Non-Ligand-Based Targeting of Hyperactive Neurons: Deep Insights of Cellular Interactions with Glucose Dendrimer

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CRS 2025 ANNUAL MEETING & EXPOSITION
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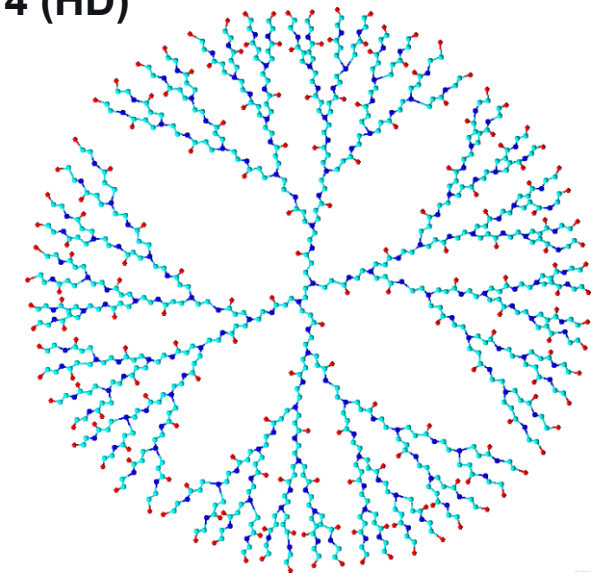
NEXT-GENERATION DELIVERY INNOVATIONS

Glucose dendrimer: Next generation platform to target neuronal cells

Poly(amidoamine) dendrimer generation 4 (HD)

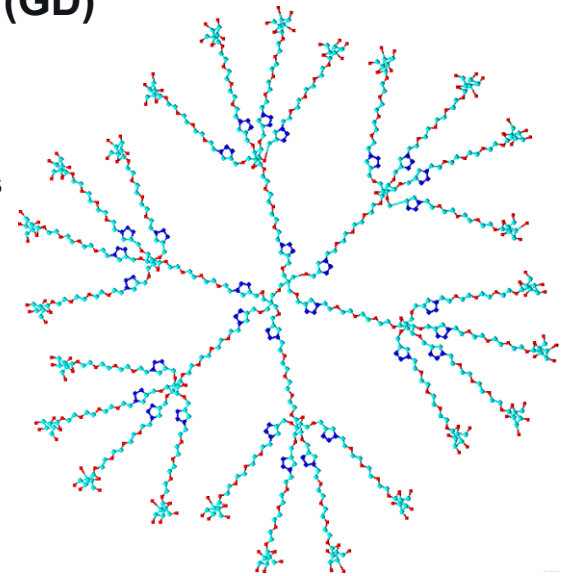


Physicochemical traits

Number of hydroxyl groups on the surface: 64
Size: ~ 4 nm
Charge: neutral / slightly negative
Polarity: highly polar

Glucose dendrimer generation 2 (GD)

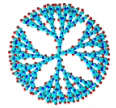
Primary made of PEG and Glucose moieties on the surface



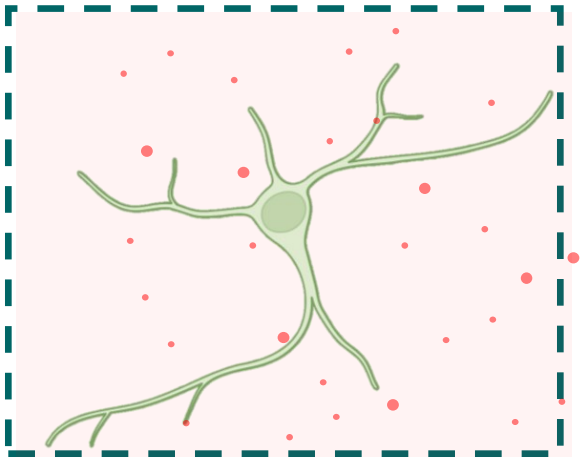
Physicochemical traits

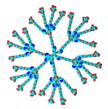
Number of hydroxyl groups on the surface: 96
Size: ~ 4 nm
Charge: slight negative
Polarity: highly polar

