GbSciences' Plant-inspired Prescription Drugs

for Parkinson's disease, COVID-CRS & Chronic Pain

GbSciences

OTCQB:GBLX

DISCOVERY

PhAROS™ Drug Discovery Platform

Pre-validates efficacy of plant-inspired mixtures for disease-targeted therapies

PIPELINE

Top 2 programs advancing to First-in-Man

5 preclinical programs

65+ discovery projects

IP PORTFOLIO

ISSUED PATENTS:

5 US &
3 PCT/WIPO

PATENT-PENDING:

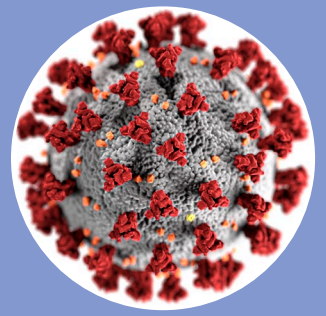
19 US &
40 PCT/WIPO

CNS PROGRAM

Parkinson's disease formulas advancing to First-in-Man,

Positive PoC data

US Patent Issued



COVID-related Cytokine Release Syndrome

Positive PoC data

Patent-Pending

CHRONIC PAIN

Oral, time-released nanoparticles

Positive PoC data

US Patent Issued

GbSciences' Drug Development Pipeline

Rx PROGRAMS	DISCOVERY	PRECLINICAL	Pre-IND	CLINICAL TRIALS: First-in-Man/ Phase I	CLINICAL TRIALS: Combined Phase I-II
Parkinson's Disease (PD)					
COVID-Cytokine Release Synd. (CRS)					
Chronic Pain (CP)					
Heart Failure (HF)					
Anxiety/Depression (Piper plant family)					
Mast Cell Activation Syndrome (MCAS)					

