Gaucher Disease - More Than Just a Lipid Storage Disease

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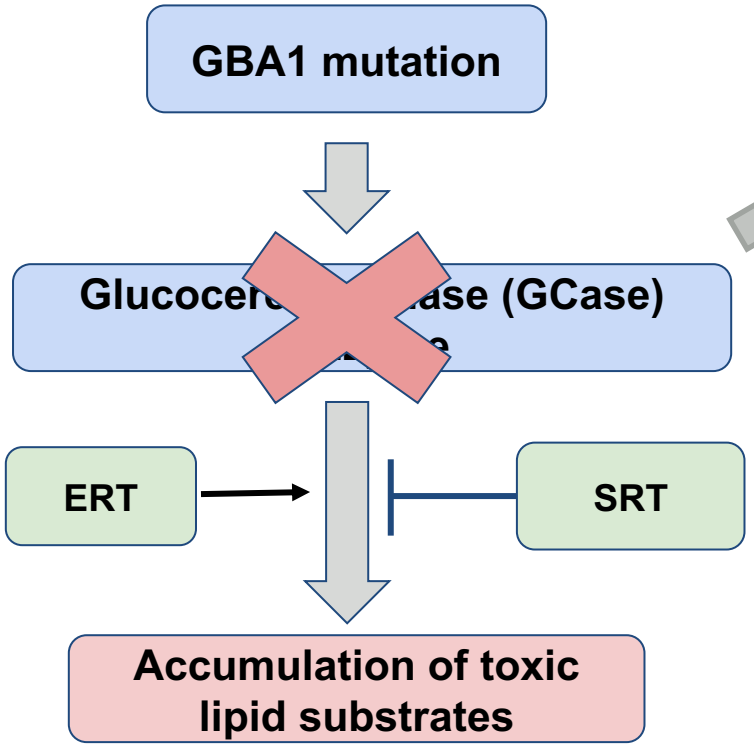
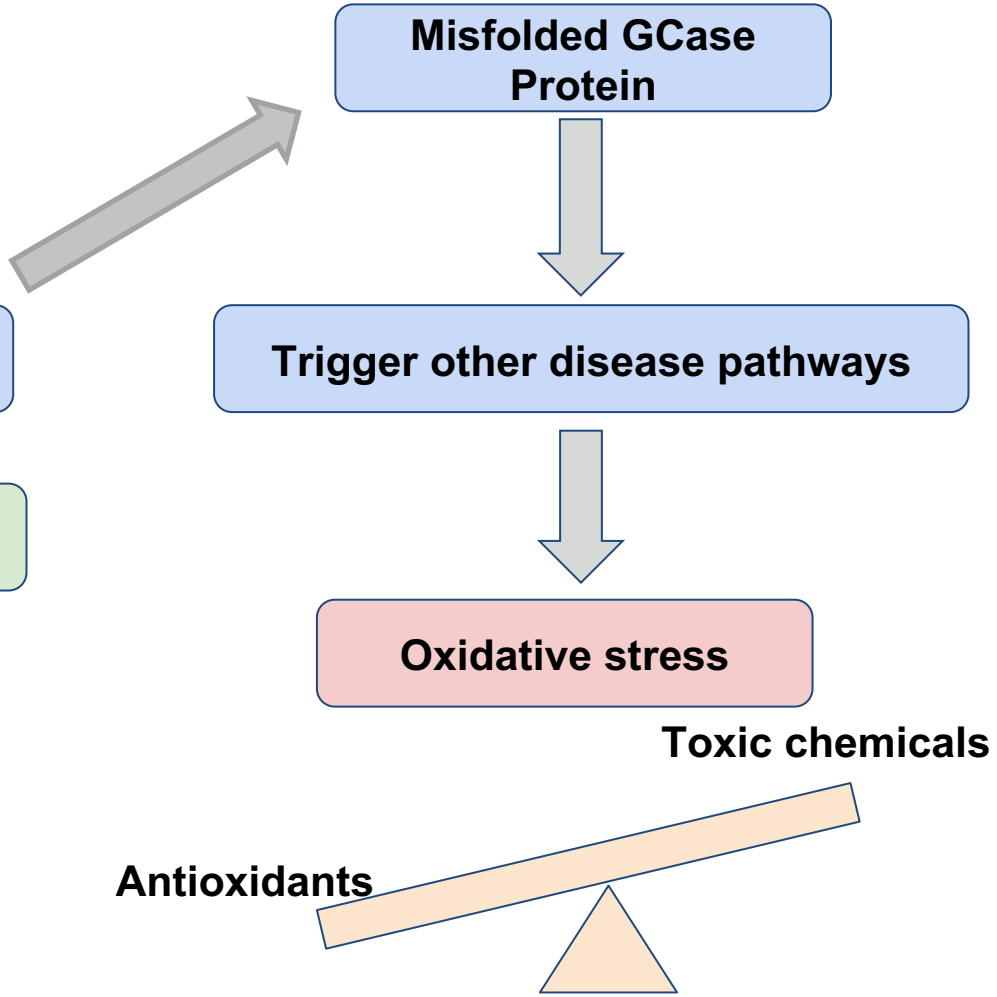
Gaucher Disease Pathophysiology