Unique features of **glucose dendrimers** compared to other nanoparticles

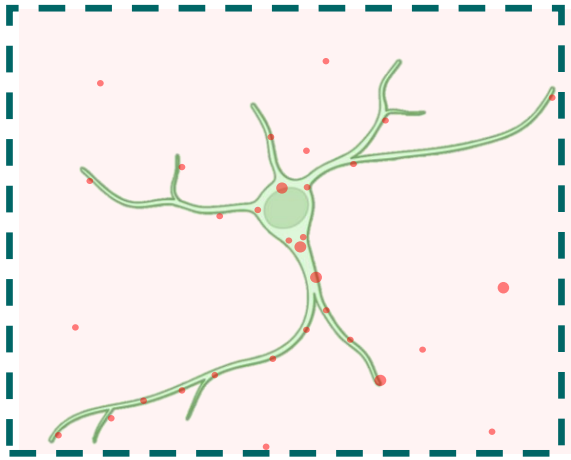


PAMAM-OH
~ 4 nm
Neutral/-
Polar

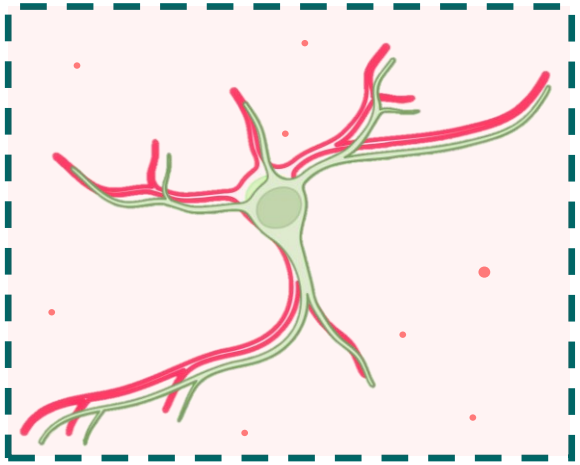




Glucose dendrimer
~ 4 nm
-
Polar



Iron oxide nanoparticle
~ 5 nm
+++
Non-polar



Poly(styrene) nanoparticle
~ 20 nm
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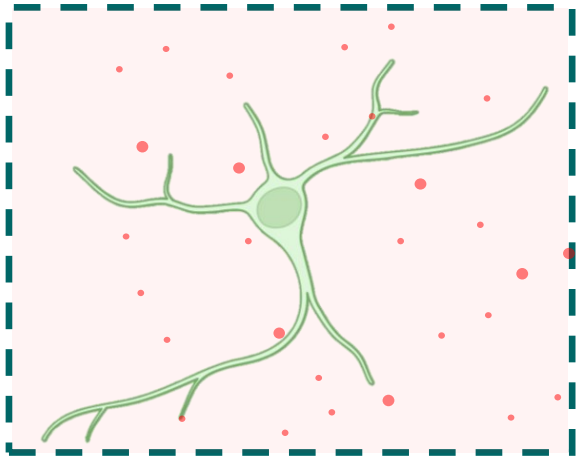
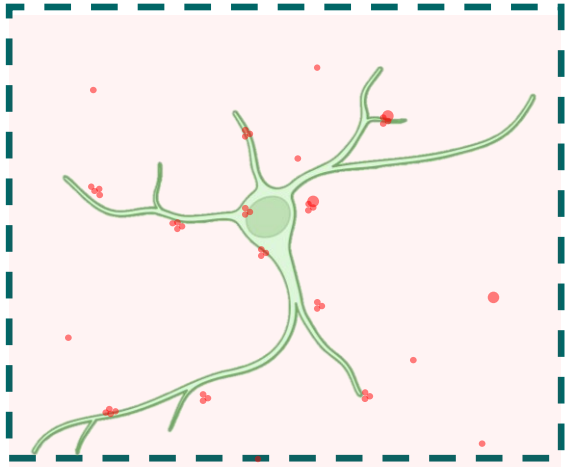
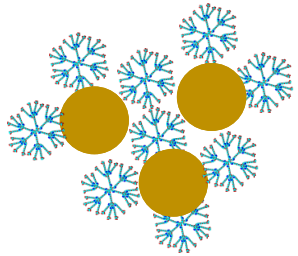
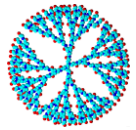
Non-polar





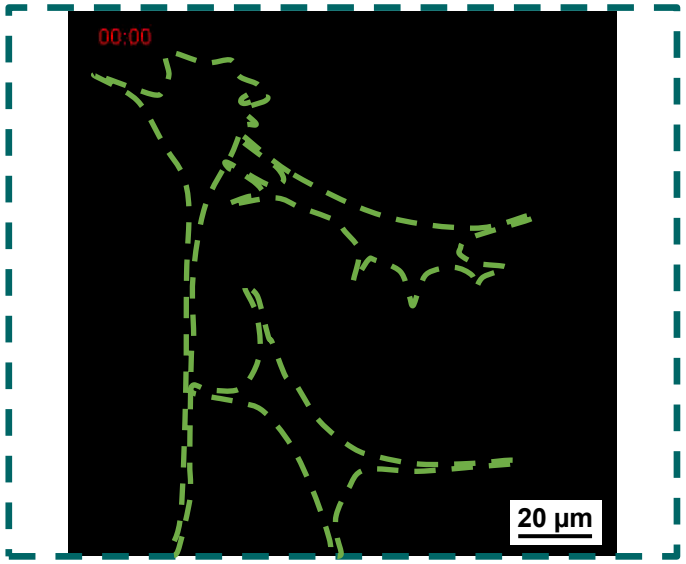


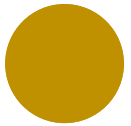
Glucose dendrimer-Iron oxide nanoparticle complex
~ 200 nm
+++
Polar



