

# Therapeutic Drug Development For Rare Diseases Implications for SLOS

***Robert D. Steiner, MD***

**Geneticist and Medical Director, Marshfield Clinic Health System**

**Chief Medical Officer, PreventionGenetics**

**Neurodel Alliance, a tTAp initiative**

**Professor (Clinical) University of Wisconsin**

**Editor in Chief, *Genetics in Medicine***

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**<https://www.fda.gov/media/91349/download> good resource**

# Rare (Orphan) Diseases Background

## RARE DISEASES by the numbers



RARE DISEASES AFFECT

**30 MILLION**  
AMERICANS

THAT'S 1 IN 10



APPROXIMATELY  
**7,000**  
DIFFERENT RARE DISEASES  
EXIST TODAY

THE FDA HAS APPROVED  
**NEARLY 500 ORPHAN DRUGS**  
SINCE THE PASSAGE OF  
THE ORPHAN DRUG ACT



IN THE LAST 5 YEARS



OF ALL NEW DRUG  
APPROVALS WERE FOR  
**RARE DISEASES**



**80%** OF RARE  
DISEASES  
ARE GENETIC IN ORIGIN



APPROVED TREATMENTS  
ARE AVAILABLE  
FOR ONLY **5%** OF  
ALL RARE DISEASES

THERE ARE  
MORE THAN

**450**  
**MEDICINES**  
IN DEVELOPMENT  
FOR RARE DISEASES

# WHAT IS THE ORPHAN DRUG ACT?



1983

The Orphan Drug Act (ODA) of 1983 is a federal law that incentivizes biopharmaceutical companies to develop drugs and biologics, known as “orphan drugs,” for individuals with **rare diseases**.



A RARE DISEASE IS ANY CONDITION AFFECTING FEWER THAN **200,000** AMERICANS

## HOW DOES THE ORPHAN DRUG ACT WORK?

There are **4** INCENTIVES in the law that encourage biopharmaceutical companies to develop orphan drugs.

**7** YEARS OF EXCLUSIVITY that prevent competitors from selling the same product

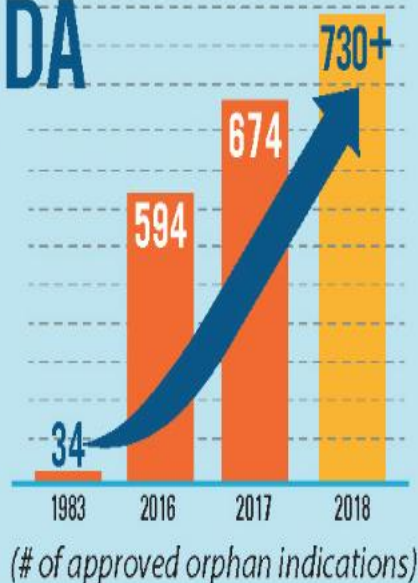
**25%** TAX CREDIT for qualified clinical testing expenses incurred in clinical trials

~ **\$18** MILLION in FDA research grant funding

~ ~~**\$2.5**~~ MILLION FDA user fees waived

HAS THE ODA  
WORKED?

YES!



BUT APPROXIMATELY

95% of rare diseases are still without any FDA-approved treatment.

PLEASE SUPPORT THE  
ORPHAN DRUG ACT!

Source: FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, IQVIA Institute, Sep 2018 for Human Data Science.

Note: The graphic was created using a curated list of indications and approvals based on the FDA Orphan Drug Database. Includes drug approvals through Aug 2018. ©2018 NORD. All rights reserved. NORD® and RareInsights® are registered trademarks of The National Organization for Rare Disorders. NORD is a 501(c)(3) charity organization. For more information, visit: [rarediseases.org](http://rarediseases.org). NRD-1159



# DRUG DEVELOPMENT PROCESS

Out of every 10,000-15,000 new compounds identified during discovery, **five are considered safe for testing** in human volunteers. **Only one of these compounds** is typically approved as a marketed drug.



