# CHAPTER 26

# Patenting Trends in Chimeric Antigen Receptor Technologies

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## INTRODUCTION

Many current therapies for chronic and life-threatening disease are minimally effective or have immediate or chronic debilitating side effects. For example, current cancer therapies (such as radiation, chemotherapy and surgical excision) may not eradicate all cancer cells, and as a result, the cancer returns in the same or another organ. Some chemotherapies are initially effective, but the cancer cells develop a resistance rendering the treatment ineffective in the long term. Other therapies, such as radiation therapy, can damage tissues adjacent to the tumour or cause cancer itself.

Immunotherapy is an emerging therapy that utilises a patient's own immune system to fight diseases. CAR cell therapy (CAR therapy) is a promising immunotherapy that mobilises immune effector cells such as T cells to inhibit the growth of or kill diseased cells. In general, CAR therapy involves the use of immune effector cells that have been modified to specifically recognise and kill diseased cells. The technology merges the exquisite cell-targeting specificity of monoclonal antibodies with the potent cytotoxicity of immune cells. In addition, the immune cells' potential for expansion provides long-term persistence. Quickly hailed as a new breakthrough for oncology patients, many academic and private institutions began to focus on this new therapeutic modality.

As an indication of the interest in and depth of the research effort, over 1600 patents applications[1] were published in the United States, Europe, Japan, and under the Patent Cooperation Treaty (PCT) by July 2018 that contain the term 'chimeric antigen receptor' as a claim term.[2] The University of Pennsylvania and inventors under the direction

[a] The co-authors thank Peter Diez, Ph.D., Foley & Lardner, LLP, for his research contributions to this chapter.

[1] Patents are one means to monitor and measure innovation. Patents also name the innovators and institutions sponsoring the innovation and therefore are useful indicators of the competitive landscape in a technology.

[2] The application number is based on an analysis of applications in filed in the US, Europe, Japan, and under the PCT using the term "chimeric antigen receptor" in the Lens Patent database, see www.lens.org Patent Database.

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of Dr. Carl June[3] are responsible for many of these early filings, as are Immatics,[4] the Department of Health and Human Services (including some of this the early work of Zelig Eshhar),[5] City of Hope,[6] Cellectis,[7] Novartis,[8] Memorial Sloan Kettering[9] and Baylor College of Medicine and Kite Therapeutics.[10]

With this in mind and using patent filings as an indicator of innovation, in this chapter, we review and report on patenting trends and identify some interesting issued patent and pending patent applications in the field of CAR immunotherapy.[11]

## PATENTS AND THE PATENT PROCESS

A patent is a property right issued by a government to an inventor or a group of inventors. The United States Patent and Trademark Office is the US governmental authority granting this property right. The patented technology is proscribed by the claims of the document and in most instances is not commensurate in scope with the claims of the application as originally filed. A US patent allows the patent holder to prevent others from making, using, importing or selling the patented claimed technology. Not every discovery is patentable; only discoveries that meet the criteria of novelty,[12] nonobviousness[13] and utility[14] are patentable. The novelty requirement ensures that the discovery is 'new' – that is, that the discovery is not a copy of an existing or prior discovery or invention. The nonobviousness requirement ensures that the discovery or invention is a significant advancement over prior known discoveries. Whether a proposed patent claim is novel and nonobvious is determined by a search and review of the 'prior art' in the field, as determined by the patent examiner. The utility requirement ensures that the invention is useful and is of a class for which the patent office is authorised to grant patents. Because of these criteria, every US patent claims and covers a unique technological advancement.

[3] See www.lens.org Patent Database. Dr. June is the director of translational research at the Abramson Cancer Center at the University of Pennsylvania (Philadelphia, PA, USA). His work led to the commercialization of tisagenlecleucel or Kymriah, an FDA-approved CD19-directed genetically modified autologous T cell immunotherapy.

[4] Immatics Biotechnologies GmbH (Tuebingen, Germany) and Immatics US, Inc. (Houston, TX, USA), see immatics.com. The information was obtained from the Lens Patent database, see www.lens.org.

[5] See www.lens.org Patent Database. Dr. Eshhar worked on the early development of the CAR concept – publishing works on the idea of a modified T cell receptor or "T-body" in the early 1990s. See, e.g., Eshhar et al. "The T-body approach" potential for cancer immunotherapy. Springer Seminars in Immunopathology 1996;18(2):199–209.

[6] City of Hope National Medical Center (Duarte, CA, USA); see www.cityofhope.org.

[7] Cellectis, Inc (New York, NY, USA); see www.cellectis.com.

[8] Also known as Novartis Pharmaceuticals Corporation (Basel, Switzerland); see www.pharma.us.novartis.com.

[9] Memorial Sloan Kettering Cancer Center (New York, NY, USA); see www.mskcc.org.

[10] On October 3, 2017, Gilead Sciences, Inc. (Foster City, CA, USA) announced that it had acquired Kite Pharma Inc. (Los Angeles, CA, USA); www.kitepharma.com.

