

# The 100 most influential studies in CAR-T: a bibliometric analysis

**Beomjun Seo**

Korea University <https://orcid.org/0000-0001-6561-0115>

**Jeeyoon Kim** (✉ [chezjeey@naver.com](mailto:chezjeey@naver.com))

<https://orcid.org/0000-0003-2939-2602>

**Seungwook Kim**

Ulsan National Institute of Science and Technology School of Business Administration

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## Research article

**Keywords:** Chimeric antigen receptors, CAR-T, citation classic, bibliometric, Web of science, VOS viewer

**Posted Date:** March 4th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-15930/v1>

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## **The 100 most influential studies in CAR-T: a bibliometric analysis**

Beomjun Seo Ph.D.<sup>1</sup>, Seungwook Kim PSM<sup>2</sup>, Jeeyoon Kim M.S.\*

### Affiliation List

<sup>1</sup> Department of Epidemiology and Medical Informatics, Graduate School of Public Health, Korea University, Seoul, South Korea

<sup>2</sup> Graduate School of Interdisciplinary Management, Ulsan National Institute of Science and Technology (UNIST), Ulsan, South Korea

### \*Correspondence Address and Information

Postal code: 13496

Department of Clinical Pharmacy, Graduate School, Cha University, Graduate School, Seoul, South Korea

Tel: 82-10-3600-3053

Email: [chezjeey@naver.com](mailto:chezjeey@naver.com)

## **Abstract**

**Background:** Bibliometric analyses are used to provide information on trends within a specific research field, along with indicators of the impact of a publication. With such an analysis, we map the scientific landscape of chimeric antigen receptor T-cell (CAR-T) research to see the emerging topics and infer directions the field might take.

**Methods:** We extracted the 100 most cited articles, published between 1945 to 2018, from the Web of Science Core Collection. Using their bibliographic details, including year of publication, country of author, funding agencies, research organization, author information, and keywords, we graph the networks created between the articles.

**Results:** Of the 100 papers identified, majority (92%) were written in the United States. US government agencies and non-profit organizations provided the most funding. It was observed that the papers funded by the NIH had the most citations, followed by those funded by the Alliance for Cancer Gene Therapy. Also notable was that 33 papers were published from the University of Pennsylvania. Regarding authors, Carl H. June participated in 30 researches, followed by Bruce L. Levine who participated in 11. As for journals, Blood (n=20) published the most papers, followed by Science Translational Medicine (n=10). Lastly, the most frequently used keywords were “adoptive immunotherapy” (n=37), “lymphocytes” (n=27), and “antitumor-activity” (n=25).

**Conclusion:** By evaluating the top 100 most cited papers in the CAR-T field, this study provides insight into the direction of the scientific growth and its trends, as well as information on the field’s network structure.

**Keywords:** Chimeric antigen receptors; CAR-T; citation classic; bibliometric; Web of science, VOS viewer

## **Introduction**

Since chimeric antigen receptors (CARs) were genetically engineered to express on T-cells three decades ago<sup>1</sup>, they have become one of the most promising targeted immunotherapy research interests. These chimeric antigen receptor T-cells (CAR-Ts) are modified to express cancer antigen-recognizing CARs, and stimulate the immune system.<sup>2-4</sup> To produce CAR-Ts, leukapheresis is performed in the patient's blood: first, the T-cell is extracted (selection and activation phase) with the virus vector (retro-/lentivirus vector), then the host T-cell is injected with the unique cancer-specific CAR DNA (CAR transduction) for cell proliferation (expansion). It is critical that these methods, such as the handling of the virus and the quality of the CAR-T, are properly verified as these manufactured CAR-Ts are reinfused into the patient, and any errors in selection may compromise their health.<sup>4-6</sup>

