Targeting pathogenic Lafora bodies in Lafora disease using an antibody-enzyme fusion

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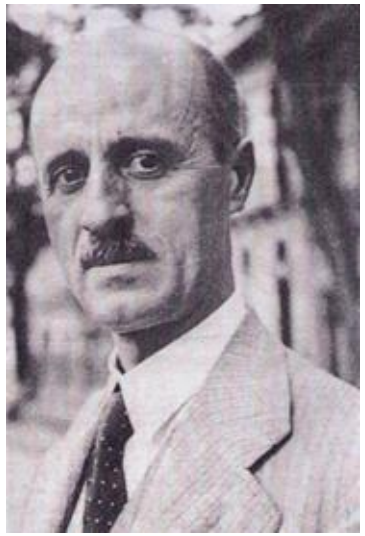
ENABLE Nijmegen
14 November 2019

Lafora disease is a fatal progressive myoclonus epilepsy

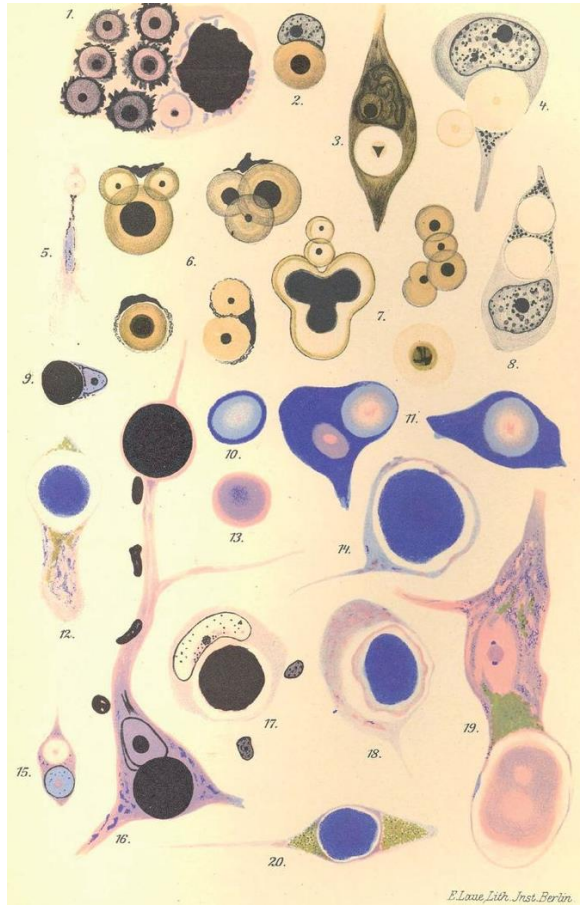
Beagle with Lafora disease





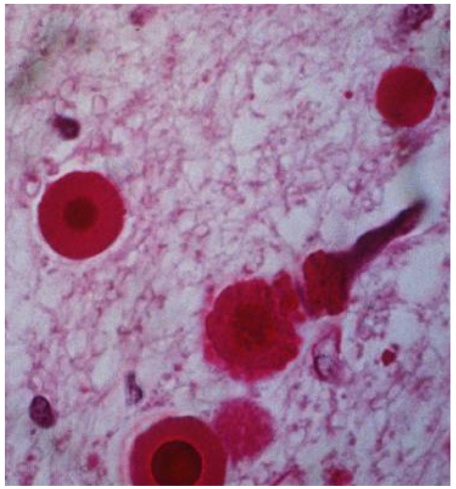


Gonzalo Rodriguez Lafora



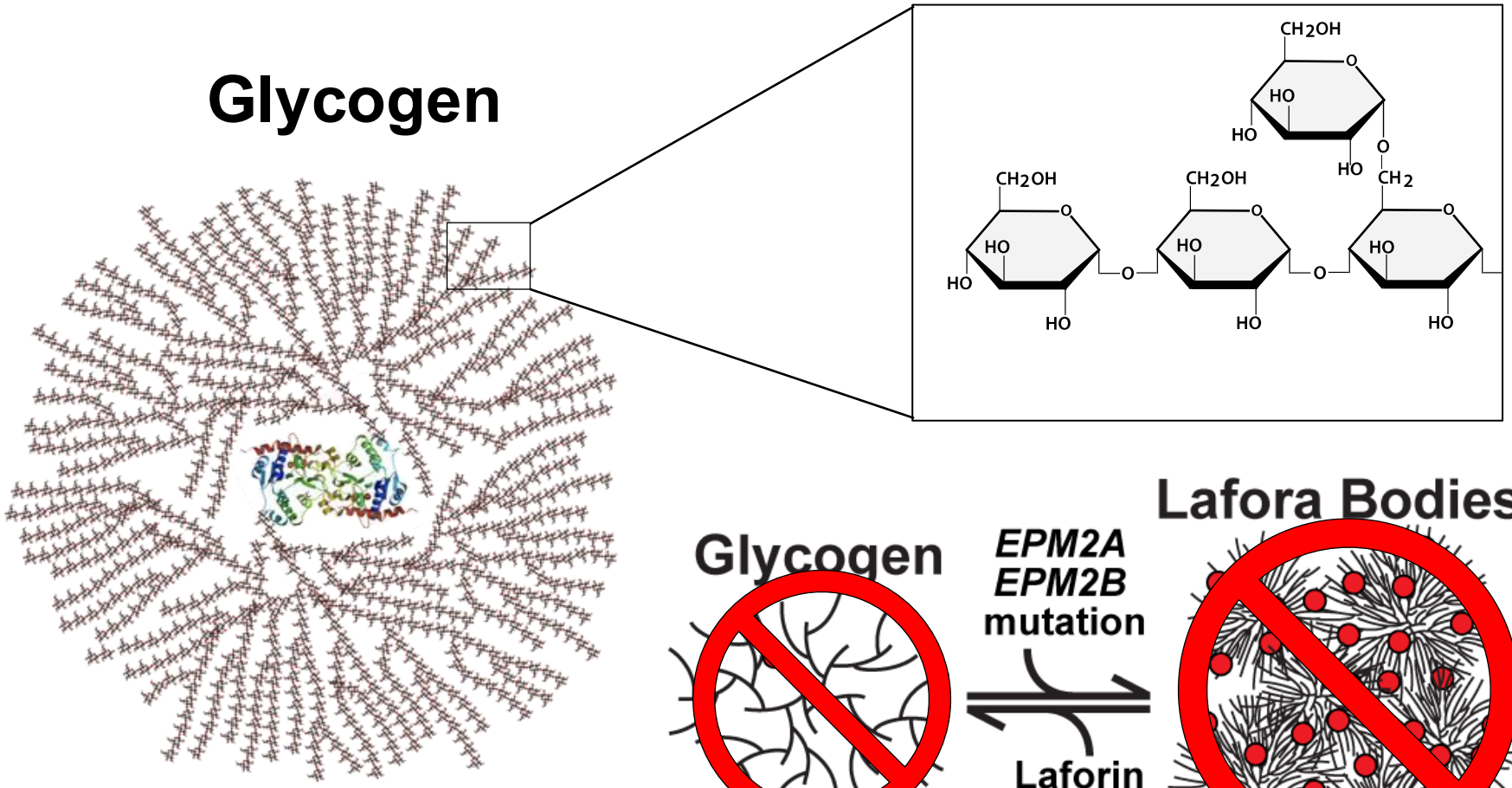
Lafora, *Virchows Arch Pathol Anat Physiol Klin Med* (1911).

