Pitfalls in patenting academic CAR-T cells therapy

Abstract

Introduction: Emerging immunotherapies are pushing the boundaries of cancer treatment, with chimeric antigen receptor (CAR)-T cell therapy being one of the most advanced. Due to the increasingly crowded CAR-T cell field, patenting and protecting the intellectual property of these CAR-T cells implies a good knowledge of the legal landscape.

Areas covered: The present manuscript focuses on the challenges regarding the patenting process of CAR-T technology, beginning with a description of the main characteristics of CAR-T cells and their functionalities, continuing with the legal landscape applicable to patenting processes, and concluding by presenting the potential strategies to overcome the impediments that can appear when trying to patent CAR-T cells. It is meant to offer insights for those who are exploring possible patenting options in CAR-T cells territory. PubMed and Patenscope databases were used for patent and literature searching (2013-2023).

Expert opinion: There is no one-size-fits-all solution in this matter and the medical evolution of this therapy will certainly bring out even more challenges. Comprehensive knowledge of the intellectual property, exposure to potential litigation, growing competition, and the high price of therapy, are strikingly relevant in the broader landscape. Future endeavors would be to take steps towards the harmonization of the CAR-T patenting procedure.

Keywords: Chimeric antigen receptor (CAR)-T cells, CAR-T cells, immunotherapy, patents, intellectual property

1. Background

The therapies that use the patient's own immune system to attack tumors, also known as immunotherapies, have emerged as a new way to treat cancer. One of the rapidly emerging immunotherapy approaches to treating cancer is adoptive cell transfer, the most advanced of which is chimeric antigen receptor (CAR)-T cell therapy (1). These types of immunotherapies work by using the ability of the host's immune system to recognize tumor antigens and effectively eradicate tumor cells (2).

An exciting new option for immunotherapy is represented by neoantigens (3). Within cancer cells there are somatic mutations that generate peptides, which are actually the neoantigens, and as such are not found in normal tissues and cells. Neoantigens are mostly tumor- and patient-specific, making them special sites of attack. In this way, the prospect of the severe toxic off-target effects which could result in damage to the normal tissues and cells is, somehow, confined (4).

In the field of hemato-oncology, which includes these immunotherapies, patents play an important part in expanding the frontier of translational biomedical research. The work that is necessary to successfully finalize a patent application can take a considerable amount of time, and even more time for the patent to be granted.

Patenting and protecting the intellectual property of CAR-T cells implies a good understanding of the legal landscape and the ability to overcome the hurdles that have been reported so far, as well as proper technical preparation of the invention. Until now, very high profits were reported for the use of these therapies and they still play an important role in expanding previous predictions. With the adoptive T cell market not only being profitable but also highly competitive, pioneers in CAR-T therapy should consider securing their intellectual property (IP) rights quite early during the development stages of these therapies, while also considering carefully the possible impact of other parties' IP (5).

Effective patent strategy requires attentive planning, especially in consideration of the increasingly crowded CAR-T field (6).

The present manuscript focuses on the challenges and possible impediments regarding the entire patenting process of CAR-T technology, beginning with a drawing of the main characteristics of CAR-T cells and their functionalities, continuing with the legal landscape applicable to patenting processes, and concluding by presenting the potential strategies to overcome the impediments that can appear when trying to patent CAR-T cells.

2. Short history of CAR-T cells emergence and patenting

2.1. Short history of CAR-T cells emergence

The remarkable advances in cancer treatment in recent times have seen a shift from a 'one-size-fits-all' approach en route to the development of technologies that are strengthening a patient's immune system against cancer cells.

Thirty years have passed since CARs were first described with one of the first published papers regarding the possible application of this type of immunotherapy in B-cell lymphoblastic leukemia and lymphomas in 2007 (7). Only in the last decade has biomedical research focused on the potential of CAR-T cells to create medicines, with ever-increasing clinical trials in progress both in hematologic malignancies and solid tumors (8,9). Some CAR-T treatments have been approved in the US: tisagenlecleucel was first to receive US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approbation in 2017 (10), followed a few months later by axicabtagene ciloleucel (11) and FDA approbation for brexucabtagene autoleucel at the end of July 2020 (12). Idecabtagene vicleucel (13) and lisocabtagene maraleucel (8) are two newer CAR-T cell therapy approved in 2021, respectively 2022. These types of CAR-T therapies are called "autologous" therapies, which work by using the patient's own T cells. The entire process takes several weeks and is quite expensive (14). New approaches to diseases require new challenges.

In order to fully understand how CAR-T cell therapy works we must first describe the design that stands behind it. The first step is to harvest white blood cells (WBC) from the peripheral blood of the patient, the T-lymphocytes with the help of leukapheresis. Furthermore, recombinant technology uses lentiviral vectors for genetic sequencing that integrate into the genome of the cell giving rise to a modified T cell with a synthetic receptor on its surface (15). T cells, normally recognize foreign antigens on tumors with the help of the T-cell receptor (TCR)-CD3 complex that binds to the peptide-HLA (human leukocyte antigen) complex and initiates T cell activation (16). The development of the CAR-T construct was achieved by assembling components such as the TCR-CD3 complex (CD3ζ) with genes borrowed from the structure of immunoglobulins (VH and VL) that form tumor-specific antigen with single-chain variable fragment (scFv) that is fused to a transmembrane domain (TMD) and then to an intracellular T cell signaling domain (such as the CD28 costimulation domain) (15,17). The end product is capable of selectively binding to different tumor tissues depending on the antigen present and activating other T-cells to achieve cytotoxic properties by means of an immunological cascade, with the possibility of persisting in the body for years contributing to immune surveillance. CAR specificity actually comes from the extracellular domain, derived from the antigen-binding site (2,18).

Steps in CAR-T development are described in **Figure 1**.

