Paul B. Beeson
Career Development Awards
In Aging Research Program

2009 Report

Featuring the 2007 Scholars

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

About Paul B. Beeson, MD
(1908-2006)

Paul B. Beeson, a distinguished physician, researcher, and teacher, was the inspiration behind the creation of the Paul B. Beeson Career Development Awards in Aging Research Program. It was his vision to increase the number of physicians with a combined clinical, academic, and scientific expertise to care for a growing older population.

At the time of his death, Dr. Beeson was professor emeritus of medicine at the University of Washington. Though "retired," he remained active in the field of aging research, attending meetings and advising many Beeson Scholars. In his long and distinguished career, he profoundly influenced the career paths of many physicians and was stalwart in his concern for the care and dignity of patients.

It is a tribute to him that to date, 152 physician-scientists throughout the United States and the Island of Ireland have emerged as leaders in the field, changing the landscape of geriatric medicine and aging research. His enduring legacy is that these leaders will not only provide the best possible care for older adults, but will also go on to train the next generation of leaders.

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American Federation for Aging Research

Message from AFAR's Executive Director

Stephanie Lederman

This report celebrates the 14th year of the Paul B. Beeson Career Development Awards in Aging Research Program and introduces the 2007 Beeson Scholars, whose work, already in progress, is enhancing academic careers in aging research, teaching, and practice.

Every year, we take pride in the extraordinary men and women whose innovative research have been selected from 40 of the nation's most prestigious medical schools and research institutions. The program remains competitive; only 152 physician-scientists have been named Beeson Scholars since 1995, an award of utmost standing in the aging research and geriatric medicine communities.

The Beeson program has become a model of cooperation between foundations and government. Our partnership with the National Institute on Aging (NIA), now in its fifth year, has allowed the program to expand and evolve into a leadership powerhouse in aging research and clinical care.

Past Beeson Scholars have made their mark in academic medicine, research, and clinical practice and we expect no less from our 2007 Scholars. Their innovative research — from the role of cognitive function in falls and depression in the elderly, to the connection between cardiac health and brain aging, to racial disparities in hospice use — already stand on their own, but combined with the work of their peers will greatly impact the health and quality of life of older adults.

Stephanie Lederman

"The Beeson program has become a model of cooperation between foundations and government."

From Innovation to Revelation: The Paul B. Beeson Career Development Awards in Aging Research Program

The rapidly expanding aging population in the U.S. and beyond requires a forward-thinking approach to addressing the strains that will be placed on our nation's healthcare system in the years ahead. This approach requires more geriatrics research and training, integrating high-quality medical and supportive care services with support of scientific research to ensure that we live healthier longer, less susceptible to disease and disability.

2008 Annual Meeting Poster Session

Nearly 15 years ago, several philanthropies realized the need to develop a program to assist in the development of future leaders in the field of aging, encouraging physician-scientists to pursue independent, ground-breaking, clinically relevant research, and deepen the commitment of academic medicine to research in aging that would translate research outcomes into advances in treatment, prevention, and service. Together, they created what today is known as the Paul B. Beeson Career Development Awards in Aging Research Program, one of the largest programs in the U.S. that supports aging research and geriatric medicine. Generously supported by the National Institute on Aging, The Atlantic Philanthropies, The John A. Hartford Foundation, The Starr Foundation, the National Institutes of Health Office of Dietary Supplements and an anonymous donor, and administered by the American Federation for Aging Research with the NIA, the Beeson award has provided nearly $80 million to 152 researchers since 1995.

With the addition of the National Institute on Aging as partner in 2004, Beeson Scholars receive between $600,000 and $800,000 over three to five years to study 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. Each year, up to 10 clinically trained investigators are selected in the U.S. and one in the Island of Ireland. The benefits of the award for Beeson Scholars are numerous and career-changing, helping them develop research during a critical period in which funding is limited. They include:

- Flexible, generous funding with ample resources to pursue an innovative research program;
- Protected time for research;
- An outstanding support system with senior faculty at each Scholar's institution serving as mentors, and Scholars matched with members of the Beeson Program Advisory Committee;
- Extensive networking opportunities within the vast network of Beeson Scholars; and
- Alumni participation through annual meetings, where Scholars can assume leadership roles in the program, including becoming mentors to the next generation of Beeson Scholars.

Since the first group of Beeson award recipients was selected, the program has blossomed into one of the nation's most well-respected career development

programs, attracting and supporting some of the brightest minds not only in aging but also in science as a whole. "The Beeson Scholars are an extraordinary group of people," says Christopher A. Langston, PhD, program director of The John A. Hartford Foundation, one of the program's founding sponsors. "All the Scholars are outstanding researchers, and in many cases, leaders in their respective disciplines."

Florence A. Davis, president of The Starr Foundation, adds that, "The Beeson award permits investigators to explore problems that previously have been neglected for lack of funding. That can make a big difference in how long and how well a person lives. The program may also encourage more scientists to pursue careers in geriatrics and gerontology."

The Beeson program has evolved to include expansion to the Island of Ireland as well as the creation of a collaborative grants program encouraging Beeson Scholars to partner and expand on their primary Beeson-supported research (see box page 5).

With funding from The Atlantic Philanthropies, the Beeson program expanded internationally in 2007, supporting junior physician faculty on the Island of Ireland, with the goal of helping to train physicians in geriatrics, build Ireland's capacity to provide high-quality care for older adults, and advance knowledge of effective geriatric care. Three physician-scientists have been named Beeson Ireland Scholars so far. "Our goals for the Beeson Ireland program are similar to the U.S. program: to take academic stars who are conducting research relevant to aging and firmly ground their careers in geriatrics," says Brian F. Hofland, PhD, director of the Ageing Programme at The Atlantic Philanthropies, also a founding partner. "Both the populations of Northern Ireland and the Republic of Ireland are rapidly aging and we want to further develop the human capital in this important field by providing an opportunity for talented faculty to make their mark and work in areas of increasing importance."

Point of View – NIA

We joined the Beeson program because of a confluence of needs, one being our alarm at the decline in professionally trained researchers obtaining NIA and NIH funding. We saw the Beeson program as a way to address that gap. We believed that the resources offered through the program coupled with the annual meetings and national mentoring would be particularly attractive to relatively newly trained clinician-scientists.

We are very pleased with the success of the program to date. At the application and award stage we continue to see a strong response to each year's solicitation and are impressed that the reviewers of the applications frequently comment on the overall strength of the applications. As we had hoped, most of the awardees are the kind of clinician-scientists that we intended to attract. Every year, the program has had awards going to all broad scientific areas in the NIA's mission – from the very basic to clinical and translational research. In terms of outcomes we have seen increasing numbers of Beeson awardees compete successfully for R01 and other research grant funding both from NIA and from other NIH Institutes and Centers.

Robin A. Barr

The vibrancy in the program is well captured at the annual meetings. These awardees share their research findings with each other and often form collaborations. Attendance from former Beeson awardees is high, showing a healthy continuing identification with the program and a welcome desire to give back, both through formal mentoring and through informal advice.

Robin A. Barr, DPhil
Director, Division of Extramural Activities
National Institute on Aging

Letter from Edward H. Koo, MD

Chair of the Program Advisory Committee

Edward Koo

I was fortunate to be among the first Beeson Scholars selected in 1995. Looking back, this was a pivotal moment in my career as it allowed me to pursue my ongoing research projects and initiate new projects unencumbered with worries about sources of funding and administrative responsibilities during a critical period of transitioning from a junior investigator to a more established one.

