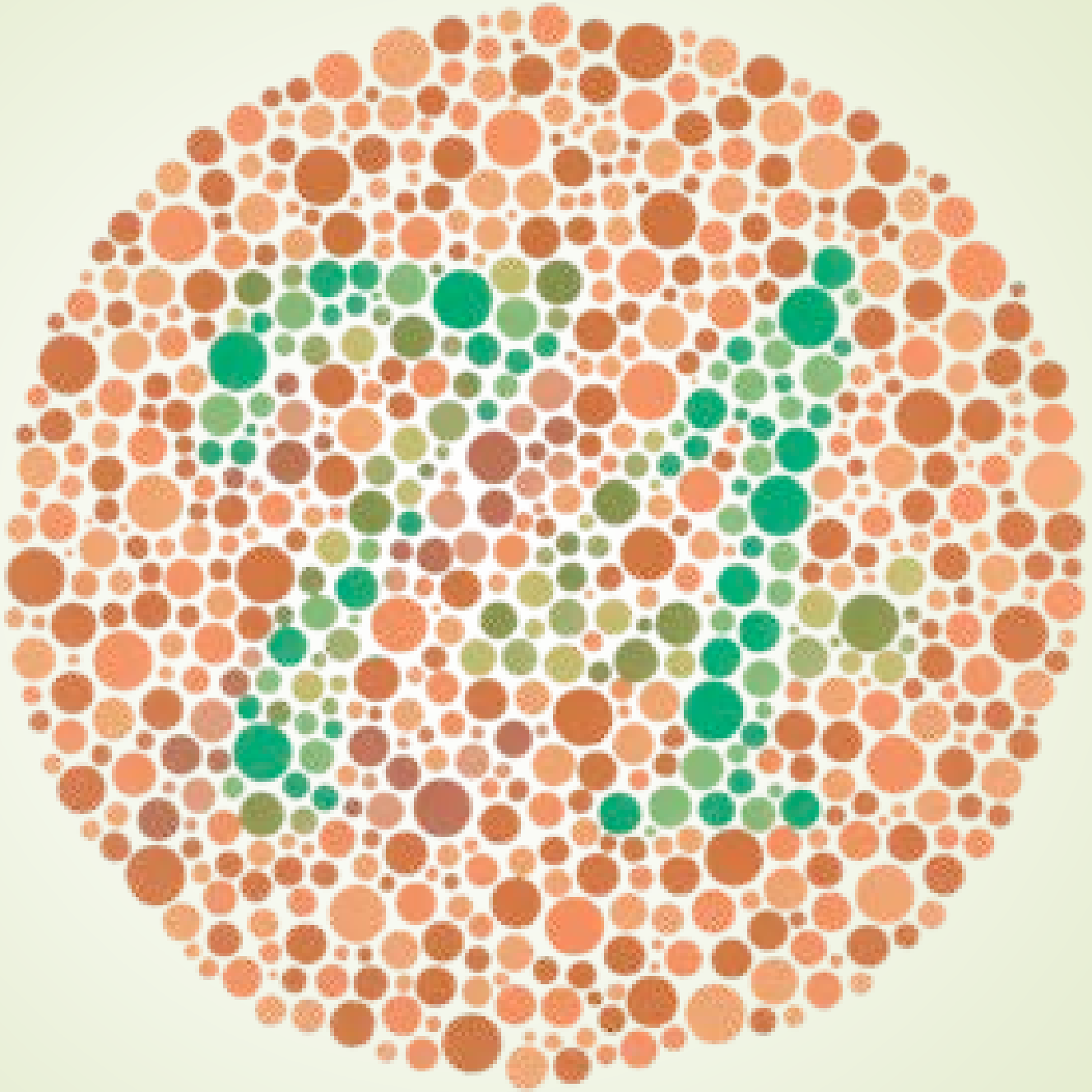
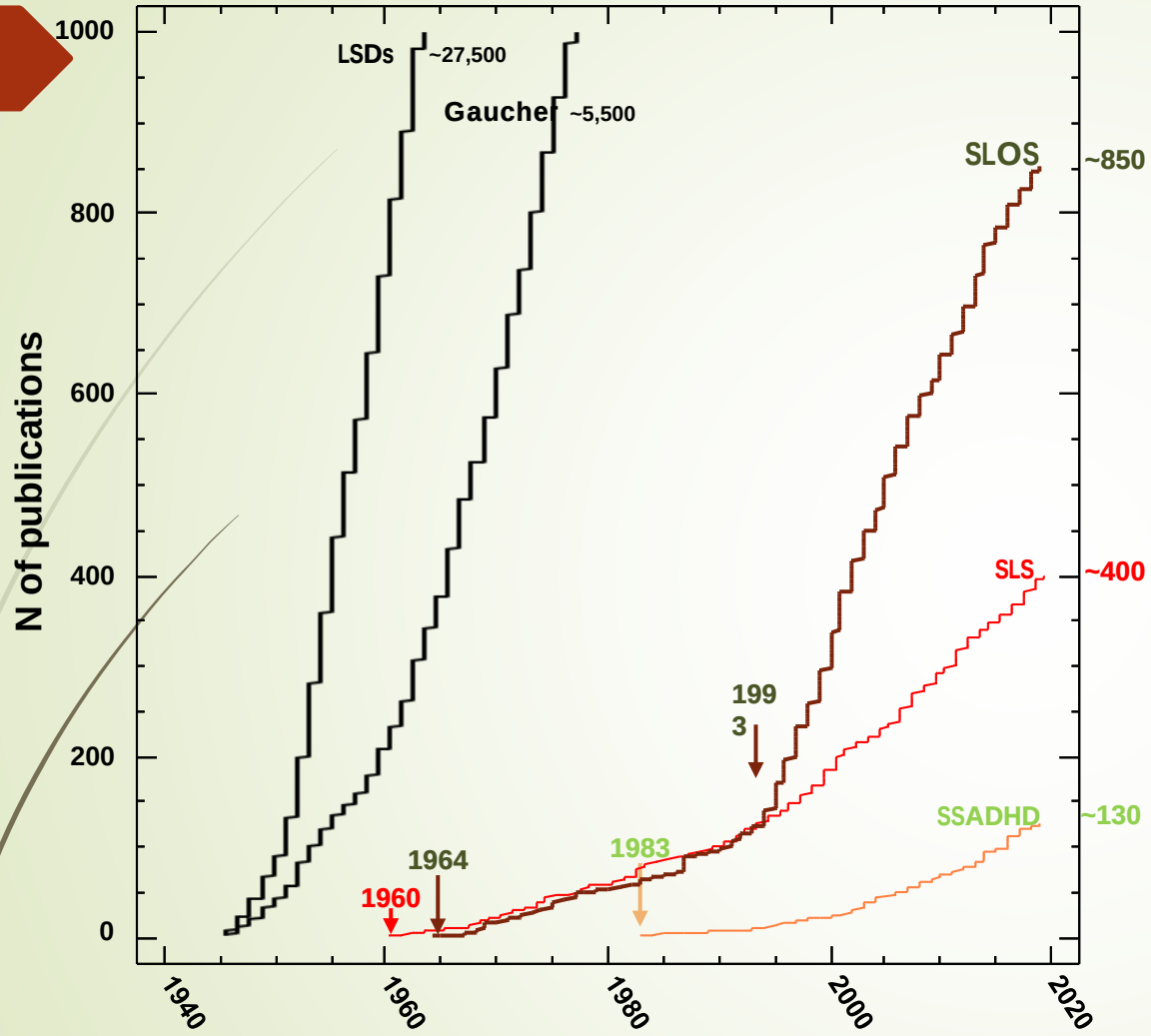
SLOS Research Studies: Historical and Current perspective

