CHAPTER 23

CAR-T: From Concepts to Products – Now What?

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HISTORY OF CAR-T CELLS

The concept of immunotherapy was created many years ago with initial experiments performed in the late 1800's (Firor et al., 2015). Some of the earliest work with CAR-T in the 1980s was targeting the creation of anti-HIV CAR-T cells (Hale et al., 2017), but this quickly evolved to oncology applications. However, it has taken many more years to understand the underlying biology of tumours to get us to the point today where we have approved cell-based therapies for cancer. The history of the technological innovations required to bring CAR-T cell products to the market can be broken down into four distinct periods (see Junghans, 2017): (1) the preclinical period, (2) the first-generation clinical studies, (3) the costimulation studies and (4) the second-generation clinical studies. The evolution of the underlying science over the last 40 years has been remarkable and has the industry poised to not only provide significant benefits to patients suffering from haematological malignancies but also hopes to successfully tackle the elusive solid tumours that have evaded the immune system.

FIRST-GENERATION CAR-T CELL THERAPIES

The first successful treatments using a CAR-based therapy occurred in 2012 after the successful case of Emily Whitehead emerged from the Children's Hospital of Philadelphia. Emily is now a 13-year-old child cured from recurrent acute lymphoblastic leukaemia; she took part in the NCT01626495 trial and has now reached 6 years of cancer-free survival with CAR-T therapy (http://emilywhiteheadfoundation.org/emily-whitehead-story/). As mentioned above, the US Food and Drug Administration (FDA), as of October 2018, has approved two CAR-T therapies (see Table 23.1) based on strong clinical benefits data, even though the trials only included a small number of young, lower-risk patients (Hartmann et al., 2017; SeekingAlpha).

Juno (acquired by Celgene, Summit, New Jersey, USA in January 2017) is on track for a 2019 submission for FDA approval of its own CAR-T cell therapy (Lisocabtagene Maraleucel; JCAR017) after its pivotal trial (TRANSCEND-001) (DeFrancesco,

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Table 23.1 Summary of FDA-Approved CAR-T Therapies.

	Kite-Gilead		Novartis	
Name	**Axicabtagene Ciloleucel [Yescarta]**		**Tisagenlecleucel [Kymriah]**	
CAR type	CD19/CD28/CD3z		CD19/4-1BB/CD3z	
Diffuse large B-cell lymphoma	Approved (ZUMA-1) (Oct. 2017)		Approved (JULIET) (May 2018)	
Follow-up	3 Months	6 Months	3 Months	6 Months
Patients	N = 101		N = 81	
Objective response rate	54%	41%	38%	37%
Complete response	36%	36%	32%	30%
Cytokine release syndrome	13% Severe 94% Any		23% Severe 58% Any	
Neurotoxicity	31% Severe 84% Any		12% Severe 58% Any	
Acute lymphoblastic leukaemia	Ph 1 (ZUMA-3/4)		Approved (ELIANA) (August 2017)	
Price per patient (USD)	$373,000		$475,000	

2017). At the 2017 annual meeting of the American Society for Hematology (ASH2017), it was reported that JCAR017 achieved much lower cytokine release syndrome (CRS) numbers (1% severe; 40% any) relative to the similar products developed by Novartis and Kite/Gilead, thus raising a case for a best-in-class therapy for non-Hodgkin lymphoma. However, there are two limitations remaining: (1) the smaller patient sample size for Juno's trial relative to their competitors and (2) the drop in complete response (CR) from 3 to 6 months in Juno's trials, questioning the durability of the treatment (June 5, 2017 press release). In addition, Juno has a broad portfolio of Phase 1/2 assets across both blood and solid tumours with first results being expected by the end of 2018.

