PATENTS

Evolution of CAR T-cell immunotherapy in terms of patenting activity

An analysis of published patent applications in chimeric antigen receptor (CAR) T-cell immunotherapy allows insight into the development of this emerging technology.

Over the past several years new cancer therapies have been developed that strengthen the power of a patient's immune system to attack tumors: cancer immunotherapy. One of the most promising techniques is CAR T-cell therapy[1,2]. This therapy is based on altering T cells to fight cancer by genetically reprogramming them to express on their surface chimeric antigen receptors (CARs), which are proteins that allow the T cells to specifically find and destroy cancer cells. The reprogrammed cells are introduced to the body, where the CARs enable the modified T cells to engage and kill tumor cells[3].

T-cell-mediated cytotoxicity has an extensive scientific history dating back at least to the early 1960s (ref. [4]). It was not until the late 1980s that CAR T cells began to be reported as showing efficacy against some hematological malignancies. These and subsequent scientifically and clinically significant observations were, and continue to be, reported in the scientific literature[5–7]. However, it was not until the mid-2000s that CAR T-cell immunotherapy as a technology became commercially established and began to be exploited, as relevant patent publications began to appear.

Patents essentially cover technical inventions, and the associated patent publications are an obvious and unique source of data regarding technical change. Especially in emerging and research-intensive sectors, patent information offers a basis for analysis where other data are limited[8,9]. Taking advantage of structured formats, statistical analyses can be conducted on an appropriately chosen 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 ranking whereas cross-reference analysis combines two fields and generates a matrix (Table 1) that can reveal valuable information for monitoring the evolution[10,11] of an emerging technology like CAR T-cell therapy.

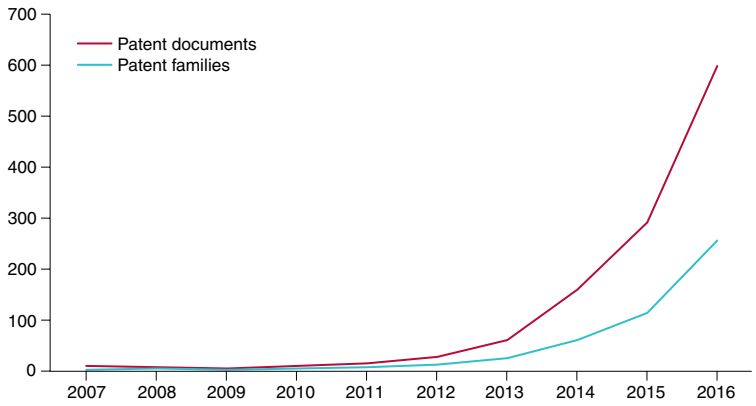

Fig. 1 | The number of CAR T-cell patents started increasing markedly in 2013.

Our literature review regarding studies that could have used patents to analyze CAR T-cell development found very few such studies. With one exception, none specifically analyzed CAR T-cell therapy. A generalized study of anticancer patents[12] did not identify instances of CAR T-cell therapy. There is an analysis of cancer immunotherapy–related patents granted by the US Patent and Trademark Office in the past decade (2006–2016)[13] and a mapping exercise of publications and patents in breast cancer immunotherapy[14]. A recent but very restricted study retrieved only ten CAR T-cell patent publications from the US Patent and Trademark Office[15].

Table 1 | Example of information that can be revealed with cross-reference patent analysis

	Applicants	Inventors	Publication year	Priority country	Patent classification
Applicants	Collaboration between applicants	Where are the inventors working	Evolution of applicants' patenting activity	Home market or most important market	Key technological areas of applicants
Inventors		Collaboration between inventors	Evolution of inventors' patenting activity	Inventors' country of origin	Research fields of the inventors
Publication year				Evolution of country patent output	Evolution of technology sector
Priority country				Collaboration between countries	Key technological areas of countries
Patent classification					Relationships between technological domains

Table 2 | Ranking of top CAR T-cell applicants (companies)