SLO Family & Medical Conference

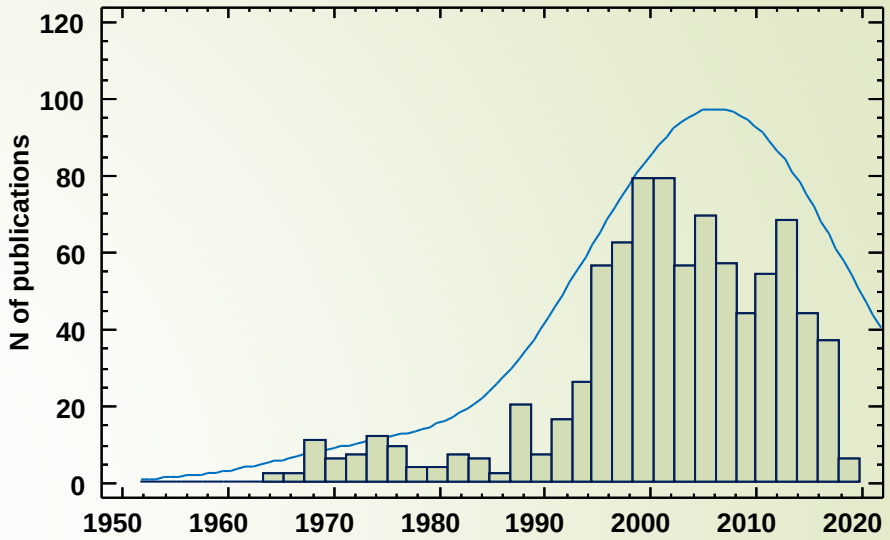
June 27-28, 2019



SLOS Research – Publications (PubMed)



