JUNE 29, 2024

Breaking Ground: Emerging Therapies on the Horizon for Glutaric Aciduria Type I

Curtis R. Coughlin II, PhD, MS, MBE
Associate Professor
Section of Genetics, Department of Pediatrics
Center for Bioethics + Humanities

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

Conflict of Interest Disclosure

I have the following conflicts to disclose:

Alnylam Pharmaceuticals

☑ Consultant (recieved consultant fees)

Member of the CHARLIE Consoritum

Changing Rare Disorders of Lysine Metabolism

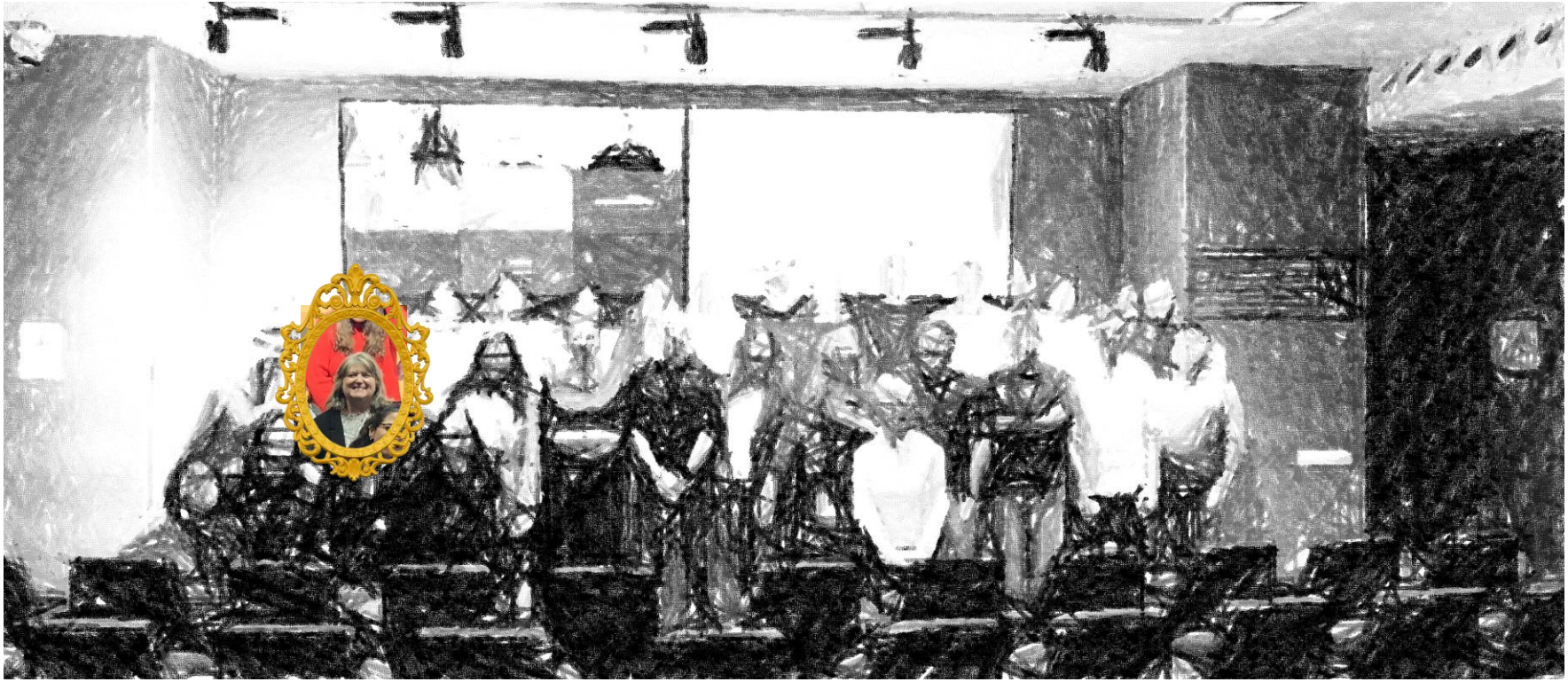
Patients, scientists, and physicians from 6 different countries working together in this project to develop and valid new therapies and biomarkers to avoid brain damage in GA1 and PDE

EUROPEAN JOINT PROGRAMME RARE DISEASES

Changing Rare Disorders of Lysine Metabolism

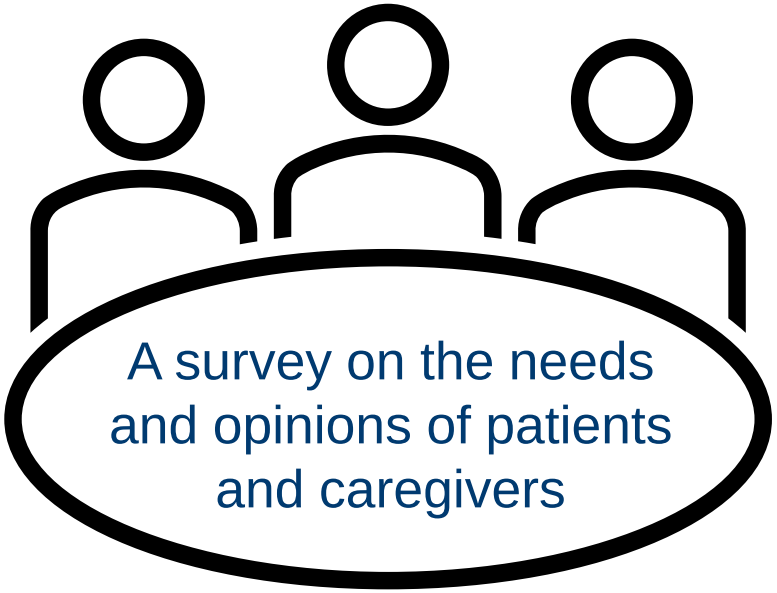
November 2022; Barcelona, Spain

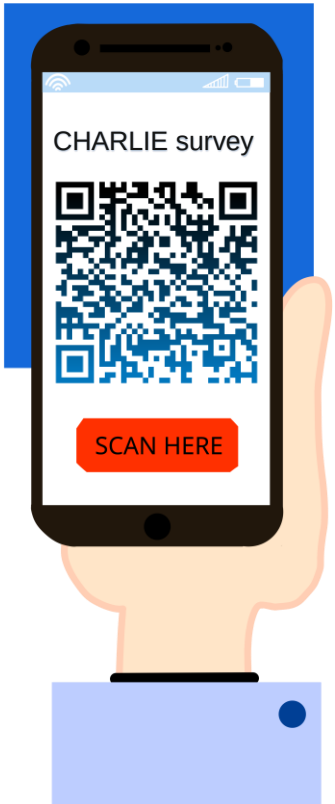
Changing Rare Disorders of Lysine Metabolism



November 2022; Barcelona, Spain

Patient & caregiver survey



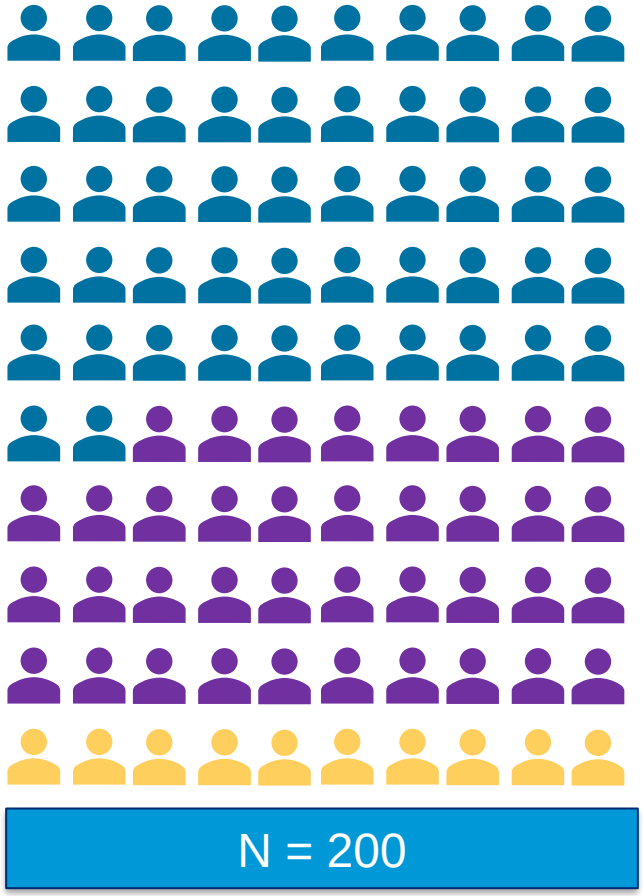


Survey responses (all)