Rank	Applicant	Inventions (No. patent families)	Patents (No. filed)
1	Novartis (Switzerland)	29	178
2	Cellectis (France)	21	165
3	Suzhou Puluoda Biological Science & Technology (China)	12	15
4	Bluebird Bio (US)	9	31
5	Eureka Therapeutics (US)	7	27
6	Sinobioway Bioeconomy Group (China)	7	7
7	Shanghai Youkadi Biological Pharmaceutical Technology (China)	6	6
8	CARSgen Therapeutics (China)	5	21
9	Beijing Marino Biotechnology (China)	5	10
10	Autolus (UK)	4	13
11	Shanghai Unicar-Therapy Bio-medicine Technology (China)	4	4
12	Celgene (US)	3	34
13	Pfizer (US)	3	18
14	Miltenyi Biotech (Germany)	3	11
15	Juno Therapeutics (US)	3	9
16	Cellular Biomedicine Group (China)	3	6
17	Kite Pharma (US)	3	6
18	Beijing Immunochina Medical Science and Technology	3	4
19	Apceth (Germany)	2	9
20	Aleta Biotherapeutics (US)	2	2

Table 3 | Ranking of top CAR T-cell applicants (universities and research centers)

Rank	Applicant	Inventions (No. patent families)	Patents (No. filed)
1	University of Pennsylvania (US)	54	428
2	University College London (UK)	15	117
3	National Cancer Institute (Department of Health) (US)	14	98
4	Memorial Sloan Kettering Cancer Center (US)	11	80
5	City of Hope Research Center (US)	8	59
6	University of Texas (US)	8	56
7	Baylor College of Medicine (US)	8	40
8	Seattle Children's Hospital (US)	6	90
9	Fred Hutchinson Cancer Research Center (US)	6	40
10	Chinese PLA General Hospital (China)	5	10
11	University of California (US)	4	32
12	Dana-Farber Cancer Institute (US)	4	17
13	University of Köln (Germany)	3	10
14	University of Washington (US)	3	10
15	University of Southern California (US)	3	4
16	University of Nagoya (Japan)	3	3
17	University of 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 (Germany)	2	14

Reviews that include CAR T-cell research output mention CAR T-cell patents in individual isolated cases, but we have found no systematic collection of patent data or patent analysis[16,17]. Although CAR T-cell immunotherapy may be about to enter the mainstream[18] and has already been the subject of legal scrutiny[19], the technique is still immature in terms of the volume of patent publications. For this reason we consider CAR T-cell therapy to be 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, we performed a technology monitoring exercise by analyzing patents related to CAR T-cell therapies. The present study reveals information about the evolution of the technology, its markets and main players (Table 2) that may be of value to R&D managers and researchers in the field. Indeed, the relatively small number of patents associated with CAR T-cell lends itself ideally to a thorough patent analytical study.

Results

A dataset of 1,914 patent documents and 399 simple patent families was generated for the statistical analysis. For the purposes of this study we consider the 'simple patent family' as multiple patent applications filed with multiple patent offices within 12 months of the first (priority filing) for the same invention. The full methodology of the study is described in the Supplementary Methods.

Overview and evolution. The analysis revealed that CAR T-cell patenting took off in 2013, with an increase in patenting of CAR T-cell related inventions from 60 filings (25 families) in 2013 to 597 filings (255 families) in 2016 (Fig. 1).

Country analysis. When analyzing countries by their number of CAR T-cell applicants (applicants with residence in these countries), the United States and China had most applicants (together more than two-thirds of the world share of CAR T-cell applicants), followed by the UK, Germany, Japan and France (Fig. 2a).

