CAR-T細胞療法全球專利格局

胡元佳
澳門大學

2021.7.31 HK

全球首個自體細胞“CAR-T”療法Kymriah的研發歷程

2017.08
獲FDA批准用於ALL治療
Phase II, 63, 83%治愈; 10:0
47.5萬美元/劑

2012.03
啓動支持性臨床試驗

2015.08
啓動主要臨床試驗研究

賓大與諾華合作共同開發

2014.07
IND申報，獲突破性療法

2017.03
獲優先審批資格

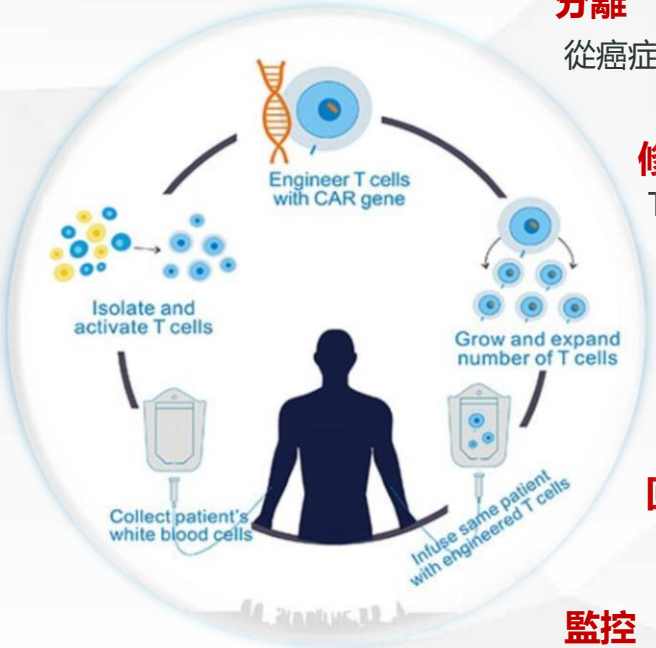
最早由賓大研發

2012 2013 2014 2015

Emily Whitehead
全球首例接受CAR-T療法的白血病患者

無癌生存8年

治療流程



分離

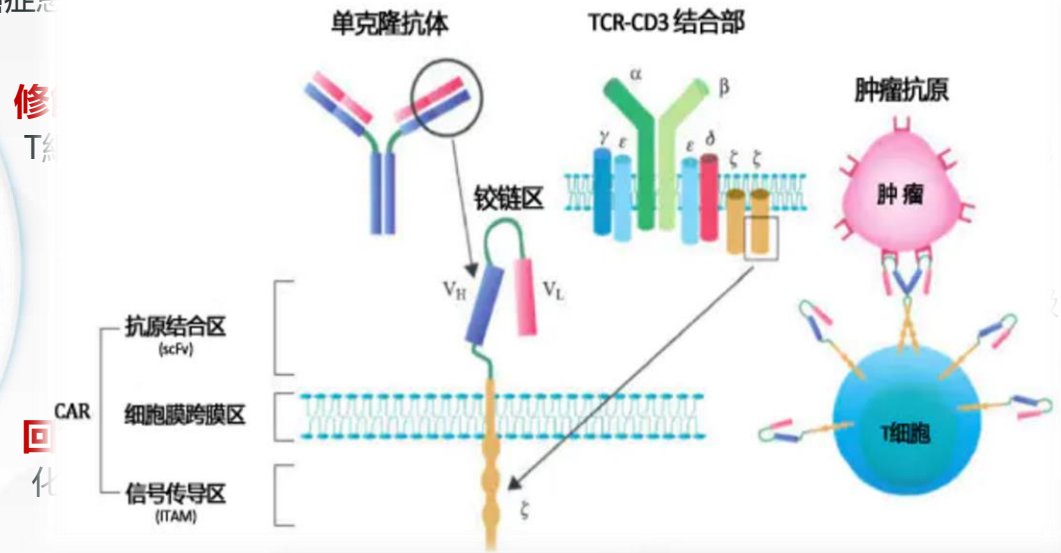
從癌症患

修

T

回

化



監控

觀察療效並嚴密監測不良反應

Value 具技術、法律、商業三種屬性，**高價值**

Volume

2018年全球專利申請總量高達332.63萬件，專利數據**容量非常大**

Velocity

全球平均每天產生近萬件專利申請，高速增长

Veracity

專利需經發明、審查、公開、批准等多個環節，虛假申請將被無效，**真實性**有保障

Variety

包含發明人、時間、引用、家族、權利請求、描述，聲明，序列表、圖紙、化學式等結構化資料、非結構化資料和圖像數據，具**多樣性**

僅2.3%的論文引用專利

數據來源： WIPO,《世界知識產權指標2019》
胡元佳, 宋瑞霖. 專利轉化：中國醫藥創新的關鍵. ***中國改革***. 2020(5): 1-5

數據樣例

地理信息：保护范围

优先权

引用：技术流动

标题；摘要；权利请求等

技术类别

靶点

治疗领域