[11] The reported information was gleaned from the United States Patent and Trademark Database, Google Patent, Total Patent, and Lens.Org.

[12] See 35 U.S.C. § 102.

[13] See 35 U.S.C. § 103.

[14] See 35 U.S.C. § 101.

Claims have varying breadth, and the value of the claim is linked to its breadth. Broader claims cast a wider exclusionary net, while narrower claims are more targeted with respect to exclusionary effect. It is not unusual for patents issued early in a field are broader as there is less prior art to be distinguished. As a field matures and the technology evolves, the number of prior art documents multiplies, and as a result, the scope of issued patent claims narrow or become more specific.

Patents are issued on classes of technology: compositions, methods of using the compositions and methods of making the compositions. Patent claims to compositions are considered of higher value because with the composition patent claim, one can also exclude all uses of the technology. In contrast, method of use claims is limited to that use and may infringe any pre-existing patent on the composition. Claims to method for making compositions are valuable if the process is the only means by which the technology can be made or if the patent is directed to a key intermediate process. The early Cohen and Boyer patent, U.S. Patent No. 4,237,224,[15] is an example of a valuable process patent because it covered methods to insert DNA into cells, a key intermediate process step in the early days of genetic engineering.

## CAR TECHNOLOGY

Initial CARs – also referred to as T-bodies – were fusions of an antibody molecule and a T cell (and so named CAR-T cells) receptor subunit and were used on T cells to mediate Major Histocompatibility Complex (MHC)-independent T cell activation. Thus CAR technology is built on an immune cell engineered by the incorporation of a targeting molecule, typically a fragment of a monoclonal antibody (mAb) designed to target the diseased cell.[16] To generate the CARs, immune cells, such as T cells and natural killer cells (NK-cells), are harvested from the patient to be treated or an allogeneic donor activated in vitro and genetically engineered to express a CAR on their surface. After genetic modification, these cells are expanded ex vivo and infused into patients for treatment.

CAR-expressing immune cells are MHC-independent and, thus, were initially proposed for use in oncotherapy, given the tendency of certain tumours to downregulate MHC expression.

[15] Cohen and Boyer, U.S. Patent No. 4,237,224, for "Process for producing biologically functional molecular chimeras, issued on December 2, 1980. The technology covered by the '224 patent and related patent filings were licensed to 468 companies. See labiotech.eu/making-dollars-out-of-the-recombinant-dna-biotech-patents/. The original Cohen and Boyer patents have now expired.

[16] See Eshhar, et al. U.S. Patent No. 7,741,465 for "Chimeric receptor genes and cells transformed herewith," issued June 22, 2010 and Eshhar et al., U.S. Patent No. 8,211,422 for "Chimeric receptor genes and cells transformed herewith," issued July 3, 2012.

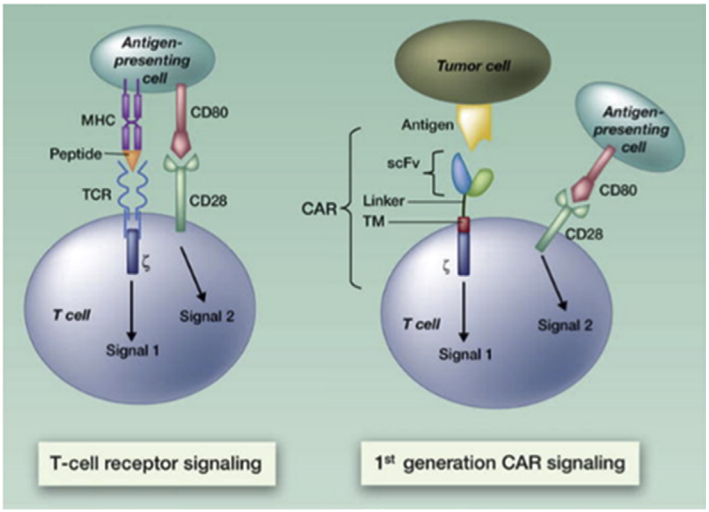


**Figure 26.1** First-generation CAR-T technology. *(Figure adapted from Clin Cancer Res 2012;18(10):2780–90.)*

## First-Generation CARs

The structures have since evolved to most commonly incorporate a single-chain variable fragment (scFv) derived from a mAb plus the signalling motif from the T Cell Receptor (TCR) ζ chain. This canonical structure is referred to herein as the 'first-generation' CAR depicted in below (Fig. 26.1).

