Mass General Brigham

World Medical Innovation Forum

In partnership with
BANK OF AMERICA

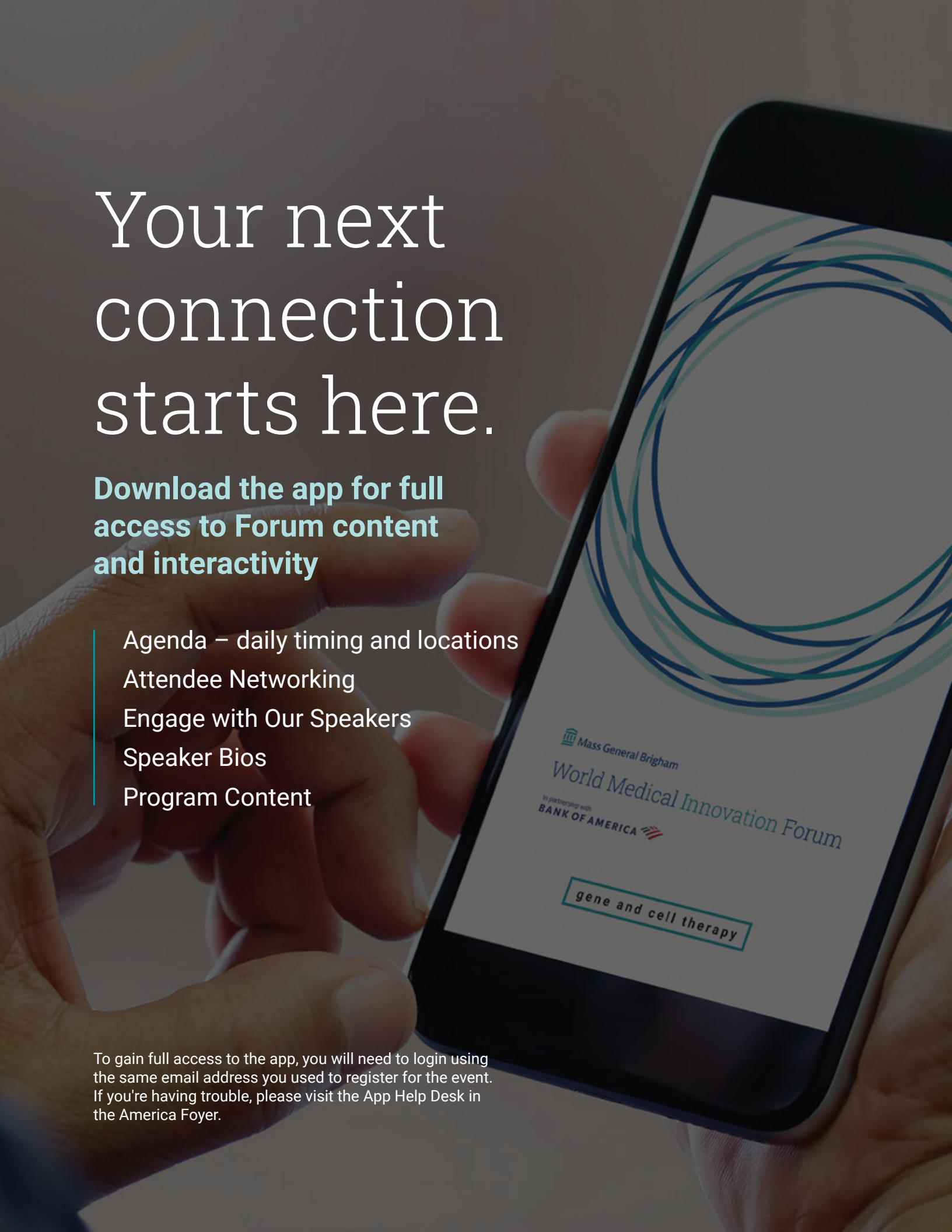
gene and cell therapy

May 2–4, 2022 | worldmedicalinnovation.org

Your next connection starts here.

Download the app for full access to Forum content and interactivity

- Agenda – daily timing and locations
- Attendee Networking
- Engage with Our Speakers
- Speaker Bios
- Program Content



To gain full access to the app, you will need to login using the same email address you used to register for the event. If you're having trouble, please visit the App Help Desk in the America Foyer.

Table of Contents

Welcome.

Welcome to the 8th annual World Medical Innovation Forum. We're glad to be able to come back together in person, as we explore new partnerships in innovation that have the power to transform the future of medicine.

We're grateful to be co-sponsoring the Forum with Bank of America, a relationship which will create new opportunities for like-minded innovators across sectors to engage with each other, toward advancing medical breakthroughs for millions of patients around the world.

This year, the Forum focuses on how gene and cell therapy is changing the game. We will explore the promise of these transformational therapies and discuss the existing challenges to their development and how we can work together to overcome them. We will address such topics as strategy in the space, clinical opportunities and patient access, economic and regulatory considerations, and manufacturing scalability.

The Forum's nearly 200 speakers include CEOs of leading companies in the GCT and biotech fields, investors, entrepreneurs, clinicians, scientists, government officials and other key influencers. Mass General Brigham's Harvard Medical School faculty will present on emerging research projects that explore GCT opportunities across a wide range of areas, from neurology, to cardiology, to oncology, and many more.

I'd like to thank Mass General Brigham's Chief Innovation Officer Chris Coburn, and the Forum's steering committee chairs Nino Chiocca, MD, PhD, Neurosurgeon-in-Chief and Chairman, Neurosurgery at Brigham and Women's Hospital; Susan Slaugenhaupt, PhD, Scientific Director, Mass General Research Institute; and Ravi Thadhani, MD, Chief Academic Officer of Mass General Brigham for their leadership in planning this exciting event, and all of our staff members who worked tirelessly to make this year's Forum a reality.

Of course, we can't get to where we want to be without each of you, our participants – leaders and innovators in your respective fields. Thank you for being an integral part of this year's event. I'm confident that the conversations held and the relationships made over the next three days will have a significant impact on the reason we're all here – to bring the promise of GCT to the benefit of our communities, faster.

Anne Klibanski, MD
President and CEO, Mass General Brigham;
Laurie Carrol Guthart Professor of Medicine,
Harvard Medical School

Thanks for joining.

On behalf of my 200,000-plus Bank of America teammates around the world—including more than 3,500 in Greater Boston—I'd like to welcome you to the 2022 World Medical Innovation Forum.

We are proud to partner with Mass General Brigham for this year's event. Through our partnership, we're helping expand access to leading healthcare technology and investment insights and, at the same time, highlighting Greater Boston's growing role as a global biotech and investment hub.

Breakthrough advancements in medicine are formed at the intersection of science, technology and investment capital. We wanted to join with Mass General Brigham so we could take the lead in bringing together CEOs, investors, innovators, academics and other leaders across the industry—to help spark the next great medical innovation.

At Bank of America, we build and nurture long-term relationships with medical innovators—from startups to large pharma companies to world-renowned research institutions—to help them launch and scale their ideas. That may begin by helping an entrepreneur open a credit card or operating account and extends across a continuum of solutions as clients expand and prosper, including advisory services, growth capital financing, and domestic and international treasury services, to name a few.

At the same time, our industry-leading Global Research Team—ranked #1 by Institutional Investor in 7 of the publication's last eleven Top Global Research Firm surveys—helps our investor clients identify breakthrough investment opportunities around the world. Our team of 44 healthcare analysts helps provide insightful research to investor clients on nearly 500 Global Health Care Equities and Credits with a combined market capitalization of nearly $11 trillion across the U.S., Europe, Latin America, Japan, China, India and Australia.

Our support for this year's Forum, which will help connect innovators to capital, is one of the many ways we are working to promote economic mobility within Greater Boston and the surrounding areas. Our partnerships with organizations such as Small Business Strong, Innovation Studio, Ascendus, and Year Up are focused on connecting our clients and communities to the tailored resources like technical assistance, financial education, access to jobs and training, and capital needed to succeed.

Thank you for participating in this important conference, and please don't hesitate to reach out to our team if we can be helpful.

Brian Moynihan
CEO, Bank of America

We're glad you're here.

Thank you for joining us. It's our pleasure to welcome you to the Forum.

Your support of the Forum solidifies the critical role we each play in directly influencing the insights and priorities critical to the future of medicine. This active participation focuses on providing the very best possible outcomes for patients and is the Forum's enduring goal.

Bank of America and Mass General Brigham have worked together to develop every aspect of the content, scope, and execution of this Forum. It is a relationship that brings together market leading financial capabilities with ground-breaking science and clinical care to help drive medical innovation, its commercial application and ultimate patient benefit.

We express our deep appreciation to the many individuals who made this Forum possible and are particularly grateful to our speakers for sharing their passion, expertise, and unique perspectives. Generous support from our sponsors including Innovation Champion sponsor Novartis, Innovation Partner sponsors Astellas and Bayer, our Media sponsor Cell & Gene, and our Content Partner Recon Strategies underpins every aspect of this event. Many thanks to the Steering Committee members whose insights made the Forum possible and the Planning Team's dedicated work.

Enjoy the Forum. We look forward to seeing you again next year on June 12–14, 2023, in Boston's Seaport District!

2022 PLANNING COMMITTEE CO-CHAIRS

Miceal Chamberlain
President of Massachusetts, Northeast Region Executive, Bank of America

Christopher Coburn
Chief Innovation Officer, Mass General Brigham

WiFi Network: **GCT2022** | Password: **WELCOMEBACK**

Connecting innovators to the capital they need

Bank of America thanks the World Medical Innovation Forum for bringing together partners from private industry and academia to improve patients' lives. Working with Mass General Brigham, we're connecting medical innovators to the capital they need to advance medical breakthroughs and helping to continue Boston's growth as a biotech and investment hub.

What would you like the power to do?®

BANK OF AMERICA

AD-04-22-0043

2019 World Medical Innovation Forum

WiFi Network: **GCT2022** | Password: **WELCOMEBACK**

Where the physicians doing the world-changing research are the ones providing care.

When you need some of the brightest minds in medicine, there is Mass General Brigham. The only healthcare system in the country with five nationally ranked hospitals, including two world-renowned academic medical centers. In Boston, where biotech innovates daily, and where our doctors teach at Harvard Medical School. It's why thousands from across the globe choose to travel to Mass General Brigham.

Learn more at massgeneralbrigham.org.

Mass General Brigham

2019 World Medical Innovation Forum

Event Guide

Monday, May 2

World Forum App

For access to the complete agenda of events, times and locations, please download the Forum App. Instructions are on page 2.

Continental Breakfast

America Foyer

First Look

Join us for 16 rapid fire presentations from Mass General Brigham researchers on the commercial opportunities for new GCT technologies. Abstracts for these technologies are located on page 26 of this event guide.

