Cannabinoid Prodrugs
Unlocking the power of cannabinoids to treat serious neurological and inflammatory disorders
Leadership
entrepreneurial team focused on biotechnology and life sciences

Robert Brooke, CEO, Co-founder
Former hedge fund analyst at Bristol Capital for over 50 direct healthcare investments; Experienced biotech entrepreneur, Founder of Genesis, now Lion Biotech (NASDAQ:L BIO), Co-Founder of Intervene Immune
B.S. in Elec. Eng., Georgia Tech; M.S. in Biomedical /Neuroengineering, UCLA

Avtar Dhillon, MD, Chairman & Co-founder
Chairman, Inovio Pharmaceuticals, Oncosec Medical, and Arch Therapeutics
Raised $200M in public markets over last 10 years
Former venture capitalist and family physician for >10 years

Brandon Zipp, PhD, Dir. of Research & Development, Scientific Co-founder
>10 years research experience with glucosyltransferase enzymes
Developer of UGT biosynthesis platform
Ph.D., Biochem & Molecular Biology, Univ. of California Davis

Richard McKilligan, JD, MBA, Controller
Ex-Morgan, Lewis, & Bockius LLP, State Bars in CA and NY, CPA (inactive)
JD from Cornell, MBA from Univ of Chicago, BS in Accounting from Univ of Illinois

Anthony Maida, PhD, MBA, Director, Chair of Audit Committee
Senior Vice President, Clinical Research, Northwest Bio
MBA, MA in Toxicology, PhD in Immunology
Company Background
In 2015, we discovered that stevia UGT enzymes could enable production of a new class of cannabinoid prodrugs.

Black = RebE (UGT SG substrate)
Green = Cannabidiol
= UGT glycosylation site

Superpositioning of a steviol glycoside with cannabidiol
Company Background
Enzymatic glycosylation breakthrough leads to novel compositions of matter with improved drug properties

Steviol
Steviol Glycosides (Reb A, D, M, etc.)

Cannabinoids (CBD, THC, etc.)
Cannabinoid Glycosides (Cannaboside Prodrugs)

Same Enzymatic Process, Diverse Commercial Implications
**Cannabinoids in Medicine**

CBD is not mind-altering and has very few side effects, making it useful as part of combination treatment regimens.

**Cannabidiol Clinical Trials**

- Epilepsy / Seizures
- Schizophrenia
- Neuropathic Pain
- Muscle spasticity (in MS)
- Inflammatory Bowel Disease
- Huntington’s Disease

Due to prior restrictions on marijuana research, the full therapeutic potential of cannabinoids is only now becoming well understood, causing a large increase in the number of clinical trials being performed.

Cannabidiol especially is proving beneficial for a variety of serious neurological conditions, including rare seizure disorders in children.
About Prodrugs

enabling a low-cost, low-risk regulatory strategy akin to specialty pharmaceutical development

Prodrugs are medications or compounds that, after administration, are converted within the body into a pharmacologically active drug, which may already have a long history of clinical investigation and use. Because the reference drug already has independent verification of its safety and efficacy, the prodrug may be approved rapidly through demonstrating similar bioavailability or bioequivalence, and at the same time a prodrug can be far more marketable due to its ability to eliminate unwanted side effects or undesirable commercial aspects. A classic prodrug example is Aspirin, acetylsalicylic acid, which was first made by Felix Hoffmann at Bayer in 1897 and is a synthetic prodrug of salicylic acid.

As of 2015, there were approximately 15 prodrugs that had been classified as blockbusters, defined as having annual sales in excess of $1 billion.
Glycoside Prodrugs

Oral prodrugs could overcome the limitations of existing drugs, enabling a proprietary and highly differentiated product

- **CONVENIENCE** – Oral prodrugs provide the ultimate option for convenience and acceptability for physicians and patients

- **TARGETED DELIVERY** – Site-specific delivery to the GI tract for treatment of inflammatory bowel disease, avoiding high concentration of THC in bloodstream and brain

- **BETTER DOSING** – Avoiding degradation in the acidic stomach could enable higher doses with fewer side effects
Site-Specific Delivery of THC Enables More Potent Local Effects

Current oral THC drugs deliver psychoactive THC into the bloodstream/brain, so low doses are always required.