U.S. Patent No. 7,741,465[17] is an example of a patent claiming a first-generation CAR. The representative claim is the broadest in the issued patent and covers a DNA construct used to generate a CAR cell. The claim recites:

> *A chimeric DNA comprising: a first DNA segment encoding a scFv domain comprising a light immunoglobulin chain (VL) linked to a heavy immunoglobulin chain (VH) of a specific antibody by a flexible linker, and a second DNA segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein, wherein said endogenous protein is expressed on the surface of lymphocytes and triggers the activation and/or proliferation of said lymphocytes, which chimeric DNA, upon transfection to lymphocytes, expresses both said scFv domain and said domains of said endogenous protein in one single, continuous chain on the surface of the transfected lymphocytes such that the transfected lymphocytes are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFv domain binds to its antigen.*

[17] Eshhar Z, et al. U.S. Patent No. 7,741,464 for "Chimeric receptor genes and cells transformed therewith," issued on June 22, 2010, with an earliest filing date of July 2, 1993. The patent nominally assigned to Cabaret Biotech Ltd. (Rehovot, Israel) and The Health & Human Services Government of the United States.

The '465 Patent was reexamined twice at the US Patent Office[18] in a 'reexamination proceeding'. After the reexamination proceedings, the initially granted claims were changed or amended from their initial issuance.[19] While initially very broad in that the representative claim does not require specificity with respect to the scFV domain, its binding partner or the activation domain, the reexamined claims now limit the second DNA segment to be derived from CD28 and CD8. A representative replacement claim resulting from the second reexamination recites:

> *A chimeric DNA comprising: a first DNA segment encoding a scFv comprising a VL linked to a VH of a specific antibody by a flexible linker, and a second DNA segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein, wherein said endogenous protein is expressed on the surface of lymphocytes and triggers the activation and/or proliferation of said lymphocytes, and wherein said endogenous protein is CD28, which chimeric DNA, upon transfection to lymphocytes, expresses both said scFv domain and said domains of said endogenous protein in one single, continuous chain on the surface of the transfected lymphocytes such that the transfected lymphocytes are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFv domain binds to its antigen.*

There is another analogous replacement claim directed to CD8 rather than CD28. The reexamined issued patent is linked to YESCARTA (axicabtagene ciloleucel), an Food and Drug Administration (FDA)-approved CAR therapy.

Another exemplary early first-generation CAR patent is US Patent No. 6,319,494,[20] which relates to the use of a CAR construct (scFv, transmembrane domain and a zeta domain)-containing cell to treat 'a viral disease or a malignancy in a mammal'. A representative claim recites:

> *A method for treating a viral disease or a malignancy in a mammal, wherein cells of said mammal express viral or tumour antigens, comprising introducing modified T cells into said mammal, wherein said modified T cells comprise a chimeric DNA encoding a membrane-bound protein comprising in the N-terminal to C-terminal direction: a single chain antibody domain that binds specifically to said viral or tumour antigen, a transmembrane domain and a cytoplasmic signal-transducing domain obtained from zeta, wherein when said single chain antibody domain binds to said viral or tumour antigen on said cell, said modified T cells kill the cells expressing said viral or tumour antigen.*

These claims are noteworthy since the malignancy terminology may encompass a variety of oncological embodiments, and the description of the CAR is very generic in that it is not limited to any specific antigen or transmembrane domain. Thus, '494 Patent is an example of a broad method of use patent.

[18] A reexamination is a process whereby a third party or inventor can have a patent reexamined by a patent examiner to verify that the subject matter it claims is indeed patentable. To have a patent reexamined, an interested party must submit prior art that raises a "substantial new question of patentability." It is a means by which third parties can challenge patent validity at the USPTO.

[19] See Reexamination Request Nos. 90/013,630 and 90/013,790.

[20] Capon, et al. U.S. Patent No. 6,319,494 for "Chimeric Chains for Receptor-Associated Signal Transduction Pathways," issued on November 20, 2001, and nominally assigned to Ani Pharmaceuticals, Inc. (Baudette, MN, USA).

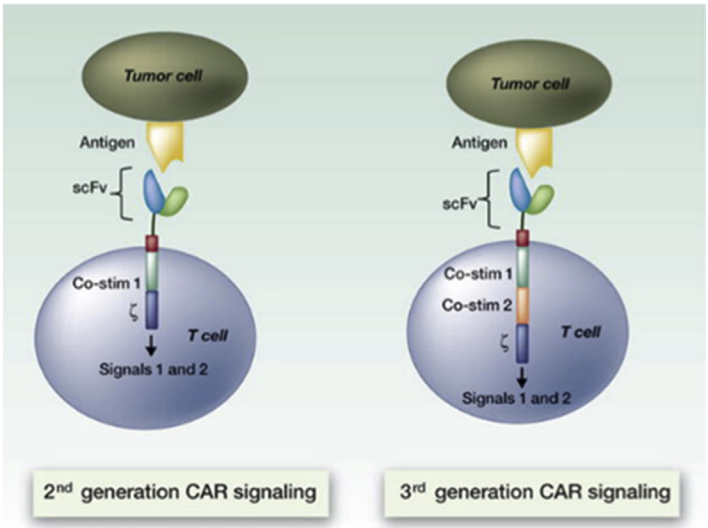


**Figure 26.2** Second- and third-generation CAR-T technology. *(Figure adapted from Clin Cancer Res 2012;18(10):2780–90.)*

