Harrington Discovery Institute

University Hospitals | Cleveland, Ohio

DISCOVERY WITH PURPOSE

2024-2025 ANNUAL PUBLICATION

DEAR COLLEAGUES,

Because heart disease remains the leading cause of death globally, new treatments for the condition remain a major unmet need. Years ago, Harrington Scholar Barry Coller, MD, Rockefeller University, endeavored to develop a drug to treat heart attacks. In 2025, the company he cofounded received the results of its Phase 3 clinical trial showing that Dr. Coller's years-long commitment had paid off; the drug zalunfiban saves the lives of patients who are having a heart attack but not yet at the hospital (i.e., in ambulance settings).

This is the type of drug discovery success that, when launching Harrington Discovery Institute in 2012, our founding team knew could take place: Our nation's corps of physician-scientists could catalyze a steady stream of successes that would benefit patients. With the goal in mind, Harrington Discovery Institute made its mission-driven focus to build a bridge over the valley of death in drug discovery, across which academic physicians and scientists with breakthrough discoveries could travel.

Today, in addition to lifesaving stories like zalunfiban's success, we have lifesaving numbers. On average, every two months a scholar or innovator Harrington supports hits an important milestone for a new medicine that may benefit patients. Either a new company is formed to commercialize a therapeutic, a breakthrough medicine moves into the clinic, or a pharmaceutical company licenses a drug discovery. Also, the pace of these successes is accelerating.

Naturally, the most meaningful successes are the patient lives to be enhanced and saved because of drugs in the making. Here are some, but not all, of the types of patients and conditions our scholars and innovators are working to help: The heart failure patient. The patient with amyotrophic lateral sclerosis. The patient with chronic obstructive pulmonary disease. The patient with Alzheimer's disease. The child with brain cancer. The patient with Rett Syndrome, a rare chromosomal disorder. The patient with IPEX syndrome, a rare immune-type condition. The patient with diabetes. The patient with Huntington's Disease. The patient with rheumatoid arthritis. The patient with Duchenne muscular dystrophy. The patient with macular degeneration. The patient with pancreatic cancer. The patient with chronic pain. The patient with addiction. The patient with depression. And more, leading to the collective potential for millions of lives enhanced and saved by breakthrough discoveries.

At Harrington Discovery Institute, we know that discovering one drug, never mind the hundreds in development, is a complex process. Hence, the purposeful simplicity of our lifesaving mission—to accelerate promising discoveries into medicines for unmet needs.

Sincerely,

JONATHAN S. STAMLER, MD
President and Co-Founder, Harrington Discovery Institute
Robert S. and Sylvia K. Reitman Family Foundation Chair
of Cardiovascular Innovation
Distinguished University Professor
Professor of Medicine and of Biochemistry
Case Western Reserve University
University Hospitals Health System

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UNITED KINGDOM

INSTITUTION WITH HARRINGTON SCHOLAR(S)

Harrington Discovery Institute
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INSTITUTION WITH OXFORD-HARRINGTON SCHOLAR(S)

Oxford-Harrington RARE DISEASE CENTRE

RON HARRINGTON
Co-Founder, Harrington Discovery Institute;
Entrepreneur and Philanthropist

Ronald G. Harrington, pictured with his family — wife Nancy, daughter Jill, and son Ron. Jr. and his wife Lydia

ON BEHALF OF PATIENTS

A trademark style Ron Harrington and his family — wife Nancy, daughter Jill, and son Ron Jr. and his wife Lydia — have long brought to Harrington Discovery Institute is a bias toward action. As a remarkably successful entrepreneur, the founding donor of Harrington Discovery Institute knew clearly what his role would be on an ongoing basis: he would help it grow to be great through ensuring it developed a highly differentiated results orientation.

"Our family knew that if discoveries sitting on shelves in academic medical centers were going to see the light of day and benefit patients, the industry needed transformation," he says.

Fast forward to 2025 when Harrington Discovery Institute's bias for action and drive toward results shone through. Harrington Discovery Institute or the Oxford-Harrington Rare Disease Centre:

- Issued calls for proposal for its five major grant programs, receiving many hundreds of applications.
- Held its annual scientific symposium convening hundreds of medical researchers from academic medical centers, in turn attracting speakers such as the former commissioner of the FDA, the former prime minister of the UK, and the CEO of the world's largest biotech industry organization.
- Supported multiple companies or drugs that entered Phase 1 clinical trials; raised millions for Phase 2 trials; inked a product deal with a pharmaceutical giant; and completed an important Phase 3 clinical trial.
- Attracted new people, including former Regeneron Pharmaceuticals and Takeda vice presidents, a former senior director of Innovations at a major healthcare system, and a luminary from Harvard Medical School's board of fellows.
- Featured speakers at major drug-discovery-related events, and Morgan Stanley's annual signature "big ideas" conference.
- Exemplify quality excellence in University Hospitals being ranked among the top academic medical centers globally.
- Reached cumulative milestones of 227 medicines in the making, 75 institutions supported, 47 companies launched, 24 medicines in the clinic and 15 licenses to pharma.

Is Mr. Harrington satisfied with the results?

"Yes," he says. "I'm really proud of the team and everyone involved." And then, "But then again, on behalf of patients, I'm never satisfied."

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The Scientific Advisory Board (SAB) helps set the science and innovation agenda in areas of unmet need. The SAB is responsible for the annual selection of Harrington Scholar-Innovators as part of Harrington's flagship physician-scientist program, as well as the annual selection of The Harrington Prize for Innovation in Medicine recipient with the American Society for Clinical Investigation.

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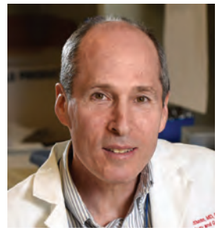
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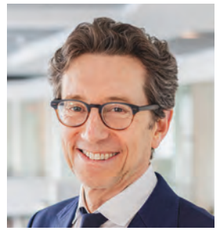
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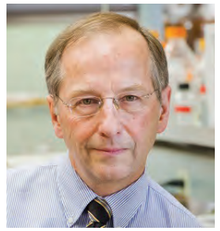
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The Harrington mission is achieved through the collective efforts of highly accomplished individuals who bring extensive experience and expertise to their roles. This collective strength enables Harrington to fulfill its purpose of transforming discoveries into medicines for patients worldwide.

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A special note of gratitude to all of our reviewers who contribute to the selection of outstanding scholars in our physician-scientist, brain health, and rare disease programs.

We thank the Harrington staff for the talent and passion they bring to work every day, and for their unwavering commitment to excellence that underpins every aspect of the institute's work.

THANK YOU

Oxford-Harrington
RARE DISEASE CENTRE

FATHERS, ADVOCATES AND THE POWER OF PARTNERSHIP

LORD (DAVID) CAMERON
Chair of the Advisory Council for the Oxford-Harrington Rare Disease Centre

Former Prime Minister of the UK, member of the House of Lords

Launched the 100,000 Genomes Project, where the genes of 100,000 patients with rare disease or cancer were sequenced

Founded Genomics England, established to deliver the 100,000 Genomes Project

President, Alzheimer's Research UK

Lord Cameron is the father of a child who suffered from Ohtahara syndrome, a rare, severe form of epilepsy.

JOHN F. CROWLEY
Member, Oxford-Harrington Rare Disease Centre Advisory Council

CEO, the Biotechnology Industry Organization (BIO)

Founder and former CEO and executive chairman, Amicus Therapeutics

Co-founder, President and CEO of Novazyme Pharmaceuticals (later acquired by Genzyme Corp.)

Mr. Crowley is the father of two children with Pompe disease, a severe and often fatal rare neuromuscular disorder.

A Partnership of

UNIVERSITY OF OXFORD

Harrington Discovery Institute
University Hospitals

Scan QR for full video of the fireside chat

On May 22, 2025, Dr. Daniel Simon, President of Academic & External Affairs and Chief Scientific Officer at University Hospitals, moderated a fireside chat between two of the most notable and accomplished leaders in rare disease. Lord Cameron and John Crowley have each made extraordinary contributions throughout their careers to support patients with rare diseases by focusing on issues such as early diagnosis, accelerating treatments, entrepreneurship, and policy and funding. Below is an excerpt from their discussion.

SIMON: David, you have a deep personal connection to rare diseases. Could you tell us a little bit about your son Ivan and how your interest in rare disease began?

CAMERON: During Ivan's all too short life, we spent so much time in hospitals, looking for treatments. But there was no genomics back then. Ivan simply relied on incredibly strong opioids to alleviate the pain.

After he passed away in 2009, and I became Prime Minister the following year, I asked the chief scientists and advisers of various departments to gather in 10 Downing Street and tell me about the latest technologies in science, healthcare and biotech. One of these was a presentation on genomics - still in a relatively early phase. Hearing about the potential led to me launching the 100,000 Genomes Project in the UK and our National Health Service and setting up Genomics England to deliver it. Both what we established and the science behind it has come such a long way since then. We now have a real chance of creating a system that will help solve problems and develop drugs faster. Through its partnership with Oxford University, the Harrington Discovery Institute is a part of that.

SIMON: John, what do you most want the physician-scientists in the room to keep in mind as they face obstacles in seeking cures?

CROWLEY: First, the human piece of this is so important. Listen to the person at the center of the disease. When my daughter Megan sat on the patient advisory council for the developers of the next generation drug for her disease, it came her turn to speak to scientists about what she most wanted. She said, "I'd like to be able to breathe for one minute without my ventilator so that when I go to college next year, I can talk clearly and more easily make friends." The developers were looking at numbers and statistics and weren't thinking about that very human level.

Second, let's work to convey the urgency of drug discovery and development. The irony is that when we're seeking cures, we're racing against time to give patients more time. We need to hold and communicate that sense of urgency.

SIMON: What do you think about the OHC's goal of 40 new treatments for rare diseases in ten years?

CROWLEY: It's ambitious but doable, and it's much needed when you consider that collectively there are 10,000 rare diseases affecting about 10 percent of people, mostly children. There's no shortage of "market opportunity." Hopefully no one will ever say Harrington Discovery Institute dreamed too small.

SIMON: What do you believe is the role of government in drug research, drug investment, and especially new drug development?

CROWLEY: First, research funding. Second, policies that support entrepreneurship. And third, regulatory bodies like the FDA, being pragmatic about the evolving state of the industry, thus cutting down timelines and bureaucratic redundancy.

CAMERON: I lost my brother to pancreatic cancer this year. He went for immunotherapy treatment in Germany, where they explained that the treatment, which derived from his own T-cells, is a unique treatment just for him. If every new, personalized treatment like this needs to go through full regulatory clearance with the FDA or the MHRA we're not going to get very far. With specific immunotherapies or gene therapies, you should have regulatory clearance for the core therapy and then very quick approval for the individual versions.

I get fired up about the way the system is changing. We now can create a genomic database, do immediate testing, get faster diagnosis, and improve drug development and licensing. The private sector will fund the opportunities that emerge, but it does require government leadership and coordination.

SIMON: Any final words before we conclude our fireside chat?

CROWLEY: You [Harrington Discovery Institute] really are at the epicenter of funding so much research that otherwise wouldn't get funded. There's nothing else like it in the world, so it needs to be successful: thank you!

CAMERON: The Oxford-Harrington Rare Disease Centre is an enormous win for parents of children with rare diseases, the children themselves and patients with rare diseases at any age. It's also a very big international win for the UK and the US continuing to be at the cutting edge of new drugs, treatments, and scientific breakthroughs. We'll only stay ahead if we keep attracting smart people, investing in drug discovery, and doing the things that the Oxford-Harrington team is doing. I'm full of excitement and optimism about the possibilities, but we need to advocate for them.

OWEN N. WITTE, MD, PhD
Distinguished University Professor and
President's Chair in Developmental Immunology
David Geffen School of Medicine
University of California, Los Angeles

Dr. Witte is internationally known for his contributions to the understanding of human leukemias and immune disorders. His work revealed the critical role of enzymes called tyrosine kinases in human disease, and his foundational discoveries of targeted therapies have transformed modern cancer treatment.

The excitement of discovery has been a powerful guiding force throughout Dr. Witte's remarkable career—a career he seems destined to have pursued.

"I became interested in science in junior high school through the good fortune of having teachers who taught science in a very active way, focusing on experiments and discovery rather than just rote memorization," Dr. Witte says.

A LIFETIME OF DISCOVERY

Dr. Witte discovered one of the first tyrosine kinases, the ABL oncoprotein, showing that its activity is responsible for causing chronic myeloid leukemia (CML), a cancer of white blood cells. He predicted that drugs that inhibit the tyrosine kinase would have therapeutic benefit.

Based on Dr. Witte's work, the drug imatinib, an inhibitor of tyrosine kinase ABL, was developed as frontline therapy. Imatinib increases the 8-year survival rate for CML from 6% to 87%.

In subsequently discovering Bruton's tyrosine kinase (BTK), Dr. Witte provided evidence that BTK's tyrosine kinase activity was important for both normal immune function (loss of BTK led to immunodeficiency disease) and white blood cell cancers, ultimately spurring the development of the BTK inhibitor drugs.

Dr. Witte defined the Bcr-Abl oncoprotein as the causative lesion in chronic myeloid leukemia, thereby validating Abl as a therapeutic target for tyrosine kinase inhibitor, and mutations in BTK as the cause of Bruton's agammaglobulinemia, validating BTK as a therapeutic target for a wide range of various B cell malignancies and autoimmune states. Dr. Witte's combined studies over 25 years firmly established the role of Bcr-Abl in Philadelphia chromosome positive leukemias and defined its kinase activity as essential for transformation.

This body of work, spanning more than a decade, led to clinical development of BTK inhibitors as treatments for B cell malignancies such as chronic lymphocytic leukemia, lymphoma and multiple myeloma. The first of these drugs, Ibrutinib, was approved by the FDA in 2013.

