This story may challenge how we think about the genetics of Mendelian disorders and complex diseases!
Blurred boundaries between simple and complex genetic disorders

“Simple” single gene disorders
Gaucher, CF, PKU, Mendelian disorders

“Complex” multi-gene disorders
PD, Diabetes, Asthma, ADHD Mendelian disorders

Single primary gene with large effect + multiple modifiers
Multiple primary genes with small effects + some modifiers

Continuum
Introduction

Gaucher Disease (GD)

- Deficiency of enzyme, (glucocerebrosidase)
- Variable age of onset
- Rare recessive, single gene disorder
- Symptoms include enlarged spleens and livers, low platelet counts, bone and brain involvement
- Multi-organ involvement

Parkinson Disease (PD)

- Loss of dopaminergic neurons + Lewy bodies (aggregates, α-syn)

Substantia Nigra
Mendelian disorders provide a window into complex disease
Diagnosis of PD

- Parkinsonism - term that describes motor features of Parkinson disease
- Parkinson disease - clinically and pathologically defined process (UK PD Society Brain Bank Criteria)

**Includes:** Bradykinesia (slowness of initiation of voluntary movement & reduction in speed and amplitude of repetitive actions)

And at least one of the following:

- Muscular rigidity
- 4-6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Parkinson Disease

- “Classic” idiopathic PD, largely sporadic
- Environmental - MPTP PD (“frozen addicts”)
- Lewy body dementias- DLB and AVLBD
- Parkinson plus
  - Multiple system atrophy (MSA)
  - Progressive supranuclear palsy (PSP)
  - Corticobasal degeneration (CBD)
  - Spinocerebellar degenerations (SCAs)
- Genetic PD: PARK1, PARK2, etc.
- Over 15 PARK genes now described-some, but not all, associated with Lewy body pathology
Autosomal Dominant

- SNCA (PARK1)= Rare cause of hereditary PD, point mutations, multiplications of α-synuclein
- LRRK2 (PARK8)= Frequent, incomplete penetrance, function unknown, variable pathologic findings

Autosomal Recessive

- Parkin (PARK2)= Early onset, slow progression, found in 10-20% in patients with early-onset (<45 y)
- PINK1 (PARK6)= Rare, onset 3rd and 4th decade, slow progression
- Kufor-Rakeb disease (PARK9)= Rare, pyramidal degeneration, cognitive dysfunction
*GBA* gene mutated in Gaucher disease

Glucocerebrosidase

Glucocerebroside + H$_2$O → Ceramide + Glucose

Macrophage

Gaucher Macrophage
The Gaucher Cell

Bone Marrow Smear

EM of a Gaucher cell showing a lipid engorged lysosome
Recognition of Gaucher disease -- 1882
Nature of the stored material -- 1935
Enzymatic defect (Dr. Brady) -- 1965
Era of molecular biology -- 1981
Enzyme replacement -- 1991
Animal model of Gaucher disease 1992
Association with parkinsonism - 2000
Clinical Manifestations of Type 1 Gaucher Disease

- Very heterogeneous in phenotype
- Presents at any age with variable progression
- Common signs and symptoms - hepatosplenomegaly, bone involvement, anemia, thrombocytopenia
- Many asymptomatic individuals
- Autosomal recessive - panethnic
- More frequent among Ashkenazi Jews
Abnormal MRI of a patient with Type 1 Gaucher disease

Enlarged spleen
Xrays showing Erlenmeyer flask deformity and osteopenia
Clinical Manifestations of Type 2 Gaucher Disease

- Stereotypic presentation
- Usually presents at 3 - 6 months, can present in the neonatal period
- Death by age 2 - 3 years
- Common signs and symptoms - hepatosplenomegaly, seizures, neurologic deterioration, may have associated ichthyosis
- Rare form
Clinical Manifestations of Type 3 Gaucher Disease

- **Heterogeneous phenotype**
- **Includes neurologic involvement**-
  - slowing and looping of horizontal saccades, may include ataxia, dementia, myoclonic epilepsy
- **Visceral and bone involvement**
- **Panethnic**, with a geographic isolate in Sweden
Gaucher Disease: A Continuum of Phenotypes

