Review Article

The global landscape of approved antibody therapies

Xiaochen Lyu[1],[†], Qichao Zhao[2],[†], Julia Hui[3], Tiffany Wang[4], Mengyi Lin[1], Keying Wang[1], Jialing Zhang[1], Jiaqian Shentu[1], Paul A. Dalby[5], Hongyu Zhang[1],[2],[*] and Bo Liu[3],[*]

[1]Big Data and Bioinformatics, Zhanyuan Therapeutics Ltd, Hangzhou, Zhejiang 310000, China , [2]Research and Development, Zhanyuan Therapeutics Ltd, Hangzhou, Zhejiang 310000, China , [3]Big Data and Discovery, Umabs Therapeutics Inc., Salem, NH 03079, USA , [4]Department of Applied Mathematics, Harvard College, Cambridge, MA 02138, USA , and [5]Department of Biochemical Engineering, University College London, London WC1E 6BT, UK

ABSTRACT

Antibody therapies have become an important class of therapeutics in recent years as they have exhibited outstanding efficacy and safety in the treatment of several major diseases including cancers, immune-related diseases, infectious disease and hematological disease. There has been significant progress in the global research and development landscape of antibody therapies in the past decade. In this review, we have collected available data from the Umabs Antibody Therapies Database (Umabs-DB, https://umabs.com) as of 30 June 2022. The Umabs-DB shows that 162 antibody therapies have been approved by at least one regulatory agency in the world, including 122 approvals in the US, followed by 114 in Europe, 82 in Japan and 73 in China, whereas biosimilar, diagnostic and veterinary antibodies are not included in our statistics. Although the US and Europe have been at the leading position for decades, rapid advancement has been witnessed in Japan and China in the past decade. The approved antibody therapies include 115 canonical antibodies, 14 antibody-drug conjugates, 7 bispecific antibodies, 8 antibody fragments, 3 radiolabeled antibodies, 1 antibody-conjugate immunotoxin, 2 immunoconjugates and 12 Fc-Fusion proteins. They have been developed against 91 drug targets, of which PD-1 is the most popular, with 14 approved antibody-based blockades for cancer treatment in the world. This review outlined the global landscape of the approved antibody therapies with respect to the regulation agencies, therapeutic targets and indications, aiming to provide an insight into the trends of the global development of antibody therapies.

> **Statement of Significance:** This article gives a comprehensive review of the global approved antibody therapies on their approval statistics in each country/region, types of engineering formats, targets and therapeutic indications, aiming to provide an insight into the trends of the global development of antibody therapies.

INTRODUCTION

Antibody therapy is a form of targeted treatment that uses antibody-based molecules to treat human diseases [1]. Monoclonal antibodies (mAbs) are immunoglobulins produced by plasma B cells as stimulated by a specific antigen. Antibodies can perform several roles in the human immune system, such as facilitating humoral and cellular immune responses to a wide range of antigens with high specificity and long-term efficacy. Thus, it has emerged as a major class of therapeutics since the approval of the first mAb, anti-CD3 OKT3 (also known as muromonab-CD3), by the United States Food and Drug Administration (US FDA) in

1986 [2]. The number of approved and marketed antibody therapies has reached 162 as of 30 June 2022, targeting a wide range of diseases including cancers, immune-related disease, infectious disease and hematological disease. The benefits of using antibody therapies stem from their high selectivity and optimal binding affinity. In addition, the safety and efficacy of antibody therapies are closely related to the characteristics of their therapeutic targets, such as expression patterns and the role they perform in the progression of disease [3]. Targets in cancers and immune-related diseases are well characterized, such as PD-1/PD-L1, CD20, tumor necrosis factor (TNF)-alpha, HER2 and CD3. As a result, the approved antibody therapies are mostly developed for the treatment of these indications, although a broader range of diseases have also been investigated [4]. Moreover, SARS-CoV-2 spike protein in COVID-19 infectious disease and calcitonin gene-related peptide (CGRP) in the central nervous system (CNS) disorders, have aroused broad interest in recent years [5, 6].

The global antibody therapies market was merely 0.3 billion USD in 1997 and rapidly increased to 186 billion USD in 2021. However, there are thousands of ongoing clinical trials and preclinical studies, and so the market is estimated to reach 445 billion USD by 2028, with a compound annual growth rate (CAGR) of 13.2% from 2022 to 2028 [7]. The market of antibody therapies has been growing fast and shows great market potential in the overall healthcare industry in the US, Europe, Japan and China. Companies with the largest number of approved antibodies and greatest share of the market are mostly located in the US due to their long-term investment into R&D. The market position of the US is followed by Europe, whereas there has been a rapid growth in the number of companies and approved antibodies in China and Japan over the past 5 years [8].

