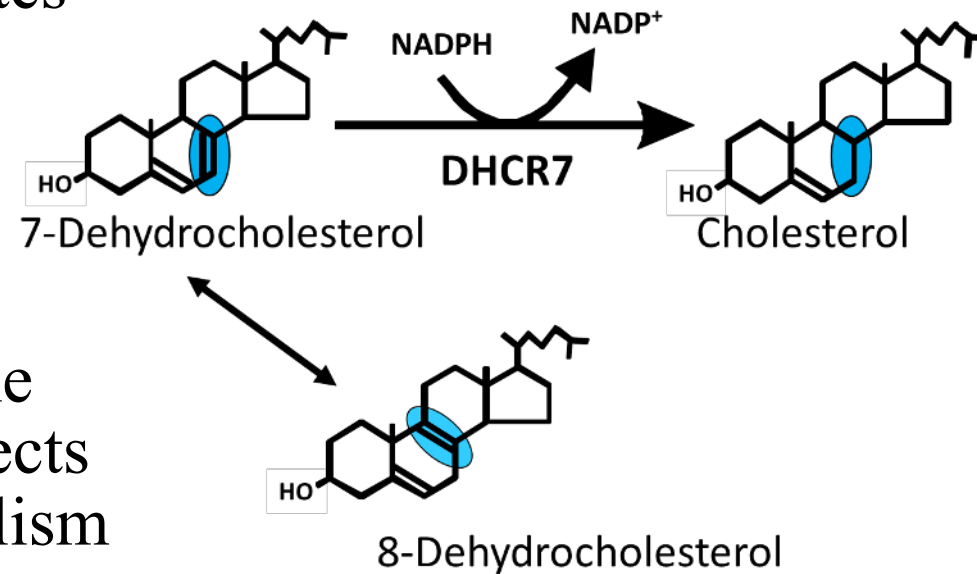


Therapy for SLOS

- SLOS

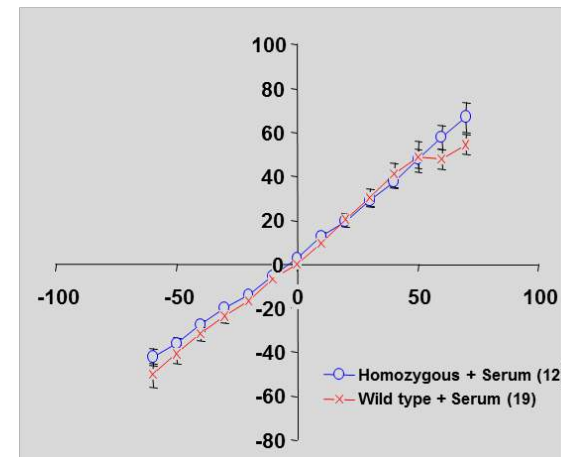
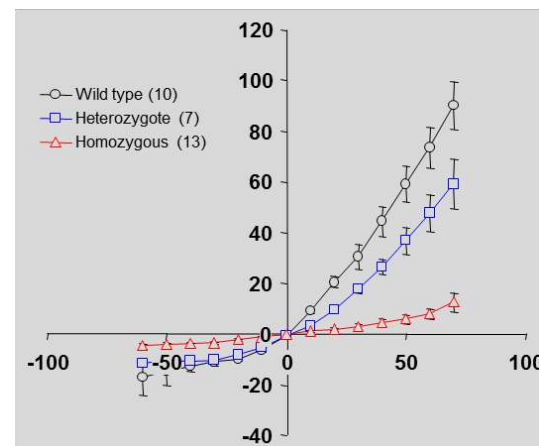
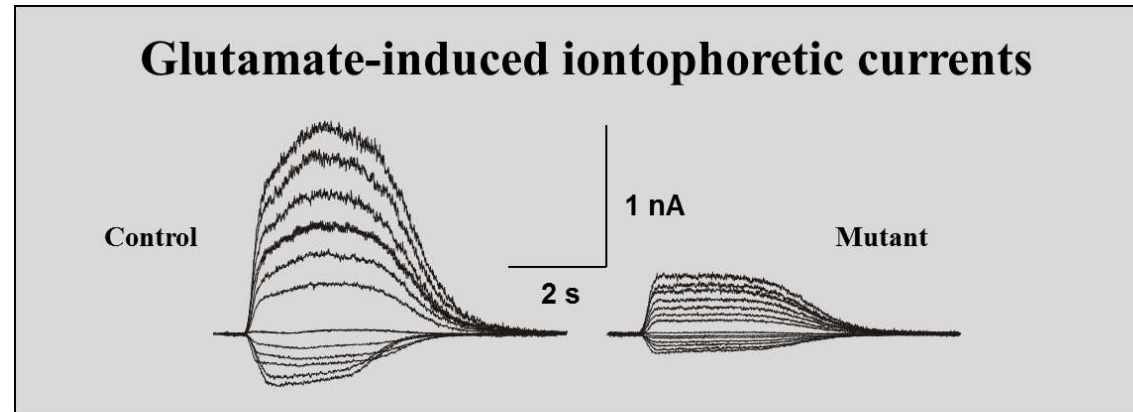
- Inborn error of cholesterol synthesis
 - Impaired 7-dehydrocholesterol reductase activity
 - Increased dehydrocholesterol
 - Decreased cholesterol
 - 7DHC metabolites