## Second-Generation CARs

'Second-generation' CARs offered an improvement over the canonical CAR structure by adding costimulatory activating motifs from costimulatory molecules (e.g., CD28, 4-1BB and/or OX-40) depicted in Fig. 26.2. Incorporating these costimulatory molecules enhanced proliferation, cytotoxicity and persistence of the CAR-expressing cells in vivo. Further innovations involved the incorporation of more than one of these motifs, optimising them in combination with a particular targeting agent or a specific antibody or antibody derivative and/or modifying the CAR-expressing cells to express additional factors that enhance therapeutic efficacy, for example, cytokines or enzymes depicted in Fig. 26.2.

Broad claims such as those nominally granted to Sloan Kettering Institute for Cancer Research in U.S. Patent No. 7,446,190[21] are exemplary of constructs comprising costimulatory molecules. The '190 Patent claims feature an early priority date of May 28, 2002, and relate to a construct comprising a binding element, a zeta chain portion and a particular CD28 transmembrane domain sequence. An exemplary claim recites:

> *A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising (1) a zeta chain portion comprising the intracellular domain of human CD3 zeta chain, (2) a costimulatory signalling region and (3) a binding element that specifically interacts with a selected target, wherein the costimulatory signalling region comprises the amino acid sequence encoded by SEQ ID NO: 6.*[22]

[21] Sadelain, et al. U.S. Patent No. 7,446,190 for "Nucleic Acids Encoding Chimeric T Cell Receptors," issued on November 4, 2008 and is nominally assigned to Sloan-Kettering Institute for Cancer Research.

[22] SEQ ID NO: 6 is described in the patent to the costimulatory signaling element from human CD28, including transmembrane and extracellular portions.

The issued claims are broad because they are not restricted to a specific antibody sequence or a specific zeta chain sequence. Despite the broad scope, the patent claims were upheld as valid by the United States Patent and Trademark Appeal Board in an *inter partes* review proceeding[23] initiated by Kite Pharma Inc. The validity decision was affirmed in late 2017 by the US Court of Appeals for the Federal Circuit.[24]

Another noteworthy second-generation CAR patent application was filed by The City of Hope in 2008. The application published as US Patent Publication No. 2012/0148552,[25] and in general claimed a tumour-specific CAR, which comprises a specific recognition element, an optional support or linker region, a transmembrane region, the signalling domain of CD3 zeta chain and the signalling domain of at least one additional costimulatory signalling receptor, which is selected from the group consisting of CD28, 4-1BB and OX-40. The application issued on September 2, 2014, as U.S. Patent No. 8,822,647. Challenged by prior art during examination, the ultimately issued claims were limited to specific amino acid CAR constructs:

*A CAR comprising the amino acid sequence of SEQ ID NO: 54.*

Thus, this patent does not dominate all second-generation CAR constructs due to prior art concerns raised during examination, and the claims are limited by the claim elements 'amino acid sequence of SEQ ID NO: 54'.

U.S. Patent No. 8,465,743[26] was filed by the U.S. government after the '647 Patent, but it issued in June of 2013. The invention was initially claimed as a CAR antigen-binding domain of a KDR-1121 or DC101 antibody, an extracellular hinge domain, a T cell-receptor transmembrane domain and an intracellular T cell receptor signalling domain. A representative claim recited '[a] CAR comprising (1) an antigen-binding domain of a KDR-1121 or DC101 antibody wherein the antigen-binding domain comprises an amino acid sequence comprising SEQ ID NO: 1 or 2; (2) an amino acid

[23] An *inter partes* review is used to challenge the patentability of one or more claims in a U.S. patent only on a ground that could be raised under 35 U.S.C. §§ 102 or 103, and only on the basis of prior art consisting of patents or printed publications. The procedure is conducted by the Patent Trial and Appeal Board (PTAB). The *inter partes* review process allows the PTAB to hold a hearing with the respective parties and make its decision on the validity of the issued patent.

[24] The decision is reported at *Kite Pharma, Inc. v. Sloan Kettering Institute for Cancer Research*, Case IPR2015-01719 (Fed. Cir. 2017).

[25] Jensen, U.S. Publication No. 2012/0148552 titled "Method and Compositions Using a Chimeric Antigen Receptor for Enhanced Anti-Tumor Effector Functioning of T Cells," which issued as U.S. Patent No. 8,227,647 on September 2, 2014.

