

Paul B. Beeson
Career Development Awards
In Aging Research Program



2005 Report
Featuring the 2003 Scholars

Tribute to Paul B. Beeson, MD

The Paul B. Beeson Career Development Awards in Aging Research Program is named after a distinguished leader in medicine who, accomplished in the art of healing and treating disease, exemplifies the word, “physician.”

Now Professor Emeritus of Medicine at the University of Washington, Dr. Beeson remains active in the field and has participated in several of this program’s annual meetings. Throughout his career, he has profoundly influenced the career paths of many young physicians, who today form the core leadership in geriatric medicine. His own career of unstinting service to medicine and unwavering commitment to geriatrics and aging research is an inspiration to all of us.



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Message from Stephanie Lederman

This report chronicles the tenth year of the **Paul B. Beeson Career Development Awards in Aging Research Program**. In particular, it focuses on the innovative work of the Beeson Scholars who have joined the program in 2003 and are now in the middle of their work in the program.

We are extremely proud of the growing number of Beeson Scholars. They are an impressive and needed group of talented physician-scientists. Since 1995, we have selected 104 Beeson Scholars from 39 of the nation's top medical schools and research institutions. In just one decade, the program has created a powerful and growing leadership network for the field of aging research.

Last year, we were pleased to welcome the support of the National Institute on Aging (NIA), which has become a powerful and strategic partner in advancing the goals of the program. With the continued support of the NIA and program's private foundation sponsors, we look forward to continuing to identify and nurture the future leaders of this important field.



Stephanie Lederman, Executive Director
American Federation for Aging Research

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An Innovative Public-Private Partnership

The Paul B. Beeson Career Development Awards in Aging Research Program

In the next few decades, the number of older adults in the United States will double, transforming our society and putting extreme pressure on our health care system. It is imperative that the nation has the ability not only to provide high quality medical and supportive care to older Americans, but that we develop the new scientific knowledge that ensures that we live longer, independently and productively as well.

Recognizing these challenges a decade ago, several major philanthropies joined together to launch what is today known as the Paul B. Beeson Career Development Awards in Aging Research Program. Today, the Beeson program continues to make a substantial investment in developing medical faculty so that we can expand our nation's capacity to train physicians in geriatric medicine and conduct aging research. In particular, we support talented physician-scientists whom we trust will devote their careers to advancing our knowledge of the basic mechanisms of aging and effective prevention and management of illness, and who will inspire successive generations of physicians to do the same. Through their diverse scientific interests and extensive teaching commitments, Beeson Scholars are developing the research and nurturing the medical professionals and researchers needed to care for a growing number of older adults.

Beeson in Action

The cornerstone of the Beeson program is the provision of significant financial and career development support for outstanding junior faculty committed to academic careers in aging-related research, teaching, and practice. Each year, the program has made approximately 10 development awards, now worth \$600-800,000, to talented physician-scientists, 104 since the program started.

In addition to providing important financial support, the program requires senior faculty members at the Scholars' institutions to serve as mentors. It also complements this support through "national" mentors chosen from among the members of the committee that advises the foundations supporting the program. These academic leaders guide Scholars' research and career development and provide access to organizations, programs, and colleagues helpful to the Scholars' growth and development.

"We support talented physician-scientists whom we trust will devote their careers to advancing our knowledge of the basic mechanisms of aging and effective prevention and management of illness..."

The critical role of mentoring is further augmented by an annual conference, which convenes all the Scholars and mentors, as well as other leaders in the field of aging research. And year-round, a Web site (www.beeson.org) enables Scholars (and people throughout the field) to learn about recent developments in the program and follow the research throughout the Beeson network.

Enduring Goals, a New Partnership

Beginning in 2004, the National Institute on Aging (NIA) joined the Beeson program as a new public partner. Along with The John A. Hartford Foundation, The Atlantic Philanthropies, and The Starr Foundation, the NIA has helped to ensure the Beeson program's sustainability, while retaining the program's mission, intent and structure. NIA and AFAR (representing the foundation partners) now serve as co-administrators of the program.

The goals of the Beeson program are to:

- Encourage and assist the development of future leaders in the field of aging by supporting faculty members who are early in their careers or who are poised to establish independent programs in aging research.
- Deepen the commitment of academic medicine to research in aging and to translating research outcomes into medical advances, treatment, prevention and service through the mentor-recipient relationship, coupled with broader networking and career development support.
- Expand medical research on aging, broadly defined as including the biology of aging, maintenance of health and independence in old age, diseases and disabilities of old age, and issues in clinical management and systems of care pertaining to elderly patients.

In sum, the Paul B. Beeson Career Development Awards continues to foster the independent research careers of clinically trained investigators. It is their life-long commitment to this research that will enhance the health and quality of life of Americans, and particularly, the growing number of older people.

“It is imperative we develop new scientific knowledge that ensures that we live longer, independently and productively.”

Letter from Mary Tinetti, M.D.

Chair of the Program Advisory Committee of the Paul B. Beeson Career Development Awards in Aging Research Program

It is once again a pleasure to introduce this year's group of Beesons. They are an impressive and dynamic group of physician-scientists, and we on the program committee are pleased that they are part of the growing cadre of scientist-leaders representing the Beeson program.

We now have one year of experience with the National Institute of Aging as our partner, and we have been extremely pleased with the initial fruits of this new arrangement. Judging from the excellent quality of the Scholars chosen, the first review and selection process has been a spectacular success. We have another highly qualified cohort of Scholars representing a broad spectrum of content, methodological expertise and research institutions (See p. 24 for a listing of these new Scholars).

From our vantage point on the Program Committee, the foundations and NIA have developed a strong working collaboration. Representatives from the two "cultures" have come together with a can-do attitude and common commitment to building an even stronger program. Nowhere was this more evident than at last year's annual meeting in Park City, Utah. NIA staff members were much in evidence, and their participation at the meeting was very well received by Scholars. For many Scholars at this point in their careers, NIA and the National Institutes of Health (NIH) in general, are a black box. Scholars know their careers are likely predicated on federal grant funding, but many are not sure of how NIA and NIH work. At the annual meeting, NIA staff members made themselves readily available to grantees, helped to describe the nuts and bolts of the federal grant process, and reinforced that NIA is a partner in their research, not simply a funding mechanism.

