Developing a New Generation of Medical Subspecialists with Expertise in Aging and Care of the Elderly

T. Franklin Williams Scholars Program

Report to T. Franklin Williams Scholars Program Evaluation Team
ASP Geriatrics Steering Committee
Integrating Geriatrics Project Evaluation Team
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Submitted by:

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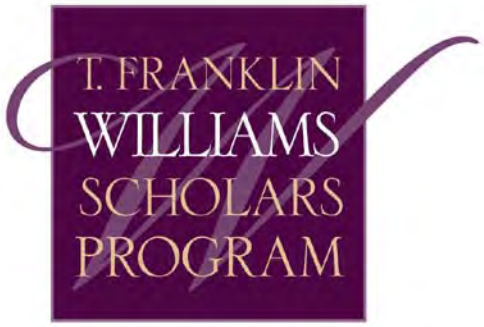

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T. Franklin Williams Scholars Program
Evaluation Report

The Association of Specialty Professors (ASP)—the organization of specialty internal medicine divisions at medical schools and community teaching hospitals in the United States and Canada—created the T. Franklin Williams Scholars Program to improve the care of older adults by identifying, training, and developing a cadre of leaders specifically focused on researching the geriatric aspect of their subspecialty.

There are currently two award structures for the T. Franklin Williams Scholars Program. Through the first structure, ASP and its partners provide two- to four-year development awards for internal medicine junior faculty at the early stages of their academic career. The total amount of the award varies from $75,000 to $225,000, and it supports the applicants' research and career development.

The second structure of the Williams Scholars award is offered in collaboration with the National Institute on Aging (NIA) through the Grants for Early Medical/Surgical Subspecialists' Transitions to Aging Research (GEMSSTAR) award program. The GEMSSTAR award, which utilizes the R03 award mechanism, will provide successful applicants up to $100,000 to support research in a geriatric aspect of their internal medicine or surgical subspecialty. To provide opportunities for professional and career development, ASP and its partners will offer the Williams Scholars awards to those GEMSSTAR applicants who have received a fundable score on their application. The Williams Scholars career development awards support applicants' plans for continued involvement in geriatrics activities or development of research skills (i.e., master's level coursework in statistical analysis). Similar to the first structure, the Williams Scholars awards provide recipients with two-years of career development support. The total amount of the award is $50,000.

For the purpose of this evaluation report, ASP is only evaluating the first structure for the T. Franklin Williams Scholars awards and will provide a summary of the administration of the second award structure.

Methods

ASP evaluates the success of the T. Franklin Williams Scholars Program through scholar questionnaires, scholar progress reports, and mentor interviews.

Williams Scholars are required to submit 12- and 24-month research and career development progress reports to ASP and the sponsoring specialty societies. In addition to the progress reports, ASP asks the scholars to complete questionnaires at six and 18 months. Through these questionnaires, ASP gathers specific information about the publication and presentation of the recipients' research, the status of grants the award recipients have applied for, and their roles in educating others about a geriatric aspect of their subspecialty. Progress reports for the 2008 and 2009 Williams Scholar are included as appendices of this report. A summary of the scholars' questionnaires is included in this report.

In addition to the above, ASP interviews the geriatrics and research mentors of the 2010 Williams Scholar at six months into the award. Mentors are asked about the progress of the scholars' research and career development plans as well as the scholar's commitment to research and education in the geriatric aspect of his or her specialty. Mentors are also asked to identify challenges or advantages that may affect the goals of the research project, comment on how the program has helped the award recipient in his or her professional development, and rate the scholar's success in comparison to other faculty at a similar stage of career development. Lastly, the mentors are asked about their role in helping the scholar implement his/her career development plan and reach independent investigator status. The mentor interviews for the 2010 Scholars are included in the appendices of this report.

Quantitative Results

Out of the 18 possible responses, 16 Williams Scholars from the 2009 and 2010 cohorts completed the six- and 18-month questionnaires. From those responses, 10 scholars have published a peer-reviewed article. In addition, seven of the 16 scholars presented on their research at a workshop or professional conference within the last year, 11 also applied for or received a grant from the National Institutes of Health in the last 12 months. Seven Scholars out of the 16 also reported involvement in a Claude D. Pepper Older Americans Independence Center, John A. Hartford Foundation Center of Excellence, or a Department of Veterans Affairs' Geriatric Research Education and Clinical Center.

In an effort to measure the long-term success of the T. Franklin Williams Scholars Program, ASP tracks the success of Williams Scholars through the collection of curriculum vitae, publication searches on PubMed, and National Institutes of Health (NIH) funding searches via the NIH Research Portfolio Online Reporting Tools Expenditures and Results database. Out of 82 T. Franklin Williams Scholars from the 2002-2010 cohorts, 43 scholars obtained extramural funding from NIH that exceeds $40 million dollars. A breakdown of the extramural funding by specialty and NIH institute or center is in Appendix x.

Qualitative Results

Interviews conducted with the scholars' geriatrics and research mentors offered additional insight on the progress, successes, and challenges faced by the 2010 Scholars. Based on the interviews, most of the scholars have started working on applications for a K08 or a K23 award, including the Paul B. Beeson Career Development Award. Since the interview was conducted during the first nine months of awards, most mentors felt that Scholars did not have the analyzed or published data to be considered a competitive applicant for an independent investigator award. However, most of the mentors felt that with the protected time from the Williams Scholars award, and the research support, that most Scholars will be ready to apply for an R01 award by the end of the Williams Scholars award (June 30, 2013).

While highlighting the successes of the scholars, it is also important to recognize the challenges they face. A challenge that several scholars faced was with their

collaborations with both internal and external stakeholders (e.g., institution center on aging and Kaiser Permanente). The challenges they face with the two stakeholders is navigating the political process of research collaborations. With internal stakeholders, the scholars' project may be delayed because it is not considered as high a priority as other senior investigators' projects. With external stakeholders, the scholar's project may be delayed because the research question does not align with the stakeholder's actual practices (e.g., trying to capture data that is not being tracked in a systematic manner). To work through that, the scholars are working with their established research and geriatrics mentors to help navigate the political processes of collaborating with various stakeholders so their project is not delayed.

Administration

The award application and selection process is now underway for the 2011 award cycle. The 2011 awards will be offered in collaboration with the NIA GEMSSTAR award program. The partners for the 2011 cycle are:

- The American Academy of Allergy, Asthma, and Immunology (AAAAI).
- The American College of Rheumatology Research and Education Foundation (ACR REF).
- The American Diabetes Association (ADA).
- The American Geriatrics Society (AGS) Foundation for Health in Aging.
- The American Society of Nephrology (ASN).
- The CHEST Foundation of the American College of Chest Physicians (ACCP).
- The Infectious Diseases Society of America (IDSA).
- The Society of Hospital Medicine (SHM).

Currently, several partner organizations have received applications and are reviewing them for a primary and an alternate candidate for the 2011 award cycle. After reviewing the applications and identifying a possible recipient, ASP's partners will submit the applications for the recommended recipients to ASP for review and approval from the ASP Geriatrics Steering Committee. Those applicants who have been identified as recipients of the T. Franklin Williams Scholar award must then submit confirmation of the matching career development award to NIA. ASP and its partners will only support those applicants who have received a fundable score by NIA, been selected by ASP and its partner, and who have made the NIA pay line cutoff. Table 2 shows the number of applications NIA received in response to the 2010 GEMSSTAR request for applications. Toward the end of 2010, ASP confirmed its partners for the 2011 T. Franklin Williams Scholars Program award cycle, one of which was with a new partner, the Society of Hospital Medicine (SHM). Since SHM was recently (September 2009) recognized as a member of ASP, this was the first year ASP offered an award with SHM under the T. Franklin Williams Scholars Program. The joint ASP-SHM award offers two years of career development support for academic hospitalists. While ASP was able to secure this new partnership, it was not able to confirm all the partners from the 2010 cycle for the 2011 cycle.

Due to the revised application review structure of the Williams Scholars awards, some of ASP's partners were not able to confirm their participation in the 2011 award cycle. In an effort to secure additional partners for the 2012 cycle, ASP is meeting with the American College of Cardiology and the American Heart Association, the Conquer Cancer Foundation of the American Society of Clinical Oncology, and the American Society of Hematology.

As in the past years, ASP has increased its marketing efforts of the T. Franklin Williams Scholars Program and its awards. In August 2010, ASP submitted a press release announcing the 2010 scholars through the American Association for the Advancement of Science's EurekaAlerts. The release received more than 2,600 hits. ASP plans to post the announcement of the 2011 T. Franklin Williams Scholars and advertise the second GEMSSTAR funding opportunity announcement to EurekAlert. It is our hope that this marketing mechanism will increase the interest and the number of applications to the GEMSSTAR award program and the T. Franklin Williams Scholars Program.

Conclusion

Through the revised T. Franklin Williams Scholars Program, ASP will support 33 Williams Scholars/GEMSSTAR Scholars by June 30, 2014. By the end of the T. Franklin Williams Scholars Program, ASP and its partners will have identified 115 leaders in aging research.

Table 1: Applications and Award Progress

	2002		2003		2004		2005		2006		2007		2008		2009		2010	
	App	Awd	App	Awd	App	Awd	App	Awd	App	Awd	App	Awd	App	Awd	App	Awd	App	Awd
Allergy	2	1	1	1	0	0	4	1	3	1	2	1	2	0	3	1	4	1
Cardiology	n/a	n/a	6	1	2	0	7	1	n/a	1	24	1	9	0	3	1	3	1
Endocrinology	n/a	n/a	4	1	3	1	1	0	1	0	3	1	2	0	7	1	2	0
Gastroenterology	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	3	1	2	1	3	1	n/a	n/a
General Internal Medicine	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2	2	2	1	3	1	4	1
Geriatrics	n/a	n/a	n/a	n/a	n/a	n/a	6	1	2	1	2	1	2	1	4	1	4	1
Hematology	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2	0	4	1	2	0	2	0
Infectious Diseases	5	1	2	1	4	2	5	1	7	1	6	2	4	1	4	1	3	1
Nephrology	2	0	3	2	3	2	1	1	5	2	1	0	3	2	2	1	0	0
Oncology	n/a	n/a	n/a	1	2	0	1	1	n/a	2	7	1	n/a	n/a	5	1	0	0
Pulmonary/ Critical Care	6	1	4	1	7	2	7	1	2	1	5	2	6	2	4	1	2	1
Rheumatology	4	1	2	2	1	0	4	2	2	1	1	1	2	2	1	1	3	1
TOTAL	**19**	**4**	**22**	**10**	**22**	**7**	**36**	**9**	**22**	**10**	**58**	**13**	**38**	**11**	**41**	**11**	**24**	**7**

Table 2: GEMSSTAR Award Program – Breakdown of Applications by Specialty

Specialty	Percent of Applications	Estimated Number of Applications (assuming 100 people applied for award)
Allergy/immunology	2%	2
Anesthesiology	4%	4
Cardiac surgery	2%	2
Cardiology	8%	8
Emergency medicine	2%	2
Endocrinology	8%	8
General surgery/endocrinology	2%	2
Geriatrics	2%	2
General internal medicine	12% (33% of these applications are focused on hospital medicine)	12 (4 applications focused on hospital medicine)
Hematology/Oncology	6%	6
Medical oncology	2%	2
Infectious diseases	12%	12
Nephrology	6%	6
Neurology	2%	2
Obstetrics and Gynecology	10% (40% of these applications are focused on gynecology-oncology)	10 (4 applications focused on gynecology-oncology)
Orthopedic surgery	2%	2
Pulmonary/critical care	6%	6
Radiology	2%	2
Rheumatology	4%	4
Surgical oncology	2%	2
Urology	4%	4
TOTAL	100%	100

T. Franklin Williams Scholars Program

ABOUT THE PROGRAM

During the 20th century, America's health care system evolved to meet the needs of a younger generation. Now, the nation's health system is facing a shift from a population dominated by young and middle-aged people to one dominated by older citizens. The Association of Specialty Professors (ASP) created the T. Franklin Williams Scholars Program to address the health care needs of this growing segment of society.

Through strong partnerships with specialty societies and the generous commitment of the Atlantic Philanthropies (USA) Inc., and support of The John A. Hartford Foundation, ASP developed a research award program for specialists in the early years of their first faculty appointment. ASP partners with 12 internal medicine specialty societies to offer the Williams awards in 12 specialties, including general internal medicine.

PROGRAM PARTNERS

Partner	Partner Since
American Academy of Allergy, Asthma, and Immunology	2002
American College of Chest Physicians	2002
American College of Rheumatology Research and Education Foundation	2002
American Diabetes Association	2003
American Gastroenterological Association Foundation	2006
American Geriatrics Society	2005
American Society of Clinical Oncology	2003
American Society of Hematology	2006
American Society of Nephrology	2002
Infectious Diseases Society of America	2002
Society of General Internal Medicine and Association of Chiefs of General Internal medicine	2006
American Heart Association	2005

SUMMARY DATA ON THE WILLIAMS SCHOLARS PROGRAM

Funding Committed to Williams Scholars Awards (2007-2010 cohorts) (including visiting professor program)	$4,670,971.07
Matching Funds (2007-2010 cohorts)	$4,305,999
Number of Applications Received for 2010 award cycle	30
Number of Awards Funded for 2010 award cycle	7
Total Number of Awards Funded through 2010 cohort	82

Breakdown of Williams by Specialty

Specialty	Total Applications 2002-2010	Funded 2002-2010
Allergy and Immunology	21	7
Cardiology	60	6
Endocrinology	23	4
Gastroenterology	8	3
General Internal Medicine	11	5
Geriatrics	20	6
Hematology	10	1
Infectious Diseases	40	11
Nephrology	23	10
Oncology	15	6
Pulmonary and Critical Care Medicine	46	12
Rheumatology	20	11
Total	**291**	**82**

Breakdown of Applications and Awards by Specialty

Specialty	% specialty applications per total applications 2002-2010 (291)	% of total awards 2002-2010 (82)
Allergy and Immunology	7.2%	8.5%
Cardiology	20.6%	7.3%
Endocrinology	7.9%	4.9%
Gastroenterology	2.7%	3.7%
General Internal Medicine	3.7%	6.1%
Geriatrics	6.8%	7.3%
Hematology	3.4%	1.2%
Infectious Diseases	13.7%	13.4%
Nephrology	7.9%	12.2%
Oncology	5.1%	7.3%
Pulmonary and Critical Care Medicine	15.8%	14.6%
Rheumatology	6.8%	13.4%
Total	**101.6%**	**99.9%**

Total Award Amount Dedicated to Award Recipients 2002-2010

Specialty	Amount
Allergy and Immunology	$1,012,500
Cardiology	$887,000
Endocrinology	$600,000
Gastroenterology	$675,000
General Internal Medicine	$750,000
Geriatrics	$900,000
Hematology	$150,000
Infectious Diseases	$1,550,000
Nephrology	$1,469,000
Oncology	$1,000,000
Pulmonary and Critical Care Medicine	$1,670,000
Rheumatology	$1,650,000
Total	**$12,313,500**

DRAWING ADDITIONAL FUNDING TO THE FIELD

The following data is based on data gathered from the database National Institutes of Health (NIH) Research Portfolio Online Reporting Tool and from scholars' curriculum vitas.

NIH Funding

Number of Scholars Receiving NIH Funding	43
Total Number of Research Awards	65
Total Amount for Research Awards	$40,831,764

Breakdown by Type of Grant

Type of grant	Total number of grants	Total Amount for grant
F32	2	$142,570
K08	6	$3,400,254
K23	25	$16,068,996
M01	10	$1,193,132
P20	1	$480,396
R01	9	$12,617,625
R03	3	$372,659
R21	5	$2,220,847
U13	1	$212,500
U54	1	$279,954
Contract	2	$3,842,831
TOTAL	**65**	**$40,831,764**

Breakdown of Applications to Institute by Specialty

Institute	Total number of awards	Total amount per specialty
National Center for Research Resources	**11**	**$1,673,528**
Allergy and Immunology	1	$271,978
Endocrinology	3	$476,003
Hematology	1	$19,712
Nephrology	1	$6,414
Oncology	2	$242,333
Pulmonary and Critical Care Medicine	2	$655,714
Rheumatology	1	$1,374
National Heart, Lung, and Blood Institute	**13**	**$9,019,501**
Cardiology	3	$1,585,561
Endocrinology	2	$1,404,550
Oncology	1	$657,450
Pulmonary and Critical Care Medicine	6	$5,091,986
Rheumatology	1	$279,954
National Institute on Aging	**19**	**$12,816,127**
Endocrinology	1	$60,652
General Internal Medicine	4	$1,978,053
Geriatrics	4	$4,035,630
Infectious Diseases	4	$2,918,310
Nephrology	1	$690,176
Oncology	2	$1,086,777
Pulmonary and Critical Care Medicine	2	$899,540
Rheumatology	1	$1,146,989

National Institute of Allergy and Infectious Diseases	**5**	**$5,804,425**
Allergy and Immunology	1	$699,744
Infectious Diseases	2	$3,107,196
Rheumatology	2	$1,997,485
National Institute of Arthritis and Musculoskeletal and Skin Diseases	**9**	**$6,432,777**
General Internal Medicine	1	$727,119
Rheumatology	8	$5,705,658
National Institute of Diabetes and Digestive and Kidney Diseases	**7**	**$4,646,526**
Endocrinology	1	$81,918
Nephrology	6	$4,564,608
National Institute of Nursing Research	**1**	**$438,880**
Pulmonary and Critical Care Medicine	1	$438,880

Dissemination of Research Findings

The data below is collected from annual questionnaires, where we ask the scholars to list the number of articles and abstracts submitted for publication and presentations on their research topic. The data is extracted from the scholars' 18-month questionnaires.

Publications

Scholar Class	2002	2003	2004	2005	2006	2007	2008	2009
Published abstracts	7	24	21	23	25	18	15	8
Published peer-reviewed articles	11	20	23	35	25	31	53	15

Presentations

Scholar Class	2002	2003	2004	2005	2006	2007	2008	2009
Presentation at another institution	N/A[1]	5	3	1	7	10	9	4
Presentation at workshop or professional conference	4	16	6	25	8	25	17	6

[1] This information was not collected during this reporting period.

Foundation for Digestive Health and Nutrition

Research Award Progress Report

I. General Information:

Abraham, Neena, S
Name (Last, First, MI)

AGA Foundation Research Scholar Award in Geriatrics — **07/01/2007-06/30/2010**
Name of Award — Dates of award period

SHARED DECISION-MAKING FOR NSAID AND CARDIOPROTECTIVE DRUG PRESCRIPTION AMONG OLDER ADULTS
Project Title

Baylor College of Medicine
Sponsoring Institution where award was held

Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd (152), Houston, TX, 77030
Office Address (or best address to reach you)

713-794-8601 — **713-748-7359**
Phone Number — Fax Number

nabraham@bcm.edu — **July 1, 2007-June 30, 2010**
E-mail — Award Term covered by this report

I certify that the foregoing information is correct, and that my research has been conducted in accordance with the Foundation guidelines.

Signature — June 17, 2010 Date

Responses to the following items should be appended on separate sheets. Please observe the space limitations, and type your name and the award type on the top right hand corner of all supplemental materials.

II. Scientific progress report:
In no more than 2 pages, summarize the scientific accomplishments of the award period. Describe how your findings relater to the specific aims of the original application, as well as any changes in research direction that occurred during the tenure of the award, or the effect that the results may have on patient care (if applicable). Describe any specific techniques or skills that you acquired as a result of this award. Progress reports must include a lay language project summary.

III. Publications, abstracts and presentations:
On separate sheets, list all publications that have resulted from this award. Do not list publications that resulted from work conducted largely prior to the award period. Enclose one copy of all listed publications.

IV. Current funding, including any additional funding obtained as a result of this award:
Using NIH format, list all current and pending support for your research activities. Identify any new awards obtained that you believe were facilitated by the support received from the Foundation.

V. Other honors:
List any prizes or other honors given to you since the start date of your Foundation funding.

VI. Personal statement:
In half a page or less, describe the personal benefits that have accrued to you from this award and not whether you are still conducting GI research (if no longer conducting research, please indicate your current position). If appropriate, please state how the award has influenced your career decisions and/or academic advancement. This statement may be submitted on personal/institutional letterhead, if preferred. *Please note: these statements may be utilized by the Foundation Developmental Department as a tool to obtain funding support for the Foundation Research Awards Program.*

II. Scientific progress report

The educational and scientific goals of this RSA were to a) learn and operationalize the Delphi panel method for consensus development to assess physician beliefs, expectations and treatment goals for nonsteroidal anti-inflammatory drug (NSAID) and cardioprotective polypharmacy (i.e., complex antithrombotic therapy [CAT]), and b) to develop and recruit an Adaptive Conjoint Analysis (ACA) survey to assess patient preferences for medication treatment strategies.

a) As a member of the steering committee and methodologist for the First International Working Party on the Gastrointestinal (GI) and Cardiovascular Effects of NSAIDs and Antiplatelet Drugs, I worked with Dr. Loren Laine, Professor of Medicine at the Keck School of Medicine, University of Southern California, to operationalize and moderate a Delphi Panel to measure physician consensus regarding the topic of my RSA. The results were published in October 2008 in the *Journal of the American College of Gastroenterology.* The expertise I gained operationalizing this Delphi panel led to an invitation to serve as a member of the joint American College of Cardiology (ACC)-ACG-American Heart Association (AHA) Consensus Panel for development of practice recommendations to reduce GI risks of antiplatelet therapy and NSAIDs. My participation on this panel resulted in two multi-society guidelines, published in the Journal of the American College of Gastroenterology, the Journal of the American College of Cardiology and Circulation in October 2008 (Bhatt et al.) and in November 2009 (Becker et al). The high-point of my RSA and the educational trajectory it permitted was my invitation to chair the ACC-ACG-AHA panel of experts in NSAIDS and antiplatelet drugs to author an Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines. This guideline is currently in revision and will be simultaneously published in the Journal of the American College of Gastroenterology, the Journal of the American College of Cardiology and Circulation in the fall of 201 0 (**Abraham NS**, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and the gastrointestinal risks of antiplatelet therapy and NSAID use. J Am Coll Cardiol; 2010). Highlights from the open peer-review process are paraphrased below:

"This is the best written document I have ever reviewed. The simplicity of the sentence structure and the consistent use of summary sentences in place of rambling trial summaries would make Hemingway proud. The reader will delight in its readability and clear summary messages. The crisp style and short length should be an example for future Guideline documents". Eric R. Bates MD, Official AHA Reviewer and Lead Reviewer

"Of all the documents similar to this that I have read over the past few years, this is-by far-the best. It is succinct, focused, and very clear. I congratulate the authors for an outstanding job." Leslie David Hillis MD. ACCF CABG Guideline Group Leader and Content Reviewer

"This is overall a superb document—clear, focused and clinically relevant. I have no major changes to recommend". Philip O. Katz MD, ACG Official Reviewer.

b) Our work eliciting preferences for NSAID and cardioprotective polypharmacy yielded excellent data which I have leveraged into my second VA Merit Award (HSRD IIR 08-028), "Complex Antithrombotic Therapy in Older Veterans: GI Risk and Preference", which began funding in September 2009. The preliminary data generated included an assessment of the influence of pharmaceutical companies on physician NSAID prescription (Am J Manag Care 2009), and an exploration of patient narrative coherence and understanding of risk associated with NSAID and cardioprotective polypharmacy (Qualitative Health Research 2010). In addition, preliminary data included ascertainment of the dominant attributes and the range of medication

attributes that are most valued by CAT patients. We confirmed our hypothesis that patients are "predictably irrational" when making decisions, overweighing rare events (i.e., excessive concern regarding potential future stroke, heart attack or GI bleed) demonstrating intense risk aversion (i.e., especially with regard to avoiding medication side-effects). This data permitted refinement of the conjoint matrix which informed the clinical trade-offs used in the Adaptive Conjoint Analysis (ACA) survey. We pilot tested and refined the resultant survey, enrolling 85 patients to complete the final survey. Analysis is ongoing to derive utilities and the strength of patient preference for specific CAT strategies. I plan to generate a summary of preferences with the inherent property of multiple trade-offs between treatment benefits, risks and management burdens. A sensitivity analysis using Monte Carlo simulations will test the robustness of predicted utilities over a wide range of potential risk-benefit estimates to determine how variation influences treatment choices. Finally, I will perform segmentation analysis to aggregate individual preference responses highlighting respondents with similar preferences.

Future plans:

I plan to submit a federal grant to use the derived summary characteristics and quantified segmented preferences to develop *patient archetypes* which can serve as an efficient method for understanding the motivational drivers of preference choice among major segments of the CAT population. The medication strategy attributes which drive or dominate the construction of archetypes, will be considered the foundation for developing *screening questions* that permit the physician to quickly segment his/her patient into an archetype. Once having a sense of what the patient's archetype might be, a physician can quickly focus his/her discussion to verify the patient's placement within that archetype. If the archetype fits, then the physician can delve into the specifics of the preferences, key motivations that would underpin that patient's likely preferences for CAT therapy; determine if there is any archetype-specific health education that needs to occur during decision-making; and use a communication-aid to engage the patient in a way that permits the patient's individual voice to come into play and encourages patient activation in the decision-making process. In short, the archetypes offer a starting point for focusing the discussion of patient values which in turn should make it easier to uncover the patient's unique preferences, thereby promoting more patient-centered care.

III. Publications, abstracts and presentations

Abstracts and presentations:

Woofter A, Naik AD, **Abraham NS**. What shapes provider behavior when prescribing NSAIDs? Am J Gastroenterol 2006; 101 (9): S397: AB 1007. (*Presented at the Annual Scientific Meeting of the American College of Gastroenterology, Las Vegas, NV, October 2006*).

Abraham NS, Hartman C, Smalley W. Mortality following NSAID-related gastrointestinal or cardiovascular event. Gastroenterology 2007; 132 (4) Suppl 2; AB 918. (*Presented at Digestive Diseases Week, Washington, DC, May 2007).*

Abraham NS, DeSilva R, Richardson P. Derivation and validation of an algorithm to identify *Helicobacter pylori* infected patients using administrative data. Am J Gastroenterol 2007; S431:AB 850. (*Presented at the Annual Scientific Meeting of the American College of Gastroenterology, Philadelphia, PA, October 2007*).

Abraham NS, Hasche J, Hartman C. Cost-benefit of PPI gastroprotection among elderly NSAID users. Am J Gastroenterol 2007; 102 (S2): S431; AB 851. (*Presented at the Annual Scientific Meeting of the American College of Gastroenterology, Philadelphia, PA, October 2007). *Awarded the Auxiliary Award for the best scientific paper submitted by a Member of the College.*

Abraham NS, Castillo DL, Naik AD. NSAID-cardioprotective drug polypharmacy: Patient beliefs and expectations of treatment goals. Journal of the American Geriatric Society 2008; 56 (4s):S49. (*Presented at the American Geriatrics Society Annual Meeting, Washington, DC, May 2008).*

Gaspard GP, Castillo DL, **Abraham NS**. Clinical knowledge gaps, formative training and safer NSAID prescription. Gastroenterology 2008; 134 (4 suppl 1): A625. (*Presented at Digestive Diseases Week, San Diego, CA, May 2008*).

Desai SV, Fitton CP, Castillo DL, **Abraham NS**. Meta-Analysis: Risk of upper gastrointestinal event with over-the-counter non-steroidal anti-inflammatory drugs. Gastroenterology 2008; 134 (4 suppl 1): A737. (*Presented at Digestive Diseases Week, San Diego, CA, May 2008*).

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Abraham NS, Naik AD, Richardson P, Hartman C. Complex antithrombotic therapy (CAT) and the risk of upper gastrointestinal events (UGIE) among vulnerable elders. (*Presented at the American Geriatrics Society Annual Meeting, Chicago, IL, May 2009*).

Abraham NS, Naik AD, Richardson P, Hartman C. Complex antithrombotic therapy (CAT) and the risk of upper gastrointestinal events (UGIE) among vulnerable elders. Gastroenterology 2009; 136 (5 suppl 1): A29. (*Presented at Digestive Diseases Week, Chicago, IL, June 2009). *Selected for inclusion in the Digestive Disease Week 2009 press program which highlights the most important and newsworthy research being presented at the meeting.*

Abraham NS, Naik AD, Kunik M, Richardson P. Colorectal cancer and the elderly: Prevalence of geriatric syndromes and implications for care. Gastroenterology 2009; 136 (5 suppl 1): A334. (*Presented at Digestive Diseases Week, Chicago, IL, June 2009).*

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Bhatt DL, Scheiman J, **Abraham NS**, Antman EM, Chan FKL, Furberg C, Johnson DA, Mahaffey K, and Quigley EM. ACCF/ACG/AHA clinical expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents. Circulation 2008; 118 (18): 1894-909.

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Castillo DL, **Abraham NS**. Knowledge management: how to keep up with the literature. Clin Gastroenterol Hepatol. 2008 Dec;6(12):1294-300.

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Sonnenberg A, Richardson PA, **Abraham NS**. Hospitalizations for inflammatory bowel disease among US military veterans 1975-2006. Digest Dis Sci, 2009;15(4):1740-5.

Dries AM, Richardson P, Cavazos J, **Abraham NS**. Therapeutic intent of proton pump inhibitor prescription among elderly NSAID users. Aliment Pharmacol Ther 2009;30(6):652-61.

Becker RC, Scheiman J, Dauerman HL, Spencer F, Rao S, Sabatine M, Johnson DA, Chan F, **Abraham NS**, Quigley EM. Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. J Am Coll Cardiol 2009; 54(24):2261-2276.

Becker RC, Scheiman J, Dauerman HL, Spencer F, Rao S, Sabatine M, Johnson DA, Chan F, **Abraham NS**, Quigley EM. Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. Am J Gastroenterol 2009; 104(12):2903-17.

Thirumurthi S, Chowdhury R, Richardson P, **Abraham NS**. Validation of ICD-9-CM diagnostic codes for inflammatory bowel disease among veterans. Dig Dis Sci 2009 Dec 24 [Epub ahead of print].

Abraham NS, Hartman C, Hasche J. Reduced hospitalization cost for upper gastrointestinal events that occur among elderly veterans who are gastroprotected. Clin Gastroenterol Hepatol 2010;8(4):350-6.

Anaya DA, Becker NS, **Abraham NS**. Global graying, colorectal cancer and liver metastasis. Crit Rev Oncol Hematol 2010 Mar 3 [Epub ahead of print].

Collins D, **Abraham NS**, Naik AD, Street RL. Understanding risk through narrative coherence: patients' stories about complex antithrombotic therapies. *In press: Qualitative Health Research 2010.*

Cheema F, **Abraham NS**, Berger D, Albo D, Naik AD. Novel approaches to assessment and longterm outcomes of older adults undergoing colorectal cancer resection. *In press: Annals of Surgery 2010.*

IV. Current Funding

1. a. Complex Antithrombotic Therapy in Older Veterans: GI Risk and Preference
   b. VA MERIT award (HSRD IIR 08-028)
   c. Principal Investigator (20% effort; no salary)
   d. 07/01/09-06/30/12
   e. $462,100
   f. Grant
2. a. Obesity, *H. pylori*, and Risk of Barrett's Esophagus
   b. 1 R01 CA116845-01 A2
   c. Co-investigator (12% effort; with salary; PI: Hashem El-Serag, MD MPH)
   d. 4/1/07-3/31/12
   e. $1,890,908
   f. Grant
3. a. PPI Therapy for the Gastroprotection of Older Patients with NSAID and Cardioprotective Polypharmacy
   b. TAP Pharmaceuticals Inc. (Investigator-Initiated Protocol)
   c. Principal Investigator (1% effort; no salary)
   d. 01/31/00-01/31/11
   e. $104,610
   f. Grant

V. Honors (2007-2010)

a. Fellow of the American Society of Gastrointestinal Endoscopy, February 16, 2007.

b. Gastroenterology Research Group and American Gastroenterological Association Young Investigator Clinical Science Award; 2007.

c. American College of Gastroenterology Auxiliary Award for the best scientific paper submitted to the Annual Scientific Meeting by a Member of the College, Philadelphia, PA, October13-17, 2007.

d. Named one of "America's Top Gastroenterologists" by the Consumers' Research Council of America, 2007 and 2008.

e. Course Co-Director, National Post-Graduate Course of the American College of Gastroenterology, Orlando, FL, October 3-8, 2008.

f. Member, American College of Cardiology -American College of Gastroenterology-American Heart Association Committee for practice recommendations/guidelines regarding the "Reduction of Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use," Washington, D.C., May 19, 2007-October 31, 2008.

g. Fellow of the American College of Gastroenterology, February 4, 2008.

h. Fulbright & Jaworski L.L.P. Faculty Excellence Award in Teaching and Evaluation, Baylor College of Medicine, Houston, Texas, August 1, 2008.

i. Chair, Educational Products Committee of the American Society of Gastrointestinal Endoscopy, 2008-2010

j. **Promoted to Associate Professor with Academic Tenure; Baylor College of Medicine, 2009**

k. Trustee, American College of Gastroenterology, 2009-2011.

l. Chair, American College of Cardiology -American College of Gastroenterology-American Heart Association Expert Consensus Panel regarding "the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update".

m. American Gastroenterological Association and United European Gastroenterology Federation ASNEMGE/AGA Exchange Program; Barcelona, Spain, October 24, 2010.

VI. Personal Statement

I believe the AGA-Sucampo-ASP Dedicated RSA in Geriatric Gastroenterology has been critical in my evolution from junior- to mid-career clinical scientist. The refinement of methodological skills and the scientific trajectory facilitated by this research scholar award was integral in securing my second federally funded grant (VA HSRD Merit Award 08-028) as a Principal Investigator, and key to my promotion to the rank of Associate Professor with Academic Tenure. During the tenure of my award (2007-2010), I have continued to develop my interest in decision-sciences as it relates to the safer prescription of NSAIDs and antiplatelet agents, especially among the elderly and the cardiac patient. I have enjoyed the opportunity to collaborate with thought leaders in gastroenterology, geriatrics and cardiology to meaningfully contribute to the literature, and consequently, impact day-to-day clinical practice. Most importantly, this funding permitted me to step away from full-time clinical practice, and continue my scientific growth. For this, I am indebted to the Foundation for Digestive Health and Nutrition, Sucampo Pharmaceuticals and the Association of Specialty Professors.

T. Franklin Williams Scholars Program 24 month progress report

Steven Coca, DO, MS
Effect of Acute Kidney Injury on Long-Term Kidney Function in Elderly Patients

A. Specific Aims:

1. To determine the factors associated with accelerated long-term decline in kidney function in elderly patients.

2. To determine if AKI-specific biomarkers can predict long-term outcomes (CKD, ESRD, death) in an elderly population.

3. To ascertain if AKI is associated with increased concentrations of urinary markers of renal fibrosis, and whether these markers predict long-term decline in kidney function.

4. To determine the association between AKI and health-related quality of life and cognitive function.

The population that was (and still is being) studied for answering these aims in the **T**ranslational **R**esearch **I**nvestigating **B**iomarkers **E**ndpoints in **A**cute **K**idney **I**njury (TRIBE-AKI) cohort of elderly patients undergoing cardiac surgery at 5 academic medical centers in North America (ClinicalTrials.gov #: NCT00774137). The TRIBE-AKI study was designed to validate the ability of novel biomarkers of AKI to predict in-hospital outcomes. 1219 adult patients were enrolled in the TRIBE-AKI study through December 2009.

B. Studies and Results: Through March 2011, 87 (7.1%) of the 1219 adult TRIBE-AKI study participants have died. We have ascertained these deaths through SSDI searches, hospital records and family contact. Of the remaining 1,132 participants presumed alive as of March 2011, we have performed phone follow-up on 610 (54%) to assess vital status, development of end-stage renal disease, hospitalizations and cause for hospitalizations, and consent for the 3 year in-person follow-up visit. We have completed in-person visits on 120 (74%) of 162 participants who have reached their 3 year anniversary since enrollment/surgery date via Hooper Holmes, Inc. At these in-person visits, the following tasks are being performed: blood draws for serum creatinine, urine collection for urinary albumin:creatinine concentrations, SF-12 for health-related quality of life, and the Montreal Cognitive Assessment for cognitive function. Thirty five (2.8%) TRIBE participants have been lost to follow-up due to either inability to contact or due to refusal to participant any further in research endeavors. Including all contact, we have 1221 patient-years of follow-up through the end of February 2011 (1 year follow-up (n=196), 2 year follow-up (n=236), 3 year follow-up (n=159), 4 year follow-up (n=19)). We are still in the process of collecting the data, thus no interim analyses on the relationships between the exposure (AKI) and the primary outcomes (CKD, ESRD, death) have been performed at this time.

The pre- and post-operative urine samples have been assayed for the following biomarkers: neutrophil gelatinase-associated lipocalin, interleukin-18, urinary albumin, kidney-injury

molecule-1 (measurements in-progress) and liver fatty acid binding protein (measurements in-progress).

In addition, as a complementary piece of work to the current prospective longitudinal study, I applied and had an ancillary study approved by the Health-ABC Executive Committee (AS09-124) with the primary goals of examining the relationship between AKI and changes in physical, cognitive, and kidney function in older persons. Leveraging the infrastructure of the existing Health-ABC longitudinal study (with 11 years of follow-up data) is an efficient and effective manner in which to examine these associations at low cost. The analyses for this project are currently in progress.

C. Significance: This prospective longitudinal follow-up study of patients with and without AKI will be unique because it will be the largest and longest follow-up study of AKI in elderly patients that has obtained specimens for biomarker assays around the time of AKI. Thus, this study will not only help to determine the risk for chronic kidney disease after AKI in elderly cardiac surgery patients, but will evaluate the ability for acute phase biomarkers of kidney injury to predict long-term outcomes, and whether AKI and/or these biomarkers are associated with decrements in health-related quality of life and cognitive function.

D. Research Plans:
1. Continue mailings and phone calls to remaining TRIBE-AKI adult participants to arrange 3 year follow-up visits via Hooper Holmes. Over the next 12 months, 598 additional TRIBE participants will reach their 3 year anniversary date and will be due the in-person visits.
2. Data collection/retrieval from Hooper Holmes staff from the visits.
3. Linkages with administrative databases (Medicare, USRDS) for assessment of dialysis, death and hospitalizations on TRIBE-AKI participants that refuse follow-up or cannot be contacted.
4. Data entry, data cleaning, and data analyses.
5. Completion and publication of the results from the Health-ABC ancillary study
6. Submission of RO1 application as Co-I with Mike Shlipak, MD (UCSF) for an ancillary study to the ancillary study to the LIFE trial (see below)

E. Publications (during the time period of this award):

1) **Coca SG**, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Risk of mortality and other adverse outcomes after acute kidney injury: A systematic review and meta-analysis. Am J Kidney Dis 2009; 53:961-73.

2) Lu JC, **Coca SG**, Patel UD, Cantley L, Parikh CR. Searching for genes that matter in acute kidney injury: a systematic review. Clin J Am Soc Nephrol 2009; 4: 1020-31.

3) **Coca SG**. Long-term outcomes of acute kidney injury. Curr Opin Nephrol Hypertens 2010;19:266-272.

4) Parikh CR, Lu JC, **Coca SG**, Devarajan P. Tubular proteinuria in acute kidney injury: a critical evaluation of current status and future promise. Ann Clin Biochem. 2010;47:301-12.

5) **Coca SG**. Acute kidney injury in elderly persons. Am J Kidney Dis 2010;31:408-481.

6) Hall IE, Yarlagadda SG, **Coca SG**, Wang Z, Doshi M, Devarajan P, Han WK, Marcus RJ, Parikh CR. IL-18 and urinary NGAL predict dialysis and graft recovery after kidney transplantation. J Am Soc Nephrol. 2010;21:189-97.

7) Park M, **Coca SG**, Nigwekar SU, Garg AX, Garwood S, Parikh CR. Prevention and treatment of acute kidney injury in patients undergoing cardiac surgery: A systematic review. Am J Nephrol 2010;31:408-418. PMID: 20375494

8) **Coca SG**, King JT, Rosenthal RA, Perkal MF, Parikh CR. The duration of acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. Kidney Int 2010 78;926-33. PMID: 20686452

9) Brown JR, Kramer RS, **Coca SG**, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg 2010;90:1142-8. PMID: 20868804

10) Go AS, Parikh CR, Ikizler TA, **Coca SG**, Siew ED, Chinchilli VM, Hsu CY, Garg AX, Zappitelli M, Liu KD, Reeves WB, Ghahramani N, Devarajan P, Faulkner GB, Tan TC, Kimmel PL, Eggers P, Stokes JB; Assessment Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury Study Investigators. The assessment, serial evaluation, and subsequent sequelae of acute kidney injury (ASSESS-AKI) study: design and methods. BMC Nephrol. 2010;11:22. PMCID: PMC2944247

11) Li, S, Krawczeski CD, Zappitelli M, Devarajan P, Thiessen-Philbrook H, **Coca SG**, Kim RW, Parikh CR; for the TRIBE-AKI Consortium. Incidence, risk factors and outcomes of acute kidney injury after pediatric cardiac surgery: A prospective multicenter study. Crit Care Med 2001 [epub ahead of print] PMC Journal- In Process.

12) Parikh CR, **Coca SG**. Acute kidney injury: defining prerenal azotemia in clinical practice and research. Nat Rev Nephrol 2010;6:641-2. PMID: 20981121

13) Shlipak MG, **Coca SG**, Devarajan P, Thiessen-Philbrook, H, Wang Z, Koyner JL, Patel UD, Garg AX, Parikh CR. (for the TRIBE-AKI Consortium) Pre-operative serum cystatin-C and risk of acute kidney injury after cardiac surgery. Am J Kidney Dis (in press). PMC Journal- In Process.

14) Molnar A, **Coca SG,** Devereauz PJ, Jain A, Kitchulu A, Luo J, Parikh CR, Paterson JM, Siddiqui N, Wald R, Walsh M, Garg AX. Statin use is associated with less acute kidney injury after major elective surgery. J Am Soc Nephrol 2011 (ePub ahead of print) PMID:21493769

15) Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, Kim RW, Koyner JL, **Coca SG**, Edelstein CL, Garg AX, Krawczeski CD,for the TRIBE-AKI Consortium. Early post-operative urine and serum biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol (in press). PMC Journal- In Process.

16) **Coca SG**, Cho KC, Hsu CY. Acute kidney injury in the elderly: predisposition for chronic kidney disease and vice-versa. Nephron (in press). PMC Journal- In Process.

17) Parikh CR, **Coca SG**, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX, for the TRIBE-AKI Consortium. Post-operative biomarkers predict acute kidney injury and poor outcomes after cardiac surgery in adults. J Am Soc Nephrol (in press). PMC Journal- In Process.

18) **Coca SG**, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. Kidney Int (submitted).

19) **Coca SG**, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of Intensive Glucose Control in Development of renal endpoints in type 2 diabetes: Systematic review and meta-analysis (submitted).

20) **Coca SG**, Jammalamadaka D, Sint K, Thiessen-Philbrook H, Shlipak MG, Zappitelli M, Devarajan P, Hashim S, Garg AX, Parikh CR. (for the TRIBE-AKI Consortium). Pre-operative albuminuria predicts acute kidney injury in patients undergoing cardiac surgery (submitted).

21) Siddiqui N, **Coca SG**, Devereaux PJ, Jain AK, Li L, Luo J, Parikh CR, Paterson M, Thiessen-Philbrook H, Wald R, Walsh M, Whitlock R, Garg AX. Secular trends in acute dialysis following major elective surgery, 1995 to 2009 (submitted).

22) Testani JM, **Coca SG**, Shannon RP, Kimmel SE, Cappola TP. Influence of renal dysfunction phenotype on mortality in the setting of cardiac dysfunction: analysis of three randomized controlled trials (submitted).

23) Testani JM, **Coca SG**, Shannon RP, Kimmel SE. Impact of changes in blood pressure during the treatment of acute decompensated heart failure on renal and clinical outcomes (submitted).

24) Hall IE, **Coca SG**, Perazella MA, Iyanam U, Luciano R, Peter P, Han WK, Parikh CR. Novel and traditional biomarkers for prognosis and etiology of acute kidney injury (submitted).

25) Testani JM, Kimmel, SE, Dries D, **Coca SG**. Prognostic importance of worsening renal function following initiation of angiotensin converting enzyme inhibitor therapy in patients with cardiac dysfunction (submitted).

26) Testani JM, McCauley BD, Chen J, **Coca SG**, Cappola TP, Kimmel SE, Shannon RP. Clinical characteristics and outcomes of patients with improvement in renal function during the treatment of decompensated heart failure (submitted).

F. Research Development (past 24 months)

1. Obtained a Masters of Science in Epidemiology and Public Health from Yale University (graduated in May of 2009).

2. Attended the American Geriatrics Society Annual Meetings in 2009 in Chicago and in 2010 in Orlando, including the T. Franklin Williams Meetings that occurred contemporaneously.

3. Attended a workshop on Acute Kidney Injury in Older Adults in May 2010 (sponsored by the ASP-ASN) in Alexandria, VA.

4. At the American Society of Nephrology (ASN) Annual Meeting (ASN Renal Week) in Denver in November of 2010, I delivered 2 invited talks as distinguished faculty on the following topics: A. “Is the Aging Kidney More Susceptible to AKI?” and B. “How Should Biomarkers Be Incorporated into Clinical Trials of AKI?”.

5. Presented at Yale Medical Grand Rounds in August 2010 (“Can We Improve Outcomes Related to Acute Kidney Injury?”).

6. Submitted my first RO1 in December 2010 as PI, entitled “Novel serum and urinary biomarkers of diabetic kidney disease” (1R01HL110394-01). The primary aim of the project is to identify novel biomarkers predictive of incident and progressive diabetic kidney disease.

7. Attended the T. Franklin Williams Scholars Alumni Meeting in January 2011 in Washington DC.

8. Attended the Yale Program on Aging Research Career Development Retreat in March of 2011.

9. I was designated by my section Chief as the faculty member at Yale to deliver conferences to the renal faculty and fellows pertaining to Geriatric Nephrology, including the following topics: renal physiology in the elderly; acute and chronic kidney disease in the elderly; and evaluation and management of the Geriatric CKD/ESRD patient. I have been delivering these conferences since 2010.

10. I was also designated by my section Chief as the faculty member at Yale to deliver conferences to the fellows on biostatistics and epidemiology. I have been delivering these conferences since 2009.

G. Research Development and Other Career Development Activities Planned for Next Year

1. Continue to attend weekly Renal Rounds, Journal Club and Research Meetings, TRIBE-AKI meetings, ASSESS-AKI consortium meetings, and the ASN Renal Week.

2. Invited to speak as faculty on the topic "Long Term Outcomes after an AKI episode" at the ASN Renal Week in November 2011 in Philadelphia, PA.

3. Invited to speak as faculty at the Society of Cardiac Anesthesiologists Annual Conference in May 2011 on the following two topics: "Novel biomarkers for early prediction of AKI" and "Why even a small bump in creatinine is important".

4. Submission of an RO1 application as Co-investigator for an ancillary study to the Lifestyle Interventions and Independence for Elders (LIFE) clinical trial to study the effect of an intense exercise intervention on the development and progression of CKD and on biomarkers of kidney injury in elderly, sedentary adults (target submission date early 2012).

5. Continue to deliver conferences to the Yale renal faculty and fellows pertaining to Geriatric Nephrology (renal physiology in the elderly; acute and chronic kidney disease in the elderly; and evaluation and management of the Geriatric CKD/ESRD patient).

6. Continue to deliver conferences to the Yale fellows on biostatistics and epidemiology.

H. Summary

I am very grateful for my experience with the Williams Scholars program. The additional funding allowed me to be extremely productive in the past two years. The results from my long-term follow-up of the TRIBE-AKI study should be published in the next 12-18 months and from the Health-ABC ancillary study in the next 6-9 months. I will acknowledge the T. Franklin Williams Award in all the manuscripts related to these projects.

Myofibroblast Fate Determination by Extracellular Matrix Interactions

2008 Geriatric Development Research Award

Jeffrey C. Horowitz, M.D., FCCP
Assistant Professor of Medicine
Department of Internal Medicine
Division of Pulmonary and Critical Care Medicine
University of Michigan

7/15/2008 - 7/14/2010

Support Provided By:

The Chest Foundation

and

Association of Specialty Professors

ABSTRACT

Idiopathic pulmonary fibrosis (IPF), a disease of the elderly for which there is no effective treatment, results from a dysfunctional repair process following lung injury. Myofibroblasts, critical effectors of fibrosis, accumulate in IPF and we have proposed that this accumulation is due, in part, to resistance to apoptosis. Our previous studies have defined mechanisms by which soluble fibrogenic mediators promote myofibroblast resistance to apoptosis, but the role of extracellular matrix (ECM) in the regulation of myofibroblast fate has not been shown.

This study was undertaken to examine how ECM biomechanics regulate fibroblast fate and to define the temporal relationships between changes in lung stiffness and the development of pulmonary fibrosis following lung injury. Using the murine model of bleomycin-induced pulmonary fibrosis, we found that there is an early decrease in lung compliance following injury. This correlates with an increase in fibronectin and precedes the establishment of fibrosis. In-vitro studies employed normal lung fibroblasts cultured on substrates engineered to have the stiffness of normal or fibrotic lungs. Cells were treated with/without TGF-β1 in the presence/absence of apoptotic stimuli and the effects on pro-survival signaling pathways and apoptosis were examined. First, we found that fibroblast apoptosis is decreased on substrates with fibrotic stiffness. Next, we discovered that the susceptibility of fibroblasts to Fas, but not plasminogen-mediated apoptosis also declines with increased substrate stiffness. Finally, the relative anti-apoptotic effects of TGF-β1 decline as stiffness increases such that TGF-β1 has a greater effect when cells are on a normal-stiffness substrate than a fibrotic-stiffness substrate.

PURPOSE

The overriding hypotheses of my research program are that (1) myofibroblast fate is a critical determinant of the outcome of lung injury and repair, and (2) myofibroblast resistance to apoptosis contributes to the pathobiology of pulmonary fibrosis. The focus of my research has been the study of the mechanisms regulating survival and apoptosis of lung mesenchymal cells. As the effector cells of wound repair, mesenchymal cells (fibroblasts and myofibroblasts) are responsible for the synthesis, secretion, organization, and remodeling of the extracellular matrix (ECM). Myofibroblasts are differentiated and activated cells which are characterized by the expression of stress fibers composed of alpha smooth muscle actin (α-SMA). Focal adhesions are the anchor points for these stress-fibers and represent the sites where the ECM is interacts with the cellular cytoskeleton convert biomechanical signals from the ECM into biochemical signals within cells (a process called mechanotransduction). The coupling between cells and the ECM allows formation of an integrated contractile apparatus that facilitates wound healing through the approximation of wound edges. Focal Adhesion Kinase (FAK) is a non-receptor tyrosine kinase that is an integral component of the focal adhesion complexes. Importantly, FAK is activated by the soluble fibrogenic mediator transforming growth factor beta-1 (TGF-β1) and is required for myofibroblast differentiation. Moreover, FAK is strongly expressed in murine lungs following bleomycin-induced injury and the loss of FAK signaling is a trigger for myofibroblast apoptosis. It follows, then, that the biomechanical properties of the ECM may modulate fibroblast fate through regulation of FAK.

Myofibroblast recruitment is a physiologic and stereotypic response to injury, but pulmonary fibrosis is associated with the abnormal accumulation and persistent activation of these effectors leading to excessive ECM deposition and, ultimately, the replacement of functional parenchyma with dysfunctional scar. The resolution of physiologic repair requires that accumulated myofibroblasts undergo apoptosis and failure of myofibroblast apoptosis is associated with a persistent wound-repair response and pathologic wound healing, or fibrosis. Recent studies demonstrate a distinct lack of apoptosis within fibroblastic foci, the presumed “active” sites of fibrogenesis within the IPF lung. Moreover, fibroblasts isolated from the lungs of patients with IPF have increased resistance to apoptotic stimuli. Although the mechanistic triggers of myofibroblast apoptosis *in vivo* have not been defined, our laboratory has shown that the soluble mediators TGF-β1 and endothelin-1, each of which has been causally implicated in the pathogenesis of pulmonary fibrosis, induce fibroblast resistance to apoptosis. However, there is little understanding of how dynamic changes in the biomechanical properties of the ECM matrix impact the fate of myofibroblasts. **Our hypothesis is that biomechanical signals, transduced by FAK, regulate myofibroblast fate and that the physical properties of the ECM are critical determinants of fibrogenesis.** The goals of this proposal were to:

1) Determine how biomechanical forces regulate FAK activity and fibroblast susceptibility to apoptosis *in vitro*.
2) Examine the temporal relationship between increased lung stiffness and pulmonary fibrosis *in vivo*.

SCOPE

Idiopathic Pulmonary Fibrosis: Idiopathic Pulmonary Fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias, a group of diffuse parenchymal lung diseases of unknown cause, with a conservatively estimated prevalence of 100,000 in the United States and a rising incidence and prevalence. The incidence of IPF increases with age, as does the risk of mortality in those diagnosed with IPF. The course of IPF tends to be progressive, and it presents with non-specific signs and symptoms of dyspnea and cough. Because of the indolent nature and non-specific symptoms, the diagnosis is commonly delayed in the elderly as the dyspnea and declining functional status are mistakenly attributed to aging and co-morbid illness. IPF has a dismal prognosis with a median survival of only 2-3 years following the diagnosis, and no pharmacologic intervention has been shown to improve outcomes. Despite the lack of proven efficacy, immunosuppressive medications (including corticosteroids) are commonly considered the "standard of care" for IPF; yet elderly patients are at significant risk for morbidity associated with these medications. Finally, lung transplantation is the only intervention in IPF that, in appropriately selected patients, confers a definitive survival advantage for patients with IPF. However, geriatric patients have an increased risk of mortality with lung transplantation and the elderly are frequently excluded from consideration for lung transplantation. Thus, in the geriatric population, IPF is an under-recognized disease with a dismal prognosis and inadequate therapeutic options. Improved understanding of disease pathogenesis is required for the development of novel strategies for treatment.

IPF Pathogenesis: The pathogenesis of IPF remains enigmatic, but current hypotheses propose that the disease results from an aberrant wound-repair response to chronic or recurrent lung epithelial injury. Fibroblastic foci are aggregates of myofibroblasts underlying phenotypically abnormal, apoptotic epithelial cells and are considered the "active" lesions in IPF. The extent of these foci correlates with mortality, supporting a critical role for fibroblasts in disease pathogenesis. Fibroblasts are necessary effectors of wound-repair; following epithelial injury, recruited fibroblasts differentiate into myofibroblasts which secrete, organize and contract the extracellular matrix (ECM). The resolution of normal wound repair, with restoration of functional tissue architecture, requires that myofibroblast apoptosis and clearance of excessive ECM coincide with the reestablishment of epithelial integrity. Failure of myofibroblast apoptosis with persistent ECM deposition is associated with pathologic scar formation and destruction of

functional tissue architecture. Thus, myofibroblast fate represents a critical determinant of the resolution of wound-repair responses.

Soluble Mediators in Fibrogenesis: Transforming growth factor beta-1 (TGF-β1) and endothelin-1 (ET-1) are soluble fibrogenic mediators that have been causally implicated in the pathogenesis of pulmonary fibrosis. Each of these mediators has potent fibrogenic effects, as they stimulate myofibroblast differentiation, ECM production, and ECM contraction. We have shown that each of these mediators protects myofibroblasts from apoptotic stimuli through the activation of pro-survival signaling pathways involving PI3K/AKT. Moreover, our published and unpublished studies show that each of these mediators induces activation of focal adhesion kinase (FAK) in lung fibroblasts. Importantly, FAK is strongly expressed in fibrotic lung tissue and in fibroblasts cultured from lung explants of mice following injury with intratracheal bleomycin. Moreover, pharmacologic inhibition of FAK attenuates bleomycin induced pulmonary fibrosis in this murine model. Collectively our studies suggest that FAK activation is associated with, and may be necessary for, lung fibrogenesis.

FAK regulates mechanotransduction: Mechanotransduction is the process by which physical forces exerted by the ECM are sensed by cells and converted into biochemical signals. The resulting cellular responses regulate the intracellular cytoskeleton to maintain an isometric balance between external and internal forces and affect cell phenotypes, including myofibroblast differentiation. Integrins are transmembrane receptors that bind the ECM and cluster in focal adhesions, the anchor points for cytoskeletal networks and stress fiber formation in myofibroblasts. FAK is a critical component of focal adhesions and mechanotransduction signaling that is activated by TGF-β1, required for myofibroblast differentiation, and promotes myofibroblast survival. Consistently blockade of adhesion mediated signals results in FAK inactivation and subsequent apoptosis, suggesting that FAK activation is critical for the maintenance of myofibroblast survival.

ECM stiffness and fibrogenesis: Pulmonary fibrosis is characterized by a progressive loss of lung compliance, and this loss of lung compliance has been correlated with the severity of underlying fibrosis. The increased stiffness of lung parenchyma has, in the past, been attributed to the deposition of excessive ECM by myofibroblasts. Recent studies in animal models of liver fibrosis have shown, however, that increases in tissue stiffness following injury actually precede myofibroblast accumulation and collagen production, calling into question the established wound-healing paradigm that increased stiffness follows from myofibroblast activation. Indeed, prior studies have shown that biomechanical tension (i.e. a “stiff” mechanical substrate), is necessary for fibroblast differentiation to myofibroblasts. The temporal relationship between lung injury, lung

stiffness, and subsequent fibrogenesis has not previously been studied. We hypothesize that, as in liver, increased lung stiffness following injury is necessary for the development of fibrosis. Additionally, we propose that increased lung stiffness may, even in the absence of soluble mediators, support the anti-apoptotic myofibroblast phenotype. If so, this would suggest that interactions between myofibroblasts and the ECM may promote the autopropagation of fibrosis in the absence of ongoing injury. The clinical implication of these hypothesis are that emerging treatment strategies for IPF would target the vicious cycle of increased matrix stiffness, myofibroblast survival and myofibroblast activation.

METHODS:

In-vitro models: To examine the effects of ECM stiffness on mesenchymal cell survival and apoptosis, we collaborated with Daniel J. Tschumperlin, Ph.D. from the Harvard School of Public Health. Dr. Tschumperlin has recently used atomic force microscopy to determine the range of parenchymal stiffness in normal and fibrotic lung (median of 400 Pa vs. 3000 Pa, respectively), and has used polymerized acrylamide and bis-acrylamide to establish hydrogels with specific sheer moduli spanning the normal and fibrotic range (100, 400, 1600, 6400 and 25600 Pa). The hydrogels were coated with monomeric collagen via a heterobifunctional crosslinker sulfo-SANPAH to allow cell attachment. For cell culture, normal human fetal lung fibroblasts (IMR-90) were seeded onto the hydrogels in DMEM supplemented with 10% fetal bovine serum and allowed to adhere for 6 hours. The media was then changed to serum-free DMEM for 24 hours, and cells were treated with or without a stimulus of apoptosis (Fas-activating ligand, the combination of Fas-activating ligand with cycloheximide, or plasminogen) and/or a soluble fibrogenic mediator (TGF-β1, 2 ng/ml) for an additional 16 hours. Protein (cell lysates) and RNA were isolated for subsequent evaluation of: 1) signaling pathway activation (via Western immunoblotting for FAK, AKT), 2) differentiation (Western immunoblotting for α-SMA expression), 3) apoptosis (ELISA for histone-associated DNA fragmentation, ELISA for caspase-3 activation, or Western immunoblotting for cleaved poly-ADP ribose polymerase), and ECM expression (quantitative real-time PCR).

In-vivo studies: To examine the temporal relationship between lung injury and lung compliance, we utilized the well described model of bleomycin-induced murine pulmonary fibrosis. In this model, bleomycin induces alveolar epithelial injury with inflammation which peaks at day 7 and is followed by the development of fibrosis which is traditionally measured as increased collagen after day 14. Wild-type C57/b6 mice were treated with intratracheal bleomycin or saline on day 0. Between days 3 and 14, assessments of lung compliance were made by: 1) in-vivo pulmonary function testing (the Cchord measurement, which reflects the mean slope of the lung compliance curve between 0-10 cm H_2O.), 2) generation of inflation and deflation air compliance curves

were with a closed thoracic cage (Pulmonary Maneuvers System ; Buxco Electronics), and 3) evaluation of tissue strips dissected from harvested lung using a tissue elastometer (Artann Laboratories). In addition, protein was isolated from lung homogenates for assessment of ECM by Western immunoblotting for fibronectin.

RESULTS

In vitro studies: Our in-vitro studies show that mechanical stiffness within the range found in the parenchyma of fibrotic lung, in contrast to the stiffness found in the normal lung, has profound effects on mesenchymal cell phenotype. First, fibrotic-range stiffness leads to a significant increase in FAK activation as determined by Western blotting for phosphorylation at tyrosine-397 (Y^{397}). This increase in FAK activation was concordant with myofibroblast differentiation (determined by Western blotting for α-SMA) and, to a lesser extent, activation of AKT (determined by phosphorylation at S^{473}). Moreover, fibrotic range stiffness was associated with increased transcriptional expression of both fibronectin and collagen.

Spontaneous rates of mesenchymal cell apoptosis declined significantly when cells were exposed to a substrate with fibrotic-range stiffness in comparison to cells cultured on stiffness within the range found in normal lung parenchyma. Interestingly, mesenchymal cells cultured on substrates with fibrotic-range stiffness were resistant to apoptosis induced by Fas-alone (compared to cells on normal stiffness substrates), but this resistance to apoptosis was lost when cells were exposed to Fas in combination with cycloheximide. Substrate stiffness had no apparent effect on apoptosis induced by plasminogen activation, suggesting that the anti-apoptotic effect of increased matrix stiffness is stimulus-dependent.

Finally, the effects of TGF-β1 on FAK activation, myofibroblast differentiation, ECM expression and spontaneous apoptosis were modulated by substrate stiffness. Surprisingly, TGF-β1 had a greater relative impact on cells cultured on normal-stiffness substrates and the stimulatory effects of TGF-β1 diminished as substrate stiffness increased into the fibrotic range. Thus, TGF-β1 effectively stimulated cells on normal matrices to express phenotypes that were similar to cells on stiff matrices in the absence of the soluble mediator; the soluble mediator had little further effect on cells cultured on substrates with fibrotic-range stiffness. These studies suggest that increased ECM stiffness is capable of sustaining an apoptosis-resistant myofibroblast phenotype even in the absence of ongoing soluble fibrogenic stimulus.

In vivo studies: Murine studies consistently showed that there is an early and sustained increase in lung tissue stiffness following lung injury. Following bleomycin treatment at day 0, there is a progressive decline in compliance, as determined by pulmonary function measurements, which becomes statistically significant by day 6. Although this initial decrease in compliance coincides with the inflammatory phase following injury, it

is notable that the decreased compliance persists with the resolution of the inflammatory phase (days 9 and 14). Similar to the pulmonary function studies, generation of inflation and deflation pressure-volume curves show a marked rightward shift at day 8 day following bleomycin, signifying decreased lung compliance. Consistent with the in-vivo measurements, examination of tissue strips harvested at baseline or at days 3, 7 and 14 days following intratracheal bleomycin demonstrate a significant increase in stiffness at day 7 which is maintained through day 14. Finally, lung homogenates show that there is a dramatic increase in fibronectin in the lungs at day 7 following injury, suggesting a strong correlation between fibronectin accumulation and increased lung stiffness, each of which precedes the collagen accumulation that signifies fibrosis.

Conclusions: In vivo studies show that increased lung stiffness is an early event following that precedes collagen accumulation following lung injury. *In vitro* studies demonstrate that the biomechanical properties of the ECM are potent regulators of myofibroblast phenotypes, including susceptibility to apoptosis. Stiffness mediated resistance to Fas-induced apoptosis, but not apoptosis induced by Fas combined with cycloheximide, suggest that ECM stiffness may regulate the transcriptional expression of inhibitors of apoptosis (IAP) such as survivin, an IAP which we have previously shown to be downregulated in association with fibroblast apoptosis. Moreover, the diminished effect of TGF-β1 on matrices with fibrotic-range stiffness, when compared to normal stiffness, supports the concept that increased matrix stiffness, alone, can maintain the myofibroblast phenotype. *Collectively, these data suggest increased lung stiffness precedes fibrosis and that biomechanical signals from a stiff ECM may promote the autopropagation of an apoptosis-resistant myofibroblast phenotype, thereby contributing to fibrogenesis.* The implications of these findings are that tissue stiffness may be a critical component in the autopropagation of fibrosis, even in the absence of an ongoing external stimulus of injury or inflammation. Accordingly, interventions targeting this cycle of autopropagation should be sought for the treatment of pulmonary fibrosis.

GENERAL BUDGET SUMMARY

Allocation of research funds were as follows:

A. $74,814 for salary and fringe benefits for the principal investigator and a research technician.
B. $23,036 for research supplies including: IMR-90 fibroblasts and cell culture reagents (tissue culture plastic, pipettes, culture media, fetal bovine serum), reagents for protein estimation and Western blotting (Bradford assay kits, gradient gels, transfer membranes, running and transfer buffers, enhanced chemiluminescence, and radiography film), assessments of apoptosis (ELISA

kits for histone-associated DNA fragments and for caspase-3 activation), antibodies for detection of total and phosphorylated FAK, total and phosphorylated AKT, α-smooth muscle actin, fibronectin and GAPDH, reagents and primers for quantitative real-time PCR to detect α-SMA, fibronectin and collagen expression.

C. $2,150 for travel (ACCP conference in 2009 and for an aging and IPF workshop organized by the ASP and the NIH meeting in August 2009.)

PUBLICATIONS/AWARDS

Awards

1. June 2009, appointed to the editorial board of the American Journal of Pathology

Publications

1. **Horowitz JC**, Martinez FJ, Thannickal VJ. Mesenchymal Cell Fate and Phenotypes in the Pathogenesis of Emphysema. *COPD* 2009; 6(3):201-210. (Review)
2. Kulasekaran P, Rogers DS, Scavone C, Arenberg DA, Thannickal VJ, **Horowitz JC.** Endothelin-1 and TGF-beta Independently Induce Fibroblast Resistance to Apoptosis via AKT Activation. *Am J Respir Cell Mol Biol* 2009; 41(4):484-93.
3. Huang S, Wettlaufer SH, White ES, Grifka H, Hogaboam C, Thannickal VJ, **Horowitz JC,** Peters-Golden M. Prostaglandin E_2 Induces Fibroblast Apoptosis By Modulating Multiple Survival Pathways. FASEB J. 2009 Dec;23(12):4317-26
4. Hecker L, Vittal R, Jones T, Jagirdar R, Luckhardt TR, **Horowitz JC**, Pennathur S, Martinez FJ, Thannickal VJ. NADPH Oxidase-4 Mediates Myofibroblast Activation and Fibrogenic Responses to Lung Injury. *Nat Med* 2009; 15(9):1077-81.
5. **Horowitz JC** and Peters-Golden M. Prostaglandin E_2's New Trick: "Decider" of Differential Alveolar Cell Life and Death. *Am. J. Respir Crit Care Med* 2010;182(1):2-3 (Editorial)

PROGRESS REPORT

Please complete all fields, sign and forward to The ASCO Cancer Foundation. Forms without signatures will not be processed.

Recipient Information

Award Recipient Name: Danelle F. James Credentials: M.D., M.A.S.

