Mass General Brigham

World Medical Innovation Forum

In partnership with
BANK OF AMERICA

June 12–14, 2023

2023.worldmedicalinnovation.org

cns • brain health | oncology | inflammation • immunology

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Agenda – daily timing and locations
Attendee Networking
Panel Q&As
Speaker Bios
Program Content

Search for 'World Medical Innovation Forum' in your respective software app store.

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 Grand Ballroom foyer.

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Welcome to the World Medical Innovation Forum. Our speakers and attendees look forward to sharing their views on the future of healthcare innovation and investment. Please be aware, that by attending this Forum, you are agreeing to abide at all times by the Forum's respectful and collaborative environment.

World Forum App

Full agenda for the 2023 World Medical Innovation Forum can be found on the Forum app

Welcome.

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

Now in its ninth year, the Forum brings together experts across sectors for in-person dialogue on new technologies. Mass General Brigham faculty and leaders from Bank of America, our presenting sponsor, share perspectives with entrepreneurs, executives, investors, and government leaders. The cross-industry connections facilitated by the Forum are critical to translating those technologies to benefit patients.

For more than 200 years, Mass General Brigham has been among the world's foremost engines of scientific discovery and medical progress. Research and innovation are central to our mission and vision for the future. The insights of our faculty have resulted in more than 300 spin-off companies in just the last decade, many of them fueled by the $500 million under management by Mass General Brigham Ventures.

These discoveries and the companies that bring them to patients are at the core of the $54 billion that Mass General Brigham contributes to the Massachusetts economy, and enable people around the world to benefit from Boston's unrivaled biotech hub.

This year, the Forum is focused on three key areas that are poised for significant breakthroughs and increased investment -- central nervous system/brain health, oncology, and immunology and inflammation. Entrepreneurs, investors, physicians, executive and government leaders will examine the newest technology for treating patients and applications in therapies, diagnostics, and software. Additionally, the Forum's more than 150 speakers are immersed in our mission to create innovation that addresses medical challenges and is accessible for patients no matter their location, economic status, or race.

I want to thank the countless individuals who collaborated to make the 2023 World Medical Innovation Forum a reality and each of you for attending and enriching these important conversations with your perspective. I am confident that the connections forged over the next three days will be invaluable for you.

Thanks for joining.

Brian Moynihan
Chair and CEO, Bank of America

Bank of America is pleased to once again partner with Mass General Brigham to welcome CEOs, investors, innovators, academics, and other leaders across the industry to Boston. Greater Boston is a global biotech and investment hub, with significant advances in medicine happening here every day. It's also home to more than 3,700 Bank of America teammates.

The World Medical Innovation Forum was founded in 2015 with the belief that collaborative innovation—industry and academia working together—ultimately drives better patient lives. This vision continues to guide the Forum and its content, and it aligns with our purpose at Bank of America: making financial lives better through the power of the connections we can help make – for our clients and in this community.

Our partnership with Mass General Brigham to bring you the World Medical Innovation Forum is just one of the ways we are promoting economic opportunity within Greater Boston and the surrounding areas. In addition to helping connect innovators to capital through the forum, we also partner with organizations including Ascendus, Small Business Strong, and Year Up to connect our clients and communities to tailored resources like technical assistance, financial education, and access to jobs and training.

We are pleased to serve clients of every size, from startups through going commercial enterprises to global pharma leaders and world-renowned research institutes. Bank of America serves clients around the world with our corporate and investment banking capabilities. Since the beginning of 2021 we have advised clients on M&A transactions with an aggregate value of over $250 billion and raised more than $60 billion of equity capital and $825 billion of debt financing for our clients globally. In addition, through both our Corporate Banking and Commercial Banking businesses, we provide a full range of treasury, lending and leasing services to companies that operate around the world, and in local markets across the United States.

Our Global Research team also provides the insights and analysis our investor clients rely upon to identify breakthrough investment opportunities in Boston and around the world. Our team of more than 40 healthcare analysts helps provide insightful research to investor clients on over 500 Global Health Care Equities and Credits with a combined market capitalization in excess of $10 trillion across the U.S., Europe, Latin America, Japan, China, India and Australia. We're proud that investors have ranked our research team number one in the world in seven of the last 12 Institutional Investor surveys.

Thank you for joining us at this important gathering, and please don't hesitate to reach out to our team if we can be helpful.

We're glad you're here.

2023 PLANNING COMMITTEE CO-CHAIRS

Miceal Chamberlain
President, Massachusetts,
Bank of America

Christopher Coburn
Chief Innovation Officer,
Mass General Brigham

Welcome to the World Medical Innovation Forum, presented by Mass General Brigham in partnership with Bank of America. Thank you for joining us to invest in the future of patient care and partaking in the idea exchange in healthcare's most dynamic areas — central nervous system/brain health, oncology, and immunology and inflammation. Your involvement in the Forum signifies the crucial role we each play in shaping the insights and priorities that will impact the future of medicine. Our shared commitment to achieving the best possible outcomes for patients is at the forefront of this interactive program.

The Forum's content, scope, and execution were developed through the collaborative efforts of our Mass General Brigham and Bank of America teams. We have one collective goal: finding solutions to clinical, operational, and economic challenges to ensure that patients benefit as soon as possible. This partnership brings together financial insights with groundbreaking science and clinical care to help bridge the innovation gap between discovery and clinical application.

We extend our deepest gratitude to all those who made this Forum possible. Additional event support has been provided by Canon, and Siemens Healthineers, and we thank them for their continued engagement. Suffolk's partnership on industry outreach has raised the Forum's visibility in Boston and beyond. We would also like to express our appreciation to the Steering Committee and Planning Team for their invaluable contributions.

We hope you enjoy the Forum!

2022 World Medical Innovation Forum

GENE AND CELL THERAPY

Opening Remarks

Moderator: **Bertha Coombs**, Reporter, CNBC

Anne Klibanski, MD, President & CEO, Mass General Brigham; Laurie Carrol Guthart Professor of Medicine, HMS

Brian Moynihan, Chair & CEO, Bank of America

Event Guide

Monday, June 12

Continental Breakfast & Boxed Lunch

Grand Ballroom Foyer

First Look

Join us for 16 rapid fire presentations from Mass General Brigham researchers on the commercial opportunities for new technologies across clinical areas. Abstracts for these technologies are located on page 32 of this event guide.

Fireside Chats

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

Sree Chaguturu, MD
Chris Viehbacher
Kate Walsh

Book Signing with Dr. Robert Waldinger

3:15pm – 3:45pm, Pavilion

Opening Reception

SPONSORED BY SIEMENS HEALTHINEERS

Pavilion

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

Tuesday, June 13

Continental Breakfast & Boxed Lunch

Grand Ballroom Foyer

Fireside Chats

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

Robert Califf, MD
Arpa Garay
David Ricks

Attendee Reception

SPONSORED BY CANON MEDICAL

Pavilion

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

World Forum App

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

Wednesday, June 14

Continental Breakfast & Boxed Lunch

Grand Ballroom Foyer

Fireside Chats

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

Mikael Dolsten, MD, PhD
Scott Gottlieb, MD

Disruptive Dozen

Don't miss the announcement of the 2023 Disruptive Dozen. This rank order of the 12 technologies that Mass General Brigham faculty feel will break through over the next 18 months offers a capstone on the Forum and reveals key discoveries for patients around the world.

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

The Doctor Is In

Join us for an immersive experience as experts from Mass General Brigham and other leading organizations take the stage to explore the forefront of medical innovation and markets. Get ready to be enlightened by interactive conversations that delve into the most cutting-edge trends and shed light on the future of healthcare.

Experts will guide you through thought-provoking discussions on various topics, including reimagining mental health clinical trials, AI's transformative power in healthcare, and the pivotal role of incubators and accelerators in the innovation ecosystem. We'll also take a deep-dive into the captivating world of inflammation and immunology, navigate the intricate economics of academic medical centers (AMCs), and uncover strategies to profoundly impact research and clinical care.

If you're hungry for knowledge and seeking to stay ahead in the ever-evolving healthcare landscape, this is an opportunity you can't afford to miss. Join us on Monday for a series of targeted breakouts that promise to elevate your understanding and leave you inspired. Remember to check the app and hallway signage for room locations. The future of healthcare awaits your exploration!

Academic Innovation's Citadel | Wellman Center's Unrivaled Translation

Renowned as a pioneer in light-based biomedical research, the Wellman Center for Photomedicine has led the way in translating its discoveries into tangible clinical applications, profoundly impacting healthcare. Its opportunity focused approach transcends boundaries and has produced an unbroken flow of first in class products. This session, led by legendary inventor and Wellman head, Rox Anderson MD, will highlight the next wave and the inspirations behind it.

Moderator: **Rox Anderson, MD**, Lancer Endowed Chair of Dermatology; Director, Wellman Center for Photomedicine, MGH; Professor of Dermatology, HMS

Conor Evans, PhD, Principal Investigator, Wellman Center for Photomedicine, MGH; Associate Professor, HMS

Lilit Garibyan, MD, PhD, Physician-Scientist, Wellman Center for Photomedicine, MGH; Associate Professor of Dermatology, HMS

Generative AI, ChatGPT, and the Rapidly Changing Role of AI in Healthcare

Delve into this thought-provoking discussion about the future of LLMs (Large Language Models) in healthcare. We'll discuss the opportunities for these cutting-edge technologies in the short- and long-term while keeping a close eye on potential biases in their development and their impact on equity in care. Discover the role of AMCs (Academic Medical Centers) in preparing for LLM integration, the ins and outs of insurance approvals and appeals, and the regulatory landscape for LLMs in clinical practice, research, and operations. Plus, we'll tap into the unique assets for building and validating LLM datasets, discuss approaches to industry collaboration, and brainstorm ways to ensure safe and liability-free LLM implementation. Don't miss this dynamic conversation!

Moderator: **Adam Landman, MD**, Vice President, Chief Information Officer, and Digital Innovation Officer, BWH

Brian Anderson, MD, Chief Digital Health Physician, MITRE

Ruth Carlos, MD, Professor of Radiology, Assistant Chair Clinical Research, University of Michigan

Munjal Shah, Co-Founder & CEO, Hippocratic AI

Varun Singh, PhD, President & Co-Founder, Moveworks

Biotech Deal Making Draws Increasingly on Accelerators and Incubators Especially in America's Innovation Hub

An increasing portion of the translation of disruptive medical innovation is occurring via the work of incubators and accelerators. Boston is home to some of the best in the business that drive commercial success and entrepreneurial outcomes around the United States and abroad. Experts will explore transformative, sustainable, and equitable solutions that emerge from these vibrant startup hubs. Panelists carve into how to optimize the return from accelerators, discuss unique benefits and challenges, and offer insights on maximizing these valuable resources' impact. Enable your inner innovator, join this engaging session!