In this review, we collected data from the Umabs Antibody Therapies Database (Umabs-DB) [9], to make a statistical analysis of the antibodies approved by at least one drug regulatory agency of the world, excluding biosimilar, diagnostic and veterinary antibodies. We firstly inspected the number of antibody therapies approved by drug regulatory agencies for each year, which shows the trend of the approval of antibody therapies in different regions. Then, the format of antibody therapies on the year of their first approval is presented, showing the historical map to the development of new antibody formats. Targets and indications of antibody therapies in each historical period are presented to show the progress of global R&D. Lastly, approvals from companies in different countries and regions are analyzed to predict the future trend in the development of antibody therapies.

GLOBAL LANDSCAPE OF ANTIBODY THERAPIES APPROVAL

As of 30 June 2022, we reviewed a total of 162 antibody therapies approved by at least one drug regulatory agency in the world, including nine that were later withdrawn. Biosimilar, diagnostic and veterinary antibodies were not included for the analysis. An overview on the number of antibody therapies approved in each year and in different regions is presented in Fig. 1 and Table 1.

Counting the number of global approvals, around 93% of approved antibody therapies were first approved by only four major drug regulatory agencies, which are the FDA in the US, the European Medicines Agency (EMA) in Europe, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the National Medical Products Administration (NMPA) in China (Supplementary Fig. 1). The remaining 7% of antibody therapies were first approved in Canada, Brazil, Cuba, India and Russia. Historically, the FDA, EMA, NMPA, and PMDA started to give antibody therapies market approval in the 1990s. For the 162 approved antibody therapies to date, the FDA has approved 122, the EMA has approved 114 (including 4 approved by European countries prior to the formal establishment of the EMA), the NMPA has approved 73, and the PMDA has approved 82. In this review, we mainly focus on the approvals by these four drug regulatory agencies. If one antibody was first approved by one of the other agencies, the first approval information was given but the approvals in other countries were not specifically listed.

Our data show that the US has had the greatest number of approvals, and is far ahead of other countries and regions. After the first antibody therapy (OKT3) was approved by the FDA in 1986, it took another 8 years to approve the second antibody therapy in 1994. This was Abciximab, a treatment of cardiovascular disease which acts by binding to the $\alpha IIb\beta 3$ integrin to prevent clotting [10, 11]. Since 2000, there has been at least one antibody therapy approved by the FDA every year. This has led the US to dominate the number of antibody therapy approvals for more than two decades.

The first antibody therapy approved in Europe was Nebacumab in 1991, which was an anti-endotoxin antibody for the treatment of sepsis [12]. Although Nebacumab was withdrawn in 1993 because it failed to reduce mortality in the following clinical performance, it was the only approved human IgM antibody to date [13]. The second antibody therapy approved in Europe in 1995 was Edrecolomab, a murine antibody targeting EpCAM for the treatment of colorectal cancer [14]. Between 1995 and 2014, the EMA only approved less than five antibodies annually, but since 2015, the number of annual approvals has increased to around 10.

Japan and China are about 10 years behind the US and Europe in terms of the number of approvals and clinical trials. However, Japan and China have witnessed rapid development in antibody therapies over the past decade. The first antibody approved in Japan was the anti-CD52 Alemtuzumab in 2001 [15], which was a humanized antibody developed by Sanofi Genzyme for the treatment of leukemia. The first locally developed antibody approved in Japan was Tocilizumab in 2005, which was a humanized antibody targeting the interleukin 6 receptor (IL-6R) for the treatment of arthritis [16]. Since then, the number of approvals in Japan has steadily increased, especially after 2014. As for China, the first antibody therapy was approved by the NMPA in 1999. This was a murine anti-CD3 antibody IOR-T3 developed by a Cuban company, for the treatment of organ transplant rejection [17]. In 2002, a locally developed antibody called Wut3, which was also a murine anti-CD3 antibody for the treatment of transplant rejection, was approved in China. Until 2017, the number

