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Patent Trend and Competitive Analysis of Cancer Immunotherapy in the United States

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Abstract

Immunotherapy has brought high hopes for cancer treatment, and attracted tremendous resources from the biopharmaceutical community. Here we analyze cancer immunotherapy-related patents granted by the United States Patent and Trademark Office in the past decade (2006-2016). A total of 2,229 patents were identified in 13 subfields. The growth of patent number in this field has outpaced the background rate, with cytokine-related therapies, immune checkpoint inhibitors, and natural killer cell therapies growing the most rapidly. The top 15 assignees possess 27.6% (616) of the patents. Amgen is the largest patent holder, followed by Novartis, and then by Chugai Seiyaku. The top assignees have focused on different subfields, and collaborated with each other for technology development. Our competitive analysis reveals that Novartis, Chugai Seiyaku, and Abbvie lead in both patent number and average quality of patents. Meanwhile, Immunomedics owns a high-quality though relatively small patent portfolio in single-chain variable fragment technology, which is not the focus of the abovementioned forerunners. Overall, our analysis illustrates an ecosystem where industry giants and smaller-size players each occupies a niche. Selection and succession are expected to continue for years in this young ecosystem.

Introduction

Immunotherapy has been heralded as our best chance to terminate cancers[1]. Surprisingly favorable clinical outcomes of cancer immunotherapy[2-7] have ignited fervent competitions to claim inventions in this field. Broadly defined, cancer immunotherapy includes cytokine-related therapies, immune checkpoint inhibitors, immune cell-based therapies (such as chimeric antigen receptor T cell, or CAR-T), cancer vaccines (active and passive), antibody-drug conjugates, oncolytic viruses, and other immunity-based technologies.

One of the most significant advances in cancer immunotherapy is the approval of check point inhibitors by the FDA (US Food and Drug Administration), including PD-1/PD-L1 inhibitors Pembrolizumab, Nivolumab, Atezolizumab, Avelumab, and Durvalumab. These entities have significantly improved on the treatment of melanoma, Hodgkin lymphoma, renal cancer, bladder cancer, non-small cell lung cancer (NSCLC), and head and neck cancer. Another class of checkpoint inhibitor targets CTLA-4, (Ipilimumab), which has been approved for the treatment of melanoma [8]. In year 2016 alone, FDA approved five new molecular entities, seventeen efficacy supplements, and five companion diagnostics

for cancer immunotherapy [9]. Despite the successes of immunotherapies in FDA clearance, these novel treatments may cause serious adverse effects in certain patients. Adequate management is required to balance between therapeutic benefits and damages to the patients [10-13]. Cancer immunotherapies other than checkpoint inhibitors have also faced challenges. For instance, the clinical benefits of several monoclonal antibodies have been called into question [13].

Recently, the scope of cancer immunotherapy has continued to expand to other therapeutic paradigms, including but not limited to personalized medicine [14,15], combination of targeted and immunotherapies [16], novel delivery methods [17], cancer stem cells [18], epigenetics [19], liquid biopsy [20], and novel biomaterials [16]. The cross-discipline integrations signify the rapidly growing influence, practicability, and adaptability of cancer immunotherapy. These exciting developments may not be reflected in the current patent landscape because of the time lapse between scientific innovation and technological implementation (and the subsequent patent application), but could possibly be observed in collaborations between key players in the field. Meanwhile, challenges remain for cancer immunotherapy. An important issue is to screen for a patient population suitable

for a certain treatment scheme. Appropriate biomarkers are required to ensure safety and efficacy of immunotherapeutics [21-24]. With increasing applications of immunotherapeutics, resistance to current drugs is expected to occur [25]. Multiple therapeutic options should be available for one indication to overcome drug resistance. This future need could further foster the development of cancer immunotherapy, which could be observed in the patenting activities in this field.

The patenting activities in different subfields reflect strategies for product development. For instance, a company may be actively patenting cell-based therapies but lacking strength in checkpoint inhibitors. Another company could partner with a business ally to co-develop a critical vaccine technology, and jointly file patent applications. The number and quality of patents owned by an industry player indicate its competitive edge in the technology field. Such information is precious yet difficult to find for the field of cancer immunotherapy.

Patenting is the most effective means of excluding market competitions. Unlike consumer electronics, a biopharmaceutical product is usually protected by a small number of

patents. Standard essential patents and patent pooling are seldom seen in the biopharma industry. The key to success of a biopharmaceutical product is to prove its safety and therapeutic benefits in clinical trials, which are stringently regulated and the outcomes are unpredictable. Such stringency and unpredictability have consumed enormous human and financial resources, and greatly increased the risk in product development.

To protect potentially massive returns, drug makers have raced to build strong patent portfolios. Patent analysis can provide a snapshot of patenting activities of the industry. A number of immunotherapy-related patent analyses have been available, covering such subfields as general anticancer therapies[26], immune checkpoint inhibitors[27,28], dendritic cell-based therapy[29], oncolytic virus[30], monoclonal antibodies[31], and antibody-drug conjugates[32]. However, the patents of other important subfields, *e.g.* T cell-based therapy, vaccine, and bispecific antibody, remain unanalyzed. Furthermore, overview of the entire filed of immunotherapy and competitive analysis are still unavailable. The Unites States of America is the largest single pharmaceutical market. The advanced US legal system for intellectual property protection further increases the nation's attraction to inventors and potential patentees worldwide. Importantly, access to patent raw data from

the United States Patent and Trademark Office (USPTO) has recently become feasible. Here we analyze US patents related to cancer immunotherapy. This analysis aims to address three important questions: (1) What is the patenting trend in each of the subfields of cancer immunotherapy? (2) Who are the major players and what are their relative strengths in the field? (3) Has any subfield or the entire field of immunotherapy been dominated by a small number of players? Our results suggest that the field of immunotherapy as a whole is still growing, with varying growth rates among different subfields. Although a few players possess relatively large numbers of patents, the field appears to remain dispersed. Joint development, cross-licensing activities, and mergers/acquisitions may occur for consolidation of this new technology field.

Results and Discussion

Patent trend

Fig 1A shows that the number of immunotherapy-related patents trended upwards from 2006. The number of patents decreases slightly in 2016 because the 2016 data were incomplete (Materials and Methods). This upward trend reflects that considerable

resources have been attracted to this promising field in recent years. The annual growth rate of immunotherapy-related patents, defined as the percentage of increase in patent number over the previous year, is shown in Fig 1B. The sharpest increase in immunotherapy-related patents occurred during 2008-2010, with an annual growth rate falling between 36-50%. Interestingly, a temporary decline in patent number followed in 2011 before the growth rate rebounded to ~20% in 2012. The background growth rate (*i.e*. the growth rate of all of the issued US patents) exhibited a similar trend, but with a smaller variation. The background growth rate peaked at 2010 (27%). The slowdown from 2011 observed for immunotherapy-related patents also occurred to the background growth rate. Overall, immunotherapy-related patents have been increasing more rapidly than patents in other fields. We have also analyzed the number of cancer immunotherapy-related publications at PubMed and patent publications. Fig. 1B shows that the growth in applications peaked at Year 2009 and Year 2014, whereas the growth of publications has been escalating since Year 2009. Academic activities usually lead industry applications by several years. The steady recent increase in cancer immunotherapy-related publication may foretell growth in patent number in the years to come.

