OFFICE OF TECHNOLOGY LICENSING

INTELLECTUAL PROPERTY NEWSLETTER

2019 Issue

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NEWSLETTER DEDICATION

This issue of the OTL newsletter is dedicated to Brian Sorrentino, MD, who died in 2018 after a battle with cancer. Dr. Sorrentino uniquely understood the urgency of the St. Jude mission, as he survived cancer as a child and grew up to lead research that is offering children throughout the world new hope for cures.

Brian Sorrentino, MD (1958-2018)

"A prodigious scientist known for his brilliance, dedication and hard work, the New York native arrived at St. Jude in 1993 after spending five years at the National Institutes of Health. Dr. Sorrentino served as director of Experimental Hematology since 2001, when he and his colleagues discovered what they believed to be the world's first 'universal' stem cell marker. The team found that expression of a gene called ABCG2/ Bcrp1 allowed researchers to identify stem cells from a variety of sources. The discovery provided scientists with a much more accurate way of identifying true stem cells than had been available in the past."

-James R. Downing, MD
President and Chief Executive Officer, St. Jude Children's Research Hospital

One aspect of Dr. Sorrentino's research resulted in a safer and more effective way to deliver gene therapy, leading to his work aimed at curing infants with XSCID. This line of research is detailed in the following article.

SUCCESSFUL TRIAL AND A COMMERCIAL PARTNER FOR GROUND BREAKING XSCID TREATMENT

X-linked severe combined immunodeficiency (XSCID, also known as bubble boy disease) is a rare genetic disorder that occurs in 1 to 2 births per 100,000. The children are born lacking the ability to produce T cells or natural killer (NK) cells; and although they have a normal number of B cells, they are not functional. As a result, XSCID patients often suffer from potentially deadly bacterial, viral, or fungal infections very early in life.

Various XSCID gene therapy clinical trials have been conducted over 20 years, both as an alternative to hematopoietic stem cell transplant (HSCT) or following a poor outcome. Transduction of normal copies of the mutated IL2RG gene into stem cells using a gamma-retroviral vector has previously resulted in reconstitution of patient NK and T cells, but not functional B cells; and early trials resulted in vector-induced leukemia in 25% of patients due to insertion of the gene-carrying retrovirus near an oncogene.

A lentiviral (LV) vector from St. Jude Children's Research Hospital is being investigated in multicenter clinical trials in conjunction with reduced-exposure busulfan conditioning. A trial was first initiated in older adolescents, and then for newly diagnosed infants with XSCID. The vector is made on our campus by our GMP facility that produces clinical grade biological products, which also re-engineers the patients' cells to carry the healthy new gene.

In the first trial, which was reported in the April 2016 issue of Science Translational Medicine, five males aged 10 to 23 years with progressively declining persistent immune dysfunction after parental HSCT in infancy were treated at the National Institute of Allergy and Infectious Diseases (NIAID). Patients all had chronic viral infections and other XSCID related health problems after HSCTs failed to fully correct their immune function.

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Previously, patients on gene therapy trials gained T cells; but still lacked B cells, NK cells, and antibodies; requiring lifelong gamma globulin therapy. Now, more than 2 years after undergoing this new gene therapy, initial patients are producing a greater percentage of immune cells, including T, B and natural killer cells. The clinical trial included a number of firsts for gene therapy of XSCID:

- The first use of a lentiviral vector
- A streamlined stable production system (increases supply)
- Novel features designed to increase safety/effectiveness
- Busulfan used to re-establish the gene-corrected stem cells

In the second trial, results for 8 patients under the age of 2 with XSCID were presented at the 21st Annual Meeting of the American Society of Gene & Cell Therapy in May 2018. In that group, 6 patients achieved reconstituted immune systems within 4 months following treatment, with 2 of the 6 patients discontinuing monthly infusions of intravenous immunoglobulin. The remaining patients, at earlier stages of recovery, continue to progress favorably. In 3 patients who had disseminated infections prior to therapy, all infections resolved completely and the therapy was well tolerated.
Both trials continue to add patients, with those under the age of 2 being treated at St. Jude, UCSF Benioff Children's Hospital San Francisco, and Seattle Children's Hospital; and older patients being treated at the NIH. Follow-up data from two older patients demonstrated immune system reconstitution and clinical improvement at 2 to 3 years following treatment. In 3 younger patients, similar levels of gene-modified immune cells were also observed at 6 to 9 months following treatment.

In 2018, the successful trials generate commercial interest which ultimately resulted in an exclusive worldwide license agreement between St. Jude and Mustang Bio to further develop and commercialize this therapy.

