Stanford University
Stanford, CA
Karl Deisseroth & Zhenan Bao
$1,000,000
June 2021

Imagine a world where we build within biological systems, rather than inserting devices. Imagine a nerve growing its own antenna to receive direct communication from physicians, or glucose-measuring cells sending instructions directly to an insulin pump, or neurons forming precisely defined new connections between two distant brain regions simply by assembling a conductive polymer pathway. Two professors at Stanford University are inventing a new field at the interface of chemistry and biology: genetically targeted chemical assembly (GTCA). They have already completed a pilot project: to instruct specific neurons to guide chemical synthesis of electrically functional polymers. With this funding from the W. M. Keck Foundation, they will broaden GTCA for use to any biological system, and create a foundation ranging from materials synthesis to assembly of brain-computer interfaces. By bridging the biological and nonliving worlds through synthetic chemistry and hierarchical assembly, GTCA may promote both understanding of fundamental biology and creation of seamlessly integrated clinical devices. The team's vision is to construct matter within life, guided by life, for healing and enhancing life. The resulting universe of opportunities will re-define the border between matter and life.

University of California, Irvine
Irvine, CA
Andrej Luptak, Jennifer Prescher & Oswald Stewart
$1,000,000
June 2021

A team of three investigators from the University of California, Irvine, plan to develop and deploy ultrasensitive luminescent probes, which they call "molecular lanterns". These new tools will allow them to trace the life history and local translation of RNAs in neurons in living mammals. Local protein synthesis at synapses plays a critical role in neuronal changes that underlie learning and memory, and neuroscience has identified circuits, cells and individual synapses that are modified during learning, but fundamental overarching questions remain unanswered: Why are some mRNAs present in abundance in neuronal dendrites (thousands of copies per dendrite) whereas other mRNAs are present at very low levels, if at all? Why are some mRNAs expressed transiently whereas others are present constitutively? Their novel molecular lantern tools will enable the investigators at Irvine to answer these and other questions about the lifecycles of mRNA, from transcription in the

nucleus to delivery to distant synapses, translation and degradation, and dynamic changes in response to synaptic signals. The team's vision is that molecular lanterns will be broadly applicable for neuroscience and lead to a mechanistic understanding of the lasting synaptic changes that underlie enduring memory.

University of Colorado Denver | Anschutz Medical Campus
Aurora, CO
Matthew Taliaferro & Chad Pearson
$1,000,000
June 2021

Centrosomes are essential cellular organelles with important functions in cell division and embryonic development. Centrosomal defects can cause cancer and other diseases. A small number of RNA molecules have been found to localize to the centrosomes, but there are thought to be many more RNAs remaining to be identified. Furthermore, the cellular functions of all of these RNAs are not known, nor how they are moved to and anchored at the centrosome. Two investigators at the University of Colorado Anschutz Medical Campus have developed an RNA proximity labeling technique called "Halo-seq", which is highly sensitive and spatially specific. Halo-seq will allow the team to purify and identify new centrosomal RNAs as well as mechanisms that govern their transport to centrosomes. They plan to image the centrosomal RNAs within cells at high resolution and then to study their functions in mitosis and cell-cycle progression. Given the connections between centrosome dysfunction and cancer, they may also identify new contributors to tumorigenesis.

Georgia Institute of Technology
Atlanta, GA
Francesca Storici & Nataša Jonoska
$1,000,000
June 2021

Before cells can divide, the DNA genome must be replicated, and when this happens, a huge number of building blocks of RNA, *ribo*nucleotides, is incorporated instead of the usual DNA monomers. These ribonucleotides are abundantly found in the DNA of living cells, from unicellular organisms (like bacteria), up to humans. The presence of these RNA subunits in the genome has been considered as random errors of DNA synthesis. A pair of investigators, one at the Georgia Institute of Technology and the other at the University of South Florida suggest that these RNA elements may be non-randomly distributed in the human genome, and furthermore that some of these ribonucleotides may serve in a specific capacity: as crucial signposts to control gene expression, DNA replication, or other biological function. The investigators will map, at single nucleotide resolution, the positions

of the RNA subunits in the human genome of cells from different tissues. They will use bioinformatic analyses and mathematical methods to search for recurring sites of ribonucleotides and sites displaying a certain sequence regularity, and how such sites may relate in the chromosome map to, and within, the genes themselves. The investigators' goal is to decode the 'cryptic language' of these RNA elements in the human genome, about which nothing is currently known.

