

2026 Finalist Abstracts

proposal name:

Modeling neuroimmune sensing of the gut microbiome

proposal team members:

Kathleen Abadie, Abhe Rajagopal, Andrew Stirn, Maximilian Heeg, Anna Globig, Grace Huynh

accelerators:

immunology, OCTO

abstract:

Healthy immunity in the intestinal tract balances appropriate activation against foreign pathogens with tolerance to dietary and commensal microbe antigens. Changes in the gut environment, including dietary alterations, changes to species and numbers of microbiota, and pathogen infection, can remodel immune organization, leading to transient or lasting effects on gut health. Chronic inflammatory conditions such as inflammatory bowel disease (IBD) represent a lasting effect of immune reorganization with known association with the microbiome. Neurons sense changes to the gut environment and signal to immune and non-immune cell populations, thus forming a critical, but often obscured, link between changes to the gut environment and resultant immune reorganization. Despite recent appreciation for the interplay between gut immune cells, microbiota, and neurons, we lack a clear understanding of their causal interactions and, importantly, how to manipulate these interactions therapeutically to correct dysfunctional gut immunity. To address this gap and reveal therapeutically actionable mechanisms by which immune cells, microbiota, and neurons interact in the healthy or inflamed gut, we propose an end-to-end experimental and computational framework for (1) multi-scale deep learning modeling of immune organization in different microbiome and nerve activation contexts, (2) in silico mechanistic interpretation to identify key cell states and receptors driving healthy immune organization, and (3) prioritized experimental testing of candidate perturbations through pooled genetic editing with in vivo spatial readouts.

impact:

Just as characterization of the immune system's anti-cancer role in recent decades has revolutionized cancer treatment with immunotherapy, understanding how the nervous and immune systems interact in health and disease could open up 'neuro-immunotherapy' as a powerful new therapeutic approach. Towards this understanding, we combine precise experimental control of nerve activation and gut environment with a novel multi-scale, multi-modal spatial ML modeling approach and scaled in vivo testing of ML predictions to elucidate how neuro-immune crosstalk shapes gut

organization. Our approach aims to identify therapeutic avenues to steer the inflamed gut to a healthy state in diseases such as IBD.

proposal name:

Engineering tissue-specific immune sentinels with synthetic enhancers

proposal team members:

Alan DenAdel, John Ray, Kasia Kedzierska

accelerators:

immunology, OCTO

abstract:

This project will develop synthetic genetic regulatory elements, called enhancers that enable precise, programmable gene activation in T cells. These enhancers will be specific to a tissue of interest (the gut) and particular inflammatory environments. To decode the genetic regulation of T cells, we will integrate massively parallel reporter assays (MPRAs) with sequence design AI models to decode and design regulatory logic that distinguishes between T cell states and T cells that are localized to specific tissues.

impact:

To be optimally effective and avoid off-target effects, gene therapies should be specific to the relevant cell populations (for example, specific to T cells actively causing autoimmunity). Synthetic enhancers, a type of regulatory element, enable cell-type specific expression of a gene therapy payload. Successful design of these enhancers will enable the engineering of immune sentinels that sense specific environments before activating. These sentinels can be used for precision immune responses and therapeutic delivery and would be transformative for engineering the immune system to behave appropriately in health (preventing autoimmunity, like irritable bowel disease) and in disease (activating the immune system to fight cancer).

proposal name:

EMPrint: Uncovering Cell-Type Signatures within the Nucleus

proposal team members:

Leila Elabbady, Chi Zhang, Kim Gruver, Marc Takeno, Jacob Quon, Geoffrey Schau, Grace Huynh, Shenqin Yao, Michael Kunst, Nuno de Costa

accelerators:

brain science, OCTO

abstract:

