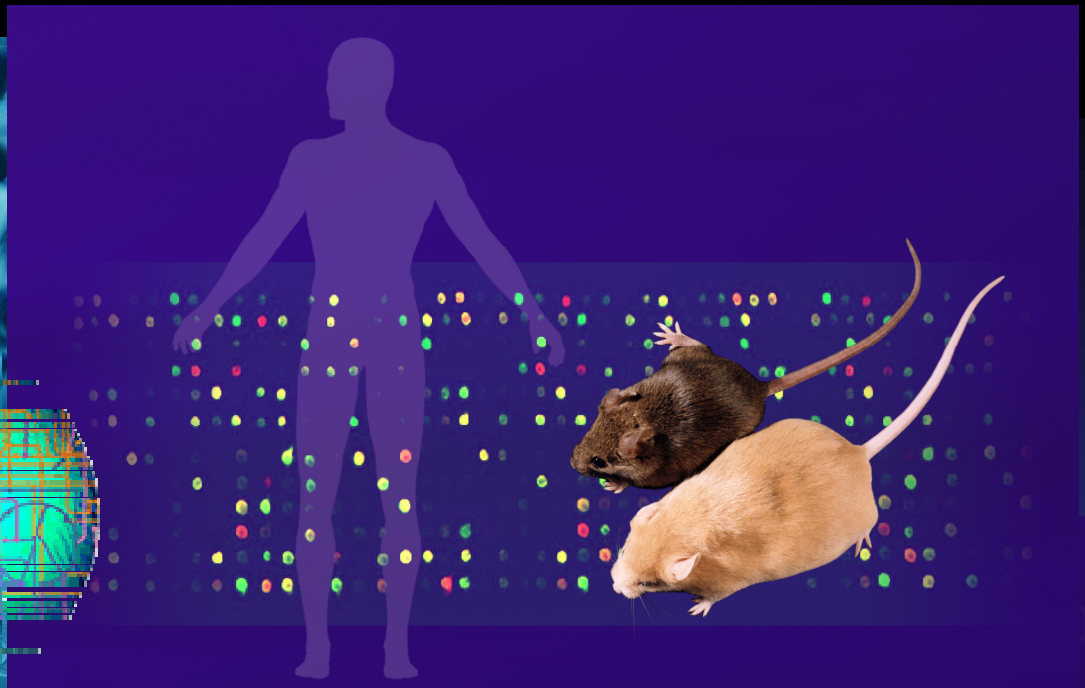
Lysosomal Storage Disorders Research Supported by NINDS



Lysosomes

- Cell's recycling centers.
- Breakdown macromolecules, such as proteins, glycoproteins, lipids, phospholipids for re-use
- Accomplished by about 70 known lysosomal enzymes, with optimal activity at acidic pH 5.0

