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A bibliometric analysis of research on chimeric antigen receptor T cells

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Abstract: **To explore the main authors, institutions, countries, hotspots and frontiers in the research field of chimeric antigen receptor T cells (CAR-T). The relevant literature on chimeric antigen receptor T cells was retrieved from Web of Science (WOS). The visualization maps were generated by CiteSpace and VOSviewer. We identified a total of 1644 articles among which 1596 articles were published in English. We observed rapid growth in the number of articles after 2010. Mol Ther had the largest number of publications, while Blood was the most co-cited journal. The USA contributed most publications. The largest numbers of papers were written by June Ch. The research in the field of CAR-T mainly focuses on the basic theory and hematological system tumors. Conclusion: The USA contributes the most studies on chimeric antigen receptor T cells. After 2010, relevant studies increased rapidly. There were active cooperations between authors, countries, and institutions. Research hotspots and further research should focus on hematological tumors and solid tumors.**

Keywords: Bibliometrics analysis; Chimeric antigen receptor T cells; Hot topics; Development trends; CiteSpace; VOSviewer

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1. Introduction

In recent years， Chimeric antigen receptor T cells(CAR-T) has become the most promising immunotherapy for cancer. In CAR-T therapy, a kind of exogenous chimeric antigen receptors are added into T cells extracted from cancer patients[1]. After amplification in vitro, the modified T cells are transfused back into the patients. CAR-T therapy has many advantages, such as limitation of non-major histocompatibility complex (MHC) [2], wide target, long survival time, long action time[3] and low rejection reaction. It has achieved remarkable achievements on the treatment of hematological tumors. Davila and his team reported that the complete remission rate of CAR-T therapy on patients with refractory and recurrent B-cell acute lymphoblastic leukemia was 88% [4]. More and more clinical trials were performed on CAR-T therapy for solid tumors. Grove and his team introduced a clinical trial of 10 patients with ovarian cancer treated with CAR-T in 2006 [5].

CiteSpace and VOSviewer are two kinds of the most influential software for information analysis in Bibliometric visualization, which were used to measure domain-specific literature and explore critical paths, knowledge break point and development trends of the scientific field[6]. In this study，we not only tried to show the general research situation of chimeric antigen receptor T cells by the software of CiteSpace and VOSviewer, including years, journals, authors, institutions, countries, keywords and references but also explore the research hotspots and frontiers.

2. Method

2.1 Data source and search strategy

The relevant literature on Chimeric antigen receptor T cells was retrieved from the Web of Science (WOS) on September 18, 2019. Retrieval strategy was: TS= ("chimeric antigen receptor" and ("T cell*" or "T lymphocyte*" or "modified T cell*" or "modified T lymphocyte*" or "transduced T cell*" or "transduced T lymphocyte*" or "engineering T cell*" or "engineering T lymphocyte*" or "transgenic T cell*" or "transgenic T lymphocyte*")) or TS= ("CAR-T"). The time period of publication was from the inception of the database to August 31, 2019. Retrieval was performed on a single day to avoid deviation caused by daily updates of databases. There were no restrictions on data types and languages. Articles were included only in this study. A total of 1644 eligible articles were retrieved.

2.2 Data analysis

The analytical function of WOS was used to analyze the publication language. The VOSviewer was used to create visualization map of authors, co-cited authors. High-frequency keywords network map and density

map was created by VOSviewer. CiteSpace was used to design visualization map for journals, the dual-map overlay for journals, countries, institutions, co-cited references and detect citation bursts for references and Timeline View. In the map, different nodes represented different parts such as authors, journals, countries, institutions. The size of nodes reflects frequency of elements. The lines between nodes represented relationship such as cooperation, co-occurrence and co-citation[7].

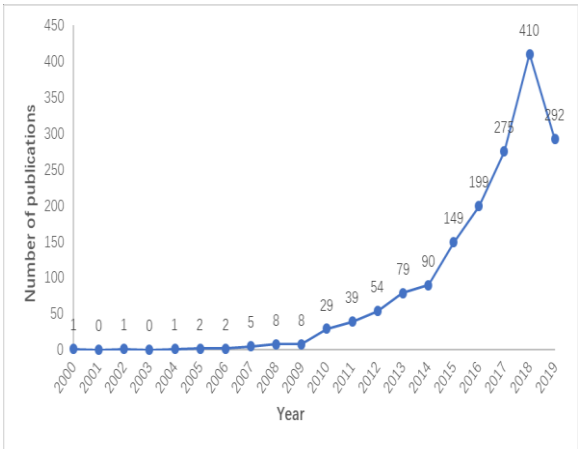

Figure 1. Publication years of chimeric antigen receptor T cells.

The fractional counting method of VOSviewer was used and customized to ignore documents with many authors (maximum number of authors per document: 25). The CiteSpace was set up as follows: time slicing (2000-2019), years per slice (2), node types (choose one at a time), selection criteria (Top 50), pruning(pathfinder: pruning the merged network).

3. Results

3.1 Publication language

A total of 1644 articles were included in the study and published in nine languages. Of 1644 articles, 1596(97.080%) were published in English, 29(1.764%) in French, 10(0.608%) in German, 3(0.182%) in Chinese, 2(0.122%) in Russian, and 1(0.061%) in Hungarian, Portuguese, Spanish, Turkish.

