Harrington Discovery Institute

University Hospitals | Cleveland Ohio

2013 – 2014

CREATING CONNECTIONS

connect

Dear Colleagues,

In the two years since the founding of the **Harrington Discovery Institute**, our leaders, administration, advisors, collaborators and physician-scientists have relentlessly pursued a single goal: enable a better drug development model in academia that can move discoveries from bench to bedside more quickly and efficiently. That commitment has made possible significant advances in a short time.

This report details the progress we have made toward our goal and features many of the individuals who have made it possible. Highpoints of our activities over the past year include:

- The Harrington Discovery Institute is now providing support to 27 physician-scientist-led research programs across the nation. We have transitioned the first of these programs to our mission-aligned for-profit, BioMotiv, and to large pharma.
- We have entered into a relationship with the Alzheimer's Drug Discovery Foundation (ADDF) that will leverage our combined expertise and resources to make a difference in this devastating disease. Two promising physician-scientist-based teams have been selected as our first ADDF Harrington Scholar awardees.
- In partnership with The American Society for Clinical Investigation, we established the Harrington Prize for Innovation in Medicine. This annual award will recognize the inventiveness and creativity that characterize physician-scientists par excellence and celebrate their role in curing diseases and improving quality of life. We announced our first awardee in February.
- In June we convene the Second Annual Harrington Scientific Symposium, bringing together national Harrington Scholars, drug development experts, our new disease foundation partners and leadership in American medicine. This symposium connects leading-edge research with the drug development expertise that is required to realize its commercial potential.

I invite you to observe our progress and witness our future successes as we advance medicine and society by enabling inventive physician-scientists to turn their discoveries into medicines that improve human health.

Sincerely,

Jonathan Stamler, MD
Director, Harrington Discovery Institute

The 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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Ronald G. Harrington: THE ESSENCE OF SUCCESS

At a time in life when most people are starting to slow down and take it easy, **Ron Harrington** is busy ramping up his family's latest venture, The Harrington Project for Discovery & Development. A hands-on leader who likes finding new challenges, he is energized by the progress the Harrington Discovery Institute and BioMotiv, its for-profit, mission-aligned consort, have made in two years.

"The essence of success comes from the quality of people, their talent, and what they can accomplish together."

"When our family got involved with this project, we expected the concept of discovering new drugs to extend life and improve people's quality of life to be well-received," Mr. Harrington says. "What we did not expect was the reception that BioMotiv has received. As a result, we are far ahead of where we thought we would be at this point."

He pinpoints his March 2012 introduction to financier-philanthropist Michael Milken as the catalyst. Mr. Milken heads the Milken Family Foundation and its spinoffs, the Prostate Cancer Foundation and FasterCures, a Washington-based think tank that removes barriers to progress against life-threatening diseases. "Mike immediately grasped the Harrington Discovery Institute financial model as well as its mission, and that's not easy to do the first time around," Mr. Harrington says.

With the mutual recognition that their two organizations are philosophically in sync, Mr. Milken began opening doors for Mr. Harrington to connect him with influential, like-minded individuals. "Mike Milken knows everyone. He introduced us to people and organizations who are interested in what we are doing with the Harrington Discovery Institute, and he continues to help us connect the dots," Mr. Harrington says.

In some respects, building the Harrington Discovery Institute into a sustainable model for drug development and commercialization resembles the path of Edgepark Surgical, the company the Harrington family transformed from a struggling durable medical equipment and supply company with 34 employees into an industry giant with eight national distribution centers and nearly 1,200 employees. Success in either endeavor ultimately depends on bringing a good product to market.

From a perspective gleaned over his years at the head of the family business, Mr. Harrington speaks with assurance about what it takes to reach that goal. "The essence of success comes from the quality of people, their talent, and what they can accomplish together," he explains. "With the Harrington Discovery Institute leadership and on our boards, we have recruited the top people with the necessary talent to achieve our mission."

The quality of the Harrington Discovery Institute's leadership and its association with University Hospitals has brought about the other essential element for success – a good product. Through a rigorous application and selection process, the Harrington Discovery Institute seeks to identify innovative drug discovery research projects across the United States that have the greatest potential for commercialization with the capability to be moved further along the path by BioMotiv and its resources.

In its first two years, the Harrington Discovery Institute has chosen these research projects wisely, Mr. Harrington believes. "We are committed to trying to support as much great discovery as we can," he notes. "Currently we select 10 to 12 of the best from the best [academic institutions] to receive Harrington Discovery Institute Grants. That's very interesting from the medical and financial aspect."

By almost any metrics, the Harrington Discovery Institute and BioMotiv have made astounding progress in a short time: 27 Harrington Scholars around the nation are progressing their projects toward a drug product; five products are already in development with BioMotiv; and institutions from around the world are coming to Cleveland to examine the Harrington Discovery Institute model firsthand. Mr. Harrington is among the first to celebrate these accomplishments, but it is the ultimate prize that keeps him motivated.

"We haven't done anything yet," he says. "We want a cure, and we want it faster and sooner rather than later."

Creating **CONNECTIONS**, Broadening **HORIZONS**

Harrington Discovery Institute Scientific Director **Mukesh K. Jain, MD**, already had an impressive resume and a full schedule when Harrington Discovery Institute Director Jonathan S. Stamler, MD, asked him in 2013 to serve as the Harrington Discovery Institute Scientific Director.

Dr. Jain, an internationally respected physician-scientist who joined University Hospitals and Case Western Reserve University School of Medicine faculty in 2006, possesses the ideal qualifications for the position. As former Director of the Program in Cardiovascular Transcriptional Biology at the Brigham and Women's Hospital, Harvard Medical School, Dr. Jain made headlines in the early 2000s when his research team discovered the essential role of proteins termed Krüppel-like factors (KLF) that regulate critical aspects of cardiovascular biology, immunity and metabolism.

> I have never seen such robust growth in an organization in such a short period of time.

At the School of Medicine, he continues to investigate and expand the understanding of the role of these factors in a broad spectrum of biological processes. Beyond his research activities, Dr. Jain is the Ellery Sedgwick Jr. Chair & Distinguished Scientist, Director of the Case Cardiovascular Research Institute, and a clinical cardiovascular disease specialist at University Hospitals. He is also President of The American Society for Clinical Investigation (ASCI) for the 2014 – 2015 term.

OPPORTUNITY OF A LIFETIME

Nonetheless, Dr. Jain seized the opportunity to be part of the Harrington Discovery Institute. "It is, in a singular word, unique. There is no other program that approximates the Harrington Discovery Institute, nationally or internationally," Dr. Jain says. "To be in on the ground floor of setting the vision for the Harrington Discovery Institute is a once-in-a-lifetime experience."

As Scientific Director, Dr. Jain added a number of significant responsibilities to his already-full plate. He is responsible for recruiting faculty to the Harrington Discovery Institute's "home base," as he calls University Hospitals and the School of Medicine, through the Harrington Distinguished Scholar program. In addition, he oversees the national Harrington Scholar-Innovator Grant program, the Foundation Scholar program, the annual Harrington Discovery Institute Scientific Symposium, and selection of the Harrington Prize for Innovation in Medicine recipient. Meanwhile, he continues his laboratory research, his clinical practice and teaching at the medical school.

That all makes for a busy life, but Dr. Jain finds the varied sectors of his professional life interrelated and personally fulfilling. "My clinical care informs my research, and my research informs my clinical care," he explains. "It is important for translational researchers to stay in touch with patient care, talk with patients and their families and teach residents."

FORGING NEW CONNECTIONS

As president of The ASCI, one of the oldest and most prestigious honor societies in the United States dedicated to the physician-scientist, Dr. Jain is excited about the synergy between the society and Harrington Discovery Institute. "The physician-scientists elected to ASCI focus on precisely the kind of research efforts that the Harrington Discovery Institute seeks to advance," he notes.

The Harrington Prize, announced in 2013 and presented for the first time in April 2014, recognizes a physician-scientist who has made scientific discoveries and translated them into clinical impact. "In my role at ASCI I have the good fortune to interact with the premier physician-scientists in the United States," Dr. Jain notes. "To have the Harrington Prize presented at The ASCI annual meeting will create a strong and enduring link between this incredible national community of elite scholars and our program." He also hopes that this alliance with The ASCI will provide opportunities to recruit the best and the brightest physician-scientists to The Harrington Project for Discovery & Development.

Establishing the Harrington Discovery Institute's baseline programs is only the beginning, Dr. Jain says. He has no doubt that the institute is capable of charting new waters. "I have never seen such robust growth in an organization in such a short period of time," he says. "That speaks volumes to Jonathan Stamler's vision, our incredible administrative team, and very enlightened institutional leadership."

Dr. Jain already is looking forward to the organization's next steps with characteristic enthusiasm. "The theme is 'broadening horizons,'" he says. He envisions growing the Harrington Scholar-Innovator Grant program through new engagements with various academic and disease-based foundations, recruiting new faculty to the Harrington Discovery Institute as Distinguished Scholars, and continuing to support the Harrington Discovery Institute's ecosystem of physician-scientist scholars across the globe.

