Mucopolysaccharidosis Types IIIA and IIIB: Translational Development at NCH
Goals for today

• Introduce the members of the MPS translational team here at NCH

• Update the MPS community on the preclinical studies supporting development of gene therapy

• Discuss expectations of the FDA

• Introduce the NCH MPSIII Natural History Study

• Discuss the route forward for gene therapy
Lync Webinar

• Please note that you are muted
• Unfortunately the Lync software does not allow “raising hands”
• Please type questions into the chat window
• We will collate and answer the most common questions in the second half of the webinar
The NCH Team

• Haiyan Fu, PhD  
  – Investigator, Center for Gene Therapy (pre-clinical)

• Doug McCarty, PhD  
  – Investigator, Center for Gene Therapy (pre-clinical)

• Kevin Flanigan, MD – Clinical Gene Therapy  
  – Investigator, Center for Gene Therapy (clinical)

• Kim McBride, MD – Medical Genetics

• Krista Kunkler, BA – Clinical Research Coordinator

• Tim Miller, PhD – President, Abeona Therapeutics
Today’s Outline

• Introduction
  – Kevin Flanigan, MD

• Basics of biology and MPS; Outcome measures
  – Kim McBride, MD

• Animal studies
  – Haiyan Fu, PhD & Doug McCarty, PhD

• The NCH MPSIII Natural History Study
  – Kevin Flanigan, MD

• Abeona Therapeutics
  – Tim Miller, PhD
Introduction

• Pediatrics (Mayo Clinic)
• Clinical/Biochemical Genetics (Baylor College of Medicine, Houston)
• Manage or consult on most lysosomal storage disease patients in central Ohio region
• Clinical trials:
  – Enzyme replacement therapy (ERT) Fabry, Pompe, Hunter (phase III/IV)
  – ERT PKU (phase I/II)
  – Natural history Hunter (MPS II), PKU

Kim L McBride, MD
Biology Introduction

• Focused on workings of cell
  – Outside of cell: extracellular matrix
  – Inside of cell: lysosome

• What goes wrong in lysosomal storage disease

• House analogy
Cell Parts & Moving In and Out

Nucelus – DNA/Genes
mRNA
Enzyme
Lysosome
Autophagosome
Endoplasmic reticulum
Golgi apparatus
Trans-Golgi network
Endocytosis
Receptor recycling to plasma membrane
Early endosome
Late endosome

Source: Nature Reviews Neuroscience 6, 713-725
(September 2005)
Outside the Cell

Source: http://www.meddean.luc.edu/lumen
Nature Reviews Cancer 2, 521-528 (July 2002)
Glycosaminoglycan (GAG) Breakdown

Lysosomal Dysfunction

Blood Brain Barrier
Cerebrospinal Fluid (CSF)

Modified from Englehardt and Sorokin,
Seminars in Immunopathology, 2009; 13:497

http://faculty.massasoit.mass.edu/whanna/201/201_assets/LA_CSFflow.jpg
Mucopolysaccharidoses (MPS)

• Collection of diseases caused by lack of specific enzyme that breaks down GAGs
• Problems depend on where the GAGs build up
• Can affect any organ
  – Varies by the specific disease
  – Generally divided into body (somatic) and brain (CNS)
Features of MPS

• Brain (CNS)
  – Intellectual decline
  – Learning disability
  – Attention problems
  – Behavior problems
  – Seizures
  – Underlying inflammation

• Facial
  – Thickened/coarse features

• Respiratory
  – Ear infections, sleep apnea
  – Restrictive lung disease

• Heart
  – Valve disease

• Liver, spleen
  – Enlarged

• Bone, joint
  – Misformed bones, stiffness

• Nerve
  – Loss of movement, feeling
MPS III - Sanfilippo

• Divided into four types (A to D) based on specific enzyme defect
  – IIIA $N$-sulfoglucosamine sulfohydrolase (SGSH)
  – IIIB $\alpha-N$-acetylglucosaminidase (NaGLU)

• Cannot tell apart based on clinical features
  – Some suggestion type A may progress faster
MPS III CNS Key Features

• First signs between 2-6 years old

• Development
  – Speech more affected than motor skills
  – Intellectual decline first (3-8 years), then motor

• Behavior problems
  – Restless, anxious, destructive/aggressive
  – Sleep disturbance: poor settling, frequent waking
MPS III Fewer Somatic Features

