

Lafora disease: a link between energy metabolism and epilepsy

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Neurology Grand Rounds
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Epilepsy: a disease of energy metabolism

EPILEPSY TREATMENT

Targeting LDH enzymes with a stiripentol analog to treat epilepsy

Nagisa Sada,[1] Suni Lee,[2] Takashi Katsu,[1*] Takemi Otsuki,[2] Tsuyoshi Inoue[1†]

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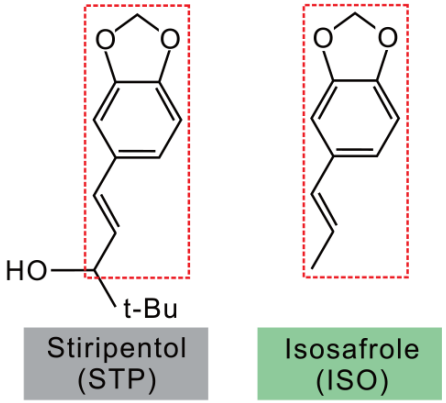
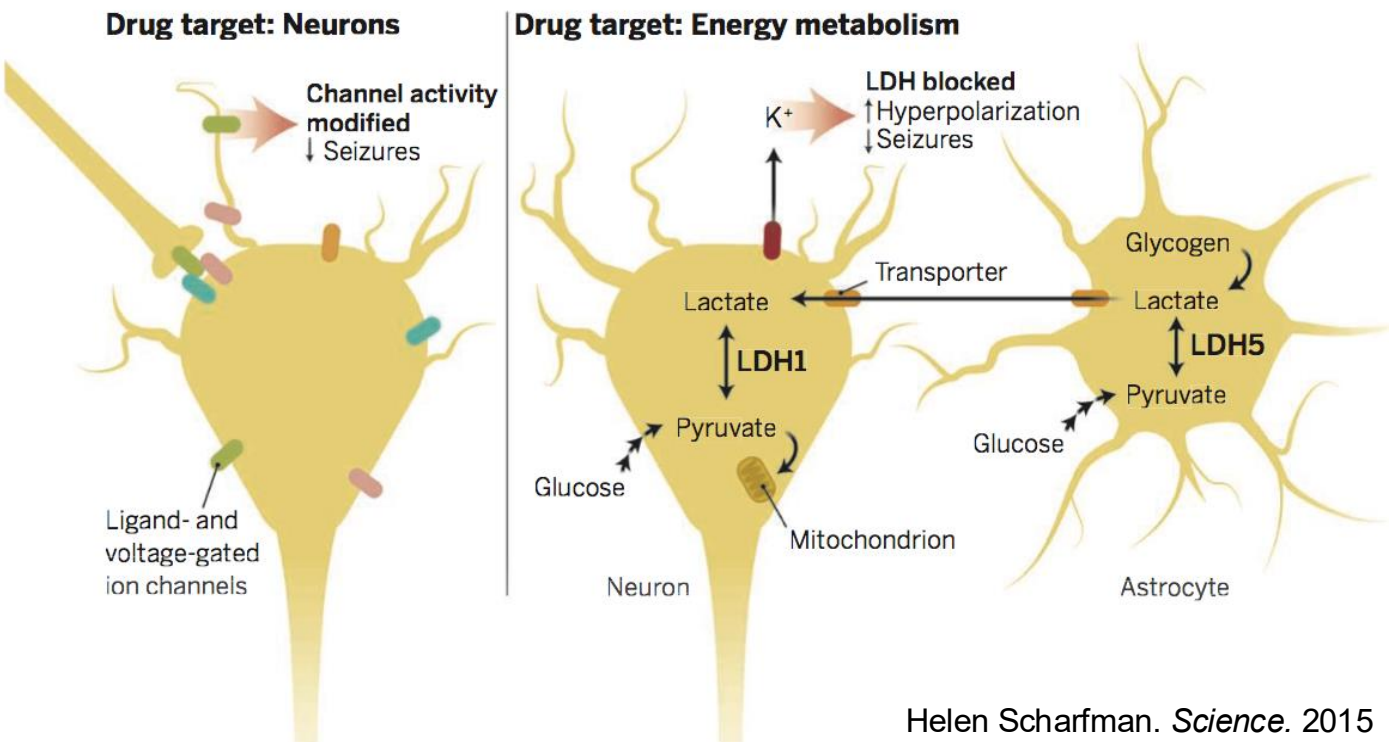
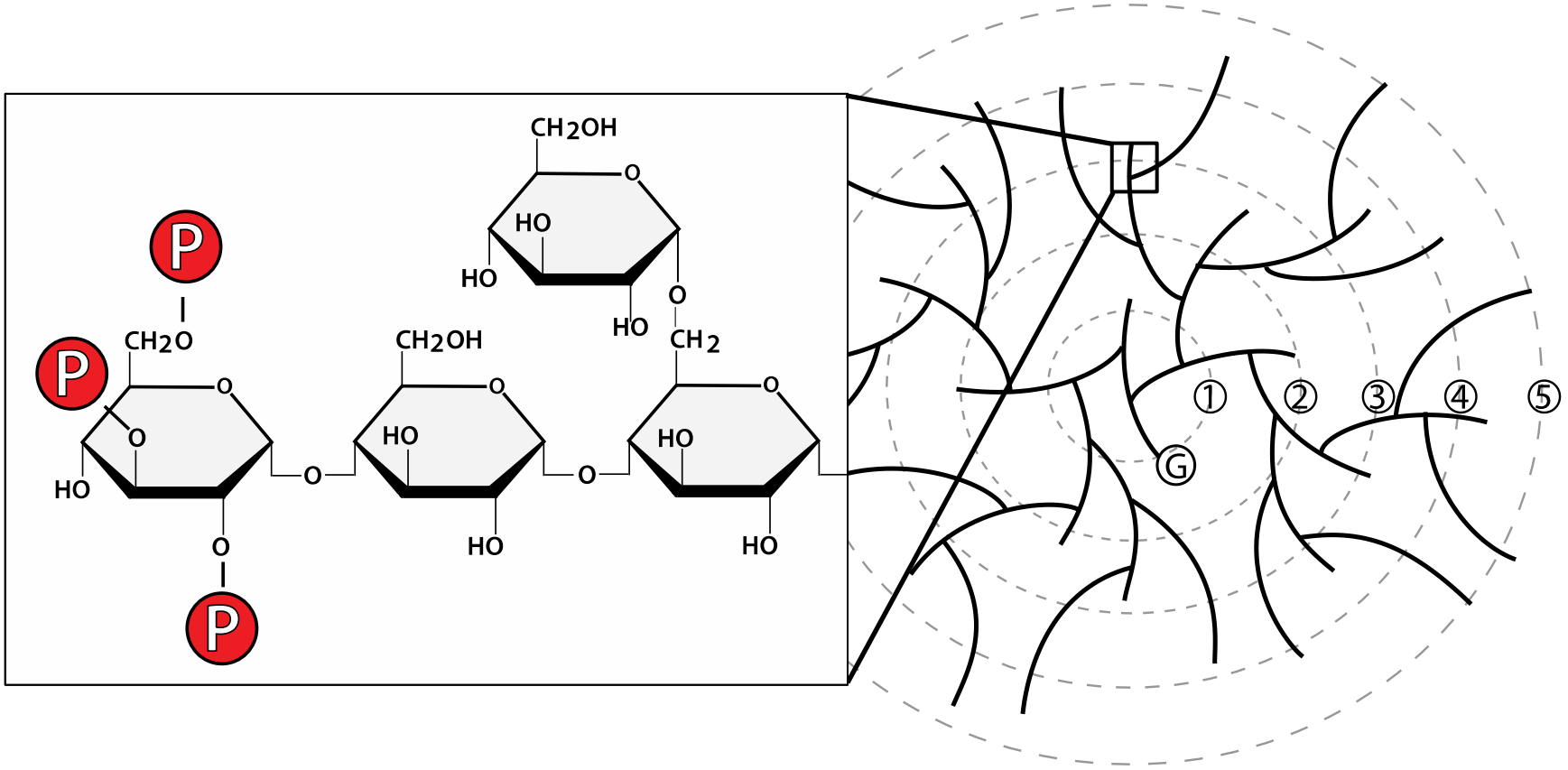


