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The research status of immune checkpoint blockade by anti-CTLA4 and anti-PD1/PD-l1 antibodies in tumor immunotherapy in China

A bibliometrics study

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Abstract

Purpose: Using bibliometrics, we analyzed the research status of immune checkpoint blockade (ICB, a popular tumor immunotherapy method represented by antibodies targeted CTLA-4 and PD-1/PD-L1) in tumor immunotherapy in China during the past 2 decades.

Methods: Articles in Science Citation Index Expanded (SCI-EXPANDED), patents in Thomson Innovation, and drugs in Cortellis Competitive Intelligence in the field of ICB for tumor immunotherapy from 1996 to 2015 were the subjects of bibliometric analysis. Using database-attached software and Excel, quantitative analyses were performed including examination of the number of documents, citation frequency, h-index, key projects, quantity of publications, public patents, and status of new drug research.

Results: The number of publications from 1996 to 2015 in the field of ICB for tumor immunotherapy that came out of China was 380, which was 14.3% of the total publications worldwide and was second only to that of the USA. In the past decade, China has rapidly increased the number of publications and patents in this field. However, indicators of publication influence, such as citation frequency and h-index, were far behind other advanced countries. In addition, the total number of patents in China was much lower than that of the USA. China has introduced 5 drugs for ICB that are being developed for the healthcare market.

Conclusion: Tumor immunotherapy research such as ICB in China has developed rapidly with increasing influence in the last 2 decades. However, there is still a relatively large gap compared with the USA. It is expected that China will have greater influence on tumor immunotherapy research in the near future.

Abbreviations: AAGR = average annual growth rate, ACPP = average citations per paper, APCs = antigen presenting cells, CTLA-4 = cytotoxic T-lymphocyte antigen 4, dMMR = mismatch repair-deficient, FDA = Food and Drug Administration, GDP = gross domestic product, HCP = highly cited papers, h-index = high citation index, ICB = immune checkpoint blockade, IF = impact factor, ISI = Institute of Scientific Information, MSI-H = microsatellite instable-high, NIH = National Institute of Health, NSCLC = non-small cell lung cancer, NSFC = National Natural Science Foundation of China, PD-1 = programmed death 1, PD-L1 = programmed death-ligand 1, SCCHN = head and neck squamous cell carcinoma, SCIE = science citation index expanded, TC = total citations, TCR = T cell receptor, TP = total paper, TPR% = the percentage of articles of journals in total publications.

Keywords: cytotoxic t-lymphocyte antigen 4, immune checkpoint blockade, programmed death 1, tumor immunotherapy

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1. Introduction

Cancer is one of the leading causes of death in the world, trailing just behind cardiovascular diseases.[1,2] Traditional strategies for cancer treatment include surgery, chemotherapy, and radiotherapy. However, these methods have serious side effects and many patients succumb to cancer due to metastasis. Targeted therapy is more specific, but drugs that are effective for cancers with the target gene mutations often have poor therapeutic effects on cancers with other gene mutations.[3] This means targeted drugs can only be used to treat certain types of cancer. In Comparison with traditional methods, tumor immunotherapy, including immunomodulator, tumor vaccine, adoptive cellular immunotherapy, and immune checkpoint blockade (ICB), can modulate the host immune system and enhance antitumor response.[4–7] Encouragingly, after decades of efforts, tumor immunotherapy has made significant progress and gained recognition in the field of tumor therapy. For instance, adoptive cellular immunotherapy and ICB in tumor therapy were recognized as some of the biggest breakthroughs of the year in 2013 by Science Magazine.[8]

One of the most important advancements in tumor immunotherapy, ICB, is based on our understanding of the interactions between T cells and tumor cells.[9] T cells are the principal immunological force in the war against tumors.[9] Interaction between B7–1 (CD80)/B7–2 (CD86) proteins on the surface of antigen presenting cells (APCs) and CD28 on the surface of T cells (a costimulating signal) is required for the T cell activation. However, T cell activation gradually leads to the expression of checkpoint molecules such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1), which acids to avoid aberrant T cell activity.[10–12] Expressed only on activated T cells, CTLA-4 has a higher affinity for B7 than CD28, and can inhibit the costimulating signal, thus reducing the T cell-dependent antitumor effect.[13,14] PD-1 (a member of B7 family) can be expressed on activated T cells and the ligand of PD-1 (PD-L1) is highly expressed on both APCs and tumor cells.[15] The interaction of PD-I and PD-L1 eventually results in T cell apoptosis, anergy, and exhaustion.[16,17] Therefore, drugs that inhibit CTLA-4 and/or PD-1/PD-L1 activity enhance the antitumor immunity response via ICB. The anti-CTLA-4 drug YERVOY (Ipilimumab) has been approved by the American Food and Drug Administration (FDA) as a first-line therapy for advanced melanoma.[18] In the last 2 decades, numerous studies on immune checkpoint blockade for tumor immunotherapy have been published. Effective way, such as bibliometrics, is needed to summarize and analyze these research advances and obtain a view of research status of ICB in tumor immunotherapy in China.

