

these undifferentiated myeloid cells traffic more effectively to tumors than terminally differentiated macrophages. In contrast to Carisma, both Myeloid and Thunder are using nonadenovirus transduction systems.

Yet, perhaps the most notable difference between the three companies' technologies lies in the intracellular signaling domain chosen for each CAR construct: CT-0508 takes advantage of CD3 $\zeta$ , part of the T-cell antigen receptor and the same domain used in first-generation CAR T-cell therapies, whereas Thunder's and Myeloid's products incorporate signaling domains from Toll-like receptors and phagocytotic receptors, respectively.

Judging by the Penn team's results, CD3 $\zeta$ , despite its usual role in T-cell stimulation, seems to prime macrophages into an M1 phenotype, O'Neill says, "but it's probably not as good as the inherent mechanism" of macrophage activation.

Carisma is now developing novel co-stimulation domains that are "rationally designed" for macrophage activation, Klichinsky says. "If we find significant improvement, those will be implemented in future iterations" of the therapy. —*Elie Dolgin* ■

## Looking to Scorpion Venom for GBM Treatment

When engineered into chimeric antigen receptor (CAR) T cells, chlotrotoxin (CLTX)—a peptide component of the deathstalker scorpion's venom—may help pinpoint glioblastoma (GBM) cells for destruction. This concept, developed by researchers at City of Hope Comprehensive Cancer Center in Duarte, CA, has shown preclinical promise and will soon enter a first-in-human study (*Sci Transl Med* 2020;12:eaaw2672).

CLTX "probably helps scorpions deliver poison into their prey's nervous system, while not being toxic itself—which is loosely reminiscent of how we're applying it now," says Michael Barish, PhD, a co-senior author. "It's evolved through predator-prey relationships to have rather exquisite specificity, with useful therapeutic outcomes for us."

CLTX's binding affinity for GBM and other neuroectodermal tumors, sparing

normal tissue, was established a couple of decades ago, says co-senior author Christine Brown, PhD. Since then, it's been developed as <sup>131</sup>I-conjugated radiotherapy for high-grade glioma, used to coat nanoparticles for targeted drug delivery, and turned into a fluorescence imaging tool, enabling more precise brain tumor resection. The imaging tool, called "Tumor Paint," was created by James Olson, MD, PhD, of Fred Hutchinson Cancer Research Center in Seattle, WA. "It's his work we're building on," Brown notes. "We wanted to get from tumor binding to tumor killing, by exploiting CLTX in CAR T cells."

Graduate student Dongrui Wang was tasked with achieving this goal, which involved going beyond the familiar terrain of antibody-based constructs (commonly targeting CD19) to ligand-receptor CARs. "We did have some experience" with the latter, he says, but pioneering an optimal design to incorporate a peptide toxin targeting the membrane-associated protein MMP2, a crucial part of CLTX's receptor complex, was challenging.

Interestingly, Wang observes that "our construct worked much better with CD28 as a costimulatory domain," instead of 4-1BB. Possible reasons why remain unknown, but the field "has had this idea for a while now that 4-1BB is a preferable design," Brown notes, "and our data seem to suggest something different."

In patient-derived xenograft models, potent anti-GBM activity and tumor regression were seen with CLTX-CAR T cells, Wang says—even when there was minimal expression of IL13R $\alpha$ 2, HER2, or EGFR, three key GBM antigens. The therapy was also active against glioma stem cells, a subpopulation that often seeds recurrence. Treatment was well tolerated, with no off-target effects or other toxicities.

Encouraging preclinical safety aside, CLTX-CAR T cells' potential immunogenicity in humans "is difficult to model," Brown says, "so it will be an important end point" in the phase I trial. "We're screening patients based on tumor MMP2 expression," she adds, "because that's essential for CAR T recognition and targeting."

Antonio Iavarone, MD, of Columbia University in New York, NY, considers CLTX-CAR T cells "a novel approach



A peptide component of the deathstalker scorpion's venom may help pinpoint glioblastoma cells.

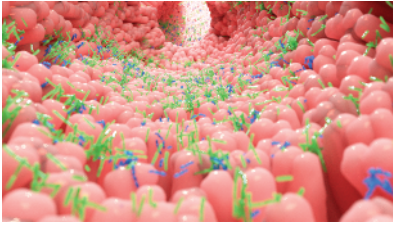
that should allow more comprehensive targeting of a highly heterogeneous cancer." In general, GBM remains a poor candidate for immunotherapy, but Iavarone and others are gradually unearthing features, in small subsets of patients, that may better predict benefit. He therefore lauds patient stratification, such as Brown's team is doing, as "absolutely key" (*Commun Biol* 2, 135 [2019]).

"The more molecular profiling up front, the more likely that even if a given trial turns out negative, it will still be informative," Iavarone says. He hopes for clinical efficacy with CLTX-CAR T cells but thinks concurrent immune checkpoint inhibition may well be necessary, based on the researchers having shown that one route of treatment resistance is PD-L1 induction.