时间：申请；公开；授权

IPC

发明人：类型；地址

剩余效期

专利权人：类型；国别

终属母公司

技术交易：转让；许可；共研；并购

专利家族：DWPI等

申请/有效/失效

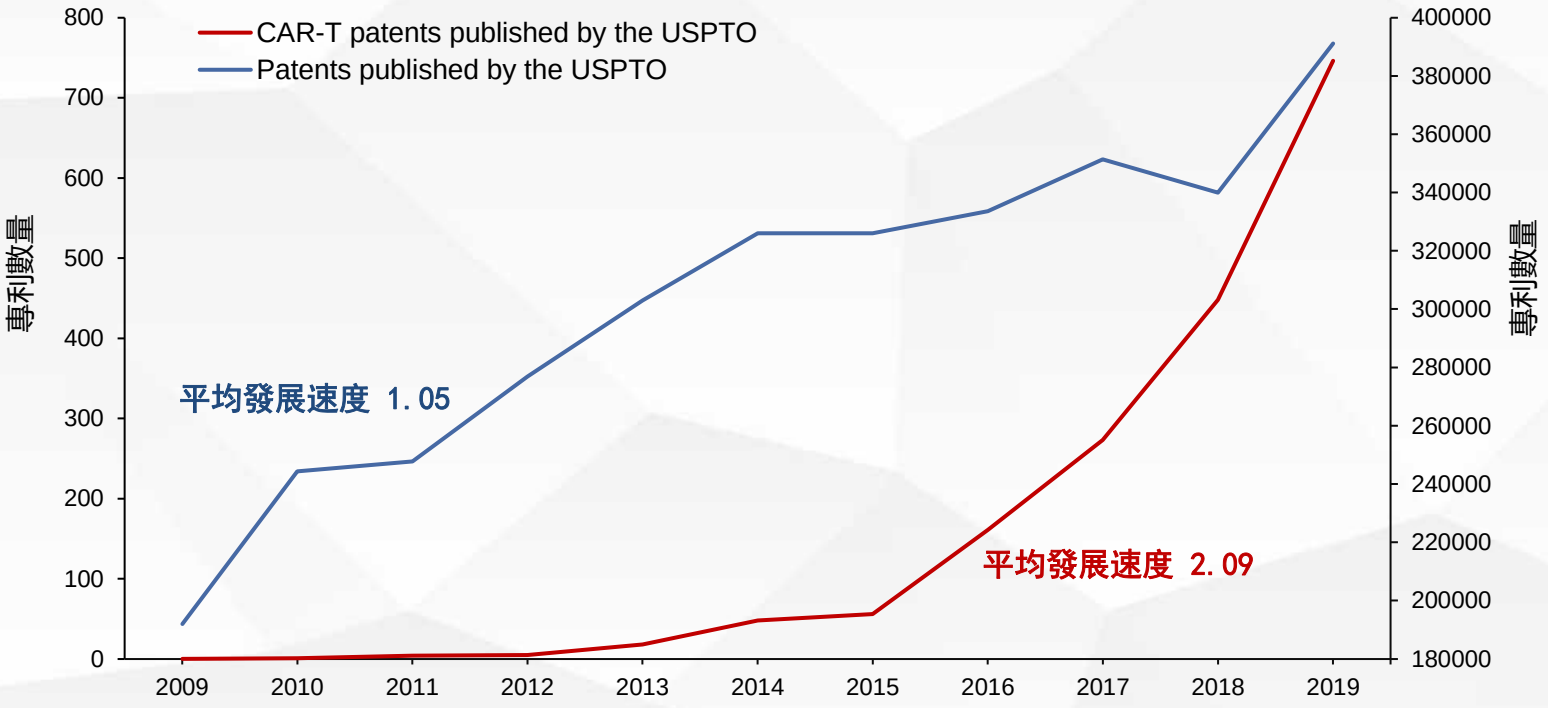
INPADOC法律状态

WIPO | PCT

(10) International Publication Number

WO 2012/079000 A1

CAR-T專利的快速增長



數據來源：美國專利局

方　法


nature > nature biotechnology > patents > article

Published: 09 November 2018

The Reporting Items for Patent Landscapes statement

James A Smith, Zeeshaan Arshad, Anthony Trippe, Gary S Collins, David A Brindley & Andrew J Carr

Nature Biotechnology **36**, 1043–1047(2018) | Cite this article

840 Accesses | 4 Citations | 5 Altmetric | Metrics

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

Article | Authors | Metrics | Comments | Media Coverage

Introduction
Terminology
Developing the PRISMA Statement
The PRISMA Statement
From QUOROM to PRISMA
Endorsement