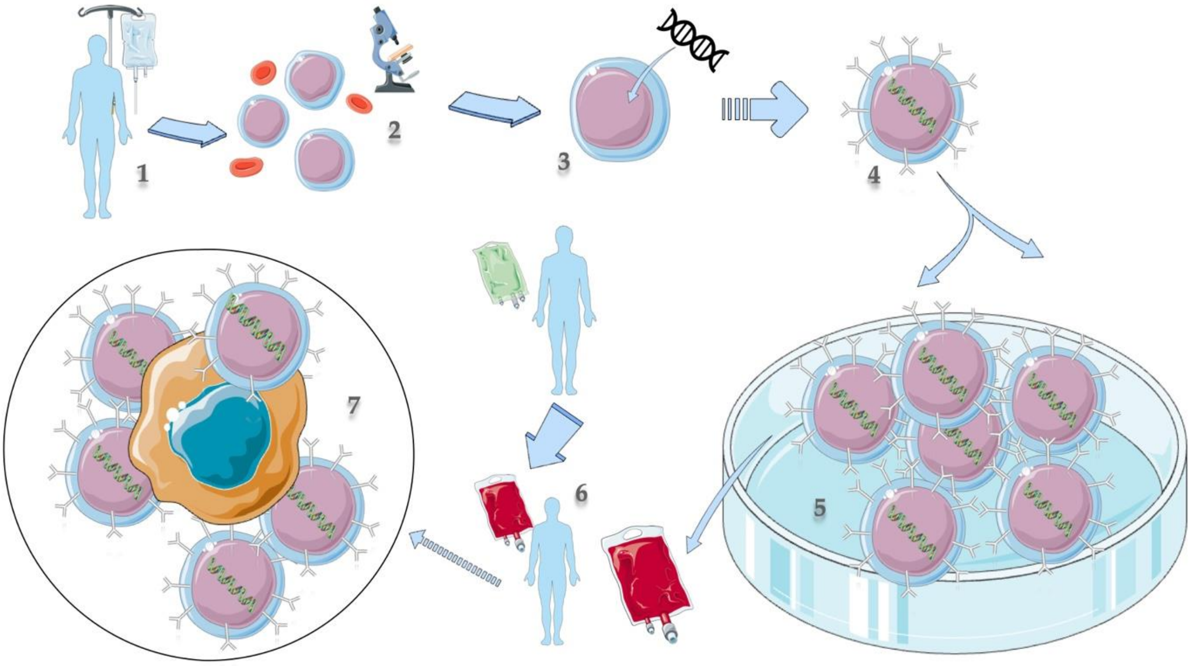

Figure 1. Steps in CAR-T development

Step 1. Removal of blood from the patient to harvest the T cells by leukapheresis.
Step 2. Study of the T cells.
Step 3. Make the CAR-T cells in the laboratory. Insert the gene for CAR by means of an inactive virus (retroviruses).
Step 4. Obtaining the CAR product.
Step 5. Multiplication of CAR-T cells until they reach millions in number.
Step 6. Infusion of CAR-T cells to the patient after the lymphodepletion chemotherapy regimen.
Step 7. CAR-T cells will bind to cancer cells by recognizing the antigens on the surface through the CAR and will kill the cells. CAR-T cells may remain in the body for some time to prevent cancer from returning.

When first-generation CARs were first produced, they consisted of only the TCR complex CD3-zeta chain domain and antigen recognition domains. The use of first-generation CARs was explored in clinical trials that included patients with several types of cancers but only showed modest efficacy mainly due to insufficient T-cell persistence *in vivo*. Subsequently, second-generation CARs were developed, which incorporated costimulatory domains, such as CD28 or 4-1BB (CD137), thus increasing the potential of CAR-T cell survival and proliferation, ultimately leading to improved antitumor efficacy. Third-generation CARs combine the CD3-zeta domain with more than two costimulatory domains; nonetheless, its superiority over second-generation CARs has not yet been completely demonstrated (17,19). (**Figure 2**)

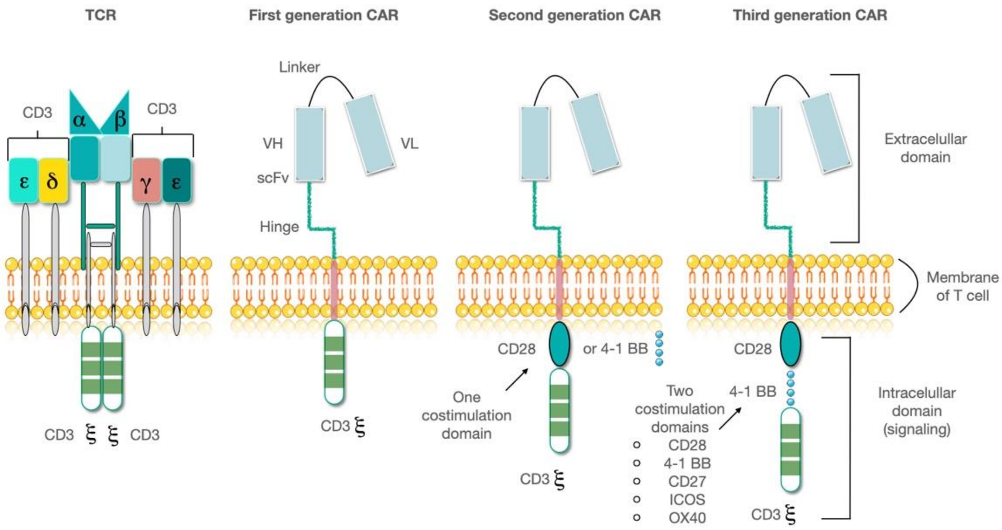

Figure 2. CAR-T cell generations and the TCR complex.

