HEALTH RESOURCES IN ACTION

Falk Catalyst Awardees

Christin Burd Ph.D. – 2025 Awardee

Associate Professor of Molecular Genetics and Cancer Biology and Genetics, The Ohio State University

"Repurposing precision medicine to prevent melanoma onset and recurrence"

Each year, thousands of Americans are diagnosed with early-stage melanoma, and more than $3 billion is spent on biopsies to detect the disease. While early detection and surgical excision are often curative, over 10% of patients with thicker melanomas experience local recurrence.

This project aims to develop a non-invasive, topical therapy to prevent the onset and recurrence of early-stage melanoma. Target populations include children with giant congenital moles, individuals with over 50 moles, and survivors of early-stage melanoma. Our approach involves repurposing oral pan-RAF inhibitors for topical application in patients with high-risk moles or previously resected melanoma. By applying the drug topically, we aim to achieve higher local concentrations while minimizing systemic toxicity. We propose two specific aims to advance this goal:

Aim 1. Determine if the short-term application of topical pan-RAF inhibitors prevents melanoma.

Aim 2. Evaluate the effect of adjuvant pan-RAF inhibitors on melanoma recurrence.

Through these aims, we will achieve several key milestones. These include developing topical pan-RAF inhibitors, determining the maximum tolerated dose, and evaluating preventative efficacy in genetically and environmentally relevant mouse models of melanoma. Our results will provide proof-of-principle for a new drug indication and support early-phase clinical trials during the project's transformational phase.

Jianguo Cheng M.D., Ph.D. – 2025 Awardee

Professor of Anesthesiology, Cleveland Clinic Lerner Research Institute

"Development of AFA-281, a First-in-Class Dual Inhibitor of Cav3 and Soluble Epoxide Hydrolase for the Treatment of Complex Regional Pain Syndrome (CRPS)"

The long-term objective of this project is to develop and clinically validate AFA-281, a novel, first-in-class dual inhibitor of T-type calcium channels (Cav3) and soluble epoxide hydrolase (sEH), as a safe, non-opioid therapy for Complex Regional Pain Syndrome (CRPS), a highly debilitating and treatment-resistant chronic pain condition. The project's specific aims are: (1) to Evaluate the Therapeutic Efficacy and Dose-Response Profile of AFA-281 in Validated Rodent Models of CRPS; (2) to Identify Neuroimmune Biomarker Changes Induced by AFA-281 through molecular, flow cytometric, and transcriptomic analyses; and (3) to Complete Preclinical Development and Prepare for Phase II Clinical Trials. The research design includes multi-dose administration of AFA-281 and inclusion of placebo controls and positive controls in rodent models of CRPS type I and type II followed by behavioral assessments, molecular profiling of the spinal cord, dorsal root ganglia, sciatic nerve, and plasma, and biomarker discovery through RNA sequencing and immunohistochemistry. With existing IND status and strong safety data from Phase I trials, the study is positioned to advance AFA-281 rapidly into clinical evaluation. This project supports transformative non-opioid therapies for CRPS and has strong translational and commercialization potential, including biomarker-driven patient stratification strategies.

Jose Debes M.D., Ph.D. – 2025 Awardee

Associate Professor of Medicine, University of Minnesota

"Assessment of Sounds Waves Via Artificial Intelligence as a Biomarker to Detect Early Stage Liver Cancer"

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide. HCC mortality occurs primarily due to late detection. Here we propose to assess sound waves of the main liver vessels through Doppler ultrasonography, to detect changes that can differentiate livers with HCC from those with no HCC. Our aims are to 1-assess the role of Doppler ultrasonography sound waves analyzed via AI in differentiating livers with cancer versus controls; and 2-to determine the efficacy of Doppler ultrasonography applicable to mobile phones in detecting HCC in resource-limited settings in a separate validation cohort.

We will first optimize the algorithm through expansion, flexibility improvement, robustness and fine-grained analysis, and later collaborate with our partners at Federal University of Porto Alegre (UFCSPA) in Brazil to apply the AI algorithm and determine its applicability in resource-limited regions. Our approach of assessing "sound waves" via AI using mobile-phone ultrasound devices is a first of a kind and completely innovative. This will remove the limitation of "operator experience" and standardize the detection of HCC for curative intervention.

Alexis Demonbreun Ph.D. – 2025 Awardee

Associate Professor of Pharmacology, Northwestern University

"Anti-LTBP4 Antibodies for the Treatment of Cardiac Fibrosis"

Cardiac fibrosis, or scarring of the heart muscle, develops after acute infarction or in chronic cardiomyopathy. Cardiac fibrosis impairs heart function, causing heart failure, and increasing risk for cardiac arrhythmias and sudden cardiac death. Cardiac fibrosis is defined by excessive deposition of extracellular matrix (ECM) proteins in the heart, especially collagen and other transforming growth factor-beta (TGF-β) scaffolding proteins. The principal goal of this project is to develop biologic therapeutics to mitigate acute and chronic cardiac fibrosis, by limiting the activation of TGF-β.

TGF-β is major driver of cardiac fibrosis, as its expression and activity are central to promoting fibrosis in many acute and chronic conditions. Latent TGF-β Binding Protein 4 (LTBP4) is an ECM protein that restricts TGF-β activation by sequestering latent TGF-β in an inactive state. In cardiac fibrosis, excess ECM protease activity cleaves LTBP4, triggering the first step of TGF-β activation and resulting fibrosis. We used genomewide signals to uncover LTBP4's mechanism, and applied this information to develop blocking antibodies that stabilize the LTBP4 latent TGF-β complex, reducing active TGF-β and fibrosis in skeletal muscle.

Under this award, we will develop the necessary preclinical data to support anti-LTBP4 antibody for the treatment of cardiac fibrosis.

John Erickson M.D., Ph.D. – 2025 Awardee

Assistant Professor of Pediatrics, Cincinnati Children's Hospital Medical Center

"Antibody sialic acid acetylation controls autoimmune arthritis"

Aberrant production of self-reactive antibodies contributes to numerous autoimmune diseases. Yet, some individuals with autoantibodies do not go on to develop symptoms. We hypothesize that one reason for this discordance is that subtle molecular changes to autoantibodies alter their ability to modulate disease. Autoantibodies in mice with collagen-induced arthritis (CIA) and humans with rheumatoid arthritis (RA) are highly sialylated on IgG Fab-region N-glycans. We have previously shown in infection models that this Fab sialic acid (Sia) can be modified by acetylation (Ac-Sia). A key gap in knowledge is whether autoantibodies also possess Fab Ac-Sia and how it modulates disease progression. Our overarching hypothesis is that arthritogenic autoantibody Fab Ac-Sia disrupts disease progression. Aim 1 will experimentally interogate how autoantibody Fab Ac-Sia modulates disease using the CIA mouse model. We will utilize transgenic mice to manipulate Sia acetylation and downstream immune modulators. Aim 2 will determine the prevalence and significance of autoantibody Ac-Sia in patients with RA. By comparing Ac-Sia levels on autoantibodies in people who do or do not go on to develop RA, we will test whether Ac-Sia predicts disease onset. These studies will establish Fab Ac-Sia as a prognostic biomarker and therapeutic target in autoimmune arthritis.

Colin Franz M.D., Ph.D. – 2025 Awardee

Associate Professor of Physical Medicine and Rehabilitation, Rehabilitation Institute of Chicago

"Rapid Restoration of Diaphragm Function: Enhancing Nerve Transfer Surgery with Axonal Fusion Technology"

High cervical spinal cord injury (SCI) often causes permanent diaphragm paralysis, leaving individuals dependent on invasive mechanical ventilation with no proven intervention to restore natural breathing. This project targets a critical barrier to recovery: the inherently slow and inefficient process of axonal regeneration following nerve transfer surgery. Our goal is to dramatically accelerate diaphragm reinnervation by integrating a novel axon fusion technology—NTX-001 (PEG-fusion)—into Spinal Accessory to Phrenic nerve (SAN →PhN) transfer, a promising surgical approach.

Unlike traditional nerve repair, which relies on donor axons regrowing over months to years, PEG-fusion directly fuses the membranes of severed axons, reestablishing continuity within minutes and preserving the distal nerve environment. We propose two specific aims: (1) determine the functional benefits of PEG-fusion in accelerating diaphragm restoration in a rat (SAN →PhN) model, and (2) assess long-term respiratory and electrophysiological outcomes. Diaphragm function will be evaluated using ultrasound, electromyography, transdiaphragmatic pressure, and neuromuscular junction analysis.

This project represents a high-reward opportunity to establish a new paradigm for early diaphragm reinnervation and ventilator liberation. Supported by a partnership with Neuraptive Therapeutics and leveraging NTX-001's FDA Fast Track Designation, the work will lay essential groundwork for a first-in-human clinical trial.

Jarrod French Ph.D. – 2025 Awardee

Associate Professor of Nucleotide Metabolism & Drug Discovery, University of Minnesota

"Drug Repurposing for a Host-Directed Treatment for Systemic Bacteremia."

The long term goal of our research program is to develop broad spectrum, host-directed therapeutics to treat deadly infections. In prior work, we demonstrated that a novel immune checkpoint, Suppressor of T Cell Signaling (Sts), acts as a negative regulator of immune signaling. Genetic inactivation of Sts potentiates the immune response and increases survival in animal models of infection without causing damaging inflammation. Rebamipide, a known therapeutic which has been used safely in Asia for several decades to treat gastritis, is a selective and potent inhibitor of Sts. We recently demonstrated that a liposomal reformulation of rebamipide can inhibit Sts in vivo, increasing the survival and rate of pathogen clearance in a mouse model of S. aureus bacteremia. The objectives of the proposed studies are to determine an optimized, shelf-stable formulation and dose of rebamipide that maximizes efficacy. Specific milestones include the demonstration of a statistically significant improvement in mean survival and accelerated bacterial clearance in infected organs, in the absence of a deleterious inflammatory response. This works forms the foundation for future IND-enabling studies and first-in-human clinical trials.

Michael Girardi M.D. – 2025 Awardee

Professor and Vice Chair of Dermatology, Yale University

"Lead Optimization of an Anti-V β 2 Antibody Drug Conjugate for T Cell Leukemias and Lymphomas"

T cell leukemias and lymphomas are some of the most aggressive and difficult-to-treat cancers. We propose targeting V β 2, a T cell receptor variant expressed in malignant T cells, as a therapy that would avoid the severe immune suppression caused by other T cell approaches. Leveraging preliminary studies demonstrating efficacy of our anti-V β 2 antibodies in cell culture and in mouse models, our aims include: 1) creating a minimally toxic, highly V β 2-specific antibody drug conjugate (ADC) with low immunogenicity, 2) confirming selective target expression and efficacy in cancer tissue, 3) demonstrating conjugate synthesis, safety testing, and functional validation, and 4) planning for CMC and regulatory strategy to enable IND submission. Accomplishing these aims will enable IND qualifying studies in advance of an investigator-initiated clinical trial. We will use patient-derived malignant cells, xenografts models and a range of analytical techniques including in vivo imaging, RNA in situ hybridization, specificity and stability screening, and flow cytometry. This project aims to overcome critical barriers to ADC development, optimizing the therapeutic window and stability to facilitate progression from preclinical research to clinical application. Successful outcomes will advance this ADC and enable the development of further anti-V β agents, transforming treatment options for T cell malignancies.

Lori Isom Ph.D. – 2025 Awardee

Maurice H Seevers Collegiate Professor of Pharmacology, University of Michigan

"Neuro-Cardiac Mechanisms of Sudden Unexpected Death in Epilepsy (SUDEP)"

The goal of this proposal is to use our novel transgenic rabbit model to test the hypothesis that cardiac and respiratory arrhythmias, in addition to seizures, contribute to the mechanism of SUDEP in Dravet syndrome (DS). This work will allow, for the first time, simultaneous study of the impact of Scn1a haploinsufficiency on brain, brainstem respiratory and cardiac centers, and cardiac physiology using an in vivo model that is more closely related to humans than are mice. This work will also test a newly developed gene-modifying ASO therapy for DS from Stoke Therapeutics, currently entering phase 3 clinical trials, for effects on brainstem respiratory and cardiac centers. This high-risk, high-reward project addresses critical scientific and therapeutic roadblocks presented by intractable developmental and epileptic encephalopathies (DEEs). If successful, our work will have high impact outcomes that open new avenues for treating, curing, and improving the lives of individuals suffering from DS and related DEEs. This work addresses all three principal areas of focus of the Falk Medical Research Trust:

1. Identification of biological markers of SUDEP,

2. Identification of targets for therapeutic intervention in the brainstem and heart,

3. Development of gene-modifying therapeutic agents to disrupt and prevent SUDEP.

Andrea Kasinski Ph.D. – 2025 Awardee

Professor of Biological Sciences, Purdue University

“From MicroRNA Biology to Clinical Breakthroughs: Advancing MicroRNAs as Anti-cancer Agents”

This project aims to develop and translate a first-in-class, tumor-targeted microRNA (miRNA) therapeutic, FM-FolamiR-34a, for the treatment of triple-negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC). The long-term goal is to overcome the historical barriers of RNA-based cancer therapeutics – namely instability, poor intracellular delivery, and off-target toxicity – by combining a fully chemically modified miR-34a with folate-mediated tumor targeting. miR-34a is a potent tumor suppressor that silences key oncogenic drivers (e.g., MYC, MET, CDK4/6, PD-L1), many of which are validated drug targets in TNBC and NSCLC.

FM-FolamiR-34a achieves a >400-fold improvement in stability and demonstrates potent, selective gene silencing in preclinical models. Folate conjugation enables selective delivery to folate receptor-positive tumors, which represent ~80% of TNBCs and NSCLCs. Preclinical efficacy studies show significant tumor regression and complete cures in xenograft models. The project has two specific aims: (1) refine miR-34a chemistry to enhance pharmacological properties; (2) benchmark FM-FolamiR-34a against standard-of-care therapies in mouse xenografts, genetically engineered mice, and PDX models.

This work will establish a novel therapeutic platform for miRNA-based cancer therapy, with FM-FolamiR-34a as the lead candidate. The successful completion of this project will enable clinical entry and redefine RNA-based therapeutics for aggressive, treatment-resistant cancers.

Irida Kastrati Ph.D. – 2025 Awardee

Assistant Professor in Cancer Biology, Loyola University of Chicago

"Preclinical evaluation of first-in-class thioredoxin reductase inhibitors for triple negative breast cancer therapy."

Triple-negative breast cancer (TNBC) is an aggressive, highly recurrent subtype lacking targeted therapies and is associated with poor prognosis. Our prior studies identified thioredoxin reductases (TXNRD1 and TXNRD2), major enzymes in redox homeostasis, as critical mediators of TNBC progression. These enzymes are upregulated in TNBC and correlate with poor patient outcomes, revealing a targetable vulnerability.

We propose a novel therapeutic strategy using first-in-class non-covalent TXNRD inhibitors (TXNRD(i)s), developed following the discovery of a unique regulatory "doorstop" pocket in a TXNRD-like enzyme. Designed and synthesized by medicinal chemist Dr. Pavel Petukhov, these inhibitors were evaluated with breast cancer biologist Dr. Irida Kastrati and showed selective anti-cancer activity in TNBC models while sparing normal breast epithelial cells.

Aim 1 will test ~40 next-generation TXNRD(i)s for potency, specificity, and safety in vitro and in healthy mice.

Aim 2 will assess anti-tumor efficacy in xenograft and syngeneic TNBC models, along with pharmacodynamic validation of TXNRD targeting.

This multidisciplinary approach leverages innovative chemical tools and mechanistic insights to address a major unmet need in TNBC therapy. The project has strong potential to advance TXNRD(i)s toward clinical development and may extend to other TXNRD-dependent malignancies.

Jin-Moo Lee M.D., Ph.D. – 2025 Awardee

Chair, Department of Neurology, Washington University in St. Louis

"Neuromodulation Using Vagus Nerve Stimulation Following Ischemic Stroke as Therapeutic Adjunct (NUVISTA) 2"

Stroke is a leading cause of death and disability worldwide. Neuroinflammation has long been recognized as an important contributor to ischemic brain injury. Acute ischemic stroke (AIS) induces pro-inflammatory cytokines which are associated with worse outcomes. The inability to effectively mitigate the inflammatory response limits our ability to reduce disability in these patients. Thus, there is critical need for novel, noninvasive, and easily accessible approaches to modulate inflammation that can be safely and rapidly deployed. Transcutaneous auricular vagus nerve stimulation (taVNS) fills this gap, suppressing the inflammatory response following AIS. In a previous pilot trial, NUVISTA-1, we found that taVNS safely reduced plasma IL-6 and other pro-inflammatory cytokines, associated with improved clinical outcomes. In this grant, we propose to randomize AIS patients to treatment with sham vs. taVNS with two aims: 1. use single-cell RNAseq from blood to identify cellular transcriptomes induced by taVNS, to elucidate anti-inflammatory mechanisms; and 2. to measure blood biomarkers of brain injury to assess early signs of efficacy of taVNS. This study will provide a go/no-go decision to proceed with a pivotal clinical trial of taVNS vs. sham for the treatment of AIS.

Aline Martin M.S., Ph.D. – 2025 Awardee

Associate Professor of Medicine, Northwestern University

"Bone Targeted Therapy for Chronic Kidney Disease – Mineral Bone Disorder (CKD-MBD)"

There is an urgent need to improve skeletal outcomes in chronic kidney disease (CKD). Virtually all 700 million patients with CKD experience severe bone loss and fracture in their lifetime. Unfortunately, therapies for post-menopausal osteoporosis fail in CKD due to different pathogenic mechanisms; the result: a 100-fold higher fracture risk, significant costs and higher mortality.

Our team is composed of worldwide leaders investigating CKD-specific mechanisms of altered bone and mineral metabolism. We successfully identified and validated dentin matrix protein 1 (DMP1) as a unique target to improve the differentiation of bone forming cells and mineralization in CKD. DMP1 would be the first drug that targets the bone and shows efficacy in CKD-associated bone disorders. In this project, we propose to 1/ test the efficacy of humanized DMP1 derivates on the production of a key circulating marker of altered bone and mineral metabolism, fibroblast growth factor 23 (FGF23), 2/ engineer DMP1 derivates of extended half-life, and 3/ validate their efficacy on bone and FGF23 against mouse DMP1 in vivo. In the longer term, the best DMP1 derivate will be tested in a phased clinical trial initially targeting patients with CKD on dialysis and expanding to patients with earlier stages of CKD.

Jeffrey Millman B.Sc., Ph.D. – 2025 Awardee

Professor of Medicine, Washington University in St. Louis

"Scalable Bioreactor-Based Production of Stem Cell–Derived Islets for Type 1 Diabetes Cell Replacement Therapy"

Type 1 diabetes (T1D) arises from autoimmune destruction of pancreatic ? cells, resulting in lifelong insulin dependence and serious complications. While stem cell-derived islets (SC-islets) offer a curative alternative, their clinical implementation is limited by poor scalability, reliance on animal-derived reagents, lack of current Good Manufacturing Process (cGMP)-compatible protocols, and the need for immunosuppression. This project aims to overcome these barriers by developing a fully defined, scalable, and hypoimmune SC-islet product using the UDC-001 cGMP-grade human induced pluripotent stem cell (hiPSC) line engineered to evade immune rejection. The specific aims are to (1) optimize a six-stage differentiation protocol using xeno-free, clinically qualified reagents to generate high-purity SC-islets; (2) implement scalable manufacturing using hybrid multilayer and perfusion bioreactor systems with cryopreservation and cold-chain shipment; and (3) rigorously characterize the identity, function, and safety of SC-islets using single-nucleus multiomics, insulin secretion assays, and long-term in vivo efficacy testing in diabetic mice. Benchmarks include generation of >10? cells per batch, >25% ? cell composition, insulin secretion >1 μIU/10^3 cells, and diabetes reversal in >80% of transplanted mice. Completion of this work will produce an IND-enabling SC-islet product for first-in-human trials and provide a scalable blueprint for regenerative therapies in T1D and beyond.