Currently, only two multinational pharmaceutical companies (Novartis and Gilead), have FDA approval for the treatment of some hematologic disorder (Table 1) and CAR-T studies registered at ClinicalTrials.gov as on-going (i.e. not yet recruiting, recruiting, enrolling by invitation, and active but not recruiting) number over 300. Among them are studies that look into the development of new combination therapeutic options for malignant blood cancer, but also solid tumors, and other immunotherapies.<sup>7-9</sup> However, not only has the number of CAR-T experiments been growing, but over 3,000 articles regarding CAR-Ts have been published according to Clarivate Analytics' Web of Science Core Collection (WoSCC; [www.webofknowledge.com](http://www.webofknowledge.com)). The WoSCC online database provides systematic literature information, including data under the scope of the Science Citation Index (SCI) and the Science Citation Index Expanded (SCIE), Social Science Citation Index (SSCI), Arts & Humanity Citation Index (A&HCI), and the Emerging Sources Citation Index (ESCI)<sup>10</sup>

Typically, citations express an author's consent to a study's presented insights, findings, and interpretations presented. Thus, citation analysis, as a quantitative bibliometric method, can be used to provide information on a study's trends, as well as an objective index of the scientific effect of publications through their citation frequency within a specific field.<sup>11-13</sup> Consequently, the most cited articles are analyzed through their bibliometrics to understand the direction of scientific growth and flow of the study area.<sup>14-16</sup>

In this study, a bibliometric network analysis will be conducted on the 100 most cited publications in the CAR-T area. Using their bibliographic information (i.e., year of publication, country, funding, institution, author information, and keywords), we can provide insights on the target cells and genes typically studied in the field, indications for major studies, and any hot topics regarding CAR-Ts after analyzing the simultaneous exposure and frequency of the core keywords. Also, the information yielded may allow us to determine potential new study fields, the opportunities available to researchers, and leading funding organizations.

## **Methods**

This noninterference study conducted a bibliometric analysis not involving any human subjects; thus, no approval was required from any institutional review board or ethics committee.

Using “chimeric antigen receptor T cell,” “CAR-T,” or “CAR T” as keywords, we found a total of 3,018 articles published in the last decade, dated between January 01, 2009 to December 31, 2018. All of them were located using the WoSCC as of July 1, 2019. This 10-year analysis period is aimed at capturing current moments in such a rapidly developing science, such as immune oncology and chemotherapy.

All publication information (i.e., journal name, funding organization, country, enhanced-organization information, author, title, publisher, keyword, PubMed ID, and citation frequency) was downloaded as Bib-Text files, then converted into the XML format. The network graph was constructed using VOSviewer 1.6.13, a software tool for visualizing and exploring network data. The VOSviewer manual by Van Eck and Waltman states that VOSviewer is a program for building and visualizing networks of scientific publications, journals, researchers, research institutions, countries, keywords or terms. It can be used to analyze bibliographic and other types of networks.<sup>17</sup> In this study, we used the function of the VOSviewer 1.6.13 version to design the network graph. For clearer network visualization, keywords can be marked more than five times, and author networks more than two times. For brevity of presentation, only information on the top 10 is included in the tables.

## Result

The publication rate and the citation frequency of the 100 most cited publications are shown in Figure 1. We observed that majority of the publications were original articles (81%), while the remaining were reviews (19%); all publications were released in English across 26 different journals. The top 100 most cited articles were published by co-authors from 18 countries—most of who were from the US (n=93), Germany (n=11), UK (n=5), Italy (n=5), Canada (n=4) and China (n=4). Concurrently, major funding bodies were US government agencies (i.e., NIH, NCI, HHS), while others were funded by research organizations or research support groups, such as the Leukemia and Lymphoma Society, and Lymphoma Research Foundation (Table 2).

The results are able to note that the United States and Germany showed the most pronounced activity (Figure 2). Hartmann<sup>18</sup> corroborates this lead the United States possesses as he cites their overwhelming percentage of next generation development and research in the rapidly developing field of CAR-T, similar to their development of new technologies and cost-intensive immunotherapies.

The articles were published across 26 journals, focusing on subjects such as blood cancer, chemotherapy research, and immune-chemotherapies; all of them were located in the US (Table 3). Notably, it was the journals Blood (n=20), Cancer Research (n=10), and Science Translational Medicine (n=10) that accounted for 40% of the publications; while the remaining 16 journals published less than 3 each—10 of which had only published 1 paper.