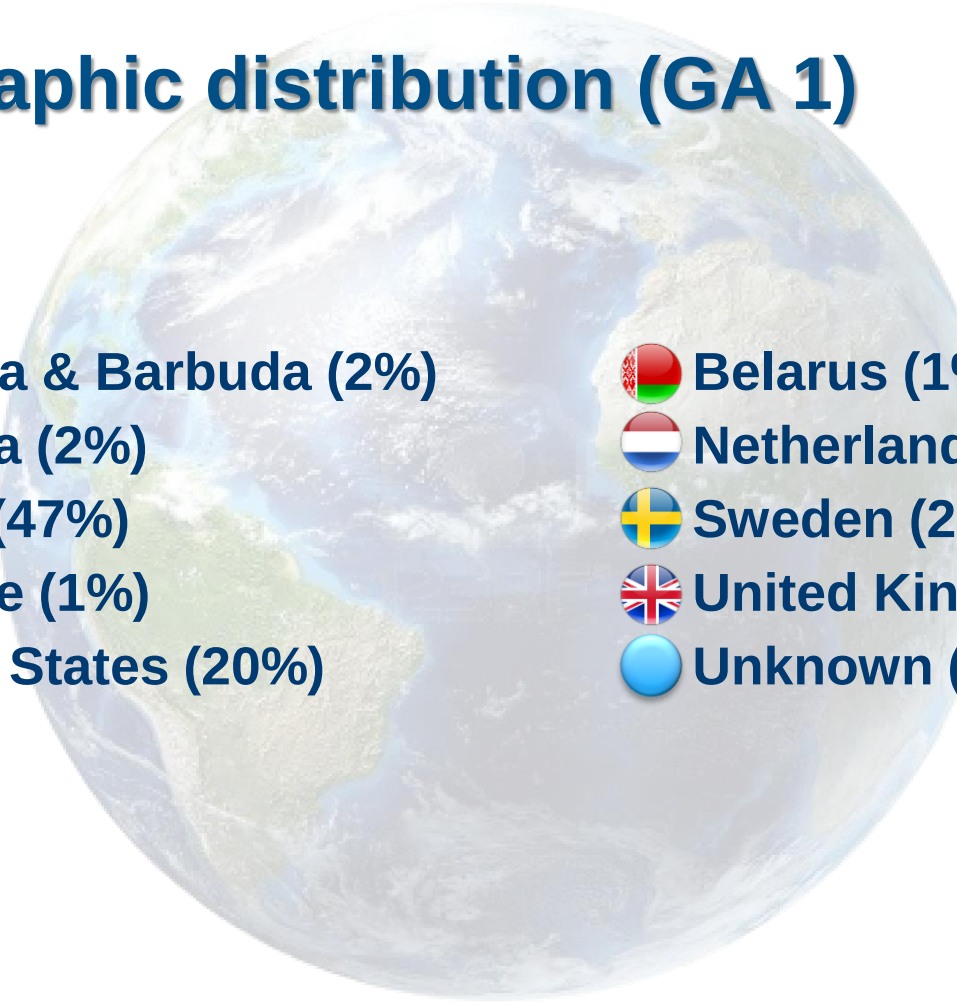
52% Glutaric aciduria type 1

38% Pyridoxine-dependent epilepsy

10% Not reported

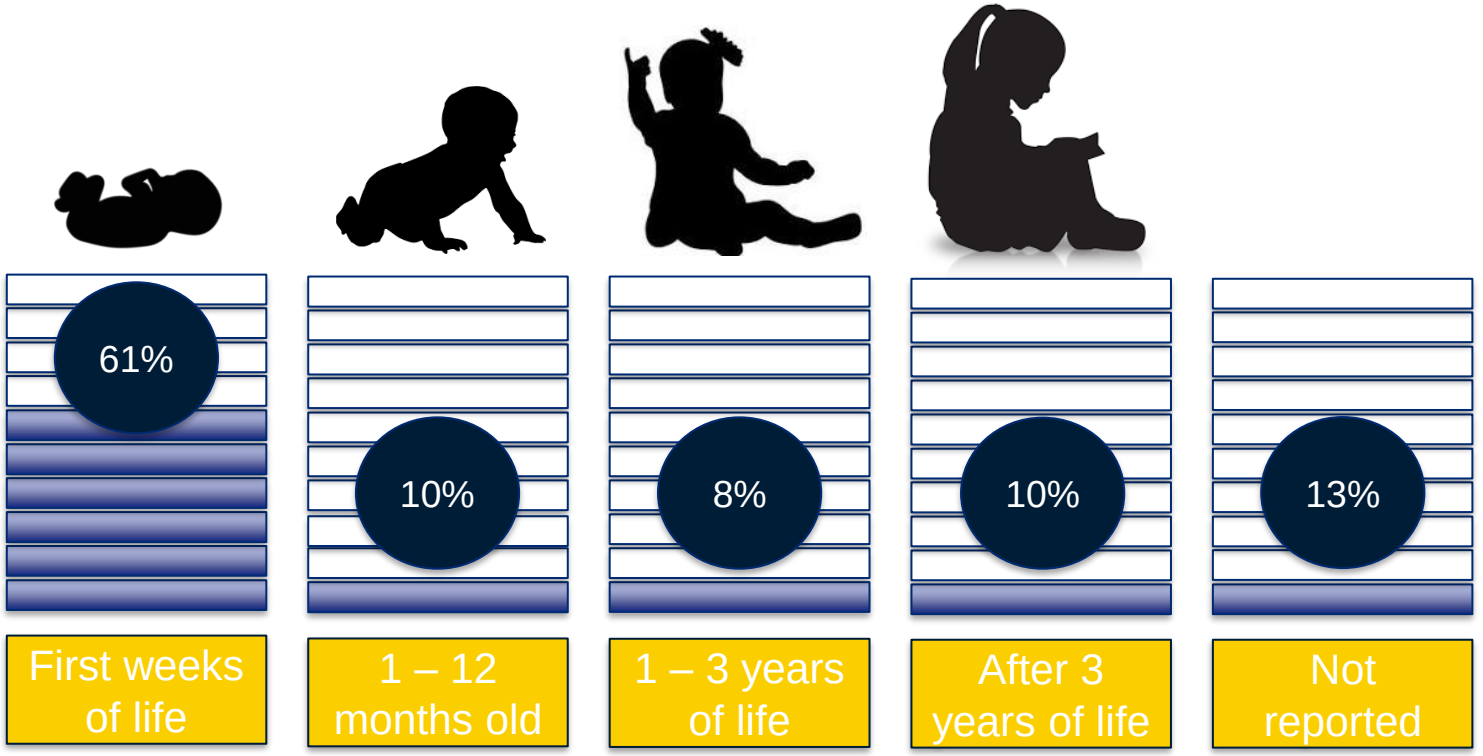


Geographic distribution (GA 1)



- Antigua & Barbuda (2%)
- Canada (2%)
- Spain (47%)
- Ukraine (1%)
- United States (20%)
- Belarus (1%)
- Netherlands (9%)
- Sweden (2%)
- United Kingdom (3%)
- Unknown (13%)

Age at start of treatment (GA 1)



Survey responses (GA 1)

"Is the patient totally asymptomatic?"

30%

"Does the patient follow a diet?"

66%

"Have you ever experienced a situation in which the patient's symptoms worsened, either because of a crisis or more gradually?"

21%

Yes

No

NA

“The unknown. Every single symptom makes me wonder if GA1 is the cause. And regardless of the cause, I wonder if she is getting the treatment needed to keep her safe.”

Q: Can you describe which aspects of the disease is bothering you?

non-English responses
translated with google translate

“…the responsibility of caring for a child with needs that could have such irreversible and life changing consequences, if not handled correctly, has been a heavy weight to bear. We spent her early months/years petrified of our daughter having a crisis and were on constant high vigilance to any minor illness.”

Q: Can you describe which aspects of the disease is bothering you?

non-English responses
translated with google translate

“We are constantly on the alert to protect against potential contagions, social and family issues in many cases. Difficult to compare with a ‘normal’ life if you live another 8 month old. Difficult to find ‘family retirement/retreat’ if you do not have personal/financial centers. It is very physical and emotional.”

Q: Can you describe which aspects of the disease is bothering you?

non-English responses
translated with google translate

Survey responses (GA 1)

"Would you be willing to participate in a clinical trail?"

50%

"Should the new therapy replace the diet?"

57%

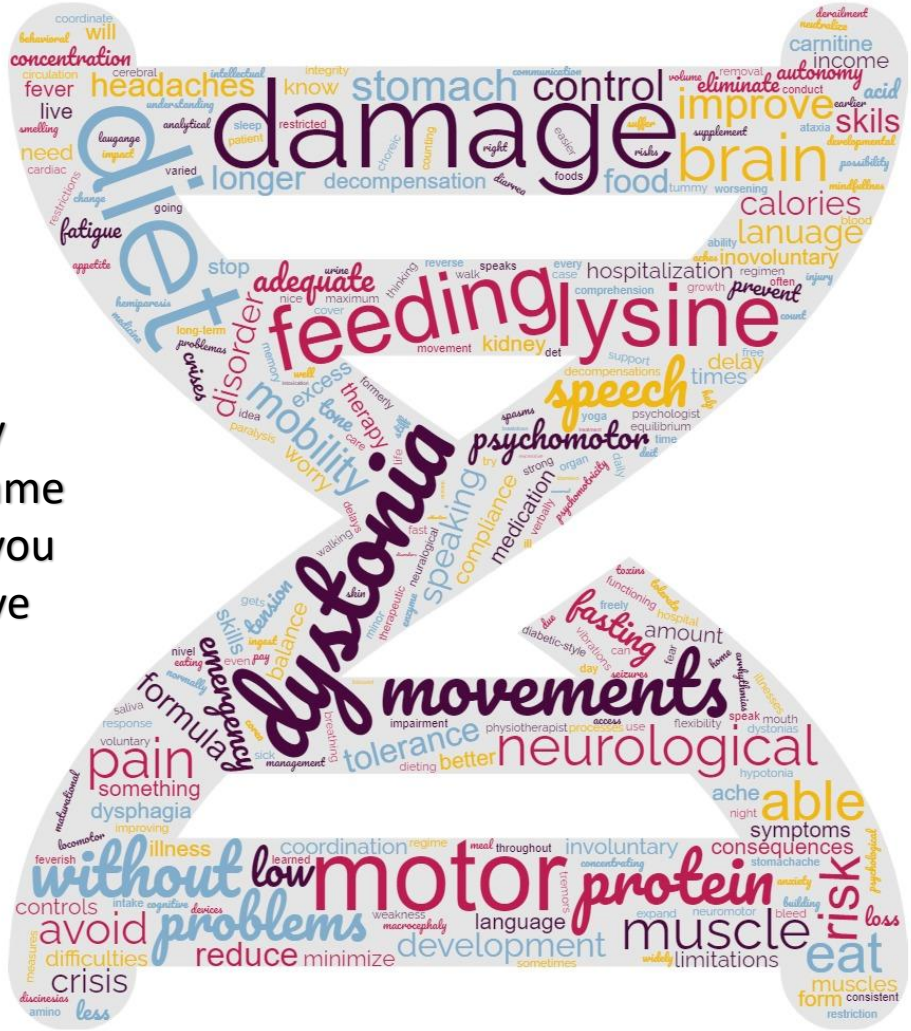
"Would your preference be for a single dose* therapy (e.g. gene therapy) or rather maintenance medication therapy?"

54%

*single dose = yes

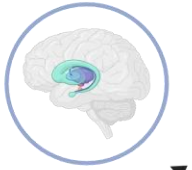
Yes | No | NA

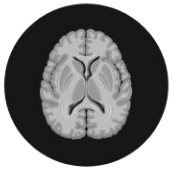
Q: If a new therapy becomes available, name the top 3 symptoms you would like to improve

