Internship Proposal

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Project Title:
Investigating dynein-2 motor regulation to identify therapeutic targets for ciliopathies

Level:

Master Student

Project Summary:

We see, hear, and smell the world around us because of cilia—microtubule-based protrusions present on most cells of the human body, not only essential for motility, signaling, and development, but also for sensory perception.

Within cilia, intraflagellar transport (IFT) functions as a bidirectional trafficking system that delivers cargoes essential for cilia assembly while also removing signaling molecules and proteins to regulate cellular pathways. IFT dysfunction is associated with severe disorders known as ciliopathies, which affect many organ systems often involving the nervous system and skeleton. However, it is still unclear how defects in IFT lead to these diseases. Studying the mechanisms of IFT regulation is thus crucial for understanding the drivers of disease and how we can treat them.

IFT is mediated by two opposing molecular motors: Kinesin-2 drives anterograde transport from the ciliary base to the tip, while dynein-2 facilitates retrograde transport, from the tip to the ciliary base. While anterograde IFT has been extensively studied, retrograde IFT remains less characterized.

This project aims to unravel the regulatory mechanisms governing dynein-2 activity to ensure efficient retrograde IFT and ciliary function. By addressing this gap, our research will provide key insights into the underlying mechanisms of dynein-2-associated ciliopathies, with implications for the development of targeted therapies.

Work to be developed by the student:

In this study, the student will use Caenorhabditis elegans as an animal model. Among many

advantages, C. elegans animals have cilia in their sensory neurons that enable environmental perception and behavioral modulation.

Since most IFT genes are highly conserved in C. elegans, we will leverage CRISPR-Cas9 genome editing to introduce ciliopathy-associated mutations and express fluorescently labeled IFT proteins.

Using fluorescent microscopy, we will visualize cilia in these genetically modified animals and track IFT dynamics to assess potential alterations. Additionally, we will conduct behavioral assays to evaluate sensory perception, providing a functional readout of cilia integrity and activity.

References:

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