Periodic acid-Schiff (PAS)



Courtesy of Jose Serratosa

Lafora bodies result from aberrant glycogen metabolism

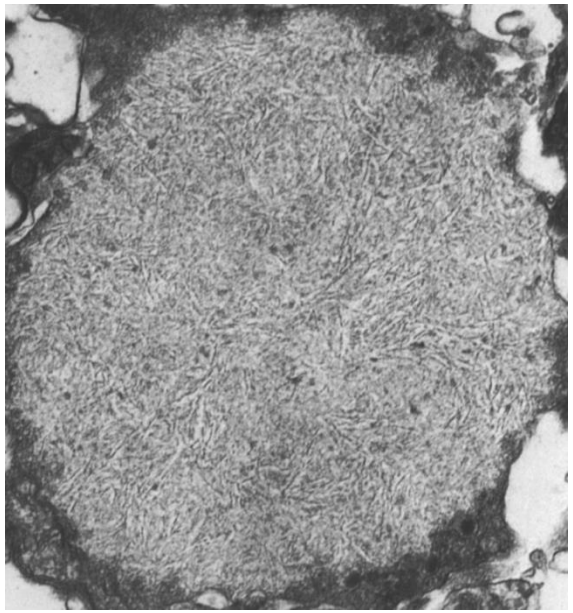


Turnbull et al., *PLoS Genetics,* 2011
Pedersen et al., *Ann Neurol,* 2013
Turnbull et al., *Ann Neurol,* 2014
Duran et al., *Hum Mol Gen,* 2014

50% reduction in glycogen synthesis eliminates epilepsy in LD mice

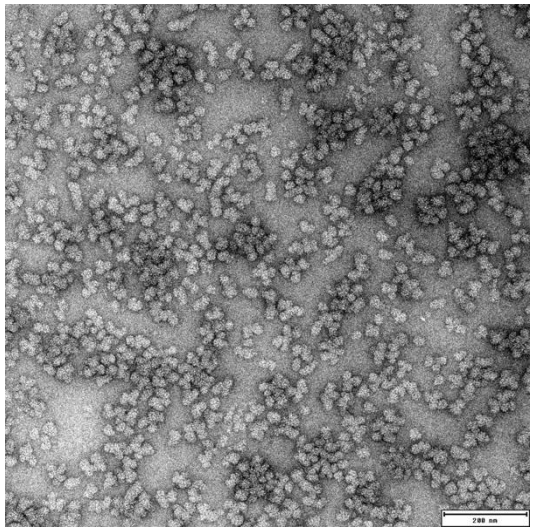
Lafora bodies resemble plant starch

Lafora Body
(2-40 µm)

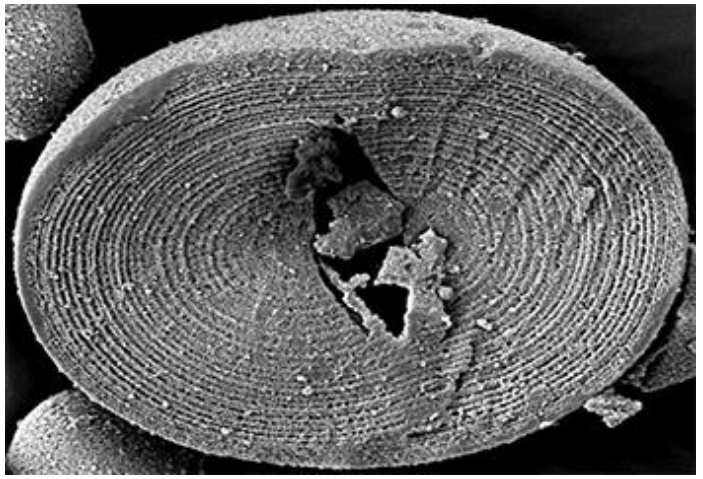


Berard-Badier et al., 1979.
Albrecht Von Graefes Arch Klin Expo Ophthalmol.

Glycogen
(25 nm)

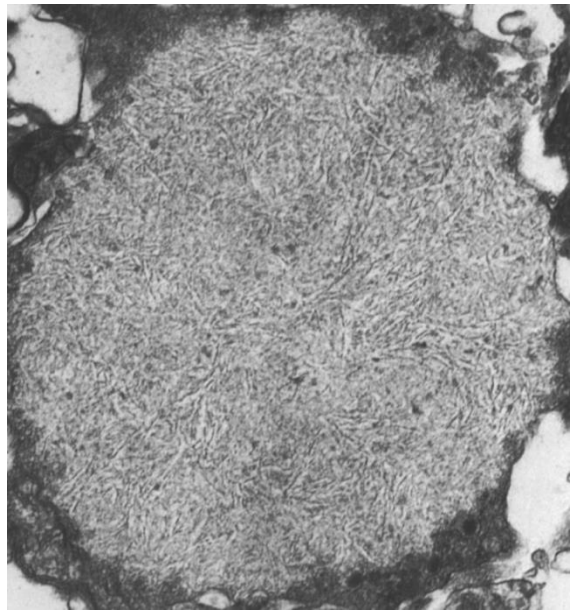


Starch
(5-100 µm)



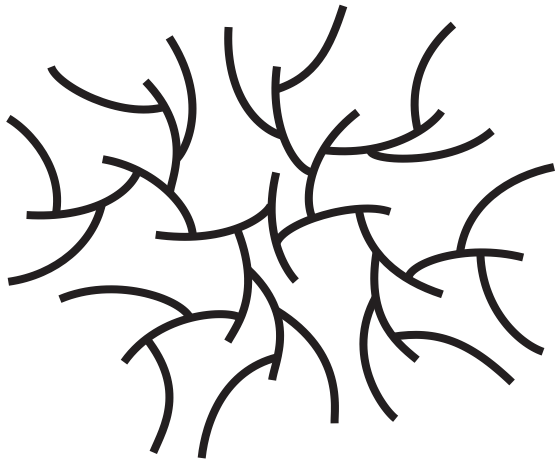
Lafora bodies resemble plant starch

Lafora Body
(2-40 µm)

