Primary Immune Deficiency Treatment Consortium

NEWSLETTER

Summer 2022 | Issue 16

Read about Crystal Cruz's experience with her son, Cyrus Bakhtiari, who is diagnosed with CGD on Page 3.

Greetings from Drs. Jennifer Puck, Chris Dvorak, and Elie Haddad, Multi-PIs

We are pleased to announce that the CGD (6908) and PIRD (6906) protocols have been approved by the UCSF IRB. The onboarding and site activation process are now in progress. The SCID (6907) protocol is also open at several sites – read more details on page 18.

We are also excited to announce that the Neurodevelopmental Outcomes in SCID study in collaboration with the Immune Deficiency Foundation has been approved for an extension until July 31st, 2023. This will allow more time to get sites onboarded and patients enrolled into this study. For additional information see page 15.

A Leadership Meeting will be held at the end of this August to prepare for grant submissions in the next two years before the end of our U54 funding cycle – it's been a great run, but we are no longer eligible for future U54 funding. We are also excited to start the planning for our PIDTC Education Day – Scientific Workshop which will be hosted by Dr. Rebecca Marsh at the Cincinnati Children's Hospital Medical Center in April 2023.

With appreciation,
Jennifer, Elie, and Chris

CGD FAMILY SPOTLIGHT: Crystal Cruz and Cyrus

by Suzanne Zuckerman

Cyrus Bakhtiari and Crystal Cruz

The medical journey of LA acupuncturist Crystal Cruz and her two-year-old son, Cyrus, reads like a laundry list of parental nightmares. However, it's all too familiar for parents of a child with Chronic Granulomatous Disease (CGD). The strength Crystal has tapped into as her son's caregiver and advocate, as a recently diagnosed CGD family, provides both a logistical roadmap and a source of inspiration.

From infancy on, Cyrus faced a series of relatively minor health problems, such as cradle cap sores that wouldn't fully heal and a perianal abscess. These incidents turned out to be anything but isolated. In fact, they were early indicators of CGD. But this was unclear to his pediatrician at first. After all, CGD is so rare, it affects only one in 250,000 people.

Cyrus's path to diagnosis began on a family vacation in Yosemite in the summer of 2021, when at 18 months old, he presented with an unusual and concerning tongue blister. Soon after, the entire family tested positive for Covid. Initially, this was a red herring. A few weeks later, Cyrus became lethargic and indicated he felt pain in his lower right quadrant. A blood test at urgent care revealed a raging infection. His parents took him to the Children's Hospital LA (CHLA) emergency room. There—because he seemed outwardly healthy—he waited hours to be admitted. "Invisible illness is wild because Cyrus is a very cute kid," says Crystal. "He looks fine. Everyone thinks he's fine. I'm like, Cyrus is not fine. Cyrus is really sick."

An ultrasound revealed an abscess on his liver that persists to this day. An initial, incorrect diagnosis of liver cancer meant that "for a day," recalls Crystal, "I thought Cyrus was going to die of cancer." The hits kept coming. Doctors found a lesion on his lungs, which led to more tests, and speculation he may have tuberculosis. The ensuing weeks-long process of ruling this out also coincided with the height of the

COVID-19 pandemic (and Cyrus was still testing positive). As a result, some medical staffers wore Hazmat-like suits with oxygen tanks, as they repeatedly poked his collapsed veins to draw vial upon vial of blood. “It was dreadful and scary and too much to handle, really,” says Crystal.

As many CGD mothers know, it’s the pain of seeing your child suffer that hurts the most, like the times Cyrus was not allowed to eat before medical procedures. “Your child is begging for food and water and milk and you cannot give it to him,” says Crystal. “This went on for days. And I had to be there, saying no to Cyrus begging for food for hours. That was one of the hardest things.” Also, the need to repeatedly draw blood meant a PICC line was surgically inserted into his arm for continuous intravenous access. For these procedures and others, Cyrus was put under general anesthesia multiple times.

After several more weeks enduring a high fever, the tide was turned by a steroid. And six weeks after he was admitted, Cyrus was discharged from CHLA. He is currently taking CGD prophylaxis, and thankfully, many of his acute health issues have resolved. But the challenge of administering his oral meds multiple times a day should not be minimized, says Crystal. There are many heartbreaking days when Cyrus just does not want to take his medication, and he cries in protest. “And I’m crying, because it’s reigniting all of my traumas and his traumas,” says Crystal.

Cyrus on the swing.

In positive news, Cyrus has a donor match for a bone marrow transplant, which Crystal hopes to schedule by this summer, provided his liver abscess continues to heal. Like all CGD parents, she is weighing the heart-wrenching risks carefully. “You just figure it out,” she says. “And you continue to keep pushing forward.”

In the meantime, Crystal has found solace in connecting with others in the CGD community through the CGDAA and sharing her experience. She has also recently learned that she is carrier of X-linked CGD, and she is in the process of understanding what that means.

Cyrus playing on the slide.

"It can be difficult for carriers of CGD to know which symptoms are carrier-related and which are not," Crystal says. "Because, in some instances, we have been living with these symptoms our whole lives."

She says being able to virtually meet other female carriers and mothers of children with CGD via CGDAA's "Coffee & Carriers" Zoom meetings has helped as well.

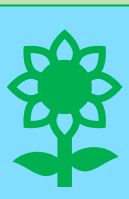
"Talking about it is reliving trauma, but it's also releasing the trauma," she says.

So how *is* Cyrus doing these days?

Well for starters, he loves opera music, dancing, and eating lobster. "Cyrus's playlist is much more sophisticated than mine," says Crystal. "He's just a joy to be around."

PAG Updates

WAS Foundation:




WAS Symposium

- Sumathi Iyengar M.D., founder of the WAS Foundation, attended the very successful WAS Symposium in Munich, Germany.
- Suhag Parikh M.D., also attended the WAS Symposium, where he shared the WAS Carrier survey information.

