Marley is a 10-year old girl diagnosed with severe Leukocyte Adhesion Deficiency Type I (LAD-I) at age 7. Her childhood was punctuated with significant recurring infections, skin lesions, and hospitalizations. LAD-I is caused by ITGB2 mutations which encode for the β2-integrin component, CD18. These mutations impair the ability of neutrophils to adhere to endothelial surfaces and extravasate to infection sites.

Marley was the first patient to enroll in an autologous ex-vivo lentiviral gene therapy trial for severe LAD-I at UCLA with Dr. Donald Kohn (NCT03812263). At baseline, her CD18, CD11a, and CD11b were < 1%. Three months post-treatment, her CD18 levels increased significantly to 45%, with comparable increases in CD11a and CD11b. Skin lesions evident at baseline also showed visible signs of improvement and no new ones have appeared. Marley continues to be stable with no new infections reported.
Greetings from Jennifer Puck and Don Kohn, PIDTC Co-PIs!

We have completed our enrollments of retrospective patients (those who were affected by immune deficiency and treated from 1968-2010). However, we are continuing our prospective studies, that is, studies that are following patients forward in time as they complete therapies and age through the lifespan. Our recent research papers examined quality of life in patients with Wiskott Aldrich Syndrome, the role of inflammatory bowel disease in chronic granulomatous disease, and transplantation success in PIRD.

People with severe immunodeficiency, including those undergoing transplants, are at high risk from all infections, and especially risk of respiratory infections, one of the most severe complications of covid-19 disease. Patients should follow the advice from their physician(s), including continuing therapies as prescribed. Precautions to prevent infections are consistent with the actions listed here: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

With appreciation,
Jennifer and Don

PIDTC continues important research work on primary immune deficiencies in challenging times
Pre-Coronavirus...

Fitz loves sitting in his backpack carrier to go hiking! He’s also a big fan of taking walks around our island and checking out all the hustle and bustle. He goes out to lunch with mama Christina a lot and loves to sit in her lap and smile at all the people passing by. He’s slowly starting to meet all his baby friends who aren’t sick and seems to enjoy just watching them do their thing. (Crying, etc.) He’s as chill as ever - except for some teething pain. He has 8 teeth already!!! 💗

Post-Coronavirus...

Being back in isolation again with Deklan is both comfortable and scary at the same time. While it’s a way of life we are used to, there are still so many unknowns. For now, we are just taking things one day at a time and staying busy doing schoolwork, having fun together and doing what we can to try to keep our family safe.
SCID Angels for Life Foundation has been doing what it can during this pandemic to connect with its members, in an effort to reassure their feeling of safety and tap into their feeling of mental security. When a family was discharged from the hospital and sent home during a “stay at home order” and basic necessities and PPE were in short supply, we sent out a request to our members for help and within 24 hrs., the necessary supplies were delivered to their home or shipped to them in the coming week (top right photo).

We’ve also supplied 50 families, from around the world, with a collection of hand sanitizer (middle right photo). We’ve hosted virtual support groups in an effort to check in on some of the SCID families who are currently hospitalized or really struggling. Also, through the generosity of one of our SCID families, we’re hosting a web series on Jin Shin Jyutsu (JSJ), which is hosted by an expert in the field with over 30 years of experience. Together, as a collection of affected SCID families, we’ve come together with our resources and done some amazing things to help one another during this difficult time. By: Heather Smith
Immune Deficiency Foundation launches new research project on COVID-19 and its effect on those with primary immunodeficiencies (PI)

IDF is in the process of a COVID-19 & PI research project. 2,200 adults with and parents of those with PI completed an initial questionnaire. The bi-weekly survey is aimed at gathering longitudinal information on the pandemic and how it may impact those with PI. Topics include things such as infection with COVID-19, access to therapies, medicines, and healthcare.

The goal of the survey is to document the impact of COVID-19 on those with PI as well as to detect and document potential problems so that IDF can advocate on behalf of the PI community. The survey will be run approximately every two weeks and continue for 12-18 months.

When the physical offices of the Immune Deficiency Foundation (IDF) closed in early March, staff and volunteers knew that their services were needed more than ever, and they started working vigilantly to continue the provision of services to the community.