The meeting in Park City was also exciting as it was the first time that the Scholars played a lead role both in planning the program and making the lion share of the presentations. This is a function of the deepening

Judging from the excellent quality of the Scholars chosen, the first review and selection process has been a spectacular success.

experience of the Scholars that have "graduated" from the program, as well as a notable example of the dynamic leadership Scholars continue to express at their own institutions and for the field more broadly.

Looking ahead, we continue to be optimistic about the Beeson program. Our partnership with NIA is not only working, but flourishing. Our cadre of talented scholars continues to expand. Most importantly, our program, as we have hoped all along, continues to create the leaders and knowledge the nation needs to improve the health and well-being of older adults.



Mary Tinetti

Meredith A. Hawkins, MD

Associate Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Mentors:

Nir Barzilai, MD
Laurie Jacobs, MD
Harry Shamoon, MD
Michael Brownlee, MD

The Role of Nutrient Excess in Mediating the Insulin Resistance of Aging

The metabolic syndrome of aging, also known as Syndrome X, is characterized by the co-existence of a specific set of unhealthy conditions, including obesity, insulin resistance, and high blood pressure. The presence of this cluster of health problems is associated with the development of a host of age-related diseases (such as diabetes, stroke, and heart disease). Understanding the metabolic syndrome, therefore, is crucial to combating or preventing these diseases. In her Beeson-supported work, diabetes researcher Dr. Meredith Hawkins is investigating the origins of the syndrome by exploring two hypotheses: that excessive nutrient intake (fatty acids and/or glucose) or excessive body fat contribute to the development of the metabolic syndrome, and that aging increases a person's susceptibility to the detrimental effects of nutrient excess.

Dr. Hawkins is primarily concerned with the activity of the hexosamine biosynthetic pathway, or HBP. A key regulator of cellular metabolism, HBP can activate proteins that lead to insulin resistance. Increased availability of nutrients, particularly glucose and fatty acids, seems to increase the HBP's activity. In addition, the pathway seems to become more active as people age. To test her hypothesis that nutrient excess and aging interact to boost or upregulate HBP, Dr. Hawkins is examining the consequences of increasing glucose and fatty acid levels in healthy young and old individuals. Half the participants are lean; half obese.

Results in young, lean individuals show that increasing blood levels of fatty acids increases levels of PAI-1, a substance related to risk of cardiovascular disease, known to be elevated in metabolic syndrome. PAI-1 gene expression is modulated by HBP. Dr. Hawkins presented these results at the American Diabetes Association meeting in June 2004. She continues to recruit subjects for the study, with a particular emphasis on recruiting more healthy older adults, which is often a challenge.

Dr. Hawkins's enthusiasm for research began when she was twelve years old, when she learned the story of insulin's discovery. Today, that interest continues unabated. "I have a fascination for research topics in metabolic disease," she says. "As long as I can continue to obtain funding, I will keep doing research until we've answered all the questions."

In addition to her research, Dr. Hawkins is a committed clinician and teacher. She sees patients every other week as part of Albert Einstein College of Medicine's Endocrinology Consulting Service. She is also very active in training and mentoring residents, postdoctoral fellows, and junior faculty. Away from the bench and bedside, she reviews papers for journals such as *Diabetes*, *the American Journal of Physiology*, and the *Journal of Clinical Investigation*; and co-chairs the Public Policy Committee for the American Federation for Medical Research.

The Beeson Award has had several tangible benefits. Dr. Hawkins says she appreciates the career development support that is part of the program. The Beeson annual meeting has also been a bonus. "Meeting and interacting with other Beeson scholars," she says, has been "both stimulating and helpful." Collaborations with her four Beeson mentors, including Dr. Nir Barzilai, a former Beeson scholar, have also strengthened her research and career trajectory, as has the positive attention around her Beeson Award. "It has brought me very favorable recognition within my institution," says Hawkins, who was recently promoted to associate professor of medicine.

Michael C. Irizarry, MD
Assistant Professor of Neurology
Harvard Medical School
Charlestown, Massachusetts

Mentor:
Bradley T. Hyman, PhD

Beta-secretase and Alzheimer's Risk with Aging

Dr. Michael Irizarry always knew he wanted to learn how the brain worked. After completing his neurology residency, he decided to concentrate on Alzheimer's disease. "There are so many unanswered questions about this disease," he explains. "How do you diagnose it? How do you treat it? It seemed like the most interesting field."

Dr. Irizarry's fascination with Alzheimer's disease has led him to split his time between conducting both basic and clinical research and seeing patients at Massachusetts General Hospital's Memory Disorders Unit. Obtaining the Beeson award has enabled him to redouble his efforts in both areas.

"The Beeson award has allowed me to build up my lab and focus on my beta-secretase research," says Dr. Irizarry, noting that the award has enabled him to double his lab space, hire an additional post-doc and technician, and spend less effort seeking new grant monies. Importantly, it has also freed up time so he can pursue a Master's in Public Health (MPH).

Dr. Irizarry expects the MPH to help him learn how best to analyze large data sets, such as those collected during his basic research studies or his involvement in a clinical trial looking for biomarkers that could help diagnose cognitive impairment and dementia. He is also learning strategies for setting up clinical trials. For example, he has begun a pilot study looking at risk factors for specific types of dementia among 200 participants in the Nurses' Health Study.

The work supported by Dr. Irizarry's Beeson award, however, is firmly within the boundaries of the laboratory. He is studying age-related changes in the activity of beta-secretase (BACE). This enzyme is known to be involved in the formation of beta-amyloid, the protein that forms clumps, or plaques, in the brains of Alzheimer's patients.

So far, Dr. Irizarry has learned that although BACE enzymatic activity increases with age, levels of the BACE protein remain the same. These results, similar for mouse, monkey, and human brain, were published in the February 2004 issue of the *American Journal of Pathology*. This suggests that the BACE protein must be modified during aging in a way that increases enzymatic activity. Dr. Irizarry is currently trying to determine what this modification is and how it occurs. He hopes that identifying this mechanism could allow researchers to develop therapies to pinpoint it, thereby slowing or stopping the development of beta-amyloid.