[26] Rosenberg, et al. U.S. Patent No. 8,465,743 for "Anti-Vascular Endothelial Growth Factor Receptor-2 Chimeric Antigen Receptors and Use of Same for the Treatment of Cancer," issued on June 18, 2013, and is nominally assigned to The United States of America, as Represented by the Secretary, Department of Health and Human Services.

sequence comprising SEQ ID NO: 3, 4 or 7; and (3) an amino acid sequence comprising SEQ ID NO: 5, 6, 8 or 9'.[27]

However, during examination, the claim was ultimately restricted to the antigen-binding domain and the specific sequence of the extracellular hinge domain, transmembrane domain and intracellular hinge domain.[28] Thus CARs that utilise an antigen-binding domain other than those of the KDR-1121 or DC101 antibodies would not fall within the scope of this patent even if they contained the remaining claim elements of an extracellular hinge domain, a T cell receptor transmembrane domain and an intracellular T cell receptor signalling domain.

The Regents of the University of California was awarded a broad second-generation CAR patent – U.S. Patent No. 9,587,020[29] in March of 2017, directed to a T lymphocyte, comprising an expression vector, which includes a nucleic acid that encodes for two polypeptides of a CAR. The first polypeptide includes an antigen-binding domain, which includes a scFV, a transmembrane domain and a first member of a dimerisation pair. The second polypeptide includes a transmembrane domain, a second member of the dimerisation pair and an intracellular signalling domain. The first and second polypeptides comprise a costimulatory polypeptide between the transmembrane domain and the member of the dimerisation pair, the costimulatory polypeptide is 4-1BB, CD28 or OX40. What is notable about this patent is the lack of specificity around the antigen-binding domain. As such, any construct with any antigen-binding domain may fall within the scope of this patent, provided the additional generic elements are present.

Memorial Sloan Kettering Cancer Center was awarded US Patent No. 9,220,728[30] in December of 2015. The patent claims are directed to treating a neoplasia by administering to the subject an effective amount of a T cell comprising (1) two exogenous costimulatory ligands that are 4-1BBL and CD80 and (2) a receptor that binds an antigen. The '728 Patent is not limited to treatment with a specific antigen-binding receptor. Specificity is defined by the use of the two costimulatory ligands. Thus any treatment method using a CAR with the two costimulatory ligands and an antigen-binding

[27] Rosenberg, et al. U.S. Patent No. 8,465,743 for "Anti-Vascular Endothelial Growth Factor Receptor-2 Chimeric Antigen Receptors and Use of Same for the Treatment of Cancer," issued on June 18, 2013, and is nominally assigned to The United States of America, as Represented by the Secretary, Department of Health and Human Services.

[28] A representative claim recites: "a chimeric antigen receptor (CAR) comprising: (a) an antigen binding domain of a KDR-1121 or DC101 antibody wherein the antigen binding domain comprises an amino acid sequence comprising SEQ ID NO: 1 or 2; (b) an amino acid sequence comprising SEQ ID NO: 3, 4, or 7; and (c) an amino acid sequence comprising SEQ ID NO: 5, 6, 8, or 9."

[29] Wu, et al. Chimeric Antigen Receptor and Methods of Use Thereof, issued on March 7, 2017, and nominally assigned to The Regents of the University of California.

[30] Sadelain, et al. U.S. Patent No. 9,220,728 for "Constitutive expression of costimulatory ligands on adoptively transferred T lymphocytes" issued on December 29, 2015, and is nominally assigned to Memorial Sloan-Kettering Cancer Center.

domain may be within the scope of this patent. Notably, this is a 'use' patent only; and therefore the patent does not cover the use of the construct for therapies beyond oncology.

Early stage filings such as the aforementioned first- and second-generation CAR filings benefitted from the lack of published literature and have resulted in generally broad patent grants potentially covering later generations and optimisations of CAR cells. Thus innovators should approach the space with caution as to freedom to operate, assessing both the coverage and expiry dates of patents from the early stages of CAR development since later generation CAR-expressing cells may contain all the components of the first- or second-generation CAR cells with additional elements.

## Third- and Fourth-Generation CARs

Despite offering the potential to overcome the challenges posed by MHC-dependent activation of immune cells, the general structure of first- and second-generation CAR-expressing cells presented therapeutic limitations. First, if the targeted antigen is also expressed on normal cells, CAR-expressing cells run the risk of off-target effects, that is, targeting and killing off too many normal cells. Second, given tumour heterogeneity, cell antigens or surface markers targeted by the CAR may not be consistently expressed on tumours, meaning the CAR cells may be minimally effective or useless. Third, rapid lysis of diseased cells by CAR-expressing cells may result in cytokine storming or other adverse immune effects. Future research and patenting will likely address this toxic side effect.

A variety of innovations have been proposed and tested in an effort to address the limitations of the earlier generations of CAR-expressing cells and to facilitate regulatory approval, that is, by enhancing safety and efficacy of CAR-expressing cells.

### *'Switches'*

To ensure specificity of expression and tight control of the duration of CAR-expressing cell activity, CAR constructs have been designed with 'switches'. A common approach is the inclusion of a 'suicide switch', such as inducible Cas9 ('iCas9'), allowing for lysis of the CAR-expressing cell once it has served its function. Alternatively, or in addition, CAR constructs may include tissue-specific promoters or other regulatory elements that allow for expression or suppression when subjected to particular stimuli.

