Therapeutic Drug Development For Rare Diseases Implications for SLOS

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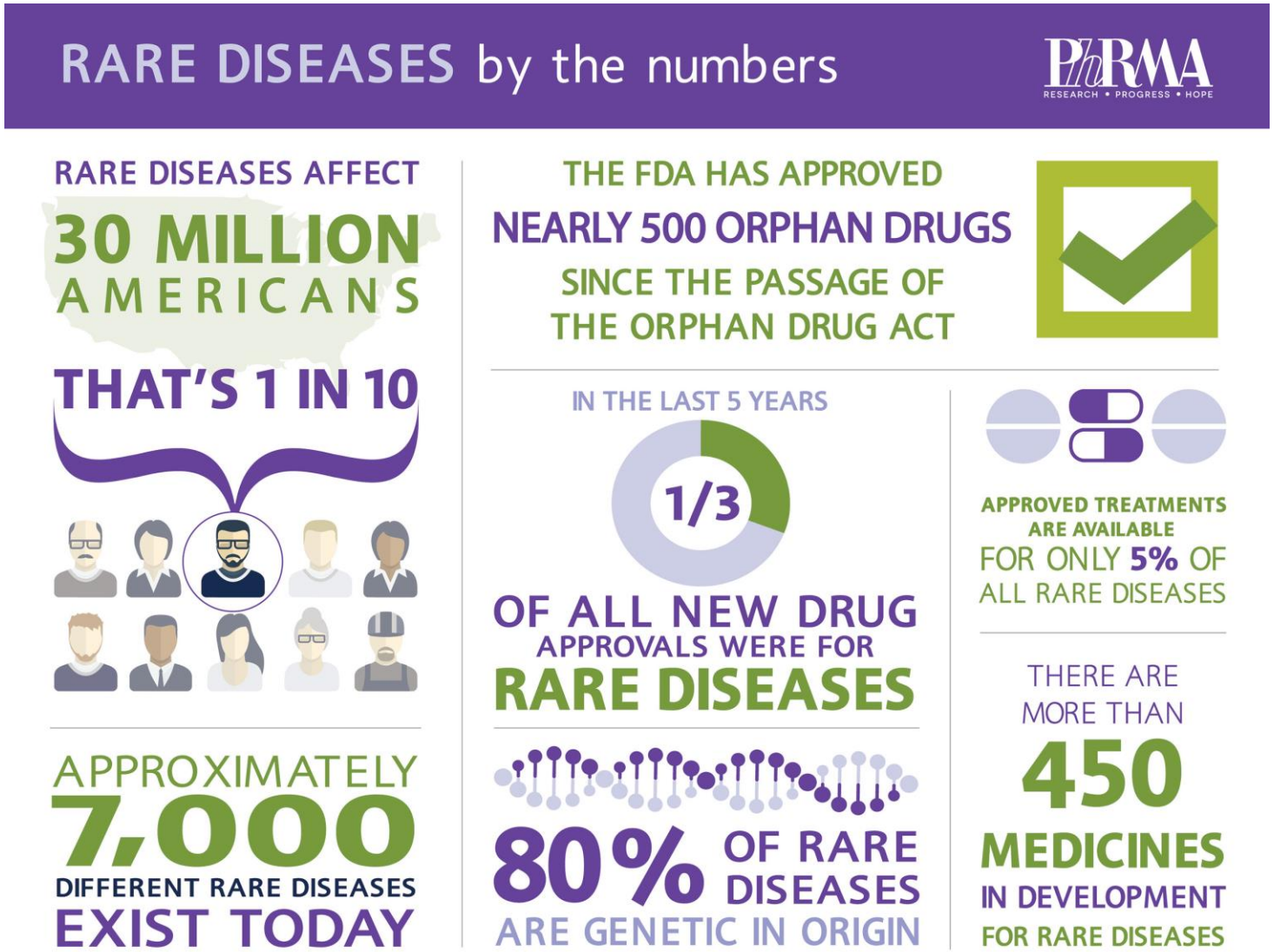
https://www.fda.gov/media/91349/download good resource

Rare (Orphan) Diseases Background



WHAT IS THE ORPHAN DRUG ACT?

NORD® RARE INSIGHTS®

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

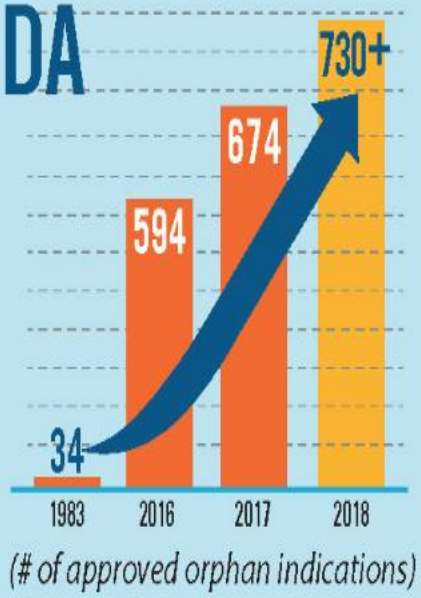
25% TAX CREDIT for qualified clinical testing expenses incurred in clinical trials

~$18 MILLION in FDA research grant funding

~$2.5 MILLION FDA user fees waived

HAS THE ODA WORKED?

