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***Is CSF GM2 a Surrogate Marker
for the GM2 Gangliosidoses?***

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Clinical Overview: GM2 Gangliosidoses

- **Tay-Sachs Disease (TSD), Sandhoff (SD), AB Variant**
 - Combined prevalence: 1:120,000
 - Lysosomal accumulation of GM2 ganglioside
- **Age of onset varies**
 - Mean age of onset of symptoms: ~5 years
 - Nature of symptoms similar
- **Variable degree of severity**
- **Primarily CNS symptoms**
 - Ambulatory impairment, incoordination, difficulty in speech, cognitive impairment, and swallowing
- **No effective treatment**
- **Natural history studies**
 - Few studies, a couple of publications

Biochemistry of GM2 Gangliosidoses

- **Deficiency in GM2 degradation**
 - β -Hexosaminidase α – Tay-Sachs Disease
 - β -Hexosaminidase β – Sandhoff Disease
 - Multiple mutations observed in each enzyme
 - Disease severity dependent on residual enzyme activity
- **Accumulation of GM2**
 - Accumulation primarily in the brain and liver
 - Accumulation in the brain contributes to the observed phenotype
 - Accessible matrix - CSF

Natural History: GM2 Gangliosidoses

- **Gait Disturbances** (ambulatory impairment)
- **Ataxia** (Incoordination)
- **Dysarthria, Anarthria** (Speech Problems)
- **Cognitive Impairment** (Developmental Delay)
- **Dysphagia**
- **Incontinence**
- **Sleep Problems**
- **Behavioral Problems**
- **Muscle Wasting**

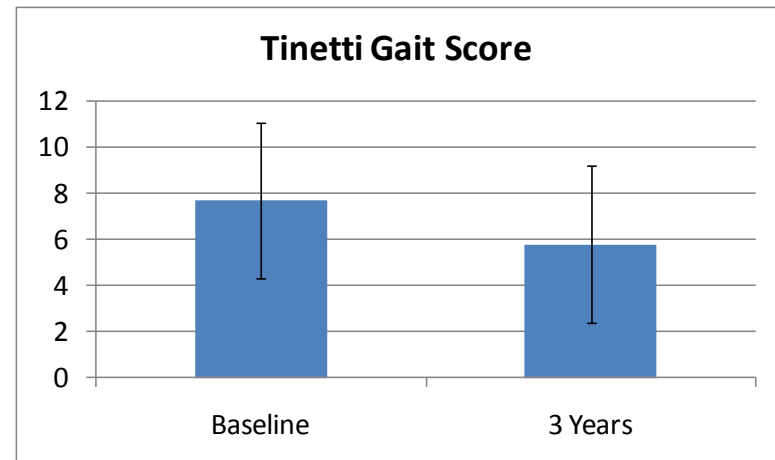
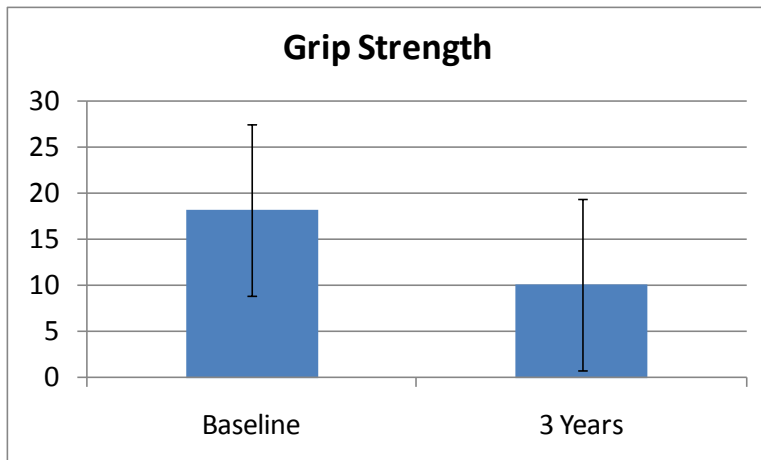


Most common
symptoms in
TSD and SD

Maegawa, et al., *Pediatrics* **118**, 2006, e1550-62

Natural History in Gangliosidoses

- **Natural Progression of Gangliosidosis**
 - Highly variable
 - Slow



Source: Miglustat clinical trial in late onset GM-2 (Shapiro et al. Genetics in Medicine. Vol. 11, No 6 June 2009).