- Type 1
  - Asymptomatic
  - Skeletal disease
  - Visceral disease
  - 2° neurologic involvement
  - Parkinsonian manifestations

- Type 2
  - Neurologic manifestations
  - Hydrocephalus, cardiac valve calcifications
  - Myoclonic epilepsy
  - Eye movement disorder
  - Progressive neurologic degeneration

- Type 3
  - Congenital ichthyosis
  - Hydrops fetalis

Visceral disease
Skeletal disease
Asymptomatic
**Glucocerebrosidase Gene (GBA) Locus on 1q21**

- Pseudogene sharing 96% sequence homology 16kb downstream
- Some mutant alleles originate from the pseudogene (rec alleles)
- > 300 mutations, point mutations, frame-shifts, deletions and insertions

**GBA # of reported mutations per exon**

<table>
<thead>
<tr>
<th>Exon</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>1</td>
<td>84GG</td>
<td>ATG1</td>
<td>ATG2</td>
<td>84GG</td>
<td>IVS2(+1)</td>
<td>N188S</td>
<td>R120W</td>
<td>G202R</td>
<td>F213I</td>
<td>R257Q</td>
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*from Hruska et al. 2008 Hum Mut*

*Pink - mutations derived from the pseudogene.*
Neither the amount of lipid stored nor the enzyme activity correlate well with the patient phenotype.

Genotype-Phenotype Studies

Some correlations exist, but:

- Clinically different patients can have the same genotype
- Clinically similar patients can have many different genotypes
- Siblings with the identical genotype exhibit different clinical manifestations and responses to therapy
Study of 32 L444P homozygotes

- All have slowed horizontal saccades
- Degree of systemic and neurological manifestations highly variable
- Residual enzyme activity between 1%-13% with no correlation to clinical symptoms
- Outcomes range from death in childhood to autism to successful college students
- Specific neurocognitive deficits noted

Studies of discordant siblings and patients with the same genotype can be used to identify factors modifying phenotype
Multiple factors impact phenotype and blur boundaries between simple and complex genetic disorders

- Contiguous genes
- Altered splicing
- Gene regulation
- "Simple" Mendelian single gene disorders
- Complex multi-gene disorders
- Chaperones
- Post-translational processing
- Modifier genes
Chapter 1

Probands with both Gaucher disease and parkinsonism
This story began my clinic in 1996, with a single patient with GD who developed parkinsonism…

- Mild Gaucher disease- diagnosed at age 19
- Tremor began at age 42 with progressive rigidity, masked facies, difficulty initiating movements and rapid deterioration of gait
- No improvement with pallidotomy or enzyme replacement therapy
- Progressive dementia -death at age 54

Was this a co-incidence?

- Other cases found in literature (Neudorfer et al 1996) and other clinics
- In 2003, we published a series of 17 such subjects
### Patients with Gaucher disease and parkinsonism

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Genotype</th>
<th>Ethnic Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>R463C/R120W</td>
<td>Canadian</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>N370S/V394L</td>
<td>Hungarian/Jewish</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>N370S/IVS2+1</td>
<td>Polish</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>L444P/D409H + dup.</td>
<td>American</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>G377S/G377S</td>
<td>Italian</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>N370S/RecNcil</td>
<td>French</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>N370S/c.84insG</td>
<td>American</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>N370S/N370S</td>
<td>Ashkenazi</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>N370S/c.1263-1317del</td>
<td>French</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>N370S/c.500insT</td>
<td>Spanish</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>N370S/?</td>
<td>Italian (sib of 12)</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>N370S/?</td>
<td>Ashkenazi</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>N370S/N370S</td>
<td>Ashkenazi</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>N370S/L444P</td>
<td>Italian</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>N370S/N370S</td>
<td>Ashkenazi</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>N370S/N370S</td>
<td>Ashkenazi</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>N370S/N370S</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Clinical data on 17 patients with Gaucher disease and parkinsonism

