MPSIII A Disease Overview

- Autosomal recessive: mutations in SGSH, encoding heparan N sulfatase; over 70 mutations described
- Live birth incidence ~ 1 in 100,000
- Enzyme defect causes accumulation of heparan sulfate
- Clinical features are overwhelmingly neurological:
  - normal early infancy
  - developmental delays often first manifestations
  - severe behavioral disturbances are a prominent feature of middle childhood
  - progressive dementia leads to a “quiet phase” of withdrawal and developmental regression
  - survival to late teens / early 20s
- No ethnic predisposition
- Primary accumulation of the glycosaminoglycan (GAG) heparan sulfate triggers poorly understood pathological cascade with primarily CNS manifestations
- Pathomechanisms invoked include: secondary accumulation of toxic metabolites, neuroinflammation, disrupted growth factor signaling, dysregulated cell death
HGT-SAN-053 Natural History Study of MPSIIIA

• Description: An observational study with no investigational treatment
• Enrollment criteria
  • Confirmed MPSIIIA diagnosis
  • Calendar age ≥ 1 yr
  • Developmental age ≥ 1yr, estimated using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
• Evaluations every 6 months for 12 months:
  • Comprehensive neurodevelopmental assessments
  • Brain imaging
  • Cerebrospinal fluid biomarkers
• Rationale:
  • To understand MPSIIIA disease spectrum
  • To measure disease progression over 12 months
  • To obtain insight into an appropriate patient population for trials of therapy
  • To identify candidate endpoints applicable in clinical trials
  • To generate a high quality set of data with potential utility as a historical control
SAN-053 Developmental Assessment

• 25 children enrolled at a single site (U Minnesota)
• Neurodevelopmental assessment using either the Bayley Scales of Infant Development III (BSID), or Kaufman Assessment Battery for Children (KABC)
• For both the BSID and the KABC a total mental age equivalent (MA) was calculated for every participant in months
• To create a developmental quotient (DQ), total mental age equivalent (MA) was divided by chronological age in months (CA): DQ (%) = (MA/CA) x 100
Baseline DQ plotted against age shows age-related decline.
Patients diagnosed after age 6 may exhibit different rate of decline.
Plot of mental age equivalence against calendar age reveals apparent plateau in mental age achieved @ 30 months in children diagnosed before age 6.
Developmental age equivalence independently assessed by VABS-II shows strong correlation with age equivalence calculated by BSID or KABC.
Automated brain magnetic resonance image (MRI) analysis using “Freesurfer” software

Data suggest decline in cerebral cortical volume with advancing age in children diagnosed before age 6

![Graph showing grey matter volume (mm³) against age (months) with data points for different age groups.](image-url)
Cerebral cortical volume correlates with DQ

Grey Matter Volume (mm³)

DQ (%)
Summary of baseline clinical and imaging data

- Children diagnosed before and after the age of 6 years exhibit different patterns of disease progression, suggesting that later diagnosis is a surrogate for a phenotypic and prognostic difference.
- In children diagnosed before the age of 6 years, cross-sectional data suggests a steady decline in DQ is evident from an early age.
- This decline appears to reflect an arrest in the acquisition of new skills beyond the age of approximately 30 months.
- Cortical grey matter volume exhibits age-dependent decline which correlates with loss of DQ.
CSF Glycosaminoglycan (GAG) levels

• Hypothesis: pathological heparan sulfate GAG accumulation in the brain is reflected in elevated GAG levels in the cerebrospinal fluid

• CSF GAGs were measured using 2 independent techniques:
  • Shire proprietary assay – measures a functional attribute of GAG
  • Zacharon assays – proprietary “Sensi-Pro” assay to measure MPSIIIA pathognomonic GAG via non-reducing end identification, as well as total heparan sulfate

• Samples collected from SAN-053 and healthy young adult controls were compared
CSF heparan sulfate levels measured using 3 different techniques reveal comparable patterns, and insight into trends over time.

