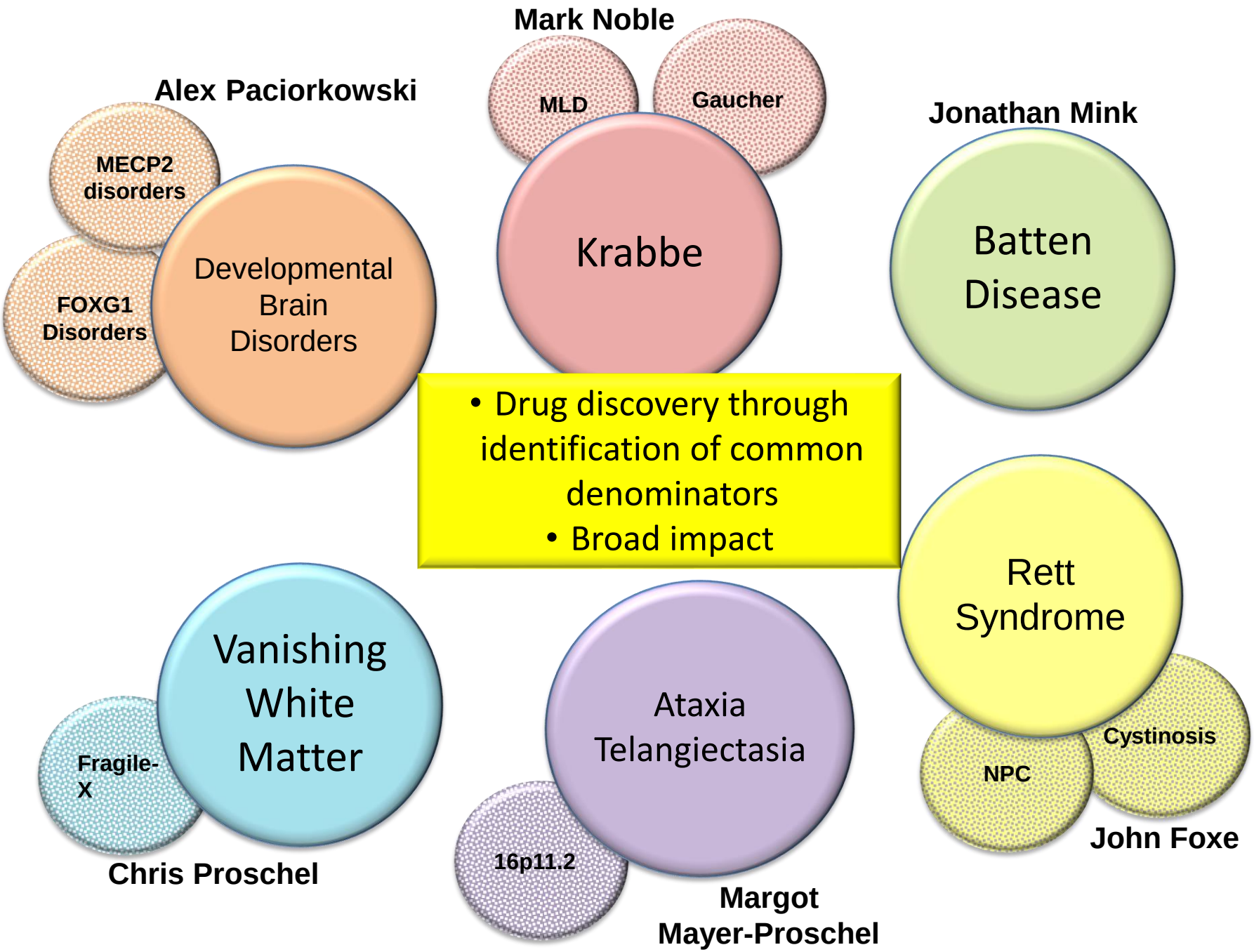
Neurodevelopmental Disorders

Focus: Rare Diseases

Margot Mayer-Proschel, John Foxe, Jonathan Mink,
Mark Noble, Alex Paciorkowski, Chris Proschel


Mark Noble
MLD
Gaucher
Krabbe
Alex Paciorkowski
MECP2 disorders
FOXG1 Disorders
Developmental Brain Disorders
Jonathan Mink
Batten Disease
• Drug discovery through identification of common denominators
• Broad impact
Rett Syndrome
Cystinosis
NPC
John Foxe
Vanishing White Matter
Fragile-X
Chris Proschel
Ataxia Telangiectasia
16p11.2
Margot Mayer-Proschel