Title: Assistant Professor Email: dfjames@ucsd.edu

Research Mentor: Thomas J. Kipps Mentor's Email: tkipps@ucsd.edu

Grant Information

Award Type (select one): YIA Year Award Received: 2009

Original Award Term: July (year) 2009 through June (year) 2010

Project Title: Age Related Differences in Immunomodulatory Therapy for Chronic Lymphocytic Leukemia

Institution Information

Institution: UCSD Moore's Cancer Center

Address: 3855 Health Sciences Drive

Address:

City: la jolla State: ca Zip: 92093 Country: USA

Institution Contact: Karen Hickey Title: contracts/grants officer

Phone: 858-534-3334 Email: khickey@ucsd.edu

Grants Officer/Administrator: Phone:

Email:

Reporting Year: Year 1 Please use *year award recieved* as anniversary date

Have you received a no-cost extension for this project? NO If YES, for how long? 6 Months

SECTION I

Progress and Results of Research

Research Proposal: (B*rief summary of your original proposal and specific aims)*

Over the last twenty years, progress in therapy for chronic lymphocytic leukemia has focused on young and healthy individuals who constitute a small fraction of individuals with this disease. Immunomodulatory therapies represent a novel approach that has the potential to be administered with less toxicity then observed with combination chemotherapy. Lenalidomide is promising in CLL, is being investigated in solid tumors, and is gaining increasing indications in a variety of hematologic malignancies. Despite the increased use of lenalidomide in diseases of older individuals, the mechanism of action of this drug, pharmacokinetics, and pharmacodynamics in the aged are not understood. We have developed an investigator initiated multi-center study to evaluate the combination of lenalidomide and rituximab for the initial treatment of progressive CLL. To enrich the study enrollment of older individuals the trial has been designed to accrue equally to two age specific cohorts, those younger than the age of 65 and those older. This study is an outstanding opportunity to gain insight into clinical and biologic characteristics and pharmacodynamic-pharmacokinetic parameters of immunomodulatory therapy in older patients. Short-term goals of this proposal are to understand the toxicity, clinical activity, and pharmacodynamic properties lenalidomide treatment in the elderly. Long-term goals of this proposal are to develop new therapeutic strategies for CLL in older individuals and to improve the use of immunomodulatory therapy in the elderly.

Aim I: Evaluate for Age Related Differences in toxicity and response to CLL therapy with Lenalidomide and Rituximab. Combination chemoimmunotherapy regimens are considered the major advance in the treatment of CLL patients. However, these combinations are typically poorly tolerated in older individuals- with age often being associated with decreased efficacy and enhanced toxicity. The clinical study of lenalidomide and Rituximab for the initial treatment of CLL enriches for an older population by evaluating two independent strata in parallel- arm A patients under the age of 65 and arm B patients 65 years and older. To improve this study's ability to assess for age related differences outside of chronology we will incorporate a pretreatment geriatric assessment and assessment of comorbidities. Patients will be followed prospectively for clinical response and toxicity to the immunomodulating therapy. Responses and toxicities will be comparatively analyzed for each group those less than 65 and those older with respect to their geriatric assessments, comorbidites, and other possible confounders. We hypothesize that the treatment will be well tolerated in older individuals. If the treatment is found to have good tolerability by older individuals regardless of the rate of complete response - future studies will be planned to utilize this combination in an older population with endpoints including quality of life and symptom improvement.

Aim II: Evaluate the pharmacokinetics of lenalidomide with respect to age, kidney function, toxicity, and response. We hypothesize that age and pretreatment kidney function will be associated with decreased clearance of lenalidomide and a lower median tolerated dose of this agent. This knowledge could guide future starting dose recommendations and dose escalation schemas and further improve the tolerability of this agent in CLL and other cancers.

AIM III: Evaluate the incidence of tumor flare reaction (TFR) in older versus younger individuals TFR is a CLL specific side effect that occurs with immunomodulatory treatment. TFR is thought to correlate with the biologic activity of these agents. Interestingly, in retrospective and historical comparative analyses there appears to be a lower incidence of tumor flare reaction in older individuals. We will explore the incidence and mechanism of the TFR induced by lenalidomide.

Results and Conclusions: *(Report the results and conclusions of your research progress in relation to each of your specific aims. You may attach an additional page or figure if needed.)*

A two arm, CLL research consortium (CRC) multi-center phase II trial of lenalidomide and rituximab for the initial treatment of patients with progressive B-cell CLL who require therapy as per current guidelines is an investigator-initiated study supported by Celgene. University California San Diego (UCSD) holds the IND from the FDA for the combination of lenalidomide and rituximab in CLL. Dr. Danelle James is the clinical principal investigator for the multi-institutional study. The study is registered on clinicaltrials.gov number NCT00628238. The study has now opened at four CRC clinical sites - UCSD, Dana Farber Cancer Institute, MD Anderson, and Long Island Jewish. The study has two strata to ensure equal accrual of older individuals, arm A for patients less than 65 years old and arm B for patients 65 years and older. Forty-two patients have been enrolled, 26 in Arm A and 16 in Arm B with total of eighty patients anticipated to be accrued to this study- 40 to each age specific strata. To improve this study's ability to assess for age related differences outside of chronology the study was amended in August 2009 to incorporate a pretreatment geriatric assessment and assessment of co-morbidities. This amendment has been approved at UCSD, and is pending local IRB approval at the other participating clinical sites.

The primary objective of the clinical study is to determine the complete response to therapy. Secondary objectives evaluate response duration, investigate mechanism of lenalidomide in CLL, lenalidomide pharmacokinetics, and the mechanism and significance of the tumor flare reaction. Patients with CLL were eligible if they had not received previous chemotherapy or monoclonal antibodies, had active disease with an indication for therapy, normal kidney function, and no history of recent thromboembolic events. All patients received lenalidomide orally at a starting dose of 2.5 mg/day, which in the absence of toxicity >= grade II was increased to 5 mg on day 8 and later to a maximum of 10 mg/day. Lenalidomide was administered for a maximum of 21 days/cycle followed by at least 7 days of rest for up to 7 cycles. Cycle 1 is 35 days with cycle 2-7 are 28 days. Rituximab was started at the end of cycle 1, was continued weekly during cycle 2, and on day 1 of cycles 3-7.

The trial is ongoing continues to accrue to a planned total of 80 patients. No patients have been removed from treatment for progressive disease. There have been no deaths. At interim analysis the criteria for continuing accrual to a total of 40 patients in each stratum were met with at least two responses in each arm. Early results of this ongoing study suggest that the immunotherapy combination of lenalidomide and rituximab is tolerable both in younger and older individuals.

Aim I: Evaluate for Age Related Differences in toxicity and response to CLL therapy with Lenalidomide and Rituximab. The median age of all subjects enrolled (n= 42) is 62 yrs. The median age in arm A is 56 years and Arm B patients have median age of 73 years. 45% (17/38) patients had advanced stage (Rai III-IV disease) with baseline cytopenias, 36% and 56% of arm A and B patients respectively. The sequence of the expressed Ig heavy chain variable region (IGHV) gene was determined on the individual patient's leukemia cell clone. Those cases that used IGHV with 98% or greater homology to a known germ-line gene were classified as using unmutated IGHV- a factor associated with poor prognosis. 51% (18/35) of patients evaluated had leukemia cells which expressed unmutated IgVH genes including 47% and 57% for arm A and B patients respectively. 15/37 patients had CLL cells with elevated expression of ZAP70 and 14/34 had elevated expression of CD38. 3 patients had chromosome 17p deletion and 3 patients had loss of 11q by FISH analysis. The most common grade III/IV adverse events were neutropenia, anemia, and thrombocytopenia occurring in 18, 5, and 4 patients respectively. There were no cases of neutropenic fever, sepsis, or bleeding. Non-hematologic grade III/IV adverse events included infections (3 patients in arm B), rash (2 patients), and pulmonary embolus (one pt in each arm). The protocol was amended to include the use of aspirin 81mg daily as thromboprophlyaxis. The most frequent adverse events (all grades) were the tumor flare reaction (TFR) (21/30), fatigue (19/30), and elevated liver transaminases (25/30).

results continue on separate page.

Future Directions: *(Summarize the next steps planned for this project)*

As the trial has enrolled only 42 of the planned 80 subjects all aspects of this grant proposal have not been completed. However, much work has been done to open all clinical sites and the study has been amended to incorporate geriatric assessments and extensive pharmacokinetics and pretreatment evaluation of kidney function. With continued accrual to 80 total patients full data on toxicity and efficacy will mature to allow for comparison of the age related differences in immunomodulatory therapy for CLL.

Long-term goals of this proposal are to develop new therapeutic strategies for CLL in older individuals and to improve the use of immunomodulatory therapy in the elderly. As such, we are designing study to be again conducted in the CRC to evaluate this non-chemotherapy, immunomodulatory strategy for relapsed and refractory patients. A subsequent follow-up frontline protocol of immunomodulatory therapy in the elderly is being planned to open after this study finishes accruing.

SECTION II

Layperson Summary of Research Results

(1-2 paragraph description of your results and conclusions in non-technical language for a general audience)

Chronic Lymphocytic leukemia (CLL) is the most prevalent leukemia in the western world and is an incurable disease. Over the last twenty years, progress in therapy for chronic lymphocytic leukemia has focused on young and healthy individuals who constitute a small fraction of individuals with this disease. Immunomodulatory therapies represent a novel approach that has the potential to be administered with less toxicity then observed with combination chemotherapy. We have developed an investigator initiated multi-center study to evaluate the combination of lenalidomide and rituximab for the initial treatment of progressive CLL. To enrich the study enrollment of older individuals the trial has been designed to accrue equally to two age specific cohorts, those younger than the age of 65 and those older. This study is an outstanding opportunity to gain insight into clinical and biologic characteristics and pharmacodynamic-pharmacokinetic parameters of immunomodulatory therapy in older patients. Short-term goals of this proposal are to understand the toxicity, clinical activity, and pharmacodynamic properties lenalidomide treatment in the elderly. Long-term goals of this proposal are to develop new therapeutic strategies for CLL in older individuals and to improve the use of immunomodulatory therapy in the elderly.

The study has opened at four different CLL Research Consortium Clinical sites and has enrolled 42 patients. Early results reveal enrollment of a spectrum of aged patients with a median age of 62 for the entire study, median 56 years in Arm A (those aged younger than 65) and 72 years in Arm B (those 65 years and older.) There is early evidence of a difference in lenalidomide dose tolerability with a median tolerated dose in arm A of 10 mg and 5 mg in arm B. This suggests a possible age related difference in the clearance of the immunomodulatory drug- which will be evaluated with extensive pharmacokinetic measures and pretreatment evaluation of kidney function. In the two age strata comparing older and younger cohorts we have noted differences in frequent toxicities of the tumor flare reaction and transaminitis. Differences in the baseline biologic characteristics associated with the development of the tumor flare reaction will be examined. No patients have been removed for progressive disease. At interim analysis the criteria for continuing accrual to a total of 40 patients in each stratum were met with at least 2 clinical complete responses in each arm. Early results of the ongoing study suggest that immunotherapy with lenalidomide and rituximab is tolerable for both elderly and younger patients with CLL.

SECTION III

Activities Related to this Grant

(List any presentations or other activities you participated in during the past year that relate to the research that was funded by this grant.)

An abstract was presented at the American Society of Hematology 51st Annual Meeting entitled, "Lenalidomide Administered for the Initial Treatment of Chronic Lymphocytic Leukemia (CLL) Patients- In Vivo Modulation of the Leukemia Cell Surface Phenotype and Association with Tumor Flare Reaction (TFR)"

An abstract was submitted to the American Society of Clinical Oncology (ASCO) annual meeting for consideration of presentation at the 2010 annual meeting. Paper #51640 " Lenalidomide and rituximab for the initial treatment of chronic lymphocytic leukemia – report of an ongoing study. "

SECTION IV

Additional Research Support Obtained Since Receipt of this Grant:

Lymphoma Research Foundation Fellowship 2010-2012 for my proposal entitled, "Targeting the CLL Microenvironment, Novel Prognostic and Therapeutic Strategies."

SECTION V

Bibliographical List of Publications Resulting from this Grant:

(Please remember to acknowledge funding from The ASCO Cancer Foundation in all publications that result from this grant)

pending.

The ASCO Cancer Foundation will review and approve this report at its discretion. Once the report has been reviewed, notification will be sent to the award recipient.
Please note, failure to submit these reports by the specified deadline may result in the disapproval of any future requests pertaining to this research project.
A Budget Summary *must* also be submitted. Please visit www.ascocancerfoundation.org/TACF/Grants to download the form.

SIGNATURE - Award Recipient _____ Date _____

SIGNATURE - Research Mentor _____ Date _____

Please email grants@asco.org with any questions or concerns.

Mail or fax form to:
The ASCO Cancer Foundation
Grants Division
2318 Mill Road, Suite 800
Alexandria, VA 22314
Fax: 571-366-9552

Results continued:

Aim I: Evaluate for Age Related Differences in toxicity and response to CLL therapy with Lenalidomide and Rituximab *continued*

Biochemical evidence of tumor lysis was observed in two patients, but there were no cases of clinical tumor lysis. Continued accrual and further analysis of toxicity and efficacy will illustrate the age related differences in toxicity and responses to this immunomodulatory therapy.

Aim II: Evaluate the pharmacokinetics of lenalidomide with respect to age, kidney function, toxicity, and response.

To accurately determine pretreatment kidney function in all subjects the protocol was amended to incorporate 24-hour urine collections to measure the creatinine clearance. Pharmacokinetic studies will be performed on consenting subjects in both arms of the study. Lenalidomide pharmacokinetic analysis will be performed in batches over two different runs. As such, results from lenalidomide PK analyses are forthcoming. Interestingly, so far the median tolerated dose for the two different strata are different. Suggesting age-related changes in lenalidomide clearance may exist. For patients who have received at least three cycles of therapy the median tolerated dose was 10 mg for patients in Arm A (those younger than 65 years) and 5mg for arm B patients (those 65 years and older).

AIM III: Evaluate the incidence of tumor flare reaction in older versus younger individuals

As previously suggested by a retrospective comparison in previously treated CLL patients this ongoing prospective study on treatment naive patients reveals a higher incidence of the TFR in younger patients compared with older individuals (p =0.0382 2-tailed Fisher exact test). In arm A TFR occurred in (88%) 15/17 patients. In the older patients tumor flare was reported less frequently with only 50% (6/12) experiencing the TFR in arm B. Interestingly, only a small fraction of patients experienced TFR following the institution of rituximab at the end of cycle 1.

	Tumor Flare Present	Tumor Flare Absent	Total
Group A (<65 yrs)	15	2	**17**
Group B (>=65 yrs)	6	6	**12**
Total	**21**	**8**	**29**

Fisher's exact test: The two-tailed P value equals 0.0382

Interestingly, the clinical pattern of liver transaminitis was very similar to what was observed in patients with the TFR. Elevation of hepatic transaminases was observed the majority (83%) of individuals (25/30), which was largely limited to grade I-II in severity. In all cases this was transient- usually limited to the first cycle of therapy and improved without treatment interruption. Elevation of liver transaminases occurred in 100% of younger individuals (17/17 patients in arm A). However, only 62% (8/13) of older individuals in arm B experienced this transient elevation of liver transaminases.

	Transaminitis Present	Transaminitis Absent	Total
Group A (<65 yrs)	17	0	**17**
Group B (>=65 yrs)	8	5	**13**
Total	**25**	**5**	**30**

Fisher's exact test: The two-tailed P value equals 0.0090

Through evaluation of serum cytokines/chemokines as well as changes in B cell activation markers and chemokine receptors biologic characteristics that might identify individuals more likely to undergo the TFR will be explored.

AMERICAN SOCIETY OF HEMATOLOGY'S (ASH)
SCHOLAR AWARDS

Year Two Evaluation

This evaluation should be accompanied by a letter from a division head or department chair (on letterhead with signature) requesting final year funding, providing assurances that the work has progressed and that both appropriate facilities and the mentor will continue to be available. Additionally, please attach a current CV or NIH bio sketch.

1. Are you still pursuing the research for which your Scholar Award was provided? If not, please explain why you are not still pursuing the research.

Yes. The ASH Scholar research project is progressing well. We have met the initial recruitment goal of 50 evaluable subjects (current N=52). We are continuing to enroll subjects through December 2010. We anticipate adequate power to evaluate the primary objective (using baseline geriatric assessment tools to predict survival) and will be able to explore change in geriatric assessment measures pre and post treatment. All available data has been entered into an electronic web-based data system. We anticipate beginning preliminary analyses by late summer 2010. All analyses including follow-up data should be completed in spring 2011. We anticipate 2 manuscript submissions within the next 12 months from these data.
Additional research activities include: 1. Submission of a Beeson K23 award in January 2010 entitled "Minimizing physical function decline in older adults receiving chemotherapy". The proposed grant built upon preliminary data from the ASH study to further investigate interventions to improve physical function among older adults receiving induction chemotherapy for AML. 2. Successful funding of an intramural grant entitled "Systemic inflammation, functional decline and treatment outcomes among older adults receiving chemotherapy for acute myelogenous leukemia (AML)". This grant provides funding to add serum measurement of systemic biomarkers of inflammation to the remaining subjects to be enrolled on the ASH study (N=20). This will provide preliminary data on the relationship between systemic inflammation and functional decline post induction chemotherapy as well as the relationship between systemic inflammation and treatment response.

2. Is 75% of your full-time professional effort devoted to research activities? If not, please explain.

☒ Yes ☐ No

3. Has your position at your institution changed during the preceding 12 months? If so, please explain.

☐ Yes ☒ No

The deadline to submit this form and other materials is Wednesday June 30, 2010
Forms can be e-mailed to Elisa Shea at *eshea@hematology.org*.

AMERICAN SOCIETY OF HEMATOLOGY'S (ASH)
SCHOLAR AWARDS

Year Two Evaluation

4. Did you submit an abstract to the 2009 ASH annual meeting as both the first and presenting author or as a senior author?

☒ Yes, as first & presenting author ☐ Yes, as senior author ☐ No

If yes, was it accepted?

☐ Yes, for oral presentation ☒ Yes, for poster presentation ☐ No

5. Have you presented your ASH Scholar Award research at any other conference since beginning your award?

☒ Yes ☐ No

If yes, where?

Preliminary data was presented at the American Geriatrics Society Annual Meeting 2010 as part of the T. Franklin Williams Poster Session.

6. Have you published the research for which your Scholar Award was provided in any journals?

☐ Yes ☒ No

If yes, where?

7. Have you received any additional funding for the research for which your Scholar Award was provided?

☒ Yes ☐ No

If yes, from who and the amount?

Yes, a 1 year intramural grant entitled "Systemic inflammation, functional decline and treatment outcomes among older adults receiving chemotherapy for acute myelogenous leukemia (AML)". This grant provides funding ($20,000) to add serum measurement of systemic biomarkers of inflammation to the remaining subjects to be enrolled on the ASH study (N=20). This will provide preliminary data on the relationship between systemic inflammation and functional decline post induction chemotherapy as well as the relationship between systemic inflammation and treatment response.

The deadline to submit this form and other materials is Wednesday June 30, 2010
Forms can be e-mailed to Elisa Shea at *eshea@hematology.org*.

AMERICAN SOCIETY OF HEMATOLOGY'S (ASH)
SCHOLAR AWARDS

Year Two Evaluation

8. Please use this space to provide any additional comments or suggestions you have:

Optional:

Name: Heidi D. Klepin, MD, MS

Checklist:

☒ Completed evaluation

☒ Letter from division head or department chair (on letterhead with signature) requesting second year funding

☒ Current CV or NIH bio sketch

The deadline to submit this form and other materials is Wednesday June 30, 2010
Forms can be e-mailed to Elisa Shea at *eshea@hematology.org*.

The Franklin Williams Research Scholars Awards Program

24-Month Narrative Progress Report

Recipient: **George C. Wang**

Project Title: **Immunologic Dysregulations and Inflammation in the Pathogenesis of Frailty of Old Age: The Role of CMV Infection**

Reporting Period: From 07/01/08 Through 06/30/10

Project Objectives:

The objectives of this project are to investigate the association between cytomegalovirus (CMV) infection and frailty in older adults by examining possible underlying mechanisms of pathogenesis, including the humoral and T-cell responses to CMV infection, autoimmunity, and restriction in T-cell receptor diversity (TCR), and to determine the temporal relationship between CMV infection and incident frailty development.

Activities and Results:

I have completed a study examining the relationship between serum CMV antibody concentration and 5-year mortality and 3-year incident frailty in older women participating in the Women's Health and Aging Studies (WHAS) I and II. CMV IgG concentration was measured in baseline repository serum specimens. We found that incrementally higher CMV IgG antibody concentration was associated with an incremental risk in prevalent frailty in a dose-response manner, after controlling for participant factors that could potentially confound the relationship between CMV infection and frailty. Plasma interleukin (IL)-6 concentration modified the effect of CMV antibody concentration on the risk of prevalent frailty, such that the magnitude of the association increased with incrementally higher plasma IL-6 levels. Over a three-year follow-up period, older women in the highest quartile of CMV IgG antibody concentration had a higher incidence of new-onset frailty compared with CMV seronegative women (hazard ratio [HR], 3.46; 95% confidence interval [CI], 1.45-8.27). Over a five-year follow-up period, older women in the highest quartile of CMV IgG antibody concentration had a higher risk of mortality compared with CMV seronegative women (HR, 3.81; 95% CI, 1.45-8.27). This association remained significant after adjusting for potential confounders (HR, 2.79; 95% CI, 1.22-6.40). CMV seropositivity alone, regardless of the level of antibody concentration, was independently predictive of a higher 5-year mortality ($P<0.05$). These findings have been published in the *American Journal of Epidemiology* (Wang GC, Kao WH, Murakami P, et al. Cytomegalovirus infection and the risk of mortality and frailty in older women: a prospective observational cohort study. Am J Epidemiol 2010;171:1144-52) and featured in a Reuters news report (http://www.reuters.com/article/idUSTRE63Q3M220100427).

I have also measured CMV viral load in 20 pairs of age-, race-, and education-matched frail and robust WHAS participants, using repository serum specimens. The CMV viral load was detectable in only one frail participant and none of the robust participants. In the same 20 pairs of participants, I have also measured a panel of autoimmune markers, with no differences between frail and robust individuals.

Despite the lack of significant differences in autoantibody prevalence in our pilot study, we focused on measuring three prevalent autoantibodies, anti-thyroglobuin (Tg), anti-thyroid peroxidase (TPO), and antinuclear antibody (ANA), in a combined WHAS I and II cohort of 641

participants. We found that older women seropositive for either Tg or TPO antibodies were less likely to be frail (odds ratios, 0.30 and 0.44; 95% CI, 0.10-0.85 and 0.20-0.96, respectively). In contrast to thyroid antibody findings, we found that women seropositive for ANA did not have decreased risks of being frail or prefrail. To our knowledge, this was the first study which demonstrated a specific, inverse association between thyroid antibodies and the frailty syndrome. Whether these findings originate from a protective role of thyroid antibodies in frailty development or reflect an exhaustion of thyroid autoimmunity, prevalent in older age, in frail older women, remains to be elucidated. These findings have been published in the *Journal of Clinical Endocrinology and Metabolism* (Wang GC, Talor MV, Rose NR, et al. Thyroid autoantibodies are associated with a reduced prevalence of frailty in community-dwelling older women. J Clin Endocrinol Metab 2010;95:1161-8).

The work in this and the previously mentioned CMV paper has allowed me to gain proficiency in cross-sectional analyses with multinomial logistic regression models and in longitudinal analyses with Cox proportional hazards models, using population-based cohort data. These skills are part of the epidemiologic skillset that I aim to develop toward the goal of becoming a capable translational investigator.

With regard to TCR diversity investigations, we hypothesized that TCR distribution in frail older adults would be represented by greater clonality and biases in TCR Vβ usage than robust older adults. In a pilot study involving 4 frail and 4 robust older adults (mean age, 86.5 ± 4.3 years), we performed spectratyping on the CDR3 region of the T-cell receptor Vβ gene in unsorted lymphocyte specimens containing total CD3+ T cells. The complementary-determining region 3 (CDR3) includes the V, D and J gene regions in the TCR β-chain and constitutes the majority of the TCR Vβ diversity. We did not detect significant differences in TCR clonality between frail and robust older adults in this small group of 8 participants. However, spectratyping yields low-resolution information for TCR diversity, since each abnormal CDR3 peak could represent either a single clone or a diverse distribution of clones. Therefore, further studies using higher-resolution techniques are indicated to definitively test the relationship between TCR diversity and frailty in older adults. Working under the guidance of Dr. Doherty, we have adopted a more rigorous, state-of-the-art approach to the assessment of TCR diversity, based on single-cell CDR3 sequencing, to examine pathogen-specific TCR diversity.

The timely and generous support from the T. Franklin Williams Award has made it possible for me to travel to the immunology laboratory of Dr. Peter Doherty, Nobel laureate at St. Jude Children's Research Hospital, where I have developed a method of investigating CMV-specific T-cell receptor repertoire diversity in humans, using single-cell TCR clonotypic analysis. This novel method of TCR repertoire investigation, being used in humans for the first time, utilizes multiplexed panels of CDR3α and CDR3β-specific primers in a nested PCR to amplify TCR transcripts derived from single epitope-specific T cells, sorted into 96-well PCR plates by a flow cytometric sorter. We have applied this strategy to characterize the repertoire of CMV-specific CD8 T cells in seven individuals and validated the clonotype-level data with those of previously reported repertoires. TCR repertoire determined by the single-cell multiplex TCR analysis has the same resolution as that offered by cloning-based procedures, but additionally provides reliable clonotype frequency data, CDR3α repertoire, and CDR3α and CDR3β co-expression data at a much lower cell-number requirement and labor intensity than currently available methods. Additional preliminary data has led to a novel observation regarding a hitherto unobserved strategy for repertoire diversification in humans, an observation that would have otherwise been impossible to make without this new method of repertoire analysis. A "methods manuscript" has been completed and will be submitted shortly.

During the past two years of the Williams Award, I have been promoted to Assistant Professor of Medicine. I have recently received the Johns Hopkins Clinician Scientist Award, and have received a fundable-range priority score for the NIH K23 Career Development Award. I am grateful to have been placed on this trajectory of success by the generosity of the Williams Award.

Principal Investigator/Program Director (Last, First, Middle): Abadir, Peter M.

Re: T. Franklin Williams Scholars Award progress report

I wish to start my progress report with a sincere thank you to the T. Franklin Williams Scholars Program administrative staff and review board. This award has enabled me to pursuit and progress in my research career at Johns Hopkins. I can honestly say that this award came at a critical time to protect my budding research career, and for that I am very appreciative and grateful. Although I was successful in obtaining few awards as detailed below to support my research, the T. Franklin Williams Scholars award is the only award that provided me with the needed research supplies and protected my research time in this very vulnerable time in my research career. I am happy to report that I was hired as an Assistant Professor of Medicine at the Johns Hopkins University. On career development aspect I have been productive along the following lines:

A. ONGOING RESEARCH PROJECTS:

Changes in Human Angiotensin system leading to development of Frailty:

a. Mentors: Jeremy Walston, Bruce Bochner, Helmy Siragy and Robert Carey
b. Objectives: To evaluate the relationships between AT1R and AT2R in immune system cells as people age, and determine how these changes might influence , chronic inflammation, frailty and late life vulnerability. Genetic and hormonal features that may contribute to the development of chronic inflammation via angiotensin receptors pathway will also be identified.
c. Study progress: We included two more control groups of robusts and frails therapeutically on AT_1R blockers. We surveyed different longitudinal studies including the WHAS and Health ABC we found a total of 110 individuals (robusts and frails) on ARBs. An abstract with preliminary results was presented to the 2010 American Geriatrics Society meeting in Orlando, Florida.

B. RESEARCH SUPPORT AND FUNDING:

i. NIA K23 award application: my original application submitted on 3/2009 was favorably reviewed, was supported with excellent enthusiasm for my candidacy (please see attached pink sheets). My initial application received a priority score of “30” (funding range was “25” for 2009 submission). I re-submitted my application on March of 2010 with an enhanced research plan, new specific aims and response to statistical and methodology question.
ii. I was selected to receive the Johns Hopkins Clinician Scientist Award which provides me with research support up to $75,000 /years in salary support.
iii. I successfully obtained support from the Johns Hopkins Claude Pepper Older American Independence center, providing me with an additional $10,000 for research support to study sub-cellular effects of angiotensin receptors.

iv. I applied to the “Johns Hopkins Claude Pepper Older American Independence Center Junior Faculty Career Development in Frailty Research” award.

C. ABSTRACTS AND CONFERENCES PRESENTATIONS:
   i. I presented three abstracts to the international association of gerontology and geriatrics conference in Paris on July 2009. I was also selected to receive a travel award to the conference.
   ii. I presented an abstract titled “The Aging Renin Angiotensin System” to the 2010 American Geriatrics Society conference in Orlando, Florida.
   iii. I will present an abstract titled “Cytokine Profiling for Aged Low Capacity Runner (LCR) Rats: A Rat Model for Human Frailty” to the Gerontological Society of America's 63rd Annual Scientific Meeting, taking place in New Orleans, LA.

D. Peer Reviewed Publications and Book Chapters:
   i. I submitted an original manuscript titled “Angiotensin II Type-2 Receptors Modulate Inflammation Through STAT3 Phosphorylation and TNFα Production” to Interferon and Cytokine Journal. The manuscript (JICR-2010-0043) focuses on the role that angiotensin receptor type 2(AT2R) plays in the production of TNFα. Our data demonstrated that stimulation of AT2R independent of AT1R through STAT3 signaling pathway leads to reduction in production of TNFα, confirming an anti-inflammatory role for AT2R. The manuscript was reviewed favorably by two experts in the field and the editor for the Journal of Interferon and Cytokine Research. On May 10th, 2010 we received reviewers and editors positive comments and we were urged to revise the submission to address a few issues; mainly clarifying two figures in the manuscript and inserting an additional control figure. The findings in this manuscript align with the hypothesis and objectives of my K23 application and it supports a potential role for changes in angiotensin system in development of inflammation in older adults. Further, it demonstrates my ongoing productivity in this field.
   ii. I authored a chapter on “ Evaluating The Older Driver” that has been published in The Oxford American Handbook of Clinical Geriatrics (Durso CS, ed.).
   iii. I also submitted a chapter on “The Frail Renin Angiotensin System” to be published in “Clinics in Geriatric Medicine.” The chapter reviews current knowledge on the effect of aging on the Renin Angiotensin System and contribution of an aged angiotensin system to development of frailty.
   iv. I co-authored an original manuscript submitted to the Journal of Experimental Medicine titled "Intrinsic Aerobic Capacity Sets a Divide for Longevity" (JEM ms. # 20100667). The manuscript was reviewed and currently is modified for re-submission.

E. Patent Application: Johns Hopkins University submitted on my behalf a provisional patent application on the protective role of angiotensin type two receptors.

Aging and Critical Illness in HIV-infected Patients

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Dates of Research Project: July 1, 2009-June 30, 2011

Funding support: Association of Subspecialty Physicians and CHEST Foundation of the American College of Chest Physicians T. Franklin Williams Award

I. Purpose:

A. Specific Aims: The specific aims remain as follows:
1. Determine risk factors for intensive care unit (ICU) admission in HIV-infected patients. The hypothesis for this aim was that older age is associated with increased ICU admission but that the effects of age were partially mediated by the burden of comorbid disease and functional status.
2. Compare indications for ICU admission in older to younger HIV-infected patients. The hypothesis for this aim was that older ICU patients are more likely to be admitted to the ICU with non-AIDS associated conditions which is partly explained by greater burden of comorbid disease and antiretroviral (ART) use.
3. Determine risk factors for poor outcomes following ICU admission in HIV-infected patients. For this aim, the hypothesis was that older age is associated with greater in-hospital mortality in HIV-infected patients admitted to the ICU which is, in part, related to pre-ICU functional status, ICU admission diagnosis, and severity of critical illness on ICU admission.

HIV-infected patients are living longer with the advent of antiretroviral therapy (ART). Older HIV-infected patients, defined as age 50 years and older, progress to AIDS faster with associated increased mortality rates compared with younger HIV-infected patients. As the HIV epidemic and HIV-infected patients themselves age, chronic comorbid medical diseases such as renal disease or liver disease are increasingly prevalent. These observations have contributed to a hypothesis of advanced physiologic aging in HIV-infected patients with progressive frailty.

In Aim 1, we sought to determine the risk factors for ICU admission in HIV-infected patients. We hypothesized that older age is associated with increased risk of ICU admission and that the effects of age on risk of ICU admission were partially mediated by comorbid diseases and functional status. The second and third aims will address the differences in ICU admission diagnoses between older and younger HIV-infected patients and risk factors for poor ICU outcomes. This research will help shift the paradigm of aging in HIV-infected patients and may identify modifiable risk factors for ICU admission and poor ICU outcomes.

II. Studies and Results:

A. Research conducted:

We evaluated the incidence of ICU admission in HIV-infected patients compared with HIV-uninfected patients using the VACS. VACS-8 is an observational cohort study conducted at 8 Veterans' Administration infectious disease and general medicine clinics located in Atlanta, Baltimore, the Bronx, Houston, Los Angeles, Manhattan/Brooklyn, Pittsburgh, and Washington, D.C.

We compared patients admitted to the ICU by HIV status. The following factors were investigated at baseline: age, sex, race, hazardous alcohol use, smoking history (ever, current, never), BMI, and functional status by Short Form-12 scores (SF-12). Medical comorbidities at study enrollment included: chronic lung disease, cardiovascular disease, liver disease, and hepatitis C coinfection. We also compared ICU admission and overall mortality using survival analysis in patients who were admitted to the ICU by HIV status.

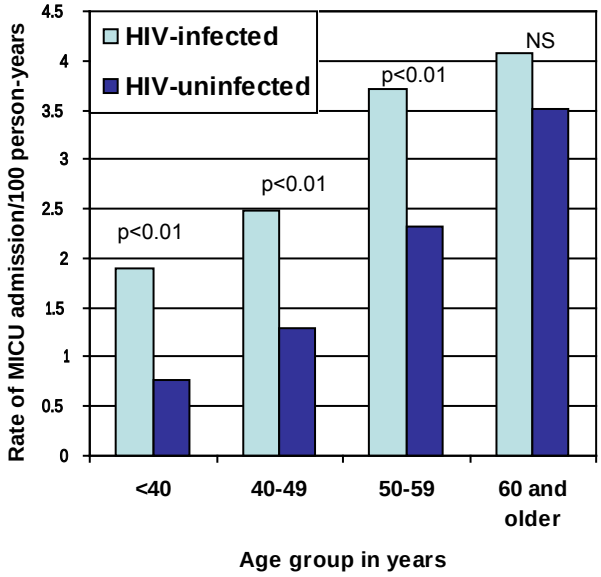
B. Preliminary Results:

1. ICU Admission Incidence and Comorbidity by HIV status

We compared incidence of ICU admission between HIV-infected patients and HIV-uninfected patients with respect to age and medical comorbidities. HIV-infected patients are more likely to be admitted to the ICU than HIV-uninfected veterans and have higher ICU admission rates except in the oldest age group (>60 years old). Finally, we found that age is an independent risk factor for ICU admission.

Table 1. Characteristics of Patients with ≥ One ICU Admission by HIV status			
Characteristic	**HIV-infected** (n=3,410)	**HIV-uninfected** (n=3,409)	**p-value**
Age in years, median (IQR)	51	53	<0.01
Current smokers, %	61	51	0.04
Cardiovascular disease, %	11	26	<0.01
Chronic renal disease, %	12	8	0.048
Hepatitis C coinfection, %	64	40	<0.01
Mortality rate following ICU admission, per 100-person years	27.8 (24.3-32)	12.6 (10.1-15.6)	<0.01

Figure 1. Rates of ICU Admission/100 Person-years by Age Groups and HIV status



2. Determine risk factors for intensive care unit (ICU) admission in HIV-infected patients. To identify risk factors for ICU admission, we compared HIV-infected patients with at least 1 ICU admission with patients without ICU admission. (Table 2)

Table 2. Characteristics of HIV-infected Patients Stratified by ICU Admission Status			
Characteristic	**ICU Admission** (n=428)	**No ICU Admission** (n=2982)	**p-value**
Age in years, median (IQR)	51 (46-55.5)	49 (43-54)	<0.01
CD4+ cells/microliter, median (IQR)	297 (138-500)	376 (215-555)	<0.01
ART use (%)	69	71	0.3

HIV RNA lop copies, median (IQR)	1580.5 (75-47,295)	507 (75-16,073)	<0.01
Body Mass Index, median (IQR)	23.8	25	<0.01
SF-12 PCS Score, median (IQR)	39 (32-49)	45 (36-54)	<0.01
SF-12 MCS Score, median (IQR)	47 (38-56)	49 (38-57)	0.3
Cardiovascular disease (%)	11	5	<0.01
Chronic renal disease (%)	12	4	<0.01
Cancer (%)	11	7	<0.01
Hepatitis C coinfection (%)	64	52	<0.01
History of Bacterial Pneumonia (%)	37	28	<0.01
History of Pneumocystic pneumonia (%)	19	14	0.01

In multivariate analysis, African American race, older age, lower BMI, lower physical function score, lower CD4+ T-cell count, higher HIV viral load, and prevalent cardiac or renal disease, cancer history, and hepatitis C infection were independent risk factors for ICU admission in HIV-infected patients. (Aim 1)

C. Problems Encountered and Further Training:

Dr. Akgün had no experience with SAS Statistical software. This was essential to perform basic analyses for this research. With the support of the Williams Award, Dr. Akgün took two on-line SAS training courses and is able to perform basic statistical analysis with SAS. In addition, after applying for additional grants during this first year of the Williams Award, it became clear that Dr. Akgün needed additional formal training in biostatistics and epidemiology. Dr. Akgün is currently auditing a summer-long Biostatistics class through the Yale University School of Epidemiology and Public Health. She has also applied and been accepted into the Masters in Epidemiology and Chronic Disease and will be enrolled in classes starting with the Fall 2010 semester.

As we investigated the differences between patients admitted to the ICU by HIV status, we needed to compare severity of illness between patients admitted to the ICU. Most ICU scales include the Glasgow Coma Score (GCS). GCS is not routinely collected in the participating VA hospitals in VACS-8. We are addressing this issue by finding mechanisms used in other ICU studies and developing a method for extracting this information from the VACS dataset without the GCS. Finally, we compared the ability of the VACS Risk Index to predict patients at high risk of ICU admission with a Reduced Index. The VACS Risk Index accounts for age, HIV biomarkers, and non-HIV comorbid disease biomarkers such as anemia, renal insufficiency, and liver fibrosis while the Reduced Index only includes age and HIV biomarkers. The VACS Risk Index will be another tool we will use to compare outcomes in older and younger HIV-infected patients while adjusting for severity of illness (Aim 3).

III. Significance:

- HIV infection is a risk factor for ICU admission.
- As HIV-infected patients age, rates of ICU admission increase. However, when compared with HIV-uninfected patients, HIV-infected patients are younger which may be related to premature physiologic aging in HIV-infected patients.

- Comorbid diseases are more prevalent in HIV-infected patients admitted to the ICU compared with those who are not admitted to the ICU.
- Despite improvements in ICU outcomes for HIV-infected patients in the current ART era, HIV-infected patients admitted to the ICU have worse outcomes compared to HIV-uninfected patients that may be partially explained by increased prevalence of non-HIV chronic, comorbid diseases which progress more rapidly and lead to more end-organ dysfunction in HIV-infected patients and, thus, premature physiologic aging.

IV. Publications, Book Chapters and Presentations:

A. Publications:

Akgün, K, Pisani, M, Crothers, K. The Evolution of HIV-Infected Patients in the Intensive Care Unit. JICM. *In press*.

B. Poster Discussion Sessions:

American Thoracic Society Annual Meeting in New Orleans, LA May 2010

- Incidence and Mortality of MICU Admission in HIV-infected and HIV-noninfected Veterans
- Risk Factors for Medical Intensive Care Unit Admission in HIV-infected Veterans

C. Presentations:

- April 2010: Yale University Pulmonary and Critical Care Medicine Research in Progress
- April 2010: VACS Annual Scientific Meeting: Predicting ICU admission in HIV-infected veterans

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Research Article

Does Gender Impact Intensity of Care Provided to Older Medical Intensive Care Unit Patients?

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Introduction. Women receive less aggressive critical care than men based on prior studies. No documented studies evaluate whether men and women are treated equally in the medical intensive care unit (MICU). The Therapeutic Intervention Scoring System-28 (TISS-28) has been used to examine gender differences in mixed ICU studies. However, it has not been used to evaluate equivalence of care in older MICU patients. We hypothesize that given nonsignificant, baseline health differences between genders at MICU admission, the level of care provided would be equivalent. *Methods*. Prospective cohort of 309 patients ≥60 years old in the MICU of an urban university teaching hospital. Explanatory variables were demographic data and baseline measures. Primary outcomes were TISS-28 scores and MICU interventions. We compare TISS-28 scores by gender using a statistical test of equivalence. *Results*. Women were older and had more chronic respiratory failure at MICU admission. Using equivalence limits of ±15% on gender-based scores of TISS-28, MICU interventions were equivalent. Supplementary analysis showed no statistically significant association between gender and mortality. *Conclusions*. In contrast with other reports from the cardiac critical care literature, as measured by the TISS-28, gender-based care delivered to older MICU patients in this cohort was equivalent.

1. Introduction

Currently 12.6% of the total population in the U.S. is 65 years of age or older [1]. This number is expected to increase to 16% by 2020. Within the 65 and older age group, 58% are women [1]. As the population ages, medical intensive care unit (MICU) utilization is likely to increase. Prior studies investigating aging and critical illness show that MICU outcomes are primarily determined by severity of illness and respiratory failure rather than age [2–4].

Initial studies examining gender differences in the ICU were conducted with cardiac patients. These studies demonstrated that women were older and sicker at the time of angioplasty or surgical bypass, receive fewer invasive procedures, such as implantable cardioverter defibrillators and heart transplants, and were less likely to receive appropriate medications during and after non-ST segment elevation myocardial infarctions [5]. These findings suggest potential treatment disparities between men and women. However, the importance of gender for MICU outcomes in older patients has not been fully established [2–4, 6, 7].

Severity of illness scores such as the Acute Physiology and Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA), and the Simplified Acute Physiology Score (SAPS II) are useful descriptors for patient acuity and predictors of mortality but do not account for the patient care-related workload required for ICU patients. The Therapeutic Intervention Scoring System-28 (TISS-28) is a simple, reliable tool for describing both the severity of illness and the intensity of nursing care delivered to ICU

patients [8, 9]. The TISS-28 has been used extensively in older ICU populations, exhibiting negative correlation with age, particularly in patients older than 85 years [10].

Whether there are gender differences in intensity of care delivered to older MICU patients using the TISS-28 has not been investigated. This study sought to determine whether there were differences in provision of MICU care and outcomes according to gender in an older cohort of patients. We also examined factors at MICU admission and during the course of the MICU stay according to gender. We hypothesized that if there were minimal or no differences in baseline health status of men and women upon MICU admission, then care provided to men and women in our MICU would be equivalent. This study is novel in using a validated scoring system (TISS-28) to formally test for statistical equivalence of MICU care between older men and women.

2. Materials and Methods

2.1. Participants and Setting. The study was a prospective cohort of 309 patients aged 60 years and older in the medical intensive care unit of Yale-New Haven Hospital (YNHH), who were enrolled from September 5, 2002 to September 30, 2004. YNHH is a 900-bed urban teaching hospital with a 14-bed medical ICU (MICU) serving a large urban community as well as a referral population. Patients were excluded if there was no identifiable proxy to provide information about the patient, if they were transferred from another hospital or ICU, or if the patients died before the proxy was identified. Informed consent for participation was obtained from the proxy and patients according to procedures approved by the Institutional Review Board of Yale University School of Medicine.

2.2. Study Procedures

2.2.1. Proxy Interviews. As previously described, proxy respondents were the primary sources of baseline information due to critical illness [11–14]. Information on premorbid functional and cognitive status was obtained.

2.2.2. Patient Factors. Charts were reviewed at the time of enrollment to obtain demographic information, admission diagnosis, preexisting depression, medication use at admission, and the Charlson Comorbidity Index (CCI) [15]. Severity of illness was assessed with the Acute Physiology and Chronic Health Evaluation II Score (APACHE II) [16].

2.2.3. ICU and Hospital Factors. Use of MICU interventions such as mechanical ventilation, vasopressors, new onset dialysis, and pulmonary artery catheterization were recorded. Total number of days in the MICU and requiring mechanical ventilation were recorded to calculate median values. The full range of days in the MICU or on mechanical ventilation for the entire cohort was measured. Patients were assessed daily for delirium. Changes in resuscitation status during the MICU admission were documented. Continuous sedative and narcotic drug administration were tracked using Infusion Administration Pumps which record total dose delivered to the patient.

2.2.4. TISS-28. The TISS-28 is a simple, validated scoring system designed to quantify severity of patient illness and therapeutic activities in the ICU in terms of nursing workload [9]. TISS-28 scores range from 1 to 78 points. Each TISS-28 point correlates with 10.6 minutes of nursing care [9]. The TISS-28 score is compiled from seven general groups: Basic Activities (dressing changes, laboratory blood draws, single medication administration, etc.), Ventilatory Support (mechanical ventilation, care of airway, intratracheal suctioning, etc.), Cardiovascular Support (arterial lines, central venous lines, vasoactive medications, intravenous fluid resuscitation, etc.), Renal Support (active diuresis, quantitative urine output, dialysis), Neurologic Support (measurement of intracranial pressures), Metabolic Support (treatment of complicated metabolic acidosis or alkalosis, enteral feeding, intravenous hyperalimentation), and Specific Interventions (pacemakers, cardioversions, endoscopies, emergencies surgeries, etc.).

For this study, the information for the TISS-28 was collected prospectively from the nurses' bedside flow sheet and the medical record. Data from the entire MICU stay, ranging from admission through discharge, were utilized in the calculation. For patients who died during their MICU stay, the TISS-28 was calculated to include all interventions through time of death.

2.3. Outcomes. We examined gender differences at three time points. We compared baseline factors at MICU admission, interventions during the MICU stay including the TISS-28 scores and outcomes including mortality and length of stay. Fifteen-month mortality was determined by follow-up telephone interview.

2.4. Statistical Analysis. Admission characteristics stratified by gender were summarized with means and standard deviations or medians and interquartile ranges for continuous variables, and with counts and percentages for dichotomous variables. Tests for baseline gender differences were made using t-tests or Wilcoxon rank sum tests for continuous variables and Pearson chi-square or Fisher's exact test for dichotomous variables. For these tests the null hypotheses assumed equality of admission characteristics for men and women.

When comparing two groups, a lack of statistical difference is a different conclusion than saying that two groups received the same treatment, the latter a much less stringent test. We wanted to evaluate if treatment between men and women was the same using a formal test of statistical equivalence. A nonparametric, Mann-Whitney test of equivalence for discrete distributions was used to compare the TISS-28 scores between men and women during their stay in the MICU. The null hypothesis in this case was that men and women received different amounts of overall critical care. We chose equivalence limits of $\pm 15\%$ to reflect the percentile differences around the median value on the

Table 1: ICU admission characteristics of patients enrolled in study ($N = 309$)*.

Characteristic	Men ($n = 145$)	Women ($n = 164$)	P value
Age in years, Mean (SD)	73.7 (8.2)	75.6 (8.6)	.046
Nonwhite race	19 (13)	32 (20)	.13
Medicaid status	13 (9)	30 (18)	.02
APACHE II Score	23.1 (6.6)	23.8 (6.2)	.36
Admitted from home	117 (81)	124 (76)	.28
Baseline Medical Status			
Body Mass Index (BMI, m^2/kg), Mean (SD)†	25.7 (6.9)	26.1 (9.8)	.88
Chronic respiratory failure	37 (25)	64 (39)	.01
Chronic heart failure	33 (23)	44 (27)	.41
Chronic renal insufficiency	28 (19)	28 (17)	.61
Hepatic Failure	1 (<1)	1 (<1)	1.0
Malignancy	10 (7)	8 (5)	.45
Depression	31 (21)	54 (33)	.02
Dementia†	42 (29)	53 (33)	.55
Antidepressants prior to ICU admission	28 (19)	49 (30)	.03
Any Impairment in Activities of Daily Living	50 (34)	61 (37)	.62
Any Impairment in Activities of Instrumental Daily Living	120 (83)	144 (88)	.21
Full Code on ICU Admission†	121 (83)	144 (88)	.27
Admitting Diagnosis			
Sepsis	23 (16)	28 (17)	.77
Respiratory	68 (47)	88 (54)	.23
Neurologic	1 (<1)	4 (2)	.38
Gastrointestinal hemorrhage	33 (23)	19 (12)	.009
Other	20 (14)	25 (15)	.72

*All variables presented as n (%) except where indicated. †Missing data present for some subjects. For BMI missing = 9; Dementia missing = 3; Code status missing = 1.

TISS-28 scale that we regard as being clinically equivalent based on clinical experience with critical care for older persons in the MICU. These equivalence limits correspond to an approximate change of ±5 points between the median TISS values of the gender subgroups. Because 4 points are assigned to intubation, a change of 5 points at the group level would reflect even larger treatment differences "on average" between individual men and women.

The equivalence test was performed using the SAS macro "mwtie_xy" written by Wellek [17] with $P \leq .05$ indicating statistical significance. In supplementary analysis we examined time to death within 15 months of MICU admission with a Cox proportional hazards multivariable model [18] that included covariates for age, APACHE II at admission, gender, TISS-28, and the interaction between gender and TISS-28. These covariates were chosen based on prior ICU studies reporting that mortality is most closely tied to APACHE II scores. Given that the TISS-28 and the interaction between the TISS-28 and gender were the primary outcomes of interest and that the TISS-28 correlates with risk of death, these were additional covariates chosen. All statistical tests were two tailed, with $P < .05$ indicating significance. Analysis was performed with SAS version 9.1.3 software [19, 20].

3. Results

3.1. Comparisons between Men and Women Admitted to the MICU. In this older MICU cohort, women were older than men (75.6 years versus 73.7 years; $P = .046$), were more frequently enrolled in Medicaid (18% versus 9%; $P = .02$), and had more preexisting chronic respiratory failure (39% versus 25%; $P = .01$). More men were admitted with gastrointestinal hemorrhage than women (23% versus 12%, $P = .008$). Women were more likely than men to have a diagnosis of depression and to be taking antidepressants prior to admission to the ICU (30% versus 19%; $P = .03$). However, there were no significant differences between men and women regarding APACHE II score on MICU admission or "Do Not Resuscitate (DNR)" or "Do Not Intubate (DNI)" orders. Additional results regarding admission characteristics for men and women enrolled are included in Table 1. There were also no statistical differences in ICU interventions such as intubation, days of intubation, or ICU length of stay between men and women (Table 2).

3.2. TISS-28 Scores, APACHE II Scores and MICU Mortality. The amount of critical care delivered to women was equivalent to men based on their respective TISS-28 scores.

Table 2: Factors related to time in ICU ($N = 309$).

Continuous Descriptors of ICU Stay	Men ($n = 145$) Median (IQR)	Women ($n = 164$) Median (IQR)	P value*
Therapeutic Intervention Score (TISS-28) Range: 9–50	25 (14)	26 (14)	Equivalent at $P \leq .05$****
Days of stay in ICU (LOS)** Range: 1–51	4 (5)	4.5 (4.5)	.38
Days of Intubation in ICU Range: 1–48	6 (8)	5 (6)	.69
	Men ($n = 145$) n (%)	Women ($n = 164$) n (%)	P value*
ICU Mortality	20 (14)	33 (20)	.14
ICU Delirium	110 (77)	129 (80)	.50
ICU readmission	13 (9)	16 (10)	.81
Intubation	78 (54)	89 (54)	.93
Use of vasopressor medications (Dopamine, dobutamine, norepinephrine, epinephrine, phenylephrine, vasopressin)	54 (17)	77 (25)	.0848
Tracheostomy	8 (5)	7 (4)	.61
Continuous Positive Airway Pressure (CPAP) or BiLevel Positive Airway Pressure (BiPAP)	30 (21)	42 (26)	.31
Pulmonary Artery Catheterization	10 (7)	19 (12)	.16
Enteral Nutrition (Nasogastric Tube or Percutaneous Endoscopic Gastrostomy Tube)	53 (37)	60 (37)	.99
Hemodialysis	7 (5)	10 (6)	.62
Continuous Veno-Venous Hemofiltration (CVVH)	5 (3)	8 (5)	.53
Change in code status to "Less aggressive"	37 (26)	45 (27)	.70

†Missing data present for some subjects. For ICU delirium missing = 5.
*Chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables were used with statistical significance defined as P value $\leq$ .05.
**Length of stay was for first admission.
***Delirium was defined by either positive ICU Confusion Assessment Method (CAM) or chart indication of delirium during ICU stay.
****A nonparametric test of equivalence rejects the null hypothesis that men and women are not equivalent at significance level 0.05 for equivalence limits of ±15% around median value. IQR (Interquartile Range, i.e., central fifty percent distribution).

The statistical test of equivalence employed equivalence limits of ±15 percent around the cohort's median value of TISS-28 scores. Additionally, there was no evidence of statistically significant differences between men and women in rates of specific MICU interventions such as intubation, tracheostomy, renal replacement therapy, or change in code status to "Less aggressive". Table 2 compares selected specific components of the TISS-28 scores related to patients in the MICU by gender. TISS-28 scores significantly correlated with APACHE II scores (Kendall Tau B 0.27311 (<0.0001) and risk of death in the MICU (Kendall Tau B 0.26377 (<0.0001). There was no evidence of gender-based differences in medication administration, or MICU or hospital length of stay.

We also examined TISS-28 scores by age category. The median (range) TISS-28 scores for patients age 60–69 ($n = 87$) was 27 (9–50), for patients age 70–79 ($n = 124$) was 25 (9–43) and for patients age 80 ($n = 98$) and older was 23 (9–46).

3.3. Patient Discharge and Fifteen-Month Mortality. In supplementary analysis women were less likely to be discharged home (42% versus 52%; $P = .13$) although the difference was not statistically significant. There was no association between gender and mortality up to 15 months after ICU admission. There was also no association between 15-month mortality and the interaction of gender and TISS score (Table 3).

4. Discussion

While gender differences in ICU care delivered have been reported in the cardiac critical care literature and some mixed medical and surgical ICUs, we did not detect any evidence of gender-based differences in rates of MICU interventions when looking at specific aspects of critical care. In addition, there was no evidence of statistically significant gender-based differences in administration of medications in the MICU. After controlling for age and severity of illness, there was no evidence of a statistically significant

Table 3: Mortality and discharge disposition ($N = 309$).

	Men ($n = 145$) n (%)	Women ($n = 164$) n (%)	P value
Death (ICU or Floor)	32 (22)	47 (29)	.17▲
Overall Mortality (15 months from ICU admission)	86 (59)	85 (52)	.76*
Discharge to skilled nursing facility, assisted living, rehabilitation unit, hospice, hospital**	54 (48)	67 (58)	.13▲

▲Chi-square or Fisher's exact tests were used for categorical variables with statistical significance defined as P value $\leq .05$.
*The P value reported pertains to the interaction term in a Cox proportional hazards multivariable model including age, APS at admission, gender, TISS-28, and the interaction between gender and TISS-28.
**Those not discharged to Skilled Nursing Facility, and so forth were discharged to home or friend/relative.
Missing data are present for some subjects. For discharge location missing = 1.

difference in ICU or 15-month mortality between men and women.

Men admitted to the MICU were younger than women, likely related to increased longevity in women in the general population. Additional differences between men and women on MICU admission included receipt of Medicaid, chronic respiratory failure and admission diagnosis of gastrointestinal bleed. Given these minimal differences between men and women on MICU admission, our conditional hypothesis that there would be equivalent care delivered to men and women if there were minimal baseline differences was supported by these study results.

Our study showed that women were more likely to have underlying chronic pulmonary disease compared to men. With increasing rates of women smoking, there has been a shift towards more women than men dying from chronic obstructive pulmonary disease (COPD) [21]. Men were more likely to be admitted with gastrointestinal hemorrhage in our cohort. This finding conforms to data that demonstrates male gender is associated with increased risk factors for gastrointestinal hemorrhage, including peptic ulcer disease, colonic polyps, or gastrointestinal malignancies [22–25].

In our study, the average TISS-28 score in our older MICU population was 25 for men and 26 for women which is consistent with the range of TISS-28 scores from other studies. In a study of mixed medical and surgical ICUs in Brazil, the average TISS-28 for all patients who stayed in the ICU for at least 24 hours was 23 with a range from 14–32 [26]. The majority of these patients were admitted to surgical ICUs. Mean TISS-28 scores in prior studies of predominantly medical ICUs range between 22–33.8 [27–29]. TISS-28 scores and in-hospital mortality have shown a positive correlation in patients older than 65 years of age [30]; our study also found a positive correlation between TISS-28 scores and APACHE II scores (Kendall Tau B 0.27311 (<0.0001) and mortality (ICU, Kendall Tau B: 0.26377 (<0.0001). Older patients may be more vulnerable to poor ICU outcomes if they receive less aggressive care despite a greater severity of illness [31].

The current study shows that the care delivered to older men and women as measured by the TISS-28 was equivalent in our MICU. Treatment disparities between men and women have been observed in other studies of critically ill patients and may impact outcomes according to level of aggressive care [5, 29, 32]. A large Belgian study of mixed medical and surgical ICU patients showed that women had a higher mortality than men, particularly women greater than 50 years old during their first days of ICU admission [33]; however, this study did not adjust for severity of illness. Another study examining gender difference in acute myocardial infarction found that while there were no differences in diagnostic or treatment procedures between men and women, female sex was an independent predictor for adverse events including reinfarction, death, in-patient stroke, and postinfarction angina [34].

Conversely, in a single-site study of a surgical ICU by Wichmann et al. where less women were referred for care in the ICU, there was no difference in mortality between men and women who were admitted to the surgical ICU [35]. A large Finnish study of surgical and medical ICUs found that men had a modest but significantly higher TISS-28 score [29]. Despite this, older men had an increased risk of death after adjusting for severity of illness. In the medical subgroup, there was no difference in mortality between men and women [29]. In another study of critically ill medical and surgical patients from Austria, men received more invasive procedures such as mechanical ventilation, renal replacement therapy, and vasoactive medications than women although women had a greater severity of illness [32]. These differences were observed in all age groups but were most pronounced in the older population (age 61–80 years). Even with the observed differences in level of care between men and women, there were no differences in outcomes or mortality between men and women in multivariate analysis [32].

While studies show equivalent or greater intensive care administered to men, other data suggests that neurohumoral changes in men may have greater adverse effects on their survival after critical illness. Testosterone has immunosuppressive characteristics with detrimental effects after trauma-hemorrhage injury in animal models, increasing susceptibility to infections or sepsis [35–37]. Men with severe infections have elevated 17β-estradiol and progesterone levels which are

associated with increased mortality [38]. Similarly, women with severe infections had higher levels of 17β-estradiol and testosterone which were also associated with higher mortality [38]. In addition to male and female sex hormones, biomarkers such as tumor necrosis factor, interleukin-10, and interleukin-6 are postulated to play a role in these gender disparities.

The main limitation of this study is that it was performed in a single ICU in a large academic medical center so results may not be representative of care provided in other subspecialty ICUs or in community hospitals. Another limitation of this study is that the TISS-28 does not account for patient preferences and acceptable levels of intensive care. In addition, the TISS scoring systems were derived to measure ICU nursing activities which may not fully correlate with aggressiveness of ICU care. Strengths include the large sample size of older ICU patients with equal numbers of men and woman along with the high participation. In addition, we collected a detailed, clinically rich prospective data set using validated instruments.

In summary, this study is novel in demonstrating that treatment of men and women in this ICU cohort is not only not different but is statistically equivalent using equivalence limits based on clinical experience in caring for older MICU patients. Finally, there was no difference in mortality between men and women in this cohort.

5. Conclusions

In contrast with prior studies, men and women in this older MICU cohort with similar baseline characteristics on MICU admission received equivalent critical care based on their TISS-28 scores. In this study, MICU and 15-month mortality were also similar between men and women. As the U.S. population ages and medical technology advances, there will be greater need and opportunity for interventions in medical ICUs. It will be valuable to use reliable measurements for the amount of care provided and weigh their impact on ICU survival. While our study did not show significant differences in MICU care or 15-month mortality between men and women, gender-based treatments and mortality should continue to be examined for biological differences between men and women, patient and cultural influences, and biases in clinician practice. Future studies will be necessary to further examine gender differences in critically ill patients.

Key Messages

(i) In this cohort of older patients admitted to a medical intensive care unit (MICU), women were older than men and had more chronic respiratory disease but had otherwise similar baseline characteristics.

(ii) Men and women in this older cohort received equivalent care in the MICU based on the Therapeutic Intervention Scoring System-28 (TISS-28).

(iii) After adjusting for age and severity of illness, there was no difference in MICU or 15-month mortality.

(iv) Contrary to prior studies in cardiac ICUs and mixed ICUs, there was no evidence of gender disparity impacting the amount of critical care delivered to this cohort of older patients.

Abbreviations

ADL:	Activities of Daily Living Scale
APACHE II:	Acute Physiology and Chronic Health Evaluation
CCI:	Charlson Comorbidity Index
COPD:	Chronic Obstructive Pulmonary Disease
IQCODE:	Informant Questionnaire on Cognitive Decline in the Elderly
IADL:	Instrumental Activities of Daily Living Scale
ICU:	Intensive care unit
SOFA:	Sequential Organ Failure Assessment
SAPS:	Simplified Acute Physiology Score
TISS-28:	Therapeutic Intervention Scoring System-28
YNHH:	Yale-New Haven Hospital.

Conflict of Interests

None of the participating authors have competing interests in the research conducted or preparation of this paper.

Author's Contributions

K. M. Akgün conducted the background research and prepared the paper. K. L. B. Araujo managed the data and prepared figures and tables for the paper. T. E. Murphy and P. H. V. Ness performed the necessary statistical research and statistical analysis for this paper. M. Pisani enrolled patients and collected the data for this study. In addition, M. Pisani mentored K. M. Akgün for study design and paper preparation.

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To: Erika Tarver, Alliance for Academic Internal Medicine

Re: T. Franklin Williams Grant - Year 1 Progress Report

Date: June 15, 2010

Scholar and institution:

Alison Huang, MD, MAS, University of California San Francisco Department of Medicine

Summary of scholar progress:

Since beginning my T.F. Williams scholars award in July of 2009, I have published 3 first-author peer-reviewed publications related to urogenital aging in women, and have given 2 research presentations at national scientific meetings of the Gerontological Society of America and the American Geriatrics Society. I received an American Geriatrics Society/Merck New Investigator Award for my research related to the clinical significance of postvoid residual bladder volume in older women. I also resubmitted an R03 grant application to the National Institute of Aging, which scored in the top 1% at its review section.

With regard to my specific T.F. Williams research project, I have administered my preliminary Day-to-Day Impact of Vaginal Aging (DIVA) Questionnaire to over 500 middle-aged and older women enrolled in the Reproductive Risks of Incontinence Study at Kaiser 3 (RRISK3) cohort. I have also re-administered the questionnaire to a subset of 100 women approximately 1 week after the initial administration, for assessment of test-retest reliability. Administration of the questionnaire to the remaining women in the RRISK3 cohort will continue in year 2 of this award, along with repeat administration to a subset of 100 women approximately 1 year after their initial administration. Using these data, I will subsequently examine the psychometric properties of the questionnaire and examine differences in the impact of urogenital atrophy symptoms by age, sexual activity status, and comorbidity status.

With regard to my T.F. Williams training plan, I have participated in works-in-progress sessions within the UCSF Division of Geriatrics in order to gain feedback from geriatrics scholars at my institution on my work. I have presented my research at meetings of the Gerontological Society

of America and the American Geriatrics Society in order to foster collaborations with other aging researchers. I have also been pursuing a course of directed reading related to assessment of comorbidity and evaluation of functional status in the elderly, in order to apply these principles of geriatrics assessment to my own work.

Publications since award date:

1) **Huang AJ**, Subak LL, Thom DH, Van Den Eeden SK, Ragins AI, Kuppermann M, Shen H, Brown JS. Sexual function and aging in racially and ethnically diverse women. *Journal of the American Geriatrics Society.* 2009 (57):1362-1368. [PMC2749599]
2) **Huang AJ**, Moore EE, Boyko EJ, Scholes D, Lin F, Vittinghoff E, Fihn SD. Vaginal symptoms in postmenopausal women: self-reported severity, natural history, risk factors. *Menopause.* 2010 (17):121-126. [PMC2806500]
3) **Huang AJ,** Luft J, Grady D, Kupperman M. The day-to-day impact of urogenital aging: perspectives from racially/ethnically diverse women. *Journal of General Internal Medicine.* 2010 (25): 45-51. [PMC2811605]

Presentations since award date:

Nov, 2009 Gerontological Society of America Annual Meeting
"Vaginal Atrophy Symptoms: Natural History and Predictors in Older Women"

May, 2010 American Geriatrics Society Annual Meeting
"Clinical Significance of Postvoid Residual Volume in Older Women"

Awards and honors since award date:

May, 2010 American Geriatrics Society/Merck New Investigator Award

Grant applications since award date:

R03 resubmitted grant application to the National Institute of Aging, entitled "The Impact of Vaginal Atrophy Symptoms on Quality of Life in Postmenopausal Women," reviewed at study section in June, 2010 (impact score = 19, percentile = 1%).

The Day-to-Day Impact of Urogenital Aging: Perspectives from Racially/Ethnically Diverse Women

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BACKGROUND: Urogenital symptoms affect up to half of women after menopause, but their impact on women's day-to-day functioning and wellbeing is poorly understood.

METHODS: Postmenopausal women aged 45 to 80 years reporting urogenital dryness, soreness, itching, or pain during sex were recruited to participate in in-depth focus groups to discuss the impact of their symptoms. Focus groups were homogenous with respect to race/ethnicity and stratified by age (for White or Black women) or language (for Latina women). Transcripts of sessions were analyzed according to grounded theory.

RESULTS: Six focus groups were conducted, involving 44 women (16 White, 14 Black, 14 Latina). Five domains of functioning and wellbeing affected by symptoms were identified: sexual functioning, everyday activities, emotional wellbeing, body image, and interpersonal relations. For some participants, symptoms primarily affected their ability to have and enjoy sex, as well as be responsive to their partners. For others, symptoms interfered with everyday activities, such as exercising, toileting, or sleeping. Participants regarded their symptoms as a sign that they were getting old or their body was deteriorating; women also associated symptoms with a loss of womanhood or sexuality. Additionally, participants reported feeling depressed, embarrassed, and frustrated about their symptoms, and expressed reluctance to discuss them with friends, family, or health care providers.

CONCLUSIONS: Urogenital symptoms can have a marked impact on sexual functioning, everyday activities, emotional wellbeing, body image, and interpersonal relations after menopause. Clinicians may need to question women actively about these symptoms, as many are reluctant to seek help for this problem.

KEY WORDS: urogenital atrophy; vaginal dryness; dyspareunia; menopause; quality of life.

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INTRODUCTION

The postmenopausal years are characterized by profound degenerative and inflammatory changes in the urogenital tissues, collectively described as urogenital atrophy[1]. In up to half of women, these changes are accompanied by symptoms such as dryness, soreness, itching, and pain during sexual intercourse that can persist for many years after menopause, causing ongoing discomfort and distress as women age[2–6].

Currently, the impact of urogenital atrophy symptoms on quality of life after menopause is poorly understood. A few studies conducted primarily in Europe have suggested that these symptoms may contribute to problems with sexual activity, body image, and psychological wellbeing[7–10]. These studies have largely been confined to white women; however, even though epidemiologic research suggests these symptoms are equally if not more prevalent in women of other racial/ethnic backgrounds[3,11], and even though women's experiences of these symptoms may be influenced by cultural attitudes toward aging and urogenital function[12–14].

To address these issues, we conducted a qualitative study of racially and ethnically diverse postmenopausal women experiencing urogenital dryness, soreness, itching, and pain with sexual intercourse. Our goal was to identify dimensions of functioning and wellbeing affected by urogenital atrophy symptoms, in order to guide future efforts to reduce their impact on quality of life. We also sought to understand women's beliefs about the etiology of their symptoms, attitudes toward discussing symptoms, and strategies for coping with symptoms, in order to understand how these beliefs and attitudes might influence their discussions with health care providers.

METHODS

Eligibility and Recruitment

Postmenopausal women aged 45 to 80 years from three racial/ethnic groups (White, Black, and Latina) who reported urogenital symptoms were recruited to participate in focus group discussions. Women were considered postmenopausal if they had not had a menstrual period in 12 months; those who had undergone hysterectomy were also required to have had bilateral oophorectomy unless they were over 70 years of age. In addition, to be eligible, women had to report moderate-to-severe urogenital dryness, soreness, itching, or pain/discomfort during sex for at least 6 months.

