2014 | 2015

EXPLORING NEW DIRECTIONS

THE HARRINGTON PROJECT
FOR DISCOVERY & DEVELOPMENT

Harrington Discovery Institute
University Hospitals | Cleveland Ohio

Dear Colleagues,

In 2014, the Harrington Discovery Institute expanded in new directions that increased opportunities for the nation's best medical inventors and validated our model for drug discovery and development.

We extended our program internationally through a partnership with Oxford University in the UK. Ranked one of the world's best universities in medicine and science, Oxford shares the Harrington Discovery Institute's commitment to innovation and scientific discovery in medicine. The Oxford-Harrington Scholarship Program currently is supporting groundbreaking research in Crohn's disease, and a new class of Oxford-Harrington Scholars will come on board shortly as part of a staged expansion of The Harrington Project across the UK.

Closer to home, we created a partnership with the Foundation Fighting Blindness, based in Columbia, Md. Through the generosity of Cleveland native Gordon Gund and his wife, Lulie, and the Harrington family, we will assist 30 Gund-Harrington Scholars over the next 10 years to turn their breakthroughs into medicines within the newly established National Center for Excellence in Fighting Blindness at University Hospitals.

We also have strengthened our financial base. Takeda, the largest pharmaceutical manufacturer in Japan, made a $25 million strategic investment in BioMotiv, The Harrington Project's for-profit accelerator. The relationship will include strong support for Harrington Scholars in the therapeutic areas of immunology and cardio-metabolic diseases.

In another endorsement of our mission, we received a $25 million grant from Ohio's Third Frontier Technology Commercialization Center, the largest award of its kind in almost a decade. The monies will help support breakthrough developments in all areas of medicine.

Our growth in new directions with regional, national and international partners validates our open model of drug development to ensure that patients get the best that medicine has to offer. That exciting promise can be found in the discoveries of our 36 Harrington Scholars, including the new class of Scholar-Innovators introduced in this publication.

I invite you to read more about the 2015 Harrington Scholar-Innovators and the institute's 2014 accomplishments in this annual review. Thank you for your continued support of our mission.

Jonathan Stamler, MD
Director, Harrington Discovery Institute
Robert S. and Sylvia K. Reitman Family Foundation Distinguished Chair in Cardiovascular Innovation
Director, Institute for Transformative Molecular Medicine
Professor, Case Western Reserve University School of Medicine

Harrington Discovery Institute

MISSION:

To advance medicine and society by enabling inventive physician-scientists to turn their discoveries into medicines that improve human health.

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Private Philanthropy and the Power to Make a Difference

Ron Harrington, founder of **The Harrington Project**, and **Gordon Gund**, chair and co-founder of the **Foundation Fighting Blindness**, have more in common than their Cleveland roots. They share a fierce dedication to using their personal wealth to make a difference in human health and inspiring like-minded individuals to do the same. In October 2014, the two visionary leaders and their organizations created the National Center for Excellence in Fighting Blindness, a Gund-Harrington Initiative, based at University Hospitals. Here, they share some of their personal philosophies about private philanthropy's role in drug discovery and development.

How does philanthropy figure into The Harrington Project's mission?

HARRINGTON: Philanthropy is essential to our mission of accelerating breakthrough discoveries into medicine for patients in need. Philanthropy is our foundation. It supports our unique model for drug discovery and development, which can attract the crème de la crème of physician-scientists, advisors and industry experts – the best in the world. Our culture of philanthropy engages individuals and families who have the fire in their belly to make a difference and are willing to take a leadership role by supporting the very best medicine has to offer.

What is the role of federal funding in support of drug development?

GUND: The cost of research from basic science through clinical trials can be billions of dollars. And a huge funding gap exists between the basic science that the NIH [National Institutes of Health] is willing to fund and commercialization. NIH and the National Academy of Sciences generally do not naturally fund translational research. That means the Harrington Discovery Institute and philanthropic foundations like the Foundation Fighting Blindness play a key role in advancing early research. Fortunately, these organizations can direct resources efficiently, so each donor can make a difference. Translational research must receive funding through private philanthropy if we are going to bring new treatments to market. This is the era of the "venture philanthropist."

Why is private philanthropy becoming more important than venture capital financing in funding medical breakthroughs?

HARRINGTON: That's simple – the conventional venture capital model for advancing breakthroughs does not work. A new approach is needed. Venture capitalists need a short-horizon timeline to achieve profitability. With early-stage discoveries, that isn't possible. We rely on venture philanthropy, also called impact philanthropy – funding that represents a philanthropist's personal commitment to making a change in the world – one that may take 10 years or more to become a reality. Our model includes a for-profit arm called BioMotiv. The success of the for-profit is essential to our mission of supporting physician-scientists and developing the next generation of treatments and cures. Philanthropy assists the for-profit so it can be successful, with the goal of making a significant difference to society.

Does private philanthropy bring an added value beyond the financial to these endeavors?

GUND: Success in drug discovery and development is as much about people and relationships as it is about finance. The key to successful collaboration is people. If you can bring together passionate people who want to see change happen, you can do almost anything, including advancing scientific discoveries from the lab to patient care.

What would you say to individuals who want to be part of The Harrington Project?

HARRINGTON: If you share our values and want to make a difference, join us. If you want to find a cure for disease, you can help. If you want to support the nation's best and brightest physician-scientists, we are your partner. And if you are an entrepreneur with a heart for doing the right thing, this is the mission-directed model for you.

"If you are an entrepreneur with a heart for doing the right thing, this is the mission-directed model for you."

Ron Harrington

Gordon Gund and William Schmidt

Foundation Fighting Blindness

In 2014, the Foundation Fighting Blindness (FFB) became the second disease-focused foundation to partner with the Harrington Discovery Institute.

Foundation Fighting Blindness

Cleveland native, entrepreneur and businessman Gordon Gund, who became blind in his early 30s due to retinitis pigmentosa, established the FFB in 1971. The FFB's singular goal is to drive the research that will provide preventions, treatments and cures for people affected by inherited retinal diseases.

As a result of their shared commitment to advancing medicines to help patients, the FFB and Harrington Discovery Institute have established the National Center for Excellence in Fighting Blindness, a Gund-Harrington Initiative, at University Hospitals. The initiative will make Gund-Harrington Scholar Awards that recognize innovators in North America whose research has the potential to advance standards of care for retinitis pigmentosa and other retinal diseases. The center will make an average of three awards per year of up to $900,000 each over three years.

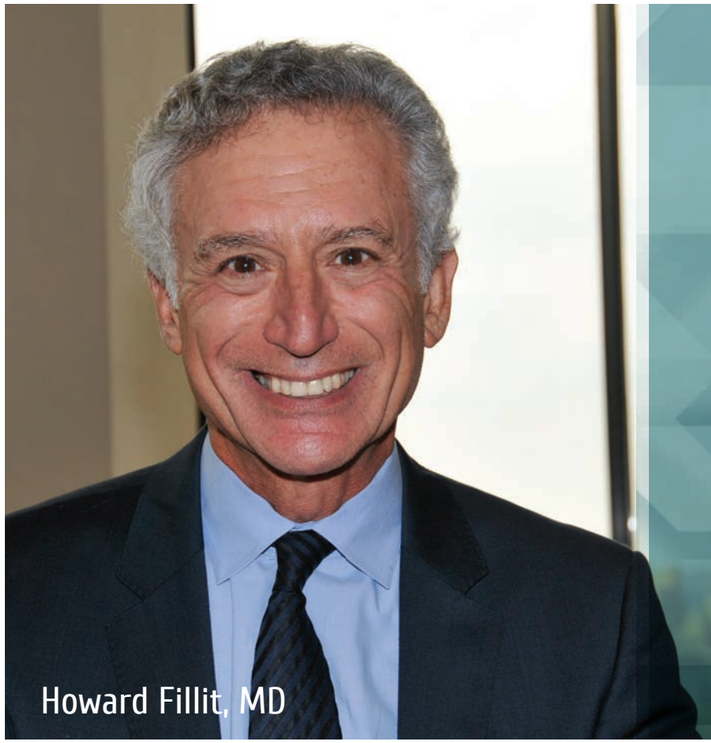
In addition to the financial support, Scholars will receive nonfinancial support in the form of project management and guidance through the Harrington Discovery Institute's Innovation Support Center. With this support, Scholars are expected to develop a lead drug candidate that has strong potential to enter clinical trials and be developed into a commercial product.

Subsequent clinical development may be supported by the Foundation's Clinical Research Institute and other commercial partners, but the Foundation looks to the alliance with the Harrington Discovery Institute to strengthen its clinical pipeline, explains William Schmidt, FFB Chief Executive Officer. "Prior to our collaboration, many of our skilled scientists lacked the resources and regulatory knowledge required to progress translational projects through the preclinical phase to the point where they could submit an Investigational New Drug Application to the FDA to initiate a clinical trial," he notes.

The FFB will look to the Harrington Discovery Institute's Innovation Support Center to develop those translational projects that need focused management. Schmidt believes that collaboration can make a life-changing difference. "It means we will speed up the process of getting translational projects to clinical trials – and to patients."

The first Gund-Harrington Scholar Awards will be announced this summer.

"It means we will speed up the process of getting translational projects to clinical trials – and to patients."



Howard Fillit, MD

A Common Vision Inspires New Directions

Since the Harrington Discovery Institute's inception, forging partnerships with disease-focused foundations that share its commitment to advancing drug discovery and development has been central to fulfilling its mission. Over the past two years, the Harrington Discovery Institute has reached out in new directions to develop relationships that multiply the power of its resources to deliver promising new drugs to patients more quickly.

Alzheimer's Drug Discovery Foundation

The Harrington Discovery Institute established its first foundation partnership in 2013 with the Alzheimer's Drug Discovery Foundation (ADDF) and selected the first two ADDF-Harrington Scholars.

Founded in 1998 by Leonard A. and Ronald S. Lauder, sons of makeup entrepreneur Estée Lauder, the ADDF provides critical seed funding to leading scientists conducting breakthrough drug discovery and clinical research focused on Alzheimer's disease treatments.

The ADDF strives to bridge the critical funding gap between the lab and commercialization for promising preclinical drug research and early-stage clinical trials. "Our approach is totally synergistic with the Harrington Discovery Institute," says Howard Fillit, MD, ADDF Founding Executive Director and Chief Science Officer and Clinical Professor of Geriatric Medicine, Palliative Care and Neuroscience, The Icahn School of Medicine at Mount Sinai. "We select and fund those projects that we believe have the greatest potential to get to clinical trials in two years. The amount of strategic advice the Harrington Discovery Institute has brought to those projects has been invaluable."

Dr. Fillit is proud to note that ADDF was the first disease foundation to partner with the Harrington Discovery Institute. "Together we explored the idea of a partnership based on the strengths of our organizations," he adds.

