



Paul B. Beeson
Career Development Awards
In Aging Research Program

2011 Report

Featuring the 2009 Scholars

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

About Paul B. Beeson, MD (1908-2005)



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

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

To date, 170 physician-scientists throughout the United States and the Island of Ireland have emerged as leaders in the field, changing the landscape of geriatric medicine and aging research. They serve as a testament to his enduring legacy, not only providing the best possible care for older adults, but also taking on the charge to train the next generation of leaders.

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Message from Stephanie Lederman

Executive Director, American Federation for Aging Research



Stephanie Lederman

The Paul B. Beeson Career Development Awards in Aging Research Program, now in its 16th year, has come to exemplify one of the most successful public-private partnerships in aging research, teaching, and clinical practice.

To be a Beeson Scholar is to join a prestigious group of emerging leaders who are improving the care of older adults and adding new

knowledge about age-related diseases and disorders. Their work is increasing our understanding of the basic mechanisms underlying age-related diseases and disorders, opening the door for potential drug trials and clinical interventions. Their work is changing the landscape of how we treat the clinical and social needs of older adults, whether it is identifying how exercise and depression affect long-term health and implementing new tools to combat it, challenging long-held assumptions that exclude older patients from clinical trials, or exposing the alarming rise of elder abuse.

Beeson Scholars are also influencing patient treatment decisions and their research findings are adding to the discourse about healthcare reform, healthcare access, public health, and health policy.

The 2009 Scholars, whose work we are highlighting and celebrating in this year's report, are studying ways to develop age- and disease-specific treatment protocols, identify new strategies to protect against neurodegenerative diseases, and reduce the high incidence of hospital-acquired infections in older adults. They are also looking at seemingly unrelated conditions such as heart disease and its impact on falls and cognitive function.

We thank our sponsors for supporting such work and that of the many other Scholars and we welcome new partners to join us to ensure that more researchers can benefit from all that is Beeson.



Stephanie Lederman

“To be a Beeson Scholar is to join a prestigious group of emerging leaders.”

Letter from Edward H. Koo, MD

Chair of the Program Advisory Committee



Edward Koo

As part of the first group of Beeson Scholars, it has been very gratifying to witness the success of the Beeson program and the leadership roles Beeson Scholars have assumed in academic medicine and aging research. This significant network of top physician-researchers with diverse and complementary interests has advanced knowledge in a broad area of scientific investigation — from

the molecular to the societal — that will impact the health and well-being of our nation's unprecedented number of older adults.

Our Scholars do not work in a vacuum. They are collaborating with their peers across multiple disciplines and educating and mentoring the next generation of leaders in geriatric medicine and aging research.

The program has remained resilient and strong despite the enormous changes that have taken place during the last two decades and the challenges affecting our healthcare system and the new funding environment.

It takes time and resources for junior faculty to establish independent research programs while meeting clinical and administrative responsibilities. Yet grant funding is more limited and there is a great deal more competition to obtain funding. These promising researchers are spending an ever increasing portion of their time seeking and writing grants, curtailing their ability to study, conduct research, and elicit new discoveries that will go from the lab to the clinic.

The strength of the Beeson award is that it provides significant financial and career development support, the latter through the annual meeting of present and former Beeson Scholars and their mentors. This allows Scholars to establish research platforms, initiate new research projects, and meet and interact with others who will not only help advance their careers by providing a launch pad for obtaining long-term extramural funding but also advance the field. An example of the success of the Beeson program — especially since this has become a joint NIH-private foundation joint venture — is that Beeson Scholars are able to convert their K08 or K23 Beeson awards to R01 grants at a much higher rate than other K award grantees. However, these are challenging times for the various funding agencies and I hope this novel and highly successful program will continue for years to come.

I am encouraged by the enormous commitment and contributions of the Beeson Scholars and the work of the 2009 awardees that is already in progress. And I am honored and pleased to introduce them.

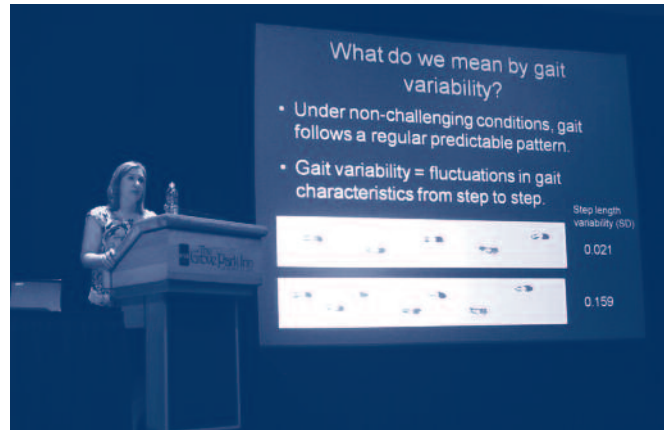


Edward H. Koo

Beeson History

To understand the enormous influence of the Beeson program is to know its history. When it was created in 1994, the field of geriatric medicine and aging research was not one that many physicians and scientists were encouraged to pursue. Medical school curricula did not put a great emphasis on training the next generation of physicians to care for what was going to be a burgeoning aging population. And there were few leaders to mentor early-career clinicians and researchers.

A 1993 report from the Institute of Medicine (IOM) highlighting the need for more physicians trained in geriatrics spurred the creation of what is now called the Paul B. Beeson Career Development Awards in Aging Research Program. Starting in 1994 with funding from The John A. Hartford Foundation, The Atlantic Philanthropies, and The Commonwealth Fund, the program has grown to be one of the largest and most successful public-private partnerships supporting development of leaders in aging



research and geriatric medicine. In 1999 The Starr Foundation joined the partnership and an anonymous donor joined in 2004. With the addition of the National Institute on Aging, also in 2004, and of more recent partners the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke, the Beeson program has benefited some 170 junior investigators to date.



Beeson Scholars are learning about and taking a larger role in advocacy and outreach efforts to inform and influence leaders, policymakers, and the public about the need for more support of aging research.



In addition, The Atlantic Philanthropies provided support from 2007-2009 for an expansion of the program to the Island of Ireland, bringing the benefits of the Beeson Program to the Republic of Ireland and Northern Ireland and supporting the academic careers of 5 additional Scholars.

