- **Mark Kaplan, Ph.D.** – 2023 Awardee

“Inhibitors Targeting Peanut-Specific Allergies Specific IgE (sIgE) on the surface of mast cells and basophils. The diversity and complexity of allergen epitopes, and high-affinity of the sIgE–allergen interaction are roadblocks in the development of allergen-specific inhibitors of allergic responses. This study presents the design of food allergen-specific sIgE inhibitors termed covalent heterobivalent inhibitors (cHBIs) that selectively form covalent bonds to only sIgEs, thereby permanently inhibiting them. We have developed peanut-specific inhibitors that have demonstrated efficacy and specificity in blocking mast cell or basophil degranulation and anaphylaxis using in vitro assays, ex vivo samples from peanut-allergic patients, and humanized mouse models. The next critical steps in moving these inhibitors to testing in humans are to manufacture GMP/GLP inhibitors for testing (Aim 1) and to perform more detailed dosing and toxicity studies in non-

- **Jonathan Kurtis, M.D., Ph.D.** – 2023 Awardee

"APOPTOSIS-INDUCING ANTI-MALARIA DRUGS TARGETING PFGARP"

The overall aim of this application is to discover novel therapeutics for Plasmodium falciparum malaria. P. falciparum is a leading cause of morbidity and mortality in developing countries, infecting hundreds of millions of individuals and killing over 300,000 children each year. The spread of parasites resistant to the artemisinin family of compounds threatens recent progress achieved by antimalarial campaigns and underscores the urgent need to identify new antimalarial drugs. In previous work, we discovered PfGARP, a previously unrecognized vaccine candidate found only in P. falciparum.

The Scientific Premise of this application is that PfGARP is a high-value druggable target based on: 1) its surface expression on infected RBCs, 2) the absence of any signific(i)-7.1 (e)-16.4 (v)14 821 ( )0.6 (s) 2

- **Reshmi Parameswaran, Ph.D.** – 2023 Awardee

"Allogeneic "off the shelf" therapy for B cell malignancies using BAFF CAR-NK cells."

CAR-T immunotherapies have produced remarkable clinical responses, but several challenges remain: disease relapse due to antigen escape, serious side effects (Cytokine Release Syndrome/neurotoxicity) and long lead times with high manufacturing costs. To address these challenges, we developed B cell activating factor (BAFF) ligand-based CAR-NK cells to target three antigens expressed by B cell cancers: BCMA, TACI and BAFF-R. With three antigen targeting, we anticipate mitigating antigen escape. Under the Catalyst award, I developed 15 new BAFF CAR designs, optimized for NK cells, and selected the CAR construct exhibiting maximum tumor killing. Preliminary data demonstrates the BAFF CAR-NK cells efficiently kill B cell cancers and secrete significantly low amounts of cytokines compared to CAR-T cells. This is expected to minimize CRS in patients without compromising the tumor killing potential. NK cells from random donors can be used to generate BAFF CAR-NK cells, enabling an "off-the-shelf" product. Manufacturing costs are significantly reduced as patient cell harvesting is eliminated. Under the Transformational Award, I will perform IND enabling efficacy and safety studies with humanized mouse models

**Hermine Brunner, M.D., M.B.A., M.Sc.** – 2022 Awardee

"Lupus Nephritis Biomarkers for Introducing Personalized Therapies and Improving Clinical Trials"

---

Our objective is to bring much needed non-invasive predictive urine biomarkers, i.e., the Renal Activity Index in Lupus (RAIL) that reflect kidney inflammation and activity with lupus nephritis (LN), into the hands of clinicians, researchers, and industry to improve LN care. Funded by the FALK Catalyst award, a multiplex assay (RAIL-MPA) was developed using cutting-edge FirePlex® technology. We also developed a RAIL-MPA using Luminex®xMAP® technology.
Methods/Approach: Collaborating with pharmaceutical companies that provide clinical data and urine samples from LN clinical trials, we will pursue generation of Laboratory Developed Tests (LDT) for the RAIL-MPAs using (1) FirePlex® technology and (2) Luminex®xMAP® technology. We will disseminate information about the value of the RAIL-MPAs among stakeholders.
Expected Results/Deliverables:

**Jeannette Messer, D.V.M., Ph.D.** – 2022 Awardee

"Crafting New Weapons for the Fight Against Infectious Diseases"