SLOS publications over time (~850) – *Source: PubMed*



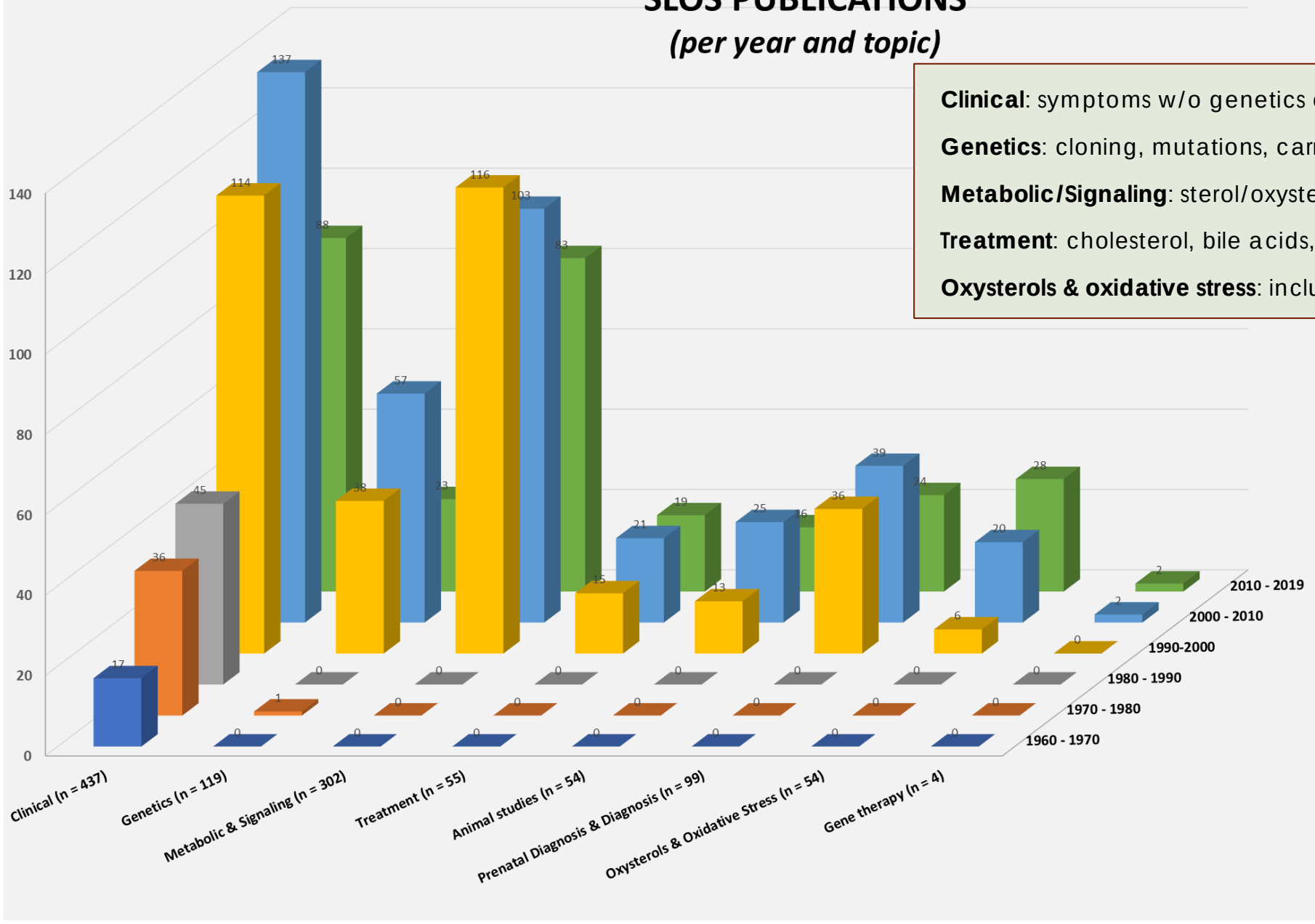
Prevalence

1. SLOS: 1:10,000-1:60,000 (*Carrier*: 1:1,600 – 1:13,500)
2. LSDs: 1:57,000 (Gaucher) – 1:4,000,000 (sialidosis)
3. SLS: 1:250,000
4. SSADHD: 1:2,000,000 (~350 cases world-wide)

Consider working with other PAGs supporting patients with other sterol-related rare diseases??

SLOS PUBLICATIONS

(per year and topic)



Clinical: symptoms w/o genetics or metabolic studies

Genetics: cloning, mutations, carriers

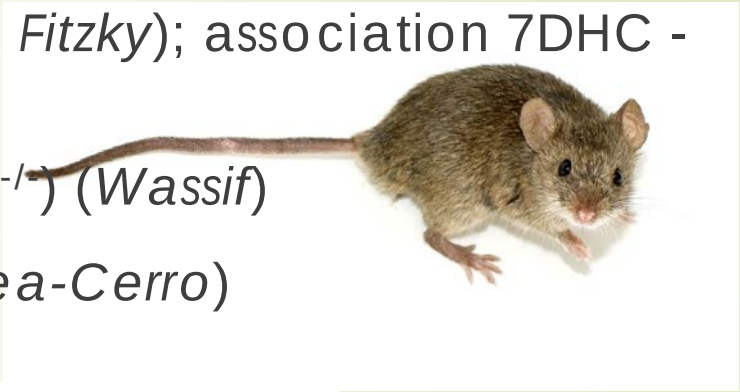
Metabolic/Signaling: sterol/oxysterol, signaling pathways

Treatment: cholesterol, bile acids, statin, antioxidants, gene, others

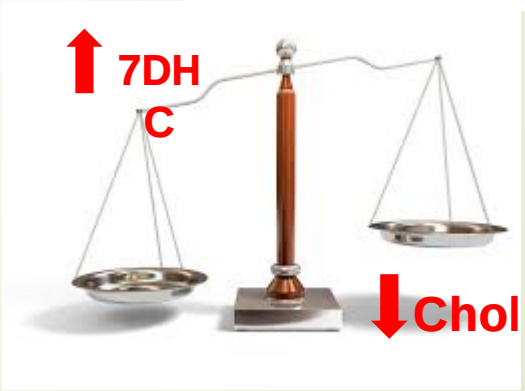
Oxysterols & oxidative stress: includes photosensitivity studies

Key Steps in SLOS Research: 1964 - 2006

- **1964**: 1st Clinical report (*Smith, Lemli, Opitz*)
- **1993**: cholesterol deficiency (*Irons/Tint*)
- **1998**: cloning of DHCR7 (*Moebius*); SLOS mutations (*Wassif, Fitzky*); association 7DHC - photosensitivity
- **2001**: development of the 1st mouse model of SLOS ($Dhcr7^{-/-}$) (*Wassif*)
- **2006**: development of the 2nd mouse model of SLOS (*Correa-Cerro*)



