Lysosomal Disease Network

P.I. Chester Whitley, Ph.D., M.D.
Co-P.I. Elsa Shapiro, Ph.D.

University of Minnesota
Lysosomal Disease Network

- Lysosomal diseases collectively affect 1 in 6,000 - significant disability and disease burden.

- Lysosomal diseases are a setting for innovative and advanced experimental treatments.

- No single medical research center can acquire sufficient numbers to test new therapies because of rarity. Multicenter collaborative research is necessary.

- The Lysosomal Disease Network brings together more than 500 researchers and clinicians across the country, Patient Advocacy Groups, and other interested partners to further research and education.
Longitudinal Studies

Project 1 – Longitudinal studies of brain structure and function in MPS disorders
P.I. Elsa G. Shapiro, University of Minnesota
Co Investigators: Gerald Berry, Boston Children's Hospital, Paul Fernhoff, Emory University, Paul Harmatz, Oakland Children's Hospital, Greg Pastores, New York University, Julian Raiman Hospital for Sick Children, Toronto, Robert Steiner, Oregon Health Science University, David Viskochil, University of Utah, Lorne Clarke, University of British Columbia.

Goals: to identify abnormalities of central nervous system (CNS) structure and function as well as to measure quality-of-life (QOL) in both treated and untreated patients with MPS disorders over time using quantitative neuroimaging, neuropsychological tests, and biomarkers.

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Project 2 – Longitudinal study of bone disease and the impact of growth hormone treatment in MPS I, II, and VI
P.I. Lynda Polgreen, University of Minnesota
Co-Investigator, David Viskochil, University of Utah

Goals: to characterize the bone health and bone architecture, density, strength, and mobility, and to document the natural progression of bone disease, to assess the efficacy of human growth hormone in a subset of the population and to standardize measurements of bone disease.

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Project 3 – CRIM Responses in Pompe disease
P.I. Priya Kishnani, Duke University
Co P.I. Dwight Koerberl, Duke University

Goals: to evaluate rare CRIM-negative Pompe disease patients on ERT +/- immune suppression, by enrolling them in a prospective/retrospective natural history study.

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Longitudinal Studies continued

**Project 4 – Longitudinal Study of Cognition in Subjects with Niemann-Pick Disease, Type C**  
P.I. Marc Patterson, Mayo Medical School, Rochester, MN  
Co P.I. Forbes Porter, National Institute of Health

Goals: to test the hypothesis that patients with NPC will demonstrate a specific pattern of neurocognitive deficits that will be present prior to development of significant neurological deficits and that will correlate with disease progression.

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**Project 5 – Clinical and Laboratory Investigations of Glycoprotein Storage Disorders**  
P.I. Sara Cathey, Greenwood Medical Center, South Carolina

Goals: to better define the disease incidences, identify clinical features which could contribute to early diagnoses, detail progression of the diseases, assess efficacy of supportive therapies currently used, and identify potential treatments.

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**Project 6 – Epidemiology and Natural History of Wolman and Cholesteryl Ester Storage Diseases**  
P.I. Greg Grabowski, Cincinnati Children's Hospital

Goals: to document and characterize the phenotypes, and their progression, as well as the determination of the genotypes of patients with lysosomal acid lipase (LAL; LPA locus) defects in the severe (WD) and attenuated (CESD) variants.

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Longitudinal Studies continued

Project 7–Assessment of Neurological Deterioration in Subjects with LINCL
  P.I. Ron Crystal, Cornell Weill Medical Center
  Co P.I. Dolan Sondhi, Cornell Weill Medical Center

Goals: to use clinical rating scales and magnetic resonance imaging methods to define the natural history of LINCL and to provide objective and sensitive surrogates for neurological status and for the assessment of the impact of experimental treatments in children with LINCL.

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Project 8–The Natural History of Mucolipidosis Type IV
  P.I. Raphael Schiffmann, Baylor Research Institute

Goals: to systematically study the neurological and retinal function over time, to characterize and quantify the clinical abnormalities of MLIV, and to increase awareness and improve diagnosis.

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Project 9–A Natural History Study of Hexosaminidase Deficiency
  P.I. Chester Whitley, University of Minnesota

Goals: to develop an index of disease progression in infantile Tay-Sachs disease by collecting longitudinal medical and developmental data in patients with infantile Tay Sachs disease and to measure change over time in underlying CNS structure and function in Juvenile and Late Onset Tay Sachs disease.

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Longitudinal Studies continued

**Project 10 –Natural History and Structural-Functional Relationships in Fabry Renal Disease**

P.I. Michael Mauer, University of Minnesota

Goals: to apply quantitative morphometric stereologic methods to 50-60 Fabry patients with a wide range of GFR with kidney biopsies performed prior to beginning enzyme replacement therapy to develop a model of structural functional relationships which most closely predicts GFR loss. These data will be used for the power calculations needed to design early intervention trials based on those structural endpoints which are most closely related to important functional outcomes in Fabry disease.

