Biotech's pursuit of next-generation CAR-T

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About the author:

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Biotech has joined the pursuit of next-generation CAR-Ts and it's not subtle. Some new, others having pivoted towards the area, there are now over 100 companies working on CAR-Ts or derivatives around the world.

With the clinical successes of first-generation autologous CAR-T cell therapies, has come a diverse and frenzied field of biotech companies, all working on next-generation products to improve patient outcomes. Despite the crowd, most do seem differentiated, so what is going on and what will the clinical landscape look like when the dust settles?

Past and present

As the industry has learnt over the past decade, cell therapy is complex and still far from perfect despite the successes. Currently, approved products are expensive[1], which is giving healthcare providers and insurers alike a headache, and can still cause significant side effects, most notably cytokine release syndrome and neurotoxicity[2]. Manufacturing is also slow and not always reliable[1], which means some patients drop out.

That is not to take away from the response and remission data those therapies have generated, as recently highlighted in Kite's addition of follicular lymphoma to their YESCARTA label[3]. However, it does mean there is plenty of space for innovation to fill in the blanks.

Best-in-class products

In comes biotech. A land of opportunity, for those who have developed novel IP in the hope to participate in the pursuit for next-generation CAR-Ts, and they come in all shapes and

sizes – each, attempting to address the different problems of these complex therapies, in a plethora of ways.

Some companies have focused on the receptor itself to improve efficacy, targeting specificity or trafficking such as inert NKG2D-CARs or T cell receptor fusion constructs, and many others iterating on T cell receptors and fourth-generation CARs.

Others are focusing on making T-cells allogeneic to create off-the-shelf products with various gene-editing technologies by knocking out the TRAC locus with TALENs, ARCUS nucleases and CRISPR/Cas9 to avoid graft-versus-host disease.

Several, that see allogeneic off-the-shelf products as the future, are working on moving away from blood-derived cells and towards induced pluripotent stem cell (iPSC)-derived immune cells. This shift is already seeing stem-cell-derived products enter the clinic, enabled and enhanced by an increasing variety of cell reprogramming techniques, such as Mogrify, which uses direct cellular conversion to produce clinically valuable cell types. This method uses computationally predicted transcription and growth factors based on next-generation transcriptomic (RNA) and epigenetic (ChIP) sequencing.

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Some are pre-empting safety issues with universal allogeneic therapies and therefore developing suicide-inducing cell switches or activation switches such as the THROTTLE and GoCAR-T platforms. Many have now looked towards other immune cells, namely natural killer and gamma-delta T cells.

And of course, several companies are bringing technologies to the process and manufacturing complex therapies, such as scalable 3D stem cell encapsulation and the automation of personalised iPSC reprogramming.

All of this innovation is extraordinarily exciting not least because it is blooming at an unprecedented rate but because a significant portion should be complementary rather competitive. Aside from those approaches which are mutually exclusive by cell type or belong to different schools of thought (allogeneic vs autologous), the hope would be for many of these technologies to be combined like CAR-T building blocks to create best-in-class multi-technology products.

What are the challenges?

There are constraints, biotech companies must prove themselves and there are templates to do so. In his early blog posts[4] Atlas partner, Bruce Booth, described the two models a biotech can adopt: drug discovery engine or asset-centric development. The former, available to platform companies with broad ambitions, requires validating that the platform can generate repeatable advances in novel biology, while the latter is based on the clinical development of a lead or investigational new drug through the clinical phases.

As Booth points out, and many blue-chip investors support, both models are based on a key principle of capital efficiency. This means relentless focus and delivery towards value inflection points, offering little room for biotech companies to explore and combine the many blocks required to build these best-in-class products.