**AVERAGE COST:** \$1 billion+

**DURATION:** 10-15 years\*

**PPD**

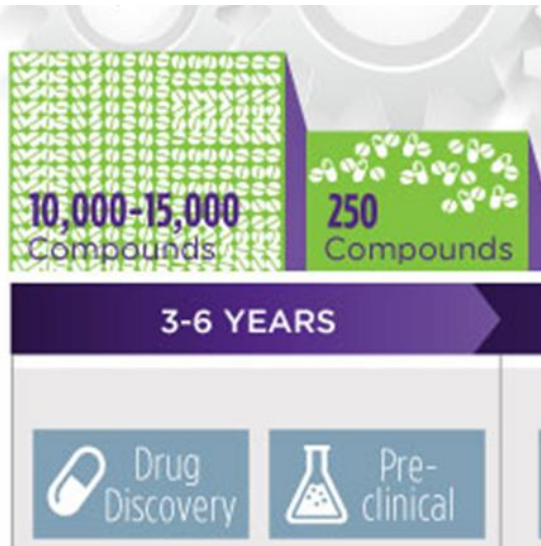
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# FDA Orphan Drug Act

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- Taking a drug to market (FDA marketing approval) can cost BILLIONS
  - Rare disease patient advocates, legislators worked with FDA to create the Orphan Drug Act to encourage Pharma to develop drugs for rare diseases which otherwise might not be profitable
  - Orphan Drugs
    - Those for whom the # patients with the disease is smaller
- Orphan Disease: "A disease or condition affecting <200,000 persons in the US"  
(In reality most rare diseases far less prevalent)
- Giving companies who develop them
    - Paths to shorten/simplify the development timeline
    - Providing them longer term protection to economically recapture the costs of development, tax incentives, etc.

# Drug Discovery: Early stage, not very visible



Highly scientific, carried out by scientists dedicated to research in academia or pharma

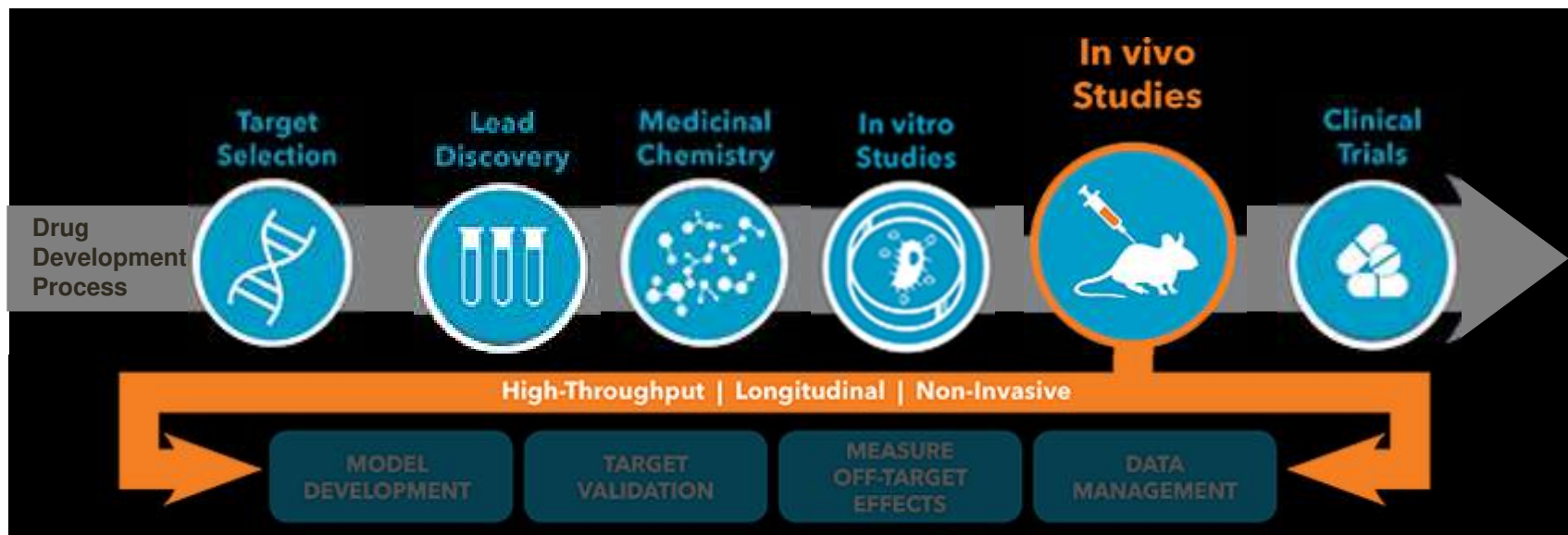
1. Theoretical research based on concepts trying to understand disease
2. Proof of Concept testing:
  - laboratory in test tubes
  - animals

