# Targeted glucose dendrimer ketamine therapy protects against refractory *status epilepticus* in mice

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NEXT-GENERATION DELIVERY INNOVATIONS

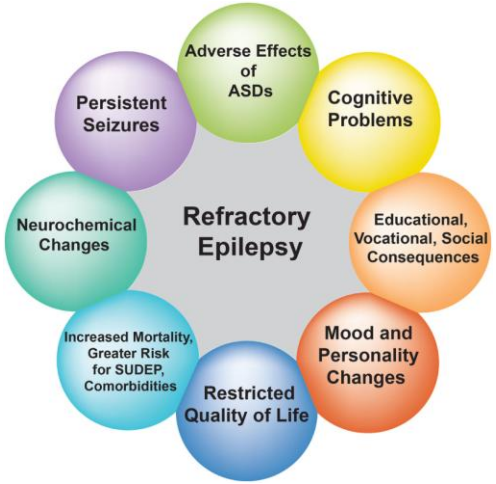
# Disclosures

- All IP related to these compounds is licensed to Samata Therapeutics, Inc. I am a co-inventor of related IP.

- All conflict of interests are managed by Johns Hopkins University.

**Patent pending**

# Ketamine is a promising NMDA antagonist, but is unsafe and impractical for broad implementation




**50 Million**

people globally had epilepsy in 2023, according to WHO, making it one of the most common neurological disorders.

**30% to 40%**

of adults with epilepsy remain refractory to pharmacological treatment, while

**Ketamine is effective and recommended for treating refractory *status epilepticus***

**Ketamine's limitations overshadow its promise**

- **Risks of dissociation, hypoventilation**
- **Inconvenient administration modalities**
- **Short half-life and low bioavailability**
- **Drug interactions and abuse potential**

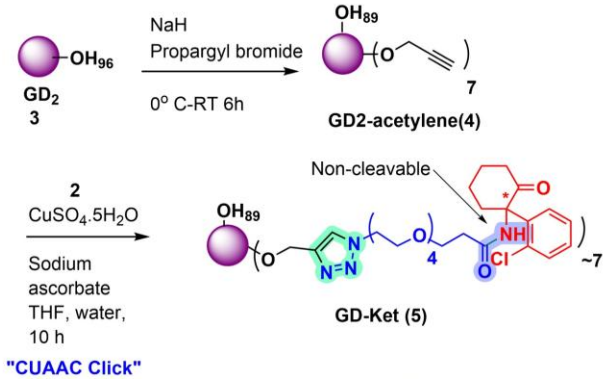
**Addressing these challenges will enable broad application in epilepsy, depression, and pain**

# GD-Ket exhibits high purity, stability and better potency than free ketamine

Patent pending

## (a) Synthesis of clickable ketamine


## (b) Synthesis of glucose dendrimer conjugate

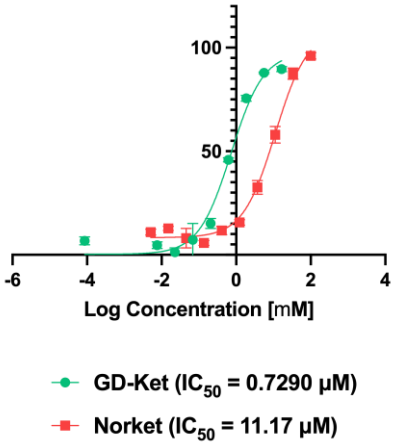



| Physiochemical Characterization | |
|---|---|
| Size | 6.2 nm |
| Zeta Potential | -0.41 mV |
| No. of attachments | 7 |
| Drug Loading | ~ 10% |
| HPLC purity | > 99% |
| Mol. Weight | 16,690 Da |

