Targeted Glucose Dendrimer- Cannabidiol Conjugates: Safe and Effective Treatment of Pain and *Status Epilepticus*

Durgadas Cherukaraveedu, Ph.D.

Spencer Shumway, Preeti Vyas, Narendra Kale, Kavichandhirakanth Murugesan, Shreevadsaa A. M, Sujatha Kannan, Kunal S Parikh, Rangaramanujam M Kannan

Center for Nanomedicine, Wilmer Eye Institute
The Johns Hopkins University School of Medicine

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CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

High demand for treatment options for post-operative and acute pain

80 million patients suffer from moderate-to-severe acute pain

40 million acute pain patients receive an opioid each year

First-line treatments have major limitations

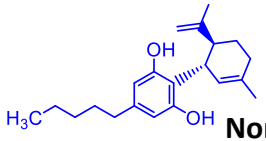
- **Ineffective in 75% of patients**
- **Disabling off-target effects**
- **Risk of dependence and addiction**
- **Patient-patient variability**

An effective, safe, non-addictive alternative will dramatically improve patient care and reduce costs.

Luby, A. O., et al. Annals of surgery 281(3):p 347-352, 2025 Lopez, et al., An Evaluation of the Prevalence of Acute and Chronic Pain Medication Use in the United States: a Real World Database Analysis, ASRA Annual Pain Meeting 2023.

Wu, C., Raja, S. Treatment of acute postoperative pain, The Lancet, 377: 9784. 2011.

Cannabidiol has promise in pain management, but formulation issues preclude broad implementation



Non-psychoactive

Cannabidiol (CBD)

CBD as an analgesic: Arthroscopic Rotator Cuff Repair

TABLE 5
Subgroup Analysis of Pain and Patient Satisfaction[a]

Variable	CBD 25 mg	CBD 50 mg	Control	*P* Value
Day 1				
VAS score	5.1 ± 2.9	3.9 ± 3.2	5.7 ± 3.2	.04
Satisfaction	5.7 ± 3.2	8.0 ± 2.5	5.6 ± 3.7	.005
Day 2				
VAS score	4.7 ± 2.7	4.7 ± 3.0	5.3 ± 2.6	.61
Satisfaction	6.5 ± 2.8	7.9 ± 2.1	6.0 ± 3.3	.02
Day 7				
VAS score	3.1 ± 2.1	2.1 ± 1.7	3.2 ± 2.7	.13
Satisfaction	7.4 ± 2.7	8.6 ± 2.4	7.9 ± 2.7	.34
Day 14				
VAS score	2.0 ± 1.4	1.1 ± 1.3	2.3 ± 2.4	.10
Satisfaction	8.3 ± 2.2	9.1 ± 2.4	8.5 ± 2.4	.58

[a]Data are shown as mean ± SD. CBD, cannabidiol; VAS, visual analog scale.

VAS, visual analog scale

Buccally absorbed CBD shows significant promise for immediate postoperative pain control.

CBD formulations can be unsafe inconvenient and ineffective

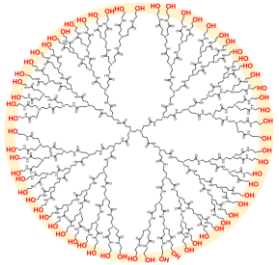
- **Delayed onset of action**
- **Inconvenient administration modalities**
- **Short half-life and low bioavailability**
- **Drug-Drug interactions and toxicity**

Addressing these challenges will enable broad application in acute and chronic pain

Alaia MJ, et al. The American Journal of Sports Medicine. 2022;50(11):3056-3063
https://www.aaos.org/aaosnow/2024/monday/research/research04/

Meissner H, Cascella M. Cannabidiol (CBD) in Clinical Care. StatPearls. Jan 2025.

