BIOCENTURY

REPRINT FROM FEBRUARY 24, 2020

BIOCENTURY & GETTY IMAGES

PRODUCT DEVELOPMENT

T regs are back - promising to do for autoimmunity what CAR Ts have done in cancer

BY LAUREN MARTZ, SENIOR EDITOR

Drug developers are giving regulatory T cells a second look as treatments for autoimmune disease. The difference this time is that they can leverage orthogonal benefits from CAR T cells in cancer, capitalizing on new tools for boosting potency and persistence, plus regulatory breakthroughs, to yield a new class of cell therapies.

Some of the tools come from gene editing, others from synthetic biology, indicating a convergence of new technologies that could lead to the first successful use of CAR T constructs outside of cancer.

Mechanistically, Tregs have the opposite effect to standard CAR T cells, serving to suppress rather than enhance immune responses. The idea is to exploit the flip-side of immuno-oncology, and counter the immune overactivation that characterizes autoimmune diseases instead of bolstering the weak immune response that exacerbates cancer.

The first generation of Tregs for autoimmune disease failed to advance because the unmodified cells weren't potent enough and were difficult to isolate and expand.

The next generation will see Tregs engineered with CAR or TCR constructs to target them to specific cells, and modifications that enhance persistence, potency and stability.

CAR Treg therapies could present a major improvement over marketed autoimmune medicines, most of which are blanket immunosuppressants, because the Tregs' suppressive effects would be much narrower. And unlike CAR Ts for cancer, engineered Tregs shouldn't kill their target cell type, or trigger

cytokine release syndrome or any of the other inflammatory risks of effector CAR Ts.

"As immuno-oncology was a large disruptive force in oncology, I think Tregs will be the next disruptive force on the other side of immunology," said Iain McGill, CEO of Quell Therapeutics Inc., a Treg-focused startup launched last May by Syncona Ltd (LSE:SYNC) with £35 million ($44.6 million).

The field is pulling investors, biopharmas and other key players.

Two newcos have launched since the start of the year. Sonoma Biotherapeutics debuted this month with a $40 million series A round, and Kyverna Therapeutics Inc. launched in January with a $25 million series A round from Vida Ventures, Westlake Village Biopartners and Gilead Sciences Inc. (NASDAQ:GILD).

TX200 is a Treg expressing a CAR against HLA-A2, gained through Sangamo's 2018 acquisition of TxCell S.A., to prevent rejection in HLA-2 mismatched kidney transplant patients. It received clearance from EMA to start clinical testing in a Phase I/II trial.

However, Sangamo SVP of Cell Therapy Jason Fontenot thinks Tregs will go beyond transplant and traditional autoimmune indications.

"There's a developing appreciation of the inflammatory component of diseases like ALS and other CNS diseases, and we're excited about the potential there," he told BioCentury.

Editing the next generation

Over the past ten years, dozens of trials attempted to use unmodified Tregs to treat autoimmune disease and transplant patients. The cells failed to provide meaningful clinical benefit and their popularity waned.

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Gilead also entered a partnership with Kyverna, combining Kyverna's synthetic Treg platform with the synthetic gene expression system synNotch from Gilead's Kite unit. Kyverna receives an upfront payment of $17.5 million and is eligible for up to $570 million in development and commercialization milestones.

Sonoma is headed by T cell pioneer Jeffrey Bluestone, who was previously president and CEO of the Parker Institute for Cancer Immunotherapy (see "Led by Bluestone, Sonoma Launches"; "Kyverna Applies Tregs, CAR Ts to Autoimmune Diseases").

Bluestone told BioCentury going in this direction is a logical next step. "My sense is that the cancer cell therapy field has gotten very crowded. Looking at how to expand cell therapy as a modality is an obvious choice."

The first indications will be in organ transplants, where the ability to engineer a Treg that selectively targets one antigen can yield short-term readouts for high-profile, well-defined disease settings.