The AJP paper is not Dr. Irizarry's only recent contribution to the scientific literature. He has published papers on beta-amyloid in *Neurology* and the *Journal of Neurochemistry*, and presented his findings on beta-secretase, Alzheimer's, and the aging brain at Grand Rounds and Colloquiums at Harvard Medical School, as well as at international symposia on neurodegenerative diseases. He says he has enjoyed attending the Beeson annual meetings, where he appreciates learning about other perspectives on Alzheimer's and aging research from other scholars and senior mentors. His own Beeson mentor, Dr. Bradley Hyman, has been accessible and supportive, offering Dr. Irizarry key knowledge about dementia as well as access to needed resources. Dr. Irizarry is also a mentor himself: he trains residents in Massachusetts General Hospital's neurology residency program, as well as medical students serving their rotation in the hospital's Memory Disorders Unit.

All of these Beeson benefits will make it easier for Dr. Irizarry to achieve his professional goals: understanding the changes that predispose the aging brain to develop Alzheimer's disease and providing more effective therapies for his patients.

Kenneth M. Langa, MD, PhD
Assistant Professor of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan

Mentors:
Jeffrey B. Halter, MD
Richard Schulz, PhD
Peter A. Ubel, MD

Long-Term Outcomes of Caring for a Disabled Spouse

Older adults with disabilities are often cared for on a volunteer basis by a spouse or other family member. Until recently, the economic costs of this type of informal, unpaid care were unrecognized, hidden from government data and policymakers. Dr. Kenneth Langa is part of a growing effort to reveal those hidden costs so the public and policymakers notice and value them. "We want to find out what it means to be a caregiver," he explains. "How much time do they spend? What are the emotional, health, and economic impacts of caregiving?"

Dr. Langa's Beeson award project is a two-pronged effort to investigate how long-term care for a disabled spouse affects a caregivers' health. Half the project is devoted to analysis of rich data sets from the University of Michigan's Health and Retirement Study (HRS), which began collecting data from couples on a biannual basis in 1992, and the related Aging, Demographics, and Memory Study.

To date, Dr. Langa and his team have published papers in the *Journal of General Internal Medicine and Social Science and Medicine*, with several other manuscripts in review or preparation. Their analyses include the surprising finding that caregivers are no less likely to seek preventive medical care for themselves than are non-caregivers. They have also found that those caring for spouses with dementia are more likely to suffer from depressive symptoms, and that the death of the spouse relieves those symptoms. Ultimately, Dr. Langa says that he suspects that while caregivers providing high levels of care experience a negative impact on their health, caregivers providing low to moderate levels of care actually experience a health benefit.

The second aspect of Dr. Langa's Beeson award addresses data quality. Traditionally, caregiving data is obtained via retrospective questionnaires. These may yield biased results as caregivers inaccurately remember their experiences. Hoping to promote improved

research methods, Dr. Langa has begun a small study that intends to gather information at numerous points during a caregiver's day via specially programmed Palm Pilots. Data obtained from each participant's weeklong turn with a Palm Pilot will be compared to surveys completed both before and after the Palm Pilot experience.

Dr. Langa hopes this data collection method, called Ecological Momentary Assessment, will improve the quality of data gathered on a range of caregiving issues. "The key challenge, of course, is making the technology accessible to older people," he notes. Initial feedback from focus groups was helpful and positive, and recruitment of the 100 participants for this study began in November 2004.

The work Dr. Langa has done so far for his Beeson award has already led to new research opportunities. His preliminary Beeson data on family caregiving for chronic disease will help support a grant proposal to renew the Health and Retirement Study. He also hopes to win a K01 award to study how changes in Medicare policy and the development of Alzheimer's medications have affected caregiving. This proposal arose out of discussions with Beeson scholar Dr. Jason Karlawish at the Beeson annual meetings. "The Beeson meetings allowed me to make connections through a national network," he says. This network includes Dr. Linda Fried, who, in addition to Dr. Langa's three Beeson mentors, has provided helpful career development advice.

The Beeson award, says Dr. Langa, has also raised his profile within the University of Michigan. Mentor Dr. Jeffrey Halter, Division Chief of Geriatric Medicine, asked Dr. Langa to plan and direct an expansion of the university's geriatric health services research. The award has also allowed him to assemble a talented research team of junior faculty and postdoctoral candidates and mentor them in work related to the Beeson grant.

Holly Lisanby, MD

Associate Professor of Clinical Psychiatry
Columbia University College of Physicians and Surgeons
New York, New York

Mentor:
Harold Sackeim, PhD

Brain Stimulation and Pharmacological Strategies to Reduce the Cognitive Side Effects of ECT in Geriatric Depression

Dr. Lisanby became interested in the challenges of electroconvulsive therapy (ECT) as a depression treatment for older adults early in her training as an academic psychiatrist. More than 50% of ECT recipients are over the age of 65, likely because older patients have a high prevalence of depression and often cannot tolerate antidepressant drugs. ECT induces seizures that stimulate the release of neurotransmitters in the brain, improving mood. However, despite its efficacy, ECT can cause memory loss and other side effects, especially in older people with pre-existing cognitive impairment. Dr. Lisanby's interest in the topic and the issue of geriatric depression more broadly, led her to a research fellowship in geriatric psychiatry with current Beeson mentor Dr. Harold Sackeim at Columbia University, where she is now an associate professor.

Dr. Lisanby has dedicated her Beeson project—and her career—to finding newer, more effective treatments for depression in the geriatric population. “We need better treatments that don't impair their cognitive function or detract from their quality of life,” she explains.

One potential treatment is a new form of brain stimulation: magnetic stimulation therapy, or MST. Like electricity, magnetic fields applied to the brain can cause seizures. Yet because magnetic fields penetrate the scalp and skull better than electricity, these seizures can be confined to specific areas of the brain, making it less likely that the treatment will induce memory problems.

In preliminary work published in *Neuropsychopharmacology* in July 2003, Dr. Lisanby, who is also Director of the Magnetic Stimulation Laboratory at the New York State Psychiatric Institute, showed that 10 patients treated with MST and ECT had fewer cognitive side effects after the MST sessions than after the ECT sessions.

She also published a case report in August 2003 in the same journal showing the antidepressant efficacy of MST in a 66-year-old depressed patient. “We have found that MST induces more focused seizures that do not spread to other areas of the brain,” she says.