**High purity**

**Stable at intracellular and extracellular conditions**

### NMDAR 1A/2B Antagonist Assay

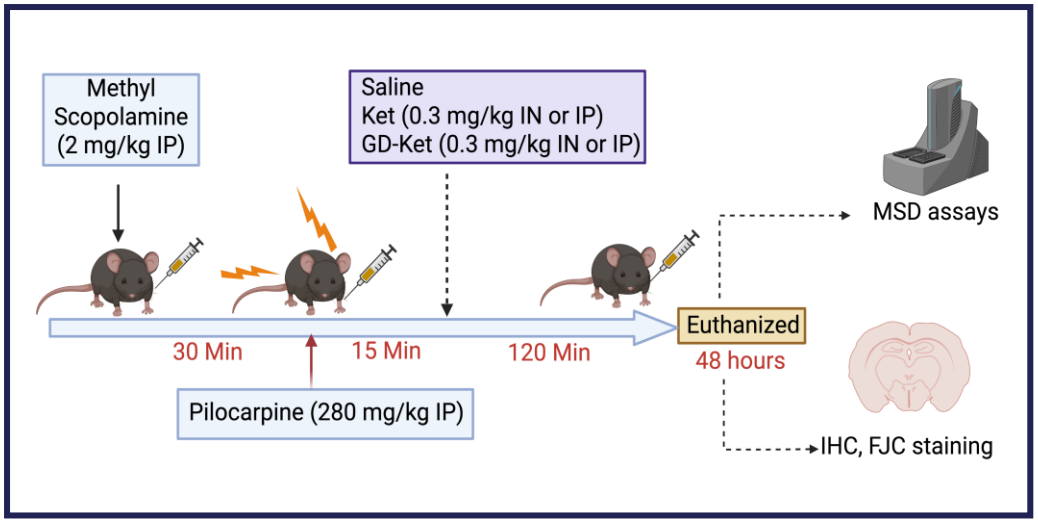


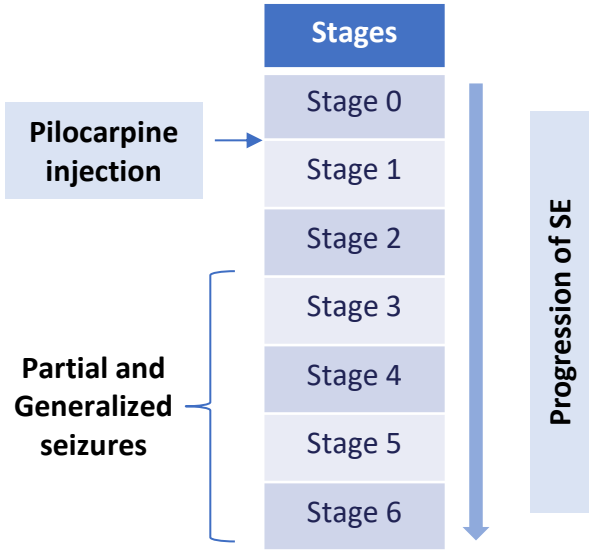

**More potent than Ketamine, superior $IC_{50}$**




Wathsala Liyanage, PhD

# Pilocarpine model of refractory *status epilepticus*



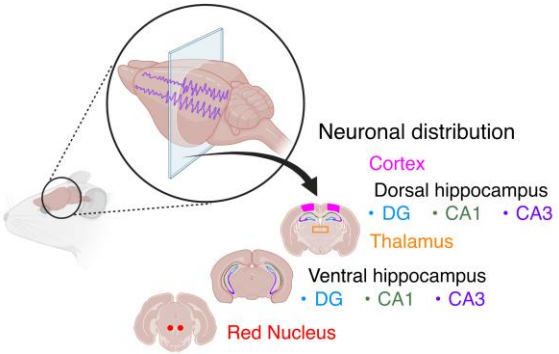

Modified Racine Scale (Racine 1972; Borges 2002)