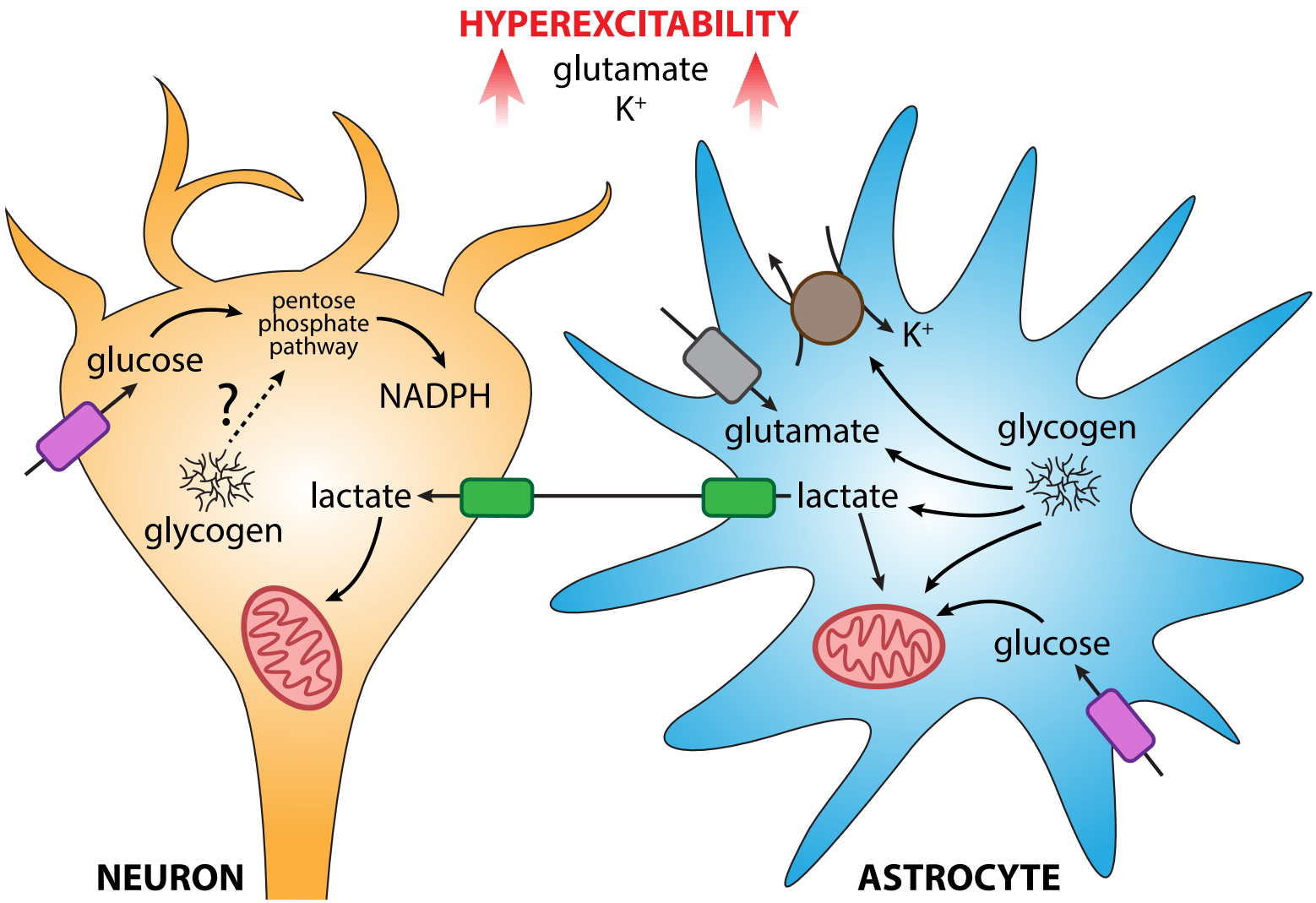


Helen Scharfman. *Science.* 2015

Glycogen plays a dynamic role in brain metabolism

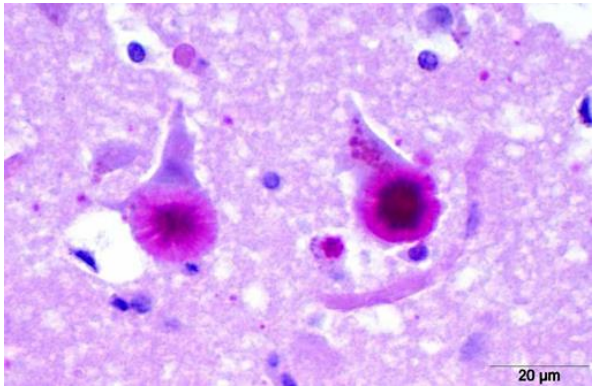


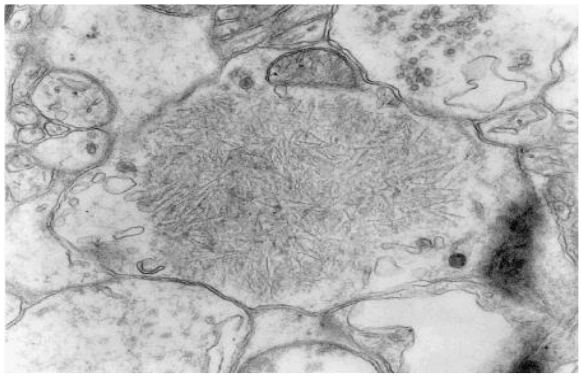
Glycogen plays a dynamic role in brain metabolism



Lafora disease is a fatal neurodegenerative epilepsy

- Autosomal recessive neurodegenerative disorder
- Manifests during adolescence, eventually leads to death
- Most common and severe progressive myoclonus epilepsy