In parallel, bluebird biosciences ($BLUE, Cambridge, MA, USA) are testing their lead assets: bb-2121 and bb-21217 in multiple myeloma trials. At ASH 2017, it was reported that the CRB-401 clinical showed a 56% CR rate and a 94% overall response (OR) rate in multiple myeloma patients. However, safety in a 21-patient trial showed that 71% of patients had CRS and 24% showed signs of neurotoxicity (Raje et al., 2018). With such high levels of toxicity, bluebird's therapeutics could only be administered in major cancer and transplantation centres that can manage CRS and neurotoxicity for in-patients. In particular, bb2121 has breakthrough therapy designation with the FDA and also PRIME eligibility by the European Medicines Agency (EMA).

THE CAR-T CELL PLATFORM NOT ONLY EXPANDS BUT ALSO EVOLVES

There are currently more than 200 ongoing clinical trials of CAR-T therapies recorded in the clinical trials database (www.clinicaltrials.gov), primarily to treat haematological cancers; nevertheless, a few trials are aimed at treating solid tumours (Hartmann et al., 2017). In addition to novel targets in solid tumours, next-generation CAR-T products include synthetic biological approaches such as synthetic gene circuits and engineered molecular switches and off-the-shelf CAR-T therapies, all of which aim to address the main limitations identified to date in the first products to have reached either the market or late-stage clinical trials, with the goal to improve safety, efficacy and manufacturing of CD-19–directed CAR-T cell therapies. Notably, beyond cancer, the CAR-T technology is potentially effective against life-threatening viruses such as HIV. Since 2012, there has been an explosion of commercial activity, and numerous CAR-T strategic partnerships, acquisitions or licencing deals have been implemented between not only biotechnology companies developing CAR-T cell-based products or large pharmaceutical companies but also with smaller emerging organisations or academic institutions developing novel and cutting-edge CAR architectures. The major novel approaches are highlighted below:

Synthetic Gene Circuits

Cell Design Labs (acquired by Gilead), founded by scientists from the University of California at San Francisco and synthetic immunology pioneer Wendell Lim, has built a toolkit of modular genetic 'parts' to fine-tune CAR-T behaviour in different tumour microenvironments. One such approach, called the synthetic Notch (synNotch) receptor, gives scientists the ability to engineer cells with finely tunable sensing and response behaviours to user-specified cell–cell and extracellular signals (Morsut et al., 2016). In the context of oncology, synNotch receptors can sense tumour antigens, deliver custom therapeutic payloads, drive T cell cytokine profiles and determine T cell fate in varying physiological environments (Roybal et al., 2016a). Another approach is combinatorial antigen-sensing circuits (Roybal at al., 2016b). Such circuits require CAR-T cells to recognise multiple antigens on a tumour prior to activation, reduce the risk of toxicity to healthy tissue and increase the scope of targetable tumour types. Combinatorial-activated circuits utilise a synNotch receptor for one tumour antigen that induces the expression of a CAR for a second tumour antigen via an AND gate, which ensures the CAR-T cells are only active when both antigens are present (Roybal et al., 2016b).

Cellular Switches

There are a number of companies currently developing molecular switch approaches in the area of CAR-T; this diversity translates into several ingenious mechanisms being pursued. For example, Bellicum Pharmaceuticals ($BLCM, Houston, Texas, USA) is

developing two molecular switch-based approaches that are currently in Phase 1 (GoCAR-T) for pancreatic cancer (BPX-601) to help control patient responses to T cell deployment in situ (http://www.bellicum.com/product-candidates/bpx-601/). The first is a suicide switch that activates caspases in the T cell, causing it to die (Di Stasi et al., 2011). The second is an inducible MyD88/CD40 activation switch, which controls how fast the cells proliferate in the body and attack solid tumours (Narayanan et al., 2011). Likewise, Ziopharm Oncology (Cambridge, Massachusetts, USA, partnered with Intrexon ($XON) Germantown, Maryland, USA) is building cellular switches that are similar in design to those developed by Bellicum (https://www.sec.gov/Archives/edgar/data/1107421/000119312518006523/d444139dex991.htm). However, the engineered cells are activated via the drug veledimex and need continued dosing of the drug to remain active. Halting administration of veledimex shuts off the T cells, but it does not induce their death. This is a clever mechanism of action as it enables their reactivation when appropriate again later and, in theory, controlled like a traditionally titrated therapeutic (Barrett et al., 2018).

