HARVARD
MEDICAL SCHOOL

Blavatnik Family Foundation Annual Report of Support

December 2024

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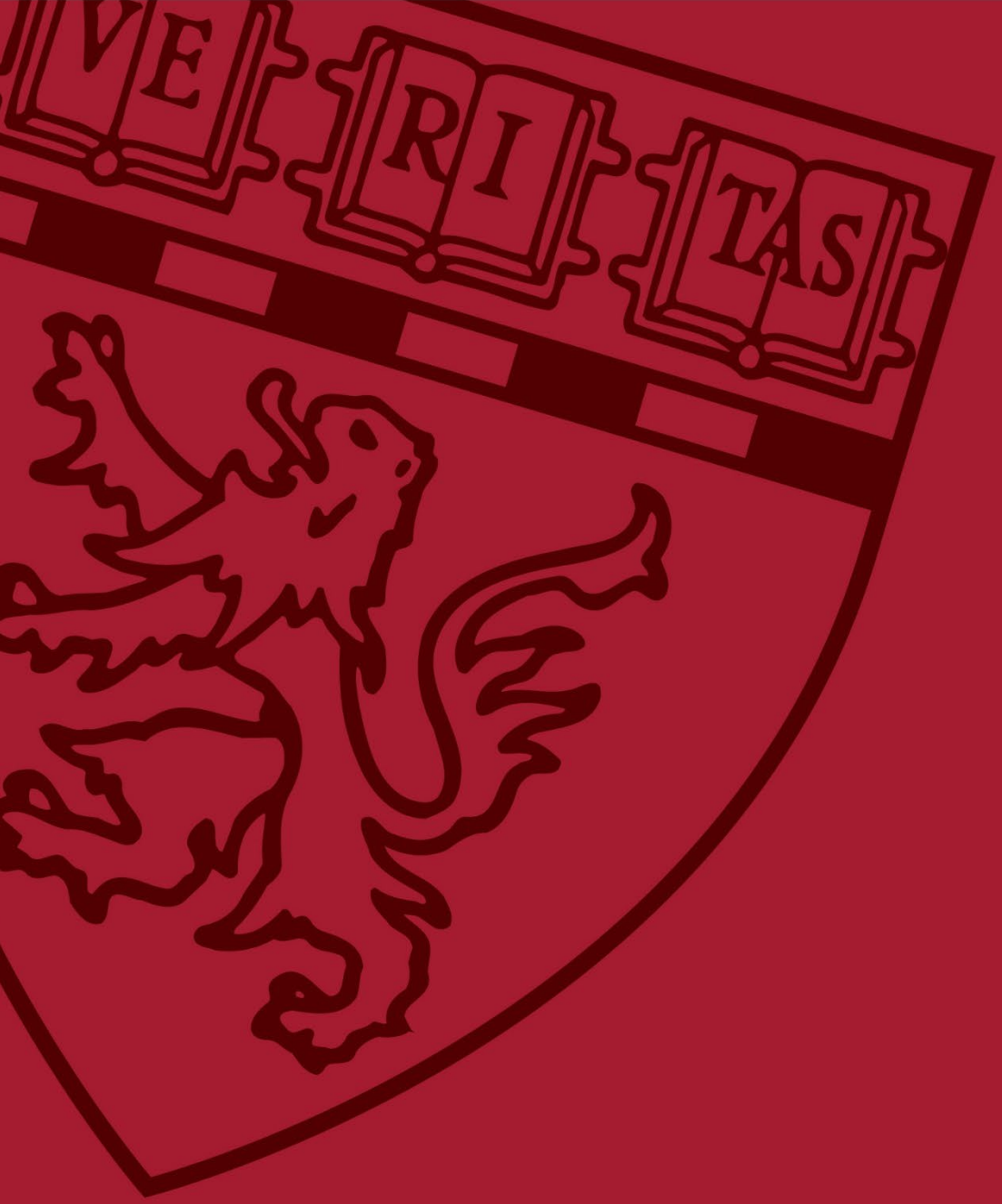


Blavatnik Dean's Discretionary Fund at Harvard Medical School

The Therapeutics Initiative

Now in its fifth year, the HMS Therapeutics Initiative recently began a new corporate alliance and is exploring novel, productive ways to collaborate with the venture community to support HMS research before company creation.

The core mission of the Therapeutics Initiative remains unchanged:

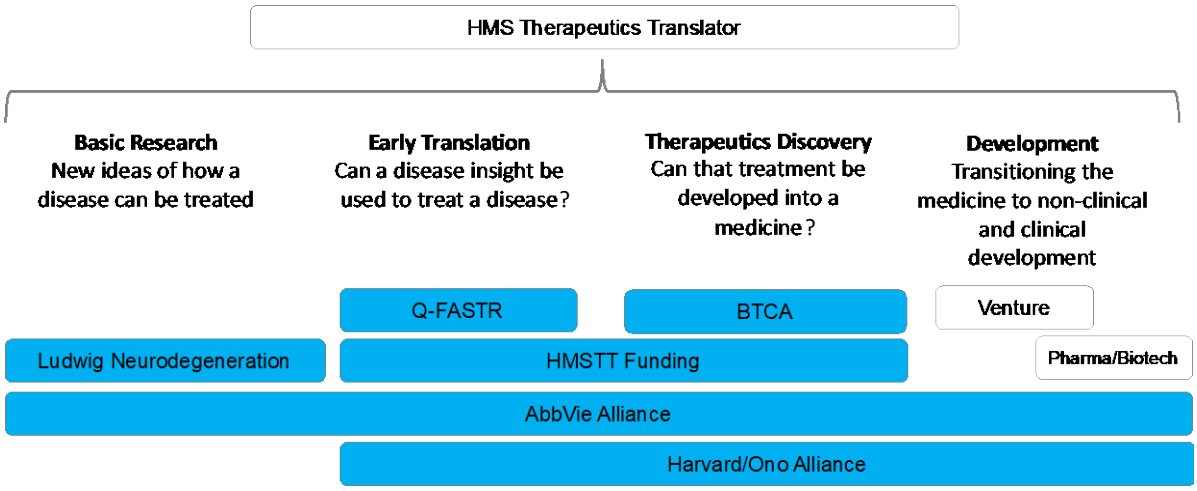
- Advance the science required to improve the effectiveness of therapeutics discovery.
- Integrate high-level therapeutic science into our community of extraordinary fundamental researchers to improve the speed and fidelity of our discoveries progressing toward medicine.
- Provide classroom and experiential learning to train and inspire tomorrow's medicine inventors.

As we enter into 2025, the Initiative will focus on seeking new funding sources to continue its critical work from the last four years, as both the AbbVie Alliance and the Blavatnik Therapeutics Challenge Award (BTCA) programs will begin to wind down in the coming year. In 2024, the Initiative launched a Harvard-wide corporate alliance with Ono Pharmaceuticals. The alliance partners with Harvard's Office of Technology Development and offers the first opportunity to apply the capabilities of the Therapeutics Initiative campus-wide.

The Initiative continued to expand its impact on translational work throughout the HMS community, ranging from generating initial ideas to supporting faculty-led formation of new companies.

HMS Therapeutics Translator

The HMS Therapeutics Translator provides the scientific and logistical support that enables researchers to identify and rapidly advance translational projects focused on developing new therapies. Importantly, these projects provide experiential learning opportunities, not just for the teams involved, but as real-time case studies in therapeutics discovery and development. The Drug Discovery Sciences Core (DDSC) has operated for two years and has made impactful contributions to translational science across the Longwood institutions, especially in small-molecule drug discovery. Five of the 20 Blavatnik Therapeutics Challenge Awards recipients and five of the 11 2024 Q-FASTR recipients worked with DDSC scientists to execute their awards.



Senior Therapeutic Scientists and Drug Discovery Sciences Core

The Translator and the associated DDSC have fully-staffed teams and are operating at full capacity. As of June 2024, the Translator and DDSC scientists had supported, or were currently supporting, 36 drug discovery efforts across HMS and its affiliated hospitals. In 2024, the team included up to five senior therapeutic scientists with expertise in small-molecule, biologic, and oligonucleotide therapies and assay development. The team supports drug discovery efforts at HMS, Dana Farber Cancer Institute, Mass General Brigham, and Boston Children's Hospital. The size and composition of the senior therapeutic scientist group will continue to be customized by Translator leadership to best meet the needs of the research community's needs, with an expansion into early non-clinical development anticipated in 2025. DDSC member Jennifer Smith, PhD, who is also the director of the ICCB-Longwood Screening Facility, oversees assay development and execution core. The Core played a critical role in compound handling and providing quality assay data to support many projects, particularly the BTCA Award projects and Translator projects.

Grant Program Highlights

From January 2020 through June 2024, the Therapeutics Initiative supported 105 HMS community projects with 88 lead principal investigators. The projects encompassed HMS and nearly every affiliated hospital and included collaborations with industry and venture. This year, the Quadrangle Fund for Advancing and Seeding Translation Research (Q-FASTR) awarded three new development awards and eight pilot awards. The final round of Blavatnik Therapeutics Challenge Awards funded three creative and impactful programs. The internal project management group continues to monitor the progress of all 20 BTCA recipients. As of August 2024, four projects have progressed to either intellectual property licensure or company creation, and several other awardees are actively engaged in business discussions.

To date, the Translator has directly funded six projects, and five of them were active during 2024. The most advanced project is with Chenghua Gu, PhD, a professor of neurobiology in the Blavatnik Institute. This project aims to validate a target to enhance central nervous system exposure for biologics and other therapeutic modalities. The lab obtained small-molecule inhibitors with sub-nanomolar potency and excellent drug-like properties, and it

will conduct critical proof-of-concept (POC) studies in the fall. A prominent local venture firm partnered with this project and funded much of the work in 2024, but because the research was in its early stages, the firm elected not to pursue licensure at this time. This opens up a variety of business options for the project if the POC studies are successful. Mark Namchuk, PhD, executive director of therapeutics translation and the Puja and Samir Kaul Professor of the Practice of Biomedical Innovation and Translation in the Department of Biological Chemistry and Molecular Pharmacology at HMS, and Ifat Rubin-Bejerano, PhD, senior director of translational research at HMS, are leading the initiative to secure a business partnership. DDSC scientists are conducting the drug discovery in the project.

Mark Namchuck. PHD

The Greenberg Lab continues to work on developing a gene therapy for emerging pain treatments. Technical difficulties, such as issues with acquiring appropriate expression of the gene therapy in IPSC dried human neurons, slowed progress. However, the critical in vivo POC study conducted this fall demonstrated that the GRE construct showed expression specifically in the targeted neurons in mice. Tom Hoock, PhD, a senior therapeutic scientist with over 30 years of research and development experience, is leading the project.

Marcia Haigis, PHD

The Blavatnik Biomedical Accelerator is co-funding a third project, in which the team is working with Marcia Haigis, PhD, a professor in the Department of Cell Biology in the Blavatnik Institute, to develop small-molecule inhibitors targeting a novel mechanism that drives resistance to anaplastic lymphoma kinase (ALK) inhibitors. DDSC scientists designed the assays, completed a screen, and identified the target's low-micromolar inhibitors. Chemists in the group completed a first round of compound optimization and provided the results from the follow-up compounds to the Haigis Lab.

