GW Pharma Overview

• **World leader in development of plant-derived cannabinoid therapeutics**
  - Proprietary cannabinoid product platform

• **Commercialized product, Sativex®**
  - Approved in 27 countries (ex-U.S.) for MS spasticity
  - U.S. Phase 3 cancer pain trials near completion

• **Epidiolex® orphan program in pediatric epilepsy**
  - Development programs in Dravet and Lennox-Gastaut syndromes
  - Approx. 400 children in FDA authorized “expanded access” program
  - First placebo-controlled trial due to commence October ‘14
  - GW retains global commercial rights

• **Promising clinical stage cannabinoid product pipeline across range of therapeutic areas**
Meet Molly

- Born 6 weeks early, on November 14, 2005 – but completely healthy
- Seizures
- Autism
- Gait Abnormality and Difficulty
- Temperature Regulation and Autonomic Dysfunction
- Motor Skills Difficulty
- Processing and Planning problems
- Anxiety
- Sleep trouble and disruption
Dravet syndrome also known as Severe Myoclonic Epilepsy of Infancy (SMEI)

- Rare and Catastrophic form of intractable epilepsy
- Usually begins in the first year of life
- Initial seizures often convulsive, associated with fever, and prolonged events
- New seizure types emerge in the second year of life
- Development remains on track initially, with plateaus and a progressive decline typically beginning in the second year of life.
- Individuals with Dravet syndrome face a higher incidence of SUDEP (sudden unexplained death in epilepsy) and have associated conditions, which include:
  - behavioral and developmental delays
  - movement and balance issues
  - orthopedic conditions
  - delayed language and speech issues
  - growth and nutrition issues
  - sleeping difficulties
  - chronic infections
  - sensory integration disorders
  - disruptions of the autonomic nervous system

*Children with Dravet syndrome do not outgrow this condition and it affects every aspect of their daily lives.*
Better treatment is needed.

- Without better treatment, individuals with Dravet syndrome and related disorders face a diminished quality of life.

- Fear of SUDEP (Sudden Unexplained Death in Epilepsy) is very real and ever present.

- The constant care and supervision of an individual with such highly specialized needs is emotionally and financially draining on the family members who care for these individuals.

- Unlike approximately 70% of epilepsies, this population has difficult to control seizure, failing drug after drug.
Dravet Syndrome
Non-profit, grass-roots organization started in Connecticut in 2009

Mission
- To aggressively raise research funds for Dravet syndrome and related epilepsies
- To increase awareness of these catastrophic conditions
- To provide support to affected individuals and families

We understand:
- The ongoing need to fund innovative research
- The urgency in finding better treatments
- The motivation of our donors to make an impact specifically in the fields of Dravet syndrome and related epilepsies
- The importance of transparency and accountability of not only our organization, but the researchers that we fund
We must work together, as at our heart, we all have the same goal – to make a better life for those with these syndromes.

We are all connected, working to find better treatments, and one day a CURE!
Treatments for Epilepsy: A large unmet need

Elizabeth A. Thiele, MD, PhD

Director, Pediatric Epilepsy Program
Massachusetts General Hospital
Professor of Neurology
Harvard Medical School
Epilepsy: Definitions

- Seizure: disturbance in the electrical activity of the brain
- Epilepsy: two of more unprovoked seizures occurring greater than 24 hours apart

Epilepsy is a spectrum of disorders:
  - Many different types of seizures
  - Many causes
  - Many syndromes and types of epilepsy
Epilepsy: Definitions

- **Medically intractable seizures**
  - Seizures that are not controlled by anticonvulsant medications, or are controlled only by medications that have significant side effects.
  - 1/3 of children with epilepsy will develop medically intractable epilepsy
Pharmacoresistant Epilepsy

Previously Untreated Epilepsy Patients (n=470)

- 47% Seizure-free with 1st drug
- 36% Seizure-free with 2nd drug
- 13% Seizure-free with 3rd or multiple drugs
- 4% Pharmacoresistant epilepsy

