Columbia University
New York, NY
Dietrich M. Egli, Juan-Manuel Schvartzman
$1,200,000

Investigating the causes of genome instability in development

Fertility treatments often fail because embryos can struggle to develop properly due to genome instability *in vitro*. An observed slowdown in DNA copying can lead to what is known as DNA replication stress, which often results in detrimental chromosomal abnormalities. Compared to other mammals, human embryos are more susceptible to these chromosomal errors, which can occur not only before but also after fertilization, during the first stages of the embryo's cell division. These mistakes in copying the DNA can disrupt normal development, result in miscarriage and disease. The investigators at Columbia University found that certain metabolites can cause DNA replication stress and genome instability in cancer cells. The team hypothesizes that there may be parallels in early human development and they plan to test this hypothesis experimentally. Their goals are to understand the causes of DNA replication stress, the full range of its consequences, and learn how to prevent the formation of chromosomal and genetic abnormalities in embryos. Understanding the root causes and consequences of DNA replication stress, as well as developing strategies to mitigate it, could translate to clinical advances, including higher success rates in fertility treatments using fewer oocytes and hormonal cycles.

University of California, Berkeley
Berkeley, CA
Ziyang Zhang, Robert Saxton
$1,000,000

Developing chemical tools to manipulate cytokine signaling in immune cells

Efficient communication of immune cells is mediated by a class of secreted “messenger” proteins called cytokines, which orchestrate nearly all aspects of immune function. Despite their essential role in host defense, cytokines can become dysregulated and contribute to diseases including chronic inflammation, autoimmunity, and cancer. The development of small molecule probes targeting signaling proteins such as kinases and G protein-coupled receptors has revolutionized our understanding of cell biology and facilitated extensive therapeutic development. However, an analogous chemical toolkit for probing cytokine-mediated immune cell signaling is lacking, due in part to the difficulty of modulating extracellular protein-protein interactions with small molecules. Two investigators at the University of California, Berkeley plan to develop a platform for the discovery of small molecule cytokine receptor modulators capable of selectively controlling immune cell communication. If successful, this approach could provide an unprecedented degree of pharmacological control over immune cell function, enabling the molecular dissection of complex immune responses in vivo and unlocking a new paradigm in immunotherapy.

University of California, San Francisco
San Francisco, CA
James Gardner, Vasilis Ntranos, Matt Spitzer
$1,300,000

Modulating novel immune tolerance mechanisms for precision immune education.

Over the past century we have become exquisitely good at teaching the immune system precisely what to attack, but we remain almost entirely unable to do the opposite – teach it what not to attack. And yet our bodies do this all the time: teaching our immune cells how not to attack our own tissues and organs. To this end, this investigator and others have discovered novel, dedicated immune-educator populations called extrathymic Aire-expressing cells (eTACs), and have defined their essential roles across a range of conditions from autoimmune diabetes to organ transplantation, healthy pregnancy, and cancer. These tolerogenic antigen-presenting populations are a common thread that traverses diverse health conditions, but they remain remarkably understudied; defining their essential biology could have broad impacts on human health. The aims of this project are: (1) define the fundamental biology of eTACs including their identity, lineage, and cellular interaction network using and building novel transgenic systems and advanced single-cell genomics; (2) define the role and function of these populations in disease states like autoimmunity and tumor immune evasion; and, (3) develop and optimize a platform for in vitro eTAC differentiation using CRISPR-screen based high-throughput optimization to interrogate the essential biology of this population and establish proof-of-concept methods of precision immune self-education. Insights from this project could define entirely novel paradigms of immune tolerance.

University of Colorado Denver – Anschutz Medical Campus
Aurora, CO
Olivia Rissland
$1,000,000

Molecular vulnerabilities in cells that produce large amounts of a single protein

Many cells in the human body produce a complex mixture of proteins, but a subset of cells turn into specialized “factories” that predominantly produce extremely large amounts of a single type of protein. Collagen is the most abundant protein in our bodies. It is produced rapidly in a process called translation and secreted in large volumes by fibroblast cells during critical biological processes, such as organ development and wound healing. An investigator at the University of Colorado Denver – Anschutz Medical Campus plans to use collagen as a test case to explore hypotheses about “ultra-dedicated” production of a single protein. She will test how cells deal with the increased demands for building blocks and translation machinery during ramped up production of collagen, which is dysregulated in many diseases and in aging. Understanding the opposing forces of supply, demand, and quality control processes involved in collagen translation could give us insight into not only strategies to modulate collagen synthesis but also the production of other essential proteins, such as insulin released by pancreatic beta cells or antibodies secreted by B cells.