Participants were recruited through newspaper notices and brochure postings in primary care and gynecology offices.

Women who had participated in other women's health studies in the San Francisco Bay Area[15,16] and expressed willingness to be contacted for other research were also invited to participate. Eligibility was determined through a screening telephone call, after which eligible women were invited to participate in a semi-structured discussion group with 6 to 10 other women.

Focus Groups

Six focus groups were conducted between April, 2007 and April, 2008 on the University of California, San Francisco campus. Each group was homogenous with respect to race/ethnicity (White, Black, or Latina). Focus groups were also stratified by either age (<60 versus ≥60 years old for White or Black women) or language (English-speaking versus Spanish-speaking for Latina women).

Focus groups were led by female moderators who were matched with respect to race/ethnicity, language, and general age with participants. Moderators were trained in interviewing and/or discussion moderation but were not clinicians. Focus group sessions were audiotaped with the participants' permission, and all sessions were directly observed by at least two investigators from behind a one-way mirror. All participants gave informed consent before their focus group.

Moderator guides were developed that encouraged women to freely express their thoughts on how urogenital symptoms affected their day-to-day activities, feelings, and relationships, using prompts derived from a review of existing studies of genitourinary conditions (Box 1). Additionally, moderators encouraged women to discuss their thoughts about the etiology of symptoms, attitudes toward discussing symptoms, and strategies for coping with symptoms in everyday life. At the end of each session, participants completed brief questionnaires assessing demographic and clinical characteristics. Participants were offered $40 compensation and reimbursement for costs of transportation or parking.

Box 1. Sample Moderator Prompts to Promote Focus Group Discussion

- In what ways have your vaginal symptoms affected or changed your day-to-day life?
- Do your vaginal symptoms affect how physically active you are or the amount or type of exercise you do? How so?
- Do you think your vaginal symptoms have changed how you feel about your life? Can you give an example?
- Do you think you have changed how often you have sex or how you have sex as a result of your symptoms?
- Have your vaginal symptoms affected your relationship with your spouse or partner? If so, how?
- Do you think your vaginal symptoms have affected your mood day-to-day? If so, how?
- How often do you find that you end up thinking about your vaginal symptoms in the course of a week?
- What are the ways in which your vaginal symptoms have affected your romantic and sexual relationships?
- What has changed about you as a person, if anything, since you developed these vaginal symptoms?
- Has your attitude toward your health changed since you developed these symptoms? If so, how?
- Were you surprised when you developed these vaginal symptoms, or did you expect to develop them?
- Do you think that having these symptoms has affected your relationship to friends or relatives other than your husband or sexual partner? If so, how?
- Have you ever talked about your symptoms with doctors, nurses, or other health care professionals about your symptoms?
- Have you ever talked about your symptoms with friends or family members? Can you tell me about some of those conversations?

Data Analysis

Focus group recordings were transcribed and, if necessary, translated into English by experienced bilingual transcriptionists. Transcripts were then analyzed according to grounded theory, a qualitative data analysis approach in which analysis codes and explanatory themes are allowed to emerge from the data[17]. Additionally, the constant comparative approach was used, in which codes identified in the first transcript (White women ≥60 years of age) were applied to subsequent transcripts, and additional codes were added as additional themes emerged from the data[18].

To minimize bias in analyses, two methods of triangulation were used: investigator triangulation (multiple investigators attended the focus groups and reviewed transcripts) and disciplinary triangulation (investigators represented different areas of expertise). Specifically, transcripts were independently read and coded by three members of the investigative team, including a nurse practitioner specializing in women's health, a PhD-trained researcher experienced in quality-of-life assessment, and a general internist with a research focus in menopause. Afterwards, investigators met to discuss and resolve differences in coding. Through this iterative process, a set of common themes observed throughout the groups was extracted and agreed upon by all investigators.

Additionally, semi-quantitative methods were used to explore potential differences in the impact of symptoms among women of different age and/or race/ethnicity. Consistent with other qualitative studies[19], we examined the frequency with which various participant responses corresponding to different coded themes occurred in each focus group session. All study procedures were approved by the institutional review board at the University of California San Francisco.

RESULTS

The mean (SD) age of participants was 58 (8) years, with a range of 48 to 75 years (Table 1). The most commonly reported urogenital symptom was dryness (66%), followed by soreness (41%), pain/discomfort during sexual intercourse (41%), and itching (36%).

Five major dimensions of functioning and wellbeing affected by symptoms were identified through analysis— sexual functioning, everyday activities, emotional wellbeing, self-concept/body image, and interpersonal relations (Table 2). With the exception of the everyday activities dimension, which did not emerge in discussion among Black women under 60 years of age, all dimensions featured prominently in discussion in all six focus groups.

Sexual Functioning

Participants from all age, racial/ethnic, and language groups described significant problems with sexual activity as a result of their symptoms (Box 2). Some women who had previously enjoyed active, satisfying sexual lives reported that their symptoms had caused them to lose interest in sex: "[I]n the last year I have only had sex twice, and both times it was extremely painful, I can remember screaming in pain.... I always loved sex, but... that is enough to disenchant me.... Because it's too painful." Some women who remained sexually

active complained that their symptoms had transformed vaginal intercourse into a primarily painful experience: "And sometimes you do it anyways, putting up with the discomfort, the pain, but you wish that the moment would pass... because you can't stand it!... Instead of having pleasure, instead of satisfaction, what you have is anguish, for it to be over."

Box 2. Participant Responses Regarding the Impact of Urogenital Symptoms on Dimensions of Functioning and Wellbeing

Sexual functioning	"I am married now, and I just feel sorry for my husband, because I just don't want to have sex anymore…. [It's] painful. Extremely painful. And… it makes me feel like I am not a good wife." "[W]ith oral sex… there is a response that promotes lubrication, and then you can have sex, and it's not very painful. It's not very comfortable, but it's not very painful. But if there is not that preamble of oral sex, it's impossible, it's too painful." "Then you worry… slipping in the KY Jelly, if it's going to be lubricated enough so that you can get pleasure, and he can get pleasure, and stop him saying, 'What's going on here, you're just a little too dry, so I can't do anything?'"
Everyday activities	"It does interfere with your day-to-day life, because it doesn't say, 'Now, I am not going to bother you now because you're around your friends or you're around other people,' you know. You have to excuse yourself and go to the bathroom, and then there is nothing in there to give you any relief." "I would feel that terrible burning so much that I couldn't sleep at night. It was a terrible burning, and I would go to the bathroom, I would put really cold water on myself, good and cold. But I would feel that I couldn't sleep, until almost one or two o'clock in the morning [when] I would fall asleep, when that pain would go away a little bit." "[T]he more water you drink, the more you go, and the more you go, you have to wipe. And if you don't have the wipes with you, you have to wet the toilet tissue, or paper towel… I remember a time when I was irritated so bad... I had to hurry, get up, and go to the restroom, wet me a paper towel, and try to cool down... Oh, gee, it's just, just irritating! Really irritating!"
Emotional wellbeing	"I think with me… it may be because [I have] health problems already, and when [vaginal dryness] happens it's one more thing, as far as pain and things like that to deal with. And that's why I know at times I do get depressed because, I think, I can't have just one thing on my body that is just OK?" "When I go to the bathroom and there's, whatever, itching, dryness, burning, I have to remember that, okay, on the larger scale of things, [I'm] pretty damn lucky. But, you know, as with anything else, I'm human, I have my weak moments, and I can sit there and feel sorry for myself and have a pity party."
Self-concept & body image	"I've always had a pretty good feeling about myself, my self-image… But as those symptoms became more obvious, I felt that three letter word, OLD, and that it put me in the category of being invisible." "[W]hen you pass 50, you start looking back at the 20 year-olds, and saying OK… we know they don't itch.… [N]ow I am 66, and I am not young anymore. I am not young anymore…. [N]ow I wish I didn't have to get older, but the alternative to getting old is to die…." "I think [that] as you get older… the dryness is going to stay there, get worse. Everything is going to get worse as you get older.… You might have other things to get in your head to tone it down. But it's going to be there. It's going to be there on the backburner."
Interpersonal relations & communication	"So when I started to suffer these things, I was embarrassed to tell even my female doctor, right? There are things that you deal with yourself, trying to cure them alone, without help from anyone, and it's terrible. Now that I feel more confident with my doctor, I've talked to her, [but] it wasn't very long ago, it's only been a few months since I was able to tell my doctor." "Yes, since it's very private, it's something that... nobody talks about. Not the neighbor, nor at school, nor at work. So then you think it's something special that you are going through." "On many occasions I had the intention to sit down with my husband… and talk to him about what I felt each time we had sexual contact, but he liked to joke a lot, he really liked to joke around, and I was embarrassed to tell him. I said to myself, 'He's going to make jokes about what I am telling him.'"

Participants who were involved in long-term sexual relationships expressed concern about being unable to be responsive to their partners as a result of their symptoms: "And I also feel very guilty vis-à-vis my husband.... He likes to make love all the time, but... I have been avoiding it... because it's uncomfortable, it's painful... and I don't want to make him aware that I have been avoiding it." Participants described furtively applying vaginal lubricants or trying to disguise their discomfort to prevent their partners from becoming aware of their problem. Some participants also reported that their problems with pain were exacerbated by the sexual problems of their partners. For example, several women complained that their need to apply lubricants made it difficult for them to respond quickly on those occasions that their partners were able to overcome their erectile dysfunction: "He's at the age where, if it's working, we're supposed to drop everything.... [I]nevitably when the mood hits him, I'm not ready with the AstroGlide, or it's far away, and I'm going, 'oh, please... give me a little notice.'"

Among women who were not currently involved in a sexual relationship, some indicated that they would be reluctant to enter into a new relationship due to fear of pain during sex: "[M]y boyfriend is 15 years older than I am, and... he's in assisted living now... so it isn't a problem at this moment. But I worry, my God, if something happens to [him], and should I find another boyfriend...would I say, "'No, I can't do it.'?" Even when women were capable of feeling desire for a new partner, some said they were reluctant to progress to intercourse due to fear of pain: "[S]ometimes I go out on a date, and you know, you could consider me a teaser, 'cause I still get the build up and the desire to want to have sex, but I am not going to put myself through the discomfort that I think I would suffer if I had it."

Table 1. Demographic and Clinical Characteristics of Participants

Characteristic	Participants (N=44)
Race/ethnicity	
White/Caucasian	16 (36%)
Black/African-American	14 (32%)
Latina/Hispanic	14 (32%)
Age	
Total age range (yrs)	48, 75
Age > 60 yrs	17 (39%)
Primary language	
English	36 (82%)
Spanish	8 (18%)
Relationship history	
Sexually active[a]	23 (52%)
Married/living with partner	17 (39%)
Work/education history	
High school graduate	38 (86%)
Full- or part-time employed	19 (43%)
Medical/surgical history	
Fair/poor self-reported health	18 (41%)
Hysterectomy	10 (23%)
Bilateral oophorectomy	9 (20%)
Moderate-to-severe urogenital symptoms[b]	
Dryness	29 (66%)
Itching	16 (36%)
Soreness	18 (41%)
Pain during sex	18 (41%)

Data are presented as number (percent). Data were missing for 1 participant for education, 3 participants for employment, and 2 participants for self-reported overall health
[a]*Sexual activity status was assessed by using the question, "Are you currently sexually active with or without a partner?"*
[b]*Indicates the number (percentage) of participants who reported a symptom as being "moderately," "quite a bit," or "extremely" bothersome*

Everyday Activities

Although some participants indicated that their symptoms were problematic only during sex, others said their symptoms

Table 2. Frequency of Participant Responses Regarding the Impact of Urogenital Symptoms on Dimensions of Functioning and Wellbeing, by Focus Group[a]

White women, <60 yrs old	White women, ≥60 yrs old	Black women, <60 yrs old	Black women, ≥60 yrs old	Latina women, English-speaking	Latina women, Spanish-speaking	All focus groups
Sexual functioning—the impact of symptoms on women's interest in and willingness to engage in sexual activity, ability to enjoy sexual activity, and ability to maintain sexual or intimate relationships with partners						
59	69	33	41	21	45	268
Everyday activities—the extent to which symptoms interfere with participation in activities of daily life, such as dressing, toileting, and exercising, as well as more complex activities or routines such as working outside the home or recreational activities						
9	6	0	15	8	12	50
Emotional wellbeing—the impact of symptoms on mood, including feelings such as depression, anxiety, or frustration, as well as the extent to which women are preoccupied by their symptoms						
15	15	5	14	13	20	82
Self-concept and body image—the extent to which symptoms affect women's feelings and perceptions about their bodies, their health, and their identities as women						
19	31	2	12	27	22	80
Interpersonal relations—the extent to which symptoms affect women's ability to socialize with friends and family, their ability to communicate with others, and their sense of connection to other people in their lives						
17	45	9	14	17	45	147

[a]*Transcripts of focus group discussions were independently read and analyzed by three investigators. Each identifiable segment of continuous speech uttered by a focus group participant was analyzed as a separate unit. Investigators assigned thematic codes to individual speech segments based on their interpretation of their content; more than one code could be assigned to speech segments that evoked more than one theme. After investigators met to resolve any differences in coding, the total number of times that each thematic code appeared in each focus group session was tabulated. Next, thematic codes were grouped into five overall dimensions of functioning or wellbeing (i.e., sexual functioning, everyday activities, emotional wellbeing, self-concept/body image, or interpersonal relations), and the total number of times that a thematic code corresponding to each of these dimensions was calculated for each session.*

interfered with other activities of daily living (Box 2). Some reported being unable to sit for prolonged periods on public transportation, go for walks, or ride a bicycle because of dryness/irritation. Participants also described being unable to go out in public due to a frequent need to retire to a bathroom to scratch or wipe. Furthermore, some participants complained that their choice of clothing was limited by their symptoms, as they could not wear pantyhose or form-fitting clothing that might irritate the urogenital area.

Women who experienced symptoms specifically during urination described being reluctant to use the toilet because of their symptoms: "Well, when I had the dryness, I didn't want to drink, because I dreaded the thought of having to urinate, because I knew it was going to burn.... There was a point there where I dreaded to have to drink.... I'd hold it, you know, because it burned so bad." Women also described elaborate rituals of washing and wiping in order to relieve their irritation with urination.

Emotional Wellbeing

Participants varied in the emotions evoked by their symptoms, with some reporting extreme depression and frustration, and others being only moderately bothered by this problem (Box 2). Some women who had not previously heard of urogenital atrophy indicated that their lack of prior knowledge increased their emotional distress upon developing symptoms: "Once I... resumed my sexual activity... I realized that I [had] this problem, and it was extremely embarrassing and frightening... I'd gone through so many things, and I'm thinking... I'm going to be able to enjoy sex... but then... I can't even have sex, and it was frightening, and it was disillusioning, and it was frustrating, and I was really angry."

Some women reported coping with their symptoms by trying to ignore their impact on their everyday lives: "I don't want to admit that there's dryness, it's kind of like, "Oh no, one more thing," and I tend to ignore it.... I want to think that I'm not dry, that those juices are still flowing...." Others complained that even when they were successful in finding ways of relieving their symptoms, they felt burdened by constantly having to think about this problem: "I've never been aware of my vagina at any other time. Suddenly there she is! And I'd rather she'd be gone most of the time...."

Self-concept and Body Image

In all six focus groups, participants tended to describe their symptoms as a sign that they were getting old or that their body was deteriorating (Box 2). As a result, their feelings about their symptoms often reflected their anxieties and concerns about growing old. Several women expressed fear or concern that they were becoming "less of a woman" as a result of these and other signs of menopause and aging: "You know, what kind of scared me was, there's a girlfriend of mine who's ten years older than me.... She's like, 'Oh, well, you know, as women age, we become more like men, because [we] don't have estrogen,' and, really, I feel myself getting horrified.... I felt like, 'Oh my God, I don't want to get old.'" Others argued that "being feminine has nothing to do with aging of the vaginal area," and insisted that their symptoms, although bothersome, had not detracted from their sense of womanhood. Several women complained that their negative feelings about their symptoms were exacerbated by social pressure to appear or act younger than their age, including pressure to maintain frequent sexual activity: "I am thinking if we weren't faced with this relentless barrage of ads... and TV shows that are... only about sex and

mean jokes about women who don't have sex, that we could be happy with our place in society as aging women."

Interpersonal Relations

Many participants were reluctant to discuss their urogenital symptoms with their husbands or partners because they were afraid of being perceived as "too old" or "not good enough" or being ridiculed for having this problem (Box 2). Some indicated that they were also uncomfortable with discussing their symptoms with female friends or relatives, even when they were accustomed to discussing other types of menopausal symptoms: "I have four or five very, very close friends.... You talk about the flashes, you talk about the fact that, OK, maybe you haven't had sexual activity in a couple of weeks.... But as far as [dryness] is concerned, we never talk about that." Because they had not discussed these symptoms with others, some participants said that they mistakenly believed that they alone had this problem: "When I got all of this, I was ignorant. I didn't know that I would get dryness, itching, irritations.... I didn't know! And I put up with it for a long time, until very recently when I told my doctor.... Could it just be me, could it be that it's not everyone?"

Participants also reported being reluctant to discuss their symptoms with health care providers, even when their symptoms significantly affected their quality of life: "I started to get these things like dryness, itchiness, irritation that was very bothersome. Sometimes when I scratched myself, even with a towel, I would bleed. But I was scared. Even with all that I wasn't brave enough to tell my doctor." Some women indicated that they were not aware that their symptoms could be caused by a medical problem until they were finally evaluated by a doctor: "I felt really isolated for a long time, because I didn't understand that this could happen. And the first time I became aware of it, I was having an exam at the doctor's office.... [T]hey're looking in there, and she said, 'You see that, that's urogenital atrophy,' and I went, 'Oh!'"

Beliefs About Etiology

Some participants attributed their symptoms to modifiable behaviors such as physical exercise or fluid intake, while others regarded their symptoms to be an unavoidable consequence of aging or menopause: "You get to be 65, your whole body dries up.... [M]y ears is dry, my nose is dry, my eyes is dry, my everything is dry." Women also expressed concerns that their symptoms were caused or exacerbated by their prior use of hormone-based therapies: "So I also felt a little punished.... Well, if you had been smarter... not taken birth control pills, maybe you wouldn't have this problem right now..." Other women believed that they had developed urogenital dryness as a side effect of other medications: "And when we get older we do take a lot of medicine.... Anybody taking some kind of pill even if it's only an aspirin a day... that aspirin could be sucking up all the water in the body."

Women also expressed conflicting views about the role of sexual activity in the etiology of their symptoms, with some believing that women who remained sexually active were less likely to be symptomatic, and others believing that sexual activity could worsen symptoms. Several expressed concern that their symptoms resulted from contracting a sexually transmitted disease: "Yes, I thought, I would say, 'Who knows where this man has gone and who knows what he's given me,' because after having sex with him, I would feel that terrible burning...." Participants also expressed concern that they had developed symptoms as a result of poor hygiene: "It's just like, are you cleaning up down there? Or, you know, is it dirty in there? So... you're putting water in the sink, and putting soap in there, and you're scrubbing and scrubbing."

Treatment/Coping Strategies

Participants described a variety of approaches to managing their symptoms, including hormone therapies, non-hormonal lubricants and moisturizers, alternative/complementary therapies, and washing and soaking techniques. Concern about the potential side effects of estrogen-based therapies emerged in all groups: "I just don't like to put all that stuff in my body, because... five or six years from now, you've got vaginal cancer or something." However, some participants argued that the relief they obtained with these therapies was worth the risks: "It's been about two years [since] I was taken off the hormone therapy, and I was getting up every night, at least three times... and dealing with dryness. So I did go back to the doctor and ask to be put back on it... And at my age, it's more important about the quality of my life than how long I live." Frustration about the inadequacy of existing treatments emerged in all focus groups, with women complaining that fewer treatments were available for problems related to women's sexual function than men's: "[W]hen men begin to have difficulties, well here is Viagra... like the perfect solution... not quite realizing that maybe there isn't as perfect a solution as Viagra to our problem."

DISCUSSION

In this study of racially/ethnically diverse postmenopausal women, we found that urogenital symptoms such as dryness, soreness, itching, and pain/discomfort with sexual intercourse had a profound and multi-layered impact on day-to-day functioning and wellbeing. For some, urogenital symptoms primarily affected their ability to have and enjoy sex, as well as their ability to be responsive to their partners. For others, symptoms restricted their choice of clothing, interfered with exercising or toileting, and limited their ability to go out in public. Participants from all age and racial/ethnic groups reported feelings of depression, frustration, or anxiety related to their symptoms, although some were more successful in coping than others. Many regarded their symptoms as a palpable sign that they were getting old or that their body was deteriorating; some also associated their symptoms with a loss of womanhood or femininity. Additionally, many described feelings of isolation or embarrassment due to a belief that they alone suffered from this problem.

Several limitations of this research should be acknowledged. First, we purposefully recruited women with moderate-to-severe urogenital symptoms to participate in our study. Our findings may not be generalizable to women with milder symptoms, who might be less likely to believe they had a problem worthy of discussion. Second, we did not require women to undergo clinical evaluation for their symptoms, and it is possible that some participants suffered from diseases other than menopause- or age-related urogenital atrophy.

Nevertheless, our findings likely have relevance to the impact of urogenital dryness, soreness, itching, and dyspareunia in postmenopausal women independent of etiology.

Several of our findings may be important to the evaluation and/or management of urogenital symptoms in older women. Many of our participants indicated they were uncomfortable seeking treatment, even when their symptoms significantly compromised their quality of life. Our findings suggest that clinicians may need to question older women actively about urogenital symptoms and initiate discussion of strategies for reducing their burden on women's day-to-day lives, rather than waiting for women to volunteer information about this problem.

Additionally, participants' subjective experiences of and responses to their symptoms were influenced by their perception of what constituted "normal" urogenital function after menopause, as well as their beliefs about the underlying cause of their symptoms. These findings underline the need for clinicians to address women's understanding of the etiology of their symptoms, including any misconceptions about the contribution of medications, hygiene, and sexual activity that may magnify the impact of symptoms on self-image and emotional wellbeing.

Third, the impact of symptoms on participants' sexual functioning varied markedly depending on whether women had a sexual partner, the nature of their relationship to that partner, and whether the partner also had physical or sexual problems. Women who felt that their partners were unable or unwilling to accommodate their symptoms appeared especially likely to feel that their sexual lives were compromised. These findings underline the need for clinicians to address the larger context of women's sexual relationships when counseling them about urogenital atrophy, as well as to tailor discussion of different types of therapies (e.g., daily maintenance therapy with a vaginal moisturizer versus use of a lubricant before intercourse) to women's priorities regarding their sexual functioning.

Finally, many participants expressed conflicting feelings about using treatments such as estrogen that could improve their symptoms but might be associated with other health problems. For women with severe or disruptive symptoms, clinicians may play a useful role in helping women to thoughtfully weigh the risks and benefits of estrogen-based treatments for urogenital atrophy.

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Progress Report - 2010

In accordance with REF reporting requirements, a progress report is to be completed each year. Please use this template in the submission of your progress report. Click in the grey boxes to insert your text for each section and fill in your name and institution in the header above. Please note that incomplete or incorrect reports will be returned. Please submit your completed progress report as an MS Word '.doc' file to Damian L. Smalls at dsmalls@rheumatology.org no later than ***March 15, 2010.***

ACR REF/ASP Junior Career Development in Geriatric Medicine Award
This award provides support for academic rheumatologists who are interested in careers focused on gerontology and the geriatric aspects of rheumatology during their transition from fellowship to first faculty appointment.

Abstract
Please provide a copy of your abstract below.
Older adults (aged 65 years or older) individuals with chronic diseases such as rheumatoid arthritis (RA), chronic lymphatic leukemia, and chronic obstructive lung disease are often treated with long-term with glucocorticoids (GC), a class of medications with adverse effects on almost all organ systems of the body.

We propose that, due to age specific factors such as frailty, GC-attributable adverse outcomes are disproportionately greater among older persons. We will use RA as the disease model for testing our hypotheses. We will study the relationship between GC use and incidence of predefined adverse outcomes among 1750 older RA patients followed for a median of 5 years in an NIH funded multi-center, long-term prospective cohort. The comparison groups will be 4082 younger RA patients, 1874 older osteoarthritis patients, and 3408 younger osteoarthritis patients. A de novo randomized trial is impractical due to financial and time constraints and hence this study design.

Our specific aims are as follows: a) To examine the GC use patterns among the older patients with RA. b) To investigate the GC-related morbidity and mortality outcomes, such as infections, fractures, diabetes mellitus, and cardiovascular events and role of age-related frailty measures c) To identify disease, treatment, and patient-specific risk factors for GC-related adverse outcomes.

Our study will show that a) GC are used more often, at higher doses and for longer duration in the geriatric age group; b) the risk-benefit ratio of long-term GC treatment will be more unfavorable among the older patients and that b) it is possible to identify those old people who are at risk for adverse outcomes. This study will lead Dr Krishnan to a Beeson-K23 grant proposal for translating our findings into preventive strategies in geriatric patients regardless of the disease diagnosis.

I. Overview of Project Proposal - *(limit to 2 pages)*

Geriatric populations**,** arbitrarily defined as those of age 65 years or older**,** have disproportionate prevalence of chronic diseases such as rheumatoid arthritis (RA), polymyalgia rheumatica, giant cell arteritis, other systemic vasculitides, chronic lymphatic leukemia, and chronic obstructive lung disease. Long-term (defined as ≥2 years) treatment with glucocorticoids (GC) is an important and sometimes the sole therapy available for these conditions. Geriatric population is

at higher risk for GC induced toxicity as they utilize GC more frequently, at higher doses and for longer duration than those studied in clinical trials(*1*). Among older patients, especially women, the impact of comorbidities and frailty, can substantially increase risk for serious and sometimes fatal adverse outcomes from chronic or long term GC use.(*2*) The available literature on long-term GC toxicity either focuses on younger population (age between 18-65 years), shorter disease duration, or use age as a mere covariate. The scope of the problem in the older populations with their inherent frailty remains unclear. We have chosen RA as disease model to study our hypotheses. In RA, remissions are rare, events are relatively frequent, and the need for immunomodulatory treatment is often lifelong.

We propose to use the multicenter cohorts of the Arthritis Rheumatism and Aging Medical Information Systems (ARAMIS) a comprehensive data source of RA. This study involves supplementing existing data by additional assessment of health outcomes and hypothesis driven statistical analyses.

Our specific aims for this proposal are:

1. *To study patterns of GC use among older patients***:** We hypothesize that older patients with RA are more likely to have greater utilization of GC, especially long-term use compared to younger RA patients. We will examine the relationship between frailty and the decision to start GC and other disease modifying anti-rheumatic drugs. Our second hypothesis is that within the older age group, women receive more GC despite having disease characteristics similar to their male peers.

2. *To study GC-related morbidity and mortality outcomes among older patients:* A priori, we hypothesize that GC has disproportionately worse adversely effects on older patients with RA in terms of morbidity and mortality and that this could be, in part explained by differences in frailty. We hypothesize that women with RA is the demographic segment most likely to suffer adverse outcomes after adjusting for other confounders.

3. *To identify patient characteristics that will enable identification of older patients at high risk for long-term GC toxicity:* Our fundamental premise is that older patients have a different albeit overlapping set of toxicity-risk characteristics compared to younger patients. We hypothesize that we can identify such a set of risk factors specific for older adults on long-term GC treatment. Additionally we hypothesize that there is a dose-threshold effect for the toxicity of GC and that such a threshold becomes lower with increasing age.

II. Progress (*limit to 2 pages)*

The research status including the reporting of your progress during the award year addressing:

- ***your research*** specific to the accomplishments of project benchmarks, including timelines and objectives completed and less on data analysis
- ***your coursework, training, and lectures,*** in a narrative format
- ***Any and all*** submitted or ***published*** articles, other grants obtained or invited reviews

Project Year (check one)**:** ☒ **1** ☐ **2**

Overview

The past year has been eventful and exciting. We have made significant progress towards completion of the work proposed in Year 1. We are almost exactly on schedule. An abstract for the American Geriatrics Society meeting has been submitted as per the ASP requirements. From a career Development point of view Dr Krishnan has secured additional funding from the NIH as a co-investigator for the NIH-Patient-reported Outcome Measurement Information System (PROMIS ™ www.nihpromis.org) with 30% FTE salary support and access to the resources of the project. Seven manuscripts have been published in peer reviewed journals and 7 abstracts were presented for the American College of Rheumatology Annual Meeting at Philadelphia. All these were made possible because of Junior Career Development Award that has protected 80% of my time.

Research Progress

This has been summarized in the table in the next section titled *'Benchmarks of Success'*. Our project primarily involved augmentation of a large database and performing detailed analyses. In order for such analyses to be performed we need to create an analysis data set- an objective that has been the main focus of our efforts for Year 1. This work has been progressing very well with the exception of one unanticipated problem- delay in verification of status of those who were lost to follow up. The number of such subjects (~70) is relatively small and ongoing work will address this issue. We believe that many of these individuals are deceased. We expect to 'catch up' with the time line over the next few months, especially when the data from the National Death Index becomes available. The following table shows some of the data that are being readied for analyses.

A snapshot of the study subjects as of March 2010

	Number of subjects				Age % at the baseline					
	At baseline	Last Follow up	Person years	% men	%age >=65	%age >=75	%age >=85	% on prednisone ever during observation period	Mean (standard deviation) daily prednisone dose	Number of deaths confirmed so far
RA	5832	962	38,587	24.0%	29.8%	8.7%	5.1%	13%	8.5 (10)	1536
OA	3408	737	18,620	24.7%	55.2%	21.0%	24.1%	62%	6.7 (5.0)	400

Career development activities

I am a co-investigator in the recent successful cooperative U01 grant awarded to Dr James F Fries to develop a PROMIS™ instrument to measure extremes of physical function. My role (305 FTE effort) in this project will be to help develop the concept of Negative Health and Frailty. application in 2010. In addition I have received a Starter grant from PhrMA foundation to develop a Frailty Index. In combination with my work in this Geriatric Career Development grant, we expect this work with PROMIS™ and PhRMA grant to enable preliminary results that can lead to a Beeson K23 grant.

Publications

The following list of publications does not relate to the research plan presented in the JCD grant application; these are the results of the projects undertaken in previous years but published during the grant period. Some part of the papers were done (revisions, editing, etc.) in the time protected by this career development grant and hence these are included. It is expected that publications directly from this research proposal will start appearing in 2011.

1. Fries JF, Cella D, Rose M, Krishnan E, Bruce B. Progress in assessing physical function in arthritis: PROMIS short forms and computerized adaptive testing. J Rheumatol 2009;36(9):2061-6.
2. Fries JF, Krishnan E. What constitutes progress in assessing patient outcomes? J Clin Epidemiol 2009;62(8):779-80.
3. Fries JF, Krishnan E, Bruce B. Items, Instruments, Crosswalks, and PROMIS. J Rheumatol 2009;36(6):1093-5.
4. Krishnan E. Hyperuricemia and incident heart failure. Circ Heart Fail 2009;2(6):556-62.
5. Schmajuk G, Bush TM, Burkham J, Krishnan E, Chung L. Characterizing systemic sclerosis in Northern California: focus on Asian and Hispanic patients. Clin Exp Rheumatol 2009;27(3 Suppl 54):22-5.
6. Shah MA, Shah AM, Krishnan E. Poor outcomes after acute myocardial infarction in systemic lupus erythematosus. J Rheumatol 2009;36(3):570-5.
7. Wu EQ, Patel PA, Mody RR, Yu AP, Cahill KE, Tang J, et al. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? J Rheumatol 2009;36(5):1032-40.
8. Krishnan E. Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. Rheumatology (Oxford).[EPUB]
9. Bhole V, de Vera M, Rahman MM, Krishnan E, Choi H. Epidemiology of female gout: 52-Year follow-up of a prospective cohort. Arthritis Rheum.[EPUB]

III. Benchmarks of Success - *(limit to 1 page)*

Complete the '***Benchmarks of Success***' table included below, listing the specific aims from your original proposal and your progress toward each. Please also list expected publication dates or dates of new appointments.

PROJECT BENCHMARKS

The benchmarks (expected status of the project at various points in time) listed below will be used to evaluate progress. The milestones should reflect the specific aims of the proposal and be presented within the context of measurable outcomes.

GOALS *(Should be listed in order of priority)*	Metrics for Success *(Projected end points)*	Expected completion
Study initiation	IRB approval Outcome verification algorithm testing (Originally expected to be completed in Sep 1,2009)	Completed Completed
Data Audit and outcome validation –Step 1	Medical records of all individuals with outcomes of interest to be obtained (Originally expected to be completed in Jan 1,2010)	Nearly complete(90%). Some additional record collection pending on lost-to follow up subjects .
Data Audit and outcome validation –Step 2	Medical record review by Dr Krishnan (Originally expected to be completed in April,2010)	Nearly complete- Held back by record collection in Step 1
Data Audit and outcome validation –Step 3	Death information collation (Originally expected to be completed in August,2010)	National Death Index data collation pending- On schedule
Initiate data analysis	Creation of analysis data set (Originally expected to be completed in Oct,2010)	On schedule
Career development grant application	(Originally expected to be completed in November, 2010)	On schedule
Completion of data analyses	Abstracts/manuscripts	On schedule

Project Discussion *(limit to 1 page)*
Complete the ***project discussion area*** explaining where revisions to the original research proposal or training plan were made and your explanation for the changes
No revisions to the research proposal and training grant have been made

IV. Distribution of Time - *(limit to 1 page)*

Complete the table below and explain how much of your ***time*** was devoted to clinical duties; research; any and all educational activities your were involved in and how your protected time is helping accomplish your goals

ACTIVITY	**% Effort**	**Explanation, if applicable**
Clinical	20	
Research	80	
REF funded Project	40	
Administrative		
Teaching		
Other*		**Requires explanation*
TOTAL	100 *(must equal 100%)*	

Narrative:

I have 2 half day clinics where I precept residents and rheumatology fellows. In addition I performed 2 weeks of inpatient Rheumatology Consultation services last year. The rest of the time has been spent entirely on research projects including that funded by the REF

V. Budget Update - *(limit to 1 page)*

Give an ***explicit Budget*** update indicating how funds are being allocated and explaining any variation from the originally approved budget (i.e. expected unobligated balance as of your last progress report)

Working as per the original budget

VI. Curriculum Vitae *(limit to 4 pages)*

Please attach or insert below a copy of your most recent ***curriculum vitae*** or ***biosketch***

Attached biosketch

VII. Experience Evaluation *(limit to 1 page)*

Provide feedback regarding your experience as it relates to this award, including any promotions or other opportunities that arose as a result of this project

This award has had a tremendously positive impact on my research career. This has also enabled gathering of preliminary data for other sources of funding.

VIII. Future Plans and Goals - *(limit to 1 page)*

Future plans and goals for next year of the award (if applicable) or narrative of future career plans

My next step is preparation of K23 Beeson grant application this Fall. I also will be working on several analyses set forth in the research proposal that will lead to abstracts and manuscripts starting Spring 2011.

IX. Mentor Statement *(limit to 1 page)*

Please provide an updated statement from your mentor or mentoring team, including their thoughts on your progress so far as well as future plans

Eswar is making excellent progress towards the research goals set out in his research grant. He has been meeting with me and other mentors in regular time intervals, as we had planned. This has enabled us to mentor him through various career development activities. Eswar is a talented young physician with all the capabilities necessary to become a successful investigator in disability and its prevention. His superb personal qualities are matched only by his intense ambition and a desire to make a difference. He is also a team player who is capable of bringing together people with different backgrounds and research interests. In research discussions, he expresses his views with clarity and consideration for other points of view. He has worked hard over the past months to make sure that the timelines are met and benchmarks reached. Currently we are waiting for the outcome assessment to be completed so that analysis datasets can be prepared.

Over the next few months we expect to generate reports of the research plan in terms of abstracts for conferences and manuscripts for publications. We have also decided to apply for the Beeson Grant that is aimed at individuals like Eswar where I will serve as the main mentor. The preliminary results from this grant and from the PROMIS™ program where he is a key person will strengthen his Beeson application.

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Epidemiology of Gout in Women

Fifty-two–Year Followup of a Prospective Cohort

Vidula Bhole, Mary de Vera, M. Mushfiqur Rahman, Eswar Krishnan, and Hyon Choi

Objective. **Despite the recent doubling of the incidence of gout among women and its substantial prevalence particularly in the aging female population, the risk factors for gout among women remain unknown. We undertook this study to evaluate purported risk factors for incident gout among women and to compare them with those among men.**

Methods. **Using prospective data from the Framingham Heart Study, we examined over a 52-year period (1950–2002) the relationship between purported risk factors and the incidence of gout in 2,476 women and 1,951 men.**

Results. **We documented 304 incident cases of gout, 104 of them among women. The incidence rates of gout for women per 1,000 person-years according to serum uric acid levels of <5.0, 5.0–5.9, 6.0–6.9, 7.0–7.9, and ≥8.0 mg/dl were 0.8, 2.5, 4.2, 13.1, and 27.3, respectively (P for trend < 0.0001). The magnitude of this association was lower than that among men (P for interaction = 0.0002). Multivariate relative risks conferred by increasing age (per 5 years), obesity (body mass index ≥30 kg/m^2), alcohol intake (≥7 ounces of pure alcohol/week), hypertension, and diuretic use were 1.24, 2.74, 3.10, 1.82, and 2.39, respectively (all P < 0.05), for women.**

Conclusion. **These prospective data with long-term followup provide evidence that higher levels of serum uric acid increase the risk of gout in a graded manner among women, but the rate of increase is lower than that among men. Increasing age, obesity, alcohol consumption, hypertension, and diuretic use were associated with the risk of incident gout among women.**

Gout, a common and excruciatingly painful inflammatory arthritis (1), has historically been considered a male disease, and most gout research has focused on men (2–9). However, growing evidence suggests a substantial disease burden of gout among older women, whose representation in the general population has grown with increasing longevity. The prevalence of self-reported physician-diagnosed gout based on the Third National Health and Nutrition Examination Survey (NHANES-III) was 3.5% in women ages 60–69 years, 4.6% in women ages 70–79 years, and 5.6% in women ages ≥80 years (10). The incidence of gout has doubled among women over the past 20 years, according to the Rochester Epidemiology project study (11). Despite this substantial and increasing disease burden, the risk factors for gout among women remain unknown.

Given the significant role of estrogen in serum uric acid levels as well as the substantial sex difference in the incidence of gout and perhaps in uric acid metabolism (12), extrapolation of data on the risk factors for gout from men to women should be done with caution. The serum uric acid level, which is the most prominent predictor and precursor of gout, has been prospectively studied in relation to the risk of incident gout among men (2), but no corresponding data among women are

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Vidula Bhole, MD, MHSc, Mary de Vera, MSc, M. Mushfiqur Rahman, MSc, Eswar Krishnan, MD, MPH, Hyon Choi, MD, DrPH: Boston University School of Medicine, Boston, Massachusetts.

Dr. Krishnan has received consulting fees, speaking fees, and/or honoraria from Savient Pharmaceuticals and UCB Pharma (less than $10,000 each) and from Takeda Pharmaceuticals (more than $10,000); he has served as a paid consultant to Cowan and Associates. Dr. Choi has received honoraria for service on the Savient Pharmaceuticals advisory board (less than $10,000) and on the TAP Pharmaceuticals advisory board (more than $10,000).

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available. The widely cited Normative Aging Study, exclusively based on men (2), showed annual incidence rates of gout per 1,000 person-years of 0.8, 0.9, 4.1, 8.4, and 49.0 for serum uric acid levels of <6.0, 6.0–6.9, 7.0–7.9, 8.0–8.9, and ≥9.0 mg/dl, respectively. It remains unknown whether these levels of serum uric acid pose the same levels of risk of gout among women.

Previous case series studies of gout in women (12–15), which have been the exclusive source for teaching and textbooks, have demonstrated higher mean uric acid levels among women with gout than among men with gout. For example, a previous study found that the mean serum uric acid levels were 9.3 mg/dl in female patients and 8.4 mg/dl in male patients ($P < 0.03$), and this difference was not explained by diuretic use, hypertension, or renal insufficiency (12). While this difference appears substantial, particularly given the lower baseline serum uric acid level among women than among men, no prospective data are available on this topic. To fill the gap in knowledge of the risk factors for gout in women, we investigated the associations between serum uric acid levels, other purported risk factors, and the risk of incident gout specifically among women in the Framingham Heart Study cohort and compared them with those among men.

PATIENTS AND METHODS

Study population. We conducted a cohort study using the prospectively collected data in the Framingham Heart Study original cohort, using the data set obtained from the National Heart, Lung, and Blood Institute (NHLBI). The Framingham Heart Study is an ongoing longitudinal study of 5,209 men and women from the town of Framingham, MA, ages 29–62 years at the time of recruitment in 1948. Subjects have been followed up biennially, and at each study examination data from a detailed medical history, physical examination, and laboratory tests were collected. Additional details of the Framingham Heart Study cohort are described elsewhere (16–18). We limited our analysis to 2,476 women and 1,951 men for whom we had complete followup data and who were free of gout at baseline. Ethics approval for this study was obtained from the University of British Columbia Behavioural Research Ethics Board.

Assessment of exposure variables. We evaluated serum uric acid levels and purported risk factors for gout that were obtained in the Framingham Heart Study, including age, education, body mass index (BMI), alcohol consumption, hypertension, medication use (diuretics, hormone replacement therapy), clinical laboratory measures (blood glucose level, blood cholesterol level), and menopause status. These factors are closely consistent with those included in the widely cited Normative Aging Study of gout among men (2). Serum creatinine levels were first measured at the 14th examination in the Framingham Heart Study and thus were not included in our primary analysis.

Serum uric acid levels were measured in the Framingham Heart Study for the first 4 examinations and the 13th examination with an autoanalyzer using a phosphotungstic acid reagent (19). Age was ascertained by self-report at the baseline Framingham Heart Study examination, and then subsequent age was calculated from the time between examinations and the baseline age. Information about education was obtained at the baseline examination. Height and weight were measured at each examination, and BMI was calculated as the weight in kilograms divided by the square of the height in meters. The information on medication use and alcohol consumption was ascertained by self-report (20). Systolic and diastolic blood pressures were measured twice in the left arm, with the patient in a sitting position, using a mercury-column sphygmomanometer positioned near eye level. The average of the 2 readings was used for each blood pressure variable. A person was classified as hypertensive if he or she had a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or was receiving antihypertensive drugs (21). Random blood glucose levels were determined using Nelson's method (22). Cholesterol levels were determined according to the Abel-Kendall method (23). Menopause was defined as the absence of menstruation for ≥1 year (24).

Ascertainment of incident cases of gout. Our end point was the first recorded event of clinically diagnosed gout. At the Framingham Heart Study examination, a clinical diagnostic impression of gouty arthritis was noted if the subject had experienced acute joint pain, accompanied by swelling and heat, lasting from a few days to 2 weeks, and followed by complete remission of symptoms (25). Evidence of gout was further confirmed when an attack of arthritis promptly responded to therapeutic doses of colchicine or other antigout medications. Since study participants were rarely seen during an acute attack of arthritis, aspiration of joint fluids for examination of uric acid crystals, considered a diagnostic gold standard, was not performed (25). Subjects with a diagnosis of gout at the baseline examination were defined as prevalent cases; subjects who were free of gout at baseline and received a diagnosis of gout at any subsequent Framingham Heart Study examination were defined as incident gout cases.

Statistical analysis. We calculated the incidence rates of gout according to serum uric acid level categories in the Framingham Heart Study. We computed person-time of followup from our study baseline (1950) to the clinical diagnosis of gout at a subsequent examination, day of the last attended examination, or end of the study period (26th biennial examination, conducted in 2000–2002), whichever came first. Individuals who died or in whom gout was diagnosed at any Framingham Heart Study examination were excluded from subsequent followup.

We used time-dependent Cox proportional hazards modeling to estimate the relative risk (RR) of incident gout associated with the most recent prior serum uric acid levels during the cohort followup. Our primary RRs for the association with serum uric acid levels were unadjusted, because serum uric acid is the direct causal intermediate for other examined risk factors to contribute to the risk of gout (e.g., alcohol causes hyperuricemia, which in turn leads to an increased risk of gout). We categorized serum uric acid levels

into the categories of <5.0, 5.0–5.9, 6.0–6.9, 7.0–7.9, and ≥8.0 mg/dl to appropriately reflect their range among women. We used ≥8.0 mg/dl of uric acid as the top category, since only 7 women in this cohort had uric acid levels ≥9.0 mg/dl at least once over the entire followup period. We assessed the trend, using the median values of uric acid level in each category, to minimize the influence of outliers.

Multivariate models were used to evaluate the following purported risk factors in a time-dependent manner: age (continuous, per 5 years), education level (below grade 12, grade 12 completed, above grade 12), BMI (<25 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2), alcohol consumption (abstinent/light [0–1 ounce, 29.57 ml, per week], moderate [2–6 ounces per week], and heavy [≥7 ounces per week] [20]), hypertension (yes or no), use of diuretics (yes or no), blood glucose level (continuous, per 10 mg/dl), blood cholesterol level (continuous, per 10 mg/dl), menopausal status (yes or no), and hormone replacement therapy (yes or no). The last 2 categories of BMI employed correspond to overweight and obesity according to the World Health Organization definition (26). The alcohol intake in ounces per week was obtained by multiplying the average amounts of alcohol in beer, wine, and spirits (mixed drinks) times the amount consumed. Total alcohol intake was categorized as abstinent/light, moderate, and heavy, as explained above (20). The same categories were used to classify intakes of beer and spirits, but the top 2 categories were collapsed for wine intake, because no woman with heavy wine intake developed gout in this cohort. We explored potential interaction by sex by testing the significance of interaction terms added to our final multivariate models. For all RRs, we calculated 95% confidence intervals (95% CIs). All *P* values are 2-sided. All statistical analyses were conducted using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

The baseline characteristics of the Framingham Heart Study cohort in this study, according to sex, are shown in Table 1. There were 2,476 women, comprising 56% of the cohort. The mean age at baseline was 47 years for women and 46 years for men. The mean baseline serum uric acid level was 4.0 mg/dl for women and 5.1 mg/dl for men.

Over a 28-year median followup period, we identified 104 incident cases of gout in women and 200 in men. The incidence of gout was 1.4 per 1,000 person-years in women and 4.0 per 1,000 person-years in men. The incidence of gout increased with increasing levels of serum uric acid among women, but the rate of increase was lower than that among men (*P* for interaction = 0.0002) (Figure 1 and Table 2). Specifically, the incidence rates of gout for women per 1,000 person-years according to serum uric acid levels of <5.0, 5.0–5.9, 6.0–6.9, 7.0–7.9, and ≥8.0 mg/dl were 0.8, 2.5, 4.2, 13.1, and 27.3, respectively (*P* for trend < 0.0001) (Table 2).

Table 1. Baseline characteristics of the subjects according to sex*

Characteristic	Women (n = 2,476)	Men (n = 1,951)
Age, mean ± SD years	47 ± 9	46 ± 9
Education level		
Below grade 12	41	45
Grade 12 completed	31	27
Above grade 12	28	28
BMI, kg/m^2		
<25	54	40
25–29.9	32	49
≥30	14	11
Alcohol consumption		
Abstinent/light	70	43
Moderate	24	32
Heavy	6	25
Hypertension	14.9	10.6
Use of diuretics†	5.6	2.7
Serum uric acid, mean ± SD mg/dl	4.0 ± 1.0	5.1 ± 1.1
Blood glucose level, mean ± SD mg/dl	82.2 ± 19.6	82.7 ± 23.6
Blood cholesterol level, mean ± SD mg/dl	229.0 ± 46.5	227.1 ± 42.7
Postmenopausal	50.4	–

* Except where indicated otherwise, values are the percentage of subjects. BMI = body mass index.
† First assessed at Framingham Heart Study examination 7 (1962).

The RRs for gout among women according to the corresponding serum uric acid categories were 1.00, 3.29, 5.49, 22.09, and 45.75, respectively (Table 2). When we moved our cohort followup baseline to the 13th examination (n = 1,465 women, ages ≥53 years, and 99.6% postmenopausal), the corresponding incidence rates were 1.3, 2.6, 3.7, 13.5, and 28.5, respectively (*P* for trend < 0.0001), and the corresponding RRs for gout were 1.00, 2.38, 3.36, 17.75, and 34.98, respectively.

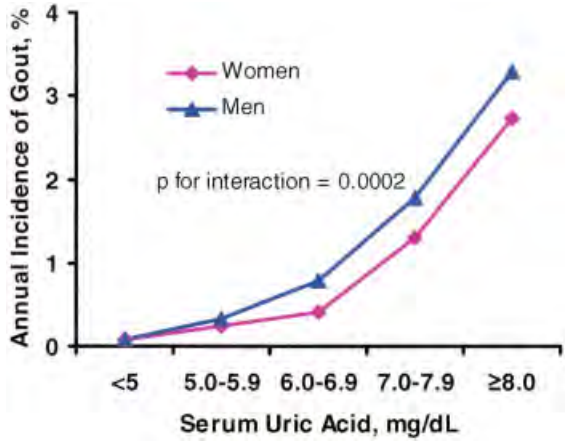

Figure 1. Relationship between serum uric acid levels and annual incidence of gout.

Table 2. Incidence rate and multivariate RRs for development of gout according to updated uric acid level (categorical and continuous for women and men)*

	Uric acid level, categorical, mg/dl					Uric acid level, continuous, mg/dl
	<5.0	5.0–5.9	6.0–6.9	7.0–7.9	≥8.0	
Women						
No. of gout cases	46	25	14	12	7	–
Person-years of followup	58,579	10,108	3,303	918	256	–
Incidence/1,000 person-years	0.8	2.5	4.2	13.1	27.3	1.4†
Univariate model RR (95% CI)	Referent	3.29 (1.98–5.45)	5.49 (2.90–10.42)	22.09 (10.98–44.43)	45.75 (19.17–109.21)	2.01 (1.79–2.26)
Multivariate model RR (95% CI)‡	Referent	2.42 (1.46–4.02)	3.41 (1.76–6.63)	12.18 (5.87–25.27)	22.53 (9.12–55.64)	1.84 (1.60–2.11)
Men						
No. of gout cases	17	56	64	42	21	–
Person-years of followup	21,979	16,549	8,046	2,359	638	–
Incidence/1,000 person-years	0.8	3.4	8.0	17.8	32.9	4.0†
Univariate model RR (95% CI)	Referent	4.54 (2.64–7.82)	12.05 (7.01–20.69)	31.01 (17.24–55.76)	61.27 (31.25–120.12)	2.66 (2.36–2.99)
Multivariate model RR (95% CI)‡	Referent	4.09 (2.37–7.07)	9.53 (5.49–16.55)	22.36 (12.31–40.61)	47.90 (24.02–95.53)	2.56 (2.25–2.91)

* RR = relative risk; 95% CI = 95% confidence interval.
† Overall incidence rate.
‡ Adjusted for age (continuous, per 5 years), education level (below grade 12, grade 12 completed, above grade 12), body mass index (<25 kg/m^2, 25–29.9 kg/m^2, ≥30 kg/m^2), alcohol consumption (abstinent/light [0–1 ounce, 29.57 ml, per week], moderate [2–6 ounces per week], heavy [≥7 ounces per week]), hypertension (yes or no), use of diuretics (yes or no), blood glucose level (continuous, per 10 mg/dl), blood cholesterol level (continuous, per 10 mg/dl), and menopausal status (yes or no).

Among the purported risk factors for gout, increasing age, obesity, alcohol consumption, diuretic use, and hypertension (all $P < 0.05$) were independently associated with the risk of incident gout in women (Table 3). The magnitudes of associations with these factors did not differ significantly from those among men, except for a stronger age effect among women than among men (P for interaction = 0.02) (Table 3). The age-adjusted RR of gout conferred by menopause was 4.18 (95% CI 0.55–31.86), and the multivariate RR was 3.54 (95% CI 0.46–27.15). When we limited our analysis to a subgroup of women who were postmenopausal at baseline (n = 1,249), the multivariate RR conferred by the use of hormone replacement therapy was 0.24 (95% CI 0.03–1.79). Furthermore, when we evaluated the potential effect of adding creatinine in our model using the creatinine values obtained at the 14th examination and later, the multivariate RRs associated with the identified factors and their significance levels did not change materially.

We also evaluated the association between individual types of alcoholic beverages and the risk of incident gout. In women, the multivariate RRs of heavy consumption were 7.10 (95% CI 1.70–29.62) for beer and 2.66 (95% CI 1.24–5.72) for spirits, whereas the corresponding RRs among men were 2.00 (95% CI 1.26–3.19) and 1.82 (95% CI 1.26–2.63). The multivariate RR of moderate or heavy wine intake was 1.46 (95% CI 0.80–2.65) among women and 1.24 (95% CI 0.84–1.84) among men.

DISCUSSION

In this prospective cohort study, based on 52 years of followup, we found that higher levels of serum uric acid increase the risk of gout among women in a graded manner. The risk of gout among women with a serum uric acid level ≥8 mg/dl was 46 times higher than that among women with a serum uric acid level <5 mg/dl. However, the magnitude of this association among women was significantly lower than that among men, indicating that at a given level of serum uric acid >5 mg/dl, women have a significantly lower risk of developing gout than men. Furthermore, we found that increasing age, obesity, intake of beer and spirits, diuretic use, and hypertension were associated with the risk of incident gout in women. The magnitude of associations with these factors among women did not

Table 3. Multivariate RRs of risk factors for incident gout according to sex*

	Women			Men		
	No. of cases	Age-adjusted RR (95% CI)†	Multivariate RR (95% CI)‡	No. of Cases	Age-adjusted RR (95% CI)†	Multivariate RR (95% CI)‡
Age (per 5 years)	104	1.32 (1.16–1.49)†	1.24 (1.08–1.43)	200	1.14 (1.04–1.24)†	1.14 (1.03–1.26)
Education level						
Below grade 12	47	Referent	Referent	84	Referent	Referent
Grade 12 completed	37	0.97 (0.62–1.51)	1.05 (0.67–1.66)	49	0.85 (0.59–1.22)	0.86 (0.59–1.24)
Above grade 12	20	0.51 (0.30–0.86)	0.58 (0.34–1.02)	67	1.08 (0.78–1.50)	1.12 (0.81–1.56)
BMI, kg/m^2						
<25	29	Referent	Referent	39	Referent	Referent
25–29.9	38	1.67 (1.03–2.72)	1.44 (0.88–2.37)	109	1.87 (1.29–2.69)	1.76 (1.22–2.54)
≥30	37	3.52 (2.16–5.72)	2.74 (1.65–4.58)	52	3.50 (2.30–5.32)	2.90 (1.89–4.44)
Alcohol consumption						
Abstinent/light	67	Referent	Referent	54	Referent	Referent
Moderate	23	1.10 (0.68–1.78)	1.30 (0.80–2.12)	61	1.45 (0.99–2.09)	1.44 (0.99–2.08)
Heavy	14	2.06 (1.14–3.71)	3.10 (1.69–5.68)	85	2.34 (1.66–3.30)	2.21 (1.56–3.14)
Hypertension						
No	19	Referent	Referent	62	Referent	Referent
Yes	85	2.91 (1.74–4.88)	1.82 (1.06–3.14)	138	2.39 (1.73–3.29)	1.59 (1.12–2.24)
Diuretics						
No	55	Referent	Referent	143	Referent	Referent
Yes	49	3.23 (2.13–4.91)	2.39 (1.53–3.74)	57	4.31 (3.06–6.08)	3.41 (2.38–4.89)
Glucose (per 10 mg/dl)	104	1.05 (1.00–1.10)	1.02 (0.98–1.07)	200	1.01 (0.97–1.05)	0.99 (0.95–1.03)
Cholesterol (per 10 mg/dl)	104	1.00 (0.96–1.05)	0.99 (0.95–1.04)	200	1.03 (0.99–1.07)	1.03 (0.99–1.06)

* 95% CI = 95% confidence interval.
† Adjusted for age (continuous); the relative risk (RR) for age is the univariate RR only.
‡ Adjusted for age (continuous, per 5 years), education level (below grade 12, grade 12 completed, above grade 12), body mass index (BMI) (<25 kg/m^2, 25–29.9 kg/m^2, ≥30 kg/m^2), alcohol consumption (abstinent/light [0–1 ounce, 29.57 ml, per week], moderate [2–6 ounces per week], heavy [≥7 ounces per week]), hypertension (yes or no), use of diuretics (yes or no), blood glucose level (continuous, per 10 mg/dl), blood cholesterol level (continuous, per 10 mg/dl), and menopausal status (yes or no).

differ from that among men, except for a stronger age effect among women than among men (P for interaction = 0.02). These associations were mutually independent of these and other potential risk factors for incident gout.

To our knowledge, our findings provide the first prospective, quantitative data on the relationship between serum uric acid levels and the risk of incident gout among women. The overall smaller magnitude of association, compared with that for men, was consistent with the aforementioned study that found a significantly higher serum uric acid level among female gout patients than among male gout patients (12). The possibility of differential ascertainment of gout between sexes is unlikely, since the sex ratio of the incidence of gout in this cohort (2.8 for men:women) was similar to that in previous studies (2.7 for the UK General Practice Research Database study [27] and 3.3 for the Rochester Epidemiology Project [11]). Similarly, the consistency between the results from the entire cohort followup of all women and those from the analysis limited to the 13th examination or later (99.6% of women were postmenopausal) does not support the presence of systematic differential misclassification of serum uric acid levels associated with aging or the menopausal transition among women. If confirmed by future studies, these findings would suggest additional reasons for the lower background incidence of gout among women that go beyond their lower baseline serum uric acid levels.

We found that obesity was associated with the risk of incident gout among women, as was the case among men in this cohort and in previous studies (28–32). Hyperuricemia has been associated with obesity via both increased production and decreased renal excretion of uric acid (33,34). Increased insulin levels associated with obesity likely play a role in the link between obesity and the increased risk of gout, since higher insulin levels are known to reduce renal excretion of urate (35–38). For example, exogenous insulin can reduce the renal excretion of urate in both healthy and hypertensive subjects (30,37,38). Specifically among women, the Coronary Artery Risk Development in Young Adults study showed that white women with a BMI >23.5 kg/m^2 have a 5.7-fold increased likelihood of hyperuricemia compared with white women with a BMI <20.8 kg/m^2 (32). In the NHANES-III, a marked in-

crease in the prevalence of the metabolic syndrome and obesity was observed at higher serum uric acid levels (39). Other factors not related to uric acid, including chronic joint trauma due to excess body weight, have also been speculated upon as potential explanations for the link between obesity and gout (34,40).

The association between hypertension and gout among women in this study is consistent with previously reported associations between hypertension and incident gout in men (2,4,28). Previous retrospective case series of gout in women showed that a higher proportion of women than men with gout had hypertension and were treated with diuretics, suggesting that these risk factors may be more important among women (12,13,41). Our prospective data also showed that these factors are more common among women with gout than among men with gout (diuretic use, 47% versus 29%; hypertension, 82% versus 69%), suggesting that these risk factors may lead to a larger population-attributable risk of the development of gout among women. Renal urate excretion was found to be inappropriately low relative to glomerular filtration rates in patients with essential hypertension (42,43). Reduced renal blood flow with increased renal and systemic vascular resistance may also contribute to increasing serum uric acid levels (44). Finally, diuretics also play an important role in the pathogenesis of gout through the combined effect of increased tubular reabsorption of uric acid and volume depletion (29,45,46). The results from our study support a significant role of diuretics in the risk of gout among women, independent of the presence of hypertension.

We found that overall alcohol intake was associated with the risk of gout in women. Among individual types of alcoholic beverages, beer and spirits were significantly associated with the risk among women. These findings were similar among men in this cohort as well as in the Health Professionals Follow-up study (5). Furthermore, our results were consistent with the associations with serum uric acid levels among US women in the NHANES-III (47). Interestingly, the same NHANES study also showed that the increase in serum uric acid levels associated with beer or spirit intake tended to be greater among women than among men (47), which was the case in the current study with incident gout as the outcome. Taken together, these data suggest potential effect modification by sex—that is, women may be more susceptible to these alcoholic beverages in terms of risk of hyperuricemia or gout—and call for confirmation by future studies.

A number of mechanisms have been implicated in the pathogenesis of alcohol-induced hyperuricemia, including both decreased urate excretion (48–51) and increased production (52,53), although the magnitude of association appeared larger among women (47). Ethanol administration has been shown to increase uric acid production by net ATP degradation to AMP (52,53). Additionally, decreased urinary excretion associated with dehydration and metabolic acidosis (34,54) may contribute to hyperuricemia associated with ethanol ingestion. Our data provide support for a substantial role of alcohol intake in the risk of incident gout among women, independent of the presence of other risk factors.

The strengths and limitations of our study deserve comment. This study was performed using community-based prospective data from the Framingham Heart Study, and thus findings are likely to be generalizable to women and men in the US. Potential recall bias was avoided in this study, because the exposure assessment of purported risk factors was done before the diagnosis of gout. The baseline mean age of 47 years for women and the infrequent occurrence of gout in the premenopausal period limited our investigation of the potential effect of menopause on the risk of gout. Nevertheless, our point estimates, although nonsignificant, appeared to be consistent with the notion of an increased risk of gout in postmenopausal women and a decreased risk associated with hormone replacement therapy (55,56).

The definition of gout was based on a clinical diagnosis of gout by examining physicians and did not require observation of urate crystals in joint fluid, as was the case in other large epidemiologic studies of gout (2–9,25,57,58), including the widely cited Normative Aging Study of men (2). However, it is unlikely that potential misclassification of the diagnosis would explain the strong associations observed in this population study. It remains conceivable that the results may be even more striking with more specific case definitions of gout, as was the case in our prospective epidemiologic study of gout for suspected associated factors (3,5). Nonetheless, confirming these results using such specific case definitions of gout would be valuable. The unavailability of creatinine data between the study baseline and the 13th examination precluded adjustment for reduced renal function in our primary analysis. However, our analysis using the creatinine values obtained at the 14th examination and later suggests that this factor did not materially confound the observed associations. Finally, our study was observational; thus, we cannot rule out the

possibility that unmeasured factors might contribute to the observed associations.

In this prospective study over 50 years of followup, higher levels of serum uric acid increased the risk of gout in a graded manner among women, but the rate of increase was lower than that among men. Increasing age, obesity, hypertension, alcohol consumption (beer and spirits), and diuretic use are also associated with the risk of incident gout among women.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Choi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Alanine Aminotransferase Decreases with Age: The Rancho Bernardo Study

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Abstract

Background: Serum alanine aminotransferase (ALT) is a marker of liver injury. The 2005 American Gastroenterology Association Future Trends Committee report states that serum ALT levels remain constant with age. This study examines the association between serum ALT and age in a community-dwelling cohort in the United States.

Methods: A cross-sectional study of 2,364 (54% female) participants aged 30–93 years from the Rancho Bernardo Study cohort who attended a research clinic visit in 1984–87. Demographic, metabolic co-variates, ALT, bilirubin, gamma glutamyl transferase (GGT), albumin, and adiposity signaling biomarkers (leptin, IL-6, adiponectin, ghrelin) were measured. Participants were divided into four-groups based upon age quartile, and multivariable-adjusted least squares of means (LSM) were examined (p for trend <0.05).

Results: ALT decreased with increasing age, with mean ALT levels (IU/L) of 23, 21, 20, and 17 for those between quartile ages 30–62, 63–71, 72–77, and 78–93 years ($p<0.0001$). Trends of decreasing LSM ALT with age and the decreasing prevalence of categorically defined elevated serum ALT with age remained robust after adjusting for sex, alcohol use, metabolic syndrome components, and biomarkers of adiposity (p-value <0.0001), and was not materially changed after adjusting for bilirubin, GGT, and albumin.

Conclusions: ALT levels decrease with age in both men and women independent of metabolic syndrome components, adiposity signaling biomarkers, and other commonly used liver function tests. Further studies are needed to understand the mechanisms responsible for a decline in ALT with age, and to establish the optimal cut-point of normal ALT in the elderly.

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Introduction

Serum alanine aminotransferase (ALT) level is frequently used as a surrogate marker for hepatocyte injury. Normal ranges vary according to the commercial kit used, but have historically been set at around 40 IU/L. This value was based on population studies conducted before the availability of blood tests for hepatitis C and before the widespread recognition of nonalcoholic fatty liver disease (NAFLD). Recently, some have suggested that not only should the upper limits of normal for ALT be lowered, but that limits should differ based on sex as well [1], [2], [3]. Since then, many other factors have been implicated in differing ALT levels. Most of these factors are features related to the metabolic syndrome, including body mass index, waist-hip ratio, dyslipidemia, and glucose intolerance [4–13]. The relationship between ALT and age, however, remains somewhat ambiguous.

The 2005 American Gastroenterology Association Future Trends Committee report regarding the effects of aging on future trends in gastroenterology states that there is no effect of age on conventional liver function tests, including serum ALT [14]. A study of serum ALT concentrations in healthy Iranian blood donors also concluded that ALT did not correlate with age [15]. However, a few studies published since that time have reported that the prevalence of elevated (abnormal) ALT decreases with age [4], [6], [7], [8], [10], [11]. Some have found this association to be true in men, but not in women [3], [5], [16]. Most of these studies were performed using retrospective chart reviews of patients who had laboratory tests, including serum ALT, for medical reasons, in self-selected populations (such as blood donors), or in Asian populations, whose liver function may differ compared to Western populations. A recent study of community dwelling elderly men (over age 70) suggested that ALT may be a novel biomarker of aging, with levels decreasing with rising age, and low levels associating with frailty and reduced survival [17].

The largest United States population-based study of ALT levels is from the National Health and Nutrition Examination Survey

(NHANES). In both the 1988–1994 [6] (elevated ALT defined as >40 U/L in men and >31 U/L in women) and the 1999–2002 [7] (elevated ALT defined as >43 U/L in both men and women) cross-sectional reports, older age was associated with a decreased prevalence of elevated ALT levels, but the conventionally higher ALT cutoff values were used in these analyses. It is therefore uncertain whether age was associated with serum ALT concentrations *within the normal range*, and whether the associations between age and the prevalence of categorically defined elevated ALT would have remained had lower ALT thresholds been applied. The latter question was answered by Ruhl and Everhart [4], who examined data from the NHANES 1988–1994 survey using both the traditionally higher ALT cutoff threshold (>43 IU/L) as well as lower thresholds (≥30 IU/L for men and ≥19 IU/L for women). They found that in univariate analysis, younger age was associated with abnormally elevated ALT activity.

Thus, there seems to be an association between younger age and increased prevalence of elevated ALT. However, it is still unclear whether serum ALT levels within the normal range decline with age, and if so, whether this decline is related to changes in body mass, central adiposity, or other plausible covariates. Additionally, it is unclear whether the threshold of extreme values of ALT (e.g. 95th percentile of ALT range for a particular age group) also varies with age.

To the best of our knowledge, this paper is the first to examine the association between serum ALT level as a continuous variable and age, including ALT levels that are within normal range as well as those that are elevated, in a well-characterized [12], [18], [19], healthy, community-dwelling cohort of older men and women residing in Southern California. We also determined whether any age-related changes in serum ALT were explained by metabolic syndrome components, adiposity-related biomarkers including leptin, adiponectin, ghrelin and interleukin-6 (IL-6), or other markers of hepatic function (bilirubin, albumin, gamma glutamyl transferase [GGT]).

Methods

Study Cohort and Setting

This cross-sectional study is based on data from participants of the Rancho Bernardo Study (RBS). The RBS cohort was established in 1972, when 82% of residents of a geographically defined suburban Southern California community were recruited to a study of heart disease risk factors. The details of the cohort, selection criteria, and purpose of the RBS have been published elsewhere [18], [19]. The current study cohort was derived from 2480 residents who attended the research clinic between 1984 and 1987, approximately 80% of the surviving, local, community-dwelling adults. Of these, 2364 participants were aged 30 years or older and had available ALT data and were included in the current analysis [12]. The RBS cohort is almost entirely Caucasian of European ancestry, most with at least some college education, and largely white-collar workers. All participants gave written informed consent; the study was approved by the institutional review board of the University of California, San Diego.