3.2 Publication years

As what is shown in Figure 1, the first article of chimeric antigen receptor T cells was published in 2000[8]. Before 2009, there were few studies in this field, with no more than 10 papers published annually. After 2010, the number of articles increased rapidly, especially after 2014. One possibility was that the effectiveness of CAR-T cells on patients with lymphoma was first reported in 2010[9]. After 2010, besides the United States, China and Europe began to register clinical trials of CAR-T cells[10]. From 2015 to 2019, 1325 articles were published which accounted for 80.59% of the total volume of publications.

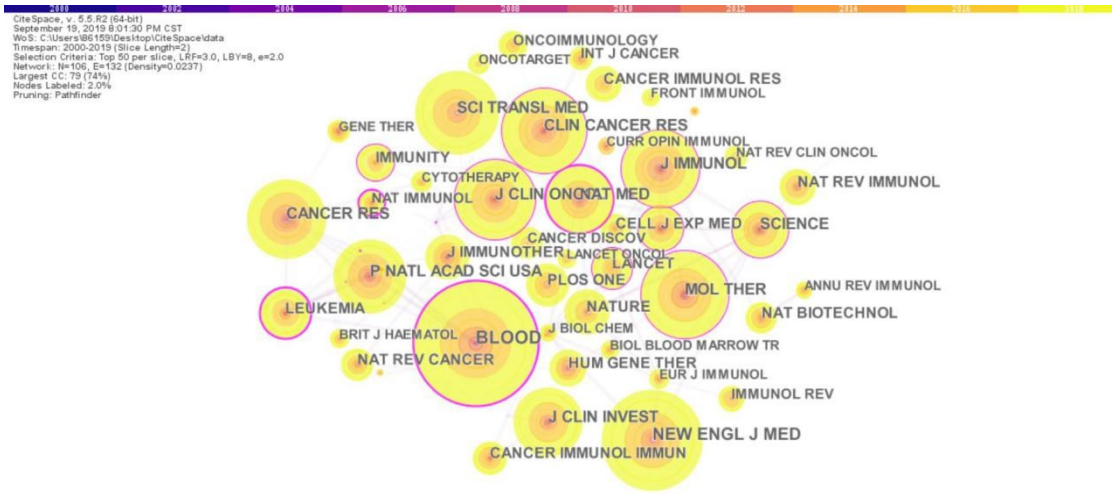

Figure 2. The map of co-cited journal for CAR-T.

3.3 Journals and co-cited journals

Co-cited journals are those often cited by scholars. Through the analysis of journals and co-cited journals, we can get the sources of knowledge in this field. All the 1644 articles were published in 435 journals. Figure 2 presents the map of co-cited journals and Table 1 shows the top 10 journals and co-cited journals in CAR-T field. Nine of the ten journals were from the United States and only one was from Norway. The top 10 journals contributed 450(27.37%) articles. The largest number of papers published is Mol Ther, which

published 82(4.988%) papers. The impact factors of six journals are more than 5.00.

All the top 10 co-cited journals were from the United States. Among the 10 top co-cited journals, 9 were cited more than 900, 9 had higher IFs than 5.00 and 5 were higher than 10.00. Blood(1430 co-citation, 86.98%) had the largest number of co-citations.

Figure 3 presents the overlay map of journals. In the overlay map, the left side represents the citing journals, and the right side is the cited journals. The colored curve is the link of citation, which completely shows the origin and development of citation[11]. There were two citation paths in the map.

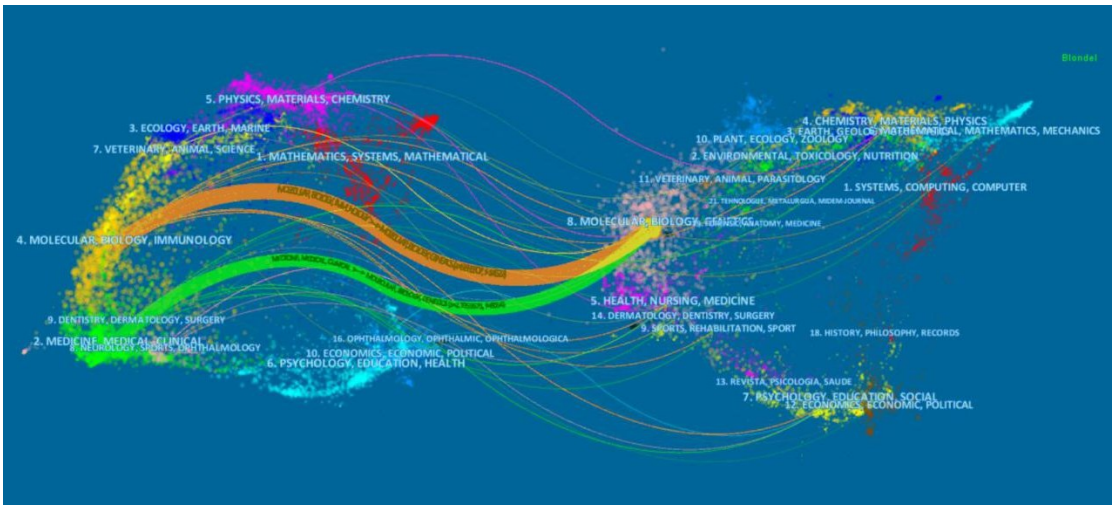

Figure 3. The overlay map of journals related to CAR-T research.