Primary Gaucher Disease Manifestations
- Most had relatively mild Gaucher disease manifestations

Primary Parkinsonian Manifestations
- Tremor
- Bradykinesis
- Rigidity
- Masked facies
- Several had cognitive decline and/or dementia

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Mean</th>
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<tbody>
<tr>
<td>Age at diagnosis of Gaucher disease</td>
<td>9-62 yrs</td>
<td>35 yrs</td>
</tr>
<tr>
<td>Age at onset of parkinsonian symptoms</td>
<td>38-63 yrs</td>
<td>48 yrs</td>
</tr>
</tbody>
</table>

Therapy
- L-Dopa response was variable
- No change with Cerezyme
Are Gaucher carriers more susceptible to parkinsonism?
Family histories reveal parkinsonism in heterozygotes

- In a prospective study, 12 of 45 Gaucher probands had relatives with parkinsonism.
- Often, this was a parent or grandparent who was a Gaucher carrier.
- This was subsequently seen in other Gaucher centers including in Jerusalem.

*Heterozygotes are at increased risk for parkinsonism*
Pedigree of a patient with Gaucher disease

- Parkinson disease
- Tremor
- Type 3 Gaucher disease (L444P/L444P)
- L444P/wt heterozygote

Proband
This time we studied patients with Parkinson disease (with no known Gaucher disease)
Identification of *GBA* mutations in PD

- Autopsy sample was donated from a subject with Gaucher disease and parkinsonism
- Tissue requested from 2 age-matched PD subjects
- Both “controls” had GCase activity in the heterozygote range and *mutations in GBA*!
- We sequenced DNA from 57 brain samples with PD- 8 carried *GBA* mutations, none in 44 controls

This has propelled the community studying the genetics of PD in a new research direction. Many replication studies published around the world.

However, many of the initial studies were greeted with skepticism due to limitations in power or controls and because GWAS did not identify *GBA*
### Studies of GBA in Different PD Cohorts

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>% GBA mutations in PD patients</th>
<th>% GBA mutations in controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nichols <em>et al.</em> 2009</td>
<td>Cincinnati</td>
<td>4.1% of 1325</td>
<td>1.1% of 359</td>
</tr>
<tr>
<td>Mitsui <em>et al.</em> 2009</td>
<td>Japan</td>
<td>9.4% of 534</td>
<td>0.4% of 544</td>
</tr>
<tr>
<td>Gan-Or <em>et al.</em> 2008</td>
<td>Tel Aviv, Israel</td>
<td>17.9% of 420</td>
<td>4.2% of 333</td>
</tr>
<tr>
<td>Bras <em>et al.</em> 2008</td>
<td>Portugal</td>
<td>6.1% of 230</td>
<td>0.7% of 430</td>
</tr>
<tr>
<td>Lesage <em>et al.</em> 2010</td>
<td>France</td>
<td>6.7% of 1391</td>
<td>1.0% of 391</td>
</tr>
<tr>
<td>Neumann <em>et al.</em> 2009</td>
<td>UK</td>
<td>4.2% of 720</td>
<td>1.2% of 257</td>
</tr>
<tr>
<td>Kalinderi <em>et al.</em> 2009</td>
<td>Greece</td>
<td>5.8% of 172</td>
<td>1.5% of 132</td>
</tr>
</tbody>
</table>

*sequenced by Green subsequent to NEJM paper
This association has persisted!

“The GBA example is an illustration of how an important genetic risk factor for a complex disease can evade detection by systematic analysis: it only came onto the radar because of astute clinical observation.”

