**1.Describe your research idea that would further an understanding of neurobiology as it relates to SUD and that is intended to be the basis for a successful start-up. (1 page)**

**Our research idea to create a start-up that focuses on novel medications for opioid abuse and chronic, treatment-resistant pain disorders, conditions that often go hand-in-hand.**

*To consider only the sensory features of pain, and ignore its motivational and affective properties, is to look at only part of the problem, and not even the most important part at that* (Melzack and Casey 1968, Fields 1999).

Recent research into the neurobiology of chronic pain has emphasized the affective and motivational dimensions of the chronic pain syndrome, the role of brain reward systems in pain chronification, and overlap between the brain areas involved in chronic pain and addiction (Porreca and Navratilova 2017). Deficits in dopaminergic functioning similar to those found in addictive disorders have been found in chronic pain (Taylor, Becker et al. 2016) and the mesolimbic reward system plays a critical role in mediating the affective and motivational aspects of chronic pain and analgesia (Finan, Remeniuk et al. 2017). Baseline structural and functional connectivity within the mesocorticolimbic system (dorsal medial prefrontal cortex-amygdala-nucleus accumbens), not areas related to pain sensation, predicted the development of chronic low back pain among patients with new onset back pain (Vachon-Presseau, Tetreault et al. 2016). Anxiety and depression are common among patients with chronic pain and are risk factors for prescription opioid abuse and overdose (Velly and Mohit. 2017). Co-prescribing of opioids and sedatives-hypnotics is common among patients with chronic pain (Larochelle, Zhang *et al*. 2015) and use of opioids with sedatives is particularly dangerous with 6.4 times the risk of overdose for opioids with sedatives and 12.6 times the risk of overdose for opioids with both benzodiazepines and muscle relaxants compared to opioids alone (Garg, Fulton-Kehoe *et al*. 2017). The affective aspects of pain are often the most bothersome and threatening for patients with chronic pain (Fields 1999) and challenging for clinicians to manage and therefore treatments that target the affective and motivational aspects of chronic pain, and the associated neurobiological alterations in the mesolimbic reward systems, may be safer and more effective than existing pain treatments.

The innovative approach for our prototype at the basis of our start-up is that a combination of a cannabinoid and an opioid partial agonist will be a safer and more effective treatment for chronic pain than existing pain medications by targeting the affective and motivational aspects of chronic pain and the underlying deficits in mesolimbic reward system functioning. Cannabidiol (CBD) is a compound found in the Cannabis genus of plants. The major psychoactive compound found in cannabis is ∆9-tetrahydrocannabinol (∆9-THC) which binds to CB1 and CB2 receptors and is thought to be responsible for many of the negative consequences of cannabis use including addiction, psychosis, cognitive impairment, weight gain, anhedonia, and rebound anxiety and insomnia. In contrast, CBD does not bind CB1 or CB2 receptors and does not have psychoactive or addictive properties and has been purported to be responsible for many of the "medicinal" properties of cannabis. In particular, CBD has anti-anxiety properties as a 5-HT1A partial agonist and is being investigated as a potential anxiolytic. Buprenorphine (BUP) is FDA-approved in a variety of formulations for sublingual administration for the treatment of opioid use disorder, opioid withdrawal, and chronic pain. Buprenorphine is a partial opioid agonist that has a lower risk of overdose compared to full opioid agonists due to a "ceiling effect" on respiratory depression. Typical sublingual dosing of BUP for opioid use disorder is between 16 mg and 24 mg a day but ultra-low doses of BUP (average dose 0.44 mg/d) reduced suicidal thinking among severely suicidal patients without substance abuse with ultra-low-dose sublingual BUP starting at 0.1 mg once or twice daily and titrated to a mean dose of 0.44 mg a day (Yoram Yovell, Gali Bar et al. 2016). Of note there was minimal physical dependence/withdrawal symptoms associated with these ultra-low-doses of BUP. Low doses of morphine reduce the affective but not sensory dimension of pain (Price, Von der Gruen et al. 1985) and in a fMRI study, low opioid

doses reduced experimental pain-induced activation in brain circuits known to process the affective dimension of pain, including the parahippocampal gyrus, the amygdala, and anterior parts of the insula, but not areas associated with the sensory dimensions of pain (Oertel, Preibisch et al. 2008). A combination of CBD and ultra-low doses of BUP in a single combination formulation for sublingual administration may be safer and more effective in reducing the affective dimension of chronic pain, including depressive and anxiety symptoms, and restoring mesolimbic reward system functioning.

