

# ADVANCES IN PEDIATRIC ONCOLOGY

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 Dr. Julia L. Glade Bender



## Gene Therapy for Thalassemia and Hemophilia Comes of Age

For years, therapies for thalassemia and hemophilia have managed to control these chronic diseases, and with care at comprehensive treatment centers, such as those at NewYork-Presbyterian/Weill Cornell Medical Center, patients can live to near normal life expectancies. “However, until recent breakthrough advances in gene therapies, there was a huge unmet need in terms of having a curative treatment for either disease,” says **Sujit Sheth, MD**, Chief, Pediatric Hematology and Oncology, and Director of the Thalassemia Center at Komansky Children's Hospital at NewYork-Presbyterian/Weill Cornell. Today, Dr. Sheth and **Catherine E. McGuinn, MD**, Director of the Hemophilia Center at Komansky Children's Hospital, share a tangible optimism that a cure for both conditions is well within reach.

“We have the largest population of patients with hemophilia and thalassemia between Boston and Philadelphia and follow some 150 patients in each program,” notes Dr. Sheth. “We're able to provide



Dr. Catherine E. McGuinn and Dr. Sujit Sheth

all of the latest therapies and state-of-the-art care for both of these chronic conditions.”

Current treatments for hemophilia prevent patients from having bleeds and also maintain them in

*(continued on page 2)*

## CAR T-Cell Therapy: A Reason to Hope in Hematological Malignancy

Chimeric antigen receptor (CAR) T-cell therapy engages an individual's own immune cells to treat cancer, and, in particular, hematological malignancies.



Dr. Prakash Satwani

In CAR T-cell therapy, T-cells are obtained from the patient and with genetic engineering, these cells are trained to identify, attack, and kill cancer cells. With the first-ever FDA approval for a CAR T-cell therapy, (CTL019), in August 2017 for children and young adults with relapsed or refractory  $\beta$ -cell acute lymphoblastic leukemia, interest in this first-in-class therapy has intensified. Developed by Novartis, Kymriah™ (tisagenlecleucel) has been tested in a number of different clinical trials in approximately 150 patients in the United States, many of who had decreases in their disease or entered a complete remission.

“This transformative treatment for cancer can help some leukemia patients who have no other options,” says **Prakash Satwani, MD**, a pediatric hematologist/oncologist in the Division of Pediatric

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## Gene Therapy for Thalassemia and Hemophilia Comes of Age (continued from page 1)

**“Experiments in animal models for both hemophilia and thalassemia have been ongoing for at least 30 years. It’s only in the last three to five years that we are able to actually apply these findings in humans.”**  
**– Dr. Sujit Sheth**

as normal a state as possible, says Dr. Sheth. “But they still have hemophilia. With gene therapy, we are looking at a cure.”

As major treatment programs for thalassemia and hemophilia, the two centers have long participated in multicenter trials of new therapies. Most recently, Weill Cornell took part in an early stage, open-label, phase 1-2a study of an experimental gene therapy for hemophilia B in 10 men who had factor IX coagulant activity of 2 percent or less of the normal value. The therapy involved the infusion of a single-stranded adeno-associated viral vector – SPK-9001 – consisting of a bioengineered capsid, liver-specific promoter and factor IX Padua transgene. This gene transfer therapy goal is to have a non-pathogenic virus deliver a hyper-expressing factor IX gene to the liver, allowing consistent expression of the factor IX clotting factor to prevent bleeding.

The results, published in *The New England Journal of Medicine* in December 2017, showed that nine of the 10 patients did not experience any bleeding episodes after the gene therapy treatment, and the one patient who needed clotting factor because of bleeding used 91 percent less than before. Participants were followed for 52 weeks and are currently enrolled in a long-term follow-up protocol.

“The adeno-associated viral vector targets the liver and produces the coagulation protein that is missing,” says Dr. McGuinn. “It is a much easier process for the patient with a one-time infusion of SPK-9001 that results in continued expression of that factor in the bloodstream compared to standard of care with twice a week peripheral intravenous infusion of clotting factor concentrate.”

Currently, the Weill Cornell investigators are participating in a multicenter trial for patients with hemophilia A, the more common form of hemophilia. Gene therapy for hemophilia A has been demonstrated as a proof of concept in early phase clinical trials and researchers are actively screening patients for participating in ongoing studies with promising results. An abstract of the researchers’ early findings was presented at the American Society of Hematology 59th Annual Meeting in December 2017.

To date, a curative treatment for thalassemia has required hematopoietic stem cell transplantation from a matched sibling. “However, only 20 percent of patients have a matched sibling, so it is not a therapy that is available to everyone,” says Dr. Sheth. “The mainstay of treatment is transfusions, which can result in iron overload, leading to complications of hemochromatosis. Over time, this can lead to diabetes, heart disease, and various endocrinopathies. And this form of treatment heavily depends on the patient’s compliance with the therapy.”