Fireside Chats

Don't miss these one-on-one discussions with the leading minds in GCT. Refer to the app for up-to-date times.

Peter Marks, MD, PhD

Albert Bourla, PhD

Opening Networking Reception

America Foyer

Join us at a networking reception open to all Forum attendees. Also, use the Forum app to connect with other attendees.

Tuesday, May 3

Bayer Continental Breakfast

America Foyer

Innovation Discovery Grants Announcement

Join us for Tuesday's Innovation Discovery Grant Award Announcements. Ten awardees will receive grants to further the commercialization and development of their research. See page 21 for a full description of the IDG program and, on May 3rd, a link to the winners' list.

Astellas Lunch

America Foyer

Fireside Chats

Be sure to attend these one-on-one discussions with the leading minds in GCT. Refer to the app for up-to-date times.

Robert Bradway

Norman Sharpless, MD

Carl June, MD

Marc Casper

Novartis Attendee Networking Reception

America Foyer

Join us at a networking reception open to all Forum attendees. Also, use the Forum app to connect with other attendees.

Wednesday, May 4

Disruptive Dozen

On the concluding day of the Forum, don't miss the announcement of the 2022 Disruptive Dozen. This rank order of the 12 GCT technologies that Mass General Brigham faculty feel will break through over the next 1-5 years offers a capstone on the Forum and reveals key discoveries for patients around the world. To access a complete list of the Disruptive Dozen, use the link on page 20 which will be released just prior to the D12 session on Wednesday, May 4th.

Times, content, location, and speakers are subject to change.

The Doctor Is In

The Future of GCT: Identifying Market Opportunities

Understanding long-term Gene and Cell Therapy investment complexities requires a keen awareness of where the science and the markets are headed. That's why "The Doctor is In" in these updates on the latest GCT technologies. Presented by Mass General Brigham clinicians and innovators from the front lines of care, the sessions are co-hosted by expert analysts from Bank of America and include interactive discussion and Q&A. Join in these concurrent lunch-time programs on Monday and Tuesday. Check the app and hallway signage for room locations.

Monday, May 2

Gene and Epigenetic Editing in the Development of Treatment for Deafness

Moderator: Geoff Meacham, PhD
Managing Director, Global Research, BofA Securities

Albert Edge, PhD
Eaton Peabody Professor of Otolaryngology, Mass Eye and Ear, HMS

Single Gene Correction in the Brain: Delivering Where it Matters Most.

Moderator: Tazeen Ahmad
Managing Director, Global Research, BofA Securities

Florian Eichler, MD
Director, Center for Rare Neurological Diseases, MGH; Associate Professor, Neurology, HMS

Repair, Replace, Regrow: The Advancement of Regenerative Medicine

Moderator: Jason Zemansky, PhD
Vice President, Global Research, BofA Securities

Joseph Bonventre, MD, PhD
Chief, Division of Renal Medicine, BWH; Samuel A. Levine Distinguished Professor of Medicine and Constantine L. Hampers Distinguished Chair, HMS

David Scadden, MD
Director, Center for Regenerative Medicine, MGH; Gerald and Darlene Jordan Professor of Medicine, HMS

Smart Materials: Non-viral Vectors for Gene Therapy

Moderator: Alec Stranahan, PhD
VP, Equity Research, BofA Securities

Natalie Artzi, PhD
Assistant Professor of Medicine, HMS

Newborn Sequencing and Prevention of Rare Diseases: A New Public Health and Biopharma Challenge

Moderator: Jason Gerberry
Managing Director, Global Research, BofA Securities

Robert Green, MD
Director, Genomes2People Research Program, BWH; Professor of Medicine, HMS

Adam Shaywitz, MD, PhD
CMO, BridgeBio Gene Therapy

Leveraging Novel Mechanisms for Accelerated Vaccine and Immunotherapy Development

Moderator: William Maughan
Associate, Global Research, BofA Securities

Mark Poznansky, MD, PhD
Director, Vaccine and Immunotherapy Center, MGH; Professor of Medicine, HMS

Tuesday, May 3

Personalizing Cancer Care through RNA Therapies

Moderator: Jason Gerberry
Managing Director, Global Research, BofA Securities

Pierpaolo Peruzzi, MD, PhD
Neurosurgeon and Principle Investigator, BWH; Assistant Professor of Neurosurgery, HMS

Designing for Success: Clinical Trial Approaches for Rare and Ultra-Rare Diseases

Moderator: Tazeen Ahmad
Managing Director, Global Research, BofA Securities

Demetrios Vavvas, MD, PhD
Associate Director of the Retina Service, Mass Eye and Ear; Solman and Libe Friedman Professor of Ophthalmology, Co-Director Ocular Regenerative Medical Institute, HMS

A New Hope: Cell Therapy and Transplantation for Parkinson's Disease

Moderator: Greg Harrison
Vice President, Global Research, BofA Securities

Bob Carter, MD, PhD
Chairman, Department of Neurosurgery, MGH; William and Elizabeth Sweet Professor of Neurosurgery, HMS

Todd Herrington, MD, PhD
Director, Deep Brain Stimulation Program, MGH; Assistant Professor of Neurology, HMS

Kwang-Soo Kim, PhD
Director, Molecular Neurobiology Laboratory, McLean; Professor of Neuroscience and Psychiatry, HMS

Jeffrey Schweitzer, MD, PhD,
Neurosurgeon, MGH; Assistant Professor of Neurosurgery, HMS

The Inner Workings of Gene Therapy Manufacturing

Moderator: Michael Ryskin
Director, Global Research, BofA Securities

Sarah Nikiforow, MD, PhD
Medical Director, Cell Manipulation Core Facility, Technical Director, Immune Effector Cell Therapy Program, DFCI; Assistant Professor, HMS

The Road Ahead: Regulatory Challenges for Gene and Cell Therapy

Moderator: Geoff Meacham, PhD
Managing Director, Global Research, BofA Securities

Peter Marks, MD, PhD
Director, Center for Biologics Evaluation and Research, FDA

The Mysterious Dark Genome

Moderator: Angela Shen, MD
Vice President, Strategic Innovation Leaders, Mass General Brigham Innovation

Moderator: Richard Young, PhD
Professor, Whitehead Institute, MIT

Rosana Kapeller, MD, PhD
Co-Founder, President & CEO, ROME Therapeutics

Josh Mandel-Brehm
President & CEO, CAMP4 Therapeutics

Amir Nashat, PhD
Managing Partner, Polaris Partners

Issi Rozen
Venture Partner, GV

Times, content, location, and speakers are subject to change.

Steering Committee

CHAIRS

Nino Chiocca, MD, PhD
Neurosurgeon-in-Chief and Chairman, Neurosurgery, BWH; Harvey W. Cushing Professor of Neurosurgery, HMS

Susan Slaugenhaupt, PhD
Scientific Director, Mass General Research Institute, MGH; Professor, Neurology, HMS

Ravi Thadhani, MD
CAO, Mass General Brigham; Professor of Medicine and Faculty Dean for Academic Programs, HMS

Bob Carter, MD, PhD
Chairman, Department of Neurosurgery, MGH; William and Elizabeth Sweet, Professor of Neurosurgery, HMS

Florian Eichler, MD
Director, Center for Rare Neurological Diseases, MGH; Associate Professor of Neurology, HMS

Meredith Fisher, PhD
Partner, Mass General Brigham Ventures

Jean-Francois Formela, MD
Partner, Atlas Venture

Pat Fortune, PhD
VP, Strategic Innovation Leader, Mass General Brigham Innovation

Lawrence Di Rita
Global Public Policy & Environmental Strategy, President, Greater Washington, DC, Bank of America

Anna Greka, MD, PhD
Associate Professor of Medicine, BWH, HMS; Director, Kidney Disease Initiative, Broad Institute of MIT and Harvard

Reid Huber, PhD
Partner, Third Rock Ventures

Ole Isacson, MD, PhD
Director, Neuroregeneration Research Institute, McLean; Professor of Neurology & Neuroscience, HMS

J. Keith Joung, MD, PhD
Robert B. Colvin, M.D. Endowed Chair in Pathology & Pathologist, MGH; Professor, Pathology, HMS

Adam Koppel, MD, PhD
Managing Director, Bain Capital Life Sciences

Elizabeth Everett Krisberg
Head of Bank of America Institute

John Lepore, MD
SVP, Head of Research, GlaxoSmithKline

Marcela Maus, MD, PhD
Director, Cellular Immunotherapy, Cancer Center, MGH; Associate Professor, HMS

Marie McDonnell, MD
Chief, Diabetes Section and Director, Diabetes Program, BWH; Lecturer, HMS

Adrian Mee
Head of Global Healthcare Investment Banking, and Chairman, Global M&A, BofA Securities

Patricia Musolino, MD, PhD
Co-Director Pediatric Cerebrovascular Service, MGH; Assistant of Neurology, HMS

Chandra Ramanathan, PhD
Global Head, Pharma R&D Open Innovation, Bayer

Alfred Sandrock, MD, PhD
CEO, Voyager Therapeutics

Bastiano Sanna, PhD
Executive Vice President, Chief of Cell & Gene Therapies and VCGT Site Head, Vertex Pharmaceuticals

Christine Seidman, MD
Director, Cardiovascular Genetics Center, BWH; Thomas W. Smith Professor of Medicine and Genetics, HMS

Angela Shen, MD
Vice President, Strategic Innovation Leaders, Mass General Brigham Innovation

Deb Sloan, CFA
SVP, Treasury, Mass General Brigham

Additional support and guidance provided by Bank of America:

Tazeen Ahmad
Managing Director, Global Research, BofA Securities

John Bishai
Managing Director, Global Investment Banking, BofA Securities

Greg Butz
Managing Director, Investment Banking, BofA Securities

Jason Gerberry
Managing Director, Global Research, BofA Securities

Derik de Bruin
Managing Director, Global Research, BofA Securities

Geoff Meacham, PhD
Managing Director, Global Research, BofA Securities

Aamir Mecklai
Managing Director, Global Investment Banking, BofA Securities

Sumit Mukherjee
Managing Director & Head of Healthcare in Equity Capital Markets, BofA Securities

Nathan Zibilich
Managing Director, Global Research, BofA Securities

Planning Committee

A special thanks to Innovation's Planning Committee and Event Team for their unstinting commitment over the last 18 months to create the 2022 World Medical Innovation Forum.