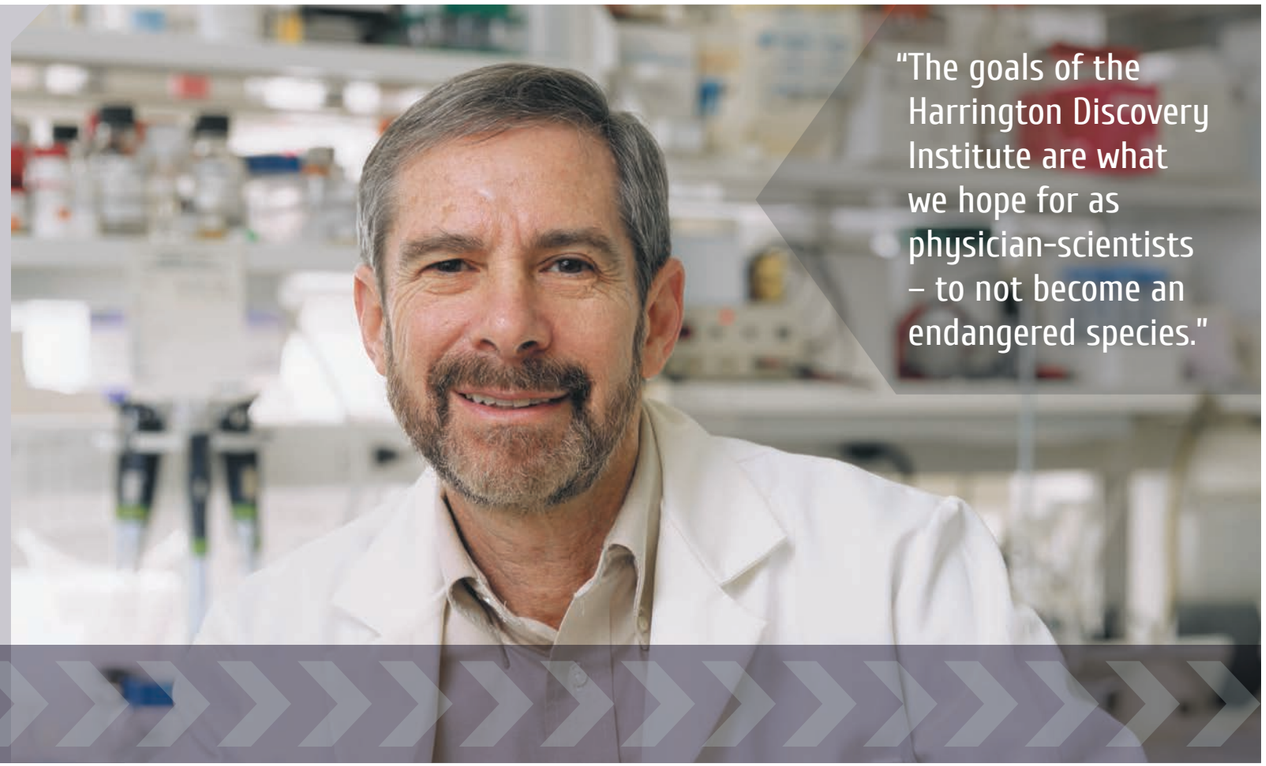
2015 RECIPIENT OF

THE HARRINGTON PRIZE FOR INNOVATION IN MEDICINE

National Institutes of Health (NIH) researcher Douglas Lowy, MD, is the 2015 recipient of The Harrington Prize for Innovation in Medicine for his groundbreaking work on the human papillomavirus (HPV) vaccine. Approved by the U.S. Food and Drug Administration in 2006, the HPV vaccine prevents cancer by warding off the viral infection that causes the disease.

In affiliation with The American Society for Clinical Investigation (ASCI), The Harrington Prize seeks to recognize individuals for achieving innovation, creativity and the potential for clinical application, explains Harrington Discovery Institute Scientific Director and ASCI President Mukesh Jain, MD. "Dr. Lowy demonstrated innovation in identifying the vaccine target and creativity in developing the antibody that has affected millions of lives. His body of work represents an extraordinary achievement, and he serves as an exemplary physician-scientist."

Dr. Lowy, Chief of the Laboratory of Cellular Oncology, Acting Director of the National Cancer Institute (NCI), and co-investigator John T. Schiller, PhD, Deputy Chief of the NCI Laboratory of Cellular Oncology and Head of the Neoplastic Disease Section, developed the vaccine technology that was licensed to pharmaceutical makers Merck and GlaxoSmithKline for development. NIH Director Francis Collins, MD, PhD, nominated Dr. Lowy for The Harrington Prize.



DOUGLAS LOWY, MD

A Meaningful Affiliation

The papillomavirus research was carried out with Dr. Lowy's long-standing collaborator and former trainee, Dr. Schiller, with whom he has co-authored more than 100 papers over the past 25 years. It is for this body of work that Dr. Lowy and Dr. Schiller have received numerous awards together, including the 2014 National Medal of Technology and Innovation Award, the 2011 Sabin Gold Medal Award and the 2007 Federal Employee of the Year Award.

Although those previous awards have been prestigious achievements, Dr. Lowy considers The Harrington Prize particularly meaningful because of its association with The American Society for Clinical Investigation. "As a member of the ASCI, I know what it is like to be a physician-scientist and how prestigious the organization's awards are," he says. "The goals of the Harrington Discovery Institute are what we hope for as physician-scientists – to not become an endangered species."

Innovation Takes Flight

A native of New York City, Dr. Lowy earned his medical degree from New York University School of Medicine in 1968. He completed his residency in internal medicine at Stanford and went on to a dermatology residency at Yale. After finishing his dermatology residency in 1973, he started worrying that he was becoming a perpetual student. "That's why I started looking for a place to start a lab and spread my wings," he recalls.

He still considers it "fortunate" that he found a position with the National Cancer Institute in dermatology and a mentor in Wallace Prescott Rowe, MD, an internationally known virologist and cancer researcher who at the time was Chief of the Laboratory of Viral Diseases at the National Institute of Allergy and Infectious Diseases.

By the early 1980s, Dr. Lowy was studying papillomaviruses and beginning what would turn into a decades-long collaboration with Dr. Schiller. The discovery in the 1980s of the human papillomavirus' connection to cervical cancer motivated them to develop their original version of the HPV vaccine in the 1990s.

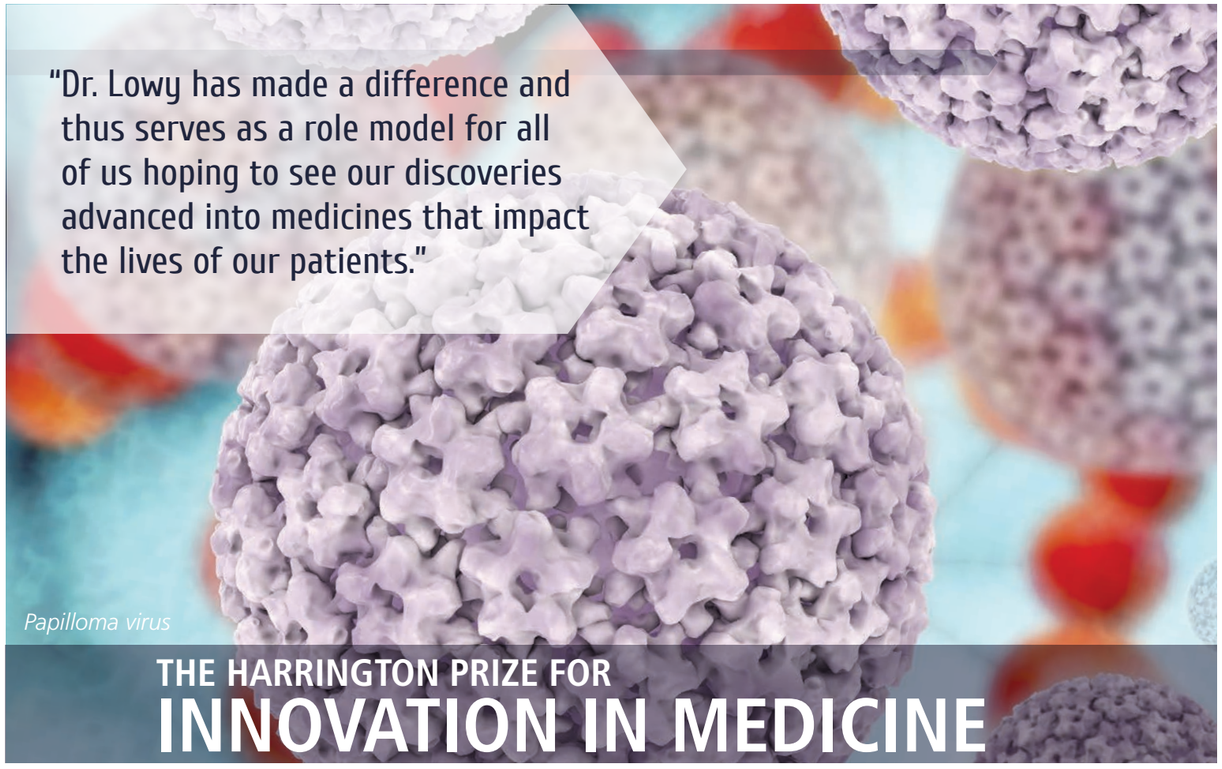
HPV is now known as the cause of virtually all cervical cancer. In the United States, nearly 13,000 women are diagnosed with cervical cancer every year, a number that has been steadily declining as cervical cancer screening has become commonplace. However, developing countries – where 80 percent of cases of cervical cancer occur – still carry a heavy disease burden.

"I was trained first as a physician. I have always thought about disease and its pathogenesis," Dr. Lowy comments. With a career spent in basic and translational research, he considers the HPV vaccine – 95 percent effective in preventing disease – his signatory contribution. "Nothing else comes close because its impact on human health is so significant."

With his roots deep in clinical practice, Dr. Lowy discovered early in his career at NIH that he "loves the rigors of scientific research and the opportunity to answer potentially important unanswered questions by looking at what everyone else has looked at and seeing what no one else has seen."

Now in his early 70s, Dr. Lowy is still energized by that scientific fervor. Not satisfied with inventing the HPV vaccine, he and Dr. Schiller now are studying the safety and efficacy of using fewer doses than the vaccine's original three-dose protocol. They are proposing a clinical trial of one or two doses, potentially in Costa Rica.

"I am as excited now as I have been throughout my career," Dr. Lowy says. "Retire? I don't know what that word means."



Papilloma virus

THE HARRINGTON PRIZE FOR

INNOVATION IN MEDICINE

The Harrington Prize for Innovation in Medicine is presented annually by The American Society for Clinical Investigation (ASCI) and the Harrington Discovery Institute to honor a physician-scientist who has moved science forward with achievements notable for innovation, creativity and potential for clinical application.

