Tribute to Paul B. Beeson, M.D.

The Paul Beeson Physician Faculty Scholars 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.
Building Physician-Scientists for Aging Research

The Paul Beeson Physician Faculty Scholars in Aging Research Program was created in 1995 to provide important financial and career support for outstanding “physician-scientists,” junior faculty committed to academic careers in aging-related research, teaching, and practice. Since its inception, the program has made three-year, $450,000 development awards to 91 talented academic physician-scientists.

The Paul Beeson Physician Faculty Scholars in Aging Research Program has three explicit goals, namely to seek to:

**Encourage and assist** the development of faculty members early in their careers to address clinically relevant research needs in the areas related to aging.

**Strengthen and expand** research and educational programs in academic centers of excellence, particularly those institutions that have demonstrated leadership and a commitment to aging research and to geriatric medicine.

**Expand medical research** on aging through focusing on the biology of aging, diseases of old age, and clinical management issues, with the aim of enhancing the health and quality of life of Americans, particularly older people.
Focus on the Future

The Paul Beeson Physician Faculty Scholars in Aging Research Program is a critically important effort. 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. Therefore, it is imperative that we as a nation have the ability not only to provide high quality medical and other care to older Americans, but that we develop the new scientific knowledge that ensures that as we live longer, we live independently and productively as well.

To this end, the Paul Beeson Physician Faculty Scholars in Aging Research Program makes a substantial investment in developing medical faculty so that we 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 continue to devote their careers to advancing our knowledge of effective prevention and management of illness and who will inspire successive generations of physicians to do the same. Through their diverse scientific interests and their extensive teaching commitments, Scholars are developing the research and nurturing the professionals that will be needed to provide care for a growing number of older adults.

In addition to providing important financial support, the Paul Beeson Physician Faculty Scholars in Aging Research Program invites senior faculty members at the Scholars’ institutions to serve as mentors. These academic leaders guide Scholars’ research and career development and provide access to organizations, programs, and colleagues helpful to the Scholars’ growth and development.

The critical role of the mentor is further complemented by an exciting annual conference, coordinated by the Alliance for Aging Research, which has convened all the Beeson Scholars and mentors, as well as other leaders in geriatrics and aging research. And year-round, two web sites (www.afar.org/beeson.html and www.beeson.org) also enable Scholars (and people throughout the field) to learn about recent developments in the program and follow the research of all the Scholars in the Beeson network. We urge you to visit these websites to find out about the exciting research conducted by the Beeson Scholars.
It is a pleasure and honor to introduce the talented physician-scientists who make up the seventh group of Paul Beeson Physician Faculty Scholars in Aging Research. We once again received a very strong and competitive group of proposals and were able to choose an extremely talented group of scientists. As you will read in the coming pages, their research is first-rate. Many Scholars are already assuming new responsibilities, heading up innovative programs and initiatives at their institutions and in national organizations and journals. They are quickly taking up their leadership in a variety of local and national forums.

While the Beeson program funds in a variety of disciplines related to aging, this latest class of Scholars reflects a re-emergence of researchers who focus on Alzheimer’s and other neurodegenerative diseases, an area well-represented in the program’s earliest cohorts. However, it is really excellence that connects this talented group of scientists, whether they are working on heart disease, back injury, care fragmentation, prion disease, delirium, cartilage breakdown, depression, or some aspect of cognitive decline and brain disease.

As I consider the broader historical arc of the program, I am heartened by the continuing and positive career growth of our Scholars as evidenced by their new appointments, publications, new funding and national awards. Even within our own program, graduated Scholars have become mentors to current Scholars and have joined us as important members of the Program Committee. An external review of the program was recently conducted, confirming our more subjective views of the program’s success.

Given the strong record and current state of the Beeson Program, it is a fitting time for me to step aside as the Chair of the Program Committee. I am extremely pleased that Mary E. Tinetti, M.D., Professor of Medicine and Epidemiology and Public Health and Chief of the Division of Geriatrics at the Yale University School of Medicine, has taken over leadership of the committee in March of 2003. Dr. Tinetti, the nation’s leading researcher on falls prevention among older adults, has served on the committee since 1994 and is a stalwart supporter of the field of geriatrics.

It has been an honor to lead this group during the last 6 years and more importantly, to contribute to a program honoring one of my mentors, and one of the great geriatricians of our time, Paul Beeson.

William R. Hazzard

Letter from William R. Hazzard, M.D.
Chair (1997-2002) of the Program Committee of the Paul Beeson Physician Faculty Scholars in Aging Research Program
More than one million older Americans suffer from Parkinson’s disease (PD) and are afflicted with muscle tremors, problems walking, and decreasing motor control. There are few medications for these symptoms and no cure for the progressive neurodegenerative disease.

Neuroscientist Dr. Asa Abeliovich, Assistant Professor at Columbia University’s Taub Institute for Alzheimer’s Disease and the Aging Brain, is aware of and concerned with this problem. He takes time out of his busy laboratory schedule every week to care for patients in the university’s Memory Disorders clinic. Frustrated by a lack of treatments for Parkinson’s patients, Dr. Abeliovich has concentrated his research efforts on probing the molecular mechanisms of several genes implicated in PD. His hope: identifying a useful target for future therapies.

