Moving Beyond Cancer to Wellness

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Optimizing the Medical Properties of Cannabis

Nephi Stella, Ph.D.

Professor in Pharmacology, Psychiatry and Behavioral Sciences, **University of Washington, Seattle WA**

Director, **University of Washington, Center for Cannabis Research**

Disclaimer

Dr. Nephi Stella is professor of pharmacology, psychiatry and behavioral sciences at the **School of Medicine**, University of Washington Seattle.

He is the founder of **Stella Therapeutics, Inc.** and is employed by **Stella Consulting LLC**.

All results were **published** in peer-reviewed journals.

Introduction: Nephi Stella, PhD

25 years of research in optimizing the medical properties of cannabis

CCR | CENTER FOR CANNABIS RESEARCH

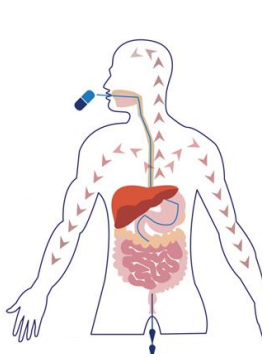
A Pharmacologist

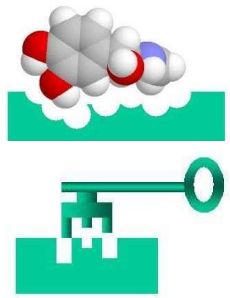
THC

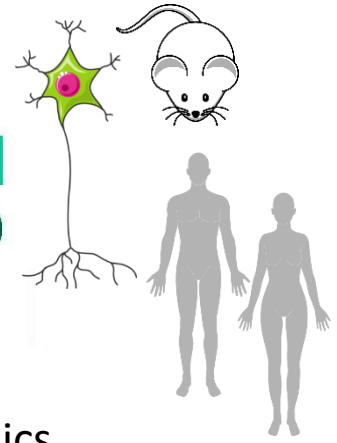
CBD

Phytocannabinoids

Small molecules







Pharmacokinetics

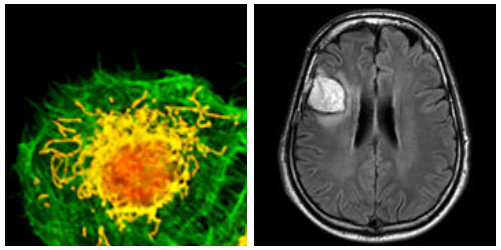
Pharmacodynamics

Laboratory model systems

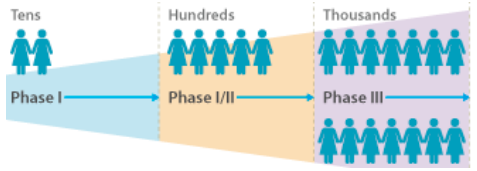
B Discover Therapeutics

Epilepsy

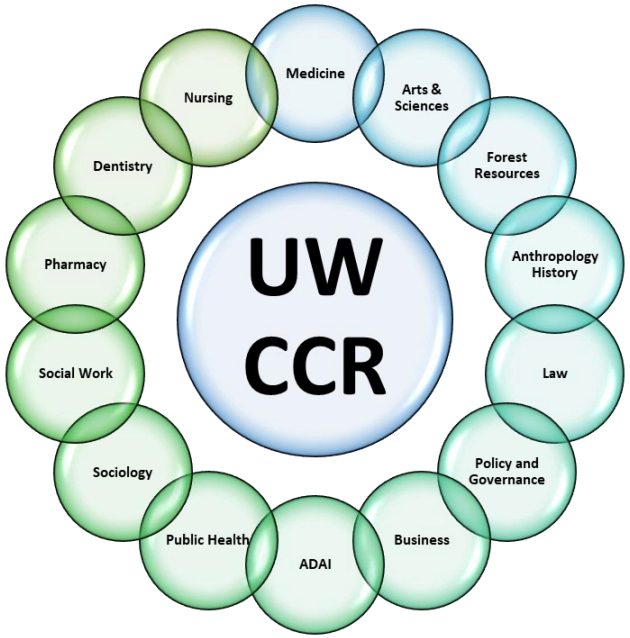
Brain Cancer



Human Trials



C Founder and Director



► Punch Line!

Agenda: Optimizing the medical properties of *Cannabis*

Become experts in Cannabis Pharmacology

Hypothesis Cannabinoids have unique medicinal properties

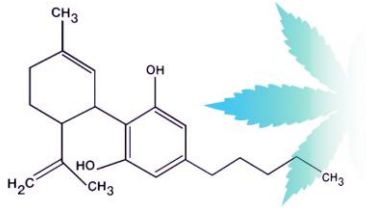
Background

- Cannabinoid Biology: From Plant to bioactivity in Humans
- Therapeutic optimization: Preclinical and Human
- Clinical Cannabis: Therapeutic Index

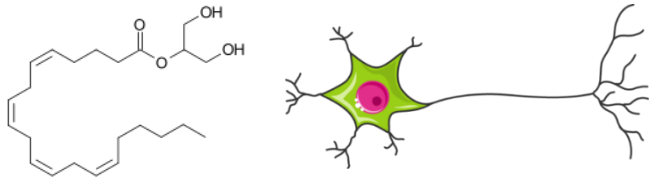
Develop Cannabinoid-based Therapeutics

- Potential Risk: **Adolescence**
- Potential Therapeutics: **Epilepsy** and **Brain Cancer**
- Conclusion, challenges and future directions

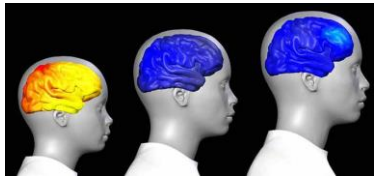
Phytocannabinoids



Endocannabinoids



THC impact on developing brain



Treating epilepsy and brain cancer

► Goal: All become experts in Cannabis and Cannabinoid Pharmacology

Bioactivity: Differences between THC and CBD

Accepted by scientific community

A Difference: chemotype!

Cannabis

THC > 0.3%

CBD?

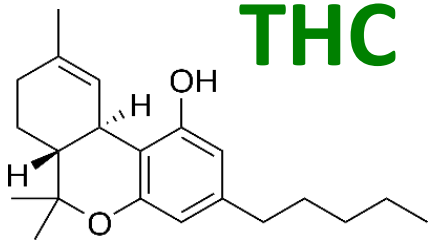
Hemp

THC < 0.3%

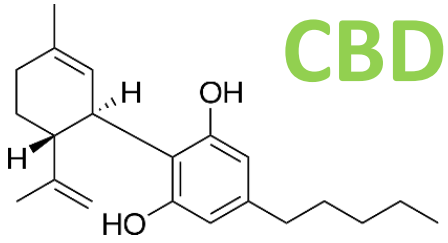
CBD?

B Phyto-Cannabinoids

THC



CBD



C Bioactivity

THC

- Psychoactive - Enhances Sensory Awareness
- Medical: Analgesic/Appetite
- Side effects: Impact Brain Development
- Side effects: "High" not always wanted

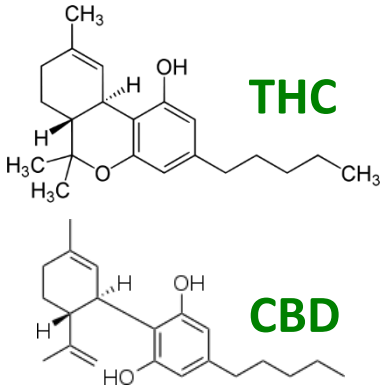
CBD

- No "high" "Tames" THC properties
- Medical: Anti-epileptic
- Medical: Anti-inflammatory
- Side effects: Different than THC!?

