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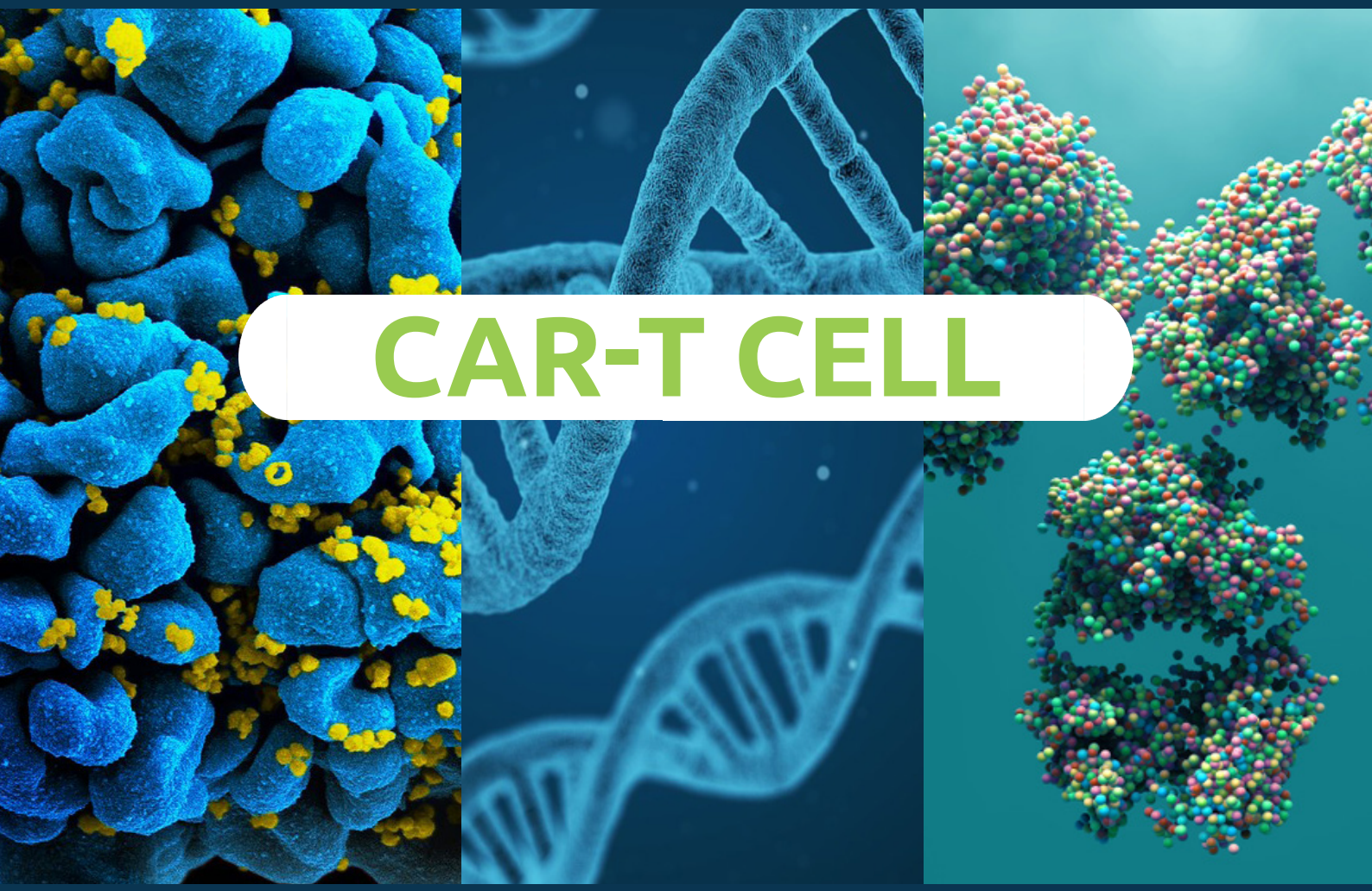

CAR-T CELL

MABDESIGN
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DISRUPTIVE CAR-T THERAPY IS DRIVING A NEW WAVE OF PATENTING CHALLENGES