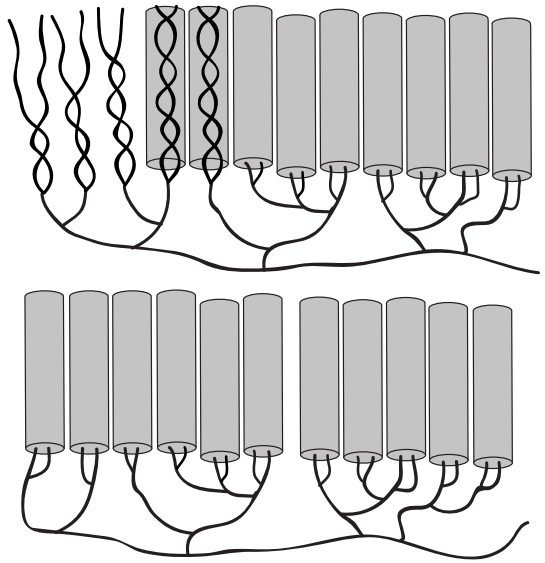


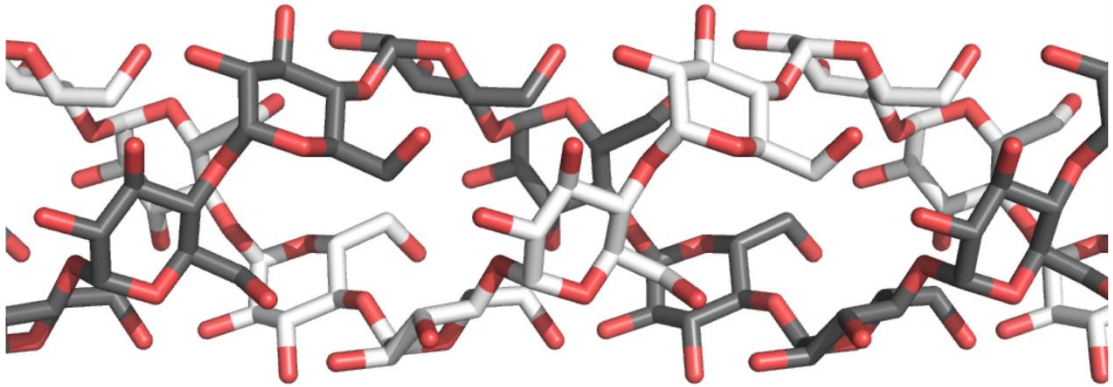
Berard-Badier et al., 1979.
Albrecht Von Graefes Arch Klin Expo Ophthalmol.

Glycogen



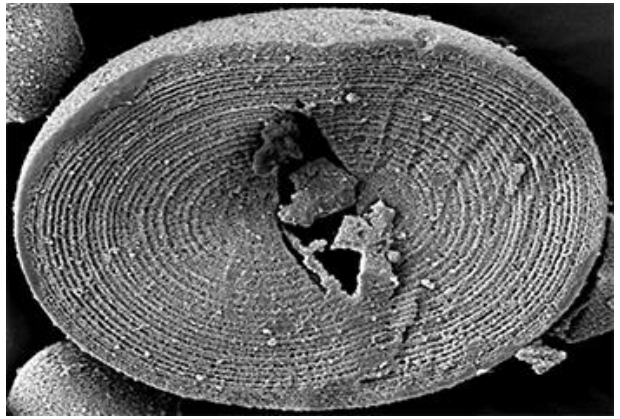
Starch

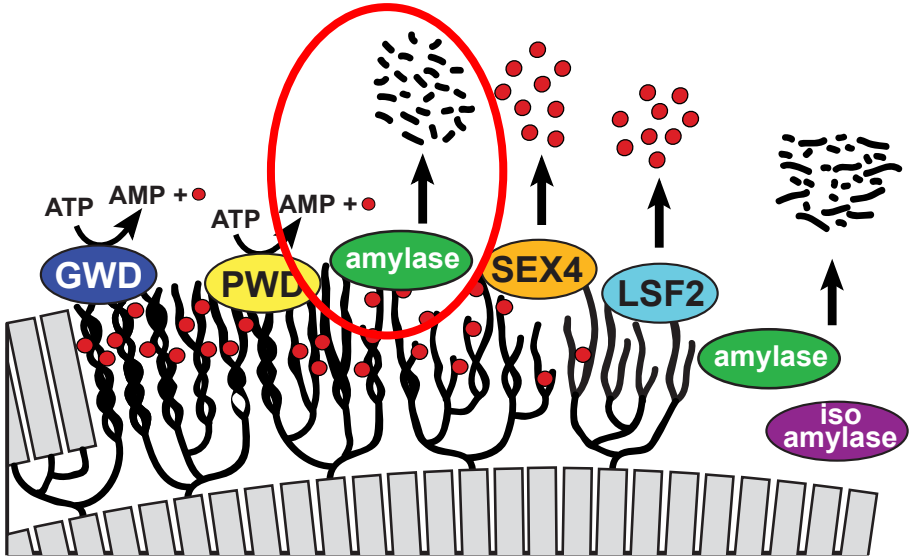




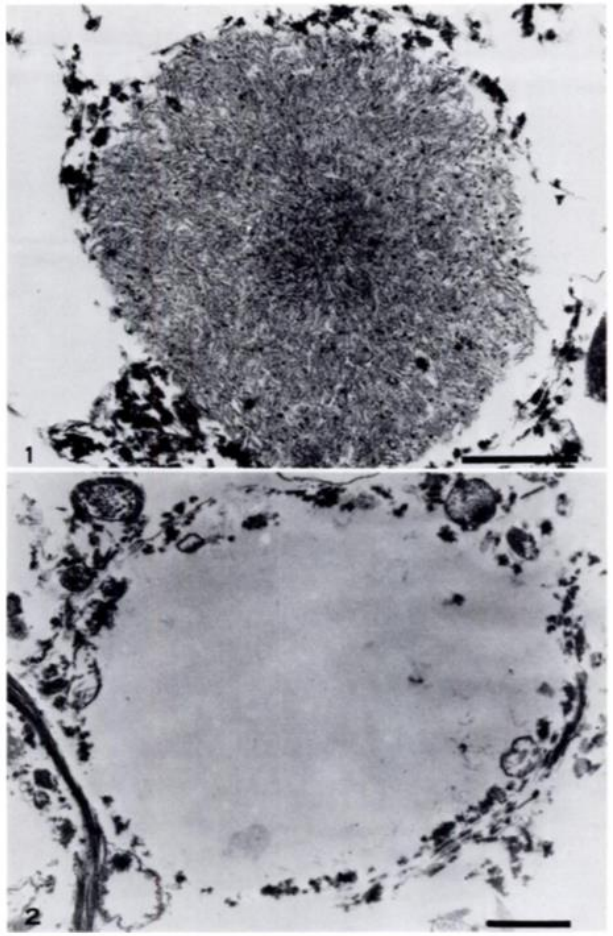
Corn starch and LBs are degraded by α-amylase