Gene therapy trials for the treatment of beta-thalassemia began several years ago with encouraging results, notes Dr. Sheth. However, recent data presented at the American Society of Hematology meeting focused on a new approach of using a lentiviral vector to transport a functioning hemoglobin gene into patients’ hematopoietic stem cells and then transfusing them back into the patients.

“The preliminary data of the new protocol is very promising and much better than the prior study,” says Dr. Sheth. “To put it into

perspective, a vector copy number indicates how many copies of the vector are present in each stem cell. A previous study had a vector copy number of .6 to .7. You need to have at least one copy per stem cell for it to work well, so at .6 or .7, it probably would not do the trick. With this new process, the vector copy number is between 2 and 3, a huge difference and the prime reason why we think it will be very successful. Treatment still requires patients to undergo a stem cell transplant, but autologous.”

“It’s very exciting to have conversations with patients where we are not talking about doing this in mice or in a primate model but are able to say that we can offer them this treatment as part of the clinical care we provide,” says Dr. McGuinn. “And now that we know that technology can deliver a new gene that can produce a protein that will function biologically, I believe this is a potential model for other diseases, such as muscular dystrophy and cystic fibrosis.”

**“It’s exciting to be part of what’s happening in gene therapy and to be able to share the latest developments with our patients that I hope will improve their quality of life.”**

**– Dr. Catherine E. McGuinn**

“Experiments in animal models for both hemophilia and thalassemia have been ongoing for at least 30 years,” says Dr. Sheth. “It’s only in the last three to five years that the technology has exploded, and we are able to actually apply findings in humans. There’s been a lot of investment in technology from the biotech companies, and many trials are opening with slightly different variations of vectors and slightly different variations of genes. Based on what we know so far, in terms of safety and efficacy, I believe gene therapies will be FDA approved for hemophilia and thalassemia within three to five years.”

Monitoring individuals for long-term results, safety outcomes, and durability of treatment is imperative, says Dr. McGuinn. “We’ve already seen that the FDA originally called for an extremely long period for follow-up studies for gene therapy trials; they’ve shortened that significantly as we’ve gotten started, so it’s been reassuring.”

“To be able to offer patients with these chronic conditions a cure is incredible,” says Dr. Sheth. “Honestly, I never thought in my professional life that I would be able to say, ‘I can cure thalassemia.’ It’s not here yet, but it’s coming.”

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### For More Information

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## Pursuing Precision Medicine in Pediatric Cancers

The pediatric oncology program at NewYork-Presbyterian/Columbia is one of the front-runners nationally instituting and implementing real-time precision oncology for patients, including the establishment in 2014 of a precision-in-pediatric sequencing program called the PIPseq Cancer Program. Led by **Julia L. Glade Bender, MD**, Associate Director, Pediatric Hematology, Oncology, and Stem Cell Transplantation, and Medical Director for PIPseq, the program works to identify the molecular drivers of each patient's cancer and use this information to personalize his or her treatment using novel, biologically targeted investigational agents.

Columbia is among only a handful of institutions nationwide providing a comprehensive sequencing platform for pediatric patients that includes not only the DNA code (whole-exome), but also the RNA message which informs protein expression (RNA-seq). In 2016, PIPseq received funding from the Sohn Conference Foundation to provide this clinical testing to any child with a high-risk cancer in the New York, New Jersey, Connecticut area. And, in 2018, the program will begin integrating the OncoTarget™ and OncoTreat™ methodologies originally developed for the adult N-of-1 program to interpret the RNA data.

“Through NewYork-Presbyterian/Columbia’s pediatric sequencing program, every child with a high-risk cancer that comes to Columbia undergoes whole-exome sequencing; the patient’s tumor also undergoes RNA-seq analysis,” says Dr. Glade Bender. “Half of the clinically applicable findings have come from the expression data; applying OncoTarget™ and OncoTreat™ add validity and depth to the analysis.”

### MATCH Trial Welcomes Pediatrics

Researchers at Columbia are major participants in the NCI-based MATCH trial – a nationwide effort to sequence 7,000 adult patients with different types of cancer. The MATCH trial has identified 30 different drugs correlated to the different genes of patients, making it possible for adult patients anywhere in the country to have access to treatment specific to the genetic makeup of their tumor.

In July 2017, the NCI-COG Pediatric MATCH trial launched with two of the eight treatment arms led by Dr. Glade Bender, and **Alice Lee, MD**, Medical Director, Pediatric Hematology, Oncology, and Stem Cell Transplantation, NewYork-Presbyterian Morgan Stanley Children’s Hospital.

The NCI-COG Pediatric MATCH trial is open for children and adolescents from one to 21 years of age with advanced solid tumors, including non-Hodgkin lymphomas, brain tumors, and histiocytoses, whose cancer has advanced while on treatment or has returned following treatment. Patients are assigned to an experimental therapy based on the genetic changes found in their tumors through genomic sequencing rather than on their type of cancer or cancer site.

