Inside the effort to bring life-saving cell therapies to the masses

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Krishnendu Roy, Robert A. Milton Chair and professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, is leading the cell manufacturing initiative. Credit: Georgia Institute of Technology

Doctors knew long before Owen Webb was born that they were racing against the clock to save his life.

Tests had confirmed the developing child suffered from Krabbe disease, a genetic disorder that causes toxins to build up in the nervous system, progressively damaging the brain.

Just days after he was delivered, a medical team at Duke University began Owen on nine days of chemotherapy. His body was then infused with stem cell-rich donor umbilical cord blood. A second dose came four weeks later, through a spinal tap, delivering millions of cells directly to his central nervous system.

The rush to save the newborn came about two months after his 10-month-old sister, Mabry Kate, died from the same disease. Christin and Kyle Webb had spent months in and out of hospitals searching for answers as to why their daughter no longer smiled and was having muscle spasms and trouble eating.

By the time she was diagnosed with Krabbe at 6 months of age, the disease had progressed too far for treatment. "We felt helpless," Christin Webb said. "As parents we were supposed to be able to help her, and we couldn't." But their search wasn't in vain. It led them to Duke and to the discovery that for Owen, it was not too late.

For years, medical researchers across the country have been working on a host of groundbreaking therapies using human cells to treat a range of diseases, from neurological leukodystrophies such as Krabbe disease, all the way to certain types of cancer.

For all of its promise, however, cell therapy still faces hurdles before it can be used to treat more than a handful of patients at a time. Challenges range from the need to standardize the way cells are manufactured to

figuring out how to produce cells faster, in greater quantities, and at lower cost. Georgia Tech researchers have embarked on a multiyear effort aimed at helping doctors and scientists address these challenges and expand cell therapies to more people and more conditions.

"The fundamental challenge is that we're dealing with a living entity," said Krishnendu Roy, Robert A. Milton Chair and professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "Classically we've always dealt with manufacturing an inanimate object, like materials or a car or an airplane. Even in biomanufacturing we have mostly dealt with a single molecule or protein, not a complete living product like a cell that can change with every manipulation you make."

In January 2016, Georgia Tech announced a research center devoted to developing processes and techniques to manufacture living cells—the Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M). Made possible by a $15.7 million grant from the Atlanta-based Marcus Foundation, the $23 million center will include a facility to produce cells under strict federal quality control protocols—referred to as a good manufacturing practices facility—and will provide the framework for partnerships with industry as well as research and clinical institutions across the country.

The cell manufacturing effort is just one of myriad research initiatives ongoing at Georgia Tech geared toward advancing manufacturing technologies to solve real-world problems in a broad range of areas.

Along with the Georgia Research Alliance, Georgia Tech is leading the National Cell Manufacturing Consortium representing dozens of research institutions, medical technology firms, and government agencies. The first initiative was to chart a coordinated approach to fully establishing the cell therapy industry over the next decade—with the

ultimate goal of making treatments such as the one Owen received available to patients across the country.

It has been nearly six decades since some of the first medical research was published on using bone marrow transplants—one of the earliest forms of cell therapy—to treat patients suffering from cancer. It took another 10 years for researchers to see success from the therapy, which today is standard care for blood cancers.

More recently, other exciting cell therapies have emerged. Immunotherapy involves infusing a patient with billions of immune-system T cells that have been genetically engineered to kill cancer. Meanwhile, therapies involving stem cells have shown promise in treating neurodegenerative conditions, brain and spinal cord injuries, diabetes, and more.

Many of the treatments involve taking cell samples from a patient or a donor and multiplying them in a lab—a tedious and time-consuming process limited to a small number of patients.

"Currently, patients who want one of these treatments need to go to one of the top clinical centers in the world where they're treating a small number of patients at a time in clinical trials," Roy said. "But a way to scale up these revolutionary therapies for the masses does not exist. We do not know how to mass manufacture these cells, while ensuring safety and clinical effectiveness."

Among the foremost goals of the MC3M is to take a process that happens traditionally in small labs and increase production capabilities to the industrial scale.

"For potentially curative therapies like these, clinical centers could get backed up for months with a line of patients unless we can significantly

increase capacity, translate this into an industry product, and improve access by ensuring reduced cost of production," Roy said. "That's a fundamental manufacturing problem, especially when we have to deal with thousands of patients."

That sentiment was echoed by Dr. Joanne Kurtzberg at Duke University School of Medicine, who heads the school's Pediatric Blood and Marrow Transplant Program and the Carolinas Cord Blood Bank, a vast repository of cord blood from unrelated donors. She has led much of the research there into therapies using stem cells from cord blood, such as the treatment Owen received.

"There are tens of thousands of patients who might potentially benefit from these treatments, but large-scale manufacturing of cells is challenging," Kurtzberg said. "That's what makes our collaboration with Georgia Tech so important. We need to find ways to produce more doses in a shorter amount of time."

The cell manufacturing roadmap outlines a number of strategies for increasing production capabilities, such as developing new large-scale bioreactors—the machines used to grow cells. Another is finding the most efficient formula for culture media, which includes the nutrients given to cells to encourage their growth.