Starch (5-100 µm)





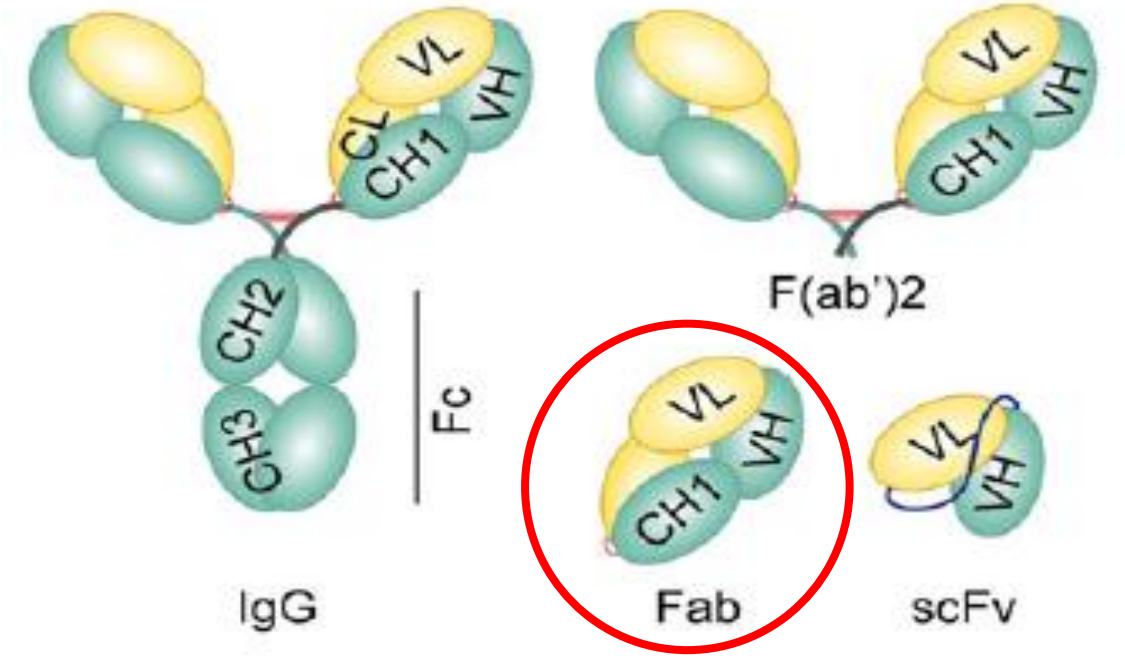
Lafora body
(fixed human tissue)



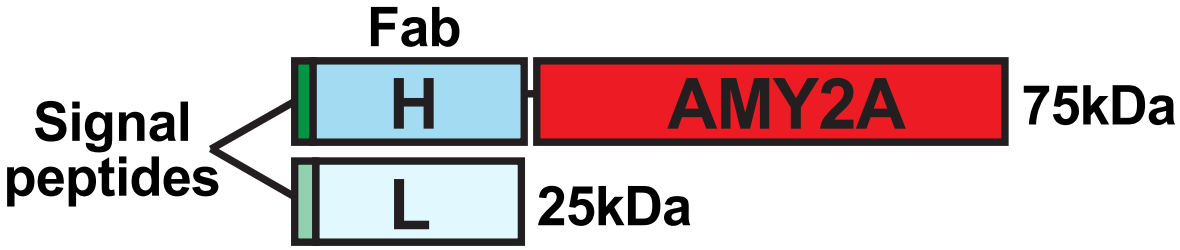
Nikaido et al. 1971. *J Histochem Cytochem.*