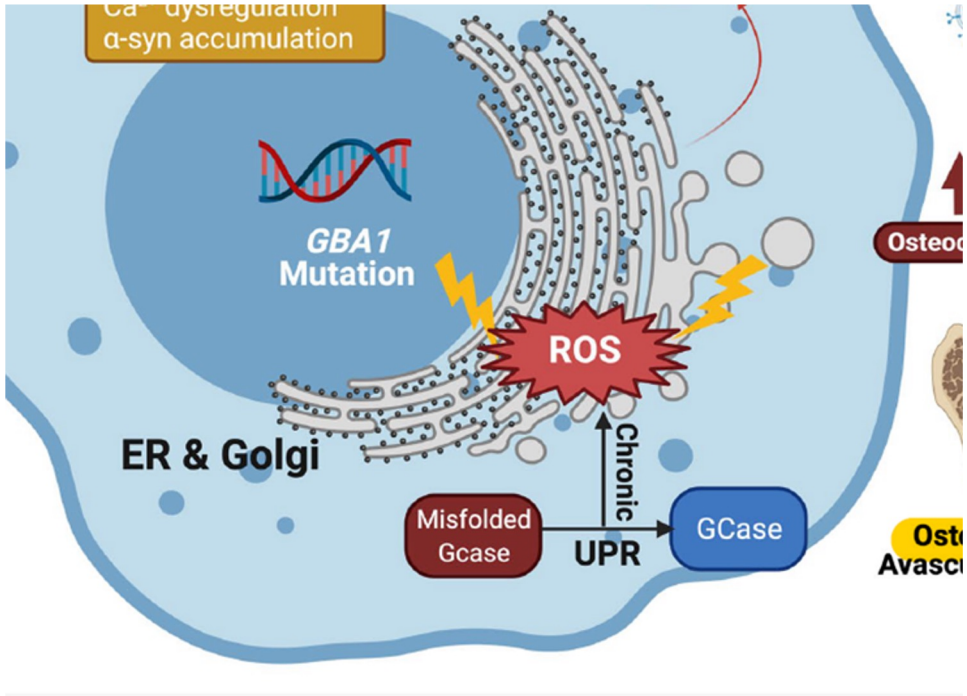
What we know



What may also be happening



Oxidative Stress



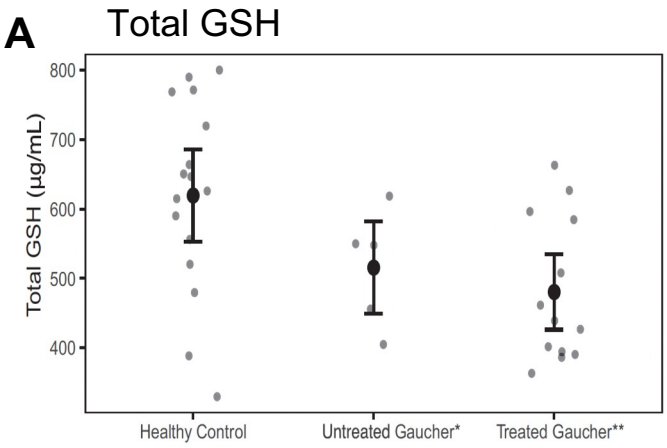
- Reactive oxygen species (ROS) are formed as a by-product of the unfolded protein response (UPR) process
- Glutathione (GSH) acts as an antioxidant
- Lead to other comorbidities

