AI-Enabled In Vivo Phenotypic Screening and Human Brain Organoid Validation to Identify Novel Therapeutics for CDKL5 Deficiency Disorder

Calum MacRae, MD PhD

Harvard Medical School

Brigham and Women's Hospital

A major barrier to developing new treatments for CDKL5 Deficiency Disorder (CDD) is the lack of scalable biological models that can be used to efficiently discover therapeutic compounds. Traditional animal models, such as mice, provide valuable insights but are time-consuming and expensive, making it difficult to screen large numbers of potential drugs. In this project we will use a powerful vertebrate model organism, the zebrafish, to rapidly identify potential treatments for CDD. Zebrafish share many genetic and neurological similarities with humans and can be studied in large numbers using automated imaging and behavioral analysis. Our team has developed artificial intelligence (AI) methods that automatically analyze zebrafish behavior and identify compounds that improve disease-related, and especially seizure-related, phenotypes. Promising compounds discovered through zebrafish screening will then be tested in human brain organoids derived from patients with CDKL5 mutations. These miniature brain models allow researchers to study human neuronal development and network activity in the laboratory, and in this context provide human validation of efficacy seen in our zebrafish model. By combining large-scale zebrafish screening with human organoid validation, this project aims to accelerate the discovery of new therapeutic candidates for CDKL5 Deficiency Disorder and establish a scalable platform for future treatment development.