Antibody-enzyme fusion (AEF) treatment platform

valerion



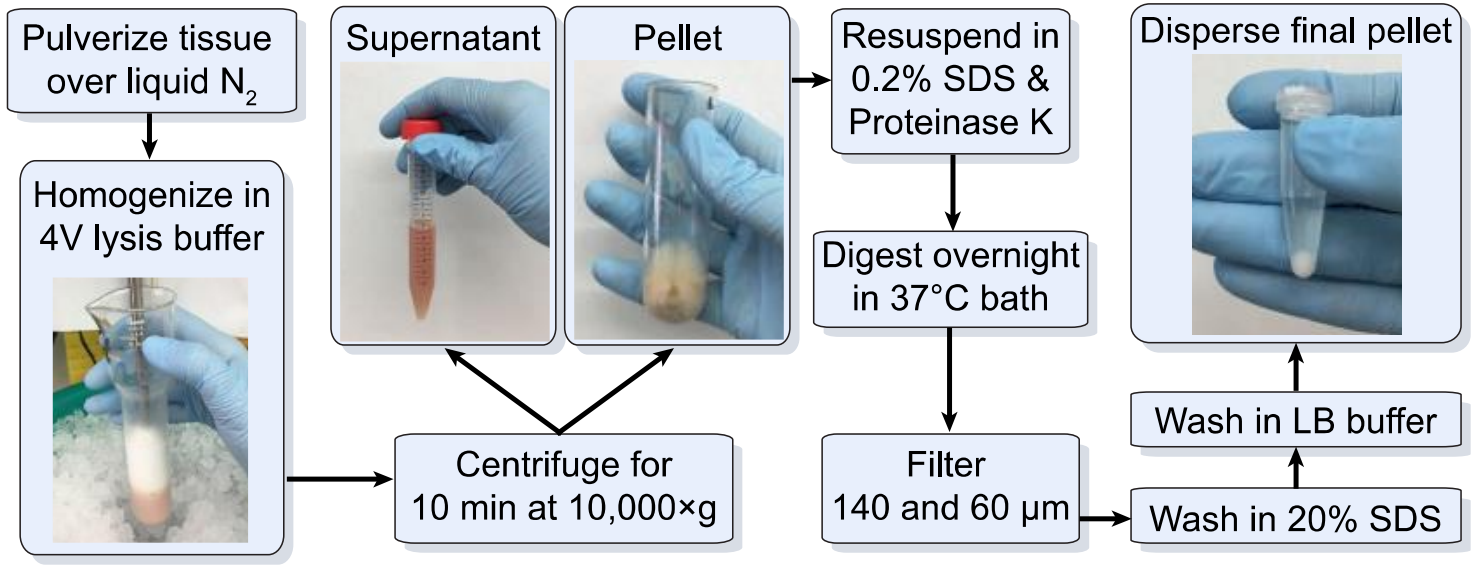
VAL-0417

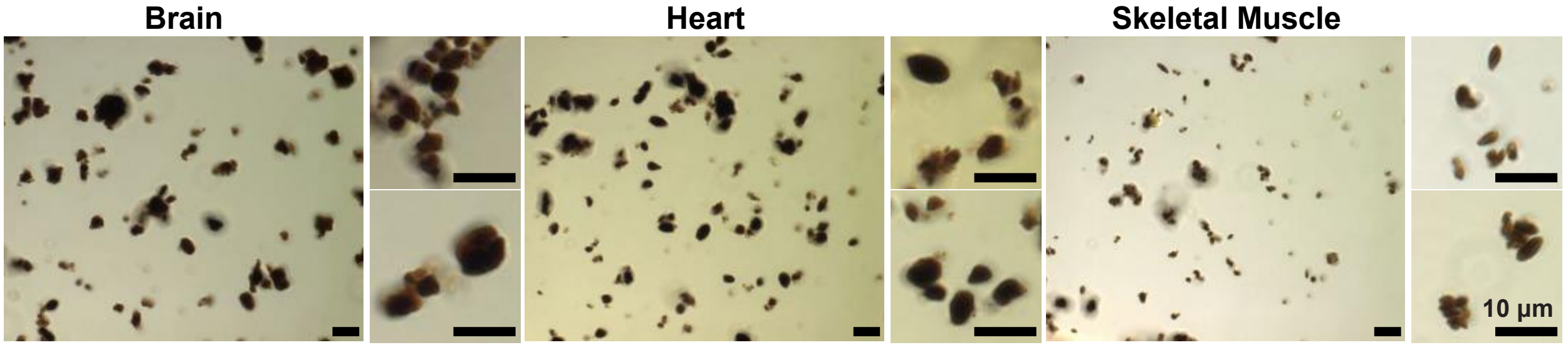


AMY2A = human amylase

Brewer et al., *Cell Metabolism* (2019).

Purification of native LBs from *Epm2a-/-* and *Epm2b-/-* mice





Brewer et al., *Cell Metabolism* (2019).

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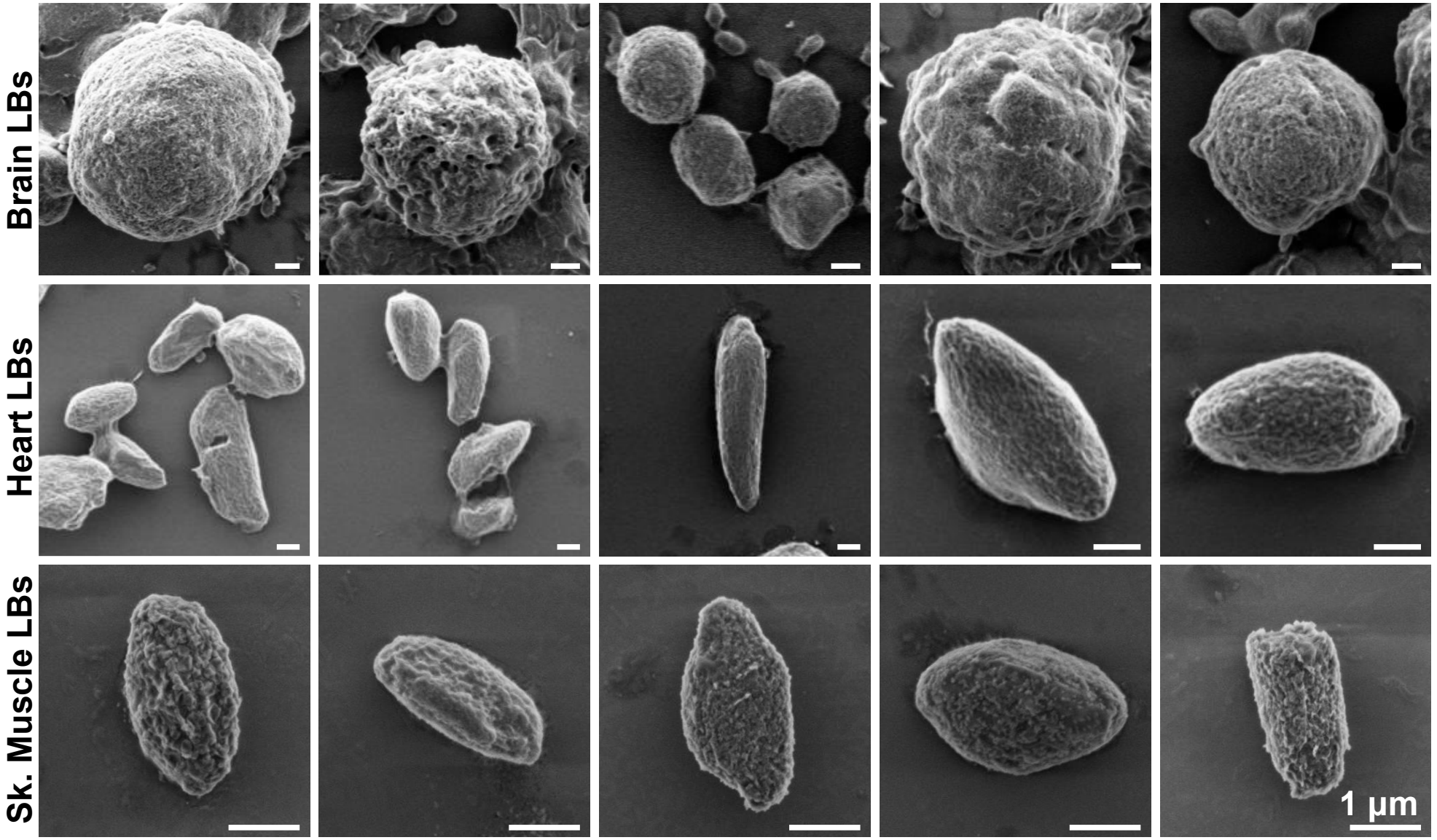
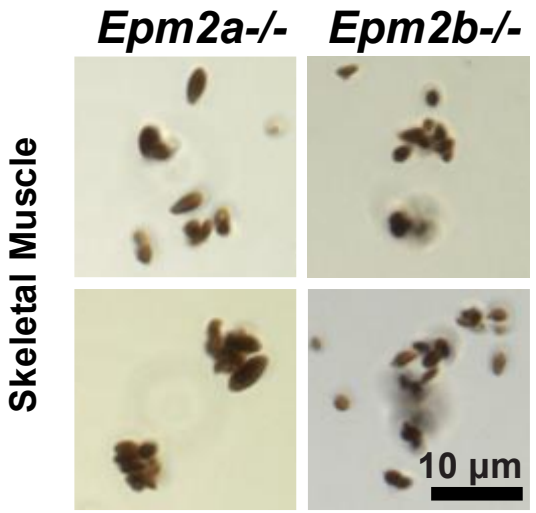
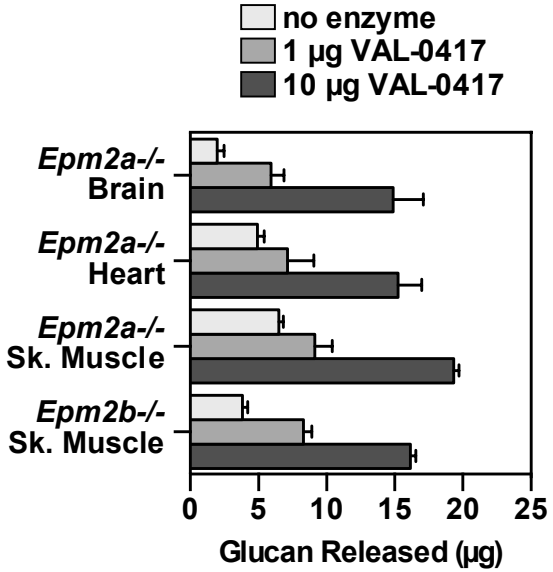
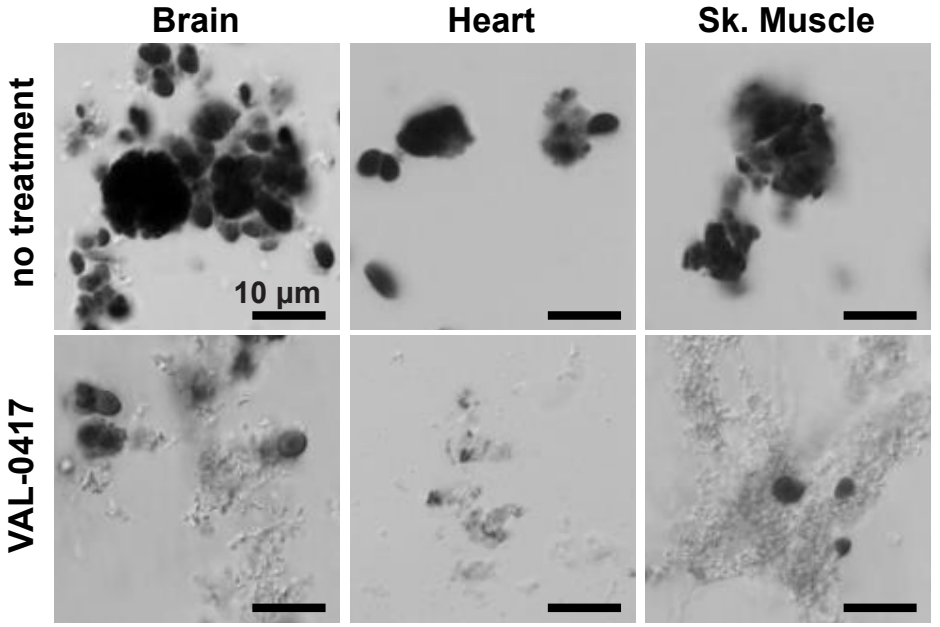


