

UW MJ Symposia: May 18th, 2018

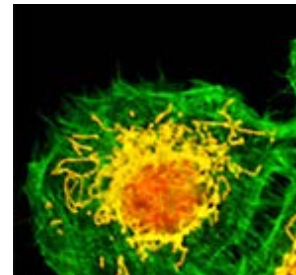
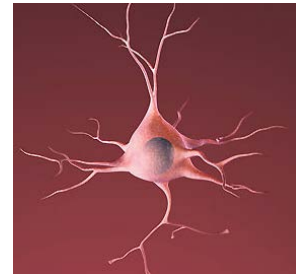
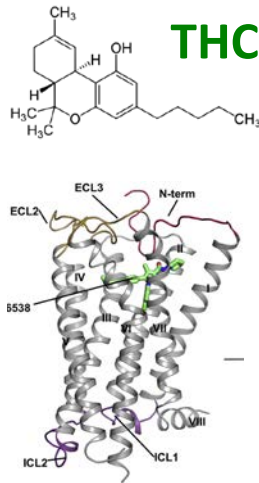
Optimizing the medical properties of cannabis:
From hypothesis to proof-of-concept

Nephi Stella

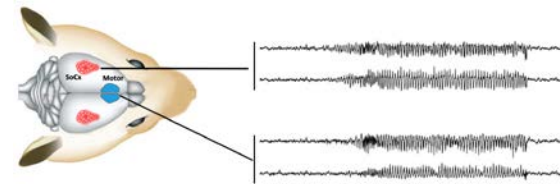
Pharmacology, Psychiatry and Behavioral Sciences
University of Washington, Seattle WA

Background:

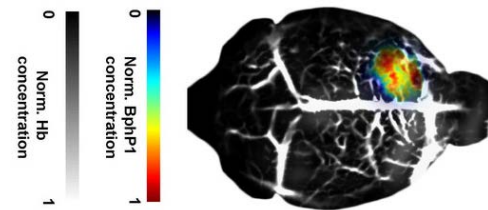
- Professor Pharmacology, Psychiatry and Behavioral Sciences



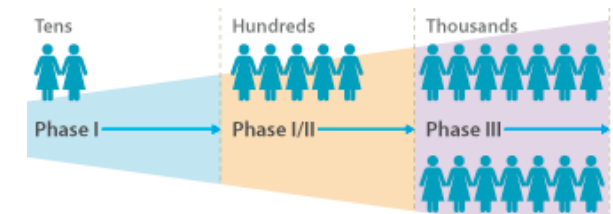
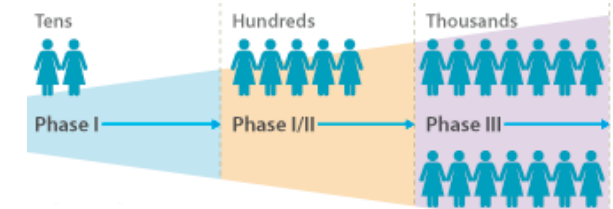
Epilepsy



Brain Cancer



Human Trials



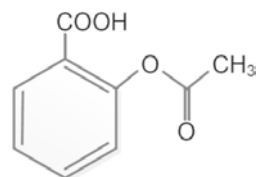
Punch line!

Scientific Approach: Pharmacology and Drug Discovery

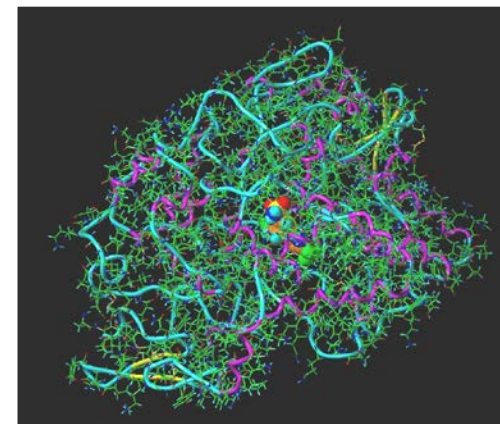
A. Aspirin & B. Morphine

A.

Willow

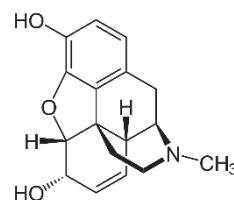


COX inhibitors

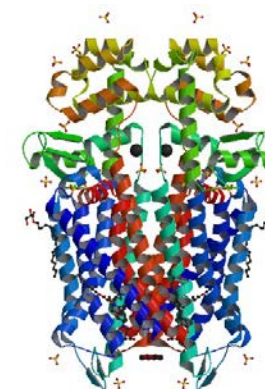


B.

