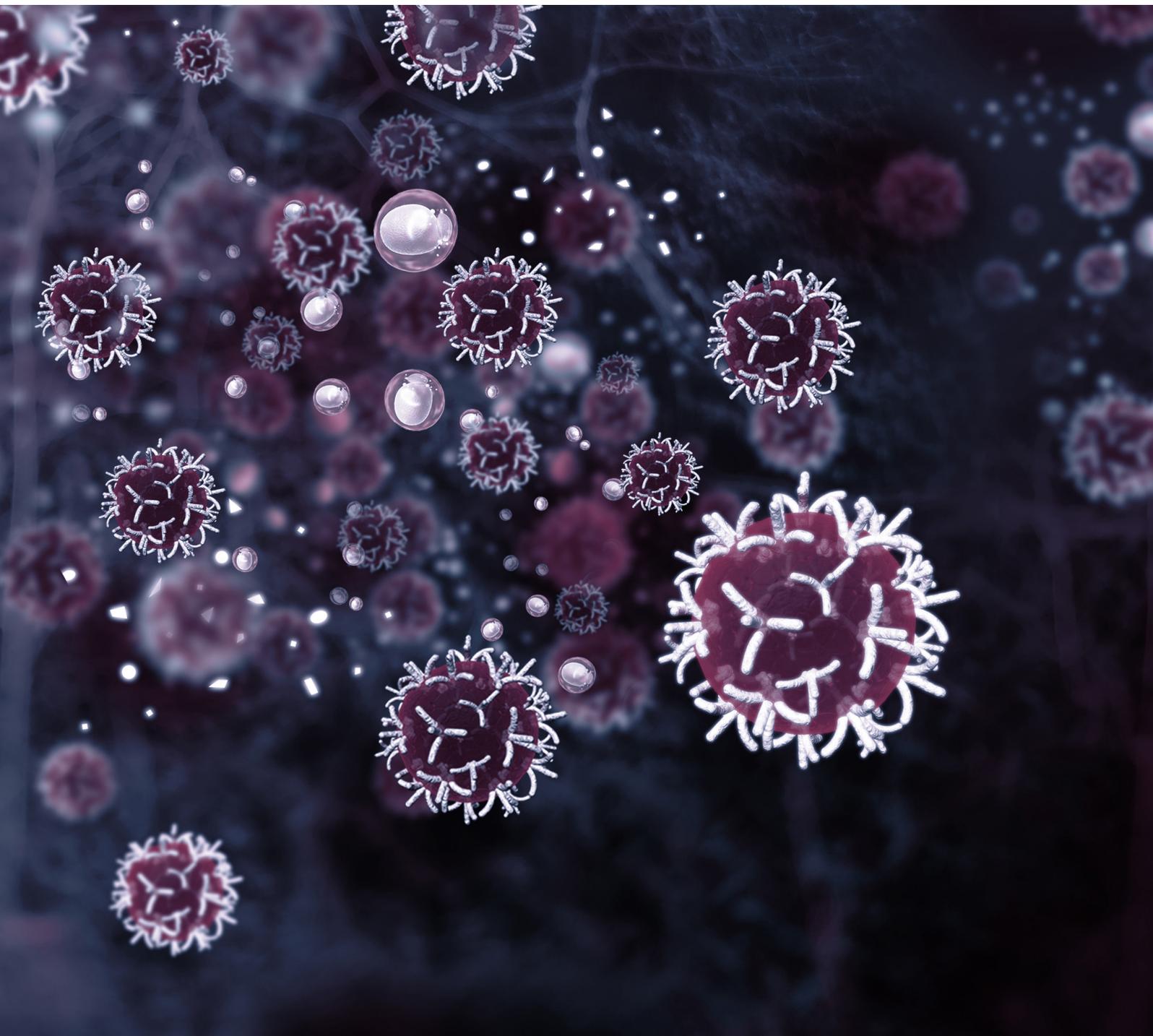




Europäisches
Patentamt
European
Patent Office
Office européen
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Landscape study on patent filing

Chimeric Antigen Receptor T-cell Immunotherapy



Abstract

This study commissioned by the European Patent Office demonstrates the application of patent information to gain insights into specific technological fields, in this case Chimeric Antigen Receptor T-cell Immunotherapy (CAR T-cell Immunotherapy). A peer-reviewed paper was published in Nature Biotechnology¹ and featured in a recent webinar².

Aim of the study

CAR T-cell therapy has captured public attention because of the remarkable responses it has produced in some patients for whom all other treatments had been ineffective. Research and development has intensified in this field over the last few years, making it a highly interesting subject for patent analysis. We present the results of our analysis on a statistically significant dataset of retrieved patent documents. We show activity of inventors and applicants, locations of inventive activity, preferred territories of patent protection and cooperation networks. Citation analysis revealed key patents. Investment in manpower (inventor count) shows the commitment of patent applicants to their R&D investment in CAR T-cell therapy.