Rogaeva and Hardy, Neurology - June 10, 2008 Editorial
International multi-center study of GBA mutations in PD

16 centers joined, contributing 5691 GBA genotypes from patients with PD and >5000 from controls

Subjects with PD are >5 times more likely to have a mutation in GBA

(Overall OR=5.43; 95%CI=3.89-7.57)
Non-Ashkenazi Jewish Patients (n=1883)

Full sequencing of GBA

- Wild Type: n=1754 (93.1%)
- Mutant Alleles: n=129 (6.9%)
  - N370S: n=28 (absent in Asians)
  - L444P: n=43 (22 are rec. alleles)
  - D409H: n=3
  - N188S: n=4
  - N396T: n=5
  - R120W: n=16
  - Other Alleles: n=30

Screening for 2 mutations would fail to detect at least 42% of mutant alleles
Clinical Characteristics of ~3000 PD Patients With and Without GBA Mutations

Subjects with GBA mutations

Subjects without GBA mutations

% Patients

Asymmetric Onset
Bradykinesia
Resting Tremor
Rigidity
Shuffling Gait
Postural Instability
Orthostatic Changes
Dyskinesias
Wheelchair Dependent
Patients with GBA mutations have an earlier onset of parkinsonian manifestations (mean 4.3 yr, p<0.001)
Conclusions from study

- Combined analysis of 5691 patients showed that subjects with Parkinson disease are >5 times more likely to have a mutation in glucocerebrosidase.

- Screening methods are crucial - in some cohorts >40% of GBA mutations are not L444P or N370S.

- Age at onset is earlier in patients with Gaucher mutations; Parkinson symptoms vary and do not differ from patients without mutations.

- Studies of a rare Mendelian disease can provide insight into a common complex disorder.

*Mutations in glucocerebrosidase are the most significant genetic risk factor for PD identified.*
23andMe study on the genetics of Parkinson disease

- “23andMe researchers run a database query based on 3,200 subjects. The results are returned in 20 minutes.”
- “The results are that people with GBA are 5 times more likely to have Parkinson’s, which is squarely in line with the NEJM paper.”
Mutations in GBA are the most significant genetic risk factor for PD identified to date!

However, the vast majority of patients with Gaucher disease and Gaucher carriers do *NOT* develop parkinsonism!

A GBA mutation is a *risk factor* for the development of parkinsonism.
Different Risk Factors Contribute to Genetic Disease

Single gene
Modifier genes
Multiple genes
Life-style
Environmental exposure
Health factors

Phenotype: The Patient
What does this finding mean for patients with Gaucher disease and GBA mutation carriers?
Estimates of the frequency of PD in patients with Gaucher disease and Gaucher carriers

**International Gaucher registry:** PD in 68 of 1130 pt > age 60. Probability of PD is 5-7% by age 70; 9-12% age 80. No predictive GD-profile. (Rosenbloom et al. 2011)

**Other studies from individual clinics:** Probability of PD is 5-13 % by age 60, 15-30% by age 80.

Better and larger studies still needed- Lifetime RR is around 5-8 X higher than general population.
Patients with GD have classic Parkinson disease, a more aggressive early-onset form and/or a familial form.

Multiple genotypes seen: N370S is common.

Most respond to Ldopa: No improvement with ERT or SRT.

Olfactory and cognitive impairment relatively common.

Among 12 patients at NIH, mean age at PD diagnosis: 49yr; mean UPDRS III Score: 26.3
Prospective patient study: Clinical features and PET imaging in subjects with \textit{GBA} mutations (Collaboration with K.F. Berman, NIMH)

Goals:

1. To better characterize the PD phenotype associated with \textit{GBA}.
2. To study F-dopa uptake and evaluate PET as a surrogate marker in subjects with \textit{GBA} mutations.
3. To establish earliest signs of PD in at-risk subjects.

\textbf{Included:}

- GD\slash PD
- PD\dash no GD
- GD with +FH of PD
- GD carriers with +FH of PD

\textbf{Clinical Studies}

- Physical exam
- Neurologic exam (UPDRS)
- Neurocognitive evaluation
- Olfactory testing
- Screens for non-motor symptoms

\textbf{Imaging Studies}

- MRI (structural abnormalities)
- F-18 Dopa PET (L-Dopa metabolism)
- 15-H2O PET (cerebral blood flow)
- Trans-cranial sonogram (TCS) (midbrain structures)
**PET studies: \(^{18}\text{F}\)-fluorodopa and \(\text{H}_2\text{\(^{15}\text{O}\)}**

Measure regional brain dopamine synthesis and resting rCBF respectively

**\(\text{Studies of 44 patients completed}\)**

**Striatal dopamine synthesis** (Ki value)

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<th>Controls &gt; PD</th>
<th>Controls &gt; GD-PD</th>
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**\(^{18}\text{F}\)-fluorodopa:** Pattern of dopamine loss in GBA-associated PD similar to sporadic PD.

