



Paul B. Beeson Career Development
Awards in Aging Research Program

2004 Report Featuring the 2002-2005 Scholars

Tribute to Paul B. Beeson, M.D.

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

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



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Message from Stephanie Lederman

This report chronicles the ninth year of what has been known as the Paul Beeson Physician Faculty Scholars in Aging Research program. In particular, it focuses on the innovative work of the Beeson Scholars who joined the program in 2002 and are now in the middle of their work in the program. As you will also see in the introductory section of this report, there are a number of exciting changes in store. Most notably, we have entered into a dynamic, new public-private partnership with the National Institute on Aging. Starting in 2004, the program will continue as the Paul B. Beeson Career Development Awards in Aging Research program.

We are extremely proud of the growing number of Beeson Scholars. They are an impressive and needed group of talented physician-scientists. Since 1995, we have selected 91 Beeson Scholars from 36 of the nation's top medical schools and research institutions. In little less than a decade, the program has created a powerful and growing leadership network for the field of aging research. With the continued support of the program's public and private sponsors, we look forward to encouraging the potential of these future leaders.



Stephanie Lederman, *Executive Director*
American Federation for Aging Research

New Partners Take on a Continuing Challenge

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

Recognizing these challenges a decade ago, several major philanthropies joined together to launch the

Paul Beeson Physician Faculty Scholars in Aging Research program. Today, the Beeson program continues to make a substantial investment in developing medical faculty so that we can expand our nation's capacity to train physicians in geriatric medicine and conduct aging research. In particular, we support talented physician-scientists whom we trust will devote their careers to advancing our knowledge of the basic mechanisms of aging and effective prevention and management of illness, and who will inspire successive generations of physicians to do the same.

Beeson in Action

The cornerstone of the Beeson program is the provision of significant financial and career development support for outstanding junior faculty committed to academic careers in aging-related research, teaching, and practice. Each year, the program has made as many as 10 three-year, \$450,000 development awards to talented physician-scientists, 91 since the program started.

In addition to providing important financial support, the program requires senior faculty members at the Scholars' institutions to serve as mentors. It also complements this support through "national" mentors who have been chosen from among the

members of the committee that advises the foundations supporting the program. These academic leaders guide Scholars' research and career development, and provide access to organizations, programs, and colleagues helpful to the Scholars' growth and development. The critical role of mentoring is further augmented by an annual conference, which convenes all the Scholars and mentors, as well as other leaders in the field of aging research. And year-round, a Web site (www.beeson.org) enables Scholars (and people throughout the field) to learn about recent developments in the program and follow the research throughout the Beeson network.

Enduring Goals, a New Public Partner

We are pleased to announce that the National Institute on Aging (NIA) has become a new partner in the Beeson program. NIA, whose staff has participated in the Beeson program's annual meetings for a number of years, was interested in modeling a new award for junior faculty career development on key elements in the Beeson program. Meetings of the staff at NIA, The John A. Hartford Foundation, The Atlantic Philanthropies, and the American Federation for Aging Research (AFAR) determined that it was feasible to merge their respective efforts into a strengthened program. The result is a novel public-private partnership in which NIA will provide important leadership and significant funding to the Beeson program. This joint support will ensure the Beeson program's sustainability, while retaining the program's mission, intent, and structure. Beginning in 2004, the program will be called the Paul B. Beeson Career Development Awards in Aging Research program. It will be co-administered by NIA and AFAR, which will be representing the program's Foundation partners (The John A. Hartford Foundation, The Atlantic Philanthropies, and The Starr Foundation).

The Beeson program will continue to:

- Encourage and assist the development of future leaders in the field of aging by supporting faculty members who are early in their careers or who are now poised to establish independent programs in aging research.
- Deepen the commitment of academic medicine to research in aging and the translation of new knowledge into advances in treatment, prevention, and service by involving mentors and Scholars in establishing and advancing Scholars' careers in aging research.
- Expand medical research on aging, broadly defined as including the biology of aging, maintenance of health and independence in old age, diseases and disabilities of old age, and issues in clinical management and systems of care pertaining to elderly patients.

The Paul B. Beeson Career Development Awards program will continue to foster the independent research careers of clinically trained investigators whose research will enhance the health and quality of life of Americans, particularly older people.

Letter from Mary Tinetti, M.D.

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

It is a pleasure and honor to introduce the physician-scientists who make up the eighth group of Beeson Scholars. Once again, we are proud to present an extremely talented group of investigators. As you will read in the coming pages, their research is focused on critically important issues—decision-making at the end of life, the connection between depression and chronic pain, the basic mechanisms of neurological conditions such as Parkinson’s and Huntington’s diseases, and much more. Away from the bench, Scholars are also providing needed leadership. They are driving new programs and initiatives at their institutions. They are spearheading major initiatives and serving in national organizations.

