Fox Chase Cancer Center
Philadelphia, PA
John Karanicolas, Siddharth Balachandran, Alfonso Bellacosa, Israel Cañadas, James S. Duncan, Jinhua Wu
$1,000,000

Many diverse proteins have been clearly and unambiguously implicated as drivers of human disease, but most are not readily druggable using currently existing approaches. Certain drug-like compounds known as “molecular glues” can tune the selectivity of E3 ubiquitin ligases, redirecting them to degrade a neo-substrate of interest. While these offer an exciting new modality for addressing hitherto undruggable targets, all molecular glue degraders reported to date have been the product of serendipitous discovery. A team of six investigators at Fox Chase Cancer Center will use cutting-edge structure-based machine learning methods to develop a platform with limitless applicability for identifying molecular glue degraders via rational design, thus broadening the space of protein targets that can be targeted for degradation. The impact of these studies will also extend far beyond degraders: the same framework can also be extended in the future to enable the design of other molecular glues for creating synthetic signaling networks, tuning epigenetic marks, and much more.

New York University
New York, NY
Eric K. Oermann, Biyu J. He
$1,200,000

One-shot learning is a critical component of human perceptual reasoning, conferring the ability to survive in environments with limited information and to maximally leverage learned experiences. The mechanisms thought to enable human one-shot perceptual learning, through the use of prior knowledge, are associated with a wide range of psychopathologies including posttraumatic stress disorder, anxiety, and psychosis. Two early career investigators at New York University will use brain surface electrodes to record local activity in neurosurgical patients, and multimodal neuroimaging to gather data from healthy human subjects, while they perform timed visual recognition tasks. They also plan to use advanced artificial intelligence/deep learning techniques to model such processes and use this to study human perception and its pathologies. The two co-investigators provide an unusual combination of expertise to the project: neuroscience, neurosurgery, and computer science. This project may establish a previously unknown, non-hippocampal pathway for human visual learning. The project may also have impact for object recognition for artificial intelligence machine vision and would add useful insights into the possibilities and limitations of such models.

Seattle Children's Hospital
Seattle, WA
John D. Aitchison, Nitin S. Baliga, Shuyi Ma, Robert L. Moritz, Michael D. Tyers
$1,300,000

Recent viral epidemics and the current pandemic have exposed the need for effective, targeted, and robust antiviral therapeutics. A team of five investigators at Seattle Children's Hospital (JDA, SM), Institute for Systems Biology (NSB, RLM), and The Hospital for Sick Children (SickKids) in Toronto (MT) proposes a unique strategy for host-based therapeutics that, if successful, will be broadly applicable and could lead to new classes of antiviral agents with high specificities and low toxicity. When viruses infect cells, they hijack and repurpose the host machinery to produce a massive number of new viral particles. This drain on cellular resources exposes vulnerabilities specific to infected cells and is akin to removing one of the legs of a four-legged table. The table can still stand on three legs but will collapse upon the removal of one of its remaining legs. The team hypothesizes that such virus-induced vulnerabilities can be exploited to selectively disable virally infected cells, thereby disrupting the viral life cycle. Their methodology combines state-of-the-art proteomics, targeted CRISPR screens in human cells that overexpress key viral proteins, and novel computational analyses specifically designed to identify host cell vulnerabilities elicited upon influenza, dengue, or SARS-CoV-2 infection. The team's overall goal is to determine if virus-induced vulnerabilities represent an untapped strategy for host-based antivirals.

The Ohio State University
Columbus, OH
Kristy Townsend, Martha Ann Belury, Andrea Tedeschi
$1,200,000

The brain regulates adipose (fat) tissue function via the peripheral nerves, and this bi-directional neural communication is crucial for maintaining metabolic homeostasis. Yet, a significantly understudied aspect of the basic biology of adipose tissue function is the communication channel via the tissue's sensory nerves, including how these nerves respond to local lipids and whether they serve as a neuronal 'fuel sensor' for the brain. It may be that these sensory neurons degenerate with age and in some common diseases, including diabetes and obesity, which could lead to critical failures of control mechanisms. A team of researchers at The Ohio State University and collaborating institutions will investigate the neural circuits connecting adipose tissue and the brain using mouse models. They will image the activity of the nerves as they respond to introduced lipids, and they will determine lipid interactions with neural receptor molecule(s), describing for the first time a 'neuro-lipidome axis'. The team will also test the function of the circuit by specifically blocking or activating subsets of nerves and observing changes in metabolic behaviors and lipid profiles. This project may lead to breakthroughs in basic physiological science and, in the longer-term, has the potential to impact the clinical management of human metabolic diseases like obesity and diabetes, which are associated with increased risk of cardiovascular disease and cancers.