DHCEO
27OH-7DHC



- Malformation syndrome
 - Developmental defects
- Inborn error of metabolism
 - Functional defects

To what extent are the mental and behavioral problems in SLOS due to fixed developmental abnormalities, versus to what extent are they due to functional problems secondary to the abnormal sterol composition in the CNS?



Therapeutic Approaches for SLOS

- Increase cholesterol
- Decrease 7-dehydrocholesterol
- Decrease 7-dehydrocholesterol metabolites

Therapeutic Approaches for SLOS

- Peripheral (Body) Therapy
 - Improved serum biochemistry
 - Improved nutritional status
 - Improved growth
- Central (Brain) Therapy
 - Cholesterol does not cross the blood-brain barrier
 - Anecdotal reports of improvement in behavior
 - Decreased irritability and Self Injurious Behavior
 - Decreased hyperactivity
 - Decreased tactile defensiveness

- Autistic Behavior

(ADI-R Criteria and Initiation of Cholesterol Therapy)

< 4 yo 2/9 22%

> 4 yo 7/8 88%

Analysis of Short-Term Behavioral Effects of Dietary Cholesterol Supplementation in Smith–Lemli–Opitz Syndrome

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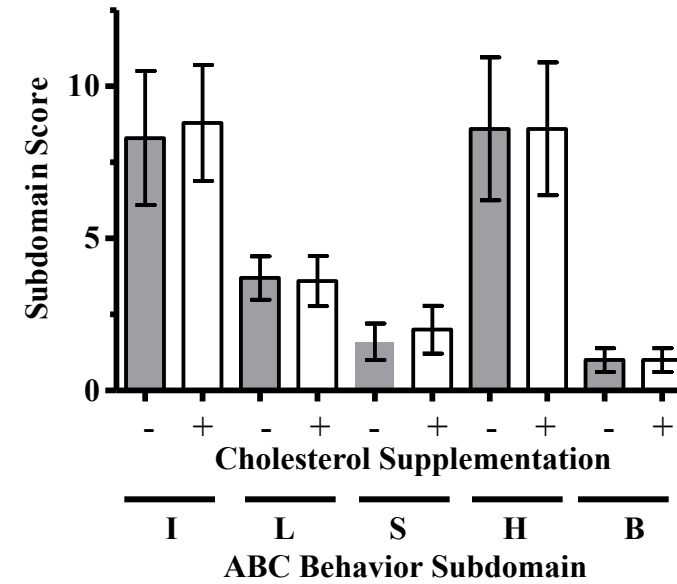
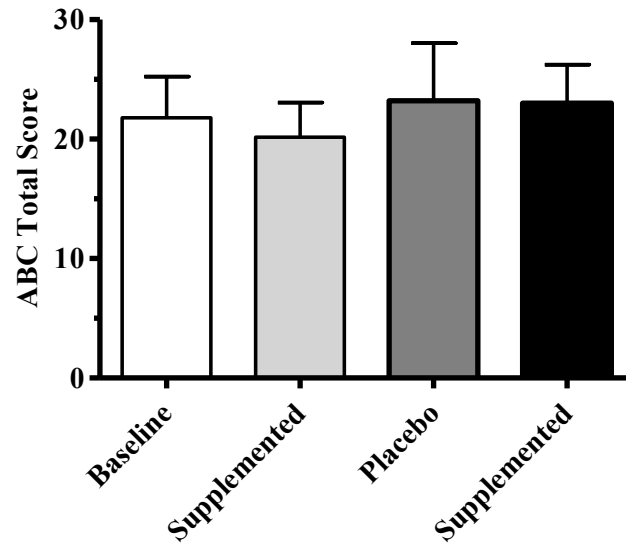
Received 15 July 2009; Accepted 12 September 2009