Table 1. Globally approved antibody

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Muromonab	Orthoclone OKT3	CD3	Canonical antibody; Rodent	1.Heart transplant rejection 2.Liver transplant rejection 3.Renal transplant rejection	EMA Europe:1986* FDA US:1986*
IOR-T3	IOR-T3, aioushan	CD3	Canonical antibody; Rodent	1.Organ transplant rejection	CECMED Cuba:1989 NMPA China:1999
Nebacumab	Centoxin	Lipid A region of endotoxin	Canonical antibody; Human	1.Sepsis	EMA Europe:1991*
Abciximab	ReoPro, Clotinab	Integrin alpha IIb beta 3 (Integrin $\alpha IIb\beta 3$)	Fab fragment; Chimeric	1.Unstable angina 2.Restenosis	FDA US:1994 EMA Europe:1995
Edrecolomab	Panorex	Epithelial cell adhesion molecule (EpCAM)	Canonical antibody; Rodent	1.Colorectal cancer	EMA Europe:1995*
Daclizumab	Zenapax, Zinbryta	CD25	Canonical antibody; Humanized	1.Organ transplant rejection 2.Multiple sclerosis	FDA US:1997* EMA Europe:1999*
Rituximab	Rituxan, MabThera	CD20	Canonical antibody; Chimeric	1.Rheumatoid arthritis 2.Chronic lymphocytic leukemia 3.Follicular lymphoma 4.Non-Hodgkin's lymphoma 5.Lymphoproliferative disorders 6.Microscopic polyangiitis 7.Nephrotic syndrome 8.Pemphigus 9.Idiopathic thrombocytopenic purpura 10.Wegener's granulomatosis 11.Granulomatosis with polyangiitis 12.Systemic scleroderma 13.Thrombotic thrombocytopenic purpura	FDA US:1997 EMA Europe:1998 PMDA Japan:2001 NMPA China:2000/3/15
Infliximab	Remicade	Tumor necrosis factor-alpha (TNF-α)	Canonical antibody; Chimeric	1.Ankylosing spondylitis 2.Psoriatic arthritis 3.Rheumatoid arthritis 4.Behcet's disease 5.Ulcerative colitis 6.Crohn's disease 7.Kawasaki disease 8.Plaque psoriasis 9.Psoriasis	FDA US:1998 EMA Europe:1998 PMDA Japan:2002 NMPA China:2006
Trastuzumab	Herceptin	Human epidermal growth factor receptor 2 (HER2)	Canonical antibody; Humanized	1.Breast cancer 2.Gastric cancer	FDA US:1998 EMA Europe:1998
Palivizumab	Synagis	Respiratory syncytial virus F protein (RSV-F)	Canonical antibody; Humanized	1.Respiratory syncytial virus prophylaxis	FDA US:1998 EMA Europe:1999

(*continue*)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Basiliximab	Simulect	CD25	Canonical antibody; Chimeric	1. Organ transplant rejection 2. Renal transplant rejection	FDA US:1998 EMA Europe:1998 PMDA Japan:2002 NMPA China:2004
Etanercept	Enbrel	Tumor necrosis factor-alpha (TNF-α)	Fc-Fusion protein	1. Ankylosing spondylitis 2. Psoriatic arthritis 3. Rheumatoid arthritis4. Plaque psoriasis 5. Juvenile rheumatoid arthritis	FDA US:1998 EMA Europe:2000 PMDA Japan:2005 NMPA China:2010
Gemtuzumab ozogamicin	Mylotarg	CD33	Antibody-drug conjugate; Humanized	1. Acute myelogenous leukemia	FDA US: 2000 PMDA Japan:2005 EMA Europe:2018
Alemtuzumab	Lemtrada, Campath	CD52	Canonical antibody; Humanized	1. Chronic lymphocytic leukemia 2. Multiple sclerosis	FDA US:2001 EMA Europe:2001 PMDA Japan:2014 NMPA China:2010
Wut3	Shudankang	CD3	Canonical antibody; Rodent	1. Graft versus host disease 2. Organ transplant rejection	
Adalimumab	Humira	Tumor necrosis factor-alpha (TNF-α)	Canonical antibody; Human	1. Ankylosing spondylitis 2. Juvenile rheumatoid arthritis 3. Psoriatic arthritis 4. Rheumatoid arthritis 5. Behcet's disease 6. Ulcerative colitis 7. Crohn's disease 8. Hidradenitis suppurativa 9. Inflammatory bowel disease 10. Plaque psoriasis 11. Generalized pustular psoriasis 12. Pyoderma gangrenosum 13. Uveitis	FDA US:2002 EMA Europe:2003 PMDA Japan:2008 NMPA China:2010
Ibritumomab tiuxetan	Zevalin, Zevaman	CD20	Canonical antibody; Rodent	1. Non-Hodgkin's lymphoma	FDA US:2002 EMA Europe:2004
Omalizumab	Xolair	Immunoglobulin E (IgE)	Canonical antibody; Humanized	1. Allergic asthma 3. Urticaria	FDA USA:2003 NMPA China:2017
Efalizumab	Raptiva, Xanelim	Integrin subunit alpha L (ITGAL)	Canonical antibody; Humanized	1. Psoriasis	FDA US:2003* EMA Europe:2004*
Anti human interleukin-8 monoclonal antibody	Enboke	Interleukin 8 (IL-8)	Canonical antibody; Rodent	1. Atopic dermatitis 2. Generalized pustular psoriasis	NMPA China:2003