KEY	
Completed	
In-Process	

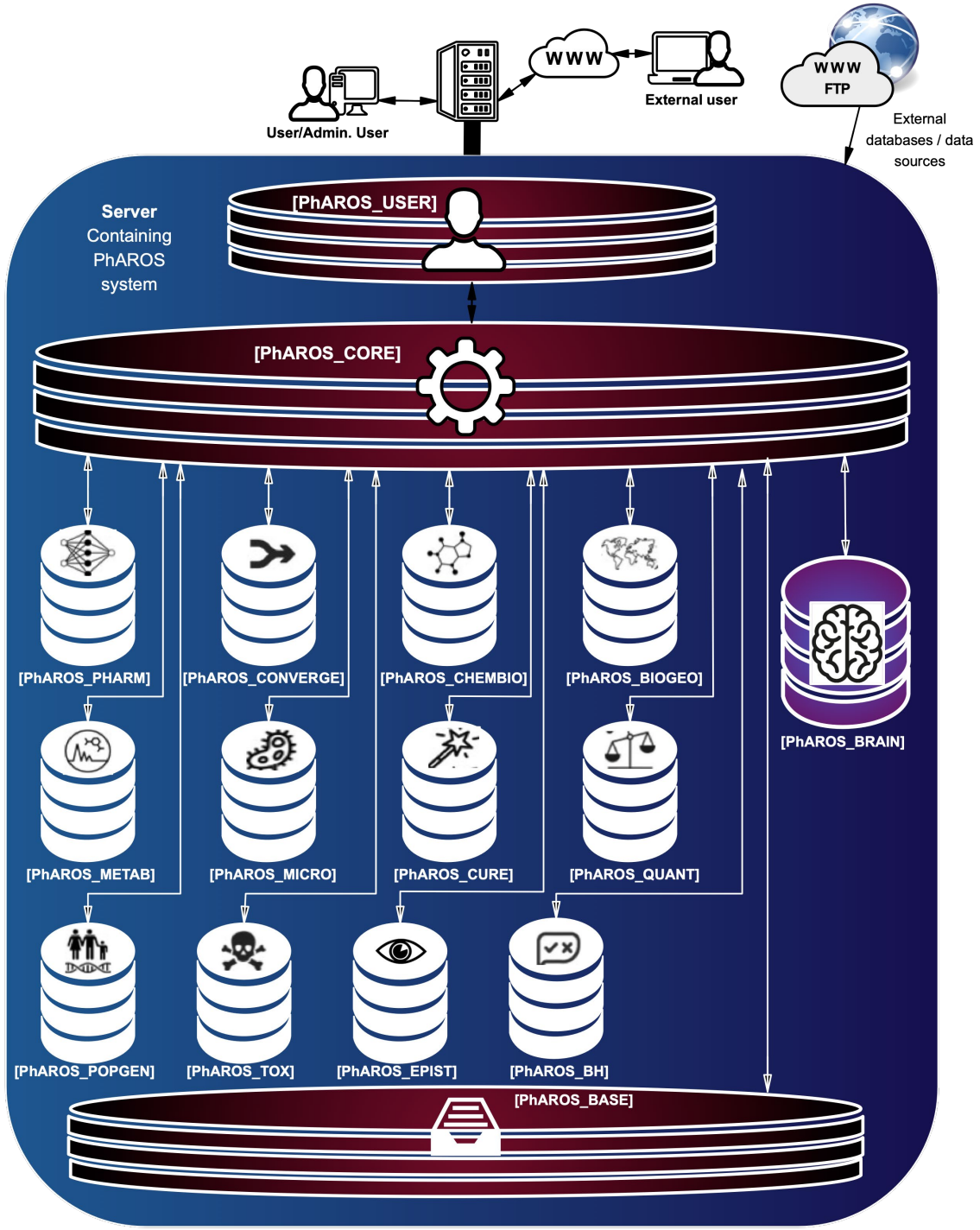
PhAROS™ Drug Discovery Platform

Phytomedical Analytics for Research Optimization at Scale

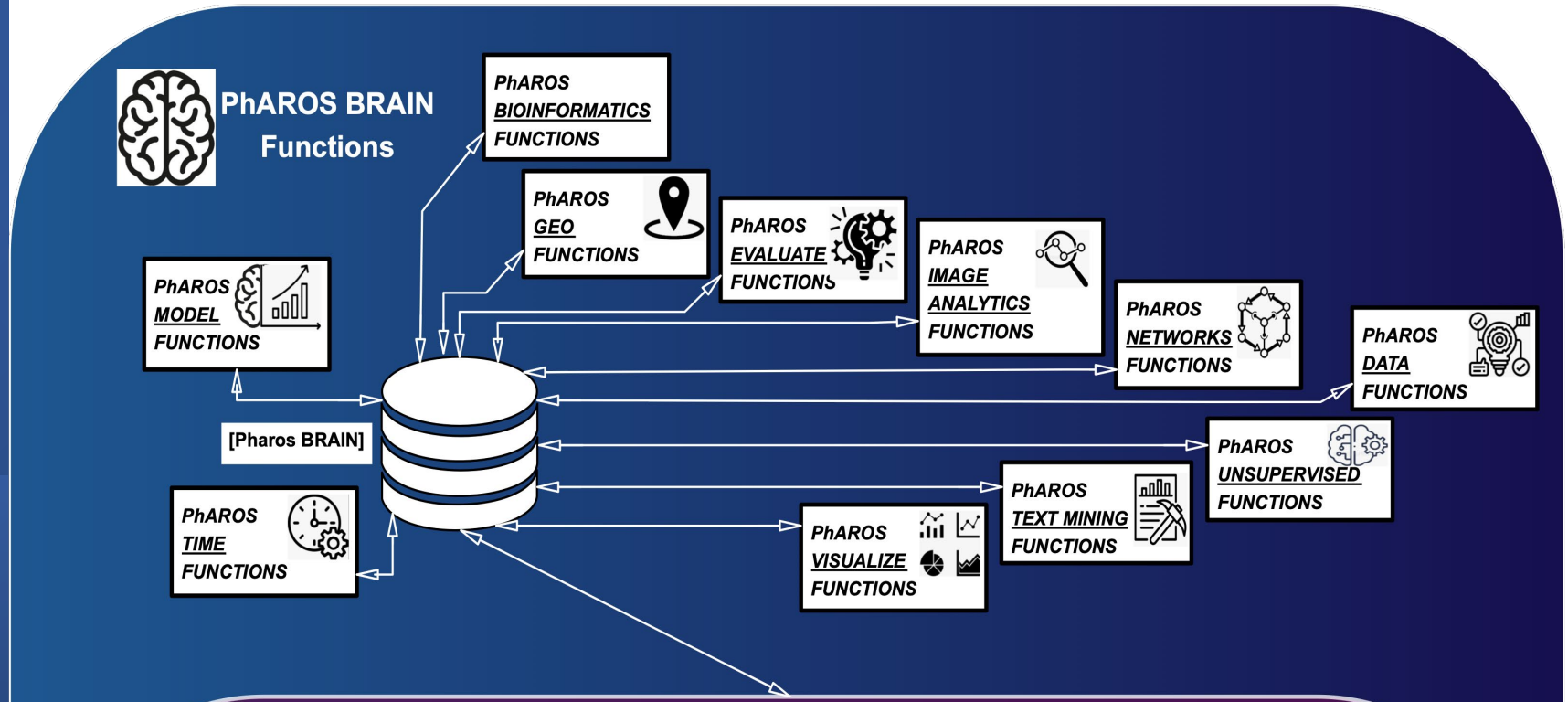
- Proprietary plant-based Rx therapies based on traditional medicine systems
- Minimum Essential Mixtures
- Pre-validates efficacy of drug-target-indication relationships
- “Transcultural Medicines” = ingredients not constrained by geography or culture
- De-risked as Rx therapies
- Multiple Uses: Novel Rx & Global Health Initiatives

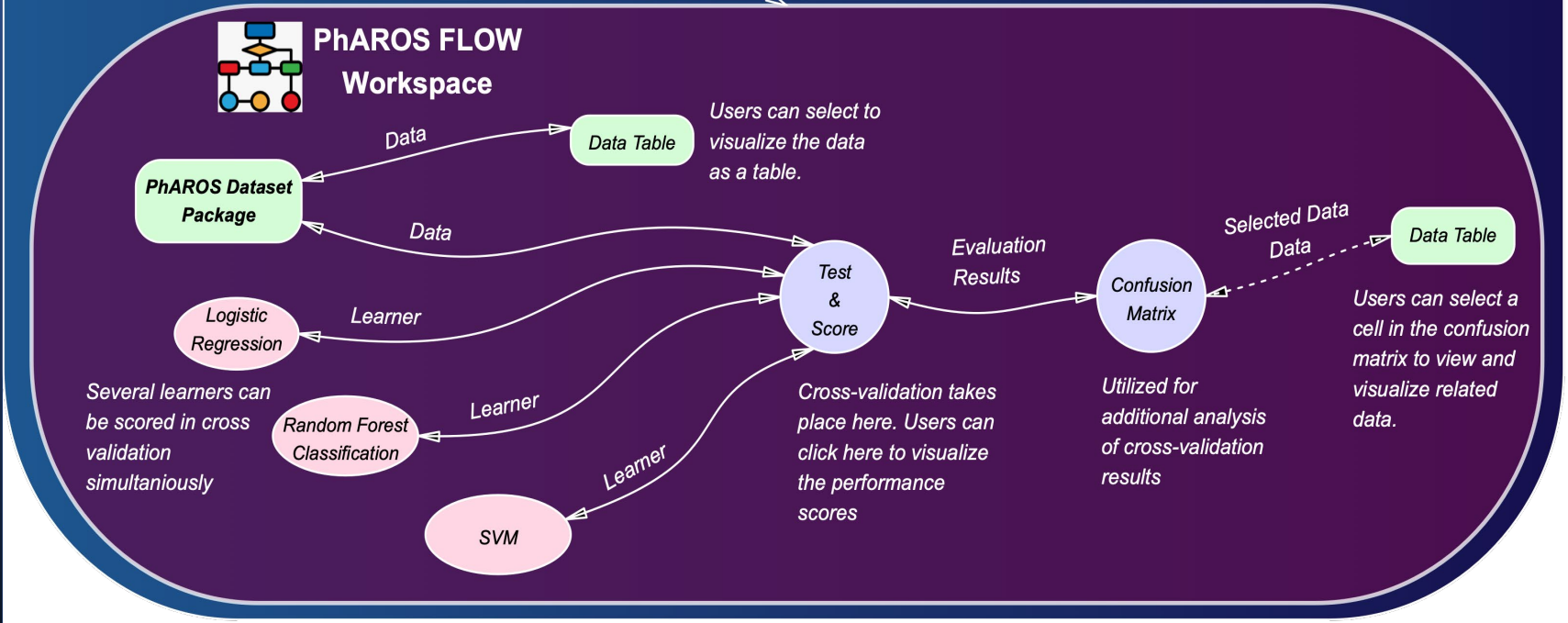
Jansen C, Baker JD, Kodaira E, Ang L, Bacani AJ, Aldan JT, Shimoda LMN, Salameh M, Small-Howard AL, Stokes AJ, Turner H, Adra CN. Medicine in motion: Opportunities, challenges and data analytics-based solutions for traditional medicine integration into western medical practice. *J Ethnopharmacol.* 2021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