Moderator: **Roger Kitterman**, Senior Vice President, Venture, Business Development and Licensing, Mass General Brigham

Cait Brumme, CEO, MassChallenge

Ann DeWitt, PhD, General Partner, The Engine

Johannes Fruehauf, MD, PhD, Founder & General Partner, Mission BioCapital; Co-Founder & President, LabCentral; CEO, BioLabs

Marc Succi, MD, Executive Director, Mass General Brigham MESH Incubator; Associate Chair of Innovation & Commercialization, Mass General Brigham Radiology; Strategic Innovation Leader, Mass General Brigham Innovation

The Future of Academic Medical Centers | Economic Challenges, Adaptation, and Opportunities

Explore the significant economic challenges facing Academic Medical Centers (AMCs) and how they will adapt over the next decade. Panelists will share insights on new models needed for AMCs to maintain economic viability and potentially thrive in the coming years. Gain strategies for supporting the clinical, research and educational missions and the potential opportunities that lie ahead.

Moderator: **Niyum Gandhi**, Chief Financial Officer, Mass General Brigham

Andrew Bressler, Managing Director, Global Research, BofA Securities

Adam Harpool, Principal, Health & Digital, Oliver Wyman

Cheryl Sadro, Chief Financial Officer, UC Davis Health

Inflammation and Immunology: Balancing the Risks and Rewards of Immune System Modulation in Treatment

Join us for our thought-provoking panel discussion where we'll unpack the complexities of inflammation and immunology. We'll be delving into the risks and rewards of using checkpoint inhibitors in cancer treatment and exploring the potential complications that arise from immune system activation. Our experts will also shed light on how inflammation can contribute to cardiovascular disease and share insights on the latest research and treatment approaches. So join us for this illuminating conversation, and let's put our immune systems under the microscope!

Moderator: **Katherine Liao, MD**, Associate Physician, Department of Rheumatology, Inflammation, and Immunity, BWH; Associate Professor of Medicine and Biomedical Informatics, HMS

Moderator: **Jeffrey Sparks, MD**, Associate Physician, BWH; Associate Professor of Medicine, HMS

Nicole LeBoeuf, MD, Chief of Oncodermatology, BHW; Vice Chair of Dermatology, Dana-Farber Brigham Cancer Center; Associate Professor of Dermatology, HMS

Brittany Weber, MD, PhD, Director, Cardio-Rheumatology Clinic, Associate Physician, Prevention Cardiology and Cardiovascular Imaging, BWH; Instructor of Medicine, HMS

Mental Health Clinical Trials I Measurable vs. Hype

It's time to rethink the approach to clinical trials in mental health and develop a new model that prioritizes measurable outcomes. Hear from experts on charting a path toward a more quantifiable and effective future for mental health clinical research that will result in more reliable trial results and lead to new treatments and improved patient care. Our panelists will share their insights as to why a shift in clinical trial design is so important to innovation in mental health and expansion of opportunities with the improved risk:benefit ratio required by investors

Moderator: **Kerry Ressler, MD, PhD**, Chief Scientific Officer, McLean Hospital; Professor of Psychiatry, HMS

Laura Germine, PhD, Co-Director of the Institute for Technology in Psychiatry, President of the Many Brains Project, McLean Hospital; Associate Professor of Psychiatry, HMS

Philip Wang, MD, DrPH, Director of the Center for Learning Health Systems, BWH; Professor of the Practice of Psychiatry, HMS

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

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Paul Ridker, MD
Director, Center for Cardiovascular Disease Prevention, BWH; Eugene Braunwald Professor of Medicine, HMS

Rudolph Tanzi, PhD
Director, Genetics and Aging Research Unit, Co-Director, McCance Center for Brain Health, MGH; Joseph P. and Rose F. Kennedy Professor of Neurology, HMS

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A special thanks to Innovation's Planning Committee and Event Team for their unwavering commitment over the last 18 months to create the 2023 World Medical Innovation Forum.

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2022 World Medical Innovation Forum

GENE AND CELL THERAPY

Gene and Cell Therapy Safety | Enduring Framework Required

Moderator: **Christine Seidman, MD**, Director, Cardiovascular Genetics Center, BWH; Smith Professor of Medicine & Genetics, HMS

Rick Fair, President & CEO, Bellicum

Alexandria Forbes, PhD, President & CEO, MeiraGTx

Sekar Kathiresan, MD, CEO, Verve Therapeutics

Rick Modi, CEO, Affinia Therapeutics


neral Brigham
Medical Innovation Forum
AMERICA

Innovation in CNS, Oncology, Inflammation/Immunology:

Primed for Growth

CNS • Brain | Oncology | Immunology • Inflammation

This year's World Medical Innovation Forum delves into three key areas of biomedical innovation and healthcare: CNS/Brain Health, Oncology, and Immunology and Inflammation (I&I). Here, we highlight emerging themes in these areas that showcase the efforts of trailblazing faculty members across the Mass General Brigham system and underscore the impact of discovery and development throughout the healthcare innovation ecosystem. The themes described below also represent fields that are on the cusp of significant growth, both from the standpoint of clinical care and healthcare investment.

Harnessing the power of biomarkers for neurodegenerative diseases

Therapeutic development in neurodegenerative disease is at a watershed moment. With recent FDA approvals in both amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD), there are now a small handful of treatment options that can, in some individuals, slow the course of disease. Mass General Brigham faculty have been a driving force in this effort, unraveling the biology of disease and its clinical manifestations, and translating that knowledge into groundbreaking therapeutics.

At the same time, the field is also rethinking its approach to drug discovery and development for neurodegenerative diseases. That includes the identification of robust molecular markers that can enable clinicians to diagnose disease at its earliest stages — before outward symptoms emerge — and also help monitor disease progression and response to therapy.

"The problem now is that neurodegenerative diseases typically aren't diagnosed until the brain has deteriorated to the point of irreversible dysfunction," said Rudolph Tanzi, PhD, Director of the Genetics and Aging Research Unit, Co-Director of the McCance Center for Brain Health and Co-Director of the MassGeneral Institute for Neurodegenerative Disease at Massachusetts General Hospital and Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School. "So, the future is really about developing methods to support early disease detection and early intervention."

Incorporating biomarkers into clinical development is a critical step that underpins recent therapeutic approvals in ALS and AD. Biomarkers provide an alternative readout to outcome-directed measures, allowing an early readout of whether a drug is likely to provide therapeutic benefit. This, in turn, reduces the likelihood of failure in an outcomes-directed trial.

A recently approved gene-based therapy for a rare genetic form of ALS caused by mutations in the SOD1 gene demonstrates the power of such biomarker-focused clinical trials. This new therapy, an antisense oligonucleotide known as tofersen, was shown in clinical trials to reduce the levels of a biomarker of neuronal injury by 50 percent; about 40 percent of patients showed functional improvements. Tofersen was approved under the FDA's accelerated approval pathway, and a large phase three confirmatory study based on outcomes is now underway to enable full approval of the drug for this indication.

"Only about two percent of ALS patients carry mutations in the SOD1 gene," said Merit Cudkowicz, MD, Chair of the Neurology Department and Director of the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital and Julieanne Dorn Professor of Neurology at Harvard Medical School. "But this drug really is a miracle for some of them."

She added, "With our FDA approval based on the use of a biomarker, this could help carve a path for future therapeutic innovations in neurodegenerative disease."

The clinical evolution of CAR T-cell therapy

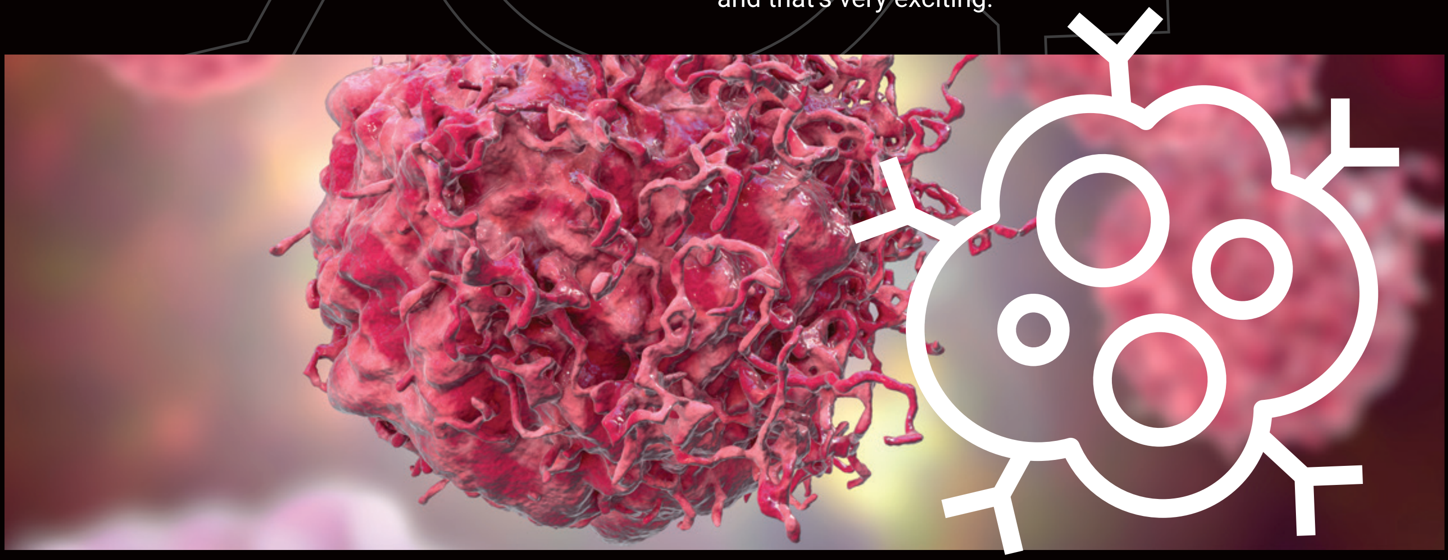
CAR T-cell therapy emerged as a groundbreaking treatment for patients with advanced forms of B-cell acute lymphoblastic leukemia (ALL) in 2017. Over the last several years, this therapeutic modality has undergone a remarkable evolution — propelled in part by the research and clinical innovations of Mass General Brigham faculty — as it has expanded to other liquid tumors and moved earlier in the recommended treatment regimens for advanced lymphomas.

"It's absolutely remarkable to watch a patient whose cancer has relapsed multiple times go from being really sick to camping outside, hiking, and planning a weeklong kayaking trip," said Matthew Frigault, MD, who is an assistant professor of medicine at Harvard Medical School and clinical director of the Cellular Immunotherapy Program at Massachusetts General Hospital. "Instead of talking about a patient's disease and very scary end-of-life things, now after successful CAR T therapy, we talk about real life. How are the kids? What are you doing this summer? It's just phenomenal to see that as a clinician."