(continue)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Alefacept	Amevive	CD2	Fc-Fusion protein	1.Psoriasis	FDA US:2003*
Iodine 131 tositumomab	Bexxar	CD20	Radiolabeled antibody; Rodent	1.Non-Hodgkin's lymphoma	FDA US:2003* EMA Europe:2003*
Cetuximab	Erbitux	Epidermal growth factor receptor (EGFR)	Canonical antibody; Chimeric	1.Colorectal cancer 2.Head and Neck cancer	FDA US:2004 EMA Europe:2004 PMDA Japan:2008 NMPA China:2005
Bevacizumab	Avastin	Vascular endothelial growth factor A (VEGF-A)	Canonical antibody; Humanized	1.Breast cancer 2.Cervical cancer 3.Colorectal cancer 4.Glioblastoma 5.Liver cancer 6.Non-small cell lung cancer 7.Ovarian cancer 8.Glioma 9.Renal cell carcinoma	FDA US:2004 EMA Europe:2005 PMDA Japan:2007 NMPA China:2010
Natalizumab	Tysabri, Antegren	Integrin subunit alpha 4 (ITGA4)	Canonical antibody; Humanized	1.Crohn's disease 2.Multiple sclerosis	FDA US:2004 EMA Europe:2006 PMDA Japan:2014
Tocilizumab	Actemra, RoActemra	Interleukin 6 receptor (IL-6R)	Canonical antibody; Humanized	1.Juvenile rheumatoid arthritis 2.Rheumatoid arthritis 3.Castleman's disease 4.Drug hypersensitivity 5.Giant cell arteritis 6.Severe acute respiratory syndrome coronavirus 2 7.Systemic scleroderma 8.Adult-onset Still's disease 9.Vasculitis	FDA US:2010 EMA Europe:2009 PMDA Japan:2005 NMPA China:2013
Abatacept	Orencia	CD80, CD86	Fc-Fusion protein	1.Psoriatic arthritis 2.Graft versus host disease 3.Rheumatoid arthritis pain 4.Juvenile rheumatoid arthritis	FDA US:2005 EMA Europe:2007 PMDA Japan:2010 NMPA China:2020
Panitumumab	Vectibix	Epidermal growth factor receptor (EGFR)	Canonical antibody; Human	1.Colorectal cancer	FDA US:2006 EMA Europe:2007 PMDA Japan:2010
Iodine 131 derlotuximab biotin	Cotara, Vivatuxin	DNA/Histone H1	Radiolabeled antibody; Chimeric	1.Lung cancer	NMPA China:2006
Iodine 131 metuximab	Licartin	CD147	Radiolabeled antibody; Chimeric	1.Liver cancer	NMPA China:2006

(continue)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Nimotuzumab	Taixinsheng, TheraCIM, Theraloc, CIMAher, BIOMAb EGFR	Epidermal growth factor receptor (EGFR)	Canonical antibody; Humanized	1.Anaplastic astrocytoma 2.Brain cancer 3.Esophageal cancer 4.Glioblastoma 5.Head and neck cancer 6.Nasopharyngeal cancer 7.Glioma	CECMED Cuba:2006 NMPA China:2012
Ranibizumab	Lucentis	Vascular endothelial growth factor A (VEGF-A)	Fab fragment; Humanized	1.Choroidal neovascularization 2.Degenerative myopia 3.Diabetic macular edema 4.Diabetic retinopathy 5.Retinal edema 6.Wet age-related macular degeneration 7.Retinopathy of prematurity	FDA US:2006 EMA Europe:2007 PMDA Japan:2009 NMPA China:2011
Eculizumab	Soliris	Complement C5 (C5)	Canonical antibody; Humanized	1.Hemolytic uremic syndrome 2.Myasthenia gravis 3.Neuromyelitis optica 4.Paroxysmal nocturnal hemoglobinuria	FDA US:2007 EMA Europe:2007 PMDA Japan:2010 NMPA China:2018
Racotumomab	Vaxira	Ganglioside GM3 (GM3)	Canonical antibody; Rodent	1.Non-small cell lung cancer	CECMED Cuba:2008
Rilonacept	Arcalyst	Interleukin 1 alpha, Interleukin 1 beta (IL-1α, IL-1 β)	Fc-Fusion protein	1.Cryopyrin-associated periodic syndrome 2.Inborn genetic diseases 3.Pericarditis	FDA US:2008
Certolizumab pegol	Cimzia	Tumor necrosis factor-alpha (TNF-α)	Fab fragment; Humanized	1.Ankylosing spondylitis 2.Psoriatic arthritis 3.Rheumatoid arthritis 4.Crohn's disease 5.Plaque psoriasis 6.Axial spondyloarthritis	FDA US:2008 EMA Europe:2009 PMDA Japan:2012 NMPA China:2019
Romiplostim	Nplate, Romiplate	Thrombopoietin receptor (TPOR)	Fc-Fusion protein	1.Idiopathic thrombocytopenic purpura 2.Acute radiation syndrome 3.Aplastic anemia	FDA US:2008 EMA Europe:2009 PMDA Japan:2011 NMPA China:2022
Canakinumab	Ilaris	Interleukin 1 beta (IL-1 β)	Canonical antibody; Human	1.Adult-onset Still's disease 2.Gouty arthritis 3.Juvenile rheumatoid arthritis 4.Rheumatoid arthritis 5.Chronic obstructive pulmonary disease 6.Cryopyrin-associated periodic syndrome 7.Familial Mediterranean fever 8.Familial periodic fever 9.Peroxisomal disorder	FDA US:2009 EMA Europe:2009 PMDA Japan:2011

