**Smith Family Foundation: Odyssey Award**
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**2025 Award Recipients**

**Ankur Jain, Ph.D.**
Assistant Professor
*Whitehead Institute for Biomedical Research*

"RNA Misfolding as a Driver of Cold-Sensitive Autoimmune Diseases"

Key words: RNA biology, Innate immune system, Cold stress

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Many tissues in the human body—such as the skin, nasal passages, and extremities—routinely experience colder temperatures than the core body temperature. Yet how cells adapt to mild cooling at the molecular level remains largely unknown. In our preliminary studies, we discovered that even modest cold exposure causes endogenous RNAs to misfold into double-stranded structures— molecular patterns normally associated with viral infection. Surprisingly, cells do not immediately activate innate immune defenses against these self-derived RNAs, suggesting that specialized mechanisms have evolved to preserve immune tolerance under cold stress. This project will investigate how temperature stress reshapes RNA folding inside cells and how the immune system adapts to recognize—and sometimes misrecognize—self. We aim to (1) identify RNAs that misfold into potentially immunogenic structures during cold exposure, and (2) define the cellular pathways that prevent inappropriate immune activation. We will combine cutting-edge approaches in RNA structure mapping, functional immunogenicity assays, and genome-wide genetic screening. By uncovering how cold stress perturbs fundamental molecular processes, this work will provide new insights into why cold exposure exacerbates autoimmune diseases and increases infection susceptibility. In the long term, these discoveries will offer a new lens for understanding how climate and environmental stressors influence human health at the molecular level.

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**Eunjung Alice Lee, Ph.D.**
*Associate Professor*
Boston Children's Hospital

"Harnessing Interactions Between Transposable Elements RNA and RNA-Binding Proteins for Personalized Splicing Modulation"

Key words: Transposable elements, RNA-binding protein, RNA splicing, DNA mutation, personalized splicing modulation

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Transposable elements (TEs) comprise nearly half of the human genome, when aberrantly exonized, drive splicing defects that contribute to cancer and rare genetic disorders. Our central hypothesis is that a regulatory network of TE-derived RNAs, RNA-binding proteins (RBPs), and cis-acting variants governs TE-mediated alternative splicing (AS), and that perturbing this network can restore normal transcriptomic profiles. To test this, we will: 1. Discover RBP regulators via genome-wide CRISPR knockout screens using novel Alu-splicing fluorescent reporters, identifying RBPs whose loss-of-function modulates TE exonization. 2. Develop and implement a computational pipeline for sensitive detection of TE-mediated alternative splicing in both short- and long-read RNA-seq, enabling transcriptome-wide mapping across diverse samples. 3. Validate top candidate regulators by quantifying splicing changes at endogenous TE loci in cultured cells and integrating TCGA and GTEx datasets with individual SNV/indel calls to uncover tissue- and genotype-specific interactions. 4. Design and evaluate splice-switching antisense oligonucleotides (ASOs) targeting RBP binding hotspots adjacent to deleterious TEs, assessing their ability to correct aberrant splicing in disease models. Our long-term goal is to define how TEs shape transcriptomic diversity and leverage TE-RBP networks to develop precision therapies for disorders driven by aberrant TE reactivation.

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**Wei Mi, Ph.D.**
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Yale University, School of Medicine

"Designing Innovative BacPROTACs to Combat Gram-Negative Bacterial Infections"

Key words: Antibiotic Resistance, Bacterial Proteolysis Targeting Chimeras (BacPROTACs), Lipopolysaccharide (LPS) Synthesis and Regulation, Deacetylase LpxC, Structure-based Drug Design, Molecular dynamics (MD) simulation, Single Particle cryoEM