Dr. Abeliovich is currently investigating two genes linked to familial, inherited forms of PD, α-Synuclein (α-Syn) and Parkin. Although mutations in these genes are responsible for only a fraction of PD cases, he believes that the pathways influenced by these genes are likely the same as those activated in non-familial PD. Experiments in mice, for example, show that the α-Syn gene helps regulate the release of dopamine, the crucial neurotransmitter deficient in the brains of PD patients.

Parkin, on the other hand, seems to be involved in the protein degradation process, called ubiquitination. “It looks like it is involved in what can be thought of as the garbage disposal system,” says Dr. Abeliovich. “Since PD involves an accumulation in the dopamine neurons of what looks like cellular garbage, there’s logic behind that.” Dr. Abeliovich’s research goal is to establish that Parkin is indeed a ubiquitin ligase (a substance that tags proteins for degradation) and discover its targets and, if they include, directly or indirectly, α-Syn.

To date, Dr. Abeliovich has demonstrated in cell culture that Parkin is a ubiquitin ligase which appears to alter the response of dopamine neurons to cellular signals. He has also identified several molecules that are activated by Parkin during ubiquitination. However, α-Syn does not seem to be one of these molecules. Dr. Abeliovich continues to test the interaction of α-Syn and Parkin to further explore the possibility that α-Syn may be indirectly activated by Parkin through other means. He is also attempting to identify additional molecular targets, or substrates, for Parkin and is checking its known substrates to determine if any might improve the survival of dopamine neurons.

An additional step in Dr. Abeliovich’s research will be to test in vivo whether mutations in Parkin and α-Syn can genetically interact to alter dopamine neuron survival. He is currently using several transgenic mouse lines for these studies, including mice that lack the α-Syn gene, overexpress α-Syn, or lack the Parkin gene. He is also working on crossing the Parkin-deficient mouse line with each of the α-Syn transgenic mouse lines.

The financial assistance provided by the Beeson Award enables Dr. Abeliovich the ability to create these mutant mice. “It can take three years to develop mice,” he points out. “You really do need outside support to do these sorts of long-term projects.” The Beeson’s financial support has also allowed him to hire a technician for his laboratory, as well as spend time mentoring two graduate students and three post-doctoral fellows.

The Beeson Scholarship has provided other, non-financial benefits, as well. In addition to the extensive mentoring Dr. Abeliovich receives from Dr. Michael Shelanski, chair of Columbia’s pathology department, he appreciates the opportunity for networking offered by the Beeson annual meeting. The meeting, he says, offers a “tremendously helpful” opportunity to meet and exchange ideas with geriatricians and researchers in his field—experts whom he would otherwise never meet.
Mechanisms of Cyclooxygenase-2-Dependent Neuronal Injury in Aging and Neurodegenerative Disease

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Mentor: Donald Price, M.D.

Neurologist Dr. Katrin Andreasson first encountered the gene cyclooxygenase-2 (COX-2), which helps regulate connections between synapses in the brain, during her postgraduate work in neurology. Recently, as evidence continues to mount indicating non-steroidal anti-inflammatory drugs, which inhibit cyclooxygenase, have a protective effect against Alzheimer’s disease, Dr. Andreasson has chosen to devote most of her research efforts determining the role of COX-2 in neuronal injury.

Recent research has shown that COX-2 levels are linked to levels of glutamate in the brain. This toxicity from skyrocketing glutamate levels is a primary cause of neuron death in stroke and neurodegenerative disease. To validate the theory that high levels of COX-2 have a deleterious effect on the brain, Dr. Andreasson has developed several animal models that overexpress COX-2.

In the first mutant mouse line she created, the Johns Hopkins professor found that levels of substances called prostaglandins, which are created through COX-2 activity, are 10 to 15 times higher than in normal mice. In a study published in the *Journal of Neuroscience* in 2001, Dr. Andreasson showed that these mice begin experiencing age-related spatial memory deficits in middle age, or 12 months. Subsequently, by testing a second mouse line in which COX-2-derived prostaglandin levels are more than 40 times normal, Dr. Andreasson established a dose-response relationship between COX-2 levels and memory decline. These highly overexpressed COX-2 mice show memory deficits as early as seven months of age. In addition, Dr. Andreasson confirmed the COX-dependent nature of the cognitive effect by treating these transgenic mice with a COX-2 inhibitor. Her team demonstrated that treated mice reversed these memory deficits.

According to Dr. Andreasson the next step in her Beeson research involves examination of the prostaglandins generated by COX-2 activity. “Our goal is to figure out which prostaglandin is damaging neurons,” she says.

“If you can figure out what the pathway is, you can develop potential therapeutic interventions to target those pathways.” Because there are five types of prostaglandins and numerous receptors to which they can bind, zeroing in on the correct combination of prostaglandin and receptor is a time-consuming process.

Dr. Andreasson notes that her efforts to identify the correct prostaglandin-receptor combination have been greatly aided by the generous financial support provided by the Beeson Award. “It’s been a godsend,” she says. “I have been able to hire some very good people for my lab, and our progress has accelerated tremendously. We’re moving so much faster than we could have before.”