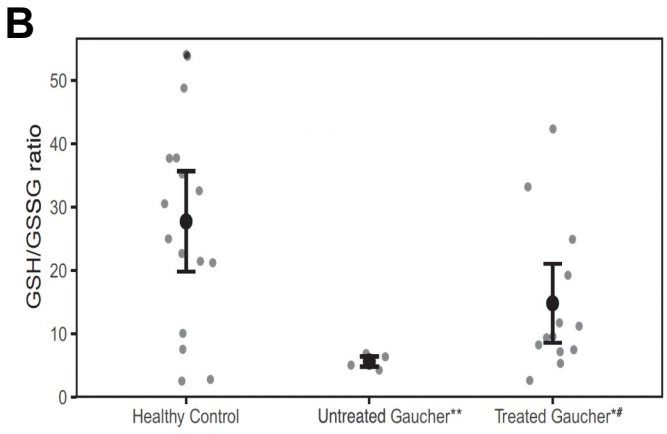
↑ ROS + ↓ GSH = ↑ Oxidative Stress (harmful to body)

Increasing GSH can protect from harmful effects

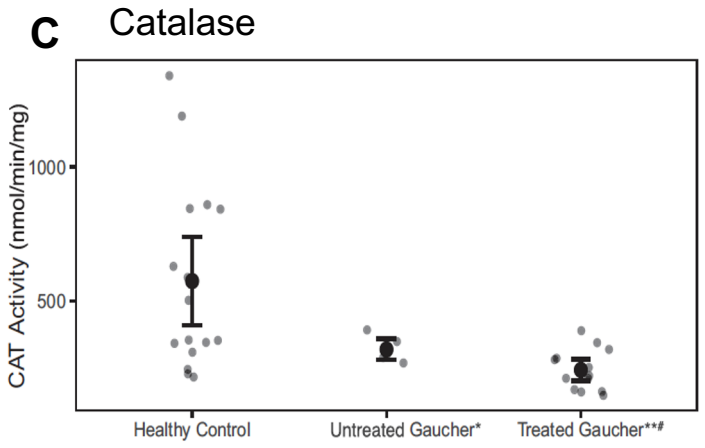
Roh, J., Subramanian, S., Weinreb, N.J. *et al.* Gaucher disease – more than just a rare lipid storage disease. *J Mol Med* 100, 499–518 (2022). https://doi.org/10.1007/s00109-021-02174-z