Poppy



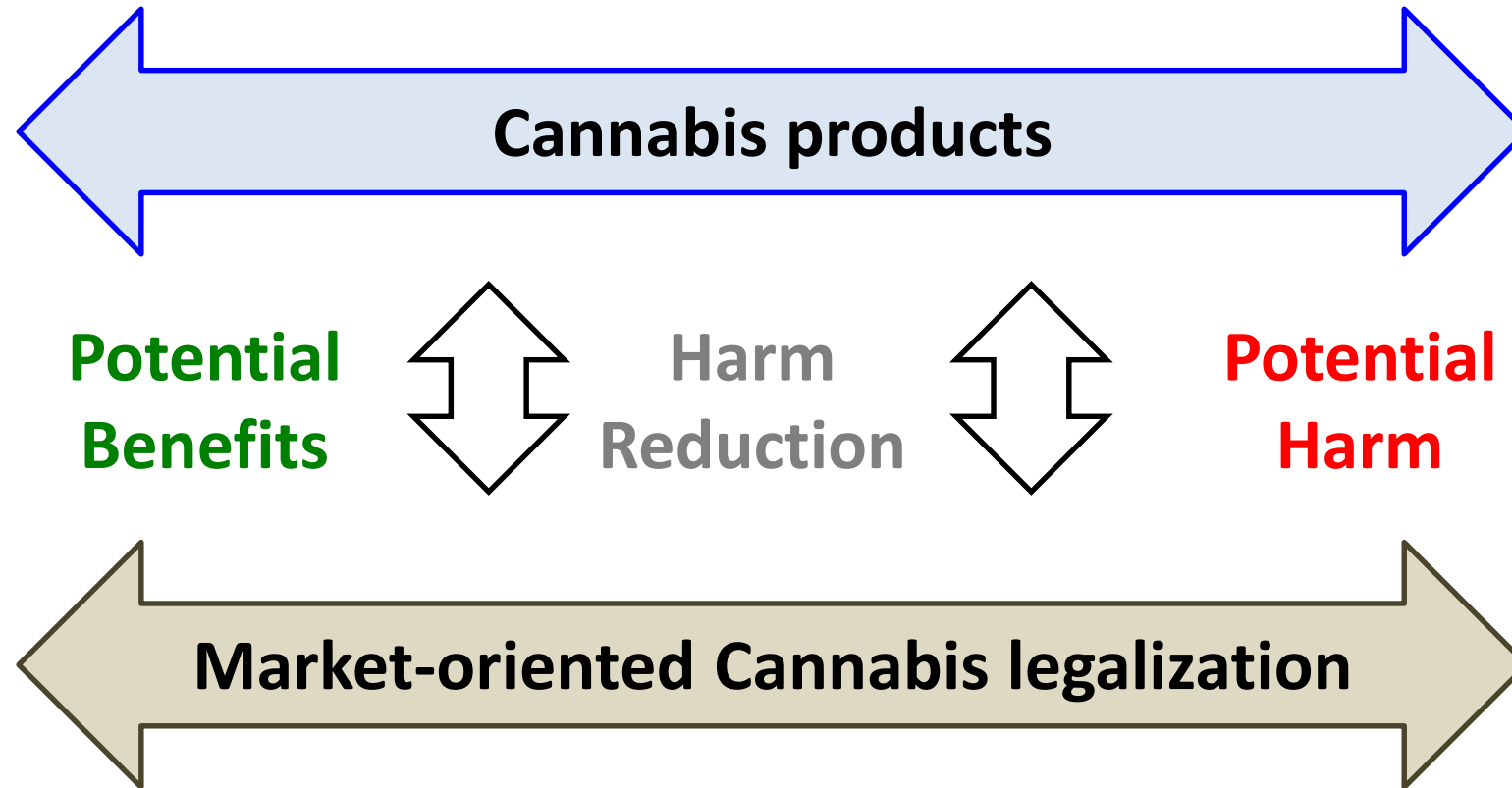
Opioid receptor agonists



Optimize Bioactive Compounds for Therapeutic Benefit

Understand Broad Impact: Short and Long Term Impacts on Humans

Time-dependent changes in impact associated with legalization

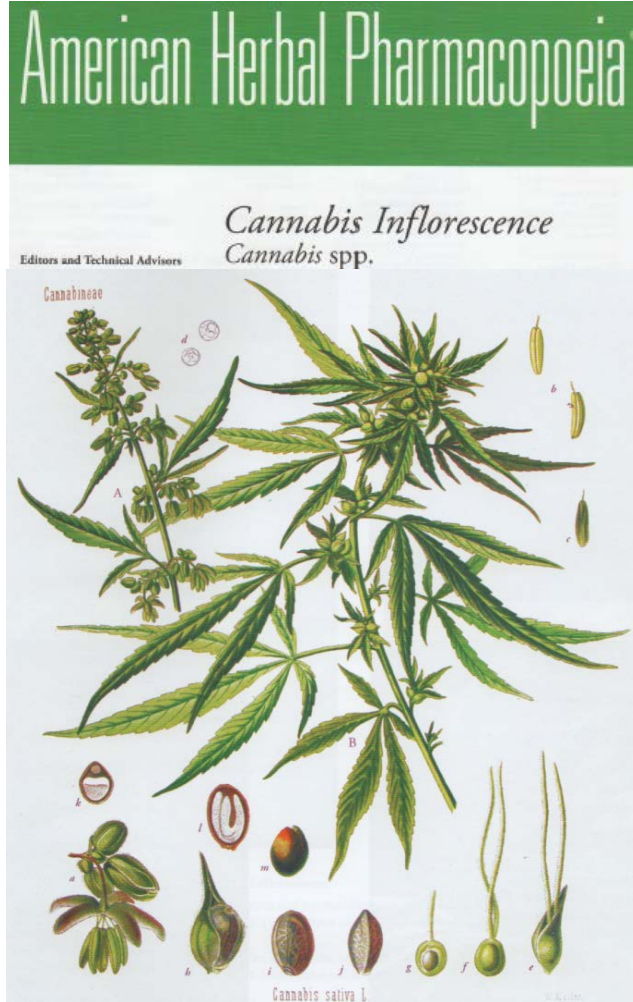


Impact Occurs Along a Continuum and is Changing

Protagonist: Cannabis Plant and Cannabinoids

Sativa versus Indica versus Hybrid strains versus Synthetics