YES!



(# of approved orphan indications)

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. NRD-1159

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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*

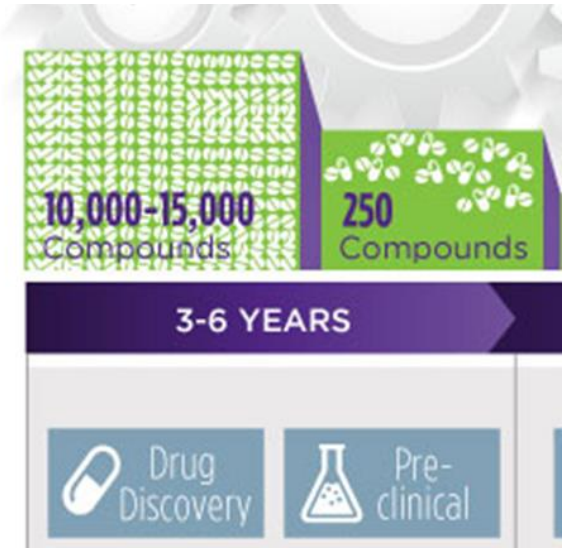
*Source: ACRO

FDA Orphan Drug Act

- 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)

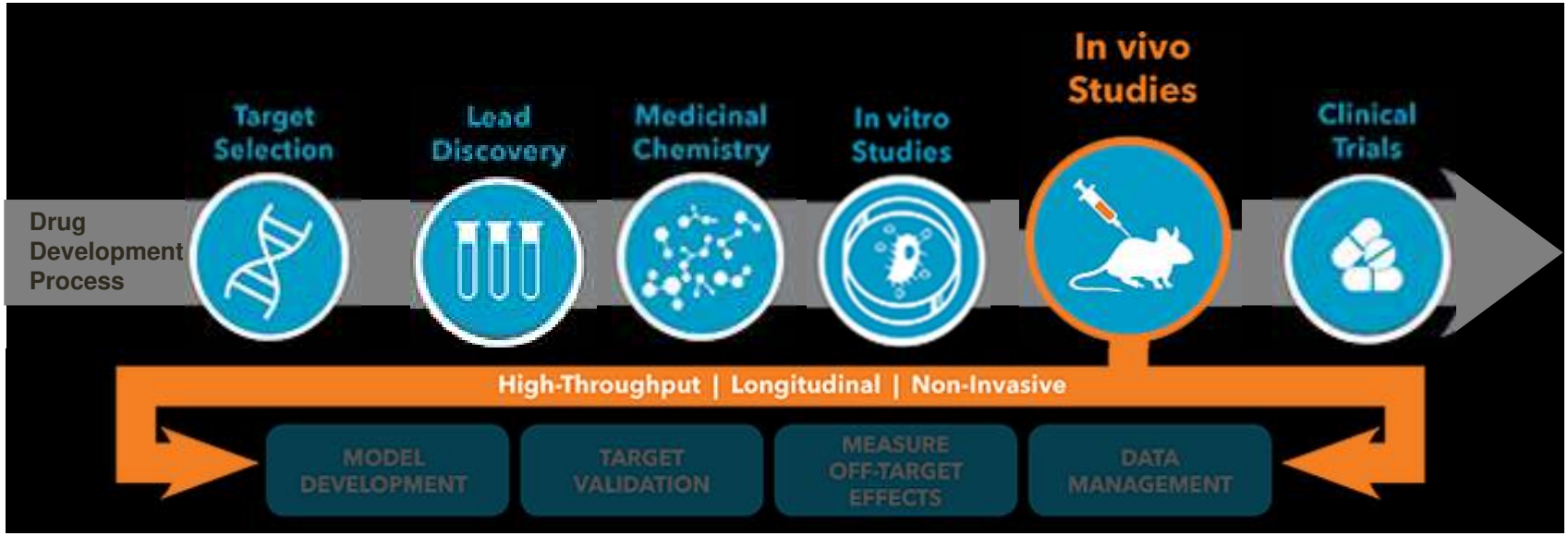
<u>Approach for Rare Diseases is typically</u>