We then analyzed countries by their number of CAR T-cell inventions (number of patent families filed by applicants based in these countries). In this case, the United States was the most productive country (209 CAR T-cell patent families), followed by China, Switzerland, the UK, Germany and France. When comparing the country output (Fig. 2b) with the

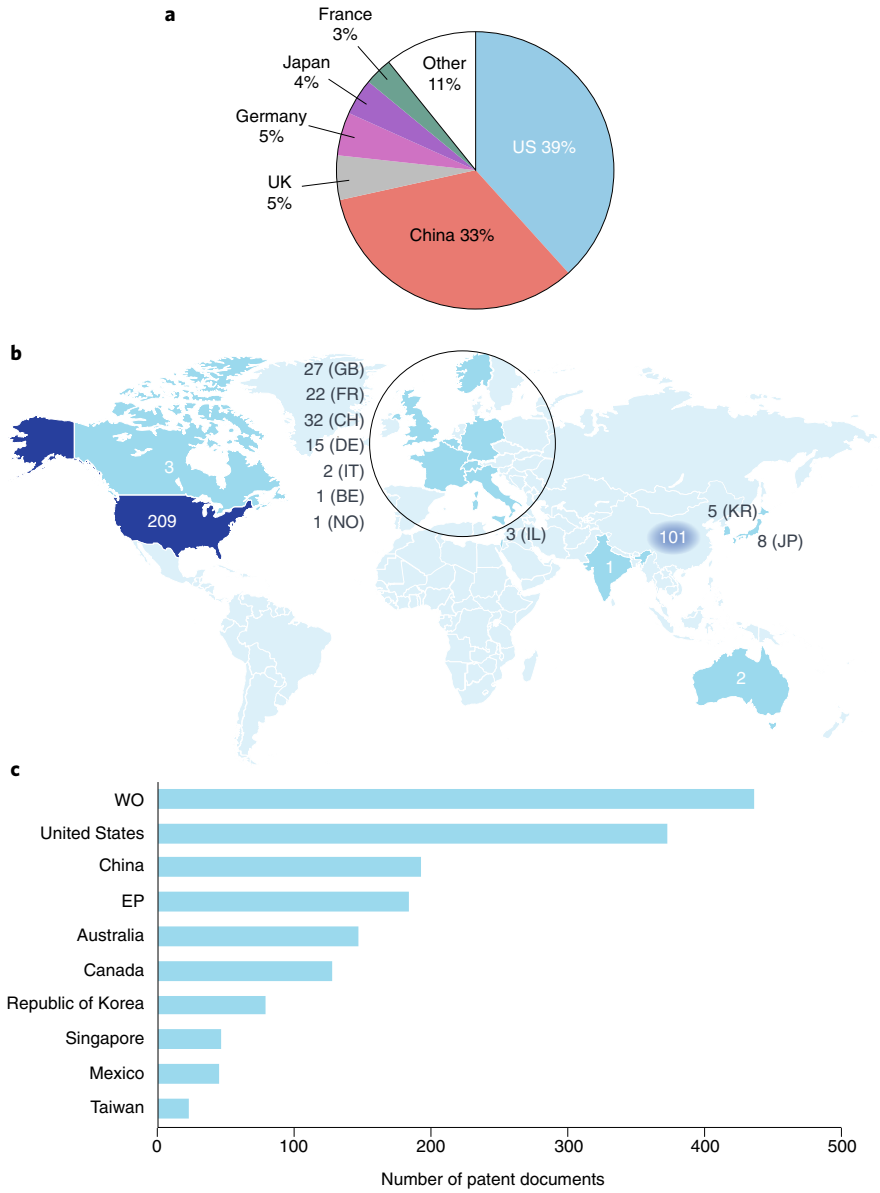

Fig. 2 | Geographical analysis of CAR T-cell patenting activity. a, Country of residence of CAR T-cell patent applicants. **b**, Most productive countries, by number of inventions (patent families). GB indicates the UK; FR, France; CH, Switzerland; DE, Germany; IT, Italy; BE, Belgium; NO, Norway; IL, Israel; KR, Republic of Korea; JP, Japan. **c**, The top ten jurisdictions where CAR T-cell patent protection has been sought (patent filings).

geographical origin of applicants (Fig. 2a), we can see similarities in the country distribution, although it is remarkable that the United States, with nearly the same percentage of applicants as China (39% vs. 33%), has originated more than twice the CAR T-cell-related inventions. In the case of Switzerland, although it has less than 3% of the world's CAR T-cell applicants, it is the country that originated the third-highest number of CAR T-cell inventions, since it has few but very productive applicants.