Other Projects

- Dr. Iyengar is working with the FDA to help assemble a stakeholder group of physicians and PAGs to gather information in the rare disease community.

For more information about the WAS Foundation click here: http://www.wiskott.org/

SCID Angels for Life Foundation:

SCID Angels For Life Foundation

SCID Angels For Life Foundation

scidangelsforlife.org

SCID Angels for Life is committed to increasing awareness, providing a safe environment for families to connect, granting family scholarships, promoting research, and providing parent and family education for those affected by Severe Combined Immune Deficiency. SCID Angels believes that through our advocacy and support we can empower every patient to strive for the highest possible quality of life.

"Knowledge is Power"

By supporting SCID Angels you help make our mission a reality. It enables families to find the emotional and oftentimes the financial support they need to live with a child with a life-threatening illness.

For many families, the emotional toll involved in the treatment of a child with SCID is a lonely and frightening journey. We aim to bring families together to emotionally support one another.

The cost of travel not only to hospitals but also to educational meetings is often too much for a family already stretched beyond its means. The cost of special education, insurance co-pays, or specialty equipment not covered by insurance can be impossible.

We aim to assist as many families as we can with these out-of-pocket expenses, but we need your help. Your donation today will ensure that families in need are not turned away.

SCID Angels For Life Foundation

scidangelsforlife.org

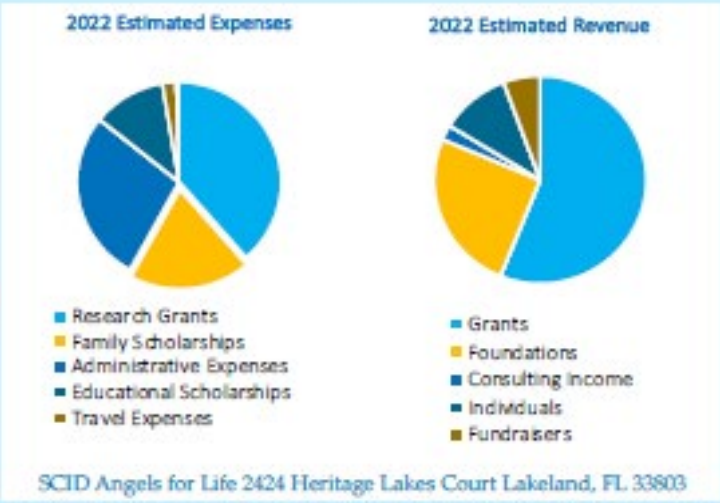
2022 Research Grant Awards | Inaugural Grant Year

For a New and Innovative Curative Treatment Approach | Dr. Donald B. Kohn, MD; UCLA | *"IL7Rα gene editing to treat IL7Rα-SCID"*

The work being performed is to develop a gene editing approach to treat IL7Rα SCID starting with the initial studies to assess elements of the gene editing reagents. These studies will provide the basis for the next set of steps, to test the optimal IL7Rα gene editing reagents. The goal is to develop an effective method to treat IL7Rα SCID using gene editing in autologous HSC.

For an Innovative Approach Targeting a Marginalized Community | Dr. Jolan Walter, MD, PhD, USF | *"Predicting the clinical phenotype and increasing awareness of a novel RAG1 p.C176F founder variant causing atypical SCID with variable immune dysregulation in U.S. Mennonite communities"*

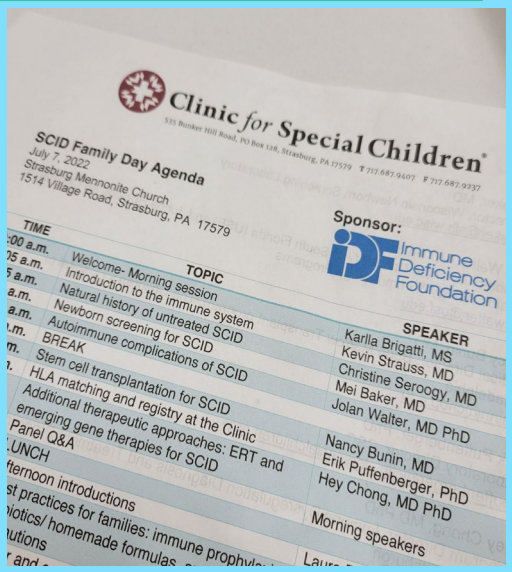
The study involves members of conservative Mennonite communities with the same homozygous RAG1 p.C176F founder variant yet highly variable disease severity. These communities reside in four states: Pennsylvania, Virginia, North Carolina and Ohio. The outcomes of the study are: increased awareness of the RAG1 founder variant among Mennonite community members and greater inclination to seek genetic screening and follow-up care. Additionally, it is anticipated that the study will lead to novel preventive and therapeutic strategies that reduce disease severity of those who inherit the RAG1 founder variant as well as other variants of atypical SCID with variable clinical presentations.



SCID Angels for Life 2424 Heritage Lakes Court Lakeland, FL 33803

SCID Angels for Life Foundation (continued…)

Clinic for Special Children's SCID Day


Clinic for Special Children

SCID Family Day Agenda
July 7, 2022
Strasburg Mennonite Church
1514 Village Road, Strasburg, PA 17579

Sponsor: Immune Deficiency Foundation

TIME	TOPIC	SPEAKER
:00 a.m.	Welcome- Morning session	
25 a.m.	Introduction to the immune system	Karlla Brigatti, MS
5 a.m.	Natural history of untreated SCID	Kevin Strauss, MD
a.m.	Newborn screening for SCID	Christine Seroogy, MD
.m.	Autoimmune complications of SCID	Mei Baker, MD
m.	BREAK	Jolan Walter, MD PhD
.	Stem cell transplantation for SCID	
	HLA matching and registry at the Clinic	Nancy Bunin, MD
	Additional therapeutic approaches: ERT and emerging gene therapies for SCID	Erik Puffenberger, PhD
	Panel Q&A	Hey Chong, MD PhD
	UNCH	
	fternoon introductions	Morning speakers
	st practices for families: immune prophyla	
	iotics/ homemade formulas	
	utions	