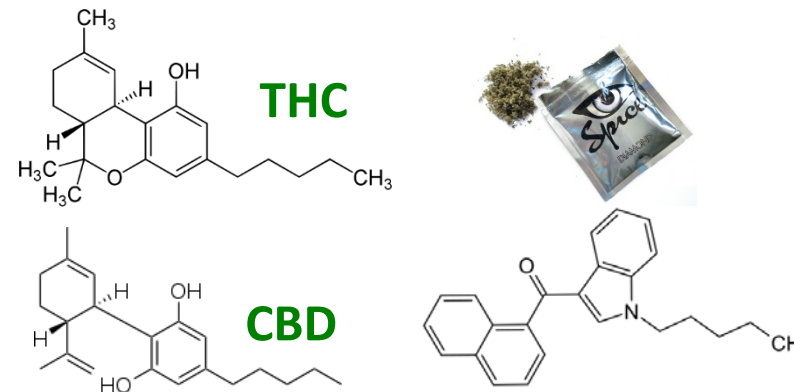
A.



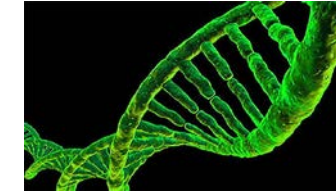
B. Strains



C. Phytocannabinoids



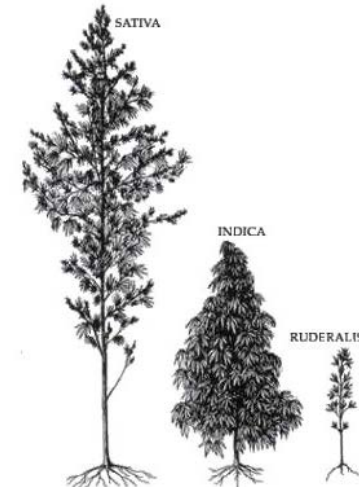
D. Genotype



E. Chemotype



F. Phenotype



In need of well-defined plants and products

Develop Therapeutic Approaches: Novel and Transformative

Pharmacology & Drug Discovery to study this unique therapeutic modality

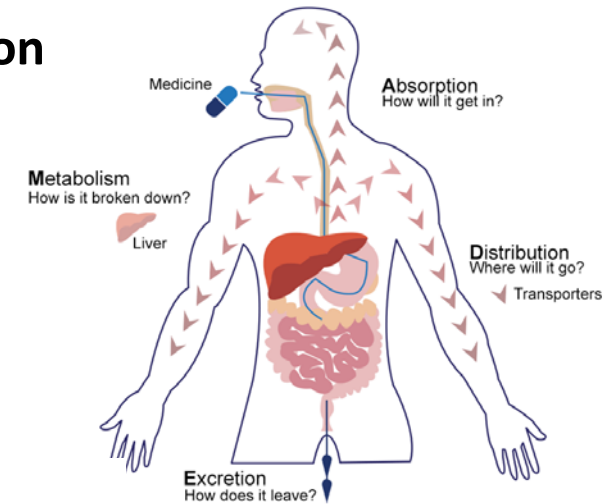
1. Reliable Source of Bioactive Compound