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

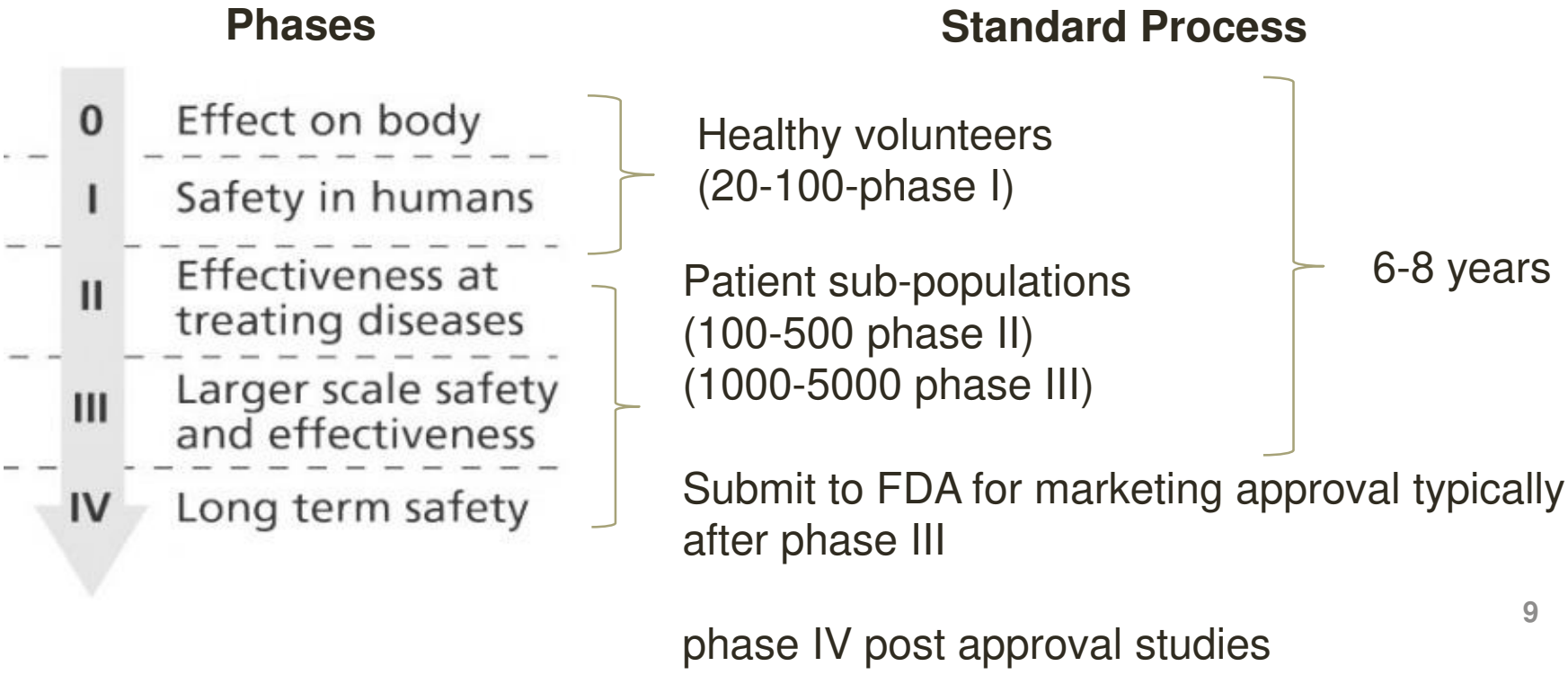
- Can we model disease? Cell or animal
- Does drug perform as expected?
- Does it cause harm? Toxic? Unexpected side effects?
- Funding critical! Will studies be strong enough to convince others (e.g. grant funders, angel investors, universities, VC, patent office, tech. transfer office, pharma, etc)?