SCID Angels' Director, Barb Ballard, attended the SCID Day presented by the Clinic for Special Children in Strasburg, PA and sponsored by the SCID Compass program. The Clinic for Special Children focuses on the unique health issues prevalent in the Amish and Mennonite Communities. The day-long event focused on providing information to local Amish and Mennonite families who have had SCID children. This topic is of particular interest as there is an unusually high incidence of SCID in this community. Attendees were able to learn the basics of the immune system from their local physician, Dr. Strauss, as well as hear Dr. Jolan Walter from University of South Florida discuss her latest findings regarding the variability she's documented in RAG1 SCID, focusing on the autoimmune complications associated with this form of the disease. Speakers from Children's Hospital of Philadelphia including Drs. Jen Heimall and Nancy Bunin gave the attendees a thorough overview of how to manage SCID patients and what to expect through a typical transplant process. The information presented by Dr. Puffenberger regarding the methods used by the clinic to develop their own proprietary donor registry and matching program was especially interesting. Emma Mertens from the Immune Deficiency Foundation presented an overview of the resources available through SCID Compass and IDF and provided printed copies of the SCID Compass Toolkits to everyone.

"Expectations and Experience: Parent and Patient Perspectives Regarding Treatment for Severe Combined Immunodeficiency (SCID)"

"Expectations and Experience: Parent and Patient Perspectives Regarding Treatment for Severe Combined Immunodeficiency (SCID)" (NIHMS1715458) is the collaboration of Heather Smith with our PAG - SCID Angels For Life Foundation, Jen Heimall and others from the PIDTC came together on the publication of a great paper regarding expectations and experience of families with SCID. This was published in Clinical Immunology last year and the manuscript is now available in PubMed Central (PMC) for public access using the following link https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8559521.

Description of the article that was written by Jill Williams with RDCRN: Severe combined immunodeficiency (SCID) is a group of rare disorders caused by mutations in different genes involved in the development and function of infection-fighting immune cells. Infants with SCID are treated with hematopoietic cell transplantation (HCT, also called bone marrow transplantation or stem cell transplantation) or gene therapy (an experimental form of treatment that uses transfer of genetic material into the cell of a patient to treat or stop disease). To test parent and patient expectations and experience with these treatments, researchers distributed 151 surveys to families of patients with SCID treated with HCT or gene therapy. They found that 37% of respondents expected the therapy would lead to a "cure" and 43% expected it would last a lifetime. Researchers found that varying interpretations of the word "cure" led to misunderstandings regarding the need for continued medical evaluations and therapies. They concluded that clear communication about the importance of lifelong follow-up, regardless of treatment outcome, is needed to optimize health and quality of life.

SCID Angels for Life Foundation (continued…)

Aisha Chaudhary Educational Scholarships

Meet the 2021 Recipients:

Myles Temple

Myles is attending the University of Texas at San Antonio. He expects to graduate in 2023 with a degree in Business. “I've enjoyed the experience of being in a classroom again as well as meeting wonderful new friends!”

Samuel Antipov

Samuel is attending the University of Oklahoma. He is planning to graduate in 2023 in Pre-Pharmacy. “I’ve enjoyed being able to live on campus, seeing all my friends! College is a tight-knit community, so hanging out with a friend is as simple as asking someone to do something with you!”

Aiden Walsh

Aiden attends Ohio University. He's studying Sport Management and Business Analytics and expects to graduate in 2023. “The thing I have enjoyed most about college has been the social experience of meeting all new people and making new friends.”

Congratulations to the 2022 Recipients: Zachary Smith, Brenna Carpenter, and Parker Sipprell!

For more information about SCID Angels for Life click here: http://www.scidangelsforlife.com/

CGD Association of America:

CGDAA Helps Sri Lankan Family Battle CGD Article

- To read about this story, click on this link: https://myemail.constantcontact.com/CGDAA-Helps-Sri-Lankan-Family-Battle-CGD.html?soid=1133213561273&aid=dXls9zEzYsg






(Above) Sasindu Gunawardana, CGD patient from "CGDAA Helps Sri Lankan Family Battle CGD" Article

Coffee & Carriers

- Jillian Button of Rochester, NY and mom to a 6-year-old son named Elliott, who is 4 years post transplant for CGD, will be joining us to chat about her foray into Vegan cooking. She will talk about her experience as a CGD carrier, a CGD Mama, and how cooking up tasty vegan dishes has helped her feel better, while encouraging her family to eat more healthy, plant-based meals.
- This session is will be held on Zoom on September 30th at 5 pm EST. All are welcome.
- Email info@cgdaa.org for the invitation link.

Coffee & Community

- First Instagram "Live" Chat on September 8! (Time:TBD)

- Liz Carlile, the host of the popular podcast "Motherhood Unstressed" will join us for our first live Coffee & Community talk on Instagram.
    - Her work is rooted in helping all people and especially women be unapologetically selfish with their self-care, so they are able to be present for their families. Liz provides uplifting conversations with brilliant minds, authors, and meditations to empower us to live with less anxiety and stress and more purpose and joy.

- This talk is open to everyone in the CGD and rare disease community who is seeking ways to address reduce anxiety, manage stress, and achieve personal growth.