The top ten jurisdictions of CAR T-cell patents are shown in Fig. 2c. 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 important markets for the CAR T-cell therapy. European patent (EP) applications under the European Patent Convention and World Intellectual Property Organization patent applications (WO) under the Patent Cooperation Treaty 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 supranational patent systems (European Patent Convention and Patent Cooperation Treaty), most patents (>100) are filed in the United States, China, Australia and Canada.

Inventorship analysis. Nearly half of all CAR T-cell-related patents are filed by private companies, followed by research centers—most of them universities, research institutes and hospitals (Fig. 3). Some patents are filed by individuals, which in most cases are researchers who are affiliated with a research center but have 100% ownership of the patent.

Of the companies, the most important players were revealed to be the Swiss pharma Novartis, with 29 CAR T-cell inventions filed in 178 patents, followed by the French biotech Cellectis, Suzhou from China, and the US companies Bluebird and Eureka (Table 2).

When analyzing universities' and research centers' filings, we identified the University of Pennsylvania as the undisputed leader, with 54 CAR T-cell-related inventions filed in 428 patents, followed by University College London, the US National Cancer Institute and Memorial Sloan Kettering Cancer Center (Table 3).

We then analyzed the patenting evolution of the five main players over the past few years. Most of them showed a constant growth in CAR T-cell patenting, with the exception of the University of Pennsylvania, whose activity fell in 2015 before rebounding (Fig. 4).

An analysis of the number of patent inventions (counting by patent family) revealed the top 20 inventors and researchers working with CAR T-cells (Table 4). The most productive was US researcher Carl June of the University of Pennsylvania.

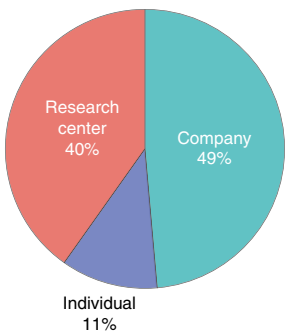

Fig. 3 | Organizational affiliations of CAR T-cell applicants.

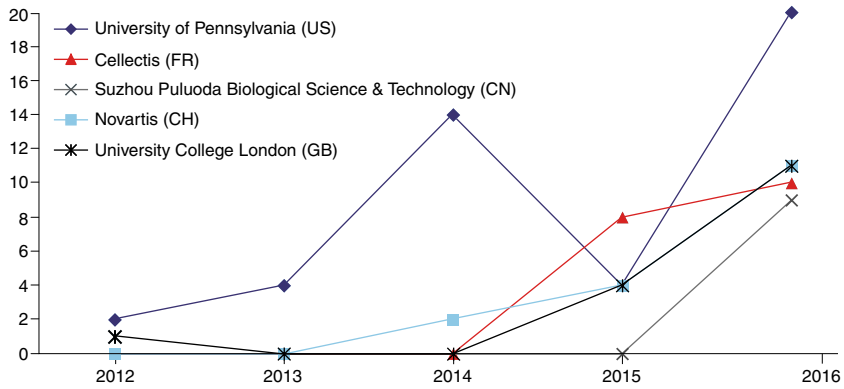

Fig. 4 | Patenting evolution of the top five CAR T-cell applicants. FR, France; CN, China; CH, Switzerland; GB, the UK.

Patent applicant collaborations can be visualized with network node maps. These types of maps can give insights into collaboration patterns between companies and/or research centers and possible licensing of inventions. The analysis reveals a strong partnership between Novartis and the University of Pennsylvania, with all CAR T-cell related patents from Novartis (29) filed in coauthorship with the University of Pennsylvania (Fig. 5). Another remarkable cooperation was between Eureka Therapeutics and Memorial Sloan Kettering Cancer Center, with five inventions in common. Examining the number of different cooperation partners, Seattle Children's Hospital was the only one that has patent co-ownership with three different other centers.