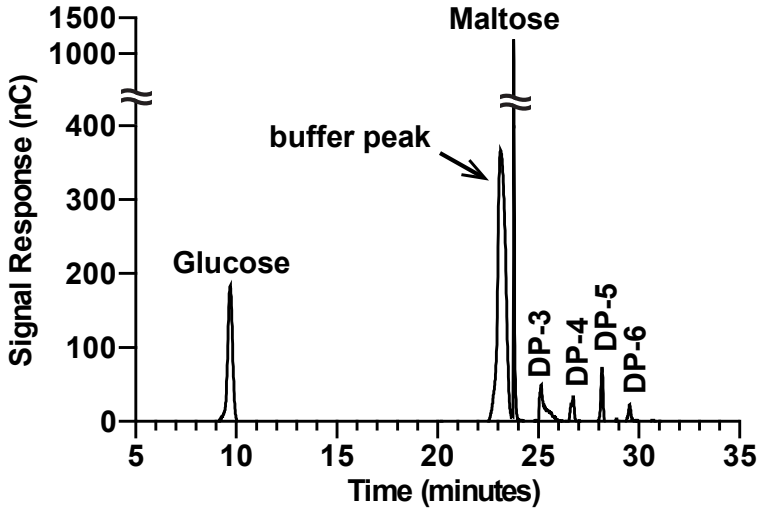
Brewer et al., *Cell Metabolism* (2019).

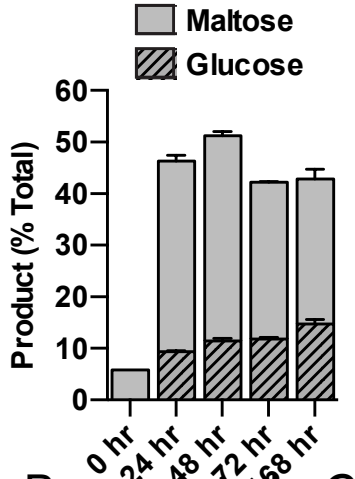
VAL-0417 degrades LBs *in vitro*







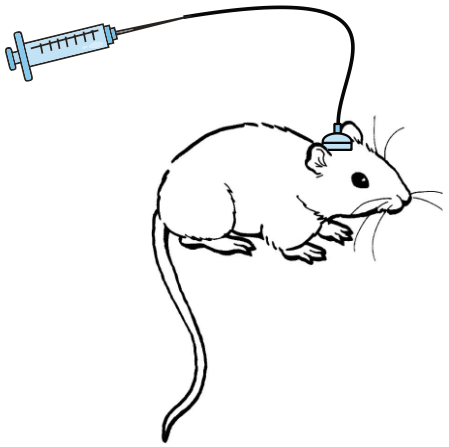




Brewer et al., *Cell Metabolism* (2019).