The majority of the analyzed patents (1,463/2,229) do not claim to target any specific cancer type. Two hundred eighty-three patents target one cancer type, while 483 patents target multiple cancer types. The top ten cancer types that are explicitly targeted by the analyzed patents are shown in Fig 2. Each of these cancer types is targeted by more than 150 patents, and the top five (colorectal cancer, breast cancer, lymphoma, lung cancer, and melanoma) are each targeted by more than 200 patents.

As expected, the 2,229 patents were mostly granted to US applicants (~1600 patents), followed by Japanese, French, German, and Chinese applicants (Fig 3A). The high percentage (>70%) of US-owned patents clearly indicates the dominance of US in this technology field. Also noteworthy is that Japan had the second largest number of immunotherapy-related patents (248), dwarfing France (122), Germany (106), Switzerland (87), and the United Kingdom (74). Of note, many biopharmaceutical companies have branches in both of the US and Europe. The observed distribution thus may not completely reflect the patenting activities of Europe-based companies.

Fig 3B demonstrates the top 20 inventors of the 2,229 analyzed patents. As expected, most (16/20) of the top inventors were US citizens. Interestingly, only one Japanese inventor (Shiro Shibayama) made to this top 20 list, even though Japanese entities owned the second largest number of immunotherapy-related patents. By contrast, three German inventors (Hans-Juergen Krause, Michael Dickes, and Lisa Baust) were listed in the top 20, despite the smaller number of patents owned by German than by Japanese entities (Fig 3A and 3B). These observations imply that the efforts in developing cancer immunotherapy technology are more scattered in Japan as compared with in Germany. In addition, the three German inventors might have been the employees of the same entity or entities undergoing a joint venture. We then analyzed the co-inventorship of these top 20 inventors. Fig 4A shows that David M. Goldenberg and Chien-Hsing Chang co-invented 10 patented technologies. Among the 10 patents, five were assigned to Immunomedics, four assigned to IBC Pharmaceuticals, and the remaining one assigned to both companies. Indeed, IBC Pharmaceuticals was founded as a result of a joint venture between Immunomedics and Beckman Coulter (http://www.immunomedics.com/ibc-pharmaceuticals.shtml). Smilarly, Carl H. June and David L. Porter, Michael C. Milone, and Bruce L. Levine co-invented in 9 patents in

University of Pennsylvania (Fig 4B). Alan J. Korman co-invented with Mark J. Selby and Mohan Srinivasan, in a variety of entities (Fig 4C). Meanwhile, the three German inventors, Krause Hans-Juergen, Dickes Michael, and Baust Lisa co-invented in 17 patents, all of which were assigned to AbbVie (data not shown). This co-inventorship analysis revealed which entities the top inventors worked for, and how they collaborated with each other in the development of immunotherapy-related technologies.

Fig 5A shows the distribution of patents among the 13 subfields of cancer immunotherapy. Cytokine-related patents accounted for the largest group (> 800 patents), followed by patents related to immune checkpoint inhibitors, natural killer cell, cancer vaccines, single-chain variable fragment, and so on. The disparity in patent numbers among different subfields partly resulted from the differences in the stage of technology development. Newly emerged therapies, such as IDO (indoleamine 2,3-dioxygenase) inhibitors, tumor-infiltrating lymphocytes (TILs), CAR-T (chimeric antigen receptor T cell) understandably included only small numbers of patents. In comparison, cytokine-related therapies have long been recognized as a potential treatment for cancer[33-35]. And the patenting activities indicate that interests in this subfield

are long-lasting. Meanwhile, oncolytic virus-related patents represented only a small group although the potential of this technology had been explored early[36-38], suggesting that the industry has not been passionate in further developing this subfield. This cautious attitude probably resulted from potential risks and unpredictable outcomes of oncolytic virus therapy[39] . The temporal development of these 13 subfields is shown in Fig 5B. The patent numbers in most of the groups increased over time, with patents related to cytokine, immune checkpoint, and natural killer cell growing most rapidly. Interestingly, year 2007-2008 seems to be a starting point of rapid growth for all these three subfields. In comparison, the growth of patents related to vaccines and T cell-based therapies seem to have slowed down since year 2010, whereas those related to antibody-drug conjugates and single-chain variable fragment continue to grow steadily.

Development strategies and relative strengths of the top 15 assignees

The next important question is which entities own the immunotherapy-related patents. Fig 6A shows the top 15 assignees of the 2,229 patents. Twelve of the entities were biopharmaceutical companies. Only three were academic institutes (the Regents of the University of California, the Trustee of the University of Pennsylvania, and the

Dana-Farber Cancer Institute). Amgen, Novartis, and Chugai Seiyaku Kabushiki Kaisha possessed the largest numbers of immunotherapy-related patents. The top 15 assignees collectively owned 616 (27.6%) of the 2,229 patents. Amgen, the top assignee, owned only 88 of the patents, which represented 3.9% of the 2,229 patents, and 14.3% of the 616 patents. This observation suggests that the patent landscape of immunotherapy has remained dispersed, and that cross-licensing, joint venture, and merger/acquisition events might increase in the years to come. Indeed, collaborations among the top 15 assignees were observed. Two patents were co-owned by Novartis and Amgen, 16 were shared by Amgen and Pfizer, and another five by Pfizer and Bristol-Myers-Squibb (Fig 6B). Table 1 lists the patents co-owned by these assignees. Apparently Amgen and Pfizer joined force to develop monoclonal antibodies against CTLA-4, CD40, and insulin-like growth factor I receptor. Meanwhile, Pfizer collaborated with Bristol-Meyer-Squibb to develop antibodies against OX40, integrin α5β1, and IL-6. This observation indicates that resourceful pharmaceutical giants have been utilizing a multi-channel development strategy by partnering with different entities.

To evaluate the relative technology strengths for each of the top 15 assignees, we generated the Radar Diagram (Materials and Methods). Fig 7 indicates that Amgen had strong standings in antibody, immune checkpoint, IDO inhibitor, and T cell-related therapies. In comparison, Novartis focused more on natural killer cell, cancer vaccines, dendritic cell, and TILs. Meanwhile, Seattle Genetics seemed to specialize in antibody-drug conjugates, while Ohno Pharmaceutical was focused on CAR-T therapies. Apparently the top 15 assignees have different roadmaps for technology development. This is consistent with our above proposition that the patent landscape of immunotherapy has remained dispersed. Further consolidation or collaborations are expected to occur.

Next, we analyzed the qualities (measured by the patent quality index “PQ6”; Materials and Methods) versus the numbers of patents owned by the top 15 assignees. The median values of patent number and PQ6 were used to delineate the data space into four quadrants (Fig 8). The upper-right quadrant included entities that had relatively large numbers of high-quality patents, including Novartis, Chugai Seiyaku Kabushiki Kaisha, Abbvie, and Seattle Genetics. These companies have the potential of becoming leaders of the relevant subfields given sufficient time or strategic alliances for development. The

lower-right quadrant harbored entities with smaller numbers of high-quality patents, including Immunomedics, Biogen Idec, and the Dana-Farber Cancer Institute. The patent numbers of these assignees would have to keep growing to join the forerunner group. Although Amgen had the largest number of patents, the average PQ6 score of its portfolio was slightly lower than the median. Nevertheless, the large patent portfolio could be a powerful weapon in the increasingly vehement competitions in cancer immunotherapy.

