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.

Better treatment is needed.

Dravet Syndrome

Non-profit, grass-roots organization started in Connecticut in 2009

DRAVET® SYNDROME FOUNDATION

Raising hope & changing lives through research

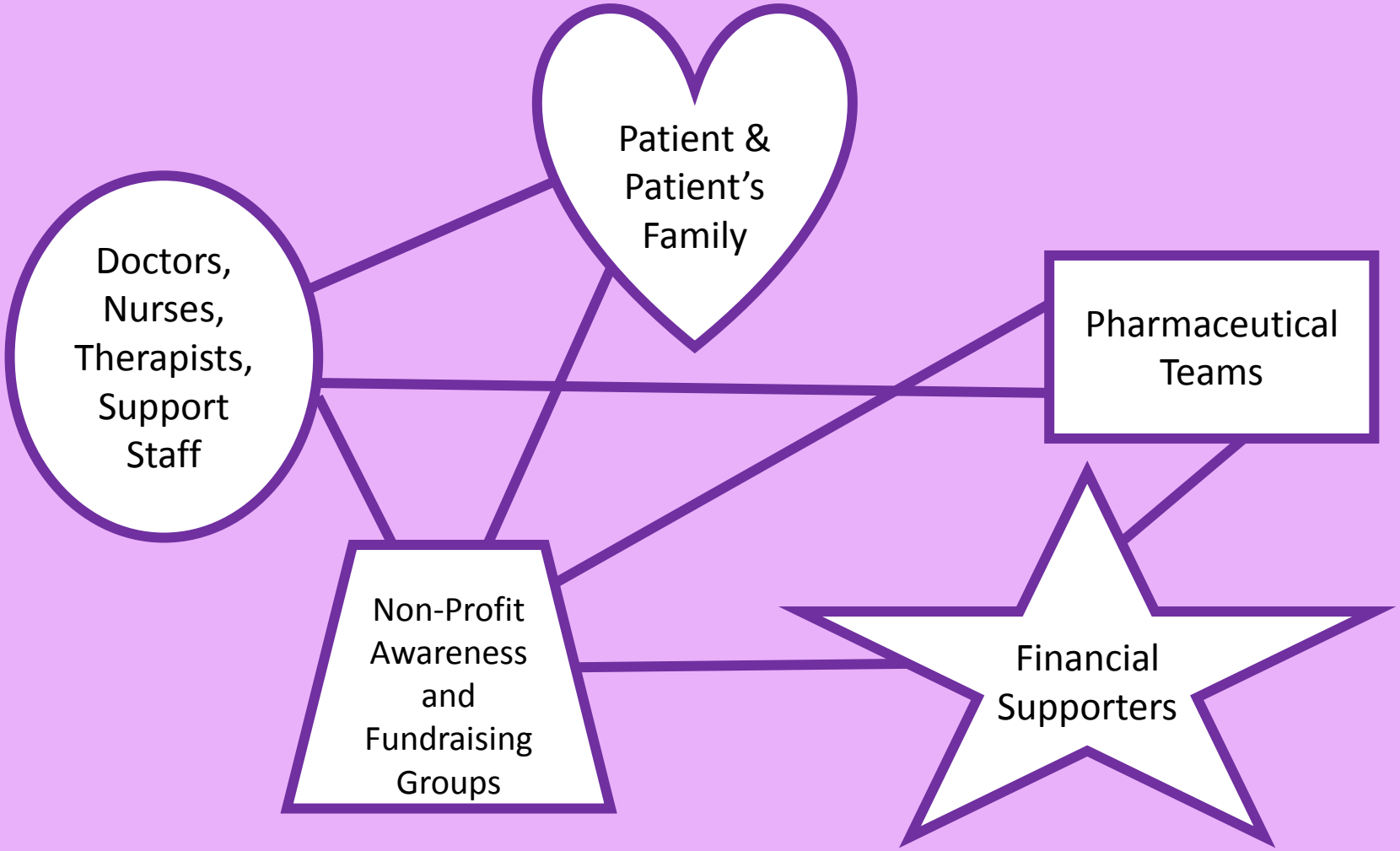
Mission

- 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*

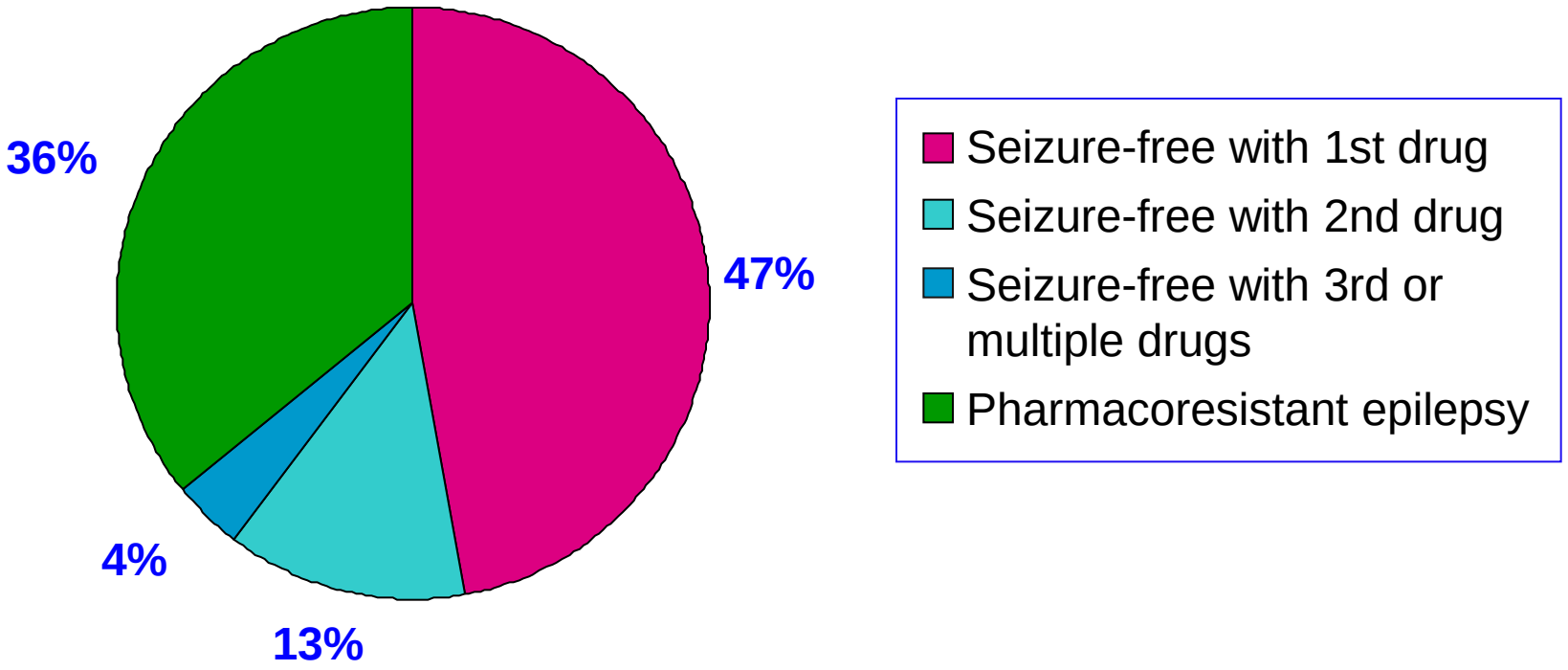
- *Epilepsy is a spectrum of disorders:*
  - Many different types of seizures
  - Many causes
  - Many syndromes and types of epilepsy

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)



Kwan P, Brodie MJ. *N Engl J Med.* 2000;342:314-319.

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

Primary Generalized

Absence

Myoclonic, Atonic, Tonic

Tonic-Clonic

Partial Onset

Simple Partial

Complex Partial

Secondary Generalized Tonic-Clonic

Ethosuximide

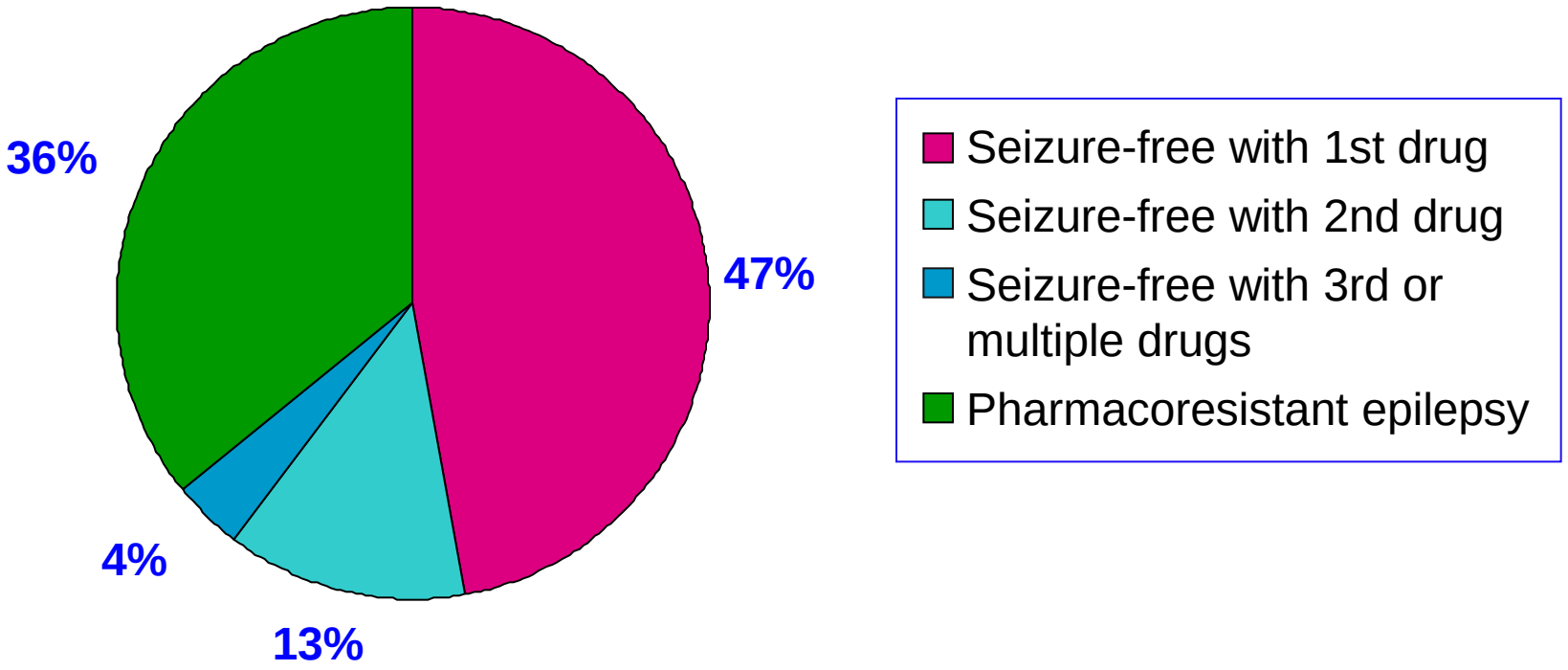
Benzodiazepines

Carbamazepine, Phenytoin, Phenobarbital, Primidone, Gabapentin, Tiagabine, Pregabalin, Oxcarbazepine, Vigabatrin, Lacosamide, Ezogabine, Parampanel, Elsicarbazepine

Valproate, Felbamate, Lamotrigine, Topiramate, Levetiracetam, Zonisamide, Rufinamide ?Lacosamide, Clobazam, ?Elsicarbazepine

Pharmacoresistant Epilepsy

Previously Untreated Epilepsy Patients (n=470)



Kwan P, Brodie MJ. *N Engl J Med.* 2000;342:314-319.

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

MGH 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

MGH Epidiolex experience:
11 year old girl with TSC

- *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

MGH Epidiolex experience:
20 year old boy with generalized epilepsy

- *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 world wide: > 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

GW pharmaceuticals

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.

