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Fresh blood in off-the-shelf CAR-T marathon

Jacob Plieth

Despite slowly mounting competition, off-the-shelf, allogeneic CAR-T therapies continue to enthral Cellectis investors. Some of them might now be wondering whether the next to enter the fray is Sangamo – a company that, despite setbacks, boasts a rival genome-editing technology, based on Zinc-finger nucleases.

The issue hinges on the quietly revealed possible granting to Sangamo of a licence to the NCI's fully human anti-CD19 CAR-T construct for allogeneic use. Sangamo's chief executive, Sandy Macrae, is blunt, however. "We are not an oncology company," he told *EP Vantage* yesterday. "We need a partner."

Whatever criteria a potential partner would have, it will not go unnoticed that – in addition to Cellectis – Kite, Novartis, Celyad and others have already touted in-house allogeneic approaches. And whether Zinc-finger nucleases have been overtaken by other genome-editing systems like Talens and Crispr/Cas9 remains an open question.

Mr Macrae was bullish: "Probably the best bit of molecular engineering I've seen [at Sangamo] is T-cell work; we can edit out the HLA region and T-cell receptor, and drop in a new gene with 80-85% efficiency." But he insisted that his immediate focus, as part of Sangamo's reboot, was on delivering four clinical trials in non-oncology indications.

First mover

Of course, any threat to Cellectis is in the longer term, and for now the group's key advantage is as a first mover. Speaking at the Jefferies conference on Wednesday Cellectis said it would file a US IND for its UCART123 project this year, aiming to take it into the clinic in 2017.

Meanwhile, in the hands of Servier and Pfizer, UCART19 is in two clinical studies, and two children with ALL who were earlier given this construct under compassionate use remain in complete remission over a year later. But it is impossible to say how much of the benefit here is due to UCART19 and how much to subsequent bone marrow transplants.

Another consideration for Cellectis is Novartis, whose academic partner University of Pennsylvania is preclinically studying a Crispr-edited allogeneic CAR. Cellectis is also in an increasingly acrimonious spat with Celyad precisely over a genome-editing patent, and last week Celyad publicly accused Cellectis's chief executive, André Choulika, of making defamatory comments.

The off-the-shelf approach has generated interest because, if successful, it could cut manufacturing cost and complexity versus autologous CARs, which rely on genetically engineering each person's own T cells. Among the unknowns is the efficiency with which allogeneic cells can have their T-cell receptor knocked out – essential to avoid alloreactivity and graft-versus-host disease.

Split licence?

Sangamo's prospective grant of a licence to the NCI construct, announced in the Federal Register in September, is itself intriguing, since the NCI already licensed this patent invention to Kite.

An NCI spokesperson explained that Kite's licence was for autologous CARs, adding: "The licence under consideration to Sangamo … is limited to the development of allogeneic T-cell therapies. These two therapeutic approaches are fundamentally different and do not overlap."

Why was Kite not interested in allogeneic use? "We felt it was too early for us," Arie Belldegrun, Kite's chief executive, told *EP Vantage* on Wednesday. In July the group struck a deal with the University of California, Los Angeles, over a cell culture system as the basis for an off-the-shelf CAR therapy.

Kite's chief medical officer, David Chang, explained that this could present a high-yield source of T cells, whereas Cellectis's off-the-shelf projects rely on cells donated by healthy individuals. Interestingly, however, he said Kite was not wedded to any specific genome-editing technology.

Disclosed allogeneic CAR-T approaches		
Group	**Genome-editing technology**	**Projects**
Cellectis/Servier/Pfizer	Talen, via RNA electroporation	UCART19 in the clinic; preclinical pipeline
Novartis/Intellia/Penn	Crispr/Cas9, via RNA electroporation	Preclinical work on TCR, HLA & PD1 knockouts
Sangamo	Zinc-finger nuclease	Subject to grant of licence to NCI's fully human CD19 CAR
Kite/UCLA	None selected	None; licence to artificial thymic oranoid as T cell source
J&J/Transposagen	Piggybac footprint-free	None disclosed
Celyad/Dartmouth College	None disclosed	None; US patent for TCR-deficient T cells
Shire/Precision Biosciences	Arcus nuclease	None disclosed
Ziopharm/MD Anderson	None disclosed*	Stem cell donor-derived CD19-directed CAR in clinical trials
*Note: *this group uses the Sleeping Beauty transposon/transposase to express the CAR, but since the project uses donor-derived T cells it is not a true, universal off-the-shelf approach.*		

As for the unusual split of the NCI licence, Mr Belldegrun said “we all got smarter. The NCI got smarter. Now the NCI is [asking] how can we slice and sub-slice everything?” He also stressed the close links he had developed with the US government body over decades, meaning that Kite effectively had an early look at anything interesting that emerged from the NCI.

Kite remains cautious as to the allogeneic timeline, with Mr Chang saying: “Hopefully we can take something to the clinic in the next five years.” And Mr Belldegrun had a similar message for Kite's potential competitor, stating: “Whatever Sangamo is doing will not bring a product in the next five years – 100%.”

Cellectis must make the most of it head start.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobPlieth on Twitter