Anticonvulsant Drug Development: “Old” anticonvulsant medications

- 1857  Bromides
- 1912  Phenobarbital
- 1920’s (Ketogenic Diet)
- 1938  Phenytoin
- 1950’s ACTH
- 1970’s Valproate, carbamazepine
Anticonvulsant Drug Development: “New” FDA approved anticonvulsants

- 1993  Felbamate, Gabapentin
- 1994  Lamotrigine
- 1997  (Vagal Nerve Stimulator)
- 1997  Topiramate
- 1998  Tiagabine
- 2000  Levetiracetam, Oxcarbazepine, Zonisamide
- 2005  Pregabalin
- 2009  Rufinamide, lacosamide, vigabatrin
- 2010  ACTH
- 2011  Ezogabine
- 2012, 2013  Clobazam, Parampanel, Elsicarbazepine
# Treatment of Seizure Types: Anticonvulsant Drugs, 2014

<table>
<thead>
<tr>
<th>Primary Generalized</th>
<th>Partial Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence</td>
<td>Simple Partial</td>
</tr>
<tr>
<td>Tonic-Clonic</td>
<td>Complex Partial</td>
</tr>
<tr>
<td>Myoclonic, Atonic, Tonic</td>
<td>Secondary Generalized Tonic-Clonic</td>
</tr>
</tbody>
</table>

- **Ethosuximide**
- **Benzodiazepines**
- **Carbamazepine, Phenytoin, Phenobarbital, Primidone, Gabapentin, Tiagabine, Pregabalin, Oxcarbazepine, Vigabatrin, Lacosamide, Ezogabine, Parampanel, Elslicarbazepine**

- **Valproate, Felbamate, Lamotrigine, Topiramate, Levetiracetam, Zonisamide, Rufinamide**
- **Lacosamide, Clobazam, Elslicarbazepine**
Pharmacoresistant Epilepsy

Previously Untreated Epilepsy Patients (n=470)

- Seizure-free with 1st drug: 47%
- Seizure-free with 2nd drug: 4%
- Seizure-free with 3rd or multiple drugs: 36%
- Pharmacoresistant epilepsy: 13%

MGH Expanded Access IND for Epidiolex

- **26 patients enrolled in March 2014**
  - 25 medically intractable epilepsy
  - 1 refractory status epilepticus
  - Ages 3-24 years of age
- **Various etiologies of epilepsy**
MGH Epidiolex experience: 13 year old girl with Doose syndrome

• **Seizure onset at 3 years of age**

• **Pre-Epidiolex (at time of enrollment)**
  » On 4 anticonvulsant medications and vagus nerve stimulator
  » Previously on 11 other ACD, ketogenic diet, and steroid course
  » Daily seizure activity, with mixed seizure disorder
    3-4 generalized tonic clonic seizures per week
    >20 focal seizures per day
    Numerous atypical absence and drop seizures
MHG Epidiolex experience:
13 year old girl with Doose syndrome

- **On Epidiolex**
  - Seizure free for 5 months
    - Previous “best seizure control” 1-2 days
  - Tolerates Epidiolex well with no apparent side effects
  - Now tapering other medications
MGH Epidiolex experience:
11 year old girl with TSC

- Onset of seizures at 4 mo with infantile spasms
- Subsequently developed refractory mixed seizure disorder, global developmental delays
- Pre-Epidiolex (at time of enrollment)
  - On 3 ACD and vagus nerve stimulator
  - Previously on 12 other ACD
  - Daily seizure activity, with mixed seizure disorder
    - 8-12 seizures per day
    - 4-6 generalized tonic clonic seizures per week
On Epidiolex

- Seizure frequency unchanged, although seizures less intense
- But, significant perceived benefits:
  - “much more alert”
  - “significantly improved eye contact”
  - “much more engaged and responsive”
- Plan to further increase Epidiolex dose after DEA okay
Onset of seizures at 4 years of age
  » Rare seizure free days since epilepsy onset

Pre-Epidiolex (at time of enrollment)
  » On 5 ACD, dietary therapy, and with vagus nerve stimulator
  » Previously on 6 other ACD and ketogenic diet
  » 10-40 seizures per day