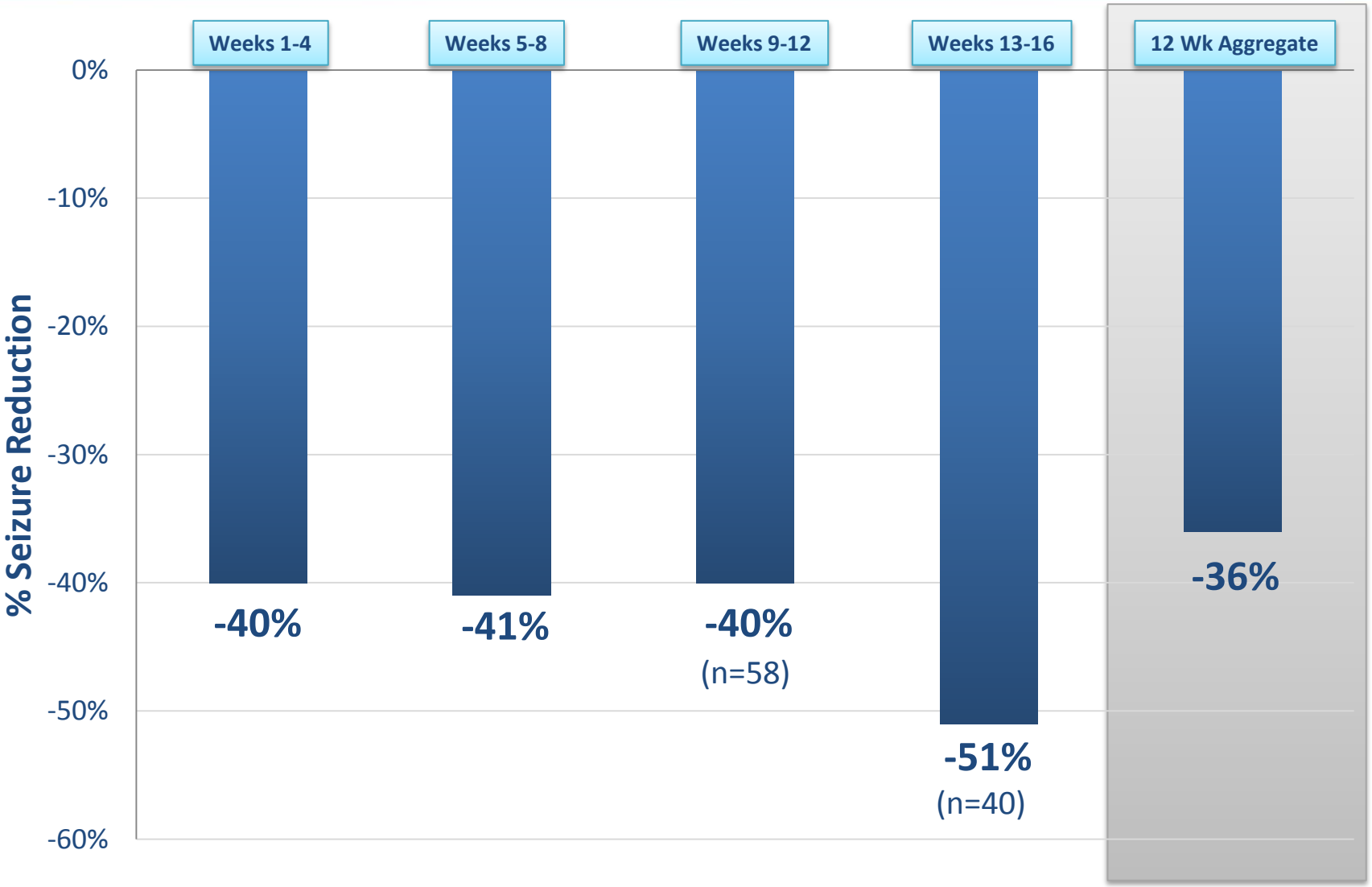
Background and Introduction

- 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

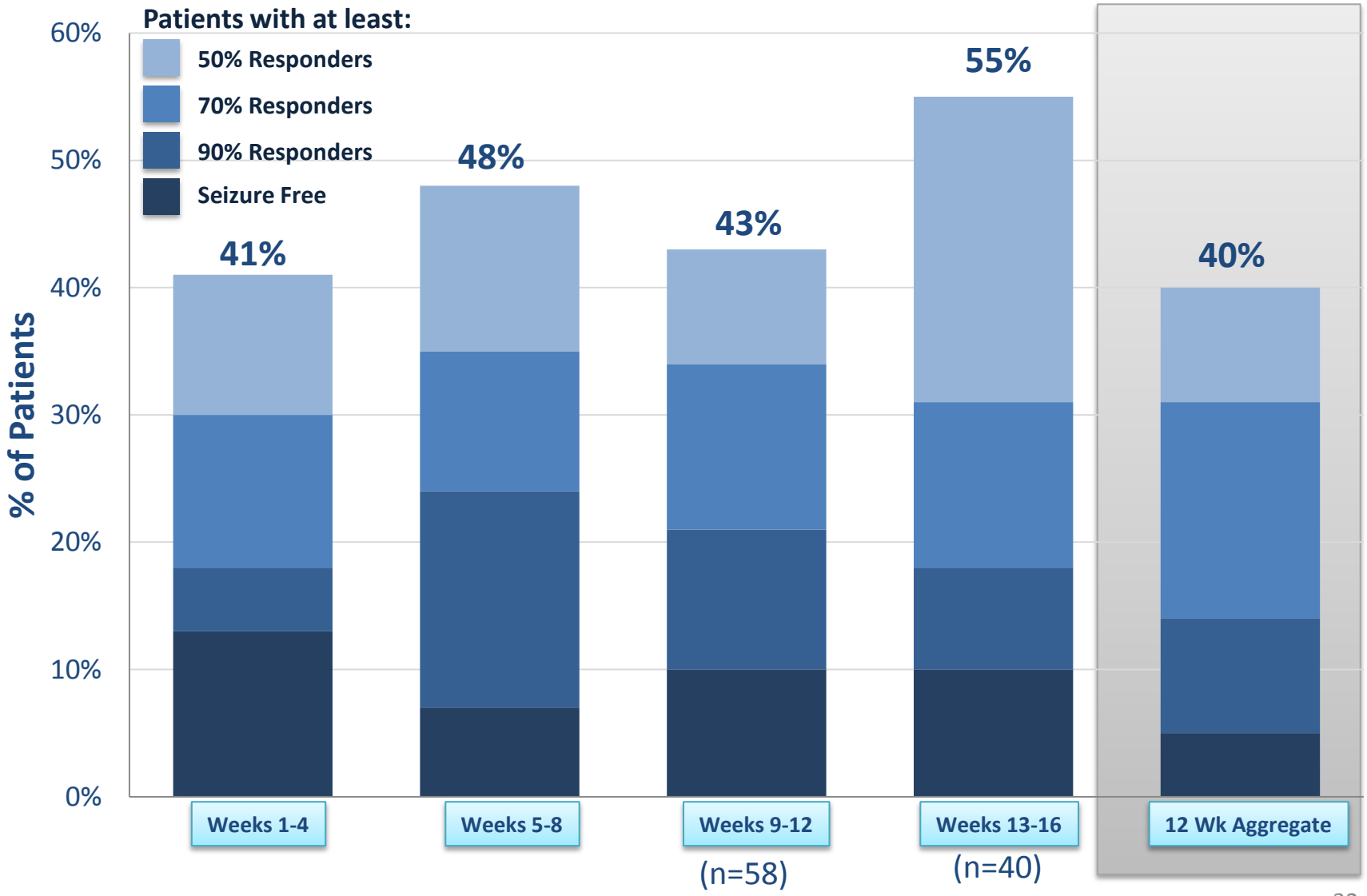
- Treatment-resistant children and young adults (mean age 11 years)
  - Epidiolex added to existing meds. Patients on average 3 other AEDs
- Patients include extreme and rare forms of epilepsy including several patients with major congenital structural brain abnormalities
- Data presented for all 58 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



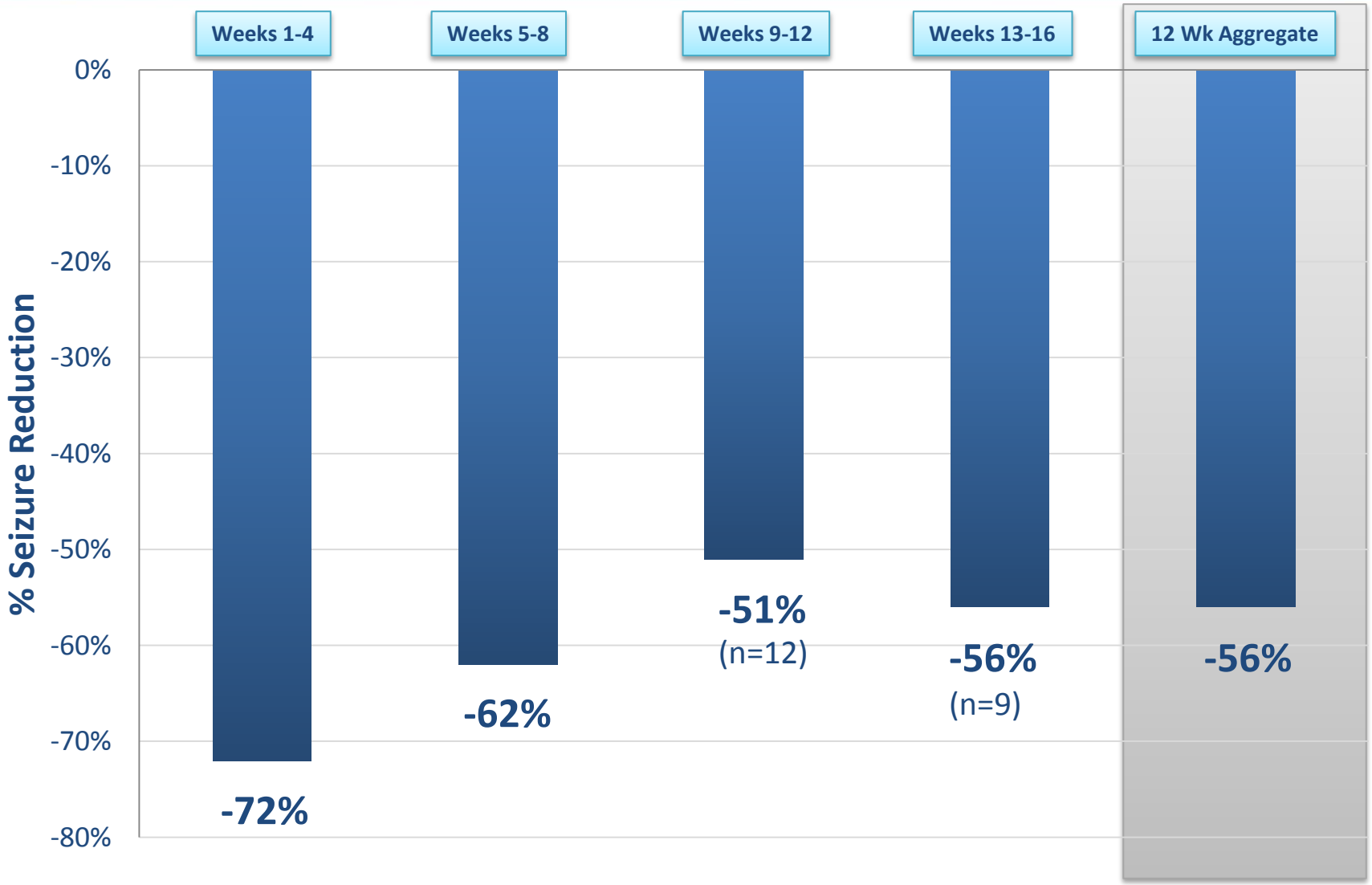
Total Seizures = Convulsive and Non-Convulsive

All Patients (n=58)
All Seizures - Responder Analysis

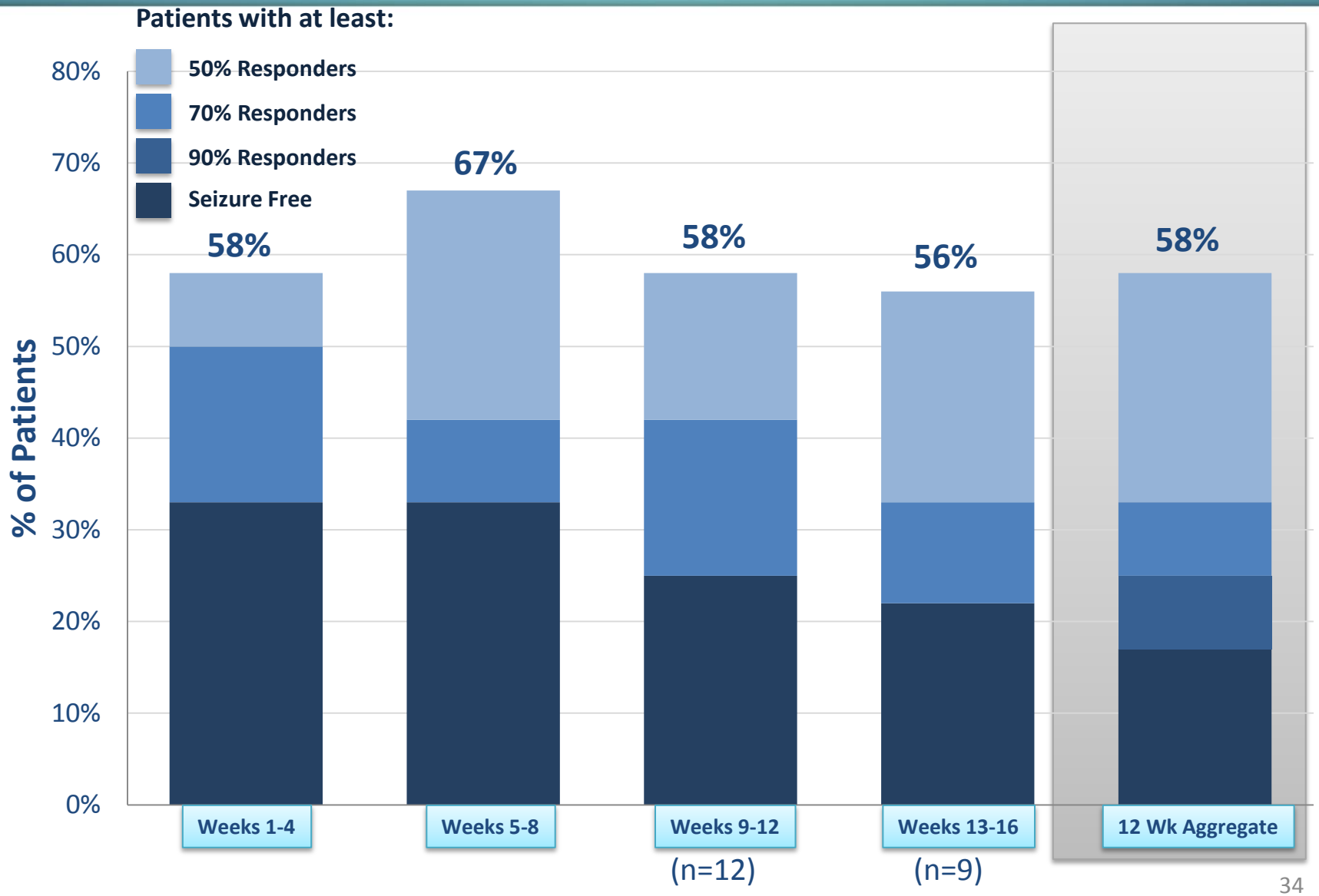


Total Seizures = Convulsive and Non-Convulsive

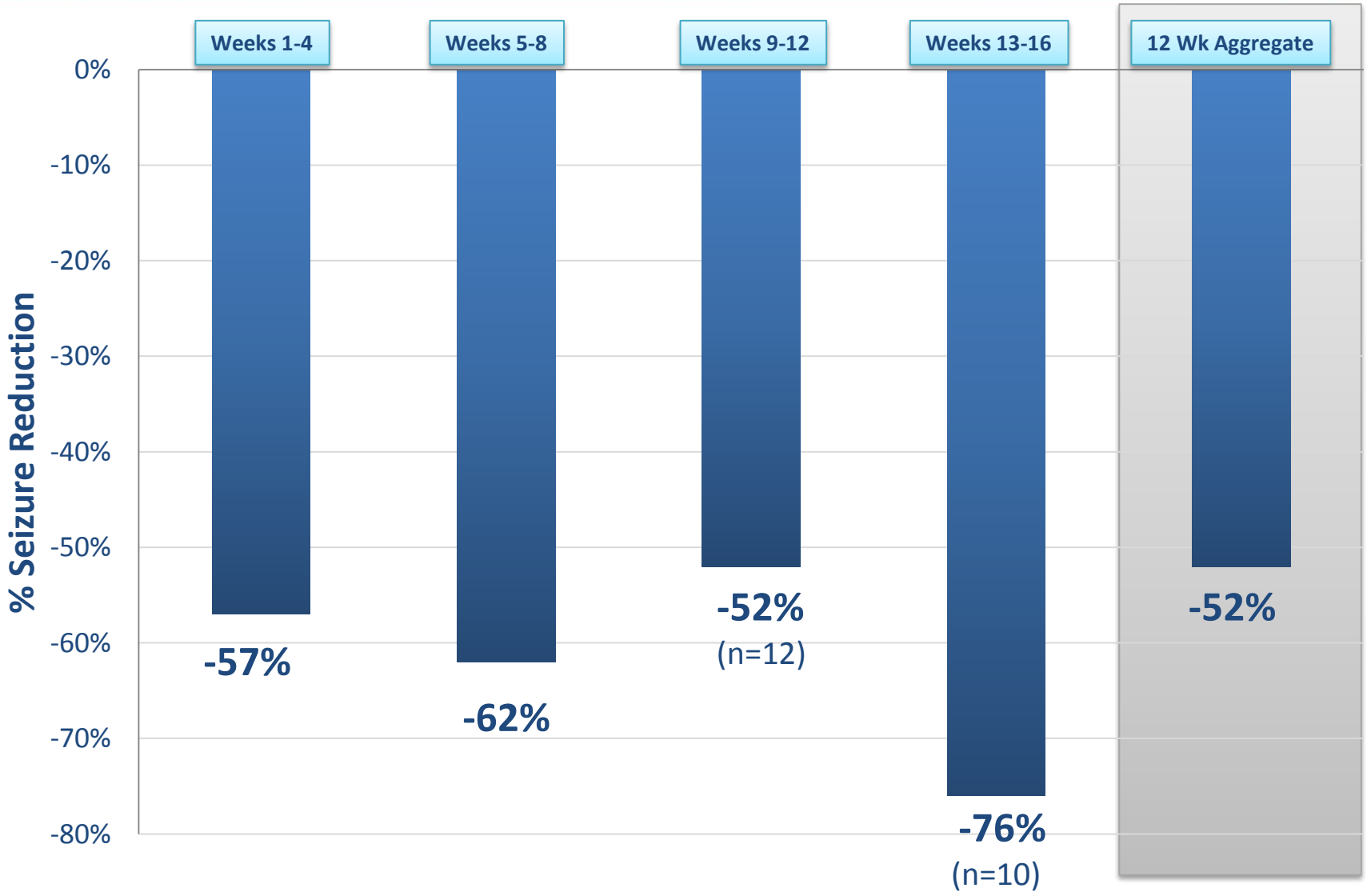
Dravet Syndrome Patients (n=12)
Median % Reduction in Convulsive Seizures