Karen Adelman, PHD

In partnership with Karen Adelman, PhD, the Edward S. Harkness Professor of Biological Chemistry and Molecular Pharmacology in the Blavatnik Institute, the Translator team completed an in vivo POC study examining the efficacy of an antisense oligonucleotide (ASO) therapy for the treatment of cancer. The study showed compelling evidence of complete tumor growth inhibition in an in vivo study (a critical issue for many ASOs tried in cancer), and the team leveraged those data to obtain a second Q-FASTR grant to continue optimizing the ASO.

Finally, a Q-FASTR project led by Mark Albers, PhD, assistant professor of neurology at HMS, received a grant to support a successful initiative where DDSC scientists developed low-nanomolar dual-target inhibitors for a novel pathway shown by genetic models of ALS and Alzheimer's disease to be neuroprotective. These findings enabled Dr. Albers to secure a Massachusetts Center for Alzheimer's Therapeutics Science grant, which will support continued work on the project.

Mark Albers, PHD

Corporate Alliances

The HMS/AbbVie Alliance recently completed its third year. The Therapeutics Initiative plays a central role in a corporate alliance with Ono Pharmaceuticals, launched in June 2024. The alliance allows for two projects, including a $1 million drug discovery-oriented grant program for relatively mature therapeutics projects across Harvard. These projects will use the resources and expertise of the Therapeutics Translator to support projects throughout the University. Senior staff from the Therapeutics Initiative will have instrumental roles in managing the alliance. Mark Namchuk is one of the two Harvard joint steering committee members for the alliance and Ifat Rubin-Bejerano is a key member of the joint operating committee. Ono has received 37 proposals for consideration, with funding decisions expected in late 2024. Ten proposals have progressed to second-stage diligence.

HMS/AbbVie Alliance

The HMS/AbbVie Alliance aims to study and develop therapies against emergent viral infections, with a focus on those caused by coronaviruses and by viruses that lead to hemorrhagic fever.

The Blavatnik Harvard Life Lab Longwood

The Blavatnik Harvard Life Lab Longwood just completed its second full year of operations and currently incubates seven start-up companies, operating at 70% capacity, which is on par with similar facilities in the Boston area. Since July 2023, the Life Lab has offered residency to seven companies through a rigorous selection committee process and onboarded three companies to date with two more in the process of contracting. Life Lab tenant company Skylark Biosciences, founded by HMS neurobiology professor David Corey, PhD, closed a $40 million funding round in April 2024 and will graduate from the Life Lab to its first commercial laboratory space in winter 2025.

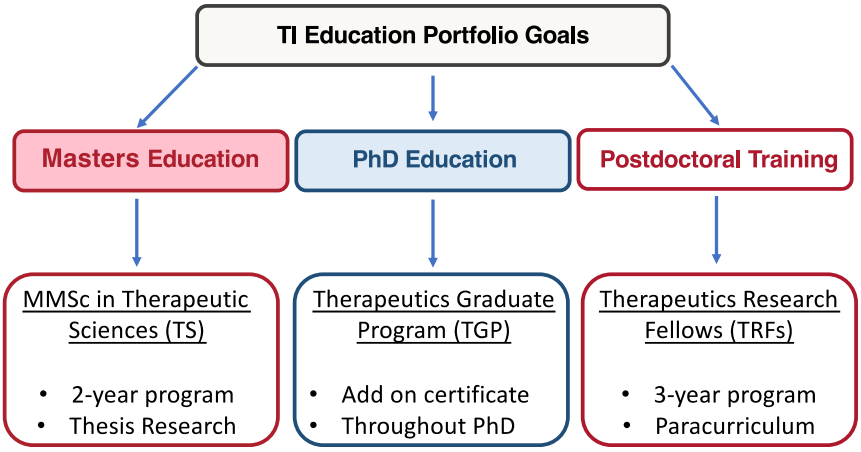
In the coming year, the Life Lab will focus on supporting and attracting new tenant companies and will partner with the Therapeutics Graduate Program (TGP) to pilot the placement of TGP students into Life Lab companies for the internship component of the program.

Therapeutics Education

Over the last year, the Therapeutics Initiative's education team, formerly the Ideation Hub team, focused on the formation and launch of two new programs: a master's program in therapeutic science that will launch in 2025, and a therapeutics research fellowship program that is in the planning stages. Catherine Dubreuil, PhD, senior director of therapeutics education, leads the creation and administration of the new education programs.

Master of Medical Sciences in Therapeutic Sciences

Harvard University approved the new Master of Medical Sciences in Therapeutic Sciences (MMSc TS) program in spring 2024 and is on track to accept its first cohort of students in fall 2025.



The Department of Biological Chemistry and Molecular Pharmacology in the Blavatnik Institute at HMS will house the program. It will focus on training individuals to become professional experimentalists in early drug discovery and to work at the leading edge of therapeutic sciences in areas of high need within the biopharmaceutical industry.

The Therapeutics Initiative education team is preparing for the first application cycle and developing a new curriculum designed specifically for this program. The new offerings include a class in the fundamental concepts of biochemistry and cell biology with a hands-on lab component (the first of its kind in graduate education at HMS), a course on data literacy and analysis, and a course focused on professional and career skills. The student experience centers around a robust lab-based thesis project on or related to drug discovery, to be completed in a Harvard faculty member's lab.

Applications to the MMSc-TS program opened in September 2024, with plans to accept 12 students per year. Mark Namchuk will serve as the inaugural faculty director for the program and Ralph Mazitschek, PhD, an HMS assistant professor of radiology based at Massachusetts General Hospital, will serve as the academic co-director.

Therapeutics Research Fellowship

The Therapeutics Research Fellowship trains postdoctoral fellows at HMS for careers in translational research in academia. This program equips the next generation of tenure-track academic faculty with the skills to secure funding for translational research from new and emerging sources, create companies, and collaborate effectively with the biopharmaceutical industry. Fellows also receive relevant training in entrepreneurship, business, and management from the Harvard Business School.

Therapeutics Graduate Program

The Therapeutics Graduate Program (TGP) is an elective certificate program for PhD students in any of the Harvard Integrated Life Sciences PhD programs, as well as in the Harvard-MIT Program in Health Sciences and Technology. The TGP focuses on pharmacology, toxicology, and drug discovery and emphasizes research in labs across Harvard and its affiliate institutions and hospitals, as well as in real-world internships. The TGP's external internship requirement aligns with its philosophy that hands-on experiences are vital to graduate education and

important for future career success. The TGP currently has 97 active students, and the program has grown steadily since its creation in 2012, from small cohorts of eight students per year to a current acceptance rate of 20–25 new students per year. Eighty-four TGP alumni have successfully found positions across the spectrum of the therapeutics-related workforce, with 32% remaining in academia post-graduation and 63% transitioning to industry, representing sectors including research and development, venture capital, consulting, and project management. The TGP's focus on career development, internships, and site visit networking contributes to the program's success.

Over the past year, the TGP has achieved several impactful financial and academic milestones. The National Institute of General Medical Sciences (NIH/NIGMS) awarded the program's T32 training grant an outstanding score and renewed it for another five years. As part of this renewal, the NIH granted the TGP two additional student spots, extending its support to 10 students per year. Fujifilm also renewed its generous contribution to the TGP. The Fujifilm Fellowships will fully support six to eight TGP students per year, who have demonstrated excellent skills in research, leadership, and community engagement.

The TGP's new program manager, John Kropowensky, MEd, is helping the TGP grow by increasing program tracking, advising, and event management, and by assisting with other initiatives. The TGP also welcomed a new curriculum fellow who will lead several curriculum projects—most importantly, the development of a new gene and cell therapy course. Lastly, the TGP is committed to building and maintaining a strong community. The program hosted several events in the past year, including its second annual in-person symposium, two site visits to local biotech companies, academic and career development panels, and new social events for the community. The TGP team will increase activity and engagement in the upcoming year to create one of the strongest interdepartmental and interdisciplinary communities on campus.

The Harvard Medical School Foundry Award Program

The Harvard Medical School Foundry Award Program aims to drive technology development and implementation across HMS by supporting innovation and research infrastructure. The Foundry primarily focuses on supporting the HMS Core Facilities and technology platforms, and aiding individual technology development projects. These shared resources build community across HMS, other Harvard schools, and HMS-affiliated institutions and provide access to highly specialized services, equipment, and staff that would be too costly for individual laboratories.

Progress

In summer 2024, the Foundry awarded funding to 10 projects to purchase new instrumentation and support operations in HMS core facilities. These Foundry investments in infrastructure continue to enable HMS to maintain the world-class facilities that are key to its research mission.

2024 Foundry Awardees

Chad Araneo, Director, Immunology Flow Cytometry Facility

Core capacity expansion

Thomas Bernhardt, PhD, Professor of Microbiology, Microscopy Resources on the North Quad (MicRoN)

STEDycon add-on for imaging microbes

Mandovi Chatterjee, PhD, Director, Single Cell Core

Upgrading existing instruments and addition of new technological capabilities

Maria Ericsson, Director, Conventional Electron Microscopy Facility

Microscope replacement

Gregory Heffron, Director, Bio-NMR Facility

Update of the 400 MHz NMR console system

Michael James, Director, Analytical Chemistry Core

Expansion of metabolomics and lipidomics capabilities

Paula Montero Llopis, PhD, Director, MicRoN core

Enhancing efficiency and expanding microscopy capabilities

Wade Regehr, PhD, Bullard Professor of Neurobiology, Neurobiology Imaging Facility

Super-resolution light microscopy for molecular analysis in situ

Robert Steen, Director, Biopolymers Facility

Next Gen Sequencing Core: Contribution toward purchase of an Illumina NovaSeq X Plus

Ulrich Von Andrian, MD, PhD, Edward Mallinckrodt Jr. Professor of Immunopathology, Immune Imaging Core

Tunable laser replacement for dual excitation multiphoton microscopy system

Dean's Innovation Awards for the Use of Artificial Intelligence in Education, Research, and Administration

The Dean's Innovation Awards for the Use of Artificial Intelligence in Education, Research, and Administration encourage innovative projects that utilize generative artificial intelligence (AI) to advance HMS's mission across education, research, and administration.

This initiative aims to:

- Sponsor innovative uses of generative AI that transform medical and graduate education, including new technologies for interactive simulation-based learning, adaptive tutoring systems, automated assessment, and other applications that enhance teaching and learning inside and outside the classroom.
- Enable groundbreaking applications of generative AI that open new frontiers in medical and biological research across disciplines such as medical imaging, drug discovery, genomics, structural analysis, and public health informatics.
- Improve administrative efficiencies and productivity through generative AI automation of workflows, development of intelligent decision support systems, improvements in data analytics and reporting, and other administrative applications.

In total, HMS distributed $2.2 million to 33 awardees to support the piloting of AI ideas, ranging from testing methods to customize medical education to developing tools for predicting biological behavior. The projects are underway and will be completed within two years.

The Center for Computational Biomedicine

In 2020, HMS launched the Center for Computational Biomedicine (CCB) to create a shared resource for data and computational expertise across HMS's Quad-based departments and labs to further enable research.

Over the last four years, the seismic progression and application of artificial intelligence (AI)—a top priority for HMS—have generated countless opportunities. However, these changes and unexpected financial challenges have compelled the team to reevaluate the center's scope and service areas. Consequently, the CCB team is transitioning the center from a standalone entity affiliated with the Department of Biomedical Informatics (DBMI) to a research core administered by the department to support science and education across the Quad.