Moreover, Autolus (London, UK), founded on advanced cell programming technology pioneered by Dr. Martin Pule, was spun out from University College London in 2014 and has three ongoing Phase 1/2 trials at the time of this writing, targeting both haematological and solid tumours. The primary technology pursued by Autolus utilises a fast-acting, permanent 'off' switch (Stavrou et al., 2018). Particularly, AUTO2 and AUTO4 incorporate RQR8, a permanent off switch activated by rituximab (McConaghie, 2018). Because of the limitations of tissue penetration and response time, the company is planning to replace the monoclonal antibody, rituximab, with a small molecule (McConaghie, 2018). The small molecule approach will require the addition of caspase 9 (rapaCasp9) into the engineered T cells, which are then shut off by rapamycin. Furthermore, F1 Oncology (San Diego, California, USA partnered with BioAtla, San Diego, California, USA) is employing BioAtla's Conditionally Active Biologics (CAB) technology initially designed for BioAtla's Biologics (https://www.bioatla.com/technology/cab/). The CAB technology activates or inactivates drugs under specific physiological conditions defined by specific cellular metabolites, in this case metabolites representative of the tumour microenvironment. In January 2018, the two companies received approval for a clinical trial in China for two CAB-CAR-T product candidates targeting Axl and Ror2 for the treatment of recurrent and refractory metastatic renal cell carcinoma, a solid tumour. Likewise, an exciting new development in the field is the technology being pursued by Tmunity (Philadelphia, Pennsylvania, USA). The company is developing the first CRISPR-edited TCR cell therapy in the United States and is working to target it to prostate cancer. The leading idea is to control T cell activation and direction in vivo (https://www.tmunity.com/). Tmunity's strategy could produce a highly efficient CAR-T production process and a long-term edge over the competition.

Allogeneic CAR-T Cells

The process of removing T cells from a patient and then isolating and reprogramming them in a highly controlled laboratory is time-consuming, extremely costly and prone to potential manufacturing errors. It is because of the aforementioned issues that some biotechnology companies are departing from autologous treatments to design 'off the shelf' or allogeneic CAR-T cells. The key difference between autologous CAR-T cells and allogeneic CAR-T cells is that the latter product class involves harvesting and genetically reprogramming immune cells from a healthy donor, with the resulting cells being subsequently used to treat any appropriate cancer patient. As with cellular switches, this is a competitive area with multiple companies developing emerging architectures and allogeneic 'immune-permissive cell chassis' designs to exploit this alternative CAR-T method. Notably, Cellectis (Paris, France) is acknowledged as the pioneer of allogeneic T cell therapy. This company has promoted the use of transcription activator-like effector nucleases (TALENs) to directly edit the genome of donor immune cells (http://www.cellectis.com/en/research/gene-editing/). Unfortunately, it has had troubling results in Phase I clinical trials to date for its UCART123 for acute myeloid leukaemia and blastic plasmacytoid dendritic cell neoplasm (BPDCN), as the FDA halted both trials in September 2017 following patient deaths resulting from therapeutic toxicity (https://immuno-oncologynews.com/2017/09/07/fda-puts-cellectis-ucart123-on-hold-after-patient-death/). However, the trials have since resumed. Although Cellectis is using TALENs as a gene-editing technology, Kite (acquired by Gilead) is using Sangamo Therapeutics' (Richmond, California, USA) zinc-finger nuclease (ZFN) technology to develop allogeneic CAR-T therapies. Despite the difficulty of ZFN protein engineering, ZFNs might be more likely to play a role in CAR-T R&D in the near future relative to CRISPR/Cas9, an otherwise more popular gene-editing tool for research laboratories. ZFNs are more accurate proteins that unlike CRISPR/Cas9 can be delivered as a one-shot gene-editing tool in RNA form (Rui et al., 2018). ZFNs have been around for 20 years and have a proven track record of clinical safety and efficacy. Furthermore, ZFNs display more target flexibility because they do not exhibit target site restrictions unlike CRISPR/Cas9 that requires the target gene sequence to be immediately upstream of a protospacer adjacent motif (Rui et al., 2018). Allogene Therapeutics (South San Francisco, California, USA) has raised $300 million in funding as part of a strategy to acquire and develop a portfolio of 16 preclinical cell therapy assets from Pfizer (New York, New York, USA). The acquisition of those assets marks Pfizer's exit from the adoptive cell therapy arena, though Pfizer maintained a 25% ownership stake in Allogene through to the Initial Public Offering (IPO) (http://fortune.com/2018/10/11/biotech-allogene-ipo/). So far, one of these UCART19 programs, which was originally developed by Cellectis, has been tested clinically. Early UCART19 data in two children were encouraging (Qasim et al., 2017). Celyad (Mont-Saint-Guibert, Belgium) has a single allogeneic asset, CYAD-101 (CAR-T NKG2D), which