A Common Denominator

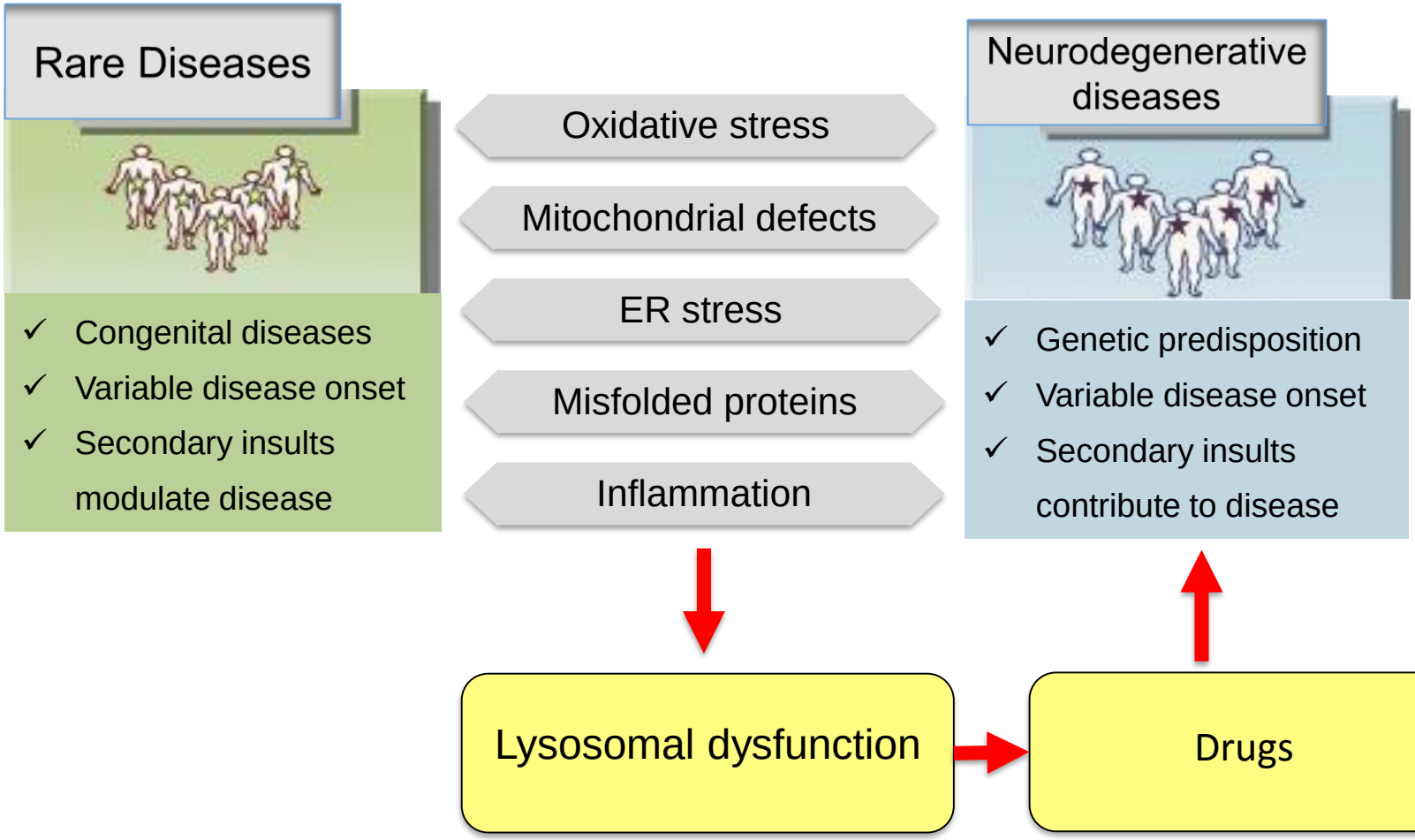
Rare Diseases

- ✓ Congenital diseases
- ✓ Variable disease onset
- ✓ Secondary insults modulate disease

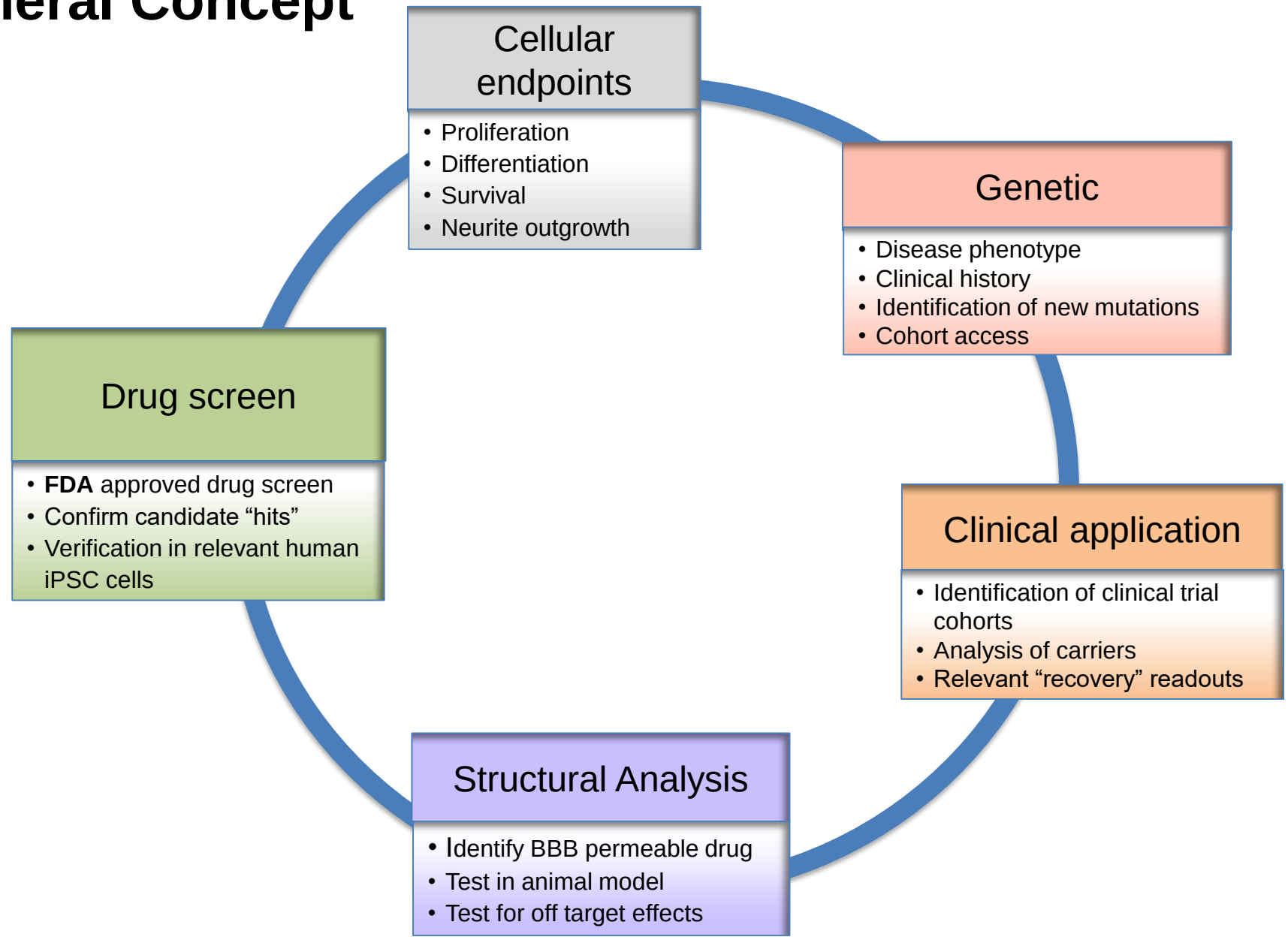
- Oxidative stress
- Mitochondrial defects
- ER stress
- Misfolded proteins
- Inflammation