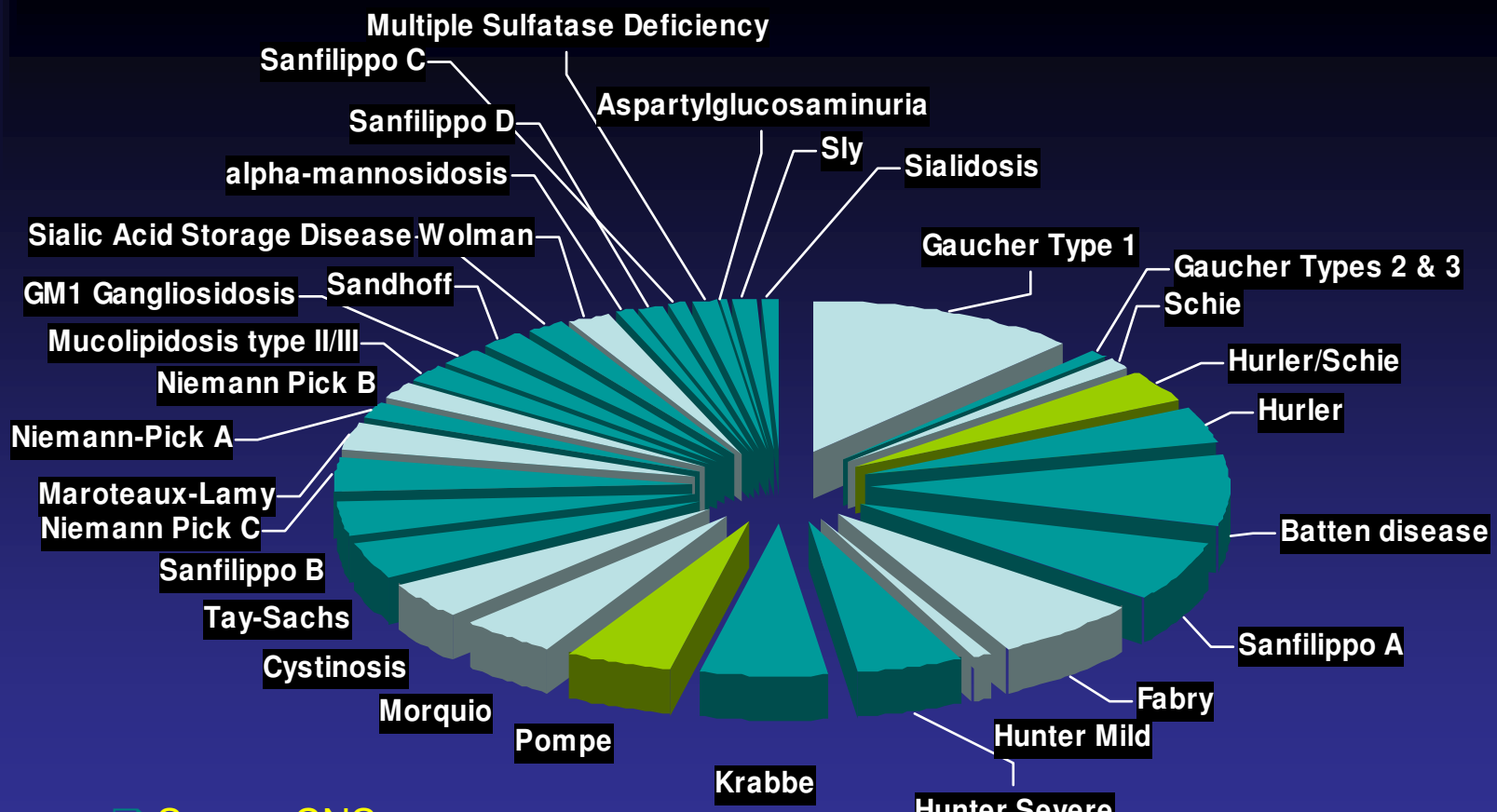
Lysosomal Storage Disorders

- Characterized by a genetic defect in one or more lysosomal enzymes or in their protein co-factors, post-translational modification or lysosomal protein transport
- Results in substrate accumulation in lysosomes
- Currently 46 different LSDs have been identified, mostly autosomal recessive (except Hunter and Fabry which are X-linked)
- Individually rare (1/50,000 – 1/4,000,000) but collectively at 1/5,000 to 1/7,500 (about 500-900 new cases/year)
- Onset typically in infancy to early childhood
- Phenotype-genotype heterogeneity
- Majority with CNS involvement

Classification of Lysosomal Storage Disorders

- Mucopolysaccaridoses (MPS I or Hurler, MPS II or Hunter, MPS III or Sanfilippo, MPS IV or Morquio, MPS VI or Maroteaux-Lamy, MPS VII or Sly, etc.)
- Glycoproteinoses (mannosidosis, fucosidosis, aspartylglucosaminuria, sialidosis, etc.)
- Glycogen storage (Pompe)
- Sphingolipidoses (Fabry, Farber, Gaucher, Tay-Sachs, Sandhoff, Krabbe. MLD, etc.)
- Neuronal ceroid lipofuscinoses (infantile, late infantile, juvenile, adult, Finnish, variant late infantile, Turkish, etc.)
- Lipid storage (Niemann Pick, GM2 Gangliosidosis, etc.)
- Multiple lysosomal enzyme defects (ML-II, ML-III, etc.)
- Transport defects (cystinosis, ML-IV, Salla, etc.)