CAR T-cell immunotherapy

One of the most recent and promising techniques for cancer treatment is Chimeric Antigen Receptor T-cell immunotherapy^{3,4}. Chimeric antigen receptors (CARs) are based on natural proteins which have been re-engineered to bind to a specific target molecule, such as one that is located on the surface of a cancer cell. This therapy is based on altering T-cells to fight cancer by genetic re-programming in the laboratory to express CARs on their surface, thereby directing the CAR T-cells to specifically bind cancer cells. The re-programmed autologous cells are introduced into the body, where the CARs enable the modified T-cells to engage and kill tumour cells.

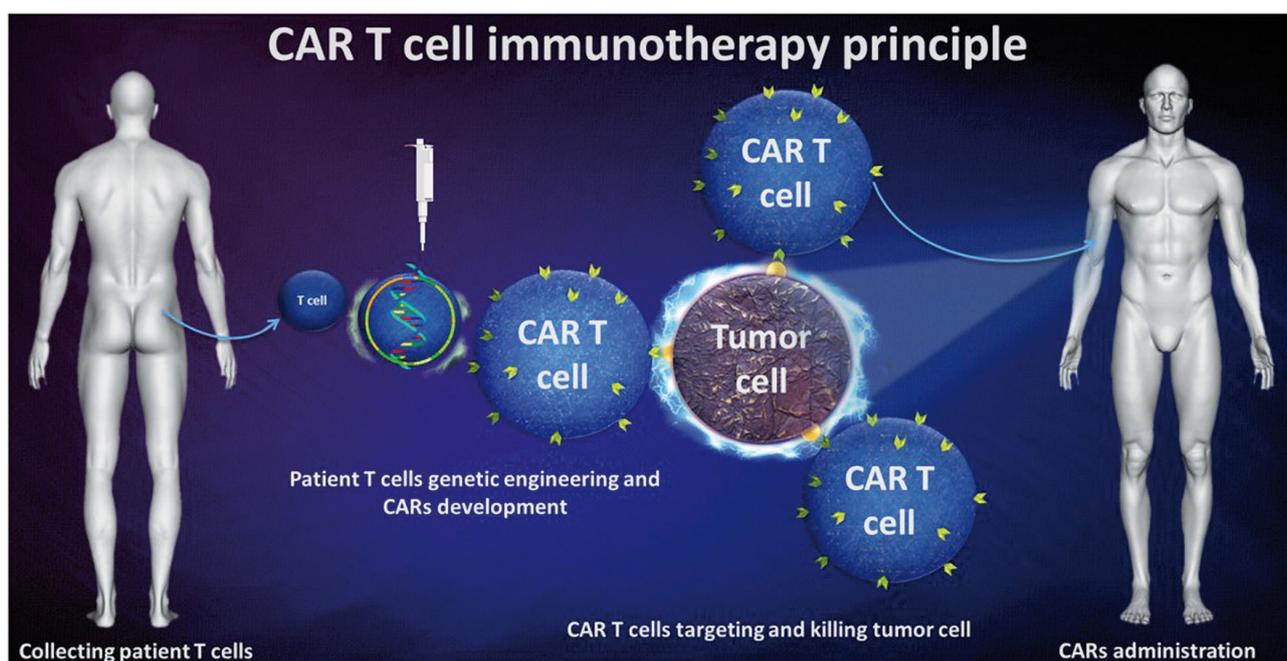
An infographic⁵ of the CAR T-cell immunotherapy principle is shown in Figure 1.

A video recording⁶ shows CAR T-cells attacking glioblastoma cells and a recent⁷ TEDx talk provides a clear explanation of the clinical, and human, relevance.

Our knowledge of T-cell mediated cytotoxicity goes back at least to the early 1960s (Golstein and Griffiths⁸ have produced a definitive timeline). It was not until the late 1980s that chimeric antigen receptor (CAR) T-cells began to be reported as showing efficacy against some haematological

Figure 1

CAR T-cell immunotherapy principle



malignancies. These and subsequent observations were, and continue to be, reported in the scientific literature. CAR T-cell immunotherapy is not only scientifically and clinically significant, but it is becoming commercially important as well.^{9,10,11}

Patent publications are an obvious and unique source of data regarding technical change. Patent information offers a basis for analysis where other data is limited, especially in emerging and research intensive sectors.^{12,13}

Taking advantage of structured formats, patent statistics are conducted on a statistically significant set of bibliographic patent references with bibliometric techniques. Those most commonly used are single field and cross-reference analysis. Single field analysis of a bibliographic patent field generates a list or a ranking, whereas the cross-reference analysis combines two fields and generates a matrix (Table 1) that can reveal valuable information for a patent landscape^{14,15} of a whole sector or a “hot” or emerging technology like CAR T-cell immunotherapy therapy.