For her Beeson project, Dr. Lisanby is continuing clinical trials of MST in order to learn more about the procedure's safety and efficacy in larger groups of patients. A key aspect of this work will be determining the optimal dose of MST required to induce seizure. Once Dr. Lisanby has determined the appropriate dose, she will compare the side effects, safety, and efficacy of MST with conventional ECT in elderly patients. She will also include a third treatment type in these experiments: ECT plus donepezil, a cholinergic drug used to slow memory decline in Alzheimer's patients. If donepezil is effective in reducing the cognitive side effects of ECT, this could be an inexpensive and accessible alternative to MST or conventional ECT.

In addition to her duties as a researcher, Dr. Lisanby is Director of the Columbia Depression Center and the New York State Psychiatric Institute's Brain/Behavior Clinic. The Beeson award has allowed her to manage these clinical responsibilities, while expanding her research. Now, most of the time she spends with patients is in conjunction with her clinical trials. “My clinical work is supportive of my research instead of detracting from it,” she says.

Dr. Lisanby has found the Beeson to be a comprehensive career development program. “It does everything from facilitating research to helping people grow in their careers, make connections, and prepare for the next stage of career development,” she notes.

Jack M. Parent, MD

Assistant Professor of Neurology
University of Michigan Medical School
Ann Arbor, Michigan

Mentor:
Roger L. Albin, MD

Stimulation of Endogenous Neural Stem Cells to Promote Recovery after Stroke

For decades scientists believed that the adult brain could not generate new neurons, fueling the assumption that significant recovery from stroke or other brain injuries was unlikely. Recently, however, experiments have shown that a small number of neurons are generated throughout life from neural stem cells. After brain injury, this neuron growth increases. Hoping to improve recovery after stroke, Dr. Jack Parent is trying to find ways to boost this natural self-repair mechanism in the brain. "Two weeks after a stroke, there are lots of new neurons, but most die within five to six weeks," he says. "We're trying to find ways to get more new nerve cells to survive."

In order to prolong these neurons' function, researchers must first gain a better understanding of what factors regulate neuron generation and survival. Dr. Parent's Beeson project is focused on two substances known to influence neurogenesis: retinoic acid (RA) and hepatocyte growth factors (HGF), which occur naturally in the brain. Examining the effect of RA on mouse neural stem cells, Dr. Parent found that not only does RA promote neurogenesis, but it is also required for the new cells to migrate to where they are needed. He found similar results with HGF, and presented both findings at the annual meeting of the Society for Neuroscience in November 2004.

Dr. Parent has also been testing RA and HGF in live mice, to determine whether supplementing these animals with additional amounts of either substance improves neurogenesis in the forebrain and improves stroke recovery. He is currently collecting data on the RA experiments, which include testing mice to determine cognitive and behavioral deficits after an induced stroke, and obtaining MRIs of their brains. Similar experiments with mice treated with supplementary HGF will begin in 2005.

This work represents a significant shift into aging research for Dr. Parent, who began his career as an epilepsy researcher. A growing interest in using neural stem cells to repair problems in the brain led him to focus his attention on stroke and other age-related neurological disorders. "Stroke is a much better model for brain repair than epilepsy," says Dr. Parent. "And most neurological diseases that can be treated with stem cells are age-related." Dr. Parent has recently expanded his interest in stem cell therapies to include embryonic stem cells, which he is studying for possible stroke therapy as part of a recent NIA grant.

Receiving a Beeson award has allowed Dr. Parent to cut back on his clinical responsibilities in favor of concentrating on his laboratory research, although he continues to see patients in the neurology clinic and hospital. In addition, he has expanded his laboratory, involved graduate students and a postdoctoral fellow in his work, and received a guarantee of laboratory space in a planned new research building. He is pleased with the guidance he has received from mentor Dr. Roger Albin, and notes that working together on the Beeson project has strengthened their relationship.

Dr. Parent hopes that his work in the laboratory will yield useful therapies for patients, and plans to become involved in transitioning discoveries made at the bench into the clinic. "There has been a lot of research on how to protect the brain from stroke, and so far that has failed," he notes. "We're trying a different approach: boosting the self-repair mechanisms that we all already have."

Henry L. Paulson, MD, PhD
Associate Professor of Neurology
University of Iowa College of Medicine
Iowa City, Iowa

Mentor:
Beverly L. Davidson, PhD

RNA Interference (RNAi) as a Novel Therapy for Age-Related Disease

Over the past decade, researchers have learned a great deal of valuable information about the molecular mechanisms underlying Alzheimer's and other age-related neurodegenerative diseases. However, scientists have not yet developed effective ways to prevent or cure these diseases. To that end, neurologist Henry Paulson, MD, PhD, is exploring a novel means of stopping Alzheimer's disease in its tracks.

During the last several years, researchers have discovered that humans and many other animals regulate the expression of genes using RNA. RNA is a similar molecule to DNA but with a slightly different structure. RNA plays an intermediary role in converting the infrastructure contained in DNA into proteins. Dr. Paulson hopes to use a technique called RNA interference (RNAi) to turn off the RNA of genes associated with the development of the plaques and tangles of Alzheimer's disease, such as APP (amyloid precursor protein), BACE (beta-secretase), and tau. His goal is to find out if RNAi technology could yield a cure for Alzheimer's disease and/or other neurodegenerative diseases of aging.

The Beeson award has already given Dr. Paulson's work in this field a helpful leg up. He was promoted to associate professor shortly after receiving the award, and work funded by the Beeson award helped him secure additional funding from the National Institute of Neurological Disorders and Stroke. He has developed a new, highly specific type of RNAi that can silence particular alleles, or versions, of genes, allowing scientists to turn off mutated copies of genes while leaving normally functioning copies untouched. A study documenting his success in silencing specific alleles of tau and APP in the laboratory with small interfering RNAs (siRNAs) was published in the February 2004 issue of *Nucleic Acids Research*. In addition, he and mentor

Dr. Beverly Davidson co-authored a review on the up-and-coming RNAi technology for the March 2004 issue of *Lancet Neurology*, and he spoke on the topic at meetings of the American Neurologic Association and the Society for Neuroscience.

Dr. Paulson calls his mentor "super-talented," and credits her as a source of energy for his work. He also enjoys sharing in the excitement of the postdoctoral and graduate students that he mentors in his laboratory. "It makes up for no longer being able to do the experiments myself," he says. He finds the Beeson meetings to be an additional source of inspiration, as they allow him to interact with experts in geriatrics and neurodegenerative disease research.