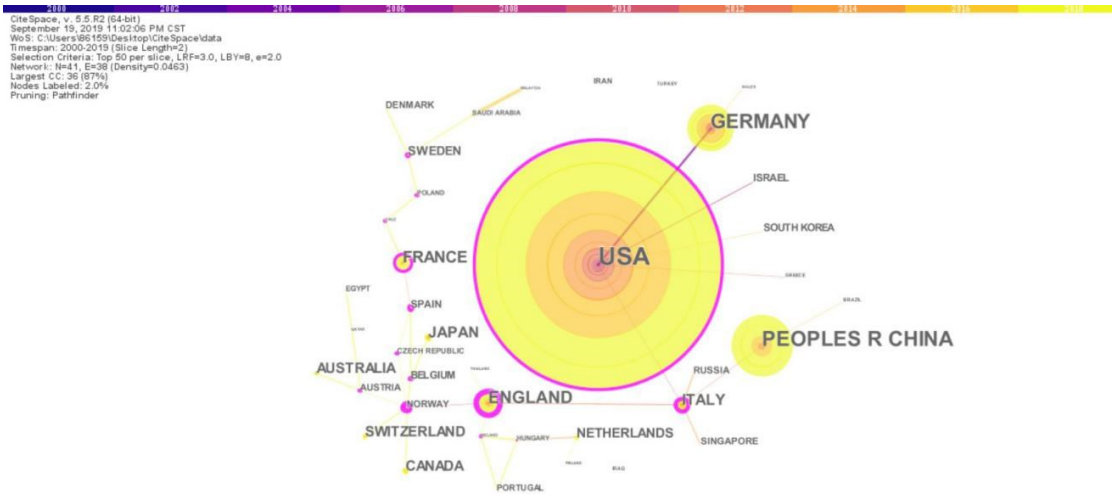

Figure 4. The map of countries for CAR-T.

3.4 Countries and institutions

A total of 54 countries have conducted CAR-T studies. Figure 4 shows the map of countries for CAR-T. There were 41 nodes and 173 links in the map. Table 2 presents the top 10 countries of CAR-T. Among the top 10 countries, the United States (1019, 61.983%) contributed to the largest number of publications. China (264, 16.058%) and Japan(51, 3.102%) ranked top two in Asia. The major European countries were Germany, England, France, Italy and Switzerland. Australia in Oceania was also doing good job. In the Americas, besides the United States, Canada also had a high frequency of publications.

Table 2 presents the top 10 institutions of CAR-T research. The top 10 institutions contributed 827(50.30%) articles. Figure 5 shows the map of institutions for CAR-T. There were 165 nodes and 651 links. In the map, Univ Penn(148 ,9.002%) mostly attract the gaze of people. It was the most influential

research institution on CAR-T. Other institutions such as NCI(107, 6.59%), Mem Sloan Kettering Canc Ctr(98, 5.961%), Baylor Coll Med(95, 5.779%) also did a lot of researches. These institutions mentioned above were all from the United States (USA).

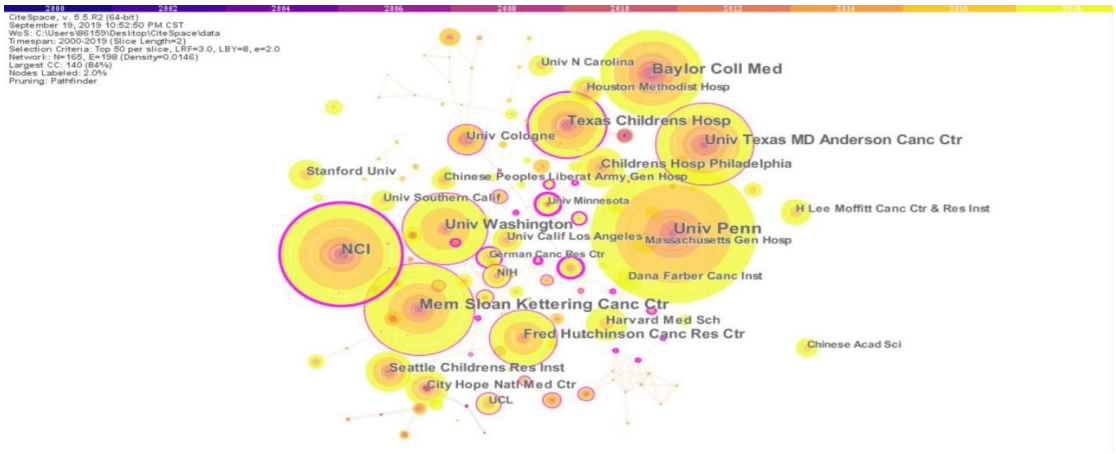

Figure 5. The map of institutions for CAR-T.