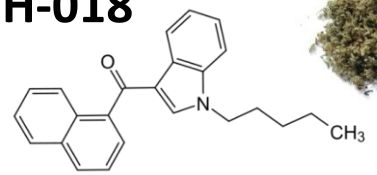
► Known: **THC** and **CBD** produce radically different biological effects (bioactivities)

Cannabinoid compounds: Chemical and Legal framework

Cannabinoids (phyto-cannabinoid & synthetic)



JWH-018



Schedule 1 ➔ 3 inclusion criteria:

- All cannabinoid compounds derived from the **Plant**
- **Synthetic** cannabinoids that Produce Psychotropic Response

National Institute on Drug Abuse (NIDA) – Drug supply:

- **Sole source** of material for academic research
- Quality and reliability of product

Schedule 1 license:

- **Arduous process and extensive legal restrictions**

Illegal to research cannabis-based products from other source:

- Produced and sold in WA state

Increase resources to study cannabinoid bioactivity

- Human research (surveys and in laboratory)
- Animal and basic science research
- NIH, Federal and State agencies

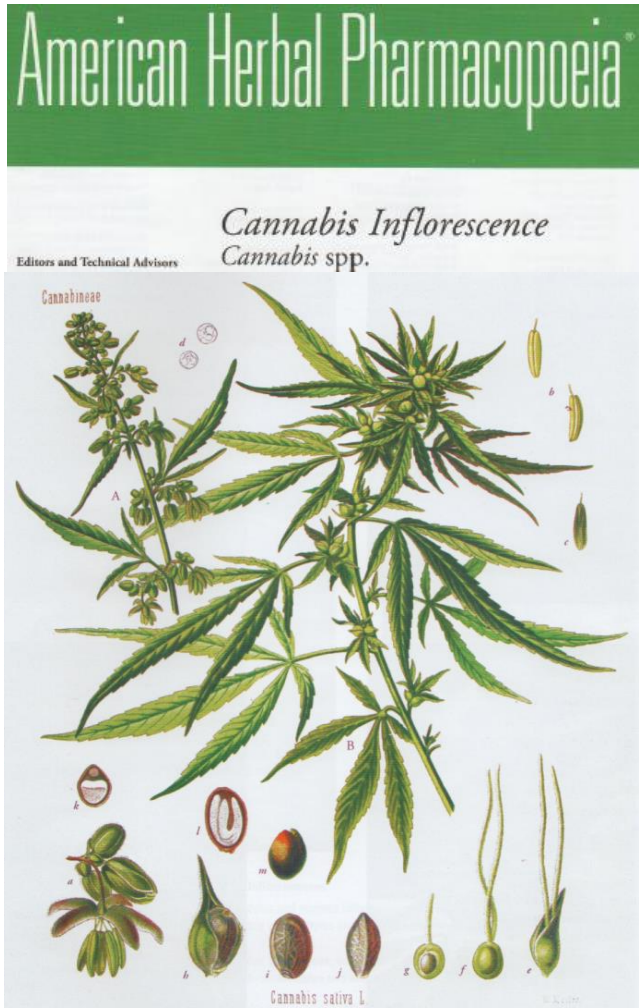
► Solution: Relieve challenges for research

➔ Explore new legal pathways to enable and foster cannabinoids research & development

Protagonists: *Cannabis* – Hemp – Cannabinoids – Terpenes

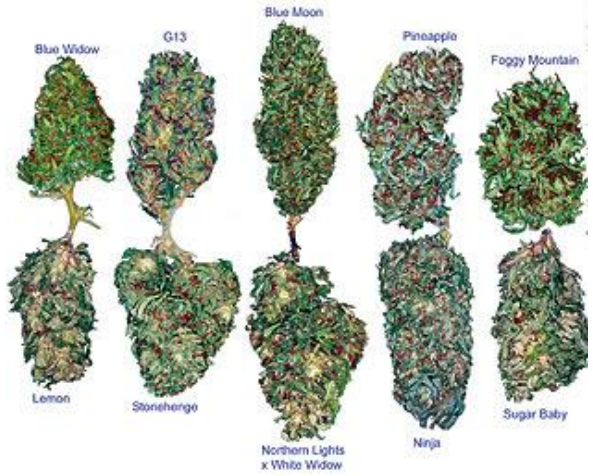
Sativa versus Indica versus Hybrid and Natural versus Artificial

A



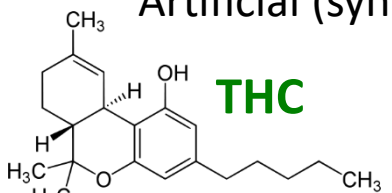
B

Strains

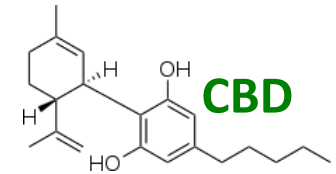


C

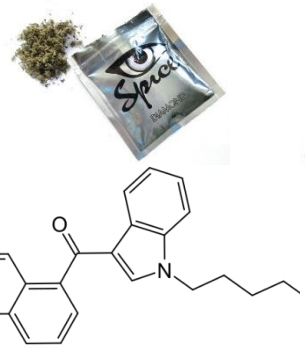
Phytocannabinoids
Artificial (synthetic)



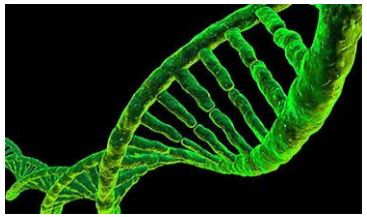
THC



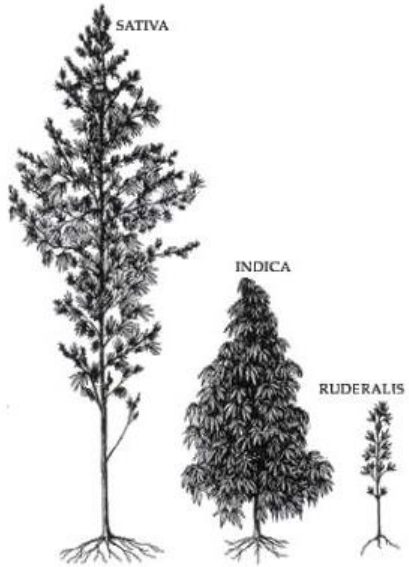
CBD



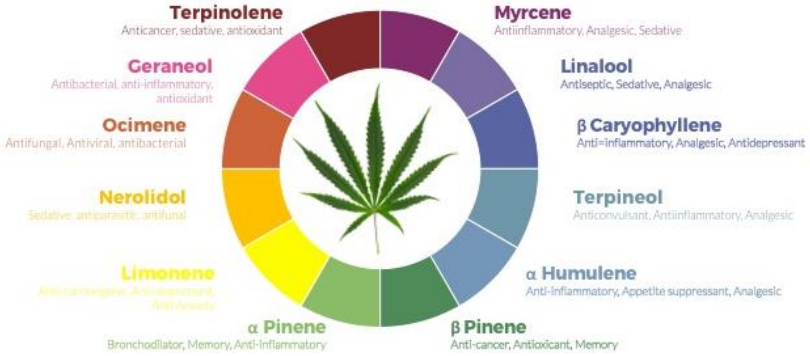
D Genotype



E Phenotype



F Chemotype



► Need: Research the biology of the plant and its bioactive compounds (phytocannabinoids and terpenes)

History of Cannabis Use: From 8.000 BC - to - Today

Historical Evidence of Clinical and Recreational Cannabis Use

2.500 BC: Earliest proof of its use is in **Chinese Medicine**.

1st century: Medical use by **Greek** and **Roman** empires.