CHAIRS

Christopher Coburn
Chief Innovation Officer,
Mass General Brigham

Lawrence Di Rita
Global Public Policy & Environmental Strategy, President, Greater Washington, DC, Bank of America

MASS GENERAL BRIGHAM

Laura Bombrun
Administrative Coordinator

Tracy Doyle
Director, Strategic Marketing

Pat Fortune, PhD
VP, Strategic Innovation Leader

Casey Frazier
Marketing and Administrative Coordinator

Michelle Grdina
Senior Project Manager, World Medical Innovation Forum

Beth Mollineaux
General Manager, Strategic Marketing and Communications

Tim Riley, PhD
Strategic Innovation Leader & EIR

Angela Shen, MD
VP, Strategic Innovation Leader

BANK OF AMERICA

Allison Greenhouse
Senior Vice President, Global Events

Katy Huertas Del Pino
Senior Vice President, Global Marketing

Frances Kelly
Vice President, Global Events

Amy Leith
Senior Vice President, Global Marketing

Amy Stroud
Senior Vice President, Global Marketing

Jon Watt
Senior Vice President, Global Marketing

John Yiannacopoulos
Senior Vice President, Media Relations

EVENT TEAM

Adviciti
Susan Bernat

Biomedical Communications
Nicole Davis, PhD

Healthcare Leadership Council
Michael Freeman

Ink Factory

Jamie Belkin Events
Jamie Belkin
Jerry Mizer
Amy Pappas
Lisa Savin

Mueller Design
Eric Castle
Hannah Chambers
Greg Mueller

NPi Audio Visual Solutions

12 Most Disruptive Technologies

The Disruptive Dozen identifies and ranks the GCT technologies that Mass General Brigham faculty feel will break through over the next one to five years to significantly improve health care.

DISRUPTIVE DOZEN

Scan on Wednesday, May 4 at 11:30 AM to see the final selections

2022 Congratulations Innovation Discovery Grant Awardees

Every day, Mass General Brigham is working to translate innovation into clinical applications that improve outcomes for patients faced with challenging diseases. The Innovation Discovery Grants, or IDG, support translation of breakthrough research from the lab to real-world products.

Since IDG's inception in 2014, 65 projects have been awarded a combined $4.2 million and together have raised more than $196 million to further their development. This includes 14 new companies actively developing IDG-supported technologies and 19 license agreements.

$4.2 million

Has been awarded to 65 projects in the first five rounds of funding

14

New companies are actively developing IDG-supported technologies

19

License agreements have been executed to further their development

>$199 million

In follow-on funding has been received to further development of IDG-supported technologies (a 47-fold increase on the funds awarded)

IDG PROGRAM

Scan on Tuesday morning, May 3rd, for the announcement of all IDG winners and descriptions of their projects. Check the app for the exact timing.

WiFi Network: **GCT2022** | Password: **WELCOMEBACK**

Mass General Brigham Ventures

Investing in Bold Transformative Innovations

$500M
Capital Under Management

54 Portfolio Companies
15 Exits
$18B Enterprise Value

Mass General Brigham Ventures is an early-stage venture firm focused on investing in life science technologies that emerge from the Mass General Brigham research community.

Founded in 2008, the firm has $500 million in capital under management with proven leadership in both venture capital investing and venture creation.

Our mission is to bring more bench-to-bedside innovations to market to solve unmet medical needs for the benefit of patients worldwide.

www.massgeneralbrighamventures.com

Mass General Brigham Innovation

The World Medical Innovation Forum is brought to you by Mass General Brigham Innovation, the 140-person business development unit responsible for the worldwide commercial application of the capabilities and discoveries of Mass General Brigham's 74,000 employees.

Be a part of a team that lives at the cutting edge of medical innovation.

Please contact us if you or someone you know would like to join our diverse team. We have positions for MDs, PhDs, JDs, MBAs and others who have a passion to improve lives by translating the insights and capabilities of our 6000 Harvard faculty.

Join us today!

DEPARTMENTS

- Business Development
- Innovation Operations
- Licensing and Innovation Management
- Market Sectors
- Open Innovation | Alliances and Fellows
- Mass General Brigham Ventures

FUNCTIONS

- Business development
- Company creation
- Industry collaborations
- Innovation management
- Licensing
- Research translation strategy and funding
- Technology marketing
- Venture investing
- Workforce capacity building

One Main Street, Suite 501 | Cambridge, MA 02142
857-307-2400 | innovation.massgeneralbrigham.org

Make an impact

We connect with innovators who share

our commitment to moving communities forward.

What would you like the power to do?®

BANK OF AMERICA

First Look

The Next Wave of Gene and Cell Therapy Breakthroughs in Health Care

Sixteen presenters from Brigham and Women's Hospital, Massachusetts General Hospital, Massachusetts Eye and Ear, McLean Hospital, and Harvard Medical School will give 10-minute presentations highlighting their discoveries and insights that will disrupt the field of gene and cell therapy. This session is designed for investors, leaders, donors, entrepreneurs, investigators and others who share a passion for identifying emerging high-impact technologies.

BWH | Brigham and Women's Hospital
MGH | Massachusetts General Hospital
HMS | Harvard Medical School

Microbiota-Informed Strategies to Combat Disease: Leveraging Human-Microbiota Molecular Mechanisms of Action in Therapeutic Applications

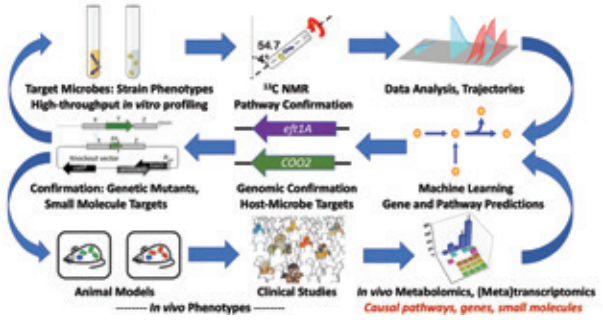
Lynn Bry, MD, PhD
Director, Massachusetts Host-Microbiome Center, BWH; Associate Professor of Pathology, HMS
lbry@bwh.harvard.edu

Dr. Bry is the Director of the Massachusetts Host-Microbiome Center (MHMC) at BWH, which promotes further understanding of host-microbiome interactions in health and disease, emphasizing a Focus-on-Function to define causative effects of the microbiota in vivo and to harness this knowledge in developing new therapies, diagnostics and further commercial applications.

Defining the molecular mechanisms by which our microbiota modulates risks for human disease has enabled new therapeutic approaches in areas ranging from gastrointestinal, immunologic and infectious to ones for cardiovascular disease, diabetes, and cancer. While the field has had a major focus on correlative aspects of microbiome signatures with disease, the MHMC seeks to identify causative effects of the microbiota on our physiology and on disease pathogenesis.

We bring unique approaches using machine learning, deep knowledge of anaerobe and host physiology and genomics, and high-dimensional muti-omic platforms that integrate pre-clinical models with human studies to provide an in vivo context for defining the causative mechanisms by which populations of colonizing microbes modulate our own physiology. Platform approaches in metabolomic analyses, anaerobe-host metabolic modeling, and longitudinal dynamics of the microbiota relative to patient factors, dietary, or druggable interventions, have progressed patented new therapeutic approaches for diseases such as human food allergies, diabetes, and reduction of infection risk in newborns and hospitalized patients.

With investment from the Massachusetts Life Sciences Center (MLSC), the MHMC has a long-standing outreach program with academic and industry partners to develop microbiota-informed applications. Example program will be presented, including underlying mechanisms by which the microbiota promotes constructive immunomodulation, as well as metabolic reprogramming of the gut nutrient environment, and use of this knowledge to inform new approaches to human disease.



A Novel Cellular Therapeutic Approach to Replacing Toxic Immunosuppressive Drugs in Kidney Transplantation

Anil Chandraker, MD
Medical Director of Kidney and Pancreas Transplantation, BWH; Associate Professor of Medicine, HMS
achandraker@bwh.harvard.edu

A recognized leader in transplantation and immunology, Dr. Chandraker is currently working on alternatives to immunosuppressive drugs currently used to prevent rejection of transplanted organs. His innovative approach is able to suppress the immune system response to a transplant without causing non-specific immunosuppression.

While kidney transplantation is usually viewed as a successful treatment, long term transplant survival has not greatly improved in many years and kidney transplant patients often require multiple transplants. The situation is even more critical for other types of transplants; median survival for a lung transplant, for example, is around 6 years. Immunosuppressive drugs needed to sustain transplants increase the risks of cancer, infection, heart disease and toxicity to the kidney (Fig 1).

Cellular therapy with T-regulatory cells (Tregs) is a promising strategy to control immune responses and restore immune tolerance in a variety of immune-mediated diseases, such as transplant rejection and autoimmunity. Multiple clinical trials are currently testing this approach, typically by using polyclonal Tregs that have been expanded prior to transplantation. However, evidence from animal models of Treg therapy has clearly shown that antigen-specific Tregs are vastly superior to polyclonal cells. Another disadvantage of the polyclonal approach is that it is essentially limited to living donation, which excludes the majority of kidney transplant recipients as well as recipients of other organs such heart, lung, pancreas and most liver transplants.

We have developed an approach that entails expanding donor antigen specific T regulatory cell enriched lines (ASTRLs) from human kidney transplant recipients. These ASTRLs can be expanded ex vivo using donor specific peptides (Fig 2). ASTRLs have been shown to significantly prolong transplant survival in a kidney transplantation animal model and demonstrate 'linked suppression' while preserving the immune system's ability to respond to infections and cancer (Fig 3). The goal is to use ASTRLs to decrease reliance on conventional immunosuppression. This approach has several advantages compared to competing technologies; it is relatively inexpensive, less complex, applicable to all types of transplants and may have application in autoimmune diseases.

We have advanced pre-clinical studies, solid IP, and are now transitioning the work from academic discovery to NewCo formation. We are working on pre-IND studies and targeting completion of our Phase I kidney trial by mid 2023.

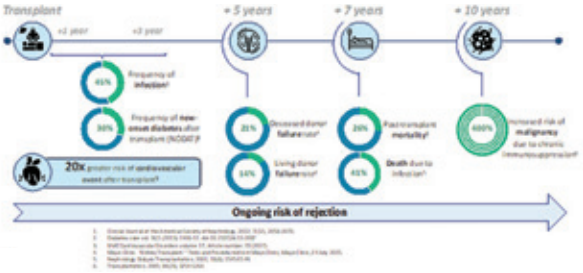


Figure 1. Current immunosuppression is the Achilles heel of transplantation. Lack of precision leads to serious toxicities and poor survival outcomes. Critical to balance immunosuppression to prevent rejection and maximize safety.

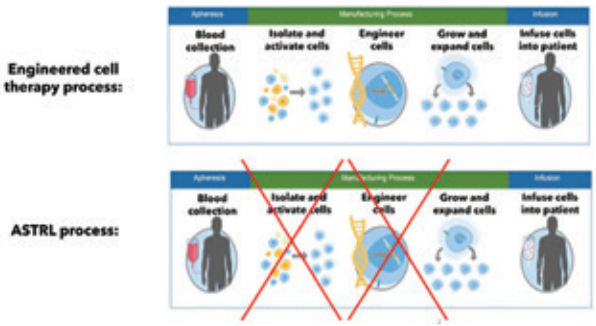


Figure 2. ASTRL manufacturing is simpler than engineered cell technologies. No cell sorting or engineering creates time and cost efficiency.

