

Harrington Discovery Institute

 University Hospitals | Cleveland, Ohio

BREAKTHROUGHS TO CURES



2020-2021 ANNUAL PUBLICATION



JONATHAN S. STAMPLER, MD

President and Co-Founder, Harrington Discovery Institute
Robert S. and Sylvia K. Reitman Family Foundation Distinguished Professor
of Cardiovascular Innovation and Professor of Medicine and of Biochemistry at University Hospitals
and Case Western Reserve University School of Medicine

DEAR COLLEAGUES,

I am both nostalgic about our first ten years and excited about an impactful upcoming decade. We have immense opportunity to improve lives, and we plan to do this through our four innovation centers, which are:

Major Diseases—Our flagship physician-scientist initiative encompasses major diseases impacting society. In 2021, we on-boarded our tenth class of scholar-innovators and second class of Harrington medical student-innovators, saw two new companies launch, and celebrated the Amgen acquisition of Rodeo Therapeutics, a biopharmaceutical company launched by Harrington Scholar-Innovator Sanford Markowitz, MD, PhD.

Brain Health Medicines—Neurodegenerative and neuromuscular disorders are areas of unmet need for patients, families and caregivers. Last year, we saw continued progress in clinical trials in a number of programs, including through our latest investment in Allyx Therapeutics, a spin-out of Harrington Scholar-Innovator Stephen Strittmatter, MD, PhD, and Yale University. If successful, the small-molecule drug would be a first-in-class disease-modifying therapy for Alzheimer's.

Rare Diseases—The Oxford-Harrington Rare Disease Centre is a cornerstone of our rare disease efforts via our transformative partnership with the University of Oxford. In 2021, we oversaw five UK Scholar programs virtually, and established Friedreich's ataxia as a priority area. Our Takeda collaboration offers additional expertise and reach. Notably, Harrington Rare Disease Scholar Ed Grabczyk, PhD of LSU Health New Orleans entered an option and license agreement with Takeda for technology to treat rare neurological diseases caused by DNA repeat expansion.

COVID-19—Among our twelve COVID-19 projects, four have advanced to the clinic, four are near Investigational New Drug status, one start-up company has been formed, and two projects have partnered with pharma. One example is Harrington Scholar Michel Nussenzweig, MD, PhD, of The Rockefeller University,

who has a novel, improved monoclonal antibody drug for COVID-19 treatment. In 2021, Rockefeller entered a licensing agreement with Bristol Myers Squibb to develop, manufacture, and commercialize the novel antibodies, which are entering late-stage trials.

Much of my role involves ensuring sustainable resources for the future, and on this front we have cultivated diverse funding sources as follows:

- **Harrington Discovery Institute Operating and Grant Funds.** Philanthropists, partners, and our parent institution provide us with charitable funds. We disburse the monies in the form of Scholar Award grants and in-kind drug development assistance.
- **Morgan Stanley GIFT Cures powered by Harrington Discovery Institute.** This is our powerful partnership with Morgan Stanley Global Impact Funding Trust. Its high-net-worth clients donate to disease areas, and Harrington Discovery Institute allocates those monies to innovators working in that area.
- **The Advent-Harrington Impact Fund.** Advent Life Sciences, a leading venture fund manager, leads this joint effort to invest in promising drug discovery assets, including projects generated by our scholars. Returns from the fund are shared with the institute to catalyze its mission.
- **Harrington Discovery Institute Seed Fund.** We have formalized a small, internal investment fund and can now invest in companies stemming from Harrington scholar projects, as well as mission-aligned projects addressing unmet need outside the Harrington community.

As I consider our *present*, my strongest sentiment is gratitude—for the opportunities our stakeholders have given us to improve human health and find cures. As I consider our *future*, my strongest sentiment is humility—about the possibility that we may do just that.

Warmly,

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OUR INNOVATION CENTERS

MAJOR DISEASES

Physician-scientist initiative encompassing major diseases impacting society

BRAIN HEALTH MEDICINES

Neurodegenerative disorders, mental health and neuromuscular disorders

RARE DISEASES

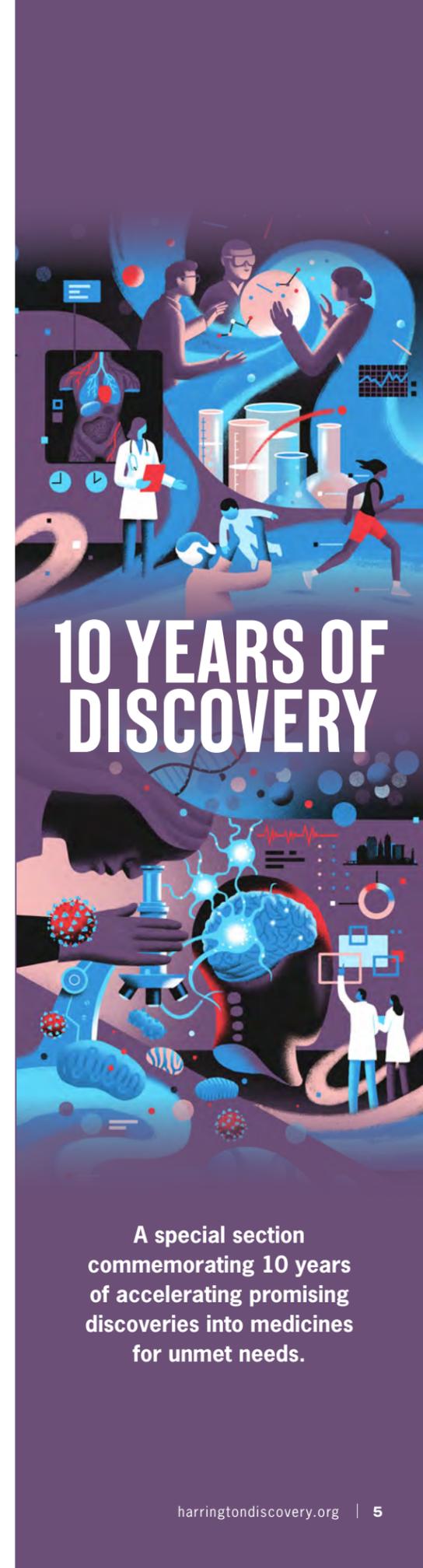
Rare and ultra-rare diseases, and rare variants of common diseases

COVID-19

Coronaviruses and pandemic-causing pathogens



FOR MORE INFORMATION:
HarringtonDiscovery.org/Centers



10 YEARS OF DISCOVERY

A special section commemorating 10 years of accelerating promising discoveries into medicines for unmet needs.

**THE HARRINGTON PROJECT
MILESTONES ACHIEVED**

162 MEDICINES IN
THE MAKING

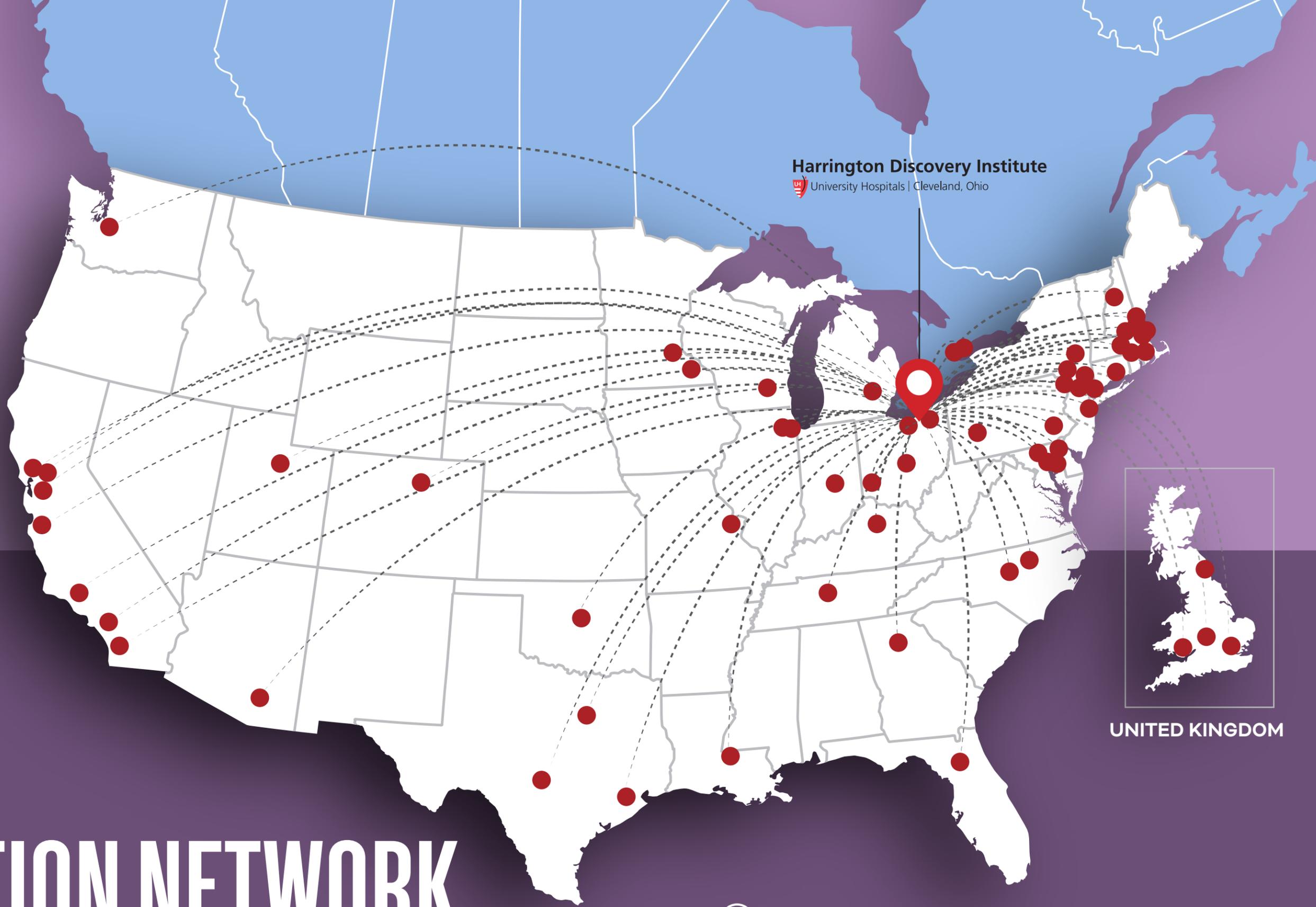
64 INSTITUTIONS
SUPPORTED

31 COMPANIES
LAUNCHED

17 MEDICINES
IN THE CLINIC

13 LICENSES
TO PHARMA

Harrington Discovery Institute
University Hospitals | Cleveland, Ohio



UNITED KINGDOM

OUR GLOBAL
INNOVATION NETWORK

HARRINGTON SCHOLAR PROJECTS SUPPORTED TO DATE

FOR MORE INFORMATION:
HarringtonDiscovery.org/Impact



“Seeing that the Harrington Discovery Institute will get new medicines into the world to help save people’s lives has moved us deeply. We feel the future is bright for discovering treatments as well as cures.”

RONALD G. HARRINGTON
Philanthropist and Entrepreneur

THE EVOLUTION OF IMPACT

The Harrington family appreciates the power of great results for motivating people; a results-orientation is part of the family story. When Mr. Harrington and his wife, Nancy, acquired a distressed medical products distributor in 1990, they knew its employees needed to create a new culture that included empowerment and generating results. If successful at that, then Edgepark Medical Supplies would thrive. If not, it would end up in bankruptcy.

Naturally, then, when the Harrington family (including children Ron M. and Jill, plus daughter-in-law Lydia) became founding donors of the Harrington Discovery Institute, they wanted a predominant focus to be on results and ultimately the impact on human health. That’s where the idea of a dashboard came in—a group of metrics that can be shown visually and that drive business success.

“Thing is, as is the case with all new organizations, our dashboard would need to evolve,” says Mr. Harrington. “Drug

development is a long-term endeavor. This meant our dashboard showed mainly organizational activities instead of global impact.” The dashboard included monies raised, people hired, and applications and nominations submitted for the inaugural Scholar-Innovator Award and the Harrington Prize for Innovation in Medicine, presented with the American Society for Clinical Investigation.

Then, acceleration began! As the Harrington Discovery Institute added programs for Alzheimer’s, rare diseases, and COVID-19, plus international linkages, a network effect and a virtuous cycle took place. Many people in the US, Canada, and the UK, were connected to the metrics, and the dashboard began to show international impact and success.

“We could post more and more progress on our dashboard,” Mr. Harrington says, “developments that may improve humanity—medicines in clinical trials and licenses to pharma, companies formed, and potential

cures.” The number of donors and dollars raised gained momentum, now surpassing \$600 million for The Harrington Project.

What started as anticipation evolved into shared excitement and momentum. Now, Harrington scholars, partners, advisory board members, and patients and their families can see the dashboard on the Harrington Discovery Institute website (both on the homepage and in the Impact section) and feel the impact being made. The numbers shown at the time of this writing will likely increase by the time stakeholders receive this publication.

As for the Harrington family business, it eventually became the largest mail-order medical products distributor in the country and enjoyed 20 consecutive years of double-digit revenue growth and double-digit profit growth—results to which everyone at the company felt connected. “Our family believes the people of Harrington Discovery Institute are poised to achieve even more impressive progress,” Mr. Harrington says.

A SELF-SUSTAINING APPROACH TO CURING DISEASES

Morgan Stanley GIFT Cures

Morgan Stanley GIFT CuresSM powered by Harrington Discovery Institute was established as the first special interest program of Morgan Stanley Global Impact Funding Trust (GIFT) in response to client demands for concrete results from their medical philanthropy. Morgan Stanley GIFT Cures provides philanthropic

funds to Harrington Discovery Institute while creating a community of like-minded donors. It is an opportunity for philanthropists, foundations, family offices and companies to learn from drug development experts and provide catalytic support to bring treatments and cures to market.

“We have created a community of like-minded donors who want to see their philanthropic dollars used to advance these promising discoveries.”

MELANIE SCHNOLL BEGUN
Managing Director

Head, Field Engagement | Morgan Stanley Family Office Resources
President, Morgan Stanley Global Impact Funding Trust



Advent-Harrington Impact Fund

The Advent-Harrington Impact Fund is a market rate investment fund in partnership with Advent Life Sciences, a leading transatlantic venture investor. The Fund invests in promising drug discovery assets, including projects generated by Harrington Scholars. Profits from the Fund are shared with Harrington Discovery Institute to catalyze additional drug development to address future unmet medical needs.

Advent’s collaboration with Harrington Discovery Institute broadens the quality of investment in academic research and commercial drug development opportunities across the globe, while increasing the amount of capital available to support these projects.



“We are delighted to have partnered with Harrington Discovery Institute to provide translational finance that will deliver real impact to patients in addition to strong financial returns.”

SHAHZAD MALIK
General Partner, Advent Life Sciences



FOR MORE INFORMATION:
HarringtonDiscovery.org/ImpactInvesting



ACCELERATING NOVEL TREATMENTS FOR
RARE DISEASES

Through its Center for Rare Diseases, Harrington Discovery Institute is addressing an enormous unmet need. The Center has three components.

Takeda Program

The Harrington Rare Disease Scholar Award, sponsored by Takeda Pharmaceuticals, supports researchers whose discoveries show promise for translation into novel medicines for rare diseases. Among 275 applications (in 2017) and 90 possible breakthrough discoveries, nine scholars were awarded a Harrington Rare Disease Scholar Award. Scholars have received grants, drug development expertise, project management support, and access to Takeda’s R&D experts. This has yielded four possible treatments that have made good progress. Especially exciting is Ed Grabczyk, PhD from LSU Health New Orleans and his platform for DNA repeat disorders, as well as a possible treatment for Rett Syndrome being investigated by Jeannie Lee, MD, PhD, of Massachusetts General Hospital.

Those with Rett Syndrome typically live wheelchair-bound for 40 years or more and require full-time care; no treatment or cure exists. Dr. Lee aims to treat the disease by reactivating a dormant X-chromosome to restore a key protein (MECP2) to the brain.

Harrington UK Rare Disease Program

In a UK-wide call for applications, nearly 50 applications from 17 institutions were received, successfully demonstrating national interest in the program. Five scholars were selected, and their rare disease projects address neurological disease, neuromuscular conditions, lysosomal storage disorders, kidney failure, and hereditary pain. They will receive funding and support to advance their research into novel treatments. One scholar is Angela Russell, DPhil,

University of Oxford, who is researching Duchenne Muscular Dystrophy. Many treatments help manage symptoms but are not disease-modifying. Further, many treatments are helpful with subsets of patients whereas Professor Russell’s possible therapy would address the underlying cause for all patients. (See page 34).

Oxford-Harrington Rare Disease Centre

The Oxford-Harrington Rare Disease Centre (OHC) is a unique partnership between the University of Oxford and Harrington Discovery Institute that combines world-class strengths in research and therapeutics development. OHC director, Professor Matthew Wood, explains, “Oxford has hundreds of brilliant scientists who work on rare disease. Harrington Discovery Institute brings deep experience in



MUKESH K. JAIN, MD
Co-Director, Oxford-Harrington Rare Disease Centre
Chief Scientific Officer, Harrington Discovery Institute
Visiting Professor, University of Oxford

FOR MORE INFORMATION:
HarringtonDiscovery.org/RareDiseases

supporting drug discovery and development. This combination will enable us to address, treat, and even cure some rare diseases.”