For more information about CGDAA click here: https://cgdaa.org/

Immune Deficiency Foundation:

Having a child who is facing a life-threatening illness such as SCID can be traumatic. Maintaining mental wellness is an essential part of the SCID journey, both as a patient and as a parent. This video shares the stories of three parents who navigated their own mental health challenges while caring for their children: https://scidcompass.org/video/parental-mental-health-experiences-across-scid-journey

*Families seeking information about severe combined immunodeficiency (SCID) who want quick access to the basics of diagnosis, treatment, and what to expect in the future can now find what they're looking for in the **SCID Compass Toolkit**. The toolkit is a downloadable summary of the website and is available in **twelve total** languages: https://scidcompass.org/parent-publications*

SCID Compass Lunch & Learn: Gene Therapy Updates for ADA SCID

- *Join IDF for the SCID Compass Lunch & Learn where Dr. Donald Kohn of UCLA will provide an update on the status of gene therapy as an available treatment option for ADA SCID.*
- *Date: Wednesday, September 14th, at 11AM-12PM PT / 12PM – 1PM MT / 1-2PM CT / 2-3PM ET*
- *Website Link: https://community.primaryimmune.org/s/event/a2S4x000000hiDDEAY/scid-compass-lunch-learn-gene-therapy-updates-for-ada-scid?filters&language=en_US*

Family Resources

- ***Families Help Shape SCID Compass Family Planning Guide***: https://scidcompass.org/news/families-help-shape-scid-compass-family-planning-guide
- ***SCID carrier discussion explores family planning, mental health:*** *https://scidcompass.org/news/families-help-shape-scid-compass-family-planning-guide*

For more information about IDF click here: https://primaryimmune.org/

Hyper IgM Foundation:

Hyper IgM Foundation Appeal for adult volunteers with X-linked Hyper IgM to contribute to clinical research in Milan

The Hyper IgM Foundation is working to drive research forward into new treatments for X-Linked Hyper IgM Syndrome. In March this year, they helped Chris Sheasby, an adult X-Linked Hyper IgM Patient living in Cambridge, UK, to donate T-cells to research conducted by Drs. Canarutto and Ferrua in Milan, Italy, on gene editing for Hyper IgM Syndrome. Chris has written a blog about his experience volunteering.

Chris's first ever selfie just after he finished his consultation at San Rafealle Hospital in Milan. (Turns out that it is harder than it looks?)

Hyper IgM Syndrome is such a rare condition; the Milan research team has had to draw on the help of volunteers from far and wide. But they still need many more volunteers to progress through the final stages of their research so that hopefully, before long, they can commence their clinical trials for gene therapy.

Researchers at San Raffaelle Hospital, Dr Daniele Canarutto (left) and Dr Francesca Ferrua (right).

In order to support this important research in Milan, working on cutting-edge new T cell gene editing, The Hyper IgM Foundation will cover all costs associated with travel and lodging in Milan. Please contact research@hyperigm.org for more information.

For more information about Hyper IgM click here: https://hyperigm.org/

Jeffrey Modell Foundation:

Genetic Sequencing Program Information

- Up to 2,500 patients have been sequenced
- 17,000 variants have been identified
- If anyone is not yet participating in this program and wishes to, send e-mail to Jessica Quinn at jquinn@jmfworld.org.
- A manuscript regarding the update of JMF's Genetic Sequencing Program, "Jeffrey's Insights", was published on June 10th in Frontiers in Immunology: Quinn J, Modell V, Johnson B, Poll S, Aradhya S, Orange JS, Modell F. Global Expansion of Jeffrey's Insights: Jeffrey Modell Foundation's Genetic Sequencing Program for Primary Immunodeficiency. Front Immunol. 2022 Jun 10;13:906540. PMCID: PMC9226364.

Meet JMF's Associate Directors of Marketing & Communications:

Stephanie Ishoo

Larissa Albright

Stephanie *(top left)* and Larissa *(top right)* are currently working on raising awareness through social media, creating diverse content, and increasing reach/growth across platforms.

For more information about JMF click here: https://www.info4pi.org/

XLA Life:

Welcome to our newest PAG, XLA Life, founded by Austin Stack!

Austin Stack, Founder of XLA Life

XLA Life is committed to fostering the unification and empowerment of the global X-Linked Agammaglobulinemia (XLA) community through education, advocacy, and initiatives that aim to improve the overall quality of life for those affected by XLA. The rare disease landscape is rapidly evolving and the future is bright. XLA Life aims to keep the patient community at the forefront of medicine by providing educational webinars, support groups, and researcher-patient family platforms. Come join us on www.xla.life

Our next Fireside Chat is August 23rd at 12pm ET (New York time). We are hosting our first international guest speakers. The leaders of the STOP XLA program in The Netherlands aim to include XLA in newborn screening programs - and they need our help! Please join this important effort by signing up for our monthly "Fireside Chats" at https://bit.ly/XLAlifeFiresideChats

To see XLA Life's previous Fireside Chats, check out our Youtube channel: https://www.youtube.com/channel/UCYwpfgjBDqAnYvwI5fNYx6Q

For more information about XLA Life click here: https://www.xla.life/

Thank you to all our PAGS!

6909 - Protocol Title: Neurodevelopmental Outcomes Following Treatment for Severe Combined Immunodeficiency (SCID)

A collaborative project funded by HRSA between the

Primary Immune Deficiency Treatment Consortium

and

Immune Deficiency Foundation

Primary aim:

- To evaluate the neurodevelopmental differences among patients who have been diagnosed following newborn screening versus those who were diagnosed following infections or via a family history of primary immune deficiencies.

Secondary aims:

- To determine the effects of chemotherapy conditioning regimen upon the neurodevelopmental outcomes.
- To determine if there is a correlation between the neurodevelopmental outcomes with the different SCID genotypes.
- To assess quality of life of patients and family members following definitive therapy.

Study Sample: Ages 6-16 years old with SCID; Enrolled in 6901 or 6902 (6902 cross-sectional only)

HRSA granted a final year no-cost extension

- 32 patients enrolled
- 10 PIDTC sites (9 US and 1 Canada) so far

Looking to enroll approximately 100 total patients by July 31, 2023

Precision Medicine World Conference (PMWC) Silicon Valley Pioneer Awardee

Congratulations to Dr. Jennifer Puck!

Dr. Puck received the **Pioneer Award** for developing the newborn screening test for Severe Combined Immunodeficiency (SCID) which is now used in all 50 states.

