Gene therapy approaches for Parkinson's disease related lysosomal disorders

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Prevail Therapeutics

Growing gene therapy landscape

- **Safety:** AAV-based therapeutics have been dosed safely in hundreds of patients and do not integrate into the host genome
- **Transformative efficacy:**
  - Spark's Luxturna first gene therapy approved in the United States
  - Avexis' AAV9-based therapy showed transformative efficacy in babies with SMA

SMA Gene Therapy Promising in Early Results

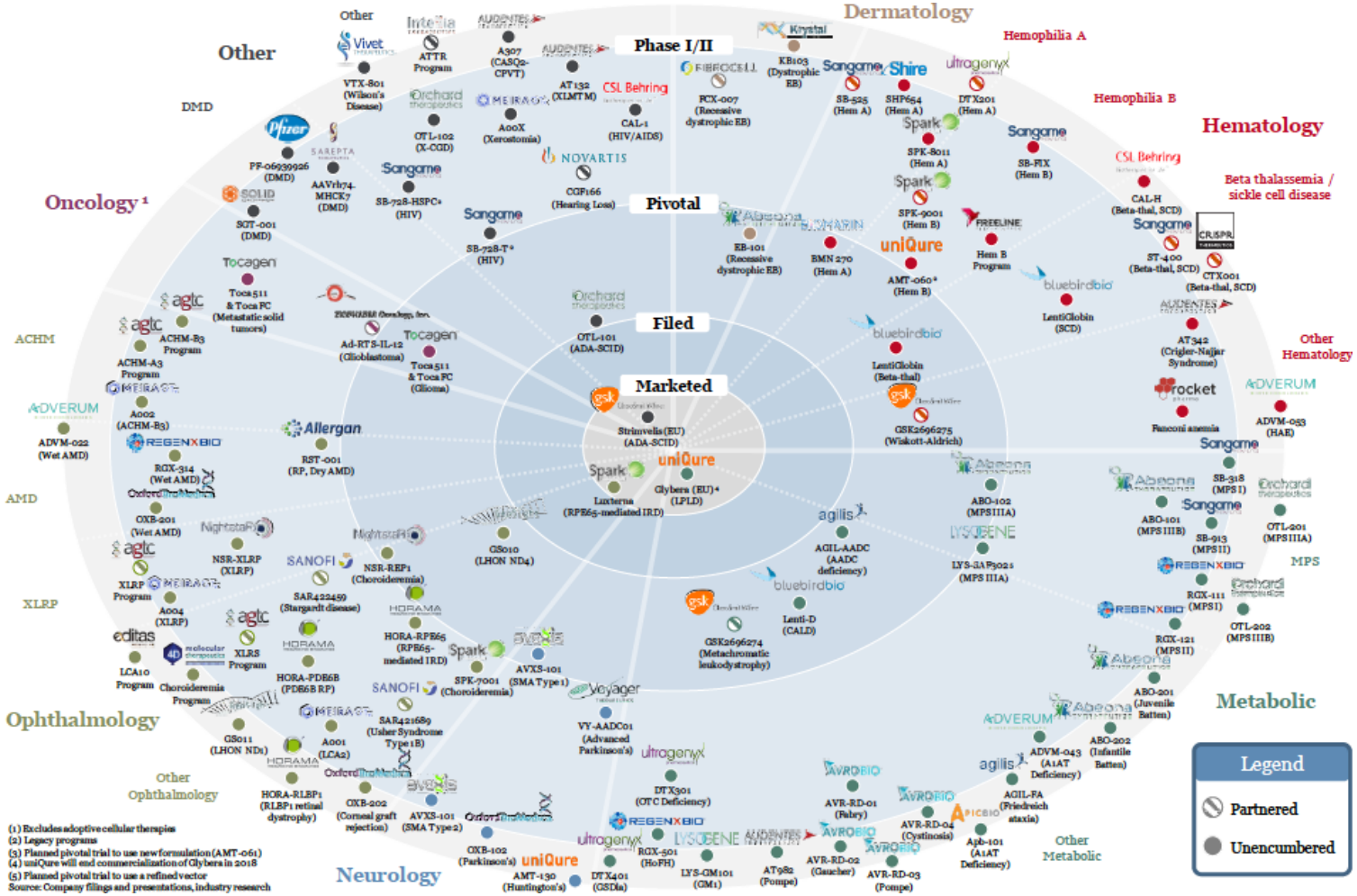
— 12 children with spinal muscular atrophy hit motor milestones in phase I trial of AVXS-101