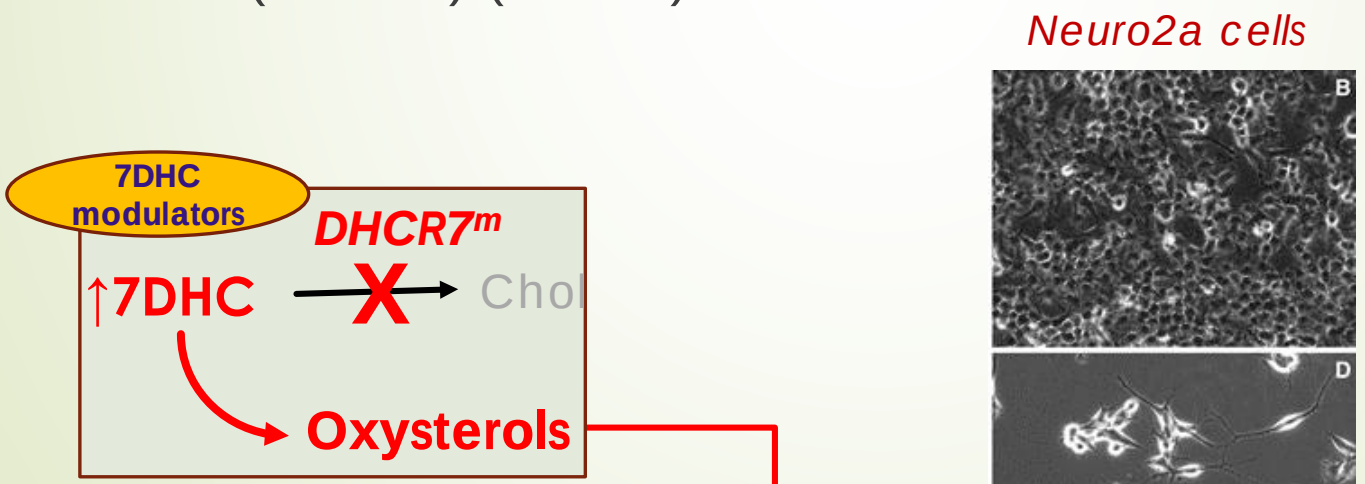
Acetate → HMG-CoA → MVA → 7DHC —(*DHCR7m*)→ Cholesterol



→ SLOS

Key Steps in SLOS Research : 2010-present

- **2010**: take off of research on 7DHC-derived oxysterols and cell toxicity (*Liu/Porter/Korade*)
- **2016**: screening of small molecules that decrease 7-DHC (*7DHC modulators*) *Korade*)
- **On-going**: screening of small molecules (fibroblasts, zebrafish, modifier genes/CYP27 (mouse) (*Wassif*)

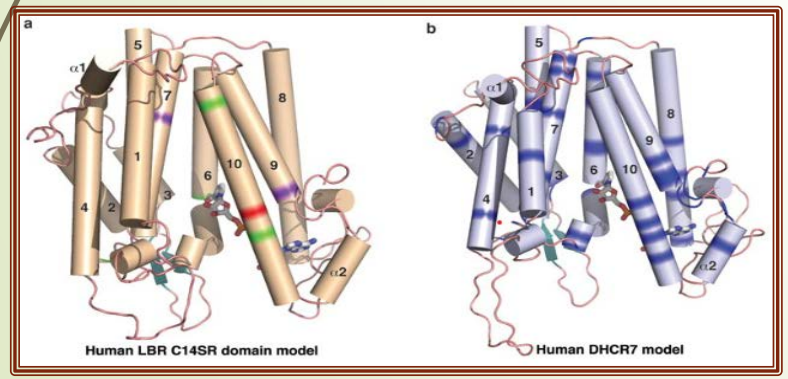


Neuro2a cells

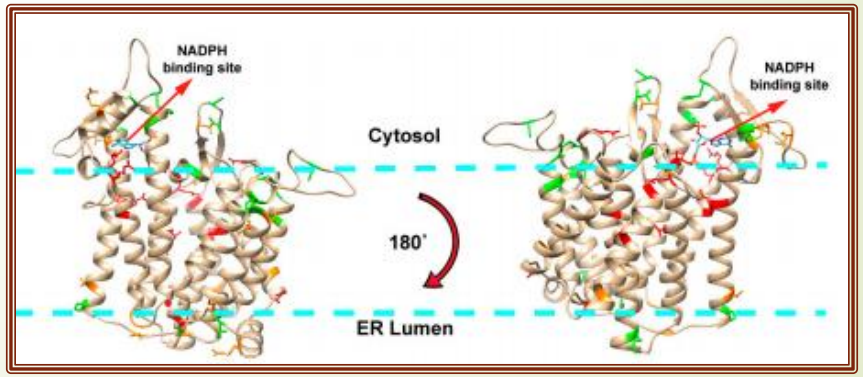
Korade, J. Lipid Res., 2010

Key Steps in SLOS Research : 2010-present

- **2015:** crystal structure of bacterial *DHCR14* (*Li*)
- **2016**: Identify amino acids responsible for cholesterol-mediated regulation of *DHCR7* (*Prabhu*)
- **2018**: in silico modeling of DHCR7, investigations of the impact of pathogenic mutations on the stability and conformation of the enzyme (*Peng*)