Of 2021, Professor Wood says “We saw tremendous progress this past year.” One accomplishment was to hone the overall focus of the OHC, determining that it will seek to find treatments and cures for rare diseases: that affect mainly children and have a genetic basis; in which the treatment may impact multiple diseases; that may fill an urgent need with great potential. Examples of this are neurological rare diseases, developmental rare diseases and rare cancers.

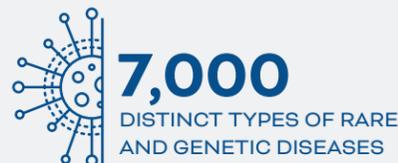
Also in 2021, the OHC named Friedreich’s ataxia (FA) as its first priority area of research. FA is a debilitating, life-shortening, degenerative neuromuscular rare disorder

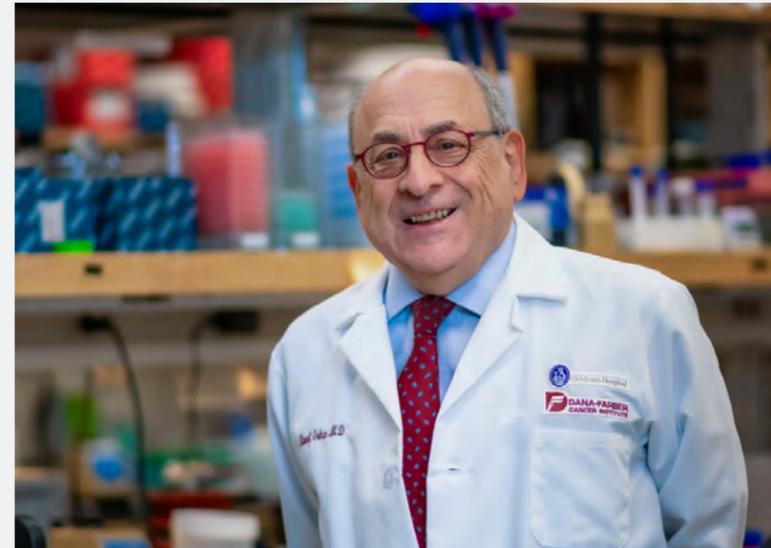
with onset during childhood. Despite high levels of existing medical research around FA, much progress is needed to advance new treatments. Setting FA as a focus area ensures that OHC will put special resources into tackling the disorder, such as partnering with relevant research associations and hiring an FA research facilitator. Ultimately, the OHC hopes to participate meaningfully in developing a therapy to treat or even cure FA.

Third, the OHC in 2021 established measurable objectives: our goal is to have 20 drugs in the clinic in 10 years. “That’s a drop in the bucket compared to the 7,000 rare diseases with no treatments or cures,” says OHC co-director, Dr. Mukesh Jain. “But for the scientists and drug development professionals, 20 drugs in 10 years is an enormous goal.”

The Oxford-Harrington Rare Disease Centre is positioned for success, and its overall strategy is to build extraordinary capabilities in finding treatments and cures for rare diseases. Dr. Jain describes the ideal future as being like a ‘one-stop-shop’. He says, “Our vision is that we can diagnose a patient, sequence the DNA to identify a cause, develop therapies, and test the therapies in clinical trials. This extends beyond science, into the business realm so we can take a medicine across the finish line.”

Professor Wood agrees, and adds, “It’s an aspirational vision. It captures the imagination, but we’ve made good strides towards achieving it.”





STUART H. ORKIN, MD
 David G. Nathan Distinguished Professor of Pediatrics, Harvard Medical School
 Principal faculty member, Harvard Stem Cell Institute
 HHMI Investigator at Boston Children's Hospital

There may be no better example of the mission of Harrington Discovery Institute than the work being done by Stuart H. Orkin, MD.

That mission—to accelerate the translation of scientific breakthroughs into life-enhancing and lifesaving new drugs—is exemplified by the work of Dr. Orkin and his colleagues. He is being honored with the seventh annual Harrington Prize for Innovation in Medicine for his discoveries that have enabled the treatment and possible cure for sickle cell disease (SCD) and β -thalassemia.

SCD affects approximately 100,000 individuals in the United States and millions of people worldwide, and β -thalassemia is one of the most common autosomal recessive disorders in the world. In β -thalassemia, adult hemoglobin production is impaired, whereas in SCD the adult hemoglobin has a single amino acid change.

Dr. Orkin's research into blood-related diseases goes back decades. Because hemoglobin is one of the first proteins that scientists understood both structurally and biochemically, it has served as an important early model of genetic diseases.

As Dr. Orkin explains, there are basically two types of hemoglobin. As fetuses, humans express the gamma or fetal chain, and as adults we express the beta or adult chain. In SCD, the adult form of hemoglobin is affected. The fetal form of hemoglobin (HbF), which is unaffected by sickle mutation, is shut off shortly after birth, leaving adults with about 1% of fetal hemoglobin.

"As both sickle cell and thalassemia are mutations in the adult beta chain, it was hypothesized that it would be of great clinical benefit—and may even be curative in some individuals—if HbF could be increased to roughly 20% from the 1% we typically have as adults," Dr. Orkin says.

To determine how the switch between fetal and adult hemoglobin is orchestrated, Dr. Orkin and his colleagues started with common genetic variation that is present in all populations, and used genome-wide association studies (GWAS) to identify genes that might correlate with the expression of HbF.

"The challenge in GWAS is going from the 3 billion bases in the entire DNA to some relevant targets," Dr. Orkin says. "We did this over a several year period, going from the entire solar system, if you will, down to a needle in a haystack of a few base pairs."

Ultimately, Dr. Orkin and his colleagues discovered how the switch between fetal and adult hemoglobin is controlled, solving a long-standing mystery and suggesting new ways to reactivate the expression of HbF. Specifically, the Orkin laboratory showed that the gene BCL11A turns off fetal hemoglobin. By blocking BCL11A,

fetal hemoglobin expression can be restored in the adult, offering a potential cure. Once the researchers understood how BCL11A was expressed, they set to work determining how it could be manipulated for therapeutic purposes.

"Our discoveries left the important question of how we can use this information to develop new treatments for blood disorders," Dr. Orkin says. "That is the promise of molecular hematopoiesis and molecular biology, and we'd like to deliver on that promise."

At Boston Children's Hospital, Dr. Orkin's colleague David A. Williams, MD, has

translated these findings to individuals with SCD in a gene therapy trial in which BCL11A expression is down-regulated.

In parallel, a biotechnology company-pharmaceutical company collaboration (CRISPR Therapeutics and Vertex) applied Dr. Orkin's findings in the first clinical trial of gene editing for human diseases to treat patients with SCD and β -thalassemia. Both approaches led to dramatic results in the patients treated to date. In the gene-targeted cells, HbF constituted ~40% of the total hemoglobin, a level well in excess of that which prevents painful crises in patients with SCD and renders those with β -thalassemia transfusion-independent.

These disease-modifying results have validated the preclinical data of Dr. Orkin and his colleagues, and they establish reactivation of HbF as a tractable and likely curative approach to genetic management of the hemoglobin disorders. To date, there has been no evidence of adverse effects or short-term toxicity.



THE HARRINGTON PRIZE FOR INNOVATION IN MEDICINE, established in 2014 by Harrington Discovery Institute and the American Society for Clinical Investigation (ASCI), honors a physician-scientist who has moved science forward with achievements notable for innovation, creativity and potential for clinical application.

THE 2021 HARRINGTON PRIZE
FOR INNOVATION IN MEDICINE

CHANGING THE STANDARD OF CARE IN

AUTOIMMUNE DISORDERS

Research typically builds on other research, resulting in the growth of shared knowledge. Warren J. Leonard, MD and John J. O'Shea, MD, two physician-scientists whose research has dramatically advanced humanity's shared knowledge and continues to spawn additional investigation and clinical advances to this day, are the co-recipients of the eighth annual Harrington Prize for Innovation in Medicine.

Drs. Leonard and O'Shea are honored for their respective contributions to the field of immunology, from fundamental discovery to therapeutic impact.

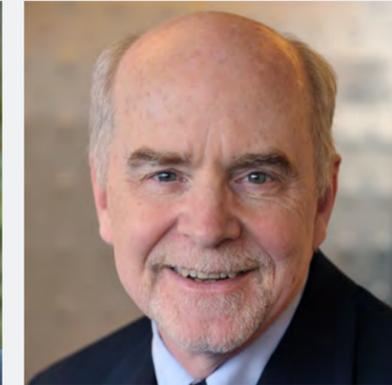
The work of Drs. Leonard and O'Shea focuses on the biology of cytokines, small proteins that modulate lymphocytes (immune cells) in the immune system. From discovery to bedside, their work has changed the standard of care for patients with challenging inflammatory and autoimmune disorders.

By modulating lymphocytes, cytokines play an important role in the body's immune response. Many cytokines were discovered in the 1970s, including interleukin-2 (IL-2), which is a member of a major group of cytokines and was shown to be central to regulating T-lymphocyte activity, representing a major advance in the field. The work by Drs. Leonard and O'Shea collectively has provided fundamental insights into IL-2-related biology, led to new diagnostics for human immunodeficiency syndromes, and resulted in a new class of therapeutics for numerous inflammatory and autoimmune disorders.

Dr. Leonard's discovery of the IL-2 receptor revealed that one component of this receptor, termed the gamma chain (IL-2R γ), was shared among receptors for numerous interleukins, and thus central to signaling within the immune system. Seminal work by Dr. Leonard in 1993 demonstrated that patients with mutations in IL-2R γ suffered

from the immune disorder X-linked severe combined immunodeficiency (XSCID). Babies born with XSCID have little to no immune protection, making them prone to developing life-threatening infections. By demonstrating that XSCID is a disease of defective cytokine signaling, Dr. Leonard's work has led to new molecular diagnostics and paved the way to gene therapy for XSCID.

"Almost anything that can go wrong will go wrong in the gamma chain gene," Dr. Leonard says. "In the Human Gene Mutation Database, there are more than 200 mutations that have been found in the gene encoding this protein. Without treatment, individuals die in the first year of life. However, successful bone marrow transplantation corrects the T-cell and NK-cell defects and allows patients to survive long-term."



(LEFT) WARREN J. LEONARD, MD
National Heart, Lung, and Blood Institute,
National Institutes of Health
NIH Distinguished Investigator

(RIGHT) JOHN J. O'SHEA, MD
Scientific Director, National Institute of Arthritis
and Musculoskeletal and Skin Diseases,
National Institutes of Health

Dr. John O'Shea discovered the signaling protein JAK3 and showed that it was essential for the immune actions of interleukins that share IL-2R γ . In collaborative papers in 1994 and 1995, Drs. Leonard and O'Shea demonstrated that JAK3 signals "downstream" of IL-2R γ leading them to predict and then demonstrate that, similar to mutations in IL-2R γ , mutations in JAK3 result in severe combined immunodeficiency.

Based on these findings, they boldly speculated that "reagents that disrupt Jak3-gc association may be immuno-suppressive" and furthermore "that any agents that inactivate JAK3 function may be potent immuno-suppressants", ideas that promoted the development of a new class of immunosuppressant molecules.

Dr. O'Shea then collaborated with industry to develop an oral JAK inhibitor for rheumatoid arthritis. This work has inspired a new field of JAK inhibitors, referred to

as "jakinibs", which are being evaluated in clinical trials for a wide range of inflammatory and immune diseases.

Today there are nine jakinibs approved for indications such as rheumatoid, psoriatic and juvenile arthritis; inflammatory bowel disease; and hematologic indications, and there are multiple trials ongoing for additional indications. Displaying their versatility, jakinibs have even been used to treat individuals affected by COVID-19.

"We are in a phase right now where we have more selective JAK inhibitors, but there's still so much more we need to know," Dr. O'Shea says. "Going forward we have the opportunity to determine how to use this class of drugs optimally, either alone or in combination with other effective drugs we've been using previously."

Receiving the 2021 Harrington Prize for Innovation in Medicine presented Dr. O'Shea

with an opportunity to step back and reflect on what he and Dr. Leonard have been able to accomplish in the field of immune system research.

"I'm very grateful for this honor and particularly pleased to be honored with my long-term NIH colleague Warren Leonard," Dr. O'Shea says. "I'm humbled and amazed that the ideas we had 25 years ago turned out to help individuals with autoimmune and allergic diseases, and now even COVID-19." Dr. Leonard echoes these feelings and is most pleased to be honored with Dr. O'Shea.



BASIC DISCOVERIES WITH
BROAD APPLICATIONS

Amidst a successful career as a tenured professor at the University of California San Diego, Dr. Seth Field chose to move to Northeast Ohio for the unique opportunity offered by the Harrington Investigator Program, which supports leading physician-scientists seeking to translate their basic science discoveries into advances in medicine.

A graduate of MIT, and Harvard where he received his MD and PhD in Genetics, Dr. Field has won numerous awards, including a prestigious NIH Director's New Investigator Award.

Dr. Field's approach to advancing medicine is predicated on the idea that simply enhancing our knowledge of fundamental cell biology will tell us how to cure diseases.

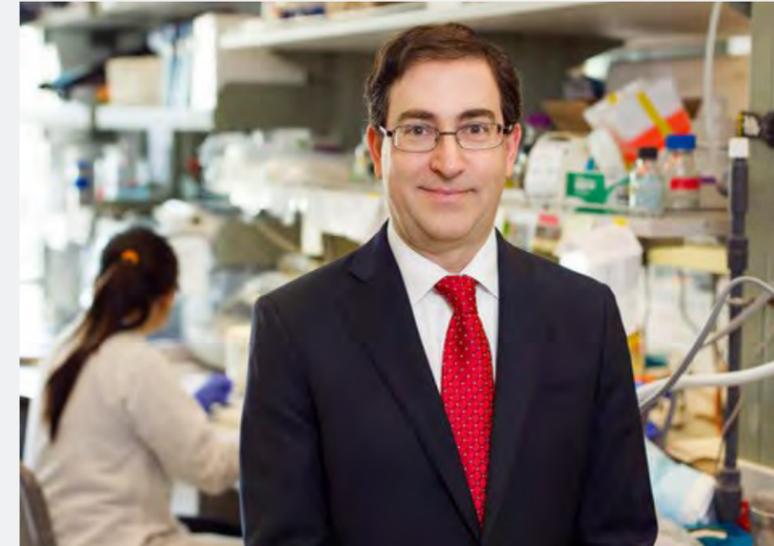
"The plain truth is, our basic understanding of how biology works, how human cells work, how the machinery of our bodies work, is very limited," Dr. Field says.

"Every time there's even a small advance in understanding the fundamental biology of, for example, how cells work, it has always led to advancements in understanding disease. So my aim is to learn new things

about how biology works, knowing that new information is going to tell us important things about one or more human diseases."

Dr. Field's approach has indeed yielded important findings. The Field Lab has developed new methods to investigate how messages are carried within the cell, which led to new discoveries that have advanced our understanding of both a childhood immunodeficiency disease and diabetes mellitus.

His work also discovered part of the cell's internal workings that export packages



SETH FIELD, MD, PhD
Harrington Investigator
Director, Physician-Scientist Program

out of the cell, the process known as secretion. The fundamental component in this cell machinery is called the Golgi apparatus, the structure that packages proteins into membrane-bound sacs before these sacs are sent to play important roles in various destinations within the body. The discovery of the Golgi secretory machinery wasn't a single "aha" moment, but rather a trajectory of discoveries that occurred over several years.

"We established that this cellular machinery serves as a hub for intracellular signaling pathways that regulate Golgi function," Dr. Field says. "Our lab is using diverse and cutting-edge approaches in cell and molecular biology, genetics, biochemistry, and pharmacology to provide new insights into the Golgi—its regulation, and its contribution to human pathophysiology."

Remarkably, they found that this cellular machinery is abnormally activated in cancer, and by inhibiting it, cancer growth ceases. Initially, the discovery suggested that a single protein component of this Golgi secretory machinery plays a role in cancer. However, many scientific papers have since identified other parts of this Golgi secretory machinery to be involved in cancer.

Driven by these discoveries, Dr. Field has implemented a state-of-the-art microscopy facility in order to peer into the smallest recesses of the cell, allowing his team to churn out data in pursuit of understanding just how activation of the cellular machinery for secretion is driving cancer growth. His lab has been developing chemicals that act to inhibit the pathway, paving the way to develop new classes of therapeutic drugs to treat cancer.



2022 BREAST CANCER
STATISTICS IN THE US

1 in 8

WOMEN WILL DEVELOP
INVASIVE BREAST CANCER
OVER THE COURSE OF
HER LIFETIME

287,850

NEW CASES OF INVASIVE
BREAST CANCER ARE
EXPECTED TO BE
DIAGNOSED IN WOMEN

2,710

NEW CASES OF INVASIVE
BREAST CANCER ARE
EXPECTED TO BE
DIAGNOSED IN MEN

"By joining Harrington Discovery Institute my lab can access unique resources to leverage our discoveries in fundamental cell biology to produce new drugs to treat human disease."