"We are pleased to join with the ASCI to honor Dr. Lowy and his team's remarkable contribution to medicine," said Jonathan Stamler, MD, Director of the Harrington Discovery Institute. "Dr. Lowy has made a difference and thus serves as a role model for all of us hoping to see our discoveries advanced into medicines that impact the lives of our patients."

Members of the ASCI Council and the Harrington Discovery Institute Scientific Advisory Board select the recipient in November each year from dozens of nominations received from around the world. In addition to receiving a $20,000 prize honorarium, the recipient delivers The Harrington Prize Lecture at the ASCI/Association for American Physicians Joint Meeting, participates at the Harrington Discovery Institute Symposium and publishes a personal essay in the Journal of Clinical Investigation.

Pediatric cardiologist and genetics researcher Harry Dietz, MD, The Johns Hopkins University School of Medicine, received the inaugural Harrington Prize for Innovation in Medicine in 2014. The ASCI, established in 1908, is one of the nation's oldest and most respected medical honor societies.

MEETING CHALLENGES WITH INSPIRATION

ALISON SIMMONS, MD, PHD

"I was very keen on being a doctor early on in my life. I knew I wanted to do something where I could challenge myself and make a lasting difference."

Oxford-Harrington Scholar Alison Simmons, MD, PhD, has turned her frustration with the limits of modern medicine into hope for hundreds of thousands of patients with Crohn's disease. In her 15 years as a gastroenterologist at Oxford's John Radcliffe Hospital in the UK, Dr. Simmons personally has cared for hundreds of patients with Crohn's, a chronic inflammatory disease of the large intestine. Crohn's disease has no known cure, leaving Dr. Simmons with no options other than treating patients for flare-ups and offering them guidance on keeping symptoms in check.

Frustrating, yes, but for Dr. Simmons, the experience also has been inspiring.

"It's very important to have a vibrant clinical department," she explains. "That's what keeps you in touch with where the translational research is needed." Gifted with an inquiring mind and a love of science and research, Dr. Simmons felt drawn to the problem of Crohn's disease as an opportunity to make a difference.

Alison Simmons, MD, PhD

University of Oxford

Oxford, United Kingdom

Choosing a Challenging Direction

"I was very keen on being a doctor early on in my life," she recalls. "When I got to the end of my specialty training after medical school in London, I knew I wanted to do something where I could challenge myself and make a lasting difference."

Her first experience in research at Oxford sealed her future. "I got hooked on research," says Dr. Simmons who is also Professor of Gastroenterology at the University of Oxford. In-depth studies related to liver disease and HIV convinced her that her destiny lay in immunology – the study of the body's defense system against viruses, bacteria or parasites.

That fascination, combined with her clinical training as a gastroenterologist, led her to the Crohn's disease research that resulted in her selection as the first Oxford-Harrington Scholar. Dr. Simmons' research focuses on the genetic risk factors for Crohn's disease; as many as 20 percent of people with Crohn's have a parent, child or sibling with the disease. New understanding about the genetics underlying the disease has the potential to impact thousands of people, she explains. In the UK, an estimated 115,000 people have Crohn's disease; in the United States, it is estimated at 700,000.

Genetic Target for Crohn's

Dr. Simmons and her team have teased out the NOD2 gene as the strongest genetic link to Crohn's disease. Normally, NOD2 defends the gut from pathogens by forming a shell around bacteria and degrading it.

"In Crohn's patients, a genetic defect prevents NOD2 from operating normally. The coating doesn't form, so the bacteria can hang around and multiply and cause damage," she explains. She hopes to discover a drug that will overcome the genetic defect to turn NOD2 back on and restore its normal function.

Although that approach seems very promising, the team is tackling the problem in the lab from the inflammation angle as well. "We have a number of paths to explore, and what will result in a treatment, we don't know," Dr. Simmons adds.

Best-case scenario, she says, would be in five years to have multiple treatment options available for Crohn's patients. With the support of the Harrington Discovery Institute, Dr. Simmons hopes to be responsible for at least one of them.

The Oxford-Harrington Scholarship Program

The Harrington Discovery Institute, in November 2014, formed an affiliation with the University of Oxford in the United Kingdom to create the Oxford-Harrington Scholarship Program. Once established, the partnership plans to expand the support of physician-scientists throughout the UK.

The Oxford-Harrington Scholarship Program will provide support to physician-scientists for promising preclinical drug research and early-stage clinical trials. Oxford-Harrington Scholars will have access to the Harrington Discovery Institute's Innovation Support Center for strategic project management that includes dedicated pharma teams that will be charged with oversight of the drug development efforts of the Oxford-Harrington Scholars. To further the transition to the commercial realm, the new alliance also includes a BioMotiv presence at Oxford.

Up to three additional awards will be made this spring to Oxford researchers working on clinical translational projects.

EXPLORING NEW DIRECTIONS

Celebrating the 2015 Harrington Scholar-Innovators and their passion for helping patients

A Strategy to Overcome Resistance

"The best part of my field is the connection between bedside and bench."

The need to take care of patients is deeply embedded in the soul of Robert A. Bonomo, MD. As an Infectious Diseases specialist at the Louis Stokes Cleveland VA Medical Center, where he is also Chief of the Medical Service, his patients are some of the sickest, usually with poor immune systems, often with multiple medical problems, complicated by one or more bacterial infections.

"My persona is like a surgeon's," he says. "I get in there and do something difficult. There is little margin for error with acute bacterial infections. It's a high-risk, high-reward field, and the rewards are very immediate. My wits are on the line with every patient."

Robert A. Bonomo, MD
Case Western Reserve University
Louis Stokes Cleveland VA Medical Center
Cleveland, Ohio
Infectious Diseases

Important Connections

When he isn't taking care of patients, Dr. Bonomo is in his lab, laboring to develop a new, better treatment for infections. "I need to do something to help people," he says, explaining his dedication to both the clinic and the lab. "The best part of my field is the connection between bedside and bench. I get samples from the patient, take it to the lab and dissect it down to find out why this organism is antibiotic-resistant."

Dr. Bonomo, who is also Professor of Medicine, Pharmacology, Biochemistry, Molecular Biology and Microbiology at Case Western Reserve University School of Medicine, has participated in the development of four drugs that are now available commercially. He believes he is on the verge of a potential fifth drug discovery with his current research project, a new beta-lactamase inhibitor. These inhibitors are commonly given with beta-lactam antibiotics like penicillin derivatives and cephalosporins to prevent the bacteria from developing drug resistance.

But the pressure is on – a recently released competing drug likewise targets beta-lactamase inhibitors. "We want ours to be better, and that's where the Harrington Discovery Institute's expertise will help us," Dr. Bonomo says. "We need the Harrington Discovery Institute because we do not know how to move our discovery to the next level."

An Unexpected Direction

A high-energy, direct-speaking man born in the Bronx in the shade of Yankee Stadium, baseball players like Mickey Mantle and Yogi Berra were the idols of his youth. A career in medicine was not even on his radar. An indifferent student through high school, he did not excel during his undergraduate career at Hamilton College.

It wasn't until he was married and working at New York University that he first considered a medical career. There, he encountered a physician-scientist who was dedicated to taking care of his patients and to developing a vaccine. For the first time, the young Robert Bonomo visualized a new world of opportunities.

He enrolled at Case Western Reserve University School of Medicine at the age of 25. As a resident at University Hospitals, he met physician-scientist and microbiologist David Shlaes, MD, PhD, and the course of his future was set. "I ended up returning for an infectious disease fellowship and became a research fellow working under Dr. Shlaes," Dr. Bonomo recalls.

Twenty years later, he hasn't lost his love for basic science or his zest for patient care. Managing both puts demands on his time and energy, but Dr. Bonomo thrives on it. "I can't imagine my life without this blend of clinical and research activities."

Cardiology with "One Foot Firmly in the Lab"

"A hotbed of new drug development." Those are the words John C. Burnett Jr., MD, uses to describe the Harrington Discovery Institute. As a Harrington Scholar-Innovator, he plans to leverage the available resources to move his lab's critical discovery – a peptide therapy for the treatment of congestive heart failure (CHF) – through the drug development pipeline as rapidly as possible.

John C. Burnett Jr., MD

Mayo Clinic

Rochester, Minnesota

Congestive Heart Failure

"Every morning, you would ask another question, and there was so much to learn that we could harness to treat patients."

In Need of Innovation

Innovation is badly needed in cardiovascular medicine, particularly for treating the 5.1 million people in the United States with CHF, notes Dr. Burnett, the Marriott Family Cardiovascular Research Professor, Mayo Clinic. Outcomes are dismal, with nearly half of people with heart failure dying within five years after diagnosis. Yet, "Despite the prevalence of CHF, there has not been a new drug to treat it in 15 years," he adds.

His proposed drug will be based on a peptide that would delay disease progression in CHF by promoting repair and regeneration of the heart. Dr. Burnett's long-range plan is to formulate the drug so it can be given as a once-a-month injection or oral medication.

He already has three biotech startups to his credit that are advancing Mayo-engineered peptides for heart failure and drug-resistant high blood pressure. But, says Dr. Burnett, who once wanted to be a lawyer or a history teacher, this latest drug would be the culmination of a career as a cardiologist spent with "one foot firmly in the lab."

A dedicated physician-scientist, he traces his passion for his field back to his cardiology fellowship under the tutelage of physiology expert and physician-scientist Franklyn Knox, MD, PhD. "That experience changed my life," Dr. Burnett says.

"There was so much that was not known. Every morning, you would ask another question, and there was so much to learn that we could harness to treat patients. That's a good life to have."

A Fresh Approach for Patients

That enthusiasm has rapidly propelled him forward with this latest discovery, which he describes as "fresh off the lab bench." Introduced at the American Heart Association annual meeting in 2013, he believes his discovery will herald a new era of CHF treatment.

With that in mind, a sense of urgency surrounds his project. "The Harrington funding comes at a sweet time, when we can put it right to use," Dr. Burnett notes. His plan is to "nail the molecular mechanism," demonstrate efficacy in large animal models, then embark on preparation for clinical testing, all on as short a timeline as possible. "That's what drives us," he stresses. "This is the future of protein therapy. At the end of the day, our goal is to have a new drug to treat CHF."

Moving in a Positive Direction

Somewhere in South Florida lives a retired high school biology teacher named Howard Weise who can pride himself on inspiring a student who is now a Harrington Discovery Institute Scholar-Innovator.

Neurologist Nicole Calakos, MD, PhD, clearly recalls the year Mr. Weise encouraged her to attend a University of Florida summer science program some 30 years ago. "When I was in high school, I was very people-oriented, and I liked science," Dr. Calakos remembers. "I credit Mr. Weise with opening a door for me by sharing an opportunity."

The summer program experience ignited in her a fervent desire to do scientific medical research. That passion carried her through her medical education and propelled her into a career as a physician-scientist.

"There's always a little serendipity in science."