The Allen Institute has produced foundational datasets characterizing brain cell-types by morphology, electrical activity, transcriptomics, and connectivity—yet translating across these modalities remains a fundamental challenge. This is particularly evident in connectomics: MICrONS, the largest mammalian connectome to date, contains more than 100,000 cells with connections and organelles resolved at nanometer precision - yet molecular identities remain out of reach. EMPrint is built on the hypothesis that the answer is already there, encoded in the structure of the nucleus—a molecular fingerprint legible at EM resolution. Using MICrONS, we have already demonstrated that nuclear shape alone can predict broad cell-types across a cubic millimeter of cortex. We propose to build upon this through a joint Connectomics-Spatial Transcriptomics effort. In the first stage: we will mine existing MICrONS and MERFISH datasets to train computational models on nuclear ultrastructure, while simultaneously using recombinase enhancer labeling to collect cell-type-specific EM datasets that directly map nuclear features to known transcriptomic identities. Together these establish whether the signal exists and provide biological ground truth. This stage functions as a feasibility gate – if the signal is sufficient, we plan to collect spatial transcriptomic and connectomic data from adjacent samples. By merging the two modalities into a unified experimental framework we would expand cross-model public resources and validate our EMPrint model. A validated EMPrint model would allow researchers worldwide to retrospectively assign molecular or connectivity identities to cells in existing EM dataset and spatial transcriptomic datasets—transforming both into cross modality annotated resources for the entire field.

impact:

This project bridges nuclear structure, connectivity and transcriptomic identify – embedding our understanding of cell types within the architecture of brain circuits. The result is a more holistic view of cell types and their microcircuits than either modality provides on its own. The clinical implications are equally significant: many neurodegenerative diseases afflict specific cell-types, yet current treatments target the brain globally. Linking connectivity and transcriptomic identity would illuminate the precise circuits disrupted in disease, pointing toward interventions and therapeutics that are targeted, more effective and less broadly damaging.

proposal name:

Rescuing the Cellular Trajectory of Huntington's Disease

proposal team members:

Mariano Gabitto, Jeff Carroll, Jane Lai, Maddie Etheridge, Alissa Cullen

accelerators:

brain health

abstract:

The goal of the computational tools developed in BHA is to accurately track disease progression in dysfunctional brain cells in neurodegenerative diseases. Ultimately, we aspire to predict a series of state changes along disease progression that can be blocked or slowed with therapeutic interventions. To date, given the lack of effective treatments for the diseases we study, it's been impossible to capture the states of rescued cells, and so to understand how well these models respond to slowed progression. Here, we propose to apply one such tool, scVIP, to a cohort of Huntington's Disease (HD) model mice being treated with a gene therapy intervention that we predict will completely rescue them from HD pathology. Completing this work will enable us to benchmark scVIP-derived disease trajectories against a top therapeutic candidate with immediate clinical relevance in Huntington's Disease.

impact:

Huntington's Disease (HD) is fatal and has no disease-modifying therapy. We pair a benchmark rescue reagent – an allele-selective zinc-finger transcriptional repressor that lowers mutant Huntingtin (HTT) – with a generative model that places each animal on a learned disease-progression trajectory. This gives a first quantitative test of whether treatment returns brain cells toward a healthy state, and a transferable framework for measuring cellular rescue across neurodegenerative diseases.

proposal name:

Making the Invisible Visible: Decoding the Second Brain

proposal team members:

Juhee Son, Adam Savage

accelerators:

immunology

abstract:

The gut contains the largest neural network outside the brain, and its dysfunction often precedes central nervous system neurodegeneration by years. Despite growing evidence that neurotransmitters in the gut shape neuroimmune communication and tissue homeostasis, we still do not know where these signals are distributed within tissue or how they change during disease. We propose to directly map neurochemical environments within intact gut tissue using MALDI-MSI in mouse disease models and human endoscopic biopsies. This work will generate the first spatial maps of gut neurochemistry and reveal the neurochemical environments that shape cellular behavior in health and disease.

impact:

Current studies of the gut-brain axis have generated important insights and established the gut as a major neuroimmune organ, largely through experimental perturbation in animal models. However, without the ability to directly observe neurochemical environments, it remains difficult to determine whether the same biology is present in human disease. Our platform enables direct observation of neurochemical remodeling during disease in both mouse models and human biopsies. Because the gut can be routinely sampled and directly treated, these discoveries may support earlier detection of disease-associated neurochemical changes, particularly during prodromal and body-first neurodegeneration, and inform development of therapies that target neurochemical dysfunction.

proposal name:

Tissue origami: modulating tissue geometry using cellular zipcodes

proposal team members:

Duncan Chadly, Jacob McCarley, Gaea Turman, Sassan Ostvar

accelerators:

cell science

abstract:

Precise control of tissue geometry is a hallmark of multicellular life. Individual cells control their shape by locally creating tension at the membrane. Coordinated application of tension across multiple cells drives tissue deformation and allows bulk changes in shape. Recently, researchers have developed optogenetic tools that allow localization of actomyosin effectors to create similar localized shape changes through targeted application of focused light. Alternatively, many efforts in bioengineering rely on bioprinting and tissue scaffolding methods to control tissue shape by setting initial conditions. While powerful, these tools require external input and cannot be integrated with cell autonomous genetic programs. In this work, we will develop a library of protein minibinders that target distinct subcellular regions in human induced pluripotent stem cells (hiPSCs), including apical, basal, and lateral surfaces among others. We will then couple these biological zipcodes to proteins that increase or reduce tension in the cell membrane through actomyosin coupling and screen the effects of localized expression in a three-dimensional spherical-shell hiPSC-based model of multicellularity. Finally, we will use physical modeling and machine learning to create a predictive framework for rational design of genetic circuits that produce on-demand multicellular structures. These tools will open new research avenues for CellScapes and be immediately of use to the broader synthetic biology and tissue engineering communities.

impact:

Building rational control of tissue geometries would improve our understanding of natural biological systems and could address a variety of clinical problems. Throughout development, tissues undergo dramatic cellular rearrangements to create diverse 3D structures across organisms. Disease frequently manifests as malformations in tissue structure, including polycystic kidney disease (polarity inversion) and neural tube defects (failed apical constriction). Understanding how to direct tissue shape could ultimately lead to novel treatments for this class of disease. The tools developed here will enable new disease modeling capabilities and establish the foundation for programmable tissue morphogenesis.

proposal name:

Turning metadata from burden into scientific asset

proposal team members:

Antoine Borensztein

accelerators:

cell science

abstract:

Modern microscopy generates enormous quantities of image data, yet the metadata needed to interpret those images are often incomplete, fragmented, or absent. Cell line, treatment conditions, sample preparation, and imaging parameters are scattered across notebooks, spreadsheets, instrument software, and researchers' memories. Awareness of this gap has grown, but most laboratories lack the infrastructure to close it, and traditional solutions such as LIMS demand a documentation effort that limits adoption. We developed Orchestra Planner and Orchestra Link, two applications that turn organized metadata into a natural by-product of everyday microscopy workflows. Rather than asking researchers to manage metadata, Orchestra helps them solve problems they already care about: planning experiments and coordinating laboratory activities. Orchestra Planner captures structured biological metadata during experiment planning, while Orchestra Link extracts instrumental metadata from image files and merges both into a complete record of each image and its experimental context. Such systematic capture is critical not only for reproducibility and data sharing, but also for computational and AI-driven analyses in which insight depends on accurate context of each image. We now propose to transform Orchestra from an internal solution into a broadly adopted community resource by: (1) releasing and disseminating it to the microscopy community, (2) expanding Orchestra Link to support additional file formats, and (3) enabling researchers to connect existing AI assistants (such as ChatGPT, or Asta) to their Orchestra data, turning accumulated experiments and metadata into a searchable laboratory memory. Together, these efforts offer a scalable pathway for metadata adoption across the microscopy community.

impact:

Although FAIR data principles (Findable, Accessible, Interoperable, Reusable) are widely recognized within the microscopy field, adoption of metadata-focused solutions remains limited because available tools are cumbersome and too expensive for most labs. This limited adoption hinders modern quantitative analysis across the microscopy field which depends on contextual information for each image in the form of metadata. Orchestra removes this adoption barrier directly by providing a user-friendly and open-source infrastructure for generating metadata. Orchestra could improve metadata capture at scale, enabling more reproducible science, easier data sharing, and

prepare the microscopy field for a future of AI-driven laboratory knowledge systems.

proposal name:

ENTIRE-FLEX: Decoding Immunity for Global Health

proposal team members:

Zach Thomson, Matt Hart, Peter Skene, Neel Kaul

accelerators:

immunology

abstract:

A defining feature of the human adaptive immune response is the T-cell receptor (TCR) repertoire, which exhibits an exponential population-level diversity estimated at up to 10^{20} unique formulations. This vast structural landscape allows the immune system to anticipate and neutralize entirely novel pathogens. Because T cells recognize target antigens via structural peptide-MHC (pMHC) interactions, mapping the predictive rules of TCR-pMHC binding represents a foundational goal in modern immunology. Traditional assays, however, lack the throughput required to capture this complexity, resulting in reference datasets that are heavily over-indexed on common viral antigens and low-diversity Caucasian cohorts. To resolve this limitation, we introduce an end-to-end multiomic pipeline, ENTIRE-FLEX, that strategically integrates next-gen, high-throughput cellular screening assays with predictive machine learning. By substituting prohibitively expensive, low-throughput physical reagents—such as commercial dextramers—with a scalable molecular screening architecture, this pipeline eliminates historical cost and throughput constraints. The platform enables parallel processing of thousands of unique peptides against diverse ethnic backgrounds, supplying the dense, high-dimensional training data required for predictive computational modeling.