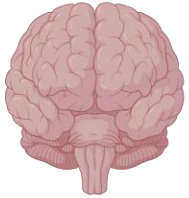


non-English responses translated with google translate

Treatment for GA 1

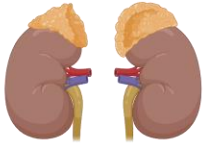


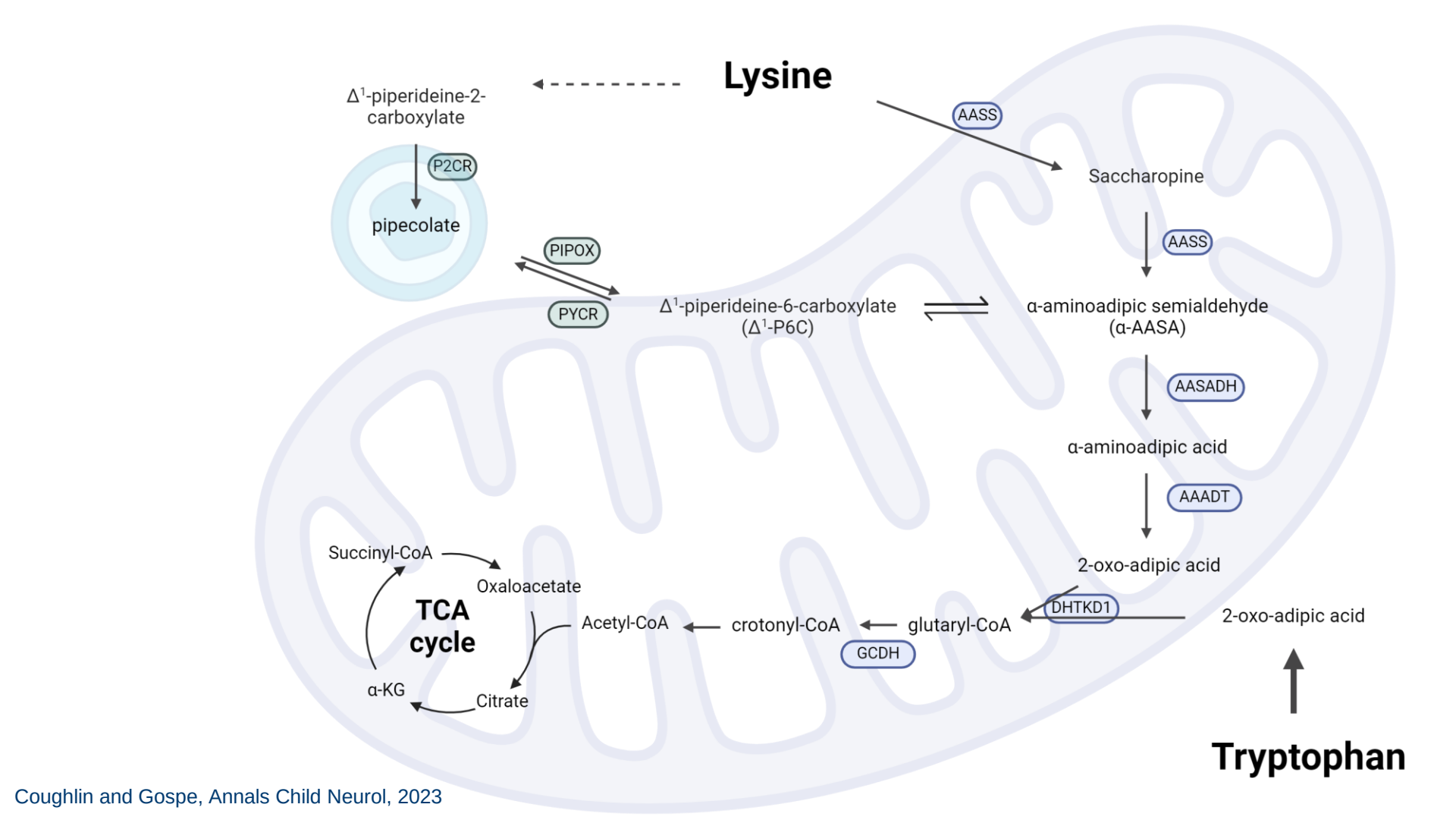



neuro  toxic

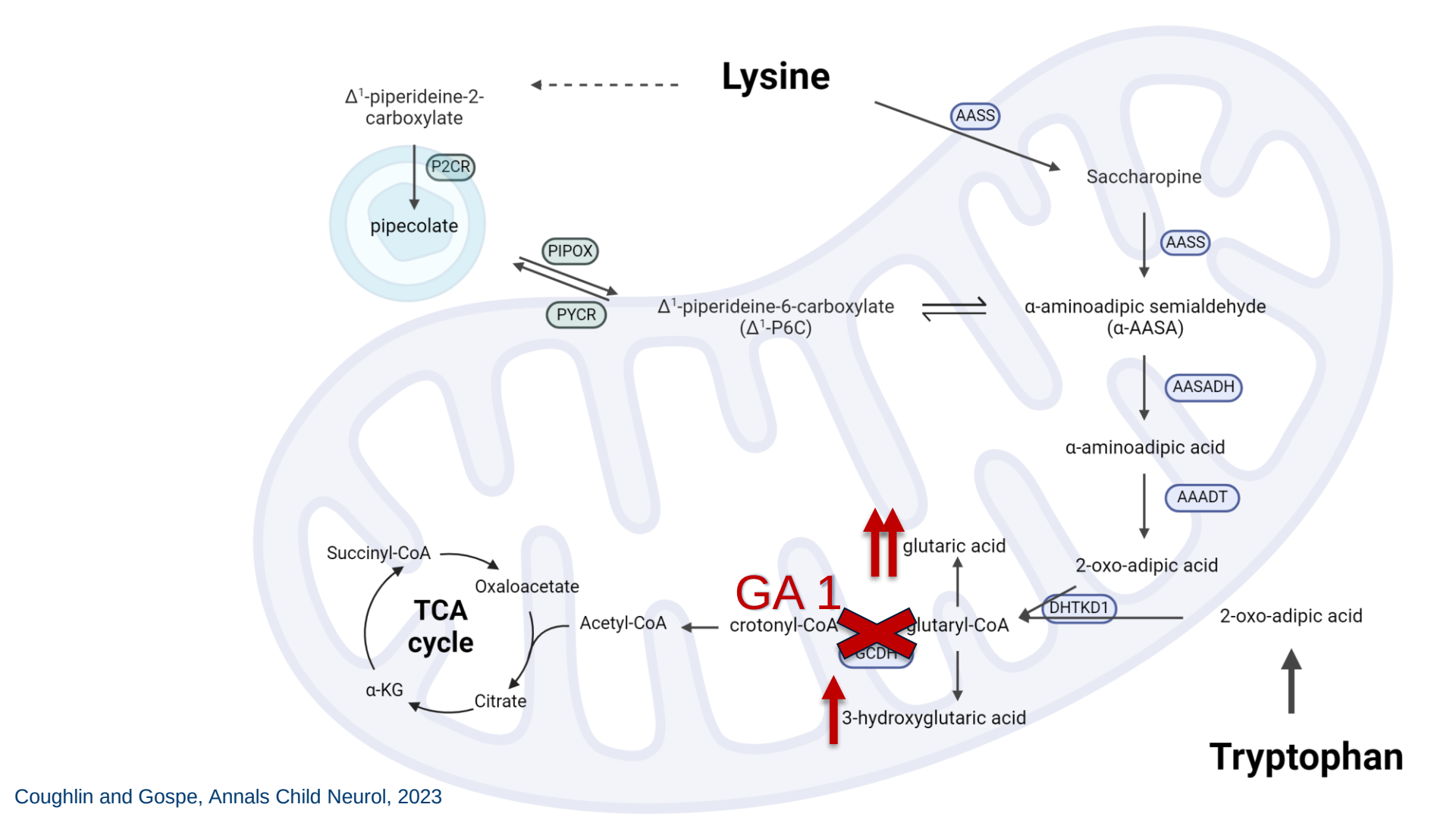
chronic or acute accumulation of

3-hydroxyglutaric acid

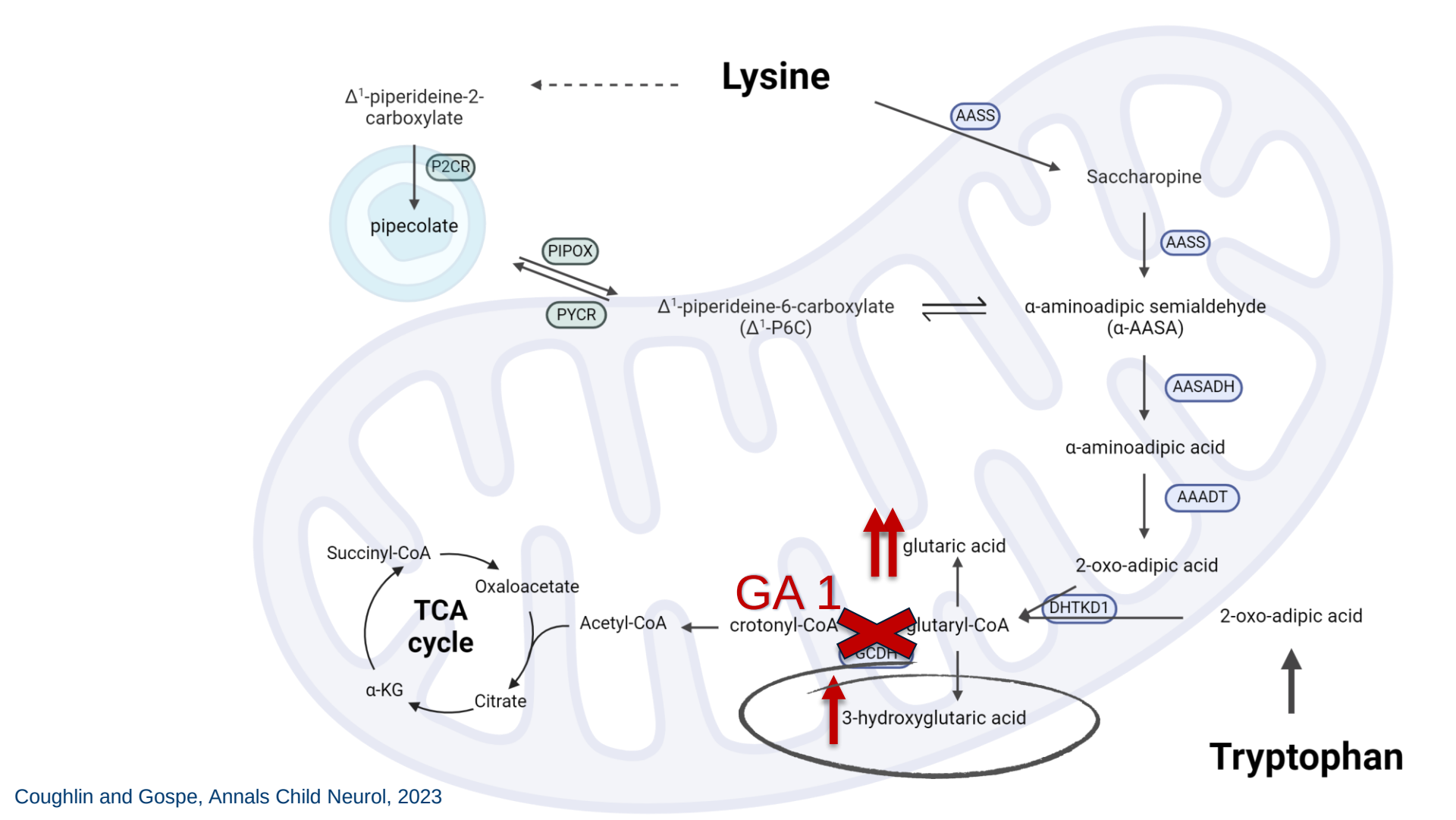




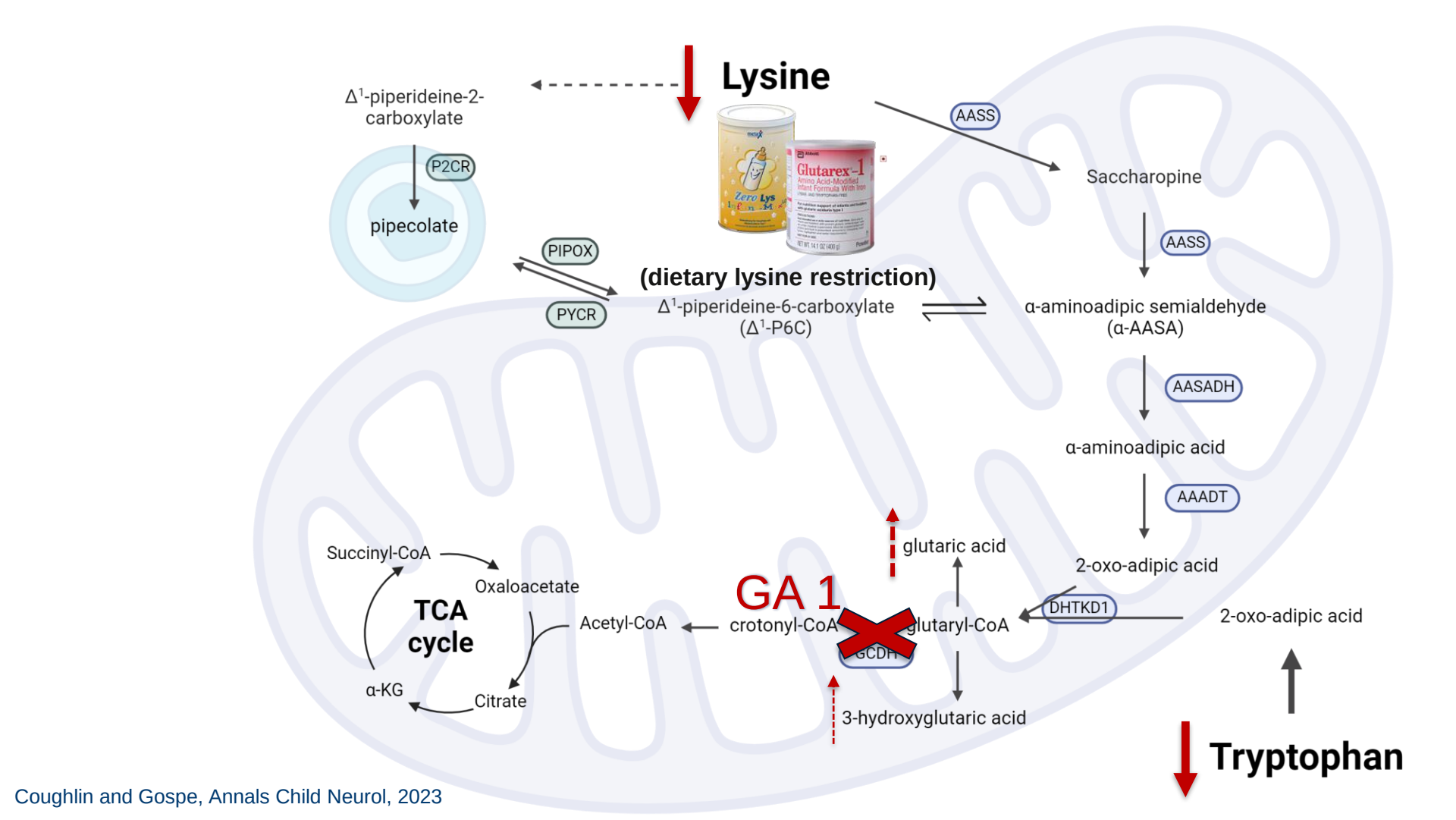
Coughlin and Gospe, Annals Child Neurol, 2023



Coughlin and Gospe, Annals Child Neurol, 2023



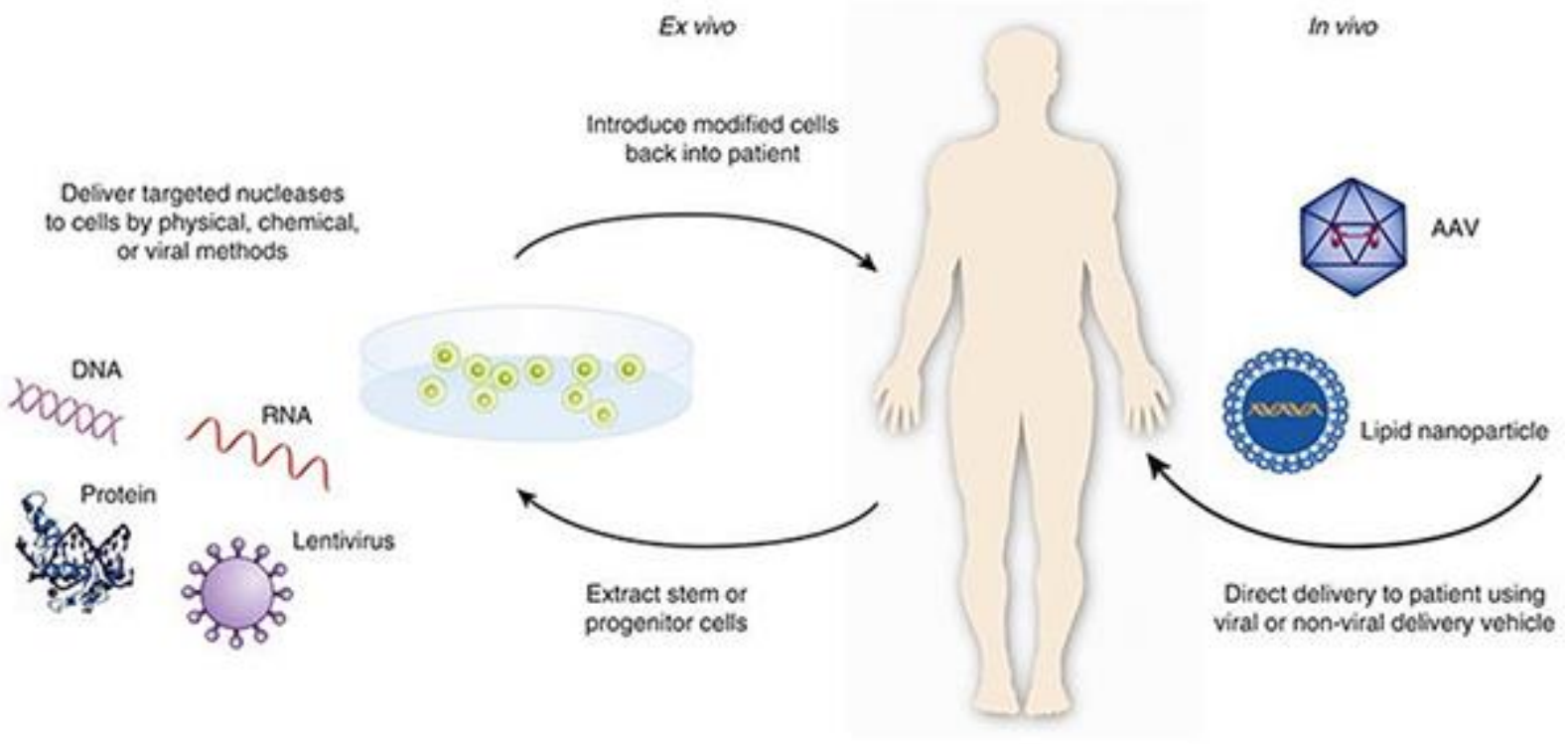
Coughlin and Gospe, Annals Child Neurol, 2023



Coughlin and Gospe, Annals Child Neurol, 2023

Gene Therapy

- gene replacement therapy
- gene addition therapy
- gene editing approaches



FDA.gov: What is Gene Therapy?

