Update: Council of Councils Working Group on Fostering Transformative Biomedical Research

Maryellen L. Giger, PhD, A.N. Pritzker Distinguished Service Professor of Radiology, Professor, Department of Radiology, Committee on Medical Physics, and The College, The University of Chicago

Huda Yahya Zoghbi, MD, Ralph D. Feigin Distinguished Service Professor, of Pediatrics, Molecular and Human Genetics, Neurology and Neuroscience, Baylor College of Medicine; Director Duncan Neurological Research Institute at Texas Children's Hospital, and Investigator Howard Hughes Medical Institute

Background

Core NIH Goal	Foster creative discoveries and innovative research strategies to protect and improve human health and wellbeing.
Transformative Research	Transformative research is essential for driving exceptionally high-impact breakthroughs that challenge established paradigms.
Catalyst Programs	Initiatives like Common Fund's *High-Risk, High-Reward Research Program* encourage bold, cross-disciplinary, outside-of-the-box thinking.
DPCPSI's Opportunity	Build on current successes and partner across NIH to advance novel approaches and human health outcomes.
Strategic Goal	Our goal is to accelerate biomedical innovation rapidly and efficiently.

Our Charge Is Multi-pronged

1. Highlight exemplars of transformational funding and key lessons from both within and outside NIH.
2. Review baseline assessment of current NIH efforts (e.g., Common Fund HRHR program).
3. Pinpoint obstacles in current funding mechanisms and explore alternative approaches.
4. Assess NIH approaches and recommend strategies to the Council of Councils.
5. Provide recommendations to DPCPSI and NIH leadership regarding portfolio balance, broad participation, disciplinary needs, and ecosystem alignment.

WG Members

Co-chairs	Maryellen L. Giger, PhD	The University of Chicago
	Ananda L. Roy, PhD	NIH / The Common Fund
Members	Ravi Basavappa, PhD	ARPA-H
	Polly Fordyce, PhD	Stanford University
	Erwin Gianchandani, PhD	National Science Foundation (NSF)
	Anders Sejr Hansen, PhD	MIT
	Preeya Khanna, PhD	UC Berkeley
	Adam Russell, PhD	USC/Information Sciences Institute
	Lauren Silvis, JD	Tempus, Inc. *(Council of Councils Member)*
	Huda Yahya Zoghbi, MD	Baylor College of Medicine / HHMI
***Ex Officio* Member**	Grace McCarthy, PhD	NIH / DPCPSI
Executive Secretary	Eva Tonsing-Carter, PhD	NIH / The Common Fund

What Is Transformative Science? Is It Different From Innovative Science?



Innovation is the "Spark": Focuses on the novelty of the idea, method, or approach—it introduces a new way of thinking or doing.

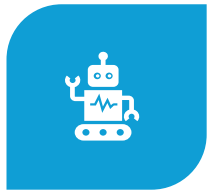


Transformation is the "Shift": Defined by the magnitude, breadth, and durability of downstream impact—it fundamentally reshapes or creates entire fields of study.



Methodology is Secondary to Impact: A project does not need to be methodologically novel to be transformative, as long as it disrupts the scientific paradigm (e.g., the Human Genome Project).

Examples of Transformative Biomedical Discoveries



Computational Biomedical & AI (e.g., AlphaFold, Medical Imaging CAD/AI, AI-enabled Diagnostics)



Single-Cell, Structural, and Imaging Technologies (e.g., Cryo-EM, fMRI)



Genomics, Gene Editing (e.g., Human Genome Project, CRISPR/Cas9)



Neuroscience Tools (e.g., Optogenetics, Neuropixel Probes)



Cell-Based & Regenerative Therapies (e.g., Organoids, iPSCs)



Therapeutic & Clinical Transformations (e.g., Immunotherapy, GLP-1 Agonists)

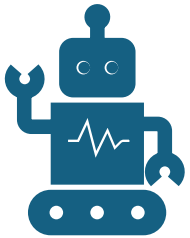
Supporting Transformative Science Starts with People



Transformative science starts with the workforce, including both the visionary and the team.



Funding graduate students, postdocs, and early-career researchers is a vital national investment that generates both novel research and the next generation of highly trained scientists.



Because transformative science increasingly spans the physical, chemical, computational, biological, and medical sciences, cultivating researchers fluent across these fields is essential.