(continue)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Catumaxomab	Removab	CD3, Epithelial cell adhesion molecule (CD3, EpCAM)	Bispecific antibody; Rodent	1.Gastric cancer	EMA Europe:2009*
Ustekinumab	Stelara	Interleukin 12, Interleukin 23 (IL-12, IL-23)	Canonical antibody; Human	1.Psoriatic arthritis 2.Ulcerative colitis 3.Crohn's disease 4.Plaque psoriasis 5.Psoriasis	EMA Europe:2009 FDA US:2009 PMDA Japan:2011 NMPA China:2017
Ofatumumab	Arzerra, Kesimpta	CD20	Canonical antibody; Human	1.Chronic lymphocytic leukemia 2.Multiple sclerosis	FDA US:2009 EMA Europe:2010 PMDA Japan:2013 NMPA China:2021
Golimumab	Simponi	Tumor necrosis factor-alpha (TNF-α)	Canonical antibody; Human	1.Ankylosing spondylitis 2.Juvenile rheumatoid arthritis 3.Psoriatic arthritis 4.Rheumatoid arthritis 5.Ulcerative colitis 6.Axial spondyloarthritis	FDA US:2009 EMA Europe:2009 PMDA Japan:2011 NMPA China:2017
Denosumab	Prolia, Ranmark, Xgeva	Receptor activator of nuclear factor kappaB ligand (RANKL)	Canonical antibody; Human	1.Corticosteroid-induced osteoporosis 2.Rheumatoid arthritis 3.Bone Metastases 4.Bone cancer 5.Bone disorder 6.Male osteoporosis 7.Malignant hypercalcaemia 8.Osteopetrosis 9.Postmenopausal Osteoporosis	FDA US:2010 EMA Europe:2020 PMDA Japan:2012 NMPA China:2019
Brentuximab vedotin	Adcetris	CD30	Antibody-drug conjugate; Chimeric	1.Hodgkin's lymphoma 2.T-cell lymphoma 3.Peripheral T-cell lymphoma 4.Anaplastic large cell lymphoma 5.Sezary syndrome 6.Mycosis fungoides 7.Primary cutaneous anaplastic large cell lymphoma	FDA US:2011 EMA Europe:2012 NMPA China:2020 PMDA Japan:2014
Belatacept	Nulojix	CD80, CD86	Fc-Fusion protein	1.Renal transplant rejection	FDA US:2011 EMA Europe:2011
Aflibercept	Zaltrap, Eylea	Vascular endothelial growth factor (VEGF)	Fc-Fusion protein	1.Branch retinal vein occlusion 2.Colorectal cancer 3.Central retinal vein occlusion 4.Choroidal neovascularization 5.Diabetic macular edema 6.Diabetic retinopathy 7.Glaucoma 8.Wet age-related macular degeneration 9.Macular edema	FDA US:2011 EMA Europe:2012 PMDA Japan:2012 NMPA China:2018

(continued)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Belimumab	Benlysta, LymphoStat-B	B cell activating factor (BAFF)	Canonical antibody; Human	1.Lupus nephritis 2.Systemic lupus erythematosus	FDA US:2011 EMA Europe:2011 PMDA Japan:2017 NMPA China:2022
Ipilimumab	Yervoy	Cytotoxic T-lymphocyte antigen 4 (CTLA4)	Canonical antibody; Human	1.Liver cancer 2.Non-small cell lung cancer 3.Mesothelioma 4.Malignant melanoma 5.Renal cell carcinoma	FDA US:2011 EMA Europe:2011 PMDA Japan:2015 NMPA China:2021
Pertuzumab	Perjeta	Human epidermal growth factor receptor 2 (HER2)	Canonical antibody; Humanized	1.Breast cancer	FDA US:2012 EMA Europe:2013 PMDA Japan:2013 NMPA China:2018
Raxibacumab	Abthrax	*Bacillus anthracis* protective antigen (*B. anthracis* PA)	Canonical antibody; Human	1.Anthrax infection	FDA US:2012
Mogamulizumab	Poteligeo	C–C chemokine receptor type 4 (CCR4)	Canonical antibody; Humanized	1.Adult T-cell leukemia/lymphoma 2.Cutaneous T-cell lymphoma 3.Peripheral T-cell lymphoma 4.Mycosis fungoides 5.Sezary syndrome	PMDA Japan:2012 FDA US:2018 EMA Europe:2018
Trastuzumab emtansine	Kadcyla	Human epidermal growth factor receptor 2 (HER2)	Antibody-drug conjugate; Humanized	1.Breast cancer	FDA US:2013 EMA Europe:2013 PMDA Japan:2013 NMPA China:2020
Obinutuzumab	Gazyvaro, Gazyva	CD20	Canonical antibody; Humanized	1.Chronic lymphocytic leukemia 2.Follicular lymphoma 3.Non-Hodgkin's lymphoma	FDA US:2013 EMA Europe:2014 PMDA Japan:2018 NMPA China:2021
Conbercept	Langmu, Lumitin	Vascular endothelial growth factor (VEGF)	Fc-Fusion protein	1.Wet age-related macular degeneration	NMPA China:2013
Itolizumab	Alzumab	CD6	Canonical antibody; Humanized	1.Cytokine release syndrome 2.Plaque psoriasis 3.Severe acute respiratory syndrome coronavirus 2	CDSCO India:2013
Blinatumomab	Blincyto	CD19, CD3	Bispecific antibody; Rodent	1.B-cell acute lymphoblastic leukemia	FDA US:2014 EMA Europe:2015 PMDA Japan:2018 NMPA China:2020

