GbSciences' Development Programs

GbSciences

OTCQB:GBLX

- Phytomedicine-based Drug Development
- Extensive Research Network: multiple universities, hospitals & CROs
- GBS' Discovery Platform: unique APIs and IP
- APIs: Synthetic homologues identical to plant compounds
- Oral delivery formulations: ODT, OTF, nanoparticles, gel capsules
- Parkinson's Disease (PD): Patent issued; IND ready Q2 2022
- Neuropathic Pain (NP): Patent issued; Animal study at NRC Canada
- Anti-Inflammatory (AI): Patent issued; Animal P of C ready
- Cytokine Release Syndrome (CRS): Patent filed; P of C study at MSU

GbSciences Drug Development Pipeline

Pre-IND

Rx PROGRAMS	DISCOVERY	PRECLINICAL	CLINICAL TRIALS			
			First-in-Man/ Phase I	Combined Phase I-II	Phase III	FDA APPROVAL
Parkinson's Disease (PD)						
Neuropathic Pain (NP)						
Heart Failure (HF)						
Cytokine Release Syndrome (CRS)						
Mast Cell Activation Syndrome (MCAS)						
Inflammatory Bowel Disease (IBD)						

KEY	
Completed	
In-Process	

GbSciences Drug Discovery Platform

HTS

High Throughput Screening System

Disease-specific cell & animal models

ISCA

In Silico Convergence Analysis

Data Analytics & Machine Learning

CTM

Plant-inspired, Optimized Therapeutic Mixtures

Synthetic cannabinoid API & IP (comp and use)

Intellectual Property Portfolio Strategy

- Plant-Inspired, Optimized Therapeutic Mixtures
  - Novel API composed of natural or synthetic homologs of plant-derived ingredients
  - Composition of Matter and Field of Use Claims
  - Combinations of Novel API and Delivery
- Current Portfolio (USPTO & WIPO/PCT)
  - 5 Issued US Patents & 3 Issued International Patents
  - 7 Nonprovisional US Patent Applications & 35 International Patent Applications
  - 3 Provisional US Patent Applications

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GbSciences Parkinson's Therapeutics

Optimized Therapeutic Mixture (OTM) Development

# mixtures	screen type	GBS screen	GBS references
>10,000	metabolomic	METABOLOMIC PROFILES 2662 *Cannabis* chemovars	PMID: 32923659
~1,000 combinations	high throughput cellular	MPTP & DOPAMINE RELEASE ASSAYS 1080 combinations of 9 cannabinoids & 13 terpenes	US Patent 10,653,640
<100	medium throughput cellular	RECEPTOR PHYSIOLOGY & MOLECULAR DOCKING STUDIES 5 cannabinoids & 6 terpenes INFLAMMATORY PROFILING 5 cannabinoids & 6 terpenes	PMID: 31096838 PMID: 31446830 US Patent App 63/067,269
<20	medium throughput animal	6-OHDA ZEBRAFISH MOTOR ASSAYS 5 cannabinoids & 6 terpenes	US Patent App 16/844,713
3	Lead Optimization	OTM.PD119, OTM.PD205, OTM.PD361 for Acute & Chronic testing in 6-OHDA mouse model	

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Chaminade University

NRC·CNRC Canada

Mixtures More Effective Than Individual Ingredients

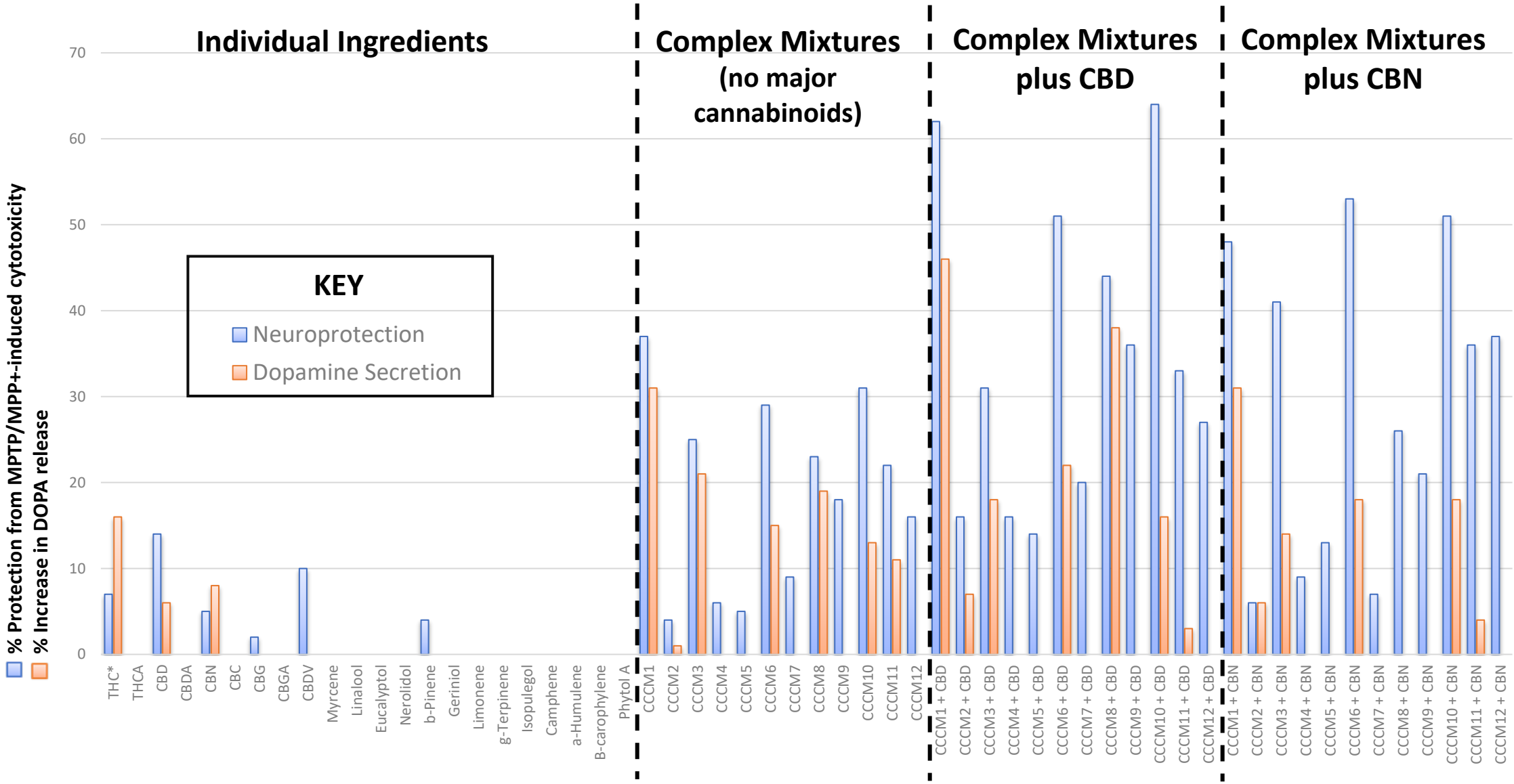

Figure 1. Mixtures were more effective than Individual Ingredients in cell models of Parkinson's disease