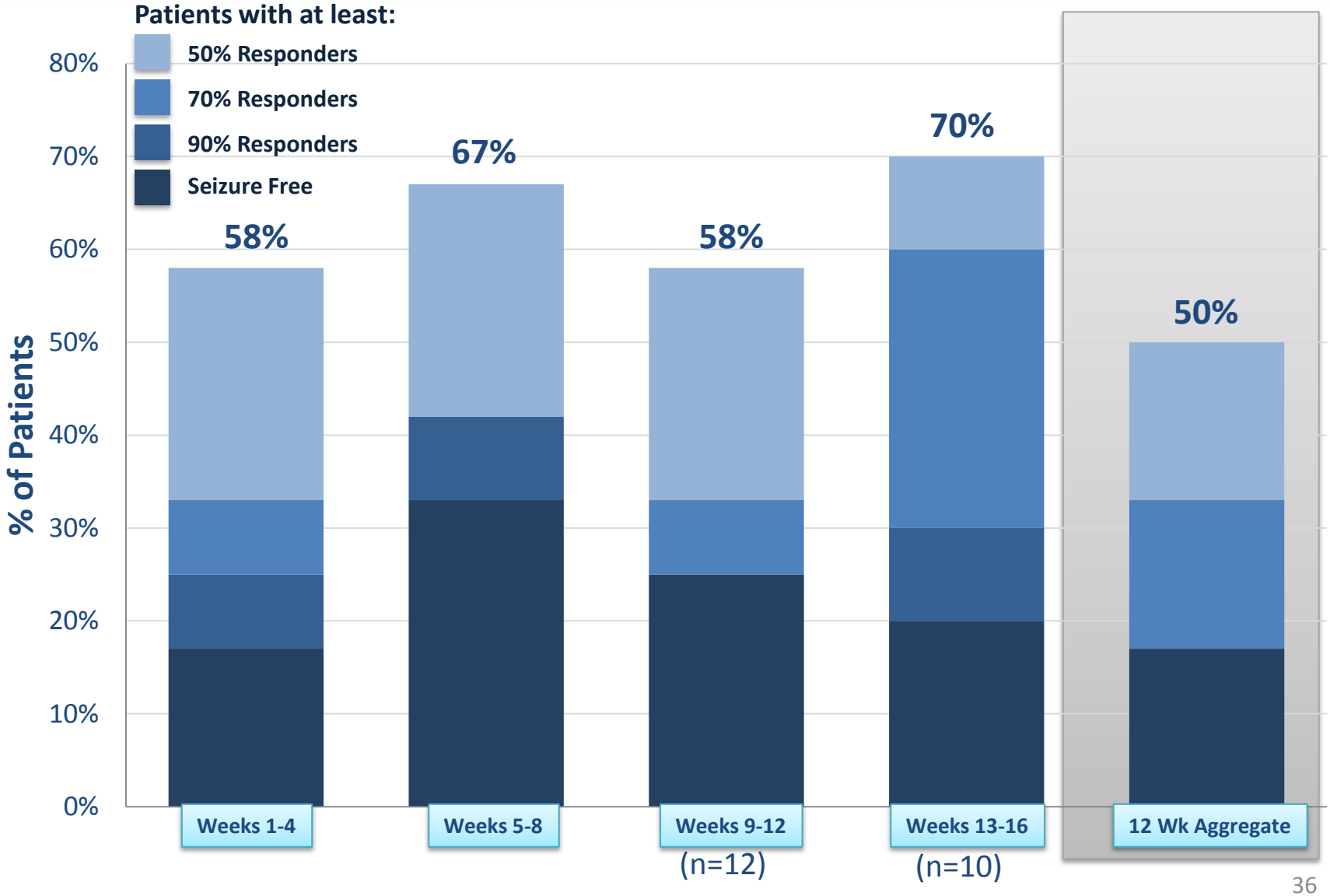
Dravet Syndrome Patients (n=12)
Convulsive Seizures - Responder Analysis



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



All Patients with Atonic ("Drop") Seizures (n=12)
Atonic Seizures - Responder Analysis



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

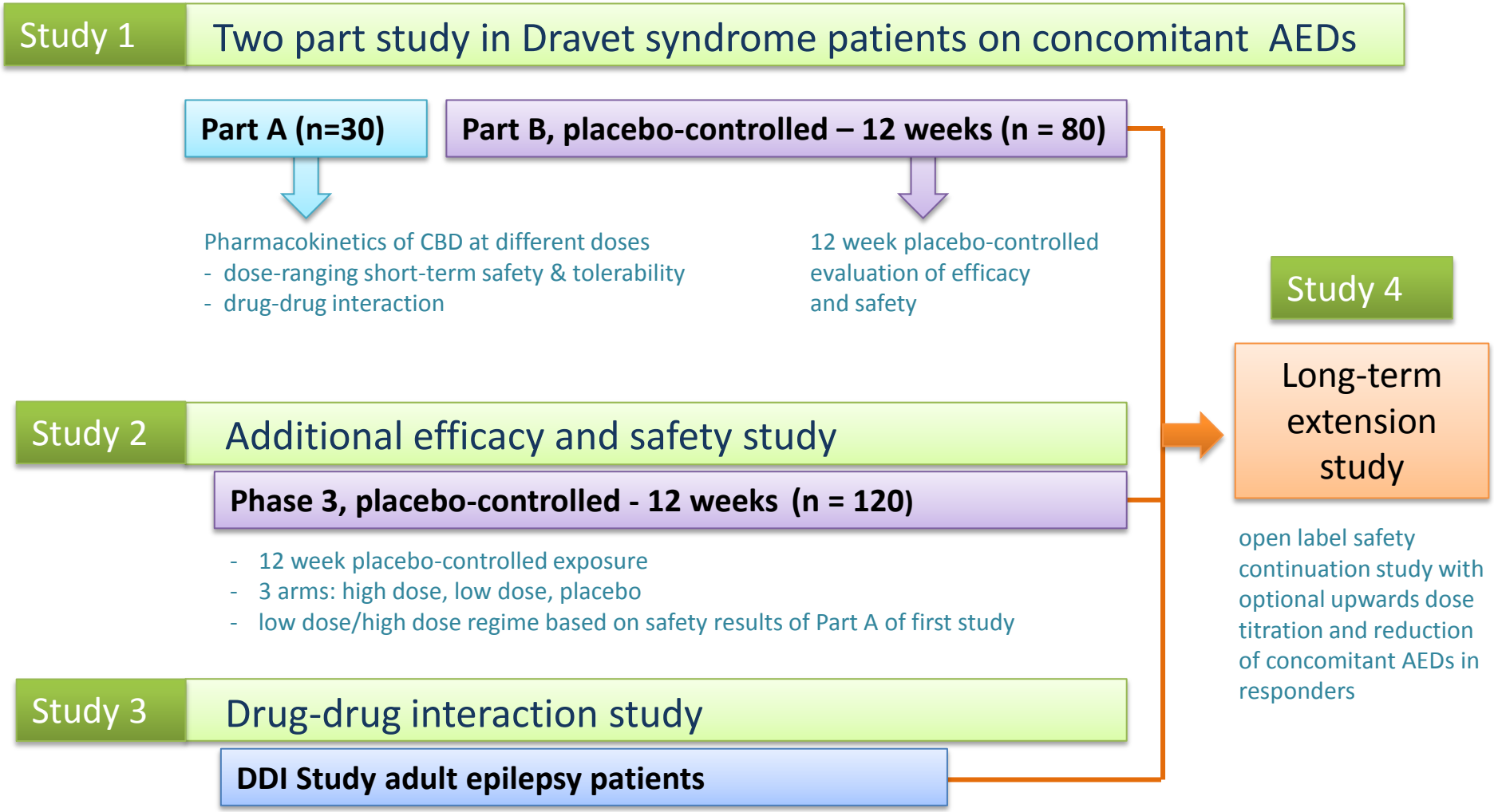
Director, NYU Comprehensive Epilepsy Center

Clinical Program

Overview

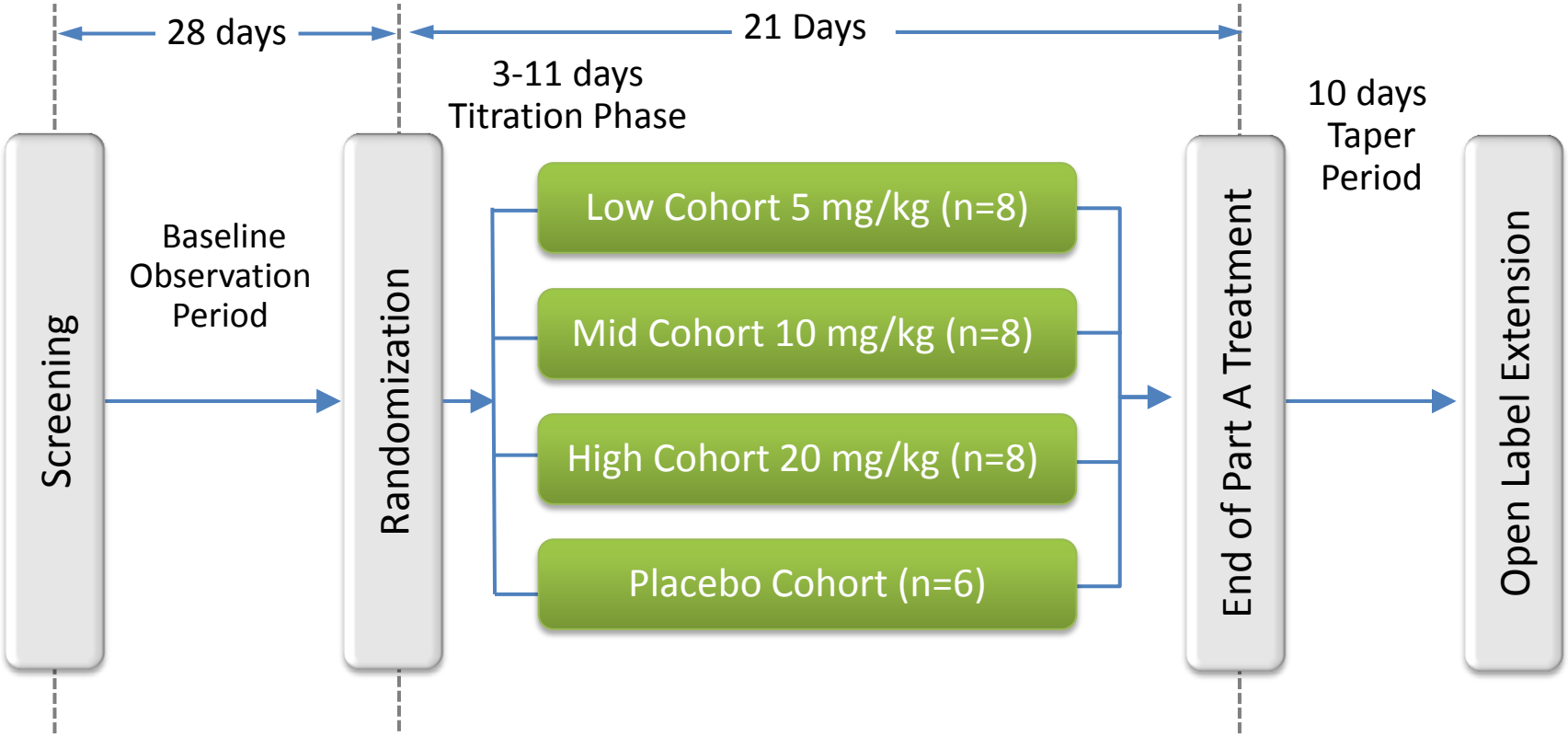
- Formal development programs for Epidiolex in both Dravet syndrome and LGS
- FDA Orphan Drug Designations for Epidiolex for both Dravet syndrome and LGS, as well as Fast Track Designation for Dravet syndrome
- A company-sponsored IND is open with the FDA
- Phase 2/3 Dravet syndrome clinical trial on 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



Epidiolex in Dravet Syndrome
Part A Trial Design

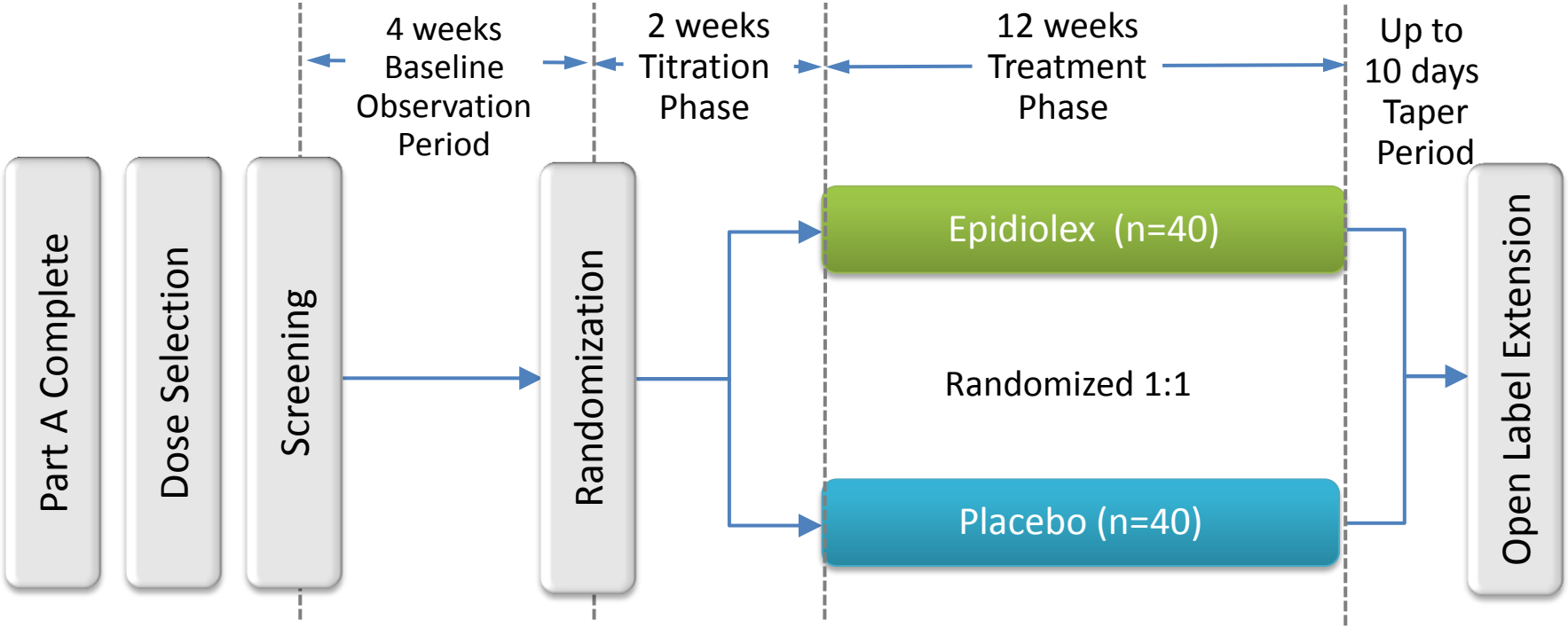
Objective: To determine the safety and dose-related pharmacokinetics of cannabidiol



