

ISCT TALKING WITH GIANTS TRILOGY



FOREWORD

Donald G. Phinney, PhD, Senior Editor

Alongside the International Society for Cell & Gene Therapy (ISCT), it is my privilege as Senior Editor of *Cytotherapy* to introduce to you this latest addition to the “Talking with Giants” series – a special “*Talking with Giants Trilogy*”. Celebrating the highly successful development of the first chimeric antigen receptor T cell (CAR-T) therapy, this novel immunotherapy, pioneered by the University of Pennsylvania, has shown remarkable clinical results, pushing the rapid approval of CAR-T therapies for treating pediatric and adult patients suffering from leukemia and lymphoma. This advancement has pushed, in turn, the development of personalized cellular therapies for treating both bloodborne and potentially tumorous cancers, offering new hope to many cancer patients.

Our trilogy begins with fellow ISCT member Dr. Carl June, MD, who almost needs no introduction. His pioneering work in T-cell immunotherapies led to the first successful CAR-T clinical trial in patients with refractory and relapsing chronic lymphocytic leukemia (CLL). Dr. June offers his insights into the rapid evolution of immunotherapy that has followed and reveals the motivation that drove him while working on this breakthrough trial.

From there, we speak with ISCT President-Elect, Dr. Bruce Levine, PhD, who, mentored by Dr. June, established a cell therapy manufacturing laboratory and pioneered the production of T cell-based therapeutics including the CAR-T cells used in Dr. June’s landmark trial. Dr. Levine provides his perspective on the trajectory of cell manufacturing and on the future of immunotherapy.

Finally, we speak with the Whitehead family, whose daughter Emily was one of the first patients treated with CAR-T cells in the breakthrough trial spearheaded by Drs. June and Levine. Emily’s story of defying the odds, and the fortitude of her parents Kari and Tom, are truly inspirational.

I am confident that you will relish this “*Talking with Giants Trilogy*” that honors true pioneers in the field of immunotherapy.

ISCT TALKING WITH GIANTS TRILOGY

PART I: CARL JUNE, MD



"You want to be persistent and continue to work on difficult problems. This is different than stubbornness, which is continuing to hit your head against the wall in the same way."

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ISCT SERIES: TALKING WITH GIANTS

"It was a long and winding road," says Dr. Carl June, the Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine and the Director of the Center for Cellular Immunotherapies at the Perelman School of Medicine at the University of Pennsylvania.

In August 2011, a team of researchers led by Dr. June published findings that detailed a new therapy in which patients with refractory and relapsed chronic lymphocytic leukemia were treated with genetically engineered versions of their own T cells. When the news broke, a flood of support for the research inundated the handful of researchers responsible.

The treatment made possible by the research performed in Dr. June's lab has expanded the field considerably. However, what people did not see were the years of behind-the-scenes work of Dr. June and his team and the lack of funding and other barriers that preceded the breakthrough that saved the lives of leukemia patients who had exhausted all other treatment options.

In the 1990s, Dr. June led an immunobiology research program at the Naval Medical Research Institute in Bethesda, Maryland. An adoptive immunotherapy proof of concept trial there showed that T cells from HIV+ persons could be expanded successfully in the laboratory, and then administered back to subjects, raising their CD4 T cell counts and immune function. Simultaneously, Dr. June's team had collaborated with Cell Genesys, a company that ran the first ever clinical trials of Chimeric Antigen Receptor (CAR) T cells in HIV and cancer. These cross-cutting technologies converged in a translational path when he was recruited to the University of Pennsylvania in 1999.

Relying mostly on philanthropy, Dr. June and his researchers were able to leverage experience in HIV begin their first CAR T cell trials in HIV, and then in cancer. Results from the 2010 CAR T cell clinical trial in cancer patients with advanced leukemia led to the blossoming of the cell and gene therapy field that Dr. June helped pioneer through his vision, creativity, and relentlessness.

Dr. June has published more than 500 manuscripts and is the recipient of numerous prizes and honors, including election to the Institute of Medicine in 2012, the William B. Coley award, the Richard V. Smalley Memorial Award from the Society for Immunotherapy of Cancer, the AACR-CRI Lloyd J. Old Award in Cancer Immunology, the Hamdan Award for Medical Research Excellence and the Paul Ehrlich and Ludwig Darmstaedter Prize. In 2014, he was elected to the American Academy of Arts and Sciences.