Clinical and Laboratory Assessment

A trained interviewer gathered information regarding medical history and current medication use. Weight was obtained with participants wearing light clothing and no shoes. Height, waist and hip circumference, and systolic blood pressure were obtained in clinic by trained investigators. Blood pressure was obtained from two morning readings with the resting participant in the seated position, using a regularly calibrated mercury sphygmomanometer, according to the Hypertension Detection and Follow-up Program protocol [20]. Alcohol use, in terms of amount, type, and frequency, was self-reported. One alcoholic drink was defined as 10 g of alcohol. Alcohol use was indirectly validated by showing a similar quantitative response to a nutritionist interviewer who obtained alcohol intake as part of a separate food-frequency questionnaire. Fasting venous blood was analyzed in a clinical laboratory. ALT, bilirubin, GGT and albumin were measured using a single assay by spectrophotometry on fresh samples. Fasting serum samples were obtained during the research visit; they were measured in all participants using the same assay and under identical testing conditions at a UCSD clinical laboratory. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using enzymatic methods in a Lipid Research Clinic-certified laboratory. Plasma glucose was measured in a hospital laboratory using the glucose-oxidase method. Diabetes was defined as a fasting glucose of ≥126 mg/dL (≥7 mmol/L) or treatment with either insulin or an oral hypoglycemic medication. Adipocytokine studies were performed on samples stored at −70°C. IL6 was measured using an enzyme-linked immunosorption assay (Quantikine HS, R&D Systems, Minneapolis, MN) on previously unthawed samples in 2000. Adiponectin, ghrelin, and leptin were measured in 2004 (samples thawed for a second time) by radioimmunoassay (Linco Diagnostics Laboratory, St. Louis, MO) as previously reported [21], [22]. The laboratory reports that there is no loss of assay sensitivity or adipocytokine degradation with two freeze-thaw cycles, and levels in our study are similar to those reported in the literature using the same assays [23], [24], [25], [26]. Adequate blood samples for serum leptin, IL-6, adiponectin, and ghrelin concentrations were available for 1565, 1843, 1572, and 1556 of 2364 individuals, respectively.

Elevated ALT was defined, a priori, as an ALT ≥30 IU/L for men and ≥19 IU/L for women as proposed by Prati et al [2].

Statistical Analysis

The cohort was divided into the following four groups based upon the age quartiles: 30–62, 63–71, 72–77, and 78–93 years. Descriptive statistics were described in participants classified into these quartile age groups. Serum ALT, bilirubin, GGT, albumin, triglycerides, IL-6, leptin, adiponectin, and ghrelin were log transformed for statistical analyses to fulfill conditions of normality. Least squares means were used to examine the trends in serum ALT, bilirubin, GGT, and albumin across the four age groups and p-value for trend was examined. Multivariate hierarchical models were used to examine the relationship between ALT and age that included: 1. Un-adjusted, 2. Multiply adjusted for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total cholesterol-HDL cholesterol ratio, triglycerides, IL-6, leptin, adiponectin, and ghrelin, and 3. Multiply adjusted with the above plus commonly used liver function tests (bilirubin, GGT, and albumin). Additionally, we conducted multivariate-adjusted models to examine the association between age and prevalence of categorically defined elevated serum ALT across these four age groups, and p-value for trend was examined. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Population Characteristics

Cohort characteristics of the 1044 men (44.2%) and 1320 women (55.8%) are shown in table 1. The mean ± standard

Table 1. Cohort Characteristics.

	Total	Age Quartile 1 (30–62 years)	Age Quartile 2 (63–71 years)	Age Quartile 3 (72–77 years)	Age Quartile 4 (78–93 years)	P-trend
No of individuals	2364	597	574	589	604	
Women (%)	55.8	57.0	57.8	58.2	50.5	.0357
BMI (kg/m^2) (Mean±SD)	24.9±3.7	25.5±4.0	25.2±3.7	24.7±3.6	24.4±3.4	<.0001
Waist-hip ratio (Mean±SD)	0.8±0.1	0.8±0.1	0.8±0.1	0.8±0.1	0.8±0.1	<.0001
Alcohol use (%)						<.0001
None	36.8	36.5	34.8	32.1	43.4	
<1 drink/day	22.0	25.0	18.8	22.6	21.4	
1–2 drinks/day	26.8	22.5	27.0	31.4	26.5	
>2 drinks/day	14.5	16.1	19.3	13.9	8.8	
Systolic blood pressure (mmHg) (Mean±SD)	138.9±21.9	124.0±18.4	136.3±18.7	144.5±19.2	150.7±21.5	<.0001
Total cholesterol (mg/dl) (Mean±SD)	219.9±40.0	218.7±36.6	228.1±41.5	219.6±40.5	213.5±39.9	.0009
HDL cholesterol (mg/dl) (Mean±SD)	61.7±18.7	60.9±18.2	62.3±19.9	62.9±20.1	60.9±16.7	.8538
Total/HDL cholesterol ratio (Mean±SD)	3.9±1.3	3.9±1.3	4.0±1.3	3.8±1.3	3.8±1.2	.0120
† Triglycerides (mg/dl) (95% CI)	102.0 (99.8–104.3)	100.2 (95.9–104.7)	111.3 (106.4–116.4)	101.7 (97.3–106.3)	95.8 (91.7–100.1)	.0245
Diabetes (%)	14.3	7.4	12.5	17.7	19.7	<.0001
†* Leptin (μg/L) (95% CI)	8.5 (8.2–8.9)	7.1 (6.6–7.8)	9.2 (8.5–9.9)	9.1 (8.5–9.8)	8.6 (8.0–9.2)	.0015
†* Adiponectin (μg/ml) (95% CI)	11.7 (11.3–12.0)	8.6 (8.1–9.2)	10.7 (10.1–11.3)	12.7 (12.1–13.4)	14.0 (13.3–14.7)	<.0001
†* Ghrelin (pg/ml) (95% CI)	1345.2 (1317.9–1373.2)	1333.3 (1272.9–1396.5)	1303.7 (1249.5–1360.2)	1367.2 (1313.8–1422.7)	1366.8 (1316.6–1418.9)	.2028
†* IL-6 (pg/ml) (95% CI)	2.4 (2.3–2.5)	1.8 (1.7–1.9)	2.3 (2.2–2.5)	2.8 (2.6–3.0)	3.1 (2.9–3.3)	<.0001
ALT (IU/L) (Mean ± SD)	20.2±15.6	22.8±14.7	20.8±13.6	19.8±21.2	17.3±10.2	<.0001
Men	22.0±19.1	26.5±14.9	22.7±15.6	21.4±30.5	17.9±9.1	<.0001
Women	18.8±11.9	20.1±14.0	19.5±11.8	18.6±10.2	16.8±11.1	.0003
†ALT (IU/L) (95% CI)	17.4 (17.1–17.8)	19.6 (18.9–20.4)	18.1 (17.4–18.9)	16.9 (16.2–17.6)	15.4 (14.8–16.1)	<.0001
Elevated ALT (%)	28.0	35.3	31.0	28.4	17.4	<.0001
Men (≥30 IU/L)	15.3	28.0	15.3	11.4	7.7	<.0001
Women (≥19 IU/L)	38.0	40.9	42.5	40.5	26.9	.0004
† GGT (IU/L) (95% CI)	9.8 (9.5–10.1)	9.7 (9.1–10.2)	10.5 (9.9–11.1)	9.9 (9.3–10.4)	9.3 (8.8–9.9)	.2000
† Bilirubin (mg/dl) (95% CI)	0.5 (0.5–0.5)	0.4 (0.4–0.4)	0.4 (0.5–0.5)	0.5 (0.5–0.5)	0.6 (0.5–0.6)	<.0001
Albumin (g/dl) (95% CI)	4.3 (4.3–4.3)	4.4 (4.4–4.5)	4.4 (4.4–4.4)	4.2 (4.2–4.3)	4.1 (4.1–4.2)	<.0001

†Geometric means.
*Smaller sample sizes: Leptin (N = 1565), Adiponectin (N = 1572), Gherlin (N = 1556), IL-6 (N = 1843).
CI = confidence interval; SD = standard deviation.
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deviation (SD) age was 69.6±10.5 years, range 30–93 years. Average (mean ± SD) BMI was 24.9±3.7 kg/m^2 and average waist-hip ratio was 0.8±0.1. 36.8% reported no alcohol use, 22% reported <1 drink/day, 26.8% reported 1–2 drinks/day, and 14.5% reported >2 drinks/day. The mean ± SD systolic blood pressure was 139±22 mmHg. The mean ± SD for total and HDL cholesterol was 220±40 mg/dL and 62±19 mg/dL, respectively. 14.3% of the cohort had diabetes. Geometric mean (95% CI) concentrations for leptin, IL-6, adiponectin, and ghrelin were 8.6 μg/L (8.2–8.9 μg/L), 2.4 pg/ml (2.3–2.5 pg/ml), 11.7 μg/ml (11.3–12.0 μg/ml), and 1345.3 pg/ml (1317.9–1373.2 pg/ml), respectively. Geometric means (95% CI) for bilirubin, GGT, and albumin were 0.5 mg/dl (0.5–0.5 mg/dl), 9.8 IU/L (9.5–10.1 IU/L), and 4.3 g/dl (4.3–4.3 g/dl), respectively.

Analysis of each of these variables by age showed a significant age trend for BMI, waist-hip ratio (marker of central adiposity), alcohol use, systolic blood pressure, elevated cholesterol, prevalence of diabetes, leptin, adiponectin, IL-6, bilirubin, and albumin with increasing age. BMI and albumin decreased with increasing age, while waist-hip ratio, systolic blood pressure, prevalence of diabetes, adiponectin, IL-6, and bilirubin increased with age. GGT did not show a significant trend with age.

ALT Trends

Serum ALT Declines With Age. For all participants combined, ALT was highest in the youngest (30–62) age group, with a mean ± SD ALT of 23±15 IU/L for that group. Subsequently, ALT decreased with increasing age, from 21±14 IU/L for those aged 63–71 years, to 20±21 IU/L for

those aged 72–77 years, and 17±10 IU/L for those aged 78–93 years.

In sex-specific analyses, ALT decreased with increasing age for both men and women. In men, the highest ALT of 26.5±14.9 IU/L was observed in the 30–62 year age group, subsequently dropping to 22.7±15.6 IU/L, 21.4±30.5 IU/L, and 17.9±9.1 IU/L for each of the progressive age subcategories (Figure 1). ALT in women started at 20.1±14.0 IU/L in the 30–62 year age group, then gradually dropped thereafter to 19.5±11.8 IU/L, 18.6±10.2 IU/L, and 16.8±11.1 IU/L for the subsequent age subcategories (Figure 2). The 95th percentile cutoff value for ALT also decreased with age, suggesting that extreme ALT values for each respective age-category declined as well (Figures 1 and 2).

Least Squares of Mean of ALT and Age. Results remained consistent when least squares means of serum ALT were analyzed across all four age groups, using p-value for trend (p-value <0.0001). After multivariable adjustment for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total cholesterol to HDL radio, triglycerides, IL-6, adiponectin, and ghrelin, the trend of decreasing least squares means of ALT with age remained consistent and statistically significant (p<0.0001). Addition of bilirubin, GGT, and albumin to the multivariable model did not significantly change the statistical association (p<0.0001) (Table 2).

Elevated ALT Declines With Age. Using elevated ALT cutoff values of ≥30 IU/L for men and ≥19 IU/L for women as proposed by Prati et al. [2], the prevalence of abnormally elevated ALT was highest in the 30–63 year age group at 35.3%, then subsequently gradually declined to 31%, 28.4%, and 17.4% for each progressive age subcategory (p<0.0001) (Figure 3).

Similarly, after multivariate adjustment of prevalence of elevated ALT for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total cholesterol to HDL ratio, triglycerides, leptin, IL-6, adiponectin, ghrelin, bilirubin, GGT, and albumin, results remained statistically significant and showed a consistent downward trend of prevalence of elevated ALT with increasing age (p = 0.0001, Figure 3).

Trends in Bilirubin, GGT, and Albumin

In unadjusted analyses, rising bilirubin (from 0.4 mg/dL in the youngest quartile to 0.6 mg/dL in the oldest quartile) and falling albumin (from 4.4 g/dL in the youngest quartile to 4.1 g/dL in the oldest quartile) were associated with increasing age, while GGT had no association. After multivariable adjustments for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total-HDL ratio, triglycerides, and adiposity biomarkers (leptin, adiponectin, ghrelin, IL-6), trends in rising bilirubin and falling GGT and albumin levels with increasing age remained significant with p-values for trend <0.05. Bilirubin increased from 0.4 mg/dL in the youngest group to 0.6 mg/dL in the oldest group, GGT decreased from 11.7 IU/L in the youngest group to 9.9 IU/L in the oldest group, and albumin decreased from 4.5 g/dL to 4.2 g/dL in those groups.

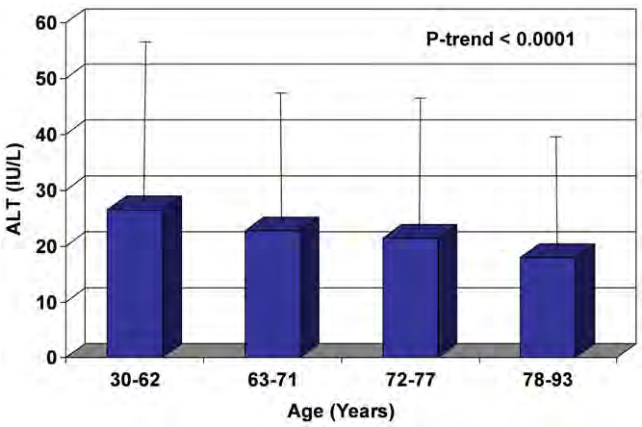

Figure 1. Effect of Age on ALT Values in Men (Mean and 95% Confidence Interval). In men, mean ALT (bars) and 95th percentile cutoff ranges (extension lines) both decrease with rising age.
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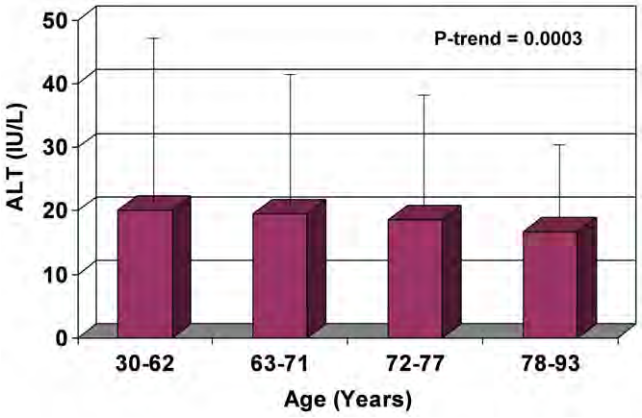

Figure 2. Effect of Age on ALT Values in Women (Mean and 95% Confidence Interval). In women, mean ALT (bars) and 95th percentile cutoff ranges (extension lines) both decrease with rising age.
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Discussion

Principal Findings

In this population-based, community-dwelling cohort of older men and women residing in Southern California, ALT levels decreased with age for both sexes. Even after multivariate adjustments for factors previously found in other studies to be associated with differing ALT levels (sex [2], [4], [7], [8], [11]; alcohol use [7]; components of the metabolic syndrome [4–11]: BMI, waist-hip ratio, diabetes, fasting glucose, total cholesterol to HDL ratio, triglycerides), for surrogate markers of adiposity (leptin [4], IL-6 [27], [28], adiponectin [29], [30], ghrelin [31], [32]), and for other markers of liver function (bilirubin, GGT, albumin), the association of rising age with decreasing ALT remained significant (p<0.0001, Table 2). Correspondingly, the extreme values of ALT (95^{th} percentile cutoff points for upper limit of ALT, Figures 1 and 2) as well as the prevalence of elevated ALT (p<0.0001, Figure 3) both decreased with rising age as well. These data suggest that age is an independent and robust predictor of serum ALT within normal range as well as of elevated serum ALT, and this association is independent of adiposity, known metabolic correlates of ALT, and possibly liver function. We also found that serum albumin declines with increase in age, perhaps related to a decline in muscle mass. Serum GGT did not decrease with increase in age in unadjusted analyses but after adjustment for metabolic correlates it also showed a decrease with age. Bilirubin increased with increasing age.

Speculations on Causes and Implications for Future Research

We initially hypothesized that perhaps this trend may be related to decreasing adiposity with advancing age, leading to a decreased

Table 2. Least Square Means of ALT by Age.

ALT	Age Quartile 1 (30–62 years)	Age Quartile 2 (63–71 years)	Age Quartile 3 (72–77 years)	Age Quartile 4 (78–93 years)	P-trend
Unadjusted	19.6	18.1	16.9	15.4	<.0001
†***Multivariate adjusted**	21.5	18.5	17.4	15.9	<.0001
†* **Multivariate adjusted with addition of GGT, bilirubin, and albumin**	20.9	18.3	17.5	16.4	<.0001

†Multi-variate adjustment for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total-HDL ratio, triglycerides, leptin, adiponectin, ghrelin, and IL-6.
*Smaller sample sizes: Leptin (N = 1565), Adiponectin (N = 1572), Gherlin (N = 1556), IL-6 (N = 1843).
Geometric means used for ALT, leptin, adiponectin, ghrelin, GGT, and bilirubin.
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prevalence of nonalcoholic fatty liver disease. In analysis of our cohort characteristics, while BMI decreased with age, waist-hip ratio, and IL-6 increased with age, suggesting that central obesity (a component of the metabolic syndrome) increased with age. This finding is somewhat contrary to our hypothesis. These age-related anthropometric and cytokine changes are complex and do not account for the decline in serum ALT. Furthermore, age retained a clinically and statistically significant association with ALT despite multivariable adjustment for these metabolic characteristics and biomarkers.

Another potential explanation is that a decrease in ALT signifies a true decrease in prevalence of liver disease. While the prevalence of significant alcohol use in our cohort did decline with older age, peak consumption occurred at ages after ALT levels started to fall. Furthermore, the trend of decreasing ALT with age persisted after adjusting for alcohol intake, suggesting that alcohol consumption alone does not account for the decrease in ALT with age.

Information regarding viral hepatitis was not available in our study cohort, therefore these participants could not be excluded. Theoretically, a higher burden of chronic viral hepatitis in younger individuals could lead to higher ALT levels in this age group. However, data from NHANES suggests that this is not the case. The prevalence of hepatitis B infection was found to increase with increasing age among Caucasians [35]. While hepatitis C prevalence decreased among Caucasians aged 50 and older, the prevalence rate was only 0.7% [36], therefore any effects of decreasing hepatitis C prevalence would be offset by increasing hepatitis B prevalence, making the overall contribution of viral hepatitis to population ALT trends minimal.

Decreased prevalence of liver disease may also reflect selective survival bias, whereby those with high levels are more likely to have died. A study of 8043 construction workers by Arndt et al. [33] found that elevated liver enzymes predicted a significantly increased risk of all-cause mortality. Adams et al. [34] found that mortality was significantly higher in community-dwelling patients with NAFLD compared to the general population. Due to the cross-sectional nature of this study, we cannot exclude this possibility. Alternatively there is a yet unidentified lifestyle or clinical factor which confers protection to liver disease as one ages.

Another possibility is that decreasing ALT signifies a decrease in the mass or function of the normal liver. This is plausible given that albumin levels decreased with age and bilirubin levels

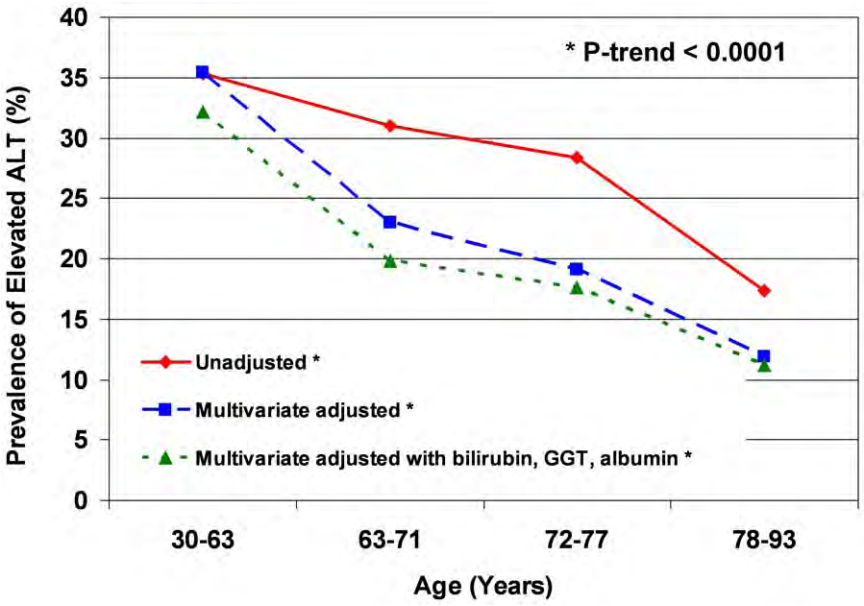

Figure 3. Prevalence of Elevated ALT by Age. The trend of decreasing prevalence of elevated ALT with rising age persists in unadjusted analysis, after adjustment for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total-HDL ratio, triglycerides, adiposity biomarkers (leptin, adiponectin, ghrelin, IL-6), and after adjustments for the above plus bilirubin, GGT, and albumin.
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increased with age. Both albumin and bilirubin provide information regarding functional status of the liver and are considered to be true liver function tests. Studies comparing young and old livers in rats showed that older livers have slower and weaker regenerative capacity, a decrease in homeostatic capacity, and a lower inflammatory response rate [37]. In rat models of liver transplantation, aged livers showed a reduced organ weight, increased hepatocyte degeneration, and increased fibrosis [38], [39]. Similarly in humans, older livers show a progressive decrease in size and blood flow, and changes related to the accumulation of oxidative stress [40], [41], [42]. In studies by Elinav et al. [43] and Le Couteur et al. [17], an ALT value below the median was a strong and independent predictor of mortality in community-dwelling elderly men. In our study, modest decreases in albumin and GGT and increases in bilirubin were observed with increasing age after adjustments for sex, alcohol use, metabolic syndrome traits, and surrogate markers of adiposity, suggesting that a decrease in liver function may indeed be present. However, bilirubin, GGT, and albumin are also complex biomarkers and may not solely reflect hepatic function. Furthermore, the trend of decreasing ALT with increasing age remained significant after adjusting for bilirubin, GGT, and albumin.

An additional possibility is that the prevalence of liver disease is the same or perhaps higher in elderly subjects, but the ALT is not a reliable marker of hepatocyte injury. In our study, age was associated with increasing central obesity, systolic blood pressure, and prevalence of diabetes, all factors associated with the metabolic syndrome and NAFLD. Although ALT is frequently used in the evaluation of NAFLD, it has been shown to correlate poorly with liver histology in subjects of all ages [44], [45]. This lack of correlation with ALT levels in the elderly could be increased in part due to a decrease in the inflammatory response of the older liver, as discussed above. Others have suggested that elderly subjects with NAFLD tend to have more fibrosis on liver biopsy compared to younger subjects who tend to have more steatosis or steatohepatitis. Frith et al. [46] examined 351 consecutive patients with biopsy-proven NAFLD, and found that age >60 was significantly associated with fibrosis. Similar results were found by Angulo et al. [47] and Miyaaki et al. [48].

Finally, ALT was a marker of age independent of other liver function tests, including bilirubin, GGT, and albumin. Others have also speculated that ALT may be a novel biomarker of aging [17].

Strengths and Limitations

The strengths of this study include the use of a population-based, well-characterized cohort of healthy, community-dwelling elderly men and women. Analysis of data obtained from a research clinic visit 12–15 years after the initial establishment of the cohort allowed the unique opportunity to study an older group of individuals. One potential limitation of our study is that information regarding chronic liver diseases, such as viral hepatitis, autoimmune hepatitis, or metabolic liver diseases, was not available, thus we were not able to exclude these individuals. However, these conditions are not so common that they would be expected to influence the results. Our study cohort is fairly uniform (predominantly Caucasian, middle to upper-middle class), suggesting good internal validity of the findings. However, generalizability of these findings in other ethnic groups or socio-economic classes would require further studies in other more diverse cohorts.

In conclusion, ALT levels were not constant, but decreased with increasing age for both men and women, independent of components of the metabolic syndrome, surrogate markers of adiposity, and other markers of hepatic function. As a consequence, an ALT value which is considered normal for a younger individual may fall outside of 2 standard deviations for an older individual. The reasons for these differences and the clinical implications of decreasing ALT with age remain to be determined. Future longitudinal studies are needed to confirm our findings and examine the factors that explain the association between the decline in serum ALT with rising age.

Author Contributions

Conceived and designed the experiments: RL. Performed the experiments: RL. Analyzed the data: RB RL. Contributed reagents/materials/analysis tools: RL. Wrote the paper: MD EBC RL. Critical review of the manuscript: EBC.

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T. Franklin Williams 12 Month Progress Report
Sharmilee Nyenhuis, MD

Over the past 1 year, the T. Franklin Williams Scholars Award has allowed me to pursue my research in examining age related changes in neutrophils during an asthma exacerbation. My career development activities for this award are categorized as follows: 1) aging research training, 2) faculty/investigator training in geriatrics, and 3) mentorship.

1). Aging research training: In the past twelve months I have advanced my knowledge of asthma in the geriatric population in several ways. I have attended relevant sessions on asthma in older adults at the national meeting of the American Association of Allergy, Asthma and Immunology, the American Thoracic Society, the American Geriatrics Society and the Association of Clinical Research Training. These meetings have fostered interactions with leaders in the field of asthma in older adults and have provided insight into my research. Though more recognition of asthma, allergic and immunologic diseases in older adults are occurring there is still a need for more attention to these conditions. This has influenced me to propose sessions at both the AGS and AAAAI national meetings, which focus on allergic disease and vaccine responses in older adults. I will be leading a session at the AAAAI and I am in the process of organizing a session at the upcoming AGS meeting. Additionally, I took advantage of the opportunity to participate in the first symposium on comparative effectiveness research (CER) in geriatrics this fall. This symposium allowed me to identify potential challenges of CER in the geriatric population and what resources are available for carrying out CER.

To increase the awareness of asthma in older adults I have given didactic sessions to the Department of Medicine, the Section of Geriatrics, a Junior Faculty Monthly meeting. The sessions were received favorably and have led to collaborations.

In order to address additional research questions of neutrophil biology I have acquired knowledge of additional laboratory techniques through my mentors Drs. Steven Ackerman and Richard Ye. Dr. Ye is world-renowned for his work in neutrophil biology and I have learned of additional techniques such as neutrophil chemotaxis assays and adhesion assays which will help in assessing age-related differences in neutrophil recruitment. By attending the lab meetings of Dr. Ackerman I have learned about quantitative RT-PCR, which will allow my to examine cytokine expression in my research project.

Finally, I have participated in weekly departmental conferences including journal club, research conference, and Grand Rounds which provide additional exposure to a variety of clinical and basic science topics in pulmonary medicine and immunology. My participation in these conferences have given me a mechanism for review and critique of my own research activities and presentation skills. Additionally, along with my mentor Dr. Ackerman, we have started a monthly multi-disciplinary asthma meeting which brings investigators from several different backgrounds (psychologist, molecular biologist, physicians, pharmacologist, geneticist) together to discuss a common interest of asthma. This allows us to learn about the ongoing research in asthma as well as helps develop collaborations which will lead to a program project grant in the future.

2). Faculty/Investigator training in geriatrics: The University of Illinois at Chicago has a Center for Clinical and Translational Science (CCTS) funded by the NIH CTSA. One of the goals of the CCTS is to provide core training for career development. The CCTS

offers an Intensive Summer Program on Clinical Research, a one week intensive course which provides an introduction to key aspects of the design and implementation of a clinical research study. I participated in this program this summer and gained a tremendous amount of knowledge which has already helped my implement my research. Additionally, they have had other seminars including one on mentorship, preparing for K award and how to use the biostatistical core at UIC. I have also completed a Biostatistics course and am enrolled in a Grant Writing course of the Spring 2011 semester. As a participant of Dr. Ackerman's laboratory meetings, Pulmonary and Geriatrics research conferences, and journal clubs, I have been giving presentations at least once a semester and with each presentation I am provided with feedback regarding the content, communication, and quality of slides and presentation materials.

3). Mentorship: My mentorship thus far as been extraordinary. I have weekly meetings with Dr. Ackerman who has been supportive and provides constructive criticism. He is readily available and has been more than willing to review any abstracts, manuscripts, or grants. Dr. Ackerman reviews the appropriateness of my research questions and experimental approaches. Dr. Christman has provided excellent career development support and also has aided in clinical research study design. Dr. Christman also provided me with additional aging biology mentorship by introducing me to Dr. Liz Kovacs. Dr. Kovacs is a professor at Loyola University in Chicago and is very well known in the field of aging biology. Her extensive knowledge of the age-related changes in neutrophils is invaluable to my research project and I will include her as a mentor when I apply for my NIH K award in June 2011. I have had several meetings with Dr. Jurivich, geriatrics mentor, who has provided me with the bulk of my geriatrics mentorship. I have maintained contact with Dr. Cindy Carlsson via telephone, email and one face-to-face meeting. Though she is not in Chicago she has made herself available to me and has given me excellent geriatric career development support. Moreover, I have maintained my monthly meetings with Dr. Sameer Mathur who has helped guide me with study design questions that have arisen through the IRB process and beyond. Dr. Richard Ye has provided mentorship in neutrophil biology and we have worked on additional assays that I will perform in my projects (ie. chemotaxis).

In conclusion, this past year has been very productive and I look forward to my next year as a T. Franklin Williams Scholar. I am currently planning to apply for NIH funding via K award mechanism in June 2011. I know that this award provides validation of my research in the field of aging asthma and will increase the awareness of the impact aging has on asthma exacerbations.

IMMUNITY & AGEING

SHORT REPORT Open Access

Characterization of leukotrienes in a pilot study of older asthma subjects

Sharmilee M Nyenhuis[1,2], Elizabeth A Schwantes[1] and Sameer K Mathur*[1]

Introduction

Asthma is a chronic inflammatory disorder of the lower airway that results in mucus secretion, airway edema and reversible airway obstruction [1]. These characteristic features lead to the clinical symptoms of asthma, which include recurrent episodes of wheezing, breathlessness, chest tightness and coughing [2]. The pathophysiology of asthma is not fully elucidated but the current paradigm involves multiple cell types (ie. eosinophils, neutrophils, mast cells, T-cells) and their mediators.

The most recent estimates of asthma prevalence in those over the age of 65 are between 4 and 8%, which may be an underestimate due to an underdiagnosis of asthma in the elderly [3]. An increase in morbidity and mortality and a reduced response to bronchodilators in the emergency department setting have been shown in older asthmatics compared to their younger counterparts [4-7]. Elderly asthmatics also have a higher rate of severe exacerbations, emergency department visits, and hospitalizations than younger asthmatics [8,9].

Leukotrienes are potent pro-inflammatory lipid mediators that have been shown to have a role in asthma [10]. Leukotrienes are a product of arachidonic acid via the 5-lipoxygenase pathway. Leukotriene B_4 (LTB_4) is a potent chemotactic agent and activator of neutrophils and is also produced mainly by neutrophils. The presence of LTB_4 in the lung results in neutrophil recruitment and activation leading to superoxide anion generation and cholinergic airway hyperresponsiveness [11]. The cysteinyl leukotrienes (CysLTs), LTC_4, LTD_4, and LTE_4, are known for their profound effect on the airway, including increased microvascular permeability and vasodilation, airway smooth muscle contraction, mucous secretion and impaired mucociliary clearance [10]. CysLTs are produced by eosinophils, basophils, mast cells, macrophages and to a lesser degree by T cells and endothelial cells [10,12]. Increased CysLT levels have been detected in the sputum of patients with asthma and have been shown to correlate with symptom severity [13].

Despite older asthmatics often having more severe disease and exacerbations, few studies have been done to characterize their asthma at a cell and/or molecular level. We have previously shown that functional differences exist in eosinophils from older adult asthmatics *in vitro*; specifically, diminished IL-5 stimulated eosinophil derived neurotoxin (EDN) release and superoxide production [14]. In this pilot study, we sought to compare pro-inflammatory lipid mediator production, specifically leukotrienes LTB_4 and CysLT, both *in vitro* and *in vivo* in young and older adult asthmatics. Identifying the inflammatory differences seen in older asthmatics may be important for the diagnosis, improving the morbidity and mortality, as well as determining optimal therapies of the disease in this growing population.

Methods

We recruited subjects in two age groups, 20 to 40 years (n = 12) and 50 to 70 years (n = 6), in a study protocol approved by the University of Wisconsin Health Sciences Institutional Review Board. Inclusion criteria included a physician diagnosis of mild to moderate asthma with a provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) of < 8 mg/mL or albuterol reversibility on spirometry of ≥ 12%. Exclusion criteria included history of tobacco use > 5 pack-years or use in the previous year, prednisone use within 1 month, donation of blood (greater than 1/2 pint) in the previous 8 weeks, FEV_1 < 60%, severe asthma, upper and/or lower respiratory tract infection in the previous 4 weeks, diabetes, pregnancy, or an active cardiovascular disease other than controlled hypertension.

At the study visit, medical history, spirometry with bronchodilator reversibility, sputum induction, allergy skin prick test, physician exam and phlebotomy were performed. Sputum processing was performed as described previously [15]. LTB_4, LTC_4 and CysLT levels in culture

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supernates or the sputum samples were measured using the LTB_4, LTC_4 and CysLT competitive EIA kits, respectively (Cayman Chemical, Ann Arbor, MI). Heparinized venous blood was lysed in a hypotonic solution and subjected to gradient centrifugation. Neutrophils were isolated from the granulocyte pellet and were > 95% pure and > 98% viable. Eosinophils were also isolated from the granulocyte pellet by negative selection using anti-CD16, anti-CD14, and anti-CD3 magnetic beads (Miltenyi Biotechnology; Auburn,CA) as described previously [16]. The eosinophils were typically > 99% pure and > 98% viable.

Results

Table 1 shows a comparison of lung function and peripheral blood characteristics for the subjects in the study. Both FEV_1 and FVC were significantly lower in the older group compared to the young subjects, which is consistent with lung volume decreases in the aging population [17]. However, percentage of predicted values, for both FEV_1 and FVC were comparable between young and older groups, suggesting similar disease severity in both age groups. There was no difference in peripheral blood eosinophil counts between young and older asthmatics. Sputum cell differentials revealed a tendency for increased percentage of neutrophils in older asthma subjects, 72(65-76)%, compared to young asthma subjects, 42(21-66)%, p = 0.09 (Figure 1A). This is consistent with our previous cohort of older asthmatics exhibiting a significantly higher percentage of sputum neutrophils [18]. The total number of eosinophils in the sputum were similar in both the young and older group [Young: 0.6 (0-1.3) × 10,000 cells/gm; Older: 0.5 (0.1-3.9) × 10,000 cells/gm; Figure 1B], while the total numbers of neutrophils apparently increased though not statistically significant [Young: 30 (4-138) × 10,000 cells/gm; Older 68 (4-304) × 10,000 cells/gm; Figure 1C].

In vivo levels of LTB4 and CysLT were measured in the induced sputum samples from young and older asthma subjects. Sputum LTB4 levels in older asthma subjects, 320 (301-397) pg/mL, were significantly decreased compared to the young subjects, 1235 (706-2259) pg/mL, p = 0.015 (Figure 2A). Sputum CysLT levels in older asthma subjects, 264 (224-269) pg/mL, were lower than in younger asthma subjects, 717 (408-1152) pg/mL; however, this only approached statistical significance, p = 0.06 (Figure 2B).

In order to determine whether these *in vivo* differences were due to an age-related diminished ability of neutrophils or eosinophils to produce leukotrienes, both puri-

Table 1: Subject Characteristics

	Young (n = 12)	Older (n = 6)
Age (years, range given)*	27 (20-35)	64 (58-70)
Duration of disease	17 (6-30)	37 (4-65)
FEV_1 (L)*	3.35 (+/- 0.81)	2.24(+/- 0.28)
FEV_1 % Predicted	86 (+/- 14.7)	81 (+/- 16.46)
FVC (L)*	4.28 (3.99-5.02)	3.24 (+/- 0.71)
FVC % Predicted	100 (+/- 12.15)	89 (+/- 12.62)
WBC (10^6cells/mL)	5.55 (4.75-6.85)	5.6 (5.13-6)
Absolute Eosinophil Count (cells/mL)	204 (+/- 127.75)	114 (+/- 82.95)
Positive Allergy Testing+	11/12	6/6
Inhaled Corticosteroid Use	6/12	4/6

Data are presented as mean values (+/- standard deviation; t-test) or median values (25%-75% interval; Mann-Whitney Rank-Sum).
*Statistically significant difference between young subjects and older subjects ($p < 0.05$). +At least one positive skin prick test result for grass, mold, ragweed, tree, cat, dog, or dust mite.

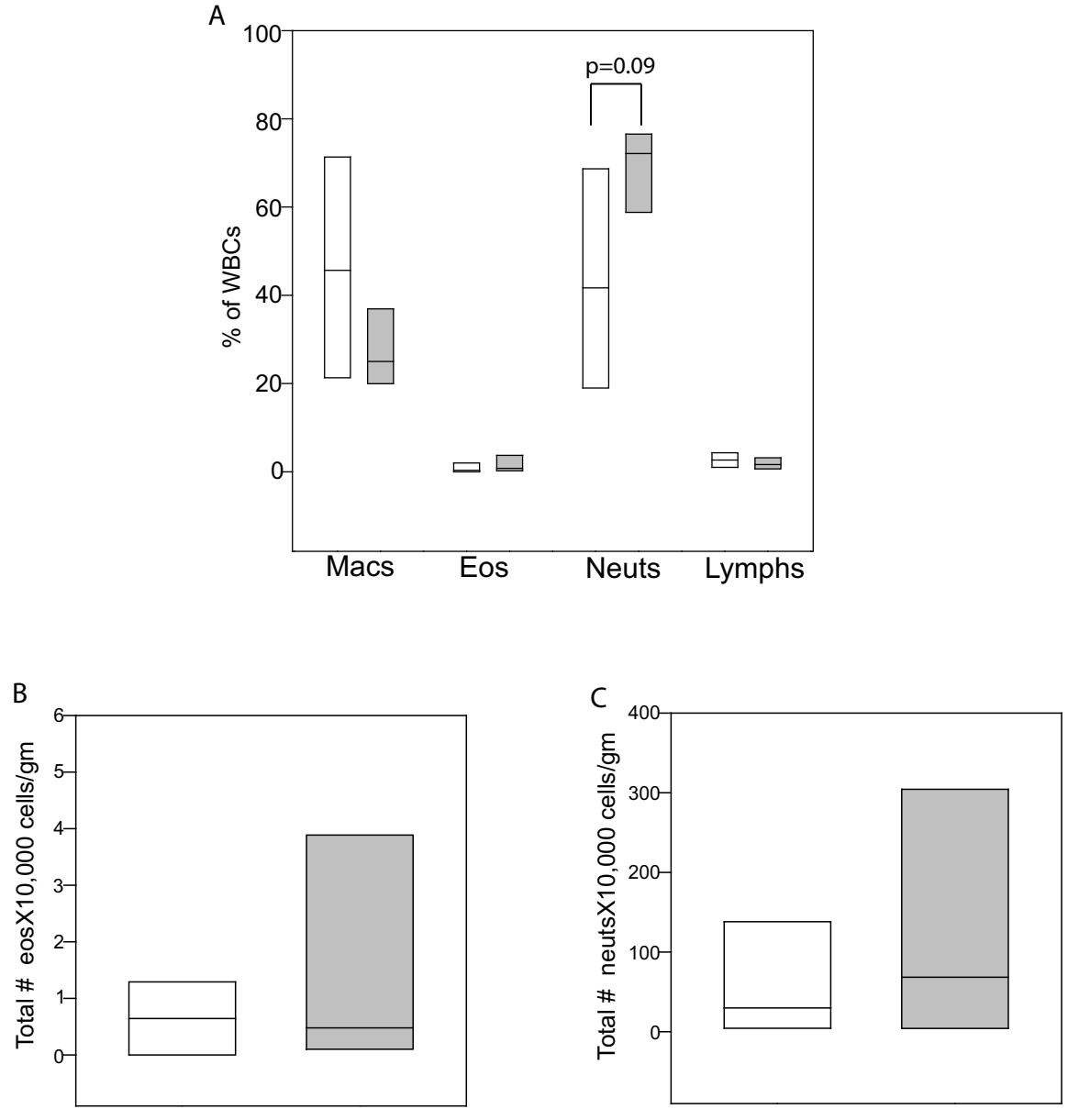

Figure 1 Sputum cell type differentials. Box plots of sputum cell percentages (**1A**) and total eosinophil (**1B**) and neutrophil (**1C**) number are shown for young subjects (white bars; n = 11), and older subjects (gray bars; n = 6). One young subject had > 80% epithelial cells in the sputum (indicating oral/salivary contamination) and was not included in the sputum differential. Comparisons between the young and older groups were performed with *t* test analysis or Mann-Whitney rank sum analysis. Statistical significance was defined at $p < 0.05$. Mac = macrophage; Eos = eosinophil; Neut = neutrophil; Lymph = lymphocyte; Median: ----- (solid)

fied neutrophils and eosinophils were treated with calcium ionophore to stimulate leukotriene production. As shown in Figure 2C, the neutrophil production of LTB_4 from older asthma subjects, 8708 ± 5326 pg/mL, was comparable to the young subjects, 10234 ± 3078 pg/mL, p = 0.45. Eosinophil production of LTC_4 from young, 5836 (3678-9512) pg/mL, and older asthma subjects, 4766 (2685-8456) pg/mL, was also similar in the two groups, p = 0.78 (Figure 2D).

Since GM-CSF can stimulate leukotriene production by neutrophils and eosinophils[11] and changes in GM-CSF mediated signaling have been shown to occur in elderly human subjects *in vitro*[19,20], we examined GM-CSF production by peripheral blood mononuclear cells (PBMCs) in the older and young asthma subjects. As

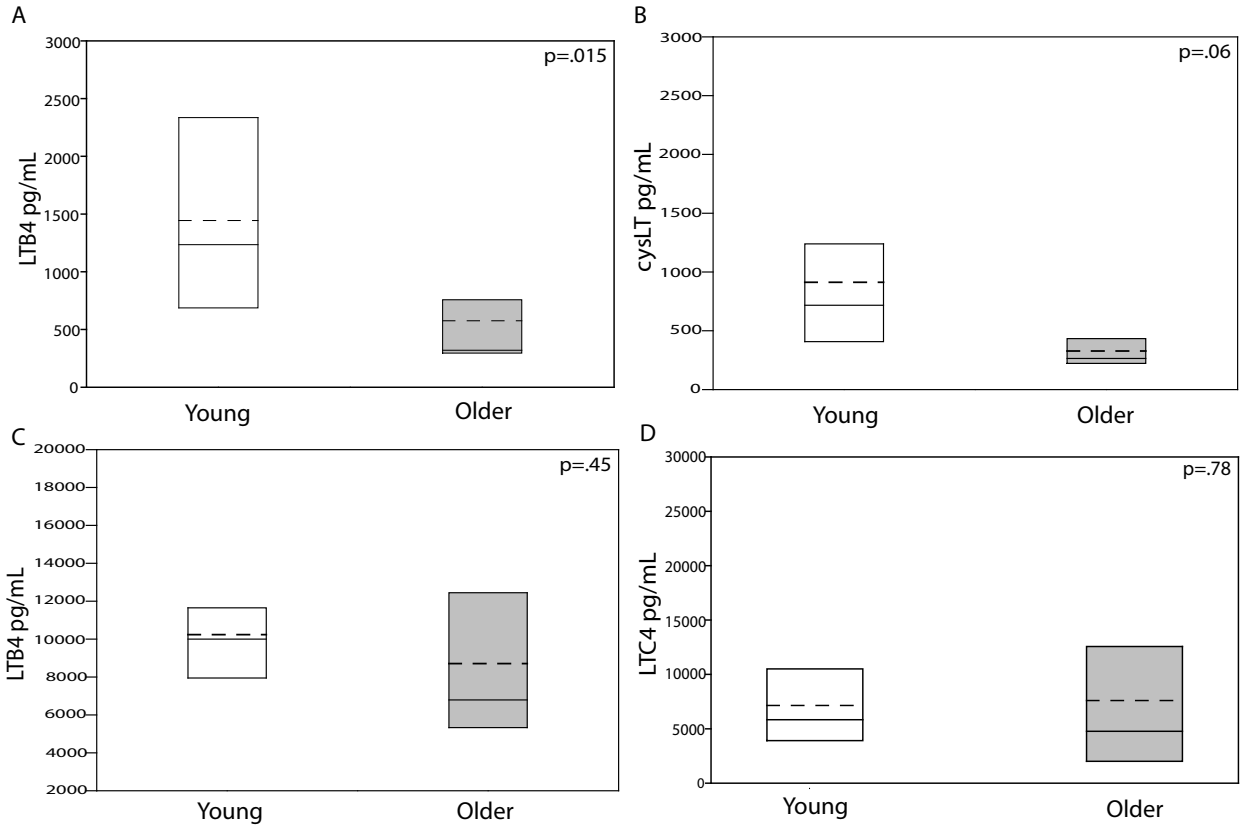

Figure 2 ***In vivo and in vitro*** **leukotriene levels**. Comparisons between the young and older groups were performed with *t* test analysis or Mann-Whitney rank sum analysis. Statistical significance was defined at $p < 0.05$. White bars: young subjects; Gray bars: older subjects Mean: - - -(dashed) Median: ----- (solid). **2A and 2B**. Sputum was processed and LTB_4 and CysLT levels were measured using the LTB_4 and CysLT competitive EIA kit, respectively (Cayman Chemical, Ann Arbor, MI). Sputolysin (Calbiochem) was added to all assay standards to represent an equivalent amount in the diluted sputum samples and run in duplicate. Standard curves for LTB_4 and CysLT were performed both with and without Sputolysin to ensure an equivalent slope was obtained. Young: n = 11 (One young subject had > 80% epithelial cells in the sputum and was not included in the biochemical analysis.); Older: n = 6. **2C and 2D**. Peripheral blood neutrophils and eosinophils were isolated and stimulated with calcium ionophore (A23187) for 60 min at 37°C. LTB_4 and LTC_4 were measured by competitive EIA kit (Cayman Chemical, Ann Arbor, MI). Young: n = 12; Older: n = 6

shown in Figure 3, GM-CSF production by unstimulated PBMC was similar; however, LPS-stimulated PBMCs from the older asthma subjects, 125 ± 118 pg/mL, produced significantly less GM-CSF than their younger counterparts, 317 ± 136 pg/mL, p = 0.01.

Discussion

To our knowledge, a characterization of leukotriene levels has not been previously performed in an older adult asthma population. In this pilot study of young and older mild-to-moderate asthmatics we found that older asthma subjects had lower *in vivo* levels of LTB_4 and CysLT in the sputum at baseline disease. This difference in leukotriene levels was not a reflection of fewer eosinophils and neutrophils in the airway as the total number of these cells in the sputum were similar or greater in our older asthmatic group. However, young and older asthma subjects produced comparable amounts of LTB_4 and LTC_4 *in vitro* when neutrophils and eosinophils, respectively, were stimulated with calcium ionophore. The observation that LPS stimulation of PBMCs resulted in less GM-CSF production in the older asthma subjects provides a potential explanation for the age-related differences in sputum leukotriene levels. Rather than an intrinsic defect in neutrophils and eosinophils, there may be less GM-CSF in the airways of older asthmatics serving as a stimulant to produce leukotrienes. However, it is possible that other age-related changes in the *in vivo* inflammatory milieu contribute to the diminished levels of leukotrienes in the airway.

There are several limitations to this study including the absence of a control non-asthmatic population, lack of subjects >65 years old, and few total number of subjects enrolled. Though multiple studies have consistently revealed increases in leukotriene production in asthmatic airways compared to controls, we cannot fully gauge the

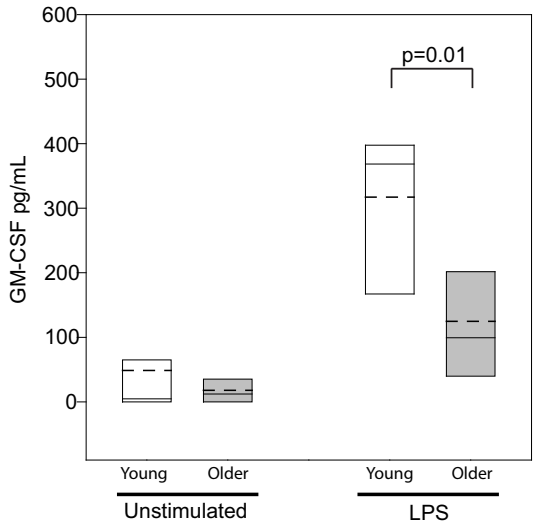

Figure 3 Production of GM-CSF in PBMCs; Peripheral blood mononuclear cells (PBMCs) were either not stimulated or stimulated with LPS (0.4 μg/mL) and supernatants analyzed by ELISA for GM-CSF. Comparisons between the young and older groups were performed with *t* test analysis. Statistical significance was defined at $p < 0.05$. White bars: young subjects (n = 12); Gray bars: older subjects (n = 6); Mean: - - - (dashed) Median: ----- (solid)

magnitude of our findings in the older asthmatic without non-asthmatic older controls [21]. It is possible though that our findings would have been more profound if we had more subjects in an even older (> 65 years old) population. Furthermore, as a pilot study, we had a limited number of subjects enrolled in order to establish preliminary observations to serve as the focus of future studies.

Calcium ionophore is a potent activator of leukotriene production in eosinophils and neutrophils. It is possible that we were unable to detect small differences in leukotriene production *in vitro* with the use of such a potent stimulator of leukotriene production. Therefore, a less potent, physiologically-relevant stimulant (such as GM-CSF) could reveal a difference in leukotriene production *in vitro*.

The use of inhaled glucocorticoids by some subjects in our study may represent a confounder as glucocorticoids can have multiple effects such as a decrease in inflammatory mediators and neutrophil apoptosis [22]. However, glucocorticoids have not been shown to affect LTB_4 formation *in vitro* and *in vivo* [23]. Also, we performed a statistical analysis of paired young and older subjects that were matched based on inhaled corticosteroid use, which continued to show statistically significant differences in the *in vivo* leukotriene levels (data not shown). Thus, the use of inhaled glucocorticoids alone cannot explain our findings.

The lower levels of CysLTs in the airways of older adults may have an impact on the effectiveness of CysLT receptor antagonists in the older population. Two studies to date have examined the efficacy of the CysLT receptor antagonists in an older adult population and concluded that their effectiveness might be limited or altered in older asthmatics [24,25]. Furthermore, the neutrophil predominance found in the airway of older asthmatics may actually represent a tendency for decreased responsiveness to glucocorticoids as has been observed in the neutrophilic phenotype of severe asthma [26].

Our findings show that aging can result in changes in the airway environment in asthmatics, specifically an increase in airway neutrophils and decreases in both LTB_4 and CysLT levels at baseline. This characterization of leukotrienes in older adult asthmatics reveals significant differences that may have clinical relevance not only in baseline asthma but also during an exacerbation of disease. Understanding the biological changes of airway inflammation in the aging population will aid in the development of future therapies and impact the increased morbidity and mortality that is associated with this phenotype of asthma.

Abbreviations

CysLTs: cysteinyl leukotrienes; LTB_4: leukotriene B_4; PBMCs: peripheral blood mononuclear cells; GM-CSF: granulocyte macrophage colony-stimulating factor; EDN: eosinophil derived neurotoxin; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; LPS: lipopolysaccharide

Competing interests

SMN received a fellowship award co-sponsored by GlaxoSmithKline, which helped fund this study.

Authors' contributions

SMN performed the leukotriene and GM-CSF immune assays, analyzed data, created graphs and drafted the manuscript. EAS performed cell separations, sputum processing, sputum differentials, assisted with immune assays, and assisted with data analysis and drafting of the manuscript. SKM conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors reviewed and approved the final manuscript.

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Twelve Month Scientific Progress Report

Award Recipient Name: Peter P. Reese, MD, MSCE - American Society of Nephrology- Association of Speciality Professors Junior Development Award in Geriatric Nephrology

Project: "Predictors of Mortality Among Older Renal Transplant Candidates and Recipients: Implications for Organ Allocation Policy in the United States"

Overall Scientific Progress

Dr. Reese's Junior Development Grant in Geriatric Nephrology focuses on optimizing organ allocation in kidney transplantation. Recent organ allocation proposals (e.g. the Life Years from Transplant, or LYFT proposal) from the United Network for Organ Sharing (UNOS) would reduce the ability of older adults to get a transplant due to lower estimated mortality benefit compared to younger individuals. Unfortunately, these proposals rely on models to predict mortality that may not adequately distinguish between individuals of the same age because important characteristics such as functional status were not included in the models. Dr. Reese, through support from this grant, is working to identify clinical and functional characteristics that predict mortality among renal transplant candidates and recipients, and to assess whether these characteristics differ across age strata. Specifically, he is examining the utility of functional status as a mortality predictor that may improve the accuracy of models such as the one used in the LYFT proposal. In the past year, Dr. Reese has made significant progress related to obtaining preliminary data, beginning preliminary analyses and submitting an NIH grant to expand the scope of this project.

The primary operational challenge of this project involves linking large datasets from Fresenius Medical Care (FMC) corporation and UNOS using patient identifiable information (including social security numbers). In the past year, Dr. Reese has received institutional review board approval from the University of Pennsylvania and developed procedures for exchanging data that that have been accepted by Penn, FMC and UNOS; these procedures have also undergone careful legal review. Working with

FMC, Dr. Reese has commenced preliminary analyses of the data to determine demographic and clinical characteristics of individuals in the dataset and distributions of values related to the Medical Outcomes Study Short-Form 36 (SF-36), which measures functional status and is the primary exposure for this study. Dr. Reese has also obtained datasets from UNOS and completed preliminary analyses of mortality and access to kidney transplantation. These data were obtained by using the funding provided by the ASN-ASP grant. Dr. Reese expects to create the final linked dataset in the next month and to commence more detailed analyses.

New grant applications

Using these preliminary data, Dr. Reese submitted his first R-01 grant to the National Institutes of Health in February 2010. His application was scored in the thirtieth percentile, which is unlikely to be funded at this time, although comments were readily addressable and the project officer was very encouraging about the prospects for a resubmission.

Professional Development

Dr. Reese's professional goals through the ASN-ASP grant include developing further skills in geriatric renal research and building relationships to collaborators with related interests and skills. Dr. Reese's attendance at the 2010 American Geriatrics Society conference provided him with an excellent opportunity to gain exposure to a diverse array of high-quality geriatrics research. The conference also provided an introduction to a collaborator at Johns Hopkins, Dr. Dorry Segev, a transplant surgeon who investigates related topics. Following discussions at the conference, Dr. Reese and Dr. Segev have commenced a health services research analysis of how kidney transplant centers respond to external review. Dr. Segev also invited Dr. Reese to speak at Johns Hopkins in Fall 2010.

Publications

An additional goal for this ASN-ASP grant is the development of a policy framework to examine the tradeoff between efficacy and fairness when rationing a finite pool of kidney allografts among the large number of renal transplant candidates. To this end, Dr. Reese and his mentor Dr. Karlawish wrote a conceptual article entitled "Should we use age to ration health care? The case of kidney transplantation" which was accepted by the *Journal of the American Geriatrics Society*. In this work, we explore the ethical dilemmas created policies (such as LYFT) in which elderly patients are deemed to have lower priority for medical care due to advanced age and lower relative mortality benefit. We argue that other forms of cost-effectiveness research, which may use survival as the primary metric of effectiveness, may disadvantage older patients. Lastly, we propose strategies to protect the interests of older patients in these situations.

Dr. Reese's research portfolio related to geriatrics also includes a study examining whether, as the population of renal transplant patients in the United States (US) ages, the population of clinical trial participants is also growing older. Given higher mortality, greater likelihood of medication side effects, and less rejection among elderly kidney transplant recipients, optimal care of these patients may require tailored decisions about transplant therapeutics. Dr. Reese has completed preliminary analyses of a decade's worth of clinical trials related to kidney transplantation. We found that a third of clinical trials had an exclusion criterion related to older age, and that the mean age of clinical trial participants was significantly younger than US renal transplant participants overall. We also found that trials involving immunosuppression were more likely to exclude patients over 65 years of age. Synthesizing these data, we express concern that the findings of many clinical trials may not be generalizable to the growing elderly kidney transplant population, and argue that the designers of future clinical trials should carefully consider

whether age-exclusion criteria are warranted. These findings were presented at the 2010 American Transplant Congress, and the manuscript will be submitted this fall to the *American Journal of Transplantation.*

Dr. Reese also studies age-related barriers to live-donor kidney transplantation. In a single center study, he found that older patients were less likely to attract live donors, and among older patients with live donors, these patients were less likely to undergo renal transplantation. This study was accepted for publication in the *Clinical Journal of the American Society of Nephrology.*

Advancing geriatric education

In the interests of promoting awareness of geriatric clinical issues and geriatric research, Dr. Reese has given a series of talks on geriatric topics at the University of Pennsylvania during the past year. He delivered renal grand rounds, focusing on the subject of facilitating the transition to end-stage renal disease care among older patients. He led a seminar for geriatrics fellows on clinical issues related to the care of elderly dialysis patients. Lastly, he delivered geriatrics grand rounds, focusing on the subject of how the LYFT proposal and subsequent policies may affect geriatric renal transplant patients.

Other

Using funds from the ASN-ASP grant, Dr. Reese also hired a research coordinator. This coordinator has excellent research skills and experience, and has been instrumental in helping Dr. Reese accomplish research goals related to this grant. His responsibilities will include updating necessary documentation for the institutional review board, preparing and presenting preliminary findings, and researching other related topics for future research efforts in geriatric nephrology.

Determinants of the Decision to Accept a Kidney from a Donor at Increased Risk for Blood-Borne Viral Infection

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Background and objectives: The use of kidneys from donors at increased risk for viral infections (DIRVI) such as HIV could increase the number of transplants and decrease waiting times. This study aimed to identify the proportion of kidney transplant candidates that would accept a kidney from a DIRVI and the factors that influenced this decision.

Design, setting, participants, & measurements: Conjoint analysis was used to assess the conditions in which renal transplant candidates would accept a DIRVI kidney. Candidates completed 12 scenarios in which the waiting time for a kidney, the donor age as a surrogate for kidney quality, and the risk of contracting HIV were systematically varied.

Results: Among 175 respondents, 42 (24.0%) rejected DIRVI kidneys under all conditions, 103 (58.9%) accepted DIRVI kidneys under some conditions, and 31 (17.7%) always accepted DIRVI kidneys. In multivariable logistic regression, patients were more likely to accept a DIRVI kidney when waiting time was longer, the donor was younger, and HIV risk was lower ($P < 0.01$ for each variable). Patients on dialysis ($P < 0.01$) and older patients ($P = 0.04$) more commonly accepted DIRVI kidneys, but self-rated sense of health was not associated with DIRVI kidney acceptance.

Conclusions: Most renal transplant candidates would accept a DIRVI kidney under some circumstances. These findings suggest that recipients can be allowed to make prospective choices regarding DIRVI kidney acceptance without hindering placement of these organs.

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The use of kidneys from deceased donors categorized as having increased risk for blood-borne viral infections (DIRVI) such as HIV could increase access to renal transplantation and decrease waiting times for everyone on the list (1–3). However, expanding DIRVI kidney use requires that transplant candidates accept the possible increased risks of such organs to gain the other benefits from transplantation. It is unknown what proportion of transplant candidates would accept DIRVI kidneys or what factors influence such decisions.

In 1994, a report from the Public Health Service (PHS) and Centers for Disease Control (CDC) advised against transplantation of organs from seronegative donors with a history of specific behaviors and health conditions associated with elevated risk for HIV infection "unless the risk to the recipient of not performing the transplant is deemed to be greater than the risk of HIV transmission and disease" (Table 1). This recommendation was based on the recognition that antibody tests for HIV used on donors have limited sensitivity, particularly during the window period after infection (4). The risk factors for viral infection published by the PHS/CDC have also been used to identify donors at higher risk of hepatitis B (HBV) and hepatitis C (HCV). However, since the PHS/CDC issued this recommendation, the wait list for kidney transplants has grown rapidly, better treatments for blood-borne viral infections have become available, and patients with pre-existing HIV and HCV have enjoyed superior outcomes from kidney transplantation than from remaining on dialysis (5–8). Additionally, nearly 10% of the overall pool of kidneys procured from deceased donors are recovered from DIRVIs (9). These facts suggest that policy and practice related to DIRVI kidney use should be re-evaluated.

A decision analysis of wait-listed patients showed that accepting DIRVI kidneys would lead to longer survival, although this strategy posed a higher risk of HIV infection compared with refusing these organs. However, this decision analysis rested on the untested assumption that 5% of the wait-listed population would accept a DIRVI kidney (2). Importantly, from the societal perspective, the benefits obtainable through the use of high-quality DIRVI kidneys are directly related to how many eligible wait-listed patients would actually accept these organs.

We hypothesized that ESRD patients would more commonly

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Table 1. Criteria for a seronegative deceased donor categorized as increased risk for HIV infection (4)

1. Men who have had sex with another man in the preceding 5 years
2. Persons who report nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years
3. Persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates
4. Men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years
5. Persons who have had sex in the preceding 12 months with any person described in items 1 to 4 above or with a person known or suspected to have HIV infection
6. Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, nonintact skin, or mucous membrane
7. Inmates of correctional systems

accept a DIRVI kidney when donor HIV risk was lower, donor age was lower, when candidate self-rated state of health was worse, and when candidate waiting time was longer.

Materials and Methods

We performed a cross-sectional study of adult kidney transplant candidates at the University of Pennsylvania. We used conjoint analysis to assess the conditions in which candidates would accept a DIRVI kidney. The University of Pennsylvania Institutional Review Board approved the study.

Pilot Study

We first developed a baseline description of the decision to accept a kidney from a DIRVI. The description included statements that a DIRVI has negative serologic tests for HIV and a risk factor for HIV infection (*e.g.*, intravenous drug use or having been a prison inmate) and that patients who consider a DIRVI kidney should weigh the benefit of getting a kidney sooner against the risk of infection. This baseline description was refined with input from decision scientists and transplant nephrologists at our institution.

Two investigators (T.T. and M.L.) presented this description to 20 kidney transplant candidates and solicited feedback regarding clarity. Additionally, using a standard series of open-ended questions, these investigators interviewed the 20 candidates about what specific factors would be most important in deciding whether to accept a DIRVI kidney. The most important factors were (*1*) risk of HIV infection, (*2*) factors related to the quality of the kidney, and (*3*) waiting time.

Questionnaire and Experimental Design

On the basis of the pilot results, we developed 12 scenarios in which we systematically varied the quality of the DIRVI kidney, the anticipated waiting time for the next offer of a kidney if the DIRVI organ was declined, and the risk of contracting HIV from the organ. We used donor age and prior history of a cerebrovascular accident (CVA) as a surrogate for kidney quality (the donor was a 55-year-old with a history of CVA or an 18-year-old). The anticipated waiting time for the next kidney offer was varied between 1, 3, and 5 years. We chose 1 year as the lower bound because re-evaluation candidates may have accumulated substantial waiting time. We chose 5 years as the upper bound because this is the median time to kidney transplantation for candidates with the longest wait (blood types O or B) in our region. We chose 3 years as the intermediate value because it corresponds to waiting time for type A blood and because an equal interval between the lower and upper bounds simplified the analysis (10).

The stated risk for HIV infection was 1 in 1500 or 1 in 10,000 on the basis of the extreme estimates for injection-drug-use donors and inmate donors that were provided in a decision analysis by Schweitzer *et al.* (2). To facilitate comprehension, we informed respondents that the 1-in-1500 risk was comparable to the lifetime probability of dying in a fire and the 1-in-10,000 risk was comparable to the lifetime probability of dying from drowning in a bathtub (11).

In each scenario, the respondent was asked to make a binary choice to accept the DIRVI kidney or to decline and continue waiting the specified time until the next organ became available.

Participants and Administration of the Instrument

We pilot-tested this instrument among nurses, physicians, and social workers to ensure the appropriateness of the content. We tested it among an additional 20 transplant candidates for clarity (Appendix 1 presents a description and an example scenario).

From September 2008 until January 2009 we recruited renal transplant candidates waiting to meet with the physicians and social workers. Before being approached for participation, candidates coming for their initial visit had listened to a 45-minute presentation about the advantages and disadvantages of accepting various types of kidneys (from expanded criteria donors, donors with cardiac death, DIRVI). Printed information about DIRVI organs was not provided. Investigators attempted to recruit all candidates, but some patients were occupied with clinical meetings or phlebotomy.

Demographic and Clinical Data

The questionnaire asked the participant to report education, income, history of dialysis, prior transplant evaluation, prior transplantation, and sense of health (by rating on a visual analog scale how well he or she felt during the past year; the scale went from 1 representing "the worst you could imagine feeling" to 10 representing "the best you have ever felt in your life").

We abstracted information about age, race, gender, cause of ESRD, HCV, and HIV infection from the electronic medical record.

Analyses

Our central analytic approach was to use conjoint analysis—a technique grounded in economic theory and developed for marketing research—to evaluate patients' global preferences for accepting a DIRVI kidney and the independent influences of the three primary attributes (12,13). All analyses were performed using Stata 10.0 (Stata Corporation, College Station, TX).

To explore the possibility of a nonlinear relationship between patient age and high-risk organ acceptance, we explored age as a continuous variable and an ordinal variable in which participants were divided into quartiles of approximately equal size. Because the continuous sense of health variable was left-skewed, we converted this variable into three approximately equal tertiles (1 to 6, 7 to 8, and 9 to 10). Education was also left-skewed and grouped into three approximately

equal categories (no college education, some college education, and finished college).

We used the *t* test to compare the means of continuous variables between scenarios in which respondents accepted or rejected a DIRVI kidney. We used the χ^2 test to compare categorical variables. We then fit a multivariable (MV) logistic regression model for the binary outcome of DIRVI kidney acceptance. We fit the model with (*1*) all variables related to our hypotheses, (*2*) those with unadjusted associations with acceptance of a DIRVI kidney in which $P < 0.15$, and (*3*) a prespecified interaction between HIV risk and waiting time. We used the robust variance estimator to account for the fact that the 12 responses of each participant were not independent (14). The Hosmer–Lemeshow goodness of fit test for calibration was acceptable for all models ($P > 0.05$).

Lastly, to evaluate how patients view a tradeoff between a higher quality organ with higher HIV infection risk *versus* a lower quality organ with lower risk, we used a χ^2 test to compare responses to scenarios in which the donor was 18 years old and HIV transmission risk was 1 in 1500 to scenarios in which donors were 55 years old with a history of CVA and the HIV transmission risk was 1 in 10,000.

Sample Size

We based our sample size estimates on the hypothesis requiring the most participants: the interaction of waiting time by risk of HIV. Enrolling only 30 participants would have provided 90% power to detect a waiting-time-by-HIV risk interaction with an odds ratio ≤0.67 or ≥1.5. This estimate accounts for the inflation required to detect statistical interactions rather than main effects (15), the expected intraclass correlation among responses within each individual (based on our pilot), and the number of scenarios administered to each respondent (12). However, we sought a sample larger than 30 to ensure power to detect between-respondent differences (*e.g.*, among men *versus* women).

Missing Data

A small proportion of participants did not provide answers to demographic and clinical questions. A total of 16 patients (9.1%) did not report income, 7 (4.0%) did not indicate sense of health, and 6 (3.4%) did not report education. For our final regression model, we used multiple imputation (using the "ice" command in Stata) (16). We also performed secondary analyses restricted to individuals with complete information and analyses in which missing data were assigned extreme values.