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

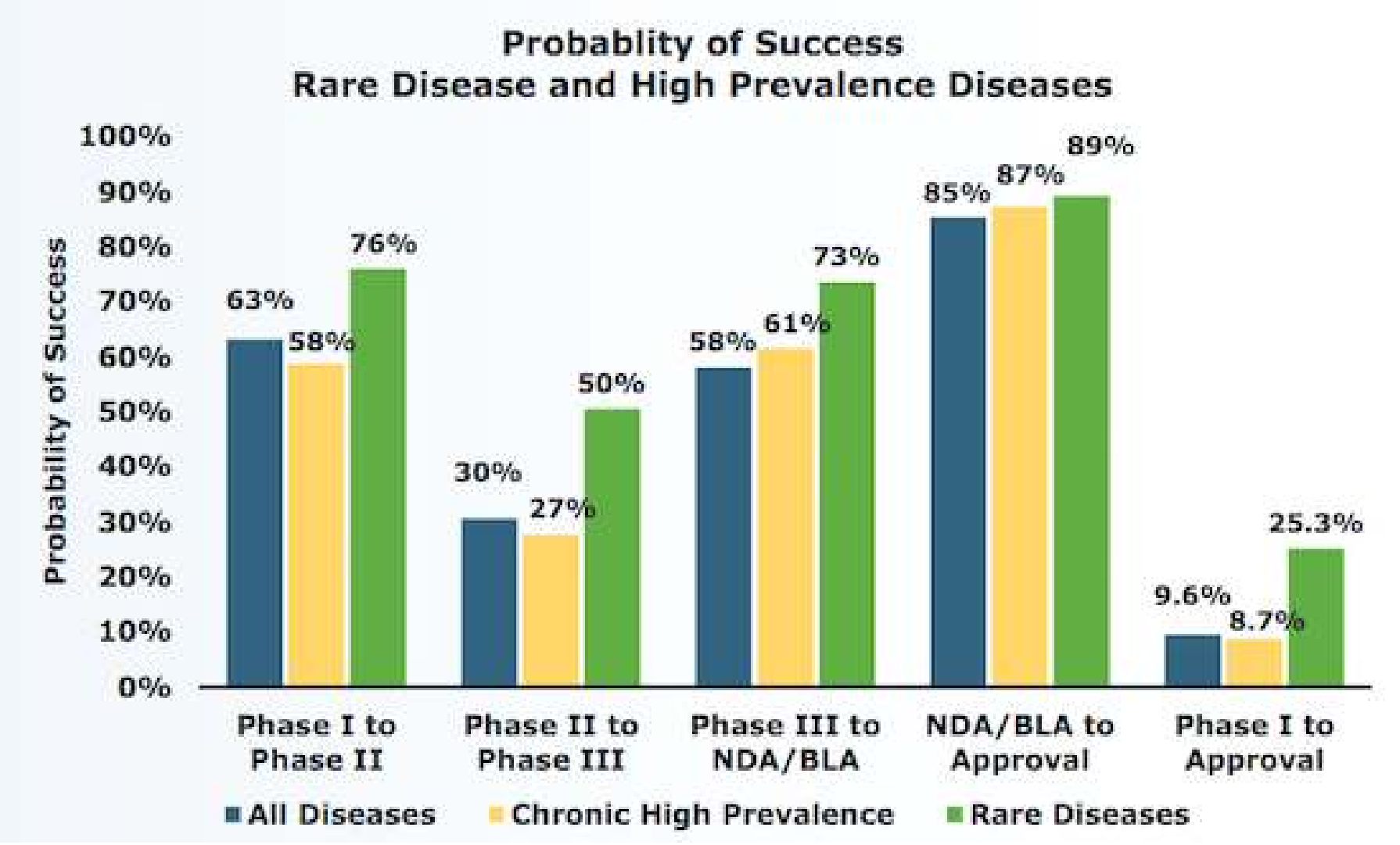
- Small populations
  - Limited # affected patients available to enroll in clinical trials
  - Few treating physicians, treatment centers
- Highly heterogeneous: Patients are affected differently
  - Wide range of severity, clinical presentation, rate of progression
  - Less well understood, natural 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)	Can Propose for Rare Diseases (~2-3 years)
I Safety in humans	Healthy volunteers (20-100-phase I)	Affected Patients Combined phase I/II -w/ small patient sample (10-12) - May seek FDA approval
II Effectiveness at treating diseases	Patient sub-populations (100-500 phase II)	
III Larger scale safety and effectiveness	Patient sub-population (1000-5000 phase III) Submit to FDA after phase III	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

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

↑ Increase brain cholesterol

↓ Decrease 7-DHCs

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

SLOS treatment ideas

Cholesterol administration:

- Dietary
- Highly concentrated IV cholesterol (e.g. fromFFP, 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

Co-PI

Roman Bielski PhD
PI – Bio Chemist

tTAp

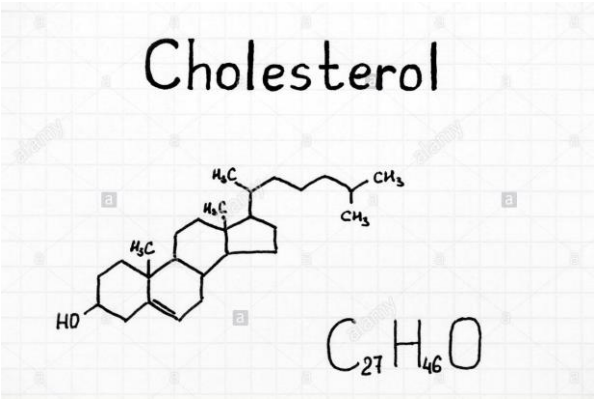
Caroline Hoedemaker
Business Management
(ex J&J, etc tTAp exec.)