Through statistical analysis of the literature, bibliometrics describes, evaluates, and forecasts the status and development of trends in science and technology.[19] Bibliometrics are widely used in clinical research, as they provide reference data that can be used to understand the dynamics of technology, determine the novelty of projects, publicize research results, and make decisions on which scientific topics to study.[19] To date, bibliometrics have been used in evaluating and forecasting trends of macro-health science and medical systems in the fields of cancer, Alzheimer's disease, and diabetes, and micro-fields such as tumor biomarkers.[19–22]

However, very few literature studies have reported on the overall research status in the field of immune checkpoint blockade in tumor immunotherapy. Information on how Chinese research in this area is compared with the global community is especially lacking. Therefore, we took advantage of databases in the Shanghai Information Center of Life Science of the Chinese Academy of Sciences, and performed both qualitative and quantitative analyses of the articles, patents, and drugs produced in the field of immune checkpoint blockade from 1996 to 2015 both worldwide and in China. We identified a rapid expansion of publications and patents from China in immune checkpoint blockade research during the last 2 decades, but also found shortcomings in these studies. Our results provide a better understanding of the research status of tumor immunotherapy and offer a reference for relevant future research in China.

2. Materials and methods

2.1. Data sources

Published data from the Shanghai Information Center of Life Sciences of the Chinese Academy of Sciences were used for our analyses. We chose the science citation index expanded (SCIE) from the database of Institute of Scientific Information (ISI) Web of Science™ as data sources in the last 2 decades (from 1996 to 2015). The impact factors reported are from the 2014 database of ISI Web of Knowledge Journal Citation Reports (updated in June, 2015).

2.2. Index strategies

Global immune checkpoint blockade research: subject term= ("CTLA-4" OR "Cytotoxic T lymphocyte antigen-4" OR "CD152" OR "PD-1" OR "Programmed death 1" OR "CD279" OR "PD-L1" OR "programmed death-ligand 1" OR "CD274" OR "B7-H1") SAME (cancer OR tumor) AND publication year=(1996–2015). Refining basis: paper type=article.

CTLA-4 target tumor immunotherapy research: subject term= ("CTLA-4" OR "Cytotoxic T lymphocyte antigen-4" OR "CD152") SAME (cancer OR tumor) AND publication year= (1996–2015). Refining basis: paper type=article.

PD-1/PD-L1 target tumor immunotherapy research: subject term= ("PD-1" OR "Programmed death 1" OR "CD279" OR "PD-L1" OR "programmed death-ligand 1" OR "CD274" OR "B7-H1") SAME (cancer OR tumor) AND publication year= (1996–2015). Refining basis: paper type=article.

Immune checkpoint blockade research in China: subject term= ("CTLA-4" OR "Cytotoxic T lymphocyte antigen-4" OR "CD152" OR "PD-1" OR "Programmed death 1" OR "CD279" OR "PD-L1" OR "programmed death-ligand 1" OR "CD274" OR "B7-H1") SAME (cancer OR tumor) AND publication year=(1996–2015) AND address=(Peoples R China). Refining basis: paper type=article.

Using the above indexing strategies, we analyze research papers in the areas of melanoma, myeloma, lymphoma, lung cancer, prostate cancer, and pancreatic cancer in China or around the world.

2.3. Data collection

Search date: March 12, 2016, SCIE database updated: March 3, 2016. The.txt data downloads from SCIE was imported into Microsoft Excel 2007 for analysis. Bibliometric indicators including publication number, citation, average citations per paper, h-index, and proportion of articles with funding sources, was extracted from the data for quantitative and qualitative analyses of the publication of ICB in cancer immunotherapy. The