DBMI senior research scientist Nathan Palmer, PhD, who recently served as director of the CCB data and analytic platforms, will lead the new HMS Core for Computational Biology. The core will focus primarily on the Quad, directly assisting investigators and departments in implementing innovative research solutions and supporting AI-enabled projects in research, teaching, learning, and administration. Colleagues in HMS Information Technology, who have made strategic investments in research computing, will closely collaborate on this important work and support HMS as it emerges as a leader in harnessing AI and machine learning.

HMS leadership is committed to working closely with Palmer, faculty advisers, and the HMS AI Steering Committee to ensure the redesignated core successfully meets its goals, supports the strategic integration of AI more broadly across HMS, and realizes the full potential of the core's productive research and education community.

The following update outlines the CCB's progress over the past year and the promising initiatives poised to advance AI-driven research and education at HMS.

Empowering Innovation in Generative AI

In 2023, the dean's office invited teams across research, education, and administration to submit proposals exploring the potential impact of generative AI in their areas of expertise. The initiative sparked significant interest, resulting in over 30 proposals receiving a year of funding to further explore and validate these concepts. The new Core for Computational Biology will support these projects in three ways:

Resource Integration

Project teams require access to various technical resources, including advanced commercial AI models like OpenAI's GPT, on-premises accelerated computing for bespoke model implementation and training, and fine-tuned open-weight models hosted on-premises. The CCB Core will be crucial in guiding these teams by identifying and connecting them to the most suitable platforms for their projects. This support is vital, especially as many teams are unaware of the extensive options available to them. Further, the core's efforts in triaging to the best platforms will ensure that each project is optimally equipped to advance successfully.

Infrastructure Setup

The new core, in collaboration with HMS IT, will develop the necessary on-premises computing infrastructure tailored to the specific needs of research projects. The core has invested in some of this infrastructure to experiment with various solutions, such as model fine-tuning, training, and retrieval-augmented inference. Through this iterative process, the core's team has guided HMS's leadership to invest in an NVIDIA AI hardware platform, positioning HMS at the forefront of academic medical research technology.

Implementation Assistance

Recognizing that many teams possess strong domain-specific expertise but may lack the necessary programming and prompting skills to develop their tools, the new core will provide essential software engineering services and support to ensure these projects succeed. Several projects, particularly in AI-assisted medical education—e.g., automated assessment quiz generation, grading, and summarization of grades for instructors and students—are now in production and performing demonstrably better than their human counterparts.

The Core for Computational Biology has built a robust support framework featuring a centralized website that offers access to essential resources such as technical tools, as well as details about office hours, and events. The core team actively maintains a GitHub organization to share software artifacts broadly with the open-source community. Additionally, team members offer regular office hours to provide targeted expertise in programming in R and generative AI prompt engineering, assisting community members with everything from general advice to specific technical issues. Core experts also lead AI training sessions, delivering one-hour educational modules that equip labs and departments with hands-on experience and practical, real-world applications for effectively integrating AI into their specialized areas.

Initiatives and Projects

Inovalon

In collaboration with several Harvard Business School (HBS) faculty members, researchers purchased the Inovalon data set, an extensive shared data repository that contains adjudicated and closed health insurance claims for over 150 million covered American lives across 11 calendar years. The repository comprises some 43 billion individual claims, 30 billion CPT procedures, 120 billion ICD diagnoses, and nine billion pharmacy claims. Thirteen labs at HMS and several more at HBS use this data.

Supporting Inovalon Data Access

The Core for Computational Biology supports the research community by giving hands-on assistance to active user groups and developing derived datasets for broader use. The core team manages vendor relationships and collaborates closely with HMS IT to design and maintain secure computing infrastructure. Additionally, the core facilitates a community platform that fosters research engagement and collaboration. The following are examples of research projects that have utilized the Inovalon data set:

- *Understanding the effects of economic shocks on health inputs and outcomes*
- *How do provider characteristics influence treatment decisions and health outcomes?*
- *Telemedicine, parity laws, and mental illness*
- *Improving Medicare in an era of change*
- *Environment, weather, and demographics in health care utilization*
- *Inter-hospital transfer*
- *Surgical outcomes*
- *Post-surgical risk of opioid misuse*
- *EHR data completeness biases*
- *Distribution of payers across providers*
- *Impact of a changing health care delivery system on the quality of oncology care*
- *Urgent care clinic ownership*
- *Robust learning approaches for assessing effects and effect heterogeneity of real-world antipsychotic treatment regimes in elderly persons with schizophrenia*
- *Disease trajectory modeling via foundational AI models over medical claims data*
- *Evaluations of increasing state investments in primary care: effects on health care spending, utilization, and quality*
- *Risk factors and impact of firearm-related injuries in the US*

Advancing Computer Vision Applications

The Core is developing versatile tools and workflows for Computational Biology in collaboration with the Harvard School of Dental Medicine, designed to be applicable across various computer vision applications. Key initiatives include:

Computer Vision Code Repository

This framework allows researchers, entrepreneurs, and clinicians with minimal machine-learning experience to apply AI techniques across various imaging modalities. Users can easily perform tasks such as image classification, object detection, and instance segmentation. The repository provides all necessary containerized infrastructure for off-the-shelf use, deployable on hardware-accelerated systems (e.g., GPU), and includes pre-built examples and comprehensive documentation to support seamless integration.

Diagnostic Tools

The core has presented and is in the process of publishing a machine learning-based tool for diagnosing periodontal disease. Traditionally, diagnosing periodontal disease requires a time-intensive and uncomfortable probing procedure for patients. This tool uses oral radiographs from routine clinical care to replicate the diagnostic process, providing a less invasive solution. The tool has generated significant commercial interest, and early discussions are underway with several companies to explore future partnerships.

Global Health Initiatives

In partnership with Ariadne Labs' Better Evidence Program, the Core for Computational Biology is developing a provider eHealth clickstream data database, focusing on low-resource settings, sourced from Wolters Kluwer's UpToDate tool, which offers clinical, drug, patient, and member content to support all health professionals. The primary goals of this initiative are to explore an innovative and cost-effective approach for epidemiological surveillance, including monitoring emerging infectious diseases, assessing regional health disparities, and evaluating the impact of health policy changes. Potential use cases for this database include:

- Monitoring infectious disease outbreaks
- Identifying new or emerging infectious diseases
- Assessing clinician knowledge gaps
- Evaluating regional health disparities
- Monitoring adverse drug events
- Identifying emerging health trends
- Tracking vaccine acceptance
- Monitoring the effectiveness of public health campaigns
- Evaluating the impact of health policy changes
- Assessing healthcare provider compliance with guidelines
- Evaluating patient education and engagement efforts to build trust in the health system
- Analyzing regional and geographic disparities

Looking Ahead

Artificial intelligence is poised to dominate the landscape of medical and biological research for the foreseeable future. While traditional analytic methods will still play a vital role, the Core for Computational Biology is committed to enhancing AI support for the research community by expanding implementation and educational resources and investing in on-premises infrastructure to support AI-driven research. Additionally, the core collaborates with HMS Information Technology to ensure that the most appropriate platforms meet the community's AI needs.

As the current GPU infrastructure approaches capacity, the core plans to acquire additional NVIDIA DXG H200 computer systems. These systems will serve a community-wide request for applications, inviting Quad researchers to apply for preferential access to the hardware. This initiative will also provide opportunities for collaboration with core experts, who will offer guidance on using the technology effectively.

The core will focus on sustaining the collaboration with HBS around shared data and computing platforms, ensuring continued progress and innovation in research infrastructure.

Special Projects Fund: Blavatnik Therapeutics Challenge Awards

Blavatnik Therapeutics Challenge Awards

In November 2019, HMS and the Blavatnik Family Foundation launched the Blavatnik Therapeutics Challenge Awards (BTCA) to advance therapeutics research projects within two years of a commercial exit. This program successfully addresses a critical gap in funding and expertise that often stalls progress in later-stage translational research programs in an academic setting. Additionally, it serves as a critical vehicle for the HMS Therapeutics Initiative to expand its impact in the broader Longwood community. HMS faculty members at the assistant, associate, or full professor level, based at HMS or its affiliated hospitals and research institutions, can apply as lead principal investigators, ensuring the Awards' broad impact across the entire HMS community. The Blavatnik Family Foundation funds awards up to $1 million each over two years, with up to five awards given annually. The grants are highly competitive.

In 2024, the BTCA program successfully concluded its fifth and final award cycle. This year, the program received 66 preliminary proposals. Ten of these were selected to advance to full proposals, which researchers crafted in collaboration with the scientific staff from the Therapeutics Initiative. A team of experts from academia, hospitals, biopharma, and the venture capital industry reviewed the pre-proposals and ultimately approved funding for three outstanding projects.

Expert principal investigators from three different institutions lead the awarded projects, which address a variety of medical conditions, including cancer, osteoarthritis, and anemia. Mark Namchuk, PhD, and Ifat Rubin-Bejerano, PhD, along with Translator scientists and scientific project managers, have assisted BTCA investigators with project planning and milestone tracking. They have also provided scientific advice and logistical support.

The emerging outcomes from the earlier cohorts of projects testify to the quality of the investigators and the rigor of the selection process. To date, none of the selected projects have failed due to invalidation of the scientific hypothesis or approach, which is a remarkable achievement. Among the 17 projects awarded during the program's first four years, four have progressed to the stage of founding a new company or licensing their technology as part of a startup. Additionally, two more projects are completing IND-enabling studies, intending to move their molecules into clinical development within the next year.

2024 BTCA Projects and Awardees

Treating Fragile X syndrome via CGG repeat contraction

Jeannie Lee, MD, PhD

Phillip A. Sharp Chair in Molecular Biology, Massachusetts General Hospital
Vice Chair of the Department of Genetics and Professor of Genetics and Pathology, HMS

Brain selective modulation of adrenergic receptors to treat Parkinson's disease

Kevin Hodgetts, PhD

Associate Professor of Neurology, HMS and Brigham and Women's Hospital

Preparation of intravenous oxygen for a first-in-human clinical trial

John Kheir, MD

Senior Associate Cardiologist, Boston Children's Hospital
Associate Professor of Pediatrics, HMS

BTCA Project Highlights

- 2020 cohort: **Steven Greenberg, MD ’88**, a professor of neurology at HMS and Brigham and Women’s Hospital (BWH), founded a new company based on his work to develop a first-in-class asthma treatment.
- 2020 cohort: **Peter Park, AB ’94, SM ’94, SM ’00 PhD**, a professor of biomedical informatics in the Blavatnik Institute, developed an antisense oligonucleotide (ASO)-based progranulin augmentation therapy, which Third Rock Ventures incorporated into the start-up RegUp. Unfortunately, despite excellent scientific progress, the company folded, and Harvard regained the IP. The Harvard Office of Technology Development (OTD) is now prioritizing licensing this promising IP.
- 2021 cohort: **David Corey, PhD**, the Bertarelli Professor of Translational Medical Science in the Blavatnik Institute at HMS, completed an $840,000 sponsored research agreement to enhance the development of his gene therapy for congenital deafness and blindness. OTD is now working on licensing this IP.
- 2021 cohort: **Vijay Sankaran, PhD ’09**, **MD ’10,** the Lodish Family Chair in the Division of Hematology at Boston Children’s Hospital (BCH), successfully completed his BTCA project to develop a gene therapy for pediatric anemia. With matching funds from BCH, the therapy completed IND-enabling studies, and plans are underway to initiate clinical development.
- 2022 cohort: **Kevin Hodgetts, PhD**, an HMS associate professor of neurology based at BWH, founded the company Modulate Bio based on his work in developing novel small molecules for the treatment of essential tremor. The company is now actively fundraising.
- 2022 cohort: **Mohammad Rashidian, PhD**, an HMS assistant professor of radiology based at Dana Farber Cancer Institute (DFCI), founded the company Koi Biotherapeutics around his BTCA-supported CAR-T engager program and is actively fundraising.
- 2023 cohort: **Michael Eck, MD, PhD**, an HMS professor of biological chemistry and molecular pharmacology based at DFCI, is completing IND-enabling studies for his EGFR inhibitor and is actively seeking funds from public and private sources to support Phase 1 clinical studies.