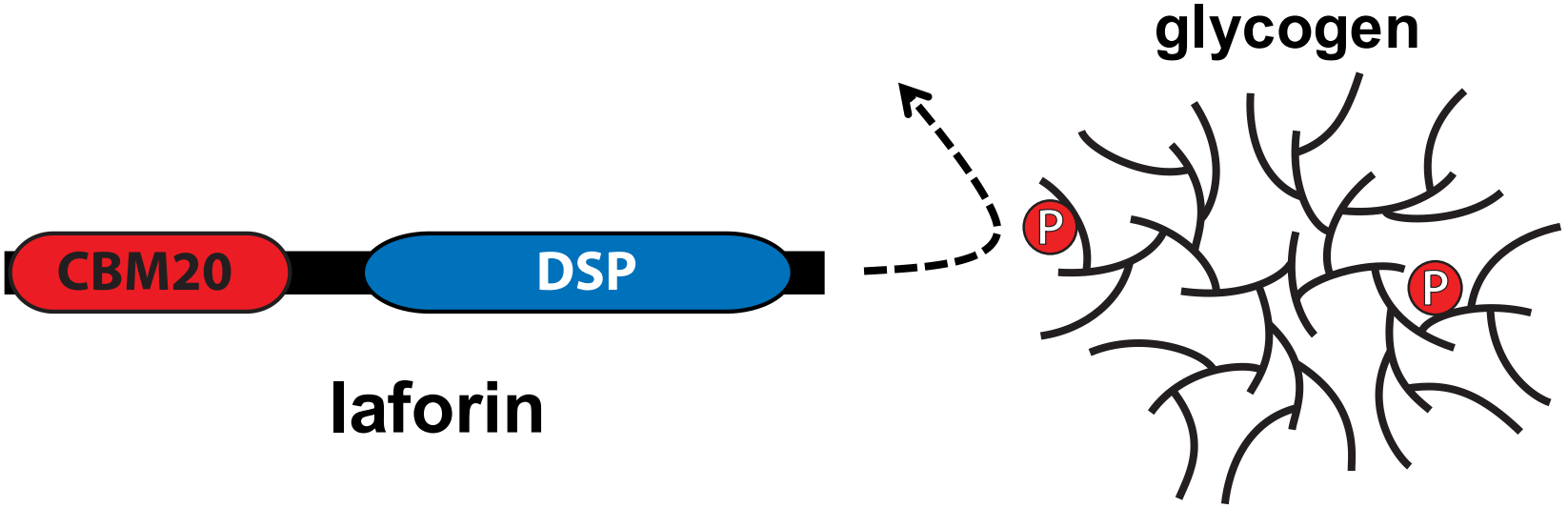
Minassian, *Pediatr. Neurol.*, 2001

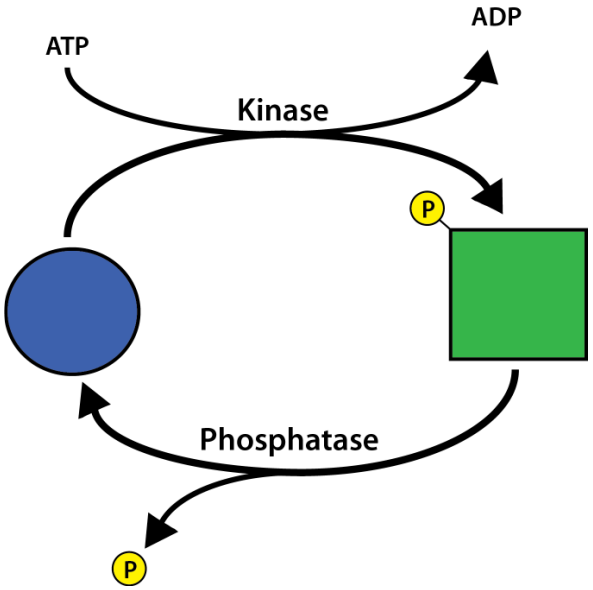


Dr. Gonzalo Rodriguez Lafora (circa 1910)