The Beeson program has grown dramatically to include more collaboration among the Scholars, addressing the multiple influences at play in aging research from the cellular to societal that require novel approaches and greater interactions among disciplines. This shared repository of information will only enhance human health as we age. An example of this is the Hartford/AFAR Collaborative Research Awards that specifically encourage collaborations between Beeson Scholars. In my case, the Beeson program brought Todd Golde, a 1997 Scholar, and me together for one of the most productive projects in my professional career. While presenting at a Beeson-sponsored symposium, we realized that our shared research interests were complementary and ripe for partnership. This led to the discovery of a new class of compounds, gamma-secretase modulators, that are now being pursued by academic laboratories and the pharmaceutical industry as a potential Alzheimer's disease treatment.

Now as chair of the Beeson Program Advisory Committee, I am honored to remain involved with the program. Funding for this distinctive program is always a top priority and in the current financial climate, there may be challenges. I have seen a number of colleagues forced to leave academic medicine during their critical formative years — the period after securing their first faculty position – with so much promise leaving with them.

Another priority is to continue the strong emphasis on mentoring, a key factor to ensuring academic success among the Scholars. Due to the lack of mentors, junior faculty members are sometimes left to succeed on their own without a strong network of teaching support. One of the duties of the Advisory Committee is to mentor incoming Beeson Scholars, providing timely professional and personal advice outside of the Scholars' institutions. The combination of funding and mentorship has a direct impact on whether talented investigators advance in their academic careers.

Lastly, we participate in the selection process that is led by the National Institute on Aging review section. We hope to continue attracting the very best clinician-investigators from some of the nation's leading academic institutions combining basic, clinical, and translational research in aging and age-associated diseases.

It is my pleasure to introduce you to the 2007 Scholars.

Edward H. Koo

Hartford/AFAR Collaborative Research Awards: Expansion of the Paul B. Beeson Career Development Scholars Program

As physician-scientists, the Beeson Scholars are uniquely positioned to play a crucial role in the transfer of findings that can transform scientific knowledge and institute changes in medical research necessary to improve the health care and independence of older Americans.

Often, the success of research efforts depends on the collaboration and exchange among researchers engaged in numerous disciplines. The Hartford/AFAR Collaborative Research Awards – created as a one time grant program — stimulates collaborations among Beeson Scholars to move beyond the confines of their own disciplines and explore new models of interdisciplinary research.

In 2007, five research teams of Beeson Scholars received $400,000 each to investigate cognition and physical rehabilitation; novel forms of therapy in the prevention and treatment of Alzheimer's disease; memory decline; the role of inflammation in cognitive decline; and the protective benefits of a previously considered toxic metabolite in aging hearts and brains.

"There are major opportunities and gaps in research on aging that no single investigator could tackle alone," said Corinne Rieder, EdD, executive director of The John A. Hartford Foundation. "Research on aging encompasses many areas of investigation and care: from the very basic biology of aging processes to the clinical and social care needs. Our Beeson Scholars are the top scientists in the nation – a brain trust to help tackle the many research and clinical challenges of geriatric medicine. The prospects for this collaborative effort are great."

"The Hartford/AFAR Collaborative Research Award encouraged us to realize that the approaches we had separately developed for promoting neurogenesis might be combined in a synergistic way. The award has made it possible for us to apply the first generation of small molecule growth factor mimetics developed in the Stanford lab in the context of the novel imaging and exercise protocols that were pioneered at Columbia University's lab. This combined approach might allow us to reverse the decline in neurogenesis that occurs during aging."

Frank M. Longo, MD, PhD
Stanford University School of Medicine
Scott A. Small, MD
Columbia University School of Physicians and Surgeons

Research Focus:
Ameliorating Age-related Memory Decline

"This award has enabled us to establish a multidisciplinary working group that includes geriatricians, psychiatrists, anesthesiologists, and surgeons who are all focused on improving outcomes in vulnerable older adults who are undergoing surgery and anesthesia. No one member of this investigative team could do this research alone. The Beeson support has allowed ideas that we developed together to flourish outside of our perceived boundaries."

Laura L. Dugan, MD
University of California, San Diego
Jeremy D. Walston, MD
Johns Hopkins University School of Medicine

Research Focus:
Systemic Inflammation and Central Nervous System Dysfunction: A Mechanistic and Translational Pilot

Randall J. Bateman, MD
Assistant Professor of Neurology
Washington University School of Medicine

MENTORS:
John C. Morris, MD
David M. Holtzman, MD

Abeta and Proteomic Analysis of Cerebrospinal Fluid in Alzheimer's Disease and Aging

Bateman

The dominant risk factor for Alzheimer's disease is increasing age. And yet, researchers know agonizingly little about the mechanism that doubles the risk every 5.5 years after a person reaches the age of 60. At least 5.2 million adults in the United States are now living with the disease, according to the Alzheimer's Association. By 2050, that number could triple. If researchers hope to reverse that trend, they may need considerable assistance from neurologists like Dr. Randall Bateman, whose research on the cause, diagnosis, and treatment of Alzheimer's focuses on how an unusual protein called amyloid-beta (Aß) is metabolized in the human brain.

"What we know is that in Alzheimer's, the protein is 1,000-fold above its normal level," Dr. Bateman says. "What we don't know is why that build-up occurs, but we're fairly confident that it leads to a cascade of events that leads to dementia." Recent research by Dr. Bateman has uncovered some tantalizing clues about how humans metabolize Aß. Younger adults, for example, can clear away about eight percent of the protein from the brain every hour, based on measuring labeled Aß in the cerebrospinal fluid.

"Our hypothesis is that as we get older, that percentage rate changes," Dr. Bateman says. "You make too much, or there's a decrease in the clearance of the Aß." To test that hypothesis, he is studying the clearance rates and cerebrospinal fluid contents in volunteers ranging from their 20s to their 90s. "By looking at all these different ages, we think we'll be able to see the effect that aging has on the protein in the brain."

For his Beeson project, Dr. Bateman will be comparing Aß metabolism in 30 healthy young adults with that of 30 healthy middle-aged adults. An *in vivo* labeling process will allow his team to tag the Aß protein as it has been made in the brain, while a lumbar catheter (similar to that used for an epidural) will sample the protein levels in the cerebrospinal fluid every hour for 36 hours. A specialized mass spectrometry technique can then sort out the slightly heavier tagged version of the protein from pre-existing Aß.

Dr. Bateman compares the challenge to calculating the flow and clearance rate of water as it enters a sink through a faucet and leaves through an open drain. Without labeling, an observer could only gauge the overall water level. But Dr. Bateman's method, akin to dyeing the water blue as it flows in from the faucet, should help his team track the Aß protein. In a separate but related study, he will compare the protein contents of cerebrospinal fluid samples taken from 50 people with Alzheimer's disease to the fluid contents of 50 comparably aged but healthy people.

Armed with the new information, Dr. Bateman hopes to learn why aging carries such a large increase in risk for Alzheimer's, and how to devise a better way of testing therapeutics to ensure they hit the right targets in the brain. "If you develop therapies where you want to lower the production rate of Aß," he says, "at least you'll know that your drug is doing what it is designed to do."

The Beeson award, Dr. Bateman says, has given him the practical means to follow his long-standing interest in how the brain works. He is especially thankful for the program's strong focus on career development and for annual meetings that he calls a highlight of his year. "You get a chance to sit down with scientists who are not in your field. There's a lot of brainstorming, think-tank activities, and that's incredibly enriching," he says. "That really brings a lot of new ideas and new excitement. The other big advantage is that you get to network with other leaders in the field. In my opinion, it's a major part of the program, which is invaluable."