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Immunotherapies, including monoclonal antibodies and checkpoint inhibitors, are a hugely promising therapeutic area, in terms of both clinical benefits and potential market size. These treatments are able to reactivate the body's own immune response to increase effectiveness in fighting diseases, particularly cancers. Among immunotherapies "adoptive immunotherapies" such as CAR-T cells (T cells engineered with chimeric-antigen-receptors (CARs)) are probably the highest hopes for patients and turn out to be a hot topic for healthcare and pharmaceutical industries. CAR-T therapy is indeed a revolutionary type of treatment which has emerged as a potent new class of therapeutics for cancer, based notably on their remarkable potency in blood cancers.

INTRODUCTION

CARs were first described more than 30 years ago. But only over the last decade has biomedical research really focused on the potential of CAR-T cells to create medicines, with an ever increasing clinical trials in progress. Three CAR-T treatments have now been approved: Kymriah® (tisagenlecleucel) was first to receive FDA and EMA approbation, followed a few months later by Yescarta® (axicabtagene ciloleucel) and FDA approbation for Tecartus® (brexucabtagene autoleucel) at the end of July 2020. All of these CAR-T therapies are "autologous" therapies, based on using the patient's own T cells. The process takes several weeks and is extremely expensive.

However, new approaches entail new challenges. effective patent strategy requires careful planning, especially in view of how increasingly crowded the CAR-T field has become. Infringement scenarios are different from those that have been traditionally considered for patents for pharmaceutical products. Companies will have to devise early on a sound patent strategy and thoroughly vet their products and processes for any freedom-to-operate issues. This article reviews the different approaches to CART-T cells patents with a focus on the European perspective. While not looking for exhaustivity, it will illustrate the complex intellectual property issues which have to be faced when trying to protect and/or commercialise CAR-T cells in Europe.

About Regimbeau

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REGIMBEAU, a French IP law firm, has been assisting companies and private and public project developers to protect, enhance, and defend their innovations and creations (patents, trademarks, designs) for more than 85 years. Fifteen partners head a team of more than 200 people whose skills are put into practice in every strategic aspect of Intellectual Property – business intelligence and information search, license agreements, IP portfolio audits, partnership negotiations, acquisition of industrial property rights, litigation. A dedicated team of technical and legal experts, with hands-on experience in tackling issues and challenges of innovation in immunology, can assist you in protecting your inventions with your best interest in mind. More info on our specific **webpage**.

CAR-T CELLS AND THEIR THERAPEUTIC USES

CAR-T cells therapy is based on *in vitro* engineering T-cells so that they express artificial receptors (called a "chimeric antigen receptor (CAR)") on the surface, thereby directing the CAR-T cells to specifically bind cancer cells.
CARs are synthetic proteins built by connecting several functional parts from different proteins, each with a specific function. A single-chain antibody variable fragment (scFv) recognises a specific protein on the surface of the malignant cells (e.g., CD19 on B-cells), thereby targeting the tumour. This antibody portion is connected via a flexible linker to a transmembrane segment which anchors the CAR at the surface of the T cell. Inside the cell, one or more domains are taken from signalling proteins, that ensures the T-cell receptor (TCR) signalling necessary to activate the effector functions of the CAR T-cell once it finds a tumour cell (cf. Figure 1).