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

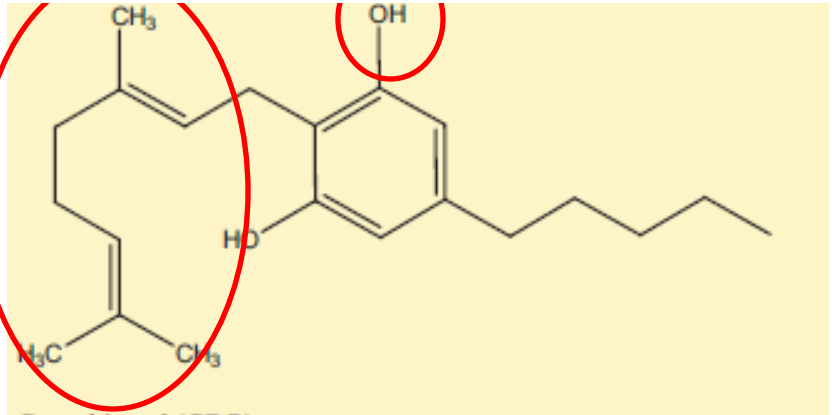
GW pharmaceuticals

British Journal of Pharmacology (2005) 146, 913–915
www.nature.com/bjp

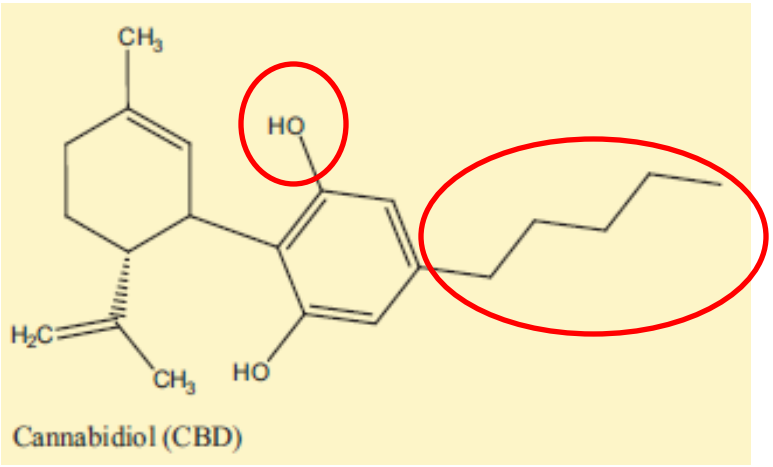
COMMENTARY

Plant cannabinoids: a neglected pharmacological treasure trove

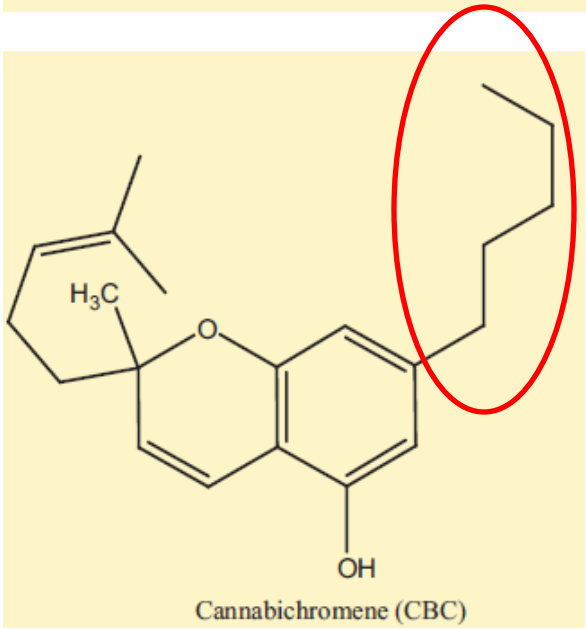
*,[1]Raphael Mechoulam



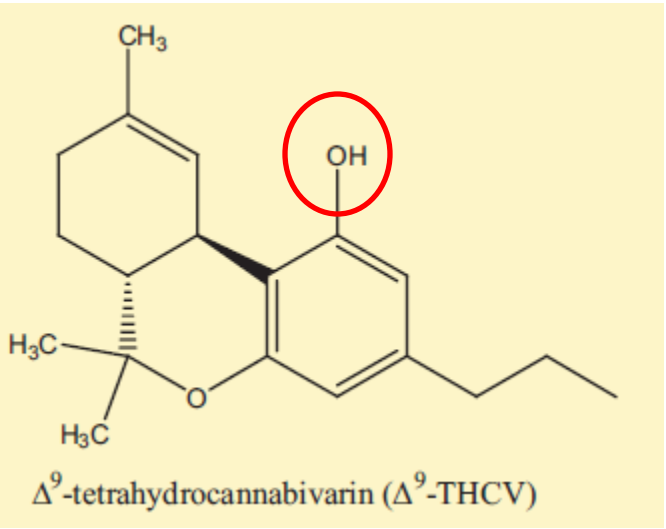
Cannabigerol (CBG)



Cannabidiol (CBD)



Cannabichromene (CBC)



Δ^9-tetrahydrocannabivarin (Δ^9-THCV)

- Propyl analogues
- Methyl analogues
- Sesquiterpene analogues
- Acid precursors
- Others
- **Over 100 phytocannabinoids**

International Research Network:

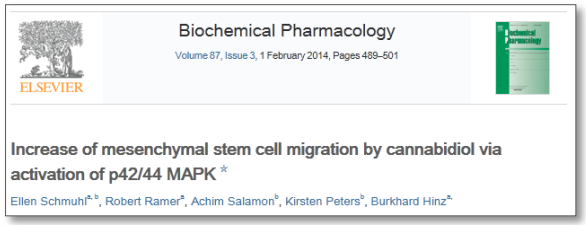
GW is a Pioneer in Funding Cannabinoid Research

Evaluate the potential for the therapeutic use of phytocannabinoids in human disease

Recent successes of the GW-sponsored consortium


The Journal of Clinical Investigation — RESEARCH ARTICLE

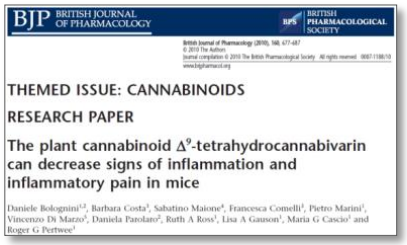
Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes


Biochemical Pharmacology
Volume 87, Issue 3, 1 February 2014, Pages 489–501

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


Caffarel et al. Molecular Cancer 2010, 9:196
MOLECULAR CANCER
RESEARCH — Open Access

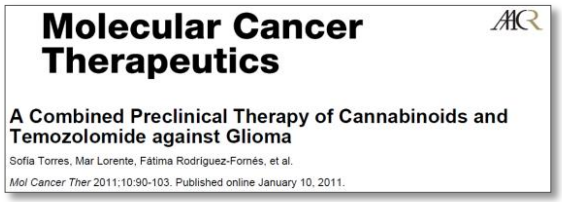
Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition


BJP BRITISH JOURNAL OF PHARMACOLOGY — BPS BRITISH PHARMACOLOGICAL SOCIETY

THEMED ISSUE: CANNABINOIDS

RESEARCH PAPER

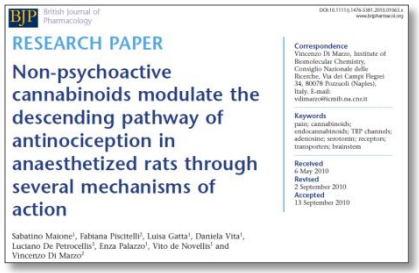
The plant cannabinoid Δ9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice


Molecular Cancer Therapeutics — AACR

A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma

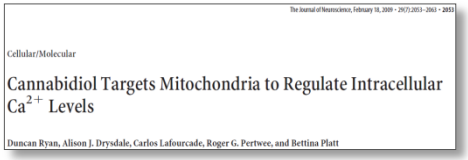
Sofia Torres, Mar Lorente, Fátima Rodríguez-Fornés, et al.

Mol Cancer Ther 2011;10:90-103. Published online January 10, 2011.


BJP British Journal of Pharmacology

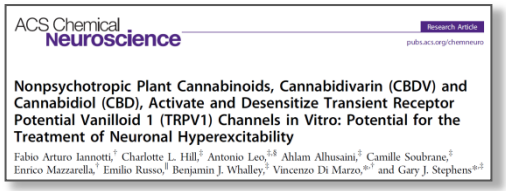
RESEARCH PAPER

Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action


Cellular/Molecular

Cannabidiol Targets Mitochondria to Regulate Intracellular Ca^{2+} Levels

Duncan Ryan, Alison J. Drysdale, Carlos Lafourcade, Roger G. Pertwee, and Bettina Platt


ACS Chemical Neuroscience — Research Article — pubs.acs.org/chemneuro

Nonpsychotropic Plant Cannabinoids, Cannabidivarin (CBDV) and Cannabidiol (CBD), Activate and Desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) Channels in Vitro: Potential for the Treatment of Neuronal Hyperexcitability

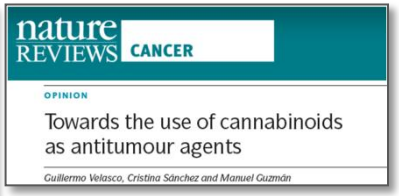

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2012) 367, 3364–3378
doi:10.1098/rstb.2011.0389

Review

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

Alline Cristina Campos[1,2], Fabricio Araújo Moreira[3], Felipe Villela Gomes[4], Elaine Aparecida Del Bel[5] and Francisco Silveira Guimarães[4,*]


nature REVIEWS CANCER

OPINION

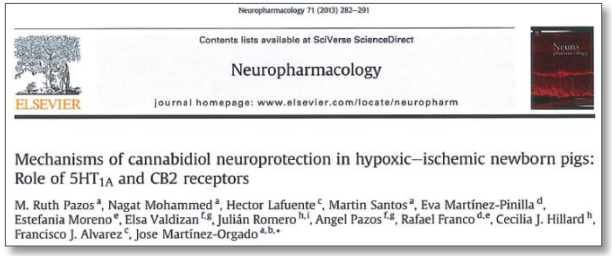
Towards the use of cannabinoids as antitumour agents

Guillermo Velasco, Cristina Sánchez and Manuel Guzmán


BJP British Journal of Pharmacology

RESEARCH PAPER

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

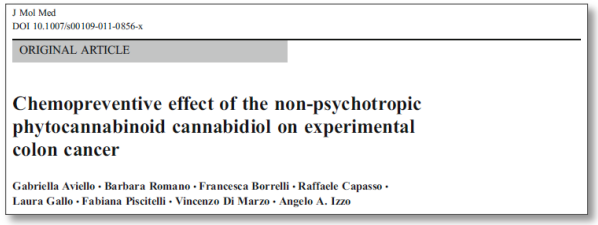

Neuropharmacology 71 (2013) 282–291

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

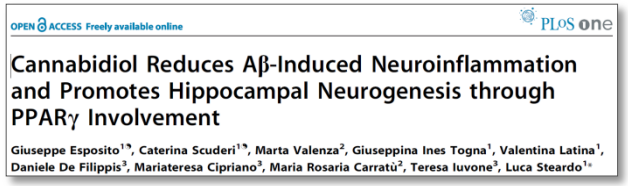
Mechanisms of cannabidiol neuroprotection in hypoxic–ischemic newborn pigs: Role of $5HT_{1A}$ and CB2 receptors


J Mol Med
DOI 10.1007/s00109-011-0856-x

ORIGINAL ARTICLE

Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer

Gabriella Aviello · Barbara Romano · Francesca Borrelli · Raffaele Capasso · Laura Gallo · Fabiana Piscitelli · Vincenzo Di Marzo · Angelo A. Izzo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Cannabidiol Reduces Aβ-Induced Neuroinflammation and Promotes Hippocampal Neurogenesis through PPARγ Involvement

Giuseppe Esposito[1☯], Caterina Scuderi[1☯], Marta Valenza[2], Giuseppina Ines Togna[1], Valentina Latina[1], Daniele De Filippis[3], Mariateresa Cipriano[3], Maria Rosaria Carratù[2], Teresa Iuvone[3], Luca Steardo[1*]

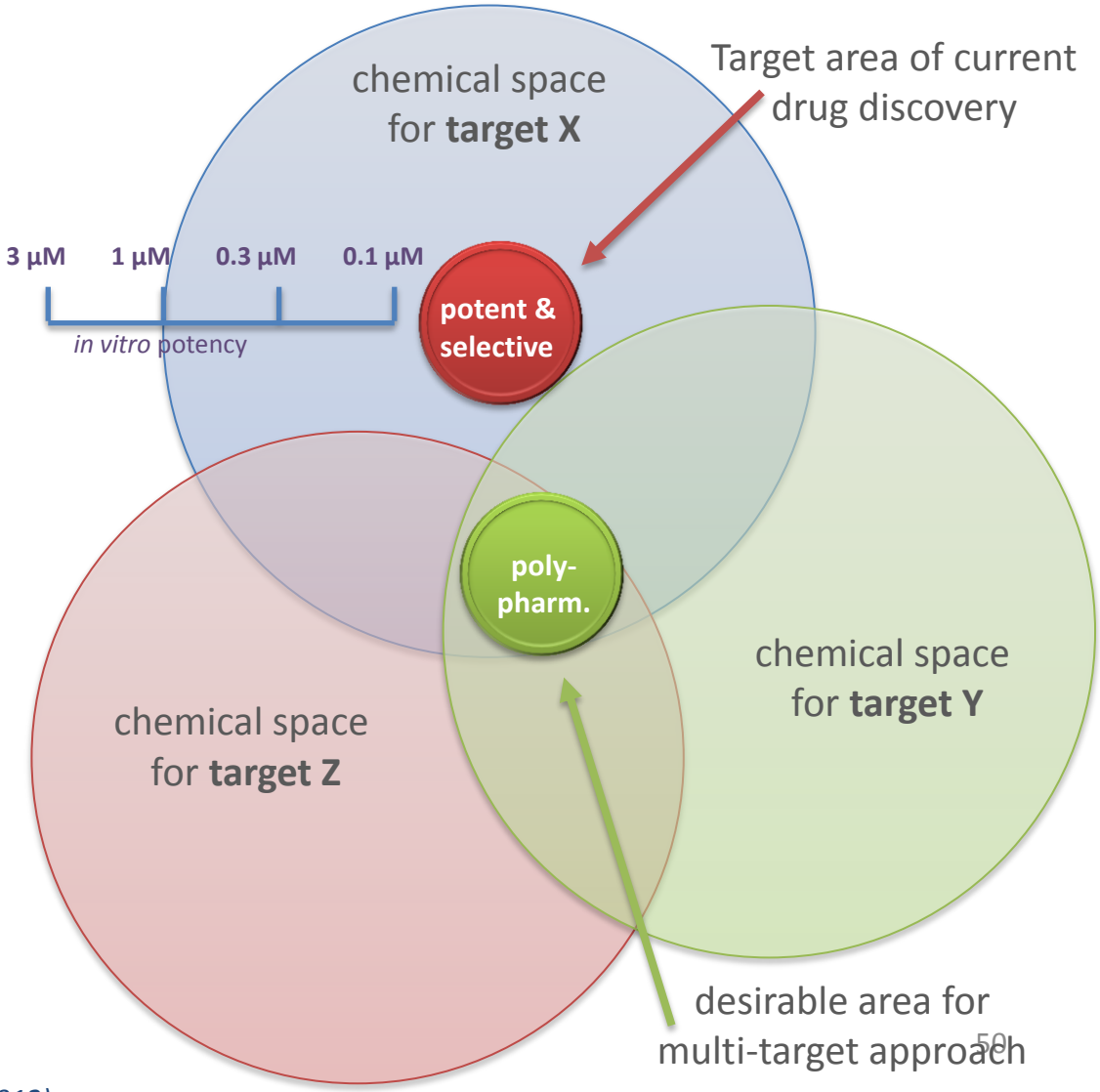
GW-sponsored preclinical studies published to date > 80