Julie P.W. Bynum, MD, MPH
Assistant Professor of Medicine and Community Family Medicine
Dartmouth Medical School

MENTORS:
Elliott S. Fisher, MD, MPH
Stephen J. Bartels, MD

Improving the Quality of Health Systems for the Very Old

Bynum

An 85-year-old woman may not want to live forever, but may care very deeply about how she dies and whether she can continue living at home until then. What would high-quality healthcare mean for her? Unfortunately, few measures exist to provide even basic indicators of quality for the nation's oldest patients, a compelling reason for Dr. Julie Bynum to ramp up her own research examining how such healthcare is delivered. "We don't know from clinical trials," she says. "And the goals of care are quite different for older people."

The key, according to Dr. Bynum, is providing care that matches a patient's stated goals. "My basic idea is that every treatment choice includes both harm and benefit. The only way to know what is right for the individual is to make sure that the individual is influencing the choice," she says. To that end, she is exploring how the United States healthcare system shapes treatment choices and care among the elderly. "The reason is that we don't have a lot of evidence for what's harmful and what's beneficial."

Even before she became a physician, Dr. Bynum knew she wanted to take care of older adults. While in medical school at Johns Hopkins University in Baltimore, she received a Medical Student Training in Aging Research award and after graduation, a John A. Hartford/AFAR Academic Geriatrics Fellowship grant to analyze Medicare expenditures and hospital use among Alzheimer's patients. Because of her early participation in two AFAR programs and contact with mentors in geriatrics, she says, the Beeson award became a goal very early in her career. Now that she is a Beeson Scholar, the award has kept her well-connected with peers and spurred "incredibly great" contacts with other experts – an important benefit to someone whose work straddles both healthcare policy and gerontology.

For one arm of her Beeson project, Dr. Bynum is looking at how older patients receive care from a network that can include primary doctors, clinics, hospitals, and nursing homes, among other providers. Most performance measures focus on locations, such as what happens within a hospital. "But I think the most important question is what happens to people, no matter where they are," she says.

Dr. Bynum has used Medicare claims to identify caregiver groups and assess a patient's overall experience. "The long-term goal is to be able to come up with measurements that can evaluate these physicians' groups in treating the oldest old," she says. But because the field of research is still in its infancy, she is building many of her own measures of care.

For a second arm of her project, Dr. Bynum is interviewing about three dozen people – all at least 80 years old – about recent doctor visits and whether they have received enough support to make informed choices. Answers from the one-on-one interview sessions may help doctors better tailor treatment options to the goals of their patients, an important consideration when weighing medical interventions that carry short-term risks or benefits that may not materialize until far into the future. Studies have revealed a surprisingly high rate of prostate-specific antigen screening among men older than 80, for example, even though the prostate cancer screens are not recommended for men older than 75. And unlike younger age groups, Dr. Bynum says, people older than 80 tend to do worse with carotid artery stents than without them.

So far, her interviews suggest that older patients know they have choices regarding surgery. "What they don't understand is that they have a role in deciding which medications are good for them or not," she says. Understanding of screening choices has been decidedly mixed. The interviews also suggest specific end-of-life issues carry more weight. "They care about how they die. They care about whether they're in and out of the hospital," she says. In short, their goals may differ markedly from other patients, and understanding those distinctions could be crucial for providing the elderly with the best possible care.

Sascha Dublin, MD, PhD
Assistant Investigator
University of Washington Group Health Cooperative

MENTORS:
Eric B. Larson, MD, MPH
Noel S. Weiss, MD, DrPH

Pharmacoepidemiology in the Elderly: Medications, Pneumonia Risk and Confounding

Dublin

Nearly 60 percent of older people in the United States take more than five medications every week, according to a 2006 study by the Slone Epidemiology Center at Boston University. But if pharmaceutical clinical trials never include the oldest and the sickest, how can doctors know whether benefits outweigh the risks for their complicated patients? "You have to be able to look at data in the real world," says Dr. Sascha Dublin, who is doing just that in a big way. An epidemiologist by training, Dr. Dublin is tapping the patient database of Seattle's Group Health for her research. "We can look at what people are actually taking, and what things happen to them," she says.

Her goal, she says, is to encourage researchers to conduct better studies on drug safety for the elderly. Given their disproportionate burden of prescription drugs and vulnerability, older people need to make informed choices. "But to make better choices, you need solid data," Dr. Dublin says. "In many cases, there isn't any data to make decisions." As a result, she says, patients may be filled with false hope or fear. For her Beeson project, she says, "one of my questions is: What do we need to know about these people, about their cognitive status, their physical and functional status, to get accurate results?"

One way Dr. Dublin is tackling that question is by assessing the impact of prescription drugs on community-acquired pneumonia risk, a particular concern for older people and those with conditions like heart and lung disease. A 2004 study suggested that acid-suppressing medications used to treat gastroesophageal reflux disease, or GERD, may increase the risk for pneumonia in the general population. The drugs work by making the stomach less acidic, but a more permissive environment for bacteria could raise the risk of aspirating pneumonia-causing bacteria into the lungs. Dr. Dublin's analysis, however, suggests the risk may be inflated by failing to adjust for factors like higher prescription rates among frailer people – including those with lung disease. "The pneumonia risk may not be that the medicine increased risk, it may be that the users have chronic lung disease, which puts them at increased risk. It may not really be about aspirating stomach contents."

Dr. Dublin is also accounting for a long list of variables to critically examine the suggestion that statin drugs, prescribed to control cholesterol levels, carry added infection and pneumonia-fighting benefits. Patients on statins are more likely to survive and less likely to get infections. But people on statins also tend to be younger and healthier, she notes, suggesting the possibility of a "healthy user bias" in which those patients are more likely to pursue healthier choices in general.

One of Dr. Dublin's favorite aspects of the Beeson program is how it promotes a cross-fertilization of ideas from all areas of aging research. "Every time I go to the Beeson meeting," she says, "I come home with new ideas and potential collaborations." Among her new collaborators is 2006 Beeson Scholar Dr. Margaret Fang, an assistant professor of medicine at the University of California at San Francisco. "We realized very quickly that we had tremendously overlapping interests, so we're doing a sub-project among elderly people with a certain heart condition and are looking at who gets warfarin and who doesn't," Dr. Dublin says. The blood thinner marketed as Coumadin carries the risk of excessive bleeding. But without it, patients risk a stroke.

Clarifying a drug's risks and benefits can lead to a rapid response, like pulling a dangerous product from pharmacies or reevaluating its use among certain patients. Some risk factors are hard to change, she says, "but it's not that hard for someone to quit using a prescription drug."

Roee Holtzer, PhD
Assistant Professor
Albert Einstein School of Medicine

MENTORS:
Joe Verghese, MD
Richard B. Lipton, MD
Laurie J. Ozelius, MD

Predictors of Gait and Falls in Aging: Linking Cognitive Control to Genes

Holtzer

When Dr. Roee Holtzer published a 2006 study that associated walking speed with multiple cognitive functions in healthy older adults, he soon began fielding calls from around the United States. He remembers one in particular: an Indiana woman who confided that she had never before thought to link together the simultaneous decline of her husband's cognitive and walking abilities.