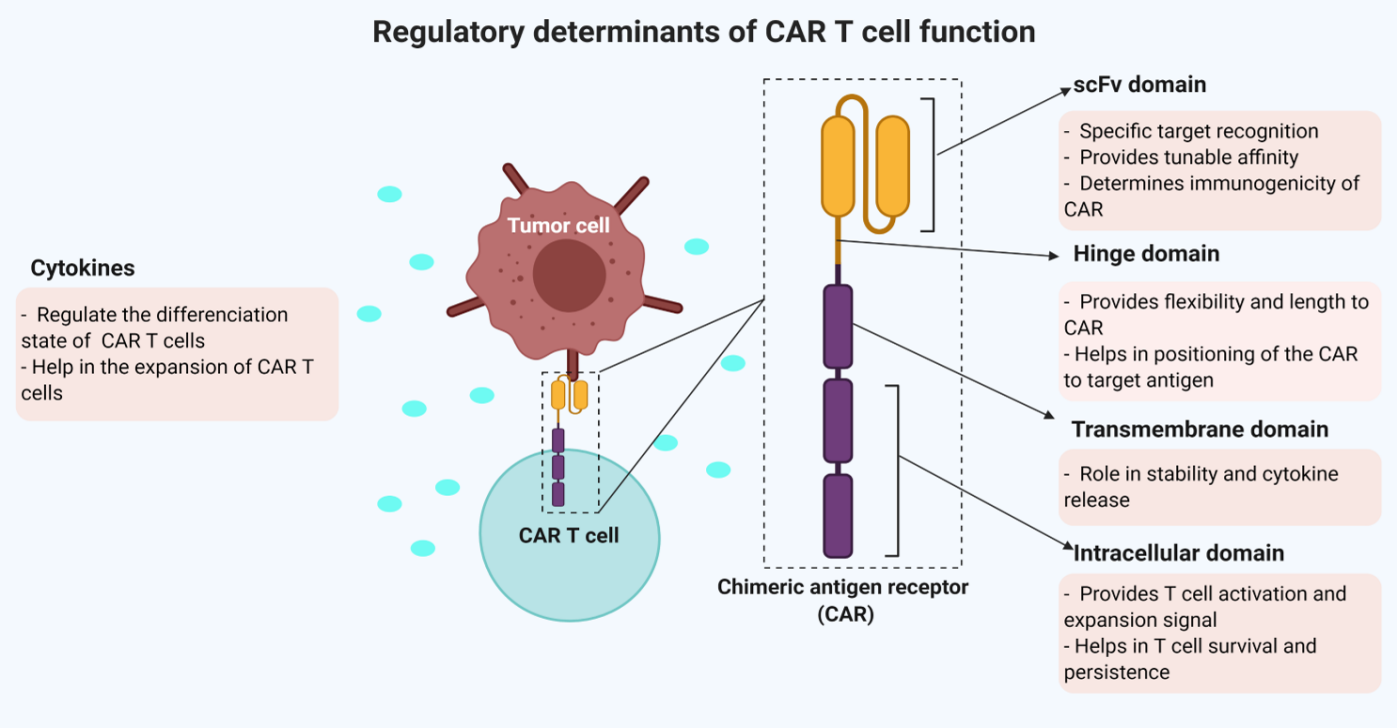

Figure 1: Structure of a chimeric antigen receptor (CAR)

In CAR-T cells therapy, individual patient's cells are collected, genetically modified, and returned to patient with new cancer-fighting properties. The various stages of this therapy are shown in Figure 2.

First, immune T cells are extracted from the patient's blood by leukapheresis. Then, the patient's T-cells are sent to the lab, where they are transfected with a recombinant vector encoding the CAR receptor, thereby making them CAR T-cells. Transfected T-cells are expanded *ex vivo* in platforms controlled for all aspects of safety and reproducibility in order to obtain enough cells for treating the patient. The cells are re-administered to the patient intravenously after chemotherapy conditioning.
The need to collect T-cells, to carry out the cell engineering and growing the genetically modified T cells, and then to return them into the patient's body, makes such a therapeutic process complicated and expensive. Collecting the T-cells from the patients and infusing back the engineered T-cells to them being performed at hospitals whereas the genetic modifications of the cells to produce CARs on their surface