Eric Morrow M.D., Ph.D. – 2025 Awardee

Professor of Biology and Psychiatry, Brown University

"Development of First-In-Class Gene Therapy for Christianson Syndrome"

Christianson Syndrome (CS) is a childhood neurological disorder caused by loss-of-function mutations in the endosomal Na /H Exchanger 6 (NHE6). CS is among the most common X-linked developmental brain disorders and is characterized by intellectual disability, epilepsy, autism, non-verbal status, motor abnormalities, and neurodegeneration. As there are currently no treatments for CS, our long-term objective is to develop an effective gene therapy to treat CS patients. Using our unique CS rat model that strongly recapitulates several core CS symptoms, we are optimizing an adeno-associated virus (AAV)-based gene therapy strategy in vivo. Our preliminary data support the feasibility of using AAV9-based gene therapy to deliver NHE6 for both long-term NHE6 brain expression and amelioration of motor dysfunction in our CS rat model. This proposal will identify the lead AAV9 vectors, routes of administration and dosages for the broadest NHE6 brain expression and improvement of motor functioning in our CS rat model (Aim 1). We will also define the long-term functional efficacy of our lead AAV9 vectors for amelioration of epilepsy-related, learning and memory, and neuropathologic outcome measures in CS rats (Aim 2). These studies are designed to advance a promising CS treatment towards first-in-human clinical trials.

Tingwei Mu Ph.D. – 2025 Awardee

Associate Professor of Physiology and Biophysics, Case Western Reserve University

"A Pharmacological Chaperoning Strategy to Treat Genetic Epilepsy"

Recent advances in genetics have identified numerous genes associated with epilepsy, among which those encoding gamma-aminobutyric acid type A (GABAA) receptors, the primary inhibitory neurotransmitter-gated ion channels in the human brain, are prominently indicated. Despite the development of numerous anti-seizure drugs, about one-third of epilepsy patients are resistant to current drug treatment, often leading to severe developmental and epileptic encephalopathy. We and other groups have revealed that proteostasis deficiency resulting from protein misfolding and inefficient surface trafficking of GABAA receptor variants is the major disease-causing mechanism for their loss of function. Recently, our cell-based screenings have identified small-molecule pharmacological chaperones that bind GABAA receptors to restore the surface trafficking and function of multiple pathogenic variants. Therefore, we hypothesized that GABAA receptor-specific pharmacological chaperones can correct the proteostasis deficiency of pathogenic GABAA receptor variants to enhance their surface trafficking and thus function, as a novel therapeutic strategy to treat genetic epilepsies. Here, we aim to optimize the potency, efficacy, and drug properties of our pharmacological chaperone hits using pharmacological and cellular approaches for the correction of GABAA variant function. Our milestone is to identify at least two preclinical small-molecule candidates for future in vivo testing.

Mark Pagel Ph.D. – 2025 Awardee

Professor of Medical Physics and Radiology, University of Wisconsin-Madison

"Improving the diagnoses of breast cancer by imaging oxygenation and vascular perfusion using Optoacoustic Imaging"

Our research will perform clinical translation of Oxygen Sensitive – Dynamic Contrast Enhanced Optoacoustic Imaging (OS-DCE OAI). This imaging method can evaluate oxygenation and vascular perfusion in tissues as deep as 4 cm from the body surface. OS OAI is already FDA-approved for imaging subjects who may have breast cancer, demonstrating that clinical OAI is feasible and the 4 cm depth of view can image >90% of breast tumors.

We have invented a DCE OAI analysis method that can image vascular perfusion in a way that avoids variable light scattering and absorbance in tissues, which is a key innovation of our research. We have developed a combined OS-DCE OAI protocol for imaging oxygenation and vascular perfusion in small animal models of cancer and wounds. We will translate our OS-DCE OAI method to the radiology clinic for improving the diagnosis of malignant breast tumors that are hypoxic and angiogenic relative to benign breast tumors and non-tumor breast lesions. We will then perform clinical studies with OS-DCE OAI vs. DCE MRI. Our benchmarks for success are to demonstrate that DCE OAI should replace DCE MRI for breast cancer diagnoses, and that OS-DCE OAI provides multiparametric information that improves breast cancer diagnoses.

Peter Tessier Ph.D. – 2025 Awardee

Albert M. Mattocks Professor of Pharmaceutical Sciences and Chemical Engineering, University of Michigan

“Peripherally-administered Antibody-C9orf72 ASO Conjugates for Improved CNS Delivery and Therapeutic Index”

A GGGGCC tandem repeat expansion in C9orf72 is the most common genetic cause of Amyotrophic Lateral Sclerosis (ALS). The use of antisense oligonucleotides (ASOs) for reducing CNS gene expression of C9orf72 repeats is limited by three challenges: i) insufficient delivery to the CNS after intrathecal administration; ii) neuroinflammation and dose-limiting toxicity, and iii) lack of targeting of both sense and anti-sense RNAs. These challenges likely contributed to the failure of the first C9orf72 ASO clinical trials and will continue to plague the ALS field unless they can be overcome. We have developed a bispecific antibody-ASO conjugate technology, which we posit will i) improve CNS delivery and biodistribution of C9orf72 ASOs; ii) reduce the required ASO dose for achieving large reductions in gene expression; and iii) improve the feasibility of targeting both sense and anti-sense RNAs. Therefore, in Aim 1, we will optimize bispecific antibody-ASO conjugate dosing for maximal C9orf72 gene silencing in humanized C9orf72 mice. Then, in Aim 2, we will evaluate the efficacy of bispecific antibody-ASO conjugates for reducing pathology in humanized C9orf72 mice. Our work is expected to improve the efficient modulation of gene expression needed for treating ALS and other neurodegenerative disorders.

William Thiel Ph.D. – 2025 Awardee

Associate Professor, University of Iowa

"Advancing Precision Medicine for Vascular Health: Targeting VSMC Growth with Cell-Specific Aptamers"

Coronary heart disease afflicts more than 18 million Americans. Current treatment options such as drug-eluting stents (DES) and coronary artery bypass grafting (CABG) are limited due to vascular smooth muscle cell (VSMC) growth causing neointimal hyperplasia, the thickening of the blood vessels. Existing options to mitigate neointimal hyperplasia impair reendo-thelialization and increase the risk of life-threatening thrombosis. Our goal is to address this problem by developing and validating an aptamer-based molecular delivery mechanism of growth-suppressing agents (such as everolimus or an anti-proliferative siRNA) precisely to VSMCs without impacting endothelial cells.

As proof-of-concept, we have developed VSMC-specific aptamers that inhibit VSMC migration and neointimal hyperplasia in both murine and pig models of vascular injury. Further work has led to aptamers with improved safety, human specificity, and intracellular therapeutics delivery. We propose to advance this lie of research, among others, by incorporating machine learning models of VSMC aptamer specificity across multiple patient disease states and VSMC subtypes and design aptamers that are precisely tuned to the aforementioned contexts.

The precise aptamer-based delivery technology will significantly improve the treatment of various vascular conditions, including atherosclerosis, aortic aneurism, and pulmonary hypertension for enhanced long-term patient health and survival.

Andre Bachmann Ph.D., M.Sc. – 2024 Awardee

Professor of Pediatrics, Michigan State University

"Development of New ODC Inhibitors to Treat Neuroblastoma, a Childhood Cancer"

Neuroblastoma (NB) is the most common extracranial solid tumor in children, with frequent relapse and poor survival rates (<50%) despite the use of multi-modal, high-dose chemotherapies.

ODC inhibitors are attractive new agents that block polyamines. DFMO, the only ODC inhibitor in the clinic, was FDA approved in 2023 for relapse prevention of NB. However, DFMO is not suitable for the treatment of aggressively proliferating tumors, due to low cytotoxic potency, short half-life, and rapid renal clearance, traits requiring frequent high drug dosing during therapy. We have optimized a new series of ODC inhibitor analogs, all structurally related to 44544, that inhibit ODC through a novel mechanism rendering them significantly more potent than DFMO, in vitro and in NB culture models. The goal of this proposal is to further optimize 44544 to generate robust proof-of-concept in vivo PK/PD and tumor efficacy data.To fulfill these goals, we will: Aim 1. Define structure-activity relationships (SAR) and further optimize activity of 44544 series. Aim 2. Conduct integrated SAR, cytotoxicity, and in vitro ADME to prioritize analogs for in vivo efficacy studies. Aim 3. Demonstrate mouse PK/PD, in vivo toxicity, and proof-of-concept efficacy of 44544 series against NB using 3 preclinical tumor mouse models.

Sara Hamilton Hart Ph.D. – 2024 Awardee

Associate Professor, University of Minnesota

"Developing IL-15 as a Malaria Vaccine Therapeutic"

Malaria, which is caused by Plasmodium parasites, remains a major global public health problem with >600,000 deaths annually worldwide. With growing antimalarial drug and insecticide resistance, highly effective and durable vaccines are urgently needed. Vaccine-induced antibodies can protect against clinical malaria disease, but liver tissue resident memory T (Trm) cells will be required for robust and durable (long-lasting) protective immunity. Whole Plasmodium sporozoite vaccines generate liver Trm cells, but financial and technical barriers prevent the number of doses needed worldwide. Using a mouse model of whole sporozoite vaccination, we identified an immune-based therapeutic – IL-15 complex – that boosts Trm cell formation and function as well as antibody production. We will define the impact of IL-15 complex on Trm cells during Plasmodium vaccination in mice (Aim 1). We will determine if IL-15 complex enhances Plasmodium vaccine efficacy in mice following sporozoite challenge (Aim 2). We will utilize a novel mouse model whereby mice are reared in the presence of natural microbial exposure, resulting in a more physiologically relevant model to investigate Plasmodium vaccination and IL-15 therapy (Aim 3). These data will inform the rational design of cutting-edge immunomodulatory strategies to improve immunization against malaria and other infections and cancer.

Jesse Hoffmeister Ph.D.– 2024 Awardee

Associate Professor, University of Minnesota

“Development of Physiologically Based Measures of Disease Severity in Adductor Laryngeal Dystonia.”

Adductor Laryngeal Dystonia (AdLD) is a disorder in which laryngeal spasms cause voice disruption, limiting the ability to communicate and degrading quality of life. There is no cure, and AdLD is symptomatically treated with injection of botulinum neurotoxin (BTX) into the larynx every 3-4 months for life. Side effects include weak voice and difficulty swallowing. A challenge to developing alternative treatments is that current assessment tools are subjective and/or have limited correlation with patient-reported measures in AdLD. This suggests important physical correlates of symptom severity go undetected and untreated. Current measures are also not specific to AdLD, resulting in average diagnostic delays of >5 years. There is thus a critical need for 1) sensitive and specific measures of disease severity to monitor treatment response, and 2) tools for objective diagnosis. We propose to meet this need by testing a novel application of high resolution manometry (HRM): measurement of upper esophageal sphincter (UES) pressure during speech to 1) quantify spasm severity and 2) determine the specificity of this measure to AdLD. Completion of this proposal will remove roadblocks that have prevented identification and vetting of potential novel treatments for AdLD.

Saad Kenderian M.D. 2024 Awardee

Assistant Professor of Medicine, Oncology, and Immunology, Mayo Clinic

"CD19-targeted chimeric antigen receptor-engineered mesenchymal stromal cells (CAR-MSC19) in systemic lupus erythematosus (SLE)."

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease mediated by pathogenic B cells. Mesenchymal stromal cells (MSCs) have regenerative, immunosuppressive properties, but adoptive therapy of unmodified MSCs has yielded mixed clinical results in SLE. CD19-targeted chimeric antigen receptor T cell (CART19) therapy for severe SLE led to disease remission and offers hope for durable disease control. However, CART19 often results in severe toxicities, requires lymphodepleting chemotherapy, and has a long manufacturing lead time. We have recently published the application of CAR technology to MSC therapies to enhance trafficking and immunosuppressive properties. Like CART19, CAR-MSC19 is a targeted therapy which specifically suppresses B cells. However, CAR-MSC19 offers the potential of being minimally toxic, off-the-shelf, and requires no conditioning regimens. This has led to our central hypothesis that CAR-MSC19 therapy is safe and shows increased therapeutic efficacy in SLE. We will test this hypothesis in two specific aims. In aim 1, we will test the efficacy of CAR-MSC19 in murine models of SLE, and in aim 2, we will study the safety of CAR-MSC19 in preclinical models of CAR-associated toxicities. The overall goal of this project is to develop CAR-MSC19 as an independent novel cellular therapeutic option in patients with SLE.

Francis McCormack, M.D.- 2024 Awardee

Professor Gordon and Helen Hughes Taylor Chair Internal Medicine, University of Cincinnati

"An Improved Method of Pleurodesis"

Our goal is to develop an improved treatment for recurrent pneumothorax and pleural effusion, conditions in which the chest cavity repeatedly becomes filled with air or fluid, causing often intolerable and sometimes life threatening breathlessness. Currently, the most effective approach is to instill talc into the pleural space to induce fibrotic fusion of the lung to the chest wall (termed talc pleurodesis), eliminating the potential space between them and reducing the risk of recurrences. Talc has several limitations, however, including dissemination, lead exposure and acute lung injury, and as a lifelong foreign body, talc causes chronic pain and excessive bleeding with subsequent thoracic surgeries. As an alternative to talc, we propose commercially available, GMP-grade hydroxyapatite microspheres(HAM) for pleurodesis. In mouse models, we have found that these bone-like particles are safer and more effective than talc, and are degraded to calcium and phosphate and cleared within 3 months. The Falk Catalyst award will be used to demonstrate that HAM pleurodesis is safe and effective in a larger animal species (pig) with a pleural structure that is more similar to humans. In the Transformational Award phase, with FDA guidance, we will conduct GLP-tox studies in two species and a first-in-man trial.

Mark Mitton-Fry Ph.D.- 2024 Awardee

Assistant Professor, Division of Medicinal Chemistry and Pharmacognosy, The Ohio State University

"Preclinical Development of OSUAB-0284: A new therapy for MRSA infections"

Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterial pathogen directly responsible for more than one hundred thousand deaths per year worldwide. We have discovered a new therapy to treat MRSA infections, the novel bacterial topoisomerase inhibitor OSUAB-0284. Our long-term goal is to bring this molecule into clinical usage in both the hospital and community settings. This project will build the deep understanding of antibacterial efficacy and safety that is required to advance '284 toward clinical development. Specifically, the Catalyst Award will enable us to: 1) determine the doses/exposures required for effective treatment in mice and refine the projected efficacious human doses, 2) prepare sufficient quantities of our new therapy for seven-day rat toxicology studies, and 3) demonstrate safety in multiday toxicology studies in rats. The critical milestone for the Catalyst Award is the demonstration of a therapeutic index (safety margin) of at least ten-fold when comparing safe exposures to those required for efficacy. Success in this project will provide the groundwork for longer duration IND-enabling safety studies during the Transformational Award, a pre-IND discussion with the Food and Drug Administration (FDA), and future human clinical trials.

Gregorio Valdez Ph.D.- 2024 Awardee

Associate Professor, Brown University

"Repurposing Clopidogrel to treat ALS"

To date, there is no cure for Amyotrophic Lateral Sclerosis (ALS), a progressive neurodegenerative disease that impairs voluntary movements and leads to paralysis and death within five years of diagnosis, and existing therapies are minimally effective. Our group recently generated exciting preclinical data indicating that Clopidogrel, an FDA-approved drug commonly known as Plavix, may be an effective therapy for ALS. We found that Clopidogrel protects the neuromuscular junction (NMJ), the synaptic connection formed between motor neurons and muscle fibers critical for all voluntary movements, from ALS-induced degeneration in mice. In this proposal, we will expand on these initial findings by defining the optimal dose at which Clopidogrel is most effective at preserving NMJs in mouse models of ALS. We will also determine the extent to which Clopidogrel treatment preserves mobility and prolongs the lifespan of mouse models of ALS. With our lab's vast experience in ALS research and our recently obtained patent for using Clopidogrel to treat ALS, we are uniquely positioned to catalyze this translational research into a revolutionary new treatment option for ALS patients in the near future.

Qigui Yu M.D., Ph.D. - 2024 Awardee

Professor of Microbiology and Immunology, Indiana University

"Advancing Traumatic Brain Injury Therapy Through Targeting CD1d-lipid Signaling"

Traumatic brain injury (TBI) is a major cause of death and disability worldwide, affecting more than 10 million people annually. Survivors of TBI often face a wide range of neurological and psychiatric complications. Unfortunately, effective therapy for TBI patients is currently lacking, highlighting the critical need for innovative strategies to improve functional recovery. Our preliminary data reveal the crucial role of CD1d signaling, a unique family of MHC-like proteins presenting lipid antigens, in orchestrating TBI-triggered neuroimmune/neuroinflammatory responses that impede tissue repair and hinder functional recovery. Blocking CD1d signaling has shown promising outcomes in ameliorating traumatic central nervous system (CNS) injuries. These findings lead us to hypothesize that CD1d signaling is instrumental in driving acute neuroimmune and neuroinflammatory cascades, ultimately resulting in functional deficits post-TBI, and targeting CD1d represents a compelling avenue for therapeutic intervention in TBI. We have two Specific Aims to validate this hypothesis: (1) Identifying the specific CD1d-positive cell type(s) within the CNS responsible for instigating neuroinflammation, tissue damage, and functional deterioration following TBI, and (2) Evaluating CD1d as a novel therapeutic target for TBI immunotherapy. Our endeavor addresses the urgent need for the development and translation of strategies aimed at treating TBI to enhance patient outcomes.

James Byrne, M.D., Ph.D. – 2023 Awardee

Assistant Professor University of Iowa

"Novel materials to improve management of hypoxic tumors"

Malignant peripheral nerve sheath tumors (MPNSTs) represent a devastating type of tumor that accounts for 5–10% of all soft-tissue sarcomas and has a 5-year overall survival rate of only 50%. Despite curative-intent treatment (surgery and/or radiotherapy) of localized MPNSTs, prognosis remains poor. The objective of the proposed research is to overcome these barriers by taking advantage of a novel series of GeMs that we recently developed to safely and tunably release gases. GeM manufacturing utilizes a simple, cost-effective and scalable technology involving components FDA classified as Generally Regarded As Safe (GRAS), and we pro-pose to develop GeMs to safely and sustainably deliver oxygen through intratumoral administration. We aim to demonstrate that mitigating tumor-associated hypoxia using intratumorally administered O2-GeMs will improve responses to radiation and immunotherapy in preclinical models of MPNSTs and is safe for use in MPNST patients undergoing neoadjuvant radiation therapy.