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**Project 11 –Longitudinal Studies in Batten disease** (already funded RO1)

P.I. Jonathan Mink, University of Rochester

Goals: to determine the natural history of JNCL quantitatively, characterize the neuropsychological and behavioral phenotype of JNCL, establish validity and reliability of a rating scale for JNCL, and determine correlations between phenotype and genotype of individual JNCL subjects.

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Pilot Studies

Pilot Project 1  
**Intrathecal ERT for cognitive decline in MPS I**
P.I. Patricia Dickson, UCLA

Pilot Project 2  
**Fabry disease identification**
P.Is. Marsha Browning, Harvard, Michael Mauer, University of Minnesota, Raphael Schiffman, Baylor Research Institute

Pilot Project 3  
**Phase I trial of Pyrimethamine to treat LOTS**
P.I. Joe Clarke, Hospital for Sick Children, Toronto

Pilot Project 4  
**Gene therapy for Tay-Sachs disease**
P.I. Chester Whitley, University of Minnesota

Pilot Project 5  
**Characterizing the neurobehavioral phenotype(s) in MPS III**
P.I. Michael Potegal, University of Minnesota

Pilot Project 6  
**Health, development, and functional outcomes in preschool children**
P.I. Michael Msall University of Chicago

Pilot Project 7  
**Pulmonary disease and exercise tolerance in boys with Fabry disease**
P.I. William Wilcox, Cedars Sinai Medical Center, Los Angeles, CA
New pilot studies

- Intravenous N-acetylcysteine for the treatment of Gaucher’s disease and Parkinson’s disease
  - James Cloyd, PharmD and Paul Tuite, MD, Co-PIs
  - Start date: September 1, 2010

- Residual Cardiovascular Risk in Mucopolysaccharidosis
  - Aaron Kelly, PhD., Raymond Wang, MD and Elizabeth Braunlin, MD, Co-Investigators
  - Start date: September 1, 2011
Education

- Director: Marc Patterson, Mayo Medical Center

- Fellowships -
  - Vera Moins - LDN fellow
  - Julie Eisengart – Minnesota LDN fellow
  - Jeanine Utz – Genzyme fellow
  - Sarah Lo – LDN fellow
  - Jonica Hazeart – Genzyme fellow

- CME meeting yearly
  - WORLD symposium – 2012 Sixth Annual San Diego CA
    - Attendance was over 500 in 2010
    - Basic, translational, and clinical science
    - New this year: Lysosomes 101 educational program

- LDN website – provide information for patients and their families, providers, researchers, and the public-at-large.
Cores

Purpose: to supply services to researchers, set standards, and provide consultation.

- **Statistical core** – John Connett; Kyle Rudser
- **Neuroimaging core** – James Provenzale; Igor Nestrasil, Alia Ahmed
- **Neurobehavioral core** – Richard Ziegler, Kathleen Delaney
- **Laboratory core** – Chester Whitley
- **Data, technology & web core** -David Erickson
- **Cell repository** - Coriell
Patient Advocacy Groups - COPA

- The National MPS Society
- National Tay-Sachs & Allied Diseases
- International Society for Mannosidosis and Related Disorders
- Fabry Support and Information Group
- Fabry Disease Foundation
- National Gaucher Foundation
- Children’s Gaucher Disease Research Fund
- Association for Glycogen Storage Disease
- Hide and Seek Foundation for Lysosomal Research
- Hunter’s Hope
- Mucolipidosis IV Foundation
- MLD Foundation
- United Leukodystrophy Foundation
- National Niemann-Pick Disease Foundation
- Ara Parseghian Medical Research Foundation
- Children’s Rare Disease Network
- Batten Disease Support and Research Association
- Acid Maltase Deficiency Association

More than any other RDCRN consortium
Functions

Collect, store and analyze data: Prepare case report forms for web-based data entry. Prepare data reports. Integrate image data.

Each consortium can access help with treatment assignment, pharmacy management, event scheduling, specimen management, adverse events monitoring, and image uploading.

Provide secure network space for LDN documents such as 1) copies of each grant document 2) protocols for each study, 3) IRB updates and other regulatory documents, 4) manuscripts.

Provide a contact registry for recruitment.

Provide web based video conferencing for each consortium.

Regulatory function; keeping IRBs up to date etc.
Part II

Longitudinal studies of brain structure and function in MPS disorders

University of Minnesota with
Oakland Children’s Hospital
Hospital for Sick Children – Toronto
Oregon Health Science University
Boston Children’s Hospital
Emory University
New York University
Goals of the study

- to identify abnormalities in brain structure and function over time
  - in treated and untreated MPS patients

- To identify distinct neuroimaging and neuropsychological patterns for each MPS disorder

- to develop quantitative measurements of change.

