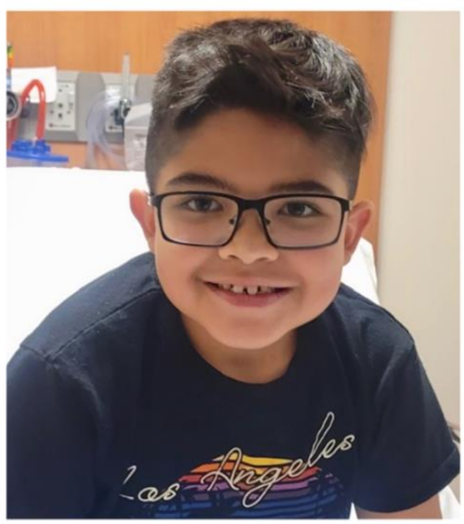
UCI Health

The Lost Enzyme Project

Mission Statement

Creating treatment to transform the lives of individuals and families affected by Beta-mannosidosis, an ultra-rare lysosomal disease



BRILLIANT FUTURE
THE CAMPAIGN FOR **UCI**

The Lost Enzyme Project

The road to a rare disease diagnosis is often long and grueling. Those diagnosed with Beta-mannosidosis arrive at a devastating prognosis**; Beta-mannosidosis is a progressive disease with no treatment.** Patients and their families have struggled to find hope for this under-researched and poorly understood disease. The Lost Enzyme Project was created by the families of those patients diagnosed in the United States, in collaboration with **Kimonis Lab** at the University of California, Irvine to complete the preclinical studies necessary for the development of an enzyme replacement therapy for Beta-mannosidosis. We are thrilled to announce **JCR Pharmaceuticals** supports our project to develop β-Mannosidase, the enzyme lost in beta-mannosidosis patients. Using its patented, state-of-the-art, J-Brain Cargo technology, which allows enzymes to be transported across the blood brain barrier (BBB), JCR will engineer **β-Mannosidase** to allow delivery of the enzyme directly to the brain and body. JCR will provide us with the experimental therapeutic to test its utility in an animal model of β-Mannosidosis. JCR has also offered to host a scientist from our lab to learn the basic technologies for this important program.

What is Beta-Mannosidosis?

Beta-mannosidosis (β-mannosidosis) is an extremely rare genetic disease that belongs to a larger group of lysosomal storage disorders (NORD, 2023). Changes in the *MANBA* gene cause metabolic abnormality, specifically a loss of a functional β-Mannosidase enzyme, resulting in the buildup of toxic materials in the cells throughout the body and brain.

Severity and progression of the disease vary widely in individuals and symptoms can appear in infancy through adulthood. Most affected individuals experience some degree of intellectual disability and delayed motor development. Other signs and symptoms include speech delay, swallowing difficulties, hearing impairment, chronic infections, seizures, gross and fine motor delay, low muscle tone, scoliosis, optic nerve atrophy, nystagmus, white matter changes to the brain (leukoencephalopathy), painful peripheral neuropathy, and behavioral and psychiatric challenges.

Oliver, a 13-year-old boy, was diagnosed with Beta-mannosidosis at the age of 4 years. He underwent an experimental bone marrow transplant at the age of 4 years, the first in medical history for Beta-mannosidosis, with the hope the transplant would slow the progression of the disease. Even with a successful transplant, Oliver symptoms continue to progress. He is now considered blind, experiences chronic pain, and has lost his ability to walk without adaptive equipment. Despite his challenges, Oliver works hard in school, loves to swim, and hopes to work for the LA Lakers one day.

Skylar, a 3-year-old girl affected by Beta-mannosidosis, showed signs and symptoms of the disease from birth, and was diagnosed the day before her 1st birthday. Skylar suffers from hearing and vision loss, chronic pain from peripheral neuropathy, cognitive delay, physical abnormalities, and chronic infections. Despite these challenges, she is eager to learn and grow. Her smile lights up the room and her joy is contagious. Skylar's sign name means "brave," because she does more than just endure, she is a fighter.

Kendreona, a 13-year-old girl, was diagnosed with Beta-mannosidosis at the age of 7 years, after white matter changes were found in her brain. Kendreona's symptoms include leukoencephalopathy, optic nerve damage, moderate hearing loss, intellectual disability, and behavioral issues. Beta-mannosidosis has dramatically impacted her family's lives, including job resignation and relocation to meet Kendreona medical needs. Kendreona loves being outdoors, dancing, and riding the school bus. She continues to find a way to smile though her mental and physical challenges, laugh, and love her life.

Dean, an 8-year-old boy, passed all newborn health screens and was meeting his milestones. Around age 6 years, he began showing symptoms of hearing loss and learning disabilities. Genetic testing was recommended, and in September 2022, Dean was diagnosed with Beta-mannosidosis. Dean now requires hearing aids and receives educational assistance in school. Despite his disabilities, Dean is an energetic and active boy. He loves karate, baseball, and hopes to become a cruise ship captain when he grows up.

Inequity in Rare Disease and Treatment

While individually, diseases like beta-mannosidosis are ultra- rare, collectively rare disease affects about 4% of the world's population, resulting in a significant number of childhood illnesses, deaths, and associated healthcare costs (Nguengang Wakap, et al., 2019). Still, low individual numbers create a treatment gap for patients who are a low priority in health advancement. Individuals with rare disease and their families often face delays in diagnosis, limited evidence-based information to guide disease management, and lack of treatment, which devastates their physical, psychosocial, and economic well-being (Baumbusch, Mayer, Sloan-Yip, 2018).