MGH Epidiolex experience:
20 year old boy with generalized epilepsy
On Epidiolex

» Initial dramatic decrease in seizure activity
  “seizure free” for several weeks

» Subsequent seizure recurrence with longer duration seizures
  Thought likely due to medication interactions, so adjustments made

» Currently, seizure control again significantly improved
Treatments for Epilepsy: a large unmet need

- Incidence of epilepsy in US per year: ~150,000 new cases
- Prevalence of epilepsy in US: ~2.2 million people
- Prevalence of epilepsy worldwide: > 65 million people

IOM report on epilepsy, 2012

- Estimate of prevalence of refractory epilepsy:
  - US: 730,000 people
  - Worldwide: 21.7 million people
Epidiolex® Expanded Access INDs
Physician Reported Treatment Effect Data

Dr Stephen Wright, R&D Director
14 October 2014
Expanded Access Studies

Expanded access studies are uncontrolled, carried out by individual investigators, and not typically conducted in strict compliance with Good Clinical Practices, all of which can lead to a treatment effect which may differ from that in placebo-controlled trials. Data from these studies provide only anecdotal evidence of efficacy for regulatory review, contain no control or comparator group for reference and are not designed to be aggregated or reported as study results. Moreover, data from such small numbers of patients may be highly variable. Such information may not reliably predict data collected via systematic evaluation of the efficacy in company-sponsored clinical trials. Reliance on such information may lead to Phase 2 and 3 clinical trials that are not adequately designed to demonstrate efficacy and could delay or prevent GW’s ability to seek approval of Epidiolex. Expanded access programs may provide supportive safety information for regulatory review. Physicians conducting these studies may use Epidiolex in a manner inconsistent with the protocol, including in children with conditions different from those being studied in GW-sponsored trials. Any adverse events or reactions experienced by subjects in the expanded access program may be attributed to Epidiolex and may limit GW’s ability to obtain regulatory approval with labeling that GW considers desirable, or at all.
Background and Introduction

• Expanded access INDs granted by FDA to individual pediatric epileptologists
  ‣ In response to unmet medical need
  ‣ In children and young adults with range of drug-resistant epilepsies

• FDA authorization received to date for approx. 400 children at 17 US hospital sites

• Significant body of data being generated
  ‣ Patients treated according to standardized treatment plan
  ‣ All seizure types
  ‣ Use of concomitant meds, blood levels
  ‣ Adverse events
Latest Data: Overview

- Treatment-resistant children and young adults (mean age 11 years)
  - Epidiolex added to existing meds. Patients on average 3 other AEDs

- Patients include extreme and rare forms of epilepsy including several patients with major congenital structural brain abnormalities

- Data presented for all 58 patients with at least 12 weeks continuous exposure
  - UCSF: 9 patients; NYU: 26 patients; Boston: 23 patients

- 16 week data presented for all 40 patients with 16 week data

- Total safety database of 151 patients
  - Total estimated exposure: 50 patient-years
All Patients (n=58) Median % Reduction in Total Seizures

-40% -41% -40% (n=58) -51% (n=40) -36%

Total Seizures = Convulsive and Non-Convulsive
All Patients (n=58)
All Seizures - Responder Analysis

Patients with at least:
- 50% Responders
- 70% Responders
- 90% Responders
- Seizure Free

- 41% of Patients
- 48% of Patients
- 43% of Patients
- 55% of Patients

Total Seizures = Convulsive and Non-Convulsive
Dravet Syndrome Patients (n=12) Median % Reduction in Convulsive Seizures

- % Seizure Reduction

<table>
<thead>
<tr>
<th>Weeks 1-4</th>
<th>Weeks 5-8</th>
<th>Weeks 9-12</th>
<th>Weeks 13-16</th>
<th>12 Wk Aggregate</th>
</tr>
</thead>
<tbody>
<tr>
<td>-72%</td>
<td>-62%</td>
<td>-51% (n=12)</td>
<td>-56% (n=9)</td>
<td>-56%</td>
</tr>
</tbody>
</table>

- Dravet Syndrome Patients (n=12)
Dravet Syndrome Patients (n=12)
Convulsive Seizures - Responder Analysis