Milan Chheda, M.D. – 2023 Awardee

Associate Professor of Medicine and Neurology, *Washington University in St. Louis*

"Genetic arming of Zika virus to treat patients with glioblastoma"

The long-term goal of this work is to genetically engineer and test a new oncolytic virus in patients with glioblastoma (GBM). Zika virus naturally targets treatment resistant GBM cells and induces a potent anti-tumor immune response. Combined, these properties are unique. We have made it safe and tested it in non-human primates. In this proposal, we will increase its efficacy by systematically modifying its genome to enable to virus to manipulate the tumor microenvironment. The proposal is high risk in that each genetic modification may adversely impact viral fitness. Even so, by the end of the proposal we will have determined our lead strain for the clinic. By completion of this proposal, we will be poised to test our lead optimized candidate in humans. We anticipate that the first human patient could receive this groundbreaking treatment within the next two years, marking a significant milestone in our mission to combat GBM and transform the landscape of cancer therapies.

Melanie Cushion, Ph.D. – 2023 Awardee

Professor of Internal Medicine, University of Cincinnati

"Targeting the Sexual Cycle of Pneumocystis for Treatment, Prevention, and Diagnosis of Pneumocystis Pneumonia"

Pneumocystis jirovecii Pneumonia (PjP) is caused by a fungal pathogen and a threat to patients receiving lifesaving immunosuppressive therapies. PjP is both difficult to diagnose and treat because there is no method to grow it outside the lungs, a standard approach that facilitates identification and candidate drug testing. This project will address both problems by taking advantage of a recent discovery we made that Pneumocystis only replicates via a sexual cycle. Treatment with the echinocandins, a new class of antifungals, disrupted the sexual cycle in rodent models of PjP but could only eliminate the infection with lengthy treatment, which is impractical for clinical use. The first objective of this project is to complement the echinocandin effect by blocking fusion of the two mating receptors with nanobodies to prevent the mating process, upstream of the echinocandin disruption. We hypothesize that such a combination will lead to a more rapid elimination of the infection. The second objective is to fluorescently label the nanobodies and deliver them to the lungs of infected mice to diagnose and track the response to therapies by live animal imaging, eliminating the need for invasive procedures such as lung lavage to obtain fluids for PCR or microscopic diagnosis.

Agnieszka Czechowicz, M.D., Ph.D. – 2023 Awardee

Assistant Professor of Pediatrics, Stanford University

"Development of Novel DNA-guided Argonaute Base Editing"

Approximately half of the known human genetic diseases are caused by single-nucleotide variants (SNVs). While CRISPR-base editing (BE) technologies offer hope in the treatment of SNV-related diseases, they can only edit certain regions of the genome and lack perfect specificity. To overcome these limitations and enable exact correction of all SNVs, we propose to develop a novel DNA-guided Argonaute (Ago) BE technology by using Ago-deaminase fusion protein as Ago base editor, facilitated by the sequence-specific strand invasion function of the peptide nucleic acid (PNA).

We will first demonstrate targeted deamination by Ago base editor (Aim 1), and then successful BE combining Ago base editor and PNA (Aim 2). The optimized Ago BE system will then be applied to correct pathogenic mutations causing severe combined immunodeficiency (SCID) in fibroblasts (Aim 3), and subsequently in mouse hematopoietic stem cells (HSCs) (Aim 4). These edited HSCs will then be transplanted to cure disease in a SCID mouse model. The feature of limitation-free binding of Ago and PNA renders this technology unprecedented applicability, and this dual binding mechanism further guarantees its accuracy. A highly versatile, accurate BE system could lead to curative treatments for millions of individuals with various disease-causing SNVs.

Pankaj Desai, Ph.D. – 2023 Awardee

Professor and Chair, Division of Pharmaceutical Sciences, University of Cincinnati

"Clinical and Correlative Translational Studies for Repurposing Letrozole as a Novel Therapeutic for Glioblastoma: Proof of Efficacy in Combination with Metronomic Temozolomide"

Our goal is to expedite repurposing letrozole, (LTZ), an aromatase inhibitor widely used for breast cancer treatment, as a novel drug for glioblastoma (GBM), a lethal brain tumor. The objective of this proposal is to conduct a "proof-of-efficacy" study as a critical first-step to support our commercialization efforts and facilitate larger confirmatory phase II trials. Our observations include: 1) the enzyme aromatase is abundantly expressed in GBM, 2) LTZ readily crosses the blood-brain barrier and exerts marked anti-GBM activity in pre-clinical models, 3) LTZ synergistically potentiates the activity of temozolomide (TMZ), the only drug approved for GBM, and, 4) in a phase 0/1 study in recurrent GBM patients (dose range, 2.5-15 mg), the 15 mg dose was identified as the Recommended Phase 2 Dose (RP2D) since it met the primary endpoint (tumoral concentration > 2 μM) with no safety concerns. Based on the Simon two-stage optimal study design, here we propose to initiate stage one efficacy study in recurrent GBM patients (N = 19) who will receive LTZ (15 mg) with metronomic TMZ (50 mg/m2). A 30% improvement in 6-month progression-free survival will meet the criteria to reject futility, confirm efficacy and establish RP2D of LTZ for further development.

Bryan Dickinson, Ph.D. – 2023 Awardee

Assistant Professor of Chemistry, University of Chicago

"Development of targeted translational activating oligos to treat SYNGAP1 deficiency-related neurological disorders"

The SYNGAP1 spectrum of neurodevelopmental disorders is caused by a genetic haploinsufficiency of SYNGAP1 that leads to abnormally low levels of this synaptic protein. Remarkable progress in gene therapy and other related technologies can now address protein overproduction, but strategies to boost protein levels, such as SYNGAP1, are comparatively lacking. We recently developed a promising new therapeutic technology to correct gene deficiencies. Translation-activating RNAs (taRNAs) are a RNA-based technology that recruits molecular machinery to enhance protein translation in model cell lines, primary neurons, and patient-derived iPSCs. This proposal aims to complete key next steps to launch taRNAs into preclinical and clinical development, furst foicused on SYNGAP1, through iterative chemical optimization to maximize stability, selectivity, and potency (Aim 1) followed by functional evaluation and prioritization in cells (Aim 2) and pharmacologic and molecular efficacy studies in animal models of SYNGAP1 (Aim 3). Successful completion of these aims will yield lead SYNGAP1- targeting taRNAs that effectively boost SYNGAP1 protein levels to within 25% of healthy-matched controls. Taken together, this will be a substantial first step toward actualization of a near-curative treatment for SYNGAP1 disorders, and will generate a broadly-applicable, programmable platform technology for addressing a broad array of other disease-causing haploinsufficiencies.

Andrea Domenighetti, Ph.D. – 2023 Awardee

Research Scientist and Principal Investigator, Rehabilitation Institute of Chicago

"Repurposing 5-azacytidine for the treatment of muscle contractures in children with cerebral palsy."

Skeletal muscle impairment and contracture development affect a third of children with cerebral palsy (CP), are often painful and limit their involvement in daily activities, school, and sports. Our long-term goal is to develop a multimodal nonsurgical treatment for skeletal muscle impairment and contracture development in children with CP. We were able to make important preclinical observations suggesting that CP muscles have lost their biological ability to grow, owing to a significant impairment of their resident stem cells, called satellite cells (SCs). We also showed that we could actually restore the muscle-growing potential of these SCs by treating them with FDA-approved 5-azacytidine (AZA). In this study we aim to start the translational process that will repurpose AZA from a blood and leukemic treatment to a muscle contractures treatment. We will perform a 3+3 dose-escalation study in children with CP (a) to determine the dose of AZA that will rescue SC physiology in contractured muscle, and (b) to determine AZA dose safety and preliminary efficacy in children. Successful completion of this study will set in motion a new paradigm for multimodal nonsurgical treatment of muscle contractures by using traditional physical therapy in combination with the biologically enabling effect of AZA.

Jacques Galipeau, M.D. – 2023 Awardee

Professor of Medicine, University of Wisconsin-Madison

"A STEM CELL CURE FOR DIABETES BY NOVEL IMMUNE EVASION TECHNOLOGY"

We have developed a gene engineering technology that allows for immune evasion of living tissues transplanted across species barriers. This technology, termed as "PIDO", consists of a novel gene composed of two potent immune-checkpoint proteins, namely PD-L1 and IDO (Indoleamine dioxygenase). Specifically, our recently published work in American Journal of Transplantation (Paul et al., 2022; Vol 22 Issue 11 p2571–2585) demonstrates that PIDO expressing allogeneic islet transplants exhibit unparalleled protection against immune rejection in a mouse Type 1 diabetes model reflective of the human condition. These data point towards the clinical potential of the PIDO technology for allowing transplantation of allogenic embryonic stem cell derived islet like cells without any companion pharmaceutical immune suppressive drugs. This represents a potentially game-changing paradigm for organ transplantation where off-the-shelf human stem cell origin can be transplanted in human subjects without rejection or need for toxic immunosuppressive drugs. In this proposal, we aim to (1) build on our previous work to further define the molecular mechanism of action of PIDO mediated localized immune evasion and (2) refine the translational use of PIDO expressing human embryonic stem (ES)-cell derived islets as a clinically deployable cell pharmaceutical.

Amir Hajrasouliha, M.D. – 2023 Awardee

Assistant Professor of Ophthalmology, Indiana University

"A Novel Minimally-Invasive Vision Restoration Method Through Continuous Slow-Release of Artificial Photoreceptors"

We have devised an innovative solution for vision loss affecting 250 million people worldwide. The root cause of the problem is deterioration of retinal photoreceptors in retinal dystrophies and degenerations. The diversity and complexity of different genes involved in these diseases have made photoreceptor replacement therapy a complex clinical challenge. We have identified a potential candidate in an artificial photoreceptor termed nanocomposite, capable of restoring sensory functions on the retina of blind mice model (rd1) and in ex vivo retina explants. However, these nanocomposites have a limited lifespan and must be renewed and replaced for the eye to maintain visual resolution. In this project, we aim to devise a method to continuously release our proven artificial photoreceptors to the retina. We propose a minimally invasive technique in which a capsule full of new nanocomposites will be injected into the eye to provide a long-time supply of replaceable artificial photoreceptors. This biodegradable capsule is slowly dissolved to release a controlled rate of artificial photoreceptors in the retina. Our Specific Aims are: Aim 1. To validate the slow-release construct of the polymer-encapsulated artificial photoreceptors. Aim 2. To assess the function of the slow-release construct to restore functional vision and its duration.

David Ingbar, M.D. – 2023 Awardee

Professor of Medicine, Pediatrics & Physiology; Assistant Dean, University of Minnesota

"Aerosolized Thyroid Hormone Treatment of Acute Lung Injury & Pulmonary Edema"

Severe respiratory failure with Adult Respiratory Distress Syndrome (ARDS) has high mortality (~40%) and morbidity, affecting 200,000 Americans annually pre-COVID. As no biologic or molecular therapies are approved for ARDS, a new therapy is high risk, high reward. Lungs of ARDS patients have very low thyroid hormone (T3) levels. T3 improves 3 key abnormalities of ARDS: pulmonary edema; lung inflammation and injury; and fibrosis. We developed a novel, patented T3 formulation (ThyrOxy) that can be safely administered directly to the lung. A Phase 1/2A clinical trial of ThyrOxy liquid instillation directly into lungs of mechanically ventilated patients with ARDS has early signs of efficacy with no treatment-related adverse events. However, this approach is limited to severely affected, ventilated ARDS patients.

With Catalyst Research Award support, we will develop an aerosolized form of ThyrOxy to treat patients at earlier or milder stages, known as Acute Lung Injury (ALI). The Catalyst phase will include preclinical pharmacokinetic, biodistribution, efficacy, and toxicology studies required to secure FDA approval of aerosolized T3 trials in non-intubated ALI patients. This formulation will expand treatment to patients with ALI and with other chronic lung and heart diseases with pulmonary edema, including congestive heart failure.

Maria Martinez Cantarin, M.D. – 2023 Awardee

Associate Professor, Thomas Jefferson University

"Chemokine antagonist to prevent progression of kidney disease"

The Fractalkine (CX3CL1)-CX3CR1 axis has been implicated as playing a key role in kidney fibrosis. CX3CR1+ macrophage infiltration contributes to disease progression, and genetic deletion decreases inflammation, reduces macrophage infiltration, and fibrotic scarring. AD-0145 is a novel small molecule CX3CR1 antagonist than in our preliminary data has been shown to decrease macrophage infiltration and fibrosis in inflammatory models of kidney disease.

The goal of this proposal is to demonstrate that AD-0145 is effective in preventing kidney function decline in animal models of CKD and using medicinal chemistry, scale up compound and developing a cellular assay to demonstrate target engagement. The addition of binding information to our demonstrated functional assays will corroborate that the effects are consistent with the proposed mechanism of action.

In specific aim 1, we will characterize the efficacy of AD-0145 in a model of crystal induced nephropathy. We will determine kidney function, fibrosis and macrophage infiltration. In specific aim 2, we will scale-up AD-0145 for use in animal models and develop a CX3CR1 nanoBRET assay to confirm target engagement in cells. Demonstration efficacy of AD-0145 is expected to significantly impact treatment of CKD, as a new drug class targeting a distinct pathological pathway than current approved therapies.

James Mathew, Ph.D., M.Sc. – 2023 Awardee

Professor of Surgery and Microbiology-Immunology, Northwestern University

"Donor-specific Regulatory T-cell Therapy for the Induction of Transplant Tolerance in Pediatric Heart Transplant Recipients"

Heart transplantation is a life-saving procedure for those with end-stage heart disease, but it necessitates lifelong use of immunosuppressive drugs with severe side effects. Inducing immunologic tolerance, where the recipient's immune system accepts the transplant as "self," is crucial, especially in pediatric patients. Our long-term objective is to achieve immunologic tolerance in pediatric heart transplant recipients.

Regulatory T-cells (Tregs) have shown promise as tolerogenic agents, promoting graft acceptance in animal models and being associated with increased Treg counts in tolerant human recipients. Tregs are typically limited in number, so they are expanded in culture and used in adult patients to induce tolerance.

Blood is the source for Tregs in adults, but obtaining sufficient quantity of blood from pediatric patients is not feasible. During pediatric heart transplantation, the thymus, a rich source of Tregs, is removed and discarded. Therefore, our proposal focuses on isolating and expanding thymic Tregs for tolerance induction in these patients.

During the Catalytic Award, we will optimize the isolation of thymic Tregs and then expand them utilizing similar methodologies employed in adults. Subsequently, during the Transformational Phase, a phase I trial will be conducted to assess the safety of infusing expanded Tregs in pediatric heart transplant patients.

Hiromitsu Nakauchi, M.D., Ph.D. – 2023 Awardee

Professor of Genetics, Stanford University

"Metabolic Pausing: Revolutionizing Affordable Organ Transplantation Globally"

Addressing the global organ shortage, our long-term goal is to economically generate universally immune-compatible organs that are readily available for transplantation, democratizing access to this life-saving resource and procedure. Liver diseases alone cause 2 million deaths annually, representing 4% of all global fatalities. In the U.S., the crisis is stark with over 100,000 patients waiting for organ transplants; tragically, 22 individuals lose their lives daily while waiting. Existing organ preservation methods are inadequate, inflicting irreversible damage, imposing geographic limitations on organ transport, and leading to the regrettable discarding of over 5,000 viable donated organs annually. Motivated by these challenges, we have turned to nature for solutions. Our previous research revealed a hibernation-like mechanism in hematopoietic stem cells (HSCs) that aids their protection. By leveraging similar survival strategies found in animal hibernation and diapause, we now aim to revolutionize organ preservation. Our project includes (A) optimizing ex vivo liver preservation through metabolic pausing, (B) evaluating this novel preservation solution's effectiveness in rodent liver transplantation, and (C) validating the technique using discarded human livers. We aspire to reduce organ metabolic damage, extend preservation time, and ultimately save numerous lives worldwide through our inexpensive but improved organ transplantation outcomes.

Sean Pitroda, M.D. – 2023 Awardee

Associate Professor of Radiation and Cellular Oncology, University of Chicago

"Validation of Tumor Aneuploidy as a Novel Predictor of Radio-Immunotherapy Response in Metastatic Non-small Cell Lung Cancer: Biomarker Analysis of a Prospective Randomized Phase I/II Clinical Trial"

Although immunotherapy has revolutionized the treatment of metastatic NSCLC, only a small fraction of patients experiences long-term survival following treatment. In a recent breakthrough, we discovered that a subset of patients with immunotherapy resistant, highly aneuploid NSCLC derive a major benefit from the addition of radiotherapy to immunotherapy leading to improved outcomes. Here, we propose to validate a novel biomarker of tumor aneuploidy and understand how radiation therapy augments the immune response to improve the efficacy of immunotherapy treatment in highly aneuploid NSCLC. We will utilize advanced tumor genomic sequencing, multiparameter spectral flow cytometric, T cell receptor sequencing, and immune cytokine profiling approaches to comprehensively characterize the immune repertoire. We will combine these data with powerful computational and statistical analyses as a secondary translational endpoint of our unique randomized phase I/II clinical trial of combination radiation therapy and immunotherapy as a first-line treatment for patients with metastatic NSCLC. We believe our tumor aneuploidy biomarker can be rapidly integrated into clinical practice to inform hundreds of ongoing radiation/ immunotherapy combination trials and can serve as the foundation for novel personalized medicine trials, which will have important implications in the paradigm-shifting curative treatment of patients with metastatic NSCLC.

Carlos Subauste, M.D. – 2023 Awardee

Professor of Medicine and Pathology, Case Western Reserve University

"CD40-TRAF2,3 Blocking Peptide for the Treatment of Ocular Disorders"

The main cause of blindness in patients with diabetic retinopathy is macular edema caused by vascular leakage. Anti-VEGF agents are used to treat diabetic macular edema. Unfortunately, many patients do not respond because vascular leakage is also driven by VEGF-independent inflammation. The objective of this application is to identify an improved approach to treat diabetic retinopathy. We hypothesize that, in contrast to anti-VEGF agents, nanoparticle-driven sustained intravitreal release of a peptide that blocks CD40-TRAF2,3 signaling will cause long-lasting reduction of VEGF and inflammatory molecules, reversing VEGF-dependent and independent vascular abnormalities (Claudin 5 redistribution) and reducing vascular leakage in diabetic mice. Using confocal microscopy and mass spectrometry, we will first establish how long the peptide is present in the retina and inhibits CD40. In the second aim, we will establish nanoparticle-assisted method of sustained delivery of the peptide and determine its duration of action in the retina. Using a mouse model of diabetic retinopathy in the third aim, we will test whether nanoparticle-associated blocking peptide is more effective than an anti-VEGF agent in reducing expression of inflammatory molecules, VEGF, vascular leakage and normalizing Claudin 5 expression. This work may result in a novel and improved approach to treat diabetic retinopathy.

Paul Turner, Ph.D. – 2023 Awardee

Associate Professor, Yale University

"Developing Innovative Phage Therapy to Target MRSA"

The rise of serious antibiotic-resistant infections caused by Staphylococcus aureus (SA) warrants development of novel therapies, which can treat MRSA (methicillin-resistant SA) and other deadly strains. One approach is phage therapy, where viruses of bacteria are used to target human infections. Our innovative method develops therapeutic phages that target virulence factors as cellular receptors. Phage-resistant bacteria modify/delete the receptor, causing virulence reduction/loss ("trade-off") that decreases bacterial pathogenicity. We discovered phage mallokai which kills SA while selecting for trade-offs that decrease virulence in surviving bacterial mutants. In Aim 1, we will use experimental evolution to develop phage variants with improved biofilm degradation, and more consistent ability to select for biofilm-growth trade-offs in clinical SA strains. In Aim 2, we will similarly evolve phage variants with improved antibiotic synergy, which consistently kill clinical strains while driving oxacillin re-sensitivity in phage-resistant mutants. Comparative genomics will identify how phages evolve improved traits, and how SA bacteria suffer trade-offs useful in clinical treatment with phages. Our proposed pre-clinical studies will further develop phage mallokai as a therapeutic that generally targets and kills problematic SA bacteria, advancing novel treatments against the worrisome rise of morbidity and mortality caused by this dangerous human pathogen.