**2. Convince the challenge reviewers of your technical competence as a biomedical scientist. Be brief, selective and persuasive. (0.5 page)**

Keith Heinzerling, MD, MPH, is an Associate Professor in the Department of Family Medicine at UCLA. Dr. Heinzerling is board certified in Internal Medicine and Addiction Medicine and has a busy academic clinical practice at UCLA. Dr. Heinzerling specializes in treating high risk patients with chronic pain and opioid problems and receives referrals of complicated patients from throughout California. Dr. Heinzerling (along with Dr. DeYoung) is one of the founding members of the UCLA Integrated Pain Management Center that is working to reduce complications of opioid therapy among patients in the UCLA Health System by providing integrated pain management, addiction medicine, psychiatric, and behavioral treatment for patients with chronic pain. Dr. Heinzerling completed a NIDA K23 award, has been Principal Investigator and Co-Investigator on multiple NIH-funded phase 1 and phase 2 clinical trials of anti-addiction medications and is recognized as an expert in medication development for stimulant use disorders. Dr. Heinzerling has active collaborations with several pharmaceutical companies (MediciNova, DeNovo) related to the early phase clinical development of medications for substance use disorder indications and has held and managed several INDs.

Dustin DeYoung, MD is board certified in Family Medicine, Psychiatry and Addiction Medicine. Dr. DeYoung has a busy outpatient psychiatric practice treating patients with co-morbid substance use and psychiatric disorders (as well as at the UCLA Integrated Pain Management Center as noted above.) Dr. DeYoung has participated in multiple NIH-funded phase 1 and phase 2 clinical trials (with Drs. Briones and Heinzerling) for anti-addiction medications. As an Addiction Medicine fellow, Dr. DeYoung received and completed an NIDA funded grant (through the Society of Teachers of Family Medicine) on online cognitive behavioral therapy for the treatment of opioid use disorders.

Marisa Briones, PhD, is the Clinical Research Director in our group in the Department of Family Medicine at UCLA. Dr. Briones has extensive experience ranging from basic and translational science to clinical research and clinical trials. She completed her graduate training on the molecular biology of HIV, supported by a NIGMS T32 Research Award in Pharmacological Sciences and a NIGMS F31 National Research Service Award. At the UCLA Center for Behavioral & Addiction Medicine, Dr. Briones serves as Clinical Research Director and co-Investigator on NIDA-supported phase 1 and phase 2 clinical trials for anti-addiction medication and oversees all regulatory, compliance and quality assurance. She has also supported numerous NIAID-sponsored phase 2 clinical trials for medication development for HIV prevention. We believe the 3 of us, with our combination of skill sets, are perfectly suited to create a start-up to develop multiple products for the treatment of opioid and other use disorders.

**3. Describe, in as many details as possible, what the prototype of your product would look like. Then, walk the Challenge reviewers through the typical use of the product, using simple terms and instructions. (1.5 pages)**

We are developing multiple pharmaceutical products combining a cannabinoid in combination with an opioid partial agonist for the treatment of opioid abuse and chronic,

treatment-resistant pain disorders. Our prototype is a combination formulation of cannabidiol (CBD) and buprenorphine (BUP) for sublingual administration. As described above, a cannabinoid-partial opioid agonist combination may be a safer and more effective treatment for the affective and motivational aspect of chronic pain than existing opioid formulations thereby improving patient outcomes and reducing complications of opioid abuse including overdose.

Pre-clinical research shows a broad range of effects of CBD, including neuroprotective, antioxidant, analgesic, anti-psychotic and anti-anxiety properties, not acting through CB receptors, but interacting with other targets (Zlebnik and Cheer 2016). Multiple studies (Zuardi, Cosme et al. 1993, Zuardi, Rodrigues et al. 2017) have shown anxiolytic effects of CBD in human volunteers when exposed to stressful situations (and chronic pain creates similar stress.) More than 90% of oral cannabinoids are metabolized during first pass. Formulation of this medication sublingually allows for an increased effect with lower doses of medication. Sublingual administration will avoid first-pass metabolism by the liver. The dose of 300 mg (Zuardi, Rodrigues et al. 2017) administered orally for anxiolytic effects appears to be effective and may be able to be reduced to sublingually. In a pharmacokinetic study of oromucosal spray (Stott, White et al. 2013), there was a moderate to high-degree of inter-subject variability for all pharmacokinetic parameters, with mean $C_{max}$ values well below those for smoked/inhaled cannabis. There were no safety concerns in this study and there was no evidence of drug accumulation with single or multiple dosing groups. In a review of patients with chronic pain and opioid use disorder (Barry, Cutter et al. 2016), 52% had evidence of a lifetime anxiety disorder, with 48% having a current disorder. High rates and persistence of anxiety disorders, among other mood disorders, can account for some of the difficulty providers have treating patients with co-occurring opioid use disorder and chronic pain. CBD may reduce anxiety, inflammation, and pain among patients with chronic pain without the serious complications associated with current opioid formulations including addiction and overdose.

BUP is a partial opioid agonist with analgesic effects and an excellent safety profile due to a lower risk of respiratory depression compared to full opioid agonists. BUP also reduced opioid-induced hyperalgesia (Koppert, Ihmsen et al. 2005, Mercieri, Palmisani et al. 2017). BUP potentiates the response of mesolimbic circuits in an fMRI study of an experimental pain model (Upadhyay, Anderson et al. 2012). Typical sublingual doses of BUP for opioid use disorder and chronic pain are in the 16 mg to 24 mg a day range (Malinoff, Barkin et al. 2005). Ultra-low doses of BUP (average dose 0.44 mg/d) reduced suicidal thinking among severely suicidal patients with minimal physical dependence/withdrawal symptoms (Yoram Yovell, Gali Bar et al. 2016). Low doses of BUP may be effective in reducing the affective and depressive symptoms and improving reward system functioning in patients with chronic pain.