To date, Dr. Andreasson’s lab has tested two prostaglandin-receptor pairs, called prostaglandin receptor agonists, and found, surprisingly, that one has a protective effect on neurons, while the other has no effect. Dr. Andreasson plans to test the two receptor agonists together to see if they have a deleterious effect in combination, as well as continue testing of the remaining prostaglandins and receptors. Once she has identified possible candidates for therapeutic intervention—those with either negative or positive effects on neurons—Dr. Andreasson intends to test what effect their absence has on mice engineered to lack those receptors. The final step will be to determine which genes are activated by these specific prostaglandin receptor agonists, hopefully yielding targets for therapeutic intervention. Dr. Andreasson has several manuscripts in progress describing her results so far. She presented two posters on her work at the 2001 meeting of the Society for Neuroscience.

Dr. Andreasson is also working on additional projects related to COX-2. With assistance from her mentor, Dr. Don Price, she has begun collaborating with a group at Vanderbilt University to examine the interactions between COX-2 and the amyloid β peptide, which is involved in plaque formation in Alzheimer’s disease. In addition, she has received an RO1 grant from the NIA to cross her COX-2 transgenic mice with the current Alzheimer’s model, APP mutant mice, to create a new, improved mouse model for Alzheimer’s disease. The new line should not only display the hallmark plaques of Alzheimer’s disease, as do APP mice, but also develop memory deficits, giving researchers an important new tool in the battle against the devastating disease.
Reducing Care Fragmentation Across Sites of Geriatric Care

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Mentor: Andrew Kramer, M.D.

Older adults often receive health care from several providers in different care settings, such as their own home, a doctor’s office, a hospital, or a nursing home. This care is rarely coordinated, and providers often unknowingly duplicate or contradict each other’s efforts. This “care fragmentation” likely contributes to medication errors, confusion and frustration for patients and caregivers, and higher costs.

Geriatrician Dr. Eric Coleman believes the most cost-effective way to reduce the negative impact of care fragmentation on older adults and the health care system is to help patients manage their own care. “By default,” he points out, “older patients are often managing their own transitions. They are asked to become conduits of information between practitioners who don’t talk to each other.” To address this problem, Dr. Coleman is developing and testing a strategy designed to give older patients the tools they need to successfully manage their own care transitions.

The intervention strategy features two self-management tools: a patient-centered medical record that includes medical conditions, care goals, and medications, and a checklist of activities that should take place before and after patients are discharged or transferred to another care setting. A geriatric nurse practitioner explains use of the tools, then provides support to patients through a follow-up visit and telephone calls in order to assist them with medication and condition management as well as care planning.

After successfully testing the feasibility of providing these tools, Dr. Coleman has begun a randomized trial in two care sites, thanks to the generous support of The John A. Hartford Foundation and the RWJ Foundation. This study compares outcomes between older adults receiving the intervention and a control group receiving standard care. He will assess the outcome of the trial via the Care Transitions Measure (CTM), a patient-centered measure which he developed to measure care fragmentation. The development and initial validation of the CTM was published in the International Journal of Care Integration in 2002.

To date, Dr. Coleman has completed about 25% of the trial’s initial enrollment, with a goal of 700 participants at each care site. Access to patients for both the feasibility study and the interventional trial has been greatly facilitated by Dr. Coleman’s collaboration with Kaiser Permanente of Colorado, with whom he holds a formal research position.

With few geriatricians engaged in research on population-based care, Dr. Coleman has benefited from the network of colleagues afforded by the Beeson program. He continues to seek guidance from senior investigators, such as mentor Dr. Andrew Kramer and Beeson Program Committee member Dr. Linda Fried. In addition, Dr. Coleman notes that the award has given an “external stamp of approval” to the importance of his research, leading to his recent promotion to Associate Professor after less than four years at the University of Colorado Health Sciences Center.

Dr. Coleman is also increasingly recognized as a leader in public health care policy. He has authored several papers on health care topics and directed a national conference on transitional care in September 2002. In addition, in a project related to his Beeson research, Dr. Coleman is using Medicare data to develop a model to predict which patients are more likely to experience numerous care transitions, thereby placing them at a higher risk for care fragmentation.

Despite his demanding schedule, Dr. Coleman continues to make mentoring geriatrics fellows and medical students a high priority. His main focus, however, remains encouraging health and managed care systems to adopt strategies to integrate care, leading to potential cost savings for health insurers and providers and improving the health and well-being of older adults.
Restoration of Senescent Cardiac Angiogenic Activity by Bone Marrow Transplantation

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Mentors: Ralph Nachman, M.D.
Ronald Adelman, M.D.

During his clinical training in cardiovascular medicine, Dr. Jay Edelberg soon realized that heart disease tended to be much more severe in elderly patients than in younger ones. Dr. Edelberg's wife, a geriatrician, urged him to consider concentrating his research on aging topics. In order to do this, Dr. Edelberg combined his interest in elderly cardiac patients with his basic research on cardiac endothelial cells. Investigating the changes in endothelial activity as cells age, he found that in older hearts, senescent endothelial cells do not express platelet-derived growth factor B (PDGF-B), a prime regulator of cardiac blood vessel growth, or angiogenesis.

Dr. Edelberg theorized that the greater severity of cardiac disease in the elderly could be due to this inability to grow new blood vessels, which would make it harder for an older person to recover from damage suffered as a result of a heart attack. He set out to find a way to restore the angiogenic pathways, ultimately hoping to develop a therapy that could help reduce heart attack damage in elderly patients. Injecting the bone marrow from young mice into old mice, Dr. Edelberg found that young endothelial precursor cells (EPCs), a type of stem cell in the marrow, restored the PDGF-B angiogenic pathway in the elderly hosts. He and his collaborators published an article describing this work in the May 31, 2002, issue of *Circulation Research*.

