Pre-ARC Proposal "Type 1 Diabetes"

**Pre-ARC Co-directors:**
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**Barbara Corkey, Ph.D., Professor of Medicine**
**Barbara Nikolajczyk, Ph.D., Associate Professor of Microbiology**

## Announcement

Drs. Dooms, Corkey and Nikolajczyk are leading a **new pre-ARC focused on Type 1 Diabetes**. The interdisciplinary group brings together investigators with expertise in Type 1 Diabetes (mouse models and clinical), human and mouse immunology, metabolism, and wound healing. The goal is to develop and experimentally test out-of-the-box ideas about the etiology of T1D, leading to the design of new approaches to prevent and treat the disease and its complications.
The group meets every second Wednesday of the month at 10 am in X714. For more information, please contact hdooms@bu.edu, bcorkey@bu.edu or bnikol@bu.edu

## Mission Statement

Type 1 Diabetes (T1D) is a disease that has been on the rise in the Western world for the past decades and for which no cure exists despite massive research efforts. Investigators in the fields of autoimmunity, metabolism, endocrinology, β-cell biology and stem cells have all contributed to understanding various aspects of the pathogenesis of T1D. However, despite this progress, the promise of effective prevention and a cure remains unmet, which is in part due to the limited cross-talk and integration of research attempting to understand this complex disease. Our vision is to bring together investigators from various disciplines with an interest in T1D to develop novel, better integrated research lines into the etiology and complications of T1D based on interdisciplinary hypotheses and expertise. It is hoped that increased knowledge of the metabolic underpinnings of autoimmune disease, the interaction of β-cells with the immune system and the capacity to correct defects in disease-causing cells with stem cell technology, will lead to new strategies for the prevention and therapy of T1D. In addition, this group will strengthen and grow the relatively modest presence of T1D research at BU/BMC.

## Significance

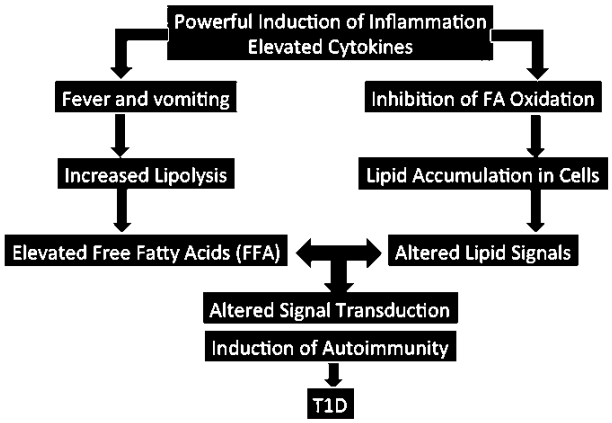
T1D is an autoimmune disease caused by destruction of the insulin-producing β-cells in the pancreas, but the initial events leading to activation of pathogenic, autoreactive T cells in susceptible individuals are poorly understood. This is a critically important problem since most healthy adults carry islet-antigen-specific T cells, indicating that the presence of these autoreactive T cells alone is not sufficient to trigger disease. Given that the concordance rate for T1D in monozygotic twins is < 40%, environmental factors likely play an important role in the breakdown of immune tolerance that causes T1D. Although a number of immune system genes (e.g. HLA, CTLA4, CD25) and environmental factors (e.g. enteroviruses) are associated with the disease, a convincing model linking the initiation of autoreactive T cell responses with an environmental insult is still missing.

Findings from the Corkey lab provide the basis for a fundamentally new concept about the etiology of T1D. Cells from individuals and mice predisposed to become diabetic show defects in metabolic pathways, resulting in inappropriate responses to elevations in cytokines and free fatty acids such as those experienced during severe infections. Hence, our pre-ARC currently works around the hypothesis that metabolic and signal transduction differences in

vulnerable cells enable the induction of autoimmunity in individuals predisposed to T1D. These differences include a hypersensitivity to elevated fatty acids and marked inhibition of fatty acid oxidation in response to cytokines. Thus, any severe illness that leads to elevated cytokines and compromised food intake, increasing free fatty acids, can trigger this hypersensitivity in susceptible individuals. We propose that aberrant behavior of metabolically altered islet-specific T cells and/or pancreatic β-cells results in the autoimmune destruction of the islets and, ultimately, hyperglycemia. Importantly, our novel concept has direct translational potential to develop new strategies for early diagnosis and prevention of T1D in at-risk individuals by measuring cellular metabolic parameters and correcting defective metabolic pathways before β-cell destruction becomes irreversible.