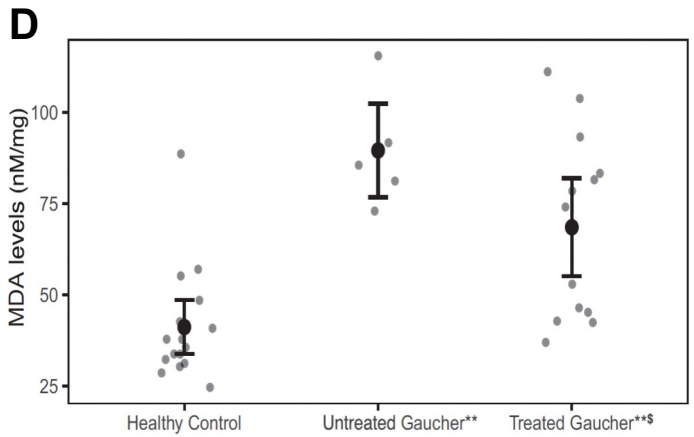
Oxidative Stress Markers





GSH redox



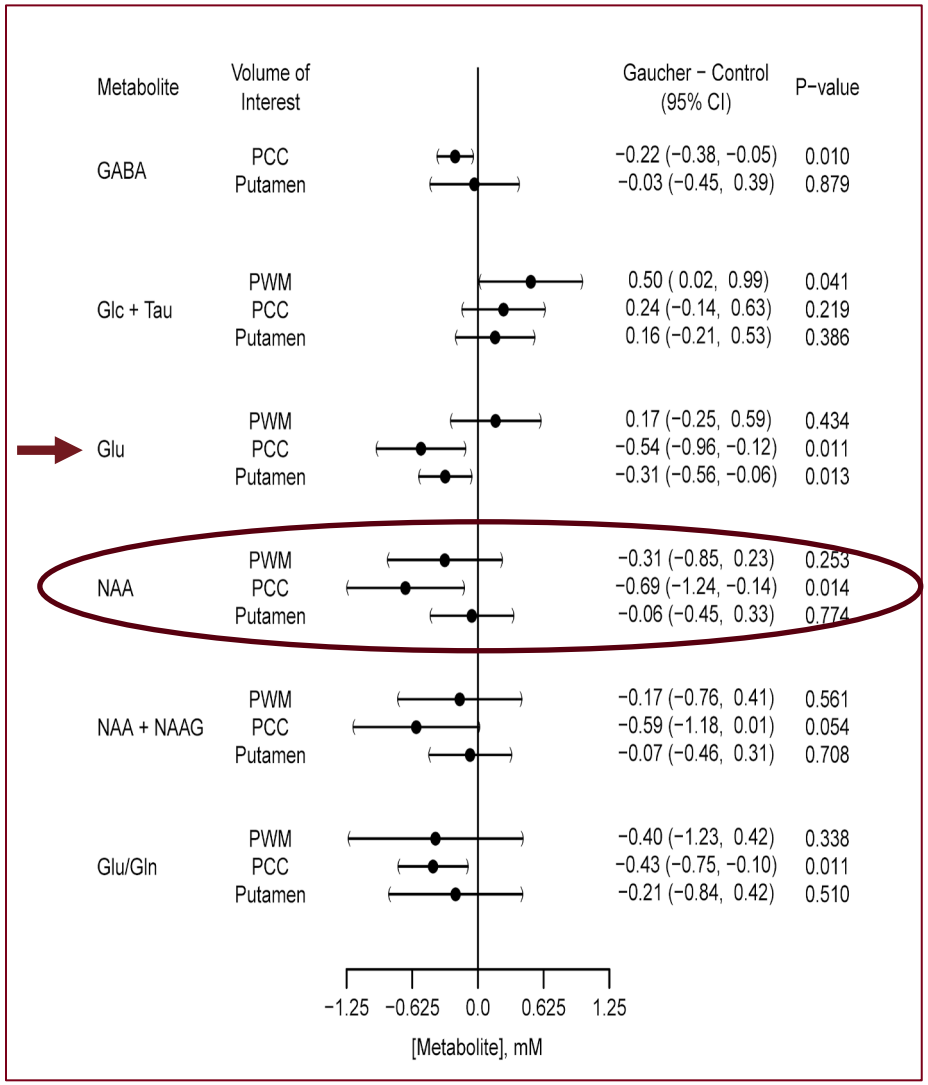


Lipid Peroxidation

Healthy n=17
Treated n=13
Untreated n=5

Kartha.RV *et al.* Mol Genet Metab Rep. 2020 Dec 9;25:100667. doi: 10.1016/j.ymgmr.2020.100667.

Mean Differences in Key Neurometabolites



NAA - neuronal health, integrity
GABA- neurotransmitter
Glu- neurotransmitter, neuronal marker
Gln - glial marker
Glc+Tau - cellular energetics
Glu/Gln - glutamate-glutamine cycling

N=12

NAA- N-acetylaspartate; NAAG- NAA glutamate; Glu-glutamate; Gln-glutamine; Glc-glucose; Tau-taurine; GABA-gamma amino butyric acid

New Therapeutic Approaches

Table 1 Current emerging interventional therapies for Gaucher disease

Name	Type	Target	Details	Dose	Outcome	Sources
Ambroxol	Pharmacological chaperone	Type 1 GD, ages 18–75, suboptimal response to ERT	Clinical trial phase 2 study	600 mg/day	Platelet count, bone mineral density, Lyso-GB1[a] biomarker	NCT03950050
N-acetylcysteine (NAC)	Antioxidants	Type 1 GD, Ages 18 years and older	Clinical trial phase 2 study	1800 mg NAC twice daily for approximately 90 days	Changes in neurometabolites, changes in blood biomarkers of oxidative stress and inflammation	NCT02583672
Coenzyme Q10 (CoQ10)	Antioxidants	Chemically induced Gaucher macrophages	In vitro cellular model	CoQ 25 μM	Improve mitochondria function and oxidative stress	[236]
Arimoclomol	Pharmacological chaperone	Type 1 or 3 GD, ages 4–60	Clinical trial phase 2 study	100, 200, 400 mg	Percentage change in serum chitotriosidase levels	NCT03746587
GuardOne	Lentiviral vector gene therapy	Type 1 GD, ages 16–35	Clinical trial phase 1/2 study	A single dose of AVR-RD-02 infusion	Treatment-emergent adverse events, GCase enzyme activity	NCT04145037
PROVIDE	Adeno-associated virus serotype 9 (AAV9) gene therapy	Type 2 GD, up to 24 months	Clinical trial phase 1/2 study	A single dose of PR001 administered intracisternally	Number of adverse events, changes in immunogenicity of AAV9 and GCase in blood & cerebrospinal fluid	NCT04411654
FLT201	AAV8 gene therapy	Type 1 GD	In vitro cellular model (human PBMCs and macrophages) & animal studies (mice, rhesus macaque)	A single dose of FLT201 infusion	Enhanced GCase expression, lowers substrate levels	[237]