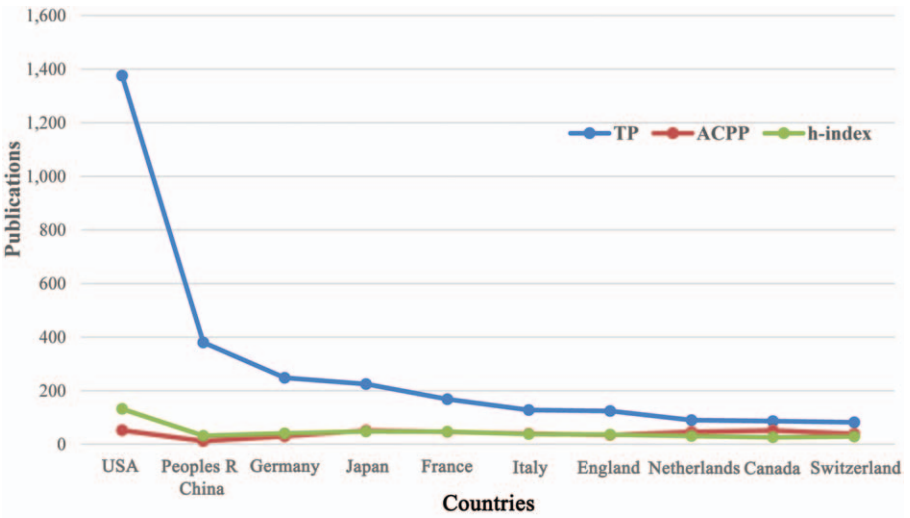

Figure 1. Comparison of the publications in the field of ICB for tumor immunotherapy. ACPP = average citations per paper, ICB = immune checkpoint blockade, TP = total papers.

journal's impact factor (IF) was based on the ISI Journal Citation Reports 2014 database.

2.4. Statistical analysis

The analysis tools of Web of Science were used to analyze the time, country and region, authors, research institution, language, document type, research direction, and funding sources. We compared the Chinese literature distribution with that of other countries and compared the output of tumor immunotherapy in different years. We also analyzed the output of tumor immunotherapy research in 2 time frames, from 1996 through 2005, and from 2006 through 2015.

3. Results

3.1. China plays an important role in the world in the research on ICB for tumor immunotherapy

From 1996 to 2015, 2648 papers on ICB for tumor immunotherapy were published worldwide. China published 380 papers, accounting for 14.3% of all publications, and ranking second behind the USA. China produced more papers than Germany, Japan, and France. However, China had room for improvement in terms of article influence. For example, in the top 10 countries or districts, China ranks the lowest for the average citations per paper (ACPP), and 7th place in the h-index (high citation index), an indicator for influence of the papers (Fig. 1).

In terms of timing, the number of publications from China in ICB for tumor immunotherapy increased rapidly in last decade compared with the previous decade. There were only 13 papers between 1996 and 2005 (3.4% of total), but the number increased to 366 papers between 2006 and 2015 (16.3% of total). In addition, the h-index increased from 8 in 2006 to 2015 to 30 in 2006 to 2015. However, the ACPP were still far behind those of many other countries (Table 1).

3.2. The number of publication in China increases annually

A total of 70 papers in the field of ICB for tumor immunotherapy were published during 2006 to 2010 (12.2%) from China. This increased to 296 papers published between 2011 and 2015 (17.5%), indicating that China made significant progress in contributing to tumor immunotherapy research. The average

Table 1

Comparison of the publications in immune checkpoint blockade (ICB) for tumor immunotherapy research in the top 10 countries from year 1996 to 2005 and 2006 to 2015.

	1996–2005					2006–2015				
Country	TP	TPR%	TC	ACPP	h-index	TP	TPR%	TC	ACPP	h-index
USA	223	57.9	27,165	121.82	80	1,153	51	44,495	38.59	106
China	13	3.4	571	43.92	8	366	16.2	3,965	10.83	30
Germany	31	8.1	2,440	78.71	18	217	9.6	5,019	23.13	36
Japan	43	11.2	5,311	123.51	28	182	8	6,223	34.19	36
France	13	3.4	1,494	114.92	12	155	6.9	6,228	40.18	43
Italy	23	6	1,870	81.3	18	105	4.6	3,216	30.63	29
England	19	4.9	1,223	64.37	14	105	4.6	3,065	29.19	29
Netherlands	12	3.1	1,744	145.33	11	78	3.4	2,398	30.74	27
Canada	13	3.4	943	72.54	11	74	3.3	3,538	47.81	22
Switzerland	6	1.6	460	76.67	6	76	3.4	2,724	35.84	28

ACPP = average citation per paper, TC = total citations, TP = total paper, TPR% = the percentage of articles of journals in total publications.

Table 2

Annual citations and paper numbers from year 2006 to 2015.