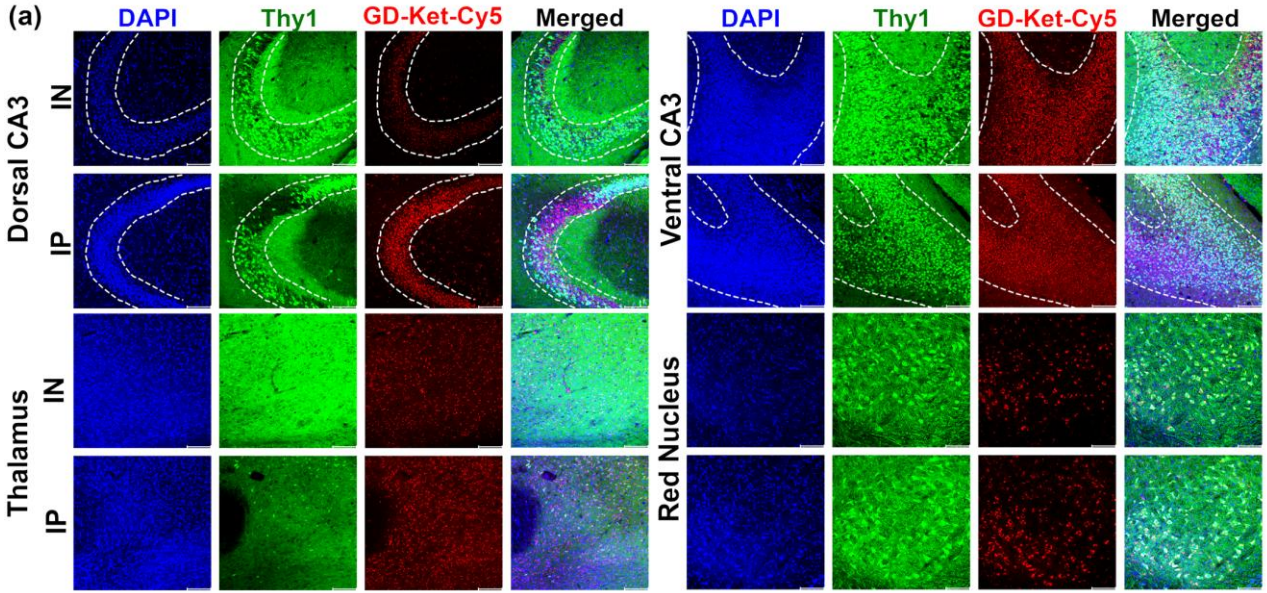
# GD-Ket targets neurons in areas associated with seizures in SE mice

