2011 Pilot & Feasibility Awards Recipients

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“siRNA Delivery Scaffold for Altering Cytokine Signaling in Diabetes Skin Wounds”

Impaired wound healing is a hallmark of diabetes, and chronic diabetic skin ulcers are the number one cause of non-traumatic limb amputations in the United States. Impaired wound closure in this setting is characterized by a cytotoxic, hyperinflammatory state and insufficient proliferation and migration of keratinocytes, fibroblasts, and vascular cells. Here, studies are proposed for development of a novel tissue scaffold for sustained siRNA delivery targeting the suppressor of cytokine signaling (SOCS) family member SOCS3. SOCS3 overexpression has been linked to hypoproliferative keratinocyte phenotype and cytotoxic (M1) activation of macrophages in the diabetic wounds. The central hypothesis of this proposal is that knockdown of SOCS3 using a controlled siRNA delivery system will induce reparative cellular phenotypes (M2 macrophage activation and keratinocyte proliferation) and promote diabetic wound healing. Aim 1 involves development of the delivery system and characterization of its siRNA release kinetics and bioactivity in vitro and in vivo. Aim 2 is to assess the functional effects of SOCS3 knockdown on macrophages and keratinocytes in vitro and on healing in a mouse diabetic skin wound model. The expected outcomes for the proposal include validation of a new platform technology for siRNA delivery to skin wounds and establishing SOCS3 as a potential target for wound therapies, with the long-term goal of reducing wound related morbidity and mortality in diabetic patients.

Daniel J. Moore, M.D., Ph.D.
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"The Microbial Ecology of Immune Tolerance in Type 1 Diabetes"

Type 1 diabetes is a relentless autoimmune disorder that afflicts over 2 million Americans and will be diagnosed in over 15,000 new children in the next year. The mechanisms that trigger this disease are unknown, but numerous epidemiologic studies point to environmental factors that may be both protective and provocative. The concept of environmental triggers is also supported by genetic studies; long-term studies on identical twins show that fewer than 60% of twins become concordant for disease even after decades of follow-up. While the circumstantial evidence for environmental effects is large, their role has not been described with mechanistic precision. Thus, interventions aimed at changing the effects of the environment remain haphazard. Recent data suggest that the human microbiome, or metagenome, may determine susceptibility to autoimmune disorders. These studies have been extended to demonstrate that the gut microbiome plays a deterministic role in diabetes susceptibility in the NOD mouse, the primary preclinical model of diabetes (Wen et al, Nature, 2008). Moreover, the microbiome can be modulated by genetic disruption of innate immune function to produce a tolerogenic state, the composition of which is not yet specified. We hypothesize that shifts in the microbiome between tolerogenic and non-tolerogenic states dictate diabetes progression and that these states can be specified and harnessed for diabetes prevention and reversal. In this proposal, we will pursue the first detailed analysis of diabetes-protective and -promoting microbiomes (Aim 1). We will further unravel the mechanisms by which innate and adaptive immunity modifies its composition by capitalizing on our recent description of a diabetes-preventing peptide inhibitor of proinflammatory signaling to the nucleus (Aim 2). These studies will lead to clinically translatable interventions that will enhance immunomodulatory therapies for T1D by identifying and correcting the autoimmunity-promoting state of the resident microbiota in genetically-prone individuals.