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 developmenbmNeeeo-10.4 (t)10.4.01114.5 (e)12.4 (n9.9 (-1)17.7)-1.6 (n)-11.5 .4 (e)2n( )32.2 (Dl d 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 c ontribute 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 extra cellular 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

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

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

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.

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