Two decades later in its 2008 report, *Retooling for an Aging America: Building the Health Care Workforce*, the IOM once again sounded the alarm that the nation was woefully unprepared to care for the growing aging population. The difference is that the age shift has arrived. The number of older adults — with multiple and complex needs — is growing faster than the number of physicians and other healthcare providers trained in geriatric medicine and gerontology. Approximately 37 million Americans are 65 and older. By 2030, it will grow to more than 71 million, accounting for nearly 20% of the population.

Benefits of Beeson

The Beeson Award has helped drive interest in geriatric medicine and aging research by attracting top physician-scientists who are not only expanding knowledge in the field but who are in turn mentoring others. Many successful collaborations among Scholars from multiple disciplines have resulted from the wealth of networking opportunities the grant provides, from the annual meetings to the Beeson website (www.beeson.org).

Most Beeson Scholars would attest to the tremendous value of the annual meeting, which is a cornerstone of the program. For example, Dr. E. Wesley Ely, a critical care specialist from Vanderbilt University Medical Center and Dr. Malaz Boustani, a geriatrician from Indiana University Center for Aging Research, first met at a Beeson annual meeting and realized that they had a shared interest in preventing delirium and its long-term effects, particularly delirium that results from stays in the intensive care unit (ICU). Their work has resulted in new treatment models being put into practice in hospitals worldwide and the creation of a new medical society — see page 5. Another example of collaboration among Beeson Scholars is that of Drs. Laura Dugan and Jeremy Walston. They developed an inflammation and cognition project which was funded and is showing promising results in initial data development.

Taking on New Roles — Advocacy and Outreach

As the political climate is changing, there is a greater need to be heard. Beeson Scholars are learning about and taking a larger role in advocacy and outreach efforts to inform and influence leaders, policymakers, and the public about the need for more support of aging research.

AFAR will establish an Outreach Fund which will provide resources to the Scholars for a range of activities to bring the issues of aging and age-related diseases and conditions to the forefront of their institutions, specialty associations, and beyond. For example, Scholars and alumni can request funds to establish or support an Aging Task Force/Special Interest Group, invite a visiting professor to come to their



institution, or organize symposia with an aging focus at specialty meetings and other societies, allowing them to present their Beeson-supported research findings and other activities to increase the visibility of aging research.

“The Beeson Scholars are powerful, strong, and becoming increasingly influential,” says Corinne Rieder, executive director of The John A. Hartford Foundation. “Their presence is widely felt in academic, clinical, and political



circles. They have helped build and promote the field of aging research and geriatric medicine far beyond peers who share common interests and goals. And they have created an excitement not just in the scientific community but the larger public.”

The Basics of Beeson

Each year, as many as ten clinically-trained researchers are awarded a Beeson grant of \$600,000-\$800,000, covering three to five years for protected time in aging-related research.

Selecting Scholars from the top medical schools and research institutions, the program invests in developing medical faculty in order to expand the nation’s capacity to train physicians in geriatric medicine and conduct research on aging. The award is often life and career-changing. Many Beeson Scholars go on to devote their careers to advancing progress in the basic mechanisms of aging and effective prevention and management of illnesses, and serve as role models for future generations of physicians.



Scholars report that the following features of the Beeson Program have been most helpful in advancing their careers:

- Flexible and generous funding with ample resources to pursue a research program.
- 75% of a Scholar’s time is protected for research.
- An outstanding support system. Senior faculty members serve as mentors and Scholars are matched with members of the Beeson Program Advisory Committee, some of the most talented leaders in geriatrics and aging research.
- Extensive networking opportunities through the Beeson annual meeting, an interdisciplinary conference for Scholars, mentors, and leaders in the field.
- Exchange of information among current and former Scholars from many disciplines.
- Alumni participation. Many Scholars continue to attend annual meetings, assume leadership roles in the program, and become mentors to the next generation.



What You Do in the ICU: Beeson Scholars Improve Health for the Long-Term

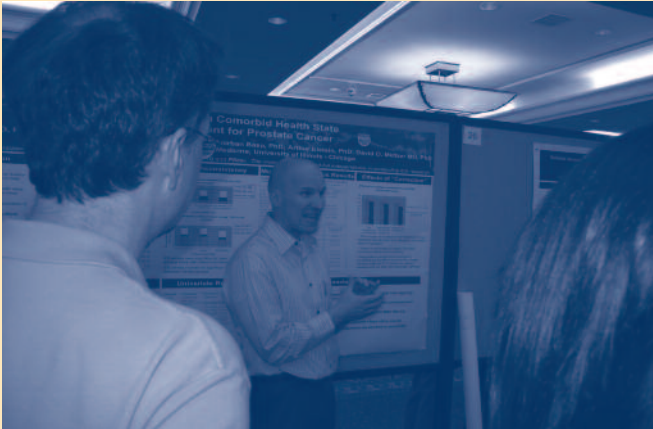
Beeson Scholars are changing the practice of clinical care. One striking example is redefining the way intensive care unit (ICU) patients are treated in order to reduce serious and long-term complications.

Traditional ICU treatments rely on heavy sedation, high doses of pain medications, machine monitoring, and keeping patients immobile. This seemingly compassionate care is aimed at reducing pain and anxiety and speeding recovery, but it also dramatically increases the incidence of delirium. ICU-acquired delirium can affect patients long after they leave the hospital in the form of reduced brain function, which is often manifested as problems with memory and executive function. ICU survivors also suffer from an intense loss of muscle mass and an increase in the incidence of depression and post-traumatic stress disorder. 2001 Beeson Scholar E. Wesley Ely, MD, MPH, professor of Medicine and Critical Care at Vanderbilt University Medical Center and associate director of Aging Research for the Tennessee Valley Geriatric Research Education Clinical Center (GRECC), explains that whether they are young or old, patients who arrive at the ICU because of complications from their primary conditions often leave with newly acquired and tremendously debilitating cognitive and functional deficits.