The driving force behind the first U.S. Food and Drug Administration–approved gene therapy product (called Kymriah), Dr. June speaks to ISCT about how the field has changed and offers advice to young researchers who are starting out in the field.

1 How is the cell and gene therapy field different now compared to when you started?

When I look back, it was really astonishing for us. The field had this lukewarm reception in 2010 when the first FDA-approved cell therapy for cancer came out. That was a dendritic cell vaccine that Dendreon had developed for prostate cancer. It did not have a successful commercial launch, primarily due to its very expensive cost of goods for manufacturing the cells. It was just not a home run.

Then we had our first three CAR T cell patients published in August 2011. It was like the dam broke, and we had floods of requests and inquiries about funding, spinoff opportunities, and pharma alliances. The field was ready for immuno-

oncology, in part because of checkpoint antibodies and the progress they had made where chemotherapy had not.

The CAR T cells really provided the first demonstration that led to breakthrough status, because the cells were genetically marked and we had striking on-target effects. The non-infectious cytokine release syndrome that was observed with very high fever was a syndrome never seen in medicine before. It was a striking toxicity that was on-target, and it allowed the mechanism of action of CAR T to be clearly ascertained because the pharmacokinetics of the CAR T cells mirrored the symptoms of cytokine release syndrome and tumor elimination. The T cells actually proliferated when they encountered tumor targets and were easily measurable because of the genetic marking in patients.

I think all that led to the realization that genetic programming of cells actually had merit beyond what people before previously thought was a dead end, and because there were so many years when it did not work.

2 Where do you see the cell and gene therapy field heading in the next five years?

In the case of cancer, I think the next-generation therapies will be combinations. One orthogonal technology that really adds so much from a synthetic biology aspect is the ability to use the various genome-editing technologies to engineer the T cells and make them resistant to toxic tumor microenvironments, provide for conditional expression, and so on. Therein lies a huge opportunity to improve the immune system over the natural immune system response, where usually responses are shut down in the context of the tumor environment. Another possibility is the evolution of using nonautologous “off the shelf” cells.

There have been examples from the Great Ormond Street Hospital in London, where they are testing third-party T cells and editing out the endogenous T-cell receptor. I think there will be many opportunities with induced pluripotent stem cells to make various immune cells such as T cells, natural killer cells, macrophages, and so on, and these will be genetically pliable and synthetically enhanced.

Additionally, there are already some interesting trials where oncolytic viruses have shown a strong synergy and potential to combine with engineered T cells. I think various oncolytic viruses can be made and used in many applications in cancers.

3 Why are you so passionate about working in the cell and gene therapy field?

I hate cancer. My dad died of lung cancer a few years ago and my first wife, at the age of 41, had metastatic ovarian cancer. I took care of her for about five years and she passed away in 2001. It changed my life forever, and probably for the good. There's a big silver lining. It made me more compassionate...

Because, at that time, I was working on both cancer and HIV immunotherapy, and I found out how hard it was to get that into trials that would treat my wife, Cindy. There were many, many barriers to early stage trials. It takes a lot of commitment and years of laser focus.

4 What are the biggest challenges facing the development of new cell and gene therapies?

The biggest challenges are in the areas of access and cost of goods. With respect to access, we need to realize that the average annual cost of all cancer drugs recently approved by the FDA was \$150,000 per year. CAR T cells cost approximately three times that, and this is due to the high cost of goods for manufacturing. However, CAR T cells only need to be given once, and most other cancer drugs are given recurrently so that cumulative costs are high. The costs of manufacturing are simply an engineering issue and will be solved by automation by the industry that is evolving to manufacture engineered cell therapies. Another potential radical solution to the access and cost issues would be if so-called “third-party” cells made from healthy donors or induced pluripotent stem cells can be shown to have efficacy.

The final barrier for a disruptive therapy like CAR T is the education of the medical workforce. At this point, CAR T cell therapies are given routinely at the tertiary cancer centers. However, there is little access to this therapy for people who live in rural areas or in less developed world economies. My group is working with investigators in Costa Rica and India, along with Bruce Levine and Stephan Grupp, to test “indigenous” CAR T cells in second-world economies.