Patent pending

**GD-Ket predominantly targets neurons in**

- CA3 regions of hippocampus
- Thalamus
- Red nucleus (nucleus rubber)
- Cortex

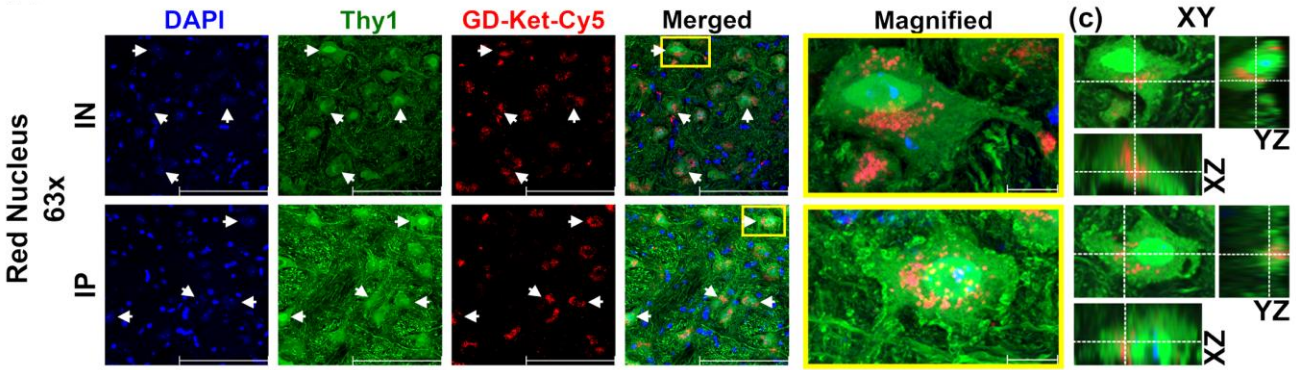


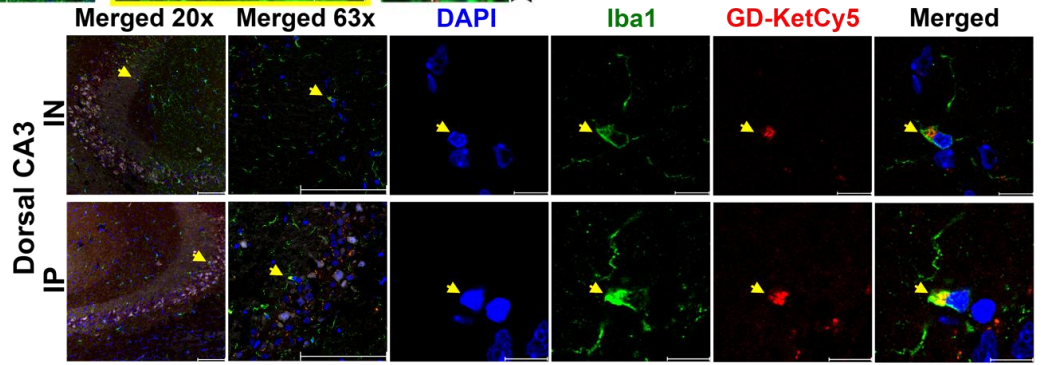

Javier Allende Labastida, MD, PhD

# GD-Ket is primarily uptaken by neurons in areas associated with SE

Patent pending




Neuronal co-localization



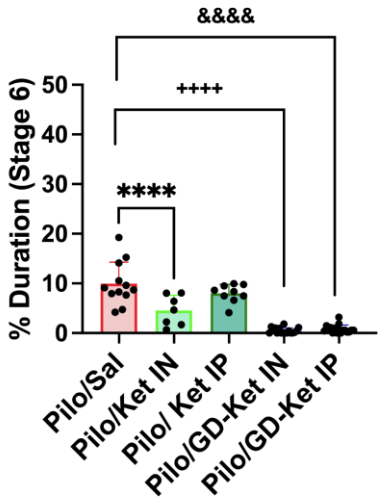

**Microglial co-localization in areas associated with neuroinflammation post-SE**

Javier Allende Labastida, MD, PhD

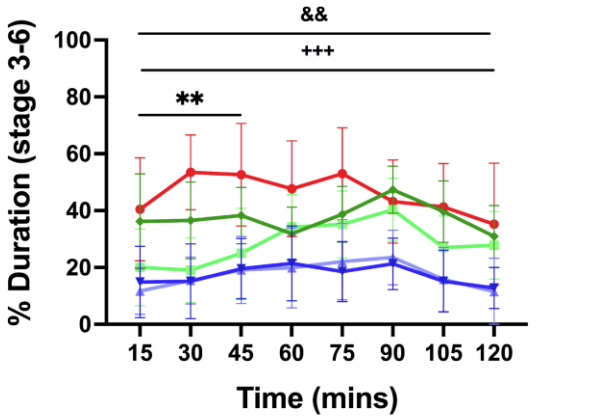
# Acute GD-Ket administration reduces seizure duration and severity

Patent pending

### % Stage 6 duration




### % Duration of Generalized seizures over time




### Recovery from SE within first hour

| | #Recovered / #Tested |
|---|---|
| Pilo/Sal | 0/27 |
| Pilo/Ket IN | 2/15 |
| Pilo/Ket IP | 0/13 |
| Pilo/GD-Ket IN | 17/21 |
| Pilo/GD-Ket IP | 16/22 |

↓ Seizure duration

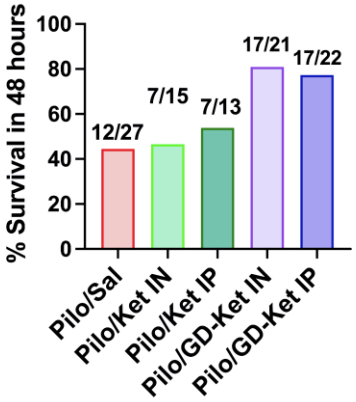
↑ Recovery from SE

* versus Pilo/Ket IN
\+ versus Pilo/GD-Ket IP
& versus Pilo/GD-Ket IP

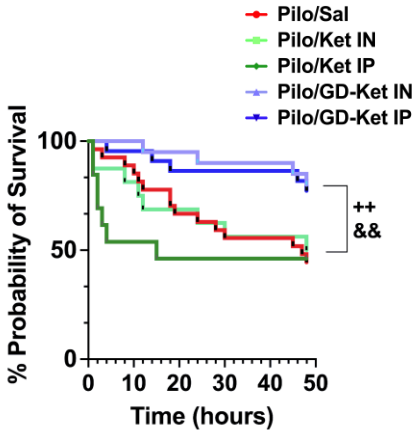
# GD-Ket improves survival and reduce seizure severity post-SE

