Dr. Ralph and Marian Falk Medical Research Trust
Transformational Award Program

Mark Feinberg, M.D. - 2016 Awardee
Department of Medicine
Brigham and Women's Hospital

"MicroRNA-based Therapeutics for Diabetic Wound Healing"

Patients with diabetes are frequently afflicted with impaired wound healing that may progress into chronic, diabetic ulcers, often leading to complications including limb amputation with increased risk of cardiovascular morbidity and mortality. Consequently, innovative medical therapies are desperately needed in the treatment of diabetic wound healing to improve patient suffering and reduce health care-associated economic burden.

Accumulating studies demonstrate that angiogenesis, or the formation of blood vessels from pre-existing ones, may promote wound healing. However, angiogenesis is impaired in diabetic patients and the mechanisms controlling this process are not fully understood. Our published and preliminary studies demonstrate important roles for specific microRNA inhibitors in mouse models of diabetic wound healing. In this proposal, we will translate these findings using novel delivery and targeting strategies in mice, human skin preparations, and larger animal models of diabetic wound healing as IND-enabling therapeutics in an effort to improve outcomes.

MicroRNAs are small, single-stranded, non-coding RNAs that suppress the expression of target genes at the post-transcriptional level and are involved in a range of disease states. By microarray profiling, we originally identified microRNA-26a (miR-26a), and its target gene Smad1, among the most differentially expressed under diabetic conditions in endothelial cells (ECs). Using diabetic wound miRNA profiling, our preliminary studies indicate that the miRNA, miR-615-5p, is also differentially expressed in diabetic wounds and functions as an anti-angiogenic miRNA in a cooperative, non-redundant manner with miR-26a. Our preliminary studies show that expression of both miR-26a and miR-615-5p are glucose-responsive miRNAs in ECs. Punch skin biopsy wounding of diabetic db/db mice revealed increased expression of both miR-26a (~2-fold) and miR-615-5p (~4-fold) compared to WT mice. Preliminary studies reveal that administration of new chemically modified inhibitors to miR-26a and miR-615-5p may more effectively promote endothelial cell angiogenic functions. Mechanistically, inhibition of miR-26a and miR-615-5p in ECs increased their respective target genes and signalling pathways, Smad1/BMP signalling and AKT/eNOS signalling. We therefore hypothesize that miR-26a and miR-615-5p may serve as critical regulators of pathological angiogenesis in diabetes and propose to study the cooperative effect of miR-26a and miR-615-5p neutralization using complementary targeting and delivery approaches on dermal wound healing in mice, pigs, and human skin models as a translatable foundation for bringing these findings closer to the clinic as IND-enabling therapeutics.

Michael Nishimura, Ph.D. - 2016 Awardee
Department of Surgery
Loyola University of Chicago

"TCR Gene Modified T Autologous Cells for Treating RCC Patients"

Renal cell carcinoma (RCC) is responsible for approximately 12,000 deaths every year in the US. When detected early, it is often cured surgically. However, most patients are diagnosed with advanced disease. Despite great progress with new treatments, metastatic RCC is generally lethal. Therefore, more effective therapies are needed for patients with this disease. Recent clinical trials using T cells that are genetically modified to express T cell receptors (TCR) or chimeric antigen receptors (CAR) have shown great promise in treating cancer patients. However, this treatment can only be used for selected malignancies because of the lack of tumor reactive TCR's and CAR's. Dr. Childs at the NHLBI/NIH isolated a HERV-E reactive T cell clone from an allogeneic stem cell transplant RCC patient. HERV-E is encoded by an endogenous defective retrovirus. While silent in normal cells, mutations in the von Hippel--Lindau (VHL) tumor suppressor gene lead to stabilization of the hypoxia-inducible transcription factor HIF-2α which is a transcription factor leading to expression of HERV-E. Therefore, we believe that targeting HERV-E has tremendous potential to be safe and effective for treating RCC.

Using Falk Foundation Catalyst funding, we identified, cloned, and characterized a TCR that targets HERV-E. T cells engineered to express this HERV-E TCR were found to recognize HERV-E+ RCC in cytokine release and killing assays. A high titer retroviral producer clone was generated and is being GMP qualified for clinical use. Based on these results, this Falk Foundation Transformative Award application proposes to conduct a phase I clinical trial to treat 12 patients with advanced RCC. The GMP compliant T cells will be prepared at Loyola by Dr. Nishimura using the Falk Foundation funding. The patients will be treated by Dr. Childs at the NHLBI/NIH using Clinical Center resources. In addition to the proposed clinical trial, we will clone a different HERV-E TCR which is HLA-A2 restricted. This second TCR will expand the use of HERV-E TCR transduced T cells to more patients.