FOR MORE INFORMATION:
HarringtonDiscovery.org/Investigators/Field

HARRINGTON SCHOLAR PROGRAMS



FOR MORE INFORMATION:
HarringtonDiscovery.org/Funding

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.

GUND HARRINGTON SCHOLAR AWARD

In partnership with Foundation Fighting Blindness (FFB)

Supports innovative researchers who seek to translate their findings in retinal degenerative diseases into new therapies to improve and/or restore vision. ELIGIBILITY: MD OR PhD; US AND CANADA.

RARE DISEASES

HARRINGTON RARE DISEASE SCHOLAR AWARD

Sponsored by Takeda Pharmaceutical Company Limited

Supports researchers whose discoveries show promise for translation into novel medicines for rare diseases. ELIGIBILITY: MD OR PhD; US.

HARRINGTON UK RARE DISEASE SCHOLAR AWARD

In conjunction with Harrington Discovery Institute's registered UK charity, Fund for Cures UK

Supports UK researchers who are advancing promising research into novel treatments for rare diseases, with the opportunity for funding and personalized drug discovery and development support. ELIGIBILITY: MD OR PhD; UK.

COVID-19

HARRINGTON SCHOLAR AWARD FOR CORONAVIRUS

Supports promising, near-term treatments for the novel Coronavirus and its co-morbidities, and accelerates next-generation vaccines to avert future pandemics, as part of a broader initiative to aid in the global fight against COVID-19. ELIGIBILITY: MD OR PhD; US, CANADA AND UK.

CONGRATULATIONS NEW SCHOLARS

2022 HARRINGTON SCHOLAR-INNOVATORS

BURTON DICKEY, MD
MD Anderson Cancer Center

LI LAN, MD, PhD
Massachusetts General Hospital

DAVID MYUNG, MD, PhD,
Stanford University

DIANA FARMER, MD
University of California, Davis

CAROLYN LEE, MD, PhD
Stanford University

BERND SCHNABL, MD
University of California, San Diego

JAMES HAGOOD, MD
University of North Carolina
at Chapel Hill

MICHAEL LIN, MD, PhD
Stanford University

LOREN WALENSKY, MD, PhD
Dana-Farber Cancer Institute

FRANCIS MCCORMACK, MD
University of Cincinnati

HANS-GUIDO WENDEL, MD
Memorial Sloan Kettering Cancer Center

2021 HARRINGTON SCHOLAR-INNOVATORS

JENNIFER CHEN, MD
University of California,
San Francisco

JOSEPH CONTESSA, MD, PhD
Yale University

AARON SCHIMMER, MD
University of Toronto

JOHN CHORBA, MD
University of California,
San Francisco

TOREN FINKEL, MD, PhD
University of Pittsburgh

JILL SMITH, MD
Georgetown University

MARIA GRAZIA RONCAROLO, MD
Stanford University

XINNAN WANG, MD, PhD
Stanford University

2021 HARRINGTON-MSTP SCHOLAR

DEREK WONG
Case Western Reserve University

2021 ADDF-HARRINGTON SCHOLARS

KAREN ASHE, MD, PhD
University of Minnesota

CHRISTIANE WRANN, DVM, PhD
Massachusetts General Hospital

MEET OUR 2020 AND 2021 HARRINGTON SCHOLARS

RIZWAN HAQ, MD, PhD
Assistant Professor of Medicine
Dana-Farber Cancer Institute



TARGETING CANCER

WHEN THERE'S NO TARGET

FOCUS: A small molecule that targets KEAP1-mutant cancers.

“To get a car to work, you need a lot of things to go right; it’s much easier to get a car not to work.” Dr. Rizwan Haq uses this analogy to illustrate the specific dilemma his lab faces in their work toward developing a drug that targets cancers.

The “car” in this parallel is a protein that drives the growth of cancer. The focus of Dr. Haq’s work are cancers that are mutated for the Kelch-like ECH-associated protein (KEAP1), a mutation that exists in approximately 30% of all lung cancers.

“Most drugs work by suppressing or obstructing an overactive protein,” Dr. Haq says. “KEAP1 is different—it is actually deleted in cancers, so there’s no active protein to target. The mutation has rendered it functionless, so to reactivate it you’d have to fix the mutation in the gene, which is very challenging, perhaps impossible.”

So Dr. Haq and his team set out to find a way of hitting other key proteins in the KEAP1 pathway. They screened more than 330,000 compounds, and one was found

to have a strong connection to loss of KEAP1 activity, and to preferentially target and kill the KEAP1-mutant tumors.

Harrington Discovery Institute is collaborating with Dr. Haq to find derivatives of this compound with more favorable potency and toxicity properties. In addition, beyond being a potential therapeutic for various cancers, the drug has also shown promise for some rare pediatric cancers where no effective therapies exist.

“It is validating that our expert Harrington advisors can envisage the possibility of our work leading to a drug that helps fight cancer.”

A PROMISING APPROACH TO TREATING

DANGEROUS AFTER-EFFECTS OF COVID

FOCUS: A drug to address infections associated with respiratory diseases.

For years Dr. Holtzman and his team have been striving to deliver a therapeutic for respiratory airway diseases such as rhinosinusitis, asthma, and COPD (chronic obstructive pulmonary disease). When the pandemic hit, they were able to pivot this work toward a potentially effective COVID-19 therapy.

For COVID patients, what occurs after the initial injury phase remains a major obstacle to better outcomes. In the weeks after a virus is cleared from the body, destructive processes may be set in motion during an infection crest. This explains why a high percentage of the many millions who have had a COVID infection are experiencing long-term disease, especially with respiratory symptoms. Some have organ damage that can cause chronic illness or even death.

Dr. Holtzman has uncovered clues to understanding how such lung damage develops. “We found that infection triggers the expression of a protein called IL-33, which in turn results in stem cells overgrowing their normal boundaries, and an increase in basal cells (found in the outermost layer of skin, they produce new skin cells), all of which increases mucus production and causes inflammation in the lung,” he says.

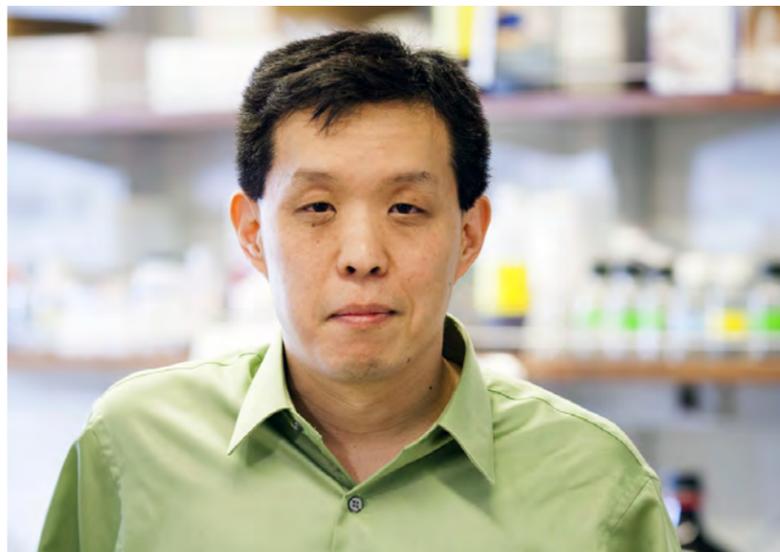
Dr. Holtzman’s team has developed a promising compound designed to target steps on the pathway between IL-33 and basal cell activation. If successful, it would form the basis of broadly effective therapies to prevent or treat lung disease caused by a variety of viruses, including COVID.



MICHAEL HOLTZMAN, MD
Division Director, Selman and Herman Seldin
Professor of Medicine
Washington University School of Medicine
in St. Louis

“Our Harrington team has been quite helpful—in particular, their toxicology expertise has helped speed development of our lead drug.”

KYU RHEE, MD, PhD
Associate Professor
Weill Cornell Medicine



BEATING A MICROBE THAT KNOWS US TOO WELL

FOCUS: New and selective inhibitors of tuberculosis.

Because tuberculosis (TB) cases typically number under 10,000 annually in the US, most Americans are unaware that nearly a quarter of all people on earth are infected with *Mycobacterium tuberculosis*, the microbe that causes TB. Before COVID, TB was the leading infectious disease killer in the world, claiming 1.5 million lives each year.

A microbe as old as humankind, it has not only figured out our immune system, but has learned how to adapt to available therapies. “Treating and eradicating TB is very challenging, and when we don’t do it right, it becomes smarter and more resistant,” Dr. Rhee says. “Further, within a person’s body it exists in multiple states, only some of which are vulnerable to antibiotics.”

Because of the scale and transmissibility of TB, it is both a cause and consequence of poverty. If it doesn’t kill a person,

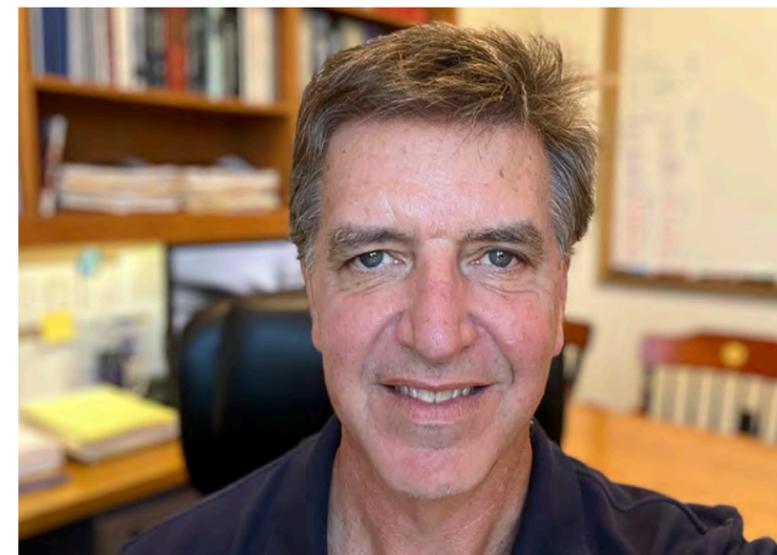
it renders them unable to work—which leads to homelessness, food insecurity, and crowding that actually promotes conditions that foster spread of the disease.

At a conference in 2018, hearing a colleague speak about work he was doing on malaria, it struck Dr. Rhee that the same targets of the malaria approach were present in TB. “The idea is to lead the parasite to think that the compound we use is a nutrient,” Dr. Rhee says. “But in fact, it is poisonous to the parasite.”

Working off of the malaria therapy model, Dr. Rhee’s team feels they have developed a formula that has strong pharmacological potential to progress into a lead compound. Harrington Discovery Institute is helping to ensure this project’s biologic studies are optimized for drug development potential.

“Harrington has ensured that our studies of biology haven’t become disassociated from the practical process of drug development itself.”

PROTECTING SYNAPSES FROM AMYLOID PLAQUES



STEPHEN STRITTMATTER, MD, PhD
Vincent Coates Professor of Neurology and
Professor of Neuroscience
Director, Cellular Neuroscience,
Neurodegeneration and Repair
Yale University

FOCUS: Prion protein antagonist for Alzheimer’s disease and Creutzfeldt-Jakob disease.

Synapse loss in Alzheimer’s disease and the corresponding cognitive symptoms of the disease have long thought to be triggered by the accumulation of a protein in the brain called beta-amyloid.

Dr. Strittmatter is investigating a previously unexplored mechanism of disease progression based on the action of two other proteins in the brain, cellular Prion Protein (PrP-C) and type 5 metabotropic glutamate receptor (mGluR5).

“Although many researchers have focused on the accumulation of beta-amyloid plaques in the brains of Alzheimer’s patients, our

attitude is that what really matters is identifying which proteins beta-amyloid interacts with on the surface of the neurons, because dysfunctional neurons are what cause people to lose learning, memory and cognitive function,” Dr. Strittmatter said.

Seeking to preserve, protect and even restore neuronal synapses in Alzheimer’s disease, Dr. Strittmatter and his colleagues have discovered a class of agents capable of blocking PrP-C and mGluR5 from binding with beta-amyloid. These agents do not alter the amount of accumulated beta-amyloid, but they do protect neuronal synapses from amyloid presence, allowing the neural

network to function normally. The approach is distinct from the common amyloid-lowering agents, though the two approaches may be synergistic.

“We now have a handle on how neurons are damaged, and we’re hoping to develop drugs that will preserve the neurons in Alzheimer’s disease—regardless of how much plaque there is in the brain,” Dr. Strittmatter said. “We believe this program offers an exciting opportunity to quickly and efficiently deliver a new therapeutic option for a very large patient population in desperate need of novel approaches.”

“Harrington Discovery Institute has been critical in helping with our research into prion protein antagonists. We’re not in the clinic yet, but we wouldn’t be bringing these compounds from animal studies toward a human trial without Harrington’s support.”



DONALD WEAVER, MD, PhD, FRCPC, FCAHS
 Director, Krembil Research Institute
 University of Toronto
 University Health Network

TAKING AIM AT NEW
ALZHEIMER'S TARGETS

FOCUS: Targeting immunopathy to treat Alzheimer's disease.

For the past two decades, most work aimed at developing a curative therapeutic for Alzheimer's disease (AD) has been focused on the clumping of beta-amyloid and tau proteins. Dr. Weaver is using a fundamentally different approach based on ample data indicating that AD may also be caused by inflammation of the brain.

Brain inflammation occurs when, for any of various reasons, molecules which mediate inflammation, such as cytokines, become overactive and kill brain cells. Dr. Weaver's team has identified two therapeutic targets

for devising AD therapeutics: IDO and FBP, two proteins which mediate the neurotoxic effects of inflammation.

IDO is a known target which has been studied for non-neurological disorders; FBP is a previously un-described receptor. To target FBP Dr. Weaver's team is using furosemide—a remarkably novel approach, since for over 60 years furosemide has been used exclusively as a diuretic. Their hypothesis is that inhibiting these receptors will down-regulate the release of inflammatory cytokines.

Harrington Discovery Institute is supporting Dr. Weaver in his work to develop molecules targeting both these receptors. "We hope that our work leads to a drug that is part of the cure, complementary to other approaches," Dr. Weaver says. "When you consider that there are many medications for a condition as simple as high blood pressure, it becomes obvious that for AD, a complex disease in the most complex part of the body, one day there will be not one, but numerous therapeutic answers."

"Working with our Harrington team, there have been more than one 'why didn't I think of that?' moments."

BREAKTHROUGHS,
INDIVIDUALIZED

FOCUS: Personalized oligonucleotide therapy for Niemann-Pick disease.

Dr. Yu is responsible for developing what is considered the world's first example of individualized genomic medicine—a drug customized solely for a single patient, designed on the basis of that patient's specific pathogenic mutation.

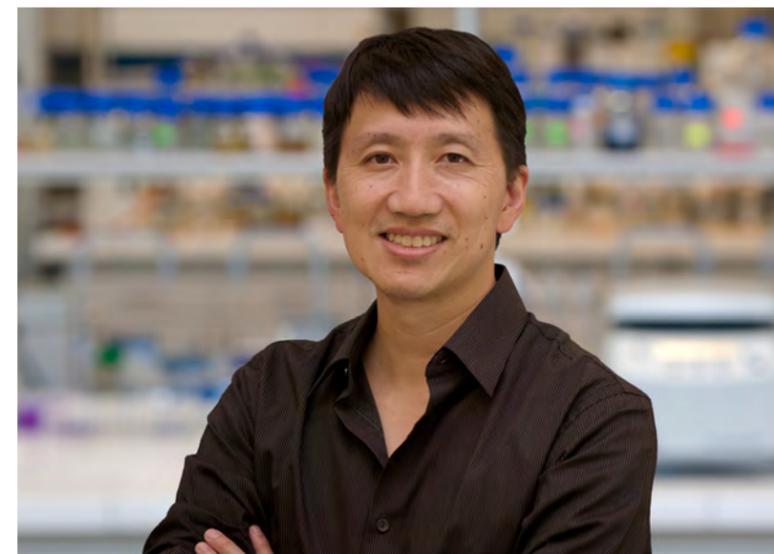
This remarkable achievement was made possible by the relatively new antisense technology, wherein small pieces of DNA or RNA, called antisense oligonucleotides (ASOs), are used to precisely target splice-altering mutations (genetic alterations in the DNA sequence) at the RNA level, restoring proper gene assembly and rescuing gene function.

Niemann-Pick type C (NPC) is a rare inherited disease that affects the body's ability to metabolize cholesterol and lipids within cells, which in turn malfunction and eventually die. NPC can affect the brain, nerves, liver, spleen, bone marrow and in severe cases, lungs.

The condition is commonly fatal within the first two decades of life. Current treatments are focused on helping people live with their symptoms.

With help from Harrington Discovery Institute, Dr. Yu and his team are designing personalized ASO therapy for NPC. "In some cases of this disease, a mutation alters RNA splicing of the NPC1 gene, resulting in loss of function," Dr. Yu says. "We have generated ASOs targeting these mutations, screening them for their ability to restore normal NPC1 splicing in patient-derived cell models."