Year	China				USA				World			
	Papers	%	TC	ACPP	Papers	%	TC	ACPP	Papers	%	TC	ACPP
2006	9	2.5	588	65.33	42	3.6	3,422	81.48	71	100.0	4,681	65.93
2007	9	2.5	187	20.78	55	4.8	4,335	78.82	101	100.0	6,637	65.71
2008	12	3.3	259	21.58	60	5.2	3,945	65.75	118	100.0	6,634	56.22
2009	21	5.7	666	31.71	76	6.6	4,908	64.58	132	100.0	6,774	51.32
2010	19	5.2	384	20.21	74	6.4	5,024	67.89	150	100.0	6,682	44.55
2011	36	9.8	641	17.81	89	7.7	2,826	31.75	180	100.0	4,710	26.17
2012	33	9.0	291	8.82	119	10.3	7,269	61.08	222	100.0	8,608	38.77
2013	38	10.4	358	9.42	144	12.5	5,991	41.6	295	100.0	8,031	27.22
2014	72	19.7	468	6.5	201	17.4	4,569	22.73	384	100.0	5,813	15.14
2015	117	32.0	123	1.05	293	25.4	2,206	7.53	609	100.0	2,654	4.36
Total	366				1,153				2,262	100.0		
2006–2010	70	12.2			307	53.7			572	100.0		
2011–2015	296	17.5			846	50.1			1,690	100.0		
AAGR		33.0				24.1				27.0		

AAGR = average annual growth rate, ACPP = average citation per paper, TC = total citations.

annual growth rate of Chinese publications was 33.0% during the past decade, while the global average was 27.0%, and the USA average was 24.1% (Table 2). We predict that in the next 5 to 10 years China will produce more researches in the area of tumor immunotherapy.

3.3. Top 10 institutions in the field of ICB for tumor immunotherapy research

The top 10 institutions publishing research in ICB for tumor immunotherapy from 1996 to 2015 were all from the USA except 1 institute from France (#8, INSERM). The top 3 institutions were Harvard University, VA Boston Healthcare System, and Dana-Farber Cancer Institute. Suzhou University (#29) had the most publications in China. However, in terms of ACPP and h-index, Suzhou University showed a significant lag behind institutes of the USA (Fig. 2).

The top Chinese contributors to this research were Universities, except for the Chinese Academy of Sciences (#6). The total number of published papers in the first 10 years (2006 to 2015) was almost same as that in the full 20 years (1996 to 2015), revealing that the publication contributions from China were mostly made in the last 10 years (Table 3).

3.4. Highly cited papers

There were 3 highly cited papers (HCP) that were published in 2011, 2014, and 2015 from China, which were from Suzhou University, Fudan University, and Sichuan University, respectively. China's HCP (3) is 1.8% of the global HCP, while the USA's HCP (140) is 82.8% of the global HCP (Table 4), indicating that China still lags a significant behind in terms of high quality papers at the global standard.

3.5. Funding in China primarily comes from the national natural science fund

Funding sources on ICB for tumor immunotherapy generally came from the National Natural Science Foundation of China (NSFC) and the 973-National Basic Research Program of China plan (Table 5).

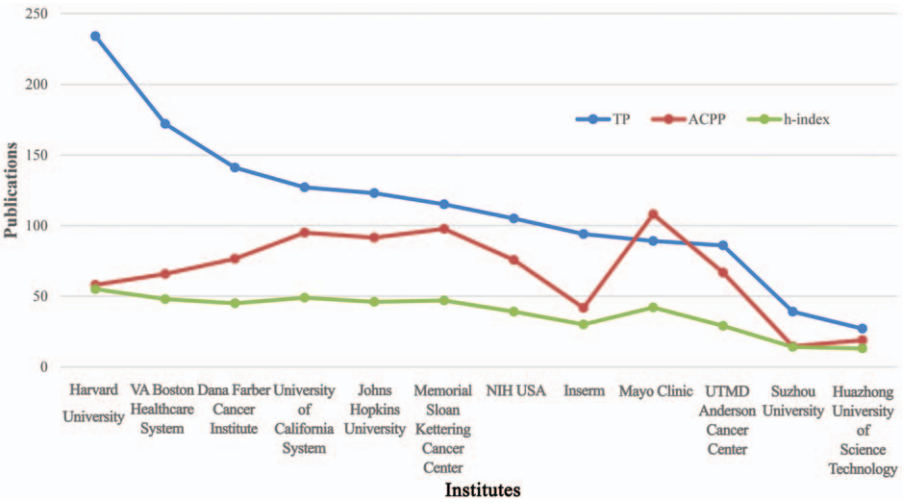

Figure 2. Top 10 institutes and some Chinese institutes in the field of ICB for tumor immunotherapy from 1996 to 2015. ACPP = average citations per paper, ICB = immune checkpoint blockade, TP = total papers.

