Chimeric Antigen Receptor Therapy in Haematology and Oncology: Current Successes and Challenges

Commercialization of cellular immunotherapies for cancer

Anthony Walker*[1] and Robert Johnson†

*Alacrita LLP, 2 Royal College Steet, London NW1 0NH, UK

†Alacrita LLC, Cambridge Innovation Center, Kendall Square, Cambridge MA 02142, USA

Abstract

Successful commercialization of a cell therapy requires more than proving safety and efficacy to the regulators. The inherent complexity of cellular products delivers particular manufacturing, logistical and reimbursement hurdles that threaten commercial viability for any therapy with a less than spectacular clinical profile that truly changes the standard of care. This is particularly acute for autologous cell therapies where patients receive bespoke treatments manufactured from a sample of their own cells and where economies of scale, which play an important role in containing the production costs for small molecule and antibody therapeutics, are highly limited. Nevertheless, the promise of 'game-changing' efficacy, as exemplified by very high levels of complete responses in refractory haematological malignancies, has attracted capital investments on a vast scale, and the attendant pace of technology development provides promising indicators for future clinical and commercial success.

The CAR-T landscape

Clinical trials have revealed spectacular efficacy in refractory leukaemia patients using anti-CD19 chimeric antigen receptor (CAR) adoptive T-cell therapy, with a 92% complete remission rate in 39 patients with acute lymphocytic leukaemia (ALL). These are transformative results which help tip the balance in the war against cancer: if the complete responses are durable, the technology raises the previously unthinkable possibility that late stage cancer can be cured.

These and other data have ignited investor interest in the biotech sector and this field in particular. In August 2012, Novartis entered into an alliance with the University of Pennsylvania (U Penn) on the back of nascent clinical data with U Penn's CD19 construct and in the context of equally pioneering work at Memorial Sloan Kettering Cancer Center and Baylor College. Novartis agreed to fund a Center for Advanced Cellular Therapies (CACT) on the U Penn campus in Philadelphia, contributing $20m. At the time of the deal, this was an extraordinary venture for Novartis which maintained a strong focus on small molecule and monoclonal targeted therapies; throwing its weight behind an autologous cell therapy was a radical departure for its typically conservative approach to deal-making. The company is looking to aggressively maintain its leadership in the field through both in-house research and continued deal-making.

Start-up companies have raised unprecedented amounts of private capital on both sides of the Atlantic, subsequently tapped equally impressive sums in IPOs and have gone on to achieve eye-wateringly high valuations on the public markets (including European companies such as Adaptimmune, Cellectis and Celyad on the NASDAQ market). Such is the appetite that important investment criteria, for example robust and clear IP have been somewhat forgiven, although this has been shifting as the sector rapidly matures.

Major partnering deals were consummated between 2013 and 2015:

- In March 2013 Celgene and Bluebird Bio announced a global strategic collaboration to advance gene therapy in

Key words: CAR-T, cellular therapy, immunotherapy, oncology, solid tumours.

Abbreviations: CAR, chimeric antigen receptor; PDAC, pancreatic ductal adenocarcinoma; U Penn, University of Pennsylvania.

[1] **To whom correspondence should be addressed (email awalker@alacrita.com).**

oncology, with a focus on CAR-Technology. Financial terms of the agreement include an upfront payment and up to $225 million per product in potential option fees and clinical and regulatory milestones.

- In June 2014 Pfizer and Cellectis entered into a global strategic cancer immunotherapy collaboration to develop CAR-T technologies. Pfizer gained access to Cellectis' allogeneic approach and Pfizer is able to select 15 targets. Cellectis received an upfront payment of $80m and milestone payments of up to $185m.
- Adaptimmune announced in June 2014 that it had entered into a strategic collaboration and licensing agreement with GlaxoSmithKline (GSK) for the development and commercialization of its lead clinical cancer programme, a TCR-engineered T-cell targeting NY-ESO-1, with payments of up to £350m over 7 years plus royalties on eventual sales.
- In January 2015, Amgen and Kite announced a strategic cancer immunotherapy collaboration, combining Amgen's oncology targets and Kite's CAR-T platform to develop new therapeutics. Kite received $80m upfront from Amgen and is eligible for up to $525m in milestones per programme.
- Celgene redoubled its commitment to the field in June 2015, announcing a 10-year collaboration with Juno (albeit after significantly narrowing its collaboration with Bluebird). Celgene gained options to commercialize Juno's programs outside North America and made an investment of $1bn.