impact:

An adult human maintains up to 100 million unique T-cell clonotypes, yet current gold-standard screenings capture fewer than 20,000 cells per assay. Attempting to scale these low-throughput, reagent-heavy methods becomes cost-prohibitive, leaving the vast immunological search space largely unmapped. Our pipeline addresses this bottleneck with a scalable architecture that drastically lowers costs while maximizing population-level breadth. By capturing dense, multi-ethnic datasets, this platform feeds predictive machine learning models that decode adaptive immunity globally. Ultimately, this framework accelerates the rational design of universally effective vaccines, high-precision T-cell therapeutics, and comprehensive maps of autoimmune cross-reactivity.

proposal name:

SciDEX - Allen Institute Discovery Exchange

proposal team members:

Kris Ganjam, Kyle Travaglini, Claire Gustafson

accelerators:

OCTO, brain health, immunology

abstract:

SciDEX is mission-steered shared intelligence infrastructure for Allen Institute teams. It links institute and public evidence into living world models, lets scientist personas and specialist agents price value of knowledge against cost, and continuously reprioritizes experiments, analyses, and collaborator paths. The one-year, OCTO-housed pilot funds a SWE II to productionize the platform for Allen Institute workflows: integrate SEA-AD and Brain Knowledge Platform assets, support OSI landscaping/de-risking/IP workflows, and route ~20 ranked decisions into collaborator follow-up through the most informative available modality for each claim. Allen Institute already has the data, collaborators, and a working prototype. This award is the wedge that turns those pieces into a cross-institute achievement engine first, while keeping open a broader external platform horizon after institute-wide value is proven.

impact:

Within Allen Institute, the bottleneck is no longer idea generation; it is deciding what to do next with scarce wet-lab time, compute, and expert attention. SciDEX gives Allen Institute an auditable, evidence-weighted way to prioritize across many artifact types and share that capability as infrastructure. It benefits patients and the scientific community by reducing wasted effort now, while keeping open a broader external path after internal value is proven.

proposal name:

ThymOS: A reusable agentic AI platform for generation of human cell types from hiPSCs

proposal team members:

Gokhan Dalgin, Geoffrey Schau, Claire Gustafson

accelerators:

cell science, immunology, OCTO

abstract:

ThymOS is a cell type agnostic agentic AI platform for understanding, directing, and learning the process of cellular differentiation. It designs, predicts, and iteratively refines protocols by synthesizing primary literature (papers, patents, clinical trials, protocols, etc.), drafting versioned protocols with explicit quantitative metrics and checkpoint predictions. The platform's value is not tied to any single lineage: any directed differentiation program can plug in by supplying its target cell type, assay readouts, and decision criteria, and each iteration compounds a shared corpus of literature, design decisions, and quantitative benchmarks reusable across programs. To demonstrate the platform end-to-end on a high value biological problem, we anchor it to iPSC to T cell differentiation, starting at the rate limiting first step: hematopoietic stem and progenitor cell (HSPC) specification. ThymOS could turn human induced pluripotent stem cell (hiPSC) differentiation from a slow, poorly documented craft into a closed-loop, data driven, reusable engineering discipline.

impact:

Directed differentiation is the slowest, most opaque, and least cross-benchmarked step in every hiPSC-based therapy program. Protocols today are human curated, take months to design, vary between labs, and rarely log the reasoning behind their parameter choices, making each new cell type a near independent invention rather than a shared engineering problem. By compressing protocol design into a closed loop of literature synthesis, falsifiable prediction, and bench driven revision, ThymOS turns directed differentiation from a craft into a reusable design and engineering discipline. The longer-term translational impact is real but downstream: allogeneic iPSC-derived cell therapies could deliver curative treatments at a fraction of the cost and cycle time of autologous CAR-T, reaching autoimmune and oncology indications that patient specific platforms cannot scale to.

proposal name:

Capturing memories of immune cells

proposal team members:

Maximilian Heeg, Anna Globig, Yoav Ben-Simon, Zack Lewis, Emily Jacobs

accelerators:

immunology

abstract:

