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.**

Marijuana is derived from the plant Cannabis sativa L. and is commonly used for medicinal purposes including use as an anti-inflammatory agent and in pain management (anti-nociceptive compound). There are over 100 different cannabinoids and over 200 different terpenoids in the cannabis plant. The primary psychoactive ingredient in marijuana is 9-tetrahydrocannabinol (9-THC) while the major non-psychoactive ingredient is cannabidiol (CBD). Terpenoids make up less than 1% of the chemical constituents, but even minute concentrations may have an effect on animal physiology, and terpenoid concentrations above 0.05% are considered to be pharmacologically relevant. While there is burgeoning interest in the effects of CBD as a medicinal agent, including its effects in pain management, there is much less information on the actions of terpenoids as compounds that alleviate pain. Moreover, there is virtually nothing known about the combined or synergistic effects of THC, CBD and terpenoids on nociception and pain. In this proposal, we present 2 Aims to approach this major knowledge deficit. The first aim proposes the use of zebrafish larvae in large-scale screens to test the ability of individual cannabinoid and terpenoid compounds to reduce pain. The second aim focuses on studying the cellular and receptor mechanisms of action by which these compounds are acting to alleviate pain. Specifically, we will examine the ability of the following 12 compounds: THCA, CBDA, THC, CBD, D-limonene, beta-Myrcene, alpha-Pinene, D-Linalool, beta-Caryophyllene, Nerolidol, Caryophyllene oxide and Phytol to prevent acetic acid-induced pain

Zebrafish embryos and larvae offer important distinct advantages over mammalian models for exposure studies, development and as a model for nociception. Embryos develop outside the mother in a chorion or egg casing, allowing one to accurately control the concentration and the time course of exposure compared with placental animals. The semi-transparent embryos can be used for whole preparation imaging and identifiable neurons can be studied throughout development. Large numbers of animals can be acquired very quickly, allowing for high throughput studies on locomotion, cardiac activity, nociception and pain. Importantly, the advantages offered by a zebrafish model for development, disease and pain studies are significant and allow for a wide range of experiments that may be difficult to perform in other preparations. Finally, zebrafish have receptors for transient receptor potential channels (TRPs), opioids, acid-sensing channels (ASICs) and toll-like receptors (TLRs). In fact, large-scale studies using zebrafish larvae for pain following treatment with acetic acid (AA), clearly indicate the exciting benefits of this animal model to study pain and nociception

This proposal directly addresses one of the critical areas of cannabinoid and terpenoid research that remains under-investigated: the combinatorial effects of cannabinoids and terpenoids on pain perception.