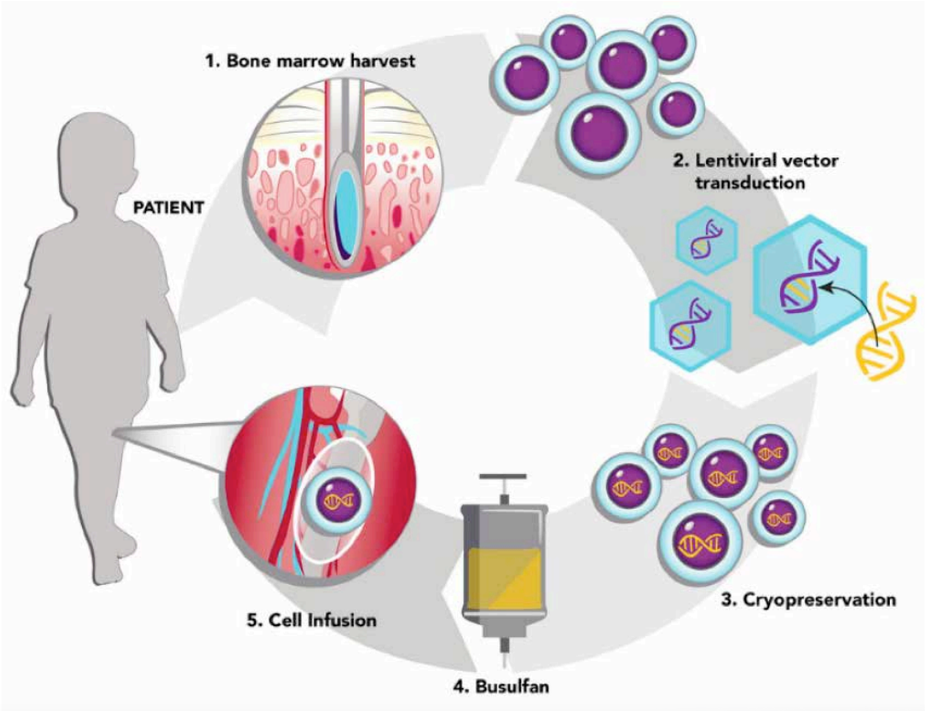
The specific genetic disorder that causes XSCID is a mutation in the gene coding for the common gamma chain (γc), a protein that is shared by the receptors for at least 6 interleukins. These interleukins and their receptors are critical for the development and differentiation of immune cells. The gene coding for γc is known as IL-2 receptor gamma, or IL2RG; and is located on the X-chromosome, resulting in almost all patients being male.

Historically, the most effective treatment for XSCID has been bone marrow transplantation, [i.e. hematopoietic stem cell transplantation (HSCT)], where a patient receives healthy blood-forming cells from a matched sibling donor, or a half-matched parental donor. Physicians have also had success using umbilical cord blood, which is rich in stem cells. Overall survival for the 10% of patients who have matched sibling donors is 95%; however, it falls to 60 to 75% with other types of transplant, with over 50% of these patients requiring lifelong intravenous immunoglobulin therapy. In addition, 28% experience acute graft-vs-host disease (GvHD), and 15% experience chronic GVHD. T-cell immunity may also decrease over time, requiring 26% of patients to undergo a second HSCT. The earlier age the treatment is provided, the better the clinical outcome, so now all 50 U.S. states and many countries screen newborns for XSCID. To the right is the St. Jude procedure to reconstitute the immune system.

"We look forward to working with St. Jude to advance this program… we are building a fully integrated cell and gene therapy company, with the goal of leveraging the transformative potential of these technologies to bring life-saving treatments to patients in need."

-Manuel Litchman

President and CEO Mustang Bio



Samuel's last visit before returning home, with (from left) Ewelina Mamcarz, MD; Samuel Evangelista; interpreter Marc Friedman; and Katie Birdsell, a nurse practitioner in Bone Marrow Transplantation and Cellular Therapy. For more information about Samuel's story, go to: https://www.stjude.org/xscid-second-chance

A PERSONAL SIDE OF THE STORY

A newborn child is precious. For Ricardo and Simone Evangelista of Sao Paulo, Brazil, the birth of their son Samuel was especially precious, as they had twice miscarried; however, at 3 months old, Sam was diagnosed with XSCID.

After learning about St. Jude Children's Research Hospital, the Evangelistas and their doctor spoke with doctors in the St. Jude Department of Bone Marrow Transplantation and Cellular Therapy, and the couple agreed to take part in the world's first lentiviral gene therapy trial for infants with XSCID.