The total citation frequencies of the articles ranged from 86 to 1052 ( $\mu=207.2$ ;  $Md=156.5$ ). Only one article (Kalos M., et al. “T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia.” Science Translational Medicine, 2011) had been referenced more than 1,020 times, while the other articles in the top 30% (>34 rank) were referenced an average of 361.2 times. Of the 100 articles published

across the decade, 58% were published in 2015 (n=20), 2016 (n=26), and 2017 (n=12), with the most referenced publications found in 2016 (Table 4).

The authorial organizations and affiliations of the top 10 are summarized in Table 5. We found that the most cited publications were authored in the University of Pennsylvania (n=33), followed by the University of Texas (n=15). However, the difference in citation frequency between the two was more than double. These are then proceeded by the Memorial Sloan Kettering Cancer Center (n=14), University of Washington (n=13), and the Fred Hutchinson Cancer Center (n=12; Table 5). The University of Pennsylvania is the top-cited publication institution; along with that, the most cited author (C. H. June; n=30). Subsequently, authors B. L. Levine (University of Pennsylvania) and S. R. Riddell (Fred Hutchinson Cancer Research Center) published 11 articles each.

All of the organizations and authors of the top 10 most cited papers were all from the US. Figure 3 then illustrates the overall institution network graph. The network centered on the University of Pennsylvania, Stanford University, and the Fred Hutchinson Cancer Center. Stanford University has published the most recent cited articles than both the University of Pennsylvania and MD Anderson. Stanford also appears to have collaborated with the Mayo Clinic and Novartis. On the other hand, the Fred Hutchinson Cancer Research Center collaborated primarily with Washington, Juno Therapeutics, and the Seattle Children Research Institution. Looking at the coauthors, they can be largely divided into Zone 1 (C. H. June), Zone 2 (S. R. Riddell), Zone 3 (G. Dotti), Zone 4 (J. N. Kochenderfer), and Zone 5 (M. Sadelain). The central groups, Zone 1 and 2, are bridged by J. C. Byrd. Zones 3, 4, and 5 each carry out separate research, and nothing links one group to another. Then, Zones 2 and 5 published research papers most often cited from the same time period (from 2016 to 2018), but also notably disagreeing with each other.

Finally, in the 100 most cited articles, the most frequently used keywords were “adoptive immunotherapy” (n=37), “lymphocytes” (n=27), and “antitumor-activity” (n=25; Table 6). The density of the keywords is also accounted for and determined by their frequency of appearance (Figure 5). Higher density keywords are represented in yellow, and lower densities are represented in blue; shorter distances between keyword nodes indicate frequent expression as co-occurring keywords.

## **Discussion**

We extracted the top 100 cited articles in the CAR-T field from the WoSCC database to analyze the field’s network characteristics. In this study, we tried to visually express the research trends and mainstream structure through the network mapping of the simultaneous exposure of countries, funding bodies, researchers’ affiliations and organizations, and keywords. Our network analysis found the United States and Germany possessed the most nodes, followed by Italy, Canada, and China. While an overwhelming amount of studies have been conducted in the United States, there appears to be an exchange with the vast majority of other countries (Figure 2).

CAR-T is a highly technological and high cost method of cancer therapy. and the top 10 funding bodies, journals, organizations, and authors were based or from the US. The US is objectively leading the development and research of the CAR-T field that is growing at an incredibly rapid rate.<sup>18–20</sup> However, these advancements are not limited only to

those dealing with CAR-T research and general cost-intensive treatments, but also with overall immuno-chemotherapy research.<sup>21</sup> The study of CAR-Ts is led mainly by three institutions: first is the University of Pennsylvania, then there is Stanford University, and the other is the Fred Hutchinson Cancer Center (Figure 3). When looking at the authorial connection and citation relationships, there seems to be a network centered around the works of C. H. June and B. L. Levine, with M. Sadelain acting as a bridging node. Another cluster of nodes centers around S. R. Riddell, and one around G. Dotti, but neither has a bridging node between them (Figure 4). This may imply that each group is being led by their respective institution directing the research, and that there is minimal to no research network cooperation in the researches listed in ClinicalTrials.gov.<sup>9</sup> Finally, the most used keyword is “adoptive immunotherapy” which lies at the center, while other keywords like “lymphocytes,” “antitumor-activity,” “persistence,” and “B-cell” were connected through multi-frequency simultaneous exposures (Figure 5).