MENTORING SCIENTIFIC LEADERS

Dr. Witte credits three individuals as important mentors in his life and career: Dr. Lawrence Slobin at Cornell University, Dr. Irving Weismann at Stanford University and Dr. David Baltimore, the 1975 Nobel laureate in physiology or medicine, at the Massachusetts Institute of Technology.

Today, Dr. Witte pays back those mentors by mentoring a steady flow of outstanding and diverse scientific leaders. He has served as the primary mentor of nearly 100 graduate students, post-doctoral fellows and clinical fellows over the past 45 years, following an approach that allows his mentees' inquisitiveness to blossom. In addition, Dr. Witte has trained numerous preeminent scientists with illustrious careers at other institutions.

LOOKING AHEAD WITH EXCITEMENT

Dr. Witte remains motivated by seeing his body of research being applied to a variety of immune-based technologies in the treatment of cancer.

"Finding the right target, employing available technology and making a difference for patients is what I've been interested in my entire career," he says. "And as long as I can raise money, bring good people to the table, have ideas for projects and entertain ideas collaboratively with my colleagues, I'm going to continue to get up and go to work every day."

Dr. Witte notes that he recently had a paper accepted for publication in the journal Science, and it gives him the same satisfaction at the age of 76 that he had when his first paper was published in the Journal of Immunology when he was 22.

"I feel no less excited about research today than I did in 1969-1970 when I worked on my first independent research project," he says.

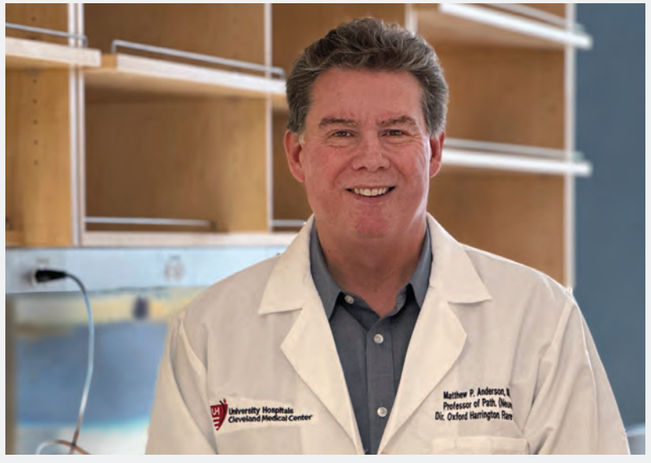
"Harrington Discovery Institute has shown they're willing to invest in ideas at an early stage and support people with ideas that are not totally established in the field, but that may change the field. This is really the way to move the needle in therapy for cancer and other diseases."

TO LEARN MORE ABOUT THE HARRINGTON PRIZE, PLEASE VISIT:
HarringtonDiscovery.org/Prize

DESIGNING DRUGS FOR

A NEW ERA IN RARE DISEASE

HARRINGTON INVESTIGATOR



MATTHEW P. ANDERSON, MD, PhD
Harrington Investigator and Co-Director,
Oxford-Harrington Rare Disease Centre
Sylvia K. Reitman Chair in Discovery and Innovation
Harrington Discovery Institute at University Hospitals
Professor of Pathology (Neuropathology),
Case Western Reserve University
Visting Professor of Neurodevelopmental Disorders,
Oxford University

Ceaselessly curious and driven by a relentless quest to improve the lives of patients and their families, Matthew P. Anderson, MD, PhD is in his element as Co-Director of the Oxford-Harrington Rare Disease Centre (OHC).

"The more I experience this program, the more excited I am about the unique approach that's been adapted for doing top-notch translational science and therapeutic development," he says. "One of my life passions is establishing a therapeutic foundation from which we can steer development of proper treatments."

An inherent advantage of the OHC model is its emphasis on genetic conditions, which generally have a single causal factor. Yet, rare diseases have intrinsic challenges and require a different business model. One approach Dr. Anderson envisions for the OHC involves combining a productive network of partnerships across academia, patient advocacy groups, and industry to broaden the scope of rare disease research to open new pipelines for delivering safe, effective, easily accessible drugs.

In his previous role as Vice President of Research and Preclinical Development, and Head of the Neuroscience Therapeutic Focus Area at Regeneron® Pharmaceuticals, Inc., Dr. Anderson led a neuroscience team of 45 people, gaining firsthand knowledge of drug development challenges.

"We need to know each of the diseases we are trying to tackle just as well as the best academic laboratories in the world, what should be measured, what outcomes we want, and how to leverage novel therapeutic strategies," he says. "Virtually all major therapeutic successes, such as immuno-oncology which has improved cancer survival rates, originated in academic laboratories where the experts work out complex problems and advance new discoveries in human disease mechanisms and targets."

While working with Professor Matthew Wood, the OHC Director and Chief Scientific Officer, to guide the OHC mission of advancing 40 new medicines into clinical development by 2034, Dr. Anderson is enjoying a return to academia as an investigator with Harrington Discovery Institute at University Hospitals and Senior Attending Physician and Professor of Pathology, Division of Neuropathology at Case Western Reserve University. As a part of the trans-Atlantic collaboration, Dr. Anderson also was recently appointed Visting Professor of Neurodevelopmental Disorders, Department of Paediatrics, Oxford University.

A long career of discovery and innovation underpin Dr. Anderson's current activities. As a PhD candidate in Physiology and Biophysics at University of Iowa College of Medicine (where he received MD and PhD degrees), his pioneering investigations under the mentorship of Michael J. Welsh, MD, illuminated the function of the CFTR chloride channel that's mutated in cystic fibrosis (CF). He earned the International Distinguished Dissertation Award for the groundbreaking study, which contributed to development of life-saving small molecule therapeutics for CF patients.

"We found out CFTR encodes a chloride channel not trafficking properly, or in some cases, at the membrane but not working properly," he says. "The discovery enabled a change in approach that took cystic fibrosis from a childhood fatal illness to a manageable disease where a patient can more or less live a full life. Having been a part of the very early stage of that process has been inspirational."

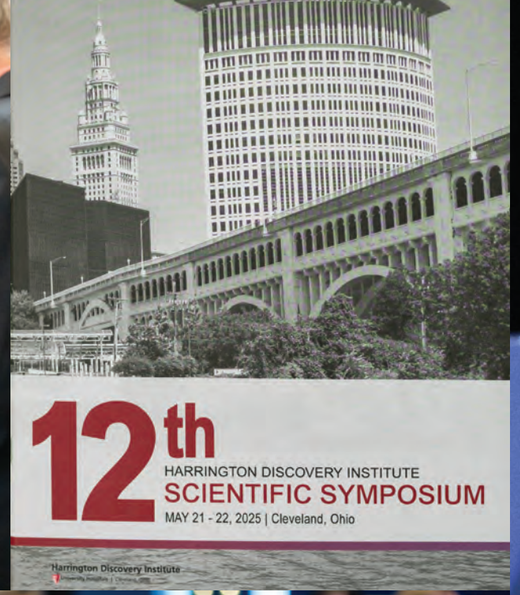
At Massachusetts Institute of Technology (MIT), he completed his postdoctoral work, delving into genetic engineering, brain circuit electrophysiology, and behavioral circuits studies in mouse models. As Chief of the Neuropathology Division at Beth Israel Deaconess Medical Center at Harvard Medical School, he ran a robust research program that yielded breakthroughs in neurological, neuropsychiatric, and neurodevelopmental diseases including epilepsy and autism. His lab has made seminal discoveries in genetic forms of autism identifying the circuits that are disrupted to impair social behavior and to increase irritability/aggression. In sporadic autism, his lab identified CD8 T-cell infiltrates causing cytotoxic injury to the astrocytes. Most recently, by studying an ultra-duplicated gene in autism, his lab identified a novel gene regulatory pathway involving retrotransposons that could underlie neurodevelopmental pathways unique to humans.

Leveraging genetic engineering and technology while orchestrating a network of relationships—patients, scientists, and industry—represents a paradigm shift in bringing cures and medicines to patients in urgent need, Dr. Anderson believes. Predictive analytics such as Google's AlphaFold, cryo-EM imaging, and large language models will be inevitable accelerators of rational drug design.

"Visualizing how a simple string of nucleotides and coding proteins transcripts are spliced and regulated enables us to take that raw data—the mutation—and apply a possible design that might be therapeutically useful," Dr. Anderson explains. "You can hit almost any gene now, even genes that lack a binding pocket for a small molecule."

"Today, we can build a virtual disease model and then target something that would be beneficial for treating the rare form, as well as the common forms."

2025 SCIENTIFIC SYMPOSIUM



2025 SCIENTIFIC SYMPOSIUM

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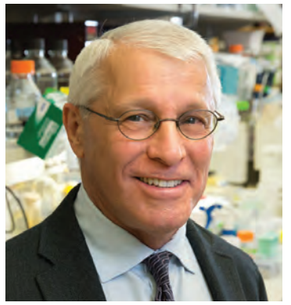

OWEN N. WITTE, MD
University of California,
Los Angeles

On May 21–22, 2025, Harrington Discovery Institute at University Hospitals welcomed scientific leaders, Harrington Scholars, advisory board members, donors, and global partners to Cleveland, Ohio, for its **12th Annual Scientific Symposium**. Over the two-day Symposium, attendees were immersed in the progress being made by Harrington Scholars in cardio-renal-metabolic diseases, cancer, rare diseases, and neurologic diseases, to advance breakthrough discoveries into new medicines.

A GLOBAL COMMITMENT TO CURES

Dr. Jonathan Stamler, President and Co-Founder of Harrington Discovery Institute, spoke of creativity and creation in his opening remarks, calling them hallmarks of the institute. He reflected on Harrington's many advancements since its inception in 2012. "We've created new models, programs, centers, symposia, honors, awards, investment funds, and most importantly, drugs and therapies — from virtually nothing. Collectively, our propensity as scientists, philanthropists, entrepreneurs, and investors to create, with creativity, has been remarkable," said Dr. Stamler.

The Harrington family's leadership in philanthropy has helped fuel this creativity and creation and inspired other philanthropists to step forward, recognizing the profound impact they too can make on accelerating cures for patients around the world.

RARE DISEASE INNOVATION

Among the initiatives highlighted was the Oxford-Harrington Rare Disease Centre (OHC), a transatlantic partnership between Harrington Discovery Institute at University Hospitals and the University of Oxford, to create new medicines for rare diseases. The OHC offers a new model for rare disease innovation that builds on Oxford University's outstanding scientific capabilities with Harrington's track record in drug development.

A Symposium highlight was the participation of **Lord (David) Cameron**, former UK Prime Minister, Chair of the OHC Advisory Council, and father of a child with a rare disease. In his welcoming remarks, he captured the urgency and potential of this mission. "The work of Harrington Discovery Institute is second to none. It's rare to find an organization that not only funds, but also surrounds, researchers with a full infrastructure to move discoveries forward. To be truly transformational, genomics requires the best of academia, life sciences, pharmaceutical companies, philanthropy and venture capital from around the world to come together," said Lord Cameron.

Lord Cameron joined **John F. Crowley**, President & CEO of BIO and fellow OHC Advisory Council member, in a fireside chat moderated by **Daniel I. Simon, MD**, President of Academic and External Affairs and Chief Scientific Officer at University Hospitals. The two leaders emphasized the power of global partnerships in advancing rare disease treatments across borders and sectors.

OTHER HIGHLIGHTS

- Keynote by **Robert M. Califf, MD, MACC**, Former Commissioner, Food and Drug Administration (FDA), on the changing ecosystem of medical product development and regulation.
- Remarks by **Cliff Megerian, MD**, CEO of University Hospitals, who affirmed Harrington Discovery Institute's integral role in University Hospitals' mission—To Heal. To Teach. To Discover.
- A message from **Ronald G. Harrington**, philanthropist and entrepreneur, reflecting on the importance of culture and the power of philanthropy to advance new treatments for patients.
- Reflections by **Owen N. Witte, MD**, University of California, Los Angeles, 2025 recipient of the Harrington Prize for Innovation in Medicine, who spoke of his scientific discoveries that have transformed modern cancer treatment.
- A presentation on the Harrington Scholar Experience from **Deepak Nijhawan, MD, PhD**, UT Southwestern, who spoke of collaborating with his Harrington team to accelerate the hit-to-lead stage and ultimately nominate a lead compound in the pursuit of novel cancer therapies.

EXTRAORDINARY POSSIBILITIES

The Symposium made one message unmistakably clear: when brilliant science is matched with committed partners and catalytic philanthropy, the possibilities for patients are extraordinary. United in purpose and propelled by a global community of innovators, Harrington Discovery Institute continues to expand what is possible in the quest for cures.

thank you TO OUR 2025 PANEL MEMBERS!

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William Murray, PhD
Lawrence Olanoff, MD, PhD

SAVE THE DATES:

MAY 20-21, 2026
MAY 26-27, 2027

"What struck me most about the Harrington Symposium was how quickly a casual scientific conversation could turn into a genuine collaboration. The Symposium brings together investigators who are not only highly accomplished in their field, but are open, generous, and eager to help move therapies forward."

JULIE SABA, MD, PhD
University of California, San Francisco
2024 Harrington Scholar-Innovator

HARRINGTON SCHOLAR PROGRAMS

Our Scholar Award programs support physicians and scientists in their development of new medicines to address unmet medical need. Our current programs are listed below by Innovation Center.

MAJOR DISEASES

HARRINGTON SCHOLAR-INNOVATOR AWARD

Supports physician-scientists whose research has the potential to change the standard of care in medicine. Each year, Harrington Discovery Institute's Scientific Advisory Board reviews applications from outstanding physician-scientists and selects those whose discoveries embody innovation, creativity and potential for clinical impact. ELIGIBILITY: MD OR MD/PhD; US AND CANADA.