Research led during the past decade by Dr. Ely and his many colleagues at Vanderbilt University's ICU Delirium and Cognitive Impairment Study Group (www.icudelirium.org) spurred the creation of a five step protocol to improve the assessment and outcomes of medical and surgical ICU patients. Called the ABCDEs of Critical Care, this quality improvement program includes measuring spontaneous **A**wakening and **B**reathing trials, **C**oordination between ICU team members, **D**elirium monitoring and management, and **E**arly mobility and exercise. This evidence-based approach ushers in some dramatic changes in the culture of care that had become standard during the past three decades. It is designed (and some elements have shown) to help standardize communication, improve interdisciplinary patient care, reduce length of hospital stay and mortality, and improve long-term cognitive and functional outcomes. Approximately 40% of hospitals have incorporated some part of the ABCDE protocol in their ICUs and the delirium tool is now translated into more than 20 languages and used worldwide.



Overall, this change in the culture of the ICU, its organization, and focus on vulnerable older patients is taking time but making progress. There are well-documented and marked improvements in patients' physical, cognitive, mental, and long-term health but on a large-scale basis, more studies and cohort data are needed.



In a recent Vanderbilt randomized, controlled trial of the ABC section of the protocol published in *The Lancet*, patients' ICU and hospital stays were reduced by four days and one-year survival rates improved by 15% (up to 65% from 50%) simply by cutting the amount of sedation in half.

"We are finding that both patients and their families are so relieved that ICU teams are now focusing on the brain both during and after the ICU stay," says Dr. Ely. In the past, we used our 'beeps and buzzers' to help patients survive, but now we are paying close attention to the quality of survival and we know that the brain is the most important organ determining that quality."

The ABCDE program is garnering a lot of attention outside of the hospital. Recently, *The Wall Street Journal* featured the ABCDEs and the work of other researchers studying the role of delirium during and post-ICU. It has also become a major focus of a national quality improvement effort led by the Institute for Healthcare Improvement (IHI) to implement the ABCDEs at hospitals across the country.

Other Beeson Scholars are adding to the knowledge that can help improve ICU and post-ICU care. A 2007 grant from The John A. Hartford Foundation allowed 1997 Scholar Helen Hoenig, MD, MPH, associate professor of medicine

at Duke University Medical Center, to collaborate with Dr. Ely on one of the first pilot studies in cognitive and physical rehabilitation of ICU survivors in the home-care setting. They evaluated functional mobility and home safety, which included exercises to improve physical impairment in strength, balance, and endurance, and cognitive training to improve decision-making and daily functioning. After 12 weeks, participants showed significant improvement in executive function and mobility.

Malaz Boustani, MD, MPH, a 2005 Beeson Scholar who is associate professor of Medicine at the Indiana University Center for Aging Research and scientist at the Regenstrief Institute, is leading a study to improve pharmacologic management of critical care ICU patients. Many medications commonly used in the ICU, such as benzodiazepines, contribute to delirium. Dr. Boustani's research seeks to create a multi-component pharmacological intervention that would include human and computer-based decision support systems to reduce drug-induced adverse events.

In July 2011, Indiana University Medical Center will open a post-ICU survivor clinic. The Critical Care Recovery Center will closely track and assess patients' cognitive and functional status at three-month intervals and develop individualized treatment protocols to improve rehabilitation. Vanderbilt University Medical Center will also open an ICU Survivor Clinic in July.

Drs. Ely and Boustani realized that they had shared interests when they first met at an annual Beeson meeting. Along with 1999 Beeson Scholar Edward Marcantonio, MD, director of Research in the Division of General Medicine and Primary Care at Harvard Medical Center, they helped found the American Delirium Society, (<http://www.americandeliriumsociety.org>) a collaborative interdisciplinary effort designed to better understand the science of delirium and its prevention, treatment, and long-term consequences.

Cynthia M. Boyd, MD, MPH

Associate Professor of Medicine
Johns Hopkins University School of Medicine

MENTORS:

Cynthia Rand, PhD
Charles Boulton, MD, MPH, MBA
Bruce Leff, MD

Treatment Burden in Older Adults with Diabetes and Multimorbidity



Boyd

Dr. Cynthia Boyd has always been drawn to older and more complex patients. During her internal medicine residency program, she says, “I went out on house calls with a geriatrics fellow and I realized very quickly that this was for me. I realized that I really loved older people, that I loved their stories and thinking about their health in

context of their whole life and their history and their relationships to other people.”

At the same time, Dr. Boyd was intrigued by the challenge of figuring out how to best medically intervene for these patients. “As these two things melded together, I was really struck by what we know about evidence-based medicine and how poorly much of it applies to people with multiple chronic conditions, particularly older people,” she says.

Early in her medical fellowship, she started a project looking at how well clinical practice guidelines for people with single diseases worked for older people with multiple chronic conditions, or multi-morbidities. “What we found backed up my hypothesis, which is that they didn’t apply very well,” she says. Only rarely did the guidelines discuss how well the evidence actually applied to older people with multiple chronic conditions or address the breadth of issues important to them. “People would end up on these incredibly complicated regimens with many, many medicines, and a lot of visits to doctors and healthcare professionals.”

For her Beeson project, Dr. Boyd is aiming to improve the lot of such patients by examining how doctors deliver their healthcare. “We want to make them feel better, we want to make them more functional, and we want to make better decisions that will directly lead to improved outcomes in a way that is patient-centered and evidence-based,” she says.

In other words, the care should account for individuals’ unique circumstances and consider variables like their medical conditions, social support, values, goals, and

healthcare preferences. To get at these personal aspects, Dr. Boyd and her team are collecting information from patients, their family members, caregivers, and physicians. With the brief assessment — essentially a short survey — busy clinical practices might be more able to identify those who should be on physicians’ radar screens. The results of that assessment could then inform follow-up conversations.

Among older patients, for example, researchers have found that adherence goes down for every medicine added. How can clinicians measure that treatment burden and use it in an appropriate way in decision-making? “It’s not just a simple matter of knowing when we’re asking patients to do too much,” Dr. Boyd says. For a patient feeling particularly burdened by a treatment regimen, the assessment could help identify priorities or ways to overcome the stumbling blocks preventing adherence. And a thoughtful approach and an open discussion regarding how much benefit various options really deliver could help patients decide which represent the best way forward for them, making them more active participants of their treatment plans.

The Beeson award, Dr. Boyd says, has granted her the “enormous privilege” of protected research time, something she considers essential for transitioning to being a leader and developing a full research program. And with “truly phenomenal” peer networking, she has developed ongoing collaborations with three other Beeson scholars. “The other thing that I think is really amazing is what you learn on a national level from people who are the mentors and the more senior researchers,” she says. “It’s really an unparalleled opportunity to develop collaborations and get mentoring nationally in aging research, which I think is very unique and wonderful.”

