2015 Pilot & Feasibility Award Recipients

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Gestational diabetes mellitus (GDM) impacts up to 1 in 10 pregnancies in the US and significantly increases the risk of complications, including infant macrosomia, neonatal hypoglycemia, preeclampsia, premature labor, and Cesarean delivery. It also increases the risk of postpartum complications in both mother and child including late onset diabetes and cardiovascular disease. Causal mechanisms explaining how GDM predisposes to these adverse outcomes are poorly defined, but the placenta is increasingly appreciated to be a target organ of diabetes. This proposal addresses a potential cause of exaggerated placental inflammation in GDM related to increased iron accumulation by macrophages within this vital organ. Placental macrophages (PMs) play an important role in normal placental development and govern maternal-fetal tolerance and tissue inflammatory tone. Notably, PM numbers increase and they take on a more pro-inflammatory phenotype in GDM. We recently found that healthy human PMs accumulate iron through undefined mechanisms. Using a mouse model of GDM, we also found increased tissue iron staining and greater macrophage infiltration in diseased placentae, along with increased fetal resorption (fewer live pups). A potential explanation for increased placental iron in GDM is the previously described higher expression of the hemoglobin-haptoglobin receptor (CD163) by PMs affected by GDM. Thus, our central hypothesis is that PMs exhibit an exaggerated proinflammatory phenotype in GDM, related to an increased accumulation of intracellular iron and enhanced CD163 expression.

This proposal brings together a new multidisciplinary team of investigators to test our hypothesis through three specific aims: In Aim 1 we will characterize the cellular immunophenotype of the mouse placenta in GDM, with a special focus on PMs, CD163 expression, and intracellular iron storage. Immunophenotyping studies in a robust mouse model of GDM will assess leukocyte phenotypes including macrophages (both M1 and M2 subtypes), CD4+ cells, CD8+ cells, NK cells (NK1.1+ or CD335+), and neutrophils (Neu7/4+). Tissue inflammation will be assessed by histology and flow cytometry and macrophage expression of CD163 and accumulation of iron will be assessed. In Aim 2 we will determine the cellular inflammatory phenotype of human placental tissues affected by GDM using archived tissue specimens linked to clinical meta-data from the electronic medical record, with a special focus on PMs, CD163 expression, and intracellular iron storage. Case and control placentae will be analyzed histologically for inflammation. Macrophage abundance, polarization, and iron accumulation will be determined by specific tissue immunostaining (and iron staining). These studies will help validate a mouse model of GDM using human tissues, while advancing our understanding of the impact that GDM has on placental biology. They will also provide critical preliminary data for externally-supported grants that can expand institutional efforts to prevent and treat GDM.

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Patients with chronic inflammatory diseases, including rheumatoid arthritis (RA), have an increased prevalence of obesity and metabolic syndrome (MetS). Little is known about the phenotype of adipose tissue (AT) in patients with RA. It is also unknown if experimental inflammatory arthritis stimulates changes in AT and metabolic derangement. An important characteristic of inflammation in both arthritis and AT is activation of the prostaglandin (PG) biosynthetic pathway characterized by markedly increased expression of cyclooxygenase -2 and microsomal PGE synthase-1 (mPGES-1). In inflamed tissues, expression of PGE2 increases disproportionately to other PGs because of coordinated regulation of these two biosynthetic enzymes. When mPGES-1 is genetically deleted in mice (KO), PG synthesis is shunted toward other terminal PG in a cell and tissue specific manner. In adipose tissues, shunting is towards alternate species that may lead to changes in AT phenotype, specifically in the capacity to develop brown-in-white or brite adipocytes. Increased brown/brite adipocyte activity is inversely associated with obesity, age, and type II diabetes. Our preliminary data demonstrate that mPGES-1 KO mice are resistant to weight gain when being fed a high-fat (HF) diet. In addition, we showed that mPGES-1 KO mice exhibit markedly increased expression of UCP-1 mRNA, the marker of brite adipocytes, in white AT and increased energy expenditure. Thus, our preliminary data suggests that mPGES KO mice could be resistant to arthritis-induced MetS due to their ability to promote “browning” of white AT. In this pilot project, we will test the hypotheses that (1) mPGES-1 deficiency reduces weight gain by stimulating brite adipocyte phenotype during HF feeding, (2) inflammatory arthritis increases AT inflammation and induces MetS, and (3) mPGES-1 deficiency blocks arthritis-associated changes in AT and MetS. This will be accomplished by determining the effect of mPGES-1 deficiency on differentiation to the brite adipocyte phenotype, obesity, and energy metabolism during HF feeding and determining if a murine model of RA increases inflammation in AT and alters energy metabolism and test whether the AT phenotype in mPGES-1 deficient mice is modulated by arthritis.

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Diabetic nephropathy (DN) is a major diabetic complication that determines the morbidity and mortality of the diabetic patients. Although clinical indicators or risk factors of this disease have been described, the currently available tests do not reliably assess its severity or progression in individual patients, making it difficult to do the targeted and intensified treatment to high-risk patients. Renal fibrosis is a hallmark of progressive DN; therefore, it is critical to evaluate the presence and extent of renal fibrosis in the diabetic

kidney to treat the patients as well as to predict their long-term outcome. However, the current clinical tests lack the sensitivity and specificity to measure renal fibrosis in diabetic kidney. Although renal biopsy can diagnose fibrosis, it is invasive and prone to sampling errors, and does not reliably measure renal fibrosis in the affected kidney. Thus, a non-invasive test that better evaluate renal fibrosis would greatly improve the assessment of this disease. In recent decade, a variety of magnetic resonance imaging (MRI) methods have been developed and applied to human disease including cancer and brain disorders. These techniques have enabled us to assess the pathological changes in disease organ at molecular and cellular levels. Magnetization transfer (MT) imaging is a MRI technique that evaluates large and immobile macromolecules distributed within the tissue and could provide a means to evaluate the pathological events that are accompanied by the changes of macromolecular components, such as fibrosis and apoptosis. However, this method is poorly applied to kidney disease including DN. Therefore, here we will evaluate the utility of MT imaging in measuring renal fibrosis in diabetic kidney using a mouse model of progressive DN (db/db eNOS -/- mice). The aims of this study are: 1) To optimize and establish the MT protocol for mouse kidney imaging; 2) To examine the correlation between MT data and histological or biochemical measures of renal fibrosis. Thus, this application explores a new MRI test to assess renal fibrosis in DN. Given the fact that this MRI technique can be translated to clinics, the present work should efficiently improve the outcome of the DN patients.