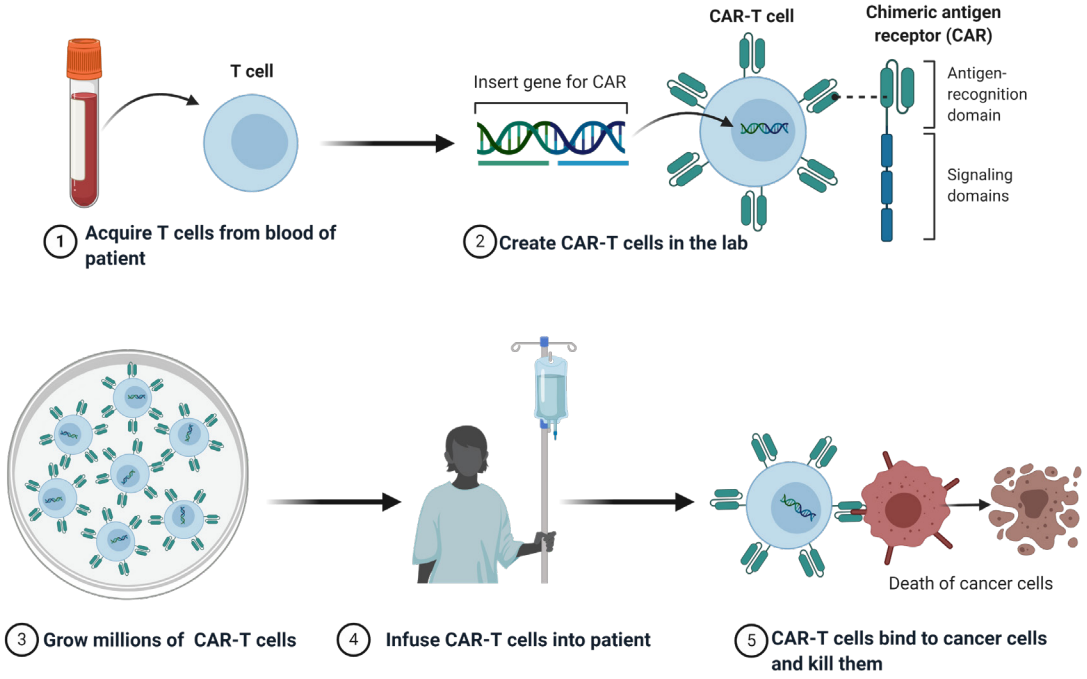

Figure 2: CAR-T Cell Therapy

is carried out by pharmaceutical industry. The key difference between conventional drugs and CAR-T cells therapies is that in the latter, each patient receives a treatment engineered specifically for them using their own immune cells, generating ambiguity around what the "drug" really is.

Due to these particularities of the treatment process, finding the more appropriate and effective patenting strategy is a real challenge, notably since this process may involve different steps being performed by distinct entities, which may furthermore not be located in the same country.

A DENSE INDUSTRIAL PROPERTY SITUATION

It is a sprint for pharmaceutical companies who are entering or continuing to do research into the development of the most optimal CAR-T cell therapy, manufacturing process and delivery method. The more patents a single pharmaceutical company can be issued that relate to CAR-T cell therapy; the greater market control a company will retain in this immunotherapy field.

As with many new biomedical developments, the firms bringing CAR-T treatments to market have filed numerous patent applications covering various aspects of these treatments. Different companies have their own proprietary CARs, with modifications in the transmembrane and endodomain co-stimulatory structures and signal peptides, in addition to the antigen recognition regions.

In April 2019, Björn Jürgens and Nigel Clarke published a study of CAR-T patenting commissioned by the European Patent Office (EPO). They found that it was in 2013 that the patenting of CAR-T inventions began in earnest with sixty filings around the world; it then increased through 2016 to 597 filings. When analysing countries by their number of CAR-T cell applicants, they found that US and China had the most applicants, with 39% and 33% respectively, followed by the UK (5%), Germany (5%), Japan (4%) and France (3%). As expected, the U.S. and China were the most productive countries, followed by the Switzerland, the U.K., Germany, and France. Parties looking today to protect their CAR-T inventions thus have to make with a very crowded patent field. As additional companies

[1] http://documents.epo.org/projects/babylon/eponet.nsf/0/5BE8186BE71C52FCC12584C100498651/$File/patent_insight_report-chimeric_antigen_receptor_t-cell_immunotherapy_en.pdf

proceed with CAR-T cell research, it is likely one will observe a steady increase in similarities between patent applications. This will inevitably lead to narrower claims being granted (if any) in many cases. However, in any case, a precise freedom-to-operate analysis cannot be omitted to fully and safely drive commercialisation of each specific CAR-T cells therapy.
Above all, the quest for the most appropriate patent protection for such an uncommon and disruptive therapies increasingly requests conceiving and designing new, imaginative patent strategies.