The program expects several additional BTCA-funded projects to complete their work in 2025, resulting in more commercial and clinical success.

Blavatnik Special Projects Fund at Harvard Medical School

Blavatnik Fund for Cryo-EM

Stephen Harrison, AB '63, PhD '68
Giovanni Armenise-Harvard Professor of Basic Biomedical Science, HMS
Faculty Director, Harvard Cryo-EM Center for Structural Biology

The Blavatnik Fund for Cryo-EM has enabled the Harvard Cryo-EM Center for Structural Biology to substantially upgrade its most powerful electron microscopes—two Titan Krios, 300 keV instruments—and to establish expertise in the major new technology, cryogenic electron tomography (cryo-ET). These two initiatives allow Harvard Medical School to remain at the cutting edge of this rapidly advancing field.

The team upgraded the two Titan Krios microscopes with new electron detectors and energy filters; active data acquisition is on-going for both instruments. Thanks to the upgrades, the team is now experiencing higher throughput and better data with the instruments. A project that previously required two days of user time now requires only a day. This advance is important, not only because of the intensive use of both microscopes but also because cryo-ET is particularly time-consuming. Additionally, operating the microscopes with the new detectors is more straightforward for users, minimizing user errors.

In cryo-ET, researchers obtain structural data, potentially at high resolution, from macromolecular complexes in situ by flash freezing an intact cell. They record data in a manner similar to a medical CAT scan—capturing a series of views of the object at regularly spaced angles around a tilt axis and using that series of projected images to reconstruct a three-dimensional one. Because cells are too thick to allow enough electrons to pass through them, researchers apply focused-ion-beam milling technology to create a very thin slab through the cell and obtain the series of tilted views through one or more regions of that slab. Two years ago, the Center acquired the relevant instrument and has since developed the expertise to regularly apply this approach to important issues ranging from fundamental questions about cell division and motility to how cells transmit certain key signals to their neighbors.

The Blavatnik Fund for Cryo-EM has allowed the center to recruit an additional staff member, who will assist users in collecting and interpreting data on the upgraded Titan Krios microscopes and accelerate the screening of samples to find preparations suitable for high-resolution interpretation. This new staff member will join the team at the end of calendar year 2024.

The appendix includes a list of papers published by Cryo-EM Center researchers between January and August 2024. Below are brief descriptions of three papers:

1. **Johnson et al.** discovered that bacteria possess a homolog of gasdermin (GSDM), a protein previously characterized only in eukaryotic cells, where it oligomerizes into membrane pores in response to a pathogen and kills the infected cell. The structure of the bacterial GSDM, together with cellular studies, supports a model for stepwise pore assembly and highlights the ancient evolutionary origin of this important class of pore-forming proteins.

2. **Pahil et al.** utilized structural, biochemical and genetic approaches to demonstrate that some newly discovered antibiotics stall the lipopolysaccharide (LPS) transporter of Acinetobacter, a gram-negative bacterium, by trapping a substrate-bound conformation. Because LPS is a critical component of the bacterial outer membrane, the transporter has long been a sought-after target for potential inhibitors. The findings identify a druggable conformation of the transporter and provide an opportunity to extend this class of antibiotics to other gram-negative bacteria.

3. Through structural analysis, **Zhao et al.** discovered that insect odorant receptors—tetrameric, ligand-triggered ion channels that contain both a conserved co-receptor subunit (Orco) and an odorant-binding subunit (OR)—have an unexpected 3:1 Orco:OR ratio. These receptors are important targets for controlling disease-bearing insects, such as the two mosquitos (Aedes aeqypti and Anopheles gambiae) from which the receptors characterized in this paper were derived. The work represents a first step toward understanding how each molecule in the vast universe of volatile odorants can produce a distinctive signal in the insect's nervous system, ultimately influencing the animal's behavior.

Blavatnik HealthTech Fellowship

Turning Health Care Challenges into Business Opportunities

The Harvard Medical School (HMS) HealthTech Fellowship is a 10-month program that trains health care's next generation of innovators to harness technology, engineering, business skills, and cutting-edge science to elevate medical care to a higher standard. This University-wide program unites the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS), Harvard Business School (HBS), and HMS to develop significant health technology innovations. This cross-disciplinary program leverages faculty mentors and resources at Harvard and HMS's affiliated hospitals.

Using a process called biodesign, a rigorous, proven framework for using direct observation in clinical settings, HMS HealthTech Fellows explore the challenges faced by medical practitioners and patients to create solutions that directly address those challenges. They embed themselves into clinical settings and receive direct exposure to the most pressing, unmet health care needs, ultimately choosing one need to focus on, then designing and testing innovative solutions. Along the way, fellows receive mentoring from Harvard faculty and guidance and feedback from health care entrepreneurs, corporate executives, and venture capitalists. The program's Extension Fund provides seed grants of up to $50,0000 to fellowship teams with high-potential business ideas, enabling them to continue working on their novel interventions post-fellowship.

> "Having the opportunity to have the HMS HealthTech Fellows embedded in our department was an incredible experience. They energized our faculty to think more creatively about innovation as they spent time in ORs, clinics, and in conversation with our surgeons. The relationships they built with our group here have been enduring and they are continuing to work with us well past the end of their term."
>
> *—Mark Varvares, MD, FACS*
>
> *Associate Chair of Otolaryngology Head and Neck Surgery, Massachusetts Eye and Ear*

The HealthTech program is expanding its impact by working directly with faculty members at Harvard-affiliated hospitals to guide them in their innovations. The program's Anatomy of Innovation course gives graduate students, postdoctoral students, residents, and researchers the opportunity to learn the biodesign curriculum experienced by fellows, helping to build the pipeline for health care innovators and STEM professionals. The Junior HealthTech Fellowship is a community engagement program that encourages students from Brooke High School in Boston, which serves a high percentage of disadvantaged students, to pursue careers in STEM disciplines. Additionally, the program hosts life science events for HMS HealthTech Fellows, Harvard and affiliate students, and other health care and life science partners to foster collaboration and relationship-building.

Program Highlights

- The 2025–2026 application cycle launched in July 2024, with a 30% increase in applications. The program will select candidates this month.
- The program's 2024–2025 clinical partner is the Massachusetts General Hospital (MGH) Department of Neurosurgery. In September 2024, Fellows began their clinical immersion, focusing on issues affecting the aging population from preoperative to post-operative care.
- The team is in discussions with the MGH Mongan Institute and Center for Aging to establish a long-term partnership that expands innovation opportunities in the aging space.
- In January 2025, fellows will join MS/MBA students for a weeklong Technology Venture Immersion course co-taught by HBS and SEAS faculty. This course uses a hands-on approach to teach essential skills for early-stage technology ventures.
- The program's Anatomy of Innovation course continues to inspire the Harvard ecosystem. A team from the last class is advancing a non-invasive solution to detect breech pregnancies before 36 weeks using advanced thermal imaging technology.
- Sixteen Junior HealthTech students have participated in the program, and four more will join between November 2024 and May 2025. They will be encouraged to work on age-related issues.

HealthTech Startup Highlights

- 2021–2022 fellows Nicky Agahari and Martin Jensen co-founded InConfidence, a company that uses smart patch technology to treat urinary incontinence and overactive bladder. In spring 2023, they received $75,000 from the Harvard President's Innovation Challenge and raised approximately $10 million.

- 2022–2023 fellows Ana Trapero-Martin and Bridget Slomka, co-founders of RhinUS, are developing a low-frequency ultrasound device designed to disrupt biofilms and treat chronic sinus infections, in collaboration with the ear, nose, throat and microbiology departments at Mass Eye and Ear. Their latest prototype shows promise by significantly reducing bacterial biofilms in vitro, marking an important step in the development of their non-invasive treatment for patients suffering from chronic rhinosinusitis. They have also advanced their market research and strategy by joining the NSF Spark I-Corps program and have built business, regulatory, and reimbursement plans through participation in multiple accelerators, including Primary VC, Nucleate, M2D2, MassMEDIC, and The Engine's Blueprint.

2025–2026 HealthTech Fellows Team

The HealthTech Fellowship program is in the final stages of confirming its 2025–2026 cohort. The candidates offered positions bring a diverse blend of skills in clinical care, research, health care technology innovation, and business leadership. Their collective strengths include deep clinical experience in fields such as urologic oncology and colorectal cancer, technical expertise in AI, experience in entrepreneurship and startup operations, and strong capabilities in business analytics and marketing. Each candidate is committed to leveraging the biodesign innovation framework to create impactful solutions, making for an exceptional cohort poised to advance health care innovation and address critical challenges in aging.

Blavatnik Fund for Longevity and Human Health

Abraham Morgentaler, AB '78, MD '82
Associate Clinical Professor of Urology, HMS and Beth Israel Deaconess Medical Center

Supported by the Blavatnik Family Faculty Fellowship in Health and Longevity, Dr. Abraham Morgentaler has continued to make a widespread impact through his educational and research activities.

In 2023, he created an educational website, T4LEducation.com (T4L), focused on testosterone deficiency and its treatment. The website provides clinicians and the public with reliable information about the topic, drawing on research by Dr. Morgentaler and others, and informed by Dr. Morgentaler's pioneering clinical experience over the past 35 years. T4L has established several educational initiatives, including a bi-annual virtual international fellowship that provides physicians with intensive training with Dr. Morgentaler. Physicians from Germany, France, the United Kingdom, South Africa, and Vietnam, participated in the fellowship, which ended in May 2025, and gave positive reviews. A new fellowship cycle began in September 2024.

Dr. Morgentaler continued his active role in the Androgen Society, an international multidisciplinary medical organization he founded eight years ago. He currently serves on the board of directors as executive secretary and provides oversight and direction for the organization, dedicated to research, education, and clinical expertise in the field of testosterone deficiency and its treatment. Many of the leading testosterone researchers from around the world participated as faculty in the most recent meeting in Boston in May 2024.

Dr. Morgentaler and his wife, Marianne Brandon, PhD, launched a new podcast, The Sex Doctors, in September 2024. The podcast's goal is to review the latest research and trends in human sexuality and translate this information to the general public.

Continuing Medical Education Course

Dr. Morgentaler directs a Harvard Medical School two-day continuing medical education (CME) course on testosterone and sexual dysfunction. In February 2024, the course sold out, attracting over 400 attendees, and receiving evaluations as one of the best CME courses offered by HMS. The course will be offered again in January 2025.