In our determination of effect and value, we only consider the citation frequency. As such, we also only consider the number of co-authorships, regardless of an author’s actual achievements and contributions. Future studies may consider the use of high quality databases that considers both qualitative and quantitative evidence for their objective analysis. Should consideration be placed on a study’s phase and design, and the author’s achievement and contribution for their analytical database, more robust results may be gained. Even now, there may be studies in press or in the process of completion that can contribute to the development of the field in spite of their low citation frequency.

## **Conclusion**

Using the 100 most cited papers in the CAR-T field, we attempted to provide insight into the direction of the scientific growth and core study areas and trends, and opportunity to understand information on the main network structure of those studies. What we observed was that CAR-T engineering is a developing technology- and cost-intensive form of immunotherapy, with most of its studies funded and led by US-based institutions and researchers.

## Acknowledgements:

**Funding:** This research did not receive any external funding.

**Disclosures:** The authors declare that they have no conflict of interest.

## References:

1. Lim WA, June CH. The principles of engineering immune cells to treat cancer. *Cell* 2017; 168(4): 724–740.
2. Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. *Nat Rev Clin Oncol* 2016; 13(6): 370–383.
3. Park JH, Brentjens RJ. Adoptive immunotherapy for B-cell malignancies with autologous chimeric antigen receptor modified tumor targeted T cells. *Discov Med* 2010; 9(47): 277–288.
4. National Cancer Institute (<https://www.cancer.gov/about-cancer/treatment/research/car-t-cells>)
5. Shi H, Sun M, Liu L, Wang Z. Chimeric antigen receptor for adoptive immunotherapy of cancer: latest research and future prospects. *Mol Cancer* 2014; 13: 219.
6. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. *PNAS* 1989; 86(24): 10024–10028.
7. Strohl WR, Naso M. Bispecific T-Cell Redirection versus Chimeric Antigen Receptor (CAR)-T Cells as Approaches to Kill Cancer Cells. *Antibodies* 2019; 8(41).
8. Newick K, O'Brien S, Moon E, Albelda SM. CAR T Cell Therapy for Solid Tumors. *Annu Rev Med* 2017; 68: 139–152.
9. Clinicaltrials.gov information ([https://clinicaltrials.gov/ct2/results?cond=CAR-T&Search=Apply&age\\_v=&gndr=&type=&rslt=](https://clinicaltrials.gov/ct2/results?cond=CAR-T&Search=Apply&age_v=&gndr=&type=&rslt=)) Searching on Jul 2019
10. WoSCC detailed information ([https://images.webofknowledge.com/images/help/WOS/hp\\_citation\\_report.html](https://images.webofknowledge.com/images/help/WOS/hp_citation_report.html)) Accessed Jul 2019
11. De Bellis N. *Bibliometrics and Citation Analysis: From the Science Citation Index to Cybermetrics*: Scarecrow Press, USA, 2009.
12. Moed HF. *Citation Analysis in Research Evaluation, Volume 9*: Springer Netherlands, 2005.
13. Moed HF. New developments in the use of citation analysis in research evaluation. *Arch Immunol Ther Exp (Warsz)* 2009; 57(1): 13–18.
14. Brandt JS, Downing AC, Howard DL et al. Citation classics in obstetrics and gynecology: the 100 most frequently cited journal articles in the last 50 years. *Am J Obstet Gynecol* 2010; 203(4): 355.e1–7.
15. Ponce FA, Lozano AM. Highly cited works in neurosurgery. Part I: the 100 top-cited papers in neurosurgical journals. *J Neurosurg* 2010; 112(2): 223–232.
16. Van Noorden R, Maher B, Nuzzo R. The top 100 papers. *Nature* 2014; 514(7524): 550–553.
17. van Eck, Nees Jan, and Ludo Waltman. “VOSviewer manual.” Leiden: Univeriteit Leiden 2013; 1.1.
18. Hartmann J, Schübler-Lenz M, Bondanza A, Buchholz CJ. Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts. *EMBO Mol Med* 2017; 9(9): 1183–1197.
19. Hoos A. Development of immuno-oncology drugs—from CTLA4 to PD1 to the next generations. *Nature Rev Drug Discov* 2016; 15(4): 235–247.

20. Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. *Ann Oncol* 2017; 29(1): 84–91.
21. Jürgens B, Clarke NS. Evolution of CAR T-cell immunotherapy in terms of patenting activity. *Nat Biotechnol* 2019; 37(4): 370–375.

Figure 1. Total CAR-T related publications vs. Top 100 cited publications from 2009 to 2018

Figure 2. The network of countries that co-published related to CAR-T from 1999 to Jun 2019

Figure 3. The network of institutions that co-published related to CAR-T from 1999 to Jun 2019

Figure 4. The network of authors that co-published related to CAR-T from 1999 to Jun 2019

Figure 5. The co-occurrence density of keyword that co-published related to CAR-T from 1999 to Jun 2019

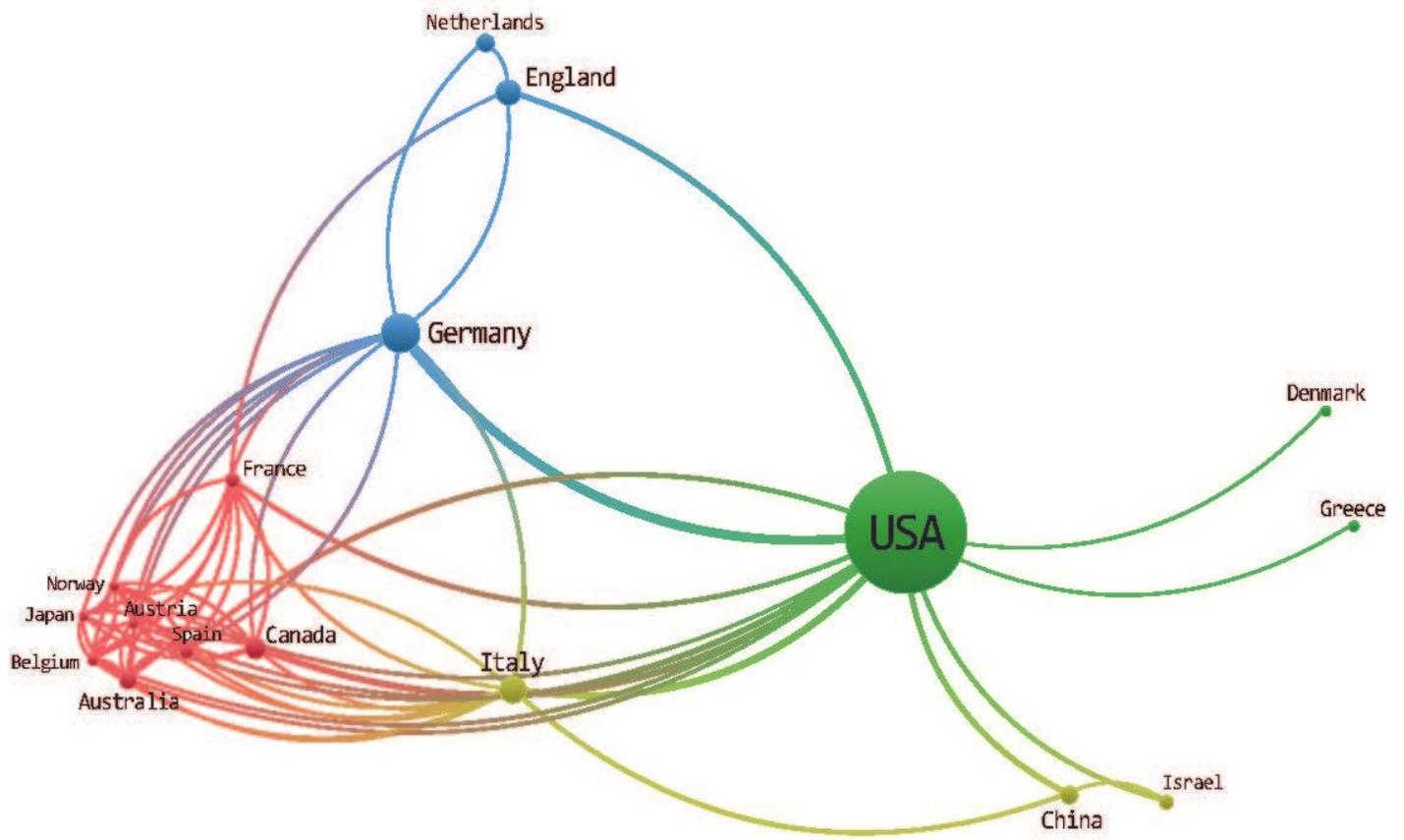
# Figures



Figure 1. Total CAR-T related publications vs. Top 100 cited publications from 2009 to 2018

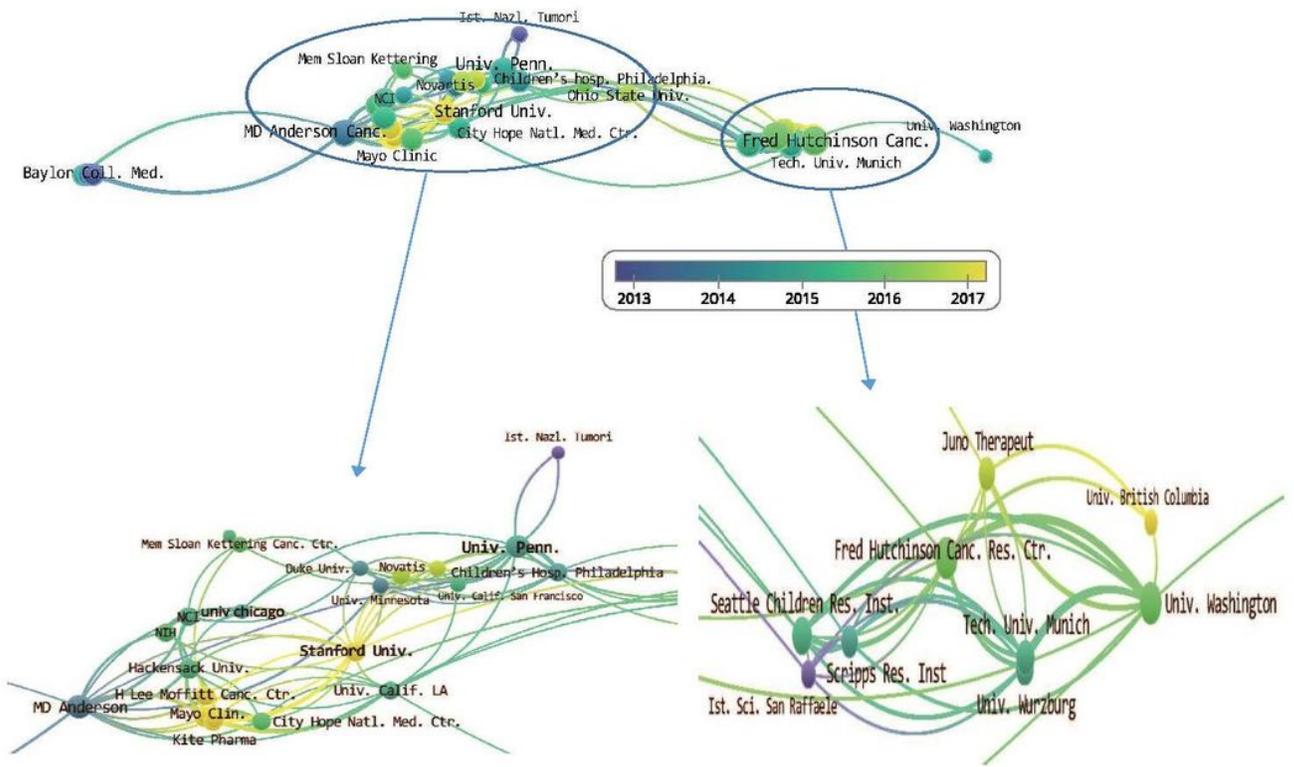
## Figure 1

Total CAR-T related publications vs. Top 100 cited publications from 2009 to 2018