Development of initial, foundational base  
Intellectual Property (IP) created (patent)

Approach for Rare Diseases is typically Opportunistic ---- *Leveraging off findings from other research*  
Futuristic ---- *Demonstrating something that can be useful for a larger disease area in the future*

# Goal: screen “ideas” to test in patients

- Can we model disease? Cell or animal
- Does drug perform as expected?
- Does it cause harm? Toxic? Unexpected side effects?
- Funding critical! Will studies be strong enough to convince others (e.g. grant funders, angel investors, universities, VC, patent office, tech. transfer office, pharma, etc)?

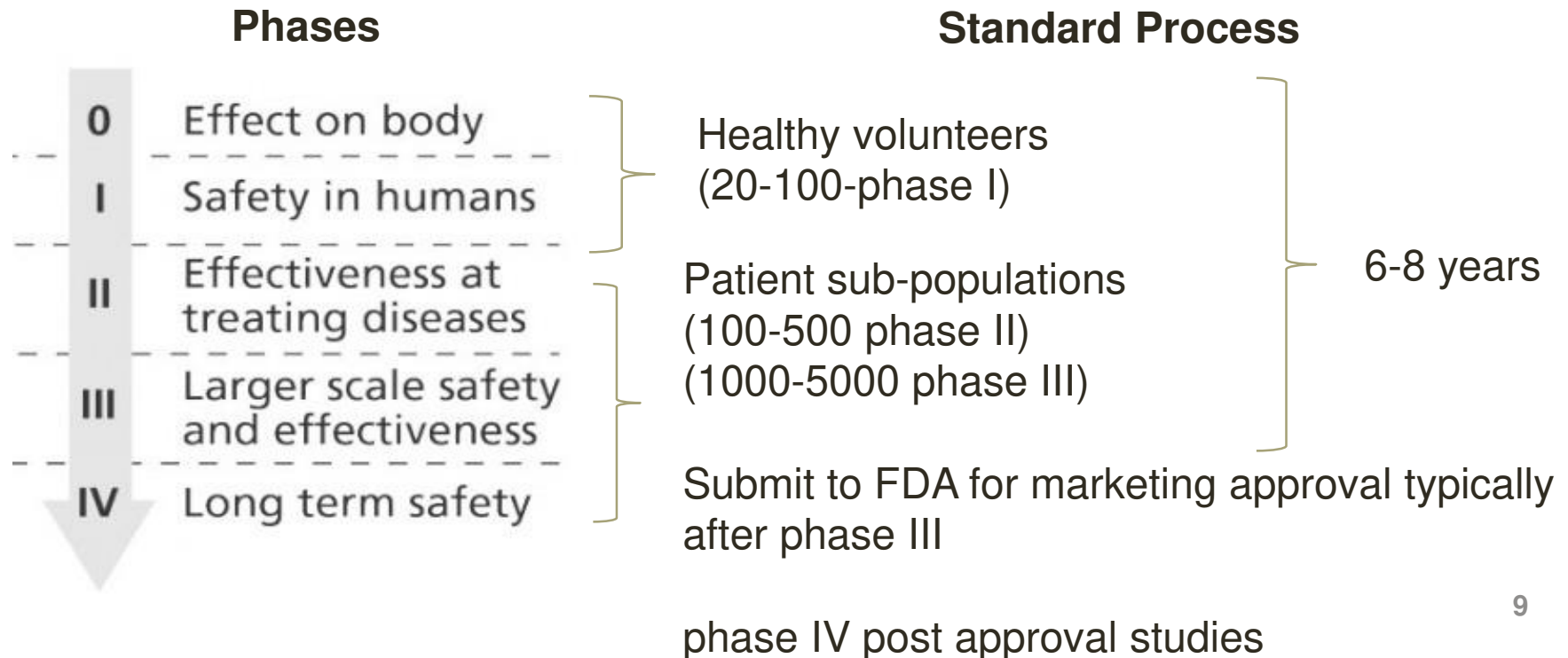




# Testing in humans done cautiously

Carried out under strict regulatory guidance

- IRB/Ethics Board: Institutional Review Board
  - Approval by hospital/institution that it is “reasonably” safe, the demonstration of prior work is compelling
- FDA: IND: Investigational New Drug application/approval
- Testing of drug done in stages...