This is not surprising news to anyone who has followed the Beeson program during the last decade. The program remains stable and strong, particularly as it is poised to enter a new phase, having entered into a partnership with the NIA (see page 3). While there is always a certain amount of angst and perhaps even confusion at times of transition, the Program Committee has been heartened by everyone’s cooperation and commitment to fulfilling the mission of the Beeson program. We trust that our work with NIA will produce a model of how the federal government and private funders can collaborate to sustain and grow an important awards program.

Going forward, we hope and trust that the Beeson program’s mission will be sustained. The program should continue to appreciate and reward innovative and even risky research. It should also continue to bring together physician-scientists with a broad range of experience and focus. We must not underestimate how important this multi-disciplinary perspective is to addressing health issues in aging. Finally, the Beeson program should continue to fill an important developmental niche. There are other sources of support for researchers at the beginning of their careers, as well as for those who are well established. The Beeson program catches scientists in that vulnerable period in between, and supports them through to their independence. It is a critical role at a critical juncture.

Looking back at the last year and looking ahead to our new collaboration with NIA, we remain energized, as always, by the important research and the talented leaders who have earned the Beeson award. Their numbers continue to grow, and along with them, our ever-expanding commitment to improving the health and well-being of older people.



Improving Decision-Making About End-of-Life Care and Promoting Earlier Referral to Hospice

Seriously ill older patients often suffer from significant amounts of pain and receive unwanted aggressive care despite the existence of palliative care and hospice programs. Dr. David Casarett, Director of the Philadelphia VA Medical Center's Palliative Medicine service, believes that more can be done to inform patients and their families about the services offered by hospice and palliative care programs.


The prestige of the Beeson Award, says Dr. Casarett, has raised awareness of end-of-life issues in his home institutions, the University of Pennsylvania's School of Medicine and Philadelphia VA Medical Center. "I think palliative care as a research topic had slipped under the radar of a lot of people until I received the Beeson Award," he notes. "This was the first prestigious career development award in end-of-life care awarded to a Penn faculty member, and I think it made people here realize that palliative care is actually a growing, important, and nationally recognized area of research."

The Beeson Award has allowed Dr. Casarett to form collaborations with other Beeson awardees working in end-of-life care or related fields, such as Dr. Terri Fried, primarily through contacts made at the Beeson annual meeting. He has also had the opportunity to formalize his relationship with long-time mentor David Asch and form a new partnership with Beeson mentor Dr. John Trojanowski, Director of the University of Pennsylvania's Institute on Aging. "The combination of Dr. Asch's wealth of methodological expertise and Dr. Trojanowski's strong leadership in aging research at Penn have provided the perfect mentoring environment," Dr. Casarett says. The award also helped Dr. Casarett gain an Advanced Research Career Development Award from the Department of Veterans Affairs, allowing him to devote 80% of his time to research.

The idea for Dr. Casarett's Beeson research was sparked when he and his colleagues noticed that patients and families informed about hospice care were more likely to enroll sooner in a hospice program. To capitalize on this observation, they created a multi-part intervention. This was designed to test whether informing nursing home residents and their families about hospice and working with them to consider their preferences for care would result in

improved palliative care and earlier referrals to hospice programs. "Palliative care and hospice programs have grown to overcome the failures and limitations of the current health care system, which we know does a poor job of handling end-of-life care," Dr. Casarett says. "If by eliciting people's preferences we can get people into comfort care sooner, we will wind up with a better quality of dying at the end of life."

Dr. Casarett originally designed his Beeson-supported intervention in three parts, to be tested with patients making outpatient visits to a geriatric clinic. Some patients would receive a brief overview of available palliative and hospice care. Others would receive that overview plus a discussion of their preferences and evaluation of their ability to make decisions. A third group would receive both the interventions, plus a presentation about hospice and palliative care using visual aids designed to increase understanding about these care options. However, pilot testing led Dr. Casarett to simplify the intervention in a number of important ways. First, because implementation in clinics resulted in a small number of primary care physicians making treatment decisions for older patients, the study was relocated to nursing homes to allow an analysis of provider effects. Second, preliminary testing indicated that the visual aids increased the intervention's complexity without improving patient comprehension. The visual aids were eliminated, and instead, all patients getting the intervention also received an overview of hospice and palliative care combined with preference discussion and a decision-making evaluation. The PRIDE study (Promoting Residents' Involvement in Decisions at End of Life) began recruiting in June of 2003.