She was not alone. Most people understand that being able to walk to the bus stop or grocery store strongly influences whether older adults can continue living independently. Likewise, many public health programs targeting the same age group focus on the risk of falls and minimizing that risk. Nevertheless, Dr. Holtzer says, "typically, one would not think to administer a cognitive battery of tests as part of a risk assessment for falls."

Due in large part to his research, that mindset may be changing. "Walking has been associated with a range of outcomes, anywhere from risk of dementia to risk for disability, so gait speed has been divined by several groups of researchers as a very important index of physical disability or frailty," Dr. Holtzer says. After his 2006 study in *Neuropsychology* strengthened that link, a follow-up showed that older individuals scoring better for a cluster of cognitive functions including attention and processing speed were at reduced risk for falling, while those who scored worse had a significantly higher risk. More recently, Dr. Holtzer has homed in on a genetic factor that may underlie gait speed.

The Beeson award, he says, has given him new ideas through meetings with other scientists and the flexibility to expand his work to include predictors of dementia through the well-respected Einstein Aging Study. A prime source of inspiration, in fact, has come from within the same building at Yeshiva University's Albert Einstein College of Medicine. Upon his faculty appointment there in 2004, he met Beeson Scholar Dr. Joe Verghese, who was conducting work on gait disorders and their links to aging and dementia.

"We began to talk and discover that we have a shared interest. And then the ball just got rolling from there," Dr. Holtzer says. Their collaboration has yielded more than a half-dozen studies so far.

For his Beeson project, Dr. Holtzer has adopted a three-level plan to tease apart the tangled relationships among declining gait, falls, and aging. Beyond administering clinical neuropsychological tests to assess deficits in specific cognitive abilities, he is pursuing a more focused computer-aided strategy that precisely measures attention by dividing it into its three subcomponents of alerting, orienting and executive attention, or conflict-resolution.

"We have demonstrated that these three attention networks do exist in aging, that they are separate and that they can be measured reliably in all people," he says. "This was not a trivial issue because in all people, with aging, the brain goes through major, major changes." That success has led to a third level of questioning: what is it about attention that predicts gait in older adults? "It's important in terms of the behavior, but also because these networks are mediated by different brain regions and also have been related to different genes," Dr. Holtzer says.

One gene in particular, COMT, has attracted notice as a potential regulator of gait in healthy older adults due to its role in degrading dopamine, a neurotransmitter that controls both cognition and movement. In a 2008 *Neurobiology of Aging* study, Dr. Holtzer and his collaborators showed for the first time that the gene may act through separate pathways in the brain's striatum and prefrontal cortex to influence gait and attention, respectively.

"I'm interested in not just understanding cognitive function for healthy individuals but relating it to outcomes and functions in an individual's daily life, from depression to the ability to function independently," he says. Ultimately, better risk assessments and interventions could help with the outcome that matters most: a better quality of life for older adults.

Angela L. Jefferson, PhD
Assistant Professor of Neurology
Boston University School of Medicine

MENTORS:
Emilia J. Benjamin, MD, ScM
Rebecca A. Silliman, MD, PhD

Cardiac Integrity and the Aging Brain

Jefferson

As a graduate student at Drexel University in Philadelphia, Dr. Angela Jefferson was studying the differential diagnosis of Alzheimer's disease and vascular dementia when an unusual clinical case crystallized the potent relationship between blood flow and brain function. A 48-year-old patient with a rare vascular disorder called moyamoya syndrome was referred to a specialist at the Hospital of the University of Pennsylvania, where Dr. Jefferson was completing a practicum. Already impacted by a stroke, the patient had so many blocked blood vessels in her brain that surgeons had to reroute her right superficial temporal artery past all the obstructions. After the surgery, Dr. Jefferson recalls, "her blood flow values practically doubled on both sides of her brain." Likewise, the patient's cognitive test scores dramatically improved.

The case, which Dr. Jefferson eventually published with four co-authors in the *American Journal of Neuroradiology*, led to her interest in studying blood flow from the heart to the brain and how it can reveal important clues about what can go wrong during the cognitive aging process. Now at Boston University School of Medicine, she is studying how a subtle reduction in heart function may accelerate cognitive decline. "We know that people with heart failure are at increased risk for Alzheimer's disease," Dr. Jefferson says. Other studies suggest that before receiving heart transplants, patients with end-stage heart disease have reduced blood flow in the brain and lower memory and cognition scores. After the transplant, cerebral blood flow can increase by 50 percent, accompanied by an increase in cognitive function. "These studies suggest that there's a relationship between heart function and brain function in patients with end-stage disease," she says. "My research focuses on what happens when you don't have end-stage heart disease. Are these relationships present when you have subtle reductions in heart function?"

To find out, Dr. Jefferson is looking for potential links between systolic function – a measure of the heart's pumping efficiency – and brain aging among 1,500 relatively healthy adults ranging in age from 35 to 85 who are participating in Boston University's famed Framingham Heart Study. For a second project, she is collecting data from people with mild cognitive impairment to see if systolic function is associated with MRI markers of early Alzheimer's disease. "We're looking for global neuronal loss, but we're also looking for neuronal loss in the hippocampus, where the earliest signs of Alzheimer's can be visualized by MRI," she says. The study also will test if systolic function is associated with vascular disease in the brain and test patients' cognitive abilities.

Dr. Jefferson credits the Beeson award for not only allowing her to spend more time on her scientific interests, but also for helping her secure a major grant from the Alzheimer's Association to expand her research. With the Beeson award in hand, she has been free to attend more career-enhancing lectures and classes. And through the extended Beeson network, she says, she has found numerous potential collaborators whom she likely would not have met otherwise.

The combined resources could go far in resolving lingering uncertainties over the impact of the vascular system on cognition. Most medical textbooks, Dr. Jefferson says, suggest that an auto-regulatory system preserves blood flow in the brain, meaning that reductions in systolic function don't impact blood flow in the brain. Although that phenomenon may be true in acute instances of reduced heart function, research in monkeys suggests that reductions in systolic function directly reduce blood flow in the brain. The big question, of course, is whether these relationships are true for humans.

So far, Dr. Jefferson's early results agree that systolic function may indeed be related to the brain's integrity. With subtle reductions, she says, lower blood flow from the heart could contribute to microvascular disease in the brain, contributing to vascular and Alzheimer's disease pathology in the elderly. With her research as a guide, perhaps such cases will end differently in the not-so-distant future.

Kimberly S. Johnson, MD
Assistant Professor of Medicine
Duke University Medical Center

MENTORS:
James A. Tulsky, MD
Richard Payne, MD, PhD

Organizational Variability and Racial Disparities in Hospice Use

Johnson

Studies show that African Americans use hospice services at a lower rate than Caucasians in the United States, even though the African American population shoulders a higher burden of terminal cancer and heart disease, the two most common conditions among those receiving end-of-life care. Research also suggests that African Americans are more likely than Caucasians to receive inadequate pain management and report poor provider communication, contributing to a lower overall satisfaction with such care. "Because hospice use is associated with improvements in the quality of end-of-life care," says Dr. Kimberly Johnson, "increasing the use of hospice care among African Americans could decrease some of the racial disparities in that care."

With her Beeson research, Dr. Johnson is shifting the focus from changing the individual to changing the service organization. "Rather than focus on why older African Americans do not use hospice care, my research looks at how hospice organizations can better meet the needs of dying African Americans," she says.

The first part of her study, a database analysis of Medicare claims in North Carolina and South Carolina, will help determine variability among individual hospices. "Some hospice organizations are reaching a larger percentage of African Americans in their service area than others," she says, and a thorough inspection of the database will help her describe that variability and begin to understand the causes. A second, complementary project will consist of surveys and qualitative interviews with the 131 hospice care providers in both states to help identify best practices geared toward reaching more African Americans.