# Rare disease challenges in drug development

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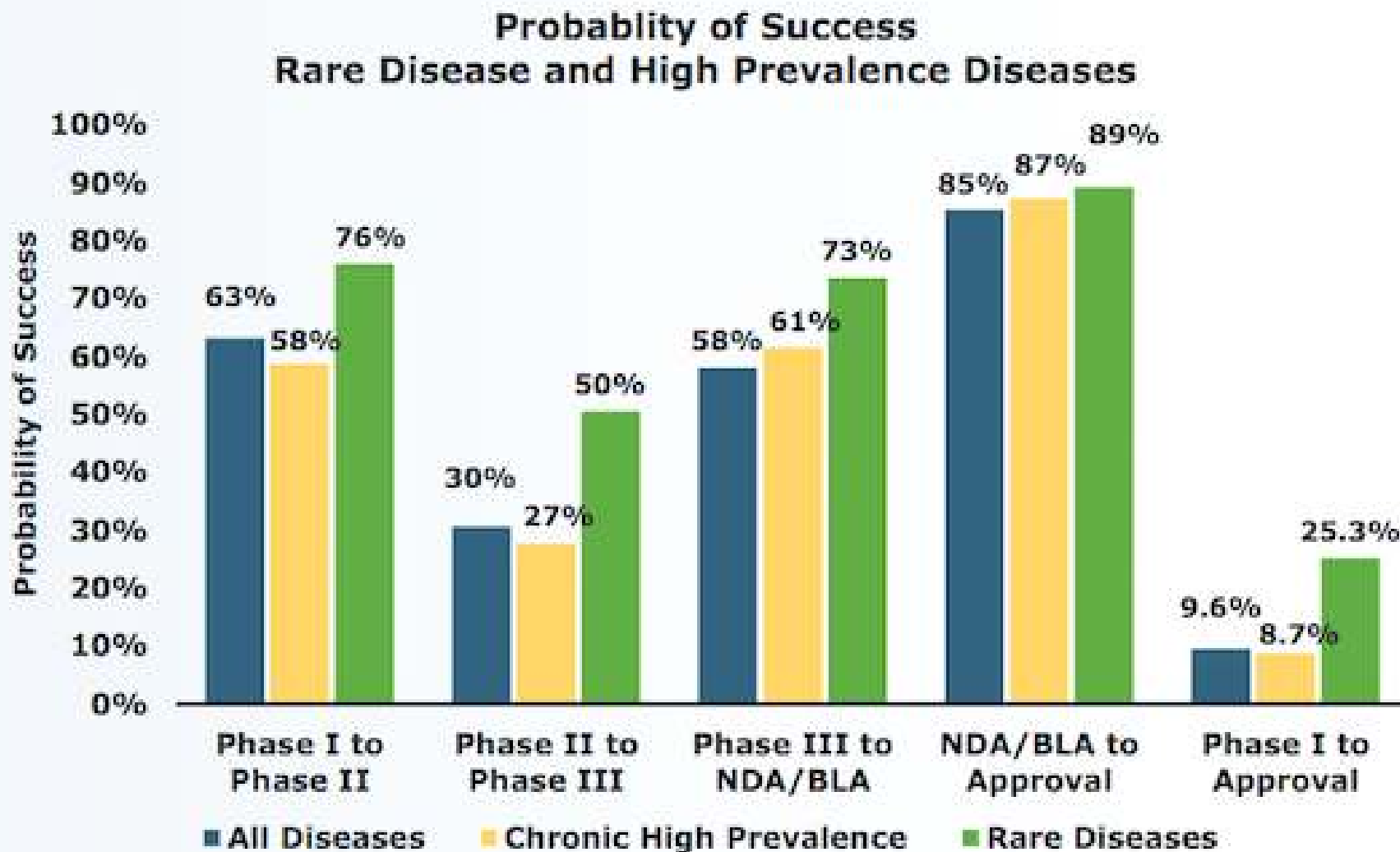
- Small populations
  - Limited # affected patients available to enroll in clinical trials
  - Few treating physicians, treatment centers
- Highly heterogeneous: Patients are affected differently
  - Wide range of severity, clinical presentation, rate of progression
  - Less well understood, natural history incompletely described
- Most serious or life-threatening,
  - Most have significant unmet medical needs
  - Lack regulatory/drug development precedent
- Unclear clinical trial outcomes to measure, validated means to measure them
- Many affect children, patients predominantly pediatric
  - Additional ethical considerations, constraints