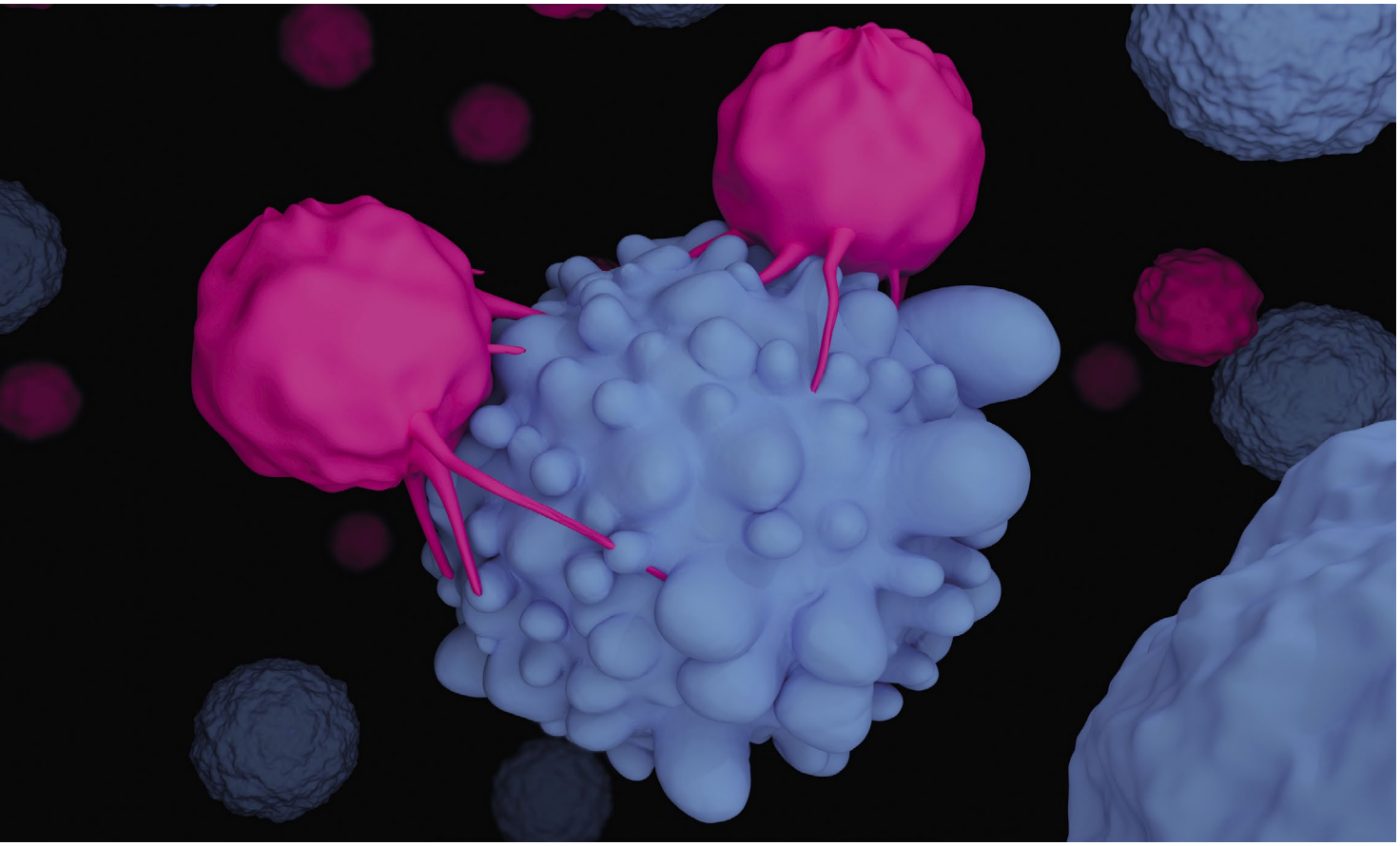
Even in 2020, when biotech was "raining SPACs or special purpose acquisition companies" and enjoying an IPO party, raising over $14 billion in 74 deals with a further $37 billion raised in follow-on equity and all-time high post-IPO stock performance[5], it would be too much for any single biotech to do. Not least because proving your technology up to clinical stages is very capital intensive, but because access to IP is necessary and biotech boardrooms are unwilling to give away large slices of their IP to "retain value", especially before they know what those slices are worth.

Meanwhile, big pharma companies mostly get involved at the later stages and often on a product-by-product basis (see Janssen-Fate deal of April 2020)[6] leaving little scope for them to build multi-technology CAR-T portfolios.

So, how will this shape the clinical landscape in the coming decade? Will we be left with a wasteland full of single/dual technology products with limited clinical differentiation and clinicians confused for choice? Or can we fast forward to fewer, optimised multi-technology product hybrids — the ultimate differentiation? And if so, how?

Collaborate and combine

The good news is, out of the exhaustive list of neoplasms, some will be well served by simpler products because they are easier targets. Haematological malignancies will most likely fall in this category as they don't present the same challenges as solid tumours. This is a double-edged sword as more companies will



> Meanwhile, biotech companies should increasingly look to collaborate with big pharma and each other through co-development

therefore also pick the former to prove their technologies.

On the other hand, where diseases require more complexity, the sector needs to innovate more efficiently than ever before. What should pharma companies be doing? Collaborate, acquire, combine — early! Before assets are stuck in tightly defined processes and reach local maxima of innovations. Meanwhile, biotech companies should increasingly look to collaborate with big pharma and each other through co-development that is aligned with their own strategies. Opting for earlier product dilution across a portfolio rather than equity dilution.

Collaborations from the early stages, working on combining a multiplicity of technologies will be the key to the long-term success and adoption of these technologies and companies.

Luckily, many are already embracing these ways of collaborating both in biotech and pharma. For example, the collaboration between Mogrify and Sangamo on iPSC derived CAR-Tregs[7], Astellas's acquisition of Xyphos[8], or yet, Kite's acquisition of Cell Design Labs[9].

In all cases, these are big bets on the future clinical potential of very early-stage technologies and assets; however, they will allow companies to go further together rather than faster alone.

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