HARRINGTON-MSTP SCHOLAR AWARD AT CASE WESTERN RESERVE UNIVERSITY

In partnership with Case Western Reserve University (CWRU)

Supports Medical Scientist Training Program (MSTP) students whose research shows innovation and creativity, and the potential for progressing from scientific discovery to a medical therapy. ELIGIBILITY: MSTP STUDENTS AT CWRU.

BRAIN HEALTH MEDICINES

ADDF-HARRINGTON SCHOLAR AWARD

In partnership with the Alzheimer's Drug Discovery Foundation (ADDF)

Supports research efforts that seek to prevent, treat, or cure Alzheimer's disease, related dementias and cognitive decline associated with aging. ELIGIBILITY: MD OR PhD; US, CANADA AND UK.

BRAIN HEALTH MEDICINES SCHOLAR AWARD

Supports researchers whose work aims to treat, prevent or cure Alzheimer's disease and related dementias. ELIGIBILITY: MD OR PhD; US, CANADA AND UK.

RARE DISEASES

OXFORD-HARRINGTON RARE DISEASE SCHOLAR AWARD

In partnership with the University of Oxford through the Oxford-Harrington Rare Disease Centre (OHC)

Supports researchers who are advancing promising rare disease discoveries from academic labs into clinical practice. ELIGIBILITY: MD OR PhD; US, CANADA AND UK.

FOR MORE INFORMATION:
HarringtonDiscovery.org/Funding

CONGRATULATIONS NEW SCHOLARS

These scholars have been recently awarded and will be profiled in our next annual publication.

MAJOR DISEASES

2025 HARRINGTON SCHOLAR-INNOVATORS

RAVIT BOGER, MD
Medical College of Wisconsin

ROBERT BONOMO, MD
Case Western Reserve University

JACOB BRENNER, MD, PhD
University of Pennsylvania

GEORGE DALEY, MD, PhD
Boston Children's Hospital

HAMED JAFAR-NEJAD, MD
Baylor College of Medicine

DANNY KHALIL, MD, PhD
Memorial Sloan Kettering Cancer Center

DEEPAK NIJHAWAN, MD, PhD
UT Southwestern

ALEXANDER ROTENBERG, MD, PhD
Boston Children's Hospital

NATHAN STITZIEL, MD, PhD
Washington University in St. Louis

LEONARD ZON, MD
Boston Children's Hospital

BRAIN HEALTH MEDICINES

2025 ADDF-HARRINGTON SCHOLARS

STEVEN ACKERMAN, PhD
University of Illinois

MARC DIAMOND, MD
UT Southwestern

RARE DISEASES

2025 OXFORD-HARRINGTON RARE DISEASE SCHOLARS

RACHEL BAILEY, PhD
University of Texas
Southwestern Medical Center

ESTHER BECKER, PhD
University of Oxford

JOSEPH BUXBAUM, PhD
Icahn School of Medicine
at Mount Sinai

MATTHEW GENTRY, PhD
University of Florida

ALBERT LA SPADA, MD, PhD
University of California, Irvine

MICHAEL LIN, MD, PhD
Stanford University

PENGFEI LIU, PhD
Baylor College of Medicine

DAVID SEGAL, PhD
University of California, Davis

ANTHONY SHUM, MD
University of California,
San Francisco

MINGSHAN XUE, PhD
Baylor College of Medicine

ENZYME THERAPY

TARGETS LUPUS

FOCUS: Enzyme therapeutics for the treatment of autoimmune and autoinflammatory disorders

Physician-scientists such as Dr. Braddock have a laudable goal: translating basic science into patient care. “Physician-scientists have a visceral understanding of medicine and disease, and knowing that patients are suffering drives us,” he says. “Seeing our research move into patient care is our ultimate goal, and there is nothing more satisfying to us professionally.”

That passion is guiding the way for Dr. Braddock and his team as they pursue enzyme therapy to treat systemic lupus erythematosus (SLE), a chronic autoimmune disease in which the body's immune system mistakenly attacks its own healthy tissues and organs.

Enzymes are proteins that facilitate virtually all chemical reactions within cells. They are essential for numerous biological processes, including digestion, muscle and nerve function, and energy production.

Enzymes enable crucial biological processes by changing one molecule into another without being consumed in the process. When the activity of certain enzymes is reduced or impaired by genetic mutations or other factors, it can begin a chain of events that triggers the production of harmful autoantibodies that characterize lupus.

To combat this, Dr. Braddock and his colleagues have developed a stable, potent and bioavailable enzyme-based biologic that has suppressed pathogenic autoantibody formation, tissue damage and death in multiple small animal models of autoimmune and autoinflammatory disease. This biologic is a novel molecular entity with IND-enabling preclinical data, paving the way for its use as a therapeutic.

“In our lab the drug has been very effective in numerous small animal models,” Dr. Braddock says. “The next logical step is proving that in the clinic, then getting it to the patients who will benefit from it.”

DEMETRIOS BRADDOCK, MD, PhD
Professor of Pathology
Yale University

“Harrington’s professional advisors are eminently skilled and qualified. I’ve learned so much from them and they were extremely helpful in many key decisions throughout this project.”

JULIANE BUBECK WARDENBURG, MD, PhD
Donald B. Strominger Professor of Pediatrics
Washington University in St. Louis

TRANSFORMING

STAPH VACCINE RESEARCH

FOCUS: Novel Staphylococcus aureus vaccine to provide infant protection

Dr. Bubeck Wardenburg’s research into developing a vaccine for Staphylococcus aureus has a very clear purpose: “I don’t want to see another child die of this disease,” she says.

S. aureus is the leading cause of bacterial pathogen-associated mortality worldwide, disproportionately affecting those younger than one year of age. Yet despite more than 30 years of vaccine development efforts, no S. aureus vaccine is available. Dr. Bubeck Wardenburg and her team are working to change that.

S. aureus makes a protein called alpha-toxin that changes the way the human immune system “sees” S. aureus, Dr. Bubeck Wardenburg explains. In effect, alpha-toxin allows the immune system to drop its guard and tolerate S. aureus.

“The goal of our research is to raise that guard through vaccination. Since all humans are exposed to S. aureus within the first few months of life, that is the window of opportunity,” Dr. Bubeck Wardenburg says.

Dr. Bubeck Wardenburg and her colleagues have engineered mutations into the alpha-toxin that makes the vaccine more effective at eliciting the desired immune response. In small animal testing, one such modified alpha-toxin variant has produced a high level of protective immunity in the host.

Dr. Bubeck Wardenburg credits her Harrington advisors for providing insight not only on the science, but also on what it will take for the science to advance toward a human intervention.

“Harrington Discovery Institute connects us with individuals who can influence the trajectory of this work moving forward, be that scientifically, financially, or from a business development perspective,” she says.

“While the path toward clinical trials of a population-level vaccine for infants and children is not anticipated to be straightforward, our commitment to this goal is unwavering.”

BREAKING OUT OF THE

‘STATIN QUO’

FOCUS: Targeting non-coding RNAs to treat atherosclerosis

Many people are familiar with statins, a class of drugs widely used to prevent accumulations of harmful cholesterol plaques in the coronary arteries. Yet despite decades of use and millions of prescriptions for statins, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide.

“Statin medications are inexpensive and effective, but there are still many people developing atherosclerosis, having heart attacks and dying from coronary heart disease,” Dr. Holley says. “So we’d love to have another tool to treat atherosclerosis that’s independent of treating cholesterol.”

This goal has led Dr. Holley and his colleagues to discover that certain small nucleolar RNAs (snoRNAs,) a class of RNA molecules that guide chemical modifications of other RNAs, are critical for atherogenesis. Further, in multiple mouse models, they found that selectively shutting down specific snoRNAs strongly mitigated atherosclerotic development regardless of serum cholesterol levels.

During their research, Dr. Holley and his team discovered that snoRNAs are not easily targeted by small molecule pharmaceuticals. They overcame this challenge by using antisense oligonucleotides (ASOs), an emerging class of drugs based on nucleic acid, to target snoRNAs for degradation.

Dr. Holley notes that because snoRNA-targeting ASOs are distinct from all other existing and emerging atherosclerosis therapies, there is no reason for them to compete with established therapies such as statins.

“Instead, our proposed therapeutic could serve as a co-first-line option for essentially all patients with ASCVD, including the more than 200 million patients worldwide currently taking statins,” he says.

CHRISTOPHER HOLLEY, MD, PhD
Associate Professor of Medicine
Duke University

“There aren’t many nucleic acid therapeutics that have been approved by the FDA. Getting expertise and insights from people like our Harrington advisors, who have done nucleic acid drug development, has been incredible.”

ANDREW HSIEH, MD
Professor, Clinical Research Division
Fred Hutchinson Cancer Research Center

NEW APPROACH TO

TARGET PROSTATE CANCER

FOCUS: Targeting mRNA-specific translation in cancer

Dr. Hsieh has two reasons for choosing to pursue prostate cancer research. The first is that every year in the United States castration-resistant prostate cancer (CRPC) affects roughly 230,000 men and results in about 30,000 deaths. The second reason is more personal: in 2009, metastatic prostate cancer claimed the life of Dr. Hsieh’s father-in-law.

For the past decade, Dr. Hsieh’s lab has been studying the interaction between mRNA translation initiation—the process through which the genetic information encoded in messenger RNA is used to build proteins in cells—and androgen receptor (AR) signaling, a crucial pathway involved in prostate cancer development and progression.

Dr. Hsieh and his colleagues found that decreased AR activity is commonly seen in CRPC patients. This decrease leads to a corresponding increase in translation initiation, specifically through a potentially cancer-causing interaction between two cellular proteins: eIF4E and eIF4G. The team is exploring eIF4E inhibitors as a potential therapeutic strategy for prostate and other cancers.

After using AI to help screen 2.7 million compounds, Dr. Hsieh’s team identified a promising drug candidate. With the support of Harrington Discovery Institute, Dr. Hsieh and his team are poised to conduct optimization of this lead compound, and in vitro and in vivo testing for efficacy in prostate and other forms of cancer, including breast, lung, and bladder.

“We think that this is an untapped opportunity,” Dr. Hsieh says. “Given the clinical need and the discovery of a lead compound, our program is poised to make a discovery with therapeutic impact.”

“Current therapies for metastatic disease can extend life, but our vision of resounding success is a cure.”

OUTSMARTING

CANCER CELLS IN THE BRAIN

DEEPAK NIJHAWAN, MD, PhD,
Associate Professor, Medical Oncology
and Biochemistry
University of Texas Southwestern Medical Center

FOCUS: Development of LSS inhibitors for the treatment of glioblastoma

There are many facets to drug discovery in cancer, the most important being efficacy (how well a drug stops tumor growth) and toxicity (a drug's ability to kill cancer cells without causing prohibitive side effects in the patient). When targeting glioblastomas, however, there is an additional challenge: the drug must be able to cross the blood-brain barrier and get into the brain in sufficient quantities to be effective.

Glioblastomas are lethal, non-metastatic tumors that exist exclusively in the brain. As Dr. Nijhawan explains, glioblastoma cells need cholesterol to survive. They must produce their own cholesterol or scavenge it from other cells. Knowing this, Dr. Nijhawan and his colleagues began investigating the mechanism of MM0299, a member of a class of organic compounds that can disrupt cholesterol synthesis.

In essence, MM0299 fights glioblastomas by tricking cancer cells into making a "decoy" cholesterol. It does this by inhibiting lanosterol synthase (LSS), a key enzyme in the cholesterol biosynthesis pathway. When LSS is inhibited, glioblastoma cells behave as if they have plenty of cholesterol, when in reality the cholesterol they need to survive has been diverted into a shunt pathway.

The researchers are now seeking ways to get MM0299 into the brain.

Dr. Nijhawan says he and his colleagues are advancing their research by "letting the science guide them."

"We saw that there was a molecule that was very potently toxic to glioblastoma cells," he says. "So, we just followed that molecule to see what it was doing and how it was doing it, and it has led us to this very promising approach."

"We really don't overlap with traditional pharmaceutical targets and discovery. Our goal is to have an independent approach and Harrington's support has helped us in that effort."

RUSSELL PACHYNSKI, MD
Associate Professor of Medical Oncology
Director of Genitourinary Oncology Research
Washington University in St. Louis

"Our Harrington advisors really understand the nuts and bolts of how to get a drug into the clinic."

RECRUITING IMMUNE CELLS

TO FIGHT CANCER

FOCUS: Novel tumor-targeted chemerin immunotherapeutic

Recent advances in immunotherapies have produced impressive responses in treating cancers such as bladder and lung cancer and melanomas. These drugs, however, have been less successful treating prostate cancer: only about 10% or less of patients with advanced prostate cancer respond to current immunotherapies. In addition, these therapies cause systemic activation of the immune system, potentially producing challenging immune-mediated toxicities.

Dr. Pachynski and his colleagues are determined to change that. They have developed an immunotherapeutic based on a tumor-fighting protein called chemerin. Chemerin is a naturally produced protein that—in part—acts to direct immune cell movement and migration. Dr. Pachynski has discovered that chemerin is "turned down" in multiple tumor types, thereby evading the immune system. By "turning up" the concentration of chemerin within the tumor, Dr. Pachynski was able to "recruit" immune cells into the tumor and significantly suppress tumor growth.

According to Dr. Pachynski, a chemerin-based therapeutic that is prostate-specific and antigen-targeted would represent a first-in-class novel immunotherapy for prostate cancer and potentially other cancers as well.

Small animal studies of chemerin have demonstrated its effectiveness as a tumor fighter in prostate and multiple other cancers. Dr. Pachynski says human prostate tumor models using the novel immunotherapy have already shown efficacy, providing the rationale for translation of his team's research into the clinic.