- Double-blind, placebo-controlled, cross-over trial



- 10 Participants completed both phases
- No Participants discontinued the placebo phase
- Aberrant Behavior Checklist (ABC)
 - Hyperactivity score

Dietary Cholesterol Supplementation

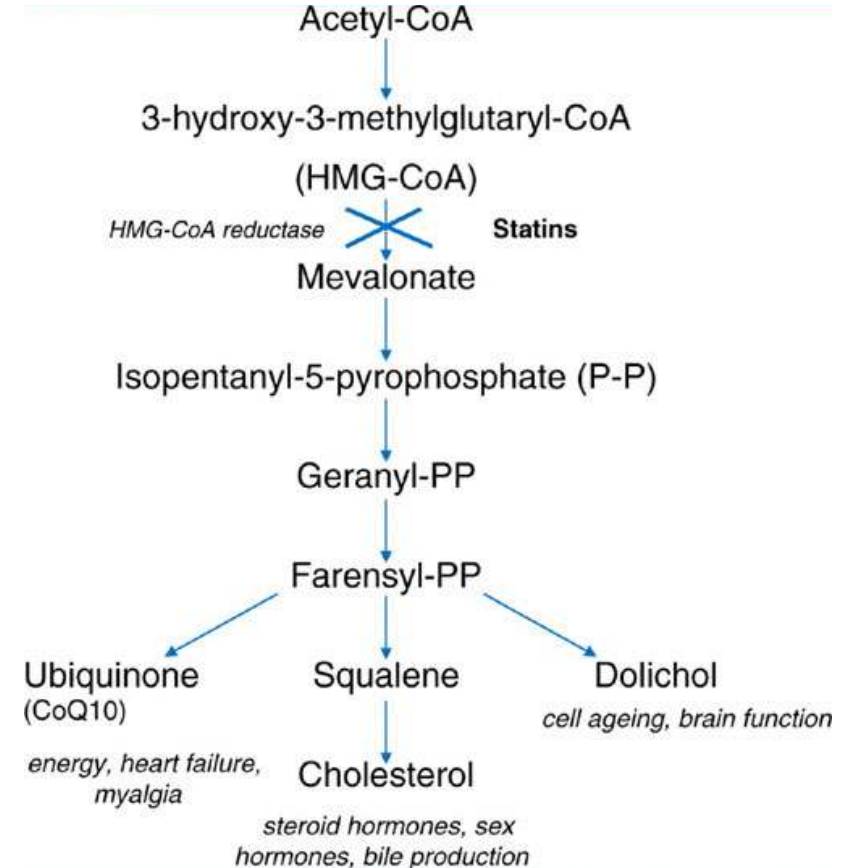
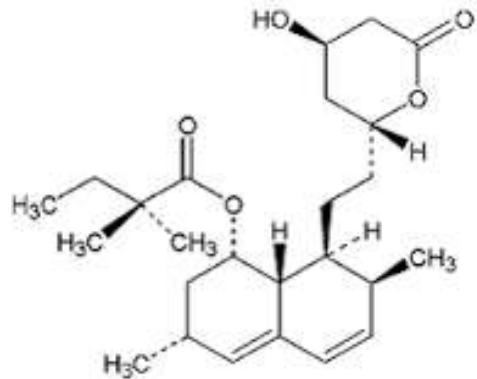