A Cure for Hemophilia within Reach

Gene Therapy for Rare Form of Blindness Wins US Approval

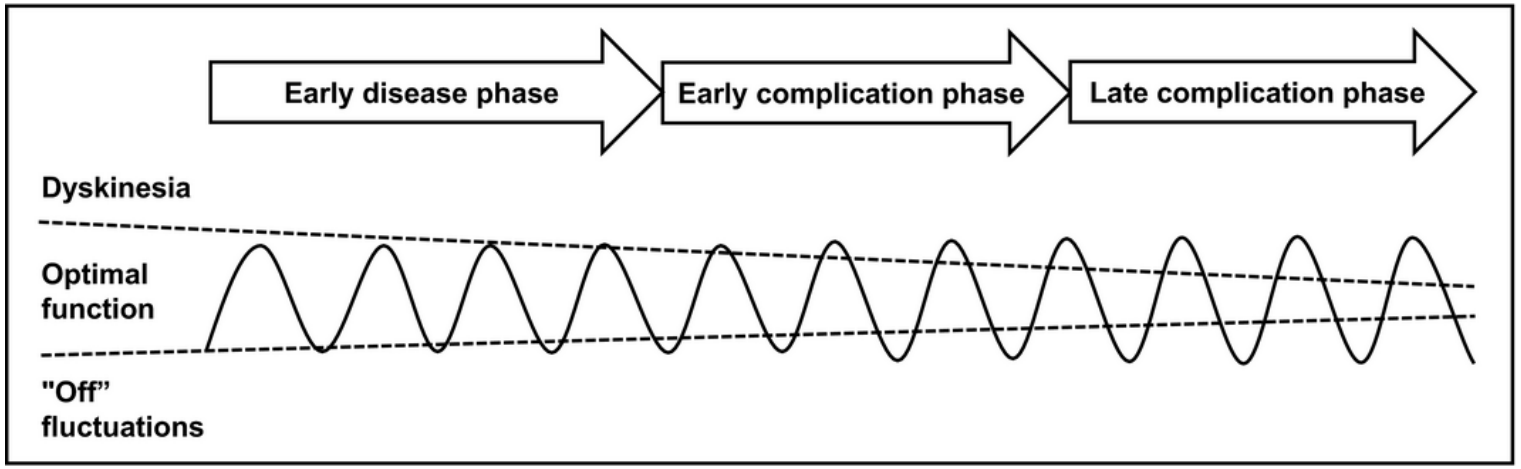
Gene therapy's new hope: A neuron-targeting virus is saving infant lives