Photo credit: Steve Ruark/PR Newswire, © HHMI

UNRAVELING THE MYSTERIES OF MARFAN SYNDROME

Harry (Hal) C. Dietz, MD, Victor A. McKusick Professor of Genetics and Medicine and Director of the William S. Smilow Center for Marfan Syndrome Research at Johns Hopkins, was a young pediatric cardiologist, just beginning his career at Johns Hopkins Medical Center, when he experienced the professional frustration that would change his life and impact the lives of thousands of children.

Johns Hopkins is recognized worldwide as a center for the treatment of Marfan syndrome, a genetic disorder of the connective tissue that causes skeletal and cardiovascular system problems, including excessive growth of the aorta. Physically, Marfan patients are unusually tall with long limbs and long, thin faces and fingers.

"I felt frustrated because my patients were not benefiting from existing treatment strategies," Dr. Dietz recalls. "Children were dying in the first year of life, and even if they had surgery, they still had problems."

His frustration peaked the day a young patient's father asked him why connective tissue weakness was causing his son's fingers and facial features to be abnormal. Dr. Dietz realized he could see the outward results of Marfan syndrome but couldn't explain them and, even more importantly, had no treatment available to control them.

CHANNELING FRUSTRATION

That encounter on top of his daily experiences in the clinic with young Marfan patients pushed Dr. Dietz to a life-altering decision. "I made the deliberate decision to walk away from my clinical practice to pursue research with the sole goal of doing better for my patients," he explains.

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PARTNERS IN PURSUIT OF A CURE

THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION

The introduction of the Harrington Prize for Innovation in Medicine brings together two organizations that share a common mission: commitment to physician-scientists and to the advancement of research that ultimately improves the treatment of human diseases.

Established in 1908, The ASCI is the most prestigious honor society dedicated to physician-scientists in the United States. Among its past and current members, the society can count 16 Nobel Prize in Physiology or Medicine winners, three Nobel Prize in Chemistry winners, 31 Lasker Award laureates, 359 Institute of Medicine members and 178 National Academy of Sciences members.

The society currently has more than 3,000 members representing physician-scientists who are at the bedside, at the research bench and at the blackboard. Many senior members are widely recognized leaders in academic medicine. Members must be nominated and elected to The ASCI and be 50 years of age or younger at the time of their election. From among the several hundred nominations The ASCI receives each year, the society elects up to 80 new members.

Harrington Discovery Institute Scientific Director **Mukesh K. Jain, MD,** is the 2014 – 2015 President of the society. He was elected to the society in 2005.

THE HARRINGTON PRIZE FOR INNOVATION IN MEDICINE

The Harrington Prize for Innovation in Medicine honors a physician-scientist who has moved science forward with achievements notable for innovation, creativity and potential for clinical application. The award recipient receives an unrestricted $20,000 honorarium, presents the Harrington Lecture at the joint meeting of The ASCI and the Association of American Physicians (ASCI/AAP) and authors a paper for publication in The ASCI's Journal of Clinical Investigation. The Harrington family of Hudson, Ohio, provides an annual honorarium to support the award.

The Harrington Prize is only the second prize The ASCI has established in its more than 100-year history. The ASCI's Stanley J. Korsmeyer Award, established in 1998, recognizes outstanding achievements of ASCI members in advancing knowledge in a specific field and mentoring. The addition of the Harrington Prize brings recognition to the second element of ASCI's mission, creating clinical impact through fundamental discovery.

Within a year of joining a laboratory dedicated to Marfan genetics, Dr. Dietz and colleagues had identified the gene responsible for the condition. He determined that the gene alteration causes changes in a specific protein, fibrillin-1, and changes in fibrillin-1 somehow cause the internal and external bodily changes associated with Marfan.

After this rapid initial discovery, Dr. Dietz and his team labored more than a decade before identifying the biological process underlying Marfan's physical characteristics. They discovered that fibrillin-1 regulates another protein, TGF-beta, transforming growth factor-beta. TGF-beta normally directs cellular performance during development, but in people born with the Marfan gene mutation, TGF-beta doesn't attach to the connective tissue as it should. Instead, unbound TGF-beta causes cells to behave abnormally, leading to the low muscle mass and excessive growth of bone and the aorta that are part of Marfan.

Knowing the cause for the abnormalities associated with Marfan, Dr. Dietz believed that finding a drug that could control TGF-beta activity was the key to making a difference in the lives of people born with the Marfan gene mutation. He and his team discovered that injecting mice with an antibody that blocks TGF-beta prevented many features of Marfan syndrome in mouse models of the disease. Coincidentally, losartan, a high blood pressure drug, also blocks TGF-beta. When tested in mice, it also prevented aortic enlargement and other features of Marfan.

> "The Harrington Prize mirrors my motivation to enter science and reflects my sense of urgency to make discoveries and explore therapeutics at the early stage."

"That was one of the most gratifying moments of my professional career," Dr. Dietz recalls. "Not only did the drug work, the magnitude of the response was unexpected." The team published their results in 2006 in a landmark paper in the journal Science.

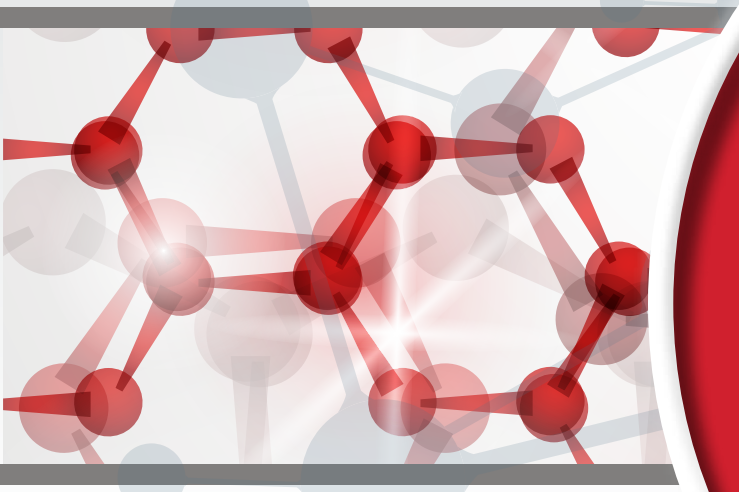
RESEARCH MEETS PATIENT CARE

Personally committed to the synchronicity between clinical care and research, Dr. Dietz continued in his role as Director of the Marfan Clinic at Johns Hopkins, among the largest Marfan clinics in the world. Regularly confronted with Marfan's effects on children, Dr. Dietz in 2006 felt compelled to try losartan in children with Marfan who had no treatment options. He and his team began treating the children with losartan, resulting in a remarkable 10-fold reduction in their aortic growth rate. In 2008, the Dietz team published their results with the children in another landmark paper in the New England Journal of Medicine.

Impressed by those results even before they were published, the National Institutes of Health in 2007 launched a clinical trial of losartan at 20 sites in the United States, Canada and Belgium, which will conclude in 2014. Trials of losartan in Marfan syndrome in other countries also have reported very encouraging results.

As a member of The American Society for Clinical Investigation and recipient of the inaugural Harrington Prize for Innovation in Medicine, Dr. Dietz feels singularly honored. "The Harrington Prize mirrors my motivation to enter science and reflects my sense of urgency to make discoveries and explore therapeutics at the early stage," he says. "These two organizations share my dedication to improving the quality and extending the length of life."

He remains tightly focused on two objectives: treating his patients and translating his research into a treatment for Marfan syndrome and related disorders. While more experience with new therapies is needed, Dr. Dietz believes that validated treatments are on the horizon for his patients and thousands of Marfan patients around the world.



Celebrating the

2014 HARRINGTON SCHOLAR-INNOVATORS

and their passion for helping patients

"To the individual who devoted his or her life to science, nothing can give more happiness than when results immediately find practical application. There are not two sciences. There is science and the application of science and these two are linked as the fruit is to the tree."

– Louis Pasteur

JAYAKRISHNA AMBATI, MD

University of Kentucky
Lexington, Kentucky

Age-Related Macular Degeneration

"It became obvious that I wanted to make a contribution to something that was a societal epidemic."

Ask Harrington Scholar-Innovator **Jayakrishna Ambati, MD**, about his goals as a physician-scientist, and he gives a surprising answer. "My ultimate goal is to put myself out of business," he responds.

Dr. Ambati, Professor and Vice Chair of Ophthalmology and Visual Sciences, Endowed Chair in Age-Related Macular Degeneration and Professor of Physiology, University of Kentucky School of Medicine, is focused intently on developing a treatment for the dry form of age-related macular degeneration (AMD). For patients with the wet form of AMD, there is still no cure, but new treatments can slow its progression at least for a few years. There is no cure or effective treatment for the dry form.

> I envision a single injection into the eye that would provide lifetime protection against AMD.