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

INBORN ERRORS OF METABOLISM

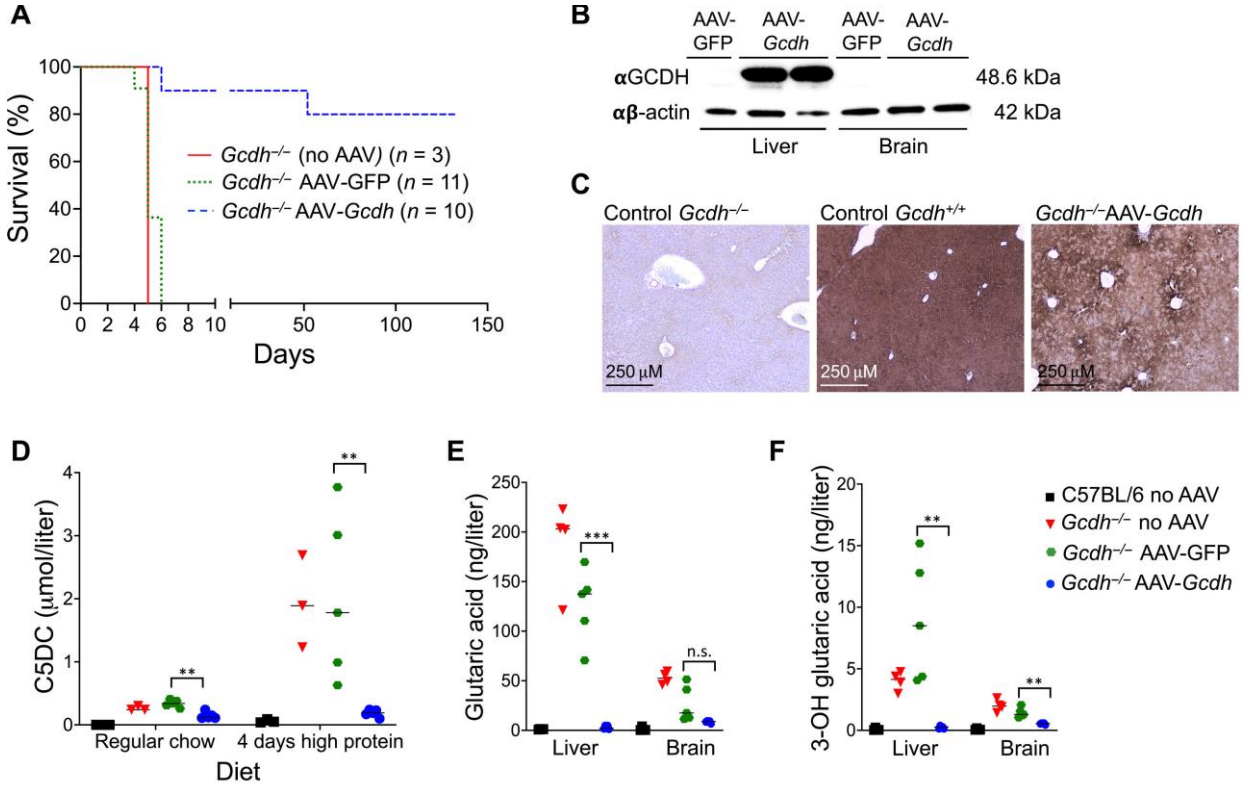
Rescue of glutaric aciduria type I in mice by liver-directed therapies

Mercedes Barzi[1], Collin G. Johnson[2], Tong Chen[1], Ramona M. Rodriguiz[3], Madeline Hemmingsen[1], Trevor J. Gonzalez[4], Alan Rosales[4], James Beasley[1], Cheryl K. Peck[5], Yunhan Ma[1], Ashlee R. Stiles[1], Timothy C. Wood[5], Raquel Maeso-Diaz[6], Anna Mae Diehl[6], Sarah P. Young[1], Jeffrey I. Everitt[7], William C. Wetsel[3], William R. Lagor[8], Beatrice Bissig-Choisat[1], Aravind Asokan[4,9,10,11], Areeg El-Gharbawy[1], Karl-Dimiter Bissig[1,6,10,11,12]*

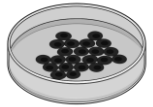
Gene replacement therapy

Improves survival

Improves biochemistry



Barzi et al, Sci Transl, 2023



www.nature.com/gt

Gene Therapy

BRIEF COMMUNICATION

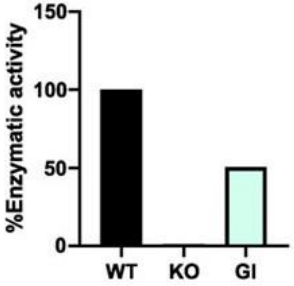
Check for updates

Modeling Glutaric Aciduria Type I in human neuroblastoma cells recapitulates neuronal damage that can be rescued by gene replacement

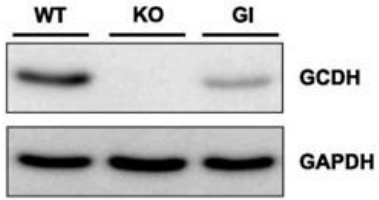
A. Mateu-Bosch[1,2,8], E. Segur-Bailach[1,2,3,8], J. García-Villoria[1,3,4,5], S. Gea-Sorlí[1,3], I. Ruiz[6], J. del Rey[6], J. Camps[1,6,7], M. Guitart-Mampel[1,2,3,5], G. Garrabou[1,2,3,5], F. Tort[1,3,5], A. Ribes[1,3,5] and C. Fillat[1,2,3]✉

Gene replacement therapy

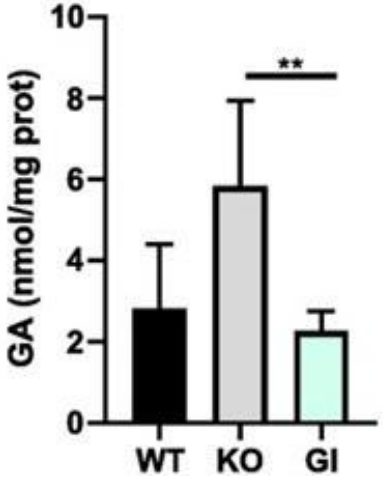
Restore enzyme activity

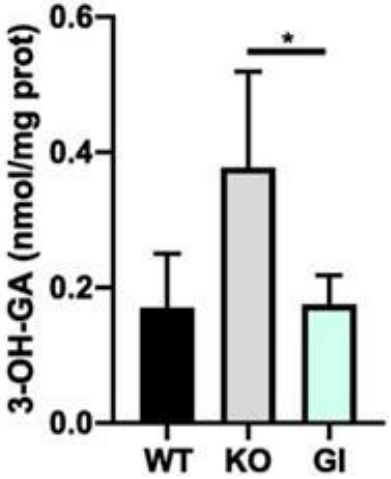


Identify GCDH protein



Normalizes biochemistry





Mateu-Bosch et al, Gene Ther, 2024

Contents lists available at ScienceDirect

Fundamental Research

journal homepage: http://www.keaipublishing.com/en/journals/fundamental-research/

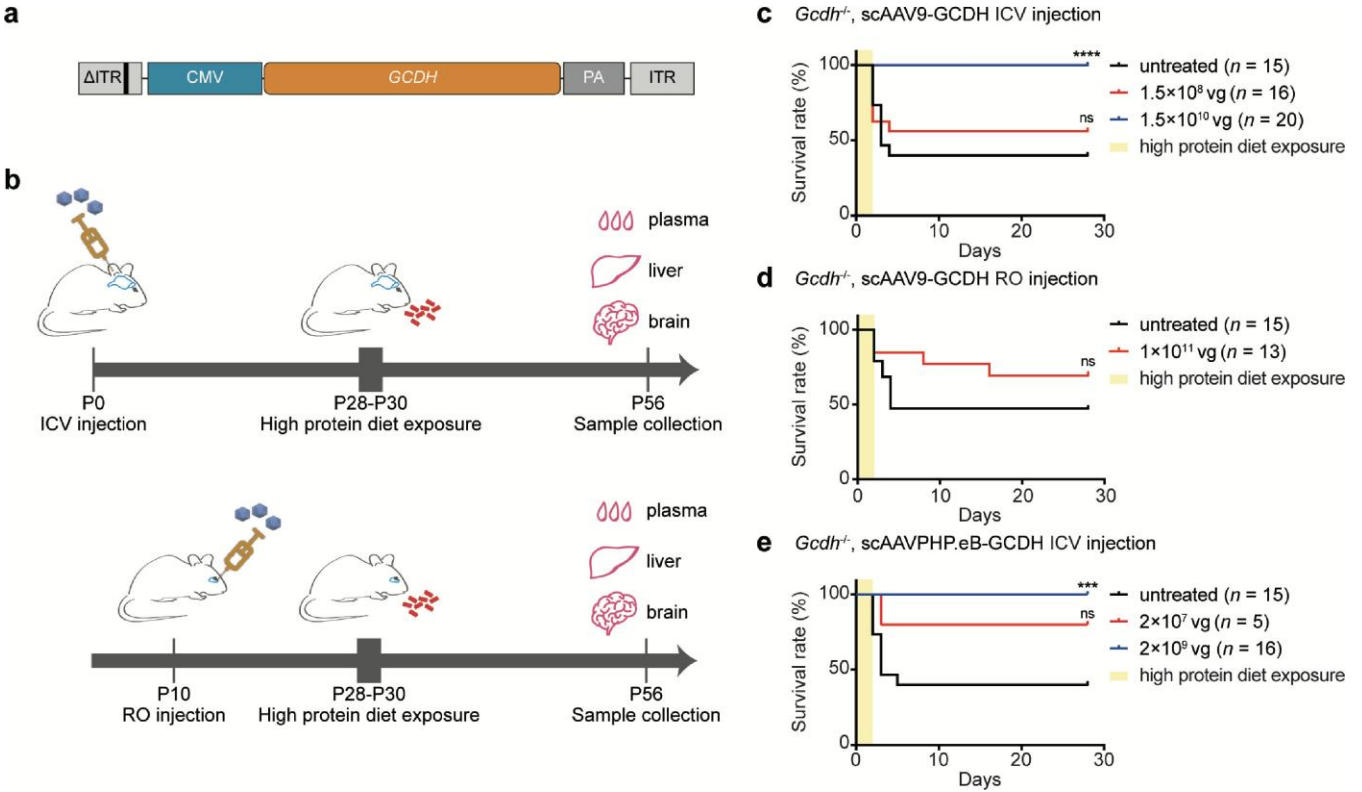
Article

Treatment of glutaric aciduria type I (GA-I) via intracerebroventricular delivery of GCDH

Lu Guo[a,b,c,1], Zhikun Li[a,b,c,1], Yuhuan Li[d,1], Bin Qu[a,b,c,1], Guanyi Jiao[a,b,c,1], Chen Liang[a,b,c], Zongbao Lu[a,b,c], Xin-Ge Wang[a,b,c], Cheng Huang[a,b,c], Hongwei Du[d], Jianmin Liang[d], Qi Zhou[a,b,c,*], Wei Li[a,b,c,*]

[a] *State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China*
[b] *Beijing Institute for Stem Cell and Regenerative Medicine, Beijing 100101, China*
[c] *University of Chinese Academy of Sciences, Beijing 100049, China*
[d] *The First Hospital of Jilin University, Changchun, Jilin 130021, China*

