MARC I. DIAMOND, MD

ALZHEIMER'S DISEASE

Washington University, St. Louis, Mo.

"Diseases like Alzheimer's… are devastating for those they affect, not only the person with the disease but also their loved ones, who watch their steady decline."

Alzheimer's disease, with its slow descent into mental, emotional and psychological oblivion, is perhaps one of the most feared diseases of the 21st century. To **Marc I. Diamond, MD**, a neurologist and the David Clayson Professor of Neurology at Washington University School of Medicine, it's also one of the most fertile areas for translational research.

In his clinical practice, Dr. Diamond regularly treats patients with neurodegenerative diseases and sees their effects on patients and families. "Diseases like Alzheimer's, Parkinson's and Lou Gehrig's are devastating for those they affect, not only the person with the disease but also their loved ones, who watch their steady decline," he says. "Better diagnostic tests and effective treatments are desperately needed."

Dr. Diamond's inspiration derives not only from his patients but also from his father, Ivan Diamond, MD, PhD, researcher and founding director of the Ernest Gallo Clinic and Research Center at the University of California, San Francisco. "My dad impressed upon me the excitement and joy of life as an academic physician, and the worthiness of the work," he says.

Devising a Game-Changer

Since joining the Department of Neurology at Washington University in 2009, Dr. Diamond has concentrated his research on neurodegenerative diseases. His laboratory was responsible for a major breakthrough in understanding the development of neurodegenerative diseases like Alzheimer's with the discovery that pathologic proteins in these diseases propagate pathology between cells, just like prion protein.

Building on that discovery, he now is exploring the development of antibodies that can target these pathologic proteins and block their spread through the brain. "If this approach is successful, it could be a game-changer in Alzheimer's treatment," he says. "Anything that would significantly slow down the disease, let alone cure it, would have enormous impact on our society."

Always considering the practical clinical application of his discoveries, Dr. Diamond sees the need for a screening tool that could detect these protein pathogens before they have a chance to cause any harm to the brain. So far, he has discovered a way to detect the pathogens in spinal fluid and blood prior to the onset of dementia.

"My dad impressed upon me the excitement and joy of life as an academic physician, and the worthiness of the work."

Exploring the Options

"It's early in the discovery process, but I am very excited by the potential implications of this work, although the corollary is that once we can detect the disease at a preclinical stage, we need to have a therapeutic intervention available," he says.

That, he notes, is the beauty of the Harrington Discovery Institute at University Hospitals Case Medical Center. "The Harrington Discovery Institute model not only provides funding, it also connects us with the expertise to bring discoveries to a point where they can be translated to patient care."

Dr. Diamond's next steps will be developing antibodies that are more effective at interfering with the pathologic process and refining the screening technique. Support from the Harrington Discovery Institute will give him the flexibility to explore different approaches, he says. "It is helping me go in directions that promise to be the most productive – and the most exciting."

ROGER A. GREENBERG, MD, PHD

HEREDITARY BREAST AND OVARIAN CANCER

University of Pennsylvania, Philadelphia, Pa.

"The support provided by the Harrington Discovery Institute is very unique and very special."

"The excitement of discovery drives me on a daily basis," says **Roger A. Greenberg, MD, PhD**, researcher in the Abramson Family Cancer Research Institute and associate professor in the University of Pennsylvania's Perelman School of Medicine. That excitement paired with years of diligent research at the laboratory bench has led Dr. Greenberg to identify the molecular basis for a potential new cancer treatment.

Targeting Hereditary Cancers

Dr. Greenberg has discovered an enzyme that is required to repair certain types of DNA damage that occur during the development of hereditary breast and ovarian cancer. He believes that he can inhibit this enzyme to create irreparable DNA damage in the cancer cells, causing the cells to die. This mechanism could be the foundation for new, more effective chemotherapy drugs.

The challenges inherent in any exploration of novel therapeutic approaches to cancer don't discourage Dr. Greenberg. In fact, the challenges intensify his interest in the research. "I think it's exciting to work on something that's novel, that's uncharted territory," he says. He plans to apply his Harrington Discovery Institute Scholar-Innovator grant to navigate through that uncharted territory with additional work on refining the use of the enzyme against breast and ovarian cancer.

Dr. Greenberg's dedication to understanding the molecular basis of disease dates back to his undergraduate years at Haverford College in Pennsylvania. As part of a Howard Hughes Medical Institute program for interdisciplinary research, he had his first taste of scientific research.

Working for several years after graduation as a scientist with DuPont-Merck Pharmaceuticals piqued his interest in drug development and medicine, leading to his decision to attend medical school. But it was his work with renowned cancer

researcher David M. Livingston, MD, at Harvard's Dana-Farber Cancer Institute after earning his medical degree that ultimately shaped his career as a physician-scientist.

