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PATENTS

The global chimeric antigen receptor T (CAR-T) cell therapy patent landscape

Global patents in the field of CAR-T cell therapy show a changing landscape with fierce competition and intensive collaboration.

As revolutionary immuno-oncology changes to cancer treatment[1], cell therapies have attracted widespread attention with their high clinical remission rate in hematological cancers. Since 2018, cell therapies have accounted for more remissions than cancer vaccines[2], with chimeric antigen receptor T (CAR-T) therapies leading the global cell therapy development race[3]. The US Food and Drug Administration (FDA) approved two CAR-T cell therapies in 2017, a milestone in immune oncology — Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel)[4]. The US Centers for Medicare & Medicaid Services made a national coverage determination[5] for FDA-approved CAR-T cell therapies on 7 August 2019, and national health insurance in England and Japan began covering Kymriah in the last two years[6,7]. There has also been an increase in patent disputes surrounding CAR-T, with the suit between Gilead Sciences' Kite Pharma division and Bristol Myers Squibb's Juno Therapeutics[8] the most notable example.

According to data from the US Patent and Trademark Office (USPTO), CAR-T patents showed sharp growth in the past decade, with an average development speed of 2.09 as compared with the baseline level of 1.05 in the patent population (Supplementary Fig. 1; average development speed is defined as the geomean of annual development speed values over the observation period, which can be calculated as the ratio of the patent count in year n to the patent count in year $n - 1$). However, no comprehensive patent analyses have been conducted in this area of rapid growth. A previous study on the patent landscape of CAR-T covered only patent applications before 2017 and did not include a systematic analysis of patent content[9]. Here, we aim to present a comprehensive overview of the landscape of CAR-T patents that differs from the existing literature by its extended search strategy (Supplementary Note) and integrated analysis from the temporal, organizational, spatial and technical perspectives. This research provides a series of key messages to support the relevant decision-making of key stakeholders, including academics, government officials, and industrial leaders.

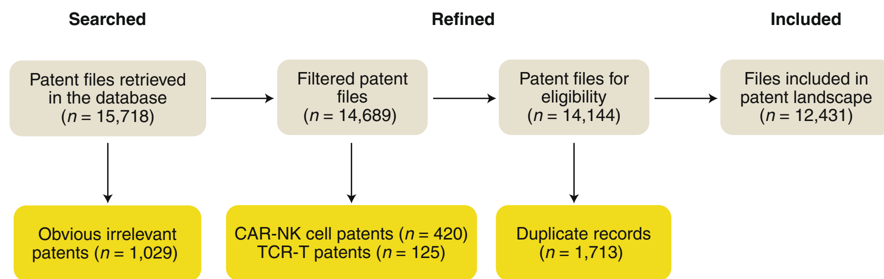

Fig. 1 | Flow diagram of patent sample. The yellow boxes show the number of excluded patent files and the relevant reasons.

Methods

To achieve the research objectives mentioned above and avoid common shortcomings in patent landscape reporting[10], we adopted the criteria of the Reporting Items for Patent Landscapes (RIPL) statement[11] and referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12] to collect all patent documents related to CAR-T worldwide. The study retrieved patents samples with a priority date before 31 December 2019 using a series of searching terms related to "chimeric antigen receptor" in Derwent Innovation (https://clarivate.com/products/derwent-innovation/), a well-known patent database. To avoid missing data, we searched for these terms in items including the title, abstract, claims and Derwent World Patents Index (DWPI) field.

For all sampled patent records, this research selected various data, such as inventor, assignee, address of the inventor, address of the assignee, citations, application year and publication year. We first excluded irrelevant patents manually and then used Derwent Innovation to deduplicate records — for example, different document types (B2, A1) of a given publication — to avoid multiple counts for the same invention. Moreover, after judging the relevance of targets to patent files by a hierarchical reading order from title, abstract, claims and full text, we added target labels to relevant patent records. In addition, we used statistical figures and tables to describe patent data and analyzed different patent networks by employing the software platforms Gephi and Cytoscape. More detailed methods are described in the Supplementary Note.

Results

In total, 15,718 patent documents were initially obtained from the database. We excluded obviously irrelevant patents ($n = 1,029$; for example, patents related to automobiles), CAR-NK cell patents ($n = 420$), and TCR-T patents ($n = 125$). We also excluded duplicate records from the database ($n = 1,713$) to avoid multiple counts for the same invention. Ultimately, 12,431 patent documents were included in this analysis of the patent landscape, involving a total of 2,783 International Patent Documentation Center (INPADOC) extended patent families[13] (Fig. 1). The patents included in this study are listed in the Supplementary Data.

Top inventors and assignees. The top 20 inventors are located in the United States, the United Kingdom and France (Table 1). Among them, Carl H. June, one of the creators of CAR-T, is an inventor on the most patents; Martin Pule and Shaun Cordoba are second and third, respectively.

