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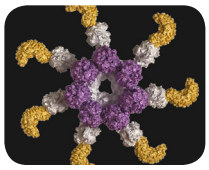
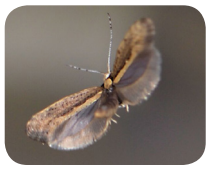


Drugmakers target the inflammasome p893



Oxitec to release GM moths in NY state p896

Pharma and 23andMe partner to tackle psychiatric disorders p897

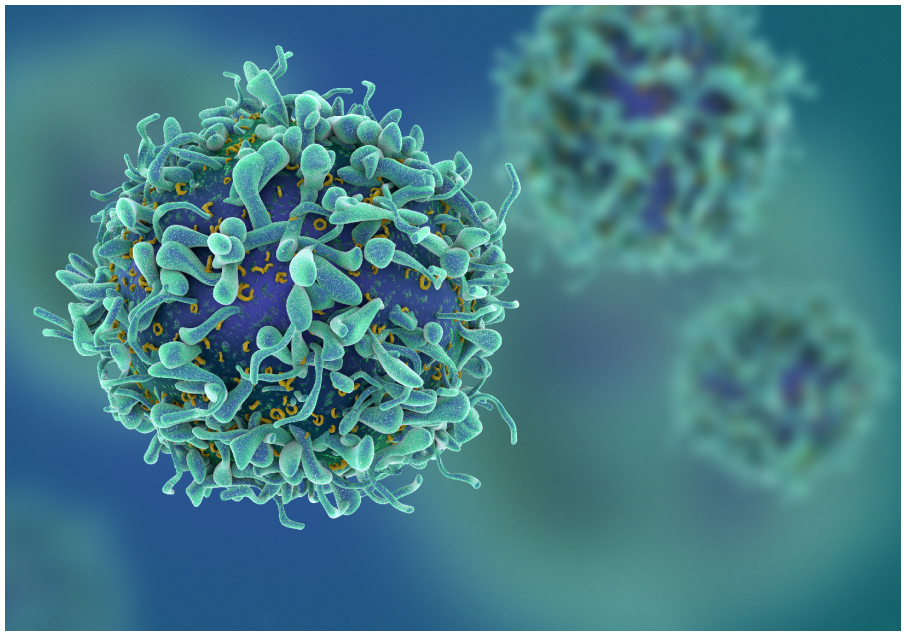
Epic $12 billion deal and FDA's approval raise CAR-T to new heights

The strategy of engineering patients' own T cells for cancer therapy got two major endorsements in late August, one financial and one regulatory. First, Gilead Sciences of Foster City, California, announced plans on August 28 to dole out $11.9 billion to acquire Santa Monica, California–based Kite Pharma, one of the leading developers of chimeric antigen receptor (CAR)-T cell immunotherapies. Then, two days later, the US Food and Drug Administration (FDA) granted approval to the country's first CAR-T cell product: Kymriah (tisagenlecleucel), an autologous CD19-directed therapy from Novartis of Basel, Switzerland (*Nat. Biotechnol.* **35**, 691–693, 2017), which the agency characterized as "the first gene therapy" approved in the US. At the same time, the FDA gave the go-ahead to fellow Swiss drug maker Roche to market its anti–interleukin-6 receptor antibody Actemra (tocilizumab) for CAR-T recipients who experience a life-threatening immune side effect known as cytokine release syndrome (CRS).

"It really marks a huge milestone for the field—and for cancer therapy as a whole—that relatively large commercial players now are in this space and are interested in providing a new kind of therapy for patients," says Marcela Maus, a CAR-T researcher at the Massachusetts General Hospital in Boston, who has consulted for both Novartis and Kite. "There's a real alignment between what's exciting for medicine, what's exciting for patients and what's exciting for business."

Novartis has priced Kymriah at $475,000 per patient with a money-back guarantee if patients don't see improvements in the first 30 days—a fee structure that Maus describes as "very innovative and creative and more than reasonable." It could also be lucrative for Novartis, especially if the therapy—which is part of the company's ongoing partnership with Carl June and his team at the University of Pennsylvania Perelman School of Medicine in Philadelphia—continues to rack up indications.