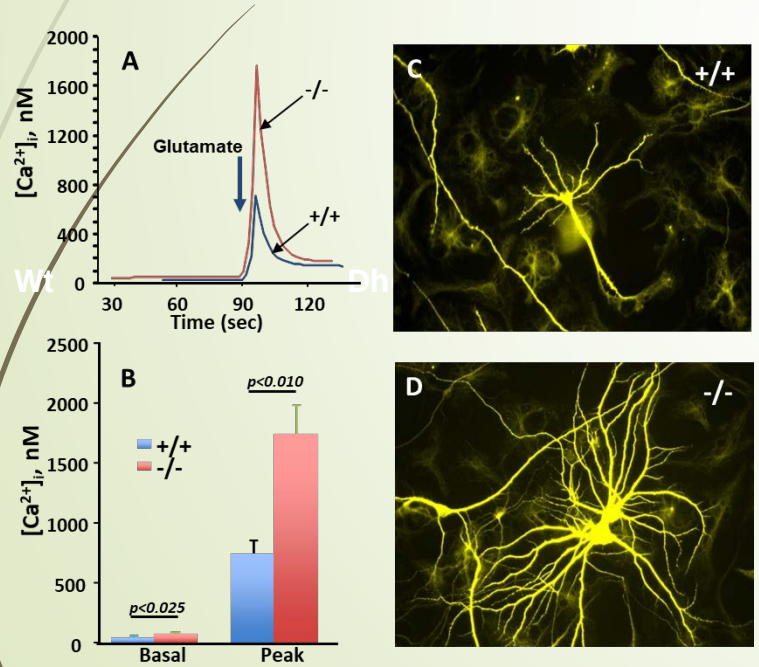
Li, 2015



Peng, 2018

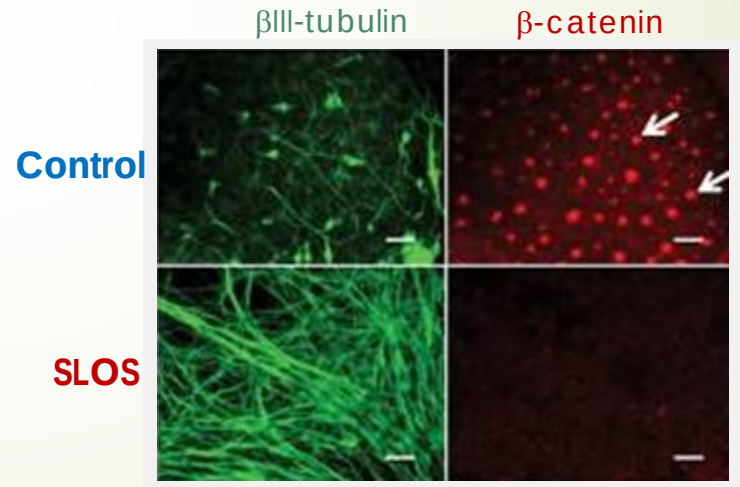
Key Steps in SLOS Research: 2010-present

- **2010**: mouse neural stem cells (*Roullet, Steiner, NIH*)
- **2016**: "Brain in the dish" – patients' fibroblast-derived iPSCs and Wnt/*β-catenin* signaling (*Francis*)
- **Ongoing….**



Mouse neural stem cells

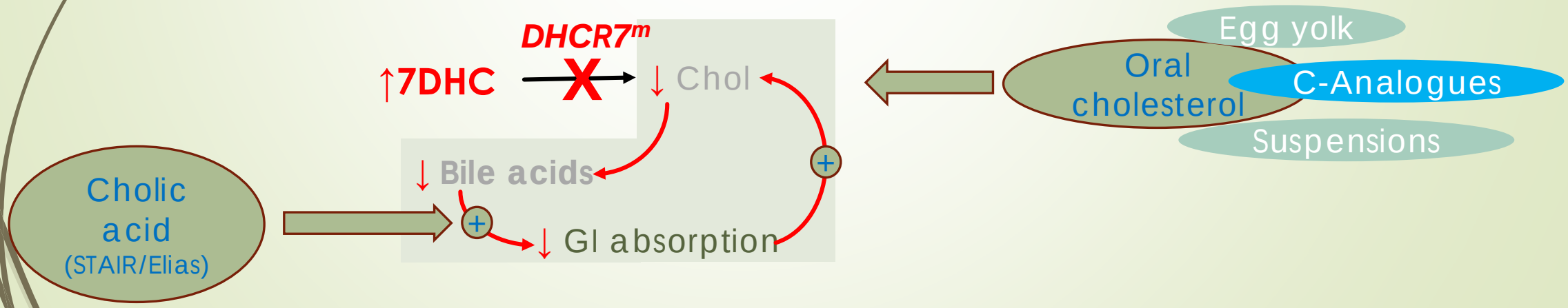
Human fibroblast-derived iPSCs



Francis, *Nature*, 2016

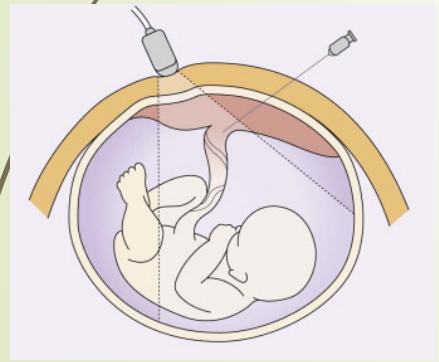
Cholesterol/Bile acid supplementation studies (1)

- **1994**: design of oral cholesterol supplementation (Acosta)
- **1996, 1997**: treatment with cholesterol and bile acids (Ullrich, 1996; Nwokoro, 1997)
- **2004**: no improvement of development progress with cholesterol supplementation (Sikora)
- **2007**: partial rescue of retinal abnormalities with cholesterol (rat) (Fliesler)
- **2009 – 2014**: *Cholesterol supplementation intervention study (STAIR 7001 – Aborted by NICHD)*
- **2019 –**: *Bile acid treatment study [primary outcomes: cholesterol, 7DHC] (STAIR 7012, Elias)*
- **Ongoing**: *BBB-permeable cholesterol analogues* (*Steiner, Neurodel*)