Combining CBD with a low or ultra-low dose of BUP is a novel approach to treating chronic pain that would be much safer than existing opioid analgesic formulations and targets the reward system dysfunction that underlies the affective and motivational aspects of chronic pain that are clinically most challenging for patients and physicians. Our prototype is a combination formulation of cannabidiol (CBD) and buprenorphine (BUP) for sublingual administration. For initial clinical studies of the prototype, we plan on a CBD-BUP sublingual formulation with the following ratios of CBD to BUP: (1) 10 mg CBD and 0.5 mg BUP; (2) 25 mg CBD and 0.5 mg BUP; and (3) 50 mg CBD and 0.5 mg BUP. Dosing would be once or twice a day sublingually. For opioid-naïve patients with chronic pain, the CBD-BUP combo product could be a first-line treatment as the low doses of BUP are well tolerated in opioid naïve patients. Patients with physical opioid dependence would taper the opioids first prior to transition to CBD-BUP. Treatment with CBD-BUP would likely be long-term in patients with chronic pain although an advantage of a CBD-BUP with low doses of BUP is that there would be minimal risk of opioid withdrawal when discontinuing treatment.

We have submitted a provisional patent application for a cannabinoid-partial opioid agonist combination for the treatment of chronic pain, opioid use disorder, and opioid withdrawal as well

as paperwork for incorporating our start-up in California. Our immediate plans for the prototype are to complete a proof-of-concept rodent study within the next 6 months to support the patent application. The aim of the study is to determine if BUP+CBD reduces pain more than BUP or CBD alone in a rodent model of chronic pain. Male Wistar rats will undergo baseline assessment of mechanical or thermal hyperalgesia (different animals will be used for each) and then undergo chronic constriction injury of the sciatic nerve (neuropathic pain model) or treatment with complete Freund's adjuvant (inflammatory pain model). Seven days after injury, rats will undergo re-assessment of mechanical or thermal hyperalgesia and then begin treatment with compound (BUP, CBD, or BUP+CBD) once daily for 7 days. Following completion of 7 days of treatment with experimental compound, rats will again undergo assessment of mechanical or thermal hyperalgesia. We hypothesize that reductions in mechanical and thermal hyperalgesia will be greatest with the BUP+CBD combinations and that adding CBD to BUP will produce similar analgesic effects with lower doses of BUP. The primary outcome variable will be mean latency to withdraw for the mechanical and thermal hyperalgesia tests for BUP, CBD, and BUP+CBD. Results of the rodent study will be used to support the submission of a non-provisional patent application prior to the expiration of the 12-month pendency period for the provisional application (November 2018).

**4. Explain the methods you will use (how, when, where, whom) to determine whether the product is needed by the target audience and whether that audience would be willing to pay for the product. (1 page)**

There is an epidemic of opioid abuse especially among patients with chronic pain. Drug overdose is the leading cause of accidental death in the US, with 55,403 lethal drug overdoses in 2015. Opioid addiction is driving this epidemic, with 20,101 overdose deaths related to prescription pain relievers. From 1999 to 2008, overdose death rates, sales and substance use disorder treatment admissions related to prescription pain relievers increased in parallel. Overdose death rate in 2008 was nearly 4 times the 1999 rate. An estimated 3.8 million people aged 12 years and older reported past month misuse (not directed by a physician) of pain relievers (opioid medications.) Approximately 2 million adults met criteria for a pain reliever use disorder in 2015. The U.S. market for opioids for chronic pain is estimated to be $10 billion and for medications to treat opioid addiction at least $1.5 billion and likely to grow due to significant drawbacks with existing opioid formulations including risk of addiction and overdose.

More than 27 million Americans use some form of marijuana each month. Legal cannabis sales in the US reached an estimated $1.7 billion nationwide. Estimates put California's medicinal use around 750,000 patients or 19.4 per 1000 population. The market for cannabis products is likely to explode as states loosen legal restrictions on marijuana use, although none of these formulations are FDA-approved and access to medical marijuana products is currently limited to the 28 US states that have legalized some form of medicinal marijuana use.

As these numbers would suggest, we believe there is a definite market for our product. The targeted audience (and desire by health care organizations and insurance companies to reduce opioid use) would insure payment for this (and other future products) for treatment of chronic pain and opioid use disorders. As with any new product, determining the target audience, evaluating other products on the market, and promoting the benefits of the new product are very important for any start-up. Looking at these core issues, we believe there is a known and defined target audience. We feel other medications currently prescribed for opioid use disorders and chronic pain have key disadvantages, which are well known, that would put us at an advantage over our competitors. Finally, given the characteristics of our target audience that we have experienced in our clinical practices and research trials, we believe our combination product would have multiple key advantages that would make it desired by the target audience, prescribing physicians, and insurance companies and other payors.