• Facial features less coarse
• Ear infections, but minimal airway disease
• Rare heart valve problems
• Liver may enlarge slightly
• Later onset & less joint stiffness, bony changes
• Later peripheral nerve changes
Specific Treatments

**NOT EFFECTIVE**
- Reduce amount of Substrate: Genistein
- Substrate: Heparan Sulfate

**PROBLEM:** Getting past BBB

**Increase Enzyme:**
- Enzyme Replacement Therapy (ERT)
- Bone Marrow Transplant

**Repair Gene Defect:**
- Gene Transfer

**Gene**
- Product GAGs
- Removal
Outcome Measures - Challenges

• Need a measure for a primary outcome for future trials
  – Direct endpoint of how patient feels, functions, survives
• Current information on disease course is incomplete
  – Very little data on repeated measures of individuals
• MPS III effects primarily CNS (intellect, behavior)
  – Many measures designed using normal children
• Place in setting of children with a disease
  – Children grow, develop
  – Disease worsens over time, but is very variable
Scoring for MPS III Disease Course

**TABLE 1** FPSS for MPS Type III

<table>
<thead>
<tr>
<th>Function</th>
<th>Performance</th>
<th>Score</th>
</tr>
</thead>
<tbody>
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<td>Motor function(^a)</td>
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</table>

\(^a\) In some patients, motor and speech development were never normal. In these case subjects, the scoring started at a score of 2.

Meyer et al. *Pediatrics* 2007;120;e1255
Chosen Outcome Measures

• Developed with Dr. Keith O. Yeates
• Intellectual abilities:
  – Need tool that can be used for those without speech or are delayed: Leiter 3rd edition
• Behavior
  – Parent survey of behavior: Adaptive Behavior Assessment System (ABAS)
• Daily function
  – Pediatric Quality of Life Inventory 4.0 (PedsQL)
• Motor function
  – Tests of walking ability
Outcomes - Biomarkers

• Something that can be measured, but is not a direct endpoint
• Spinal fluid
  – Assess enzyme activities, signs of inflammation
• Urine
  – GAGs
• MRI of brain
  – Look for changes in brain white matter
CNS Gene Delivery for treating Neuropathic Lysosomal Storage Diseases

Haiyan Fu, Douglas McCarty

Center for Gene Therapy
Haiyan Fu, PhD
Training in Medicine (China)
Ms. in Medical Microbiology (China)
PhD. in Virology (UK)
Postdoc in Gene Therapy (UNC-CH)
Investigator (NCH-RI)

Gene therapy for MPS IIIB (1998-)

Gene therapy for MPS IIIA (2011-)

Doug McCarty, PhD
PhD. In Molecular Biology (UF)
Postdoc in AAV Biology (SUNY)
Director of Vector Core (UNC-CH)
Investigator (NCH-RI)
Gene therapy for MPS III

- Treat root cause: gene defect of lysosomal enzyme
- Long-term
- Secreted enzyme: no need to treat 100% cells

Major challenge: blood-brain-barrier (BBB)
Favored vector for gene therapy: AAV

- Nonpathogenic.
- Latent in cells after initial infection
- **AAV9** has the ability to cross the **BBB** and can reach the entire brain and spinal cord via intravenous injection.
MPS III gene therapy approaches

- **Missing enzyme**
  
  MPS IIIA: SGSH  
  MPS IIIB: NAGLU

- **Gene therapy vectors**
  
  MPS IIIA: AAV9 carrying human SGSH gene  
  MPS IIIB: AAV9 carrying human NAGLU gene

- **Vector delivery**: intravenous injection
MPS III mouse models resemble human diseases

- Lack of enzyme activity
- Lysosomal storage pathology in cells
- Severe progressive neurological disorders
- Mild somatic involvement relative to other forms of MPS
- Shortened lifespan:
  - MPS IIIA: 7-16 months
  - MPS IIIB: 8-12 months
  - Normal: 18-32 months
Therapeutic benefits of a single intravenous injection of AAV9 vector for treating MPS IIIA and IIIB in mouse models

- Restoration of enzyme activity in the central nervous system and somatic tissues
- Correction of lysosomal storage lesions
- Improvement in behavior
- Extension of survival
Correction of lysosomal storage pathology: reduction of LAMP-1 (MPS IIIB)
Correction of neuroinflammation (MPS IIIB)

Cerebral cortex  Thalamus  Striatum

NT (7mo)

AAV9 (End)
Reduction of lysosomal storage in the CNS and Somatic Tissues (10 days pi)

MPS IIIA

Brain

Liver

MPS IIIA + AAV9
Significant increase in survival

*Significant increase in survival also observed in MPS IIIA mice treated with an IV injection of AAV9-hSGSH vector
Current status of MPS IIIB gene therapy projects

- Prepare for Phase I clinical trial

  - **MPS IIIB**: Pre-IND meeting with the FDA on Aug. 23, 2013

  - **MPS IIIA**: Submit Pre-IND request to the FDA in 2-3 months

- MPS III natural history study

- Clinical team:

  Dr. Kevin Flanigan (PI)
  Dr. Kim McBride
Thanks!