To date, Dr. Casarett has already interviewed more than 130 residents and/or their families at five participating nursing homes and expects to enroll 600 residents, along with their families, by the end of the study. Residents and their families are randomly assigned to receive either usual care or the intervention. In addition to determining whether or not the intervention does indeed increase rates of referral to hospice care, Dr. Casarett hopes to use the study to identify subgroups of older patients who could most benefit from the intervention. 

In Vitro and In Vivo Models of Synucleinopathies

As a young man, Dr. James Galvin watched the slow, years-long decline of his grandfather after he developed Parkinson's disease. After losing much of his ability to move, the older man developed dementia, which affects about one-third of Parkinson's patients. As Dr. Galvin made his way through his medical training, this personal experience helped to stimulate his interest in the neurological disorders of aging. Today, much of his work is clinical in nature, including seeing demented patients, heading Washington University's memory disorder clinics, and conducting clinical research on cognitive screening and social attitudes toward dementia.

However, Dr. Galvin never forgot his initial interest in Parkinson's disease, which is characterized by the accumulation of filamentous alpha-synuclein (AS) protein aggregates called Lewy bodies in certain areas of the brain. He believes that Lewy body disorders, which are the second most common cause of dementia, are under-researched. He hopes to discover what effects Lewy bodies have on neurons and why AS aggregates in the first place.

"The overall goal is to understand the mechanisms whereby Lewy bodies form, so you can potentially find a cure for the disease," says Dr. Galvin. "But first, you need to develop tools so you can do truly hypothesis-driven research." The tools, in this case, are cell lines and mice that develop AS protein aggregates like Lewy bodies, allowing researchers to test different hypotheses. Although some cell and animal models exist that express an abnormally high amount of alpha-synuclein, there are only a few models that actually form filamentous AS protein aggregates. Creating and improving on such models is the first step of Dr. Galvin's Beeson research.

To create an improved cell line model of Lewy body disease, Dr. Galvin plans to add a mutant type of AS prone to aggregation, A53T, to a neuronal cell line. This cell line will also include a biochemical "switch" that will allow researchers to turn AS expression on and off. Once experiments with the neuronal cell line are complete, Dr. Galvin hopes to create a similar model using neuron cells from mice whose AS gene has been turned off, or "knocked out."

These AS knockout mice will also form the basis of Dr. Galvin's new mouse model of Lewy body disease. Instead of expressing murine AS, the mice will overexpress human mutant A53T AS, as well as other substances that will encourage excess AS to aggregate in the areas of the brain typically affected by Parkinson's disease. Dr. Galvin hopes that creation of improved models of Lewy body disease will enable him and other scientists not only to determine the consequences of Lewy body aggregation, but also to tease out the underlying mechanism causing this aggregation.

Dr. Galvin's research efforts have been greatly aided by the Beeson Award. In addition to gaining his own research lab, he also obtained an appointment in the Departments of Anatomy and Neurobiology, improving his access to graduate students for his laboratory work. This has given him opportunities to mentor junior faculty and train more medical and graduate students. His Beeson research has also led to the publication of papers in the *Archives of Neurology* and *Neurochemical Research*, as well as a book chapter on dementia in Parkinson's and Lewy body disease. "The Beeson Award has given me the protected time and resources to really develop my lab, which is now bigger, to a fuller extent," says Dr. Galvin. "It has also given me the opportunity to network with other awardees and potentially find projects in common, and to make those important career development connections that help everyone." ➤

Functions of the Werner Syndrome Family of Proteins in Telomerase-Deficient Mice and Yeast

Researchers interested in probing the biology of aging are drawn to Werner syndrome, a rare genetic defect that causes premature aging in young adulthood. Dr. Brad Johnson has been interested in aging since enjoying childhood conversations with his centenarian great-grandmother. He believes that Werner syndrome provides an excellent vehicle for examining the role of telomeres in aging biology.


Telomeres are repeating DNA strands capping the ends of chromosomes. When a human cell divides and reproduces, its telomeres shorten. Eventually, when a cell's telomeres reach a critically short length, the cell can no longer reproduce. It enters a non-dividing state called senescence. In cell culture, the telomeres of Werner syndrome cells, which lack the Werner protein, dwindle more rapidly than those of normal cells, and they reach senescence sooner.

"Right now," explains Dr. Johnson, "we know that telomere shortening leads to changes in cell function in the culture dish and that telomeres shorten inside of intact people. What isn't clear is whether telomere shortening is really causing age-associated pathology in humans. If we can establish a clear role for the Werner protein in telomere maintenance, that will provide some indication of what role telomeres may play in the aging process."