Lysosomal dysfunction → Drugs

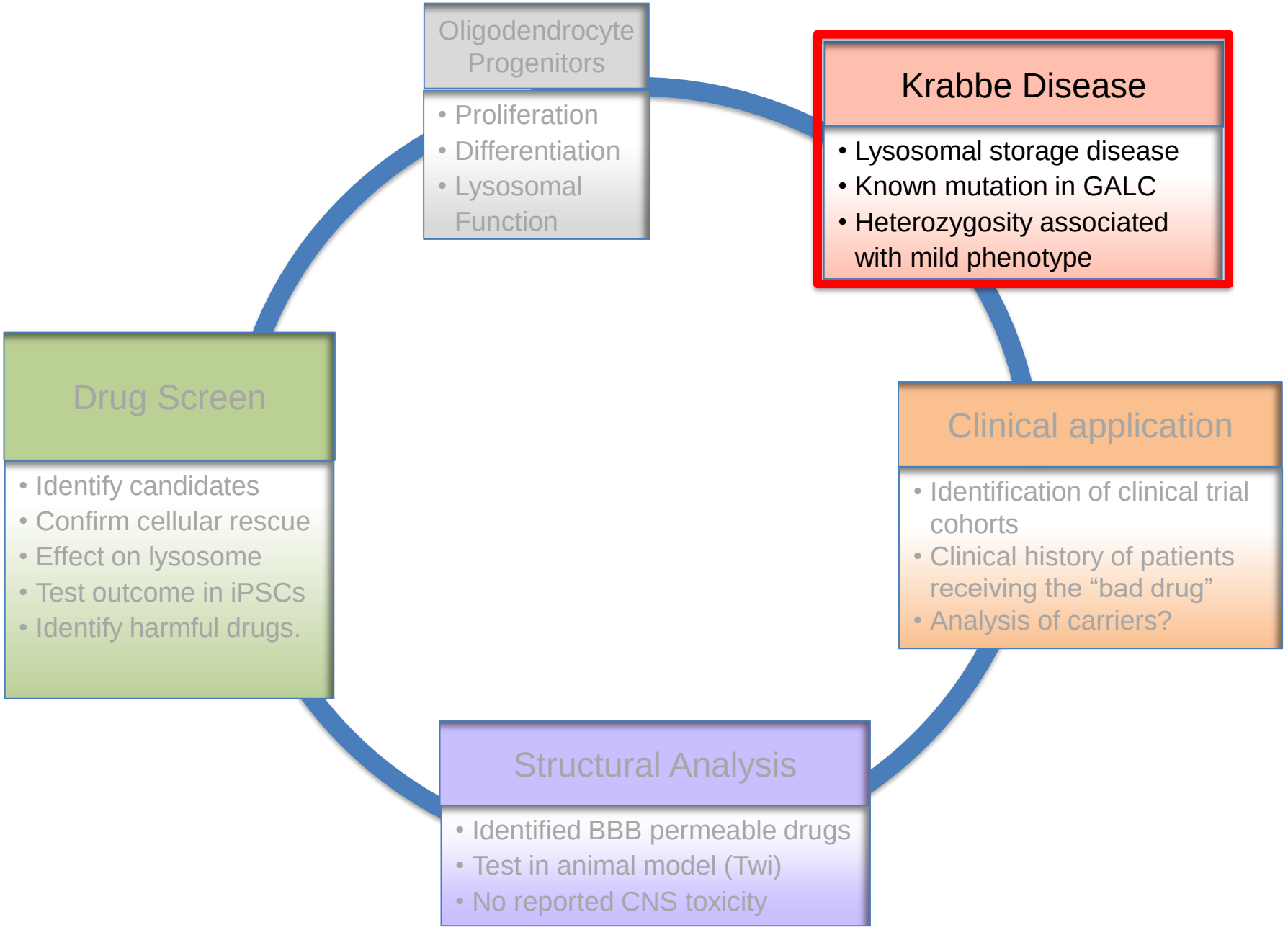
A Broader Impact



General Concept

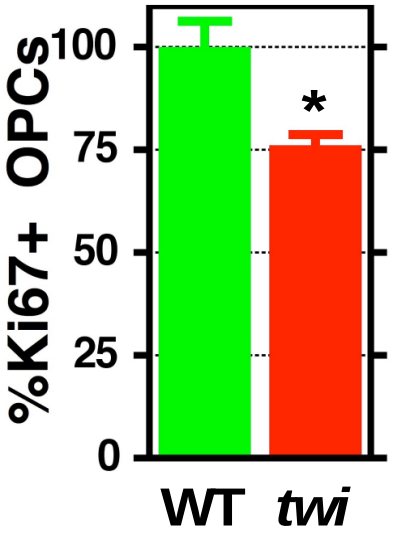


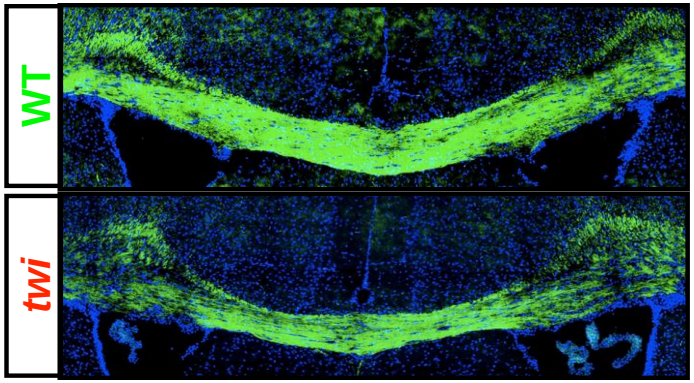
A Specific Example



Krabbe Disease:

- Severe, progressive loss of myelin & neurodegeneration
- Enzymatic deficiencies (mutations) in galactocerebrosidase (GALC)
- Accumulation of the toxic lipid ***Psychosine (Psy)***
- *Twitcher* mouse: a pathologically/genetically authentic murine model





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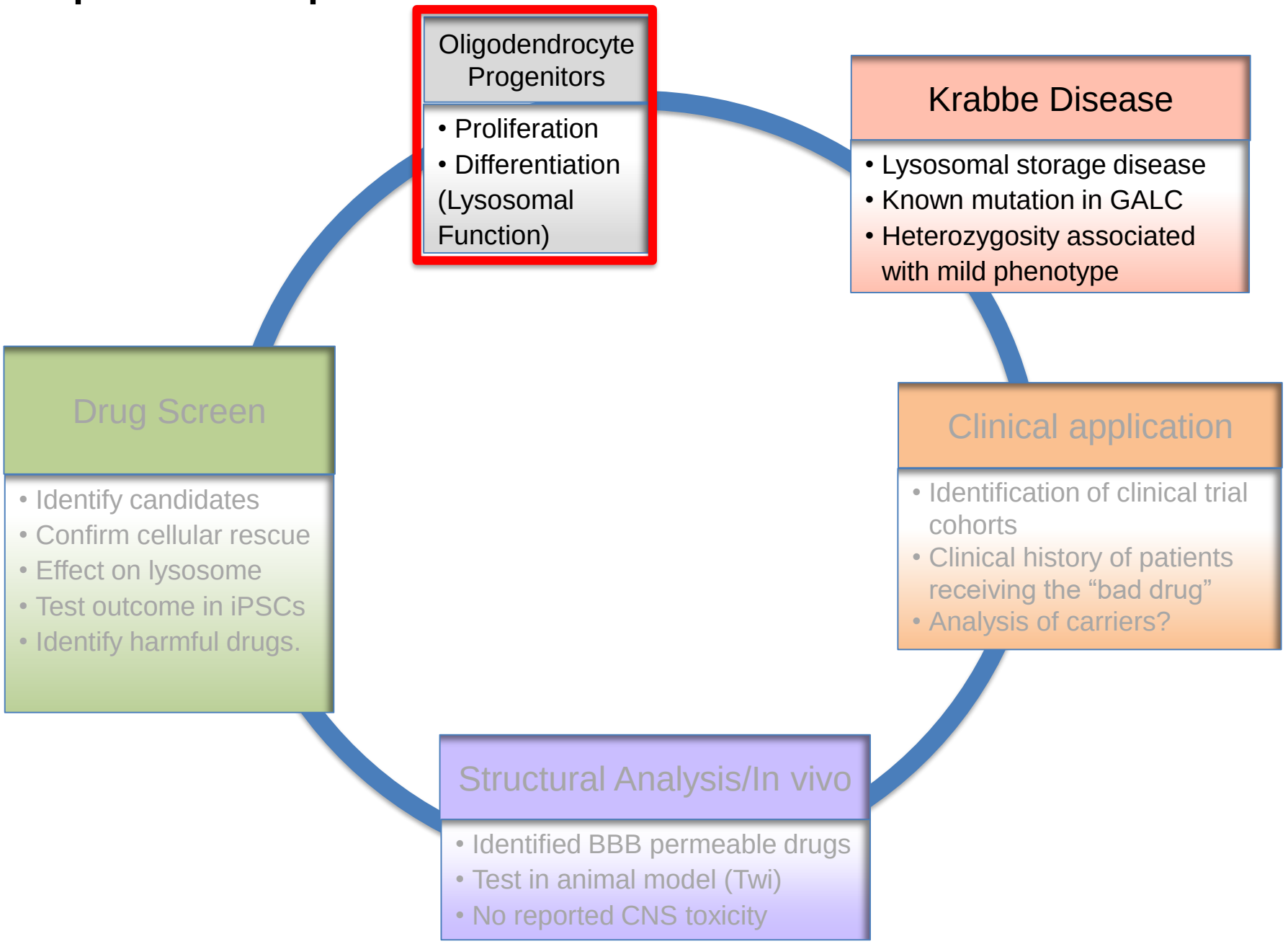
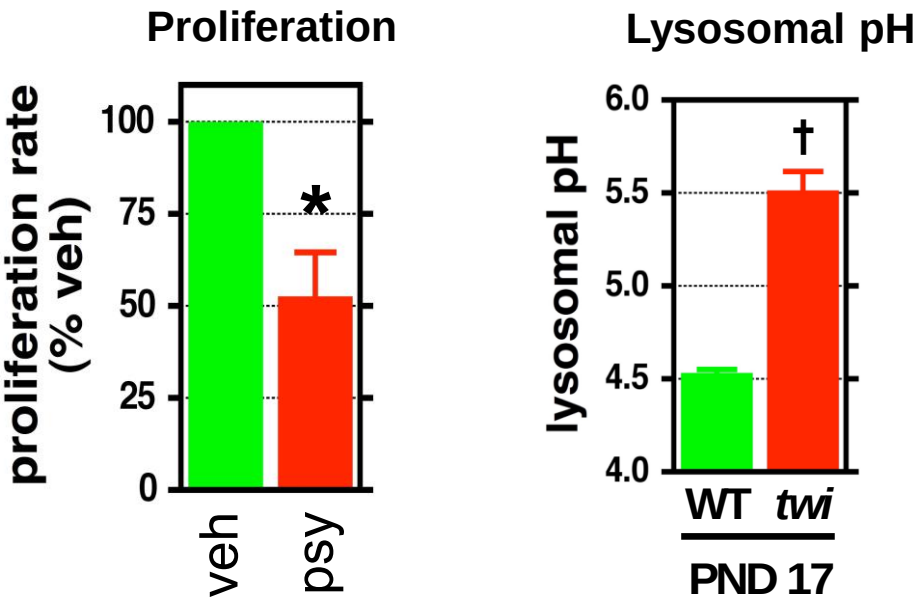