Higher local concentrations of cannabinoids could then enable more potent cannabinoid treatments for pain and inflammation within the gastrointestinal tract.

“CB2 receptors represent a braking system for... the resolution of inflammation and many of its symptoms.”
Avoiding Mouth Lesions In Users of Alcohol-Based Cannabis Sprays

Oral lesions may form in users of alcohol-based cannabis sprays, coupled with reported stinging, bad taste, and dry mouth.

Solubility:
Oral cannabosides with improved solubility could enable better tasting formulations that do not require harsh organic solvents such as ethanol in high concentrations.

Avoiding Complications of Topical Patches or Gels

Transdermal delivery routes can in some cases lead to hives/skin irritation, and typically deliver relatively small drug dosages.

Oral delivery:
Oral cannabosides that avoid this problem could enable far more convenient delivery of cannabinoids in a form that is fast-acting, convenient, and that works at high dose for maximal effect.

Kaptanoglu, Journal of Neurological Sciences, 2011
Targeted Drug Delivery

Glycoside prodrugs can selectively target different tissues, including the colon through oral delivery, and the brain (I.V.).

Distribution of ibuprofen after intravenous injection of ibuprofen and glycoside prodrugs in rats (Chen et. al., 2009)

Independent studies have demonstrated reliable targeting to the colon upon oral delivery of glycoside prodrugs, as well as higher permeation of brain tissue upon IV or alternative routes of drug administration.
Cannabinoid Prodrugs

A blockbuster cannabinoid drug must overcome existing deficiencies, and be differentiated from medical marijuana

<table>
<thead>
<tr>
<th>Barriers that Prodrugs Can Overcome</th>
<th>Sativex® (nabiximols)</th>
<th>Marinol® (dronabinol)</th>
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</thead>
<tbody>
<tr>
<td>Favorable taste, for better patient compliance</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lack of stomach degradation, to enable reliable dosing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Avoid high concentrations of THC in bloodstream and brain</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Highly differentiated from effects of medical marijuana</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Synthetic cannabinoid drug sales estimated at $133 million in 2014 by IMS Health, while legal marijuana estimated at $2.57 billion in 2014, and projected to grow to $10.2 billion in several years

*Sativex® is owned/marketed by GW Pharma, and Marinol®/dronabinol is marketed by multiple drug companies.*
Cannabinoid prodrugs
Glycosylation has reliably led to improvements in drug solubility and stability in novel class of cannabosides

Patents pending for more than 20 novel cannabinoid glycoside prodrugs, known as “cannabosides” 

(prodrugs of CBD, THC, CBDV, and more)
Intellectual Property

Patent applications covering compositions of matter for more than 20 cannabinoid prodrugs with modified solubility and stability, including glycoside prodrugs of THC, CBD, and CBDV

Manufacturing system for glycosides, geared for low-cost efficient production of steviol and cannabinoid glycosides

Legacy patents and patent applications related to stevia production through enzymatic processing and combined stevia-sugarcane processing
Cannabinoid Prodrugs

Cannaboside prodrugs enable the site-specific delivery of cannabinoids to the large intestine upon oral ingestion.
Clinical Development Pipeline

Oral cannabosides - drug formulations including a novel class of cannabinoid glycoside prodrugs (CBD, THC, CBDV, etc.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Indications</th>
<th>Status</th>
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<tbody>
<tr>
<td>VB100</td>
<td>Inflammatory Bowel Disease</td>
<td>Phase 1/2 Studies to initiate in 2017</td>
</tr>
<tr>
<td>VB210</td>
<td>Neuropathic Pain, Irritable Bowel Syndrome, Fibromyalgia, Muscle Spasticity in Multiple Sclerosis</td>
<td>Phase 1/2 Studies to initiate in 2017</td>
</tr>
<tr>
<td>Additional Cannaboside Formulations</td>
<td>Epilepsy, Schizophrenia, Huntington’s, Guillain-Barré</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Pursuing low-risk approvals for established clinical uses of cannabinoids, with exploratory use in large market indications

Vitality may benefit from results of clinical studies that were initiated and paid for by independent clinical investigators, including studies that were performed or are currently still in process for many large market clinical indications: epilepsy, neuropathic pain, multiple sclerosis, inflammatory bowel disease, schizophrenia, and Huntington’s disease
## Treatment of Inflammatory Bowel Disease

Clinical data describes use of Cannabis for remission of Crohn’s, weaning off steroids, and symptomatic relief.