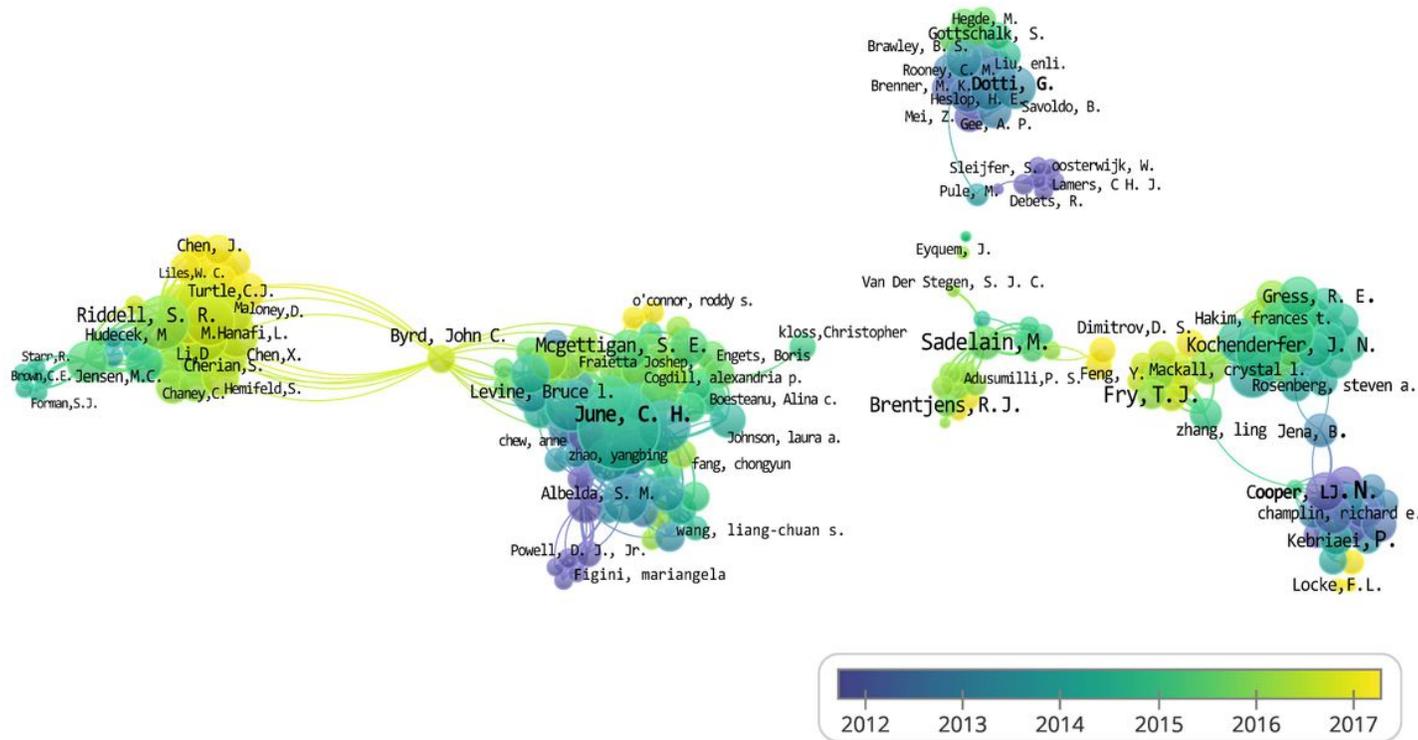
**Figure 2**

The network of countries that co-published related to CAR-T from 1999 to Jun 2019



**Figure 3**

The network of institutions that co-published related to CAR-T from 1999 to Jun 2019



**Figure 4**

The network of authors that co-published related to CAR-T from 1999 to Jun 2019