Dietary Cholesterol Supplementation

- Limitations
 - Under powered Study needs to be larger
 - Short-term Study needs to be longer
- No controlled studies showing a benefit of dietary cholesterol supplementation on either behavior or learning

Simvastatin Therapy in SLOS

- HMG-CoA reductase inhibitor
 - Rational: Decrease 7DHC levels



Simvastatin Therapy in SLOS

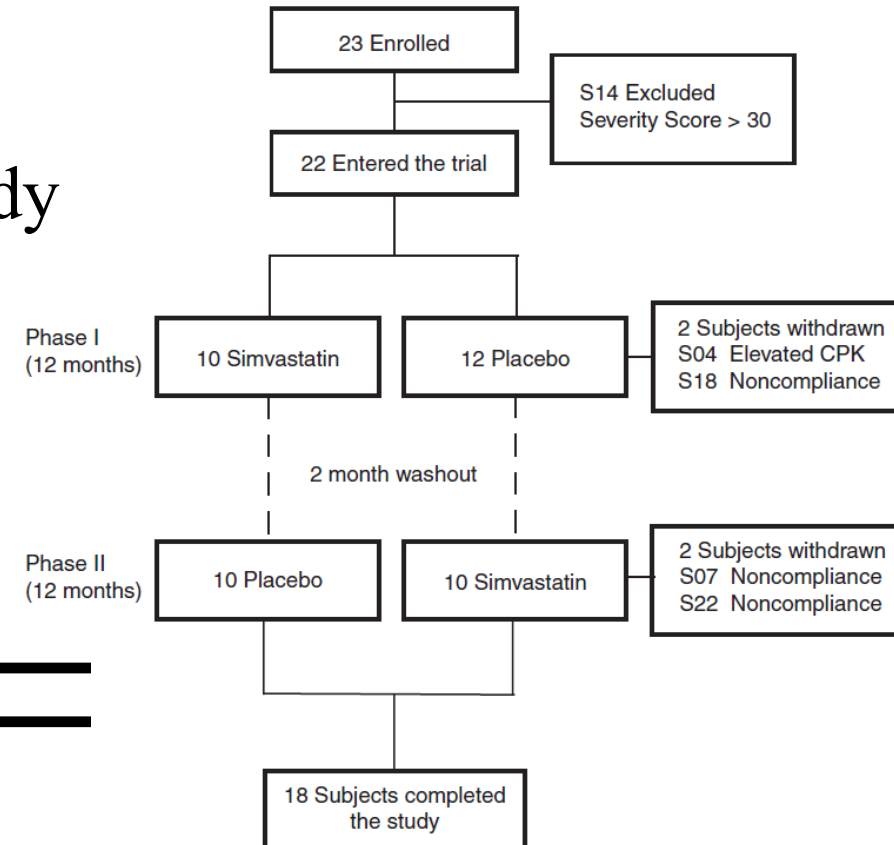
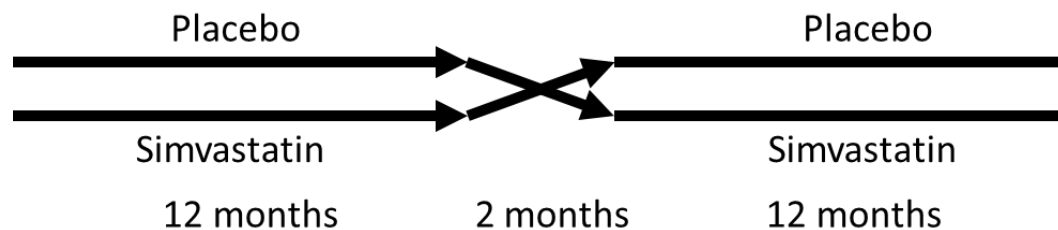
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ORIGINAL RESEARCH ARTICLE | Genetics
inMedicine

A placebo-controlled trial of simvastatin therapy in Smith-Lemli-Opitz syndrome

Christopher A. Wassif, PhD¹, Lisa Kratz, PhD², Susan E. Sparks, MD^{1,3}, Courtney Wheeler, MS⁴,
Simona Bianconi, MD¹, Andrea Gropman, MD⁵, Karim A. Calis, PharmD, MPH⁶,
Richard I. Kelley, MD, PhD⁷, Elaine Tierney, MD⁴ and Forbes D. Porter, MD, PhD¹