Key Funding Themes from Exemplar Biomedical Transformative Discoveries

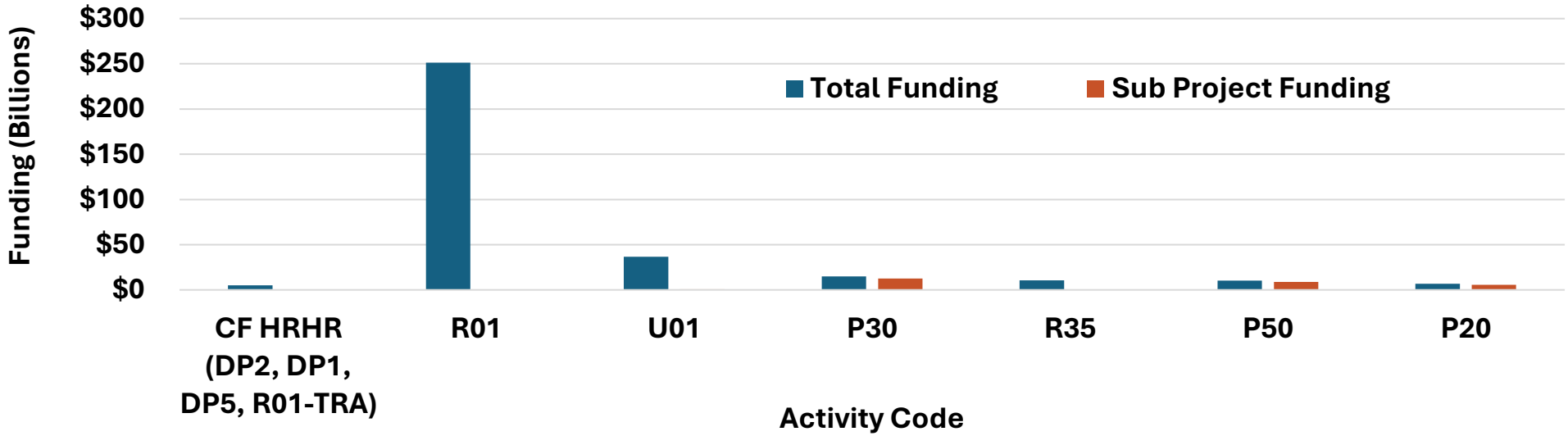
1. NIH is the Bedrock of Discovery - NIH funder/co-funder of 22 of the 26 discoveries analyzed. It supported the basic science for decades before commercial or clinical applications.
2. Philanthropy Funds High-Risk, High-Reward Science - The Howard Hughes Medical Institute (HHMI) was a critical funder in 8 of the 26 discoveries (31%). This is highly significant as HHMI funds a small, select group of investigators, not projects, giving them the freedom to pursue bold ideas.
3. Industry Translation and Commercialization - In nearly every case, from GLP-1 agonists (Novo Nordisk) to CAR-T therapy (Novartis) and TAVR (Edwards Lifesciences), industry partners built on early research and turned discoveries into approved products and novel tools by bringing manufacturing expertise.
4. A Global and Collaborative Effort – Several key discoveries originated and were funded abroad, including iPSCs (Japan), Cryo-EM (UK, Switzerland), Organoids (Netherlands), and TAVR (France).
5. Some Transformative Ideas Nearly Failed to Receive Funding - The initial CRISPR research by Francisco Mojica was repeatedly rejected for grant funding.

Summary of HRHR-related Program* Themes (FY19-FY25)

***49 ICO-reported NIH HRHR/Transformative Programs**

Theme Category	# of Programs	Example Programs
Transformative & Pioneering Research	19	NIAID New Innovators Awards, NIDDK Catalyst Awards, NIH HRHR Program, NINDS HEAL "New Innovator"
Technology & Tool Development	8	NCATS Quantum (Qu-BIT), ODSS Multimodal AI, NIMH Labs to Optimize Digital Health
Investigator & Program Support	8	NIGMS MIRA, NIDCR SOAR Award, NIMH SBIR/STTR, NCATS ASCETTS
Clinical & Translational Innovation	6	NHLBI Cure Sickle Cell Initiative, NIAID Clinical Trial Implementation, NCATS Tissue Chips
Foundational Datasets & Infrastructure	4	NIDA Adolescent Brain Cognitive Development (ABCD) Study, NINDS BRAIN Initiative (BICAN, CONNECTS)
Interdisciplinary & Team Science	4	NIDCR Collaborative Science, NIMH Conte Centers, NIEHS PRIME Program