Results

Three hundred and seven renal transplant candidates came to clinic on recruitment days and 220 were approached about study participation. Among this group who were approached, 27 refused to participate, 9 left the clinic without returning the study materials, 5 did not respond to all scenarios, and 4 could not read English and no translator or family member was present to help. The study cohort consisted of the remaining 175 (79.5%) candidates.

There were no differences between study participants and patients who did not enroll in terms of their age, gender, race, HIV or HCV infection, diabetes as a cause of ESRD, or history of prior transplantation. Participants were less likely than nonparticipants to be in clinic for annual re-evaluation *versus* a primary transplant evaluation (44.0% of participants *versus* 71.2% of nonparticipants were coming for a re-evaluation, $P < 0.01$).

The mean age of participants was 52.4 years (±1.0) and 116 (66.3%) were men. One hundred one participants (57.7%) were white. The median education level was having completed some years of college. Sixteen participants (9.1%) had a history of a prior failed kidney transplant (Table 2).

Table 3 reports the percentage of participants who would accept the kidney in each of the 12 scenarios presented. Forty-two (24.0%) would not accept a DIRVI kidney in any scenario, 103 (58.9%) would accept a DIRVI kidney in some scenarios, and 31 (17.7%) would accept a DIRVI kidney in all scenarios.

Unadjusted Analyses

Lower donor HIV risk; younger donor age; increased waiting time for the next offer; and participant characteristics of nonblack race, being on dialysis, never having had a prior transplant or undergone evaluation at another institution, and com-

Table 2. Demographic and clinical characteristics of study cohort

Characteristic	Final Cohort (n = 175)
Age in years (SEM)	52.4 (1.0)
Male (%)	116 (66.3)
Race (%)	
white	101 (57.7)
African American	58 (33.1)
Hispanic	6 (3.4)
other	10 (5.7)
Cause of ESRD (%)	
diabetes	60 (34.3)
GN	48 (27.4)
hypertensive nephrosclerosis	19 (10.9)
polycystic kidney	14 (8.0)
other (%)	34 (19.4)
HCV positive (%)	14 (8.0)
HIV positive (%)	1 (0.6)
Median educational level	Some college
Median annual household income	$25,000 to 49,999
Dialysis (%)	101 (58.7)
if dialysis, number of years (SEM)	2.16 (0.11)
Evaluation status at our center (%)	
new evaluation	98 (56.0)
re-evaluation	77 (44.0)
Prior transplant evaluation at another center (%)	47 (27.8)
Prior renal transplant	16 (9.1)
Median sense of health in past year (1 to 10 scale)[a]	7

[a]Patients indicated their health on a visual analog scale, with 1 representing "the worst you could imagine feeling" and 10 representing "the best you have ever felt in your life."

Table 3. Percentages of participants by scenario who would accept a kidney offer

Scenario Number	Scenario Attributes			Outcome
	Risk of HIV Infection	Donor Age (years)	Waiting Time (years)	Percent Who Would Accept
1	1/1500	18	5	61.7
2	1/1500	18	3	55.4
3	1/1500	18	1	24.6
4	1/10,000	18	5	73.7
5	1/10,000	18	3	70.3
6	1/10,000	18	1	42.9
7	1/1500	55[a]	5	45.1
8	1/1500	55[a]	3	42.3
9	1/1500	55[a]	1	25.1
10	1/10,000	55[a]	5	56.6
11	1/10,000	55[a]	3	56.6
12	1/10,000	55[a]	1	32.6

[a]These donors were also specified to have died from a CVA.

ing for initial evaluation (*versus* an annual re-evaluation) were associated with greater likelihood of accepting DIRVI kidneys (all $P < 0.01$).

There were steady increases in the proportions of patients accepting DIRVI kidneys across age quartiles: acceptances rates were 38.6% for individuals aged 20 to 45 years, 46.6% for ages 46 to 55 years, 50.5% for ages 56 to 62 years, and 61.6% for ages 63 to 82 years ($P < 0.01$). Similarly, there were steady increases in the acceptability of a DIRVI kidney across health tertiles: acceptance rates were 45.2% among those with the worst self-reported health *versus* 48.2% among those with intermediate health and 56.1% among those with the highest self-rated health ($P < 0.01$). Age and sense of health were entered as ordinal variables in our final model.

Income was not linearly associated with likelihood of accepting a DIRVI kidney. Among individuals with income <$15,000, 41.3% of DIRVI kidney offers were accepted *versus* 42.6% of offers among those with income between $15,000 and $24,999, 53.0% of offers among those with income between $25,000 and $49,000, 51.1% of those with income between $50,000 and $74,999, and 55.3% of those with income ≥$75,000 ($P < 0.01$). Because of the change in likelihood of accepting a DIRVI kidney among individuals with income ≥$25,000, we categorized income as a binary variable (defined by this threshold) in our MV regressions.

Participant education, gender, and HCV infection were not associated with DIRVI kidney acceptance. Only one patient was HIV infected, so we did not examine the association of this attribute with the outcome. The association of diabetes with DIRVI kidney acceptance met our criterion for inclusion in the MV model ($P = 0.07$).

An almost equal proportion of participants accepted DIRVI kidneys in scenarios presenting a younger donor (higher quality) with higher HIV risk (47.2%) as compared with scenarios with an older donor (lower quality) and lower HIV risk (48.6%, $P = 0.67$).

Multivariable Logistic Regression

Longer waiting time ($P < 0.01$), lower donor age ($P < 0.01$), lower donor HIV risk ($P < 0.01$), participant being on dialysis ($P < 0.01$), and older participant age ($P = 0.04$) remained associated with the outcome (Table 4).

Secondary Analyses Related to Missing Data

Sensitivity analyses and secondary analyses restricted to patients with complete data showed similar results to those from the primary model.

Secondary Analyses of Education and Lack of Variation in Responses to Scenarios

We evaluated whether education level was associated with choosing a dominant response to the questionnaire; that is, to accept or reject all kidney offers regardless of scenario. We reasoned that if less educated participants had less comfort handling numerical concepts, they would be more likely to make the same choice regardless of the risks; however, no association was found between education and the probability of a dominant response ($P = 0.57$).

Discussion

The high mortality of ESRD and the rising waiting time for a kidney transplant have created an urgent need to expand the pool of kidneys for transplantation (6,17,18). Increasing DIRVI kidney use could improve access to kidney transplantation, but only if candidates are willing to accept these organs. Our results reveal that people make rational tradeoffs between the risks conferred by DIRVI kidneys and their virtues (*e.g.*, shorter waiting times).

These empirical results indicate that kidney transplant candidates can be allowed to make prospective choices regarding DIRVI kidney acceptance without hindering placement of these organs (1). Specifically, at the time of transplant evaluation, physicians and patients should discuss

Table 4. Characteristics associated with acceptance of a DIRVI kidney in MV logistic regression

Characteristic	Odds Ratio	Confidence Interval	*P* Value
5-year waiting time[a]	4.20	2.97 to 5.94	<0.01
3-year waiting time[a]	3.50	2.57 to 4.75	<0.01
Dialysis	2.88	1.71 to 4.84	<0.01
Lower risk of HIV infection from kidney[b]	2.12	1.61 to 2.81	<0.01
18-year-old donor[c]	1.78	1.43 to 2.23	<0.01
Participant age (per additional quartile of older age)	1.28	1.02 to 1.63	0.04
Higher income[d]	1.33	0.79 to 2.22	0.28
Sense of health (per additional tertile of feeling healthier)[e]	1.29	0.90 to 1.87	0.17
Cause of ESRD: diabetes	1.27	0.76 to 2.13	0.37
Interaction of level of HIV risk and duration of waiting time[f]	0.97	0.91 to 1.03	0.28
Re-evaluation[g]	0.93	0.55 to 1.59	0.79
Prior transplant or evaluation elsewhere[h]	0.71	0.41 to 1.23	0.22
Black race	0.71	0.42 to 1.22	0.21

[a]Reference group: 1-year estimated waiting time until next offer of a kidney transplant.
[b]Lower risk = 1 in 10,000, *versus* reference group of 1 in 1500 chance of HIV.
[c]Reference group: 55-year-old donor with history of CVA.
[d]Income was dichotomized as ≥$25,000 or not.
[e]Sense of personal health was divided into three strata with higher strata representing better health; the odds ratio represents the odds associated with increasing one health stratum.
[f]The odds ratio of the interaction term assesses the extent to which the effect of HIV risk and waiting time on the outcome is more or less than the additive effect of these two variables in the model.
[g]Patients returning to center for annual evaluation.
[h]Patient had undergone prior renal transplant evaluation at another institution (leading to a prior failed transplant or to getting a second opinion at our institution).

whether or not the patient wishes to be considered for DIRVI or other nonstandard kidneys and listed accordingly. These discussions should incorporate the best available estimates of what the patient's current and projected quality of life is and what his wait time for an organ might be based on blood type and other relevant factors. Additionally, because waiting time and quality of life can change, transplant candidates should be encouraged to readdress their decisions to accept or decline DIRVI organs during interval evaluations as needed.

The finding that patients on dialysis were more likely to accept DIRVI kidneys may reflect their heightened desires for change given the low overall quality of life associated with hemodialysis (19). The fact that self-rated sense of health was not also associated with DIRVI kidney acceptance in MV analysis may be due to the insensitivity of this measurement or to its close correspondence with other more determinative predictors of organ acceptance (*e.g.*, age).

Older transplant candidates in our study may have been more likely to accept the potential risks associated with DIRVI kidneys because they are often encouraged (in our center and others) to consider expanded criteria donor kidneys that also involve tradeoffs of risk and benefit. Alternatively, older candidates may recognize that age is a risk factor for deterioration in health while waiting for a kidney transplant. These observations merit further study to clarify the roles of current health and quality of life in guiding organ acceptance decisions.

We found that patients were equally likely to accept a DIRVI kidney from a younger donor with higher chance of HIV infection and from an older donor with a lower chance of having HIV. Given that donor age is a powerful predictor of the likelihood of poor allograft outcomes, participants appeared willing to choose a substantially greater risk of allograft failure to avoid a tiny increase in absolute risk of HIV infection. This finding may reflect aversion to any possibility of HIV infection and its associated stigma or could represent a lack of understanding about increased likelihood of allograft failure and delayed graft function with kidneys from older donors. Alternatively, it is possible that our study design, which included only two levels of infection risk and donor age, was not sufficiently sensitive to determine the combined effects of these factors on patient decision-making.

A prior study by our group revealed that DIRVI kidneys are used by many transplant centers, but this usage varies widely (20). Our results indicate that a much greater proportion of transplant candidates would consider a DIRVI kidney than previously suggested (2). Efforts to maximize the appropriate use of DIRVI kidneys will depend on several factors, including processes of informed consent, procurement decisions by donor service organizations, education about the relative benefits and hazards posed by DIRVI and other organ types, readiness of transplant physicians to offer DIRVI kidneys, and recipient willingness to accept a DIRVI kidney (9,21). In particular, further study of the readiness of transplant professionals to use these organs is needed to understand variation in their use.

Our study has limitations. First, our results consist of responses to hypothetical scenarios. However, participants were those patients for whom the decision is relevant, and the results were largely consistent with our clinical intuitions about what patients would do in real settings. Second, we compared the one-time risks of contracting HIV from a kidney donor to the lifetime risks of dying in a fire or drowning in a bathtub. It is possible that these dissimilar time horizons could have made the scenarios seem less plausible, but we believe this approach clarified the meaning of small risks, particularly for participants with limited numeracy. Our results also indicate that participants were paying close attention to differences in HIV transmission. Third, our scenarios only focused on HIV risk, although accepting a DIRVI kidney may pose higher risk of exposure to other blood-borne viruses such as HCV and HBV. We presented the risks this way for simplicity and because we believed that, for participants, the social stigma and health hazards of HIV infection were at least as great as those of other infections. Nonetheless, transplant professionals counseling patients about DIRVI kidney use should also discuss the risk of HCV and HBV. Fourth, we studied participants from a single center. Although it is possible that results might not be generalizable to all other centers, our center performs approximately 200 kidney transplants a year and attracts a racially diverse population from a large geographic area. We also acknowledge that our results may not be generalizable to patients undergoing re-evaluation because study participants were more likely to be coming for a primary evaluation than nonparticipants. On the other hand, the lower participation by re-evaluation patients may have been attributable to the shorter times required for re-evaluation visits and hence reduced opportunities for us to request participation from these patients rather than differences in willingness to accept a DIRVI kidney.

Our study also has strengths. We designed the scenarios after considerable pilot testing. We had a large sample size. In addition, we used conjoint analysis—a statistically powerful approach that has advantages over simple questionnaires in that participants reveal, rather than express, preferences while simultaneously considering multiple factors that may influence complex decisions (13,22).

In conclusion, despite recent negative publicity about donor-derived viral infections, most renal transplant candidates would consider accepting DIRVI kidneys under some conditions. When listing patients for kidney transplantation, transplant physicians should openly discuss the possibility of being listed as eligible to receive DIRVI organs—with the benefits and risks associated with this choice—without fearing that such conversations will undermine the ability to place these organs.

Appendix 1

Introductory Narrative and Example of a Scenario[a]

Kidney transplants improve the quality of life for patients with severe kidney disease and help them live longer. However, there are not enough kidneys for all of the people who need them. One way to get a kidney transplant sooner is to accept a kidney from someone with a higher chance of being infected with a virus, like HIV.

We are interested in learning more about whether you would be willing to accept a kidney that was donated by someone with a chance of having a viral infection such as HIV. We want to know how you think about this tradeoff. Of course, everyone would prefer to receive a kidney that had no risk of transmitting an infection. But what if that meant you couldn't get a kidney at all? Would you be willing to settle for a kidney that had a slightly higher chance of transmitting an infection?

These kidney donors are called Centers for Disease Control "increased risk" donors. The donors are called "increased risk" because of recent behavior—such as intravenous drug use or having gone to prison—that might have exposed them to a virus. *We are not talking about kidneys that we know are infected with HIV*. We test for HIV, and *no one uses kidneys from donors who test positive*. But it turns out that the HIV tests are not perfect, and so the safest approach is also to avoid kidneys from people who test negative for HIV, but who have engaged in behaviors that might mean they actually have HIV although the test is negative.

The chance of getting HIV from one of these "increased risk" donors is very small. Remember, these donors have negative tests for HIV. Doctors are not sure what the exact risk of infection is with these donors, but one study estimated that a patient who receives a kidney from a donor who was an intravenous drug user would have a **1 in 1500** chance of getting HIV. That study also estimated that a patient who receives a kidney from a donor who has gone to prison has a **1 in 10,000** chance of getting HIV.

Please look through the following 12 scenarios. Each scenario will ask you if you are willing to accept a kidney from an "increased risk" donor.

Scenario 1

Imagine that you are on dialysis.

Your doctor now calls to offer you a kidney transplant from an **18-year-old man**.

This kidney donor has a **1 in 1500** chance of being infected with HIV. In other words, 1499 people out of the same 1500 will *not* get HIV. This risk is similar to your lifetime risk of dying in a fire.

Your doctor predicts that you will be on the wait list for **5 more years** before receiving another offer for a kidney transplant.

What Will You Do?

1. I will accept this kidney.
2. I will wait for a normal-risk kidney. I understand that I will probably wait 5 more years before I receive an offer for a normal risk kidney. I understand that I may get sick or even die while waiting for another kidney.

[a]Each study participant was presented 12 scenarios in which the donor age, chance of infection, and anticipated years on the waiting list before another offer of a transplant were varied.

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Disclosures

None.

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Specific Aims

Specific Aim 1. Test the hypothesis that a novel CMR-based prediction model developed from the ICELAND MI cohort improves prediction of: 1) mortality, and 2) either sudden cardiac death or ICD shock, compared to models with only clinical indices.

Progress:

This aim requires the interpretation and measurement of a variety of CMR covariates. We (myself and others) have meticulously quantified the size (expressed as % of LV mass) of all infarcts in the ICELAND MI cohort using a post processing tool (Feature Analysis and Combined Thresholding—'FACT') validated against histologic gold standards as previously reported (Hsu,L-Y, et al. JRMI 2006; Hsu,L-Y, et al. JRMI 2006). The border zones remain to be measured for these infarcts but involve simply rerunning the FACT algorithm using the same regions of interest, but lowering the threshold (Schmidt A, et al. Circulation 2007;). We also have completed both semi quantitative visual scores of infarct size (Wagner A, et al. Lancet 2003). Non myocardial infarction-related scar has previously been noted for all 950 participants. Ejection fraction and left ventricular mass have also been measured and recorded previously.

Specific Aim 2. Test the hypothesis that the novel CMR based prediction model(s) developed above will generalize to our local University of Pittsburgh (validation) cohort. While there will be clear differences compared to Iceland subjects, we hypothesize that outcomes nonetheless will be governed more by CMR findings (phenotypes) than clinical variables.

Progress:

We have enrolled ~480 subjects in our local registry which permits long term follow-up, reflecting the growth of the local (clinical) CMR program at the University of Pittsburgh. At this rate, we should enroll over 2500 subjects in the local validation cohort by the project's end. Annual volume is >800 cases, and we have been enrolling >95% of the clinical caseload into our local research cohort.

We have encountered an unanticipated problem. The web based computer system that we will use for reporting and archiving CMR reports as well as all of the associated patient 'point of care' demographic and comorbidity data has not yet become operational, in part due to the complexities and resources needed for integrating it into the UPMC IT infrastructure that serves multiple hospitals. Importantly, this reporting system renders exporting subject data into statistical software (SAS) a very simple procedure. Dr. Rasu Shrestha, Medical Director of Digital Imaging Informatics has prioritized this project as an enterprise application and has assigned computer programmers to execute the local integration of this software. I expect to go live with our new CMR reporting system in late July. Yet, the backlog of 420 subjects already scanned and enrolled in our registry will need to manually entered into the system to compile the data electronically to make it accessible for statistical for analysis. I will devote whatever resources I have (including seed funds) to ensure that this matter is resolved successfully.

Specific Aim 3. Test the hypothesis that novel CMR measures of diffuse interstitial fibrosis and adverse cardiac remodeling (i.e. the gadolinium partition coefficient, lambda) will improve further the CMR prediction model developed above. Diffuse myocardial fibrosis alters the electromechanical properties of the myocardium and leads to anisotropic conduction. Techniques for measuring diffuse interstitial myocardial fibrosis have only recently emerged. Fibrosis causes gadolinium to accumulate in the myocardium thus shortening T1 relaxation and increasing lambda. Thus, CMR may be able to quantify myocardial fibrosis comprehensively. Whether measuring lambda of non infarcted myocardium without evident scarring further refines risk stratification is unknown.

Progress:

We currently measure the myocardial partition coefficient of gadolinium contrast routinely and reliably. Initially, we encountered some challenges, but we have since successfully overcome a series of unanticipated problems after extensive validation work. First, we discovered that using signal intensity as a surrogate for T1 relaxation as described by Thornhill et al. (MRM 2004) was not at all robust. The main issue was that the blood pool precontrast signal intensity was highly variable due to artifacts presumably related to flow in the ventricular cavity of even the descending aorta. This artifact resulted in poor reproducibility and inaccuracy, and ultimately a lack of confidence in the signal intensity-based measurement. Of course, this problem did not appear in preliminary studies involving static phantoms which cannot generate a flow-related artifact.

Since signal intensity on T1 weighted images was a poor surrogate to actual T1 measures, we resorted to using T1 measurements to compute the partition coefficient (Jerosch-Herold M, et al. AJP-HCP 2008):

Lambda=change in myocardial relaxivity/change in blood pool relaxivity
where change in relaxivity=(1/postcontrastT1) - (1/precontrastT1)

However, since our Siemens scanner was one the first in the world to receive the newer operating system (VB17) in July 2009, we essentially upgraded out of all research pulse sequences, including the modified Look-Locker inversion recovery pulse sequence ('MOLLI;' Messroghli D, et al. JMRI 2007) used to measure myocardial and blood pool T1 used to compute the partition coefficient.

We finally received the pulse sequence in January 2010 and fortunately had all of the requisite paperwork in place to permit its use (IRB protocol, Master Research Agreement between Siemens and the University of Pittsburgh, etc). Since then, we have established that this pulse sequence (described in detail by Messroghli D, et al. MRM 2004) works very well for T1 measurement. Since this pulse sequence employs an inversion pulse with an SSFP readout (where the signal intensity is governed by the ratio of the square root of T2/T1), we validated the ability of this pulse sequence to measure T1 by creating CuSO4 phantoms-agar phantoms with both T1 and T2 values nearly identical to myocardial and blood T1 and T2 pre and post contrast. We compared the 'MOLLI' T1 to the 'gold standard' method of T1 measurement using a spin echo inversion recovery sequence where the radio frequency inversion pulses are spaced 10 seconds apart (to allow complete recovery and avoid saturation between inversion

pulses), where one line of k space is acquired per inversion pulse. Results were very similar using MOLLI instead of spin echo (clinically impossible since each T1 measurement takes ~6 hours) yielded a slight underestimation of the partition coefficient, rendering the MOLLI slightly less sensitive compared to the spin echo ideal. We also demonstrated that sampling T1 recovery with 6-7 heart beats was at least as effective as 11 heart beats (i.e., 5+1 or 4+2+1, versus 3+3+5 as has been previously used by Messroghli et al., see attached Figure). This finding is very important to extend T1 measurements to sicker subjects in our cohort who might find breath holding too challenging (for 11 versus 6-7 heart beats).

We computed T1 for myocardial and blood pool regions of interest by fitting plots of signal intensity against effective inversion times employing custom Matlab code using a Marquardt-Levenberg least squares fitting algorithm (Deichmann R and Haase A, J Magnetic Resonance, 1992) courtesy of Dr. Sanjeev Shroff, (Chair of Bioengineering, University of Pittsburgh) who provided the Matlab code.

Next, armed with robust T1 measurement methods, we measured myocardial and blood partition coefficients in volunteers by establishing steady state using a gadolinium contrast bolus following an infusion. Steady state was identified when the slope of serial T1 measures were zero. Importantly, we found an identical partition coefficient regardless of whether it was measured during steady state infusion or after a bolus. This finding confirms that equilibration occurs rapidly between the blood pool and myocardium compared to the relatively slow renal clearance of contrast; achieving steady state is a prerequisite for accurate measurement. This finding is also critically important for integrating partition coefficient measurement into clinical use since it can easily be integrated into routine CMR scanning protocols most of which typically include a bolus of gadolinium contrast rather than a tedious infusion. We also have demonstrated in healthy volunteers as well as patients that the partition coefficient is stable for the 10-45 minutes after the contrast bolus and highly reproducible. We usually obtain a standard deviation of <1% for repeated measures in any given patient or subject. All data indicate that lambda is independent of time and dose of contrast

Lastly, since the hematocrit may influence the partition coefficient, we have been routinely collecting hematocrits at the time of CMR scanning for measuring the extracellular, extravascular volume fraction, ‘Ve’ (which increases as fibrosis expands the extracellular, extravascular volume fraction, ‘Ve’). I believe Ve is the measure of choice for measure diffuse interstitial fibrosis since lambda is influenced by the hematocrit which displaces gadolinium contrast from the blood pool, but not from the myocardial extracellular space. The partition coefficient lambda and extracellular, extravascular volume fraction, Ve, are related by the following equation (see Jerosh-Herold M, et al. AJP-HCP 2008 for derivation): Ve=[Lambda x (1-hematocrit) x 1.05] – 0.045. Hematocrit and Ve are measured on all patients participating in our local registry since January 2010.

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RESEARCH Open Access

Myocardial extravascular extracellular volume fraction measurement by gadolinium cardiovascular magnetic resonance in humans: slow infusion versus bolus

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Abstract

Background: Myocardial extravascular extracellular volume fraction (Ve) measures quantify diffuse fibrosis not readily detectable by conventional late gadolinium (Gd) enhancement (LGE). Ve measurement requires steady state equilibrium between plasma and interstitial Gd contrast. While a constant infusion produces steady state, it is unclear whether a simple bolus can do the same. Given the relatively slow clearance of Gd, we hypothesized that a bolus technique accurately measures Ve, thus facilitating integration of myocardial fibrosis quantification into cardiovascular magnetic resonance (CMR) workflow routines. Assuming equivalence between techniques, we further hypothesized that Ve measures would be reproducible across scans.

Methods: In 10 volunteers (ages 20-81, median 33 yr, 3 females), we compared serial Ve measures from a single short axis slice from two scans: first, during a constant infusion, and second, 12-50 min after a bolus (0.2 mmol/kg gadoteridol) on another day. Steady state during infusion was defined when serial blood and myocardial T1 data varied <5%. We measured T1 on a 1.5 T Siemens scanner using a single-shot modified Look Locker inversion recovery sequence (MOLLI) with balanced SSFP. To shorten breath hold times, T1 values were measured with a shorter sampling scheme that was validated with spin echo relaxometry (TR = 15 sec) in CuSO4-Agar phantoms. Serial infusion vs. bolus Ve measures (n = 205) from the 10 subjects were compared with generalized estimating equations (GEE) with exchangeable correlation matrices. LGE images were also acquired 12-30 minutes after the bolus.

Results: No subject exhibited LGE near the short axis slices where Ve was measured. The Ve range was 19.3-29.2% and 18.4-29.1% by constant infusion and bolus, respectively. In GEE models, serial Ve measures by constant infusion and bolus did not differ significantly (difference = 0.1%, $p = 0.38$). For both techniques, Ve was strongly related to age ($p < 0.01$ for both) in GEE models, even after adjusting for heart rate. Both techniques identically sorted older individuals with higher mean Ve values.

Conclusion: Myocardial Ve can be measured reliably and accurately 12-50 minutes after a simple bolus. Ve measures are also reproducible across CMR scans. Ve estimation can be integrated into CMR workflow easily, which may simplify research applications involving the quantification of myocardial fibrosis.

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Introduction

Emerging techniques in cardiovascular magnetic resonance (CMR) offer new and important opportunities to quantify pathologic myocardial fibrosis but require further understanding to optimize their integration into CMR workflow routines. Myocardial fibrosis, characterized by expansion of the myocardial extracellular matrix and accumulation of interstitial collagen, is the hallmark of pathologic remodeling [1]. This derangement alters electrical and mechanical function. Extracellular collagen, the principal constituent of the expanded extracellular matrix [1], blocks electrical conduction [2-7], constitutes the substrate for reentry and lethal ventricular arrhythmia [8], and stiffens the myocardium [1].

While CMR with late gadolinium enhancement (LGE) can detect large macroscopic foci of myocardial fibrosis [9], it cannot detect the full spectrum of myocardial fibrosis. LGE relies on relative differences in signal intensities expressed in arbitrary units and employs the myocardium with lowest signal intensity as a reference for normality, regardless of the degree of fibrosis contained within. Two lines of evidence underscore a need for alternative techniques beyond LGE. First, a recent study indicated that collagen biomarkers were more sensitive than LGE for detecting early myocardial fibrosis in hypertrophic cardiomyopathy [10]. Second, roughly half of the excess collagen in the setting of dilated cardiomyopathy is deposited diffusely between myocytes as opposed to focally [11], therefore undetectable by LGE.

Standard extracellular gadolinium (Gd) contrast tracks collagen at the microscopic level with high fidelity without an apparent critical mass needed for detection [12], thereby offering an opportunity to use Gd concentration as a robust indicator of myocardial fibrosis burden. Indeed, recently developed methods [13-15] assess the volume fraction of extravascular extracellular matrix (Ve) in human myocardium (with standard contrast agents) by exploiting the linear relationship between change in relaxivity and Gd concentration. These methods, however, require steady state equilibrium between the plasma and myocardial interstitium for successful Ve measurement. Whether a lengthy continuous intravenous infusion is needed to achieve steady state, or whether a simple bolus is sufficient to achieve steady state equilibrium remains uncertain, but an important issue for several reasons: First, introducing a lengthy infusion imposes additional burden on patients and considerable constraints on routine CMR workflow routines. Second, these data are important to interpret results from studies employing either the bolus [13,15] or infusion [14] techniques. Third, if the Gd dose reserved for LGE is lowered (e.g., halving a 0.2 mmol/kg dose to 0.1 mmol/kg bolus) [14] to allocate a portion for the subsequent infusion, the sensitivity of LGE may decline since doses as low as 0.1 mmol/kg have reduced sensitivity for myocardial infarction [16].

Given the slow renal clearance of Gd, its low molecular weight, and rapid dispersion throughout tissues [17,18], we tested whether a simple bolus permits accurate Ve measurement. We hypothesized that the equilibrium between plasma and the interstitium contrast concentrations would be maintained during slow renal clearance so that the ratios of Gd in myocardium and blood, the change in their respective relaxivities, and Ve would remain constant and similar to measures acquired during steady state infusion. If indeed Ve measurement was not related to technique, we further hypothesized that Ve measures would also be reproducible between scans. We compared the accuracy of serial Ve measures from two different CMR scans (at 1.5 T) in each subject, the first involving a continuous infusion to demonstrate the attainment of steady state equilibrium, and the second involving a simple intravenous bolus as is typically performed for LGE imaging.

Methods

T1 and T2 Measurement in Phantoms

CMR-based Ve measurement requires robust measurement of T1. Therefore, we compared 2 different methods of T1 measurement in phantoms with varying concentrations of CuSO4 and Agar to produce similar T1 and T2 of myocardium and blood, before and after Gd administration. Physiologic T2 values are important for sequences with steady state free precession readouts because signal intensity varies by T2/T1. All measurements were acquired with a 1.5 Tesla Siemens Magnetom Espree (Siemens Medical Solutions, Erlangen, Germany) with a 32 channel phased array cardiovascular coil. To obtain T1 values from CMR data, we used a 3 parameter model to describe signal intensity (SI) as a function of inversion time (TI): $SI = | A - B \cdot e^{(-TI/T1^*)} |$, where $T1 = T1^*((B/A)-1)$ [19]. T2 values were obtained using a 2 parameter model describing SI as a function of echo time (TE): $SI = A \cdot e^{(-TE/T2)}$. Least square estimates of model parameters were obtained using the Levenberg-Marquardt algorithm in Matlab® (The MathWorks, Inc., Natick, Massachusetts).

T1 and T2 Relaxometry

For a reference standard, T1 was measured by spin echo inversion recovery experiments, acquiring 1 k-space line per readout (i.e., echo train = 1), TR = 15 s, TE = 10 msec, FA 90 degrees, with 10 inversion times ranging from 25 - 8000 msec. T2 was measured by spin echo experiments, acquiring 1 k-space line per readout, TR = 15 s, FA 90 degrees, with 10 TE times ranging from 10 - 400 msec.

T1 using MOLLI

We measured T1 using an ECG-gated single-shot modified Look Locker inversion recovery (MOLLI) sequence as described by Messroghli et al. [20] with simulated heart rates. Typical parameters were FOV 360 × 270 cm, matrix 256 × 128, 6 mm thickness, FA 35 degrees, 6/8 partial Fourier k-space sampling, parallel processing factor (GRAPPA) 2, and initial effective inversion time (TIeff) 90 msec with a TIeff increment of 80 msec. To sample T1 recovery, serial single shot diastolic images were acquired every heart beat after 3 nonselective adiabatic inversion pulses (i.e., 3, 3, and 5 images after each inversion pulse, totaling 11 images), and 3 dummy heart beats separated inversion pulses [20]. We refer to this sampling approach as "Classic MOLLI."

We also used a shorter sampling scheme to minimize breath hold times. A shorter sampling scheme may also minimize potential T1 measurement error due to effects related to repeated excitations prior to complete recovery of magnetization between serial inversion pulses. For longer *precontrast T1 recovery* of myocardium and blood (~950 and 1500 msec, respectively), we adjusted the above sampling scheme to employ only 2 nonselective adiabatic inversion pulses with a 5 and 1 sampling scheme (6 images total).

For *post contrast T1 recovery* that demonstrates faster relaxation rates, we employed 3 inversion pulses with a 4, 2, and 1 sampling scheme (7 images total). This approach attempted to ensure adequate sampling of the initial portion of the T1 recovery curve where the rate of relaxation was highest given the constraints imposed by sampling limited to diastole. Hence, additional data points were sampled during early T1 recovery for post contrast T1 measures. Furthermore, in contrast to precontrast sampling, we reasoned that the sample from 5th heart beat was unnecessary because most post contrast T1 values were approximately 500 msec or less, meaning that 99% of the magnetization had recovered by four heart beats (i.e., 2.5 sec, or 5 multiples of post contrast T1 if the R-R interval was ≥625 msec). We refer to this overall shortened T1 sampling approach adapted to the anticipated precontrast or post contrast T1 recovery curve as "Hybrid MOLLI." Using "Classic" and "Hybrid" MOLLI, we compared T1 data from phantoms against the spin echo derived values at slower (68 bpm) and faster simulated heart rates (92 bpm). Each of the 7 phantoms had 5 measurements by each MOLLI technique.

Monte Carlo Simulation

To explore how variable sampling of the T1 recovery curve affected the precision of T1 measures, we used Monte Carlo simulations to compare the root mean square error associated with the "Classic" and "Hybrid" sampling schemes mentioned above. Importantly, this simulation did not measure effects related to incomplete magnetization recovery between serial excitation pulses (whereas the phantom studies did), and thus was not used to assess accuracy. For simulation, we assumed a maximum signal amplitude (A.U.) of 250 and added noise with a standard deviation of 10. We performed 128 trials for each set of parameters, varying the heart rate from 50-100 beats per minute (5 bpm increments) and sampled T1 ranges from 200-500 msec and 800-1500 msec (100 msec increments).

Subjects

After Institutional Review Board approval and written informed consent, ten volunteers received CMR exams. Six were young adults who were under age 35, healthy, without symptoms or known comorbidity. Since renal function declines with age [21], these young subjects represented those with the highest renal function, fastest Gd clearance, and thus the greatest potential to disrupt equilibrium (and also Ve measures) after a bolus. Data were also acquired from four older subjects with ages ranging from 66-81 years, all clinically stable and asymptomatic, but with significant comorbidity. These older subjects represented those with a potential to disrupt equilibrium not from robust renal clearance, but from 1) a larger volume of distribution for Gd contrast, and 2) less capillary density [22-24] which occurs with older age and associated comorbidity. Together, the larger interstitial reservoir for Gd to accumulate and the diminished capillary density might prevent steady state equilibrium between plasma and myocardium after a bolus.

T1, lambda, and Ve measurement in Subjects

Infusion

We modified the intravenous infusion protocol outlined by Thornhill et al. [25] to constrain the total contrast dose to be 0.2 mmol/kg. For the infusion CMR scan, we gave a loading dose (0.1 mmol/kg gadoteridol bolus (Prohance, Bracco Diagnostics, Princeton, NJ)) followed by a 200 mL/hr infusion for ~1 hr with 0.1 mmol/kg diluted in 200 mL saline. Assuming a baseline myocardial blood flow of ~1 mL/g/min and an extraction efficiency of 0.6, this strategy should attain plasma-interstitium equilibrium for a wide range of Ve by ~25 minutes [26]. We arrived at the final infusion protocol by further iterative adjustments in 4 additional volunteers. T1 measures were obtained precontrast and repetitively during the 1-hour period after the initiation of contrast infusion. We defined steady state equilibrium during infusion when T1 values of both blood and myocardium varied by <5% [14].

Bolus

For the bolus CMR scan acquired on a different day, subjects received a 0.2 mmol/kg intravenous bolus of

gadoteridol. T1 measures were obtained precontrast and repetitively during the 12-50 min period after the receipt of the contrast bolus. We delayed Ve measurement for 12 minutes after the bolus to ensure full dispersion and equilibration of Gd contrast between tissues, which occurs after at least 5 minutes [13].

Ve measurement

We measured Ve as outlined by Jerosch-Herold et al. [13] Specifically,

$$Ve = \left[\lambda \cdot \rho \cdot (1\text{-hematocrit}) \right] - Vp$$

where Ve is the myocardial extravascular extracellular volume fraction, ρ is the specific density of myocardial tissue (1.05), Vp is the myocardial plasma volume fraction (assumed to be a constant 0.045 [13,27-29], reflecting capillary density), and $\lambda = [\Delta R1_{myocardium}] / [\Delta R1_{bloodpool}]$ pre and post Gd contrast (where R1 = 1/T1) [30,31]. Hematocrit was measured from blood samples drawn at the time of each CMR session. We carefully localized one mid ventricular short axis slice per subject for T1 measurement to match slice position across different scans. Blood pool regions of interest were intentionally large to average any inhomogeneity related to diastolic blood flow. Images were analyzed with Siemens multimodality workstations. When drawing circumferential regions of interest in the myocardium with computer assisted planimetry, care was taken to avoid the very edges of myocardium to avoid contaminating the measurement with partial volume averaging from voxels straddling the myocardial-blood pool border [12].

Late Gadolinium Enhancement

We acquired late gadolinium enhancement images 10-30 minutes after the 0.2 mmol/kg gadoteridol bolus in all subjects in the usual fashion [32]. To optimize detection of grossly evident scar or myocardial infarction, we used a phase sensitive segmented gradient echo inversion recovery [33] pulse sequence to increase signal to noise ratios, correct for surface coil intensity variation, and render signal intensity proportional to T1 recovery.

Statistical Analysis

T-tests compared continuous variables. Linear regression compared the mean Ve for subjects (given unequal number of measurements for bolus and infusion) according to measurement technique; Bland-Altman plots assessed overall agreement and bias between Ve measurement techniques [34]. Generalized estimating equations (GEE) with exchangeable correlation matrices to account for serial measures compared the linear regression slopes of individual classic and hybrid MOLLI T1 measurements against spin echo T1 measurements. GEE also summarized any differences between the infusion (at steady state equilibrium) and bolus techniques for Ve measurement, adjusting for repeated Ve measures across individuals over time. To assess for an interaction between time and Ve measures, a time variable and a variable representing the product of Ve and time was entered into the model. Analyses were performed using SAS (Cary, NC) and Microsoft Excel (Redmond, Washington).

Results

Monte Carlo Simulation

Monte Carlo simulation revealed no difference in the root mean square error (RMSE) between classic and hybrid MOLLI for T1 values between 200-500 msec (RMSE 14 vs. 14, p = 0.51, paired t test). At higher T1 values of 800-1500 msec, classic MOLLI exhibited better precision than hybrid MOLLI (RMSE 29 vs. 45, respectively, p < 0.001). It should be noted that this simulation scheme did not account for effects related to repeated excitation pulses as did the phantom data below.

Phantom Studies

Phantom T1 and T2 values measured by spin echo relaxometry closely approximated the expected range of physiologic values before and after contrast administration. The phantom representing blood before contrast had T1/T2 values of 1535 msec/172 msec. Two precontrast myocardium phantoms had T1/T2 values of 909 msec/44 msec and 887 msec/38 msec. Postcontrast blood phantoms had T1/T2 values of 309 msec/187 msec and 251 msec/171 msec. Postcontrast myocardial phantoms had T1/T2 values of 342 msec/53 msec and 260 msec/53 msec.

Correlation plots and Bland-Altman analysis demonstrated that hybrid MOLLI exhibited better agreement with spin echo T1 relaxometry measures than classic MOLLI. At a relatively low heart rate of 68 bpm, serial T1 measures (5 repetitions per phantom for each technique; thus 70 total measures) by ECG gated MOLLI were highly correlated with the spin echo 'gold standard' measures (Figure 1). The regression line for hybrid MOLLI had a slope of 0.98 (95%CI 0.91-1.06), that was not significantly different from unity (p = 0.66). In contrast, the regression line for classic MOLLI had a slope of 0.95 (95%CI 0.91-0.99), significantly less than unity (p = 0.007). These differences were more pronounced at higher heart rates (i.e., 92 bpm) where the regression line slopes for hybrid and classic MOLLI were 0.95 (95% CI 0.89-1.01; p = 0.12) and 0.88 (95% CI 0.87-0.89; p < 0.001), respectively. At higher heart rates, Bland-Altman analysis revealed that the classic MOLLI approach underestimated T1 when T1 was long but overestimated T1 when T1 was short. This bias compresses the dynamic range of the T1 differences. Hybrid

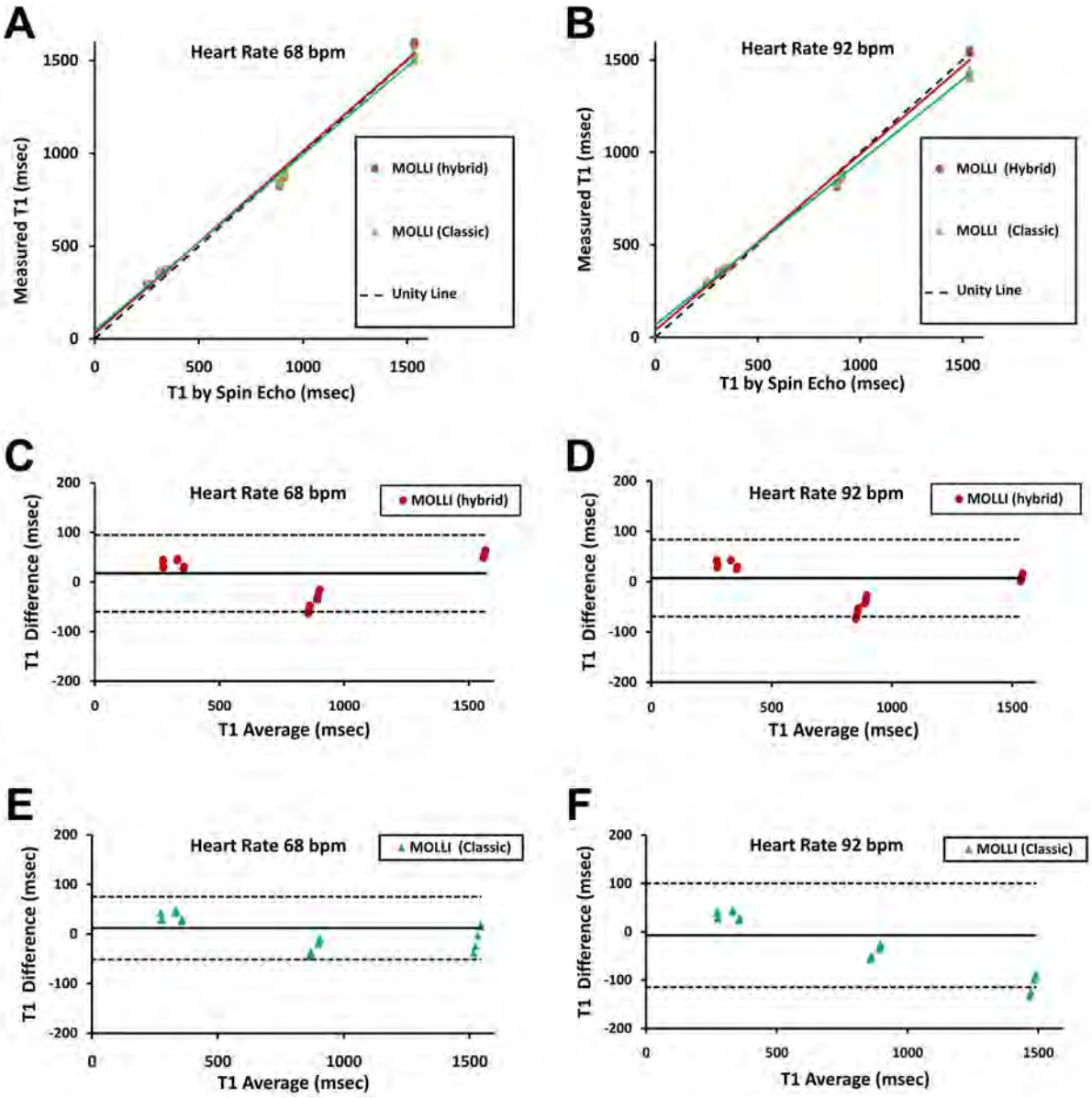

Figure 1 Comparison of "Classic" MOLLI (i.e., 3+3+5 uniform sampling scheme) and "Hybrid" MOLLI (i.e., 5+1 precontrast or 4+2+1 post contrast sampling scheme) with spin echo T1 measures (gold standard) in CuSO4-Agar phantoms with T1 and T2 values similar to myocardium and blood before and after contrast (see text for details). Both exhibit excellent correlation with spin echo measures. "Hybrid MOLLI" exhibits slightly better correlation (panels A and B) and better agreement with less bias (panels C and D) compared to "classic" MOLLI (Panels E and F), especially at higher heart rates. Each of the 7 phantoms had 5 serial measurements.

MOLLI exhibited less bias and generally yielded better agreement.

Both the hybrid and classic MOLLI acquisitions demonstrated excellent reproducibility for repeated measurements. The coefficients of variation for all phantoms were <1.6%. At a heart rate of 68 bpm the mean coefficient of variation was 0.55% and 0.59% for hybrid versus classic MOLLI, respectively; at a heart rate of 92 bpm the mean coefficient of variation was 0.53% and 0.61% for hybrid versus classic MOLLI, respectively. The coefficients of variation for each phantom measured by either technique are plotted as a function of T1 for both a slow and faster heart rate in Figure 2. Given the better correlation and agreement with T1 measurement compared to the spin echo gold standard as well as the comparable precision in phantom studies (but not

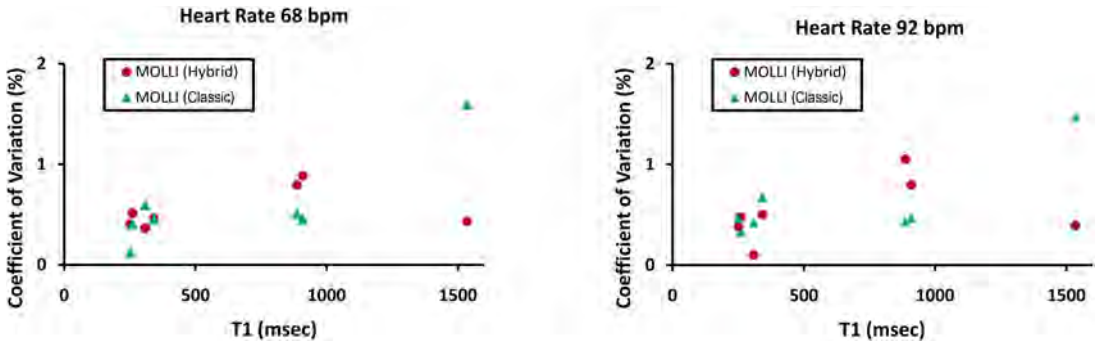

Figure 2 Coefficients of variation for phantoms measured by "Classic" MOLLI and "Hybrid" MOLLI techniques (see text for details). Both techniques exhibit excellent reproducibility (<2%), but the hybrid MOLLI technique exhibits more precision at higher T1 values.

simulation studies), hybrid MOLLI techniques were selected for T1 measurement in human subjects as demonstrated in Figure 3.

Subjects

Median age of the 10 subjects was 33 years (range 20-81 yrs), and 3 were female. All subjects were free of cardiac symptoms. Characteristics of the subjects are shown in Table 1. The six younger subjects were healthy without any associated comorbidity. No subject exhibited abnormalities on late gadolinium enhancement images in the slice position used for Ve measurement; one subject with a history of myocardial infarction exhibited late gadolinium enhancement remote from myocardium used for Ve measurement.

Representative images used for T1 measurement are shown in Figure 3. Signal intensity versus inversion time plots indicate good fit to the T1 recovery curves. Post contrast T1 curves for blood and myocardium indicate magnetization has nearly completely recovered after 4 heart beats (hence the 4+2+1 "hybrid" post contrast sampling scheme). Before contrast, 5 heart beats are needed to sample the full span of the longer T1 recovery curve.

Older subjects had higher mean Ve from infusion compared to younger subjects under age 35 (21.1 ± 1.1% vs. 25.3 ± 2.4% by the infusion technique and 20.8 ± 1.8% vs. 25.2 ± 2.1% by the bolus technique, respectively; $p \leq 0.03$ for both). Similarly, for each technique, regression analysis of mean Ve values for each subject also yielded a significant relation between Ve and age regardless of whether the infusion technique or the bolus technique was employed (Figure 4). Because heart rate may exert slight effects on T1 measurement by MOLLI, we created a multivariable GEE regression model that adjusted for heart rate. Regardless of technique, Ve remained significantly related to age ($p < 0.01$ for both), even after adjusting for heart rate which was not significant predictor ($p \geq 0.2$). Whether high Ve values were related to age alone or associated comorbidity or both is beyond the scope of this work.

Comparison of Ve Measurement by Infusion and Bolus Techniques

Baseline *precontrast* T1 measures for the "infusion" scan and the "bolus" scan permit assessment of T1 variability across scans. There was no significant difference between T1 measures of blood (1534 vs. 1502 msec, $p = 0.41$) and myocardium T1 (946 vs. 948 msec, $p = 0.83$). Yet, the median of the absolute value of T1 *differences* in individual subjects between the scans was 20 msec for myocardium (2.1% of mean myocardial T1) and 55 msec for blood (3.6% of mean blood T1), indicating variability attributable solely to T1 measurement *between scans*. This precontrast T1 variation across two scans was greater than T1 variation within one scan. For the infusion scan, precontrast blood and myocardium T1 were measured twice. The median of the T1 *differences* in individual subjects for an extra T1 measurement during the infusion scan was 12 msec for myocardium (1.3% of mean myocardial T1) and 20 msec for blood (1.3% of mean blood T1), indicating the variability of T1 measures *within one scan*.

Despite the variability in precontrast T1 measurements, Ve data from both methods (i.e., during continuous infusion with steady state defined by stable blood and myocardial T1 and after a simple bolus) yielded similar results. Because the clearance of Gd contrast is slow relative to its equilibration between tissues, both T1 and the $\Delta R1$ changed gradually, and the partition coefficient, λ, remained constant. The stability of infusion- and bolus-based Ve estimation is illustrated in Figure 5. This observation would only occur if steady state between interstitium and plasma was maintained

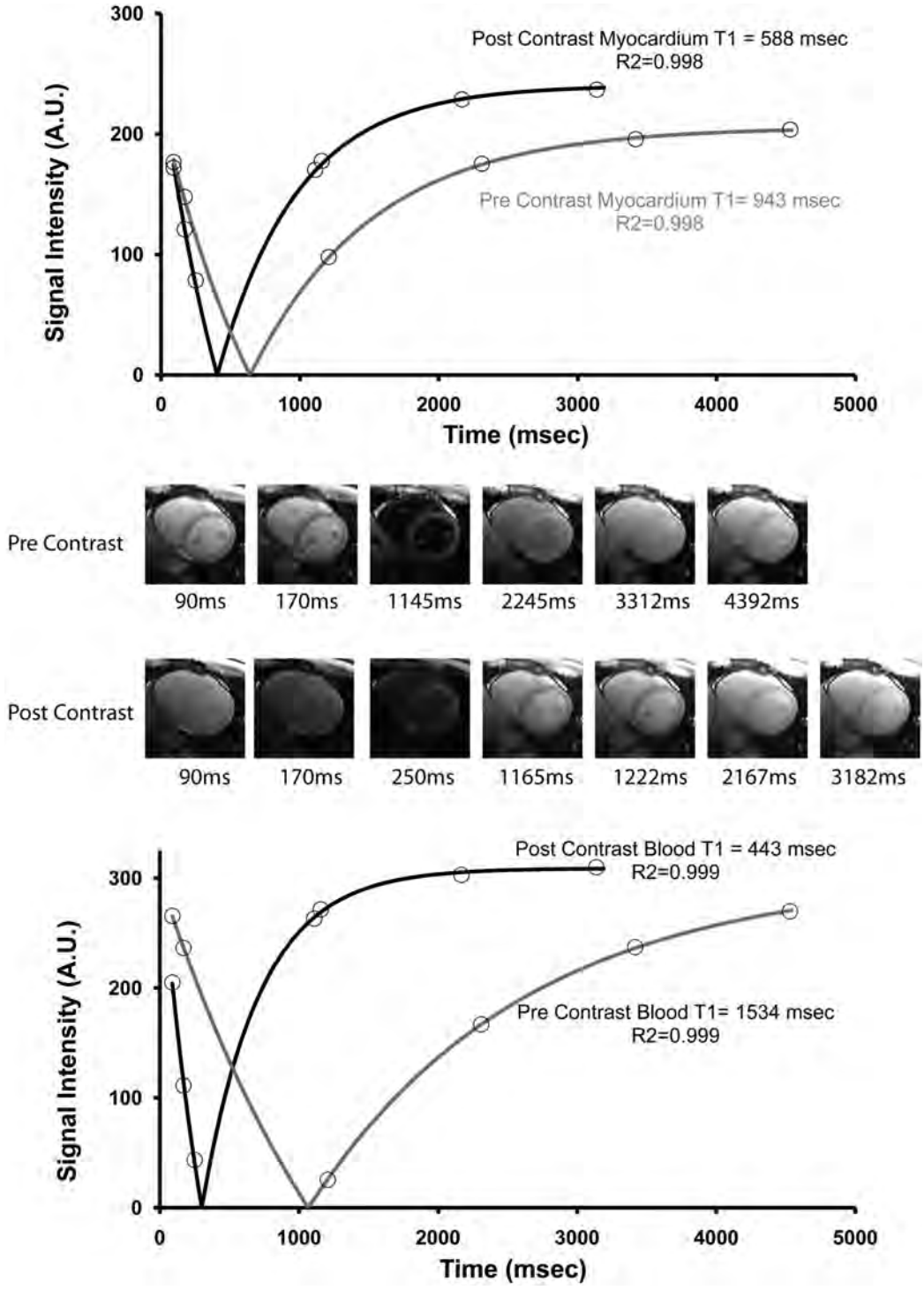

Figure 3 Representative T1 values of myocardium and blood in a subject before and after contrast can be measured with a modified Look Locker pulse sequence employing single shot SSFP imaging within a single breath hold. Signal intensities are plotted against effective inversion time. A three parameter fitting of the data with a correction for read-out attenuation yields T1 values (see text for details). The top panel shows myocardial T1 curves before and after contrast whereas the lower panel shows the blood T1 curves before and after contrast. Most of the magnetization recovers after 4 heart beats *after* contrast administration. Pre and post contrast thumbnails corresponding to the myocardium and blood pool data points in the curves are also shown in order of effective inversion times.

Table 1 Characteristics of subjects undergoing assessment of the extravascular extracellular volume fraction (Ve)

Age	Gender	Comorbidity	Mean Infusion λ (SEM)	Infusion hematocrit (%)	Mean Bolus λ (SEM)	Bolus hematocrit (%)
20	male	none	0.452 (0.002)	47.7	0.424 (0.007)	46.1
21	male	none	0.399 (0.002)	41.2	0.392 (0.004)	41.9
21	female	none	0.434 (0.004)	39.6	0.424 (0.004)	38.9
22	male	none	0.398 (0.002)	41.0	0.401 (0.003)	42.1
31	male	none	0.412 (0.002)	40.4	0.424 (0.003)	42.3
34	male	none	0.437 (0.001)	42.7	0.448 (0.002)	41.5
66	female	Ulcerative colitis, colectomy, diabetes, left bundle branch block, recurrent infections	0.451 (0.002)	30.0	0.442 (0.002)	29.8
68	female	Diabetes, obesity, hypertension	0.453 (0.002)	38.0	0.461 (0.003)	38.9
69	male	Myocardial infarction, hypertension	0.473 (0.006)	44.4	0.474 (0.009)	44.0
81	male	Atrial fibrillation	0.460 (0.002)	41.2	0.459 (0.004)	40.4

Subjects were either healthy young adults or older individuals with significant comorbidity.

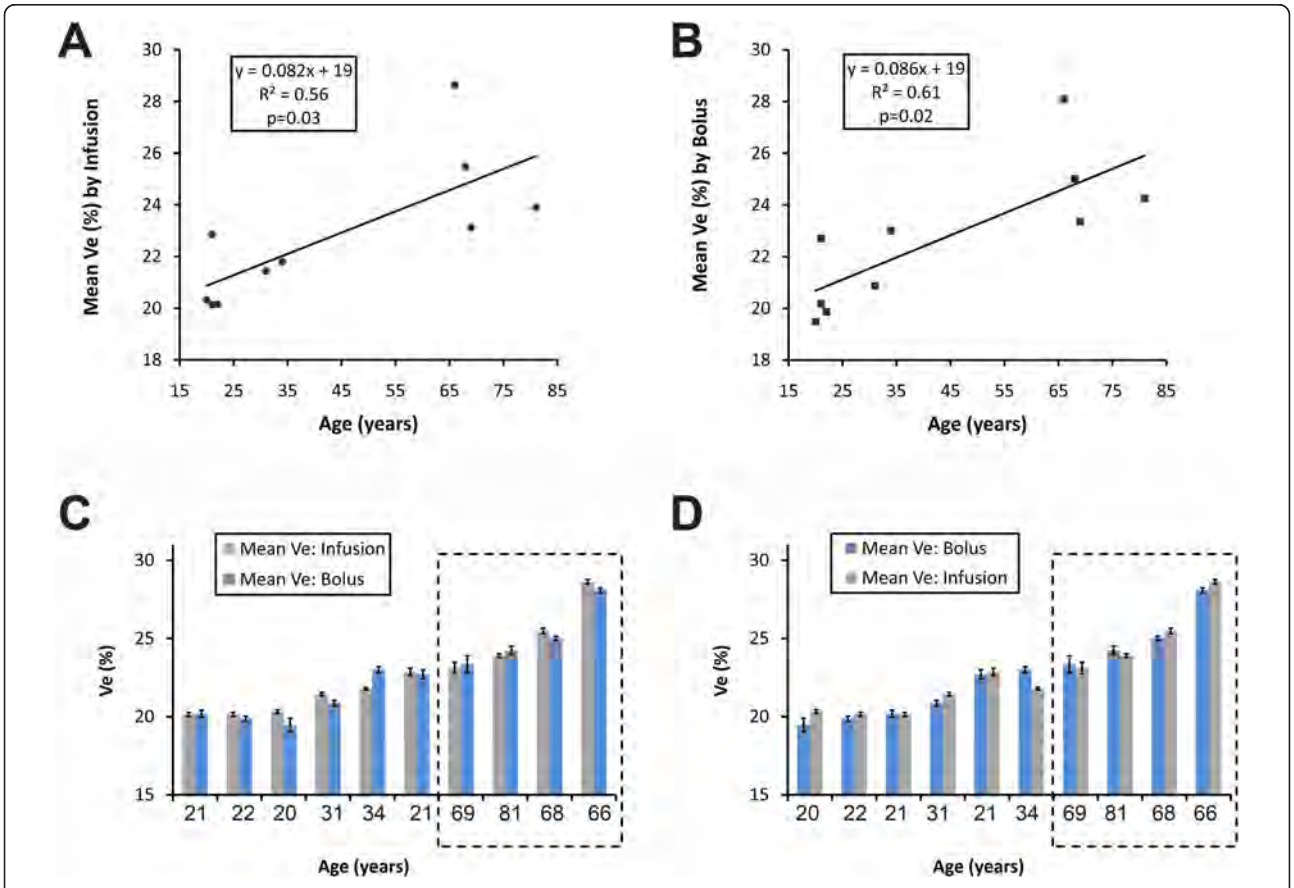

Figure 4 The Ve spectrum in volunteers by age was similar regardless of technique. As expected, Ve values were significantly higher in older subjects with significant comorbidity. Ve data from either the infusion technique (Panel A) or the bolus technique (Panel B) yielded similar linear regression results where both techniques detected significantly higher Ve with increasing age. When the same Ve data were then sorted in order of ascending Ve (sorted by Ve from infusion technique in Panel C; sorted by Ve from bolus technique in Panel D), both techniques identically sorted the older subjects with higher mean Ve (dashed boxes). Error bars in the bar graphs indicate the standard error of the mean for repeated Ve measures by each technique in each individual.

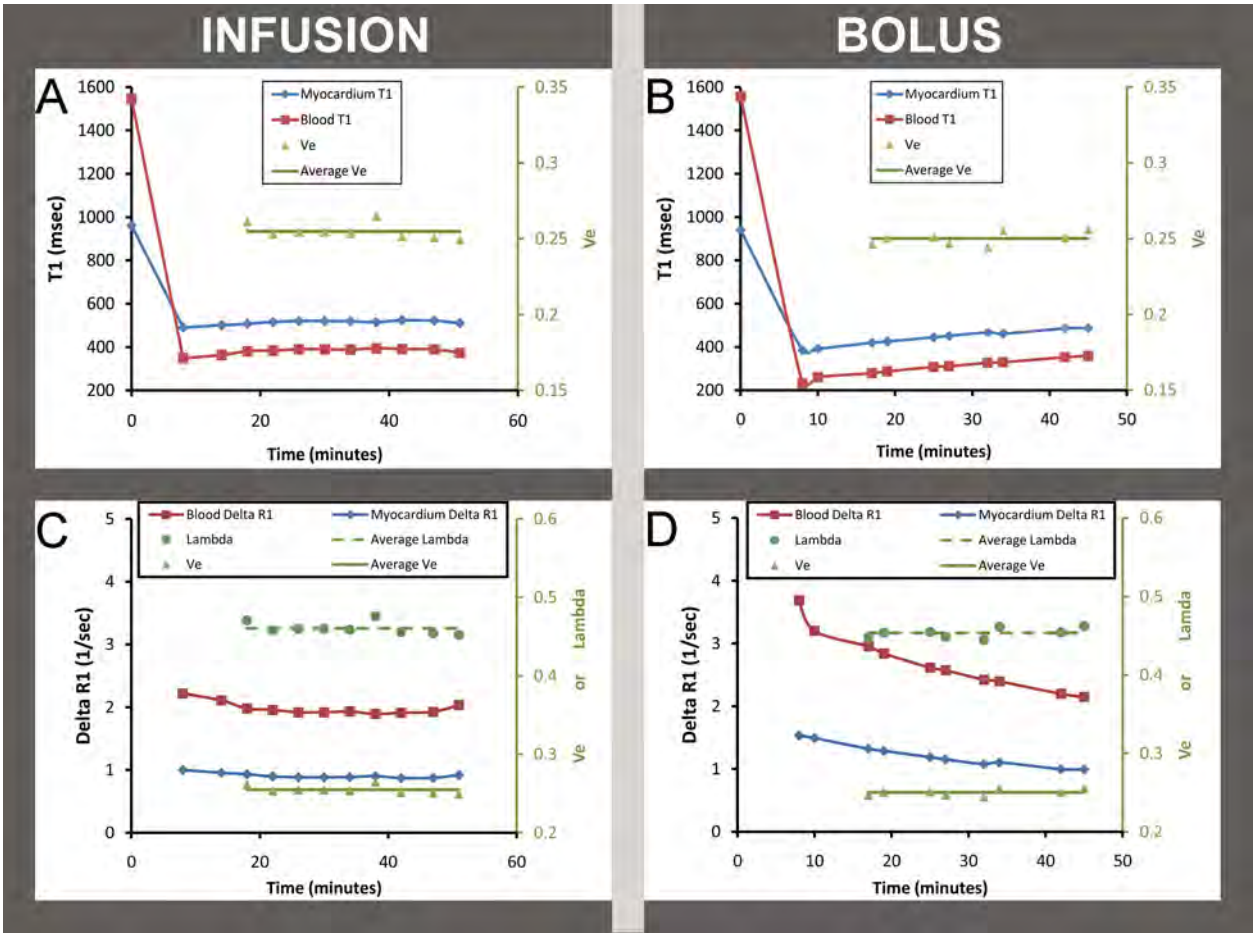

Figure 5 Ve measurements in a 68 year old female subject with diabetes and hypertension remain constant over time with a constant infusion or with a bolus. Panel A shows T1 values for blood and myocardium during a constant infusion; the T1 values with associated Ve measures become level and remain relatively constant with <5% variation. Panel B, however shows ever increasing T1 values following a single bolus as gadolinium contrast is cleared. Yet the Ve data (expressed as a proportion, green triangles) yield similar mean Ve values (green line) for each technique. In Panels C and D, the same data (for infusion and bolus, respectively) are expressed as the *change in relaxivity* (delta R1) which linearly relates to gadolinium contrast concentration. T1 and delta R1 do not change rapidly indicating relatively slow clearance. As such, it becomes evident that the ratio of myocardial delta R1 to blood delta R1–the principal determinant of Ve, after adjustment for the hematocrit–remains constant. The ratio is expressed as the partition coefficient lambda (expressed as a proportion, green circles with the green dotted line represents the mean lambda). Indeed, the Ve measures for both the infusion and bolus techniques remain nearly constant at 0.25 (right vertical axis). This finding demonstrates steady state equilibrium between plasma and the myocardial interstitium even as the T1 changes in both tissues during the slow renal clearance of contrast.

during the clearance of gadolinium contrast. Of note, this 68 year old subject had excellent renal function with a serum creatinine of 0.8 and a preserved glomerular filtrate rate of 71 mL/min/1.73 m^2.

With the *infusion technique*, the range of individual Ve measures among subjects was 19.3%-29.2% with a SD≤0.9% for repeated measures (n = 110) in the 10 subjects. Similarly, the range of individual Ve measures among subjects measured by the *bolus technique* was 18.4%-29.1%, with a SD≤1.3% for repeated measures (n = 95). In GEE regression models that adjusted for the clustering of repeated measurements in subjects, serial Ve measures by bolus or infusion did not differ significantly (Ve difference between techniques = 0.1%, p = 0.38). Moreover, when the mean Ve for each subject measured by bolus was plotted against the mean Ve measured by infusion, the regression line had a slope similar to unity, an intercept of nearly zero, and a high R^2 value (Figure 6). Importantly, Bland-Altman plots did not reveal significant bias introduced by the bolus technique. Given the lack of a statistically significant difference in Ve measurements related to technique, Ve measurements across CMR scans were therefore reproducible.

The variation between the techniques was similar to the variation within each technique. As shown in the

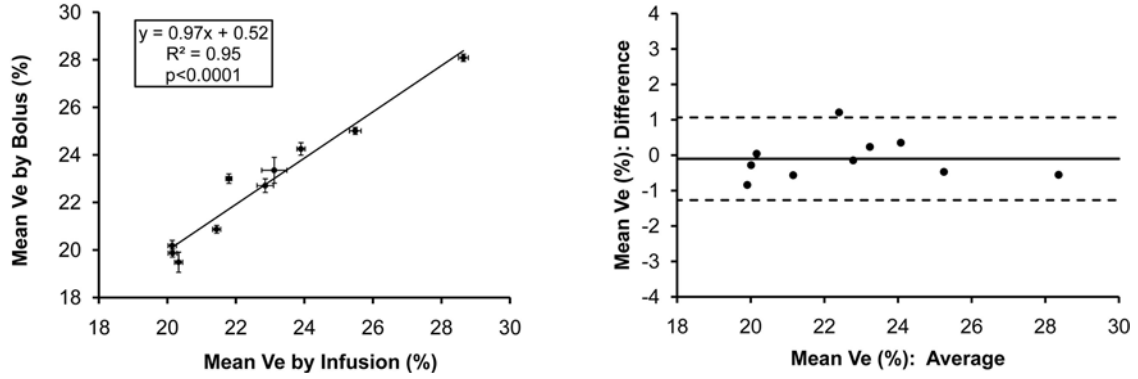

Figure 6 Correlation and Bland-Altman plots of mean Ve measures for each of the ten subjects by infusion or bolus techniques. Ve measures by either technique are highly correlated without evidence for significant bias. The correlation plot includes bars representing the mean Ve ± standard error for each subject by bolus or infusion. Bland Altman analysis depicts the mean difference between the bolus or infusion technique (solid line) ± 1.96 SD (dotted lines). The 95% confidence intervals of ± 1.2% for the mean Ve *difference* between bolus and infusion techniques in Bland Altman analysis are comparable to the average 95% confidence intervals for repeated Ve measures by infusion alone (± 1.0%) or by bolus alone (± 1.4%).