Team Approach

Now at the Duke Institute for Brain Sciences and the Duke Movement Disorder Clinic, Dr. Calakos says she is in an ideal situation for a physician-scientist. "You train a long time for this job," she says. "Duke is among the top in neuroscience in the country, and here I have the ability to be well-integrated into the heart of the neuroscience and clinical neurology communities."

That accessibility is important to her research on advancing a novel class of drugs that may help treat dystonia, a brain disorder that causes involuntary twisting movements and abnormal postures. "There's always a little serendipity in science," Dr. Calakos says, explaining how she came to her discovery. "I was trying to figure out why a person in clinic had this disease and whether it was related to an unusual mutation in one of his genes."

Her subsequent research led Dr. Calakos and her team, including collaborators at the National Center for Translational Sciences (NCATS), to develop an automated screening test that quickly evaluates the biological or biochemical activity of thousands of drug-like compounds. Through this screening, they were able to identify potential treatments that would fix the unusual protein distribution that occurs in the presence of the dystonia gene mutation.

Next Steps

With support from the Harrington Discovery Institute, she plans to complete two major objectives that will move her discovery closer to clinical trials. First, she will identify how these drugs normalize the mutant protein's distribution and, secondly, she hopes to solve the problem of how to formulate an improved drug that can readily penetrate the brain.

Although Dr. Calakos recognizes there are still many hurdles between this discovery and having a treatment for her patients, she says she also is highly optimistic. "When you work with patients, it keeps you focused on the need to make a difference."

Nicole Calakos, MD, PhD

Duke University

Durham, North Carolina

Nervous System Movement Disorders

David R. Clemmons, MD

University of North Carolina
Chapel Hill, North Carolina
Osteoporosis

"I can live for a week on the positive results of a clinical trial, knowing that a discovery will make a difference in people's lives."

In Search of Strength

David R. Clemmons, MD, is one of those fortunate people who discover their direction in life early and never veer from it. Now an endocrinologist and the Sarah Graham Kenan Professor of Medicine at the University of North Carolina at Chapel Hill, he was a young medical student there when he first experienced what would become his lifelong love of medical research.

"I dropped out of medical school between my second and third years to do research in endocrinology, and that was it," Dr. Clemmons recalls. "I knew then that research was it for me."

Of Mice and Bones

The pathway to the osteoporosis project that has earned him a Harrington Discovery Institute Scholar-Innovator award has been less direct. Call it serendipity, a side effect or an accident, Dr. Clemmons discovered the osteoporosis drug he is developing when he was researching diabetes.

"We were studying diabetic nephropathy [kidney disease] in mice when we noticed that their bones were very thin and would break easily," he explains. Those fragile bones led Dr. Clemmons and his team eventually to discover a peptide (a short amino acid chain) that plays a role in stimulating bone formation and inhibiting bone resorption.

For Dr. Clemmons that was an exciting revelation. He immediately saw the potential application in osteoporosis, a possibility that spoke to his heart as well as his mind. In that peptide, Dr. Clemmons envisioned hope for the elderly women with osteoporosis he sees every week with their pain, difficulty moving, broken bones and fractures that occur simply because their bones are so weak. "These are the very patients I want to help with this discovery," he says. Among all the currently available osteoporosis drugs, only one regenerates bone, and it has limitations, he adds.

The Harrington Discovery Institute grant will help Dr. Clemmons and his team validate their discovery in laboratory animals and optimize the peptide structure. From there, a French pharmaceutical company has expressed interest in identifying the best form for the drug and moving it through the toxicology studies and other testing needed to advance it to clinical trials.

Positive Energy

Although clinical trials are at least three years in the future, Dr. Clemmons already is looking forward to them. "Seeing those results is what keep me going and energized," he says. "I can live for a week on the positive results of a clinical trial, knowing that a discovery will make a difference in people's lives."

The osteoporosis drug would give Dr. Clemmons a trio of discoveries in clinical trials. His other successes, a monoclonal antibody for diabetic nephropathy and a compound that inhibits coronary artery disease in diabetes, are currently in clinical trials.

Dr. Clemmons is modest about his achievements as a physician-scientist, but he is quietly proud of what could be his legacy. "If all three compounds make it as therapeutics," he considers, "that would be a pretty good accomplishment."

"When you get to an obstacle, you have to choose whether to go over, around, under or through it."

A Revolutionary Approach

Barry S. Coller, MD, the David Rockefeller Professor of Medicine, Rockefeller University, New York, still vividly remembers the patient who, more than 40 years ago, sparked his interest in stroke and heart attack research and unknowingly set his life's direction.

"It was 1970, and I was a fourth-year medical student at New York University School of Medicine on a neurology rotation. One of the patients who'd had a stroke had an artificial heart valve," Dr. Coller recalls. As he began researching more about the patient's treatment with the anticoagulant drug warfarin, he started to dig deeper into the role of platelets – the blood component responsible for clotting – in stroke.

Dr. Coller was intrigued, particularly because researchers at the time knew little about platelets and their activity. His quest for more information eventually led him to Marjorie Zucker, PhD, an internationally renowned platelet expert at NYU. Under her tutelage, he studied a platelet test that became the basis in 1971 of his first published scientific paper, co-authored with Dr. Zucker when he was just a year out of medical school.

That experience sowed the seeds of his passion for research and a lifelong fascination with platelets and their role in heart disease and stroke.

Emergency Preparedness

Four decades later, the fascination continues. As a Harrington Scholar-Innovator, he envisions a totally new approach to prehospital treatment for heart attack based on his small molecule RUC-4, which prevents platelets from aggregating and initiating clots. "RUC-4 is extremely soluble and so could be given by auto-injector by emergency medical service personnel to a person having a heart attack, thus preventing further heart damage," Dr. Coller says, explaining his eventual plan for the compound. But support for projects at this early stage, Dr. Coller knows, is hard to come by. "We have not had a lot of exposure to industry, and the economic model for this compound is complex," he notes. "We need a business model that will make it possible to partner with a large pharmaceutical company for Phase II and III studies." He is hopeful that the Harrington Discovery Institute, Innovation Support Center and BioMotiv will help him make those connections.

In the ensuing years between that first paper in 1971 and the RUC-4 project, Dr. Coller has learned to accept the challenges of research. "When you get to an obstacle, you have to choose whether to go over, around, under or through it," he says.

Long Road to Success

His first experience with drug discovery and development put that perseverance to the test. It began in 1981 with his discovery of a monoclonal antibody that blocks platelet binding sites to prevent blood clotting. That discovery led to 14 years of basic research, clinical testing and regulatory submissions in collaboration with scientists at Centocor.

The U.S. Food and Drug Administration approved abciximab, the drug based on Dr. Coller's discovery, in 1994. It is used around the world to prevent platelets from initiating blood clots in high-risk patients undergoing metal stent placement in a coronary artery.

Dr. Coller is now resolved to find a treatment that fills the gap in care between home and hospital for heart attack victims. "We need a revolution in advancing prehospital care for people with heart attacks," he explains. He believes that RUC-4, with help from the Harrington Discovery Institute, holds the promise of advancing that revolution.

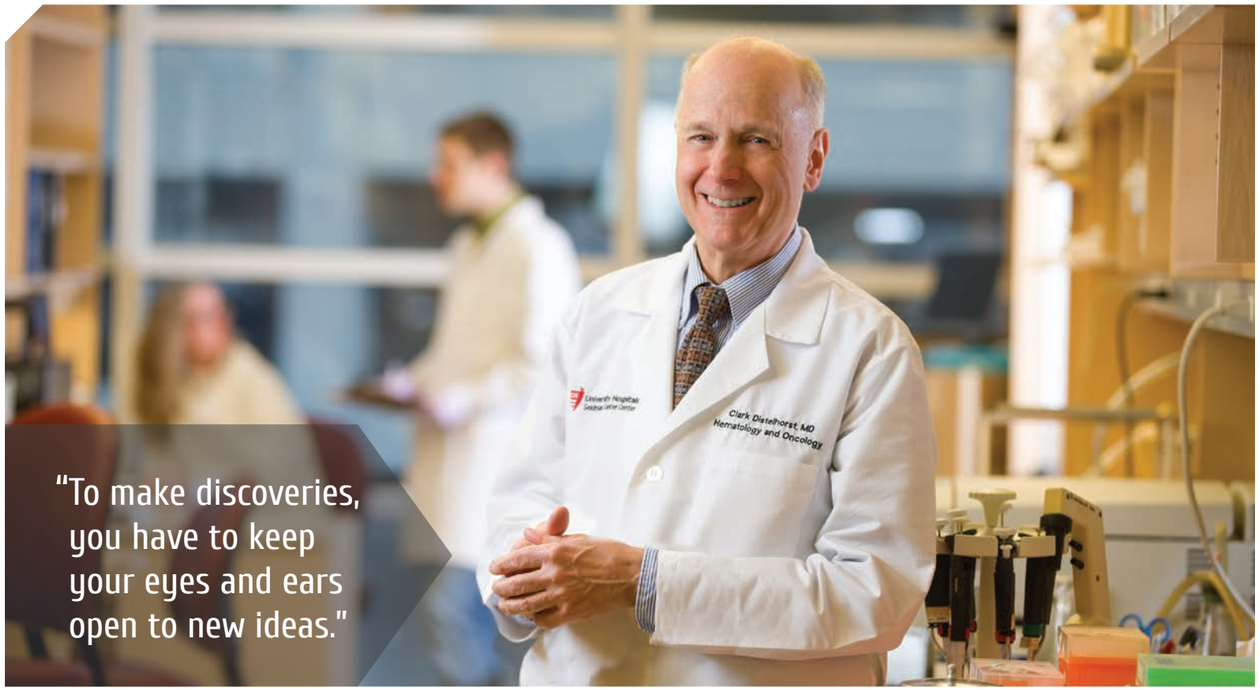
Barry S. Coller, MD
Rockefeller University
New York, New York
Myocardial Infarction

Clark W. Distelhorst, MD
Case Western Reserve University
Cleveland, Ohio
Blood Cancers

JOURNEY OF DISCOVERY: From Back-Porch Latin to a Cure for Cancer

For Clark W. Distelhorst, MD, spending summers on the back porch of his childhood home translating Latin with his mother, a high school Latin teacher, is one of his favorite memories. Who can tell whether it was that early interest in Latin, the kindly, local family doctor or both that sparked his interest in medicine, but Dr. Distelhorst remembers telling his parents at a young age of his desire to be a doctor.

That early certainty eventually took him to medical school at The Ohio State University College of Medicine where he discovered a world beyond the family doctor's sphere. "In medical school, I learned there are so many diseases we don't have treatments for," he recalls. That realization resonated with him, shaping his decision to specialize in hematology and, ultimately, his career as a physician-scientist.



"To make discoveries, you have to keep your eyes and ears open to new ideas."

A Passionate Pursuit

His clinical practice as a hematologist at University Hospitals Case Medical Center and his laboratory research have a natural synergy. "I am very interested in taking care of patients and in understanding the disease they have," he explains.