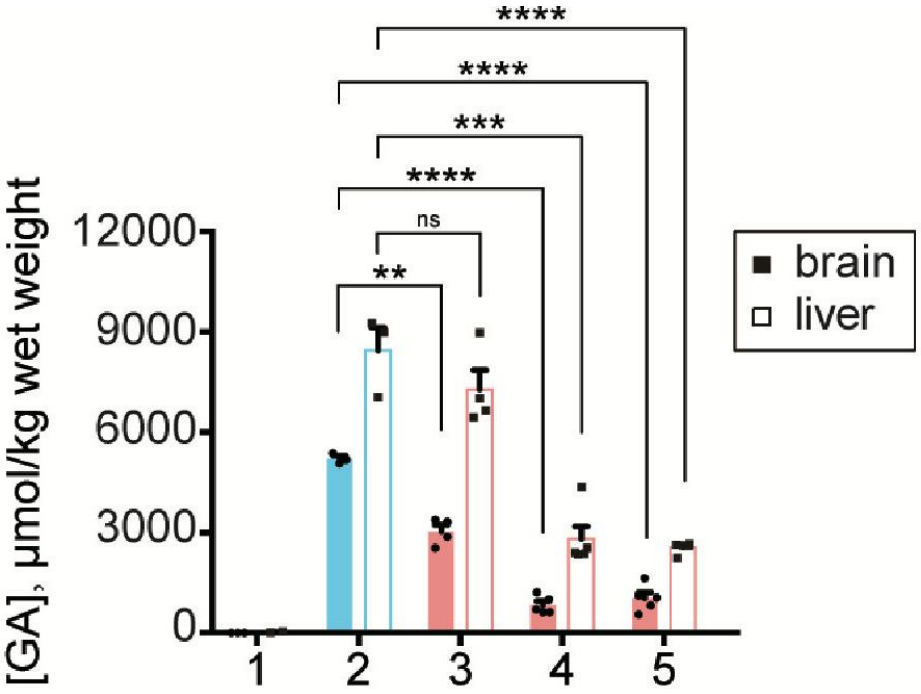
Improves survival



ICV: intracerebroventricular
RO: retro-orbital

Guo et al, Fund Res, 2022

Improves biochemistry



1: WT

2: *Gcdh*$^{-/-}$, untreated

3: *Gcdh*$^{-/-}$, 1.5×10^{8} vg scAAV9, ICV

4: *Gcdh*$^{-/-}$, 1.5×10^{10} vg scAAV9, ICV

5: *Gcdh*$^{-/-}$, 2×10^{9} vg scAAVPHP.eB, ICV

Guo et al, Fund Res, 2022

ClinicalTrials.gov

RECRUITING

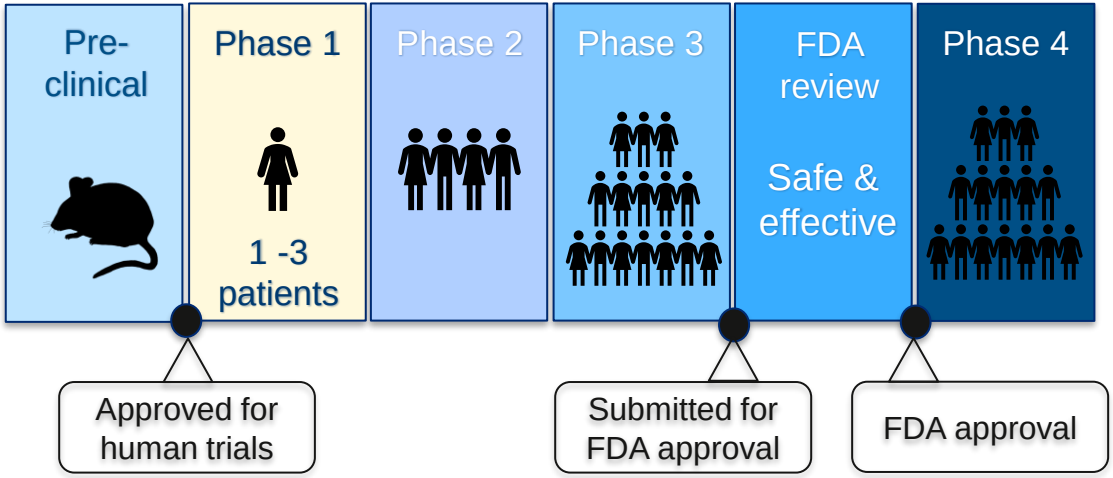
A Study to Evaluate the Tolerability, Safety and Efficacy of VGM-R02b

ClinicalTrials.gov ID NCT06217861

Sponsor Shanghai Vitalgen BioPharma Co., Ltd.

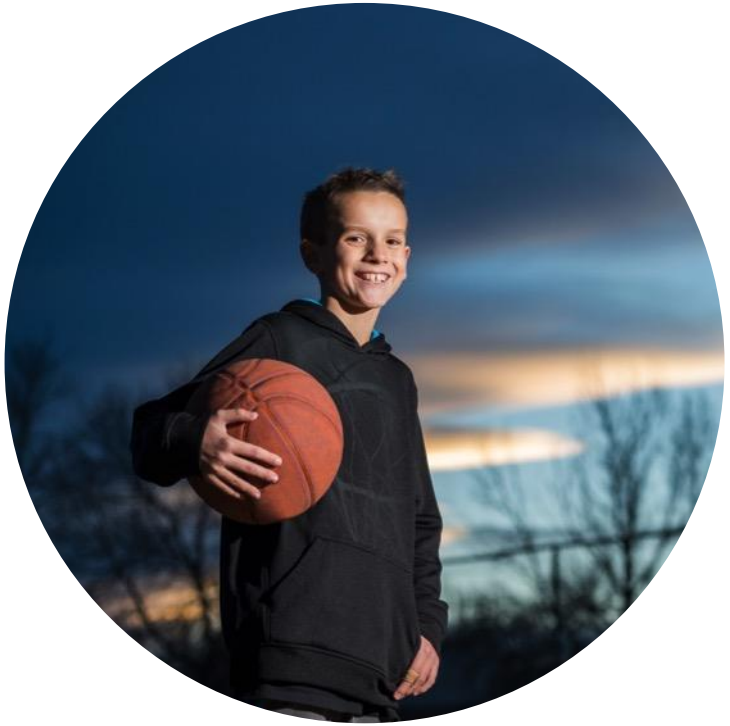
Information provided by Shanghai Vitalgen BioPharma Co., Ltd. (Responsible Party)

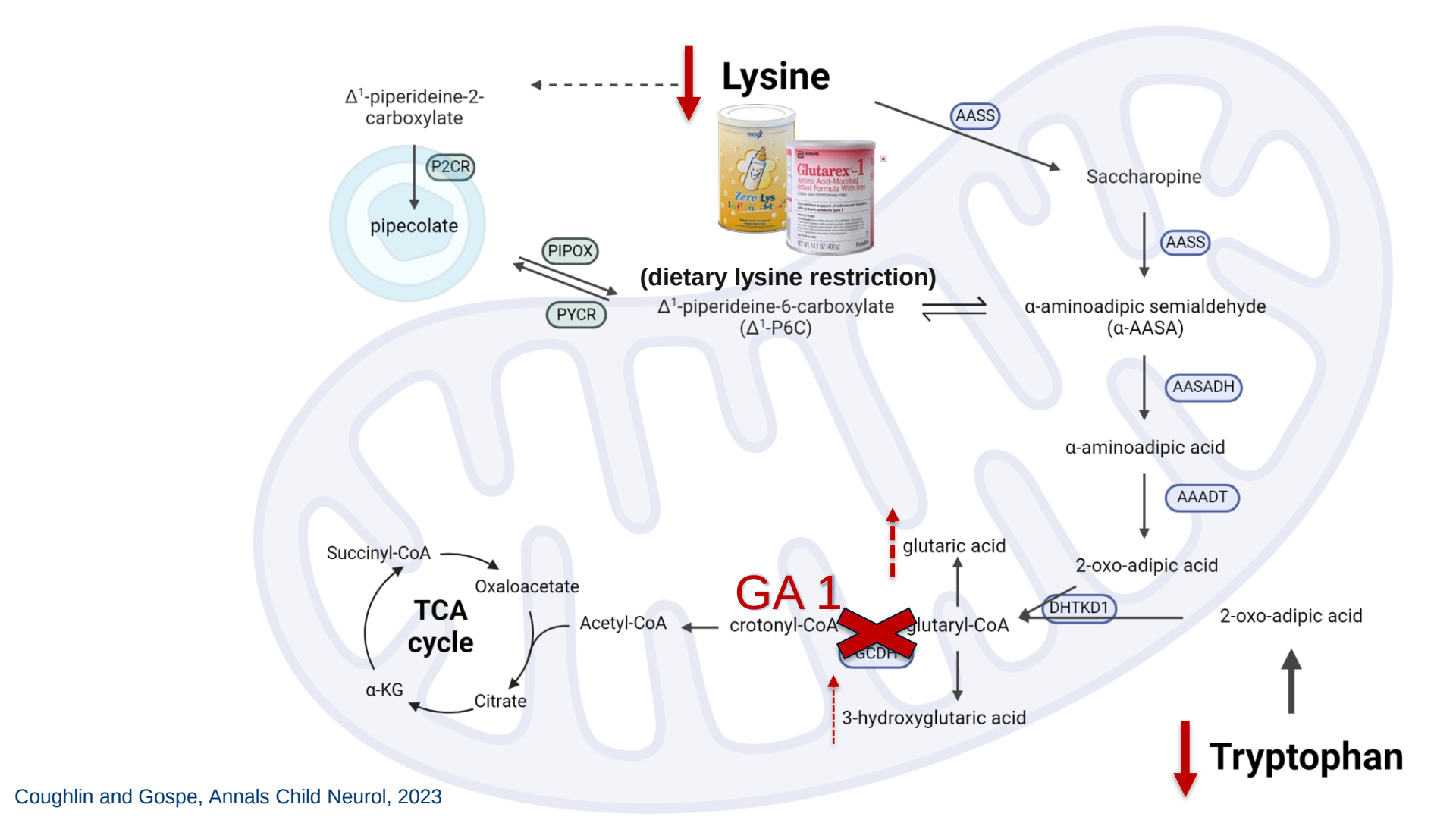
Last Update Posted 2024-05-17



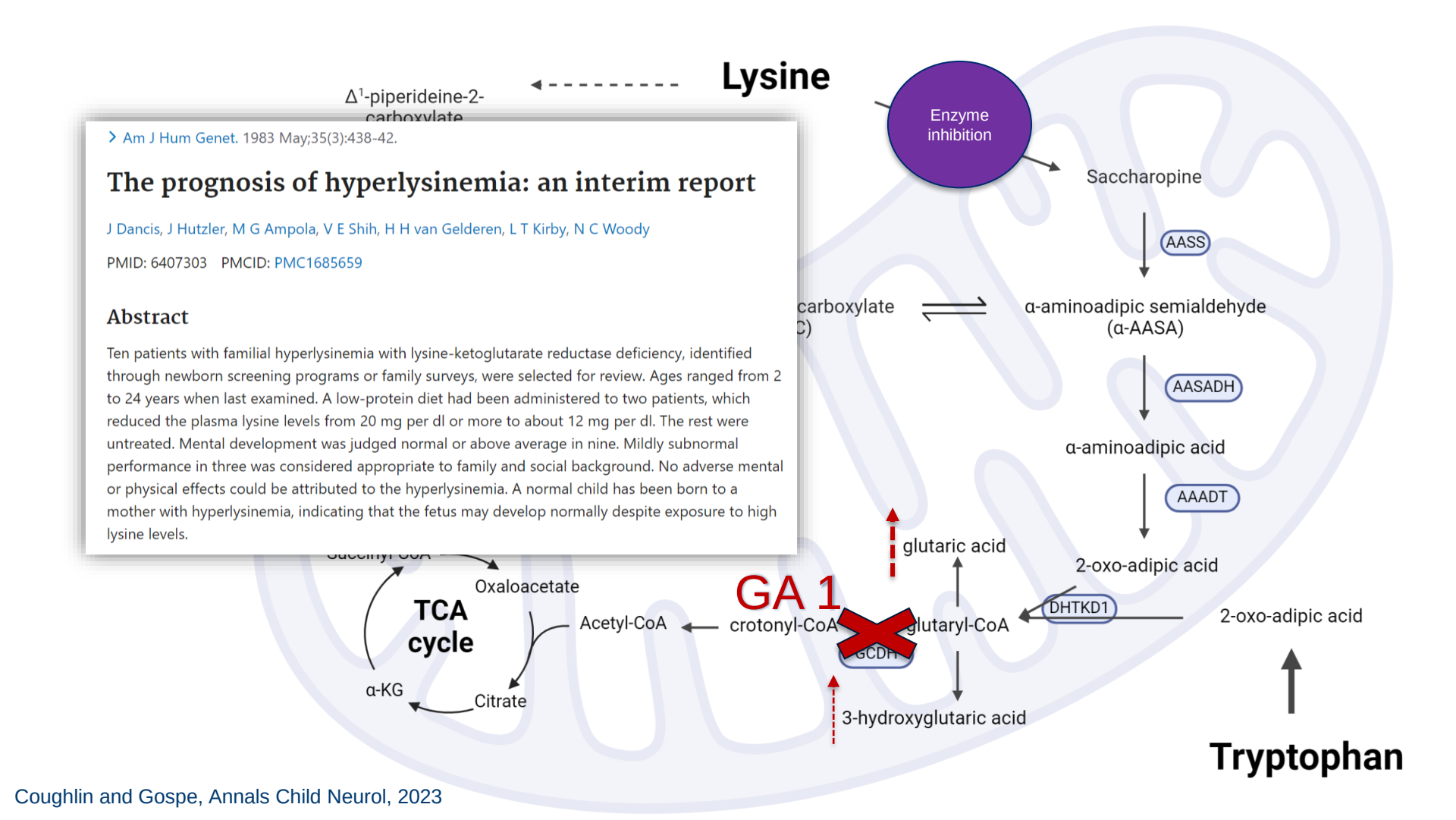
substrate reduction therapy

- upstream enzyme inhibition





Coughlin and Gospe, Annals Child Neurol, 2023



> Am J Hum Genet. 1983 May;35(3):438-42.