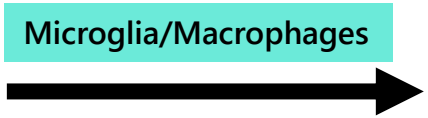
Next-generation nanotherapeutic platform enables cell-targeted drug delivery



HD with 64 hydroxyl groups and a size of ~ 4nm, in contrast, a typical nanoparticle is 100 nm

Hydroxyl Dendrimer

Microglia/Macrophages

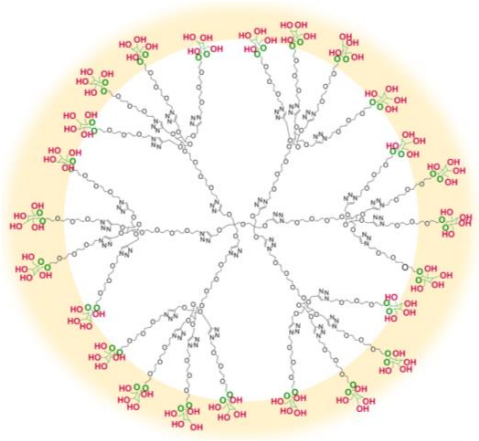


Based on enhanced endocytosis at site of pathology

Evaluated in 50 models, 7 species, and 6 Phase I and 2 Phase II trials

Kannan Lab & Ashvattha Therapeutics (co-founded by Prof. Kannan Rangaramanujam and Prof. Sujatha Kannan)

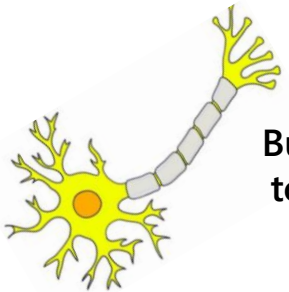
Novel glucose dendrimer(GD) targets neurological disorders



Glucose Dendrimer

***Click chemistry: State-of-the-Art Synthesis* from Kannan Lab**
~4nm with 96 hydroxyl groups

Neurons

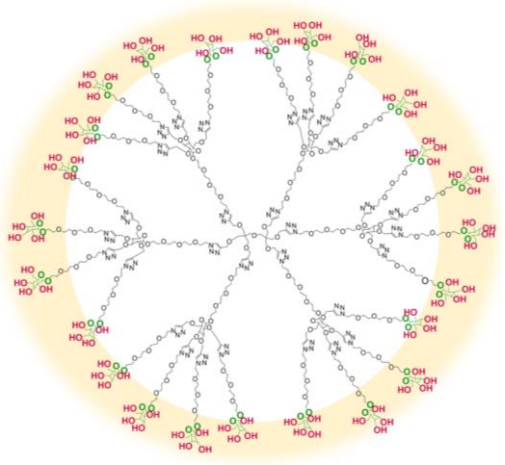


Builds on prior learnings to address neurological disorders

Based on dysregulated glucose metabolism at the site of pathology

Sharma et al., Bioeng Transl Med. 2024;e10655. ,https://doi.org/10.1002/btm2.10655
IP and Patent, Kannan Lab, JHU

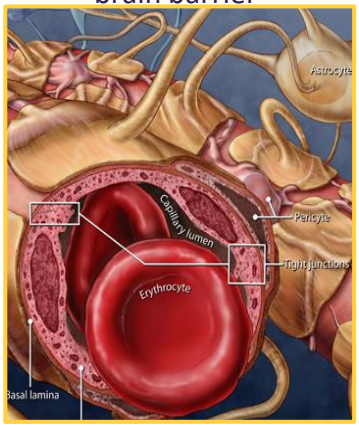
Glucose dendrimer overcomes longstanding impediments to neurological drug delivery



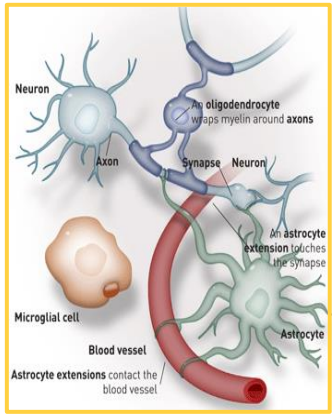
Glucose Dendrimer

Nanomedicine is designed (size, charge, hydroxyl density) to overcome physiological barriers safely and specifically enter neurons due to the glucose composition

