ENDPOINTS FOR GENE THERAPY CLINICAL TRIALS: Pompe Disease

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Endpoints for Pompe disease

Overview

- Liver depot gene therapy for Pompe disease
- Challenges with developing endpoints
- Validated endpoints for Pompe disease
- Applying endpoints in gene therapy

Conflict of Interest

Disclosures

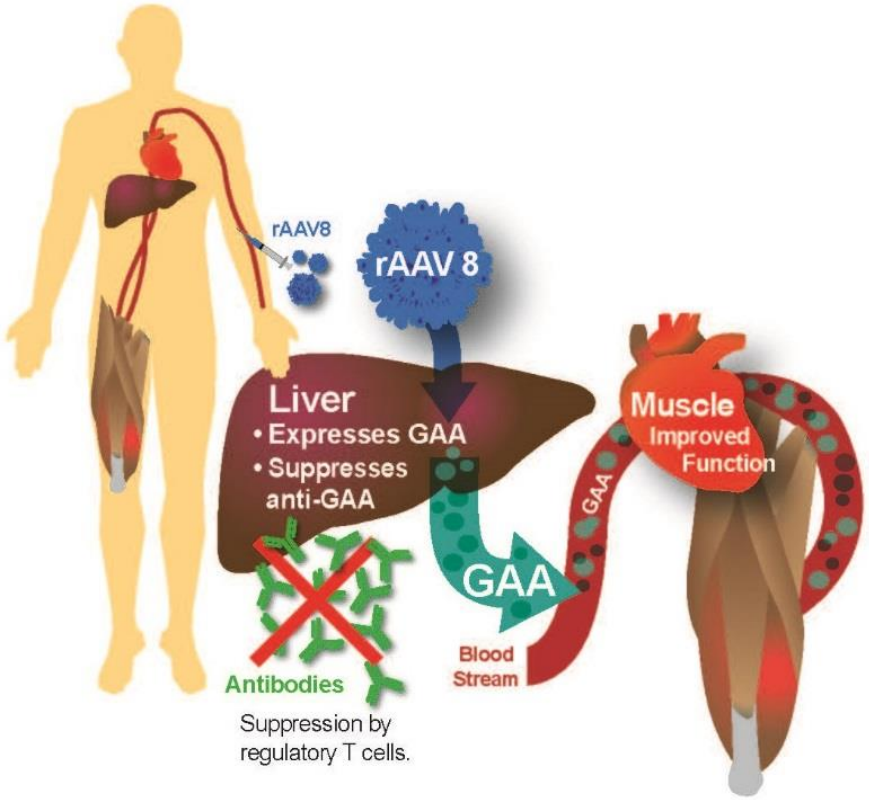
- Dr. Dwight Koeberl and Duke University might benefit financially, if the experimental treatments discussed here prove effective and are successful commercially.
- Dr. Koeberl has served as a consultant for Sangamo Therapeutics and for Genzyme Sanofi, Amicus, and Vertex.
- Dr. Koeberl has received grant support from Viking Therapeutics, Genzyme Sanofi, Roivant Rare Diseases, and Amicus.
- Dr. Koeberl has equity in Actus Therapeutics, which is developing gene therapy for Pompe disease.