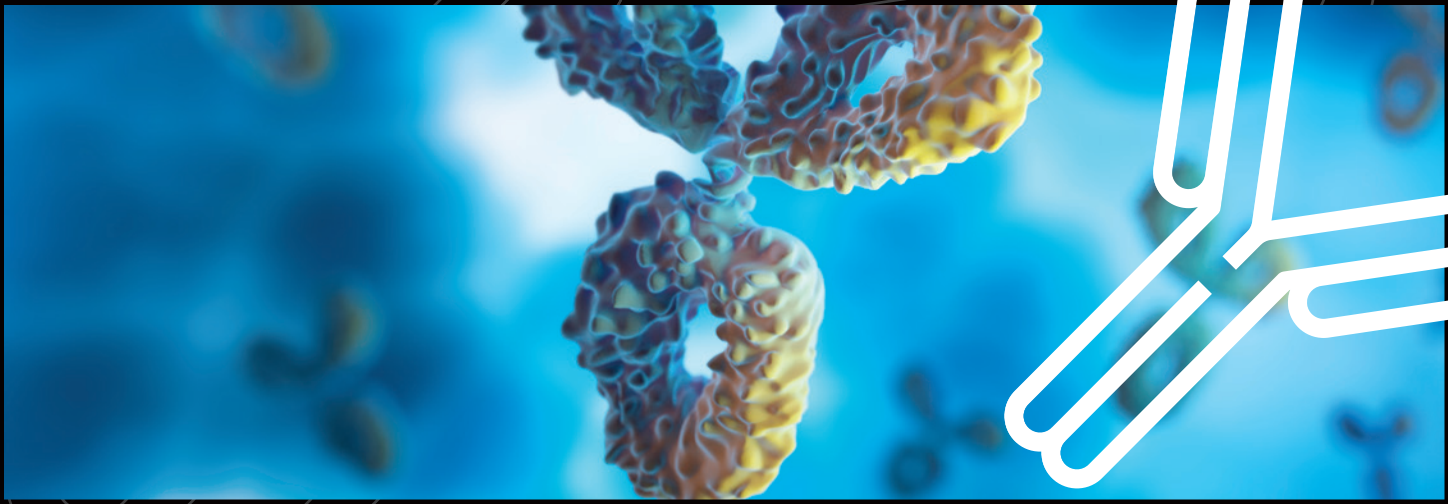
As game-changing as CAR T-cell therapy is for some patients, not every patient responds to the treatment. Moreover, the therapy is complex, and comes with a host of challenges. "It's important to remember that these are really complicated therapies to manufacture and administer — and for patients, to receive," said Frigault.

That complexity means that current autologous CAR T-cell therapies require significant time and resources in order to perform properly and a whole new clinical enterprise to deliver them to patients. As more patients become eligible for these treatments, researchers are working to devise ways to reduce that complexity — from overcoming regulatory challenges, to streamlining manufacturing, to exploring allogeneic options. Mass General Brigham's Gene and Cell Therapy Institute (see Sidebar) is dedicated to holistically advancing these and other GCT technologies.

We're really just beginning to uncover the potential of these therapies," said Frigault. "But already, CAR T-cells are becoming a mainstay of cancer therapy and that's very exciting."



The Gene and Cell Therapy Institute (GCTI) was established to unify the more than 400 Mass General Brigham researchers and clinicians working on gene and cell therapy innovations. The objective of the Gene and Cell Therapy Institute is to translate the scientific discoveries made by these researchers to first-in-human clinical trials. Working within the Mass General Brigham health care system, the Gene and Cell Therapy Institute is dedicated to delivering innovative targeted treatments that potentially can cure disease or halt its progression.



Stoking the fires in heart disease

There is an increasing recognition that inflammation underlies the development of chronic diseases linked with aging. Mass General Brigham faculty have been at the forefront of this field, uncovering the myriad intersections between inflammation and disease, and how therapeutic interventions can potentially disrupt them. Over the last few decades, one key area of work includes heart disease, a condition also fueled by elevated levels of blood cholesterol.

"Our data are clear — if we only lower cholesterol, we're not going to beat this disease," said Paul Ridker, MD, Director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital and Eugene Braunwald Professor of Medicine at Harvard Medical School. "We've got to target vascular inflammation as well."

Ridker has been a pioneer of this concept since the 1990s, when the prevailing belief was that high cholesterol — causing the buildup up of fatty plaques in the blood vessels, known as atherosclerosis — was the only driver of heart disease. His early research, which revealed that middle-aged men with high levels of an inflammatory protein, called C-Reactive Protein (CRP), were at increased risk for heart disease regardless of their blood cholesterol levels, proved to be a watershed moment in the field.

After a series of large clinical trials, including CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study,) Ridker and other Mass General Brigham researchers demonstrated that certain targeted anti-inflammatory therapies can substantially lower the risk of heart attacks and strokes without changing cholesterol levels — and also reduce the risk of developing other serious diseases such as lung cancer. Their efforts as well as others have focused attention on a key immune signaling pathway that includes the NLRP3 inflammasome, IL-1, and IL-6. Inhibition of IL-6 has become a major therapeutic priority.

Now, Ridker and his colleagues are leading two other international clinical trials, including ZEUS (Zlitivekimab Cardiovascular Outcomes Study), which is assessing the ability of ziltivekimab, a monoclonal antibody that targets the IL-6 ligand, to reduce the risk of heart disease.

"Lipid lowering and inflammation inhibition are not in conflict, but are in fact synergistic," said Ridker. "In the future, the combined use of aggressive LDL-lowering and inflammation-inhibiting therapies may well become standard of care for almost all atherosclerosis patients."

First Look

The Next Wave of Breakthroughs in Health Care

Sixteen presenters from Brigham and Women's Hospital, Massachusetts General Hospital, Massachusetts Eye and Ear, and McLean Hospital will give 10-minute presentations highlighting their discoveries and insights that will disrupt the fields of CNS/brain health, oncology, and inflammation & immunology. This session is designed for investors, leaders, donors, entrepreneurs, investigators, and others who share a passion for identifying emerging high-impact technologies.

TYK2 as a novel therapeutic target in a subset of Alzheimer's Disease with neuroinflammation

Mark Albers, MD, PhD
Frank Wilkens Jr and Family Endowed Scholar in AD Research, MGH;
Assistant Professor of Neurology, HMS
albers.mark@mgh.harvard.edu

Neuroinflammation is a pathological feature of several neurodegenerative diseases, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), raising the possibility of common therapeutic targets. However, triggers of innate immune signaling in these disease processes remain elusive.

We previously established that cdsRNA, an established trigger of innate immunity, is spatially coincident with cytoplasmic phosphorylated TAR DNA-binding protein 43 (pTDP-43) inclusions, a pathologic hallmark of ALS and AD, in neurons of patients with C9ORF72-mediated ALS. Up to 50% of brains with AD pathology harbor cytoplasmic pTDP-43 aggregation. We also found that cdsRNA is spatially coincident with pTDP-43 inclusions in brain cells of patients with AD, a striking pathological similarity to ALS. Consistent with this finding, RNA sequencing analysis on AD patients further showed that type-I interferon signaling is significantly elevated in brain regions affected by AD.

Cytoplasmic inclusions of pTDP-43 may confer nuclear hypofunction of TDP-43, which increases expression of cryptic exons in STMN2 and UNC13A. Thus, we modified our machine-learning pipeline, DRIAD (Drug Repurposing In Alzheimer's Disease), to incorporate cryptic exon detection as a proxy for pTDP-43 inclusions. Using DRIAD, we demonstrated that baricitinib and ruxolitinib (FDA-approved JAK inhibitors that block interferon signaling) show a protective signal only in cryptic exon-expressing brain regions. These results indicate that targeting JAK-mediated immune responses is not only relevant in ALS but also in the cdsRNA/pTDP-43-positive subset of AD.

We conducted a CRISPR screen in an in vitro model of cdsRNA-mediated death in differentiated human neural cells lacking microglia to identify genes whose ablation rescues the phenotype. Both the interferon receptor subunit IFNAR2 and the JAK family member TYK2 were top hits. Experimentally inhibiting the activity of IFNAR2 and TYK2 (using a blocking antibody and an FDA-approved inhibitor, respectively) rescued the cdsRNA-induced toxicity, validating these two hits and supporting further efforts to target this pathway. Together, these findings demonstrate the potential for brain-penetrant TYK2 inhibitors as drug candidates for some forms of AD, ALS, and potentially other incurable neurodegenerative diseases.

Extracellular vesicle engineering to counteract age-related cognitive declines

Fabrisia Ambrosio, PhD
Atlantic Charter Director of the Discovery Center for Musculoskeletal Recovery, Schoen Adams Research Institute, Spaulding Rehabilitation Hospital; Faculty, HMS
fambrosio@mgh.harvard.edu

Innovative medical advances have increased the average lifespan but, unfortunately, these improvements have not been satisfactorily accompanied with advances in healthspan, particularly with respect to brain health and cognition.

Physical activity is increasingly recognized to play a role in maintaining brain health. Exercise attenuates age-related cognitive declines, including loss of brain volume, impaired neurogenesis, decreased attention and learning. These benefits are attributed, at least in part, to the function of skeletal muscle: muscle contractile activity is critical for the secretion of myokines into the bloodstream, and these myokines work in a hormone-like fashion to influence the health and function of distal organs, including the brain. Identification of these exercise-induced factors can aid in the development of novel therapeutics to promote brain health with aging.

Findings from our laboratory suggest that circulating extracellular vesicles (EVs) play a major role in the non-cell-autonomous regulation of tissue aging. EVs are a broad class of membrane-bound nanoparticles that can target and reprogram cells to regulate physiological functions or pathological processes. EVs are particularly promising for central nervous system therapies because they can cross the blood–brain barrier.

We have shown that blood serum from young donors enhances muscle regeneration and cognition in aged animals. However, this effect is diminished when the serum is depleted of EVs, suggesting that circulating EVs play a central role in in this process (Figure). Our work further suggests that exercise may promote more youthful cargoes in aged circulating extracellular vesicles.

Building on these studies, we are developing novel EV engineering approaches designed to counteract the effect of aging on cognitive health. Specifically, our focus is on identifying age- and exercise-responsive EV cargoes critical for enhancing brain vitality. This work will allow us to engineer autologous EVs to express and deliver these optimized cargoes across the blood–brain barrier to neural tissues.