Building on this success, Dr. Edelberg is working to further understand the molecular pathways activated by bone marrow transplantation, as well as examining differences in genes expressed by older versus younger heart cells. Because of the problems presented by bone marrow transplantation in humans, such as finding a young, matching donor, Dr. Edelberg hopes to find alternative methods of activating the PDGF-B pathway—such as targeting a receptor with a specific molecule.

Dr. Edelberg’s lab has made some progress in this regard. Looking for differences in receptor activity in old compared to young heart cells, his team has found that older hearts have a markedly reduced capacity to bind tumor necrosis factor α (TNF-α). TNF-α promotes the expression of PDGF-B in endothelial cells. Dr. Edelberg is conducting further investigations of this receptor, as well as testing the efficacy of bone marrow transplantation in aging animal models. This testing is being performed to make certain that bone marrow transplantation does decrease the extent of cardiac damage inflicted by a heart attack. Results in mice show that this is indeed the case.

Dr. Edelberg notes that the Beeson Award has made a major impact on his career. “It has been unbelievable,” he says. “It has provided professional recognition, both here at Cornell and nationally.” This increased recognition has led to additional funding, as Dr. Edelberg has recently been awarded three grants from the NIA and has won awards from the American Heart Association and the American Geriatrics Society. In addition, he has been recognized as an expert on aging in stem cells and has received several invitations to present on the topic. The support from the Beeson Award has also allowed Dr. Edelberg to increase his training of young researchers. Last year he added three fellows and two medical students to his staff. He also directs a translational research seminar series, developed with the help of one of his mentors, Dr. Ronald Adelman.

The professional contacts afforded by the Beeson Award are, to Dr. Edelberg, one of its most valuable assets. “This is a great group of researchers that understands and appreciates this type of work. With aging research still less established than other disciplines, it’s wonderful to have access to such outstanding mentorship, particularly as a non-geriatrician.”
Respiratory failure primarily strikes elderly patients. Unfortunately, those patients who survive an extended stay in an intensive care unit (ICU) connected to a mechanical ventilator, often return home with a marked decline in mental function. A growing number of researchers, including Dr. Wesley Ely, believe that delirium—a condition of mental confusion and hallucinations common among hospitalized elderly—may be a contributing factor in this cognitive decline as well as other poor clinical outcomes, such as loss of functional independence and even death.

The aim of Dr. Ely’s Beeson-supported research is threefold. His intent is to determine: how often delirium occurs among mechanically ventilated ICU patients and its association with clinical outcomes; if the type of drugs given and a patient’s sensitivity to medication affect the development of delirium; what factors influence lingering cognitive deficits after discharge from the ICU.

In order to measure these outcomes, Dr. Ely and his colleagues developed an assessment method that can detect delirium in nonverbal patients. Validation of the Confusion Assessment Method for the ICU, or CAM-ICU, has been published in several medical journals, including the Journal of the American Medical Association, and the measure has been adopted and recommended by the Society of Critical Care Medicine.

Analyzing results from his initial cohort of 276 elderly, mechanically ventilated patients, Dr. Ely found that 90% developed delirium in the ICU and that delirium is the strongest independent predictor of mortality and length of hospital stay, even after adjustment for severity of illness and other factors. He continues to add patients to the study, with a goal of 1,000 participants by 2003. During each patient’s ICU stay, Dr. Ely collects data on delirium and sedation levels and tracks medication use. Upon patient discharge, as well as two and six months after discharge, Dr. Ely measures factors such as depression, post-traumatic stress disorder, and cognitive function.

Once analysis of results from the current study has been completed, Dr. Ely expects to conduct an interventional trial to test the hypothesis that reducing delirium by targeting modifiable risk factors will improve patient outcome. He hopes to begin the randomized, controlled trial in 2004 or 2005.

The ultimate goal of Dr. Ely’s research is to help patients who survive their stay in the ICU to regain their normal lives. “What we’re finding right now,” he says, “is that when people come off the ventilator, they can’t balance their checkbook, go to work, or do the things they really want to do because they’re so neurologically impaired. Our goal is to continue to provide supportive care for people with failing organs while modifying that care to improve the likelihood of them going on to lead functional, meaningful, productive lives.”

Dr. Ely calls the Beeson Award a “major door opener” and a significant factor in his growing reputation as an expert on delirium in ICU patients. Not only has he been asked to make several presentations on delirium at national meetings, he has recently been named Vanderbilt’s Associate Director of Research for the Geriatric Research Education and Clinical Center of the Veterans Affairs Tennessee Valley Healthcare System.

Dr. Ely has also benefited from the mentorship and networking opportunities afforded by the award. Discussions with experienced geriatricians and his Beeson Award colleagues have helped him improve the scope of data collection in his research. In turn, he has been passing on his expertise to the next generation of investigators by mentoring fellows and AFAR Medical Student Geriatric Scholars, as well as becoming involved with a recently formed Student Geriatrics Interest Club.
Targeting Signaling Pathways in Aging Hearts by Gene Transfer

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Mentor: G. William Dec, M.D.