(continue)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Pembrolizumab	Keytruda	Programmed cell death 1 (PD-1)	Canonical antibody; Humanized	1.Breast cancer 2.Cervical cancer 3.Colorectal cancer 4.Esophageal cancer 5.Gastric cancer 6.Head and neck cancer 7.Liver cancer 8.Non-small cell lung cancer 9.Diffuse large B-cell lymphoma 10.Hodgkin's lymphoma 11.Pancreatic cancer 12.Squamous cell carcinoma 13.Urogenital cancer 14.Malignant melanoma	FDA US:2014 EMA Europe:2015 PMDA Japan:2016 NMPA China:2018
Eftrenonacog alfa	Alprolix	Factor VIII	Fc-Fusion protein	1.Hemophilia B	FDA US:2014 PMDA Japan:2014 EMA Europe:2016 NMPA China:2021
Vedolizumab	Entyvio, Kynteles	Integrin alpha4 beta7 (Integrin α4β7)	Canonical antibody; Humanized	1.Ulcerative colitis 2.Crohn's disease	FDA US:2014 EMA Europe:2014 PMDA Japan:2018
Secukinumab	Cosentyx, Scapho	Interleukin 17A (IL-17A)	Canonical antibody; Human	1.Ankylosing spondylitis 2.Psoriatic arthritis 3.Non-radiographic axial spondyloarthritis 4.Plaque psoriasis 5.Generalized pustular psoriasis	PMDA Japan:2014 FDA US:2015 EMA Europe:2015 NMPA China:2019
Ramucirumab	Cyramza	Vascular endothelial growth factor receptor 2 (VEGFR-2)	Canonical antibody; Human	1.Colorectal cancer 2.Gastric cancer 3.Liver cancer 4.Non-small cell lung cancer	FDA US:2014 EMA Europe:2014 PMDA Japan:2015 NMPA China:2022
Efmoroctocog alfa	Elocta, Eloctate	Factor IX	Fc-Fusion protein	1.Hemophilia A	FDA US:2014 PMDA Japan:2014 EMA Europe:2015
Siltuximab	Sylvant	Interleukin 6 (IL-6)	Canonical antibody; Chimeric	1.Castleman's disease	FDA US:2014 EMA Europe:2014 NMPA China:2021
Nivolumab	Opdivo	Programmed cell death 1 (PD-1)	Canonical antibody; Human	1.Colorectal cancer 2.Esophageal cancer 3.Gastric cancer 4.Head and neck cancer 5.Non-small cell lung cancer 6.Hodgkin's lymphoma 7.Mesothelioma 8.Squamous cell carcinoma 9.Urogenital cancer 10.Malignant melanoma 11.Renal cell carcinoma	PMDA Japan:2014 FDA US:2014 EMA Europe:2015 NMPA China:2019

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Elotuzumab	Empliciti	SLAM family member 7 (SLAMF7)	Canonical antibody; Humanized	1.Multiple myeloma	FDA US:2015 EMA Europe:2016 PMDA Japan:2016
Alirocumab	Praluent	Proprotein convertase subtilisin/kexin Type 9 (PCSK9)	Canonical antibody; Human	1.Hypercholesterolemia 2.Hyperlipoproteinemia Type IIa	FDA US:2015 EMA Europe:2015 PMDA Japan:2016
Mepolizumab	Nucala	Interleukin 5 (IL-5)	Canonical antibody; Humanized	1.Asthma	FDA US:2015 EMA Europe:2015 PMDA Japan:2016 NMPA China:2021
Necitumumab	Portrazza	Epidermal growth factor receptor (EGFR)	Canonical antibody; Human	1.Non-small cell lung cancer	FDA US:2015 EMA Europe:2016 PMDA Japan:2019
Idarucizumab	Praxbind	Dabigatran	Fab fragment; Humanized	1.Blood coagulation disorders	FDA US:2015 EMA Europe:2015 PMDA Japan:2016 NMPA China:2018
Dinutuximab	Unituxin, Qarziba	GD2 ganglioside (GD2)	Canonical antibody; Chimeric	1.Nephroblastoma	FDA US:2015 EMA Europe:2015 PMDA Japan:2021 NMPA China:2021
Daratumumab	Darzalex	CD38	Canonical antibody; Human	1.Multiple myeloma	FDA US:2015 EMA Europe:2016 PMDA Japan:2017 NMPA China:2019
Evolocumab	Repatha	Proprotein convertase subtilisin/kexin Type 9 (PCSK9)	Canonical antibody; Human	1.Coronary artery disease 2.Hypercholesterolemia 3.Hyperlipoproteinemia Type IIa 4.Myocardial infarction 5.Stroke	FDA US:2015 EMA Europe:2015 PMDA Japan:2016 NMPA China:2018
Atezolizumab	Tecentriq	Programmed cell death 1 ligand 1 (PD-L1)	Canonical antibody; Humanized	1.Breast cancer 2.Liver cancer 3.Non-small cell lung cancer 4.Small cell lung cancer 5.Urogenital cancer 6.Malignant melanoma	FDA US:2016 EMA Europe:2017 PMDA Japan:2018 NMPA China:2020
Olaratumab	Lartruvo	Platelet-derived growth factor receptor alpha (PDGFRA)	Canonical antibody; Human	1.Soft tissue sarcoma	FDA US:2016* EMA Europe:2016*
Bezlotoxumab	Zinplava	*Clostridium difficile* Toxin B	Canonical antibody; Human	1.*C. difficile* infection	FDA US:2016 EMA Europe:2017 PMDA Japan:2017