- A single-chain variable fragment (scFv) is generated by linking the variable region heavy and light chains (VH and VL). This extracellular domain is fused to an intracellular domain via a transmembrane sequence. The intracellular domain is designed to recapitulate the normal series of events by which T cells are activated. In addition, the incorporation of costimulatory signals to the CAR makes CAR-T cells less susceptible to negative regulation by the host cells, which occurs in normal immune responses against cancer.
- Starting from left to right - TCR structure; the first generation of CARs which are composed of CD8/CD3ζ fusion receptors and T bodies; the second generation of CARs that provide double signaling; the third generation of CARs more complex in structure by having three or more signaling domains.

The fourth CAR generation is still in its early development and has some particularities consisting in incorporating other genes to empower the antitumor activity of CAR-T cells (20). Recently, other genetic modifications (i.e. receptor design or different vectors used for gene delivery) have been evaluated in pre-clinical (*in vitro* or *in vivo* biological testing) and clinical trials but these remain to be seen (21).

Following systemic infusion, CAR-T cells recognize tumors that express the target antigen, cluster around them, multiply and eliminate them through a cytotoxicity mechanism – the release of cytokines, perforins, and granzymes that initiate apoptosis (22). (**Figure 3**)

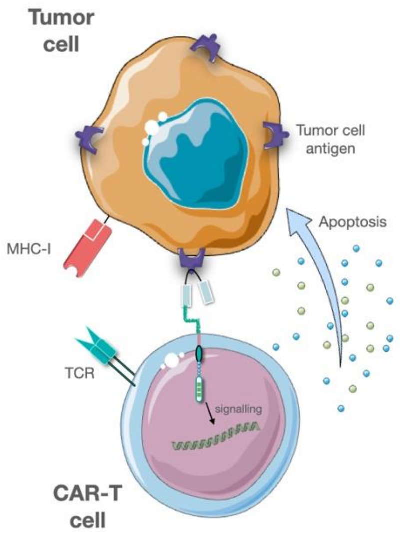

Figure 3. CAR-T construct and tumor-cell interaction.

In 2013, the patenting of CAR-T inventions began in earnest with sixty filings around the world, before being increased through 2016 to 597 filings. When analyzing countries by their number of CAR-T cell applicants, the US and China had the most applicants, with 39% and 33% respectively, followed by the UK (5%), Germany (5%), Japan (4%), and France (3%). The U.S. and China were the most productive countries, followed by Switzerland, the U.K., Germany, and France (23,24). Parties looking today to protect their CAR-T inventions thus have to make with a very crowded patent field.

Noteworthy, combinations of immunotherapies, for example CAR-T cells and immune checkpoint inhibitors, for boosting the efficacy of therapy, could become subject of future patents (25–27).

Although, at first sight, it would seem that CAR-T therapies follow the drugs ordinary pathway, actually they display substantial differences from the pharmaceutical patenting and cannot be considered a "product" as such. Patenting CAR-T products does not follow the typical path of patented medicines mainly because they are personalized therapies, that include multiple steps involving collecting a patient's own T cells, modifying them using genetic technology, multiplying them in the process, and then infusing the same cells back into the patient.

2.2. CAR-T cells patents

The search query using the Patentscope database and the International Patent Classification (IPC) field, along with C07K14/705 and A61K35/17 combined with the terms "CAR T" or "chimeric antigen receptor" gave relevant results for CAR-T cell patents. The inquiry revealed that patenting in the field of CAR-T cell significantly increased after 2013 (**Figure 4**) and peaked in 2022.

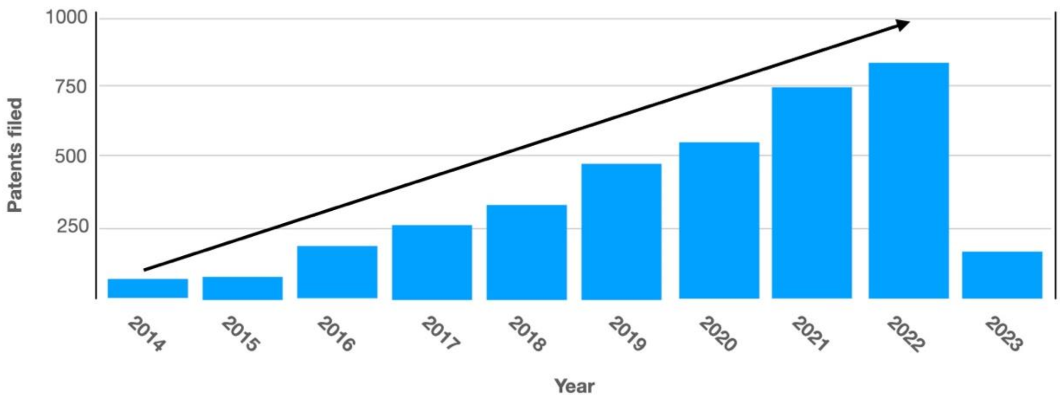

Figure 4. Patenting evolution of CAR-T cell therapy (source: WIPO analysis based on search results).

For instance, one the first published patents in 2014, notably US20140322183 - Targeting cytotoxic cells with chimeric receptors for adoptive immunotherapy, and WO2014184143 - CD19 SPECIFIC CHIMERIC ANTIGEN RECEPTOR AND USES THEREOF, were focused on obtaining a type of chimeric antigen receptor (CAR) wherein the CAR is termed a "KIR-CAR" which is a CAR design comprising a component of a receptor naturally found on natural killer (NK) cells, respectively Chimeric Antigen Receptor in which extracellular ligand binding is a scFV derived from a CD19 monoclonal antibody, preferably 4G7. The last one mentioned is particularly useful for the treatment of B-cells lymphomas and leukemia.