Funding Allocation by Mechanism (FY2005–2025) – NIH RePORTER (https://reporter.nih.gov/)



Activity Code	Projects	Total Funding	Sub Projects	Sub Project Funding
CF HRHR (DP2, DP1, DP5, R01-TRA)	5,488	$5,150,756,520		
R01	595,319	$251,397,574,299	73	$18,393,740
U01	39,716	$36,760,890,192	1,004	$710,962,622
P30	13,404	$15,011,110,196	62,133	$12,536,238,770
R35	22,393	$10,531,335,739		
P50	6,346	$10,272,722,212	32,313	$8,723,442,050
P20	4,700	$6,653,652,697	21,387	$5,668,552,753

What Is The Current Landscape of Transformative Science Across NIH?

Strategic Area	Current Reality & Landscape Dynamics
Funding Skews Standard R01s	The vast majority of NIH funding supports R01s.
The "Underfunded" Gap	Other investigator-led transformative science (DP1, DP2, DP5, TRA) represents a very small share of the portfolio.
Alternative Funders	ARPA-H, DARPA, and Foundations provide alternative funding approaches. HHMI supports longer-term, flexible support.
Review Culture	Review culture may not favor transformative research ideas.
The Timeline Mismatch	Transformative outcomes typically require 10–20 years to mature, directly conflicting with the standard 3–5 year NIH award cycle.

Focus Area 1 — Realign the Review Culture



Realign reviewer training to include risk tolerance.



Redesign study sections to become adept at assessing interdisciplinary work as well as research from less-represented disciplines.



Reinforce reviewer training (i.e., HRHR study sections should not apply prior “R01-like” mindset, and R01 study sections should embrace HRHR grants)

Focus Area 2 — Funding Timescale, Approach, and Impact

1

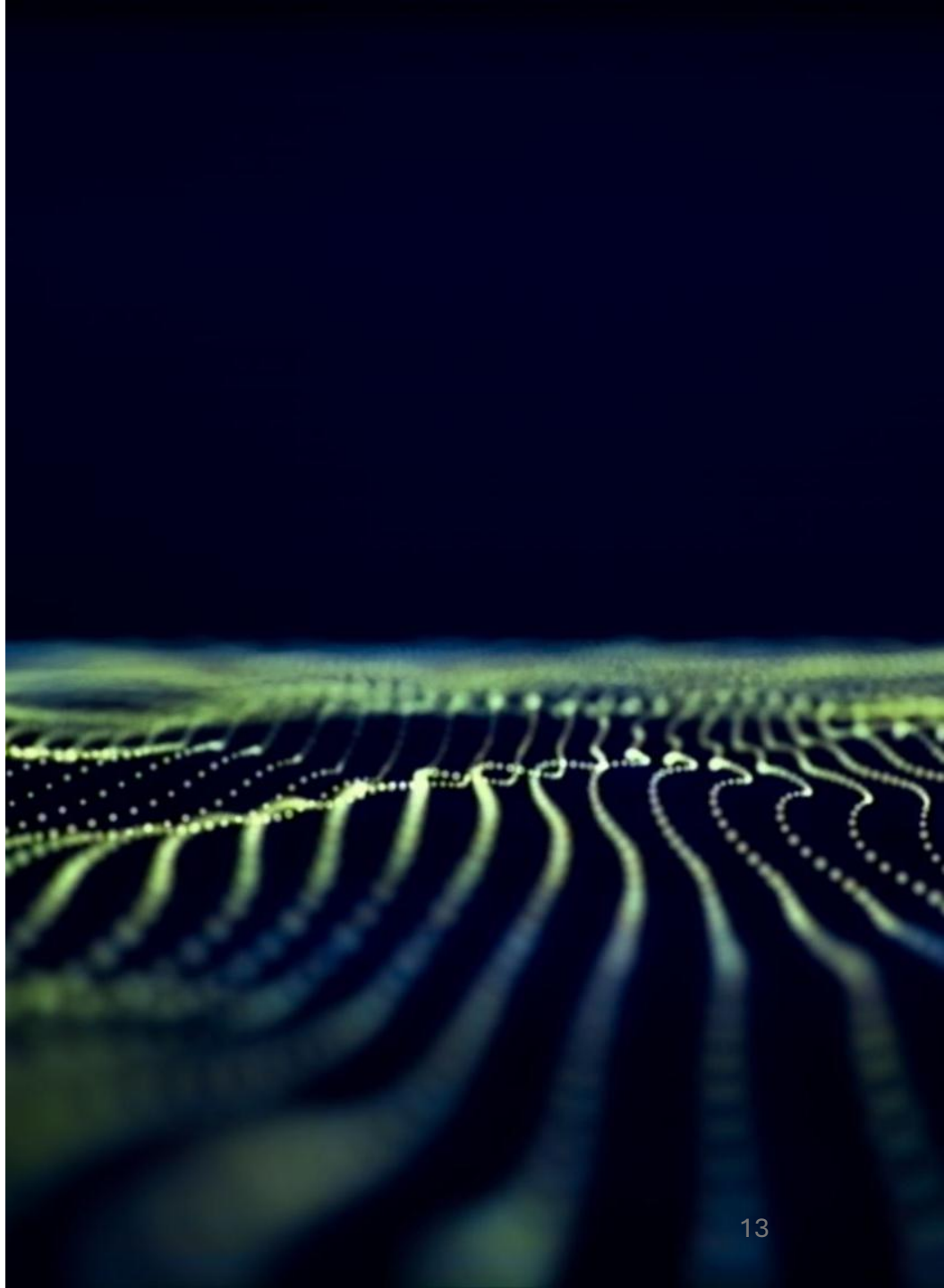
Recognize the limitations of 3-to-5-year grant cycles on work that historically requires a 10-to-20-year horizon to mature.