PAMAM-OH

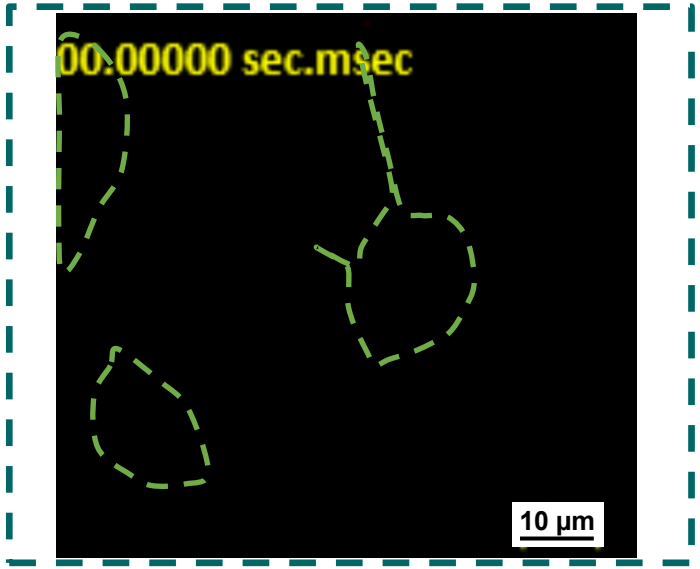
~ 4 nm
Neutral/-
Polar

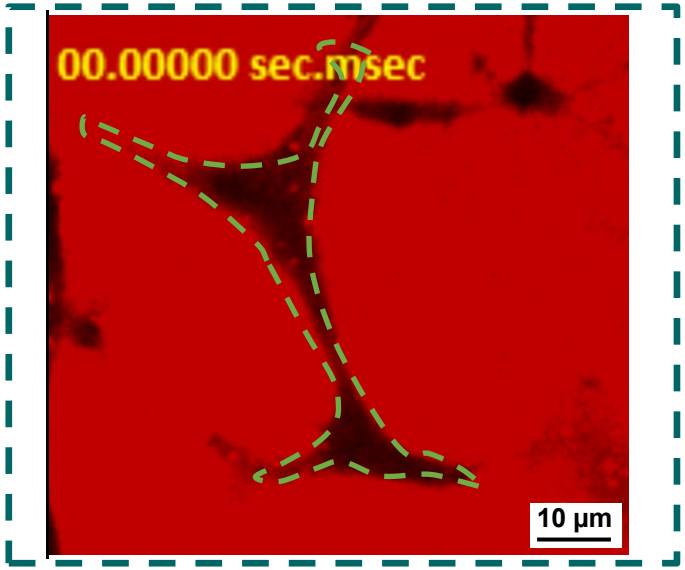


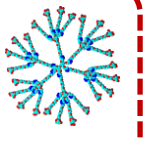


Iron oxide nanoparticle

~ 5 nm
+++
Non-polar

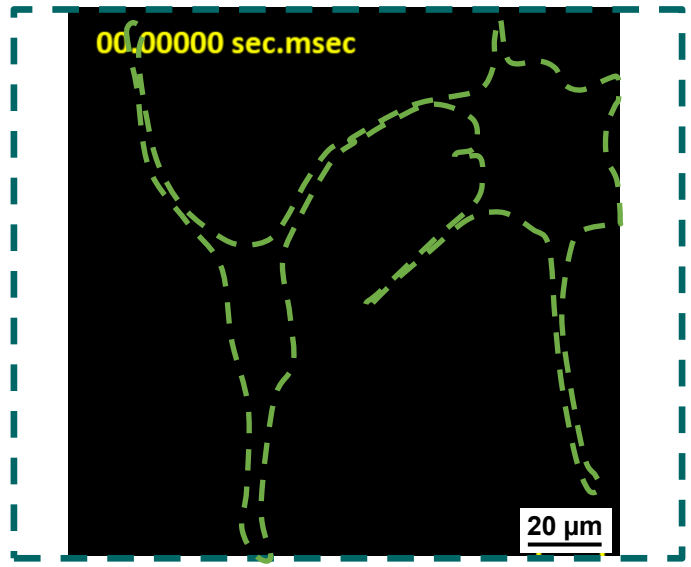






Glucose dendrimer

~ 4 nm
-
Polar



Poly(styrene) nanoparticle

~ 20 nm
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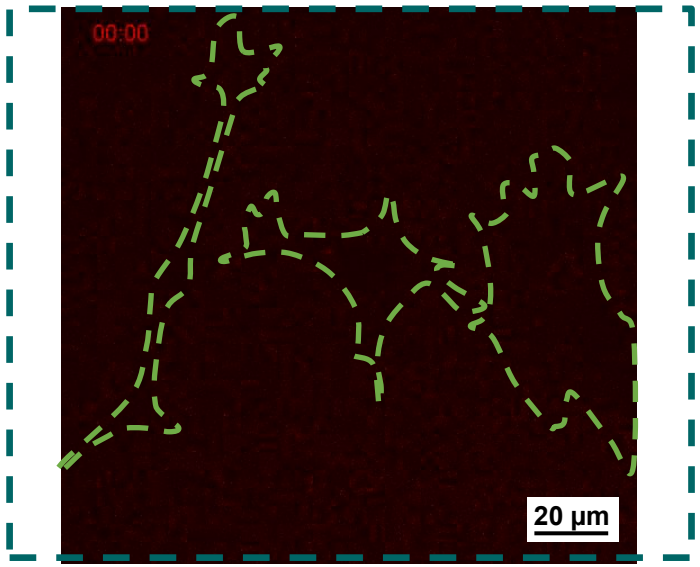
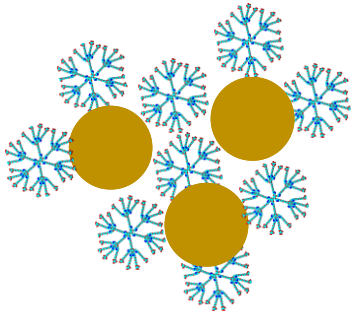
Non-polar