Our dedicated literature review regarding studies that could have used patents to analyse the CAR T-cell development revealed that very few such studies have actually been published so far. With one exception, none specifically analysed CAR T-cell therapy. A generalised study of anticancer patents

by Dara and Samgawar¹⁶ did not identify instances of CAR T-cell therapy. The work of Chia-Lin and Feng-Chi¹⁷ analysed cancer immunotherapy-related patents granted by the United States’ Patent and Trademark Office (USPTO) in the past decade (2006-2016) and the article by Anaya¹⁸ described a mapping exercise of publications and patents in breast cancer immunotherapy. A recent, but very restricted study retrieved only ten CAR T-cell patent publications from the USPTO.¹⁹

Reviews which include CAR T-cell research output, only mention CAR T-cell patents in individual isolated cases, but we have found no systematic collection of patent data or patent analysis.^{20,21}

Although CAR T-cell immunotherapy may be about to enter the mainstream²² and has already been the subject of legal scrutiny²³ and discussion²⁴, the technique is still immature in terms of the volume of patent publications. For this reason, we consider CAR T-cell therapy as an emerging technology.

In view of the lack of a coherent and comprehensive overview of CAR T-cell patents, and the present, relatively small, but growing number of patent publications, the aim of our research was to perform a landscaping exercise by the analysis of patents related to CAR T-cell therapies. The present

Table 1

Information that can be revealed with cross-reference patent analysis

	Applicants	Inventors	Publication Year	Priority Country	Classes
Applicants	Collaboration between organisations	Where are the researchers working	Evolution of filing activity	Home market or most important market	Key technological areas of applicants
Inventors		Collaboration between researchers / inventors	Evolution of inventors patenting activity	Inventors country of origin	Research fields of the inventors
Publication Year			Evolution of the activity per country	Evolution of country patent output	Evolution of technology sector
Priority Country				Collaboration between countries	Key technological areas of countries
Classes					Relationships between technological domains

study thus reveals valuable information (as shown in table 2) about the evolution of the technology, its markets and main players. Indeed the current relatively small amount of patent data associated with CAR T-cell lends itself ideally to a thorough patent analytical study.

Materials and Methods

Search query

One of the first steps, as is common in patent landscaping, is the definition of a search strategy in order to retrieve the most relevant set of documents. These documents, at a later stage, will form the data set to be analysed. The search strategy is usually based exclusively on keywords, but in the case of patent documents, which include patent applications and patent specifications, we have the advantage that patents are classified according to technological field, the most significant classification schemes being the International Patent Classification (IPC)²⁵ and the Cooperative Patent Classification (CPC).²⁶

CPC is a joint classification scheme developed by the European Patent Office (EPO) and the United States' Patent

and Trademark Office (USPTO) and is based on IPC but has significantly deeper levels of hierarchy and thus can define and resolve the technology in patents in finer detail. Unfortunately not all patent documents are classified with CPC whereas most patent documents from most patent authorities worldwide are classified with IPC. Therefore two search queries were used, the first to retrieve relevant patents classified with CPC and the second to retrieve relevant CAR T-cell patents which are only classified with IPC. However, more IP authorities are starting to apply CPC to their own publications.²⁷

In order to identify classifications that best describe CAR T-cell related patents we consulted EPO patent examiners who gave input on relevant keywords and patent classifications as follows:

The first query identified CAR T-cell patents that were classified with C07K2319/03 in combination with either C07K2317/622 or C07K2317/55 (Table 2). This combined CPC search gave very relevant results, so that no further search restriction with keywords was needed.

The second query identified relevant CAR T-cell patents that were not classified with CPC but only IPC. We used the IPC classes mentioned in Table 3 and combined the query with a search of the terms "CAR T" or "chimeric antigen receptor" in the title or abstract in order to retrieve relevant results.

Table 2

CPC symbols used for the CAR T-cell query

CPC symbol	Description
C07K2319/03	Fusion polypeptide – containing a transmembrane segment
C07K2317/622	Immunoglobulins specific features – characterized by non-natural combinations of immunoglobulin fragments – comprising only variable region components – Single chain antibody (scFv)
C07K2317/55	Immunoglobulins specific features – characterized by immunoglobulin fragments – Fab or Fab'

Table 3

IPC symbols used for the CAR T-cell query

IPC symbol	Description
C07K14/705	Receptors; Cell surface antigens; Cell surface determinants
A61K35/17	Blood; Artificial blood- Lymphocytes; B-cells; T-cells; Natural killer cells; Interferon-activated or cytokine-activated lymphocytes

Databases and tools

The study used the DocDB bibliographic patent database²⁸ which is the master documentation database with worldwide coverage from the EPO. Global Patent Index (GPI)²⁹ from the EPO, and Matheo Patent 30 from Matheo Software, were the retrieval, analytical and visualisation tools used for this study. GPI is a subscription patent database that uses DocDB as its data source and Matheo Patent is a commercial patent analysis software tool that is capable of downloading patents from the EPO's free-to-use Espacenet³¹ search platform (which also uses DocDB data). The tools were selected because of their mutual complementarity. GPI was used as a powerful search tool, which allowed complex patent searches, whereas Matheo Patent was used for statistics and for the data correction / harmonisation process (mainly the applicant names and country assignments). This is a typical and time-consuming task in every bibliometric exercise, and since patent data originates from multiple patent authorities worldwide, it is quite common to find misspellings and different name variations, which have to be harmonised, or compensated for.