Overcomes the blood-brain barrier



Uptake into specific disease associated cells

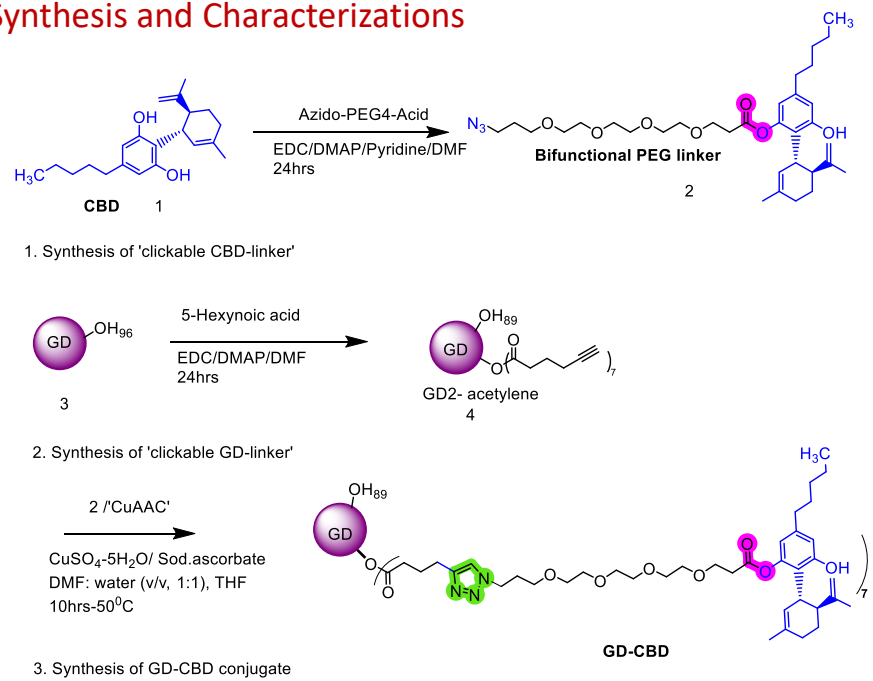


- Glucose dendrimers specifically localize in activated or dysfunctional immune cells and neurons in the brain that mediate neurological and mental health disorders.
- Drug payloads can be conjugated to the dendrimer and delivered specifically to these cells, significantly improving efficacy and safety (reducing off-target effects).

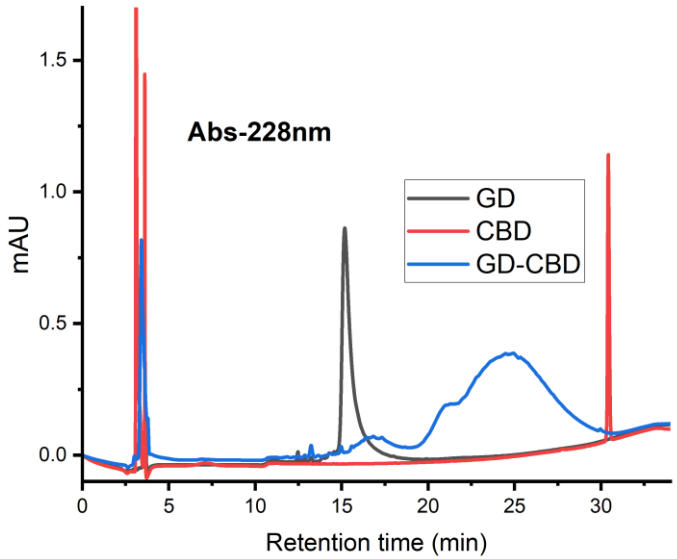
Tech Session VII: Nanomedicine and Nanoscale Delivery (Focus: Bioengineering)
Dr. Narendra Kale, Novel glucose dendrimer approach to target hyperactive neurons in vivo: mechanistic insights
Friday, July 18, 2025 , 9:16 AM - 9:27 AM EDT , Location: 121 B/C

Synthesis of highly water-soluble glucose dendrimer-cannabidiol (GD-CBD) conjugates