Liver Depot Gene Therapy Strategy

- A <u>one-time gene therapy treatment</u>

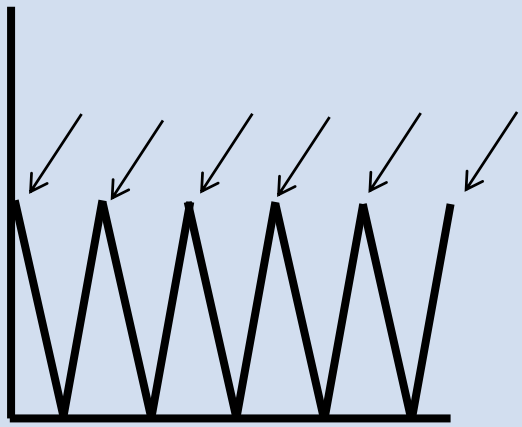
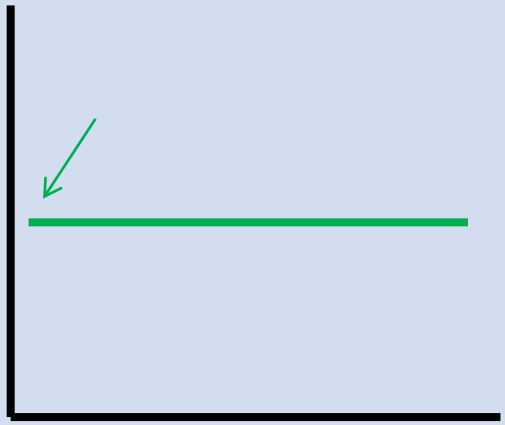
  Can be used with enzyme replacement therapy to reduce immunogenecity

  Liver targeted delivery and expression.
- Activation of regulatory T cells.
  - Suppress previously formed anti-rhGAA antibodies.
  - Enhanced efficacy.
- Orphan Drug Designation



Gene Therapy with AAV8-LSPhGAA. Treatment with rAAV8 converts the liver depot for continuous secretion of the enzyme therapy (rhGAA) correcting the GAA deficient. Liver expression induces immune tolerance to rhGAA, by reducing antibodies through suppression by regulatory T cells

Comparison of ERT and Liver Depot Gene Therapy

	ERT	AAV8-LSPhGAA*
Stability	Short half-life in blood	Continuous GAA in bloodstream
GAA delivery to muscle	Lack of uptake in skeletal muscle	Increased delivery to muscle
Immune Responses	High titer antibody response	Immune tolerance induction
Population	Some patients fail to respond	Larger patient population
Efficacy	Partial	More complete correction
Mortality	Yes	Decreased
Administration	Every 1-2 weeks 	Single dose 

*Gene therapy data from laboratory studies, not a clinical trial

Experiment (Gene therapy vs. ERT)

- Comparison of 3 groups
  - AAV8-LSPhGAA (8E+11 vg/kg)
  - ERT
  - No treatment
- Evaluate after one month
- Muscle GAA activity and glycogen content