Background: We have identified a conserved amino acid motif (CAMo-1) with an associated molecular feature in adherence proteins from a range of microbes. In our preliminary work, we identified this novel drug target and validated it experimentally by showing that a protein

**Lonnie Shea, Ph.D.** – 2022 Awardee

**Sarah Slavoff, Ph.D.** – 2022 Awardee

“Targeted degradation of a melanoma transcription factor”

Invasive melanoma kills thousands of Americans each year because nearly half of patients fail to respond to, become resistant to, or experience adverse events as a result of current treatments. Novel therapeutic strategies are therefore desperately needed. Innovative new technologies have enabled access to previously “undruggable” cancer-driver proteins, including the development of cell-

**Allan Brasier, M.D.** - 2021 Awardee

"Smart Nanoparticles Targeting the Myofibroblast Epigenome for First-In-Class Treatment of Idiopathic Pulmonary Fibrosis"

Idiopathic Pulmonary Fibrosis (IPF) affects over 3 M people. Triggered by smoke and other injuries, IPF is an unrelenting process of airway destruction and repair leading to death by asphyxiation within 3-4 years. No effective treatments are available. Here, structural changes are produced by bromodomain containing protein 4 (BRD4)-activated myofibroblasts that secrete extracellular matrix (ECM), such as fibronectin (FN). Advances from our Falk Ca Tw 0 -1.214 T1jeda[T2 a6noda[4 (a)7.2(6n)-7.8tNh deestidF)-6.2 dgg r a-actD0(59.106eTc 30.016 T

Chaitan Khosla,

**Takanori Takebe, M.D., Ph.D.** - 2021 Awardee

"Developing Human Liver Organoid Therapy"

The foundation of this proposal lies in the recognition that breakthrough discoveries cannot change the world if they never leave the laboratory. Our team's long-standing commitment to basic science research has enabled key discoveries in organ development and function, resulting in cutting-edge iPSC (induced pluripotent stem cell) technology and team science supporting the generation of human organoids from human stem cells.

Through the Catalyst Award using lab-scale manufacturing protocol, we demonstrate the remarkable therapeutic potential of human liver organoid (HLO) to rescue urea cycle disease in a rodent model, the most common inborn error of hepatic metabolism. The data highlights the immense transformative potential of HLOs that supports the overarching vision of ORGANOID therapy - life saving treatments and therapies that can exponentially increase the survival rate of people suffering from liver disease, especially infants. The first step towards this goal is to focus on IND-enabling studies for first-in-human use of iPSC-derived organoids to replace damaged and diseased liver (focused on an ornithine transcarbamylase deficiency, or OTCD). We will develop clinical-grade and large-scale manufacturing protocols and preclinically identify risk/benefit profiles of mass-produced HLO. This work will establish a preclinical proof-of-concept for cell therapy approach by bringing ORGANOID CURE concept, allowing us to extend the therapeutic potential to other pediatric liver disease conditions that currently have limited treatment options.

**Shirit Einav, M.D.** - 2020 Awardee

"Towards Predicting and Preventing the Development of Severe Dengue"

Dengue virus (DENV) is a threat to global and child health for which no effective vaccines or approved antivirals exist. 5-20% of symptomatic patients progress to severe dengue (SD), associated with morbidity and mortality. There are no accurate means to predict which patients will progress to SD. This project's goals are to: i. elucidate the cellular and molecular factors contributing to SD and decipher why children have worse disease outcome; ii. translate this knowledge into prognostic tools to identify patients at risk for progression to SD and countermeasures to prevent or treat SD.

We collected blood samples from 288 children and 163 adults prior to progression to SD in Colombia. Moreover, we developed a virus-inclusive, single-cell transcriptomic (viscRNA-seq) platform and a multi-cohort analysis to monitor host gene expression dynamics in the course of natural infection, while capturing tissue and real-

**Nicholas Leeper, M.D.** - 2020 Awardee

"Precision Nanotherapies for Cardiovascular Disease"

Atherosclerosis is the process underlying heart attack and stroke. Despite recent advances, atherosclerotic cardiovascular disease (CVD) remains the leading cause of death in the United States. Most current therapies are directed against cardiovascular risk factors (such as hypertension and elevated cholesterol). However, much of the population's risk of developing disease occurs independently of traditional risk factors. Therapies that directly target the plaque would instead address the root cause of disease and could fundamentally transform how CVD is treated.