"Beyond Niemann-Pick disease, this work has the exciting potential of fulfilling a longstanding dream of using genetic tools not just to diagnose but to accelerate the development of drug treatments, rapidly get them FDA-approved, and made available to children with rare conditions."



TIMOTHY YU, MD, PhD
 Attending Physician, Division of Genetics and Genomics
 Boston Children's Hospital
 Associate Professor of Pediatrics
 Harvard Medical School

"Harrington Discovery Institute is an exemplar of what's needed to jumpstart the development of medicines for rare diseases."

UNRAVELING A BIOLOGICAL MYSTERY

FOCUS: Exploiting novel small molecule pharmacology to treat inflammatory diseases.

In insects and vertebrates, nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1) are ancient regulators of the cell growth and differentiation, which allow for creation of all structures in the body. There is a great deal of support for the idea that their activities are especially important to the immune system, and their dysfunctions lead to devastating pathologies in cancer and immunity.

Mr. Chen and his team are working with SP100030—a lab-made small molecule inhibitor of NF-κB and AP-1. SP100030 has been used for transplant rejections and lung fibrosis in animals and has great promise in the treatment of inflammatory

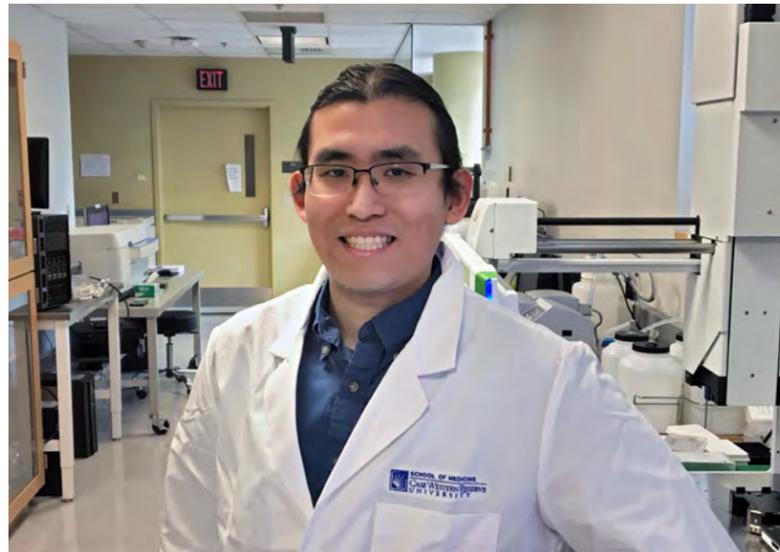
and autoimmune-related diseases. “Traditionally we deal with an overactive immune system by shutting down all of the functions involved; this works reasonably well, but with very undesirable side effects,” Mr. Chen says.

“SP100030 is unique because of its remarkable efficacy with very few side effects compared to mainstream options. What is this magic that enables this molecule to treat various disease models with no apparent side effects?”

Mr. Chen is working with Harrington Discovery Institute to answer this question, and to design potent, safe

new molecules that behave like SP100030 but improve on its current limitations.

“To understand how the SP100030 molecule does what it does and discover new insights into our immune system would be exciting developments in drug discovery,” Mr. Chen says. “It would open the door to next generation therapies for many diseases with unmet clinical need.”



YI FAN CHEN
MD/PhD Candidate
Case Western Reserve University

“I relish the expertise that our Harrington advisors bring to our project.”

10 YEARS OF DISCOVERY

Harrington Discovery Institute
University Hospitals | Cleveland, Ohio



Innovation

Integrity

Passion

Tenacity

Results

Impact

Harrington Discovery Institute

 University Hospitals | Cleveland, Ohio

Thank you VISIONARIES AND EARLY BELIEVERS



The Harrington Family

A \$50 million transformative gift in 2012 from Ron and Nancy Harrington and their children Jill and Ron, and daughter-in-law Lydia Harrington, made possible the vision of Dr. Jonathan Stamler to support physician-scientists. The gift established Harrington Discovery Institute as a key part of a pioneering global initiative—The Harrington Project for Discovery & Development—which combines a non-profit organization with impact investing partners to form a powerful system for drug development.

Jonathan S. Stamler, MD

An internationally acclaimed physician-scientist known for the discovery of protein S-nitrosylation, a global post-translational modification of proteins that is widely involved in both physiology and disease, Jonathan understood the pivotal role physician-scientists play in advancing discovery. He established Harrington Discovery Institute with the Harrington family and University Hospitals to support physician-scientists (later to include all scientists in areas of unmet need) with financial and human capital in the form of expert industry guidance. The vision was to enable a better drug development model in academia that could move discoveries from bench to bedside more quickly and efficiently.



Achilles Demetriou, MD (Deceased)

The late Dr. Achilles Demetriou was University Hospitals' first executive vice president and chief operation officer. He helped launch The Harrington Project and helped Dr. Stamler hire Baiju Shah to lead BioMotiv. Achilles was an exemplar of the physician-scientist that The Harrington Project intended to support. He was an acclaimed surgeon and researcher, and his passion was around helping patients and improving the standard of care.

David U'Prichard, PhD (Deceased)

The late Dr. David U'Prichard held an instrumental role in The Harrington Project for Discovery & Development by building world-class drug development capability and leading a search for new medicines. His career spanned academic research, biotech, pharma company leadership, venture capital, and extensive experience on the boards of public and private US, UK, European and Indian companies. After Jonathan convinced Dr. U'Prichard to join the BioMotiv team, David quickly mobilized his network of pharma leaders to assist Harrington Discovery Institute, and tapped other colleagues who shared his commitment to drug development to join the BioMotiv Advisory Board.



Daniel Simon, MD

As the Director of the UH Harrington Heart & Vascular Institute in 2009, Dr. Dan Simon recruited Jonathan Stamler from Duke University to University Hospitals. With his close relationship to the Harrington family and his belief in the vision for Harrington Discovery Institute and The Harrington Project, Dan quickly became a staunch supporter. His sponsorship continued as he was promoted to increasing levels of responsibility within the UH system, including President of UH Cleveland Medical Center and Chief Clinical & Scientific Officer for the entire health system.

Baiju Shah

Baiju Shah helped launch BioMotiv in 2012 as Harrington Discovery Institute's first mission-driven, for-profit accelerator partner under The Harrington Project. Baiju was at that time President & CEO of BioEnterprise, a Cleveland-based business formation, recruitment, and acceleration initiative designed to grow healthcare companies and commercialize bioscience technologies. Baiju saw the need and opportunity that The Harrington Project was addressing and later signed on as BioMotiv's CEO. He helped establish its unique business and investment platform that creates and operates biotech companies, providing capital, operating expertise and partnerships to speed the development of drug discoveries into medicines.





Mukesh Jain, MD

When Jonathan Stamler asked Mukesh Jain to serve as Scientific Director in 2013 (later he became Chief Scientific Officer), Mukesh seized the opportunity to be in on the ground floor of managing operations for Harrington Discovery Institute. Mukesh, an internationally respected physician-scientist who joined University Hospitals and Case Western Reserve University School of Medicine faculty in 2006, assumed responsibilities for recruiting faculty, overseeing Harrington Scholar programs and the annual Scientific Symposium, as well as the selection of the annual Harrington Prize recipient.

Becca Braun

A successful tech entrepreneur, Becca had led many new ventures including co-founding and serving as COO of JumpStart, a nationally recognized venture development firm in Cleveland. When Jonathan Stamler told her, "We have a great opportunity here, but we have a lot of work to do," she knew exactly what was required. She proceeded to systematically help create and 'productize' the Harrington Scholar programs and establish important processes, that are in use today. Becca continues to act as staff liaison to the Scientific Advisory Board.



Perry Molinoff, MD

Dr. Perry Molinoff first heard about Harrington Discovery Institute and The Harrington Project over dinner one evening with his neighbor in Philadelphia, David U'Prichard. Soon after Perry stepped in and helped launch the Innovation Support Center (now the Therapeutics Development Center), which has become the "secret sauce" that sets the Harrington model apart. He further expanded the model by recognizing that in many cases the initial grant funds awarded were not enough to reach meaningful milestones. As a result he worked with Jonathan Stamler to establish a process for scholars to apply for supplemental funding, now called Stage 2 funding.

John Rice, PhD

"Would you come over and talk to Jonathan about your background?" This was the question from BioMotiv's Bajju Shah that led to John Rice's involvement with Harrington Discovery Institute. Shortly after Bajju posed the question, John found himself across the table from Jonathan discussing the Innovation Support Center (now the Therapeutics Development Center), and the need for an advisory group that would oversee post-award investment decisions. A seasoned leader and advisor in med-tech, life sciences, and pharma, John was well-suited to chair the new Investment Advisory Board.



Thank you
SCIENTIFIC ADVISORY BOARD

- David Ginsburg, MD
- William G. Kaelin Jr., MD
- Barbara B. Kahn, MD
- Andrew Marks, MD
- Solomon Snyder, MD, D.Phil., DSc.
- Michael Welsh, MD
- Doug R. Lowy, MD (Government Liaison)

Emeritus

- Irwin Fridovich, PhD (Deceased)
- Beth Levine, MD (Deceased)
- Charles Sawyers, MD

INVESTMENT ADVISORY BOARD

- June Almenoff, MD, PhD
- Stephen Burley, MD, D.Phil
- Nancy Chang, PhD
- Peter Grebow, PhD
- Graeme Martin, PhD
- John Rice, PhD
- Jonathan Stamler, MD
- Jesse Treu, PhD

THERAPEUTICS DEVELOPMENT CENTER TEAM

FOR A COMPLETE LISTING OF ADVISORS AND PROJECT MANAGERS, VISIT: HarringtonDiscovery.org/TDC

HARRINGTON TEAM

FOR A COMPLETE LISTING OF HARRINGTON DISCOVERY INSTITUTE TEAM MEMBERS, VISIT: HarringtonDiscovery.org/Team

DISCOVERY AND FUNDING PARTNERS



Individual Philanthropic Contributors

The Harrington Family

WE CURE DISEASES *together!*



YOUR HELP TODAY ENSURES

PATIENT IMPACT TOMORROW



In 2000, doctors at University Hospitals helped save my life. The care and skill they brought to the diagnosis of a heart condition transformed my family and me into grateful patients. The Harrington Heart & Vascular Institute became a testament to our gratitude.

By 2011, our family had the good fortune to meet with a tremendously accomplished University Hospitals physician-scientist, Dr. Jonathan Stamler. We were told he had a benevolent, philanthropic idea for improving drug discovery and development. Did he ever! We were taken with his entrepreneurial spirit. We knew right away that the combination of philanthropy, science, and innovation that he envisioned could lead ultimately to cures for disease. We shared his vision and thought the model he articulated was creative and exciting.

Ten years later, it is our family's joy and pride to see that all those involved with the Harrington Discovery Institute have built something special. Donations from generous philanthropists have brought us here, and so too will a wide range of donations take us to our next major milestones in the coming decade.

The reality is this: donations are the only way we can fund discovery of treatments and cures that improve human health. Through a suite of options, people can join or continue with our growing circle of family and friends.

Here are several examples:

- **Donate to, or name, an Innovation Center.** For example, you can support possible breakthrough treatments for Alzheimer's or for COVID-19 medicines that fill gaps in existing pandemic treatment capabilities.
- **Make a disease-specific gift.** For example, support new therapies for retinal diseases causing blindness or possible treatments for rheumatoid arthritis.
- **Become an impact investor.** Impact investors can make "bridge investments"—philanthropic monies that position a project to receive commercial funding to advance to clinical trials.
- **Be a pioneer with Morgan Stanley GIFT Cures.** Make a significant impact and join a community of committed medical philanthropists through this pioneering Morgan Stanley Global Impact Funding Trust—Harrington Discovery Institute program. The model elegantly combines Wall Street prowess, unfunded science, and unmet medical need.
- **Support International Scientific Collaboration.** Support the Oxford-Harrington Rare Disease Centre and accelerate novel treatments for rare diseases.

Our network of scholars represents hundreds of chances for treatments and cures. We have painstakingly built a portfolio of opportunities and an ecosystem for success, an approach that strengthens our chances at finding treatments and cures. We can only enjoy additional success in the upcoming decade through your financial support. Please help us accelerate promising discoveries into medicines that will impact human health and reduce suffering.

Warmly,

BELIEVERS

MAKING AN IMPACT



Longtime UH Supporters Fund New Treatments for Alzheimer's

Linda and Les Vinney committed \$1.25 million to establish the Linda and Les Vinney Scholar Program in Alzheimer's Disease at Harrington Discovery Institute's Center for Brain Health Medicines, which will support new treatments for patients. The gift also creates the Linda and Les Vinney Acceleration Awards, which will assist the Vinney Scholars with their research.



A Family Builds Community in its Pursuit of a Cure for FBX011

Rusty Cooper, Senior Vice President at Morgan Stanley, and his family have much needed hope to help their 7-year old grandson who lives with an ultra-rare disease caused by a mutation of the FBX011 gene. Through the Oxford-Harrington Rare Disease Centre and Morgan Stanley GIFT Cures powered by Harrington Discovery Institute, they are helping to raise awareness and create a community of families supporting the advancement of novel treatments for rare and ultra-rare diseases.



A Visionary Supports the Future of Medicine and International Collaboration

A \$1 million gift from the late Norman Wain, a pillar in the Cleveland community, helped support Harrington Discovery Institute's entrepreneurial pursuit of drug development collaborations around the world. When the Oxford-Harrington Rare Disease Centre was established in 2019, the gift funded critical start-up needs, including transatlantic travel, to support the successful partnership between the University of Oxford and Harrington Discovery Institute.



500

TREATMENTS EXIST FOR

10,000+

DISEASES



10M

PEOPLE WORLDWIDE ARE LIVING WITH PARKINSON'S DISEASE



12.7M

AMERICANS AGED 65 AND OLDER ARE PROJECTED TO HAVE ALZHEIMER'S DISEASE BY 2050



Only 5%

OF THE 7,000 IDENTIFIED RARE DISEASES HAVE TREATMENTS

RE-ENFORCING A BARRIER TO

PROTECT AGAINST ALZHEIMER'S

FOCUS: Restoration of healthy Wnt signaling to prevent and/or allay Alzheimer's disease.

With more than 50 million people worldwide living with Alzheimer's disease (AD), its tragic results are impacting countless lives. A therapy that halts or slows the progress of this disease is one of humankind's most significant unmet needs.

The blood-brain barrier (BBB) controls what nutrients get into the brain from blood (e.g. glucose that provides energy). With AD, the BBB no longer functions properly, and the brain receives insufficient glucose while allowing blood proteins to penetrate, causing inflammation. Preventing this loss of function could be a valuable therapeutic approach for AD.

"Wnt" are signaling proteins that are important in maintaining a healthy BBB, keeping nerve cells healthy, and promoting the clearance of toxic proteins like tau and amyloid.

Dr. Fish and his team have identified an enzyme at the BBB, called Notum, which prevents Wnt signaling by removing an essential palmitoleate group (fatty acid) from Wnt proteins. "We have found that Notum is increased in mouse models of AD and in post-mortem brain samples from AD patients," Dr. Fish says.

"Thus, we hypothesize that inhibiting the increased Notum will help to restore Wnt signaling, the result being a healthy BBB in AD patients."

Dr. Fish has indeed developed a potential drug that can inhibit Notum. He and his collaborators have reason to believe this drug may even have the potential for use in other conditions such as colorectal cancer. With insights from his Harrington Discovery Institute team, their drug is being rapidly progressed to testing in animal models of AD and safety studies to determine its suitability for treating AD patients.



PAUL FISH, PhD
Professor and Head of Chemistry
Alzheimer's Research UK UCL
Drug Discovery Institute

"An invaluable asset in working with our Harrington team is being able to have critical and supportive peer reviews as we develop this drug."



PAUL WORLEY, MD
Professor of Neuroscience
Johns Hopkins School of Medicine

ENLISTING NEURONS TO

FIGHT ALZHEIMER'S

FOCUS: Preserving NPTX2 and memory in Alzheimer's disease.

Dr. Worley is examining connections between Alzheimer's disease (AD) and the basic biology of memory. There is strong evidence that successful memory requires a sequence of events over many hours mediated by a set of genes that function at synaptic connections between neurons in the brain.

In the AD brain, the expression (transcription of DNA into mRNA and protein translation) of one of these memory genes, NPTX2, which has vital functions such as supporting information processing and preventing excessive excitability, is prominently reduced.

"Patients with AD have much less NPTX2 in their brains compared to healthy individuals," Dr. Worley says. "We are also examining less severe but significant reductions of NPTX2 in normative aging. There are several lines of evidence to suggest that preventing

reduction of NPTX2 can protect neurons, preserve synapses, and prevent memory failure. We don't know why neurons decide to destroy their NPTX2 mRNA, but our therapeutic approach seeks to prevent NPTX2 mRNA degradation."

If rescue of NPTX2 expression can prevent memory failure, it would support the concept that the ongoing memory process, acting in the absence of NPTX2, is a principal driver of AD. Astoundingly, this would mean that the memory process may cause AD, rather than the long-assumed other way around.