2

Assess whether funding could follow an investigator's vision rather than a prescriptive project plan;
confront concerns about institutional equity and elitism.

3

Assess milestones suited to long-horizon science, tracking adoption by the field, patents, company formation, and translation.



Focus Area 3 — Strategic Portfolio Improvements

- Create mechanisms to capture transformative ideas, which current review might miss; for example, an Office of the Director fund reserved for unconventional but scientifically plausible proposals.
- Set expectations for geographic distribution of transformative awards.
- Address less-represented disciplines.
- Support trainees, early-career researchers, and non-traditional scientific communities.
- Design study sections suited for interdisciplinary research.

The Path Forward

- Ongoing Assessment: The Working Group will continue to analyze current mechanisms, barriers, and alternative models for transformative research.
- Formulating Solutions: We are now shifting from data collection to strategy formulation.
- Final Deliverable: The Working Group will return to the Council of Councils with a comprehensive written report summarizing strategic recommendations for DPCPSI and NIH leadership’s consideration, aimed at strengthening the future of transformative biomedical research.

Discussion

Appendix

WG Members Continued

WG Role	Name	Affiliation	Research Experience and Focus Areas
Co-chairs	Maryellen L. Giger, PhD	The University of Chicago	Maryellen Giger is a medical physicist, has been a pioneer of AI methods and systems in medical imaging since the 1980's (CAD: computer-aided diagnosis). Her AI research in cancer, neuro-imaging, and other diseases for risk assessment, diagnosis, prognosis, and therapeutic response has yielded various translated components, including "virtual biopsies". She has developed and translated, through regulatory to the clinical arena, multi-modality breast cancer imaging AI. She is also contact PI on the NIBIB & ARPA-H-funded Medical Imaging and Data Resource Center (MIDRC).
	Ananda L. Roy, PhD	NIH / The Common Fund	Ananda L Roy is currently an Assistant Director of Transformative Science and Discovery at the NIH Common Fund/Office of Strategic Coordination within DPCPSI and the Office of the NIH Director. In this role, Ananda oversees a number of large programs focusing on paradigm shifting science, and novel tools and technology development. He is also involved in establishing the new Office of Research Validation and Application (ORIVA) within DPCPSI. Ananda maintains a research program studying transcriptional signatures during immune activation and inflammatory responses.