VAL-0417 reduces cerebral LB load *in vivo*

Intracerebroventricular (ICV) administration

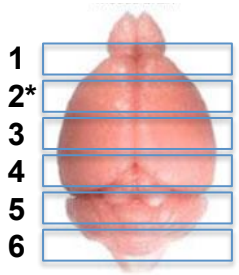


5 month old *Epm2a-/-* mice

Continuous infusion of VAL-0417 (0.08mg/day) or PBS for 28 days via ICV catheter

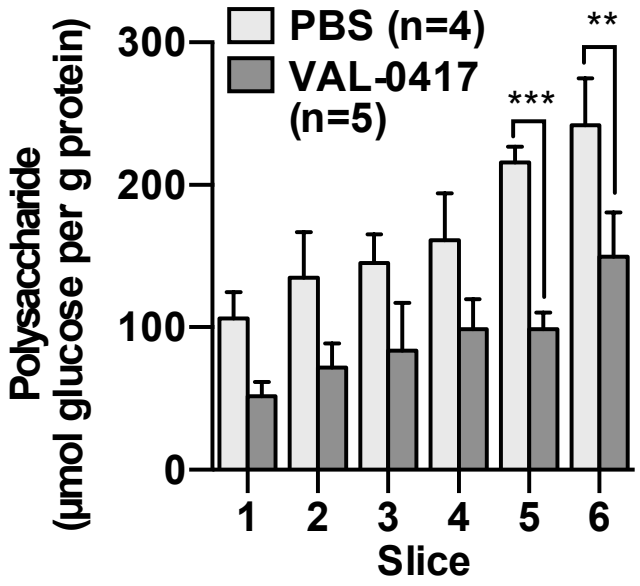
NBR
Northern Biomedical Research, Inc.

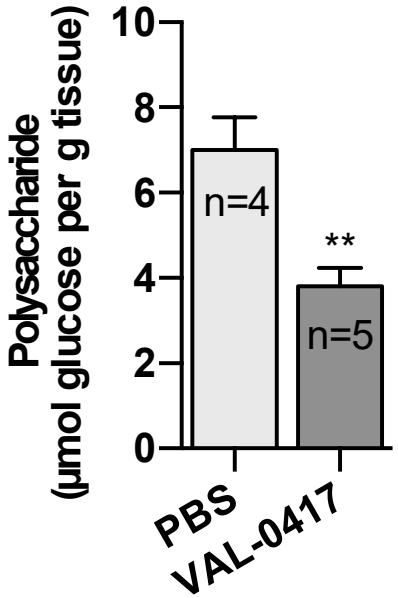
→ **Euthanized on 29th day Brains sectioned**



→ **Polysaccharide content determined**

Whole brain



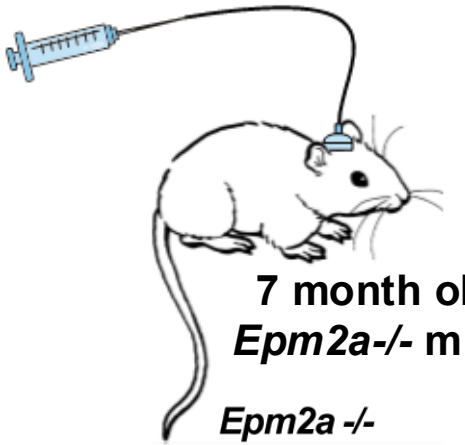


** p < 0.01
*** p < 0.001

Brewer et al., *Cell Metabolism* (2019).

VAL-0417 reduces cerebral LB load *in vivo*

Intracerebroventricular (ICV) administration



7 month old *Epm2a-/-* mice

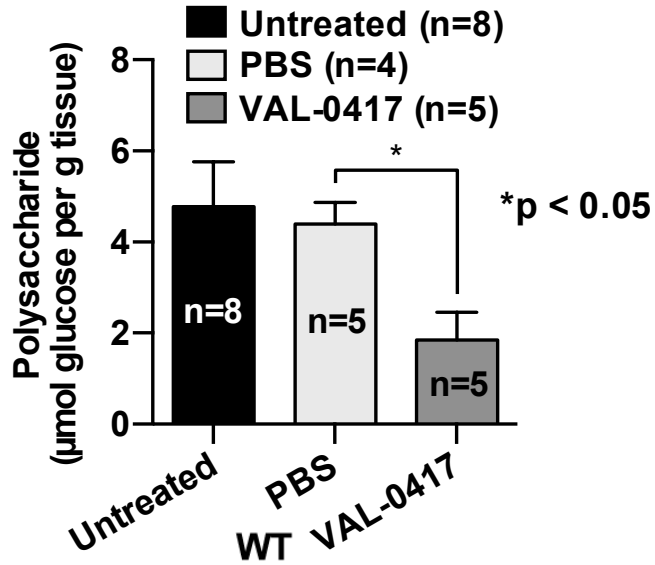
Continuous infusion of VAL-0417 (0.08mg/day) or PBS for 8 days

NBR Northern Biomedical Research, Inc.

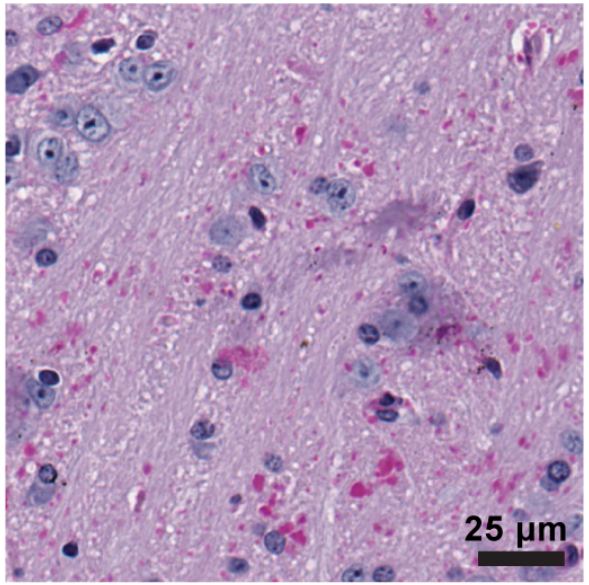
→ Euthanized on 9th day → Polysaccharide content