Patent pending

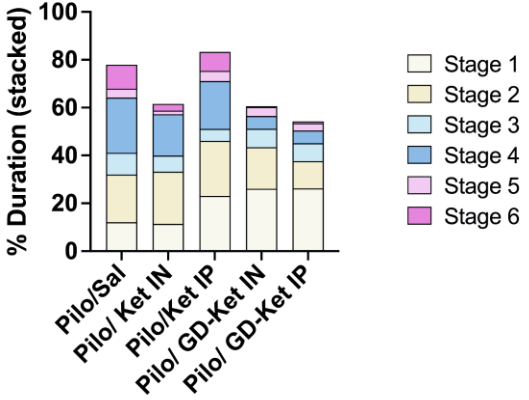
**% Survival 48 hours post-SE**



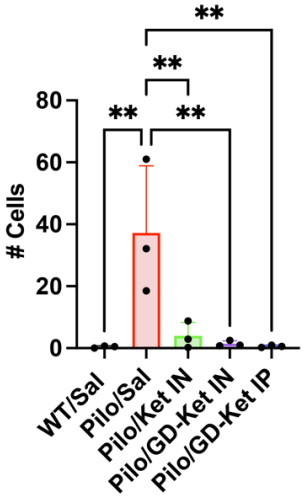

**Survival proportions**




**% Duration of seizure stages (stacked)**




**FJC $^{+}$ cells per hippocampus**



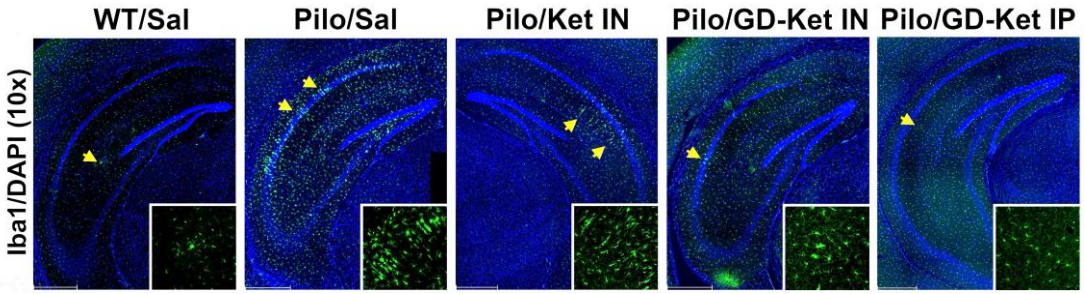

↑ Survival post-SE

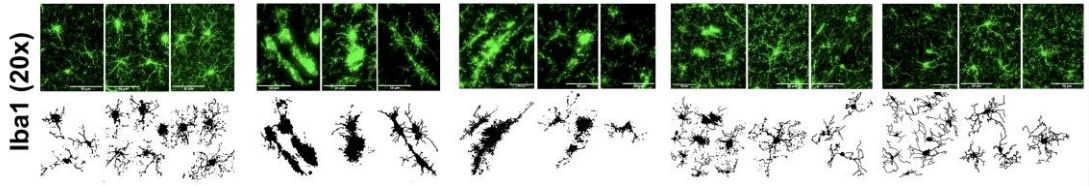
↓ Seizure severity

↓ Reduce neurodegeneration

# GD-Ket protects against hippocampal inflammation post SE

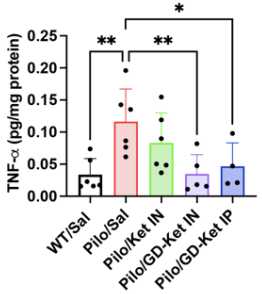
Patent pending



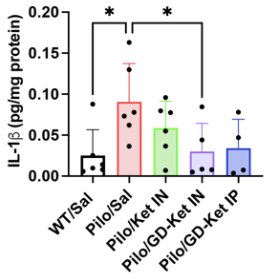




Reduces glial activation

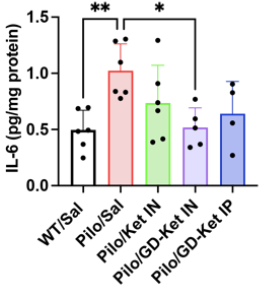
TNF-α levels




IL-1β levels




IL-6 levels

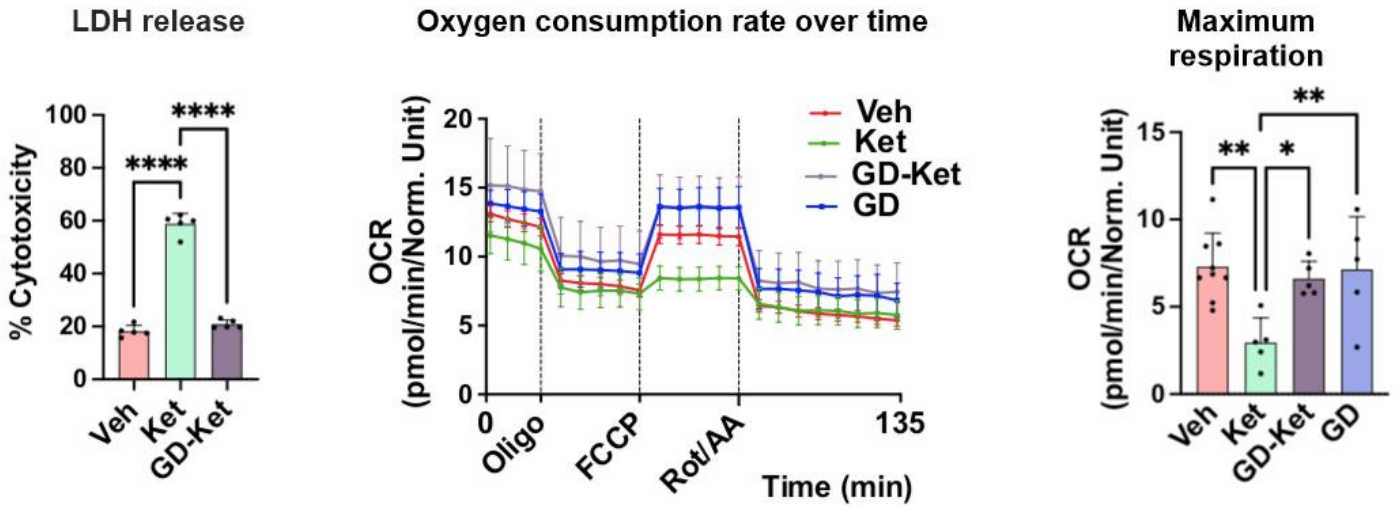



Reduces Cytokine release

Reduces Neuronal inflammation

# GD-Ket does not exhibit *in vitro* toxicity of ketamine

Patent pending




GD-Ket does not show the *in vitro* toxicity in differentiated neurons, unlike Ketamine. Abnormal mitochondrial respiration noted with ketamine but not GD-Ket