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

Concept – Increase cholesterol in the brain

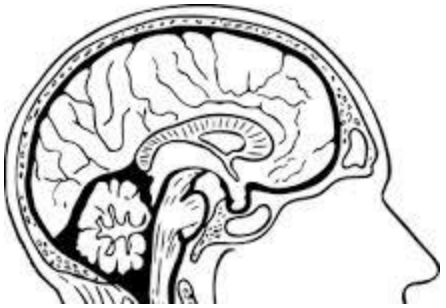
CHALLENGE:

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

GOAL: INITIAL PROOF OF CONCEPT

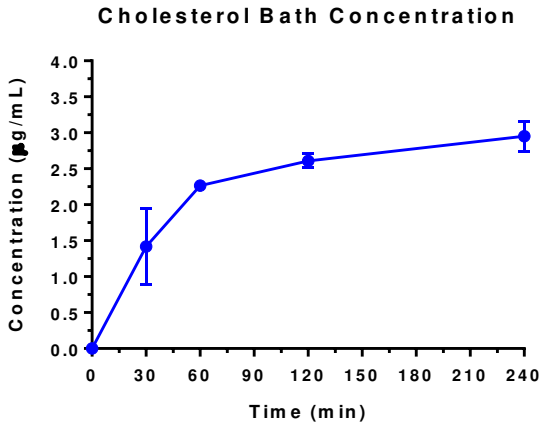
DRUG MODIFICATIONS AS NEEDED

- *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

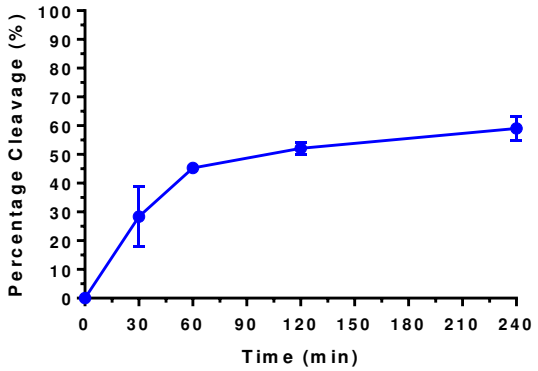
Will the compound increase Cholesterol?

