Title of Project	From patient to molecular mechanism: understanding pathogenic mutations of the cytoskeleton
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Summary of project

Mutations to cytoskeletal proteins are associated with a wide range of human genetic disorders and cancers. However, the mechanisms underlying pathogenesis can be profoundly different than for other disease-associated proteins. In particular, they are often associated with dominant inheritance related to the misassembly of mutant proteins into cytoskeletal filaments or associated molecular motors. For example, dominant-negative mutations that can interfere with assembly have been seen in alpha tubulin (causing amyotrophic lateral sclerosis or lissencephaly), kinesins (causing mental retardation) and dynein (causing spinal muscular atrophy). Moreover, our own analyses have revealed that current computational approaches are markedly worse at predicting dominant pathological mutations in cytoskeletal proteins.

This project will seek to integrate computational and experimental strategies in order to: 1) investigate the molecular mechanisms underlying dominant pathogenic mutations of cytoskeletal proteins; and 2) develop a model to predict them.

First, the student will perform a systematic computational analysis of mutations in cytoskeletal proteins to identify pathogenic mutations and prioritise mutations incorrectly predicted by current approaches. Next, the student will test pathogenic mutations experimentally, focusing on candidates such as tubulin and microtubule motor proteins to analyse the molecular mechanism underlying the pathogenic phenotype using cell biology, single molecule reconstitution and structural biology as suitable. Finally, the student will develop a new model for predicting pathogenic mutations. They will use machine-learning methods to integrate the evolutionary properties of mutations with the mechanistic insights underlying the experimental and disease phenotypes, in order to develop gene-family specific models for predicting pathogenesis.