Immunotherapy team harnesses cellular systems to fight diseases

January 5 2017, by Toni Morrissey

Mario Otto, MD, PhD, (right) leads research on processes used in immunotherapy in his lab. Credit: University of Wisconsin-Madison

Four decades ago, researchers at the University of Wisconsin School of Medicine and Public Health had the right idea—to pursue a theory that they could harness patients' own immune systems to fight and defeat cancer. Their perseverance and hard work are paying off, as they've recently made great strides in cellular immunotherapy, along with colleagues in myriad medical fields.

"It's an exciting time for our team—and especially for Dr. Paul Sondel and me because we've been working on this for a long time," reflects Ken DeSantes, MD, professor, School of Medicine and Public Health Department of Pediatrics, and director, Pediatric Hematology, Oncology and Bone Marrow Transplant Program, American Family Children's

Hospital.

"Forty years ago, we didn't understand enough about how the immune system works, nor about how cancer cells can thwart the immune system, for us to make immunotherapy work. We felt vindicated when we were able to mastermind how to get the immune system to attack cancer."

A dedicated army of UW-Madison researchers is perfecting the use of immunotherapy. Ken DeSantes, MD; Paul Sondel, MD, PhD '75 (PG '80); Peiman Hematti, MD; Christian Capitini, MD; Mario Otto, MD, PhD; Douglas McNeel, MD, PhD; Jacques Galipeau, MD; and many others synergistically have combined forces around the newest frontier in the war on cancer and other diseases.

"This field is changing so fast that it's hard to keep up. A lot of it sounds like science fiction, but this is very real," notes Capitini, assistant professor, Department of Pediatrics, who is investigating novel therapies, particularly chimeric antigen receptor (CAR)-T cell therapy for refractory acute lymphocytic leukemia.

CAR-T cell therapy uses a patient's T cells that researchers have reprogrammed to express the chimeric antigen receptor, which—to treat leukemia—hunts down and destroys cells that express a CD19 antigen. The therapy is offered at just a handful of academic research centers.

"CAR-T cell therapy will be evaluated in 2017 by the Food and Drug Administration. Approval would be an important advance in immunotherapy for patients with relapsed leukemia because they have no good options. Many people, particularly under-represented minorities, don't have donor matches for bone marrow transplants," explains Capitini.

Hematti adds, "In my opinion, CAR-T cell therapy is one of the most

exciting developments in cancer treatment and potentially a game-changer for the field of cellular immunotherapy."

The medical director of the University Hospital Clinical Hematopoietic Cell Processing Laboratory and a professor in the School of Medicine and Public Health Department of Medicine, Hematti calls the method "cellular immunotherapy 2.0" because it's a huge improvement over standard bone marrow transplants with a matched donor.

Instead, these advances allow experts to collect a patient's immune cells and re-engineer them before infusing them back into the patient—eliminating the risk of some side effects, such as graft versus host disease (GVHD).

Aiming to outsmart potentially lifethreatening side effects of CAR-T cell therapy, such as cytokine release syndrome, UW-Madison researchers are tackling this next challenge, too. Through a National Science Foundation grant, Capitini and co-principal investigators Kris Saha, PhD, and David Beebe, PhD '94, are exploring ways to improve the manufacturing of CAR-T cells to make them safer and more effective. Saha is an assistant professor of biomedical engineering, and Beebe is a professor of biomedical engineering in the UW-Madison College of Engineering.

Similarly, Hematti recently received an award from the Wisconsin Alumni Research Foundation's Accelerator Program to extend a line of research that could further optimize CAR-T cell therapies. This work—conducted by Debra Bloom, PhD, in Hematti's lab—was originally supported by the Crystal Carney Fund in Leukemia Research and the Don Anderson GVHD Fund.

Additionally, cancer immunotherapy and GVHD-countering innovations have been discovered, in part, in Otto's lab. An assistant professor in the

Department of Pediatrics, Otto and collaborators created a technology that selectively removes GVHD-causing alpha beta T cells from blood-derived stem cell grafts, but retains important immune cells along with stem cells. This allows just the carefully selected cells to be infused back into the patient.

Otto is leading a related Phase 1 clinical trial that involves a haploidentical stem cell transplant for pediatric patients who have relapsed solid tumors or leukemia. In this trial, the patient's immune system is destroyed with high-dose chemotherapy; stem cells and immune cells (the graft) are obtained from a half-matched donor (usually a parent or adult sibling, eliminating the need to search for an unrelated donor); and the alpha beta T cells are removed from the graft using the technology co-developed by Otto. This process calls upon magnetic beads that attach to a protein so a magnet can remove the tagged cells. When the immune cell graft is infused into the patient, the cells can immediately attack cancer and decrease the risk of life-threatening infections—a critical factor for these highly immunocompromised patients. About 10 to 14 days after receiving the graft, the new stem cells begin making blood and immune cells that destroy cancer.

"Seven months after treatment, the first patient in the trial shows no signs of cancer. This patient had neuroblastoma, a deadly childhood cancer," says Otto. "We consider him disease-free, but it is still too early to say this treatment is curative. Nevertheless, we are very encouraged by patients' quick recovery in the trial so far."