- 22 patients entered trial
- 18 subjects completed the study
- Cross-over design
 - 12-month phases
 - 2-month washout



Simvastatin Therapy in SLOS

Inclusion/Exclusion

- Age: 4-18 yrs
- SLOS Severity Score ≤ 30
- Fibroblast residual cholesterol synthesis $\geq 10\%$

Demographics

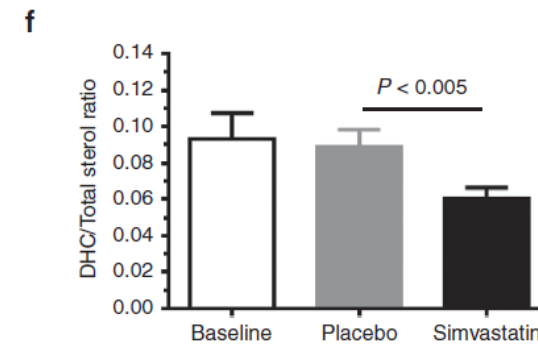
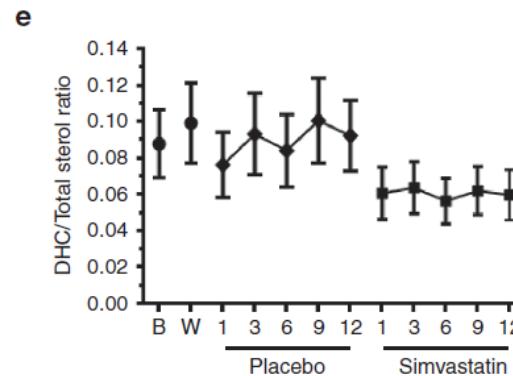
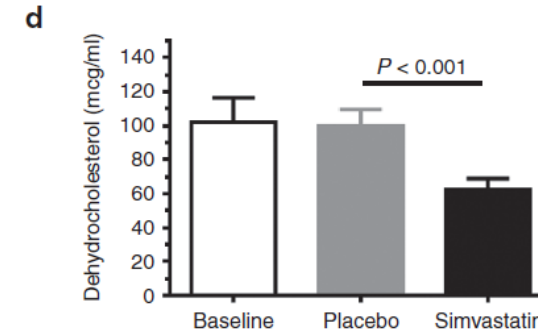
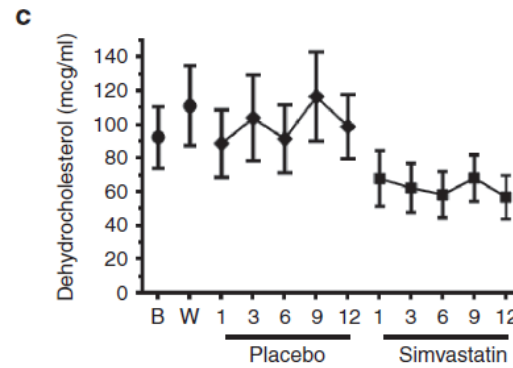
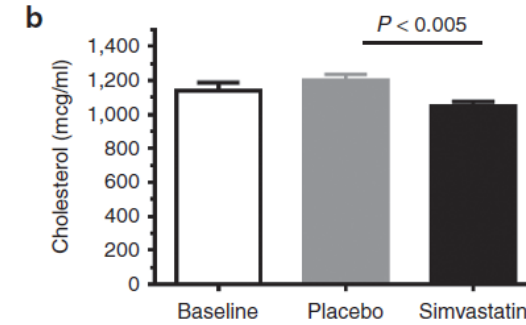
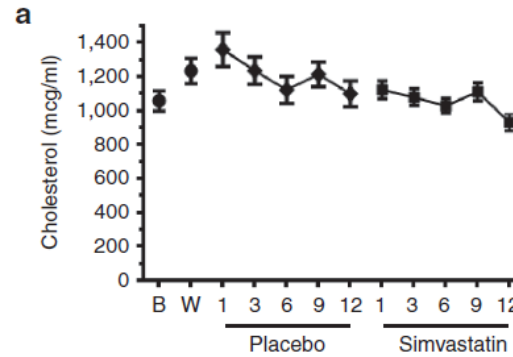
- Mean 8.2 yrs Range 4.0-17.5 yrs
- Mean 13.2 Range 6-28
- Mean 37% Range 11-76%
- Male/Female 13/9