Although her analysis is just beginning, anecdotal data and expert opinion have suggested some practices that are likely to work. "Number one is partnerships," she says, especially between hospices and institutions in the African American community like churches. Church-based outreach and education are critical for building trust, she says, "because spirituality is such an important part of African American culture." The presence of a diverse staff that reflects the community it serves also may make a big difference. "Some terminally ill patients may be more comfortable with care providers who share their beliefs, values, and culture," Dr. Johnson says.

Reaching out to African American media also may help increase access to hospice care for older members of the community, as can backing flexible hospice policies with regard to chemotherapy and radiation therapy, hospitalizations, feeding tubes, and transfusions. Hospices that do not restrict those interventions, Dr. Johnson says, may be more attractive to African Americans who value such end-of-life services more than other patient groups for spiritual or cultural reasons.

Prior to receiving the Beeson award, Dr. Johnson conducted a number of small projects while spending the bulk of her time in geriatrics and palliative care. Through her work, she saw how the beliefs and priorities of older African American patients and their families were often at odds with those of the medical team, and she frequently found herself being sought out as a mediator to help resolve conflicts. The Beeson award, she says, has given her the protected time and resources to pursue a research agenda delving more deeply into how those conflicts might be avoided within a hospice setting. "I like to think of the Beeson award as a toolkit that provides everything necessary to build a career as a successful researcher," she says. "The Beeson award has thought of everything."

As her research expands, she says, "I'm hoping to engage more in community-based research, to help hospices implement interventions which include best practices in reaching older African Americans." North Carolina and South Carolina are convenient places for her to begin applying what she has learned. "But the hope is that we will develop a model of best practices that can be used anywhere," she says, "and ultimately have a significant impact in improving the quality of care for African Americans facing terminal illnesses."

Kejal Kantarci, MD
Assistant Professor of Radiology
Mayo Clinic College of Medicine, Rochester

MENTORS:
Ronald C. Petersen, MD, PhD
Clifford R. Jack, Jr., MD

Proton MRS Markers of MCI Syndromes and Common Dementias

Kantarci

Dr. Kejal Kantarci has been fascinated with medical imaging ever since she was a budding radiologist at Marmara University Medical School in Turkey. Now an assistant professor of radiology at the Mayo Clinic, she has called upon her neuroimaging expertise to identify the danger signs of early cognitive decline. "What I'm after is identifying quantitative imaging markers for the early diagnosis of dementia," Dr. Kantarci says. Among people with mild cognitive impairment, early detection could lead to interventions for a range of dementias, but only if the warning signs are truly predictive.

One of the best bets for reaching that goal may be proton magnetic resonance spectroscopy (1H MRS). In 2000, Dr. Kantarci and colleagues used the imaging technique to show that an inflammation-associated metabolite known as myo-inositol is present at higher than normal levels in mildly cognitively impaired patients at increased risk for developing Alzheimer's disease. Initially, she focused on imaging only one or a few select regions of the brain. "Now I'm expanding that to five regions of the brain because there are other early dementia pathologies in patients with mild cognitive impairment that may progress to more serious conditions, and we need to look at different regions of the brain to detect them," she says. "When we are supplying treatment, we need to know which dementia pathology is the underlying cause of the mild cognitive impairment."

Metabolites, or the biochemical products of metabolism, contain protons that render them detectable by 1H MRS. When properly tuned, a single imaging run can detect five or six of the biochemicals and measure how a specific metabolite's levels change early in the course of declining cognitive function. "So it's a quantitative marker that we can track in individuals who don't yet have dementia," Dr. Kantarci says. The big question is whether the metabolites have a future in prediction and early diagnosis of that dementia. Then, can they be used as reliable markers for disease progression and for the effectiveness of treatments in clinical trials? "We're hoping these biological markers that are more closely related to the pathology in the brain will more precisely detect disease progression than our standard clinical measures," she says.

To get at the metabolite levels, Dr. Kantarci has zeroed in on precisely framed regions of the brain that can be imaged with 1H MRS. Among her targets, she is focusing on the medial temporal lobe and the posterior cingulate gyrus, areas involved in memory function and linked to Alzheimer's. Another area, the frontal lobe, has been associated with frontotemporal dementia. Metabolites in yet another, the occipital lobe, can change in people diagnosed with what is known as dementia with Lewy bodies.

Despite the advanced nature of neuroimaging, Dr. Kantarci believes the technology has yet to reach maturity – an exciting opportunity to help shape an open field. Having abundant resources at her disposal certainly helps. Her Beeson mentor, Dr. Ronald Petersen, is director of the Mayo Clinic Alzheimer's Disease Research Center, one of the nation's largest centers and her other mentor, Dr. Clifford Jack, is the director of the Aging and Dementia Imaging Laboratory at the Mayo Clinic. Dr. Kantarci also has direct access to data from the Mayo Study of Aging, which is analyzing the incidence and prevalence of mild cognitive impairment in Minnesota's Olmstead County.

Even so, a project of such magnitude would have been hard to pull off without the support of the Beeson award. With it, she says, "I was able to write new grants to continue my funding and to put together a solid foundation for the future." Having a majority of her time protected for Beeson-funded research and training "is definitely crucial to be able to do something like this." The award also has spurred new collaborations, including a proposal she recently submitted with a mentor to another Beeson Scholar, Dr. Sanjay Asthana, associate director of the Wisconsin Alzheimer's Institute at the University of Wisconsin School of Medicine and Public Health. Receiving the Beeson award, Dr. Kantarci says, "has definitely lifted my career in many ways."

Patricia M. Kearney, MBBChBAO, PhD, MPH
Clinical Research Fellow
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MENTORS:
Rose Anne Kenny, MD
Ivan Perry, MD, PhD

Biopsychosocial Factors and Vascular Disease in an Ageing Cohort of Irish Adults


Kearney

A straightforward lesson in salt reduction fueled Dr. Patricia Kearney's faith in the power of preventive medicine. As a medical student at University College Cork, Ireland, Dr. Kearney took an elective in epidemiology at Johns Hopkins University, where Irish native Dr. Paul Whelton explained how a program encouraging hospital patients to reduce their salt intake could have a huge impact on reducing cardiovascular disease. "It just stuck with me as a medical student: The recognition that prevention is incredibly powerful."

Now a doctor herself, Dr. Kearney says, "I find that approach in promoting health to be incredibly exciting." Her excitement over preventive medicine could receive a significant boost with The Irish Longitudinal Study on Ageing, or TILDA, a groundbreaking study spearheaded by Trinity College Dublin that aims to enroll 7,000 to 10,000 Irish adults over the age of 50. Her participation in the study could yield a gold mine of information about the factors contributing to cardiovascular disease, a particular risk for older people. Most of the focus to date has been on known risk factors like higher blood pressure, smoking, obesity, diabetes, and lack of physical exercise, she says, "but there's also the social gradient, and that's what I want to explore." With the TILDA study, she says, "we'll have all that data, and be able to look at how those factors interact with each other."

One of the potentially critical elements that Dr. Kearney hopes to address is whether study participants are minimizing risk factors such as hypertension. The gap between self-reporting and objective measures is thought to be higher among people who are less educated and belong to a lower social class, she says. A combination of objective measures – including height, weight, and blood pressure – and a thorough questionnaire collecting economic, social, and behavioral data may help her better understand whether education, social class, or other factors influence any self-reporting discrepancies.