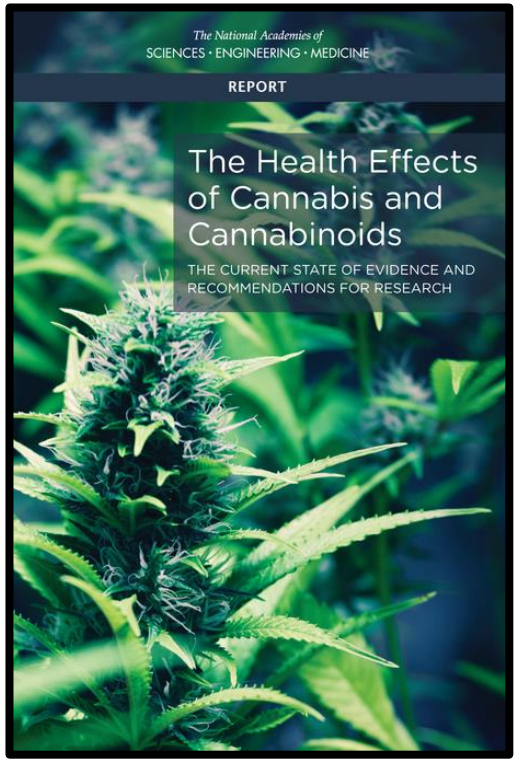
19th century: Europe and US.

- **O'Shaughnessy** conduct medical cannabis experiments.
- "Tilden's Solution" (= an **alcoholic** extraction) used for euphoric properties.

20th century:

- 1920: Increase use of Cannabis use during alcohol **prohibition**.
- 1970: US Supreme court declared cannabinoids **Controlled Substances**

  ➔ **Schedule 1** = no medicinal properties!
- 1997: FDA and DEA allow research on Medicinal properties.
- 2017: National Academy of Science
  - **Therapeutic effects**: Nausea, Chronic pain and Multiple sclerosis
  - **Risk**: Mental Health issues, Cannabis abuse and Psychosocial impairment



► Urgent need: Define medical properties, euphoria, intoxication, impairment!?

Behavioral effects: Poly-modal responses In humans

Acute response of Cannabis *use depends on individuals and prior experience in using cannabis*

somatic	perceptual	cognitive
light-headedness	euphoria	introspective states
"floating" feelings	loss of time sense	rapid flow of thoughts
pulse rate increases	increased body awareness	dreamy
palpitation	distortions of vision	loss of concentration
sweating	decreased hearing	disrupted memory
tremulousness	paying attention	anxiety
weakness	mental confusion	incoordination
numbness	dizziness	sleepiness
	blurring	difficulty in thinking
	fatigue	difficulty in speaking
		difficulty in reading
		difficulty in remembering

▶ Need: Better understand behavioral effects in humans

THC bioactivity: Biological response occurs along continuum

Strong evidence accepted by scientific community

Pain / Sleep
Anxiety / Stress

Opioid addiction

Cognitive Impairment
Cannabis Use Disorder

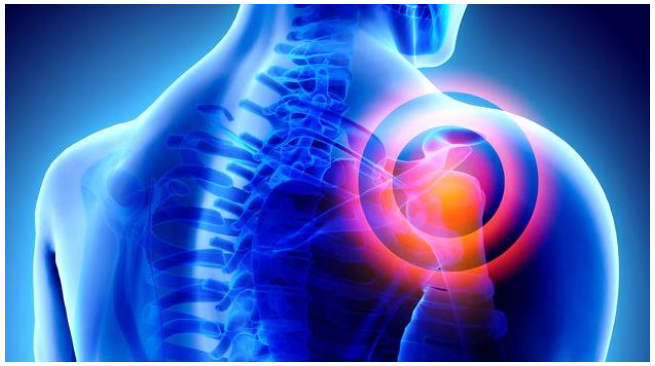
Use of cannabis products

Potential Benefits **Harm Reduction** **Potential Harms**

CBD bioactivity: Biological response occurs along continuum

Strong evidence

Epilepsy
Autism



Pain
Inflammation

Side effect?
Dose/Interaction with other drugs

Use of cannabis products

Potential Benefits — **Harm Reduction** — **Potential Harms**

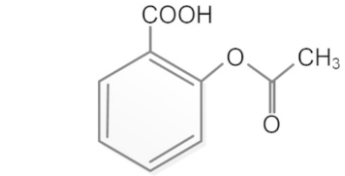
Scientific Approach: Pharmacology and Drug Discovery

Historical success stories: Aspirin & Morphine

A

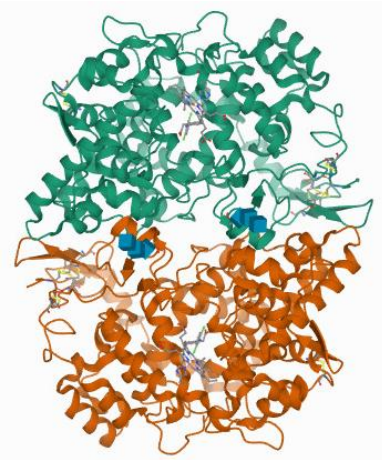
Willow

Therapeutic *Version 1.0*



Therapeutic *Version 2.0*

COX 1-2 inhibitors

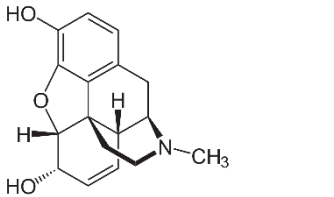


Therapeutic *Version 3.0*

B

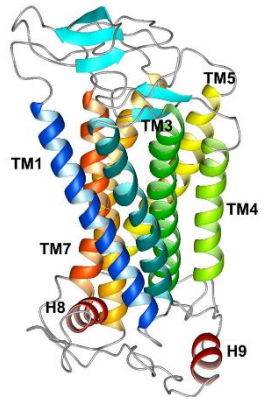
Poppy

Therapeutic *Version 1.0*



Therapeutic *Version 2.0*

Opioid receptor modulators



Therapeutic *Version 3.0*

► Goal: Optimize natural bioactive compounds for **therapeutic benefit while reducing harm**

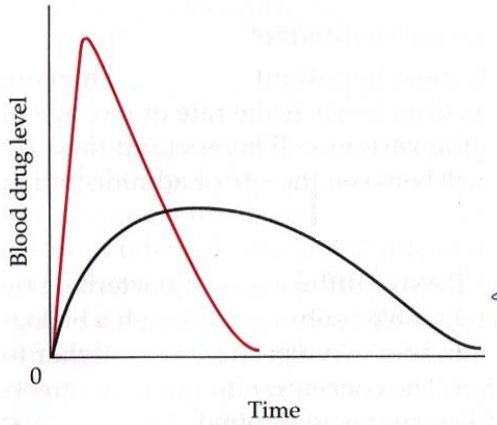
Evidence-based drug development: Transformative therapeutic approach

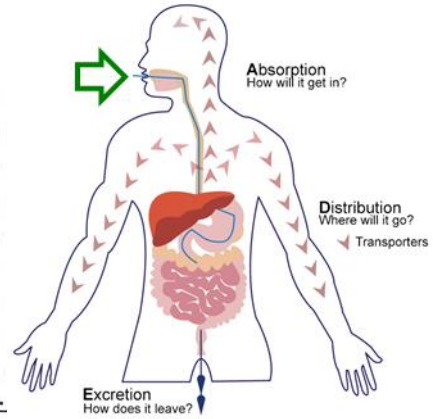
Combine Pharmacology & Drug Discovery to study this unique therapeutic modality