Figures

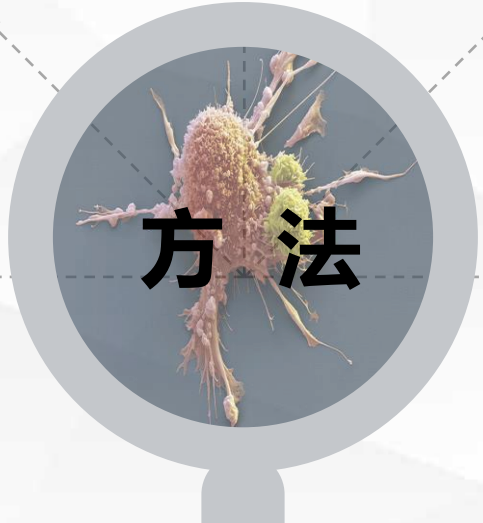
優先權年截至
2019年12月3日

時間
範圍

處理
標準

數據
搜集

Derwent™
A Clarivate Analytics company



Chimeric
antigen
receptor

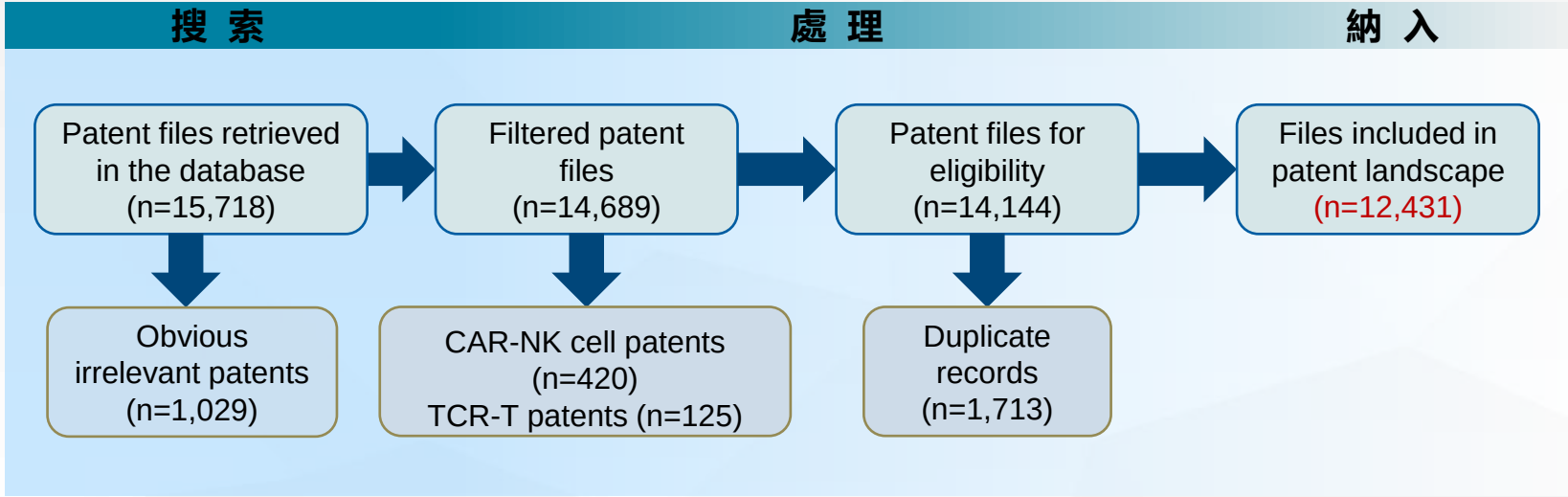
搜索
策略

軟件
分析

Gephi

Cytoscape

數據處理流程


搜 索
處 理
納 入
Patent files retrieved in the database (n=15,718)
Filtered patent files (n=14,689)
Patent files for eligibility (n=14,144)
Files included in patent landscape (n=12,431)
Obvious irrelevant patents (n=1,029)
CAR-NK cell patents (n=420)
TCR-T patents (n=125)
Duplicate records (n=1,713)

挖掘15,718件專利：自動去重；人工降噪；技術標引；重點解讀.....

1 / 454

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(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
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WIPO | PCT

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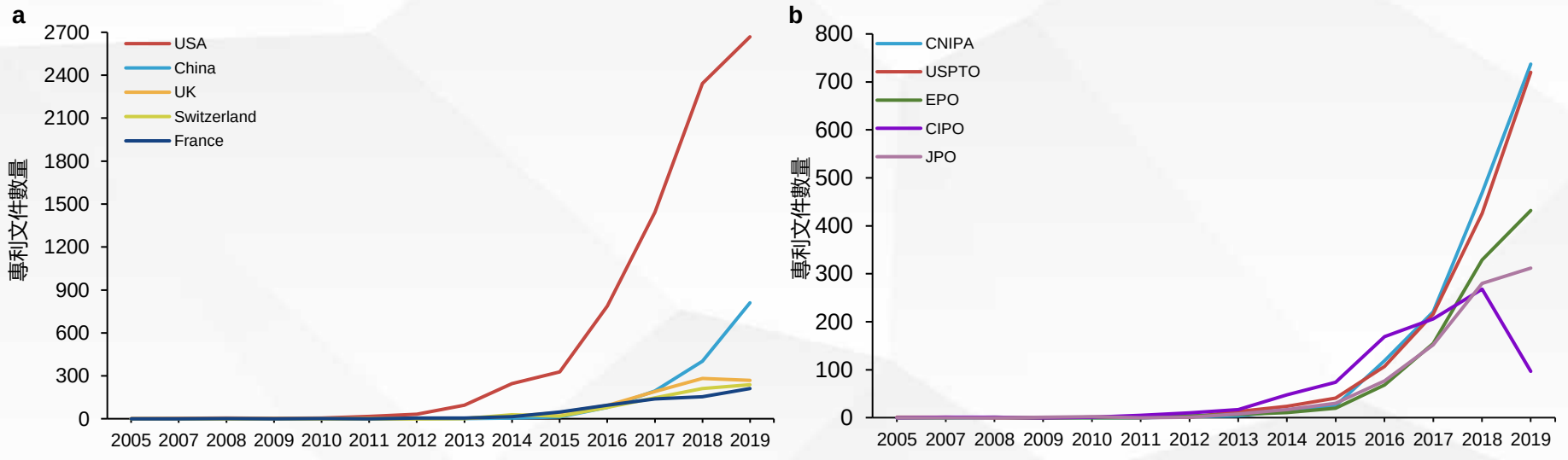
61/953,783 15 March 2014 (15.03.2014) US