Growing gene therapy landscape



Bishai, Petti, Bounoutas Wells Fargo 2018

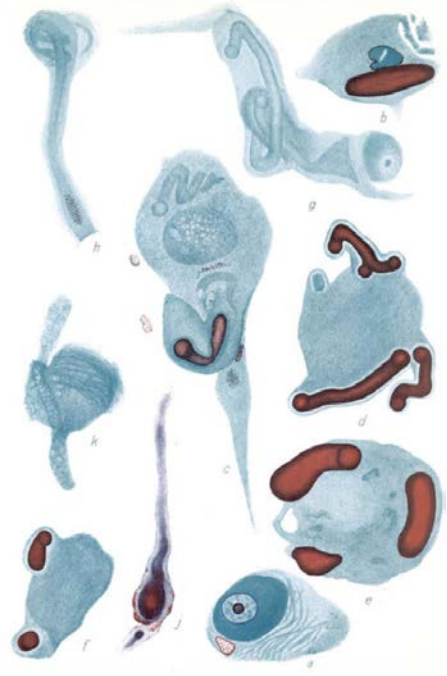
Parkinson's disease: the unmet need

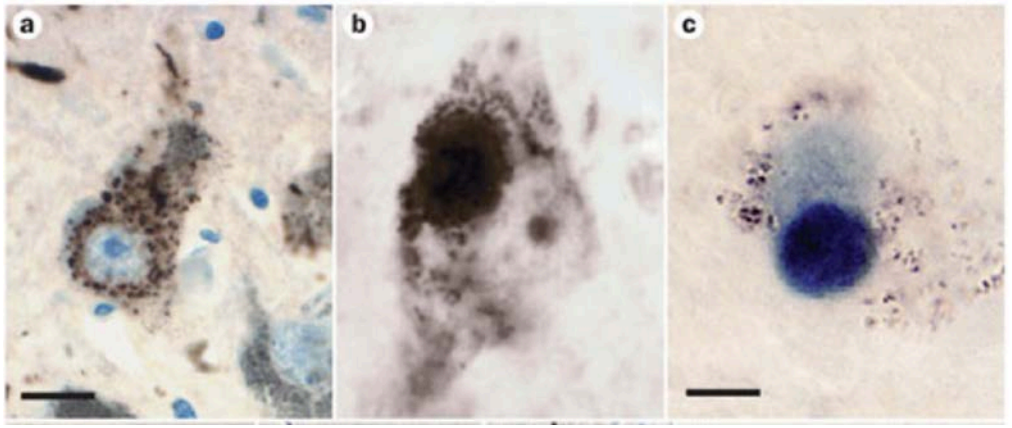


- Parkinson's is the most common progressive motor disease of aging
- Many Parkinson's patients initially experience a "honeymoon period" with good response of their motor symptoms to symptomatic dopaminergic therapy, but this response wanes
- Genetically-defined Parkinson's patient subpopulations (such as with glucocerebrosidase [GBA1] mutations) progress rapidly and with a more aggressive course
- **No existing therapies modify or halt the progression of Parkinson's disease**

Source: eMedicine, Michael J. Fox Foundation, Timpka et al. Movement Disorders – Clinical Practice (2016)

PD Pathology: Lewy Body Inclusions





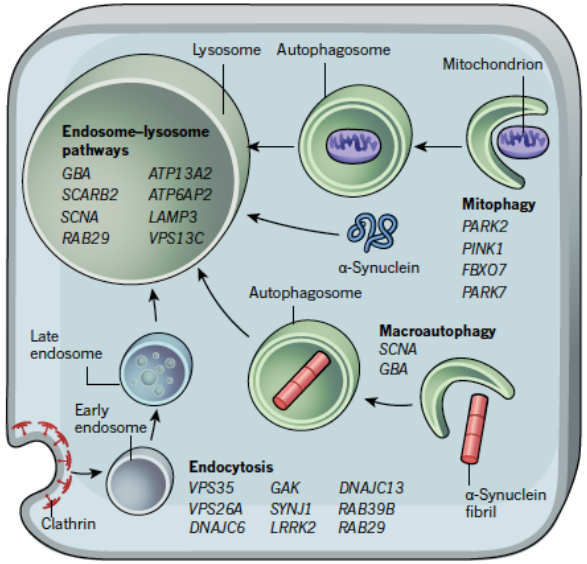
← Fritz Lewy

Braak and Del Tradici, 2009

Key human genetics insight: lysosome dysfunction underlies age-associated neurodegeneration in Parkinson's disease

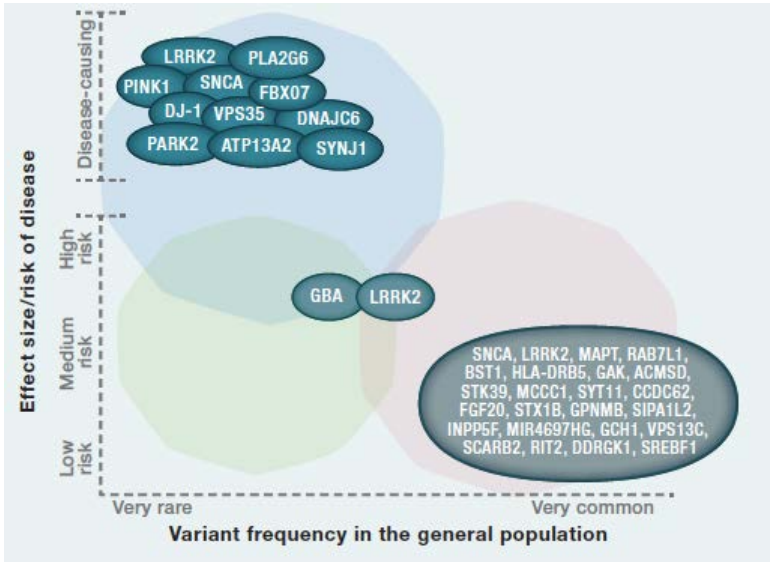
- Human genetic studies, including genome wide association and deep sequencing, have identified causative genes for age-related neurodegenerative disorders such as Parkinson's disease
- Parkinson's disease is now known to be strongly impacted by over 40 genes
- **Many of these PD-associated genes play a direct role in lysosome function and trafficking, such as GBA1 which encodes glucocerebrosidase (Gcase)**

