



Project Title: Preclinical Development of Cannabis-derived Medicines for Drug-Resistant Epilepsy		Code: SOMS3
Host School / Institute: School of Medical Sciences/ Brain and Mind Centre		Address: Building F, Level 6, Brain and Mind Centre
Certificates & Clearances required: No		
Primary Supervisor: A/Prof Jonathon Arnold		
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Co-Supervisor/team: The Lambert Initiative provides national and international leadership both in the science of medicinal cannabis and in the discovery and development of cannabis-based medicines. Our activities extend from plant science and cannabinoid production, through cellular and preclinical pharmacology, to medicinal chemistry and drug discovery, including human laboratory studies and clinical trials. We also act in an advocacy and educational capacity, see https://sydney.edu.au/lambert/		
Project Type: Laboratory based		
Project Category: Pharmacology		
Skills / Attributes of a successful student: A genuine interest in a research career. Ideally the student would already have experience working in a research laboratory, although this is not mandatory. Knowledge of pharmacology and/or neuroscience. Problem-solving skills and attention to detail		
Project Keywords: Cannabis; Cannabinoids; Epilepsy; Animal models		
<p>Project Description: Epilepsy is a common neurological disorder with a lifetime prevalence of 2-5%. While many epilepsy patients achieve adequate seizure control with prescription anti-epileptic drugs (AEDs), about 30% of patients remain refractory to treatment. Childhood epilepsies, including the orphan diseases Lennox-Gastaut and Dravet syndrome, are particularly drug-resistant and more effective treatments for these conditions are urgently needed. Treatment-resistance is associated with an unrelenting seizure burden causing developmental delays in cognition, speech and motor skills, as well as increased mortality. In desperation, many parents have turned to illicit cannabis extracts to treat their children, with widespread media coverage of individual cases where spectacular outcomes have been achieved. Lending some credence to these anecdotal reports are results from recent randomised controlled trials (RCTs) showing that cannabidiol (CBD), a non-intoxicating plant-derived cannabinoid (phytocannabinoid), reduces seizure frequency in childhood epilepsy. These trials indicate promise for the development of cannabinoids as novel AEDs.</p> <p>A/Prof Arnold and colleagues have recently commenced a research program around the discovery and development of phytocannabinoid AEDs. To date this program has identified four phytocannabinoids with anticonvulsant properties more potent than CBD. The present project will build on these recent discoveries using an innovative phenotypic drug discovery platform, namely the Scn1a+/- genetic mouse model of childhood epilepsy. We aim to screen further novel phytocannabinoids using this model and to further validate existing findings. Additionally, given that phytocannabinoids as a class often have poor bioavailability, lead compounds will be structurally modified in a systematic fashion to improve pharmacokinetic properties, potency and efficacy. We will also explore the role of active metabolites of lead molecules in producing anticonvulsant effects. Finally, despite the recent promising results with compounds such as CBD in treating epilepsy, their mechanism of action (MOA) remains unclear. Here we will test the hypothesis that phytocannabinoids, and their derivatives, act to overcome inherent dysregulation of the endocannabinoid system (ECS) in epilepsy. Taken together, these approaches will provide a rational drug design approach to cannabinoid AED development.</p>		