As part of his Beeson research, Dr. Johnson is investigating the effects a missing Werner (WRN) gene and a related gene called BLM have on the phenotype and telomeres of mice. Dr. Johnson crossed mice lacking telomerase with mice with mutations in WRN and BLM. Mice with telomerase mutations alone show impairments such as small body mass, higher levels of cell death, chromosome problems, and atrophy of the testes by the sixth or seventh generation after loss of telomerase. Mice mutants for WRN and BLM alone show few problems, but mice mutant for telomerase, WRN, and BLM develop severe defects as soon as the third or fourth generation. This supports Dr. Johnson's hypothesis that the Werner and Bloom proteins become particularly important as telomeres shorten. Dr. Johnson is currently examining the cells of these mice to characterize their telomere damage.

Work in yeast cells is allowing Dr. Johnson to further analyze the function of the Werner protein. Yeast cells contain a homologue, or equivalent, to the WRN protein called SGS1. Dr. Johnson has gathered evidence that SGS1 is involved in a process of telomere maintenance called recombination, in which short telomeres copy longer telomeres to lengthen themselves. Work from several labs has shown that this process allows some cells to survive senescence. Dr. Johnson has identified several areas of SGS1 required to prevent cells from rapidly senescing as they do in Werner syndrome. Eventually, Dr. Johnson hopes to identify rare mutations or overexpressed genes that allow cells to survive senescence when all of the known telomere repair pathways are eliminated. Finding such genes, he says, might allow scientists to manipulate them, either turning them on to repair telomeres and reverse age-associated pathology, or turning them off to prevent cancer cells from surviving through these pathways.

Dr. Johnson has enjoyed the opportunities provided by the Beeson meetings to broaden his interest in and knowledge about aging research and aging issues. He is working to expose medical students to such issues by co-organizing a new aging overview course at the University of Pennsylvania School of Medicine. "This is something that I think is becoming increasingly important and interesting to people in academic institutions," says Dr. Johnson. "Medical students need to learn about the biology of aging because a growing proportion of our population is elderly."

The Beeson Award has given a major boost to Dr. Johnson's research, allowing him to pursue higher risk experiments and attract postdoctoral students to his laboratory. Since receiving the award, he has presented abstracts of his work at meetings at Cold Spring Harbor Laboratory and given several invited talks on Werner syndrome and telomere biology at the University of Washington, Swarthmore College, and the International Workshop on Werner Syndrome, among others. Dr. Johnson expects to continue focusing his research on solving basic questions about the biology of aging. He hopes to one day become involved in translating findings from laboratory work into therapies that could help older adults combat the diseases of aging. 

Development of Therapies for Polyglutamine Neurodegeneration and Related Disorders


Alzheimer's disease is only one of many neurodegenerative disorders. One subset of these neurodegenerative disorders are referred to as the polyglutamine repeat diseases due to their abnormally long sequences of the amino acid glutamine. The most well-known example is Huntington's disease. Like most other neurodegenerative diseases, including Alzheimer's and Parkinson's, polyglutamine repeat disorders also feature misfolded protein fragments that accumulate in the brain, damaging neurons.

By studying a mouse model of spinocerebellar ataxia type 7 (SCA7), a rare polyglutamine repeat disease, Dr. Albert La Spada hopes to learn more about the mechanisms by which proteins become misfolded, how select groups of neurons die in neurodegenerative disorders, and how therapeutic agents can correct these problems. SCA7, unlike most other neurodegenerative diseases, causes visual deterioration, allowing researchers to track deterioration in the relatively simple context of the retina.

Dr. La Spada is attacking the disease on several fronts. In SCA7, certain genes fail to express properly due to a failure in the system that copies DNA information to RNA. Dr. La Spada has narrowed this failure down to the disease's interference with a group of enzymes called histone acetyltransferases, which play an important role in allowing DNA to be transcribed into RNA. In order to combat this problem, Dr. La Spada plans to introduce compounds called histone deacetylase inhibitors (HDAC I's) into the cerebrospinal fluid of SCA7 mice.

Dr. La Spada's second therapeutic strategy holds the widest application to most neurodegenerative diseases: refolding aberrant proteins so they can be cleared normally, avoiding toxic accumulation. Heat shock protein 70 is his first candidate, as it is believed to refold polyglutamine peptides. He intends to deliver the therapy via a subretinal injection, and has refined the technique so the gene therapy can be delivered to young mice, giving it time to take hold before the disease can develop. He also continues to monitor the latest research in order to identify potential therapeutic compounds, and plans to test cannabinoids as a possible therapy for both SCA7 and Huntington's disease.

