EXECUTIVE SUMMARIES OF PROGRESS REPORTS

Awardees of the 2019 Consortium grants cycle

Paul A. Borsa, PhD
Associate Professor
College of Health and Human Performance

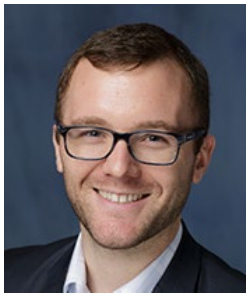
Efficacy of a controlled short-term trial of CBD ingestion on reducing symptomatic response and facilitating recovery after induced muscle injury

Executive Summary: Is a controlled short-term trial of CBD ingestion effective in reducing symptomatic response (e.g. musculoskeletal pain and pain-related anxiety) and facilitating functional recovery (strength loss) following induced muscle injury? Secondarily, are the therapeutic effects dose-dependent? We have secured IRB approval from UF and are still in the process of obtaining an Investigational New Drug (IND) status from the Food & Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). Our application is presently on clinical hold status pending additional information requested by CDER. We are in the process of securing collaboration with a Florida-based CBD company (SunFlora, Inc, St. Petersburg, FL) who has agreed to source our hemp-derived CBD for the project as well as assist in the generation of additional information requested by the FDA. We expect to obtain and IND this summer and begin data collection pending approval from the University to reinstate clinical laboratory operations.

Helen Bramlett, PhD
Professor
Miller School of Medicine

Therapeutic dosing of a cannabinoid (CBD) after mild and moderate brain injury for translation to the clinic

Executive Summary: Cannabidiol (CBD), a type of cannabinoid, has been shown to have anti-inflammatory, neuroprotective effects that may be a therapeutic strategy in the treatment of traumatic brain injury (TBI). The objective of this study is to rigorously assess two therapeutic doses (3 or 5mg/kg) of CBD using a clinically-relevant oral administration regimen in two pre-clinical models of brain injury. At this time, we have completed 50% of our preclinical injuries using either the moderate fluid percussion injury (FPI) model or blast TBI model. Animals were orally administered 5 mg/kg CBD in peanut oil or vehicle (Veh; peanut oil alone) for 7 days after TBI or sham surgery. The FPI and Blast TBI groups have undergone their respective behavioral testing paradigms and tissue has been processed for histological analyses. The next steps will include completing the animal groups for both the Blast and FPI models with oral administration of two different concentrations of CBD. This includes conducting and analyzing neurocognitive, sensorimotor, hearing, and vestibular behavioral outcome measures, as well as histological analyses evaluating neuro- and cytoprotection and inflammatory responses. By the end of the award, with completion of proposed specific aims, we anticipate oral administration of CBD will mitigate some of the behavioral deficits and histopathological consequences resulting from FPI and Blast TBIs.



Joshua Brown, PharmD, PhD, MS
Assistant Professor
College of Pharmacy

Characterizing community and physician-level factors associated with medical marijuana prescriber registration and patient access

Executive Summary: The charge of the Florida Consortium for Medical Marijuana Clinical Outcomes Research is to engage in research to evaluate the clinical outcomes of medical marijuana use in Florida residents. While one facet of these evaluations are the outcomes associated directly with use of medical marijuana products, many other factors can influence the outcomes experienced by Florida's medical marijuana patients. Thus, assessing these external factors is important to produce impactful research. Our research to date has utilized multiple extant data resources to gather, combine, refine, and map information on relevant external factors such as community health ratings, physician access, and dispensary locations. We have created interactive Tableau® based maps that provide county-level stratification of these factors to enhance understanding of their interplay. With the remaining project period, we will continue to refine these interactive maps and data visualizations, including use of a Google API, to map physician and dispensary locations with greater precision. The final product will include merging of all publicly available data sources to create a downloadable resource that can be used by other researchers. At the end of the award, we are on-track to deliver a continuously improving resource and are preparing to migrate these tools to be an open-access dashboard hosted by the Consortium and made available to the broader research community as well as the public and policymakers in Florida. Ultimately, the goal is to capture and understand the additional ecological factors that may influence an individual's access to medical cannabis as well as the outcomes they experience.

Andrea Cippitelli, PhD
Research Assistant Professor
College of Medicine

Cannabidiol: A potential treatment for migrainelike pain, negative emotion and photophobia

Executive Summary: Based on the beneficial effects of cannabidiol (CBD), we aimed to investigate if CBD has therapeutic role in migraine pathology. Using nitroglycerin (NTG), we completed conditioned place aversion (CPA) experiments, Von Frey assay of allodynia in the paw, and grimace face assay with no significant findings. Due to multiple failed attempts and time restraints using NTG, we moved to a calcitonin gene-related peptide (CGRP) migraine model. We successfully modeled aversion in CGRP groups, however pretreatment with CBD showed no effect. The grimace face assay produced acute spontaneous pain with visible symptoms from CGRP, such as eye squinting and downward pointing of the face and we will repeat using pretreatment with CBD. A reliable method for detecting facial allodynia in the periorbital region using Von Frey filaments has proven challenging with failed attempts following acute NTG treatment and restraining/holding apparatus development difficulty, however we are now able to detect thresholds of allodynia similar to those reported in the literature. Our next steps include combination of acute CBD and CGRP treatment in all models, and well as chronic administration of CBD prior to CGRP induced migraine. Finally, we are ready to begin facial allodynia analysis, which will be measured for acute and chronic administration of CBD. By the end of the award, we are confident we will have insight into whether or not CBD may play a role in mouse models of migraine.