Analysis and Perspective

The challenges of cancer immunotherapy also bring opportunities for technological innovations. First, current cancer immunotherapies are usually effective only in a subgroup of patients. Obviously, novel diagnostics are required to identify the patient population suitable for a certain immunotherapy scheme. To this end, liquid biopsy, novel biomarkers, omics-based tests, and the broad concept of precision medicine are expected to converge with cancer immunotherapy. Second, the adverse drug effects of immunotherapies suggest that adjunctive therapies to ameliorate such effects without compromising the efficacy of the primary therapy are needed. Alternatively, researchers may also consider developing future therapies with smaller side effects, or novel delivery

methods to limit the range of drug actions. Third, the possibility of drug resistance foretells the needs for multiple therapeutic options, combinatorial therapies, and next-generation immunotherapies for each cancer type. This also indicates joint developments between major players of different expertise in the field. All of these directions are expected to emerge in the future patent landscape of cancer immunotherapy.

Concluding Remarks

The development of cancer immunotherapy is clearly on the rise (Fig 1), yet subfields differ from each other in patent number and growth rate (Fig 5), reflecting uneven resource allocation by the community to different subfields. Meanwhile, major players in cancer immunotherapy apply divergent strategies in technology development, and specialize in different subfields (Fig 7). Joint development thus may be mutually beneficial, as can be observed in the collaborations between top patent assignees (Fig 3 and 5B, Table 1). The biotech giant, Amgen, has so far harvested more patents than any other competitors in the field of immunotherapy. Other companies, such as Novartis, Chugai Seiyaku Kabushiki Kaisha, and Immunomedics have fewer but relatively high-quality patents. (Fig 8). The dynamic patent landscape of cancer immunotherapy is

expected to keep changing rapidly in the foreseeable future, and is worth close attention from stakeholders in the field.

Methods

Patent search and classification

Fig 9 summarizes the analysis flow. To begin with, all of the patent documents in XML format were downloaded from the USPTO website at https://bulkdata.uspto.gov/. The XML files were then parsed using an in-house PERL script. The patent number, abstract, assignee(s), inventor(s), international patent classification codes, and claims were retrieved and dumped into an in-house MySQL database. Two rounds of keyword searches were then conducted in this database. The search space was limited to patents issued between January 2006 and October 11, 2016, and patents under IPC categories A、C、G01N and G06F. The first round of search (downward arrow from "In-house DB") was based on immunotherapy-related keywords retrieved from a review article authored by Kohrt and colleagues (2016)[2]. The synonyms, abbreviations, alias and/or full names of these keywords were retrieved from GeneCards and Wikipedia (S1

Table). The S1 Table keywords were then used to search against the title, abstract, and claims of each patent in the in-house database, which yielded Result (1). Note that certain keywords must be capitalized to be considered as correct keywords when appearing in a patent document. These include 19A, CD2, CLA, MICA, ML, NAIL, NK, SELL, PVR, TRAP, LIGHT, BLAST, T1, APRIL, H1, and TDO. A total of 4,491 patents were thus identified.

The second round of search (rightward arrow from “In-house DB”) was based on company names. The companies known to be developing immunotherapy were retrieved from a business intelligence report[40]. Merger and acquisition histories of interested companies were retrieved from Wikipedia. The names of immunotherapy-related subsidiaries of major companies were also considered. These company names were searched in the “assignee” column of the patent documents. Cancer-related wildcard keywords (cancer, tumor, tumour, *noma, *ioma, *toma, *sarcoma, leukemia, and *moma) and immunotherapy-related keywords (immune*,immune, antibod*, interferon, killer cell, NK cell, adoptive T, vaccine, cytokine, IDO inhibitor, CAR T, chimeric antigen receptor, indoleamine-2,3-dioxygenase, IL-1R, IL-2R, IL-7R, c-KIT, CCR, CXCR, and

CX3CR1) were used to further limit the scope of the search space. 1,267 patents were identified by using this approach (Result (2)).

Results (1) and (2) were combined. The total of 5,758 (4,491+ 1,267) patents were manually curated to further screen out irrelevant and distantly related patents. Finally, 2,229 patents were retained. These patents were then classified into 13 groups based on subfield-related keywords (S2 Table)[2]. Note that one patent can be classified into multiple groups. The sum of patent numbers across the 13 groups was thus larger than 2,229.

Patent quality analysis

Patent quality was measured by PQ(6)[41,42]. PQ(6) is the average of six normalized measurements: number of forward citations, number of backward citations, number of claims, family size, generality index, and grant lag. The numbers of forward citations, backward citations, and claims were retrieved from the downloaded patent data. Family size, defined as the number of patents in an INPADOC family (https://www.epo.org/searching-for-patents/helpful-resources/first-time-here/patent-famil

ies/inpadoc.html), was obtained from the Espacenet Patent Search web page (http://www.epo.org/searching-for-patents/technical/espacenet.html#tab1). Family size, the number of forward/backward citations, and the number of claims were separately normalized by dividing the measure of the interested patent by the maximal measure of the patent cohort. Note that a maximal family size of 490 is given by the Espacenet if the actual size exceeds this number. A total of 15 out of the 616 patents that belonged to the top 15 assignees were given the family size of 490. The generality index[42] was defined as

$$\boldsymbol{Generality_p = 1 - \sum_j S_{pj}^2}$$

where S_{pj} is the percentage of forward citations received by patent p from 4-digits IPC technology class j.

Grant lag was defined as:

$$\boldsymbol{Grant_{\mathrm{pi}} = 1 - \frac{\Delta t}{Max_{\Delta ti}}}$$

where Δt was the time between the date of filing and the date of issuance (days);

MaxΔti was the maximal Δt of patent cohort i. Both grant lag and the number of backward citations were extracted from the downloaded patent documents.

Relative strength analysis

Radar Diagrams were used to exhibit the relative strengths of the top 15 patent assignees in different subfields. The patents owned by the top 15 assignees (total 616 patents) were classified into 13 subfields as mentioned above. For an assignee, the strength in a subfield was defined as the proportion of the assignee's patents over the total number of patents owned by the top 15 assignees in this subfield. Therefore, each assignee had 13 strength measures, with each corresponding to one subfield.

Author Contributions

FCC conceived of and designed the study. CPL conducted data collection and analysis. CPL and FCC drafted the manuscript.

Declaration of competing interests

The authors declare that they have no competing interests.