CNS Involvement in LSDs



Research in LSDs

- Challenges
  - Rare disorders
  - Single gene defects but clinically heterogeneous
  - Accurate and timely diagnosis
  - Current therapeutic approaches have limited efficacy on neurologic symptoms due to blood-brain barrier
- Opportunities
  - Most genes or metabolic pathway have been identified, generally single gene defect
  - Mostly autosomal recessive inheritance so ‘loss of function’ amenable to enzyme replacement, gene therapy, substrate reduction, stem cell transplantation
  - Small and large animal models exist (mice, dogs, cats, sheep, etc.)
  - Cross-correction

Approaches to Treatment of LSDs

- Stem cell transplantation
- Enzyme replacement therapy
- Substrate reduction therapy
- Enzyme enhancement therapy (chaperones)
- Gene therapy
- Drug screen for read through compounds
- Protein re-engineering

Recent NINDS Initiatives on LSDs

- Workshops
  - Batten Disease: Basic Biology and Therapy
  - The Mucopolysaccharidoses: Therapeutic Strategies for the Central Nervous System
  - Glutamic Acid Decarboxylase (GAD) Autoimmunity in Batten Disease
  - The Glycoproteinoses: An International Workshop on Advances in Pathogenesis and Therapy
  - NINDS Workshop on Glycosphingolipids in Health and Disease
  - Towards Clinical Progress in the Mucopolysaccharidoses
  - 9th Int. Congress on Neuronal Ceroid Lipofuscinosis
  - Tenth International Congress on Ceroid Lipofuscinoses
  - Brain Uptake and Utilization of Fatty Acids and Lipids
  - WORLD Lysosomal Research Network Annual Symposium
  - Lysosomal Disease Network-2nd Annual WORLD Symposium
- Funding Opportunity Announcements
  - PAS-04-120: CNS THERAPY DEVELOPMENT FOR LYSOSOMAL STORAGE DISORDERS
  - PAS-06-202: CNS Therapy Development for Lysosomal Storage Disorders (R21)
  - PAS-07-195: CNS Therapy Development for Lysosomal Storage Disorders (R01)
- Worked with advocacy and voluntary groups
  - Helped form the LSD Research Consortium, governed by an MOU
  - LSD Research Consortium :The National MPS Society, Inc.; National Tay-Sachs & Allied Diseases Association, Inc.; The Canadian Society for Mucopolysaccharide & Related Diseases, Inc.; The Sanfilippo Syndrome Medical Research Foundation, Inc.; Hunter's Hope Foundation; National Niemann-Pick Disease Foundation
- Worked with researchers, academic institutions, private companies
  - Helped form Lysosomal Disease Network

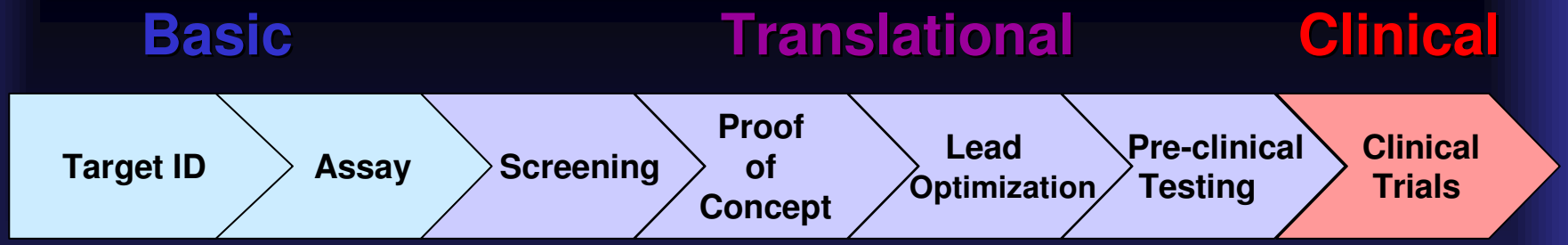
CNS Therapy Development for Lysosomal Storage Disorders