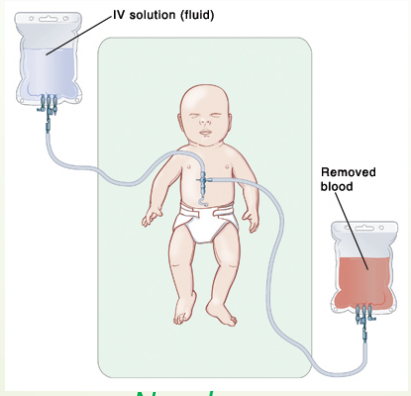


Cholesterol supplementation studies (2)

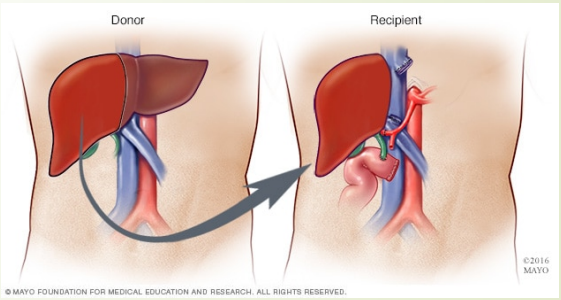
- **1999**: Antenatal therapy with fetal i.v. and i.p. transfusion of fresh frozen plasma (*Irons*) *[feasibility]*
- **2014**: Fresh frozen plasma transfusion in SLOS newborn (*Boctor*) *[feasibility]*
- **2019**: liver transplant in a young boy (6 months?) – remarkable increase in metabolic profile and fine motor skills (tacrolimus) (*Ertugrul*)



Fetus



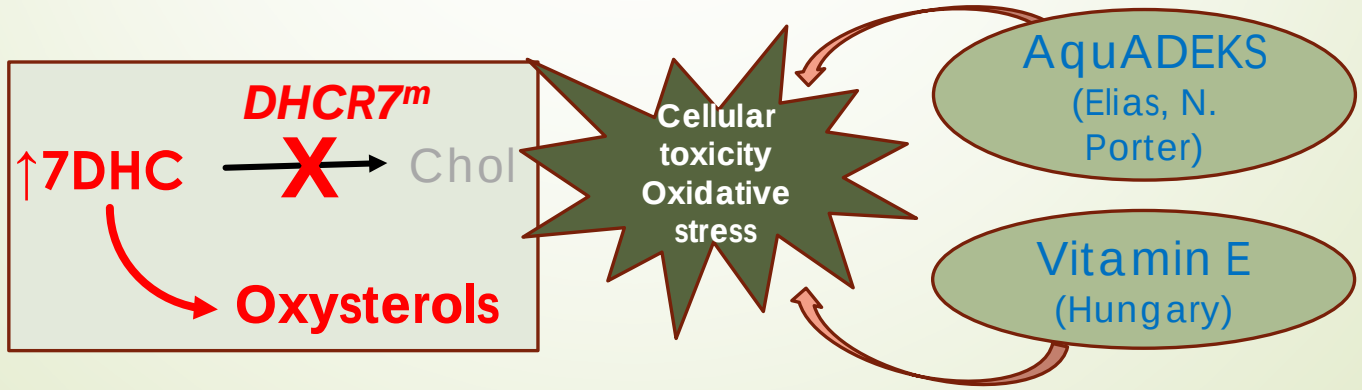
Newborn



Infant

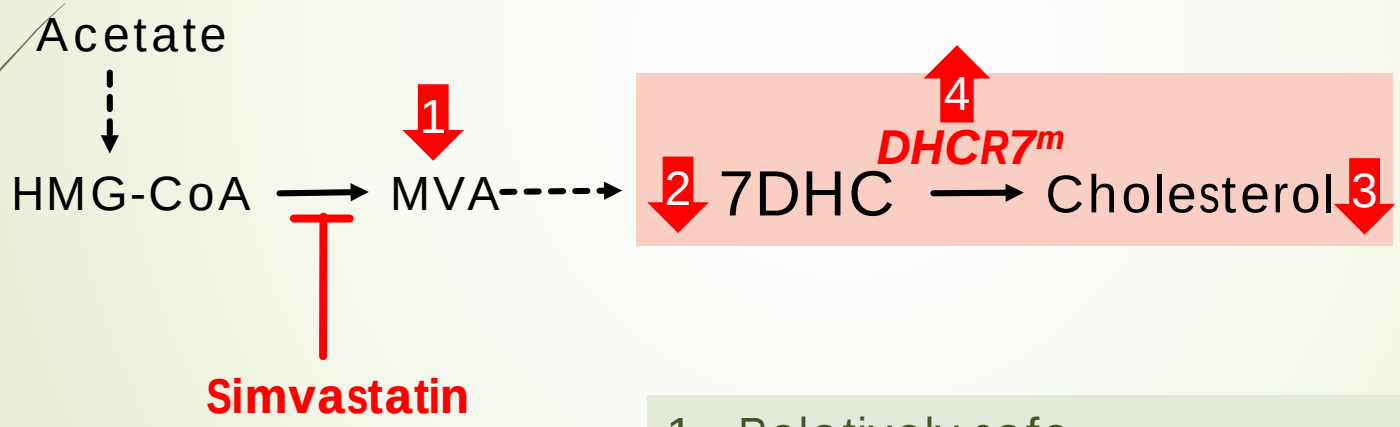
Antioxidant studies (~20 Years)