DeSantes, the patient's oncologist, recalls, "Ten years ago, we had no meaningful treatments to offer. These children would have needed hospice care."

Hematti points to a similar clinical trial being conducted by Vaishalee P.

Kenkre, MD, assistant professor, Department of Medicine.

"My trial uses alpha beta T cell and CD19 B cell depletion with haploidentical donors. The trial is open to adults with relapsed/ refractory lymphoma," explains Kenkre. "There is virtually no data on this cellprocessing mechanism in adult lymphoma patients, and we're not aware of this type of study happening anywhere else. We are excited about having this option for patients who otherwise do not have viable options."

UW Carbone Cancer Center's pediatric immunotherapy efforts have resulted in the development of several investigator-initiated trials, offering therapies available only at American Family Children's Hospital and UW Health, as well as participation in multicenter "Pediatric Oncology Dream Team" studies. That alliance represents unique collaborations across multiple disciplines at eight U.S. and Canadian academic medical centers. It was created in 2013 when Stand Up to Cancer, the American Association for Cancer Research and St. Baldrick's Foundation established a four-year grant.

Another novel clinical trial will begin in early 2017 at all eight Dream Team sites. DeSantes will lead the trial at all sites, investigating the role of an antibody targeting the B7-H3 "checkpoint" molecule, which is expressed on the surface of many pediatric cancers. This genetically engineered antibody, MGA-271, activates tumordestroying Natural Killer (NK) cells that are programmed to eradicate cancer cells and prevents B7-H3 from dampening the immune response to cancer cells.

"Our bodies contain immune cells that kill bacteria and viruses, but if the immune system is active all the time, it can get out of control and attack healthy cells," says DeSantes. "It's sometimes necessary to dampen down the immune response, so a number of checks and balances are built into the system."

Yet, some cancer cells can co-opt that system by over-expressing checkpoint molecules and telling the immune system to stop its attack. MGA-271 binds and blocks the checkpoint molecules and allows the immune system to recognize that the signal has been activated, in turn letting the immune system destroy the cancer.

This type of checkpoint blockade figures into two other potential clinical trials that cause great excitement for Sondel, the Reed and Carolee Walker Professor in Pediatric Oncology.

One of the trials, which could open for melanoma patients in spring 2017 with leadership from Mark Albertini, MD (PG '87, '91), professor, Department of Medicine, and Zach Morris, MD, PhD (PG '12), assistant professor, Department of Human Oncology, will combine a dose of radiation—too small to shrink a tumor but large enough to stimulate immune cells— with a separate antibody that recognizes cancer cells and serves as a checkpoint blockade. The combination has cured mice with large tumors.

A similar trial, also to start in spring 2017 for children with high-risk neuroblastoma, will be led by Sondel and DeSantes; it includes a collaboration with hospitals in London; Southampton, United Kingdom; and Greifswald, Germany.

In separate work that lays the foundation for simpler, more cost-effective immunotherapy, Douglas McNeel, MD, PhD, professor, Department of Medicine, and director, Solid Tumor Immunology, UW Carbone Cancer Center, has been investigating T cell-activating therapies, or vaccines, as treatments for prostate cancer. The concept with this approach is generating tumor-fighting immune cells directly, without having to prepare them in the laboratory and infuse them back into patients. Over the past 15 years, McNeel and his team have conducted several clinical trials with two vaccines that are currently in

testing at the Carbone Cancer Center and elsewhere in the United States.

Cellular immunotherapy has been remarkable for cancer treatment, and School of Medicine and Public Health experts are taking it far beyond cancer.

For instance, Hematti is working with Dixon Kaufman, MD, PhD, the Ray D. Owen Professor and chief, Division of Transplantation, Department of Surgery, on a novel cellular immunotherapy using donor stem cells.

"We take stem cells from a kidney donor and do a stem cell transplant after the kidney transplant," says Hematti, adding that findings could lead toward eliminating the patients' need for immunosuppression drugs after solid organ transplantation.

The research is rapidly moving from animal models toward human clinical trials, both supported by grants from the National Institutes of Health. Hematti and Kaufman are collaborating with scientists at Stanford University to make this treatment a reality for patients at UW Health.

Through the UW-Madison Stem Cell and Regenerative Medicine Center, Hematti also has worked for more than a decade with Amish Raval, MD, associate professor, Department of Medicine, on cardioimmunotherapy. Recently, the duo has focused on using immune cells, specifically macrophages, to repair cardiac damage in animal models, and they hope to move their research into human clinical trials soon.

Whether it's for cancer treatment, organ transplants or cardiac tissue repair, cellular immunotherapy is exploding.

"Today, immunotherapy is approved as a first-line treatment for adult patients with widespread melanoma, lung cancer and several other forms of high-risk cancers in adults and children," says Sondel.

He predicts that within the next 10 years, treatment of nearly all cancers that are not being cured by surgery alone will integrate immunotherapy.

Sondel knows that concept will take intense teamwork over time but states that the School of Medicine and Public Health and UW Carbone Cancer Center have world-class reputations for research being done by outstanding faculty who collaborate internally and throughout the nation—and they are making great strides in the fight against deadly diseases.

Provided by University of Wisconsin-Madison