[a]Alternate name for Lyso-GL1

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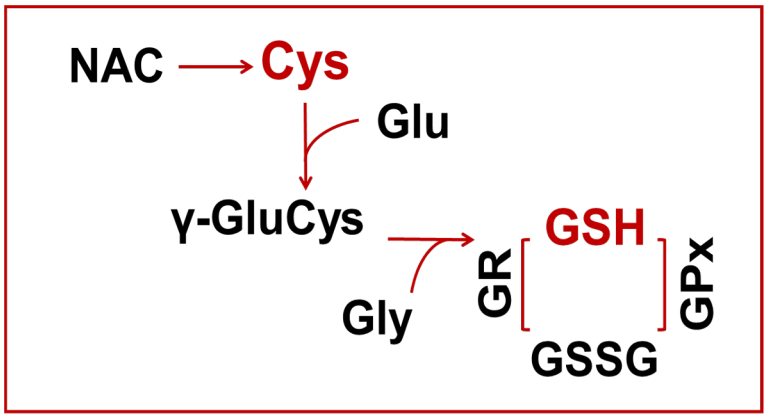
N-acetylcysteine (NAC)

- Pulmonary disorders – Mucomyst (acetylcysteine oral solution); approved in 1963; mucolytic agent
- Acetaminophen overdose – Acetadote (intravenous solutions); *Orphan drug designation* in 2004
- Over the counter supplements (capsules, effervescent tablets)



- A safe, effective, low-cost antioxidant/anti-inflammatory that would offer patients a new, adjunctive therapeutic option

Oral NAC as Adjunctive Therapy

Study design

Baseline: In patients and healthy subjects; blood samples collected at 3 different time points over ~90 days; imaging.

Intervention: Patients are given PharmaNAC™ @ 3600mg/day for 90 days. Blood collected at 3 time points; a second scan at the end of therapy and PK blood sampling.

Follow-up: End of study visit 3 months after intervention.

Blood Analysis	Analytes
Oxidative Stress markers	Total GSH, antioxidant enzymes, lipid and protein modifications
Inflammatory markers	Anti- and pro-inflammatory markers
Pharmacokinetic Analysis (exposure-response modeling)	Total NAC, Cysteine, GSH