(74) Agent: COLLAZO, Diana M.; Lando & Anastasi LLP, Riverfront Office Park, One Main Street, Suite 1100, Cambridge, MA 02142 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,

CAR-T專利公開趨勢



(a)專利申請國　(b) 專利受理地. CNIPA –中國國家知識產權局. USPTO - 美國國家知識產權局. JPO - 日本知識產權局. CIPO – 加拿大知識產權局. EPO – 歐洲專利局

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3	Shaun Cordoba (UK)	279	41
4	Philippe Duchateau (France)	268	35
5	Laurent Poirot (France)	260	26
6	Michael C. Milone (US)	256	22
7	Roman Galetto (France)	225	12
8	Jennifer Brogdon (US)	218	19
9	Michael C. Jensen (US)	214	19
10	Bruce L. Levine (US)	203	9
11	Julianne Smith (US)	184	12
12	Michael D. Kalos (US)	178	7
13	Simon Thomas (UK)	173	27
14	Cheng Liu (US)	169	16
15	Saar Gill (US)	159	15
16	Steven A. Rosenberg (US)	154	12
17	Laurence J.N. Cooper (US)	148	19
18	Alexandre Juillerat (US)	146	16
19	Yangbing Zhao (US)	141	15
20	Julien Valton (US)	140	15