Simvastatin Therapy in SLOS

- Safety and Adverse Events
 - No drug related serious adverse events during the study*
 - No significant changes in serum transaminase or creatine phosphokinase levels
 - Anthropomorphic measures
 - No significant changes in growth parameters
 - Behavioral changes
 - Increased aggression and self-injurious behavior in one subject during the open-label extension
 - *One subject developed cataracts after the study while on off-label simvastatin

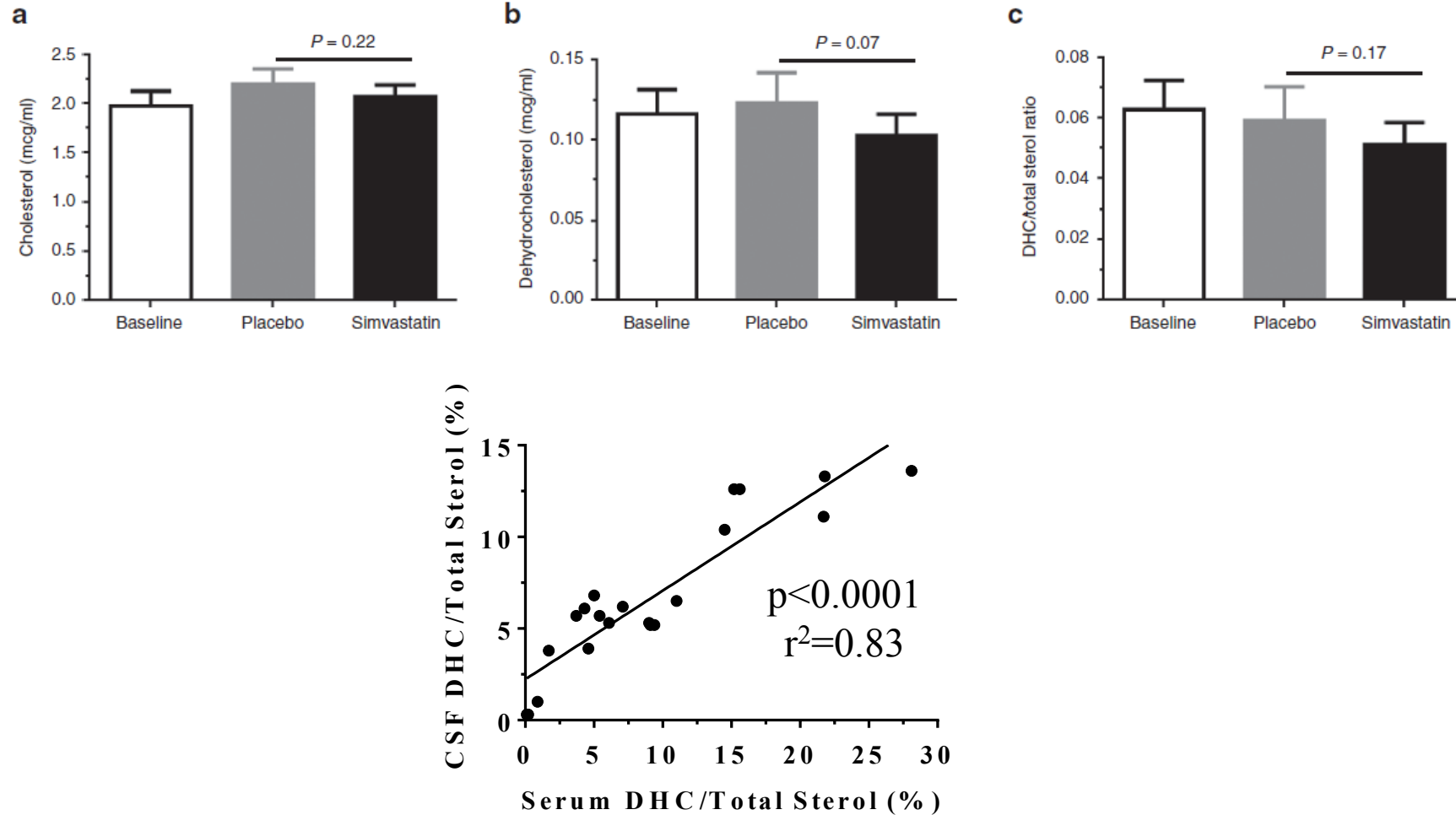
Simvastatin Therapy in SLOS

Sterol Biochemistry Serum



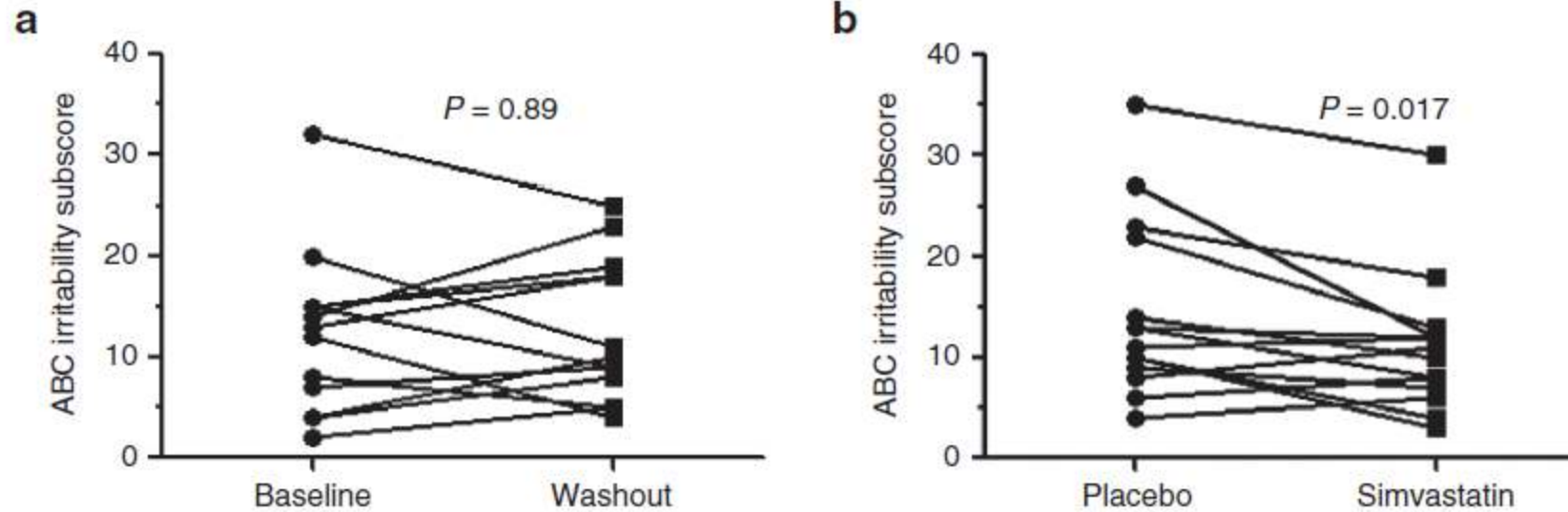
Simvastatin Therapy in SLOS

Sterol Biochemistry Cerebral Spinal Fluid



Simvastatin Therapy in SLOS

Clinical Outcome Measures
Aberrant Behavior Checklist-Irritability Subscore
(14 Subjects)



Simvastatin Therapy in SLOS

- First controlled study to demonstrate improved behavior in SLOS subjects in response to a therapeutic intervention
- Statistical significance versus clinical significance
- Limited ability to push the simvastatin dose
- Proof-of-concept
 - Increased *DHCR7* expression
 - Proteostasis modulators

Therapy for SLOS

- Basic Science
 - Model systems
 - High-throughput drug screens
 - Biomarker identification and characterization
- Clinical research
 - Natural history
 - Detailed phenotyping
 - Biomaterial collection
 - Therapeutic trials
- Family and patient support

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- All our collaborators Nationally and Internationally
- All the SLOS families and patient support.