Once her assessment tool has been refined, she hopes to test its interventional utility in the clinic. This evidence-based approach could help fill in some critical knowledge gaps about which approaches are most likely to help older and more complicated individuals. “It’s really a very exciting field because there’s so much that we don’t know,” Dr. Boyd says, “and it’s very relevant to so many patients.”

Dena Bou Dubal, MD, PhD

Assistant Professor of Neurology

University of California, San Francisco Medical School

MENTOR:

Lennart Mucke, MD

Collagen VI: Novel Mechanisms and Functions in Alzheimer's Disease



Dubal

As the world's aging population rapidly increases, humans are living longer than ever before, with the World Health Organization calculating an unprecedented global life expectancy of 68 years for babies born today. That longevity, however, comes amid a disturbing uptick in the prevalence of Alzheimer's disease among

seniors. A century after it was first described, the disease is quickly reaching epidemic proportions, with no effective prevention or treatment options yet in sight. "So very simply, the bottom line of my research is to understand the disease process so that we can develop strategies to prevent and treat the disease," says Dr. Dena Dubal.

Dr. Dubal's efforts are focused on a little-known factor called collagen VI, which exists beyond the confines of brain cells as something called an extracellular matrix protein. "What we discovered is that it's very highly expressed in the brains of Alzheimer's disease patients and in mouse models of Alzheimer's disease," she says. "And so we sought to ask, 'Why is this protein that lives outside the cells so highly expressed, why is it so abundant, and what is it doing in the disease?'" So far, the emerging story suggests that by producing the protein, brain cells are protecting themselves against Alzheimer's-associated toxins. In particular, Dr. Dubal and her colleagues have found that collagen VI can bind to amyloid-beta — a toxin believed to play a critical role in Alzheimer's disease — and effectively keep it from attacking neurons.

As part of her Beeson project, Dr. Dubal is characterizing the potential effects of collagen VI in mice, in mouse neurons grown under lab conditions, and in Alzheimer's-impacted brain tissue taken from human patients. The work spans everything from biochemical and molecular investigations of the disease pathway to studying impacts on behavior and cognition in mice treated with collagen VI. "The hypothesis is that if we were to increase this factor even further, we would see a protection against the

disease, and if we were to take away that factor, we would see a worsening of the disease," she says.

Dr. Dubal says her strong passion for aging research goes back to her days as an undergraduate student, when aging was a common theme bridging her studies in medical anthropology and neurobiology. A subsequent class on the physiology of aging, she says, had her on the edge of her seat and brought home the "urgent need for scientific discoveries to prevent these devastating dementias that affect people of all cultures." At that point, she developed a strong commitment to become a physician-scientist. She began by working to identify protective strategies against diseases of aging in the brain, and eventually specialized in dementias as a clinician.

With all of her accomplishments, Dr. Dubal calls the Beeson Award one of her greatest to date. "It has enabled me to really develop into an independent investigator," she says. "It's enabled me to spearhead burning questions to really begin a line of independent research in the field of aging and degeneration. It's opened many, many doors in terms of scientific networking and career development." In short, she says, the award has been a seminal turning point in her career.

"I come into this award with a very strong background in neurology, neuroscience, and aging. But to really become an independent investigator and leader in the field of Alzheimer's disease, I needed some very specific training and mentoring expertise," Dr. Dubal says. The Beeson award has given her that opportunity to learn cutting-edge approaches and techniques through her exposure to world-renowned experts.

The therapeutic potential of collagen VI, she notes, is still unclear. "But as we understand what can protect the brain against disease, we can begin to understand how to increase those factors," she says. "It opens wide the possibilities of really promising targets for prevention and therapy."

Chie Wei Fan, MD, RCPI

Senior Research Fellow

Trinity College Dublin, Ireland

MENTOR:

Rose Anne Kenny, MD

Age-related Autonomic Dysfunction and its Impact on Cognition, Gait and Falls



Fan

An ill or dehydrated person who stands up too quickly in the morning may feel a temporary bout of dizziness. For many older adults, that sensation never goes away until they sit down — or pass out — and Dr. Chie Wei Fan wants to understand why.

The physical act of going from a lying to standing position causes a pint of blood to flow from the chest to the abdomen, dropping the blood pressure and spurring a compensatory increase in the heart rate. Patients with a condition known as orthostatic hypotension, however, are deficient in their response to this blood pressure drop, whether in a diminished rise in the heart rate or in a decreased constriction of the veins in the abdomen and lower limbs. The result is a temporary reduction in blood supply to the brain and an accompanying feeling of dizziness.

Prolonged dizziness and a higher risk of falling result from the body's autonomic failure, as it is called. The phenomenon increases with age, and as studies are increasingly suggesting, more ominous implications may include lower mental function, higher risk of cardiovascular disease, and greater odds of death from all causes. "A poorer response of blood pressure to standing seems to be related to a lot of physical failings and maybe include cognitive failings — and it may even be related to mood," Dr. Fan says.

Standard blood pressure readings lack the sensitivity to detect rapid changes. For her Beeson project, Dr. Fan is using a more sophisticated tool known as a Finometer. "It's able to measure blood pressure on a beat-to-beat basis, so every heartbeat will produce a blood pressure measurement," she says. With the equipment, she and her colleagues can scrutinize how patients respond to standing up from a lying down position within five seconds.

Tellingly, the researchers have identified three main responses. In younger, healthy volunteers, a quick recovery follows the initial drop in blood pressure. In

older people, however, Dr. Fan's team found that the recovery is often delayed — a subtle but important difference missed by standard blood pressure tests. And for a patient with autonomic failure, commonly seen in someone with Parkinson's disease or diabetes, the blood pressure never returns to normal.

One Parkinson's patient in particular triggered her curiosity: a 62-year-old man who attended her clinic because of falls and blackouts. Every time he stood up, his dizziness increased so much that he was forced to sit down. While standing, his vision was blurred, his hearing muffled, and his breathing labored. Dr. Fan and her colleagues adjusted his medications and helped him make some lifestyle changes to improve his cardiovascular health, thereby improving his blood pressure recovery enough so that he could take a vacation to Spain.