The prognosis of hyperlysinemia: an interim report

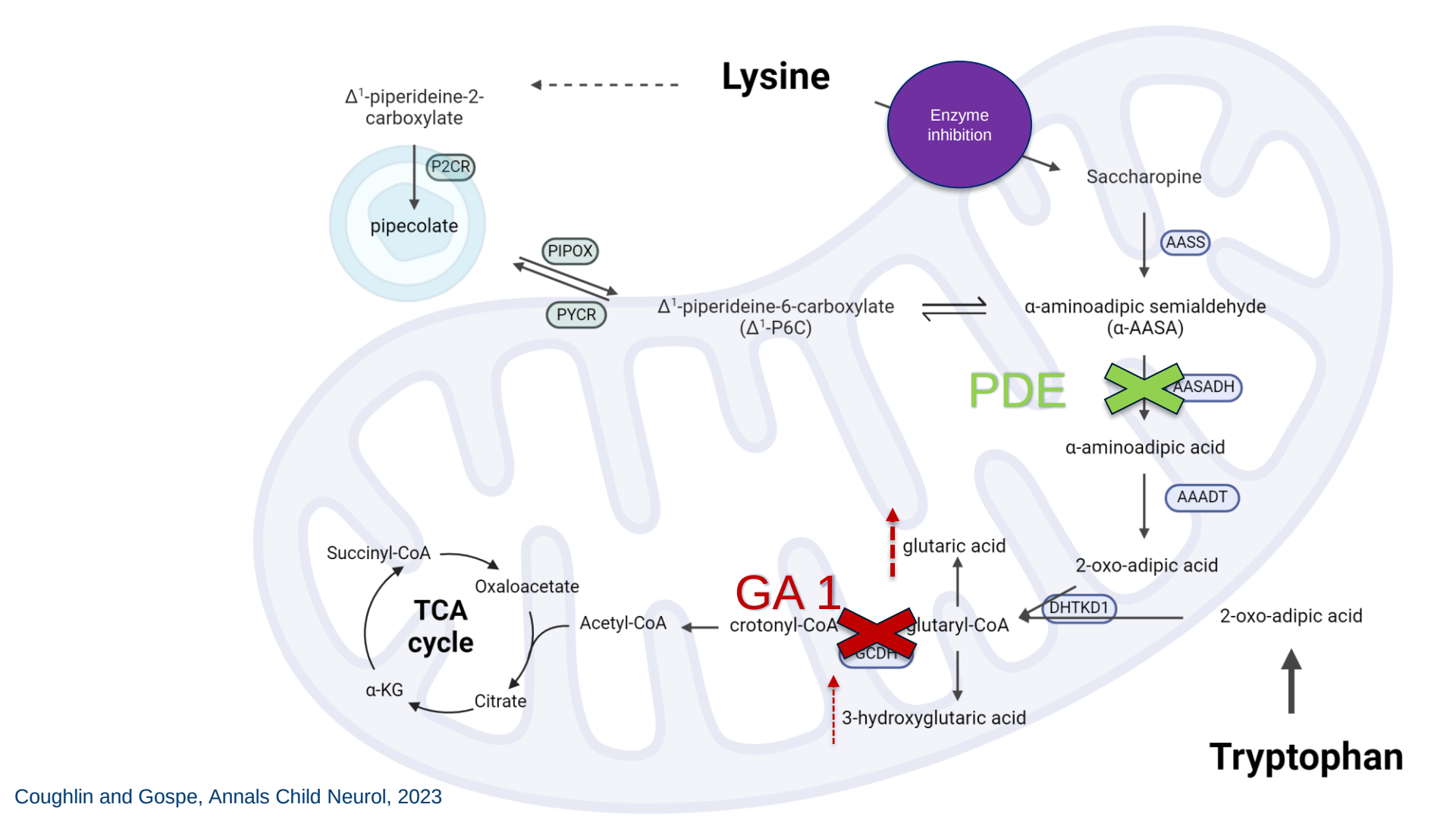
J Dancis, J Hutzler, M G Ampola, V E Shih, H H van Gelderen, L T Kirby, N C Woody

PMID: 6407303 PMCID: PMC1685659

Abstract

Ten patients with familial hyperlysinemia with lysine-ketoglutarate reductase deficiency, identified through newborn screening programs or family surveys, were selected for review. Ages ranged from 2 to 24 years when last examined. A low-protein diet had been administered to two patients, which reduced the plasma lysine levels from 20 mg per dl or more to about 12 mg per dl. The rest were untreated. Mental development was judged normal or above average in nine. Mildly subnormal performance in three was considered appropriate to family and social background. No adverse mental or physical effects could be attributed to the hyperlysinemia. A normal child has been born to a mother with hyperlysinemia, indicating that the fetus may develop normally despite exposure to high lysine levels.

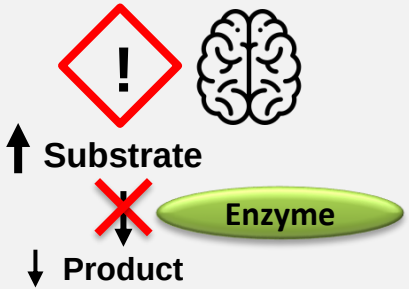
Coughlin and Gospe, Annals Child Neurol, 2023

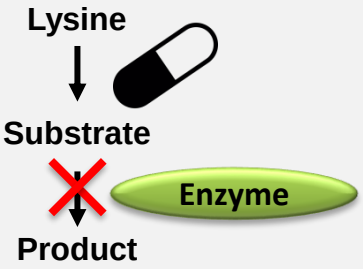


Coughlin and Gospe, Annals Child Neurol, 2023

Development of an oral substrate reduction therapy medication for Glutaric Aciduria Type 1

Glutaric Aciduria Type 1

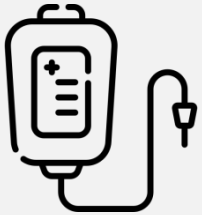




Glutaric aciduria type 1
Inherited defect in an enzyme involved in lysine degradation
Substrate accumulation is neurotoxic

Current treatment

&



New treatment is a small molecule drug that prevents the formation of the toxic substrates

See also OAA Newsletter Winter 2023

sander.houten@mssm.edu

Received: 27 April 2020 | Revised: 4 June 2020 | Accepted: 17 June 2020

DOI: 10.1002/jimd.12276

RAPID COMMUNICATION

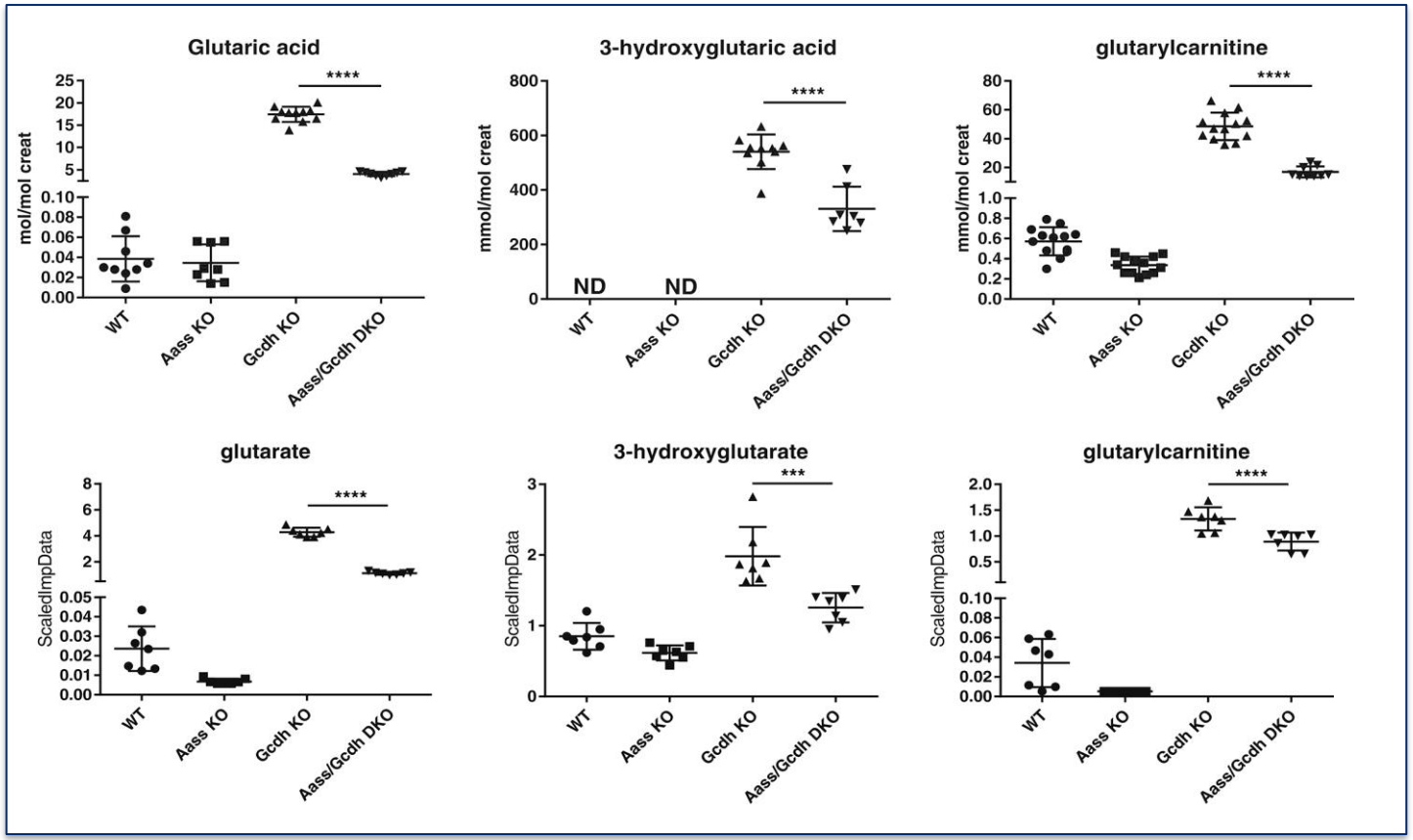
JIMD SSIEM WILEY

Deletion of 2-aminoadipic semialdehyde synthase limits metabolite accumulation in cell and mouse models for glutaric aciduria type 1

João Leandro[1,2] | Tetyana Dodatko[1,2] | Robert J. DeVita[3,4] | Hongjie Chen[1,5] | Brandon Stauffer[1,5] | Chunli Yu[1,5] | Sander M. Houten[1,2]