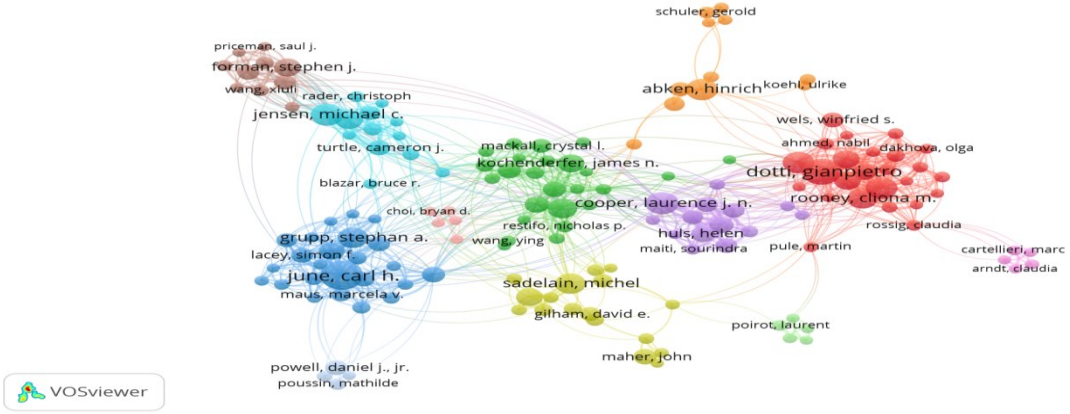

Figure 6. The map of authors for CAR-T.

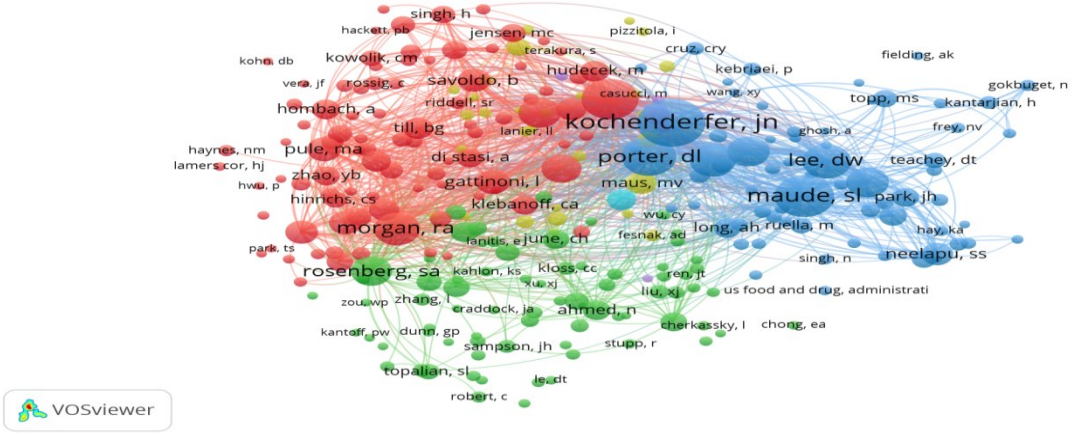

Figure 7. The map of co-cited authors for CAR-T.

3.5 Authors and co-cited authors

By VOSviewer, the maps of the authors and co-cited authors were generated. And they will provide information about influential research group and potential collaborators in CAR-T field. 1644 articles were published by 8505 authors. Table 3 shows the top 10 authors and co-cited authors. The top 10 authors contributed 456 articles (27.73%). The largest number of papers were written by June Ch (77, 4.684%) and other authors such as Dotti G (60, 3.650%), Cooper LJN (44, 2.676%), Abken H (42, 2.555%) were also very active in this field.

In the map of author for CAR-T, 158 authors were included, forming 1009 lines and 12 clusters(Figure 6). There were close connection between the authors, especially among the authors in the same cluster. The co-cited authors map was shown in Figure 7. There were 268 nodes and 28218 links in the map. All the top 10 co-cited authors had citations higher than 400. Kochenderfer JN(1084) ranked first, followed by Maude SL(838), Brentjens RJ(783), Porter DL(692), Lee DW(547).