**rCBF:** Less activity in areas affected in neurodegenerative disorders like AD (inf parietal lobules & precuneus bilat)- may explain cognitive impairment in GD-PD.

Among 14 pt with GD and 7 carriers (no PD, but +FH), only 2 showed evidence of dopamine loss. Longitudinal studies needed. *(Brain 2012)*
Brain samples from patients with GD and parkinsonism show Lewy bodies, inclusions characteristic of PD and related disorders.

Patients also have gliosis of hippocampal CA2-4- regions also affected in Lewy body dementia.
Studies of mechanism: Glucocerebrosidase is found in Lewy bodies in patients with GBA mutations.

ACTA Neuropath 2010

Brain samples stained with antibody; GCase, α-synuclein and ubiquitin
Multicenter analysis of GBA in Dementia with Lewy bodies (DLB) JAMA Neuro In Press

GBA genotypes from 11 centers
721 cases with DLB, 1962 controls.

450 cases were autopsied, 80% of cases had full GBA sequencing
Significant association found.

Odds ratio = 8.28 (95%CI = 4.78 – 14.88).

Age at diagnosis ~ 5 years earlier in GBA carriers with DLB.
Mutations associated with higher PD scores (H&Y, UDPRS).

GBA mutations play a larger role in DLB than PD!

Pilot studies of GBA mutations in MSA and Essential Tremor have not shown a similar association.
Why would being a carrier for one genetic disorder put you at risk for another unrelated illness?
Carriers for other Mendelian disorders are at risk for other complex diseases

<table>
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<tr>
<th>Disorder</th>
<th>Disease</th>
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<tbody>
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<td>Methyltetrahydrofolate reductase</td>
<td>Atherothrombotic disease</td>
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<tr>
<td>Factor V &amp; prothrombin</td>
<td>Stroke, recurrent miscarriages</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CFTR</td>
<td>Obstructive azospermia, chronic pancreatitis</td>
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<tr>
<td>Glycerol kinase</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Glucocerebrosidase</td>
<td>Parkinson disease</td>
</tr>
<tr>
<td><strong>TREM 2 (Nasu–Hakola disease)</strong></td>
<td>Alzheimer disease</td>
</tr>
</tbody>
</table>
Protein misfolding

Missense mutation
Conformation change in protein (misfolding)

Unstable protein
- Organelle dysfunction
- Degradation
- Functional defect

Stable protein
- Altered transport and/or protein-protein interactions
- Traffic jam
- Aggregation
- New function
- Dominant negative effect

Gain of toxic function
How can mutations in a metabolic enzyme lead to parkinsonism?

**Gain-of-function:**
- PD in GBA heterozygotes
- GCase in LBs

**Loss-of-function:**
- Null alleles
- CBE effect

Formation of insoluble $\alpha$-synuclein aggregates

Organelle dysfunction: decreased aggregate clearance

Increased aggregate formation

Mutant glucocerebrosidase may lead to...

- Unstable or deficient protein
  - Degradation
  - Not enough enzyme = Lipid accumulation

Neuronal cell death
A) Lysosomal GluCer promotes formation of soluble α-syn oligomers and fibrils
B) Increased α-syn oligomers block ER-Golgi trafficking of GCase
C) Decreased lysosomal GCase amplifies increased GluCer and stable α-syn

However, questions remain since Gaucher carriers do not have GluCer accumulation and lysosomal dysfunction. Story may still be more complicated.
A molecular link between α-synuclein and glucocerebrosidase

Collaboration with J. Lee, NHLBI (JBC 2011)

A) Dns-136-α-syn + GCase-spectrum shifts indicate physical interaction.

B) NMR shows interaction is at C-terminus of α-synuclein.