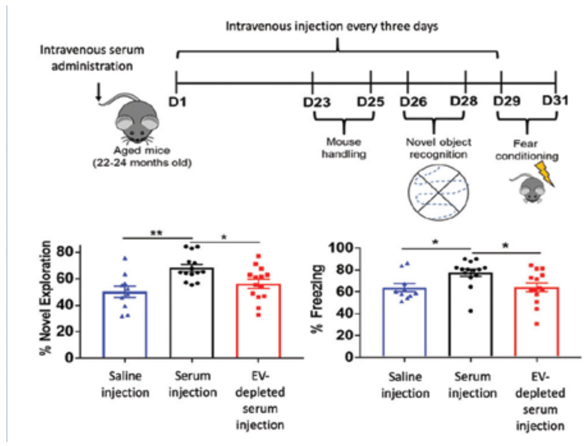


Fig. Circulating extracellular vesicles contribute to the beneficial effect of young serum on cognitive function in aged mice. (Top) Schematic of the experimental paradigm for cognitive testing in aged mice following intravenous injections of saline, young serum, or young serum depleted of EVs. (Left bottom) Quantification of % novel exploration memory test across the three groups. (Right bottom) Quantification of % freezing memory test across the three groups.

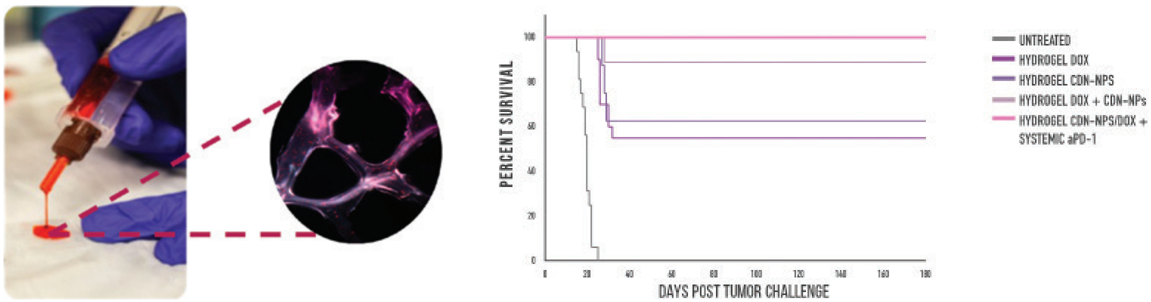


Fig. 1: Left: injectable adhesive hydrogel delivered via a double-barrel syringe; Right: Kaplan-Meier curves of orthotopic GL261 glioblastoma tumors for different treatment groups delivered locally via the adhesive hydrogel.

Delivering on the promise of immunotherapy for the treatment of brain cancer

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The Artzi lab is designing biomaterials that enhance precise drug delivery to enhance therapeutic outcomes in a range of diseases. Immune modulatory drugs can help regulate the immune system and generate a 'living,' long-lasting response. To realize the full potential of immunotherapies, there is a need for non-viral delivery systems targeted delivery and enhanced uptake to specific cells. Yet, when biological barriers to delivery limit drug accumulation in particular organs, such as in the brain, the combination of nonviral nanomaterials with macroscopic materials that can be injected in a particular site may expand the therapeutic window. We engineered an injectable dendrimer:dextran-based adhesive hydrogel that gels rapidly upon application and adheres to a tissue target. This hydrogel can be loaded with a therapeutic drug to enable localized and sustained drug delivery, bypassing the barriers associated with systemic administration.

Potential applications of this technology include autoimmune diseases and cancer, including glioblastoma (GBM)—an aggressive form of brain cancer with a median overall survival rate of 15 months. Treatment for GBM involves surgical resection followed by chemotherapy and radiation therapy. Yet, tumor recurrence is inevitable as it is impossible to eliminate all tumor cells with current strategies. The development of more efficacious therapies is hindered by the low permeability of the blood brain barrier (BBB) to systemic therapies, GBM's diffuse and infiltrative nature, and the immune quiescence in the brain. Local delivery enables the use of drugs irrespective of their ability to cross the BBB and enhances their therapeutic efficacy and tolerability.

We leveraged our injectable, adhesive hydrogel to mediate controlled local delivery of chemoimmunotherapy in the brain for GBM (Fig. 1). We demonstrated the use of this system for local and sustained release of the immunogenic chemotherapy doxorubicin in combination with a proprietary nanoparticle formulation of cyclic dinucleotides, which are stimulator of interferon genes (STING) agonists that promote an immunostimulatory tumor microenvironment. In vivo experiments in immunocompetent clonotypic murine models of GBM demonstrated that local hydrogel-mediated delivery of this chemoimmunotherapy eliminated tumors in 90% of the mice and generated anti-tumor immune memory (Fig. 1). In contrast, intratumoral delivery of the same chemoimmunotherapy resulted in rapid drug clearance and did not elicit immune memory, demonstrating the value of sustained immunotherapy delivery. This platform technology can be exploited to deliver a range of combination therapies, overcoming delivery barriers and enhancing therapeutic outcomes while minimizing side effects in GBM and other oncology and autoimmune diseases.

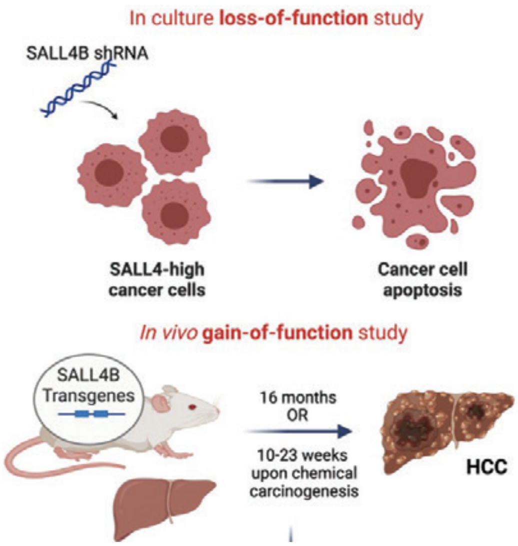

Fig. 1: SALL4B is the dominant oncogenic isoform.

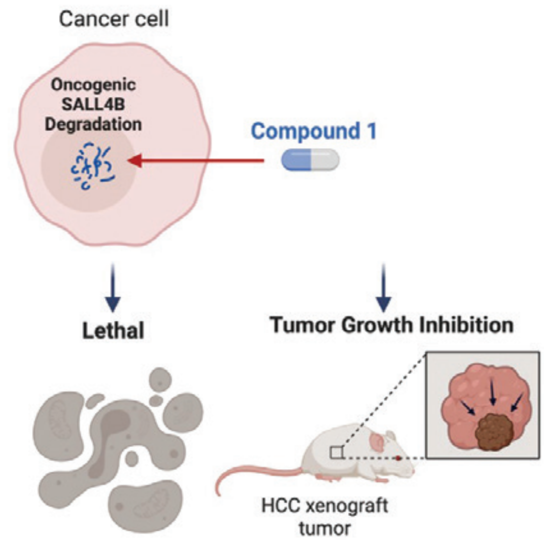

Fig. 2: Discovery of a non-IMiD SALL4 degrader.

Novel mechanism and compound targeting oncogenic transcription factor SALL4 in cancer

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Research in the Chai lab focuses on transcription factors (TFs), gene regulation, and their therapeutic applications. Oncogenic TFs, critical for cancer development and survival, historically have been viewed as “undruggable”. However, recent breakthroughs and successes have highlighted TF degradation as one of the most exciting new frontiers in the development of novel cancer drugs. Dr. Chai has led a team studying an oncogenic TF protein, SALL4, for the last 20 years.

The zinc finger TF protein SALL4 is mainly expressed in fetal tissues and silenced in most adult tissues. However, it is aberrantly re-expressed in approximately one-third of cancer patients across almost every human cancer type. We have uncovered direct evidence of the causative role of SALL4 in cancer using SALL4 transgenic mice that develop leukemia and/or liver tumors. Loss-of-function studies by knocking down SALL4 using shRNA showed cell growth inhibition and cell death in leukemias and SALL4-expressing solid tumors in both cell culture and in vivo xenotransplants. These findings demonstrate the significant potential of SALL4 as a cancer target. Further, we expect that SALL4 can be targeted with limited toxicity due to its limited expression in normal tissues.

Immune-modulatory imide drugs (IMiDs) are molecular glues that drive protein degradation; several IMiDs are approved for hematological malignancies. The mechanism of action of IMiDs involves degradation of several TFs, including SALL4. However, IMiDs do not inhibit proliferation of SALL4-expressing cancer cells. We recently discovered that IMiDs only degrade the SALL4A isoform and not SALL4B, which is likely essential for SALL4-mediated cancer cell survival. We have shown that SALL4B knockdown increases apoptosis and inhibits cancer cell growth. Further, SALL4B gain-of-function leads to liver tumor formation in mice (Fig. 1). Through a novel screening approach, we identified a new non-IMiD SALL4 degrader that can also target SALL4B via proteasomal degradation. This compound exhibits potent anticancer activity in cell culture and inhibits in vivo tumor growth by 62% (Fig. 2). This TF-targeting approach represents a promising novel IMiD-independent mechanism for cancer therapy.

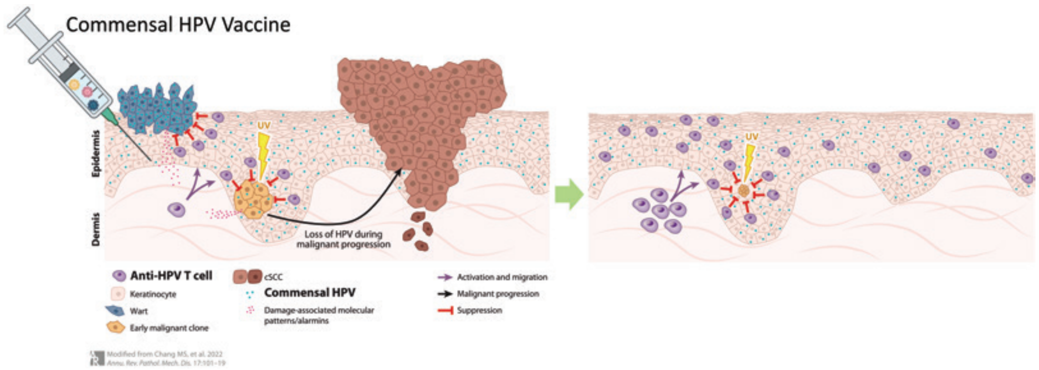

Fig. 1: T Cell Immunity to Commensal Human Papillomaviruses (HPVs) Cross-Protects Tissues Against Cancer. HPV broadly colonizes human skin cells. In the immunocompetent setting, skin cells colonized with HPV trigger T cell responses that prevent warts and block skin cancer development from malignant cells. In immunocompromised and elderly patients, the immune response to HPV is diminished, which leads to a marked increase in skin cancer risk. Thus, commensal HPV immunotherapy to boost T cell immunity in the skin can control malignant clones and prevent/treat skin cancer in the at-risk population.