plasma

brain

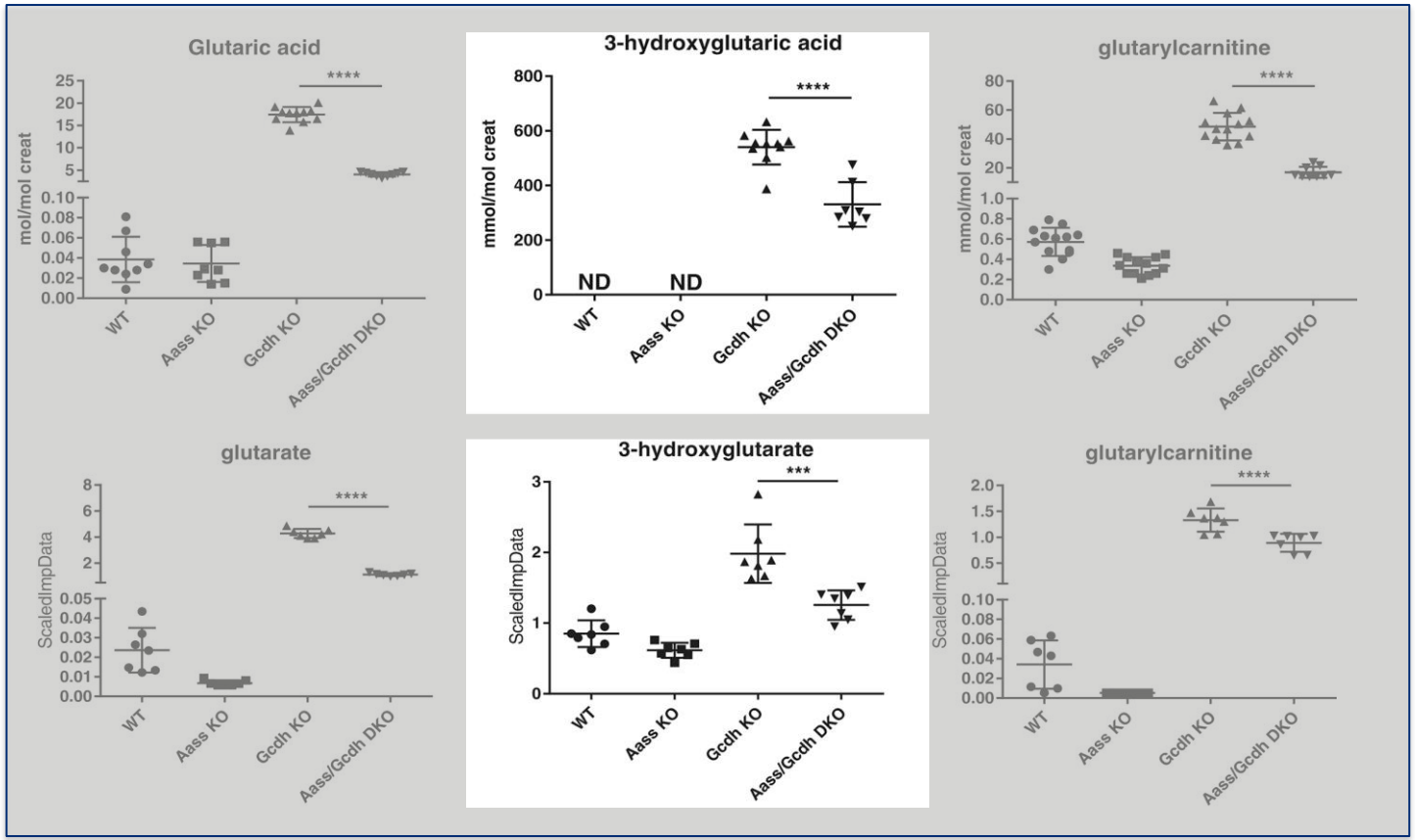


Leandro et al, J Inherit Metab Dis, 2020

Improves biochemistry

plasma

brain



Leandro et al, J Inherit Metab Dis, 2020

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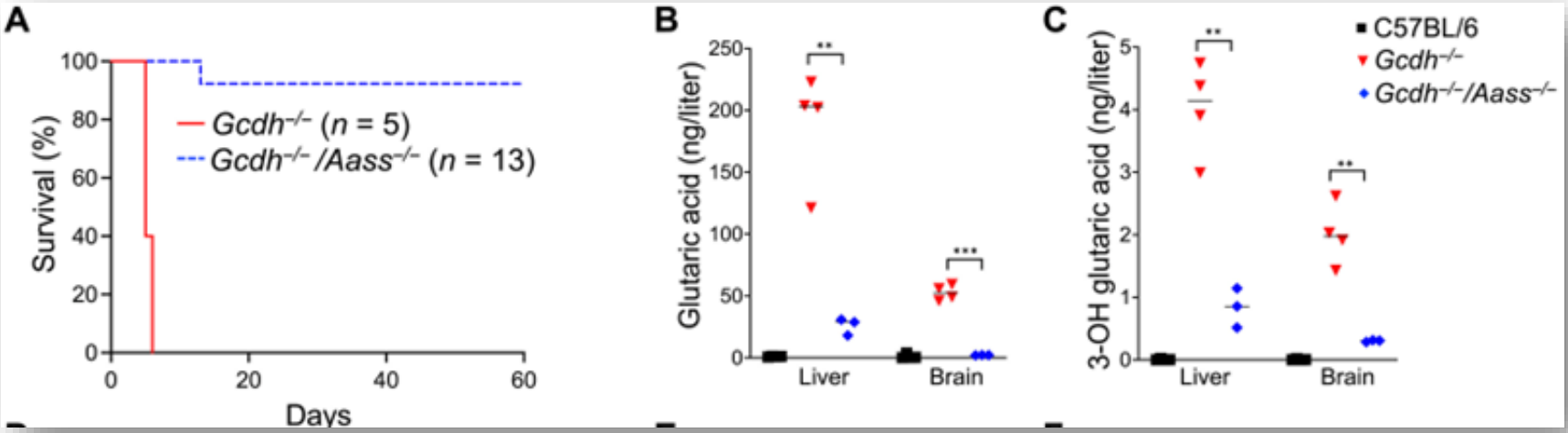
Improves survival

Improves biochemistry

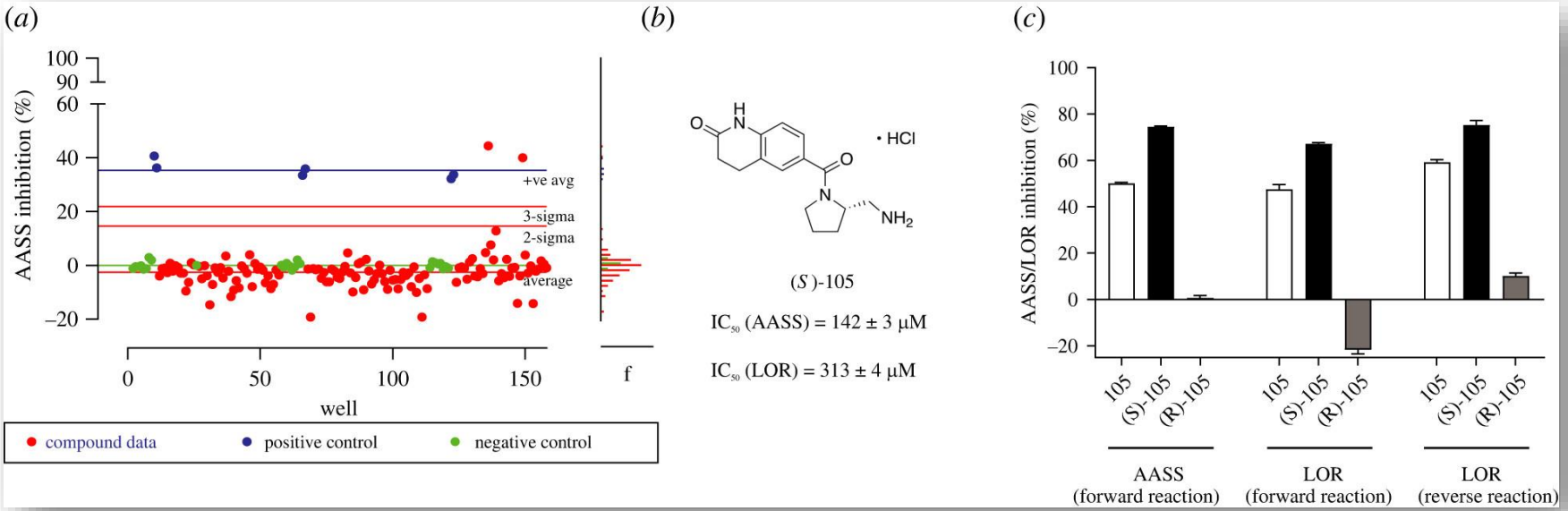


Barzi et al, Sci Transl, 2023

Stratagies to inhbit AASS

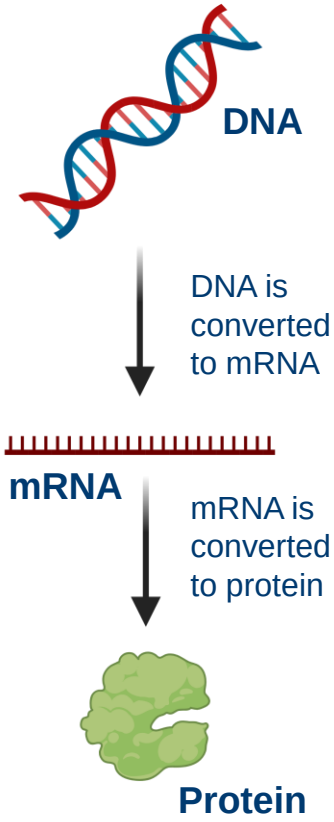
- Repurpose FDA approved drugs
- Antisense oligonucleotides (ASO)
- miRNA inhibition
- Gene editing (i.e. CRISPR)

Repurposing drugs to target AASS

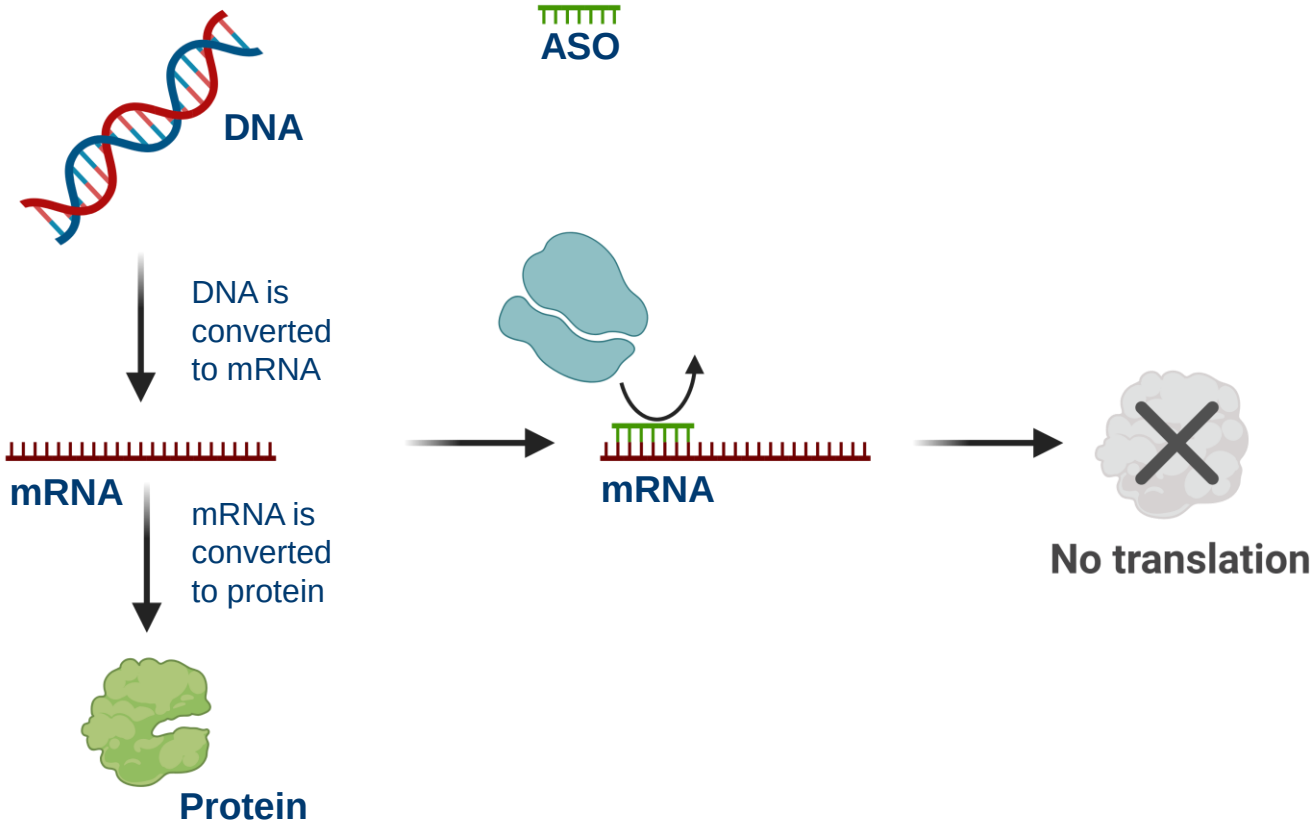


Leandro et al, Open Biol, 2022

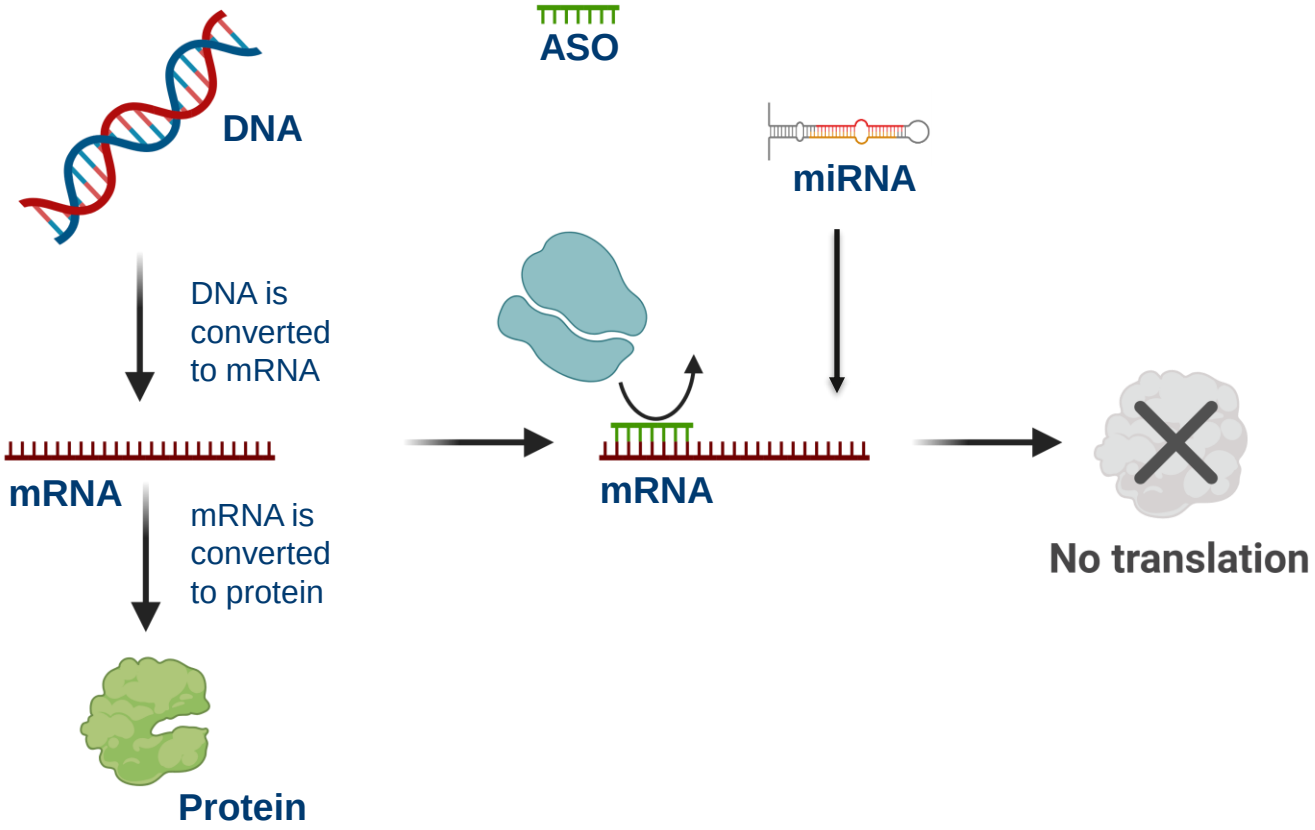
Antisense Oligonucleotide (ASO)