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

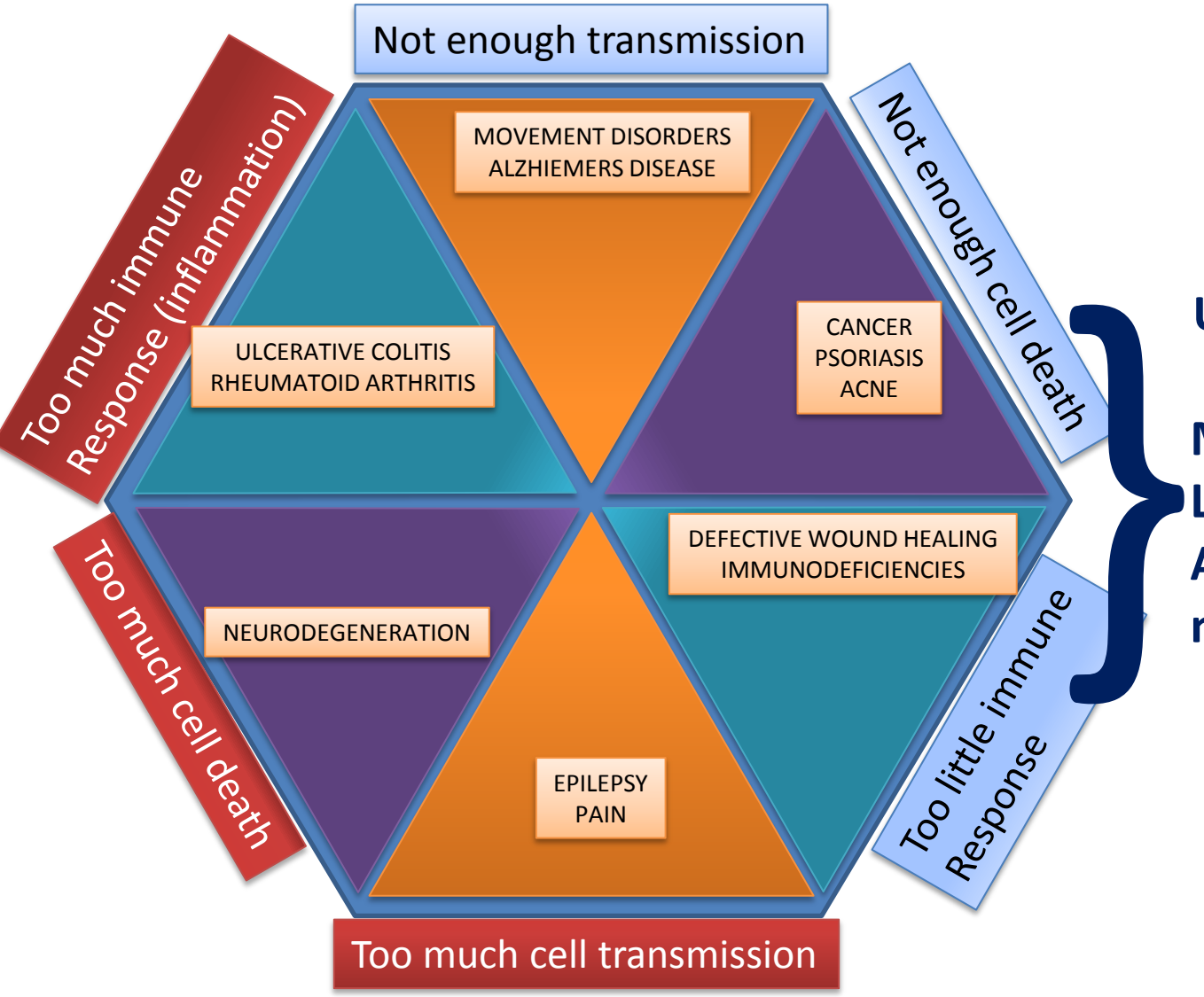
- 1 single ultra-potent “selective” compound->1 target ->1 disease only seldom works
  - Wrong assumption, a magic bullet may treat one of many relevant targets but this is not enough to affect a disease
  - Instead it may cause homeostatic unbalance in organs in which that target is not malfunctioning,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

Revisiting an old Paradigm to Treat Disease



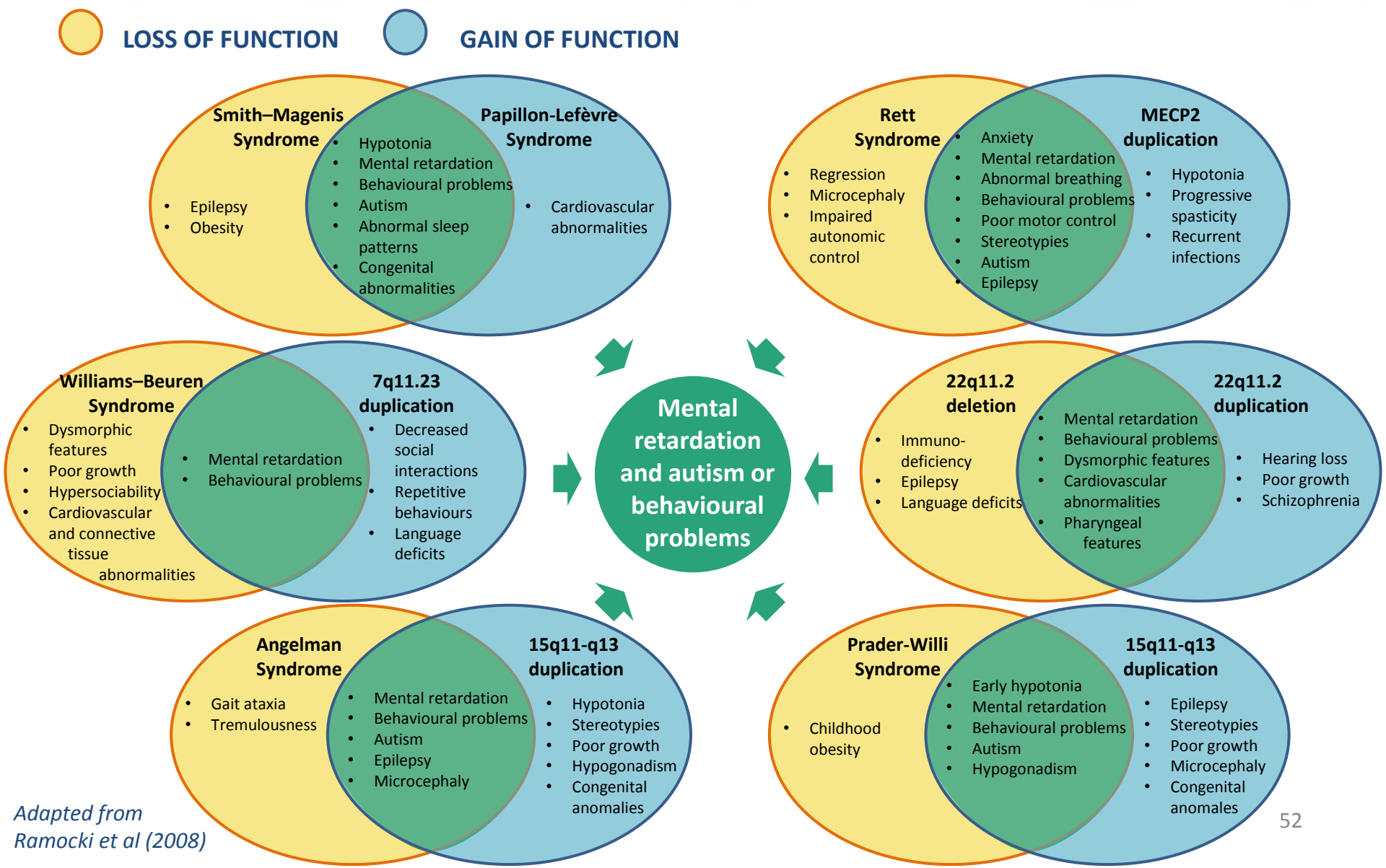
Adapted from Pang et al. (2012)

Diseases are at the opposite ends of unbalanced physiological "modes" (in a time and organ-dependent manner)



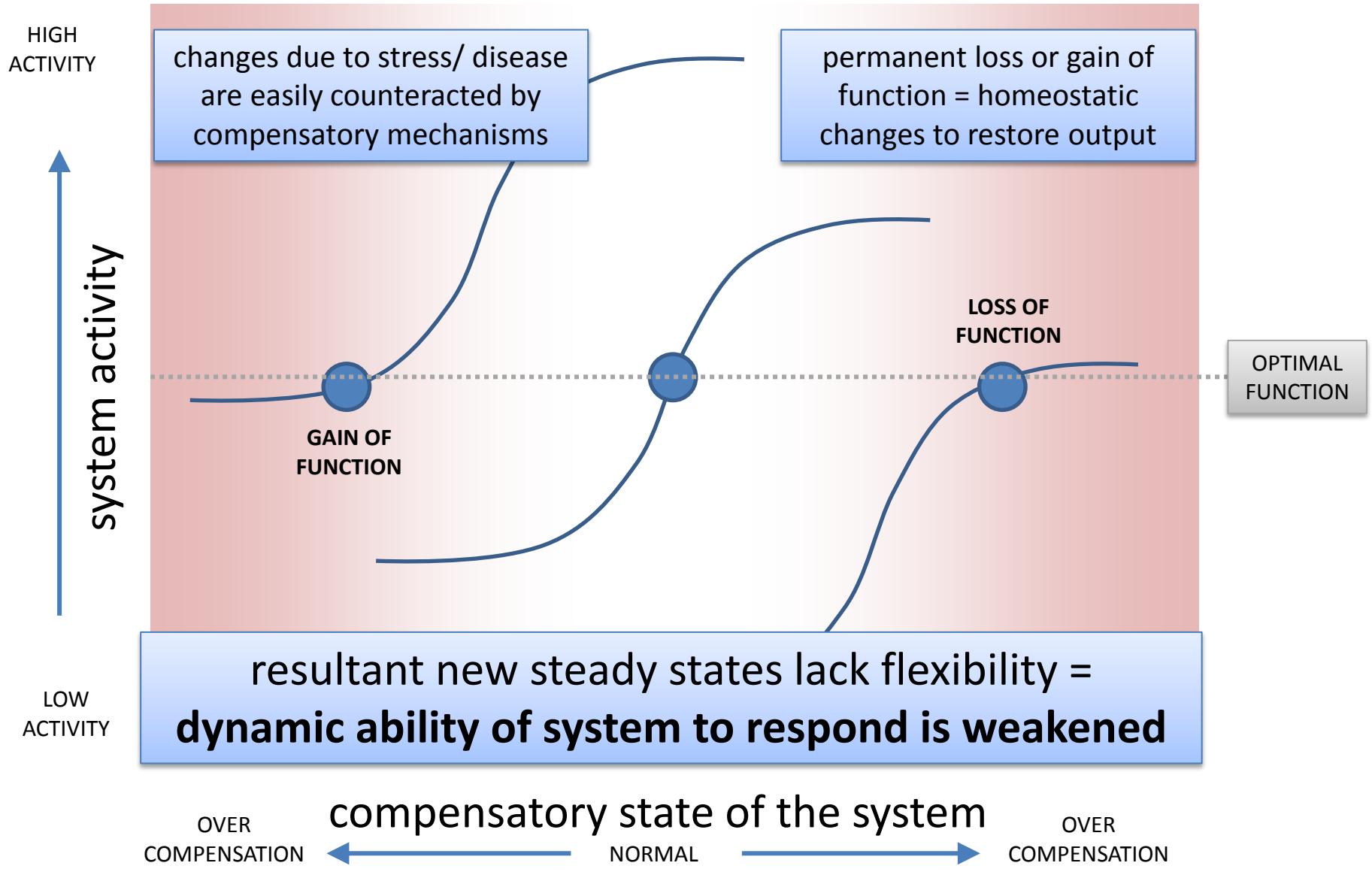
UNBALANCED ENERGY CONTROL:
Mitochondrial &
Lysosomial activity
Autophagy
mTOR activity

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

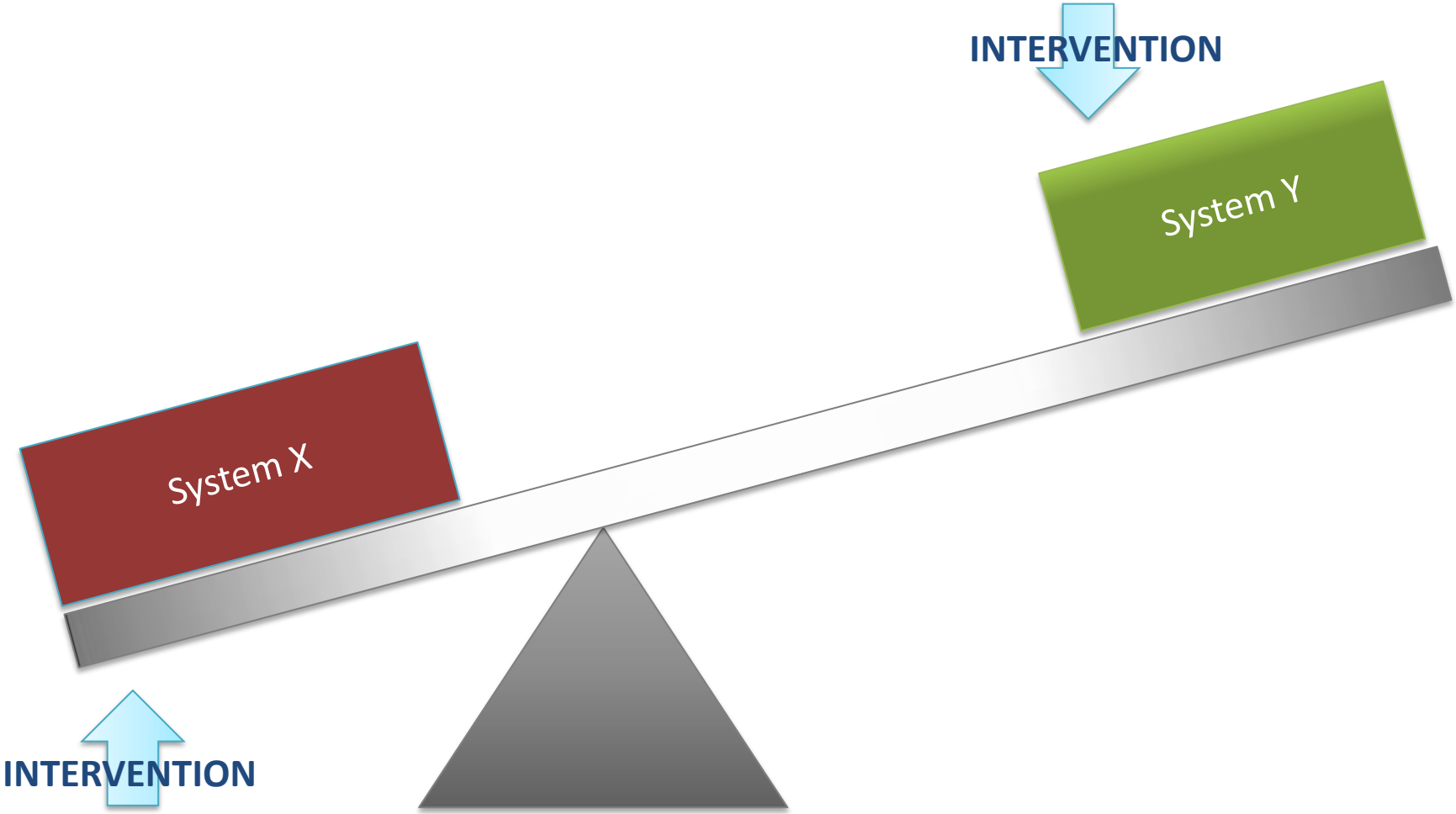


Adapted from Ramocki et al (2008)