Why all the attention to social or economic status and self-reporting? "There has been a perception that a lot of cardiovascular risk is well-explained," Dr. Kearney says. But for all the accumulated knowledge, many people still carry a heavy load of risk factors and are not being treated for them, or are being treated inappropriately. For any public health programs to succeed, researchers will need to understand what is blocking adherence to a treatment regimen and how to overcome it. Is social isolation, for example, a true risk factor, or is it a marker for a deeper problem? The question is especially important for older adults, because loneliness and social isolation tend to increase with age.

In the face of the study's magnitude, Dr. Kearney credits the Beeson award with helping her maintain her enthusiasm and focus. At the 2008 annual meeting, she was particularly struck by a group brainstorming session in which participants presented their research challenges and solicited advice. One of her concerns was being able to answer enough questions in the grant's allotted three-year timeframe. The feedback, she says, sent a clear message. "The Beeson program had invested in me, not just in my research, but in me as a clinical researcher, as someone who is going to contribute to the future."

With fewer medical researchers in Ireland to call upon for advice, Dr. Kearney says she particularly welcomed the meeting's "incredibly nurturing" atmosphere and sense of community. "I came back from the meeting totally revved up for my research and incredibly invigorated." A second pilot study for TILDA is now underway, and with the larger study's eventual results, she says, she hopes to help older adults chart out a better course for containing their hypertension and diabetes risk and for following through on sound prevention advice. "The bottom line is that we're trying to improve the health of people as they age," she says. "And we are going to have more and more older people."

M. Bernadette McGuinness, MD, MRCP
Senior Clinical Research Fellow
Queen's University Belfast

MENTORS:
Anthony P. Passmore, BSc, MD, FRCP
Janet A. Johnston, PhD

Platelet ß-secretase in Mild Cognitive Impairment

McGuinness

As a specialist in geriatric medicine, Dr. McGuinness has long been attracted to caring for older people. After receiving her medical degree, she began studying the neuropsychological changes in patients with vascular dementia and Alzheimer's disease (AD) – and more recently, to developing an early indicator for elevated Alzheimer's risk. "My emphasis is on early diagnosis or detection, and correctly classifying patients with mild cognitive impairment," Dr. McGuinness says. "If we can devise methods of finding those patients most at risk of disease progression, that would be very useful. This would be particularly exciting if new treatments become available."

For her Beeson research, she is zeroing in on an enzyme called ß-secretase. Initial work by her research team at Queen's University Belfast led to the development of a novel quantitative assay of platelet ß-secretase activity. This enzyme is involved in cleaving amyloid precursor protein to produce beta-amyloid, which is deposited in the brains of people with AD. Activity of this enzyme was significantly higher in patients with AD but did not correlate with cognitive decline as measured by the Mini Mental State Examination (MMSE). This led Dr. McGuinness and her colleagues to wonder if activity was elevated before the onset of symptoms.

In a small pilot study, Dr. McGuinness and her colleagues found that ß-secretase activity was 27 percent higher in patients with mild cognitive impairment (MCI) than in age-matched controls, suggesting the enzyme may indeed be a marker of early disease. This straightforward test that measures enzyme's activity in blood platelets spares patients from more invasive cerebrospinal fluid sampling. Could the assay pave the way for a blood test gauging Alzheimer's risk? "That would be the hope," she says.

With the Beeson award, Dr. McGuinness says, she is well-positioned to reach that goal. "This is the first time it was given in Ireland, so it means a lot to the university, and it's also enabled me to meet a lot of influential researchers in America through the annual meeting," she says. "It's given me a better foundation in the university." Building on her earlier findings, she has launched a major study in which she is carefully classifying patients with MCI, a very heterogenous disorder that may be the underlying cause of AD, vascular dementia, depression, and other forms of dementia.

Dr. McGuinness will perform a battery of neuropsychological tests on 150 recruited patients to more accurately define their cognitive deficits. One hundred fifty controls will also be recruited. The patients will be tested for platelet ß-secretase activity and be genotyped for the APOE gene, one form of which has been associated with a higher risk for late-onset Alzheimer's. The rigorous sorting and follow-up over the course of a year, she hopes, may better define those most at risk, such as patients with amnestic mild cognitive impairment. Studies suggest that 12 percent of these memory-deficient patients progress to Alzheimer's disease every year. "The ones with forgetfulness – are they the ones who have the highest ß-secretase activity, or is ß-secretase activity higher in all patients with mild cognitive impairment?" Dr. McGuinness asks. "We don't know the answer." Patients will be followed yearly with repeat neuropsychological and blood tests so we can ascertain what happens over time.

In a similar vein, she is pursuing an imaging technique abbreviated FDG-PET, which uses an analog of glucose that can be radioactively labeled and then used to scan the brain. "The whole brain is imaged, and if there is reduced tracer uptake in the medial-temporal lobe, that would be in line with mild cognitive impairment and patients who are more at risk of Alzheimer's disease," she says. With the neuropsychological results, the FDG-PET and the ß-secretase platelet assays, she hopes to more accurately predict those at risk of progression. "I suppose in dementia research, there's not going to be one test that you can use," she says. But together, they could be invaluable.

Nicolas Musi, MD
Associate Professor of Medicine
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MENTORS:
Arlan G. Richardson, PhD
Ralph A. DeFronzo, MD

Role of IKK/IkB/NFkB Signaling in Insulin Resistance in Aging Muscle

Musi

Insulin resistance is a major contributor to type 2 diabetes, the fifth leading cause of death in the United States. Research has likewise linked aging to a higher risk for diabetes, due to factors such as a decline in the amount and function of muscle mass and a drop in the ability of the muscle to metabolize fuels like sugars and fat. The big question, according to Dr. Nicolas Musi, is what age has to do with it at a molecular level.

Some key answers could be forthcoming from Dr. Musi's Beeson research comparing adults between the ages of 18 and 30 with adults older than 65. "Basically, we are taking tissue from both groups and we are comparing a series of genes and proteins that are responsible for maintaining muscle mass and metabolizing sugars and fats," he says. "We hypothesize that the older group will have altered function of certain genes and proteins that are important to maintain muscle mass and function."

The underlying abnormality, he believes, is an age-associated dysfunction among the muscle cells' energy-producing mitochondria, whose decline triggers a series of cellular cascades leading to a reduction in muscle mass, function, and glucose metabolism. Preliminary studies in rodents and humans suggest that aging triggers the excessive activation of a cellular pathway abbreviated IKK/IkB/NFkB, and that the pathway's molecules negatively impact muscle cell function.

Insulin normally stimulates the transport of sugar from the blood into the muscle cells, thereby helping to maintain blood sugar levels within a controlled range. With mitochondrial dysfunction leading to an over-activation of the IKK/IkB/NFkB pathway, Dr. Musi says, the muscle becomes resistant to insulin and too much sugar remains in the blood, instead of moving into the muscle reservoir. Decreasing the muscle mass only compounds the problem. "If you have less muscle, then you have less space where the glucose is going to get in and be metabolized," he says.

A second aspect of the research will test whether exercise can reset the normal mitochondrial function and whether that correction restores the normal activity of the molecular pathway. Exercise is already known to help maintain muscle mass, muscle function, and the ability to metabolize sugars, and although the ability of muscle to respond to insulin declines with age, Dr. Musi says, "most often, the patients' muscle will respond to exercise in terms of improving insulin sensitivity." Under the training regimen, patients will exercise on a stationary bicycle three to four times a week for three months. Studies suggest the aging population adheres well to exercise and lifestyle interventions, raising his hope that the Beeson-funded research will point toward a significant diabetes mitigating factor among the elderly.