Richard Vile, Ph.D. – 2023 Awardee

Professor of Immunology,Mayo Clinic

"In Vivo Generation of Persistent, Memory and Effector CAR T Cells from Naïve T Cells as a Platform for Treating Solid Tumors"

Activation of naïve T cells by pathogens induces differentiation into memory T cells that can both produce and replenish the supply of effector cytotoxic T cells. CAR T cells (CAR T) are engineered to express a Chimeric Antigen Receptor (CAR) which directs the T cell to kill tumor cells. Clinically produced CAR T primarily contain effector cells for tumor killing with few replenishing memory CAR T, leading to tumor escape once effector CAR T die. We engineered dendritic cells (DC) ex vivo to release a CAR vector during presentation of an immunogenic epitope to naïve T cells. Activation of naïve T cells is coupled with infection of T cells by the CAR vector, producing populations that differentiate into effector CAR T (to kill tumor) and memory CAR T to replace lost effectors. We hypothesize that direct in vivo administration of a DC-targeting vector will enable DC-based generation of both CAR T populations in situ from naïve T cells. We will (1) compare vectors for delivery of CAR/packaging functions to DC, T cell targeted CAR vector release in vivo, and potential toxicities; (2) test anti-tumor efficacy in vivo and (3) identify IND-enabling studies to prepare for IND application to clinical trial.

Robert Abramovitch, Ph.D. – 2022 Awardee

Associate Professor of Microbiology and Molecular Genetics, Michigan State University

"Development of New MmpL3 Inhibitors to Treat Mycobacterial Infections"

Tuberculosis (TB) remains a global health crisis causing ~1.5 million deaths per year. To cure TB, treatment requires daily, multidrug therapy for 6 months. However, with the evolution of drug resistant Mycobacterium tuberculosis (Mtb), current therapies are inadequate to control multi-drug resistant TB.

MmpL3 inhibitors are attractive new agents functioning against drug susceptible and resistant Mtb. We have discovered a new class of MmpL3 inhibitors called HC2099. We optimized and found an orally bioavailable analog that is efficacious in vivo in an acute murine Mtb infection model. However, we encountered a barrier to development caused by in vivo metabolism of HC2099, leading to a short half-life. We have identified the metabolic liability presenting a clear path forward to overcome this barrier to development.

The goal of this proposal is to further optimize the HC2099 series to generate proof-of-concept in vivo efficacy data showing its utility for once daily dosing.

To fulfill these goals, we will complete:

Specific Aim 1. Define structure activity relationships and optimize activity of HC2099 series.

Specific Aim 2. Conduct integrated SAR and pharmacokinetic studies to prioritize compounds for in vivo efficacy studies.

Specific Aim 3. Demonstrate proof-of-concept in vivo efficacy of HC2099 series against Mtb infection.

Drew Adams, Ph.D. – 2022 Awardee

Associate Professor, Dept. of Genetics; Thomas F. Peterson Jr Professor of Novel Therapeutics, Case Western Reserve University

"Targeting Exportin-1 to Block T Cell Activation in Autoimmune Diseases"

My laboratory seeks to validate new targets for drug discovery, and our past work has led to high-impact publications and commercialization. Recently we identified Exportin-1 (XPO1) as the target of multiple small molecules that suppress T cell activation, an important immune process that goes awry in autoimmune diseases. XPO1 is a validated drug target, but safety considerations limit the existing XPO1-targeting drug's use to late-stage cancer patients. In contrast, molecules we have identified show a unique 'low cytotoxicity' profile that suggests XPO1 may have potential as a drug target in autoimmune diseases where cytotoxicity is undesirable. Our goal is now to demonstrate that this novel class of XPO1-targeting molecules is effective in animal models of autoimmune disease and demonstrates diminished toxicity relative to the established XPO1-targeting drug. Our Aims entail 1) using medicinal chemistry to generate an optimized in vivo-active tool molecule, and 2) evaluating both the efficacy of this tool molecule in mouse models of autoimmune disease and its cytopenic effects relative to the approved XPO1 drug. Demonstrating that our novel class of XPO1 modulators is efficacious but also shows a distinct safety profile in vivo will inspire expanded drug discovery efforts toward a new class of immunomodulatory drugs.

Nita Ahuja, M.D. – 2022 Awardee

Chair of Surgery, Yale School of Medicine

"Bedside Liquid Biopsy for Pancreatic Cancer"

Pancreas cancer (PC) is lethal and detected in advanced stages. Early-stage PC detection is the only potentially curative modality. Screening has been recommended in high-risk individuals (HRIs) with significant familial and/or genetic risk. There is no approved screening test, and surveillance relies on imaging modalities (CT scans) or invasive procedures (endoscopic ultrasound). These approaches are available only in selected centers, are expensive, invasive, and prone to interval cancer detection. DNA methylation biomarkers have recently been approved for cancers (Cologuard, SEPT9 for colon cancers) and show promise as cost-effective and safe approaches for PC surveillance

Our blood-based DNA methylation biomarkers (ADAMTS1/BNC1/LRFN5/PXDN) have diagnostic accuracy of 94% for early-stage PC detection. Optimizing the panel with pancreas-specific "tissue of origin" marks may increase diagnostic accuracy from 94% to 99%. We also propose using our DNA methylation panel to monitor HRIs in a pilot study.

An affordable bedside test with excellent diagnostic accuracy will support early detection efforts and identify early curable stage PC, thereby extending patient longevity. If this project succeeds, it can be applied in routine health care. Our proficient multidisciplinary team is led by Dr. Ahuja, a surgeon-scientist with a two-decade history of blood-based biomarkers development.

Ethan Anderson, Ph.D. – 2022 Awardee

Associate Professor of Experimental Therapeutics, University of Iowa

"Development and validation of a piezoelectric immunosensor to rapidly detect a novel biomarker of morbidity and mortality risk in sepsis patients."

Approximately one million people in the U.S. develop sepsis each year and nearly 30% from it. Recent sepsis care guidelines emphasize that a major barrier to improving patient outcomes is early identification of those at greatest risk of organ failure and mortality, so that they can be aggressively treated and closely monitored. We have exciting preliminary evidence that a mitochondrial membrane protein measured with our validated ELISA in blood samples obtained from patients within 24 hours of sepsis diagnosis, is associated with organ failure and mortality. The objective of this project is to validate this biomarker in sepsis mouse models and patients, and then develop a rapid test for this protein using a piezoelectric immunosensor. Preliminary studies suggest that this approach is feasible. Work in Aim 1 will establish the range of this protein's serum concentration in sepsis mouse models and patients to model organ failure and mortality risk. In Aim 2 we will determine the technical specifications of the immunosensor required for rapid detection and quantification of the protein in serum. This project will be the first steps toward development of a point-of-care biosensor which could rapidly identify high-risk patients early in the progression of a very deadly condition.

Fariba Behbod, PharmD, Ph.D. – 2022 Awardee

Professor, University of Kansas Medical Center

"Elucidating the Role of Enhancer Reprogramming in DCIS Malignancy"

Having no reliable biomarkers for risk stratification of ductal carcinoma in situ (DCIS) has resulted in overtreatment of indolent disease as well as undertreatment for a small subpopulation at high risk for metastasis. We hypothesize that the evolution of DCIS epithelial cells into invasive and metastatic cancer cells is associated with enhancer reprogramming and subsequent acquisition of an epithelial stem-like signature.

Aim 1. Study the epigenome and transcriptome associated with evolving breast epithelial cells during the transition of DCIS to invasive breast cancer using simultaneous scATAC/scRNA-sequencing in patient derived DCIS models that evolve into invasive and metastatic cancers versus those which remain indolent. Established algorithms (CytoTRACE) will be used for predicting cellular stemness.

Aim 2. Investigate the role of BCL9 and its binding partners (pS-STAT3 and CREBBP) in enhancer reprogramming, epithelial stemness and DCIS invasive and metastatic progression using RNA- and ChIP-sequencing.

Impact: The development of biomarkers for risk stratification in DCIS. Absence of biomarkers of epigenome reprogramming and cellular stemness may identify women at low risk who do not require further treatment avoiding overtreatment. Additionally, the presence of DCIS cells which have acquired epigenome reprogramming and cellular stemness may justify early systemic therapy including drugs that target the epigenome.

Luisa Escobar-Hoyos, Ph.D. – 2022 Awardee

Assistant Professor of Therapeutic Radiology, Yale School of Medicine

"Making cancer cells look like bacteria: Developing antigen-mimicry cancer vaccines."

Our objective is to create a vaccine that can induce the clearance of tumors in pancreatic cancer. The most lethal malignancies uniquely express the neoantigen K17, and we have found that patients with prior exposure to the pathogenic bacterium, Streptococcus pyogenes, lack K17-expressing tumors. This led us to identify bacterial antigens that mimic K17, and, using cell cultures, we showed that T cells from donors or patients with previous exposure to S. pyogenes can eliminate K17 cancer cells. Thus, we will test the hypothesis that anti-S. pyogenes immunity or anti-K17 immunity can cause clearance of K17-expressing cancer cells. We will carry out critical proof-of-concept vaccination studies in animal models of pancreatic cancer using mRNA-based expression of bacterial and K17-derived antigens, and a drug delivery system based on GMAB immunoglobulin, which we have shown can deliver mRNA efficiently to tumors in vivo, a condition that is required to elicit immunoclearance at the tumor site. If successful, we will demonstrate elimination of K17-expressing tumors in mice, paving the way for development of a vaccine to treat the large proportion of patients who have the most aggressive form of pancreatic cancer.

Amanda Garner, Ph.D. – 2022 Awardee

Assistant Professor of Medicinal Chemistry, University of Michigan

"Decoding the Druggable Transcriptome"

Following completion of the Human Genome Project, it was revealed that only ~2% of our genome encodes for proteins, and the overwhelming majority of our transcribed genome is comprised of often highly conserved non-coding RNAs. Through expanded exploration of RNA biology, a diversity of structure and function has been revealed putting RNA at the forefront of medicine, making the targeting of RNAs with small molecules attractive as a novel therapeutic strategy. Yet, despite significant efforts in the field, our ability to directly drug RNA molecules has been wrought with challenges. We believe that this lack of success is due to the use of reductionist-based approaches that are in contrast to what we know about RNA biology: that it is a complex and underexplored area of science. To match this complexity of cellular RNA structure-function, through the aims proposed, we seek to develop an integrated chemotranscriptomic pipeline to facilitate the target agnostic discovery of RNA-binding small molecules with disease-relevant cellular phenotypes allowing us to finally decode the druggable transcriptome and enable the systematic discovery of RNA-targeted small molecule therapeutics.

Justin Lathia, Ph.D. – 2022 Awardee

Associate Professor of Cellular and Molecular Medicine, Cleveland Clinic Lerner Research Institute

"Development of an anti-cancer stem cell therapy for glioblastoma by targeting the epigenetic state via WDR5"

Our long-term objective is to synthesize a brain penetrant, WDR5 inhibitor with sufficient potency to decrease cancer stem cell (CSC) proliferation, self-renewal, and viability. We plan to accomplish this goal through (1) structure informed compound design and (2) rigorous experiments designed to evaluate drug efficacy in vitro and in vivo. In Aim 1, we will develop new compounds altering motifs known to enhance brain permeation, increase potency, and decrease off-target effects based on a WDR5 tool compound. We will evaluate drug properties central to brain penetrant compounds such as plasma protein/tissue binding, target affinity, predicted clearance, solubility, and brain specific pharmacokinetics. In Aim 2, we will evaluate our top compounds for inhibition of cancer cell growth, induction of cell-death, disruption of the WRAD complex, reduction of the methylation that promotes CSC growth, and increasing survival in preclinical glioblastoma models. We also evaluate predicted mechanism of action through a variety of in vitro assessments and tumors isolated from in vivo studies. These studies will facilitate the development and translation of novel brain penetrant WRD5 inhibitors to attenuate CSCs in glioblastoma and can be expanded to other cancers in which the WRAD complex drives CSCs and tumor growth and brain metastasis.

Craig Levin, Ph.D. – 2022 Awardee

Professor of Radiology, Physics, Electrical Engineering, and Bioengineering, Stanford University

"Multiplexed Positron Emission Tomography Imaging of Promising Biomarkers for Immune Checkpoint Inhibitor Therapy"

Immunotherapy has revolutionized medical oncology. The use of immune checkpoint inhibitors (ICIs) has demonstrated revolutionary results in cancer treatment, but only a portion of patients can achieve complete disease remission. Current diagnostic imaging based on the tumor size measurement alone is not adequate to assess initial response to immunotherapy and disease evolution. Therefore, there is an urgent need for the development of new non-invasive imaging assays that can tell whether a patient's cancer responds to the immune treatment at an earlier timepoint than that allowed by the current methods. A commonly explored approach to imaging immune response uses radiolabeled antibodies targeting membrane associated markers, but this single biomarker imaging strategy has not yet demonstrated reliable prediction of treatment response. In this project, a team of investigators will bring expertise in chemistry, physics, engineering, molecular imaging, and cancer immunology to develop a novel non-invasive multiparametric imaging assay that can sensitively detect two (or even three) biomarkers in the tumor in response to the immune therapy. This new imaging assay will be evaluated in a preclinical mouse model of colorectal cancer and the results will pave the way to future clinical translation for more efficacious selection and accurate monitoring of cancer immunotherapy.

Karen Liby, Ph.D. – 2022 Awardee

Professor of Pharmacology and Toxicology, Michigan State University

"Novel RXR Agonist for Neurofibromatosis"

Neurofibromatosis type 1 (NF1) is a complex disease driven by inactivation of the NF1 gene, leading to constitutive RAS activation, uncontrolled cell growth and immune cell infiltration. Our novel compound, MSU42011, suppresses tumor growth, drives immune cells toward an anti-tumor phenotype, and decreases p-ERK expression in a RAS-driven lung cancer model, but has never been tested for NF1. We hypothesize that MSU42011 will inhibit tumor growth in NF1 mouse models and target immune cells that drive disease progression. Macrophages co-cultured with conditioned media or NF1 cells will be treated with MSU42011. Macrophage activation and polarization will be analyzed by measuring cytokine expression and cell surface markers via qPCR, ELISAs and flow cytometry. To explore complex interactions in the tumor microenvironment, effects of drug treatment on immune phenotypes will be evaluated using tri-cultures of macrophages, T cells and tumor cells. In vivo efficacy of MSU42011 will be tested in mice with established neurofibromas or malignant peripheral nerve sheath tumors. Tumor growth and toxicity will be monitored and immune cell populations in tumors quantified by flow cytometry and immunohistochemistry. The pharmacokinetic profile and selectivity of MSU42011 will be evaluated. These studies are designed to advance MSU42011 into the clinic.

Feng Lin, B.Sc., Ph.D. – 2022 Awardee

Professor of Molecular Medicine, Cleveland Clinic Lerner Research Institute

"Development of a New Drug for Patients With T Cell Lymphoma"

T-cell lymphomas (TCL) are complex clusters of aggressive blood cancers with unsatisfactory management options. In pilot studies, we identified CD6 as a novel therapeutic target for TCL. We developed an antibody-drug conjugate (ADC) specific for CD6 (CD6-ADC) using a conventional anti-CD6 monoclonal antibody (mAb) and found that this ADC is highly effective in selectively killing TCL cells both in vitro and in vivo. Nanobodies, heavy-chain only antibodies produced in camelids, are the next generation of mAb-based therapeutics. Given the many advantages that nanobodies have over the conventional mAbs, especially their excellent tumor penetrating capacity, we are developing the next generation of CD6-ADC using nanobody technology. We have immunized an alpaca and identified more than 120 anti-CD6 nanobody candidates. In this project, we will rigorously characterize these candidates to identify the best anti-CD6 nanobodies, use them to develop the next generation of CD6-ADC, and evaluate their treatment efficacy and potential adverse effects both in vitro and in vivo in a preclinical model of TCL. These high-risk studies, if successful, will generate the next generation of CD6-ADC and provide the required proof of concept to translate it into a much-needed new drug for patients with TCL.

Jonathan Marchant, Ph.D., M.A. – 2022 Awardee

Professor, Medical College of Wisconsin

"IDENTIFYING NEW DRUGS TO TREAT AN INFECTIOUS DISEASE OF POVERTY"

Diseases caused by parasitic flatworms impact millions of people. These infections cruelly target some of the most disadvantaged, with an especial burden on children worldwide. Many infections are treated with a drug called praziquantel (PZQ), the sole clinical agent available, but not an ideal treatment: for 40 years we have not understood how PZQ works, and it is not effective against every parasitic disease. Therefore, discovery of new anti-parasitics is a priority.

Our team recently identified the target of PZQ, overcoming a long-standing roadblock. The target is an ion channel, named TRPMPZQ, responsible for PZQ-dependent worm paralysis and elimination. Our discovery explains why PZQ is effective against some diseases and not others, as the TRPMPZQ binding site differs between parasites. With this knowledge in hand, we are optimally placed to discover novel drugs.

Therefore, in this 'Catalyst' proposal, we will take two independent, but parallel approaches to identifying novel chemotypes active at TRPMPZQ. We will take a rational drug engineering approach (Aim 1) and an unbiased drug screen (Aim 2). By adhering to 10 quantitative metrics that benchmark success of our assays, we aim within 18 months to discover novel agents that can be further progressed in subsequent work.

Tay Netoff, Ph.D. – 2022 Awardee

Professor of Biomedical Engineering, University of Minnesota

"Rational, Targeted Electrical Brain Circuit Intervention for Mental Illness"

We will demonstrate a new approach to treating mental illnesses, based on directly changing the underlying biology (activity in defined brain circuits) through targeted electrical stimulation. Brain stimulation is a rapidly growing approach to treating a range of illnesses, but has a fundamental limitation: it is difficult to determine the "dose" that will produce a desired circuit change. Patients' self reports are often inaccurate and change too slowly to be useful for tuning stimulation.

We have developed a new approach, based on a core insight: many mental disorders are characterized by "stuck", inflexible thought/behavior patterns. We have developed a way to measure that behavioral inflexibility in seconds, using computer-based testing. We have further developed electrical stimulation methods that reverse the deficit and make patients more flexible– and patients feel less anxious or depressed when we do. To bring these methods into trials, we need to turn them from academic lab code into a robust and tested application that can meet FDA Investigational Device Exemption requirements. In our Catalyst project, we will perform that development and testing, engage with FDA to verify that our tests meet their criteria, and formalize the design of a clinical trial in major depression.