# Addressed by modifying clinical trial requirements

Phases	Standard Process (6-8 years to approval)	<u>Can Propose</u> for Rare Diseases (~2-3 years)
I Safety in humans	Healthy volunteers (20-100-phase I)	Affected Patients
II Effectiveness at treating diseases	Patient sub-populations (100-500 phase II)	Combined phase I/II -w/ small patient sample (10-12) - <b>May seek FDA approval</b>
III Larger scale safety and effectiveness	Patient sub-population (1000-5000 phase III) <b>Submit to FDA after phase III</b>	Simplified phase III IF required - Not randomized Rx vs. no Rx - 20-150 patients
IV Long Term Safety	phase IV are post approval studies	Phase IV often required post approval

**SMALLER AND FASTER**

# Drug development probability of success



# Current treatment, clinical management of SLOS

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- 1. Oral cholesterol supplementation often used (egg yolk, cholesterol suspension, commercially available cholesterol formulations), so far no evidence cholesterol supplementation is effective “treatment”**
- 2. Cholesterol-lowering drugs (statins) have been tried based on animal & human cell studies showing statins increase DHCR7 activity, reduce 7DHC accumulation (see results from Porter study)**



**No effective specific treatment, no cure to date**

# Goals of SLOS Treatment

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↑ Increase brain cholesterol

↓ Decrease 7-DHCs



- Feeding, growth
- Development, cognition/IQ
- Behavior
- Autistic features

# SLOS treatment ideas

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## Cholesterol administration:

- Dietary
- Highly concentrated IV cholesterol (e.g. from FFP, apheresis)

## Applied therapeutics:

- Statins/ Antioxidants/ Bile acids

## Cholesterol or Enzyme delivery to brain

- Across BBB/ propagation in brain (Stem Cells)

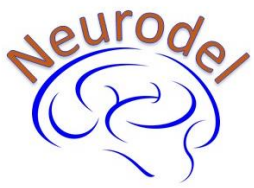
## Prenatal Rx:

- Maternal high cholesterol diet
- Cholesterol delivery to amniotic fluid or fetus (umb. vein, IP)

Organ/Bone Marrow Transplant, Gene therapy

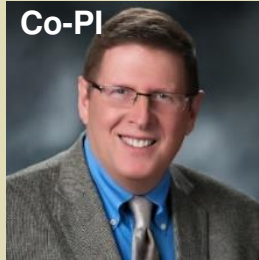
# Our Current Collaborative Research





# Bringing cholesterol to the brain - to treat SLOS

**CLINICAL NEED:**  
Deliver cholesterol  
to the brain



Robert D Steiner, MD,  
Pediatrician/Geneticist  
Univ. of Wisconsin



Craig Smith, MS  
Product Development  
(ex. Sanofi)

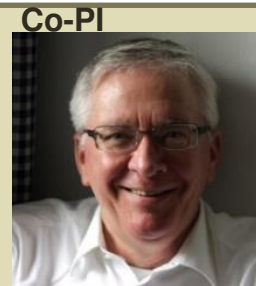


**SOLUTION EXPERTISE:**  
How do we get a  
compound in the brain

And to release  
cholesterol



ZJ Wbigniew, PhD  
Chemist

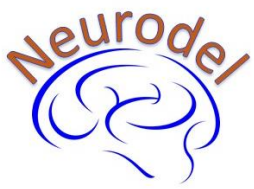


Roman Bielski PhD  
PI – Bio Chemist



Caroline  
Hoedemaker  
Business  
Management  
(ex J&J, etc  
tTAp exec.)