<table>
<thead>
<tr>
<th>IBD Symptoms Improved</th>
<th>Patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>83.9%</td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td>76.8%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>48.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28.6%</td>
</tr>
</tbody>
</table>

In 8 weeks of *Cannabis* treatment, 5 of 11 Crohn’s patients entered remission (CDAI<150)

Storr et al., *Inflammatory Bowel Diseases*, 2014

Clinical Gastroenterology & Hepatology, 2013
Clinical Development Strategy
Low-cost data for initial drug approvals, and simultaneous proof-of-concept in large market disease indications

First-in-man clinical studies of proprietary cannabinoid glycosides “cannabosides”

Phase 1/2 Trial Design in Inflammatory Bowel Disease
Trial of multiple agents for initial evaluation of pharmacokinetics and symptomatic relief of IBD (e.g. abdominal pain, intestinal cramping, etc.)

Symptomatic relief will be pursued, along with secondary endpoints

Proprietary molecules and manufacturing process developed internally
Use of enzyme biosynthesis process for biotransformation of cannabinoids for production of cannabinoid prodrugs of CBD, THC, CBDV, and more
Serious Unmet Need in MS
Clinical trial designs include use of cannabosides in combination with approved drugs in order to attempt reversal of neurological damage.

~80% of MS patients have muscle spasticity, which may be treated with cannabinoids, but often neurological deficits are irreversible.

No approved drugs for functional recovery or brain repair/remyelination.

Vitality testing approved drugs to be used in combination with symptomatic treatments in large market and serious disease indications.
Cannabinoid Reference Drug
Approved for Muscle Spasticity in MS

Nabiximols, an oral spray of THC and CBD, is already approved in more than 25 countries for treatment of muscle spasticity in MS.

An oral spray of THC and CBD has been used in Phase 2 and 3 studies that were double-blind, randomized, and placebo-controlled involving 1,294 patients, with the results published in peer-reviewed journals.

Figure 2. 0–10 Numeric Rating Scale (NRS) spasticity scores during the study (intention-to-treat analysis).

*(Novotna, European Journal of Neurology, 2011)*

*Sativex®*(nabiximols) is owned/marketed by GW Pharma
CBD’s Role in Neuroprotection

Cannabidiol and endocannabinoids are involved in key aspects of neuroprotection & remyelination, a regenerative process in the brain.

Cannabidiol has been shown to be protective of oligodendrocyte progenitor cells, which seem critical for brain repair in multiple sclerosis, and it reduces the severity of multiple sclerosis in preclinical models (Mecha et. al., 2012, Kozela 2011).

“Cannabidiol... represents a rare, if not unique, compound that is capable of affording neuroprotection by the combination of different types of properties e.g., anti-glutamatergic effects, anti-inflammatory action, and antioxidant effects” (Iuvone et. al., 2009)
Additional Programs

Vitality has mature biosynthesis technologies for stevia production, which we aim to monetize through partnerships.

**BIOSYNTHESIS PLATFORM** with related intellectual property for stevia production and use as zero-calorie, plant-derived sweetener:

- Commercial: Stevia program utilizes same manufacturing platform used for CB glycoside production, obtained preliminary FDA GRAS review
- R&D: Next-gen steviol glycosides with improved taste profile, including proprietary bioprocessing methods

**RESEARCH PRODUCTS & TOOLS**, commercializing assay kits and research reagents:

- Commercial: provider to major research universities, and further distributed through international distribution network and open-source communities
Company Highlights

- Developing proprietary cannabinoid pharmaceuticals prodrugs, enabling a low-cost, low-risk regulatory strategy akin to specialty pharmaceutical risk profile

- Intellectual property covering more than 20 cannabinoid prodrugs including modifications of non-psychotropic CBD, THC, and CBDV, a new class of cannabosides

- Proven management and board with track record of building value in drug development

- Focused on using cannabinoid prodrugs to treat serious neurological and inflammatory conditions, such as inflammatory bowel disease and multiple sclerosis