Table 1 | Top CAR-T cell inventors

Rank	Inventor	Patents	
		No. of files	No. of families
1	Carl H. June (United States)	562	44
2	Martin Pule (United Kingdom)	493	61
3	Shaun Cordoba (United Kingdom)	279	41
4	Philippe Duchateau (France)	268	35
5	Laurent Poirot (France)	260	26
6	Michael C. Milone (United States)	256	22
7	Roman Galetto (France)	225	12
8	Jennifer Brogdon (United States)	218	19
9	Michael C. Jensen (United States)	214	19
10	Bruce L. Levine (United States)	203	9
11	Julianne Smith (United States)	184	12
12	Michael D. Kalos (United States)	178	7
13	Simon Thomas (United Kingdom)	173	27
14	Cheng Liu (United States)	169	16
15	Saar Gill (United States)	159	15
16	Steven A. Rosenberg (United States)	154	12
17	Laurence J. N. Cooper (United States)	148	19
18	Alexandre Juillerat (United States)	146	16
19	Yangbing Zhao (United States)	141	15
20	Julien Valton (United States)	140	15

By statistics on types of assignees, commercial companies are dominant, accounting for 61% of the total, while universities and hospitals account for 25%, non-profit organizations for 13%, and individuals for 1%. In the top 20, there are one assignee each from France, Switzerland and China, two from the United Kingdom, and the remainder from the United States (Table 2). The University of Pennsylvania is the highest-ranking assignee, followed by Bristol Myers Squibb.

The ranking of inventors and assignees by family counts is shown in Supplementary Tables 4 and 5. Statistics on patent family size by country are shown in Supplementary Table 6.

Institutional and regional collaboration. The main collaborative relationships and patterns among assignees (Fig. 2a) shows 136 nodes (assignees) and 199 edges (co-ownership relationships among assignees). For better visualization performance, the network only displays large clusters with more than five institutional members and gives label names of active institutions with the most partners. For an information-rich institutional collaboration network, see Supplementary Fig. 2.

The University of Pennsylvania and Novartis have the closest collaboration (Fig. 2a). Many organizations with a large number of patents, including Bristol Myers Squibb, the US Department of Health and Human Services, and Memorial Sloan Kettering Cancer Center, have such cooperative relationships, forming a huge collaboration network. We divided the organizations in the information-rich institutional collaboration network into non-commercial institutions and commercial companies and explored the cooperative relationships between them. This analysis showed that collaboration involving non-commercial institutions accounts for 82% of the total.

European organizations have formed a collaboration network centered on the French National Institute of Health and Medical Research (Institut National de la Santé et de la Recherche Médicale, or Inserm), the French National Center for Scientific Research (Le Centre National de la Recherche Scientifique, or CNRS) and University College London. Asian assignees play a weaker role in the collaboration network.

To characterize regional collaboration in CAR-T patents, we transformed the institutional network into a regional network by merging assignees whose headquarters are located in a same region (Fig. 2b). In this network, nodes denote regions and edges denote collaborative relationships between co-assignees, weighted by summing relevant counts at the institutional level. In total, the network across regions includes 16 nodes and 24 edges. The United States is dominant in developing wide partnerships with different countries; United States–Switzerland is a distinct collaborative pair that hit the highest collaboration frequency of 66 — far higher than the other pairs. By contrast, despite being the second largest node behind the United States, China has relatively few partners and collaborations with neighboring countries Japan and Korea. Europe seems to lack a centralized mechanism to develop CAR-T technologies: European countries are parallel-connected with the United States central node in the network, with the only exceptions being France and the United Kingdom linking neighbors (Fig. 2b). Nevertheless, France and the United Kingdom have cultivated their own distinct clusters (Fig. 2a).

Geographic distribution. To distinguish where patents come from and where they go (technological origination and market destination), we drew line charts of CAR-T patent documents by the location of assignees and the jurisdictions that are filing patents. Figure 3a indicates the annual growth of CAR-T patent documents by the top five assignee countries. As the first mover, the United States first developed CAR-T patents in 2005, with France and other leading countries following in 2008 and 2012, respectively. Chinese assignees have filed the second largest number of patents since 2017, though they still represent less than one-tenth of the total for the United States. Other leading countries have shown relatively slow development.

Figure 3b shows annual changes in CAR-T patent documents by the top five patent offices. The USPTO and the China National Intellectual Property Administration (CNIPA) have consistently filed similar numbers of patent applications; China ($n = 119$) exceeded the United States ($n = 107$) for the first time in 2016. Patent applications in the European Patent Office and Japan Patent Office have maintained a relatively stable growth trend. However, patents received in Canada have shown a sharp decrease since 2018.

CAR-T targets. Figure 4 shows the top 20 targets of CAR-T by patent families and the relevant leading countries. CD19 is the most frequent target, followed by BCMA and CD20. Assignees in the United States