However, the technology faces big questions to live up to stratospheric expectations, with at least two major issues facing the field. First, can these technologies be commercialized at reasonable cost (CAR-T technologies use autologous cells, a major logistical challenge); until very recently, commercial activity in the field comprised academic investigator led trial activity with manufacturing housed within academic facilities, resulting in the need for large-scale investments in manufacturing infrastructure. The second major issue is whether the technology can be applied to cancers beyond leukaemia; a technology that delivers equally impressive results in a range of solid tumours would surely mark a milestone in the history of medicine.

Addressing solid tumours

Although successful treatment of advanced haematological malignancies would represent a major clinical win, commercial success relies on conquering solid tumours which represent over 90 % of the oncology sector. There is a dearth of clinical data; the most impressive to date include:

- A 60 % response rate in ten synovial sarcoma patients treated with NY-ESO-1 specific T-cells produced by Adaptimmune, with a durability of response ranging from 2 to 9 months [1];
- The U Penn group treated patients with pancreatic ductal adenocarcinoma (PDAC) with CAR-T-cells recognizing mesothelin, an antigen overexpressed on PDAC cells. Two of six patients experienced stable disease by RECIST 1.1 with disease control off-therapy seen in one patient for >4 months. In one patient, abnormal 18FDG avidity seen in liver metastases at baseline was no longer detected at 1 month after therapy [2].

While providing encouraging preliminary signs of efficacy, these results fall well short of the possibly unreasonable 'game-changing' benchmarks that many investors and some Big Pharma have come to expect from adoptive cellular immunotherapy.

Major technical challenges remain, not least homing of sufficient engineered T-cells to the tumour site(s) to provide an adequate effector:target ratio for meaningful potency. Beyond this, the microenvironment of a solid tumour may prove to be far more hostile to CAR-T-cells than circulating tumours, and induction of anergy may become an efficacy-limiting factor regardless of CAR-T-cell persistence which in itself may be an issue. Finally, the emergence of CAR-T resistant disease through antigen escape loss mechanisms already seen in studies of cancer vaccines [3] may limit the durability of any responses to CAR-T therapy and, as discussed below, this could severely restrict reimbursement for this modality.

Manufacturing and logistical hurdles

Most CAR-T and TCR-engineered T-cells are currently made by a cumbersome and bespoke process involving:

- Leukapheresis to extract T-cells from a cancer patient who is connected by two intravenous tubes to an apheresis machine for several hours. This is not comfortable for the patient, incurs a substantial cost, and ultimately, large-scale adoption of autologous CAR-T therapy may become rate limited by availability of apheresis capacity.
- Activation and transduction of T-cells. The original CAR-T processes used anti-CD3 anti-CD28 Dynabeads for T-cell activation; Novartis made an early move to secure exclusive commercial access to this reagent for CAR-T production to reinforce its proprietary position in the field. Since then, alternatives to Dynabeads have been successfully implemented and this no longer represents a commercial hurdle. Transduction is usually by retroviral or lentiviral vectors, although non-viral systems are also used.
- Expansion of transduced T-cells over an approximately 2-week period in a cytokine (typically IL-2) supplemented tissue culture medium.
- Washing and concentrating the T-cells prior to administration. For CAR-T products made at central facilities and transported to remote treatment centres, cryopreservation protocols have been developed.
- QC release assays are conducted for each batch of CAR-T product.

The entire process has to be conducted under environmentally controlled GMP compliant conditions which are

Table 1 | **Top level pros and cons of manufacturing models**

	Pro	Con
Centralized	- Economies of scale (albeit limited)	- Extremely complex logistics increases risk of production failures/errors - Higher risk of production outages in the event of plant contamination, etc.
Decentralized	- Enables use of fresh, non-cryopreserved product which is likely to be inherently superior - Maximizes local clinician buy-in to the therapy - Potentially harnesses existing investments in cleanrooms at major cancer centres	- Need to demonstrate comparability of manufacturing at each site: complex, time consuming, costly - Validating any process change at each site multiplies the efforts required compared with a centralized setting

expensive to maintain and run. As each CAR-T product is made from starting materials (T-cells) from the patient to be treated, there are no substantial economies of scale: increasing manufacturing capacity requires the addition of extra production 'pods' or 'booths' in parallel. The earliest production processes were lab-based, fully manual and involved open tissue culture manipulations in biological safety cabinets and/or isolators: although workable for very early stage clinical research, this approach is clearly not appropriate for commercial purposes. An industrial grade manufacturing process needs to be conducted in sealed systems (zero open manipulations) and should be automated as far as possible, primarily to reduce the human variability from a complex process but also to reduce costs. A fully sealed system could arguably be situated in a Grade D cleanroom (EU cGMP classifications), although individual regulatory agencies will scrutinize this in great detail and may require Grade C conditions which increases complexity and cost. At present, the only commercially available system that meets the criteria of a closed system automated manufacturing device is the Miltenyi CliniMACS Prodigy [4]. Even then, not every process can be implemented on that system (for example, it currently appears better suited to lentiviral transduction than retroviral, and this depends on the details of each specific process which will not be discussed here).