As a hematologist, leukemia and lymphoma are his major clinical and research interests because of the need to develop new treatments, particularly for acute myeloid leukemia (AML) with its high mortality rate. Treatment and outcomes for AML have not changed significantly in the past 30 years, a fact that Dr. Distelhorst takes as practically a personal challenge as a physician and a scientist. He has devoted more than 30 years to understanding how to develop novel treatments for these malignancies.

One of his major goals is to understand the Bcl-2 protein, which leukemia and lymphoma cells use to stay alive. A few drugs do block Bcl-2 and thus kill cancer cells, but these drugs block only one of the mechanisms that Bcl-2 uses to keep leukemia and lymphoma cells alive. In 1990, Dr. Distelhorst and his team discovered another Bcl-2 mechanism. They developed a small peptide, BIRD-2, that blocks this mechanism and kills leukemia and lymphoma cells, including AML cells.

An Accidental Discovery

The team discovered Bcl-2's second mechanism – which holds the promise of being a major treatment target for certain cancers – almost by accident while they were studying corticosteroids, Dr. Distelhorst notes, adding, "Science isn't always programmed. To make discoveries, you have to keep your eyes and ears open to new ideas."

Since the BIRD-2 discovery, Dr. Distelhorst and his team have identified two drug-like compounds that mimic the peptide's action. They have demonstrated that using one of their compounds along with existing drugs causes more cancer cell death. One of their compounds appears very promising against AML cells.

With the Harrington Discovery Institute's support through the Innovation Support Center, Dr. Distelhorst hopes to improve the compounds and develop them into drugs that can be tested in preclinical models. Ultimately, he looks ahead to the day when one of the team's compounds is in clinical trials with leukemia and lymphoma patients, especially AML patients.

Legacy of Integrity

At the end of the day, Dr. Distelhorst says two things are most important to him: believing that he tried to do his best for every patient he encountered and seeing that his research has some degree of importance and was well and honestly done.

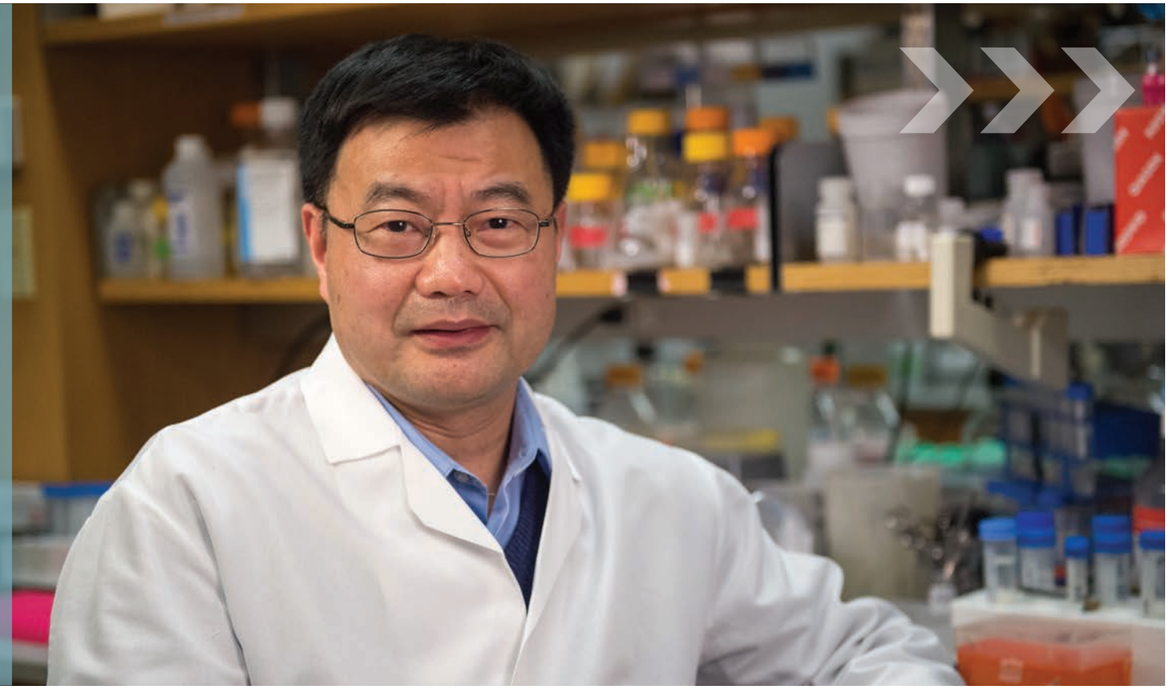
For now, he is impatient but persistent – impatient in that he wants a drug for patients that works but persistent in doing the painstaking, meticulous work it takes to be successful. "Science takes time. It's not a source of instant gratification," he says. "We want to make sure we get it right."

Xianxin Hua, MD, PhD
University of Pennsylvania
Philadelphia, Pennsylvania
Type 1 Diabetes

Life Lessons in Patience

When Xianxin Hua, MD, PhD, a professor at the Perelman School of Medicine, University of Pennsylvania, isn't in his lab, he's likely to be found casting his line in a peaceful river or a lake. Something of a philosopher besides being a physician-scientist and a fisherman, he draws a parallel between science and fishing. "Like in fishing, with science it takes a long time to discover something," he explains.

"This is science on the cutting edge of research, and it has led us to discovering a potential new drug."



An Unexpected Change in Direction

He keeps that in mind as he looks back on the path that has brought him to a Harrington Scholar-Innovator award. It was 2006 when he and his team were studying the tumor suppressor effects of a specific gene. To their surprise, in addition to the gene's role in regulating the growth of endocrine cells, they found that acutely deleting the gene resulted in the rapid proliferation of beta cells, the specialized cells in the pancreas that manufacture insulin. In people with diabetes, beta cells are damaged or not functioning normally, leading to the abnormal blood sugar levels that characterize the disease.

"I vividly remember reviewing the data that morning with a student," Dr. Hua recalls. "That was the moment it dawned on us that wow, this is a direct effect."

For the first time, Dr. Hua's lab had provided scientists with evidence of the direct relationship between this gene and type 2 diabetes. When their findings were published and communicated in the American Society of Molecular Biology, it was hailed as a groundbreaking discovery.

The team has continued studying the role of a protein called menin, which is encoded in the gene they deleted in the beta cells, and how it regulates the expression of genes that control a beta cell's capability to regenerate. "This is science on the cutting edge of research, and it has led us to discovering a potential new drug," Dr. Hua says.

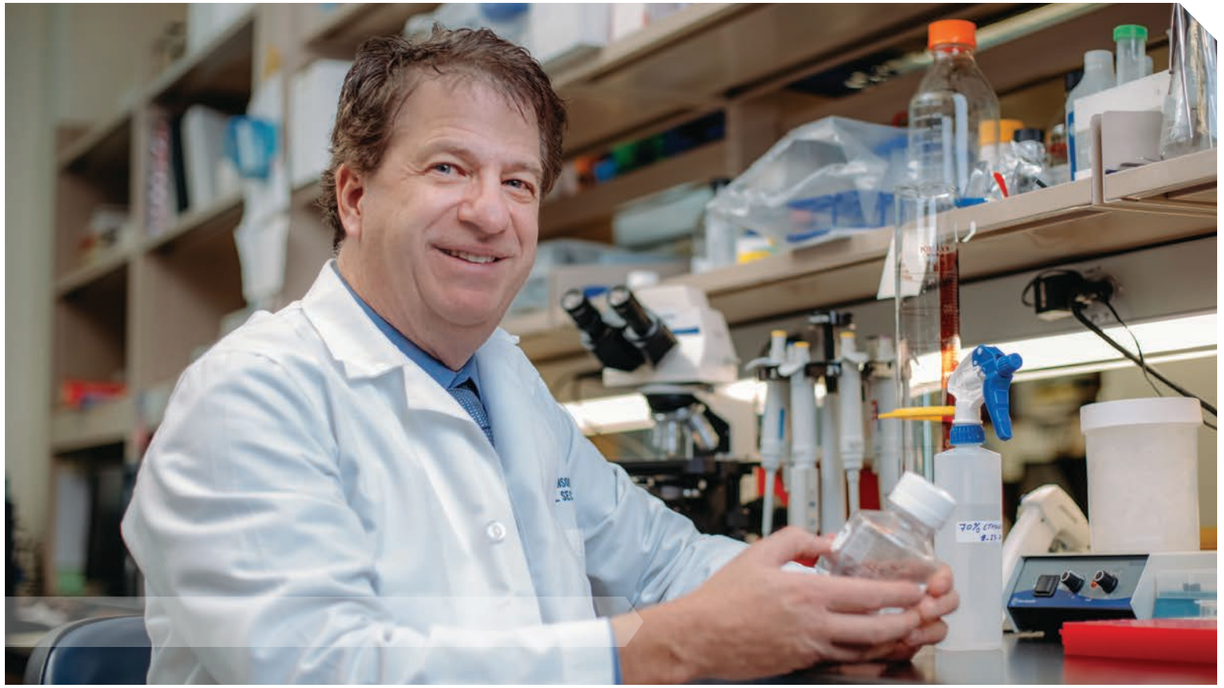
Open to the Unexpected

Like a fisherman eager to try an untried fishing spot, Dr. Hua believes it is important as a physician-scientist to stay open to the unexpected discovery. "I follow my passion to see where it leads and whatever difference it might make," he explains. "A discovery that would improve people's lives has always been my dream."

So far the team's exploration has led to development of a small molecule inhibitor that may restore normal blood sugar levels in laboratory animals with high blood sugar or diabetes.

If the research continues to unfold as it has so far, "it would be a radical leap forward in the treatment of diabetes," Dr. Hua says. "A small molecule drug could be used to treat diabetes by tapping into the diabetic patient's own ability to regenerate beta cells."

His hope is to use the Harrington Discovery Institute resources to develop a better, more powerful molecule that can eventually be advanced to clinical trials. He knows that reaching that goal is still years in the future. Fortunately, patience is a quality he has cultivated during quiet hours with his rod and reel along the water's edge.



Richard J. Johnson, MD

University of Colorado Denver,
Health Sciences

Denver, Colorado

Obesity and Diabetes

"If we can pull this off, the day is coming when we will be able to reverse the current epidemics of obesity and diabetes."

Turning Off the Fat Switch for Good

Richard J. Johnson, MD, the Tomas Berl Professor of Medicine, and Chief of the Division of Renal Diseases and Hypertension at the University of Colorado Denver, Health Sciences has been dubbed the "sugar researcher" in the media, interviewed by popular health and nutrition writers and radio hosts, featured on websites and published two books available on Amazon.com. Considered controversial, compelling and creative among the scientific community, there's no doubt that Dr. Johnson's research on sugar and obesity has captured the attention of even the nonscientist public.

