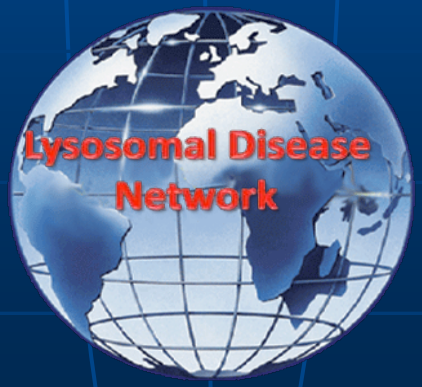
Lysosomal Disease Network

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

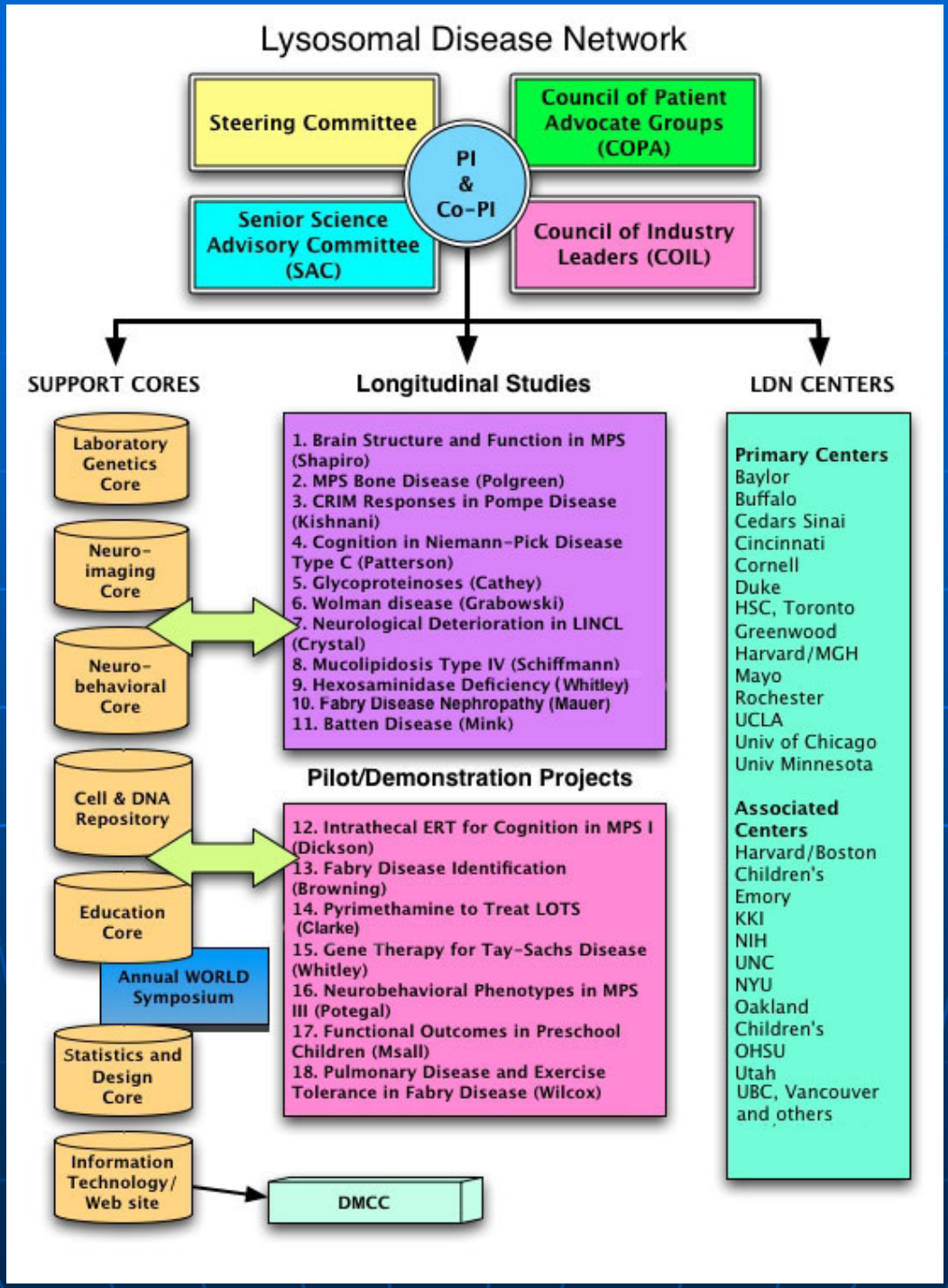
University of Minnesota

24th Annual National MPS Society Family Conference



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


Lysosomal Disease Network
Steering Committee
Council of Patient Advocate Groups (COPA)
PI & Co-PI
Senior Science Advisory Committee (SAC)
Council of Industry Leaders (COIL)
SUPPORT CORES
Longitudinal Studies
LDN CENTERS
Laboratory Genetics Core
Neuro-imaging Core
Neuro-behavioral Core
Cell & DNA Repository
Education Core
Annual WORLD Symposium
Statistics and Design Core
Information Technology/ Web site
DMCC
1. Brain Structure and Function in MPS (Shapiro)
2. MPS Bone Disease (Polgreen)
3. CRIM Responses in Pompe Disease (Kishnani)
4. Cognition in Niemann-Pick Disease Type C (Patterson)
5. Glycoproteinoses (Cathey)
6. Wolman disease (Grabowski)
7. Neurological Deterioration in LINCL (Crystal)
8. Mucolipidosis Type IV (Schiffmann)
9. Hexosaminidase Deficiency (Whitley)
10. Fabry Disease Nephropathy (Mauer)
11. Batten Disease (Mink)
Pilot/Demonstration Projects
12. Intrathecal ERT for Cognition in MPS I (Dickson)
13. Fabry Disease Identification (Browning)
14. Pyrimethamine to Treat LOTS (Clarke)
15. Gene Therapy for Tay-Sachs Disease (Whitley)
16. Neurobehavioral Phenotypes in MPS III (Potegal)
17. Functional Outcomes in Preschool Children (Msall)
18. Pulmonary Disease and Exercise Tolerance in Fabry Disease (Wilcox)
Primary Centers
Baylor
Buffalo
Cedars Sinai
Cincinnati
Cornell
Duke
HSC, Toronto
Greenwood
Harvard/MGH
Mayo
Rochester
UCLA
Univ of Chicago
Univ Minnesota
Associated Centers
Harvard/Boston Children's
Emory
KKI
NIH
UNC
NYU
Oakland Children's
OHSU
Utah
UBC, Vancouver
and others

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.

* * * * *

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.

* * * * *

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.

* * * * *

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.

* * * * *

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.

* * * * *

- 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.

* * * * *

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.

* * * * *

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.

* * * * *

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.

* * * * *

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.

* * * * *

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.

* * * * *

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

Education

- Director: Marc Patterson, Mayo Medical Center
- Fellowships -
  - Vera Moins- LDN fellow
  - Julie Eisengart – Minnesota LDN fellow
  - Jeanine Utz – Genzyme fellow
- CME meeting yearly
  - WORLD symposium – 2011 Sixth Annual Las Vegas, NE
    - Attendance was over 400 in 2010
    - Basic, translational, and clinical science
- 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 – Christine Eng
- 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

Data Management and Coordinating Center
University of South Florida

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.