C) In brain extracts, GCase co-immunoprecipitates with α-syn.

All 3 occur at pH 5.5 (not at pH 7, with N370S GCase or with α-glu).

Model: C-terminal region of α-syn interacts with GCase (glowing). N-terminal helix bound to a glycolipid-rich vesicle in lysosomes.

Membrane bound α-syn interacts with GCase and inhibits activity

Could this binding at lysosomal pH facilitate α-synuclein degradation or prevent aggregation?
Needed: Better models for studies

Mouse models do not mimic the human phenotype.

Skin fibroblasts, used in some studies don’t show lipid storage.

**Patient-derived induced Pleuripotent Stem cells (iPSCs cells)**

IPSCs are reprogrammed adult fibroblasts that can grow for extensive periods and be used to form any cell type.
Development of Gaucher iPSC cells

- iPSCs generated from type 2 GD fibroblasts (L444P/IVS2+1).
- Differentiated into Gaucher macrophages - show lipid storage.
- Neurons now generated. Will make iPSC lines from patients with PD and Gaucher disease.

Control

Gaucher type 2

hiPSC –derived macrophages
(fed with labeled ghost cells)

DAPI
Bodipy-GlcCer

Aflaki et.al. submitted
Normal GCase

Proteosomal and/or mitochondrial pathways

Normally functioning lysosome

α-syn

GCase

Degraded α-syn
Neuronal cell death

Diminished GCase

Lysosome with mutant GBA

Mutant GCase

α-syn aggregates

With aging:
- Decrease in lysosome number
- Decrease in lysosome function
- Increase in α-syn

Degraded α-syn

Neuronal cell death
Chapter 4
Implications for therapy
Enzyme Replacement Therapy

**Results:**
- Hemoglobin levels in 4-6 months
- Platelet counts
- Splenic and hepatic volume
- Feeling of well-being & growth velocity

- High cost ($100,000 - $400,000/patient/year)
- Response is highly variable; IV preparation
- Does not alter CNS manifestations

We have been working with NCGC to develop small molecule therapies.
Chemical chaperone therapy for Gaucher disease

A) GCase is synthesized in the ER, glycosylated and folded, attaining functional tertiary structure in the lysosomes.

B) However, mutant GCase may be misfolded and degraded.

C) Chemical chaperones may bind to the active site and enhance folding, allowing delivery to the lysosome.

*Chemical chaperones may partially correct the enzyme deficiency in Gaucher disease.*
High Throughput Screening (HTS)

Screen Goal:
- To identify activators and inhibitors of glucocerebrosidase
- To find potential pharmacological chaperones

Assay Development:
- Use commercially available enzyme
- Miniaturize enzymatic assay
- Fluorogenic readout
- Homogenous assay in 1536-well plate format

Primary Screening:
HTS with 7-point concentration-response curves for all compounds in library collection (60,000-500,000)
New GCase chaperones as therapy for GD

New screening approach: (Goldin et al. PLoS One 2012)

- Patient spleen- source of mutant GCase (N370S/N370S).
- HT Screen performed with 250K compounds.
- New compounds identified: both activators & inhibitors.
- Lead compound reverses lipid storage and enhances enzyme activity.
- Plan to advance development through NIH TRND and/or with partners in industry.

Small molecule therapy may stabilize and/or activate mutant GCase and be used to treat GD as well as GBA-associated PD
Results with lead compound

GCase activity with lead activator in four different assays

Storage is cleared by compound

Compound is selective for GCase and did not activate other hydrolases.
Understanding the links between the two disorders

Gaucher Disease

Parkinsonism

Pathogenesis of both disorders

Genetic counseling

Therapeutic strategies
Complexity in Mendelian disorders

A window into complex disorders
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Collaborators

Ari Zimran- Jerusalem  Mark Cookson- NIA
Jennifer Lee- NHLBI  Andy Singleton- NIA
Wei Zheng- NCATS  Mark Hallett- NINDS
Benoit Giasson- U. Florida  Ricardo Feldman UMD
Richard Youle- NINDS  Karen Berman- NIMH
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