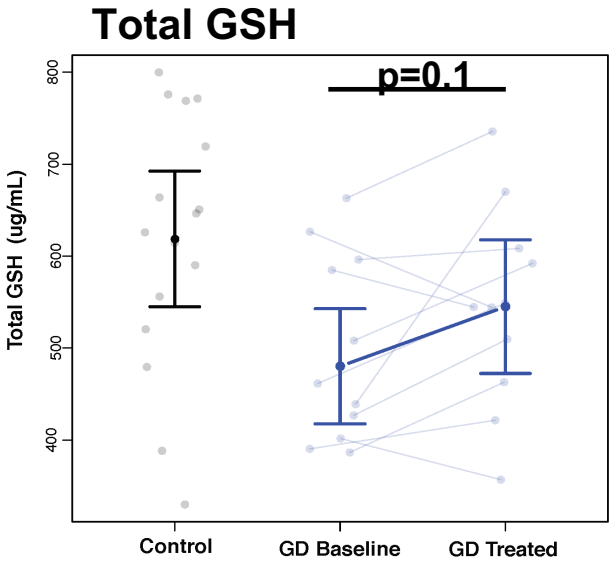
Participant Characteristics

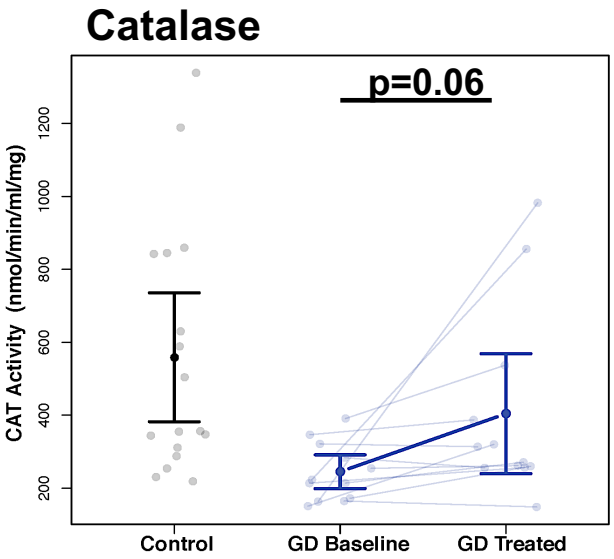
Covariate	Control (n = 17)	GD1 (n = 13)
Age (years)	38.8 (14.9)	46.9 (12.0)
Female	9 (50.0%)	8 (61.5%)
Caucasian	12 (75.0%)	12 (92.3%)
Mutation status	NA	
N370S/N370S		5 (38.5%)
N370S/L444P		5 (38.5%)
N370S/unknown		1 (7.7%)
N370S/R463C		1 (7.7%)
Unknown		1 (7.7%)
Years on therapy	NA	16.1 (8.3)
ERT		6 (46.1%)
SRT		7 (53.8%)

Baseline Pain and Fatigue Assessments

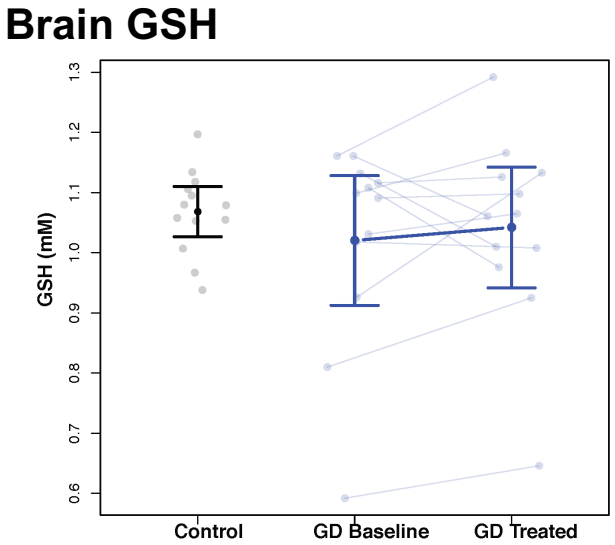
Variables		GD1 (n = 13)
Brief Pain Inventory(BPI) Average pain; 0-10	0-2 (Mild pain)	8 (61.5%)
	3-6 (Moderate pain)	5 (38.5%)
Brief Fatigue Inventory (BFI) Usual fatigue in the last 24 hours; 0-10	1-4 (Mild-moderate fatigue)	9 (69.2%)
	5-8 (Moderate-severe fatigue)	4 (30.8%)
History of analgesic use for chronic pain		6 (46.2%)

Preliminary Results





Improved Antioxidant Defenses



Improvement following NAC therapy	N (%)
Average Pain	5 (38.5%)
Usual Fatigue	8 (61.5%)

Continue enrollment with a higher dose

Effect on Glucocerebrosidase (GCase) Activity

- NAC and Cys can increase GCase activity in patient-derived skin cells.
- Anecdotal report from a physician (n=3; GBA1 carriers)

Carrier Mutations	% change in GCase activity
N370S (mild)	67% increase
IVS 2+1 (null)	37.4% increase
IVS 2+1 (null)	19.6% decrease

- Indicate mutation-specific chaperone effect.

Inflammatory Markers in GD1

- Extension of Oxidative Stress study (NCT02437396)
- Characterize novel inflammatory markers
- Enroll 10 untreated and 5 treated patients with GD1
  - 3 visits over a 3-month period
  - Provide a tablespoon of blood at each visit
    - We will run inflammatory assays
  - Home visit by a nurse/phlebotomist