PROGRESS AGAINST AMD

Four years ago, Dr. Ambati and his team discovered in their laboratory that an enzyme deficiency in the eye causes cell death in the retina in dry AMD. Two years ago, they figured out the destructive process the enzyme deficiency causes.

Now, they are in pursuit of a way to block this process as a treatment for dry AMD. They have found an inhibitor. With the assistance of the Harrington Discovery Institute, they will increase its potency and develop it into a gene therapy. "I envision a single injection into the eye that would provide lifetime protection against AMD," Dr. Ambati explains.

His drive to solve puzzles and create solutions to problems comes to him naturally as the son of a mathematics professor and an Indian literature scholar. Growing up in India and, later, upstate New York, "Education was worshipped in our household," he recalls. "I had an affinity for seeking out knowledge and a penchant for solving mathematics problems, so I am not surprised by how my career evolved."

After graduating from high school at age 14, he earned his undergraduate degree in electrical engineering at The Johns Hopkins University at 17, and his MD from SUNY Health Science Center at Brooklyn at 23. Settling early on a career in ophthalmology, he completed a residency at the University of Rochester and a retina fellowship at Harvard Medical School.

A PERSONAL CONNECTION

"As I went through medical school and my training, it became obvious that I wanted to make a contribution to something that was a societal epidemic," Dr. Ambati says. "There are as many people with AMD as with all solid tumors combined." He sees the results of the disease – the progressive vision loss, the depression and loss of independence – firsthand in his clinic. "Macular degeneration is life-altering for the patient and family," he stresses.

Because AMD is a lifelong disease, he develops strong relationships with his patients and their families, some of them stretching back to 2001 when he came to the University of Kentucky. As much as he is enriched by those long-term relationships, he also finds them frustrating – the reason he continues to see these patients is because there is no cure.

Dr. Ambati has made it his personal mandate to improve diagnosis and develop a treatment for AMD, and he has set his own timetable. The father of two young girls, he says, "By the time my girls go to college, I hope to have a drug available."

DARREN CARPIZO, MD, PhD

Rutgers Cancer Institute of New Jersey
New Brunswick, New Jersey

Cancer

When **Darren Carpizo, MD, PhD**, an Assistant Professor of Surgery and Surgical Oncology at Rutgers' Robert Wood Johnson Medical School, first considered a career in medicine, he didn't give much thought to becoming a researcher. "I went into medicine because I wanted to take care of sick people," he says.

Looking back, he can see that his decision to be a doctor was the first step along a path that would lead him into the world of cancer drug development. A biology major in college, he was "intellectually curious" about the cancer process.

"The compounds we are testing against p53... represent the essence of personalized medicine."

CATCHING THE BUG

His path became clearer during medical school at the University of Illinois at Chicago. There he entered a program for medical students interested in research, initially as a means of paying his tuition, but soon discovering that he loved the work. "I caught the research bug," he says. "I discovered I really liked it and decided to pursue a career as a physician-scientist."

> I caught the research bug... and decided to pursue a career as a physician-scientist.

From there, he elected to serve his surgical residency at the University of California, Los Angeles (UCLA), in part because of the program's track record for training physician-scientists. From the beginning, he was interested in pursuing a career as a surgical oncologist. "My interest gravitated toward diseases with the most negative impact because that's where doctors are really needed," Dr. Carpizo explains. "I felt it would be most rewarding to interact with patients whose cancers were diagnosed rather early and in whom surgery would have a possibility of cure."

Dr. Carpizo understood early on that to be successful in research, formalized training in the discipline is necessary. This led him to UCLA's Specialty Training in Advanced Research (STAR) program. Through STAR, he completed a PhD in Molecular, Cell and Developmental Biology.

While completing a fellowship in surgical oncology at Memorial Sloan-Kettering Cancer Institute, Dr. Carpizo developed an interest in liver, pancreatic and bile duct cancers, appreciating the complexity of the operations. Also during this time, he decided that his research career would focus on drug development. "The biggest problem that we face in managing patients with these types of cancer is recurrence, and recurrence requires drug treatment," he notes. "Unfortunately, the drugs we have available for these cancers are largely ineffective."

BREAKTHROUGH AFTER 30 YEARS

Now at Rutgers Cancer Institute of New Jersey, he divides his time between operating on patients with liver, bile duct or pancreatic cancer and laboratory research focused on developing new cancer therapeutics. The research that earned Dr. Carpizo recognition as a Harrington Scholar-Innovator focuses on mutation of the p53 gene, the most frequently mutated gene in human cancer. A p53 mutation disables the gene's normal mechanism for preventing cancer cells from multiplying.

"From over 30 years of research on p53, we know that it is one of the most important genes in cancer biology, yet we still do not have a drug available that targets p53, although some are now in clinical trials," he says.

He and his team have discovered one of the first drugs that targets mutant p53. Their drug makes the mutant p53 protein normal again, so it can do what it is supposed to do – kill cancer cells.

He looks to the Harrington Discovery Institute for guidance in moving his team's most promising compound along the pathway to trials in humans. "The compounds we are testing against p53 are consistent with the current trend to find drugs that act on tumors with specific mutations," he explains. "This is the essence of personalized medicine."

GARRET FITZGERALD, MD

University of Pennsylvania
Philadelphia, Pennsylvania

High Blood Pressure, Atherosclerosis

"I have always kept a clinical interest as part of my research."

The name **Garret FitzGerald, MD**, is not exactly a household word, but millions of people are familiar with at least one of his research findings – low-dose aspirin as prevention for heart attacks and stroke. Dr. FitzGerald demonstrated this in clinical trials in the 1980s, and it has been standard practice ever since. In 1999, he became known as the first physician to raise questions about the cardiovascular risks of COX-2 inhibitors like the blockbuster drugs Celebrex and Vioxx.

Born in Dublin, Ireland, where he earned his medical degree at University College Dublin, Dr. FitzGerald embraced translational research long before it was in vogue. "I started being involved in clinical research, then went to the lab to learn about biochemical assays," he explains. "I have always kept a clinical interest as part of my research, so when people started talking about translational research, I realized we seemed to be doing it."

> I look up to those who demonstrate intellectual rigor.

THE MEDICINE-SCIENCE CONNECTION

Now Professor and Chair of Pharmacology, McNeil Professor in Translational Medicine and Therapeutics at the University of Pennsylvania Perelman School of Medicine, Dr. FitzGerald established the Institute for Translational Medicine and Therapeutics there in 2005 – the first such institute and a model for the subsequent National Institutes of Health (NIH) Clinical and Translational Science awards. "We wanted to develop an institute that embraced the kind of medicine and science we practiced," he explains.

Over the years he has built a reputation as a physician-scientist who looks at existing clinical knowledge and practice and uses science to question it. His inspiration, he says, comes from leaders in medicine and science such as John Oates, MD, at Vanderbilt University, who is credited with leading the launch of clinical pharmacology. Dr. FitzGerald began his career in the United States at Vanderbilt when he and his wife emigrated in 1980. "I saw people there who were trained to bring science to medicine," he says. "I look up to those who demonstrate intellectual rigor."

FROM SCIENCE TO BUSINESS

As a Harrington Scholar-Innovator, Dr. FitzGerald will continue his exploration of prostaglandins as a novel therapy for high blood pressure and atherosclerosis. Prostaglandins are a type of biochemical signaling fat produced in the body, some of which specifically protect the heart.

"The NIH does not see it as very exciting to advance drug discovery to the next stage, where the Harrington Discovery Institute promotes this type of research," Dr. FitzGerald notes. "A bonus is access to the [Harrington Discovery Institute's] intellectual capital of people experienced in developing drugs, not just the science but also the business aspects."

In a career that spans more than 30 years, Dr. FitzGerald has done it all. He has received numerous honors, including the 2013 Grand Prix Scientifique from the Lefoulon-Delalande Foundation of the Institute of France, considered the world's most prestigious award in cardiovascular research; the 2013 Jay and Jeanie Schottenstein Prize in Cardiovascular Sciences from The Ohio State University; the 2012 Lucian Award from McGill University, a semiannual award that recognizes seminal advancement in cardiovascular research; and the 2005 Boyle Medal of the Royal Dublin Society, which honors outstanding scientists. He has been interviewed by media ranging from CNN to Forbes to leading medical publications.

Even after these many accomplishments, Dr. FitzGerald is still eager for the next scientific challenge. What is it that keeps the spirit of discovery fresh for him? "That's easy," he says. "I'm inquisitive. I like doing science."

MARK HUMAYUN, MD, PhD

University of Southern California
Los Angeles, California

Blindness

As a student at Duke University Medical School in the 1980s, **Mark Humayun, MD, PhD**, witnessed his grandmother's progressive vision loss and eventual total blindness. "I was very close to my grandmother, and when she went blind, it made me rethink my career," Dr. Humayun says. "I got interested in ophthalmology and completed my residency training at Duke Eye Center followed by a fellowship in retinal diseases at Johns Hopkins Wilmer Eye Institute."