PhAROS™ Platform: Phytomedicine Analytics for Research Optimization at Scale



PhAROS_BRAIN houses many data analytics, AI/ML-functions & visualization tools

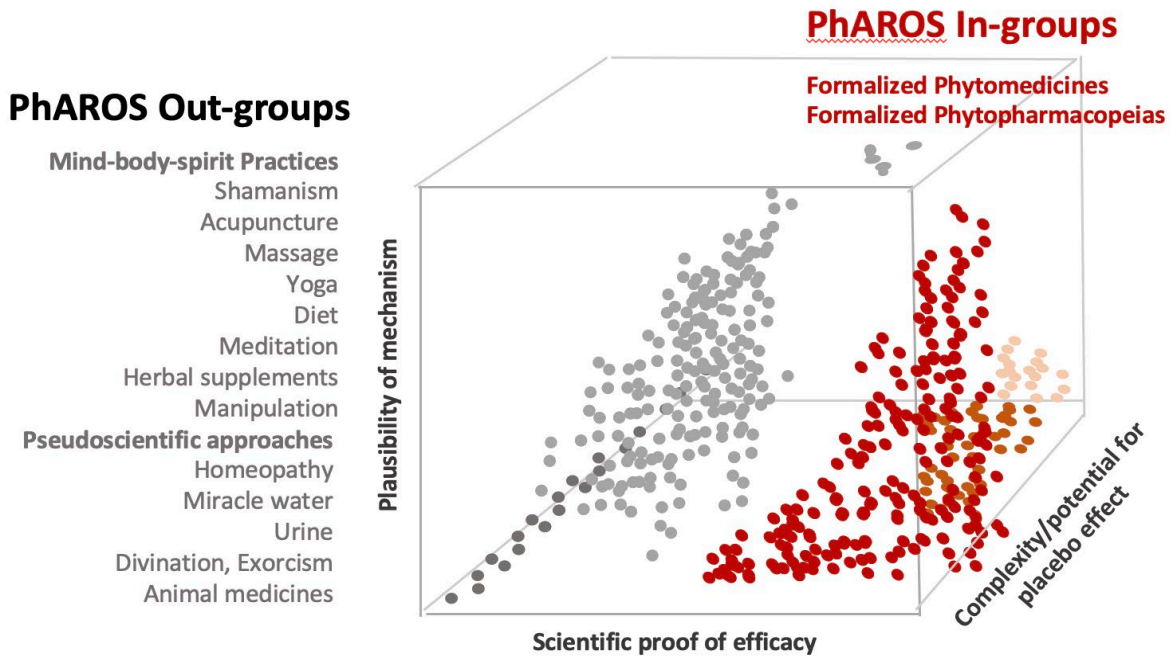


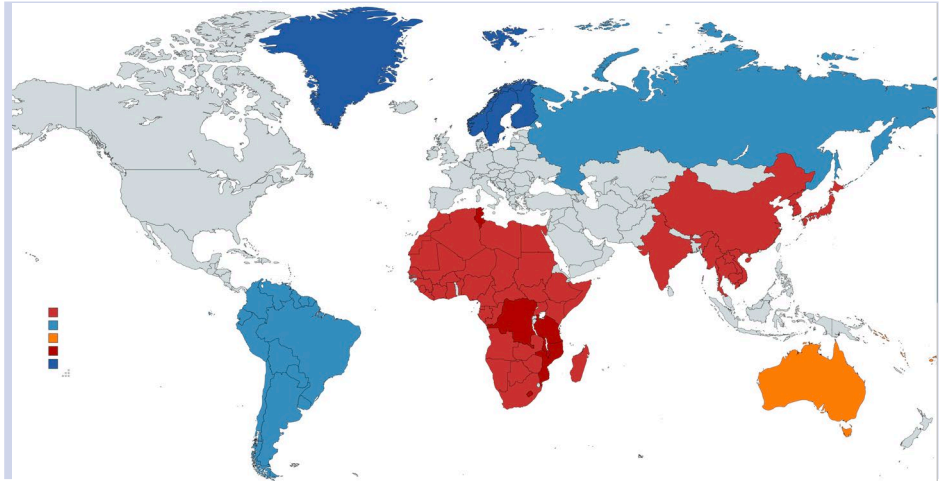


PhAROS_PHARM: Transcultural Database

Figure 1: PhAROS_PHARM is a single computational space comprised of multiple traditional medical (TMS) systems

PhAROS_PHARM Phase I					
Medical Systems	5	**Biogeography**	16.8M sq. m	**Inclusion Criteria (Phase I)**	
Chemical components	84,665	**Timeframe**	300 YR BCE-current	**In-group**	Formalized pharmacopeias
Formulations	22,153	**Countries**	113		Phytomedicines
Ingredient Organisms	13,648	**Cultures/ethnic groups**	>3000		Plants, fungi, associated microbiomes (prokaryotic and eukaryotic)
				Out-group	Shamanistic/hallucinogenic traditions
					Animal/mineral medicine
					Oral traditions/knowledge systems
					Western medicine





PhAROS™ Platform Objectives

1. MINIMUM ESSENTIAL MIXTURES (MEM™):

- **Improve Existing TMS Therapies by reducing the numbers of components to the Minimum Essential**
- **Substitution of Ingredients across TMS (free from biogeographical & cultural boundaries) to increase efficacy/decrease side effects**
- **De Novo Design of a new class of 'Transcultural' Medicines, integrating phytomedical intelligence for a particular indication across geographically and culturally distinct pharmacopeias**

2. EFFICACY PREDICTIONS: IN SILICO CONVERGENCE ANALYSIS

3. SUPPLY CHAIN SOLUTIONS: 'BIOEQUIVALENT' PLANTS

PhAROS™: Pain Formulation Example

Figure 2. PhAROS. Transcultural Formulation Assembly of Minimum Essential Mixtures based on Epistemology

CATEGORIES

opioid/alkaloid candidate analgesics

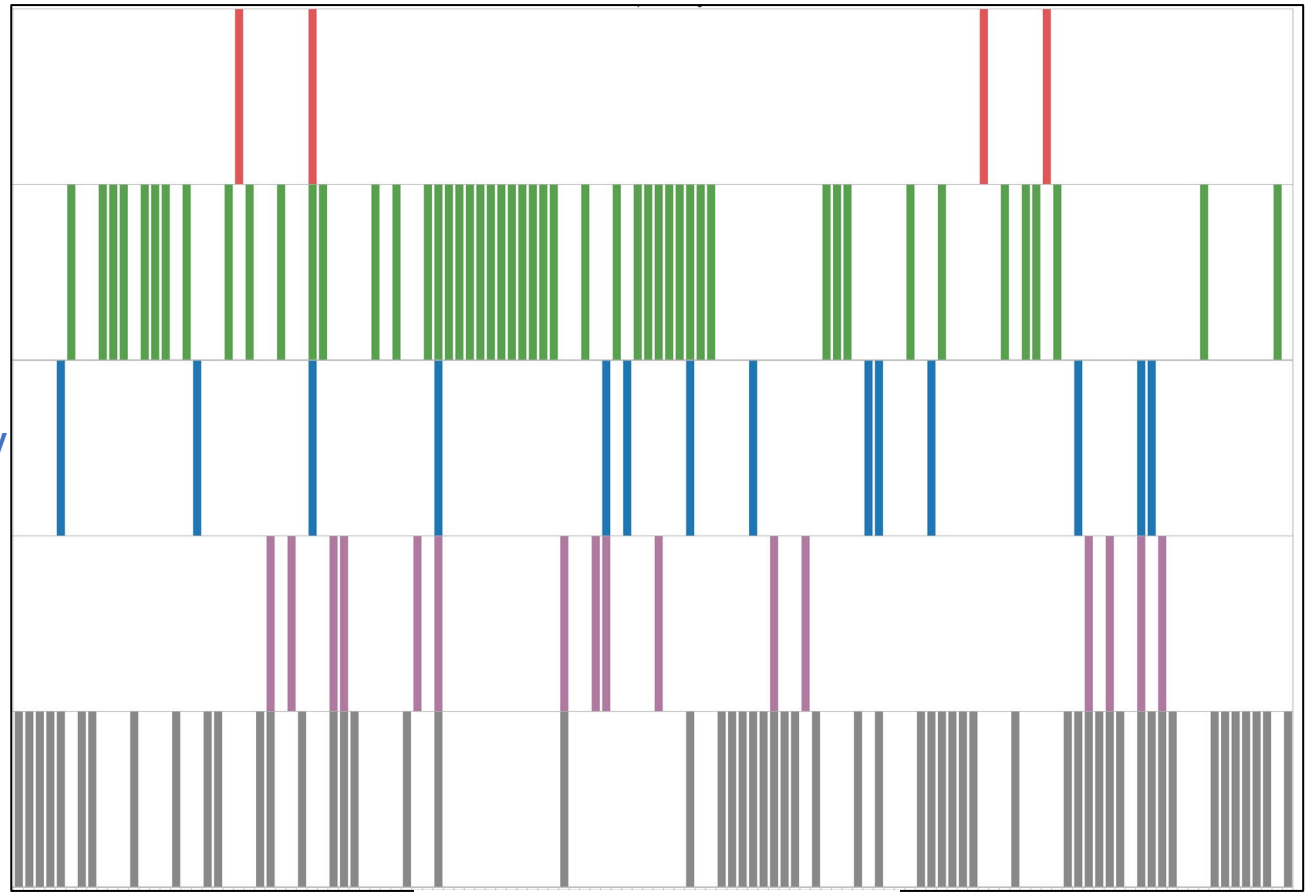
ligands for nociceptive ion channels
e.g., terpene ligands for nociceptive TRPs