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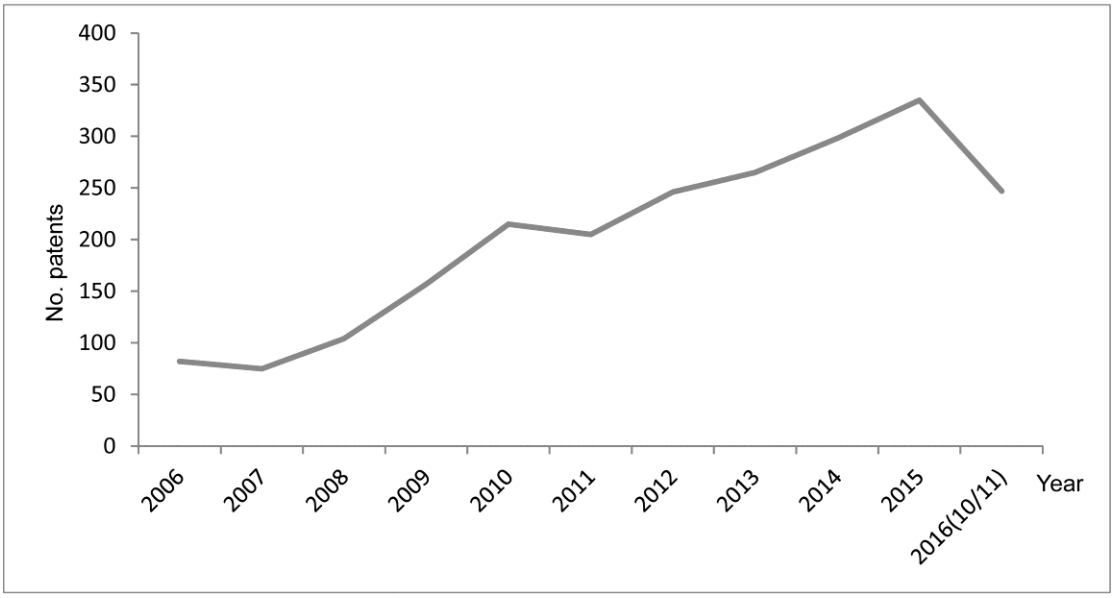
Figure legends

Figure 1. (A) The numbers and of cancer immunotherapy-related US patents (B) the annual growth rates of cancer immunotherapy-related US patents, patent applications, and PubMed publications from Year 2006 to 2016, as compared with the growth rate of all issued US patents. Note that no growth rate is available for 2006 (the first year of the dataset) and 2016 (data incomplete).

A.



B.

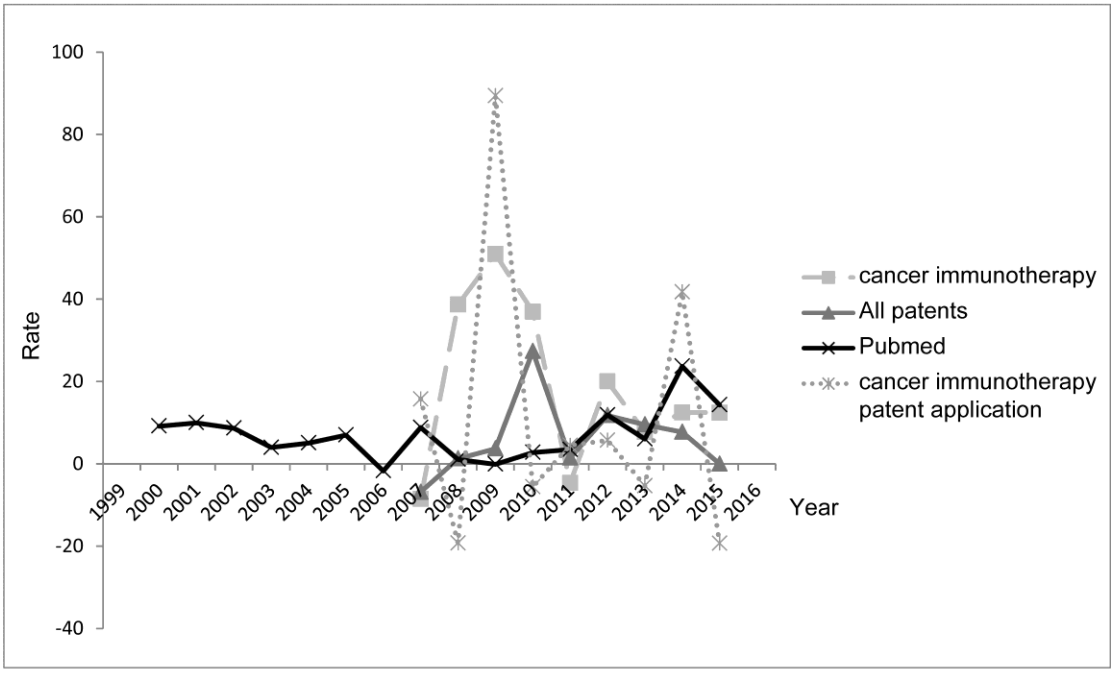


Figure 1

Figure 2. The number of patents that claim to target specific cancer types. Note that one patent can claim to target multiple cancer types.

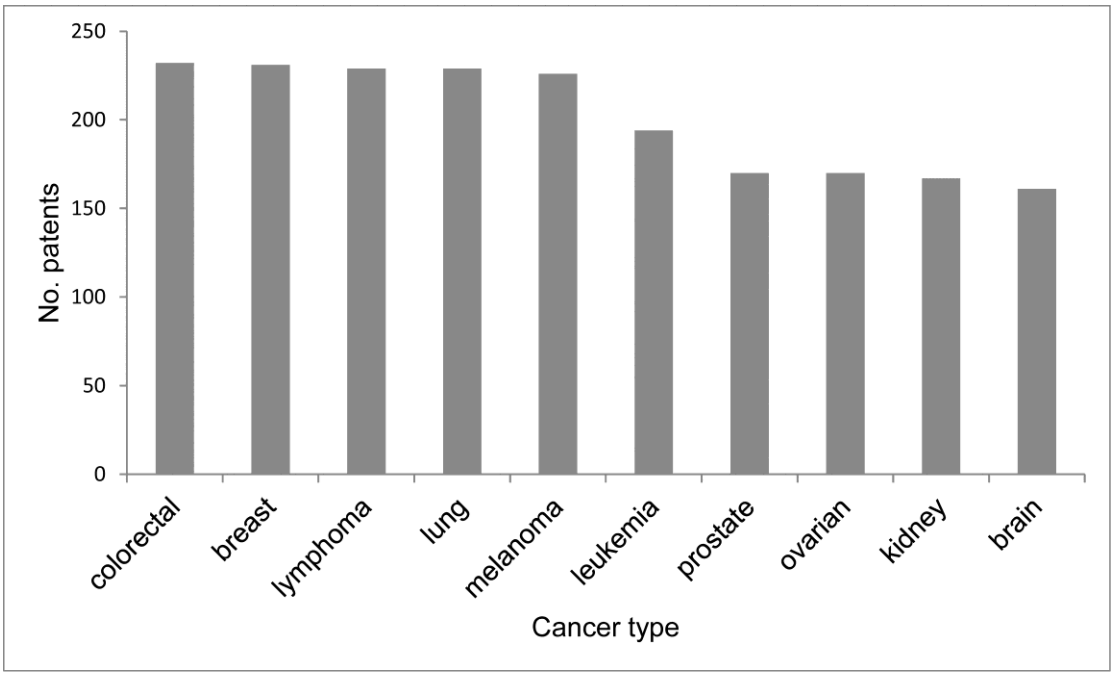
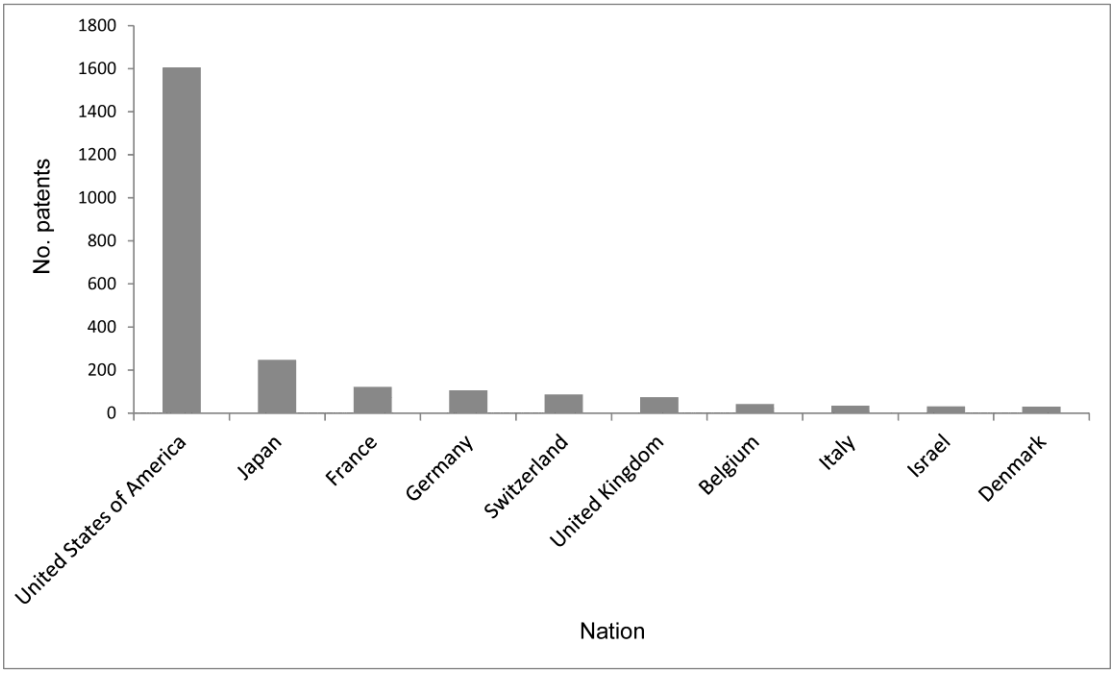