Gregory McManus, PhD
Associate Professor
College of Arts and Sciences

Florida Gulf Coast University

Rapid identification and quantification of heavy metals and microplastics in CBD oil

Executive Summary: There are substantial uncertainties surrounding the nature and content of contaminants in cannabis plants. An in-depth understanding of plant contaminants and toxin effects on the stability of plant compounds and the effect on human health is necessary. The goal of this project is to develop reliable, rapid, efficient, inexpensive techniques for the determination of key contaminants within the cannabis plant and to accelerate research in this promising industry to ensure consumer/patient safety. We have begun developing and refining our methods for the testing of CBD oil samples for heavy metals and microplastics contaminants. After accomplishing the aims in this proposal, we will continue to expand the scope of our research to determine contaminates present in the marijuana vaping products using coupled Thermal Gravimetric analysis, Gas Chromatography and Mass Spectroscopy (TGA-GC-MS) techniques. For this purpose, we will seek funding through the NIH R21 program. At the conclusion of this project, we will have an understanding as to whether or not Wavelength-Dispersive X-ray Fluorescence and coupled Differential Scanning Calorimetry – Thermal Gravimetric Analysis are effective tools for identifying contaminants in CBD oil. We will have collected data on a variety of CBD oil samples and determined whether heavy metal and microplastic contaminants are present in concentrations that would pose a danger to public safety. This project will have also supported the training of two undergraduate research students during the summer of 2020.

Mandip Singh Sachdeva, PhD
Professor
College of Pharmacy

FAMU Florida Agricultural and Mechanical University

Hyaluronic acid functionalized, Cannabidiol-loaded Mesenchymal Stem Cells (MSC)-Derived Exosomes for Drug Resistant Cancers

Executive Summary: Triple negative breast cancer (TNBC) represents an important clinical challenge, as these tumors often develop resistance to conventional chemotherapeutics. Anti-cancer potential of cannabidiol (CBD) is well demonstrated in various cancers but poor solubility and increased metabolism by CYP enzymes limit its bioavailability. We hypothesize that therapeutic usage of hyaluronic acid (HA) functionalized human umbilical cord stem cell derived exosomes (hUCMSCs-EX) will serve as a delivery platform not only for increasing the bioavailability but also for overcoming resistance of docetaxel (DTX) in MDA-MB-231 (i.e., CB1, CB2, and CD44 receptors expressing) cells. Synthetic CBD (Purisys™, GA; GMP grade) decreased proliferation of MDA-MB-231, MDA-MB-468 and Doxorubicin (DOX) resistant MDA-MB-231 cells. CBD could also increase sensitization of DTX and DOX to MDA-MB-231 (by 8.2 and 2.5-fold respectively) and MDA-MB-468 (by 4.6 and 3-fold respectively) cells. We also developed stable formulation of CBD loaded exosomes (CBD-EX) by using sonoporation technique. CBD-EX significantly decreased the proliferation of TNBC cells. We will further investigate the therapeutic efficacy of CBD-EX after their functionalization with HA in both wild type and drug resistant TNBC cancers. Molecular studies such as whole transcriptome analysis are currently in progress to delineate the mechanisms responsible for CBD induced-cell death. The PI expects to have stable HA-functionalized CBD-EX, which can show anti-cancer effects and enhance the sensitivity of DTX in 2D and 3D cultures of TNBC cells.

Jacqueline Sagen, PhD, MBA
Professor
Miller School of Medicine

UNIVERSITY OF MIAMI

Evaluation of medical marijuana for the treatment of chronic spinal cord injury pain using a rat central neuropathic pain model

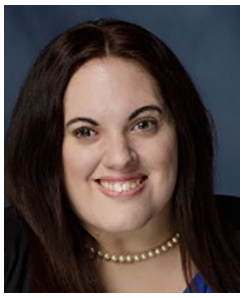
Executive Summary: Although the most frequently reported use of medical marijuana is for pain relief, there has been a paucity of preclinical studies evaluating the effects of Cannabis components in chronic pain models. Chronic pain following spinal cord injury (SCI) occurs in a majority of patients and can be so severe that it is their top quality of life concern. Despite anecdotal observations from SCI patients reporting substantial pain relief from marijuana and medicinal extracts, progress in the field has been hampered by lack of solid supporting preclinical evidence. Thus, the goal of this study is to rigorously evaluate the effects of the two major but mechanistically distinct Cannabis components, CBD and THC, and their potential synergistic pain-relieving combination, using a preclinical SCI rodent model. Towards this goal, both male and female rats have undergone a spinal cord compression injury and tested for onset and maintenance of neuropathic pain using a battery of sensory and motor outcome measures. Results showed a gradual onset of neuropathic pain following SCI, similar to the time course observed in SCI patients. A key observation was the similarities in pain development and expression in both sexes. We have also applied for and received FDA/CSS approval for DEA Schedule 1 Researcher, but the regional field office review has been delayed due to the COVID-19 crisis. Once completed, we will test CBD/THC combinations on chronic pain reduction, dose-ranging, and daily dosing to provide the essential preclinical foundation for further guidance on medical marijuana in the treatment of chronic neuropathic pain.

