ACD
ASSOCIATION FOR CREATINE DEFICIENCIES

BUILDING STRENGTH
changing lives

May 22, 2024

Regarding: CIRM Application Review Subcommittee - May 30, 2024 | TRAN1-16011

Dear Committee Members,

I am writing as a patient advocacy leader and parent in my strong support of Dr. Gerald Lipshutz's proposal, TRAN1-16011 for the development of a gene therapy for GAMT Deficiency.

BACKGROUND ON GAMT Deficiency:
GAMT Deficiency is a recessive, inborn cerebral creatine deficiency syndrome caused by mutations in a single gene- GAMT. GAMT enzyme is needed for the body to synthesize creatine and is lacking in GAMT Deficiency. Creatine is critical for brain and muscle development. When GAMT enzyme is not present, a **neurotoxic** substance, guanidinoacetate (GAA), builds up in the brain and periphery; often 2,000% higher than reference ranges. Long term exposure to this compound causes **irreversible neurological damage**.

NEED FOR ADVANCEMENTS IN GAMT TREATMENT OPTIONS:
Patients with GAMT often present with weak muscles, global developmental delays, intellectual disability, self-injurious behaviors, autistic-like features, severe speech impairments, and epilepsy. While a reduction of symptoms is possible by orally administering creatine, the **neurotoxic GAA remains elevated**. Creatine and other amino acids prescribed combine to make a brackish, horrific tasting treatment that is difficult to administer with many children experiencing diarrhea, vomiting, and behavioral problems as a result. A low protein diet is sometimes advised as an additional approach at reducing GAA but again this is difficult for parents to implement, results in great distress, and does not normalize GAA.

I've observed two unsafe extremes in our patient community. Due to the emotional struggles and often violent behaviors brought on by treatment aversion, some parents choose to stop supplements. The treatment battle ends, but the disease progresses in intensity, especially seizure frequency. Other families restrict diets so intensely that new symptoms of malnourishment appear in addition to existing issues.

Diagnosis at birth has the greatest patient treatment compliance but once again, GAA is never normalized and there is great concern for the long-term impacts of an elevated neurotoxin. The rate and range of neurological decline these patients will face over time is not yet known.

A PERSONAL EXAMPLE:
My oldest child, Sam, appeared to be healthy at birth. She had no dysmorphic features or alarming symptoms. By age 3, she had developed no speech, her body had become more "floppy", and her interest in social interactions and play had disappeared. She received a mild autism diagnosis and we were told to go to speech and occupational therapies and be patient. Unfortunately she wasn't improving and when she was 5 she began to have seizures. The seizures led us to a diagnosis of GAMT Deficiency.

Today, Sam is 20. Seizure falls have broken her bones and teeth, dented walls, caused massive facial swelling, and sent her parents into a state of paralysis watching over every little sign of oncoming seizures. One of these signs is aggression and violence from our otherwise gentle daughter. We know what is wrong with Sam but we can't fix her elevated GAA and the three anti-seizure medications she is currently taking only make her tired and irritable. We need help.

THE PROMISE OF THIS GRANT & WHY WE NEED THIS TREATMENT:
GAMT is a single gene disorder. Time and time again, I have been told what a promising disorder this is to treat, "Single gene disorders are the simplest," yet there is very little interest from pharma in helping these patients because the prevalence of GAMT Deficiency is low and the promise of financial return is low. Dr. Lipshutz has invested years of his career meticulously researching GAMT, the proposed gene therapy, including many vectors and dosages, and the impacts of elevated guanidino compounds that are a hallmark of the disorder.

When creatine is restored to the brain, patients experience immediate improvements. When GAA is lowered a small amount, there are additional improvements. Caregivers are hopeful for the day that GAA can be NORMALIZED, their children experience the best health possible, and seizures stop. Dr. Lipshutz's data show restoration of creatine and reduction of GAA in a mouse model and this is the treatment we need. We need this treatment.

DEI:
GAMT is the newest disorder to be approved by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and the U.S. Secretary of Health and Human Services for additional to the Recommended Uniform Screening Panel (RSUP). This means states are advised by the federal government to add GAMT to their newborn screening panels. California plans to begin screening for GAMT in all newborns in June 2024. Over 99% of newborns born in the U.S. receive the mandated newborn screen shortly after birth. Screening is mandated and paid for by the state, insurance, or medicaid. This means that identification of GAMT is blind to patient demographics such as race and income. The only patient advocacy group for GAMT is the Association for Creatine Deficiencies (ACD) and ACD has proactively contacted every newborn screening program in the U.S. to ensure that patients are able to immediately find support and access to resources once a positive screen occurs.

SUMMARY:
In summary, Dr. Lipshutz is dedicated, experienced in developing and advancing AAV vectors, has developed an effective therapeutic that the majority of GAMT caregivers are excited to see advance, and quite honestly this therapy is our only hope. We are a rare disease group and our children require the hard work of an individual like Dr. Lipshutz and the forward thinking investment of an organization such as CIRM that understands the value of each individual life over net profits.

Best Regards,

Heidi Wallis, ACD Executive Director and GAMT parent