Initially, the FDA gave its blessing to Kymriah only for treating relapsed B-cell acute lymphoblastic leukemia (ALL) in patients 25 and under, a relatively rare cancer diagnosed in around 3,000 children and young adults annually in the US, only a few hundred of whom don't respond to existing treatment options and would be eligible for the CAR-T therapy. Novartis hopes to add diffuse large B-cell lymphoma (DLBCL)—the most common form of non-Hodgkin lymphoma, diagnosed in more than 20,000 US citizens each year, up to 60% of whom relapse on existing therapies—to Kymriah's label sometime next year. But among CAR-T players, the first to market for DLBCL is widely anticipated to be Gilead, which expects to hear by November 29 whether Kite's anti-CD19 product axicabtagene ciloleucel (axi-cel) wins approval for chemorefractory DLBCL.



cgtoolbox

The FDA announced the first gene therapy approved in the United States is a genetically modified T cell. It is not clear how this relates to Amgen's melanoma therapy T-Vec, a herpes simplex virus 1 (HSV-1) engineered for selectivity in neoplastic cells approved in 2015, or Provenge, a mixture of CD52-enriched immune cells engineered with granulocyte-macrophage colony-stimulating factor hooked up to prostatic acid phosphatase, which was approved in 2010.

Commercialization could then pose the first stress test of the Gilead–Kite deal, says Jerry Cacciotti, an advisor to life sciences companies at AT Kearney in San Francisco. Given the side effect profile of axi-cel—cases of both CRS and neurotoxicity were tied to patient deaths in Kite's trials—Gilead will need to strike the right balance between getting axi-cel to the thousands of eligible patients and pushing the therapy so aggressively that it kills a large number of recipients. "This treatment requires careful clinical deployment," Cacciotti says. "And you're going to have to teach physicians how to do that, particularly those outside of the handful of centers where CAR-T has been studied extensively."

Analysts seem to think the company is up to the task. Consensus forecasts put peak annual sales of axi-cel at around $2 billion, an amount that could help Gilead offset some the declining proceeds from its hepatitis drug franchise (*Nat. Biotechnol.* **35**, 623–629, 2017). "But doubts arise whether the near- to mid-term revenues that Kite can deliver will justify the purchase price to stock analysts' satisfaction," says Anthony Walker, a managing partner at Alacrita, a consulting firm in London.

All eyes are therefore on Kite's next-generation technologies and manufacturing processes—assets that, according to Gilead spokesperson Nathan Kaiser, "will serve as a platform for Gilead's efforts to build an industry-leading cell

therapy franchise in oncology." And although Kaiser declined to discuss the management structure of the future merged company, saying only that Kite's research and manufacturing centers in the Los Angeles area "are very important and will continue on after the transaction has been completed," some CAR-T experts think Gilead should take a back seat and let Kite take the lead. "Management matters," says Ronald Dudek, a consultant for CAR-T cell development who also directs technology development and marketing at Lentigen Technology in Gaithersburg, Maryland. "I wouldn't mess with success."

After axi-cel, Kite's two most advanced products are a second-generation anti-CD19 CAR-T cell product (huCAR-19) that's already under evaluation in a phase 1 trial for B-cell malignancies, and an anti-BCMA CAR-T for multiple myeloma (KITE-585) that's scheduled to enter clinical testing before the end of the year. Both contain only human parts—unlike axi-cel or Kymriah, which include single-chain variable fragments (scFv) derived from mouse antibodies, components that have been shown in trials to elicit immune responses to the transgene product. huCAR-19 also differs in its delivery mechanism. It relies on lentiviral transduction, whereas axi-cel is incorporated into T cells by a gamma retrovirus. (The viral vector for KITE-585 has not been publicly disclosed.)

But the biggest difference between huCAR-19 and Kite's other clinic-ready products lies in the hinge and transmembrane domain, a part of the CAR that serves as a bridge between the antigen-binding moiety on the outside of the engineered T cell and the co-stimulatory domain on the inside. Axi-cel and KITE-585 use CD28 for this section (as well as for the co-stimulatory domain), whereas huCAR-19 incorporates CD8α for the hinge and transmembrane region while still retaining CD28 for costimulation. This structural change "generally delivers a weaker activation stimulus to the T cells, so there's less cytokine release, but it still maintains its activity against CD19-positive target cells," says James Kochenderfer, a physician–scientist at the US National Cancer Institute (NCI) in Bethesda, Maryland, who signed a collaborative agreement with Kite last year to develop huCAR-19. That deal builds on a previous one inked with the NCI's Stevevn Rosenberg, whose work underpins the company's technology portfolio (*Nat. Biotechnol.* **32**, 229–238, 2014).

The reduced immunogenicity of huCAR-19 could be seen both in preclinical experiments published by Kochenderfer's team in late July (*Mol. Ther.* http://dx.doi.org/10.1016/j.ymthe.2017.07.013, 2017) and in early safety data from the NCI's phase 1 trial of the therapy presented at last year's American Society of Hematology meeting. Compared to axi-cel, "it appears that this CAR has less neurological toxicity," Kochenderfer says.