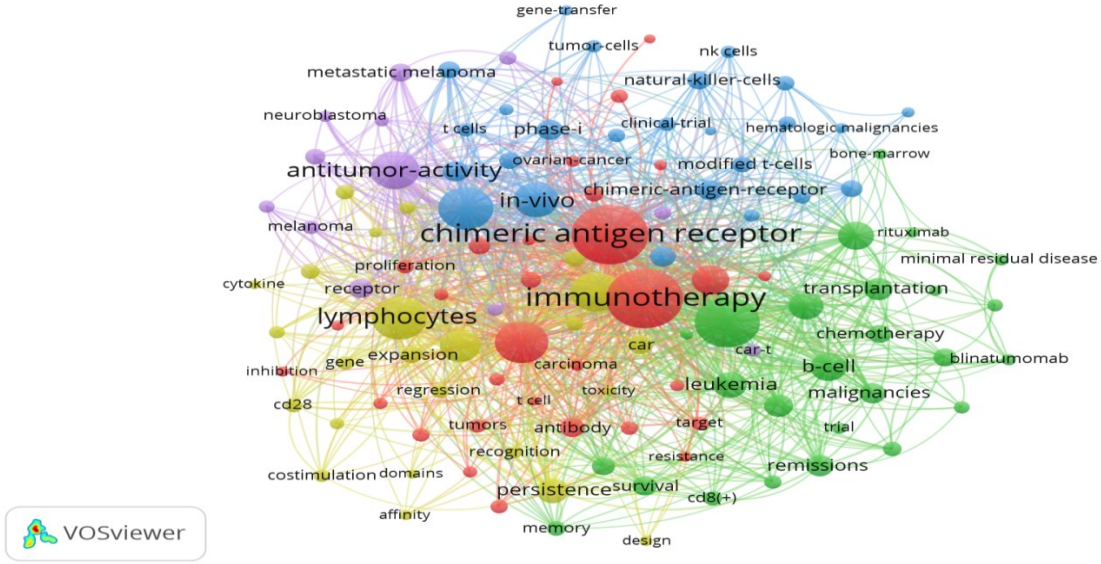

Figure 8. The map of keywords for CAR-T.

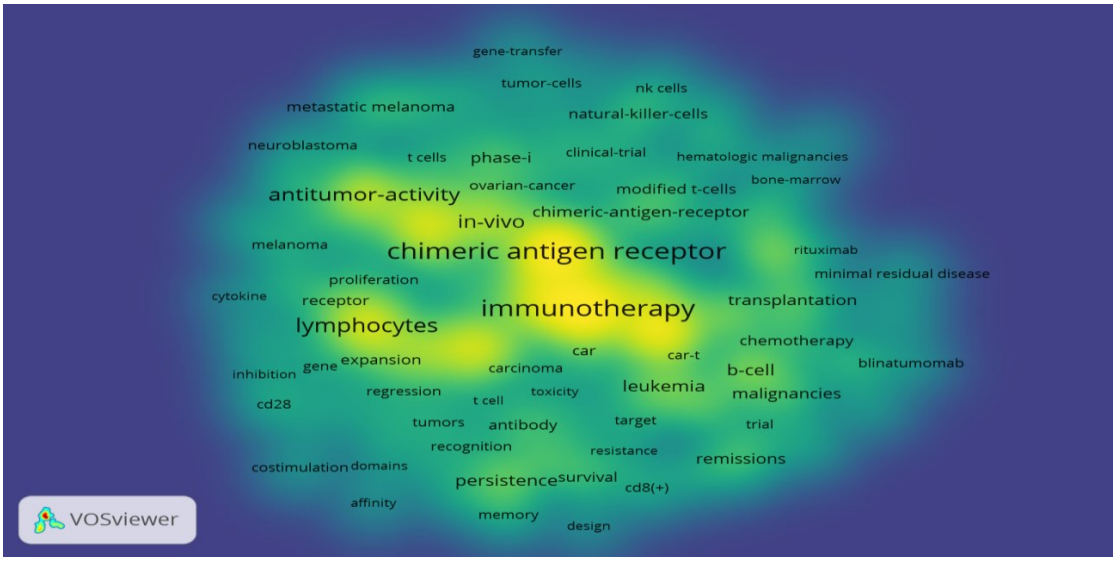

Figure 9. The density map of keywords for CAR-T.

3.6 Keywords and cluster analysis

A total of 4763 keywords were extracted from 1644 articles. Table 4 shows the top 20 of keywords. Chimeric antigen receptor(478, 10.03%) was the most important keyword, followed by immunotherapy(470, 9.86%), therapy(369, 7.74%), lymphocytes(279, 5.85%), adoptive immunotherapy(274, 5.75%), expression(270, 5.66%) and cancer(243, 5.10%). Among the top 20 keywords, chimeric antigen receptor，lymphocytes，t-cell，and chimeric antigen receptors were related to retrieval strategy. Immunotherapy, therapy, adoptive immunotherapy, expression, antitumor-activity, transplant and CD9 constituted the theoretical basis of CAR-T. Acute lymphoblastic-leukemia, lymphoma, and leukemia represented hematological tumors.

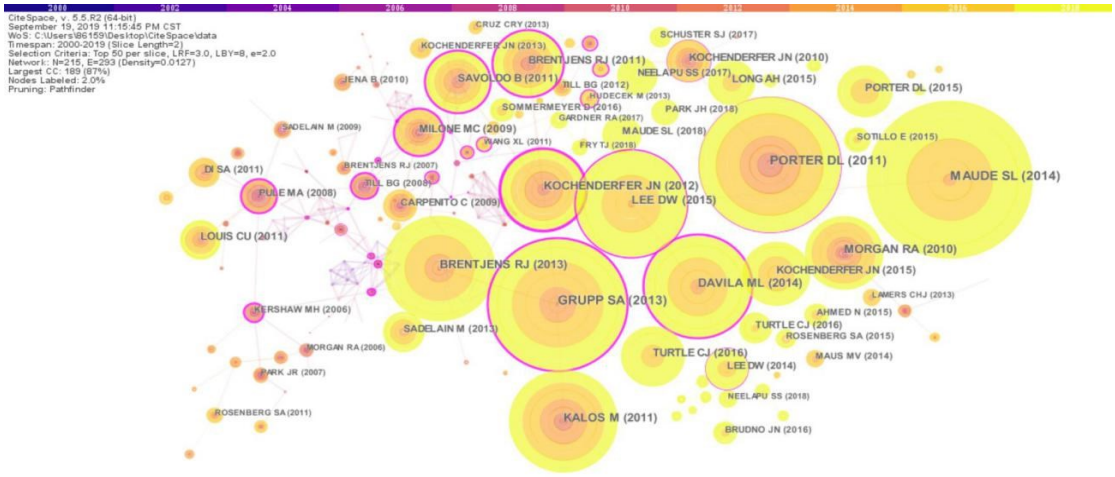

Figure 10. The density map of keywords for CAR-T.