Fast-forward 25 years to 2013. The U.S. Food and Drug Administration (FDA) approves the Argus II. Known as a "bionic eye," it is a bioelectronic implant that restores vision to people with retinitis pigmentosa, an inherited disease that eventually causes blindness by destroying the retina's rods and cones, its imaging receptors. Inventor: Dr. Mark Humayun, now the Cornelius J. Pings Chair in Biomedical Sciences, Professor of Ophthalmology, Biomedical Engineering, and Cell and Neurobiology, Director, Institute for Biomedical Therapeutics, and Co-Director, USC Eye Institute, University of Southern California.

> Thus far there hasn't been anything that isn't doable based on the laws of physics, biology and chemistry.

MEDICINE MEETS ENGINEERING

Driven to develop a device that could restore some degree of vision for the blind, Dr. Humayun's early efforts led only to frustration. "I tried my best to solve the problem of my grandmother's blindness with engineers, but when we sat across the table from each other it was like we spoke two different languages," he recalls. That frustration led him to earn a doctorate in biomedical engineering so he could not only speak the same language as the engineers but also personally take on the engineering and technical design for his invention.

But even the success of his Argus II device for blindness caused by retinal degeneration like in retinitis pigmentosa did not satisfy Dr. Humayun. "Diabetic retinopathy as a cause of blindness was always in the back of my mind," he says. "Systemic diabetes leads to small vessel disease that results in lack of oxygen to the retina, a different cause than retinitis pigmentosa."

That determination led him to invent what he refers to as "a metabolic prosthesis" for the retina, the project he will pursue as a Harrington Scholar-Innovator. The first device to receive Harrington Discovery Institute support, Dr. Humayun describes his invention as "sitting in the realm between device and drug."

AN INGENIOUS SOLUTION

The microscopic device splits water into its component hydrogen and oxygen by electrolysis and delivers a metered amount of metabolic oxygen to the retina. By reducing the oxygen deficit in the retina, the device potentially could restore vision for people with diabetic retinopathy.

With support from the Harrington Discovery Institute and other funding, Dr. Humayun will continue refining the electrolysis for the system. So far, he says, testing results are encouraging. "Thus far there hasn't been anything that isn't doable based on the laws of physics, biology and chemistry."

Dr. Humayun and his team can leverage their work with the Argus II to help engineer most of this new device. But, Dr. Humayun notes, "Since this type of implant has never been engineered, to be successful still requires discovery." As the device moves through its journey, closer to the preclinical testing stage, Dr. Humayun will look to the Harrington Discovery Institute experts also to assist him in building the business side of his invention.

When his newest invention ultimately gains FDA approval, it will bring Dr. Humayun the dual satisfaction of honoring his grandmother's memory and helping millions of patients in his clinic and worldwide. Finally the circle will be completed.

JOHN KHEIR, MD

Harvard University
Cambridge, Massachusetts

Oxygen Deprivation

As a pediatric intensive care specialist at Boston Children's Hospital, **John Kheir, MD**, treats infants and children every day who have every type of extreme need, "but oxygen deprivation is the most poignant," he says. "Without oxygen, cells cannot produce the energy they need to perform their functions, so even brief periods of oxygen deprivation are very poorly tolerated."

"I hope to work together with the Harrington experts to bring a product to market in less than five years."

“Research takes all of your soul.”

AN INSPIRED INVENTION

He was first inspired to find a solution for the problem by a little girl who sustained a severe brain injury caused by pneumonia that resulted in severely low oxygen levels. The child died from oxygen deprivation, even as the medical team connected her to a heart-lung machine.

“That experience reinforced to me the need for a clinical application that could quickly deliver oxygen in an emergency,” Dr. Kheir explains. He began thinking through the clinical issues that would be involved in delivering oxygen to the bloodstream through an intravenous line in a form that the body could easily use.

Since 2006, he has been on a mission to translate those ideas into a viable product. The result is injectable oxygen, the project that he now will continue as a Harrington Scholar-Innovator. He is working on development of a microparticle made of fatty molecules surrounding oxygen gas with the particles suspended in a liquid.

Stored in a preloaded syringe, oxygen can be delivered almost instantaneously through an intravenous line. Dr. Kheir envisions the syringes being stored on every code cart in a hospital, ambulance or transport helicopter to help stabilize patients who are having difficulty breathing until a clinician can safely insert a breathing tube or perform some other lifesaving therapy.

DRAMATIC EVIDENCE

In some of his earliest experiments, Dr. Kheir and his team members knew they were onto something when they drew their own blood, mixed it in a test tube with the microparticles, and watched blue blood turn immediately red. They then demonstrated that an infusion of these microparticles could keep an animal alive for 15 minutes without a single breath. With that proof of concept, the team has been working with chemical engineers, particle scientists and other clinicians to identify the optimal microparticle that will make the safest, most effective drug.

With the help of the Harrington team, Dr. Kheir hopes to fast-track his discovery. “I hope to work together with the Harrington experts to bring a product to market in less than five years,” he says.

As a physician-scientist, Dr. Kheir considers himself 100 percent clinician and 100 percent researcher and believes there is a synergy between the two. “You have to be an extremely good clinician because understanding the physiology is critical,” he explains. “You have to be a foremost expert on your clinical problem before you can propose a solution to it.”

At the same time, successful research requires total dedication, he says. “Research takes all of your soul. You must think about it 24/7, think outside the box and create a unique solution that no one else has thought of.”

RAHUL KOHLI, MD, PhD

University of Pennsylvania
Philadelphia, Pennsylvania

Antibiotic Resistance

Harrington Scholar-Innovator **Rahul Kohli, MD, PhD**, has had a problem on his mind since medical school at Harvard.

"Thinking about the problem of drug resistance was in my head then. I already knew we needed a new approach," he explains. During his doctoral studies in biochemistry at Harvard where he worked on understanding many of the antibiotics in common use today, the innovation gap was obvious to him. The idea stayed with him through his training.

"It's a daunting task to translate an academic idea to the clinical and practical realm."

> We have just been running to stay in place when it comes to trying to combat antibiotic resistance.

DEFYING CONVENTIONAL THINKING

Now Assistant Professor, Division of Infectious Disease, Departments of Medicine and Biochemistry and Biophysics, University of Pennsylvania Perelman School of Medicine, Dr. Kohli four years ago decided it was time to pursue his passion. "Starting by setting aside the belief that drug resistance by microorganisms is inevitable was the launching point for our program," he says.

The typical, accepted approach to preventing resistance to antibiotics is to modify the antibiotic, he explains. In response, the bugs mutate again, and there is a never-ending battle between superbugs and new antibiotics. "We have just been running to stay in place when it comes to trying to combat antibiotic resistance," Dr. Kohli says.

Turning the problem over in his mind while treating his infectious disease patients, Dr. Kohli was drawn toward a totally different solution.

Instead of trying to build a better antibiotic, he asked, why not focus on the bugs' ability to acquire resistance instead? The research project he will pursue as a Harrington Scholar-Innovator aims to target the very pathways in the bacteria that let them adapt to antibiotics and evolve resistance.

"We hope to identify a molecule that can disrupt the pathway that allows bacteria to acquire drug resistance," Dr. Kohli explains. His ultimate goal is to develop a drug that could make bacteria more sensitive to existing antibiotics or slow or prevent them from acquiring antibiotic resistance. Either approach would have value in clinical applications.

DESPERATE CLINICAL NEED

The idea of going after the superbugs by targeting their evolution "has been floating in the field for some time," he adds. His lab's work has helped to isolate a target that might make this strategy possible, and their work caught the attention of the Harrington Discovery Institute selection committee. "The committee members are aware that infectious disease is a field with a desperate clinical need," Dr. Kohli says. "They saw our proposal as an out-of-the-box idea that is simultaneously founded on solid science."

At almost the same time last year as the Harrington Discovery Institute was reviewing Dr. Kohli's proposal, pharmaceutical giant GlaxoSmithKline was evaluating the concept in its Discovery Fast Track competition. Glaxo selected Dr. Kohli as one of eight winners in the competition and will provide support for some of the work in his lab.