Results

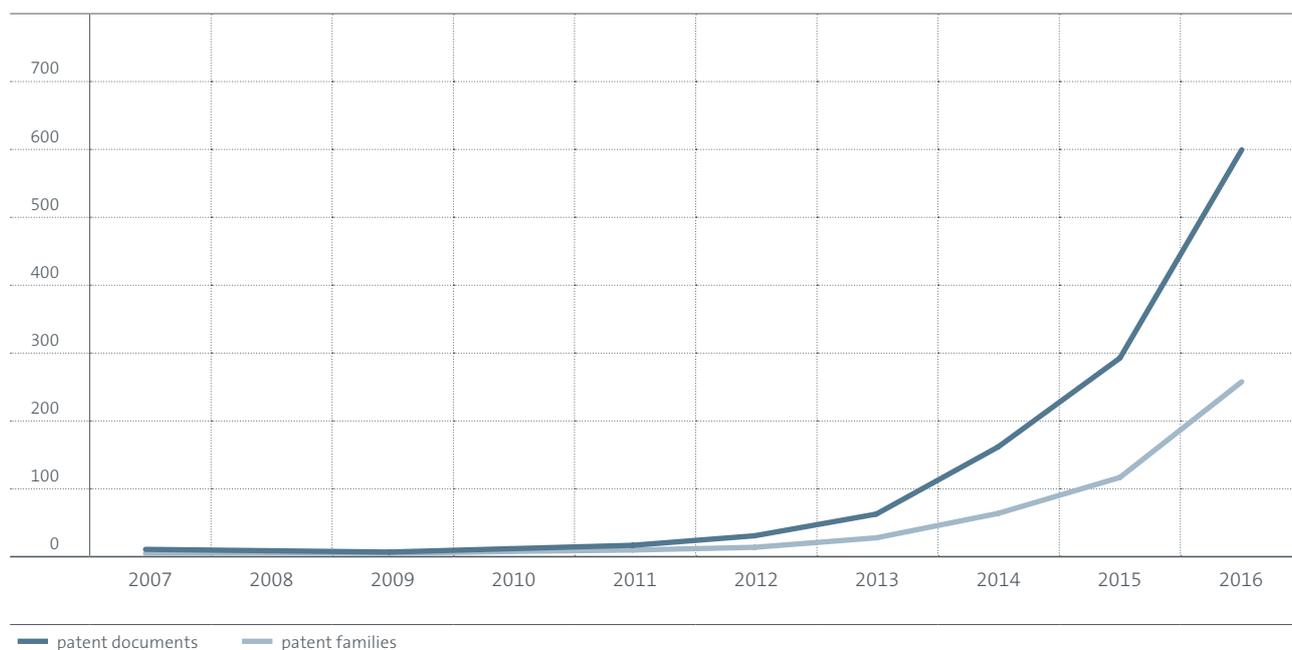
Both of the search queries which were described earlier, were combined and, after the data harmonisation process, a dataset of 1914 patent documents and 399 simple patent families was generated for the statistical analysis. For the purposes of this report, we consider the "simple patent family" as multiple patent applications filed with multiple patent offices, within 12 months of the first-filed application (priority filing) for the same invention.

Overview and evolution

The analysis revealed that CAR T- cell patenting accelerated after 2013 with a significant increase in patenting of CAR T-cell related inventions from 60 filings (25 families) in 2013 to 597 filings (255 families) in 2016 (Figure 2).

Figure 2

CAR T-cell patenting evolution



Country analysis

While analysing countries by their number of CAR T-cell applicants (applicants with residence in these countries), we identified that US and China have most applicants (together more than two-thirds of the world share of CAR T-cell applicants), followed by the UK, Germany, Japan and France (Figure 3).

We then analysed countries by their number of CAR T-cell inventions (number of patent families filed by applicants based in these countries). In this case, the USA was shown to be the most productive country (209 CAR T-cell patent families), followed by China, Switzerland, UK, Germany and France. When comparing the country output (Figure 4) with the geographical origin of applicants (Figure 3), we can see similarities in the country distribution, although it is remarkable that the USA, with nearly the same number of applicants as China (39% vs. 33%), has originated more than double the number of CAR T-cell related inventions. In the case of Switzerland, although it has less than 3% of the world share of CAR T-cell applicants, is the country from which the third highest number of CAR T-cell inventions originated, since it has few but very productive applicants (mainly the company Novartis, see also Table 4).