With support from Harrington Discovery Institute, Dr. Worley and his team are working to evaluate compounds that markedly increase the ability of neurons to make NPTX2.

"It's more than just their scientific expertise—Harrington has helped us with complicated patent protection issues."

INTRODUCING

HARRINGTON UK RARE DISEASE SCHOLARS

In January 2020, Harrington Discovery Institute and its registered UK charity, Fund for Cures UK, Ltd., issued a call for proposals for the inaugural Harrington UK Rare Disease Scholar Award. Modeled after its US programs, this Award seeks to advance promising research into novel treatments for rare diseases.



CALL FOR PROPOSALS YIELDS NEARLY

50

SUBMISSIONS FROM

18

ACADEMIC INSTITUTIONS

8

DISCOVERIES ADVANCED

5

POTENTIAL TREATMENTS SELECTED

PIETRO FRATTA, MD, PhD
MRC Senior Clinical Fellow
University College London



A MUSCLE-BOUND THERAPY

TO STOP A RARE DISEASE

FOCUS: A muscle-targeted gene therapy for Kennedy's disease, a rare neuromuscular disease.

Kennedy's disease (KD), or Spinal Bulbar Muscular Atrophy, is a rare, slowly progressing adult onset neuromuscular disorder characterized by the degeneration of neurons within the spinal cord and brainstem, accompanied by atrophy of skeletal muscle. Only males are affected, developing progressive weakness and wasting of muscles in arms and legs, as well as in the facial region, resulting in difficulty with swallowing and speech. There are currently no effective treatments.

A genetic disease, KD is caused by an abnormal expansion of DNA in the androgen receptor gene (AR) found on the X chromosome. Studies have shown that silencing the androgen receptor gene in muscles is able to fully rescue the disease. However, this approach may reduce AR in other tissues and organs, inducing significant side effects.

"We are developing a virally-delivered gene therapy approach where the AR gene is silenced only in muscles,"

Dr. Fratta says. "Thus, benefits would be provided to the neuromuscular symptoms while avoiding the threat of side-effects. This method would require just one dosage, which is a godsend for such a long-term condition."

As Dr. Fratta's lab is among the largest KD clinics in the world, they are also working on providing biomarkers and outcome measures that will allow for more effective clinical trials with this disease.

"Our Harrington team is brilliant—and so involved, following the project step by step."

FROM FAILURE TO

POTENTIAL BREAKTHROUGH

FOCUS: Small molecule AhR antagonists for the treatment of Duchenne muscular dystrophy.

Duchenne muscular dystrophy (DMD) is a severe muscle-wasting disorder that primarily affects boys. Muscle weakness usually begins around the age of four, typically in the thighs and pelvis, followed by the arms. It worsens quickly, eventually affecting all muscles. Individuals with this disease don't often reach the age of 30.

DMD is caused by a defect in a particular gene that makes dystrophin, an important protein that acts as a shock absorber in muscles, protecting muscle fibers from damage that would otherwise result from normal contraction and exercise.

Fortunately, there is another protein encoded in one's genome that makes a protein called utrophin, which is similar to the protein that's absent in DMD, dystrophin. Dr. Russell and her team developed a compound, ezutromid, designed to treat DMD by increasing the amount of utrophin in muscle.

"Our clinical trial of ezutromid showed promising results, but wasn't effective over a long period," Dr. Russell says. "But we then sought to understand just how ezutromid works, and found that it binds to and switches off a protein

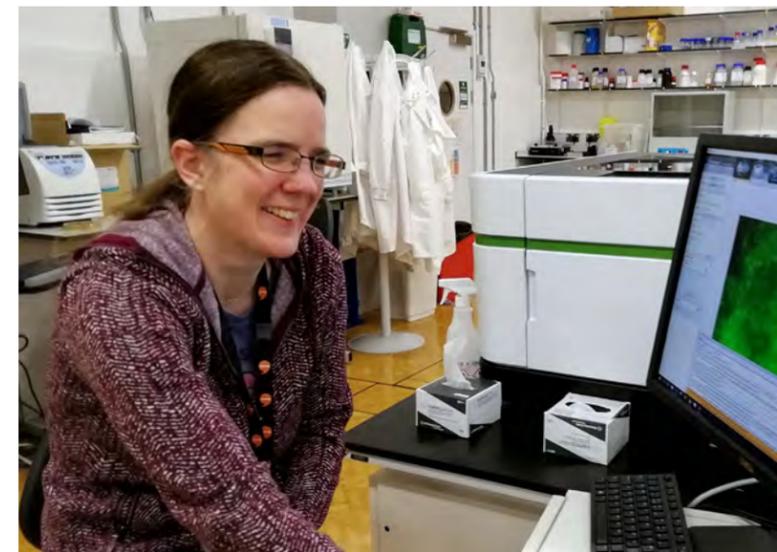
called the arylhydrocarbon receptor (AhR), which leads to more utrophin production."

Since then, Dr. Russell's lab has discovered two new molecules that switch off AhR and increase production of utrophin, both with better efficacy and improved properties compared to ezutromid. She is optimistic that this work will result in a drug candidate for utrophin replacement therapy, which in turn could be applicable to other inflammatory diseases such as cancer and arthritis.



ANGELA RUSSELL, DPhil
Professor of Medicinal Chemistry
University of Oxford

"Our Harrington team has been absolutely wonderful in helping us conduct all the right experiments and make progress toward the clinic."



"There are no rare disease experts in my institute, and so the Harrington rare disease expertise has been invaluable."

HELEN WALLER-EVANS, DPhil
Neuroscience Lecturer,
Medicines Discovery Institute
Cardiff University

70 RARE DISEASES.

ONE POTENTIAL BREAKTHROUGH

FOCUS: Treating lysosomal storage disorders, causes of widespread organ damage.

Lysosomes are organelles containing enzymes that break down many kinds of biomolecules. Lysosomal storage disorders (LSDs) are a group of more than 70 rare genetic diseases caused by defects in lysosomal proteins. Although LSDs have a collective frequency of less than one in 5,000 live births, they are the most common cause of childhood neurodegeneration.

Disease-modifying therapies are available for just 16 LSDs, but even these are not suitable for all patients. LSD therapies in development are mostly gene and enzyme replacement therapies, each targeting just a single one of these disorders.

Dr. Waller-Evans' work takes a different approach, focusing on toxic lysosphingolipids, common to nearly all LSDs. Lysosphingolipids are formed via degradation of accumulated sphingolipids—lipids that play important roles in cell recognition and transduction (when cells convert one signal or stimulus into another).

"Sphingolipids are basically fat with sugars on top," Dr. Waller-Evans says. "Normally these fats get taken into a part of cells called lysosomes, where enzymes chop up these fats, which the cells reuse to build different fats. In LSDs, there may be a defect that negatively affects that chopping process or makes the lysosome less efficient, and so these fats accumulate and are then converted to more toxic lysosphingolipids by the enzyme acid ceramidase (AC)."

It has recently been shown that in one LSD, Krabbe disease, inhibiting AC activity prevented production of lysosphingolipids, which in turn normalized LSD cells. Dr. Waller-Evans and her team have uncovered good reasons to believe that this approach would be effective in at least four other LSDs—and of course, the hope is for efficacy in 66 more.

THE ANSWER TO A RARE KIDNEY DISEASE MAY BE IN THE LIVER

FOCUS: Inhibitors of primary hyperoxaluria, a cause of kidney failure.

Primary hyperoxaluria type 1 (PH1) is a rare kidney disease caused by a genetic defect on the liver enzyme AGXT. Kidney stones are the most common symptom of PH1, although it can also affect the eyes, skin, and heart. The usual treatment for PH1, liver and kidney transplantation and lifelong immunosuppression, is associated with high risk of morbidity and mortality.

This buildup of kidney stones is due to the defective metabolism and consequential accumulation of the molecule glyoxylate. Professor Yue and his team have developed a promising strategy to mitigate this accumulation.

“In the human body, a sort of metabolic conveyor belt is responsible for manufacturing a certain chemical substance from raw materials, through a number of enzyme steps. Each enzyme catalyzes a reaction that transforms a precursor substance (known as the

substrate) to the next substance,” Professor Yue says. “If a certain enzyme becomes defective and less active, slowing down this conveyor belt, the key is to inhibit (slow down) the enzyme that’s before the defect—this is known as substrate reduction.”

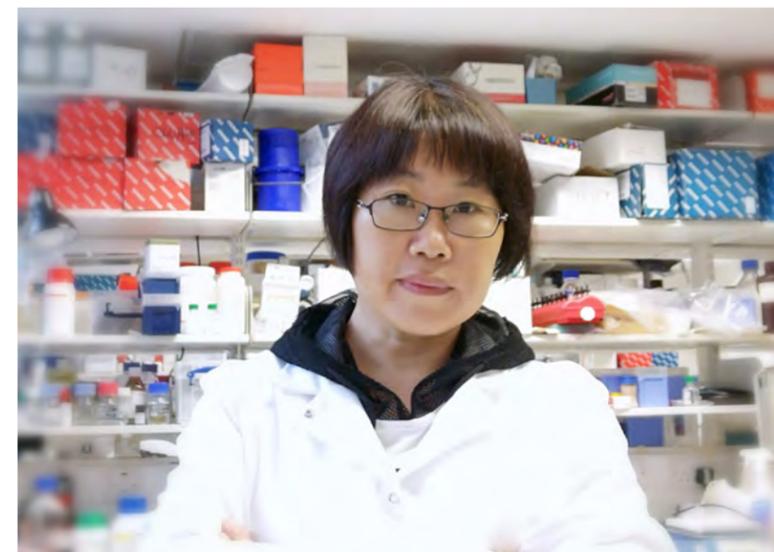
“We were able to pinpoint the enzyme, HAO1, which comes before the defective liver enzyme, AGXT. Inhibiting HAO1 will tune the manufacturing process to be in sync with the less active AGXT enzyme. The hope is that doing so will prevent the accumulation of molecules harmful to kidneys.”

Harrington Discovery Institute is helping Professor Yue and his team to design drugs specifically targeting HAO1, and with the ability to efficiently reach liver cells. The substrate reduction approach has interesting potential for the treatment of many other metabolic disorders.



WYATT YUE, PhD
(Formerly at University of Oxford)
Professor of Structural Biology
Newcastle University

“Adding Harrington’s deep drug development expertise to our experience in protein structure and function makes for a powerful combination.”



HAIYAN ZHOU, MD, PhD
Associate Professor, Genetics
& Genomics Medicine Department
University College London
Great Ormond Street Institute of Child Health

A NEW APPROACH BRINGS A FEELING OF HOPE

FOCUS: Developing novel nucleic acid therapy for a hereditary nerve damage disorder.

Hereditary sensory neuropathy type I (HSN1, also known as HSAN1) is a rare disorder of peripheral nerves that results in severe loss of sensation to temperature, pressure and pain. Symptoms typically begin in the late teens and worsen over time, often leading to painless injuries and mutilating skin ulcerations, at times leading to amputation.

This condition has been reported in residents of the United Kingdom, Europe, Australia, Canada and the United States. Currently, no effective treatment for HSN1 is available.

The disorder is most commonly caused by mutations in the SPTLC1 gene, which provides instructions for making one part of an enzyme involved in making certain fats. This genetic error creates a new metabolite that is toxic to nerves and shouldn’t stay in the body.

Antisense oligonucleotides (ASOs) are short, synthetic, chemically-modified chains of nucleotides (the building blocks of RNA and DNA) that have the potential to target any gene of interest.

Dr. Zhou and her team aim to develop a new therapy for HSN1 by using ASOs to selectively reduce the production of the toxic metabolites. They are testing specifically-designed RNA compounds in cells from HSN1 patients’ skin. If successful, the lead compound(s) will move on to animal models and eventually into humans. Harrington Discovery Institute is helping Dr. Zhou facilitate the preclinical development of these potential therapeutics.

“From the very first meeting I could feel the wonderful, professional and selfless support being provided by my Harrington Therapeutics Development team.”

INTRODUCING

HARRINGTON SCHOLARS FOR CORONAVIRUS

In April 2020, Harrington Discovery Institute launched a major initiative to galvanize its transatlantic network of academic institutions, foundations, and philanthropic partners to respond to the global coronavirus pandemic. By June 2020, it had built one of the world's largest portfolios of breakthrough COVID-19 therapies.



CALL FOR PROPOSALS YIELDS NEARLY

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SUBMISSIONS FROM

122

ACADEMIC INSTITUTIONS IN

3

COUNTRIES

12

POTENTIAL TREATMENTS SELECTED

8

CURRENTLY IN PRE-CLINICAL STAGE AND

4

CURRENTLY IN CLINICAL TRIALS

STOPPING COVID IN ITS TRACKS

FOCUS: Novel vaccine against COVID-19.

Typically, when COVID-19 infections first occur, there is only one or a few virus particles present. This would be the critical point at which to stop the infection before the virus expands exponentially. However, since COVID-19 vaccines are injected into the muscle, they miss the opportunity to generate a robust barrier of protection at the sites of entry—the nose and lungs.

Dr. Barry has hypothesized that intranasal vaccination would provide this needed barrier of protection, and has engineered a new type of vaccine called a single-cycle adenovirus, specifically for intra-nasal immunization.

“Generally, in a vaccine setting, the more protein you can make, the stronger the protection you’ll get,” Dr. Barry says. “The protein that triggers an immune response against COVID-19 is delivered into a cell using a carrier vaccine, or vector. Once it arrives, the vector produces the pathogen protein to generate the immune response

against the threat. Creating a barrier at the earliest steps of an infection makes it much easier to stop a virus than after it amplifies to millions of SARS viruses spreading to the lungs.”

This single-cycle vaccine is engineered to be substantially stronger than other adenovirus vaccines currently being used against COVID, in that it can produce 100 times more proteins for the immune system to detect, therefore provoking significantly stronger immune responses.

By making vaccines more potent, this platform technology could provide patients with greater protective benefit per dose, while enabling manufacturers to stretch vaccine supplies. Further, for the areas of the world experiencing vaccine shortages, this could unlock the potential to use fewer vaccines and inoculate more people.



MICHAEL BARRY, PhD

Director, Vector and Vaccine Engineering Laboratory
Mayo Clinic—Rochester

“Our Harrington team really challenges us, helping us to do smart experiments and think about next steps.”

KATHERINE FITZGERALD, PhD, MRIA
Worcester Foundation for Biomedical
Research Chair III, Professor
University of Massachusetts Medical School



BREAKTHROUGHS

BEHIND THE COVID LINES

FOCUS: Fumarate-based therapeutics for COVID-19 patients to reduce ICU admissions, ventilator use and the overall burden on patient care.

The news cycle has been dominated by coronavirus disease 2019 (COVID-19) case numbers and fatality rates and topics around vaccine distribution and immunization. Meanwhile, far less focus was devoted to the crucial work being done to create drug therapies aimed at addressing the symptoms of the virus.

The inflammatory response to infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) often leads to Acute Respiratory Distress Syndrome (ARDS), a life-threatening injury of the lungs.

Dr. Fitzgerald and her team hypothesized that a drug already FDA-approved, dimethyl fumarate (DMF), can be repurposed to treat severe COVID-19 infections. Known to have anti-inflammatory properties, DMF is used to treat multiple sclerosis and has few side effects.

The body's hyper-inflammatory response to COVID-19 can damage the airways, leading to significant tissue damage in the lungs. Dr. Fitzgerald proposes that DMF would block this phase, thus protecting the lungs from tissue damage.

"We aim to use DMF to target and inactivate Gasdermin D, an inflammatory protein that mediates cell death and the release of inflammatory cytokines (substances secreted by immune system cells) that are known to promote the onset of ARDS in COVID-19," Dr. Fitzgerald says.

The data for DMF look promising—not just in the treatment of COVID-19 and Delta variant patients, but also as a mechanism to dampen the inflammatory response in diseases such as arthritis, cardiovascular disease, and diabetes.

"Harrington's team of experts, clinicians and drug developers have provided invaluable help in our dealings with the FDA."

GETTING COVID PATIENTS OFF VENTILATORS

FOCUS: Novel agent to accelerate ventilator weaning for patients with COVID-19 lung infection.



BENJAMIN GASTON, MD
Billie Lou Wood Professor of Pediatrics
Indiana University

When COVID-19 infections are fatal, it is often due to severe viral pneumonia. For these patients, mechanical ventilation is necessary, and the longer they require mechanical ventilation, the greater the chance that they will experience complications and die.

Unfortunately, the opioids these COVID patients need to suppress pain and anxiety also suppress their respiratory drive. Doctors often have to wake patients in order to get them to breathe off the ventilator, causing further pain and anxiety. In addition, prolonged mechanical ventilation during the pandemic has

resulted in the terrifying dilemma of insufficient numbers of ventilators.

Dr. Gaston and his team have developed molecules that stimulate breathing, which could help patients get off ventilators without requiring that their pain control medicine be stopped.

"Our lead agent, Sudaxine, is a novel respiratory stimulant that bypasses the bad effect of opioids and helps the body sense that it needs to increase breathing," Dr. Gaston says. "We have found that Sudaxine appears to increase nerve signaling, which in turn increases both

the size of, and the number of breaths they take." Sudaxine achieves this by targeting proteins in the brainstem, as well as the respiratory control sensor in the carotid body (a cluster of cells in the neck). These ultimately send signals to the muscles that control respiration.