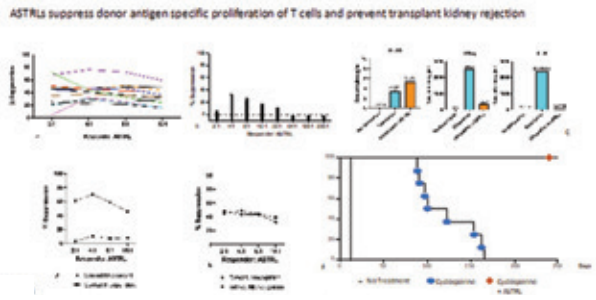


Figure 3. A.) ASTRLs from patients suppress donor antigen specific proliferation of T effector cells. B.) One ASTRL cell can suppress many T cells. C.) Inflammatory cytokine production is reduced by ASTRLs. D.) Suppressive ability of ASTRL is contact dependent. E.) ASTRL manufactured with one donor antigen suppress all donor antigen responses. F.) ASTRL prolong transplant survival in a rat kidney transplant model.

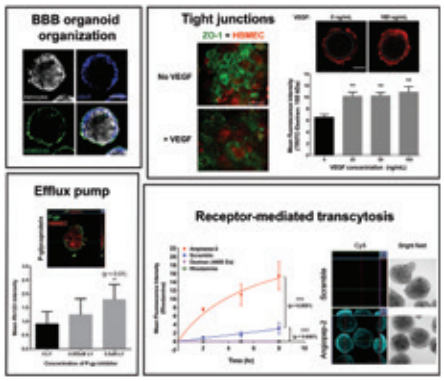


Figure 1. BBB organoids. (a) Spatial distribution of NVU cells in BBB organoid. (b) VEGF disrupts tight junctions (ZO-1) and increases organoid permeability to dextran. (c) P-gp efflux pump inhibition increases influx of rhodamine-123 (P-gp substrate). (d) Transcytosis of angiopep-2 (a BBB-permeable peptide).

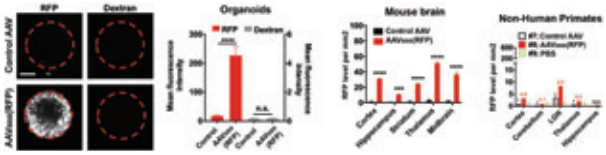


Figure 2. Translation of permeability of a novel BBB-penetrant AAV variant in BBB organoids to mouse and non-human primate models.

3D Human Blood-Brain-Barrier Organoids for Modeling Therapeutic Delivery to the CNS

Choi-Fong Cho, PhD
Assistant Professor of Neurosurgery, BWH
ccho@bwh.harvard.edu

Dr. Cho's work focuses on designing precision medicines with improved tumor-killing efficacy. In conjunction with that work, her lab has pioneered an organoid platform to model the blood-brain-barrier. This innovative and accessible approach addresses limitations of current 2D models, offering the potential for significant improvements in screening and analysis of brain-penetrant drugs.

The inability of most therapeutics to cross the blood–brain barrier (BBB) is a major roadblock to effective treatment of diseases in the central nervous system (CNS). In vitro BBB models continue to play critical roles in prioritizing CNS drug candidates prior to in vivo studies. However, brain endothelial cells (BECs) tend to rapidly dedifferentiate and lose their BBB characteristics when they are grown as monolayer cultures, resulting in the lack of expression of key BBB modulators and leaky paracellular barrier function. The mid-throughput 2D transwell BBB model is used widely, though it is associated with several limitations including barrier leakiness and loss of BBB marker expression. 3D microfluidic BBB systems have been developed to better simulate the BBB morphology, however these devices have limited throughput and require either purchase of a commercial device or construction of one, making them relatively inaccessible to many laboratories.

We have developed a high-throughput, versatile and robust 3D human BBB organoid platform for studying BBB functions and modeling therapeutic delivery. These miniature organoids are formed through the self-assembly of neurovascular unit cells co-cultured under low-adherence condition: Human BEC encase the organoid outer surface together with associating human brain pericytes (HBP), while the core consists mostly of human astrocytes (HA) (Fig. 1a).

The organoids are easy to culture, made from highly accessible cells, and reproduce key BBB biological characteristics and functions, as well as predict drug permeability. We show that the surface of the organoids recapitulates key BBB features, such as: 1) Tight junctions that exclude fluorescent dextran of various molecular weights (Fig. 1b), 2) Functional drug efflux pumps such as P-glycoprotein (Fig. 1c), 3) Receptor mediated transcytosis (Fig. 1d) to facilitate entry of specific molecules, and 4) Lipid transporter and transcytosis inhibitor MFSD2A. Furthermore, as in vivo rodent models continue to face challenges in the field with interspecies differences, we have recently demonstrated that the permeability of a novel AAV-based vector for gene delivery translates from organoids to both mice and non-human primates (Fig. 2). These data highlight the BBB organoid model as a promising in vitro screening tool to mitigate failure risk at a later state of drug development.

Restoration of Hearing and Vision with Gene Therapy

David Corey, PhD
Bertarelli Professor of Translational Medical Science, Neurobiology, HMS
david_corey@hms.harvard.edu

The Corey Laboratory has made fundamental advances in our understanding of the process of auditory transduction, including the recent identification of a pivotal sensor protein. This groundbreaking work has transformed our understanding of hearing and hearing loss and lays the groundwork for precision-targeted therapies to treat genetic deafness and blindness.

"Hair cells" of the inner ear are the receptor cells that convert a physical stimulus such as sound into neural signals that the brain can understand. Many different proteins are involved; when one or another of these has a mutation, hair cells cannot convert the sound and the person is deaf. Protocadherin-15 (PCDH15) is one such protein. PCDH15 is also used in the photoreceptor cells of the eye, so patients with PCDH15 mutations become blind over a period of about 30 years. Their combined deafness and blindness is known as Usher syndrome type 1F.

To develop a therapy for Usher 1F, we and collaborators have explored different methods to deliver a functional copy of the PCDH15 gene to hair cells of the inner ear and photoreceptor cells of the retina. We engineered a "mini-PCDH15" gene that would fit in an AAV vector. We also developed a line of PCDH15 conditional knockout mice that are deaf like Usher 1F patients. We injected AAV9-PHP.B vectors carrying the mini-PCDH15 gene into the inner ears of newborn deaf mice and tested hearing after four weeks. The mice receiving the mini-PCDH15 gene retained most of their hearing. With light and scanning electron microscopy, we found that the hair cells in untreated Usher 1F mice degenerated, but hair cells in treated mice had normal morphology.

If gene therapy with mini-PCDH15 works in the demanding environment of the inner ear, it is likely to also work to prevent the progressive blindness. We are testing efficacy of mini-PCDH15 in retinas of a zebrafish model of Usher 1F, and will test mini-PCDH15 delivery in nonhuman primate retinas to assess proper localization in photoreceptor cells and to evaluate toxicity.

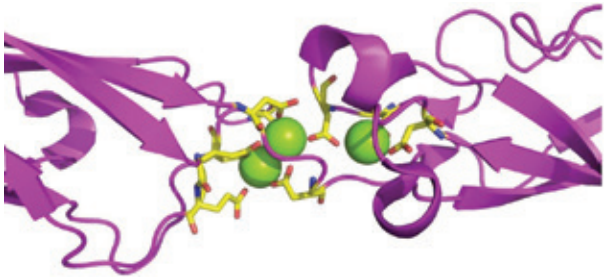


Figure 1. Engineering mini-PCDH15 based on atomic structure. PCDH15 has 11 EC repeats in its extracellular domain; to make a mini version we removed 5 of them. Adjacent EC repeats are each linked by three calcium ions (green) coordinated by side chains of aspartate and glutamate residues (yellow). Design of mini-PCDH15 required careful replication of this architecture in a synthetic EC-EC junction. Image: Sotomayor et al., 2012

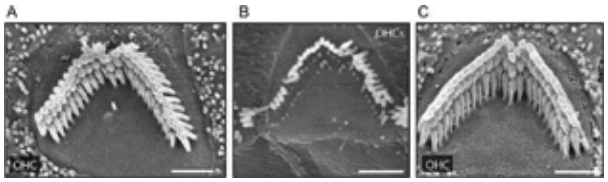


Figure 2. Rescue of hair cells with mini-PCDH15. A. Top of a normal hair cell showing the cilia bundle. B, Bundle of a PCDH15 knockout mouse at P30. The bundle is degenerating and the cell will die. C. Bundle in a mouse treated at P0 with an AAV encoding mini-PCDH15. Morphology is normal. scale bar = 1 μm Image: Maryna Ivanchenko

Genetic Studies of the NCLs: A Window into New Therapeutic Strategies for the NCLs and Related Neurodegenerative Disorders

Susan Cotman, PhD
Assistant Professor, Center for Genomic Medicine, MGH; Assistant Professor of Neurology, HMS
cotman@helix.mgh.harvard.edu

The Cotman laboratory applies genetics and cell and animal biology to the study of lysosomal dysfunction in neurodegenerative disease. The neuronal ceroid lipofuscinoses (NCLs) encompass a group of single gene neurodegenerative disorders that lead to vision loss, seizures, progressive dementia and loss of motor function, and there is significant genetic and cell biological overlap between the NCLs and other neurodegenerative diseases including frontotemporal dementia and Parkinson disease. By investigating single gene NCLs, we aim to enhance a mechanistic understanding of these disorders and to drive gene, cell-based, and small molecule therapy development for the NCLs and related forms of neurodegenerative disease.

While several forms of NCL are due to lysosomal enzyme deficiencies, a significant proportion arise from loss-of-function mutations in genes encoding transmembrane proteins of the secretory pathway and the endolysosomal system. Restoring the lost function of these membrane proteins in a sufficient number of brain and retinal cells using a classical gene therapy approach is challenged by current technology. Advancements in gene therapy vectors will improve this outlook. Combination gene, cell and small molecule-based approaches are an alternative to classical gene therapy with substantial potential to advance effective therapy development for the NCLs and related disorders.

We recently identified early disease stage abnormalities in ion regulation associated with autophagy and lysosomal function in CLN3 disease, one of the most common genetic subtypes of NCL. Mechanistic studies on these pathways have identified novel targets for therapy that are now in preclinical testing in CLN3 disease models, using gene and small molecule, as well as combination therapy approaches. The role of these pathways in neuronal and glial cells and how this contributes to the CLN3 neurodegenerative disease process is also now a major focus of our research.