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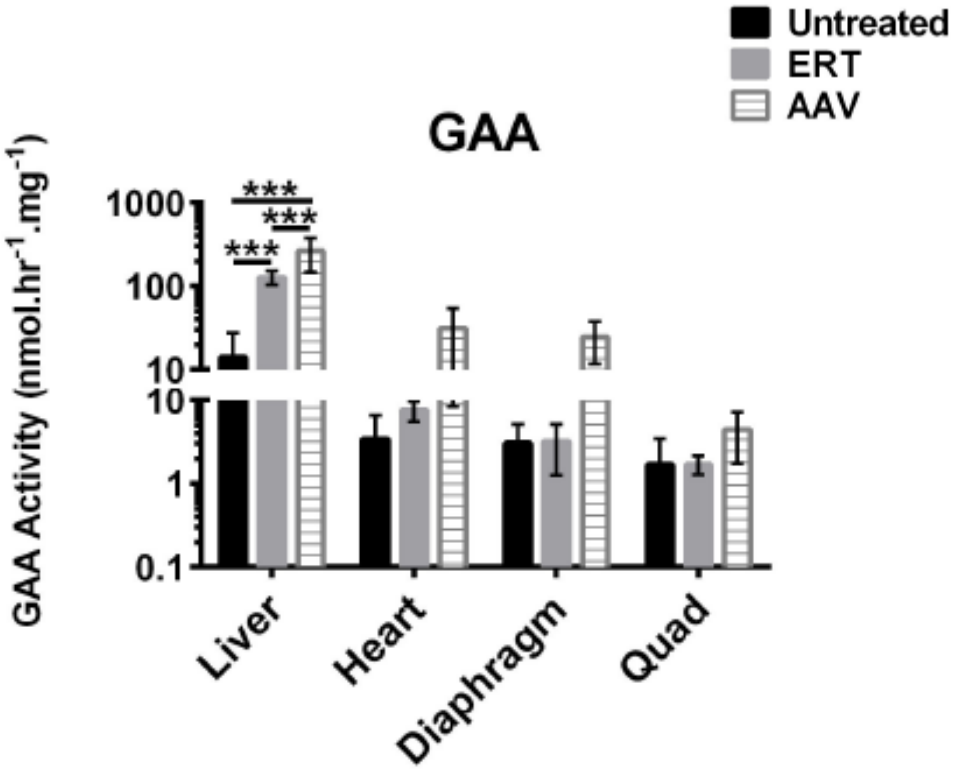
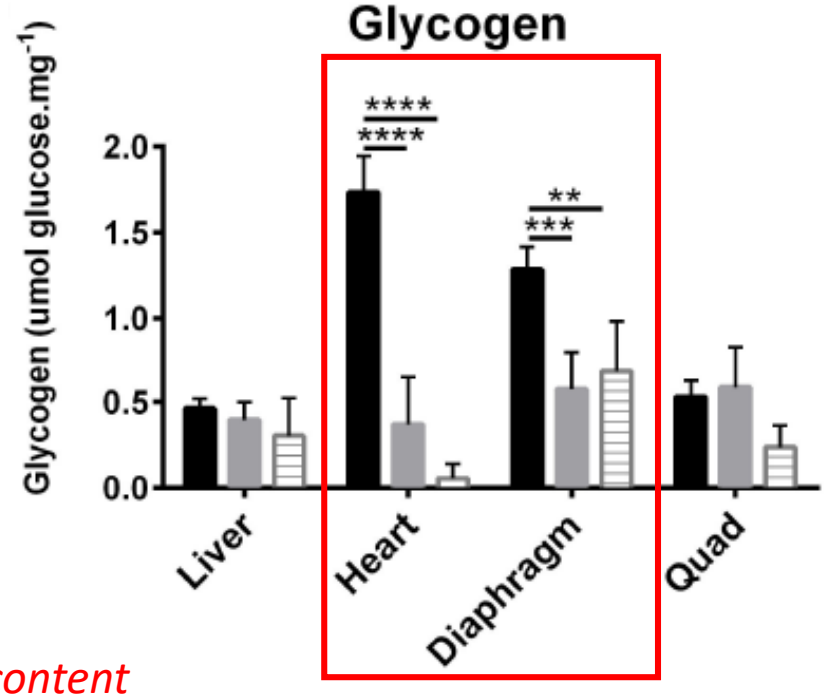
Direct Comparison of AAV8-LSPhGAA With ERT

Molecular Therapy
Methods & Clinical Development
Original Article

Low-Dose Liver-Targeted Gene Therapy for Pompe Disease Enhances Therapeutic Efficacy of ERT via Immune Tolerance Induction

Sang-oh Han,[1] Giuseppe Ronzitti,[2] Benjamin Arnson,[1] Christian Leborgne,[2] Songtao Li,[1] Federico Mingozzi,[2,3] and Dwight Koeberl[1,4]





Increased GAA activity and decreased glycogen content

Challenges with developing endpoints

AAV8-LSPhGAA in Adults with Pompe Disease

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Challenges with developing endpoints

- Standard of care should not be withheld
- Overlapping effects with gene therapy
- Goal is a standalone

