

Title of Project:	Defining and predicting the molecular basis for male infertility
Cell Mechanism Supervisor Name	Julie Welburn
Quantitative Supervisor Name	Joseph Marsh

Summary of project
<p>While the genetics and molecular mechanisms underlying male infertility remain poorly understood, mutations in &gt;75 human protein-coding genes have already been confidently linked to male infertility. Many of these genes are related to microtubule and cilia biology. However we predict many more cytoskeletal proteins may cause male infertility. The project combines the expertise of the Welburn lab in mechanistic cell biology of cytoskeletal motors with the expertise of the Marsh lab in structural and computational biology (Bergendahl et al, 2019) to understand how mutations in protein complexes, often hard to predict, can affect protein function in health and disease.</p> <p>In this project, the student will focus on germ cell enriched-cytoskeletal <math>\alpha</math>8-, <math>\delta</math>- and <math>\epsilon</math>-tubulins. The student will first define the properties of <math>\alpha</math>8-, <math>\delta</math>- and <math>\epsilon</math>-tubulin phenotypically and biochemically using phylogeny, cell biology, biochemistry and in vitro reconstitution. They will determine how these isoforms differ from other <math>\alpha/\beta</math>-tubulin to create specificity in cell types.</p> <p>Then, the student will compile a mutation database for these classes of tubulins from clinical studies based on the infertility phenotype and from flagella defects in other species which have similar isoforms. The student will then use computational prediction algorithms to identify and predict mutations that are specific to germ line tubulin. If there is time, these mutations will be tested experimentally. These studies will inform us about the role of tubulin isoform and microtubule function in specialized cell types in health, fertility and disease.</p>

What quantitative skills will the student acquire or develop during their PhD project?
<ul style="list-style-type: none"> <li>• imaging (single molecule, confocal, v-DIC, etc..) and data analysis (tracking, scripting)</li> <li>• molecular and cell biology</li> <li>• advanced biochemical techniques and in vitro reconstitution of dynamic protein complexes</li> <li>• protein structure analysis</li> <li>• statistics</li> <li>• mathematical and computational methodologies for genomic and structural data analysis</li> <li>• machine learning to integrate quantitative imaging data with molecular modelling, protein structure and genomics, in order to develop computational models for</li> </ul>