PROTECTING CAR-T CELL PRODUCTS

Patent laws around the world grant patents for two broad types of inventions: inventions relating to products (or "composition of matter") and inventions relating to methods. Product claims offer the broadest protection and are thus the most valued. They provide to the pharmaceutical companies a full ownership on the compound which is commercialised, whatever the uses thereof. Product claims should therefore be sought in any patent strategy for protecting CAR-T inventions.
For example, patent protection could also be sought for the CAR-T-cells themselves. However, this strategy is complicated by the very nature of the product. The fact that the treatment is unique and specific to each patient makes it difficult to define structurally. Obtaining a patent directed to CAR-T cells will probably be a long and arduous process. Moreover, even if this patent is granted, the real challenge will arise at the point of enforcement. CAR-T cells are individually produced for each patient. Therefore, infringement would, in principle, need to be established on a patient-by-patient basis. As a result, proving infringement will likely be complex. If testing is needed to check whether they fall under the claims in the patent, that will cause difficulties not encountered with mass-produced medicines. Another challenge will reside in the determination of the infringing sales, which are in turn used by the courts for setting the damage. And of course, preliminary injunction is out of the picture, since lives are directly at stake.
Alternatively, protection could be sought for specific CAR construct designs or their component parts. An example of such a claim is represented by claim 1 of European Patent EP2 935 321:

> *"1. A polypeptide comprising (i) a transmembrane domain from CTLA4 or PD-1, (ii) a CD3ζ intracellular signaling domain, and (iii) an extracellular domain that binds to an antigen on a tumor cell, wherein said polypeptide is a chimeric antigen receptor (CAR) and a T lymphocyte expressing said polypeptide is activated or stimulated to proliferate when said polypeptide binds to said antigen, and wherein if the transmembrane domain is from CTLA4, the extracellular domain of said polypeptide is not from CTLA4; and if the transmembrane domain is from PD-1, the extracellular domain of said polypeptide is not from PD-1."*

Many patent applications are thus directed to particular CAR constructs, and/or CAR-encoding polynucleotides. Such claims are highly valuable, as shown in a recent case in which Kite Pharma's Yescarta was found to infringe Juno Therapeutics' patent directed to a CAR-encoding polynucleotide. However, it is increasingly difficult to obtain broad claims in view of the accrual of publications and patent applications in the field. Even protecting a specific CAR construct may be challenging if this receptor does not possess an unexpected property, i.e. a feature which distinguishes this CAR from the prior art and could not have been predicted from said art.
This is because, oftentimes, the claimed construct will be built with the same basic domains (an scFv, a flexible linker, a transmembrane domain, a signalisation module) in the same arrangement, as CAR of the prior art. Furthermore, the claimed

[2] Juno Therapeutics, Inc. et al. v. Kite Pharma, Inc., No. 2-17-cv-07639 (C.D. Cal.).

construct's target will most often be a protein already known and characterised in the art. In such situations, the EPO will conclude that, absent an unexpected property, it is obvious to combine and try all these different protein sequences.
This objection can be overcome if the claimed construct possesses an advantage over the prior art which could not be foreseen. Note that it must be at least plausible that the claimed receptor does indeed possess this property. As of now, each CAR construct needs empirical testing for evaluation; indeed, small modifications can have major consequences on the therapeutic outcome. However, supporting experimental data will be needed to convince the examiner. Thus, one major focus for patenting activity is the development of new CARs with new characteristics. Among these features CAR-T cells with modified or added intracellular components, which result in improved or altered biological activities, including better activation of the CAR-T cells in response to target binding together with bispecific targeting strategies, and an improved capacity to kill target cells are of a significant interest. Besides, mitigating the off-target toxicities of CAR-T cells involves a variety of mechanisms to be discovered but which are essential for maintaining the brilliant potentials for CAR-T cells therapy and thus potentially represents a new avenue for patenting. Moreover, applying CARs to the treatment of solid cancers is also among the exciting new advancements which could significantly improve the patentability of a CAR.