The IDF team has fielded hundreds of questions through the Ask IDF portal, updated its COVID-19 announcement page several times each week, launched text alerts to those who sign up for mobile updates and created a portal for those seeking updates in Spanish.

In just one month, the organization pivoted to offering Get Connected Groups, Education Meetings and its annual Advocacy Day on virtual platforms. Be on the lookout for exciting changes to the IDF Walk for Primary Immunodeficiency to include a virtual component for participants. For more information about events, visit primaryimmune.org/events.
Thank you to our Patient Advocacy Groups for their continued support and collaboration!

More PIDTC Patients and Families

It is spring break for the kids, so they are enjoying the free time. Here are the proud artists with their work. 8-year old triplets Jason, Emily and Lauren (in that order from left to right). Jason has X-SCID and was treated at a PIDTC site.
**CONGRATULATIONS Awardees!**

**Research Training Grants 2020-2021**

Dr. Matthew Kan, MD, PhD (UCSF) for his project is titled “Sequence-based lymphocyte receptor diversity: a biomarker of immune reconstitution after hematopoietic cell transplantation for SCID”

Dr. Alice Chau, MD, MSE (Seattle Children’s Research Institute) for her project titled “Characterizing activated PIK3CD in primary human B-cells”

Dr. Ori Scott, MD (University of Toronto) for her project titled “Interrogation of STAT1 Gain-of-Function in a Novel Mouse Model and Development of a CRISPR/Cas9-Based Therapeutic Modality”

**Pilot Project 2020**

Dr. Fabien Touzot has been awarded the PIDTC Pilot Project Award for 2020 for his study "Deciphering the pathophysiology of inflammation in chronic granulomatous disease”.

Dr. Touzot is trained as a clinician-researcher in pediatric immunology and hematology. He developed a gene therapy program for hematopoietic cells for immuno-hematological pathologies. His laboratory at CHU Sainte-Justine in Montreal, Canada, also works on deciphering the pathophysiological mechanism of inflammasome dysregulation in auto-inflammatory diseases.

Dr. Aristine Cheng, MD (NIAID) for her project titled Targeting plasma cells in refractory immunodeficiency associated with Neutralizing anti-interferon-g autoantibodies”
PIDTC 2020 Scientific Virtual Workshop, Wednesday, April 29, 2020

**Virtual Workshop Stats**

- 206 Zoom call-ins
- 162 completed registration survey
- 70% Female, 30% Male

**Attendance by specialty (left)**
THANK YOU to all our attendees!
## Protocol Updates-6901, 6902, 6903, 6904

### Severe Combined Immunodeficiency (SCID) - 6901/6902

**Updates:** Thank you to our PIs Chris Dvorak, Elie Haddad and Jen Heimall for leading the SCID team on cleaning up the 6901 and 6902 datasets, finalizing the new 6907 protocol and overseeing the numerous manuscripts that are in the works. We thank our outstanding statistician team, led by Brent Logan, for their efforts pulling together this data. Be on the lookout for data cleanup queries from Sharon Kidd and Katie Chang.

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

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### Chronic Granulomatous Disease (CGD)-6903

**Updates:** The CGD is hard at work finalizing the 6908 protocol which will be led by PI Jen Leiding, and Co-Pis Harry Malech, and Dani Arnold. The entire 6903 team, especially Elizabeth Kang, Stephanie Si, Kanwal Malhi, Rebecca Marsh and Suhag Parikh have been busy cleaning the 6903 dataset in preparation for an overall manuscript. Thank you to our statisticians Rachel Wu and Brent Logan for all their efforts!

**Enrollment:** Do not miss enrolling your 6903 Prospective CGD patients. Enter in your Eligibility CRFs in the South Florida database and then email Elizabeth Dunn to finalize patient eligibility via email.

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### Wiskott-Aldrich Syndrome (WAS)-6904

**Updates.** Congrats to Lauri Burroughs and the 6904 Protocol Working Team who recently published a manuscript in Blood on WAS patients transplanted 2005-2015. The WAS team is now working on data clean-up, data analysis and manuscript writing for the a 6904 paper a larger “N” of patients. We especially want to thank investigators David Shyr, Blachy Davila, Jessie Barnum, and Ami Shah and our talented statisticians Ruta Brazauskas, and Joy Liu.