The network map (Figure 8) and density map (Figure 9) of keywords were created by VOSviewer. Figure 8 shows keywords that appear more than 25 times. 118 keywords and 4801 links were involved in the network map of keywords. In the density map, the yellow areas represented keywords with high frequency. As what is showed in Figure 8 and Figure 9, 118 keywords formed 5 clusters. Red nodes represent cluster 1, which was the largest cluster. Cluster 1 contained 31 keywords, including chimeric antigen receptor, immunotherapy, expression, breast-cancer, glioblastoma, ovarian-cancer, and solid tumors. Green nodes belong to the cluster 2, which included 26 keywords. It related to acute lymphoblastic-leukemia, cytokine release syndrome, leukemia, lymphoma, malignancies, and minimal residual disease. Blue nodes represented cluster 3. It has 25 keywords, including acute myeloid-leukemia, adoptive immunotherapy, CD28 costimulation, chronic lymphocytic-leukemia, gene-therapy, hematologic malignancies, and multiple-myeloma. Yellow nodes represent clustering 4 and consist of 24 keywords, which were activation, adoptive cell therapy, cancer immunotherapy, CD28, cytokine, CAR, expansion, and specificity. Cluster 5 is composed of purple nodes and contains 12 key words. It mainly related to antitumor-activity, cancer regression, melanoma, metastatic melanoma, and neuroblastoma.

.7 Co-cited references and references with citation bursts

Co-cited references are the basis of research in a field[12]. CiteSpace was used to create the map of co-cited references for CAR-T(Figure 10). There were 215 nodes and 939 links in the map. Table 5 presented the top 10 co-cited references about CAR-T. The top 10 references were all co-cited more than 200 times. One reference was co-cited more than 500 times, two references were co-cited between 400 and 500 times, seven references were co-cited between 200 and 400 times.

The most frequently co-cited reference was Maued SL's "Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia" published in 2014. In this article, the authors introduced the treatment of CD19 CAR-T cells in 30 patients with acute lymphoblastic leukemia (ALL) and followed up for a long time. The results showed that the complete remission rate was 90% and the remission rate lasted for 2 years[13].

“Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia” published by Porter DL and his team in 2011, ranked second. This article described Porter and his team used CD19 CAR-T cells for treating a patient with chronic lymphoblastic leukemia (CLL)[14].

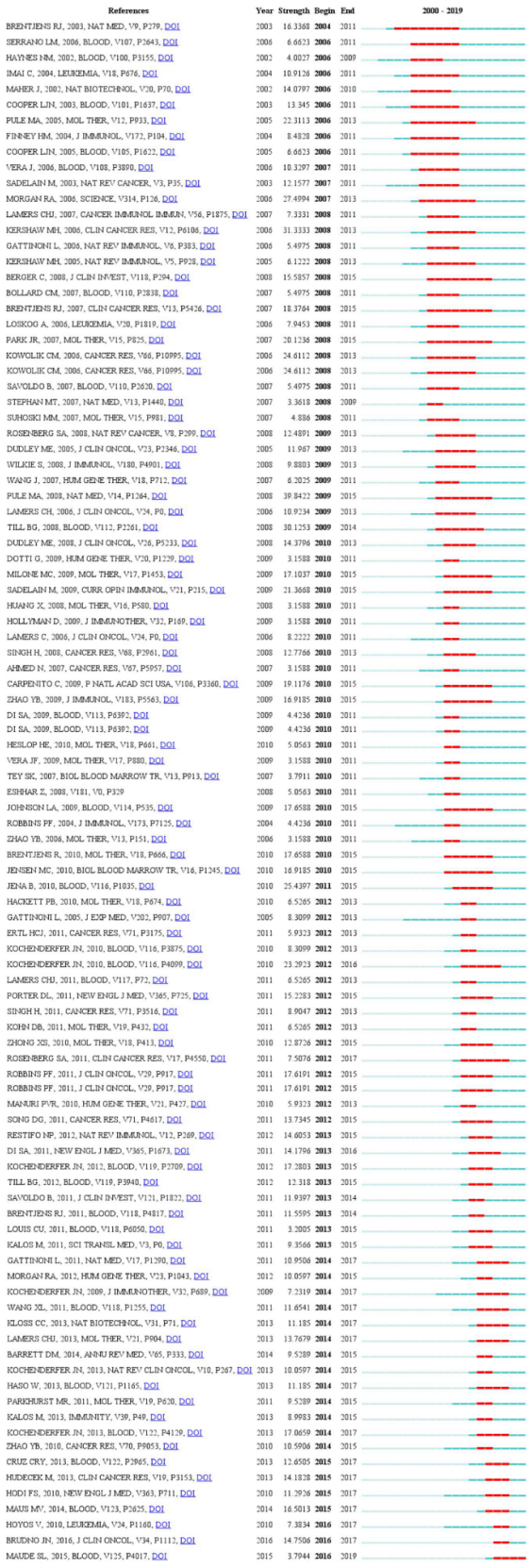

Figure 11. The map of references with citation bursts.