To find out more about Dr. Puck's accomplishments and the award, click on this link:

https://www.pmwcintl.com/speaker/jennifer-puck_ucsf_2022sv

Dr. Jennifer Puck (right) receiving the Pioneer Award from Dr. Kevin Shannon (left).

ASTCT/CIBMTR Tandem Meeting Presentations

We had several presentations and posters based on PIDTC data that were accepted to the ASTCT/CIBMTR Tandem Meetings. See more details about the presentations below.

Congratulations to Dr. Geoff Cuvelier for winning 1st Place and Dr. Danielle Arnold, for winning 2nd place for the best Pediatric Oral Abstracts at the ASTCT/CIBMTR Tandem Meeting!

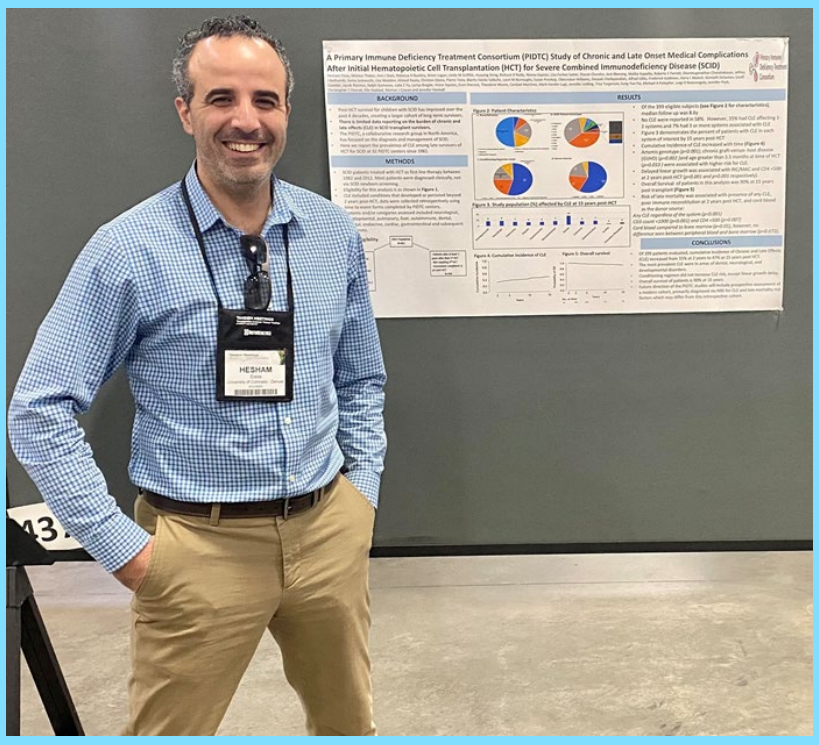
Dr. Geoff Cuvelier
1st Place Winner for Abstract Titled:
Outcomes After Hematopoietic Cell Transplant and Gene Therapy for Adenosine Deaminase (ADA) Deficiency

Dr. Danielle Arnold
2nd Place Winner for Abstract Titled:
Hematopoietic Cell Transplantation in 240 Patients with Chronic Granulomatous Disease: a PIDTC Report

In order to view the PIDTC participants contributions to the Tandem Meeting click on this link:
https://ucsf.box.com/s/t3fvt1oupokzo6dc94f9y7w7onkt0vdr

ASTCT/CIBMTR Tandem Meeting Presentations (continued…)

We are also pleased to share that Dr. Hesham Eissa provided a poster presentation. See more information below.



(Left) Dr. Hesham Eissa standing next to the Late Effects Team's poster at the ASTCT/CIBMTR Tandem Meeting.

(Below) The poster of *A Primary Immune Deficiency Treatment Consortium (PIDTC) Study of Chronic and Late Onset Medical Complications After Initial Hematopoietic Cell Transplant (HCT) for Severe Combined Immunodeficiency Disease (SCID)* presented by Dr. Eissa, on behalf of the Team.

A Primary Immune Deficiency Treatment Consortium (PIDTC) Study of Chronic and Late Onset Medical Complications After Initial Hematopoietic Cell Transplantation (HCT) for Severe Combined Immunodeficiency Disease (SCID)

Hesham Eissa, Monica Thakar, Ami J Shah, Rebecca H Buckley, Brent Logan, Linda M Griffith, Huaying Dong, Richard O'Reilly, Neena Kapoor, Lisa Forbes Satter, Sharat Chandra, Jack Bleesing, Malika Kapadia, Roberta E Parrott, Shanmuganathan Chandrakasan, Jeffrey J Bednarski, Soma Jyonouchi, Lisa Madden, Ahmad Rayes, Christen Ebens, Pierre Teira, Blachy Dávila Saldaña, Lauri M Burroughs, Susan Prockop, Olatundun Williams, Deepak Chellapandian, Alfred Gillio, Frederick Goldman, Harry L Malech, Kenneth DeSantes, Geoff Cuvelier, Jacob Rozmus, Ralph Quinones, Lolie C Yu, Larisa Broglie, Victor Aquino, Evan Shereck, Theodore Moore, Caridad Martinez, Mark Vander Lugt, Jennifer Leiding, Troy Torgerson, Sung-Yun Pai, Michael A Pulsipher, Luigi D Notarangelo, Jennifer Puck, Christopher C Dvorak, Elie Haddad, Morton J Cowan and Jennifer Heimall

Primary Immune Deficiency Treatment Consortium

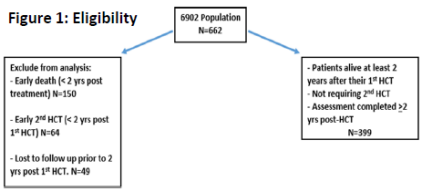
BACKGROUND

- Post-HCT survival for children with SCID has improved over the past 4 decades, creating a larger cohort of long-term survivors.
- **There is limited data reporting on the burden of chronic and late effects (CLE) in SCID transplant survivors.**
- The PIDTC, a collaborative research group in North America, has focused on the diagnosis and management of SCID.
- Here we report the prevalence of CLE among late survivors of HCT for SCID at 32 PIDTC centers since 1982.