Half of all hospital admissions among people over age 65 are due to congestive heart failure. One of the main explanations for the condition’s alarming prevalence among older people is that during the aging process, the heart undergoes changes making it more susceptible to disease. In particular, an older heart is more prone to diastolic abnormalities than a younger heart because it does not fully relax during dilation. While in medical school, Dr. Hajjar began probing the causes of this change. He discovered that the older heart somehow misuses calcium. Since then, Dr. Hajjar has focused his research on using gene therapy to boost expression of nonfunctional genes in the aging heart, seeking a calcium-related, therapeutic strategy for treating congestive heart failure.

In 2001, Dr. Hajjar published a validation of this gene therapy approach to heart failure in the journal Circulation. He showed that both survival and short-term diastolic function in aging rats with heart failure could be significantly improved by boosting expression of the gene for the sarcoplasmic reticulum calcium ATPase pump (SERCA 2a) via gene transfer. SERCA 2a pumps calcium out of the heart, a key component of diastolic function. Dr. Hajjar intends to further test the efficacy of overexpressing SERCA 2a by examining the long-term effects of the procedure in a rat model. In addition, he hopes to use gene transfer to modify metalloproteinases (MMPs) and their inhibitors (TIMPs) in aging hearts. Metalloproteinases create fibrosis in the heart, and an imbalance between MMPs and TIMPs could be responsible for the increased stiffness of older hearts. “Our goal,” says Dr. Hajjar, “is to make the aging heart look like the adult heart.”

Before Dr. Hajjar conducts these experiments, he must first identify the best possible vector for the delivery of genetic material. After settling on an adenovirus vector and a catheter delivery system, Dr. Hajjar and his lab spent the last year testing the efficacy of the vector in aging heart cells. To their surprise, they found that aging heart cells are more resistant to infection by the adenovirus vector than are normal adult cells. Exploring the causes behind this setback, they found another enigma. Despite their resistance to the adenovirus, the aging cells actually expressed more receptors for the virus than did adult cells. Dr. Hajjar has now identified decreased expression of integrins—glycoproteins that affect how cells bind to other substances—as a likely culprit for decreased susceptibility to infection in older heart cells.

Dr. Hajjar is confident his team can overcome this unexpected hurdle. They have already found that adding a substance called laminin to the aging cells improves the lack of effect of the adenovirus vector. “There are ways of enhancing the efficiency of gene transfer,” he explains. “We can modify the adenovirus to make it genetically easier to transfer.”

Dr. Hajjar’s work is greatly aided by the efforts of several postdoctoral students, who have contributed to papers published in Circulation, the Proceedings of the National Academy of Science, and Physiologic Genomics. He notes that the Beeson Award has led him to focus more on aging and gerontology, and that he is now attracting fellows and medical students who are interested in gero-cardiac research. In fact, he has three such post-doctoral fellows and students in his laboratory. This narrowed focus has led Dr. Hajjar to greater involvement with Harvard’s Division of Aging, and his growing research program has led to his appointment as director of the Cardiology Laboratory of Integrative Physiology and Imaging at Boston’s Massachusetts General Hospital. In addition, Dr. Hajjar is frequently invited to speak at conferences and Grand Rounds both nationally and internationally on the subjects of gene therapy and novel treatments for heart failure.
Aging and the Misfolded Protein: Prion Disease as a Model for Disaggregating the Aggregate

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Mentors: Raymond Roos, M.D.
John Trojanowski, M.D., Ph.D.

Scientists have been finding increasing evidence that the development of many neurodegenerative diseases—which most often strike older persons—involves a usually normal brain protein that becomes misfolded. This protein spreads its abnormal structure by latching onto other, normal proteins of its former type and transforming them into copies of itself. These misfolded proteins then begin to aggregate, or clump, into fibrils and eventually plaques that compromise brain function. In an effort to find treatments applicable to Alzheimer’s and other age-related neurodegenerative diseases, Dr. James Mastrianni is using prion disease as a model to explore ways to halt or prevent this protein aggregation.

In order to understand aggregation, Dr. Mastrianni is testing two different versions, or conformations, of the misfolded prion protein, PrPSc, in a yeast model that he developed. He is interested in observing how these different conformations interact with the normal prion protein (PrPC) and each other. He has found in both yeast and mice that prion disease progresses much faster when the sequence, which predicts conformation, of PrPSc matches that of PrPC it is trying to convert. In some cases, when the PrPSc and PrPC are mismatched, the disease does not seem to transmit at all. Dr. Mastrianni suspects this means that PrPSc tries to bind to an exact match of PrPC and, if a section of the protein doesn’t match, this dislocation could slow the progress of the disease, possibly offering an avenue for treatment.

Dr. Mastrianni is also trying to pinpoint the segments of the PrPSc protein responsible for aggregation. To find them, he is deleting likely segments of the central domain of PrP and testing the effect of each deletion on aggregation. To date, one deletion mutant has shown a decreased ability to aggregate, as the fibrils it forms are less compact. Ultimately, Dr. Mastrianni hopes to find a region or regions of PrP to target with peptides that will bind to PrPC and prevent PrPSc from binding to it and generating fibrils. His lab has already manufactured a peptide that has an effect on aggregation in vitro. Eventually, he hopes to transfer these aggregation-halting techniques from prion disease to Alzheimer’s disease.

“Alzheimer’s disease is one step after prion disease, and a study of Alzheimer’s will have a bigger impact on the aging population,” he says. “However, prion disease is such a good model for aggregation that it’s worth studying, because you can determine [its folding] mechanisms much more quickly.”