Within 2 days of traveling to St. Jude, 11-month-old Samuel spiked a fever. Bacteria used in a vaccine commonly given to newborns in Brazil to prevent tuberculosis had triggered an infection in the shoulder. Because Samuel lacked an immune system, this was a life-threatening complication. Surgeons at St. Jude performed an operation to remove the infection from his shoulder before Samuel was treated with his own genetically re-engineered cells to treat XSCID.

Samuel was one of 6 who achieved reconstituted immune systems within 4 months after gene therapy. He received his last immunoglobulin infusion in January 2018. At 16 months, Samuel Evangelista returned home to Brazil in January 2018 with no activity restrictions, though his parents will bring Samuel back to St. Jude every 3 months for checkups.

LOOKING BEYOND XSCID

The St. Jude XSCID clinical trials provide insights for treating other disorders, which include Wiskott-Aldrich Syndrome, a disorder that causes infections and reduces the ability to form blood clots, and sickle cell disease, which affects about 100,000 Americans. St. Jude cares for around 1,000 pediatric sickle cell patients, and the gene therapy platform could potentially be curative for these patients as well as for many other devastating immune disorders in the future.

ABOUT THE GMP

In 2003, St. Jude was the first pediatric cancer research center in the U.S. to open an on-site Good Manufacturing Practice (GMP) facility to play a critical role in moving discoveries from St. Jude laboratories into the clinic. The GMP allows St. Jude to develop and test innovative treatments in patients without the need for investment or interest from pharmaceutical companies. The diverse products manufactured in the facility include novel vaccines, gene therapy products, monoclonal antibodies, and recombinant proteins. Since opening, the GMP has produced 8 biologics used in clinical trials. All these products have improved the outcome of patients. Beyond producing biopharmaceuticals discovered by researchers at St. Jude, GMP staff also manufacture products that arise from research conducted by St. Jude faculty and outside collaborators. Prior to the XSCID therapy, the GMP manufactured an AAV Factor IX product that has been used to successfully treat adult Hemophilia B patients as a collaborative effort between St. Jude, University College London and the Royal Free Hospital. Recent projects include the FDA approved application for a lentiviral CD19 CAR product, and a monoclonal antibody (Hu14.18 K322A) used to treat neuroblastoma patients. The GMP also manufactures 1 to 2 new avian influenza seed stock vaccines each year. Thankfully these seed stocks have not yet been needed. The GMP most frequently works with Bone Marrow Transplant, Hematology and Infectious diseases. The Office of Technology Licensing looks forward to working with the GMP and all departmental collaborators to move treatments to the next step, from the clinic to licensing them to a company that can pursue FDA approval and broad commercial use to maximize patient impact.

TECHNOLOGY TRANSFER PROFESSIONALS DAY

Wednesday, December 12, St. Jude celebrated the Association of University Technology Managers (AUTM) Technology Transfer Professionals Day in the Marlo Thomas Center for Global Education and Collaboration. This was the 38th anniversary of the Bayh-Dole Act which dramatically expanded the profession by engaging academic institutions in the technology transfer process. Guests learned about disclosing inventions, the licensing process, and ways to partner, participate and earn money. The OTL also distributed exclusive stainless steel mugs to inventors of recently awarded patents, and gave out small candy filled "bright idea" light bulbs.

ACTIVITIES AND IMPACT

The Office of Technology Licensing received 46 invention disclosures in FY2018, and completed over 900 Agreements. The Office of Technology Licensing also managed 232 active licenses, with over $3.4M in license income allocated to 118 inventors. Through the process of technology licensing, research initiated at St. Jude has contributed to a number of pending and approved therapies and diagnostics that are improving the lives of our own patients as well as the general population. The following table summarizes the impact of four technologies that have been adopted and used broadly:

TECHNOLOGY	INDICATION	PATIENT IMPACT
Plasmid Rescue Flu Vaccine	Influenza	100 Million+ vaccine doses manufactured/yr.*
ALK Inhibitors: Xalkori/Zykadia/Alunbrig	ALK positive Cancer	45,000+ patients treated/yr.
CAR Cell Therapy	Cancer (ALL, CLL, NHL)	1,000+ treated in clinical trials (50+ w/FDA approved Kymriah®)
Thiopurine tolerance (TPMT) and B-cell test (CD-19 MAb)	Diagnostics	500,000+ tests sold/yr.

**Our process is also used to make flu vaccine for animals*

Contact us to find out more about the technology transfer process, and benefits

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