Patients with at least:
- 50% Responders
- 70% Responders
- 90% Responders
- Seizure Free

% of Patients

- 58% of Patients
- 67% Responders
- 58% of Patients
- 56% of Patients
- 58% of Patients

Weeks 1-4
(n=12)

Weeks 5-8
(n=12)

Weeks 9-12
(n=9)

Weeks 13-16

12 Wk Aggregate
All Patients with Atonic ("Drop") Seizures (n=12) Median % Reduction in Atonic Seizures

Week 1-4: -57%
Weeks 5-8: -62% (n=12)
Weeks 9-12: -52%
Weeks 13-16: -76% (n=10)
12 Wk Aggregate: -52%
All Patients with Atonic ("Drop") Seizures (n=12)
Atonic Seizures - Responder Analysis

Patients with at least:
- 50% Responders
- 70% Responders
- 90% Responders
- Seizure Free

<table>
<thead>
<tr>
<th>Weeks</th>
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<th>70% Responders</th>
<th>90% Responders</th>
<th>Seizure Free</th>
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</thead>
<tbody>
<tr>
<td>1-4</td>
<td>58%</td>
<td></td>
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<tr>
<td>5-8</td>
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<td>67%</td>
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<td>9-12</td>
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<td></td>
<td>58%</td>
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<tr>
<td>13-16</td>
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<td>70%</td>
<td></td>
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<tr>
<td>12 Wk Aggregate</td>
<td></td>
<td></td>
<td></td>
<td>50%</td>
</tr>
</tbody>
</table>

(n=12) (n=10)
Safety Data
(151 patients, approx. 50 patient years treatment)

• Most common AEs – all causes (10% or more of patients)
  - Somnolence 19%
  - Fatigue 11%

Other AE’s in 5% or more of patients are diarrhea, decreased appetite, convulsion

• 2 withdrawals due to AEs

• 4 withdrawals due to lack of clinical effect

• Serious AEs reported in 26 patients (incl 2 deaths, one from SUDEP and one from respiratory failure due to aspiration). None deemed related to Epidiolex
Conclusions

• New data on additional patients is consistent with previous data on initial 27 patients
• Epidiolex treatment is associated with a meaningful reduction in seizure frequency in a high proportion of patients with otherwise drug-resistant epilepsy
• The response seen in the first month of treatment is maintained (and possibly increased) with increasing duration of treatment
• Seizure freedom is seen in a portion of responders
• Patients with Dravet syndrome have shown an encouraging response
• Epidiolex treatment is associated with a reduction in drop seizures, the seizure type considered for primary efficacy in LGS trials
• Few patients withdrawing from treatment due to side effects or lack of clinical effect
Epidiolex® Clinical Observations

Dr. Orrin Devinsky
Professor of Neurology, Neurosurgery, and Psychiatry, NYU School of Medicine
Director, NYU Comprehensive Epilepsy Center
Clinical Program
Overview

• Formal development programs for Epidiolex in both Dravet syndrome and LGS

• FDA Orphan Drug Designations for Epidiolex for both Dravet syndrome and LGS, as well as Fast Track Designation for Dravet syndrome

• A company-sponsored IND is open with the FDA

• Phase 2/3 Dravet syndrome clinical trial on track to commence this month

• An additional Phase 3 Dravet syndrome clinical trial is expected to commence in early 2015

• Two Phase 3 trials in LGS expected to commence in Q1 2015
Epidiolex in Dravet Syndrome
Clinical Trials Program

Study 1
Two part study in Dravet syndrome patients on concomitant AEDs

Part A (n=30)
- Pharmacokinetics of CBD at different doses
  - dose-ranging short-term safety & tolerability
  - drug-drug interaction

Part B, placebo-controlled – 12 weeks (n = 80)
- 12 week placebo-controlled evaluation of efficacy and safety

Study 2
Additional efficacy and safety study

Phase 3, placebo-controlled - 12 weeks (n = 120)
- 12 week placebo-controlled exposure
- 3 arms: high dose, low dose, placebo
- low dose/high dose regime based on safety results of Part A of first study