Table 3

Top 10 institutes in ICB for tumor immunotherapy in China from year 1996 to 2015.

	1996–2015					2006–2015				
Institution	Rank	TP	TC	ACPP	h-index	Rank	TP	TC	ACPP	h-index
Suzhou University	29	39	568	14.56	14	26	38	546	14.37	13
Huazhong University of Science Technology	50	27	509	18.85	13	53	23	341	14.83	9
Sun Yat Sen University	57	24	303	12.62	7	48	24	303	12.62	7
Second Military Medical University	60	23	454	19.74	12	58	21	409	19.48	11
Fudan University	68	22	643	29.23	10	61	21	339	16.14	9
Chinese Academy of Sciences	80	20	327	16.35	10	66	20	327	16.35	10
Third Military Medical University	83	19	152	8	7	81	18	137	7.61	7
Zhejiang University	97	17	142	8.35	7	84	17	142	8.35	7
Shanghai Jiao Tong University	99	17	144	8.47	7	87	17	144	8.47	7
Wuhan University	104	16	25	1.56	3	90	16	25	1.56	3

ACPP = average citation per paper, ICB = immune checkpoint blockade, TC = total citations, TP = total paper.

Table 4

Highly cited papers (HCP) for ICB in tumor immunotherapy in China from year 2006 to 2015.

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	All	2006–2010	2011–2015
Highly cited papers	4	5	5	8	11	8	15	37	37	39	169	33	136
HCP in China	0	0	0	0	0	1	0	0	1	1	3	0	3
HCP in USA	4	3	4	8	10	5	13	29	29	35	140	29	111
China vs World %	0.0	0.0	0.0	0.0	0.0	12.5	0.0	0.0	2.7	2.6	1.8	0.0	2.2
USA vs World %	100.0	60.0	80.0	100.0	90.9	62.5	86.7	78.4	78.4	89.7	82.8	87.9	81.6
China HCP corresponding author	0	0	0	0	0	1	0	0	1	0	2	0	2

ICB = immune checkpoint blockade.

3.6. The main application of ICB for tumor immunotherapy in China was on melanoma, lung cancer, and pancreatic cancer

The main application of tumor immunotherapy in China was on lymphoma, lung cancer, and pancreatic cancer. The USA exhibited major advantages in melanoma, myeloma, lymphoma, lung cancer, prostate cancer, and pancreatic cancer. Blockade of CTLA-4 has been primarily used to treat melanoma, lymphoma, lung cancer, and prostate cancer in China, whereas it has been largely used to treat melanoma, prostate cancer, and pancreatic cancer in the USA. Blockade of PD-1 has been primarily used to treat melanoma, lymphoma, and lung cancer, with fewer treatment attempts for myeloma, prostate cancer, and pancreatic cancer in China, whereas it has been used with a focus on melanoma, myeloma, and prostate cancer in the USA (Table 6).

3.7. Applied research of ICB for tumor immunotherapy grew rapidly in China

A patent search was conducted to analyze the application of research regarding ICB for tumor immunotherapy. There were 233 patent families in China between 2006 and 2015, accounting for 25.5% (233/914) of patent families in the world. This represented the second highest number of patents after the USA (525 patent families, 57.4%). The number of public patents from China doubled from 8.4% in 2006 to 16.7% in 2015 (Fig. 3). Among the top 20 organizations generating global public patents, Suzhou M Conj Biotech Co Ltd. is the only Chinese company (Table 7). Among the top institutions generating public patents, Univ Zhengzhou (the University of Zhengzhou) of China ranked No. 6 (Table 8).

Table 5

Funding sources for ICB for tumor immunotherapy research in China from year 2006 to 2015.

Ranking	Funding organization	Publication	Percentage
1	NSFC-National Natural Science Foundation of China	178	48.50%
2	973 Program-National Basic Research Program of China	29	7.90%
3	USA NIH-National Institutes of Health	24	6.50%
4	863 Program -National High Technology Research and Development Program of China	9	2.50%
5	Special Program for Key Basic Research of the Ministry of Science and Technology	5	1.40%

ICB = immune checkpoint blockade.

Table 6

Disease distribution related to ICB for tumor immunotherapy research.