components with other demonstrated neuroactivity
e.g., NACHE pathways

components with bioactivity associated with pain
e.g., ROS/RNS targeting anti-inflammatories

compounds with other types of bioactivity

PhAROS OUTPUT: CONVERGENT COMPOUNDS FOR PAIN ACROSS 5 TMS

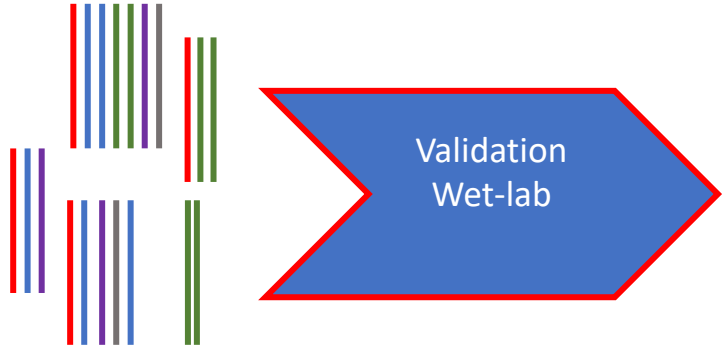


Convergent compound CIDs

PhAROS IMPACT:

New formulations can be designed that are

- **Transcultural Formulations** *(result from integrated knowledge across cultures and biogeographies)*
- **Minimal Essential Mixtures** *(reduce complexity by including components from each part of the hierarchy)*
- **Polypharmaceutical** *(retain non-Western medical architecture and polypharmacy)*



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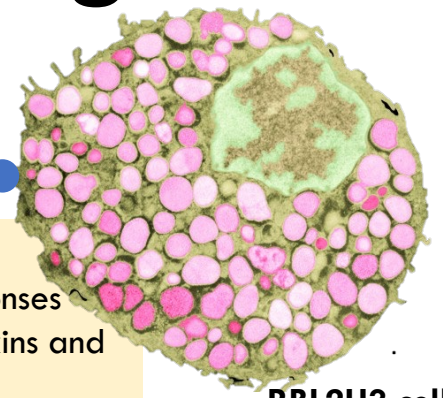
VALIDATION:High-Throughput Cell Models

Inflammation/Allergy Model

Other Disease-specific Models

Inflammation

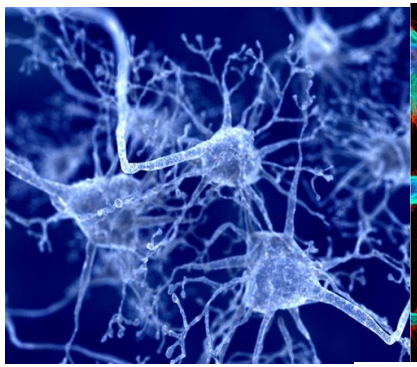
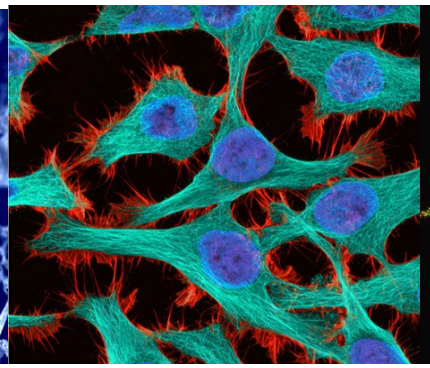
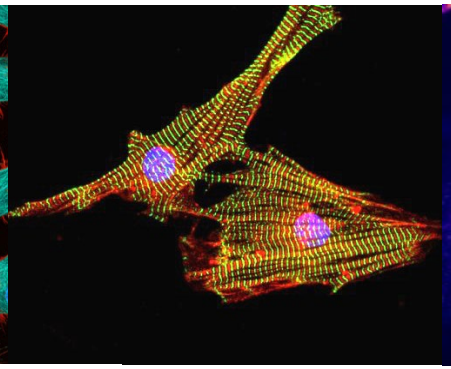
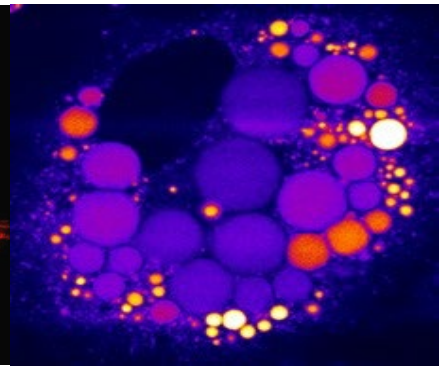


Located in barrier tissues,
Coordinate allergic/inflammatory responses
Release histamine, leukotrienes, interleukins and
Other inflammatory molecules

[Ca $^{2+}$]i and TRPV electrophysiology
[cAMP]
Leukotriene assays
Histaminergic/inflammatory
Flow Cytometry

RBL2H3 cells and primary human immune cells (MSU)

Parkinson's	Breast Cancer	Heart Disease	Metabolic Syndrome
Cath.a neurons	**MDAMB435**	**Heart Muscle cells C2C12**	**Human Adipose 3T3-L1**

[Ca $^{2+}$]i and TRPV electrophysiology

[cAMP]

proliferation

MPTP
[DOPA]
aggresomal

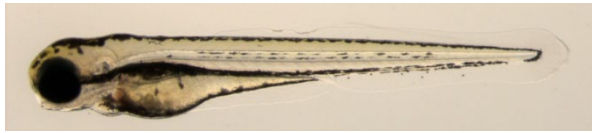
pro-apoptosis
anti-autophagy
anti-angiogenic

stretch
hypertrophy WGA

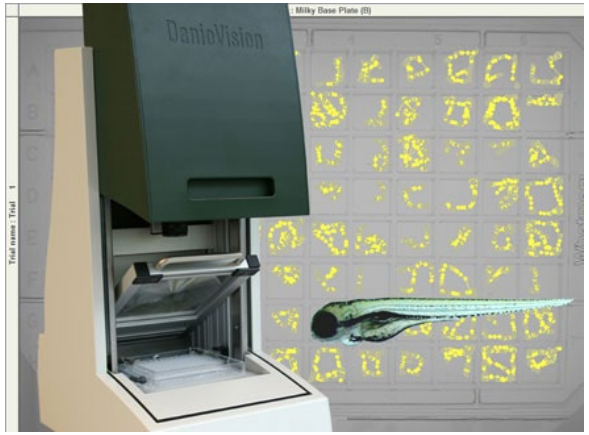
Oil Red O

VALIDATION:High-Throughput Animal Models

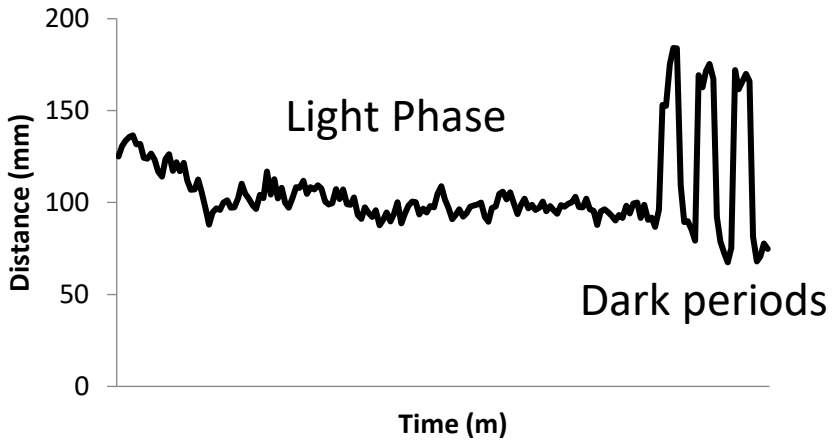
Hundreds of larvae per female



Body patterning established by 5dpf



High throughput screening
-up to 96 well plates



Stimulus induced behavioral responses

GbS' Intellectual Property Assets

- PhAROS™ Platform & Rx Formulations
- Plant-Inspired, Minimum Essential 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)
  - Patents Issued: 5 US & 3 International
  - Patent-Pending Applications: 19 US & 40 International