"There's a huge need for effective immunotherapies in prostate cancer," Dr. Pachynski says. "This deficit is sad and disheartening for patients and providers who know the great potential of immunotherapy, so we are working hard to change that with this therapeutic platform."

KNOW YOUR ENEMY: UNDERSTANDING THE

ORIGINS OF MENINGIOMAS

FOCUS: A novel humanized antibody inhibiting NOTCH3 stem cells in meningioma

Despite being the most common primary intracranial tumors and a significant source of neurological morbidity and mortality, meningiomas—tumors that arise from the lining of the brain and spinal cord—remain poorly understood. There are no standard-of-care medical therapies for these tumors (standard treatments are restricted to surgery or radiotherapy) and recent trials of molecular or biologic treatments have failed to improve outcomes for meningioma patients.

"On a very fundamental level, we don't understand the cellular origin of meningiomas," Dr. Raleigh says. "So our project started off trying to understand the cellular architecture of meningioma evolution, and in doing so we were able to find a new therapeutic target and build a drug to hit that target."

The target Dr. Raleigh cites is NOTCH3, a receptor protein that plays a significant role in the maintenance and function of stem cells by regulating their self-renewal and differentiation.

Unfortunately, NOTCH3 also drives meningioma initiating capacity, meningioma cell proliferation, meningioma angiogenesis, and meningioma resistance to radiotherapy—all of which increase meningioma growth and reduce patient survival.

Dr. Raleigh and his team identified a selective mouse antibody, aNRR3, that blocks NOTCH3-induced meningioma formation and sensitizes meningiomas to radiotherapy, reducing tumor growth and improving survival in preclinical models. They humanized and optimized 16 novel aNRR3 antibodies and then reduced that number to two for a window of opportunity clinical trial in patients with recurrent meningiomas.

Dr. Raleigh notes that in addition to intracranial tumors, NOTCH3 has been implicated in lung, colon, and breast cancer stem cells, and in arthritis pathology.

"Successful completion of this proposal sets the stage for clinical translation to myriad oncologic and inflammatory conditions," he says.

DAVID RALEIGH, MD, PhD
Assistant Professor
Robert and Ruth Halperin Endowed Chair in Meningioma Research
Brain Tumor Center Principal Investigator and Preclinical Therapeutics Core Director
Departments of Radiation Oncology and Neurological Surgery
University of California, San Francisco

"A large part of our progress has been enabled by Harrington Discovery Institute. This organization is a truly unique and wonderful effort to address what's often referred to as the translational 'Valley of Death' for new cancer therapies."

JULIE SABA, MD, PhD
Professor of Pediatrics
John and Edna Beck Chair in Pediatric Cancer Research
University of California, San Francisco

FACING OFF AGAINST

A TOUGH FOE

FOCUS: A life-saving treatment for sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS)

Dr. Saba trained as a cancer doctor and researcher, but when she first encountered sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS), she knew it was the disease she was meant to face.

"The need seemed so obvious. I immediately incorporated it into my research goals," she says. "I realized there could be no better purpose for me."

Dr. Saba picked a tough foe. SPLIS is a rare and deadly kidney disorder. The disease mostly affects children, and infantile SPLIS carries a 70% mortality rate by age five. There is no cure; kidney transplantation represents the only lifesaving intervention.

SPLIS is caused by a mutation in a single gene. Dr. Saba explains that once the gene has mutated, it becomes inactive and no longer can encode sphingosine-1-phosphate lyase (SGPL1), an enzyme that is essential to sphingolipid metabolism. Sphingolipids are a class of lipids that perform crucial roles in cells, including regulating processes such as cell growth and death.

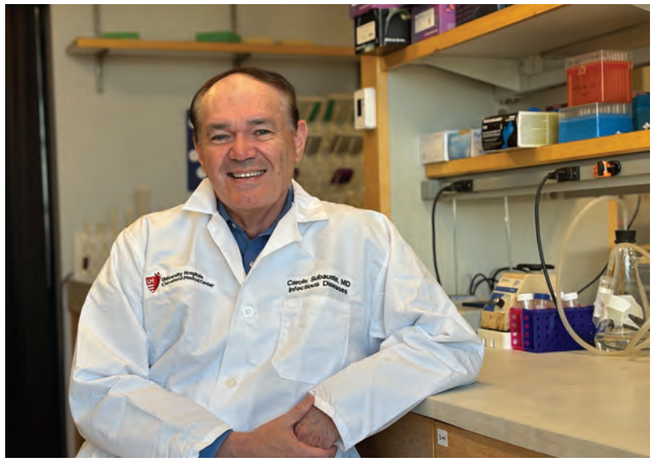
Dr. Saba discovered the first SPLIS gene and has been studying its function in various model organisms. Now, she and her team have developed a potentially curative intervention: adeno-associated virus-mediated SGPL1 gene therapy (AAV-SPL).

"AAV-SPL addresses the root cause of SPLIS," she says. "We have established proof-of-concept in a mouse model and are now exploring ways to optimize the efficacy and potency of AAV-SPL."

With the support of Harrington Discovery Institute, Dr. Saba hopes to create an armamentarium of treatments that can be personalized for each patient.

"All of our efforts are worthwhile simply because every child is unique and beautiful," she says.

"Rare diseases often unlock the puzzles to much more common diseases by teaching us the genes and the pathways that are involved in their physiology."



CARLOS SUBAUSTE, MD
Professor of Medicine,
Ophthalmology and Pathology
Case Western Reserve University

TAKING A NEW PATH AND

BREAKING NEW GROUND

FOCUS: Small molecule inhibitors of CD40 for the treatment of inflammatory disorders

A major advance in the treatment of inflammatory/autoimmune disorders may come from an unlikely source. Dr. Subauste is an infectious disease specialist who was studying intracellular parasites when his lab made discoveries that may lead to new treatments for patients with autoimmune disorders.

"My work has always been in infectious diseases and immune response, and now my lab is developing a drug for treating inflammatory bowel disease (IBD)," Dr. Subauste says. "That's why science is so exciting. You never know what paths you're going to follow and where they will lead you."

Dr. Subauste explains that a protein called CD40 plays a crucial role in the immune system. Expressed by many cell types, CD40 is required for protection against many pathogens. When CD40 is overactive, however, it drives inflammatory and autoimmune disorders such as IBD.

Dr. Subauste and his colleagues identified a small molecule (CCI2260) that blocks a specific pathway downstream of CD40, reducing pro-inflammatory responses without affecting mechanisms of protection against pathogens. It diminishes intestinal inflammation in mouse models of IBD and does not make mice susceptible to an opportunistic pathogen.

With the support of Harrington Discovery Institute, Dr. Subauste proposes to expand his team's efforts to develop an optimized inhibitor and a biomarker that will be used in subsequent in vivo studies.

"I'm not an IBD expert and have never attempted direct drug development," he says, "but the purpose of my work is helping patients, and I absolutely would consider my career to have been fulfilling if I were able to create a new drug for the treatment of autoimmune disorders."

"I am very impressed by the high caliber of the scientists that are members of the Harrington team. I find their input to be extremely helpful and I believe it is accelerating the progress of the grant."

TARGETING

THE TOUGHEST CANCER

FOCUS: Novel pharmacologic approaches to target wild-type IDH1 in pancreatic cancer

Pancreatic cancer is a notoriously challenging malignancy with an often-grim prognosis.

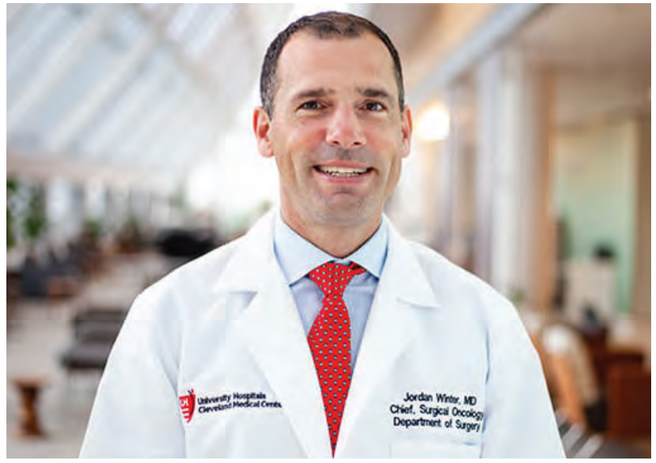
A mutant form of the enzyme isocitrate dehydrogenase 1 (IDH1) is a well-established drug target for pancreatic cancer. According to Dr. Winter, however, the "wild-type" enzyme produced by the IDH1 gene—not the mutant type—predominates in 99% of cancers. A wild-type enzyme is the standard form of an enzyme found in nature, possessing its original structure and typical function.

Dr. Winter says the wild-type of IDH1 is especially important for cancer cell survival in the nutrient-limited tumor microenvironment, which is a hallmark of pancreatic cancer. He and his colleagues, therefore, set out to target the wild-type enzyme and have developed a series and a lead compound of wild-type IDH1 inhibitors.

"My clinical and research interests have always been around pancreatic cancer," Dr. Winter says. "It's the hardest cancer to treat, it's the most lethal cancer, and it's a cancer where there are no effective novel therapies. So there's a void in the clinical space for novel drugs, and there's an opportunity to make a big impact."

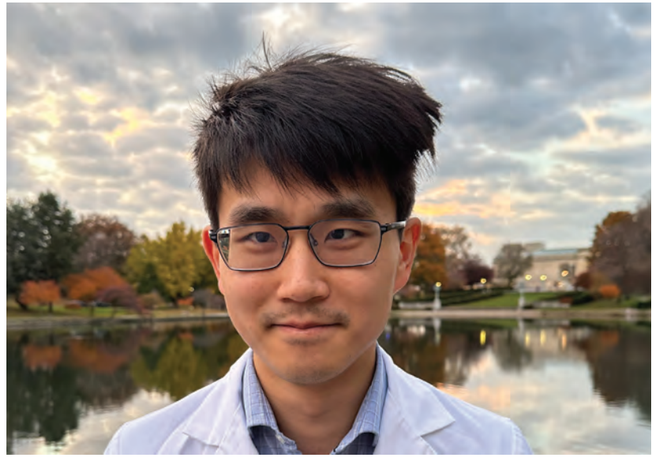
The next steps in Dr. Winters' research include taking the promising data from murine studies of the lead compound and continuing to carry out pre-IND protocols to prepare for the clinic.

"The ultimate goal is to cure pancreatic cancer, but I think it would be a major victory for Harrington Discovery Institute, for my lab, and for this project if our lead compound could progress through clinical trials and demonstrate efficacy in improving survival in patients," Dr. Winter says.



JORDAN WINTER, MD
Chief of Surgical Oncology
University Hospitals Cleveland Medical Center
Professor
Case Western Reserve University

"We want to help people with this very aggressive disease and provide them with better treatment options. That's what drives us from day to day."



"Ultimately, the goal is to selectively turn off a portion of a patient's immune system when it's acting up and make people well again."

DAVID YAN
Medical Scientist Training Program Doctoral Candidate
Case Western Reserve University

A NOVEL T CELL INHIBITOR FOR AUTOIMMUNE DISEASE

FOCUS: Blocking XPO1-chromatin binding interactions disrupts T cell activation in autoimmune diseases

Autoimmune disorders affect 15 million Americans, challenging them with chronic pain, fatigue, flare-ups, and other physical symptoms, along with frustration and stress. Current treatment with immunosuppressive drugs can trigger side effects that make many patients feel worse, not better. Harrington Scholar and Case Western Reserve University (CWRU) Medical Scientist Training Program (MSTP) student, David Yan, hopes to restore normal living to these individuals by selectively blocking the transport protein, Exportin-1 (XPO1).

While Mr. Yan was an undergraduate among the researchers in CWRU's Adams Laboratory, they discovered something unusual about XPO1. It was interacting with chromatin, the fibrous material that gives form to six feet of DNA strands and proteins neatly coiled inside the cell nucleus.

"This was not what XPO1 had been known to do for the past two or three decades of research," Mr. Yan says. "Its roles in moving molecules, including proteins and RNA, from the cell nucleus into the cytoplasm were well understood but its involvement with T cell activation was not."

As the lab began designing small molecules to target XPO1, Mr. Yan applied his problem-solving background in synthetic chemistry and biology.

"We designed small molecules that selectively inhibited XPO1's chromatin interaction without affecting its nuclear transport function thus preserving normal cellular functions," he explains. "Our small molecules are potent anti-inflammatories—good at turning off T cells without causing cell death—which could be helpful in T cell-driven diseases such as graft versus host disease (GVHD), pulmonary fibrosis, and rheumatoid arthritis, or even Type 1 diabetes."

Leveraging insights from his Harrington advisors, Mr. Yan aims to refine a promising lead compound (B-001) for further testing while unraveling XPO1's mysteries.

AGING WITH GRACE—A POTENTIAL THERAPY TO STALL ALZHEIMER'S DISEASE

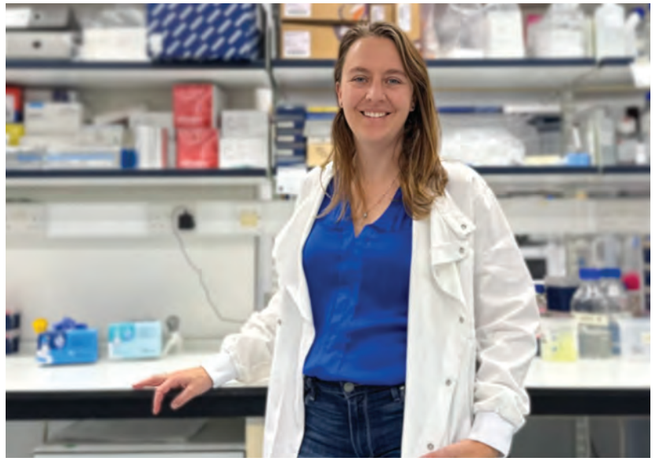
FOCUS: Validating a method to uncover and progress small molecule correctors of ApoE4

The prevalence of Alzheimer's disease (AD) in people over 65 years results from a complex web of biological processes. Focused on a "risk gene" that's been implicated in late-onset AD, Dr. Jackson hopes to develop a therapy to delay cognitive decline and give people more good years.