Building on his successful Beeson-funded *in vitro* studies, Dr. Paulson is currently working to determine if the technique will be effective in suppressing disease genes in mouse models of Alzheimer's disease and frontotemporal dementia. "It is fairly easy to do this in cell culture," notes Dr. Paulson. "Now we need to find out if we can do this in a tolerable, safe way in the mammalian brain." He will test whether viral delivery of siRNAs into mice can slow or even halt the neurodegeneration caused by these diseases. He hopes to find out if RNAi can be used as a treatment for neurodegeneration in humans.

In addition to his Beeson project, Dr. Paulson is also studying the role of proteins in the brain, including how the brain "tidies up" flawed proteins. "We are studying the brain's protein quality control machinery," he says. "This is how the brain fends off disease." All these studies of the brain are essential to Dr. Paulson's career goals to help patients suffering from neurodegenerative disease while pursuing his fascination with the molecular processes of the human brain.

Elizabeth A. Phelan, MD

Assistant Professor of Medicine

University of Washington School of Medicine
Seattle, Washington

Mentor:

Edward H. Wagner, MD, MPH

Improving Primary Care of Older Adults

During her two years as a Robert Wood Johnson Clinical Scholar in the late 1990s, Dr. Elizabeth Phelan found that she enjoyed caring for older patients more than any other age group. Concerned about the glaring lack of research on strategies for maintaining health in older adults, Dr. Phelan decided to focus her career on using evidence-based research to improve health and prevent disability.

Dr. Phelan is particularly interested in conducting interventions and trials in primary care settings, where the majority of health providers have little formal training in geriatrics, but where older people receive most of their care. She is currently a co-investigator on a randomized trial investigating the impact of an interdisciplinary geriatric team on the functional outcomes of older patients. Her Beeson project takes this trial a step further by measuring the impact of this intervention on the providers themselves, including their satisfaction with the geriatric team and whether the intervention has influenced how they treat older adults. "To get the patients to the team, the providers have to be on board," Dr. Phelan explains. "We're trying to find out if the providers welcome the team, or if they view it as unhelpful or intrusive."

The best outcome, says Dr. Phelan, would be that the presence of the interdisciplinary team, consisting of a gerontologic nurse practitioner, a pharmacist, and a geriatrician, encourages primary care providers to adopt "geriatric principles of care." These include screening for age-related conditions, careful use of prescription drugs, and management of chronic diseases. She also hopes that physicians will feel more confident in managing their older patients and express satisfaction with the support system the geriatric team offers.

Although Dr. Phelan has collected one-year data on physician confidence and satisfaction, they have not yet been analyzed. Follow-up data will be collected again at 24 months. Initial observations show mixed results depending on the care setting. In a group-model clinic, the intervention has been so popular that the clinic has hired the study's geriatrician full-time. On the other hand, the team geriatrician practicing in a fee-for-service setting often has to prompt the primary care providers to refer patients to the team. "We have already learned a lot about how relevant some aspects of the team are for the primary care providers," says Dr. Phelan. "There is a role for the team working alongside the physicians, but not duplicating their efforts."

The Beeson Award has been instrumental in allowing Dr. Phelan to expand her research program. Not only did it fund a full-time research coordinator, but it ensured her appointment to assistant professor and secured office space for her support staff despite scant availability at the University of Washington. "The award gives me more leverage to ask for the things I need to grow," she says.

Despite her busy schedule, which includes seeing patients and providing mentorship to young investigators interested in clinical research, Dr. Phelan has been pleased to make time to attend the Beeson annual meeting. She finds it focused and very responsive to the needs of current scholars. Her Beeson mentor, Dr. Edward Wagner, has been very helpful as well. "He has been unflinchingly supportive," she says. "He is there when I need him, but is also trying to increase my independence for decision-making. I can't say enough about him."

Wendy Post, MD

Associate Professor of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Mentors:

Gary Gerstenblith, MD
Alan Shuldiner, MD

Vascular Properties and Genetics Associated with Longevity in the Amish

The Amish of Lancaster County, Pennsylvania, are among the most studied populations in the United States. Because they are genetically homogenous and lead similar, agrarian lifestyles, it is easier to determine genetic correlations to health characteristics in the Amish than in a population of average Americans. Working with mentor Alan Shuldiner, MD, a former Beeson scholar and principal investigator of the Amish Longevity Study, Dr. Wendy Post is studying the Amish to determine if certain measures of heart health are associated with long life. Along with colleagues, Drs. Post and Shuldiner published a review in the October 2004 issue of *Mechanisms of Ageing and Development* discussing the utility of the Amish population in identifying longevity genes.

"My goal," says Dr. Post, "is to identify genes that might be related to vascular aging, and design interventions that prolong advanced life." To do this, she is recruiting the offspring of long-lived Amish for her study, with their spouses to serve as the control group. She is measuring several indicators of heart health in these participants, including vascular, or blood vessel, stiffness; intima media thickness, which measures the thickness of the carotid artery; coronary artery calcification, which correlates to plaque build-up; and LDL and HDL cholesterol particle sizes. The latter is a recent addition to her Beeson work, inspired by the work of another former Beeson scholar, Dr. Nir Barzilai. In a study of Ashkenazi Jews, another homogenous population, Dr. Barzilai found that long-lived individuals have larger cholesterol particle sizes than controls.

As of fall 2004, Dr. Post has recruited more than 100 subjects into the study and performed many of the planned measurements of cardiovascular health. Although she does not yet have enough participants for data analysis, she expects to find that long-lived individuals have superior cardiovascular health as compared to controls.

The next step will then be to determine whether certain areas of relevant longevity genes, such as those known to influence HDL cholesterol, are associated with any of the heart indicators she is measuring.

The Beeson award has special meaning for Dr. Post. "My other work involves collaborations with other researchers, but it's so important to have independent funding," she says. "The Beeson gives me my own funds, and more recognition among colleagues and the faculty who make decisions about my career." That recognition has already had an effect on her career path; Dr. Post was promoted to associate professor in fall 2004. She was also invited to be an ad hoc member of the scientific review committee for the National Institute of Aging's Aging Systems and Geriatrics section.