With support from Harrington Discovery Institute, Dr. Gaston and his team seek FDA approval for an investigational new drug application. If all goes well, the result will be a therapeutic that helps get COVID-19 patients, and other patients with respiratory failure, off of ventilators.

"Our Harrington team has provided invaluable support for our lab work and our translation, as well as with preclinical manufacturing development."



JEFFREY GLENN, MD, PhD
Joseph D. Grant Professor and
Professor of Microbiology and Immunology
Stanford University School of Medicine

“Our Harrington team is very helpful in finding solutions and breaking down barriers that we encounter in the practical aspects of moving our products forward.”

A LAB THAT WAS PREPARED FOR COVID

FOCUS: Single dose antiviral therapeutic for COVID-19.

In 2018, Dr. Jeffrey Glenn was named a Harrington Scholar-Innovator for his work toward developing a single-dose therapeutic to treat all strains of Influenza A virus—an endeavor fueled by Dr. Glenn’s commitment to preventing the first major influenza epidemic since 1918.

Exciting progress was being made, when suddenly another type of virus began spreading across the globe.

Fortunately, perhaps no lab in the world was in a more advantageous position to pivot from its current work to solving the challenges of COVID-19.

The viral genome consists of various stems and loops called the RNA

secondary structure. “Many viruses encode critical regulatory signals in these RNA secondary structures,” Dr. Glenn says. “My thinking was that these structures, which are highly conserved (relatively unchanged through the eons) are clearly very important; if a drug disrupted them, that could inhibit the virus from developing resistance.” Dr. Glenn and his team immediately redirected and modified this groundbreaking approach to influenza toward developing a therapeutic for COVID.

By employing a similar strategy, they identified molecules capable of preventing clinical symptoms in mice when given before or after a SARS-CoV-2 infection. Potentially, this therapeutic could also be used by someone at risk of being exposed to

COVID, and would mitigate the disease for someone already infected.

Importantly, because his molecules target the virus outside of the region used to make COVID vaccines, Dr. Glenn accurately predicted his approach would work equally well on both regular viruses and vaccine-resistant variants.

“Because our approach can be applied to any virus of interest, this work could be important for future pandemics, which as a virologist I can tell you, will occur,” Dr. Glenn says.

A COCKTAIL TO POTENTIALLY SHUT DOWN COVID

FOCUS: Multi-virus therapy for COVID-19 and other pandemic-causing viruses.

COVID-19 is caused by the novel coronavirus SARS-CoV-2, which is an RNA virus. This means that unlike in humans and other mammals, the genetic material for SARS-CoV-2 is encoded in ribonucleic acid (RNA).

The COVID vaccines the world has come to know are mRNA (messenger RNA) vaccines. In effect, these drugs teach our cells how to make a protein, or a piece of a protein, that triggers an immune response inside our bodies. Dr. Khvorova and her team have been working with small interfering RNAs (siRNA), a different RNA drug approach that shows great promise as a therapeutic for COVID.

When siRNAs enter cells, RNA-degrading protein machinery present in cells is redirected to bind to and destroy viral RNA.

Thus a virus can no longer replicate inside cells or infect other cells, effectively treating the disease and preventing further infection.

“Infection of epithelial cells of the two major compartments in the lungs seems to be a main cause of COVID-19 development,” Dr. Khvorova says. “In animal studies, we have seen success in silencing COVID in lung epithelia — so we have potentially found a way to significantly reduce the initial rate of infection of COVID and other pandemic-causing viruses, as well as slow disease progression, and convert severe cases to moderate or mild. Further, since viruses can mutate and escape vaccines or other therapeutic interventions, we have developed ‘cocktails’ of various siRNAs that target different regions of the virus, and so improve the chances of effectively combating multiple strains of the virus.”



ANASTASIA KHVOROVA, PhD
Professor, RNA Therapeutics Institute
University of Massachusetts Medical School

“Harrington provided a great deal of help in exploring various ways of delivering the drug, and formulating our clinical advancement strategy.”

A BREATH OF FRESH AIR IN THE FIGHT AGAINST ARDS

FOCUS: Novel therapy for acute respiratory distress.

Acute respiratory distress syndrome (ARDS) is a lung disease where protein-rich fluids leak into the lung airways, breathing becomes difficult and oxygen cannot get into the body. ARDS is the leading cause of death among patients with severe cases of COVID-19. With no effective therapies for ARDS, there is an urgent need for novel strategies able to improve the clinical outcomes of this disease.

At the interface between the bloodstream and lung tissue, pulmonary endothelial cells play key roles in orchestrating the gas exchange, and in mediating processes

involved in lung homeostasis, many of which are disrupted in ARDS.

After years of research related to the microtubule cytoskeleton (a network of hollow cylinder-like structures in the cytoplasm of living cells), the work of Dr. Komarova and her team resulted in a novel drug candidate, VT-109, which binds to microtubules that regulate the endothelial barrier.

“Our compound seems to tighten the endothelial barrier that separates circulating blood from lung tissue, thus restoring physiological function of the pulmonary

endothelium to support gas exchange in the lung,” Dr. Komarova says. “Our hope is that this discovery will lead to an effective intravenous treatment for COVID-19 respiratory illness.”

Dr. Komarova’s Harrington Discovery Institute advisory team provided feedback on pre-clinical studies, identified potential gaps in the studies, and will help procure interest from pharmaceutical companies. In addition, pre-clinical data shows that VT-109 has the potential to be protective against other causes of ARDS including bacterial pneumonia, endotoxemia, and mechanical ventilation.



YULIA KOMAROVA, PhD
Associate Professor of Pharmacology
The University of Illinois at Chicago

“Conversations with our Harrington team yield important feedback and insights, and they help us stay on track.”



ANNE MOSCONA, MD
Professor of Pediatrics, Physiology & Cellular
Biophysics and Microbiology & Immunology
Columbia University

THINKING OUTSIDE THE ENVELOPE TO PREVENT COVID INFECTIONS

FOCUS: Intranasal agent to block COVID-19 infection.

Long before the pandemic hit, Dr. Moscona had made many discoveries about the mechanisms of action of the proteins in the viral envelope, which in many viruses is the outermost layer of the viral particle. These envelope proteins are responsible for the entry of viruses into the target cell and delivery of viral genes into the cell during infection.

Eventually this research fueled her design, together with her co-investigator Dr. Matteo Porotto, of specific lipopeptides (lipids connected to peptides, short strings of amino acids, the building blocks of proteins)

that prevent viruses including Nipah, measles, and influenza from fusing with a target cell membrane. This membrane fusion is a necessary step for many enveloped viruses, including SARS-CoV-2, to infect cells.

“The process of the viral envelope fusing with the lung cell membrane is mediated by the virus’ spike glycoprotein,” Dr. Moscona says. “For COVID-19, we are developing peptides that will be able to recognize the spike and prevent its protein from adopting the shape necessary for fusion. What makes this antiviral strategy

different from other approaches is that it directly attacks the virus at the earliest stage of getting into a person and starting an infection. Imagine a nasal spray taken once a day, protecting you from COVID.”

Further, Dr. Moscona and Dr. Porotto have tested the efficacy of their lipopeptides against a range of COVID variants, and found that the compound prevented the spike protein of all variants from fusing with the cell membrane—heartening news as variants of COVID continue to be documented.

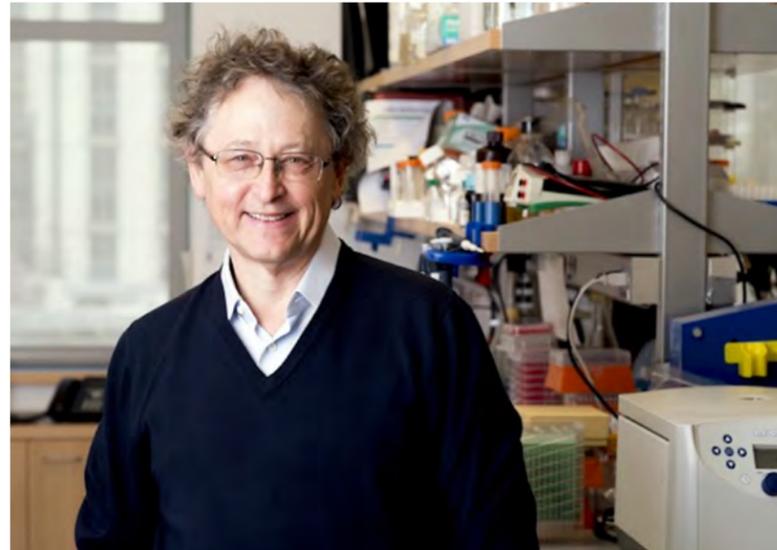
“Our Harrington team has been essential in helping us advance from successful experiments to the steps necessary for making our discoveries a reality.”

MICHEL NUSSENZWEIG, MD, PhD

Investigator, HHMI

Zanvil A. Cohn and Ralph M. Steinman Professor

The Rockefeller University



FIGHTING COVID WITH HUMAN ANTIBODIES

FOCUS: Human antibodies to prevent and treat COVID-19.

Human antibodies are produced by B lymphocyte cells which circulate in our blood. In 2009 Dr. Nussenzweig, working on treatments for HIV-1, invented a method whereby within a blood sample, a bait is used to isolate and capture the B lymphocyte cells making the specific antibodies of interest.

RNA can be made from those cells, then antibodies cloned from that RNA. An antibody's DNA sequence can then be used to produce a protein used for lab tests on a given disease or condition.

The method has also been applied to individuals infected by a series of other pathogens including Zika and Hepatitis B viruses.

Early in 2020 amidst the burgeoning pandemic, Harrington Discovery Institute provided support to Dr. Nussenzweig's lab to apply its novel "capture" method to SARS-CoV-2. "We already knew how to take an antibody from identification, through testing, through production for human use, and on to phase one human trials—we had done all that with HIV

antibodies," Dr. Nussenzweig says.

"For COVID-19, we used the same trick, but with a different bait—a piece of the SARS spike protein—and we were able to clone the antibodies very rapidly. In fact we're done with recruitment for phase two clinical trials, hoping to move on to phase three."

Immediately following a COVID diagnosis, this method would provide a treatment for unvaccinated individuals, as well as the immune-compromised who don't respond to vaccines, such as transplant recipients, cancer patients and others.

"It is very helpful to be able to discuss various aspects of the work with the world-class experts on our Harrington Therapeutics Development team."

A CHANCE TO RENDER COVID LESS HARMFUL

FOCUS: First multipurpose drug to improve lung and heart function in COVID-19 patients.

A major cause of death in COVID-19 patients is the inability to utilize oxygen. This is seen both in the breathing problems (requiring ventilators or oxygen-supportive therapies) and disruptions in blood flow, which compromises oxygen delivery within the body. Both of these aspects of oxygenation are regulated by a class of molecules called S-nitrosothiols (SNOs). During infection, SNOs appear to decrease, so oxygen delivery is reduced and breathing becomes difficult. Dr. Reynolds and his team believe they've found a novel drug, ethyl nitrite (ENO) that can enhance and restore SNO bioactivity.

"In lung diseases, it seems that the level of SNOs goes down, and it takes a while for levels in the lungs and red blood cells to be increased, if at all," Dr. Reynolds says. "Blood flow disruptions from COVID-19 occur throughout the body, leading to kidney and heart injuries. From previous and ongoing clinical trials, we have found that the administration of ENO can increase SNOs, leading to improvements in lung function and oxygen delivery."

With significant assistance from Harrington Discovery Institute, Dr. Reynolds and his

team secured FDA clearance to test ENO in COVID-19 patients who are receiving oxygen support but are not yet on a ventilator. Dr. Reynolds expects to enroll the first series of patients at University Hospitals Cleveland Medical Center. The next step will be to secure additional FDA clearance for testing ENO in COVID-19 patients who are on ventilators.

**JAMES REYNOLDS, PhD**Professor of Anesthesiology
& Perioperative Medicine
Case Western Reserve University
University Hospitals Cleveland

"Our Harrington advisory group provided invaluable insight in helping navigate the FDA approval process for testing new COVID-19 therapies."

JOSEPH VINETZ, MD, FACP, FIDSA, FASTMH, BS
 Professor of Medicine (Infectious Diseases)
 and Anthropology
 Yale University



Photo credit: Robert Lisak

REPURPOSING A DRUG TO **PREVENT COVID DEATHS**

FOCUS: Antiviral clinical effects of camostat mesylate in early COVID-19 outpatients.

ACE2 is a transmembrane protein, found on cells of the upper and lower respiratory tract, heart and vasculature, kidneys, and gastrointestinal tract. As the receptor for the SARS-CoV-2 virus, the pandemic has put ACE2 at the center of research being conducted by many Harrington Scholars and in laboratories around the world.

SARS-CoV-2 exploits the ACE2 to access and infect human cells. First, a protein on the viral surface, called the spike, attaches to the ACE2. Then another human protein, TMPRSS2, cleaves the spike protein, allowing the virus to fuse with the cell and begin to replicate inside it.

TMPRSS2 is a serine protease—an enzyme that cleaves peptide bonds in proteins. It so happens that camostat mesylate, a drug which for decades has been licensed to treat pancreatitis in Japan and South Korea, is a potent serine protease inhibitor. Dr. Vinetz believes camostat mesylate may be effective in lowering the amount of SARS-CoV-2 carried by virus patients, thus lessening the seriousness of their disease and helping to prevent its spread.

Dr. Vinetz has completed a phase II clinical trial of camostat mesylate, and with support from Harrington Discovery Institute, his work

is progressing toward a Phase III trial, where safety and efficacy of the treatment will be studied.

“Our research has shown exciting potential for the use of camostat mesylate for the treatment of COVID-19,” Dr. Vinetz says. “Our work has also revealed potential pathways for re-purposing antivirals or developing new antivirals for other respiratory viral diseases.”

“Our Harrington team has stimulated deep, rigorous and invaluable thinking about the development of our drug.”

LAYING A TRAP **FOR COVID**

FOCUS: Novel multi-target antibodies for COVID-19 infection.

In the race to address COVID-19, Dr. James Wells and his team have come up with two exciting and novel therapeutic strategies for those who have recently realized they contracted COVID, have symptoms, and are in a high-risk group.

The angiotensin-converting enzyme 2, or “ACE2 receptor”, is a protein on the surface of many cell types. The virus uses its spike proteins (the protruding bumps seen in coronavirus imagery) to bind to an ACE2 protein on the victim’s cell, thus gaining entry.

Dr. Wells’ team created a soluble, genetically-rearranged form of the ACE2 receptor itself, and used it as a decoy to block viral entry. “The virus knows how to bind to ACE2, but it can’t distinguish between

the actual ACE2 and the manufactured version,” Dr. Wells says. “Thus the virus becomes coated with this ACE2 receptor ‘trap’, preventing it from entering the cell.”

In addition, the Wells Lab made another advancement that helps prevent the virus from entering cells. The virus attaches to the ACE2 receptor thanks to an adhesive quality called affinity. Dr. Wells and his team increased that affinity by mutating the ACE2 trap, engineering it so that the virus binds more tightly to the trap.

Either of these approaches could lead to an injectable biologic able to block the COVID virus from entering, let alone infecting, human cells.



JAMES WELLS, PhD
 Professor, Pharmaceutical Chemistry
 Chair, Pharmaceutical Chemistry
 University of California, San Francisco

“Harrington has been great at always helping us determine the best next step in our drug discovery process.”



JAMES WILSON, MD, PhD
Director, Gene Therapy Program
Rose H. Weiss Professor and Director
Orphan Disease Center
Professor of Medicine and Pediatrics,
Department of Medicine
Perelman School of Medicine at
University of Pennsylvania

PROGRAMMING CELLS TO
PROTECT AGAINST COVID

FOCUS: A novel intranasal vaccine alternative for COVID-19 treatment.

An adeno-associated viral (AAV) vector is a virus engineered to safely deliver DNA to specific target cells. Long before the COVID-19 pandemic, Dr. Wilson’s lab had spent years researching how AAV could be effective against respiratory viruses. During the fateful month of February 2020, it was proposed that Dr. Wilson pivot this work toward a therapy for COVID.

Unlike current vaccines in use, which use a portion of the given virus to immunize patients, Dr. Wilson’s approach begins directly with the given antibody—actually, a cloned characterized protein/antibody—which he can isolate and study until there is confidence it will be effective against the virus. This antibody is then incorporated into the gene for that particular antibody—not to elicit an immune response, but to program a person’s own cells to express the antibody.

“A person doesn’t even need an immune system for this method to work,” Dr. Wilson says. “Because we’ve already isolated the antibody through other work, and we’re asking non-immune cells to express the antibody—cells in the nose and mucosa, since that’s where COVID is transmitted. This can be done via an aerosol spray into the nose, where the cells lining the passages take the gene up and express it. That way, when the virus comes in, it’s blocked.”

As there are reasons to believe that variants of SARS-CoV-2 will continue to emerge and threaten the efficacy of first-generation vaccine and monoclonal antibody therapeutics, Dr. Wilson’s strategy could be an invaluable tool against any flu, and serve as a crucial pandemic countermeasure in coming years.