Isolated progenitor cells recapitulate in vivo defects



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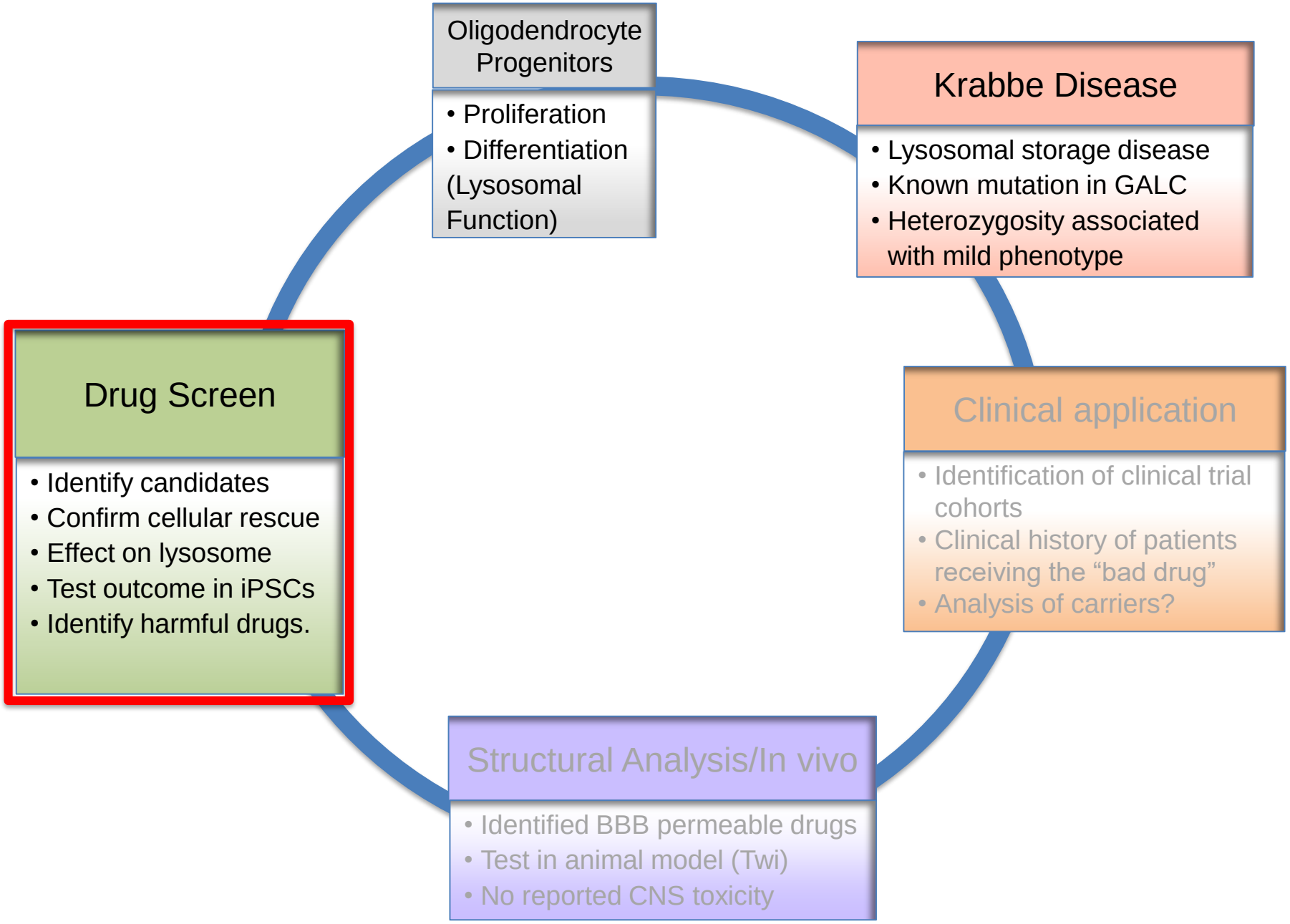
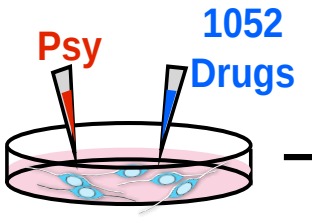


Unbiased screening

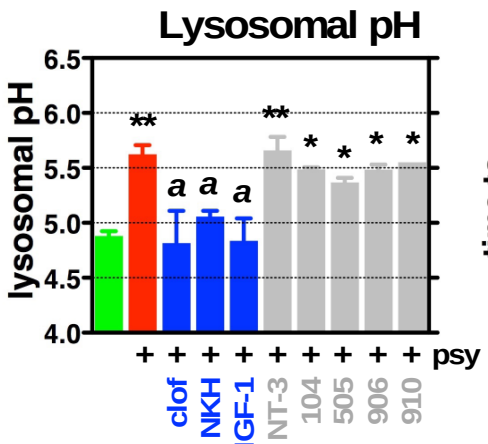
Focus on correcting important cellular behaviors, not on specific proteins or genes

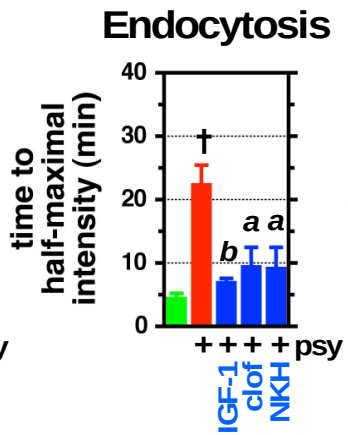


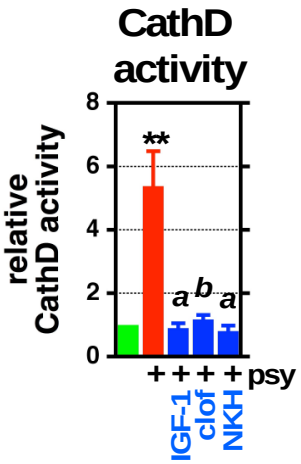
Cell division

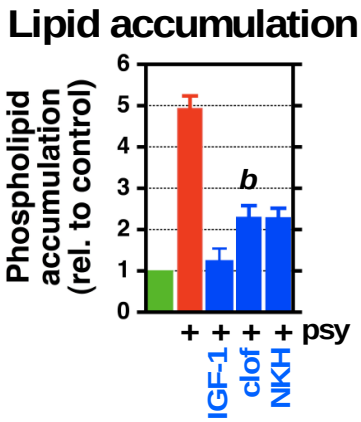
Validation of 'hits'

Restoration of lysosomal function?



