Evaluate Vantage

March 07, 2019

Off-the-shelf approaches keep cell therapy investors keen

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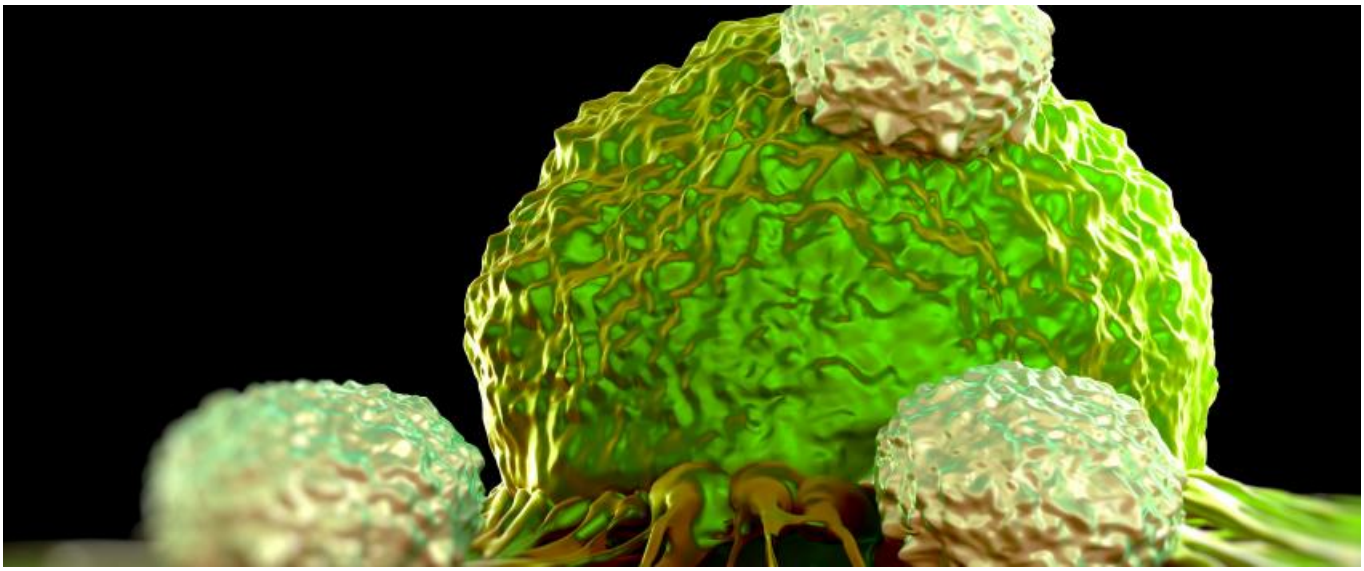

Five months after Allogene's flotation there are few signs of waning interest in new issues of cell therapy companies, and they all have one thing in common.

Late-stage and commercially available cell therapies have a had a rough time of it. Novartis's Kymriah is mired in manufacturing problems, while Kite and Juno are causing their acquirers all sorts of headaches.

Nevertheless, the rush to back version 2.0 of the technology continues, as evidenced by continued support for cell therapy company flotations this year: think Poseida, TCR2 and just last week Precision Biosciences. Like Allogene, whose IPO raised over $300m last year, all the new entrants are looking at allogeneic approaches that reduce the complexity of adoptive cell therapy.

Still, only Precision has this as its primary goal. This company boasts a gene-editing technology that uses arcus nucleases and hopes to rival Allogene/Cellectis's meganucleases and the likes of Crispr/Cas9.

Allogeneic cell therapies require gene-editing to eliminate the threat of graft-versus-host disease, typically by editing out the T cells' endogenous T-cell receptors. The jury is still out on what the most accurate and efficient technology is, not to mention the fact that their respective intellectual property positions are unclear.

In a strange chain of events, rights to Precision's technology and lead asset, PBCAR0191, have ended up with Servier. This is particularly noteworthy as the French company already has rights to the most advanced allogeneic CAR-T therapy, Cellectis/Allogene's UCART19, through a deal dating back to five years ago.

PBCAR0191 was one of six CAR-T assets that were first licensed by Precision to Baxalta, a company with no cell therapy expertise, when that group was already in the process of being acquired by Shire. Once in Shire's hands, it was divested along with legacy oncology assets to Servier, just before Shire itself was bought by Takeda (*Shire taunts Takeda with oncology sale, April 16, 2018*).

Precision filed last week to raise $100m in an IPO whose price has yet to be determined. Its allogeneic CARs target antigens that are well known in haematology: CD19, CD20, BCMA and CLL-1.

Poseida's splash

Targeting BCMA has recently become an extremely crowded field, and the players here include Poseida, which made a splash at the JP Morgan conference by announcing plans to raise $115m in a flotation. However, things have gone quiet since, and the proposed offering has still not been priced.

Poseida calls its gene-editing technology Cas-Clover, and this appears to be a variation of Crispr/Cas9. Its most advanced allogeneic asset is P-BCMA-ALLO1, but this will not enter the clinic until late 2019 or 2020.

Its lead is an autologous BCMA-directed CAR, P-BCMA-101, which is in phase I and which Poseida has put on an ambitious US approval timeframe, revealing at Ash that it would be filed next year. This asset uses the virus-free Piggybac system – similar to Ziopharm's Sleeping Beauty – to transduce the T cells without using a viral vector, and the same iCasp9/rimiducid-based safety switch that Bellicum claims is its own.

Poseida has licensed Johnson & Johnson's Centyrins technology to develop CAR-T binding domains that are not based on antibody motifs. A separate J&J tie-up, with Poseida's parent company, Transposagen, and covering the joint development of CAR-T therapies, was terminated two years ago.

TCR2 or just old-school CAR-T?

The final member of the new entrant trio, TCR2 Therapeutics, has already pulled off a Nasdaq listing, raising $75m last month and seeing its stock climb 28% since, resulting in a $450m market cap.

TCR2 is developing what it calls TRuC-T cell constructs. These look like a cross between CARs and engineered T-cell receptors (TCRs), being structurally similar to the latter but using a different region for binding the antigen, and the company boasts of being able to target irrespectively of patients' HLA type.

But this is precisely what CAR-T itself can do, and TCR2 is not claiming to target intracellular antigens – the main theoretical advantage of an engineered TCR approach. Indeed, its targets are mesothelin, Muc16, CD19 and CD22 – typical extracellular proteins that a CAR can hit. TCR2's selling point seems to be the ability to "harness the entire TCR signalling complex".

The group has not revealed its allogeneic strategy, and remarkably it has yet to start a single human trial: its autologous lead, TC-210, will only enter clinical trials this year. The ability of a company to reach a half-billion dollar valuation without any clinical data speaks volumes about the market's continuing fascination with cell therapies.