US Patent No. 9,624,276,[31] assigned to The California Institute for Biomedical Research, is directed to kits containing both a switch and a CAR-effector cell. The switch includes a peptidic antigen comprising a yeast transcription factor GCN4 that binds to and activates the CAR-effector cell by binding to the CAR. The monomeric

[31] Young, et al. U.S. Patent No. 9,624,276 for "Peptidic Chimeric Antigen Receptor T Cell Switches and Uses Thereof," issued on April 18, 2017, and assigned to The California Institute for Biomedical Research (La Jolla, CA, USA).

structure of the switch, in this case, was key to patentability over the cited art, in which the switch was dimeric. A representative claim recites:

> *A kit comprising (1) a CAR-effector cell switch comprising: (a) a peptidic antigen comprising a yeast transcription factor GCN4 peptide that binds to and activates an anti-GCN4 CAR on an effector cell; said GCN4 peptide comprising a portion of SEQ ID NO: 2 that is at least 12 amino acids and (b) a targeting moiety that binds a cell surface molecule on a target cell and (2) a CAR-effector cell comprising an anti-GNC4 CAR that binds to the peptidic antigen of the CAR-effector cell switch.*

Currently, Novartis Institutes for BioMedical Research, Inc. is pursuing claims to regulatable CARs including two switch domains in US Patent Publication No. 2016/0311907.[32] The switch domains comprise an FKBP-FRB[33]-based switch.

Another interesting pending patent application that includes a switch was filed by Fate Therapeutics, Inc. In US Patent Publication No. 2018/01557171,[34] Fate is pursuing claims to induced pluripotent stem cells that express a T cell receptor, a CAR and one or more genes expressing a safety switch protein (a TCR promoter) that controls the expression of the CAR, effectively controlling activity through the cells endogenous TCR promotor.

Thus the specific structure, binding targets and components of the cell incorporating the switch are important features limiting the scope of protection obtained or being pursued in existing patents or applications directed to CAR-T cell/switch technology. However, innovators looking to use these features in CAR research should be aware that such features may not only be covered in the CAR space but also in broad patents relating more generally to these 'switch' elements for use in recombinant expression constructs.

### *Cotherapies*

A variety of CAR cotherapies have been proposed. In some cases, regimens involving sequential or simultaneous administration of two different CAR-expressing cells or a multiple CAR-expressing cell have been proposed to address tumour heterogeneity. Furthermore, the use of known agents targeting the disease of interest, for example, chemotherapeutic drugs or antibodies for cancer, has been proposed to reduce the disease burden to be addressed by the CAR-expressing cells. Additional cotherapies have been proposed to reduce the immunogenic effects of particular CAR-expressing cells. The CAR constructs can be further engineered to have positive or negative feedback 'switches' based on the effect of the particular cotherapy.

[32] Brogdon, et al. U.S. Patent Publication No. 2016/0311907 for "Regulatable Chimeric Antigen Receptor."

[33] FKBP-FRB is described in the patent application as a switch domain comprising an FRB binding fragment or analog of FKBP and a switch domain comprising an FKBP binding fragment or analog of FRB, and the FKBP binding fragment or analog of FRB comprises one or more mutations that enhances the formation of a complex between an FKBP switch domain, an FRB switch domain, and the dimerization molecule, or a mutation described in application.

[34] Noble, et al. U.S. Patent Publication No. 2018/01557171 for "Genomic Engineering of Pluripotent Cells."

An example of a cotherapeutic approach is claimed in US Patent No. 9,855,298,[35] assigned to Kite Pharma Inc. and the National Institutes for Health and directed to a method of treating a patient having a tumour comprising administering cyclophosphamide, fludarabine and CAR-T cells to the patient.[36] The cotherapeutic treatment improves the efficacy of the CAR-T therapy. The method is limited to specific dose ranges for the three components administered over a specific period of treatment; these parameters were required to overcome novelty and obviousness rejections during prosecution. A representative claim recites:

> *A method of treating a patient having a tumour comprising (1) administering to the patient a dose of cyclophosphamide at about 500 mg/m$^2$ day to about 600 mg/m$^2$ day and a dose of fludarabine at about 30 mg/m$^2$ day and (2) administering to the patient a therapeutically effective amount of from about $1 \times 10^6$ to about $5 \times 10^6$ engineered CAR-T cells/kg; wherein the dose of cyclophosphamide is administered daily for 3 days.*

US Patent No. 9,688,760,[37] nominally assigned to Amgen Research (Munich) GmbH, is directed to a method of ameliorating, treating or preventing a clinical adverse event in a patient caused by administering blinatumomab to the patient, the method comprising administering to the patient an effective amount of pentosane polysulfate or a pharmaceutically acceptable salt thereof, minocycline, or natalizumab, and administering genetically engineered CAR-T cells. During prosecution of the patent, the scope of the cotherapies to minocycline or natalizumab instead of a generic CD3-binding compound was included to overcome an enablement rejection.