"Once we've shown our therapy is safe in people, we do want to start a combination study," Brown agrees. She's encouraged that despite the disease's seeming intractability, "there are more CAR T trials for GBM than any other solid tumor. It should accelerate our understanding of what can be achieved, therapeutically, for this population." —*Alissa Poh* ■

## Microbiome Predicts Blood-Cell Transplant Success

A large multicenter international study concludes that the composition of the intestinal microbiome in patients undergoing allogeneic hematopoietic-cell transplants (HCT) for leukemia and other blood cancers can predict treatment success. The



Artist's rendering of the intestinal microbiome.

findings may help assess patients' transplantation-related mortality risk and aid in developing strategies to prevent or mitigate microbiome changes that influence HCT outcomes.

Investigators conducted PCR amplification of bacterial 16S ribosomal RNA genes and sequencing to analyze the microbial composition of 8,767 fecal samples from 1,362 patients undergoing HCT at four centers in the United States, Germany, and Japan. They found similar patterns of microbiota disruption across centers and geographic regions and identified an association between lower intestinal diversity and higher risk of transplantation-related death, mostly due to graft-versus-host disease (GVHD; *N Engl J Med* 2020;382:822–34).

"We observed that the diversity within the microbiome changes rapidly within a few days, and actually starts in the first week before transplantation," says lead investigator Marcel van den Brink, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY. "Patients with the most diversity loss had the worst outcomes."

Notably, patients had lower-diversity microbiomes both before transplantation and for about 14 days after—during the time of neutrophil engraftment, he says. Diversity loss prior to transplant is likely tied to taking broad-spectrum antibiotics that are often prescribed for emergent infections during chemotherapy and radiation.

Smaller, single-center studies have noted associations between the gut microbiome and treatment responses, notes David Fredricks, MD, who leads the Microbiome Research Initiative at Fred Hutchinson Cancer Research Center in Seattle, WA. The much larger size and scope of this study

builds on those observations and provides a strong scientific rationale for pursuing new treatments based on manipulating the microbiome.

For example, fecal microbiota transplantation prior to HCT or at the time of neutrophil engraftment might restore diversity and improve outcomes, he says. In addition, several research groups are testing engineered microbial communities and dietary manipulation to modulate GVHD risk.

Future studies should determine whether microbial diversity is a driver or a marker of clinical outcomes, notes Fredricks. For now, these findings suggest that the microbiota could be a useful biomarker for calculating patients' risk and identifying those who may require more intense interventions to prevent or treat GVHD.

The study also suggests a rationale for improving antibiotic stewardship to minimize or prevent diversity loss prior to transplantation. For example, investigators noted that less diverse microbiomes were often dominated by certain bacteria, particularly enterococcus and streptococcus, with corresponding loss of anaerobic gut bacteria.

"Providers tend to use very broad-spectrum antibiotics when we don't know the source of an infection in order to have the biggest impact," says Fredricks. "However, these findings suggest that we might first consider more narrow-spectrum antibiotics that target common causes of bloodstream infections in order to preserve gut bacterial diversity."

The findings have implications beyond HCT, he adds. For example, patients undergoing treatment with immune checkpoint inhibitors often have enhanced antitumor responses when they have a particular gut microbiota. Trying to preserve beneficial gut microbiota in these patients might enhance therapeutic response.

"There is still a lot we need to learn about this area before we jump on clinical strategies," van den Brink cautions. "However, our findings suggest that microbiota composition is an important risk factor to consider before transplant." —*Janet Colwell* ■

## NOTED

### Gilead will buy Forty Seven for \$4.9 billion.

In the deal, Gilead will gain access to Forty Seven's anti-CD47 agent magrolimab, which is being tested in blood cancers such as acute myeloid leukemia (AML) and diffuse large B-cell lymphoma. Forty Seven is also developing antibodies that target SIRP $\alpha$  and cKIT.

### The FDA approved the CD38 inhibitor isatuximab-irfc (Sarclisa; Sanofi) plus pomalidomide (Pomalyst; Celgene) and dexamethasone in patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor. The approval was based on the phase III ICARIA-MM trial, in which patients who received the triplet had a median progression-free survival of 11.5 months, compared with 6.5 months in patients who received a pomalidomide-dexamethasone regimen.

The agency also issued a final rule requiring new health warnings on cigarette packages and advertisements that consist of text and images of lesser-known health risks of smoking, such as heart disease and diabetes. Beginning in June 2021, the warnings must cover 50% of the front and back of cigarette packages, and at least 20% of the area at the top of cigarette advertisements.

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### Tolero Pharmaceuticals will join the Beat AML Master Trial, a multiarm umbrella trial run by the Leukemia and Lymphoma Society in which patients newly diagnosed with AML are matched to targeted agents based on genomic sequencing of their tumors. Tolero's AXL receptor tyrosine kinase inhibitor duberminib will be available to patients with TP53 mutations and/or complex karyotype.

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### Prostate-specific membrane antigen (PSMA) PET-CT may be better at identifying metastases in men with prostate cancer than CT and bone scans (Lancet 2020 Mar 22 [Epub ahead of print]). Researchers assigned 302 men to undergo either PMSA PET-CT or standard CT and bone scans. They found that PMSA PET-CT was more accurate at detecting metastases than conventional imaging—92% vs. 65%, respectively.

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For more news on cancer research, visit *Cancer Discovery* online at <http://cancerdiscovery.aacrjournals.org/CDNews>.