Section 2: Non-Confidential Abstract

Please provide a scientific abstract of the Project. Clearly state the problem you are trying to solve, your hypothesis and approach, and expected results. **Please Note: This section may be provided to a diverse set of stakeholders including the public.**

Chronic pain and itch can be debilitating medical conditions that have a high prevalence in the Canadian population and are often associated with comorbidities such as anxiety and depression. Besides reducing the quality of life of affected individuals, the economic costs of chronic pain conditions in Canada are estimated to be in excess of $ 60 Billion. Although numerous pain medications are on the market, chronic pain conditions in many patients remain poorly managed, and there remains a need for effective treatment avenues without adverse effects. Cannabis and its bioactive compounds have shown promise for some chronic pain patients, however, the analgesic actions of cannabis are accompanied by psychoactive effects. Therefore, the development of cannabinoid derivatives that retain their analgesic properties, but are devoid of side effects is desirable. It is well established that cannabinoids act primarily on CB1 and CB2 cannabinoid receptors. However, there is emerging evidence that the endocannabinoid anandamide and the phytocannabinoids THC and CBD also effectively block voltage gated T-type calcium channels. These channels are known to be important for the transmission of pain signals, and there is surprising evidence that they are essential for the analgesic effects of these cannabinoids. This is further supported by our own drug discovery efforts which show that cannabinoid derivatives that block T-type channels but lack CB1 receptor activity are efficacious in preclinical chronic pain models and in the treatment of histamine-induced itch in mice.

Our core hypothesis thus posits that cannabinoids mediate significant analgesic effect independently of their actions on cannabinoid receptors, and that development of selective T-type antagonists and mixed T-type channel/CB2 receptor ligands constitute a viable therapeutic approach to chronic pain and itch conditions. This hypothesis will be tested in four research Aims. Aim 1 will use CB receptor and T-type channel knockout mouse models to test the analgesic effects of phytocannabinoids in neuropathic pain models. Aim 2 will expand our ongoing efforts to develop cannabinoid derivatives that selectively act on T-type calcium channels and test their efficacy in chronic pain models. Aim 3 will examine the interplay between cannabinoid receptors and T-type calcium channels, and Aim 4 will test selected compounds in mouse models of chronic itch.

At the end of the proposed funding period, we expect to have validated the molecular mechanism by which phytocannabinoids meet their analgesic actions. Furthermore, we expect to have identified a cannabinoid derived lead compound for further clinical development as a pain and itch therapeutics. In the long term, this work will therefore have a major impact on the life of Albertans and beyond, through increased efficacy of treatment of neuropathic pain and pruritus conditions, with reduced potential for adverse effects. These impacts will manifest themselves in the form of increased well-being, reduced incidence of comorbidities, and increased ability to engage in daily activities, including work. This in turn has the potential for major economic and socioeconomic impacts.