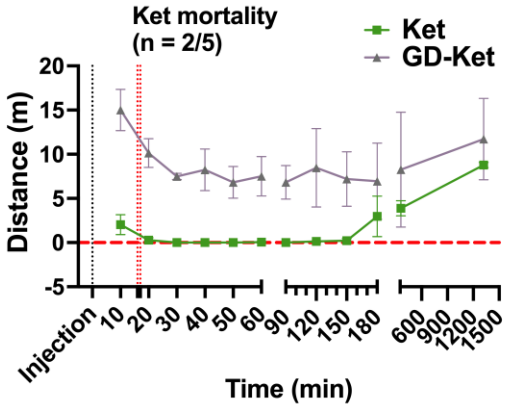



Bruno Henrique, PhD
Milan Paul, PhD
Narendra Kale, PhD

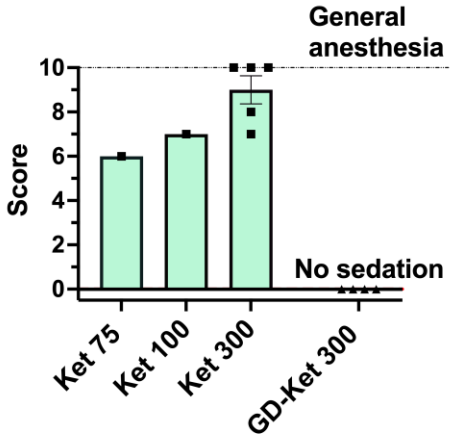
# Cell specific targeting of GD-Ket reduces off-target effects of free ketamine