PD-related genes associated with trafficking to the lysosome



Abeliovich and Gitler, Nature 2016

Genetic landscape of Parkinson's disease

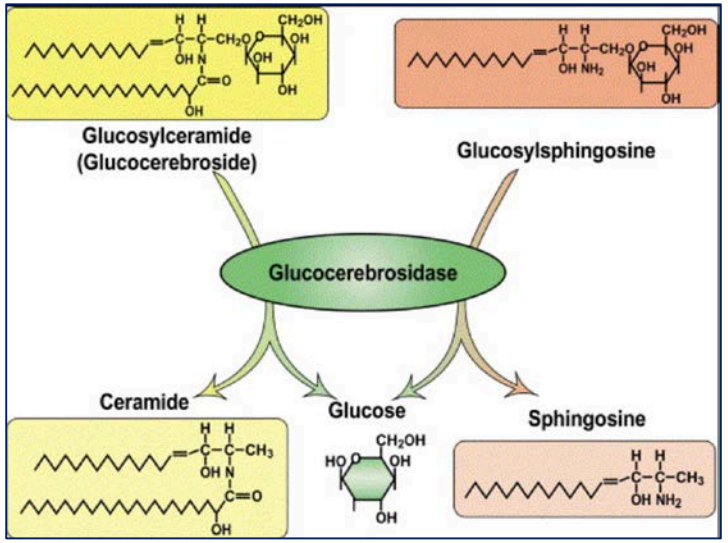


Bras, Guerreiro, Hardy, Cell 2015

Gcase deficiency and glycolipid substrate accumulation are causative in Gaucher and Parkinson's disease pathology

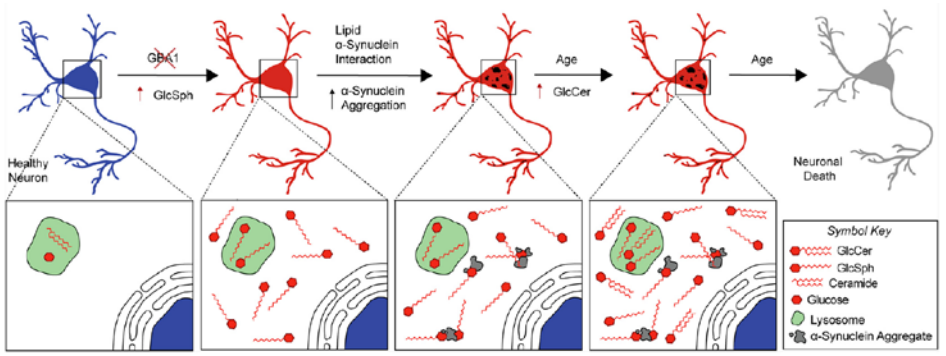
- Glucocerebrosidase (Gcase) deficiency has long been known to lead to the accumulation of toxic glycolipids in Gaucher disease, which is a multi-organ disease that can include CNS symptoms
- Recent human genetics breakthroughs demonstrate that relatively modest reduction (~20%) in Gcase can cause age-associated Parkinson's disease
- Gcase substrate accumulation induces α-synuclein pathology and neuronal loss, which typifies the Parkinson's disease brain

Gcase deficiency leads to accumulation of toxic glycolipids such as glucosylsphingosine



Sidransky, Molecular Genetics and Metabolism 2004

These glycolipids induce accumulation and aggregation of α-synuclein, which further impairs lysosomal trafficking

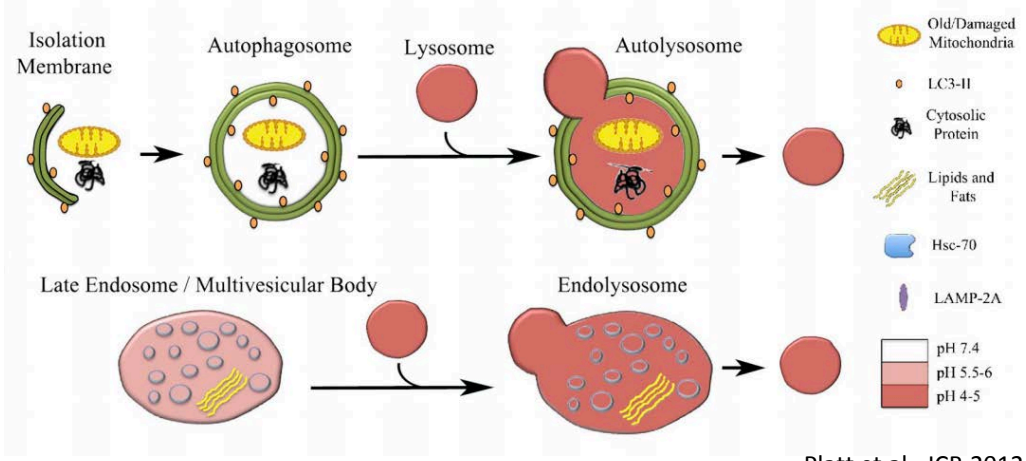


Taguchi et al., J. Neurosci 2017

Lysosomes play an essential role in degradation and recycling of macromolecules

- Lysosomes are considered the cell's "recycling center" and recycle proteins, lipids, sugars, aggregates, etc.
- Lysosomes play an especially critical role in long-lived cells, such as CNS neurons, and in aging cells
- Deficiencies in many lysosome enzymes can induce accumulation of toxic materials, leading to severe childhood syndromes termed lysosomal storage disorders (LSDs)