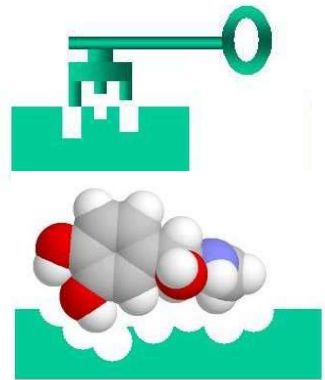
2. Delivery System



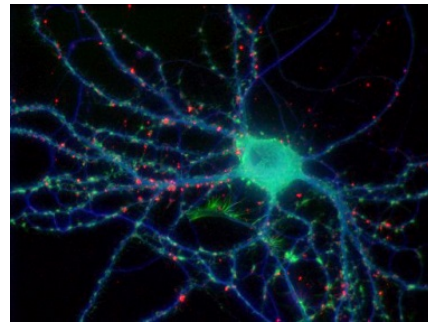
3. Body distribution Pharmacokinetics



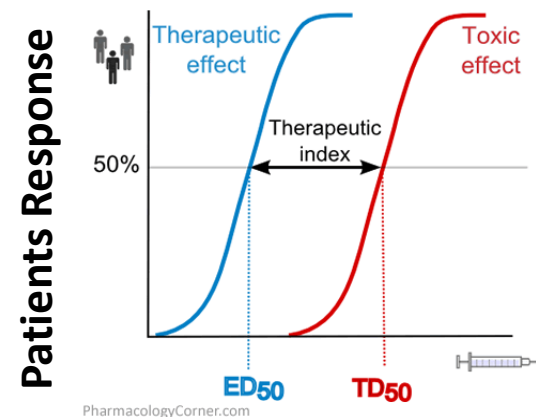
4. Molecular Mechanism



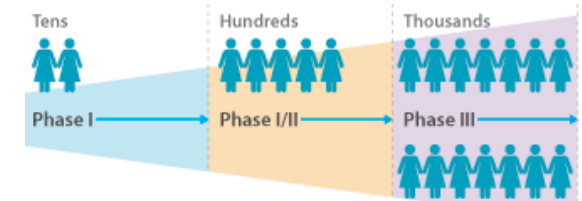
5. Cell response



6. Therapeutic Index



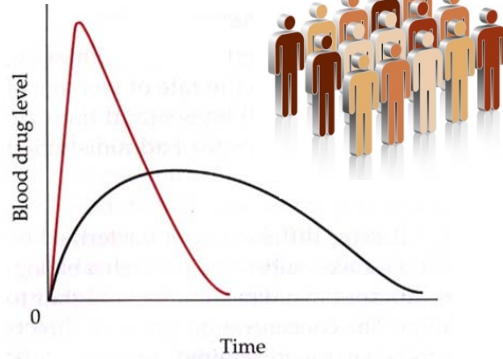
7. Human Clinical Trials



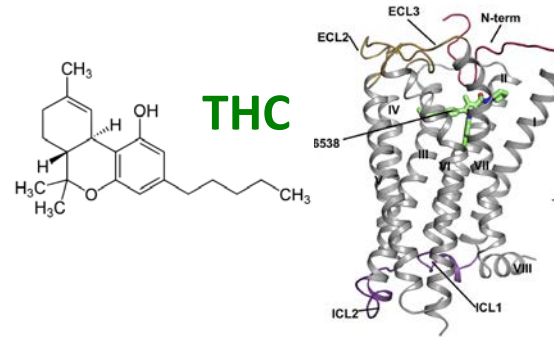
Current Cannabinoid Research Understanding: CB₁ and CB₂ Receptors

Cell membrane receptors that regulate multiple physiological functions

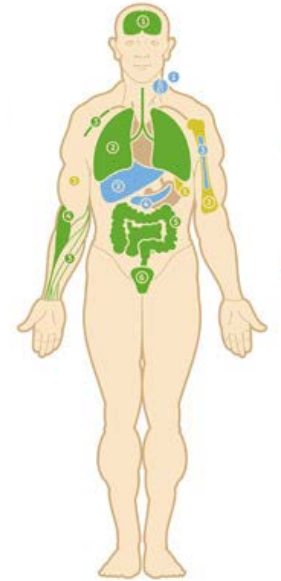
A. Cannabinoid Pharmacokinetics



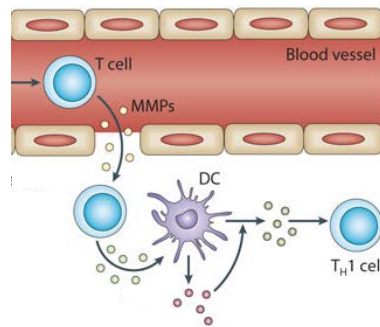
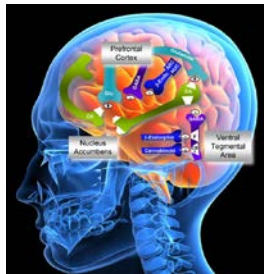
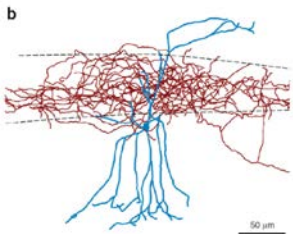
B. CB₁ & CB₂ receptors