Validated endpoints for Pompe disease

Clenbuterol in Adults with Pompe Disease

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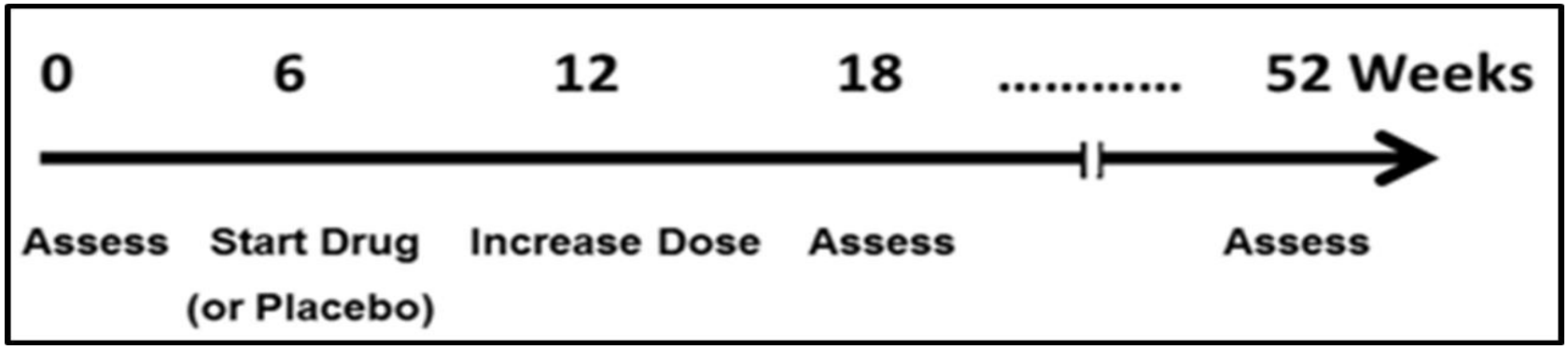
Phase I/II Clinical Trial of Clenbuterol



- Baseline: Assess
- Week 6: Start clenbuterol
- Week 12: Dose increase
- Week 18: Assess
- Week 52: Assess

Molecular Therapy
Original Article

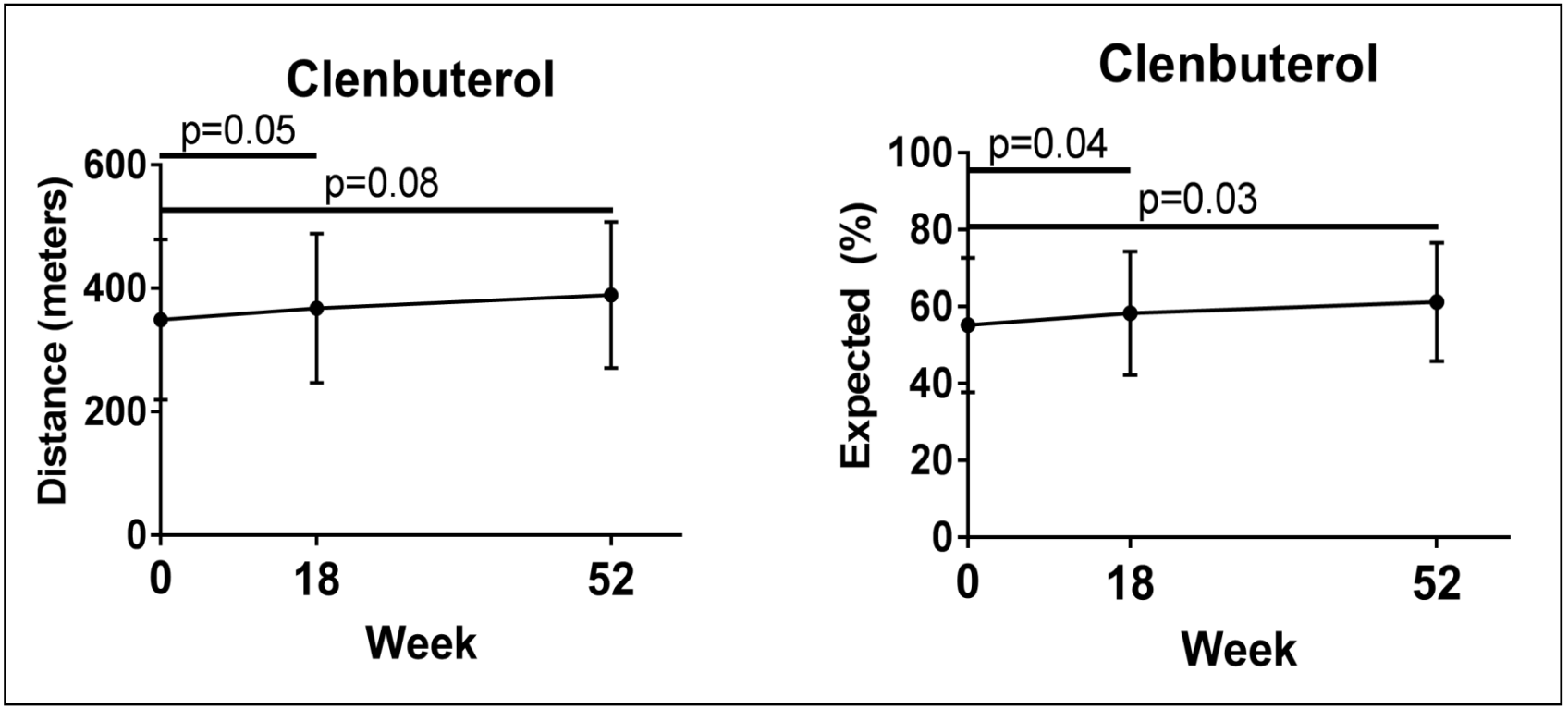
Correction of Biochemical Abnormalities and Improved Muscle Function in a Phase I/II Clinical Trial of Clenbuterol in Pompe Disease