Figure 3

Geographical origin of CAR T-cell applicants

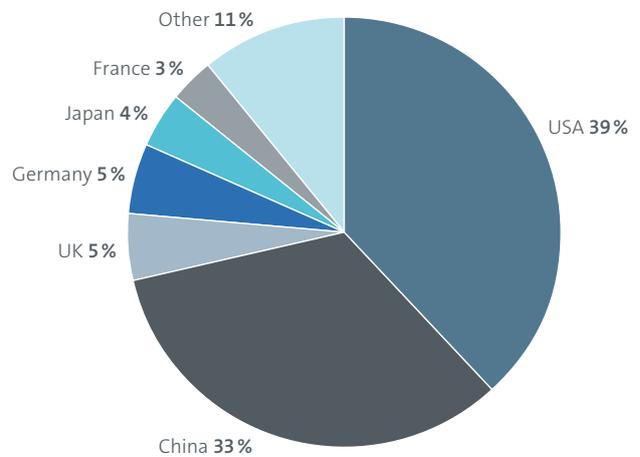


Figure 4

Most productive countries

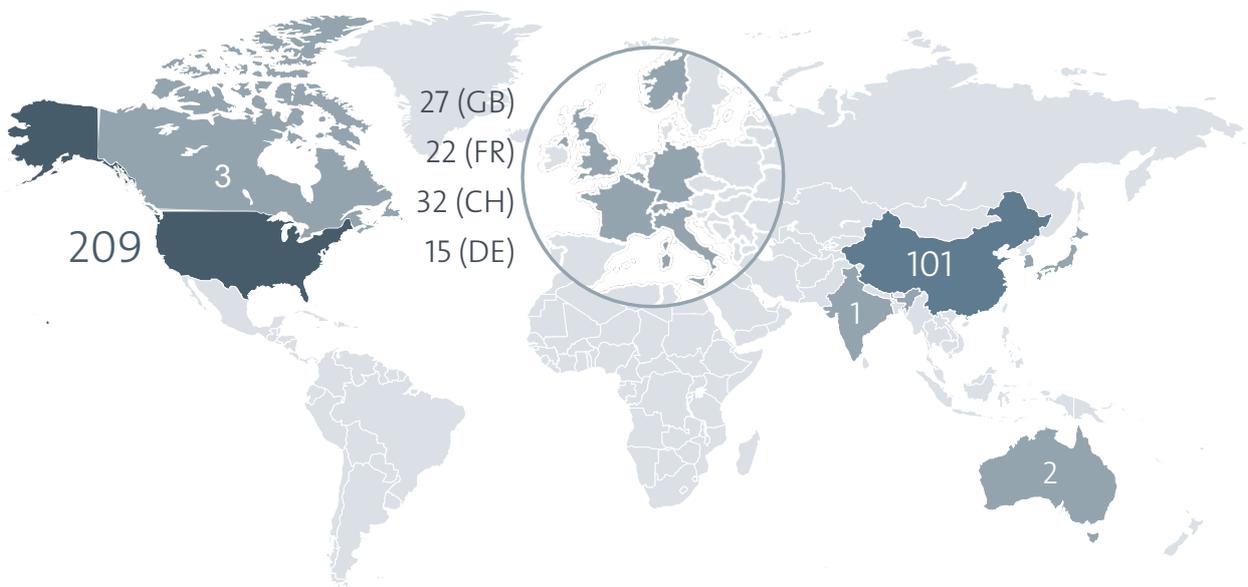
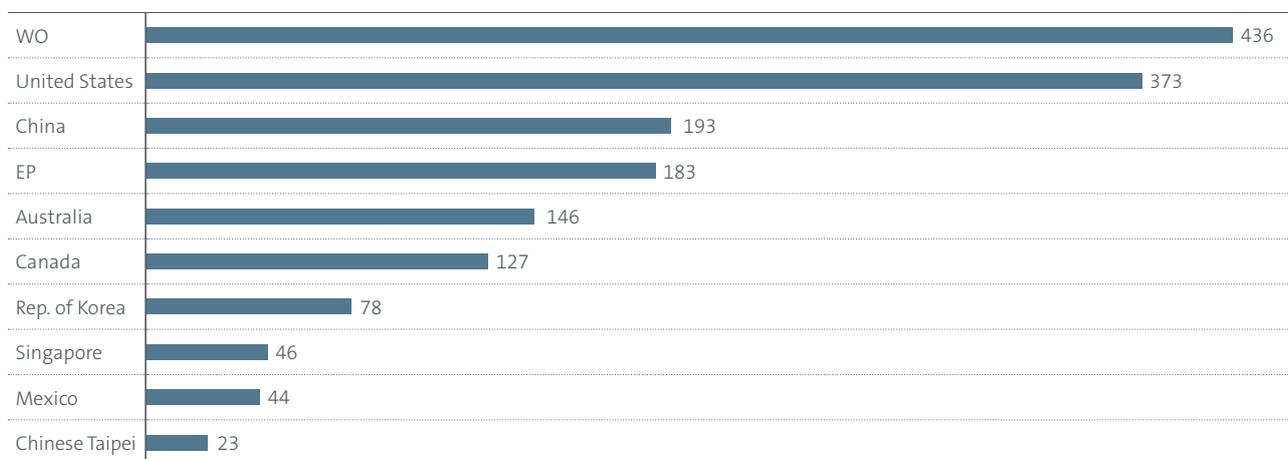