Patent value analysis. We also analyzed several patent indicators that can help measure the potential value of a patented CAR T-cell related invention. We studied the five patents with most family members (Fig. 6a). This is an important indicator for the value of the patent because it shows that the applicant is willing to absorb the high costs of patenting in multiple countries.

The number of inventors or researchers participating in an invention is another indicator that can help measure the importance of a patent because the investment in manpower shows the commitment of patent applicants to their R&D investment. Our analysis revealed that the top five CAR T-cell patents with most inventors were all filed by the University of Pennsylvania in co-ownership with Novartis (Table 5). Most of the inventors or researchers are US residents, and therefore we can assume that most of the research was done at the University of Pennsylvania. Table 6 shows the top five patents with most applicants in co-ownership. All of these turned out to originate from the same country (no international collaboration detected).

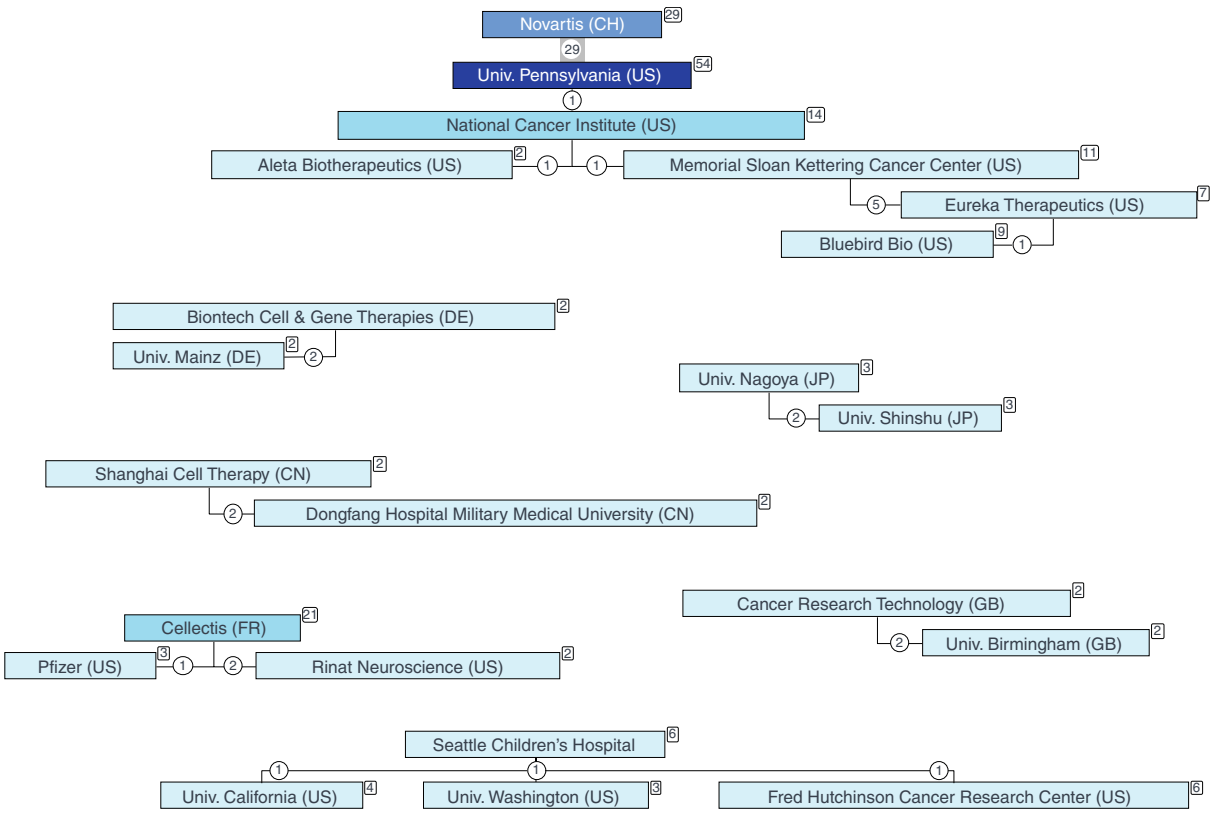

Fig. 5 | Network node map of CAR T-cell applicants. Applicants are shown with their respective CAR T-cell patent portfolio (number of patents, right superscript box) and the numbers of these patents that are in co-ownership with another applicant (connecting line with number of coauthored patents). CH, Switzerland; CN, China; DE, Germany; FR, France; GB, the UK; JP, Japan.