The study of prion disease is an expensive undertaking. Unlike other neurodegenerative diseases, prion disease is infectious. The biohazard represented by infected cells requires a lab carefully constructed to meet government regulations. Dr. Mastrianni is thankful that the Beeson Award—which he calls “the cream of development awards”—came at a crucial transition period in his work. The timing of the award lent credibility to his efforts, and lead to expanded lab space and supported his reappointment at the University of Chicago. With the support of his mentors, Drs. Roos and Trojanovksi, Dr. Mastrianni is gaining recognition as an expert on dementia caused by prion disease. This increased recognition has lead to engagements to write several book chapters and review articles as well as an appointment as advisor to the FDA on prion disease in beef, better known as “mad cow disease.”

In addition to pursuing this exciting research agenda, Dr. Mastrianni remains dedicated to the clinical care of elderly patients with dementia and co-directs the Center for Comprehensive Care and Research on Memory Disorders at the University of Chicago. He also receives high marks as an instructor; he was recently named the university’s “2002 Pfizer Instructor of the Year” for his role in mentoring psychiatry residents at the Memory Center.
Matrix Homeostasis and Gene Expression in Aging Cartilage

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Mentors: Robert Reddick, M.D.
Arlan Richardson, Ph.D.

Approximately 80 to 90% of Americans age 65 and older suffer from osteoarthritis (OA), an age-related disease in which the cartilage protecting the joints gradually deteriorates. Noting the impact this disease has on his older patients, as well as the lack of treatment for the condition beyond pain management or joint replacement surgery, pathologist Dr. Michael Naski has focused his research efforts on understanding how aging affects cartilage cells, or chondrocytes.

A protein called aggrecan regulates the growth of the matrix of cartilage that protects joints, and substances called aggrecanases, which cleave aggrecan, affect degradation of the matrix. Dr. Naski is concentrating on the effects of aging on these aggrecanases, as well as surveying how aging affects overall gene expression in chondrocytes. He hopes to identify other genes and gene products that affect cartilage matrix homeostasis. “First,” says Dr. Naski, “we want to understand how the cartilage matrix deteriorates during the development of OA. Second, we want to understand the pathway that contributes to matrix synthesis. We hope that this will allow us to design strategies for cartilage repair or regeneration.”

Early in his research on aggrecan, Dr. Naski received some surprising results: in aging mice, aggrecan levels are elevated, rather than decreased. As this would normally lead to additional matrix synthesis rather than the degradation seen in osteoarthritis, it suggests that additional deterioration mechanisms may be at work in aging cells. Although he has not yet determined those mechanisms, Dr. Naski has made considerable progress characterizing the pathways by which aggrecan is activated and up-regulated, or increased. He has recently pinpointed the section of the aggrecan gene that triggers aggrecan expression, which will facilitate understanding of how the gene is turned on. In addition, he has begun to identify several substances involved in aggrecan activation and up-regulation.

The aggrecan expression pathway involves a number of different substances working in concert. Calcineurin, a type of calcium required for aggrecan expression, enters the cell via the activity of a substance called ionomycin, which regulates intracellular calcium. Calcineurin, in turn, activates NFAT, a transcription factor, as well as p38. Both NFAT and p38 induce aggrecan activity. Dr. Naski’s description of this aggrecan-triggering pathway was published in abstract form in Molecular Biology of the Cell in 2001. He is continuing his research in this area to determine if NFAT directly turns on the aggrecan gene or if yet another signaling molecule is involved in the process. He is also working to characterize the effects of fibroblast growth factor 1 (FGF1) and bone morphogenetic protein 2 (BMP2) on aggrecan, which have been shown to up-regulate aggrecan in chondrocytes.

Dr. Naski’s research efforts have received a significant boost from the Beeson Award. His laboratory space has more than doubled since he received the award, and one of his co-mentors, Dr. Robert Reddick, has allowed him additional protected time to pursue his research and train postdoctoral research fellows. Dr. Naski also appreciates the guidance of Dr. Arlan Richardson who has placed many valued resources at Dr. Naski’s disposal. One of those resources is the mouse model of osteoarthritis that Dr. Naski is using in his research.

Dr. Naski says he is convinced that the key to devising effective treatments for osteoarthritis lies in understanding how aging affects cartilage cells. “Osteoarthritis is poorly understood,” he notes, “and there are no treatments that alter the course of the disease. Consequently, there is much need for research in this area. I believe that understanding OA will require a deeper understanding of the aging process.”
Determining the Impact of Back Pain on Physical and Social Disability Among Older Adults

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Weill Medical College of Cornell University
New York, New York

Mentors: Mary Tinetti, M.D.
John Concato, M.D., M.S., M.P.H

For most of his life, Dr. Cary Reid has been interested in caring for the elderly. After initially focusing his career on examining the effect of alcohol use on older patients’ health, he has expanded his research interests to include developing ways to better treat and manage chronic pain in older adults.

Because of its prevalence among older adults, Dr. Reid has chosen to concentrate his investigations on chronic back pain. Although it is generally assumed that back pain leads to disability, it is not well documented in studies of older adults. Further, the risk factors influencing the development of chronic back pain are not well substantiated in older populations. Dr. Reid’s Beeson project is designed to determine two outcomes; whether back pain is a risk factor for disability and; whether psychological factors such as depression and poor coping skills contribute to back pain and increase the risk for subsequent pain-related disability. He also hopes to identify the prevalence and patterns of back pain in older adults. “The goal of my research is to identify risk factors for pain-related disability among older persons,” says Dr. Reid. “In particular, we want to target factors we can do something about.”