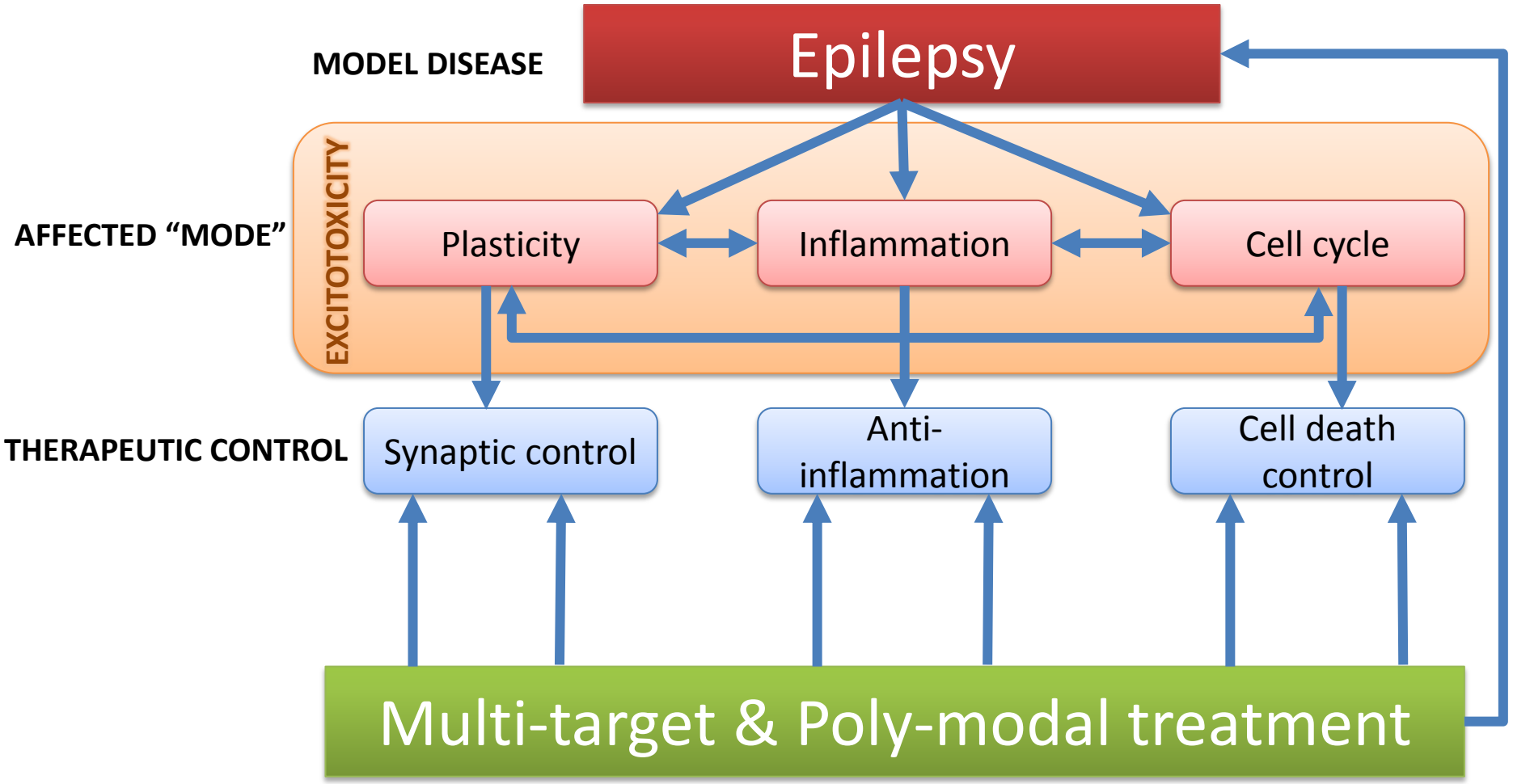
Homeostatic perturbations change the system set-point thus making treatment more complicated



Homeostatic perturbations change the system set-point thus making treatment more complicated



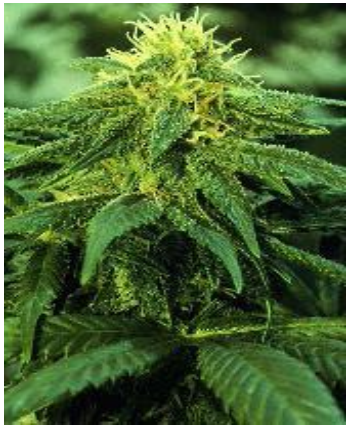
Epilepsy as a model disease to investigate the advantages of polymodal medicines

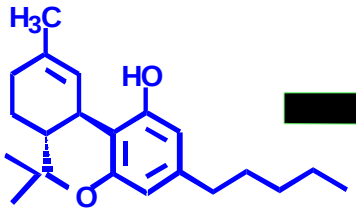


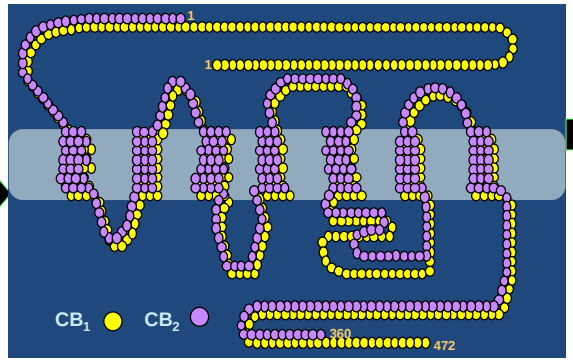
Summary 1: the "ideal" pharmacological treatment for multi-factorial disorders

- 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 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 inbalance of more physiological "modes" (cell plasticity, cell cycle, immune response, energy control). *This may clash with the idea of tissue-selective drugs*

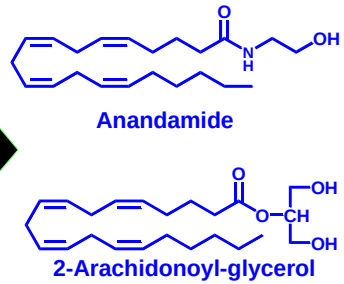
Plant cannabinoids: THC and the endocannabinoid system (ECS)





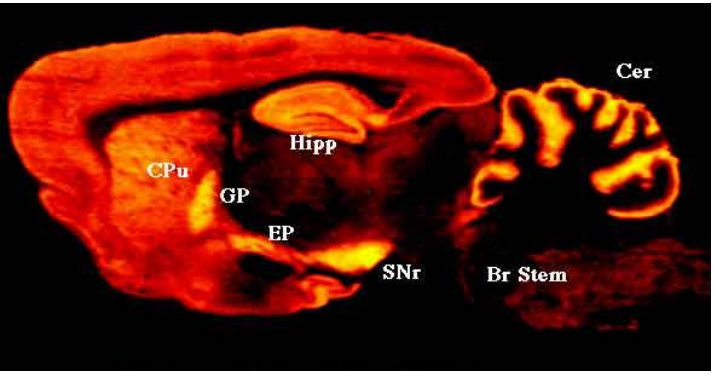


Cannabinoid receptors

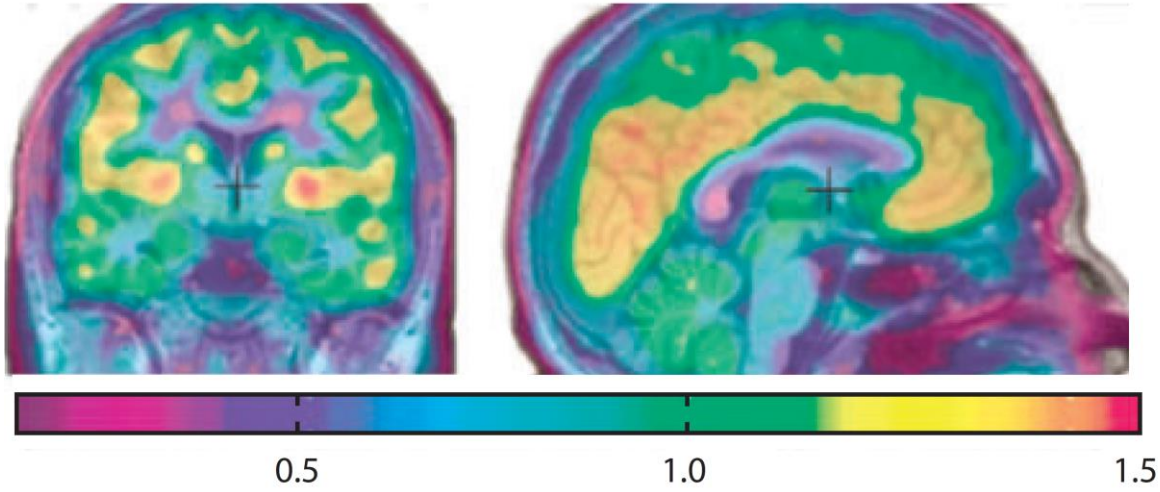


Endocannabinoids

Rat



Human



Endocannabinoids and the regulation of their tissue levels

Endocannabinoids:

1) are produced "<u>on demand</u>"

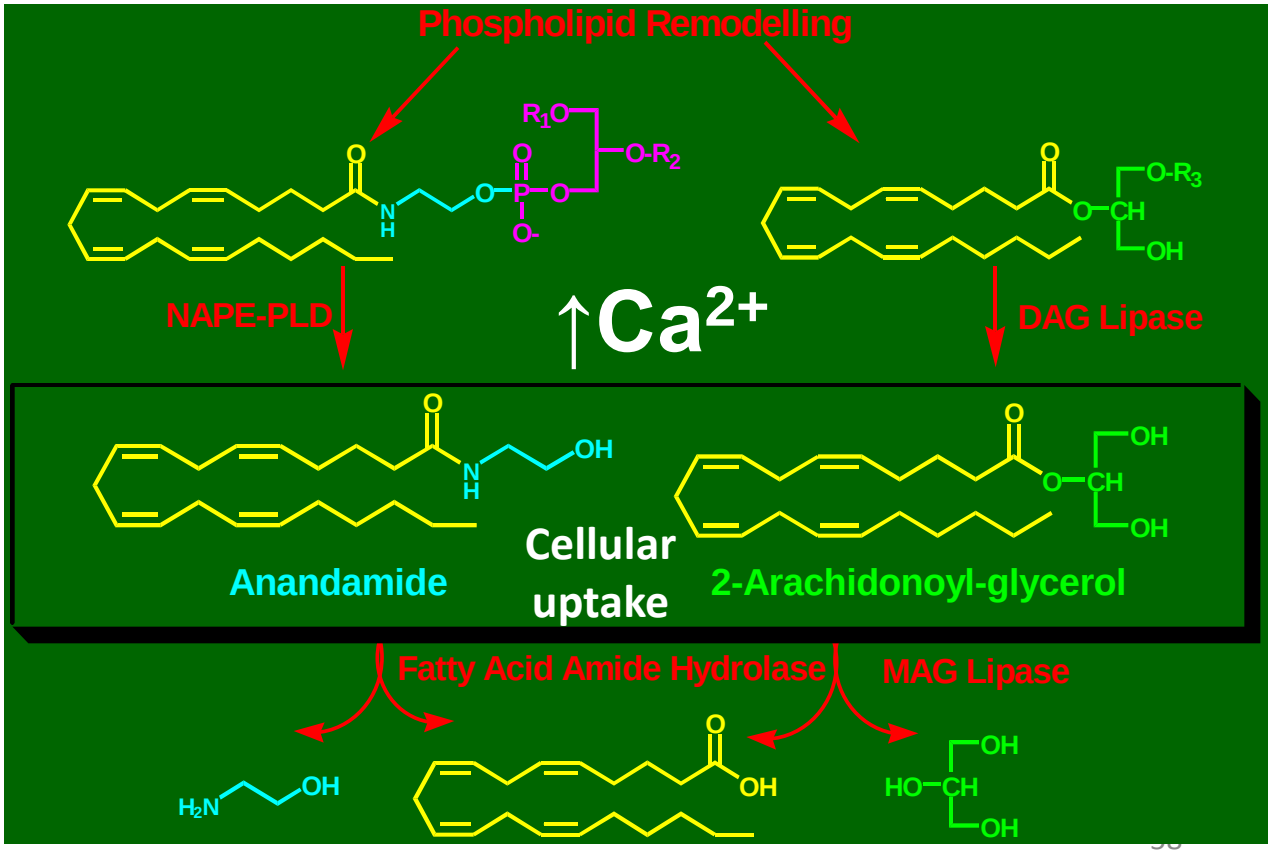
2) activate cannabinoid CB_1 and CB_2 receptors <u>locally</u>

3) are immediately <u>metabolized</u>

Phospholipid-derived precursors

Endocannabinoids

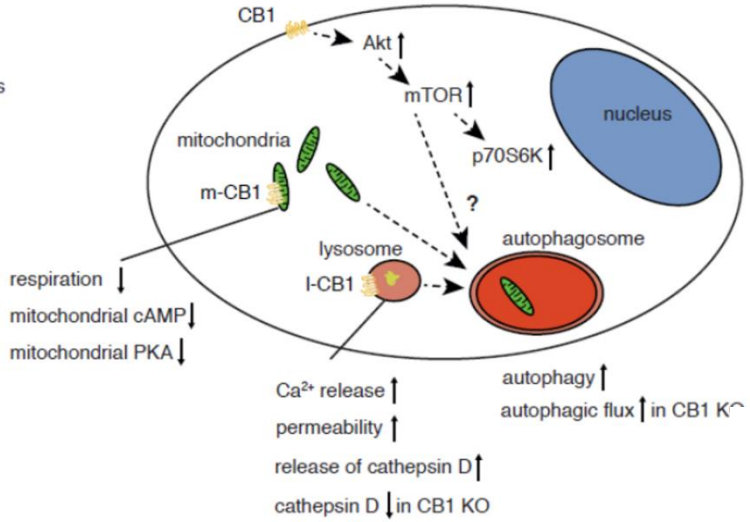
Degradation products



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

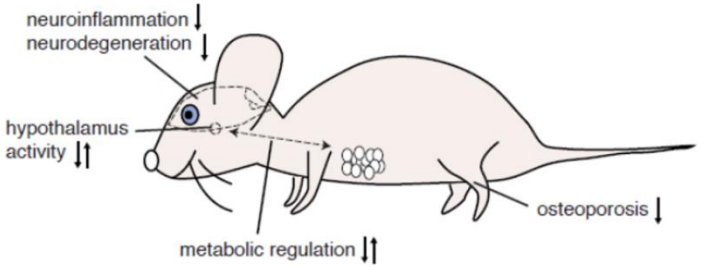
A Cell level

impaired mitochondrial functions
disrupted proteasis
disrupted nutrient sensing pathways