Due to the scope of protection of existing patents requiring specified compounds coadministered with CAR-expressing cells or specific dosages of these compounds, there exists opportunity to uncover and use novel combinations of CAR-expressing cells with various therapeutics for the treatment of disease. However, from a freedom to operate standpoint, innovators should keep in mind that patents directed to the drug element of the drug/CAR cell combination may have dependent claims drafted broadly to cover combination products and may require actual data to establish the utility of the claimed cotherapy.

[35] Bot, et al. U.S. Patent No. 9,855,298 for "Methods of Conditioning Patients for T Cell Therapy, issued on January 2, 2018," and assigned to Kite Pharma, Inc. and The United States of America, as Represented by the Secretary, Department of Health and Human Services.

[36] Cyclophosphamide is an immunosuppressant medication used in the treatment of cancers. Fludarabine is a chemotherapeutic used in the treatment of cancers.

[37] Kufer, et al. U.S. Patent No. 9,688,760 for "Anti-Leukocyte Adhesion for the Mitigation of Potential Adverse Events caused by CD3-Specific Binding Domains," issued on June 27, 2017, and assigned to Amgen Research (Munich) GmbH (Munich, Germany).

## GENETIC ENGINEERING AND 'UNIVERSAL' CAR-EXPRESSING CELLS

The process of generating autologous CAR-expressing cells is relatively cumbersome and expensive, requiring extraction of cells from a patient, subsequent transfection, activation and reintroduction into the patient. The multistep process, requiring the use of autologous cells, limits administration of the therapy to an approved hospital setting and increases the cost of the therapy as the technology is not leveraged across multiple providers. Recent CAR technologies aim to remove the need for autologous transfer and reduce its cost.

One approach applies current gene-editing technologies to the CAR cell. An interesting example of the application of new gene-editing technologies to a CAR is US Patent No. 9,890,393,[38] assigned to Cellectis. The '393 Patent claims a method of introducing RNA encoding an endonuclease into T Cells to create genetically modified T cells, while a further dependent claim comprises introducing a CAR into the genetically modified T cell. The patent discloses that the claimed methods allow for the generation of allogeneic T cells obtainable from donors to make them suitable for immunotherapy purposes using RNA-guided endonucleases such as Cas9/CRISPR. The patent also claims that the methods allow the precise modification of the genome of T cells by inactivating or replacing genes involved in MHC recognition and/or immune checkpoint proteins. The methods also provide specific relevant targets sequences in the genome for the guide RNA to inactivate components of TCR without provoking death of the cells.

This 'universal' approach aims to address each of the drawbacks of CAR-expressing cells by generating a CAR backbone that can be modified to be target- and patient-specific without having to specifically modify the cells. Rather than include the antigen-targeting domain in the CAR itself, the 'universal' approach incorporates a domain that binds to an exogenous ligand. When an antigen-targeting domain, such as an antibody or antibody derivative is bound to the ligand and introduced to the CAR-expressing cells, the ligand binds the domain on the 'universal' CAR. Thus the specificity of the CAR can be altered based on the needs of the patient. This modular system also has the potential to be an 'off-the-shelf' option for CAR-expressing cells.

## NONCANCER TARGETS

Recently, there has been an effort to apply the CAR approach to other diseases involving immune dysregulation or dysfunction and autoimmune disorders. One approach used CAR-T cells to target adipocytes as a treatment for obesity. US Patent No. 9,163,258[39] to Riddell is directed to a method of eliminating adipocytes in a subject,

[38] Duchateu, et al. U.S. Patent No. 9,890,393 for "Methods for engineering T cells for immunotherapy by using RNA-guided CAS nuclease system," issued on February 13, 2018.

[39] Riddell, et al. U.S. Patent No. 9,163,258 for "Method for the treatment of obesity," issued October 20, 2015.

comprising administering a therapeutically effective amount of a composition comprising isolated T lymphocytes modified to express a target-specific CAR, wherein the target is a cell surface antigen preferentially expressed on an adipocyte. The term 'preferentially' was required to overcome an enablement rejection. Adipocytes express a variety of antigens found in other cells, thus without this term, the scope would extend to targeting cells beyond adipocytes for which the application was not enabled. With regard to targeting adipocytes, this claim is particularly broad.

Immunomedics, Inc. has filed a patent application[40] that applies the CAR approach to treat disorders other than cancer, such as autoimmune disorders. The approach is similar to targeting cancer cells but requires predosing the patient with an unconjugated antibody against a disease-associated antigen and then administering a CAR that contains a targeting antibody fragment against the same antigen. The patent filing asserts that this approach prevents the development of cytokine storm.

IFM Therapeutics, Inc. filed a patent application[41] that uses a CAR approach to treat infectious disease by increasing the resistance of a T cell (such as a CAR-T cell) or an innate immune cell to at least one immunosuppressive cytokine. The T cell or the innate immune cell is cultured in the presence of an NLRP3 activator.