(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

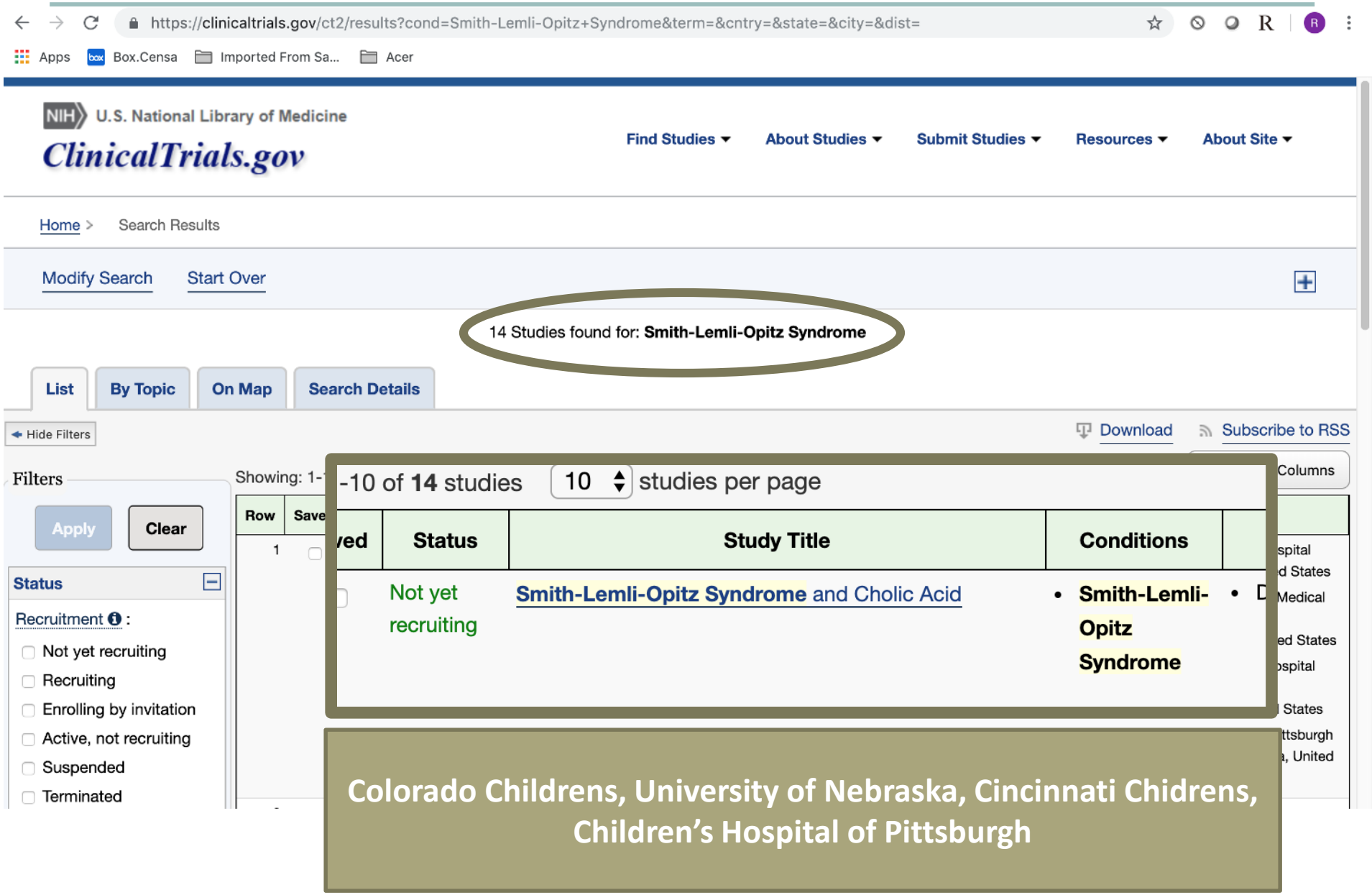
Status and Next Steps

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

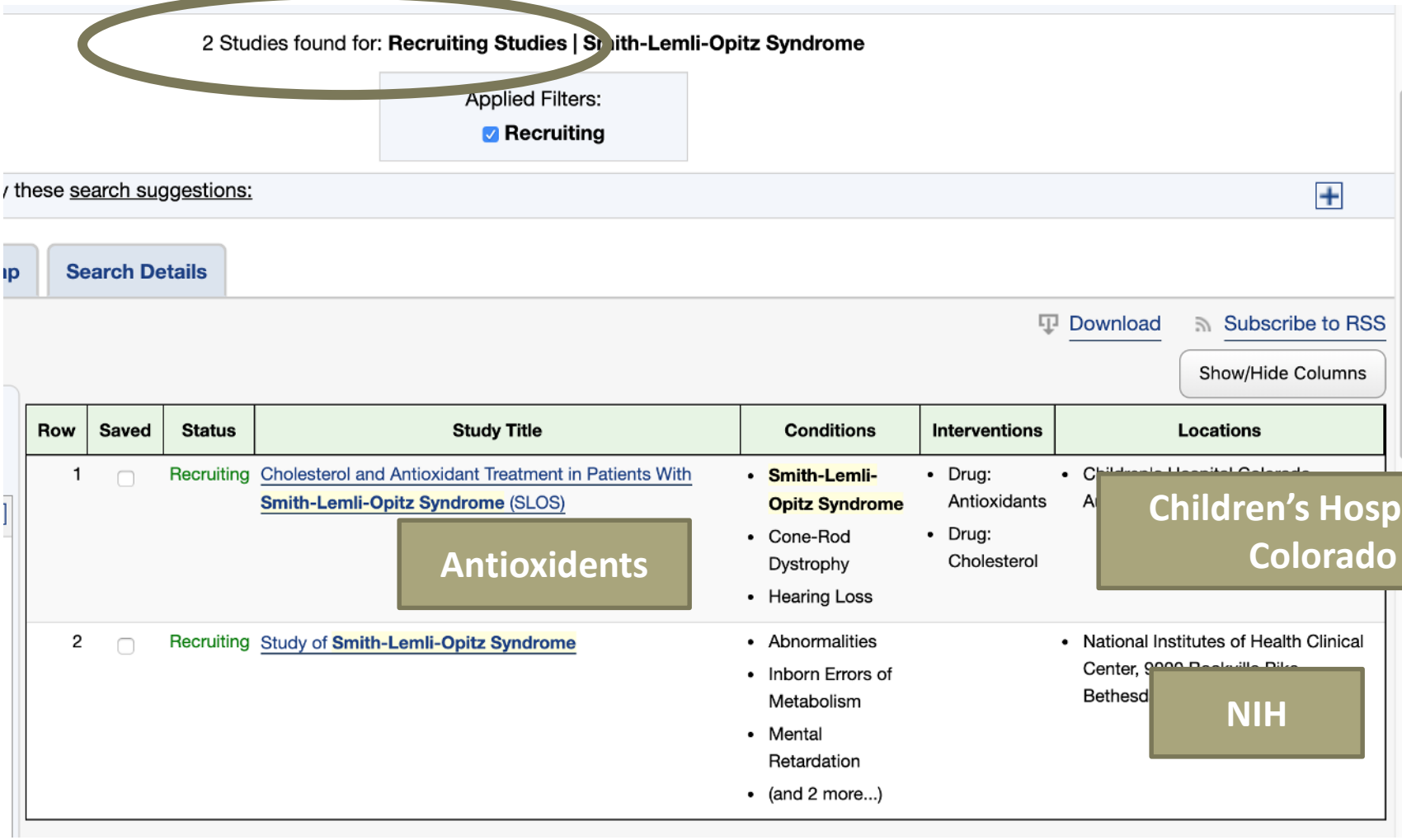