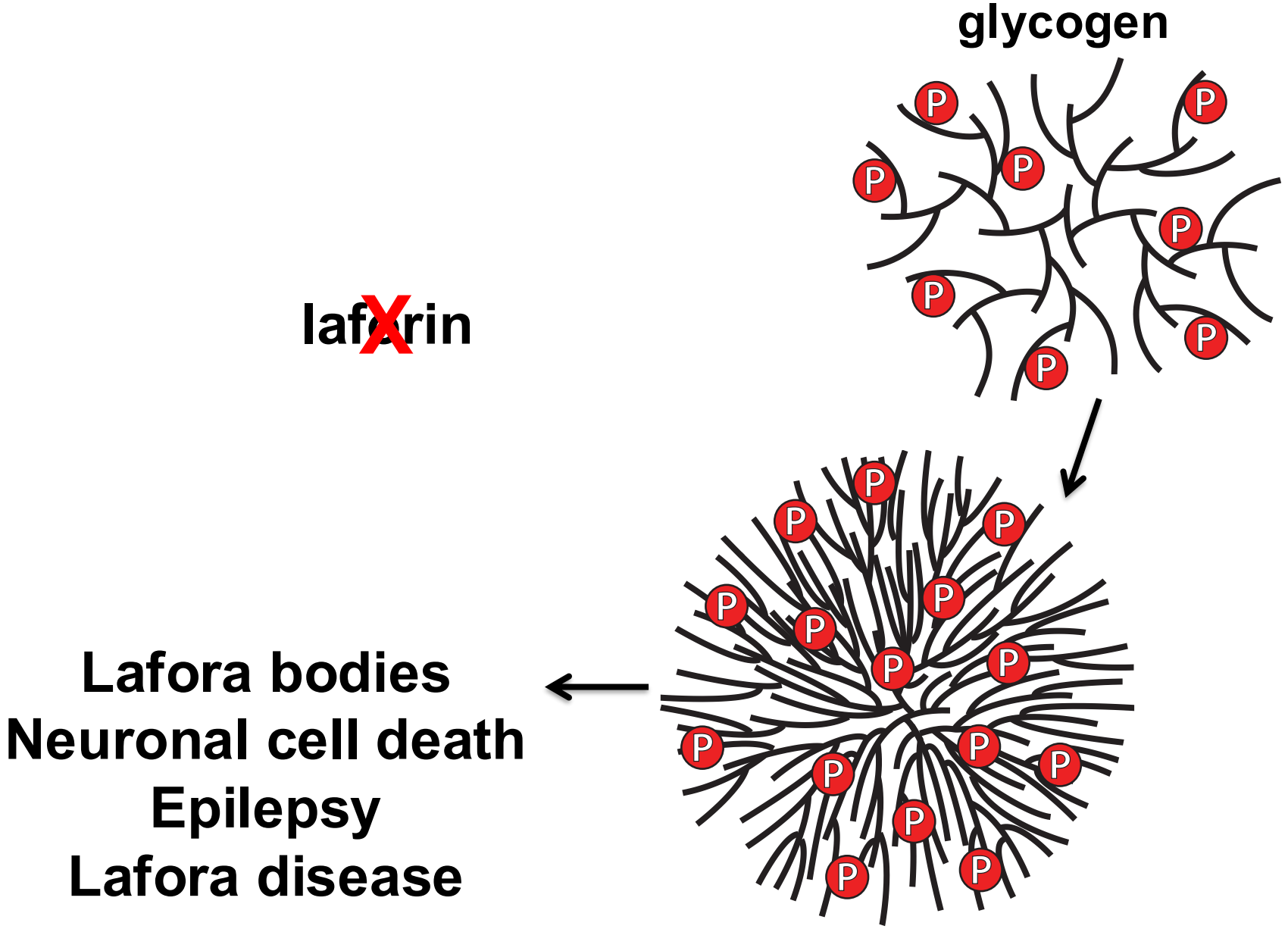


Glycogen hyperphosphorylation leads to Lafora disease

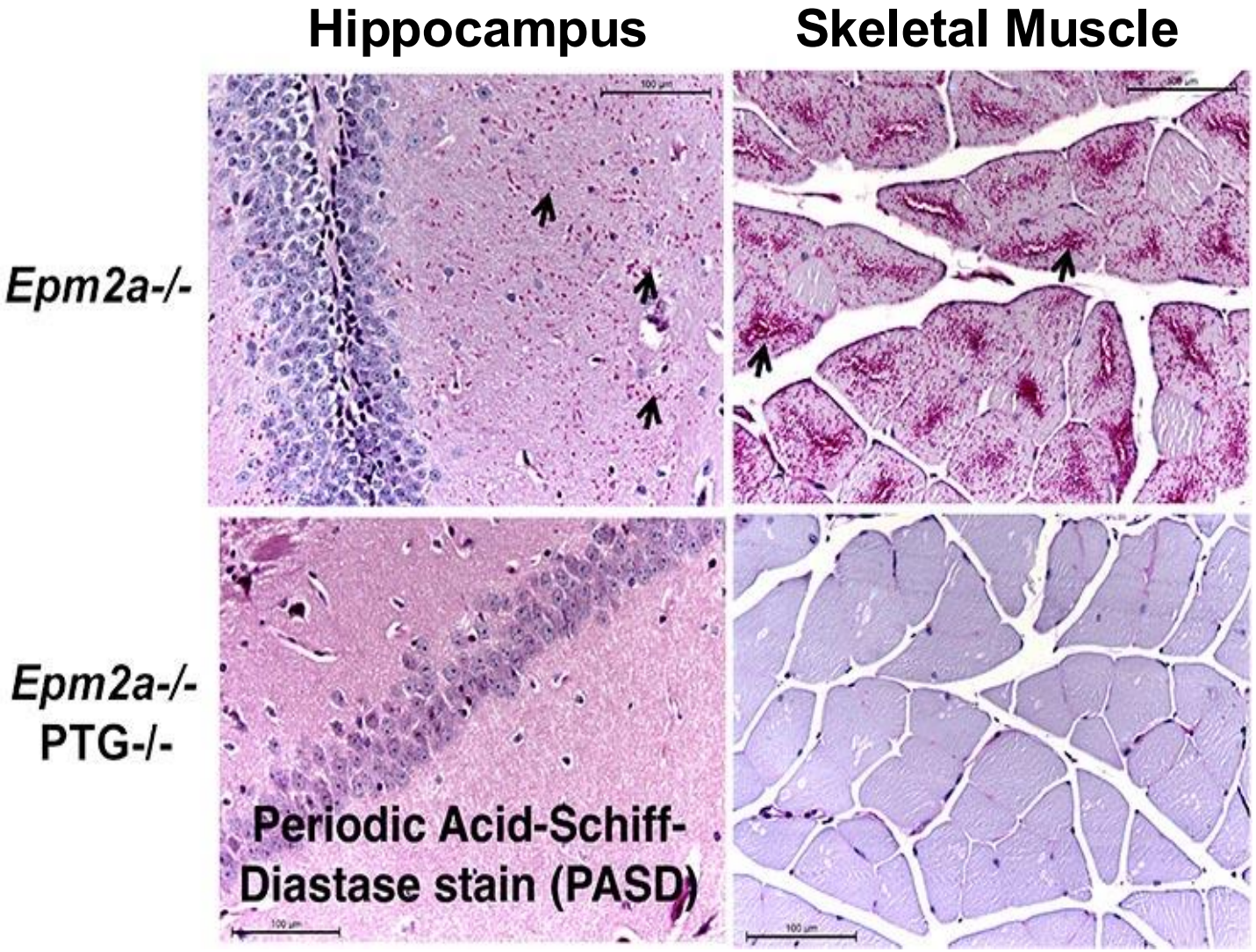