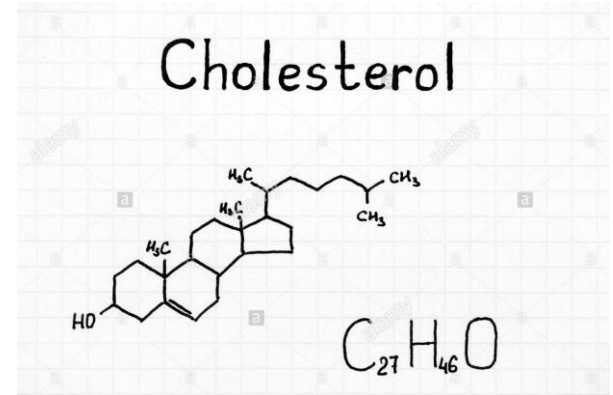
**Thank you for the 2018 SLOS/RSH Foundation grant  
permitting our work!**



# Concept – Increase cholesterol in the brain

## CHALLENGE:

1. Free cholesterol circulating in the blood cannot cross Blood Brain Barrier (BBB)
2. For SLOS patients there is not enough cholesterol in their brain



## Neurodel - IDEAL COMPOUND:

1. Is delivered via injection (or orally)
2. Travels over the Blood Brain Barrier
3. Increases brain based cholesterol
4. Cholesterol is then available for cellular interaction in the brain



# Specific Aims of Neurodel/SLOS Foundation Grant

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*GOAL: INITIAL PROOF OF CONCEPT*

*DRUG MODIFICATIONS AS NEEDED*

- *Cholesterol Increase:*

- Quantify the degree to which a therapeutic increases cholesterol in the brain
- Successful achievement of this aim will indicate the ability of the therapeutic agent(s) to increase cholesterol in an environment simulating brain chemistry

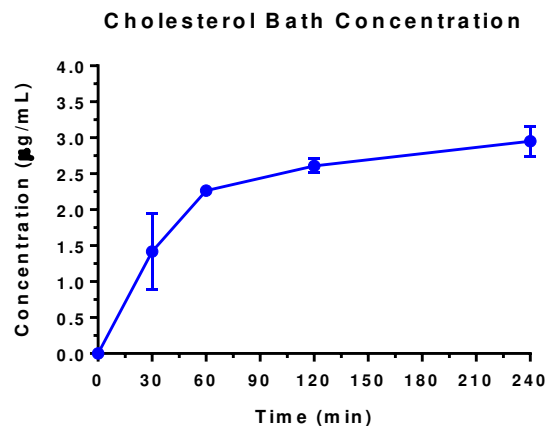
- *Therapeutic Delivery across the BBB:*

- In mice determine the accumulation of cholesterol in brain tissue following IV administration of the more promising compound
- Successful achievement of this aim will indicate the ability of the lead compound to successfully reach the brain following delivery of the therapeutic agent(s) intravenously and increase brain cholesterol

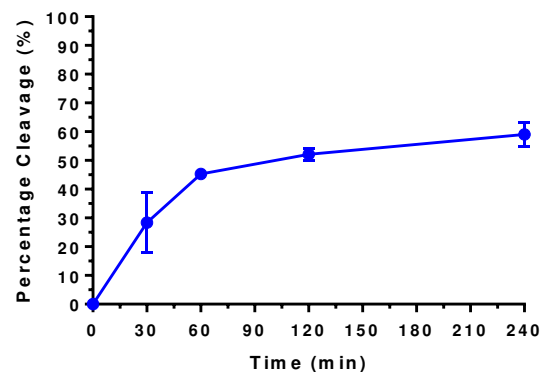
# Will the compound increase Cholesterol?

(In Vitro (ie. test tube) Assessment)

Our lead compound was put into a test tube simulating brain chemistry

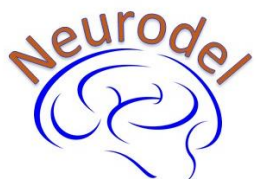


Showed an increase of Cholesterol from 0 over 4 hours



Showed what percentage of the compound was used to increase Cholesterol

Under in vitro, cell free conditions, well over half of the compound was used to increase cholesterol in a measurable fashion



# Status and Next Steps

Stage of Drug Development	Key testing model	Task achieved/proven
Hypothesis	Chemical Development	ND001, ND002 synthesis
Proof of Concept	In Vitro (test-tube)	-Increases brain based cholesterol -Stability of compound -Reproducibility of compound
	In Vivo (normal mice)	-Stability in Blood -Cross the Blood Brain Barrier
Optimization	-Chemical development and repeat testing of variations - GMP manufacturing	Stability, performance, half life, ADME: absorption, distribution, metabolism, elimination etc
Safety and Toxicity studies	In Vivo (normal mice) In Vivo (SLOS model mice, rats)	Standard tests Cause no harm
Phase I clinical study	Humans	