A Reliable Source of Bioactive Compound

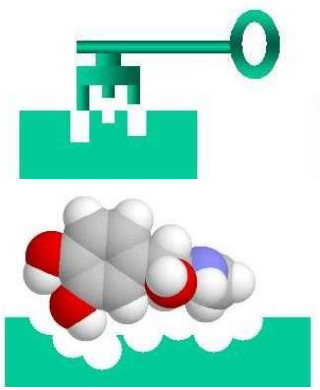
B Delivery System

C Body Distribution Pharmacokinetics

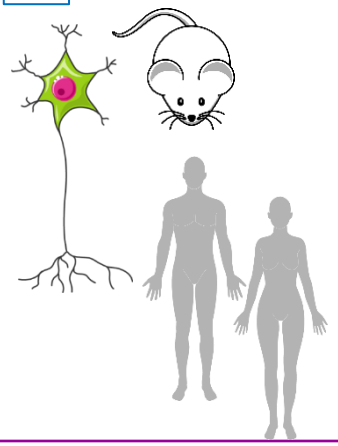




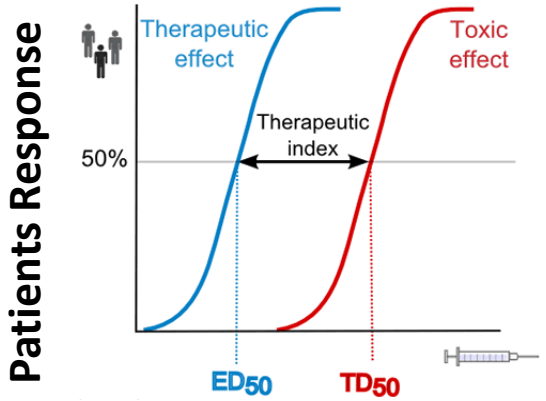
D Molecular Mechanism



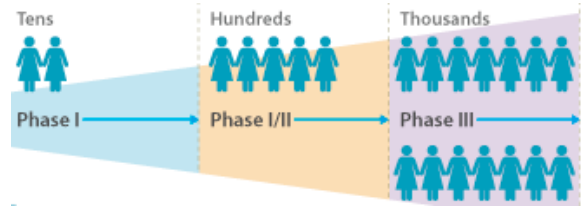
E Bioactivity



F Therapeutic Index



G Human Clinical Trials

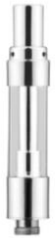
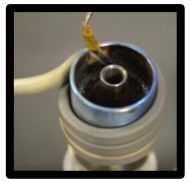