Table 2 | Top CAR-T cell assignees

Rank	Assignee	Patents	
		No. of files	No. of families
1	University of Pennsylvania (United States)	908	108
2	Bristol Myers Squibb (United States)	507	82
3	Novartis (Switzerland)	499	71
4	Cellectis (France)	495	52
5	Memorial Sloan Kettering Cancer Center (United States)	482	60
6	Department of Health and Human Services (United States)	457	67
7	University College London (United Kingdom)	428	40
8	Fred Hutchinson Cancer Research Center (United States)	244	40
9	Eureka Therapeutics (United States)	226	24
10	Baylor College of Medicine (United States)	223	36
11	University of California (United States)	220	45
12	Gilead Sciences (United States)	220	27
13	Bluebird bio (United States)	211	27
14	City of Hope National Medical Center (United States)	203	27
15	Dana-Farber Cancer Institute (United States)	192	36
16	Seattle Children's Hospital (United States)	176	15
17	Autolus Therapeutics (United Kingdom)	172	39
18	CARsgen Therapeutics (China)	150	30
19	University of Texas (United States)	150	24
20	Roche Holding (Switzerland)	134	12

and China not only cover all targets, but also lead in almost all top targets. Assignees in Switzerland focus more on CD19, BCMA, CD20, CD22 and mesothelin, while the United Kingdom focuses more on CD33 and PD-1/PD-L1, and France more on CD123. Germany, Korea and Canada focus respectively on CD30, CEA and MUC1; HER-2, EGFR and GPC3; and HLA. Japan and Singapore hit one top target, GPC3, while Finland hits only MUC1.

Citation network and milestone patents. We linked CAR-T patent families by citations to form a citation network (Fig. 5) in which there are 2,784 nodes and 7,057 edges. Figure 5a visualizes a landscape of CAR-T inventions by highlighting clusters and key inventions within clusters, coupled with the evolution process of clusters shown in Fig. 5b. The yellow clusters, which contain the most patents, are centered on WO2012079000 and WO2014153270, which focus mainly on the construction of early CARs and the application of the target CD19, which are cited by the most subsequent patents. The purple cluster contains the second largest number of patents, and the patents appear later, mostly cited after 2013. In this cluster, the types of patents are complicated, such as the improvement of the domain (WO2017025038), potential commercial targets (WO2016014789 and WO2016094304) or a conditionally activatable CAR that can be controlled pharmacologically (WO2014127261). The blue cluster is also at the center of the citation network and contains several patents that have been cited many times. For example, WO2013123061 mentions two antigen-specific targeting regions, and WO2012129514 is related to genetically modified CD4$^+$ T cells. The main cited patents in the pink cluster focus on allogeneic cells and related methods, such as WO2013176915 (methods for engineering allogeneic and immunosuppression-resistant T cells for immunotherapy), WO2014191128 (methods for engineering T cells for immunotherapy by using an RNA-guided Cas nuclease system) and WO2014039523 (multi-chain chimeric antigen receptor and uses thereof). The three patents have the same assignee, the French biopharmaceutical company Cellectis. In addition, 42.76% patents in the relatively young green cluster were filed by Chinese assignees, and the share of Chinese assignees in this cluster is much higher than in other clusters (more details in Supplementary Table 7). For an information-rich citation network, see Supplementary Fig. 5.

On the basis of the citation network, we generated a timeline of CAR-T research and development with milestone patents (Fig. 6). This highlights milestone patents and relevant assignees, thereby showing the most important historical patents in terms of citation numbers (see Supplementary Note for details). The University of Pennsylvania has three milestone patents and St. Jude Children's Research Hospital, City of Hope National Medical Center and Novartis, as patentees, have two each.

Discussion

We identified several patterns of CAR-T-relevant patents, including the geographic scope, the scale of organizational assignees, their involvement in co-patenting activities, and technological connections among patents, all of which followed the trend of rapid increases in patenting activities. Box 1 summarizes key points.

Temporal. In the past decade, CAR-T technology has developed rapidly. The number of CAR-T patent applications per publication year has increased annually since 2010, which is consistent with the publication dates of breakthrough literature in this field[14,15]. CAR-T entered a period of rapid development after 2015 (Fig. 3a,b), which may be the result of the main developers in this field (namely, Novartis, Gilead Sciences' Kite Pharma and Bristol Myers Squibb's Juno Therapeutics) obtaining breakthrough designations by the US FDA in 2014 and 2015. In particular, Novartis announced its phase 2 clinical data of CAR-T targeting CD19 molecules in the treatment of refractory and recurrent acute lymphoblastic leukemia, with complete remission rates reaching 93% and 92%, respectively, at the 57th American Society of Hematology Annual Meeting and Exposition in 2015, which caused a boom in research and development in this field[16]. In the same year, Kite Pharma and Juno Therapeutics were involved in patent disputes[8].

Organizational. In the CAR-T field, close collaborations have been established between a variety of organizations, including hospitals, universities, research institutes and pharmaceutical companies. The analysis of cooperative relationships between different types of assignees in institutional networks showed that non-commercial organizations dominate cooperation related to CAR-T patents.