University of Florida
Gainesville, FL
Jason Smith (UF), Borna Mehrad (UF), Karen Garrett (UF) & Stephen Van Den Eeden (Kaiser Permanente) & Leda Kobziar (U. Idaho)
$1,200,000
June 2021

A multidisciplinary team of five investigators from the Universities of Florida and Idaho, and from Kaiser Permanente Northern California, will explore the relationship between wildland fire smoke and emerging mycotic diseases. They will focus on California and neighboring regions with high population densities and accelerating wildfire frequency and severity. Previous research on the effects of wildfire smoke on human health has focused primarily on the context of fine particulate matter, various chemical species, and respiratory and general health outcomes. However, living microbes, notably fungi, have been found in the smoke particulate matter from wildfires. Habitats in the western U.S. where wildfires burn are known to harbor fungal species that can act as human pathogens and aeroallergens, including Cryptococcus gattii (which causes cryptococcal meningitis), Coccidioides spp. (Valley fever), and the fungicide-resistant Aspergillus fumigatus (invasive aspergillosis). The investigators hypothesize that such fungi aerosolized and transported by wildland fires are linked to increased human health risks. They will work to link a series of threats, from the source of smoke borne fungi, to combustion-aerosolization and transport, to exposure, and finally to pathogenicity. They will integrate the data using advanced machine-learning analysis to develop epidemiological models to predict the consequences of smoke-derived fungal pathogens on human health.

Rice University
Houston, TX
Jacob Robinson (Rice) & Celina Juliano (UC Davis)
$1,000,000
June 2021

An interdisciplinary team of two investigators: an engineer from Rice University and a biologist from the University of California, Davis, will use the small freshwater cnidarian *Hydra* to test the idea of building custom neural circuits in a living animal. This approach

they refer to as “synthetic neurobiology” will involve using genetic techniques to define synthetic inputs and connections between cells. As one example, the team will eliminate all but two neuronal cell-types that they will then connect to create an amplifier circuit. By creating the foundational technologies that allow scientists to artificially define the connections between neurons and muscle cells the team aims to make it possible to create designer neural circuits that drive programmed behaviors in a living animal. The investigators’ greater goal is to use this engineering approach of “design-build-test cycles” to better understand the connection between neural circuit activity and behavior in living animals.

University of Washington
Seattle, WA
Kelly Stevens, Raymond Yeung & Daniela Witten
$1,000,000
June 2021

The liver is the only visceral organ in humans with the capacity to fully regenerate. But the liver is not able to regenerate if it is severely diseased. While many biochemical factors have been identified that contribute to liver regeneration, an interdisciplinary team of three investigators from the University of Washington hypothesize that mechanobiology is a major missing piece in this field. This hypothesis is borne from numerous clinical studies which have shown that the environment surrounding cells in the liver becomes mechanically stiffer in liver disease. To address this technique, the investigators will introduce highly parallel tissue grafting (HPTG) to greatly expand the number of conditions that can be tested in parallel for liver regeneration studies. The investigators will use their funding form the W. M. Keck Foundation to perform hundreds of simultaneous human liver regeneration experiments and uncover how mechanical cues govern human liver regeneration under diverse settings of human disease. The technical innovations developed in this proposal will also be broadly useful across diverse fields of biomedicine, such as cancer, cardiovascular disease, and kidney disease.