Study 3
Drug-drug interaction study

DDI Study adult epilepsy patients

Study 4
Long-term extension study
- open label safety continuation study with optional upwards dose titration and reduction of concomitant AEDs in responders
Epidiolex in Dravet Syndrome
Part A Trial Design

Objective: To determine the safety and dose-related pharmacokinetics of cannabidiol

**Part A Trial Design**

- **Screening**
- **Baseline Observation Period**: 28 days
- **Randomization**
- **Titration Phase**: 3-11 days
- **High Cohort 20 mg/kg (n=8)**
- **Mid Cohort 10 mg/kg (n=8)**
- **Low Cohort 5 mg/kg (n=8)**
- **Placebo Cohort (n=6)**
- **End of Part A Treatment**
- **10 days Taper Period**
- **Open Label Extension**

Each dose cohort randomized 4:1 Epidiolex: Placebo
Epidiolex in Dravet Syndrome
Part B Trial Design

Objective: Provide pivotal evidence of safety and efficacy

Primary Endpoint: Average % change from baseline in convulsive seizure frequency

Secondary Endpoints:
- % change non-convulsive seizures
- Change in seizure subtypes
- % seizure freedom
- Responder rate
- Cognition
- Daytime sleepiness scale
- Night time sleep disruption
- Caregiver Global Impression of Change
- Palatability of the drug product
- Quality of Life
Cannabinoid medicines as the response to the need for polymodal therapies

Vincenzo Di Marzo, PhD
Director of the Institute of Biomolecular Chemistry, National Research Council of Italy, and Coordinator of the Endocannabinoid Research Group, Naples, Italy
Director of Preclinical Research, GW Pharmaceuticals
Plant cannabinoids: a neglected pharmacological treasure trove

Raphael Mechoulam

- Propyl analogues
- Methyl analogues
- Sesquiterpene analogues
- Acid precursors
- Others
- Over 100 phytocannabinoids
Evaluate the potential for the therapeutic use of phytocannabinoids in human disease
Recent successes of the GW-sponsored consortium

Molecular Cancer Therapeutics
A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma

ACS Chemical Neuroscience
Nonpsychotrophic Plant Cannabinoids, Cannabidiol (CBD) and Cannabidiol (CBD). Activate and Desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) Channels in Vitro: Potential for the Treatment of Neuronal Hyperexcitability

Journal of Clinical Investigation
Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes

Biomedical Pharmacology
Increase of mesenchymal stem cell migration by cannabidiol via activation of p42/44 MAPK

Research Paper
Non-psychotrophic cannabinoids modulate the descending pathway of antinoceptive in anaesthetized rats through several mechanisms of action

Review
Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabinoids in psychiatric disorders

Neuropsychopharmacology
Mechanisms of cannabinoid neuroprotection in hypoxic–ischemic newborn pigs: Role of SHT1A and CB2 receptors

Nature Reviews Cancer
Towards the use of cannabinoids as antitumour agents

Nutrients
Chemopreventive effect of the non-psychotrophic phytoconstituent cannabinoid cannabidiol on experimental colon cancer

Cannabidiol Targets Mitochondria to Regulate Intracellular Ca²⁺ Levels

Symptom-relieving and neuroprotective effects of the phytocannabinoid Δ⁹-THCV in animal models of Parkinson’s disease

Cannabidiol Reduces Aβ-Induced Neuroinflammation and Promotes Hippocampal Neurogenesis through PPARγ Involvement

GW-sponsored preclinical studies published to date > 80
Some General Considerations on Disease

• Aethiopathology of multi-factorial diseases
  ▸ Even in the rare case in which diseases are due to the malfunctioning of one gene-one protein, pathological states perturb the homeostasis of several targets, tissues and organs

• 1 single ultra-potent “selective” compound->1 target ->1 disease only seldom works
  ▸ Wrong assumption, a magic bullet may treat one of many relevant targets but this is not enough to affect a disease
  ▸ Instead it may cause homeostatic unbalance in organs in which that target is not malfunctioning, or in those that express off-targets for the compound
Revisiting an old Paradigm to Treat Disease

chemical space for target X

potent & selective

in vitro potency

chemical space for target Z

poly-pharm.

desirable area for multi-target approach

chemical space for target Y

Target area of current drug discovery

Adapted from Pang et al. (2012)
Diseases are at the opposite ends of unbalanced physiological "modes" (in a time and organ-dependent manner).