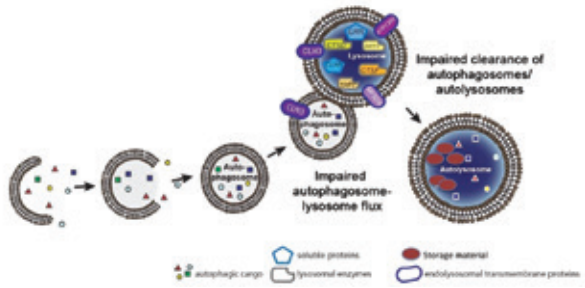


Figure 1. NCL-related proteins function in the autophagy-lysosomal pathway. The figure (adapted from Butz et al., BBA-Molecular Basis of Disease, 2020, 1866(9):165571) highlights lysosomal enzymes and soluble and transmembrane NCL lysosomal proteins in autophagosomal and lysosomal compartments and the impact of the loss of NCL protein function on the autophagolysosomal pathway. Additional NCL-related proteins localize to the endoplasmic reticulum and cis-Golgi membranes (CLN6 and CLN8, not shown) where they function to regulate the lysosomal targeting of NCL-related and other lysosomal proteins. Combination gene, cell, and small molecule-based approaches are being developed that target this pathway in the NCLs and related disorders.

Overcoming Gene Therapy Development Barriers for Ultra-Rare Diseases

Yulia Grishchuk, PhD
Assistant Investigator, Center for Genomic Medicine, MGH;
Assistant Professor of Neurology, HMS
ygrishchuk@partners.org

Dr. Grishchuk leads a lab working on therapy development for rare pediatric neurologic diseases. Her work focuses on the neurobiology of the lysosomal storage disorder mucolipidosis type VI (MLIV) and related conditions. Current efforts are focused on developing a gene therapy for MLIV as well as understanding the applicability to the broader family of lysosomal diseases.

Current advances in drug development and personalized medicine bring new hopes of creating curative therapies for patients with rare diseases and high unmet needs. Of the roughly 7,000 rare diseases, approximately 80% are caused by a single gene defect, making them ideal candidates for gene therapy development, however, less than 5% currently have a treatment. The challenges of ultra-rare disease gene therapy development include high upfront expenses of vector manufacturing and safety/toxicology studies, often incomplete natural history data, poorly established genotype/phenotype correlation, and a limited number of patients available for clinical studies. To overcome these limitations, innovative approaches are needed to allow development of gene therapy for small patient populations.

The laboratory at the MGH Center for Genomic Medicine and Department of Neurology is focused on the understanding of two cellular processes, autophagy and lysosomal function, in the context of brain health and disease, and on using this knowledge to develop new therapies. More specifically, the laboratory is developing AAV-based therapies for two ultra-rare neurologic pediatric diseases, an autophagy disease Beta-propeller protein-associated neurodegeneration (BPAN), and mucolipidosis IV (MLIV), a lysosomal storage disease. Both have very high unmet medical need.

For MLIV, the laboratory has generated robust proof-of-concept data showing efficacy of AAV9-mediated gene replacement therapy approach to reverse neurological decline and extend survival in the MLIV animal model. Working closely with the MLIV patient advocacy group, the Mucolipidosis IV Foundation, and the MLIV clinical team at MGH, translational efforts are underway to advance this program to the clinic. Using insights from this work, the laboratory is exploring whether the MLIV gene therapy vector can be efficacious in other ultra-rare indications and lysosomal diseases. This “pathway engagement” gene therapy approach offers the potential to reduce drug development expenditures for individual gene therapies, increasing the commercial attractiveness of targeting ultra-rare diseases.

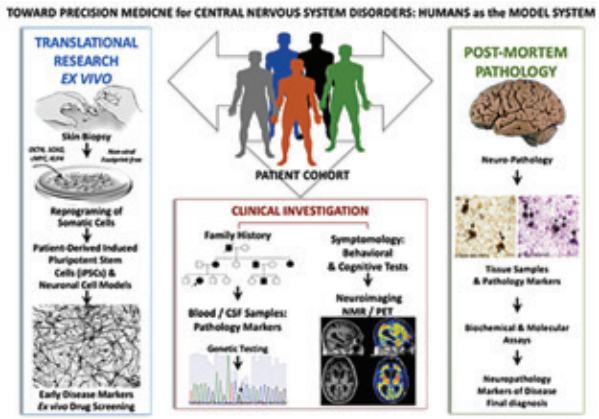


Figure 1. Toward precision medicine for CNS disorders. Humanized CNS drug discovery based around genetically accurate and pathophysiologically relevant cell types generated from the directed differentiation of induced pluripotent stem cells (iPSCs) and integration of neuropathology and clinical investigation using genetics and neuroimaging.

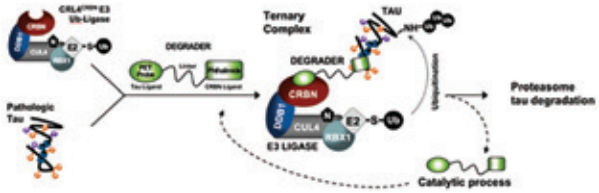


Figure 2. Strategy for Tau Targeted Protein Degradation. Degrader compounds are heterobifunctional molecules composed of a phthalimide derivative, which is recognized by CRBN in the CRL4 E3 ubiquitin ligase complex, and a moiety that recognizes human Tau (endogenous) in neuronal cells. The degrader recruits Tau into proximity of the CRBN-CRL4 E3 ubiquitin ligase complex for ubiquitination and subsequent irreversible degradation by the proteasome, allowing it to have catalytic-like activity and participate in multiple rounds of targeted degradation.

Precision Medicine for Dementia: Patient-Derived Stem Cell Models & Targeted Protein Degradation

Stephen Haggarty, PhD
Director, MassGeneral Chemical Neurobiology Laboratory, Center for Genomic Medicine, MGH; Associate Professor of Neurology, HMS
shaggarty@mgh.harvard.edu

Dr. Haggarty's overall research interest is to gain a fundamental understanding of the molecular and cellular mechanisms of neuroplasticity that enable the nervous system to sense, adapt, and respond to a variety of internal and external stimuli. His long-term goal is to translate this knowledge into the discovery of novel targeted therapeutics for the treatment and prevention of neuropsychiatric disorders.

Alzheimer's disease and related dementias are one of the leading causes of death worldwide. Current treatments are symptomatic in nature and neither prevent cognitive decline nor neuronal loss. Consequently, the burden to grow, with a cost estimate of over $1 trillion in the US alone by 2050. This burden provides a strong impetus for the discovery of effective disease-modifying and preventative treatments that target the core pathological features of Alzheimer's disease including the accumulation of aberrant protein aggregates and neurofibrillary tangles composed of microtubule-associated protein Tau. In support of Tau as a driver of disease pathogenesis, mutations in the MAPT gene encoding Tau are known to be sufficient to cause forms of frontotemporal dementia, and common genetic variation in the MAPT locus is associated with elevated risk for a range of tauopathies. However, as an intrinsically disordered, highly abundant, and predominantly intracellular protein, efforts to use immunotherapies and conventional small molecules to target Tau have encountered challenges.

Using a 'humanized' early-stage CNS drug discovery platform built around genetically accurate, patient-derived stem cell models generated via cellular reprogramming technology, our team has generated tauopathy patient-derived stem cell models (Figure 1). In collaboration with partners,), using this platform we have developed a novel pharmacological strategy for targeted degradation of Tau that exploits conformational changes of pathological, misfolded forms of Tau. This targeted protein degradation (TPD) strategy relies on a bifunctional molecule that simultaneously binds the target protein of interest and recruits an E3 ubiquitin ligase leading to proteasomal degradation (Figure 2). On-going studies seek to further leverage the principle of proximity and apply the power of TPD to other causal drivers of proteinopathies and CNS disorders. Translational efforts focused on advancing optimized 2nd generation Tau degraders are now being led by Proximity Therapeutics, with seed support from Mission Biocapital and the Mass General Brigham Innovation Fund.

cGMP Methodology and Clinical Trial Preparations for Cell Therapy using Autologous iPSCs for Parkinson's Disease

Ole Isacson, MD, PhD
Director, Neuroregeneration Research Institute, McLean; Professor of Neurology & Neuroscience, HMS
isacson@mclean.harvard.edu

Dr. Isacson and the Neuroregeneration Research Institute (NRI) at McLean Hospital are at the forefront of research into regenerative medicine for brain disorders. We are dedicated to discovering better treatments for patients with Parkinson's and Alzheimer's disease and dementia. The NRI's expertise spans a full spectrum of approaches from preventive molecular treatments to restorative cell-based therapies.

Whilst Parkinson's disease (PD) patients benefit from pharmacological substitution of dopamine (DA) that is missing in the part of the brain that controls and initiates motor function, the benefits are transient and eventually result in loss of these effects and additional side effects, such as abnormal movements. We believe a better solution is the one-time cell replacement by autologous dopamine neurons derived from induced pluripotent stem cells (iPSCs) (Figure 1), which will provide substantial clinical benefit long term over decades.

Recently, some teams have approached this type of cell therapy for PD primarily as allogeneic sources for the DA neurons (fetal or embryonic stem cells). For medical and scientific reasons, we consider the cells with the identical makeup (autologous to the patient) will work better than allogeneic. Specifically, there is a lack of immune response to the implanted autologous cells and therefore the patients will not require immune suppression. Moreover, biological studies indicate that the autologous cells integrate better than allogeneic do. The DA neuron differentiation method we have invented is protected by patents and has been shown to work in IND-enabling studies as well as in prior primate studies (Figure 2). Currently, our IND-enabling studies have been completed (Figure 3) and we look forward to receiving IND approval to initiate an NIH funded study in 6 patients at Mass General Brigham (MGB).

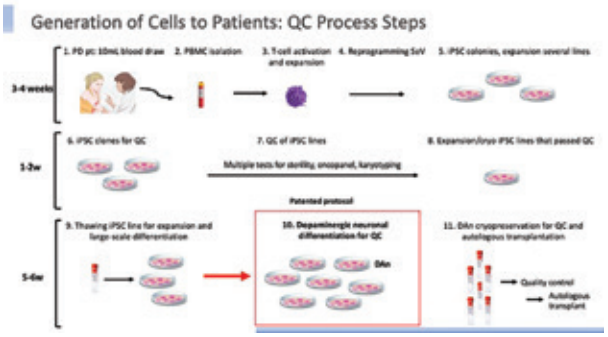


Figure 1. Generation of autologous cells for transplantation.

