Board of Directors:

Akiva Zablocki, MPH
President

Amanda Zablocki
Secretary

David Hagin, MD, PhD

Tiffany Hill

Pras Ranaweera

Scientific Advisory Committee:

Troy Torgerson, MD, PhD,
Committee Chair

Charlotte Cunningham-Rundles, MD, PhD

Antonio Condino-Neto, MD, PhD

Ramsay L. Fuleihan, M.D.

Andrew Gennery, MD

October 10th, 2019

Mr. Jonathan Thomas
The Independent Citizen's Oversight Committee
California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Dear Mr. Thomas,

I am the President of the Hyper IgM Foundation, a rare disease patient advocacy organization whose mission is to improve the treatment, quality of life and the long-term outlook for children and adults living with Hyper IgM Syndrome ("Hyper IgM") through research, support, education, and advocacy to families and patients. I am writing this letter on behalf of our entire patient community in support of Dr. Caroline Kuo's TRAN1 grant application to the California Institute for Regenerative Medicine (CIRM). We urge you to approve Dr. Kuo's research grant request for funding to support her research into gene editing as a possible cure for X-Linked Hyper IgM ("XHIGM") for the reasons set forth in this letter. We thank you in advance for your consideration to this critical matter.

Hyper IgM is a combined Immune deficiency that affects the function of t-cells and others parts of the immune system. There are different forms of Hyper IgM, but in many respects, XHIGM is the most severe form. Individuals with XHIGM cannot produce antibodies, do not respond to vaccines, and are very susceptible to infections. Those living with XHIGM face a significantly shortened life span, multiple hospitalizations, and a high risk of secondary cancers. XHIGM children and adults are especially vulnerable to opportunistic bacteria, fungi, and viral infections, they are often advised to live in isolation, put on a regimen of antibiotics along with weekly or monthly infusions of immunoglobulin replacement therapy. Sadly, even with these preventative treatments, the mean life expectancy for a patient with XHIGM is less than 25 years, with 50% of our patients not making it past age 24 and 80% not making it to 30.

The treatment for XHIGM is a combination of immunoglobulin therapy and various prophylaxis antibiotics to address the inability to make antibodies; however, this only addresses the risks associated with the lack of antibodies, and does nothing to protect patients from secondary cancers and opportunistic infections, which can pose even greater threats. The only known "cure" for XHIGM is a stem cell transplant, which carries life-threatening risks and has shown itself to be less effective for XHIGM patients than patients with other forms of immune deficiency.

Board of Directors:

Akiva Zablocki, MPH
President

Amanda Zablocki
Secretary

David Hagin, MD, PhD

Tiffany Hill

Pras Ranaweera

Scientific Advisory Committee:

Troy Torgerson, MD, PhD,
Committee Chair

Charlotte Cunningham-Rundles, MD, PhD

Antonio Condino-Neto, MD, PhD

Ramsay L. Fuleihan, M.D.

Andrew Gennery, MD

By way of background, my wife and I started the Hyper IgM Foundation in 2015 after our son was diagnosed with XHIGM when he was 8 months old, following three weeks of intubation in the ICU for a rare and deadly pneumonia. Our life changed dramatically after the diagnosis as we had to retreat into a clean and germ-free bubble and await a bone marrow transplant, the only potential effective treatment for XHIGM, which came with its own very high risks. A recent paper on 130 XHIGM Transplant patients shows a mortality rate of 22%. As parents, faced with a decision to save their first-born baby boy, a more than one in five chance of death was a dire choice.

We started the Foundation to raise money and find a cure that could be long-lasting and safe for our patients. We connected to hundreds of families around the globe with XHIGM and cultivated an active support group. Sadly, as our group grew, so did the horror stories. We have witnessed many children in our group die from complications of bone marrow transplant. We have witnessed young adults and older patients die suddenly from central nervous system infections and liver cancer. We have watched our families struggle to find the right course of treatment for their children, struggle with telling their daughters that they are carriers and would one day face the choice for their sons' of a life-threatening bone marrow transplant or a near certainty of a lifetime of complications and a shortened life span.

One family in Arizona comes to mind in particular, as we personally grew quite close to them. Their first son, Oliver, was diagnosed just one year after our own son, with a very similar hospitalization experience and pneumonia. Despite complications with CMV infections and graft-vs-host disease (GVHD) during his bone marrow transplant, Oliver survived and is living with enough donor cells to provide him with a protective immune system. When his brother Liam was born only a few months later and also diagnosed with XHIGM, his parents again had to make an unbearable decision. Liam had a bone marrow transplant at 9 months. By the age of 13 months, every organ in his body was plagued with complications from transplant. He succumbed to a fungal infection, and passed away. While one child survives, the loss of another has been a tragedy for this young family. Oliver is doing well today, but has only a small percentage of donor cells circulating in his bone marrow. There is no guarantee these donor cells will stay for the rest of his life, and if his graft slips any further, he risks returning to a disease state.

Recent studies have shown that XHIGM is "tricky" to transplant. XHIGM are prone to reject the graft, and the success rate is very low. Several of our families (my own included) have had to undergo two transplants in order to achieve a successful graft. And those are the lucky ones. For every child lucky enough to have a donor, there are several more that have no available donor or who are too old or otherwise medically challenged to a point that it is unlikely they would even survive the transplant let alone be cured. For many, a transplant is simply not an option.

Dr. Kuo's gene-editing research is the one cure that our whole community is desperately waiting to receive. XHIGM is an extremely rare disease affecting only one in a million boys. There is a dearth of research into XHIGM, and the fact that Dr. Kuo is

Board of Directors:

Akiva Zablocki, MPH
President

Amanda Zablocki
Secretary

David Hagin, MD, PhD

Tiffany Hill

Pras Ranaweera

Scientific Advisory Committee:

Troy Torgerson, MD, PhD,
Committee Chair

Charlotte Cunningham-Rundles, MD, PhD

Antonio Condino-Neto, MD, PhD

Ramsay L. Fuleihan, M.D.

Andrew Gennery, MD

interested in finding a cure in this disease has brought immeasurable hope to this struggling community. Not only does it appear to carry far less risks than transplant, it would also create a path to a cure for those for whom transplant is not an option. Funding for this research is therefore of utmost importance, as her treatment would mean a safer and long-term cure for our patients, young and old. As representatives of a rare disease community, we feel extremely lucky that a renowned researcher such as Dr. Kuo has taken interest in Hyper IgM Syndrome and is working on a potential cure. Our community as a whole is supportive of her work and is desperately waiting for this cure.

My own son spent the first 5 years of his life in isolation either at home or in the hospital. He underwent the first transplant in 2013, suffered from acute skin GVHD and was treated with high dose steroids only to see his graft rejected and fail within the first year. The second transplant in 2016 seems to have been successful, but he has mixed chimerism with donor cells in the 50% range. We live in a constant state of fear that he will lose his donor's immune system and revert back to a disease state. Together with the rest of our families, we hope that Dr. Kuo's research will lead to a real cure for our son and all our boys. Funding for this work is essential, and we hope you can provide her research the needed funding to find a cure for Hyper IgM Syndrome.

Best,

Akiva

Akiva Zablocki, MPH
President
Hyper IgM Foundation
akiva@hyperigm.org