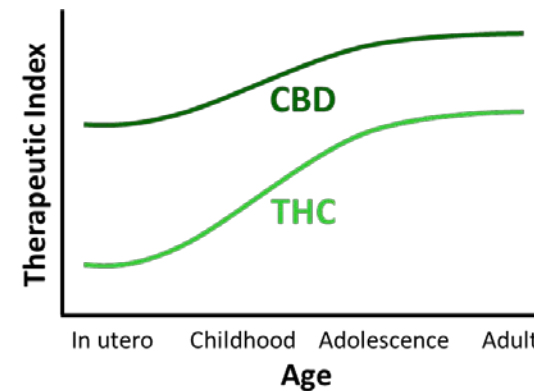
C. Expression Pattern



D. Cellular and Physiological Responses



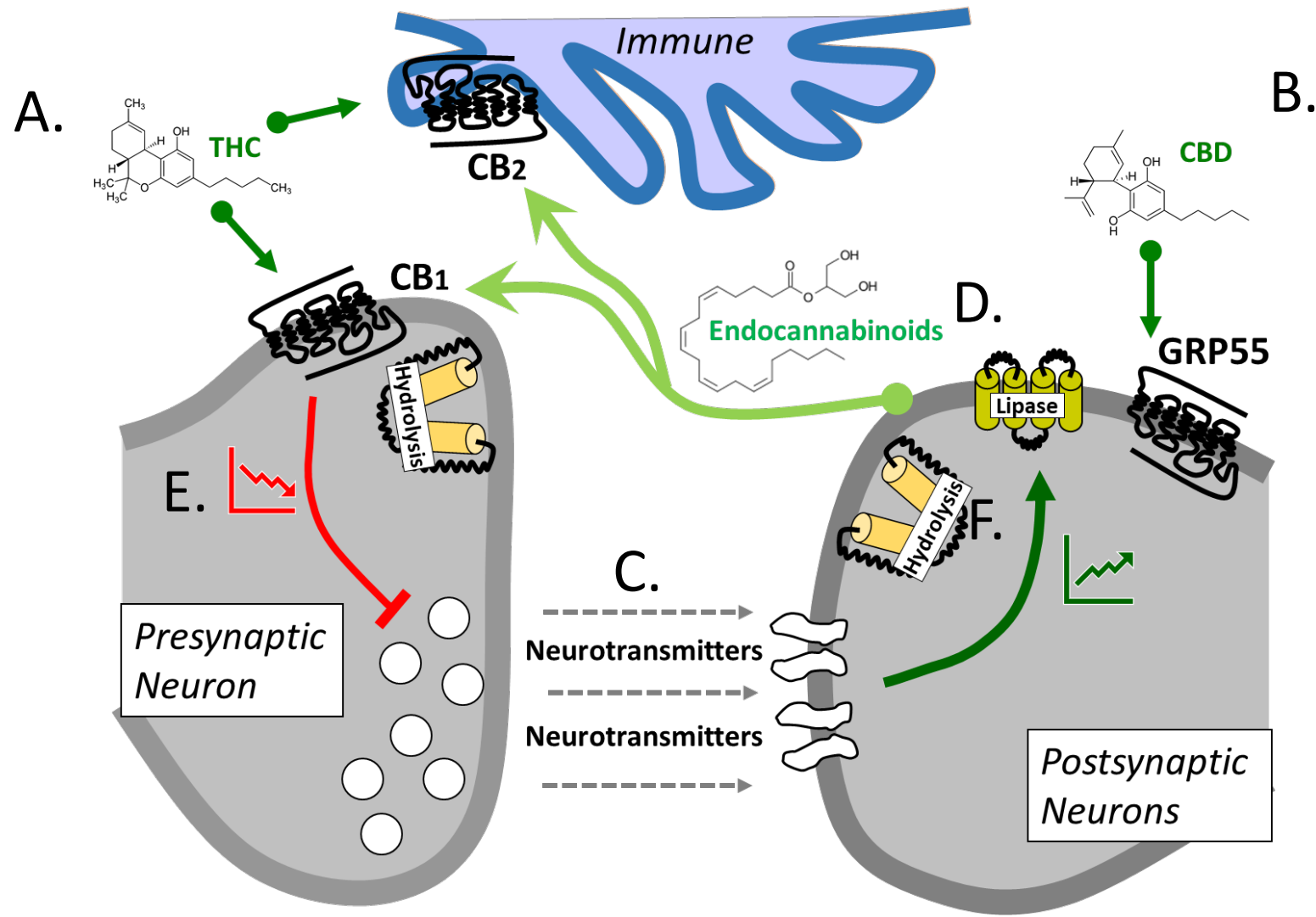
E. Dynamic Therapeutic Index



Anatomy, cellular, molecular and atomic understanding

Endocannabinoids: Signaling System uses Cannabinoid-like Molecules

Used by multiple cell types in brain and periphery to regulate physiology



Potential Harm: Pregnancy and Young adults

Urgent need to study Toxicity Profile of Cannabis-based Products and Educate People