"Dr. Livingston's focus is on the molecular pathogenesis of breast and ovarian cancer. The four years I spent with him deeply inspired my work at U Penn," Dr. Greenberg says. Working with Dr. Livingston, Dr. Greenberg developed his research skills along with a special interest in DNA repair processes and their potential relationship to cancer treatment.

Laying the Groundwork

Now, after more than a decade of research, Dr. Greenberg believes that his work is at a crucial stage. Through the relationship-building opportunities that the Harrington Discovery Institute at University Hospitals Case Medical Center offers the Harrington Scholar-Innovators, he hopes to lay the groundwork for translating his laboratory discoveries into a powerful new cancer treatment.

"To develop the necessary expertise to do this on our own would be tremendously time-consuming, difficult to assemble and prohibitively expensive," he notes. "The support provided by the Harrington Discovery Institute is very unique and very special."

It's important to Dr. Greenberg that the Harrington Discovery Institute Scholar-Innovator grant allows him free rein to follow his research wherever it leads, into that uncharted territory. "I get to apply what I love to do, which benefits humankind and is exciting on an intellectual level," he says. "That is what really makes this very rewarding."

"I think it's exciting to work on something that's novel, that's uncharted territory."

GEOFFREY C. GURTNER, MD, FACS

DIABETIC WOUND HEALING

Stanford University, Stanford, Calif.

"This is an area that can only be funded by an organization such as the Harrington Discovery Institute, where it's not necessarily just hard-nosed businessmen worried about the bottom line."

In the 25 years since his graduation from medical school at the University of California, San Francisco, **Geoffrey C. Gurtner, MD, FACS**, a plastic surgeon and professor at Stanford University, has earned a reputation as a physician, a scientist and an entrepreneur. He maintains a busy plastic surgery practice, is engrossed in leading-edge research in wound healing, has authored nearly 200 articles in the medical literature and brought innovative products to market in the diverse fields of aesthetic plastic surgery, cardiovascular surgery and wound healing.

Starting with the Basics

To Dr. Gurtner, translational research – "where surgery meets science," in his words – offers the opportunity to make a difference through discovery. "In medicine you really have to go back to the lab and understand what causes a problem and try to brainstorm a solution or better ways of doing things," he explains. "My research has always been very translationally focused on clinical needs that are unaddressed by current technologies, companies or drugs."

In his latest research, Dr. Gurtner and his team at Stanford University have discovered a negative correlation between high blood sugar and tissue regeneration and fibrosis. He believes that this irreversible disruption of the healing process at the molecular level is responsible for the development of nonhealing wounds in patients with diabetes.

With support from the Harrington Discovery Institute at University Hospitals Case Medical Center, Dr. Gurtner hopes to translate this research into a prophylactic treatment that would prevent wounds in people with diabetes, paraplegics and other patient populations prone to chronic wounds. This is a field where he believes research lags behind the clinical need. In particular, he says, "It is the patients that I deal with who have seemingly unsolvable problems that are the real imperative."

In parallel with his work on the molecular basis for chronic wounds, Dr. Gurtner is developing a skin patch delivery system for his eventual wound-prevention drug. Ultimately, he aims to have 10,000 patches produced for testing in clinical trials.

Taking a Risk

He describes his research as innovative and high risk – two descriptors that can spell sudden death in the land of funding support. "This is an area that can only be funded by an organization such as the Harrington Discovery Institute, where it's not necessarily just hard-nosed businessmen worried about the bottom line," Dr. Gurtner says. That kind of thinking leads only to small, incremental change, he adds. "If we only listened to the business perspective, we would still be going across the sea in steamships."

Despite years of personal experience in securing start-up funding and navigating through the maze of regulations on the way to commercializing a discovery, Dr. Gurtner welcomes the expertise of the Harrington Discovery Institute's advisory boards. "Having an organization that says translation is important, that they will help you figure out the regulatory pathway for the drug, device or biologic and, at a minimum, has a network of people willing to work on it – that is pretty unique."

"My research [is] very translationally focused on clinical needs that are unaddressed by current technologies, companies or drugs."

SANFORD D. MARKOWITZ, MD, PHD

COLON CANCER

Case Western Reserve University School of Medicine, Cleveland, Ohio

"The biggest challenge for any academic laboratory is to get beyond the lab and develop a therapy."

For **Sanford D. Markowitz, MD, PhD**, an oncologist at University Hospitals Seidman Cancer Center and the Markowitz-Ingalls Professor of Cancer Genetics at Case Western Reserve University School of Medicine, cancer research has a personal dimension. Early in his medical career, his father developed colon cancer, inspiring in Dr. Markowitz a desire to fight back against this disease.