Current status, 2023 wise, the patent applications are more focused on upgrading the constructs, for example, US20230085834 - Chimeric Antigen Receptors Comprising Interleukin-9 Receptor Signaling Domain, and US20230092787 - CAR T CELLS TARGETING THE INTEGRIN ALPHAV BETA3 EXHIBIT ROBUST ANTI-TUMOR RESPONSES AGAINST GLIOMAS AND OTHER SOLID TUMOR MALIGNANCIES, where the spectrum of activity is wider, focusing on clinical applicability, even targeting solid tumors.

If at the beginning of patenting in the CAR-T field, the focus was on obtaining different relatively functional constructs used especially in hematology, in the current landscape the object of protection is focused on constructs that are used against a broader spectrum of diseases, as we have mentioned earlier.

3. Patenting requirements and pitfalls in patenting academic CAR-T cells therapy

3.1. General aspects regarding the patent application process

Before applying for any kind of patent, it is important to know what inventions and patents are. An invention can be, for example, a product, a process, or an apparatus. To be patentable, it must be new, industrially applicable, and involve an inventive step.

Patents are valid in individual countries for specified periods. They are generally granted by a national patent office or a regional one like the European Patent Office (EPO). Patents confer the right to prevent third parties from making, using, or selling the invention without their owners' consent (28).

With very few exceptions, any patent application consists of a request for a grant, a description of the invention, claims, drawings (if any), and an abstract.

Even if the procedure from the date of deposit (the date on which a patent application was filed to a certain Office and which gives the priority date) until the granting of a patent is substantial and can raise several challenges, the focus will be on the conditions to be fulfilled for the application part, in order to set the highest chances for a patent to be granted.

3.2. Invention categories

Patent laws around the world define several categories of invention, including the composition of matter, article of manufacture, and process. There is some debate within the patent field regarding the category of the invention into which CAR-T-cells fall and the answer might change the ability of a granted patent to protect a CAR-T invention. Firstly, CAR-T cells may be considered physical entities, and as such would be categorized as compositions of matter or articles of manufacture. From this point of view, patent applications and patents regarding CAR-T cells would be evaluated in terms of the structural features of the CAR-T cells and their components. Moreover, because CAR-T cells express chimeric antigen receptors, which are artificially engineered, they should not be viewed as a product of nature and should accordingly satisfy the threshold eligibility for patent protection in most jurisdictions (29). Secondly, based on the way that they are produced, CAR-T cells – particularly autologous CAR-T cells – may be considered an activity (i.e., a therapeutic process or use). The argument supporting this perspective is that, in the CAR-T production process, T-cells are removed from a patient followed by an *ex vivo* genetic improvement to generate modified and multiple CAR-T cells, and administered back to the same patient. These steps define a method of treating each specific patient, not manufacturing a product for more general sales and commercial use.

3.3. CAR-T technology type of claims

Patents and applications covering CAR-T technology may include product claims for the CAR-T cells themselves, product claims for components of the CAR-T cells, process claims (30), methods of manufacturing CAR-T cells, and methods of treatment claims, and even methods of treating particular conditions with CAR-T cells (31).

As a rule in the biopharmaceutical field, product claims offer the broadest protection and are thus the most valued. They provide full ownership of the compound which is commercialized, whatever the uses thereof. Product claims should therefore be sought in any patent strategy for protecting CAR-T inventions (32).

However, seeking protection for the CAR-T cell itself can be challenging by the very nature of the product. Protection could be sought for specific CAR construct designs or their component parts with many patent applications are thus directed to particular CAR constructs, and/or CAR-encoding polynucleotides. Protecting a specific CAR construct may be challenging if this receptor does not possess an unexpected property, i.e. a feature that distinguishes this CAR from the prior art and could not have been predicted from said art. This is the main reason that determines the claims in such patent applications to not be very broad. Oftentimes, the claimed construct will be built with the same basic domains (an scFv, a flexible linker, a transmembrane domain, and a signalization module) in the same arrangement, as CAR of the prior art. The construct will most often be a protein already known and characterized in the art. In such situations, usually, the EPO concludes that, absent an unexpected property, it is obvious to combine and try all these different protein sequences (33). This objection can be overcome if the claimed construct possesses an advantage over the prior art which could not be foreseen. Every CAR construct needs empirical testing for evaluation because, in fact, even tiny changes might have a significant impact on the treatment result. To persuade the examiner, you will need to present supporting experimental evidence. Thus, the creation of new CARs with novel properties is a key area of patenting activity.

The genetic sequences that contain the code for these polypeptides may also provide protection for the CARs and the parts that make them up. Given that the CAR is only expressed in the patient's cells, it will be difficult to demonstrate infringement of a polypeptide claim. However, before transfection, the nucleic acid can be synthesized and purified in bulk, much like any other small molecule or biotech item. Thus, a patentee can prove infringement for that polynucleotide in general. In addition, patent protection should be sought for newly developed functional subunits of a CAR, such as targeting moieties and co-stimulatory domains. For example, it was recently reported that a peptide fragment of scorpion chlorotoxin can be used to effectively target glioblastoma cells (34). This targeting mechanism can receive large protection from drafting the claims in a manner that ensures viable association between peptide fragments and other functional fields of a CAR.

Protecting the cells themselves can be obtained by drafting a patent application for the composition of matter. This frame position is very similar in the matter of advantages to the biopharmaceutical patents. The most important effect is the protection given directly to the product (i.e. the cells themselves) regardless of the process driven in order to obtain them, so even if a third party uses another method but achieves the same outcome, that third party would be in the position of infringing the composition of matter patent claim.