The Secret Switch

His body of work presents convincing evidence that obesity is triggered by a "switch" in our metabolism that makes us want to eat more and exercise less. "Our work focuses on how diet (and in particular fructose) may have a role in the epidemics of obesity, diabetes, hypertension and kidney disease, and how those sugars may cause their metabolic effects by raising uric acid levels," Dr. Johnson explains.

He hypothesizes that fructose metabolism turns on what he calls "the fat switch" by raising uric acid levels, which in turn cause oxidative stress inside cells in the energy factories known as mitochondria. As a result, the cells' ability to metabolize fat is blocked and cellular energy output is reduced. The energy deficit causes cells to signal the brain to eat more. The person eats more and starts packing on the pounds.

"We have very powerful data from animals that demonstrate that fructose increases food intake while reducing the metabolic rate," Dr. Johnson explains. The result is what he terms "a perfect storm for how fructose may cause obesity, insulin resistance, kidney damage and fatty liver."

Unfazed by Controversy

His portrayal of fructose as the criminal in obesity is admittedly controversial. But skepticism doesn't faze Dr. Johnson, who holds that his scientific evidence, anthropology, evolution, comparative physiology, biology, molecular biology and history all support his conclusions. "The data are the data," he says.

Unfortunately, the obesity solution is not as simple as reducing added sugars (table sugar and high fructose corn syrup that are the main sources of dietary fructose) since the body also can make fructose. The key, Dr. Johnson believes, is inhibiting the fructose metabolic pathway.

He and his team are trying to build such an inhibitor that is safe and effective in humans, leading, they hope, to development of the first drug to block sugar's metabolic effects. A self-described workaholic, Dr. Johnson says he already has compounds that work in the test tube. The next step is to identify the optimal one and refine it into a marketable drug. "I hope to work with some top-gun scientists with the Harrington Discovery Institute to get there," he says optimistically.

Despite his confidence, Dr. Johnson admits, "It's not a slam-dunk. But," he adds, "if we can pull this off, the day is coming when we will be able to reverse the current epidemics of obesity and diabetes."

Marikki Laiho, MD, PhD
The Johns Hopkins University
Baltimore, Maryland
Cancer

Unexpected Discovery Leads to a Fresh Direction

A distinguished researcher, instructor and physician in the United States and her native country of Finland with a host of impressive degrees and titles, Marikki Laiho, MD, PhD, Professor of Radiation Oncology and Oncology in the Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University, is remarkably approachable and down to earth. Possibly it's having three children in the teen – young adult age range (ages 15, 17 and 20) or the close family ties across three generations of family in the United States and Finland that keep her grounded.

Whatever it is, Dr. Laiho has the gift of being able to readily translate the complexities of her research on RNA polymerase I transcription into easily understandable terms. "RNA polymerase I transcription is a key process that helps cells synthesize proteins," she explains. "Cancer cells are so hooked on this process that if the transcription is switched off, cancer cells die. This has uncovered a new way to target the cancer cells."

A Watershed Discovery

The project that earned Dr. Laiho a Harrington Discovery Institute Scholar-Innovator award began with her research on p53, a protein that protects cells from DNA damage. If a cell loses the function of p53, it loses its safeguards against genetic damage and tumor growth is uncontrolled. Her original search was to find a small chemical molecule that could reactivate the p53 pathway. "When we realized our molecule went beyond that and could kill cancer cells independent of p53, that was a watershed," she says.

As a Harrington Scholar-Innovator, Dr. Laiho plans to tap into the Innovation Support Center Advisory Panel's expertise in early-stage drug development to define the next steps for her project. At this stage, she is tentatively targeting her drug toward advanced prostate cancer, one of her longtime clinical interests.

Although Dr. Laiho's days now are devoted primarily to research, she is thankful for her clinical background. The realities of treating patients is another facet to her life that, like her family, keeps her grounded. "It helps me ask questions from the disease side that bridge between the basic science and the patient," she notes.

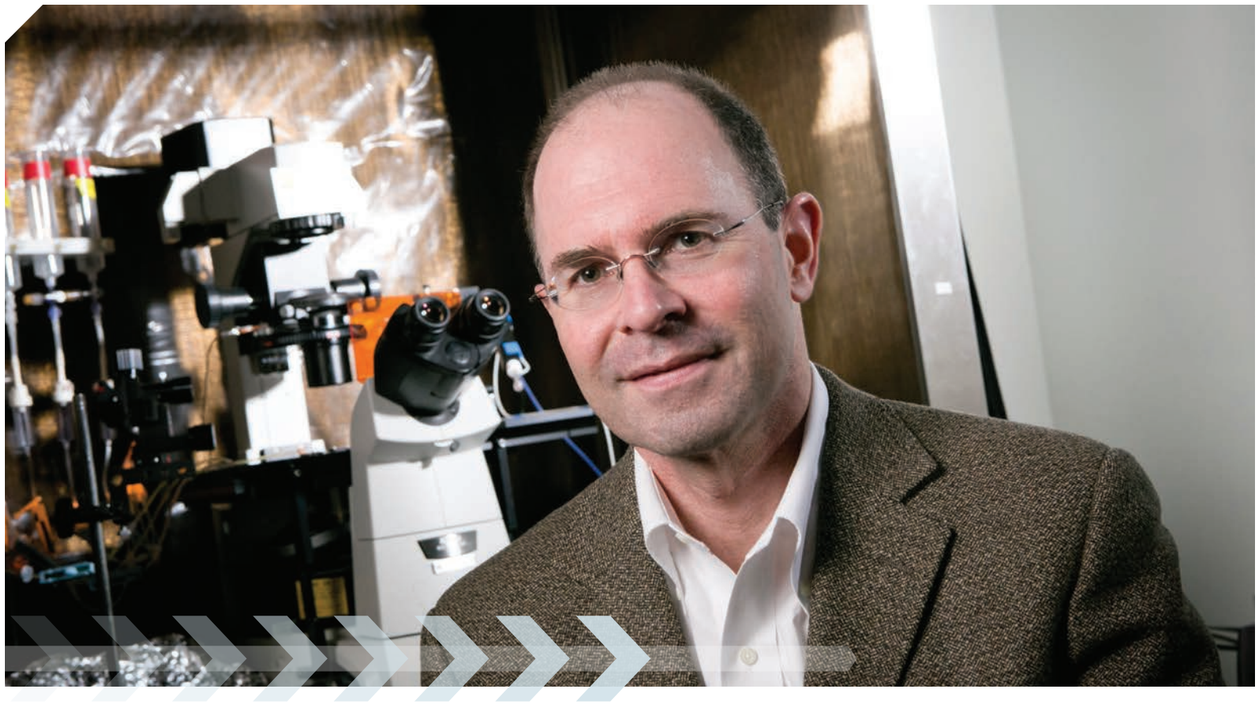
Driven by the Need for Answers

Dr. Laiho's medical interest veered toward cancer early in her career, while still in medical school, as the fledgling understanding of cancer and genetics was unfolding. "As a scientist, I ask what is the biologic reason? When the answer was I don't know, that's what drove me to research."

Now she finds herself at the threshold of not only a new phase in her career as she participates in drug development for the first time but also a new era in cancer treatment. "Our discovery is fundamental because the RNA polymerase I pathway has not received any attention as a therapeutic target," she says. Proceeding down an unproven path is risky, Dr. Laiho adds, but quitting is not an option.

"There are few times in your life when you realize that you have to lead the field and see what happens. We must go ahead."

"As a scientist, I ask what is the biologic reason? When the answer was I don't know, that's what drove me to research."



In Pursuit of Discovery

"The secret to inspiration and serendipity is to reach deep into the areas that fascinate and enliven you and wake you up in the morning."

The Little Book of Thinking Big, Richard Newton

Geoffrey S. Pitt, MD, PhD

Duke University
Durham, North Carolina
Osteoporosis

Geoffrey S. Pitt, MD, PhD, Professor of Medicine, Duke University, is privileged to live that wisdom every day. "I love discovery. That's what takes me to work in the morning," he explains.

The pursuit of discovery brought Dr. Pitt to Duke and its nationally renowned Division of Cardiology in 2007 and likewise to his induction into the prestigious American Society for Clinical Investigation the same year. As Director of the interdepartmental, multidisciplinary Ion Channel Research Unit at Duke, Dr. Pitt explores the role of ion channels in heart disease and many other disease systems.

"At Duke, the multidisciplinary approach of the Ion Research Channel Unit leads to cross-pollination," Dr. Pitt explains. "By working together with other investigators studying development and calcium signaling, we're starting to understand fundamental and unexpected roles for calcium channels in a number of different organs."

Unexpected Directions

As a cardiologist, Dr. Pitt continually seeks connections between patients and his lab research with the goal of translating his research into patient treatments. When he read a report that a number of patients with arrhythmia (heart rhythm disorder) caused by a cardiac calcium channel disorder also had syndactyly, a fusion of their fingers, it triggered his scientific imagination. "I began to wonder how that calcium channel disorder in the heart affects limb development," Dr. Pitt says.

A link between bone and calcium channels in the heart became obvious as he and his team delved deeper. They discovered how the cardiac calcium channel disorder was associated with other physical defects in arrhythmia patients, such as a large lower jaw. They also discovered that the calcium channel disorder could produce thicker bones.

That led Dr. Pitt to speculate on the possibility of a therapeutic application in osteoporosis, the brittle bone disease. Based on this research, Dr. Pitt identified certain calcium channels as a target for a new drug. With a number of drugs targeting calcium channels already available, "Our initial strategy is to tweak existing drugs to target the desired calcium channels in bone," he explains.

From there, he hopes to synthesize and test new compounds with support from the Harrington Discovery Institute and the Innovation Support Center and, ultimately, design a new drug to treat osteoporosis, a disease that affects some 50 million Americans. Dr. Pitt views his relationship with the Harrington Discovery Institute as a "wonderful opportunity" to move discovery from the lab bench to the clinic and make a lasting difference in the everyday lives of possibly millions of people.

"Discovery [is] what takes me to work in the morning."

Ira Tabas, MD, PhD

Columbia University
New York, New York
Diabetes and Atherosclerosis

Dedicated to Discovery, Determined to Help People

A 30-year career in medical research has sharpened the sensitivities of Ira Tabas, MD, PhD, and altered his motivation. "I began as a basic scientist in cellular biochemistry, and for the first 20 years of my career, I was driven by the love of discovery," he explains. "As I have gotten older, I still love discovery, but I am driven more by an interest in making my research translational. Will it do any good for people?"

A Resounding Yes

The potential for his current project to answer that question with a resounding "yes" is what excites him about it, he says. Dr. Tabas, who is Richard J. Stock Professor & Vice-Chairman of Research, Department of Medicine at Columbia University, has discovered a new biologic pathway in the liver that appears to be central to the development of diabetes. After five years of testing promising inhibitors to that pathway, he found a compound that in animal models delivered the desired result.