*“Our Harrington team is comprised of incredible advisors—
first-rate pharma folks who solely have our success in mind.”*

INVESTING IN OUR FUTURE

EXPERTISE LEADING US INTO THE FUTURE



DIANA R. WETMORE, PhD
Vice President
Therapeutics Development
Harrington Discovery Institute

Seeing a new drug through from discovery to availability is a long process that requires a large amount of funding. Even more importantly, however, it requires expertise—and providing that expertise is the role of the Therapeutics Development Center.

The Therapeutics Development Center (TDC) comprises 30-plus advisors who have spent their careers in drug discovery. They provide the know-how that a pharmaceutical company would bring to a new technology and, together with Harrington's project managers, create a "virtual Pharma" drug development team around Harrington's Scholars.

The drug development path is complicated and requires some very specific areas of expertise. For example, an advisor for toxicology studies and preclinical animal

"The Therapeutics Development Center brings Pharma know-how to the scholar in a very hands-on way."

studies will typically have a Doctorate in Veterinary Medicine (DVM) as well as a PhD and many years of experience conducting such studies in a broad range of therapeutic areas.

Once a novel new chemical entity has been selected as a drug candidate, kilos of it need to be manufactured—and the kilos need to be the same level of purity every single time to the satisfaction of the FDA. That calls for chemists who specialize in designing and streamlining the manufacturing process. Oftentimes they will devise a different synthetic pathway to manufacture the same molecule at kilo scale compared to the original synthetic route that was used in the early stages of discovery.

Other chemists specialize in formulation. The active agent must be combined with other ingredients to make it stable so that it has a reasonable shelf life, or to make it compressible into a pill form, or soluble enough to be given with an inhaler. TDC expertise also includes pharmacometrics, which is the use of mathematical formulae to evaluate experimental data for anticipating how much of the active drug is going to get into the tissues of interest in the body. If the drug is taken as a pill, will enough of it get to the cells that need it to address the source of the illness?

Harrington also provides its scholars with guidance from regulatory affairs specialists. These experts know the FDA rules and regulations inside and out, so when the inventor of a new technology makes an application to start testing a new therapy in humans, he or she is prepared to have a productive conversation that will lead to the FDA giving them the go ahead for human studies. Once human studies are under way, the toxicology specialist helps the clinical team interpret the results. And there are other specialists and experts involved along the way.

"Our project managers work directly with our experts to help us efficiently determine what expertise our scholars need. The TDC essentially becomes part of the scholar's extended team, all of us working to advance these breakthrough technologies towards clinical studies," said Dr. Wetmore, Vice President of Therapeutics Development.

"Over the years we have built our drug development capabilities to bring expertise to our scholars as quickly and efficiently as possible," Dr. Wetmore adds. "Even so, the COVID-19 pandemic changed the landscape and led to the launch of our COVID-19 Rapid Response Initiative. Through this program we provide grant funding and expert drug development support to advance

next-generation vaccines and vaccine alternatives."

Although Harrington has had antibacterial and anti-infective programs from day one, it was often very difficult to find commercial investors for them. The pandemic, however, led to a dramatic industry-wide change in focus for new drug discovery and a renewed interest in developing anti-infectives. In addition, the FDA prioritized processing applications for COVID-related therapies, which contributed to a fast path to the clinic.

"We're seeing the coronavirus projects get into clinical studies while they're still active in our grant program, and we are expanding our expertise to include more depth on regulatory affairs, clinical planning, clinical trial design, and clinical trial management," Dr. Wetmore says.

This past year also saw the selection of the first class of five inaugural Harrington UK Rare Disease Scholars representing four top academic institutions in the UK. Much like the COVID pandemic, these UK-based rare disease projects have created the need for additional new capabilities from the TDC team.

Providing the best advisors in the world to guide scholars is a winning formula, and as Harrington Discovery Institute moves into the future, the TDC eagerly looks forward to the constantly evolving role it will play in the decades to come.

Q AND A

PARTNERING WITH ACADEMIA

We spoke with Patrick E. Reed from Louisiana State University Health Sciences Center (LSU Health) in New Orleans, an institution that provides sophisticated infrastructure for scientific investigation undertaken by its faculty and learners. Edward Graczyk, PhD, associate professor of genetics at LSU Health, was awarded a Harrington Rare Disease Scholar Award in 2018 to further his research into Friedreich's ataxia (FA).

HOW IS THE HARRINGTON GRANT HELPING OVERCOME SPECIFIC CHALLENGES?

In addition to the financial support, the team at Harrington Discovery Institute has deep expertise in the translation and commercialization of innovative research. Their guidance and network of potential licensees was invaluable in getting LSU Health's technology closer to the market for public benefit.

CAN YOU DESCRIBE YOUR EXPERIENCE WORKING WITH THE HARRINGTON TEAM?

Their commercialization team was instrumental in helping us navigate interest received from potential industry partners. Their support and assistance helped LSU Health's Office of Innovation & Partnerships make sound commercialization decisions and, hopefully, create a long-lasting relationship with an industry partner.



PATRICK E. REED, RTTP
Assistant Vice Chancellor, Innovation & Partnerships
LSU Health New Orleans

WHAT ARE THE BENEFITS OF RECEIVING A HARRINGTON GRANT AWARD?

It enabled Dr. Graczyk's research both by direct support and by leveraging the expertise of his small lab by arranging contract research that complemented their work. That, along with the input by members of Harrington's therapeutic development team, really helped move the project forward.

HOW DO YOU MEASURE THE VALUE OF A HARRINGTON GRANT?

The value is multiplied far above the nominal dollar amount. A therapy that saves lives will be of incalculable value to the patients suffering from FA.

IS THERE ANYTHING ELSE YOU WOULD LIKE TO ADD?

Harrington Discovery Institute is visionary in their treatment of intellectual property created under their grants. Not burdening new industry partners with ownership issues made this a pleasant and fruitful experience that will likely advance therapeutic options for patients suffering with rare DNA repeat expansion disorders.



FOR MORE INFORMATION:
HarringtonDiscovery.org/TDC

JESSE TREU, PhD
Partner Emeritus
Domain Associates



POSITIONING HARRINGTON DISCOVERY INSTITUTE FOR THE FUTURE

The Investment Advisory Board (IAB) helps Harrington Discovery Institute succeed in its dual quest of moving promising therapeutics from bench to bedside, while also securing resources to fund new discoveries in the future. The IAB draws on its decades of industry knowledge and venture funding experience to advise Harrington Discovery Institute's leadership on investment decisions following initial grant award funding.

"Harrington occupies a very unique and exciting space," said IAB member Jesse Treu, PhD, Partner Emeritus of Domain, an international venture capital firm focused on life sciences that has been involved in the formation of more than 220 companies.

"By making investments in the projects they've backed with grants, the projects get critical support and some of the benefit

can also flow back to Harrington to keep it operating in an evergreen fashion."

Treu, who was drawn to Harrington Discovery Institute by his longstanding friendship with President Jonathan Stamler, MD, and IAB Chairman John Rice, PhD, said the definition of a successful project has changed during his seven years on the IAB.

"In the beginning, the definition of success was any kind of a deal around an asset," he explained. "For example, if an asset that Harrington supported was licensed to a drug company, that was considered a successful project. As Harrington moved on to the idea that it was in effect investing in its own future, it became apparent that we needed to strike a balance between simply 'moving the ball down the field' and incorporating the kinds of criteria that a venture capital fund would use to due diligence an investment. Success is

now also assessed by an investment's ability to deliver returns for Harrington's mission."

This has led to an evolution for the IAB, Treu noted, as it constantly balances the demands of venture capital and grant-making—while always considering the impact of the research on human health. The real challenge, he said, will be to maintain Harrington's unique appetite for promising early-stage discoveries while also supporting projects closer to the clinic.

"The integration of the charitable grant process and an investment process takes some finesse," Treu said. "There are going to be projects that are clearly good investment opportunities, and others that may be less likely to make money but that are obviously very important to patients and society. The IAB's role is to successfully analyze and navigate the spaces in-between."

"In the beginning, the definition of success was any kind of deal around an asset... Success is now also assessed by an investment's ability to deliver returns for Harrington's mission."

HARRINGTON INVESTMENT ADVISORY BOARD



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FOR MORE INFORMATION:
HarringtonDiscovery.org/IAB



HARRINGTON INVESTMENT ADVANCES ALZHEIMER'S TREATMENTS

Stephen Strittmatter, MD, PhD, a physician-scientist at Yale University and one of the nation's preeminent Alzheimer's disease researchers, was named a 2020 Harrington Scholar-Innovator for his research into a novel therapy that could lead to a first-in-class disease-modifying therapy for Alzheimer's. Exciting opportunities identified from that relationship led the Harrington Discovery Institute to support Dr. Strittmatter's work by making an equity investment in Allyx Therapeutics, a clinical-stage biotechnology company co-founded by Dr. Strittmatter.

Much of Alzheimer's disease research to date has focused on reducing the accumulation of beta-amyloid plaques in the brain, but amyloid-lowering attempts have either failed or had minimal effects in numerous clinical trials over several decades. Dr. Strittmatter's laboratory took a unique approach focusing on how amyloid, tau and inflammation synergize to cause synapse loss, and hence neural network failure, in Alzheimer's brains. Rather than

clearing out the multiple damaging factors, the approach targets synapses to protect them from these otherwise toxic influences. Moreover, Dr. Strittmatter's research at Yale and Allyx offers three different therapeutic approaches to target a common pathway of disease progression: a large molecule, or 'polymer', a small molecule, and an antibody (see sidebar).

Harrington's impact investment in Allyx has the potential to be significant. In the US, more than six million people are living with the debilitating effects of Alzheimer's disease; by 2050, that number is projected to rise to nearly 13 million.

"The goal of our research is to protect, preserve, and even restore neurons in Alzheimer's and other related neurodegenerative diseases," Dr. Strittmatter said. "And our approach is not relegated to one subset of patients. If we're successful, our therapies may be broadly applicable to the millions of people in the world suffering from Alzheimer's."

BUILDING A RELATIONSHIP

When Dr. Strittmatter began his two-year term as a Harrington Scholar-Innovator, he was assigned a team from the Therapeutics Development Center (TDC) for his polymer project. The team consisted of drug development advisors and a dedicated project manager. Lead advisor William Murray, PhD, a veteran drug development professional (including as former Head of Chemistry, Johnson & Johnson Pharmaceutical R&D) and Senior Project Manager Michael Hallen were excited by Dr. Strittmatter's technology. (See page 25).

"In Harrington it's our job to recognize true innovation and help the investigator develop it so that it attracts interest from pharma partners or the venture community," Dr. Murray said. "Unusual modalities can often be dismissed by risk-averse investors. We help provide the strategy to overcome those issues."

As the TDC team worked collaboratively with Dr. Strittmatter, a strong working relationship

DR. STRITTMATTER'S CORE TEAM



MICHAEL HALLEN, MS
Senior Project Manager



WILLIAM MURRAY, PhD
Lead Advisor, Therapeutics Development Center



LENKA FEDORKOVA, PhD
Vice President, Business Development and Strategic Alliance Management

was formed. With the collective goal of moving the polymer project towards clinical trials, TDC advisors proposed—among other recommended steps—an administration pathway where it could be demonstrated that the activity in the brain was indeed due to the action of the polymer.

"We know from experience what factors are likely to lead to success, and the stars really aligned with Dr. Strittmatter," Hallen said. "Not only is he a leading investigator with a breakthrough discovery, he viewed the Harrington team as a partner and was very receptive to the direction provided."

As the project progressed, Hallen and Murray brought in business development support to assist with commercialization of the polymer. When Dr. Strittmatter suggested Harrington Discovery Institute participate in a Series A funding round for the two other Alzheimer's therapies under control of Allyx Therapeutics, Harrington's business development team supported the idea. After all, Allyx would be an ideal home for Dr. Strittmatter's new third drug.

TRUST LEADS TO OPPORTUNITY

Lenka Fedorkova, PhD, Vice President of Business Development and Strategic Alliance Management at Harrington Discovery Institute, oversaw the investment in Allyx. "In addition to Dr. Strittmatter's practicality and focus, Allyx has an experienced management team and brought together a quality syndicate of investors. Alzheimer's patients today do not have effective treatment options, and if successful in the clinic, Allyx's therapies could really move the needle in tackling neurodegeneration," Fedorkova said.

Dr. Fedorkova added that the "trust factor" that exists between Harrington Discovery Institute and its Scholars helped create the opportunity for Harrington's investment in Allyx. "Our reputation carries a lot of weight with our external relationships," she said. "Researchers and investors alike welcome our participation and value our drug development expertise and business support. This helps propel our relationships into new areas of opportunity."



"From our first discussions with Harrington Discovery Institute, we have appreciated that the Harrington team is driven by science and innovation first. As Allyx Therapeutics develops novel treatments to protect neuronal synapses and memory in Alzheimer's disease, they are an ideal thought and financial partner."

STEPHEN BLOCH, MD, CEO, ALLYX THERAPEUTICS

"Sharing a common goal and collaborating with the highly experienced team at Harrington has been a joy. They have been very helpful in bringing us closer to our goal to develop first-in-class therapies for synapse protection to slow or stop the progression of Alzheimer's disease."

STEPHEN STRITTMATTER, MD, PhD, SCIENTIFIC FOUNDER, ALLYX THERAPEUTICS

THREE PROMISING APPROACHES. ONE GOAL.

In Alzheimer's and other neurodegenerative diseases, misfolded protein aggregates, such as beta-amyloid, interact with other proteins in the brain—cellular prion protein (PrPC) and metabotropic glutamate receptor 5 (mGluR5)—to damage synapses and destroy the functional connections between neurons. Attempts to lower beta-amyloid levels have met with at best limited success, therefore Dr. Strittmatter's research seeks to preserve synapses and neural networks no matter how much beta-amyloid or other misfolded proteins pile up in the brain.

Dr. Strittmatter's research offers three different approaches to targeting a common possible pathway of disease progression.

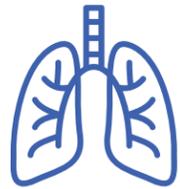
Harrington Scholar-Innovator Award

- The research supported by Harrington Discovery Institute's Scholar-Innovator Award has led to the creation of a polymer that modulates PrPC. It is currently being tested in mice. (See page 25).

Allyx Therapeutics

- Harrington's investment in Allyx Therapeutics is helping advance ALX-001, a first-in-class small-molecule silent allosteric modulator of mGluR5. The investigational new drug is currently in phase I clinical trials. The small molecule is licensed from Yale and Bristol Myers Squibb to Allyx Therapeutics.

- Allyx Therapeutics' portfolio also includes Dr. Strittmatter's work on an antibody to PrPC. The antibody targets the same PrPC protein as the polymer, but attaches to PrPC in a different way. Allyx is advancing the preclinical development of this antibody via non-dilutive grant funding from the NIH's SBIR program.



LIVING AND BREATHING THERAPEUTIC ADVANCES

Physician-scientists who are awarded a Harrington Scholar-Innovator Award benefit from a two-year term of financial, drug development, project management and business development support. But Harrington's impact does not end there. Scholars working on promising therapeutics gain access to Harrington Discovery Institute's mission-aligned partners—through The Harrington Project for Discovery & Development—to ensure that their programs have the greatest potential to advance into the clinic.

The first of such partners is BioMotiv. Harrington Discovery Institute uses its philanthropic funding and drug development expertise to refine a Scholar's aims and work plan so that the technology progresses to a stage where BioMotiv can help further de-risk the discoveries into medicines that improve the current standard of care for particular diseases.

An excellent example of this model is the work being done by Allinaire Therapeutics LLC (Allinaire) as it pursues a novel biologic approach to treating pulmonary arterial hypertension (PAH). PAH has a three-year mortality rate of greater than 50%, even with the several classes of pulmonary vasodilator treatments, often used in combination, that are the current standard of care.

Irina Petrache, MD, Chief of Pulmonary, Critical Care, and Sleep Medicine, National Jewish Health, became a Harrington Scholar-Innovator in 2014 when she was at Indiana University for her work on a treatment for chronic obstructive pulmonary disease (COPD) focusing on the pulmonary vasculature.

Working with colleagues at Indiana University, Dr. Petrache provided evidence that a protein in the body, endothelial-monocyte activating

polypeptide II (EMAP II), causes inflammation, small airways damage, and apoptosis of the lung endothelial cells—events that are pathological features of COPD. Dr. Petrache and her colleagues, including Matthias Claus, PhD, patented EMAP II as a target in COPD and formed a company, Emphymab LLC.

As a Harrington scholar, Dr. Petrache's work was brought to the attention of BioMotiv. Upon learning of Dr. Petrache's work and Harrington's support of it, and after extensive due diligence, BioMotiv recommended investment in this exciting discovery in 2016, and obtained an exclusive license from Indiana University. At this time Allinaire was formed by BioMotiv to progress the technology and has worked with Dr. Petrache and her colleagues since then.

Douglas Hay, PhD, working with BioMotiv, was part of the team that performed the due diligence on Emphymab. According to Hay,

“We are grateful to Harrington Discovery Institute and BioMotiv for their support. Without it we wouldn't have been able to get this far.”