His may be an extreme form of the condition, but Dr. Fan says the success story suggests many others also might be helped. By using more sophisticated equipment, she says, "We may be able to detect early changes. And if we intervene then, perhaps you'll stop the person from progressing to significant autonomic failure."

Dr. Fan has been able to tap into The Irish Longitudinal Study on Ageing (TILDA), a rich clinical database that may help her answer the larger question of why increasing age brings an associated delay in blood pressure recovery. With beat-to-beat measurements, she may be able to chart the long-term health trajectory of TILDA patients who show an early impairment in their lying-to-standing recovery period.

The Beeson award, she says, has raised the profile of aging research both at her university and throughout Ireland, and the yearly conference has given her the rare opportunity to directly interact with the field's world leaders. As a result, Dr. Fan has been able to focus on solving an increasingly important clinical mystery.

"It's a fascinating area," she says. "Finding that treatment of low blood pressure can improve somebody's concentration or their mood or their ability to interact with people, and improve their quality of life — it's been very rewarding."

Ronan Mullan, MBChB, PhD

Senior Lecturer in Rheumatology
University College Dublin

MENTOR:

Douglas Veale, MD

Acute Phase Serum Amyloid-A (A-SAA) in Ageing, Arthritis and Obesity - Potential Common Mechanism for Cardiovascular Disease



Mullan

Dr. Ronan Mullan has seen a disturbing phenomenon among many of his patients with rheumatoid arthritis, an autoimmune disease marked by chronic joint inflammation. "Rheumatoid arthritis patients die younger than healthy people in the population," Dr. Mullan says, "and in large part that seems to be due to an acceleration

in the rates of atherosclerosis in these patients."

With a range of related maladies, he says, rheumatoid arthritis patients actually appear older. "Their muscles almost waste away, much like an older person's would. So it's kind of accelerated aging, really."

Doctors have long known that obese people are at higher risk for strokes and heart attacks. So are rheumatoid arthritis patients, but Dr. Mullan says those with a highly active form of the disease — marked by badly inflamed joints — are more likely to be significantly underweight. So why do some gaunt rheumatoid arthritis patients suffer the same fate as overweight people?

A common denominator, Dr. Mullan says, may be the activity of an inflammation-linked protein produced by the liver, known as serum amyloid A. Among rheumatoid arthritis patients, he has found, those with high levels of the protein are at greater risk of developing cardiac complications. Other studies suggest the protein is involved in primary atherosclerosis and linked to obesity-related cardiovascular disease.

For his patients, Dr. Mullan wants to understand how pro-inflammatory serum amyloid A may be tying together these disease pathways — and indeed, could be a key player in a cardiovascular disease mechanism observed in obesity, arthritis, and aging. Accumulating research already suggests that among some obese individuals and rheumatoid arthritis patients alike, fat is actively broken down into harmful byproducts. "Part of my work is looking at fat tissue in rheumatoid patients to see how it's behaving, because it's never really been looked at before," he says. "There's probably

something in the tissue that under certain circumstances can potentiate inflammation."

Amid a challenging economic climate in Ireland, Dr. Mullan says, the Beeson Award has been highly beneficial to his ongoing research. "I just wouldn't have had the same opportunities without it," he says. "From a professional point of a view, it has raised my standing enormously in the university. You have instant recognition that you didn't before." At the annual meetings, he says, he's been welcomed with open arms and exposed to an exciting range of aging research beyond the immunology field. "I've had a great experience."

For one arm of his Beeson-supported project, Dr. Mullan is collecting fat tissue from the inflamed joints of rheumatoid arthritis patients and analyzing the rich stew of molecules linked to inflammation. By comparing this tissue to fat collected elsewhere from the patients' bodies and from other patients with a non-inflammatory form of arthritis, he hopes to characterize the unique traits of rheumatoid arthritis-associated tissue. His team can grow the tissue samples in the lab and assess the effects of deliberately blocking the activity of serum amyloid A or other inflammation-linked molecules.

For a second arm of the research, Dr. Mullan and his team are compiling demographic information and cardiovascular risk profiles for rheumatoid arthritis patients. Simultaneously, they're measuring the serum amyloid A levels and inflammatory disease activity in the patients' joints, as well as their total body percentage fat mass and lean body mass using a technique called whole body densitometry. Essentially, Dr. Mullan aims to correlate each patient's clinical history, genetic profile, and behavioral risk factors for cardiovascular disease with lab tests providing objective evidence of the overall cardiovascular risk. The patients can then be followed over time to investigate links between rheumatoid arthritis and cardiovascular disease outcomes.

Eventually, Dr. Mullan hopes his work might help scientists figure out how to neutralize the serum amyloid A protein or block a link in the pathway, thereby helping rheumatoid arthritis patients avoid a potentially deadly consequence of the disease.

Christiane Reitz, MD, PhD

Assistant Professor of Neurology

Columbia University College of Physicians and Surgeons

MENTOR:

Richard Mayeux, MD, MSc

Mapping Causative Factors in the Sortilin-related Pathway in Alzheimer's Disease



For late-onset Alzheimer's disease, the cast of genetic culprits contributing to the condition may number in the dozens. Research by Dr. Christiane Reitz, however, suggests that a family of five genes may play a central role in susceptibility to the disease.

Reitz

In Alzheimer's, a normal nerve cell constituent known as amyloid precursor protein is chopped up and transformed into a toxic byproduct called beta-amyloid. Eventually, these protein fragments stick together and form telltale clumps in patients' brains. "The main reason that there's no therapy is that we really don't yet understand how this accumulation of proteins in the brain happens," Dr. Reitz says.

In 2007, she and her colleagues took a big step toward clarifying the disease pathway by showing that a gene known as *SORL1* inhibits a key enzyme from cutting up amyloid precursor protein into its destructive derivative. Curtailing the cleaving activity of this enzyme, called gamma-secretase, allowed fewer toxic breakdown products to form instead.

In contrast, too little *SORL1* boosted the secretase enzyme's activity, increased the levels of clump-prone beta-amyloid fragments, and heightened the risk of Alzheimer's disease. Since then, Reitz and her lab have identified four related genes that all seem to behave the same way. Her ongoing investigation into how these genes function, supported by the Beeson award, has contributed more clues to the murky disease process.