▶ Drug development: Evidence base *versus* Practice base

Pharmacokinetics: Current products and delivery systems

Delivery Systems: Lungs and digestive system

A

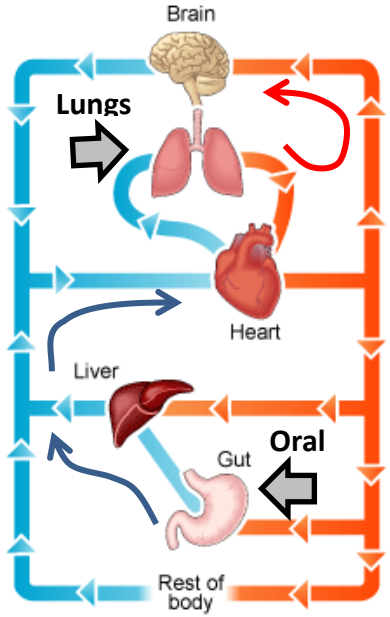
Burn flower		Vape oil	Dab resin
			
THC 5-10%	25-35%	70-80%	90-95%

B

Capsules	Eatables	Drinks	Illegal
			
THC 10 mg/dose	10 mg/dose	10 mg/servings	100-250 mg

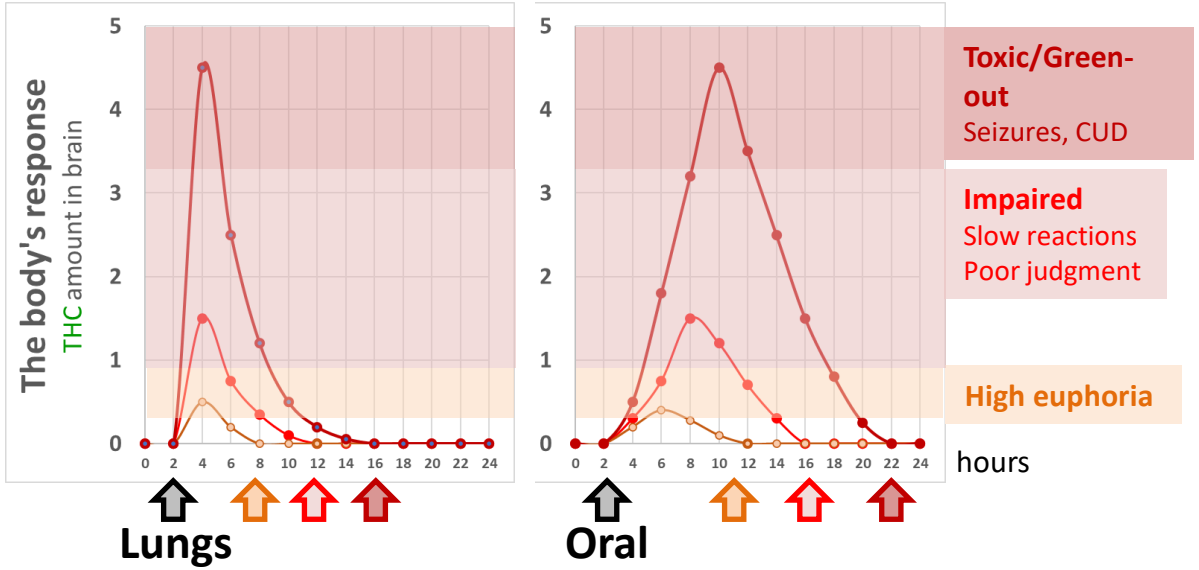
C

Distribution in the body: *Lungs/Oral*



D

Amount of **THC** in body **and** body's response

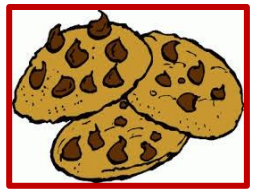


▶ Thus: It's all about who, dose and regimen *(how much and how often?)*

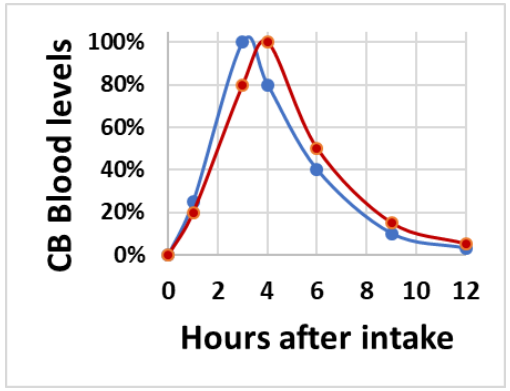
Current Understanding: Pharmacokinetics

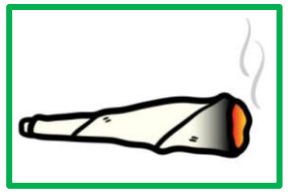
Multiple parameters control PK profile

A Delivery Systems: Model

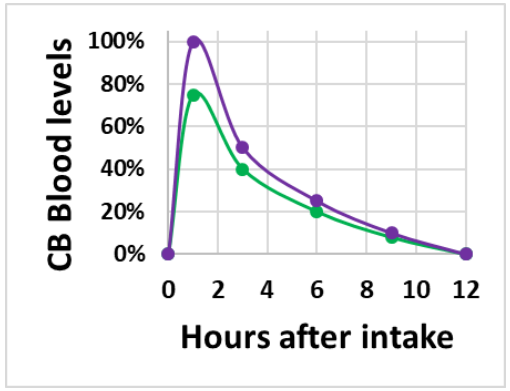


Cookie - Capsule



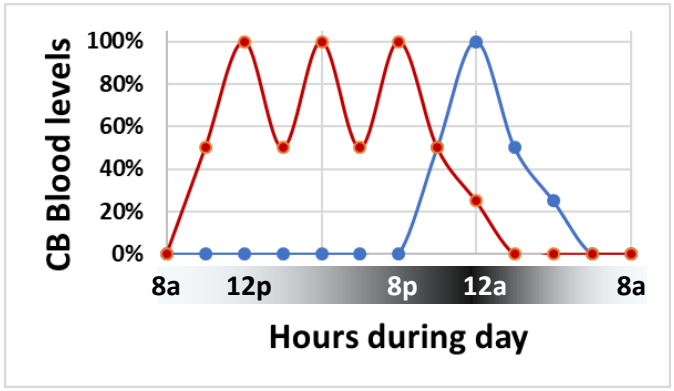


Vape/Dab - Smoke

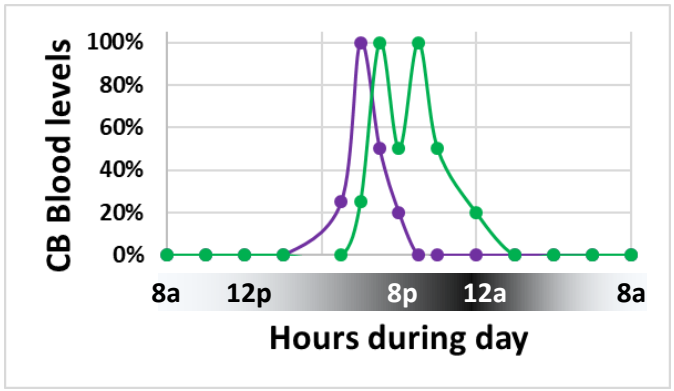


B Indication: Model

Day pain - Fall asleep

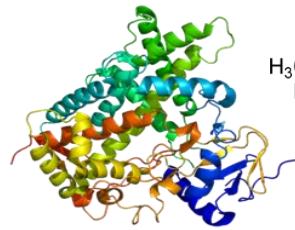


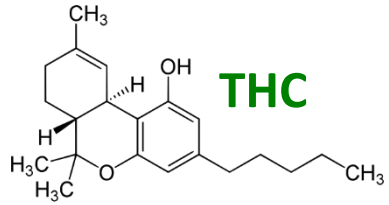
Upper - Relaxing



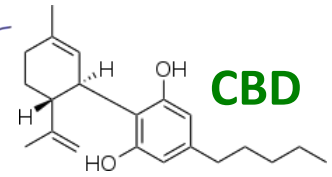
C Individual diversity

Liver metabolism (P450)





THC



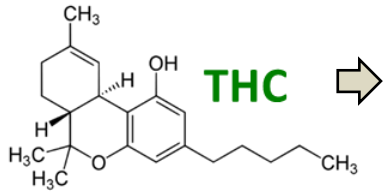
CBD

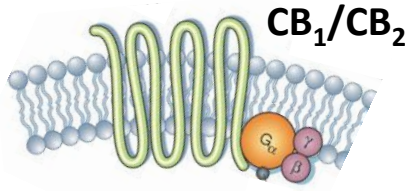
Multidimensional pharmacokinetics of cannabinoids

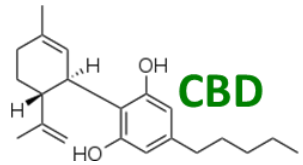
Pharmacodynamics: Bioactivity from molecular to human physiology

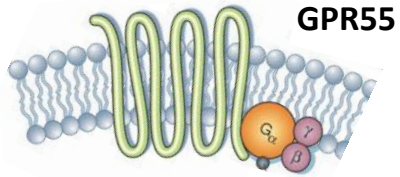
*Differences between **THC** and **CBD** action on cannabinoid receptors*

A Cannabinoid receptors

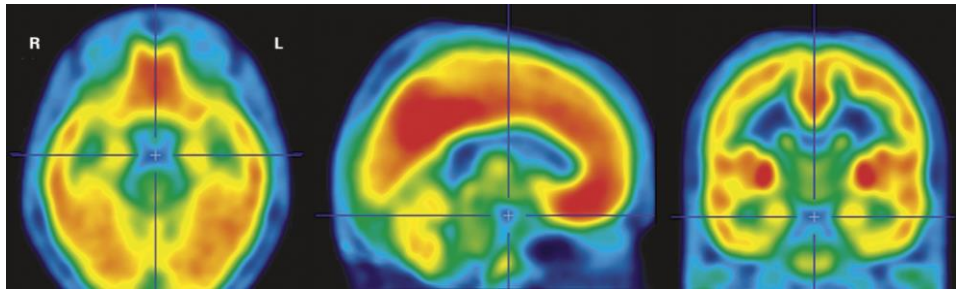


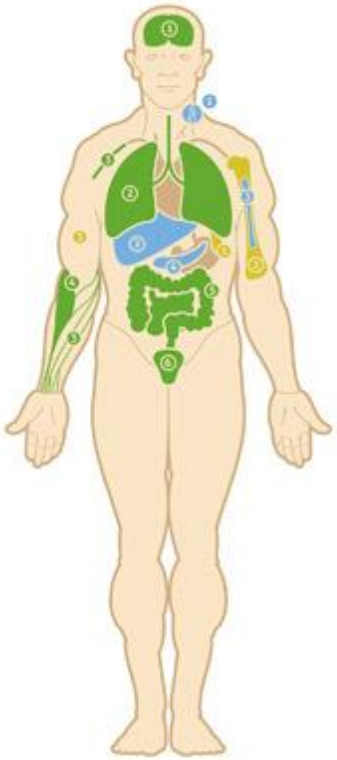






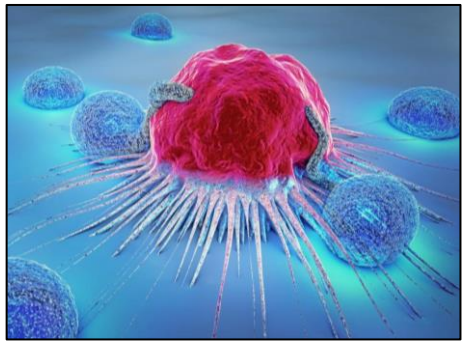
B CB receptors expression throughout the body