is still in preclinical development (https://www.celyad.com/). CYAD-101 targets the same mechanism of action as their current lead asset (CYAD-01), which is in Phase I trials and uses engineered T cells that express NKG2D, a molecule originating from natural killer (NK) cells. NKG2D binds to any of its eight naturally occurring ligands, which are known to be overexpressed on more than 80% of tumours (Schmiedel and Mandelboim, 2018). This is distinct from most CAR-T therapies, which bind to a single tumour-associated antigen. Celyad believes that the theoretically improved efficacy from a multitargeted approach to tumour eradication could outweigh the potential for off-target effects relative to more precise CAR-T therapies.

In Situ Reprogramming

Because of the complexity of organisation and materials required to produce CAR-T cells in vitro, it would be a great leap forward to develop methods where reprogramming of a patient's own T cells to express CARs could be performed in situ as this would be cost effective and also achieve 'on-demand' personalised care at the time of need. A step in this direction was recently taken by which it was shown that circulating T cells can be rapidly reprogrammed in situ using DNA-carrying polymer nanoparticles to introduce CD19-targeting CAR genes into T cell nuclei (Smith et al., 2017; Olweus, 2017). This type of approach, while being a necessary step forward, still requires derisking of the potential major side effects (primarily CRS and neurotoxicity).

CAR-T CELLS WORKFLOWS

The uses of the CAR-T technology can be broadly placed into two categories: in vitro and in vivo. This fundamental choice determines the business models and the type of products that a company in the field may follow or develop. In the case of in vitro CAR-T cell products, a patient's cells are sent to a centralised laboratory that carries out the gene editing and propagation, with the CAR-T products being subsequently sent back to the oncology clinic where the patient receives the transfusion. This model carries a high cost of goods, with costs per procedure alone being often well in excess of $100K per patient (Brigand et al., 2018). Moreover, such high costs favour larger companies such as Novartis, Gilead or Celgene for commercialisation. Despite this, Kite and Tmunity are making large investments in bottom-up manufacturing processes. Personalising such in vitro CAR-T production cannot be easily made cheaper, but other in vitro approaches, such as allogeneic CAR-T therapies, offer such possibilities. However, it remains to be fully demonstrated whether, compared with personalised treatments, the allogeneic CAR-T products will have comparable effectiveness as the autologous therapies. The alternative approach to in vitro CAR-T is the in vivo approach, where a company sells to a transfusion clinic a premade serum specific to a patient's cancer profile for the endogenous T cells to be transformed into CAR-T cells at the treating hospital laboratories. Given the heterogeneity of any T cell population, however, clinicians lose

control over which CAR-T variants are selected; this inherently brings the risk of unknown toxicity. One other advance in CAR-T therapeutics on the horizon is the use of on-demand single-cell sequencing and protein as well as metabolite detection. Companies such as 10x Genomics (Pleasanton, California, USA) and Genalyte (San Diego, California, USA) have technologies that can be applied to this way of working. It is possible that such single-cell approaches could be applied for the production of personalised therapeutics in the future and thus enable treatments to be better optimised for the patient through better alignment to an individual's cell profile.