Stephen Strittmatter, M.D., Ph.D. - 2016 Awardee
Cellular Neuroscience, Neurodegeneration & Repair
Yale School of Medicine

"Therapeutic Targets to Rescue Synapse Loss in Alzheimer's Disease"

Central to the pathophysiology of cognitive dysfunction in Alzheimer's disease (AD) is the loss of synapses, with an impairment of plasticity at surviving synapses. Therapeutic efforts to intervene in AD have focused on the Amyloid-beta peptide as an upstream trigger for synaptic disease, but clinical trials have been disappointing so far. Additional validated targets for AD therapy are needed, in particular those focused more directly on synaptic deficits.

One approach to target identification for AD is to study the biochemical basis for Amyloid-beta oligomer (A-beta-o) toxicity in neurons. We defined an A-beta-o --PrP-C--mGluR5--Fyn cascade that damages synapses in AD models. In this cascade, mGluR5 is a druggable target. Here, we seek to develop specific mGluR5 agents that preserve physiological function while blocking Aßo pathophysiology. A lead compound has been effective in reversing memory and synaptic deficits in mouse transgenic models during the Catalyst stage.

A second approach to identify targets for AD therapy with direct clinical relevance is through genetic studies of Late Onset AD (LOAD) risk. The largest GWAS analysis of LOAD identified a short list of genes whose common variants alter risk, providing potential new targets for AD therapy. We considered whether any of these might be directly linked to synaptic dysfunction in AD. Nearly all of the LOAD risk genes are hypothesized to bind A-beta, to alter A-beta metabolism, to regulate endocytosis, or to modulate immune function. Therefore, their action on synaptic dysfunction must be indirect. From the list of AD genetic risk factors, Pyk2 (also PTK2B or FAK2) is the only gene recognized to encode a protein concentrated at post-synaptic densities with direct effects on synaptic plasticity. Of note, the Pyk2 protein physically associates with mGluR5 and Fyn, so its study is supported by our biochemical approach as well. Our second goal is to develop Pyk2 inhibition as a therapy for disease modification in AD. In the catalyst stage, both genetic and pharmacological tools demonstrated the efficacy of this approach in mouse transgenic models.

This Falk Transformational project seeks to advance the success of mGluR5 and Pyk2 agents during the Catalyst phase towards a full drug development program to preserve synapses in AD. We will verify disease-modifying activity, validate with additional models, examine dual benefit for Tau pathology and provide toxicological safety information to advance these novel agents as potential disease-modifying drugs in AD.

Olufunmilayo Olopade, M.D. - 2015 Awardee
Department of Medicine
University of Chicago

"Genomics, Metabolomics and Epigenetic Regulation in Breast Cancer"

This application represents the output from a fully integrated team of scientists, clinicians and community advocates who are committed to finding new cures for the most aggressive types of breast cancer by establishing a new Center for Innovation in Global Health. Global health is an area for study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide. Breast cancer is a heterogeneous disease and the morbidity and mortality from the disease has no geographic boundaries. The basal-like breast cancer subtype is unique in its aggressive behavior and overrepresentation in young women and women of African ancestry who have been underserved and understudied for too long. The cross-continent comparative studies that we have conducted over the past decade suggest that both genetic factors, which are common among Africans and African Americans, and environmental/lifestyle factors contribute to the aggressiveness of breast cancer in both populations. Our long-term goal is to reduce global disparities in breast cancer outcomes by developing novel strategies for screening, early detection and treatment of basal-like breast cancer in high-risk populations. We leverage our institutional strengths in in chemistry, human genetics, systems biology, advanced imaging and experimental therapeutics. These advantages, together with our location in the ethnically diverse south side of Chicago and our exciting new collaborators make this a truly unique Transformative Research Program. Our overall goals are in two interrelated thematic areas with the following specific aims: 1) To personalize risk prediction for prevention and early detection of aggressive basal-like breast cancer. We will deploy tools for cancer risk assessment within a large network of primary care providers and examine whether population-specific polygenic risk scores can be used to stratify women into more meaningful risk categories so that our interventions to reduce risk can be better targeted and be more effective than current standards; 2) To find novel pathways that are dysregulated and potentially druggable in basal-like breast cancer. We will perform genome-wide gene expression, whole genome methylation sequencing and metabolomics profiles in early and late stage breast tumors. By performing chemical screens for drugs that target metabolic pathways, we will test two compounds in vitro and in vivo as potential new treatments for the most lethal subtype of breast cancer.

The University of Chicago has a unique history of organizing around research questions and cross-disciplines, which provides a robust foundation for the transformational program.