On the other hand, the composition of matter claims linked to CAR-T cells has to overcome some inherent threats that biopharmaceutical homologous don’t, with these threats being related to the fact that CAR-T cells are developed individually for each patient. So, establishing infringement on a patient-by-patient basis is almost impossible. These kinds of challenges are not present in the biopharmaceutical domain, where a certain medicine is produced for general use or at least for a certain category of patients. Also, the CAR-T cells need infusion into the patient in a very short amount of time from the moment they are made, therefore analyzing to what extent the cells are infringing is another matter that causes a lot of difficulties. From this point of view, developing and patenting CAR-T cells has to distance itself from the traditional path in the biopharmaceutical field and method claims should take a front seat in the patent strategy, but this has to be considered in relation to the purpose of patenting and the will to enforce the patent protection.

Methods of manufacturing are generally eligible for patent protection in most jurisdictions throughout the world, therefore method claims can be taken into consideration as well. Indeed, in some jurisdictions, they may be the only option for protecting a medical invention. However, this type of claim faces challenges that composition of matter claims do not. First, they do not specifically cover the CAR-T product, only the method of making it. Accordingly, to the extent that a competitor can make the same CAR-T product using a different method, it will avoid infringing the claims of the method patent. Further, the manufacturing process for CAR-T cells involves several different actors, potentially employed and controlled by different entities. The process for producing a specific CAR-T cell is performed for each patient, even though the resulting product is personalized for the specific patient. The special consequences of choosing the protection through the method of manufacturing claims should be kept in mind and carefully analyzed before applying for the patent.

3.4. Particularities

Unfortunately, many difficult problems remain, despite the fact that CAR-T cell immunotherapy has acquired quite remarkable clinical effects in oncology and hematology. For example, a perspective that may constitute a solid ground for challenging a CAR-T patent is the argument that CAR-T cells are not patentable subject matter since they are acquired from the T cells in a patient's own blood and for an invention to be patented is necessary to have a result that did not naturally exist in the recognized field of endeavor prior to the development of the invention (35). However, this principle of an "artificially created state of affairs" is valid in Australia and should be a reason to carefully explore the conditions of the various territories where patenting is desired. Patent law is still territorial law.

CAR-Ts' medical literature is spawning, creating a context for challenging patents on the basis of obviousness. As debated above, the non-obviousness requirement means that the invention, after analyzing the patentable subject matter and the novelty, has to present an inventive step. Hence, if disclosures in the prior art would have directly led a skilled person to the invention claimed, in the expectation that it might well produce a useful alternative, the invention cannot be patented. So, having strong arguments concerning the fulfillment of this condition even before starting the application would be advisable, because most probably, it will be necessary to overcome the non-obviousness requirement.

It is possible to be argued that CAR-T developers should also consider seeking a method of treatment claim. Nonetheless, such claims don't qualify for patent protection in many jurisdictions, with the notable exception of the United States of America. More accurately, US patent law limits the extent to which healthcare professionals and their employers are liable for infringing a method of treatment claim. Accordingly, to recover damages for infringement of a method of treatment claim in the United States, a patentee must establish that the CAR-T manufacturer or seller knowingly contributed to or induced infringement. As a rule, a method of treatment claim requires the action to be taken by a healthcare professional and apparently some jurisdictions maintain this prohibition and at the same time they tie some exceptions to it related to the manufacturing methods and use-limited compositions of matter. The United States has adopted a unique statutory immunity from infringement for medical practitioners and healthcare organizations but is otherwise likely to uphold patents on medical treatments. Other countries, though they have not enacted specific legislation limiting medical treatment patents, have taken a range of judicial positions that have failed to uphold such patents on the grounds of lack of industrial application.

For the method of treatment claims, the novelty might be challenged on the basis of clinical trial-related documents that were (a) publicly available before the priority date and (b) hypothesize that CAR-T cells may be useful to treat the particular condition of the subject of the patent (even where the hypothesis has not yet been validated in trials). In this respect, innovators should take care to protect the confidentiality of clinical trial-related documents where possible (e.g. through appropriate confidentiality agreements) and only disclose what is strictly necessary before filling a priority application.

Granting particular inventors exclusive rights over methods of medical treatment has been an issue and a subject of debate even from the very early stages of patenting. Objections to the patenting of medical treatments have their roots in basic moral principles—it is wrong to limit the availability of potentially life-saving treatments to individuals in need—as well as ethical precepts of the medical profession (36).

The European Patent Convention (EPC) (37), the legal framework within which the European Patent Office carries out its activity, initially stipulated the exclusion of medical treatments in Article 52. However, along with other significant amendments adopted in 2000 which came into force in 2007, that was moved to Article 53, which included exceptions for inventions "the commercial exploitation of which would be contrary to the public order or morality". The final text of the EPC exclusion for medical treatments, as it exists today, is: "Article 53 – Exceptions to Patentability. European patents shall not be granted in respect of (. . .) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods." The EPO Boards of Appeal have subsequently confirmed that the exclusion of methods of medical treatment from patentability is "based on social-ethical and public health considerations" and that "physicians should be free to choose the best medical treatment for a patient without being prevented by exclusive patent rights." Likewise, courts in Europe have confirmed this focus, holding that "patent law should not interfere with the saving of human life or the alleviation of human suffering". Therefore, the patentability of medical treatments is effectively prohibited or limited throughout much of the developed world.

Considering the extensive limitations on patenting medical treatments around the world, it should be clarified the situation of CAR-T in the matter of whether they are or should be considered medical treatments and consequently, subject to such limitations. Over the years, the courts and the EPO, including the EPO's Boards of Appeal, have interpreted Article 53(c) exclusion (including its precursor under Article 52[4]) and its subcomponents.