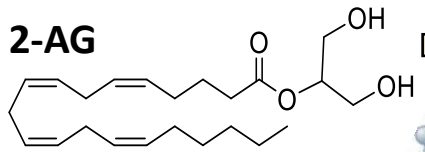


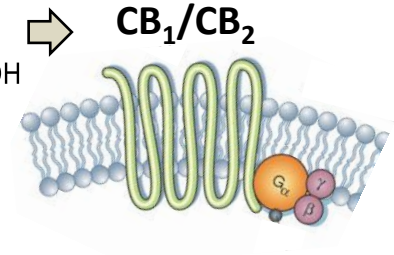
C Action on neurons

D Action on immune cells



E Endocannabinoids





▶ **THC**, **CBD** and *endocannabinoids* act differently at multiple receptors

11) Vulnerable Population: Age and subpopulations

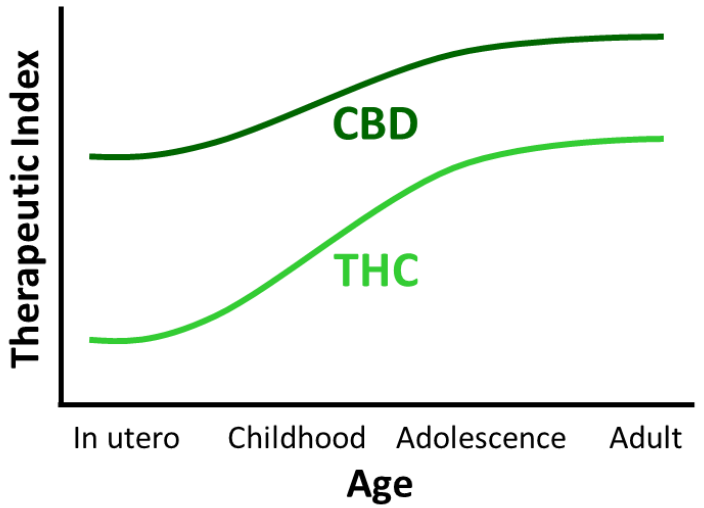
Brain development represents a vulnerable time period

A

Cannabis Use by Adolescents

- Most wide used "illegal" drug (i.e., Age 21).
- High THC affects young brain development
- Consequences on adult cognitive function
- Concerns with high potency rapid onset THC products!

B



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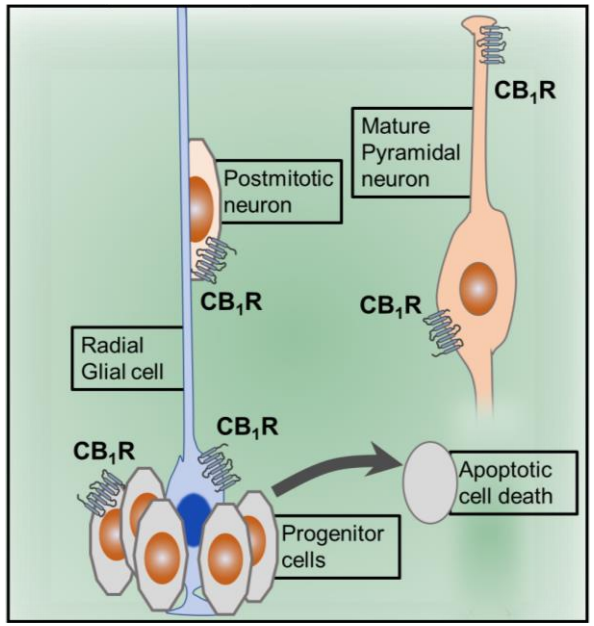

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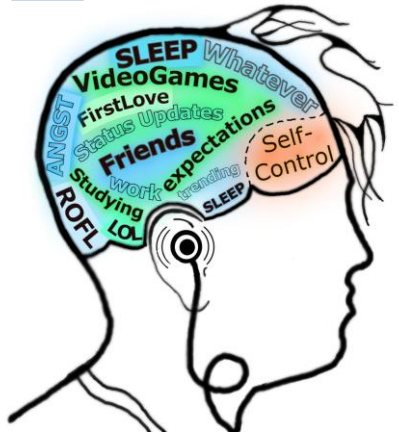


► Urgent Need: Understand the impact of THC use on vulnerable populations?

12) THC: Impact on adolescent brain ➔ Loss of CB_1R in VTA

Adolescent rats/mice, voluntary oral consumption in rodent preclinical models


Jeremy Clark


Lauren Kruse

A Gelatin edibles containing THC consumed during **adolescence**

Kruse et al. (2019) Neuropsychopharm

B Regiment: Ado ➔ Adulthood

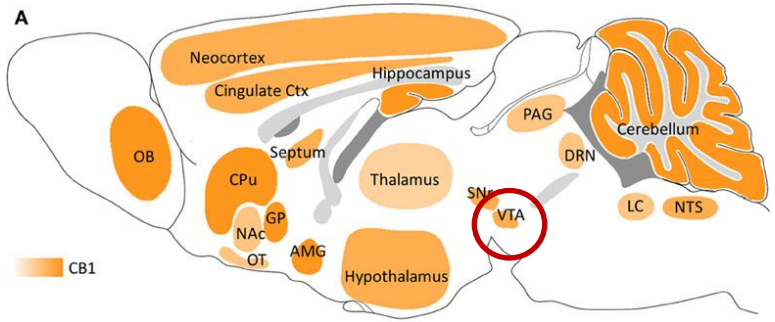
Adolescent rodents
(3 weeks of age)

THC consumption
(3 times/week for 5 weeks)

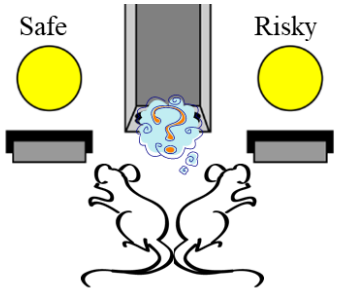
Stop consumption (5 weeks)

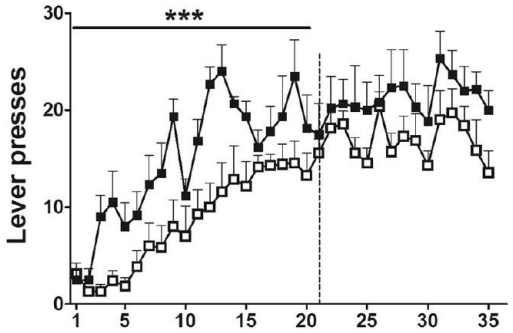
Adult rodent testing
(brain anatomy and reward behavior)

D CB_1 receptor downregulation in adulthood



E Increased reward response in adulthood





▶ Chronic use of High potency THC during adolescence impacts adulthood brain anatomy and behavior

Kruse L. (2019) ***Neuropsychopharm***

13) Cannabinoids Reduce Seizures: From basic science to FDA approval

Study and optimize the anti-seizure properties of phyto-cannabinoids

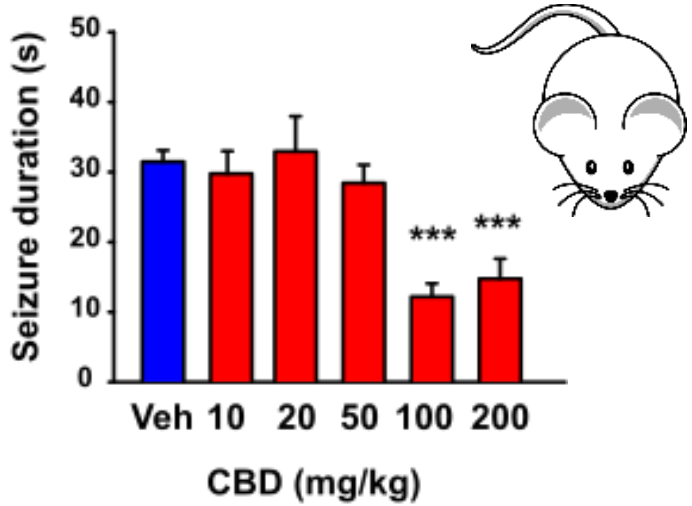
Preclinical evidence that Cannabinoid reduce seizures

- 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
- Validate in preclinical models

Charlotte Figi



Bill Catterall

Cannabis Clinical Trials

- Open-label interventional trial
- GW Epidiolex **FDA approval** June 25, 2018

► Urgent need: Optimize therapeutic properties of CBD (**forward predictive research** instead of *reverse reactive research*)