**Goals**

***1/ Metabolism & autoimmunity.*** The initial goal is to build upon the unique finding in Dr. Corkey's lab that fibroblasts from T1D patients are metabolically altered. We have brought together a group of investigators with diverse expertise (metabolism, immunology, Type 1 Diabetes) to use these data as the basis for an innovative, broad project to elucidate the etiology of T1D, uncover the missing link between environmental, genetic and immunological contributors and translate the findings into new methods for prediction, prevention and reversal of the disease. We meet monthly as a pre-ARC to ensure a vivid generation and sharing of ideas for the benefit of the project. We (Dooms, Corkey, Nikolajczyk and Steenkamp) are currently performing pilot experiments to establish whether metabolic abnormalities are present in PBMCs from T1D patients and various lymphocyte subsets isolated from spleen, pancreatic lymph nodes and pancreas of NOD mice at various stages of diabetes development. These preliminary data will help us to prepare a joint R01 application around the theme "Dysregulated cellular metabolism predisposes to Type 1 Diabetes".




***2/ Wound healing.*** Delayed skin wound healing is one of the most common complications in patients with both Type 1 and Type 2 Diabetes. Diabetes-related problems with wound healing are the leading cause of non-traumatic amputations of the lower limbs in the US. Wound healing is an extremely complex process requiring synchronized functional contributions of both blood and stromal cell types. We will investigate whether metabolic abnormalities associated with T1D contribute to impaired wound healing. There is some rationale for this in the literature, for example, reports that structurally diverse antioxidant compounds, each known to be active in the mitochondria and suppress mitochondrial injury, profoundly improve healing in wound-impaired rodent models. The Corkey lab's novel finding of dysregulated metabolism in human skin fibroblasts from patients susceptible to T1D is of particular interest. Wound closure requires the specialized differentiation of skin fibroblasts into the contractile myofibroblast and there is evidence that, in other impaired healing models, this process can be modulated pharmacologically. The key role of the readily accessible skin fibroblast in wound healing should enable in vitro studies employing both mouse T1D model- and patient-derived cells. Furthermore, in vivo studies in mouse T1D models will assess wound closure effects of any

promising interventions, including those modulating immune function, identified by other T1D preARC investigations.

***3/ Direct conversion.*** Use of nuclear reprogramming to correct the metabolic defects observed in individuals predisposed to T1D. In order to prevent or cure established T1D we need to know if the disease is genetic or epigenetic (environmental). To find out it is necessary to reprogram the T1D skin cells to eliminate epigenetic effects and determine if differences still remain. A recent study was able, by a brief demethylation step, to convert adult human skin fibroblasts into insulin-secreting cells (PNAS 110:8948, 2013). Replicating this finding would permit comparison of insulin secreting cells from diabetic and non-diabetic subjects.

Further broad questions may include:

- What environmental factors contribute to susceptibility to T1D?
- Can markers be identified that predict disease development?
- Why are ß-cells the target of the autoimmune response?
- How is genetic susceptibility linked to environmental factors, specific markers or ß-cell specificity?

**Timeline**

May 2014: submitted DOM pilot grant

May – September 2014: collect preliminary data for research area 1 and draft R01 proposal

June – December 2014: continue monthly meetings and identify most innovative and integrated research projects in wound healing and stem cells, define need for additional collaborators and expertise.

December 2014: T1D mini-symposium

**Current members**

| **Name/Title** | **Rank** | **Department/Section** | **email** |
|---|---|---|---|
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