Lectures

In 2024, Dr. Morgentaler gave several high-profile lectures, including a plenary session at the annual meetings of the American Urological Association and the Androgen Society and grand rounds at the University of California, Irvine, and the University of Chicago.

Awards

Dr. Morgentaler received the prestigious Grandmaster in Testosterone Award at the Androgen Society's annual meeting.

Publications

Dr. Morgentaler is working on chapters for two medical textbooks. In addition, he has published the following peer-reviewed articles in medical journals:

1. Morgentaler A, Traish AM, Dhindsa S, et al. Androgen Society Position Paper on Cardiovascular Risk with Testosterone Therapy. Mayo Clinic Proceedings, in press.

2. Morgentaler, A., & Hanafy, H. M. (2024). The testis, eunuchs, and testosterone: a historical review over the ages and around the world. Sexual Medicine Reviews, 12(2), 199-209.

Blavatnik Fund for Sensory Disorders Research

Project updates from the current awardees

Visual Restoration in Cortical Blindness: A New Protocol to Promote Fast Recovery

Lorella Battelli, PhD
Associate Professor of Neurology, HMS and Beth Israel Deaconess Medical Center

Chinfei Chen, MD '91, PhD '91
Associate Director of the Harvard Program in Neuroscience
Professor of Neurology and Professor of Neurobiology, HMS and Boston Children's Hospital

The leading cause of cerebral blindness (CB) is stroke. CB is a lesion in the primary visual cortex, which produces vision loss for both eyes in the visual field opposite the side of the stroke. After experiencing early, spontaneous partial recovery, the majority of patients still have large, persistent visual deficits. Currently, there is no effective clinical rehabilitation procedure. The Battelli Lab has demonstrated that combining non-invasive brain stimulation with visual discrimination training (Fig. 1A) can significantly increase the rate of visual learning in both visually intact participants and those with stroke-induced CB. The lab collected data from 10 stroke patients with partial CB and randomly assigned the patients to active or control stimulation conditions. The clinical trial aims to reduce the blind area after behavioral training combined with non-invasive brain stimulation and promote the recovery of simple and complex visual discrimination within the trained area. The clinical trial is double-blind—researchers do not know who received real or sham stimulation—but the researchers have performed some preliminary analyses of the patients' data.

The patients were divided into two groups, treatment A and treatment B. Eight of these patients were defined as chronic (more than six months post-stroke) and were equally divided into groups A and B, while two were subacute post-stroke (less than six months post-stroke) and placed in treatment B. Patients in the subacute group showed improvement at a rate consistent with published research, which indicates that individuals in the subacute phase of stroke are more likely to have vision improvements compared to those in the chronic phase. In addition, patients maintained their level of performance when tested three months after the end of training. This is also true for some chronic patients (Fig. 1B, representative patient).

The lab is collecting data before and after the two-week training procedure to observe potential changes in fMRI-based population receptive field mapping after training. The lab will analyze changes in luminance detection sensitivity with retinotopic fMRI activity before and after visual discrimination training. The lab hypothesizes that pre-training activity at the stroke site will predict the amount of recovery.

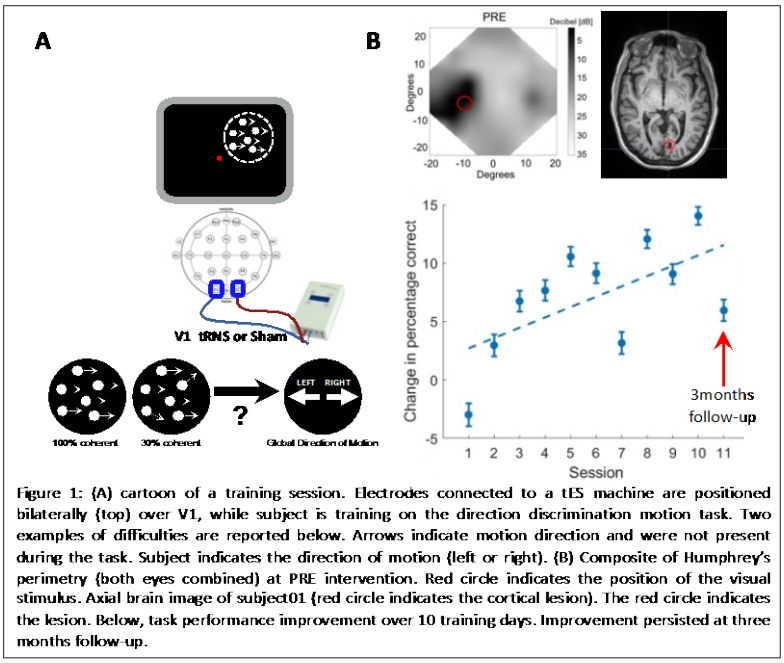


Figure 1: (A) cartoon of a training session. Electrodes connected to a tES machine are positioned bilaterally (top) over V1, while subject is training on the direction discrimination motion task. Two examples of difficulties are reported below. Arrows indicate motion direction and were not present during the task. Subject indicates the direction of motion (left or right). (B) Composite of Humphrey's perimetry (both eyes combined) at PRE intervention. Red circle indicates the position of the visual stimulus. Axial brain image of subject01 (red circle indicates the cortical lesion). The red circle indicates the lesion. Below, task performance improvement over 10 training days. Improvement persisted at three months follow-up.

To understand the circuit mechanisms underlying recovery from stroke, the Chen Lab developed an animal model to assay visual recovery in response to cortical lesions. Lab members are optimizing a two-alternative forced choice task to assay visual perception in mice by training the animals to distinguish between two sets of images or videos. The lab first validated this task by training mice to distinguish between horizontally and vertically oriented bars. Adult mice learned this task within three weeks. The lab subsequently decreased the angle differences between the two images to measure perceptual thresholds and found that mice performed similarly to previously published reports. Lab members are currently testing moving dot stimuli in this behavioral task to use stimuli similar to those that the Battelli Lab uses to assay human motion perception. Now that the Chen lab established this behavioral assay, they plan to (1) measure visual recovery in animals with cortical lesions (Fig. 2A), (2) determine how visual training (Fig. 2B) and electrical stimulation affect visual recovery in response to cortical lesions, and (3) test if recovery is associated with a plasticity response in the visual thalamus. Establishing this animal model will pave the way for understanding molecular and circuit mechanisms underlying visual recovery after stroke.

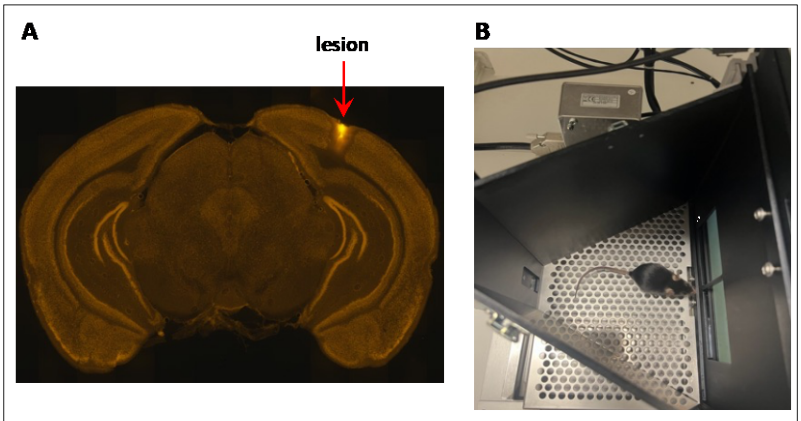


Figure 2. (A) Mouse stroke model. Example of ibotenic acid lesion circumscribed to V1 in the coronal section of the mouse brain. (B) Top-down view of the 2- alternative forced choice task. Mice are trained to distinguish between two stimuli presented on touch screens and rewarded with the correct choice. The Chen lab is training mice to distinguish subtle differences in visual stimuli between the two screens.

In Vivo Correction of a Common Hereditary Deafness Mutation Using Prime Editing

David P. Corey, PhD
Bertarelli Professor of Translational Medical Science, HMS

Benjamin Kleinstiver, PhD
Assistant Professor of Pathology, HMS
Associate Investigator, Massachusetts General Hospital

Mutations in more than 100 genes may cause a hereditary hearing deficit in more than one in 1,000 children. The mutation of a single gene, GJB2, most commonly causes the condition, and the 35delG mutation, characterized by the deletion of a single letter G in the DNA, is one of the most frequent mutations of GJB2. In the United States, as many as 700 children are born deaf each year because they carry a 35delG mutation. For this project, Corey, an expert in the inner ear, and Kleinstiver, a pioneer in gene editing, collaborated to find a treatment for GJB2-35delG-related deafness. The Corey and Kleinstiver labs developed a therapy and tested it in a mouse model of 35delG deafness by using a prime editor enzyme delivered in AAV vectors to correct the gene defect in cells of the mouse's inner ear. As a result of this work, the team has received new funding to take on related projects, filed a new IP, and attracted interest from industry partners to carry the technology to the clinic.

First, the labs created a mouse model for DFNB1 deafness and established a baseline for mutant mouse pathology. Because the mice are completely deaf, researchers can use them as an effective platform for testing prime editors.

To develop optimal prime editors, researchers can test them more quickly in cultured cells in a dish. The labs created a model 35delG cell line using HEK 293T cells. They obtained both heterozygous and homozygous HEK 293T clones bearing the 35delG mutation and used them to assess hundreds of combinations of prime editors and pegRNAs. They tested different CRISPR-Cas9 enzymes and reverse-transcriptase domains for the prime editor construct, and screened hundreds of parameters for the pegRNA, including the lengths of the sequences encoding the edit and bearing homology to the genome. The team discovered several highly efficacious combinations through extensive screening, achieving over 75% precise correction of the 35delG mutation in human cell culture.

Because an editor must be both safe and effective, the researchers sequenced other genomic sites to check for off-target editing. The data suggest that the 35delG correction approach is highly specific, showing no detectable off-target edits in cells. These unprecedented results, demonstrating highly efficacious on-target correction with no unwanted off-target edits, gave the researchers confidence to advance to further testing of the 35delG correction approach in animal models.

The team set three goals for testing the optimized prime editor in the mouse model:

1. To package the editor in an AAV virus.
2. To deliver the virus to the inner ear of the mouse model.
3. To assess the editing with both sequencing and functional preservation of hearing.

First, because the coding sequence of the prime editor and pegRNAs is too large to fit into a single AAV vector, they explored various approaches to configure the prime editing components into two AAV genomes. Once inside the same cell, the two AAV genomes drive the production of the two halves of the editor, and these two proteins self-join through the fusion and subsequent removal of an "intein" peptide. The labs conducted extensive in vitro tests to identify new intein "split" points in the prime editor that are more optimal than those previously described in the literature. This effort resulted in highly efficacious expression of prime editor and pegRNA expression, leading to effective prime editing in cultured cells when using the AAV vectors. These results motivated the team to test the AAV-based prime editing approach in their humanized Gjb2 35delG mouse model.

Second, they packaged the two parts of the editor in different AAV capsids and injected both AAVs into the inner ears of the mice the day after birth, utilizing methods standard in their laboratory. After 14 days, the researchers harvested DNA and mRNA from the cochlea. They sequenced the DNA and mRNA to determine whether the genomes of affected cells in the cochlea had been corrected—specifically checking if the missing G of the 35delG had been correctly inserted. The researchers discovered an extraordinarily high editing rate, approaching 80%, in the cells that typically produce the GJB2 protein. This rate matches or exceeds any prime editing achieved for any disease model.

