| **Project Title: Developing new mass spectrometry-based assay for hereditary transthyretin amyloidosis** | **Code: WCS4** |
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| **Host School / Institute**: Westmead Clinical School | **Address:** Department of Clinical Immunology & Allergy, Westmead Hospital; Westmead Institute for Medical Research; Children's Medical Research Institute; Sydney Mass Spectrometry Facility, Charles Perkins Centre, Darlington Campus |
| **Certificates & Clearances required:** No | |
| **Primary Supervisor:** Dr Mark Taylor | |
| **Phone:** 043 424 963 | **Email:** mtay2576@uni.sydney.edu.au |
| **Co-Supervisor/team:** Professor Graeme Stewart. Mass spectrometry training will be provided by scientists in the Proteomics Facility in CMRI and in the Sydney Mass Spectrometry Facility. | |
| **Project Type:** Laboratory based; Data Analysis | |
| **Project Category:** Cardiovascular; Chronic Diseases/Illness | |
| **Skills / Attributes of a successful student:**<br>-Keen interest in proteomics, cardiovascular medicine and biochemistry. Practical experience in proteomics and mass spectrometry would be welcomed but not essential. The student will be trained in all aspects of laboratory methods.<br>-Diligent and motivated with attention to detail. Inquisitive with problem-solving skills, as well as good time management skills.<br>-Enthusiasm, dedication, willingness to work hard and ask lots of questions<br>-Preferred science / biomedical science / current medical student background | |
| **Project Keywords:** Proteomics; Assay development; Neurosciences; Ageing | |
| **Project Description:** Transthyretin amyloidosis (ATTR) is an increasingly-diagnosed cause of heart failure with preserved ejection fraction (HFpEF), with up to 30,000 individuals in Australia with HFpEF secondary to ATTR. It is a systemic disorder with other manifestations of autonomic and peripheral neuropathy, carpal tunnel syndrome, and spinal canal stenosis. ATTR may arise in those with the wildtype TTR gene (wtATTR), or less commonly, in those with pathogenic mutations in the TTR gene, causing hereditary ATTR or hATTR, with autosomal dominant inheritance. Best clinical practice screens all patients with transthyretin amyloidosis for amyloidogenic TTR gene variants in order to qualify patients for new therapeutics such as tafamidis, patisiran, and inotersen, and to screen asymptomatic family members of TTR mutation carriers. TTR gene variants are currently diagnosed in Australia using molecular genetic testing.We have established TTR mutation detection using MALDI-TOF mass spectrometry from transthyretin purified from patient serum/plasma as a less expensive and more rapid test with comparable sensitivity and specificity to molecular genetic testing.<br>The proposed research project will:<br>(i) extend the new transthyretin variant mass spectrometry assay to higher resolution mass spectrometers such as Q-TOF and orbitrap instruments to improve assay sensitivity<br>(ii) develop a new, robust method for transthyretin immunoenrichment from serum/plasma<br>(iii) express and purify recombinant transthyretin variants using engineered Escherichia coli<br>(iv) perform a large-scale evaluation of this assay on approximately 100 patient plasma samples, comparing the mass spectrometry assay to existing gold-standard molecular genetic results.<br><br>In addition to developing a new mass spectrometry diagnostic assay with the goal of implementation into Australian clinical practice, the research scholar will acquire experience in protein chemistry, multiple cutting edge proteomic mass spectrometry techniques, and pathology assay development and evaluation. While predominantly focusing on the transthyretin mutation detection assay development, there is the potential for the research scholar to become involved in any of the other three research projects depending on interest and time. | |