Leveraging the human virome to combat cancer, autoimmunity, and other age-associated diseases

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To date, several immunotherapies have proven efficacious against late-stage cancers; however, the immune system's role in controlling the early development of cancer remains uncertain. The Demehri laboratory studies the immune system's role in maintaining tissue homeostasis and regulating the early stages of cancer development. In particular, the objective is to harness the beneficial functions of the human virome and immune system. Our research has elucidated the mechanisms that drive immune activation sufficient to prevent cancer formation from pre-cancerous lesions. This approach raises an excellent opportunity to discover novel immune pathways that can be leveraged in cancer prevention and therapy.

To realize the immune system's potential in maintaining tissue homeostasis, we study the pathways that lead to immune system activation against early phases of abnormal cellular differentiation and malignant transformation. These efforts have led us to discovering the critical role that commensal virome plays in our body. Commensals are microbes that ubiquitously reside in the body without harming human health.

Our innovative discovery posits that commensal eukaryotic viruses (e.g., HPVs and HPyVs) can play a beneficial role in maintaining healthy immune (antigen-driven) responses. Further, their absence underlies the emergence of cancer as well as aging and autoimmune diseases. With the goal of harnessing this potential, we have conducted pioneering studies on the impact of commensal virus–immune system interplay on organs exposed to environmental carcinogens and aging. We aim to determine how the immune system's control of the commensal virome regulates the homeostasis of virus-colonized tissues. The beneficial functions of the commensal virome revealed through this effort could ultimately be applied to prevent and treat cancer and other age-associated diseases.

We have generated robust proof-of-concept data showing the efficacy of commensal virome immunotherapies to combat epithelial cancers, eliminate aging cells, and protect against autoimmunity. Based on our paradigm-shifting concept, we have also developed a Discovery Engine that will feed a product pipeline of virome-directed therapeutics.

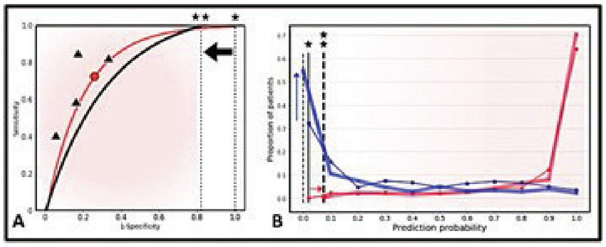

Fig. 1: Accelerating Patient Care with Innovative Triage: Our novel approach allows medical facilities to rapidly triage a vast number of normal patients, streamlining the prioritization process and greatly enhancing throughput for a more efficient healthcare experience.

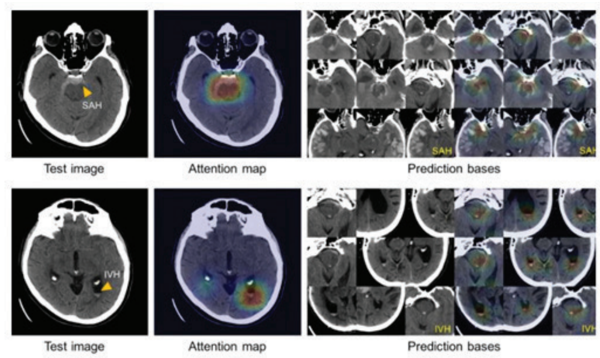

Fig. 2: An AI Solution to Repurpose SafeAI: Employing explainable AI for the detection of acute intracranial hemorrhage using a small dataset (Nature Biomedical Engineering, 2019)

SafeAI: Live Error-free or Die

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Healthcare professionals often care for numerous patients in high-pressure situations, even for brief moments. Even minor mistakes or delays can negatively impact a patient's life and lead to substantial economic losses. As a result, these skilled professionals frequently experience heavy workloads and burnout.

AI technology was expected to help mitigate this issue, but widespread implementation in real clinical environments has yet to be realized. The FDA has approved over 500 healthcare AI algorithms, most of which achieve 95% AUROC or higher or 80% sensitivity/specificity. However, this still leaves room for error, which raises the question: who will detect these errors and who is accountable for them? If AI is to be implemented systematically, its use should not make a doctor's life more difficult.

To address this concern, we have developed SafeAI, an algorithm that “eliminates mistakes while swiftly identifying only normal cases.” This doctor-friendly solution can be used independently or as a complementary addition to existing AI applications, providing extensive coverage and excellent scalability.

Our SafeAI is specifically engineered to operate at 100% sensitivity and will not function if this threshold is not met. Therefore, SafeAI can swiftly confirm normal or non-urgent outcomes. In potentially positive or equivocal cases, SafeAI avoids making an inaccurate prediction. Instead, it communicates uncertainty to the user by stating, “I don’t know.”

This technology is a product of Explainable AI, Zero Error Tolerance AI, and Continuous Learning AI, which have been extensively researched in our laboratory. We published related content in three Nature portfolio journals in 2022: focusing on identifying the sources of prediction uncertainty [1], automatically labeling necessary data in open datasets [2], and repurposing existing AI for new applications [3].

With over 10 IPs secured, we are in the process of commercializing this technology. We are currently seeking funding to submit two algorithms for FDA approval. SafeAI is groundbreaking in that it enables AI to be leveraged to improve diagnostic throughput in healthcare settings for handling 60–80% of cases that are normal or non-urgent while minimizing false negatives.

[1], Chua, M., Kim, D., Choi, J., Lee, N. G., Deshpande, V., Schwab, J., ... & Do, S. (2022). Tackling prediction uncertainty in machine learning for healthcare. Nature Biomedical Engineering, 1-8.

[2], Kim, D., Chung, J., Choi, J., Succi, M. D., Conklin, J., Longo, M. G. F., ... & Do, S. (2022). Accurate auto-labeling of chest X-ray images based on quantitative similarity to an explainable AI model. Nature communications, 13(1), 1867.

[3], Chung, J., Kim, D., Choi, J., Yune, S., Song, K., Kim, S., ... & Do, S. (2022). Prediction of oxygen requirement in patients with COVID-19 using a pre-trained chest radiograph xAI model: efficient development of auditable risk prediction models via a fine-tuning approach. Scientific Reports, 12(1), 21164

Astrocyte-derived SPP1 prevents age- and glaucoma-related loss of vision

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Glaucoma is characterized by the progressive loss of retinal ganglion cells, the neurons that connect the retina to the visual centers in the brain. The main risk factors are age, elevated intraocular pressure (IOP), and genetic factors. Currently, the mainstay of glaucoma therapy is lowering IOP, but this is not successful in all cases. Thus, alternative neuroprotective therapies are needed.

Experimental evidence shows that the first signs of ganglion cell degeneration occur in the optic nerve head, where the ganglion cell axons exit the globe to form the optic nerve. In this region, the axons come into direct contact with astrocytes, a type of supporting glial cell in the central nervous system. Optic nerve astrocytes react to many types of injury—including elevated IOP—with changes in their morphology and gene expression pattern. This astrocyte reactivity is a protective response that aims to re-establish equilibrium and prevent further damage to the ganglion cells (at least in the early stages of glaucoma). This suggests that astrocytes, or astrocyte-derived factors, could be used as a neuroprotective therapy for glaucoma and potentially other neurodegenerative diseases.

Using RNA sequencing, we have identified genes that are upregulated after damage to the optic nerve and screened several of them for neuroprotective activity. One of our leading candidates is a cytokine-like factor called SPP1, which is produced by astrocytes after optic nerve injury. Further investigation in animal models of glaucoma revealed that overexpressing SPP1 in the retina and optic nerve results in robust protection of retinal ganglion cells and visual function. Long-term expression of SPP1 slows the normal age-dependent loss of retinal ganglion cells in all mammalian retinas and, moreover, is apparently well tolerated and does not cause negative side effects in the eye. This suggests that the SPP1 protein may be a promising protein drug candidate for neuroprotection in glaucomatous and aging eyes.

Evaluating Novel Cancer Therapeutic Strategies Using Living Tumor Biopsies

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Nearly half of all cancer patients are eligible for treatment with immune checkpoint blockade (ICB) cancer immunotherapy, but only about 10% of patients derive a durable clinical benefit. Hundreds of ICB-based therapeutic combinations have undergone clinical testing in recent years. However, the vast majority of these trials have failed to demonstrate meaningful benefit over established ICB agents. The lack of representative pre-clinical models of human tumor immunity has been cited as a key contributor to the failure of these therapeutic approaches and remains a major unmet need in the field.

My lab uses patient-derived organotypic tumor spheroids (PDOTS), a novel biomimetic technology platform to study tumor–immune system dynamics in a patient-specific manner (Jenkins et al. Cancer Discovery 2018). PDOTS are living tumor biopsies comprising patient-derived cancer cells and tumor-infiltrating immune cells that are grown in a 3D microfluidic culture device to closely mimic normal physiologic conditions.

PDOTS offer an opportunity to evaluate the sensitivity of a patient's tumor to existing ICB agents and/or novel therapeutic agents using clinically relevant biospecimens. We have confirmed the utility of dynamic PDOTS evaluation in examining novel therapeutic strategies to overcome ICB resistance (Sun et al. Nature 2023). We aim to expand our efforts to evaluate patient-specific sensitivity to existing, marketed ICB therapies for patients with ICB-responsive cancers (e.g., melanoma) in the next year.

In the near term, PDOTS offers clear value in pre-clinical drug testing to evaluate novel therapeutic strategies to overcome ICB resistance. Xsphera Biosciences, a Boston-based startup, currently offers PDOTS testing for commercial partners. In addition, my lab is planning a clinical trial using PDOTS to test combinations of immunotherapies and inform rational drug combinations for future development. Our long-term vision is to develop PDOTS as a functional precision medicine platform to help oncologists optimize and prioritize therapies for their patients.

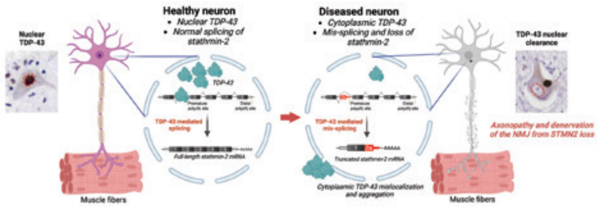

Fig. 1: Loss of nuclear TDP-43 in neurodegenerative diseases leads to misplicing of stathmin-2, axonopathy and denervation of the neuromuscular junctions.