Finally, the researchers tested the mice's hearing after a 30-day waiting period following similar treatment. While untreated mice remained profoundly deaf, the treated mice demonstrated improved hearing. However, the improvement did not match the high success rate of DNA editing. They suspect the editing may not occur quickly enough to prevent cell degeneration in the 35delG mouse model. As a result, they are now testing mice in which degeneration occurs more slowly, providing better models for human patients. The labs remain optimistic about achieving good preservation of hearing in these mice.

The Cellular and Molecular Substrates for Treating Hidden Hearing Loss

Lisa Goodrich, AB '91, PhD

Professor and Vice Chair of Neurobiology, HMS

People use their sense of hearing to navigate the world, from avoiding oncoming danger to appreciating music. Hair cells in the cochlea detect sounds, and spiral ganglion neurons (SGNs) encode the detected sounds. These neurons receive sound information through synapses with the inner hair cells. Typically, circuits in the inner ear can capture and localize sounds that vary tremendously in frequency and intensity. However, exposure to excessively intense stimuli, such as the roar of a jet engine, can permanently damage a subset of the synapses that link hair cells to SGNs. This "synaptopathy," which also occurs as animals age, degrades the cochlea's ability to accurately encode sound information and likely contributes to difficulties in hearing in noisy environments. Cochlear synaptopathy interferes with the encoding of sound information, rather than with sound detection, unlike other types of deafness that prevent normal sound detection. Because most audiological tests measure detection, changes in auditory function associated with synaptopathy are referred to as "hidden hearing loss." In these cases, patients and doctors may not recognize the root cause of hearing challenges, which would not be improved by wearing hearing aids. Identifying a way to prevent cochlear synapse loss could maintain normal hearing both after noise exposure and as people age, significantly enhancing quality of life.

In this project, researchers studied two complementary mechanisms that offer endogenous protection from acute and chronic noise exposure. They also tested the protective benefits of a neuroprotective molecule known to prevent axon degeneration. All three lines of work yielded valuable insights and provide a foundation for future translational investigations. First, they investigated how natural differences among SGNs influence their vulnerability to acoustic trauma. Researchers believe that one subtype of SGNs, called the Ic SGNs, experiences greater synapse loss than the Ia SGNs. This idea is based entirely on physiological and anatomical criteria, leaving the question of whether molecularly defined Ia, Ib, and Ic SGNs differ in their resilience. For instance, it is possible that the observed loss of SGNs with low activity levels, thought to correspond to the Ic's, is due instead to a compensatory increase in activity that makes those SGNs behave more like Ia SGNs, which typically exhibit high levels of spontaneous activity.

In the first series of experiments, the researchers tested which SGN subtypes are more likely to lose their synapses after exposure to high-intensity stimuli. They leveraged their knowledge of molecular differences by using a genetic approach to label Ib and Ic SGNs. Then, they quantified the proportion of all synapses made with Ib and Ic SGNs after noise exposure or with age. If Ib and Ic SGNs are more vulnerable, the proportion of Ib/Ic synapses is predicted to decrease. Although the researchers are still conducting the final analysis, the pilot study suggested that Ia synapses are the most resilient. To understand how this resilience relates to the properties of Ia, Ib, and Ic synapses, they utilized a genetic mouse model in which Ib and Ic SGNs take on Ia identities, as indicated by the morphology of their synapses and their contributions to auditory nerve activity. Although the analysis is incomplete, they have found no obvious differences. If this result holds up, they can conclude that factors other than synaptic size and position affect whether a synapse survives acoustic trauma. **Collectively, these results will help the researchers understand what makes a synapse more vulnerable, which is important for developing effective therapeutics.** The team is finalizing the analysis and plans to publish these results by the end of the year.

In parallel to their work on the SGN subtypes, the researcher team is also studying how inputs from other neurons influence SGNs' response to acoustic trauma. SGN activity is initiated by the signals SGNs receive from hair cells and modulated by signals from olivocochlear neurons in the central nervous system. Olivocochlear neurons are located in the brainstem and extend their axons to terminate either on the Type I SGNs (the lateral olivocochlear neurons, LOCs) or on the outer hair cells (the medial olivocochlear neurons, MOCs). Researchers have proposed that both MOCs and LOCs play important roles in limiting the effects of acoustic trauma, potentially acting through independent mechanisms. For instance, when MOCs activate OHCs, they could dampen cochlear activity overall, preventing signaling from hair cells to SGNs from becoming excitotoxic. Alternatively, LOCs could modulate SGNs to directly prevent excess activity. Previous efforts relied on methods that could not selectively access either LOCs or MOCs, making it difficult for researchers to identify the site or mechanism of any protection that is offered.

The researchers overcame this roadblock by devising a genetic method allowing selective ablation of many LOCs. They tested how LOC-ablated mice are affected by noise exposure. They found that, after acoustic trauma, LOC-ablated mice had worse hearing than their non-ablated littermates. Unexpectedly, the hearing loss was not caused by a loss of synapses: LOC-ablated and non-ablated animals retained equal numbers of synapse after noise exposure. Instead, the results suggest that LOCs normally enhance auditory nerve activity after noise exposure, thereby improving hearing sensitivity in challenging scenarios.

To learn more about the nature of LOC-mediated effects on the cochlea, the researchers asked how LOCs respond to trauma at the molecular level. Characterization of gene expression programs in LOCs one day and one week after noise exposure revealed that increased expression of transcripts encoding several neuropeptides is one of the dominant outcomes. In contrast, gene expression barely changed in MOCs. This finding suggests that noise exposure primarily causes LOCs to release neuropeptides onto the SGNs or surrounding cells. Researchers have found that many cells in the cochlea express receptors for these neuropeptides, including the macrophages of the immune system. Thus, this project inspired a new project in the Goodrich lab focused on regulating neuropeptide expression and how this change affects cochlear function and resilience. The researchers are particularly interested in exploring the possibility that the LOCs influence immune responses, similar to the effects of neuropeptides elsewhere in the body.

Finally, the research team also investigated an endogenous neuroprotective molecule and its ability to mitigate the effects of damage. Bcl-w belongs to a large family of proteins determining whether neurons live or die. Rosalind Segal, AB '79, MD, PhD, a collaborator on the project, demonstrated that Bcl-w is unusual in its ability to also prevent axon degeneration in somatosensory neurons. Previously, the researchers found that Bcl-w is expressed in SGNs and that Bcl-w mutant mice have fewer synapses than their wild-type littermates. In the current project, they established a line of transgenic mice that conditionally expresses extra Bcl-w. In addition, they used viruses to increase Bcl-w levels throughout life. The data suggest that enhanced levels of Bcl-w can partially offset the effects of noise exposure on cochlear function. They are currently investigating whether Bcl-w achieves this effect by preventing synapse loss. If the final results confirm the initial pilot study, they can explore the possibility of preventing hidden hearing loss with treatments using molecules that either mimic Bcl-w or stimulate enhanced Bcl-w activity.

This project has advanced the understanding of the neural response to acoustic trauma by examining both intrinsic differences among SGNs and the extrinsic impact of LOCs. The team is well-positioned to determine whether targeting Bcl-w could lead to the development of therapies that protect inner ear circuits, thereby preventing noise-induced and age-related hearing loss, which affects over half of the population over the age of 70.

Developing Novel Therapies for Neuropathic Pain

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Peripheral neuropathic pain occurs when trauma, infection, inflammation, metabolic disorders, or exposure to cancer chemotherapeutic agents damage sensory axons. However, existing FDA-approved therapies manage neuropathic pain poorly, as they have low efficacy and numerous side effects. The project aimed to identify targets that would enable the development of novel treatments for neuropathic pain. The researchers used three different approaches:

1. Identify and target the specific mechanisms that maintain chronic neuropathic pain.
2. Develop strategies to prevent neuropathy that causes neuropathic pain.
3. Promote recovery of nerve injury by enhancing axon regeneration.

In the first approach, they successfully developed a novel model of spontaneous neuropathic pain in mice and identified ion channels expressed by injured nociceptor cells, the sensory neurons that trigger pain. The researchers conducted high-throughput ion flux and electrophysiology screens using large chemically diverse libraries and identified compounds that act selectively on these target ion channels. They tested the activity of these hit compounds on human stem cell-derived nociceptors and ensured that the compounds had little or no activity on motor neurons, cortical neurons, or heart cells. The researchers then tested the most promising compounds on mouse models using machine-learning technologies to automatically measure pain-related behaviors and analgesic efficacy. The neuroma model revealed that injured axons in neuromas drive spontaneous neuropathic pain through voltage-gated sodium channels, which arises late after nerve injury. Compounds blocking these ion channels substantially reduce neuropathic pain.

To prevent neuropathy, the researchers screened for neuroprotective agents that would prevent the development of chemotherapy-induced peripheral neuropathy (CIPN) in response to cancer therapeutic agents like paclitaxel. The researchers used human sensory neuron assays and identified three kinases whose inhibition prevents chemotherapy-induced toxicity in these neurons without interfering with the anticancer action of the chemotherapeutic agents.

Finally, the researchers screened promoters of axon regeneration on human stem cell-derived neurons and discovered that inhibition of non-muscle myosin II (NMMII) ATPase promotes robust axonal regeneration both in vitro and in vivo. They are now optimizing these promising hits as potential clinical candidates in collaboration with medicinal chemists.

Using the human neuron phenotypic assays, the researchers identified promising hits for the ion channels that drive neuropathic pain, the kinases that lead to CIPN, and the inhibitors of NMMII that promote axon regeneration. They aimed to develop novel therapeutic strategies that would enable physicians to suppress ongoing neuropathic pain, prevent the development of neuropathy, and enhance nerve repair. Furthermore, the kinase inhibitors that protect against CIPN also act on models of Alzheimer's disease, suggesting a broader neurological utility than initially anticipated.

A Neuronal Electrical Excitability Recording System for Improved Diagnosis and Biomarker Assessment of the Therapeutic Impact of Drugs in Peripheral Sensory and Pain Disorders

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Nancy Lurie Marks Professor of Neurology, HMS
Chief of Neurology, Beth Israel Deaconess Medical Center

Brian Wainger, MD, PhD
Associate Professor of Anaesthesia and
Associate Professor of Neurology, HMS
Attending Physician, Massachusetts General Hospital

Rutkove and Wainger have created a new system to assess peripheral nerve electrical excitability, aiming to measure the severity of sensory disorders caused by neuropathies from chemotherapy, diabetes, or genetics. In addition to assessing the nerve fibers typically measured with nerve conduction studies (myelinated, large-diameter axons), they have included a second component called microneurography, which focuses on assessing the more challenging-to-quantify unmyelinated, small diameter axons. This system can potentially quantify nerve impulses associated with sensory loss and pain, as well as motor dysfunction, and could serve as a useful tool in assessing drug therapies for a variety of neurological conditions.

The system they developed is based on a system created by Professor Hugh Bostock at University College London more than 20 years ago. Bostock's system had very basic software, but researchers around the world continue to use it because no one had previously made an effort to create a dedicated system for this purpose.