Bland-Altman plots, the 95% confidence intervals of ± 1.2% for difference between mean Ve measures by bolus versus infusion in the were similar to the 95% confidence intervals for repeated measures by either technique. The average 95% confidence interval for Ve measured by infusion was ± 1.0%, and the average 95% confidence interval for Ve measured by bolus was ± 1.4%. Finally, we detected a very small, but statistically significant ($p < 0.001$) interaction between time and Ve measurement after a bolus. Ve increased slightly by 0.6% over 30 minutes, which was well within the 95% confidence intervals for serial Ve measurements by either infusion (± 1.0%) or bolus (± 1.4%) as shown in Figure 6. There was no time interaction for Ve measures by the constant infusion technique ($p = 0.17$).

Discussion

The bolus technique simplifies Ve measurement in humans. With the MOLLI-based T1 computation, Ve can be measured with a simple Gd contrast bolus as accurately as with an infusion, but with slightly less precision, i.e., ± 0.4% absolute difference in the 95% confidence intervals for Ve. Steady state equilibrium is achieved with both methods as evidenced by the stable Ve measures, even as the Gd contrast concentrations changes slowly in myocardium and blood from renal clearance. While we did detect a small, statistically significant time interaction with the bolus technique, the magnitude of the time interaction was well within the 95% confidence intervals for Ve measurement by either technique and therefore of questionable *clinical* significance. Indeed, both methods could easily sort the sample and robustly identify the order of the higher Ve values in older subjects with significant comorbidity, even in the absence of evident late gadolinium enhancement. Since Ve measures obtained from scans performed on different days were not significantly different, Ve measures are therefore reproducible.

The importance of myocardial fibrosis in heart disease has been recognized for decades [1]. A variety of studies indicate that myocardial fibrosis generally represents a final common pathway to a variety of insults [11,35-37]. As such, the human validation study recently published by Flett et al. [14] provides an important tool to those investigating the role of the "interstitial heart disease."[1] Their study established that quantitative Ve measures correlate highly with picrosirius red measures of the collagen volume fraction. Others who employed a bolus strategy for Ve measurement have also shown that Ve values are abnormal in defined patient populations [13,15].

Our work highlights the validity of these previously reported Ve measures based on a bolus strategy [13,15]. We demonstrate that Ve measures are reproducible and reasonably precise from scan to scan with good confidence intervals for Ve estimates, regardless of whether a bolus or infusion technique is employed. We also observe that the range of our Ve data from healthy controls (21.1 ± 1.1% vs. 25.3 ± 2.4% by the infusion technique, and 20.8 ± 1.8% vs. 25.2 ± 2.1% by the bolus technique for young healthy versus older with comorbidity, respectively; $p \leq 0.03$ for both) were remarkably similar to the Ve range in controls (mean age was 45 years) reported by Jerosch-Herold et al. [13] (24% ± 3% vs. 31% ± 5% for unaffected family members vs. patients with idiopathic dilated cardiomyopathy, $p = 0.002$). Similarly, by transforming the "fibrosis index" reported by Broberg et al. [15] to Ve values [where fibrosis index

= λ·(1-hematocrit)], we find that healthy controls from this study had Ve values of 21.5% ± 2.1%. Therefore, normal Ve values appear to be approximately 25% or less, but further work is needed to ascertain "normality" for Ve measures. Note, the only difference between Ve as computed both in our manuscript as well as the manuscript by Jerosch-Herold et al. [13] compared to the "myocardial volume of distribution" described by Flett et al. [14] or the "fibrosis index" described by Broberg et al. [15] is that the Ve measure simply multiplies these latter measures by the specific density of myocardium, ρ (1.05), and then subtracts the plasma volume fraction in myocardium which is assumed to be constant at 4.5%.

The bolus strategy to measure myocardial Ve simplifies the Ve data acquisition protocol and facilitates its integration into routine CMR practice. We believe these features will accelerate investigation in the role of the interstitium in health and disease by minimizing the burden on patients and investigators imposed by Ve assessment. Furthermore, the reproducibility of Ve measures between CMR scans is important for studies examining factors that affect changes in Ve over time (e.g., as a result of intervention).

In support of our conclusions, Thornhill et al. also found similar results for partition coefficients of infarcted and noninfarcted myocardium measured with either a constant infusion technique or a simple bolus [25]. Our work builds on their results in several ways. First, we used Ve as a myocardial extravascular extracellular space marker which is inherently more accurate than partition coefficients since the latter vary significantly as a function of hematocrit for a given Ve as shown graphically in Figure 7. Similarly, for a measured partition coefficient, the resultant Ve will depend on the hematocrit (Figure 7). Thus, hematocrit variation will confound myocardial fibrosis comparisons across subjects if partition coefficients (or even T1 measures) are employed as surrogate fibrosis measures. Second, we measured the partition coefficient and Ve using actual T1 measurements as opposed to signal intensity surrogates (which do not vary linearly with Gd concentration) generated from pulse sequences (spoiled gradient echo) with lower signal to noise ratios than SSFP [38]. Third, we employed a statistical modeling approach to adjust for clustering of non independent repeated measures in subjects and also identify subtle time interactions. Lastly, we studied a fundamentally different population with a narrower spectrum of myocardial disease characterized by more subtle degrees of myocardial remodeling than frank myocardial infarction. Still, we were nonetheless able to identify higher Ve values from older individuals with comorbidity as compared to the lower Ve values from younger healthy subjects with without known comorbidity.

Ve measurement techniques have been developed specifically to quantify the full spectrum of myocardial fibrosis, including diffuse fibrosis not detectable with conventional LGE images that may be difficult to distinguish from background noise [13-15]. Even though none of the subjects exhibited enhancement in the myocardium used for Ve measurement, both techniques identically stratified older individuals with higher comorbidity based on the higher Ve in older subjects with comorbidity. Although not the primary aim of this study, this specific finding is important because it confirms the remarkably robust ability of CMR to detect age-related

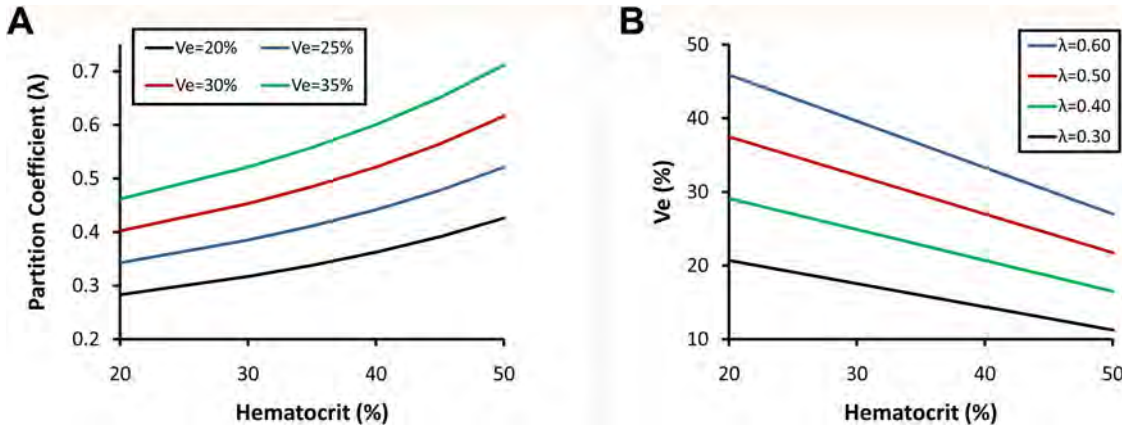

Figure 7 Hematocrit exerts a significant influence on the relationship between Ve and the partition coefficient, λ. Ve (expressed as a percentage) is defined here as the following: Ve = [λ · (1-hematocrit) · ρ] - Vp where Ve is the myocardial extravascular extracellular volume fraction, ρ is the specific density of myocardial tissue (1.05), Vp is the myocardial plasma volume fraction (assumed to be a constant 0.045, reflecting capillary density), and $\lambda=[\Delta R1_{myocardium}]/[\Delta R1_{bloodpool}]$ expressed as a decimal). Since anemia is common in various conditions (e.g., heart failure), obtaining the hematocrit is essential for accurate Ve measurement. Panel A shows how λ will vary nonlinearly with the hematocrit for a range of Ve values. Similarly, panel B shows how Ve will vary inversely with the hematocrit for a range of λ values.

change in the interstitium directly, in the absence of frank LGE. Other noninvasive techniques lack this capability. Thus, CMR can demonstrate a spectrum of interstitial changes within the myocardial interstitium itself that otherwise remain unappreciable with conventional imaging techniques. We believe Ve measures will provide an important tool to investigate the relationship between age, myocardial fibrosis, and other age-related changes described previously [23,24,39-41].

Accurate Ve measurement relies heavily on robust T1 measurement. MOLLI techniques with balanced steady state free precession (SSFP) are excellent methods to measure the T1 of myocardium and blood before and after contrast from which Ve is calculated. Use of this pulse sequence yielded excellent agreement to T1 values as measured by spin echo relaxometry at both slower and faster heart rates. Our sampling scheme of the T1 recovery curve intentionally used fewer data points for T1 curve fitting than others [13,20,30]. We attempted to minimize breath hold time for human subjects and also minimize disturbing the recovery of magnetization after inversion pulses by 1) minimizing repetitive inversion pulses generated prior to complete T1 recovery, and 2) minimizing repetitive sampling of the magnetization vector which can lead to systematic errors [42]. In fact, the shorter "hybrid MOLLI" scheme that we employed for Ve measurements in human subjects was based upon better accuracy and precision for T1 measurement in phantoms than the conventional T1 sampling scheme [20]. We note that Piechnik et al. who also have recognized the limitations of "classic MOLLI" have recently published similar accuracy data whereby shorter MOLLI sampling schemes are less heart rate dependent [43]. We also note that their "conditional" T1 sampling approach is conceptually similar to the "hybrid MOLLI" technique whereby sampling is adapted to T1 curve.

We attempted to minimize disturbance of the magnetization vector recovery by employing balanced SSFP. Compared to other T1 measurement techniques that employ spoiled gradient echo readouts, balanced SSFP offers higher signal to noise ratios and minimal disturbance of the magnetization vector that may produce systematic errors in T1 measurement, especially at higher heart rates [19,42]. In addition, SSFP is less susceptible than gradient echo to flow artifact in the blood pool [38] which can also perturb T1 measurements. Indeed, the magnitude of variation in precontrast T1 blood values was not much larger than the variation in precontrast myocardium T1 values. Moreover, MOLLI data can be obtained in a single breath hold, rendering the acquisition fast and patient friendly. In contrast, segmented T1 measurement techniques require 7-8 breath holds per T1 measurement [14]. If an individual is unable to breath hold, MOLLI images can still be obtained without respiratory motion ghosting artifact typical of segmented images (but potentially at the expense of through plane motion). This feature is particularly important in the setting where arrhythmia is present or where patient comorbidity prevents successful breath holding. Unlike segmented T1 measurement techniques [14], MOLLI can be applied to the full spectrum of patients, regardless of comorbidity, thus avoiding potential selection biases. Nonetheless, efforts to optimize T1 measurement strategies upon which Ve is based continue to evolve [43].

Our work has some limitations. First, we could not obtain histologic validation to corroborate our Ve measures because our subjects had no indication for heart surgery or endomyocardial biopsy. Nonetheless, Flett et al. have previously demonstrated excellent correlation of Ve values with the collagen volume fraction in human subjects [14]. They used a different method to measure T1, but we have demonstrated that our T1 measures agree very well with meticulous T1 relaxometry measures obtained from phantoms with representative T1 and T2 values. Second, to compare bolus versus infusion Ve measures, we also did not sample the entire spectrum of myocardial remodeling as evidenced by the absence of late gadolinium enhancement abnormalities in our subjects. We cannot exclude that individuals with very large areas of fibrosis/necrosis with low capillary density might not exhibit steady state pharmacokinetics with a bolus. Yet, Thornhill et al. did not find evidence of different partition coefficients measured with either bolus or infusion techniques within the extremes of grossly infarcted myocardium or apparently normal myocardium [25]. Thus, we believe the simple bolus strategy is valid across the fibrosis spectrum, with one notable exception: systemic amyloidosis. This condition is characterized by marked interstitial expansion from deposition of amyloid proteins and very rapid, presumably extrarenal clearance of Gd contrast from the blood pool [44], and we suspect that a bolus might not yield accurate Ve measures under such conditions. Third, we did not measure renal function in some of the younger subjects although there was no indication of renal impairment. Fourth, our Ve measures excluded the edges of the myocardium due to concerns about partial volume error in the setting of limited spatial resolution [12]. This approach will not detect fibrosis limited to the subendocardium or subepicardium. Myocardial fibrosis in nonischemic cardiomyopathy is a generally diffuse process [11], but ischemic cardiomyopathy demonstrates more fibrosis in the subendocardium [36]. Lastly, we, like other investigators [13-15], did not account for any variation in myocardial plasma volume

fraction (Vp) across individuals; this issue requires further study using additional techniques beyond the scope of this manuscript.

Conclusions

Ve measurement did not differ significantly between techniques employing a simple contrast bolus or a smaller bolus followed by a lengthy infusion to demonstrate steady state. Both methods identified similarly strong relationships between Ve and age. Both methods could easily sort the study sample and robustly identify the order of the higher Ve values in older subjects. Ve measures were also reproducible since we could not identify a statistically significant difference between Ve measures from different scans. Because the bolus strategy simplifies Ve measurement, these data may facilitate integration of Ve measurement into routine CMR practice. This strategy may accelerate investigation of the role of Ve in health and disease by avoiding the burden imposed by an infusion on patients and investigators. The reproducibility of Ve measures across scans is also important for studies examining changes in Ve measures.

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Authors' contributions

All authors read, critically edited the initial manuscript, added intellectual content, and approved the final version. EBS and TCW designed the study, created the phantoms, acquired, and analyzed the phantom data. EBS and BLJ conducted the statistical analyses. EBS conceived of the "hybrid" method, performed all CMR scans, and drafted the initial manuscript. SMT, CGM, WJC, JEL, AJB, analyzed the human data. PK assisted with pulse sequence optimization and wrote the simulation program. DRL modified and performed the final simulation. SGS wrote the fitting algorithm for T1 measures and assisted with data analysis and interpretation. BLJ wrote the code for statistical analysis and assisted with implementation and interpretation. DS assisted with the initial study design, data analysis, and added critical manuscript content.

Competing interests

Dr. Schelbert has served as an unpaid scientific advisor to Siemens Medical Solutions which provided the MOLLI sequence. The remaining authors declare that they have no competing interests

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Progress Report

The addition of the T. Franklin Williams Scholar program has led to a very productive year for both research and career development.

Research Progress:

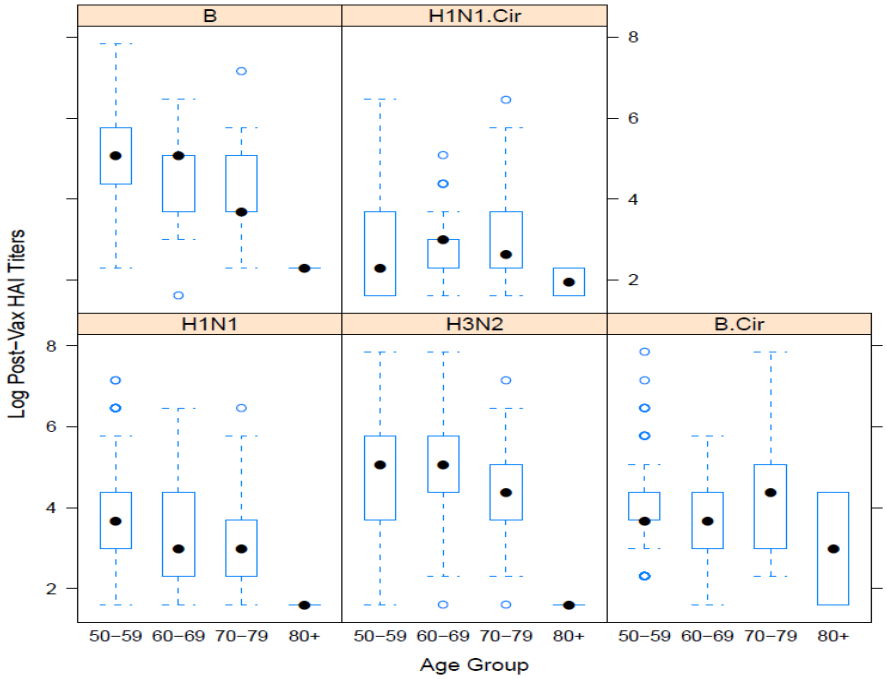
Brief Summary of Methods:

As part of a multi-site CDC-funded study to describe the cellular immune responses of older adults to influenza vaccination with trivalent inactivated influenza vaccine (TIV), this study was developed to determine which responses provide protection. Serum and peripheral blood mononuclear cell (pbmc) specimens were collected from enrolled subjects to measure cellular and humoral activity pre- & post-influenza vaccination. After influenza season, subjects were invited to return for a third blood draw to look for serological evidence of influenza infection during the season. During the second year of the study (2009-2010), subjects were followed during influenza season & had a nose/throat swab obtained at the time of influenza-like illness.

Results

During the 2008-2009 season, 591 adults provided serum samples; 205 adults also provided pbmc samples & 182 of these individuals returned in the spring for a serologic sample to seek evidence of influenza infection. HAI testing on serologic samples has been completed (Figure 1). Six episodes of influenza were diagnosed by serology. Cellular immune studies are beginning. During the 2009-2010 season, 509 subjects were enrolled & all had samples collected for both serum & pbmc testing. To date approximately 65 nose/throat swabs have been collected during episodes of influenza-like illness and one was positive for pandemic H1N1.

Figure 1: Post-Vaccination Antibody Responses to Vaccine and Circulating Influenza Strains



"B" = B/Florida/4/2006; "B. Cir" = B/Malaysia/2506/2004; "H1N1 Cir" = A/California/7/2009 "H1N1"= A/Brisbane/59/2007 "; H3N2"= A/Brisbane/10/2007

Plans:
Completion of PBMC testing is planned this summer. Since very few influenza cases were diagnosed during the 2008-2009 season, analyses will focus on frailty and the relationship to immune response. 2009-2010 samples are being prepared for testing.

Career Development

This past year has provided several opportunities for career development. Each one has augmented a different part of my career and has enabled me to meet or interact with several influential people.

The Clinical Infectious Diseases Journal invited me to write a review paper[1] on the diagnosis of viral respiratory diseases in older adults. This became an amazing opportunity to work with Dr. Ann Falsey at the University of Rochester to re-review all of the data and to work with Dr. Falsey. This article was so interesting to the Vanderbilt's geriatric division that it has been chosen as a journal club and for a topic at the upcoming local Quality in Long-Term Care Conference.

During the 2010 American Geriatric Society meeting I had the opportunity to meet Dr. Al Shaw, Associate Professor at Yale, who does immune senescence work in regard to influenza vaccination. He will be visiting me December 10, 2010 as part of the Visiting Professor Program. I am looking forward to this visit to discuss current and future projects. In addition to meeting Dr. Shaw, I also had the opportunity to meet Dr. Ken Schmader, Professor at Duke University. He is a geriatrician with experience n vaccine clinical trials. We will be collaborating on a future high dose influenza vaccine study in nursing home patients.

This past year I was able to present some of my clinical trial data a the13th Annual Conference on Vaccine Research where I was able to interact with many that are working on immunologic aspects of vaccine and vaccine responses. I learned a great of immunology, and began exploring some new research ideas. At the same meeting I was also awarded the Maurice R. Hilleman Early-stage Career Investigator Award for Vaccinology by NFID 2010 which will allow me to attend the 14th Annual Conference on Vaccine Research.

As mentioned previously, the CID article on diagnosing viral respiratory disease captured the interest of the 2010 Quality in Geriatric and Long-Term Care Conference planning committee. Hence I will be holding a workshop at Vanderbilt University Medical Center on September 24, 2010.

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Safety and Immunogenicity of Inactivated, Vero Cell Culture-Derived Whole Virus Influenza A/H5N1 Vaccine Given Alone or with Aluminum Hydroxide Adjuvant in Healthy Adults

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Abstract

Dosage-sparing strategies, adjuvants and alternative substrates for vaccine production are being explored for influenza vaccine development. We assessed the safety and immunogenicity of a Vero cell culture-grown inactivated whole virus influenza A/H5N1 vaccine with or without aluminum hydroxide adjuvant [$Al(OH)_3$] in healthy young adults. Vaccines were well tolerated, but injection site discomfort was more frequent in groups receiving $Al(OH)_3$. Dose-related increases in serum antibody levels were observed. Neutralizing antibody titers varied significantly when tested by two different laboratories. $Al(OH)_3$ did not enhance HAI or neutralizing antibody responses, and contributed to increased injection site pain. Because influenza antibody titers vary significantly between different laboratories, international standardization of assays is warranted.

Keywords

Influenza A/H5N1 vaccines; cell culture; adjuvant; aluminum hydroxide

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http://clinicaltrials.gov/ct2/show/NCT00382980?term=H5N1%2C+adjuvant&rank=5

1. INTRODUCTION

Global efforts are underway to develop vaccines for a potential influenza pandemic, particularly for influenza A/H5N1 [1]. In the decade since the emergence of the H5N1 avian strain, clinical vaccine trials have demonstrated the need for large quantities of H5 hemagglutinin (HA) and/or inclusion of an adjuvant to generate adequate immune responses in humans [2]. This observation has stimulated the search for antigen-sparing strategies such as use of more potent adjuvants, alternative methods of vaccine administration (e.g., intradermal injection), and use of whole virus (WV) preparations. Furthermore, efforts continue to develop methods other than growth in eggs for more efficient and controlled production of both pandemic and interpandemic influenza vaccines.

The potential of conventional aluminum hydroxide adjuvant [$Al(OH)_3$] to enhance immunogenicity has been evaluated repeatedly in clinical trials of H5N1 vaccines [3-5]. In earlier trials, $Al(OH)_3$ failed to confer clinically significant increases in immune responses when formulated with egg-grown subvirion (SV) inactivated vaccines. However, promising results with $Al(OH)_3$ have been reported with WV H5N1 vaccines [6-8]. Earlier studies suggested that some, but not all WV vaccines were more immunogenic than SV vaccines [9,10].

Results of a recent trial of a WV influenza A/H5N1 vaccine demonstrated that most subjects given a standard dosage developed detectable neutralizing (Neut) antibody responses, and that the inclusion of $Al(OH)_3$ did not enhance responses [11]. The purpose of our study was to assess safety and immunogenicity of the same WV H5N1 vaccine in a placebo-controlled trial in which a higher dose of vaccine antigen was evaluated. The vaccine evaluated in this report was also unique since it was constructed using a wild type (wt) seed virus grown in tissue cell culture, as opposed to using genetically altered recombinant viruses grown in eggs or purified recombinant hemagglutinin (HA) produced in cell culture systems [12,13]. In addition, neutralizing antibody responses were determined in a subset of subjects by two different laboratories in order to compare assay results directly.

2. MATERIALS AND METHODS

2.1 Vaccines

Ultraviolet and formalin-inactivated WV influenza A/H5N1 vaccine was prepared using wt A/Vietnam/1203/04 grown in Vero cells [14; Baxter]. Six study groups were compared. Two dosage levels (7.5 and 15μg of HA/0.5mL dose) were pre-formulated with or without aluminum hydroxide [$Al(OH)_3$] adjuvant; a dose of 45μg of HA/0.5mL was formulated without $Al(OH)_3$. The $Al(OH)_3$ content in the adjuvanted vaccines was 350μg per dose. Saline placebo was used as the control vaccine. Vaccines were prepared in single-dose prefilled syringes.

2.2 Study Design and Subjects

A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted at four NIH-funded Vaccine Treatment and Evaluation Unit sites. Written informed consent was obtained from potential subjects prior to screening. Healthy non-pregnant females and males between the ages of 18 and 40 years who had no history of severe reactions to influenza vaccines, no known suppression of the immune system, and who had not previously received an influenza A/H5 vaccine were eligible. The study was conducted in accordance with protocols approved by Institutional Review Boards at each of the participating study sites.

2.3 Study Procedures

The study was conducted in two stages. During stage 1, prior to vaccination, eligible subjects had to demonstrate normal laboratory assessments, including total white blood cell count, hemoglobin, platelet count, alanine amino-transferase, and creatinine. Subjects were randomized to one of the 6 vaccine groups (approximately 15 subjects per group). Subjects received two doses of vaccine in the deltoid muscle approximately 28 days apart. Vaccinations were administered by unblinded vaccinators who were not involved in safety assessments. Subjects were observed for 30 minutes after each immunization. For seven days after each immunization, subjects recorded their oral temperature and the presence and severity of injection site reactions (pain, tenderness, redness and swelling) and systemic symptoms (fever, malaise, myalgia, headache, and nausea) on a memory aid. The severity of solicited adverse events (AEs) was scored on a scale from 0 to 3: 0=absence of the symptom; 1=mild symptom that did not interfere with activity; 2=moderate symptom that interfered with activity; and 3=severe, prevented daily activity. Injection site redness and swelling were graded on the diameter of measurement, with 0=none; 1=small (<2 cm); 2=medium (2-5 cm); and 3=large (>5 cm). Fever was defined as an oral temperature ≥100°F. Serious adverse events (SAEs) were defined as life-threatening AEs, or AEs that resulted in significant or persistent disability, congenital anomalies, hospitalizations, or death. All AEs reported during the first 2 months after enrollment were recorded, and SAEs were reported during the entire 7-month study period.

Subjects were seen in the clinic on days 2 and 8 after each immunization to review their memory aids. Blood samples for laboratory safety assessments (as described above for screening) were repeated on day 7 after each immunization in Stage 1. One month after each immunization and 6 months after the second dose, interim medical history was reviewed and serum samples for antibody assays were collected

Seven-day clinical and laboratory safety data in Stage 1 participants were reviewed by the Safety Monitoring Committee prior to enrollment of subjects into Stage 2. In Stage 2 of the study (approximately 35 subjects per group), identical procedures were performed, with the exception that blood samples for laboratory screening were not collected.

2.4 Laboratory assays

Hemagglutination-inhibition (HAI) and neutralization assays were performed at Southern Research Institute (SR), as described previously [15,16]. For both assays, a significant antibody response, or seroresponse, was defined as a four-fold or greater increase in antibody titer after immunization (if antibody was detectable in the preimmunization sample) or an increase in titer from <10 before immunization to ≥40 after immunization [17]. Neutralization antibody assays were performed at both SR and Baxter [11]. The SR reference laboratory assayed all serum samples, while the Baxter laboratory assayed only a subset of 100 subjects who had consented to the future use of their specimens and who were randomly selected based on the SR results to be representative of the SR titer distribution, specifically limiting the selection to include only 5 placebo recipients. Both laboratories were blinded to sample identity. A brief overview of the two neutralizing antibody assay procedures is provided in Table 1.

2.5 Statistical analyses

The primary objectives of the study were to determine the dose-related safety of a Vero cell culture-grown WV inactivated H5N1 vaccine with or without $Al(OH)_3$ in healthy adults; and to assess the potential for $Al(OH)_3$ to enhance immune responses after immunization. The primary reactogenicity endpoints were the frequency and severity of AEs and SAEs after immunization. The primary immunogenicity endpoints included the proportion of

subjects in each dose group achieving a serum HAI or neutralizing antibody titer of ≥40 against the influenza A/H5N1 virus 28 days after receipt of the second dose of vaccine; and the geometric mean titer (GMT) and frequency of ≥4-fold rises in HAI and neutralizing antibody titers in each group one month after receipt of dose 2. Secondary endpoints were immune responses at 1 month after receipt of the first dose and six months after the second dose.

Solicited reactogenicity was analyzed by taking the most severe response over the follow-up period and dichotomizing into a binary variable: none versus mild/moderate/severe. Overall comparisons among treatment groups were made using Fisher's exact test. Further analyses were conducted using multivariate logistic regression separately for each vaccination and each symptom.

Immune responses were summarized in terms of H5-specific neutralization and HAI antibody titers, transformed to a logarithmic scale for analyses, and the proportion of subjects achieving a neutralization titer ≥40 at 28, 56, and 208 days after the initial vaccination was noted. Fisher's exact test and ANOVA (F test) were used to compare differences among treatment groups for 4-fold rise and GMT, respectively. Univariate and multivariate logistic regression and linear regression were conducted for 4-fold responses and GMT, respectively. The Cochran-Armitage trend test was performed to explore the dose response. The scores of the dosages for this test were defined as 7.5, 15 and 45. One-sided exact p values were selected.

Neutralization assays were performed at both SR and Baxter, and comparisons of GMT and 4-fold rises were made. A paired t-test was utilized to determine the confidence intervals and p-values of the GMTs; while for ≥4-fold rises, Fisher's exact test was performed. Pearson and Spearman correlation coefficients were also calculated with no adjustments made for multiple comparisons.

3. RESULTS

Enrollment into the trial was rapid, with stage 1 beginning in October 2006 and stage 2 enrollment completed during January 2007. A total of 308 subjects were enrolled (93 in stage 1, and 215 in stage 2), with 299 (98%) receiving both doses of vaccine and providing a blood sample 1 month after the second dose, and 293 providing a blood sample 6 months after receipt of the second dose. Baseline demographic characteristics and preimmunization serum HAI and neutralizing antibody GMTs of enrolled subjects are shown in Table 2 and did not differ among the six vaccine groups.

3.1 Safety and Reactogenicity

Safety—All 6 vaccine formulations were safe and well tolerated; no subjects refused the second dose as a result of injection site or systemic reactions following receipt of the first dose. Only three SAEs were reported during the study period, and none was considered vaccine-related (one subject was hospitalized for multiple traumatic fractures; one for surgical repair of a foot fracture, and one for histoplasmosis in an immunocompetent subject).

Injection Site Reactogenicity—One subject in the 45μg without $Al(OH)_3$ vaccine group developed a large area of injection site redness (maximum diameter of 5.4 cm) on days 1 and 2 after receipt of the second dose of vaccine; this subject had previously developed an area of injection site erythema of 3.8cm in diameter after the first dose. No other grade 3 injection site reactions were reported.

Injection site pain and tenderness were the most common solicited AEs during the week after each vaccination. The percentages of subjects reporting any injection site tenderness after receipt of dose 1 are shown in Figure 1. Although the frequency of injection site tenderness was significantly lower in the group given placebo when compared with the other vaccine groups combined ($p<0.05$; Fisher's exact test), there were no significant differences among the other vaccine groups ($p=0.28$; Fisher's exact test). Most reactions were mild, peaked on day 1-2 after vaccination, and resolved within a day or two (data not shown). In multivariate analyses, increasing dosage level was associated with significantly more injection site swelling after dose 1 only. Female gender and younger age were also associated with more injection site tenderness after the first dose ($p<0.05$ for each; data not shown), and after dose 2, dosage level ($p<0.05$), and female gender and younger age ($p<0.01$ for each) were associated with a higher frequency of injection site tenderness (data not shown).

Systemic Reactogenicity—Three subjects experienced grade 3 systemic reactions during the week after receipt of dose 1, but only 1 was considered vaccine-related (malaise on day 0 in a subject given the 15μg without $Al(OH)_3$ vaccine formulation). Three other subjects experienced grade 3 systemic reactions during the week after dose 2, and two of these were considered vaccine-related: 1 reported malaise, headache and myalgia on days 2, 3 and 6 after vaccination; and the other developed headache on day 2 after vaccination. Both of these subjects were in the 7.5μg with $Al(OH)_3$ group. Fever during the week after immunization was uncommon (0-3 persons/vaccine group after each dose). In multivariate analyses, younger age was associated with a higher frequency of nausea after the first dose of vaccine, and female gender was associated with a higher frequency of nausea after the second dose of vaccine ($p<0.05$ for both; data not shown).

3.2 Immunogenicity

Dose-Response Relationships—Serum antibody responses one month after each dose of vaccine, determined in the SR lab, are shown in Table 3 and Figure 2. The highest responses after the second dose of vaccine were seen in the group given 45μg without $Al(OH)_3$, with 40% and 44% of subjects in this group developing four-fold or greater increases in HAI and neutralizing antibody titers, respectively. One month after each dose of vaccine, statistically significant increases in HAI and neutralizing antibody responses from baseline values in terms of GMTs, proportions of subjects with a ≥4-fold increase in titer, and the proportions of subjects with a titer ≥40 were noted among all vaccine groups ($p\leq 0.01$ for each comparison).

In the groups given vaccine containing $Al(OH)_3$, dose-related increases in the GMTs of serum HAI antibody after the first dose ($p<0.05$), and increases in GMTs of neutralizing antibody after the second dose ($p<0.01$) were observed. For the non-adjuvanted vaccine groups, significant dose-responses for HAI and neutralizing antibody were seen after the second dose of vaccine in terms of GMTs, proportions of subjects with a ≥4-fold increase in titer, and the proportions of subjects with a titer ≥40) ($p<0.02$ for all comparisons). At six months after receipt of the second dose, dose-related increases in antibody responses persisted among groups receiving non-adjuvanted vaccines for all HAI and neutralizing antibody response parameters, with the exception of GMT of HAI antibody ($p<0.05$ for all comparisons). In contrast, dose-response relationships among groups given adjuvanted vaccine persisted only for GMT of neutralizing antibody ($p<0.05$).

Effect of $Al(OH)_3$ Adjuvant on Immune Responses—HAI and neutralizing antibody GMTs were significantly higher ($p<0.05$ for both) after the first dose containing 7.5μg without $Al(OH)_3$ when compared with group given 7.5μg with $Al(OH)_3$. Neutralizing

antibody GMTs were significantly higher in the group given 15μg without $Al(OH)_3$ when compared with group given 15μg with $Al(OH)_3$ after the first and second doses ($p<0.03$ for each), and in the group given 7.5μg without $Al(OH)_3$ when compared with the group given 7.5μg with $Al(OH)_3$ after the second dose ($p<0.02$). At six months after receipt of the second dose of vaccine, GMTs of neutralizing antibody were significantly greater among groups given 7.5 or 15μg without $Al(OH)_3$ when compared with subjects given the same dose with $Al(OH)_3$.

Serum Antibody Response Frequencies Using an Alternative Definition— While the EMEA and FDA have harmonized definitions of serum HAI antibody responses as outlined in the Methods section [17,18], traditional definitions of a four-fold or greater increase in antibody titer did not require attainment of a titer of at least 40 after immunization. Therefore, an increase in titer from undetectable before immunization (<10) to ≥ 20 after immunization was considered a seroresponse. To bridge results from prior influenza vaccine studies (including earlier pandemic vaccine evaluations) using more traditional definitions of seroresponse, the frequencies of HAI and/or neutralizing antibody responses were recalculated such that no minimum post-immunization titer was required: 0, 38%, 53% and 77% of subjects given 0, 7.5, 15 and 45μg doses without $Al(OH)_3$ responded, compared with 16% and 38% of subject given 7.5 and 15μg doses with $Al(OH)_3$ (Figure 3). Once again, dose-related increases in antibody responses were observed, and the inclusion of $Al(OH)_3$ reduced the frequencies of all immune responses.

Comparison of Neutralizing Antibody Results Obtained from Two Different Laboratories—A subset of sera collected from 100 subjects before and 1-month after each dose of vaccine was assayed in both a reference laboratory (SR) and in the laboratory of the vaccine manufacturer to bridge the results of clinical trials being conducted in the U.S to those conducted in Europe [11, current study]. Sera collected from 5 placebo subjects and 14-22 subjects from each of the 5 vaccine groups were tested.

Clear dose-response relationships in GMTs were observed in assays performed in both the SR and Baxter laboratories (data not shown); however, a significant dose-response relationship in ≥4-fold responses was observed in the SR assay only. For example, among subjects given 7.5, 15 or 45μg of vaccine without $Al(OH)_3$, 5.9 (0.1, 28.7), 28.6 (8.4, 58.1) and 45.5 (24.4, 67.8) percent (95% C.I.) developed a 4-fold or greater rise in neutralizing antibody titer after 2 doses in the SRI assay ($p<0.01$; Cochran-Armitage trend test). The corresponding percentages and 95% C.I. for the Baxter assay were 23.5 (6.8, 49.9), 42.9 (17.7, 71.1) and 50.0 (28.2, 71.8) ($p=0.08$; Cochran-Armitage trend test). Neutralizing antibody GMTs were significantly higher ($p<0.05$; paired t-test) using the Baxter assay when compared with the SR assay at all timepoints (before and 1 month after each immunization), with the exception of the pre-immunization titer in the group given 45μg without $Al(OH)_3$ (data not shown). When results for all 100 subjects are considered, the titer ratios (Baxter/SR) for GMT (95% CI) were 1.3 (1.2, 1.4); 2.23 (1.9, 2.6); and 1.89 (1.7, 2.1) before and 1 month after dose 1, and after dose 2, respectively ($p<0.01$ for all comparisons; paired t test). In general, the assay results were highly correlated for GMT (Spearman correlation coefficient=0.835 after 2 doses; Figure 4).

Because starting dilutions for the 2 assays differed, direct comparisons between the proportions of subjects who achieved a neutralizing antibody titer of at least 20 after receipt of 2 doses were made (Figure 5). Although no placebo recipient achieved a titer ≥20 after 2 doses in either assay, significant dose-related increases in the proportions of subjects with a titer ≥20 after 2 doses were observed with the SR assay only ($p< 0.01$; Cochran-Armitage trend test). The proportions of subjects who achieved a titer ≥20 using the Baxter assay were higher when compared with the SR assay ($p<0.01$; Fisher's Exact test), and a marginal dose-

response relationship was observed (p=0.054; Cochran-Armitage trend test). After 2 doses of vaccine or placebo, 30 subjects achieved a titer ≥20 in the Baxter assay but not the SR assay; 1 achieved a titer ≥20 in the SRI assay but not the Baxter assay; 42 achieved a titer ≥20 in both assays; and 27 failed to achieve a titer ≥20 in either assay. These responses were highly non-concordant between the two laboratories (p<0.01; McNemar's test).

4. DISCUSSION

Our data confirm that this novel inactivated whole virus vaccine prepared in Vero cells using a wild type influenza A/H5N1 virus was safe and immunogenic when administered to healthy adults. Dose-related increases in injection site reactogenicity were observed; however, all dosage levels were well tolerated. Inclusion of AlOH was associated with a somewhat higher frequency of injection site reactogenicity in the absence of increased systemic reactogenicity, as noted in previous studies using this preparation, as well as other adjuvanted subunit influenza vaccines [3,4,11]. Dose-related increases in serum antibody responses were observed, with the 45 μg dose without $Al(OH)_3$ providing the highest responses. Responses were significantly lower among subjects given vaccines containing $Al(OH)_3$ when compared with those given the same dosage of vaccine without adjuvant. Other reports have shown similar suppression of immune responses with the addition of $Al(OH)_3$ [3,4,11].

Serum HAI and neutralizing antibody response frequencies were moderate, even at the highest dosage level using current definitions, similar to results from other recent trials of SV influenza A/H5N1 vaccines [4,12]. Nevertheless, more than 50% of subjects given two-15μg doses without $Al(OH)_3$ responded using a more traditional definition of seroresponse, and 77% of subjects given two 45μg doses without $Al(OH)_3$ had a 4-fold or greater increase in HAI and/or neutralizing antibody. In spite of these immune responses, fewer than half of subjects receiving the highest amount of antigen achieved the putative protective HAI titer of 40 after two doses. Antibody responses against drifted H5 variants were not assessed in this study; however, it is likely these responses would be lower than those seen when measured against the homologous vaccine antigens [19]. Similar trends have been observed with candidate H5N1 vaccines where higher levels of antibody to the vaccine virus are associated with somewhat lower levels of antibody directed against drifted variants [11,20,21]. Because the precise pandemic strain is unknown, efforts must continue to develop prepandemic vaccines capable of eliciting antibody against both homologous and drifted variants.

The results of our study extend those reported by Ehrlich and colleagues using the same vaccine [11]. However, in contrast to the previous report, definite dose-responses were observed in both HAI and neutralizing antibody assays. In order to bridge the results between clinical trials conducted in different parts of the world, neutralizing antibody assays were performed on a subset of sera in the two laboratories responsible for assessing vaccine immunogenicity for the two clinical trials. Interestingly, the Baxter assay appeared somewhat more sensitive than the SR assay. The reasons for this are not known, but there are significant differences in assay methods. For example, the virus used in the Baxter assay is the wild type (wt) virus, in contrast to the SR assay, which uses a recombinant virus. As the vaccine was prepared using wild type virus, the match between test antigen and vaccine antigen is likely closer for the Baxter assay. Hoschler et al. previously demonstrated that use of wt virus yielded higher GMT values when compared with rg viruses (22). Another major difference is the longer duration of the incubation period with the Baxter assay, likely contributing to greater sensitivity. Nevertheless, clear dose-response relationships for GMTs were noted in both assays (data not shown). Our results underscore the complex issues related to comparing serologic results obtained in different laboratories. Conclusions

regarding the immunogenicity of a vaccine are highly dependent on the assays used to assess endpoints used, and the definitions of significant response and putative protective titer. Stephenson et al. recently reported comparisons of serum HAI and neutralizing antibody assays against interpandemic influenza strains in different laboratories using aliquots of the same serum samples and noted considerable inter-laboratory variability with greatest differences in the neutralizing antibody values [23]. With the necessity of comparing results of clinical trials of candidate pandemic influenza vaccines around the world, an international collaborative effort is in progress to develop an international H5N1 antibody standard that should reduce inter-laboratory variability. Alternatively, head-to-head comparative trials of various vaccines with serology measured in a single lab could be performed. Differences in assay methods and results obtained in different laboratories pose challenges to regulatory authorities who must determine which vaccines to license, purchase and stockpile.

Our study did not explore several issues that are relevant for the use of WV vaccines. First, although the vaccine formulations were well tolerated in the adults studied, safety and reactogenicity issues still need investigation in pediatric age groups, especially young children. Previous administration of egg-grown A/ New Jersey/76 (H1N1) WV vaccines to young children resulted in a high frequency of fever and systemic reactions [24]. Another area needing investigation is a direct comparison of the safety and immunogenicity of the WV vaccine with that of a corresponding subvirion (SV) preparation. Although WV vaccines have been considered more immunogenic than SV vaccines, comparisons of the immunogenicity of the two products have not been performed using well-standardized assays.

The results of this and other recent clinical trials of candidate pandemic influenza vaccines raise concern about the value of including $Al(OH)_3$ adjuvant in WV and SV influenza vaccines. While modest enhancement of immunogenicity has been observed in some trials at some antigen dosage levels, the lack of an adjuvant effect in this trial as well as the increase in local reactions are problematic. Other novel adjuvants, including ASO3 and MF59, have markedly enhanced immune responses to H5 and H9 vaccines in earlier studies [20,21,23,25,26] and would be interesting to assess with this vaccine. Cautious evaluation of this and other WV preparations in other age groups, particularly children, is warranted.

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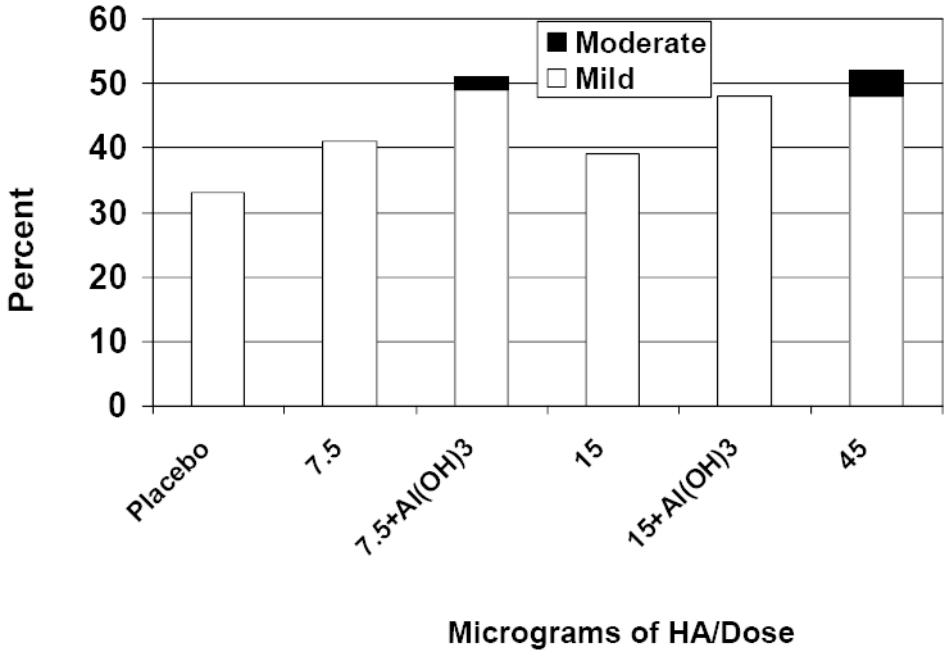


Figure 1.
Percent of Subjects with Injection Site Tenderness after the First Dose

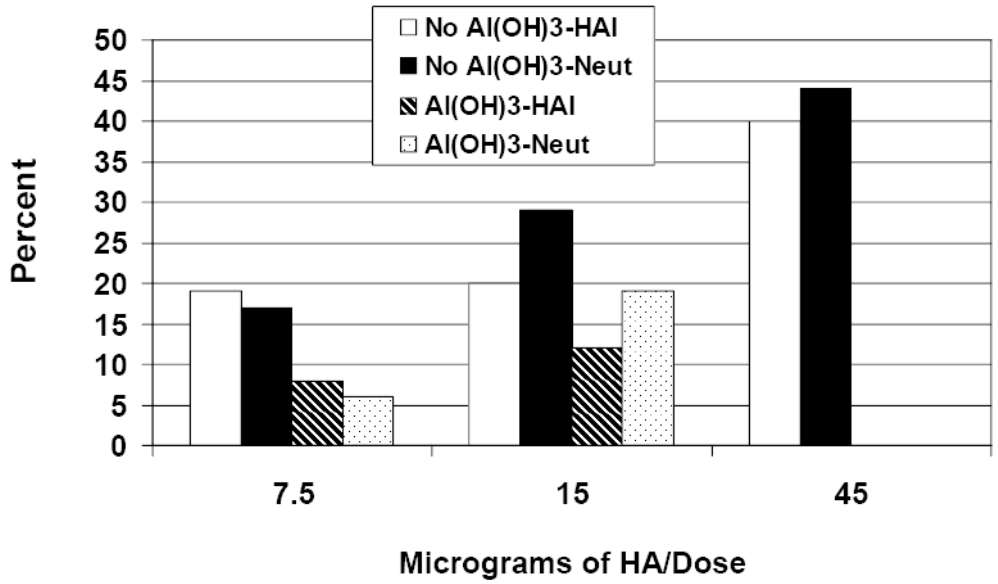


Figure 2.
Percent of Subjects with Serum HAI and Neutralizing Antibody Titer ≥40 after Two Doses

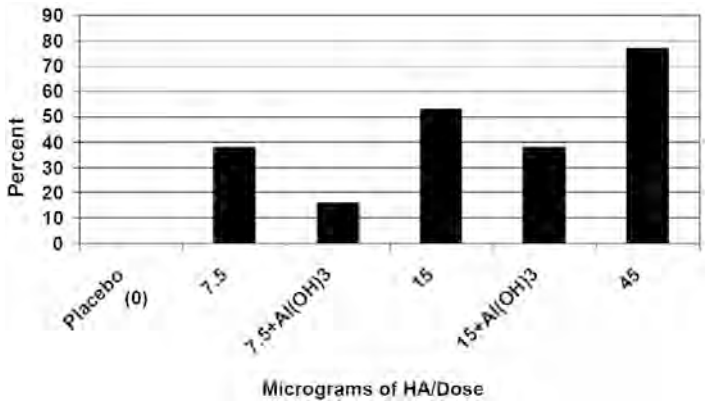


Figure 3.
Percent of Subjects with ≥ 4-Fold Increase in Serum HAI and/or Neutralizing Antibody Titer after Two Doses (No Minimum Post Vaccination Titer Requirement)

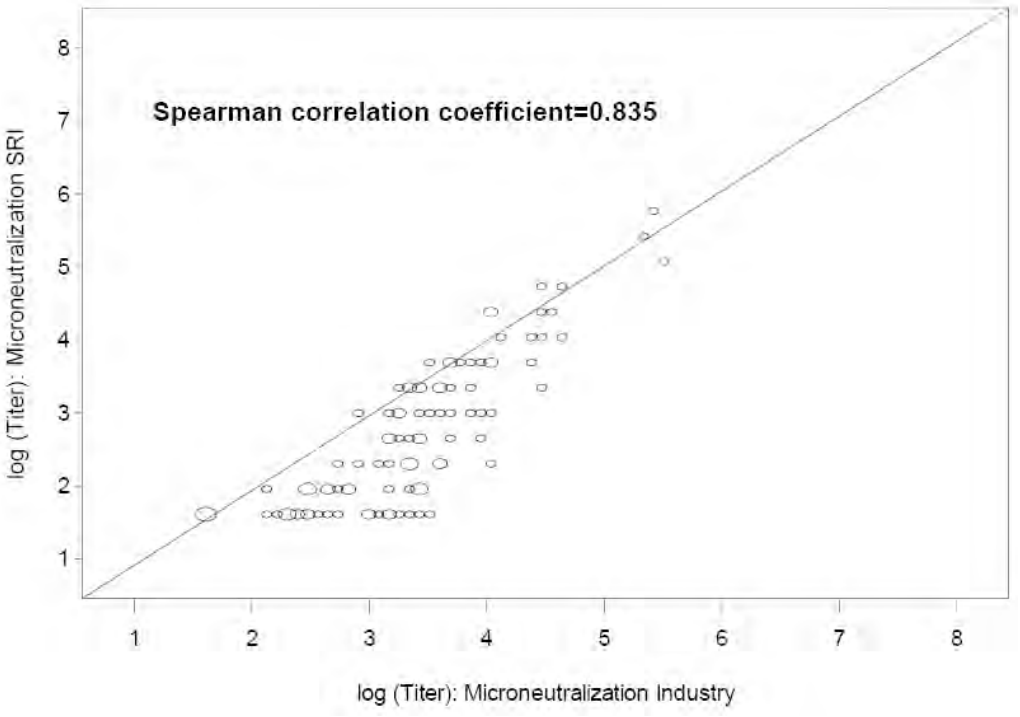


Figure 4.
Correlation between Serum Neutralizing Antibody Titers When Comparing Results Using Two Different Assays

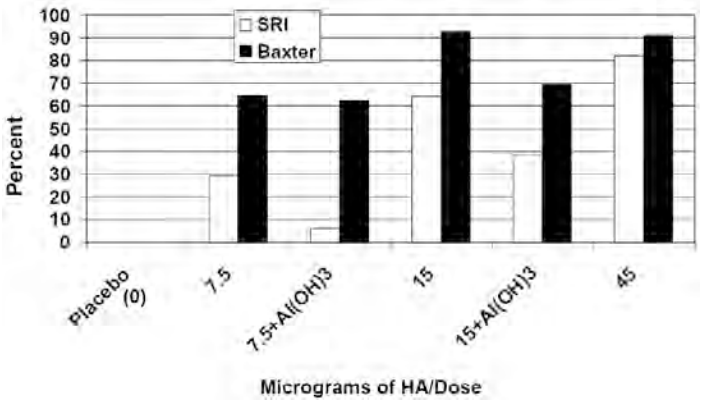


Figure 5.
Percent of Subjects with a Neutralizing Antibody Titer ≥20 after Two Doses: *SR vs. Baxter Results*

Table 1

Comparison of SR Laboratory and Baxter Laboratory Neutralizing Antibody Assay Methods

Parameter	Baxter Lab	SR Lab
Virus Type, Growth Substrate	Wild type, Vero cells	Reverse Genetics, Egg-derived
Initial Serum Dilution	1:5	1:10
Dilution Factor	2-fold	2-fold
Diluent	Cell culture medium	DMEM
Virus Inoculum	100 $TCID_{50}$	100 $TCID_{50}$
Initial Incubation Time* and Temperature	1 hour (Room temperature)	2-2.5 hours (37° C)
Assay Substrate	Vero cells; monolayer	MDCK cells; suspension
Second Incubation	5 days (37° C)	19-21 hours (37° C)
Assay Endpoint	Cytopathic effect (50%)	ELISA: Detection of nucleoprotein
Replicates	8/sample	2/sample

*Neutralization time with virus-serum mix

Table 2

Baseline Characteristics of Enrolled Subjects

	VACCINE GROUPS						
	7.5 μg (N= 49)	**7.5 μg +Al(OH)$_3$ (N= 51)**	**15 μg (N= 51)**	**15 μg + Al(OH)$_3$ (N= 50)**	**45 μg (N= 54)**	**Placebo (N= 51)**	**p-value**
Gender – N (%)							0.079
Male	19 (39)	27 (53)	25 (49)	23 (46)	24 (44)	22 (43)	
Female	30 (61)	24 (47)	26 (51)	27 (54)	30 (56)	29 (57)	
Ethnicity – N (%)							0.45
Non-Hispanic	38 (78)	42 (82)	41 (80)	46 (92)	46 (85)	44 (86)	
Hispanic	11 (22)	9 (18)	10 (20)	4 (8)	8 (15)	7 (14)	
Race – N (%)							0.23
Asian	5 (10)	8 (16)	4 (8)	3 (6)	8 (15)	8 (16)	
Hawaiian/Pacific Islander	0	0	1 (2)	1 (2)	2 (4)	0	
Black/African American	3 (6)	3 (6)	5 (10)	5 (10)	6 (11)	6 (12)	
White	31 (63)	36 (71)	39 (76)	37 (74)	31 (57)	35 (69)	
Multi-Racial	3 (6)	1 (2)	1 (2)	3 (6)	5 (9)	0	
Other/Unknown	7 (14)	3 (6)	1 (2)	1 (2)	2 (4)	2 (4)	
Age							0.28
Mean (STD)	26.5 (4.6)	28.7 (5.9)	27.5 (5.4)	27.4 (6.3)	28.2 (5.8)	26.6 (5.6)	
Antibody Level*							
HAI GMT (CI)	5.0 (5.0,5.1)	5.0 (-)	5.3 (4.7,5.9)	5.5 (4.8,6.2)	5.0 (-)	5.1 (4.9,5.9)	0.42
Neut GMT (CI)	5.0 (-)	5.1 (4.9,5.2)	5.4 (4.8,6.1)	5/5 (4.9,6.1)	5.2 (4.9,5.6)	5.4 (4.9, 5.9)	0.57

*As determined in the SR Laboratory

Abbreviations: $AlOH_3$=aluminum hydroxide; HAI=hemagglutination inhibition; Neut=neutralizing; GMT=geometric mean titer

Table 3

Serum HAI and Neutralizing Antibody Responses One Month after Each Dose of Vaccine or Placebo and Six Months after the Second Dose

Parameter		Dosage Level (μg of HA)					
		7.5		15		45	Placebo
$Al(OH)_3$ Adjuvant		No (N=48)	Yes (N=50)	No (N=49)	Yes (N=48)	No (N=54)	NA (N=50)
HAI Antibody	GMT-dose 1*	6.2 (5.0,7.7)	5.0 (-)	8.2 (5.9,11.3)	6.1 (5.0,7.4)	10.1 (7.1,14.2)	5.0 (5.0,5.1)
	GMT-dose 2	10.5 (7.0,15.7)	6.7 (5.4,8.4)	9.4 (6.6,13.4)	8.1 (6.2,10.6)	18.1 (12.1,27.0)	5.0 (5.0,5.1)
	GMT-6 months	5.5 (4.8,6.2)	5.3 (4.8,5.8)	6.4 (5,2,8.0)	6.5 (5.1,8.2)	7.3 (5.8,9.2)	5 (-)
	% Responding-dose 1**	8	0	12	2	17	0
	% Responding-dose 2	19	8	18	8	40	0
	% Responding-6 months	2	2	8	4	13	0
Neut Antibody	GMT-dose 1*	6.8 (5.5,8.5)	5.2 (4.9,5.5)	9.3 (7.0,12.3)	6.1 (5.1,7.2)	10.6 (7.6,14.7)	5.4 (4.9,5.8)
	GMT-dose 2	13.4 (9.6,18.9)	8.3 (6.8,10.1)	19.7 (14.9,26.2)	12.7 (9.8,16.4)	31.3 (23.9,40.9)	5.4 (5.0,5.9)
	GMT-6 months	9.1 (7.0,11.7)	5.8 (5.2,6.4)	11.3 (8.8,14.4)	7.6 (5.9,9.6)	19.2 (15.7,23.5)	5.5 (4.9,6.0)
	% Responding-dose 1**	10	0	10	0	19	0
	% Responding-dose 2	17	6	27	17	44	0
	% Responding-6 months	6	0	10	6	25	0

*Geometric mean titer (95% confidence intervals)

**Four-fold or greater increase in titer when compared with preimmunization titer and titer ≥40 after immunization.

2009 T. Franklin Williams Scholars
18-Month Questionnaire

Presentation and publications

1. Presentation at institution within division of geriatrics. (Seven responses)
   Zero – 3 (43%)
   One – 1 (14%)
   Two – 2 (29%)
   Three – 1 (14%)

   Description of presentation(s)

- Talked about immune responses in our center research meeting and also talked about viral pneumonias in older adults to the geriatric continuing education conference.
- Presented at the University of Pennsylvania, Geriatrics Grand Rounds, Geriatrics Division/Spring 2010 on the topic of "Kidney transplantation for the elderly." Also presented at a Fellow lecture series for the Geriatrics Division on the topic of "Considerations in renal replacement therapy for elderly individuals."
- Presented data on the topic of "Management of type-2 diabetes in elderly patients" at the 2010 Quality in Geriatric and Long-Term Care Conference - September 24, 2010. Also gave talk to geriatric residents on "Lipid metabolism and aging, how to live beyond 100," which is given twice-yearly to geriatric residents. Presented to the Geriatrics Division on, "Aging, obesity and risk of cardiovascular disease"

2. Presentation at your institution within specialty. (Seven responses)
   Zero – 1 (14%)
   One – 3 (43%)
   Two – 2 (29%)
   Three – 0
   Four – 1 (14%)

   Description of presentation(s)

- Gave a presentation on Phenotyping Frailty"
- Presented at a General Internal Medicine Research Conference
- Presented at Renal grand rounds on the subject of "Age rationing in kidney transplantation"
- Presented at the Second Annual Cardiovascular Research Day, as an invited speaker, on the topic of "Glucose as a Driver of Postmenopausal Dyslipidemia." Also presented at the:
  - Endocrine Grand Rounds: "Aging, Obesity and Cardiovascular Disease: Are we too fat, or not fat enough?"
  - Geriatrics talks to Endocrine Fellows: "Geriatric Considerations in General Endocrinology" Geriatrics talks to Endocrine Fellows: "Lipid metabolism in aging"

- Presented at Geriatrics Grand rounds and Pepper center review on the topic of "Age related changes of angiotenisn receptors."

3. Presentation or workshop at a professional conference or another institution. (Eight responses)
   Zero – 3 (37.5%)
   One – 0 (0%)
   Two – 2 (25%)
   Three – 2 (25%)
   Four – 1 (12.5%)

Description of presentation(s)

- Presented research at the Gerontological Society of America Annual Meeting and the American Geriatrics Society Annual Meeting
- Presented at Johns Hopkins University School of Medicine on "The ethics of age-rationing in kidney transplantation" Will be giving invited talks at the Mayo Clinic and Drexel University in March 2011 and will speak on the topic of my Williams research
- Gave oral presentation on the "Management of type-2 diabetes in elderly patients" and a poster presentation on "Context-Dependent Role of CETP in a mouse model of Postmenopausal Dyslipidemia" at the American Geriatrics Society 2010 Annual Meeting.
- Presented two posters titled, "Epidemiology of ICU admission in HIV-infected vs. uninfected patients," and "Risk factors and role of HIV in ICU admission: Risk with age in HIV-infected patients" at the American Thoracic Society (ATS) International meeting. Also:
    - Presented at the Veterans Aging Cohort Study annual meeting (closed meeting) on aging HIV-infected patients
    - Recently accepted abstract for ATS 2011 further investigating impact of age on ICU admission and survival in HIV-infected patients
- Presented a poster at the at the AAAAI national meeting in New Orleans.
    - Presented a poster at the ACRT national meeting in Washington, DC.

4. Publication of a peer-reviewed article. (Eight responses)
   Zero – 1 (12.5%)
   One – 2 (25%)
   Two – 4 (50%)
   Three – 0
   Four – 0
   Five – 1 (12.5%)

   Citation of peer-reviewed publication(s)

- Talbot HK, Falsey AR. The Diagnosis of Viral Respiratory Disease in the Older Adults. Clinical Infectious Diseases; 50(5):747-51, 2010. PMID: 20121411 PMC2670238
    - Talbot HK, Griffin MR, Chen Q, Zhu Y, Williams JV, Edwards KE. Effectiveness of Seasonal Vaccine in Preventing Confirmed Influenza-Associated Hospitalizations Community Dwelling Older Adults. JID in press.

- Huang AJ, Subak LL, Thom DH, Van Den Eeden SK, Ragins AI, Kuppermann M, Shen H, Brown JS. Sexual function and aging in racially and ethnically diverse women. Journal of the American Geriatrics Society. 2009 (57):1362-1368. [PMC2749599]
    - Huang AJ, Moore EE, Boyko EJ, Scholes D, Lin F, Vittinghoff E, Fihn SD. Vaginal symptoms in postmenopausal women: self-reported severity, natural history, risk factors. Menopause. 2010 (17):121-126. [PMC2806500]
    - Huang AJ, Luft J, Grady D, Kupperman M. The day-to-day impact of urogenital aging: perspectives from racially/ethnically diverse women. Journal of General Internal Medicine. 2010 (25): 45-51. [PMC2811605]
    - Huang AJ, Subak LL, Wing R, West DS, Hernandez AL, Macer J, Grady D. An intensive behavioral weight loss intervention and hot flushes in women. Archives of Internal Medicine. 2010 (170): 1161-1167. [PMID 20625026]
    - Farhat GN, Cummings SR, Chlebowski RT, Parimi N, Cauley JA, Rohan TE, Huang AJ, Vitolins M, Hubbell A, Manson JE, Cochrane BB, Lane DS, Lee JS. Sex hormones and risk of estrogen receptor-negative and estrogen receptor-positive breast cancer. Journal of the National Cancer Institute (in press).
- Reese PP, Caplan AL, Abt P, Bloom RD, Karlawish J: Should we use age to ration health care? The case of kidney transplantation. Journal of the American Geriatrics Society. Sept 9 2010 [Epub ahead of print]
    - Blosser CD, Huverserian A, Bloom RD, Abt PD, Goral S, Thomasson A, Shults J, Reese PP. Age, exclusion criteria and generalizability of randomized trials enrolling kidney transplant recipients. Accepted by Transplantation.
- Wu, K., D. Cappel, M. Martinez, and J.M. Stafford. 2010. Impaired-inactivation of FoxO1 contributes to glucose-mediated increases in serum VLDL. Endocrinology. 115 (8): 3566-3576.
- Journal of Intensive Care medicine: epidemiology of HIV in the ICU (review in press)
    - Proceedings of the American Thoracic Society: antiretroviral therapy in the ICU (review in press)
- Angiotensin II Type-2 Receptors Modulate Inflammation Through Signal Transducer and Activator of Transcription Proteins 3 Phosphorylation and TNFα Production. Abadir PM, Walston JD, Carey RM, Siragy HM. J Interferon Cytokine Res. 2011 Feb 2.
- Nyenhuis, SM, Schwantes EA, Evans M, Mathur SK. "Airway Neutrophil Inflammatory Phenotype in Older Asthma Subjects" J Allergy Clin Immunol, 2010; 125: 1163-1165.
    - Nyenhuis, S.M., et al., Characterization of leukotrienes in a pilot study of older asthma subjects. Immunity and Ageing, 2010, 7:8. These publications were from data collected during my fellowship, prior to my TFW award.

5. Other publications (Eight responses)

Zero – 7 (87.5%)

One – 1 (12.5%)

Description of publication

- Aging and lung disease in HIV-infected patients (book chapter, submitted)

6. Published abstracts. (Eight responses)
   Zero – 4 (50%)
   One – 2 (25%)
   Two – 0 (0%)
   Three – 2 (25%)

   Citation for abstract(s)

   - Blosser C, Huverserian A, Bloom RD, Abt P, Goral S, Reese PP.: Exclusion of Elderly Kidney Transplant Recipients from Randomized Clinical Trials. American Transplant Congress, San Diego, CA, Poster presentation. May 2010.
   - Context-Dependent Role of CETP in a mouse model of Postmenopausal Dyslipidemia. Poster Presentation at American Geriatrics Society Annual Meeting. Orlando FL. May 2010.
     - Impaired inactivation of FoxO1 contributes to glucose-mediated increases in serum VLDL. Oral Presentation at Triglycerides and Triglyceride-Rich Particles in Health and Disease. Big Sky Montana. January 2010.
     - Glucose-mediated VLDL production requires impaired insulin action. American Diabetes Association, New Orleans, Louisiana. 2009
   - American Thoracic Society (ATS) International meeting 2010: 2 poster presentations on epidemiology of ICU admission in HIV-infected vs. uninfected patients and risk factors and role of HIV in ICU admission, risk with age in HIV-infected patients.
     - Recently accepted abstract for ATS 2011 further investigating impact of age on ICU admission and survival in HIV-infected patients.
   - Nyenhuis, SM, Schwantes EA, Mathur SK. "Neutrophil Inflammatory Mediators in Older Asthma Subjects" J Allergy Clin Immunol. 2010; 125 (2): Supplement AB46.

Grants

1. What grants have you applied for and received in the last 12 months?
   - Submitted a grant to UCB Pharma on "Screening for ankylosing spondylitis"
     - Submitted an application to NIA on "Immunobiology of Aging."
     - Submitted an R01 to NIAID/NIH, not funded. Currently resubmitting
   - NIA R03 grant- funded for $42,000 per year for 2 years.
     - Pfizer IIR grant - funded for $160,000 total direct.
     - Beeson career development award- review pending.
     - NIDDK R01 grant - review pending
   - Submitted grant application to the American Society of Transplantation to study outcomes among older live kidney donors (pending review).
   - Received AHA grant in aid (Role of hepatic estrogen signaling in postmenopausal dyslipidemia).
     - Have R01 in review (Mechanisms for enhanced VLDL secretion with obesity).
     - Applied for VA MERIT (Bypassing Hepatic Insulin Resistance to Improve Obesity-Associated Dyslipidemia), scored but not funded, will re-submit.
   - Received VISN-1 early CDA x2 (VA award) for 75% salary support.

    - Received Yale Center of Clinical Investigations award which will provide 75% salary plus an additional $30,000.
- Submitted grant application to the NIA R03 GEMSSTAR for "Asthma in the Aging Immune System: Eosinophils to Socio-environmental Context" $50,000/year for 2 years (not awarded)
    - UIC Chancellor's Grant "Exploring Asthma in the Aging Immune System: From Eosinophils to Social Networks", $20,000/year for 2 years, not awarded
- Received a NIA K23 award ($806,625 over 5 years) to explore the changes of the renin angiotensin system with aging.
    - Johns Hopkins Clinician Scientist Award 75% salary support for two years.
    - I received a small pilot grant(10,000) and salary support for junior faculty(20%) to support my research studies of the effect of aging on the renin angiotensin system.

2. What grants have you applied for as an independent investigator?
    - Applied for a grant from Pfizer, Inc.
    - Resubmitted an R01 application on the research from my Williams Scholars grant, where I am PI, to NIDDK R-01.