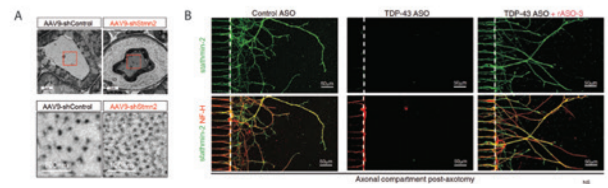

Fig. 2: Stathmin-2 is essential for axonal maintenance and regeneration. A) In vivo loss of stathmin 2 leads to collapse of mature axons with shrinkage in inter-neurofilament spacing and tearing of outer myelin layers. B) Restoration of axonal regeneration by rescuing stathmin-2 levels iPSC-derived motor neurons with TDP-43 depletion (from Baughn et al. Science 2023).

Targeting disruption of stathmin-2 in neurodegenerative diseases

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Alteration of RNA metabolism has emerged as a central theme in neurodegenerative diseases. Mutations and/or mislocalization of RNA-binding proteins, including TDP-43, have been implicated in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease. TDP-43 is involved in fundamental RNA processing activities including RNA transcription, splicing, and transport.

Recognizing the crucial role of TDP-43 in neurodegeneration, we have used genome-wide approaches to characterize how it regulates the expression and splicing of its RNA targets. We recently demonstrated that the human RNA most affected by loss of nuclear TDP-43 encodes a neuronal growth-associated factor called stathmin-2. Reduced nuclear TDP-43 results in abnormal usage of cryptic splice and polyadenylation sites in pre-mRNAs from the STMN2 gene, leading to loss of stathmin-2 protein.

Experiments in iPSC-derived TDP-43-depleted motor neurons show that stathmin-2 loss results in diminished nerve regeneration after axotomy (severing). Remarkably, although TDP-43 broadly affects the expression levels or splicing of many RNAs, restoration of stathmin-2 alone is sufficient to rescue the axonal regeneration capacity of these cells following axotomy. Stathmin-2 is also essential to maintain the axonal architecture and the connection between motor neurons and muscles. Reduced stathmin-2 level is a hallmark of sporadic and familial ALS and FTD, suggesting that restoring stathmin-2 expression is an attractive therapeutic strategy in the vast majority of patients with ALS and FTD.

We developed two approaches to block cryptic splicing of stathmin-2—one by using the CRISPR effector dCasRx and another using antisense oligonucleotides (ASOs) that bind to stathmin-2 pre-mRNA—to rescue the axonal regeneration capacity of human motor neurons with TDP-43 deficiency. We generated "humanized" stathmin-2 mice with constitutive mis-splicing of stathmin-2 and demonstrated that ASO injection into their cerebral spinal fluid rescues stathmin-2 mRNA levels. Further, we used pharmacological and genetic screens to identify modulators of stathmin-2 expression as potential novel targets for translational drug development in neurological diseases.

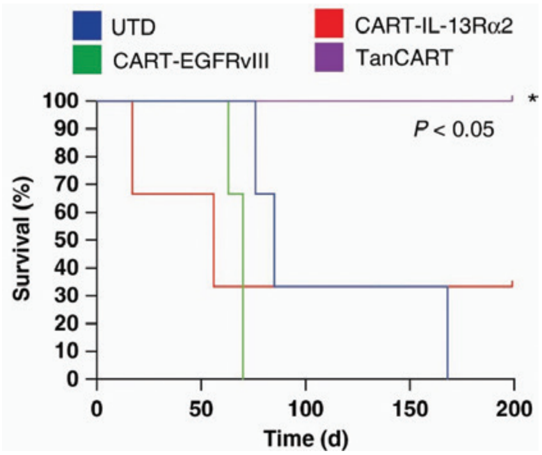

Fig. 1: Kaplan-Meier survival analysis demonstrating survival of TanCART-treated GBM patient-derived xenograft mice compared to untransduced and monospecific CAR-T cell groups, CART-EGFRvIII and CART-IL-13Rα2. Statistical significance

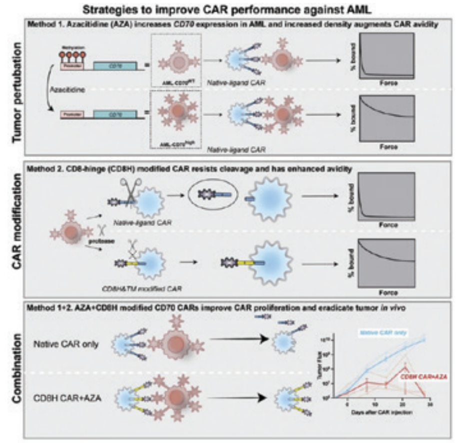

Fig. 2: Strategies to overcome CAR performance against AML

Novel CAR-T cells engineered to overcome obstacles observed in the clinic

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Using the immune system as a cancer treatment, T cells can specifically kill target cells they recognize and can persist in the body for many years, presenting the potential for long-term protection. CAR-T therapies comprise T cells that are re-engineered to produce chimeric antigen receptors (CARs), which help the T cells target specific antigens on cancer cells. CAR-T therapies have shown great promise for B cell malignancies (e.g., leukemia and lymphoma) in the clinical setting, but barriers remain, and their successful application to other cancers likely requires refinements in the molecular and clinical technologies.

The Maus laboratory and the MGH Cellular Immunotherapy Program use genetic engineering to overcome obstacles observed in the clinic, creating a pipeline of next-generation CAR-T therapies. We are developing novel receptors targeting multiple antigens on tumor cells to better attack heterogenous tumor cell populations, prevent antigen-negative relapse, and decrease effects on healthy cells. In a recent study, we developed a tandem CAR-T (TanCART) cell that simultaneously targets both EGFRvIII and IL-13Rα2, two tumor antigens that are abundant on glioblastoma (GBM) cells but absent from normal brain tissues. In patient-derived heterogeneous GBM xenografts, TanCART achieved long-term, complete, and durable responses while monospecific CAR-T cells did not (Fig. 1).

Leveraging studies that shed light on mechanisms of CAR-T resistance in the inhibitory tumor microenvironment, we aim to re-engineer CAR-T therapies with enhanced resilience. For example, acute myeloid leukemia (AML) resists CD27-ligand-based CAR-T therapy by secreting an enzyme that cleaves the CD27 ligand responsible for targeting the CD70 expressed on AML cells; this cleavage renders CAR-T cells inactive. To overcome this barrier, we modified the most potent previously described CAR targeting CD70 to stabilize its binding to CD70, leading to more potent in vivo activity (Fig. 2).

We envision next-generation CAR-T cells working synergistically with other drugs to enhance their efficacy. For example, we combined the modified CD70-targeted CAR-T therapy described above, which was only modestly effective against AML in animal models, with an FDA-approved AML drug, azacytidine, that increases the density of the CD70 antigen on cancer cell surfaces. This combination exhibited significantly greater efficacy than the CAR-T alone (Fig. 2). In the future, we aim to discover and test additional drug–CAR-T combination therapies with improved safety and efficacy.

Targeting neutrophils for T cell-mediated anti-tumor immunotherapy

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Oncology practice has been transformed in recent years by advances in T cell-focused immunotherapy, including immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T cells. Unfortunately, progression free survival in patients with solid tumors is observed in only a minority of ICI-treated patients and only in a subset of cancer types. CAR-T cell therapy is largely ineffective and not FDA approved for non-hematopoietic tumors.

Durable cancer eradication by T cells requires antigen presenting cells (APCs) to induce clonal expansion of tumor antigen-specific CD8 T cells capable of acquiring effector functions, infiltrating tumors, and generating memory T cells (Fig. 1). Intratumoral APCs also directly induce T cell influx into tumors. However, several solid tumors have an immunosuppressive tumor microenvironment (TME) that inhibits T cell infiltration into the tumor, thus limiting the impact of current T cell-focused immunotherapies. Therapies that directly target antigen to conventional dendritic cells (cDCs), canonical professional APCs are restricted by their low abundance and dysfunction as the tumor progresses and the need for toxic adjuvants to induce their immunogenicity.

Neutrophils, the most abundant circulating leukocytes in humans, can acquire APC functions in vitro and neutrophils with markers of APCs are detected in cancer patients. We developed an antibody-tumor antigen conjugate (AAC) targeting human FcγRIIIB (expressed almost exclusively on neutrophils), which delivers antigen to neutrophils, and turns a subset of them into highly immunogenic APCs that activate CD8 and CD4 T cells without the need for adjuvants. In a mouse model of melanoma with an immunosuppressive TME, this AAC therapeutically expands and induces the tumor infiltration of T cells and natural killer cells (Fig. 2), thus achieving a major goal in immunotherapy of TME reprogramming. Further, AAC significantly reduces tumor growth, the ICI anti-PD-1 has no effect and AAC combined with anti-PD-1 further decreases tumor growth compared to either agent alone (Fig. 3). The combination therapy also induces the intratumoral accumulation of memory T cells known to have durable anti-tumor properties.

The developed AAC elicited T cell-mediated acquired immunity in melanoma as a representative example has the potential to treat a range of other solid tumors upon conjugation of anti-FcγRIIIB to applicable tumor antigens. This approach has several advantages over existing immunotherapies as it can be used to non-invasively generate a large pool of highly immunogenic tumor antigen-carrying APCs from abundant neutrophils and be achieved in the absence of adjuvants. Further, this approach provides the groundwork for transformative combination treatments with ICIs.

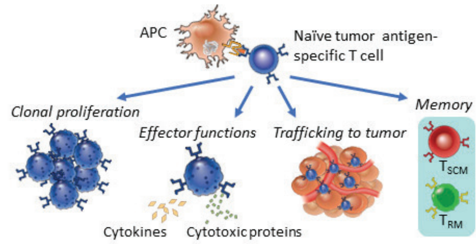


Fig. 1: APC induced T cell functions required for anti-tumor immunity. T_{SCM}, T_{RM} ; memory T cell subsets.

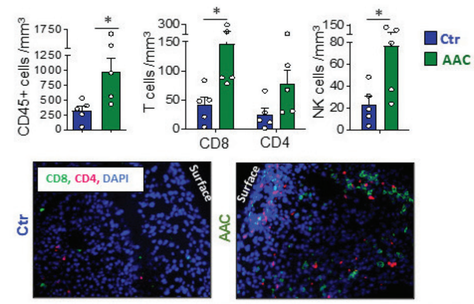


Fig. 2: Targeting neutrophils to induce tumor infiltration of T cells and NK cells. AAC, consisting of an anti-FcγRIIIB (which engages neutrophils of FcγR humanized mice) conjugated to Ovalbumin (Ova), a model T cell dependent antigen, was given to mice with a day 5 established B16F10 melanoma expressing Ova. The tumors were harvested on day 15 and analyzed by flow cytometry (top panels) for total leukocytes (CD45+), CD8 and CD4 T cells, and NK cells per mm3 volume of tumor. Tumors were also harvested for immunohistochemistry (bottom panels) to localize CD8 and CD4 T cells. DAPI; nuclear stain.