There are two schools of thought regarding the location of CAR-T manufacturing. The Big Pharma industrial mind-set favours large, centralized facilities capable of processing T-cells from many thousands of patients per year. The alternative is a decentralized model with manufacturing co-located with the specialist treatment centres (e.g. university hospitals, major cancer treatment centres). Theoretical models of the scaling of an autologous production module can show that there are optimum size thresholds for a production module at different dose numbers per year. Economies of scale are non-linear: i.e. there are scenarios where two 'small' production modules in parallel, each capable of producing say 500 doses per year, are more efficient than a 'medium' module scales for 1000 doses per year. These considerations clearly play a large role in the decision between the two models (and indeed the degree of decentralization; i.e. what would the optimum number of sites be in the USA; 25, 50, 100?).

Top level pros and cons of each model include are listed in Table 1.

Pricing, reimbursement and market access

Whichever manufacturing model is chosen, manufacturing costs for autologous CAR-T-cell therapies are likely to be in the range of $25–35000 per patient, even after maximum process efficiencies have been exploited. Note that this is just the cost of manufacturing the therapy, and in fact a course of treatment incurs substantial additional costs for patient preparation (most current protocols call for lymphodepletion prior to CAR-T administration, an expensive and time consuming in-patient procedure), CAR-T administration and follow up care costs (notably the resources required for monitoring and treating the severe side effects e.g. cytokine storm often associated with CAR-T therapy). Total treatment costs may therefore be as high as those for autologous bone marrow transplantation (currently approximately $360000 in the USA) plus the price of the CAR-T therapy. Until such time as this type of treatment can be given on a purely outpatient basis, total costs of therapy will remain extremely high.

In the immediate aftermath of the Novartis deal with U Penn, financial analysts were estimating that CAR-T therapies would be priced at $250000 per patient and possibly higher. As no CAR-T products have been launched on to the market yet, future pricing remains speculative, but many analysts are now basing forecasts on price ranges between $150000 and $300000 per patient. Even the lower end of this range is above current annualized medication costs for newly-launched cancer drugs. At first glance, this appears to fly in the face of the growing debate about the *Justum Pretium*, or Just Price, of cancer drugs [5], voluble clinician resistance to perceived excessive drug pricing (arguably started in October 2012 when physicians at the Memorial Sloan-Kettering Cancer Center announced in the New York Times that their hospital would not be using Zaltrap, a new VEGF-targeted cancer treatment for metastatic colorectal cancer) and the increasing use of Health Technology Assessment (HTA) to restrict the use of high priced treatments. A recent study assessing an original dataset of 58 anticancer drugs approved between 1995 and 2013 found that launch prices, adjusted for

inflation and drugs' survival benefits, increased by 10 %, or approximately $8500, per year [6]. Thus, in 2004 bevacizumab was launched for patients with late stage colorectal cancer at a price of $50000 per treatment episode and was associated with an incremental increase in overall survival of 5 months. Seven years later in 2011, ipilimumab was approved for treatment of melanoma, associated with an incremental increase in life expectancy of 4 months, and launched at a price of $120000 per treatment episode. It is clearly untenable for this trend to continue indefinitely in an already budget-constrained healthcare environment.

The key question therefore is: will payers be prepared to fund CAR-T treatment at these levels? This is key to understanding the commercial prospects for the technology as a whole. The answer simply is that it will depend on the level of clinical efficacy that can be achieved with this new modality. In the most optimistic (but probably unrealistic) scenario, a single CAR-T administration would induce long term remission, say 5–10 years. Using the UK's NICE benchmark of £30000 ($47000) per quality-adjusted life year, this would amount to a maximum reimbursable price of $235–470000. This would have to be adjusted downwards to account for the fact that cancer patients' quality of life is less than perfect, but that still may allow a price for CAR-T treatment of $118–235000. Allowing for the observation that NICE's approach is among the most stringent in mainstream pharmaceutical markets, and UK prices for pharmaceuticals tend to be significantly lower than in the US (the main market) and other countries, it is possible that the HTA-accepted prices for CAR-T therapy will be above this range and therefore in line with current analyst projections. However, any shortfall in efficacy below a durable 5-year remission would necessarily reduce these calculated price ranges. This may perhaps be an overly sophisticated way of saying that CAR-T therapies will be paid for only if they work in the clinic, but the serious conclusion is that the benchmark for commercially-viable efficacy is going to be much higher than for less complex modern oncology drugs such as monoclonal antibodies. Unless CAR-T therapy, in its current patient-specific autologous approach, can induce long term durable remissions in a high proportion of treated patients, the chances of commercial success are low.