METHODS

- SCID patients treated with HCT as first line therapy between 1982 and 2012. Most patients were diagnosed clinically, not via SCID newborn screening.
- Eligibility for this analysis is as shown in **Figure 1.**
- CLE included conditions that developed or persisted beyond 2 years post-HCT, data were collected retrospectively using time to event forms completed by PIDTC centers.
- Systems and/or categories assessed included neurological, developmental, pulmonary, liver, autoimmune, dental, skeletal, endocrine, cardiac, gastrointestinal and subsequent neoplasms.

Figure 1: Eligibility



RESULTS

Figure 2: Patient Characteristics

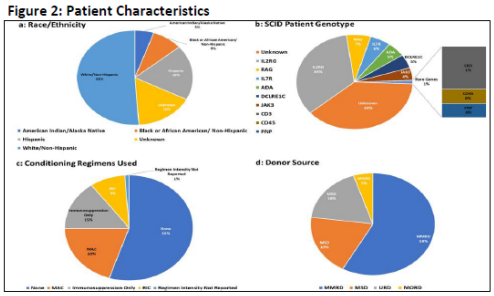
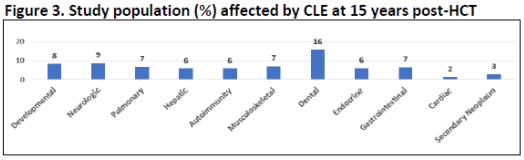


Figure 3. Study population (%) affected by CLE at 15 years post-HCT



- Of the 399 eligible subjects **(see Figure 2 for characteristics)**, median follow up was 8.6y
- No CLE were reported in 58%. However, 35% had CLE affecting 1-2 systems and 7% had 3 or more systems associated with CLE
- Figure 3 demonstrates the percent of patients with CLE in each system of interest by 15 years post HCT
- Cumulative Incidence of CLE increased with time **(Figure 4)**
- Artemis genotype *(p<0.001)*, chronic graft-versus- host disease (GVHD) *(p=0.002)*and age greater than 3.5 months at time of HCT *(p=0.033)* were associated with higher risk for CLE.
- Delayed linear growth was associated with RIC/MAC and CD4 <500 at 2 years post-HCT *(p<0.001 and p=0.001* respectively).
- Overall Survival of patients in this analysis was 90% at 15 years post transplant **(Figure 5)**
- Risk of late mortality was associated with presence of any CLE, poor immune reconstitution at 2 years post HCT, and cord blood as the donor source:

Any CLE regardless of the system (p<0.001)
CD3 count <1000 (p<0.001) and CD4 <500 (p=0.007)
Cord blood compared to bone marrow (p=0.01), however, no difference seen between peripheral blood and bone marrow (p=0.672).

Figure 4: Cumulative incidence of CLE

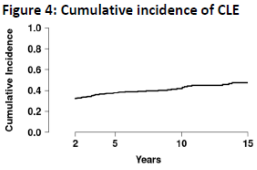
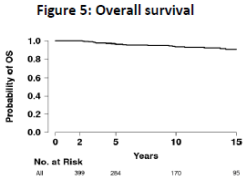


Figure 5: Overall survival



CONCLUSIONS

- Of 399 patients evaluated, cumulative incidence of Chronic and Late Effects (CLE) increased from 31% at 2 years to 47% at 15 years post HCT.
- The most prevalent CLE were in areas of dental, neurological, and developmental disorders.
- Conditioning regimen did not increase CLE risk, except linear growth delay.
- Overall survival of patients is 90% at 15 years
- Future direction of the PIDTC studies will include prospective assessment of a modern cohort, primarily diagnosed via NBS for CLE and late mortality risk factors which may differ from this retrospective cohort.

In order to view the PIDTC participants contributions to the Tandem Meeting click on this link:
https://ucsf.box.com/s/t3fvt1oupokzo6dc94f9y7w7onkt0vdr

Protocol Updates

Severe Combined Immunodeficiency (SCID) – 6901/6902/6907

Updates:
Thank you to our Protocol PIs, **Drs. Chris Dvorak**, **Elie Haddad** and **Jen Heimall** for leading the SCID team, finalizing the new 6907 protocol and overseeing the numerous manuscripts that are in the works. We thank our outstanding statistics team, led by **Dr. Brent Logan,** for its efforts pulling together this data.

The consents are UCSF IRB–approved and we began the process of onboarding many of our PIDTC sites in January. UCSF Benioff Children's Hospital, CancerCare Manitoba, Chu Sainte-Justine, Hackensack, Children's of Alabama, are our current activated sites.

Goals: Do not miss enrolling your 6901 Prospective SCID patients (while awaiting onboarding) during the DMCC transition period! Enter your eligibility data into the CRFs in the South Florida database and then email Elizabeth Dunn at Elizabeth.dunn@ucsf.edu, to finalize patient eligibility via email.

Chronic Granulomatous Disease (CGD) – 6903/6908

Updates: The 6908 Protocol has been approved by the UCSF IRB. The entire 6903 team, especially **Drs. Jen Leiding**, **Harry Malech**, **Dani Arnold, Elizabeth Kang, Suhag Parikh, Eyal Grunebaum, Kanwal Mallhi, Deepak Chellapandian and Rebecca Marsh,** have been busy preparing a manuscript using the overall data. Thank you to our statistician, **Dr. Brent Logan,** for all his efforts!

Enrollment: Do not miss enrolling your 6903 Prospective CGD patients. Enter in your Eligibility data into the South Florida database and then email Elizabeth Dunn at Elizabeth.dunn@ucsf.edu to finalize patient eligibility.