Fu Lab
Darren Murrey
Bart Naughton
Jason Duncan
Aaron Meadows
Tierra Ware
Julie DiRosario
Smruti Killedar

McCarty Lab
Doug McCarty
Kim Zaraspe
Marcela Cataldi

Ben’s Dream

McCarty Lab
Kevin Flanigan
Kim McBride
Keith Yeates
Reed Clark
Viral vector Core
Chris Shilling
Cindy McAllister
Laurie Goodchild
Vivarium

Jerry Mendell

NIH/NINDS (U01NS069626, R21NS 081173)
Mucopolysaccharidosis types IIIA & IIIB

Kevin Flanigan
Clinical Trial Readiness/Natural History Study

- Our current timeline anticipates performance of phase 1/2 clinical trials of both MPS IIIB and IIIA gene transfer to begin 2014/2015.

- In anticipation for those studies, we are beginning a natural history study with the following goals:
  - To identify individual rates of decline in motor and cognitive function in a cohort of potential clinical trial patients.
  - To study the natural history of outcome measures in order to assess their appropriateness as outcomes in an eventual trial.
  - To establish baseline functional data in patients who will be potential candidates for an eventual trial.
  - To identify biomarkers of disease progression over a 12-month interval, including changes in brain MRI and in cerebrospinal fluid.
“Direct” Endpoints

- Clinically meaningful endpoints that directly measure how a patient feels, functions, or survives
- Endpoints that in themselves represent or characterize the clinical outcome of interest
  - Objective: survival, disease exacerbation, clinical event (e.g. MI, stroke), etc.
  - Subjective: symptom score, “health related quality of life” (validated instrument), etc.
- Customarily, the basis for approval of new drugs

Note: The term “direct” is used here to distinguish from “surrogate” endpoints, but this term is not uniformly utilized. Others may refer to these as “true” or “clinically meaningful” endpoints
Surrogate Endpoints

- A surrogate endpoint is a laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint.
- Ideally, the surrogate should exist within the therapeutic pathway between the drug and meaningful benefit
  - i.e. the drug results in the therapeutic benefit by virtue of its effect on the surrogate
- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.
Surrogate Endpoints

- Surrogate endpoints can be used for drug approval:
  - if well validated, or
  - under Subpart H (21 CFR 314.500-560; “accelerated approval” for serious and life-threatening illnesses; 1992)
    - requires adequate and well controlled trials
    - requires demonstrated effect on surrogate endpoint that is “reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit” or, demonstrated effect on a clinical endpoint other than survival or irreversible morbidity
    - requires that the Applicant carry out, with due diligence, further adequate and well controlled studies to verify and describe the clinical benefit of the surrogate (where there is uncertainty as to the relation of the surrogate to the clinical benefit)
Biomarkers

- A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
- In clinical practice, biomarkers may be used in the diagnosis/staging of a disease, or to predict/monitor response to a therapy.
- In clinical trials, biomarkers may be used to
  - explore the effects of an investigational drug
  - determine the promise of a drug in early development (e.g. P2)
    - Does the investigational drug exert the expected pharmacologic activity? And, at what dose?
- Biomarkers cannot establish a clinically meaningful benefit.
What challenges do we face?
The three phases of mucopolysaccharidosis type III (MPS III) and associated signs and symptoms

Normal development for 1-2 years, then:

1. ~1-2 year: Developmental delay becomes apparent
2. ~3-4 years: Severe behavioral problems, progressive mental deterioration → severe dementia
3. Behavioral problems slowly disappear; motor retardation with swallowing difficulties and spasticity

Death by end of second/beginning of third decade

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The timing of the disease course in attenuated patients is more variable than that seen in severe patients, but progression through these phases is common to all MPS III patients.