For example, as relevant for CAR-T cells, the EPO Guidelines for Examination address the *ex vivo* modification of body tissues and fluids and provide that they "are not excluded from patentability as long as these tissues or fluids are not returned to the same body". Because autologous CAR-T cells are returned to the same body from which they were obtained, their use in a therapeutic method would, at present, seemingly be excluded from patentability. By contrast, allogeneic CAR-T cells would not be excluded from patentability because the cells are not returned to the same body from which they were obtained. Therefore, characterizing CAR-T cells as a therapeutic process may severely limit the ability to obtain patent protection for them, particularly in many jurisdictions outside the United States. Further, as therapeutic processes, the CAR-T cells would be evaluated in terms of the actions taken to make or use them, and different actions from those recited in the patent claims could avoid infringement (29).

3.5. CAR-T technology litigation

The litigation landscape is not a rich one yet due to the emergence of these therapies which still are on an ascendant rise.

Kite Pharma (now part of Gilead), Novartis, and Juno Therapeutics (now part of Bristol-Myers Squibb) were among the first in the CAR-T industry. Juno sued Kite, alleging that Kite was infringing their patent through the use, sale, offer for sale or importation of Kite's axicabtagene ciloleucel. Juno's patent at issue, U.S. Patent No. 7,446,190 ('190 patent), relates to a nucleic acid polymer encoding a three-part chimeric antigen receptor (CAR) for a T cell. There were four claims in issue in this case. Juno alleged that Kite infringed these claims and obtained a judgment for $1.1 billion at trial.

The United States Court of Appeals reversed the trial judgment on the basis that no reasonable jury could find Juno's patent written description sufficiently demonstrates that the inventors possessed the full scope of the claimed invention, in other words, the specification at issue was not sufficient. The U.S. patent law states that the specification must contain a written description of the invention, and the hallmark of the written description is the disclosure. On August 26, 2021, in *Juno Therapeutics, Inc v Kite Pharma, Inc.*(38) the United States Court of Appeals for the Federal Circuit reversed the judgment against Gilead's Kite Pharma for infringing Bristol-Myers Squibb's Juno Therapeutics cancer immunotherapy patent. After the appeals court overturned a $1.2 billion verdict against Gilead, Bristol-Myers Squibb has filed a petition to the US Supreme Court in which they claim that the US Court of Appeals ruled for a very restrictive patent stance.

Novartis and Juno also settled a patent dispute concerning a different US patent licensed by Juno (also relating to axicabtagene ciloleucel) in 2014. The terms of that settlement involved Novartis paying $12.25 million USD to Juno, as well as milestone payment and royalties on future sales of certain CAR-T therapies.

This practice will definitely be relevant in others to come, even though the applicable patent legislation will have priority in dealing and ruling with CAR-T infringement cases.

4. Potential strategies

The increasingly crowded landscape from the intellectual property point of view means that broad patents will become harder to obtain. However, the number of clinical challenges still to be met means there remains huge scope for new filings. The number of competitors in this field, and the high stakes involved, mean that further litigation should be expected before too long. This will require developing strategic patent portfolios, firm approaches for procurement, cross-transfer, setting up licensing for patents, identifying opportunities, and framing up the IP portfolio in an effective manner.

As an alternative, this information can be kept confidential. CAR-T developers may take into account the opposite alternative to applying for a patent, which is keeping relevant information confidential. To be put in place this strategy specific legal measures have to be taken such as identifying all the relevant recipients of the sensitive information, limiting the number of recipients to the minimum necessary, and concluding strong confidentiality agreements. Patenting involves full disclosure of the invention to be patented so, particularly for proprietary manufacturing processes if the innovator considers it will be possible to keep the relevant information out of the public domain (by reason of regulatory restrictions), and that competitors are unlikely to independently develop an equivalent process, the confidentiality route seems the rational option. By keeping such information confidential, an innovator will potentially enjoy a longer effective period of exclusivity than the 20-year monopoly afforded by a patent.

Regardless of the chosen path, it is crucial to have a freedom-to-operate analysis, meaning the ability to use or commercialize a product or process without infringing another party's valid intellectual property rights, usually patents. In particular, a business may seek a freedom-to-operate analysis and opinion in order to identify patent infringement risk and provide a potential defense to a willful infringement or inducement of an infringement claim before launching or developing a new product or process or after receiving a patent notice letter (39). Players who activate in the field of developing new CAR-T therapy need to reduce any risks associated with potential infringement litigations by determining their freedom-to-operate in concern of other patent applications or granted patents. A personalized therapy does not equate to being free of rights from third parties. In fact, the number of patents involving CAR-T therapy, covering all aspects from the subdomains of receptors to the dosage regimen of specific CAR-T cells, is already staggering and continues to grow. Being part of an infringement litigation as a defendant, which is the case when a patent holder appreciates that by developing a certain CAR-T its own patent is infringed, is still a costly and time-consuming process even in the best-case scenario when the court decides that no infringement has occurred.

The question of freedom-to-operate is thus a necessary prerequisite in any activity involving developing and using CAR-T therapy. When performing a freedom-to-operate search the keywords and phrases used are paramount. The most obvious search terms to start with would be “CAR-T” “CAR-T therapy”, “CAR-T cells”, and “chimeric T-cell”, but this will not exhaustively solve the matter considering that terms like “recombinant protein” or “synthetic T-cells” are quite frequently used, and they don’t even mention the “CAR-T” root. An effective search comprises many levels of actioning (a keyword search mixed with one taking into consideration the sequences) so that even the ambiguous patents get to be included.

CAR-T inventions cover several aspects, each of which may be protected independently of its role in a CAR-T context. Each part of the constituents of the receptor may be covered independently, so a specific evaluation must be carried out for each of them. Likewise, it should be cautiously checked for each step of the manufacturing method if it falls within the scope of a third-party patent. Specific medical uses should also be evaluated for their freedom-to-operate, including such aspects not directly related to CAR-T as preconditioning of patients (before administration of CAR-T cells). Therefore, any comprehensive freedom-to-operate analysis should include an evaluation of patents directed to these various, more general aspects of CAR-T therapy. Freedom-to-operate assessment of a new CAR-T invention may significantly add to the overall costs, but when considering the risks of not doing so, appears to be a wise choice. Failure to properly check that an aspect of a CAR-T invention is free may result in a highly relevant patent not being identified and facing a litigation suit later on, once the therapy is on the market: in the Yescarta infringement suit, Juno Therapeutics (BMS) was awarded 1.1 billion dollars in damages from Kite Pharma (Gilead), as described in the previous section (30,40).