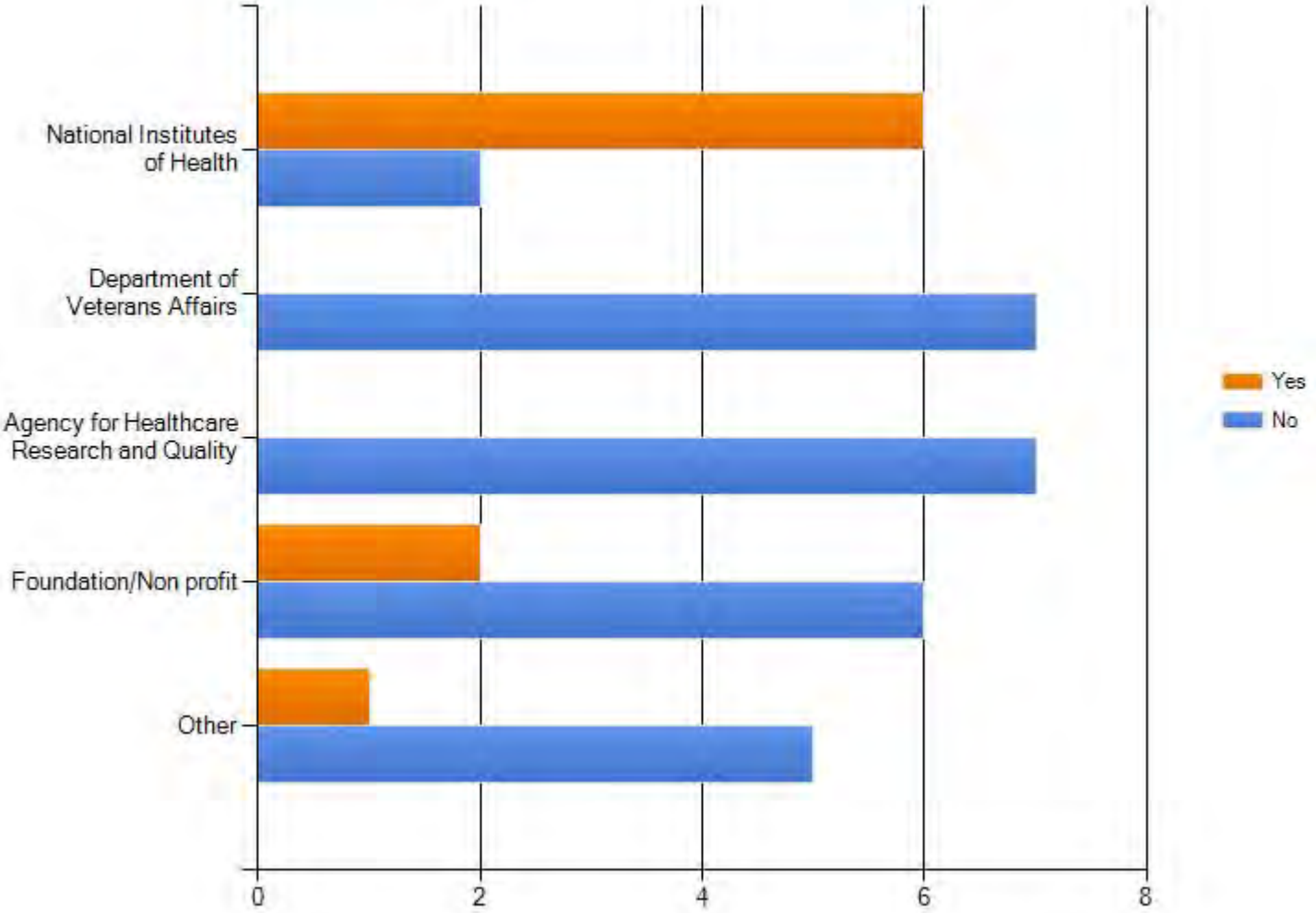
3. Please list the grants that you submitted as part of a research team.
    - Resubmitted an R01 application looking at age related disparities in access to kidney transplantation to NIDDK for a project where I am Co-I
        - I will submit a second grant as a Co-I to the NIDDK.
    - Submitted an R01 application to NCCAM for $997,000 in total funds (awaiting council review).

Career Development Activities

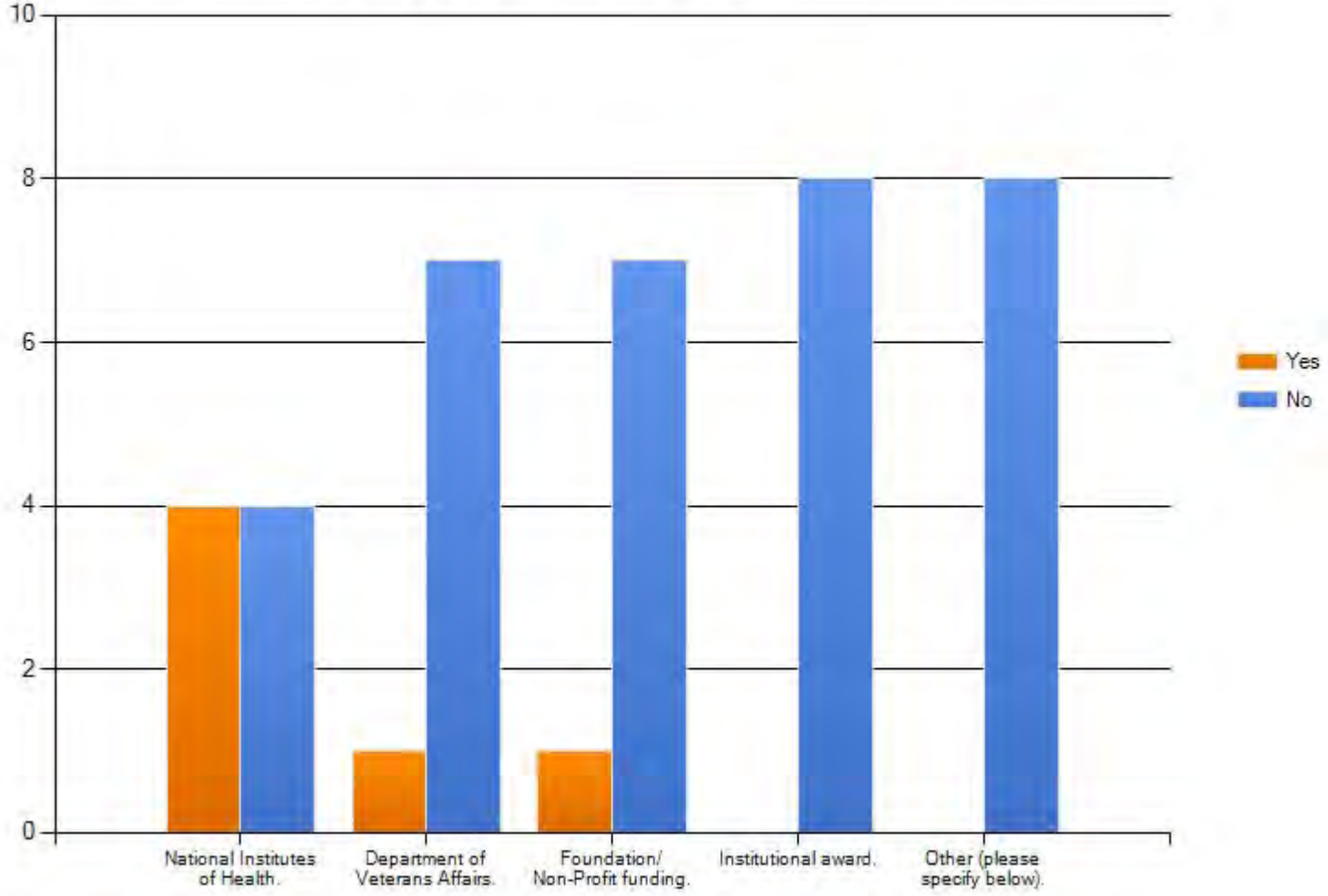
1. Please describe your role and level of involvement at an OAIC, GRECC, or COE.
    - Teaching Geriatrics Residents. I also have mentorship from Dr. James Powers in clinical aspects of Geriatrics at the TVHS GRECC
    - Attend lectures and discuss analytic plans with biostats people at the Pepper Center.

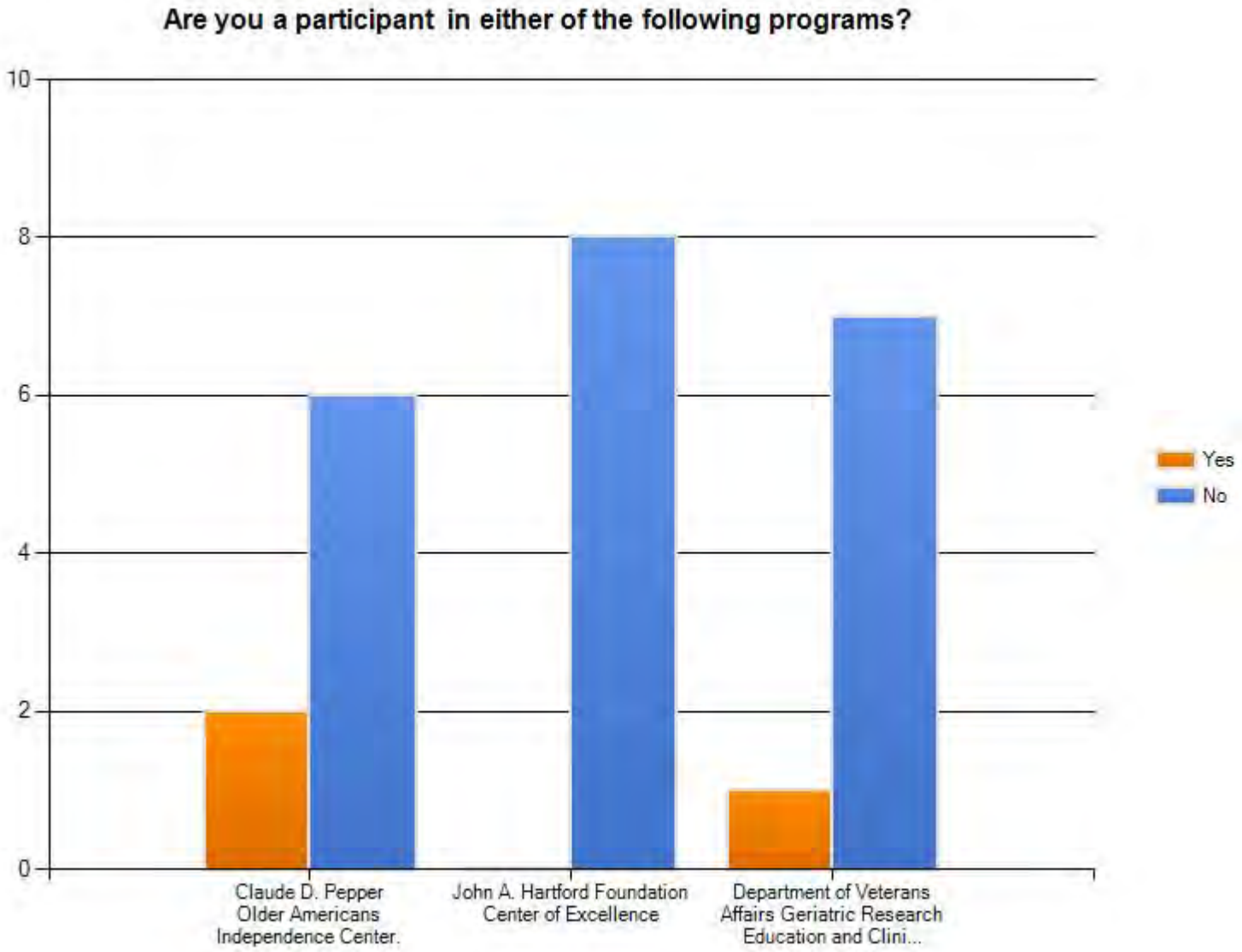
2. Please describe the educational activities in which you are involved.
    - I have been involved with mentoring a fellow to do geriatric research and informal discussions at resident lectures and infectious disease conferences.
    - I have had one of the geriatric fellows in endocrine clinic with me on several occasions to teach geriatric aspects of endocrinology.
        - I frequently discuss geriatrics cases at rounds.
        - I teach endocrine and geriatric fellows topics in aging and endocrinology as outlined in other areas
    - I have been involved in informal discussion of geriatric topics in clinics.

Have you applied for an independent investigator award from one of the following institutions?

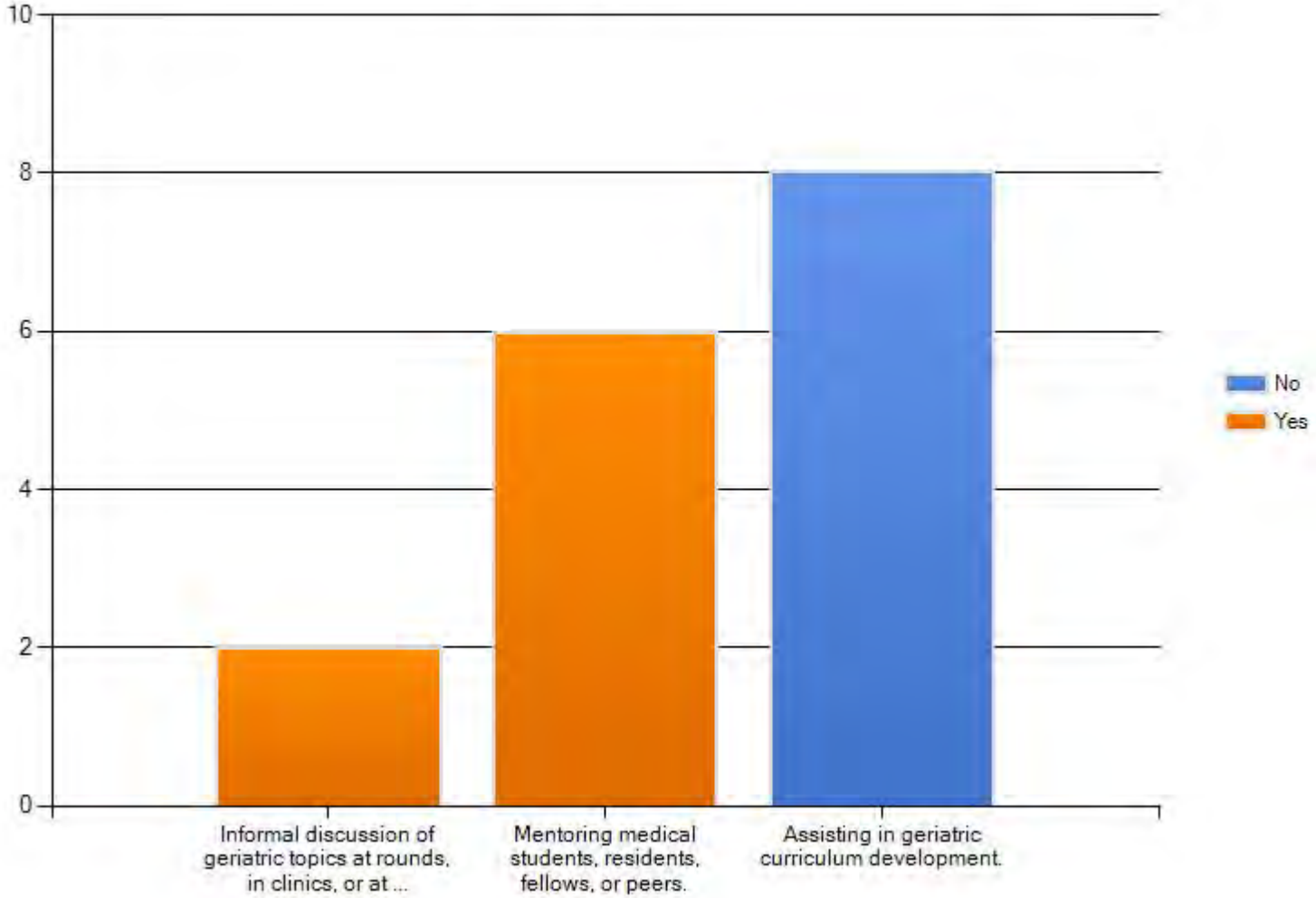


Have you been a member of a research team that has applied for or received grants or awards to support research or career development activities in the last 12 months from any of the following sources?

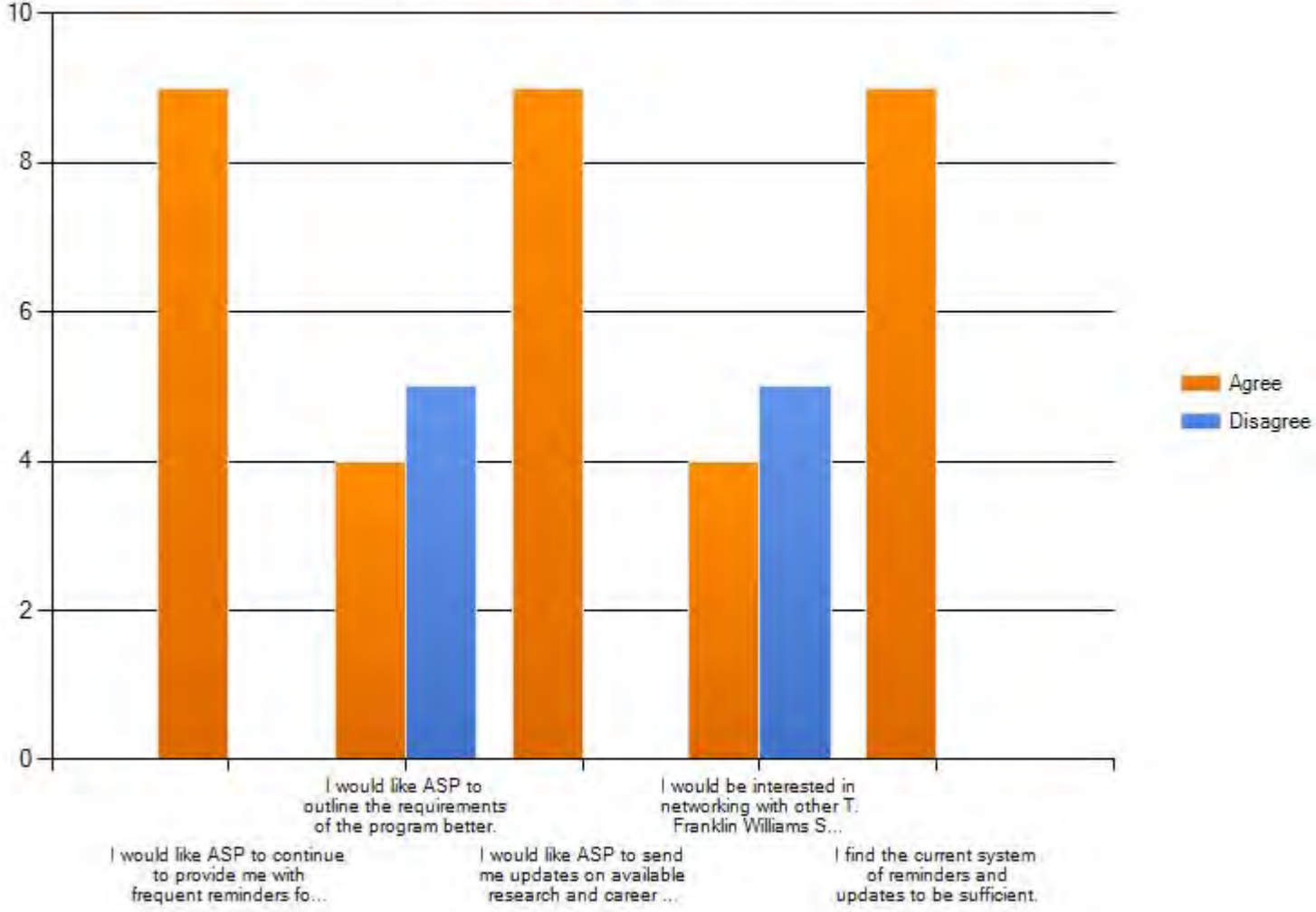



Are you a participant in either of the following programs?
10
8
6
4
2
0
Yes
No
Claude D. Pepper Older Americans Independence Center.
John A. Hartford Foundation Center of Excellence
Department of Veterans Affairs Geriatric Research Education and Clini...

Please indicate which of the following educational activities you have been involved with:



Is there any additional information or assistance you would like ASP to provide you during your award term?



T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: William Dale, MD

Award Recipient Name: Kellie Hunter Campbell, MD

Project: "Referral Patterns and Associated Clinical Outcomes for Older Adults with Chronic Kidney Disease"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Campbell has written and submitted three manuscripts, one to the *Journal of the American Geriatrics Society* and the *British Medical Journal of Nephrology*. In addition to the manuscripts, Dr. Campbell is working with researchers at Kaiser Permanente to pull together a cohort of patients who received referrals for renal therapy.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

Dr. Campbell has faced a major challenge with the cohort study with Kaiser Permanente. The researchers at Kaiser felt that there was not enough information to answer the question posed in Dr. Campbell's research award. To overcome this challenge, Dr. Campbell is working with the same cohort but measuring new issues, functional and cognitive status on patients undergoing dialysis.

The advantage of going through this challenge with Kaiser is that Dr. Campbell has developed a partnership with some of the researchers and analysis.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Over the past year, Dr. Campbell has received additional research support from a John A. Hartford Foundation Center of Excellence, and has been selected to attend the National Institute on Aging's summer session.

Has created and started up a geriatric nephrology clinic at institution. Primary care
Was selected to go to NIA summer session and learned

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

3.5: Dr. Campbell is doing well and is learning how to effectively multi-task between publications, grants, and clinical responsibilities. Even though Dr. Campbell is doing well, Dr. Dale feels as though she needs to increase her pace for submitting manuscripts and grants.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
It is difficult to rate compare Dr. Campbell to others, since she was on maternity leave from November 2010 to February 2011. While she is doing well with her research, there is more that she could be doing to publish.

2d. What are the potential next career steps for the award recipient?
The next career steps for Dr. Campbell is to get a K award, be it a KL2/K12 or a K23.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
4.5: Education is Dr. Campbell's strength. She has played an integral role in integrating geriatrics into the division of nephrology. She participates in nephrology journal clubs and is a seen as an advisor to the nephrology division for older pre-transplant patients.

3b. Describe the award recipient's role in educating or influencing his/her peers.
See response to 3a.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Campbell is a geriatrician.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
5: Receiving the Williams Scholars award, and the Hartford Center of Excellence award, were critical to help Dr. Campbell maintain a faculty position in the clinical research track.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
The Williams Scholars Program has helped Dr. Campbell's professional development in that she has developed collaborations with leaders in the field of geriatric nephrology and leaders on the University of Chicago's CTSA award. These collaborations had a significant impact on Dr. Campbell being promoted.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
Dr. Campbell is a geriatrician.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?

Dr. Campbell is not yet ready to apply for the Beeson award, but she should work on securing another career development award.

Question 6

6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?

Dr. Dale meets once a week with Dr. Campbell to discuss and outline career development and research tasks. They also participate in a research team meeting every Tuesday, with the Kaiser Permanente researchers once a month, and as a whole team once a quarter.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.

Dr. Dale is learning to become a mentor, but he is working with Dr. Campbell to ensure that she is always looking for professional development opportunities. Dr. Dale is also teaching Dr. Campbell how to select opportunities that will help her professional or research goals and how to say no to other opportunities.

6c. Please discuss your efforts to help the scholar reach independent investigator status.

See response to 6b.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?

Not yet. She should be early in her K award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Nicole Stankus, MD

Award Recipient Name: Kellie Hunter-Campbell, MD

Project: "Referral Patterns and Associated Clinical Outcomes for Older Adults with Chronic Kidney Disease"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

She has almost completed the preparatory work which involves Kaiser Permanente who will be analyzing the question on referral patterns, and what covariates matter. Kaiser Permanente has identified a sample of patients and they are working closely with Dr. Campbell to review her analysis plan.

In addition to her research, Dr. Campbell has just submitted a revised manuscript to the *International Geriatric Nephrology* and *Urology* journal.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

Dr. Campbell has established a strong mentorship team and is good at keeping with communicating with all of them, even those at a distance (e.g., Ann O'Hare, MD). The one challenge that Dr. Campbell had was with the cohort data from Kaiser. The challenge was that Kaiser Permanente was not tracking or documenting physicians' referral process for patients with chronic kidney disease. As a result of this one challenge, Dr. Campbell will change her research focus a bit, but Dr. Stankus does not anticipate that it will dramatically affect her timeline.

On the other hand, an advantage with working with Kaiser is that they have been able to do the preferred method of contacting patients in that rather than having a paper trail, they have been contacting patients and physicians by phone. This change may cause insight into the real practice of referral.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Campbell was scheduled to participate in several courses, but she took some time off for maternity leave. Before maternity leave, Dr. Campbell did complete a course on writing scientific manuscripts.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

4.5: Dr. Campbell is very dedicated and motivated. She has great organizational skills and is able to motivate a research team. During the first year of the award, she has had to learn how to

multi-task her research, teaching, clinical practice, coursework, and personal life. Dr. Stankus feels that this need to multi-task has matured Dr. Campbell as an investigator.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
4: In order for Dr. Campbell to be a 5, she needs other sources of career development funding like a K23.

2d. What are the potential next career steps for the award recipient?
Dr. Campbell is working on an R21. She will also be working publishing more manuscripts to ensure that she has the data to apply for a K23.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
4: As mentioned before, Dr. Campbell was on maternity leave, so she has been away from the university for a while. Since she has been back, Dr. Campbell participates in clinical rotation for fellows and residents. She is also active as an advisor on geriatric advisory group and as an educator to a kidney transplantation group. She provides the transplant group with information on what to look for in elderly kidney transplant recipients. Dr. Campbell is also leading the geriatrics segment of a joint geriatric and nephrology journal club.
In the coming year, Dr. Campbell will be presenting at the division of nephrology's grand rounds and will present on geriatric functional status analyses at a nephrology fellows lecture series.

3b. Describe the award recipient's role in educating or influencing his/her peers.
See response to question 3a.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Campbell is a geriatrician.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
Dr. Campbell is a geriatrician.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
The T. Franklin Williams Scholars award has provided Dr. Campbell with the support to protect her time so she is able to conduct her research.

Question 5

5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
Dr. Campbell is a geriatrician.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
5: Dr. Campbell is very qualified to apply for the Paul B. Beeson Career Development Award, but it is critical for her to complete her research with Kaiser Permanente before considering applying for this award.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. Campbell and Dr. Stankus formally meet every month, but they have many informal meetings to discuss Dr. Campbell's research goals.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
Through Dr. Stankus' role on the faculty, she is able to get Dr. Campbell more involved in clinical work as a geriatric consultant to the nephrology division. Dr. Campbell has also assisted Dr. Stankus with developing a geriatric nephrology curriculum.
Since Dr. Campbell is a geriatrician conducting research on renal diseases, Dr. Stankus is helping her to think as a nephrologist, and as she is working on manuscripts, to write like a nephrologist rather than a geriatrician. Dr. Stankus is also helping Dr. Campbell identify the best nephrology journals and prepare manuscripts to fit the nephrology style.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
Dr. Stankus has helped Dr. Campbell with submitting the R21 application.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
Before Dr. Campbell applies for an R01, Dr. Stankus feels she needs to secure the R21 award. The R21 award would help Dr. Campbell become familiar with the NIH process for reviewing applications.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Kenneth E. Schmader, MD

Award Recipient Name: Jessica Chia, MD

Project: "Role of Aging and Endoplasmic Reticulum Stress in the Pathogenesis of Pulmonary Fibrosis"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

The focus of Dr. Chia's research is to develop a model for pulmonary fibrosis through several mouse studies. Even though the fibrosis model is not working out like she hoped, Dr. Chia has developed new ideas based on the endoplasmic reticulum dysfunction in cells. This new model will still look at endoplasmic reticulum and its impact on pulmonary fibrosis. The findings from her revised study have led to a new research grant.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

In addition to the challenge mentioned above, Dr. Chia had a little difficulty gaining access to older mice. To overcome this challenge, Dr. Chia is working with Dr. Greg Sempowski, who has access to NIH animals, which includes older mice.

Dr. Chia is in a great situation at Duke University, because she has the support of her division, who ensures that she has the time and space to conduct research. An example of this support is that Dr. Chia is able to condense her clinical responsibilities to one week while she dedicates the remaining time to research.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Chia attends the Pepper Center research seminars on presenting novel ideas in research. Her participation in the Pepper Centers allows her to hear other scientists' viewpoints on basic research.

In addition to attending the Pepper Center seminars, Dr. Chia is supported by a Pepper Center pilot study grant and she is developing an Ellison grant.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

4: Dr. Chia has the potential to thrive at Duke. She is learning to make the transition to a career in bench research and has been extremely successful. She is regarded as a great lab researcher.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
5: Dr. Chia is doing a great job with securing funding to support her research (e.g., Williams Scholars grant and Duke grant) and career development (Pepper Center grant).

2d. What are the potential next career steps for the award recipient?
The next steps for Dr. Chia are to apply for a K08 award.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
Dr. Chia has given a talk at the Pepper Center on endoplasmic reticulum stress and the aging lung. She will also be giving a talk at the geriatrics and pulmonary grand rounds on the aging lung.

3b. Describe the award recipient's role in educating or influencing his/her peers.
See response to 3a.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Chia attends on the intensive care unit, so she does not have a clinic specifically focused on older adults.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
5: The Williams Scholars award changed Dr. Chia's career path in that she was not really focused on this issue and its impact in the elderly before the award.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
The research supported by the Williams Scholars award provided the foundation for another research and career development grant.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: Dr. Chia is genuinely interested in geriatrics and is really excited about conducting research on conditions that are prevalent in the elderly.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?

3: Dr. Chia's competitiveness for a Beeson award would depend on how interested the reviewers would be in her research. Dr. Chia needs to publish more to make sure that she is disseminating the results of her research.

Question 6

6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?

Dr. Schmader formally meets with Dr. Chia every month at Pepper Center meetings, but he also has informal meetings with her to discuss her research and career development goals.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.

Dr. Schmader is providing Dr. Chia with guidance on the gerontological aspects of the research. He is also encouraging her to submit applications for Pepper Center grants.

6c. Please discuss your efforts to help the scholar reach independent investigator status.

See response to 6b.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?

Not yet. Dr. Chia needs more data and publications before she can apply for an R01.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Paul Noble, MD

Award Recipient Name: Jessica Chia, MD

Project: "Role of Aging and Endoplasmic Reticulum Stress in the Pathogenesis of Pulmonary Fibrosis"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Chia has made significant research progress. She is working on an interesting model system that looks at the relationship between aging and endoplasmic reticulum stress responses. In particular, the endoplasmic reticulum stress pathway's ability to handle various insults derived from environmental exposure.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

A major challenge Dr. Chia is facing is that she is looking at this research question in old mice, and in order to access aged mice, she has to have a grant directly with NIA. She was working with an investigator at her institution to who had access to the mice, but the investigator has since closed the NIA grant. While this has slowed down Dr. Chia's research progress, it won't keep her from conducting the study.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Over the past year, Dr. Chia has successfully applied for an internal grant which will provide her with support after her Williams Scholars award. This one-year grant will allow Dr. Chia to analyze her data and submit it for publication.

Dr. Chia also participates in the monthly meetings for fellows of the SCORE program, which focuses on host-defense mechanisms in the lung. By attending these meetings, Dr. Chia is able to present her research methods and data to the group.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

5: Dr. Chia is uniquely talented in two areas; she is very good in the lab and is a great writer. Her skills will help her to secure additional research and career development grants.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.

4: Dr. Chia is ahead of where most of her colleagues. The most important thing for her to focus on in the next six months is to get a paper published.

2d. What are the potential next career steps for the award recipient?
As mentioned above, the next steps for Dr. Chia are to publish. She is looking at submitting a manuscript to Cell Molecular Biology journal. In addition to publications, Dr. Chia plans to submit a K08 application in the next two years and she is developing her skills with isolating epithelial cells from lungs of patients who have undergone lung transplant.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
4: Dr. Chia has presented on her research at the annual American Thoracic Society meeting. She also interacts with medical students and house staff on pulmonary fibrosis.

3b. Describe the award recipient's role in educating or influencing his/her peers.
See response to 3a.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Chia's clinical work is exclusively in the intensive care unit, where there are a lot of elderly patients. However, Dr. Chia does not have a pulmonary fibrosis geriatrics clinic.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
5: The Williams Scholars award helped to validate Dr. Chia's research and it helped her to receive the internal grant.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
See response to 4a.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: Dr. Chia is too committed to aging-focused research. Research in this population allows Dr. Chia to create a niche in pulmonary fibrosis research.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
Dr. Chia is not yet qualified to apply for the Beeson award program.

Question 6

6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. Noble holds a lab meeting with Dr. Chia every week, and a formal research and career development meeting every week. In addition to the formal meetings, Dr. Chia and Dr. Noble meet informally to discuss research challenges.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
Dr. Noble is working with Dr. Chia to review and submit manuscripts.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
As the division chief, Dr. Noble is providing Dr. Chia with protected time and lab space to conduct her research.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
No. Dr. Chia does not have the results or the publications needed for an R01 award. At the end of this award, she will focus on applying for a K08 award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Herbert Sier, MD

Award Recipient Name: Seong Cho, MD

Project: "Age-Related Differences in Inflammatory Mechanism of Chronic Rhinosinusitis"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Cho is doing well. Through his research he has found that the presence of nasal polyps is much higher in older adults than younger adults. He is starting to look at the indicating markers of chronic rhinosinusitis (CRS). Dr. Cho has presented at one of the Bueller Aging Conferences within the geriatrics division. He also presented on his research project at the annual AAAAI meeting in San Francisco.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

A challenge with Dr. Cho's research is that he does not have much interaction with older patients with CRS, since most patients referred to his clinic are younger adults. Since Dr. Cho was planning on recruiting participants for his study through his clinic, he is working with faculty on the geriatrics division to encourage them to refer patients with sinus problems to his clinic. Dr. Sier believes that with this marketing strategy and with the guidance of the allergy and immunology division chief, the number of elderly patients in Dr. Cho's clinic will increase.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Cho has made great progress towards his career development plan. He attends weekly sinus conferences, monthly geriatrics clinics, and monthly Bueller Aging Conferences. He also participates in a multi-disciplinary research consortium and in the development of a geriatrics review syllabus.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

5: Dr. Cho is a strong researcher and has a track record for meeting his research goals. He is being considered for promotion from an instructor to an assistant-level faculty.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.

It is difficult to rate Dr. Cho's comparison to others because he is older than most instructors, but since he has had more training (was an ear, nose, and throat physician in Korea) he is more mature in his research than his colleagues.

2d. What are the potential next career steps for the award recipient?
Dr. Cho is coming to a point in his research where he is considering applying for a Beeson award, so the next steps will be to secure a Beeson award.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
4: As mentioned above, Dr. Cho has presented on his research at the Bueller Aging conference in the geriatrics division and at a multidisciplinary research consortium. Dr. Sier believes that as Dr. Cho's knowledge of geriatrics increases then there will be more opportunities for him to teach on CRS.

3b. Describe the award recipient's role in educating or influencing his/her peers.
See response to 3a.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Cho has elderly patients integrated into his practice, but he does not have a clinic specifically focused on the elderly.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
5: The Williams Scholars award has been extremely valuable for Dr. Cho. Without the award, he would not have had the opportunity to have this exposure to geriatrics. Few allergists receive this level of geriatrics training.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
The Williams Scholars award was significant in the consideration of his promotion to an assistant-level faculty member.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: Dr. Cho has expressed a great interest in geriatrics, but it may not be the only aspect of his research.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
3.5: Dr. Cho is planning on applying for the Beeson award, but it is necessary for him to have more publications on his research before he can apply.

Question 6

6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?

Dr. Sier formally meets with Dr. Cho every month.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.

Dr. Sier is working with Dr. Cho to make sure that he is active in the Bueller Aging conferences, which will provide him with opportunities to present his research to the geriatrics division.

6c. Please discuss your efforts to help the scholar reach independent investigator status.

Dr. Sier is working with Dr. Cho to help him develop more geriatric-focused grants.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?

Dr. Sier is confident that Dr. Cho will be well positioned to apply for an R01.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Robert Schleimer, PhD

Award Recipient Name: Seong Cho, MD

Project: "Age-Related Differences in Inflammatory Mechanisms of Chronic Rhinosinusitis"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Cho is focused on his current research and is doing very well. Dr. Cho is looking at the pathogenesis of chronic rhinosinusitis (CRS) disease in the elderly and the non-elderly. Dr. Cho has written a paper on his research and will present on it at the American Academy of Allergy, Asthma, and Immunology (AAAAI) annual meeting.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

A challenge that Dr. Cho faces is finding samples from elderly patients with CRS. Dr. Cho's research is focused on reviewing samples gathered from his institution's ear, nose, and throat (ENT) surgical practice. In addition, Dr. Cho has defined elderly as patients who are 60+ years of age, so this limits the number of samples he is able to review as there are fewer individuals 60+ who visit the ENT surgical clinic.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Cho was recruited as faculty member in Dr. Schleimer's division. He has applied for a K award and is working to revise and resubmit it for funding. Help people become independent and hope they want to collaborate with you in the end.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

4-4.5: Dr. Cho has been successful in receiving funding to support his research; however, Dr. Schleimer feels that Dr. Cho has other challenges around his career path. Dr. Cho is older than most colleagues at his level because he did his training as an ENT surgeon in South Korea and had to redo his residency and internship when he came to the United States. While these are challenges that Dr. Cho has faced, Dr. Schleimer does not believe they will impact his opportunity for professional achievement at Northwestern University Feinberg School of Medicine.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.

4: As an instructor, Dr. Cho has been successful with having his publications and oral abstracts accepted for publication and presentation. However, for his age, Dr. Cho is behind where he should be for career development.

2d. What are the potential next career steps for the award recipient?
The next career steps for Dr. Cho will be to submit an application for a K award or an R21 award. Dr. Schleimer believes that if Dr. Cho's research produces enough data, then Dr. Cho will be well positioned to receive an R21 award.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
3.5: Dr. Cho is a good educator and takes advantage of every opportunity to teach clinical trainees and faculty. He has presented his research during the division grand rounds. Dr. Schleimer feels that Dr. Cho will improve as an educator as he continues to spend more time on it.

3b. Describe the award recipient's role in educating or influencing his/her peers.
Similar to what is mentioned above, Dr. Cho always ensures that he is added to the division programs to discuss his research and educate his allergy and immunology colleagues.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Cho sees elderly patients but he does not have a specific clinical designated to elderly patients.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
4.5: The ASP-AAAAI award was instrumental in supporting Dr. Cho's research on CRS in the elderly. Without the award, Dr. Cho would not have had the protected time to conduct research.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
See the response to 4a.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
3.8: Dr. Schleimer believes that Dr. Cho's research will continue to focus on the geriatric population. Whether or not it is solely on the elderly population depends on Dr. Cho's research findings and funding opportunities available to him.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides

$600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
4: Dr. Cho is qualified for the Beeson Program, and Dr. Schleimer will encourage him to apply once he analyzes his data from the Williams Scholars award.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. Schleimer meets with Dr. Cho very often. Dr. Schleimer has an "open door" policy so Dr. Cho is encouraged to speak with him as he needs.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
Dr. Schleimer is doing everything he can to work with Dr. Cho on his grant applications, manuscripts, and his research.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
See response to 6b. Dr. Schleimer believes that it is his role as a mentor to truly develop junior faculty into great physician-scientists.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
At the completion of the ASP-AAAAI award, Dr. Cho will be ready to apply for a K award or a R21, but not an R01.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Jeff Williamson, MD

Award Recipient Name: Vera Luther, MD

Project: "Critical Physician Decision Factors Influencing Appropriate Antimicrobial Prescribing in the Hospitalized Elderly"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Luther is making great strides in her research. In November 2010, she received IRB approval to conduct a follow up of older patients who received an antibiotic treatment during a hospital visit. As a result of the IRB approval, Dr. Luther has gained access to an administrative database that she will use to answer her research questions.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

Dr. Luther is faced with the challenges that most researchers encounter, but they are not severe enough to affect her research goals. Dr. Luther is part of an excellent division where the division chief ensures she has the time needed to conduct research.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Luther has made great progress on her career development goal. She has put in place a mentoring structure with both her geriatrics and research mentor. The mentoring structure, based on the Claude D. Pepper Older Americans mentorship form, will allow Dr. Luther to track her research progress and career development milestones.

In addition to developing the mentorship structure, Dr. Luther is working with Dr. Williamson and Dr. High to prepare an application for the Pepper Center junior faculty award. If awarded, Dr. Luther would receive four years of career development support.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

4: Dr. Luther's research is focused in an area that is very unpredictable and challenging. Because of these potential conflicts, she is at a slight disadvantage than her colleagues focused on more bench or basic research.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.

4.5: Dr. Luther is considered an emerging leader within her division. Viewed as an influential leader with residency and fellowship trainees, Dr. Luther was asked by the department chair to participate in the development of the residency curriculum.

2d. What are the potential next career steps for the award recipient?
The next career steps for Dr. Luther would be to work on her application for the Pepper Center junior faculty career development award.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
5: Dr. Luther plays a critical role in the curriculum for second and third year internal medicine residents, so she is able to integrate geriatrics and gerontology into the curriculum. In addition, Dr. Luther gives lectures to geriatrics fellows and attends on inpatient service.

3b. Describe the award recipient's role in educating or influencing his/her peers.
In addition to what is listed above, Dr. Luther plans on presenting her research during the geriatrics and infectious diseases grand rounds.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Luther does not have a specific clinic focused on the geriatric population, but she does have a in-patient consultation service for older adults who are using antibiotic therapy inappropriately.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
5: Receipt of the T. Franklin Williams Scholars award was extremely helpful for Dr. Luther's career in that it raised her visibility in the infectious diseases division. The research that Dr. Luther is proposing will lay the foundation for future research applications to federal agencies, like AHRQ.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
See response to 4a.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: The Williams Scholars Program has brought out Dr. Luther's interest in research. As mentioned before, Dr. Luther is conducting research in a very challenging area and if she continues a research career, then it is likely (4) that she will continue to focus on the elderly population.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
4: At this point, Dr. Luther is not yet ready for a Beeson award. By the time she completes her Williams Scholars award, she will right on the cusp of being ready to apply for the Beeson.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. Luther meets formally with Dr. Williamson on a monthly basis and with Dr. High and Dr. Williamson on a quarterly basis.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
Dr. Williamson is helping Dr. Luther with her grant writing and with identifying the best funding opportunities. In addition, he is providing her with guidance on her research goals.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
See response to 6b.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
Dr. Williamson believes that Dr. Luther will definitely be ready to apply for an R01.

OTHER:

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Kevin P. High, MD

Award Recipient Name: Vera Luther, MD

Project: "Critical Physician Decision Factors Influencing Appropriate Antimicrobial Prescribing in the Hospitalized Elderly"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Luther's research is focused on identifying and characterizing physician behavior that leads to inappropriate antibiotic prescribing and use. To access the data on inappropriate antimicrobial prescribing, Dr. Luther is reviewing past patient records. In order to do this aspect of her research, Dr. Luther received a certificate of confidentiality from the National Institutes of Health. This certificate helped her receive IRB approval to continue her proposed project.

Dr. Luther is currently working on validating and cross-validating a questionnaire, which she developed, that will assess physicians' comfort level of uncertainty with prescribing antibiotics.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

A challenge that Dr. Luther is encountering with her research is that she is trying to create a psychological profile for physicians and compare it to what is actually done with patients. To work through this challenge, she has met with and received support from the institution's information systems department.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Luther has made great progress on the milestones in her career development plan. She participated in the T. Franklin Williams Scholars Alumni Meeting, and continues to participate in the Pepper Center's Research, Condition, and Disease Categorization group, and the journal club.

The greatest challenge Dr. Luther has is that she is almost too good in some areas and so she is sought after to participate in or lead different initiatives. Dr. High is working with her to provide her with the skills to say "no" to the initiatives.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

5: Dr. Luther will be an academic success. She is currently the associate program director for the infectious diseases fellowship.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
4.7: As mentioned above, Dr. Luther is a fellowship Associate Program Director and is sought after for participating in or leading institution-led initiatives.

2d. What are the potential next career steps for the award recipient?
The next career steps for Dr. Luther will be for her to apply for K08 award through AHRQ's PCORI program. Another opportunity for research support may be through the American Medical Directors Association or the Department of Veterans' Affairs.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
5: Dr. Luther is an associate program director for the infectious diseases fellowship, so her major responsibilities are in education.

3b. Describe the award recipient's role in educating or influencing his/her peers.
Dr. Luther is the only infectious diseases physician who serves on the advisory board for Wake Forests' Center for Antimicrobial Utilization, Stewardship, and Epidemiology. As a member of the advisory board, Dr. Luther provides medical staff with education on the proper use of antimicrobial agents.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Luther does not have a specific clinic dedicated to geriatric patients.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
5: The Williams Scholars award was helpful in providing Dr. Luther with the financial support to develop a research team and to collaborate with other faculty (e.g., mentors and information systems staff). The Williams Scholars award was a needed complement to Dr. Luther's existing Brook's Scholarship award.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
In addition to the points listed in 4a, the Williams Scholars award was Dr. Luther's first extramural award.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
4.5: Dr. Luther has a great interest in aging, and has already published a manuscript on HIV and aging. This shows that Dr. Luther has an existing and an ongoing interest in the elderly population.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
While Dr. Luther is qualified to apply for the award, this type of research does not align with research previously supported by the Beeson Career Development Awards.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. High holds formal quarterly one-on-one meetings with Dr. Luther, but they meet informally to review Dr. Luther's research and career development goals.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
In addition to teaching Dr. Luther the skills to say "no," Dr. High brought leaders in this research field to the institution to meet with Dr. Luther.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
Dr. High is working with Dr. Luther to develop and submit manuscripts to journals that are methods-based (e.g., the Journal of the American Geriatrics Society and Clinical Infectious Diseases). In addition, Dr. High is the division chief for the infectious diseases division, so he is able to ensure that Dr. Luther has protected time to conduct research.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
Dr. Luther is not yet ready to apply for an R01 award, but she will be ready to apply for a R21 award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Thomas Gill, MD

Award Recipient Name: Una E. Makris, MD

Project: "Epidemiology of Restricting Back Pain in Older Adults"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Makris is making steady progress towards her research goals. The first aim of work has been completed and a publication on the first aim has been submitted and accepted in the *Journal of the American Geriatrics Society.* Dr. Makris is doing a series of qualitative interviews on back pain that restricts daily activities. To date, she has completed 18 interviews and is in the process of scheduling 10 additional interviews.

Dr. Makris has established a collaborative relationship with a research group based at Cornell University. Through this collaboration, she has received additional funding to hold a series of focus group discussions on restrictive back pain for individuals in New York. This collaboration is with Terri Reid, MD.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

There are several advantages that will help Dr. Makris reach her research goals. She is currently using the cohort from the Precipitating Events Project for qualitative interviews. The PEP cohort is supported by a grant to Yale where Dr. Gill is the principal investigator. Dr. Makris also has additional resources to support a biostatistician.

The one challenge Dr. Makris is facing is that she may have to switch institutions due to personal reasons.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Makris is making great strides towards her career development goals. She has submitted an R03 award application and received a favorable score but not a fundable score. Was on NIA training grant and has maintained presence in geriatrics. As a past recipient of an NIA training grant, Dr. Makris actively participates in geriatrics and rheumatology conferences and forums (e.g., research seminars). Dr. Makris also participated in the visiting scholar program by inviting Dr. Reid to Yale University.

Over the next few months, Dr. Makris will submit an application to attend the NIA Summer Institute.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.
5: Dr. Makris continues to demonstrate high levels of motivation and has immense support from her division. Dr. Gill can see a clear academic pathway for her in rheumatology.
If Dr. Makris is able to stay at Yale University, then he will encourage her to apply for support from the Pepper Center and the Center on Aging.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
4-5: Dr. Makris is more successful than her colleagues because she has a track record with research, having completed two years as a research postdoctoral fellow. Dr. Makris has also been active with submitting grants (R03 application). While Dr. Makris is making progress on her research and with preparing manuscripts for publication, she had a slight delay due to being on maternity leave.

2d. What are the potential next career steps for the award recipient?
The next steps for Dr. Makris will be to submit and have manuscripts accepted for publication. In addition, she needs to work on securing another career development award and the R03 award.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
4: Dr. Makris is participating in forums for medical student teaching and physical diagnosis. She has been viewed as a role model by research and clinical rheumatology fellows.

3b. Describe the award recipient's role in educating or influencing his/her peers.
Dr. Makris has provided expertise to staff in the geriatrics division on issues pertaining to arthritis.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Makris does not have a clinic dedicated to older adults, but since she deals with rheumatology, most of her patients are older.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career trajectory?
5: The Williams Scholars award was Dr. Makris' mechanism to come on board as rheumatology faculty. At Yale University, it is necessary for new faculty to have their own grant support. The Williams Scholars award provided Dr. Makris with the recognition of early grant success, and as a result is now receiving various research support from the rheumatology and geriatrics divisions.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
See response to 4a.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: It is very likely that Dr. Makris will continue to conduct research in geriatric aspects of rheumatology. As proof of this likelihood, Dr. Makris considered doing a clinical year in geriatrics. While she didn't pursue the clinical year, her consideration reflects her interest in geriatrics and pursuing additional training in aging.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
5: Dr. Makris is qualified for the Beeson award, but if she has to move institutions, then she will not be ready to apply for the award in 2013. However, if she is able to stay at Yale University, then she will be well prepared to submit and secure a Beeson award.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. Gill meets formally with Dr. Makris every other week. Since her office is right down the hall from his, they also meet informally to discuss Dr. Makris research and career development. In addition, Dr. Gill participates in a mentorship team meeting with Dr. Fraenkel and Dr. Makris.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
Dr. Gill uses his influence to get Dr. Makris invited to national conferences (e.g., comparative effectiveness research conference) and he assists her with the development of her manuscripts.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
Dr. Gill is helping Dr. Makris to network with other rheumatology investigators, specifically those on the MOST study. In addition, he is working with her to provide her information on how to effectively write NIH grant applications.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
Dr. Makris will not be ready for an R01 at the end of the award, but hopefully she will have a K23 award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Rheumatology Research Mentor Name: Liana Fraenkel, MD

Award Recipient Name: Una E. Makris, MD

Project: "Epidemiology of Restricting Back Pain in Older Adults"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Makris has made great progress on her research goals. She has already gathered results on the first aim of her project and is working with a statistician to develop a risk factor? analysis for the restrictive back pain. Dr. Makris has presented the project results, to date, at the November 2010 American College of Rheumatology annual meeting. In addition, she has had a manuscript accepted for publication in the *Journal of the American Geriatrics Society.*

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

Dr. Makris has a very supportive research environment, and she meets very regularly with her mentors. The one challenge that Dr. Makris is faced with is the timely analysis of the data from the Yale Precipitating Events Project. She is working to overcome this challenge and the biostatistician and data manager on her team have been able to spend more time on this project.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Makris has been making great strides towards establishing her career as a geriatric rheumatologist. She is participating in the Yale Center on Aging's career development training programs, presenting her research at the Yale Pepper Center retreat, serving as a member of the Williams and Jahnigen Scholars career development session, and is submitting an application for the National Institute on Aging's summer leadership program. Dr. Makris also applied for the GEMSSTAR award and is working on revising another RO3 application for resubmission.

In addition to the career development courses and grant submissions, Dr. Makris also participated in the ASP visiting professor program and invited Dr. Cary Reid to visit Yale University to meet with Dr. Makris and her mentors. As a result of the visiting professor program, Dr. Makris has developed a collaborative research relationship with Dr. Reid.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

5: As mentioned above, Dr. Makris has made great strides to publish her work and secure additional research funding. She is very adept at navigating networking relationships with researchers within and outside of her institution.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
5: Dr. Makris is very knowledgeable about what is needed to succeed as a physician-scientist and as a researcher at Yale University and she is well on her way to achieve those things. To guide her along the way, Dr. Makris is taking courses on grant writing and qualitative research.

2d. What are the potential next career steps for the award recipient?
The next career steps for Dr. Makris are to apply for and secure a K career development award and to have manuscripts accepted for publication.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
5: Dr. Makris does an excellent job educating medical students, residents, and fellows on geriatric aspects of rheumatology. In particular, she conducts a special tutoring session for medical students. She is viewed as a senior fellow who has successfully navigated the academic pathway and is revered for it.

3b. Describe the award recipient's role in educating or influencing his/her peers.
Dr. Makris is highly respected within the geriatrics and rheumatology divisions. She often serves as a rheumatology consult for geriatricians.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Makris does not have a geriatrics clinic. However, Dr. Makris has only one clinic and it is at the Veterans Affairs Medical Center and most of her patients fit within the elderly category.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
10: The receipt of the T. Franklin Williams Scholar award was extremely valuable to Dr. Makris. Without the award, she could not have stayed at Yale University. Unfortunately, there are not many funding opportunities that provide bridge funding between fellowship and the first K award for rheumatology fellows, and this award was critical for providing that opportunity.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
The Williams Scholars Program has provided Dr. Makris with the mentorship and networking opportunities needed to be a successful geriatrics-focused researcher.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.

5: Dr. Makris has found her research niche. There are few clinical rheumatologists who focus on geriatrics, so it is likely that Dr. Makris will continue to pursue research in this population.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
3: Dr. Makris is not yet ready to apply for the Beeson award. She needs about 18 months to have the data from her qualitative research before she is ready for a K23 award.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. Makris meets once a month with her mentorship team which consists of Dr. Gill and Dr. Fraenkel. Dr. Fraenkel also meets with Dr. Makris, formally and informally, between the monthly meetings, to discuss her research.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
Dr. Fraenkel is helping Dr. Makris learn how to find possible solutions to research problems before submitting the issues to her mentorship team. In addition, Dr. Fraenkel is helping Dr. Makris develop new research projects, write grants, network, and review manuscripts for submission.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
See the response to 6b.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
Dr. Fraenkel feels that by the end of the award, Dr. Makris will be ready to submit an application for a K award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Ken Covinsky, MD

Award Recipient Name: Alexander K. Smith, MD

Project: "Palliative Concerns of Frail Elders from Diverse Communities"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Smith's research is looking at the quality of life in frail older adults, and he has made a lot of progress towards his research goal. In addition, he has been active submitting manuscripts. Of his many published papers, one was accepted for publication in the *Annals of Internal Medicine*. Dr. Smith will also present on his research during the AGS 2011 Annual Scientific Meeting Presidential Poster session.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

The one challenge that Dr. Smith has faced is that he was trained as a palliative medicine physician, so he has had to learn geriatrics. Dr. Smith has overcome this challenge and is doing well with bringing together geriatric medicine and palliative care medicine.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

As a trained palliative care physician, Dr. Smith has become very active in the palliative medicine community. He has been invited to be grant reviewer at the national palliative medicine annual meeting.

Dr. Smith is also the co-founder of a blog called Geri-PAL, which bridges geriatrics and palliative medicine. With about 1,000 subscribers to the blog, Dr. Smith just received an award for the best clinical medicine blog. Building on the efforts of Geri-PAL, Dr. Smith has joined the Society of General Internal Medicine social media medical bloggers.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

5: Dr. Smith has the potential to really excel at the University of California, San Francisco, School of Medicine. His research in palliative medicine is considered novel in that it is looking at how quality of life factors impact different racial and ethnic communities.

Dr. Smith is also referred to as an emerging leader in palliative medicine. Even as a junior faculty, Dr. Smith holds a leadership role in the American Academy of Hospice and Palliative Medicine.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
5: Dr. Smith is well ahead of where he "should be" as an assistant professor.

2d. What are the potential next career steps for the award recipient?
Dr. Smith holds a National Palliative Medicine career development award and has received a KL2 award and a Greenwell Faculty Award in Ethics. The next steps for Dr. Smith are to secure an R01 award and publish more manuscripts.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
5: The University of California, San Francisco, School of Medicine started a palliative medicine fellowship this year, and Dr. Smith is very active in teaching and attends on the service. Dr. Smith is also working with residents and medical students as a mentor.

3b. Describe the award recipient's role in educating or influencing his/her peers.
See response to 3a.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Smith does not have specific geriatric clinic, but he covers nursing homes as part of his clinical coverage.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
4.5: The Williams Scholars award helped galvanize Dr. Smith's interest in geriatrics. When Dr. Smith first started working on faculty, he was focused on health outcomes in palliative medicine and oncology. The Williams Scholars award has helped him to link geriatrics, palliative medicine, and oncology back together.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
See response to 4a.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: Dr. Smith's research focus is really on the geriatric population, so it is very likely that he will continue conducting research in the elderly.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
5: Dr. Smith is well qualified to receive the Beeson award.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Dr. Covinsky's and Dr. Smith's offices are right down the hall from each other, so they meet informally to discuss Dr. Smith's research and career development plans. In addition to the informal meetings, Dr. Covinsky and Dr. Smith have a formal meeting with the entire mentorship team once a month.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
Dr. Covinsky is working with Dr. Smith to focus on submitting manuscripts to more prestigious scientific journals.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
Dr. Covinsky is helping to develop Dr. Smith's knowledge of geriatrics and geriatrics issues. Dr. Covinsky is also assisting Dr. Smith with the development of his research grant applications.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
Dr. Smith will definitely be ready to apply for an R01 by the end of his Williams Scholars award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Louise C. Walter, MD

Award Recipient Name: Alexander K. Smith, MD

Project: "Palliative Concerns of Frail Elders from Diverse Communities"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Smith has made outstanding progress on his research goals, which includes trying to understand what quality of life is and how it differs between different racial and ethnic groups. He has completed his interviews of 56 frail older adults for his research and has begun analyzing the data. Dr. Smith has used the data from the interviews to write three publications.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

Dr. Walters does not feel that there are any challenges that will keep Dr. Smith from reaching his research goals.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Dr. Smith has made great progress on his career development plan. He has already had a manuscript published in the *Annals of Internal Medicine* and has one in-press for the *Journal of General Internal Medicine.* In addition, Dr. Smith has submitted a K23 application for the Paul B. Beeson Career Development Award.

Dr. Smith is also the co-founder and developer of a geriatric-focused blog for palliative care called, GeriPAL. Dr. Smith's blog just received an award as one of the top medical education blogs.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

5: Dr. Smith has a potential to excel at the University of California, San Francisco, School of Medicine, with the progress of his research and career development. In particular, the GeriPAL blog has brought Dr. Smith a lot of recognition.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.

5: Dr. Smith has been very successful with securing grants to support his research, and with publishing data on the research.

2d. What are the potential next career steps for the award recipient?
The next steps for Dr. Smith are to secure additional career development awards and continue to publish his research findings.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
5: Dr. Smith has been very effective with educating medical professionals, at all levels, on geriatric aspects of palliative care medicine. As one of the primary authors of GeriPAL, Dr. Smith provides information to more than 1,000 subscribers. In addition to GeriPAL, Dr. Smith teaches a session on end-of-life matters to the general internal medicine division.

3b. Describe the award recipient's role in educating or influencing his/her peers.
Dr. Smith has played a vital role in developing the palliative care section of the general internal medicine curriculum at the university.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Smith does not have a specific clinic focused on older adults, but he works mostly at the Department of Veterans' Affairs Medical Center and attends at hospital's hospice and palliative care service.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
5: The Williams Scholars award was extremely valuable because it provided Dr. Smith with the resources needed to complete his research in this area. He is using the data from his Williams Scholars-supported research to apply for the Paul B. Beeson Career Development Award.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
The T. Franklin Williams Scholars award was extremely valuable in determining Dr. Smith's promotion to the accelerated tenure faculty track.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: Dr. Smith's research focus is really on palliative care and general internal medicine. He is interested in looking at how older adults from different racial and ethnic backgrounds discuss their medical prognosis. In short, he is reviewing the existing construct of successful aging.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?

5: Dr. Smith has already applied for the Beeson Career Development award.

Question 6

6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?

Dr. Walters meets with Dr. Smith and other members of his mentorship team weekly. Dr. Walters and Dr. Smith also hold one-on-one two-three times a year to discuss career development. Dr. Walters uses a career development plan template to monitor Dr. Smith's success towards his research and career development goals.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.

As the planning chair for the SGIM national meeting, Dr. Walters is working with Dr. Smith to hold a meeting on using social media for medical education. She is also providing Dr. Smith with feedback on his research goals.

6c. Please discuss your efforts to help the scholar reach independent investigator status.

Dr. Walters is helping Dr. Smith stay focused on his research and career development goals. She is also reviewing Dr. Smith's manuscripts and providing him with guidance on where to submit the manuscripts.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?

Dr. Walters believes that Dr. Smith will be ready to apply for an R01 by the end of his Williams Scholars award, if he receives the Beeson award in the second year of his Williams Scholars award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Mark A. Supiano, MD

Award Recipient Name: Michael E. Widlansky, MD

Project: "Effect of a Combined Pedometer/Computerized Feedback Intervention on Vascular and Left Ventricle Function in Older Adults"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Widlansky began enrolling patients for his study in October and has recruited 20 patients. Dr. Widlansky's research is a 12-week study where he is looking at two different intervention methods. Now that he is at the end of the first part of the study, Dr. Widlansky will begin analyzing the results from the first cohort. Based on this information, Dr. Supiano believes that Dr. Widlansky is on track to achieve his research goals.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

One challenge that Dr. Widlansky faces is his geriatrics mentor, Dr. Supiano, is based at the University of Utah School of Medicine. To work through this challenge Dr. Supiano connected Dr. Widlansky with the Medical College of Wisconsin Chief of the Division of Geriatrics, Edmund Duthie, MD. Dr. Duthie is working with Dr. Widlansky to provide him guidance in his research.

On the other hand, Dr. Widlansky has the advantage of having his division chief, Michael Cinquegrani, MD, fully support of his research. Dr. Cinquegrani provides Dr. Widlansky with the time needed to conduct research.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

In line with his career development goal, Dr. Widlansky has been focused on his K23 and ASP-AHA research projects. Dr. Widlansky submitted an application for an R01 award in the fall of 2010, so he is on track to become an independent investigator.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

Dr. Supiano is based at the University of Utah School of Medicine, so he cannot comment on Dr. Widlansky's potential for professional achievement at the Medical College of Wisconsin.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.
4.5: Dr. Widlansky is two years into his K23 award, so he is probably more successful than others at a similar stage of career development.

2d. What are the potential next career steps for the award recipient?
The next career steps for Dr. Widlansky would be to continue publishing and to secure an R01 award. As mentioned above, Dr. Widlansky submitted an application for an R01 award in the fall of 2010.

Question 3
3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?
The Medical College of Wisconsin has protected a lot of Dr. Widlansky's time for research, so he does not have much interaction with clinical trainees. When Dr. Widlansky attends in the hospital or presents at clinical conferences, he emphasizes the geriatrics aspect of cardiology during clinical rounds, and during presentations.

3b. Describe the award recipient's role in educating or influencing his/her peers.
See the response to 3a.

3c. Does the award recipient's clinical practice include a focus on elderly patients?
Dr. Widlansky does not have a specific geriatric cardiology clinic, but he primarily sees older patients in the hospital.

Question 4
4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?
4: The Williams Scholars award was valuable in providing support to protect time for Dr. Widlansky to conduct research. Dr. Widlansky has always had an interest in geriatrics, but the Williams Scholars award allowed him to sustain his interest in geriatric cardiology.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?
The Williams Scholars Program has provided Dr. Widlansky with opportunities to network with other geriatric cardiologists.

Question 5
5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.
5: As mentioned in 4a, Dr. Widlansky has always had an interest in geriatric cardiology. While in medical school at the University of Michigan Medical School, Dr. Widlansky applied for and received a medical student summer research award from AFAR. As part of this program, Dr.

Widlansky focused his research on the beta-adrenergic responses in the elderly with Dr. Supiano as his mentor.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?
Dr. Widlansky is not eligible to receive the Beeson award since he is mid-way through his K23 award.

Question 6
6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?
Since Dr. Widlansky and Dr. Supiano are based at different institutions, they do not meet on a regular basis. Dr. Widlansky and Dr. Supiano communicate periodically to discuss the status of the research project and to discuss Dr. Widlansky's career development. Dr. Supiano plans to sit down with Dr. Widlansky at the American Geriatrics Society 2011 Annual Scientific Meeting to discuss Dr. Widlansky's research.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.
As mentioned in 1b, Dr. Supiano has helped Dr. Widlansky develop a relationship with the geriatrics division at the Medical College of Wisconsin.

6c. Please discuss your efforts to help the scholar reach independent investigator status.
Dr. Supiano plays an active role in reviewing Dr. Widlansky's grant applications and publication submissions.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?
Dr. Widlansky has already applied for an R01 award.

T. Franklin Williams Scholars
Six-Month Mentor Interview

Geriatrics/Research Mentor Name: Scott Strath, MD

Award Recipient Name: Michael Widlansky, MD

Project: "Effect of a Combined Pedometer/Computerized Feedback Intervention on Vascular and Left Ventricle Function in Older Adults"

Question 1

1a. Describe the award recipient's progress in his/her research activities since receiving this award in July 2010.

Dr. Widlansky is on a fast trajectory to reach his research goals. He has developed his research team and has already begun enrolling participants. Dr. Widlansky is a little ahead of where he thought he would be for his research.

1b. Do you perceive certain challenges or advantages that would affect the goals of the scholar's research? (For example, a lack of cooperation between the geriatrics and subspecialty divisions.)

Like most junior faculty researchers, one challenge that Dr. Widlansky faces is not having enough time to conduct his research and still meet his professional development and clinical goals. Even though Dr. Widlansky is faced with the responsibility o f juggling all of the duties of a physician-scientist, he does have the advantage of having a mentorship team that is very aging focused. In addition, the mentorship team is working together as a team and encouraging him to work collaboratively with other CTSA institutions.

Question 2

2a. Describe the award recipient's career development progress since July 2010.

Since the beginning of his award, Dr. Widlansky has been putting together reviews and other publications. As a highly regarded geriatric-focused cardiologist, Dr. Widlansky has been asked to serve as a journal reviewer for cardiology publications.

2b. On a scale of 1-5 (1=low potential, 5=high potential), please rate the scholar's potential for professional achievement at your institution.

5: Dr. Widlansky is a dedicated physician-scientist and is on a trajectory to become a leader in geriatric cardiovascular medicine at his institution.

2c. On a scale of 1-5 (1=less successful, 5=more successful), please rate the scholar's overall success in comparison to others at a similar stage of career development.

5: Dr. Widlansky is ahead of where most of his colleagues are at this stage of their career. He has successfully received this ASP-AHA award and used the data to submit an R01 application to NHLBI effective interventions for cardiovascular health in aging.

2d. What are the potential next career steps for the award recipient?

The next career steps for Dr. Widlansky are to secure a larger independent research grant.

Question 3

3a. On a scale of 1-5 (1=no effect, 5=high effect), how effective has the scholar been in educating faculty, fellows, residents, or medical students on the geriatric aspect of his/her subspecialty?

4: Dr. Widlansky is working with several medical students to expose them to cardiovascular health in the aging population at an early stage in their medical training. In addition, he is mentoring several fellows who are working in the same area within the elderly population.

3b. Describe the award recipient's role in educating or influencing his/her peers.

Dr. Widlansky spoke at geriatrics grand rounds on his Williams Scholars-supported research.

3c. Does the award recipient's clinical practice include a focus on elderly patients?

Dr. Widlansky does not have a clinic designated for elderly patients, but he does run a weekly echocardiogram laboratory.

Question 4

4a. On a scale of 1-5 (1=not valuable, 5=very valuable), how valuable was receiving the T. Franklin Williams Scholars Award in determining the scholar's career in aging-focused research?

5: The Williams Scholars award helped to focus Dr. Widlansky's research in the geriatric population. The award also provided Dr. Widlansky with confirmation that his research area was of interests to other cardiologists and geriatricians. The award also provided Dr. Widlansky with the support needed to protect his time for research.

4b. How has the T. Franklin William Scholars Program helped this individual in his/her professional achievement?

See response to 4a.

Question 5

5a. On a scale of 1-5 (1=not likely, 5=very likely), please rate the scholar's likelihood of pursuing interests in the geriatric aspect of his/her subspecialty.

5: Dr. Widlansky is very likely to continue research in the elderly population. In particular, he is interested in how the interventions will help to prevent, treat, and reverse cardiovascular ailments in this population.

5b. On a scale of 1-5 (1= not qualified, 5=very qualified), how qualified is the scholar for the Paul B. Beeson Career Development Award in Aging Research Program (provides $600,000-$800,000 for three to five years to outstanding physician-scientists interested in teaching and research in the field of aging)?

Dr. Widlansky already holds a K23 award, so he is not eligible to apply for the Beeson award.

Question 6

6a. How often do you meet with the scholar? Is this a one-on-one meeting or does a mentoring team meet?

