Bench to Bedside & Back: Smith Lemli Opitz Syndrome as Paradigm

- Syndrome of multiple congenital anomalies/mental retardation 1st described by Smith et al., 1964
- Autosomal recessive genetic disorder
- Observed incidence: 1/40,000-1/20,000; proposed carrier frequency ~ 1%-2%
- Gene not yet identified at start
Clinical Features

- Characteristic craniofacial appearance
- Cleft palate
- Microcephaly & brain malformations
- Growth & developmental retardation
- Limb anomalies (syndactyly)
- Genital anomalies
- Congenital heart defects
- Feeding difficulties
- Behavioral difficulties
Plasma Sterol Profile by GLC
Fig. 1. Cholesterol biosynthetic pathway
Research Goals

Identify molecular genetic etiology, define whole body sterol metabolism, evaluate potential therapies

SLOS natural model for learning about sterol metabolism in general

Hypothesis: Cholesterol supplementation will prove beneficial to children with SLOS

- ameliorate cholesterol deficiency
- lower 7-DHC synthesis by feedback inhibition
Molecular Genetic Studies

- SLOS gene had not been identified
- Tentatively mapped to 7q32 or 7q34; patients with chromosomal translocations
- Various approaches to identify the gene
  - positional cloning based on translocation patients
  - protein purification, amino acid sequence identification, oligo probes/hybridization
Mutations in the Human Sterol Δ⁷-Reductase Gene at 11q12-13 Cause Smith-Lemli-Opitz Syndrome

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Hypotheses

The defects in SLOS result from:

• Cholesterol deficiency in tissues
• Toxicity of 7-DHC

Whole body cholesterol synthesis *is reduced* in SLOS patients

Total sterol synthesis in SLOS *is not reduced* (i.e. cholesterol + 7-DHC + 8-DHC)

Bile acid synthesis *is reduced* in SLOS
Results: Sterol & Bile Acid Synthesis in SLOS

Steiner, R. D. et al. J. Lipid Res. 2000;41:1437-1447
CHOLESTEROL SUPPLEMENTATION DOES NOT IMPROVE DEVELOPMENTAL PROGRESS IN SMITH-LEMLI-OPITZ SYNDROME

Darryn M. Sikora, PhD, Mark Ruggiero, MD, Kersti Pettit-Kekel, BS, Louise S. Merkens, PhD, William E. Connor, MD, and Robert D. Steiner, MD

(J Pediatr 2004;144:783-91)

The Near Universal Presence of Autism Spectrum Disorders in Children With Smith–Lemli–Opitz Syndrome

Darryn M. Sikora, Kersti Pettit-Kekel, Jennifer Penfield, Louise S. Merkens, and Robert D. Steiner

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Current/Future

• New Assessments: Brain MRI, ERG
• New treatments
  – TUDCA, Antioxidants, Statins
• New Disorders: SLS(J-BR), MA/HIDS, CTX
• Newborn Screening
GOAL: Make Newborn Screening Available for Sterol and Bile Acid Disorders

- Newborn screening (NBS) programs in US alone save thousands of children annually from death and serious morbidity through early detection
Separation SLOS From Normal Possible

- Unaffected subjects (n= 50, shaded circles)
- SLOS-affected patients (n=4, open circles; replicate analysis)
- Untreated CTX-affected patients (n=4, shaded triangles)
- Unaffected 3-day old newborn (open triangle)
Other research

- PKU: Neuropsych and brain imaging
- Osteogenesis Imperfecta (OI, Brittle Bone Disease): LCRC, registries, clinical trials, RDCRN grant
- Autism: SLOS, Cholesterol, Synapse
  - Autism Treatment Network (ATN, Autism Speaks)
- Purified Human Fetal Neural Stem Cells as Rx for Human Disease
Other research

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- **Purified Human Fetal Neural Stem Cells as Rx for Human Disease**
Human Neural Stem Cells for Neuronal Ceroid Lipofuscinosis

Two forms of NCL available for study, amenable to stem cell therapy

- CLN1...PPT1 (palmitoyl-protein thioesterase1)
- CLN2...TPP-I (tripeptidyl peptidase1)

HuCNS-SC

Absence of enzymes

Enzymes→ Lysosomes via MPR

10-20% Secreted

Uptake by M6PR

Accumulate storage material

Reduce storage material

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Vision

- Rare Diseases: Expertise at OHSU
- Autism: $500 million in Federal Research Funding next 5 years
- Rare Disorders Exp Therapeutics Center: Need and Opportunity
Rare Disease Research at OHSU

• Background: Bill Gahl, OCTRI EAC
• Much expertise
• Great interest
• Some progress
• OHSU RDRC (Rare Disorder Research Consortium) Hayflick, Knafl, Steiner, others
• RDCRN-NIH: Steiner DSMB member
  – RDCRN Grant: Sterol/isoprenoid disorders. Research, Education, Training, Alliance with Support Group
• Chair Rare Disease WG CTSA POC
Rare Disease Experimental Therapeutics Center

• The Opportunity: Infrastructure in place from Stem Cells trial to carry out cutting edge phase I clinical trials

• The Problem: That infrastructure could go away once trial ended. Industry sponsored.

• The Need: Huge gap in translational research—bringing advances in the lab to the clinic.
Rare Disease Experimental Therapeutics Center (cont.)

- Translational research gap: Many investigators doing basic science research develop exciting potential therapies, but lack interest or know-how or both to bring these therapies to the patients. E.g. gene therapy, stem cell therapy, small molecule therapies
- Proposal: Develop a RDETC with philanthropic and institutional support
- Grateful patients, OCTRI, OHSU research
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