5 What would you advise young researchers starting out now in the field?

Have a passion for what you want to do. You have to realize that meaningful results require many years, and possibly decades, so that means you have to have patience.

One unifying quality of successful researchers is that they have a high tolerance for failure. You have to remember that baseball players are outstanding if they succeed only one out of three times while at the plate in baseball. In medical research, the failure rate is much higher: most experiments don't work, but when they do, the emotional high is incredible.

Probably the hardest thing in science is learning when to quit. In this area, I had to learn the difference between “persistence” and “stubbornness.” You want to be persistent and continue to work on difficult problems. This is different than stubbornness, which is continuing to hit your head against the wall in the same way. So, if you have persistently looked at different ways to solve a problem and failed, it may be that it is not currently solvable with current technologies and it is time to move to a new problem!

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PART II:

BRUCE LEVINE, *PhD*



“Often the greatest advancements come when we integrate knowledge and integrate fields.”

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Growing up in the Apollo era, Dr. Bruce Levine thought he wanted to be an astronaut or astronomer. Thankfully for us, he decided against that after finding out “how much math was involved.” Dr. Levine, the Barbara and Edward Netter Professor in Cancer Gene Therapy and founding director of the Clinical Cell and Vaccine Production Facility (CVPF) and the Abramson Cancer Center at the University of Pennsylvania (Penn). In the Penn Center for Cellular Immunotherapies, he is the Deputy Director, Technology Assessment and Innovation. Dr. Levine completed his undergraduate education at Penn and, rather than applying to medical school, wanted to take a career path in translational or applied medical research. He went on to complete his doctoral degree in Immunology and Infectious Diseases at Johns Hopkins University. A postdoctoral fellowship at the Naval Medical Research Institute in Bethesda, MD, under Dr. Carl June’s mentorship, soon followed.

If not for Dr. June’s request that he set up a cell therapy laboratory to manufacture cells for clinical trials in the early 1990s, we might not have seen the beginnings of the methods for clinical cell manufacturing that have since become the foundation for more than 80 subsequent clinical trials in HIV and various cancers. Dr. Levine returned to Penn to establish the CVPF. To this day, the laboratory develops and tests novel cell and gene therapies in clinical trials in patients with hematologic malignancies, solid tumors, HIV infection, and genetic disease.

In 2010, Dr. Levine oversaw a pilot clinical trial to test CAR T cells in cancer on leukemia patients with poor prognosis, leading to remarkable positive results reported in 2011. Thousands of cancer patients flocked to inquire about enrolling in the leukemia clinical trial.

Dr. Levine is co-inventor of the first FDA approved gene therapy (Kymriah), chimeric antigen receptor T cells for leukemia and lymphoma, licensed to Novartis. He is also a co-founder of Tmunity Therapeutics, a biotherapeutics company focused on delivering T cell immunotherapy treatments to patients with devastating diseases in collaboration with UPenn.

Dr. Levine spoke to us about how the field has transformed and set the stage for many more remarkable discoveries that have clearly only just begun in cellular immunotherapies.

1 How is the cell and gene therapy field different now, compared to when you started about 25 years ago?

It’s a transformation. When we started, we were working with tools and equipment that were for research use only or created for other fields and other uses. Now, we have dedicated technologies—new technologies, new companies, new therapeutic companies, new tools and equipment companies—and financing from institutions and companies beyond the grants that we relied on, along with some philanthropy, in the early days. So, it’s a totally different world that is accelerating the work. And we have massively parallel discovery engines and academia and industry working together.

2 Where do you see the cell and gene therapy field heading in the next five years?

I think we're moving beyond the first generation of therapies to combination therapies and therapies with discreet control mechanisms. As we begin to learn more about the clinical mechanisms of action, we can incorporate new tools that deliver and guide cells to the spot in the body that we want, that turn cells on and off, that enable cells to turn left and right when we want them to. Also, there's work on mechanisms to improve potency. So, all of that will enable further progress in diseases that have so far been difficult to tackle.

