- **Cristina Aguayo-Mazzucato, M.D., Ph.D.**
  Assistant Professor of Medicine
  Joslin Diabetes Center

"Targeting Beta-Cell Senescence in Diabetes"

Key Words: Beta-cells, Type 2 diabetes, Aging, Senescence, Exercise, Senotherapeutics, P21Cip1

Insulin producing beta-cells play a central role in the development of T2D and my work has shown that at any given time there are differently aged beta-cells in the pancreas. Insulin resistance accelerates aging, as characterized by increased proportions of aged or senescent beta-cells. Senescent beta-cells are characterized by altered gene expression and secretion of senescence associated secretory phenotype (SASP) factors. If senescent beta-cells are specifically targeted through senotherapeutic interventions, the remaining cells improve their function, cellular identity and blood glucose levels. I propose to understand beta-cell senescence and its effectors to identify interventions that target senescent cells as a novel strategy to treat T2D.

The specific aims are: Aim 1. Identify the senotherapeutic mechanism that enhances beta-cell function and proliferation. This aim will explore whether it is necessary to completely remove senescent beta-cells or whether blocking their SASP secretion is enough to obtain the benefits of senotherapeutics. This will be done using transgenic models and drugs that target either the antiapoptotic pathways upregulated by senescent beta-cells to drive them into apoptosis or pathways that inhibit SASP secretion. Aim 2. Elucidate the molecular effectors and progression of beta-cell senescence and SASP. This aim will test whether p21Cip1 is the main driver of premature beta-cell aging in T2D by using gain- and loss-of-function approaches in vitro and in vivo. Aim 3. Identify the mechanism through which exercise acts as a beta-cell senotherapeutic intervention. This aim will elucidate the molecular mechanism through which exercise, which decreases beta-cell senescence, activates AMPK to achieve this effect. This will be done by measuring changes of specific plasma metabolites and hormones to test their variation with exercise and whether these can activate intracellular AMPK using western blot and immunohistochemistry.

- **Sanghyun Lee, Ph.D.**
  Assistant Professor of Molecular Microbiology and Immunology
  Brown University

"A Focused Approach to Identify Entry Factors for Pathogenic Enteric Viruses Using CRISPR Activation Screening"

Key Words: CRISPR activation, CRISPR screen, Surface proteins, Norovirus, Rotavirus, Astrovirus, Cellular receptor, Entry factor

---

Acute enteric viral infection causes significant mortality in patients under 5 years of age. Human norovirus, astrovirus and rotavirus are leading causes of gastroenteritis, causing most non-bacterial gastroenteritis outbreaks worldwide. To develop vaccines or therapeutics for a viral pathogen, a fully permissive virus-replicating cell line is the essential foundation. However, challenging viruses, such as human norovirus, do not accept growth in traditional cell lines, leaving researchers without a starting material. We hypothesize that the enteric viruses, human norovirus, rotavirus and astrovirus, utilize certain proteinaceous receptors, yet present culture systems appear not to offer these cellular receptors. There is a total of ~1200 genes known or predicted as cell surface membrane proteins. Here, we propose a targeted gene-activation screening of all known cellular surface proteins using the CRISPRa technique with three specific aims. Aim 1. Perform a focused CRISPRa screen for enteric viruses by flow sorting and by virus infection induced cell death. Aim 2. Characterize the mechanism of virus entry with the candidate genes. Aim3. Develop an in vitro cultivation model for the virus

- **Liang Liang, Ph.D.**
  Assistant Professor of Neuroscience
  Yale University

  “Early Visual Centers Coordinate to Shape the Flow of Information”

  Key Words: Salience, Vision, Visual thalamus, Superior colliculus, Integration, Visual detection, Functional organization, Visual processing, Synergy, Two-photon microscopy, Optogenetics

---

Our long-term goal is to systematically understand how neural computation in the early visual system shapes information flow and supports visual perception. The brain is constantly flooded with visual stimulation that must be rapidly gated to allow us to focus on the most critical inputs. However, it remains unclear how selective filtering of information occurs prior to the visual cortex. The visual thalamus is crucial in determining the visual signals conveyed to the cortex. In addition to receiving inputs from a diverse population of retinal ganglion cells, it is also innervated by the midbrain superior colliculus, another early visual center known for ‘saliency computation’. Could these prominent early visual centers work synergistically to selectively route salient information for rapid processing? To test this hypothesis, we will utilize innovative imaging and behavioral approaches to characterize the fine-scale convergence between collicular and retinal axons, to determine the collicular influences on thalamic visual function and on visually guided behavior. Our findings will elucidate new mechanistic insights into how distinct neural circuits coordinate to prioritize salient visual inputs and how early visual processing shapes visual sensitivity. Our work will also form basis for assessing structural and functional disruption in neurological and psychiatric disorders in which information processing is impaired.