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### PIDTC Protocols

<table>
<thead>
<tr>
<th>Rare Disease</th>
<th>2014-2019 (current)</th>
<th>2019-2024</th>
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<tbody>
<tr>
<td>Severe Combined Immune Deficiency (SCID)</td>
<td>6901 – Prospective</td>
<td>Merged to continue as 6907, “Severe Combined Immune Deficiency: Prospective and Longitudinal Study of Genotypes, Management and Outcomes”</td>
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<tr>
<td></td>
<td>6902 – Retrospective and Cross-sectional</td>
<td></td>
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<tr>
<td>Chronic Granulomatous Disease (CGD)</td>
<td>6903 – Prospective, Retrospective and Cross-sectional</td>
<td>6908, “Chronic Granulomatous Disease: Determinants of Auto-Inflammation and Complications following Hematopoietic Cell Transplantation”</td>
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<tr>
<td>Wiskott-Aldrich Syndrome (WAS)</td>
<td>6904 - Prospective, Retrospective and Cross-sectional</td>
<td>Completed (WAS patients with dysregulated immunity will be studied in PIRD)</td>
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<tr>
<td>Primary Immune Regulatory Disorders (PIRD)</td>
<td>N/A</td>
<td>New – 6906, “Primary Immune Regulatory Disorders: Clinical Presentations, Treatments and Outcomes”</td>
</tr>
</tbody>
</table>
**The PIDTC does not endorse these studies, but provides this information to our readers as a courtesy.**

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

This trial is open and enrolling at Boston Children’s Hospital and Mattel Children's Hospital UCLA, 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@childrens.harvard.edu); Los Angeles PI: Donald Kohn, MD (dkohn1@mednet.ucla.edu); Sponsor: David A. Williams, MD (david.williams2@childrens.harvard.edu).

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**UCSF Artemis SCID Gene Therapy**

In this research study, children with ART-SCID receive a treatment called “lentiviral gene transfer,” also called “gene therapy.” This method inserts a normal copy of the DCLRE1C 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 ART-SCID so that functioning T and B lymphocytes can develop.

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).

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**CSIDE**

CSIDE is open to enrollment 12 sites and 6 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@childrens.harvard.edu), Mike Pulsipher (mpulsipher@chla.usc.edu), and Jenny Vogel (jvogel@nmdp.org).

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**UCSF / Stanford Transplant Anti-c-KIT Transplant Protocol**

This Phase I study is a single arm, open label, dose escalation trial being conducted at 2 centers: UCSF Benioff Children’s Hospital and Lucile Packard Children's Hospital at Stanford. The study objective is to evaluate the safety and tolerability of tandemly purified allogeneic CD34+CD90+ human stem cells (HSC) in patients with Severe Combined Immune Deficiencies (SCID) conditioned for transplantation with AMG 191, a monoclonal antibody that targets human CD117.

For questions regarding the trial please contact Julie Shizuru, MD (jshizuru@stanford.edu), or Christopher Dvorak (Christopher.dvorak@ucsf.edu).

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**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).
New Clinical Studies

**The PIDTC does not endorse these studies, but provides this information to our readers as a courtesy.**

### UPMC clinical trial: BOLT-BMT
The University of Pittsburgh, sponsored by NIAID, is conducting a study for patients with primary immunodeficiency (PID) and end-stage lung disease. In this study, patients receive a lung and bone marrow transplant (BMT) from the same donor. Lung transplant prior to BMT would allow for restoration of pulmonary function prior to BMT, allowing PID patients to proceed to BMT, which would be curative for the patient’s underlying immunodeficiency. For more information, please contact Dr. Paul Szabolcs at paul.szabolcs@chp.edu or Shawna McIntyre at...