Opportunities exist for targeting other cell types based on their unique surface antigen profiles and acquiring a broad protection scope for CAR-T cells targeting other cell types.

## PERSPECTIVES: ADVICE FOR INNOVATORS

While there has been a lot of patenting in the CAR space, innovation and patenting will continue. Those wishing to protect innovation by the use of any patent system, US or other patent office, be aware of the challenges that face patent procurement.

In light of the explosive research and patenting effort to date, the biggest challenge will continue to be prior art – which can be an inventor's own prior work and the work of others in the field. As noted previously, a patent is issued only after the inventor has established that the invention as defined by the claims is novel, useful and nonobvious. The United States Patent and Trademark Office (USPTO) will also evaluate the patent description to determine if it was sufficiently detailed to enable a skilled researcher to reproduce the drugs or compositions claimed in the application, and where a therapy has been claimed, sufficient information to reproduce the therapy. While the USPTO may grant a patent when the patent description does not provide evidence of actual use of

[40] See Change, et al. US Patent Application No. 2016/0361360 for "Disease therapy with chimeric antigen receptor (CAR) constructs and T cells (CAR-T) or NK cells (CAR-NK) expressing CAR contructs," filed December 15, 2016, with a priority date of July 17, 2015.

[41] See Glick, et all. US Patent Application No. 2017/0056448 for "Immune cells having increased immunity or resistance to an immunosuppressive cytokine and use of the same," filed March 2, 2017, and having a priority date of September 1, 2015.

the claimed technology, where there is a reasonable question as to whether the therapy will work for its intended purpose, patent applicants may be required to file evidence of successful use, or likelihood of successful use, by the USPTO. This evidence can be generated after the original patent filing and typically is not required to be actual human clinical results.[42]

This review has shown that there are a number of early patent filings that feature broad claims. A closer look at this patent literature shows that these early patent filings also 'claim the field', that id, featuring laundry lists of diseases and targets for which CAR therapy might be relevant. This is especially true if one is seeking to apply the use of a known antibody or antibody fragment to a CAR approach. In that situation, if the other features of the CAR are known, it will be challenging to merely substitute a new antibody fragment into a CAR construct and establish nonobviousness and perhaps, novelty. This is compounded by the fact that many of the early patent filings contain prophetic examples speculating on how CAR therapies might be tested for efficacy and utility with minimal supporting data. While these patent applications ultimately may not issue as a patent, they can serve as a wall of prior art over that inventors must overcome before being granted a patent. This challenge is compounded by the wealth of research publications in the CAR cell space also provides ample fodder for a patent office to challenge a patent claim. Conversely, if an inventor has developed a new antibody with exceptional specificity to a target antigen, consideration should be given to whether an appropriate fragment of that antibody would also be suitable for CAR therapy.

Recent changes in case law also offer new hurdles with respect to the requirements of written description (conveying possession of the invention) and enablement (conveying how to make and use the invention). Whereas in the past, patent applicants could rely on disclosures of a novel antigen to claim a binding domain thereto, this so-called 'antibody exception' has been overruled by the US Court of Appeals for the Federal Circuit's recent decision in *Amgen Inc. v. Sanofi.*,[43] 872 F.3d 1367 (Fed. Cir. 2017). In accordance with this decision, the disclosure of a novel antigen no longer provides sufficient written description to support a claim to the corresponding antibody. Rather, the patent application must provide a representative number of antibodies or derivatives to support the broad claim to the binding domain. While on one hand, this change may limit an inventor's claims to particular antibodies described by very specific sequences, on the other, it may conversely open the door to challenges against the broader patents granted under the more favorable written description standard.

The general trend in the United States is for more specificity in issued patent claims, for example, with respect to one or more elements of the construct or platform patents. To determine what scope of patent to pursue, innovators are encouraged to

[42] The USPTO will accept evidence of successful use in a scientifically valid animal model.
[43] *Amgen Inc. v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017).

(1) characterise whether their findings relate to a new target or a new construct, (2) determine what is already known relative to the proposed innovation, (3) determine what the data may support and (4) balance the desired scope of protection with what protection can actually be expected in view of the prior art and supporting data. As a general rule of thumb, the more generalisable the data, the better chance of getting broad claims absent prior disclosure. To support more specific claims in a crowded prior art field, data showing 'unexpected results' relating to the particular innovative combination is helpful. In such cases, the unexpected results should be commensurate in scope with the claims being pursued. What is more, a strong rationale for why the results are 'synergistic' rather than 'additive' is helpful to push these cases forward.

CAR is an exciting field that is providing great hope and promise to many patients. Patents support this innovation by describing in detail the technology so that others can benefit from the work of the inventors and subsequently apply the work after the patent has expired while providing a time-limited monopoly to preserve incentives to innovate and to invest in innovation.

## DISCLAIMER