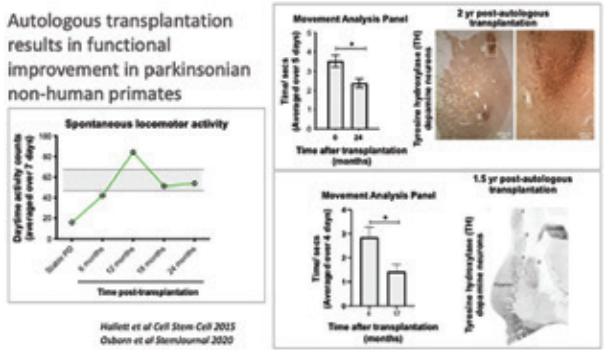


Figure 2. Autologous transplantation results in functional improvement and robust survival of dopamine neurons in parkinsonian non-human primates.

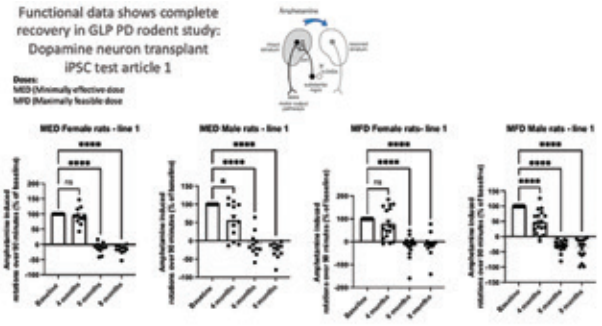


Figure 3. Functional data shows complete recovery in GLP Parkinson's disease model rodent study.

Programming Cell Therapies with Targeted Protein Degradation

Max Jan, MD, PhD
Assistant Professor, Center for Cancer Research, MGH
mjan@mgh.harvard.edu

The Jan Laboratory seeks to build clinically suitable synthetic biology technologies by reprogramming elegant and powerful cellular protein degradation machinery. With bespoke tools, we then design and test smart, next-generation cellular immunotherapies targeting unmet clinical needs.

Gene-modified cellular immunotherapies are transformative advances in the care of people with B cell cancers. However, toxicity, high rates of intensive care, and cost limit both patient outcomes and the accessibility of these autonomous, living therapies. While synthetic biology platforms to predictably tune and regulate cellular behaviors have enormous potential to refine cell-based therapies, toolkits of molecular parts, modules, and circuits designed for clinical use are in short supply.

Using lenalidomide, an FDA-approved anti-cancer drug that acts as a molecular glue to recruit select target proteins to an E3 ligase for ubiquitination and subsequent proteasomal degradation, we engineered lenalidomide-inducible dimerization and degradation systems. With these tools, we have developed drug ON- and OFF-switch chimeric antigen receptor (CAR) and cytokine systems to enable user control over anti-tumor and proliferative functions of cellular immunotherapies with small molecule pharmacokinetics. Current work in the lab aims to develop additional technologies at the interface of targeted protein degradation drug development and cell engineering, as well as to define the catalog of attractive space- and time-limited genetic perturbations to immune cells. Clinical development goals include using degrader synthetic biology to 1) alleviate risks associated with higher potency cellular immunotherapies and 2) safely deploy cell therapies as routine outpatient modalities.

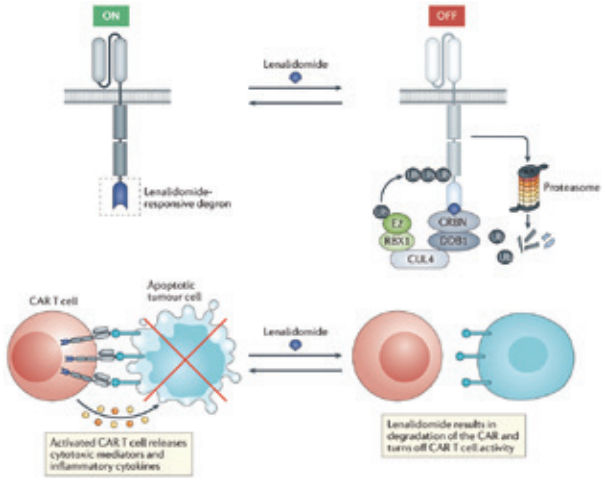


Figure 1. Molecular switch control of genetically engineered cell therapies. Incorporation of a lenalidomide-responsive degron tag into a chimeric antigen receptor (CAR) enables drug-dependent degradation mediated by the ubiquitin-proteasome system. Pharmacologic control can be used to mitigate CAR T cell hyperactivation toxicities or to tune CAR signaling. Image credit: Nature Reviews Clinical Oncology.

Development of RNA-Targeting Therapies for Malignant Brain Tumors

Anna Krichevsky, PhD
Associate Professor of Neurology, BWH
akrichevsky@bwh.harvard.edu

Dr. Krichevsky's lab focuses on small regulatory RNA molecules, microRNAs, their role in brain tumors, and potential as novel therapeutic targets and biomarkers. RNA-mediated intracellular communication between brain tumors and normal cells of their microenvironment is also a main focus of research. Dr. Krichevsky's goal is to develop basic RNA research toward a cure for glioblastoma (GBM) and other brain tumors.

Until recently, biomedical research has entirely focused on proteins and protein-coding genes as building blocks and enzymatic factors underlying human physiology and pathology. Consequently, all current precision medicine approaches are based on protein targeting. However, in recent years it became clear that the human genome is vastly transcribed to non-protein-coding RNA (ncRNA) that play diverse and multiple regulatory functions. In contrast, only 2% of the genome is protein-coding. Targeting regulatory ncRNA species would expand the repertoire of therapeutic targets and the space for drug development tremendously.

The mission of the Krichevsky lab is to explore diverse types of regulatory RNAs in the most devastating human neurologic diseases, including neurodegenerative diseases (such as Alzheimer's) and malignant brain tumors (such as GBM). Our immediate goal is to target GBM dependencies on molecular circuits controlled by regulatory RNAs. The talk will illustrate the potential of ncRNA targeting using microRNA-10b and associated long ncRNAs as an example. Possible therapeutic strategies rely on antisense oligonucleotides and CRISPR-Cas9 gene editing and will pave the road for similar approaches for other malignancies and neurologic disorders.

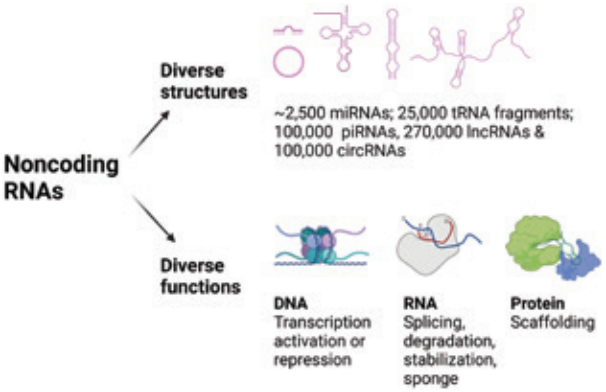


Figure 1. Hundreds of thousands of non-coding RNAs, short and long, with diverse regulatory functions, are expressed from the human genome.

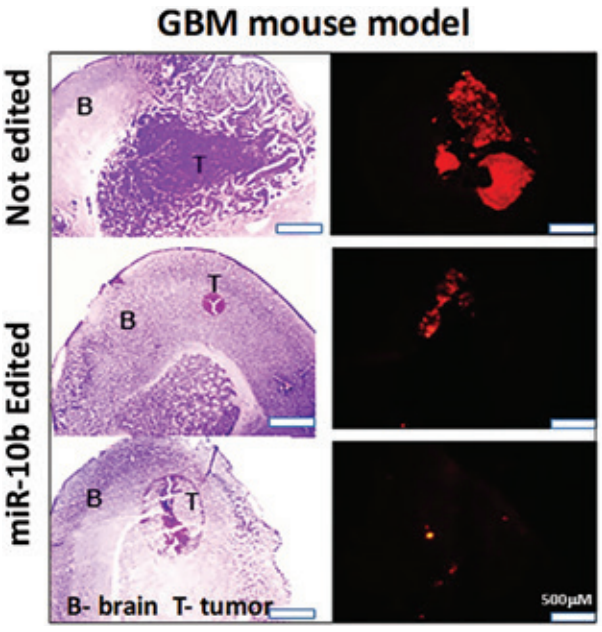


Figure 2. Gene editing of essential miRNA-10b in orthotopic glioblastoma in vivo reduces tumor growth and extends animal survival (El Fatimy … Krichevsky, Mol Therapy 2017).

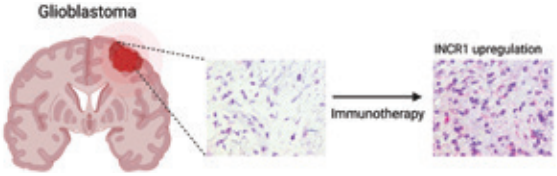


Figure 1. INCR1 is upregulated in patients treated with immunotherapy.

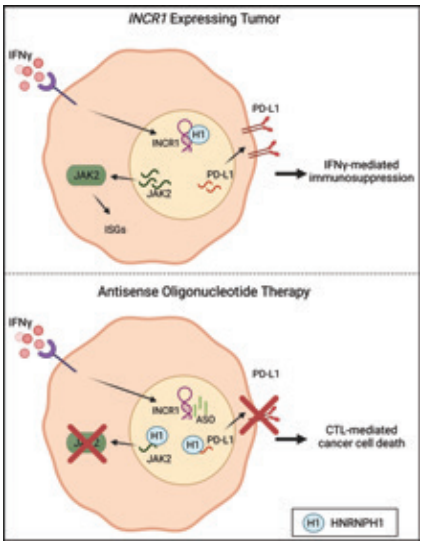


Figure 2. INCR1 regulates tumor interferon signaling.

Antisense Oligonucleotides for Cancer Immunotherapy

Marco Mineo, PhD
Instructor in Neurosurgery, BWH
mmineo@bwh.harvard.edu

Dr Mineo's work is focused on developing a new approach to treatment of glioblastoma. His work brings together his understanding of the tumor microenvironment with his expertise in long noncoding RNA, his work uses gene therapy to manipulate tumor cells in a way that will make them more susceptible to attack by immunotherapies. Dr Mineo has demonstrated the effectiveness of this strategy in animal models and is working on pre-IND studies.

Cancer is the second leading cause of death worldwide. Despite the significant advances in tumor targeted therapy and the development of novel drugs, there remain a large number of cancer patients who do not respond to therapy. In addition, personalized treatments available may be toxic for some patients. As a result, there is an urgent need to identify new therapeutic options. The need for novel therapies is even higher in certain cancers, such as glioblastoma, in which the standard of care has not advanced beyond maximum possible resection, radiation, and chemotherapy. For these patients, the median survival remains only few months. Immunotherapies have been shown to be effective in some types of cancer, such as melanoma, but remain mostly ineffective in glioblastoma, which is characterized by a highly immunosuppressive microenvironment.