- Too much cell transmission
  - MOVEMENT DISORDERS
  - ALZHEIMERS DISEASE
  - ULCERATIVE COLITIS
  - RHEUMATOID ARTHRITIS
  - NEURODEGENERATION
  - EPILEPSY
  - PAIN

- Too little cell transmission
  - DEFECTIVE WOUND HEALING
  - IMMUNODEFICIENCIES
  - CANCER
  - PSORIASIS
  - ACNE
  - NEURODEGENERATION
  - ULTHERATIVE COLITIS
  - RHEUMATOID ARTHRITIS

- Not enough transmission
  - IMMUNODEFICIENCIES
  - CANCER
  - PSORIASIS
  - ACNE

- Not enough cell death
  - DEFECTIVE WOUND HEALING
  - IMMUNODEFICIENCIES
  - CANCER
  - PSORIASIS
  - ACNE

UNBALANCED ENERGY CONTROL:
- Mitochondrial & Lysosomal activity
- Autophagy
- mTOR activity

Response to...
Diseases caused by opposite alterations of one gene may cause overlapping behavioral consequences.

Adapted from Ramocki et al (2008)
Homeostatic perturbations change the system set-point thus making treatment more complicated.

Changes due to stress/disease are easily counteracted by compensatory mechanisms. Permanent loss or gain of function = homeostatic changes to restore output. Resultant new steady states lack flexibility = dynamic ability of system to respond is weakened.
Homeostatic perturbations change the system set-point thus making treatment more complicated.
Epilepsy as a model disease to investigate the advantages of polymodal medicines

MODEL DISEASE

EXCITOTOXICITY

Plasticity

Inflammation

Cell cycle

THERAPEUTIC CONTROL

Synaptic control

Anti-inflammatory

Cell death control

Multi-target & Poly-modal treatment
Summary 1: the “ideal” pharmacological treatment for multi-factorial disorders

- Should be a rationalized “multi-target” drug, or a combination of drugs, possibly designed using models predictive of both efficacy and safety. *This clashes with the idea of target-selective drugs*

- Should be “pro-homeostatic”, designed to preserve the time- and tissue-specificity of homeostasis and possibly cope with its maladaptive adjustments (which occur much more rapidly, e.g., in a developing brain). *This clashes with the idea of ultra-potent drugs administered no matter when*

- Should be “multi-modal”, in order to deal with the often concurring imbalance of more physiological “modes” (cell plasticity, cell cycle, immune response, energy control). *This may clash with the idea of tissue-selective drugs*
Plant cannabinoids: THC and the endocannabinoid system (ECS)
Endocannabinoids and the regulation of their tissue levels

Endocannabinoids:
1) are produced “on demand”
2) activate cannabinoid CB₁ and CB₂ receptors locally
3) are immediately metabolized

Phospholipid-derived precursors

Endocannabinoids

Degradation products
Endocannabinoid regulation of homeostasis at the cellular, tissue and systemic level
Endocannabinoid regulation of homeostasis at the cellular, tissue and systemic level

A restricted population of CB₁ cannabinoid receptors with neuroprotective activity

Anna Chiarlone¹, Luigi Bellocchio¹, Cristina Blázquez¹, Eva Resel¹, Edgar Soria-Gómez², Astrid Cannich³, José J. Ferrero⁴, Onintza Sagredo⁵, Cristina Benito⁶, Julián Romero⁷, José Sánchez-Prieto⁸, Beat Lutz⁹, Javier Fernández-Ruiz⁶, Ismael Galve-Roperh⁴, and Manuel Guzmán¹,²

