MSUD FAMILY SUPPORT GROUP RESEARCH AGENDA

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WE ARE A RARE DISEASE!

- Worldwide incidence is estimated at 1:185,000
- It is estimated that fewer than 30 babies are born with MSUD in the US each year*
- More prevalent in
  - the Mennonite population - 1:380
  - MidEast Arab– estimated 1:10,000-1:15,000**
  - Ashkenazi Jews – 1:26,000

*https://newbornscreening.hrsa.gov/conditions/maple-syrup-urine-disease

**Expanded Newborn Screening Program in Saudi Arabia: Incidence of screened disorders: Saudi Newborn Screening Program. Alfadhel 2017

AIM OF OUR RESEARCH AGENDA

- To drive research in MSUD
- To be purposeful in our approach to supporting research
  - Prioritize projects
- To improve the lives of those with MSUD

HOW CAN WE IMPROVE THE LIVES OF THOSE WITH MSUD?

- **Find a cure!**
- **Improve treatments**
  - Improved BCAA control
  - Reduced reliance on formula/increase tolerance to protein
  - Support for cognitive and emotional difficulties
- **Develop a home monitor** to:
  - ID elevated leucine levels rapidly
  - ID blood leucine trends
  - ID response to treatment in real time
  - Understand within-day fluctuations in blood leucine levels
- **Understand how MSUD affects the aging process**
  - Young adults → old age

MSUD SCIENTIFIC ADVISORY BOARD

formed in 2020

- Plays a key role in developing our research agenda
- Reviews requests for proposals
- Meets biannually to discuss current projects and suggest new directions

MSUD SCIENTIFIC ADVISORY BOARD MEMBERS

- **Lindsay Burrage**, Baylor College of Medicine
- **Andrea Gropman**, Children's National
- **David Fischler**, Xyzagen
- **Irini Manoli**, NIH
- **Kevin Strauss**, Clinic for Special Children
- **Dan Wang**, University of Massacheusetts
- **Tilla Worgall**, Columbia University
- **Richard "Max" Wynn**, UT Southwestern Medical Center

MSUD SCIENCE SUMMIT 2024

- Our scientific advisors and other invited scientists from around the globe met yesterday to discuss:
  - Gene therapy
  - MSUD and the brain
  - Therapeutic agents
- 1st convened in 2022

MSUD PATIENT REGISTRY: Key to our research goals

- Essential to understanding the lived experience of those with MSUD worldwide
- Will help us understand the challenges of living with MSUD and how that changes over a lifetime
- Sharing your health data and experiences will accelerate research

Recent Projects Supported by the MSUD FSG

- **Gene therapy**
  - Dr. John Counsell
  - Dr. Kevin Strauss
- **MSUD and the brain**
  - Dr. Rebecca Ahrens-Nicklas
  - Dr. Jessica Gold
  - Dr. Andrea Gropman and Kosar Khaksari
- **Leucine monitor**
  - Dr. Lital Alfonta: Ben Gurion University of the Negev
  - Dr. Milan Stojanovic: Columbia University

OTHER THERAPIES IN THE PIPELINE

<u>Goal</u>: to allow for more protein in the diet and help reduce the risk of a metabolic decompensation with illness

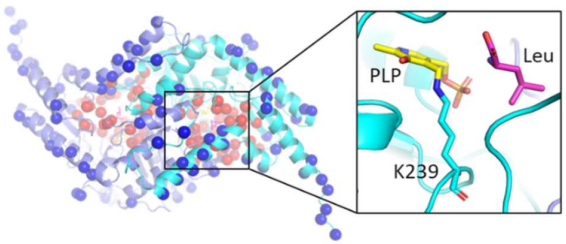
- **Kinase inhibitors**
  - Na Phenylbutyrate
  - Zevra (previously Acer)
- **Enzyme therapy**
  - Oral administration of leu decarboxylase to break down leu in GI tract
  - Syntis Bio (previously Codexis)

Syntis is advancing a portfolio of potential MSUD solutions

SYNT-203*

- ✓ **Oral Leucine Decarboxylase (LDC)**
- ✓ **Targets Leucine (Leu) in the GI tract**
- ✓ **Active throughout the GI tract**
- ✓ **Control systemic Leu & KIC levels**

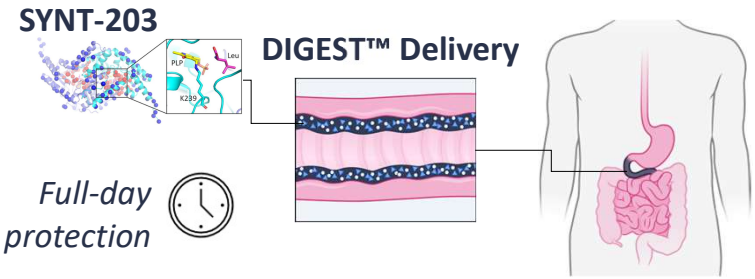
Engineered for GI-activity



**Formerly CDX-6210*

SYNT-213

- ✓ **Once-daily oral LDC**
- ✓ **Targets Leucine in the GI tract**
- ✓ **Sustained duodenal activity**
- ✓ **Maximum Leu & KIC control**