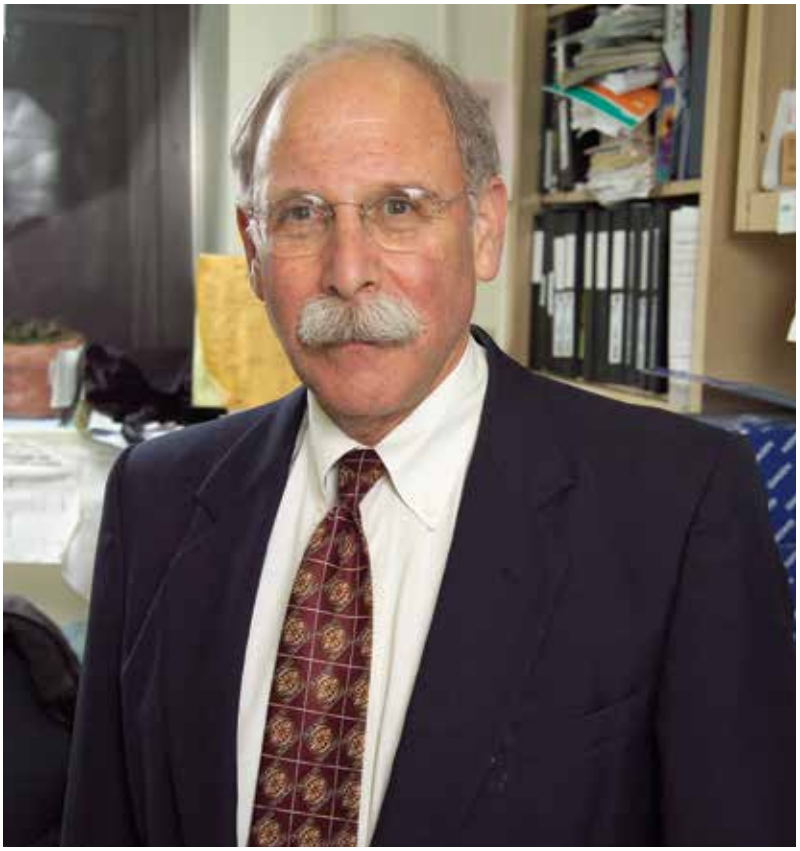
His laboratory also is gaining renown for parallel research under way to identify the role of purposeful mutations on the other side of the host-pathogen divide. The team has published several articles in scientific journals about how the immune system uses such mutations to strengthen itself.

For Dr. Kohli, what sets the Harrington Discovery Institute apart from other awards is the group of scientists and industry experts it has collected to move drug discoveries forward. "It's a daunting task to translate an academic idea to the clinical and practical realm," he notes. "We are grateful for as much advice as we can get."

GAVRIL PASTERNAK, MD, PhD

Memorial Sloan-Kettering Cancer Center
New York, New York

Cancer Pain



As a young medical student at Johns Hopkins, **Gavril Pasternak, MD, PhD,** discovered in himself an innate love of research that has continued to motivate him for 40 years. "Research is like a giant mystery novel that never stops," he says. "Every time you think that you have the answer, Nature explains that you are not as smart as she is. As you go on, the problems get more interesting."

"The Harrington grant provides an opportunity to explore new drugs in a way that the NIH wouldn't support."

> Research is like a giant mystery novel that never stops.

UNDERSTANDING PAIN

As a cancer physician, Dr. Pasternak, the Anne Burnett Tandy Chair of Neurology at Memorial Sloan Kettering Cancer Center, is moved by the suffering of patients who need pain relief. As a scientist, he is intrigued by the question of whether the positive effects of the opiate drugs frequently prescribed for cancer pain could be separated from their known negative effects.

He is all too familiar with pain and its impact. "The best treatment for pain is to take away its source, but we can't always do that," he explains. "The next best thing is to relieve their suffering as much as possible. But pain can become so overwhelming that the person cannot enjoy life, and that is a tragedy."

For four decades, Dr. Pasternak has pursued research to advance the understanding of pain and the opiate drugs used to treat it. The National Institutes of Health (NIH) has funded his work since 1979 through the National Institute on Drug Abuse, and he and his team have published extensively in medical journals about how pain drugs work so that they can be used more effectively.

Through this body of work, Dr. Pasternak has gained intimate knowledge about the risks and side effects associated with opiates, ranging from dizziness, nausea, vomiting and constipation to addiction and breathing problems. Yet, with a dearth of new painkillers coming on the market, opioids like hydrocodone and morphine are among the most frequently prescribed painkillers for everything from oral surgery to cancer.

IN SEARCH OF AN ALTERNATIVE

Dr. Pasternak set out to develop an alternative – a painkiller as effective as the opiates without the nasty side effects. Now, he and his team have generated in the laboratory what they believe may be the answer – a new class of drugs derived from opiates that block pain signals in the brain without the risks.

The next step in their research is to identify the best targets in the brain for the compounds they have created. Through the support of the Harrington Discovery Institute, Dr. Pasternak is hopeful that the research team will be able to progress several of the compounds to clinical trials.

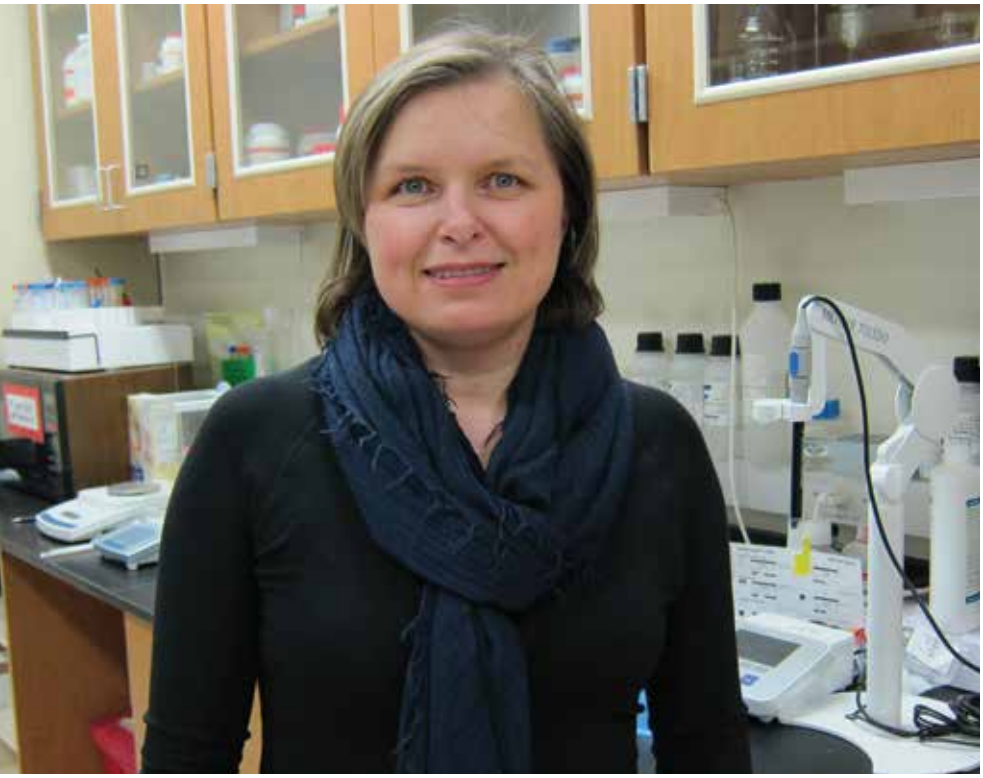
He notes that the NIH has been generous with funding, but focuses on basic laboratory research. "The Harrington grant provides an opportunity to explore new drugs in a way that the NIH wouldn't support," he says. "It will help us take our work one step closer to patients rather than leaving it in an academic journal."

Dr. Pasternak's deep personal commitment to making a lasting impact on the future is apparent when he speaks of his involvement with the Harrington Discovery Institute as the culmination of 40 years of research. He says simply, "I get enormous personal fulfillment from the knowledge that we can do something to make a difference."

IRINA PETRACHE, MD

Indiana University
Indianapolis, Indiana

Chronic Obstructive Pulmonary Disease



As a former Alpine skier for the national team in her native Romania, **Irina Petrache, MD,** Dr. Calvin H. English Professor of Medicine, Indiana University School of Medicine, has an affinity for speed. Now as a Harrington Scholar-Innovator developing a treatment for emphysema, speed is still her objective.

"Using the resources of the Harrington Discovery Institute, we want to move this discovery faster to the bedside as a diagnostic and therapeutic tool," Dr. Petrache says.

"It is a two-way street as I pass on my experience and knowledge, I also learn and get a lot of energy from my mentees."

> We want to move this discovery faster to the bedside as a diagnostic and therapeutic tool.

EXPANDING THE OPTIONS

Dr. Petrache's specialty is investigating the underlying mechanism that damages the small blood vessels in smokers' lungs. "When smokers get chronic obstructive pulmonary disease [COPD], there are limited treatment options available," she explains. "It is a prevalent disease that becomes devastating when severe."

Smoking is the number one cause of COPD, including emphysema and chronic bronchitis. Dr. Petrache, a pulmonary medicine specialist, practices at the Indianapolis, Ind. Richard Roudebush VA Medical Center, where she sees "far too many" cases of COPD. "Stopping smoking remains the most effective intervention, but sadly, many affected people continue to suffer from COPD, even if they stop smoking," she says.

Dr. Petrache believes that she and her team are getting close to expanding the treatment choices for these patients. She and her collaborator, Indiana University researcher Matthias Clauss, PhD, have identified a protein in the body that causes inflammation and death of the cells that line the inside of blood vessels – two events that occur in COPD. They have patented this protein – EMAP II – as a target in emphysema and had several grants, including from the National Institutes of Health, to help move it closer to human testing. With assistance from the Harrington Discovery Institute's industry experts, Dr. Petrache believes that a drug to treat COPD based on EMAP II may be tested in less than a decade.