Other Current SLOS Research

Clincaltrials.gov is a place to look

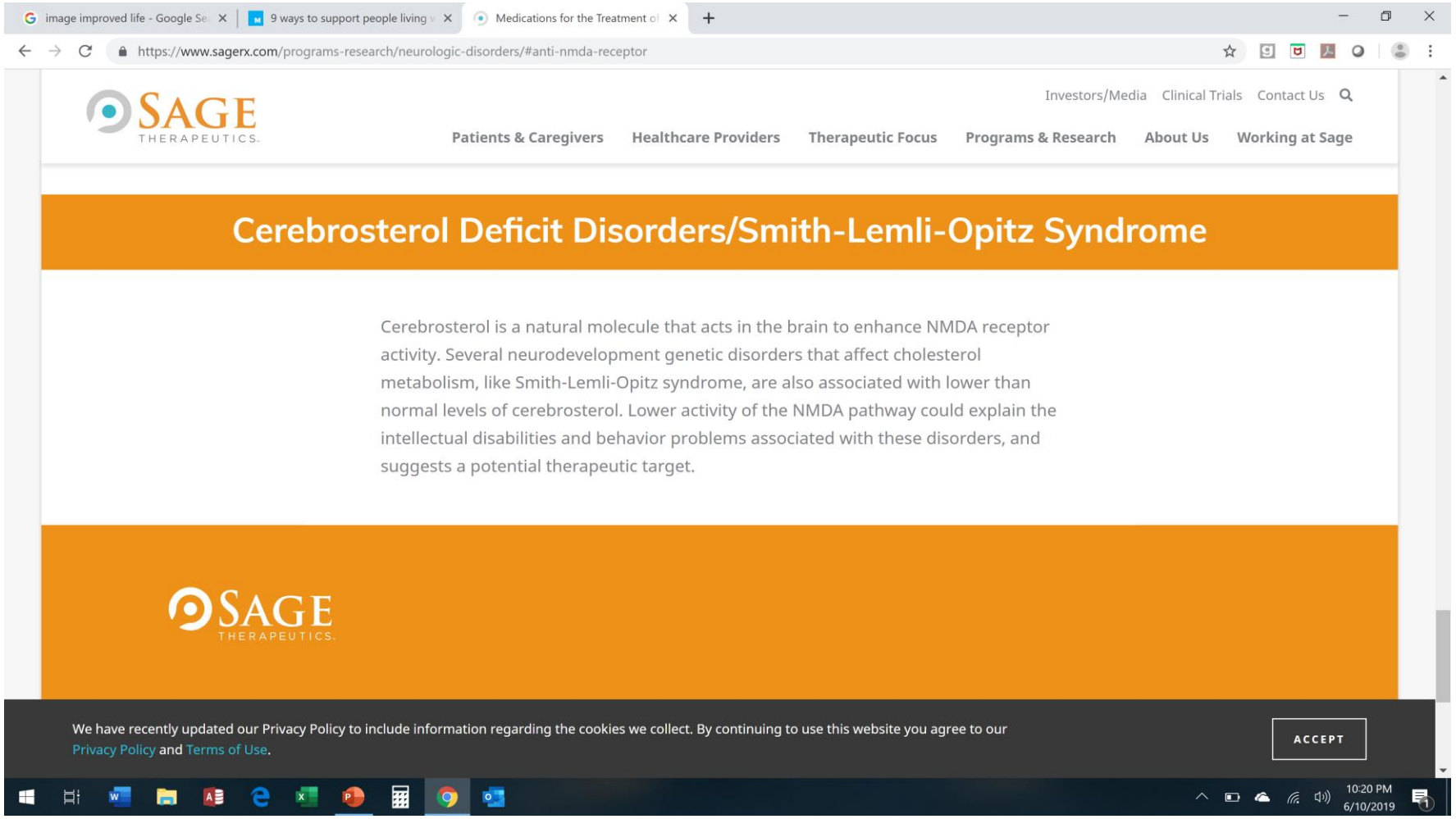


Colorado Childrens, University of Nebraska, Cincinnati Chidrens, Children's Hospital of Pittsburgh