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排名	專利權人	專利	
		文件數	家族數
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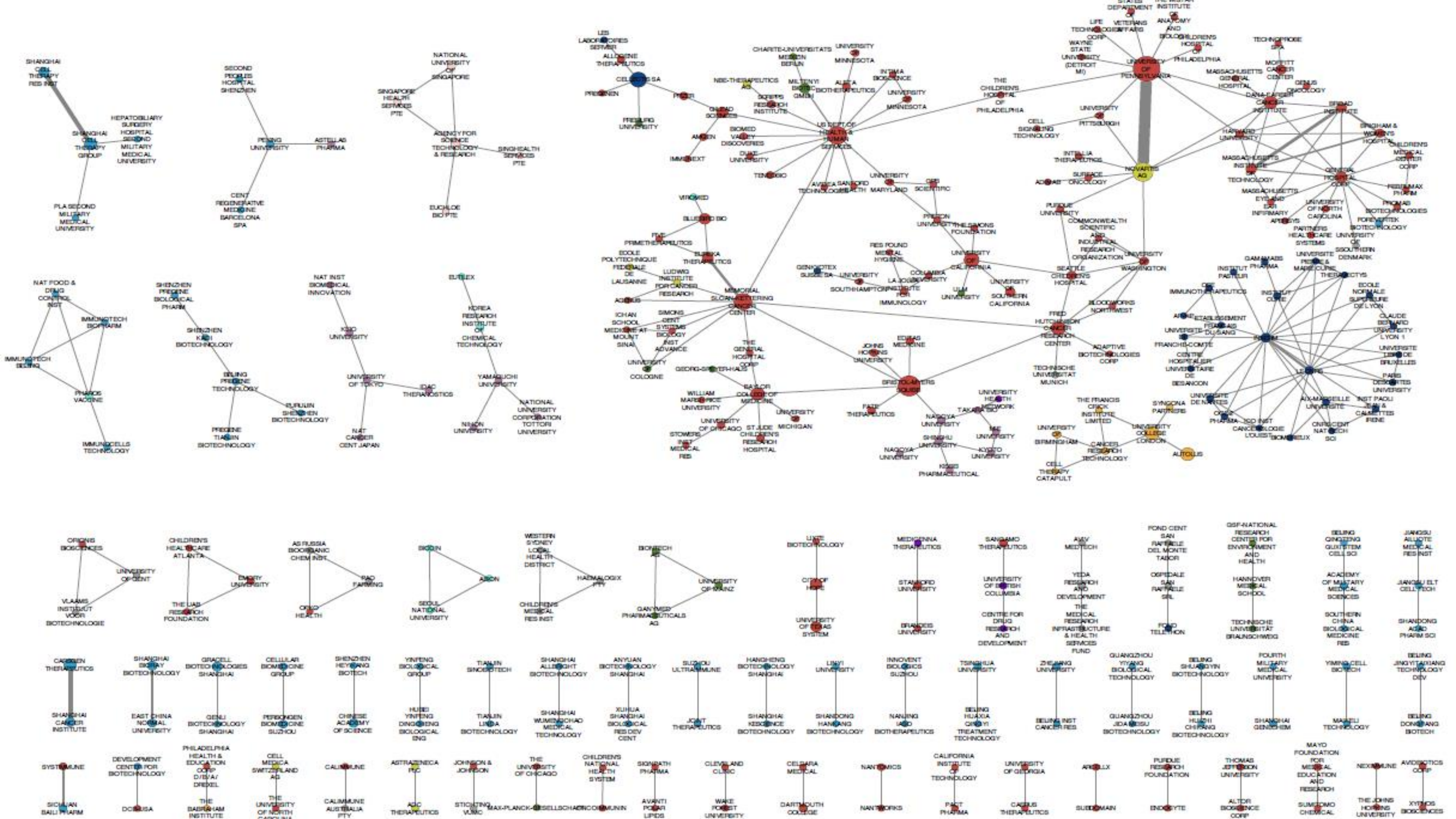
2	美國百時美施貴寶公司	507	82
3	瑞士諾華	499	71
4	法國Cellectis生物製藥公司	495	52
5	美國紀念斯隆· 凱特琳癌症中心	482	60
6	美國衛生與公眾服務部	457	67
7	英國倫敦大學學院	428	40
8	美國弗雷德· 哈欽森癌症研究中心	244	40
9	美國優瑞科生物技術公司	226	24
10	美國貝勒醫學院	223	36
11	美國加利福尼亞大學	220	45
12	美國吉利德科學公司	220	27
13	美國藍鳥生物公司	211	27
14	美國希望之城國家醫療中心	203	27
15	美國達納法伯癌症研究所	192	36
16	美國西雅圖兒童醫院	176	15
17	英國Autolus生物製藥公司	172	39
18	科濟生物醫藥（上海）有限公司	150	30
19	美國德克薩斯大學	150	24
20	美國羅氏控股	134	12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PLA SECOND MILITARY MEDICAL UNIVERSITY
SECOND PEOPLES HOSPITAL SHENZHEN
PEKING UNIVERSITY
ASTELLAS PHARMA
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GANYMED PHARMACEUTICALS AG
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SANGAMO THERAPEUTICS
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TSINGHUA UNIVERSITY
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SYSTIMMUNE
SICHUAN BAILI PHARM
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THE UNIVERSITY OF NORTH CAROLINA
CALIMMUNE
CALIMMUNE AUSTRALIA PTY
ASTRAZENECA PLC
JOHNSON & JOHNSON
THE UNIVERSITY OF CHICAGO
CHILDRENS NATIONAL HEALTH SYSTEM
SIGNPATH PHARMA
AVANTI POLAR LIPIDS
CLEVELAND CLINIC
WAKE FOREST UNIVERSITY
CELGARIA MEDICAL
DARTMOUTH COLLEGE
NANTOMICS
NANTWORKS
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UNIVERSITY OF GEORGIA
APEXELLX
PURDUE RESEARCH FOUNDATION
ENDOCYTE
THOMAS JEFFERSON UNIVERSITY
MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH
NEXIMMUNE
THE JOHNS HOPKINS UNIVERSITY
AVIDBIOTICS CORP
XYPHOS BIOSCIENCES