Mark Paterno, P.T., Ph.D. – 2022 Awardee

Professor of Sports Medicine, Children's Hospital Medical Center dba Cincinnati Children's Hospital Medical

"Identifying Early Indicators of Outcome to Inform Novel Rehabilitation Paths"

The healthcare system is failing young patients who suffer musculoskeletal (MSK) injuries and seek to return to prior levels of function as many suffer subsequent injuries and few are able to return to pre-injury levels of activity. Our long-term objective is to improve outcomes for youth who sustain MSK injury by reducing the incidence of subsequent injury and enabling patients to return to and maintain pre-injury levels of activity through an innovative and personalized rehabilitative care pathway. To achieve this, the focus of this observational cohort study is to validate current discharge criteria and identify key modifiable biomarkers, present early in the rehabilitation process, as indicators of poor outcome. This important step towards our long-term goal is foundational to the development of a paradigm shift in standard care, specifically a shift towards a personalized, adaptable, algorithmic rehabilitation process. This work has the potential to create accessible and objective clinical metrics that personalize return to sport clearance and improve long-term health of millions of young patients who sustain acute MSK injury annually.

Arjun Raman, M.D., Ph.D. – 2022 Awardee

Assistant Professor, University of Chicago

"The 'statistical' design of synthetic microbiomes"

Complex microbial communities ('microbiomes') are ecosystems that critically contribute to human physiology. A major goal is to design such communities to unlock their immense potential in addressing challenges affecting human health. However, it is remarkably difficult to rationally engineer microbiomes due to their immense complexity—the number of possible interactions between the thousands of component microbes is astronomical. Thus, what strategy can be used to design functional microbiomes? We have developed a 'top-down' approach that combines the ability to print thousands of microbiomes in parallel and emerging mathematical inference methods with the goal of designing microbial communities that perform specific functions. As a first instance of using our approach, we created two designed microbial consortias (DMCs) comprised of 24 and 46 bacterial strains that suppress Klebsiella pneumoniae—a pathogen that is resistant to many antibiotics and causes severe disease. Our goals are (i) to mechanistically understand why our DMCs work, (ii) investigate whether we can deduce a 'core' set of bacterial members to reduce the size of our DMCs, and (iii) apply the general approach of creating DMCs to suppress other antibiotic resistant pathogens. Ultimately, we hope to define DMCs as novel therapeutic modalities for a range of health-relevant conditions.

Jeffrey Schneider, Ph.D. – 2022 Awardee

Assistant Professor, Rush University Medical Center

"Glycoengineering Anti-HIV antibodies to increase delivery to the brain and block viral egress from the CNS"

There is no cure for HIV despite great strides in combination anti-retroviral therapy(cART) to control HIV/AIDS. Once cART is interrupted, HIV re-emerges from sanctuary sites to reseed the body. One such site is the central nervous system (CNS). Our recent chimeric human brain mouse model demonstrates that HIV egresses from the brain to peripheral organs following cART cessation. Therefore, it is critical to develop therapies targeted to the brain to block this egress if a viable cure strategy is going to be achieved. We propose to target anti-HIV neutralizing antibodies to the brain to block this egress. CNS antibodies have a distinct glycosylation profile to support their retention in the CNS in comparison to bulk IgG. We propose a novel methodology to target antibodies to the brain, involving engineering antibodies to be more "CNS like" through glycosylation and subclass manipulation (Aim 1). We will assess these "CNS like" anti-HIV antibodies for CNS penetration and potential to block HIV viral egress following cART cessation in our chimeric human brain mouse model (Aim 2). Collectively, these studies will explore the validity of engineering CNS-like antibodies to increase penetration to the brain and ability to block viral egress following cART cessation.

Jennifer Woyach, M.D. – 2022 Awardee

Assistant Professor of Internal Medicine, The Ohio State University Wexner Medical Center

"Optimizing BTK Inhibitor Therapy in CLL"

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia. Covalent Bruton's Tyrosine Kinase inhibitors (BTKi) ibrutinib and acalabrutinib have been paradigm-shifting in CLL, however, patients do relapse. Our previous work has identified that the vast majority of patients with ibrutinib-refractory CLL develop mutations in BTK or its immediate downstream target PLCG2. New approaches to therapy in patients who relapse on these agents are of critical importance.

In this proposal, we evaluate a novel selective inhibitor of BTK which can bind the protein both covalently and noncovalently. This allows for differential binding with wild type (covalent) vs mutant (noncovalent) BTK. A dual inhibitor may represent a strategy which prevents resistance, thereby significantly extending remissions. In this project, we will perform preclinical work on this BTKi, NW775 to evaluate efficacy in CLL cells as well as mouse models. We will also use CRISPR screens to evaluate potential combination partners, which we will extensively validate.

At completion, we will have preclinically evaluated a promising new agent for CLL and performed validation studies for potential combinations. We expect that this project will lead to clinical studies with the potential of this mechanism to change the standard approach for patients with CLL.

Xiaoyu Zhang, Ph.D. – 2022 Awardee

Assistant Professor of Chemistry, Northwestern University

"Discovering and developing neoantigen inducers as new and effective cancer immunotherapeutics"

Cancer immunotherapy relies on cytotoxic T lymphocytes (CTLs) to recognize proteins or mutation-derived peptides displayed on cancer cell surfaces in order to eliminate cancer cells. Mutation-derived peptides, or neoantigens, that display on major histocompatibility complex I (MHC-I) on cancer cell surfaces are particularly relevant to effective cancer immunotherapy. Although exome sequencing and in silico algorithms are used to predict MHC-I-associated neoantigens, only a handful of neoantigens have been identified experimentally. Given that protein turnover rate is correlated with MHC-I antigen presentation, I hypothesize that the neoantigens presented under physiological conditions represent only a small fraction of all potential neoantigens, most of which may exist in an unprocessed state. Inducing the presentation of those otherwise 'invisible' or insufficiently presented neoantigens by small molecules, or neoantigen inducers, has the potential to convert immunologically silent cancer into an immunosensitive state. In Aim 1, we will demonstrate the therapeutic potential of inducing the presentation of a CDK4_R24C neoantigen to elicit CTL responses. In Aim 2, we aim to discover a new knowledge of cancer on a genome-wide scale – the presentability of cancer neoantigens. In Aim 3, We will develop neoantigen inducers to induce the presentation of 'invisible' cancer neoantigens.

Franziska Bleichert, Ph.D. - 2021 Awardee

Molecular Biophysics and Biochemistry, Yale School of Medicine

"Targeting DNA Replication Initiation for Cancer Therapy"

Harnessing DNA replication stress to induce cell death has been a successful approach in cancer therapy. One attractive but underexplored strategy to selectively enhance replication stress in cancer cells is to inhibit the licensing of replication origins, i.e., the loading of replicative helicases onto DNA. We hypothesize that origin licensing inhibitors would serve as powerful cancer drugs, either in stand-alone or combination therapy, as they sensitize cancer cells to replication stress through a mechanism distinct from established chemotherapeutics, eventually causing cell death. Here, we propose to use high-throughput biochemical screening to identify small-molecule origin licensing inhibitors. Positive hits will be tested in biochemical and cellular assays to establish dose-responses and identify compounds that are most effective at inhibiting DNA replication initiation. These studies will be combined with X-ray crystallography and cryo-electron microscopy to understand the structural mechanisms by which identified compounds selectively inhibit replicative helicase loading. The outcomes of these efforts will pave the way for the development of the first origin licensing inhibitors as anticancer therapeutics and, in the long term, have the potential to yield a novel class of cancer drugs.

Vladimir Bogdanov, Ph.D. - 2021 Awardee

Internal Medicine, University of Cincinnati

"Preclinical Development of a First-In-Class Humanized Antibody Targeting Alternatively Spliced Tissue Factor"

This proposal is focused on pancreatic ductal adenocarcinoma (PDAC) – a highly lethal cancer with poor treatment options. We study alternatively spliced Tissue Factor (asTF), a protein whose expression is high in tumor tissue and blood of patients with PDAC. asTF activates integrins, which promotes proliferation, migration, and metastasis of cancer cells. We developed 1) a humanized, inhibitory monoclonal anti-asTF antibody termed hRabMab1 with a favorable pharmacokinetic profile and tumor-suppressing properties in vivo; and 2) asTF-specific ELISA. The Specific Aims we propose are: 1. Test the hypothesis that hRabMab1, a first-in-class biologic, may help treat PDAC. Our preliminary data shows that hRabMab1 suppresses the growth of pre-formed, orthotopically grown PDAC tumors when administered intravenously as a single agent. We will assess hRabMab1's ability to suppress the growth of several PDAC cell lines and patient-derived xenografts in combination with standard-of-care regimens; and hRabMab1's ability to impede metastases. 2. Test the hypothesis that measuring circulating asTF may help evaluate response to therapy. We found that asTF levels in plasma drop post-treatment; this extends our earlier findings that plasma asTF levels are high in PDAC patients compared to healthy subjects, and positively correlate with non-resectability. In this aim, we will determine if asTF levels rise with recurrence post-surgery. In partnership with investigators conducting a Phase II trial examining an adaptive approach to neoadjuvant therapy, we will determine if plasma asTF rises in those subjects who recur, and whether said rise precedes the emergence of conventional signs of recurrence. Our studies will help us validate asTF as a new target and a biomarker in PDAC, bringing this technology closer to the clinic.

Karlene Cimprich, Ph.D. - 2021 Awardee

Chemical and Systems Biology, Stanford University

"A Novel Biomarker for the Detection of Genomically Unstable Cancers"

Early cancer detection is a critical factor in patient survival. However, sensitive and specific diagnostic tools are limited. Many cancers exhibit genome instability, a hallmark of cancer. Among the causes of genome instability are mutations in DNA repair genes, including the hereditary breast cancer susceptibility genes, BRCA1 and BRCA2. Mutations in BRCA1/2 lead to elevated levels of R-loops, nucleic acid structures that form when nascent RNA hybridizes to the template DNA. Although R-loops have regulatory roles in the cell, their deregulation causes DNA damage and genome instability. We have identified RNA-DNA hybrids as a product of R-loop processing, which accumulate in the cytoplasm of cells lacking BRCA1/2. We hypothesize that these hybrids could be a circulating biomarker suitable for liquid biopsy and thus, early cancer detection. Our approach has three aims with the overarching goal of evaluating hybrids in the serum of BRCA1/2-deficient high-risk individuals. We plan to detect and sequence extracellular hybrids from BRCA1/2-deficient cell lines (aim 1) and serum samples (aim 2), and test a quantitative qPCR-based assay for serum hybrid analysis (aim 3). A highly sensitive, non-invasive, and inexpensive method for early cancer detection in individuals of elevated genetic risk would transform current management and surveillance schemes.

Swetha Gowrishankar, Ph.D. - 2021 Awardee

Anatomy and Cell Biology, University of Illinois College of Medicine at Chicago

"Evaluation of the In Vivo Efficacy of Novel Autophagy Activators for Amelioration of AIzheimer's Disease Pathology in the 5xFAD Mouse Model"

AIzheimer's disease (AD) is a progressive neurodegenerative disease that affects over 5 million people in the United States and is characterized by amyloid plaques, tau tangles, loss of synapses and ultimately, neuronal death. FDA-approved drugs for AD treat the symptoms of the disease but do not improve the underlying cell damage that leads to disease progression, highlighting the need for novel neuroprotective therapeutic options. Dysfunction in the autophagic and lysosomal pathways, which are critical for protein and organelle homeostasis in neurons, is associated with different stages of the disease, and thus modulation of autophagy has emerged as a new strategy for developing AD-targeted drugs. To this end, we have identified novel, small-molecule autophagy activators in a high-throughput screen that rescued key pathological features in human neuronal culture models of the disease. We hypothesize that these novel activators will restore optimal autophagy, clear protein aggregates, prevent disease progression, and ameliorate AD symptoms in the 5xFAD mouse model. We will test this hypothesis through determination of the drug metabolism and pharmacokinetic parameters of these two autophagy activators to identify a lead compound and evaluation of the in vivo efficacy of this compound in 5xFAD mice.

Nikki Johnston, Ph.D. - 2021 Awardee

Otolaryngology, Medical College of Wisconsin

"Aerosolized HIV Inhibitors for the Treatment of Laryngopharyngeal Reflux (LPR)"

More than 20% of the US population suffer from LPR with no effective medical therapy. We have identified two, well tolerated, drugs which hold promise for the treatment of LPR. While the FDA has approved a proof-of-concept clinical trial using the high dose oral formulation (Transformational Application), the long-term objective is to develop a metered inhaler for local delivery. Local administration of a low dose to the laryngopharynx can achieve the same therapeutically effective drug level as the high dose, oral formulation. It follows that the use of a lower dose will be associated with fewer and/or less severe side effects. We therefore propose to:

Specific Aim 1: Develop a water-based formulation of fosamprenavir and darunavir that is amenable for inhalation administration in humans, and

Specific Aim 2: Compare the dose response of oral and inhalation administration of fosamprenavir and darunavir for pepsin-mediated laryngeal epithelial damage in our established LPR in vivo mouse model.

Aerosol formulation offers the potential for generating Intellectual Property and thereby the means to connect with an industrial partner to carry out the detailed drug product development needed for an effective treatment for the millions of people in the US that suffer from LPR.

Mark Kaplan, Ph.D. - 2021 Awardee

Microbiology and Immunology, Indiana University

"Inhibitors Targeting Peanut-Specific Allergic Reactions"

Allergies are a result of allergen proteins cross-linking allergen-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 have impaired 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 step in moving these inhibitors to testing in humans is more formal toxicology analysis and establishing efficacy of the inhibitors for cutaneous anaphylaxis as a prelude to testing inhibition of skin prick testing. Thus, the specific aims of this application are to 1. Validate the inhibitory potential of cHBIs for cutaneous reactivity in humanized mouse models; and 2. Assess the cHBI toxicity and pharmacokinetics in non-human primate models. Together, these Aims will provide the critical data required to move forward with IND approval and preparation for phase I clinical trials.

Jonathan Kurtis, M.D., Ph.D. - 2021 Awardee

Pathology and Laboratory Medicine, Brown University

"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 1. The spread of parasites resistant to the artemisinin family of compounds 2 threatens recent progress achieved by antimalarial campaigns and underscores the urgent need to identify new anti-malarial drugs.

In previous work, we discovered PfGARP, a previously unrecognized vaccine candidate found only in P. falciparum. Antibodies to the highly invariant carboxyl-terminal of PfGARP (PfGARP-A, aa 411-673) inhibit parasite growth in vitro by 99% compared to controls ($P < 0.001$) by killing trophozoite stage parasites. In confocal and transmission electron microscopy studies, PfGARP localized to the exofacial surface of the RBC membrane in trophozoite and early schizont infected RBCs, but not to other parasite stages or uninfected RBCs. Importantly, the growth inhibition assays are performed in the absence of any immune effector molecules (complement) or cells- thus the remarkable anti-parasite effect of anti-PfGARP results from antibody binding alone. This is further supported by the killing effect of recombinant mAb (KD 2.9 nM, (95% CI = 1.3 – 5.9 nM)) and its rec monovalent Fab that target aa 443-459 (VKNVIEDEDKDGVEIIN) of PfGARP.

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 significant amino acid homology with human host proteins, and 3) the ability of antibody binding to PfGARP to kill essentially all parasites within 12-24 hours.

In the current proposal, we will: 1) conduct a targeted, high-throughput drug screen to discover drugs which mimic the lethal activity of antibodies recognizing PfGARP, 2) optimize and down select these candidates, and 3) validate these new drug candidates in a humanized mouse model of P. falciparum.

Kelvin Lee, M.D. - 2021 Awardee

Medicine, Indiana University

"Targeting PIM2 and its Regulation of the c-Myc Oncogene in Multiple Myeloma and Other Cancers"

Multiple myeloma (MM) is a malignancy of plasma cells that is the second most common hematologic malignancy (20% of all cases), and remains incurable for almost all patients. The primary cause of treatment failure is upregulation of pro-survival resistance mechanisms, and identifying these mechanisms remains key for new therapeutic development. We have recently reported that the serine-threonine kinase PIM2 has a major pro-survival role in MM, and that inhibition of PIM2 with a first-in-class PIM2-selective non-ATP-competitive kinase inhibitor JP11646 (JP) caused significant MM cell death in vitro and in vivo in preclinical MM models. Unexpectedly, JP was much more effective than the ATP-competitive PIM kinase inhibitors due to JP's unique ability to downregulate of PIM2 gene and protein expression. This has led to our findings that PIM2 has critical but previously unrecognized kinase-independent (KI) functions, which would be a change in paradigm. One such PIM2 KI function that is inhibited by JP is induction of the expression (mRNA and protein) of the c-Myc oncogene, which is dysregulated in ~50% of all human cancers, including MM. Our additional findings suggest a completely novel mechanism where JP disrupts PIM2 interaction with a partner protein (possibly c-Myc itself) that results in downregulation of c-Myc expression and loss of c-Myc driven PIM2 gene expression, collapsing a self-reinforcing loop that sustains both PIM2 and c-Myc expression. Targeting c-Myc expression through PIM2 inhibition represents an entirely unexplored therapeutic approach. The overall goal of this proposal is to develop JP11646 for the treatment of refractory/relapsed MM, and potentially for other cancers. The Specific Aims of the proposal are:

Aim 1. Define the kinase-independent mechanisms by which PIM2 supports MM survival, and how JP11646 inhibits these.

Aim 2. Conduct preclinical and IND enabling studies for a phase I clinical trial of JP11646 in refractory/relapsed multiple myeloma.

Tristan Maerz, Ph.D. - 2021 Awardee

Orthopaedic Surgery, University of Michigan

"Targeting Pathological Rspo2-mediated Wnt/β-Catenin Signaling as a Novel Treatment for Osteoarthritis"

Recent evidence has associated overactivation of canonical Wnt signaling through β-catenin(cWnt) with multiple pathological processes in osteoarthritis (OA). The cWnt agonist, R-spondin 2 (Rspo2), is a soluble ligand that our preliminary data demonstrates is sufficient to induce joint degeneration in vivo, making it a promising therapeutic target. The antidepressant drug Mianserin was recently identified as an Rspo2 inhibitor by blocking Lgr5 binding.

Our overall objective is to elucidate the role of Rspo2 in OA pathogenesis and test the efficacy of sustained intra-articular Rspo2 inhibition using Mianserin-loaded polymeric microspheres. We will:

Aim 1: Demonstrate the joint-protective effect of Rspo2 ablation. We hypothesize that joint injury-induced Rspo2 potentiates OA by activating cWnt signaling in multiple intra-articular cell types, promoting pathology. Using a global, inducible Rosa26-CreERT2; Rspo2flox mouse, we will globally ablate Rspo2 at the time of injury (Rspo2cKO) and comprehensively evaluate OA severity.

Aim 2: Test the efficacy of sustained intra-articular Rspo2 inhibitor therapy as a novel OA treatment. We will formulate PLGA microspheres to deliver the Rspo2 inhibitor Mianserin to the joint, assessing dose-dependent pharmacokinetics and pharmacodynamics of Mianserin release in vivo. Then, we will test the OA disease-modifying effects of Mianserin-loaded PLGA-MS in mice, benchmarking against repeated direct Mianserin injections.