Dr. Reitz is systematically asking the same questions for each gene: "What happens if we really alter this gene in the cell? Does it lead to the toxic form of amyloid being generated less or more?"

So far, her research suggests that for *SORL1* and its four relatives, lower-than-normal gene activity does indeed yield higher concentrations of Alzheimer's-associated protein plaques. If her results hold up to further scrutiny, "then of course, all of those genes would be a target for therapy," Dr. Reitz says.

In medical school, Dr. Reitz instantly gravitated toward neurology, and subsequently obtained her PhD in genetics so she could focus on better understanding the genetic basis of Alzheimer's and neurodegenerative diseases. "With the Beeson award, it gives you the possibility to network with people who are from other top universities and working on other aging-related diseases," she says.

The rare opportunity to receive direct feedback from leading experts has helped her refine her grant proposals and has highlighted potential connections with other researchers. "Scientifically, there's a lot of development and a lot of collaboration," she says. "But then in addition, it's the mentoring part which is just very helpful."

To characterize the role of *SORL1* and its relatives in Alzheimer's, Dr. Reitz has pursued multiple strategies. Initially, her team collects DNA samples from and conducts neurological examinations of recruited volunteers to detect signs of the disease. Using powerful assays, the researchers measure each gene's relative activity in healthy volunteers and in Alzheimer's patients, and identify genetic variants that may be affecting those levels.

Significant differences between the two patient populations can be further investigated by tinkering with each gene's relative activity in human nerve cells grown in Petri dishes. By artificially switching a gene on or off, the researchers can observe the impact on the gamma-secretase enzyme and on the buildup of beta-amyloid plaques. Finally, Dr. Reitz is examining whether these same genes are turned on at lower levels in cells from the donated brains of patients who died of Alzheimer's disease.

All the tests support the same emerging story: when fully functional, these five genes seem to keep the secretase enzyme in check, preventing it from cutting amyloid precursor protein. Fewer amyloid-beta plaques result, which may translate to a reduced risk of Alzheimer's.

"The next step for those five genes — and others, probably — is how do they interact and what is the pathway?" Dr. Reitz says. With her extensive training, budding collaborations, and encouraging results, she's well on her way to finding out.

Mara Schonberg, MD

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MENTORS:

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Rebecca Silliman, MD, PhD
Ellen McCarthy, PhD, MPH

Benefits and Burdens of Screening Oldest-old Women: The Case of Mammography



Schonberg

When she was diagnosed with early-stage breast cancer at the age of 79, one of Mara Schonberg's grandmothers made the difficult decision to not pursue radiation therapy. Meanwhile, Dr. Schonberg's other grandmother steadfastly refused to receive another mammogram after she turned 87. Watching them grapple with their respective choices, Dr. Schonberg was reminded how little information is available to help older women through the decision-making process for breast cancer screening and treatment.

Clinical data on the effectiveness of mammography screening has typically included only women younger than 75, leaving older women with little guidance. When Dr. Schonberg was a medical resident, the common default for doctors was to continue mammograms regardless of age, with no prior discussion of whether they were truly warranted. "We're not trained on how to have these conversations," Dr. Schonberg says. "Nor is there a lot of data on how to do it."

Dr. Schonberg is hoping to help fill that void through two related Beeson projects. One is aimed at better understanding the psychological impact and decision-making process of older women as they consider breast cancer screening and treatment options. For a second project, Dr. Schonberg is developing an accessible tool to help those women make informed decisions based on their own values and preferences.

Overall, experts estimate that about two-fifths of breast cancers are over-diagnosed, meaning that the tumors would never be clinically significant in a woman's lifetime. But Dr. Schonberg says that number is likely higher for older women who may have slow-growing cancers and multiple competing illnesses. "If that breast cancer is never going to show up and never cause significant morbidity or mortality, then finding it may not be a good thing for all women," she says.

To hear from the women themselves, she is comparing the experiences of two groups who received abnormal mammograms and were recommended for a breast biopsy: those aged 75 and older and those aged 65 to 74. For the observational study, Dr. Schonberg is surveying both groups after their initial mammogram and again after 4 to 6 months to assess their decision-making process, quality of life, and other markers of well-being.

Although her results are still preliminary, the data suggest that women aged 75 and older are more likely to feel that their physician made their treatment choices for them and to feel less satisfied. Because the older women tend to rely on their primary care providers more than younger women, Dr. Schonberg says one lesson is that those physicians should be better informed about the intricacies of breast cancer treatment.

For her related project, Dr. Schonberg is developing a decision aid to help older women decide whether to continue receiving mammograms. To create the accessible pamphlet, she interviewed experts in fields ranging from geriatrics and oncology to epidemiology and communications. Using visual cues, the pamphlet explains the average outcome of women who do or do not continue with breast cancer screening, and includes a scored questionnaire that estimates overall risk of death. Women who score higher have a greater overall risk of death, and are less likely to benefit from mammography screening. Most importantly, the tool is designed to help them think about what they value most.

Dr. Schonberg is testing the tool in a primary care-based clinic to see whether it improves older women's knowledge about the pros and cons of screening and whether they consider it useful. She hopes that with balanced information about options and outcomes and an approach that considers patients' personal values, women will become more active participants in discussing the best course of action with their doctors and their loved ones.

Dorry Segev, MD, PhD

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Jeremy Walston, MD

Access to Kidney Transplantation in Elderly Patients



Segev

With more than half of all kidney dialysis patients now over the age of 65, doctors are seeing an increasing number of older candidates for kidney transplants. Yet most studies of kidney transplant outcomes have all but excluded this subpopulation. Older adults may have cognitive issues and multiple chronic conditions, further complicating the task of predicting who may do best after a transplant.

Dr. Dorry Segev, was among the doctors confronted by a lack of data and struggling with the question of whether certain patients were good transplant candidates. "I saw some older adults do fantastically well after kidney transplants, and I saw some older adults do quite poorly," Dr. Segev says. "It was frustrating to me to not have been able to predict those outcomes."

After talking with geriatricians, he realized that better predictions would come only with a fuller understanding of the geriatric-specific issues faced by older patients. His Beeson award, Dr. Segev says, has let him focus on a challenging aspect of his field with major implications for assisting individual decision-making and informing policy discussions on how donated organs should be allocated to older transplant candidates.

