In La Jolla Institute for Immunology
La Jolla, CA
Miguel Reina-Campos, Ferhat Ay
$1,300,000

Leveraging histones as reservoirs of cellular energy to boost antitumor T cells

One of the most significant obstacles in cancer immunotherapy is T cell dysfunction caused by nutrient-depleted environments. So far, every approach to reinvigorate exhausted T cells does not tackle the root problem: the lack of suitable nutrients. Two investigators at the La Jolla Institute for Immunology will attempt to power T cells from within, transforming their epigenome into a strategic metabolic asset they can leverage under situations of nutrient starvation. Histones are one of the most abundant cellular proteins and they harbor large amounts of post-translational modifications. Acetylation stands out as a particularly prevalent modification among these. An acyl chain can be removed by histone deacetylases into acetate and converted to acetyl-CoA, a key versatile metabolite. Histone acetylation levels reflect changes in environmental nutrient availability, and specific histone modifications do not always correlate with gene transcription. Thus, the team hypothesizes that histones can store large quantities of useful metabolites, potentially acting as a cellular nutrient reservoir. Integrating novel functional genetic screens, histone modification mapping, metabolic tracing, metabolomics, and new tools to monitor the epigenome's architecture, they aim to demonstrate the potential of "harvesting" histone acetylation and to deploy an engineered epigenetic system to improve the persistence and function of T cells in immunotherapies.

Montana State University
Bozeman, MT
Dana Rashid, Susan Chapman, Kimberly Coope
$1,000,000

Defining the role of inflammation in vertebrate bone fusion

Inflammation, often viewed as a blight on our health, is known as a response to infection, trauma, or disease. A team of three investigators at Montana State University, Clemson University, and University of California, San Diego hypothesizes that inflammation is a universal driver of vertebrate postnatal bone fusion events. They discovered a critical role of inflammation in normal skeletal maturation that drives vertebral fusion in the avian tail and sacrum, and this fusion is inhibited by anti-inflammatory drugs. To investigate whether inflammation is a widespread bone fusion mechanism, the team will expand their studies to mammals. Kangaroo rat-like rodents called jerboa are ideal for this study as they have extensive axial and peripheral skeletal fusions. The goal is to identify those postnatal bone fusion events in chicken and jerboa that involve inflammation and are vulnerable to anti-inflammatory drugs. The team is also investigating the contribution of necroptosis, an inflammatory type of cell death, to bone fusions in development and disease. For a broader perspective, they will apply an evolutionary lens to examine inflammation as an instigator of evolutionary adaptation. Humans, like other terrestrial vertebrates, undergo extensive postnatal skeletal fusions that have arisen as evolutionary adaptations. Their data suggests that fusion events could be unintended targets in the clinical application of anti-inflammatory drugs, carrying significant health implications.

Memorial Sloan-Kettering Cancer Center
New York, NY
Chrysothemis Brown, Christina Leslie, Santosha Vardhana
$1,500,000

Recruiting neuronal communication pathways for immune tolerance

The immune system's ability to avoid attacking the very tissues it is designed to protect is critical to preventing autoimmune diseases. Elucidating the regulatory mechanisms underlying this immune tolerance will open the door to better treatments for many of these debilitating diseases. Accordingly, three Memorial Sloan Kettering Cancer Center (MSKCC) investigators seek to advance the field of immune regulation by showing how the immune system senses and controls self-reactive T cells, thereby suppressing autoimmunity. MSKCC investigators recently discovered a lineage of tolerance-inducing antigen presenting cells (APCs), named Thetis cells, which have provided tantalizing clues into novel pathways of immune tolerance. Based on their investigation of tolerogenic APCs, the investigators hypothesize that T cells utilize a classical neurotransmission pathway to convey information about their self-reactivity to APCs, which in turn respond by releasing molecules that induce T cell tolerance. While communication between neurons and immune cells is well known, establishing a role for neurotransmitters at the immunological synapse would reveal a new pathway of APC–T cell communication. By determining the role of "neurotransmission" in T cell tolerance, the investigators aim to establish a new pathway of immune regulation that will facilitate advances in therapies for autoimmune disease and cancer.