“We have taken a leadership role in the NCI Pediatric MATCH trial,” says Dr. Glade Bender, who is a member of the trial’s Steering Committee. “I’m very passionate about getting more adolescents and young adults on clinical trials. In many ways, we’re using our own in-house platform to screen patients who we think are likely candidates for MATCH. If we find the genetic alterations that lend themselves to therapy in the MATCH trial, then we can get our kids access to those targeted drugs.”

The first enrollment step of the trial involves screening the patient’s tumor sample to determine if there is a genetic change that could be targeted by one or more of the drugs being studied. Researchers plan to screen the tumors of 200 to 300 patients each year, until 1,000 have



Dr. Julia L. Glade Bender

been screened. Current research suggests that one out of 10 patients who enroll in the screening phase will have a genetic change that matches one of the targeted drugs undergoing testing. Patients will also undergo testing to determine whether any genetic change in their tumor was hereditary. The information gleaned can help physicians advise families about possible additional genetic testing, counseling, and follow-up.

Those patients whose tumors have a genetic change that can be targeted by a MATCH study drug may go on to the second step, which is to enroll in a treatment arm if they meet other eligibility criteria. Patients who enroll in a treatment arm will continue to receive the experimental treatment as long as their tumors are stable or getting smaller. At least 20 patients will be enrolled in each treatment arm in the testing of a different drug, all of which have been donated by pharmaceutical companies that have partnered with NCI. While the drugs are experimental in children and adolescents, they have been tested in, or in some cases approved for, adults and have shown activity against tumors with specific genetic changes.

“I’m running the trial of olaparib, which is a PARP inhibitor, and we’ll be giving that to patients who have genetic alterations in their DNA damage repair genes,” says Dr. Glade Bender. “Dr. Lee is running the erdafitinib arm that is targeting gain-of-function mutations and fusions of the genes encoding FGFR, the fibroblast growth factor receptors.”

“There are a lot more agents out there,” adds Dr. Glade Bender. “The push for the future is to figure out through biomarkers which patient needs which therapeutic approach, be it immunotherapy, chemotherapy, biologically targeted therapy, or a combination. Creating big data sets of these patients and looking at their N-of-1 experiences should help us to predict what therapy might be of greatest benefit for the next patient.”

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**CAR T-Cell Therapy: A Reason to Hope in Hematological Malignancy** *(continued from page 1)*

Hematology, Oncology, and Stem Cell Transplantation at NewYork-Presbyterian/Columbia University Irving Medical Center. Dr. Satwani developed the CAR T-cell treatment program at Columbia for children with acute lymphoblastic leukemia. The program is one of 32 centers in the country and one of only two in New York approved by Novartis to offer this treatment.

“The FDA has established strict guidelines for eligibility for the treatment,” says Dr. Satwani. “Patients must be younger than 25 years old with refractory acute lymphoblastic leukemia. The second indication is for patients with leukemia who have undergone two separate cycles of chemotherapy, bone marrow transplant, or another treatment and the cancer has returned each time. If the patient meets these criteria, then we next want to make sure that he or she has good organ function – their lungs, kidneys, and heart all need to be in good shape before they go for this therapy.”

**An Exacting Treatment Process**

The process for administering CAR T-cell therapy is a rigorous one. It begins with collecting the patient’s T-cells through leukapheresis. Once the T-cells are extracted they are shipped to Novartis to be genetically engineered, which takes approximately three weeks.

“There are two parallel paths,” explains Dr. Satwani. “While the patient’s cells are with Novartis, we are preparing the patient to receive the cells. This involves administering lymphodepleting chemotherapy to help reduce the amount of leukemia cells present in the blood and bone marrow. This protocol is individualized to each patient with a goal of minimizing toxicity to enable them to receive the CAR T-cells.”

When the cells are ready, Novartis ships the cells in frozen vials to Columbia’s stem cell lab. The patient is given another round of chemotherapy to deplete any remaining T-cells. “We don’t want the patient’s own T-cells to fight the genetically engineered T-cells, so we want a very low lymphocyte level in circulation.”

The patient is then given Kymriah through IV infusion and then discharged to a location no farther than two hours from the Hospital for the next four weeks for close monitoring.

“After the first 72 hours, some patients will start to develop a fever, and nearly half will require admission to the intensive care unit,” says Dr. Satwani. “As the genetically engineered T-cells begin to fight the leukemia cells, they become very active, begin to multiply, and will release chemicals – a phenomenon called cytokine release syndrome. When cytokines are released in a very high quantity, the patient may get very sick. Novartis only chose a few centers with strong intensive care unit support to do the therapy because this cytokine release syndrome can be very severe.”

Dr. Satwani notes the success rate based on the studies that have been published indicate that 50 percent of patients will be leukemia free at one year. “What makes this so amazing,” he says, “is that the patients who are going to be treated by the CAR T-cells usually have a less than 10 percent chance of surviving. This offers a huge increase in their survival rate for leukemia-free survival.”

**For More Information**

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