CAR-T cell therapy is a vibrant and developing field and this is shown clearly by the active number of companies in the area. In Table 23.2 are summarised the main companies pursuing this therapy, their technological approach and disease targets.

SAFETY CONSIDERATIONS

Although CAR-T cell therapy has shown impressive clinical benefit, it is associated with a variety of toxicities that can be life threatening. For example, Kymriah and Yescarta have the capacity to cause adverse events and toxicities such as CRS (CRS was seen in up to 30% of patients). CRS occurs as T cells secrete massive amounts of cytokines especially IL-6 (Lee et al., 2014) causing severe fever, nausea, fatigue, difficulty breathing, low blood pressure and organ swelling. Current treatment includes steroids (Davila et al., 2014; Lee et al., 2015), but these drugs can result in ablation of the infused CAR-T cells, thus limiting the desired antitumoral effect (Davila et al., 2014). A currently preferred alternative way to manage CRS is with tocilizumab, a therapeutic IL-6 receptor–blocking antibody, which does not affect CAR-T cell persistence (Davila et al., 2014; Maude et al., 2014). However, one death case has been reported due to severe CRS with multiorgan failure resulting 3 days after the CAR-T cell infusion, despite treatment with tocilizumab, the TNFα inhibitor etanercept and corticosteroids (Turtle et al., 2016).

In addition to CRS, CAR-T cell therapies may cause neurological toxicity with several death cases being reported due to cerebral oedema (Turtle et al., 2016; DeFrancesco, 2017). Reversible neurological symptoms such as delirium, expressive aphasia and seizures have also been reported in several studies (Brentjens et al., 2011; Maude et al., 2014; Kochenderfer et al., 2015; Lee et al., 2015; Turtle et al., 2016). The potential causes for the occurrence of neurotoxicity are under debate, and pathophysiological mechanisms including cytokine diffusion and the translocation of activated CAR-T cell across the blood–brain barrier have been postulated.

Finally, the antigens used in the current CAR-T therapies are not restricted to tumour cells and as such they target healthy tissues as well. Therefore, 'on-target/off-tumour' toxicity occurs throughout the treatment. Of particular note, B-cell aplasia is a common adverse event in CAR-T cell trials targeting B-cell malignancies (Kochenderfer et al., 2015; Maude et al., 2014; Turtle et al., 2016).

Table 23.2 CAR-T Cell Therapy Companies.

Company Name	CAR-T Technology	Disease Targets
AbbVie and Calibr	'Switchable' CAR-T cells that use antibody-based switch molecules	Haematological and solid tumour cancers
Agios Pharmaceuticals and Celgene	Small molecule anticancer therapeutics targeting cancer cell metabolism through the growth factor pathway	Metabolic immune oncology
Allogene Therapeutics (Cellectis/Pfizer/ Servier)	Sixteen preclinical CAR-T assets and UCART19, an allogeneic CAR-T therapy that is currently at Phase 1	Acute myeloid leukaemia, acute lymphoblastic leukaemia and blastic plasmacytoid dendritic cell neoplasm
Amgen and Kite Pharma/Gilead	Kite's engineered autologous cell therapy together with Amgen's broad array of cancer targets	Haematological and solid tumour cancers
Atara Biotherapeutics	Off the shelf, allogeneic T cells broadly targeted to recognise Epstein–Barr virus and cytomegalovirus viral antigens and the tumour-associated antigen Wilms tumour 1	Cancer, autoimmune, viral diseases
Autolus Ltd.	Anti-GD2 CAR-T cells	Paediatric neuroblastoma
BioAtla and F1 Oncology	Conditionally Active Biologics (CAB) CAR-T technology	Recurrent/refractory metastatic renal cell carcinoma
Bellicum Pharmaceuticals	CIDeCAR and GoCAR-T Technology	Haematological and solid cancers
Bluebird Bio and Celgene	bb2121	Multiple myeloma
Carina Biotech	CAR-T cells targeting a molecular marker expressed on a wide range of cancer cells	Solid cancers including paediatric and rare cancers
CARsgene Therapeutics	Commercialising CAR-T cell therapies	Haematological malignancies and solid tumours
Cartherics Pty Ltd. and Mesoblast	Allogeneic CAR-T cells from induced pluripotent stem cells (iPSCs)	Solid cancers
Cell Design Labs and Gilead Sciences	Switches: Throttle and synNotch technologies	Anticancer therapies
Cell Medica	CAR and TCR (T cell receptor) technology	Cancer immunotherapy
Celularity	CAR-T/natural killer products	Cancer immunotherapy
Celyad	Natural killer receptor T cell platform	Cancer immunotherapy
Fate Therapeutics	CAR-T cell product from iPS	Solid tumours
Fortress Bio and Mustang Bio	CD20-directed CAR-T and CRISPR/Cas9-enhanced CAR-T technologies	Relapsed or refractory B-cell non-Hodgkin lymphoma