Statistically Significant PD-Symptom Reduction

Parkinson's Animal Study—NRC Canada

- Zebrafish model of Parkinson's Disease-72 hr OHDA Exposure
  - Restored overall movement levels (measured based on total distance moved)
  - Normal startle response (Light/Dark)
  - Reduced "resting tremor"(measured frequency & duration of shifts in activity states)
- Tested Multiple OTMs
  - Safety/Toxicology
  - Proof of Concept: Acute Symptomatic Relief
  - Mechanism of Action: Neurostimulatory, Neuroprotectant, Anti-Inflammatory
- Animal Data to support IND application to US FDA and Health Canada

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NRC·CNRC Canada

Statistically Significant PD-Symptom Reduction

Frequency of Switching & Duration of Activity State

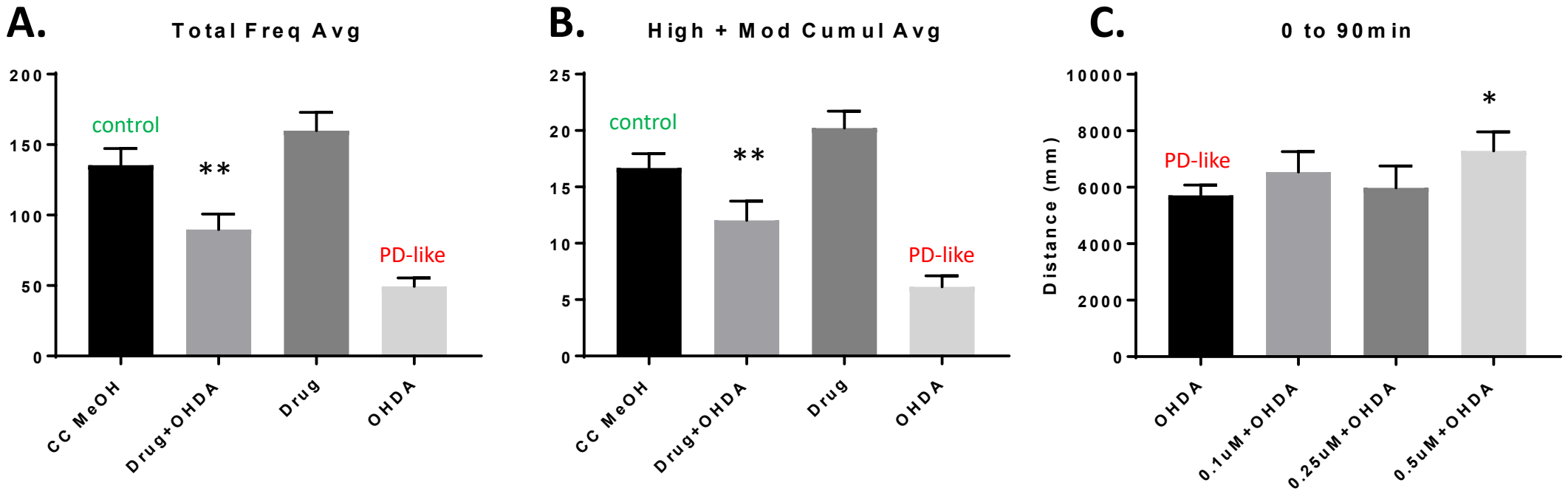

Figure 2. Statistically significant reduction in PD-like symptoms was achieved when 0.5 µM of OTM.PD119 was exposed to the PD-like animals (Drug + OHDA); Panel A. Total frequency of activity state switching; Panel B. % Time in the "ON" (or not low) Activity State, Panel C. Total distance traveled; * = t-test $p < 0.05$ for OHDA + Drug vs OHDA; ** = t-test $p < 0.01$ for OHDA + Drug vs OHDA

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NRC·CNRC Canada

PD Clinical: Orally Disintegrating Tablets (ODT)

Zydis™ Orally Disintegrating Tablets (ODT)

- Unique, freeze-dried oral solid dosage
- Instant oral dispersion – typically less than 3 seconds

OTM.PDXXX in Zydis™ ODT

- Convenient dosing solution for PD patients
- Greater than 50% of PD patients have swallowing problems

Clinical Advantages

- Improved bioavailability
- Increased patient compliance
- Rapid onset through Buccal/Sublingual Absorption

Figure 3. Zydis™ Orally Disintegrating Tablets (ODT)

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Catalent®

Parkinson's OTM Study Synopsis

Name of Sponsor/Company: GB Sciences, Inc.

Name(s) of Investigational Products: OTM.PD119, OTM.PD205, OTM.PD361

Title of Study: A Randomized, Double-Blinded, Cross-Over Study Designed to Evaluate the Safety and Preliminary Efficacy of OTM.PD119, OTM.PD205, GBS.PD361 in Mild to Moderate Parkinson's Disease (PD).

Study Center(s): Two potential sites identified, pending further discussions.

Study Type: Interventional

Study Design: Allocation-Randomized; Interventional Model-Crossover Assignment; Masking-Double (Participant & Outcomes Assessor); Primary Purpose: Safety, Tolerability, and Preliminary Efficacy

Total Duration of Study: For each subject, the duration of the treatment is 12 weeks (3 treatments x 4 weeks each). The estimated duration for the entire protocol is approximately 18 weeks based on a two-week run-in period and two, two-week wash out periods (TBD) between treatments.