"The first goal was to try to figure out, using a large national database, who are the appropriate older candidates for transplantation?" Dr. Segev says. Secondly, he wondered, how many of those predicted to be good candidates actually have access to transplantation?

"Under the hypothesis that we will find some discrepancy between medical appropriateness and access to transplantation, then the question is, 'What are the barriers to getting appropriate older adults listed for transplants?'" he says. That question may have been less urgent 10 to 15 years ago, when older patients often didn't fare well after receiving a donated kidney. But better immunosuppression medication and more clinical experience with older patients have markedly improved post-transplant survival for many.

To help with the predictive modeling, Dr. Segev tapped into a rich database of nearly 7,000 older patients linked to the Organ Procurement Transplantation Network. He and his collaborators have used advanced computer modeling techniques that take into account the varying interactions that can occur among a patient's multiple chronic conditions. "We're able to categorize people by how good of a candidate they would have been for a transplant," he says, "and then we can go back to the whole dialysis population and say, 'What percentage of the good candidates actually had access and what percentage did not have access?'"

Preliminary results have pointed to some eye-opening findings. The top tier of kidney transplant candidates over the age of 65, for example, collectively have a 90% chance of surviving at least three years after receiving a kidney transplant. But Dr. Segev's initial analysis shows that fewer than 25% of these "excellent" candidates have had access to one.

His work also has suggested a host of misconceptions. People who are less likely to pursue a transplant, for example, are more likely to think they will do better than predicted on dialysis. Conversely, they're more likely to think a transplant will be riskier than predicted for them. Older patients say they don't want to burden their family members or society, and have more doubts about whether they could handle additional medications.

The Beeson award has allowed Dr. Segev to receive formal training in geriatric issues and to create a network of geriatrics colleagues and mentors who have helped him understand how those issues apply to his own research. "Since I got my Beeson award, I've received a PhD in clinical investigation, and I was promoted to associate professor," he says. "With the protected time that it's given me, it's really opened for me an opportunity to grow significantly in my career."

His ultimate goal, he says, is to ease the delicate process of determining whether a patient might benefit from a kidney transplant. "If we can be more objective about this," he says, "then it would help people understand that they may be good candidates and encourage them to seek out the transplant that would help them."

Edmond Teng, MD, PhD

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Assessment of Biomarkers and Behavior in a Transgenic Rat Model of AD



Teng

A particularly cruel aspect of Alzheimer's disease is the slow erosion of memory and thinking abilities. By the time patients make their first worried trip to the doctor, changes in the brain may have been brewing for a decade. The gradual deterioration has presented a challenge for researchers who have little else to

help gauge the potential of candidate therapies during expensive clinical trials. "Right now, our clinical trials are stretching out to 18 months or two years to be able to see if we're making a difference," says Dr. Edmond Teng.

Scientists have identified a few biological markers that may indicate early signs of the disease in a patient's cerebrospinal fluid — and potentially in the blood. Dr. Teng is asking whether researchers also can detect further changes in these markers that could be used as a proxy for disease progression. If so, he says, interventions that prevent or slow the disease might yield effects on the biomarkers that appear long before changes in more traditional measures of patient behavior.

"Even though it might take us 18 months to see a difference in memory and thinking, if we could see a difference within two or three months or sooner in blood or spinal fluid, we'd at least know we were on the right track," Dr. Teng says. "We could identify treatments that seem to be working earlier, and identify patients who seem to respond to those treatments earlier as well." One difficulty, though, is knowing whether changes in biological markers really reflect changes in disease severity. To address that uncertainty, he is studying laboratory rats that have been modified with an introduced genetic mutation that leads to Alzheimer's-related symptoms relatively quickly.

As part of his Beeson project, Dr. Teng is examining two markers in the rats' cerebrospinal fluid that can distinguish between those that have Alzheimer's and those that don't. For these disease-linked proteins,

amyloid-beta and tau, he is testing the ability of each to track the improvements in memory and cognition that researchers have seen in treated animals. If a candidate intervention has a clinical effect in rats and also significantly changes the levels of tau or beta-amyloid in the animal's cerebrospinal fluid, researchers might be encouraged to test the same strategy in humans. "So it would help make sure we could prioritize the treatments that are most promising," he says.

Dr. Teng became fascinated with memory during a psychology course in college, when he heard the story of a famous patient named H.M. To control H.M.'s epileptic seizures, doctors removed the majority of a structure called the hippocampus from both sides of his brain. The operation worked, but H.M. was left with severe long-term memory problems. In graduate school, Dr. Teng studied the memory-robbing impacts of hippocampal damage in monkeys and humans. Later, in medical school, he saw patients whose memories had likewise been stolen — this time by Alzheimer's disease. With two family members afflicted by the incurable disease, "it really strikes that personal chord with me," he says.

With the crucial support of the Beeson Award, Dr. Teng has been applying his research knowledge to help address a clinical epidemic that is expected to affect an estimated 16 million Americans by 2050. "The Beeson Award has been totally awesome," he says, citing the program's emphasis on mentorship and career support. At the annual meeting, he says, "you're getting a lot of feedback from your peers but also feedback from more senior members on a much more personal level than you might get at the bigger scientific meetings."

Although he had secured some smaller grants during his medical fellowship, Dr. Teng was faced with making the career jump from being a trainee to running his own lab. "And if I hadn't gotten the Beeson Award I probably wouldn't have been able to make that jump," he says. "So the award has been, I think, absolutely essential for me being able to continue to pursue a career in academic medicine."

Heidi L. Wald, MD, MSPH

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Elizabeth Capezuti, PhD, RN
Peter Lindenauer, MD, MSc

Reducing Urinary Tract Infections in the Hospitalized Older Patient



Wald

Urinary tract infections are by far the most common of all hospital-acquired infections, with an estimated incidence of more than 500,000 cases every year. Researchers have blamed about 80 percent of these infections on the use of a urinary catheter, and Dr. Heidi Wald is training a spotlight on the avoidable harm that such infections can inflict on older patients.

“My timing is lucky because there’s a big focus nationwide at this point in time on hospital-acquired conditions, and specifically hospital or healthcare-acquired infections,” Dr. Wald says. “Catheters have been used fairly cavalierly in all patients, but in particular in elderly patients.”