On the one hand, the demand for collaboration between non-commercial

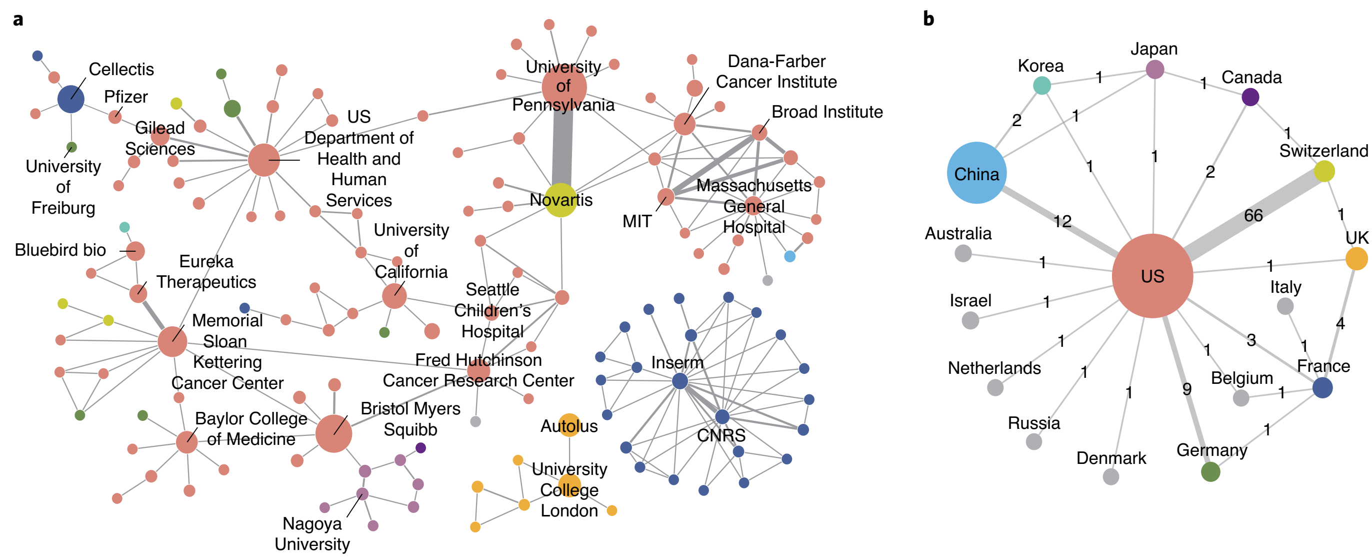

Fig. 2 | **Collaboration networks of CAR-T patents. a**, Institutional collaboration network, in which nodes denote assignees and edges represent co-assignee relations. **b**, Regional collaboration network. Nodes denote regions in which assignees are located, and edges corresponding collaborations based on co-assignee relations. Node size is scaled to the number of patent families, while the thickness of edges represents collaboration frequency (also given as a numerical value). Red, United States; light blue, China; dark blue, France; yellow, Switzerland; lilac, Japan; gold, United Kingdom; green, Germany; purple, Canada; aquamarine, Korea; gray, other countries: Australia, Belgium, Denmark, Israel, Italy, the Netherlands and Russia.

Box 1 | Key messages

Temporal. With rapid development in the past decade, CAR-T immunotherapy has become a hot area in which commercial organizations compete fiercely and universities and industry collaborate intensively.

Organizational. An open innovation model has been well established in the CAR-T area due to the intrinsic demand for non-commercial organization–industry partnerships and strong technological complexity. Non-business institutions played a more positive role by shifting the collaborative mode from technology assignment or licensing to co-development or joint ownership, as seen in the most frequent collaboration pair — the University of Pennsylvania and Novartis.

Spatial. As the most dominant country in CAR-T cell therapy, the United States holds the most patents, is linked to other countries most widely, covers all relevant targets, and has a majority of the top inventors and assignees. As the country on track to have the most patenting activity, China has attracted the most worldwide patent applications, though no therapy has yet been launched.

Technical. CD19 is the most frequent target, while exploring multiple targets, universal CAR-T cells and industrial preparation have become new research hotspots.

organizations and pharmaceutical companies is based on the complexity of CAR-T technology. As CAR-T cells are an autologous living cell drug, manufacturers are cooperating directly with designated hospitals instead of selling through traditional channels. In the collaboration network, collaborative relationships between non-commercial organizations and pharmaceutical companies are often established through their affiliated hospitals, as in the collaborations between Memorial Sloan Kettering Cancer Center and Eureka Therapeutics, the US Department of Health and Human Services and Gilead Sciences, and University College London and Autolus Therapeutics[17]. Many pharmaceutical companies have closed their traditional R&D bases and opened new R&D centers in close proximity to world-class academic institutions.

On the other hand, non-commercial organizations can benefit from close collaboration with pharmaceutical companies[18]. Partnerships between industry and academia have been developing since 2000[19]. However, traditional collaboration models, such as the transfer of achievements in scientific research or sponsorship from commercial companies, cannot fully meet the needs of non-commercial organizations. Especially in the CAR-T field, non-commercial organizations are actively transforming their mode of collaboration through resource sharing, collaborative R&D and joint patents. For example, the early patent collaboration between the University of Pennsylvania and Novartis was realized through technology transfer and licensing. After 2012, the mode of collaboration between the two changed to joint patent holding. At the same time, the University of Pennsylvania and Novartis are co-assignees of 422 patents (55 patent families), which puts them at the core of the collaboration network (Fig. 2a); they also share some milestone patents (Fig. 6). Similarly, in the United Kingdom, University College London and Autolus Therapeutics not only have many patents, but also work closely together.