Dwight D. Koeberl,[1] Laura E. Case,[2] Edward C. Smith,[3] Crista Walters,[1] Sang-oh Han,[1] Yanzhen Li,[4] Wei Chen,[5] Christoph P. Hornik,[6] Kim M. Huffman,[7] William E. Kraus,[8] Beth L. Thurberg,[9] David L. Corcoran,[5] Deeksha Bali,[1] Nenad Bursac,[4] and Priya S. Kishnani[1]

Characteristics of Study Population

	Clenbuterol (n=8)	Placebo (n=5)
Age (median)	52	32
Gender	5M:3F	2M:3F
Duration of ERT, months (median, range)	75 (38-102)	21 (15-72)
Baseline FVC, % predicted (median)	50	89
Baseline 6MWT, meters (median)	350	450
Baseline 6MWT, % predicted (median)	51	72

Effect of Clenbuterol on 6MWT



- *Distance walked trended higher at Week 18*
- *Predicted 6MWD (%) significantly higher at Weeks 18 and 52*

No change seen in placebo group

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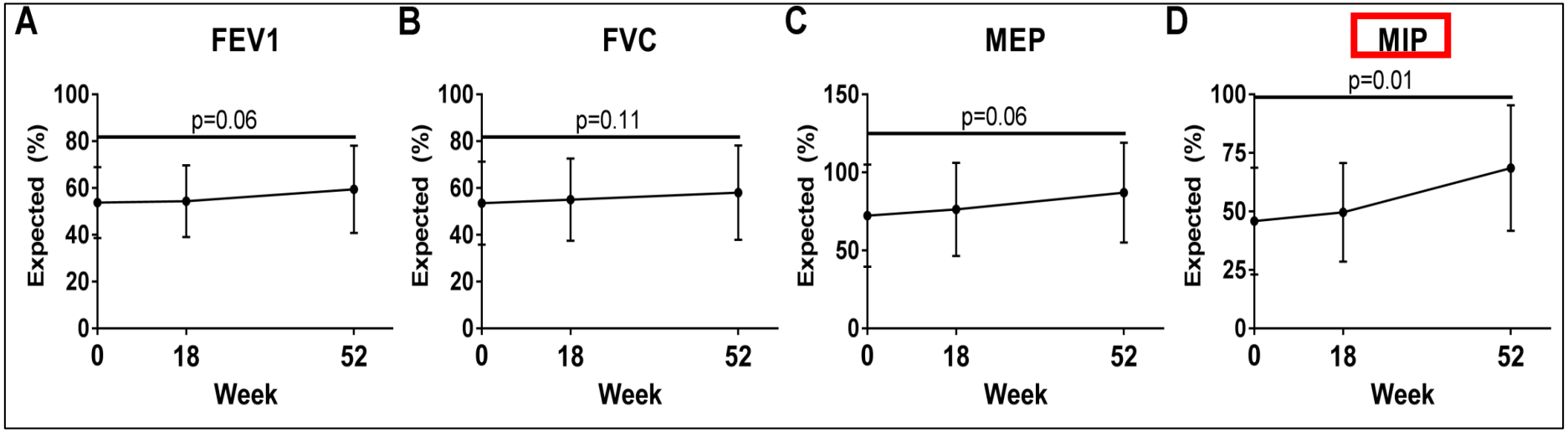
Effect of Clenbuterol on PFTs