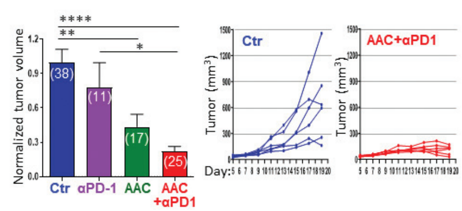
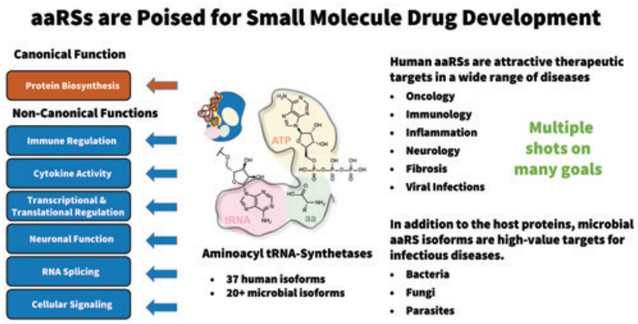


Fig. 3: AAC significantly reduces tumor growth and in combination with anti-PD-1 markedly regresses melanoma. Mice with a 5-day established B16F10-Ova were treated with isotype-control conjugated to Ova (Ctr), anti-PD1, AAC or a combination of AAC plus anti-PD1. The measured volume (mm³) of tumors harvested at day 19 were normalized to the average of the control (Ctr) group. The number of mice per group are in parentheses. Profiles of tumor growth over time of independent mice in control and AAC+anti-PD-1 from one representative experiment are shown.



Unlocking aminoacyl-tRNA-synthetases as novel drug targets for first-in-class therapeutics

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As a chemical biologist, Dr. Mazitschek's research interests center on investigating biological systems at the molecular level using modern chemistry tools. Motivated by Sidney Brenner's famous quote, "progress in science depends on new techniques, new discoveries and new ideas, probably in that order," the Mazitschek lab seeks to develop innovative small-molecule approaches to modulate physiological processes to establish therapeutic strategies for previously unmet medical needs.

Aminoacyl-tRNA synthetase (aaRS) enzymes are central to protein homeostasis, connecting RNA and protein domains in the central dogma. Because of their assumed role as mere housekeeping enzymes, traditional aaRS drug development efforts have primarily focused on antimicrobial agents targeting bacterial, fungal, and parasitic organisms. However, recent advanced omics studies have begun unveiling the many non-canonical roles of individual isoforms in human health and disease, including autoimmune disorders, cancer, and neurological diseases. Unfortunately, despite offering multiple highly-druggable features, the exploration of human aaRSs for translational research has been hindered by an almost complete lack of chemical leads and robust pharmacological tools for systematically interrogating mammalian aaRSs in disease settings - a scenario reminiscent of the kinase field in the 1980s.

To overcome this challenge, we have leveraged our novel CoraFluor high-throughput screening (HTS) assay technology, which has enabled previously elusive experimental designs and provided access to a versatile aaRS discovery platform. Our robust and facile assay strategy is suitable for all 37 human aaRS isoforms and allows for quantitative and comprehensive ligand characterization, eliminating existing bottlenecks and greatly accelerating systematic drug discovery and development. We have validated our approach for multiple aaRS targets, including the rational development of novel prolyl-tRNA synthetase inhibitor classes, and demonstrated their inhibitory efficacy in vivo. We aim to transform this work into a comprehensive and systematic discovery engine, streamlining the process for efficient aaRS-targeted drug development and establishing a direct path to first-in-class therapies, resolving unmet medical needs in various human disease areas.

Figure legend: In addition to their canonical role in protein homeostasis, aminoacyl-tRNA synthetases (aaRSs) exhibit a variety of non-canonical functions that are often isoform-specific and cell-type dependent. These non-canonical functions play critical roles in various cellular processes and have significant implications for human health and disease. The growing understanding of these diverse functions has identified aaRSs as potential therapeutic targets for various diseases, including autoimmune disorders, cancer, and neurological conditions. Along with their microbial homologs, aaRSs represent a large group of underexplored targets with highly druggable features for next-generation therapeutics that can address unmet medical needs.

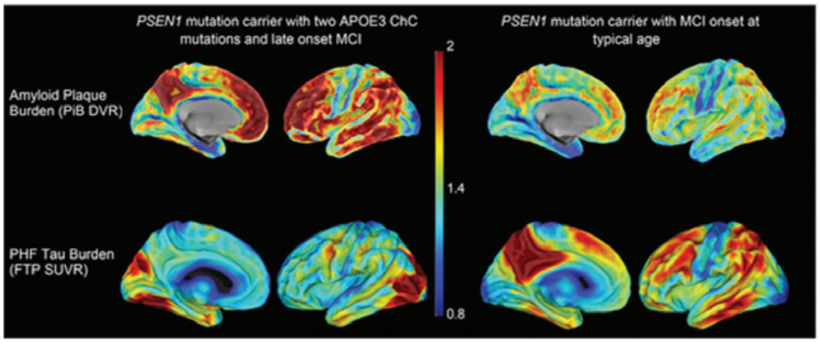

Fig. 1: Brain imaging shows limited tau pathology and neurodegeneration despite high amyloid-β plaque burden in an individual homozygous for the APOE3 Christchurch variant

Untangling the role of rare genetic variants in protection against Alzheimer's disease: From biomarkers to novel therapeutic targets

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For the past two decades, Dr. Quiroz and the Mass General Familial Dementia Neuroimaging Lab have followed an extended family of 6,000 individuals with a known Alzheimer's disease (AD) genetic mutation, PSEN1 E280A. The work with this family has revealed key details about the genetics and early brain changes associated with AD.

In 2014, Quiroz launched the COLBOS (Colombia-Boston) project, an international collaborative longitudinal biomarker study to identify the earliest in vivo pathological and functional abnormalities associated with autosomal dominant AD. Dr. Quiroz and her team have identified a few COLBOS study participants who, despite carrying the PSEN1 mutation, remained cognitively unimpaired until a relatively old age compared with others with the same mutation, who exhibit cognitive impairment at a median age of 44 years prior to developing dementia at 49 years. These rare occurrences yield insights into potential protective factors against the neuropathogenesis of AD and possible avenues for therapeutic targets.

One of these late-onset COLBOS study participants was a woman who began showing signs of AD thirty years after the expected age of clinical onset. Clinical and PET imaging studies of this individual showed an extremely high amyloid level but a tau burden and neurodegeneration lower than expected for her age. These findings suggest a disconnection of amyloid pathology from tau pathology, neurodegeneration and cognitive impairment (Arboleda-Velasquez… Quiroz, Nature Medicine, 2019) (Fig. 1). Genetic analyses revealed a homozygous rare variant of APOE3 (R136S substitution, known as the Christchurch variant, APOECh), which plays a role in binding to lipoprotein receptors and heparin sulfate proteoglycans (HSPG). Experimental studies showed that this mutation impairs heparin binding to ApoE. Our findings suggest that antibodies or small molecules binding to the R136S-containing APOE region or otherwise modulating APOE-HSPG interactions could reproduce this potentially protective effect of APOE3Ch, representing a promising novel target for AD therapies.

Case studies like this APOE3Ch case have a high sensitivity for novelty: they may reveal critical, previously unrecognized pathways and mechanisms of cognitive resilience and resistance to AD and ultimately lead to novel, patient-inspired therapies for AD and other neurodegenerative diseases.

Preventing post-traumatic stress disorder: Novel pharmacological approaches based on the neuroscience of fear

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Post-traumatic stress disorder (PTSD) is a prevalent, debilitating and sometimes deadly consequence of exposure to severe psychological trauma. Interventions are limited and new approaches to prevention and therapy are much needed. Given our knowledge of the memory consolidation that occurs in the aftermath of trauma experiences, timely intervention is thought to be paramount as it is in myocardial or cerebrovascular infarction. Thus, we are working towards interventional approaches in the emergency department or on the battlefield to prevent the long-term sequelae of PTSD.

In the past few years, technological advancements have allowed the observation and perturbation of the macrocircuits and microcircuits thought to underlie PTSD-related symptoms. These findings have evolved our understanding of the dysfunctional brain circuits underlying PTSD and provided translational knowledge about the condition, including insights into the mechanisms of risk and resilience.

Our lab has focused on the intersection of human genetics, neurobiology, postmortem biology, and mouse brain utilization to understand neural and molecular mechanisms of trauma memory consolidation. Our ultimate goal is to develop novel neurobiologically derived targets for the prevention of PTSD. In one promising avenue of research, we discovered that the Tac2 gene (TAC3 in humans), which is expressed in neurons specifically within the centromedial amygdala (CeM), is required for consolidating fear memories. Furthermore, the Tac2 product, neurokinin B (NkB), and its specific receptor, Nk3R, are also involved in the consolidation of fear memories. We showed that increasing Tac2 expression via lentiviral transduction in the CeM or via PTSD-like stress induction enhances fear consolidation. This effect is blocked by Nk3R antagonists. Concordantly, silencing of Tac2-expressing neurons in the CeM with DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) impairs fear consolidation.

Together, these studies provide a deeper understanding of the role of the Tac2 gene and the CeM in fear processing. We are working to translate this new knowledge into more successful, scientifically informed and rationally designed biomarker- and neurobiologically-driven interventions for disorders of fear regulation, including anxiety disorders and PTSD.

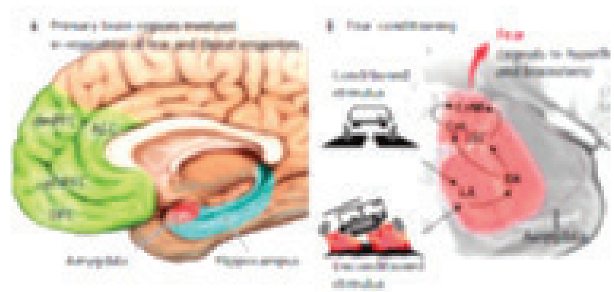

Fig. 1: Schematic of Trauma Memory Brain Circuits. A) The prefrontal cortex and hippocampus are the primary brain regions that regulate amygdala activity with fear/threat processing. B) Trauma exposure leads to synaptic plasticity events resulting in the consolidation of trauma memories within the amygdala, with the centromedial amygdala (CeM) as the primary output node eliciting the fear/threat reflex.