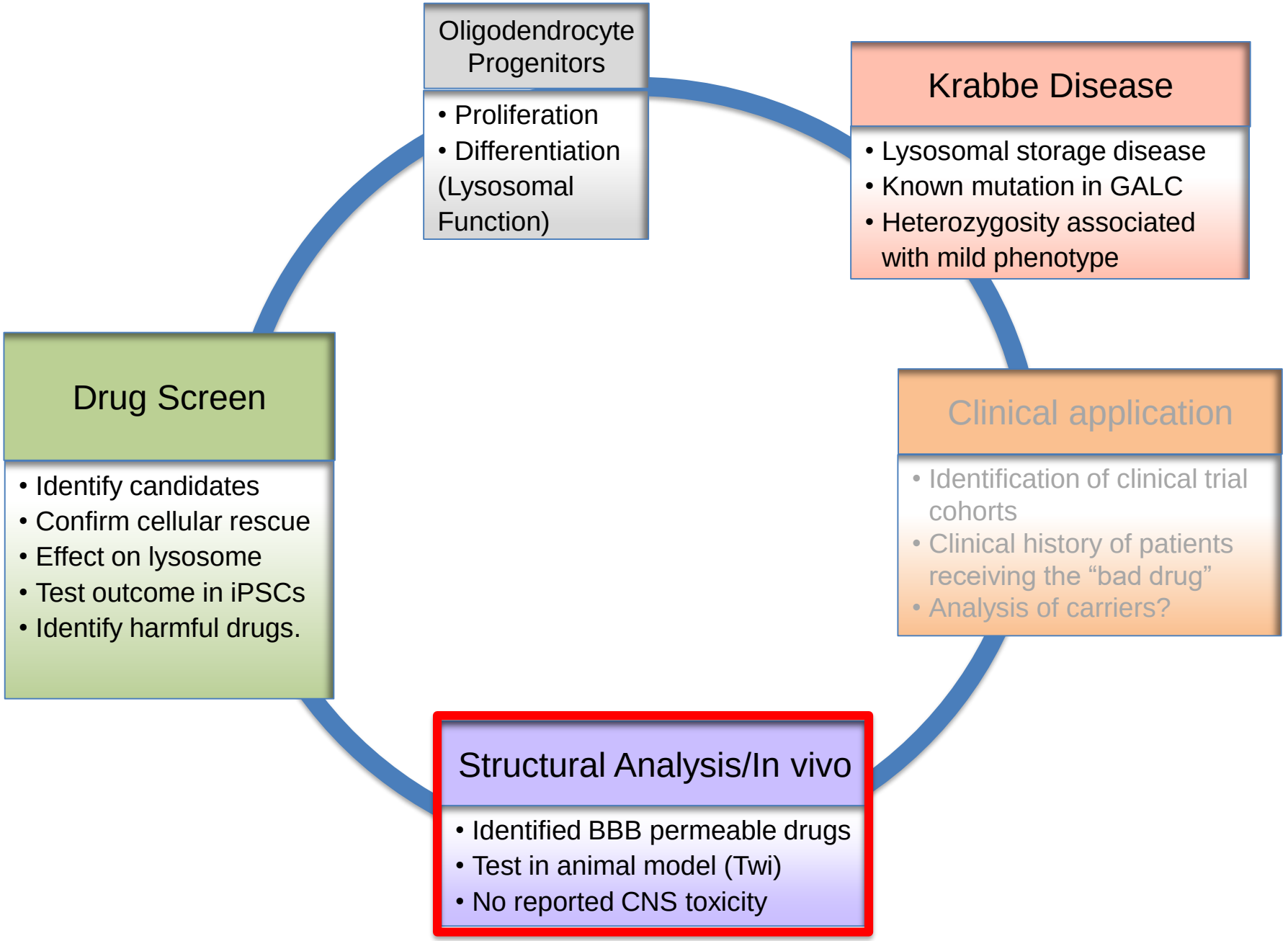






Top hits rescue cellular defect associated with lysosomal dysfunction in vitro

A Specific Example….