Patent pending

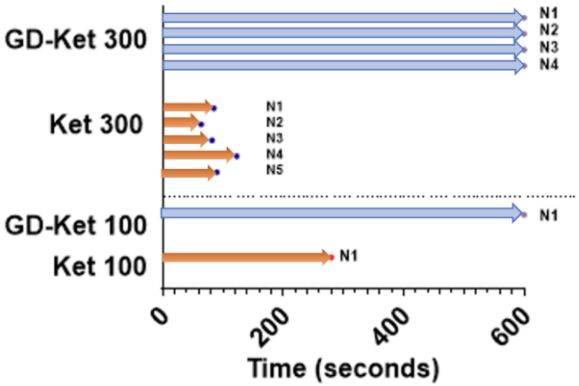
### Activity post-administration




### Composite sedation score



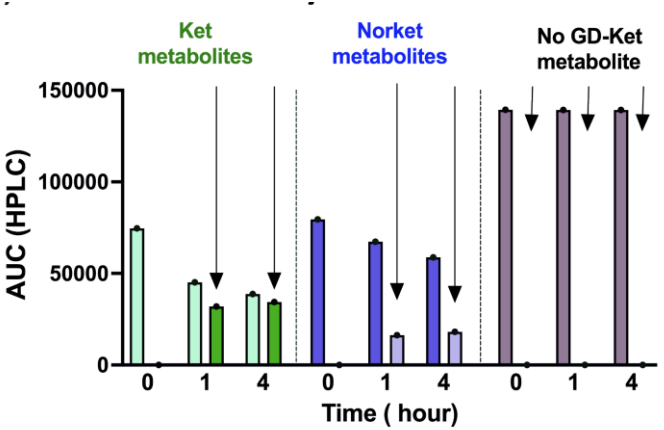

### Latency to deep sedation

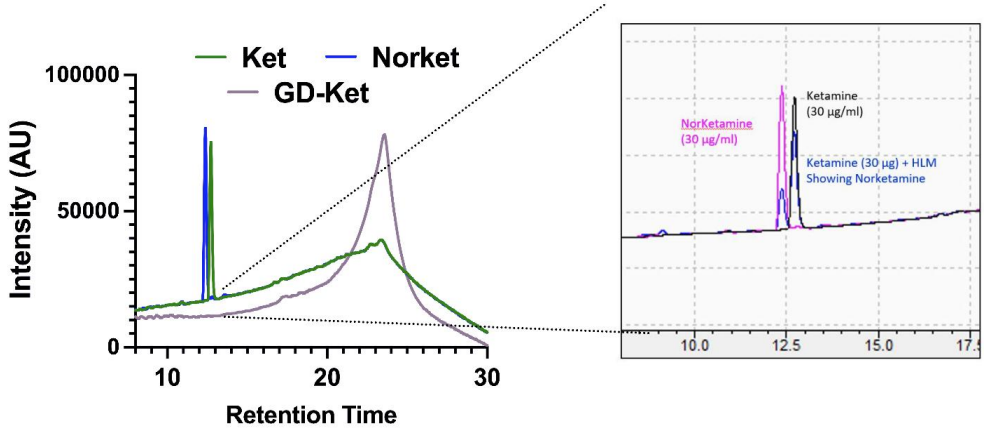



**GD-Ket targets the site of pathology without the off-target effects at high doses.**

# GD-Ket is not metabolized by liver enzymes unlike ketamine and norketamine

Patent pending



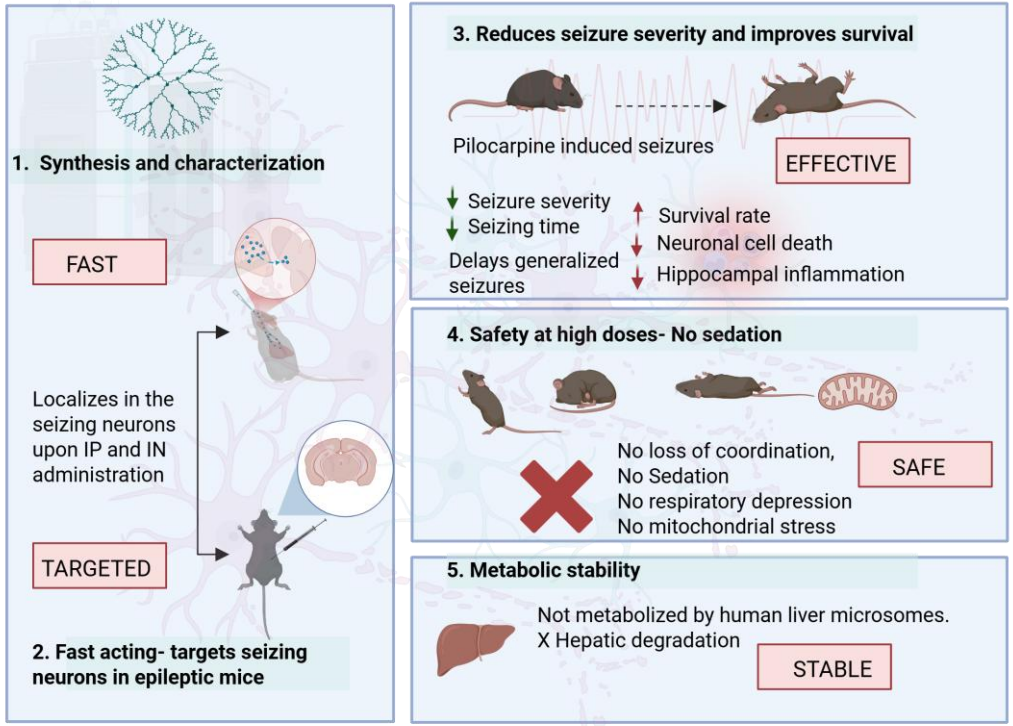