Increased respiratory muscle strength based upon significantly improved performance on the MIP test

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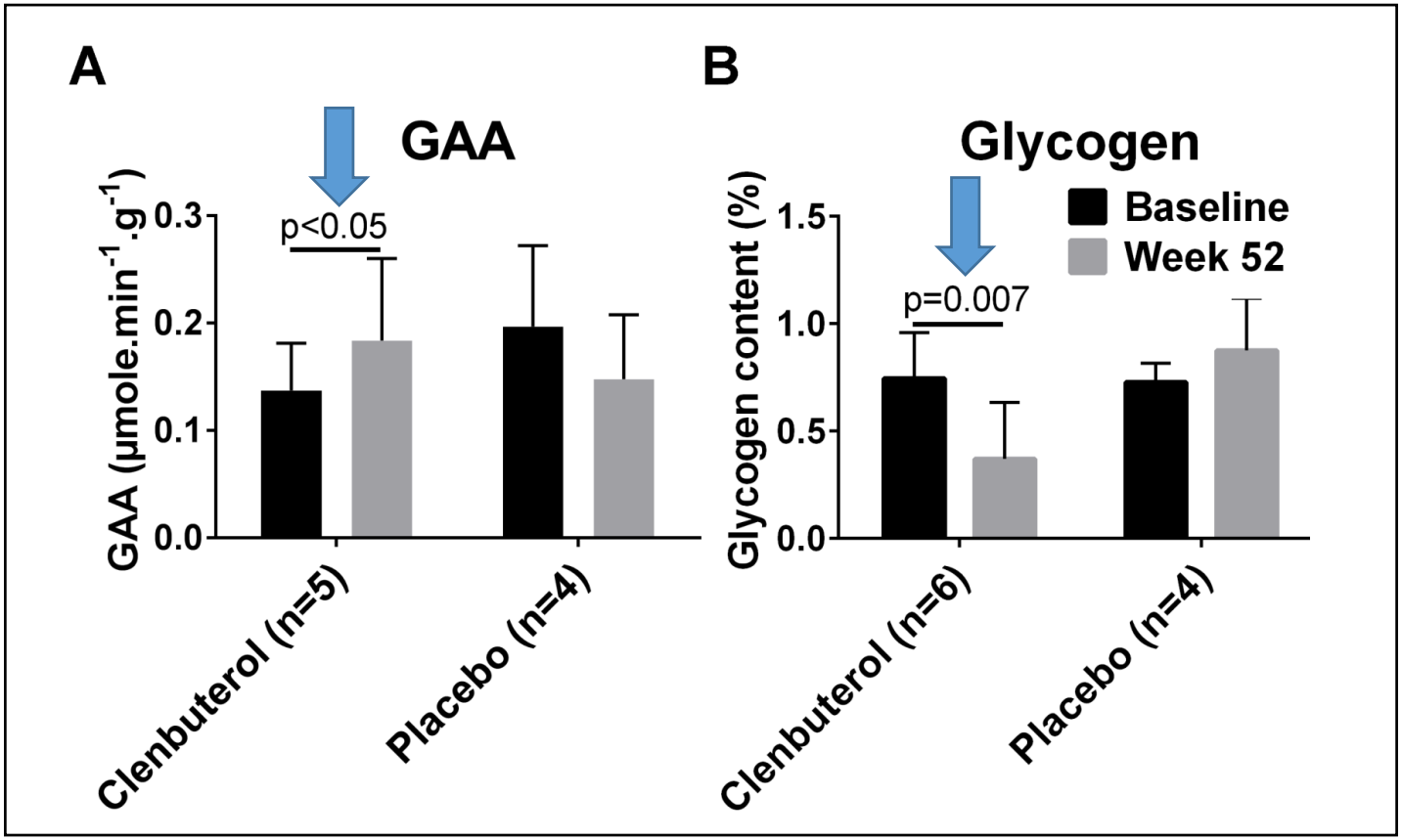
Effect of Clenbuterol Upon Biochemical Correction



