GbSciences’ Development Programs
GbSciences

• 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
# Drug Development Pipeline

**Rx PROGRAMS**
- Parkinson's Disease (PD)
- Neuropathic Pain (NP)
- Heart Failure (HF)
- Cytokine Release Syndrome (CRS)
- Mast Cell Activation Syndrome (MCAS)
- Inflammatory Bowel Disease (IBD)

<table>
<thead>
<tr>
<th>Rx PROGRAMS</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>First-in-Man/Phase I</th>
<th>Combined Phase I-II</th>
<th>Phase III</th>
<th>FDA APPROVAL</th>
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<tbody>
<tr>
<td>Parkinson's Disease (PD)</td>
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<td>Neuropathic Pain (NP)</td>
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**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
  • 3 Provisional US Patent Applications
# Optimized Therapeutic Mixture (OTM) Development

<table>
<thead>
<tr>
<th># mixtures</th>
<th>screen type</th>
<th>GBS screen</th>
<th>GBS references</th>
</tr>
</thead>
</table>
| >10,000                   | metabolomic high throughput cellular | METABOLOMIC PROFILES  
2662 Cannabis chemovars  
MPTP & DOPAMINE RELEASE ASSAYS  
1080 combinations of 9 cannabinoids & 13 terpenes | PMID: 32923659  
US Patent 10,653,640 |
| ~1,000 combinations       | high 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  
| <100                      | medium throughput cellular         | 6-OHDA ZEBRAFISH MOTOR ASSAYS  
5 cannabinoids & 6 terpenes |                                |
| <20                       | medium throughput animal           | OTM.PD119, OTM.PD205, OTM.PD361 for Acute & Chronic testing in 6-OHDA mouse model |                                |
| 3                         | Lead Optimization                 |                                                                             |                                |
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
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
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)
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: Intervventional

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
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

<table>
<thead>
<tr>
<th>Group</th>
<th>Run-in</th>
<th>Treatment 1</th>
<th>Wash-out</th>
<th>Treatment 2</th>
<th>Wash-out</th>
<th>Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>placebo</td>
<td>OTM.PD119</td>
<td>placebo</td>
<td>OTM.PD205</td>
<td>placebo</td>
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<td>B</td>
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<td>OTM.PD361</td>
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<td>OTM.PD119</td>
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<td>C</td>
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<td>OTM.PD361</td>
<td>placebo</td>
<td>OTM.PD119</td>
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<td>OTM.PD205</td>
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<tr>
<td>Weeks</td>
<td>1 &amp; 2</td>
<td>3, 4, 5, 6</td>
<td>7 &amp; 8</td>
<td>9, 10, 11, 12</td>
<td>13 &amp; 14</td>
<td>15, 16, 17, 18</td>
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</tbody>
</table>
GbSciences Neuropathic Pain OTM
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.
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.


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


**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
-体 patterning established by 5dpf

- High throughput screening
- Light Phase
- Dark periods

- Stimulus induced behavioral responses
<table>
<thead>
<tr>
<th>Condition</th>
<th>Highlights from 2020</th>
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<tbody>
<tr>
<td><strong>Parkinson’s disease</strong></td>
<td>US Patent Issued Statistically-significant reduction of Parkinsonian movement in animal model</td>
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<td>OTM.PD119, OTM.PD205, OTM.PD361</td>
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<tr>
<td><strong>Neuropathic pain</strong></td>
<td>US Patent Issued Promising Preclinical Results in Midterm Research Report</td>
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<td>OTM.NP110, OTM.NP121, OTM.NP139</td>
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<tr>
<td><strong>Mast Cell Activation Syndrome</strong></td>
<td>US Patent Issued Rare disease, Regulatory Advantages</td>
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<td>OTM.MC122, OTM.MC128</td>
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<tr>
<td><strong>Cytokine Release Syndrome</strong></td>
<td>US Patent Application Filed Preclinical Proof-of-Concept Studies</td>
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<td>Multiple OTM.MCAS</td>
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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

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
Contact Information

Andrea Small-Howard, Ph.D., M.B.A.
Chief Science Officer & Director

GB Sciences, Inc.
3550 West Teco Avenue
Las Vegas, Nevada 89118
www.gbosciences.com
andrea@gbosciences.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