**Status** →

# Other Current SLOS Research

# Clinicaltrials.gov is a place to look

https://clinicaltrials.gov/ct2/results?cond=Smith-Lemli-Opitz+Syndrome&term=&cntry=&state=&city=&dist=

Apps Box.Censa Imported From Sa... Acer

Home > Search Results

Modify Search

Start Over



14 Studies found for: **Smith-Lemli-Opitz Syndrome**

List

By Topic

On Map

Search Details

Download Subscribe to RSS

Hide Filters

Filters

Apply

Clear

Status

Recruitment ⓘ :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated

Showing: 1-

10 of 14 studies 10 studies per page

Row	Save	ed	Status	Study Title	Conditions
1	<input type="checkbox"/>		Not yet recruiting	<a href="#">Smith-Lemli-Opitz Syndrome and Cholic Acid</a>	<ul style="list-style-type: none"><li>Smith-Lemli-Opitz Syndrome</li></ul>

Colorado Childrens, University of Nebraska, Cincinnati Childrens, Children's Hospital of Pittsburgh

# Can filter for recruiting studies

2 Studies found for: **Recruiting Studies** | Smith-Lemli-Opitz Syndrome

Applied Filters:

**Recruiting**

/ these search suggestions:



Search Details

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Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Recruiting	<a href="#">Cholesterol and Antioxidant Treatment in Patients With Smith-Lemli-Opitz Syndrome (SLOS)</a>	<ul style="list-style-type: none"><li>Smith-Lemli-Opitz Syndrome</li><li>Cone-Rod Dystrophy</li><li>Hearing Loss</li></ul>	<ul style="list-style-type: none"><li>Drug: Antioxidants</li><li>Drug: Cholesterol</li></ul>	<ul style="list-style-type: none"><li>Children's Hospital Colorado</li></ul>
2	<input type="checkbox"/>	Recruiting	<a href="#">Study of Smith-Lemli-Opitz Syndrome</a>	<ul style="list-style-type: none"><li>Abnormalities</li><li>Inborn Errors of Metabolism</li><li>Mental Retardation</li><li>(and 2 more...)</li></ul>		<ul style="list-style-type: none"><li>National Institutes of Health Clinical Center, 9000 Rockville Pike Bethesda</li></ul>

