Master project: Derivation and characterization of pacemaker cells from human pluripotent stem cells for investigation of cardiotoxicity

Drug-induced cardiovascular toxicity is one of the leading causes of drug attrition during preclinical and clinical development. We are in need of better predictive in vitro models that allow detection of adverse cardiac liabilities early on in the drug discovery process. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) typically used in in vitro assays are differentiated using protocols that produce a mixed population of cells, the majority of which have ventricular characteristics. This excludes their usefulness to detect drug-induced cardiotoxicity within other heart specific cell types, including atrial and sino-atrial (SA) nodal cells. SA nodal cells, located within the sinoatrial node (SAN) of the heart, generate spontaneous rhythmic action potentials that excite cardiac muscle to contract, enabling the heart to pump blood throughout the body. In this graduate project you will be at the forefront of innovative medicines working with experts across global multi-disciplinary teams in the fields of cardiac and stem cell biology, to develop, evaluate and utilize hiPSC differentiation protocols to produce SA nodal cells. This will be followed by their pharmacological evaluation using cutting edge technology, which will ultimately allow us to understand mechanisms of atrial fibrillation (a form of cardiac arrhythmia) and potassium/sodium hyperpolarization-activated cyclic nucleotide-gated ion channel 4 (HCN4) mediated pharmacology. From this cutting-edge work there is the potential for publication in high-impact journals and to influence the future direction of the cardiovascular safety strategy within AZ.

Preferred previous experience: We seek master student candidates with a strong bioscience background, preferably with cell culture and molecular biology experience. We are looking for a highly motivated person with an interest in novel breakthrough technologies and a willingness to work in global multi-disciplinary teams.

Central placement objectives: 1. Establish a SAN cell differentiation protocol and characterise the cells in terms of phenotype and functionality. 2. Perform cellular assays to understand their robustness to detect compounds causing atrial fibrillation or HCN4 driven pharmacology.

Contact: Linda Starnes at linda.starnes@astrazeneca.com

Start date: Fall of 2020