Figure 2

Figure 3. The numbers of cancer immunotherapy-related patents (A) assigned to entities from different countries and (B) issued to top 20 inventors.

A.



B.

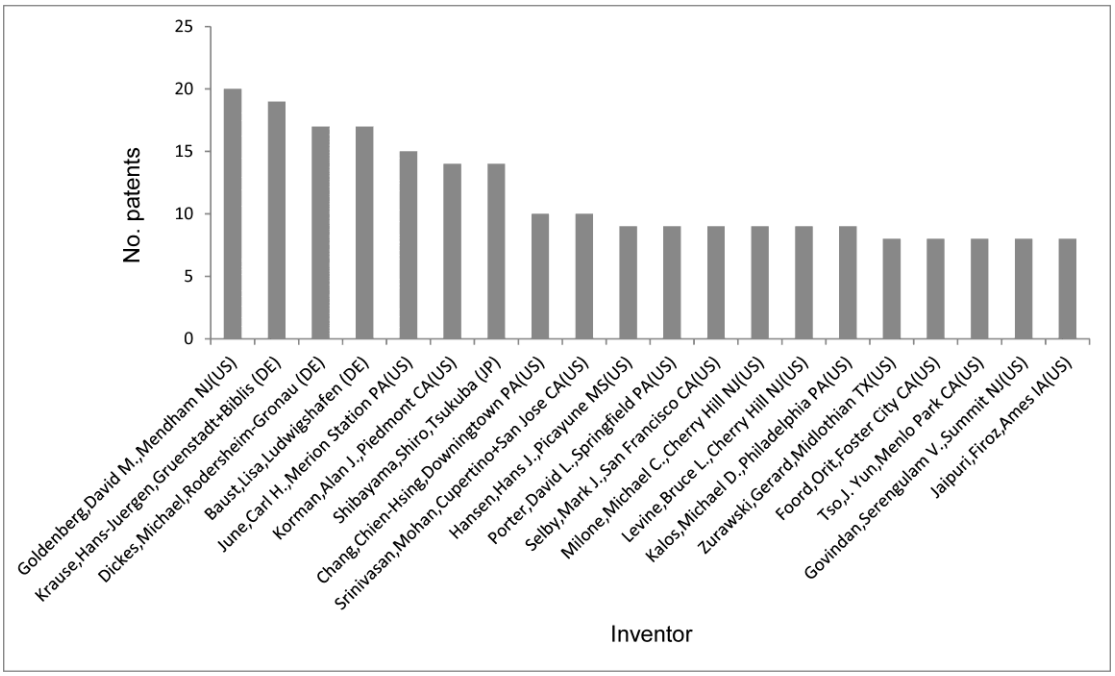


Figure 3

Figure 4. The co-inventorship among the top 20 inventors. The names of the inventors are shown on both sides. The company/institution names in the middle indicate the assignees of the relevant patents. The numbers in the parentheses represent the numbers of patents when the inventors were affiliated with the company/institution.