The Beeson Award has bolstered Dr. La Spada's career in numerous, concrete ways, leading to more laboratory space and a growing staff of promising postdoctoral fellows. He has published several papers and a book chapter since 2002, as well as two reviews in the journal *Neuron*. One of his most recent original publications was the cover feature of the January 1, 2004, issue of the journal *Human Molecular Genetics*. In the March 4, 2004, issue of the journal *Neuron*, Dr. La Spada was the senior author of an article that reported reduction of a growth factor as an early event in spinal and bulbar muscular atrophy, a motor neuron disease. He has also presented his work on numerous occasions, such as at the 2002 meeting of the American Society of Human Genetics and in seminars at the Buck Institute for Aging, Emory University, and UCLA Medical Center. Of particular note, Dr. La Spada was a featured speaker in the Spinocerebellar Ataxia session at the 2nd Gordon Conference on CAG Repeat Disorders held in Barga, Italy in 2003 and at the 4th International Conference on Unstable Repeats and Human Disease.

In addition, Dr. La Spada is impressed by the Beeson's intangible benefits, particularly the Beeson meetings. He believes that the fundraising, media relations, and leadership workshops he attended at the meetings will prove very helpful as he works to develop the Center for Neurogenetics and Neurotherapeutics at the University of Washington, of which he was recently named Director. The Beeson meetings have also given Dr. La Spada an "appreciation of the aging problem as a compelling intellectual pursuit. Before the Beeson Award, I had not carefully or critically thought about how neurodegeneration was linked to aging. Now, I see that there are lines of investigation in neurodegeneration and aging that come together nicely." As a result, with assistance from his mentor Dr. Bird, Dr. La Spada's lab has been increasingly focusing on neurodegenerative diseases more specific to old age, such as Lewy body dementia and Parkinson's disease. 

Mitochondrial DNA Mutations in Aging and Alzheimer's Disease

Many researchers believe that oxidative damage within our cells, caused by byproducts of normal metabolism, is a primary contributor to aging and age-associated disease. Neurologist Dr. Michael Lin, introduced to the importance of mitochondrial dysfunction by his current Beeson mentor Dr. M. Flint Beal, is interested in determining if oxidative damage to mitochondria is a significant contributor to age-associated changes and the most well-known neurodegenerative disease, Alzheimer's.


The generous financial support provided by the Beeson Award has enabled Dr. Lin to hire more staff and increase the productivity of his laboratory. He has recently published papers in *Experimental Neurology* and *Neurobiology of Aging*, among other journals. Yet he sees the other benefits of the Beeson Award as being just as valuable as financial support, namely, the networking opportunities it offers. "I enjoy meeting other researchers at the Beeson meeting, where we can share common interests and get ideas," he comments. "And there are people here at Cornell I probably would not have met without the Beeson Award, some of whom I am now collaborating with." He also credits the award with injecting a new emphasis on aging into his research.

Dr. Lin is keenly interested in introducing students to neurology and geriatrics. In 2003, he received the Neurology Department's Fred Plum Award for excellence in graduate staff teaching and mentoring. He has mentored several Samuels/AFAR medical student scholars, teaches a neurology course in the medical school, and is involved in organizing the neurology resident core curriculum. He also continues his clinical practice through weekly visits with patients in the Memory Disorders unit as well as an annual month-long stint on the neurology consult service.

At the bench, Dr. Lin found a compelling link between mitochondrial mutations and neurodegenerative disease in a preliminary study comparing the mitochondrial mutation burden of subjects carrying two ApoE4 alleles to those carrying none or one. The ApoE4 gene is associated with a greater prevalence of Alzheimer's disease and accelerated age-related cognitive decline. He found that subjects with two ApoE4 alleles had significantly more mutations in mitochondrial DNA (mtDNA) than subjects with only one or no ApoE4 genes.

Hoping to identify how mutation burden affects mitochondrial function, Dr. Lin created cell hybrids, called cybrids, by removing the mtDNA from cells and replacing it with the well-characterized mtDNA from his ApoE4 experiments. Surprisingly, he found no differences in mitochondrial respiratory activity between cybrids with high levels of mtDNA mutations and those with low levels. These results imply that although mtDNA mutations rise with age, they may not be a cause of age-related decline.

On the other hand, Dr. Lin has found links between oxidative damage and accumulation of beta-amyloid, the abnormal protein responsible for forming damaging plaques in the brains of Alzheimer's patients. Dr. Lin crossed APP mice, an Alzheimer's disease model which manufactures beta-amyloid, with mice that have a reduced amount of an important mitochondrial antioxidant, MnSOD. Compared to APP mice with MnSOD production intact, APP mice missing MnSOD had significantly greater amounts of beta-amyloid plaques in their brains at four months of age.