GbSciences' Parkinson's Disease MEM™

Parkinson's Disease MEM™ Therapeutic Development

# mixtures	screen type	GbS screen	GbS references
>100,000	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 & 5 terpenes INFLAMMATORY PROFILING 5 cannabinoids & 5 terpenes	PMID: 31096838 PMID: 31446830 US Patent App 63/067,269
<25	medium throughput animal	6-OHDA ZEBRAFISH MOTOR ASSAYS 5 cannabinoids & 5 terpenes	US Patent App 16/844,713
3	lead optimization	MEM.PD119, MEM.PD205, MEM.PD361 for Acute & Chronic testing in 6-OHDA mouse model	

Figure 3. Reducing Complexity Identifies Minimal Essential Mixtures of Compounds for Parkinsonian Movement Disorders

GbSciences

Chaminade University

NRC·CNRC Canada

Mixtures More Effective Than Individual Ingredients

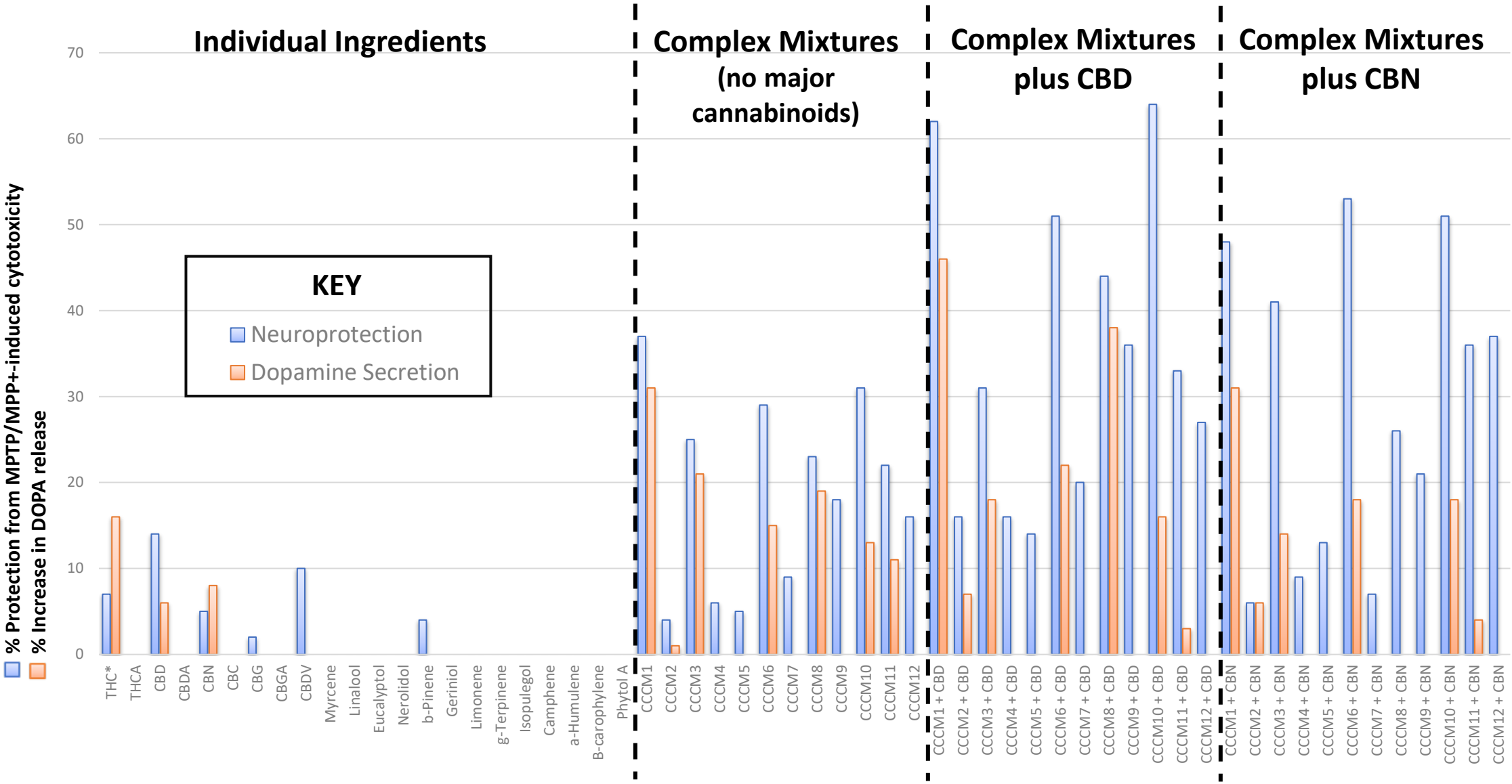


Figure 4. Mixtures were more effective than Individual Ingredients in cell models of Parkinson's disease

Chaminade University

Statistically Significant PD-Symptom Reduction

PD MEM™ in 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)
  - Reduced "resting tremor"(measured frequency & duration of shifts in activity states)
  - Normal startle response (Light/Dark)
- Tested Multiple Therapeutic Mixtures for Parkinson's disease
  - 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

GbSciences

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

Gb's PD Mixtures 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 5. Zydis™ Orally Disintegrating Tablets (ODT)

GbSciences

Catalent®

Next Steps & Milestones

1. Dose-Response Study in Rodents – University of Lethbridge
2. Clinical Prototypes of PD Mixtures in Zydis® ODT—Catalent Pharma
3. Tox & ADME Clinical Prototypes
4. Engage CRO
5. Pre-IND Application with US FDA
6. Pre-IND Meeting with the US FDA
7. First-in-Man Clinical Trial

GbCOVID-related Cytokine Release Syndrome MEM™

Can MEM™ Reduce Viral-Induced Hyper-Inflammation?

Overview

Co-Culture Human Immune Cells

4 Treatment Groups

- Untreated (no inflammatory stimulus)
- Inflammatory Stimulus (viral-CpG or bacterial-LPS)
- Positive Control=Inflammatory Stimulus + vehicle
- MEM™ + Inflammatory Stimulus

Measure Cytokine & Inflammatory Markers

All 24 MEM™ achieved Statistical Significance

Clinical Categories Created for Development

Overview of COVID-related CRS Results

All 24 MEM™ achieved Statistically Significant Immunomodulation

- **8 MEM™ = 'Selective' Anti-Inflammatory Drugs**
  - ✓ **7 MEM™ = Decreased key COVID-19 related cytokines & preserved anti-viral immune responses**
  - ✓ **1 MEM™ = Reduced Pro-Inflammatory Mediators from a Single Immune Cell Type**
- **16 MEM™ = 'Broad-Spectrum' Anti-Inflammatory Drugs**
  - ✓ **Unmet need for novel, plant-inspired, anti-inflammatory drugs**
  - ✓ **One sub-category shows promise for chronic inflammatory conditions**

Molecular Synergies in COVID-CRS MEM™

Components	MEM A	MEM B	MEM C	MEM D
Cannabinoid 1	1 μM	1 μM	1 μM	1 μM
Cannabinoid 2		5 μM	5 μM	5 μM
Terpene 1			0.001 μM	0.001 μM
Cannabinoid 3				0.01 μM

Figure 6. Both the number and kind of components in the MEM determined their anti-inflammatory potential.