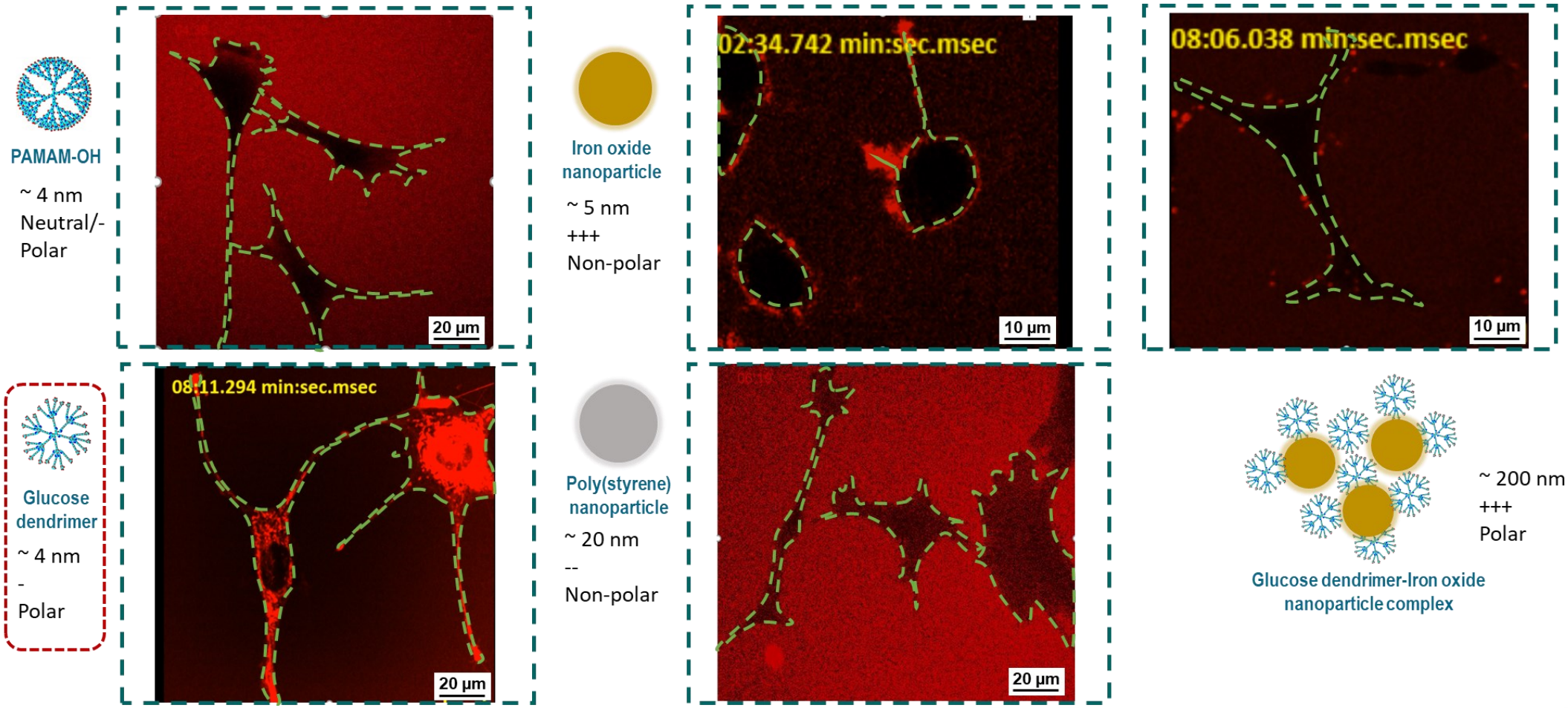




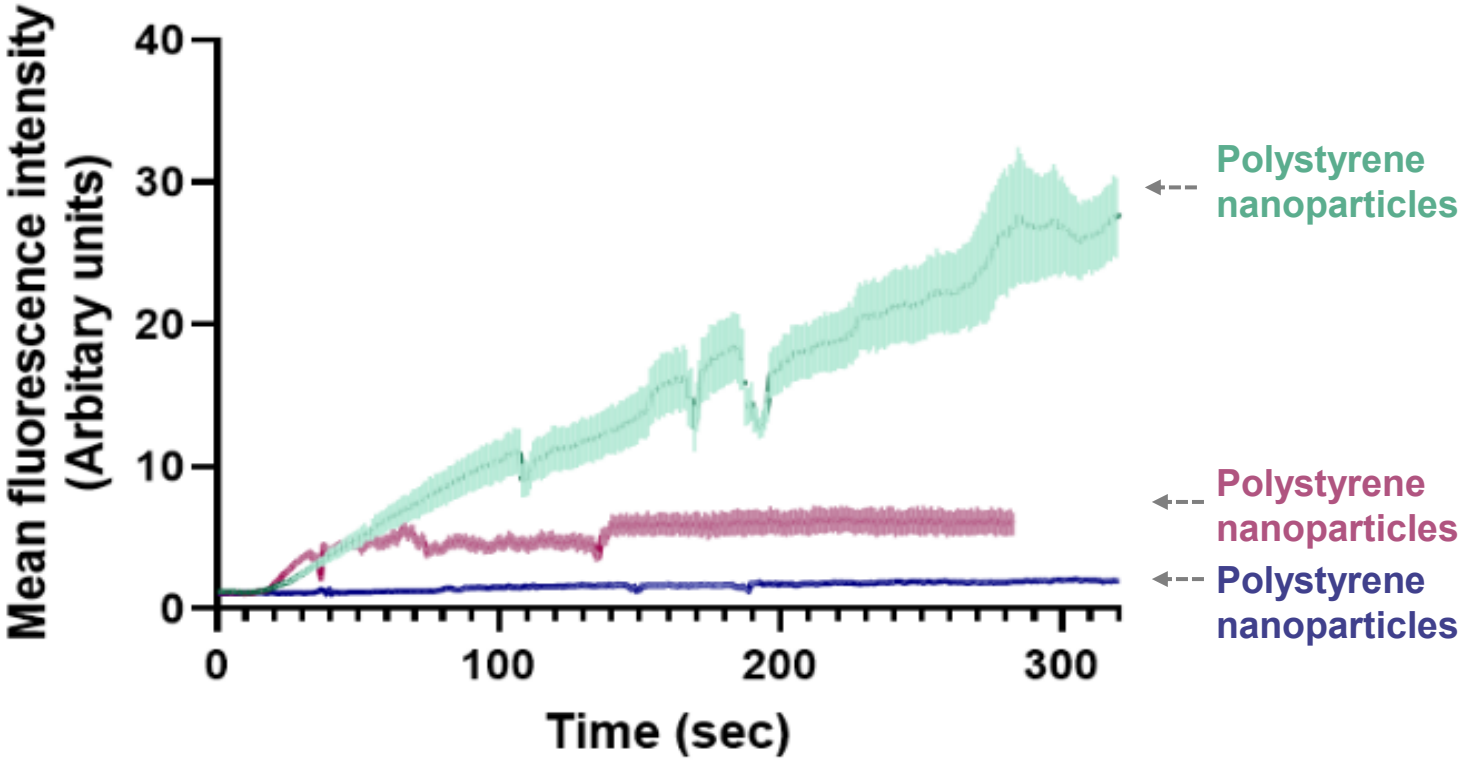
Glucose dendrimer-Iron oxide nanoparticle complex

~ 200 nm
+++
Polar

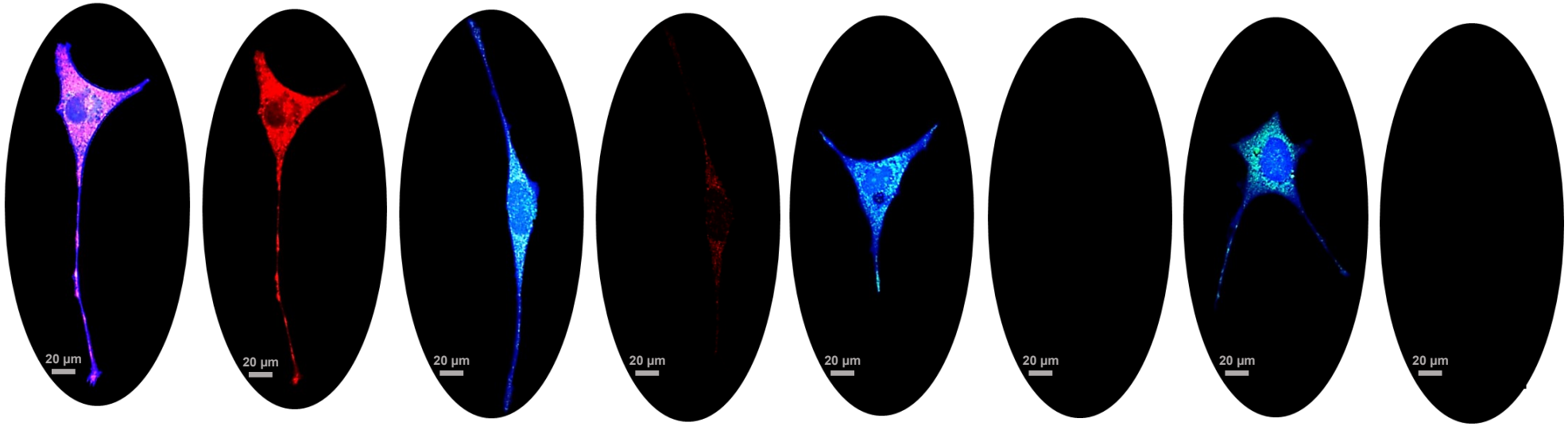
Glucose dendrimer **rapidly up-taken** by hippocampal **neuronal cells**



Glucose dendrimer uptake was **~13 fold higher** than conventional poly(styrene) nanoparticles **within 300 seconds** of exposure



Preferential uptake of Glucose Dendrimer in **hyperexcited neurons**



CellTracker + GD-Cy5 (30 min) | GD-Cy5 (30 min)

With Glutamate activated

CellTracker + GD-Cy5 (30 min) | GD-Cy5 (30 min)