As his next step, Dr. Lin plans to conduct a feeding study of young APP mice to determine whether dietary antioxidants can delay plaque accumulation. He also plans to test if APP mice that overexpress MnSOD accumulate less plaque than APP mice with normal MnSOD production. "This research suggests that we could try boosting antioxidant capacity in people before they develop Alzheimer's disease, perhaps through diet or vitamin supplements," Dr. Lin explains. "Even if that doesn't cure Alzheimer's, just putting off the disease by five years could have a huge epidemiological impact." 

Oxidative Stress and Telomere Maintenance: *In Vitro* and *in Vivo* Studies

Dr. Robert Marciniak, trained in hematology/oncology but primarily conducting research in the biology of aging, is using his Beeson Award to explore a fundamental question in molecular gerontology: why do we age?

Two current theories include the “oxidative damage” theory, which proposes that aging is primarily due to the damaging effects of oxygen free radicals on our cells; and the “telomere” theory, which holds that aging is a result of a reduction during cell division in the length of chromosome-capping DNA sequences called telomeres. As telomeres become shorter, a cell loses function and eventually stops dividing, reaching a state called senescence.


Dr. Marciniak believes that these theories are not mutually exclusive. “As we continue to learn, we will find more and more that these are not independent processes,” he says. “I’m looking at the effect of oxidative damage on telomere sequence loss and how this may contribute to age-related changes in humans.”

A possible key to the unification of the two theories is Werner syndrome, a rare premature aging syndrome linked to a genetic defect. Persons with Werner syndrome show signs of aging, such as wrinkled skin, arthritis, and heart disease, in adolescence or early adulthood. In the laboratory, Werner cells show an increased rate of telomere shortening and reach senescence sooner than normal cells. Dr. Marciniak suspects this is because Werner cells are more susceptible to oxidative damage than normal cells, perhaps because the protein missing in Werner syndrome is vital to the repair of damaged telomeres. Exposing normal and Werner cells to hydrogen peroxide, which increases oxidative stress, Dr. Marciniak found that the Werner cells are indeed more sensitive to oxidative stress than normal cells, although this difference is only observed when the cells are not growing. This sensitivity difference vanishes when the cells are treated with telomerase, which regrows telomeres, suggesting that telomere shortening is responsible for the Werner cells’ increased sensitivity.

To test his hypotheses *in vivo*, Dr. Marciniak is breeding several types of mice. Using mice that cannot produce telomerase, he is creating mice that additionally lack the

Werner protein and/or who undergo higher levels of oxidative stress due to a mutation of the gene that produces superoxide dismutase (SOD), an antioxidant. He expects the Werner variants to experience increased rates of telomere sequence loss, with those rates being particularly high in mice that also have an SOD mutation. In the meantime, he has been refining available technology to yield more precise measurements of telomere length.

Dr. Marciniak hopes his experiments will not only yield insights into the nature and function of the Werner protein, but also illuminate the influence of oxidative stress on the rate of telomere loss in humans. The work could even lay the foundation for eventual therapeutic treatments to combat aging. “If telomeres are lost simply due to end replication, we are unlikely to be able to improve upon that,” he notes. “But if telomere loss is due to DNA damage, then we might be able to intervene.” Dr. Marciniak has presented abstracts of his findings at several meetings on the genetics and biology of aging.

The Beeson Award, says Dr. Marciniak, has smoothed his transition from junior investigator to full independence, enabling him to apply for and receive additional funding from the NIA and the Veterans Administration. This transition has also been greatly aided by his mentors. Dr. Hornsby offers weekly advice, and Dr. Richardson helped him obtain the telomerase knockout mice he needed to pursue his experiments. In addition to his research, Dr. Marciniak remains active in hematology/oncology as Assistant Chief of the Division of Medical Oncology and as Co-Director of the University of Texas Health Science Center’s Geriatric Clinical Oncology Training Program. There he helps train clinician-scientists, not only to treat elderly cancer patients, but also to design and implement much-needed clinical trials involving older patients. 

Lifespan Extension of Vascular Cells for Tissue Engineering

Each year, more than one million older Americans improve their health via coronary artery bypass surgery, in which doctors take a vein from elsewhere in a patient's body and transplant it into the heart to bypass a blocked artery. However, says Dr. Laura Niklason, "there are probably about 100,000 patients a year who wish they could have a bypass, but who don't have enough replacement vessel of their own to undergo the procedure." To help these patients, most of whom are older, Dr. Niklason has been working on techniques for growing replacement arteries in the laboratory from the patients' own vascular cells.