Wiskott–Aldrich Syndrome (WAS) – 6904

Updates. The WAS team is now working on data analysis and manuscript writing for the second 6904 paper with a larger "N" of patients. We especially want to thank investigators **Drs. Lauri Burroughs, David Shyr**, **Blachy Davila Saldana, Jessie Barnum**, **Sung-Yun Pai** and **Ami Shah,** and our talented statisticians **Dr. Ruta Brazauskas**, and **Huaying Dong**. We would also like to thank **Dr. Sumathi Iyengar** for her advice and active participation in our protocol calls.

Primary Immune Regulatory Disorders – 6906

Updates : The 6906 Protocol has been approved by the UCSF IRB. The PIRD team is led by Protocol PIs Drs. **Troy Torgerson, Alice Chan and Rosa Bachetta**. Plans for networking with Adult Immunology providers is underway to capture many adults with PIRD that might otherwise be missed.

Ongoing Clinical Studies

C-SIDE

CSIDE is open to enrollment at 48 sites and 24 patients have been enrolled to date. More centers are currently being activated! If you have any questions about getting your site on board, please email **Sung-Yun Pai, MD** (sung-yun.pai@nih.gov) **Mike Pulsipher** (mpulsipher@chla.usc.edu), and **Janelle Olson** (jolson@nmdp.org).

As you remember, the purpose of this trial is to test the efficacy of regimens containing busulfan targeted to 30 mg*h/L vs 60 mg*h/L in patients with X-linked SCID, JAK3 SCID, RAG1/RAG2 SCID. To date 13 IL2RG/JAK3 and 10 RAG1/RAG2 patients have been enrolled. The vast majority of patients have done very well with reconstitution of T cells and varying degrees of humoral immune reconstitution. We encourage all sites to be sure to offer enrollment on CSIDE to every eligible patient. You can also feel free to contact Sung-Yun or Mike with any questions on potentially eligible patients, and/or bring cases for discussion to the monthly PI meetings.

UCSF Artemis SCID Gene Therapy

In this trial, newly diagnosed or previously treated patients with insufficient immunity due to ART-SCID receive "lentiviral gene transfer," also called "gene therapy." A normal copy of the DCLRE1C gene is inserted into blood-forming stem cells that grow and develop into all blood lineages. The inserted gene provides correct instructions to the defective stem cells so that functioning T and B lymphocytes can develop. So far 10 patients have been treated.

For eligibility or more information about the study, please contact: **Mort Cowan, MD** (Mort.Cowan@ucsf.edu) or **Jennifer Puck, MD** (Jennifer.Puck@ucsf.edu).

Gene Therapy Trial to Treat X-linked Severe Combined Immunodeficiency

This trial is currently enrolling at St. Jude's, Seattle, and UCSF Benioff Children's Hospital. In this research study, boys with SCID-X1 will receive a treatment called "lentiviral gene transfer," also called "gene therapy." This method inserts a normal copy of the SCID-X1 gene into blood-forming cells or "stem cells" from bone marrow that grow and develop into all blood cell types. The inserted gene will provide correct instructions to the defective stem cells in SCID-X1 so that functioning lymphocytes can develop.

For eligibility or more information about the study, please visit: stjude.org/LVXSCID-ND, or contact **Ewelina Mamcarz, MD**(ewelina.mamcarz@stjude.org), **Aleksandra Petrovic, MD** (Aleksandra.Petrovic@seattlechildrens.org), or **Mort Cowan, MD** (Mort.Cowan@ucsf.edu)

LAD-I gene therapy trial

This Leukocyte Adhesion Deficiency Type I (LAD-I) gene therapy trial is currently enrolling patients at UCLA (US). Additional treatment centers will include UCL/GOSH (UK) and Hospital Infantil Universitario Niño de Jesús (Spain). The trial is sponsored by Rocket Pharmaceuticals, Inc., and funded by the California Institute of Regenerative Medicine (CIRM). For more information, please contact LADclinicaltrial@rocketpharma.com or visit https://clinicaltrials.gov/ct2/show/NCT03812263?term=NCT03812263&rank=1 or https://www.rocketpharma.com/lad-i-clinical-trial-for-health-care-providers/

Viral CTL Consortium (VIRCTLC)

Principal Investigator Mitchell S. Cairo, MD and Study Chairs Julie Talano, MD and Nancy Bunin, MD, are studying (funding by the FDA) the safety, efficacy and biology of viral CTLS derived from related donors by the Cytokine Capture System using the Prodigy device in patients with immunodeficiencies either secondary to HSCT or primary immunodeficiencies with refractory CMV, ADV and/or EBV or intolerant to anti-viral therapy. If you and your institution are interested in participating in this clinical trial, please contact **Dr. Mitchell S. Cairo** (Mitchell_cairo@nymc.edu).

Lentiviral gene transfer for SCID-X1 with low dose targeted Busulfan conditioning

This trial is open and enrolling at Boston Children's Hospital, Mattel Children's Hospital UCLA, Cincinnati Children's, Children's Hospital of Atlanta, as well as at Great Ormond Street Hospital in London. For eligibility or more information about the study, please contact:

Overall PI: **Sung-Yun Pai, MD** (sung-yun.pai@nih.gov); Boston PI: **Susan Prockop** (susan.prockop@childrens.harvard.edu) Los Angeles PI: **Donald Kohn, MD** (dkohn1@mednet.ucla. edu); Atlanta PI: **Shanmuganathan Chandrakasan** (shanmuganathan.chandrakasan@emory.edu); Cincinnati PI: **Sharat Chandra** (sharat.chandra@cchmc.org); Sponsor: **David A. Williams, MD** (david.williams2@childrens.harvard.edu).

A Study of Mavorixafor in Participants With Severe Congenital Neutropenia and Chronic Neutropenia Disorders

This Phase 1b study will determine the safety and tolerability of mavorixafor in participants with severe chronic idiopathic neutropenia (CIN) and selected congenital neutropenia disorders. The anticipated enrollment is up to 25 participants.

For questions regarding the trial, please email clinicaltrialinfo@x4pharma.com or call 857-529-5779.