Table 23.2 CAR-T Cell Therapy Companies.—cont'd

Company Name	CAR-T Technology	Disease Targets
Humanigen Inc.	Humaneered platform	Rare haematologic cancers
Immune Therapeutics	Chimeric Super Antigen Receptor T cell cocktail therapy	Various application
Janssen Biotech and Legend Biotech	Manufacturing and commercialising experimental CAR-T cell therapy LCAR-B38M	Multiple myeloma
Juno Therapeutics and JW Therapeutics and Celgene	CAR and TCR technologies; JCAR015 in Phase 2	Anticancer therapies
Kite Pharma and Gilead	CAR-T cell therapy approval by the US FDA (Yescarta)	Relapsed or refractory large B-cell lymphoma
Lion TCR Pte Ltd. and Technical University, Munich	CAR-T cell therapy	Viral-related cancer and chronic hepatitis B
Medisix Therapeutics Pte Ltd and National University of Singapore	CAR-T technologies	T cell malignancies
Nanjing Legend Biotech and Johnson and Johnson	CAR-T products	Haematological and solid tumours
Novartis	World-first Kymriah became the first CAR-T cell therapy to be approved by the US FDA	B-cell acute lymphoblastic leukaemia
Obsidian Therapeutics	On-off CAR switch, refresh circuits for CAR	Haematological malignancies and solid tumours
Precision Biosciences and Baxalta/Shire	Allogeneic CAR-T cells using ARCUS genome editing technology	Haematological malignancies and solid tumours
Poseida Therapeutics	P-PSMA-101 (PSMA-specific stem cell memory CAR-T drug candidate)	Prostate cancer
Sangamo Therapeutics and TxCell	Zinc-finger nuclease technology to develop allogeneic CAR-T therapies	Prevent organ rejections and autoimmune diseases
Sorrento Therapeutics and TNK Therapeutics Inc.	Nonviral CAR-T cells	Liver metastases
TC Biopharm	ImmuniCell/gamma delta CAR-T cells	Haematologic and solid tumour targets
Tmunity	CRISPR-edited TCR cell therapy	Prostate cancer
Xyphos Inc.	Convertible CAR technology	Various targets
Ziopharm and Intrexon andand MD Anderson Cancer Center	Nonviral Sleeping Beauty platform towards point of care for rapid manufacturing genetically modified CAR-T cells	Recurrent glioblastoma

The biggest challenges for the development of next-generation CAR-T will be to improve safety and demonstrate efficacy in solid tumours. Beyond achieving solid tumour infiltration and penetration, it will be critical to decrease or better still eliminate CRS and neurotoxicity due to CAR-T. In the current landscape, biotechnology companies cannot compete with large pharmaceutical companies, and so it will be essential to expand CAR-T beyond the existing few targets and blood cancers, as this will open up the possibilities for more biotechnology companies to enter the space.