Still, if patenting is the chosen path, it is important that firstly, a prior art search be made. A prior art search is undertaken to ascertain whether an invention is new and non-obvious, or not. A prior art search will bring to light any knowledge existing prior to the invention at hand. This knowledge might include, but may not be limited to, patent applications, scientific theses, and industrial know-how. Once this knowledge is acquired, an inventor will get an accurate idea of just how novel and non-obvious the invention is. Later, the inventor can, accordingly, re-work his invention and patent application to enable the grant of a patent for the invention. Thus, a prior art search will help distinguish between what is already known (prior art) and what is new (invention) (41). This must be done before spending significant amounts of time and money on trying and starting to patent the idea.

Alternatively, steps could be taken to try to prevent a patent from being granted, or to challenge a granted patent, to try to clear the way, but this should be assessed on a case-by-case basis with the careful monitoring of the patent applications.

As CAR-T patenting does not fit into the traditional model of patentable therapy, it is indeed necessary to explore new strategies. Infringement circumstances are also different from those that have been traditionally considered for patents in the pharmaceutical field.

Unfortunately, due to expanding number of applications regarding patenting in CAR-T cells field, which harbors immense therapeutic opportunities, an increasing number of patent litigation is expected in the following years.

Each strategy has its own strengths and weaknesses. Researchers and inventors hoping to protect CAR-T-related inventions should consider as soon as possible a comprehensive and global plan at the outset to pursue each patenting strategy to the fullest extent possible.

5. Conclusions

There are endless opportunities for intellectual property protection, but the bigger challenge is the arduous complexity of running a process of this nature. In the case a patent cannot be obtained on a particular biologic product, there remains a prospect of patenting the method of using such a product. The frontline for personalized medicines is very different from single-molecule and biological drugs. The future is pictured as new start-ups and innovators who are competing to develop new ways to perfect the technique. CAR-T universe is spinning quite quickly and gathers pace in progress which will result in many of the patents filed today becoming worthless in several years. The quick progress of science is one of the main challenges in intellectual property for these products. Probably the ultimate goal of CAR-T cell therapy would be allogeneic CAR-T cells which can be given to any patient.

Article highlights

- There is a dire need for insights into the intellectual property for those who are exploring possible patenting options in CAR T-cells territory.
- Avoiding pitfalls in patenting CAR-T requires an overall understanding including the concept, history, claim drafting approach, current status in patenting, and case law, all integrated into a personalized strategy.
- Patenting efforts need to be directed towards a more creative approach due to the overcrowded field of CAR-T technology.
- The patenting trend in the matter of CAR T-cells is on the ascending path, with growing interest for applicability in different diseases, including solid tumors.
- Several strategies need to be taken into account as a checklist before filing a patent application
- There is no one-size-fits-all solution in this matter and the evolution of CAR T-cells therapy will certainly bring out even more challenges.

References

1. Wang Z, Wu Z, Liu Y, et al. New development in CAR-T cell therapy. J Hematol Oncol. 2017 Feb 21;10(1):53.

2. Tomuleasa C, Fuji S, Berce C, et al. Chimeric Antigen Receptor T-Cells for the Treatment of B-Cell Acute Lymphoblastic Leukemia. Front Immunol. 2018;9:239.

3. Shang S, Zhao Y, Qian K, et al. The role of neoantigens in tumor immunotherapy. Biomed Pharmacother Biomedecine Pharmacother. 2022 Jul;151:113118.

4. Gupta SL, Basu S, Soni V, et al. Immunotherapy: an alternative promising therapeutic approach against cancers. Mol Biol Rep. 2022 Jun 27;

***Details some of the immunotherapies available**

5. Aggarwal S, Chandra A. Patentability challenges associated with emerging pharmaceutical technologies. Pharm Pat Anal. 2021 Jul;10(4):195–207.

6. Moretti A, Ponzo M, Nicolette CA, et al. The Past, Present, and Future of Non-Viral CAR T Cells. Front Immunol. 2022;13:867013.

7. Numbenjapon T, Serrano LM, Chang WC, et al. Antigen-independent and antigen-dependent methods to numerically expand CD19-specific CD8+ T cells. Exp Hematol. 2007 Jul;35(7):1083–90.

8. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet Lond Engl. 2022 Jun 18;399(10343):2294–308.

9. Qi C, Gong J, Li J, et al. Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. Nat Med. 2022 Jun;28(6):1189–98.

10. Liu Y, Chen X, Han W, et al. Tisagenlecleucel, an approved anti-CD19 chimeric antigen receptor T-cell therapy for the treatment of leukemia. Drugs Today Barc Spain 1998. 2017 Nov;53(11):597–608.

11. FDA Approves Second CAR T-cell Therapy. Cancer Discov. 2018 Jan;8(1):5–6.

12. Beyar-Katz O, Gill S. Advances in chimeric antigen receptor T cells. Curr Opin Hematol. 2020 Nov;27(6):368–77.

13. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021 Feb 25;384(8):705–16.

14. Golumba-Nagy V, Kuehle J, Abken H. Genetic Modification of T Cells with Chimeric Antigen Receptors: A Laboratory Manual. Hum Gene Ther Methods. 2017 Dec;28(6):302–9.