Understanding the molecular mechanisms of resistance may pave the way for more effective immunotherapeutics that overcome current limitations. We have recently identified the interferon-stimulated noncoding RNA 1 (INCR1) as a novel long non-coding RNA transcribed from the PD-L1 locus, and showed that INCR1 is highly inducible in tumor cells stimulated with interferon-γ. We demonstrated that INCR1, through the interaction with the ribonucleoprotein HNRNPH1, regulates tumor interferon signaling and the expression of different immunosuppressive molecules. Moreover, we showed that silencing INCR1 could improve effectiveness of different immunotherapies, such as CAR T and IL-12 therapy. INCR1 functions can be therapeutically blocked using antisense oligonucleotides (ASOs), which are currently FDA-approved for the treatment of a variety of disorders. We recently designed ASOs targeting INCR1, and showed their ability to inhibit the expression of INCR1 and reduce the levels of immunosuppressive molecules. Therefore, our results suggest the use of ASOs targeting INCR1 as potential immunotherapeutic strategy for the treatment of cancer.

yBOTs: Self-Tunable Engineered Yeast for Controlled Therapeutic Delivery

Francisco Quintana, PhD
Professor, Neurology, Ann Romney Center for Neurologic Diseases, BWH; Kuchroo Weiner Distinguished Professor of Neuroimmunology, HMS
fquintana@bwh.harvard.edu

The Quintana Laboratory is focused on the characterization of signaling pathways that control the activity of the immune system, with the ultimate goal of identifying novel therapeutic targets and biomarkers for immune-mediated disorders.

Current therapeutic approaches are limited to a passive, one-size-fits-all modality that is oblivious to the changing needs of each individual patient, failing to rapidly adapt to changes in disease state and often leading to adverse effects. To address this unmet clinical need, we engineered yBOTs (yeast robots), which provide a new therapeutic platform capable of sensing disease-associated molecules and responding with the release of a therapeutic compound at the right dose, at the right time and in the right location. Specifically, yBOTs are yeast cells modularly engineered to quantitatively detect disease-associated stimuli and respond with the release of therapeutic effector molecules in a self-tunable manner.

We first evaluated the potential of yBOTs-based therapies on Inflammatory Bowel Disease (IBD), a chronic disorder of the gastrointestinal (GI) tract where most available therapies suppress the immune system systemically, increasing the risk of infections and cancer, while not benefiting all patients. Using three independent pre-clinical IBD preclinical models, we demonstrated that yBots could significantly reduce GI tract pathology by targeting 3 important contributors to the disease process: 1) Inflammation driven by innate and adaptive immune cells; 2) fibrosis; and 3) dysbiosis. These findings support the use of yBOTs for the treatment of GI tract inflammation. In addition, yBOTs can be engineered to detect multiple disease markers and release multiple therapeutic effectors.

yBOTs provide a tunable platform for controlled therapy delivery, which can be designed to treat GI and/or systemic inflammation, metabolic and genetic disorders, as well as gut-brain axis related CNS disorders.

Gene Therapy for Tuberous Sclerosis Complex

Vijaya Ramesh, PhD
Co-Director, Neuroscience,
Associate Geneticist in Neurology, MGH;
Professor of Neurology, HMS
ramesh@helix.mgh.harvard.edu

The Ramesh Laboratory has been investigating the pathophysiology of Neurofibromatosis 2 (NF2) and Tuberous Sclerosis Complex (TSC) for almost two decades. Our work on NF2 in human arachnoidal and meningioma cells discovered that NF2 protein merlin is a novel negative regulator of mTORC1 signaling. This work has been translated into clinical trials with RAD001 for NF2 and sporadic meningiomas. We have also established CRISPR-Cas genome editing technology in human arachanoidal cells, Schwann cells and iPSCs and have used this technique to create/correct mutations in NF1, NF2, TSC1 and TSC2 generating isogenic sets of human lines for drug screening.

TSC is a multisystem disorder that includes epilepsy, autism spectrum disorder (ASD), intellectual disability (ID), and hamartomas in many organs. TSC is caused by mutations in the TSC1 or TSC2 gene, encoding proteins hamartin (TSC1) and tuberin (TSC2), respectively. The TSC proteins act as a central hub relaying signals from diverse cellular pathways to control mammalian/mechanistic target of rapamycin complex 1 (mTORC1) activity, which regulates cell growth and proliferation. The aberrant activation of mTORC1 in TSC has led to treatment with mTORC1 inhibitor rapamycin analogs as a lifelong therapy since discontinuation leads to increase in growth of the TSC-associated lesions, and further treatment or lack of it can potentially compromise early brain development.

Therefore, there is a clear need to identify other therapeutic approaches for TSC. Toward this goal, gene therapy was evaluated in collaborative efforts between our laboratory and the Breakefield and Maguire laboratories at MGH, employing TSC2-patient-derived neural progenitor cell models (NPCs) and a mouse model of TSC2 using an AAV vector carrying a "condensed" form of tuberin (cTuberin). Functionality of cTuberin was first verified in human cellular models. A mouse model of TSC2 was generated by AAV-Cre recombinase disruption of Tsc2-floxed alleles at birth, leading to a shortened lifespan and brain pathology consistent with TSC. When these mice were injected intravenously on day 21 with AAV9-cTuberin, the mean survival was very significantly extended with reduction in brain pathology. This study demonstrates the preclinical efficacy of a single intravenous injection of AAV9-cTuberin, setting the stage for IND-enabling studies and clinical translation.

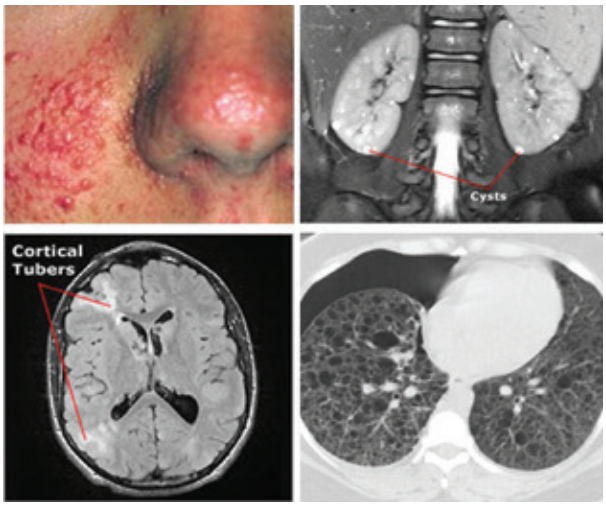


Figure 1. Tuberous Sclerosis Complex (TSC) is a multisystem disorder characterized by tumors affecting multiple organs as well as autism, epilepsy and intellectual disability.

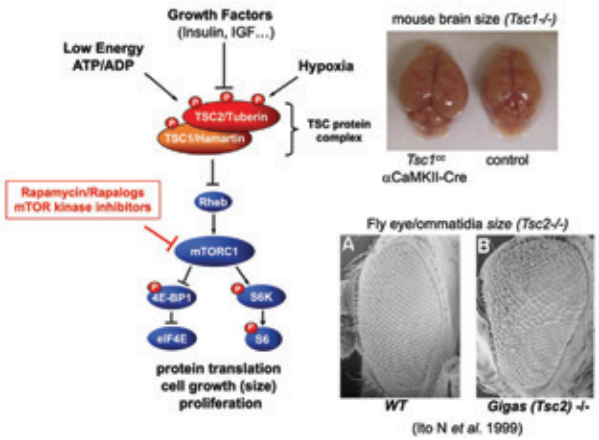


Figure 2. TSC protein complex is a master negative regulator of mTORC1 signaling, a key cellular sensor pathway integrating upstream external signals with downstream protein translation, cell size and proliferation.

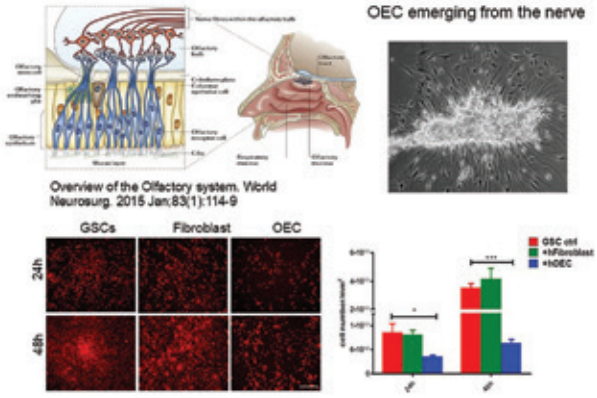


Figure 1. OEC inhibit patient-derived glioma stem cells (GSCs) self-renewal and proliferation.

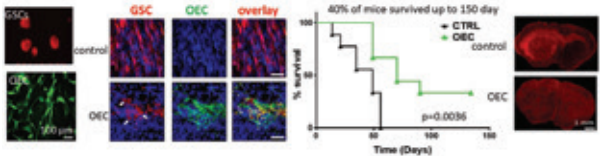


Figure 2. OECs migrate to GBM through the nasal pathway and induce striking cytotoxic anti-cancer effect and increase survival with 40% of mice survived >150 days and were cancer free.

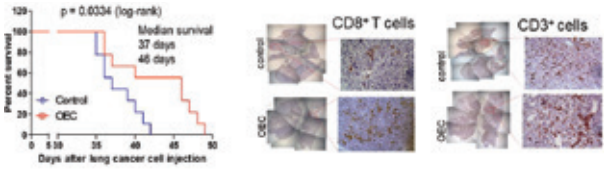


Figure 3. OEC induces cytotoxic effect in an aggressive lung cancer model.

Olfactory Ensheathing Glia: An Unconventional Cell for Cancer Gene/Cell Therapy

Bakhos Tannous, PhD
Director, Experimental Therapeutics Unit, Director, Viral Vector Core, MGH;
Associate Professor of Neurology, HMS
btannous@mgh.harvard.edu

Dr. Tannous is focused on developing experimental therapeutics against malignant pediatric and adult brain tumors including diffuse intrinsic pontine gliomas (DIPG) and glioblastomas (GBM). His recent work includes the novel approach of using olfactory cells to carry anticancer therapy to deadly brain tumors. Advanced animal studies have shown the approach is effective in reducing tumor size and prolonging survival.