(A) *Significantly* ***increased GAA activity (34%)***

(B) *Significantly* ***decreased glycogen content (50%)*** *in the clenbuterol group.*

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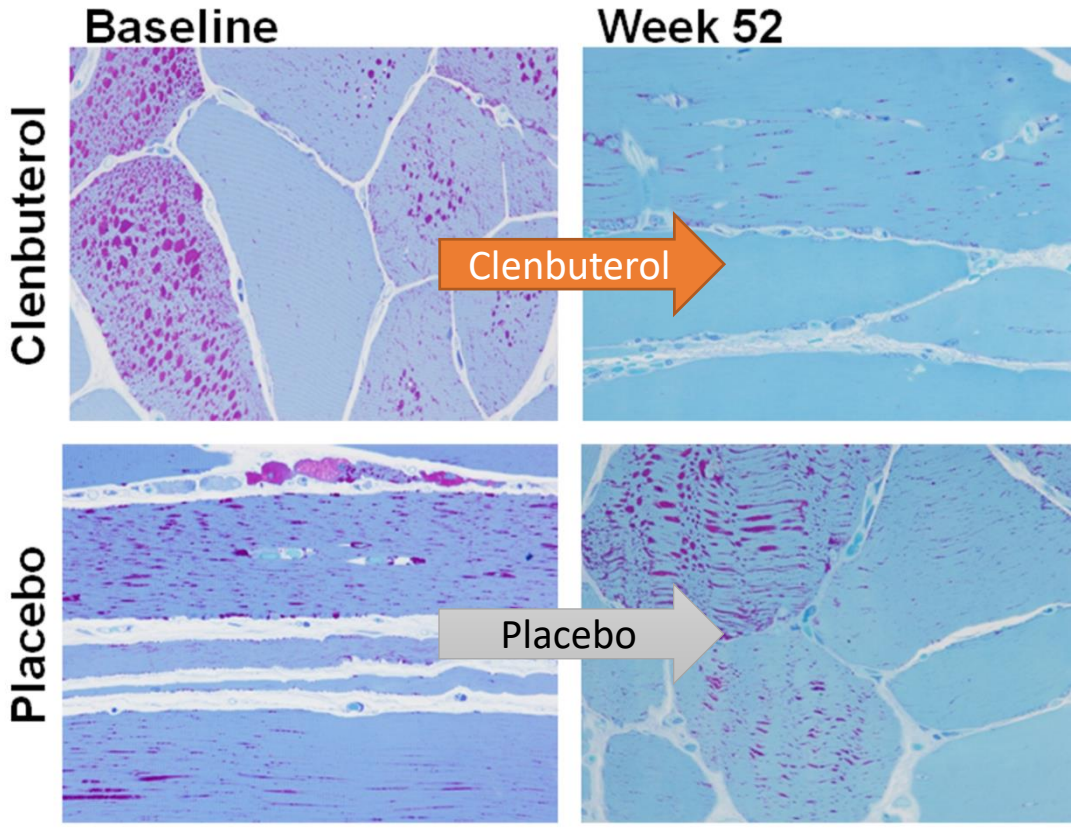
Effect Of Clenbuterol On Muscle



Applying endpoints in gene therapy

AAV8-LSPhGAA in Adults with Pompe Disease

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Phase I Clinical Study

- 6 Adult patients, 3x2 design (Low and Higher Dose)
- Safety (primary endpoint):
  - Incidence of adverse events (AE) and serious AE
  - Clinical laboratory abnormalities
- Efficacy (secondary endpoints):
  - Muscle function (6 minute walk and pulmonary function testing)
  - GAA activity in muscle biopsy and serum
  - Antibody formation
  - Urinary biomarker

Validated Endpoints

- **Our data reveal *favorable initial safety and efficacy data* for adjunctive clenbuterol therapy in LOPD patients**