FINANCING HISTORY OF LEADING COMPANIES

Since 2012, billions of dollars have been poured into the development of CAR-T therapeutics from large pharmaceutical companies and venture capitalists eager to create strategic and financial returns from this paradigm-changing technology. The funding history of a few of the major players in the CAR-T space is reviewed below.

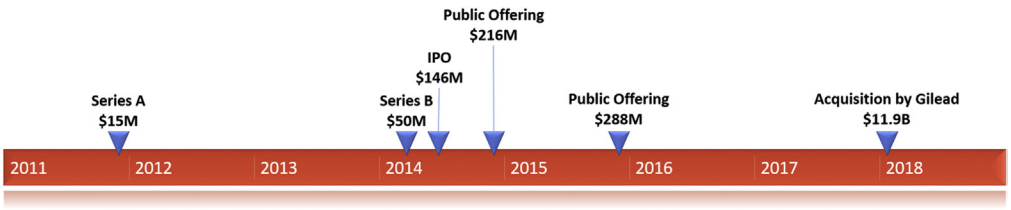
The Incumbents

Novartis

Novartis kick-started major commercial investment in CAR-T therapy when it licenced technology from the Children's Hospital of Pennsylvania in 2012 based on early clinical trial output from just a few patients, given the breakthrough clinical benefits they exhibited. That initial investment became Kymriah, the first FDA-cleared CAR-T therapy (Anonymous, 2017a). Although Novartis has not published the amount of money invested in CAR-T, former CEO Joe Jimenez stated that the cost to develop Kymriah was over $1B.

Gilead (Kite Pharma)

Kite Pharma was founded in 2009 and raised its first round of venture capital in 2011, a $15M Series A. Two years later Kite sold an additional $35M of Series A stock (Press Release, 2013a). In April 2014, Kite completed a $50M mezzanine round of financing. This was followed by an initial public offering in June 2014 that raised $146M in capital and a secondary offering in December 2014 totalling $216.4M. Kite raised an additional $287.6M on the public market in December 2015. Backed by strong clinical data, Kite was acquired by Gilead Sciences in August 2017 for $11.9 billion ($180.00 per share) (Press Release, 2017) preceding FDA approval of Yescarta in October 2017 (Anonymous, 2017b).

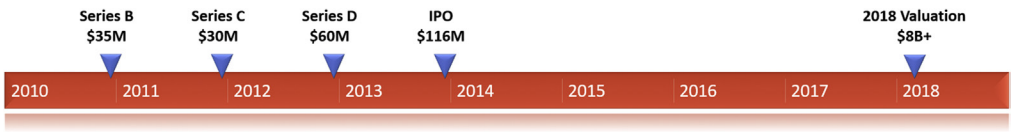


Celgene (Juno Therapeutics)

In 2017, Celgene announced its agreement to acquire Juno Therapeutics for $9B, officially marking its foray into the CAR-T therapy market. Juno launched in 2013 with $120M in Series A cash was led by investors ARCH Venture Partners and Alaska Permanent Fund and completed its Series A with an additional $56M in early 2014 (Press Release, 2014a). Later in 2014, Juno raised $134M in Series B funding and then went on to complete the year with an initial public offering in which it added $265M to its coffers, bringing the total funds raised to nearly $600M in slightly more than 12 months, an astonishing sum in the biotech industry. The acquisition of Juno by Celgene was completed in January 2018 (Press Release, 2018a).

Bluebird Bio

Bluebird bio is a major player in the CAR-T therapy space, but with a unique background to the other incumbents. Originally named Genetix Pharmaceuticals, the company was first founded in 1993 as a gene therapy company, then restarted in 2004 and capitalised with $23M in Series A funds between 2004 and 2010. That is the year when things really heated up for the company, which was rebranded as bluebird bio with an infusion of $35M in Series B financing led by Third Rock Ventures, then an additional $30M in 2011 and $60M in 2012. In 2013, bluebird bio announced its initial foray into the CAR-T space via a collaboration with Celgene, leveraging its expertise in gene therapy to genetically engineer T cells to treat cancer. The Celgene collaboration has infused additional cash into bluebird, including payments of $25M and $15M in 2015 and 2017, respectively (House, 2018). Bluebird then raised $116M at its 2013 IPO (Press Release, 2013b), and its shares have risen from $17 per share at the time of its IPO ($389M valuation) to a peak of more than $230 per share in March 2018 ($8B+ valuation). Bluebird has hundreds of millions more available in upcoming milestone payments and is also widely considered to be a major acquisition target.