Richard Pestell, M.D., Ph.D. - 2015 Awardee
Cancer Biology
Thomas Jefferson University

"Targeting CCR5 In Cancer Treatment"

The repurposing of FDA approved drugs may provide a more rapid path to new treatments for cancer patients. Our objective is to define the role of CCR5 in breast cancer progression and metastasis and to carry out a biomarker-driven clinical trial using a CCR5 inhibitor for high-risk breast cancer patients. To ensure the completion of this objective we have assembled a national collaborative team of experts who have worked successfully together for many years, including the Falk Catalyst Award. For the analysis of human breast cancer molecular mechanisms of therapy resistance (Dr. Pestell, Thomas Jefferson University), for the quantitative analysis of annotated breast cancer patient samples for target protein expression (Dr. Rui, Medical College of Wisconsin), and for breast cancer circulating tumor cells (CTC) and breast cancer clinical trials (Dr. Cristofanilli, Northwestern University).

Metastasis is the primary cause of death in breast cancer patients. No treatments are directed specifically to the metastatic process. We provide strong evidence that CCR5 is expressed in human breast cancer, and that CCR5 inhibitors, previously developed and FDA approved for treatment of HIV, can effectively block breast cancer metastasis in preclinical models. Our studies from the current Falk Catalyst award show >50% of human breast cancer patients express CCR5 in their tumor. Thus a very large number of patients are candidates for CCR5 inhibitor therapy.

Understanding the mechanisms of resistance to current breast cancer chemotherapeutic agents is an urgent matter of broad importance to our patients. Breast tumor initiating cells (BTIC) are resistant to chemo- and radiation-based therapeutics. Our studies from the Falk Catalyst award demonstrate that CCR5 promotes BTIC formation. We show that the CCR5+ cells within the breast cancer are sufficient to drive breast cancer metastasis. Furthermore, we show CCR5 induces DNA repair in breast cancer cells after chemotherapy or irradiation. CCR5 inhibitors reduce the DNA repair response. Combination therapies aimed at reducing the DNA repair response selectively in tumors would be a highly favorable addition to current therapies.

In order to conduct an expedited clinical trial it is advantageous to identify a marker for the therapeutic target in the peripheral blood. During the Falk Catalyst Award we identified CCR5 on the surface of patient's CTC, to identify and monitor the candidate patients for treatment with CCR5 inhibitors. Our proposed studies provide the rational basis for repurposing of CCR5 inhibitors for CCR5+ human breast cancers that are resistant to current therapies.

Menachem Shoham, Ph.D. - 2015 Awardee
Department of Biochemistry
Case Western Reserve University School of Medicine

"Novel Antivirulence Agents against MRSA and other Bacterial Pathogens"

MRSA is the most widespread bacterial pathogen in the developed world. In the US, MRSA caused 75,309 severe infections, resulting in 9,670 deaths in 2012. MRSA is resistant to most antibiotics and strains have emerged that are even resistant to vancomycin, the antibiotic of last resort. Thus, resistance to antibiotics and decline in the development of new antibiotics create an urgent unmet medical need to search for novel unconventional agents to prevent and treat MRSA.

Antivirulence agents present an alternative or an adjuvant to antibiotics. In contrast to antibiotics, antivirulence agents are not bactericidal and not even bacteriostatic. Their mechanism of action is based upon disarming the pathogen of toxins and virulence factors without killing it, thereby decreasing the pressure on the pathogen to develop resistance.

During the Catalyst Award period we have developed small-molecule inhibitors of the S. aureus quorum sensing response regulator AgrA, a transcription factor that drives the expression of a series of disease-causing toxins. Lead compounds F12 and F19 promote healing of MRSA-contaminated wounds in mice. F19 reduces bacterial load on kidneys in a murine MRSA model. Remarkably, F12 and F19 sensitize MRSA to beta-lactam and fluoroquinolone antibiotics, to which MRSA is resistant in mono therapy. This finding opens the possibility of reintroducing "old" antibiotics, such as penicillin, into the clinic. Preliminary toxicity studies have established F12 and F19 safety up to 200 micromolar concentration. This data forms the basis for the development of safe and potent novel treatment option against MRSA infections.

We now propose to further develop the preclinical data package of compounds F12 and F19 in vivo by exploring efficacy against an already established infection, extending the applicability to lung infections in wild type and cystic fibrosis mice, exploring protection of implants against infection in a murine MRSA graft model, and broadening the spectrum to other Gram-positive pathogens. Efficacy against Gram-negative pathogens will be explored by combination therapy with antibiotics. Possible emergence of resistance will be probed in vitro and in vivo. Medicinal chemistry will be employed to improve F12 and F19 solubility, stability and spectrum of applicability.

Antivirulence therapy has the potential to revolutionize treatment of MRSA and other bacterial infections.
A Falk Transformational Award will enable us to generate preclinical data for an IND application to the FDA and subsequent clinical trials.