(*continue*)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Brodalumab	Siliq, Kyntheum, Lumicef	Interleukin 17 receptor alpha (IL-17 RA)	Canonical antibody; Human	1. Ankylosing spondylitis 2. Psoriatic arthritis 3. Erythrodermic psoriasis 4. Plaque psoriasis 5. Psoriasis 6. Axial spondyloarthritis 7. Generalized pustular psoriasis	PMDA Japan:2016 FDA US:2017 EMA Europe:2017 NMPA China:2020
Ixekizumab	Taltz	Interleukin 17A (IL-17A)	Canonical antibody; Humanized	1. Ankylosing spondylitis 2. Psoriatic arthritis 3. Erythrodermic psoriasis 4. Plaque psoriasis 5. Generalized pustular psoriasis 6. Non-radiographic axial spondyloarthritis	FDA US:2016 EMA Europe:2016 PMDA Japan:2016 NMPA China:2019
SII rmab	Rabishield	Rabies virus glycoprotein (Rabies virus GP)	Canonical antibody; Human	1. Rabies virus infection	CDSCO India:2016
Reslizumab	Cinqair, Cinqaero	Interleukin 5 (IL-5)	Canonical antibody; Humanized	1. Asthma	FDA US:2016 EMA Europe:2016
Obiltoxaximab	Anthim	*B. anthracis* Protective antigen (*B. anthracis* PA)	Canonical antibody; Chimeric	1. Anthrax infection	FDA US:2016 EMA Europe:2020
Inotuzumab ozogamicin	Besponsa	CD22	Antibody-drug conjugate; Humanized	1. B-cell acute lymphoblastic leukemia	EMA Europe:2017 FDA US:2017 PMDA Japan:2018 NMPA China:2021
Sarilumab	Kevzara	Interleukin 6 receptor (IL-6R)	Canonical antibody; Human	1. Rheumatoid arthritis	HC Canada:2017 FDA US:2017 EMA Europe:2017 PMDA Japan:2017
Dupilumab	Dupixent	Interleukin 4 receptor alpha (IL-4RA)	Canonical antibody; Human	1. Asthma 2. Atopic dermatitis 3. Nasal polyps 4. Eosinophilic esophagitis	FDA US:2017 EMA Europe:2017 PMDA Japan:2018 NMPA China:2020
Durvalumab	Imfinzi	Programmed cell death 1 ligand 1 (PD-L1)	Canonical antibody; Human	1. Non-small cell lung cancer 2. Small cell lung cancer	FDA US:2017 PMDA Japan:2018 EMA Europe:2018 NMPA China:2019
Avelumab	Bavencio	Programmed cell death 1 ligand 1 (PD-L1)	Canonical antibody; Human	1. Merkel cell carcinoma 2. Urogenital cancer 3. Renal cell carcinoma	FDA US:2017 EMA Europe:2017 PMDA Japan:2017
Emicizumab	Hemlibra	Coagulation factor IX, Coagulation factor X (Factor IX, Factor X)	Bispecific antibody; Humanized	1. Hemophilia A	FDA US:2017 EMA Europe:2018 PMDA Japan:2018 NMPA China:2018