As people age, Apolipoprotein E (ApoE), a lipid-transporting protein, plays increasingly significant roles in brain health. Dr. Jackson has been studying a specific gene variation—ApoE4. It's considered the "risk gene" and has been shown to be the strongest genetic factor for developing AD. A large study of post-mortem brains has shown that an estimated 60% of late-onset AD patients are ApoE4 carriers.

"Another variation, ApoE3, differs from ApoE4 by a single amino acid, yet the structural difference causes changes in many biological pathways," Dr. Jackson explains. "People who inherit two copies of ApoE4 are more likely to develop AD and be more susceptible to the consequences." With Harrington support, Dr. Jackson is screening small molecule compounds for a lead candidate that could act as an "ApoE corrector," making ApoE4 function more like ApoE3. Potentially, her approach could replace current AD medications that cause side effects in ApoE4 individuals. "The challenge is getting a small molecule compound past the blood brain barrier," Dr. Jackson says. "Once we do that, there's hope for slowing AD at middle-age and improving quality of life in later years."

ROSEMARY JACKSON, PhD
Principal Investigator
University of Dundee



"Adding ten good years to people's lives would make a big difference."

THE SHIP1 PROTEIN–PUTTING THE BRAKE

ON ALZHEIMER'S DISEASE

FOCUS: Lead optimization of SHIP1 inhibitors and biomarker development for the treatment of Alzheimer's disease

Today's approved drugs for Alzheimer's disease (AD) can be traced to research on amyloid plaque—an abnormal level of a naturally occurring protein that forms plaques in the brain that are believed to cause neuronal disruptions. Although these medications help slow cognitive decline, their effectiveness is limited. With a novel approach, Dr. Richardson is targeting SHIP1, a protein involved in regulating microglia, the brain's key immune cells.

SHIP1 is involved in neuroinflammation, which is associated with memory loss, confusion, and other AD symptoms. How the protein regulates microglia may be important in whether, and how fast, AD develops.

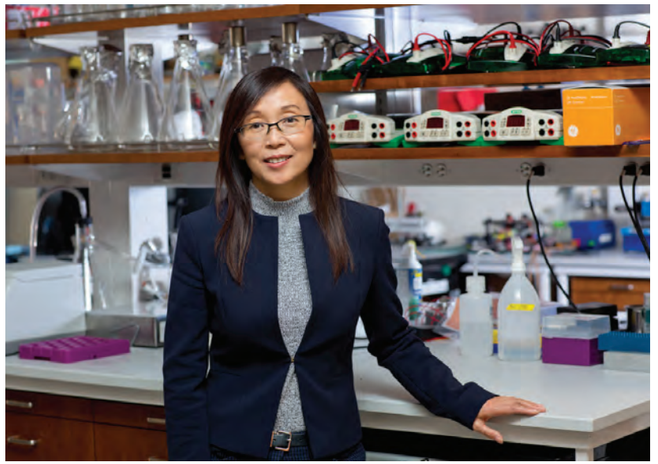
"Microglia are a double-edged sword," Dr. Richardson says. "They can defend against or contribute to neurodegenerative processes. The SHIP1 protein plays an important regulatory role in the microglia. We believe it restrains microglial protective functions enabling processes that lead to neuroinflammation."

"There are 'super agers' over 100 years old who have immune systems that are slightly more responsive than normal, yet the inflammation doesn't cause AD," he continues. "It's the individuals whose microglia aren't dealing well with amyloid plaque who are more susceptible to AD."

Dr. Richardson and his team have demonstrated success in inhibiting SHIP1, releasing microglial protective mechanisms to clear amyloid and other neurotoxins without causing harmful inflammation in mouse brains. With Harrington's support, they aim to validate SHIP1 as a therapeutic target with a small molecule compound. With potential to advance to clinical trials and beyond, Dr. Richardson sees a future where AD is much better understood, preventable—and easily treated.

TIMOTHY RICHARDSON, PhD
Senior Research Professor of Medicine
Indiana University

"Essentially, our approach is to encourage microglia to protect the brain. With early detection, a patient could take a medicine that maintains cognition for the rest of their life."



LI GAN, PhD
Professor and Director
Helen and Robert Appel Alzheimer's Disease Research Institute
Weill Cornell Medicine

"I'm a biologist, not a chemist. I study molecules, disease mechanisms and biological processes. But to turn those findings into drugs, we need chemistry expertise. That's the type of expertise that Harrington excels at providing."

TARGETING TAU TO

REDUCE COGNITIVE DECLINE

FOCUS: Evaluation of a novel human cGAS inhibitor to treat tauopathy

Much of Alzheimer's disease research has focused on anti-amyloid immunotherapy. Some newer therapies that target accumulations of amyloid-beta plaques in the brain have been shown to reduce cognitive decline by 30% in patients with very mild disease.

Although that's a positive step, Dr. Gan says simply, "That means our job is not done. We need therapies that can improve cognitive function. Not just slow it down, but stabilize and reduce cognitive decline. And we need these therapies for more patients."

To that end, Dr. Gan and her colleagues are exploring a treatment pathway that targets tau. Tau is a protein found in brain cells that drives cognitive decline by inducing inflammation.

Dr. Gan's team is developing small molecule inhibitors of the DNA-sensing cGAS enzyme, which plays a crucial role in maladaptive immune response and chronic neuroinflammation caused by tau tangles. According to Dr. Gan, cGAS inhibitors could complement existing beta-amyloid therapies, bringing benefits to a larger group of patients—potentially even those with moderate cognitive decline.

Dr. Gan and her team are seeking to evaluate two human cGAS inhibitors using human iPSC (induced pluripotent stem cells). They anticipate that the cGAS inhibitors will reduce tau-induced inflammation in human iPSC-derived organoids.

Dr. Gan notes that an intriguing aspect of tau research is that patients who have amyloid-beta plaques do not always experience memory loss. Patients who have memory loss, however, always have inflammation caused by tau.

"That's why I've been working on tau for the past 20 years," Dr. Gan says. "cGAS inhibitors will temper the chronically inflamed brain. That will help the brain heal and stop the memory loss. Finding that solution is what drives me."

FORGING A DIFFERENT PATH

IN ALZHEIMER'S DISEASE

FOCUS: CK2 inhibition as a promising target in Alzheimer's

Several processes are known to contribute to the development and severity of Alzheimer's disease. These processes, which include inflammation, abnormal metabolic activity and pathological cellular modifications, contribute to neuronal death, although they typically precede cognitive decline.

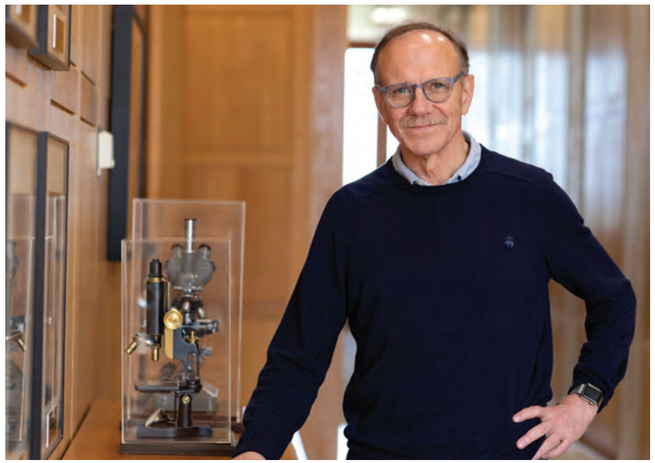
Dr. Gage and his team have found that the protein kinase CK2 activity is abnormally elevated in the brains of Alzheimer's disease patients and in patient-derived models, making CK2 inhibition a promising therapeutic target. Protein kinases are enzymes that play a crucial role in regulating various cellular processes.

Dr. Gage notes that much Alzheimer's research has focused on clearing beta-amyloid plaques in the brain, but he says that drugs targeting beta-amyloid have only been marginally effective in treating neurodegenerative disease in humans. He says his team's purpose is to find new and better options for patients.

"There is a real search for new and different compounds that work through different mechanisms that might be more promising," Dr. Gage says. "We're part of the new vanguard of therapies that are targeting biological problems associated with the disease rather than targeting the pathology."

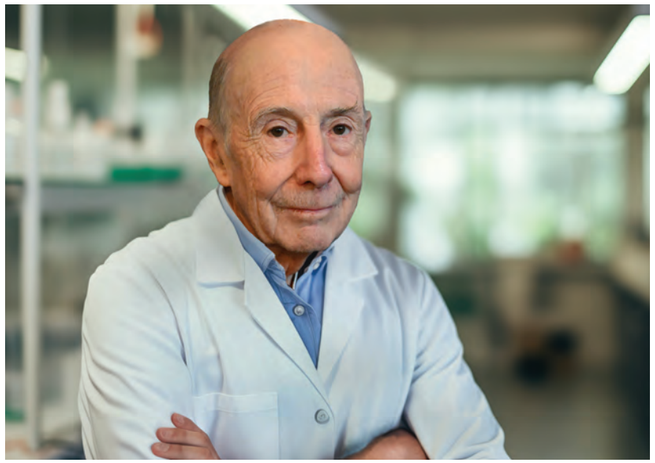
With the support of Harrington Discovery Institute, Dr. Gage plans to accelerate his research into CK2 inhibitors. He and his team, Dr. Ioana da Silva and Dr. James Tucker, have generated more than 350 novel compounds, and their lead compound, TAL606, has shown tolerability and proof-of-concept efficacy in reducing neuroinflammation, boosting neurogenesis and rescuing dendritic loss in mice.

"CK2 inhibition shows promise for combating Alzheimer's and other neurodegenerative diseases, and could be used with existing beta-amyloid therapies in a dual-targeted approach, and could be used either early or late in the course of therapy," Dr. Gage says.



FRED 'RUSTY' GAGE, PhD
Professor
Salk Institute for Biological Studies

"Harrington's support is strong and ongoing; they make many good recommendations, and they're only a phone call away."



BRUCE HAMMOCK, PhD
Distinguished Professor
University of California, Davis

"Soluble epoxide hydrolase inhibitors show great potential for neurodegenerative diseases."

BOOSTING NATURAL CHEMICAL MEDIATORS

TO TREAT ALZHEIMER'S DISEASE

FOCUS: Development of novel inhibitors of soluble epoxide hydrolase specifically to treat Alzheimer's disease

Dr. Hammock has gained a wealth of insight in his more than fifty years of scientific journeys exploring entomology, biochemistry, physiology, toxicology, pharmacology, and experimental therapeutics. In a career accentuated with numerous discoveries and innovations, the pioneering biological chemist is internationally recognized for his contributions to healthier plants, people, and pets. Now, with Harrington Discovery Institute support, he and a dream team of collaborators aim to slow, prevent, or reverse Alzheimer's disease (AD) by blocking a target enzyme he discovered—soluble epoxide hydrolase (sEH).

"The sEH regulates the activity of anti-inflammatory fatty acids, the body's natural chemical mediators that also are involved in blood pressure and pain," Dr. Hammock explains. "In animal models we found that inhibiting sEH increases levels of natural chemical mediators that reduce vascular inflammation and neuroinflammation, both hallmarks of Alzheimer's disease. We also observed that sEH inhibition increased clearing of toxic plaques."

Today, 150 million individuals worldwide have AD. Aging populations and increasing diagnoses heighten the need for improved treatment options, yet almost 99% of drugs taken to clinical trials fail. The anti-plaque drugs that reach the market are contraindicated in patients with vascular issues. Potentially, sEH inhibitors could be combined with monoclonal antibodies therapy for those patients.

"Recently, multiple genome-wide association studies (GWAS) have targeted the sEH locus as a prime therapeutic target for Alzheimer's," Dr. Hammock says. "We are optimizing a very promising lead compound, which we hope to accelerate to clinical trials, initially in patients with diabetes-driven dementia."

Eventually, Dr. Hammock hopes to translate his discovery into a life-changing drug that can be easily taken by patients.

SETTING SIGHTS ON GENE THERAPY TO

TREAT A DEADLY EYE CANCER

FOCUS: A novel adeno-associated virus (AAV) gene therapy approach for the treatment of rare uveal melanoma tumors

Oxford-Harrington Rare Disease Scholar, Dr. Jacquelyn Bower, is working to develop potential therapies for a rare, aggressively metastasizing eye cancer—uveal melanoma (UVM). Difficult side effects accompany standard immunotherapy and radiation treatments, and eye removal doesn't always stop the spread. Cruelly, UVM can strike again after a long remission. Dr. Bower hopes to develop a targeted gene therapy using a viral vector to help save sight and lives.

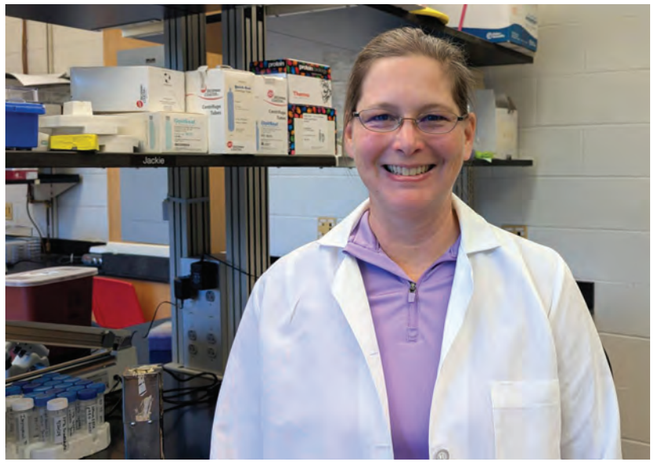
"In cell culture studies, we used an adeno-associated virus (AAV)-based vector to silence two mutated genes, GNAQ or GNA11—two closely related tumor drivers found in 90% of UVM patients," Dr. Bower explains.