Dr. Strath and Dr. Widlansky hold formal meetings once a month, but they meet throughout the month to discuss research and career development progress.

6b. How are you assisting in implementing the career development plan outlined in the mentee's application.

Dr. Strath is providing Dr. Widlansky with guidance on those efforts or initiatives have the potential to be successful. Specifically, he is helping Dr. Widlansky to look at community-based and physician-based intervention to ensure tat he is addressing the efficacy of his study.

6c. Please discuss your efforts to help the scholar reach independent investigator status.

Dr. Strath is working with Dr. Widlansky to map out a five- and 10-year plan for applying for extramural grants from private and public foundations and the federal government.

6d. At the completion of this award do you believe the scholar will be ready to apply for an independent investigator award (e.g., R01)?

Dr. Widlansky has already submitted an R01 application.

OTHER:

2010 T. Franklin Williams Scholars
Six-Month Questionnaire Responses

Presentations and Publications

1. Presentation at your institution within the division of geriatrics.
   Zero – 4 (57%)
   One – 3 (43%)

Description of presentation(s)

- Presented at the Center on Aging in Diverse Communities, the NIA-funded Resource Center for Minority Aging Research at UCSF.
- Presented at the Yale Program on Aging to a diverse group of clinical and basic science aging researchers on "Back Pain in Community-Living Older Persons."
- Presented an overview of the background, rationale, hypothesis, and preliminary data of project, titled "Role of Aging and Endoplasmic Reticulum Stress in the Pathogenesis of Pulmonary Fibrosis" at my institution's Pepper Center Research Meeting.

2. Presentation at your institution within your specialty.
   Zero – 5 (71%)
   One – 0 (0%)
   Two – 2 (29%)

   Description of presentation(s)
   - Rheumatology Grand Rounds
     - Hosted a Visiting Scholar, Cary Reid from Weill Cornell, January 5, 2011 Dr. Reid presented at Rheumatology Grand Rounds and at the POA Aging Research Seminar
   - Presented to the IM Residency Program Chief Medical Officer on study design.
   - Conducted a class on B cell biology for the Immunology course.
     - Held a topic course on airway remodeling in asthma.

3. Presentation or a workshop at a professional conference or another institution.
   Zero – 5 (71%)
   One – 1 (14.5%)
   Two – 1 (14.5%)

   Description of presentation(s) or workshop(s)
   - Selected to participate in US Bone and Joint Decade Young Investigators Workshop in Toronto, Canada, October 29-31, 2010. This is a two-year grant-writing mentorship work-shop with the intention of working closely with experts in the fields of rheumatology/orthopedics in order to submit a successful grant application.
     - Received a Junior Scholar Travel Grant for: Integrating Geriatrics into Comparative Effectiveness Research (CER) conference, sponsored by Geriatrics-for-Specialties Initiative (GSI)/AGS, Maryland, November 2-3, 2010

- Works in Progress (WIP) Seminar sponsored by the Cornell Translational Research Institute on Pain in Later Life (TRIPLL), October 20, 2010 "Understanding the Impact of Restricting Back Pain in Community-Living Older Persons: A Mixed-Methods Approach."
    - Presented a podium presentation at the American College of Rheumatology 2010 National Meeting on "Epidemiology of Restricting Back Pain in Older Persons and Associations with Age, Sex, Obesity, and Depressive Symptoms"
    - Presented at a Special Session: REF Marshall J. Schiff, MD, Memorial Lectureship: Everything a Rheumatologist Should Know About Spine Surgery but Was Afraid to Ask. Moderated by Stephen A. Paget, MD.
- Presented preliminary data, in abstract form, at the annual Society for Medical Decision Making Annual Meeting.
- Presented at the American College of Allergy, Asthma, and Immunology during the Rhinoscopy workshop.

4. Publication of a peer-reviewed article.
   Zero – 3 (43%)
   One – 2 (28.5%)
   Two – 2 (28.5%)

   Citation for peer-reviewed publication
   - Thijssen DH, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, Parker BA, Widlansky ME, Tschakovsky ME, Green DJ. Assessment of flow mediated dilation (FMD) in humans: a methodological and technical guideline. *Am J Physiol Heart Circ Physiol*. 2010 Oct 15. PMID: 20952670 2.
        - Babar G, Zidan H, Widlansky ME, Hoffmann R, and Alemzadeh R. Impaired Endothelial Function in Preadolescent Children with Type 1 Diabetes. *Diabetes Care* 2011, in press.
   - Makris UE, Fraenkel L, Han L, Leo-Summers L, Gill TM. Epidemiology of Restricting Back Pain in Community-Living Older Persons. *J Am Geriatr Soc* (in press, accepted October 4, 2010)
   - Review article: Ohl CA, Luther VP. Antimicrobial Stewardship for Inpatient Facilities. *Journal of Hospital Medicine*. 2011 Jan;6(S1):S4-S15
        - Invited Commentary: Luther VP, Crandall SJ. Ambiguity and Uncertainty: Neglected Elements of Medical Education Curricula? *Acad Med*. 2011; [In Press]
   - Cho SH, Kang J, Lyttle CS, Harris KE, Daley B, Grammer LC, Avila PC, Kumar R and Schleimer RP. Elevated Plasma Levels Of Plasminogen Activator Inhibitor-1 Are Associated With Diminished Lung Function In Asthma" *Ann Allergy Asthma Immunol* 2011 (in press). NIHMS262431

5. Published abstracts.
   Zero – 6 (86%)
   One – 0 (0%)
   Two – 0 (0%)
   Three – 1 (14%)

   Citation for abstract(s)
   - Lee SH, Eren M, Vaughan DE, Schleimer RP, Cho SH. A specific PAI-1 inhibitor, PAI-039, reduced airway inflammation and collagen deposition in an OVA-challenged murine model of chronic asthma. *J Allergy Clin Immunol.* (in press)
     - Habib A, KIM J, Lee S, Boushey H, Ward T, Liu J, Schleimer RP, Avila P, Cho SH. Elevation of sputum plasminogen activator inhibitor-1 levels in the subjects with asthma. *J Allergy Clin Immunol* (in press)
     - Hong S, Han B, Suh L, Conley DB, Chandra R, Kern RC, Grammer LC, Schleimer RP, Cho SH. Age-related differences in the pathogenesis of chronic rhinosinusitis. *J. Allergy Clin Immunol* (in press)

Grants

1. Please describe any funding opportunities you have applied for or secured to support your research.
   - "Understanding the Impact of Restricting Back Pain in Community-Living Older Persons: A Mixed-Methods Approach" NIA GEMSSTAR RO3 (RFA-AG-11-007), requested $100,000 (pending).
     - "Understanding the Impact of Restricting Back Pain in Community-Living Older Persons: A Mixed-Methods Approach" Brookdale Foundation Leadership in Aging Fellowship; requested $188,792 (pending).
     - "The Clinical Course and Functional Outcomes of Back Pain in Older Persons" Yale Center for Clinical Investigation (YCCI) pilot project for the promotion of T3 research, requested $48,315 (pending.
   - Wake Forest University Baptist Medical Center, Brooks Scholarship Fund; $41, 530 (funded).
   - Applied for a K08 award to NHLBI (pending).
     - Applied for an AHA Scientist Development Award (pending).
   - Applied for institutional career development award for junior faculty (2011 Barton Haynes Research Award Early Career Grant, $75K, one year). (pending)
     - Applied to Duke Center for the Study of Aging and Human Development RFA on the basic biology of aging initiative ($50K, one year). (pending)

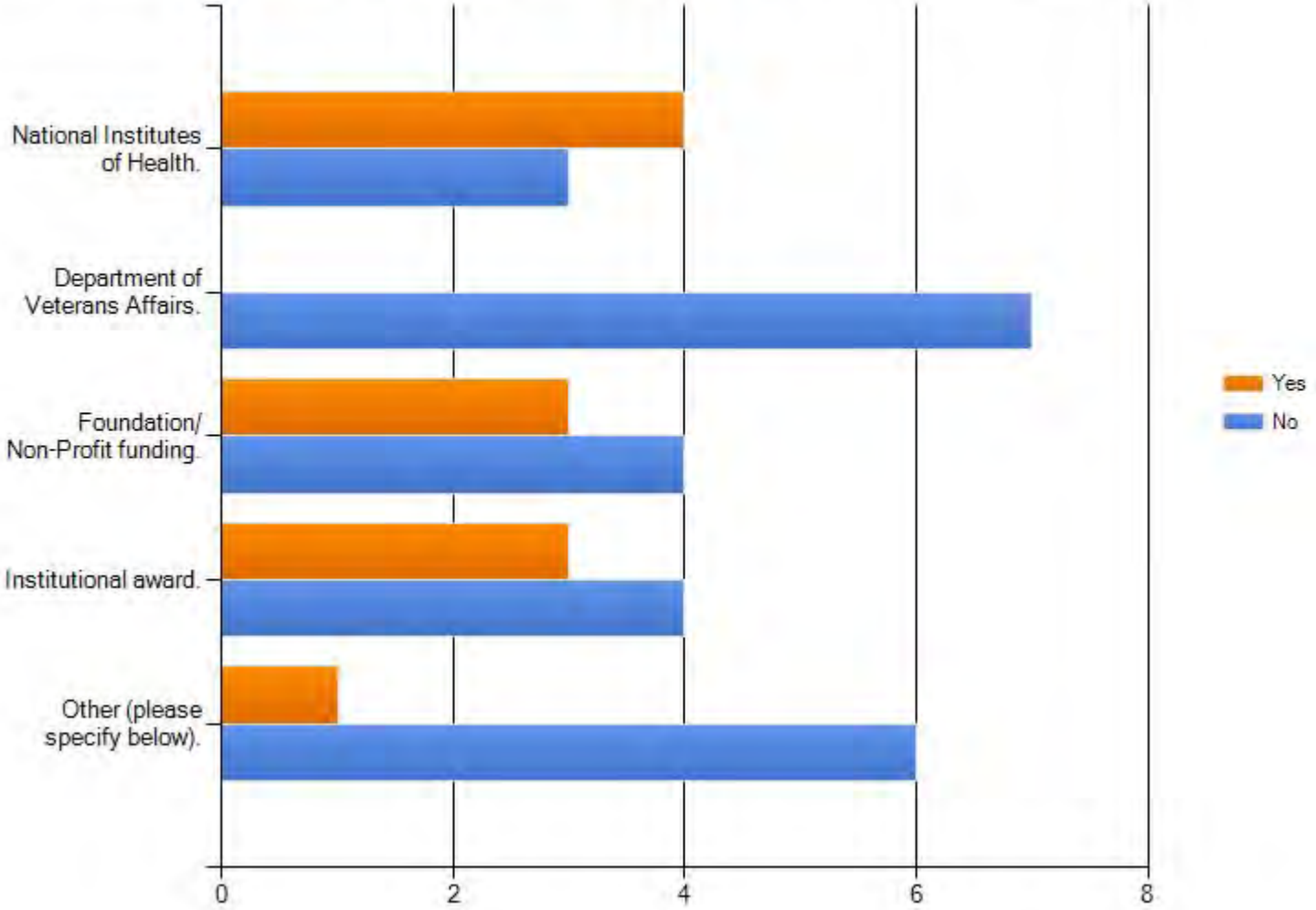
2. Please describe your role or the support you received from a team research grant.
   - Requested funding for a pilot study on "Understanding the Impact of Restricting Back Pain in Diverse Community-Living Older Persons" from Cornell Columbia Translational

Research Institute on Pain in Later Life (TRIPLL) (approved by Cornell, awaiting Yale G&C review).

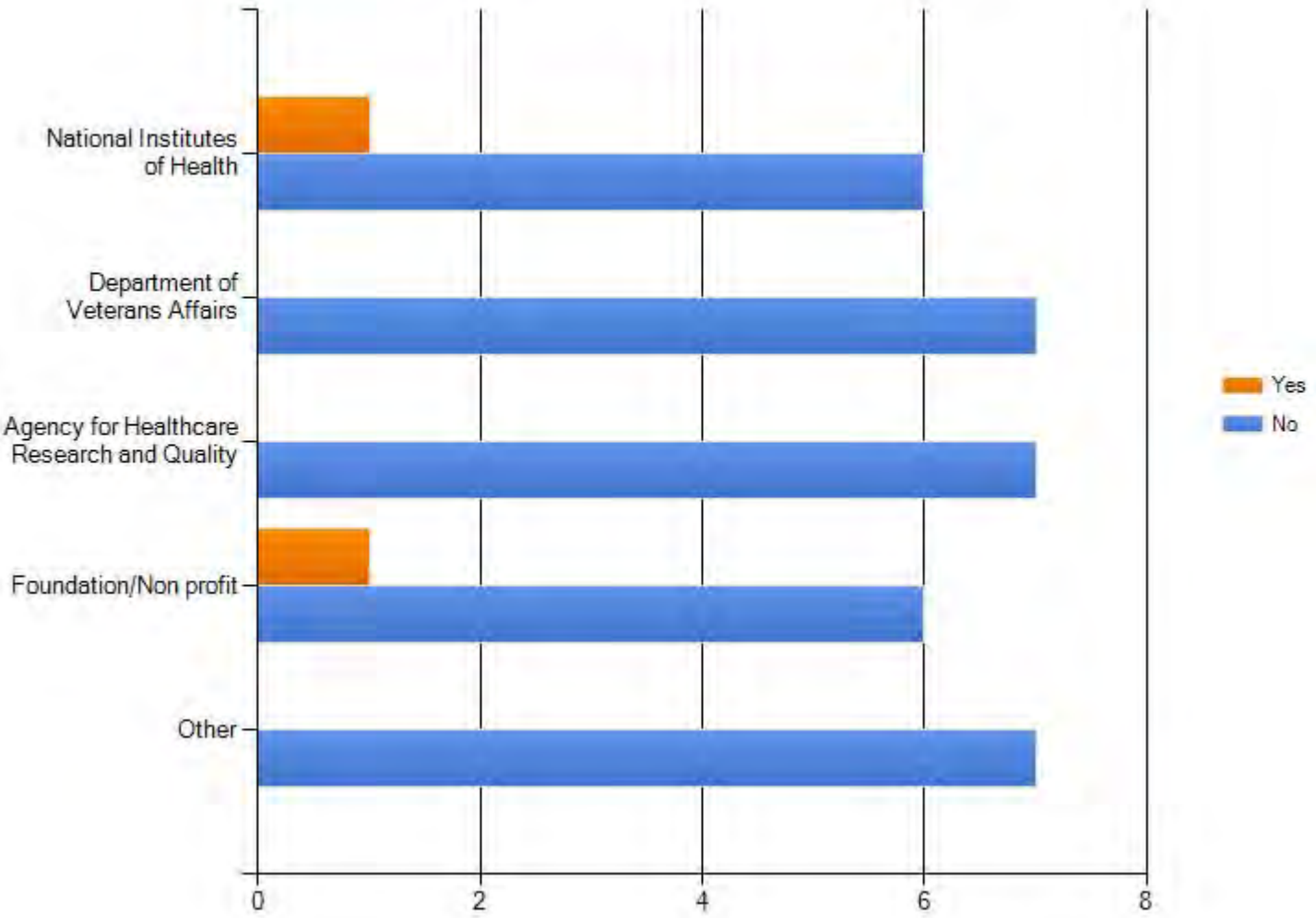
Career Development Activities

1. Please describe your role and level of involvement in an OAIC, GRECC, or COE.
    - I am a scholar in UCSF's Hartford Center of Excellence. I received funding to support the work I am doing for the TFW award, as well as dissemination and education about geriatrics and palliative care through a blog I co-founded, GeriPal.
    - My research, currently utilizing the Yale Precipitating Events Project (PEP, PI is Thomas Gill), is conducted at the Yale Program on Aging/Claude D. Pepper Older Americans Independence Center.
        - Initiated a substudy at OAIC on "Understanding Back Pain in Older Persons: a qualitative study."
    - I am a mentee and a participant in a bi-weekly conference.
    - Received pilot study funds from Duke Pepper Center.
        - Attend monthly Duke Pepper Center Research meetings.

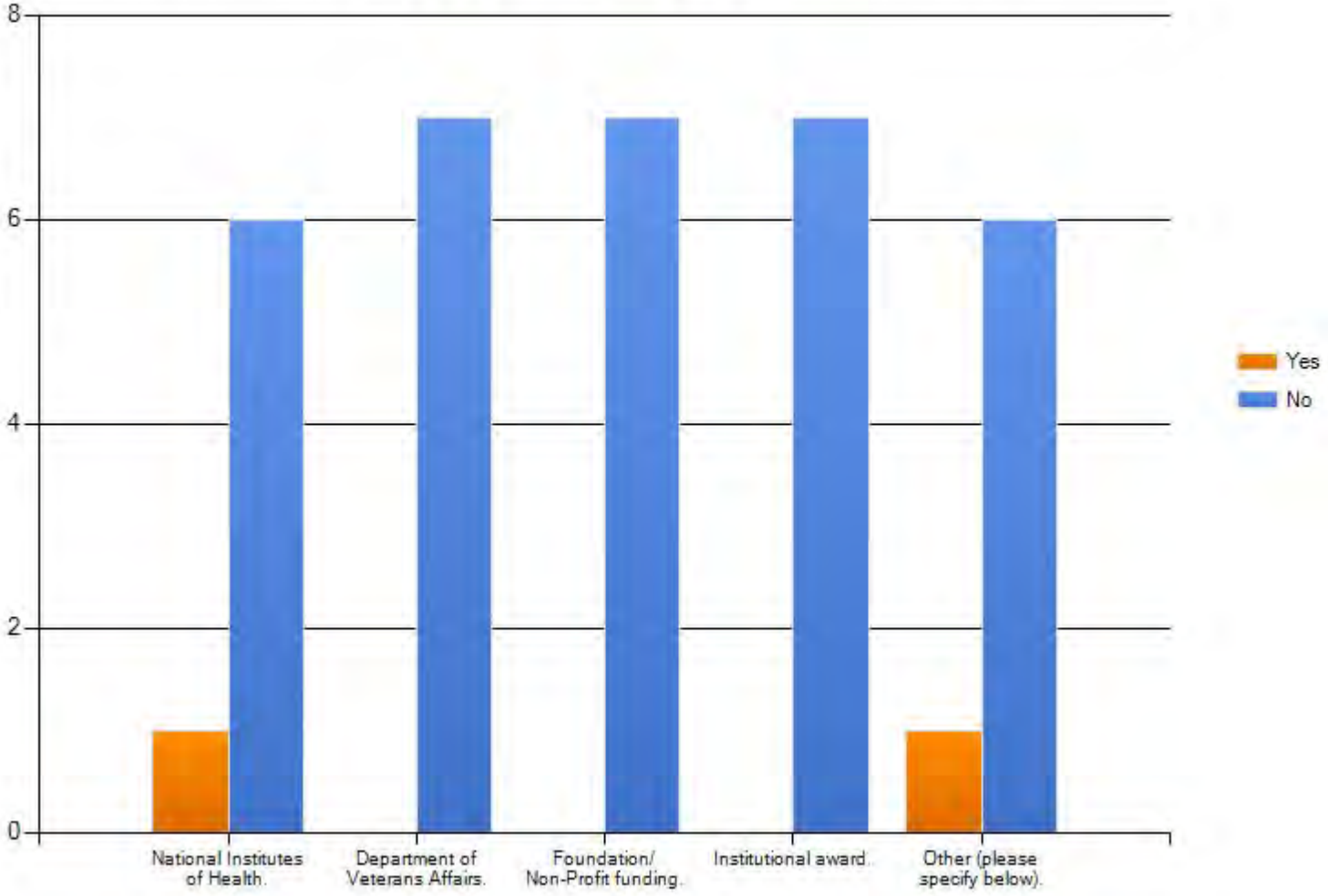
Have you applied for or received grants or awards to support your research or career development activities in the last six months from any of the following sources?

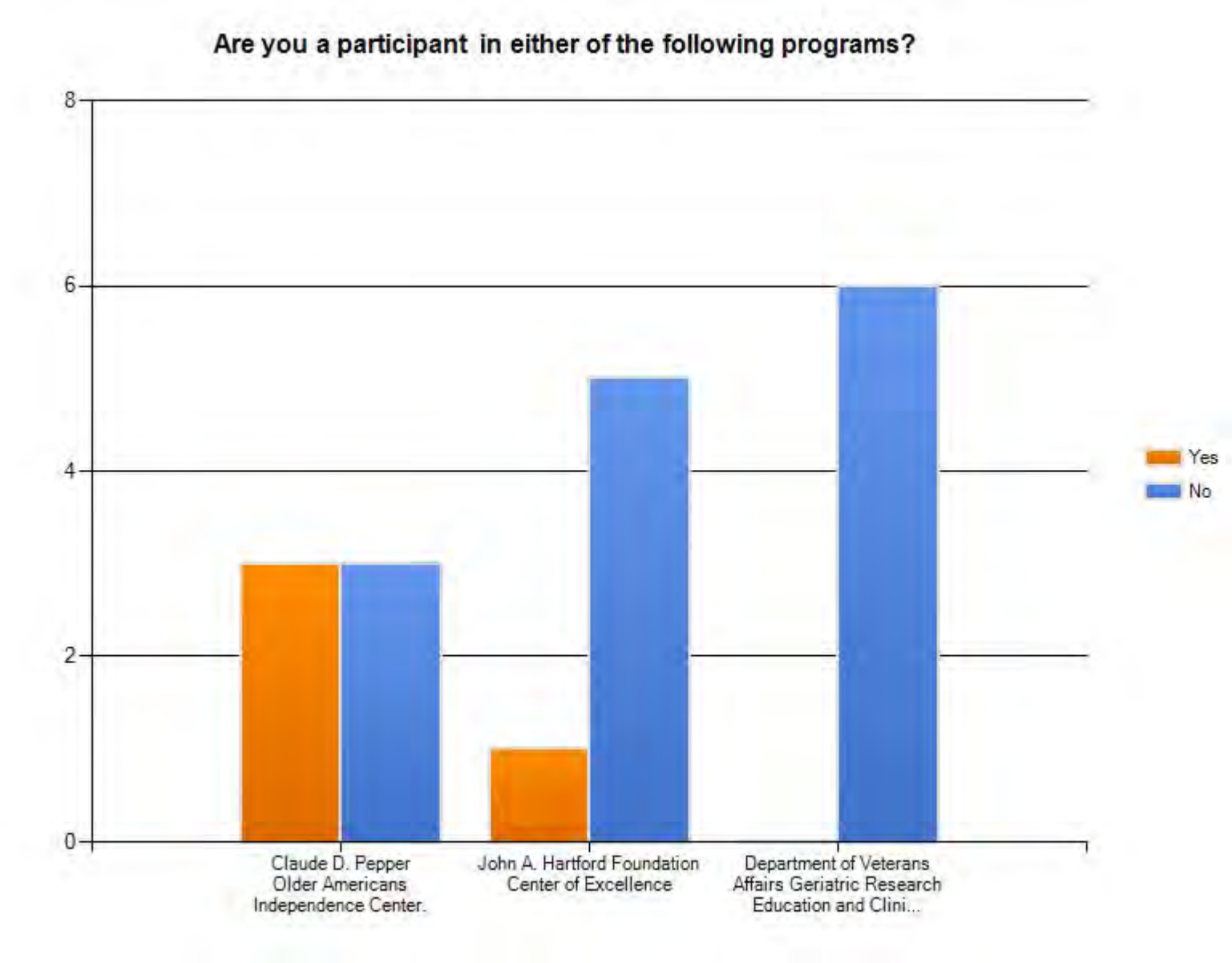


Have you applied for an independent investigator award from one of the following institutions?

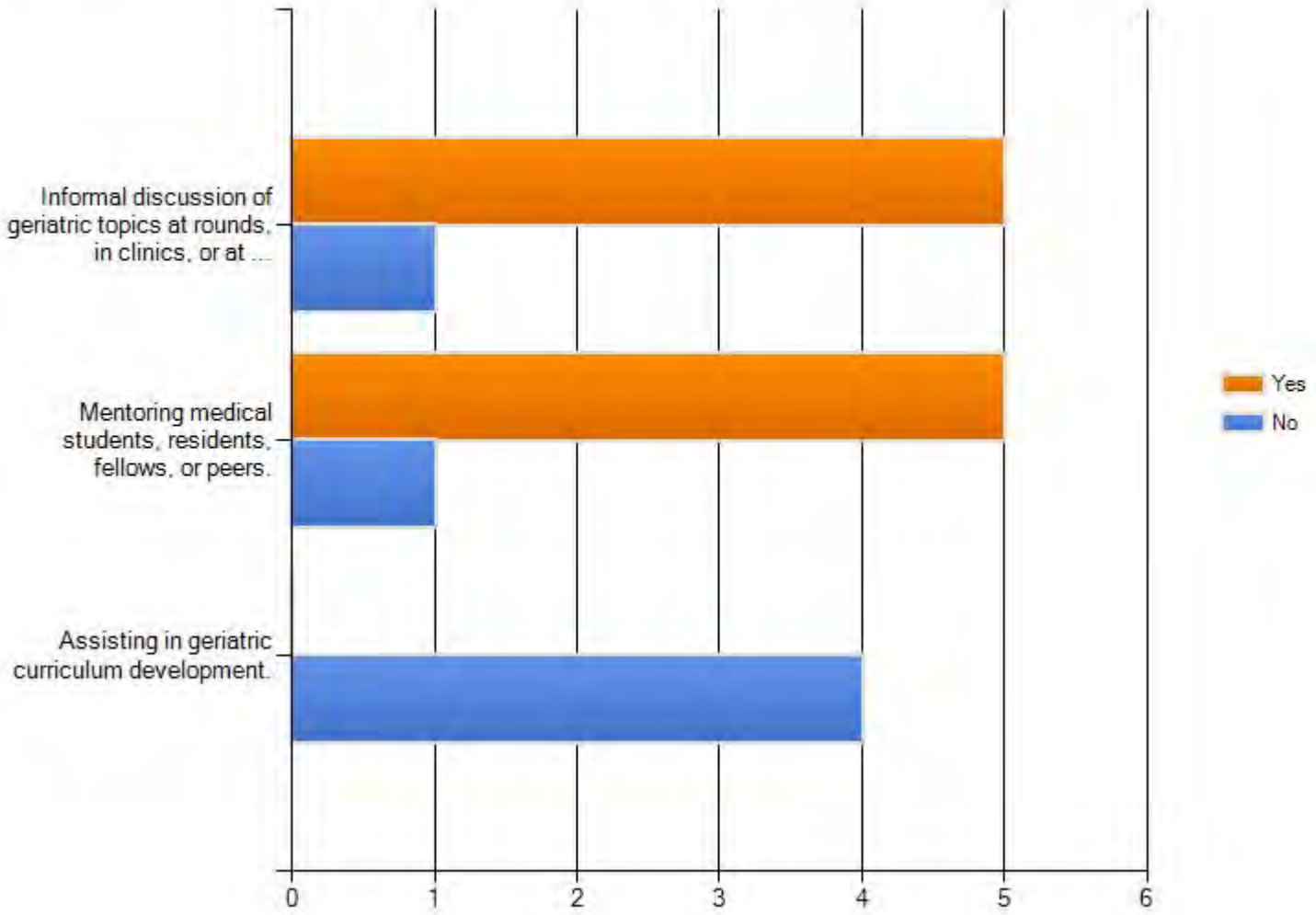


Have you been a member of a research team that has applied for or received grants or awards to support research or career development activities in the last six months from any of the following sources?

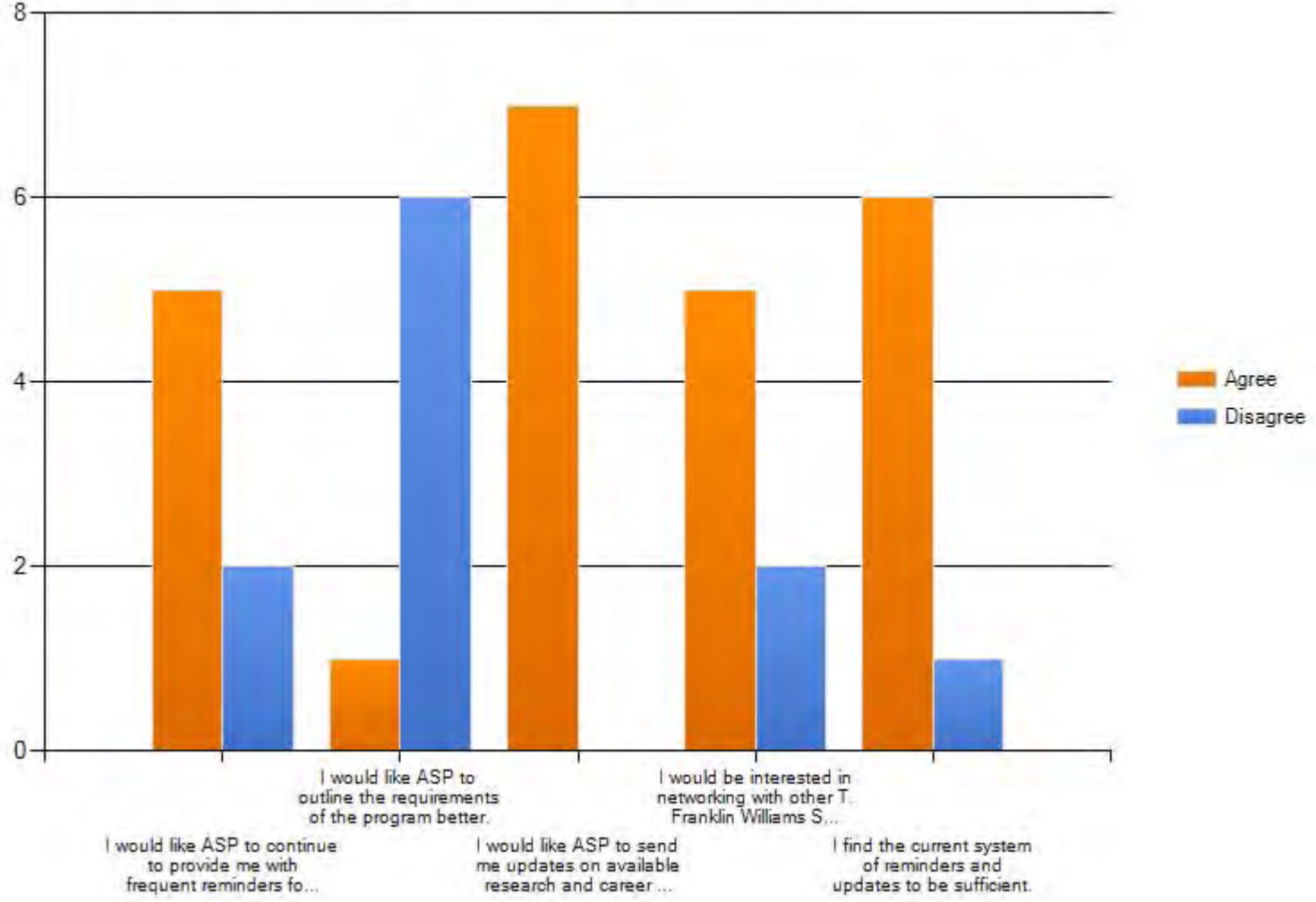



Are you a participant in either of the following programs?
8
6
4
2
0
Yes
No
Claude D. Pepper Older Americans Independence Center.
John A. Hartford Foundation Center of Excellence
Department of Veterans Affairs Geriatric Research Education and Clini...

Please indicate which of the following educational activities you have been involved with:



Is there any additional information or assistance you would like ASP to provide you during your award term?



Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov)

Components of Participating Organizations
National Institute on Aging (NIA), (http://www.nia.nih.gov)

Title: Grants for Early Medical/Surgical Subspecialists' Transition to Aging Research (R03)

Announcement Type

New

Request for Applications (RFA) Number: RFA-AG-11-007

NOTICE: Applications submitted in response to this Funding Opportunity Announcement (FOA) for Federal assistance must be submitted electronically through Grants.gov (http://www.grants.gov) using the SF424 Research and Related (R&R) forms and the SF424 (R&R) Application Guide.

APPLICATIONS MAY NOT BE SUBMITTED IN PAPER FORMAT.

This FOA must be read in conjunction with the application guidelines included with this announcement in Grants.gov/Apply for Grants (hereafter called Grants.gov/Apply).

A registration process is necessary before submission and applicants are highly encouraged to start the process at least four (4) weeks prior to the grant submission date. See Section IV.

Apply for Grant Electronically

A compatible version of Adobe Reader is required for download. For Assistance downloading this or any Grants.gov application package, please contact Grants.gov Customer Support at http://grants.gov/CustomerSupport.

Catalog of Federal Domestic Assistance Number(s)
93.866

Key Dates
Release/Posted Date: August 3, 2010
Opening Date: October 3, 2010 (Earliest date an application may be submitted to Grants.gov)
Letters of Intent Receipt Date(s): October 3, 2010
NOTE: On-time submission requires that applications be successfully submitted to Grants.gov no later than 5:00 p.m. local time (of the applicant institution/organization).
Application Due Date(s): November 3, 2010
Peer Review Date(s): February/March 2011
Council Review Date(s): May 2011
Earliest Anticipated Start Date(s): July 1, 2011
Additional Information to Be Available Date (Activation Date): Not Applicable
Expiration Date: November 4, 2010

Due Dates for E.O. 12372

Not Applicable

Additional Overview Content

Executive Summary

- **Purpose.** This program provides two years of support for small research projects to allow early career physicians trained in medical and surgical subspecialties to establish a research track record in geriatric aspects of their subspecialty. The award will provide an opportunity to gain skills and experience in aging research and help the investigators establish an independent program of research in this field.
- **Mechanism of Support.** This FOA will utilize the R03 award mechanism.
- **Funds Available and Anticipated Number of Awards.** NIA will provide $1.5 million in total costs in FY2011 to support 18-20 awards.
- **Budget and Project Period.** $50,000 per year in direct costs and a project period of up to two years may be requested through this funding opportunity.
- **Application Research Strategy Length:** The R03 application Research Strategy section of the PHS398 may not exceed 6 pages, including tables, graphs, figures, diagrams, and charts. See Table of Page Limits.
- **Eligible Institutions/Organizations.** Institutions/organizations listed in Section III, 1.A. are eligible to apply.
- **Eligible Project Directors/Principal Investigators (PDs/PIs).** Clinically trained individuals with the skills, knowledge, and resources necessary to carry out the proposed research who have completed their medical or surgical specialty and are in the early stages of their first faculty appointment are invited to work with their
- institution/organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.
- **Number of PDs/PIs.** More than one PD/PI (i.e., multiple PDs/PIs) may be designated on the application.
- **Number of Applications.** Applicants may submit only one application in response to this FOA.
- **Resubmissions.** Resubmissions are not permitted in response to this FOA. **Renewals.** Renewal applications are not permitted in response to this FOA.
- **Special Date(s).** This FOA uses non-standard due dates.
- **Application Materials.** See Section IV.1 for application materials.
- **General Information.** For general information on SF424 (R&R) Application and Electronic Submission, see these Web sites:
    - SF424 (R&R) Application and Electronic Submission Information: http://grants.nih.gov/grants/funding/424/index.htm
    - General information on Electronic Submission of Grant Applications: http://era.nih.gov/ElectronicReceipt/
- **Hearing Impaired.** Telecommunications for the hearing impaired are available at: TTY: (301) 451-5936

Table of Contents

Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

The National Institute on Aging (NIA) offers this initiative to promote research conducted by physicians trained in medical or surgical subspecialties who are entering careers as clinician-scientists in geriatric aspects of their subspecialty.

The recent Institute of Medicine Report "Retooling for an Aging America: Building the Health Care Workforce" (April 2008) (http://www.iom.edu/Reports/2008/Retooling-for-an-Aging-America-Building-the-Health-Care-Workforce.aspx) has emphasized the emergent need for additional health care personnel to address the medical needs of a growing population of older Americans with complex medical problems. Effective approaches to this impending health care crisis involve not only increasing the number of practicing physicians trained in geriatrics and in subspecialty fields related to the health problems of elders, but also fostering the development of the next generation of physician-scientists whose clinical research will lead to improved care and more effective treatment options for older patients with complex medical conditions.

A pivotal point in the development of clinician-scientists is the completion of training in a medical or surgical subspecialty and the first faculty appointment. At this early stage, limited research experience and publication record preclude competitiveness for many kinds of advanced research opportunities. This transition stage may be particularly difficult for a subspecialty-trained physician focusing on geriatric aspects of his/her subspecialty, as multidisciplinary research entails training that is rarely available in conventional programs. Thus, mechanisms that allow these physicians to begin research projects and establish a research track record are a priority for cultivating the next generation of clinician-scientists, particularly at the interface of geriatrics and medical/surgical subspecialties.

Program Goal

The goal of the Grants for Early Medical/Surgical Subspecialists' Transition to Aging Research **(GEMSSTAR) program is to promote** future leaders in clinical aging research through support to clinically trained faculty members early in their professions. To accomplish this goal, NIA will provide two years of support for small research projects to physicians trained in medical and surgical subspecialties who seek to become clinician-scientists in geriatric aspects of their subspecialty. As described below, research support through this initiative will be contingent on the applicants' demonstration of acceptable professional development activities and support.

Through this proposed initiative, physicians trained in medical and surgical subspecialties who seek to bridge both geriatrics and clinical subspecialty disciplines can receive research project support through this NIH R03 mechanism. Research projects responsive to this initiative will combine aging with subspecialty clinical areas to focus on clinical or translational questions relevant to aging and/or the aged. Research may involve pilot or feasibility studies, secondary analysis of existing data, development of research methodology, or development of new research technology. Projects should be appropriate to the background and level of experience of the applicant.

R03 awardees must have concurrent professional development support to receive this award. Documentation should not be included in the R03 application, but rather, submitted as "Just-in-Time" information upon request (see section IV.6. Other Submission Requirements). Professional development support activities might include mentorship plans, didactic training in geriatrics or subspecialty areas, coursework in pursuit of a research degree or other structured learning experience, and/or participation in existing institutional training opportunities. Support for these professional development activities may be provided through a variety of sources, alone or in combination, including the following:

- The applicant's sponsoring institution and/or its affiliated Veteran's Administration hospital
- Clinical Translational Research Award (CTSA)
- NIH K12 or R25 program
- Specialty Societies including the Association of Specialty Professors (ASP) (http://www.im.org/About/AllianceSites/ASP/Pages/Default.aspx) and the Surgical Section of the

American Geriatrics Society (AGS) (http://www.americangeriatrics.org/) (Both of these organizations have agreed to coordinate their support with this initiative)
- Older Americans Independence Center (OAIC) Research Career Development Core (RCDC)
- Other government, public, or private sources

As this award is intended for investigators in the early stages of their research careers, proposed research projects may be expected to include at least one collaborator or consultant with expertise appropriate to the proposed research.

See Section VIII, Other Information - Required Federal Citations, for policies related to this announcement.

Section II. Award Information

1. Mechanism of Support

This FOA will use the R03 award mechanism. The Project Director/Principal Investigator (PD/PI) will be solely responsible for planning, directing, and executing the proposed project.

This FOA uses "Just-in-Time" information concepts (see SF424 (R&R) Application Guide). It also uses the modular budget format (see http://grants.nih.gov/grants/funding/modular/modular.htm).

2. Funds Available

The National Institute on Aging intends to commit approximately $1.5 million in FY 2011 to support:

- 18-20 awards are anticipated;
- Awards will be made for two years.
- Applicants may seek up to $50,000 (direct costs) per year.

Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of NIA provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds.

Facilities and Administrative (F&A) costs requested by consortium participants are not included in the direct cost limitation. See NOT-OD-05-004.

NIH grants policies as described in the NIH Grants Policy Statement will apply to the applications submitted and awards made in response to this FOA.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

The following organizations/institutions are eligible to apply:

- Public/State Controlled Institutions of Higher Education

- Private Institutions of Higher Education
- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions
- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Small Businesses
- For-Profit Organizations (Other than Small Businesses)
- State Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribally Designated Organizations
- County Governments
- City or Township Governments
- Special District Governments
- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- U.S. Territory or Possession
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Organizations)
- Other(s):
    - Eligible Agencies of the Federal Government
    - Faith-based or Community-based Organizations

1. B. Eligible Individuals

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the PD/PI is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Applicants must be clinically-trained individuals who have completed their medical or surgical specialty.

More than one PD/PI (i.e., multiple PDs/PIs), may be designated on the application for projects that require a "team science" approach and therefore clearly do not fit the single-PD/PI model. Additional information on the implementation plans and policies and procedures to formally allow more than one PD/PI on individual research projects is available at http://grants.nih.gov/grants/multi_pi. All PDs/PIs must be registered in the NIH electronic Research Administration (eRA) Commons prior to the submission of the application (see http://era.nih.gov/ElectronicReceipt/preparing.htm for instructions).

The decision of whether to apply for a grant with a single PD/PI or multiple PDs/PIs is the responsibility of the investigators and applicant organizations and should be determined by the scientific goals of the project. Applications for grants with multiple PDs/PIs will require additional information, as outlined in the instructions below. When considering the multiple PD/PI option, please be aware that the structure and governance of the PD/PI leadership team as well as the knowledge, skills and experience of the individual PDs/PIs will be factored into the assessment of the overall scientific merit of the application. Multiple PDs/PIs on a project share the authority and responsibility for leading and directing the project, intellectually and logistically. Each PD/PI is responsible and accountable to the grantee organization, or, as appropriate, to a collaborating organization, for the proper conduct of the project or program, including the submission of required reports. For further information on multiple PDs/PIs, please see http://grants.nih.gov/grants/multi_pi.

2. Cost Sharing or Matching

This program does not require cost sharing as defined in the current *NIH Grants Policy Statement*.

3. Other-Special Eligibility Criteria

Number of Applications. Applicants may submit only one application in response to this FOA.

Resubmissions. Resubmission applications are not permitted in response to this FOA.

Renewals. Renewal applications are not permitted in response to this FOA.

Section IV. Application and Submission Information

To download a SF424 (R&R) Application Package and SF424 (R&R) Application Guide for completing the SF424 (R&R) forms for this FOA, use the "Apply for Grant Electronically" button in this FOA or link to http://www.grants.gov/Apply/ and follow the directions provided on that Web site.

Registration:

Appropriate registrations with Grants.gov and eRA Commons must be completed on or before the due date in order to successfully submit an application**. Several of the steps of the registration process could take four weeks or more.** Therefore, applicants should immediately check with their business official to determine whether their organization/institution is already registered with both Grants.gov and the Commons. All registrations must be complete by the submission deadline for the application to be considered "on-time" (see 3.C.1 for more information about on-time submission).

A one-time registration is required for institutions/organizations at both:

- Grants.gov (http://www.grants.gov/applicants/get_registered.jsp) and
- eRA Commons (http://era.nih.gov/ElectronicReceipt/preparing.htm)

PDs/PIs should work with their institutions/organizations to make sure they are registered in the NIH eRA Commons.

Several additional separate actions are required before an applicant can submit an electronic application, as follows:

1) Organizational/Institutional Registration in Grants.gov/Get Registered

- Your organization will need to obtain a Data Universal Number System (DUNS) number and register with the Central Contractor Registration (CCR) as part of the Grants.gov registration process.
- If your organization does not have a Taxpayer Identification Number (TIN) or Employer Identification Number (EIN), allow for extra time. A valid TIN or EIN is necessary for CCR registration.
- The CCR also validates the EIN against Internal Revenue Service records, a step that will take an additional one to two business days.
- Direct questions regarding Grants.gov registration to:
  Grants.gov Customer Support
  Contact Center Phone: 800-518-4726
  Business Hours: M-F 7:00 a.m. - 9:00 p.m. Eastern Time
  Email support@grants.gov

2) Organizational/Institutional Registration in the eRA Commons

- To find out if an organization is already Commons-registered, see the "List of Grantee Organizations Registered in NIH eRA Commons."
- Direct questions regarding the Commons registration to:
  eRA Commons Help Desk
  Phone: 301-402-7469 or 866-504-9552 (Toll Free)
  TTY: 301-451-5939
  Business hours M-F 7:00 a.m. – 8:00 p.m. Eastern Time
  Email commons@od.nih.gov

3) Project Director/Principal Investigator (PD/PI) Registration in the NIH eRA Commons: Refer to the *NIH eRA Commons System (COM) Users Guide*.

- The individual(s) designated as PDs/PIs on the application must be registered also in the NIH eRA Commons. In the case of multiple PDs/PIs, all PDs/PIs must be registered **and be assigned the PI role** in the eRA Commons prior to the submission of the application.
- Each PD/PI must hold a PD/PI account in the Commons. Applicants should not share a Commons account for both an Authorized Organization Representative/Signing Official (AOR/SO) role and a PD/PI role; however, if they have both a PD/PI role and an NIH Internet Assisted Review (IAR) role, both roles should exist under one Commons account.
- When multiple PDs/PIs are proposed, all PDs/PIs at the applicant organization must be affiliated with that organization. PDs/PIs located at another institution need not be affiliated with the applicant organization, but must be affiliated with their own organization to be able to access the Commons.
- This registration/affiliation must be done by the AOR/SO or his/her designee who is already registered in the Commons.

Both the PDs/PI(s) and AOR/SO need separate accounts in the NIH eRA Commons since both are authorized to view the application image.

Note: The registration process is not sequential. Applicants should begin the registration processes for both Grants.gov and eRA Commons as soon as their organization has obtained a DUNS number. Only one DUNS number is required and the same DUNS number must be referenced when completing Grants.gov registration, eRA Commons registration and the SF424 (R&R) forms.

1. Request Application Information

Applicants must download the SF424 (R&R) application forms and the SF424 (R&R) Application Guide for this FOA through Grants.gov/Apply.

Note: Only the forms package directly attached to a specific FOA can be used. You will not be able to use any other SF424 (R&R) forms (e.g., sample forms, forms from another FOA); although some of the "Attachment" files may be useable for more than one FOA.

For further assistance, contact GrantsInfo -- Telephone 301-435-0714; Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY: (301) 451-5936

2. Content and Form of Application Submission

Prepare all applications using the SF424 (R&R) application forms for this FOA through Grants.gov/Apply and in accordance with the SF424 (R&R) Application Guide (http://grants.nih.gov/grants/funding/424/index.htm).

The SF424 (R&R) Application Guide is critical to submitting a complete and accurate application to NIH. Some fields within the SF424 (R&R) application components, although not marked as mandatory, are required by NIH (*e.g., the "Credential" log-in field of the "Research & Related Senior/Key Person Profile" component must*

contain the PD/PI's assigned eRA Commons User ID). Agency-specific instructions for such fields are clearly identified in the Application Guide. For additional information, see "Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications."

The SF424 (R&R) application has several components. Some components are required, others are optional. The forms package associated with this FOA in Grants.gov/APPLY includes all applicable components, required and optional. A completed application in response to this FOA includes the data in the following components:

Required Components:
SF424 (R&R) (Cover component)
Research & Related Project/Performance Site Locations
Research & Related Other Project Information
Research & Related Senior/Key Person
PHS398 Cover Page Supplement
PHS398 Research Plan
PHS398 Checklist
PHS398 Modular Budget or Research & Related Budget, as appropriate (See Section IV.6 regarding appropriate required budget component.)

Optional Components:
PHS398 Cover Letter File
Research & Related Subaward Budget Attachment(s) Form

Foreign Organizations (Non-Domestic [non-U.S.] Entities)

NIH policies concerning grants to Foreign (non-U.S.) organizations can be found in the *NIH Grants Policy Statement* at: http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part12.htm#_Toc54600260.

Applications from Foreign organizations must:

- Request budgets in U.S. dollars;
- Prepare detailed budgets for all applications (that is, complete the Research & Related Budget component of the SF424 (R&R) application forms – not the PHS398 Modular Budget component)(see NOT-OD-06-096);
- Not include any charge-back of customs and import fees;
- Comply with the format specifications, which are based upon a standard U.S. paper size of 8.5" x 11" within each PDF;
- If appropriate, request funds for up to 8% administrative costs (excluding equipment) (see NOT-OD-01-028, March 29, 2001);
- Comply with Federal/NIH policies on human subjects, animals, and biohazards; and
- Comply with Federal/NIH biosafety and biosecurity regulations (see Section VI.2., "Administrative and National Policy Requirements").

Proposed research should provide special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions in other countries that are not readily available in the United States (U.S.) or that augment existing U.S. resources.

SPECIAL INSTRUCTIONS

Applications Involving Multiple Institutions

When multiple PDs/PIs are proposed, NIH requires one PD/PI to be designated as the "Contact" PI, who will be responsible for all communication between the PDs/PIs and the NIH, for assembling the application

materials outlined below, and for coordinating progress reports for the project. The contact PD/PI must meet all eligibility requirements for PD/PI status in the same way as other PDs/PIs, but has no other special roles or responsibilities within the project team beyond those mentioned above.

Information for the Contact PD/PI should be entered on the SF424 (R&R) Cover component. All other PDs/PIs should be listed in the Research & Related Senior/Key Person component and assigned the project role of "PD/PI." Please remember that all PDs/PIs must be registered in the eRA Commons prior to application submission. **The Commons ID of each PD/PI must be included in the "Credential" field of the Research & Related Senior/Key Person component. Failure to include this data field will cause the application to be rejected.**

Multiple PD/PI Leadership Plan: For applications designating multiple PDs/PIs, the section of the Research Plan entitled, "Multiple PD/PI Leadership Plan", must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, and should include communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Award (NoA).

Applications Involving a Single Institution

When all PDs/PIs are within a single institution, follow the instructions contained in the SF424 (R&R) Application Guide.

3. Submission Dates and Times

See Section IV.3.A. for details.

3. A. Submission, Review, and Anticipated Start Dates

Opening Date: October 3, 2010 (Earliest date an application may be submitted to Grants.gov)
Letters of Intent Receipt Date(s): October 3, 2010
Application Due Date(s): November 3, 2010
Peer Review Date(s): February/March 2011
Council Review Date(s): May 2011
Earliest Anticipated Start Date(s): July 1, 2011

3. A.1. Letter of Intent

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research.
- Name, address, and telephone number of the PD(s)/PI(s).
- Names of other key personnel.
- Participating institutions.
- Number and title of this funding opportunity.

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed in Section IV.3.A.

The letter of intent should be sent to:

Ramesh Vemuri, Ph.D., Chief
Scientific Review Branch
National Institute on Aging
7201 Wisconsin Avenue, Room 2C212
Bethesda, MD 20892-9205
Telephone: (301) 496-9666
FAX: (301) 402-0066
Email: VemuriR@nia.nih.gov

3. B. Submitting an Application Electronically to the NIH

To submit an application in response to this FOA, applicants should access this FOA via http://www.grants.gov/applicants/apply_for_grants.jsp and follow Steps 1-4. Note: Applications must only be submitted electronically**. PAPER APPLICATIONS WILL NOT BE ACCEPTED.** All attachments must be provided to NIH in PDF format, filenames must be included with no spaces or special characters, and a .pdf extension must be used.

In order to expedite the review, applicants are requested to notify the NIA Referral Office by Email: VemuriR@nia.nih.gov when the application has been submitted. Please include the FOA number and title, PD/PI name, and title of the application.

3. C. Application Processing

3.C.1 Submitting On-Time

Applications **may** be submitted on or after the opening date and **must** be successfully received by Grants.gov no later than **5:00 p.m. local time** (of the applicant institution/organization) on the application due date(s). (See Section IV.3.A. for all dates.) If an application is not submitted by the due date(s) and time, the application may be delayed in the review process or not reviewed. All applications must meet the following criteria to be considered “on-time”:

- All registrations must be complete prior to the submission deadline
- The application must receive a Grants.gov tracking number and timestamp (or eRA help desk ticket confirming a system issue preventing submission) by 5:00 p.m. local time on the submission deadline date.
- Any system identified errors/warnings must be corrected and the submission process completed within the “error correction window.”

Please visit http://era.nih.gov/electronicReceipt/app_help.htm for detailed information on what to do if Grants.gov or eRA system issues threaten your ability to submit on time.

Submission to Grants.gov is not the last step – applicants must follow their application through to the eRA Commons to check for errors and warnings and view their assembled application!

3. C.2 Two Day Window to Correct eRA Identified Errors/Warnings

Once an application package has been successfully submitted through Grants.gov, NIH provides applicants a two day *error correction window* to correct any eRA identified errors or warnings before a final assembled application is created in the eRA Commons. The standard error correction window is two (2) business days, beginning the day after the submission deadline and excluding weekends and standard federal holidays. All

errors must be corrected to successfully complete the submission process. Warnings will not prevent the application from completing the submission process.

Please note that the following caveats apply:

- Initial application submission must be “on-time.”
- The AOR/institutions is expected to enforce that application changes made within the error correction window are restricted to those necessary to address system-identified errors/warnings. NIH may reject any application that includes additional changes.
- Proof of “on-time” submission (e.g., Grants.gov timestamp and tracking number) and description of all changes made within the window must be documented in the PHS 398 Cover Letter component of the application.

3. C.3 Viewing an Application in the eRA Commons

Once any eRA identified errors have been addressed and the assembled application has been created in the eRA Commons, the PD/PI and the Authorized Organization Representative/Signing Official (AOR/SO) have two weekdays (Monday – Friday, excluding Federal holidays) to view the assembled application before it automatically moves forward to NIH for further processing.

- If everything is acceptable, no further action is necessary. The application will automatically move forward to the Division of Receipt and Referral in the Center for Scientific Review for processing after two weekdays, excluding Federal holidays.
- Prior to the submission deadline, the AOR/SO can “Reject” the assembled application and submit a changed/corrected application within the two-day viewing window. This option should be used if it is determined that some part of the application was lost or did not transfer correctly during the submission process, the AOR/SO will have the option to “Reject” the application and submit a Changed/Corrected application. In these cases, please contact the eRA Help Desk to ensure that the issues are addressed and corrected. Once rejected, applicants should follow the instructions for correcting errors in Section 2.12 of the SF 424 (R&R) application guide, including the requirement for cover letters on late applications. The “Reject” feature should also be used if you determine that warnings are applicable to your application and need to be addressed now. Remember, warnings do not stop further application processing. If an application submission results in warnings (but no errors), it will automatically move forward after two weekdays if no action is taken. Some warnings may need to be addressed later in the process.
- If the two-day window falls after the submission deadline, the AOR/SO will have the option to “Reject” the application if, **due to an eRA Commons or Grants.gov system issue,** the application does not correctly reflect the submitted application package (e.g., some part of the application was lost or didn’t transfer correctly during the submission process). The AOR/SO should first contact the eRA Commons Helpdesk to confirm the system error, document the issue, and determine the best course of action. NIH will not penalize the applicant for an eRA Commons or Grants.gov system issue.
- If the AOR/SO chooses to “Reject” the image after the submission deadline for a reason other than an eRA Commons or Grants.gov system failure, a changed/corrected application still can be submitted, but it will be subject to the NIH late policy guidelines and may not be accepted. The reason for this delay should be explained in the cover letter attachment.
- Both the AOR/SO and PD/PI will receive e-mail notifications when the application is rejected or the application automatically moves forward in the process after two weekdays.

Upon receipt, applications will be evaluated for completeness by the CSR and responsiveness by the IC. Incomplete and/or non-responsive applications will not be reviewed.

There will be an acknowledgement of receipt of applications from Grants.gov and the Commons. The submitting AOR/SO receives the Grants.gov acknowledgments. The AOR/SO and the PI receive Commons acknowledgments. Information related to the assignment of an application to a Scientific Review Group is also

in the Commons.

Note: Since email can be unreliable, it is the responsibility of the applicant to check periodically on the application status in the Commons.

The NIH will not accept any application in response to this FOA that is essentially the same as one currently pending initial merit review unless the applicant withdraws the pending application. The NIH will not accept any application that is essentially the same as one already reviewed. However, the NIH will accept a resubmission application, but such application must include an Introduction addressing the critique from the previous review.

4. Intergovernmental Review

This initiative is not subject to *intergovernmental review*.

5. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement.

Pre-award costs are allowable. A grantee may, at its own risk and without NIH prior approval, incur obligations and expenditures to cover costs up to 90 days before the beginning date of the initial budget period of a new award if such costs: 1) are necessary to conduct the project, and 2) would be allowable under the grant, if awarded, without NIH prior approval. If specific expenditures would otherwise require prior approval, the grantee must obtain NIH approval before incurring the cost. NIH prior approval is required for any costs to be incurred more than 90 days before the beginning date of the initial budget period of a new award.

The incurrence of pre-award costs in anticipation of a competing or non-competing award imposes no obligation on NIH either to make the award or to increase the amount of the approved budget if an award is made for less than the amount anticipated and is inadequate to cover the pre-award costs incurred. NIH expects the grantee to be fully aware that pre-award costs result in borrowing against future support and that such borrowing must not impair the grantee's ability to accomplish the project objectives in the approved time frame or in any way adversely affect the conduct of the project (see the *NIH Grants Policy Statement*).

This initiative requires the R03 applicant to provide evidence that he/she is eligible to apply for and receive support for mentoring and professional development, including sufficient protected time consistent with the specific aims of the R03 award and the need for professional development. Documented professional development support must be in place prior to and coincident in time with the award of the R03.

6. Other Submission Requirements

Applicants receiving a score within a potential funding range will be invited to share their professional development plan with the NIA staff as “Just-in-Time” information. The plan should describe professional development activities in the geriatric aspects of clinical aging research within the applicant’s medical or surgical subspecialty, including proposed mentors and activities designed to enhance their research and research career skills (e.g., additional didactic training in geriatrics or specialty areas; participation in existing institutional training opportunities such as Pepper Center seminars, CTSA training, NIH K12 or R25 programs, etc.).

Acceptable and documented support for professional development activities must be in place prior to award of the R03 and must remain active during the entire R03 award period. Applicants for this initiative are strongly encouraged to seek professional development support prior to the expected start date of the R03 award. Acquiring support for professional development is the responsibility of the R03 applicant.

As applicants for this initiative will be in the early stages of research careers, proposed research projects should include at least one collaborator or consultant with expertise appropriate to the proposed research. The collaborator(s) or consultant(s) may be the same individual(s) who will provide support for the proposed professional development activities in the complementary program.

PD/PI Credential (e.g., Agency Login)

The NIH requires the PD(s)/PI(s) to fill in his/her Commons User ID in the "PROFILE – Project Director/Principal Investigator" section, "Credential" log-in field of the "Research & Related Senior/Key Person Profile" component.

Organizational DUNS

The applicant organization must include its DUNS number in its Organization Profile in the eRA Commons. This DUNS number must match the DUNS number provided at CCR registration with Grants.gov. For additional information, see "Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications."

PHS398 Research Plan Component Sections

All application instructions outlined in the SF424 (R&R) Application Guide are to be followed, incorporating "Just-in-Time" information concepts, and with the following additional requirements:

- Specific Aims is limited to 1 page.
- Research Strategy, including tables, graphs, figures, diagrams, and charts is limited to 6 pages. See Table of Page Limits.

Budget Component

U.S. applicants submitting an application with direct costs in each year of $250,000 or less (excluding consortium Facilities and Administrative [F&A] costs) must use the PHS398 Modular Budget component.

U.S. applicants requesting more than $250,000 in annual direct costs and all foreign applicants must complete and submit budget requests using the Research & Related Budget component.

Appendix Materials

Applicants **must** follow the specific instructions on Appendix materials as described in the SF424 (R&R) Application Guide (See http://grants.nih.gov/grants/funding/424/index.htm).

Do not use the Appendix to circumvent the page limitations. An application that does not comply with the required page limitations may be delayed in the review process.

Resource Sharing Plan(s)

NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing, this should be explained in the Resource Sharing section of the application (see http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.)

(a) *Data Sharing Plan*: Regardless of the amount requested, investigators are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible. Applicants are encouraged to discuss data-sharing plans with their NIH program contact (see Data-Sharing Policy or http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html.)

(b) *Sharing Model Organisms*: Regardless of the amount requested, all applications where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms and related resources or state appropriate reasons why such sharing is restricted or not possible (see Sharing Model Organisms Policy, and NOT-OD-04-042.)

(c) *Genome-Wide Association Studies (GWAS):* Regardless of the amount requested, applicants seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or provide an appropriate explanation why submission to the repository is not possible. A genome-wide association study is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (e.g., blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (go to NOT-OD-07-088, and http://grants.nih.gov/grants/gwas/.)

Foreign Applications (Non-Domestic [non-U.S.] Entities)

Indicate how the proposed project has specific relevance to the mission and objectives of the NIH/IC and has the potential for significantly advancing the health sciences in the United States.

Section V. Application Review Information

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1. Criteria

Only the review criteria described below will be considered in the review process.

2. Review and Selection Process

Review Process

Applications that are complete and responsive to this FOA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the National Institute on Aging and in accordance with NIH peer review procedures (http://grants1.nih.gov/grants/peer/), using the review criteria stated below.

As part of the scientific peer review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific and technical merit, generally the top half of applications under review, will be discussed and assigned an impact/priority score;
- Receive a written critique; and
- Receive a second level of review by the National Advisory Council on Aging

The R03 small grant supports discrete, well-defined projects that realistically can be completed in two years and that require limited levels of funding. Because the research project usually is limited, an R03 grant application may not contain extensive detail or discussion. Accordingly, reviewers should evaluate the conceptual framework and general approach to the problem. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or from investigator-generated data. Preliminary data are not required, particularly in applications proposing pilot or feasibility studies.

The mission of the NIH is to support science in pursuit of knowledge about the biology and behavior of living systems and to apply that knowledge to extend healthy life and reduce the burdens of illness and disability. As part of this mission, applications submitted to the NIH for grants or cooperative agreements to support biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

Overall Impact

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five scored review criteria, and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance. Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? To what extent does the proposed project introduce age-related research questions to medical and surgical subspecialty areas?

Investigator(s). Are the PD/PIs, collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project? Does the team of investigators have complementary and integrated expertise in aging and geriatrics appropriate for the project? Is the role of the collaborator(s) appropriate to advance the specific aims of the project and supplement the skills of the PI?

Innovation. Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach. Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment. Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements? Does the environment provide sufficient research resources relevant to geriatrics and the subspecialty field of investigation?

Additional Review Criteria

As applicable for the project proposed, reviewers will consider **the following additional items in the determination of scientific and technical merit, but will not give separate scores for these items**.

Protections for Human Subjects. For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials.

Inclusion of Women, Minorities, and Children. When the proposed project involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children.

Vertebrate Animals. The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information, see http://grants.nih.gov/grants/olaw/VAChecklist.pdf.

Biohazards. Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmission Applications. Resubmissions are not allowed for this FOA. ***Renewal Applications.*** Renewals are not allowed for this FOA.

Revision Applications. Revisions are not allowed for this FOA.

Additional Review Considerations

As applicable for the project proposed, reviewers will address each of the following items, but will not give scores for these items and should not consider them in providing an overall impact/priority score.

Applications from Foreign Organizations. As applicable for the FOA or submitted application, reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agents Research. Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans. Reviewers will comment on whether the following Resource Sharing Plans, or the

rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan (http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm); 2) Sharing Model Organisms (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html); and 3) Genome Wide Association Studies (GWAS) (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html).

Budget and Period of Support. Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

Selection Process

Applications submitted in response to this FOA will compete for available funds with all other recommended applications submitted in response to this FOA. The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.
- The degree to which the proposed project represents a significant first independent research effort as opposed to an additive research experience for the principal investigator

This award includes special terms and conditions. See Section IV.5. “Funding Restrictions.”

3. Anticipated Announcement and Award Dates

Not Applicable

Section VI. Award Administration Information

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1. Award Notices

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the NIH eRA Commons.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the *NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General*.

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization. The NoA signed by the grants management officer is the authorizing document. Once all administrative and programmatic issues have been resolved, the NoA will be generated via email notification from the awarding component to the grantee business official.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs. See Section IV.5., “Funding Restrictions.”

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* as part of the NoA. For these terms of award, see the *NIH Grants Policy Statement* Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities.

3. Reporting

Awardees will be required to submit the Non-Competing Continuation Grant Progress Report (PHS 2590) annually and financial statements as required in the *NIH Grants Policy Statement*.

A final progress report, invention statement, and Financial Status Report are required when an award is relinquished when a recipient changes institutions or when an award is terminated.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research (program), peer review, and financial or grants management issues:

1. Scientific/Research Contact(s):

Basil A. Eldadah, MD, PhD
Program Officer, Geriatrics Branch
Division of Geriatrics and Clinical Gerontology
National Institute on Aging
7201 Wisconsin Avenue, Suite 3C-307
Bethesda, MD 20892-9205 (for FedEx use 20814)
Phone: 301-496-6761
Fax: 301-402-1784
Email: eldadahb@nia.nih.gov

2. Peer Review Contact(s):

Ramesh Vemuri, Ph.D., Chief
Scientific Review Branch
National Institute on Aging
7201 Wisconsin Avenue, Room 2C212
Bethesda, MD 20892-9205 (for FedEx use 20814)
Phone: (301) 496-9666
Fax: (301) 402-0066
Email: VemuriR@nia.nih.gov

3. Financial/Grants Management Contact(s):

Ms. Pam Adewunmi
Grants and Contracts Management Branch
National Institute on Aging
7201 Wisconsin Avenue, Suite 2N212
Bethesda, MD 20892-9205 (for FedEx use 20814)
Phone: (301) 496-1472
Email: Adewunmp@mail.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:
Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm) as applicable.

Human Subjects Protection:
Federal regulations (45 CFR 46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm).

Data and Safety Monitoring Plan:
Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity and dose-finding studies (Phase I); efficacy studies (Phase II); efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants ("NIH Policy for Data and Safety Monitoring," *NIH Guide for Grants and Contracts*, http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (http://grants.nih.gov/grants/policy/data_sharing). Investigators should seek guidance from their institutions, on issues related to institutional policies and local institutional review board (IRB) rules, as well as local, State and Federal laws and regulations, including the Privacy Rule.

Policy for Genome-Wide Association Studies (GWAS):
NIH is interested in advancing genome-wide association studies (GWAS) to identify common genetic factors that influence health and disease through a centralized GWAS data repository. For the purposes of this policy, a genome-wide association study is defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition. All applications, regardless of the amount requested, proposing a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or provide an appropriate explanation why submission to the repository is not possible. Data repository management (submission and access) is governed by the Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088. For additional information, see http://grants.nih.gov/grants/gwas/.

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the *NIH Grants Policy Statement*. Beginning October 1, 2004, all investigators submitting an NIH application or contract proposal are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Access to Research Data through the Freedom of Information Act:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are: (1) first produced in a project that is supported in whole or in part with Federal funds; and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this funding opportunity in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Inclusion of Women And Minorities in Clinical Research:
It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the SF424 (R&R) application; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects (http://grants.nih.gov/grants/funding/children/children.htm).

Required Education on the Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for Federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-116.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (http://escr.nih.gov/). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research.

NIH Public Access Policy Requirement:
In accordance with the NIH Public Access Policy, *investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central* (see

http://www.pubmedcentral.nih.gov/), *an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication.* The NIH Public Access Policy is available at (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html). For more information, see the Public Access webpage at http://publicaccess.nih.gov/.

Standards for Privacy of Individually Identifiable Health Information:
The Department of Health and Human Services (HHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule", on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the HHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. For publications listed in the appendix and/or Progress report, Internet addresses (URLs) or PubMed Central (PMC) submission identification numbers must be used for publicly accessible on-line journal articles. Publicly accessible on-line journal articles or PMC articles/manuscripts accepted for publication that are directly relevant to the project may be included **only** as **URLs** or **PMC submission identification numbers** accompanying the full reference in either the Bibliography & References Cited section, the Progress Report Publication List section, or the Biographical Sketch section of the NIH grant application. A URL or PMC submission identification number citation may be repeated in each of these sections as appropriate. There is no limit to the number of URLs or PMC submission identification numbers that can be cited.

Healthy People 2010:
The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This FOA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

Loan Repayment Programs:
NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: http://www.lrp.nih.gov/.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Office of Extramural Research (OER)
National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892
Department of Health and Human Services (HHS)

Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, Audio or Video files, see Help Downloading Files.