Reshmi Parameswaran, Ph.D. - 2021 Awardee

Medicine, Case Western Reserve University

"BAFF CAR-NK Cells: An Efficacious and Safe Immunotherapy for B Cell Cancers"

CAR-T immunotherapies have produced remarkable clinical responses, but several challenges remain including disease relapse due to antigen escape/decreased CAR-T persistence, fatal side effects (cytokine release syndrome, neurotoxicity), the cost and time to produce CAR-T cells. We have developed novel B cell activating factor (BAFF) ligand-based BAFF CAR with multi-receptor specificity to target BAFF receptors (BCMA, TACI, BAFF-R) expressed by B cell cancers. We deliver BAFF-CAR to human NK cells using a non-viral TcBuster transposon platform, enabling safer, simpler, and more cost-effective CAR-NK production. Our preliminary data demonstrates in vitro and in vivo cytotoxicity of BAFF CAR-T cells against human malignant B cell lines. The overall objective of this proposal is to develop, optimize and evaluate BAFF-CAR NK cell therapy for the treatment of B cell malignancies. Aim 1: Achieve stable, non-viral integration of various BAFF CAR constructs in human NK cells. Aim 2: In vitro functional validation and characterization of BAFF CAR-NK. Aim 3: In vivo evaluation of dosing and efficacy of BAFF-CAR-NK cells using mantle cell lymphoma (MCL) xenograft NSG mouse model. Persistence of engineered NK cells will be evaluated in parallel with efficacy, as well as examination of preliminary safety endpoints and disease relapse.

Richard Pomerantz, Ph.D. - 2021 Awardee

Biochemistry, Jefferson Medical College of Thomas Jefferson University

"PROTACs for Targeting BRCA-Deficient Cancers"

DNA polymerase (Polq) is a unique polymerase-helicase DNA repair protein that has recently been validated as a synthetic lethal drug target in cancer cells harboring mutations in BRCA1 or BRCA2 (BRCA) tumor suppressor proteins. Polq promotes DNA repair via the microhomology-mediated end-joining (MMEJ) pathway (also referred to as alternative end-joining). Polq is essential for BRCA-deficient cells, but is dispensable for normal cells and Polq null mice show no phenotypes. Thus, Polq is synthetic lethal with BRCA1/2. Consistent with this, recently published Polq inhibitors (Polqi) selectively kill BRCA-deficient cells, while showing no effects in BRCA-proficient cells. Yet, whether these early stage Polqi will lead to clinically effective drugs is unknown.

Towards the goal of developing a clinically effective Polqi, our laboratory and collaborators have taken a different approach for targeting Polq: to develop a Proteolysis Targeted Chimera (PROTAC) Polq degrader to completely abolish all Polq activities in cancer cells. Because Polq null mice are healthy with no phenotypes, simultaneous inactivation of Polq polymerase (Polq-pol) and helicase (Polq-hel) enzymatic domains is expected to be a safe and a highly effective therapeutic method. Based on this rationale, we plan to develop a Polq PROTAC targeting the Polq-pol domain as a unique therapeutic for treating BRCA-mutant cancers.

Ying Sun, Ph.D. - 2021 Awardee

Human Genetics, Children's Hospital Medical Center dba Cincinnati Children's Hospital Medical

"Novel Brain-penetrable and Orally-available Small Molecule Pharmacological Chaperones to Treat Gaucher Disease and Parkinson's Disease"

Our drug discovery effort seeks to develop brain-penetrable and orally available small molecule pharmacological chaperones to restore defective acid β-glucosidase (GCase) as a new disease-modifying treatment for neuronopathic Gaucher disease and Parkinson's disease. We have identified novel small molecules that are non-inhibitory chaperones capable of improving multiple important endpoints: a) GCase activity, b) GCase substrate reduction and c) penetration through the blood brain barrier. We are presently at the critical optimization stage and will select lead compounds to advance as drug candidates for preclinical studies. In this proposal, we will optimize our lead compounds to improve activity and bioavailability. Newly designed compounds will be screened to increase GCase activity using cell-based multi-well screening platform. The chaperone property of selected compounds will be evaluated in fibroblasts and neurons carrying common GBA1 mutations found in Gaucher disease and Parkinson's disease patients. Selected compounds will be assessed for CNS drug properties, biodistribution, and preclinical evaluation in our diseased mouse models. Upon completion of the proposed milestones, we will have identified promising drug candidates of non-inhibitory chaperones that will be implemented for IND-enabling studies and advance a drug candidate into clinical trials to test the compound's benefit for patients with Gaucher and Parkinson's diseases.

Sherry Thornton, Ph.D. - 2021 Awardee

Rheumatology, Children's Hospital Medical Center dba Cincinnati Children's Hospital Medical

"Biomarkers for the Advancement of Targeted Therapies for Children with Juvenile Arthritis"

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease of childhood, affecting 1:1,000 children worldwide. This prevalence is about the same as juvenile diabetes. Currently, physicians lack laboratory tests to support them in the initial choice and sequence of medications prescribed to a child with JIA. This deficiency increases not only health care cost but also adversely impacts the prognosis of children with JIA. What is needed is a JIA-Rx Biomarker Panel, i.e., a comprehensive, yet concise group of biomarkers that helps anticipate the response of a child with JIA to a given immunosuppressive treatment. Over the next 1 year, we will (1) delineate serum biomarkers that individually, or in combination, forecast response of JIA therapy; (2) develop a mathematical algorithm to provide a numeric estimate for the probability of experiencing response to therapy, and (3) test the performance of these candidate biomarkers and algorithm in children with JIA who are newly started on TNF-blocking medications. We will use serum samples, gene expression RNAseq data, and clinical information from 187 children with JIA who participated in a 44-week, double-blinded international clinical trial (NCT02592434) of tofacitinib. Data and samples have been donated by Pfizer to CCHMC Rheumatology. We will enroll 60 children with JIA who are newly prescribed TNF inhibiting medication and study them prospectively. We expect to delineate an actionable JIA-Rx Biomarker Panel and interpretation rules to immediately support treatment decisions for children with JIA.

Wei Xu, Ph.D. - 2021 Awardee

Oncology, University of Wisconsin-Madison

"CARM1 Inhibition Enhances Immunotherapy Response in Triple-Negative Breast Cancer"

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer. Treatment options for this subtype are limited, as it is lacks expression of ER, PR, and HER2. Immune checkpoint inhibitors (ICI) have shown promising effects, but response rates are low, underscoring the need for combination therapy. However, there are many critical roadblocks for developing combination regiments, including identifying which combinations will be effective, and identifying biomarkers to select patients that are most likely to benefit from treatment.

This project is based on our groundbreaking discovery of the role of CARM1-mediated BAF155 methylation in modulating the efficacy of immunotherapy. We found that pharmacological inhibition of CARM1 boosted host immune responses by enhancing cytotoxic T cell activity and tumor infiltration, leading to tumor regression. Moreover, a combination of CARM1 inhibitor with ICI synergistically inhibited tumor growth. CARM1 is overexpressed in TNBC and is a druggable enzyme with several pharmaceutical inhibitors. Our studies suggest that inhibiting CARM1 methylation of BAF155 primes tumors to become immunologically 'hot', and sensitizes BC to ICIs.

Furthermore, methylated BAF155 (me-BAF155) is readily detected in circulating tumor cells of metastatic BC patients, making me-BAF155 a potential biomarker for selecting patients for the combined CARM1i and immunotherapy.

Hongwei Yu, M.D. - 2021 Awardee

Anesthesiology, Medical College of Wisconsin

"A Novel Analgesic Approach for Chronic Pain: Small Peptide Inhibition of Nav1.7 in Anatomically Targeted Sensory Neurons"

The peripheral nervous system is an appealing site for devising new analgesic treatments since primary sensory neurons (PSN) play a central role in the development and maintenance of chronic pain, and can be safely medicated in a highly targeted fashion. The Nav1.7 sodium channel plays fundamental roles in mediating pain, so development of PSN-targeted NaV1.7 inhibitors could provide highly effective analgesia. However, success in creating small molecule NaV1.7 inhibitors remains elusive. For a new approach, we propose a strategy in which small peptides derived from Nav1.7 ion channels are developed as interfering peptide aptamers (iPAs) for highly effective and selective blockade of pain signaling. These will be delivered selectively to anatomically targeted sensory neurons by recombinant adeno-associated viral (AAV) vectors to achieve analgesia without side effects or addiction potential. Candidate peptides will be identified by combined computational and experimental strategies and tested for selective and effective NaV1.7 channel blockade. Analgesic efficacy will be tested in established animal pain models representing neuropathic and arthritis pain, following AAV-NaV1.7iPA injection into peripheral segmental nerves. Preliminary observations with a prototypic NaV1.7iPA candidate predict highly safe and effective analgesia. Achievement of these goals will provide candidate agents suitable for development in the subsequent transformational phase.

Jennifer Yu, M.D., Ph.D. - 2021 Awardee

Cancer Biology, Radiation Oncology, Cleveland Clinic Lerner Research Institute

"Targeting Hypoxic Cancer Stem Cells to Improve Glioblastoma Treatment"

Glioblastoma is an incurable primary brain tumor that is characterized by regions of hypoxia and marked resistance to radiation. A major roadblock in the treatment of glioblastoma is the inability to kill the cells that give rise to disease recurrence, the glioma stem-like cells (GSCs). GSCs are highly resistant to standard cytotoxic treatments, have a high capacity for self-renewal, and are frequently located in hypoxic areas, which renders them even more difficult to kill with radiation and chemotherapy. Here, we propose to develop a new therapeutic strategy to kill these GSCs, with the long-term goal of extending glioblastoma patient survival. We have found that the long non-coding RNA (lncRNA) Lucat1 is an important regulator of GSC response to hypoxia. Lucat1 is frequently overexpressed in glioblastoma and is associated with poor prognosis. Our data support that Lucat1 is induced by hypoxia and forms a positive regulatory loop to promote HIF1alpha-mediated signaling. Lucat1 helps to maintain GSCs in hypoxia and promote tumor growth. By targeting Lucat1, GSCs fail to adapt to hypoxia, resulting in cell death. Silencing Lucat1 extends animal survival in mouse models of glioblastoma. Importantly, our data suggest that targeting Lucat1 has fewer side effects than direct inhibition of hypoxia regulator HIF1alpha. In this study, we propose to develop and optimize novel anti-sense oligonucleotide (ASO) therapeutics that inhibit Lucat1-HIF1alpha signaling and test the efficacy of these ASOs in mouse models of glioblastoma. Our findings will provide a new therapeutic approach for targeting GSCs in hypoxia to improve glioblastoma control.

Hermine Brunner, M.D., M.B.A., M.Sc. - 2020 Awardee

Pediatrics, Division of Rheumatology, Children's Hospital Medical Center dba Cincinnati Children's Hospital Medical

"Lupus Nephritis Biomarkers for the Advancement of Therapies for Lupus Nephritis"

Lupus, incurable autoimmune disease affects round 1.5 million persons living in the United States. Among the main risk factors for poor disease outcome is the presence of lupus nephritis (LN). The applicants have discovered and initially validated a panel of LN-biomarkers [NGAL,MCP-1,Kim-1,ceruloplasmin,adiponectin,hemopexin]. Considering the urine levels of these LN-biomarker we delineated an algorithm, the Renal Activity Lupus Index (RAIL), where higher scores reflect more kidney inflammation as seen on kidney biopsy. Changes in RAIL scores allow us to predict LN flares and LN response to therapy at least 3 months earlier than when using current clinical tools. Further, our pilot studies suggest that the RAIL score can be used to refine the dosing of current LN therapies; we observed that high-dose intravenous steroids lead to a dramatic reduction of the RAIL score that does not occur when only daily oral steroids are used for LN therapy.

Critical Scientific Roadblock to be addressed: To enable the application of these highly promising LN-biomarkers and the RAIL algorithm in clinical care and for research, following work needs to be conducted: (1) development of a high-quality multiplex assay (RAIL-MPLA) to rapidly measure all of the LN-biomarkers concurrently; (2) additional validation of the RAIL in an independent cohort of adults and children.

Approach: Working together with Ethos Research & Development and pharmaceutical companies, we will: (1) develop a RAIL-MPLA; (2) define changes of RAIL scores that reflect clinically relevant improvement of LN and reference values for absent, controlled and active LN across age-ranges; and (3) test the hypothesis that high-dose intravenous steroids result in a significantly higher reduction of the RAIL score compared to standard doses of oral steroids alone.

Expected Results/Deliverables:

- Develop a novel clinically actionable multiplex assay that accurately quantifies the biomarkers used in the RAIL within 4 hours of sample receipt.
- Increase the usability of RAIL by refining the interpretation of RAIL scores
- Immediately advance the treatment of LN by providing the scientific underpinning for the preferred use of intravenous rather than oral steroids alone.

Christina Curtis, Ph.D. - 2020 Awardee

Medicine, Stanford University

"Identifying and Targeting the Drivers of Metastasis and Resistance in High-Risk of Relapse Estrogen-Receptor Positive Breast Cancer"

Women with early-stage estrogen receptor-positive (ER+) breast cancer face a persistent risk of distant recurrence and breast cancer death up to 20 years post diagnosis. We have recently reported the 20 year follow-up of nearly 2000 early-stage breast cancer patients with accompanying tumor molecular profiling. This work identified 11 integrative clusters (ICs) of breast cancer, defined based on integration of genomic copy number alterations and transcriptional profiles, with markedly variable risk of recurrence over time. Four of these ICs had exceedingly high risk of recurrence – over 40 percent 20 years post diagnosis – and together comprised nearly one-quarter of ER+/HER2- patients. Importantly, each of these ICs harbored a characteristic and putatively targetable gene amplifications. We hypothesize that therapy targeted at the driver genes present in each of the high-risk ER+/HER2- IC groups will reduce tumor cell proliferation, providing a path forward to design targeted therapeutic strategies aimed at preventing recurrence and reducing mortality associated with lethal metastatic breast cancer. Having identified and validated biomarkers of breast cancer relapse, several of which themselves represent potential new therapeutic targets, we propose to functionally characterize the drivers of the high-risk Integrative Clusters (ICs), to uncover their oncogenic dependencies and to elucidate mechanisms of resistance to endocrine and targeted therapies. Accordingly, we will leverage advances in CRISPR technology to perform pooled multiplexed CRISPR/dCas9-interference (CRISPRi) screens in representative 2D cell lines and 3D spheroid cultures to delineate 3D-specific vulnerabilities (Aim 1). In tandem we propose reciprocal experiments in which we oncogene engineer non-malignant mammary cells via CRISPR/dCas9-activation (CRISPRa) pooled screens to define the genes that promote malignant growth (Aim 2). Further, we will exploit a powerful cellular barcoding techniques to trace clonal dynamics during treatment and delineate the functional determinants of response to targeted and endocrine therapies in representative patient-derived organoid models (Aim 3). These complementary approaches will systematically define novel therapeutic targets and mediators of drug sensitivity in aggressive ER+ breast cancer, thus informing subsequent clinical trials.

Richard Harvey, M.D. - 2020 Awardee

Physical Medicine and Rehabilitation and Physical therapy and Human Movement Sciences

Rehabilitation Institute of Chicago

"HUMMINGBIRD: Advancing Technology for Motor Recovery in Hand and Fingers for Stroke and Spinal Cord Injury"

The purpose of this project is to develop a usable bedside hand therapy device that that takes advantage of early neuroplasticity following stroke and cervical spinal cord injury (SCI) to retrain functionally relevant movement in individual fingers of the neurologically impaired hand. It is well established in neuroscience that neural recovery and neuroplasticity at the level of cortex in animals and humans is dependent on active motor practice. In this Catalyst project we will determine and assure that the second-generation device we have develop, which has not yet been used in humans, is usable in the clinical setting and that patients with stroke and cervical SCI find it a meaningful tool for relearning hand movement. We will also assess whether use of the device daily for 2 weeks results in improved functional hand use, improve finger strength and improved ability to control individual finger movements. Although these abilities are foundational to functional manipulation of objects with the hand, there is presently no specific therapeutic interventions, nor time available in conventional early (acute) rehabilitation to address these goals. Thus, early intensive hand recovery is an obvious but unmet need in neurorehabilitation. Our goals for this one-year project are determine if the device:

1. can facilitate improve hand function.

2. can improve finger strength and individuation.

3. is usable in a clinical setting and serves as a meaningful therapy tool to patients with stroke and cervical SCI.

If successful, this project will lead to a refined therapy protocol in preparation for a larger clinical trial to establish efficacy of this training approach for both stroke and cervical spinal cord injury. We chose to study both patient populations as we believe this tool can have benefit for both groups and to study both provides generalizability to a wider group of patients needing rehabilitation. If we achieve our long-term goal, this device will evaluated in a large multi-center pivotal trial in preparation for transition to the clinical marketplace as new rehabilitation technology that has proven scientific evidence supporting its efficacy in early hand rehabilitation.

Hannelore Heemers, Ph.D. - 2020 Awardee

Cancer Biology, *The Cleveland Clinic*

"Developing Citron Kinase Inhibition As A Mechanistically Novel Approach To Overcome Cancer Treatment Resistance"

Treatment resistance causes nearly all cancer deaths. Novel treatments that bypass this resistance and inhibit the biology that drives cancer progression are needed to improve patient survival. Using prostate cancer (CaP) as model, we isolated citron kinase (CIT) as a target for such a therapy. CIT is a previously unrecognized novel druggable target that is functionally distinct from current targets yet is a critical determinant of cancer cell proliferation and induces cancer growth and treatment resistance. CIT silencing inhibited growth of cell lines and xenografts representing different stages of CaP progression and diverse forms of treatment resistance but not of benign epithelial prostate cells. CIT's stimulation of cancer progression relied entirely on its kinase activity, isolating CIT's kinase activity as a completely new target. A specific CIT inhibitor has not yet been developed. By analyzing the target spectrum of kinase inhibitors and CIT kinase assays, we identified 3 multikinase inhibitors that inhibit CIT, decrease CaP cell proliferation and inhibit CIT substrate phosphorylation. Because these drugs are not selective for CIT and thus not likely to succeed as cancer therapies, we developed a lead compound that inhibits CIT at low doses, has improved CIT selectivity and promising DMPK.

Our objective is to develop our lead compound into first-in-class selective CIT inhibitor as a novel cancer treatment. We hypothesize that novel CIT inhibitors will overcome acquired resistance to conventional cancer therapies, which will be reflected in the phosphorylation status of CIT substrates. We will test 2 Specific Aims:

1. To determine the therapeutic efficacy of novel CIT inhibitors during cancer progression using multiple chemistry and crystallography approaches and kinome screens to improve CIT specificity and DMPK and verifying growth inhibition of clinical relevant treatment-resistant cancer models.

2. To determine the substrates by which CIT kinase action conveys aggressive cancer behavior using integrated state-of-the-art biotin-based proximity ligation assays, kinase substrate arrays, and mass spectrometry approaches.

We expect these studies to have a significant positive impact because they will provide CIT inhibition as an entirely new and functionally diverse cancer treatment and the phosphorylation status of CIT substrates as a treatment-specific biomarker of response.

David Hildeman, Ph.D. - 2020 Awardee

Pediatrics, Division of Immunobiology

Children's Hospital Medical Center dba Cincinnati Children's Hospital Medical

"IL-10 Blockade to Boost Influenza Vaccination in Non-human Primates"

Declining immune function is well described in the elderly, and leads to increased risk and severity of infection, poorer control of cancer, and impaired responses to vaccination, all major public health concerns. Further, the elderly population is at high risk of mortality if infected with new viral pathogens, such as SARS-CoV2. So, even if vaccines are quickly developed against emerging pathogens, they are likely to have reduced efficacy in the elderly. Thus, there is an urgent need to identify strategies to increase vaccine responses in elderly humans.

