**Gladstone Institutes**
*San Francisco, CA*
*Isha Jain*
*$1,300,000*

Oxygen is both vital and toxic for life. Interestingly, the cities with the longest-lived populations exist at high altitude where oxygen levels are lower. The lifespan of model organisms, such as worms, flies, and yeast, can be increased experimentally by simply reducing the amount of oxygen in the air they breathe, a condition called hypoxia. Anecdotal evidence also suggests that hypoxia can alleviate many "hallmarks of aging." These cellular hallmarks represent biochemical signatures that unify all aging-related processes and lead to the demise of an organism over time. A key such hallmark is the accumulation of defective mitochondria, organelles that produce energy and perform many other fundamental functions. Mitochondrial dysfunction is also observed in Parkinson's disease and age-associated neurodegeneration. Remarkably, chronic hypoxia (equivalent to living at an altitude of 4,500 meters) has been shown to be curative in a mouse model of mitochondrial dysfunction and premature aging. In this project, an investigator and her collaborators at the Gladstone Institutes and at the University of California, San Francisco will explore the therapeutic potential of hypoxia using stem-cell derived neurons and animal models. Their work has the potential to transform our understanding of the aging process and inspire new ways of alleviating age-associated neurodegeneration by simply "turning the oxygen dial."

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**Johns Hopkins University**
*Baltimore, MD*
*Takanari Inoue, Shigeki Watanabe, Jeffrey Gray, David Meyers, Benjamin Rost*
*$1,200,000*

Progressive loss of information transfer at the neuronal junctions known as synapses is a hallmark of many neurological and neurodegenerative diseases. While restoring synaptic structure and function could, in theory, treat these disorders, this task is daunting due to the plethora of biomolecular components that would need to be properly reassembled. Current therapeutic approaches are thus limited and symptomatic, and usually lack precision to target functionally distinct synaptic subtypes. A multidisciplinary team at Johns Hopkins University (TI, SW, JG, DM) and at the Charité - Universitätsmediz Berlin (BR) will take a radical synthetic biology approach to design and realize the minimal and alternative molecular principles of synaptic transmission, and to build a synthetic synapse. In particular, they will construct a series of custom-made molecular parts that uniquely utilize chemical, optical and electrical signals in an autonomous manner, and that could

replace the vast majority of elaborate native processes. In the longer term, since the molecular parts of the synthetic synapse are modular and scalable, there is potential to expand the system to mimic higher-order synaptic properties such as experience-dependent plasticity, or establish informational transfer schemes at other cellular junctions such as neuromuscular junctions and immune synapses.

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**University of California, San Diego**
*La Jolla, CA*
*Scott Sternson, Olivier George, Michael Michaelides*
*$1,300,000*

Addictive drugs hijack brain circuits associated with natural rewards by promoting a positive feedback cycle of drug-seeking and ingestion. In principle, a temporally concurrent negative feedback process could counteract the cycle of addiction, but there are no tools to alter neuron activity in a manner that precisely mirrors the complex dynamics of addictive drug ingestion and brain pharmacokinetics. A team of three investigators at the University of California, San Diego (SS, OG) and at the National Institute on Drug Abuse (MM) will pursue a new method to gain unprecedented control over brain-to-body chemical signaling processes that guide animal behavior. The team will develop a synthetic physiology approach that installs artificial chemical negative feedback loops operating at the level of entire organisms, which they term negative feedback chemogenetics. This concept will be developed initially to investigate the neurobiology of addiction in a new way. Negative feedback chemogenetics involves creating receptors for addictive drugs that will control neuron activity only when a drug is in the brain, which enables evaluating individual cell types for their ability to blunt reinforcement processes underlying drug addiction. Because these tools are specific for drugs, they may eventually lead to gene therapies selective for addiction without affecting enjoyment of natural rewards.

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**University of Texas at Austin**
*Austin, TX*
*Lief Fenno*
*$1,000,000*

Approaches to understand brain function in laboratory animals and to treat brain disease in patients have little in common: molecular neuroscience tools turn specific neurons on or off, while psychiatric medications modulate the flow of information through neural circuits–a difference akin to a building's main circuit breaker and a dimmer switch. While today's neuroscience tools have driven progress in understanding the structure-function relationship of the brain, they have not advanced the treatment of human patients. The reason is clear: aberrant brain activity associated with psychiatric disease is not driven by inappropriate activation or inactivation of specific neurons, but instead by problematic transmission of information between neurons. Causal investigation of psychiatric disease in model organisms requires a new approach enabling direct control of neural circuit information flow. To achieve this goal, an investigator at the University of Texas at Austin is developing circuit-targeted and genetically encoded artificial neurotransmission systems. Artificial neurotransmission combines the mechanism of psychiatric medications with the cell-type specificity of molecular neuroscience tools and will open new frontiers to understand–and eventually treat–a broad range of neuropsychiatric diseases.

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**Vanderbilt University**
*Nashville, TN*
*Charles Sanders, Roy Zent*
*$1,200,000*

Two investigators at Vanderbilt University School will test an approach to identifying human genes with critical functions, based on evolutionary logic. While human genome sequencing has revealed over twenty thousand protein-coding genes, only a minority of them have identified functions in human physiology or development. The investigators have found that a very small fraction of human genes (1.3%, or 257 of the ~20,000 genes) have significant stretches of invariant sequences of amino acids (in a database of ~16,000 genomes), which they call "Zero-Tolerance Proteins." These highly conserved genes may be particularly important for normal human function. The investigators will work with three zero-tolerance domain containing genes that have not been well-studied to date. They will look for critical functions for the three genes and their encoded proteins biochemically, and then study their function in human cells and mice. If the team succeeds in finding important functions for these genes, there could be very high impact for basic human genetics, leading many investigators to focus their studies on other genes in which natural selection does not tolerate variations in the human population.

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