Evaluate Vantage

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Allogene and the need for a reliable cell source

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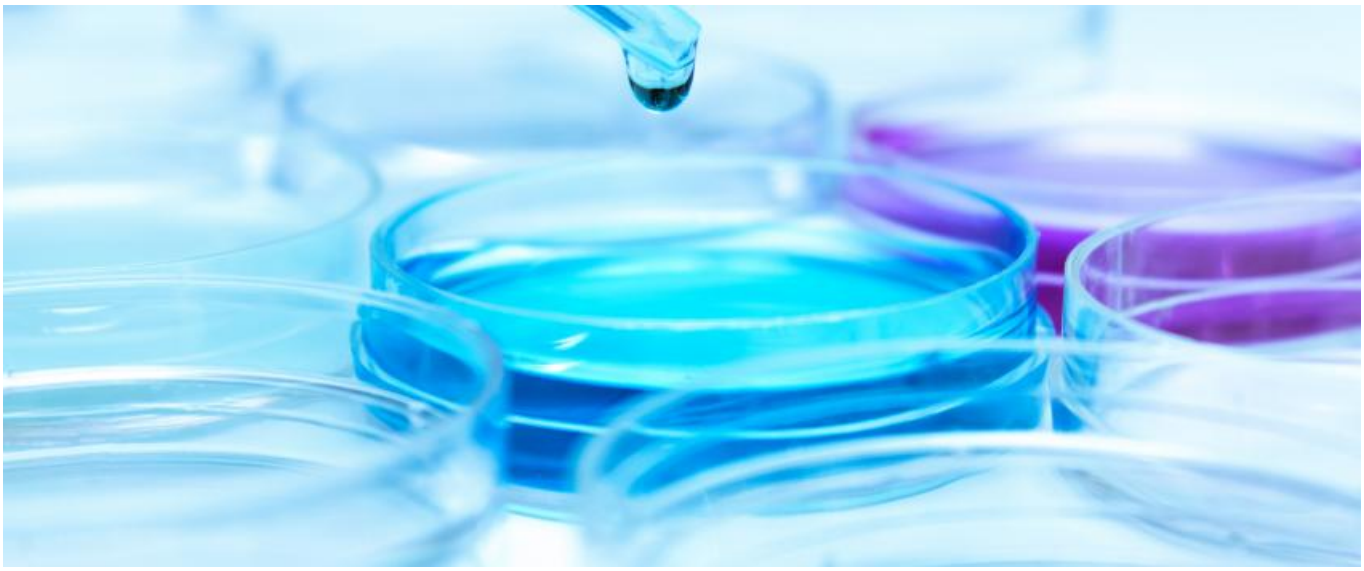

A recent technology deal with Notch points to a problem that all allogeneic cell therapy players might sooner or later have to tackle.

David Chang saw the end goal early. As chief medical officer of Kite Pharma, before that company was ever in allogeneic cell therapy, he did a deal with UCLA to secure a supply of pluripotent stem cells. Now, as chief executive of Allogene, he has repeated the trick, licensing in Notch Therapeutics' stem cell technology this month.

Speaking to *Vantage* at this week's Jefferies conference in London Mr Chang said that within a month of Allogene's creation he recognised the need to secure cell supply – and of course he had done it before, at Kite. "Any allogeneic cell therapy company at some point has to start thinking about renewable cell source," he states.

Since the 2017 approvals of Kymriah and Yescarta the development of autologous cell therapy products has stalled, and many investors see allogeneic, or off-the-shelf, therapy as the breakthrough that will move the needle.

However, the first generation of allogeneic players have hit production bottlenecks, and have struggled with cells derived from healthy donors; these tend to be heterogeneous and of variable quality – not what is needed when the goal is to produce a reliable, universal product.

Single cell

Using induced pluripotent stem cells (iPSCs) as the source, however, is likened by another player in this field, Fate Therapeutics, to going by monoclonal antibody principles: starting from a single cell line.

The idea is that virtually any adult cell can, in a petri dish, be regressed to an iPSC phenotype, and this, using clever science, can then be reprogrammed into a defined mature cell that can be infinitely expanded.

What the iPSC is differentiated into depends on each developer's focus: Allogene is clearly working on T cells, whereas Fate is initially targeting NK cell therapeutics. Each comes with its own degree of difficulty, and Mr Chang argues that "differentiating iPSCs into NK cells is possibly easy".

He says Allogene actively went out to source such a technology, and there were several potential partners, though of course the UCLA work was no longer available. Without going into scientific minutiae, the Notch team's "underlying concept is the same" as that of UCLA, says Mr Chang.

However, the Notch approach is a “serum-free, cell-free system to differentiate iPSCs”. The UCLA technology, pioneered by Dr Gay Crooks and also known as an “artificial thymic organoid”, uses so-called feeder cells on top of which the desired iPSC-derived cells are differentiated.

Selected allogeneic cell therapy players		
Company	**Cell source**	**Mature cells desired**
Cellectis/Allogene	Healthy donors	T cells
Poseida	Healthy donors	T (SCM) cells
Precision Biosciences	Healthy donors	T (N/SCM & CM) cells
Gilead/UCLA	"Artificial thymic organoid", iPSC, feeder cells	T cells
Notch/Allogene	iPSC, cell-free	T cells
Fate Therapeutics	iPSC, feeder cells	NK cells & T cells
Kiadis/Cytosen	Universal adult donor, no tumour cells in final product	NK cells
Nkarta	Adult donor, feeder cells	NK cells
Source: company presentations.		

All that said, the Notch deal caused a degree of consternation, with some Allogene investors seeing it as demonstrating a lack of confidence in Cellectis’s donor-derived approach.

Mr Chang says he was taken aback by such pushback, and stresses that the transition from autologous to allogeneic is not a bet on a single technology but a “stepwise” process. Nevertheless, the clear implication is that, in time, Cellectis's current healthy donor cell source approach will become obsolete.

Though Mr Chang accepts that the science is “not quite there” to implement the Notch technology into clinical programmes, he says: “The way we see the future, whether it’s five or 10 years down the line, is in the renewable cell source.”