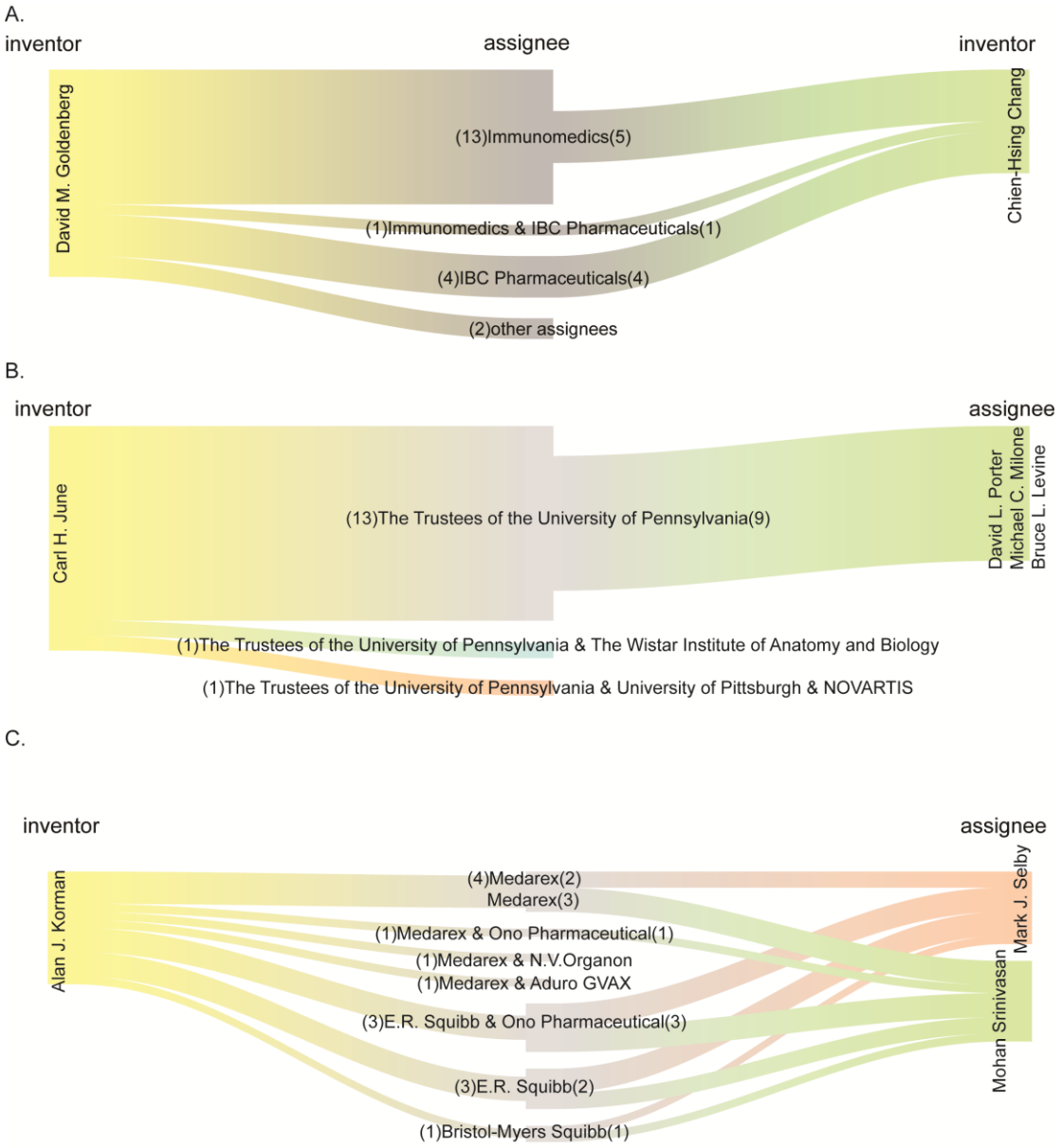
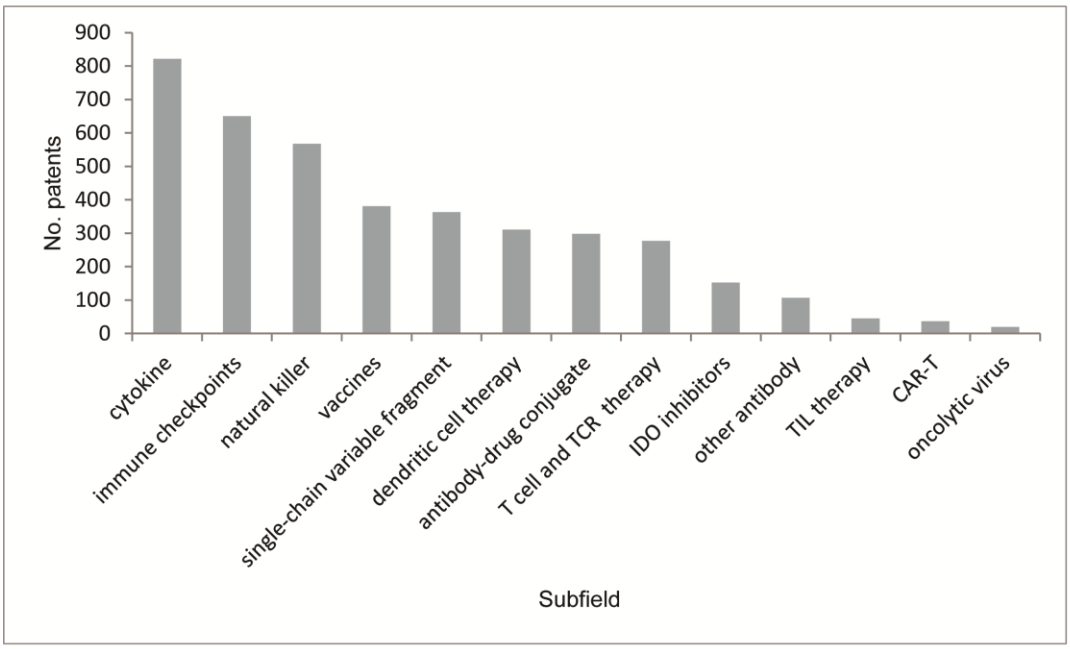


Figure 4

Figure 5. The total numbers (A) and yearly numbers (B) of cancer immunotherapy-related patents in 13 different subfields.

A.



B.

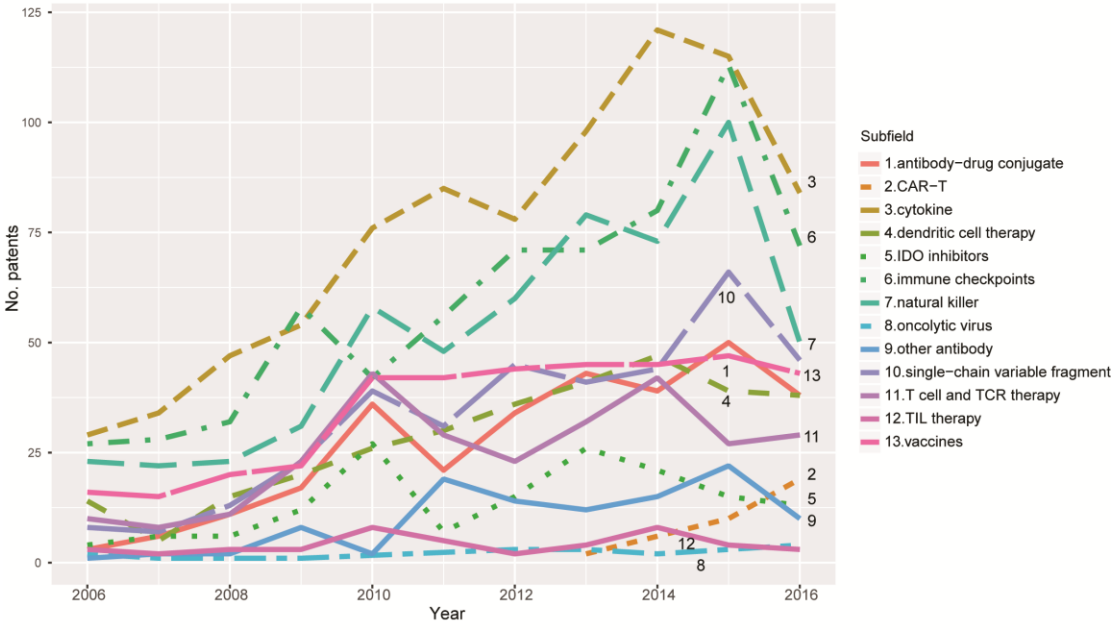
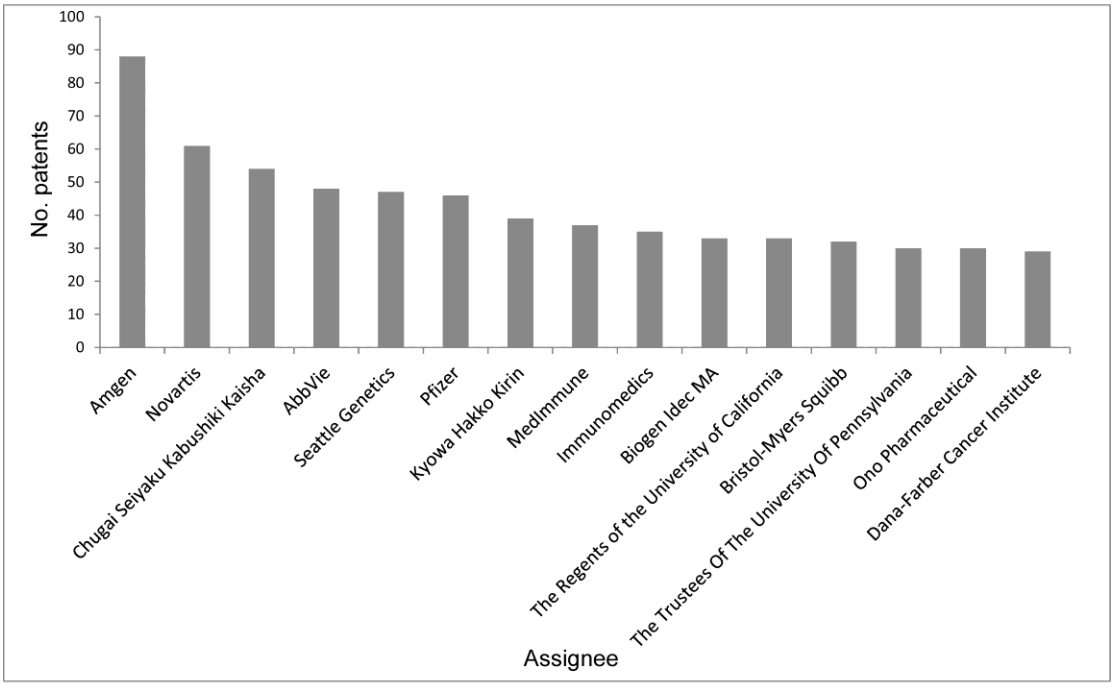