IRINA PETRACHE, MD

Dr. Petrache's Scholar-Innovator grant played an important role in BioMotiv's decision to invest in the technology.

“We would not have known about the work being done by Dr. Petrache if it hadn't been for the relationship between Harrington and BioMotiv,” said Hay, who today is Allinaire's CEO and CSO. “And we probably would not have taken the project directly from the founders, because that would have entailed a much higher risk. So the grant was really key for us, and it led us to a project with outstanding science and researchers, and the possibility of discovering a first-in-class disease-modifying biologic, an anti-EMAP II mAb, for cardiopulmonary diseases.”

BioMotiv's support continued as the focus of Allinaire's research shifted from COPD to pulmonary arterial hypertension (PAH). Allinaire is now targeting PAH as the first clinical indication, based upon the strong target validation data, and massive unmet medical need for novel treatments that are non-pulmonary vasodilators, and will slow disease-progression. There is also the potential to expand to other cardiopulmonary diseases, such as COPD and viral-induced acute lung injury, for which there are supportive preclinical data.

“Even though we are still in the preclinical stage, there is a strong level of input and interest from various industry partners, including large pharma,” said Satish Jindal, PhD, CEO of BioMotiv, and Chair, Allinaire. “This is one option among many options to advance the project in the clinic.”

“We discovered that the cytokines that are increased in COPD are also increased in PAH, and that gave us a more specific target that we believe will be easier to push forward with than a heterogeneous disease such as COPD,” Dr. Petrache added. “We have a clear pathway of moving the target forward, and we are grateful to Harrington Discovery Institute and BioMotiv for their support. Without it we wouldn't have been able to get this far.”

Allinaire has developed about 20 humanized anti-EMAP II mAbs. The next step is lead optimization, and biological and developability characterization of the new mAbs, ultimately leading to the selection of a clinical development candidate. The company hopes to complete that work in late 2023, then move on to manufacturing and safety testing of the selected antibody.



COMPANY UPDATE

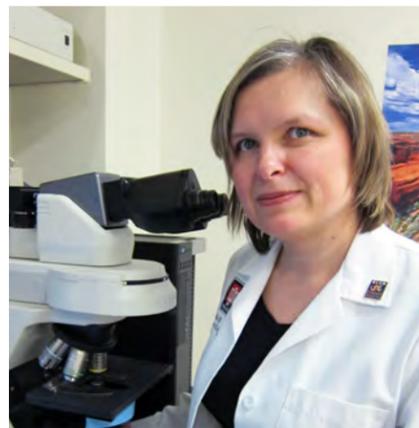
Parma, Italy and Cleveland, OH, USA
May 2nd, 2022

Chiesi Farmaceutici S.p.A. (Chiesi Group), the international research-focused pharmaceutical and healthcare group, announced it has entered into an agreement with Allinaire Therapeutic, LLC, a company founded by BioMotiv, to acquire the world-wide rights to a portfolio of therapeutic monoclonal antibodies (mAbs) against endothelial monocyte-activating polypeptide II (EMAP II) for the potential treatment of PAH.

Harrington Discovery Institute catalyzed project success with initial grant funding and therapeutic development services to one of the scientific founders, Irina Petrache, MD (Harrington-Scholar Class of 2014) and colleagues at Indiana University and National Jewish Health, together with early seed stage and follow on investments in the company.



SATISH JINDAL, PhD
CEO, BioMotiv
Chairman, Allinaire



IRINA PETRACHE, MD
Scientific Co-Founder, Allinaire
2014 Harrington Scholar-Innovator



DOUGLAS HAY, PhD
CEO and CSO, Allinaire



2021 SCIENTIFIC SYMPOSIUM



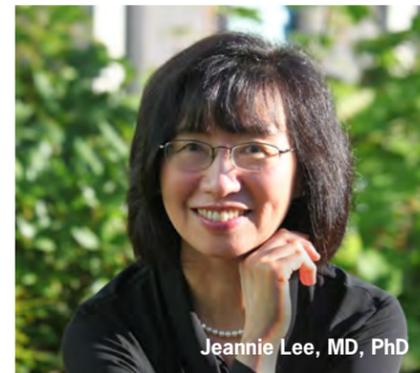
Jonathan S. Stamler, MD



Ronald G. Harrington



Mukesh K. Jain, MD



Jeannie Lee, MD, PhD



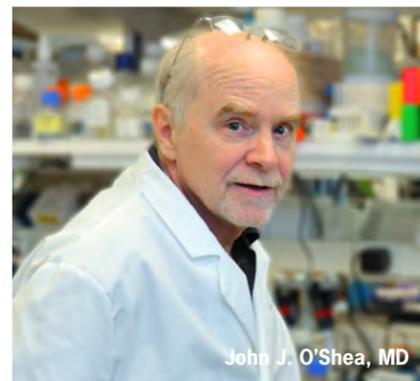
Justin Ichida, PhD



Sir John Bell



Stuart H. Orkin, MD



John J. O'Shea, MD



Warren J. Leonard, MD

A SYMPOSIUM RE-IMAGINED

The 8th Annual Harrington Scientific Symposium was held virtually with speakers and audience members from the US, UK, Japan, Canada, Greece, and Switzerland tuning in May 26-27, 2021. More than 200 attendees participated in the two-day online event.

“In 2020 we gained critical clarity around who we are and what we are called to do. We have pioneered new models for biomedical innovation and for impact investing. We developed a track record of innovation that is vital in contemporary academic medicine and in serving patient needs. And finally, we have helped change the drug discovery culture in medicine,” said **Jonathan S. Stamler, MD**, President, Harrington Discovery Institute, during the Symposium’s opening remarks.

Harrington Discovery Institute Chief Scientific Officer **Mukesh K. Jain, MD**, served as emcee for the event, introducing speakers and presenting a new addition to the Symposium of recorded Scholar updates.

Harrington Project founder **Ronald G. Harrington** welcomed attendees to the Symposium and reflected on the three key areas of Harrington Discovery Institute—partners, progress and culture. He shared his thoughts on the importance of innovation and entrepreneurship and how culture helps drive the institute’s focus on enhancing and saving lives.

Other speakers included global leaders in science, medicine and academia.

Sir John Bell, Regius Professor of Medicine at the University of Oxford, delivered the Keynote Address, Creating New Opportunities for Biomedical Innovation: The Oxford-Harrington Alliance.

Stuart H. Orkin, MD, Harvard Medical School, presented his breakthrough discoveries in red blood cells that offer new treatments for patients with sickle cell disease and beta-thalassemia, for which he was awarded the 2020 Harrington Prize for Innovation in Medicine. **Warren J. Leonard, MD, NHLBI**, and **John J. O’Shea, MD, NIAMS, NIH**, gave the 2021 Harrington Prize Lecture, which was awarded to the co-recipients for their respective contributions to the field of immunology, from fundamental discovery to therapeutic impact.

The audience heard from two Harrington Scholars on their experiences within a Harrington program. **Jeannie Lee, MD, PhD, Massachusetts General Hospital** shared her work on the treatment of the rare disease Rett Syndrome, and the collaboration with her Harrington Therapeutics Development advisors. **Justin Ichida, PhD, University of Southern California** presented exciting advances in the pursuit of a new therapeutic for ALS patients.

Harrington Scholars from the Scholar-Innovator, ADDF-Harrington and Gund-Harrington programs presented their projects in a closed session. Members of Harrington’s Scientific Advisory Board, **William G. Kaelin, Jr., MD, Barbara B. Kahn, MD, Andrew Marks, MD**, and **Michael Welsh, MD**, participated in panels where they provided feedback and posed questions to the scholars on their work. Therapeutics Development Center Advisors **Jim Bryson, PhD, Larry Olanoff, MD, PhD, Jan Rosenbaum, PhD**, and **George Trainor, PhD**, also served on the panels and addressed commercial aspects of the scholar projects.

“This was one of the best virtual conferences I’ve attended.”

SCOTT OAKES, MD

Professor of Pathology,
Vice Chair Of Research & Academic Affairs
University Of Chicago
2013 Harrington Scholar-Innovator

Thank you!

TO OUR 2021
PANEL MEMBERS

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William G. Kaelin, Jr., MD
Barbara B. Kahn, MD
Andrew Marks, MD
Michael Welsh, MD

THERAPEUTICS DEVELOPMENT CENTER

Jim Bryson, PhD
Larry Olanoff, MD, PhD
Jan Rosenbaum, PhD
George Trainor, PhD

SAVE THE DATES:

 **MAY 24-25, 2023**
MAY 22-23, 2024

 FOR MORE INFORMATION:
HarringtonDiscovery.org/Events

2021 HARRINGTON UK RARE DISEASE SCHOLARS

PIETRO FRATTA, MD, PhD
University College London

ANGELA RUSSELL, DPhil
University of Oxford

HELEN WALLER-EVANS, DPhil
Cardiff University

WYATT YUE, PhD
*University of Oxford

HAIYAN ZHOU, MD, PhD
University College London

2020 HARRINGTON SCHOLARS FOR CORONAVIRUS

MICHAEL BARRY, PhD
Mayo Clinic

KATHERINE FITZGERALD, PhD
University of Massachusetts

BENJAMIN GASTON, MD
Indiana University

JEFFREY S. GLENN, MD, PhD
Stanford University

ANASTASIA KHVOROVA, PhD
University of Massachusetts

YULIA KOMAROVA, PhD
University of Illinois

ANNE MOSCONA, MD
Columbia University

MICHEL NUSSENZWEIG, MD, PhD
The Rockefeller University

JAMES REYNOLDS, PhD
University Hospitals of Cleveland/
Case Western Reserve University

JOSEPH VINETZ, MD
Yale University

JAMES WELLS, PhD
University of California,
San Francisco

JAMES WILSON, MD, PhD
University of Pennsylvania

2021 HARRINGTON-MSTP SCHOLAR

DEREK WONG
Case Western Reserve University

2020 HARRINGTON-MSTP SCHOLAR

YI FAN CHEN
Case Western Reserve University

2022 HARRINGTON SCHOLAR-INNOVATORS

BURTON DICKEY, MD
MD Anderson Cancer Center

DIANA FARMER, MD
University of California, Davis

JAMES HAGOOD, MD
University of North Carolina
at Chapel Hill

LI LAN, MD, PhD
Massachusetts General Hospital

CAROLYN LEE, MD, PhD
Stanford University

MICHAEL LIN, MD, PhD
Stanford University

FRANCIS MCCORMACK, MD
University of Cincinnati

DAVID MYUNG, MD, PhD,
Stanford University

BERND SCHNABL, MD
University of California, San Diego

LOREN WALENSKY, MD, PhD
Dana-Farber Cancer Institute

HANS-GUIDO WENDEL, MD
Memorial Sloan Kettering
Cancer Center

2021 HARRINGTON SCHOLAR-INNOVATORS

JENNIFER CHEN, MD
University of California,
San Francisco

JOHN CHORBA, MD
University of California,
San Francisco

JOSEPH CONTESSA, MD, PhD
Yale University

TOREN FINKEL, MD, PhD
University of Pittsburgh

MARIA GRAZIA RONCAROLO, MD
Stanford University

AARON SCHIMMER, MD
University of Toronto

JILL SMITH, MD
Georgetown University

XINNAN WANG, MD, PhD
Stanford University

2020 HARRINGTON SCHOLAR-INNOVATORS

RIZWAN HAQ, MD, PhD
Dana-Farber Cancer Institute

MICHAEL HOLTZMAN, MD
Washington University

KYU RHEE, MD, PhD
Weill Cornell Medicine

STEPHEN STRITTMATTER, MD, PhD
Yale University

DONALD WEAVER, MD, PhD, FRCPC, FCAHS
University Health Network

TIMOTHY YU, MD, PhD
Boston Children's Hospital

2019 HARRINGTON SCHOLAR-INNOVATORS

ROBERT E. ANDERSON, MD, PhD
University of Oklahoma

ROSA BACCHETTA, MD
Stanford University

GERALD W. DORN, II, MD
Washington University

JOACHIM HERZ, MD
UT Southwestern

PAUL W. HRUZ, MD, PhD
Washington University

PENG JI, MD, PhD
Northwestern University

V. VINOD MOOTHA, MD
UT Southwestern

DAWN M. WETZEL, MD, PhD
UT Southwestern

T.C. WU, MD, PhD
Johns Hopkins University

ELLEN YEHL, MD, PhD
Stanford University

2018 HARRINGTON SCHOLAR-INNOVATORS

SUNEET AGARWAL, MD, PhD
Boston Children's Hospital

JEFFREY S. GLENN, MD, PhD
Stanford University

WAYNE I. LENCER, MD
Boston Children's Hospital

ROBERT O. MESSING, MD
University of Texas at Austin

VICTOR L. SCHUSTER, MD
Albert Einstein College
of Medicine

BHUVANESH SINGH, MD, PhD
Memorial Sloan Kettering
Cancer Center

DAVID B. SYKES, MD, PhD
Massachusetts General Hospital

MARC N. WEIN, MD, PhD
Massachusetts General Hospital

ADRIAN WIESTNER, MD, PhD
NHLBI/NIH

MONE ZAIDI, MD, PhD
Icahn School of Medicine
at Mount Sinai

2017 HARRINGTON SCHOLAR-INNOVATORS

PAUL L. BOLLYKY, MD, PhD
Stanford University

AMBROSE L. CHEUNG, MD
Geisel School of Medicine
at Dartmouth

GIULIO F. DRAETTA, MD, PhD
MD Anderson Cancer Center

SETH J. FIELD, MD, PhD
*University of California,
San Diego

TODD D. GOULD, MD
University of Maryland
School of Medicine

JOHN J. LETTERIO, MD
Case Western Reserve University

DAVID B. LOMBARD, MD, PhD
University of Michigan

DARUKA MAHADEVAN, MD, PhD
*University of Arizona

DEEPAK NIJHAWAN, MD, PhD
UT Southwestern

STUART H. ORKIN, MD
Boston Children's Hospital

DANIEL S. ORY, MD
Washington University

2016 HARRINGTON SCHOLAR-INNOVATORS

NUNZIO BOTTINI, MD, PhD
*La Jolla Institute for
Allergy and Immunology

STANLEY N. COHEN, MD
Stanford University

BENJAMIN M. GASTON, MD
*Case Western Reserve University

RAMA K. MALLAMPALLI, MD
*University of Pittsburgh

M. PETER MARINKOVICH, MD
Stanford University

DAVID J. MILAN, MD
Massachusetts General Hospital

KEVIN D. NISWENDER, MD, PhD
Vanderbilt University

SUSAN P. PERRINE, MD
Boston University

ANN MARIE SCHMIDT, MD
NYU School of Medicine

GERALD I. SHULMAN, MD, PhD
Yale University

2015 HARRINGTON SCHOLAR-INNOVATORS

ROBERT A. BONOMO, MD
Case Western Reserve University

JOHN C. BURNETT, Jr., MD
Mayo Clinic

NICOLE CALAKOS, MD, PhD
Duke University

DAVID R. CLEMMONS, MD
University of North Carolina

BARRY S. COLLIER, MD
The Rockefeller University

CLARK W. DISTELHORST, MD
Case Western Reserve University

XIANXIN HUA, MD, PhD
University of Pennsylvania

RICHARD J. JOHNSON, MD
University of Colorado

MARIKKI LAIHO, MD, PhD
Johns Hopkins University

GEOFFREY S. PITT, MD, PhD
*Duke University

IRA A. TABAS, MD, PhD
Columbia University

2014 HARRINGTON SCHOLAR-INNOVATORS

JAYAKRISHNA AMBATI, MD
*University of Kentucky

DARREN R. CARPIZO, MD, PhD
*Rutgers Cancer Institute
of New Jersey

GARRET A. FITZGERALD, MD
University of Pennsylvania

MARK S. HUMAYUN, MD, PhD
University of Southern California

JOHN N. KHEIR, MD
Boston Children's Hospital

RAHUL M. KOHLI, MD, PhD
University of Pennsylvania

IRINA PETRACHE, MD
*Indiana University

DAVID H. ROWITCH, MD, PhD
University of California,
San Francisco

JEAN Y. TANG, MD, PhD
Stanford University

DAVID WALD, MD, PhD
Case Western Reserve University

2013 HARRINGTON SCHOLAR-INNOVATORS

MARC I. DIAMOND, MD
*Washington University

ROGER A. GREENBERG, MD, PhD
University of Pennsylvania

GEOFFREY C. GURTNER, MD, FACS
Stanford University

RICHARD N. KITSIS, MD
Albert Einstein College of Medicine

WOLFGANG B. LIEDTKE, MD, PhD
Duke University

SANFORD D. MARKOWITZ, MD, PhD
Case Western Reserve University



FOR MORE INFORMATION:
HarringtonDiscovery.org/Scholars

*Scholar institution at time of award

HARRINGTON SCHOLARS 2013–2022

SCOTT A. OAKES, MD
*University of California,
San Francisco

FEROZ R. PAPA, MD, PhD
University of California,
San Francisco

**JONATHAN D. POWELL,
MD, PhD**
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We work in areas that have great influence on human health and improve our world.

Tenacity

We persevere through adversity in order to grow and make an impact.

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