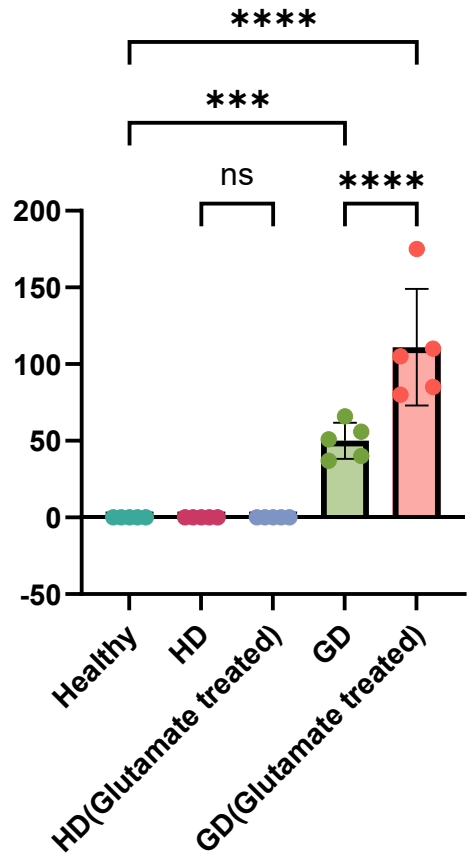
Without Glutamate activated

CellTracker + HD-Cy5 (30 min) | HD-Cy5 (30 min)

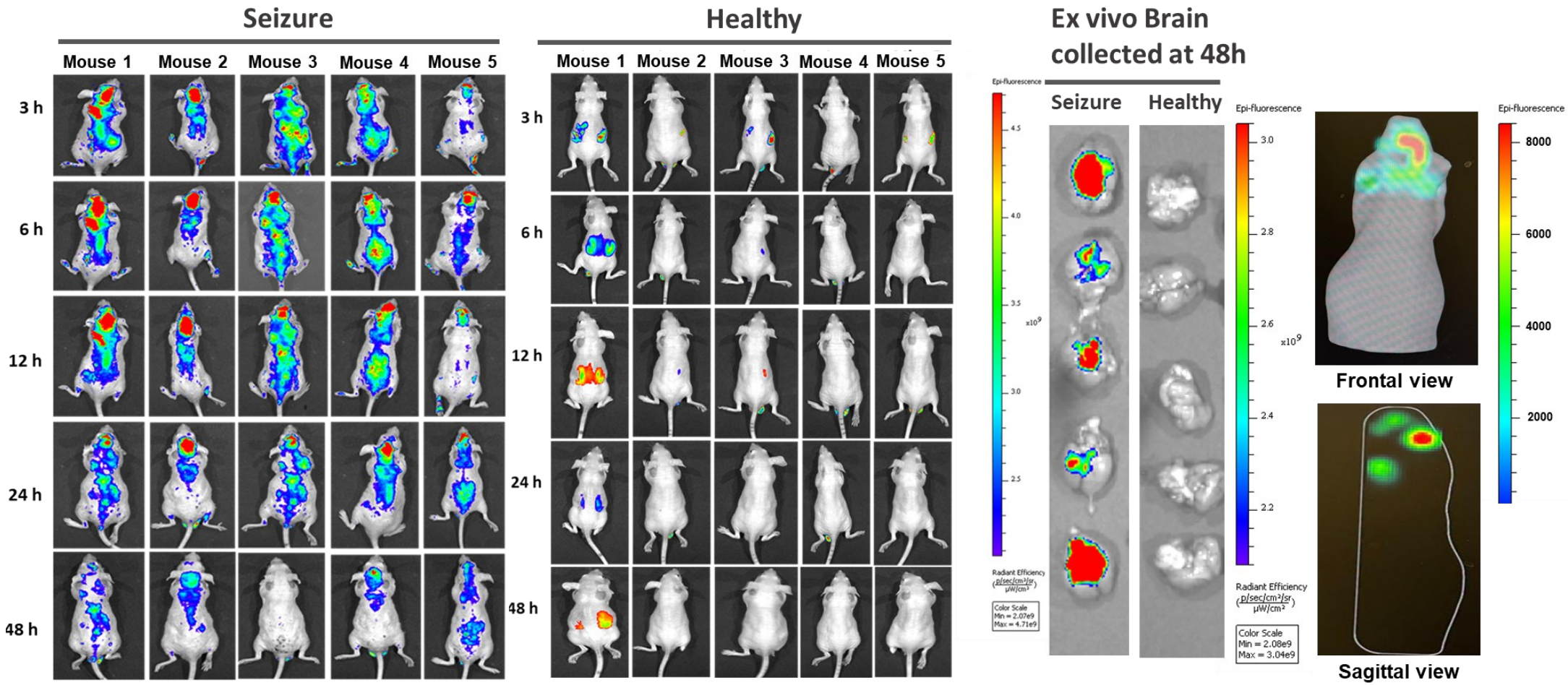
With Glutamate activated

CellTracker + HD-Cy5 (30 min) | HD-Cy5 (30 min)