DIGEST™ is an orally delivered synthetic tissue lining engineered to sustain enzyme activity in the small intestine

Syntis Bio

Skvorak et al., 2023; Li et al., 2020; KIC: α-ketoisocaproate

MSUD Program Status

SYNT-203*

Engineered Leucine decarboxylase (LDC) targets Leu in the GI tract

**Formerly CDX-6210*

IND-Enabling Studies

Demonstrated baseline Leu maintenance with protein challenge in MSUD mice

Currently advancing to IND-enabling Tox studies.

SYNT-213

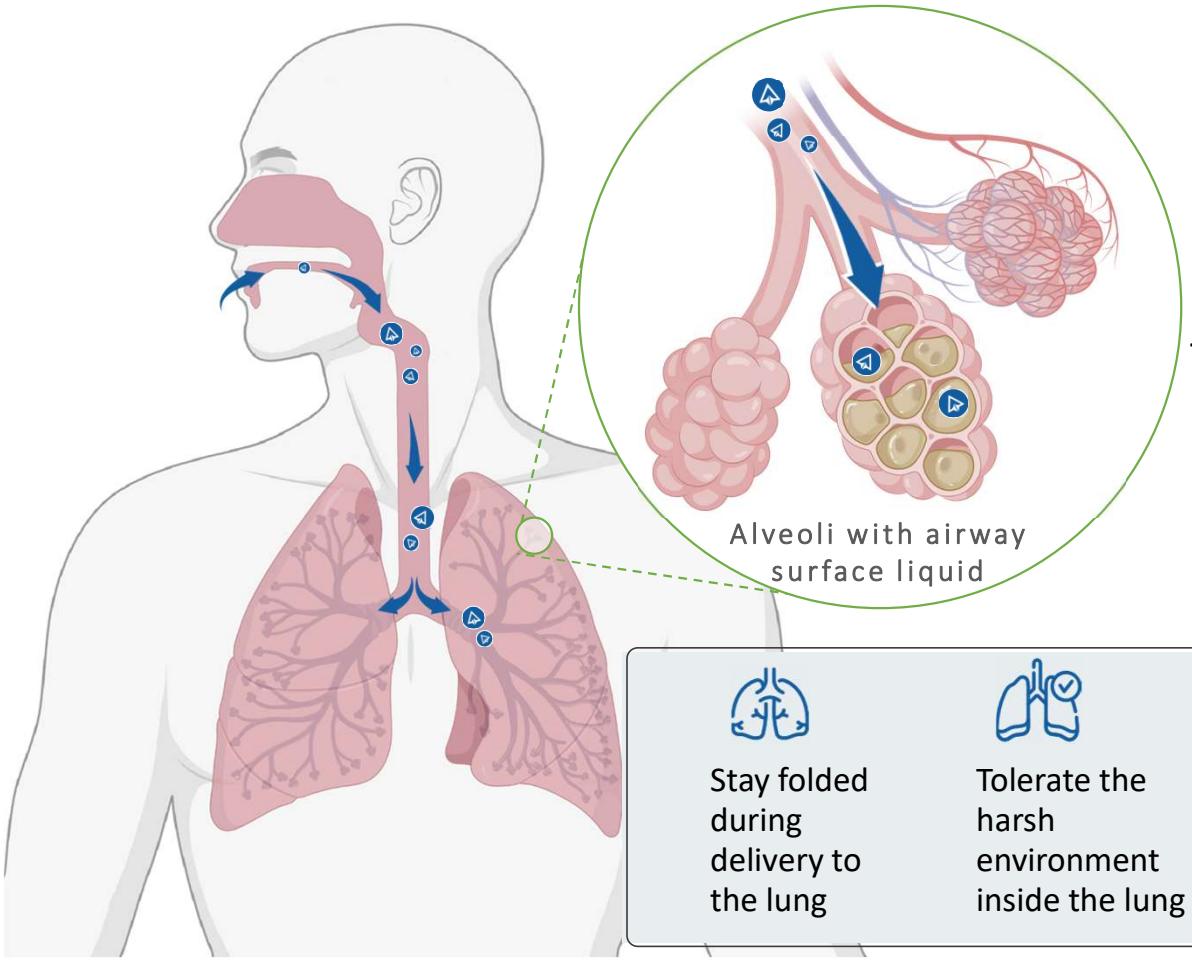
Next-generation 202 formulation with DIGEST™ extended-release technology