For example, Sangamo Therapeutics Inc. (NASDAQ:SGMO), which currently leads the field with its TX200 therapy, is starting in kidney transplants.

Companies now think they have the tools in hand to engineer more powerful Treg therapies than the previous round of candidates.

"We've been able to create the next generation of Tregs because of the learnings from CAR Ts in oncology that have spilled over, and the suite of engineering tools that have been developed in recent years," said Quell's McGill.

The early studies used Tregs taken straight from a patient's blood. Isolating and expanding those cells was an accomplishment in itself, because Tregs represent a small percentage of peripheral blood cells and are difficult to manipulate in culture.

However, the cells are polyclonal, meaning they collectively target a broad mix of antigens; this weakens their effect. "You don't know what antigens those Tregs are going to recognize and therefore you have a mix of Tregs with different specificities," said Kyverna CEO Dominic Borie.

"Some of those cells will target the antigen of interest, but the effect will be diluted because so many of the cells won't be active against the target," Borie added.

Adding a CAR or an engineered TCR to the cells allows them all to home to the target cell type or tissue, a strategy the new programs are employing.

However, additional modifications will likely be needed to improve the cells' potency and persistence.

The companies that spoke with BioCentury declined to share the specific engineered changes, but described broad strategies the field is considering.

One is to take advantage of the effect of IL-2 in promoting Treg function and durability. Though IL-2 broadly stimulates T cells, including effector T cells, low doses of the cytokine have a net immune-tolerizing effect in preclinical models.

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Several clinical trials are testing IL-2 mimics as monotherapies to increase Treg activity systemically, which could give an early read on whether stimulating Tregs can help treat autoimmune diseases.

These mimics "can validate the idea that Tregs can be used to treat these diseases," said Sangamo's Fontenot.

Fontenot thinks IL-2 could also be incorporated into Treg therapies, for example, by engineering Tregs to secrete IL-2 and overexpress an IL-2 receptor on their surface.

Another strategy is to overexpress the transcription factor FOXP3, which serves as a master regulator of Treg development and function, to promote persistence.

Casebia Therapeutics is taking that approach, developing FOXP3-overexpressing Treg cell therapies for undisclosed autoimmune indications. Casebia is a former JV between CRISPR Therapeutics AG (NASDAQ:CRSP) and Bayer AG (Xetra:BAYN), that is now managed by CRISPR.

A different strategy is to exploit naturally persistent Treg clones, or engineer the attributes of naturally persistent clones into other Treg cells.

"When you look at some of the early work being done in diabetes with a polyclonal Treg product, the Tregs were dosed in a short time frame and most disappeared very quickly, but a few stuck around. "There's a lot we can learn about the phenotype of the cells that stick around," said McGill.

Safer than CAR Ts?

Although CAR Ts in cancer paved the way, the risk profile for Tregs therapies in autoimmunity is vastly different, as is the risk tolerance of the patients.

"You can argue that creating a regulatory pathway was already done for oncology, and I think that will help, but the risks and benefits of autoimmune diseases will be different, and that's something we need to consider in our clinical development plan," said Borie.

Across the board, autoimmune indications have a higher safety bar than cancer because they're lifelong conditions, and because they're not as immediately life-threatening.

But the standard of care has severe drawbacks as well, because it imposes a perpetual immune suppression.

"These patients will be moving from a globally immunosuppressed state, which raises the opportunity for all sorts of malignancies and infections, to a system where you are immunosuppressed in a very specific location or tissue. The risk is much lower," said McGill.

However, it's not clear whether Tregs can maintain their immunosuppressive phenotype over the long term, because the cells show high plasticity. In culture and *in vivo*, Tregs evolve into other types of T cells, which is a problem when they are being directed to an already inflamed tissue.

"Tregs have the ability to morph in their phenotype. If a cell transduced with a CAR and directed toward a tissue moves from a suppressive to an effector attacking phenotype, that's one of the worst things that can happen. You're weaponizing cells against that target you're trying to protect," said McGill.