Molecular Synergies in COVID-CRS MEM™

Components	MEM E	MEM F	MEM G	MEM H
Cannabinoid 1	1 μM	1 μM	1 μM	1 μM
Cannabinoid 2	5 μM	5 μM	0.01 μM	0.01 μM
Cannabinoid 4	5 μM	5 μM	5 μM	5 μM
Cannabinoid 5		0.01 μM		0.01 μM

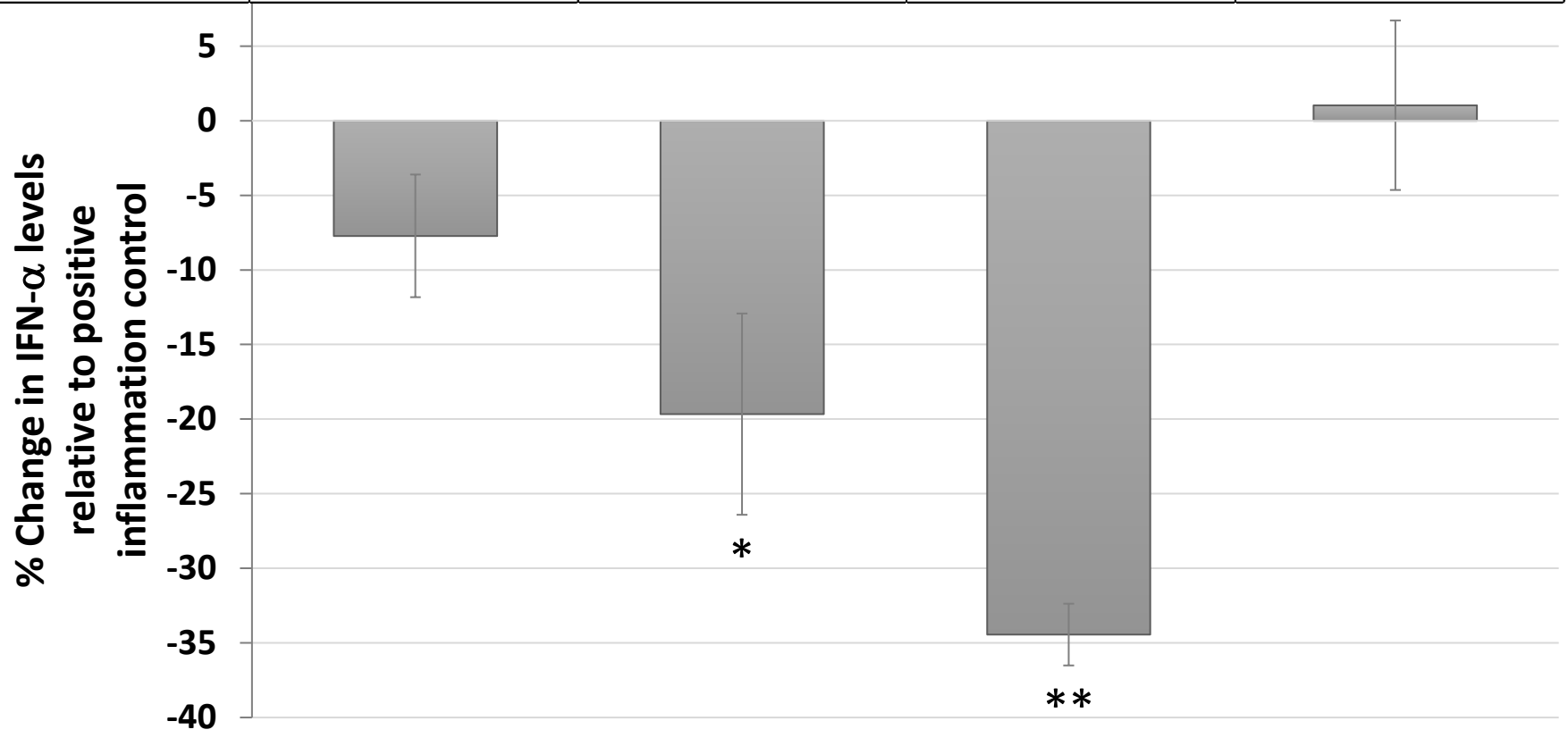
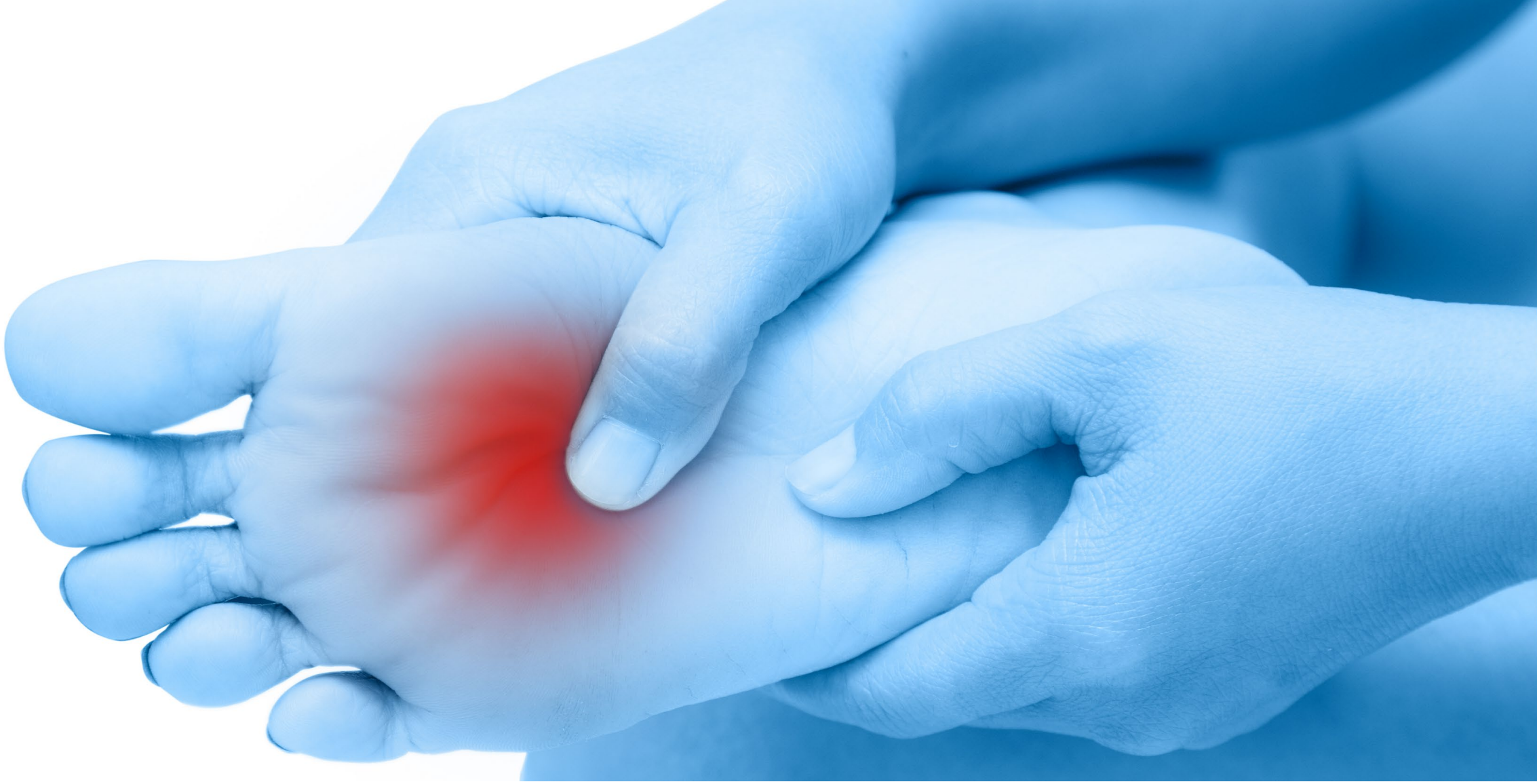