Synthesis and Characterizations

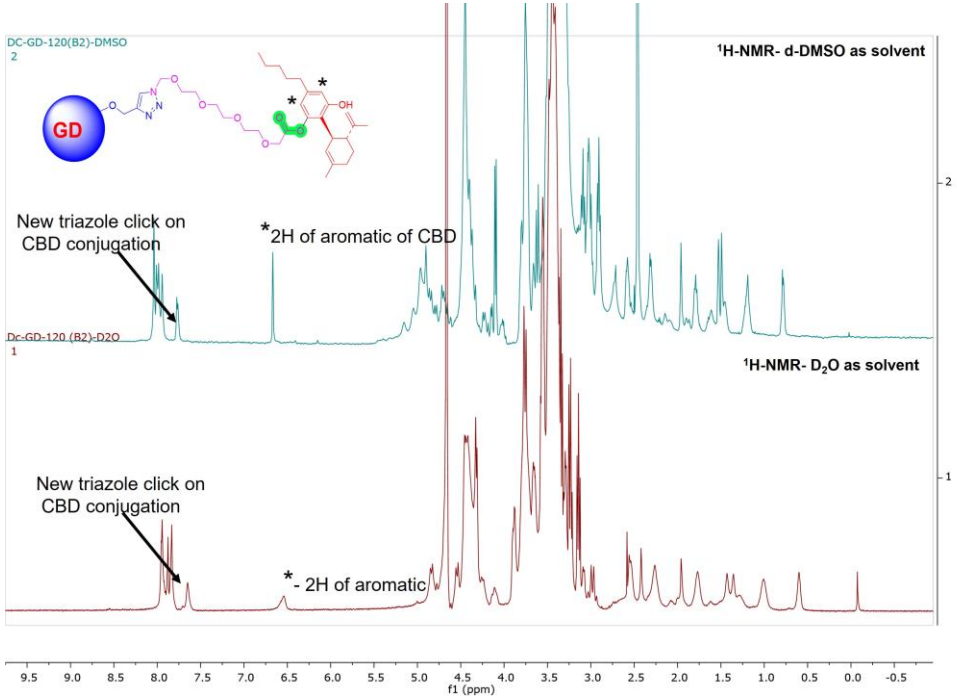


GD-CBD showed purity ≥98.5 % by HPLC



Patent filed

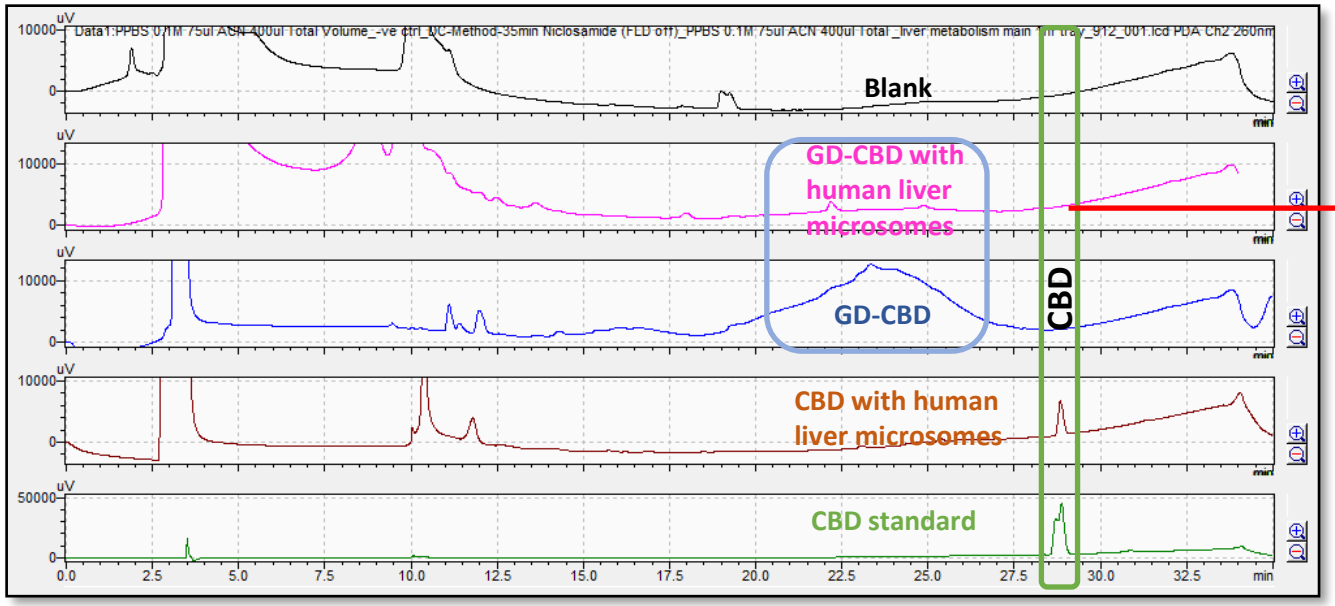
GD-CBD has high purity, aqueous solubility, and CB2 binding