Since the last report, the research team has worked closely with the engineering firm iOrbit Ltd., and made substantial progress in developing the new excitability testing system, including both stimulation and amplification paradigms. All standard design protocols were implemented to ensure that the system meets FDA and EMA requirements. Figure 1 shows the original Bostock and microneurography systems. Figure 2 shows the new system, termed Nerve Electrical Excitability Recording System (NEERS) is shown in Figure 2. NEERS has been tested and modified several times in the past year. The team is beginning to conduct testing on healthy subjects and patients with various peripheral nerve disorders.

In addition to developing new hardware, the research team has created a new software suite to drive data collection and analysis. This system includes dedicated firmware as well as the actual user interface. Figure 3 shows the original software from the Bostock system and the new interface.

With the work completed here, the team has started commercializing the technology to bring it to laboratories and clinics worldwide. **The teams established a company, Boston Axon, LLC, and applied for a small business innovative research grant through the National Institutes of Health (NIH) and the NIH's new Blueprint MedTech program.** The researchers are meeting with pharmaceutical companies in the neurological disease space, including those focusing on sensory pain disorders and amyotrophic lateral sclerosis, to gauge their interest in funding further development of the system for full commercialization and FDA approval.

The team will continue testing the new system developed with support from the Blavatnik Family Foundation and will publish the results while seeking further investment and funding to bring this important technology to the broader neurological and pharmaceutical communities.

Figure 1. At left is the legacy research system built from off-the-shelf components and developed more than 20 years ago. The standard setup includes multiple cables, a stimulator, a National Instruments analog-to-digital card, an amplifier, and noise-filtering devices. **The right** image shows a standard microneurography setup including amplifiers and stimulators.

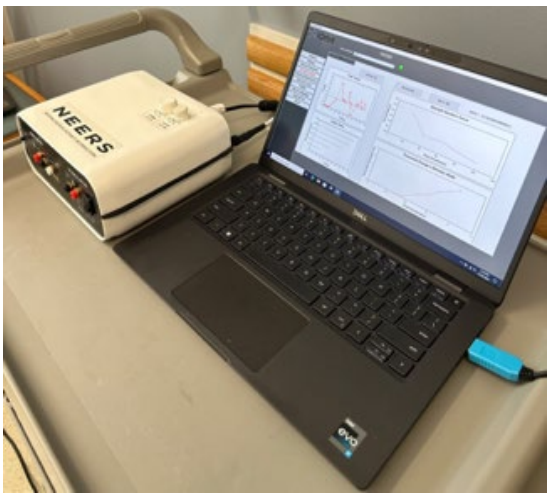


Figure 2. At left is the new Neuronal Electrical Excitability Recording System (NEERS), which takes both above systems and combines them into one small device connected to a laptop computer that runs the software. (The software is shown in Figure 3). **Above** is the front panel of the device with controls and connectors.

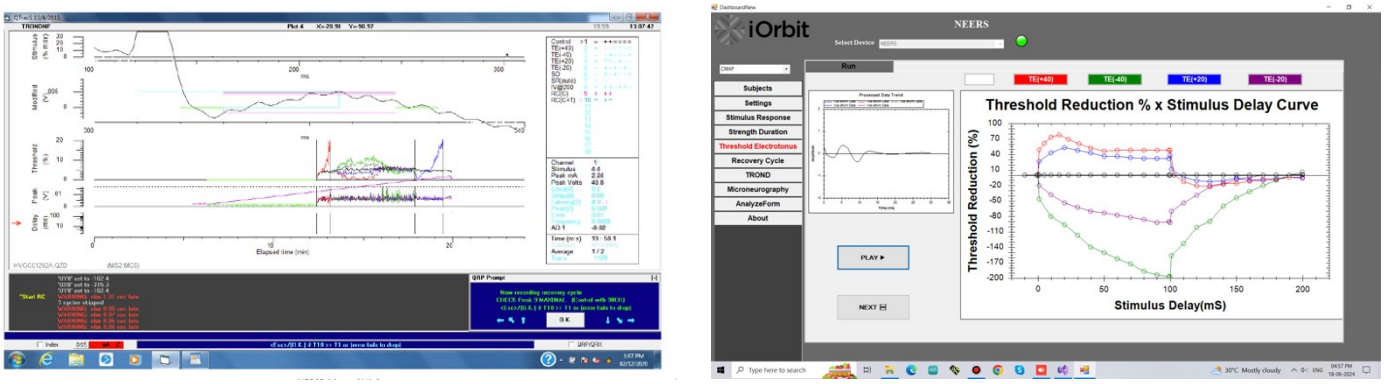
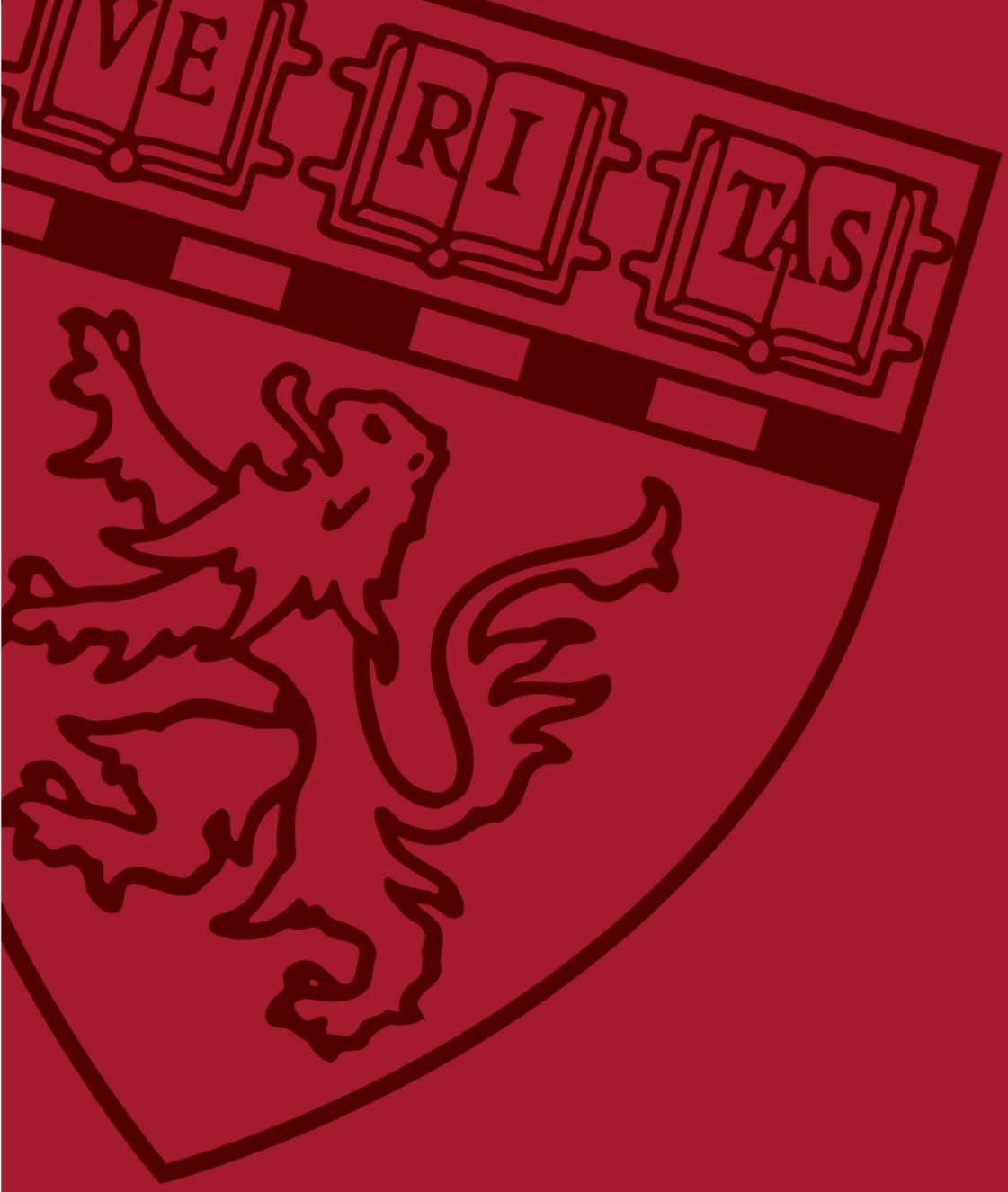


Figure 3. The left image shows the legacy Bostock system software; note the extreme complexity and non-intuitiveness of the graphic user interface. All the protocols appear on a single screen, making it exceptionally challenging to understand. **The right** image shows the new software with a recording from one testing protocol (threshold electrotonus) obtained on a healthy individual.



Appendices

Blavatnik Fund for Cryo-EM Publications

Research Articles

January–August 2024

1. Benning FMC, Jenni S, Garcia CY, Nguyen TH, Zhang X, Chao LH. 2024. Helical reconstruction of VP39 reveals principles for baculovirus nucleocapsid assembly. Nat Commun 15:250.

2. Coelho JPL, Yip MCJ, Oltion K, Taunton J, Shao S. 2024. The eRF1 degrader SRI-41315 acts as a molecular glue at the ribosomal decoding center. Nat Chem Biol 20:877-884.

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4. de Sautu M, Herrmann T, Scanavachi G, Jenni S, Harrison SC. 2024. The rotavirus VP5*/VP8* conformational transition permeabilizes membranes to Ca2. PLoS Pathog 20:e1011750.

5. Dong Y, Bonin JP, Devant P, Liang Z, Sever AIM, Mintseris J, Aramini JM, Du G, Gygi SP, Kagan JC, Kay LE, Wu H. 2024. Structural transitions enable interleukin-18 maturation and signaling. Immunity 57:1533-1548 e10.

6. Du G, Healy LB, David L, Walker C, El-Baba TJ, Lutomski CA, Goh B, Gu B, Pi X, Devant P, Fontana P, Dong Y, Ma X, Miao R, Balasubramanian A, Puthenveetil R, Banerjee A, Luo HR, Kagan JC, Oh SF, Robinson CV, Lieberman J, Wu H. 2024. ROS-dependent S-palmitoylation activates cleaved and intact gasdermin D. Nature 630:437-446.

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8. Freag MS, Mohammed MT, Kulkarni A, Emam HE, Maremanda KP, Elzoghby AO. 2024. Modulating tumoral exosomes and fibroblast phenotype using nanoliposomes augments cancer immunotherapy. Sci Adv 10:eadk3074.

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10. Li YD, Ma MW, Hassan MM, Hunkeler M, Teng M, Puvar K, Rutter JC, Lumpkin RJ, Sandoval B, Jin CY, Schmoker AM, Ficarro SB, Cheong H, Metivier RJ, Wang MY, Xu S, Byun WS, Groendyke BJ, You I, Sigua LH, Tavares I, Zou C, Tsai JM, Park PMC, Yoon H, Majewski FC, Sperling HT, Marto JA, Qi J, Nowak RP, Donovan

KA, Slabicki M, Gray NS, Fischer ES, Ebert BL. 2024. Template-assisted covalent modification underlies activity of covalent molecular glues. Nat Chem Biol doi:10.1038/s41589-024-01668-4.

11. Mercer JAM, DeCarlo SJ, Roy Burman SS, Sreekanth V, Nelson AT, Hunkeler M, Chen PJ, Donovan KA, Kokkonda P, Tiwari PK, Shoba VM, Deb A, Choudhary A, Fischer ES, Liu DR. 2024. Continuous evolution of compact protein degradation tags regulated by selective molecular glues. Science 383:eadk4422.