In early AAV studies using tumor cell cultures, Dr. Bower and her team decreased the survival of UVM cells—a big win. AAV effectively delivers nucleic acids that can target specific sequences of mutated genes, providing an advantage over chemical inhibition. The "G" family of proteins has been considered largely undruggable because chemical inhibitors have difficulty discerning between the normal and mutant proteins and therefore can be highly toxic in normal cells.

"With Harrington support, we are optimizing a combination of AAV-expressing shRNAs (artificial RNA molecules) targeting the mutant G proteins that drive 80-90% of UVM initiation and progression," she says. "We'll then test lead candidate vectors in genetically engineered UVM mice, targeting GNAQ and GNA11, as well as exploring additional gene therapy strategies for the remaining 10% of UVM cases."

Survival rates for primary UVM tumors have improved with early diagnosis and treatment. But in about half of the patients the tumors return, and once metastasized, survival rates plummet to zero.

"Our number one hope is that AAV can treat both primary and metastatic tumors," Dr. Bower says.



JACQUELYN BOWER, PhD
Research Assistant Professor of Ophthalmology
University of North Carolina at Chapel Hill

"Combining an AAV therapy with other UVM-fighting treatments has the potential to enhance current treatment options."

LOUIS CHESLER, MD, PhD
Professor
Centre for Pediatric Oncology Experimental Medicine
The Institute of Cancer Research

"Our current work is on the right track to improving cancer survivability."

FLIPPING A SWITCH

WITH CAR T CELLS

FOCUS: Engineering Chimeric Antigen Receptors fused to a high-efficiency lenalidomide-degradable Tag to control CAR T cell activity - iTAG3

Pediatric oncologist, Dr. Chesler, wants to treat childhood cancer using methods to reduce side effects that accompany high-dose treatments. The Oxford-Harrington Rare Disease Center Scholar and his co-investigator John Anderson, PhD, are equipping chimeric antigen receptor (CAR) T cells with molecular on/off switches that are sensitive to and compatible with other cancer drugs. The collaborators are testing molecular toggles, called iTags, activated by ImIDs (immunomodulatory drugs currently used in cancer therapy) to stop tumor growth.

The CAR T target is the B7H3 (CD276) cell-surface receptor, expressed on both adult and childhood cancer cells, which plays a key role in cancer development as an immune checkpoint. Because B7H3 has little to no expression on normal tissues, the approach minimizes side effects and allows normal physical growth in the children. To counter relapse and T cell exhaustion that occur with immunotherapies given to children with solid and brain tumors, the inventors are building in CAR T rest and recovery phases. The technology also enables specific targeting of CAR T to each tumor type, broadening the range of cancers that could be treated to include solid and brain tumors.

"Immunotherapies such as CAR T are showing real promise in the clinic," Dr. Chesler says. "We are designing CAR T that could work optimally together with other effective drugs in order to maximize the effectiveness of immunotherapy."

Although the approach using ImIDs and iTags to counter CAR T exhaustion is in the theoretical stage, Dr. Chesler and Dr. Anderson are continuing to experiment while awaiting critical data that will determine next steps.

"The ability to precisely control CAR T lifespan and prevent their exhaustion is a key tool for the use of cellular immunotherapies to effectively treat solid and brain cancers. We hope that our technological advances make CAR T therapy safer, more durable and effective to help move these exciting treatments forward more rapidly," Dr. Anderson says.

STOPPING HODGKIN LYMPHOMA

WITH SUPERCHARGED T CELLS

FOCUS: Epigenetically enhanced cell therapy for Hodgkin lymphoma

A chemical engineering background is an indirect pathway to biomedical engineering, but for Dr. Gersbach, the combination further ignited his passion for problem solving. As an Oxford-Harrington Rare Disease Scholar, he hopes to translate next-generation CAR T cells to end Hodgkin lymphoma (HL), a lymphatic cancer faced by almost 9,000 new patients each year.

"My PhD focused on applying engineering principles to building, restoring or regenerating damaged or diseased tissues," Dr. Gersbach begins. "I loved asking questions like, if we want to treat disease, what do we have to change inside tissues? What is driving the cells to function abnormally? Which molecules are involved, and what parts of our DNA are encoding the relevant genes? Then, how do all those different genomic regions coordinate to result in disease?"

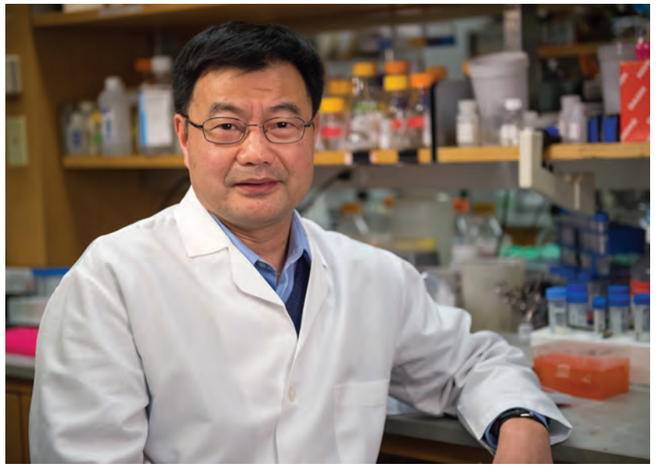
More recently, Dr. Gersbach began exploring epigenetics—the changes to genome structure that control genes turning on and off—and scrutinizing subtle mechanisms of gene expression that ultimately lead to disease. Using sophisticated high-throughput genetic screens, the Gersbach Lab made a novel discovery—overexpressing a single transcription factor called BATF3 (Basic Leucine Zipper ATF-Like Transcription Factor 3) reprograms T cells and enables them to keep killing cancer instead of succumbing to exhaustion or becoming unresponsive.

Dr. Gersbach is applying this knowledge in animal models to see how upregulating BATF3 expression improves the activity of T cells targeting of the CD30 protein, a marker highly selective for HL cells.

The approach could prevent relapse and T cell exhaustion in HL patients treated with CAR T cell therapies. Of the HL patients treated with first generation CD30-targeted CAR T therapies, ~80% see their cancer progress in under two years. Dr. Gersbach and his team hope to reduce that statistic dramatically by arming T cells to keep circulating and protecting.

CHARLES GERSBACH, PhD
Director, Duke Center for
Advanced Genomic Technologies
John W. Strohbehn Distinguished Professor
of Biomedical Engineering
Duke University

"We are manipulating the regulation of a genome in a way that can lead to more successful therapies and human clinical trials."



XIANXIN HUA, MD, PhD
Professor of Cancer Biology
University of Pennsylvania

"A scalable, off-the-shelf product has potential to transform CAR T cell therapy for AML."

REDEFINING CAR T THERAPY FOR

ACUTE MYELOID LEUKEMIA

FOCUS: Novel bispecific CAR T cells for treating acute myeloid leukemia via mRNA/lipid nanoparticle delivery

Imagine packing a two-micron-long molecule into a container thousands of times smaller than a tiny section of human hair. This describes nanotechnology, which Dr. Hua is employing to arm and deliver an innovative acute myeloid leukemia (AML) treatment—biCAR T. The approach packs chimeric antigen receptor (CAR) mRNA in lipid nanoparticles (LNPs) to target CD13/TIM3—two cell surface proteins on antibodies upregulated in the blood cancer.

Rare and aggressive, AML develops when defective white blood cells created in the bone marrow multiply, crowding out healthy red blood cells and white blood cells necessary for supplying oxygen and fending off invaders. Individuals may mistake chronic tiredness, dizziness, bone pain, and frequent infections for flu that doesn't go away. For some of the nearly 150,000 diagnosed annually, treatment arrives too late.

While chemotherapy achieves remission rates of 60-80% in younger patients, rates in older patients are lower (30-50%). In certain patients, AML is refractory—unresponsive. Relapsed and refractory patients have few effective therapy options—they need a readily available, effective, and less toxic alternative. Dr. Hua's nanotechnology approach would eliminate costly and time-consuming conventional in vitro CAR T manufacturing steps by packaging CD13/TIM3-targeting CAR mRNA (bi CAR) into lipid nanoparticles (LNP) and then injecting the mRNA/LNP cargo directly into a patient's body. When biCAR is expressed in the patient's T cells, it specifically seeks and destroys AML stem cells carrying CD13 and TIM-3 receptors while sparing normal cells and reducing toxicity.

"We demonstrated proof-of-concept in vitro," Dr. Hua says. "Next, we will test human cell-derived biCAR T in mice, and if that's successful, we will test in larger animals, then move to clinical trials in humans."

Dr. Hua envisions the biCAR T treatment readily available worldwide for most AML patients, regardless of age and disease stage.

HOPE FOR CHILDREN WITH

CTNNB1 SYNDROME

FOCUS: Identifying a lead compound for efficacious treatment of CTNNB1 syndrome

Babies born with the rare genetic disorder, CTNNB1 syndrome, seem fine at first. Then, parents notice they don't hit developmental milestones (babbling, crawling, sitting up, walking). Mobility and cognitive impairments often put them behind in school and many require life-long caretaking. Dr. Jacobs has met some of the parents and understands their heartache. Having proof-of-concept data demonstrating therapeutic effectiveness of a small molecule compound in CTNNB1 mouse and human cell models, she aims to identify a lead drug candidate for clinical trials.

"Currently, there are about 500 diagnosed CTNNB1 cases worldwide," Dr. Jacob says. "CTNNB1 syndrome, first identified as a genetic disorder in 2012, requires genetic testing for definitive diagnosis. More testing is expected to increase the number of CTNNB1 cases."

The disorder results from sporadic loss-of-function mutations in the CTNNB1 gene, which encodes for beta-catenin, an essential protein for nervous system function. As one CTNNB1 gene allele is mutated, beta-catenin levels are about half of what they should be. Normalizing beta-catenin levels provides a therapeutic opportunity for this unmet medical need.

In collaboration with Broad Institute and an NIH innovation accelerator hub, Dr. Jacob is identifying a lead therapeutic compound. Her drug studies in a preclinical mouse model show that the compound, BRD0320, a high selectivity inhibitor of the endogenous negative regulator, glycogen synthase kinase 3 (GSK-3), significantly normalizes b-catenin levels and cognitive and motor phenotypes—even with treatment initiated after symptom onset.

"With Oxford-Harrington Rare Disease Centre input and support, we are conducting essential CTNNB1 patient derived neural cell studies of GSK inhibitor lead candidates," Dr. Jacob shares. "The results are extremely encouraging!"

Michele Jacob (standing back left) with CTNNB1 syndrome families visiting her lab.

MICHELE JACOB, PhD
Professor, Director of Biomedical Therapeutics
PhD program, Dept. of Neuroscience
Tufts University School of Medicine

"Seeing a mother's tears made me determined to help."

BOWEN LI, PhD
Assistant Professor, Leslie Dan Faculty of Pharmacy
University of Toronto
Canada Research Chair in RNA Vaccines & Therapeutics

"Our goal is to provide safe, effective, and lasting relief for cystic fibrosis patients who lack therapeutic options."

DEPLOYING PRECISION MEDICINE WITH NANOTECHNOLOGY

TO TREAT CYSTIC FIBROSIS

FOCUS: Development of a novel tRNA therapy for cystic fibrosis caused by nonsense mutations

In the past 20 years, small molecule drugs developed for cystic fibrosis (CF) have improved quality of life—and extended life—for 90% of patients who inherit the disease. But for Dr. Li and his team at University of Toronto (U of T), that's not enough. Sometimes the drugs lose effectiveness, cause side effects, and in 10% of patients, they don't work. The Li team is optimizing a novel therapeutic using lipid nanoparticle (LNP) technology to deliver transfer RNA (tRNA) that potentially could help all patients live normal lives.

In CF, a premature stop codon (DNA error) in the CF transmembrane conductance regulator (CFTR) gene creates what's known as a nonsense mutation. The gene cannot make a full, working protein to control movement of salt and water in and out of cells, resulting in a thick, sticky mucus in lungs and intestines. CF patients suffer chronic breathing difficulty, gut discomforts, exhaustion, and infections requiring antibiotics and hospitalization. The disease affects more than 40,000 people in the United States and 105,000 people worldwide.

Moving forward from successful safety and efficacy studies in mice and CF patient cells, Dr. Li and his team are working to produce a safe, effective inhalable spray. They're also investigating using the novel LNP/tRNA platform to treat other diseases.

"Only three types of stop codons cause nonsense mutations, but they're implicated in thousands of different genetic disorders affecting the lungs, liver, eyes, brain, and muscles," Dr. Li says. "Lipid nanoparticles can be precisely engineered, so theoretically, we could load tRNAs that recognize each of these stop codons to restore protein production across many of these conditions."

RESCUE FOR HPDL-DRIVEN

MITOCHONDRIAL DISORDERS

FOCUS: Treating HPDL encephalopathies with CoQ10 headgroup intermediates

In the United States, about 200 babies and young children have been diagnosed with rare, genetic HPDL-driven mitochondrial disorders. Parents watch, heartbroken, as their children exhibit delayed development, epileptic seizures, muscle spasms, or even die without a cure. Now, an effective therapeutic, and possibly a cure, is within reach. A first-in-human treatment developed by Oxford-Harrington Rare Disease Scholar, Dr. Pacold restored mobility and playfulness—in just two months—to an eight-year-old boy suffering rapid decline.