Physicochemical characterization	
Size (DLS)	6.04 ± 0.81 nm
Charge(zeta potential)	-6.8 ± 0.6 mV
Drug loading (NMR)	12.5%
Mol. Weight (MALDI -TOF)	17.6 kDa
Purity (HPLC)	>98.5%
Solubility	>200 mg/mL
CB2 EC50	7.8 µM

Unlike free CBD, the GD-CBD did not metabolize by human liver microsomes

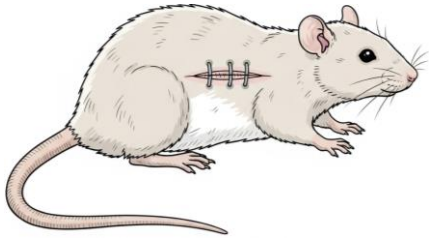
One hour incubation with human liver microsomes



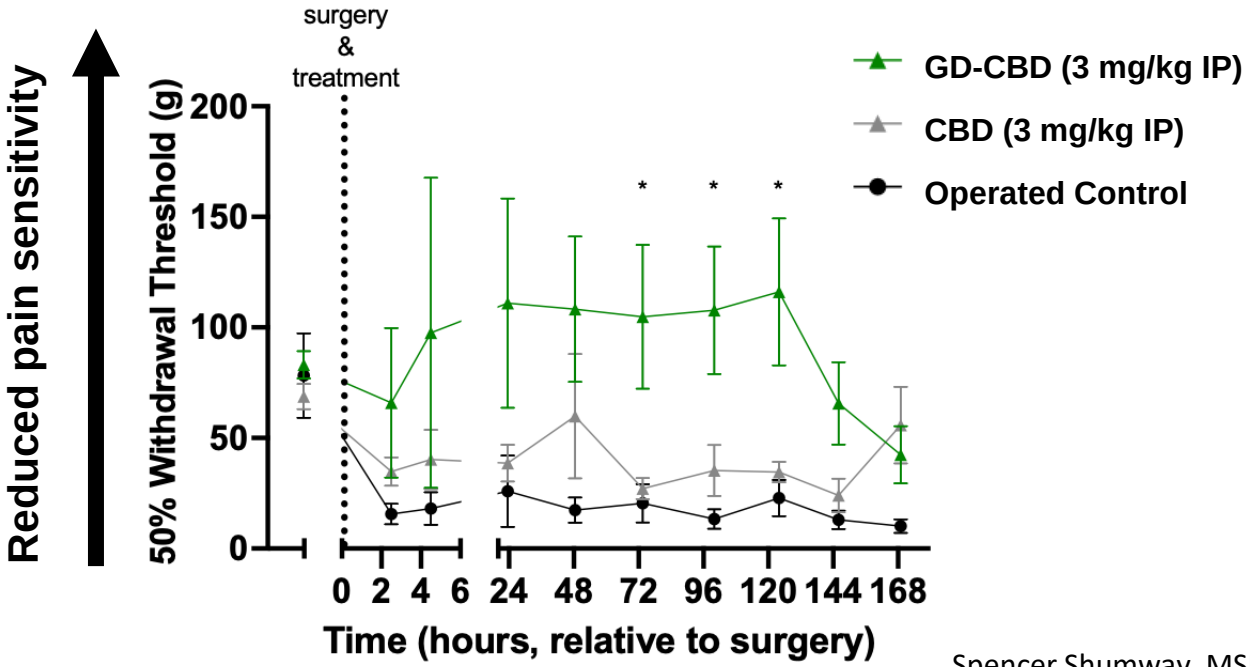
GD-CBD on incubation with human liver microsomes -No free CBD observed by HPLC