Our exciting and newly published data show that levels of IL-10, an immune suppressive cytokine, are increased dramatically with age. Further, we found that the majority of this IL-10 is produced by a population of cells called T follicular helper (Tfh) cells, which are normally critical for productive antibody responses. Notably, these aged, IL-10-producing Tfh cells are found in both mice and humans. Strikingly, neutralization of IL-10R signaling in aged mice substantially increases antibody responses, nearly to the levels observed in young mice. In monkeys, we defined the pharmacokinetics of an IL-10 neutralizing antibody as well as a soluble receptor. Given these compelling data, we hypothesize that Tfh10 cells play an important role in impaired age-related vaccine responsiveness that is conserved between mice, monkeys, and humans. Here, we propose to determine if short-term IL-10 blockade will restore Flu vaccine responsiveness in aged macaques. We propose an iterative approach, assessing whether concomitant blockade of IL-10 alongside flu vaccination will: (i) increase anti-influenza neutralizing antibody responses in response vaccination without increasing systemic inflammation (ii) promote resistance to influenza challenge. These studies will likely have important translational implications, as a short-term blockade of IL-10 signaling could be envisioned to improve vaccine responsiveness in elderly humans. Our long-term goal is to develop therapeutic strategies to enhance protective immune responses in the elderly.

Evangelos Kiskinis, Ph.D. - 2020 Awardee

Neurology, Northwestern University Feinberg School of Medicine

"Development of Spherical Nucleic Acid-Based Anti-Sense Oligos for the Therapeutic Treatment of Pediatric Epilepsy Disorders"

Heterozygous mutations in KCNQ2, which encodes a pore-forming K+ channel subunit responsible for neuronal M-current, cause neonatal epileptic encephalopathy (EE), a complex disorder presenting with severe early-onset seizures and impaired neurodevelopment. The condition is exceptionally difficult to treat, partially because the effects of KCNQ2 mutations on the development and function of human neurons are unknown. Using induced pluripotent stem cells (iPSCs) and gene editing we have established KCNQ2-EE disease model systems, and measured the functional properties of patient-derived neurons using electrophysiological and optical approaches at single-cell resolution. We find that patient-derived excitatory neurons develop intrinsic and network hyperexcitability that mimics epileptic electroencephalogram (EEG) activity. Using heterologous expression systems, we have also found that some disease-causing variants exhibit a dominant-negative effect, reducing the channel activity by more than 50%. We hypothesize that deleting the mutant transcript will restore channel activity and alleviate the associated neuronal firing defects. Here, we propose to collaborate with Exicure Inc, to design, screen and test allele-specific antisense oligonucleotides (ASOs), which will target and degrade the mutant KCNQ2 allele. Exicure, is a clinical-stage biotechnology company developing spherical nucleic acid (SNA) based ASOs for genetic disorders. We will assess the specificity of ASOs using established digital droplet PCR assays and examine the efficacy of ASOs by measuring their ability to restore the firing activity of patient-derived neurons. If successful, our work will provide a rational therapeutic approach for this devastating disease.

Eric Morrow, M.D., Ph.D. - 2020 Awardee

Molecular Biology, Cell Biology and Biochemistry, Brown University

"Development of a Preventative Treatment for a Novel Neurometabolic Disorder in Childhood"

Intellectual disabilities are common and carry high lifetime costs to families. We have identified a new neurodevelopmental disorder caused by loss-of-function mutations in the mitochondrial enzyme glutamate pyruvate transaminase 2 (GPT2). GPT2 disease involves postnatal microcephaly, cognitive disability, epilepsy, and progressive spastic paraplegia. GPT2 localizes to mitochondria and catalyzes the reversible addition of an amino group from glutamate to pyruvate, yielding alanine and alpha-ketoglutarate, a metabolite in the tricarboxylic acid (TCA) cycle. Metabolic diseases in children, such as GPT2 disease, may be amenable to treatments, via dietary restrictions or supplements, that can prevent intellectual disabilities when treated early. With the prospect of newborn screening supported by genome-wide sequencing on the horizon, there will be new opportunities to intervene in childhood brain disease. Therefore, we rapidly need to determine which new neurometabolic diseases may be amenable to interventions in early childhood. Our preliminary data provide support for disease mechanisms wherein GPT2 plays a critical role in alanine synthesis, as well as in neuronal anaplerosis. Anaplerosis (filling-up) is the metabolic process whereby TCA cycle intermediates are replenished. Anaplerosis is important during high biosynthetic demand, such as during brain development, when TCA cycle intermediates are consumed for synthesis of macromolecules for cell growth. We have established potential treatment strategies for GPT2 disease that may be implemented in the near term. To guide these interventions, we propose to complete needed pre-clinical studies. Our overriding hypothesis is that GPT2 is required for metabolic mechanisms central to neuronal and axonal growth during brain development, particularly in long projection neurons of the motor system. In Aim 1, we will test mechanism-based treatments in our mouse model of GPT2 disease. Our Gpt2-null mouse recapitulates key aspects of disease, such as motor abnormalities, akin to spastic paraplegia seen in patients. In Aim 2, to translate our basic findings to the clinic, we will establish the infrastructure and collaborations, including with industry, to develop a protocol for biomarker studies and a clinical trial in patients. The impact of this research is that we will establish the basis for therapeutics in a childhood disease for which there is no current treatment.

Lonnie Shea, Ph.D. - 2020 Awardee

Biomedical Engineering, University of Michigan

"A Cell Capture Implant to Predict Acute Cardiac Allograft Rejection"

Over 36,000 solid organ transplants are conducted annually in the US, costing $30 billion. Immunosuppressive drugs protect these donor grafts from acute rejection but increase the risk of opportunistic infections and cancer, especially in pediatric transplant recipients, who require immune suppression for decades. As there is no method for determining which grafts will be rejected, immunosuppression is aggressively applied in a one-size-fits-all approach.

We have developed a novel implantable scaffold device to monitor recipient immune response to the transplant that would enable the use of personalized immunosuppression while maintaining graft acceptance. We employed these scaffold devices in a murine skin allograft model to develop a highly sensitive and specific scoring system from a 19 gene biomarker signature to distinguish between recipients with healthy grafts and recipients with rejecting grafts.

In heart transplantation, organ scarcity requires that clinicians remain vigilant in preventing acute cardiac allograft rejection (ACAR) through frequent graft biopsy and aggressive immunosuppression, at the expense of toxicities due to over-suppression. A novel surveillance method is urgently needed to calculate the early risk of transplant rejection to allow personalized immunosuppression regimes. Here, we present a novel subcutaneous scaffold implant that collects biomarkers of graft health that will predict ACAR onset to preserve graft function while reducing the need for frequent graft biopsy and overly aggressive immunosuppression. In this proposed work, we will employ these minimally-invasive cell capture scaffolds in four cohorts of heterotopic heart transplants in mice in which we will identify a signature gene panel of graft rejection, validate this scaffold biomarker signature, assess the predictive power of the signature, and employ the biomarker signature to monitor the immunosuppression response. We hypothesize that the dynamic changes captured in the scaffold device as the allograft is recognized as non-self by the recipient immune system will enable the development of a novel predictive biomarker panel for ACAR. This minimally-invasive immune cell-capturing scaffold could prove transformative in directing and personalizing immunosuppression in solid organ transplant recipients.

David Spiegel, M.D., Ph.D. - 2020 Awardee

Chemistry, Yale School of Medicine

"Development of Bifunctional Molecules that Cross the Blood-Brain Barrier and Degrade Pathogenic Neurological Proteins"

Unique challenges are presented when treating neurological disease due to the physical obstacle formed by the Blood-Brain Barrier (BBB). Many neurodegenerative diseases result from the accumulation of pathogenic proteins and could potentially be avoided with the early detection and removal of these species. The Spiegel lab is developing a novel class of bioactive molecules that can bind proteins non-covalently and chaperone them across the BBB. These small molecules will be used for the removal of pathogenic proteins from the brain as a novel therapeutic approach to the treatment of neurological diseases. The bifunctional small molecules consist of a protein-targeting motif and a motif for the transport of the target protein across the blood-brain barrier, and subsequent degradation.

Stephen Strittmatter, M.D., Ph.D. - 2020 Awardee

Neurology, Yale School of Medicine

"Neural Repair for Spinal Cord Injury by Axon Regeneration"

Devastating and persistent functional deficits occur after Spinal Cord Injury (SCI), despite survival of nearly all neurons. Partial recovery would be adequate for patients to gain a level of independence in wheelchair transfers, bowel and bladder management, and locomotion. Today, there is no approved medical therapy for the over 300,000 individuals in the USA with SCI, rendering therapy a totally unmet medical need. Because the primary cause of disability is disconnection of networks by axon transection, axon regrowth has the potential to provide recovery by restoring connectivity, without requiring "new" cells. Unfortunately, without therapeutic intervention, the adult brain and spinal cord produce extremely limited reparative axon growth after damage.

We surveyed the mouse genome in an unbiased approach for loci with undiscovered functions in axon regeneration. This screen identified 400 genes whose suppression yielded greater axon regeneration in vitro. In Preliminary Studies, we leveraged the in vitro results to identify pathways that might be targeted to improve CNS neural repair in vivo using a simple optic nerve crush model. In control eyes, very few axons regenerate, but knockdown of 40 of the in vitro hit genes produced significantly increased regeneration. These genes were validated gene editing using CRISPR/Cas9 in vitro and in vivo.

In the current proposal, we will test two of these novel regeneration genes as attractive therapeutic candidates for their ability to promote axon growth and behavioral recovery after spinal cord injury in mice. We hypothesize that their demonstrated axon regeneration activity will translate into improved neural repair. Validation of this hypothesis will support development of their potential in translational research.

Ross Summer, M.D. - 2020 Awardee

Medicine, Thomas Jefferson University

"Preventing De-condensation of Nascent Chromatin in the Treatment of Pulmonary Fibrosis"

The goal of this project is to develop an effective therapy for Idiopathic pulmonary fibrosis (IPF), a devastating lung disease that progressively scars the lung and has a prognosis worse than many aggressive cancers. A defining feature of IPF is the differentiation of fibroblasts into myofibroblasts, followed by the production of massive amounts of extracellular matrix (ECM) and the formation of collagen-rich scars, which restrict movement of the lung and impede respiratory gas exchange. While two anti-fibrotic drugs are approved to treat IPF, neither therapy is highly effective. Our long-term objective, and the focus of this high-risk, high-yield application is to develop a new, effective therapy for IPF. Previous work has shown that differentiation of embryonic and hematopoietic stem cells requires the transient decondensation of chromatin at sites of repressed genes and that failure to do so prevents the binding of critical differentiation transcription factors (TF). The hallmark of condensed arrays of nucleosomes in chromatin is H3K27me3, and transient global removal of this mark is required for activating repressed genes during differentiation of stem and progenitor cells. The same mechanism was also found in more differentiated naïve T cells during their differentiation into Th1 and Th2 helper cells, leading us to hypothesize that removal of H3K27me3 chromatin marks might also dictate the differentiation of fibroblasts into myofibroblasts. Because transient de-condensation of the H3K27me3-marked chromatin is achieved by the activities of the H3K27me3 de-methylases (KDM) UTX and JMJD3, we hypothesized that inhibiting these enzymes via a small molecule 'epigenetic' inhibitor GSKJ4 would arrest pulmonary fibrosis. In preliminary studies presented here, we show that GSKJ4 effectively blocks the formation of myofibroblasts in vitro and limits the production of extracellular matrix genes in experimentally induced IPF mouse models. We now wish to extend these observations in hopes of moving this concept to the clinic. To achieve this goal, we propose 3 rationally designed Specific Aims that are mechanistically link but fully independent. Studies in this application aim to challenge current approaches to the treatment of IPF and provide support for targeting nascent chromatin in the treatment of a wide assortment of fibrotic diseases.

Allan Brasier, M.D. - 2019 Awardee

Medicine, University of Wisconsin-Madison

"Targeting the Myofibroblast Epigenome for First-In-Class Treatment of Chronic Obstructive Pulmonary Disease, COPD"

Chronic Obstructive Pulmonary Disease (COPD) affects 13.5 million (M) people in the US with a regional age-standardized death rate that will be the 4th leading cause of death by 2020. This obstructive lung disease is characterized by acute episodic decompensations, "exacerbations" associated with increased symptoms that result in substantial morbidity and costs through unscheduled hospital visits. Importantly, exacerbations are associated with more rapid declines in pulmonary function for which no effective therapies exist. These patients suffier substantially reduced quality of life and over half will die of acute-on-chronic respiratory failure.

COPD is initially triggered by oxidative airway injury that results in the activation of a pathogenic mesenchymal myofibroblast population in the small bronchioles of the airway. Myofibroblasts produce fibronectin and collagen that reduce the normal elastic properties of the lung and impair gas exchange.

The broad goal of this Catalyst Award is to advance first in-class therapeutics that target myofibroblast transdifferentiation. This advance will come in two stages, each a focus in this application. First, there are no high resolution, non-invasive methods for detection of airway remodeling or determination of therapeutic response. We will validate an integrated proteomic and imaging diagnostic for airway remodeling based on our unbiased pharmacoproteomics study of inhibiting BRD4 in airway remodeling. Quantitative selective reaction monitoring assays of a panel of airway remodeling proteins will be paired with minimally invasive optical imaging of mucosal collagen deposition using optical coherence tomography (OCT). Second, we will advance a lead highly selective BRD4 inhibitor to an aerosol formulation encapsulated in proprietary Dendron Micelles. Understanding that foci of myofibroblasts are initially formed in the small bronchioles, we will develop aerosolized therapeutics that target fibronectin-rich foci. Nanoparticle formulation have additional advantages that they will enhance duration of effect, and reduce potential systemic toxicity. We will demonstrate enrichment using advance mass spectrometry based imaging, and demonstrate efficacy in an established model of COPD.

By advancing, in parallel, minimally invasive biomarkers and targeted therapeutics, we will be uniquely poised to translate these into first-in human studies

John Bushweller, Ph.D. - 2019 Awardee

Molecular Physiology and Biological Physics, University of Virginia

"RUNX1-ETO Targeted Small Molecule Therapy for t(8;21) Acute Myeloid Leukemia"

The gene encoding RUNX1 (AML1) is disrupted by the t(8;21) that is associated with 4-12% of adult acute myeloid leukemia (AML) patients and ~13% of pediatric AML patients. The t(8;21) results in a fusion protein containing the N-terminus of RUNX1, including the Runt domain, fused to almost all of ETO. The RUNX1-ETO (also called AML1-ETO) fusion protein acts as a dominant repressor of RUNX1 function, dysregulating the expression of multiple genes required for normal hematopoiesis and, in cooperation with secondary mutations, leads to the development of leukemia. The RUNX1-ETO fusion protein has clearly been established as the primary driver of t(8;21) AML. About 60-70% of t(8;21) patients are alive at 5 years, however disease recurrence is the major treatment failure with 30-40% of these patients relapsing after standard intensive chemotherapy, highlighting the need for new approaches to treatment. The standard chemotherapy used to treat these patients has serious long-term side effects, which is particularly problematic for pediatric patients who will deal with these effects throughout their lives as well as for older patients who can't tolerate standard chemotherapy as well. In order to overcome this, it is essential to develop drugs which directly and selectively target the RUNX1-ETO fusion protein driver to treat the disease.

We propose to develop small molecule inhibitors of RUNX1-ETO that block its ability to bind to DNA and which selectively inhibit RUNX1-ETO while having minimal if any effect on wildtype RUNX function. Such a high level of selectivity of action has rarely been achieved, but we have previously done so in targeting the CBFβ-SMMHC fusion protein driver in inv(16) AML. We are proposing to develop a hetero-bivalent compound which targets both the Runt domain of RUNX1 (DNA binding domain) and the TAF domain of ETO (the nearest ETO domain to the Runt domain in the fusion protein). We have screened and optimized a compound which binds to the TAF domain displacing HEB with a low μM IC50. We have identified compounds which covalently react with Cys residues on the Runt domain. For this grant, we will focus on covalently linking the TAF domain inhibitor to optimized Cys reactive compounds. Linker length and chemical structure will be varied to identify optimal linkers. Compounds will be evaluated in t(8;21) cell lines for their ability to inhibit growth, alter the expression of RUNX1-ETO target genes (qPCR), and ability to inhibit binding of RUNX1-ETO to its genomic sites (ChIP).

Lin Guo, Ph.D. - 2019 Awardee

Biochemistry and Molecular Biology, Thomas Jefferson University

"Developing Therapeutic Agents to Rescue Neurotoxicity of FUS Aberrant Phase Transition"

It is now universally appreciated that accumulation of misfolded proteins, which can acquire alternative proteotoxic states, causes a series of deleterious molecular events resulting in numerous lethal neurodegenerative diseases. Among these, amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease. There are no effective therapies for ALS and very few treatment options. Therefore, new therapeutic target and strategies are greatly needed. ALS-linked mutations have been discovered in several prion-like domain (PrLD) containing nuclear RNA-binding proteins (RBPs) including FUS, which is a stress granule (SG) component. Cytoplasmic mislocalization and inclusion formation, which are common pathological features of FUS proteinopathies, have been connected to persistent SGs. Upon stress, ALS disease proteins are recruited to SGs, which are reversible cytoplasmic membraneless organelles that form through Liquid-liquid phase separation (LLPS) and behave like liquid-droplets. Because SGs condensate ALS disease proteins such as FUS that are intrinsically aggregation-prone, if SGs are not cleared in time, FUS can go through aberrant phase transition to form solid fibrils that can induce toxicity and neurodegeneration. The long-term goal of this project includes understanding the molecular mechanisms underlying the aberrant phase transitions of SGs and leveraging our understanding of aberrant phase transition to develop therapeutic agents to mitigate the neurotoxicity of these pathological events. This proposal focuses on developing two types of therapeutic agents to rescue FUS neurotoxicity caused by aberrant phase transition. We have discovered a novel function of nuclear import receptor-Kapbeta2 in reversing FUS aberrant phase transition and aggregation. However, ALS-causing mutations in FUS PY-NLS such as P525L reduces Kapbeta2's activity as protein disaggregase. Therefore, the first goal of the proposal is to discover small molecules that can enhance Kapbeta2's activity to reverse FUS P525L aberrant phase transition. Kapbeta2 reverses FUS aberrant phase transition by binding to the nuclear localization signal PY-NLS in the C-terminus of FUS. Thus, other FUS-binding biomolecules might also prevent and reverse FUS LLPS and aggregation. Indeed, our preliminary data show FUS-binding RNA can prevent and reverse FUS aggregation. Therefore, the second aim of the proposal focuses on developing RNA oligonucleotides to reverse FUS aberrant phase transition and defining their therapeutic potential in mitigating FUS neurotoxicity. The in vitro activities of the agents developed in this proposal will be characterized using pure protein biochemical and biophysical assays. Top ranking agents will then be validated in iPSC-derived motor neurons for their ability to mitigate FUS aberrant phase transition and the resulted neurotoxicity.

Yogendra Kanthi, M.D. - 2019 Awardee

Internal Medicine, Division of Cardiovascular Medicine, University of Michigan

"Combating Venous Thrombo-Inflammation with Precision Bio-functional Therapies"

Venous thromboembolism (VTE), comprised of deep venous thrombosis and secondary pulmonary embolism, affects 900,000 people and is the third leading cause of cardiovascular death. Current therapies are limited to anticoagulation, which carries significant bleeding risks and don't address the inflammatory processes that initiate and propagate VTE. Therapies that directly target inflammatory processes would address the underlying catalyst of disease and have the potential to fundamentally transform the treatment of VTE.