¹Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas, Instituto Ramón y Cajal de Investigación Sanitaria, 28040 Madrid, Spain; ²Department of Biochemistry and Molecular Biology I, Instituto Universitario de Investigación Neuroquímica, Complutense University, 28040 Madrid, Spain; ³NeuroCentre Magendie U862, Endocannabinoids and Neuroadaptation, Institut National de la Santé et de la Recherche Médicale, 33077 Bordeaux, France; ⁴NeuroCentre Magendie U862, University of Bordeaux, 33077 Bordeaux, France; ⁵Department of Biochemistry and Molecular Biology IV, Complutense University, 28040 Madrid, Spain; ⁶Department of Biochemistry and Molecular Biology III, Instituto Universitario de Investigación Neuroquímica, Complutense University, 28040 Madrid, Spain; ⁷Research Unit, Hospital Universitario Fundación Alcorcón, 28922 Madrid, Spain; and ⁸Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, 55099 Mainz, Germany

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Genetic rescue of CB₁ receptors on medium spiny neurons prevents loss of excitatory striatal synapses but not motor impairment in HD mice

Alipi V. Naydenov¹, Marja D. Sapers³, Katie Swinney⁴, Lynn A. Raymond³, Richard D. Palmiter⁵, Nephi Stella⁶,*
Plant cannabinoids are multi-target
Plant cannabinoids are multi-modal pro-homeostatic compounds.

Indeed, depending on the molecular mechanism of action, cell type and basal conditions of the cell, cannabinoids can both inhibit and stimulate:

1) mTOR and autophagy
2) mitochondrial function
3) ROS formation
Cannabidiol pharmacological fingerprint “shakes hands” with the aethiopathology of epilepsy

Polypharmacological Fingerprint

- Keppra
- Valproate
- Cannabidiol
- CBD + Keppra
- CBD + Valproate

Aetiopathophysiological Fingerprint

- Activate Target
- Repress Target

beneficial

detrimental
Cannabidiol pharmacological fingerprint “shakes hands” with the aethiopathology of epilepsy
Two is better than one.....

Clinically:
- Sativex (THC+CBD) has an improved therapeutic index in clinic:
  - Improved safety profile: less intoxication
  - Better efficacy than pure THC at reducing cancer pain
  - No statistically significant difference between placebo and high THC extract

  (Johnson et al, 2010):

Preclinically:
- THC+CBD more effective than THC alone in reducing glioma cell growth in the presence of temozolomide (Salazar et al. 2009)
- CBD+CBG more potent than each alone at inhibiting human prostate and breast carcinoma cell growth (unpublished)
Two is better than one....
Cannabinoids are effective in models of epilepsy.
GWP42006 (CBDV)
Epilepsy
Progress to date

• Pre-clinical profile shows a broad spectrum of anti-seizure activity
  ‣ Different profile from Epidiolex®

• Pre-clinical pharmacology and toxicology shows a benign toxicology profile

• Phase 1 single rising dose and multiple dose oral and IV pharmacokinetics study completed
  ‣ Pk defined
  ‣ Safety very good up to 800 mg daily dose in multiple dosing

• Phase 2a proof of concept study planned
  ‣ Dose ranging
  ‣ Efficacy and safety
  ‣ Partial onset seizures in adults
  ‣ Target start date H1 2015
Epilepsy = Model CB Responsive Disease

**Neurotoxicity with behavioural complications**

**Neural plasticity**

**Inflammatory response**

**Neurotoxicity**

**THE ECS HAS A FUNDAMENTAL ROLE IN EACH OF THESE SYSTEMS**

**AFFECTED SYSTEM**

**MODEL DISEASE**

**THERAPEUTIC CONTROL**

**Synaptic control**

**Anti-inflammation**

**Control cell survival**

**Cannabinoid treatment**
The spectrum of cannabinoid pharmacology

Neurotoxicity with behavioral complications

Neural plasticity

Inflammatory response

Neurotoxicity

Synaptic control

Anti-inflammation

Control cell survival

MODEL DISEASE

AFFECTED SYSTEM

THERAPEUTIC CONTROL

CURRENT PIPELINE

Schizophrenia

IBD

Glioma

FUTURE ORPHAN PIPELINE

Autism

DMD/ALS

NHIE

Cannabinoid treatment