No adverse metabolic effect on the liver by GD-CBD

A single dose of systemic GD-CBD effectively reduces post-operative pain sensitivity for five days

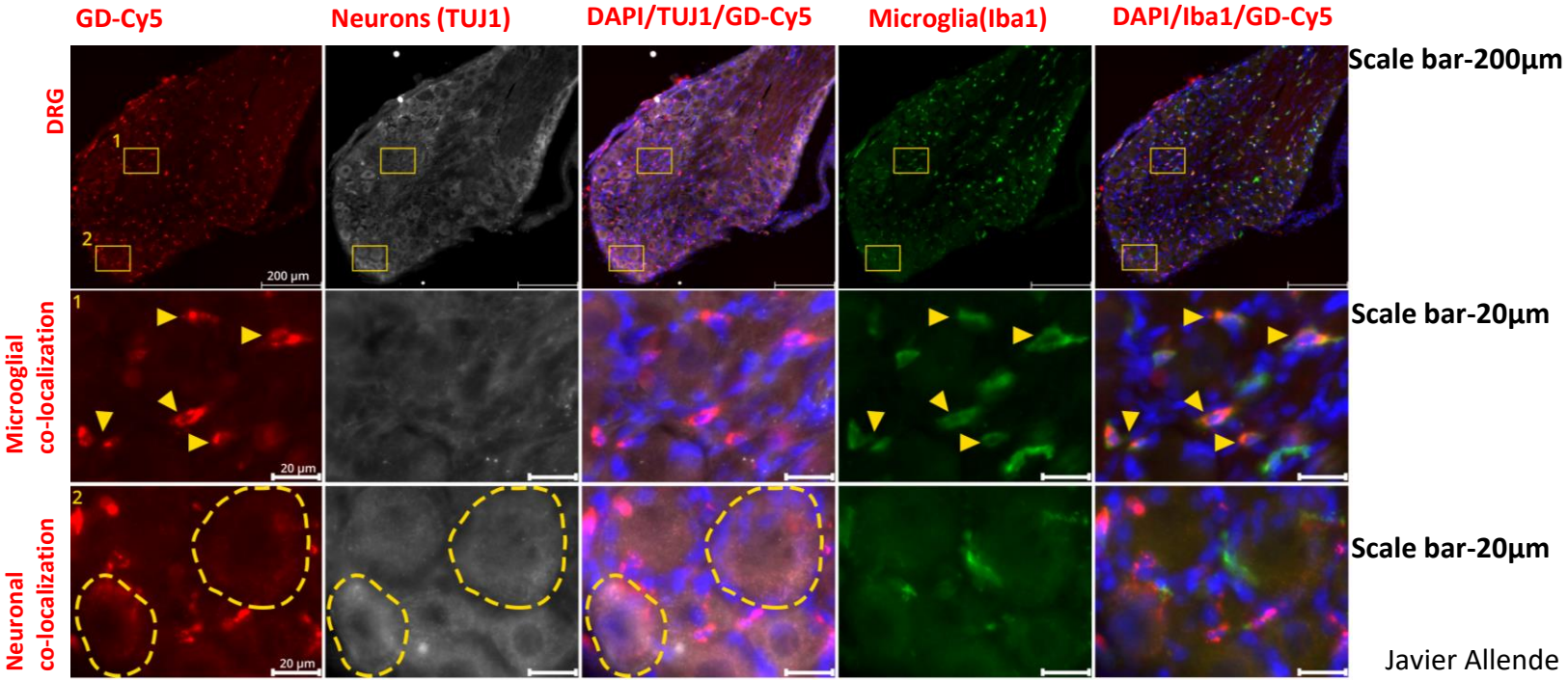


Rat- Flank incision model



Spencer Shumway, MSE

GD targets neurons and immune cells in the injured (post-operatively) rat DRG

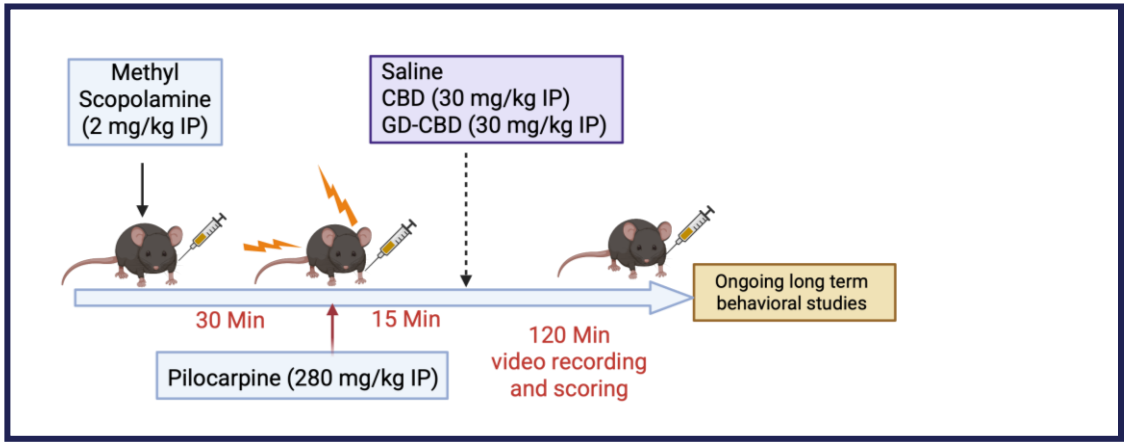