Glycogen hyperphosphorylation leads to Lafora disease



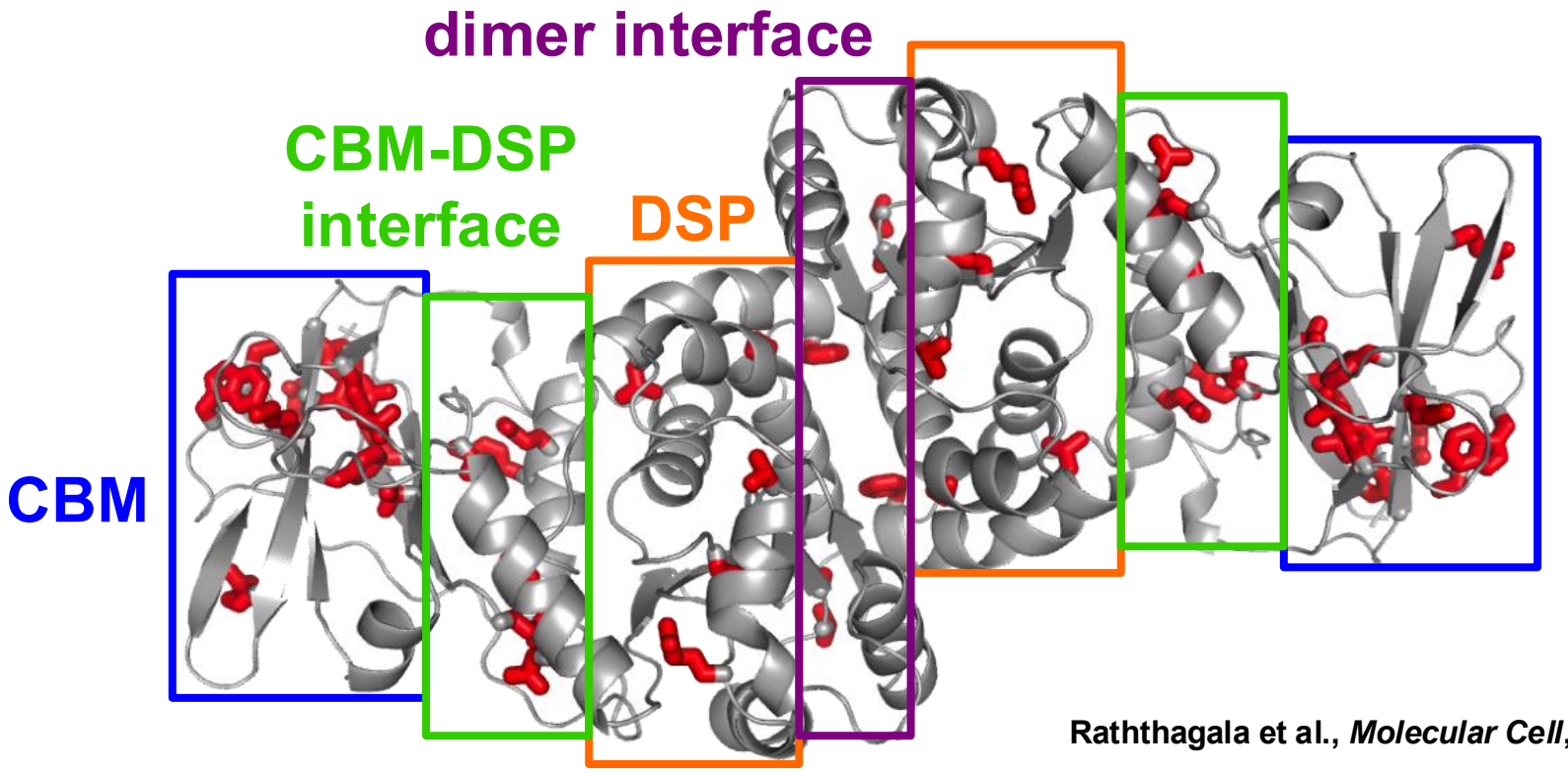
Glycogen depletion rescues Lafora disease