The third place was "Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia" published by Grupp SA in 2013. This paper reported that the use of CTL019 in the treatment of two children with refractory and recurrent acute lymphoblastic leukemia (ALL). It showed that CTL019 not only had a strong anti-leukemia effect, but also had a powerful ability of amplification. CTL019 was detected in the bone marrow and cerebrospinal fluid of the children[15].

In the paper "CD19- targeted T cells rapidly induce molecular remissions in adults with chemotherapy refractory acute lymphoblastic leukemia" published in 2013, Brentjens RJ pointed out that 19-28Z CAR modified T cells had significant antineoplastic effect on acute B-lymphoblastic leukemia (B-ALL), and could achieve complete molecular biological remission, which served as a bridge for allogeneic hematopoietic stem cell transplantation[16].

The feasibility, toxicity and maximum tolerable dose of CD19 CAR-T cells in 21 children and adults with acute lymphoblastic leukemia were discussed in the report "T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukemia in children and young adults: a phase 1 dose-escalation trial" published by Lee DW in 2015[17].

CiteSpace was used to create the map of references with citation bursts (Figure 11). Reference with citation bursts represented a change in a field. It was shown by red nodes. Brentjens RJ's[18] article published in 2003 was the first reference with citation bursts to appear. The strongest burst was Pule MA's[19] article published in 2008. A large portion of references had citation bursts between 2005 and 2015. The latest reference with citation burst occurred in 2016.

3.8 Timeline of co-cited references

CiteSpace was used to create Timeline view of co-cited references (Figure 12). In the map, references with the same cluster were placed on the same horizontal line. The rise, prosperity and decline of a clustering study can be obtained by Timeline view, and the temporal characteristics of this field can be further obtained.

According to Figure 12, the development and evolution of CAR-T cells can be divided into two stages. The first stage, from 2000 to 2009, is the initial stage of development of chimeric antigen receptor T cells, which is in the stage of basic experimental research. The concept of CAR-T first appeared in Linda L's[8] article in 2000. The second stage is from 2010 till now. It is the flourishing stage of chimeric antigen receptor T cells, which is in the stage of clinical trials. In 2010, Rosenberg and his team first published the results of CAR-T clinical trials. They reported in their article "Eradication of B-lineage cells

and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19" that a patient with advanced follicular lymphoma had a marked remission after CAR-T treatment[20]. Since then, reports on clinical trials of CAR-T cells therapy for cancer patients have been emerging

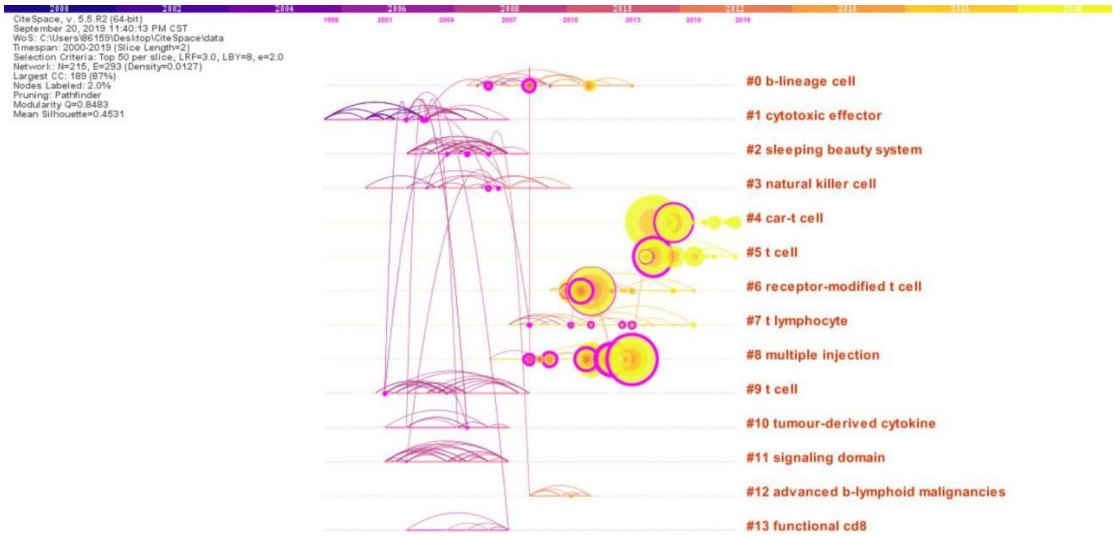

Figure 12. Timeline view of co-cited references.