- to examine the degree to which risk factors influence brain and Quality of Life outcomes

- To establish risk/benefit analysis for treatments
Coordination with other LDN studies

- Patricia Dickson – Harbor UCLA - Intrathecal ERT for cognitive decline in MPS I
  - Provide cognitive and MRI eligibility and treatment effects of intrathecal enzyme

- Lynda Polgreen - UMN - Longitudinal study of bone disease and the impact of growth hormone treatment in MPS I, II, and VI
  - Provide cognitive and MRI data to help monitor effects of growth hormone
Methods

- 100 children/adults will be enrolled/followed in 7 centers over 5 years; 60 MPS I, 20 MPS II (primarily attenuated), 20 MPS VI.

- Seen yearly for a total of at least 3 or possibly 4 follow-up visits.

- Data: Quantitative neuroimaging (DTI, volumetrics) and neuropsychological tests, and medical history

- Samples collected for a biomarker developed by Lorne Clark (HCII-T)

- MRI data analysis (volumetrics and DTI) will be analyzed at the University of Minnesota through the neuroimaging core of the LDN.*

*cofunded by the National MPS Society
### Participants recruited and data collected as of 7/15/2011

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Mean Age</th>
<th>Mean IQ</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I H Under age 6</td>
<td>18</td>
<td>3.1</td>
<td>86</td>
<td>All HCT and ERT</td>
</tr>
<tr>
<td>MPS I H Over age 6</td>
<td>13</td>
<td>12.2</td>
<td>75</td>
<td>All HCT</td>
</tr>
<tr>
<td>MPS IH Total</td>
<td>32</td>
<td>7.1</td>
<td>81</td>
<td>18 HCT+EERT, 13 HCT, and 1 ERT</td>
</tr>
<tr>
<td>MPS I attenuated</td>
<td>19</td>
<td>16.9</td>
<td>90</td>
<td>ERT - all</td>
</tr>
<tr>
<td>MPS II</td>
<td>11</td>
<td>13.7</td>
<td>98</td>
<td>ERT - all</td>
</tr>
<tr>
<td>MPS VI</td>
<td>11</td>
<td>16.8</td>
<td>94</td>
<td>4 HCT, 5 ERT, 2 failed HCT</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>23.3</td>
<td>88</td>
<td></td>
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</tbody>
</table>
Baseline data outcome

- Baseline data for 45 MPS I patients at Minnesota

- These patients include both MPS IH patients who have been transplanted and MPS I attenuated patients with both Hurler Scheie and Scheie syndromes.

- Comparison with MPS II attenuated and MPS VI

- IQ, Vinelands and CHQ data.
  
  - Comparison of MPS IH patients who have had transplant with the attenuated patients who have been on ERT
IQ and adaptive functions

- Compared to other attenuated forms of MPS disorders (MPS II and VI), MPS I patients have more cognitive impairments; they are similar to MPS IH patients who have had transplant.
  - MPS IH patients are about 1 ½ standard deviations below the mean and attenuated patients are 1 standard deviation.
- Attenuated patients have very low adaptive function, even lower than transplanted MPS IH children.
What is Health-Related Quality of Life?

- The World Health Organization defined QOL as “a state of complete physical, mental and social well-being and not merely the absence of diseases or infirmity.”

- However, QOL is a perception, not an attribute. The perception is of the parent, the child, or the health care provider; and they may be discrepant from one another. Often to determine ‘true’ QOL these different perceptions need to be merged.

- For children with chronic illness, QOL often refers to how much the illness interferes with the psychological and physical functioning of the child.
What is the Child Health Questionnaire?

A 50 item parent questionnaire that assesses the parent’s perception of the child’s physical and psychosocial functioning, including pain, general health, mental health, self esteem, behavior, and impact on parents and family cohesion.
## Child Health Questionnaire (QOL)