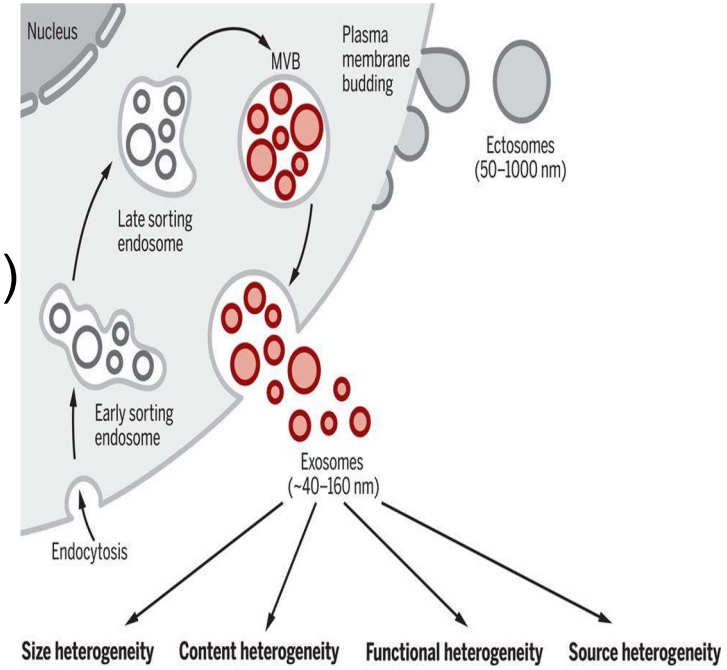
Extracellular Vesicles (EV) Study

- Characterize whether having a GBA1 mutation can change the quantity or content of small microparticles vesicles

- Enroll 10 patients with untreated GD1
  10 obligate carriers
  10 healthy volunteers

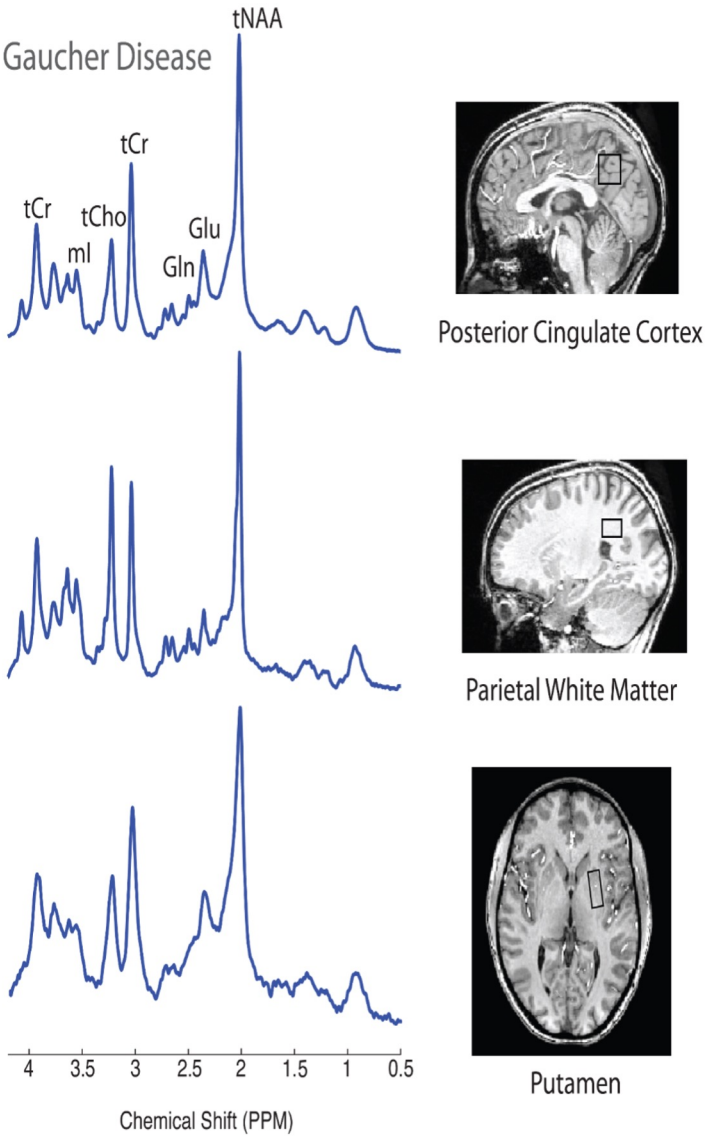
- Provide 2 fasting samples in 3 months
  - Genetic testing (whole GBA sequencing)
  - EV characterization

- Home visit by a nurse



Magnetic Resonance Spectroscopy in GD3

- Characterize MRS profiles in GD3
- Enroll 5 patients with GD3
- One visit to the UMN to provide a blood sample and complete the scan



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- Pfizer
- Takeda
- All Participants with GD1

RARE DISEASES
CLINICAL RESEARCH NETWORK

Questions?

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