Phase of development: Phase 0/First-in-Man

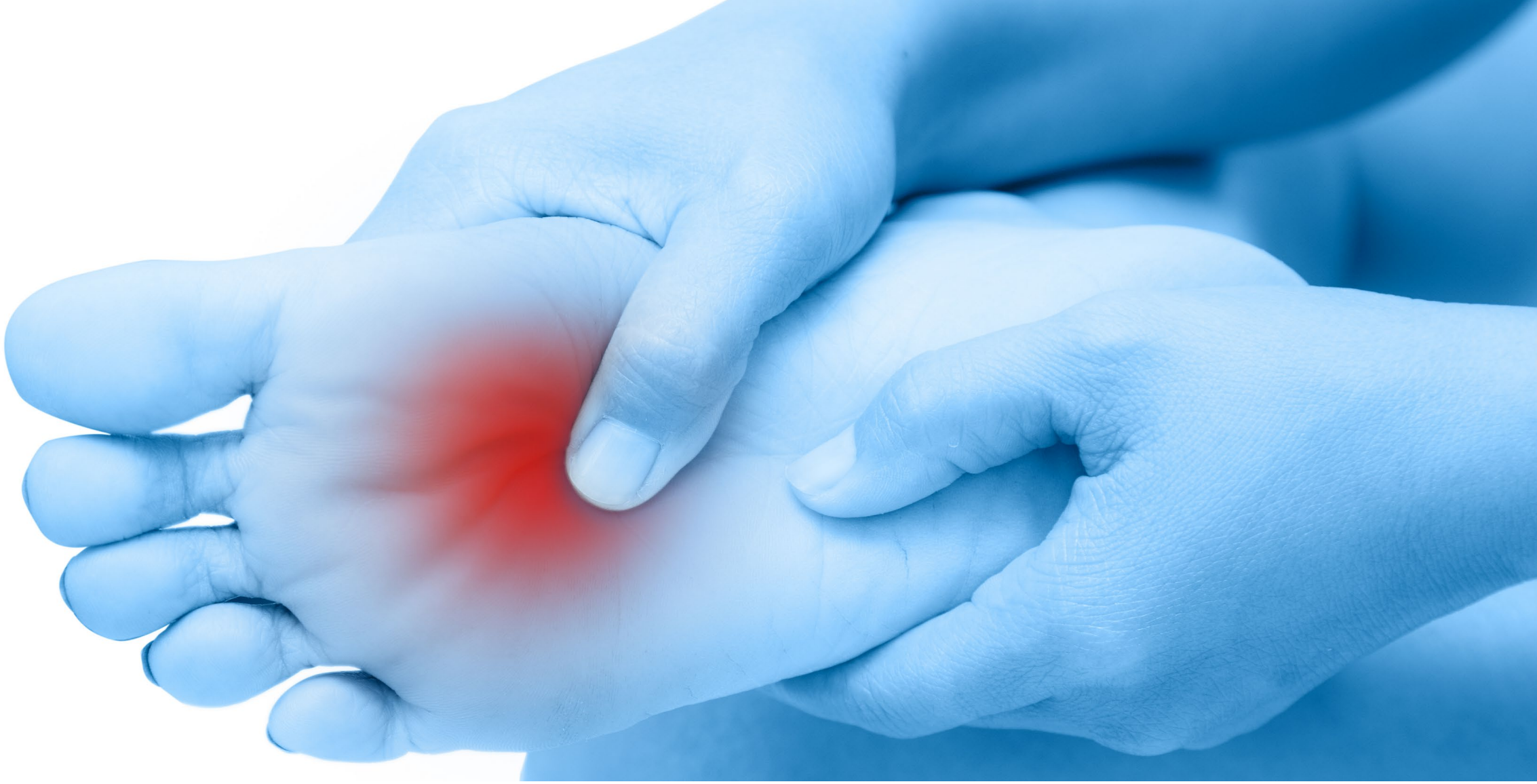
Parkinson's OTM Study Synopsis

Randomized to one of three study groups (1:1:1)

- Group A (n = 8)
- Group B (n = 8)
- Group C (n = 8)

Cross-over Design

Group	Run-in	Treatment 1	Wash-out	Treatment 2	Wash-out	Treatment 3
A	placebo	OTM.PD119	placebo	OTM.PD205	placebo	OTM.PD361
B	placebo	OTM.PD205	placebo	OTM.PD361	placebo	OTM.PD119
C	placebo	OTM.PD361	placebo	OTM.PD119	placebo	OTM.PD205
Weeks	1 & 2	3, 4, 5, 6	7 & 8	9, 10, 11, 12	13 & 14	15, 16, 17, 18



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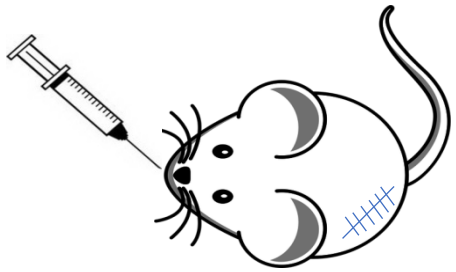
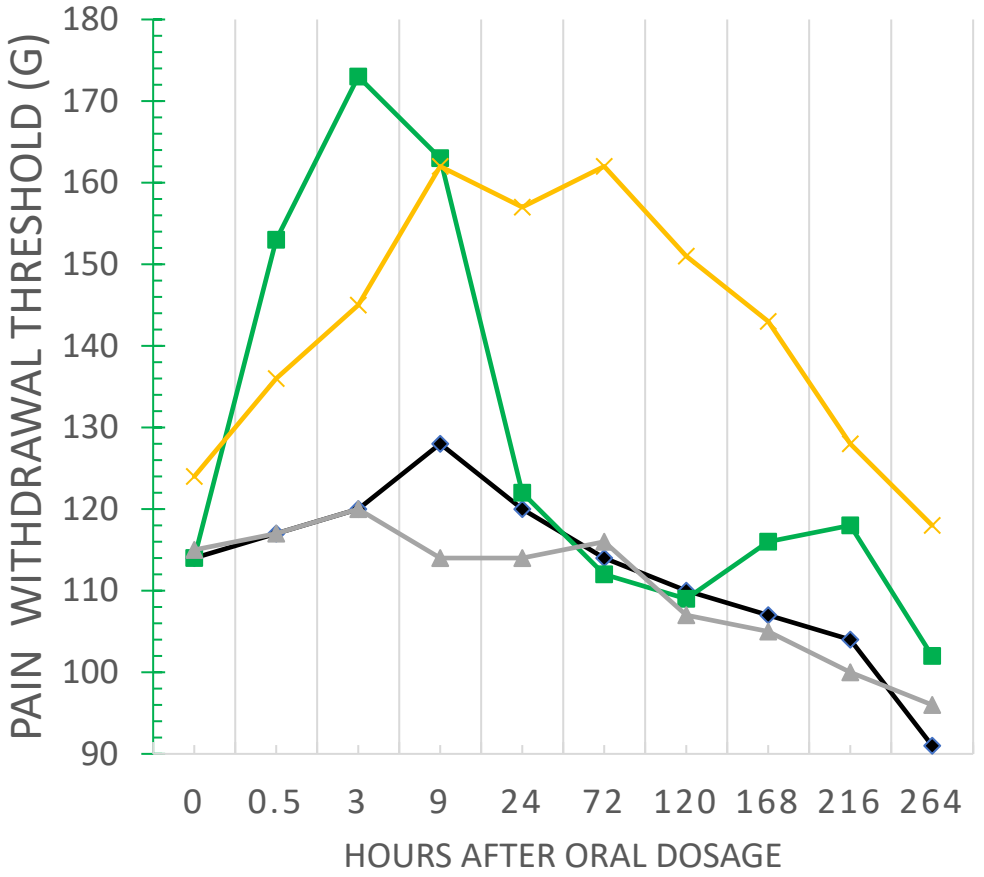
GbSciences Neuropathic Pain OTM