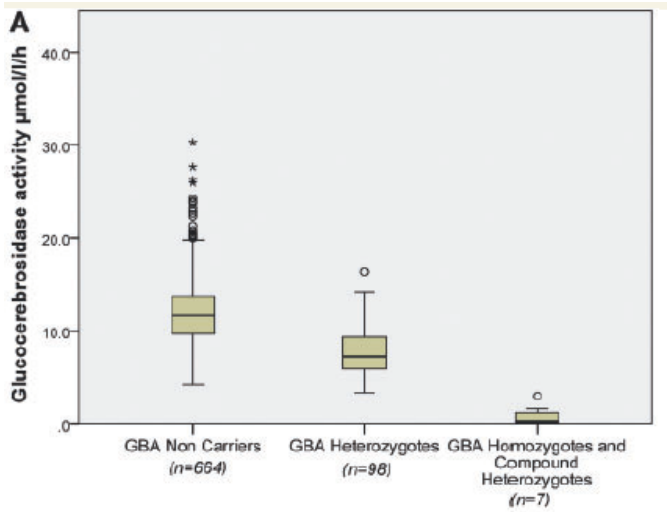
Lysosomes degrade components from the cell cytoplasm (through autophagic trafficking) or from membranes or the cell exterior (through endosomal trafficking)



Platt et al., JCB 2012

Gcase insufficiency
Contributes to PD-GBA and "sporadic" PD

- Reduced blood Gcase activity in PD-GBA and sporadic PD patients
- Dose effect: homozygotes/compound heterozygotes < heterozygotes < non-carriers
- Mildest mutations (E326K) with ~20% reduction
- "Modifiable therapeutic target"

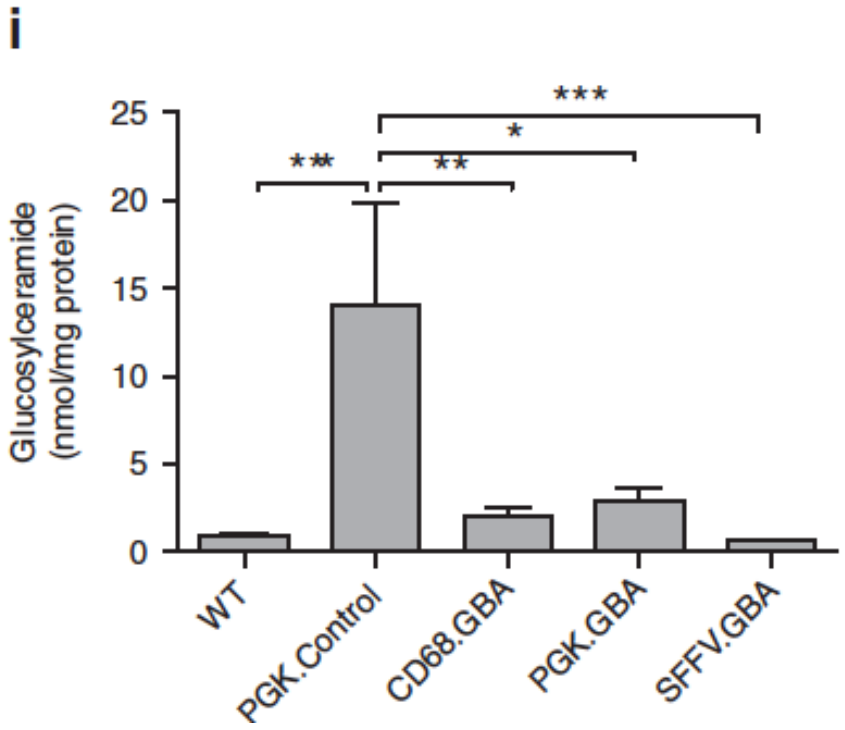


Mutation status	*n*	Mean glucocerebrosidase enzymatic activity in µmol/l/h (SD)
GBA homozygotes and compound heterozygotes	7	0.85 (1.11)
N370S	40	6.42 (1.72)
L444P	8	7.66 (2.28)
84GG	4	7.13 (1.29)
R496H	4	8.10 (2.52)
IVS2 + 1	2	7.97 (1.00)
E326K	16	9.81 (2.87)
T369M	9	7.64 (1.71)
LRRK2 G2019S[b]	36	13.69 (4.84)
Non-*GBA* and non-*LRRK2* carriers	628	11.93 (3.21)