Among Dr. Post's many scientific collaborations was one with a third-year medical student who spent 10 months in Dr. Post's lab in 2004. The student completed two manuscripts with Dr. Post, one of which, a study of the association of the gene ABC A1 with coronary calcification, she presented at the 2004 meeting of the American Heart Association. The study analyzed data from the Multi Ethnic Study of Atherosclerosis (MESA), on which Dr. Post is a co-investigator. "I enjoyed being a role model for her," says Dr. Post.

Dr. Post is also collaborating with her other mentor, Dr. Gary Gerstenblith, on a project to study the association between vascular age and atherosclerosis. All of her scientific work, as well as her clinical work with patients interested in preventing heart disease, is aimed at improving older adults' chances to age successfully by slowing blood vessel aging. With 40% of people over the age of 65 in the United States dying from cardiovascular disease, her insights will be critically important to the nation's health and longevity in the decades ahead.

Norman E. Sharpless, MD

Assistant Professor of Medicine and Genetics
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Mentor:

Terry Magnuson, PhD

The Role of the Tumor Suppressor $p16^{INK4a}$ in Mammalian Aging

Dr. Norman Sharpless became interested in aging in his childhood, when he had responsibility for caring for his demented elderly grandmother each afternoon after school. He had to re-introduce himself daily, as his grandmother's short-term memory had failed. "It was remarkable," he said, "that this retired English professor could quote Robert Service from rote but could not remember her grandchildren." This early interest in aging led him to focus first on gastrointestinal oncology, then on the relationship between cancer and aging.

It is well known that most cancers primarily affect older people—the majority of the gastrointestinal cancer patients whom Dr. Sharpless sees in his weekly clinic visits are over 70. Recently, he and other scientists have begun to suspect that cancer and aging share something more than time frame, namely gene activity. The actions of tumor suppressor genes to curb cell proliferation may be responsible for promoting some of the deficits in tissue repair that seem to underlie much of aging.

Scientists know that mice lacking the tumor suppressors $p16^{INK4a}$ and/or *arf*—two similar genes encoded practically on top of one another—are much more tumor-prone than their normal counterparts. Dr. Sharpless is interested in discovering if these mice are also resistant to aging. As part of his Beeson project, he modified a tumor-resistant strain of mice to lack one or both alleles of $p16^{INK4a}$. However, as several of the mice died of tumors before one year of age, he suspects that too many of the animals will succumb to tumors to make $p16^{INK4a}$ deletion a viable strategy for extending lifespan.

The second part of his Beeson project may be able to make up for this problem. He is working to create mice in which the $p16^{INK4a}$ gene can be turned off in

specific tissues only. He will then observe the mice to see if tissue-specific loss of the gene reduces age-related decline in those tissues without a significant increase in tumor formation.

In a related experiment, Dr. Sharpless has also characterized the expression of $p16^{INK4a}$ in aging mice. In an article published in the November 2004 issue of the *Journal of Clinical Investigation* (JCI), he describes findings showing that expression of this gene increases with aging and that this expression is reduced in certain tissues when the mice are placed on calorie-restricted diets. Caloric restriction is known to slow aging in mammals. This makes $p16^{INK4a}$ a potential biomarker of aging. "P16/arf expression marks physiologic age very well," says Dr. Sharpless. "Having a good biomarker of aging could shorten the time needed to conduct studies of anti-aging therapies and could help physicians determine whether an older cancer patient can tolerate chemotherapy." This paper merited considerable attention from other scientists, and was highlighted in editorials published in the same issue of *JCI* and on the scientific Web site SAGE KE (<http://sageke.sciencemag.org>).

Dr. Sharpless is grateful to the Beeson award for providing funding for these novel and somewhat risky experiments. Completion of the preliminary work allowed him to successfully apply for R01 funding from the NIA. The award also persuaded the University of North Carolina to allot Dr. Sharpless 17% more space for housing his mice, allowing him to pursue additional experiments. And perhaps most important, the award has allowed Dr. Sharpless to move from cancer to aging research. "The Beeson has given me credentials as an aging researcher," he says. "I hope to continue to study the razor's edge between cancer and aging."

Michael G. Shlipak, MD, MPH

Associate Professor of Medicine, Epidemiology,
and Biostatistics

University of California, San Francisco School of Medicine
San Francisco, California

Mentors:

Seth Landefeld, MD, MPH

Barry M. Massie, MD

Glenn M. Chertow, MD, MPH

Preventing Heart Failure in Elderly Persons with Chronic Renal Insufficiency

Chronic renal insufficiency (CRI), common in older people, doubles the risk of heart failure in older adults and also makes it much more likely that older adults who have heart failure will die from it. Yet almost no information is available on how to treat these two conditions when they present together because patients with CRI, and indeed all older adults, are regularly excluded from heart failure trials.

Dr. Michael Shlipak is working to eliminate this dearth of information about CRI and heart failure in older adults. His paper, "Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals," published in the April 16, 2003 issue of the *Journal of the American College of Cardiology* highlighted renal insufficiency as a risk factor for congestive heart failure, cardiovascular disease, and stroke among older adults. A more recent paper, published in the *Journal of the American Society of Nephrology* in August 2004, found that heart disease patients suffering from CRI were more likely than patients with normal renal function to die or be hospitalized. "Now there is greater recognition of the importance of kidney function in heart disease treatment," Dr. Shlipak notes, "and the American Heart Association now recognizes kidney disease as a risk factor for cardiovascular disease."

These papers are among several whose preparation has been supported by the Beeson award. Dr. Shlipak, who was recently promoted to associate professor, says, "The Beeson award helped fund some papers that were critical in establishing the national reputation that is required for promotion, and allowed me to pursue more risky, exciting experiments."

Among these exciting experiments are the discovery that a new marker of kidney function, cystatin-C, has an improved correlation to heart failure, cardiovascular

disease, and mortality than the current marker, creatinine. He presented these findings at the American Society of Neurology meeting in October 2004, and calls cystatin-C a "major breakthrough, with the potential to be very useful clinically." He has also found, by analyzing data from the Cardiovascular Health Study, that elderly persons with CRI are more likely to be frail than those without CRI, suggesting that they are at risk for progressing to a number of disabling health outcomes. This data was published in the *American Journal of Kidney Disease* in May 2004.