The institutional landscape in the field of CAR-T has been remarkably impacted by mergers and acquisitions (M&A) in recent years. Kite Pharma was bought by Gilead in 2017, Juno Therapeutics by Celgene in 2018, and Celgene by Bristol Myers Squibb in 2019. As a result, Bristol Myers Squibb has become the second largest node and occupies a prominent position in Fig. 2a. The acquisition of Kite also provided a platform for Gilead's efforts to build an

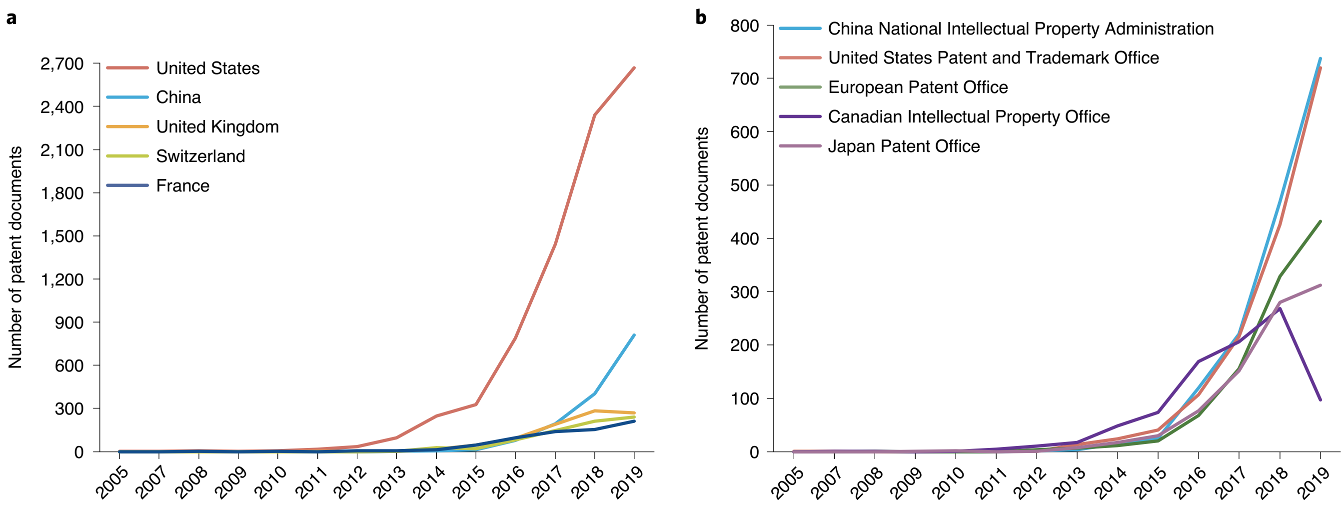

Fig. 3 | Publication trend of CAR-T patents. a, CAR-T patent documents by publication year and by the top five regions in which assignees are located. **b**, CAR-T patent documents by publication year and by the top five patent offices in which patents are filed. The cumulative numbers by all involved regions and patent offices are shown in Supplementary Figs. 3 and 4, respectively.

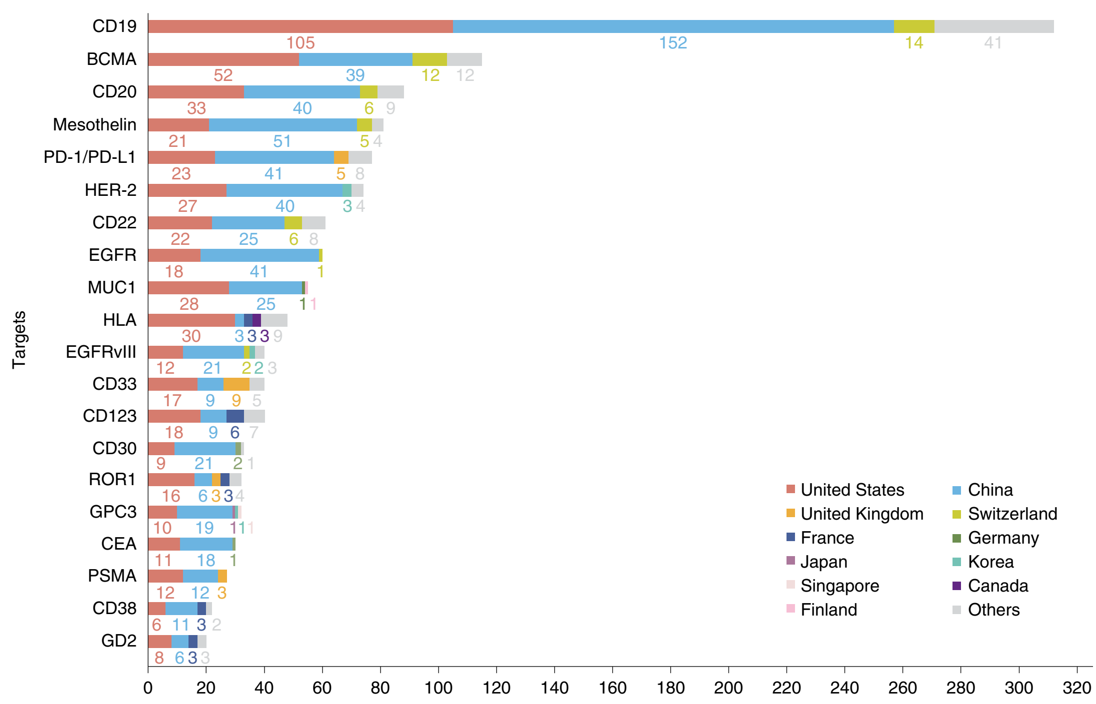

Fig. 4 | Top 20 targets in CAR-T patents.

industry-leading cell therapy franchise in oncology[20]. M&A is not uncommon in the pharmaceutical industry, and pharmaceutical companies are keen on growing their R&D capabilities by complex and expensive business activity in which patents are usually important[21]. The wide influence of M&A deals on the CAR-T institutional landscape may be masked if we neglect the fact that target companies in these transactions are pioneer institutions with core patents.