Without Glutamate activated

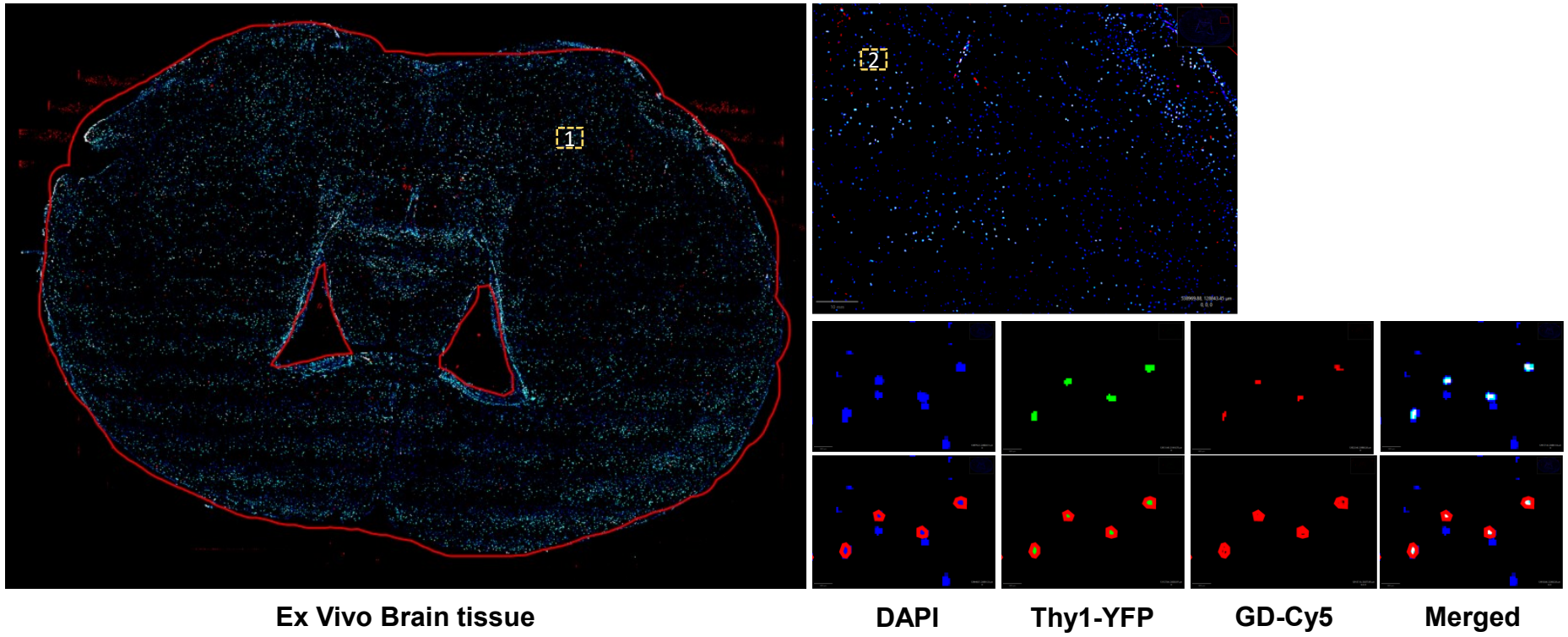


Glucose Dendrimer **localizes in Seizure-affected brain regions** with **no uptake** in **healthy mice**



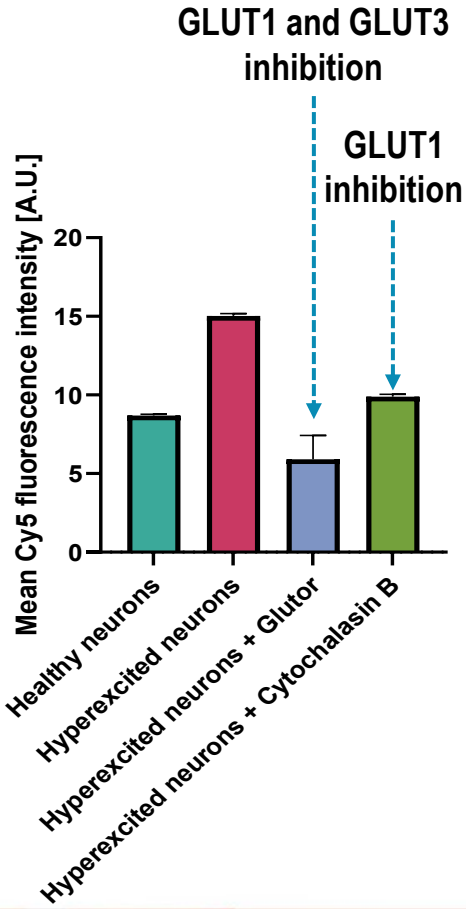
One-hour uptake of Glucose Dendrimer Is significantly reduced by glucose transporter (GLUT) Inhibition in Ex Vivo Brain tissue