A distinguishing feature of VTE is the recruitment of leukocytes to the thrombus. We discovered that this is driven by marked neutrophil activation, the expulsion of DNA as neutrophil extracellular traps (NETs), and inflammasome activation to release a potent inflammatory cytokine, interleukin 1-beta(IL-1beta). This phenomenon further polarizes the vascular environment in a self-amplifying loop culminating in VTE. We showed that hyperactive neutrophils are more prone to form NET 'scaffolds' for thrombus expansion, and that systemic delivery of anti-IL-1beta antibodies (Ab) can markedly reduce neutrophil activation during thrombogenesis. There is currently no therapeutic approach to specifically target neutrophils, and systemic IL-1beta inhibition is limited by suppression of other innate immune functions essential in host-defense. This represents a critical roadblock in the translation of our findings into the clinic for patients with VTE.

Our goal in this Falk Catalyst proposal is to overcome this current roadblock by developing a synthetic bio-functional molecule to precisely target neutrophils for inhibition during thrombogenesis. This proposal builds on an existing collaboration between experts in venous thrombo-inflammation and vascular-targeting drug carrier design to develop a neutrophil-tropic particle that directs to the inflamed neutrophil and arrests thrombosis expansion. The Aims outlined here will optimize our novel nanoparticles to exclusively target to neutrophils (Aim 1, Particle optimization); and determine whether this approach effectively reduces in vivo and in vitro neutrophil activation and venous thrombogenesis (Aim 2, Efficacy). Our proposal is driven by our innovative discoveries, expert cross-disciplinary collaboration, and strong preliminary data, with the long-term objective of developing a neutrophil-inhibiting 'precision' therapy for patients who suffer from venous thromboembolism. The results of these studies will provide a solid rationale for us to translate our discoveries during the Transformational phase of this Award, and form the basis of an innovative and more complete strategy to treat one of the leading cardiovascular diseases.

The University of Michigan has a unique history of organizing around research questions across disciplines, providing a robust foundation for the Catalyst and Transformational phases of this program.

Chaitan Khosla, Ph.D. - 2019 Awardee

Chemistry, Stanford University

"A Novel Therapeutic Approach for Major Depressive Disorder"

Major depressive disorder (MDD) is among the leading causes of illness and disability worldwide. It is a severe and life-threatening disease. Childhood trauma and insulin resistance are known risk factors for MDD. The pathophysiology of MDD remains poorly understood, and there is a serious dearth of new druggable biological targets to guide the development of improved therapeutics. This proposal outlines a research plan to identify a fundamentally new drug therapy for MDD.

In rodent models of depression, the biomolecule acetyl-carnitine promotes a rapid anti-depressant response. Endogenous acetyl-carnitine levels are also lower in the plasma of patients with MDD compared with age- and sex-matched healthy controls. Several older studies involving human subjects have also reported neurophysiological and neuropharmacological effects of oral acetyl-carnitine, although these studies were either uncontrolled or under-powered. While not a typical drug-like substance, acetyl-carnitine has properties that make it a promising lead for our purposes. It is classified as a Generally Regarded as Safe (GRAS) substance by the FDA, and is orally bioavailable, while also being transported across the blood-brain barrier.

Our goals for this Catalyst Research Award are to assemble a multidisciplinary team of researchers with relevant backgrounds in chemistry, neuropharmacology, and psychiatry to launch a comprehensive drug discovery effort aimed at optimizing the activity of acetyl-carnitine in MDD. Our technical aims are to: (1) Implement robust in vitro and in vivo assays based on our model for the mode of action of acetyl-carnitine in MDD; (2) Design and synthesize acetyl-carnitine analogs, and test them in the above assays; and (3) Compare the activity of the most promising analog vesus acetyl-carnitine in a rodent model of depression. If successful, these team-building and technical achievements will pave the way for a more intensive pursuit of a safe and effective drug candidate for MDD therapy under the Transformational Research Award Program.

Jeannette Messer, D.V.M., Ph.D. - 2019 Awardee

Inflammation and Immunity, The Cleveland Clinic

"Crafting New Weapons for the Fight Against Infectious Diseases"

Infectious diseases caused by bacteria, viruses, fungi, and single-cell parasites kill millions of people worldwide, each year. Although these microorganisms are very different in many ways, the first step of infection with each of them is microbial adherence to human or host tissues. Regardless of the microorganism, adherence essentially always involves binding between a protein on the surface of the microbe and a carbohydrate ligand on the host. Without this binding, microbes cannot infect host tissues and cause disease. It is clear that blocking microbial adherence mechanisms shared among microbes would be a powerful and nearly universal way to treat or prevent infectious diseases. However, no conserved aspects of microbial adherence have ever been identified and there are no proposed strategies to target this type of dangerous microbial behavior.

We have identified a conserved amino acid motif (CAMo-1) with an associated molecular feature in a large number of adherence proteins from bacteria, viruses, fungi, and protozoa. In our preliminary work, we identified this novel drug target and validated it experimentally by showing that a host protein binding to this structure blocks microbial adherence to human cells. The goal of this study is now to identify and develop small molecules that bind to this structural feature and block microbial adherence to host cells for treatment and prevention of these infectious diseases. We hypothesize that we can identify specific small molecules that bind to microbial adherence proteins at CAMo-1 to block the attachment of pathogenic microbes to human tissues. We will test this hypothesis using three different screening approaches as outlined in our specific aims: Aim #1) Use purified recombinant proteins to identify small molecules that bind to microbial adherence proteins at CAMo-1. Aim #2) Use bead-based microbial mimics to identify small molecules that prevent microbial adherence protein binding to host cells. Aim #3) Use live microbes to identify small molecules that prevent microbe binding to host cells. In each of these aims we will be performing primary and secondary screens using diversity and fragment small molecule libraries. Successful completion of this study would provide small molecule leads for development of a completely new type of antimicrobial drug designed to target dangerous microbial behaviors, regardless of the microorganism. This would be a paradigm shift in how these diseases are conceptualized and treated and a major advance towards our long-term objective to provide cures for infectious diseases in which no cures currently exist.

Jon Parquette, Ph.D. - 2019 Awardee

Chemistry and Biochemistry, The Ohio State University

"Antioxidant Nanoscaffold Technology for Combinatorial Treatment of Diabetes"

Diabetic patients often develop neuropathies and have a greater risk for vascular or Alzheimer's dementia compared to those without this disease. The epidemic of these diseases indicates a need to improve the treatment of diabetes and reduce neurodegeneration. Patients with diabetes must use increasingly higher doses of therapeutics over time, which increases the risk for side effects. These side-effects are partly a consequence of the fact that insulin is a growth factor that recruits glucose for anabolic processes. Consequently, diabetic patients treated with insulin are prone to weight gain and dyslipidemia that increases the risk of cardiovascular mortality. In this work, a series of short peptides are being designed and synthesized, which undergo self-assembly into nanofibers upon exposure to physiological conditions. The positive charge on the nanofibers electrostatically binds negatively charged molecules, including insulin, and can concomitantly bind to critical receptors, i.e. LepR, to stimulate glucose uptake as a cytokine. One peptide, AAC2, alone and bound to insulin, rescued mice from T1D and T2D in preliminary studies. These preliminary data provide the basis for a central hypothesis/question to be tested in this work: Can these peptides improve glucose tolerance and reduce neurodegeneration related to diabetes, based on their interaction with LepR? The overall goal is to develop and optimize this class of therapeutics with dual properties: (1) as a scaffold to bind and stabilize hormones, such as insulin, and (2) as a concomitant activator of LepR to improve glucose uptake, energy balance, and to reduce associated neurological complications. The specific aims of this work are: (1) to optimize the structure of AAC, (2) to modulate the length and stability of the AAC nanofibers, (3) to examine the glycemic and antioxidant effects of AAC variants in vitro, and a future aim will be to (4) to determine the pharmacokinetic and pharmacodynamic profile of the candidate AAC molecule in Akita mouse models of T1D and high-fat diet induced model of T2D.

Anne Rowley, M.D. - 2019 Awardee

Pediatrics Ann & Robert H. Lurie Children's Hospital of Chicago

"A New Human Hepacivirus as an Etiologic Agent of Kawasaki Disease"

Kawasaki Disease (KD) is the leading cause of acquired heart disease in children in developed nations. KD can result in coronary artery aneurysms that can lead to lifelong heart disease, myocardial infarction, and death. The clinical and epidemiologic features support an infectious etiology in genetically susceptible children, but the cause has eluded more than 50 years of study. Delayed and missed diagnoses increase the risk of coronary artery aneurysms. The development of urgently needed diagnostic tests and improved therapies are dependent upon identifying the etiology. In this study, we propose to determine if a new human hepacivirus is an etiologic agent of KD. Recent studies have shown that 1-2 weeks after infection with any specific pathogen, 75% of peripheral blood plasmablasts target that specific infection. In preliminary studies, we analyzed the peripheral blood plasmablast response at 1-3 weeks after KD fever onset using single cell RT-PCR and made 61 monoclonal antibodies (Mab) from these plasmablasts. We used these Mab to determine their target antigens. We found that 33/61 Mab, derived from 9/11 KD patients, identify intracytoplasmic virus-like inclusion bodies (ICI) in ciliated bronchial epithelium of KD children but not infant controls. Using a viral peptide discovery array and/or ELISA, we found that 6 of the 33 (18%) Mab, derived from 3 KD patients with coronary artery aneurysms, recognize multiple similar peptides of hepacivirus non-structural protein 4A (NS4A). An optimized NS4A peptide completely blocks binding of these Mab to KD ICI, indicating the presence of a hepacivirus-like protein in the ICI. We hypothesize that at least a subset of KD cases are due to a previously unidentified hepacivirus. To test this hypothesis, we will identify the KD-associated hepacivirus using a specifically designed pathway for bioinformatics analysis of our KD tissue RNAseq dataset containing >4 billion reads. In addition, we will obtain additional viral proteome data by screening viral peptide arrays/phage display libraries with KD Mab that bind to KD ICI but do not recognize NS4A. We will test KD patients and childhood controls for serologic response to and presence of KD-associated hepacivirus. These studies will lead to improved diagnosis and treatment of KD, enable prevention, and reduce healthcare costs from the long-term consequences of coronary artery aneurysms arising in young childhood.

Sarah Slavoff, Ph.D. - 2019 Awardee

Chemistry, Yale School of Medicine

"Targeted Degradation of a Melanoma Transcription Factor"

Melanoma, the deadliest skin cancer, was diagnosed in approximately 90,000 Americans and led to over 9,000 deaths in 2019. While BRAF inhibitors and checkpoint inhibitors have revolutionized treatment of metastatic melanoma, these therapies are limited by rapid development of resistance and low response rates, respectively. New therapies, and entirely novel drug targets, are therefore critically needed, ideally targeting not only melanomas but also congenital giant nevi that are precursors to melanomas and are currently removed by repeated surgery. An innovative approach originally developed by Prof. Craig Crews at Yale University, leverages molecules called proteolysis targeting chimeras, or PROTACs, to degrade – rather than inhibit – previously "undruggable" classes of proteins, including transcription factors. PROTACs also have the potential to enhance immunotherapy because the proteolytic peptides arising from target protein degradation are immunogenic. In this work, we propose development of PROTACs targeting a melanocyte-specific transcription factor, SOX10, that is required for melanoma cell, normal melanocyte and nevus cell proliferation. PROTACs consist of a ligand to the protein of interest, a flexible linker, and an E3 ubiquitin ligase ligand. We will therefore first develop a ligand to SOX10 using two high-throughput screening approaches for which preliminary feasibility has been established (Specific Aim 1). While ligand development is in progress, we will utilize a previously reported biotechnology-based strategy to demonstrate that PROTAC-mediated degradation of an engineered SOX10 fusion protein kills melanoma cells (Aim 2). Finally, we will create a small PROTAC library based on our novel SOX10 ligands, from which optimal members will be selected based on their ability to induce degradation of the transcription factor, inhibit melanoma cell, normal melanocytes and nevus cell proliferation, and eliminate melanocytes from human skin tissue in organotypic culture (Aim 3). In the future, we envision that the best PROTACs identified in this study will be further optimized and elaborated into drug candidates for testing in animal models prior to translation to the clinic. More broadly, this work will advance current cutting-edge efforts to drug transcription factors that have been refractory to traditional inhibitor development.

Fei Song, M.D., Ph.D. - 2019 Awardee

Neurology and Rehabilitation, University of Illinois College of Medicine at Chicago

"Therapeutic Targeting of Disease Progression in ALS"

ALS patients desperately need new approaches and directions to combat this disorder. While motor neuron loss in the spinal cord has been a central area of research focus for this disease, there is extensive pathology in ALS that spans from the neuromuscular synapses to the spinal cord, to the lateral corticospinal tract, and to the cerebral cortex. It is still not known how and where this disease begins nor the molecular mechanisms of how the disease progresses once it starts.

This application represents an innovative and uniquely humanized, collaborative approach for human ALS. It will combine clinical and basic research on rapidly-acquired human postmortem tissues to identify and validate new targets for drug development using a novel injury based model of disease progression. While gene mutations in animal models that rely on rarer forms of the disease with distinct genetic abnormalities have been used extensively, these animal models have not yielded effective therapeutics. The unique aspect here is that we instead focus on targeting disease progression once the disease has already begun, as it does when our patients first present with their disease. Our central hypothesis to be tested here is that the degree of pathological change will correlate with a distinct group of genes, proteins, and biological pathways that will lead us to novel drug targets of disease progression. Currently, we have leads to suggest that inflammation is key to this as well as a custom designed, patented fusion protein that targets this. Targeting disease progression offers a 'final common pathway' approach to treat ALL ALS patients, not just those with rare genetic abnormalities.

The catalyst phase will bring together a diverse team for genomic analysis and mining of our novel tissue repository. Our group has pioneered human tissue functional genomics, cellular predictions, biomarker identification, and drug target identification from human tissues. In parallel, it will build a new animal model of ALS disease progression by bringing together a multidisciplinary team to test targets generated from the human tissue data. These parallel teams will come together for the transformational phase where our top drug targets will be translated into small molecular and/or biologic therapeutics to test on the new animal model of ALS disease progression. In this later phase, our goal will be to select our top three drugs for preclinical testing, toxicology, and filing of IND applications.

Takanori Takebe, M.D., Ph.D. - 2019 Awardee

Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center

"Novel Human Organoid Transplant Therapy Against Pediatric Liver Disease"

Disorders affecting urea metabolism are among the most common inborn errors of metabolism in the liver. Defects in metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules lead to elevated blood ammonium level that causes neurotoxicity and can be fatal. Currently, low protein diets and liver transplantation are the only available therapies for disorders of urea metabolism. Procurement of cadaveric livers or use of hepatocytes/stem cell-based replacement therapies, has remained a significant challenge, driving intense research towards developing alternative liver regeneration strategies for human application. Our own current focus leverages a "self-condensation" culturing methodology wherein human induced pluripotent stem cells (hiPSC) are developmentally specified and together with vascular progenitors, self-organized into 3-D vascularized miniature livers ("organoids"). Our success with this approach is highlighted by rescue of a mouse model of liver disease using these cultured hiPSC-derived human liver organoid (hiPSC-HLO) transplants.

More recently we showed that hiPSC-HLO can be produced at a scale and purity for detailed testing in animal models. Building on this recent success, we now propose to conduct a preclinical study for the treatment of newborns who have congenital rare urea cycle disorders, more specifically, ornithine transcarbamylase deficiency (OTCD). The initial goal is to provide bridge therapies during the waiting period for liver transplants when surgery is not yet feasible and a liver not available. Our interim goals are (1) To determine if hiPSC-HLO transplants provide pivotal efficacy in alleviating urea cycle disease in our rodent models, and (2) To assure safety without tumorigenic complications by defining critical quality attributes (CQAs) in the hiPSC-HLO manufacturing process. The proposed analyses utilizing urea cycle disorder mice (generated under a severely immunocompromised background) will make it possible to determine the efficacy for correcting hyperammonemia, survival and behavioral deficits. Concurrent monitoring of tumor formation will ensure safety of our proposed organoid based approach.

In addition to providing preclinical assessment of utility of hiPSC-HLO in the OTCD model, our proposal has broader implications for efficacy in multiple hepatic dysfunctions related to protein metabolism, bile acid synthesis and export, and coagulation factor synthesis. This will expand the utility of our methodology for many other clinical indications such as liver cirrhosis, which is a significant cause of global health burden with more than one million deaths per annum.

Hongwei Yao, Ph.D. - 2019 Awardee

Molecular Biology, Cell Biology & Biochemistry, Brown University

"Identification of Carnitine Palmitoyltransferase 1A as a Novel Target for Bronchopulmonary Dysplasia"

Ventilatory support, including oxygen supplementation, has saved countless premature infants, yet these therapies have also led to bronchopulmonary dysplasia (BPD) in premature babies, which can persist into adolescence and adulthood. The pathology of this disease is characterized by alveolar and vascular simplification in the lungs. Although current therapies, including antennal steroids and surfactant, have greatly improved survival of premature infants, the prevalence of BPD and its consequences on the lung have not been reduced. My long-term objective is to develop effective drugs to prevent or treat BPD.

Carnitine palmitoyltransferase 1 (Cpt1), a rate-limiting enzyme of the carnitine shuttle system for beta-oxidation during fatty acid oxidation (FAO), may be key for developing these drugs. Cpt1 has three isoforms: Cpt1a, Cpt1b and Cpt1c, of which Cpt1a has acyltransferase activity and a high affinity to carnitine to generate acylcarnitine for mitochondrial transport. My previous studies showed for the first time that hyperoxic exposure reduces levels of Cpt1a and FAO in neonatal lung endothelial cells (ECs), leading to apoptosis. Pharmacological inhibition or genetic deletion of Cpt1a aggravates hyperoxia-induced alveolar and vascular simplification, characteristics of BPD, in neonatal mouse model of BPD. This proof-of-concept study suggests that Cpt1a reduction causes hyperoxic lung injury in neonates. Nevertheless, whether enhancing Cpt1a attenuates neonatal hyperoxic lung injury remains unclear.

We hypothesize that enhancing Cpt1a level and activity in neonatal mice ameliorates hyperoxia-induced persisting lung injury into adulthood. To test this hypothesis, we propose two Specific Aims using pharmacological activators (i.e., C89b and L-carnitine) and genetic approaches (i.e., Cpt1a gene knockout and overexpression) to determine their impact on lung injury and repair.

Aim 1: Determine whether overexpression and activation of Cpt1a reduces hyperoxia-induced lung EC dysfunction in vitro. We will genetically overexpress and pharmacologically activate Cpt1 to determine whether this attenuates hyperoxia-induced lung EC dysfunction, including apoptosis, reduced proliferation, migration, and angiogenesis.

Aim 2: Validate whether targeting Cpt1a protects against hyperoxia-induced persisting lung injury in mice. We will expose neonatal mice (<12 h old) to different concentrations of hyperoxia for 3 days, and allow them to recover in air until adulthood. These mice will be treated with L-carnitine or C89b, or Cpt1a plasmids will be transfected into lungs to determine whether this ameliorates hyperoxia-induced lung function decline as well as alveolar and vascular simplification.

These proposed studies will set the groundwork for Cpt1a as a novel therapeutic target for preventing BPD, potentially impacting tens of thousands of lives.