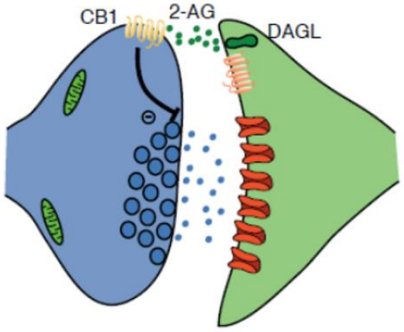
C Organism level

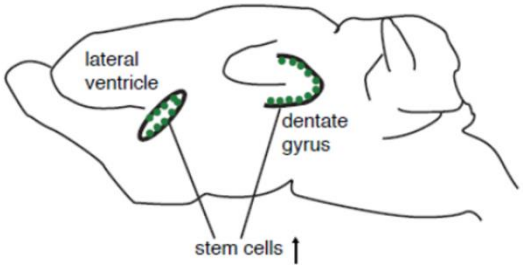
inflammaging
dysregulated homeostasis



B Tissue level

impaired intercellular communication
stem cell exhaustion





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

PNAS

A restricted population of CB_1 cannabinoid receptors with neuroprotective activity

Anna Chiarlone[a,b,1], Luigi Bellocchio[a,b,1], Cristina Blázquez[a,b], Eva Resel[a,b], Edgar Soria-Gómez[c,d], Astrid Cannich[c,d], José J. Ferrero[e], Onintza Sagredo[a,f], Cristina Benito[g], Julián Romero[g], José Sánchez-Prieto[e], Beat Lutz[h], Javier Fernández-Ruiz[a,f], Ismael Galve-Roperh[a,b], and Manuel Guzmán[a,b,2]

[a]Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas, Instituto Ramón y Cajal de Investigación Sanitaria, 28040 Madrid, Spain; [b]Department of Biochemistry and Molecular Biology I, Instituto Universitario de Investigación Neuroquímica, Complutense University, 28040 Madrid, Spain; [c]NeuroCentre Magendie U862, Endocannabinoids and Neuroadaptation, Institut National de la Santé et de la Recherche Médicale, 33077 Bordeaux, France; [d]NeuroCentre Magendie U862, University of Bordeaux, 33077 Bordeaux, France; [e]Department of Biochemistry and Molecular Biology IV, Complutense University, 28040 Madrid, Spain; [f]Department of Biochemistry and Molecular Biology III, Instituto Universitario de Investigación Neuroquímica, Complutense University, 28040 Madrid, Spain; [g]Research Unit, Hospital Universitario Fundación Alcorcón, 28922 Madrid, Spain; and [h]Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, 55099 Mainz, Germany

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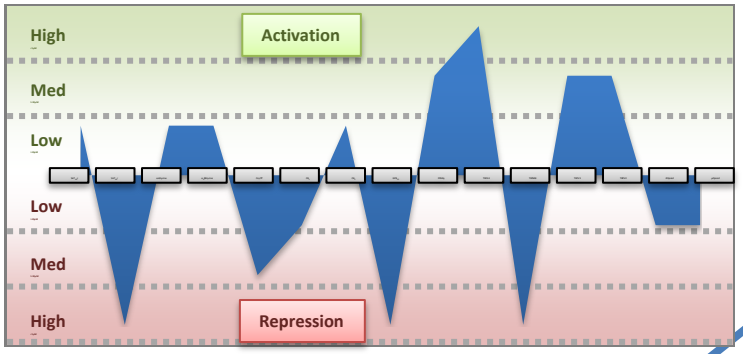
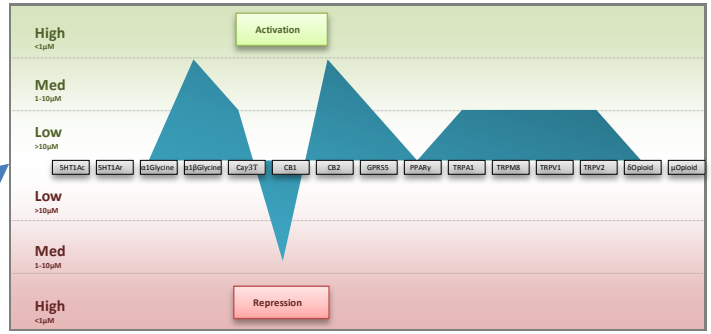
ELSEVIER

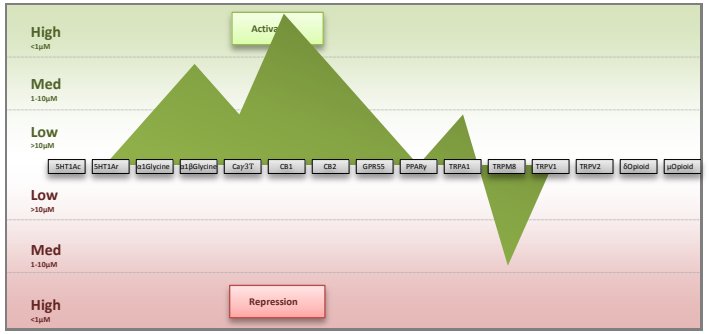
Genetic rescue of CB_1 receptors on medium spiny neurons prevents loss of excitatory striatal synapses but not motor impairment in HD mice

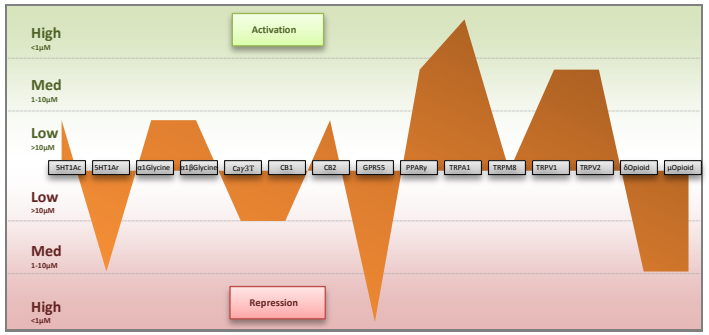
Alipi V. Naydenov [a,b], Marja D. Sepers [c], Katie Swinney [d], Lynn A. Raymond [c], Richard D. Palmiter [e], Nephi Stella [d,*]

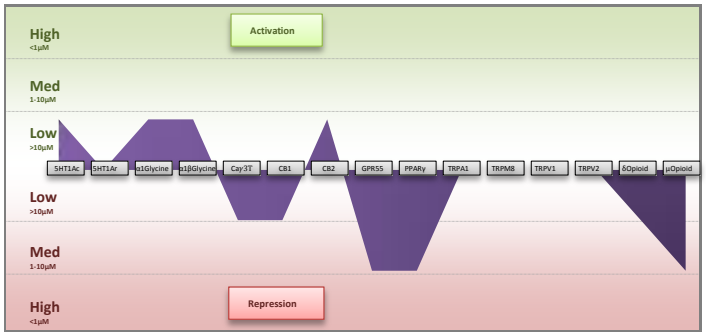
Plant cannabinoids are multi-target

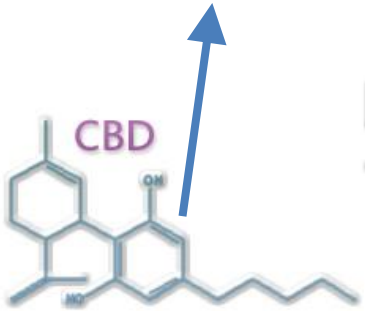


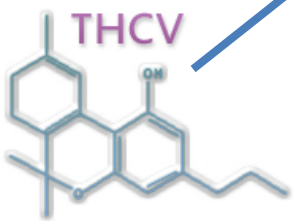


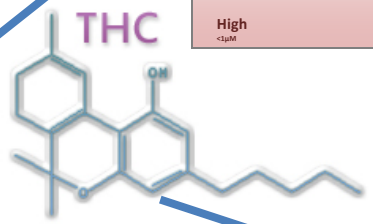


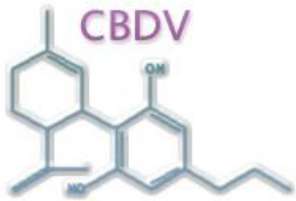




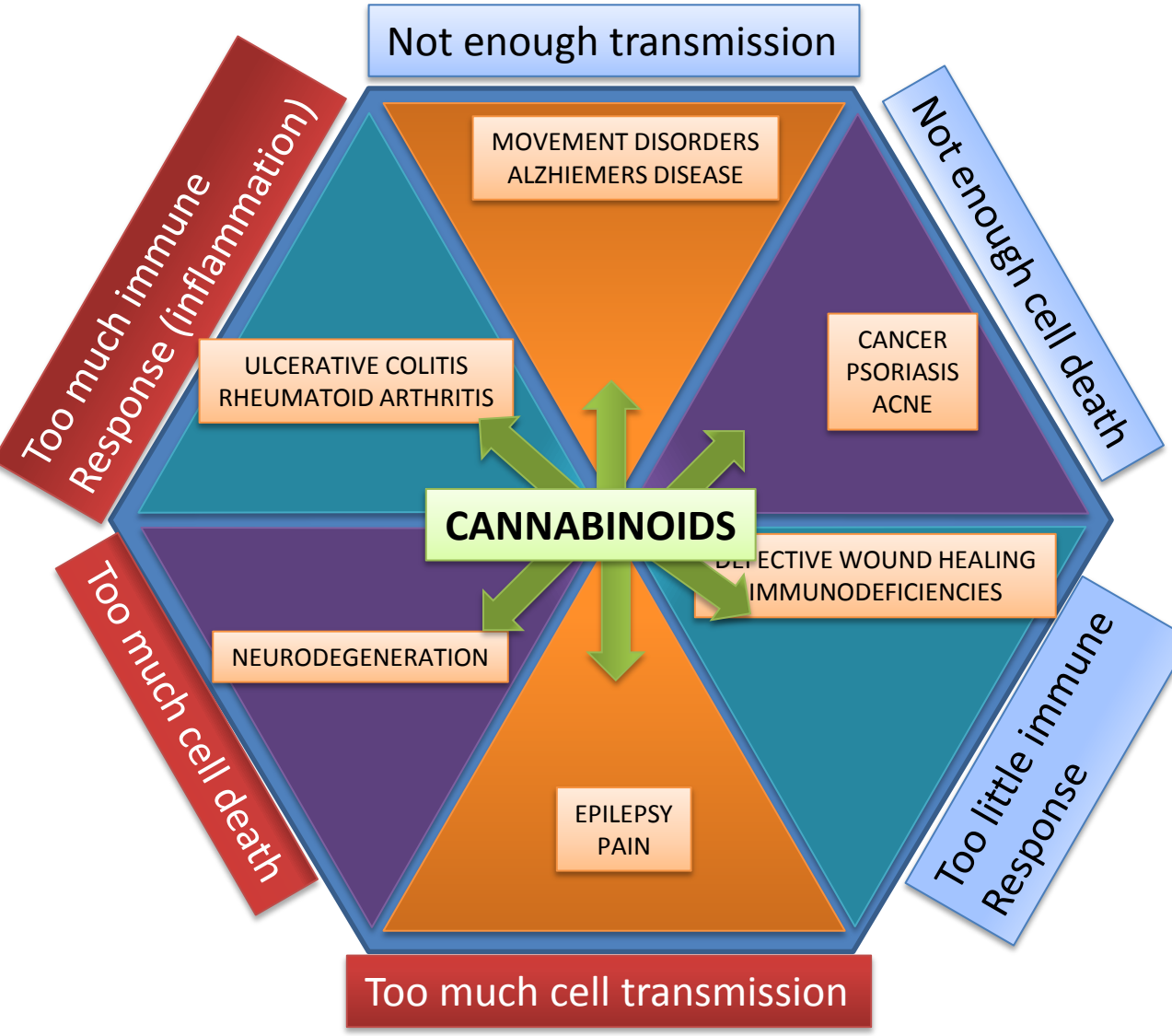








Plant cannabinoids are multi-modal pro-homeostatic compounds



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

1) **mTOR and autophagy**
2) **mitochondrial function**
3) **ROS formation**

Cannabidiol pharmacological fingerprint “shakes hands” with the aethiopathology of epilepsy

Keppra

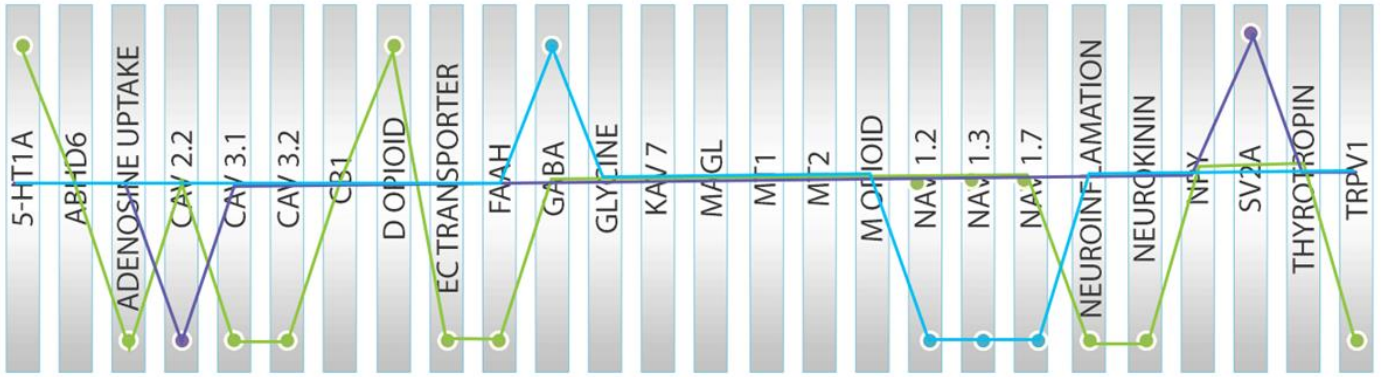
Valproate

Cannabidiol

CBD + Keppra

CBD + Valproate

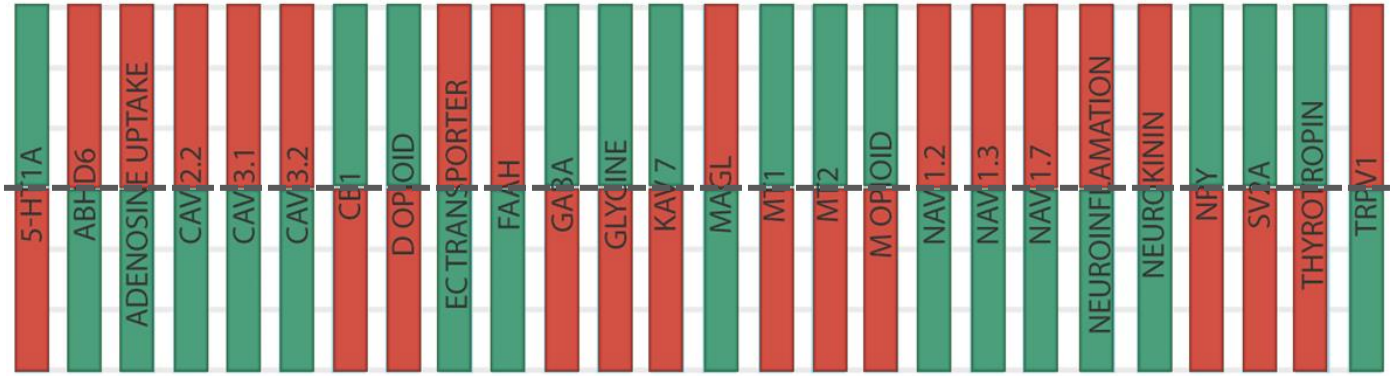
POLYPHARMACOLOGICAL FINGERPRINT



AETIOPATHOPHYSIOLOGICAL FINGERPRINT

ACTIVATE TARGET

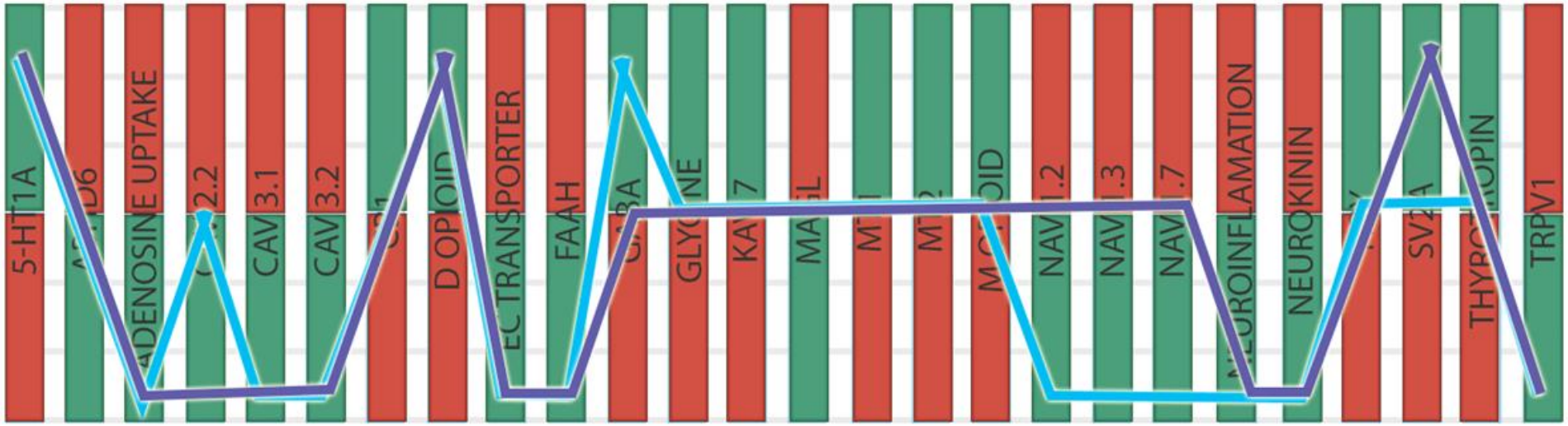
REPRESS TARGET



beneficial **detrimental**

Cannabidiol pharmacological fingerprint “shakes hands” with the aethiopathology of epilepsy