<table>
<thead>
<tr>
<th>Shire Heparan Sulfate</th>
<th>Zacharon Sensi-Pro NRE</th>
<th>Zacharon Sensi-Pro Total Heparan Sulfate</th>
</tr>
</thead>
</table>

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0  6  12  Time on Study (Months)

0  100000  200000  300000  Time on Study (Months)

0  50000  100000  150000  200000  250000  300000  350000  Time on Study (Months)

CSF GAG (ng/mL)  Sensi-Pro NRE (UAC)  Sensi-Pro Total Heparan Sulfate (AUC)

Dx < age 6  Dx ≥ age 6  Healthy Controls

To be as brave as the people we help
Correlation between 3 different heparan sulfate assays (baseline samples only)

<table>
<thead>
<tr>
<th>Assay Comparison</th>
<th>Pearson r</th>
<th>95% Confidence Interval</th>
<th>P value (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shire GAG - Sensi-Pro NRE (UAC)</td>
<td>0.4174</td>
<td>0.01679 to 0.7026</td>
<td>0.0424</td>
</tr>
<tr>
<td>Shire GAG - Sensi-Pro Total Heparan Sulfate (AUC)</td>
<td>0.7090</td>
<td>0.4280 to 0.8650</td>
<td>0.0001</td>
</tr>
<tr>
<td>Zach_pGAG - Sensi-Pro Total Heparan Sulfate (AUC)</td>
<td>0.7175</td>
<td>0.4499 to 0.8669</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
CSF Heparan Sulfate levels appear similar between sibling pairs.
Identification of disease-associate biomarkers in MPSIIIA – a work in progress

- “Selected Proteomics” by multiplexed immunoassays (luminex platform by Myriad / Rules-Based Medicine ~245 analytes)
  - RBM Discovery MAP 1.0 187-190 analytes
  - Selected markers from RBM OncoMAP 45 analytes
  - RBM Custom Neuro/LSD Multiplex 13 analytes

- Discriminant analysis performed, comparing data from MPSIIIA patients data with data from CSF collected prospectively from 20 young adult controls
Hepatocyte Growth Factor
• Key role in regulation of dendritic spine morphology and synaptogenesis
• Receptor is c-Met – pathway implicated in mental retardation / ASD / macrocephaly complexes

Calbindin D
• Expressed in Purkinje cells & striatum
• Possible predictor of dementia in patients at risk for Alzheimer’s Disease (Craig-Shapiro et al PLoS one 2011 6:e18850)
Total tau and phosphorylated tau

Total tau protein
• Elevated in several adult neurodegenerative diseases

Phosphorylated tau (p181)
• Age-dependent increase reported in brain of MPSIIIb mouse (Ohmi et al PNAS 2009 106:8332)
Conclusions and questions

• Baseline data from 25 MPSIIIA patients suggest arrest in cognitive development occurs in the majority of children, at around age 30 months
  • Does this correspond to a particularly vulnerable process in neurodevelopment – e.g., synaptogenesis?
  • What are the implications for the optimal timing of therapy?
• Cognitive decline correlates with brain cortical volume
  • Could cortical volume be an objective indicator of the pathological process with utility as a clinical trial endpoint?
• CSF heparan sulfate levels are elevated, and appear to remain at relatively constant levels for up to 12 months
• Preliminary screen identifies biologically plausible, disease-related candidate biomarkers
How do these preliminary results from the Natural History study help us to think about developing a therapy for MPSIIIA?

• **Rationale:**
  - To understand MPSIIIA disease spectrum
    - *Baseline data suggest 2 phenotypic patterns, with patients distinguished by age of diagnosis (genotype/phenotype studies will follow)*
  - To measure disease progression over 12 months
    - *Preliminary longitudinal data (not shown) suggest that interim conclusions inferred from the cross-sectional analysis are valid*
  - To obtain insight into an appropriate patient population for trials of therapy
    - *Attainment of a developmental plateau suggests that for maximal efficacy, treatment should be initiated as early during the plateau phase as possible*
  - To identify candidate endpoints applicable in clinical trials of experimental therapy
    - *Preliminary identification of biologically plausible CSF biomarkers and brain MRI patterns suggests that these may be useful adjuncts to clinical evaluation in assessing the impact of therapy*
  - To generate a high quality set of data with potential utility as a historical control
Acknowledgements

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- Nitin Nair

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To be as brave as the people we help

Grey Matter Volume (mm$^3$)

DQ (%)

- Green dots: CTX vol $\geq$ 3.5y
- Green circles: CTX vol < 3.5yrs
- Red dots: CTX Dx $\geq$ 6yr