Alcalay et al. Brain 2015

- In CSF, reduced Gcase activity (Balducci et al Mov Disord 2007; Parnetti et al Mov Disord 2014)
- In brain tissue (post-mortem), reduction of Gcase activity and mRNA (Cegg et al. Ann Neurol 2012; Murphy et al. Brain 2014, Chiasserini et al. Mol Neurodeg 2014)

Cell and gene therapies: lentivirus ex vivo



original article

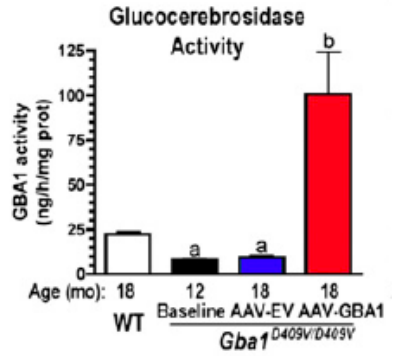
Lentiviral Gene Therapy Using Cellular Promoters Cures Type 1 Gaucher Disease in Mice

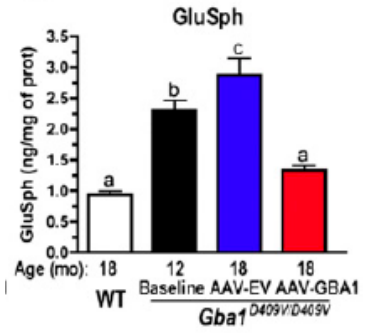
Maria Dahl[1,2], Alexander Doyle[1,2], Karin Olsson[1,2], Jan-Eric Månsson[3], André RA Marques[4], Mina Mirzaian[4], Johannes M Aerts[4], Mats Ehinger[5], Michael Rothe[6], Ute Modlich[6], Axel Schambach[6] and Stefan Karlsson[1,2]

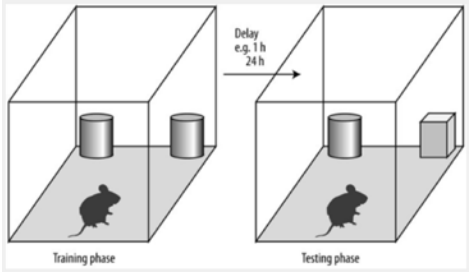
GBA1 gene therapy in a mouse model of Gaucher demonstrated rescue of cognitive dysfunction

Intrahippocampal injection of AAV1-GBA1 reduced substrate accumulation in a Gaucher disease genetic mouse model

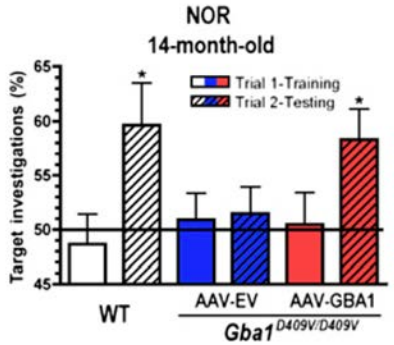
AAV1-GBA1 reversed deficits in Novel Object Recognition (NOR) task after injection at 4 or 12 months, assayed at 6 or 14 months respectively







Brodziak A, Kołat E, Różyk-Myrta A, Med. Sci. Monit. (2014)