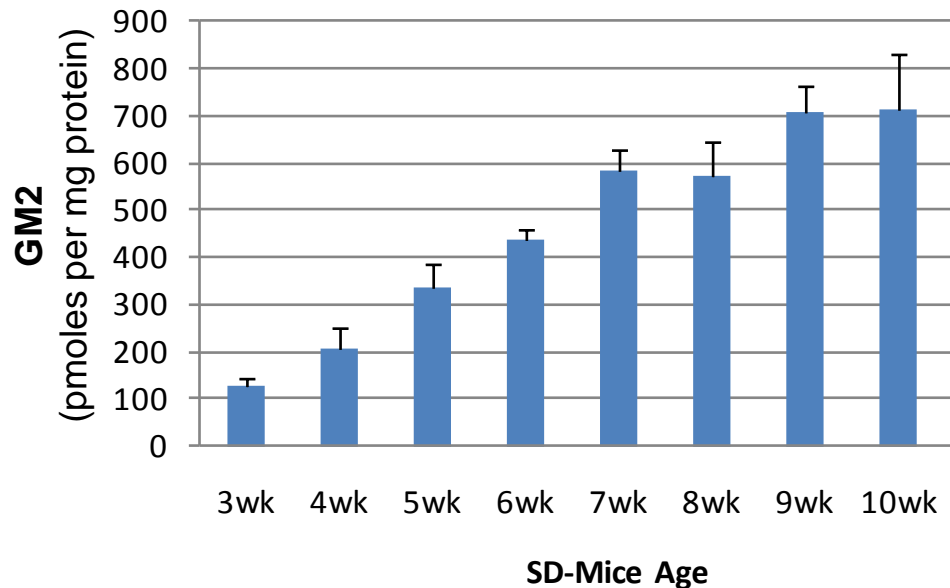
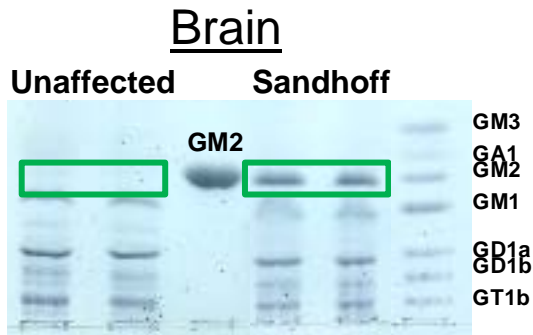
GM2 Content in Preclinical Models

- **GM2 is Elevated in All Preclinical Models**
 - Tay-Sachs mouse
 - Sandhoff mouse
 - AB variant mouse
 - Sandhoff dog
 - Tay-Sachs flamingo
 - Tay-Sachs sheep
 - Sandhoff cat

GM2 Content in Preclinical Models

■ Mouse Sandhoff Disease Model

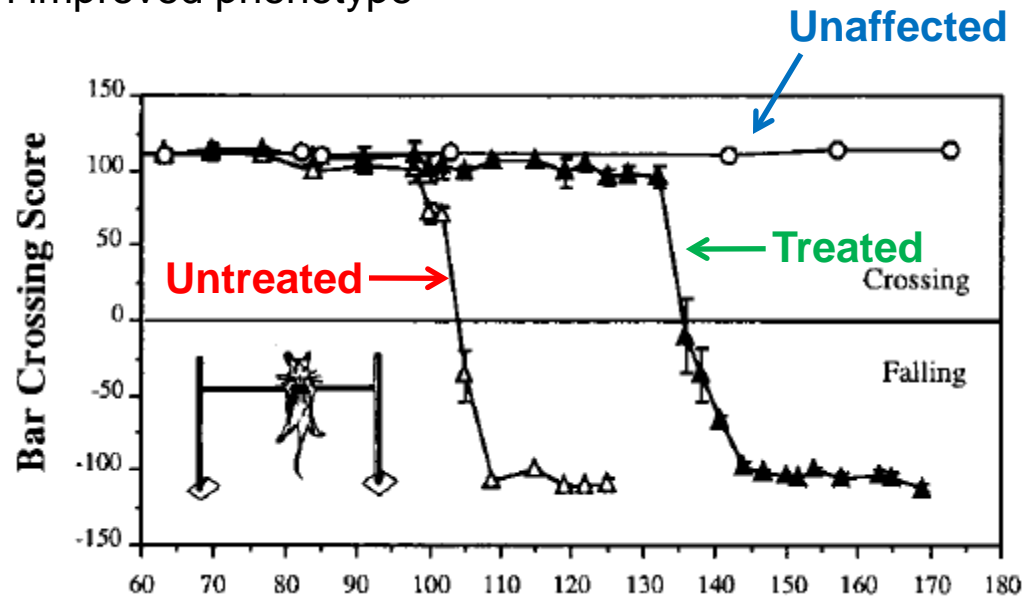
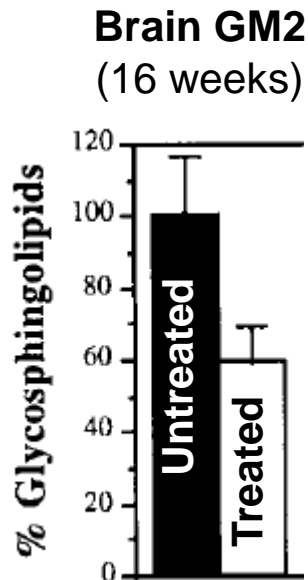
- Brain GM2 content correlates with disease progression
 - Low levels at birth
 - Steady increase through the course of disease