We propose to adapt the Allen Institute's enhancer-AAV paradigm to achieve selective genetic access to functional CD8 T cell states. Using chromatin accessibility data (internal generated scATAC, ImmGen, and published datasets), we will identify short cis-regulatory elements that drive state-biased expression in Terminal Effector (TE), Memory Precursor (MP), Central Memory (TCM), or Effector Memory (TEM) cells. We will clone the top 20 candidates into lentiviral barcoded reporter vectors, perform a pooled screen in mouse CD8 T cells, and validate the best hits by single-cell RNA-seq identity assignment. The product is a ranked enhancer toolkit of 3–5 payload-ready vectors with documented state specificity, coverage, and functional neutrality. Work will be carried out in collaboration with Yoav Ben-Simon at AIBS, leveraging AIBS single-cell and vector infrastructure.

impact:

No tools currently exist for selective genetic access to individual CD8 T cell differentiation states. Such tools would enable precise dissection of state-specific biology in cancer immunotherapy and chronic infection, support ex vivo T cell engineering with state-restricted payloads, and establish a cross-disciplinary platform extending the Allen enhancer paradigm from stable neuronal identities to dynamic immune-cell states. This cross-accelerator effort directly advances Allen's strategic goal of translating foundational research into tools that impact human health.

proposal name:

Continuous-Scan Immersion Interface: Enabling High NA TDI Imaging

proposal team members:

Alex Cahoon, Adam Glaser, Mike Taormina

accelerators:

brain science, neural dynamics, admin

abstract:

High-numerical-aperture (high-NA) microscopy resolves fine cellular and tissue detail but requires a liquid immersion medium bridging objective and specimen. Imaging a large specimen – a whole brain section for MERFISH or in situ sequencing – currently means stop-and-go tiling: the stage halts at every field, and the accumulated dead time bottlenecks throughput. The route past this bottleneck is continuous scanning with time-delay-integration (TDI) line sensors, which needs two advances: a custom large-field high-NA immersion objective, and a way to maintain immersion during scanning. This proposal delivers the second advance: an oil-compatible immersion interface using active meniscus control to hold a stable, bubble-free immersion bridge as the objective sweeps the specimen. A perimeter seal shapes the meniscus; an integrated system recovers fluid behind it. Because nothing is added to the beam path, the objective stays unmodified – identical to conventional immersion, diffraction-limited, no NA penalty. The architecture adapts the immersion seal proven in semiconductor lithography, which operates $\sim 25\text{--}50\times$ faster than we require. We will demonstrate it on a standard high-NA objective at a conservative $1\text{--}2\text{ cm/s}$. We target upright microscopes, whose geometry suits large imaging chambers and large-displacement motion platforms. A custom chamber with an oversized coverslip gives the fluid-management hardware room to travel alongside the objective, enabling single-session, high-NA scanning of large tissue volumes. Being objective-agnostic, the same proof de-risks the custom-objective effort that unlocks full throughput.

impact:

By holding a high-resolution optical link intact during continuous scanning, this interface images large, intact tissue sections in a single uninterrupted pass. A half-coronal human brain section – roughly $150 \times 100\text{ mm}$, today impossible to capture in one piece at high-NA resolution – could be scanned several-fold to roughly an order of magnitude faster than move-and-settle tiling, the larger gains for thin, few-plane spatial-omics imaging. Imaging the section whole eliminates the dissection, stitching, and distortion that fragment current datasets. This accelerates large-volume neuroscience, cell biology, and immunology across the Allen Institute and strengthens the foundation for high-resolution, AI-assisted tissue analysis.

proposal name:

Massively multiplexed metabolic engineering towards augmented cellular therapies

proposal team members:

Julie Trolle, Sudarshan Pinglay, Sylvain Simon

accelerators:

seahub/seabridge, AI Bio Design

abstract:

Engineered T cell therapies have transformed the treatment of blood cancers, providing a curative option for patients with otherwise limited therapeutic options. However, these treatments remain ineffective in solid tumors, where hostile conditions experienced within the tumor microenvironment (TME) impair T cell persistence and tumor heterogeneity facilitates antigen escape. Achieving durable anti-tumor activity will require T cells that can withstand environmental stressors (nutrient deprivation, hypoxia, acidosis, buildup of toxic metabolic waste products) while maintaining robust tumor-targeting capacity. Engineering T cells with such capacities will require the introduction of synthetic programs, powered by the precise coordination of multiple genetic components. To address this need, we propose the integration of two recent advances, namely (1) Shotgun Genetic Engineering (SGE), a pooled, multiplexed screen enabling the parallelized sampling of millions of multi-gene constructs in a single experiment, and (2) the chimeric TCR (ChTCR) platform, which overcomes antigen escape through highly sensitive, multi-antigen targeting. SGE will initially be applied towards the engineering of essential amino acid biosynthetic pathways in ChTCR cells, enabling them to outcompete tumor cells in conditions with limited amino acid availability. This work builds upon preliminary results demonstrating that Jurkat T cells can be engineered to grow in the absence of valine. We will further extend this approach to rewire hypoxia-response programs in ChTCR cells with the goal of sustaining T cell activity in low-oxygen settings. Together these complementary efforts will yield metabolically resilient immune cells, establishing a foundation for next-generation immunotherapies.

impact:

This work is expected to yield significant clinical and industrial impact. Successful implementation of engineered resilience in T cells would unlock the immense progress that has been made towards optimizing immune cell tumor-targeting capacity. This will have direct implications for patient populations while establishing engineering principles that can be translated to (a) other cell therapy platforms, and (b) to address desired resilience phenotypes beyond nutrient starvation and hypoxia. Beyond cellular therapy, the ability to engineer resilience phenotypes would also enable increasingly robust mammalian cell-based manufacturing pipelines for antibodies and viral vectors. Increased productivity of these bioprocesses would enable broader

access to these treatment modalities, which constitute fast-growing, cost-prohibitive segments of the medication market.

proposal name:

BRIDGE: Brain-wide, Interpretable, Dynamical, Generative Engine

proposal team members:

Ulises Pereira, Mathew Summers, Andrew Shelton

accelerators:

neural dynamics

abstract:

Classical mechanics gave us $F=ma$. Three letters that explain why apples fall, planets orbit, and bridges stand. Neuroscience has nothing like it. We have built world-leading atlases of connectivity, genetic diversity, and brain-wide activity, but no equations of motion. The race to build foundation models for neuroscience has two failure modes. LLM-like models that predict neural activity without explaining it, and biophysical models so detailed they do not generalize. Neither asks the right question. Which few variables govern the system, and what can we throw away? We build interpretable foundation models that are mechanistic by construction. Grounded in the physics of complex systems, we use AI to recover the collective variables driving brain dynamics, mapping them onto connectivity, cell types, and behavior. The model tells you what matters and what it coarse-grained away. We have shown this on two large-scale recordings in behaving mice, where the model generalizes to held-out perturbations, predicts behavior under unseen conditions, and yields interpretable dynamics. We propose a proof of concept that integrates cell-type-specific calcium imaging, brain-wide anatomical connectivity, and large-scale electrophysiology into a single mechanistic model. The pilot seeds a larger Institute capability. No accelerator owns cross-modal mechanistic modeling today. Once demonstrated, it becomes the modeling layer that Neural dynamics, Brain Science, and Brain Health build on, anchoring an Institute-wide effort to extract the principles of brain circuits. Someone will write $F=ma$ for brain circuits. We have the data and modeling approach. It should be us.

impact:

Psychiatric and neurological disorders are increasingly understood as circuit disorders: deficits in connectivity, or in particular cell types, that cascade into brain-wide dysfunction. Yet we have no principled way to link these deficits to their behavioral consequences. Interpretable foundation models close that gap. By mapping cell types and connectivity onto the variables that govern brain-wide dynamics, they predict how a deficit propagates, and how to counteract it. These models provide the missing quantitative layer between the multimodal data collected by brain research Allen Institute accelerators and rational, circuit-level therapy.

proposal name:

ForgeLoop: Autonomous Biology, Human Guided

proposal team members:

Mialy DeFelice, Zach Stevenson, Alex Heubeck, Peter Wittig

accelerators:

immunology, seahub/seabridge, OCTO

abstract:

Plasmids are a cornerstone of synthetic biology, enabling applications from gene tracking to delivering therapeutic genes, yet their design remains stubbornly manual and expert dependent. Compounding this, constructing plasmids can be time consuming and expensive. ForgeLoop integrates PlasmidForge, OCTO's AI-powered plasmid design tool, with the Immunology Accelerator's automation suite to create a lab-in-the-loop system. At its core, this proposal connects Claude directly to physical Hamilton and Tecan liquid handling instruments, enabling real-time instrument control and bidirectional feedback between in silico design and in vitro execution. Experimental results flow back to PlasmidForge to inform updated designs; PlasmidForge in turn revises protocols dynamically – closing the loop. The system supports end-to-end autonomous library preparation and experimentation, with a defining feature: users can intervene and re-enter the loop at any stage, preserving meaningful human oversight without disrupting the autonomous workflow. We will validate ForgeLoop through a two-stage experimental plan. We first benchmark the pipeline by reproducing a published MPRA, establishing end-to-end reproducibility against a known result. Having demonstrated reliability, we will deploy the validated system in the second year to design and execute a novel CRISPRa MPRA, probing the sequence features that drive synthetic gene activation. Together, this work establishes ForgeLoop as a reusable, AI-guided automation framework that accelerates the path from biological hypothesis to experimental insight.

impact:

This project demonstrates the potential of AI agents to automate the plasmid design-build-test-learn cycle, by removing the most human-intensive friction from synthetic biology workflows. Beyond efficiency, this codifies design logic and troubleshooting expertise into a shareable, reproducible framework. Successful completion will allow scientists to move faster -- running experiments overnights and weekends, and proposing improvements in design or experimentation -- to help scientists get to results and discoveries quicker. Scientifically, our experiments using ForgeLoop for CRISPRa MPRA will advance our understanding of how guide RNAs drive gene expression, independent of genomic context.

proposal name:

Evolving rabies to map the brain

proposal team members:

Yoav Ben-Simon, Zack Lewis, Anna Globig, Maximilian Heeg, Jada Roth, Emily Jacobs

accelerators:

brain science, immunology

abstract:

Rabies viral vectors are an essential resource in the neuroscientist toolkit, as they can be used to map connections between distinct cell types across the brain. However, their neurotoxic effects limit their application to structural connectivity experiments that can be completed before labeled neurons die. To produce a non-toxic variant, we propose to leverage the virus's high mutation rate to develop an in-vitro directed evolution scheme for selection of non-toxic variants. By co-culturing rabies-transduced neurons and primed immune cells, we will be able to track in real time the emergence of fast-proliferating, immune-evasive variants and use their naturally occurring mutations to create the next generation of rabies viral vectors.

impact:

Understanding the logic underlying the relationship between identity of different brain cell types and how they are connected, both locally and distally, is one of the institute's overarching goals. Rabies viral vectors are currently the one of few genetic tool that can bridge the gap between cell identity and whole brain connectivity and the only one which can accomplish it in behaving animals, but the ability to fully use its potential is stunted by its toxicity. Solving this problem will usher in a new wave of experiments that will further our understanding of how the brain is wired and how this affects its function.

proposal name:

A Scalable Platform for Functional Imaging of Living Neural Systems

proposal team members:

Adam Glaser, Jianin Lin, Walter Mwaniki

accelerators:

neural dynamics

abstract:

We will develop a next-generation large-field-of-view, high-speed fluorescence imaging platform for high-throughput functional phenotyping of living neural systems. The microscope is designed to capture membrane potential, calcium dynamics, and other physiological signals across large brain slices, organoids, and cell cultures while preserving cellular detail. By combining broad spatial coverage with rapid image acquisition, the platform will enable simultaneous measurement of neuronal and non-neuronal cell activity across vastly larger populations of cells than can be observed using existing approaches. Unlike conventional imaging systems that interrogate only small regions of a biological sample at a time, this platform will enable functional measurements across entire tissue preparations within a single experiment. Researchers will be able to visualize activity within individual cells while simultaneously quantifying large-scale patterns of activity, connectivity, synchronization, and signal propagation. The system will support both calcium and voltage imaging, enabling measurements ranging from slow cellular dynamics to millisecond-scale electrical signaling. The technology is intended as a scalable platform for neuroscience research, functional genomics, and therapeutic discovery. Potential applications include studies of neuron-glia interactions, astrocyte signaling, circuit physiology, developmental and disease models, pharmacological perturbations, and optogenetic experiments. The platform will be particularly well suited for high-content screening workflows, including CRISPR- and perturbation-based genetic screens, where large-scale functional measurements can be used to identify genes that regulate cellular activity, connectivity, and network behavior. These capabilities can also be applied to drug discovery, target validation, toxicity assessment, and evaluation of gene and cell therapies.

impact:

This capability has the potential to transform neuroscience research. Scientists will be able to investigate how communication between brain regions supports cognition, how neural activity changes during development and aging, and how these patterns become disrupted in disorders such as neurodegenerative disorders and epilepsy. The platform will also provide a powerful tool for evaluating new therapeutics by enabling direct observation of how drugs, genetic interventions, and neuromodulation strategies alter brain function across large neural networks. Beyond its scientific impact, this technology has significant commercial potential. Pharmaceutical and

biotechnology companies could use the platform for drug discovery, toxicity testing, target validation, and phenotypic screening, generating comprehensive functional measurements from living brain tissue. By bridging cellular and systems neuroscience, this technology could accelerate both fundamental discoveries and the development of new therapies for brain disorders.

proposal name:

Robotic Platform for Chronic Neural Probe Implantation

proposal team members:

Serol Turkyilmaz, Carl Schoonover, Peter Groblewski, Alan Guthrie, Mike Soroka, Ben Ouellette, Alex Cahoon, Matt Hicks

accelerators:

neural dynamics

abstract:

Current implantation of ultraflexible neural probes is a highly specialized and operator-dependent procedure that is often difficult, lengthy, and prone to failure, limiting reproducibility, scalability, and broader adoption of long-term neural recording technologies. We propose to develop an automated robotic implantation platform that standardizes probe handling, alignment, positioning, and insertion. The system will integrate precision motion control, machine vision, and software-guided workflows to improve implantation accuracy and consistency while reducing dependence on operator expertise. This project focuses exclusively on robotic deployment technologies and does not include probe development. The primary objective is to evaluate the feasibility of automated probe deployment workflows and validate key concepts related to probe handling, alignment, and insertion. The work will reduce critical technical risks and inform future development of scalable and reproducible implantation approaches for chronic neural recordings.

impact:

Long-term neural recordings are essential for understanding learning, development, aging, and neurodegenerative disease, yet implantation of neural probes remains a major bottleneck. By transforming implantation from a challenging, failure-prone manual procedure into a reproducible engineering process, this project will improve recording reliability, increase experimental reproducibility, and reduce dependence on highly specialized operators. The resulting platform will help enable broader adoption of chronic electrophysiology.

proposal name:

Next-generation probe for long-term, brain-wide neural recordings

proposal team members:

Carl Schoonover, Serol Turkyilmaz, Peter Groblewski, Chong Xie

accelerators:

neural dynamics

abstract:

The vertebrate nervous system operates on submillisecond timescales, continuously, for up to several decades. That range spans more than ten orders of magnitude in time, yet typical measurements of brain activity last just one or a few hours. Therefore, most of what the brain does unfolds outside the narrow temporal window during which we typically observe it. This timescale mismatch imposes a ceiling on what the field can access, and is keeping fundamental phenomena related to development, memory, and disease beyond our reach. To close this gap this project will produce an ultraflexible, high-channel-count, high-density, nanoelectronic neural probe capable of making arbitrarily long recordings. The current standard for the field, the Neuropixels 2.0 probe, is fabricated on a rigid, 24-micron-thick silicon substrate. The mechanical mismatch between rigid silicon probes and soft brain tissue leads to micromotion-induced tissue damage and hinders stable, long-term neural recordings. A 15-year engineering effort led by our external collaborator, Prof. Chong Xie (Rice University), has culminated recently in a fabrication process to pattern circuits on an ultraflexible thin film whose mechanical properties approach those of brain tissue, allowing it to move with the brain rather than resist it. This project will leverage this fabrication process to produce a probe that matches the form factor and electrode-site geometry of Neuropixels 2.0 but realized on a 2-micron-thick, ultraflexible substrate. The probe will support uninterrupted observation of the submillisecond activity of ~1,000 individual neurons over arbitrarily long periods (>year), simultaneously in multiple regions of the mouse brain. Validation in the rodent will lay the groundwork for future translation to humans.

impact:

Extending the time domain of neuroscience by several orders of magnitude will transform both fundamental research and clinical care. How does the brain retain a memory for years when it can also acquire a new one in an instant? How does the assembly of circuits over development give rise—or fail to give rise—to precisely tuned sensory systems and coordinated motor control? How does the nervous system shape, and how is it shaped by, slow processes such as immune responses, gestation, menopause, or metabolic adaptation? What do the trajectories of Alzheimer's or Parkinson's look like at single-cell resolution, across multiple regions, and in real time? How are these trajectories halted or reversed during therapeutic intervention?