WG Members Continued

WG Role	Name	Affiliation	Research Experience and Focus Areas
Members	Ravi Basavappa, PhD	ARPA-H	Ravi Basavappa has a background in biophysics and structural biology. He previously oversaw the Common Fund High-Risk, High-Reward Research Program from 2010 – 2022 and is currently a Senior Advisor at ARPA-H.
	Polly Fordyce, PhD	Stanford University	Polly Fordyce is an Associate Professor of Bioengineering and Genetics and Institute Scholar of ChEM-H at Stanford, where her lab develops and applies new microfluidic platforms for quantitative and high-throughput biophysics and biochemistry. Her work has been recognized by an NSF CAREER Award, NIH New Innovator and Pioneer Awards, the Eli Lilly Award in Biological Chemistry, and a Schmidt Sciences Polymath Award. She is also a cofounder of Velocity Bio (a venture-backed startup), a Chan Zuckerberg Biohub Investigator, and a Fellow of the AIMBE and AAAS.

WG Members Continued

WG Role	Name	Affiliation	Research Experience and Focus Areas
Members	Erwin Gianchandani, PhD	National Science Foundation (NSF)	Erwin Gianchandani is the U.S. National Science Foundation's inaugural assistant director for Technology, Innovation and Partnerships, leading the newly established TIP Directorate. Gianchandani has led the development and launch of several new NSF initiatives, including NSF Engines, NSF X-Labs, NSF Tech Accelerators, Pathways to Enable Secure Open-Source Ecosystems, Translation to Practice, AI-Ready America, Smart & Connected Communities, Civic Innovation Challenge, Platforms for Advanced Wireless Research, and National Artificial Intelligence Research Institutes.
	Anders Sejr Hansen, PhD	MIT	Anders Sejr Hansen is an associate professor of biological engineering at MIT and his research focuses on understanding how 3D genome folding regulates gene expression. Towards this goal, his lab develops new technologies across genomics, computational biology, machine learning, and super-resolution and single-molecule live cell imaging methods.

WG Members Continued

WG Role	Name	Affiliation	Research Experience and Focus Areas
	Preeya Khanna, PhD	UC Berkeley	Preeya Khanna's research focuses on understanding how the brain integrates sensory and motor information to support skilled, dexterous movement, with an emphasis on corticothalamic circuits and sensorimotor neural dynamics. She combines systems neuroscience, neural engineering, computational modeling, and neurotechnology—including chronic neural recordings, wearable sensing, and closed-loop stimulation—to investigate motor control and develop technologies to restore movement following neurological injury and disease.
Members	Adam Russell, PhD	USC/Information Sciences Institute	Adam is a Distinguished Principal Scientist in the AI Division and is currently on IPA assignment to the National Science Foundation's Technology, Innovation and Partnerships (TIP) Directorate to lead their X-Labs initiative. Before joining TIP, Adam was the AI Division Director, where he was responsible for helping to set the Division's strategic direction and supporting the AI Division's faculty, staff, and students. Prior to coming to ISI, Adam was Chief Scientist at UMD's Applied Research Laboratory for Intelligence and Security (ARLIS). While at UMD, Adam served on an IPA to help stand up and launch the Advanced Research Projects Agency for Health (ARPA-H).

WG Members Continued

WG Role	Name	Affiliation	Research Experience and Focus Areas
Members	Lauren Silvis, JD	Tempus, Inc. *(Council of Councils Member)*	Lauren Silvis serves as Senior Vice President of External Affairs at Tempus, overseeing regulatory, public policy, government affairs and strategic communications. She has held a number of senior career public health roles, serving as a Senior Advisor at the Department of Health and Human Services, Chief of Staff of the Food and Drug Administration and Deputy Center Director for Policy in FDA's Center for Devices and Radiological Health. She currently serves as a member of the Council of Councils.
	Huda Yahya Zoghbi, MD	Baylor College of Medicine / HHMI	Huda Y. Zoghbi is a physician-scientist who uses human genetics and animal models to uncover the molecular basis of neurological disease — most notably the *MECP2* mutations causing Rett syndrome and the CAG-repeat expansion in *ATXN1* causing spinocerebellar ataxia type 1. Her lab has since shown how precise dosage of disease-driving proteins governs neuronal function, work that extends to regulators of tau and α-synuclein as therapeutic entry points for Alzheimer's and Parkinson's disease. She translates these findings toward therapy — her antisense oligonucleotides for *MECP2* duplication syndrome are now in clinical trials. She is the Founding Director of the interdisciplinary Jan and Dan Duncan Neurological Research Institute and an HHMI Investigator at Baylor College of Medicine.