Antioxidants

Children's Hospital of Colorado

NIH

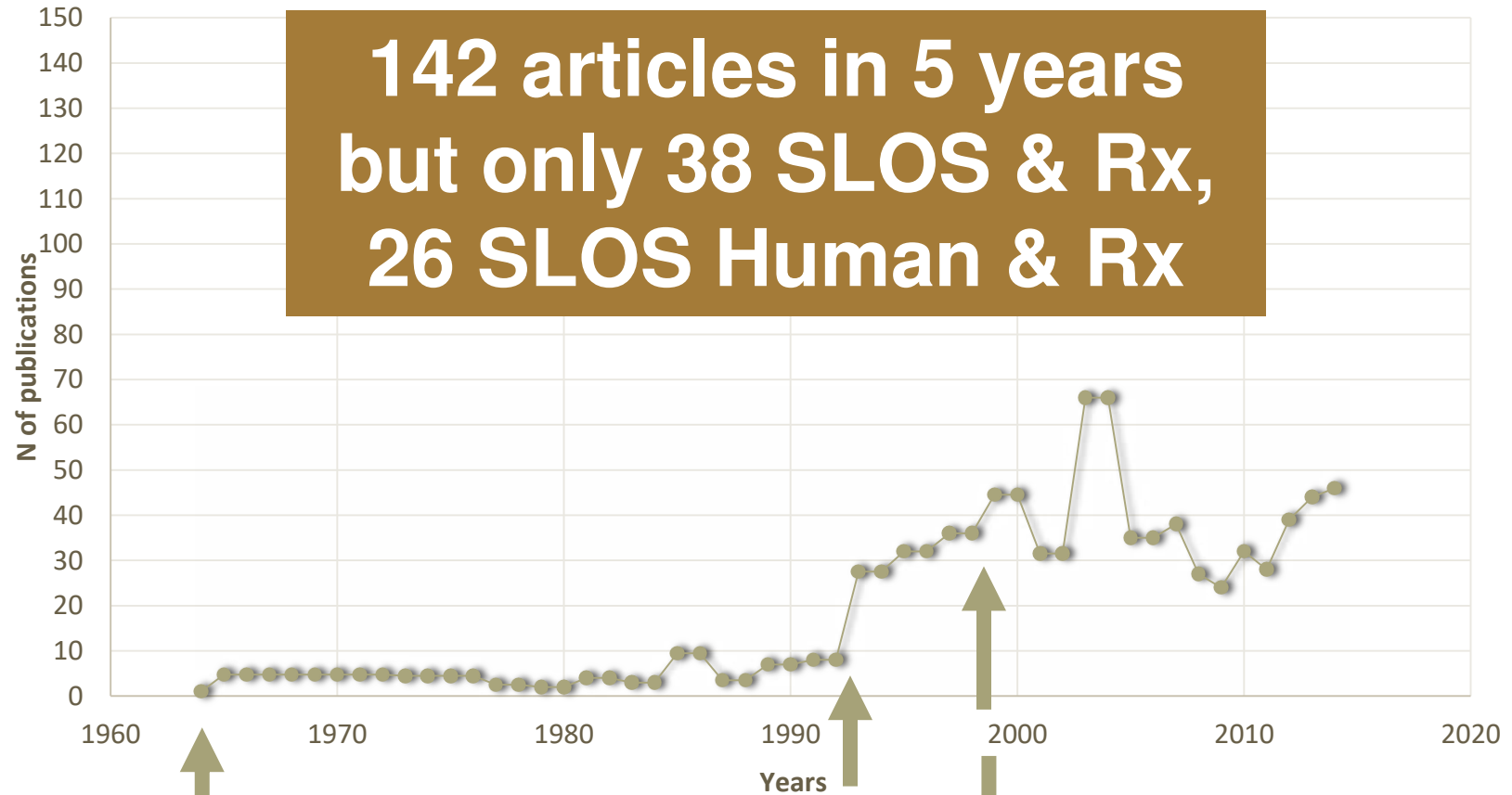


# Pharma beginning to show interest in SLOS

The screenshot shows a web browser window with the following elements:

- Browser Tabs:** "image improved life - Google Se...", "9 ways to support people living...", "Medications for the Treatment of...".
- Address Bar:** "https://www.sagerx.com/programs-research/neurologic-disorders/#anti-nmda-receptor".
- Website Header:** SAGE THERAPEUTICS logo on the left. Navigation links on the right: "Investors/Media", "Clinical Trials", "Contact Us", "Patients & Caregivers", "Healthcare Providers", "Therapeutic Focus", "Programs & Research", "About Us", "Working at Sage".
- Section Header:** "Cerebrosterol Deficit Disorders/Smith-Lemli-Opitz Syndrome" in white text on an orange background.
- Text Content:** "Cerebrosterol is a natural molecule that acts in the brain to enhance NMDA receptor activity. Several neurodevelopment genetic disorders that affect cholesterol metabolism, like Smith-Lemli-Opitz syndrome, are also associated with lower than normal levels of cerebrosterol. Lower activity of the NMDA pathway could explain the intellectual disabilities and behavior problems associated with these disorders, and suggests a potential therapeutic target."
- Footer:** SAGE THERAPEUTICS logo on an orange background.
- Privacy Notice:** "We have recently updated our Privacy Policy to include information regarding the cookies we collect. By continuing to use this website you agree to our [Privacy Policy](#) and [Terms of Use](#)." with an "ACCEPT" button.
- Taskbar:** Windows taskbar at the bottom showing icons for various applications and the system clock displaying "10:20 PM 6/10/2019".

# We still need more SLOS research



**142 articles in 5 years  
but only 38 SLOS & Rx,  
26 SLOS Human & Rx**

**1<sup>st</sup> Report  
(SLOS, 1964)**

**Defect in cholesterol  
synthesis  
(Irons, Elias, et al 1993)**

**DHCR7 Cloning,  
SLOS mutations  
(Moebius, Wassif, Fitzky, 1998)**

# The Importance of Research Funding

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- Challenges in SLOS
  - Small population
  - Diverse presentation, impact, life expectancy
  - Animal models imperfect
  - Challenging physiology (BBB)

- Needs in Research
  - Basic Understanding
  - Delivery
  - Animal Models

- Goal

- Find a Cure
- Improve Lives
- **Funding from Advocacy groups like yours absolutely critical!**