12. Pahil KS, Gilman MSA, Baidin V, Clairfeuille T, Mattei P, Bieniossek C, Dey F, Muri D, Baettig R, Lobritz M, Bradley K, Kruse AC, Kahne D. 2024. A new antibiotic traps lipopolysaccharide in its intermembrane transporter. Nature 625:572-577.

13. Park PMC, Park J, Brown J, Hunkeler M, Roy Burman SS, Donovan KA, Yoon H, Nowak RP, Slabicki M, Ebert BL, Fischer ES. 2024. Polymerization of ZBTB transcription factors regulates chromatin occupancy. Mol Cell 84:2511-2524 e8.

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15. Shankar S, Pan J, Yang P, Bian Y, Oroszlan G, Yu Z, Mukherjee P, Filman DJ, Hogle JM, Shekhar M, Coen DM, Abraham J. 2024. Viral DNA polymerase structures reveal mechanisms of antiviral drug resistance. Cell doi:10.1016/j.cell.2024.07.048.

16. Skiba MA, Sterling SM, Rawson S, Zhang S, Xu H, Jiang H, Nemeth GR, Gilman MSA, Hurley JD, Shen P, Staus DP, Kim J, McMahon C, Lehtinen MK, Rockman HA, Barth P, Wingler LM, Kruse AC. 2024. Antibodies expand the scope of angiotensin receptor pharmacology. Nat Chem Biol doi:10.1038/s41589-024-01620-6.

17. Velez B, Walsh RM, Jr., Rawson S, Razi A, Adams L, Perez EF, Jiao F, Blickling M, Rajakumar T, Fung D, Huang L, Hanna J. 2024. Mechanism of autocatalytic activation during proteasome assembly. Nat Struct Mol Biol 31:1167-1175.

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19. Zhao J, Chen AQ, Ryu J, Del Marmol J. 2024. Structural basis of odor sensing by insect heteromeric odorant receptors. Science 384:1460-1467.

Harvard Medical School
Blavatnik Endowment Fund

Market Value and Income

FY24: July 1, 2023–June 30, 2024

Beginning Market Value[1]	$	330,448,050
Total Distribution[2]		(11,988,079)
Appreciation		30,692,800
Ending Market Value[3]	**$**	**349,152,772**

Notes:

1. Market value as of July 1, 2024.
2. Total distribution per University policy. Determined by average principal units held over investment period June 1, 2022–May 31, 2023.
3. Market value as of June 30, 2024.

Harvard Medical School
Blavatnik Endowment Fund

Program Income and Expenditures

FY24: July 1, 2023–June 30, 2024

Beginning Balance[1]	$	4,641,609
Interest Income[2]		92,832
Treasurer's Distribution		11,988,079
Expenses[3]		(16,722,519)
Ending Balance[4]	**$**	–

Notes:

1. Beginning balance represents expendable cash at July 1, 2023, prior to the FY24 distribution.
2. Interest income is credited to the fund based on the July 1 beginning balance. The interest rate for FY24 was 2%.
3. Expenses include research activity as well as assessments for the essential infrastructure that allows Harvard Medical School programs and initiatives to succeed.
4. Ending balance represents cash available for expense in a future fiscal year.

Harvard Medical School
Blavatnik Fund for Cryo-EM

Financial Activity

FY24: July 1, 2023–June 30, 2024

Market Value on June 30, 2024	$	5,550,212
Operating Income		
Beginning Balance[1]	$	–
Interest Income[2]		–
Treasurer's Distribution[3]		86,606
Program Expenses[4]		–
Operating Expenses-administrative[5]		(24,252)
Ending Balance[6]	**$**	**62,354**

Notes:

1. Beginning balance represents expendable cash at July 1, 2023, prior to the FY24 distribution.
2. Interest income is credited to the fund based on the July 1, 2023 beginning balance. The interest rate for FY24 was 2%.
3. Total Distribution per University policy is determined by the average principal units held over the investment period June 1, 2022–May 31, 2023.
4. Program expenses are the direct costs for the Cryo-EM Center.
5. Administrative expenses are assessments for the essential infrastructure that allows Harvard Medical School programs and initiatives to succeed.
6. Ending balance represents cash available for expense in the following fiscal year.

Harvard Medical School Blavatnik Fund for Longevity and Human Health

Financial Activity

FY24: July 1, 2023–June 30, 2024

Market Value on June 30, 2024	$	5,132,873
Operating Income		
Beginning Balance[1]	$	122,563
Interest Income[2]		2,451
Treasurer's Distribution[3]		251,508
Program Expenses at Affiliate[4]		(301,109)
Operating Expenses-administrative[5]		(70,429)
Ending Balance[6]	**$**	**4,983**

Notes:

1. Beginning balance represents expendable cash at July 1, 2023, prior to the FY24 distribution.
2. Interest income is credited to the fund based on the July 1, 2023 beginning balance. The interest rate for FY24 was 2%.
3. Total distribution per University policy is determined by the average principal units held over the investment period June 1, 2022–May 31, 2023.
4. Program expenses are the direct costs of research and education program at the affiliate during FY24.
5. Administrative expenses are assessments for the essential infrastructure that allows Harvard Medical School programs and initiatives to succeed.
6. Ending balance represents cash available for expense in the following fiscal year.

Harvard Medical School Blavatnik Dean's Discretionary Fund

Financial Activity

FY24: July 1, 2023–June 30, 2024

Beginning Balance	$	39,552,066
Interest Income[1]		791,041
Operating Expenses[2]		(14,118,769)
Capital Projects Expenses[3]		(2,236,679)
Ending Balance	**$**	**23,987,660**

Expense Detail-operating

LifeLab	(741,686)
i-Hub	(1,067602)
Translator	(2,325,722)
Foundry	(873,576)
Center for Computational Biomedicine	(4,635,570)
AI Projects and Investments	(4,294,287)
Support Costs	(180,326)
$	**(14,118,769)**

Notes:

1. Interest income was credited to the funds based on the July 1, 2023 beginning balance. The interest rate for FY24 was 2%.
2. Operating expenses include programmatic expenditures for personnel, supplies, services, research operations, IT, and support for essential infrastructure.
3. Capital projects expenses include construction and financing, including released encumbrances, for Lifelab and Blavatnik Research Institute projects during the fiscal year.

Harvard Medical School
Blavatnik HealthTech Fellowship

Financial Activity

FY24: July 1, 2023–June 30, 2024

Operating Income		
Beginning Balance	$	5,065,559
Interest Income[1]		101,311
Program Expenses[2]		(366,035)
Ending Balance	**$**	**4,800,836**

Notes:

1. Interest income is credited to the fund based on the July 1, 2023 beginning balance. The interest rate for FY24 was 2%.
2. Program expenses include actual expenses for personnel, programming, and overhead.

Harvard Medical School Blavatnik Fund for Sensory Disorders Research

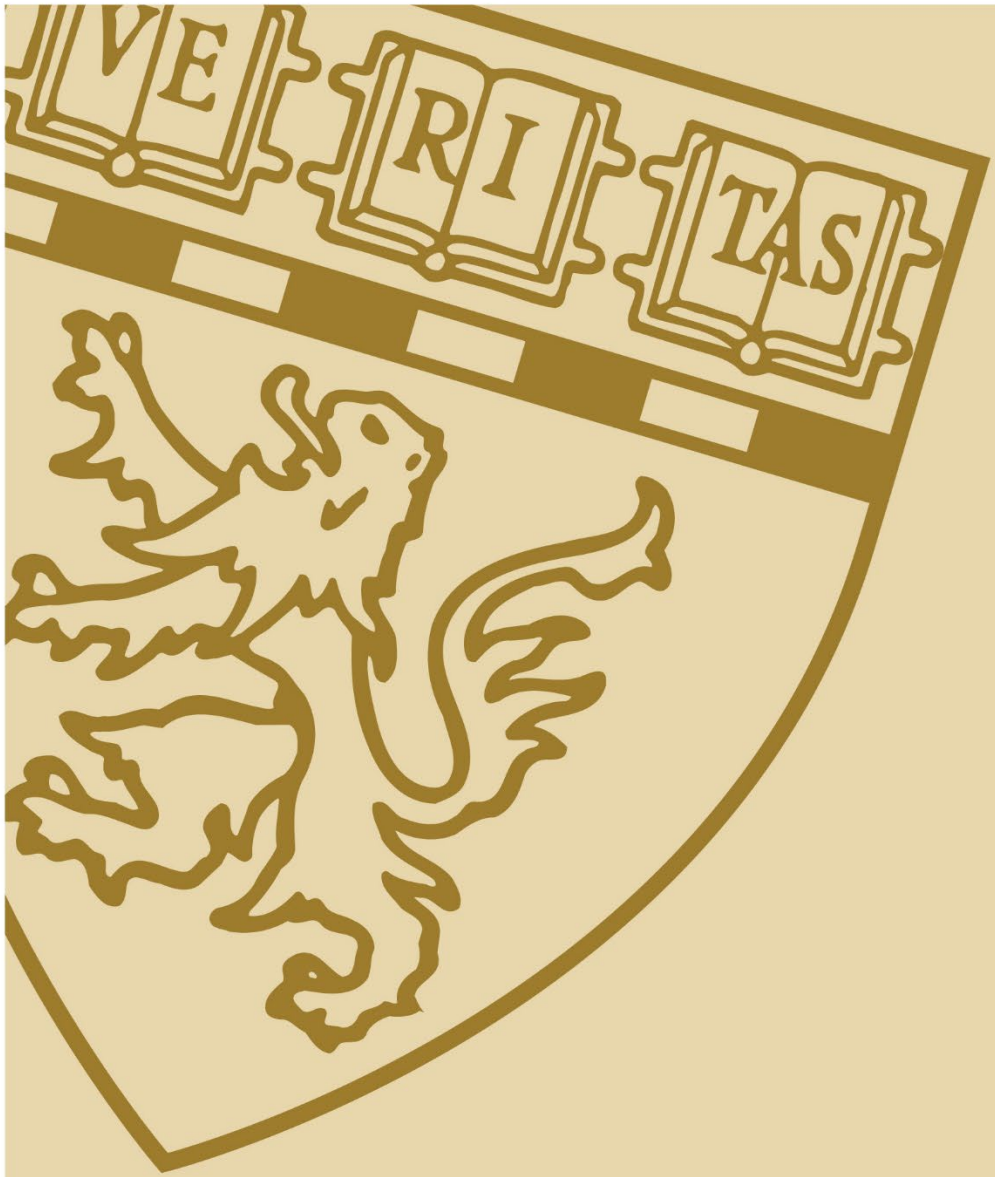
Financial Activity

FY24: July 1, 2023–June 30, 2024

Operating Income		
Beginning Balance	$	2,949,700
Interest Income[1]		58,994
Program Expenses[2]		(1,889,155)
Ending Balance	**$**	**1,119,539**

Notes:

1. Interest income is credited to the fund based on the July 1, 2023 beginning balance. The interest rate for FY24 was 2%.
2. Program expenses include actual expenses for personnel, supplies, services, research operations, and overhead.
3. $732,000 remains encumbered for on-going projects at the end of FY24.



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