Figure 5

Figure 6. The numbers of cancer immunotherapy-related patents (A) owned individually and (B) co-owned by top 15 assignees. Note that the co-owned patents in (B) were counted as one patent assigned to each of the two co-owners in (A).

A.



B.

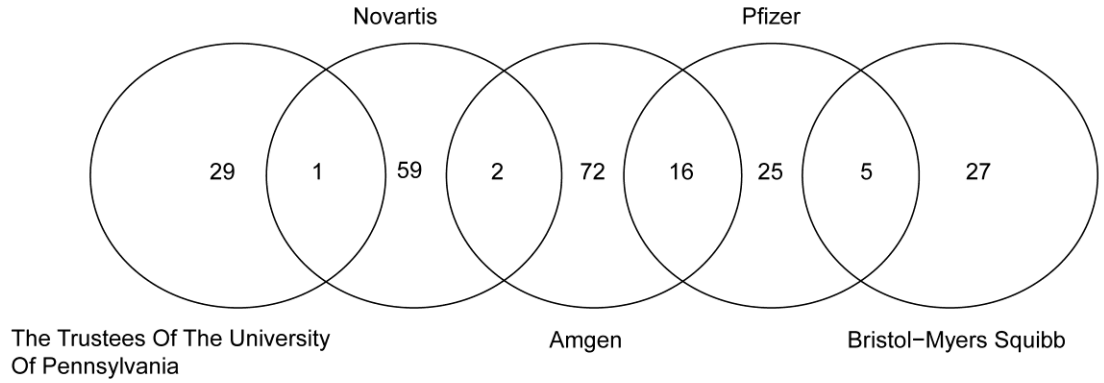


Figure 6

Figure 7. The relative strengths of the top 15 assignees in the 13 different subfields.

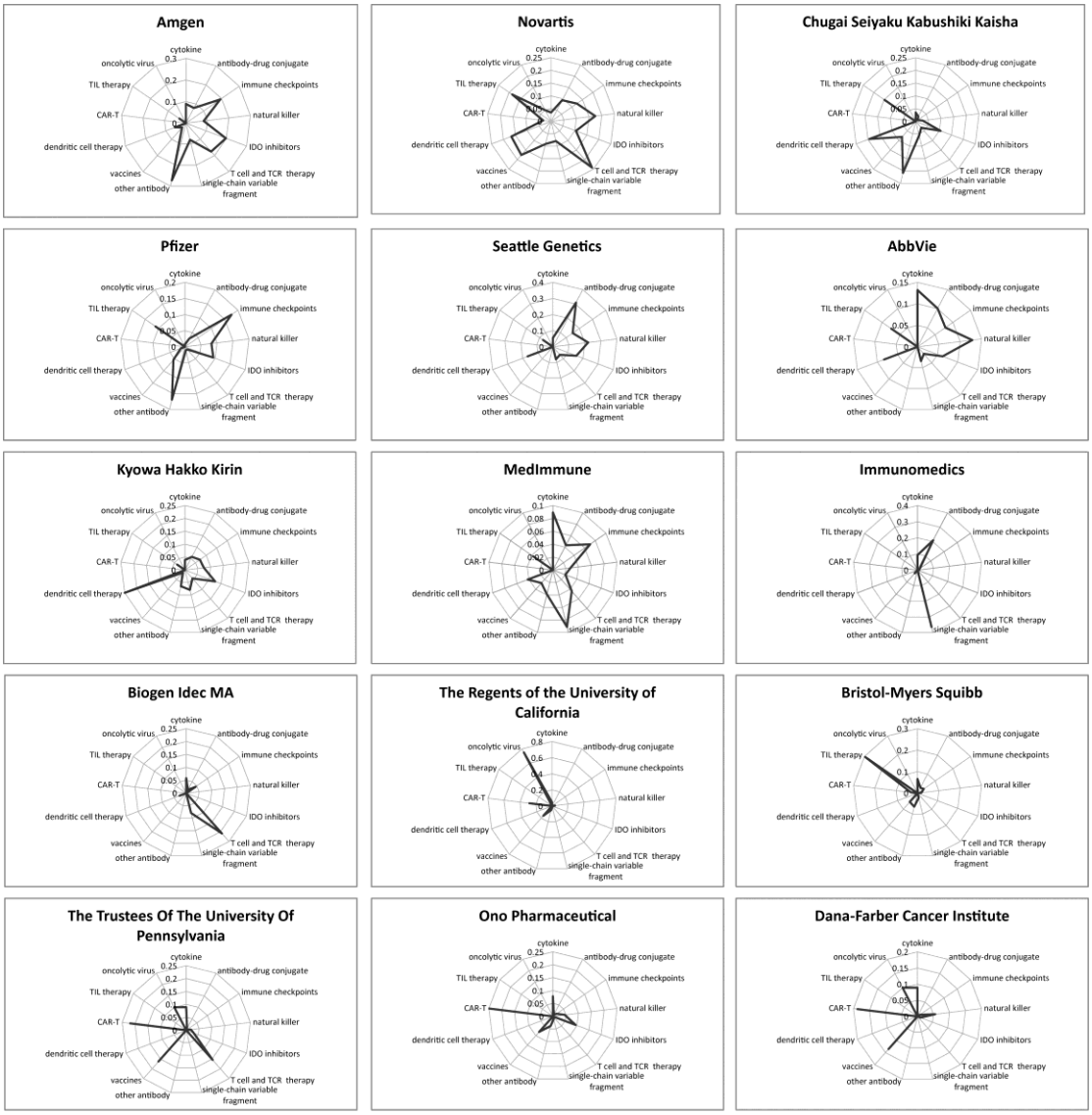


Figure 7

Figure 8. Competitive analysis of the top 15 assignees. The X-axis and Y-axis, respectively, indicates patent quality (PQ(6)) and the number of patents. The horizontal and vertical red line, respectively, represents the median value of patent number and PQ6.