POLYNUCLEOTIDES AND PROTECTING CAR-T CELL PRODUCTS

The CARs and their components may also be protected by virtue of the genetic sequences encoding these polypeptides. Actually, with infringement in mind, one may conclude that polynucleotides claims have a greater utility than claims directed to polypeptides. Proving infringement of a polypeptide claim will present a challenge, since the CAR is only expressed in the patient's cells. The nucleic acid, on the hand, may be prepared and purified in bulk before transfection, like any small molecule or biotech product. A patentee will thus be able to establish infringement for that polynucleotide generally. In this regard, it is worth noting that the claims found to be infringed in a California court by Kite Pharma (Gilead) were directed to nucleic acids encoding CARs :

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

PROTECTING METHODS USING CAR-T CELLS

Although product claims have traditionally been a priority for pharmaceutical companies in terms of patent strategy, obtaining and/or enforcing such claims in relation to CAR-T inventions may probably be difficult as detailed above. At least for these reasons, applicants may want to consider method claims, as they have an increasing significant value, even more so than product claims, for protecting these personalised medicines.

In particular, patent claims directed to methods of manufacturing CAR-T-cells may be particularly valuable. This is because the same process for producing a specific CAR-T cell is performed for each patient, even though the resulting product is personalised for the specific patient. Methods of manufacturing are generally eligible for patent protection in most jurisdictions throughout the world. Any process by which the manufacturing process can be made more efficient, make a

[3] Board of Appeal decision T 1329/04
[4] U.S. Patent No. 7,446,190

better product or do it more cheaply is likely to provide competitive advantages. Claims covering all or part of a process that becomes a *de facto* standard required by the health authorities would be especially valuable.
An example of a manufacturing claims is represented by claim 1 of European Patent EP 3 134 095:

> *"An in vitro method for manufacturing a T cell therapeutic comprising: a) providing a population of human peripheral blood mononuclear cells (PBMCs) that comprises T cells and antigen presenting cells (APCs); b) culturing the population of PBMCs for 16 hours to 32 hours prior to transduction in a cell culture medium comprising i) interleukin-2 (IL-2), ii) an anti-CD3 antibody or CD3-binding fragment thereof, and iii) an anti-CD28 antibody or a CD28-binding fragment thereof, B7-1 or a CD28-binding fragment thereof, or B7-2 or a CD28-binding fragment thereof, wherein the culture activates and stimulates the T cells; c) transducing the population of PBMCs activated in step b) with a lentiviral vector encoding a chimeric antigen receptor (CAR); and d) culturing the population of PBMCs in a cell growth medium to expand the transduced T cells; thereby manufacturing the T cell therapeutic."*

Claims directed to methods of manufacturing face challenges, however, that product claims do not. First, they cover the commercialised CAR-T product only inasmuch as it is produced by the claimed process. If a competitor manages to make the same CAR-T cell by a different process, then it will avoid infringing the claims of the method patent. Further, the manufacturing process of CAR-T cells involve different actors, such as e.g. the medical practitioners who collect the patient's T cells and inject the CAR-T cells, the manufacturing plant where the vector carrying the CAR gene is produced and purified at a pharmaceutical grade, the facility wherein the T cells are transfected by the vector, etc. It is probable that not all of these actors are under the same control. The most useful claims will have to define methods in such a way that all steps will be performed by the same party (i.e. there is a direct infringement).
A further level of complication is reached when considering that steps relating to manipulation and processing of the cells are likely to take place in a number of different countries, particularly as manufacturing processes are scaled up. Successful enforcement of the patent may then depend on the jurisdiction. Demonstrating that infringing processes are being carried out in other jurisdictions is a potentially difficult and costly exercise. When drafting and prosecuting claims for CAR-T therapies, applicants should therefore consider carefully the practicalities of how and where steps of the therapeutic process will be performed.
CAR-T developers should also consider pursuing claims directed to methods of treatment with the CAR-T cells. These claims are allowed, in one format or the other, in the most commercially-important jurisdictions. They are particularly useful against manufacturers of generics and biosimilars, because these companies sell copies of the commercialised CAR-T product and in the same indication as authorised by the relevant health agencies. On the other hand, their scope is narrow. Hence, if the claimed medical use does not encompass the authorised indication, difficulties in enforcing these claims will arise. In addition, it will be difficult to use such claims against an originator developing a related CAR-T product in a different medical indication.