Test	Baseline	Week 52	Change	P value
6MWT (m)	373	389	4%	0.08
6MWT (%)	58	61	5%	0.03
GSGC (pt)	16	14	-13%	0.004
QMFT (pt)	40	47	18%	0.007
FEV1 (%)	58	65	12%	0.06
FVC (%)	60	64	7%	0.11
MEP (%)	40	54	35%	0.06
MIP (%)	51	69	35%	0.004

Molecular Therapy
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Correction of Biochemical Abnormalities and Improved Muscle Function in a Phase I/II Clinical Trial of Clenbuterol in Pompe Disease

Dwight D. Koeberl,[1] Laura E. Case,[2] Edward C. Smith,[3] Crista Walters,[1] Sang-oh Han,[1] Yanzhen Li,[4] Wei Chen,[5] Christoph P. Hornik,[6] Kim M. Huffman,[7] William E. Kraus,[8] Beth L. Thurberg,[9] David L. Corcoran,[5] Deeksha Bali,[1] Nenad Bursac,[4] and Priya S. Kishnani[1]

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Problem: Standard of care

Issue

- Ongoing benefits
- Fluctuating GAA
- Need to stop ERT

Response

- Stably treated
- Timing of visits
- Criteria for withdrawal

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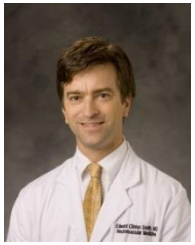
Surrogate Endpoint: Muscle Glycogen?

- Pompe disease is a glycogen storage disease; glycogen accumulation is integral to pathogenesis
- Decreased glycogen correlated with bioactivity and/or efficacy
  - Proof of concept experiments
  - Preclinical experiments
  - Clinical trial of clenbuterol
- Initial validation in Phase I/II clinical trial of clenbuterol

Project Team

Clinical Investigators



Edward Smith
Clinical Investigator
Neuromuscular Specialist

Laura Case
Physical therapy
-Muscle testing
-Pompe expertise

Clinical Laboratories

Sarah Young
Biochemical genetics
-CAP, CLIA laboratory
-Biomarker analysis

Deeksha Bali
Glycogen storage disease
-CAP, CLIA laboratory
-GAA and glycogen testing

Lead Investigators

Dwight Koeberl
-Leads gene therapy program
-Multiple investigator-initiated clinical trials

Priya Kishnani
Co-Investigator
-Internationally recognized expertise

Translational Team

Erika Segear Johnson
Regulatory Affairs

Ashley Richardson
Office of Corporate Research Collaborations

Dennis Thomas
Office of Licensing and Ventures

Summary

- Phase I study of liver depot gene therapy in Pompe disease
- Secondary endpoints validated in Pompe disease
- ERT interacts with gene therapy
- Address by understanding the dynamics of Pompe disease therapy

Acknowledgements

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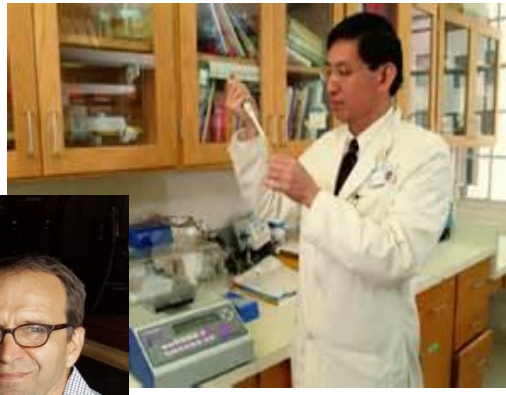
Medical Genetics



- Jennifer Bond
- Edward Smith
- Laura Case
- Sang-oh Han
- Songtao Li
- Crista Walters
- Baodong Sun
- Sarah Young
- Deeksha Bali
- Baodong Sun
- Priya Kishnani
- Y-T Chen

Funding

- NIAMS (U01-AR071693)
- NHLBI (HL081122)
- NICHD (HD054795)
- Alice and Y.-T. Chen Center for Pediatric Genetics and Genomics (generally)
- Askbio

Mouse Models

- Dr. Nina Raben (NIAMS)

AskBio

Gene Therapy Resources Program (GTRP)