Abstract Title: New clinical science of Gaucher disease, biomarkers, and therapeutic targets

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Abstract: The phenotype diversity resulting from biallelic mutations in GBA1 in Gaucher disease has been delineated mostly in type 1 Gaucher disease, usually with at least one copy of a founder mutation from Eastern Europe, Asp409Ser. However, there are orders of magnitude more significant numbers of patients with Gaucher disease in the rest of the world with unique genotypes and phenotypic expression (Sheth J et al., 2022, Lysosomal storage disorders: from biology to the clinic in India). Accordingly, there has been a resurgence of translational research to decipher disease mechanisms, biomarkers, and therapeutic targets.

The foundational research by Dr. Roscoe Brady and colleagues at the NIH in delineating genetic deficiency of lysosomal acid β-glucosidase and macrophage-centric disease pathology underpinned the development of transformative enzyme replacement therapy for type 1 Gaucher disease. Pathological accumulation of glucosylceramide in cells triggers systemic inflammation and neuroinflammation, involving the innate and adaptive immune system and complement activation. Inflammatory activation of cells involves prominent induction of UDP-glucose ceramide glucosyltransferase, UGCG, that leads to increased production of glucosylceramide, paradoxically amplifying the accumulation of glucosylceramide resulting from GBA1 mutations.

A homeostatic cellular response to accumulating glucosylceramide is the activation of an alternative metabolic pathway via acid ceramidase to generate deacylated glucosylceramide, glucosyl sphingosine, a more soluble lipid that exits the lysosomes and plasma membrane. Serum glucosyl sphingosine levels are a validated Gaucher disease biomarker that fulfills Koch's postulates and is now routinely used in the clinic and clinical trials. Glucosylsphingosine is even more inflammatory than glucosylceramide, prominently causing B cell proliferation and generation of anti-GlcSph antibodies, which, if unchecked, can lead to B cell malignancies. This pathway involves CD1-mediated presentation of GlcSph lipid antigen to T cell receptors of type 2 NKT cells exhibiting follicular helper phenotype, potent inducers of B cell lymphoproliferation.

Neuroinflammation is also central to neurodegeneration in neuronopathic Gaucher disease (CGD). Here, the primary cellular targets are microglia and astrocytes. However, the blood-brain barrier in nGD allows systemic immune cells to traverse into the brain parenchyma, amplifying neuroinflammation.

The disciplined approach to translational research is matched by rigorous decades-long efforts to develop safe and effective therapies to best to serve the needs of this rare disease patient population.