Cannabis Use During Pregnancy

- Stop Nicotine/Alcohol
- Anti-nausea
- CB receptors are involved in brain development

Cannabis Use by Young Adults

- Most wide used “illegal” drug
- Effect on Cognitive Function
- CB receptors in setting up neuronal connections



Vulnerable Population

Harm Reduction and Therapeutic Benefits: Opioids and Epilepsy

Strong Scientific Evidence to combat these Devastating Medical Problems

Opioid Epidemic

- Patients develop addiction to opioids/heroin
- Scientific evidence on the therapeutic effects of THC in **opioid-sensitive indications** (e.g. pain)
- **Opportunity:** Use cannabis as a **substitute** to opioid use



Epilepsy

- 65 million individuals (**1% of population under 20**)
- **Standard of Care** (Palliative treatment and Debilitating **side effects and resistance**)



Current Very Promising Research Venues and Several to Discover

Cannabinoids Reduce Seizures: From basic science to FDA approval

Study and optimize the anti-seizure properties of phytocannabinoids

Preclinical evidence that Cannabinoid reduce seizures

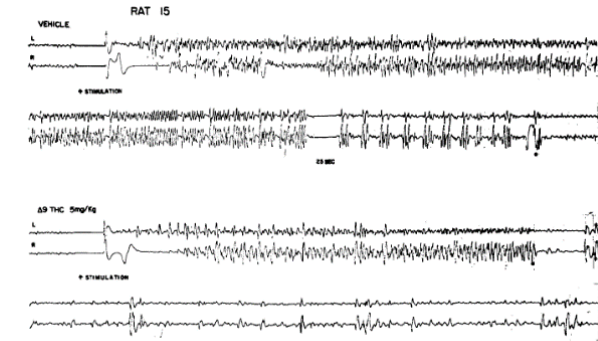
- THC in rodent models of epilepsy (1970s)
- CBD in rodent models of epilepsy (2000s)

Cannabis Use by epilepsy patients

- Clinical reports
- Charlotte had **>100 seizures/week**
- Colorado and Charlotte's Web

Cannabis Use by epilepsy patients

- Open-label interventional trial
- GW Epidiolex **FDA approval** Summer 2018



Charlotte Figi



Effect on seizures: Cannabidiol and Dravet Syndrome

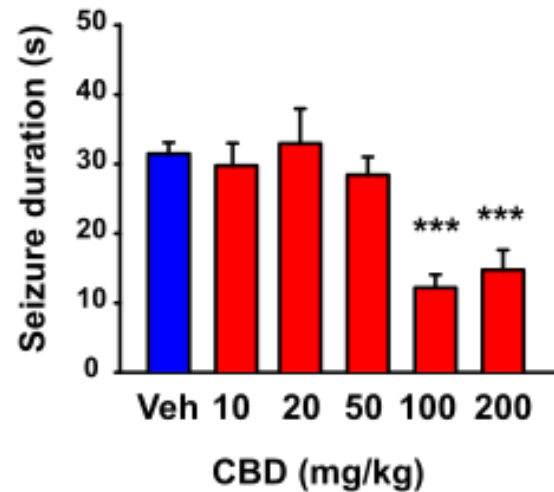
Acute and chronic anti-seizure activity of CBD in DS mice

A.



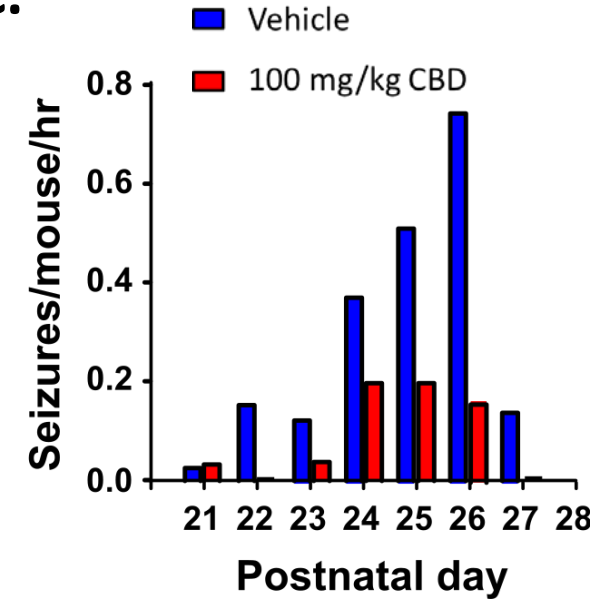
Preclinical mouse model of Dravet Syndrome

B.



Acute efficacy on temperature-induced seizures

C.