Figure 5

Top 10 jurisdictions where CAR T-cell patents have been filed



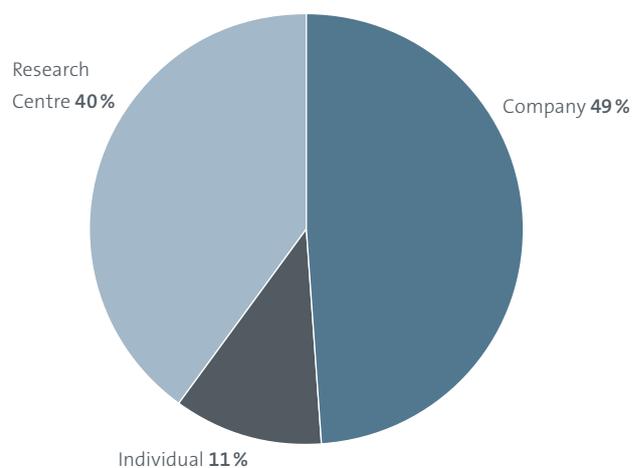
The top 10 patent jurisdictions of CAR T-cell patents are shown in Figure 5. Patent jurisdictions are the countries where a patent has been filed and thus where the applicant wants the invention to be protected. This gives us information about countries that are considered by the applicant as an important market for the CAR T-cell therapy. European patent applications (EP) under the European Patent Convention (EPC) and patent applications (WO) under the Patent Cooperation Treaty (PCT) allow patent applicants, via a single patent filing, to obtain patent protection in multiple countries in Europe and internationally, respectively. The analysis revealed that, apart from the supra-regional patent systems (PCT/WO and EP), most patents (>100) are filed in the USA, China, Australia and Canada.

Inventorship analysis

Nearly half of all CAR T-cell related patent applications are filed by private companies, followed by research centres, most of them universities, research institutes and hospitals (Figure 6). Some patent applications are filed by individuals, which in most cases are affiliated researchers, but who have 100% ownership of the patent rights.

Figure 6

Affiliations of CAR T-cell applicants



The most important commercial players were revealed to be the Swiss pharmaceutical Novartis, with 29 CAR T-cell inventions filed in 178 patents, followed by the French Cellectis, the Chinese Suzhou, and the US companies Bluebird and Eureka (Table 4).

Table 4

Ranking of top CAR T-cell applicants (Companies)

Rank	Applicant	Inventions (# patent families)	Patents (# filed)
1	Novartis AG (CH)	29	178
2	Cellectis SA (FR)	21	165
3	Suzhou Puluoda Biological Science and Tech Co Ltd (CN)	12	15
4	Bluebird Bio Inc (US)	9	31
5	Eureka Therapeutics Inc (US)	7	27
6	Sinobioway Bioeconomy Group Co Ltd (CN)	7	7
7	Shanghai Youkadi Biological Pharmaceutical Tech Co Ltd (CN)	6	6
8	Carsgen Therapeutics Ltd (CN)	5	21
9	Beijing Marino Biotechnology Co Ltd (CN)	5	10
10	Autolus Ltd (GB)	4	13
11	Shanghai Unicar-Therapy Bio-Medicine Tech Co Ltd (CN)	4	4
12	Celgene Corp (US)	3	34
13	Pfizer Inc (US)	3	18
14	Miltenyi Biotec GmbH (DE)	3	11
15	Juno Therapeutics Inc (US)	3	9
16	Cellular Biomedicine Group Ltd (CN)	3	6
17	Kite Pharma Inc (US)	3	6
18	Beijing Immunochina Medical Science & Tech Co Ltd (CN)	3	4
19	Apceth GmbH & Co KG (DE)	2	9
20	Aleta Biotherapeutics Inc (US)	2	2

We identified the University of Pennsylvania as the clear leader in the research sector with 54 CAR T-cell related inventions filed in 428 patents, followed by the University College of London in the United Kingdom, and the National Cancer Institute and the Memorial Sloan Kettering Cancer Center, both US. (Table 5).