Cellectis

French drugmaker Cellectis went public in 2015 with a $228M IPO to fund clinical studies of its off-the-shelf CAR-T products. Previously the company announced a strategic collaboration with Servier (and indirectly Pfizer) centred around development of its lead product candidate and additional products (Press Release, 2014b). The company raised an additional $175M through a secondary offering in 2018 (Press Release, 2018b).

Bellicum

Bellicum raised $140M in a 2014 IPO to fund CAR-TCR research and development (Press Release, 2014c).

The Rising Stars

In addition to the multibillion dollar companies firmly entrenched in the CAR-T market as of 2018, there is a plethora of emerging companies, some of which are briefly described below.

Allogene Therapeutics

Allogene was launched in 2018 by former Kite Pharma executives with $300M in Series A funding and a portfolio of CAR-T immuno-oncology assets acquired from Pfizer (Press Release, 2018c). This was followed by a $120M Series B and then a $324M IPO in October 2018 (Press Release, 2018d). The company is initially focused on off-the-shelf allogeneic CAR-T treatments.

Celularity

Celularity spun out of Celgene with $250M in capital to develop allogeneic cell therapies derived from postpartum placenta (House, 2018). Taking the assets developed by Celgene Cellular Therapeutics over 15 years (2003–18), Celularity was launched with established and unique technology and is actively pursuing CAR-T therapy as well as additional applications in immuno-oncology and other indications. The founding of Celularity is discussed in detail in another chapter of this monograph.

Carisma Therapeutics

Initially called Carma Therapeutics, Carisma raised $53M Series A in June 2018 to spin out of the University of Pennsylvania to apply CAR technology to macrophages (Press Release, 2018e).

Tmunity

Founded by Carl June and focused on using CAR-T to target solid tumours, Tmunity raised $135M in the first half of 2018 (Press Release, 2018f).

Autolus

Autolus is developing controlled T cells and raised $173M in private funding before going public with a $150M IPO in 2018 (Press Release, 2018g).

What Is Next on the Horizon?

There are many areas for improvement of the current CAR-T approaches. Two areas of focus for companies in this space are first, improving current efficacy and/or safety data in haematologic tumours that are a primary focus for current therapies and second, identifying novel targets in solid tumours to bring the benefits of these therapies to all oncology patients. The two goals have the potential to revolutionise the way that different tumours are treated in the future. Different approaches for achieving success in these areas have been summarised previously (Sadelain et al., 2017). Some of these include exploration of neoantigens, intracellular antigens, biomarkers for patient population stratification, solid tumour penetration and combination therapies.

PERSPECTIVES

A complex mix of exciting developments such as FDA approval of two CAR-T treatments in 2017, continual advances in the precision of gene editing, rapidly declining costs for gene synthesis, the success of potentially complementary immuno-oncology treatments, large mergers and acquisitions and a massive influx of capital have pushed CAR-T research and development to the forefront of the oncology world. While cellular therapy is becoming faster, cheaper and better, the 'elephant in the room' is how to make them affordable and accessible to all patients. Thus, companies that manage to lower production costs and shorten the time from blood draw to infusion without sacrificing quality will advance faster to FDA approval and create commercially successful therapies. However, this remains somewhat elusive to date with autologous-based approaches.

The other challenge in this space is the large number of companies pursuing a relatively limited (as of today) number of patients in the haematological malignancies. Effectively targeting solid tumours will open significant new opportunities for these new companies. This is the holy grain in CAR-T. Many are working to solve these fundamental challenges and, with time, these will be overcome.

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