The source of data for Dr. Reid’s research is the ongoing Precipitating Events Project (PEP), a three-year longitudinal study of over 700 older persons. After a baseline examination, each participant is questioned monthly regarding recent episodes of injury and pain. Each is asked if and how these incidents have affected his/her usual activities. After analyzing 12 months of data, Dr. Reid has confirmed that symptoms of depression and poor coping skills, both at baseline, increase the risk of an older person developing disabling back pain. He is also working with statisticians to find ways to analyze the PEP data to establish patterns of frequency and distinctive types of back pain among older adults.

To complement his Beeson project, Dr. Reid has begun designing several components for possible intervention. For example, in a 12-week pilot study, Dr. Reid found cognitive-behavioral therapy to be effective, safe, and feasible for older adults suffering from chronic low back pain. He also plans to conduct a 10-week study on the feasibility of a stretching and aerobic program for treating older persons with this pain. His primary goal is to design a form of intervention targeting multiple, modifiable risk factors such as depression and low level of physical activity in an effort to prevent or reduce disability in at-risk older adults.

The Beeson Award gives Dr. Reid the opportunity to spend 75% of his time on his research, mentor two medical students and a geriatrics fellow, pursue collaborations with colleagues, and network with researchers in similar fields. He also receives excellent mentorship from Drs. Tinetti and Concato. These factors are instrumental for Dr. Reid to obtain his goal as an independent investigator.

Dr. Reid recently moved from Yale University to Weill Medical College of Cornell University. His main focus continues to be improving medical care for his elderly patients. “I’m frequently frustrated by the fact that as an internist/geriatrician I do not have the adequate tools to effectively treat pain in older persons,” notes Dr. Reid. “I would like to be able to help contribute to the development of what I think will be effective treatment approaches for chronic pain in older persons.”
Mechanisms of Association Between Depression and Poor Health Outcomes

Mary Whooley, M.D.
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University of California, San Francisco
San Francisco, California

Mentors: Warren Browner, M.D., M.P.H
C. Seth Landefeld, M.D.

Dr. Mary Whooley’s interest in the health consequences of depression in the elderly began during her fellowship training in Clinical Epidemiology at the University of California, San Francisco. Alongside mentor Dr. Warren Browner, Dr. Whooley analyzed data gathered from a long-term study of 10,000 older women. During 6 years of follow-up, she found that depression was associated with poor health outcomes, and in particular, death from cardiovascular disease. However, when researching the existing scientific literature to find out why depression leads to worse health outcomes, Dr. Whooley found that although many potential mechanisms had been suggested, the reasons for these findings were not evident.

“Many previous studies have linked depression to subsequent cardiovascular events, including heart attacks and stroke,” says Dr. Whooley. “But no one has figured out why depression is associated with these poor health outcomes.” Hoping to solve this mystery, Dr. Whooley launched the novel “Heart and Soul Study,” an observational cohort study that is the primary focus of her Beeson Award. This project is designed to determine what factors explain the relation between depression and poor health outcomes in older adults, and Dr. Whooley is collecting data on a host of interesting variables that may contribute to this association.

Dr. Whooley has already completed her plan to enroll 1,000 older patients in the Heart and Soul Study. Each participant has been evaluated for depression, functional status, quality of life, and severity of heart disease. Her baseline assessment has focused on three main groups of factors that have previously been suggested as potential mediators in the relation between depression and heart disease: biological factors, such as elevated levels of certain inflammatory markers and platelet reactivity or “stickiness”; psychosocial factors, such as high levels of anxiety, anger, or low socioeconomic status; and treatment factors—whether patients are taking antidepressants or heart medications, such as aspirin, beta blockers, or ACE inhibitors—that may explain why depression leads to worse health outcomes in older patients.

During the next three years, Dr. Whooley will conduct annual interviews with each participant to record recent medical history, coronary events, depression, and functional status.

Although Dr. Whooley will not have results from the Heart and Soul Study for several years, her baseline data has already proven a gold mine for fellows and residents working with her at UCSF. For example, one fellow has found that elderly people with elevated levels of C-reactive protein, a marker of inflammation, are more likely to have myocardial ischemia. A second fellow has found that, despite its proven usefulness as a diagnostic test for heart failure in patients who have shortness of breath, B-type natriuretic peptide is not a useful diagnostic test in older patients who do not have symptoms of heart failure. Yet another fellow has found that psychosocial factors, including depression, are a greater predictor of perceived quality of life than the severity of heart disease symptoms in older patients with coronary disease.

Aside from enabling her to pursue this huge data collection effort, Dr. Whooley states that the Beeson Award has provided her with tremendous professional support. She cites her mentors, Drs. Browner and Landefeld, as critical sources of guidance in designing her groundbreaking study. Dr. Whooley also notes that the annual Beeson meeting affords her a “fabulous opportunity” to obtain career advice from senior investigators and to establish ongoing contacts with fellow Beeson Scholars.