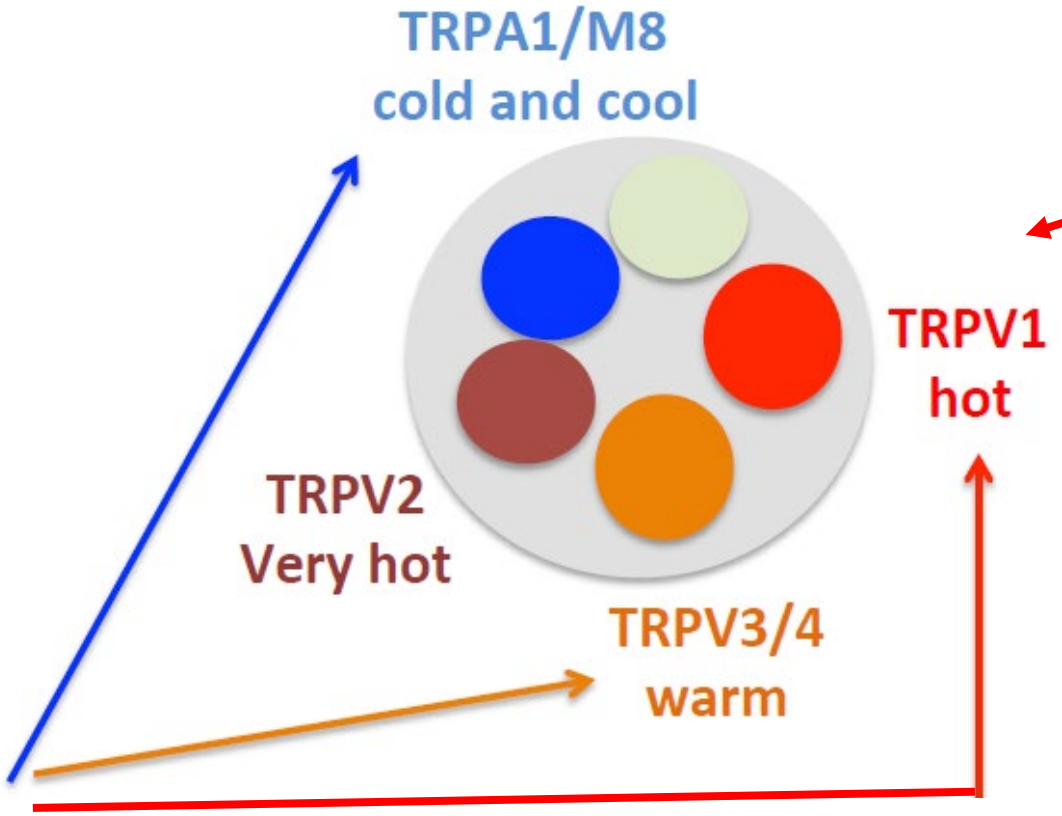
Figure 7. In MEM E and MEM G, the relative concentrations of API affected their anti-inflammatory potential. Both positive (MEM F) and negative (MEM H) synergies occurred with the addition of the fourth ingredient.



GbSciences' Novel Chronic Pain MEM™

Chronic Pain Strategy: Multiple TRP Channels

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 8. Both computational analyses and wet lab experiments reveal that our MEM™ have the potential to target multiple receptors in the bundle to increase their net effectiveness at chronic pain relief.

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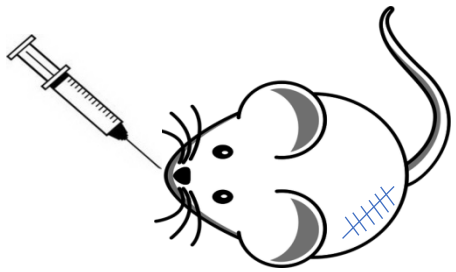
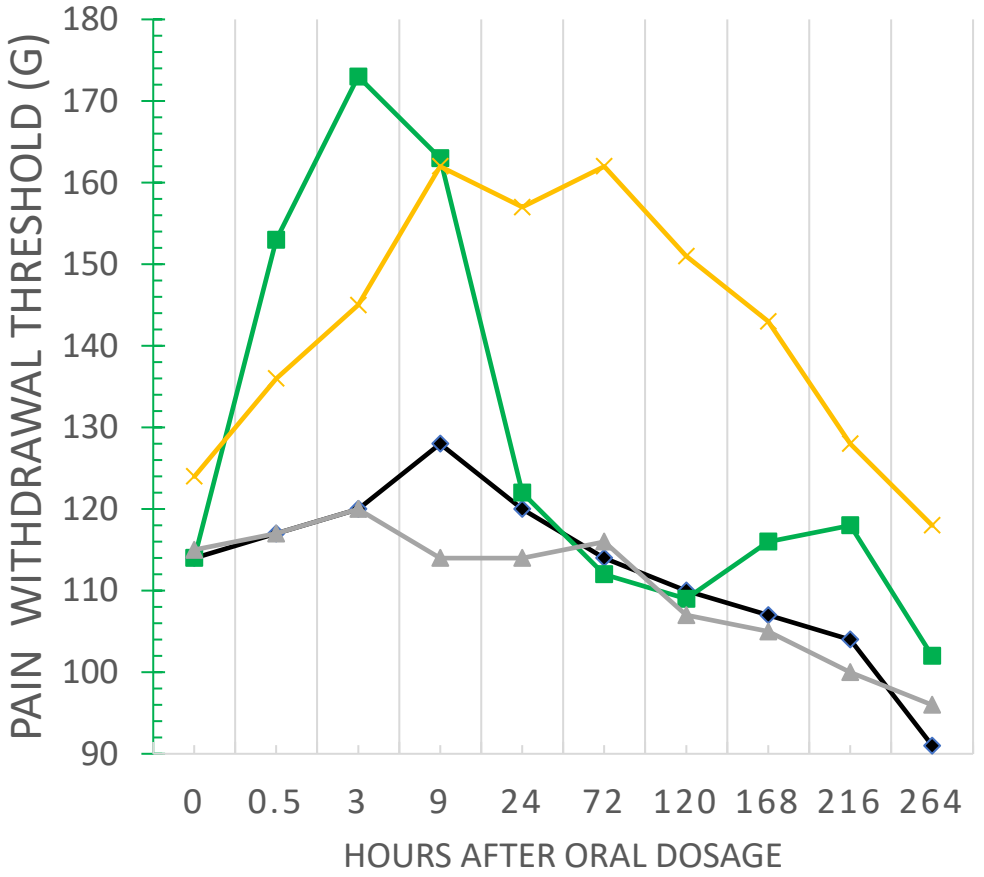
Chaminade University