Table 4 | Ranking of top CAR T-cell inventors

Rank	Inventor	Inventions (No. patent families)	Patents (No. filed)
1	Carl June (US)	31	315
2	Michael Milone (US)	19	168
3	Martin Pule (UK)	17	119
4	Jennifer Brogdon (US)	14	118
5	Andreas Loew (US)	12	92
6	Luo Ruixue (China)	12	15
7	Zhao Yangbing (US)	11	91
8	Shaun-Paul Cordoba (UK)	11	71
9	Wu Qilong (US)	10	76
10	Joan Mannick (US)	10	74
11	Leon Murphy (US)	10	74
12	Daniel Powell (US)	10	56
13	Roman Galetto (France)	9	85
14	David Glass (US)	9	70
15	John Scholler (US)	8	81
16	Philippe Duchateau (France)	8	56
17	Qi Wei (China)	8	8
18	Yu Lei (China)	8	8
19	Saar Gill (US)	7	61
20	Stephen Forman (US)	7	45

Table 5 | Top five patents with most inventors in coauthorship

Patent title and applicant	No. of inventors and their country of residence
CD20 therapies, CD22 therapies and combination therapies with a CD19 chimeric antigen receptor expressing cell (Novartis & University of Pennsylvania)	16 (United States) 1 (China)
Treatment of cancer using anti-CD19 chimeric antigen receptor (Novartis & University of Pennsylvania)	17 (United States)
Phosphoglycerate kinase promoters and methods of use for expressing chimeric antigen receptor (Novartis & Novartis China & University of Pennsylvania)	12 (United States) 2 (China) 2 (Switzerland)
Regulatable chimeric antigen receptor (Novartis & University of Pennsylvania)	14 (United States) 1 (China)
Treatment of cancer using a CLL-1 chimeric antigen receptor (Novartis & University of Pennsylvania)	14 (United States) 1 (China)

Table 6 | Top five patents with most applicants

Patent title and number (family representative)	No. of applicants and their country of residence
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 (UK)

The patent "Use of chimeric antigen receptor modified T cells to treat cancer" (WO2012079000) from the University of Pennsylvania is not only the one with most family members but also the most cited (Fig. 6b), followed by a patent co-owned by the Fred Hutchinson Cancer Research Center and the Seattle Children's Hospital.

Conclusions

The results of our analysis confirm the existence of an analytically viable corpus of CAR T-cell patent literature. We have used patent data and patent analytical techniques to produce a perspective on CAR T-cell technology that would be unavailable from the analysis of conventional scientific literature. We have deliberately excluded litigation, deals and corporate financial aspects from our study to concentrate on the emergence and development of the technology per se.

We have shown that CAR T-cell immunotherapy is emerging from scientific and clinical interest and evolving into technological and commercial significance. We have identified the most prolific inventors and patent applicants. Our study shows the geographical locations where invention activity is greatest and the territories in which patent protection is sought; the two are not necessarily congruent. We have furthermore shown the existence of national and international collaborations and corporate and individual partners. By means of citation analysis, we have identified the most significant breakthroughs in CAR T-cell technology.

We observe that substantial CAR T-cell patent filing activity began in 2012–2013 and that most applicants resided in the United States and China. Although the two countries had comparable numbers of applicants, the United States had twice as many CAR T-cell inventions. The Patent Cooperation Treaty is the most frequent filing route. Industry applicants are more numerous than research centers and universities, with the most prolific applicants being Novartis and the University of Pennsylvania, respectively. The most prolific inventor is Carl June 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.