Ultimately, Dr. Musi says the underlying mechanism must be deciphered. "If we're going to intervene pharmacologically, we need to understand what's happening at the molecular level," he says. "Not everyone can exercise. Exercise is always promoted, but perhaps finding new treatments that have an exercise-like effect would be very desirable."

Dr. Musi's research has merged his interests in gerontology, endocrinology, and exercise physiology, and he credits the Beeson award as a "fundamental" support in helping him create a successful blend. "This study could not have been done without the Beeson award," he says, noting that it has fostered other aspects of his work, including career development and networking with annual meeting participants. The support, he hopes, will help him further demonstrate how exercise "really has a series of very robust effects on our bodies, and that some of these effects can be seen from the very first exercise session." With evidence that it works like medicine – or better, perhaps people will be encouraged to exercise more and healthcare providers will design better exercise interventions that truly make a difference between life and death, whether for diabetes or for some other disease.

Neil A. Segal, MD
Assistant Professor of Orthopaedics and Rehabilitation
University of Iowa College of Medicine

MENTORS:
Robert Wallace, MD
James C. Torner, PhD
H. John Yack, PhD

Optimizing Mobility in Elders With Knee Osteoarthritis: Gait and Power Training

Segal

In college, Dr. Neil Segal volunteered to spend evenings with residents of a nursing home, who were more than happy to get out of their rooms and do something active. He began thinking about mobility, an idea that grew during his year as a Fulbright Scholar in Japan, where he studied 14 types of health and welfare facilities for the country's elderly. "When I compared all of those at the end of the year, I noticed that the facilities that focused on mobility and functional activity were the ones that were more successful in getting people back to their homes," he says.

A medical career was born. Dr. Segal initially focused on how central and lower body obesity – an "apple" versus a "pear" body shape – might put someone's knees at a biomechanical disadvantage. Eventually, he became interested in how knees function in people with osteoarthritis and used computerized motion analysis to determine what people who walk better do that lower-functioning people with knee osteoarthritis do not.

For his Beeson research, Dr. Segal is expanding on his studies to determine the benefits of two intensive rehabilitation interventions for adults over the age of 60 who have painful knee osteoarthritis. Specifically, he is examining whether functional activities with a weighted vest or a physical therapy program to reduce knee joint forces during walking are effective in improving mobility. The findings, he says, could lead to better rehabilitation and more accurate indicators of which older adults might benefit from each type of therapy.

The first of three arms in the randomized year-long study is a gait-training program that uses a high-tech treadmill. "We use a computerized camera to track where their body is in space. From sensors, we can study the forces touching the treadmill, and so gauge the forces on the knees, ankles, hip joints, and back."

As a patient walks, so does a stick figure on a computer screen, displaying the real-time force in the knee joints. "So if a therapist tells the patient to turn his toes outward more, he would be able to see the real-time reduction in the force on his knees," Dr. Segal says.

In the power-training intervention, other study participants wear a weighted vest and do mobility exercises, like walking up stairs or standing up from a chair. "With resistance training or strength training, you're activating the muscle for a specific force. If your vest is 10 pounds, you're just lifting the vest," Dr. Segal says. "But power training adds velocity, encouraging the patients to stand up from a chair or walk up stairs as quickly as they can."

Dr. Segal's hypothesis is that either intervention will deliver a better outcome than the study's third arm, in which knee osteoarthritis patients receive no special training at all. "It would be great, though, if the low-resource weighted vest intervention showed good results for some participants," he says. That would mean patients wouldn't need to rely on a technologically advanced treadmill that exists in few places.

Becoming a Beeson Scholar, Dr. Segal says, has "affected every aspect of what I'm doing. I leveraged funding from this award to obtain matching funding to hire more assistants. And that allowed me to successfully compete for several other grants. My whole program just blossomed." Meeting other Beeson Scholars, he says, has been another "amazing opportunity." From talking with 2004 Beeson Scholar Dr. Catherine Sarkisian at UCLA, "I was able to develop an interview protocol to motivate patients to continue to do the exercises that I've been teaching them." They're not alone in being newly inspired. "I feel more motivated seeing Scholars at every level of the Beeson program," Dr. Segal says. "It also motivates me to help others with less research experience. I get so much help from the Beeson family that I want to help others."

Manjula Kurella Tamura, MD, MPH
Acting Assistant Professor of Medicine
Stanford University School of Medicine

MENTORS:
Kristine Yaffe, MD
Glenn M. Chertow, MD
C. Seth Landefeld, MD

Mechanisms of Cognitive Impairment in Chronic Kidney Disease

Tamura

Dr. Manjula Kurella Tamura's research really emerged from a growing frustration in her clinical practice as a nephrologist. "I was seeing more and more elderly patients in my clinic with advanced chronic kidney disease and inevitably we would address the issue of dialysis and whether they should start," she says. "I really felt ill-prepared to talk to them about the pros and cons of dialysis." How would it affect her patients' quality of life? What were the other downsides? In short, what was the bigger picture?

By studying the oldest and sickest patients, Dr. Kurella Tamura hopes to better illuminate how dialysis may affect that small but rapidly growing group. In 2007, she co-authored a study in the *Annals of Internal Medicine* concluding that for patients 80 and older, dialysis initiation rates increased 57 percent between 1996 and 2003. Nearly half of those patients died within one year of beginning the procedure. "The operative angle of this is that the vast majority of people starting dialysis in the United States are elderly," she says. "And we really don't have a good handle on what some of the functional consequences of being on dialysis are."

As she became more interested in the geriatrics aspects of her specialty, Dr. Kurella Tamura had a startling realization. Patients with kidney failure are predisposed to early heart disease, stroke, bone fractures, menopause, and muscle wasting, among other complications, suggesting a faster rate of aging in these patients. To understand how chronic kidney disease may contribute to this phenomenon, she has now focused on studying the link between kidney failure and cognitive decline. Studies by her and others have demonstrated that up to 30 percent of patients with chronic kidney disease on dialysis have impaired cognitive function, though the reasons why are unknown. Perhaps more surprisingly, even patients with very mild chronic kidney disease not on dialysis appear to be at higher risk for cognitive decline.

With her Beeson award, Dr. Kurella Tamura is using MRI scans to image the brains of older patients with chronic kidney disease on dialysis and collecting blood samples to measure metabolic waste products that accumulate because of the disease and that may contribute to inflammation and brain dysfunction. "There are very few data right now on what the brain looks like in those patients," she says. With more data in hand, she hopes to find new connections between chronic kidney disease and cognitive decline.
The award, she says, has provided a big boost toward that goal by providing funds for the expensive but informative MRI scans and granting invaluable access to experts in geriatrics who have offered her guidance and new insights. To develop this area of research, Dr. Kurella Tamura has worked closely with her mentor, Dr. Kristine Yaffe, also a Beeson Scholar and a leading clinical researcher in dementia and cognitive impairment at the University of California, San Francisco. "Dr. Yaffe's work, especially in diabetes and cognitive impairment, has really provided a framework for some of my studies."

For a second study, part of a larger National Institutes of Health-backed effort, Dr. Kurella Tamura is examining the link between dietary protein intake, levels of metabolic waste products, and cognitive function in a randomized trial of dialysis done three times a week versus six times a week.