Website: https://www.x4pharma.com/patients/chronic-neutropenia/

Anti-c-KIT (JSP191) Transplant Protocol

This Phase I study is a single arm, open label, dose escalation trial being conducted at multiple PIDTC centers, including: UCSF Benioff Children's Hospital, Lucile Packard Children's Hospital at Stanford and Memorial Sloan Kettering Cancer Center in New York. The study objective is to evaluate the safety and tolerability of allogeneic CD34+ human stem cells (HSC) in patients with Severe Combined Immune Deficiencies (SCID) conditioned for transplantation with JSP191, a monoclonal antibody that targets human CD117. The trial is open for both patients in need of repeat HCT as well as newly-diagnosed patients undergoing first HCT. For questions regarding the trial please contact Wendy Pang (wpang@Jaspertherapeutics.com).

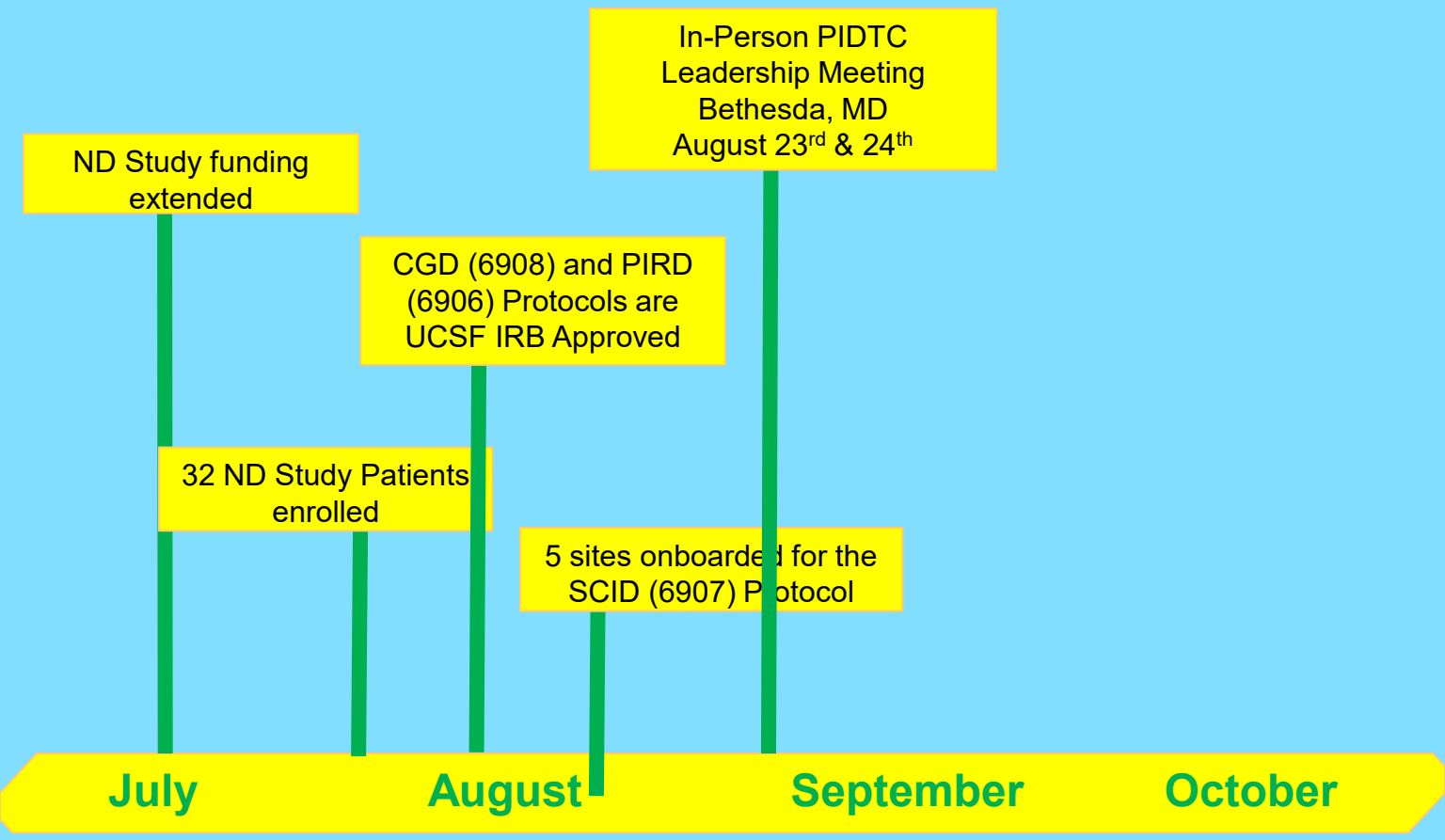
Clinical Trial at Mayo for LADII Deficiency

A Phase 3 Randomized, Double-blind Crossover Study to Assess the Efficacy and Safety of AVTX-803 in Subjects with Leukocyte Adhesion Deficiency Type II (LAD II; also called SLC35C1-CDG) enrolled the first patient at Clinical Genomics, Mayo Clinic Rochester. The study enrols LAD II patients older than 6 months receiving a dietary supplement containing L-Fucose, and randomizes patients in to a two-period study with a withdrawal phase (placebo) and treatment phase (L-Fucose) with crossover.
Patients with abnormal sialyl-Lewis antigen and history of recurrent infections are eligible for the study. Please see the attached study design summary and link for more information

Website: https://clinicaltrials.gov/ct2/show/NCT05462587?term=NCT05462587&draw=2&rank=1

For questions regarding the trial please contact Senior Program Coordinator, Kaitlin Schwartz (email: Schwartz.Kaitlin@mayo.edu or call 507-293-9114.

PIDTC: Summer/Fall 2022



Newsletter brought to you by the PIDTC Program Management Team. Thank you to our partners at the RDCRN/DMCC!

Got announcements?
Email: kiana.soriano@ucsf.edu