Krishna Vaddiparti, PhD, MPE, MSW
Research Assistant Professor
College of Public Health and Health Professions & College of Medicine

UF UNIVERSITY of FLORIDA

A feasibility study of real-time monitoring of Posttraumatic Stress Disorder related sleep disturbances and other symptoms among patients on medical marijuana

Executive Summary: The goal of this pilot grant is to recruit and retain patients with Posttraumatic Stress Disorder (PTSD) on medical marijuana (MMJ) in a prospective study and examine in real-time, using Ecological Momentary Assessment (EMA) software, how MMJ affects PTSD related sleep disturbances and recovery from PTSD symptoms and distress. At this point of time there is very little scientific indication on appropriateness of marijuana as a therapy for PTSD. As of May 18th, 2020, we have 12 participants enrolled in the study and fulfilling study requirements. Most participants have been able to reach the threshold of completing 90% of the EMA surveys and have had no issues completing the REDCap surveys. Data collection is ongoing. After 20 participants have completed the study components, data will be exported from the EMA software and the REDCap database. To compare daily sleep quality, affect, PTSD symptoms, and side effects (e.g., mood, agitation) before and after starting MMJ treatment, a multilevel model will be constructed to detect changes over time for each outcome variable. We will examine the contribution of sleep disturbances to next day PTSD symptoms, after accounting for the previous evening's PTSD symptoms. To compare sleep quality, positive/negative affect, PTSD symptoms, and well-being pre and post MMJ treatment, repeated measure ANOVA will be calculated.



Jenny L. Wilkerson, PhD
Research Assistant Professor
College of Pharmacy

Marijuana-derived terpenes for the treatment of chemotherapy-induced pain

Executive Summary: My current award seeks to examine cannabinoid receptor and immune mechanisms underlying the anti-allodynic and anti-depressive-like effects of terpenes and minor cannabinoids in a chemotherapy induced peripheral neuropathy (CIPN) model of neuropathic pain. I proposed to test terpenes: γ-terpinene, α-terpineol, β-caryophyllene, and the minor cannabinoids cannabichromene (CBC), cannabinol (CBN), found in marijuana in a well-characterized mouse model of CIPN. I have two subaims for the currently funded project: **Sub-aim a:** Determine systemic effects of terpenes and minor cannabinoids, and mediation of effects by cannabinoid 1 receptor (CB_1R), cannabinoid 2 receptor (CB_2R) and Secreted Phosphoprotein 1 (SPP1) in the CIPN model of neuropathic pain. **Sub-aim b:** Determine protein changes associated with mechanisms of select terpenes and minor cannabinoids in the CIPN model of neuropathic pain. Sub-aim a is complete. Sub-aim b will be completed in the months following the resumption of animal research activities at UF. The data that this grant funding has already produced are being used to submit a R21 grant next month (June 2020), with the intention of scaling up research to submit an R01 in following NIH grant cycles. Excitingly, the NIH grant proposal will leverage newly founded collaborations in pharmacokinetics and medicinal chemistry within UF. These collaborations came from presenting at the UF SPAR conference. Further, a publication with the data collected thus far is currently in preparation.

Ali Yurasek, PhD
Assistant Professor
College of Public Health and Health Professions

The Relationship between State Medical Marijuana Laws, Substance Use and Mental Health Disorder Diagnoses, and Associated Health Care Costs

Executive Summary: The purpose of this project is to investigate trends regarding substance use diagnosis, mental health diagnosis, and treatment utilization in states with and without medical marijuana laws. *Progress*- IRB materials for the secondary data collection were submitted. The protocol received an exempt review by the University of Florida IRB and was approved. Specific activities conducted include: recruiting and training research assistants, developing a medical marijuana database (e.g., number of dispensaries, approved conditions, etc.), working with data provider, HCCI (Health Care Cost Institute), and initial identification of variables needed from NSDUH dataset. One aspect of this study (related to Aim 1) that is behind schedule is the data acquisition from the HCCI (see next section). While our request for the no cost extension is pending, a study mirroring the larger study we proposed in Aim 1 is in progress, focusing on the state of Florida. The IRB protocol is currently under review. This will allow us to obtain the relevant data, albeit on a reduced scale, and investigate one of the core hypotheses. *Next Steps*- 1) Finalize contract with the HCCI data provider; 2) Begin secondary data analyses with a national data set 3) finish the county level marijuana law/dispensary data for Florida and other states; and 4) Conduct GIS (Geographic Information System) analysis. *Anticipated Outcomes*- Findings will demonstrate the influence of MML on health care utilization for substance use and mental health diagnoses and inform health care policy and state specific medical MJ policy and implementation.