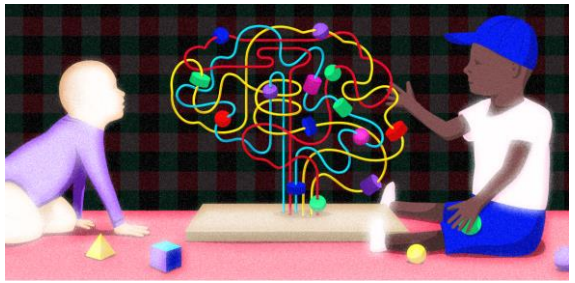
Kaplan et al. (2017) ***PNAS***

14) Therapeutic activity: CBD

Evidence in humans and rodents

Autism

A



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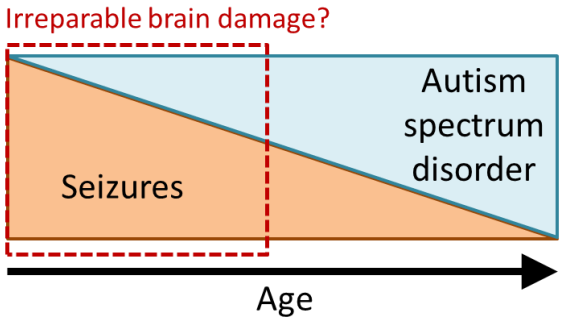

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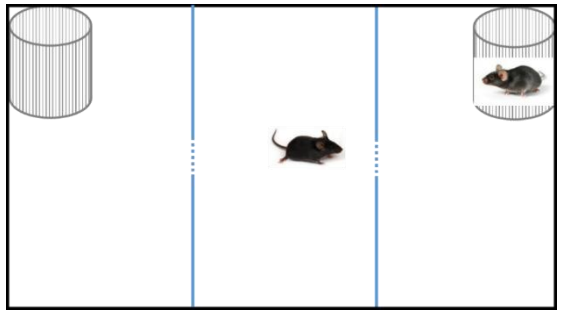

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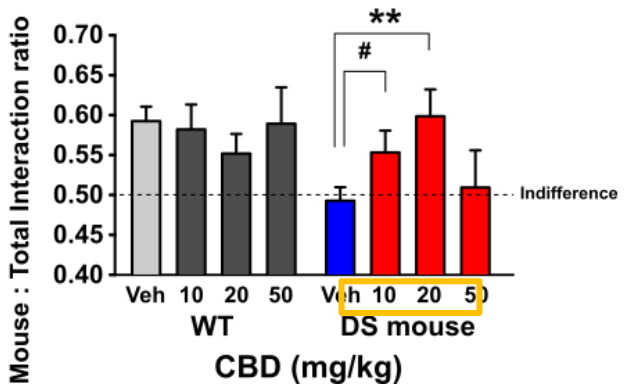
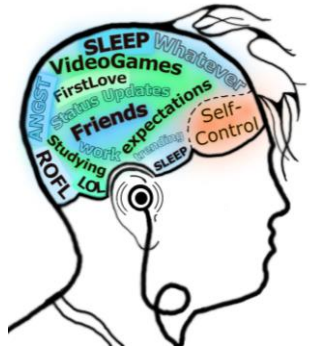


Sleep

Anxiety

Cannabis Use Disorder



► Urgent need: Optimize therapeutic properties of CBD for the treatment of devastating diseases

14) Therapeutic promises of cannabinoids: THC and CBD

Considerations and Major indications

Promises

1. Help with: Stimulating eating, Pain, Sleep.
2. Appropriate dosing is well tolerated
3. Complements other therapeutic approaches because different mechanism.

Challenges

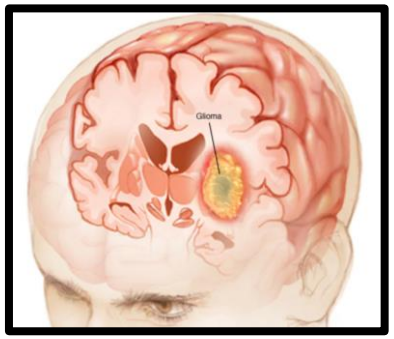
1. Concerns about anti-inflammatory with respect to immuno-therapy.
2. Find individualized delivery method, dose and regimen
3. Children are vulnerable to cannabinoids: therapeutic index
4. Stigma of select individuals (older generations?)

Solutions

1. Educate patients and care givers (medical board?).
2. Optimize cannabinoid-based therapeutics via basic and clinical research

Cannabinoids kill cancers: THC anti-tumor activity

Initial scientific reports



A

1975: Phytocannabinoids inhibit cancer cell division

Journal Nat Cancer Institute

THC inhibits lung tumor growth

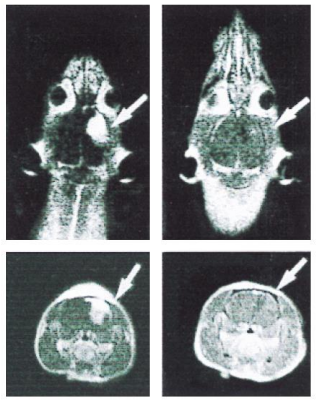
1. 50% in vitro cancer cell proliferation
2. 70% in mouse model

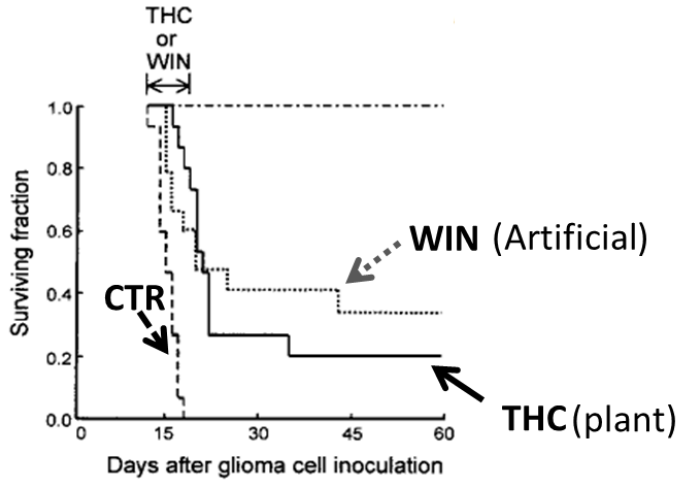
► 10 days at 200 mg/kg/day

B

2000: Phytocannabinoids and synthetic cannabinoids kill GBM tumors in rat model

Nature Medicine

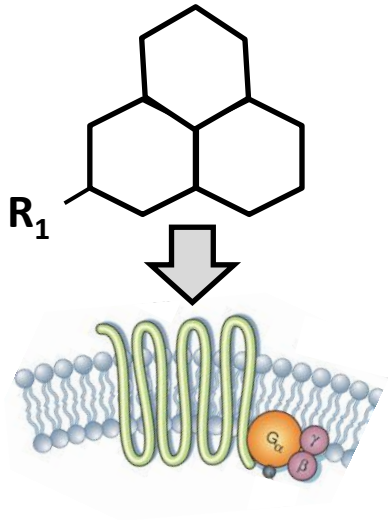




C

Cannabinoid

Small molecule scaffold



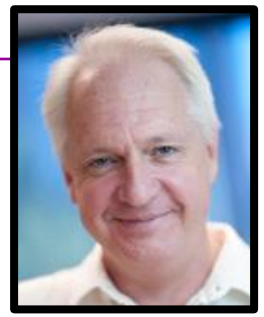
► Hypothesis: Novel anti-cancer activity, mechanism and drugs?