Princeton University
Princeton, NJ
Andrew Leifer, Mala Murthy, Sebastian Seung, David Tank
$1,200,000

Technology for measuring neural signal propagation at brain-scale

Understanding how neural signaling arises from the brain's neural network is critical for revealing how healthy brains function or fall into dysfunction. This requires relating two different maps of the brain, an anatomical map of neural wiring and a functional map of neural signaling. After years of investment, anatomical maps of neural wiring are now being measured for larger and more complex brains. But there remains a large gap in our ability to interpret these wiring diagrams and compare them to signaling, especially because no established method exists for measuring neural signal propagation at scale. Yet such comparisons are critical. Signal propagation in response to stimulation reveals causal relationships between neurons that go beyond what is visible from anatomy or even from passive observations of correlated activity. While an anatomical map reveals potential paths through which information may flow, a signal propagation map reveals where and how signaling actually occurs. To close this gap, the investigators will develop new techniques to measure signal propagation throughout the brain of the fruit fly *Drosophila*, and compare these signals to newly generated anatomical maps of its wiring. The project opens a new frontier of whole brain neural signaling measurements in large and complex brains at unprecedented resolution, throughput, and scale that will provide new fundamental principles of how a brain's connectivity relates to it's signaling.

Salk Institute for Biological Studies
La Jolla, CA
Terrence Sejnowski, Gerald Pao, Jack Gallant
$1,600,000

Mapping human brain dynamics with generative manifold networks

Three investigators at the Salk Institute, the Okinawa Institute of Science and Technology, and at the University of California at Berkeley, will collaborate to decipher human behavior using a computer model derived from functional magnetic resonance imaging (fMRI). The team aims to generate the same complex human behaviors from their computer model as is created from the recordings. The investigators will use a novel mathematical method called generative manifold networks, which is based on techniques from dynamical systems theory to determine all the cause-and-effect relationships between all the recorded brain areas. These relationships will then be transformed into mathematical objects called manifolds, which will recapitulate the flow of information in the brain. Compared to other methods, this approach aims to capture the essence of biological computing with much less data and fine-tuning, does not require extreme numerical precision, and can tolerate incomplete observations and distorted data without collapsing so long as the relevant information is present. As a proof of concept, the team has recapitulated fly walking and larval zebrafish swimming behaviors from whole-brain optical recordings. High-resolution fMRI recordings will be obtained from humans playing increasingly complex virtual reality video games, and the investigators will then test the model’s generated behaviors playing the same games.

Stanford University
Palo Alto, CA
Michael Z. Lin, Brian Kobilka, Vivianne Tawfik
$1,400,000

Developing bioluminescent probes for visualizing GPCR ligand release in the whole body

G protein-coupled receptors (GPCRs) and their ligands play critical roles in governing the intricate physiology of the body. Communicating between organ systems and along the brain-body axis, they maintain homeostasis, respond to threats, and adjust metabolism to needs and resources. However, understanding the functions of GPCR ligands in specific tissues remains elusive due to our inability to track their presence in real time. A team of three investigators at Stanford University will develop a novel method for real-time whole-body imaging of GPCR ligands using bioluminescence. They will first demonstrate noninvasive imaging of autonomic nervous system responses to food intake in body organs using prototype GPCR ligand bioluminescent indicators. They will also engineer new reporters for endocannabinoids and opioids, analgesia-promoting GPCR ligands whose regulation is still poorly understood. Using these new reporters, they will investigate how natural experiences such as exercise and injury regulate endocannabinoid and opioid release. This work will enable a holistic approach to understand how GPCR ligands shape healthy adaptive responses and how they may be dysregulated in disease.

University of Oregon
Eugene, OR
John Postlethwait, Adam Miller
$1,500,000

Finding the parameters that govern transcriptional adaptation to enable novel RNA-based therapeutics

One in seventeen people have a rare genetic disease, but there are few effective therapies for them. Two investigators at the University of Oregon aim to develop a broad-based therapeutic approach based on a recently discovered phenomenon that provides feedback from mutant RNAs to DNA to upregulate compensating genes and thus decrease harmful impacts. This poorly understood phenomenon is called transcriptional adaptation (TA). The investigators plan to define the types of genes, mutations, and disease states that respond to TA. They will perform high-throughput CRISPR mutagenesis on hundreds of disease-associated genes in zebrafish to characterize the properties and roles of TA in development and physiology. Then they will define the parameters for TA-mediated rescue for specific disease-associated cases, beginning with ten human disease genes that display TA in fish and thus mask a disease-related phenotype. These studies will identify disease-associated cell types, chromatin states, and adapting genes responsible for ameliorating mutant symptoms, revealing fundamental principles and cellular mechanisms of genetic robustness that combat disease. The goal is to develop a practical and safe new approach to genetic therapy, by harnessing TA with small mRNA fragments.