"Anyone who has experienced the acute terror of having cancer strike a family member, who has dreaded that every ache, pain or ailment was the beginning of the end, understands this desire to do something to make a difference," he says. Now, years after his father's illness, the patients he treats in his oncology practice provide a continuing source of motivation. "I've seen patient after patient, and I wanted to be able to help but lacked the means to do so," he adds.

Identifying a Genetic Control

Dr. Markowitz, who heads the cancer genetics program in the Case Comprehensive Cancer Center at Case Western Reserve University, is dedicated to understanding the genetic basis for colon cancer as the key to developing better treatments. He and his team have identified a genetic "switch" that controls cell division and tissue growth in colon cancer. Theoretically, turning off this genetic switch should prevent a tumor from growing. Turning it on potentially would promote tissue growth, a situation that could be useful in promoting new tissue growth following organ transplant.

So far, he and his team have tested more than 100 compounds and identified two specific compounds that regulate the gene switch – one that turns it off and one that turns it on. Laboratory tests of the "on" compound have shown some success in tissue regeneration.

With the Harrington Discovery Institute Scholar-Innovator grant, Dr. Markowitz plans to continue testing the compound in animal models, ultimately hoping it will have application in the treatment of colitis and inflammatory bowel disease as well as liver and bone marrow transplantation. To conduct this next stage of research, Dr. Markowitz first will develop an analog of the compound that has a longer half-life so that therapeutic blood levels can be maintained longer.

Beyond the Lab

As exciting as he finds the basic research process, Dr. Markowitz is keenly aware of the need to translate scientific discoveries into commercially viable treatments – and the barriers to making that happen. "The biggest challenge for any academic laboratory is to get beyond the lab and develop a therapy," he explains.

"You need collaborators, pharmaceutical companies, biotechnology companies that can produce compounds according to FDA safety standards. In general, academicians do not have access to those kinds of organizations."

The Harrington Discovery Institute at University Hospitals Case Medical Center, with its two advisory boards and relationships with the pharmaceutical industry and venture investors, does have that access. "The contact with experts who can help ensure that a new treatment is deliverable, stable and meets federal safety standards can make a critical difference in whether a new drug is successful," Dr. Markowitz says. "By connecting academics with industry experts, the Harrington Discovery Institute is giving our ideas a fighting chance to succeed."

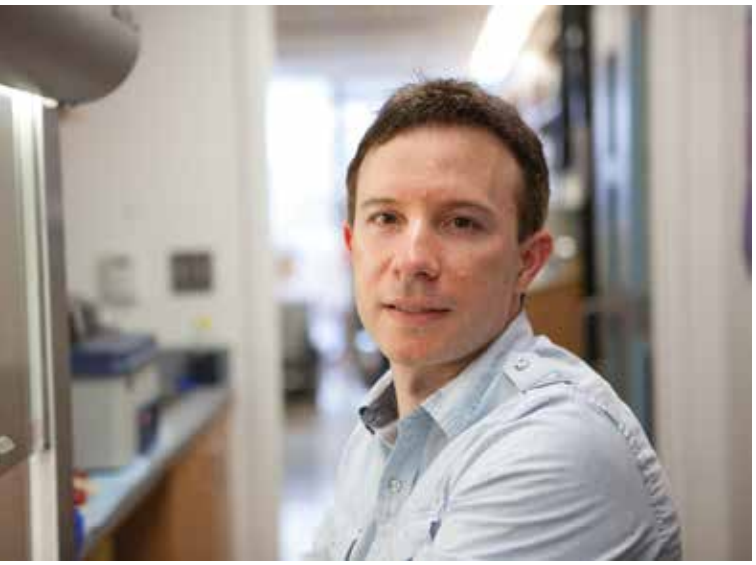
"By connecting academics with industry experts, the Harrington Discovery Institute is giving our ideas a fighting chance to succeed."

SCOTT A. OAKES, MD

FEROZ R. PAPA, MD, PHD

NEURODEGENERATIVE DISEASES AND DIABETES

University of California, San Francisco



Scott A. Oakes, MD

Feroz R. Papa, MD, PhD

Scott A. Oakes, MD, and **Feroz R. Papa, MD, PhD**, associate professors at the University of California, San Francisco (UCSF), prove the truth of the old adage "Two heads are better than one." Coming from two different perspectives and trainings – Dr. Oakes is a pathologist in the UCSF Diller Family Comprehensive Cancer Center; Dr. Papa is an endocrinologist within the UCSF Diabetes Center – the two put their heads together to discover new details about the causes and mechanisms of cell death.

Converging on a Fresh Approach

"We were working on the same problem from two different ends – Feroz was studying one end of the problem and I was studying the other end," Dr. Oakes says. His research focuses on the mechanism for cell death in response to cell injury. Dr. Papa is studying how the cell detects stress and transmits those signals to the cellular death-promoting machinery. Eventually, they hope these two vantage points will converge on a new understanding of diseases that are caused by cell degeneration under unchecked cell stress, such as diabetes, Alzheimer's disease, Parkinson's disease and Lou Gehrig's disease.