Spatial. Patent collaboration networks at the national level are rarely mentioned in patent landscapes, although such networks can convey a great deal of useful information. We found the United States at the center of the collaboration network, with cooperative relationships with other countries. The United States has the greatest collaboration with Switzerland, followed by China and Germany. Most of the collaboration between the United States and Switzerland is between the University of Pennsylvania and Novartis. The close collaboration between the United States and France is mainly due to Cellectis and its partners in the United States (for example, Pfizer).

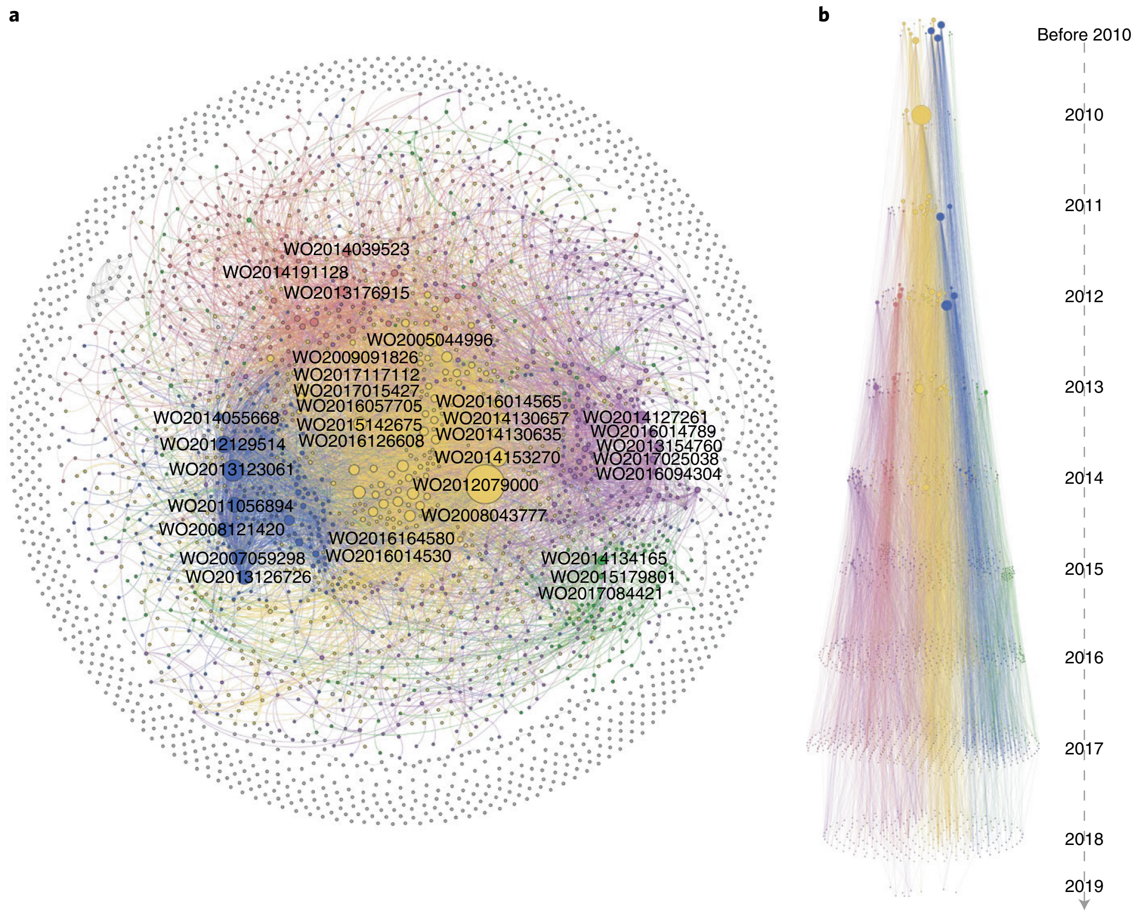

Fig. 5 | Patent citation network on CAR-T. a, The whole citation network. Each node represents a patent family as defined by the International Patent Documentation Center (INPADOC). Nodal size was set according to out-degree value (that is, the number of forward citations). Thus, the greater the out-degree, the more citations a patent received and the larger the node size. Network clusters were detected using the Louvain modularity method and further marked by different colors. The largest cluster (yellow) accounts for 20.73% in total; purple, 14.83%; pink, 10.02%; blue, 7.90%; green, 5.46%; gray, others. The color of the edge is the same as the color of the patent being referenced. Important nodes are labeled with patent family numbers. **b**, Time slice chart of the citation network. According to the earliest priority year, we divided it into 11 time slices for the top to bottom (before 2010 and every ordinal year from 2010 to 2019).