- **1998**: Skin photosensitivity – 7DHC (Charman)
- **1999**: 7DHC-derived oxysterol toxicity in rat (Gaoua)
- **2001**: Oxysterols in patients' plasma (Björkhem)
- **2012**: Oxidative stress markers in the rat (Korade)
- **2013**: Antioxidant supplementation in cells and mouse – vitamin E (Korade)
- **2013 - present**: *Cholesterol & Antioxidant Treatment in Patients with SLOS (Elias, N. Porter)*
- **Ongoing (in Hungary):** *3-year prospective study (n = 6 patients) with antioxidant (vitamin E): positive clinical signs observed in 3/6 patients with low baseline 7DHC/cholesterol ratio (comm. by Dr. Korade)*



7-DHC Modulator Studies – Simvastatin (16 Years)

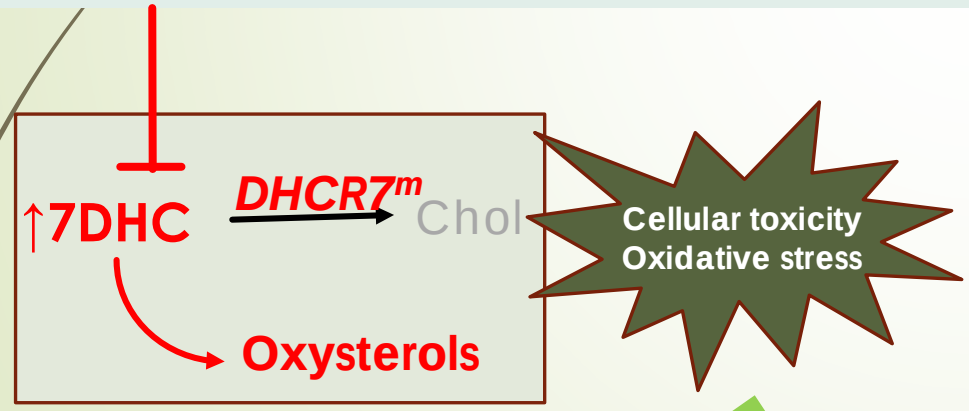
- **2000**: Proposed therapy with simvastatin (Jira)
- **2016**: *Simvastatin study in patients receiving cholesterol supplementation (Wassif, Genet. Med., 2016)*



1. Relatively safe
2. Improves 7DHC/Chol ratio
3. Improves irritability symptoms in some patients

7-DHC Modulator Studies (2)

- **2005/2010**: modulation of DHCR7 by antipsychotic/antidepressant drugs (clozapine/CPZ/haloperidol) (Fernø, 2005; Lauth, 2010)
- **2013**: antidepressants (aripiprazole, trazodone) increase 7DHC (Hall)
- **2016: screening of small molecules capable of decreasing 7DHC in DHCR7-deficient cells (Korade)**
- **2018**: recently approved psychotropic drugs (brexpiprazole, cariprazine) increase 7DHC in cells and mice (Genaro-Mattos)



- **2017**: susceptibility of mutation carriers (1-3% of population) to psychotropic drugs that increase 7DHC (fibroblasts) (Korade)
- **2019**: maternal exposure to psychotropic drugs alters embryonic development (mouse studies) (Genaro-Mattos)

7-DHC Modulator Studies: Take home message

- Simvastatin may not provide significant clinical benefits
- Some drugs used in patients or carriers increase 7DHC - clinical toxicity needs to be carefully examined
- Other drugs decrease cellular 7DHC – *PROMISING* research *BUT* potential clinical benefits need to be evaluated

Other Research with therapeutic potential

Gene *(DHCR7)* Therapy

- **2005**: Beginning of gene rescue attempts (mouse) (*Yue*)
- **2010**: Gene therapy study in the mouse with AAV/i.v. (*Matabosch*)
- **2014**: Gene therapy in the mouse with AAV/i.v. – systemic but no brain effect on cholesterol (*Ying*)
- **2015**: Gene therapy in the mouse with AAV/intrathecal inj. – partial rescue of brain cholesterol (*Pasta*)

Other potential therapeutic targets

- **2008**: Placental **ABCA1** as potential target for in utero therapy of SLOS (*Lindergaard*)
- **2013**: **ABCA1** is a genetic modifier of SLOS clinical severity(*Lanthaler*)
- **2016**: **Wnt/β-catenin** pathway (*Francis*)

The Future: Gene Editing?

- Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-318 in Subjects With MPS I, ClinicalTrials.gov Identifier: NCT02702115
- Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-913 in Subjects With MPS II, ClinicalTrials.gov Identifier: NCT03041324

Clinical Studies Registered at https://clinicaltrials.gov

Status	Study title	Intervention, enrollment, age	Locations	Contacts
Active studies				
Not Yet recruiting	SLOS and Cholic Acid	Cholic acid N = 15 2-25 years	Colorado Children's Hospital, UNMC, CCHMC, CHP	Ellen Elias, MD; 720-777-5401; Ellen.elias@childrenscolorado.org
Recruiting 2008 - present	Cholesterol and Antioxidant Treatment in Patients with SLOS	AquADEKS N = 100 0 – 65 years	Colorado Children's Hospital	Ellen Elias, MD; 720-777-5401; Ellen.elias@childrenscolorado.org
Recruiting 1998 - present	Study of Smith-Lemli-Opitz syndrome	Observational N = 200 0 – 100 years	NIH	Forbes D. Porter, MD; 301-435-4432; fdporter@mail.nih.gov Margarita Raygada, PhD: 301-451-8822; mr346@nih.gov
Completed, terminated studies				
Terminated 1995-2014	Dietary cholesterol for Smith-Lemli-Opitz syndrome	Cholesterol/Chol-free ~30 (?) patients enrolled	OHSU	Robert Steiner, MD
Completed 1998-2011	Treatment of the cholesterol defect in SLOS	Crystalline cholesterol oil-based suspension (23 patients enrolled)	Boston Children's Hospital	Mira Irons, MD
Completed 2003 - 2010	Simvastatin therapy in SLOS	Simvastatin (cross-over; placebo-controlled) 23 patients enrolled	NICHD	Forbes D. Porter, MD
Completed 2005-2009	Short-term behavioral effects of cholesterol therapy in SLOS	On/Off-cholesterol supplementation (egg yolk)	NICHD	Forbes D. Porter, MD
Completed 2009-2013	Cholesterol in autism spectrum disorders	[efficacy of cholesterol supplementation	NIH	Forbes D. Porter, MD
Terminated 2009-2015	STAIR 7001	Dietary cholesterol (egg, suspension) (21 patients enrolled)	OHSU, CCHMC, UPMC, U Manitoba, NICHD	Robert Steiner, MD Jean-Baptiste Roullet, PhD