Tumor Types	Overall			CTLA-4			PD-1		
	World	China	USA	World	China	USA	World	China	USA
Melanoma	931	56	577	586	20	365	477	38	297
Myeloma	47	4	22	19	0	9	33	4	16
Lymphoma	285	34	124	74	12	34	228	23	101
Lung cancer	269	64	121	104	19	48	203	52	96
Prostate cancer	175	15	136	134	11	108	71	7	50
Pancreatic cancer	70	18	33	27	5	17	53	13	23
Total	1,777	191	1,013	944	67	581	1,065	137	583

Note: ("CTLA-4" OR "Cytotoxic T lymphocyte antigen-4" OR "CD152") SAME (cancer OR tumor): **1035**. ("PD-1" OR "Programmed death 1" OR "CD279" OR "PD-L1" OR "programmed death-ligand 1" OR "CD274" OR "B7-H1") SAME (cancer OR tumor): 1472.
ICB = immune checkpoint blockade.

3.8. Preliminary results of tumor immune drug research

According to a Cortellis CI search result, 30 drugs that targeted CTLA-4, 37 drugs that targeted PD-1, and 2 drugs that targeted both CTLA-4 and PD-1, have been tested worldwide.

Three drugs that targeted CTLA-4 were from China. Among the institutes designing CTLA-4 drugs, 4 were from China, including 1 in Taiwan. In addition, there were 14 institutes in the United States; 2 each in the United Kingdom, Germany, Switzerland, and Japan, and India; and 1 each in France and Sweden (Table 9). Twenty-two out of 30 drugs are still in the development stage, including 3 in China, 8 in USA, 4 in UK, 2 in Switzerland, 2 in Japan, 1 in Germany, 1 in France, and 1 in Sweden (Table 10). During this time period, 3 important drugs came out of China. Ipilimumab biosimilar was produced by Hualan Gene Engineering Ltd. and is currently in development. Ipilimumab was originally produced by Medarex Inc., and was further developed by Bristol-Myers Squibb Co. and Ono Pharmaceutical Co. Ltd. Its application included genitourinary tract tumor, glioblastoma, Hodgkin's disease, and hormone dependent prostate cancer, etc. Yervoy (active ingredient: Ipilimumab) was approved by the US FDA on March 25, 2011. It is used to treat late stage (metastatic) melanoma. Bristol-Myers Squibb Company announced that the FDA approved YERVOY (ipilimumab) at 3 mg/kg for the treatment of patients with unresectable (inoperable) or metastatic melanoma. Another drug is Anti-CTLA-4 monoclonal antibody that has been in development by Aida Pharmaceuticals Inc. since January 2006. However, there was no development update report until December 2009. The last drug, anti-CTLA-4/anti-PD-1 bispecific humanized antibody (tumor), has been developed by Akeso Biopharma Inc. since November 2014. Notably, and this drug targets both CTLA-4 and PD-1.

Among the drugs that targeted PD-1, 4 drugs were from China. China had 2 original research and development institutes, while there were 24 in the USA, 5 in the UK, 2 in Germany, 2 in India, 1 in France, and 1 in Australia (Table 9). In addition, 33 drugs was currently being developed in the world, including 3 in China, 17 in USA, 7 in UK, 2 in Germany, 2 in India, 1 in France, and 1 in Japan (Table 10). Four drugs were being developed in China. KD-033 was developed by Jinghua Pharmaceutical Group Co. Ltd. and US Kadmon Pharmaceuticals LLC for cancer. This drug was in the discovery phase now. KD-033 was originally made by Kadmon Pharmaceuticals LLC. Later, Jinghua Pharmaceutical Group Co. Ltd. cooperated with Kadmon Pharmaceuticals LLC in October 2015 to further develop this drug (http://finance.qq.com/a/20151022/046411.htm). B7-H1 vaccine (cancer) was originally developed by State Key Laboratory of Cancer Biology

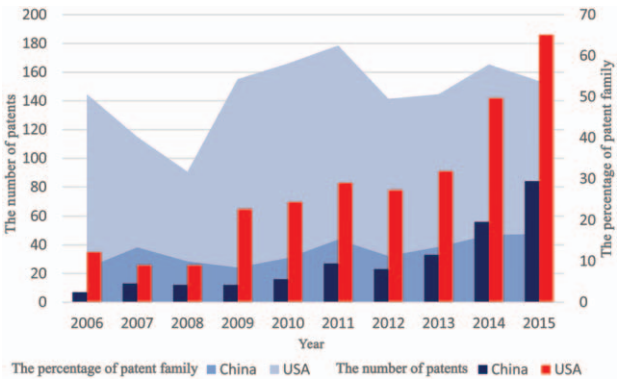

Figure 3. Annual number of patents in ICB for tumor immunotherapy from 2006 to 2015. ICB = immune checkpoint blockade.