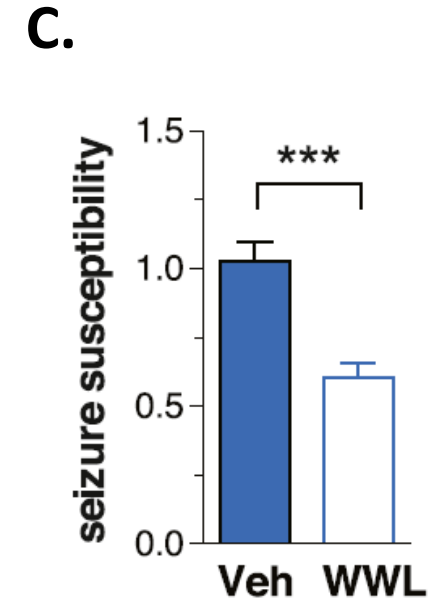
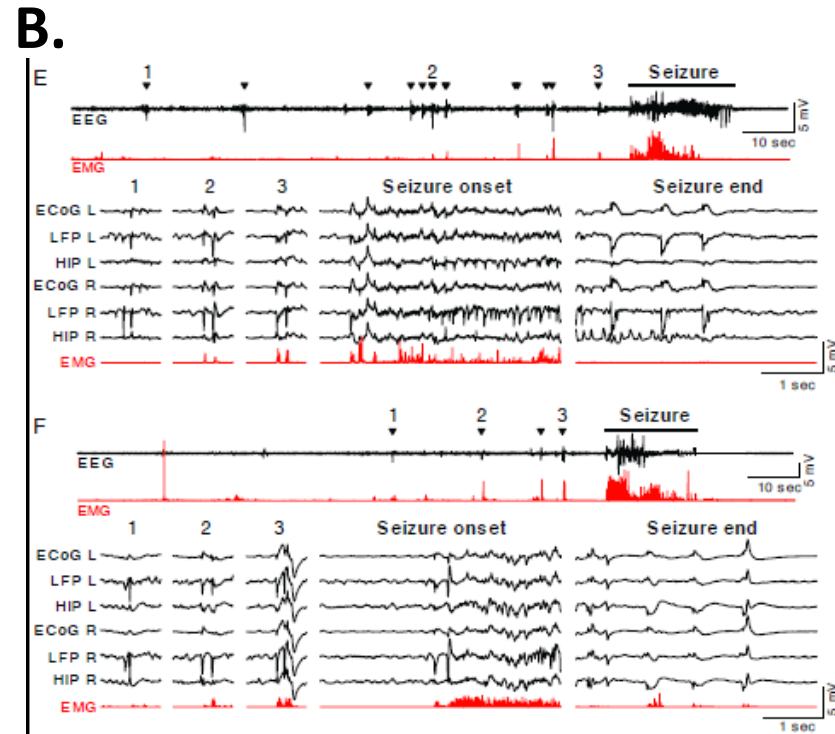
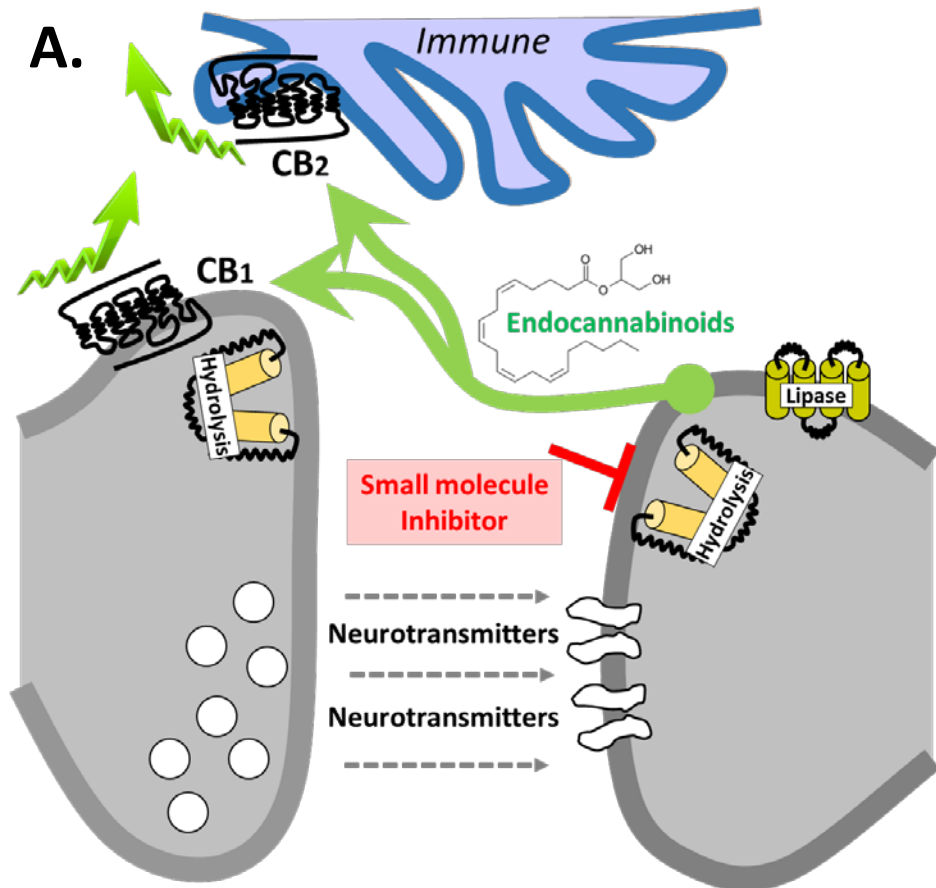