Dr. Niklason has already made great strides. In 1999, she published a groundbreaking article in *Science* detailing her success in growing arteries from bovine vascular cells. In 2001, she was named by *U.S. News & World Report* as one of 21 Innovators for the 21st century for her work in tissue engineering. However, she found that while she could grow blood vessels from human neonatal cells with relative ease, older cells could not divide enough times in cell culture to create adequate blood vessels, due to the biological cap on the number of times a cell can divide in its lifetime. She theorized that adding telomerase, which allows cells to divide indefinitely, would allow formation of usable vessels.

The technique is potentially risky. Telomerase is believed to be a major contributor to cancer because it allows mutated cells to divide unchecked. Adding telomerase to the vascular cells could promote tumor growth. Dr. Niklason believes that cancer in these blood vessels is unlikely, for two reasons. First, telomerase cannot cause cancer on its own. Mutated cells must already be present for cancer to occur. Second, cancer in the vascular smooth muscle cells used for these experiments is exceedingly rare, implying that cancer-causing mutations in these cells are equally rare.

Dr. Niklason first tested the procedure in cells from a two-year-old child, as they were unlikely to harbor any mutations. She found that cells treated with telomerase did indeed continue to divide indefinitely and showed no changes as compared to untreated control cells. The treated cells formed much thicker, stronger blood vessels than the untreated cells. These results were published in *EMBO Reports* in June 2003. Dr. Niklason is now repeating this

experiment using cells from older donors. In nine cell lines studied so far, she has found that older cells treated with telomerase grow robustly in culture and show no mutations or changes in function as compared to older control cells. The treated cells also seem to form stronger blood vessels than those grown from elderly control cells, as expected. Dr. Niklason will continue to carefully screen the cells for potential tumor-causing changes. She hopes to collect cells from 100 different older donors to improve her chances of detecting rare mutations.

Due to the controversial use of telomerase in this project, Dr. Niklason believes she would not have received funding from other sources. "If I hadn't received the Beeson Award, I probably couldn't have done this work at all," she says. "The Beeson Award has had a huge impact on what I've been able to do scientifically on this project." She cites her mentors, Drs. Friedman and Cohen, as instrumental in making sure she has protected time to run her laboratory, which currently employs 14 people. These include medical students and junior faculty, to whom she offers mentoring, advice, and assistance with grant preparation.

Dr. Niklason enjoys attending the Beeson meetings and notes that their focus on aging provides her with unexpected insights into her own work. She retains a commitment to developing treatments that will provide a tangible benefit for the elderly. She also remains in contact with older patients by running the Duke University Medical Center's surgical Intensive Care Unit for one week out of five throughout the year. ➤

Sorting Out Clues to Parkinson's Disease: Caffeine, Postmenopausal Estrogen, and Addiction

Epidemiological studies are increasingly linking the risk of Parkinson's disease (PD), which affects 3% of Americans over age 65, with chemicals in the environment. While certain chemicals, such as pesticides, may increase the risk of PD, certain habit-forming substances, such as caffeine and nicotine, seem to be associated with a decrease in Parkinson's risk in men. Dr. Michael Schwarzschild, who has dedicated his career to the study of PD and other age-related neurological diseases, is currently investigating the link between these "addictive" substances and a reduced risk of PD, with a focus on caffeine.

In preliminary experiments with mice afflicted with dopamine neuron injuries through the use of the neurotoxin MPTP, thereby mimicking PD, Dr. Schwarzschild and his colleagues showed that caffeine seems to reduce dopamine neuron injury by blocking the activity of receptors for adenosine, a neuromodulator. Other adenosine receptor antagonists are currently undergoing clinical trials for treatment of movement disorders in later stage PD, with positive results thus far. Dr. Schwarzschild believes his work could expand the utility of these drugs. "If we can show that blocking the receptor can also prevent cell death, this would be an argument for also using these drugs in early-stage disease," he explains.

To further explore the interactions between caffeine and other adenosine receptor antagonists and PD, Dr. Schwarzschild's research group repeated the experiments with caffeine in a different mouse model of PD, created by application of the pesticides maneb and paraquat. They are currently analyzing the mouse brains and expect results shortly. In a second set of experiments, Dr. Schwarzschild's laboratory examined the effect of estrogen on the neuroprotection provided by caffeine to explore the rationale behind why epidemiological studies show an apparent association between caffeine and reduced PD risk only in men. Experimenting on ovariectomized MPTP mice, they found that adding estrogen reduced the neuroprotective effect of caffeine.

In a third line of investigation, Dr. Schwarzschild is exploring the possibility that the relationship between addictive substances and reduced PD risk is not causal, but rather mediated by a genetic factor that may independently

lessen the likelihood of using addictive substances while increasing the risk of PD, or vice versa.