Proof of Concept: Extended-Relief Nanoparticles

Esther Berrocoso, PhD, Raquel Rey-Brea, MS, Mercedes Fernández-Arévalo, PhD, Juan Antonio Micó, MD, PhD, Lucía Martín-Banderas, PhD. 2017. Single oral dose of cannabinoid derivate loaded PLGA nanocarriers relieves neuropathic pain for eleven days. Nanomedicine: Nanotechnology, Biology, and Medicine. 13 (2017) 2623-2632.

Oral Administration (one dose)





Cannabinoid-containing Nanoparticle

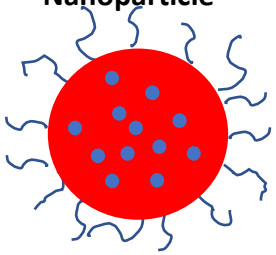
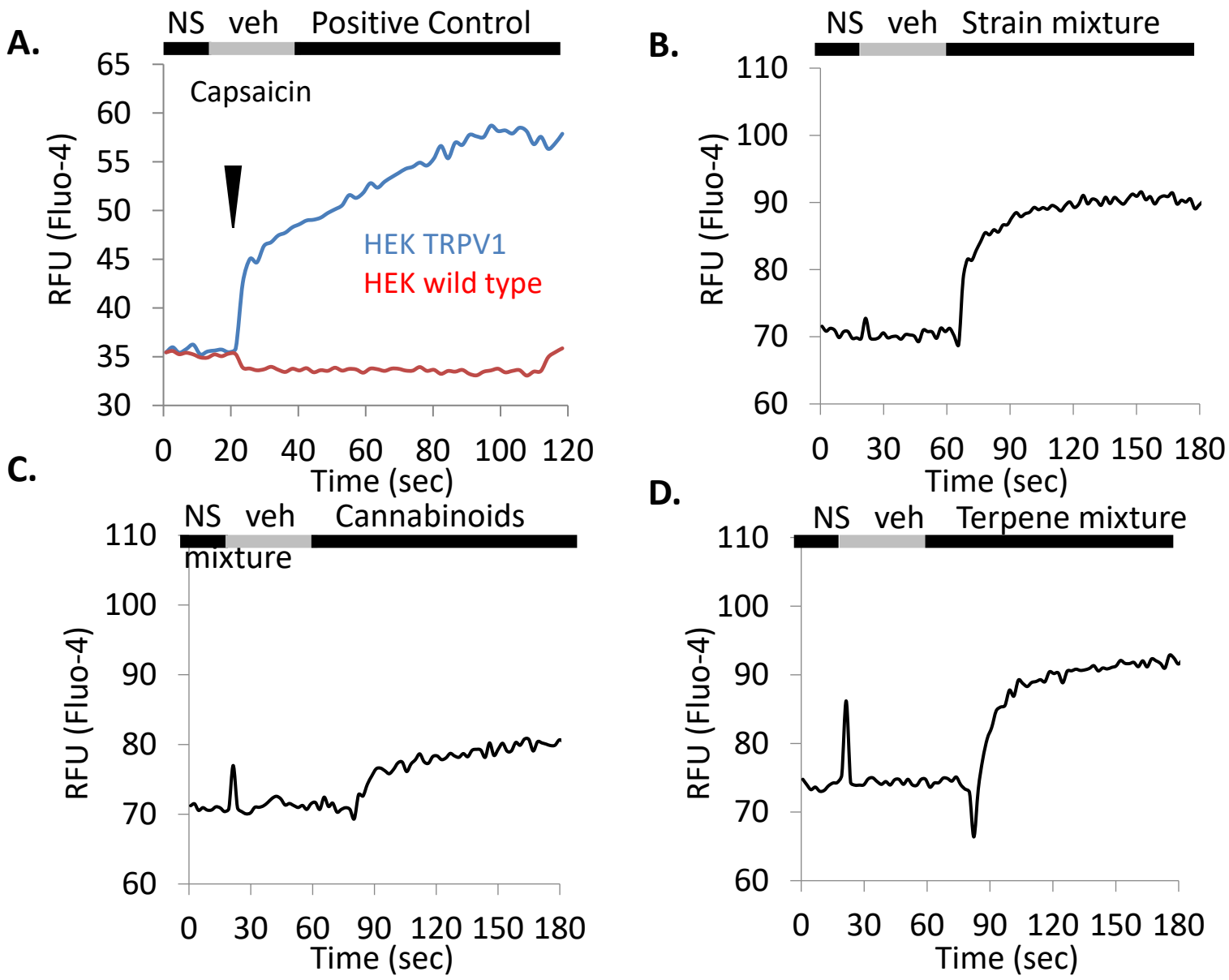


Figure 4. Single oral doses of cannabinoid-containing nanoparticles relieve pain for up to 11 days compared to less than 1 day of pain relief from free (unencapsulated) cannabinoids at the same dosage. The peak effectiveness of the free cannabinoids was between 0.5 and 9 hours; whereas, the cannabinoid-containing nanoparticles remained maximally effective between 1 and 9 days.

Pain:TRP Channel Responses to Cannabis Compounds

Figure 5. Terpenes contribute significantly to calcium fluxes via TRPV1 induced by *Cannabis*-equivalent mixtures relative to the effects of the whole strain, the cannabinoid mixture and a Capsaicin control



Starkus, J., Jansen, C., Shimoda, L.M.N., Stokes, A.J., Small-Howard, A.L., Turner, H. (2019) Diverse TRPV1 responses to cannabinoids. *Channels* 13(1):172-191. doi: 10.1080/19336950.2019.1619436.