Table 7

Top 20 organizations in number of global public patents in ICB for tumor immunotherapy from 2006 to 2015.

Rank	Applicants	Patents (family)	Percentage
1	Squibb Bristol Myers Co.	24	2.6
2	Univ Johns Hopkins	23	2.5
3	Dana Farber Cancer Inst Inc.	23	2.5
4	Univ Pennsyl Vania	23	2.5
5	Genentech Inc.	22	2.4
6	Medarex Inc.	21	2.3
7	Immunomedics Inc.	17	1.9
8	Merck Sharp&Dohme	16	1.8
9	Hoffmannla Roche	15	1.6
10	Mayo Foundation	15	1.6
11	Sloan Kettering Inst Cancer	12	1.3
12	Amplimmune Inc.	12	1.3
13	Univ California	12	1.3
14	Pfizer	10	1.1
15	Aurigene Discovery Tech Ltd.	10	1.1
16	Ono Pharmaceutical Co.	9	1
17	Medimmune Ltd.	8	0.9
18	Zymogenetics Inc.	8	0.9
19	Univ Emory	7	0.8
20	Suzhou M Conj Biotech Co. Ltd.	7	0.8

Total patent family number worldwide was 914, and the percentages were calculated by the patent family number from each institute vs total patent family number worldwide.
ICB = immune checkpoint blockade.

Table 8

Top 20 organizations in number of public patents in China in ICB for tumor immunotherapy research from year 2006 to 2015.

Rank	Applicants	Patents (family)	Percentage
1	Hoffmannla Roche Hoffmann La Roche	13	4.2
2	Medarexinc Medarex Inc.	13	4.2
3	Dana Farber Cancer Inst Inc.	11	3.5
4	Amgen Inc Amgen Inc.	11	3.5
5	Univ Johns Hopkins	9	2.9
6	Univ Zhengzhou	9	2.9
7	Univ Emory Univ	7	2.3
8	Squibb Bristol Myers Co.	6	1.9
9	Univ Pennsyl Vania Univ	6	1.9
10	Harvard College Harvard College	5	1.6
11	Postech Acad Ind Found	5	1.6
12	Ono Pharmaceutical Co.	4	1.3
13	Univ Texas	4	1.3
14	Trubion Pharmaceuticals Inc.	4	1.3
15	Zymogenetics Inc.	4	1.3
16	F Star Biotech Forsch & Entw	4	1.3
17	Immunomedics Inc	4	1.3
18	Genexine Inc.	4	1.3
19	Amplimmune Inc.	3	1
20	Wyeth Corp.	3	1

ICB = immune checkpoint blockade.

in the Fourth Military Medical University PLA of China in November 2013. This drug is still in the discovery stage. Anti-PD-1 bispecific antibodies (cancer) were originally developed by Innovent Biologics Inc. in October 2015. It is also in the discovery stage. The US Eli Lilly & Co. (http://www.innovenbio.com/) has also participated in the development of this drug. Another anti-PD-1 drug from China was originally developed by US Sorrento Therapeutics Inc. and is now being developed in cooperation with Lee's Pharmaceutical Holdings (Hong Kong, China) Ltd. (http://www.leespharm.com/en/). Anti-CTLA-4/ anti-PD-1 bispecific humanized antibody (tumor) targeted both CTLA-4 and PD-1. It was developed by Akeso Biopharma Inc. in November 2014 and is presently in the discovery stage.

At present, 2 PD-1 drugs were approved by US FDA. In 2014, Opdivo (Nivolumab) was firstly approved for patients with unresectable melanoma in Japan, and US FDA granted accelerated approval to it for patients with advanced melanoma.[23] In 2015, FDA expanded its application for patients with advanced renal cell carcinoma.[24] Then, it was approved for the treatment of patients with head and neck squamous cell carcinoma (SCCHN) in November 2016[25] and for advanced urothelial carcinoma in February 2017.[26] Keytruda (Pembrolizumab) was approved by the FDA for treatment of unresectable or metastatic melanoma in 2014.[27] It is the first PD-1 inhibitor approved by FDA. In 2015, it was approved as the first-line treatment of advanced melanoma.[28] In 2016, it was approved for first-line therapy for advanced non-small cell lung cancer (NSCLC) patients with high expression (more than 50%) of PD-L1.[29] In 2017, it was approved for unresectable or metastatic, microsatellite instable-high (MSI-H), or mismatch repair-deficient (dMMR) solid tumors.[30] Overall, China has made progress developing drugs for ICB for tumor immunotherapy, but the number of effective drugs is still lower than those produced in the USA and UK.