"It was a clear 'aha' moment," Dr. Tabas says. "The first time we used it in animal models, it lowered blood sugar and reduced insulin. We thought, 'This could develop into something.'"

Now he and his team are working on a new compound that acts the same in the body, but is safer and easier to use in humans. Eventually the team will test this compound to define its structure and develop it further.

Meanwhile, the team must answer the basic question of whether inhibiting their target pathway in the liver is safe in people. With support from the Harrington Discovery Institute, they will evaluate the effects on the heart, fat metabolism and potential unintended consequences.

Potential Worldwide Impact

Dr. Tabas believes the concept of inhibiting the liver pathway has great possibility for success as a treatment to prevent diabetes.

On average, 37 percent of U.S. adults aged 20 or older have prediabetes. In people age 65 and older, that percentage rises to 51 percent, meaning the potential for making a major impact on human health is staggering, Dr. Tabas notes. "We know the pathway is activated in prediabetes. We are testing to see if we could treat these people and prevent diabetes from developing."

Dr. Tabas is optimistic about this project, particularly because the drug attacks the fundamental mechanisms of diabetes in the liver. The drug's heart-safety profile is another reason for optimism, he notes. "All new diabetes drugs have to go through heart safety trials before approval," he explains. "The evidence to date suggests that this approach is not only heart-safe but may actually benefit the heart directly."

No Room for Discouragement

But Dr. Tabas tempers optimism with caution. "You have to constantly confront failure," he says. "But if you get discouraged, you will never get anywhere. You have to believe in what you are doing."

That commitment, coupled with the funding and resources available from the Harrington Discovery Institute and the Innovation Support Center, could propel a potentially powerful diabetes treatment to clinical trials as soon as five years from now.

"But if you get discouraged, you will never get anywhere. You have to believe in what you are doing."

Innovation Support Center Delivers on Its Promise

Two years ago, Gavril Pasternak, MD, PhD, the Anne Burnett Tandy Chair of Neurology at Memorial Sloan Kettering Cancer Institute, had a discovery that he believed had the potential to revolutionize pain management.

Dr. Pasternak and his team had synthesized a compound in the lab that is as effective as opioid-based drugs for pain relief, minus the common side effects. He knew it was exciting and promising, but he faced a conundrum – taking his compound from laboratory to patient care would require resources and expertise that are not readily available in the academic environment.

Selected as a Harrington Scholar-Innovator in 2014, Dr. Pasternak sought assistance from the Harrington Discovery Institute's Innovation Support Center. "They have the resources to look at essentials like intellectual property, patents and marketing as well as expertise in medicinal chemistry," Dr. Pasternak explains. "The more I dealt with them, the more I realized their value."

He made a crucial connection with Innovation Support Center Advisory Panel member John Piwinski, PhD, a former vice president and research chemist with Schering-Plough and now a consultant to the pharmaceutical industry. He suggested critical changes in the compound's structure that would minimize potential cardiac side effects to strengthen its commercialization potential.

Dr. Piwinski finds working with the Harrington Scholar-Innovators to be a unique experience. "It's very exciting to try to give them guidance that might be helpful in commercializing their discoveries," he says. In the year he has been working with Dr. Pasternak, Dr. Piwinski's enthusiasm for the pain reliever project continues to grow. "If this translates into humans, it will be transformational," he notes.

Strategic Assistance

Robert Lipper, PhD, has been consulting with 2014 Harrington Scholar-Innovator and Stanford University researcher Jean Tang, MD, PhD, on her skin cancer topical gel project. Dr. Lipper, whose experience includes 24 years in formulation research and development at Bristol-Myers Squibb, is an expert in designing compounds that are "developable" – meaning, he explains, that "you can optimize the compound to be potent and effective while retaining properties favorable for getting it to the site of action in the body."

Dr. Tang is working with a drug that is an effective treatment for basal cell carcinoma (a type of skin cancer) but which has serious side effects when given as a pill. At the time Dr. Tang and Dr. Lipper first met, she already was developing its formulation as a topical gel for direct application to the skin. "Our role was to help her think through some of the strategic considerations on how to move her project forward," Dr. Lipper says.

A Unique Model

Medicinal chemistry consultant William Greenlee, PhD, a veteran of both Merck and Schering-Plough, developed an almost instantaneous rapport with 2013 Harrington Scholar-Innovators Scott Oakes, MD, and Feroz Papa, MD, PhD, at their first meeting in July 2013.

"The Innovation Support Center is the most unique thing about this award," Dr. Oakes notes. "Most awards are money and it's up to you to figure out how to use it to advance your project. The truth is, we in academia don't know how to do that. The Innovation Support Center helped us identify those barriers."

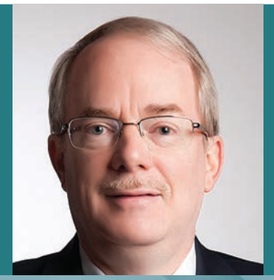
In early discussions, Innovation Support Center Chairman Perry Molinoff, MD, suggested Drs. Oakes and Papa consider changing their target from diabetes to retinitis pigmentosa, an eye disease that causes blindness. The pair considered his reasoning – mainly that pursuing a utility drug for use in the eye would be a more-straightforward path to approval – and changed their plan accordingly.

During monthly teleconferences over the next 18 months, Dr. Greenlee and other Innovation Support Center experts helped the physician-scientists optimize the potency of their lead compound, discover additional hits in their screen and obtain additional funding from the Harrington Discovery Institute for developing a formulation for delivery into the eye. Innovation Support Center business advisors provided guidance on matters such as patent strategy and intellectual property.

"I feel really good about the contributions of the Harrington Discovery Institute on this project," Dr. Greenlee says. "It has been one of the best, and working with Scott and Feroz has been a lot of fun."

For the physician-scientists, interaction with Innovation Support Center advisors smooths the journey from lab bench to patient care. Dr. Pasternak sums up the advisors' contributions: "Without them, moving my project along would be like trying to cross the Atlantic in a rowboat with a 5 hp motor. I'd get there but I would have to do a lot of bailing and take a few detours."

"I feel really good about the contributions of the Harrington Discovery Institute on this project."



William Greenlee, PhD

John Piwinski, PhD

"It's very exciting to try to give them guidance that might be helpful in commercializing their discoveries."

"If we truly want to deliver medical breakthroughs to patients for whom therapeutic options are currently limited, or absent, it is vital to forge these close relationships among innovators, expert resources and pharmaceutical companies at the earliest opportunity."

Baiju Shah

Unfolding the Pathway to Drug Development

BioMotiv, the less-than-three-year-old mission-driven accelerator associated with The Harrington Project for Discovery & Development, already is demonstrating its talents for innovation and attracting the interest of major pharmaceutical companies.

In September 2014, BioMotiv announced a strategic partnership with Takeda in the cardio-metabolic and immunological therapeutic areas. The partnership includes a $25 million investment in BioMotiv.

In December 2014, Orca Pharmaceuticals entered into a development partnership with AstraZeneca, becoming the first BioMotiv company to partner with a major pharmaceutical company. BioMotiv launched Orca in September 2013 to progress the research of Dan Littman, MD, PhD, New York University, on a potential drug therapy for autoimmune diseases such as psoriasis and rheumatoid arthritis. The goal of the Orca-AstraZeneca agreement is to advance an oral drug for these diseases based on Dr. Littman's work. The deal includes an up-front payment and milestone payments totaling $122 million and royalties.

The partnerships are gratifying at several levels, notes BioMotiv CEO Baiju Shah. "The Takeda and the AstraZeneca events exemplify that major pharmaceutical companies are interested in breakthrough science that is expertly developed," he says.

Scott Oakes, MD

Feroz Papa, MD, PhD

On the Fast Track

Scott Oakes, MD, and Feroz Papa, MD, PhD, University of California, San Francisco (UCSF) physician-scientists who were named Harrington Scholar-Innovators in 2013, aspire to a similar goal for their up-and-coming drug therapy for retinitis pigmentosa. In February 2015, BioMotiv, UCSF and the University of Washington collaborated to launch Optikira. Based in Cleveland, Optikira will move the Oakes-Papa discoveries forward toward patient care.

The Optikira company name reflects the change in direction that happened shortly after the researchers received the Harrington grant. "When we proposed the project [to the Harrington Discovery Institute], it was focused on diabetes and Lou Gehrig's disease. Retinitis pigmentosa wasn't even on our radar, but it quickly became an opportunity," Dr. Papa says.

Their small molecule therapeutic prevents cell death caused by misfolded or unfolded proteins. It is built on the scientific framework that misfolded proteins in a cell stress the cell, activating the unfolded protein response (UPR) pathway, which tries to refold the proteins.

When the UPR pathway gets saturated with too many misfolded proteins, the excess misfolded proteins accumulate and cause cellular death through hyperactivating a UPR protein called IRE1. Drs. Oakes and Papa discovered that hyperactivation of IRE1 during catastrophic protein misfolding is a common thread that causes cell damage across seemingly unrelated diseases like diabetes, Lou Gehrig's disease and retinitis pigmentosa.

Experts Share Invaluable Insights

The UCSF researchers engaged with Harrington Discovery Institute's Innovation Support Center experts shortly after their selection as Harrington scholars. "It was all hands on deck, very quickly," Dr. Oakes recalls. One of the first decisions was to change the therapeutic target from Lou Gehrig's disease, a neurologic condition, to retinitis pigmentosa, an eye disease.

The eye offers a simpler therapeutic target than the pancreas or the larger space of the central nervous system, Dr. Papa explains. "It's a confined space, so there isn't a concern about systemic side effects, and we had some positive data about the IRE pathway in the eye."

From that point, they moved on to working with an Innovation Support Center medicinal chemist, William Greenlee, PhD, to improve their small molecules as drugs. Other Innovation Support Center experts assisted the two Harrington Scholars in assembling a commercialization package for their discovery.

With Drs. Oakes and Papa still engaged in their search for the compound with the most promise as a drug, BioMotiv entered into discussions with the inventors, UCSF and their collaborators, to form a company, license the intellectual property, and advance the project to the next phase.

"There are always challenges, and we are still working through them. If and when we put our drug in the clinic, that will be the culmination of the work."

Maximizing Potential

"The Harrington Discovery Institute often starts with discoveries that have great potential but are not yet ready for clinical use," Shah explains. "The compounds need to be optimized for improved pharmaceutical characteristics to enhance the safety and efficacy before they can be advanced into clinical testing."

Although Drs. Oakes and Papa still have years of work ahead before their compound becomes a drug, they are pleased with the progress their project has made in just two years. Through the assistance of the Innovation Support Center, the Saltzman family, who generously supported their work as Harrington Scholars, and now BioMotiv shepherding their project through preclinical development, "everything is moving ahead faster than we otherwise would have been able to do it," Dr. Oakes notes.

