Synthetic CBD Analogs (SCAs) for Pain and Inflammation

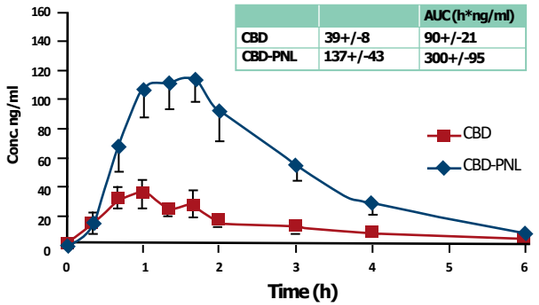
Led by Marc Feldmann, key players Mechoulam, Gallily, Domb

Developing proprietary compounds which aim to be:

- Safe & non-psychoactive
- Formulated to offer improved oral bioavailability (> three-fold)
- Rigorously tested in clinical trials for inflammatory pain (efficacy and dosing)
- Granted market approval by FDA, EMA and others
- A real alternative to unregulated consumption of medical cannabis or OTC CBD (no clinical evidence, not FDA approved, unreliable composition, unpredictable dosing and safety)

Problems with MM / OTC CBD	Our Solution
× **Variable composition, potency,** and may contain **undesirable contaminants**	✓ We will use **SYNTHETIC** >99.5% **pure** SCAs
× **Side effects** can be triggered by THC (e.g. psychosis)	✓ We will use synthetic CBD Analogs (SCAs) – **no THC**
× **Little clinical data** from approved drugs exist (outside of epilepsy) to determine dosing	✓ Planning blinded clinical trials initially in musculoskeletal pain and arthritis
× **Variable uptake and low absorption** (~4 - 9%) due to lipophilic properties of CBD / CBD-like	✓ Developing novel, patented ProNanoLipospheres (PNL) which **enhance bioavailability**

CBD-PNL Enhances Bioavailability > 3fold[1]



- CBD and CBD-PNL administered orally to rats & plasma levels assessed over time
- CBD-PNL >3x absorption compared to CBD alone
- CBD-PNL safe and well tolerated
- Additional methods to improve absorption are being patented under a recently completed agreement with HU

(1) Cherniakov I, et al. (2017) European J of Pharm. Sci 109:21-30

Platform Description

Non-psychoactive CBD analogs (SCAs) are anti-inflammatory, and elicit analgesic effects Studied by Mechoulam, Gallily, Feldmann since 1998 (Malfait et al, PNAS 2000)

HOW DOES IT WORK?

- CBD signals through multiple GPCR receptors, e.g. **CB2R, TRPV-1, 5HT1a, GPR55, GPR18** and others
- Anti-inflammatory, analgesic and anxiolytic properties

OUR PRODUCTS:

NON-PSYCHOACTIVE SCAs

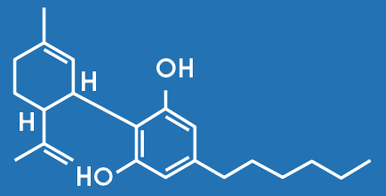
- Scientifically formulated analogs of CBD (SCAs) have been synthesized and patented, new formulations under analysis
- Analysed in animal models of inflammation and pain

WHY MAN-MADE?

- High purity (>99.5%)
- CBD from plants are typically ≤ 98% pure, contain THC, minor cannabinoids, terpenes, flavonoids etc.
- Consistent across batches, more favourable for obtaining regulatory approval

OUR DRUGS

1. HU-436 (1)
2. Domb patent 1 (2)
3. Mechoulam patent 2 (3)
4. Mechoulam patent 3 & others (3)



(1) Patented drug we licensed from HU, but expect to discover superior drugs from ongoing research
(2) CBD derivative, patent being filed, agreement with Domb & HU completed
(3) Not yet filed

Oral CBD: A Superior Treatment for Arthritis?

PROBLEM

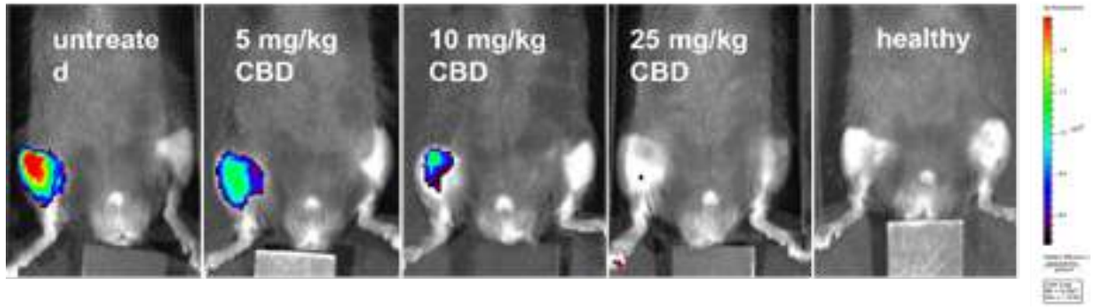
- Persistent pain & swelling in many anti-TNF partial responder RA patients, also in very early RA
- Nonsteroidals do not help, can increase TNF
- Existing therapies are suboptimal

SOLUTION?

- Novel synthetic CBD analogues (SCAs) being developed
- Effective anti-inflammatory (better than NSAIDs)
- Effective analgesic

➢ Trials planned for residual pain in RA,
- SCA in combination with anti-TNF (CBRx)

CBD reduces inflammation in knee arthritis

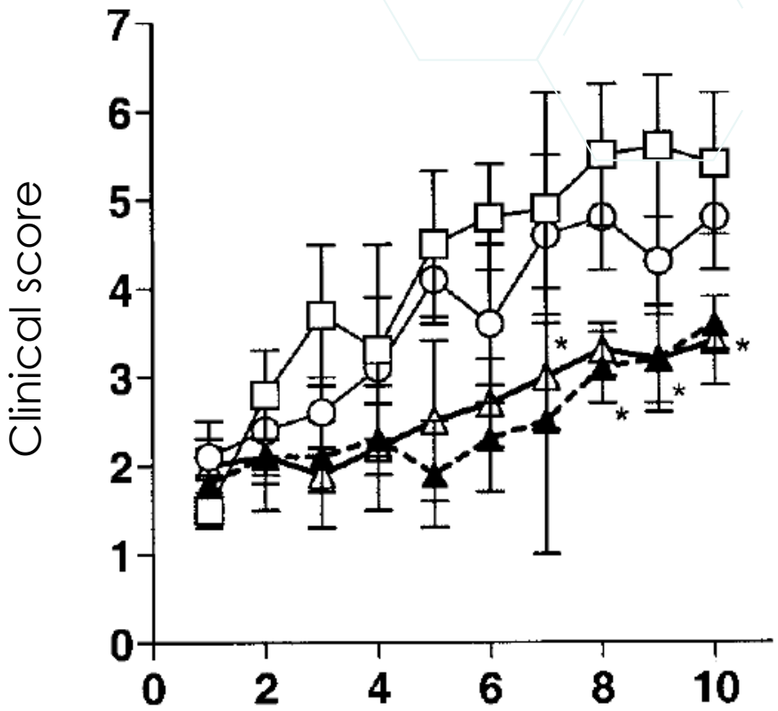


Zymosan induced arthritis in left knee

Louise Topping, Oxford

Oral CBD ameliorates arthritis in mouse RA

A. M. Malfait, R. Mechoulam, M. Feldmann, R. Gallily
PNAS 2000;97:17:9561-9566



Mice given CBD orally at onset of arthritis.
50 mg/kg (△), 25mg/kg (▲), or 10 mg/kg (o).