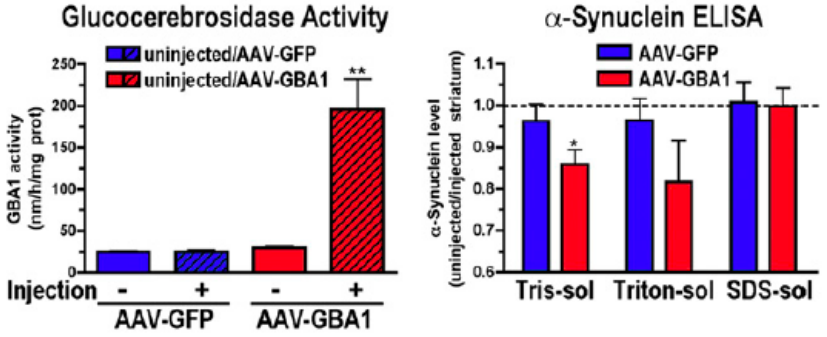


Sardi et al., PNAS 2013

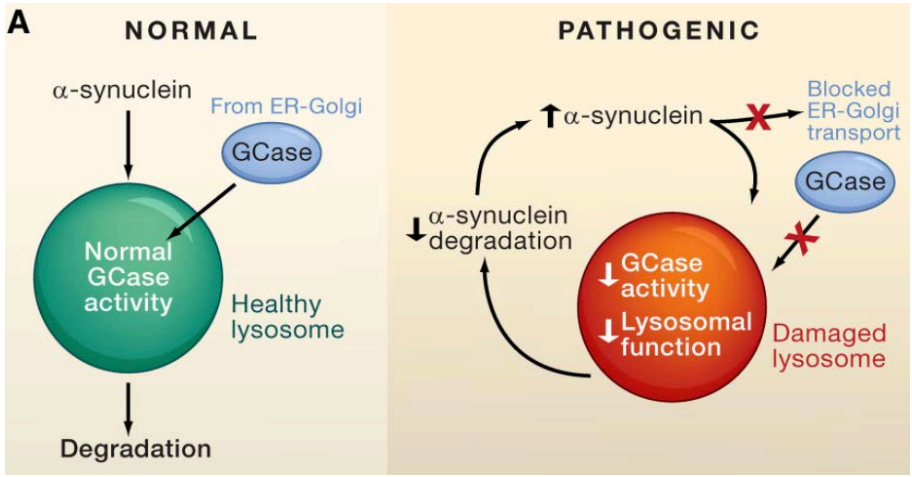
GBA1 gene therapy in a mouse model of Parkinson's disease demonstrated reduced α-synuclein accumulation

Intrastriatal injection of AAV1-GBA1 leads to enzyme accumulation and a reduction in α-synuclein accumulation

These α-synuclein transgenic mice have ~20-30% reduction in Gcase activity which is rescued by treatment