Gene/Cell therapy has been heralded as a potential revolution in medicine, however, when it comes to cancer in general and brain tumors in particular, this therapeutic strategy had shown limited efficacy due to the restricted delivery to the tumor site. The olfactory ensheathing cell (OEC) is a fully differentiated (not stem cell) glial cell type that closely accompanies the axons as they grow from the olfactory epithelium into the olfactory bulb. OECs naturally migrate from the peripheral nervous system to the central nervous system (CNS). Owing to their strong ability to migrate to the injury site in the brain and their neuroprotective, and immunomodulatory properties, the potential of OECs in neuronal regenerative medicine and spinal cord injury in animal models and the clinic has been widely investigated but were not studied in the context of cancer. Our group was the first to show that OECs can target GBM cells and stem-like cells in the brain of mice upon intranasal injection, the natural route of OECs to CNS, and can efficiently deliver therapeutic transgene to gliomas. We also show that OECs on their own can modulate cancer stemness, proliferation, and activate phagocytosis and anti-tumor immunity in aggressive brain cancer (pediatric and adult) as well as lung cancer models. In addition, we engineered OECs to secrete a single chain antibody against PD-1 and showed that these modified OECs can activate both cancer innate and adaptive immunity leading to efficient immune checkpoint blockade at the tumor site.

OEC offer several advantages over typical stem cell therapy: (1) OECs can be easily obtained from the olfactory epithelium and/or olfactory bulb, a very simple procedure, allowing autologous transplantation; (2) no toxic or tumorigenic potential (since they are fully differentiated cells) with OEC transplantation have been reported to date; (3) OEC natural migration to CNS during olfactory receptor turnover and injury gives them an additional advantage for brain tumor therapy; (4) OECs can also be injected systemically and treat tumors outside the brain, including lung.

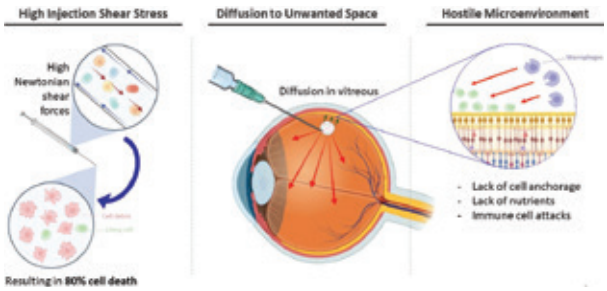


Figure 1. Key reasons why a small percentage of viable cells make it to the target site.

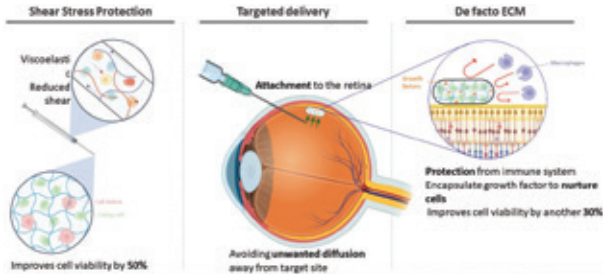


Figure 2. InGel addresses the challenges of cell delivery in the eye with its technology.

A New Hydrogel for Ocular Delivery

Michael Young, PhD
Director, Minda de Gunzburg Center for Retinal Regeneration, Associate Scientist, Schepens Eye Research Institute, Mass Eye and Ear; Associate Professor of Ophthalmology, Co-Director, Ocular Regenerative Medicine Institute, HMS
michael_young@meei.harvard.edu

Dr. Young's work focuses on the degeneration that occurs in the retina during disease or injury. He is currently studying human retinal stem cells with the goal of transplanting these cells to the diseased eye to establish functional connectivity between donor retinal stem cells and the mature, diseased host retina.

The Young Lab developed InGel technology to address the challenge of delivering stem cell therapies to the eye due to the low viability and attachment of transplanted cells. The huge efficacy gap seen between in vitro cell study and in vivo transplantation is caused by the use of phosphate buffer saline as an excipient for cell injection. To address this problem, we have created a biomimetic delivery system which enhances the viability and attachment of cells both in vitro and in vivo. This matrix possesses a low-immunogenicity, and can be finely tuned for the encapsulation of various types of therapeutics (stem cells, small molecules, or proteins) offering a sustained release (from five days to five months) and targeted delivery in the eye.

In vitro preliminary data showed a consistent improvement in retinal stem cells (photoreceptor progenitors, ganglion cells, RPE, fetal retina, hRPC) viability and phenotype when cultured in our biomatrix. Proof of concepts for safety and efficacy in vivo have been performed in multiple rodent studies (three rodent models) for various indications including Retinitis Pigmentosa and Glaucoma, which require stem cell transplantation for regenerative medicine. Low-immunogenicity has been shown with the injection of our matrix in both the vitreous and subretinal space without detectable immune reaction.

An AAV-based Single Dose, Thermostable Vaccine Platform that Provides Durable Immunogenicity

Nerea Zabaleta, PhD
Principal Investigator, Grousbeck Gene Therapy Center, Mass Eye and Ear; Instructor in Ophthalmology, HMS
nerea_zabaletalasarte@meei.harvard.edu

Dr. Zabaleta is focused on improving AAV-based gene therapies for infectious diseases. She is currently working on a novel, gene-based COVID-19 vaccine that leverages a unique AAV platform. This approach was highly effective at eliciting neutralizing antibody responses and cellular immunity from a single dose.

The SARS-CoV-2 pandemic has had a disastrous impact on health and economy globally. Although several vaccine candidates have shown to be effective in combating SARS-CoV-2, logistical, economical and sociological aspects limit vaccine access and effectiveness globally. Additionally, mRNA vaccines present limitations that include the need for several doses to induce high immunogenicity, limited durability of responses, and cold-chain requirements. In the light of these limitations highlight the need for improved vaccine platforms, for the current, as well as future, pandemics.

We have developed and characterized an adeno-associated virus (AAV)-based genetic vaccine for COVID-19 and validated this across different SARS antigens. After a single, low dose administration in non-human primates (NHP), our vaccines induce high humoral and cellular immune responses to the antigen, conferring near-complete protection against a live SARS-CoV-2 viral challenge. Additionally, neutralizing antibody responses remain at peak levels for at least 20 months after single dose vaccination, with no signs of waning immunity. Cellular responses to the antigen were also found to be high, polyfunctional and durable. We further demonstrated a rapid and robust programmability of our vaccine platform to express different SARS antigens, which elicit potent and protective immunogenicity against several variants of concern. Finally, we demonstrated that AAV-based vaccines can be manufactured at scale and are stable for 1 month at room temperature and for at least 3 months refrigerated, considerably reducing cold chain requirements.

In conclusion, AAV-based vaccines present ideal features for the development of vaccines: a single and low dose that elicits high and durable immunogenicity, and room temperature stability. High circulating antibody responses and protection from SARS-CoV-2 challenge suggest that our platform has the potential to confer protective immunity against respiratory infection as well as other mucosal or systemic viruses.

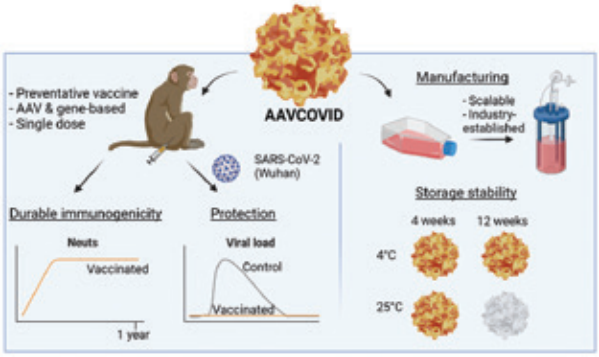


Figure 1. Graphical abstract that summarizes some important attributes of AAV-based vaccines.

WWW.RECONSTRATEGY.COM

Recon Strategy is a consulting firm focused on strategy in life sciences and healthcare.

We work with biotech, diagnostics, and medical device clients across a broad set of topics from R&D to commercial to corporate strategy, and ranging from single assets to robust portfolios and franchises.

Our experienced partners work closely with our clients to bring a unique blend of clinical, scientific, and business perspectives to every assignment, essential in areas like cell and gene therapy that are pushing the boundaries of our understanding of human biology.

BIOTECH | THERAPEUTICS | DEVICES | PAYERS | PROVIDERS | AI | DIGITAL HEALTH

Sponsors

Presenting

BANK OF AMERICA

Bank of America
Charlotte, NC

Bank of America is one of the world's leading financial institutions, serving individual consumers, small and middle-market businesses and large corporations with a full range of banking, investing, asset management and other financial and risk management products and services. The company provides unmatched convenience in the United States, serving approximately 66 million consumer and small business clients with approximately 4,300 retail financial centers, approximately 17,000 ATMs, and award-winning digital banking with approximately 41 million active users, including approximately 32 million mobile users. Bank of America is a global leader in wealth management, corporate and investment banking and trading across a broad range of asset classes, serving corporations, governments, institutions and individuals around the world. Bank of America offers industry-leading support to approximately 3 million small business households through a suite of innovative, easy-to-use online products and services. The company serves clients through operations across the United States, its territories and approximately 35 countries. Bank of America Corporation stock (NYSE: BAC) is listed on the New York Stock Exchange.

www.bankofamerica.com

Innovation Champion

Novartis
Basel, Switzerland

Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 110,000 people of more than 140 nationalities work at Novartis around the world.

www.novartis.com

Innovation Partner

Astellas
Tokyo, Japan

Astellas Pharma Inc. is a pharmaceutical company conducting business in more than 70 countries around the world. We are promoting the Focus Area Approach that is designed to identify opportunities for the continuous creation of new drugs to address diseases with high unmet medical needs by focusing on Biology and Modality. Furthermore, we are also looking beyond our foundational Rx focus to create Rx+® healthcare solutions that combine our expertise and knowledge with cutting-edge technology in different fields of external partners. Through these efforts, Astellas stands on the forefront of healthcare change to turn innovative science into value for patients.

www.astellas.com

Bayer
Leverkusen, Germany

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to drive sustainable development and generate a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world.

www.bayer.com

Media

Cell & Gene
Erie, PA

Cell & Gene provides actionable information to professionals involved in the development and commercialization of cell and gene therapies. Through the original editorial published on the site, Cell & Gene facilitates the sharing of insights on challenges, trends, and best practices in this burgeoning field. Cell & Gene's editorial scope spans the entire product lifecycle from basic research to commercialization.

www.cellandgene.com

Content Partner

Recon Strategy
Cambridge, MA

Recon Strategy is a healthcare and life sciences focused consulting firm founded in 2010 by alumni of the Boston Consulting Group. The firm works with biotech, diagnostics, and medical device clients on a broad set of topics from R&D to commercial to corporate strategy, and ranging from single assets to portfolios and franchises.

www.reconstrategy.com

Join us in

2023

Registration is now open.

Full registration, discounted at $699, is available until May 9, 2022. Register online or at the Forum registration desk to take advantage of this special conference week discount.

June 12–14, 2023

Boston, MA | The Westin Boston Seaport District

worldmedicalinnovation.org

Scan Now to Register

Mass General Brigham

World Medical Innovation Forum

In partnership with
BANK OF AMERICA

Mass General Brigham Innovation
innovation.massgeneralbrigham.org