Although the number of patients on dialysis in the U.S. is still relatively small, more than eight million American adults have chronic kidney disease not yet requiring dialysis, and Dr. Kurella Tamura's studies may ultimately help to reduce the risk for cognitive decline in this larger group as well. A holistic view indeed.

Lihong Wang, MD, PhD
Assistant Professor of Psychiatry
Duke University Medical Center

MENTORS:
David C. Steffens, MD
Ranga R. Krishnan, MB ChB

fMRI Prediction of Mild Cognitive Impairment in Geriatric Depression

Wang

As a geriatric neurologist in China, Dr. Lihong Wang saw numerous patients incapacitated by stroke or Parkinson's disease at Hebei Provincial Hospital. "Many of them had frontal lobe dysfunction and I didn't know how to deal with it," she recalls. The more she thought about it, though, the more intrigued she became – a growing interest that led her to Yokohama City University School of Medicine in Japan to study how Parkinson's disease affects the brain's frontal lobe. Fascinated with the ability of neuroimaging techniques to highlight brain function and dysfunction, she eventually moved on to Duke University as a post-doctoral fellow under the supervision of Dr. Gregory McCarthy where she has used functional magnetic resonance imaging (fMRI) to scrutinize the cognitive and emotional systems of patients with depression.

For her current Beeson research, she is working closely with her mentors Drs. David Steffens and Ranga Krishnan. Dr. Wang hopes to sort out the fuzzy relationship between depression and mild cognitive impairment, both of which are common among the elderly, and each of which may influence the other. In particular, she is interested in using fMRI to predict mild cognitive impairment in older patients with depression. As she notes, the imaging technique can reveal alterations in the neural system long before any clinical symptoms appear. So far, fMRI has not been applied as a clinical diagnostic tool, but Dr. Wang believes it is more sensitive to cognitive changes than neuropsychological assessments and that it shows great potential for reliably predicting cognitive impairments.

In people diagnosed with depression, altered activation in the brain's prefrontal cortex has been linked to abnormal executive function, which controls higher-order processes such as working memory, planning, and decision-making. Abnormalities in another area called the hippocampus have been tied to mild cognitive impairment. And changed activity in the limbic system, including the amygdala, has been associated with deficits in emotional processing – and more recently, in emotional memory. Dr. Wang's work could clarify those links and whether changes in the amygdala and hippocampus of patients with depression might help predict mild cognitive impairment. The overall goal, she says, is to identify which neuroimaging markers are most predictive so that effective early interventions can be pursued.

To reach that point, she will examine how fMRI compares to the gold standard of a neuropsychological battery of tests in detecting and predicting cognitive decline in older patients being treated for depression. During an initial phase, the patients are asked to remember a group of pictures depicting positive, negative, or neutral emotions. Three hours later, the patients undergo fMRI scans while viewing the old pictures mixed with a set of new ones, some of which are repeated once. "We ask them which ones they've seen previously outside the scanner, and which ones have just been repeated recently," Dr. Wang says.

The experiment gauges working memory as well as emotional response. In depressed patients, the hippocampus and amygdala light up less for positive or emotionally neutral pictures, but more for negative ones. Newly repeated pictures, meanwhile, elicit a lower activation of the prefrontal cortex. Repeating the same test with different pictures one year later could identify patients whose cognitive impairment remains even after successful treatment for depression. "As you treat depression, the depressive symptom is improved but those who still have memory dysfunction may fall into mild cognitive impairment," Dr. Wang explains. Importantly, a low baseline activation in the amygdala and hippocampus of patients viewing old negative and positive pictures during the experiment's first phase could predict who might develop mild cognitive impairment.

Beeson Scholars: News from the Bench

Family Surrogates and Informed Consent

With their decision-making abilities impaired, many aging patients with Alzheimer's are unable to give informed consent to participate in research studies. Beeson Scholars **Jason Karlawish, MD** (2000), and **Kenneth Langa, MD, PhD** (2003), investigated the issue of surrogate consent in a study published in the January 2009 *Neurology*. Drs. Karlawish and Langa surveyed older Americans, finding that the majority of subjects would allow a family surrogate to give consent and would participate in surrogate-based research. Since Alzheimer's research is often stalled by the complicated issue of consent, this study could be an important indicator of the general acceptance of family surrogates and move the process forward. Dr. Karlawish, of the University of Pennsylvania, and Dr. Langa, of the University of Michigan also had their work featured in a January 14, 2009, article by *Insciences*.

Cheers! To a Longer Life

On January 21, 2009, CNN highlighted the research of 1998 Beeson Scholar **Alison Moore, MD, MPH**, of the University of California, Los Angeles. Dr. Moore's study found that moderate alcohol consumption had positive effects for seniors. By analyzing self-reported data from men and women over 50, Dr. Moore saw that healthy seniors who drank fewer than 15 alcoholic beverages a week had reduced odds for developing physical disabilities or dying in the next five years. Further investigation is necessary to explore the specific cause of this relationship, but researchers suggest that alcohol's effect of decreasing atherosclerosis or raising good cholesterol levels may explain the connection between alcohol consumption and improved health. Dr. Moore's study was recently published in the January 15, 2009 issue of the *American Journal of Epidemiology*.

Understanding Diabetes, Body and Mind

The research of 2000 Beeson Scholar **Scott Small, MD**, of Columbia University, was cited in a January 6, 2009, *New York Times* story about links between blood sugar levels and declining memory. Dr. Small led a team of investigators to explore the neurological effects of blood sugar spikes, which appear to influence a particular part of the brain connected to memory-formation. Using MRIs to examine brain activity, researchers found that elevated blood sugar levels corresponded with reduced blood flow in the dentate gyrus, a region of the hippocampus. Not only does this study have implications for understanding the relationship between diabetes and aging, but Dr. Small's research also emphasizes the importance of physical exercise to regulate glucose levels and care for the aging brain. Dr. Small's research about memory and aging has also been highlighted in *Time*.

Prescribing a New Direction for Treatment

In a study published in the December 2008 issue of *Clinical Interventions in Aging*, research led by 2005 Beeson Scholar **Malaz Boustani, MD, MPH**, reviewed clinical trials of cholinesterase inhibitors to assess their value in treating behavioral problems exhibited by Alzheimer's patients. Dr. Boustani and colleagues at Indiana University found that cholinesterase inhibitors, typically prescribed for cognitive symptoms of Alzheimer's disease, were also effective in managing patients' accompanying psychological and behavioral symptoms. Dr. Boustani is eager to use this study to connect physicians with progressive treatments for their Alzheimer's patients. Dr. Boustani's study findings were profiled in several publications, including *Science Daily* and *U.S. News & World Report*.

Inheriting Good Health

A November 25, 2008, article in the *New York Times* profiled the research of 2005 Beeson Scholar **Dellara Terry, MD, MPH**. Dr. Terry's investigations showed that older adults whose parents lived 100 years or longer were healthier than others their age and were at much lower risk for heart attacks, strokes, or diabetes. The study monitored the health of centenarian offspring over three to four years and found that this group had 78% lower risk for heart attack, 83% lower risk of stroke, and 86% lower risk for diabetes than their peers. These results, published in the September 2008 *Journal of the American Geriatrics Society*, are consistent with Dr. Terry's previous research, which suggested that the avoidance or delay of cardiovascular disease and cardiovascular risk factors may play an important role in living to a very old age. Dr. Terry, of the Boston University School of Medicine, co-authored this research with 1996 Beeson Scholar **Thomas Perls, MD, PhD**.

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About the American Federation for Aging Research (AFAR)

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