New technology to drive commercial success

A number of technologies on the horizon appear set to greatly improve the clinical and commercial prospects for adoptive cellular immunotherapy. Some of these approaches aim at enhancing the efficacy of CAR-T-cells, for example by boosting the homing of infused cells to tumour sites, the lack of which is believed to be a major reason why efficacy of CAR-T-cells in solid tumours is significantly below that in circulating tumours. There are also approaches to enhancing the endurance of CAR-T-cells not just in terms of the length of duration in the circulation, but also the retention of an active, non-anergized phenotype. Combination studies, for example with immune checkpoint inhibitors, are also underway in a number of centres with similar objectives. Additionally, some researchers are assessing methods to build in defences against tumour mechanisms that evade or disable the immune system; such 'anti-missile missiles' may have a lot of mileage in boosting CAR-T efficacy.

Another set of approaches focus on the safety of CAR-T therapies. Although there is some evidence that cytokine release syndrome is at least associated, if not correlated with clinical efficacy, there may be methods to blunt the severity of the reaction without too much of an efficacy hit. Reducing the need to treat the side effects of CAR-T therapy in an intensive care unit would clearly be better for patients, more practical for treatment centres and much more attractive to payers.

Perhaps the most fundamental approach to improve cellular immunotherapy will be to transform it from a bespoke, patient specific process to a mass-produced product. This would reduce lead times for treatment (the product would be available off-the-shelf), have an inherently lower production cost (allowing for reductions in pricing without overly sacrificing profit margins) and would be more in line with the model of product distribution by the pharmaceutical industry. The first step toward this is the use of allogeneic T-cells from healthy donors, for example gene edited to eliminate the endogenous T-cell receptor and thus prevent the possibility of a potentially lethal graft compared with host reaction, and where one donor can provide enough cells to treat multiple patients. Ultimately, we foresee that this approach will extend to immortalized T-cell lines that can be cultured in bulk on an industrial scale, eliminating the need for T-cell donors altogether. An immortalized, allogeneic mass-produced CAR-T-cell capable of inducing durable (5 years or more) remissions remains a pipe dream, but at least is on the radar for a number of well-resourced research groups and thus stands a reasonable chance of becoming a reality.

References

1 Merchant, S., Cristea, M.C., Stadtmauer, E.A., Tap, W.D., D'Angelo, S.P., Grupp, S.A., Holdich, T., Binder-Scholl, G., Jakobsen, B.K., Odunsi, K. et al. (2015) Genetically engineered NY-ESO-1 specific T cells in HLA-A201 + patients with advanced cancers. J. Clin. Oncol. **33** (suppl abstr TPS3102),
2 Beatty, G.L., O'Hara, M.H., Nelson, A.M., McGarvey, M., Torigian, D.A., Lacey, S.F., Melenhorst, J.J., Levine, B., Plesa, G. and June, C.H. (2015) Safety and antitumor activity of chimeric antigen receptor modified T cells in patients with chemotherapy refractory metastatic pancreatic cancer. J. Clin. Oncol. **33** (suppl abstr TPS3007),
3 Johnson, R.S., Walker, A.I. and Ward, S.J. (2009) Cancer vaccines: will we ever learn? Expert Rev. Anticancer Ther. **9**, 67–74 CrossRef PubMed
4 MACS Miltenyi Biotec, CliniMACS Prodigy® System Mastering the complexity of cell processing (accessed 2015) PubMed
5 Hagop, M., Kantarjian, H.M., Fojo, T., Mathisen, M. and Zwelling, L.A. (2013) Cancer drugs in the United States: Justum Pretium – the just price. Am. Soc. Clin. Oncol. **31**, 3600–3604 CrossRef
6 Howard, D.H., Bach, P.B., Berndt, E.R. and Conti, R.M. (2015), Pricing in the Market for Anticancer Drugs. National Bureau of Economic Research, Working Paper 20867, http://www.nber.org/papers/w20867, (accessed 2015)

Received 4 February 2016
doi:10.1042/BST20150240