A CLEVELAND CONNECTION

Dr. Petrache's connection with the Harrington Discovery Institute has brought her career full circle. She still recalls with pleasure her residency at former St. Luke's Hospital, affiliated with Case Western Reserve University School of Medicine. "I spent four beautiful years of my life in Cleveland. The training and support I received from the Department of Medicine faculty at Saint Luke's were critical for my career," she says.

After completing her training, she was on the faculty at The Johns Hopkins University for six years where she began studying cellular damage and potential treatment targets in COPD. Now as a physician-scientist at Indiana University, Dr. Petrache strives to mentor young physicians as she was mentored early in her career.

She appreciates being surrounded by young people eager to learn, ranging from high school students to junior faculty. "It is a two-way street as I pass on my experience and knowledge, I also learn and get a lot of energy from my mentees." She adds, "I cherish this opportunity."

Dr. Petrache refers to the medical students, residents and junior faculty members whom she mentors as her Plan B. "If my contributions are not sufficient," she explains, "the people I am training may be smarter and make that high impact on patient care that I am striving to make."

DAVID ROWITCH, MD, PhD

University of California
San Francisco, California

Neurologic Damage in Premature Infants

Photo credit: Andy Kuno/PR Newswire, © HHMI

"Survival rates today are better for preemies than they were 20 years ago, but the complication rates in the brain are about the same."

David Rowitch, MD, PhD, spends his days and often his nights taking care of the tiniest, most fragile patients – preterm infants.

His dedication to helping his little patients survive and thrive has led Dr. Rowitch, Chief of Neonatology and Professor of Pediatrics and Neurological Surgery at the University of California – San Francisco (UCSF), to be a pioneer in his field. During his residency and fellowship at Children's Hospital in Boston, the importance of brain injuries suffered by newborns, which can have life-long consequences, captured his interest. Soon after completing his training in pediatrics, he established a neurosciences lab at Dana-Farber Cancer Institute (Harvard School of Medicine).

> Premature babies are very vulnerable.

BABIES AND BRAIN INJURIES

In 2006, he moved to UCSF to begin a research program focused on newborn brain injury. With pediatric neurologist Donna Ferriero, MD, he co-directs the Newborn Brain Research Institute and opened the nation's first Neurointensive Care Nursery at UCSF Benioff Children's Hospital, providing special care for babies with neurological injuries. At UCSF, in collaboration with neuroscientist Arturo Alvarez-Buylla, PhD, he performed the first detailed molecular analyses of autopsied human brains to better understand neurologic development and how it is impacted by injury.

The daily realities of trying to save babies push Dr. Rowitch to pursue practical and clinical applications for his basic science discoveries. "Day to day I am resuscitating babies, but I cannot guarantee they will have the best long-term outcome," he says. "Survival rates today are better for preemies than they were 20 years ago, but the complication rates in the brain are about the same."

Dr. Rowitch cites statistics that report a 25 to 50 percent risk of learning deficits and other cognitive problems in premature infants. "Premature babies are very vulnerable," he explains. "They face a high risk of brain injury from inflammation, infection or oxygen deprivation because their lungs are not fully developed." Ironically, steroids given to preemies after they are born to help their breathing can damage the developing brain.

MORE WORK TO BE DONE

Despite advances in other areas of neonatal medicine, knowledge about brain development in very young infants is still sketchy, Dr. Rowitch notes. Motivated by the desire to help preemies get the best possible start in life, he hopes to develop a drug that protects their brains from harm and allows them to develop normally.

By investigating genetic factors that control brain development and the brain's response to injury, he and colleagues in the UCSF Newborn Brain Research Institute were able to zero in on a particular biologic pathway that normally protects the developing brain. When injury to an infant's brain disrupts that pathway, it prevents normal brain growth and neurologic development.

Within two years of that discovery, Dr. Rowitch and his team identified a drug that can protect the preemie brain from injury. He believes it will reduce the risk of cerebral palsy and other neurologic damage.

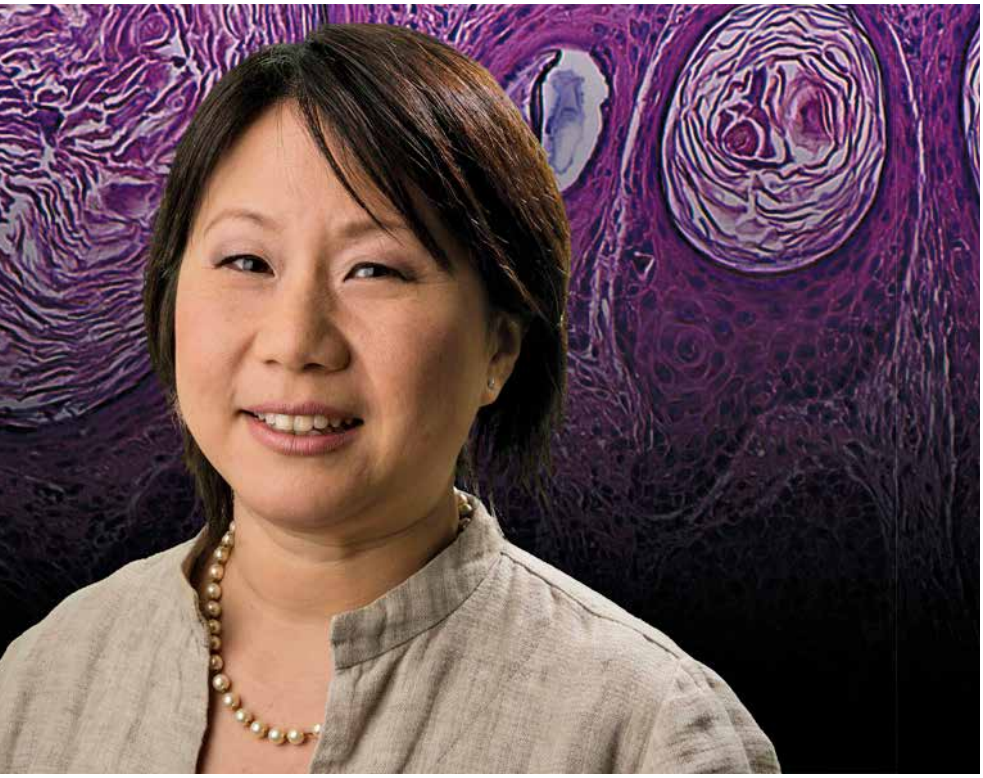
"The drug works in the laboratory, now we need to know if it is safe for infants and can it work against low oxygen and steroids," he explains. "Once we answer these basic questions with the support of the Harrington Discovery Institute, the momentum is building for it to go into human testing."

In a career studded with firsts, this could be one of Dr. Rowitch's most important.

JEAN TANG, MD, PhD

Stanford University
Stanford, California

Basal Cell Carcinoma



"You have to be humble and know when you need help. I...don't have the experience in developing a drug product...that the Harrington experts will provide."

In the world of medical scientific research, much of the work is slow and painstaking, often unrewarding on a day-by-day basis. But the moment when an experiment works, a hypothesis is validated or the results are positive – that eureka moment – is the payoff for months and years of diligent application of the scientific method.

For Harrington Scholar-Innovator **Jean Tang, MD, PhD,** Associate Professor of Dermatology at Stanford University Medical Center, the eureka moment occurred when patients with skin cancer who she had treated with a new drug returned cancer-free in less than two months. "For the patients, it changes their lives," she says. "There is no better motivation for me."

> I prefer science at a later stage, when the impact on humans is known.

ON A DIFFERENT PATH

As a dermatologist in sunny California, Dr. Tang sees many patients with basal cell carcinoma, a skin cancer that historically has been treated by radiation or surgery to remove the tumors. In 2012, the U.S. Food and Drug Administration (FDA) approved vismodegib (Erivedge) to treat inoperable basal cell carcinomas. Developed by pharmaceutical giant Genentech, "vismo" is the first class of drugs approved by the FDA that works by inhibiting the hedgehog molecular signaling pathway, a key regulator in human development before birth and a major contributor to cancer in adults when it goes awry.

Vismo is a valuable treatment but cannot be used by many of Dr. Tang's patients who are unable to take medications or can't tolerate the side effects from taking it orally. Those patients and their issues motivated Dr. Tang, who participated in vismo's clinical trials in 2007, to pursue a topical inhibitor of the hedgehog pathway using another drug, itraconazole.

Although she respects Genentech's 20 years of painstaking research to create vismo, Dr. Tang is on a different path. "I am not a patient person," she says. "I prefer science at a later stage, when the impact on humans is known." Her PhD in DNA repair and cancer biology plus postdoctoral training in clinical trial design help her move scientific findings through basic science and into clinical trials more quickly, she says.

CONNECTING WITH EXPERTS

Having said that, Dr. Tang adds, "But you have to be humble and know when you need help. Physicians are good at publishing, presenting, mentoring and teaching," she explains. "But I personally don't have the experience in developing a drug product and a company that the Harrington experts will provide."

As a physician-scientist, she says that her greatest fear would be to make a significant discovery that could benefit patients but lack the commercial experience and knowledge to be able to move it ahead.