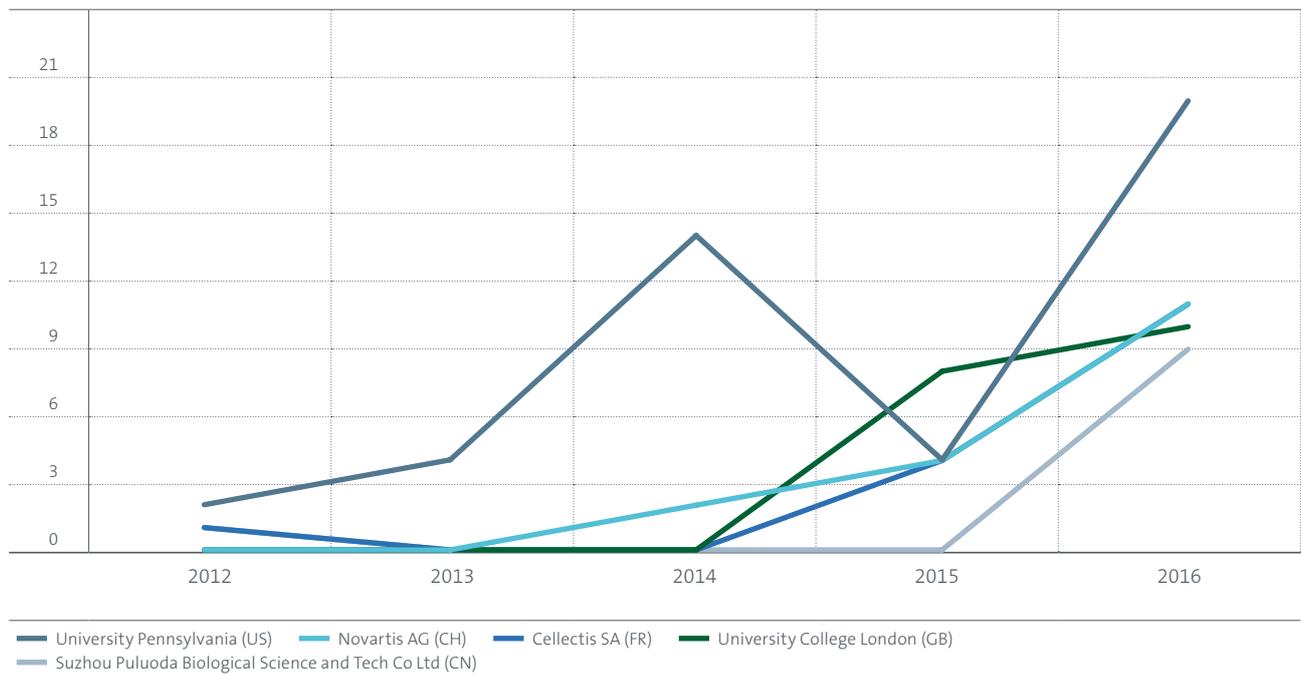
Table 5

Ranking of top CAR T-cell applicants (Research Centres)

Rank	Applicant	Inventions (# patent families)	Patents (# filed)
1	University Pennsylvania (US)	54	428
2	University College London (GB)	15	117
3	National Cancer Institute (Us Health Dep) (US)	14	98
4	Memorial Sloan-Kettering Cancer Center (US)	11	80
5	City Of Hope Research Center (US)	8	59
6	University Texas (US)	8	56
7	Baylor College Of Medicine (US)	8	40
8	Seattle Childrens Hospital (US)	6	90
9	Fred Hutchinson Cancer Research Center (US)	6	40
10	Chinese Pla General Hospital (CN)	5	10
11	University California (US)	4	32
12	Dana-Farber Cancer Institute (US)	4	17
13	University Köln (DE)	3	10
14	University Washington (US)	3	10
15	University Southern California (US)	3	4
16	University Nagoya (JP)	3	3
17	University North Carolina (US)	3	3
18	Roger Williams Medical Center (US)	2	16
19	Ohio State Innovation Foundation (US)	2	14
20	Forschungsinstitut Georg-Speyer-Haus (DE)	2	14

We then analysed the patenting evolution of the five main players over the last years, as shown in Figure 7, most of them showed a positive growth in CAR T-cell patenting, with the exception of the University of Pennsylvania that had a peak in patenting in 2014.

Figure 7
Patenting evolution of top 5 applicants (Companies and Research Centres)



An analysis of the number of patent inventions (counted by patent family) identified the top 20 CAR T-cell inventors and researchers (Table 6). The most productive individual is the American researcher Carl June. He is one of the CAR T-cell pioneers working at the University of Pennsylvania.

Patent applicant collaborations can be visualised with network node maps. These types of maps can give insights into collaboration patterns between companies and/or research centres and possible licensing of inventions.

Figure 8 shows the applicants and their respective CAR T-cell patent portfolio (number of patents, right superscript box)

and the numbers of these patents that are in co-ownership with another applicant (connecting line with number of co-applied patents).

The analysis revealed a strong partnership between the company Novartis and the University of Pennsylvania, with all CAR T-cell related patents from Novartis (29) filed in co-authorship with the University of Pennsylvania. Another remarkable cooperation is between the US company, Eureka, and the Memorial Sloan-Kettering Center, with 5 inventions in common. Taking into account the number of different cooperation partners, the Seattle Hospital is unique, having patent co-ownership with 3 other different centres.

Table 6

Ranking of top CAR T-cell inventors

Rank	Applicant	Inventions (# patent families)	Patents (# filed)
1	June Carl (US)	31	315
2	Milone Michael (US)	19	168
3	Pule Martin (GB)	17	119
4	Brogdon Jennifer (US)	14	118
5	Loew Andreas (US)	12	92
6	Luo Ruixue (CN)	12	15
7	Zhao Yangbing (US)	11	91
8	Cordoba Shaun-Paul (GB)	11	71
9	Wu Qilong (US)	10	76
10	Mannick Joan (US)	10	74
11	Murphy Leon (US)	10	74
12	Powell Daniel (US)	10	56
13	Galetto Roman (FR)	9	85
14	Glass David (US)	9	70
15	John Scholler (US)	8	81
16	Duchateau Philippe (FR)	8	56
17	Qi Wei (CN)	8	8
18	Yu Lei (CN)	8	8
19	Gill Saar (US)	7	61
20	Forman Stephen (US)	7	45

Figure 8

Network node map with applicants



Patent value analysis

In this study we also analysed several patent indicators which can help us to estimate the potential value of a patented CAR T-cell related invention.

We studied the 5 patents with most family members. “Family” means more than one application for the same invention filed with different patent authorities (Figure 9). This is an important indicator for the value of the patent, since the applicant is assumed to be willing to absorb the correspondent high costs of patenting in multiple countries.