4. Discussion

A total of 1644 articles were included in this study, published in nine languages. 97.080% were published in English. All the 1644 articles were published in 435 journals. Nine of the top 10 journals were from USA, while all the top 10 co-cited journals were from the United States indicating that American journals not only published a lot of researches, but also attracted many scholar's common citation. Only one journal had an impact factor greater than 10.000 and five co-cited journals had impact factor higher than 10.000. This indicated that journals with high impact factors played an important role in CAR-T field. Through the analysis of the overlay map of journals, we can conclude that CAR-T field is gradually developing from molecular, biology and genetics to immunology and medical clinic.

Through the analysis of the time distribution of the papers publication and the Timeline view, we know that the CAR-T field can be divided into two stages. The first stage, from 2000 to 2009, is the initial stage of development of chimeric antigen receptor T cells, which is in the stage of basic experimental research. The second stage is from 2010 till now. It is the flourishing stage of chimeric antigen receptor T cells, which is in the stage of clinical trial. In 2010, a team reported for the first time that CD19 CAR-T cell therapy was effective in a patient with lymphoma. Before 2010, the registration of clinical trials of CAR-T was mainly concentrated in the United States. Since then, China, Europe and other countries have joined the research of CAR-T.

A total 1644 articles were published by 1711 institutions from 54 countries. USA had the largest number of publications. The main research forces in Asia were China and Japan. The major European countries were Germany, England, France, Italy and Switzerland. Oceania was mainly in Australia. In the Americas, besides the United States, Canada also had a high frequency of publications. The top 10 institutions were all from the United States. This shows that the United States is ahead of other countries in the development of CAR-T field.

1644 articles were published by 8505 authors. None of the authors have published more than 100 articles，which indicates that there are few researchers in CAR-T field. Kochenderfer JN is the author cited most frequently, which shows that he has laid the foundation for the development in this field. From the map of authors, we can see a close connection between authors.

Research hotspots are a topic of common concern to researchers in a certain field. The function of keywords is to express the main content of the paper clearly and intuitively, and to embody the main purpose of the article[21]. 4763 keywords were extracted from 1644 articles. Chimeric antigen receptor was the most important keyword. Cluster analysis of keywords showed that there were five clusters in this field. Cluster 1 is the largest cluster, which contain 31 keywords, including chimeric antigen receptor, immunotherapy and expression. It is related to the basic experiment of CAR-T. Cluster 2 is associated with hematological tumors and adverse reactions of CAR-T. Cluster 3 and 4 mainly explain the mechanism

of CAR-T. The frequency of CD28 costimulation was high. The second generation of CAR adds costimulatory molecules such as CD28 to the first generation, which enhances the utility of T cells[22]. Therefore, the second generation of CAR can live longer in vivo and kill tumor cells more effectively[23]. The third and fourth generation of CAR own more costimulatory molecules[24], but considering the safety and effectiveness, the second generation of CAR-T cell therapy is still the main method in most clinical trials[25]. Cluster 5 is mainly related to solid tumors, but there are only 12 keywords. Through the analysis of key words, it is concluded that the research in the field of CAR-T mainly focuses on the basic theory and hematological system tumors. Less research has been done on solid tumors.

Research frontier refers to potential theoretical trends and new topics, while co-citation network constitutes the knowledge base. Through the analysis of co-cited references, we can draw the following conclusions: On the one hand, the highly cited references on CAR-T are mostly about hematological tumors, and are still in the stage of clinical trials. This indicates that the future trend in the field of CAR-T cells is still the study of hematological tumors[26]. On the other hand, chimeric antigen receptor T cells have significant anti-tumor effects on hematological tumors in vivo, but also have adverse effects such as cytokine-related toxicity[27]. This indicates that chimeric antigen receptors still need to be explored, innovated, optimized and modified to benefit more cancer patients.

Reference with citation bursts represented a change in a field. Brentjens RJ's article published in 2003 was the first reference with citation bursts to appear. This article described that in the presence of CD80 and interleukin-15, tumor-responsive T cells retaining functional phenotypes could be amplified by amplifying peripheral blood T cells targeting CD19 antigen[18]. The strongest burst was Pule MA's article published in 2008. This article introduced that by engineering Epstein-Barr virus (EBV)-specific CTLs, which proved that virus-specific CTLs could be modified to function as tumor directed effector cells[19].

5. Conclusions

CAR-T is a non-MHC adoptive immunotherapy, which is a new type of cancer immunotherapy. CAR-T has achieved tremendous success in the treatment of hematological malignancies， which has given the patients with malignant tumors a glimmer of light. It is considered to become the most probable method to cure malignant tumors. CAR-T has become the fastest-growing immunotherapy and has attracted more and more attention. It can be concluded from this paper that chimeric antigen receptor T cells mainly focus on hematological tumors. Severe adverse reactions such as cytokine-related toxicity occur in the treatment of hematological tumors, and less investment has been made in the study of solid tumors. This indicates that CAR-T cell technology needs further exploration and innovation, enhancing the proliferation of CAR-T cells, enhancing the specificity of CAR-T target, prolonging the survival time in vivo, and reducing adverse reactions. Thus, this technique can not only play an indispensable role in hematological tumors, but also benefit more patients with solid tumors.

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Conflicts of interest

All the authors declare there is no conflict of interest regarding the publication of this paper.

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