The Beeson award has also helped Dr. Shlipak focus more on aging. Although he has always been interested in treating older adults, it wasn't until he attended the Beeson annual meeting that he began to think of reduced kidney function as an aging syndrome.

He also enjoyed the exposure to basic research he received at the meetings. "It helps round out the field," he says. "It gave me a different perspective on how to incorporate basic science findings into clinical medicine."

Aside from his research, Dr. Shlipak practices clinical medicine as head of the division of General Internal Medicine at the San Francisco VA Medical Center. He hopes to help his patients by making sure, he says, that "there is a greater recognition of the importance of kidney function in the clinical care of older people. Then the next step will be improving detection and management of kidney failure in older adults." His remaining Beeson work includes plans to develop better markers for heart failure risk looking at cystatin-C as well as markers of inflammation, and to study what type of heart failure CRI patients usually develop, ultimately hoping to develop better treatments for older adults afflicted with CRI and heart failure.

Reisa Sperling, MD

Assistant Professor of Neurology
Harvard Medical School
Boston, Massachusetts

Mentors:

Marilyn Albert, PhD
Dennis Selkoe, MD

Investigating the Neural Underpinnings of Memory Impairment in Aging and Early Alzheimer's Disease

Dr. Reisa Sperling wears many hats as a clinician and researcher at Harvard Medical School and at Brigham and Women's Hospital in Boston. As an assistant professor of neurology, she helps train residents and fellows in geriatric neurology and dementia, teaches medical students in the neurology rotation, and lectures primary care physicians on Alzheimer's disease. One day a week, she treats patients in the Memory Disorders Clinic, where she is also Director of Clinical Research. In that capacity, she leads trials of potential Alzheimer's disease treatments. In addition to all of these duties, she also performs considerable research in the field of neuroimaging.

Dr. Sperling sees her work in clinical trials and neuroimaging as complementary. "I want to pull together my clinical and imaging work, and learn about new imaging techniques," she says. "Neuroimaging can potentially help us screen candidates for clinical trials and do early evaluation of how well treatment is working in preliminary trials."

One of the most promising neuroimaging techniques is functional magnetic resonance imaging, or fMRI. Rather than just revealing brain structure, fMRI allows scientists to pinpoint which areas of the brain are activated during mental tasks. For her Beeson project, Dr. Sperling is using fMRI to investigate how brain activation changes between normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD).

Within the last few years, fMRI studies have demonstrated that AD patients show reduced activity in the hippocampus, an area of the brain crucial for memory. Confirming a handful of previous studies, Dr. Sperling has also found that, paradoxically, patients suffering from MCI, a phase of slightly worsened cognition that often precedes AD, have increased, rather than dimin-

ished function in the hippocampus and other memory-related areas of the brain. Dr. Sperling theorizes that this increase could reflect the brain's attempt to compensate for deteriorating brain function during the early stages of memory loss. This seems likely, as she confirmed that patients with full-blown AD show decreased activation and atrophy of these brain regions. She presented these findings at the 2004 International Alzheimer's Congress, and is currently preparing a manuscript.

Dr. Sperling has also been investigating whether brain activation differs between young and old healthy subjects and cognitively impaired older subjects during successful and failed attempts to remember face-name pairs. This work, presented at the 2003 meeting of the Society for Neuroscience and under review at *Neurobiology of Aging*, shows that hippocampal activation is specific and normal in healthy older individuals. Dr. Sperling is now working to modify the memory tasks so experiments with cognitively impaired older persons will yield the same ratio of successful to failed memory tests as those with younger persons. This will allow her to study the difference in brain activation between success and failure.

Dr. Sperling credits the Beeson award with giving her the opportunity to pursue this novel line of research. "Using event-related imaging to study Alzheimer's disease is still a bit of a stretch—the Beeson gave me the freedom to pursue more speculative work," she says.

As for her own Beeson mentors, Drs. Marilyn Albert and Dennis Selkoe, Dr. Sperling hopes that her current work will lead to even more integration of neuroimaging into clinical trials, improving researchers' ability to track drug efficacy and thereby shorten the time needed to conduct preliminary trials.

The Beeson Annual Meeting 2004

Park City, Utah

The 2004 Annual Meeting of the Beeson Program took place amid the snow-capped peaks of Utah's Wasatch Mountains in Park City. Each year, the Annual Meeting affords Scholars the opportunity to learn about other areas of aging research outside their own disciplines, providing insight into the field as a whole.

As the pool of Scholars has grown, so has their involvement in the Beeson meeting. Early gatherings were presided over by outside, leading experts in the fields of aging. Now, former and current Beeson scholars play pivotal roles in the Annual Meeting's advisory committee, and Scholars organize and give many of the meeting's lectures and presentations.



Cary Reid, 2001 Scholar



Holly Lisanby (2003 Scholar) and
Dan Blazer (Member Program Advisory Committee)

At the 2004 meeting, Scholars heard from Judy Campisi, PhD, of the Lawrence Berkeley National Laboratory, who examined the relationship between cancer processes and aging, in a keynote presentation, entitled, "Friend and Foe: Cellular Senescence Links Tumor Suppression and Aging." Beeson mentor David Reuben, MD, of the University of California, Los Angeles, moderated a panel on "Leadership Principles and Practice," which drew on the experience of four Beesons—Frank Longo, MD, PhD (1995), University of North Carolina-Chapel Hill; Lina Obeid, MD, (1995) Medical College of South Carolina; Jurgen Unutzer, MD (2002), University of Washington; and Eric Coleman, MD (2001) University of Colorado Health Science Center.

Anna McCormick, PhD, and Robin Barr, PhD, from the National Institute on Aging (NIA) provided Scholars with an overview of the funding mechanisms available through NIA and the National Institutes of Health (NIH). Breakout sessions explored "Getting Your First R01" and "Beyond the First R01," offering a more in depth look at how Scholars can maximize their interactions with NIH and accelerate their career development.