<table>
<thead>
<tr>
<th></th>
<th>MPS IH (N=16)</th>
<th>MPS I Attenuated (N=9)</th>
<th>Overall (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>9.9 (3.5)</td>
<td>13.2 (3.7)</td>
<td>11.1 (3.8)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>-1.1 (1.7)</td>
<td>-2.2 (2.1)</td>
<td>-1.5 (1.9)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>-0.3 (1.1)</td>
<td>-0.8 (1.7)</td>
<td>-0.5 (1.3)</td>
</tr>
<tr>
<td>Behavior</td>
<td>0.5 (0.7)</td>
<td>0.0 (0.5)</td>
<td>0.3 (0.7)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>0.3 (1.0)</td>
<td>-0.1 (0.7)</td>
<td>0.2 (0.9)</td>
</tr>
<tr>
<td>Self Esteem</td>
<td>-0.3 (1.1)</td>
<td>-0.8 (1.4)</td>
<td>-0.4 (1.2)</td>
</tr>
<tr>
<td>Physical Function Summary</td>
<td><strong>36.1 (11.8)</strong></td>
<td><strong>30.5 (14.4)</strong></td>
<td><strong>34.1 (12.8)</strong></td>
</tr>
<tr>
<td>Psychosocial Function</td>
<td><strong>51.4 (7.4)</strong></td>
<td><strong>46.8 (7.0)</strong></td>
<td><strong>49.7 (7.5)</strong></td>
</tr>
</tbody>
</table>
Quality of Life and Adaptive Function in Hurler and Attenuated MPS I

- Overall the attenuated MPS I patients on ERT have a lower quality of life than MPS IH patients who had HCT. Most of the difficulty is physically based not psychologically based.

- What explains this difference?
  - Age- attenuated group is older; more adolescent issues
  - More physical disability; e.g. HCT better for orthopedic problems than ERT?
  - Differing expectations; attenuated MPS did not expect to have lingering orthopedic problems. Cord compression seems more common in the attenuated group
  - Variability of disease severity in attenuated group
Physical Functioning is a major challenge for almost all MPS I patients.

- challenges in communication, daily living, and socialization
- Impact on the Quality of Life of the child
- Impact on parents who report that it is difficult both time-wise and emotionally to deal with their children’s problems

Psychosocial (behavior, mental health etc.) Functioning is surprisingly normal given the physical challenges. These children are positive emotionally, optimistic, and socially connected in the face of obstacles. However, during adolescence a small subset develop mental health problems- what presages this?
CORRELATION OF FUNCTION WITH CLINICAL SCANS IS POOR

7 year old boy with MPS II

IQ = 128
No cognitive abnormalities
CORRELATION OF FUNCTION
WITH CLINICAL SCANS IS POOR

Image Examples- MPS II

Abnormal appearance of a brain of a 7 year old MPS II patient who has an IQ of 128

Virchow Robin spaces in thalamus; this 8 year old MPS II patient has an IQ of 93
Image Examples - MPS I

2.5 year-old girl with MPSIHIH. Early HCT. All cognitive functions average,

14 year-old boy with MPSIHIH. Early HCT. Cognitive, memory, attention low average, visual spatial below average,

16 year-old girl with MPSIA. Cognitive, visual spatial, memory (long and short term) impaired (attention test – unable to do.)
DTI (white matter connectivity) is associated with attention in MPS IH.
Initial studies have shown...

- Cognitive abnormalities were found in all MPS I subjects, not just MPS IH (Hurler syndrome).
- Attenuated MPS I patients have a poorer quality of life and poorer adaptive skills than other patients with MPS disorders.
- Hippocampus volume may be a key site of neuropathology in MPS I associated with learning/memory impairments.
- White matter tract organization is affected in MPS I with MPS IH more impaired.
- MPS IH is associated with poor attention and processing skills.

Lower callosal FA in MPS IH likely results from HCT treatment (chemotherapy).
Research needs

- to do better predictive analysis once we get medical and genotype data
- to examine the role of various risk factors—may be very deleterious to outcomes
- to further examine the role of age on these outcomes
- to find out why MPS I attenuated patient have such poor outcomes—lower than expected
- to further study those adolescents who have mental health problems
MPS study team

Thanks to the many MPS patients who have participated in our study and to the National MPS Society for their support and counsel.

- Kyle Rudser, Ph.D. Biostatistics
- Kathleen Delaney, Study Coordinator
- Julie Eisengart, Ph.D., Neuropsychology
- Kelly King, Ph.D., Neuropsychology
- Igor Nestrasil, M.D. Neuroimaging
- Alia Ahmed, M.D. Neuroimaging
- Brianna Yund, Data management and testing assistant
- Lorne Clarke, M.D., Ph.D., Biomarkers
- Chester Whitley, Ph.D., M.D. Lysosomal Disease Network PI
- Brenda Diethelm-Okita – IRB/administration LDN

- Julian Raiman, MD, Eva Mamak, PhD HSC, Toronto
- Paul Harmatz, MD, Rita Jeremy, PhD Oakland Childrens (UCSF)
- Paul Fernhoff, MD, Nadia Ali PhD Emory
- Robert Steiner, MD, Mina Nguyen-Driver PhD Oregon Health Sciences Univ
- Gerald Berry, MD, Susan Waisbren, Ph.D. Boston Childrens
- Greg Pastores, MD William MacAllister, PhD New York University

CENTER FOR neuroBEHAVIORAL DEVELOPMENT

lyosomal Disease Network