Chronic efficacy on spontaneous seizures

Kaplan et al. (2017) PNAS

Target endocannabinoid signaling: Identification of novel enzymes

Inhibitor of endocannabinoid inactivation to increase signaling tone

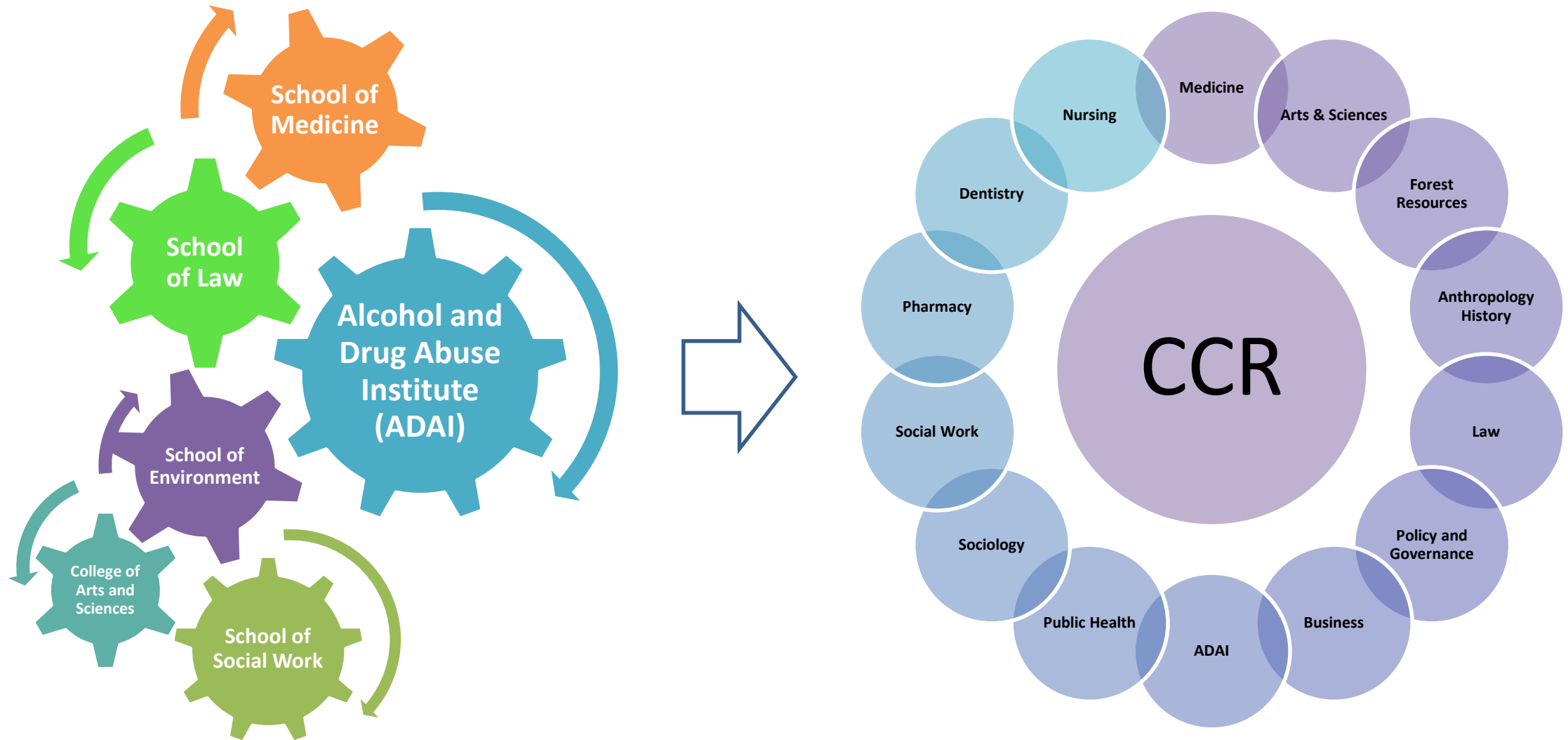


New class of small molecules as anti-epileptic therapy

Naydenov et al. (2014) Neuron

UW Center for Cannabis Research (CCR): Foster Innovation and Solidify Science

Organize world-leading expertise in multiple areas by creating affinity groups



Become a Model of Innovation in Cannabis Research



Our world changing quickly!

We need to make sure that we assure
maximal benefits with minimal side effects
at every level