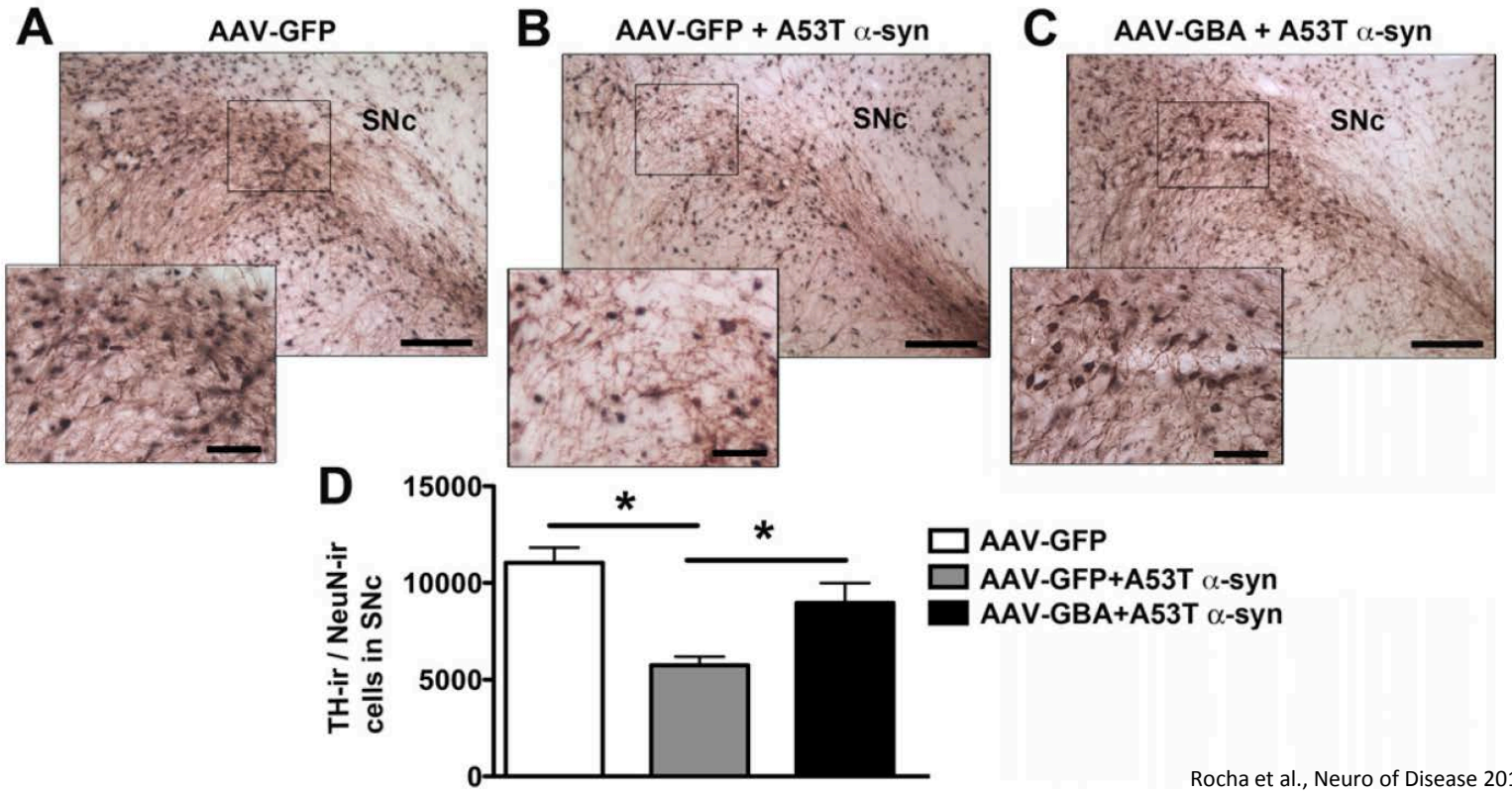
Sardi et al., PNAS 2012



Cookson, Cell 2011

GBA1 gene therapy in a second mouse model of Parkinson's disease rescues dopamine neuron loss

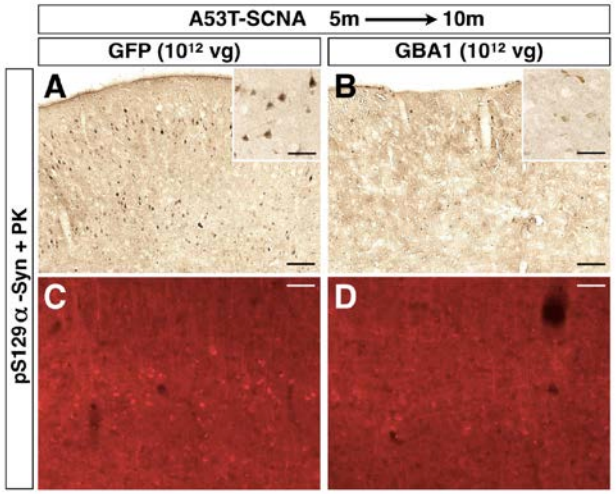
- AAV5-GBA1 vector injected into the substantia nigra rescues dopamine neuron loss in an AAV-based mutant α-synuclein animal model of Parkinson's disease

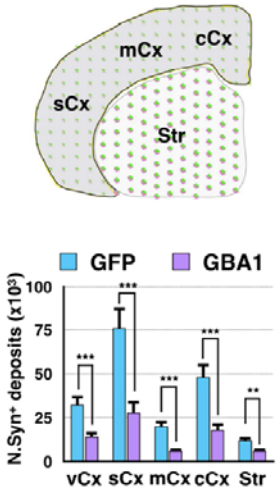


Rocha et al., Neuro of Disease 2015

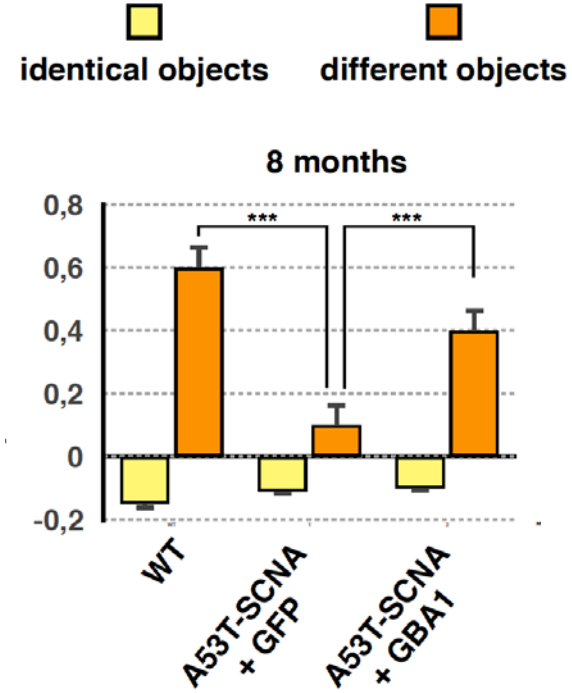
GBA1 gene therapy in a third mouse model of Parkinson's disease rescued cognitive dysfunction

- Variant AAV9-GBA1 delivered intravenously leads to rescue of α-synuclein inclusion phenotype in a different α-synuclein transgenic model
- Also rescues novel object recognition cognitive task





Transduction at 5 months, analysis at 10 months



Transduction at 5 months, analysis at 8 months

Source: Morabito et al., 2017

Thank you!