15. Sadelain M, Rivière I, Riddell S. Therapeutic T cell engineering. Nature. 2017 May 24;545(7655):423–31.

16. Ochi T, Fujiwara H, Okamoto S, et al. Novel adoptive T-cell immunotherapy using a WT1-specific TCR vector encoding silencers for endogenous TCRs shows marked antileukemia reactivity and safety. Blood. 2011 Aug 11;118(6):1495–503.

17. Sadelain M, Brentjens R, Rivière I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013 Apr;3(4):388–98.

18. Bunse M, Höpken UE. Generation of Redirected Engineered Human Chimeric Antigen Receptor (CAR) T Cells. Methods Mol Biol Clifton NJ. 2022;2521:67–83.

19. Zhang X, Zhu L, Zhang H, et al. CAR-T Cell Therapy in Hematological Malignancies: Current Opportunities and Challenges. Front Immunol. 2022 Jun 10;13:927153.

20. Duan D, Wang K, Wei C, et al. The BCMA-Targeted Fourth-Generation CAR-T Cells Secreting IL-7 and CCL19 for Therapy of Refractory/Recurrent Multiple Myeloma. Front Immunol. 2021;12:609421.

21. Charrot S, Hallam S. CAR-T Cells: Future Perspectives. HemaSphere. 2019 Mar 19;3(2):e188.

22. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Rev. 2019 Mar;34:45–55.

23. Abinader L, Contreras J. The Patentability of Genetic Therapies: CAR-T and Medical Treatment Exclusions Around The World. Utah Law Fac Scholarsh [Internet]. [cited 2023 Mar 26]. 2019 Jun 1; Available from: https://dc.law.utah.edu/scholarship/160

24. Jürgens B, Clarke NS. Evolution of CAR T-cell immunotherapy in terms of patenting activity. Nat Biotechnol. 2019 Apr;37(4):370–5.

****Details the CAR-T cell patent trend**

25. Grosser R, Cherkassky L, Chintala N, et al. Combination Immunotherapy with CAR T Cells and Checkpoint Blockade for the Treatment of Solid Tumors. Cancer Cell. 2019 Nov 11;36(5):471–82.

26. Hosseinkhani N, Derakhshani A, Kooshkaki O, et al. Immune Checkpoints and CAR-T Cells: The Pioneers in Future Cancer Therapies? Int J Mol Sci. 2020 Nov 5;21(21):8305.

27. Liu D. CAR-T "the living drugs", immune checkpoint inhibitors, and precision medicine: a new era of cancer therapy. J Hematol OncolJ Hematol Oncol. 2019 Nov 8;12(1):113.

28. Guidelines for Preparing Patent Landscape Reports [Internet]. [cited 2023 Mar 26]. Available from: https://www.wipo.int/publications/en/details.jsp?id=3938

***Details guidelines for preparing patents**

29. Patent issues in CAR-T technology [Internet]. [cited 2023 Mar 26]. Available from: https://www.iam-media.com/global-guide/global-life-sciences/2020/article/patent-issues-in-car-t-technology

30. US appeals court rules in favour of Kite in Gilead-BMS patent dispute [Internet]. Pharmaceutical Technology. 2021 [cited 2023 Mar 25]. Available from: https://www.pharmaceutical-technology.com/analysis/us-appeals-court-kite-gilead-bms-patent/

31. Methods of medical treatment patentable in Australia; infringement by cross-label use fact-dependent - Knowledge - Clayton Utz [Internet]. [cited 2023 Mar 25]. Available from: https://www.claytonutz.com/knowledge/2013/december/methods-of-medical-treatment-patentable-in-australia-infringement-by-cross-label-use-fact-dependent

32. Rai AK. Fostering Cumulative Innovation in the Biopharmaceutical Industry: The Role of Patents and Antitrust. Berkeley Technol Law J. 2001;16(2):813–53.

33. European Patent Office, Japan Patent Office and United States Patent and Trademark Office, Trilateral Project B3b: Mutual Understanding in Search and Examination: Report on Comparative Study on Biotechnology Patent Practices (2001), Annex 2, 43. 2001.

34. Dardevet L, Rani D, Aziz TAE, et al. Chlorotoxin: a helpful natural scorpion peptide to diagnose glioma and fight tumor invasion. Toxins. 2015 Mar 27;7(4):1079–101.

35. Isolated genetic material confirmed as patentable [Internet]. [cited 2023 Mar 26]. Available from: https://www.allens.com.au/insights-news/insights/2014/09/isolated-genetic-material-confirmed-as-patentable/

36. Varkey B. Principles of Clinical Ethics and Their Application to Practice. Med Princ Pract. 2021;30(1):17–28.

37. Office EP. The European Patent Convention [Internet]. [cited 2023 Mar 26]. Available from: https://www.epo.org/law-practice/legal-texts/epc.html

38. United States Court of Appeals for the Federal Circuit - JUNO THERAPEUTICS, INC., SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH, Plaintiffs-Appellees v. KITE PHARMA, INC., Defendant-Appellant [Internet]. [cited 2023 Mar 26]. 2021. Available from: http://cafc.uscourts.gov/sites/default/files/opinions-orders/20-1758.OPINION.8-26-2021_1825257.pdf

****Details the CAR-T cell lawsuit**

39. Freedom to Operate (FTO) [Internet]. Practical Law. [cited 2023 Mar 26]. Available from: http://uk.practicallaw.thomsonreuters.com/2-511-4689?transitionType=Default&contextData=(sc.Default)&firstPage=true

40. Gillet R, Bouquin N. DISRUPTIVE CAR-T THERAPY IS DRIVING A NEW WAVE OF PATENTING CHALLENGES. 2020;10.

41. Prior Art Search - IPTeL, IISc [Internet]. [cited 2023 Mar 26]. Available from: https://iptel.iisc.ac.in/prior-art-search/