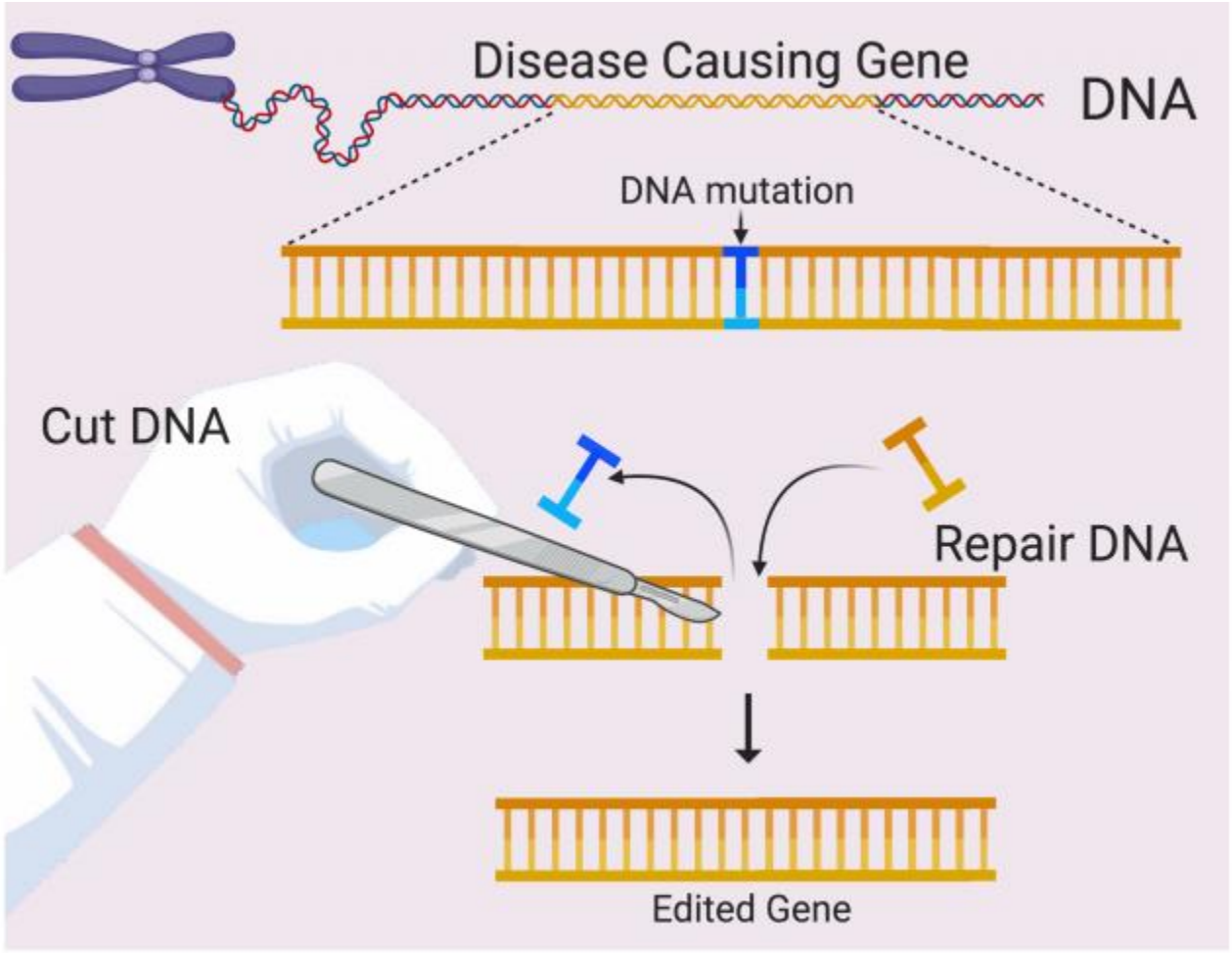


Antisense Oligonucleotide (ASO)



Antisense Oligonucleotide (ASO) and miRNA



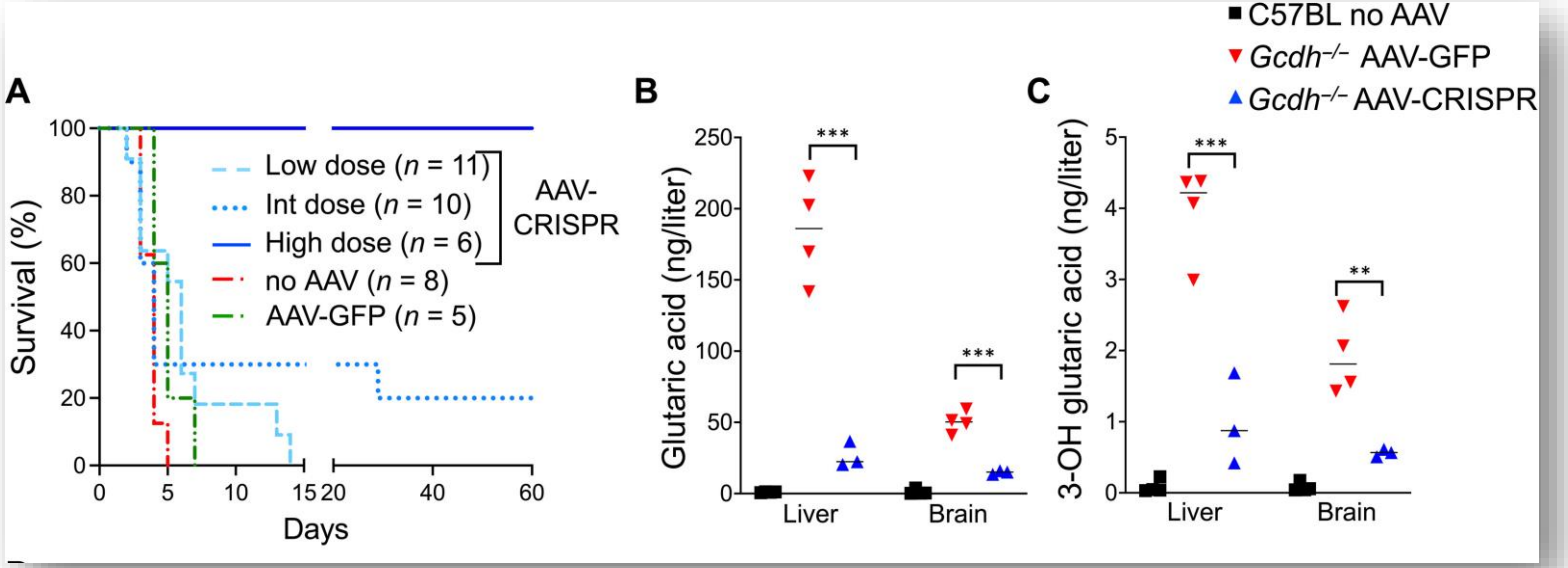


Courtesey of UCL.ac.uk: Genome Editing

CRISPR targeting (to inhibit) AASS

Improves survival

Improves biochemistry



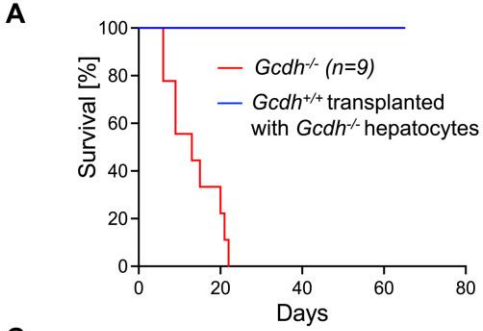
Barzi et al, Sci Transl, 2023

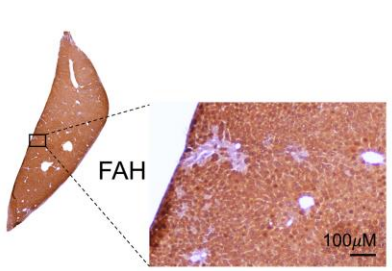
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

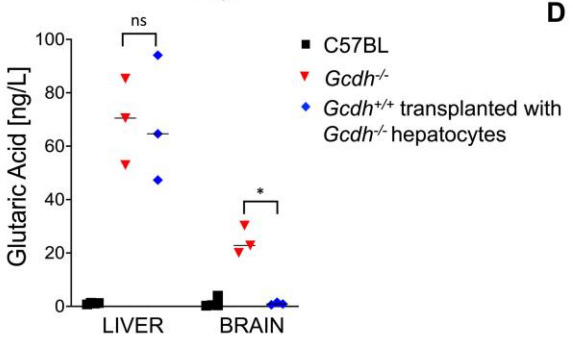
INBORN ERRORS OF METABOLISM

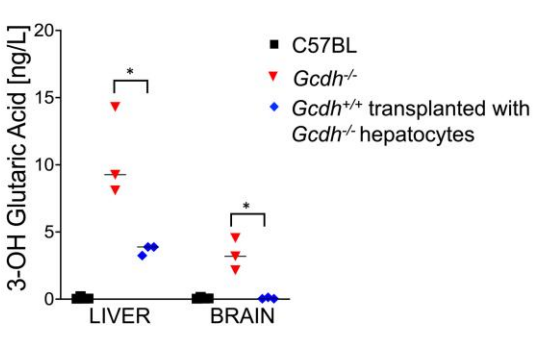
Rescue of glutaric aciduria type I in mice by liver-directed therapies

Mercedes Barzi[1], Collin G. Johnson[2], Tong Chen[1], Ramona M. Rodriguiz[3], Madeline Hemmingsen[1], Trevor J. Gonzalez[4], Alan Rosales[4], James Beasley[1], Cheryl K. Peck[5], Yunhan Ma[1], Ashlee R. Stiles[1], Timothy C. Wood[5], Raquel Maeso-Diaz[6], Anna Mae Diehl[6], Sarah P. Young[1], Jeffrey I. Everitt[7], William C. Wetsel[3], William R. Lagor[8], Beatrice Bissig-Choisat[1], Aravind Asokan[4,9,10,11], Areeg El-Gharbawy[1], Karl-Dimiter Bissig[1,6,10,11,12]*









E

Strain	Gcdh-/-/Aass+/+ mouse	Gcdh-/-/Aass+/+ mouse	Gcdh-/-/Aass-/- mouse	Gcdh-/-/Aass-/- mouse	Gcdh+/+/Aass+/+ mouse
Transplantation	none	Gcdh +/+/Aass+/+ cells	none	Gcdh-/-/Aass+/+ cells	Gcdh-/-/Aass+/+ cells
Outcome	☠	☺	☺	☠	☺

JIMD
JOURNAL OF INHERITED METABOLIC DISEASE
SSIEM

EDITORIAL | Free Access

Is it time to start to consider treating the liver in glutaric aciduria type 1?

Sander Houten, Curtis R. Coughlin II

First published: 10 May 2023 | https://doi.org/10.1002/jimd.12623

When is the cure available?

- **Improvement in survival**
- Mice are not people
- Eating very HIGH lysine diets
- Only ~50% of these mice get sick or die

- **Improvement in biochemistry**
- Is the improvement enough?

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

Can I help?

Cross sectional study

- Curtis.Coughlin@cuanschutz.edu
- kristine.pauly@cuanschutz.edu
- Coughlinlab.org

CHARLIE patient & caregiver survey

RARE DISEASES
CLINICAL RESEARCH NETWORK

Coughlin laboratory

- **Kristie Pauly, BS, MPH**
- Michael Woontner, PhD

Clinical colleagues

- **Clara van Karnebeek, MD, PhD** (Netherlands)
- **Sidney Gospe Jr, MD, PhD** (WA)
- Jose E. Abdenur, MD (CA)
- Nicola Longo, MD, PhD (CA)
- Phillipa Mills, PhD (United Kingdom)
- Laura Tseng (MD/PhD student, Netherlands)
- International PDE consortium members

Research collaborators

- **Clara van Karnebeek, MD, PhD** (Netherlands)
- Valerie Gailus-Durner, PhD (Germany)
- Cristina Fillat (Spain)
- Stefan Kölker, MD (Germany)
- Blair Leavitt (Canada)
- Carole Linster, PhD (Luxemburg)
- Giancarlo la Marca (Italy)
- Ron Wevers (Netherlands)
- The CHARLIE consortium members

Colorado collaborations

- Sommer Gaughan, RD
- Johan Van Hove, MD, PhD
- Michael Wempe, PhD
- Tim Wood, PhD
- Section of Clinical Genetics and Metabolism

Foundations, Consortiums, Funding Sources

Organic Acidemia Association

Charlie

CurePDE Foundation
Empowering Families and Igniting Possibilities

PDE
Pyridoxine Dependent Epilepsy
Pdeonline.org

VKS

umd·nl united for metabolic diseases

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Colorado Clinical and Translational Sciences Institute (CCTSI)
UNIVERSITY OF COLORADO DENVER | ANSCHUTZ MEDICAL CAMPUS

EUROPEAN JOINT PROGRAMME RARE DISEASES

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Patients and families