Deeper in Kite's pipeline are what the company calls its "control CARs," with on/off switch technologies that should boost the safety of the therapy even further. "The idea is that when it looks like the patient is nosediving into trouble, the physician would be able to administer a drug, and the CAR-T cells would then either be turned down, like a rheostat, or turned off entirely," says Brian Atwood, president and CEO of Cell Design Labs, an Emeryville, California–based startup that licensed the technology to Kite. The first of these control CARs targets C-type lectin-like molecule-1—an antigen identified as part of a co-discovery pact with Amgen of Thousand Oaks, California. An investigational new drug application to test this therapy, KITE-796, in patients with acute myeloid leukemia is expected next year.

The mix of pipeline candidates and first-movers on the market means that, for now, Novartis and Kite/Gilead remain the biggest players in the CAR-T space, with Seattle-based Juno Therapeutics a distant third place after a spate of toxicity-related deaths derailed the company's lead program of an anti-CD19 therapy for adult ALL (*Nat. Biotechnol.* **34**, 1079–1081, 2016). As a result, the key academic partners for these companies—June and Rosenberg—have been thrust into the spotlight, often overshadowing the contributions of Michel Sadelain, a scientific cofounder of Juno and one of the earliest pioneers of CAR-T technologies at the Memorial Sloan Kettering Cancer Center in New York.

Among his landmark discoveries, Sadelain led the teams that first engineered co-stimulation domains in tumor-targeted T cells and demonstrated the therapeutic efficacy in mice of CD19 as a target. So, for Sadelain, "it's a huge compliment to us that both groups pursued CD19 and used our general CAR design," he says, adding that "the NCI went even further by utilizing our sequence and substituting the antigen-binding scFv to conduct their trials." (Lawsuits are ongoing between Kite and Juno over various patent claims.) But as Sadelain points out, this first batch of market-ready CARs are far from perfect. "They have toxicities and vulnerabilities that result in relapse," he says. "There definitely is room for better products to come to market."

There are also many challenges in manufacturing scale-up to overcome, notes Bruce Levine, founding director of the University of Pennsylvania's Clinical Cell and Vaccine Production Facility, part of the Novartis–Penn Center for Advanced Cellular Therapeutics opened last year. "The field is in the spotlight," he says. "And to be able to have something that is sustainable and can be available to more patients—not only in hematologic malignancies, but also solid cancers—we've got to make progress in manufacturing sciences, analytics, logistics and infrastructure."

Kymriah had already received a Breakthrough Designation, allowing accelerated approval. But an interesting corollary to the FDA's decision to consider the engineered cell therapy a "gene therapy" is that the agency has also provided an unambiguous signal that CAR-T therapies now fall under the Regenerative Medicine Advanced Therapy (RMAT) designation, created by the 21st Century Cures Act last year. For an RMAT approval, a product requires only preliminary clinical evidence of efficacy in an unmet need for a serious or life-threatening disease. Importantly, unlike drugs with a Breakthrough designation, products do not have to show "substantial improvement on a clinically significant endpoint over available therapies".

Elie Dolgin *Somerville, Massachusetts*

"What they're doing is patently unethical. There's a reason why researchers rely on these protections [safety protocols for clinical trials]. People can die." Jonathan Zenilman, chief of Johns Hopkins Bayview Medical Center's Infectious Diseases Division, comments on an offshore clinical trial of an experimental herpes vaccine, spearheaded by wealthy libertarian businessmen. (*GenomeWeb*, 30 August 2017)

"It sucked the life out of me, on an integrity level. It got more and more corrupt." Rhonda Frantz-Smith, former manager at Proove Biosciences, a genetic testing company under FBI investigation, that was peddling a test for predicting a person's chance of becoming an opioid addict, refers to the practice of coercing patients to take the test, among other questionable business practices. (*STAT*, 31 August, 2017)

"While I appreciate the fear [that children will be treated like commodities], I think we need to realize that with every technology we have had these fears, and they haven't been realized." R. Alta Charo, a bioethicist at University of Wisconsin, Madison, and co-leader of the NAS committee that looked at germline engineering comments on fears about designer babies. (*The New York Times*, 4 August 2017)

"'The validity of your patents is subject to review, unless you pay off some Indian tribe' does not seem like a good way to run an intellectual property system." Blogger Derek Lowe's take on Allergan's transferring its property rights to their blockbuster eye product Restasis to the St. Regis Mohawk Indian Nation which, as a sovereign state, makes them immune to challenges to their patents. (*In the Pipeline*, 11 September 2017)