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)





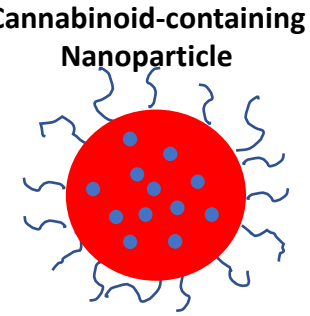


Figure 9. Single oral doses of cannabinoid-containing nanoparticles relieve pain for up to 11 days compared to less than 1 day of pain relief from free (unencapsulated) cannabinoids at the same dosage. The peak effectiveness of the free cannabinoids was between 0.5 and 9 hours; whereas the cannabinoid-containing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

CP MEM™:Surface-Modified PLGA Nanoparticles

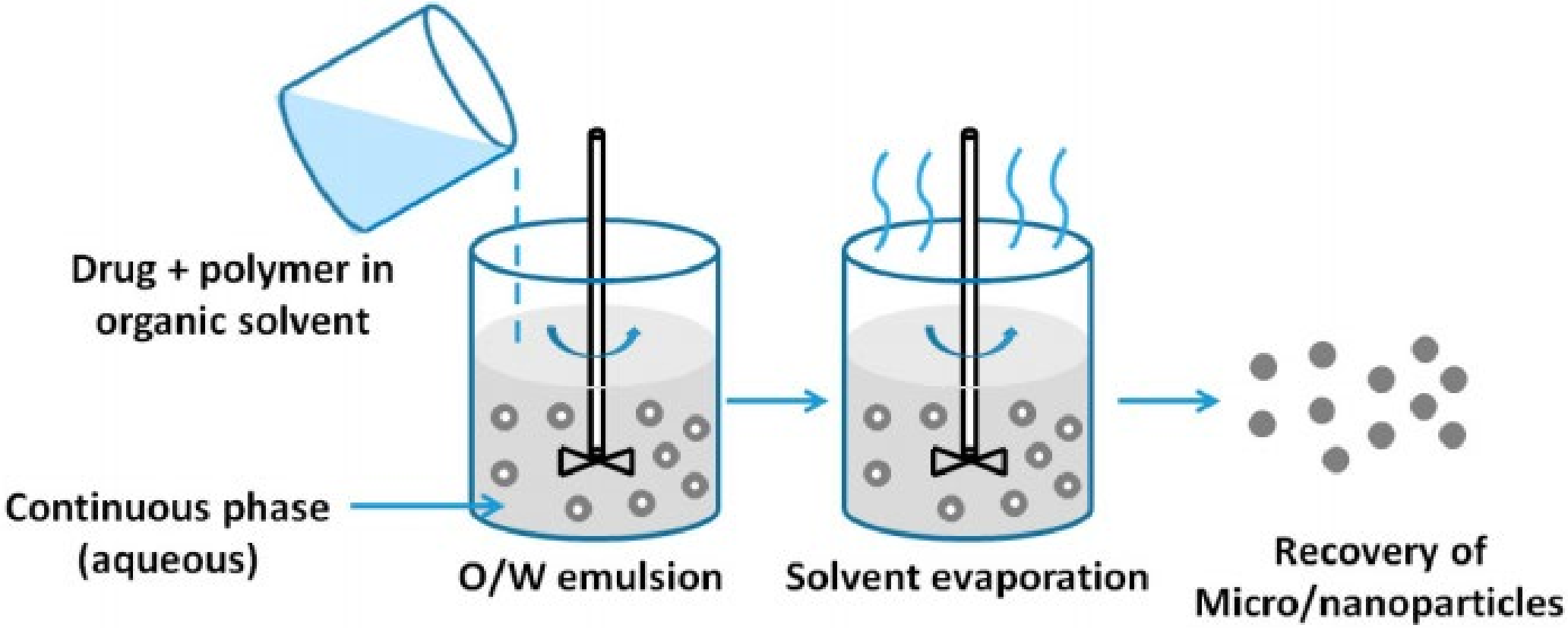


Figure 10. Schematic representing the encapsulation process for creating Poly-Lactic-co-Glycolic Acid (PLGA) Nanoparticles containing cannabinoids and/or terpenoids.

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.

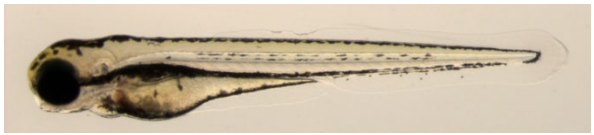
CURRENT: Testing Chronic Pain MEM in zebrafish

Chronic Pain MEM™ +/- NPs

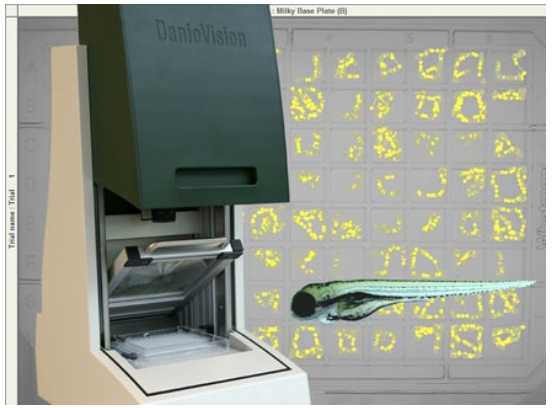
- Testing Single Compounds
  - Within nanoparticles
  - Non-encapsulated
- Testing MEM™
  - Within nanoparticles
  - Non-encapsulated
- 2 zebrafish nociceptive models
  - Place preference
  - Nociception[1]

- *Danio rerio*

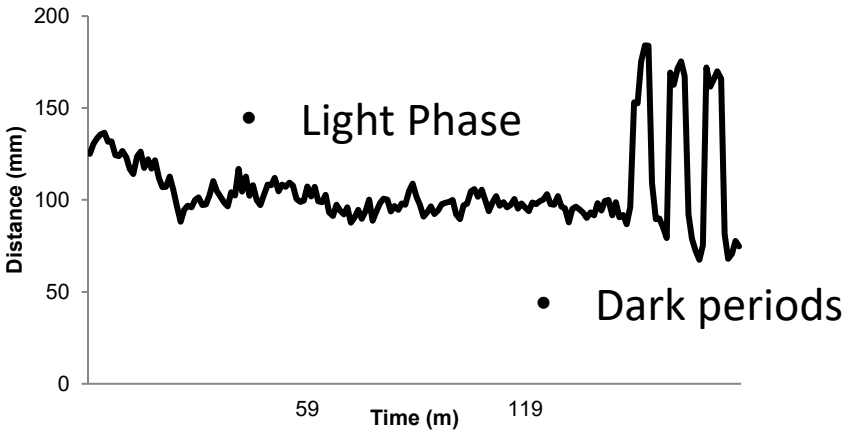
- Hundreds of larvae per female



- Body patterning established by 5dpf



- High throughput screening



- Stimulus induced behavioral responses

[1] 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.

GbSciences' Research & Development Partners

Contact Information

Andrea Small-Howard, Ph.D., M.B.A.
President, Chief Science Officer & Director
GB Sciences, Inc.
3550 West Teco Avenue
Las Vegas, Nevada **USA** 89118
www.gbsciences.com
andrea@gbsciences.com

Michael Farley, Ph.D.
President & Director
GBS Global Biopharma Inc.
200-900 Morrison Drive
Ottawa, Ontario, **CANADA** K2H 8K7
www.gbsglobalbiopharma.com
michael@gbsglobalbiopharma.com

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