China, which has the second largest number of patent applications, only has 15 co-assigned patent families involving international collaboration. By comparison, Germany, which has few patents, has 10 patent families that show international collaboration (Fig. 2b). The number of patents filed by China has increased since 2015, with single assignees remaining commonplace. Compared with earlier European and US organizations that developed this technology, there is less collaboration between Chinese patent assignees. It is worth discussing the potential reasons for this phenomenon. In the Chinese pharmaceutical industry, problems such as small scale, a large number of companies, duplication of construction and vicious competition have always plagued development of the industry. Moreover, the long-term constraints of laws and regulations, the market system, technical barriers and other factors may result in insufficient in-depth collaboration in China[22].

Even so, the economic benefits brought by the excellent clinical efficacy of CAR-T technology and the market demand brought by China's large population base have aroused great enthusiasm and interest from researchers and companies worldwide. The number of patent documents published by the CNIPA ($n = 119$) exceeded those published by the USPTO ($n = 107$) for the first time in 2016. More than half of the patents ($n = 61$) were submitted by non-Chinese assignees. The current trend suggests that China is about to surpass the United States and become the market with the highest patent activity. This trend is similar to that seen in the related field of CRISPR patents[23].

Nevertheless, China's patent system also has a great impact on other countries' access to China. Based on our data, China has granted a total of 160 CAR-T-related patents, of which 130 have Chinese assignees, and only 30 patents have been granted from other countries. For example, Novartis and the University of Pennsylvania began applying for patents in China in 2011. CN103492406 (one of the patent family members of WO201207900, filed on December 9, 2011) was rejected after four reviews and claims revisions. Other patents of the same family, such as CN108103085 and CN106220739, were also not granted. Clinical trials of Novartis's tisagenlecleucel (CTL-019) were approved in China in August 2019, and its second clinical application was filed in February 2020, but Novartis still has no patents granted in China. A question that hangs over CAR-T market development in

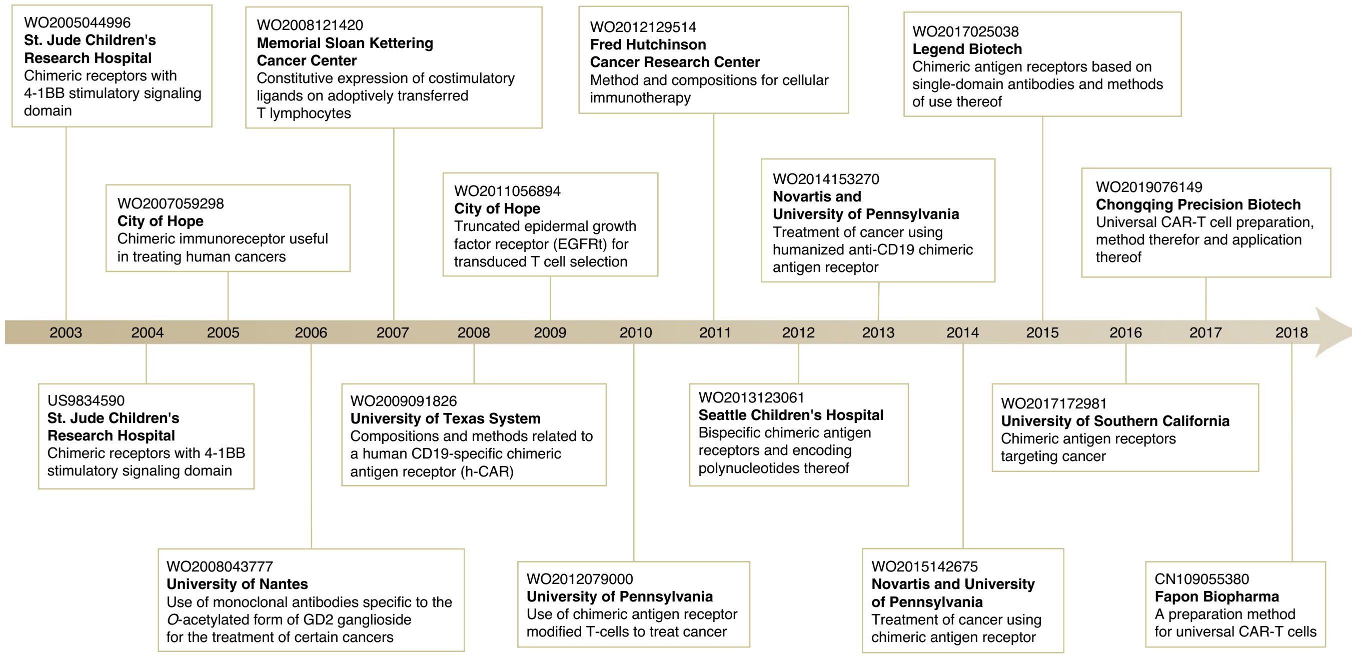

Fig. 6 | Milestone CAR-T patents. Milestone patents were identified by patent citation analysis. Patent number, assignee and title are shown.