Not all signs and symptoms may be present in any individual patient.
Cognitive development in patients with Mucopolysaccharidosis type III (Sanfilippo syndrome)

Flow diagrams of MPS III patients included in the study.

Developmental age in all tested patients with MPS III according to age. The straight dotted line indicates the normal developmental pattern.

Developmental age in patients with MPS IIIA (n = 33). The straight dotted line indicates the normal developmental pattern.

Developmental age in patients with MPS IIIB (n = 23). The straight dotted line indicates the normal developmental pattern.

### TABLE 1  FPSS for MPS Type III

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<sup>a</sup>In some patients, motor and speech development were never normal. In these cases, the scoring started at a score of 2.

**FIGURE 1**
Regression of abilities as assessed by the FPSS (0–3) divided into average age score for motor function, speech, cognitive function, and the TDS of the MPS IIIA study population (N = 71).
Clinical Trial Readiness/Natural History Study

• Our current timeline anticipates performance of phase 1/2 clinical trials of both MPS IIIB and IIIA gene transfer to begin 2014/2015.

• In anticipation for those studies, we are beginning a natural history study with the following goals:
  – To identify individual rates of decline in motor and cognitive function in a cohort of potential clinical trial patients.
  – To study the natural history of outcome measures in order to assess their appropriateness as outcomes in an eventual trial.
  – To establish baseline functional data in patients who will be potential candidates for an eventual trial.
  – To identify biomarkers of disease progression over a 12-month interval, including changes in brain MRI and in cerebrospinal fluid.
Study Population

- We will enroll at 15 patients with each of two diseases (MPSIIIA and MPS IIIB) who meet inclusion criteria, including males and females of any ethnic or racial group.

**Inclusion criteria**
- Age 2 years old or greater
- Confirmed diagnosis of MPSIIIA or MPSIIIB by either of two methods:
  - No detectable or significantly reduced NAGLU or SGSH activity in serum or leukocyte assay.
  - Genomic DNA mutation analysis demonstrating a homozygous or compound heterozygous mutations in the NAGLU gene
- Clinical history of or examination features of neurologic dysfunction.

**Exclusion criteria**
- Inability to participate in the clinical evaluation
- Presence of a concomitant medical condition that precludes lumbar puncture or use of anesthetics
- Inability to be safely sedated in the opinion of the clinical anesthesiologist
Natural History Study

• Months 0, 6, and 12:
  – Neurocognitive and parental rating assessments
  – Timed functional motor tests
  – Standard laboratory assessments
  – Serum/leukocyte NAGLU or SGSH activity
  – Urine GAG

• Months 0 and 12:
  – Brain MRI (including DTI and $^1$H spectroscopy)
  – CSF for standard chemistries/cell counts and NAGLU or SGSH activity
Sanfilippo Registry

- https://connect.patientcrossroads.org/?org=SanfilippoRegistry
Important points about enrollment

• Important to know that **no one has yet been enrolled in the natural history study.**

• Participation in the natural history study does not guarantee a spot in any eventual trial

• We cannot guarantee that all subjects in the natural history study will have been in the natural history study.
Important points about enrollment

• Please contact Krista Kunkler at:
  krista.kunkler@nationwidechildrens.org

• She will return calls and ask some detailed questions about the child

• We will be contacting subjects and inviting them to participate
Important points about enrollment

• Costs of travel to Columbus will be covered
• Clinically-approved data will be returned to parents
• We are committed to rapid publication and transparent data sharing thereafter (benefit to the MPS community)
• Participation in any other natural history study is not exclusionary, but treatment (with recombinant enzyme, for example) is exclusionary
Anticipated gene transfer trial

• Intravenous infusion of AAV9.NAGLU at two doses (n=3 each)

• Assessments at baseline and at 6 months of:
  – Neurocognitive and parental rating assessments
  – Timed functional motor tests
  – Standard laboratory assessments
  – Serum/leukocyte NAGLU or SGSH activity
  – Urine GAG
  – Brain MRI (including DTI and $^1$H spectroscopy)
  – CSF for standard chemistries/cell counts and NAGLU or SGSH activity

• Primary outcome: safety

• Primary efficacy outcome: increase in the CSF:serum NAGLU ratio at 6 months post-treatment
Questions about a gene transfer trial

• We do not yet have a protocol – the FDA will have to approve it

• Compassionate use questions are premature – we do not yet know if it is safe or efficacious.