Double KOs
Laforin / PTG ✓
Laforin / GS ✓
Malin / PTG ✓
Malin / GS ✓

Turnbull et al. *PLoS Genetics.* 2011

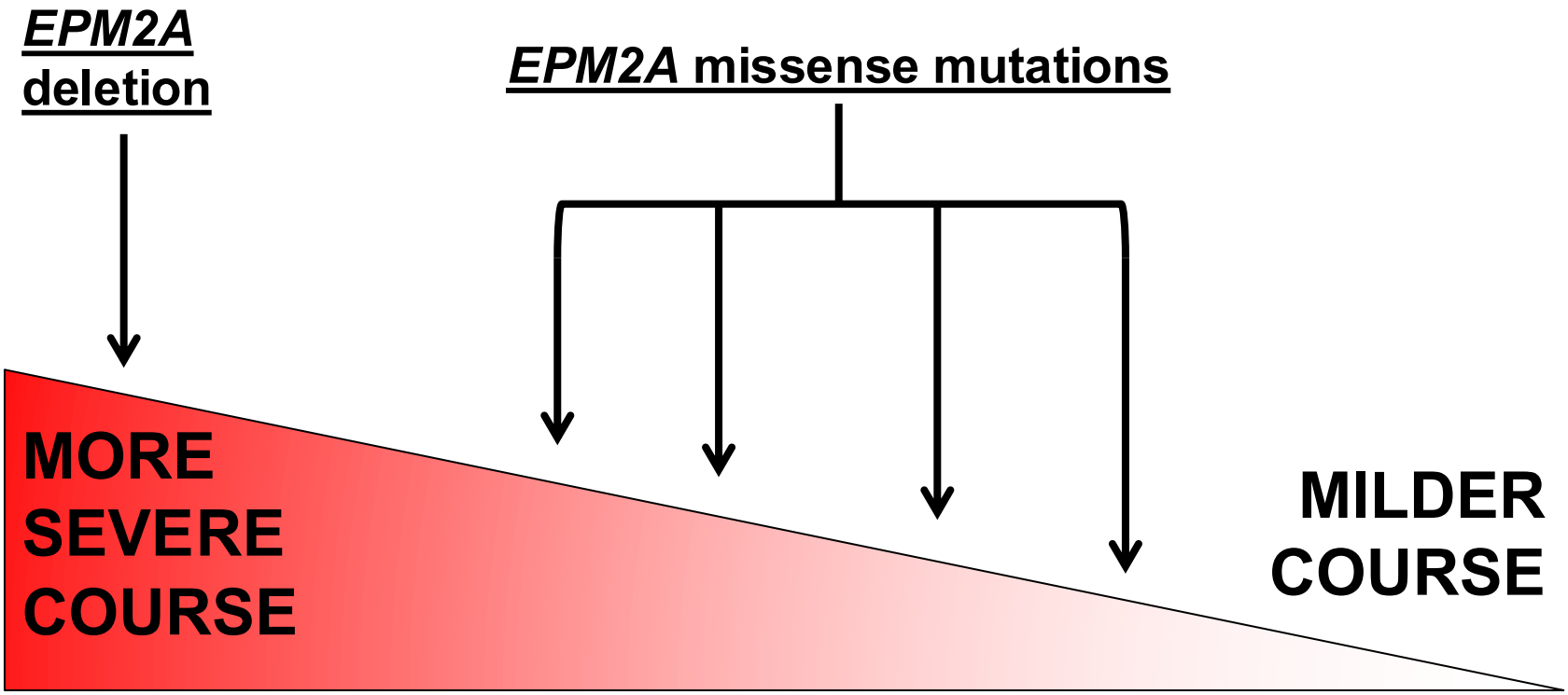
Personalized diagnosis of Lafora disease mutations



Raththagala et al., *Molecular Cell*, 2015

	CBM	DSP	CBM-DSP interface	dimer interface
glycogen binding	SEVERELY REDUCED	normal	normal	normal
phosphatase activity	VARIES	SEVERELY REDUCED	REDUCED	REDUCED
C3/C6 ratio	ALTERED	normal	ALTERED	normal
stability	REDUCED	normal	SEVERELY REDUCED	SEVERELY REDUCED
dynamics	normal	normal	ALTERED	normal
dimerization	normal	normal	normal	ALTERED