→ PAS staining

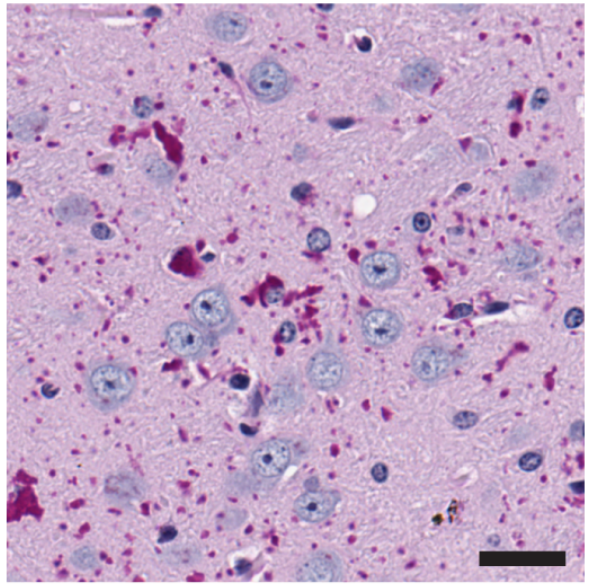
→ Metabolomics via GCMS



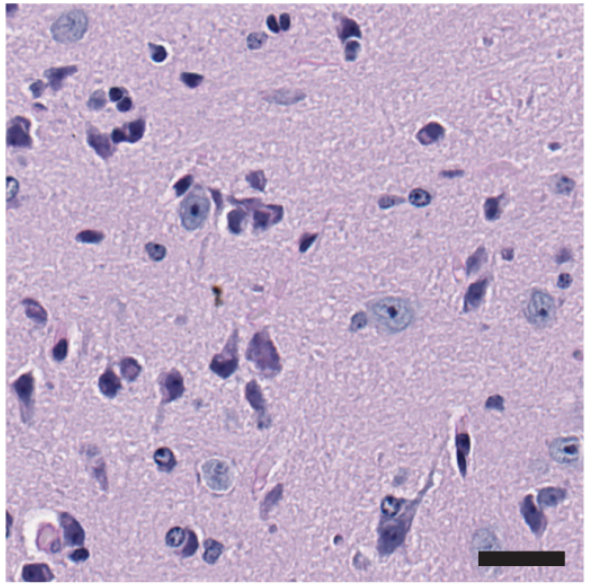
Epm2a -/- Untreated



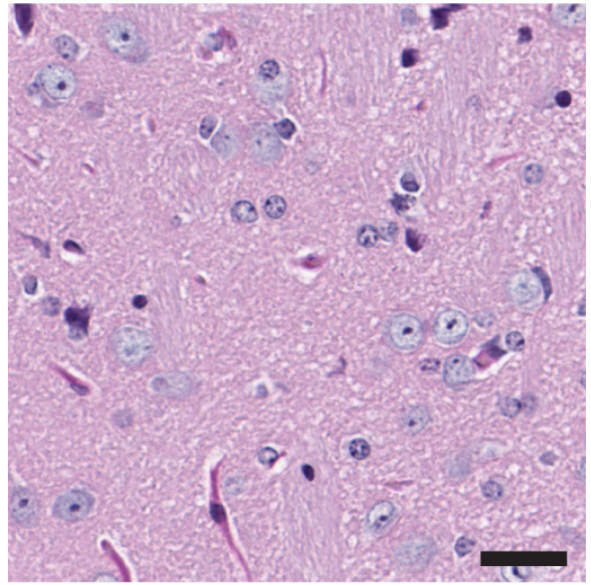
Epm2a -/- PBS



Epm2a -/- VAL-0417



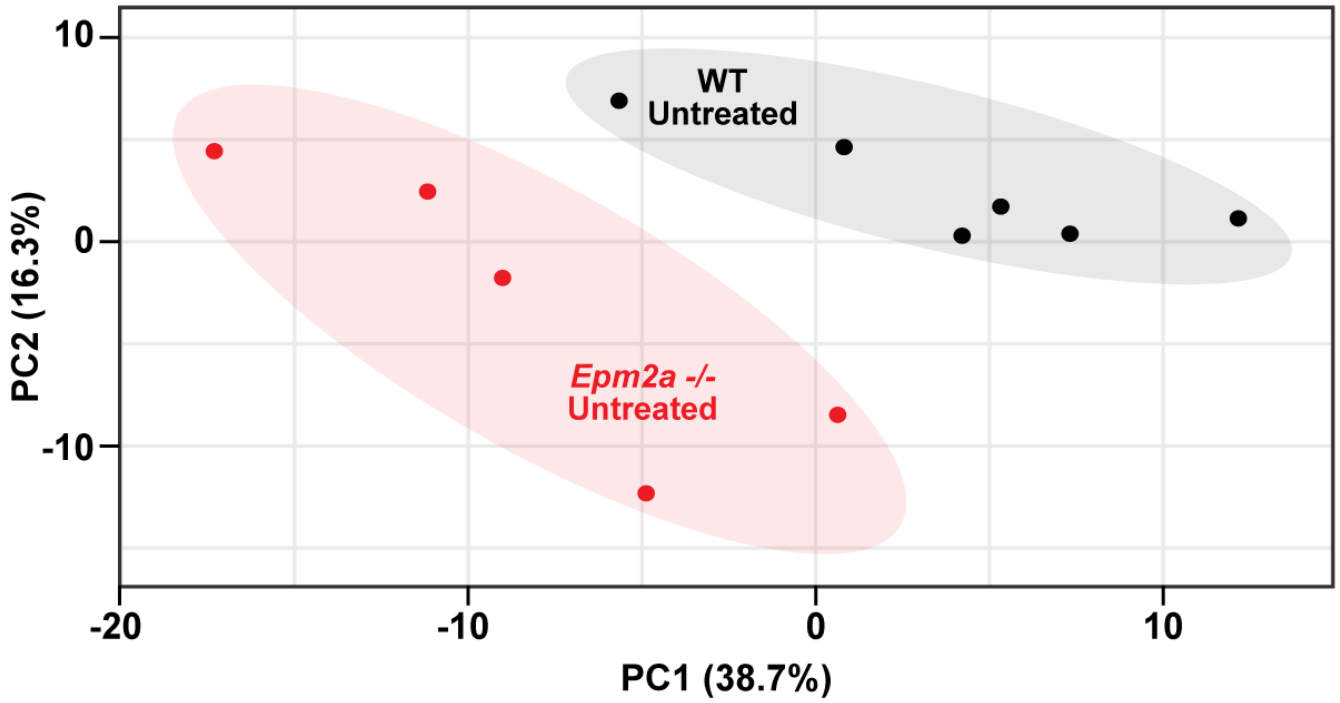
Untreated



Brewer et al., *Cell Metabolism* (2019).

VAL-0417 reverses metabolic derangement in LD mice

Principle Component (PC) analysis



Brewer et al., *Cell Metabolism* (2019).

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