Jansen, C., Shimoda, L.M.N., Ang, L., Bacani, A.J., Baker, J.D., Speck, M., Badowski, C., Stokes, A.J., Small-Howard, A.L., Turner, H. (2019) Myrcene and Terpene Regulation of TRPV1. *Channels* 13(1):344-366. doi: 10.1080/19336950.2019.1654347

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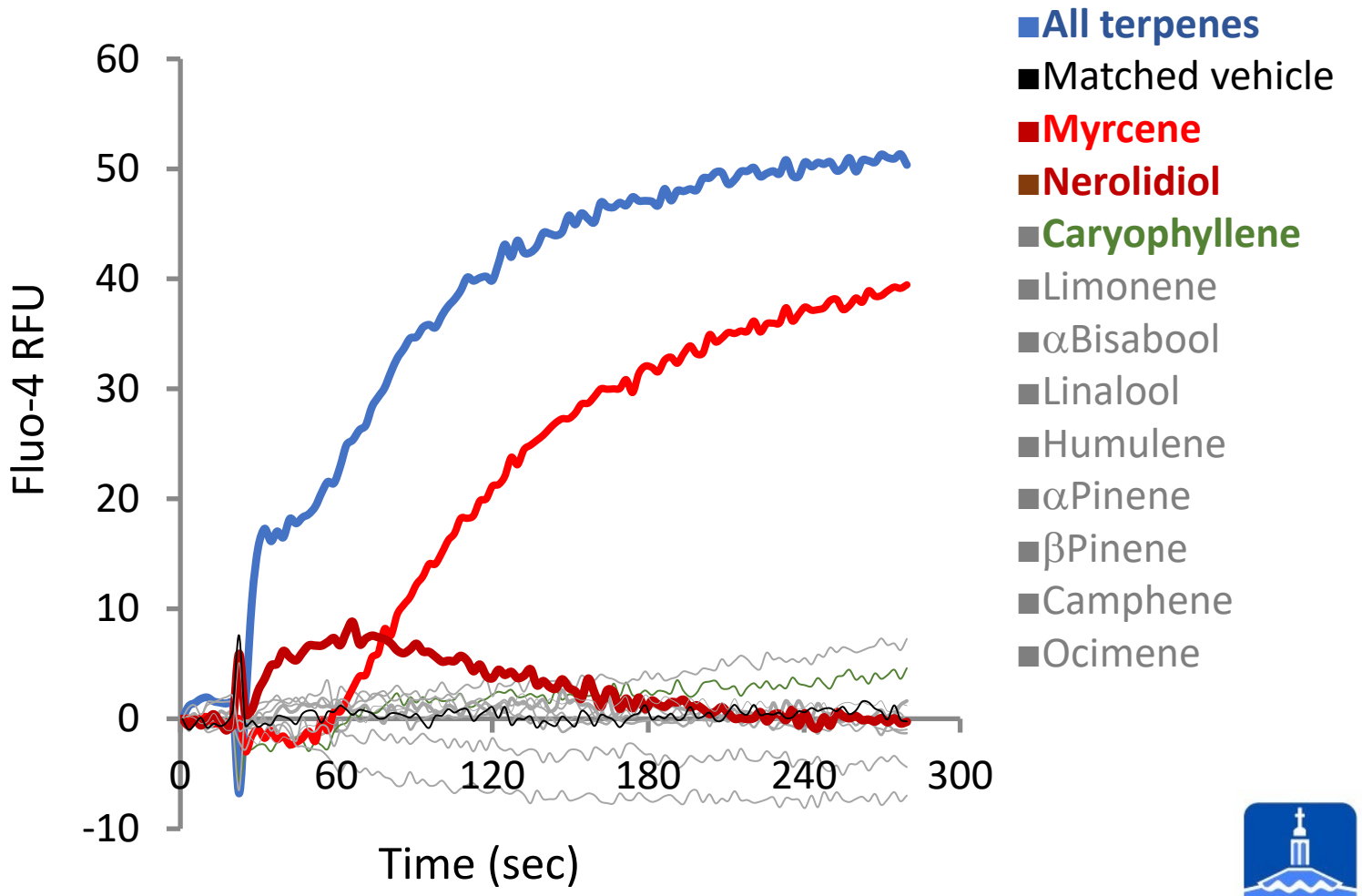
Chaminade University

Pain: Myrcene dominant TRPV1 responses

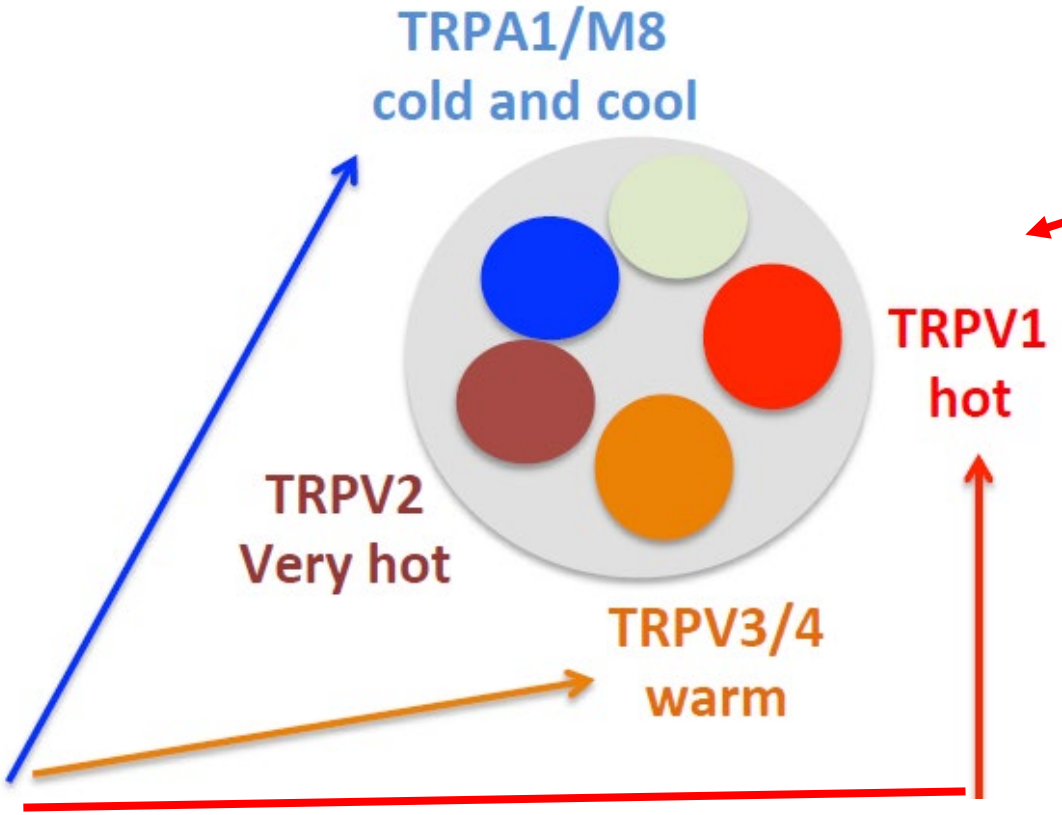
Jansen, C., Shimoda, L.M.N., Ang, L., Bacani, A.J., Baker, J.D., Speck, M., Badowski, C., Stokes, A.J., Small-Howard, A.L., Turner, H. (2019) Myrcene and Terpene Regulation of TRPV1. *Channels* 13(1):344-366. doi: 10.1080/19336950.2019.1654347

Figure 6. Myrcene and Nerolidol are the major contributors. Individual terpenes contribute differentially to terpene mixture-induced calcium responses. HEK-TRPV1 were loaded with Fluo-4 and population-based calcium assays were conducted in the presence of 1mM external calcium. After a matched vehicle exposure (veh) period to establish a baseline, cells were stimulated at 20s with the indicated terpenes.