Stephen Strittmatter, M.D., Ph.D. - 2015 Awardee
Cellular Neuroscience, Neurodegeneration & Repair
Yale School of Medicine

"Medical Therapy To Promote Neural Repair And Functional Recovery From Spinal Cord Injury"

Devastating and persistent neurological deficits occur after Spinal Cord Injury (SCI), despite survival of nearly all neurons. The primary cause of disability is disconnection of networks by axon transection. Even without full-blown regeneration, studies of electrical stimulation and weight-supported training demonstrate important gains from the few surviving, but otherwise silent, circuits in clinically complete patients. Thus, neuroplasticity and sprouting of axons are as important as regeneration per se, and medications to enhance all forms of axon growth are expected to be strongly synergistic with stimulation and training regimens. Recovery of some movement would be adequate for patients to gain a level of independence in wheel chair transfers, bowel and bladder management, and locomotion. Today, there is no approved medical therapy for the 300,000 to 1,200,000 individuals in the USA with SCI.

Our axonal growth studies included discovery of Nogo and Nogo Receptor (NgR1). We demonstrated their role in preventing axonal sprouting, regeneration and recovery after injury. With Falk Trust support, we have demonstrated that NgR1(310)-Fc is efficacious for recovery from SCI, even when treatment starts months after damage. It is being developed for human SCI trials with CSF administration. A small molecule therapeutic could broaden utility and reduce complications. With exciting preliminary data from the Catalyst period, we will advance a drug-like antagonist to rodent SCI efficacy testing.

While specific factors, such as NgR1, limiting axon regeneration have been identified, they provide an incomplete explanation for poor adult mammalian CNS regeneration. We completed a genome-wide shRNA screen for endogenous genes limiting mammalian CNS axon repair. We also conducted experiments to identify conserved genes that affect axon regeneration in the model organism C. elegans. Factors common to both systems are expected to identify fundamental regeneration mechanisms likely to benefit human patients. We aim to study and develop the translational potential of such mechanisms here.

One pathway is bioinformatically the most enriched gene set in the mammalian screen, and also regulates regeneration in C. elegans. The relevance of this pathway will be tested in preclinical models of traumatic SCI. Both gene deletion strains and pharmacological inhibition will be studied to provide a validated pathway for future therapeutic development. The findings will have high relevance for the development of novel therapeutics for SCI.

Michael Whitfield, Ph.D. - 2015 Awardee
Dartmouth Scleroderma Center of Excellence
Geisel School of Medicine at Dartmouth

"Mining genomic data to identify novel therapeutics for systemic sclerosis"

Autoimmune diseases have a variable presentation and progressive course. Many are difficult to treat and their root causes are elusive despite the significant health burden they impose worldwide. Among the most difficult to treat is systemic sclerosis (SSc), a disease whose hallmark is skin fibrosis, but internal organ fibrosis and vascular disease are the main causes of death. One in three patients dies within 10 years of diagnosis giving SSc the highest fatality rate of any systemic autoimmune disease. There are no validated diagnostic markers and no curative treatments. SSc represents a significant unmet medical need, making it an ideal target for the Falk Transformational Medical Research Program (FTMRP). Finding effective therapies is critical and is the focus of this proposal.

SSc progresses through multiple molecular states of inflammatory, fibroproliferative and normal-like, that are identifiable by our recently discovered gene expression subsets. The ability to prescribe targeted therapies that modulate the underlying deregulated molecular pathway(s) in each patient is key. We have developed diagnostic strategies that identify underlying aberrant molecular pathways in patient skin. We have also shown that analyses of skin gene expression provide a window into SSc internal organ disease. In our Catalyst grant, we identified the macrophage/dendritic cell axis as being a central cell type in SSc.

The trigger(s) for SSc are unknown, although several studies have suggested the root cause may be immune surveillance of cancer or aberrant immune responses triggered by viral or fungal infections, within the context of a predisposing genetic background. Our hypothesis is that SSc results from an aberrant immune response mediated in part by pro-fibrotic macrophages, triggered by an environmental stimulus.

Our interdisciplinary team will address the four principal focus areas of the FTMRP by providing insight into the basic disease process, identifying biological markers of disease and therapeutic targets, and developing novel methods for therapeutic intervention.

Our aims are:
Aim 1: Develop biomarkers of disease activity and progression into a marketable diagnostic test.
Aim 2: Leverage our SSc multi-tissue network to better understand the pathways modulated in SSc drug trials and the critical cell types driving disease; use the network to reposition FDA approved drugs.
Aim 4: Characterize tissue resident macrophages in SSc skin, lung and esophagus both immuno-phenotypically and using RNA-seq.
Aim 5: Develop a strategy to therapeutically target alternatively activated profibrotic macrophages using CAR-T cell technology and / or bi-specific antibodies.