已上市產品

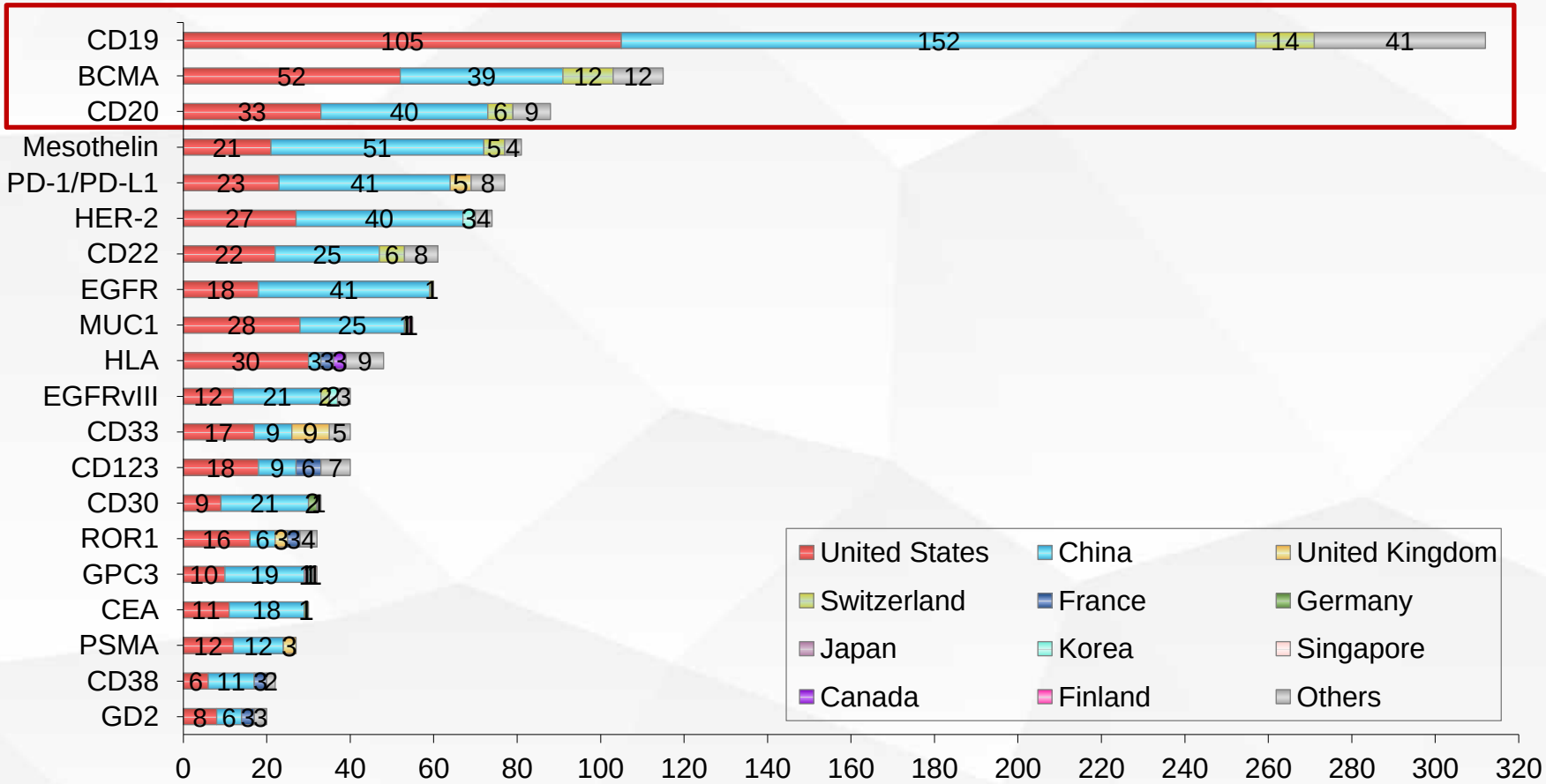
序號	商品名	靶點	企業	獲批時間	適應症
1	Kymriah	CD19	Novartis	2017-8	主要運用於治療3~25歲復發或難治性急性淋巴細胞白血病（ALL）的患者
2	Yescarta	CD19	Kite(Gilead)	2017-10	用於既往接受二線或多線系統治療的複發性或難治性大B細胞淋巴瘤（LBCL）成人患者的治療。
3	Tecartus	CD19	Kite(Gilead)	2020-7	用於治療復發/難治性套細胞淋巴瘤(MCL)成人患者
4	Breyanzi	CD19	Juno(BMS)	2021-2	用於治療復發或難治性套細胞淋巴瘤（R/R MCL）成人患者
5	Abecma	BCMA	Juno(BMS)	2021-3	用於治療復發或難治性多發性骨髓瘤成人患者