Neuropathic Pain Strategy

Within a nocioceptive sensory neuron bundle, different neurons express multiple TRP channels, so they are able to respond to different stimuli



Conventional capsaicin pain therapy targets only TRPV1 and leaves other neurons in the bundle untouched

Figure 7. In silico network pharmacology and wet lab experiments reveal that OTM.NP mixtures have the potential to target multiple receptors in the bundle to increase their net effectiveness.

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Surface-Modified PLGA Nanoparticles

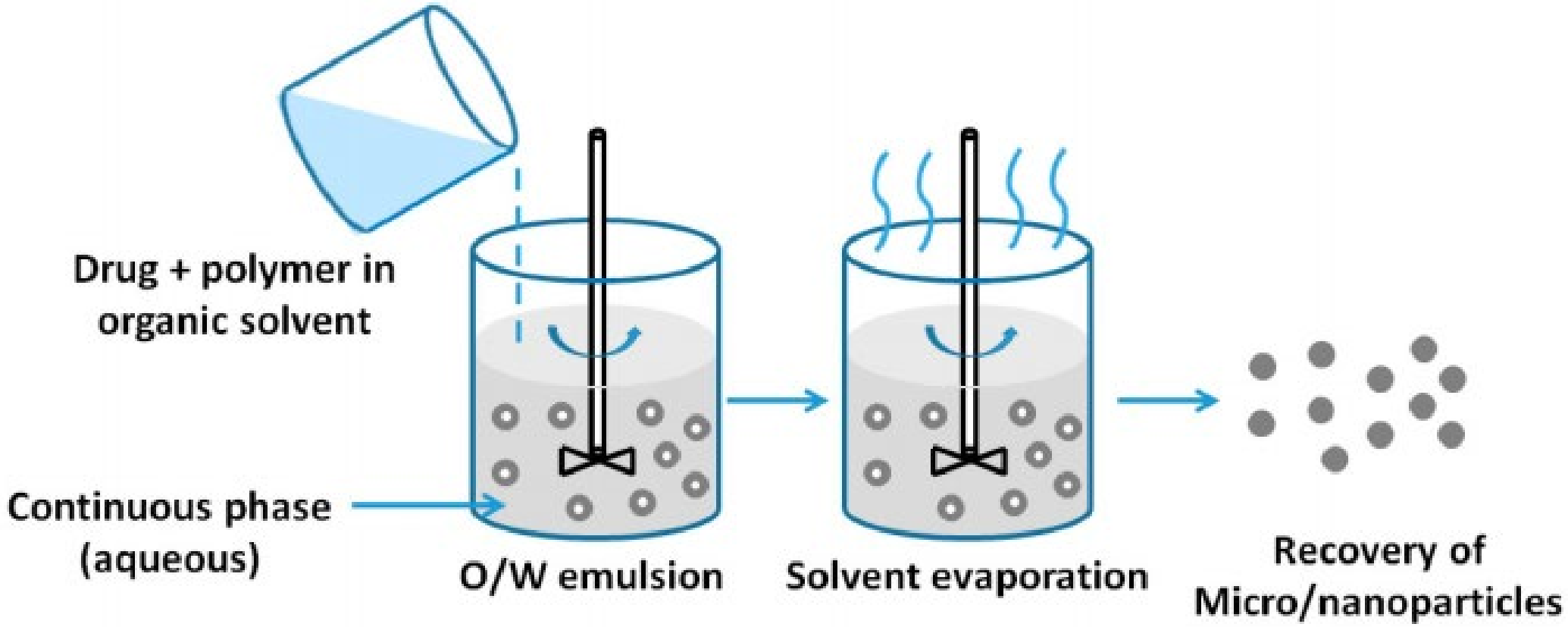
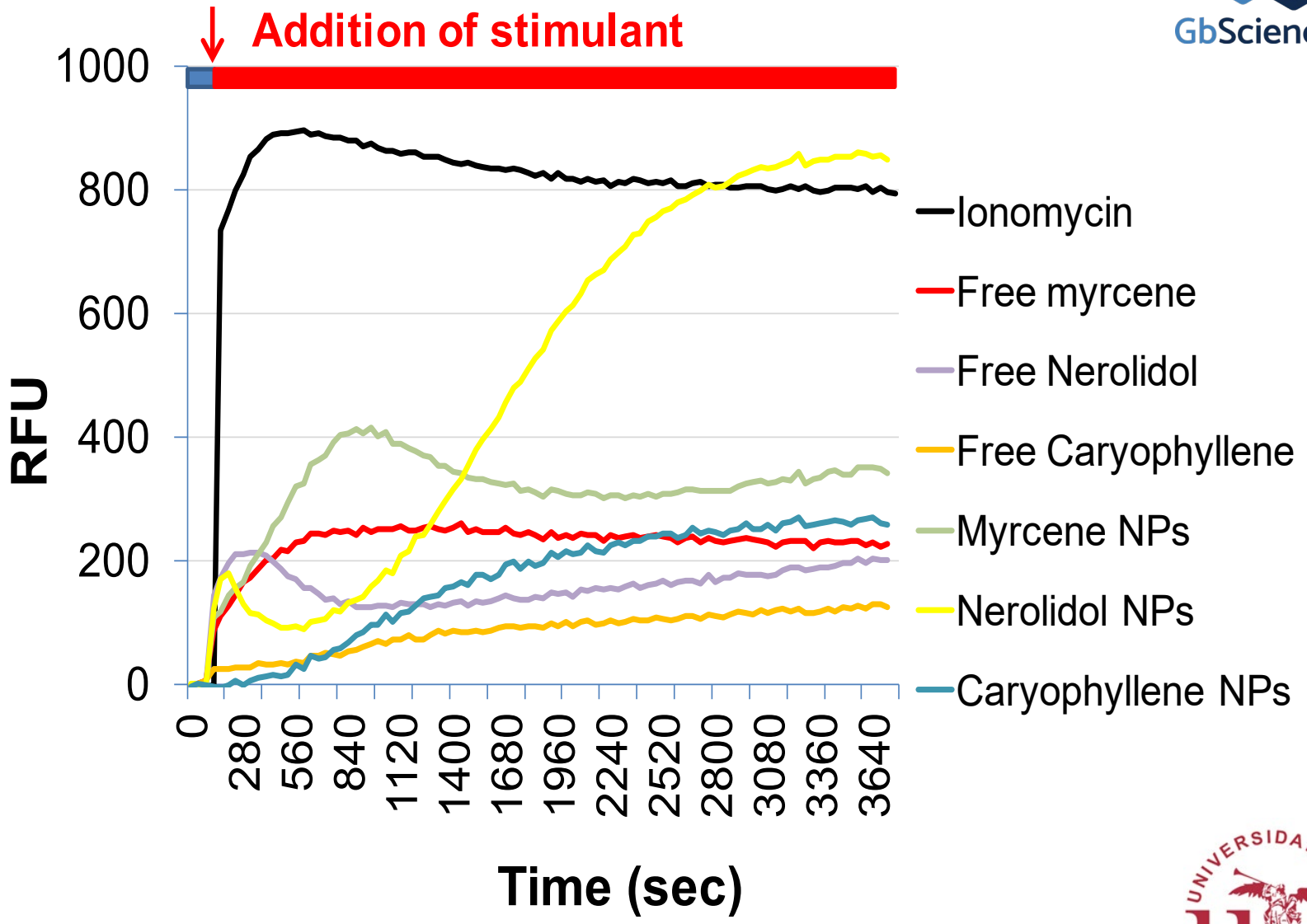