### 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).

### 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/

Got announcements? Contact Sharon at sharon.kidd@ucsf.edu
Research survey for rare disease patients and their families about impacts of COVID-19

Rare disease patients or their caregivers are invited to complete a 20-minute online survey from home about the ways the novel coronavirus pandemic is impacting people with rare diseases and their families.

Impacts can be related to physical health, emotional health, availability of supplies, access to care, or other problems. Your responses may help researchers understand the impacts of COVID-19 on the rare disease community.

The Rare Diseases Clinical Research Network (RDCRN) is conducting this study. The network is funded by the National Institutes of Health. It includes 23 research teams working to advance diagnosis and treatment of groups of rare diseases. The PIDTC is one of the teams funded through the RDCRN. To complete the survey or learn more, visit the study page here: https://www.rarediseasesnetwork.org/COVIDsurvey Questions? Email the study team at rd.covid19@cchmc.org.

PIDTC : Spring/Summer Timeline 2020

**March:** Many PIDTC sites start shelter-in-place. Work on protocols continues to the best of the ability of sites.

**Apr. 10:** Pilot Project award given to Dr. Fabien Touzot of CHU Sainte-Justine, Montreal, Canada

**Apr. 21:** Training awards given to Drs. Matthew Kan, Alice Chau, Ori Scott and Aristine Cheng

**Apr. 29:** PIDTC virtual workshop held via Zoom

**GOALS THIS SUMMER:** Add finishing touches to the 6906, 6907, 6908 protocol and CRF modules & submit to the IRB

**May:** DMCC E-Reg binder will go live
Welcome New PIDTC Sites!

University of Miami, FL

PI: Gary Kleiner

Expected enrollment: 16 patients/year
  • A leading PID Treatment center in the Southeastern US
  • Will capture South Florida’s diverse population (>85% under-represented minorities)

Columbia University, NY

PI: Larisa Broglie

Expected enrollment: 3 patients/year
  • Recent hiring of new faculty to develop a new immune dysregulation program

UCSD Rady Children’s Hospital, CA

PI: Eric Anderson

Expected enrollment: 5 patients/year
  • UCSD Genomic Center’s ultra-rapid (48 h) WGS will allow for unique PIDTC collaborations

University of Iowa

PI: Arun Modi

Expected enrollment: 3 patients/year
  • Only site for SCID NBS+ patients in Iowa
  • Only pediatric transplant center in Iowa
As a new mother, she didn’t know to look for blue-tinged lips. She could just tell her baby’s color was off. On a chest X-ray, the clean, white-against-dark curves of his ribs were obscured, clouded by fluid. Pneumonia. That tipped Ray Ballard’s physicians off: He had a form of severe combined immunodeficiency — SCID, for short — a genetic mutation that hampered the growth of crucial immune cells, leaving him utterly vulnerable to infection.

The best fix was a transplant of his mother’s bone marrow. “The attitude was that in three to six months, you should be able to go back to normal life,” recalled his mom, Barb Ballard.

That was true — at least sort of. He got two more booster transplants before he hit 10. An antibiotic left him with hearing loss, and a virus with digestive tract damage. His lack of B cells meant he needed regular injections of other people’s antibodies, and his T cell counts were never ideal. But he was healthy enough to go to public school, to move through the hallways high-fiving half the guys, to slowly inhale and take aim during rifle team practice.

“His T cells had to be working well enough that he wasn’t coming down with everything that walked into the classroom,” Ballard said.

Then, when Ray was around 18, his immunity began to wane. For him, it came in the form of a norovirus he couldn’t shake. For others with the same rare disease, it appears as pneumonia or gastrointestinal trouble or an unexpected T cell decline. Over the last 10 years, the trend has become increasingly clear: The bone marrow transplants that kept certain babies with SCID alive sometimes stop working after years or decades of providing fairly reliable immune defenses.

Now, to patient advocates, this has become an urgent lesson in the language people use to talk about treatment — and not just for SCID. They see their community’s experience as a cautionary tale for anyone developing or receiving a therapy that’s marketed as potentially curative.

“There’s an expectation and a hope: When they hear about bone marrow transplants, it sounds like a lifetime deal, a forever fix,” said John Boyle, president and CEO of the Immune Deficiency Foundation. “We’ve discovered, as a result of this issue, that bone marrow transplant ended up not being the forever fix we thought it was.”