• We do not yet know what the enrollment criteria will be
  – Depends in part upon the natural history study results
Haiyan Fu, PhD
Doug McCarty, PhD
K. Reed Clark, PhD
Chris Shilling
Kim McBride, MD
Keith Yeates, PhD
Marco Corridore, MD
Nick Zumberge, MD
William Sheils, MD
Krista Kunkler
Susan Gailey

NIH/NINDS (U01NS069626)
Co-Recipient of the 2013 Global Genes “Champions of Hope” award
About Abeona Therapeutics

- Abeona was founded in March 2013 to develop gene therapies for children with born Sanfilippo Syndrome Type A and Type B

- Abeona will hold an exclusive license to develop Sanfilippo based gene therapies discovered at Nationwide Children’s Hospital.

- Abeona is raising funds to complete preclinical development of the programs and to advance Phase I/II clinical trials for both diseases in partnership with Nationwide Children’s Hospital.

- Offices located in Cleveland, OH, USA
Abeona Management Team

Tim Miller, PhD
President & CEO
tmiller@abeonatherapeutics.com

• 16 years of scientific research, product development and clinical operations expertise,
• Focus on transitioning novel biotherapeutics through pre-clinical phases and into Phase 1 and 2 human clinical trials.
• Helped raise over $5 million in grants, VC and angel funding for startup biotechnology companies
• Direct experience engaging the FDA and NIH advisory agencies on multiple IND submissions
• Led multiple teams focused on developing early-stage cardiovascular, wound healing, gene therapy and peripheral vascular disease therapies for clinical implementation.
• PhD in Pharmacology with a focus on Gene therapy from Case Western University, a B.S. in Biology and M.S in Molecular Biology from John Carroll University

Al Hawkins
Chairman
ahawkins@abeonatherapeutics.com

• Orphan disease focused biotechnology entrepreneur.
• Most recently CEO-in-Residence at BioEnterprise, where he launched and helped secure funding for spin-out companies from academic institutions.
• Previous Director of New Ventures at Boston University, where he managed spin-out companies
• Managed the $40 million BU Venture Fund and also led BU’s Launch Award program
• Founding CEO of Milo Biotechnology, a clinical stage gene therapy company targeting muscular dystrophy
• VP of Business Development at BioMotiv, a therapeutics-focused venture accelerator
• Received an MBA from the University of Wisconsin and an SM in BioMedical Enterprise from MIT.
How are new therapies developed?

<table>
<thead>
<tr>
<th>Drug R&amp;D</th>
<th>Clinical Trials</th>
</tr>
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<tbody>
<tr>
<td>1-2 years</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Target ID &amp; Validation</td>
<td>1 year</td>
</tr>
<tr>
<td>Hit Generation</td>
<td>20-100 people</td>
</tr>
<tr>
<td>1-2 years</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Lead Gen &amp; Optimization</td>
<td>100-300 people</td>
</tr>
<tr>
<td>1-2 years</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Pre Clinical Animal Studies</td>
<td>1,000-3,000 people</td>
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<td>1 year</td>
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<td>Phase 1: Safety</td>
<td>FDA Review &amp; Approval</td>
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<tr>
<td>Phase 2: Efficacy Safety</td>
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<tr>
<td>Phase 3: Efficacy Safety</td>
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**Abeona/NCH Treatments for Sanfilippo A & B**

- Link disease and target Biomarkers
- High-throughput screening
- Rational Design
- In silico screening
- Hits Confirmation
- Potency & cytotoxicity
- Prelim animal efficacy
- Initial SAR
- Potency Studies
- Selectivity Studies
- PK/ADME-Tox properties
- SAR pharmacophore modeling
- Pharmacological profile
- Administration route
- Drug interactions
Gene therapy clinical trials

The Journal of Gene Medicine, © 2013 John Wiley and Sons Ltd www.wiley.co.uk/genmed/clinical
Rare disease gene therapy trials <5%
Abeona & Nationwide Children’s Hospital

- Partnership to develop therapies for lysosome storage diseases

- Raising funds for Clinical trials for Sanfilippo A & B in 2014
Partners in developing treatments for Sanfilippo syndrome

SF4K  USA

The Sanfilippo Children's Research Foundation  Canada

Sanfilippo Foundation  Global/USA

Fondation Sanfilippo Suisse  Switzerland

The Children's Medical Research Foundation, Inc.®  USA

Ben's Dream  USA

Stop Sanfilippo  Spain
For more information, please contact:

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President & CEO
Abeona Therapeutics

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