Figure 8. Schematic representing the encapsulation process for creating Poly-Lactic-co-Glycolic Acid (PLGA) Nanoparticles containing cannabinoids and/or terpenoids.

El-Hammadi M, Small-Howard A, Fernández-Arévalo M, Martín-Banderas L. Development of enhanced drug delivery vehicles for three cannabis-based terpenes using poly(lactic-co-glycolic acid) based nanoparticles. *Industrial Crops and Products*. 2021:164. 113345. 10.1016/j.indcrop.2021.113345.

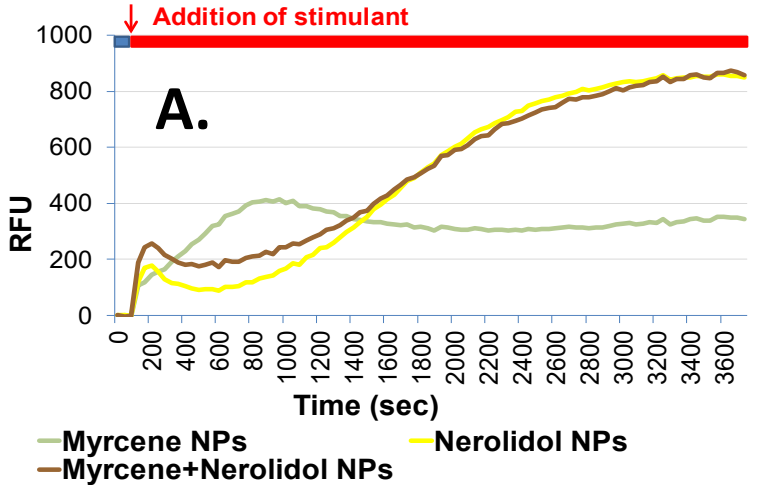
Pain: Terpene-Encapsulated Nanoparticles

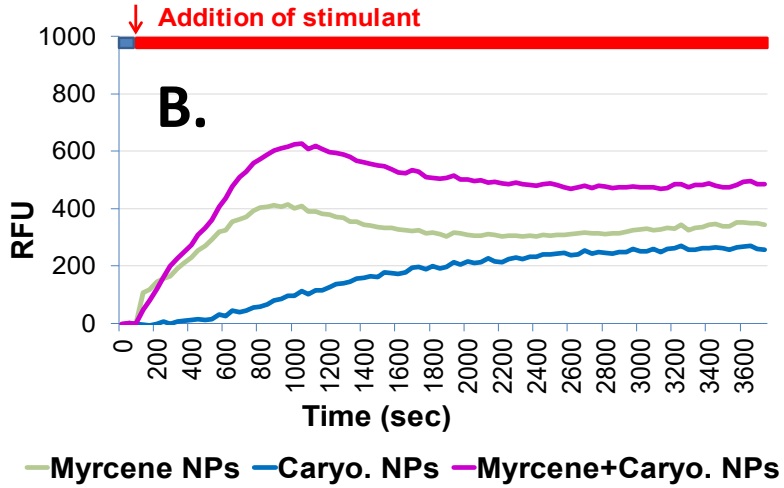
Figure 9. Encapsulated terpenoids trigger larger calcium flux at TRPV1 than non-encapsulated terpenoids. Fluorescence changes measured using Fluo-4 calcium signaling assay after treatment of inducible HEK TRPV1 cells with both free and encapsulated terpenes.