Crawford et al., unpublished results

GM2 Content in Preclinical Models

- **Mouse Sandhoff Disease Model**
 - Brain GM2 content responds to therapy
 - Substrate reduction therapy
 - Reduces brain GM2
 - Correlates with improved phenotype



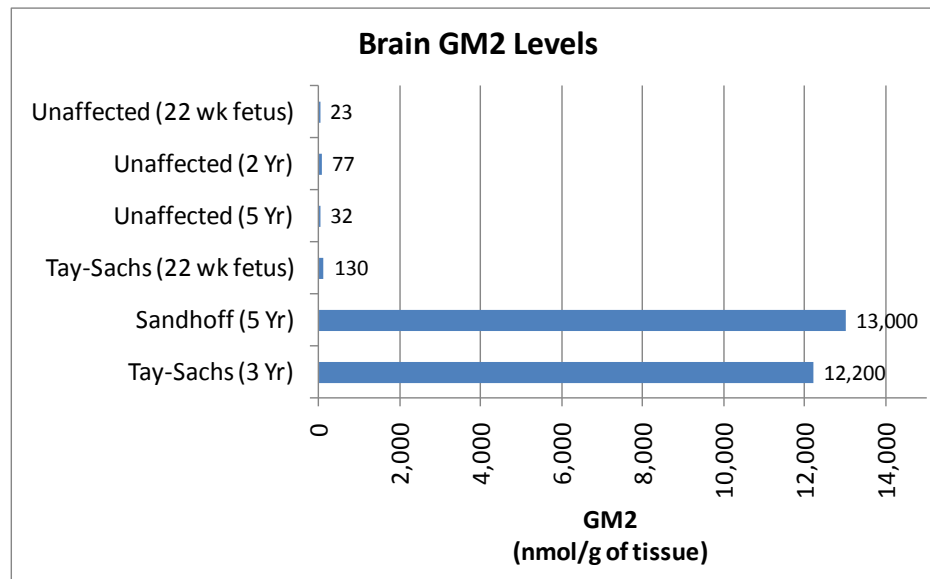
Jeyakumar, et al., *PNAS* 96 (1999) 6388-6393

GM2 Content in Preclinical Models

- **Mouse Sandhoff Disease Model**
 - Brain GM2 content responds to different therapies
 - Substrate reduction therapy
 - Gene transfer strategy
 - Martino et al. Human Molecular Genetics 2005, Vol. 14, No.15
 - Viral vector gene therapy
 - Cachon-Gonzalez et al., PNAS 2006, Vol. 103, No. 27
 - Enzyme replacement therapy
 - Tsuji, et al., Annals of Neurology, 2011, Vol 69
 - BMT and ERT combination therapy
 - Jeyakumar et al., Blood, 2001 Vol. 97
 - Neural stem cell transplantation
 - Jeyakumar et al., Stem Cells, Vol. 27