A characteristic feature of the atherosclerotic plaque is the pathological accumulation of diseased and dying cells in the necrotic core. We discovered that this phenomenon is driven by the marked upregulation of a key 'don't eat me' molecule known as CD47. This renders vascular cells 'inedible' and resistant to 'efferocytosis' (programmed cell removal). We showed that systemic delivery of anti-CD47 antibodies (Ab) could reactivate efferocytosis within the lesion, thus reducing plaque size and inflammation. However, systemic antibody-based therapy also caused off-target clearance of red blood cells. This induces an anemia which represents a critical roadblock in the translation of our findings into the clinic.

Accordingly, we used the Falk Catalyst award to partner with experts in nanomedicine, bioengineering, and immune cell biology during to develop a 'precision' nanoparticle that could specifically target the diseased blood vessel. We generated an exciting new 'Trojan horse' therapy that homed to the inflamed macrophage, reactivated phagocytosis in the plaque, and potently prevented atherosclerosis without any off-target toxicity in mouse models.

Having achieved each of the milestones set forth in our Catalyst application, we now have the broad, long-term objective of fully translating these insights from bench-to-bedside. During the Transformational phase, we aim to test whether our nanoparticle retains its exquisite cell-specificity in explanted human arteries (Specific Aim 1- human), and validate its safety and efficacy in a large animal model of established CVD (Specific Aim 2– pig). Building upon robust preliminary data, we believe these final proof-of-principle studies will

**Anita Shukla, Ph.D.** - 2020 Awardee

"Advancing Bacteria-Triggered Hydrogel Therapeutics to Combat Antibiotic Resistance"

Antibiotic resistance is a global public health threat. With the lack of government and private

**Mark Kay, M.D., Ph.D.** - 2019 Awardee

“Enhanced rAAV Mediated Genome Editing Using Ribonucleotide Reductase Inhibitors”

The goal is to safely co-deliver an FDA approved ribonucleotide(RNR) reductase small

**Ari Melnick, M.D.** - 2019 Awardee

"SIRT3 Targeted Therapy for B-Cell Lymphomas"

Our goal is to develop curative therapeutic regimens for the most aggressive forms of B-cell lymphoma, without unacceptable toxicity and in a manner that is widely applicable to patients regardless of access to the highest complexity health care. We propose that SIRT3 targeted therapy is important step to achieve this goal. Our preliminary data show that i) [illegible] maintain their

**Xin Qi, Ph.D.** - 2019 Awardee

"Enhancers of Mitochondrial Function as Candidate Therapeutics for Huntington's Disease"

Mitochondrial dysfunction is an early prominent feature in patients with neurodegenerative diseases such as Alzheimer's (AD), Parkinson's (PD) and Huntington's disease (HD). Significantly, we recently reported in vitro and in vivo proof of concept that suppression of mitochondrial impairment is therapeutically effective in various models of these diseases. We used rationally designed peptides to demonstrate that improving either impaired mitochondrial dynamics or aberrant mitophagy was protective both in neurons derived from patient induced pluripotent stem cells (iPSCs) and in mouse models of these diseases, in particular HD. Because peptides often face challenges during drug development, we identified small molecules, including CHIR99021, that increase mit

**Markus Müschen, M.D., Ph.D.** - 2018 Awardee

"CD25 as a Therapeutic Target in Refractory B-cell Malignancies"

Studying gene expression and clinical outcome data from 136 clinical trials for patients with

**Harikrishna Nakshatri, Ph.D., B.V.Sc.** - 2018 Awardee

"The Effect of Extra Physiologic Oxygen Shock/Stress (EPHOSS) on Cancer Stem cell and Drug Sensitivity Measurements"

Preclinical studies of primary cancer cells are done after cells are removed from patients or animals at ambient atmospheric oxygen ($O_2$, ~21%) yet, $O_2$ concentrations in organs are in the ~3-10% range, with most tumors in hypoxic environment in vivo. While effects of $O_2$ tension on tumor cell characteristics in vitro have been studied, typically at 1% $O_2$, it is only after the cells were first collected in ambient air. Dr. Broxmeyer's lab showed that hematopoietic stem cells exposed to ambient air within minutes undergo irreversible differentiation through a phenomenon termed extra physiologic oxygen shock/stress (EPHOSS). Studies conducted during our catalyst award collaboratively by Drs. Broxmeyer and Nakshatri showed that EPHOSS affects cancer stem cell differentiation through diminished expression of stemness-