In the past, progress has been limited, to a great degree, by the funding available. We have more of that now than we did. Of course, additional funding always accelerates some of the things that we find limiting the work now, as well as trained technicians, investigators, and other roadblocks to facilitate clinical trial development. As we look to these new technologies that are coming out of the research labs, the big question is how we can best integrate those into clinical development. Also, post-regulatory approval, and how do we integrate improvements in technologies in cell and gene therapy?

We now have approval for a type of gene modified cell therapy called Chimeric Antigen Receptor T cells (also known as CAR T cells) in pediatric and young adult acute lymphoid leukemia, and in adult diffuse large B cell lymphoma. I think, this year and next, we will see more regulatory approvals in hematologic malignancies in the US. Probably also in myeloma. We'll see more progress in solid tumors over the next couple of years, and hopefully before not too long, some solid cancer regulatory approvals, as well.

It's a very exciting time to be in the field, not only because people outside science and the larger public community are becoming aware of these therapies, but because we have at our disposal so many more technology tools than we did before, and it creates an engine of discovery when you have access to these new tools.

3 Why are you so passionate about working in the cell and gene therapy field?

The patients. Seeing the impact that we can have in patients that have no other options, to see that we have clinical responses, to see that they're durable for years. And to think about using a word that scientists and clinicians and these investigational fields are generally uncomfortable using: a cure. When we have patients that are seven years out, nine years out, we begin to think that we may have enabled potential cures.

But, at the same time, we have to be very careful in our clinical trials not to promise things inappropriately. We have to abide by the conventions for informed consent so we can be excited by what we've seen and excited by what we've been doing, but very careful in how we speak about this to patients. We have to make clear that there is a good chance that what we're doing may not work, and the same goes for communicating to the public and to the media.

4 What are the biggest challenges facing the development of new cell and gene therapies?

Technologies are accelerating what we're doing, but in some cases we're limited by being able to recruit enough people fast enough to work on manufacturing and clinical development. In some cases, it's deciding how to integrate those new technologies and new research findings into clinical development. In other words, when is the right time to proceed to pivotal trials and regulatory submission, knowing that there are still some improvements that could be made to the product sooner or later?

5 For young people just starting out in this field now, what would be the one piece of advice you would give them based on your wealth of experience?

Be excited about what you are doing. Realize that in the early stages of research and development, failures are frequent. In clinical development and clinical trials, the consequences of failure are severe, which is why understanding and implementing robust quality systems including GLP, GMP, GCP and FACT and JACIE accreditation are so important.

I think, in addition to staying abreast of new research findings, my advice is to network and present your work and engage with investigators not only in your particular area of expertise, but in related areas of expertise. Social media is a great tool for networking, and staying abreast of the latest developments in the field. Join the ISCT LinkedIn group, follow ISCT on Twitter @ISCTGlobal, and follow me @BLLPHD.

I think often the greatest advancements come when we integrate knowledge and integrate fields. What we've been seeing over the past number of years is the integration of engineering with biology, for example. We have engineers learning about immunology and cell and gene therapy, and we have investigators in cell and gene therapy, thinking about scale up and automation and engineering.

ON THE SHOULDERS OF GIANTS TRILOGY

PART III: THE EMILY WHITEHEAD STORY



*“I only remember
leaving the hospital
and going home.”*

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To almost everyone, it seemed hopeless. After eighteen months of undergoing chemotherapy, suffering multiple relapses, and almost losing her legs, Emily's cancer was still aggressively resisting.

An Unconventional Treatment

Acute lymphoblastic leukemia had come for Emily when she was five. But nobody could have foreseen the outcome that would ultimately play out after chemotherapy, the usual weapon against cancer, failed to help her.

Her parents, Kari and Tom, had researched one last hope: a clinical trial in a new immunotherapy that had never been done before on a child.

Called chimeric antigen receptor (CAR) T cell therapy, it would be their only chance to save Emily's life. After being told to take their daughter to hospice and enjoy the remaining days they had left with her, Kari and Tom Whitehead were desperate and knew they were out of options—except this.

The three pillars of surgery, chemotherapy or radiation would not help her. Truly at the end of their rope, but still clinging to hope, the Whiteheads knew they had nothing left to lose. They enrolled Emily in the clinical trial.