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Antibiotic resistance is a critical global health threat, especially in Gram-negative bacteria protected by their outer membrane's lipopolysaccharide (LPS) component. LpxC, a zinc-dependent deacetylase essential for the initial step in LPS biosynthesis, is highly conserved in Gram-negative bacteria and has no human homologs, making it an excellent antibiotic target. However, LpxC inhibitors have consistently failed in clinical trials due to bacterial compensation mechanisms that stabilize LpxC, requiring higher inhibitor concentrations and increasing the risk of resistance and toxicity. To address this, we propose using bacterial Proteolysis Targeting Chimeras (BacPROTACs) to selectively degrade LpxC by recruiting it to the ClpXP protease. BacPROTACs will be designed by linking LpxC inhibitors to a degron tag recognized by ClpXP. Structural information and molecular dynamics simulations will be used to identify the optimal tag linkage site, followed by biochemical validation. Subsequently, BacPROTACs will be synthesized and evaluated in vitro. If successful, this approach will not only produce a new class of antibiotic candidates targeting LPS biosynthesis but also establish a versatile platform for selectively degrading essential bacterial proteins, offering a novel paradigm for antibiotic development.

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**Xin Tang, Ph.D.**
*Assistant Professor*
Boston Children's Hospital

"GABAergic inhibition of brain tumor progression"

Key words: Brain tumor, GABA, neuroimmue-competent brain organoid, cancer immunology, cancer neuroscience

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This project will launch a novel research direction aimed at halting the progression of brain tumors by leveraging the brain's intrinsic inhibitory system — GABAergic signaling. Emerging evidence from my lab and others has revealed that brain tumors hijack the GABAergic pathways to fuel their growth and infiltration. Building on my lab's extensive expertise in GABAergic inhibition in the context of neurodevelopmental disorders and epilepsy, we aim to elucidate the mechanisms by which GABAergic signaling contributes to brain tumor pathogenesis and harness these insights to drive therapeutic innovation. Our studies will focus on diffuse midline glioma (DMG), a universally lethal pediatric brain tumor. To model the complex tumor microenvironment (TME), we will utilize a human stem cell-derived organoid model recently developed in my lab, which faithfully recapitulates key cellular components of the DMG TME, including glutamatergic neurons, GABAergic interneurons, microglia, astrocytes, and tumor cells (Sarnow et al., Neuro-Oncology, 2025). In parallel, we will assess the therapeutic potential of a brain-penetrant small molecule drug, also developed in my lab, designed to restore GABAergic inhibition in the TME and suppress tumor progression. This project will lay the foundation for a research program exploring GABAergic cancerneuron interactions to drive discoveries and expedite onco-therapeutic development.

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**Xu Zhou, Ph.D.**
*Assistant Professor*
Boston Children's Hospital

"Intracellular Environment Engineering in Immune Modulation"

Key Words: PH, PH regulation, Macrophage, Inflammation, BRD4, Transcriptional condensates, Engineering, Imaging, Epigenetics

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The pH inside cells has long been considered stable and passively maintained by a repertoire of proton pumps and transporters. Our recent findings challenge this prevailing notion. This project aims to establish intracellular pH (pHi) as a critical regulator of immune cell function by characterizing novel pH-sensing mechanisms and developing tools to modulate pHi for therapeutic applications. Our recent discovery of BRD4 as an intracellular pH sensor through its histidine-rich intrinsically disordered regions represents a new paradigm for understanding how cells detect and respond to environmental changes. In Aim 1, we will define the molecular determinants of pH-sensing by systematically identifying features within BRD4 necessary for pH-dependent transcriptional condensate formation, characterize the transcriptional outcomes of engineered pH-sensitive/resistant variants, and explore additional condensate-based pH sensors. In Aim 2, we will develop synthetic and genetic tools for precise pHi modulation, define how pHi influences macrophage activation and polarization, and characterize tissue pH dynamics in vivo using a novel conditional reporter mouse model. By elucidating principles of intracellular pH sensing and developing approaches to engineer it, this work will uncover fundamental mechanisms of immune regulation and establish pHi manipulation as an innovative strategy to reprogram immune responses in inflammatory diseases and cancer.