PI Name	Institution	Title
BEDWELL, DAVID M	UNIVERSITY OF ALABAMA AT BIRMINGHAM	Suppression of the Idua-W402X mutation in an MPS I-H mouse
DICKSON, PATRICIA I	LA BIOMED RES INST/ HARBOR UCLA MED CTR	Intrathecal enzyme therapy for mucopolysaccharidosis I
DUNCAN, IAN D	UNIVERSITY OF WISCONSIN MADISON	The role of microglia/macrophages and their therapeutic use in Krabbe's disease
ESTEVES, MIGUEL S	MASSACHUSETTS GENERAL HOSPITAL	Gene delivery methods for global therapy in the CNS
NEUFELD, ELIZABETH F.	UNIVERSITY OF CALIFORNIA LOS ANGELES	Aptamer-directed crossing of the blood barrier for enzyme therapy of LSDs
SEYFRIED, THOMAS N	BOSTON COLLEGE	Glycosphingolipids in murine neurodegenerative diseases
WALKLEY, STEVEN U	YESHIVA UNIVERSITY	Substrate Reduction Therapies for Niemann-Pick C Disease
YUN, KYUSON	JACKSON LABORATORY	MPS VII CNS Gene Therapy Using Neuronal Stem Cells

NINDS Translational Research Program:
Four Coordinated Program Announcements

- NINDS **Exploratory/Developmental Projects** in Translational Research (R21)
- NINDS **Cooperative Program** in Translational Research (U01 and U54)
- NINDS Cooperative **Small Business Awards** in Translational Research
- NINDS Mentored Research and **Clinical Scientist Development** Awards in Translational Research
- Milestone-driven projects with clear go, no-go criteria for continuation of funding

Funding and Resources



NINDS Translational Research Funding Program

Exploratory/Developmental R21's

Cooperative Agreement U's

NO Mechanistic Studies

Translational Research Program: Cooperative Agreements

- Investigator-initiated
  - Any disease area within NINDS portfolio
  - Any type of therapy: drugs, biologics, devices
- Entry: in vivo efficacy data
- IND-directed therapy development projects
  - Single-component projects, multi-component projects, & resource centers
- Pre-application consultation with NINDS program
- Special review environment (special criteria and study section)

NINDS Funding Opportunity Announcements

- Training
  - Mentored Clinical Scientist Development Award (K08)
  - Mentored Research Scientist Development Award
  - Mid-Career Investigator Award in Patient-Oriented Research (K24)
  - Independent Scientist Award (K02)
  - Mentored Quantitative Research Career Development Award
  - Mentored Patient-Oriented Research Career Development Award (K23)
  - Midcareer Investigator Award in Patient-Oriented Research (K24)
- Basic
  - Novel Approaches to Enhance Animal Stem Cell Research
  - Neuroprotective CNS Barriers in Neurological Diseases
- Resources
  - NIH Small Research Grant Program (R03)
  - NINDS Institutional Center Core Grants to Support Neuroscience Research
- Translational
  - NINDS Cooperative Program in Translational Research
  - NINDS Mentored Research Scientist Development Awards in Translational Research
  - NINDS Exploratory/Developmental Projects in Translational Research
  - NINDS Cooperative Small Business Awards in Translational Research
  - Notice of Availability of Administrative Supplements for Roadmap Assay Development for HTS Awards (NIH Blueprint) for Neuroscience Research)
- Clinical
  - NINDS Clinical Trial Planning Grant (R34) Program
  - Preliminary Investigations Leading to Optimal Trials in Neurology

NINDS Research Resources

- Animal Models
  - KOMP, GENSAT, Neuromice
- Reagents
  - NeuroMab
- Gene Expression
  - GENSAT, Microarray consortium
- Cells/Tissues/DNA
  - Harvard Brain Bank, Genetics Repository