Frail, older patients may suffer disproportionately from catheter-associated urinary tract infections, with studies linking the infections to decreased mobility, a higher risk of falls, and in some cases, even death. “Infections associated with catheters have previously been seen as part of doing business in hospitals,” she says. “And the paradigm has really changed over the last couple of years in that the thought is, ‘You know, these are probably largely preventable and we haven’t been doing everything that we can to prevent this additional harm to patients.’”

With the support of the Beeson Award, Dr. Wald is developing a new method to reduce these infections through a collaboration with 20 hospitals enrolled in the NICHE (Nurses Improving the Care of Health System Elders) Program. One aim of the project is to test an automated surveillance system that helps hospitals track how they use urinary catheters and how often such use leads to infections among their patients.

In return for compiling and sending data collected through the surveillance system, each participating hospital receives a report and either an immediate or delayed interventional strategy in the form of education and feedback. Dr. Wald can then assess whether early intervention helps hospitals improve patient care. If the system proves

reliable, it could be distributed more widely to help hospitals reduce the infections.

Although Dr. Wald is applying a technical solution to the problem, she says the project has broad implications. “Obviously, the main goal is to improve patient outcomes by reducing catheter use and urinary tract infections,” she says. But by advancing the knowledge of electronic surveillance and how it can be used, her approach also might help lower other hospitalization-associated risks, such as pressure ulcers (sometimes known as bedsores).

An automated surveillance system, Dr. Wald says, can free hospitals — many of them already short on personnel — from the time-intensive task of manually tracking catheter use and associated urinary tract infections. By informing hospitals how often catheters are really used, and often overused, she hopes the system might encourage staff to rely on them less and in so doing reduce the risk of infection.

An influential 1999 Institute of Medicine report on the high rate of medical errors spurred her interest in patient safety, and led to a new career trajectory that began with fellowships in geriatric medicine and primary care research. Eventually, Dr. Wald says, she saw a natural synergy between the patient safety movement and the core values of geriatric medicine. Based on her clinical experience, she started focusing on urinary tract infections as a form of preventable harm. The Beeson award, Dr. Wald says, has given her the welcome luxury of protected time to continue working on her research and career development. “It really provides me with a lot of independence and flexibility that I would not have otherwise had,” she says.

Once the issue of patient safety and hospital-acquired infections burst onto the national scene as a major point of discussion in the larger debate over healthcare quality, “all of a sudden, people started to really understand what I was doing,” Dr. Wald says. Now, hospitals and patients around the country stand to benefit from her expertise.

Jonathan Wanagat, MD, PhD

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University of California, Los Angeles School of Medicine

MENTORS:

David Reuben, MD

Steven Clarke, PhD

Mitochondrial Genetics in Skeletal Muscle Aging



Wanagat

Every few months, Dr. Jonathan Wanagat hears one of his patients talk about the difficulties of getting old. As a geriatrician, Dr. Wanagat has learned to ask an important but often neglected follow-up question: What challenges are you facing?

“The vast majority of the time, the answer to that question, regardless of their medical problems or their

societal or economic background, has been that they can’t do what they did when they were younger,” he says. Maintaining mobility and the ability to live independently are two major concerns among aging seniors, and Dr. Wanagat says an underappreciated condition may have an enormous role in undermining both. “The impact I see in clinic every week is that individuals primarily lose their independence through a variety of mechanisms — weakness, falls, gait or balance problems, changes in metabolism — because they’re losing their muscle mass.”

This age-associated muscle loss, or sarcopenia, seldom appears on the medical charts listing a patient’s primary problems. Dr. Wanagat, however, believes that understanding the mechanism underlying this progressive wasting away of muscle cells could be key to preventing or at least delaying a major source of disability among older Americans.

For his Beeson project, he is focusing on the potential role of the cell’s energy factories, or mitochondria, in age-related sarcopenia. Mitochondria contain their own DNA, which can acquire sporadic mutations throughout the aging process. Mutations in the mitochondria may spread within each thread-like muscle cell, or muscle fiber, killing off the cell and gradually winnowing away the muscle mass. “In that model, one can envision different points of intervention that might either prevent the mutation, prevent the spread of a mutation or prevent the negative outcome of that mutation, namely, the fiber being lost from the population,” Dr. Wanagat says.

Using genetically modified mice, he is testing the hypothesis that halting an early step, a DNA mutation in

the mitochondria, may shield older animals from muscle fiber loss. Dr. Wanagat’s lab mice contain a powerful antioxidant enzyme that has been redirected to the mitochondria to help protect against DNA-damaging molecules. Other research found that these mice live 25 percent longer than their unmodified peers, and Dr. Wanagat has determined that the animals also appear to be better safeguarded against sarcopenia. “We see a lower mutation rate,” he says. “I find fewer of these mitochondrial abnormalities in the muscles, and the muscles are a little bit larger in the oldest mice.”

Dr. Wanagat’s work represents an extension of his graduate research, which focused on mitochondrial aberrations and other abnormalities in the muscle cells of aging rats. “The Beeson Award for me has been critical mostly because I’m both a practicing geriatrician and a scientist,” he says. Without the protected time that allows him to pursue his research, he says, moving forward in his investigation of mitochondria and muscle loss would have been extraordinarily difficult. The tight-knit group of Beeson Scholars and geriatricians also provides a crucial support network. “I think there’s a great camaraderie there,” he says. “Academic geriatrics in general is quite small, and the subset of those individuals who do basic science is even smaller. So it’s great to have a way to be connected to those people for resources or help with protocols or collaborations.”

With firmer evidence tying mitochondria to muscle wasting, he says, researchers may gain a better handle on diagnosing sarcopenia, perhaps through telltale changes in biological markers. More clarity also might help clinicians devise interventions beyond exercise, which isn’t always realistic for patients who are recovering from a fall or don’t feel comfortable walking in unsafe neighborhoods. And mitochondria, he says, may present a better therapeutic target for antioxidants than giving patients general antioxidant supplements like vitamin E, a strategy that has been largely unproven in clinical trials.

“Hopefully, some of my work will uncover some of these basic mechanisms,” Dr. Wanagat says, “and give us targets to start preventing the changes or slowing them down.”

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