Experts have known for years that some of these transplants wouldn’t provide full immune protection over the course of a SCID patient’s entire life. They say clinicians should have avoided the word “cure.” But even scientific papers that hinted at such complications called the treatment “curative.” Just this year, an Immune Deficiency Foundation employee was given the unenviable task of sifting through the organization’s
thousands of pages of online material, scrubbing out every “cure” that popped up. It was only there a handful of times — sometimes in quotes from clinicians, Boyle said — but it was there and it needed to be removed.

The language patients hear can sometimes even change their outcomes. “We’ve heard of cases where, years later, they realized their immune system isn’t as healthy as they thought, but nobody was tracking that because they hadn’t maintained a relationship with the physician, or the physician didn’t maintain a relationship with them,” explained Ballard. “The word cure, it gives them a false sense of security.”

At a time when seemingly every biotech is promoting the idea of “one-and-done” therapies — and setting prices accordingly — these advocates hope companies, too, will be more wary. “One of the things I’m trying to make them very aware of is the need for lifelong follow-up,” said Heather Smith, who runs the SCID Angels for Life foundation. For her, it’s personal: This summer, her son took part in a clinical trial for a gene therapy in the hope that it would provide the immune protection that his decades-old bone marrow transplant no longer could. “My son will be followed for 15 years,” she said. “But what about after that?”

Part of the issue with bone marrow transplants from one person to another is the natural genetic variation between us, particularly in the proteins that help our bodies distinguish its own cells from foreign ones. Receiving cells from someone whose proteins don’t match yours could cause a civil war within you. That’s why bone marrow transplants began back in the 1950s with identical twins: Sharing those genes meant increasing the likelihood of harmony between the body and the graft.

But the vast majority of people don’t have a protein-matched sibling, let alone an identical twin. So researchers set about figuring out how to transplant bone marrow from a parent to a child — in spite of only sharing half of their genes — and from a matched unrelated donor to a stranger. Like cooks intent on refining recipes to their taste, the doctors who adapted the technique for SCID often did so slightly differently from one another. Over the past 35 years, those idiosyncrasies have hardened into habits. “Right now, everybody transplants their patients their way,” said Dr. Sung-Yun Pai, an immune deficiency researcher and co-director of the gene therapy program at Boston Children’s Hospital.

Perhaps the most vociferous controversy has been about whether to use chemotherapy to wipe out the existing stem cells within a recipient’s bone marrow to make room for the donors’. The doctors who do use chemo before a transplant might prescribe different doses; others forego it entirely.

The arguments were sound on both sides. On the one hand, the toxic drugs could clean out the niches within our bone and increase the chances that the donor’s cells take root. On the other, these chemicals could hamper growth, brain development, and fertility, could make an infant who was already sick even sicker, and could increase the likelihood of certain cancers later in life. “It’s like being exposed to a bunch of X-rays and sunlight, or other DNA-damaging agents,” Pai explained.

Because SCID is so rare — the most common subtype is thought to occur in 1 out of every 50,000 to 100,000 newborns — and because every hospital was doing transplants slightly differently, it was hard for physicians to systematically study what was working best. But even early on, they could tell that some of the infants who’d gotten no chemo were developing incomplete immune systems. They didn’t produce their own B cells, for instance, and so needed regular injections of antibodies collected from other people’s blood.

In healthy infants, stem cells migrate from the crevices of the skeleton to an organ in the chest called the thymus, where they’re trained to become T cells. In these infants, the T cell counts grew after transplant — but it wasn’t necessarily because the sludge was securely taking hold in the niches of their bones. Rather,
immunologists say, the donor’s progenitor cells were only transient. Some were able to head toward the thymus for schooling. Some graduated and started fighting off infections. But as those populations were depleted with age, there weren’t robust reserves of stem cells in the bone marrow that could arrive to produce more. To Pai, it’s like trying to fill a kindergarten class in a neighborhood where no one’s having babies.