Javier Allende Labastida, MD, Ph.D.

GD-CBD as a safer therapeutic option for *status epilepticus* (SE)

Our approach to *status epilepticus (SE)* treatment with GD-CBD

Pilocarpine model of refractory *status epilepticus*

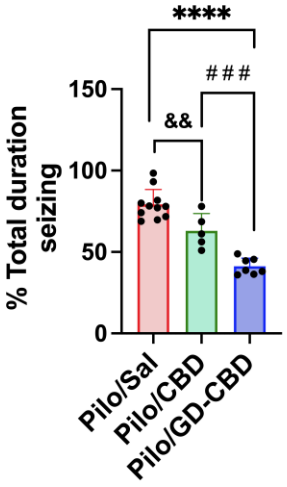


GD-CBD therapy after establishing the seizure circuit.

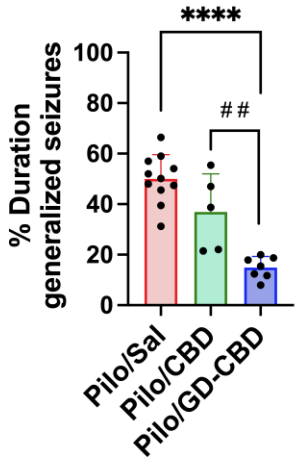
Preeti Vyas, Ph.D.