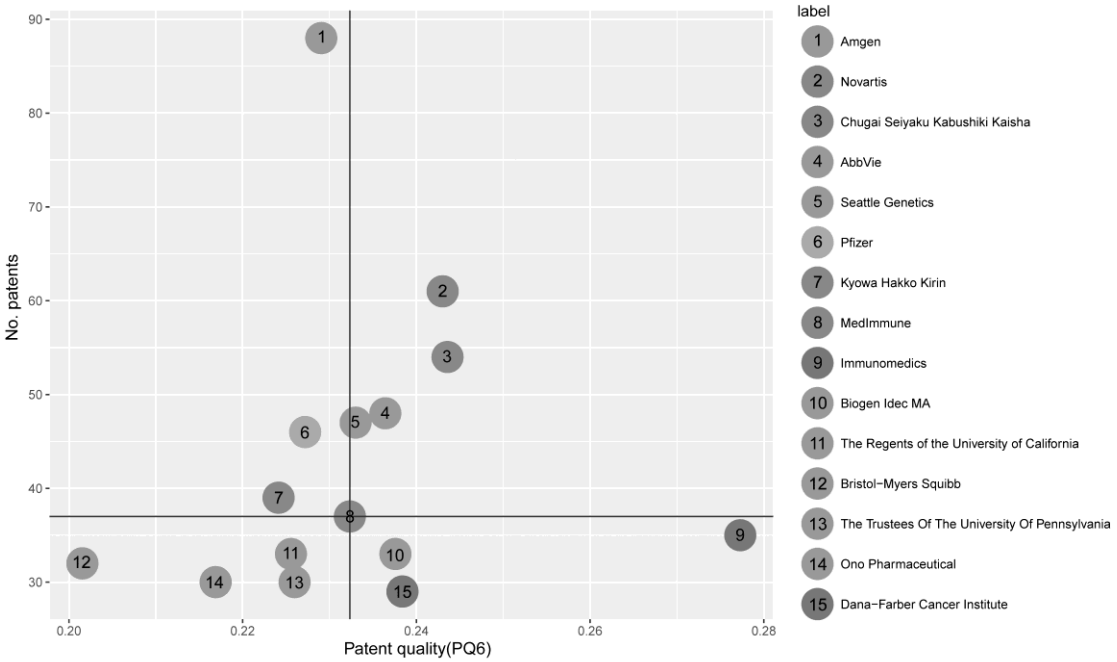


Figure 8

Figure 9. The identification process of cancer immunotherapy-related patents.

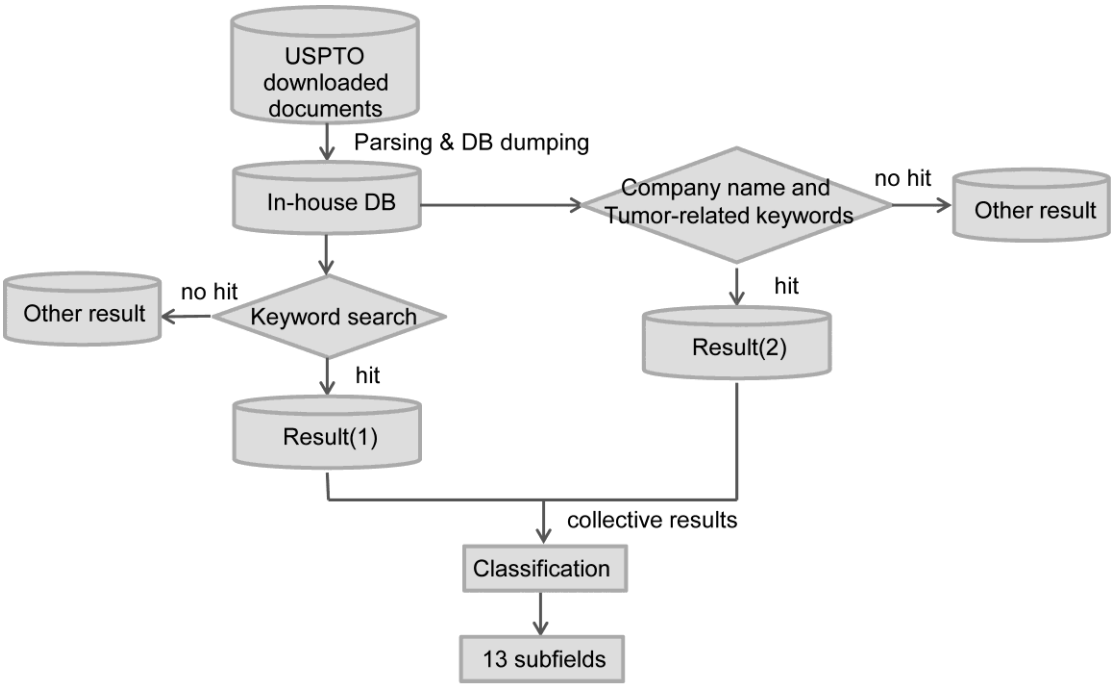


Figure 9

Tables

Table 1.

cooperation company	Number of patent	patent title
Amgen & Pfizer	US7132281	Methods and host cells for producing human monoclonal antibodies to CTLA-4
	US7618633	Antibodies that bind CD40 and methods of treating cancer and enhancing immune responses
	US8388971	Antibodies that bind CD40 and methods of treating cancer and enhancing immune responses
	US7626012	Nucleic acid molecules which encode antibodies that bind CD40
	US7700742	Antibodies to insulin-like growth factor I receptor
	US7815907	Antibodies to insulin-like growth factor I receptor
	US8642037	Antibodies to insulin-like growth factor I receptor
	US9234041	Antibodies to insulin-like growth factor I receptor
	US7807797	Human monoclonal antibodies to CTLA-4
	US7824679	Human monoclonal antibodies to CTLA-4
	US8143379	Human monoclonal antibodies to CTLA-4
	US8883984	Human monoclonal antibodies to CTLA-4
	US8163280	Antibodies to c-Met
	US8491895	Methods of treating cancer with human monoclonal antibodies to CTLA-4
	US8821869	Treatment methods using c-Met antibodies
	US9221915	Human monoclonal antibodies to activin

		receptor-like kinase-1
Bristol-Myers Squibb & Pfizer	US7960515	Binding molecules to the human OX40 receptor
	US9028824	Binding molecules to the human OX40 receptor
	US8039596	Alpha 5-beta 1 antibodies and their uses
	US8399647	Alpha5-beta1 antibodies and their uses
	US8846037	Antibodies to IL-6 and their uses
The Trustees Of The University Of Pennsylvania & Novartis	US9394368	Treatment of cancer using humanized anti-EGFRvIII chimeric antigen receptor