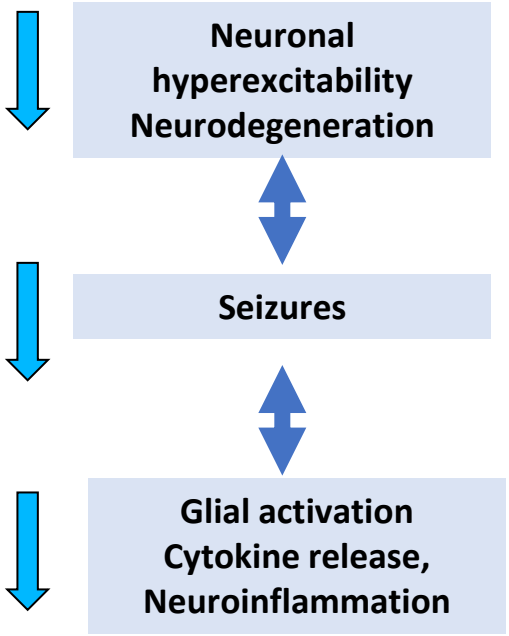

- Ket
- NorKet
- GD-Ket
- Ket metabolite
- Norket metabolite
- GD-Ket metabolite

**Dendrimer conjugation prevents hepatic degradation** → **Enhanced Metabolic stability** → **No hepatotoxicity No toxic effects due to metabolites**

Kavichandhirakanth Murugesan, MSE

# GD-Ket shows clinical potential as a convenient, safe, and effective treatment of refractory SE.



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