Table 9

Institutes that are engaged in originally designing ICB drugs.

Institutes	CTLA-4	PD-1
USA	14	24
China	4	2
United Kingdom	2	5
Germany	2	2
Switzerland	2	0
Japan	2	0
India	2	2
France	1	1
Sweden	1	0
Australia	0	1
Total	30	37

CTLA-4 = cytotoxic T-lymphocyte antigen 4; ICB = immune checkpoint blockade; PD-1 = programmed death 1.

Table 10

Drugs in discovery stage for ICB in tumor immunotherapy.

Drugs in discovery stage	CTLA-4	PD-1
USA	8	17
China	3	3
United Kingdom	4	7
Germany	1	2
Switzerland	2	0
Japan	2	1
India	0	2
France	1	1
Sweden	1	0
Australia	0	0
Total	22	33

CTLA-4 = cytotoxic T-lymphocyte antigen 4; ICB = immune checkpoint blockade; PD-1 = programmed death 1.

4. Discussion

Immune resistance in tumor microenvironment makes it hardly trigger effective immune response for tumor antigens. As the core executor of anti-tumor response, T cells were firstly activated by the capture of tumor antigens by TCR and regulated by a range of costimulation signals and coinhibition signals. These coinhibition signals are immune checkpoints that facilitate the maintenance of immune tolerance and the inhibition of autoimmune responses. Tumor cells can escape immunosurveillance by upregulating coinhibition signals and suppressing T cell activities. Therefore, T cell activation, induced by methods such as ICB, are critical for cancer therapy. Indeed, after decades of effort, ICB made great progresses in cancer immunotherapy, and have gradually been applied in clinic. Here, we used the bibliometrics method to provide a comprehensive overview of research status of ICB in tumor immunotherapy in china and worldwide during the past two decades. Notably, the number of papers about ICB in China increased rapidly in the past 2 decades, especially in the recent 10 years that increased from 13 to 366, and the total number of papers (379) just lay behind USA. In addition, the average annual growth rate of Chinese publications was 33.0% during the past decade, which is above the global average (27.0%) and the USA average (24.1%). However, greater efforts are needed to improve the quality of ICB papers from China. For instance, though the h-index increased from 6 in 2006 to 2015 to 30 in 2006 to 2015, China still ranks the lowest for the ACPP and 7th place for the h-index during the past 2 decades in the top 10 countries. Similarly, in terms of HCP, China's HCP (3) is 1.8% of the global HCP

while the USA's HCP (140) is 82.8% of the global HCP. Consistent with the increase in paper number in ICB, the number of public patents from China also increased rapidly, which doubled from 8.4% in 2006 to 16.7% in 2015. More encouragingly, China also makes progress in the research and development of drugs for ICB.

The potential reasons for the rapid development of China's tumor immunotherapy research may include the following: first, Chinese GDP maintained double-digit growth since 2000 and the medical industry income kept a 20% growth rate for the past 10 years. In addition, the pharmaceutical industry experienced strong development as well. Second, the steady increase in government investment in drug development contributes to the rapid growth of ICB for tumor immunotherapy research in China. The Chinese public financial investment in health insurance increased since 2004 when Beijing allowed health insurance to cover tumor immunotherapy. Total funding by the National Natural Science Foundations of China (NSFC) grew rapidly, and NSFC has devoted 20.71 million Chinese Yuan (RMB) to 60 projects since 2000. There was also a significant amount of funding from national special research fundings, such as "863" and "973" projects, and some local committees of science and technology. Meantime, this increase in research quality attracted funding from institutes of foreign countries, such as the National Institute of Health (NIH) of USA. However, the funding is still not adequately in line with the brisk growth of China's national gross domestic product (GDP), the growing and aging population, and the urgent health needs of cancer patients. To continue improving the quality and global influence of Chinese research on tumor immunotherapy and to promote translational research and precision therapy, a persistent increase of investment from governments, including the central and local governmental agencies, will be imperative. In addition, the financial support from non-government sources needs to be enthusiastically developed.

To conclude, ICB has developed rapidly with increasing influence in the last 2 decades in China. However, there is still a relatively large gap compared with the USA. This work represents the first bibliometric assessment of research quantity and quality in ICB literature. However, there are several limitations of the present study. Firstly, all the papers we collected were from PubMed database, while the papers from other databases and Chinese journals are not included. Secondly, the drugs for ICB we searched are focused on CTLA-4 and PD-1/PD-L1, while drugs target for other immune checkpoint molecules are lacking. Finally, all the data were only dated back to 1996.

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