Once the UCSF researchers prove their compound's efficacy in the lab, BioMotiv will begin exploring potential pharma company interest. The entire process, from lab to commercialization, is fraught with potential setbacks, but the physician-scientists keep their eyes on the prize. "There are always challenges, and we are still working through them," Dr. Papa says. "If and when we put our drug in the clinic, that will be the culmination of the work."

Shared Strengths, Commitment Bind BioMotiv, Takeda

Japanese pharmaceutical giant Takeda announced a strategic investment in BioMotiv in September 2014. The partnership will leverage the strengths of the two companies to identify and develop pioneering medical innovations from bench to bedside.

Takeda's initial investment is $25 million over five years. The agreement gives Takeda exclusive rights to develop therapeutic candidates sourced by BioMotiv in the areas of immunology and inflammation and cardio-metabolic diseases such as diabetes and heart disease.

"This strategic relationship with Takeda provides for a seamless continuum of expertise to aggressively advance physician-scientist-derived therapeutic innovations through proof of concept and into clinical development and eventual commercialization," notes BioMotiv CEO Baiju Shah. "If we truly want to deliver medical breakthroughs to patients for whom therapeutic options are currently limited, or absent, it is vital to forge these close relationships among innovators, expert resources and pharmaceutical companies at the earliest opportunity."

Adds Tetsuyuki Maruyama, General Manager of Takeda's Pharmaceutical Research Division, "Participation in The Harrington Project offers an important opportunity to stay closely connected to physician-patient dialog and work with a broader community of individuals committed to truly impactful medical innovation."

Takeda's investment brings BioMotiv's total market capitalization to more than $90 million.



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Scientific Symposium

MAY 20 – 21, 2015

The third annual Harrington Discovery Institute Scientific Symposium brings together Harrington Discovery Institute leadership and Scientific Advisory Board, Harrington Scholars, drug development experts of the Innovation Support Center and BioMotiv, leadership of The American Society for Clinical Investigation, and leadership of national foundations to celebrate the transformation of medical discovery and the crucial role of physician-scientists. The symposium presents the latest research by Harrington Scholars and connects them with the drug development expertise that is essential to realize the commercial potential of their groundbreaking discoveries.

David Ginsburg, MD, James V. Neel Distinguished University Professor of Internal Medicine and Human Genetics, Member of the Life Sciences Institute at the University of Michigan Medical School, Howard Hughes Medical Institute Investigator, and member of the Scientific Advisory Board, will deliver the Keynote Lecture to open the symposium. Dr. Ginsburg, an internationally known expert on the clotting mechanism and coagulation disorders, cloned the gene for von Willebrand factor as a post-doctoral fellow. His contributions to the field also include the discovery of the genes responsible for combined factor V and VIII deficiency (LMAN1, MCFD2) and thrombotic thrombocytopenic purpura, (ADAMTS13).

Highlights of the scientific sessions include opening remarks on the importance of physician-scientists to medicine and society by Andrew Schafer, MD, Professor of Medicine in Hematology-Oncology and Director of the Richard T. Silver Center for Myeloproliferative Neoplasms, Weill Cornell Medical College. The Cleveland Institute of Music in University Circle again will be the setting for the scientific presentations by the 2015 Harrington Scholar-Innovators, the second class of Oxford-Harrington Scholars, and the Alzheimer's Drug Discovery Foundation-Harrington scholars. Mukesh Jain, MD, Harrington Discovery Institute Scientific Director, and Daniel Simon, MD, President, UH Harrington Heart & Vascular Institute, will moderate the sessions. Special guest Tadataka "Tachi" Yamada, MD, Chief Medical & Scientific Officer, Takeda Pharmaceutical Company, will deliver remarks during the luncheon at the Cleveland Botanical Garden.

Symposium events also feature remarks by Thomas F. Zenty III, University Hospitals CEO, and entrepreneur and philanthropist Ronald Harrington and discussons of the Harrington Scholar experience by 2013 and 2014 Harrington Scholar-Innovators. The day will conclude with a dinner honoring the Harrington Scholars and personal reflections provided by Douglas Lowy, MD, Acting Director, National Cancer Institute and 2015 awardee of The Harrington Prize for Innovation in Medicine.

For more information about the Harrington Discovery Institute's annual Scientific Symposium, visit HarringtonDiscovery.org.

HARRINGTON SCHOLARS 2013 – 2015

2015 Harrington Scholar-Innovators

Robert Bonomo, MD
Case Western Reserve University
Bacterial Drug Resistance: Novel antibacterial agents to treat drug-resistant infections

John Burnett Jr., MD
Mayo Clinic
Congestive Heart Failure: Novel peptide therapy for heart failure

Nicole Calakos, MD, PhD
Duke University
Nervous System Movement Disorders: Novel targeting of the ER stress response pathway to treat movement disorders

David Clemmons, MD
University of North Carolina
Osteoporosis: Novel class of drugs to treat osteoporosis

Barry Coller, MD
Rockefeller University
Myocardial Infarction: A new prehospital drug to treat heart attack

Clark Distelhorst, MD
Case Western Reserve University
Blood Cancers: Targeting a new pathway to treat blood cancers

Xianxin Hua, MD, PhD
University of Pennsylvania
Type 1 Diabetes: A drug that regenerates pancreas cells to treat diabetes

Richard Johnson, MD
University of Colorado Denver, Health Sciences
Obesity and Diabetes: A novel drug class to treat obesity and diabetes

Marikki Laiho, MD, PhD
The Johns Hopkins University
Cancer: A first-in-kind small molecule that targets an essential mechanism of cancer cell survival

Geoffrey Pitt, MD, PhD
Duke University
Osteoporosis: A novel class of drugs that increase bone mass

Ira Tabas, MD, PhD
Columbia University
Diabetes and Atherosclerosis: Targeting a new pathway common to diabetes and atherosclerosis

2014 Harrington Scholar-Innovators

Jayakrishna Ambati, MD
University of Kentucky
Age-related Macular Degeneration (AMD): Development of novel therapeutics to treat AMD, a major cause of blindness in the elderly

Darren Carpizo, MD, PhD
Rutgers Cancer Institute of New Jersey
Cancer: Development of a first-in-kind anticancer drug that restores the function of a commonly mutated gene found in cancer

Garret FitzGerald, MD
University of Pennsylvania
Hypertension and Atherosclerosis: Development of a novel therapeutic for hypertension and atherosclerotic disease

Mark Humayun, MD, PhD
University of Southern California
Ischemic Retinal Diseases: Development of an innovative oxygen delivery device to treat ischemic retinal diseases, a leading cause of blindness worldwide

John Kheir, MD
Harvard University
Hypoxemia and Cardiac Arrest: Development of an injectable form of oxygen to prevent life-threatening hypoxemia in medical emergencies such as cardiac arrest

Rahul Kohli, MD, PhD
University of Pennsylvania
Bacterial Drug Resistance: Development of a novel approach to circumvent bacterial antibiotic resistance in diseases such as cystic fibrosis, tuberculosis and hospital-acquired infections

Gavril Pasternak, MD, PhD
Memorial Sloan-Kettering Cancer Center
Pain Management: Development of a novel class of analgesics more potent than morphine, but lacking the negative side effects and abuse potential

Irina Petrache, MD
Indiana University
Chronic Obstructive Pulmonary Disease (COPD): Development of a first-to-market disease-modifying therapy for patients with COPD, the third leading cause of death in the U.S.

David Rowitch, MD, PhD
University of California, San Francisco
Neonatal Brain Injury and Stroke: Development of a novel therapeutic approach to treat neonatal brain injury, Down syndrome and stroke

Jean Tang, MD, PhD
Stanford University
Basal Cell Carcinoma (BCC): Development of a novel topical drug for the treatment and prevention of BCC, a common form of skin cancer that affects millions worldwide

David Wald, MD, PhD
Case Western Reserve University
Acute Myeloid Leukemia (AML): Development of a novel therapeutic to treat AML, the most common form of leukemia in adults

2013 Harrington Scholar-Innovators

Marc Diamond, MD
UT Southwestern Medical Center
Alzheimer Disease: Development of a novel "anti tau" antibody therapy for the treatment of Alzheimer disease and other dementias

Roger Greenberg, MD, PhD
University of Pennsylvania
Cancer: Development of new class of anti-cancer drugs for breast and ovarian cancer, using a novel drug screening technology

Geoffrey Gurtner, MD, FACS
Stanford University
Wound Healing: Development of a novel topical drug to heal wounds, particularly in diabetic populations

Richard Kitsis, MD
Albert Einstein College of Medicine
Myocardia l Infarction: Creation of a first-in-class drug to reduce heart cell damage from acute myocardial infarction

Wolfgang Liedtke, MD, PhD
Duke University
Pain Control: Development of a new class of drugs that inhibit the pain response in skin, with potential application in many painful skin conditions

Sanford Markowitz, MD, PhD
Case Western Reserve University
Pulmonary Hypertension and Liver Regeneration: Discovery of a novel compound that increases tissue prostaglandins to treat pulmonary hypertension, liver failure and cancer

Scott Oakes, MD, and Feroz Papa, MD, PhD
University of California, San Francisco
Retinitis Pigmentosa and Diabetes: Discovery of a novel life-death switch in cells caused by protein misfolding and leading to novel drugs for retinitis pigmentosa and diabetes

Jonathan Powell, MD, PhD
The Johns Hopkins University
Diabetes: Development of a novel class of drugs that treat diabetes and obesity

Larry Schlesinger, MD
The Ohio State University
Tuberculosis: Development of a new class of anti-TB drugs that shorten he duration of TB treatment and prevent development of resistance

Robert Wilson, MD, PhD
University of Pennsylvania
Cancer: Identification and optimization of novel RNA-based drugs that treat all classes of cancer

Harrington Distinguished Scholar (Early Career Award)

Goutham Narla, MD, PhD
Case Western Reserve University
Cancer: Activating anti-cancer genes as a novel approach to treatment of a range of cancers, including leukemia, prostate and lung

2014 Alzheimer's Drug Discovery Foundation-Harrington Scholars

Thota Ganesh, PhD, Principal Investigator
Allen Levey, MD, Physician Collaborator
Emory University
Alzheimer's disease: Development of a novel anti-inflammation drug for the treatment of Alzheimer's disease

Chien-Liang Lin, PhD, Principal Investigator
Douglas W. Sharre, MD, Physician Collaborator
The Ohio State University
Alzheimer's disease: Development of novel drugs that modulate neurotransmission as potential therapeutics for Alzheimer's disease

2014 Oxford-Harrington Scholar

Alison Simmons, MD, PhD
University of Oxford
Crohn's disease: Development of new drugs that work by modifying the body's immune system to reduce inflammation

To be announced soon:

2015 Alzheimer's Drug Discovery Foundation-Harrington Scholars

2015 Gund-Harrington Scholars

2015 Oxford-Harrington Scholars

For more information, visit **HarringtonDiscovery.org**

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FOR DISCOVERY & DEVELOPMENT

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