FREEDOM-TO-OPERATE

It is important for actors willing to develop a new CAR-T therapy to mitigate the risk of future infringement litigations by assessing their freedom-to-operate with respect to third-party patents and patents that may issue from pending applications. That a therapy is personalised does not mean it is 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 dosage regimen of specific CAR-T cells, is already staggering and continues to grow. Moreover, even if an infringement suit is not successful, it may be extremely costly, thereby draining vital financial resources away from ongoing research projects. It makes the question of freedom-to-operate more pressing.

The earliest CAR-T patents are the broadest and should be monitored carefully. But that does not mean that more recent patents, especially those covering manufacturing methods or medical uses, should be ignored. It must also be emphasised that CAR-T inventions cover several aspects, each of which may be protected independently of its role in a CAR-T context. For example, each of the constituents of the receptor may be covered independently, so that 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 in 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.

Of course, freedom-to-operate assessment of a new CAR-T invention will significantly add to the overall costs of the whole project. However, when considering the risks of not doing so, verifying that all aspects of the invention are free from third-party patents appears to be money well spent. 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. The backlash then will most probably be severe: in the Yescarta infringement suit, Juno Therapeutics (BMS) was awarded 1.1 billion dollars in damages from Kite Pharma (Gilead).

CONCLUSIONS

Investments and researches in the CAR-T therapy field are continuously growing; however, with the numerous technical challenges, significant challenges in obtaining appropriate patent protection remain.

Due to the highly personalised approach and very specific targeting issues, CAR-T cells cannot be manufactured by the drug development path as usually practiced in the pharmaceutical field. The way by which the pharmaceutical companies will protect their investments through patenting must be adapted. As it does not fit into the traditional model of patentable therapy, it is indeed necessary to explore new strategies.

Still, infringement circumstances are also different to those that have been traditionally considered for patents in the pharmaceutical field. With such innovative and huge therapeutic properties associated with a growing number of patents and applications in this field, a large amount of patent litigation is expected in the years to come.

Conversely, as with any nascent technology, research is intensively underway, especially to discover how to expand such therapy to additional patients and offer valuable patenting opportunities. For example, as the CAR-T therapies approved up to now are “autologous” therapies, i.e. based on using the patient’s own T cells, the process takes several weeks and is extremely expensive. Researchers are already working on “off-the-shelf” or “allogeneic” products, that use donor CAR-T cells and would allow the treatments to be made available more quickly and cheaply. Allogeneic CAR-T cells procedures could thus provide significant advantages in manufacturing, including reducing costs and simplifying the supply chain.

With this way of scientific advancements, which in a sense un-personalised such therapy, patenting approaches could come back a few closer to those traditionally practiced. Only innovative future will let us know but patenting experts are for sure ready in the starting line!

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Raphaëlle GILLET is a French and European Patent Attorney. She has a Ph.D. in Molecular and Cellular Biology (Institut Cochin de Génétique Moléculaire, Paris), a MS in Cellular and Molecular Biology Development (Hôpital Necker, Paris) and she has a CEIPI Graduate (Distinction in Patents and Trademarks). She started her career in Industrial Property in 2001. After an initial experience in a biopharmaceuticals start-up, followed by twelve years' experience in an IP Law firm, Raphaëlle joined **REGIMBEAU** in 2014. She assists her clients and supports them in the development, management and defense of their portfolio. Raphaëlle also provides seminars and courses on Intellectual property, in order to make IP accessible to all.

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