Rising Hope

The new treatment would transform Emily's immune system into a re-engineered weapon against the cancer. Emily, just before her seventh birthday, became the first pediatric patient enrolled in a clinical trial investigating CAR T cell therapy, a technology that Dr. Carl June had been developing for twenty years.

Doctors told Kari and Tom that they truly did not know what would happen during the clinical trial. “We were scared but hopeful,” recalls Tom.

It was during this time that the Whiteheads met Dr. Bruce Levine, in whose lab the cells would be re-engineered. Dr. Levine visited Emily in her hospital room on the second day of her T cell infusion and spoke to Emily, Kari, and Tom.

Facing Fear of the Unknown

Six days after receiving her re-engineered t-cells, Emily started to go downhill. Her blood pressure dropped dangerously while she experienced dehydration and breathing difficulties. Once admitted to the paediatric intensive care unit, Emily lay in a coma while doctors worked throughout the night to figure out how to save her.

After doctors discussed what was going on with Emily's immune system with Dr. June, he suggested giving Emily tocilizumab, an immunosuppressive drug used mainly in the treatment of rheumatoid arthritis, within hours Emily's condition improved drastically.

"Dr. June saved Emily's life," says Tom.

And what had started out as a family's last hope turned into a triumphant and tantalizing breakthrough for the world: After battling the cytokine storm, Emily awoke from her delirium on her seventh birthday, cancer-free.

"It was by far the scariest, most painful, and toughest time of our lives," says Tom. "But on May 2, 2012, Emily woke up from her coma. It was a miracle."

The world was shocked. A little girl had defeated cancer.

Defying the Odds

Looking back, Tom says: "The therapy saved our family. We don't know where we'd be without it. We're very, very thankful—every single day."

Not only did it save the Whitehead family, the clinical trial's triumph against cancer in a child of seven inspired the world into renewed focus on cancer treatments.

Kari and Tom point out that it was researchers who were at the core of the success of the CAR T cell therapy. They're grateful to Dr. June, who was nearly out of funding by the time Emily enrolled in the clinical trial, and particularly for his persistence and passion.

It is a new world, with many teams now confirming the results of this radical new treatment, a drastic change from the times of struggling for funding and interest. It just goes to show how quickly things can change.

Tom's advice to early career researchers is simple: "You can change the world if you really believe you can. You're the only one that can limit what you can achieve. You've got to just keep pushing forward to have these big breakthroughs and not let the obstacles stand in your way. Look at opportunities more than you look at the obstacles."

Tom stands firm in his belief that making a difference is possible. "Do not be afraid to go for the big ideas and be creative in how they could make a difference," he says, "Because it really can save lives all over the world."

Gratitude Leads to Giving Back

Tom and Kari have also dedicated themselves to this very philosophy of making a difference in a big way.

As clinical successes have progressed to worldwide regulatory approvals and researchers and scientists have worked hard to transform the treatment of cancer, the experiences of the patients and their families have not been forgotten—and certainly not by Kari and Tom.

After Emily woke up in intensive care, Kari and Tom asked to visit the lab where the T cells were re-engineered to fight the cancer for Emily. Surprised, doctors granted them permission to visit Dr. Levine's lab at the University of Pennsylvania. Dr. Levine gave them a tour. Tom recalls tearing up during the tour and feeling immensely grateful for Dr. Levine and the rest of his team. He and Kari knew they wanted to make a difference as well.

They founded the Emily Whitehead Foundation as a means of giving back and to support patients and their families and raise awareness of childhood cancer research. Telling their story helps.

"We had friends in the hospital during Emily's time there who didn't make it," says Tom. This drives the family to continue their mission of giving children the chance to live healthy lives, just as Emily now does.

The Memory that Remains

Now fourteen years old, Emily enjoys drawing and painting. She nurtures a budding interest in filmmaking. Most recently, she spent time on the set of Steven Spielberg's latest movie, learning how a scene is filmed.

Emily has blocked out some of the more painful parts of her times in the hospital, says her father, but she still remembers happier moments, including playing with child life specialists. When asked what memory stands out the most of her experience, Emily simply says:

"I only remember leaving the hospital and going home."