"His parents previously had lost two children to HPDL encephalopathy," Dr. Pacold recalls. "When it appeared their one surviving child was heading that way, they were terrified." The boy's experimental treatment stems from a 2021 study conducted by Robert S. Banh, PhD (then a postdoctoral fellow in Pacold Lab), tracing the path of oxygen in cellular metabolism. The work shed new light on molecular pathways inside the mitochondria—the cell's energy generator involving the HPDL protein, its metabolites, and Coenzyme Q10 (CoQ10), whose synthesis is lost in HPDL deficiency.

As a 2023 Harrington Discovery Institute scholar, Dr. Pacold targeted the HPDL pathway in pancreatic cancer. Then, the first reports of patients with neurologic diseases caused by loss of HPDL were published. The Pacold team quickly obtained HPDL-deficient mouse models that mimicked HPDL-deficient patients and which responded to HPDL-produced metabolites, achieving stunning results with virtually no toxicity. Next, a unique partnership with pediatric neurologists, Claire Miller, MD, PhD and Giuletta Riboldi, MD, PhD, also at NYU Langone, enabled FDA approval of single treatment and compassionate care for a child with HPDL deficiency. A larger study to test the approach is planned.

MICHAEL PACOLD, MD, PhD
Assistant Professor
Department of Radiation Oncology
New York University

"Miraculous recovery is rare, but that's what we strive for in science."

CARLO RINALDI, MD, PhD
Professor, Molecular and Translational Neuroscience
University of Oxford

"Our goal is to transform the SBMA landscape and bring real hope to patients."

TURNING THE SWITCH ON SPINAL AND

BULBAR MUSCULAR ATROPHY

FOCUS: An isoform-switch oligonucleotide therapy for spinal and bulbar muscular atrophy

Spinal and Bulbar Muscular Atrophy (SBMA) is an inherited adult-onset neuromuscular disorder affecting 1 in 40,000 men worldwide. In this condition, specialized nerve cells controlling skeletal muscular movement degenerate gradually. Arm and leg muscles weaken and atrophy, and patients become wheelchair-bound within 15 to 20 years of onset. No cure exists for the fatal disorder—today's drugs relieve symptoms only.

SBMA is caused by a DNA mutation resulting in a pathological expansion in a cytosine-adenine-guanine (CAG) repeat in a gene called the androgen receptor (AR). This defect sets off a pattern that disrupts the motor unit functioning.

Dr. Rinaldi is testing an innovative approach based on splice-switching oligonucleotides (SSOs) to silence the mutant AR while promoting the production of an alternative, harmless AR isoform. His goal is to restore patient strength and mobility.

"The CAG segment normally repeats up to 36 times, but in SBMA individuals, the repeat is longer, typically 40 or more," Dr. Rinaldi explains. "The encoded AR protein containing the extra segments results in toxic protein functions, which ultimately damage motor neurons and muscles. The patient progressively loses muscle strength and mobility. To reduce the mutant AR protein toxicity, our approach employs an antisense oligonucleotide switch to promote expression of an AR isoform (AR2)—a closely related, harmless protein—at the expense of the canonical isoform. AR2 acts as a decoy in the transcription process and restores normal nerve and muscular functioning."

Dr. Rinaldi and his team are screening and validating SSOs in patient-derived cells, as well as performing in vivo tests in SBMA mouse models, to identify lead candidates for a novel genetic therapy.

A PIVOTAL INNOVATION

BRINGS NEW HOPE

FOCUS: ASO treatment for KCNT1-associated developmental epileptic encephalopathy

Harrington Discovery Institute has been supporting Dr. Yu's research since 2020 in multiple projects, including personalized antisense oligonucleotide (ASO) therapy for developmental epileptic encephalopathy (DEE) caused by genetic changes in the KCNT1 gene. KCNT1- related DEE is an ultra-rare, infant-onset seizure disorder caused by mutations in brain-expressed potassium channels. Severe forms of KCNT1-related DEE can cause dozens of seizures per day, with devastating neurodevelopmental consequences.

Dr. Yu's KCNT1-targeting ASO program demonstrated target engagement and disease rescue in cultured patient-derived neurons, as well as a mouse model of disease. Dr. Yu was able to obtain FDA permission to advance the program into the clinic for two KCNT1-related DEE patients. In this pilot trial, the treatment initially elicited remarkable seizure reductions in both individuals, demonstrating the promise of this approach. However, both patients subsequently developed hydrocephalus, leading one family to make the difficult decision to withdraw from the trial and seek comfort measures.

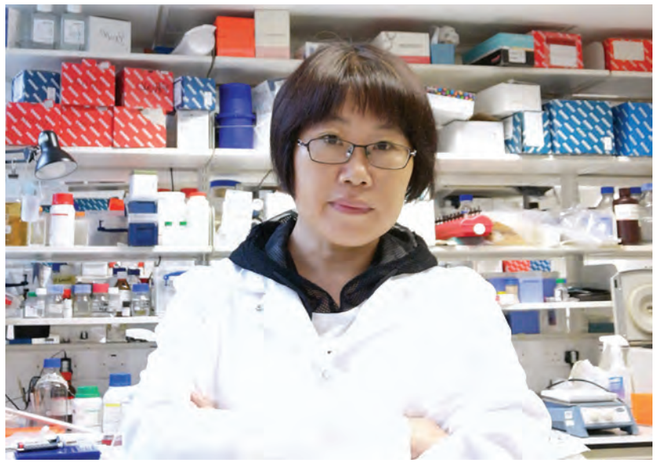
Despite this setback, the trial was able to continue, leading to a pivotal innovation: Dr. Yu's team successfully switched from intrathecal to intracerebroventricular (ICV) dosing. This has allowed for safe use of the drug at lower doses and has elicited a 75% reduction in seizures.

Dr. Yu's pioneering research into ASOs and the ongoing support from Harrington Discovery Institute and the Oxford-Harrington Rare Disease Centre are creating a roadmap for researchers developing therapeutics for other ultra-rare diseases.

"Oxford-Harrington's steadfast commitment to research into all genetic diseases, not just the handful that are highly prevalent, is so important," Dr. Yu said.

TIMOTHY YU, MD, PhD
Physician and Research Investigator
Boston Children's Hospital

"The Oxford-Harrington Rare Disease Centre is helping us advance new models that can work for all children with genetic disease."



HAIYAN ZHOU, MD, PhD
Professor of Genetic Medicine
University College London

"The ASO strategy has potential for other peripheral nervous system disorders."

NUCLEIC ACID THERAPY TO

TREAT A RARE NEUROPATHY

FOCUS: Nucleic acid therapy to treat loss of sensation and neuropathic pain caused by a rare genetic defect

Hereditary sensory and autonomic neuropathy type 1, or HSN1A, is a progressively debilitating disorder typically starting in late teen or young adult years. Patients lose the ability to feel physical sensations properly, leading to unbearable shooting pain, numbness, skin ulcers, and in the more severe cases, requiring amputation. No effective treatment exists. Dr. Zhou is focused on developing an antisense oligonucleotide (ASO)-based genetic therapy to treat HSN1A.

The disorder has been traced to the Serine Palmitoyl Transferase Long Chain base subunit 1 (SPTLC1) gene, which provides instructions for serine metabolism and production of sphingolipids, essential for brain and nerve functioning. Genetic defects in SPTLC1 change the enzyme function in that metabolic process, resulting in a buildup of neurotoxic metabolites that eventually lead to nerve damage.

A big challenge in ASO development is to identify the most efficacious and safest product in appropriate modeling systems for translation to patients. Dr. Zhou is excited about the results of testing in mice, human skin cultures, and human-derived neurons that support her approach.

"In the humanized mouse models, we achieved exciting and promising therapeutic outcomes as measured in various affected organs, without affecting the wild-type transcripts," Dr. Zhou says. "Our data provided the first proof-of-concept for ASO-mediated mutant allele-specific silencing for the treatment of SPTLC1-related HSN1. Now we are testing our lead ASO candidates for further studies on efficacy and safety, towards the clinical translation."

More than 70 adults and 100 children in the United Kingdom are affected by SPTLC1-HSN1A. Other cases exist in Canada, Australia, and the United States.

PROGRESS FOR PATIENTS

STEPS IN TIME TO TREAT

HPDL ENCEPHALOPATHY

MICHAEL PACOLD, MD, PhD
Assistant Professor
Department of Radiation Oncology
New York University

Good news is always welcome, but more so when it reaches parents anxious for a treatment or cure for a child in great need. When parents of an 8-year-old boy with a neurologically and physically debilitating genetic disorder—HPDL encephalopathy—heard about a startling discovery, their hopes rose. Studies by Dr. Michael Pacold and his team showed that mouse models with a deficiency in Coenzyme Q10 (CoQ10) headgroup synthesis recovered mobility after treatment with 4-hydroxymandelate (4HMA) or 4-hydroxybenzoate (4HB). Within a year, the boy received 4-HB treatment, which restored nearly 70% of his mobility.

The boy, who had been an active, normal child riding his bike and playing soccer, had begun falling. Leg spasms and paralysis, and loss of endurance and strength made walking difficult. Urgent help was needed.

"The couple had previously lost two children to HPDL encephalopathy and thought their child had escaped that fate," Dr. Pacold recalls. "Genetic sequencing confirmed that their child actually had the same HPDL variants that cause encephalopathy. They were terrified."

THE COQ10-HPDL CONNECTION

In 2021, Robert S. Banh, PhD (then a postdoctoral student in the Pacold Lab), traced the path of oxygen in cellular metabolism. Like a missing puzzle piece, Dr. Banh's work shed light on a metabolic byproduct (metabolite), 4-hydroxymandelate, or 4HMA.

"The 4HMA metabolite stood out because it incorporates oxygen more than any other metabolite," explains Dr. Pacold. "Previously, 4HMA was unknown in mammalian cells. Dr. Banh also showed that 4-HMA was the first committed metabolite in CoQ10 headgroup synthesis."

As a 2023 Harrington Discovery Institute Scholar-Innovator, Dr. Pacold and his team focused on treating pancreatic cancers by inhibiting 4HMA production. Then, Dr. Pacold became aware of studies in which HPDL mutations in mice mimicked the symptoms in children with the severest form of the disease—seizures, muscle spasticity, and early death.

"We contacted the NIH mutant mouse repository, got the mice into our lab, and quickly found they had exactly the same symptoms as the HPDL patients," Dr. Pacold recounts. "On a Friday, one of our pancreatic study authors treated a mouse with 4HMA. When we came back on Monday, the mouse was standing up."

The scientists continued administering 4HMA to that animal and, at 30 days, it showed abnormal gait but was very much alive. By contrast, the untreated control animal died after two weeks. The team expanded the experiment to 90 mice with 4HMA as well as 4HB, also crucial to CoQ10 synthesis. Encouragingly, 85% of those animals recovered mobility and lived at least a year or more.

FIRST-IN-HUMAN HPDL TREATMENT

In late 2023, the patient's condition was rapidly deteriorating. The parents reached out to Dr. Pacold, who connected them with two pediatric neurologists at Langone Institute of New York University, Claire Miller, MD, PhD and Giuletta Riboldi, MD, PhD. The neurologists took precise measurements of the boy's spasticity and endurance, and recorded video of his movement. They decided to treat the patient with 4HB, with Drs. Miller and Riboldi objectively evaluating study endpoints.

After 60 days of treatment, the patient's symptoms began to subside. His feet and leg muscles regained function, and he began to walk again. A year later, still on the 4HB regimen, he continues to improve.

Dr. Pacold's discovery and research toward a novel pancreatic cancer treatment has opened the door to new therapies for rare neurological disorders, as well as cancer.

"If you want to really move the needle on patient care, you have to go fundamental. You have to understand how biology works at an atomic and molecular level."

200+
PATIENTS IN THE US, AND THOUSANDS GLOBALLY, LIVE WITH HPDL-RELATED DISORDERS

ZERO
ESTABLISHED TREATMENTS EXIST FOR HPDL-RELATED DISORDERS

71%
OF PATIENTS WITH HPDL-RELATED DISORDERS SHOW MOTOR DEVELOPMENT DELAY

STEM CELLS FIND A STEPWISE APPROACH

FOR SPINAL CORD INJURY

DIANA FARMER, MD
Distinguished Professor of Surgery
University of California, Davis

Dr. Diana Farmer had been operating on babies before birth with spina bifida for years when she asked a critical question: Could surgery before birth be even better in improving outcomes? The resounding yes that came as an answer to that question, with the first successful surgeries in bulldogs with the paralyzing condition spina bifida, led Dr. Farmer to ask a new one: If there was room for some improvement, was there room for even more?

So began the Cellular Therapy for In Utero Repair (CuRE) Trial*, launched in 2021 to treat fetuses diagnosed with spina bifida with engineered placental mesenchymal stromal/stem cells (PMSCs) in utero. "When we saw how profoundly this therapy restored function in animals, we knew we owed it to patients living with other types of paralysis to explore additional applications," Dr. Farmer recalls.

That imperative was central to Dr. Farmer's 2022 Harrington Scholar-Innovator project, which coalesced former FDA leaders, drug development specialists, biomanufacturing experts, and others to extend her breakthrough stem cell therapy to the 1.5 million Americans living with acute spinal cord injury (SCI).

BEYOND PRECLINICAL PROMISE

Dr. Farmer came to Harrington with remarkable preclinical data: engineered PMSCs that could dramatically and consistently cure paralysis in fetal lamb models of spina bifida. If the same strategy could be adapted for traumatic SCI, the therapeutic potential would be enormous.

But remarkable preclinical data doesn't automatically translate to clinical success; what was needed was a translational strategy and the expertise to navigate it.

First, the multidisciplinary Harrington advisory team helped Dr. Farmer identify the central barrier to the stem cells' application to acute SCI: the time required to produce a patient-ready dose of PMSCs.