The problem is compounded by the fact that Treg therapies need to be long acting, due to the chronic nature of autoimmune diseases, McGill added. "You're looking for a one-off treatment to create a lifelong change."

Still, he believes companies have the tools to mitigate these risks, and said Quell is incorporating an undisclosed modification in its cells that locks them into the Treg phenotype. Other Treg developers are taking similar steps.

Choosing the right indications

According to McGill, the cells will be most useful and most easily adapted to autoimmune and inflammatory conditions driven by a T cell response. Examples include organ transplants, Type 1 diabetes, multiple sclerosis (MS) and rheumatoid arthritis (RA).

"When you look at what Tregs do, they predominantly control the T cell response, so you have to be looking at disease states that are predominantly T cell driven," he said.

"There are ways in which a Treg can read over to the B cell compartment, but if a disease is characterized by plasma cells pumping out autoantibodies, that's not where a company wants to start," McGill added.

Organ transplants are a good starting point because they offer a built-in target antigen. When an organ that expresses HLA-A2 is transplanted into a patient who doesn't, the new organ will be the only tissue in the body that expresses the HLA-A2 protein, so a CAR directed to the protein will be extremely selective.

Quell thinks liver transplants are ideal because, unlike the kidney, the liver can be biopsied repeatedly to monitor what's happening with the cells, and it can regenerate, which decreases the risk to patients.

"Liver transplant isn't the biggest of the transplant indications," said McGill, but "if the therapy doesn't work and the patient rejects the transplant, you can reintroduce immunosuppressive therapies and it will regenerate. There's no downside to a patient consenting. If a kidney transplant is rejected, you get irreparable damage to the nephrons."

Quell hasn't disclosed a timeline for clinical development.

Kyverna, Sonoma and Casebia have yet to disclose their lead indications.

Autologous focus

While the success of CAR Ts in cancer might depend on the ability to create off-the-shelf treatments, autologous therapies will dominate in autoimmunity, at least while the technology gets of the ground (see "CAR Ts Can Move Well Beyond Cancer").

Creating an allogeneic Treg will be much harder than creating an allogeneic effector CAR T, and the benefits of an off-the-shelf therapy are less critical in the autoimmune setting, according to the companies who spoke with BioCentury.

"Having something off-the-shelf is a nice to have, but on the other hand, the two-to-three weeks that you might save in manufacturing really aren't critical in the context of autoimmune diseases," said Borie.

He said with the exception of a life-threatening flare, most autoimmune disease patients aren't under the same urgency to begin a cell therapy treatment.

McGill added that the high price tag that accompanies autologous cell therapies in autoimmune diseases is justified if they can persist long term, and he thinks the cells can be engineered to last for the life of the patient.

However, the math changes for each disease state, how well the disease is managed with current therapies, and the price of the standard-of-care biologic.

"There's no doubt that people would love to do a universal product instead of an autologous one, and like any other company in the space, that's part of our technology plan to look at over time, but I really think allogeneic cell therapies are a long way off," said McGill.

He said the science will need to come from effector CAR Ts, and additional steps will need to be made to apply it to Tregs.

"Persistence is so important for Tregs and will be harder to achieve with an allogeneic product because it's a more challenging editing pathway," he said.

Fontenot added that autoimmune patients are unlikely to undergo the same heavy lymphodepletion as cancer patients, making it even harder to evade the immune system with an allogeneic product.

Sangamo is interested in eventually developing allogeneic Tregs using its zinc finger nuclease (ZFN) gene editing technology and expertise gained through its collaboration with the Kite Pharma Inc. unit of Gilead Sciences Inc. (NASDAQ:GILD) to create allogeneic effector CAR Ts. bc

TARGETS

FOXP3 - Forkhead box P3
IL-2 - Interleukin-2

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