First mechanism involved with uptake of Glucose Dendrimer



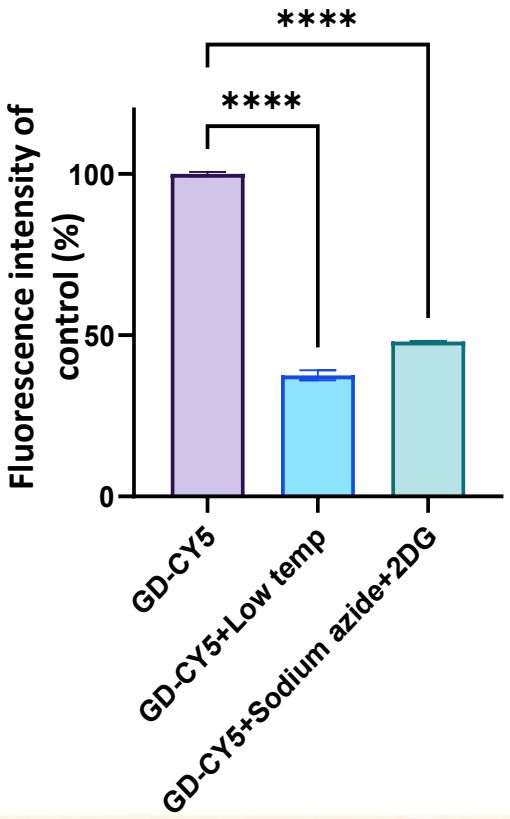
Ex Vivo Brain tissue

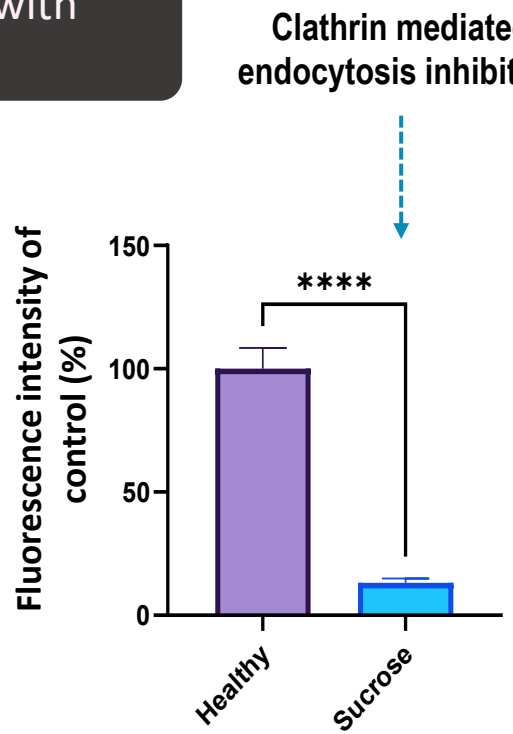
DAPI Thy1-YFP GD-Cy5 Merged

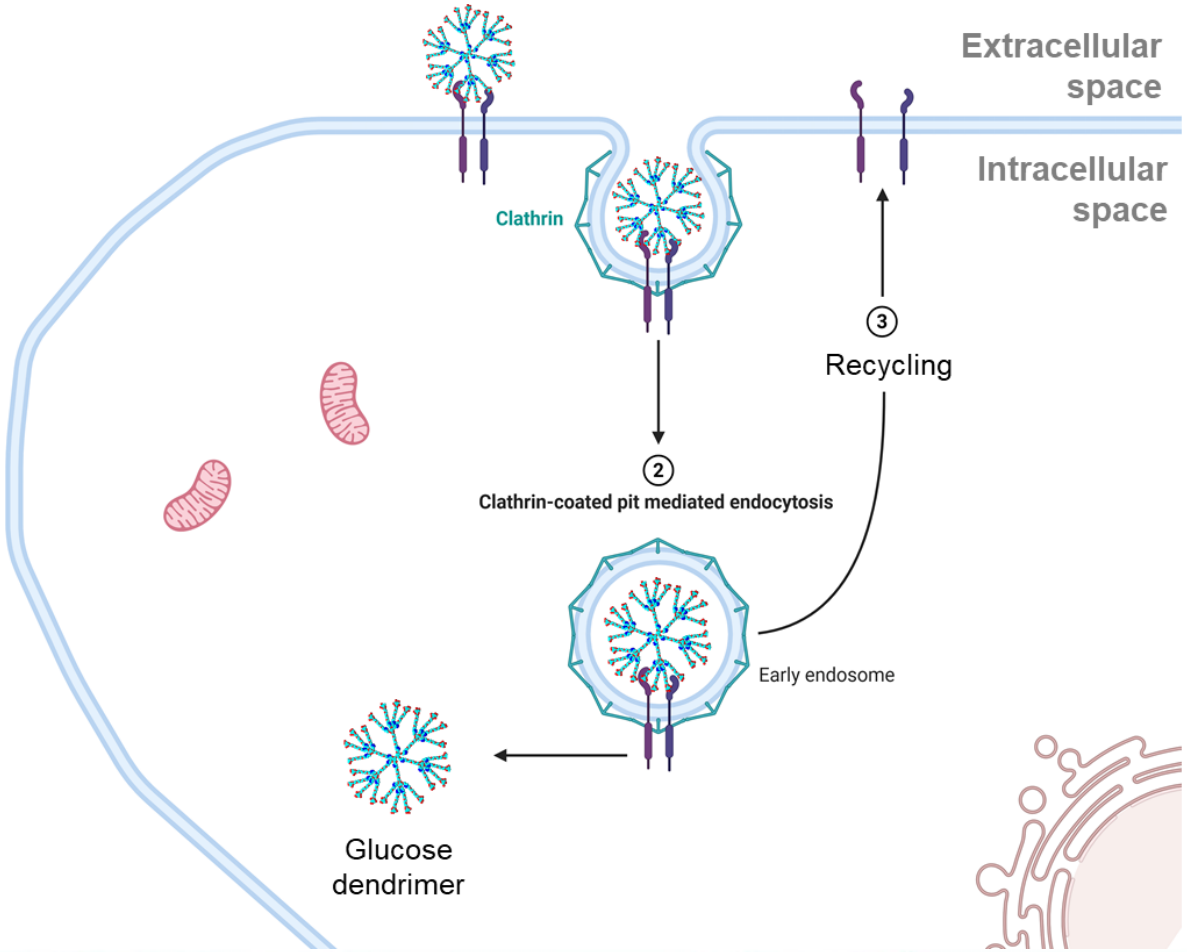


Glucose dendrimer uptake by **GLUT** initiated **clathrin** mediated endocytosis

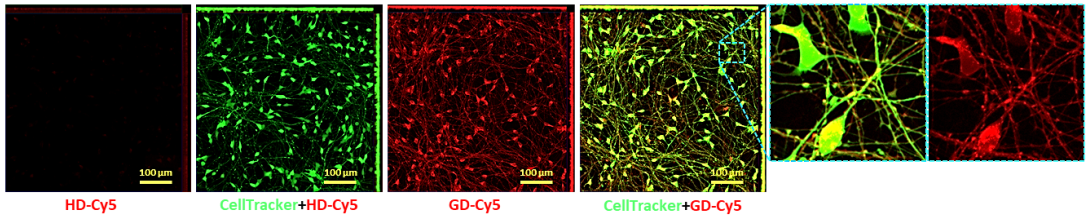
Second mechanism involved with uptake of Glucose Dendrimer

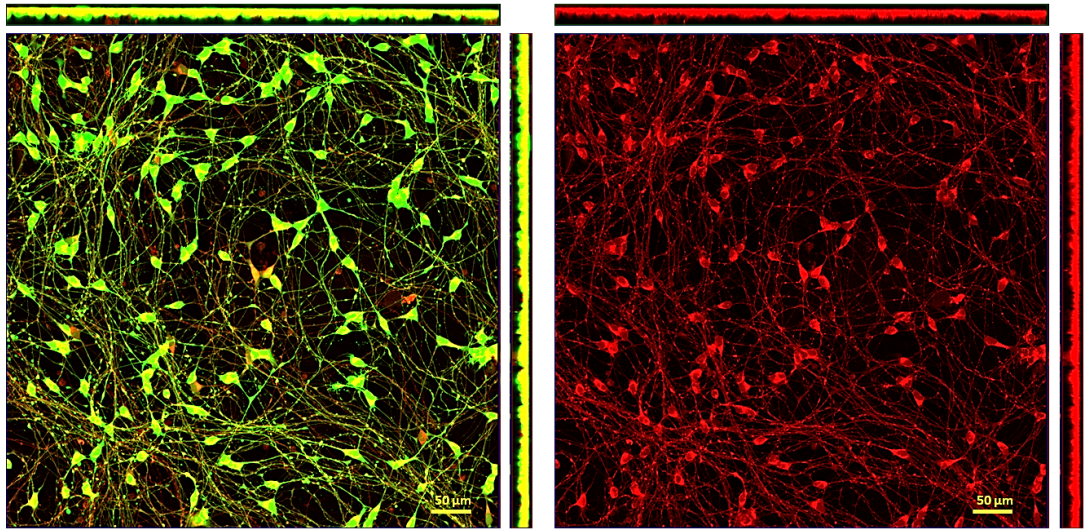




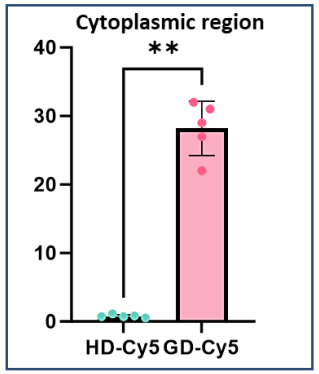


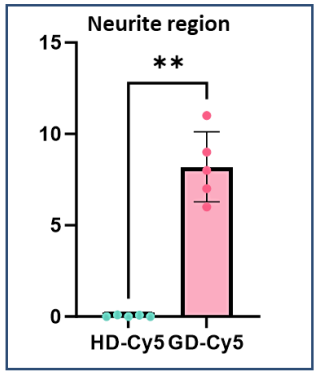
Glucose dendrimer shows significantly higher uptake than hydroxyl dendrimer in **hRGCs**