Dr. Whooley eventually intends to expand her work on depression in older adults. Her plan is to investigate other possible consequences of the condition, such as functional decline and heart failure. But with both depression and cardiovascular disease among the top five chronic disorders afflicting the elderly, any answers Dr. Whooley’s current study can provide may mean a significant difference in quality of life and health for the millions of older adults suffering from these common and serious problems.
Determinants of Cognitive Change and its Outcomes in African-American and White Elders

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One in 10 Americans over age 65 has some form of cognitive impairment, and the risk of developing this condition rises with age. Yet there are few studies investigating what constitutes normal cognitive decline and how age-related cognitive decline varies among ethnic groups. Dr. Kristine Yaffe, a psychiatrist and neurologist with a long-standing interest in diseases of the brain and their effect on cognition, intends to change that. Dr. Yaffe’s research program is aimed at identifying risk factors for cognitive decline and Alzheimer’s disease in the elderly, and specifically to try to identify modifiable risk factors. By designing interventions to reduce or eliminate the impact of certain risk factors, Dr. Yaffe hopes to help the more older adults preserve their independence.

The main focus of Dr. Yaffe’s Beeson project is analysis of data from the ongoing Health, Aging, Body Composition Study (Health ABC) to identify factors that predict cognitive decline in African-American and white elderly adults. Baseline data from the study, now in its sixth year, show that African-American older adults have lower baseline cognitive scores than whites. Most of this discrepancy can be attributed to differences in social factors such as education, income, and health care. Dr. Yaffe will analyze subsequent data to determine whether these baseline scores are linked to different rates of cognitive and/or functional decline.

Dr. Yaffe has also begun her search for risk factors among the Health ABC data. Examining a hypothesis that inflammation may be linked to cognitive decline, she has found that the inflammatory markers IL-6, TNF-alpha, and CRP are associated with an increased risk of cognitive decline, particularly if multiple markers are present. Once collection of the study’s five-year data has been completed, Dr. Yaffe intends to use longitudinal analysis to identify other risk factors for cognitive decline. She also intends to analyze if African Americans and whites show similar rates and patterns of cognitive decline as well as how cognitive decline impacts functional, psychological, and social outcomes in older patients.

Thanks to the generous financial support of the Beeson Award, Dr. Yaffe has also been able to pursue interests in related areas. For example, her research on the relationship between sex hormones and cognitive decline has revealed that higher levels of testosterone in older men are associated with better cognitive function, and that a selective estrogen receptor modulator, raloxifene, may help prevent cognitive decline in older women. In collaboration with Dr. Kenneth Covinsky, a fellow Beeson Scholar, she has also conducted a study of risk factors for nursing home placement in patients with advanced dementia. Results show that the likelihood of a patient being placed in a nursing home depends on the degree of burden on the primary caregiver as well as the severity of the patient’s cognitive impairment and behavioral problems. She has published the results of two of these studies in the Journal of the American Geriatrics Society and the Journal of the American Medical Association.

The respect the Beeson Award commands in the scientific community has opened doors for Dr. Yaffe. She has received an invitation to serve on the Research Committee of the American Association of Geriatric Psychiatry as well as on several NIH study sections. Her career trajectory has also been enhanced by the guidance provided by her mentors. Dr. Seth Landefeld, her primary mentor, has been readily available for discussion, and Dr. Tammy Harris, the leader of the Health ABC study at the National Institute on Aging, has provided Dr. Yaffe with insight on running a large cohort study.

An additional highlight of the Beeson program, says Dr. Yaffe, is the opportunity for clinical researchers such as she to talk with and exchange ideas with basic scientists. “I think we can all learn a lot from each other,” she explains. Dr. Yaffe is also committed to educating future aging researchers. She is currently mentoring geriatrics and epidemiology fellows pursuing projects related to mental health and cognitive decline in older populations.
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<td>In Vivo Magnetic Resonance Microscopy and Alzheimer’s Disease: Defining and Staging the Progression of Alzheimer’s Pathology in Transgenic Mice Overexpressing Beta Amyloid Protein</td>
<td>SUNY Stony Brook Health Sciences Center</td>
</tr>
</tbody>
</table>

### 2000-2002 Scholars

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Research Area</th>
</tr>
</thead>
<tbody>
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<td>Thomas Perls, M.D., M.P.H.</td>
<td>Familiality of Extreme Longevity and Mitochondrial Longevity-Assurance Genes in Centenarian Subjects</td>
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<td>Kerrie Rek, M.D., M.P.H.</td>
<td>Molecular Ophthalmology</td>
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<td>Alvin J. Rosenthal, M.D.</td>
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<tr>
<td>Brian T. Roberts, M.D., M.P.H.</td>
<td>Autoantibodies in Motorneuron Injury in ALS</td>
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<tr>
<td>Charles A. Thornton, M.D.</td>
<td>Pathophysiology of Myotonic Dystrophy: A Progeroid Syndrome</td>
<td>University of Rochester School of Medicine and Dentistry</td>
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The Paul Beeson Physician Faculty Scholars in Aging Research Program is managed by the American Federation for Aging Research (AFAR), a leading, national nonprofit organization dedicated to supporting biomedical research to promote healthier aging. The Annual Meetings have been organized and conducted by the Alliance for Aging Research, a leading citizen advocacy organization for research to improve the health and independence of older Americans. This publication is produced by AFAR and made possible through the generous funding of The John A. Hartford Foundation.

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We would like to thank the Beeson Scholars for reviewing this report for scientific accuracy.