Rare Diseases

Rare diseases, though individually rare, affect a large fraction of our population. There is a growing realization of the need for effective, affordable and accessible therapies and/or management strategies for rare diseases in India. Rare disease research is a key focus area at DRILS. Activities include a) model creation and fundamental research for a diverse set of diseases b) chemistry approaches for drug development and c) drug repurposing. We are interested in working with the industry, clinicians and academics towards making the most impactful contribution in rapidly moving treatments to rare disease patients.

Rare Diseases & Zebrafish

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Fragile X syndrome: New insights from a zebrafish model

Fragile X syndrome (FXS) is the leading cause of intellectual disabilities in males and a major monogenic cause of ASD (Autism spectrum disorders). FXS is caused due to the loss of FMR protein (FMRP). FMRPs role in adult neurons is well studied; however, its role during embryonic development is not. Dr. Aarti's lab have created an FMRP knockout line in zebrafish using CRISPR technology and are using this to investigate FMRP functions during ovarian development as well as embryonic development.

Understanding disease mechanism using a zebrafish model for Glutaric Aciduria Type I

Inborn errors of metabolism (IEM) are a group of inherited metabolic disorders caused due to a defect in a single gene which codes for an important metabolic enzyme. The most common IEMs in India are organic amino acid disorders and fatty acid oxidation disorders. Glutaric aciduria type I (GA1) is an autosomal recessive IEM disorder that arises due to mutations in the enzyme Glutaryl Co-A dehydrogenase (GCDH), and is found to occur with high frequency (~1:5000) certain ethnic groups including the states of AP and Telangana, India. Children with GA1 usually present with macrocephaly at birth, and a trigger such as fever or infection in early childhood results in acute encephalopathic crises and striatal damage, leading to severe dystonia and dyskinesia. There is so far, no way to predict the susceptibility to striatal damage

or prevent it, especially in the pre-symptomatic stages. Aarti's team hypothesized that imbalance in molecular pathways in GA1 patients in the gestation or new born stages, could predispose some patients to such striatal damage and our objective is to use a larval zebrafish model of GA1 to identify such molecular changes. We have created a GCDH knockout line in zebrafish using CRISPR technology, and find that it mimics certain human GA1 phenotypes. We are currently characterizing the model and exploring avenues for therapeutic interventions.

Exploring the role of Dystrophin in neuronal development using a novel Dystrophin knockout zebrafish line

We have created a Dystrophin knockout zebrafish line, which displays symptoms characteristic of DMD patients such as muscle degeneration, decreased locomotion and eventually loss of life. We are currently using this model as a tool for drug screening to identify repurposing candidates or NCEs for DMD therapy. In addition to its important role in the muscle, Dystrophin is also believed to contribute to neural development and healthy neuromuscular junctions, and a fraction of DMD patients display cognitive dysfunction. Dr. Aarti and her group are interested in understanding the basis of this defect and plan to use our zebrafish DMD line to study the function of Dystrophin in the CNS.

Investigating the role of Phosphatidylserine decarboxylase (PISD) in Spondyloepimetaphyseal dysplasia (SEMD) using Zebrafish as model organism

Mutations in Phosphatidylserine decarboxylase (PISD) gene leads to a skeletal disorder Spondyloepimetaphyseal dysplasia (SEMD) with abnormal vertebral bodies and epimetaphyseal abnormalities. PISD is an enzyme which converts phosphatidylserine (PS) to phosphatidylethanolamine (PE), a major phospholipid, constituting 20-50% of total phospholipid content in mammals. PE is present abundantly in the cellular membranes, and is especially enriched in the mitochondrial membrane. PE formed via the PISD route is critically important to maintain mitochondrial structure and function, and therefore is essential for life. Genetic changes leading to reduced PISD activity cause changes in the mitochondrial membrane integrity and function, which leads to mitochondrial diseases with severe bioenergetics dysfunction. It is not yet understood how a general defect in mitochondria due to lack of PISD results in very specific skeletal phenotypes in SEMD. Dr. Aarti groups objective is to understand the functional contribution of PISD to the process of bone and skeletal development using zebrafish as a model.