- **Kara McKinley, Ph.D.**
  Assistant Professor
  Harvard University

  “Molecular Mechanisms Underlying Uterine Regeneration”

  Key Words: Uterus, Endometrium, Endometriosis, Endometrial cancer, Stem cell, Epithelium, Microscopy

---

The uterus has the unique ability to support the growth, development, and eventual delivery of offspring. The non-pregnant uterus is no less remarkable: the uterine lining (endometrium) undergoes repeated cycles of shedding during menstruation and subsequent repair, ultimately regenerating approximately 400 times over the reproductive lifespan. The mechanisms that underlie this immense regenerative capacity are unclear. In particular, little is known about the adult stem cells responsible for repair of the endometrial epithelium after menstruation. A major challenge for the field is that humans belong to a very small group of mammals that exhibit unique uterine functions, including menstruation, limiting the use of traditional animal models to study these processes. The goal of this project is to identify the molecular and cellular basis for regeneration of the menstruating endometrium. Aim 1 is focused on identifying candidate endometrial epithelial stem cells. In Aim 2, we will identify and test lineage relationships in the endometrial epithelium. The successful completion of these aims will reveal the fundamental mechanisms that underlie the unique regenerative capacity of the endometrium. These studies will also yield insights into endometrial abnormalities including endometriosis, endometrial cancers, and infertility, and identify new avenues for therapeutic management of these widespread conditions.

- **Gowthaman Uthaman, Ph.D.**
  Assistant Professor of Pathology
  University of Massachusetts Medical School

  "Regulation of Anaphylactic IgE Promoting Tfh13 Cell Subset in Allergic Sensitization"

  Key Words: Allergy, IgE, Anaphylaxis, T follicular Helper Cells, Group 2 Innate Lymphoid Cells, GATA3

Allergies to food and environmental antigens have steeply grown to epidemic proportions. IgE antibodies are key mediators of allergic disease, including life-threatening anaphylaxis. The T cell subset that is necessary for promoting IgE to allergens is thought to be the Th2 cells. Our recent work challenged this paradigm and demonstrated that a subset of T follicular helper (Tfh) cells, namely interleukin-13 producing Tfh13 cells but not Th2 cells or other Tfh cell subsets, promote the production of high-affinity, anaphylactic IgE antibodies in B cells. Why certain individuals progress to an allergic state post allergen exposure, while others do not remain one of the big open questions in immunology. Our discovery that allergen specific Tfh13 cells were exclusively found in allergic patients suggests that Tfh13 cell induction may be a critical checkpoint to ultimately drive the allergic disease state. The goal of our proposal is to elucidate pathways that lead to Tfh13 cell differentiation program. The core hypothesis of this proposal is that activated group 2 Innate Lymphoid Cells and GATA3 expression in Tfh cells are extrinsic and intrinsic regulators of Tfh13 cell differentiation respectively. We will use T cell adoptive transfer and allergic sensitization models that we have developed, in combination with conditional deletion approaches to 1) define the role of ILC2s in Tfh13 cell differentiation and 2) investigate the role of GATA3 in Tfh13 cells. If successful, our work to understand how Tfh13 cells are induced and differentiate during allergic sensitization will not only uncover novel biology of this rare cell type responsible for anaphylactic IgE induction, but also identify new therapeutic modalities to block the induction or function of Tfh13 cells and thus anaphylactic IgE to allergens.

- **Seychelle Vos, Ph.D.**
  Assistant Professor of Biology
  Massachusetts Institute of Technology

  "Elucidating How Genome Organization Influences Gene Expression"

  Key Words: Transcription, Genome Compaction, Gene Expression, RNA Polymerase II, Cohesin, Cryo-Electron Microscopy, FRET

Genomes of all living organisms are organized from individual DNA base pairs to whole chromosomes. Genome organization across these scales results in genome compaction. Cells need to coordinate genome compaction with accessibility to determine which genes are expressed in a particular cell. The first step of gene expression is transcription of the DNA template into RNA. When genome compaction and transcription are not properly coordinated, cancer, intellectual disability, and developmental disorders arise. A mechanistic understanding of how transcription and genome compaction are coupled is essential for understanding how cell type specific gene expression is achieved and how disease disrupts this coupling.
Here, we aim to understand how one genome compacting complex, cohesin, influences gene expression. Cohesin is thought to regulate gene expression and genome organization by forming loops in the genome that segregate active regions from repressed regions. Cohesin is frequently mutated in cancer and intellectual disability syndromes, and these mutations appear to perturb appropriate gene expression. The molecular basis and consequences of cohesin loop formation on gene expression are unknown. Here, we propose to directly investigate the cohesin complex and its role in gene expression by (1) determining how cohesin forms DNA loops and (2) determining how transcription impacts and is influenced by loop formation. We will determine how DNA loops are formed by reconstituting cohesin-DNA complexes in vitro and determining their 3D structures by cryo-electron microscopy. We will then assess how cohesin affects transcription function by establishing a biochemical assay to simultaneously observe looping and transcription. This study will provide the molecular basis to understand how cohesin directly affects gene expression and how genome organization generally is employed to regulate cell fate in both healthy and diseased cells.