China is whether innovative developers can achieve patent approvals in China to block potential competitors before market access.

Technical. The distribution of targets shown by the patents is consistent with clinical studies[2], in which CD19 is the most popular target. However, subtle differences still exist that facilitate predictions for future drug development. In clinical studies, the BCMA target in theT cell field was relatively understated compared to its second place in patents (Fig. 4), though the target holds potential for the treatment of multiple myeloma[24]. CD20 is mainly used to treat melanoma, and there are 88 patent families for this target, including 33 in the United States, 40 in China and 6 in Switzerland.

Furthermore, the clustering obtained in the patent citation network can help us to see the relationship between patents (Fig. 5). The main patents in the yellow cluster were applied for by Novartis and the University of Pennsylvania. They are highlighted below.

1. Patents focused on targets. The core patents in the cluster are WO2014130635 (effective targeting of primary human leukemia using anti-CD123 CAR engineered T cells), WO2014130657 (treatment of cancer using a humanized anti-EGFRvIII CAR), WO2014153270 (treatment of cancer using a humanized anti-CD19 CAR) and WO2016014565 (treatment of cancer using a humanized anti-BCMA CAR), which focus on the application of CD19, BCMA and CD123 targets, respectively, in the fields of myeloma and glioma.
2. Combination with specific inhibitors. This can enhance antitumor effect; for example, WO2016164580 (combination of CAR therapy and amino pyrimidine derivatives) and WO2016014530 (combinations of low, immune-enhancing doses of mTOR inhibitors and CARs).
3. Bispecific CAR-T. This is an important branch occurring in the cluster; for example, WO2016126608 (CAR-expressing cells against multiple tumor antigens and uses thereof). Clinical studies have demonstrated that dual-targeted CAR-T cells are a strategy for cellular immunotherapy that avoids the loss of a single target antigen and enhances the affinity of CAR-T cells for tumor cells[25].
4. Basic research on the periphery of core technologies. A few examples include WO2017015427 (methods for improving the efficacy and expansion of immune cells), WO2017117112 (methods of making CAR-expressing cells) and WO2016057705 (biomarkers predictive of therapeutic responsiveness to CAR therapy and uses thereof). From the preparation of T cells to their purification to personalized immunotherapy, patent WO2016057705 has been repeatedly cited by other patents in the cluster.

As for patent applications in the CAR-T technology field, Novartis has not only focused on the selection and regulation of targets, but they have also paid more attention to trends in upstream and downstream process development related to commercialization and clinical application. This deserves to be noted as an example by other pharmaceutical companies.

Partnerships are more likely to produce high-quality results and accelerate technology diffusion and technology innovation. The main patents in the blue cluster in Fig. 5a were filed by Memorial Sloan Kettering Cancer Center (WO2014055668 and WO2008121420), Seattle Children's Hospital (WO2013123061) and Fred Hutchinson Cancer Research Center (WO2012129514), and the cluster also includes many highly cited patents. The aforementioned organizations are also closely linked in the collaboration network (lower left cluster).

In addition, the development history of CAR-T technology can be seen from milestone patents (Fig. 6). Generally, CARs are referred to as first-generation CARs (containing an extracellular binding domain, a transmembrane domain, a hinge region and intracellular signaling domains), second-generation CARs (adding a co-stimulatory domain), third-generation CARs (combining multiple co-stimulatory domains) or fourth-generation CARs (further enhancing T cell expansion, persistence and antitumor activity)[16]. This trend is similar in patent activity, from the rise of the early basic technology (for example, WO2005044996 and US9834590) to the exploration of different applicable targets (for example, WO2008043777, WO2009091826 and WO2011056894) and the development of optimization technology (for example, WO2012079000, WO2014153270 and WO2017025038). The most cited patents now begin to explore new universal CAR-T cells (for example, WO2019076149 and CN109055380). These patents seek to improve the safety, killing effect and side effect profile of CAR-T technology.

Moreover, in terms of the importance of tracking the patent landscape in areas of rapid development, this research provides a methodological basis for patent landscape analysis, including the use of baseline comparisons to reflect patent activity, a combination of automatic searching and manual checking, exploration broken down into temporal, organizational, spatial and technical aspects, network visualization and analysis, and standard reporting coverage.

Finally, we note that this research cannot cover all patents related to CAR-T, although we have tried to use as comprehensive a search strategy as possible. We recognize that the kind of patent landscape supported by objective data is of great importance to real-world decisions, but we do not neglect the significance of expert opinions. In fact, the integration of objective patent landscape into domain expertise can improve and assist decision-making more effectively.

Conclusions

CAR-T immunotherapy is a field of cancer treatment with great potential, and the number of patent applications is growing rapidly. An open innovation model highlighting academia–industry partnerships has been well established in the CAR-T area. The United States is in a leading position and holds the most patents, is most widely linked to other countries, covers all relevant targets, and has the majority of top inventors and assignees. China is attracting increasing numbers of patent applications and overtook the United States in this metric for the first time in 2016, even though no therapy has been launched thus far. CD19 is the most frequent target, while exploring multiple targets, universal CAR-T cells, and industrial preparation have become new research hotspots.

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Competing interests

The authors declare no competing interests.

Additional information

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