RESEARCH PROGRAM

Medical Research Abstracts for Grants Awarded in June 2019

City of Hope
Duarte, CA
Saswati Chatterjee
$1,000,000
June 2019

Gene editing is revolutionizing research from medicine to agriculture. It is enabled by nuclease-based platforms, such as CRISPR, which predominantly use error-prone non-homologous-end-joining DNA repair, leading to unintended on-target mutations. Repair of nuclease-induced double stranded DNA breaks via the highly precise homologous recombination (HR) pathway is rare. Additionally, nuclease-based editing platforms carry the burden of promiscuous off-target cleavage, resulting in the potential for genome-wide mutagenesis. Thus, significant challenges persist with current editing platforms. Adeno-associated virus (AAV)-based vectors have previously been shown to mediate genome editing without the requirement for exogenous nucleases. However, genome editing efficiencies were too low to be useful. Investigators at City of Hope recently reported that AAVHSC, a novel class of human stem cell (HSC)-derived AAV, mediate precise and efficient HR-based genome editing requiring no exogenous nucleases and no genomic scarring. Genome editing is guided only by homology arms. However, although this method is effective, little is known about the underlying processes by which any AAV, including AAVHSC, mediate gene editing. In this project, the team will investigate the mechanisms by which AAVHSC executes this unique, efficient, HR-based editing. Specifically, they will study the interactions between AAVHSC editing genomes and cellular DNA repair proteins and the role of the AAVHSC capsids in potentiating the efficiency of HR. Additionally, they will investigate how AAVHSC mediates HR in non-dividing cells. This study is expected to reveal novel cellular mechanisms that may be harnessed for a range of genomic applications including novel therapies.

Johns Hopkins University
Baltimore, MD
Abdel Hamad, Thomas Donner, Chunfa Jie, Ruhong Zhou, Mario Suva
$1,000,000
June 2019

More than 1% of the world's population currently lives with an autoimmune disease. In individuals affected by these conditions, immune cells fail to distinguish between self and foreign antigens, leading to immune attacks on the body itself, with often devastating consequences. Intense efforts have been directed toward understanding the fundamental mechanisms underlying this abnormal immune response so that effective protective and therapeutic interventions can be developed for the nearly 100 known autoimmune diseases. Yet critical gaps remain in our understanding of autoimmunity, including the identification of all cell types involved. These deficiencies are reflected in the failures of recent clinical trials aimed at protecting those at risk of one of the most prevalent autoimmune diseases – type 1 diabetes (T1D). The goal of this project is to test the hypothesis that a previously unknown immune cell type – the X cell – plays a central role in driving autoimmunity and holds the key to future treatments. Investigators at Johns Hopkins University discovered X cells during their quest for rare pathogenic cells in T1D patients. The team found that these cells are a hybrid between T and B cells, the two known distinct arms of the adaptive immune system. The Johns Hopkins investigators, in collaboration with researchers from Des Moines, Columbia and Harvard Universities, aim to confirm the unique identity of X cells by characterizing the genes that are commonly and differentially expressed in X, B and T cells. They will also investigate the role of X cells in the pathogenesis of T1D, challenging the current dogma that T and B cells are the sole adaptive immune cells driving autoimmunity. It is expected that the information learned here would shed light on a possible wider role of X cells in other autoimmune diseases.

Texas A&M University
College Station, TX
Michael Golding, Tracy Clement, Ivan Ivanov
$900,000
June 2019

Clinical studies report that 75% of fetal alcohol spectrum disorder (FASD) children have biological fathers who were either heavy drinkers or chronic alcoholics. However, the role of male alcohol use in the development of fetal alcohol syndrome birth defects remains unexplored. This is largely due to the misconception that sperm do not transmit heritable information beyond the genetic code. Using a mouse model, investigators at Texas A&M University have linked preconception male alcohol use to fetal growth restriction, placental dysfunction, and long-term deficits in the metabolic health of the adult offspring. These phenotypes are similar to those

reported in children with FASD and reveal male alcohol use to be an unrecognized contributing factor in the development of alcohol-induced growth defects. Using state-of-the-art sequencing technologies, this project aims to define the epigenetic mechanisms by which alcohol-induced errors in developmental programming transmit to the offspring and determine how long these environmentally induced effects persist after the males stop drinking. Subsequently, the investigators will examine why the offspring of alcohol-exposed males become growth restricted. This proposal challenges the prevailing paradigm, which exclusively focuses on maternal alcohol exposures and examines a novel hypothesis that considers paternal contributions to FASD birth defects. This study will be among the first to explore the role of sperm-inherited alterations in epigenetic programming in the development of a pediatric disorder and will develop biomarkers of exposure that will offer the opportunity to significantly enhance the health of future pregnancies.

Tulane University
New Orleans, LA
James McLachlan, John McLachlan, Franck Mauvais-Jarvis
$1,000,000
June 2019

Across the animal kingdom, it is well-known that males and females exhibit different immune responses with females responding more robustly in nearly all cases. The reasons for this difference are not entirely understood. For females, this disparity may be beneficial in combatting infections, but can also be detrimental due to a greater incidence of many autoimmune diseases. A team of Tulane University investigators serendipitously discovered that males and females appear to have evolved the ability to trigger immunity differently in traditional (lymphoid) and non-traditional (non-lymphoid) organs throughout the body. To help decipher these responses, the team proposes to investigate how immune cells in these organs are differentially activated by a variety of challenges and how hormones and sex chromosomes regulate the unique differences of immune cells in these distinctive tissues. A better understanding of the contribution of lymphoid and non-lymphoid organs to alterations in immunity between sexes will provide a greater awareness of how these immune systems have evolved and will allow for improved precision when treating men and women for various diseases.

Vanderbilt University Medical Center
Nashville, TN
Kasey Vickers, MacRae Linton, Ryan Allen, Quanhu Sheng
$1,000,000
June 2019

As the leading cause of death worldwide, cardiovascular disease (CVD) affects one in three people. For decades, plasma cholesterol levels have been considered the leading risk factor for CVD, with low density lipoprotein-cholesterol (LDL-C) as the primary prevention target. But cholesterol is only part of the equation, as millions of individuals with clinically normal cholesterol levels, managed by statins, still have risk for CVD. This residual risk is likely conferred by vascular inflammation, which prompts a crucial question: what are the pro-inflammatory stimuli that drive the development of atherosclerosis? Cholesterol is the best-known cargo carried by circulating lipoproteins; however, researchers at Vanderbilt University Medical Center discovered that lipoproteins also transport small non-coding RNAs (sRNAs). Strikingly, the majority of sRNAs on lipoproteins are not human, but microbial, and originate from the host microbiome, diet or other environmental exposure to micro-organisms. The biological function of microbial sRNAs on lipoproteins is completely unknown. Could sRNAs be the previously unidentified inflammatory stimuli of atherosclerosis? Vanderbilt University Medical Center Investigators hypothesize that this previously unmeasurable cargo trafficked on LDL particles engages pro-inflammatory gene regulatory networks to drive atherosclerosis and other metabolic diseases with underlying inflammation. To test this hypothesis, the researchers will determine how lipoproteins acquire microbial sRNAs, define the biological relevance of microbial sRNAs on lipoproteins, and determine the underlying mechanisms of lipoprotein-mediated cross-kingdom gene regulation. The discoveries could redefine and disrupt long-held paradigms linking dyslipidemia and inflammation and establish a new field of study for lipoprotein function and extracellular RNA applicable to many chronic diseases.