# RESEARCH PROGRAM

# Medical Research Abstracts
# for Grants Awarded in December 2021

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*Davis, CA*
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*$1,000,000*
*December 2021*

Altered neurochemical signaling is a crucial feature of all human neurological and psychiatric disorders. Hence, a critical challenge for developing therapeutic neural drugs without undesired side effects is the lack of understanding of when and where neurochemicals release and how these complex signals shape the function and structure of neural circuits. Neurochemical neurons are densely confined in relatively small deep-brain areas but extensively project to many other distant brain regions. Two collaborators at the University of California, at Davis and at Berkeley, will develop and test new protein sensors for these neural signals. Their new reagents will report the presence and time-course of three neural signals (glutamate, dopamine and serotonin), by emitting light in the far-red and near-infra-red. The sensors will be tested in mice to reveal the activity of these deep brain structures, because red light penetrates farther through tissue than is possible with existing reagents.

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Cartilage is a critical flexible connective tissue that provides mechanical support in structures such as the ear, nose, respiratory tract, and on the surfaces of joints. Most types of cartilage are formed by cells called chondrocytes, characterized by large amounts of secreted extracellular matrix (ECM). Two investigators at the University of California, Irvine will focus on characterizing an understudied cell type called the lipo-chondrocyte (LC), which secretes a small amount of ECM but contains a prominent lipid-filled vacuole, much like a fat cell. The investigators hypothesize that lipogenesis is critical for the structure-function relationship in LCs and that, analogous to "bubble wrap," a tissue can acquire cartilage-like biomechanics via tightly packed, lipid-filled cells instead of voluminous, "packing foam"-like ECM. LCs will be

characterized for their biomechanical properties, and planned genetic experiments in mice are aimed at understanding the molecular mechanisms underlying the formation of these cells. LCs are also transiently present during human gestation and may have an important role in the correct development of permanent cartilage in humans. The findings of this project could add a significant new dimension to cartilage mechanics and a better understanding of the development of human cartilage for regenerative medicine.

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*Oregon Health & Science University*
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*December 2021*

Living cells are densely packed with thousands of types of protein molecules, which makes the individual molecules hard to image. However, their spatial and dynamic relationships are important for their biological function. Two investigators at the Oregon Health & Science University will develop a new microscope which will use an array of laser beams together with machine vision and deep learning to quantify and connect these molecular behaviors to cellular functions. The new system will enable the investigators to label and track many individual, fluorescently tagged, protein molecules, at the same time, in living cells. This project aims to overcome current technological barriers and capture high-density, high-speed molecular information across the entire cytoplasm. The investigators will first apply this approach to molecular condensates, which are proposed to be aggregates of proteins and/or RNAs that constitute a phase separation, like oil droplets in water.

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*Salk Institute for Biological Studies*
*La Jolla, CA*
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*December 2021*

Although they are incredibly powerful and useful tools for studying gene function, genetically engineered mice and other model organisms are slow and costly to generate and maintain in the lab. An investigator at the Salk Institute for Biological Studies proposes to develop a novel molecular technology platform to study gene expression and function in the tissues of living animals, bypassing the need for genetically engineering the organism. This is based on a novel RNA detection system, which uses a two-part "transcriptome-reader" to detect a specific target

RNA molecule expressed by a cell type. The investigator will develop the optimal RNA sequences for different transcriptome-readers and establish generalizable programming rules that allow the technology to target any gene marking a cell type of interest. Then, various transcriptome-readers will be tested in mice, by targeting transgene expression to specific neuronal subtypes within the spinal cord and use them to study locomotor circuitry. The system will be delivered in vivo using viral vectors which opens its applicability to a variety of organisms.

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*$1,000,000*
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Heterogeneity among cells, even those that superficially seem identical, occurs at all levels of biology from single cells to humans. While vital for normal physiology, heterogeneity reveals a sinister side in diseases such as cancer. Conventional thinking considers single cancer cells in a tumor as combatants in a survival of the fittest competition with rare "winners" that survive and metastasize. However, tumors consistently maintain heterogeneous subpopulations of cancer cells, some of which appear less able to grow and spread. This paradox suggests cancer cells may collaborate to cause disease and not just compete. Causes of single-cell heterogeneity and conditions that motivate cancer cells to collaborate remain critical, unresolved problems. A team of six investigators at the University of Michigan will investigate these problems using large, single-cell data sets in combination with inverse reinforcement learning, an artificial intelligence method typically applied to discover motivations for human behaviors, and computational models inferred from the physics and chemistry of cell signaling and migration. This project aims to develop a new path to understand and treat cancer.