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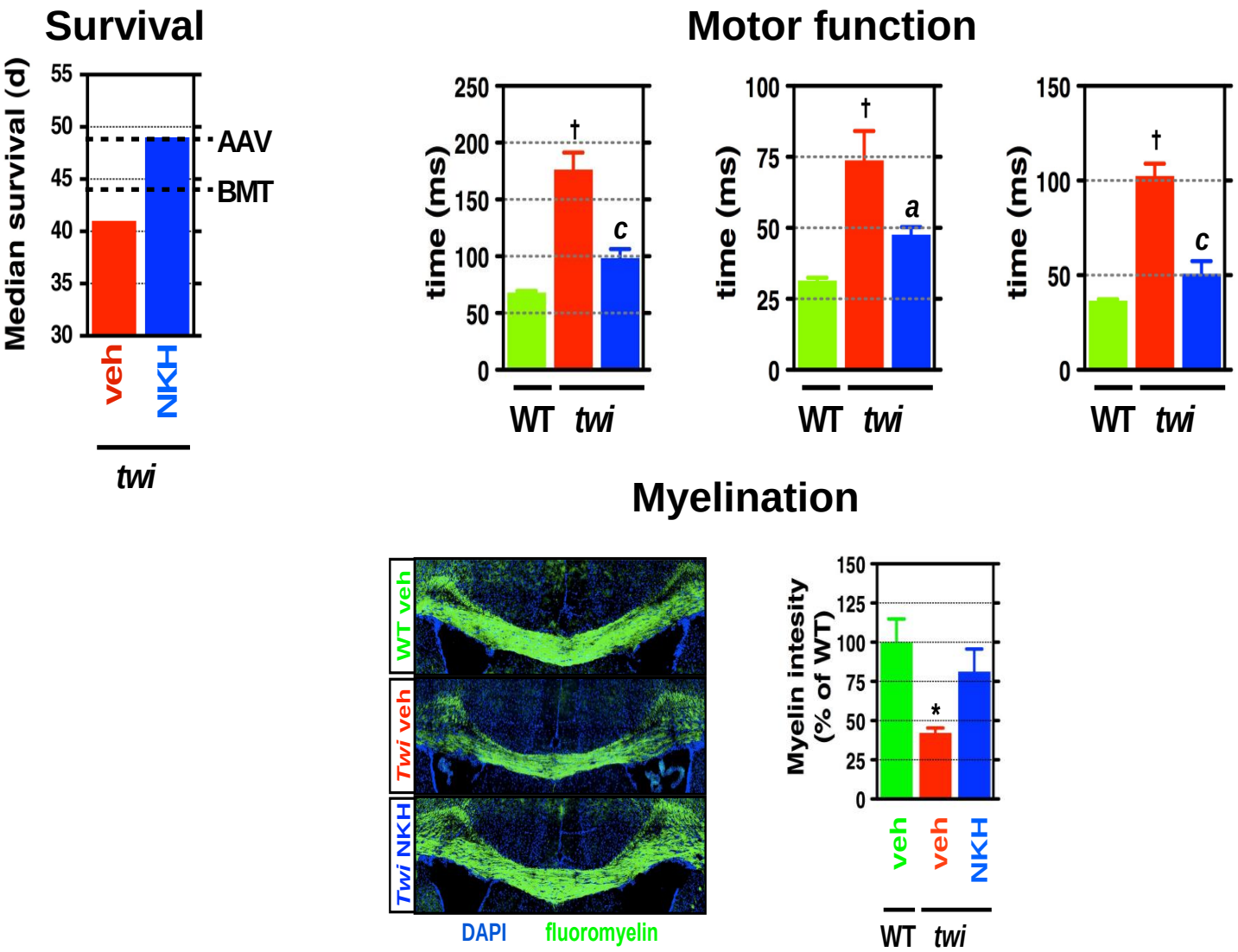

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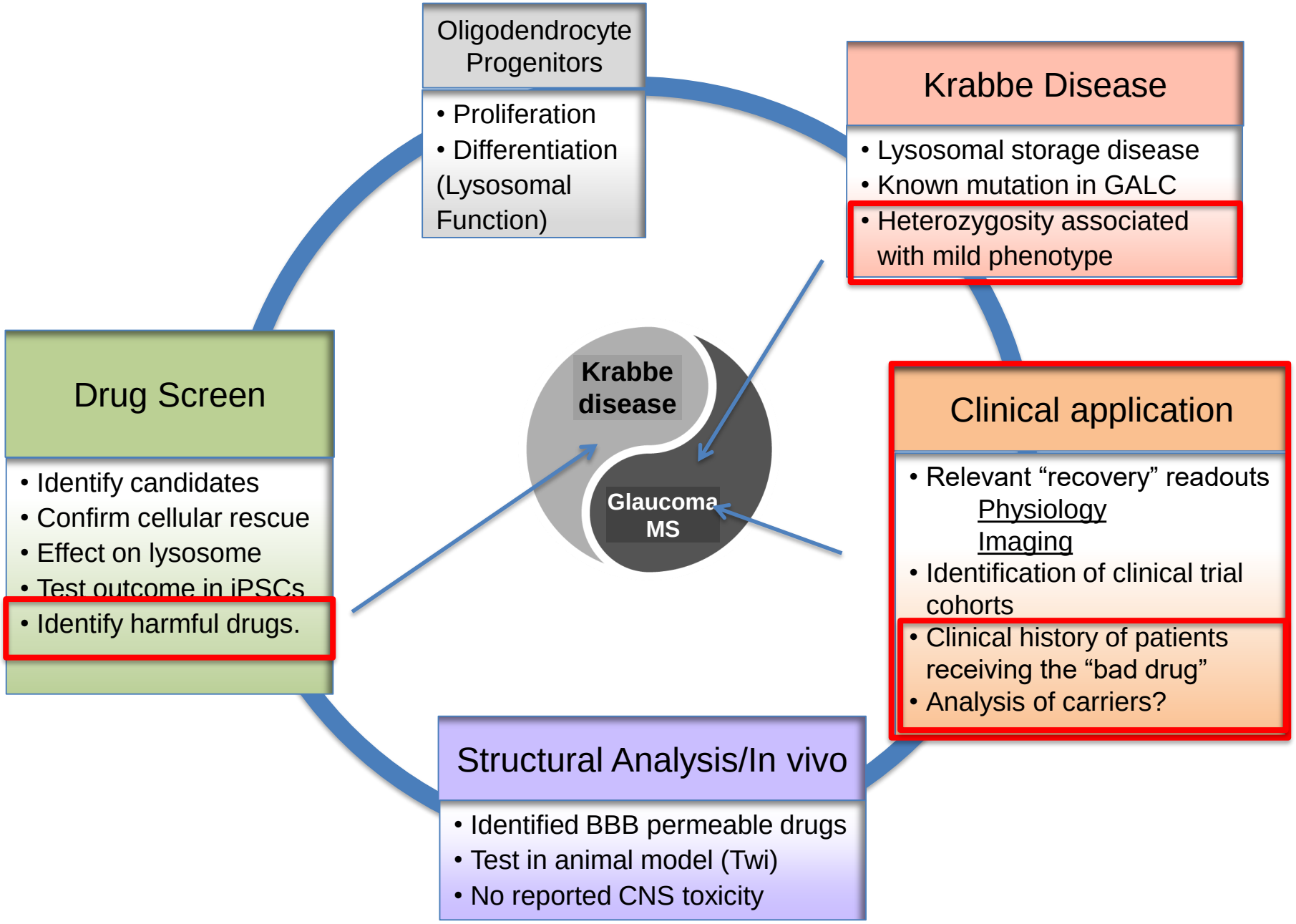
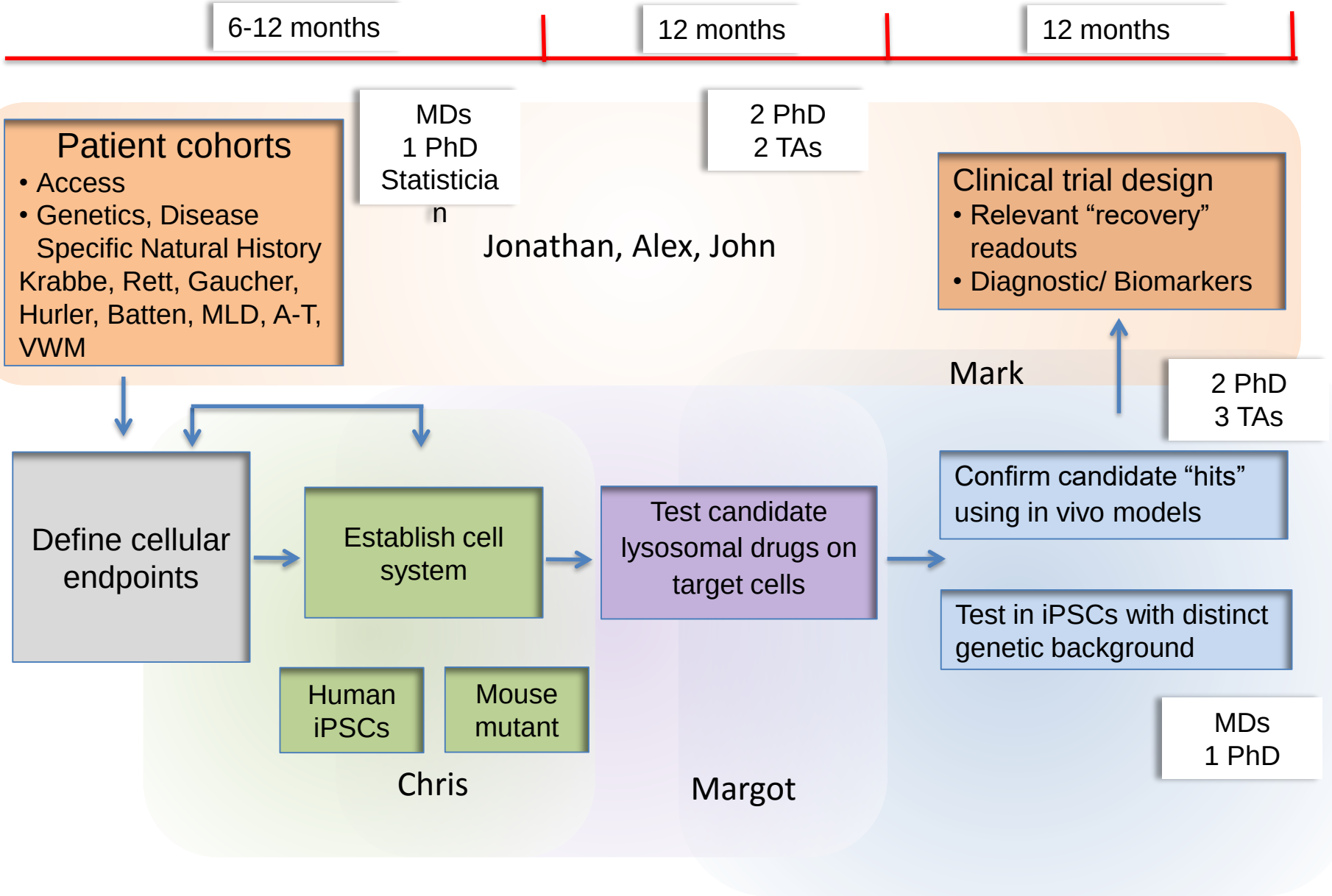