SLOS-Relevant funded NIH Research studies

(NIH RePORTER Database – Active Projects)

Grant type	Title	PI	Location	Institute	Amount
5R01ES024133-03	Sterols, neurogenesis and environmental agents	Ned Porter	Vanderbilt University	NIEHS	$353,250
5R01HD064727-09	SLOS and neuronal environmental stress	Ned Porter	Vanderbilt University	NICHD	$432,819
5R01HD092659-02	Oxysterols in SLOS neurodevelopment: pathological role and therapy	Libin Liu	University of Washington	NICHD	$391,101
5R01HL122906-03	Mechanisms of DMP development and atrioventricular septation	Arno Wessels	Medical University of South Carolina	NHLBI	$373,750
5U54 HD061939-10	*Sterol & Isoprenoid Research (STAIR) consortium*	*William Rizzo*	*UNMC*	*NICHD/NCATS*	*$600,000*
1ZICHD0088921-07	Gene function, expression and regulation in zebrafish	Carmen Feldman	NIH	NIDCD	$1,144,874
1ZIAHD008825-12	Clinical investigations of Smith-Lemli-Opitz syndrome	Forbes, D. Porter	NIH	NICHD	$1,070,046
1ZICMH002961-02	Neurodevelopmental and behavioral phenotyping	Audrey Thurm	NIMH	NIMH	$373,750
P20GM10362006	Regulation of cell fate and function by sterol homeostasis	Kevin Francis	Sanford Research/USD	NIGMS	$304,319

*, DMP: Dorsal Mesenchymal Protrusion

Research Support by the SLO/RSH Foundation: 2009 - 2019

On-going research supported by the Foundation

2018 Steroid phosphoesters (ionotropin) in SLOS and carriers	Fred Chasalow, PhD (IOMA LLC)	$10,000
2018 Utilizing SLOS patient-derived iPSCs to investigate the therapeutic potential of small molecule modulation of Wnt signaling	Jordan Sheets, PhD, Kevin Francis, PhD (Sanford Health)	$25,000
2018 Development of CTA-1 and 2 as Therapeutic Agents for Treatment of Smith Lemli Opitz Syndrome	Roman Bielski, PhD, Robert D Steiner, MD (Neurodel, VALUEDsolutions LLC)	$25,000

Grant Review Process

- Potential **significance** of the research
- **Feasibility** of the project given the investigators involved and the resources to be used
- **Likelihood that long-term funding** can be obtained for additional research

Previous research funded by the Foundation *(past decade)*

2015 Travel grant (for patients to participate in STAIR 7001)	Roullet (WSU)	*[$23,000]*
2009-2013 STAIR Consortium (Training, Cholesterol intervention study)	Steiner, Roullet (OHSU)	$125,000
(2013) Proteomics of Cerebrospinal Fluid in SLOS	Stephanie Cologna (NICHD)	$15,000
2009 Placental Cholesterol Homeostasis	Laura Woollett (CCHMC)	$37,500
2010-2011 [*Growth charts/Brain imaging*]	Ryan Lee (KKI)	$48,000

Emotional experience in parents of children with Zellweger spectrum disorders: A qualitative study (STAIR Trainee Mousumi Bose, 2019)

- nearly a third of ZSD caregivers described their overall emotional experience as a “rollercoaster.” Feeling overwhelmed and devastated were the most frequently described emotional responses.
- The *most common coping strategies* were acceptance of limitations of the diseases, redefining “normal” in the parenting experience, and advocating on behalf of the child and the patient community.
- This study underscores the profound emotional impact on parents who are caregivers for children with ZSDs, highlighting the utility of patient community feedback and qualitative approaches to fully characterize the overall family experience.
- Simple, targeted approaches focusing on improved communication between healthcare professionals and families, as well as offering resources for emotional support may greatly improve the lives of families living with ZSD and other rare pediatric diseases.

https://www.sciencedirect.com/science/article/pii/S2214426919300060

Some Take home messages…..

- Significant progress on many fronts in the past 55 years (clinical, molecular/metabolic mechanisms; identification of oxysterols as potential therapeutic targets, development of cellular and animal-based drug screening tools)
  - Continue supporting research on pathogenesis – will lead to the identification of new therapeutic targets
- No comprehensive characterization of SLOS natural history
  - *Need to further engage the patient community in natural history studies, supporting central biorepository, expanding QOL research…*
- No cure, no targeted therapeutics, uncertainty about effectiveness of cholesterol supplementation
  - *Continue supporting research with therapeutic potential*
- Trend toward decrease in SLOS research publications in the past 5 years
  - Consider teaming up with other Patient Advocacy Groups representing other rare diseases caused by sterol disorders or other rare disorders to increase representation and raise more funding.