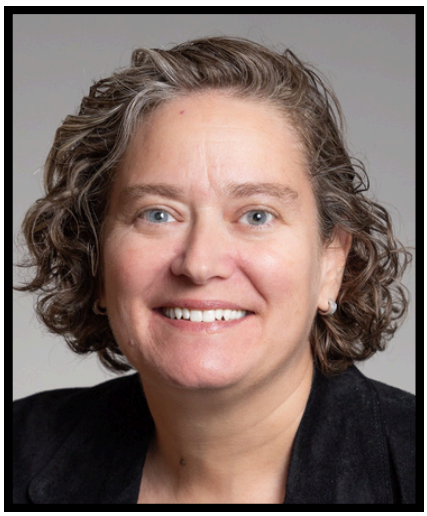
Pilot Projects on Early Drug Discovery & Artificial Intelligence



Sara Cherry, PhD
Scientific Director, High-throughput Institute for Discovery (HIT-ID)

Marylyn Ritchie, PhD
Director, Institute for Biomedical Informatics

On behalf of the High-throughput Institute for Discovery (HIT-ID) and the Institute for Biomedical Informatics (IBI), three pilot awards were selected. These awards are supported by the Stephen J. Heyman Fund for Artificial Intelligence Innovation and PSOM Dean's Innovation Fund.

A Generative AI Platform for Selective Peptide Antagonist Discovery Targeting CNS GPCRs

Primary Investigators:

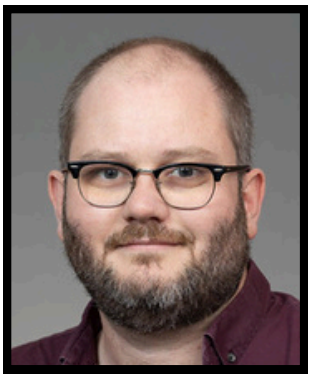
Julie Blendy, PhD
(SPATT, PSOM)

Pranam Chatterjee, PhD
(Bioengineering, EAS)

Abstract: We propose to develop and apply a generative AI framework for multi-objective therapeutic peptide discovery, to identify selective Orexin-1 receptor (OX1R) antagonists for the treatment of substance use disorder (SUD). OX1R is a validated, non-opioid target for relapse prevention, but peptide-based therapeutics have remained elusive due to the challenge of jointly optimizing for affinity, selectivity, and CNS-relevant drug-like properties. This framework integrates three recent algorithms from our work: PepTune, a masked discrete diffusion model for cyclic peptides; MOG-DFM, a discrete flow matching model for linear sequences; and BindEvaluator, a motif-specific interaction model that is embedded directly into the generative scoring loop to enforce OX1R targeting and penalize predicted off-target binding to OX2R. We will generate over 10,000 candidate peptides and select top-performing sequences using Pareto optimization across seven properties, including solubility, stability, oral bioavailability, and blood-brain barrier permeability. Lead peptides will be synthesized and experimentally validated through the PSOM High-Throughput Screening Core. This pilot will establish a constraint-aware, end-to-end generative system for CNS-targeted peptide hit discovery and enable future translational development of AI-designed peptide therapeutics.

Structure-guided discovery and optimization of novel pan-influenza inhibitors

Primary Investigators:



George Burslem, PhD
(BCBP)

Yi-Wei Chang, PhD
(BCBP)

Abstract: Influenza viruses remain a global health concern, necessitating the development of innovative antivirals that overcome both existing and emerging resistant strains. Recent cryo-electron microscopy studies from our laboratories (Peng, Xu et al, 2025 Science) have revealed a druggable interface within the evolutionarily conserved influenza ribonucleoprotein (RNP) complex, which is essential for viral replication. Three small molecule leads have been identified that inhibit this interface in vitro, but each requires optimization of potency and pharmacological profiles. In this pilot project, we will integrate large-scale AI-powered compound design and virtual screening, synthetic chemistry-informed lead prioritization, and systematic batch synthesis to generate improved RNP inhibitors. We will utilize the Penn High-Throughput Screening Core to evaluate hundreds of newly synthesized analogs and guide an iterative structure-activity relationship pipeline. By combining Dr. Chang's expertise in structural biology with Dr. Burslem's chemical biology proficiency, our multidisciplinary approach aims to deliver higher-affinity, drug-like molecules that robustly block influenza RNP assembly as potential broad-spectrum inhibitors across virus subtypes. Findings from this pilot will lay the groundwork for a multi-PI NIH proposal involving further animal model examinations to eventually providing new medicines toward addressing pandemic threats posed by influenza viruses.

Artificial Intelligence/ Machine Learning (AI/ML) based Lead Expansion for Duchene Muscular Dystrophy (DMD) therapeutics.

Primary Investigators:

Donna Huryn, PhD
(Chemistry, SAS)

Tejvir Khurana, MD, PhD
(Physiology, PSOM)

Andrew Zahrt, PhD
(Chemistry, SAS)

Abstract: Duchenne Muscular Dystrophy (DMD) is a fatal, incurable disease caused by DMD gene mutations leading to an absence of dystrophin protein. DMD is devastating for patients, their families, and society, with boys typically losing their ability to walk in their early teens and dying in the third decade of their lives. While the FDA has conditionally approved Splice Skipping Oligos for specific mutations (~ 30% of patients) and AAV μdystrophin gene therapy, these therapeutics face numerous problems such as delivery, immune rejection and toxicity (including fatalities) as well as lack of demonstrated efficacy in clinical studies. Indeed, at the time of writing the proposal (June 25, 2025) the FDA has suspended shipments and paused clinical trials of the DMD gene therapy Elevidys due to fatalities. Thus, there remains a great unmet clinical need since currently there is no safe and effective disease modifying therapy available for all DMD patients.