The number of inventors/researchers participating in an invention is another indicator which can help us to measure the importance of a patent, since the investment in

manpower is interpreted as the commitment of patent applicants to their R&D investment.

Our analysis revealed that the top 5 CAR T-cell patents with most inventors are all filed by the American University of Pennsylvania, in co-ownership with the Swiss pharmaceutical Novartis (Table 7). Most of the inventors/researchers are US residents so we assume that most of the research work was done in at the University of Pennsylvania.

Table 8 shows the top 5 patents with most co-applicants, all of these were shown to originate from the same country (no international collaboration detected).

Figure 9

Top 5 patents with most family members

University Pennsylvania (US) Use of chimeric antigen receptor-modified T cells to treat cancer (WO2012079000)	62
University Washington/Seattle Childrens Hospital Production of engineered t-cells by sleeping beauty transposon coupled with methotrexate selection (WO2015157386)	59
University College London Cell (WO2015075468)	28
Cellectis SA Use of pre t alpha or functional variant thereof for expanding tcr alpha deficient t cells (WO2013176916)	25
Memorial Sloan-Kettering Cancer Center Antibodies to muc16 and methods of use thereof (WO2011119979)	24

Table 7

Top 5 patents with most inventors in co-authorship

Patent title and applicant	# of inventors and their country of residence
Cd20 therapies, cd22 therapies, and combination therapies with a cd19 chimeric antigen receptor expressing cell (Novartis and University Pennsylvania)	16 (United States) 1 (China)
Treatment of cancer using anti-cd19 chimeric antigen receptor (Novartis and University Pennsylvania)	17 (United States)
Phosphoglycerate kinase promoters and methods of use for expressing chimeric antigen receptor (Novartis, Novartis China and University Pennsylvania)	12 (United States) 2 (China) 2 (Switzerland)
Regulatable chimeric antigen receptor (Novartis and University Pennsylvania)	14 (United States) 1 (China)
Treatment of cancer using a clt-1 chimeric antigen receptor (Novartis and University Pennsylvania)	14 (United States) 1 (China)

Table 8

Top 5 patents with most applicants

Patent title and number (family representative)	# of applicants and their country
Lentiviral vectors for regulated expression of a chimeric antigen receptor molecule (WO2016012623)	5 (France)
Claudin-6-specific immunoreceptors and t cell epitopes (WO2015150327)	3 (Germany)
Kappa myeloma antigen chimeric antigen receptors and uses thereof (WO2016172703)	3 (Australia)
Anti-ror1 chimeric antigen receptors (WO2016187216)	3 (United States)
Chimeric antigen receptor (WO2017158337)	3 (United Kingdom)

The patent application entitled “Use of chimeric antigen receptor modified T Cells to treat cancer” WO2012079000 from the University of Pennsylvania has most family members and also the most citations (Figure 10), followed by a patent that is in co-ownership with the Fred Hutchinson Research Centre and the Seattle Children’s Hospital (both US).

Figure 10

Top 5 patents with most citations received

University Pennsylvania (US) Use of chimeric antigen receptor-modified T cells to treat cancer (WO2012079000)	101
Fred Hutchinson Cancer Research Center & Seattle Childrens Hospital (US) Method and compositions for cellular immunotherapy (WO2014031687)	39
Dartmouth College T cell receptor-deficient T cell compositions (WO2011059836)	36
Novartis & University Pennsylvania Treatment of cancer using humanized anti-cd19 chimeric antigen receptor (WO2014153270)	29
Novartis & University Pennsylvania Treatment of cancer using chimeric antigen receptor (WO2015142675)	27

Conclusion

This analysis confirms that the corpus of CAR T-cell patent literature we extracted is analytically viable. We have used patent data and patent analytical techniques to produce a perspective on CAR T-cell technology which would be unavailable from the analysis of conventional scientific literature.

We have deliberately excluded litigation, deals, and corporate financial aspects from our study in order to concentrate on the emergence and development of the technology per se.

We have shown that CAR T-cell immunotherapy is emerging from a subject of scientific and clinical interest to become a field of high technological and commercial significance. We have identified the most prolific inventors and patent applicants. Our study shows the geographical location where inventive activity is greatest and the territories in which patent protection is sought, and that the two are not necessarily congruent.

We have established the existence of national and international collaborations, and the corporate and individual partners. By means of citation analysis we have identified the most significant breakthroughs in CAR T-cell technology. We observe that significant CAR T-cell patent filing activity increased noticeably in 2012-2013. The USA is the country with the largest number of patent applicants in the field, closely followed by China. However, the USA has more than double

the CAR T-cell inventions. The PCT is the most frequent filing route. Industry applicants are the most numerous followed by research centres (universities, hospitals, charities etc.) The most prolific industry applicant is Novartis, and the University of Pennsylvania is the most prolific academic research applicant. Carl June is the most prolific inventor (University of Pennsylvania) and the largest CAR T-cell patent family includes WO201207900, which is also the most frequently cited patent application. The largest collaborative team of inventors is that of Novartis and the University of Pennsylvania.

A summary of this study was presented in a workshop at the Phar East Conference in Singapore 28 February to 2 March 2018³².

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