Discovery

DIGEST™ achieved benchtop proof of concept for extended enzyme activity in ex vivo tissues

Syntis Bio

Aperiam Bio expands metabolism by transforming the lung into an auxiliary metabolic organ



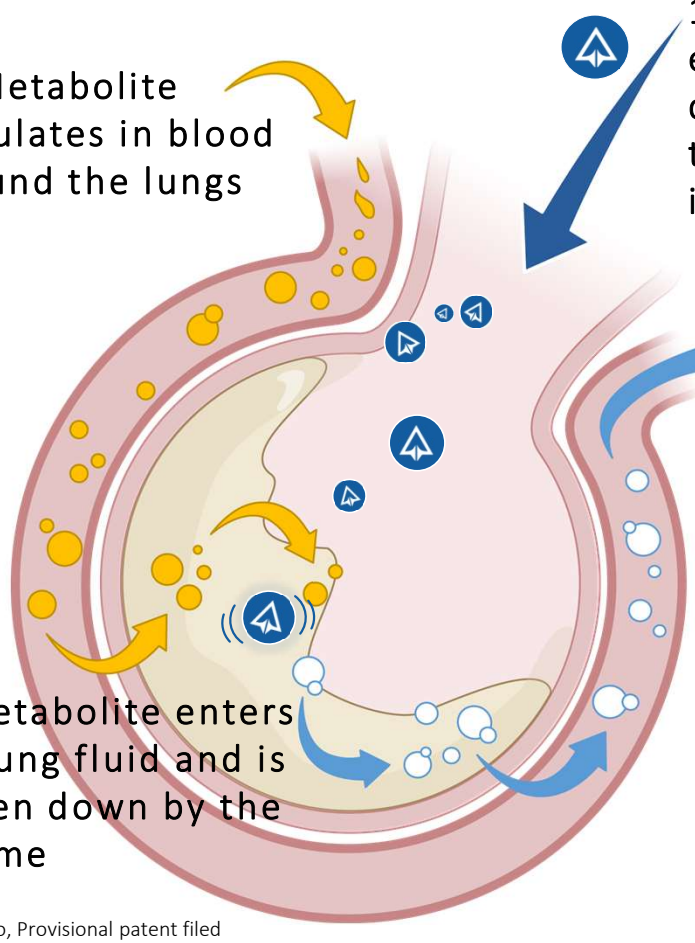
Legend

Aperiam enzymes

Therapeutic enzymes could be delivered via nebulizer or dry powder inhaler

- Stay folded during delivery to the lung
- Tolerate the harsh environment inside the lung
- Unlock many metabolic disease treatments

Therapeutic enzymes deposited in the lung could deplete targeted metabolites circulating in blood



Legend

- Metabolite (ex. Leucine)
- Aperiam enzymes
- Metabolic Product

1. Deliver enzyme to lung fluid
2. Enzyme degrades metabolite in lung fluid
3. Decreased metabolite in lung fluid creates a dialytic gradient between lung fluid and blood
4. Osmotic pressure drives metabolites from blood into lung fluid

Aperiam Bio, Provisional patent filed

GUIDING AN AGING MSUD POPULATION

- Little information available:
  - Life expectancy?
  - Risk for developing chronic diseases?
  - Physical activity recommended to prevent sarcopenia but impact on BCAA metabolism is unclear
  - What are optimal blood leucine levels for adults?

- Adult concerns:
  - Impact of cognition and executive functioning concerns on independent living
  - Metabolic decompensation may be confused with substance abuse or psychiatric illness

CALL FOR

RESEARCH PROPOSALS

AND

APPLICATION GUIDELINES

MSUD Family Support Group

www.msud-support.org

The MSUD Family Support Group (MSUD-FSG) works to improve the lives of individuals with Maple Syrup Urine Disease (MSUD) through support, research, and advocacy. The MSUD Research Fund is a campaign of the MSUD-FSG to advance the science of MSUD by funding the most promising research that will lead to new therapeutic discoveries and a cure. We seek proposals that will help us meet the above strategic goals as well as close existing gaps in the knowledge and science of MSUD.

Our primary interests are:

- Identifying the impact of MSUD on the brain and developing therapies to improve neuro-psychological health.
- Developing therapies to improve the leucine tolerance of those with MSUD and reduce the toxic effects of elevated leucine and keto-acids.
- Developing a home monitor to assess blood leucine levels.
- Developing gene therapies to repair the defect in amino acid metabolism which causes MSUD.

We will, however, entertain any proposal which can be reasonably expected to advance treatments and improve the lives of those with MSUD.

Applicants are invited to submit project proposals meeting these goals using the guidelines presented in its *Request For Proposals*.

https://bit.ly/3Y9ruUV

For questions related to MSUD research, contact MSUD Family Support Group Research Lead Karen Dolins at karen.dolins@gmail.com or 914-391-2982.