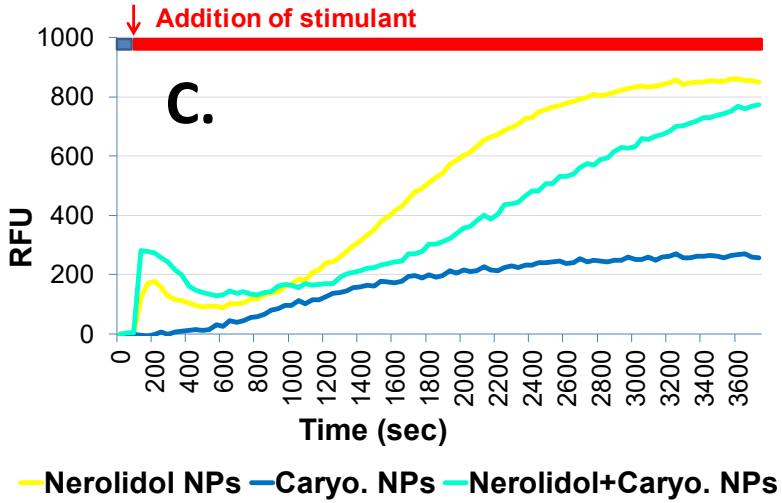


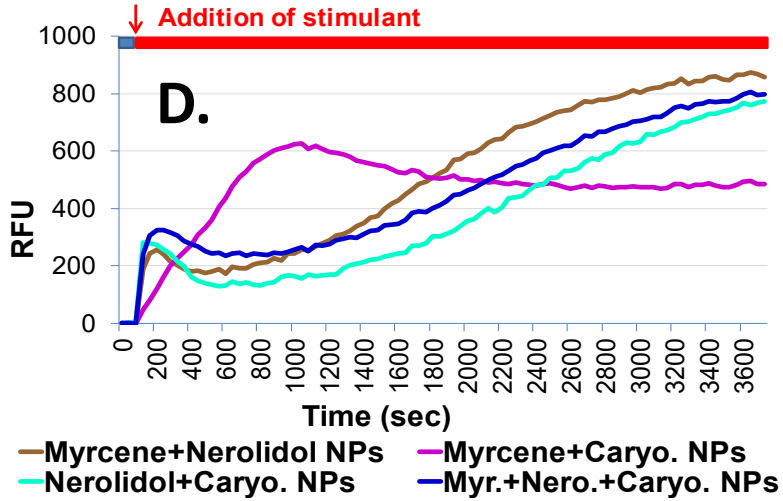
Synergy: Terpene-Encapsulated Nanoparticles

Figure 10. Synergies are revealed between encapsulated NPs. Calcium responses of individual terpenes NPs in comparison with their corresponding combinations. A: Myrcene NPs, nerolidol NPs, and their combination; B: Myrcene NPs, caryophyllene NPs, and their combination; C: Nerolidol NPs, caryophyllene NPs, and their combination; D: NPs of the three terpenes, and their combination.









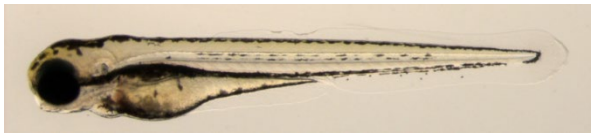
In Vivo: Terpene-Encapsulated Nanoparticles

Ellis, L.D., Berrue, F., Morash, M., Achenbach, J.C., Hill, J., McDougall, J.J. (2018) Comparison of cannabinoids with known analgesics using a novel high throughput zebrafish larval model of nociception. *Behavioral Brain Research* 337:151-159.

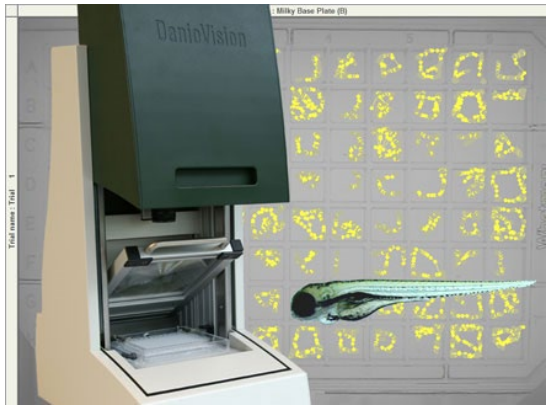
Neuropathic Pain NP

- Testing Single Compounds
  - Within nanoparticles
  - Non-encapsulated
- Testing Complex Mixtures
  - Within nanoparticles
  - Non-encapsulated
- 2 zebrafish nociceptive models
  - Place preference
  - Nociception

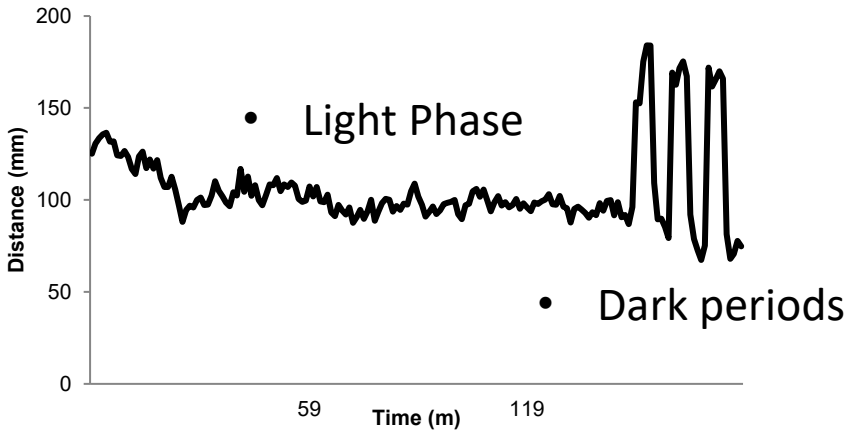
- Hundreds of larvae per female



- Body patterning established by 5dpf



- High throughput screening



- Stimulus induced behavioral responses

GbSciences: Key Milestones

	Highlights from 2020
Parkinson's disease OTM.PD119, OTM.PD205, OTM.PD361	US Patent Issued Statistically-significant reduction of Parkinsonian movement in animal model
Neuropathic pain OTM.NP110, OTM.NP121, OTM.NP139	US Patent Issued Promising Preclinical Results in Midterm Research Report
Mast Cell Activation Syndrome OTM.MC122, OTM.MC128	US Patent Issued Rare disease, Regulatory Advantages
Cytokine Release Syndrome Multiple OTM.MCAS	US Patent Application Filed Preclinical Proof-of-Concept Studies

PhAROS™ Drug Discovery Platform

Phytomedical Analytics for Research Optimization at Scale

Science Gateway & Virtual Research Environment for Drug Discovery

- Transformative data integration, analytic methods, & visualization tools for the meta-analysis of non-Western medical knowledge systems
- In Silico Convergence Analysis
- Pre-validates efficacy
- Drug-target-indication relationships
- US patent application filed Oct 16, 2020

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Jansen C, Baker JD, Kodaira E, Ang L, Bacani AJ, Aldan JT, Shimoda LMN, Salameh M, Small-Howard AL, Stokes AJ, Turner H, Adra CN. Medicine in motion: Opportunities, challenges and data analytics-based solutions for traditional medicine integration into western medical practice. *J Ethnopharmacol.* 2021 Mar 1;267:113477. doi: 10.1016/j.jep.2020.113477. Epub 2020 Oct 21. PMID: 33098971; PMCID: PMC7577282.

GbSciences Research & Development Partners

Chaminade University

University of Lethbridge

UCA

Purisys™

Catalent®

SUMMARY

- Novel drugs for unmet clinical needs & major markets
- Proprietary discovery engine: plant-inspired, optimized therapeutic mixtures (OTM)
- Active ingredients = synthetic copies of plant compounds
- First drug expected to enter clinic Q3 2022
- Four drugs in preclinical phase
- Experienced team, lean operations, outsourcing strategy

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