Proposed time line and human capital



Challenges

- Specific cellular targets might not been known (aka ASD)
- Lysosomal defects might not be a general cellular pathology
- Patient material might not be readily available for iPSC cell derivation
- Genetic profile might not be sufficient to identify relevant pathways

Solutions

- An unbiased approach might identify novel targets (see A-T work)
- In addition to lysosomal defects we can screen cells for mitochondrial and ER defects
- Crisper/Cas technology might allow to introduce defects in normal cells overcoming the need for patient material
- Proteomic or/and lipidomic analysis can be added to the genetic profiling

Collaborative published work:

- *Lysosomal Re-acidification Prevents Lysophingolipid-induced lysosomal impairment and cellular toxicity.* Folts C, Scott-Hewitt N, **Pröschel C, Mayer-Pröschel M, Noble M**. PLOS Biology. 2016

- *Epilepsy causing sequence variations in SIK1 disrupt synaptic activity response gene expression and affect neuronal morphology*. **Pröschel C**, Hansen JN, Adil A, Tuttle E, Michelle Lacagnina M, Georgia Buscaglia G, and Marc Halterman M, **Paciorkowski A.** Eur J Human Genetics, *in press*

- *Mutation of ataxia-telangiectasia mutated is associated with dysfunctional glutathione homeostasis in cerebellar astroglia*. Campbell A, Bushman J, Munger J, **Noble M, Pröschel C, Mayer-Pröschel M.** Glia. 2016 Feb;64(2):227-39.

- *A novel mouse model for ataxia-telangiectasia with a N-terminal mutation displays a behavioral defect and a low incidence of lymphoma but no increased oxidative burden.* Campbell A, Krupp B, Bushman J, **Noble M, Pröschel C, Mayer-Pröschel M.** Hum Mol Genet. 2015 Nov 15;24(22):6331-49.

- *EIF2B5 mutations compromise GFAP+ astrocyte generation in vanishing white matter leukodystrophy.* Dietrich J, Lacagnina M, Gass D, Richfield E, **Mayer-Pröschel M, Noble M,** Torres C**, Pröschel C**. Nat Med. 2005 Mar;11(3):277-83

A Value-Added
Rare Disease Center

1. Common denominator

Drug discovery

2. Broad Impact