Another challenge researchers face is finding a way to develop standardized protocols and processes for manufacturing each type of cell to achieve consistency across the industry.

"While their names may be the same, cell therapies may be very different from clinic to clinic," Roy said.

Even if researchers start with the same cell, the way they manufacture it could dramatically change its properties.

"When we do something as simple as move cells from one petri dish to another, their properties change," Roy said. "So it's very difficult to reproduce the same cell from one center to another, or from one hand to another hand."

If the goal is for cell therapy to be as consistent as a tablet of aspirin from one drug maker to the next, it makes sense to take a pharmaceutical approach to manufacturing cells, he explained. His team is studying cell therapies to find critical quality attributes—what makes each cell therapy effective.

"We know very little about what property of that cell makes it work," Roy said. "If I were making an airplane fuselage, I would know what type of mechanical strength I need, what type of fatigue resistance I need. But we know little about that for a cell. I know that if you put it in certain patients, it works. We know that these cells have some properties or markers, but we don't know correlation between those properties."

That research could have implications much broader than the cell manufacturing process itself; it is information that could help shape the development of cell therapies across the medical field in years to come.

Pinpointing the scientific basis for each cell therapy and standardizing treatments will help revitalize the cell therapy industry, said Dr. Fred Sanfilippo, director of the Emory-Georgia Tech Healthcare Innovation Program and medical director of the Marcus Foundation.

"That's one of the real values in creating this center—to address the issue of consistency and making sure the cells are being used for what they are intended," Sanfilippo said.

The initiative will also help add transparency to the industry and potentially improve patient understanding of the various treatments, he

said.

Already, Roy's team is working on projects with medical researchers at other institutions, such as the University of Miami and University of Pennsylvania. Another example is a project with Duke University School of Medicine, where doctors have developed a cell therapy using donated umbilical cord blood to treat patients with certain leukodystrophies—genetic disorders in which the white matter of the brain degenerates.

Kurtzberg, who is also a pediatric hematologist-oncologist at Duke, has pioneered a therapy that treats leukodystrophies caused by the deterioration of the myelin sheath, a barrier that protects nerve cells. Kurtzberg's team has focused on using a cell manufactured from cord blood called DUOC-01, which resembles cells in the brain that help maintain the myelin sheath.

The treatment, which can be used to fight Krabbe disease, involves taking a sample of cord blood, isolating DUOC-01, and growing it in a bioreactor for 21 days. Then, the cells are transplanted into a patient through a spinal tap. Once the cells engraft in the patient's nervous tissue, they appear to help rebuild the myelin sheath.

The goal of the Georgia Tech-Duke project is to fine tune that process, potentially finding a way to accelerate cell culturing so that patients could receive treatment faster.

"It's a cell that's very hard to manufacture, and so Krish's group is trying to figure out how the cell attaches to things like plastics, to come up with a more efficient way to manufacture them and get a bigger yield," Kurtzberg said. "Because it stimulates the re-myelination of the brain, the cell may have a lot of other applications besides the rare disorders we're treating right now, but to bring it to that level we have to make

more."

It's hard to overstate the impact of the treatment on the Webb family. For all the joy that came with the birth of their first child, Mabry Kate, in March 2014, it was the start of one of the most agonizing and heartbreaking periods for Christin and Kyle, who have been together since they were middle school sweethearts.

The Webbs first reached out to Kurtzberg while searching for treatment for Mabry Kate. While the infant's symptoms could not be reversed by that point, for Owen, whose due date was still months away, it was a different story.

"Dr. Kurtzberg wanted to have him delivered as soon as his lungs were ready," Webb said. "The earlier the treatment can begin, the better."

As the couple were making plans to travel from Tennessee to Durham, North Carolina, for Owen's birth, they were also coping with Mabry Kate's declining health. Not wanting her to be confined within the four walls of their home, the Webbs made a point of taking Mabry Kate out to spend time with friends and relatives and to games of the local high school girls basketball team, which Christin and Kyle coach together.

"We had planned on celebrating her first birthday just before her brother's birth in March, and to bring her with us to Duke for the long process," Webb said. "God had other plans."

Mabry Kate passed away in her parents' arms on a Saturday night in early February 2015. Seven weeks later, Owen was delivered, and after spending a few days in intensive care, he was admitted to the Pediatric Blood and Marrow Transplant Unit at Duke Children's Hospital to begin treatment.

It's been more than a year since Owen's therapy at Duke, and the Webbs have watched their son grow into a healthy, cheerful child who spends many of his days playing happily with his cousins, smiling for selfie photos with his parents, and learning to crawl at his family's home in Powell, Tennessee, a town on the outskirts of Knoxville.

The G-tube his parents use to deliver supplemental nutrition every day at mealtime is one of the last remaining clues to the 110 days Owen spent in the hospital.

"It's really exciting to see the new things he's doing every day," Webb said. "His personality is coming out, and he's really funny and happy."

Watching their son's development has also been bittersweet. While every milestone is a reminder of one their daughter never reached, the Webbs are thankful that Mabry Kate's struggle with Krabbe illuminated the path to save her little brother.

"It seems crazy to me to look at him and think that he has the same disease that Mabry had," Webb said. "It's night and day difference."

Provided by Georgia Institute of Technology

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