GD-CBD administration reduces acute seizure duration and severity

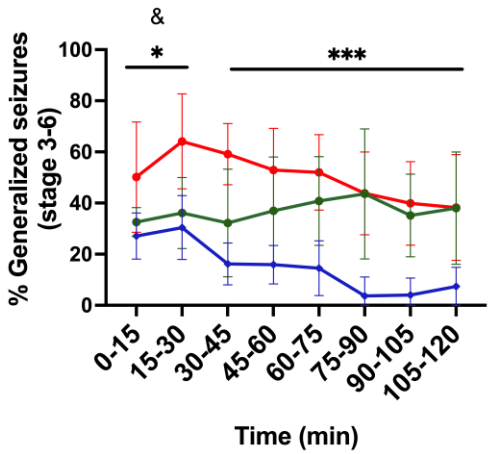
% total duration seizing

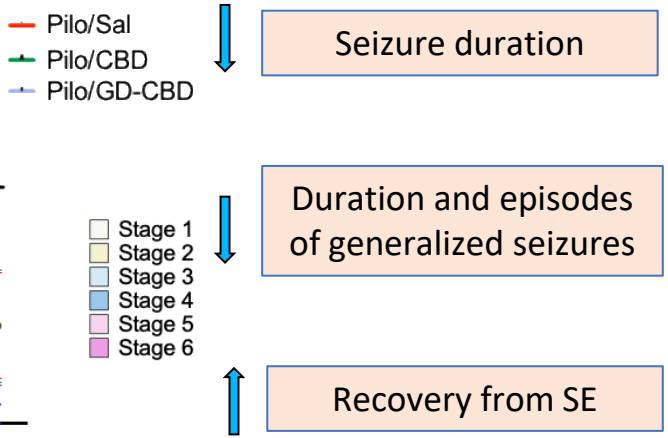


% Duration of Generalized seizures



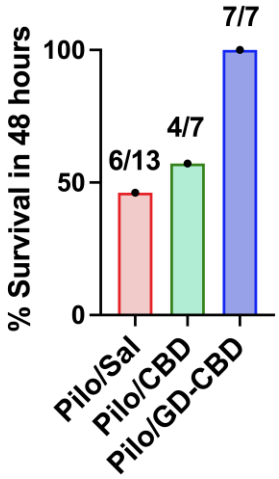
% Duration of Generalized seizures over time



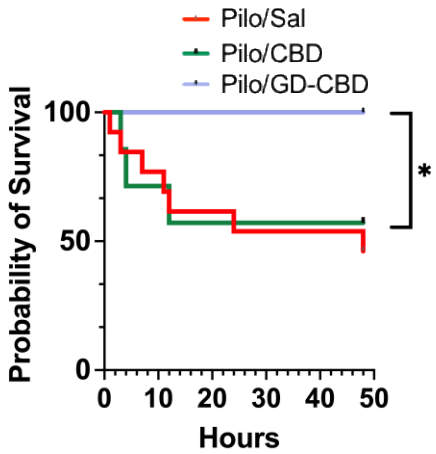


GD-CBD improves survival and reduces seizure severity post-SE

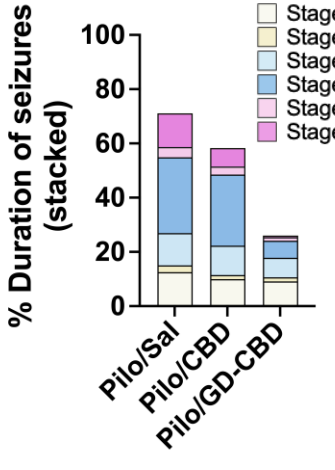
% Survival 48 hours post-SE



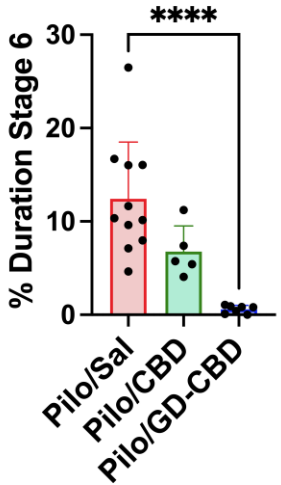
Survival proportions



% Duration of seizure stages (stacked)



% Duration stage 6



Survival post- SE

Seizure severity

Conclusion and Perspectives

GD-CBD: A safer and efficient CBD delivery to treat pain and *status epilepticus*

- Developed via click chemistry for targeted nervous system delivery

- Single systemic dose:
  - 5-day relief from post-op pain
  - Reduced seizure severity and improved survival in acute SE with sustained efficacy.

Perspectives: A **systemic GD-CBD** therapeutic formulation with safety and effectiveness for pain and seizure management

Acknowledgements & collaborations

Funded by Samata Therapeutics

Rangaramanujam M. Kannan, Ph.D.

Sujatha Kannan, MD

Kunal S. Parikh, Ph.D.

Wathsala Liyanage, Ph.D.
Narendra Kale, Ph.D.
Milan Paul, Ph.D.
Dohyun Kim, Ph.D.
Ruma Ghosh, Ph.D.
Kavichandhirakanth Murugesan, MSE
Shreevadsaa A. M, BS

Preeti Vyas, Ph.D.
Javier Allende Labastida, MD, Ph.D.
Maria Paula Avalos, Ph.D.
Diego Almodiel, BS

Spencer Shumway, MSE