Cannabinoid-based small molecule: Tumor-killing activity

Distinct bioactivities differentiated by innovative new chemical entities

Stella Therapeutics

2011-2017

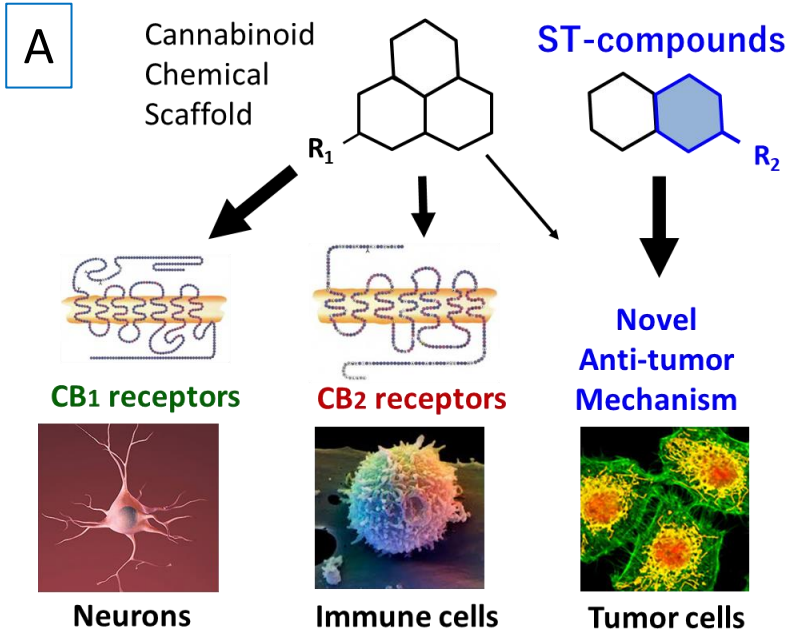


Eric C. Holland

STELLA THERAPEUTICS

Stella Therapeutics

A



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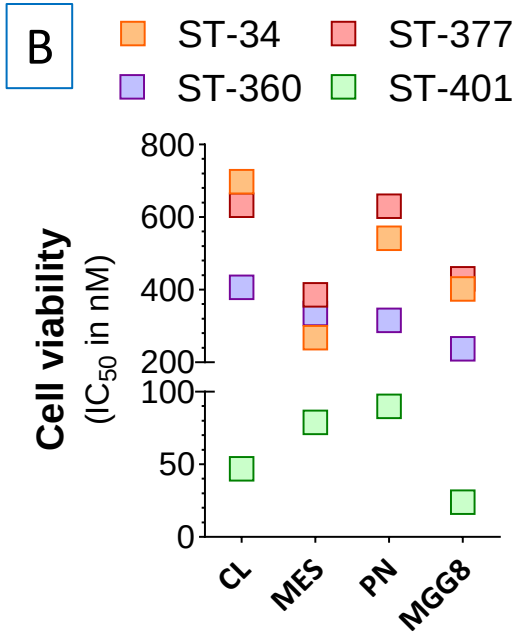


► **Artificial** small molecules: **ST-401**

- **Nanomolar** potency at killing tumors
- Pass the **blood brain barrier**
- Promising **safety** in rodents
- **Novel** anti-tumor mechanism and bioactivity
- **Indications:** Glioblastomas, melanoma and colorectal cancer

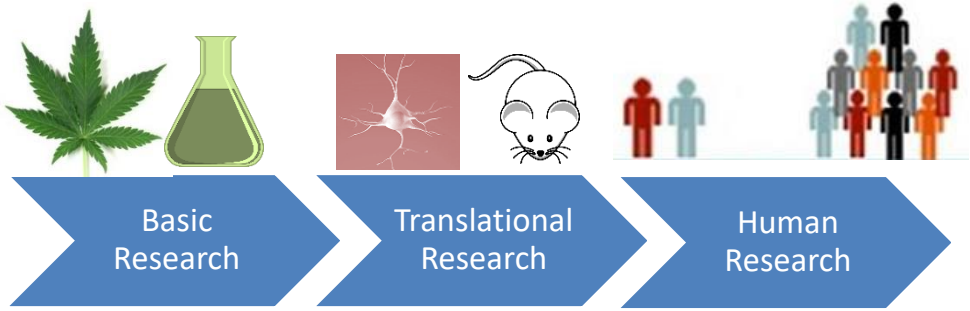
Horne *et al.* (2021) **Neuro-Onc Adv**

► Vision: Develop a transformative anti-cancer therapeutics!

Optimizing Medical properties of Cannabis: Evidence- and practice-based

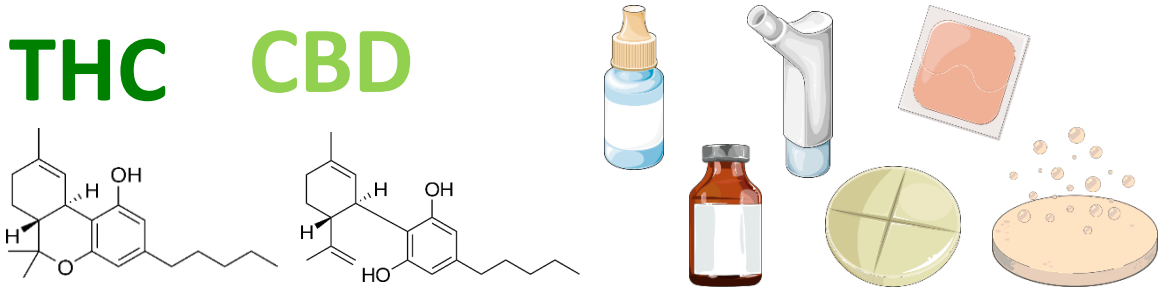
*Move from **reverse reactive** research to **forward predictive** research*

A Evidence based

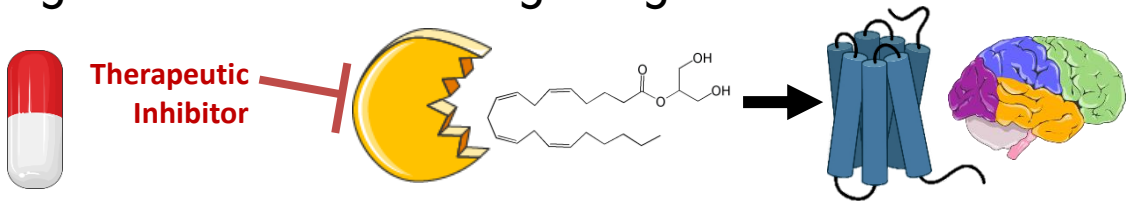


B Practice based

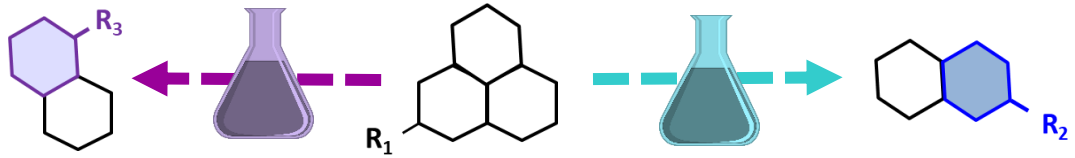
C Analogues, other phyto-CBs, formulations/devices



D Target endocannabinoid signaling



E Discover and synthetize cannabinoid-based therapeutics



► We need more research to gather a better understanding of molecular mechanism to optimize therapeutic promises and avoid side effects

Questions?


WHEN? WHY? WHEN? WHERE?
WHAT? HOW? WHY?
WHEN?
WHO? WHAT? WHERE?
HOW? HOW? WHEN?
WHERE? WHEN? WHERE?
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