THE ULTIMATE SUCCESS

With the Harrington Discovery Institute's support, she will work to develop an itraconazole cream that is effective without the risks and side effects associated with an oral drug. The oral form already has proven the efficacy of the medication's main ingredient in treating basal cell carcinoma, and Dr. Tang hopes to see the results of her research on the topical form in a relatively short time.

Her dramatic experience with basal cell carcinoma patients and vismo has set the stage for positive expectations. "We gave them the drug and the cancer went away because the drug shut down the [molecular] pathway," she says. "It doesn't get any better than that."

DAVID WALD, MD, PhD

Case Western Reserve University School of Medicine
Cleveland, Ohio

Acute Myeloid Leukemia, Colon Cancer

"I discovered that pathology and drug discovery research match with my interest in being hands-on in the lab."

Cancer researchers, even the most distinguished ones such as Harrington Scholar-Innovator **David Wald, MD, PhD**, pathologist and Assistant Professor at Case Western Reserve University School of Medicine, are used to disappointment. Day after day, week after week, year after year, they pursue the discovery that may lead to a new cancer treatment. Or not.

"I usually have multiple projects going on, knowing that most won't work – but one could," Dr. Wald says. It's that single possibility that motivates him – the potential to help millions of people by making an impact on a devastating disease.

That's why the reaction of a Harrington Discovery Institute Innovation Support Center chemist to one of Dr. Wald's projects made an impression. "That interaction got me excited because he was excited," Dr. Wald says. "It made me think that we are on to something."

> I usually have multiple projects going on, knowing that most won't work – but one could.

DEVELOPING A NATURAL TREATMENT

The chemist was reviewing Dr. Wald's research on securinine, an organic nitrogen-containing compound found in plants. Considered one of the 50 fundamental herbs used in Chinese herbal medicine, securinine has been used in China and Russia to treat neurological conditions such as amyotrophic lateral sclerosis, poliomyelitis and multiple sclerosis.

Dr. Wald and his team are working to modify securinine to make it effective against acute myeloid leukemia (AML) and colon cancer. It has never been tested as an anticancer agent, but Dr. Wald was intrigued by reports demonstrating that securinine causes cell death in leukemias with a specific genetic mutation and may be active against infections. The same genetic mutation as AML appears in colon cancer, leading Dr. Wald and his team to pursue a parallel path for their modified securinine, testing it as treatment for both diseases.

A HANDS-ON RESEARCHER

Dr. Wald remembers being interested in AML while still a medical student at Case Western Reserve University School of Medicine. "I realized even then that there was a need for new cancer drugs," he recalls, and he began considering a career in research.

That interest solidified during his residency in clinical pathology at UH Case Medical Center and his postdoctoral research. By then, his career path was set. "I am very research oriented," he says. "I discovered that pathology and drug discovery research match with my interest in being hands-on in the lab."

His cancer drug research already has attracted the attention of the Ohio Cancer Research Alliance, leading to a $60,000, two-year seed-money grant in 2011. That grant enabled Dr. Wald and his team to secure an additional $2.62 million in research funding, including $1.9 million from the National Institutes of Health and $720,000 from the American Cancer Society.

"My research has been well-received by funding agencies," Dr. Wald says. "I think it is because they can see the direct translational effects of it as a potential cancer treatment." The Harrington Discovery Institute grant with its connections to drug development experts, he says, will provide the industry expertise he needs to move his discovery ahead.

He already has conducted a small Phase I clinical trial with AML patients. "That has been the most satisfying, to see the trial of a potential new treatment come out of my lab work," he says.

"You know that 99 percent of what you try won't work out. It's that 1 percent that makes everything worth it."

EXPERT GUIDANCE

through the Valley of Death

Perry Molinoff, MD, considers the Harrington Discovery Institute Innovation Support Center that he heads a breath of fresh air blowing across the "Valley of Death," the void between drug discovery and commercialization where many discoveries languish forever. In a career that spans four decades in academics and the pharmaceutical industry, Dr. Molinoff, now Director of the Innovation Support Center, has seen firsthand the need for a fresh new model for drug development.

"We know the current model for drug discovery is broken," he says. "The Harrington Discovery Institute isn't going to cure it, but we can make a difference by bringing along a highly selective set of the most promising projects."

FILLING IN THE GAPS

The Harrington Discovery Institute Innovation Support Center provides the Harrington Scholars with the pieces of the process that are missing in the typical academic environment, where physician-scientists spend most of their time. "The Harrington Scholars understand human biology, physiology, pharmacodynamics, chemistry and genetics," Dr. Molinoff explains. "What they don't understand – because they have never been involved in it or exposed to it – is the specialization of drug development."

To ensure that elite level of specialized expertise is available to the scholars, Dr. Molinoff and Jonathan Stamler, MD, Director of the Harrington Discovery Institute, hand-select potential candidates for the Innovation Support Center Advisory Panel. The selection criteria are strict, Dr. Molinoff says, including specific experience in the pharmaceutical industry. The Advisory Panel comprises exclusively drug development business people – no academics.

BENEFITS OF EXPERIENCE

The Advisory Panel's express function is to bring together the panel's veteran investigators and the Harrington Scholars in one-to-one mentoring relationships.

Through the panel members' expertise in esoteric specialties ranging from medicinal chemistry and pharmaceutical development to regulatory affairs, they shepherd the physician-scientists through the myriad of complex stages involved in transitioning a new drug from the laboratory to commercial development. The scholars appreciate the panel's hands-on approach, Dr. Molinoff notes. "Panel members meet personally with their assigned scholars, follow their progress and consult by phone once a month. If the scholar has a question in between, all he has to do is call or send an email."

Advisory Panel members don't hesitate to offer advice. They may encourage a Harrington Scholar to continue on his or her current path. At other times, an advisor may recommend changes in the scholar's game plan such as selecting a different therapeutic target or narrowing the focus to a specific target.

The Innovation Support Center works with each Harrington Scholar for two years to prepare a discovery for the next stage with BioMotiv or another drug development company. The process is intense at times, when deadlines loom or a challenge crops up, but rewarding for scholars and Advisory Panel members.

As fulfilling and exciting as they all find the process, Dr. Molinoff and the Advisory Panel never lose sight of their purpose. "This is an exciting way to potentially revolutionize the way drugs are brought to market," Dr. Molinoff says. "But the final measure of our success will be the transformation of a scientific project into a commercialized product that can help people."

REFLECTIONS ON **PROGRESS**

Sanford Markowitz, MD, PhD, shares the progress he has made in the year since being named to the Harrington Discovery Institute's first class of Scholar-Innovators.

MAKING A DIFFERENCE FOR CANCER PATIENTS

Sanford Markowitz, MD, PhD, UH Seidman Cancer Center oncologist and Markowitz-Ingalls Professor of Cancer Genetics at Case Western Reserve University School of Medicine, is engaged in leading-edge cancer research that has a personal dimension for him.

Early in Dr. Markowitz's medical career, his father developed colon cancer. That experience has been one of the inspirations for Dr. Markowitz's work on an innovative drug that appears to hold the promise of better outcomes for cancer patients.

After years of research, Dr. Markowitz and his team have developed a first-generation drug that has been proven in laboratory animals to support tissue regeneration, resulting in faster recovery from surgery and better survival from cancer. With assistance from the Harrington Discovery Institute Innovation Support Center advisors, Dr. Markowitz is transforming his discovery from a laboratory compound into a commercially viable human drug.

"This is why we are excited," he says. "To be able to consult with individuals with real-world drug formulation experience who can teach us what we don't know and connect us with the right people and companies – this is indispensable."

Alzheimer's Drug Discovery Foundation

HARRINGTON SCHOLARS

The Harrington Discovery Institute announced a partnership with the Alzheimer's Drug Discovery Foundation (ADDF) in October 2013. The two organizations share a common purpose: fund leading scientists who are conducting the most promising, innovative drug research with the goal of finding cures. This is the first in what the Harrington Discovery Institute expects to be a series of collaborations with like-minded disease-centered foundations.

Since 1998, the ADDF has been providing seed funding for promising, innovative early-stage Alzheimer's research worldwide that may otherwise go unfunded. Like the Harrington Discovery Institute, the ADDF seeks to bridge the gap between preclinical research or early-stage clinical trials and support from pharmaceutical companies or other potential partners.

In the new partnership, physician-scientists with some of the most promising Alzheimer's research will be selected to become ADDF Harrington Scholars. Scholars will receive funding from the ADDF plus staged support from the Harrington Discovery Institute Innovation Support Center's experts in pharmaceutical development and commercialization. ADDF researchers previously have not had access to this specialized expertise.

ADDF Harrington Scholars also will have priority access to BioMotiv, the for-profit, mission-aligned company associated with the Harrington Discovery Institute. BioMotiv licenses a drug discovery from a researcher when the Innovation Support Center has laid the groundwork for progressing the product to the first stages of commercialization.