Dr. Schwarzschild describes this last area of investigation as "tricky." "This is the most high-risk arm of my research project," he says. "These are expensive, long, demanding experiments. I wouldn't have funding for them if it weren't for the Beeson Award." The Beeson Award has also had a significant impact on Dr. Schwarzschild's career. During the first year of the award, he received a promotion to Associate Professor and a 50% increase in laboratory space. In addition, the Beeson annual meeting has led him to focus more on aging, from using older mouse models in his research to forming partnerships with other investigators in aging research.

Despite his increased research responsibilities, Dr. Schwarzschild remains committed to teaching. He is training two postdoctoral research fellows in his laboratory, co-organizes the Neurology Department's neuroscience seminar series, and mentors young people interested in science careers. He also dedicates one day a week to seeing Parkinson's patients in his movement disorders clinic. He credits this clinical work with inspiring his laboratory studies. ➤

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Improving Care for Chronic Pain and Late Life Depression

When he began his psychiatry residency, Dr. Jürgen Unützer thought he wanted to become a child psychiatrist. After a six-month stint in a geriatric psychiatry inpatient unit, he changed his mind. “I just fell in love with working in that setting and with that population. I like the overlap between mental and physical disorders that you find in older adults. I find it clinically challenging.”

That interplay between physical and mental ailments in older adults is precisely what Dr. Unützer hopes to address with his Beeson project. He is working to devise an intervention that would more effectively manage treatment for older patients suffering from depression and chronic pain, which are among the most common health problems affecting older persons. The two conditions are interrelated, often exacerbating each other and leading to increased functional disability. Unfortunately, both depression and chronic pain are often under-diagnosed and under-treated in this population.

The Beeson Award has already helped bring Dr. Unützer national recognition for his work. Since receiving the award, he has been invited to participate on advisory boards for two NIH-funded research centers, serve as program chair for the 2004 meeting of the American Association of Geriatric Psychiatry, and join an NIH panel on cancer symptom management. He has been able to meet and forge collaborations with other leading geriatricians and geriatric psychiatrists.

The award also led to a promotion to full professor and a change of employment for Dr. Unützer, who moved from UCLA to the University of Washington in October 2003. In addition to his research, he directs Psychiatric Services at the University of Washington Medical Center, a program that tries to improve access to mental health care by making mental health professionals available in primary care and medical specialty clinics. Dr. Unützer also hopes to further improve care management for the elderly by developing the first national fellowship program in geriatric mental health services research. “I think we actually have pretty good treatments for many of the disorders the elderly are faced with,” he points out. “What we need to do is organize our care system so we can use the treatments we already know about more effectively.”

Dr. Unützer’s planned Beeson intervention builds on the IMPACT study, which tested the effectiveness of a collaborative care intervention for depression in eight different health care organizations. The results, published in the December 11, 2002, issue of the *Journal of the American Medical Association*, showed that older adults who were treated by a team including a care manager and psychiatrist, in addition to their primary care physician, reported twice as much improvement in their depressive symptoms and quality of life as study participants receiving usual care.

Over half of the IMPACT study participants suffered from chronic pain, and further analysis of the IMPACT data has yielded valuable information on chronic pain in elderly depressed patients. Dr. Unützer and colleagues found that although the IMPACT intervention did not specifically target pain, older adults who received the intervention reported a reduction in the severity of their pain as well as improvement in physical function. These results were published in the November 12, 2003, issue of the *Journal of the American Medical Association*. Dr. Unützer also found that care for chronic pain varies widely, with up to five-fold differences in analgesic use across the eight health care organizations that participated in the study. These results, he notes, suggest tremendous opportunity for standardizing and improving care for chronic pain in older adults.

Like the IMPACT study, the new pain intervention supported by the Beeson Award will feature a team treatment approach, including a trained nurse care manager, the patient’s primary care provider, and consulting specialists in psychiatry and pain management. Components of care will include systematic use of medication, counseling, behavior modification such as exercise, and problem-solving. The intervention will be pilot-tested in the Fall of 2004, and if successful, will be tested in a wide range of health organizations. ➤

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Between 1994 and 2003, the Paul Beeson Physician Faculty Scholars in Aging Research Program was managed by the American Federation for Aging Research (AFAR), a leading nonprofit organization dedicated to supporting biomedical research to promote healthier aging. The Annual Meetings were 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 generous funding from The John A. Hartford Foundation.

Beginning in 2004, the program will be called the Paul B. Beeson Career Development Awards in Aging Research Program. It will be co-administered by the National Institute on Aging and AFAR, which will be representing the program's Foundation partners, including The John A. Hartford Foundation, The Atlantic Philanthropies, and The Starr Foundation.

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