資料來源：美國FDA

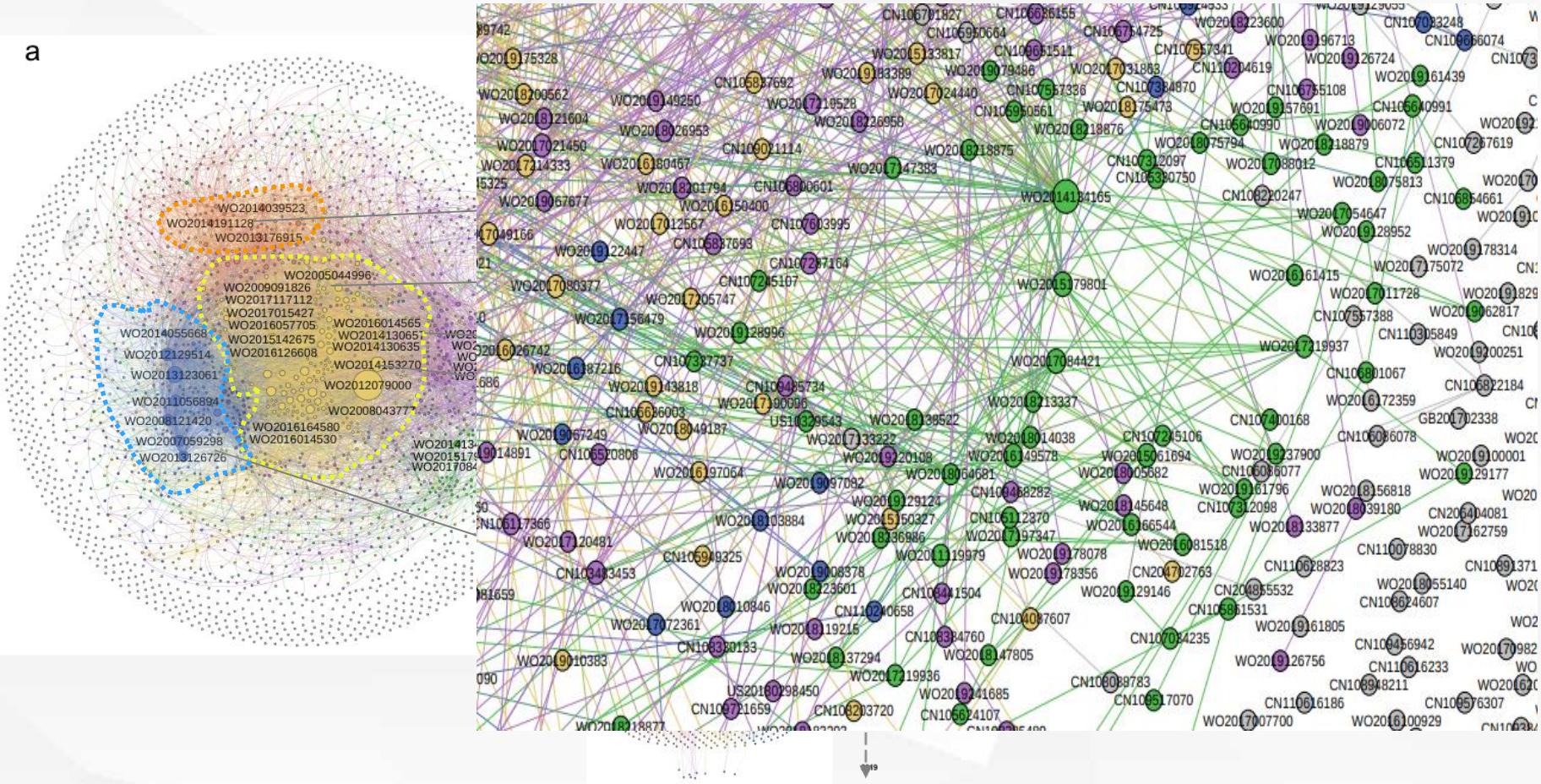
CAR-T專利家族規模國際對比

國家/地區	平均家族規模	專利	
		家族數	文件數
芬蘭	16.00	2	32
新西蘭	9.00	2	18
法國	7.68	88	676
瑞士	7.20	101	727
英國	6.77	133	901
比利時	6.40	5	32
新加坡	6.15	26	160
美國	5.84	1366	7977
意大利	5.67	12	68
日本	5.42	48	260
瑞典	5.00	3	15
德國	4.52	65	294
加拿大	4.39	28	123
丹麥	4.33	3	13
以色列	4.00	25	100
澳大利亞	3.95	19	75
韓國	3.89	36	140
荷蘭	3.67	6	22
愛爾蘭	3.25	4	13
俄國	3.00	1	3
挪威	2.60	5	13
印度	2.33	3	7
西班牙	1.67	3	5
中國	1.65	913	1506
奧地利	1.00	1	1
智利	1.00	1	1

CAR-T專利的前20個靶點



全球技術格局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WO2008121420
WO2007059298
WO2013126726
WO2016014565
WO2014130635
WO2014153270
WO2012079000
WO200804377
WO2016164580
WO2016014530

里程碑專利

WO2005044996
具有4-1BB刺激信號域的嵌合受體

WO2007059298
用於治療人類癌症的嵌合免疫受體

WO2008121420
共刺激配體在過繼轉移T淋巴細胞上的組成性表達

WO2011056894
截斷型表皮生長因數受體（EGFRt）在T細胞選擇中的應用

WO2012129514
用於細胞免疫治療的方法和組合物

WO2014153270
人源化抗CD19嵌合抗原受體治療腫瘤

WO2017025038
基於單域抗體的嵌合抗原受體及其使用方法

WO2019076149
通用型CAR-T細胞及其製備方法和應用

2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

US9834590
具有4-1BB刺激信號域的嵌合受體

WO2008043777
對GD2神經節苷脂的o-乙醯化形式特異的單克隆抗體在治療某些癌症中的應用

WO2009091826
與人CD19特異性嵌合抗原受體（h-CAR）相關的組合物和方法

WO2012079000
嵌合抗原受體修飾T細胞在腫瘤治療中的應用

WO2013126061
雙特異性嵌合抗原受體及其編碼的多核苷酸

WO2015142675
嵌合抗原受體治療腫瘤

WO2017172981
靶向腫瘤的嵌合抗原受體

CN109055380
一種通用型CAR-T細胞的製備方法

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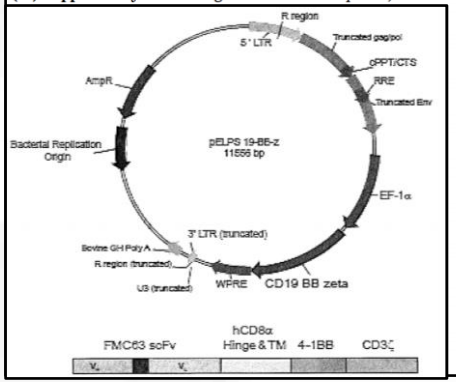