“You and I continue to have a slow trickle of new T cells coming out,” said Dr. Harry Malech, a senior investigator at the National Institutes of Health, who sits on the board of a gene therapy company, Orchard Therapeutics, but does not receive any financial compensation. “Instead of a torrent becoming slower, in these patients it goes from a trickle to practically nothing.”

That’s why immunity starts to wane in kids like Ray Ballard. To many immunologists, it isn’t a surprise, though they still aren’t sure why chemo-less transplants last longer for some of these kids than others. They can also understand how some families and clinicians might have viewed this treatment as a lifetime fix.

As Malech put it, “If I said to you, ‘Your child, instead of dying in infancy, will likely get to adulthood, go to school, have a normal life,’ you might think the word ‘cure’ in your mind.”

Even for parents who knew the protection might not last forever, the failure of a long-ago bone marrow transplant puts them in a bind. If they do nothing, their child will once again be vulnerable to any passing infection, which could prove fatal. They can try another round of the same procedure, though booster transplants sometimes come with added complications. Or they can try getting their child into a research trial for gene therapy, which comes with the risks of any experimental treatment.

Some feel an irrational guilt when the bone marrow they donated to their child stops functioning. “It’s your cells, and if it doesn’t work, you failed them,” said Ballard, who lives in Clifton, Va., about a 40-minute drive from Washington, D.C. Her son Ray had already had three transplants as a child. When his immune system started to fail again in early adulthood, gene therapy at the NIH seemed like the only reasonable choice.

That would involve researchers removing cells from his bone marrow, using an engineered virus as a kind of molecular syringe to slip in a healthy copy of the gene in which he had a defect, and then threading these corrected cells back into his veins — a bone marrow transplant to himself. But preparing a virus can be tricky, and there were delays.

Meanwhile, Ray’s condition was getting worse. His norovirus was preventing him from absorbing much nutrition, and as Ballard put it, “his bone structure was just crumbling at that point.” His doctors told her he had the skeleton of an 85-year-old.

He died this past February, at 25 years old. One friend got his birth and death dates tattooed onto her shoulder. Another painted a portrait of him for Ballard, in which his arms are crossed, his lips pressed together in a wry smile.

At Boston Children’s, Pai is now helping to lead a randomized trial to better understand what dose of chemo works best for SCID patients receiving transplants. Over the last decade or so, she, Malech, and many
other clinicians have also teamed up to track the long-term results of immune deficient patients\textsuperscript{17} who’ve received someone else’s bone marrow.

Pai is hopeful that knowing about the phenomenon of waning immunity will give gene therapies a better shot at becoming a durable fix. “They probably have a better chance of achieving a one-time, lifelong cure, but it’s never wrong to be humble,” she said. “Only after decades more and hundreds or thousands of patients will we know for sure.”

Patient advocates point out that even then, these patients will still have the capacity of passing on their SCID causing gene to future generations, and so the word “cure” is overly optimistic. “That’s why I like the word ‘remission,’” said Smith. “That still gives you the hope. If you were given a cancer diagnosis, you wouldn’t go through treatment and then just forget about it for the rest of your life.”

As Boyle put it, “We’ve seen the promise and then we’ve seen the reality. Everyone who is looking at a transformational therapy should be optimistic, but also realistic, and not assume that this is truly one and done.” (Boyle’s foundation has received financial support from Orchard Therapeutics, which is developing a gene therapy for a form of SCID.)

To Amy Saada, of South Windsor, Conn., that isn’t theoretical. Her son Adam is now 12, and the immunity from the bone marrow transplant he got as a baby is wearing off. He isn’t yet sick, but his parents know they need to decide between gene therapy or another transplant soon. She has a very clear memory of how long and uncertain the recovery from treatment felt. In some ways, she wishes she didn’t know quite as much as she does; that way, she would feel less trepidation about what lies ahead.

“Our heart kind of sinks,” she said. “You’ve already been through it once, and it was hell. It’s harder the second time.”

About the Author

\textbf{Eric Boodman}\textsuperscript{3}
General Assignment Reporter
Eric is a general assignment reporter.
\texttt{eric.boodman@statnews.com 18}
@ericboodman 4

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Got announcements? Email: Sharon.kidd@ucsf.edu