The meeting's final session, "Translation and Cardiovascular Disease," was moderated by 1998 Scholar, Eric Peterson, MD, Duke University Medical Center. It featured cutting-edge presentations by Jay Edelberg, MD, PhD (2001), Weill Cornell Medical Center, on "Cardiac Stem Cell-based Approaches for Older hearts"; Joshua Hare, MD (2000), Johns Hopkins University, on "NO and Cardiovascular Function and Aging"; Laura Niklason, MD, PhD (2002), Duke University Medical Center, on "Telomerase-assisted Engineering of Vascular Grafts"; and Roger Hajjar, MD (2001), Harvard Medical School, on "Molecular Therapies for Congestive Heart Failure."

In addition to these high quality talks, the meeting, as is customary, provided heavy doses of networking time. More formally, Scholars presented their research in a poster session and received multi-disciplinary feedback from their peers, mentors, NIA staff and other experts in the field.

These interactions are much of what make the Beeson Annual Meeting so special, creating a unique sense of community and fostering professional relationships and collaborations that can have important implications for Scholars' careers and research.



Poster Session, 2004 Annual Meeting

Scholars learn about other areas
of aging research outside their
own disciplines, providing insight into
the field as a whole

Beeson Scholars

1995 Scholars

Ashley I. Bush, MD, PhD
Associate Professor of Psychiatry
Harvard Medical School

Ted M. Dawson, MD, PhD
Professor of Neurology and Neuroscience
Johns Hopkins University School of Medicine

David M. Holtzman, MD
Professor and Chair, Department of Neurology
Washington University School of Medicine

Edward H. Koo, MD
Professor, Department of Neurosciences
University of California, San Diego, School of Medicine

Mark S. Lachs, MD, MPH
Co-Chief, Division of Geriatrics, and Professor of Medicine
Weill Medical College of Cornell University

Frank M. Longo, MD, PhD
Professor of Neurology and Chair
University of North Carolina, Chapel Hill, Medical School

Richard A. Marottoli, MD, MPH
Associate Professor of Medicine
Yale University School of Medicine

Lina M. Obeid, MD
Professor of Medicine
Medical University of South Carolina

Peter D. Reaven, MD
Staff Endocrinologist, Director, Diabetes Program
Carl T. Hayden VA Medical Center

Alan R. Shuldiner, MD
Professor and Head, Division of Endocrinology,
Diabetes and Nutrition
University of Maryland, Baltimore, School of Medicine

1996 Scholars

Christopher M. Callahan, MD
Professor of Medicine
Indiana University School of Medicine

Robert W. Doms, MD, PhD
Professor of Microbiology and Chair
University of Pennsylvania School of Medicine

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Associate Professor of Psychiatry
Duke University Medical Center

Harlan M. Krumholz, MD
Professor of Medicine of Epidemiology and Public Health
Yale University School of Medicine

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Jackson Medical Clinic

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Professor of Medicine (Rheumatology) and Biochemistry
Rush University, Rush-Presbyterian-St. Luke's
Medical Center

Karen M. Prestwood, MD
Associate Professor of Medicine
University of Connecticut Health Center

May J. Reed, MD
Associate Professor of Medicine
University of Washington School of Medicine

R. Glenn Smith, MD, PhD
Associate Professor of Medicine and Neurology
University of Texas Medical Branch

1997 Scholars

Nir Y. Barzilai, MD

Professor of Medicine and Molecular Genetics
Albert Einstein College of Medicine

Michele F. Bellantoni, MD

Associate Professor of Medicine
Johns Hopkins University School of Medicine

James R. Burke, MD, PhD

Associate Professor of Medicine
Duke University Medical Center

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University of California, Berkeley

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Yale University School of Medicine

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Senior Scientist and Director
Retina Foundation of the Southwest

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Mayo Clinic, Jacksonville

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Columbia University College of Physicians and Surgeons

Charles A. Thornton, MD

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University of Rochester School of Medicine and Dentistry

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Professor of Anesthesiology
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Hillblom Chair in Geriatric Medicine
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University of Michigan

Jeremy Walston, MD

Associate Professor of Medicine
Johns Hopkins University

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University of Michigan

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Harvard Medical School

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Stanford University School of Medicine

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R. Sean Morrison, MD
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2002 Scholars

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James Galvin, MD

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Washington University School of Medicine

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Michael Schwarzschild, MD, PhD

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Jürgen Unützer, MD, MPH

Professor of Psychiatry
University of Washington Medical Center

2003 Scholars

Meredith Hawkins, MD
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Albert Einstein College of Medicine

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Harvard Medical School

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University of Michigan

Henry Paulson, MD, PhD
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University of Iowa

Elizabeth Phelan, MD
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University of Washington

Wendy Post, MD
Associate Professor of Medicine
Johns Hopkins University School of Medicine

Norman Sharpless, MD
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Michael Shlipak, MD, MPH
Associate Professor of Medicine, Epidemiology, and Biostatistics
University of California, San Francisco

Reisa Sperling, MD
Assistant Professor of Neurology
Harvard Medical School



left to right: Corinne Rieder (The John A. Hartford Foundation), Brian Hofland (The Atlantic Philanthropies), Judith Salerno (National Institute on Aging)

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Sandy Chang, MD, PhD

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Lee Goldstein, MD, PhD

Assistant Professor of Psychiatry
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Assistant Professor of Medicine
Yale University

John Lehman, MD

Instructor in Medicine
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University of Michigan

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Assistant Professor of Neurology
Oregon Health Sciences University

Joe Verghese, MD

Assistant Professor of Neurology
Albert Einstein College of Medicine



General Session, 2004 Annual Meeting

Program Advisory Committee Members



Standing from left to right: Dan Blazer, Edward Koo
Seated from left to right: Lewis Lipsitz, Mary Tinetti,
William Hazzard, Lina Obeid, Linda Fried.

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John Trojanowski, MD, PhD (until 2004)
University of Pennsylvania School of Medicine

About the American Federation for Aging Research

The American Federation for Aging Research (AFAR) is a private, nonprofit organization whose charge is to support biomedical research into aging. It is devoted to creating the knowledge that all of us need to live healthy, productive, and independent lives. Since 1981, nearly \$80 million has been awarded to more than 2,000 talented scientists as part of its broad-based series of grant programs. Its work has led to significant advances in the understanding of the aging process, age-related diseases, and healthy aging practices. The American Federation for Aging Research communicates news of these innovations to the public through publications such as the newsletter *Lifelong* and two educational Web sites, *Infoaging* (www.infoaging.org) and *Health Compass* (www.healthcompass.org).

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