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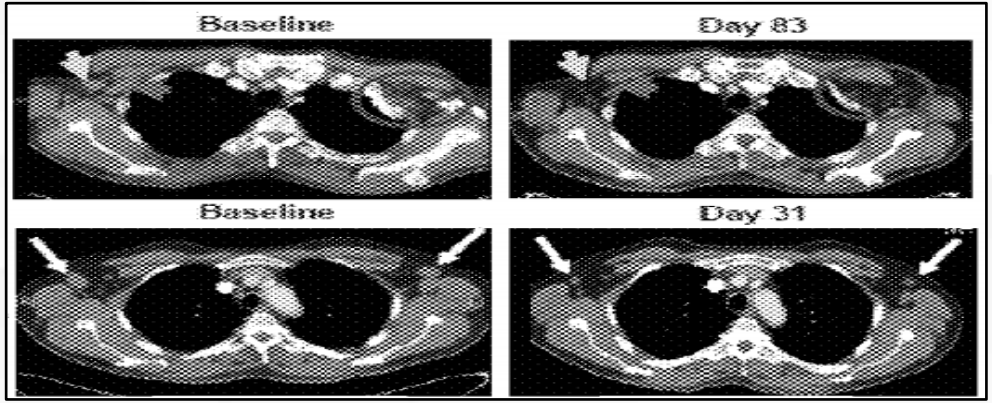
題目: 嵌合抗原受體修飾的T細胞在治療癌症中的用途

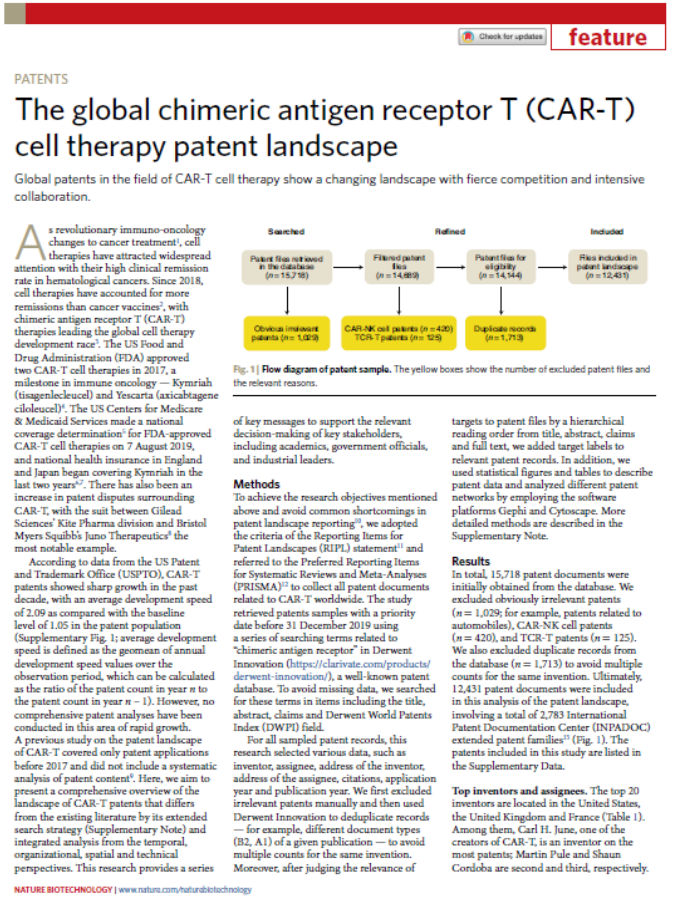
發明人: Carl H. June等

專利權人: The Trustees of the University of Pennsylvania

家族规模: 超過50個國家

權利要求: 53項，其中包括一種分離的編碼嵌合抗原受體（CAR）的核酸序列，其中所述CAR包含抗原結合結構域，跨膜結構域，共刺激信號傳導域和CD3ζ信號傳導域， CD3ζ信號傳導域包括氨基





feature

PATENTS

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

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

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

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

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

Methods

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

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

Results

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

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

資料來源: L.Y. Lyu, Y. Feng, X. Chen, Y.J. Hu*, Patent landscape of global chimeric antigen receptor T (CAR-T) cell therapy. ***Nature Biotechnology***, 38:1387-1394, https://rdcu.be/cbFlW, 2020.


高价值专利
过期专利
通用CAR-T
PD-1/PD-L1
CD19
BCMA
最新专利
诺华-宾大
实体瘤
M&A
中国
产学研合作
发明人
专利权人
Vaccines
TCR-T
mAb
iPSC
CRISPR

- “自细视大者不尽，自大视细者不明”——《庄子·秋水》
- 从细小的角度看待庞大的事物总看不全面，从宏大的角度看细小的事物总看不清楚

Endoscope

Telescope

致 謝

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