WG Members Continued

WG Role	Name	Affiliation	Research Experience and Focus Areas
***Ex Officio* Member**	Grace McCarthy, PhD	NIH / DPCPSI	Grace McCarthy is a biomedical scientist and health science policy analyst with a Ph.D. in Cancer Biology, whose research has spanned pancreatic cancer therapeutics and tumor microenvironment biology, including work on nanocarrier drug delivery and RNA-binding protein targets. At NIH, her work bridges bench science and federal research strategy, translating scientific findings into policy and funding decisions for strategic initiatives across areas such as Down syndrome research and COVID-19.
Executive Secretary	Eva Tonsing-Carter, PhD	NIH / The Common Fund	Eva Tonsing-Carter is a pharmacologist with a background in cancer biology. At NIH's Common Fund, she currently serves as the Chief of Staff/Senior Advisor to the Acting Director. Prior to joining The Common Fund, she served as a Scientific Program Manager at the National Cancer Institute (NCI). In this role, she directed the Human Cancer Models Initiative (HCMI), a major international collaboration dedicated to developing up to 1,000 next-generation, patient-derived cancer models—such as organoids and conditionally reprogrammed cells.

Exemplar Transformative Biomedical Discoveries

Transformative/HRHR Discovery	Discovery Area	Funding Sources
Human Genome Project	Genomics, Gene Regulation, and Editing	NIH (NHGRI), DOE
GWAS & noncoding variation	Genomics, Gene Regulation, and Editing	NIH (NHGRI, NHLBI, NCI)
CRISPR/Cas9	Genomics, Gene Regulation, and Editing	NIH (NIGMS, NHGRI), NSF, HHMI, Wellcome Trust
Prime editing	Genomics, Gene Regulation, and Editing	NIH (NIGMS, NHGRI), HHMI
RNAi	Genomics, Gene Regulation, and Editing	NIH (NIGMS), HHMI
3D chromatin organization	Genomics, Gene Regulation, and Editing	NIH (NIGMS, NHGRI), NSF
Single-cell genomics & imaging	Single-Cell, Structural, and Imaging Technologies	NIH (NIGMS, NHGRI, BRAIN Initiative)
Cryo-EM	Single-Cell, Structural, and Imaging Technologies	NIH (NIGMS), DOE, HHMI
FACS	Single-Cell, Structural, and Imaging Technologies	NIH, NSF
CT	Single-Cell, Structural, and Imaging Technologies	Industry
MRI	Single-Cell, Structural, and Imaging Technologies	NIH (NIGMS, NHLBI, NIBIB, NINDS)
fMRI	Single-Cell, Structural, and Imaging Technologies	NIH (NIMH, NINDS, NIBIB, BRAIN Initiative)
AlphaFold / protein structure prediction	Computational Biology, AI, and Data Infrastructure	DeepMind (industry), public databases funded by NIH/EMBL
Medical Imaging CAD; AI-enabled diagnostics	Computational Biology, AI, and Data Infrastructure	NIH (NCI, NIBIB), ARPA-H (emerging), DoD
All of Us Research Program	Computational Biology, AI, and Data Infrastructure	NIH (OD, NHGRI)
BRAIN Initiative	Computational Biology, AI, and Data Infrastructure	NIH (multi-IC), DARPA
Optogenetics	Neuroscience Tools and Systems Biology	NIH (NIMH, NINDS), NSF, HHMI
Neuropixel probes	Neuroscience Tools and Systems Biology	NIH (BRAIN Initiative), Wellcome Trust, industry partnerships
iPSCs	Cell-Based, Regenerative, and Genetic Therapies	Japanese Government Funding (JSPS, MEXT, PRESTO/JST), HHMI, private foundations
Organoids	Cell-Based, Regenerative, and Genetic Therapies	European Public Funding (ERC, NOW, FWF), HHMI, Wellcome Trust
CAR-T therapy	Cell-Based, Regenerative, and Genetic Therapies	NIH (NCI), NCI intramural, industry
Antisense oligos / splicing therapies	Cell-Based, Regenerative, and Genetic Therapies	NIH, industry
Immunotherapy	Therapeutic and Clinical Transformations	NIH (NCI)
Oncogene discovery	Therapeutic and Clinical Transformations	NIH (NCI, NIGMS), NSF, ACS, HHMI
GLP-1 agonists	Therapeutic and Clinical Transformations	NIH (NIDDK), industry
Transcatheter aortic valve replacement (TAVR)	Therapeutic and Clinical Transformations	NIH, DoD, industry