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

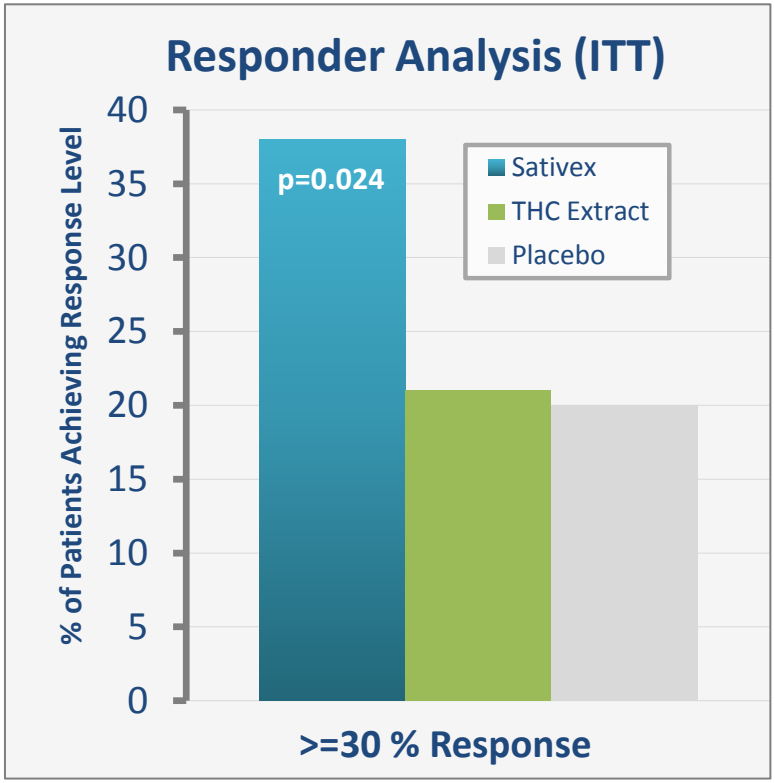


Two is better than one…..

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

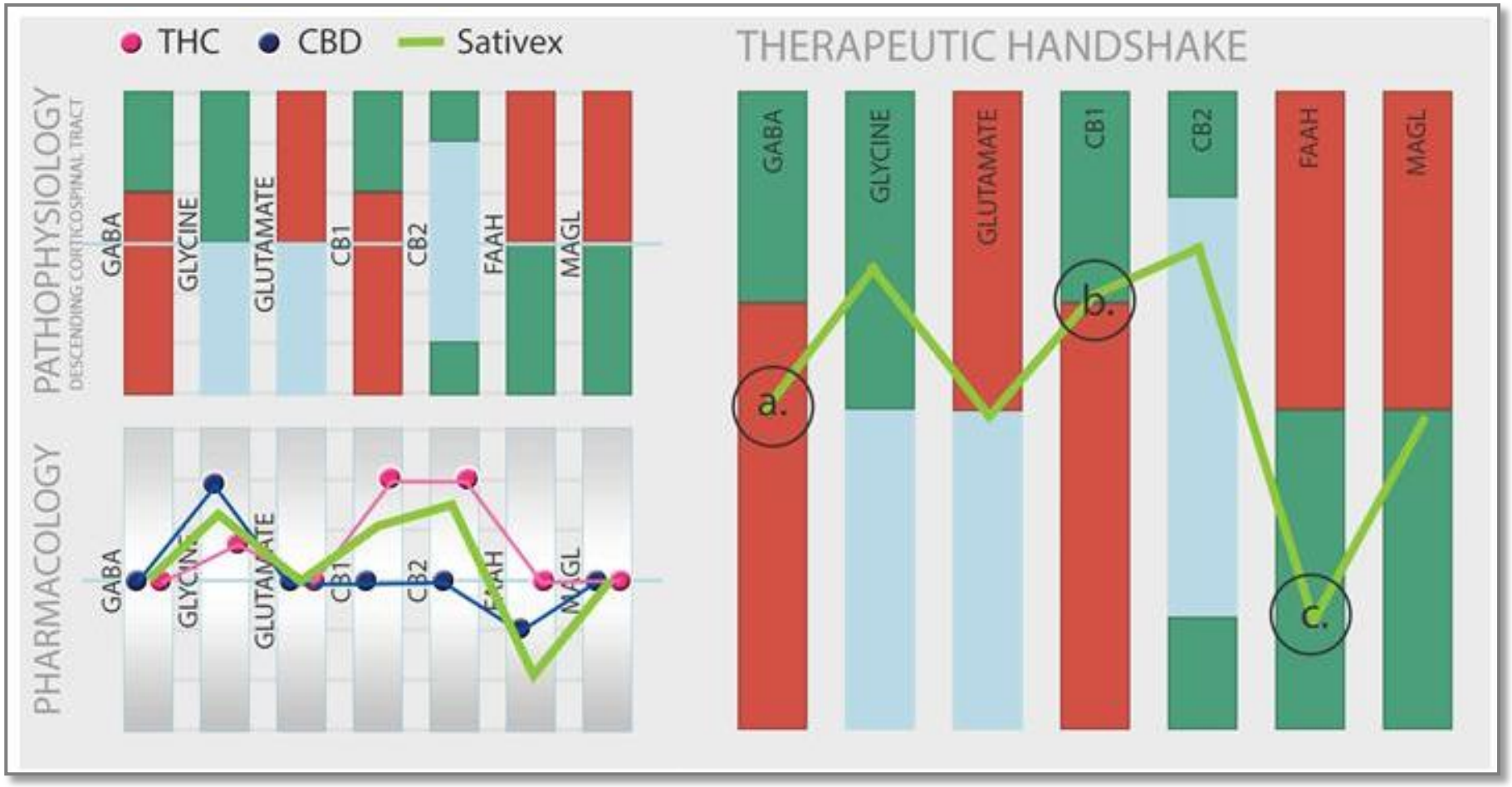
(Johnson et al, 2010):



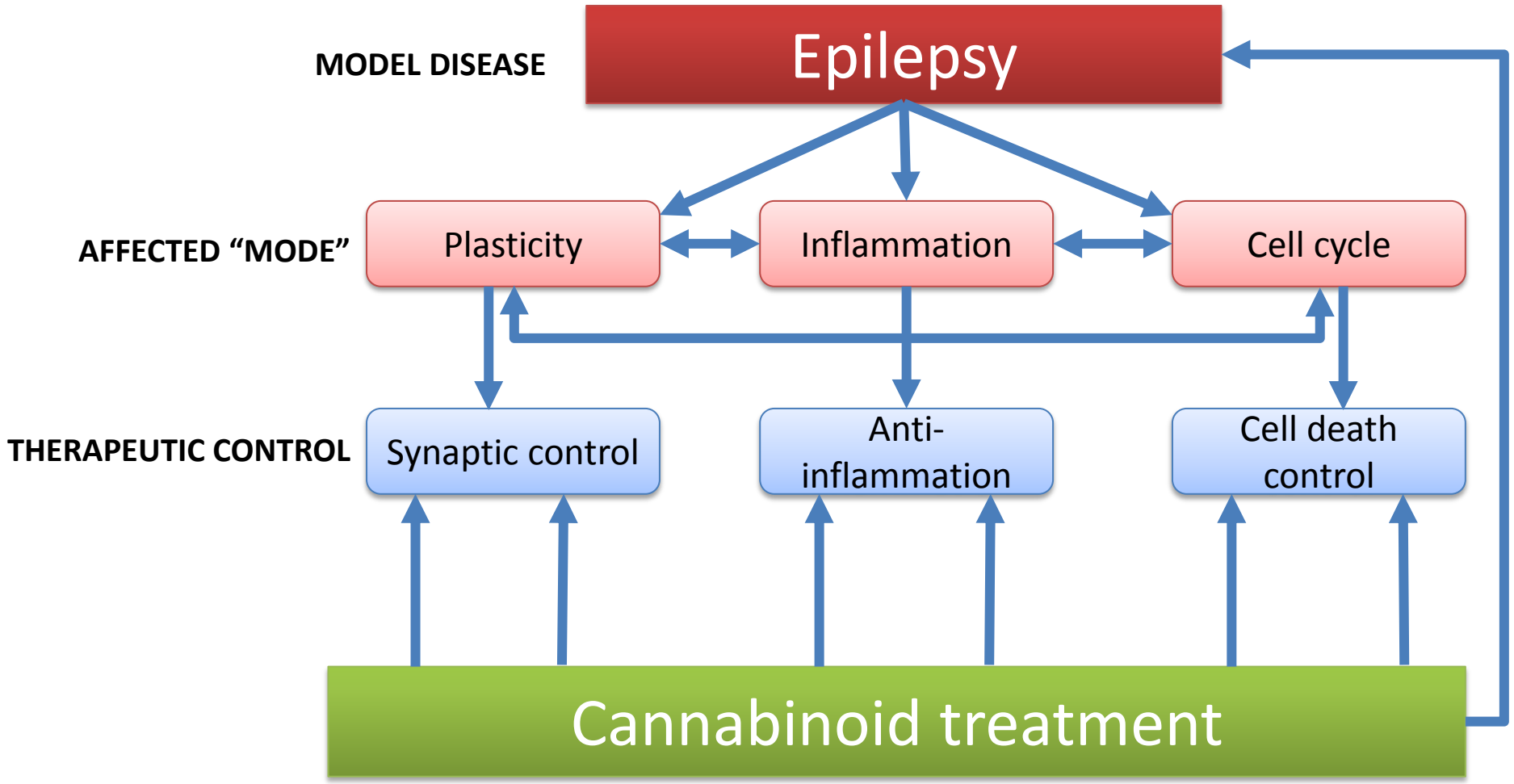
Preclinically:

- 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

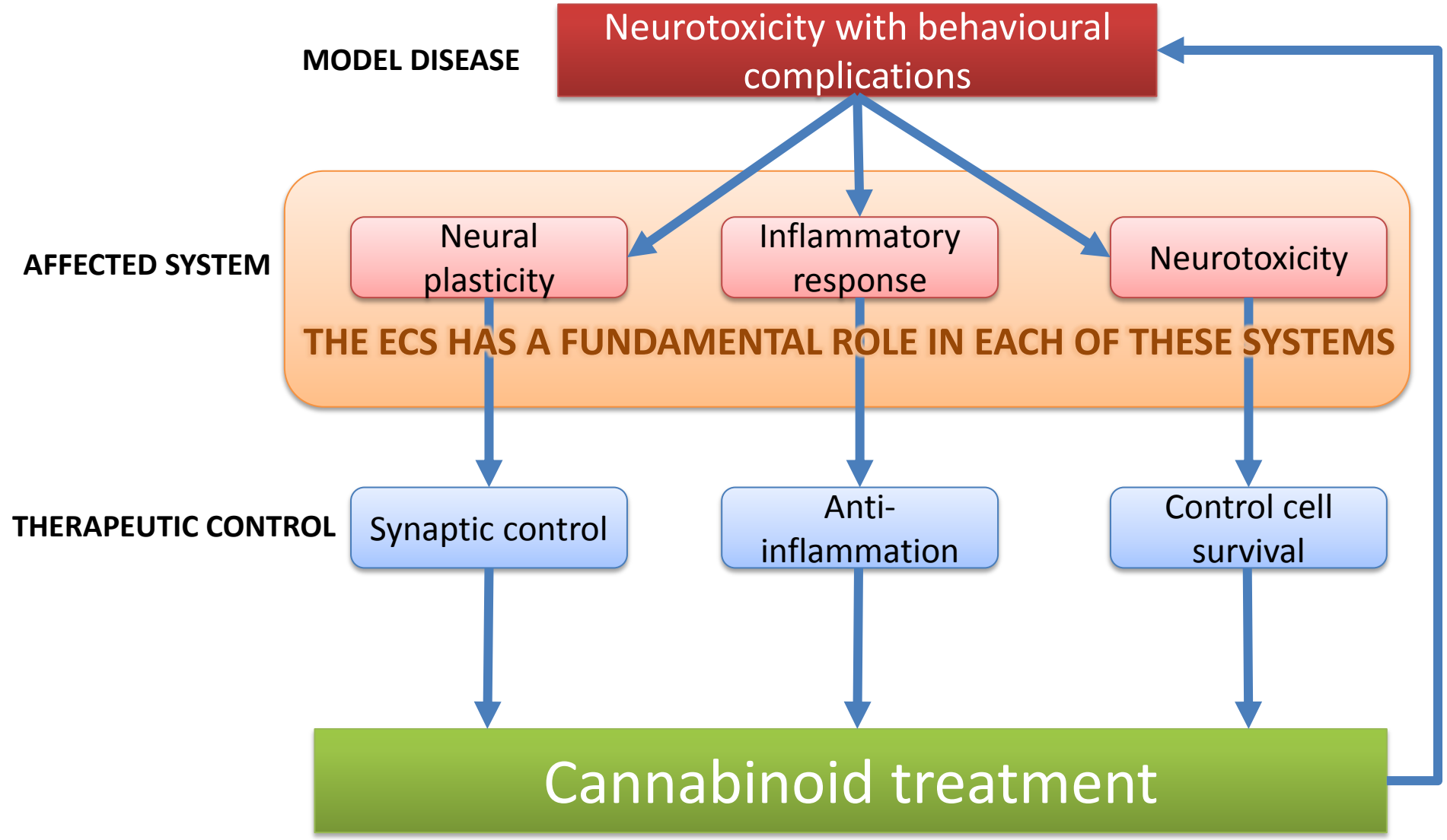


GWP42006 (CBDV)
Epilepsy

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



The spectrum of cannabinoid pharmacology