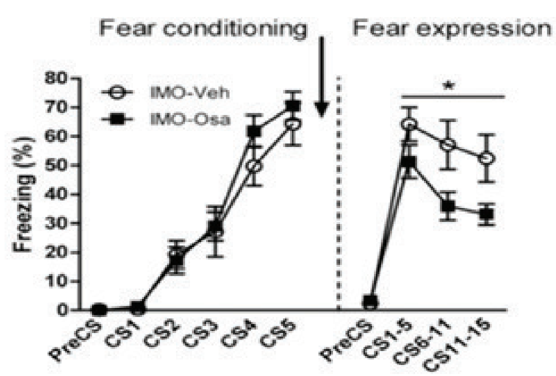

Fig. 2: Nk3R/TACR3 antagonist diminishes threat memory consolidation when given after threat exposure. Left) Acute stress/trauma model (foot shock in mice following immobilization stress) leads to fear memory responses (freezing). TACR3 antagonist is given up to 1 hour (systemically or within the CeM) after fear conditioning. Right) When tested on subsequent days, mice given osanetant (an Nk3R antagonist) exhibit diminished threat responses/freezing.

Using big data and AI to advance precision psychiatry and suicide prevention

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Dr. Smoller's research focuses on understanding genetic and environmental determinants of psychiatric disorders to develop innovative methods of better preventing and managing mental health disorders. A major component of our work is leveraging AI and the vast resource of real-world health data to enhance risk prediction and treatment selection for psychiatric illness and suicide.

1.7M people attempt suicide annually in the US. Suicide is the second leading cause of death among young people and overall suicide rates have increased by over 30% in the past 20 years. Most people who attempt or die by suicide were seen by a healthcare provider in the preceding month, presenting a crucial opportunity for risk assessment and intervention in healthcare settings. However, research by our group and others shows that clinicians do little better than chance at predicting suicide-related behaviors.

To address this unmet need, we applied AI to electronic health record (EHR) data to identify individuals at high risk of suicide attempt and death. Using longitudinal data from 1.7M patients in the MGB system, we developed and validated an algorithm that successfully identified 45% of suicide attempts and deaths with 90% specificity on average 2–3 years in advance. We subsequently validated this approach and achieved similar performance in five independent health systems across a total of 3.7M patients.

In a prospective study of 2,000 patients in a psychiatric emergency department (ED), our EHR risk algorithm coupled with a brief point-of-care survey outperformed clinicians' suicide attempt predictions up to 6 months following discharge. Of patients in the top decile of predicted risk, 40% attempted suicide within 1 month and nearly 60% attempted suicide within 6 months. Health economic analyses show that implementation of our suicide prediction models, when coupled with evidence-based interventions, is cost-effective for targeting interventions to high-risk patients. 86% of clinicians in a pilot implementation of our survey-based suicide risk scores in the ED found this information clinically valuable.

We have now refined our tool through clinician focus groups and developed a clinical decision support application that can be integrated into EHRs. The app enables point-of-care suicide risk assessment and guides clinicians through personalized care pathways. Following larger-scale clinical trials in ED settings, we plan to bring this app into production and scale its implementation to address the critical unmet need for improved suicide prevention.

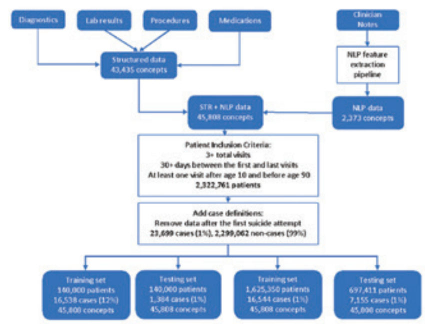

Fig. 1: Illustrative EHR model training/validation workflow

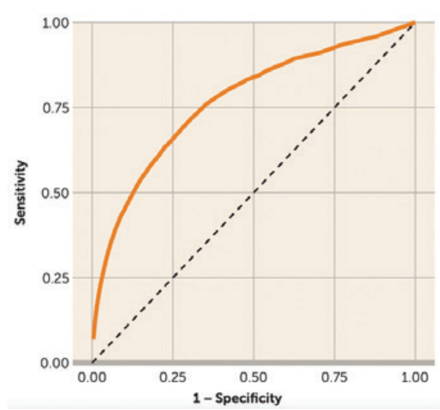

Fig. 2: Model discrimination (AUC = 0.77)

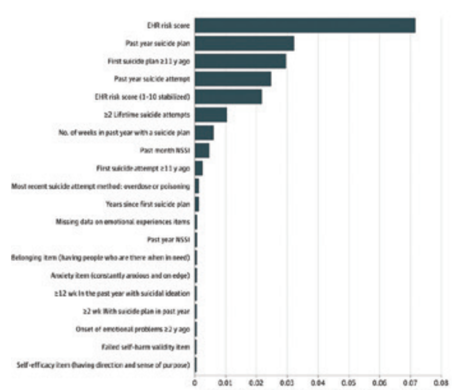

Fig. 3: Predictor importance (SHAP values) for top 20 predictors

Precision gene therapy for treating severe pain

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Chronic pain is a major socioeconomic problem. It affects more than 25% of adults in the US, costs over $500 billion annually, and drives the opioid epidemic. Human genetic evidence based on the voltage-gated sodium channel NaV1.7 and independent confirmation in mouse models together demonstrate that reducing the firing of first-order nociceptors (pain-sensing neurons) is sufficient to abrogate pain. Estimates from rodent studies using inhibitory optogenetic constructs suggest that silencing as few as 15% of nociceptors would be sufficient to yield a marked reduction in pain. However, efforts focusing on NaV channels have faced substantial challenges in translational development.

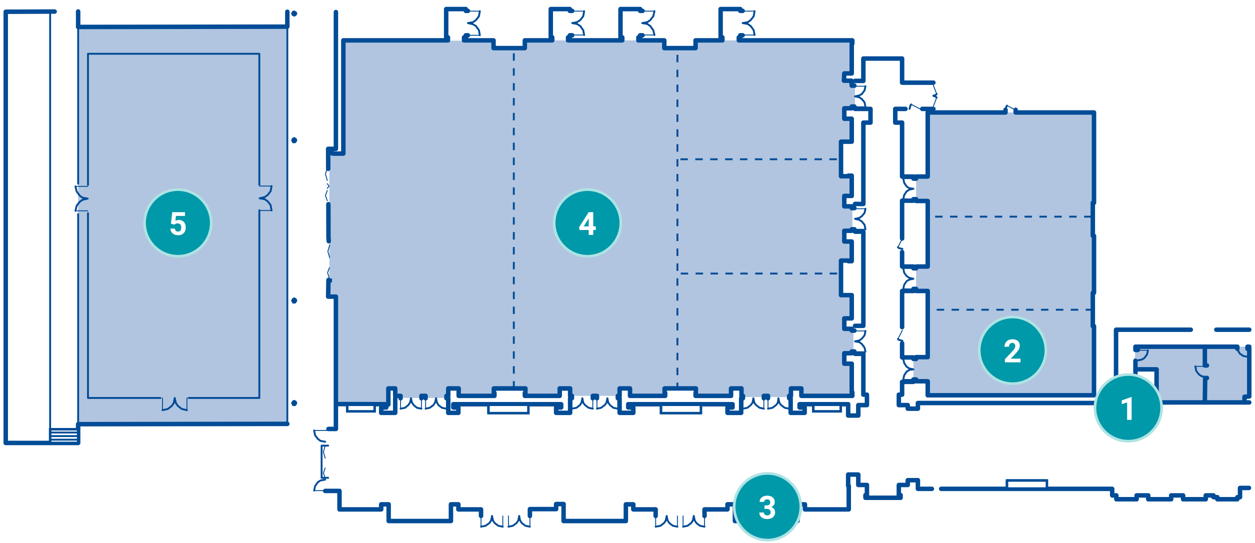
We propose an AAV-based gene therapy strategy to overexpress potassium channels in nociceptors and block pain. Potassium channels hyperpolarize the neuronal membrane potential and thereby decrease firing. Human genetic evidence supports this strategy as potassium channel gain-of-function haplotypes are protective in several pain conditions.

Our gene therapy strategy will allow us to address critical limitations in current pain treatment: although most severe pain complaints are focal, almost all existing therapies are systemic and therefore associated with side effects and limited efficacy. Such concerns are particularly important in elderly patients and those with medical comorbidities, who have a greater risk of side effects from systemic medications. Our AAV-based approach enables focal injection to spatially target potassium channel overexpression in order to treat pain aggressively while minimizing side effects. To further precisely target our gene therapy to nociceptors specifically, we identified human short promoter segments that facilitate nociceptor-specific payload expression but are small enough to fit together with the potassium channel in a standard AAV vector.

Thus, our dual spatial and cell-type precision strategy offers a highly targeted approach supported by human genetic evidence to treat severe focal pain conditions while minimizing adverse effects.

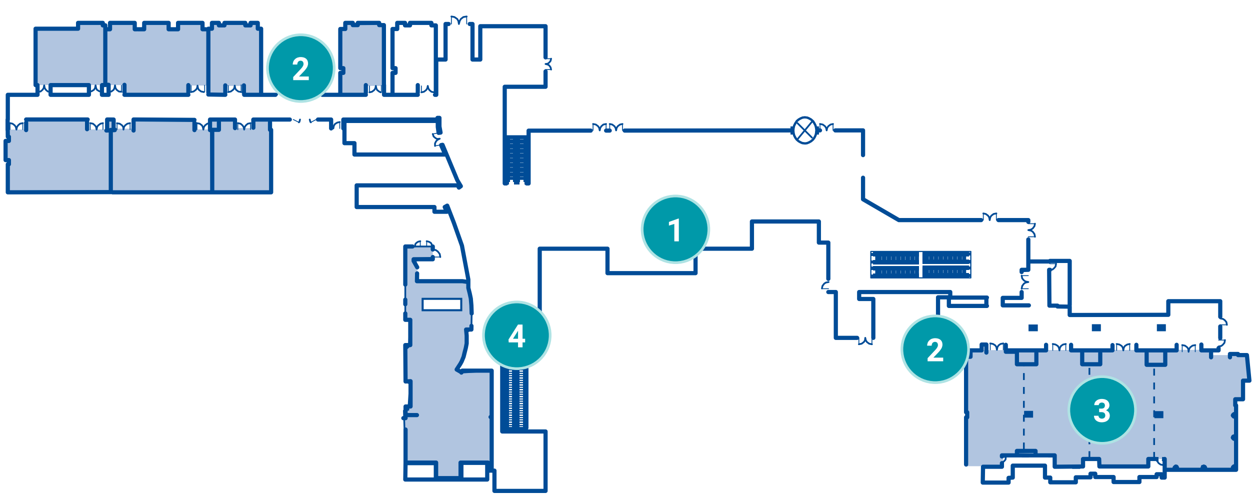
Maps

Concourse Level



1. Restrooms
2. Speaker Check-In
3. Registration
4. Grand Ballroom – General Session
5. Pavilion – Networking, Overflow & Receptions

Lobby Level



1. Hotel Registration
2. Restrooms
3. Dr. Is In Sessions (Marina Ballroom and Harbor Level)
4. Escalator to Conference

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