GM2 Content in Human Brain

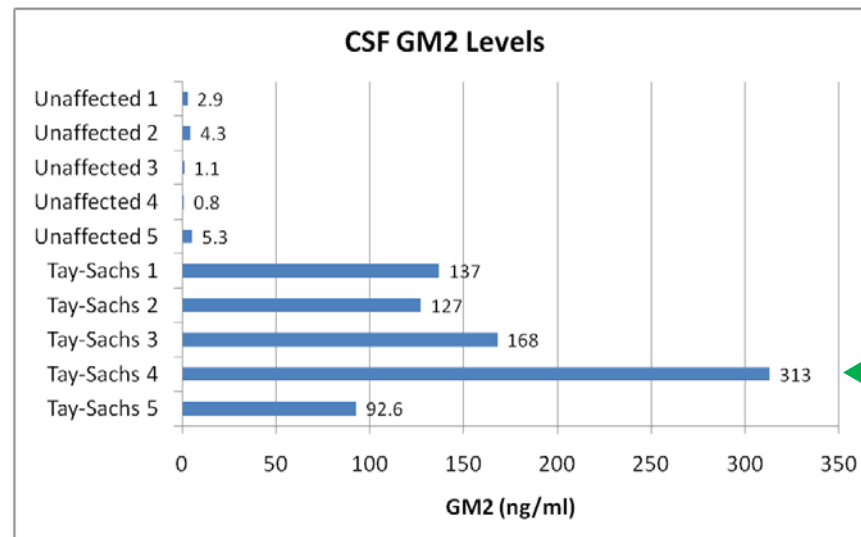
- **Brain GM2 Content Clearly Differentiates Disease from Normal**
 - Low levels in unaffected (20-70 nmol/g of tissue)
 - 200-500 fold higher levels in GM2 Gangliosidosis
 - Similar level of accumulation of GM2 in TSD and SD



Rosengren, et al., *J. Neurochem.* **49**, 1987, 834-840

GM2 Content in Human CSF

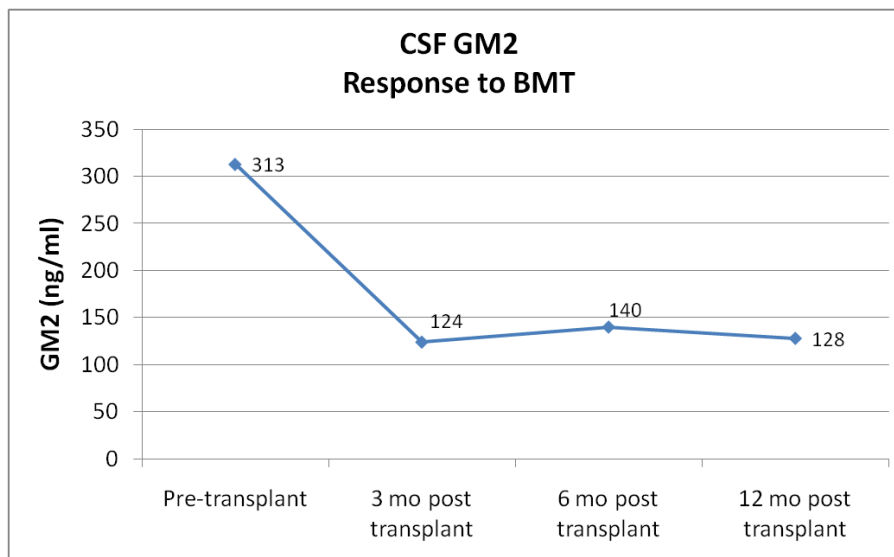
- **CSF GM2 Content Clearly Differentiates Disease from Normal**
 - Low levels in unaffected (1-5 ng/mL of CSF)
 - 60-100 fold higher levels in TSD (>100 ng/mL)



← This patient underwent BMT

GM2 Levels in Human CSF

- **CSF GM2 Content Can Detect Partial Response to Therapy**
 - Tay-Sachs patient received BMT
 - GM2 goes down by 2.5 fold
 - Lower levels maintained for 12 months



Gu, et al., *Clin. Biochem.* **41**, 2008, 413-417

Summary: Role of GM2 in Gangliosidoses

- **GM2 accumulation is the primary pathological event in GM2 Gangliosidoses**
 - Defect in hexosaminidase responsible for degrading GM2
- **GM2 is a biomarker of the disease**
 - Very low in unaffected
 - Significantly elevated in disease (200-500 fold)
- **GM2 accumulation increases with disease progression**
 - Observed in human and animal models
- **GM2 responds to therapy**
 - SRT, ERT, or gene therapy
- **Animal models indicate that GM2 predicts response to therapy**
 - GM2 reduction is a prerequisite for long term clinical benefit

Is CSF GM2 a Surrogate Marker for GM2 Gangliosidoses?

- **Is the available data in patients and animals sufficient to support GM2 as a surrogate marker for GM2 Gangliosidoses?**
- **What additional data in animals and/or patients would be helpful?**