"Our work and passions brought us together, and Scott and I developed a collegial relationship that provides a sense of fulfillment and gratification that adds to the work that we do," Dr. Papa says. The two researchers share resources, research teams and responsibilities. "That spirit of camaraderie, that working relationship has trickled down to the people that work for us," he adds.

Drs. Oakes and Papa have been working together since 2007 and are making progress at "saving cells" that they believe has significant potential for translation into clinical care. They have identified IRE1, a protein that plays a critical role in many biological processes, as a regulator of cell fate. IRE1 is a cellular stress sensor that normally protects cells from death when stress levels are low and manageable. But, under prolonged conditions of high cellular stress, it can activate a series of biologic events that actually causes cell death instead.

Survival Under Stress

Through collaboration with chemist Dustin Maly, PhD, an associate professor at the University of Washington, the researchers have identified several IRE1 inhibitors that can tilt the cellular balance toward survival under stress conditions. "We expect that these compounds will be powerful tools to investigate connections between cell stress and cell death," Dr. Papa explains. "We currently are advancing these compounds through medicinal chemistry to make them more drug-like and useful for animal and preclinical studies."

Their long-term goal is to develop new drugs that reduce cell stress and cell death to treat many cell-stress-related degenerative diseases. Their target list includes the neurodegenerative diseases and other diseases of cell loss such as type 2 diabetes, as well as certain types of cancer in which cells fail to die appropriately in response to stress. With the basic science behind their therapeutic vision steadily gaining traction, Drs. Oakes and Papa are positioned to take advantage of the resources that the Harrington Discovery Institute at University Hospitals Case Medical Center can offer for moving their discoveries from bench to bedside.

"We were working on the same problem from two different ends – Feroz was studying one end of the problem of cell death, and I was studying the other end."

– Dr. Scott A. Oakes

"We expect that these compounds will be powerful tools to investigate connections between cell stress and cell death."

– Dr. Feroz R. Papa

JONATHAN D. POWELL, MD, PHD

DIABETES

The Johns Hopkins University, Baltimore, Md.

Jonathan D. Powell, MD, PhD, an oncologist and associate professor of oncology at The Johns Hopkins University School of Medicine, set his sights on a career that combined medicine and research while he was still an undergraduate at Dartmouth College. "I entered Dartmouth as a pre-med student and planned to go to medical school, but participating in research as an undergraduate slightly changed my plans," he explains.

His desire to integrate medicine with research led him to pursue a dual MD/PhD degree at Emory University instead of the MD degree he originally planned. After finishing both degrees at Emory, Dr. Powell completed a residency at The Johns Hopkins University followed by a clinical fellowship at Harvard. He then went on to a post-doctoral fellowship in immunology at the National Institutes of Health in Bethesda, Md., an experience that helped set a direction for his research that continues today with his studies of T-cell function in his lab at Johns Hopkins.

Following Where the Research Leads

That work recently has led Dr. Powell in still another direction. He was conducting basic research into the role of T-cells in the body's immune system using laboratory mice. During the course of these studies, Dr. Powell and his team noted that a group of mice with genetically altered immune cells became obese.

Analysis revealed that the obese mice were generating brown adipose tissue, a type of fat that plays a role in regulating body weight and metabolism, including glucose tolerance and insulin sensitivity – two important factors involved with the development of diabetes. The mice with the "brown fat" were resistant to type 2 diabetes and exhibited favorable blood levels of cholesterol and triglycerides.

"By studying the immune system, we believe we have uncovered a potentially new approach to treating diabetes."

"By studying the immune system, we believe we have uncovered a potentially new approach to treating diabetes," Dr. Powell says. "Our finding is a nice example of how, by supporting basic research, unexpected spin-offs into translational research can emerge."

The excitement of these unexpected new findings has led Dr. Powell and his team to pursue this new line of inquiry further, a temporary departure from their typical research in immunology. Dr. Powell believes that his discovery could have a significant impact on treating diabetes, obesity and heart disease.

Opening Doors to a New Approach

His team already has identified a candidate gene that they believe likely promotes the creation of brown fat. "If this turns out to be the case, it might lead to the development of a completely novel approach to treating type 2 diabetes and, potentially, obesity and hyperlipidemia," Dr. Powell says.

He sees the Harrington Discovery Institute at University Hospitals Case Medical Center as offering him a unique opportunity to rapidly develop this exciting line of inquiry. "Not only does it provide funding through the Harrington Scholar-Innovator grant to support our experiments," he says, "it also provides the scientific and business resources to develop our findings into a drug."