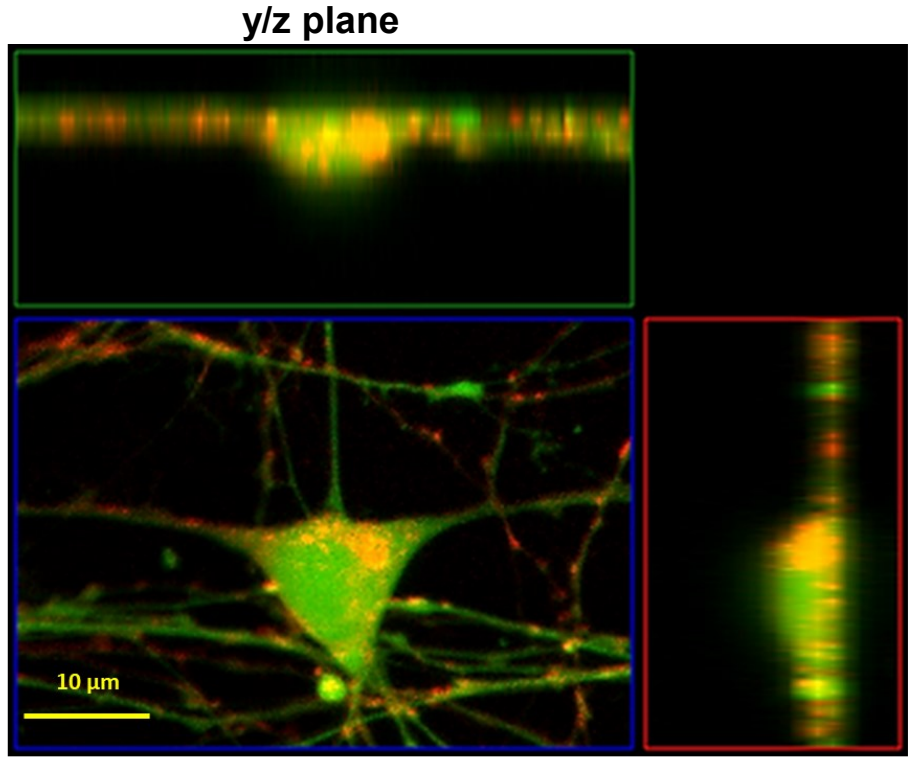




CellTracker + GD-Cy5 GD-Cy5





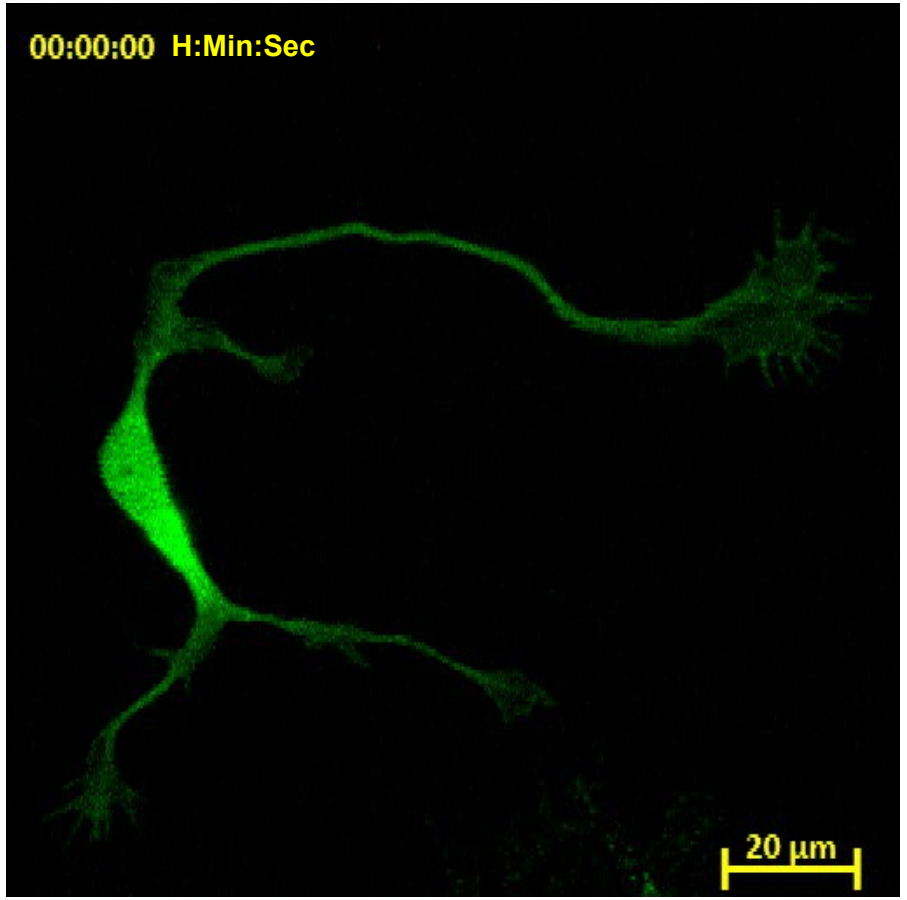


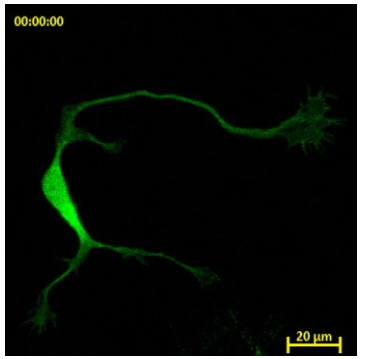
CellTracker + GD-Cy5

Rapid uptake of glucose dendrimer in human retinal ganglion cells (**hRGCs**)

Glucose dendrimer (GD-Cy5) (10 µg/ml)

tdTomato labelled RGC + GD-Cy5





Summary

- **Targeted localization** to pathologically impaired neurons ***in vivo.***
- **Ligand-Free Targeting**: Targeting driven by **GD's affinity for glucose transporters** (GLUTs), which are overexpressed during neuronal hyperactivity.
- Mechanism: **Glucose transporter** initiated **clathrin** mediated **endocytosis.**
- Strong potential for **clinical translation.**

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