Personalized medicine: phenotype vs. genotype



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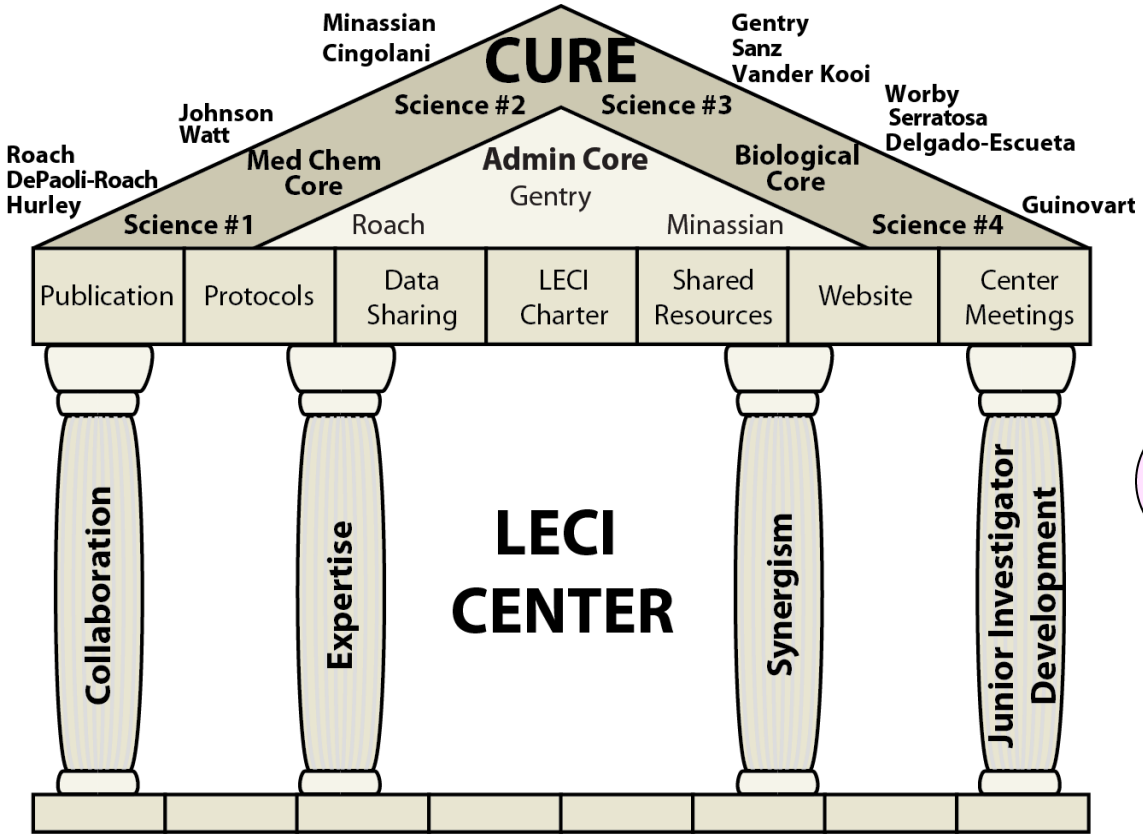

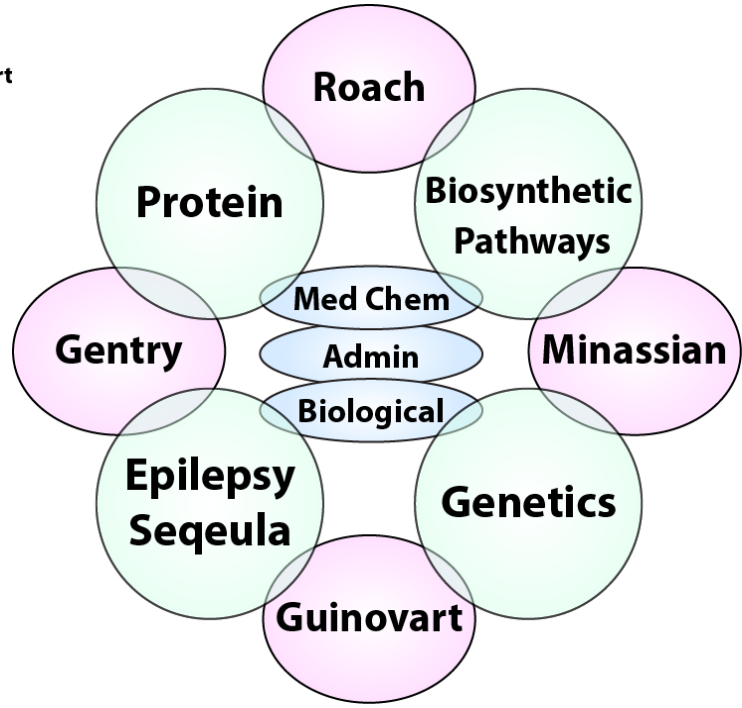

Project #1: Personalized diagnosis - defining how glycogen metabolism and proteost
impact LD

Project #2: Genome editing, mRNA suppression and glycogen chain termination to i
glycogen storage as therapy for LD

Project #3: Suppressing glycogen storage with small molecule inhibitors as a therape
approach

Project #4: Defining the therapeutic window for the treatment of LD

Metformin as a treatment for Lafora disease

Mol Neurobiol (2016) 53:1296–1309
DOI 10.1007/s12035-015-9091-8

Pharmacological Interventions to Ameliorate Neuropathological Symptoms in a Mouse Model of Lafora Disease

Arnaud Berthier · Miguel Payá · Ana M. García-Cabrero · Maria Inmaculada Ballester · Miguel Heredia · José M. Serratosa · Marina P. Sánchez · Pascual Sanz

EPM2B -/- mice treated with 4-phenylbutyric acid and metformin for 2 months displayed:

- Decreased polyglucosan inclusions
- Decreased polyubiquitinated aggregates
- Decreased neurodegeneration and gliosis
- Improved locomotion and motor coordination

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