There is no individual treatment for Beta-mannosidosis. To date, the disease has been minimally researched in humans and is thought to be significantly underdiagnosed. The **Kimonis Lab**, at the University of Irvine, has embarked on a pioneering study to better understand Beta-mannosidosis and research the effects of enzyme replacement therapy.

JCR Pharmaceuticals has partnered with our project to develop β-Mannosidase, the enzyme lost in Beta-mannosidosis patients, using its patented, state of the art, **J-Brain Cargo technology**, which will cross the blood brain barrier (BBB) and deliver this life-saving enzyme directly to the brain and body. JCR Pharmaceuticals revolutionary and humane approach to medicine centers on creating advanced, lifesaving treatment for **all** who need it, so that no person is left behind due to the rarity of their disease.

Preclinical Studies and Research Funding

Our project, working the with Kimonis Laboratory at the **University of California Irvine**, has set a goal of raising $520,925.00 by August 1, 2025, to fund the preclinical studies and research necessary to move into enzyme development with **JCR Pharmaceuticals**.

The project's design is intended to:

- **GOAL 1:** Clinical characterization and Natural history studies
- **GOAL 2:** Utilization of Fibroblast cell lines for translational (treatment) studies
- **GOAL 3:** Translational studies in neuronal cell lines derived from patient iPSCs
- **GOAL 4:** Conduct animal studies

Finally, we gladly acknowledge that **JCR Pharmaceuticals** has led the way in creating groundbreaking therapeutics. This life-saving treatment could not be developed without their vision, innovation, and compassion.

Kimonis Lab at the University of California, Irvine

We are UCI Health: a devoted team of nationally regarded physicians and nurses, researchers and clinicians, educators and students united by a single calling – to improve the lives of the people in our community and beyond. At UCI Health, we do not just practice medicine, we create it.

Advances in medical knowledge make this the perfect time to push for solutions to rare diseases, and UCI Health's contributions to that progress make us the ideal place to lead the charge in research that translates into treatments and cures.

However rare each condition is, taken together, they affect countless lives —not just of patients, but also their loved ones. In the aggregate, rare diseases — and their more common disease relatives — present a vast need for new therapies and cures. Thanks to scientific and technological advances, the promise of life-changing research outcomes has never been greater.

The members of UCI Health Kimonis Laboratory are vital to fulfilling that promise — from investigations that translate into innovations benefiting patients to leading-edge education. We all have a common cause: to free the children of current and future generations from the threat of rare diseases. Together, we can — and will — make this happen. With your support, UC Irvine Health will revolutionize how rare diseases are researched, diagnosed, treated — and prevented.

How to Donate

Please make all checks payable to: **UCI Foundation** and write "***Lost Enzyme Project"*** in the Memo Line.

Please mail donations to:
UCI Health Advancement
Attn: Carley Fox
3800 West Chapman Ave. Ste #3300
Orange, CA 92868

To donate online, please visit: bit.ly/lostenzyme or scan the QR code.

We are working in partnership with the Kimonis Laboratory at University of California Irvine. The University of California, Irvine (UCI Foundation) is a 501(c)3 organization, Tax ID 95-2540117. Your gift may be tax-deductible to the extent permitted by law. Please consult your tax adviser. No goods or services will be provided in exchange for your contribution. All donors will be recognized on our website.
We thank ***you*** for donating to our project. The groundbreaking enzyme replacement treatment will transform the outcomes of people diagnosed with Beta-mannosidosis around the world.

If you or a loved one are affected by Beta-mannosidosis, please consider:

1. Registering for our CoRDS Longitudinal Study at: **https://research.sanfordhealth.org/rare-disease-registry,** by clicking "Enroll Now," which will take you to the Activation Form where you can specify the disease you are registering for, Beta-mannosidosis.
2. Registering to the International Society for Mannosidosis and Related Diseases (ISMRD) by sending your name, name of affected individual, address, phone number, email, and diagnosis to: **info@ismrd.org**

For More Information

If you have any questions concerning this project, please email them to Laurel Gregier at **laurelgregier@gmail.com**. Please consider watching the short **video** of several US children affected by the disease, interrogative with Dr. Virginia Kimonis, Head of Project Research.

Dr. Virginia Kimonis & Children with Beta-mannosidosis: bit.ly/lostenzyme


Dodgers

UCI Health

☑ **Yes, I would like to make a gift to the UCI Department of Pediatrics Rare Disease Fund in support of the Lost Enzyme Project.**

Contact Information:

Name: ____Class Year: _____________

Address: ____

City/State/Zip: ____

E-mail: ____________________ Home Phone: _____________ Mobile: _____________

I would like to make a contribution of:

❒ **$5,000** ❒ **$2,500** ❒ **$1,000** ❒ **$500** ❒ **$250** ❒ **Other _______**

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Donor Signature ______________________________________Date_____________

THANK YOU FOR YOUR GENEROUS SUPPORT!

To learn more about the UCI Department of Pediatrics contact Carley Fox at foxc@uci.edu or (714) 456-6226. Your donation is tax-deductible to the full extent allowed by law. Please consult your tax advisor.

Internal Use: Rare Disease Fund: 3821

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