THE HARRINGTON DISCOVERY INSTITUTE AND THE ALZHEIMER'S DRUG DISCOVERY FOUNDATION ANNOUNCED THE FIRST ADDF HARRINGTON SCHOLARS IN APRIL. THEY ARE:

- Emory University's **Thota Ganesh, PhD**, Principal Investigator, and **Allen Levey, MD**, Physician Collaborator, whose research focuses on a novel anti-inflammation drug for the treatment of Alzheimer's disease
- The Ohio State University's **Chien-Liang Lin, PhD**, Principal Investigator, and **Douglas W. Sharre, MD**, Physician Collaborator, who will develop novel drugs that modulate neurotransmission as potential therapeutics for Alzheimer's disease

SETTING THE PACE FOR
DRUG DEVELOPMENT

ac·cel·er·ate:
to cause faster or
greater activity,
development, progress,
advancement

This single word capsulizes the vision and spirit of BioMotiv, the mission-aligned, for-profit company associated with The Harrington Project for Discovery & Development, and its CEO, Baiju Shah.

Less than two years since its launch, BioMotiv has surged to the forefront of early-stage pharmaceutical development. The company's portfolio of products already includes potential breakthrough technologies in preclinical testing for psoriasis and other autoimmune diseases, leukemia and other cancers, and inflammatory bowel diseases, as well as a promising discovery-stage project for treating retinitis pigmentosa.

POSITIONED FOR SUCCESS

Mr. Shah attributes the company's early momentum to having three essential conditions in place from the beginning. "Having a mission-focused approach that guides the strategy and organization, leading-edge technologies from great physician-scientist innovators and a team and advisory board of pharmaceutical development experts lays the foundation for success," he notes.

That positioned BioMotiv for a fast start, and in September 2013 the company announced the formation of Orca Pharmaceuticals, a biotechnology startup focused on treating autoimmune diseases, particularly psoriasis, by commercializing technology developed at New York University in collaboration with individuals in the United Kingdom. The company is located in Oxford, England, and funded by BioMotiv and the New York University Innovation Venture Fund.

"Dr. Dan Littman at New York University discovered the important role of a nuclear hormone receptor that has catalyzed a frenzy of pharmaceutical activity because of its implication in many autoimmune diseases," Mr. Shah says. "That discovery and the development of novel compounds that target the receptor led us to license and continue developing the technologies as Orca Pharmaceuticals."

MAINTAINING MOMENTUM

A month after announcing Orca, BioMotiv announced Dual Therapeutics in collaboration with the Icahn School of Medicine at Mt. Sinai in New York City. Dual Therapeutics' co-founders include lead inventors Goutham Narla, MD, PhD, the 2012 Harrington Distinguished Scholar and Assistant Professor of Medicine at Case Western Reserve University School of Medicine; Michael Ohlmeyer, PhD, Associate Professor of Structural and Chemical Biology, and Matthew Galsky, MD, Associate Professor of Medicine, Hematology and Medical Oncology, both at Icahn School of Medicine at Mount Sinai.

"We were excited about this program from the time we met with the team and started working with them in late 2012. Dual Therapeutics is developing an innovative product with applications for leukemia, prostate cancer and lung cancer and a goal of initial patient use in 2015," Mr. Shah says.

MAKING NEW CONNECTIONS

In November 2013, BioMotiv announced a funding partnership with Foundation Fighting Blindness with the two organizations co-funding a discovery-stage project that could lead to a treatment for retinitis pigmentosa. The discovery emanates from the Johns Hopkins' laboratory of Donald Zack, MD, PhD, a leading physician-scientist innovator in ophthalmology.

The latest addition to BioMotiv's portfolio is Kodosil Bio, a company formed to advance an antibody compound for the treatment of inflammatory bowel diseases and other autoimmune conditions. In February 2014, BioMotiv licensed the worldwide rights to develop and commercialize the compound.

With the goal of managing a broad portfolio of projects at any given time, BioMotiv continues to seek the most promising therapeutics from research institutions, industry sources, disease foundations and Harrington Scholars.

Learning the Pharma Business **FROM THE EXPERTS**

"The BioMotiv experts will help move our discovery forward better and faster than we could."

When he was selected as the 2012 Harrington Distinguished Scholar (Early Career Award), **Goutham Narla, MD, PhD,** Assistant Professor in the Case Western Reserve University School of Medicine Institute for Transformative Molecular Medicine, wasn't exactly sure what to expect. A highly skilled and experienced cancer biology researcher, Dr. Narla leads a team at the School of Medicine that is re-engineering an existing cancer drug series to boost effectiveness and reduce side effects.

But the world of drug development for commercialization that Dr. Narla is experiencing with BioMotiv is new to him. BioMotiv launched Dual Therapeutics for the express purpose of bringing his team's product to market and has licensed the rights to develop the product from his team.

"The BioMotiv Advisory Board's knowledge is invaluable," Dr. Narla says. As part of what he calls his "learning process," he is following the board's direction on due diligence, compound selection, compound safety evaluation and filing an Investigative New Drug application with the U.S. Food and Drug Administration.

"The BioMotiv experts will help move our discovery forward better and faster than we could," Dr. Narla notes. "Good science gets you so far, but then you need the right partner."

He anticipates filing the paperwork to start clinical trials by the middle of 2015.

THE HARRINGTON DISTINGUISHED SCHOLAR PROGRAM

The Harrington Discovery Institute at University Hospitals set the bar high with the selection of **Goutham Narla, MD, PhD**, Assistant Professor in the Department of Medicine and the Institute for Transformative Molecular Medicine, Case Western Reserve University School of Medicine, as the first Harrington Distinguished Scholar (Early Career Award).

Dr. Narla exemplifies the quality of physician-scientist the Harrington Discovery Institute is seeking to recruit as Harrington Distinguished Scholars – outstanding promise, leading research that has the potential to transform the standard of care, and possessing passion for the physician-scientist's central role in drug development. In the two years since Dr. Narla's recruitment, the Harrington Discovery Institute has assisted him in advancing his research on genetics and biologic pathways in cancer to early-stage commercial development through BioMotiv, the Harrington Discovery Institute's for-profit consort.

LIKE DR. NARLA, FUTURE HARRINGTON DISTINGUISHED SCHOLARS WILL RECEIVE:

- A faculty appointment to the School of Medicine and a staff position at University Hospitals Case Medical Center
- State-of-the-art laboratory space and access to unparalleled technical and scientific facilities
- Resources to support a significant laboratory-based research program, including personnel, salaries, supplies and capital equipment
- Research programs augmented by a robust drug development infrastructure, including:
  - Harrington Discovery Institute Innovation Support Center project management, resources and support
  - Facilitated access to BioMotiv
  - Additional grant funding

Over the next decade, the Harrington Discovery Institute aims to recruit at least one physician-scientist each year to the Harrington Distinguished Scholar program. They are actively recruiting exceptional physician-scientists for consideration. For complete information, visit **HarringtonDiscovery.org**.

Harrington Discovery Institute Scientific Symposium:

ADVANCING MEDICAL DISCOVERY

JUNE 5 – 6, 2014

Scientific Symposium

The annual **Harrington Discovery Institute Scientific Symposium** brings together Harrington Scholars, Harrington Discovery Institute leadership, Scientific Advisory Board, Innovation Support Center and BioMotiv drug development experts, and leadership of national disease foundations to celebrate the transformation of medical discovery. Over the two days of the symposium, physician-scientists engage in leading-edge research connect with the drug development expertise that is essential to realize the commercial potential of their groundbreaking discoveries.

In recognition of the Harrington Discovery Institute's new partnership with The American Society for Clinical Investigation (ASCI) and the inaugural Harrington Prize for Innovation in Medicine, the Harrington Discovery Institute will welcome ASCI leadership to the symposium. The first Harrington Prize awardee, **Harry Dietz, MD**, Victor A. McKusick Professor of Medicine and Genetics, The Johns Hopkins University School of Medicine, will present personal reflections following dinner Thursday evening at the historic Shoreby Club on the shores of Lake Erie in nearby Bratenahl, Ohio.

William G. Kaelin Jr., MD, Professor of Medicine, Harvard Medical School and member of the Scientific Advisory Board, will deliver the Keynote Lecture Thursday evening to open the symposium. The Cleveland Institute of Music in University Circle will be the setting for Friday's scientific presentations by the 2014 Harrington Scholar-Innovators and a panel discussion on accelerating cures by disease foundation Directors and CEOs, moderated by **Baiju Shah**, CEO, BioMotiv. **Beth Levine, MD**, Professor, Internal Medicine and Microbiology, University of Texas Southwestern Medical Center and member of the Harrington Discovery Institute Scientific Advisory Board, will deliver the closing Keynote Lecture.

FOR MORE INFORMATION ABOUT THE HARRINGTON SCIENTIFIC SYMPOSIUM, VISIT **HARRINGTONDISCOVERY.ORG**.

Harrington Discovery Institute

University Hospitals | Cleveland Ohio

Among the nation's leading academic medical centers, University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a nationally recognized leader in medical research and education.

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