In carrying out this research, we have demonstrated the applicability of our methodology to the emerging CAR T-cell therapy technology. We are confident that we can apply the same patent

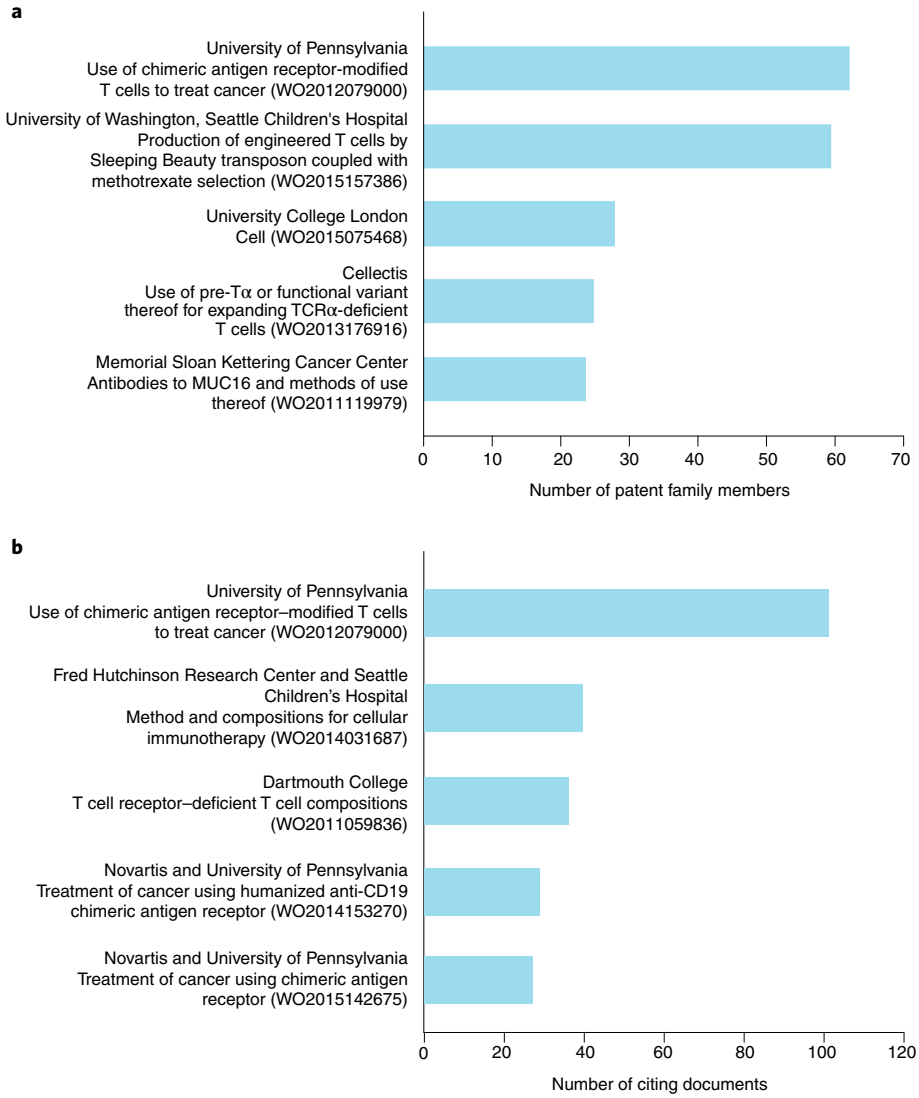

Fig. 6 | CAR T-cell patent value analysis. a, Top five CAR T-cell patents with the most family members. **b**, Top five CAR T-cell patents with most citations received.

analytical methodology to other emerging technologies. A summary of this study was presented by one of us (N.S.C.) in a workshop at the Phar East Conference in Singapore in 2018 (28 February to 2 March; http://www.terrapinn.com/exhibition/phar-east/speakers.stm).

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Competing interests

The authors declare no competing interests.

Additional information

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