THE 24-HOUR IMPERATIVE

Spinal cord injury posed a fundamentally different challenge than spina bifida. In fetal surgery, Dr. Farmer's team has days, even weeks, to prepare cells for a planned intervention. In acute SCI—following accidents or trauma—treatment must occur within 24 hours to prevent permanent paralysis. "We had to rethink everything—manufacturing, regulation, and logistics," notes Dr. Farmer, "to abbreviate our existing process from four days to a matter of hours."

This meant more than marginal optimization; it required a fundamental reimagining of how to produce and deliver a cellular therapy. Harrington's biomanufacturing advisors drew on commercial experience to map a reengineered process that successfully compressed production time to 48 hours, while maintaining safety and quality. With this milestone reached, Dr. Farmer is now working to further calibrate the manufacturing process and reduce the therapy's production time to the necessary 24 hours.

A REGULATORY WAY FORWARD

Manufacturing was only one piece of the puzzle. Dr. Farmer's team also needed FDA expertise to accelerate approval. The FDA provides several incentives to encourage drug developers to create new therapies for rare diseases. Harrington advisors created a strategy to enable Dr. Farmer to benefit from these incentives, helping her to obtain both rare pediatric disease designation for spina bifida and orphan drug designation for the engineered PMSC therapy.

These designations accelerated the spina bifida approval timeline and created a regulatory foundation for extending the therapy to other indications like adult SCI, while also securing seven years of market exclusivity. "Harrington helped us think strategically about how success in one indication could accelerate work in another," Dr. Farmer says.

FROM PROMISE TO PATIENTS

Dr. Farmer's team is now testing whether the benefits of engineered PMSC cells can be replicated in adult spinal cord injury. This stepwise approach—proving efficacy in one indication, building a regulatory foundation, then extending to another—reflects the translational strategy that emerged from collaboration with Harrington advisors.

It also embodies Dr. Farmer's fundamental conviction: if there is room for some improvement, there must be room for more.

***For details on the study, visit: clinicaltrials.gov/study/NCT04652908#study-overview**

1 IN 2,875
BIRTHS IN THE US ARE SPINA BIFIDA PATIENTS

95%
OF BABIES WITH SPINA BIFIDA ARE BORN TO PARENTS WITH NO FAMILY HISTORY

15M+
PEOPLE GLOBALLY ARE LIVING WITH SCI

DISCOVERY OF A NEW TARGET IN ALZHEIMER'S DISEASE AND TRAUMATIC BRAIN INJURY:

A HARRINGTON PHYSICIAN-SCIENTIST COLLABORATION

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Harrington Discovery Institute
Director, Harrington Discovery Institute's
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Psychiatrist, Louis Stokes VA Medical Center

A decade ago, 2013 Harrington Scholar and gastrointestinal cancer pioneer, Dr. Sanford Markowitz, and Case Western Reserve University School of Medicine Dean, Dr. Stan Gerson, identified a little-known enzyme,15-hydroxyprostaglandin dehydrogenase (15-PGDH), as a major culprit in suppressing healing and promoting inflammation of damaged tissues. With support from Harrington Discovery Institute, they went on to develop a new small molecule (SW033291) that they'd discovered could potently inhibit 15-PGDH. Demonstrating remarkable therapeutic results in mouse models of ulcerative colitis, bone marrow transplantation, and lung fibrosis, the physicians licensed SW033291 to a global pharmaceutical company, for further development.

The drug recently showed additional potential as a treatment for neurodegenerative diseases, particularly in cases of traumatic brain injury (TBI) and Alzheimer's disease (AD). This discovery occurred through a unique collaboration between Dr. Markowitz and Dr. Andrew A. Pieper, psychiatrist and neuroscientist in the Department of Psychiatry at Case Western Reserve University and University Hospitals Cleveland Medical Center, and Director of Harrington Discovery Institute's Brain Health Medicines Center.

A NEW UNDERSTANDING OF THE BLOOD-BRAIN BARRIER

Among the three known risk factors of AD—genetics, aging, and traumatic brain injury (TBI), TBI is gaining more attention. Drs. Markowitz and Pieper focused on the novel approach of inhibiting 15-PGDH to protect the blood brain barrier (BBB) in these conditions.

"The BBB is a highly dynamic, energy intensive, interrelated set of cells involving the vasculature, immune, and nervous systems that is constantly adjusting and repairing itself," Dr. Pieper notes. "What our laboratories collaboratively discovered is that two important inflammatory immune cells at the blood brain barrier—microglia and perivascular macrophages—are highly enriched in the 15-PGDH enzyme that Dr. Markowitz has been studying."

Elevated 15-PGDH in the BBB got the physician-scientists thinking. Would blocking the enzyme heal the BBB? What other therapeutic effects might that have?

NOVEL PROTECTION AGAINST NEURODEGENERATION

"With the levels of 15-PGDH in the BBB as our focus, we tested SW033291 in mice with TBI," Dr. Markowitz recounts. "We found that inhibiting 15-PGDH with SW033291 protected the mice from neurodegeneration and cognitive impairment even when the drug was given a full day after injury. By blocking 15-PGDH, we prevented brain inflammation, which preserved BBB integrity, thereby blocking neuronal damage."

The same therapeutic pathway also worked in a mouse model of AD, showing potential for a novel treatment. Currently approved AD drugs are amyloid-targeting antibodies developed to prevent the accumulation of amyloid plaque, a sticky substance that's found in the brains of AD patients. Yet, post-mortem studies have revealed that plaque build-up in the brain does not always lead to AD.

"It's recognized that some fortunate individuals are endowed with as-yet unclarified compensatory protective mechanisms that allow them to remain cognitively intact despite developing extensive Alzheimer's amyloid pathology. Our results suggest that preventing 15-PGDH-derived neuroinflammation and thereby protecting the BBB could be one such protective factor," explains Dr. Pieper.

"Although SW033291 did not influence the amyloid plaque pathology in the mouse model we tested, it was completely protective for other pathologic and symptomatic aspects of AD," he continues. "Without reducing any of the amyloid plaque buildup in the Alzheimer's mice, SW033291 prevented amyloid induced brain inflammation. That blocked amyloid from inducing BBB degradation, which thereby stopped all other signs of Alzheimer's disease in the brain, and thus preserved normal cognitive function."

Drs. Markowitz and Pieper hope to one day see SW033291 offered in pill form for protective treatment in patients developing Alzheimer's disease and in those who are within 24 hours of a TBI, potentially saving millions of people from the heartache and hardships of these currently untreatable and chronic neurodegenerative diseases.

7M+
AMERICANS ARE LIVING WITH ALZHEIMER'S DISEASE

2.9M
TBI-RELATED EMERGENCY DEPARTMENT VISITS EACH YEAR IN THE US

1 in 9
PEOPLE AGE 65 AND OLDER HAVE ALZHEIMER'S DISEASE

FROM SCHOLAR DISCOVERY

TO CLINICAL IMPACT

CeleCor THERAPEUTICS

Chair, Medical & SAB; Co-Founder: **Barry S. Coller, MD**
President & CEO; Co-Founder: **Robert Hillman, PhD**
Co-Founder; Member, Board of Directors: **Andreas Ritzi**
Member, Board of Directors: **Jack Lief**

Promising results from a pivotal Phase 3 clinical trial of an investigational heart attack drug were announced November 10, 2025, as part of the late-breaking sessions at the American Heart Association Scientific Sessions in New Orleans. Data from the CeleBrate study show that rapid treatment with CeleCor Therapeutics' investigational heart attack drug, zalunfiban (Disaggpro™), resulted in higher levels of blood flow to the heart and an approximately 21% reduction in a patient's risk of experiencing a larger myocardial infarction or one complicated by death, stroke, reinfarction, stent thrombosis or heart failure.

CeleBrate involved patients who suffered STEMI (ST-segment elevation) heart attacks—the most severe form of heart attack, in which blood flow to a portion of the heart is almost always cut off by a blood clot. The results of the pivotal CeleBrate study, which met both its primary efficacy and safety endpoints, were also published in The New England Journal of Medicine Evidence.

CeleCor Therapeutics was co-founded by Harrington Scholar Barry S. Coller, MD, Robert Hillman, PhD, and Andreas Ritzi, to improve the treatment of STEMI heart attacks at the first point of medical contact.

"Zalunfiban was designed to be easily administered by a healthcare professional and to act within minutes to block the receptor platelets used to clump together. As a result, the platelets are severely limited in their ability to start the clotting process," said zalunfiban lead inventor Barry S. Coller, MD, David Rockefeller Professor, head of the Allen and Frances Adler Laboratory of Blood and Vascular Biology, vice president for medical affairs and physician-in-chief at The Rockefeller University.

"Its effects wear off after about two hours—when it is no longer needed, because by that time, the cardiologists in the hospital have opened the artery and inserted a stent to keep the artery open," Dr. Coller added.

The vast majority of discoveries in academia fail to advance into new therapies. When Dr. Coller received a Harrington Scholar-Innovator award in 2015, he needed support to take the investigational drug into clinical testing. The award helped advance the goal of developing and testing zalunfiban in the pre-hospital setting.

Initially, the proposed route of administration for zalunfiban was intramuscular. Input from Dr. Coller's Harrington Therapeutics Development team changed that to subcutaneous (under the skin) administration, opening the potential of using an autoinjector. The team also helped build a business case for the new drug.

"My Therapeutics Development advisory team at Harrington Discovery Institute played a crucial role in where we are today. They offered access to experts in multiple disciplines, which led us to reconsider the route of administration and initiate much-needed reimbursement strategies. This positioning was instrumental in attracting new funding to advance the medication into clinical trials," Dr. Coller said.

CeleBrate was a pivotal Phase 3 prospective, blinded, randomized, placebo-controlled trial designed to assess the safety and efficacy of a single subcutaneous injection of zalunfiban in STEMI patients in the pre-hospital setting. It enrolled 2,467 patients at 45 sites in the United States, Canada, Mexico, and Europe. Eligible STEMI patients were enrolled in the ambulance or in a hospital emergency department.

For more information on CeleCor and the study results, visit **CeleCor.com**.

QUINTEN AND VICTORIA TIFFT

TRACING A FAMILY'S LIFELONG COMMITMENT TO GLOBAL HEALTH AND PHILANTHROPY

The Tifft family's philanthropy follows the same strategic bent as their professional lives: targeted, partnership-focused, and oriented toward systems-level impact.

Victoria Tifft's deep sensitivity and determination related to global health is rooted in service, science—and personal experience. As a young adult, she contracted malaria while serving in the Peace Corps in West Africa. Lying in a hospital bed, battling fever, chills, and other symptoms, she was kept from doing what she'd gone there to do—help people. She made a decision. First, get well. Next, spend her life fighting diseases in ever more impactful ways.

Along with her husband, Quinten Tifft, Victoria raised three children while nurturing a lifetime partnership centered on family, entrepreneurialism, scientific rigor, and strategic philanthropy. Their shared journey spans the Peace Corps, building clinical research businesses, and supporting cutting-edge medical research.

A LEGACY TO IMPROVE GLOBAL HEALTH

"It's unusual, though not rare for a couple to share a worldview and mission in addition to an array of complementary skills in business management, finance, human resources and scientific knowledge," Victoria begins. "Our vision extends beyond ourselves. We strove to make a multi-generational commitment to improving health outcomes around the world."

Quinten and Victoria's three adult children have inherited their parents' passion for global research—all are actively engaged in work or philanthropy that advances scientific understanding and health equity.

PARTNERS WITH A GLOBAL MISSION

In the early 1990s, the Tiffts established Clinical Research Management, a Contract Research Organization (CRO) they guided until they sold the firm in 2016. Under their leadership, the company specialized in infectious disease research in both the United States and Africa, growing to more than 500 employees, while building significant institutional partnerships.

Near the start of the 2014-15 global Ebola outbreak, the Tiffts teamed with Kenyan colleagues to create another CRO, ACE Research, with headquarters in the United States and Kenya. Both Clinical Research Management and ACE Research worked closely with the Gates Foundation and several pharmaceutical companies and international academic institutions (including University Hospitals) that ultimately would support the efforts first line responders and patients in Liberia, Sierra Leone, and Guinea in vulnerable areas. ACE Research continues today, operating in over 30 countries across Africa and the United States.

Quinten sums up the Tifft's approach to achieving impact.

"Whether it's leadership in research, entrepreneurship, or philanthropy, it's based on investing in high-quality science, building durable institutional partnerships, and supporting models that translate discoveries into real-world treatments," he says.

PHILANTHROPIC FOCUS: RARE DISEASES AND BRAIN HEALTH

Visits with Drs. Jonathan Stamler, Matthew Wood, and Matthew Anderson cemented the family's decision to provide generous support to Harrington Discovery Institute.

"As an entrepreneurial family, we are impressed with the unique strategy and goals of Harrington Discovery Institute," Victoria says. "We know firsthand about the costs and challenges of accelerating research, conducting studies, and bringing new therapeutics from bench to bedside. The focus on advancing therapeutics for rare diseases, major diseases, and brain health is timely—and doable."

"We are proud to support Harrington Discovery Institute's approach to bring 40 drugs into clinical trials by 2034 through the Oxford-Harrington Rare Disease Centre."

VICTORIA TIFFT

"Harrington Discovery Institute has developed a distinctive business model that blends scientific rigor with entrepreneurially minded support for translational research."

QUINTEN TIFFT

MAJOR DISEASES

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Case Western Reserve University

BRUCE HAMMOCK, PhD
2025 Harrington Brain Health
Medicines Scholar
University of California, Davis

VALENTINE MACAULAY,
MD, PhD, FRCP
2016 Oxford Scholar
University of Oxford

GAVRIL W. PASTERNAK,
MD, PhD
2014 Harrington Scholar-Innovator
Memorial Sloan Kettering
Cancer Center

***Scholar institution at time of award**

FOR MORE INFORMATION:
HarringtonDiscovery.org/Scholars

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