University of North Carolina at Chapel Hill
Chapel Hill, NC
Adam Hantman, Ian Shih, John Krakauer
$1,300,000

Understanding network switching to rescue damage in the central nervous system

When solving a problem, we can become stuck iterating on a suboptimal strategy. However, occasionally we reach a breakthrough, uncovering a novel way to attain a desired goal. How does our nervous system identify new solutions? A team of three investigators at the University of North Carolina and at Johns Hopkins University will study how the brain produces a network switch signal that directs the engagement of new circuits. But sometimes, this switching signal fails to activate. This is all too common following brain damage that impacts our motor system, leaving impaired movements that never completely recover. The team's findings suggest that lingering deficits can be due to a maladaptive tendency to cling to dysfunctional circuits, rather than abandon them for intact neural regions. The investigators have produced an experimental regime that uses optogenetics to completely inactivate a motor circuit, seemingly forcing the brain to issue network switch signals that in turn marshal effective compensatory responses in distant brain areas. This finding now allows them to uncover the source of the switch signal and the brain regions that take over function. To enable an unbiased search, they have invented an fMRI sequence that allows them, for the first time, to record whole-brain activity as mice perform skilled behaviors. The investigators will combine fMRI and electrophysiology to continuously monitor the nervous system as it recovers from loss of motor function. They will then modulate switch signals and compensation areas to either hinder recovery or possibly enhance functional rehabilitation following cortical stroke. This experimental platform paves a new pathway to explore neural resilience and harness endogenous plasticity mechanisms to enhance our recovery capacity.

University of Utah
Salt Lake City, UT
Deborah Neklason, Aaron Quinlan, Nicola Camp
$1,500,000

Understanding the genetic and epigenetic control of aging: the Keck/Utah Genetics Reference Project

Twenty-five years ago, the W.M. Keck Foundation and the University of Utah embarked on the Utah Genetic Reference Project (UGRP), a unique collection of large, three-generation families, not selected for disease, with 180 characteristics measured to study the genetics of human variation. The UGRP families were a backbone of the Human Genome Project, have served the international community in landmark genetic studies, provided an essential reference for hundreds of medical discoveries, and are technical standards for most new genetic technologies. Now, a team of three investigators will further advance genome science by sequencing the genomes of these well-studied families to understand the extent and dynamics of variation in the epigenetic chemical modifications to DNA. These epigenetic modifications do not change the DNA sequence itself, yet they modulate the expression of genes. Importantly, these chemical modifications are reversible, and change in individuals over time and through generations, thus providing an opportunity to treat disease and enhance healthy lifespans. The investigators will sequence and analyze the genomes of ten large UGRP families using technology that can accurately determine the genetic code of long stretches of DNA and simultaneously detect epigenetic modifications. The team is uniquely positioned to answer these and other open questions with fundamental and translational impact: Which epigenetic changes are inherited, and do they affect traits and gene expression? Which types of genes have variable epigenetic inheritance? And what epigenetic changes are associated with aging? In addition, they will establish an essential reference of epigenetic variation for studying health conditions.

Vanderbilt University
Nashville, TN
Cody Siciliano
$1,300,000

Study of neural circuits that link oral sensation to drinking behavior

Oral chemesthesis, the sensation associated with chemical activation of nerve fibers in the mouth, contributes to a broad range of behaviors such as preference for spicy foods, attraction to alcoholic beverages, and avoidance of chemically contaminated food sources. Despite its behavioral importance, very little is known about the brain mechanisms that give rise to oral chemesthesis. To address this, an investigator at Vanderbilt University plans to study the neural circuits that specifically function in oral chemesthesis of alcohol, drive decision-making, and then affect drinking behavior in a rodent model. The project applies advanced neuroscience techniques to enable long-term observation of neuronal activity while simultaneously testing animal behaviors, and genetic manipulation of neural circuits at a very fine scale by laser ablation. By elucidating the fundamental biological mechanisms underlying this sensory modality, their work promises to contribute significantly to the broader field of sensory neuroscience. The study could potentially provide insights into more effective behavior modification in patients suffering from addictions such as alcoholism.