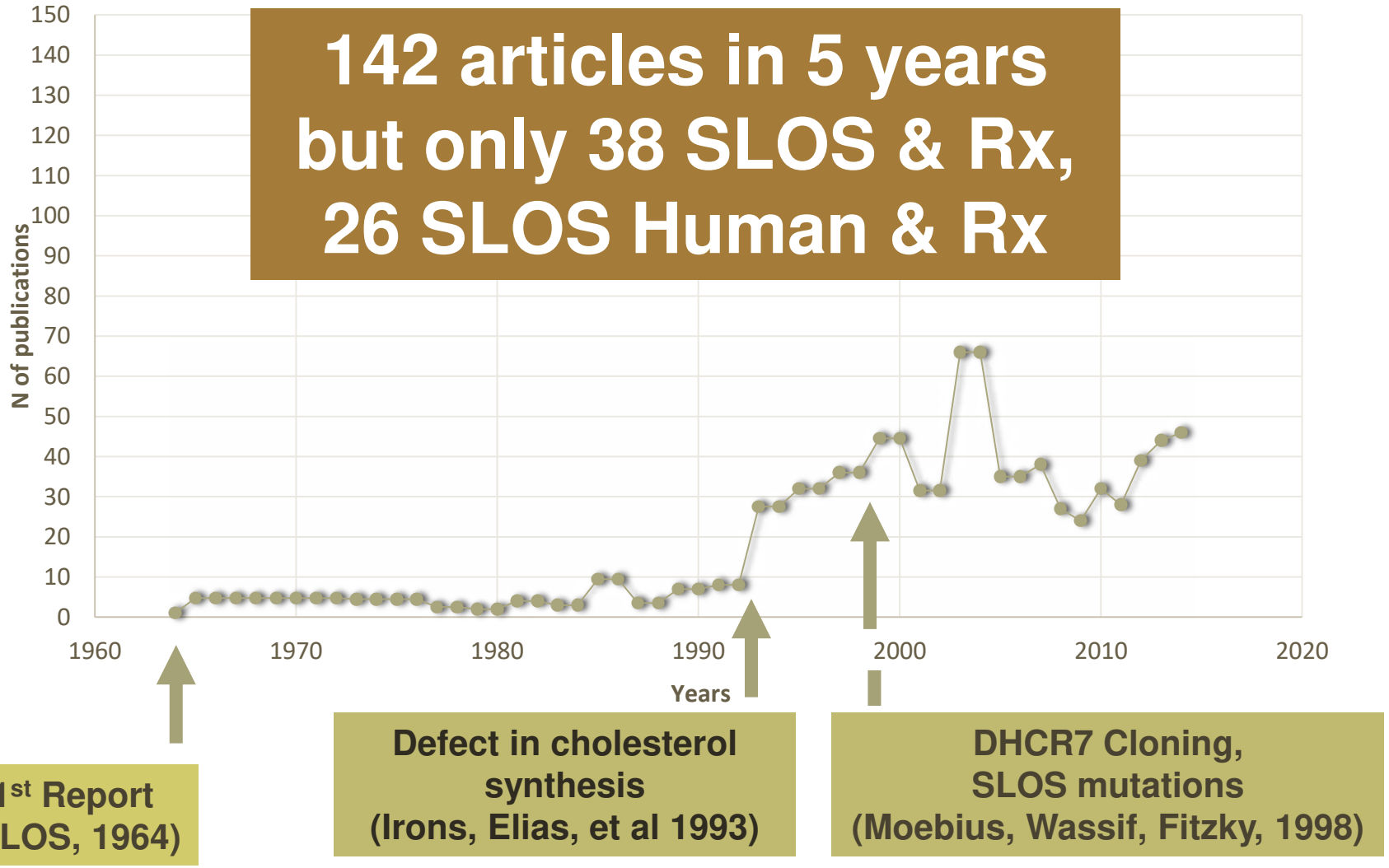
Can filter for recruiting studies



Pharma beginning to show interest inSLOS



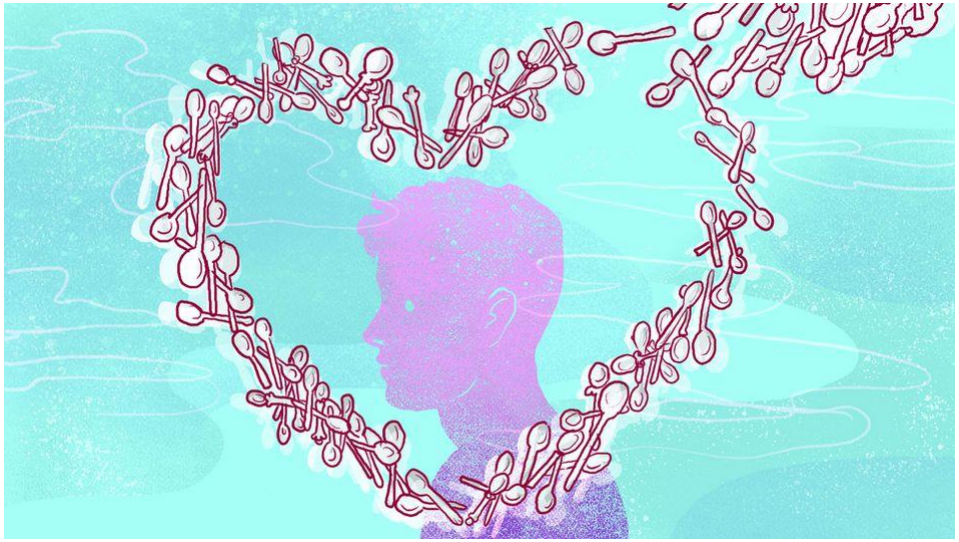
We still need more SLOS research



The Importance of Research Funding

- 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!**