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Benralizumab	Fasenra	Interleukin 5 receptor subunit alpha (IL-5RA)	Canonical antibody; Humanized	1.Asthma	FDA US:2017 EMA Europe:2018 PMDA Japan:2018
Ocrelizumab	Ocrevus	CD20	Canonical antibody; Humanized	1.Multiple sclerosis	FDA US:2017 EMA Europe:2018
Guselkumab	Tremfya	Interleukin 23 p19 (IL-23p19)	Canonical antibody; Human	1.Psoriatic arthritis 2.Erythrodermic psoriasis 3.Plaque psoriasis 4.Palmoplantar pustulosis 5.Generalized pustular psoriasis	FDA US:2017 EMA Europe:2017 PMDA Japan:2018 NMPA China:2019
Erenumab	Aimovig	Calcitonin gene-related peptide receptor (CGRP-R)	Canonical antibody; Human	1.Migraine	FDA US:2018 EMA Europe:2018 PMDA Japan:2021
Moxetumomab pasudotox	Lumoxiti	CD22	Immunotoxin; Rodent	1.Hairy cell leukemia	FDA US:2018 EMA Europe:2021
Ravulizumab	Ultomiris	Complement C5 (C5)	Canonical antibody; Humanized	1.Haemolytic uraemic syndrome 2.Myasthenia gravis 3.Paroxysmal nocturnal hemoglobinuria	FDA US:2018 PMDA Japan:2019 EMA Europe:2019
Fremanezumab	Ajovy	Calcitonin gene-related peptide (CGRP)	Canonical antibody; Humanized	1.Migraine	FDA US:2018 EMA Europe:2019 PMDA Japan:2021
Sintilimab	Tyvyt, Daboshu	Programmed cell death 1 (PD-1)	Canonical antibody; Human	1.Gastric cancer 2.Esophageal cancer 3.Liver cancer 4.Non-small cell lung cancer 5.Hodgkin's lymphoma	FDA US:2018 EMA Europe:2019 PMDA Japan:2021 NMPA China:2018
Ibalizumab	Trogarzo	CD4	Canonical antibody; Humanized	1.HIV infection	FDA US:2018 EMA Europe:2019
Galcanezumab	Emgality	Calcitonin gene-related peptide (CGRP)	Canonical antibody; Humanized	1.Cluster headache 2.Migraine	FDA US:2018 EMA Europe:2018 PMDA Japan:2021
Tildrakizumab	Ilumetri, Ilumya	Interleukin 23 p19 (IL-23p19)	Canonical antibody; Humanized	1.Plaque psoriasis	FDA US:2018 EMA Europe:2018 PMDA Japan:2020
Emapalumab	Gamifant	Interferon gamma (IFN-γ)	Canonical antibody; Human	1.Hemophagocytic Lymphohistiocytosis	FDA US:2018 NMPA China:2022 EMA Europe:2021
Cemiplimab	Libtayo	Programmed cell death 1 (PD-1)	Canonical antibody; Human	1.Basal cell carcinoma 2.Non-small cell lung cancer 3.Squamous cell carcinoma	FDA US:2018 EMA Europe:2019

(continue)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Toripalimab	Tuoyi	Programmed cell death 1 (PD-1)	Canonical antibody; Humanized	1.Nasopharyngeal cancer 2.Urogenital cancer 3.Malignant melanoma	NMPA China:2018
Caplacizumab	Cablivi	von Willebrand Factor (vWF)	VHH-VHH, Humanized	1.Thrombotic thrombocytopenic purpura	EMA Europe:2018 FDA US:2019
Lanadelumab	Takhzyro	Kallikrein	Canonical antibody; Human	1.Hereditary angioedema	FDA US:2018 EMA Europe:2018 NMPA China:2020 PMDA Japan:2022
Burosumab	Crysvita	Fibroblast growth factor 23 (FGF23)	Canonical antibody; Human	1.Osteomalacia 2.X-linked hypophosphatemia	EMA Europe:2018 FDA US:2018 PMDA Japan:2019 NMPA China:2021
Tislelizumab	Baizean	Programmed cell death 1 (PD-1)	Canonical antibody; Humanized	1.Liver cancer 2.Non-small cell lung cancer 3.Hodgkin's lymphoma 4.Nasopharyngeal cancer 5.Squamous cell carcinoma 6.Urogenital cancer	NMPA China:2019
Risankizumab	Skyrizi	Interleukin 23 p19 (IL-23p19)	Canonical antibody; Humanized	1.Psoriatic arthritis 2.Plaque psoriasis 3.Psoriasis 4.Crohn's disease	PMDA Japan:2019 FDA US:2019 EMA Europe:2019
Trastuzumab deruxtecan	Enhertu	Human epidermal growth factor receptor 2 (HER2)	Antibody-drug conjugate; Humanized	1.Breast cancer 2.Gastric cancer	FDA US:2019 PMDA Japan:2020 EMA Europe:2021
Brolucizumab	Beovu	Vascular endothelial growth factor A (VEGF-A)	ScFv fragment; Humanized	1.Wet age-related macular degeneration	FDA US:2019 EMA Europe:2020 PMDA Japan:2020
Crizanlizumab	Adakveo	P-selectin	Canonical antibody; Humanized	1.Vaso-occlusive crisis	FDA US:2019 EMA Europe:2020
Enfortumab vedotin	Padcev	Nectin Cell Adhesion Molecule 4 (Nectin 4)	Antibody-drug conjugate; Human	1.Urogenital cancer	FDA US:2019 PMDA Japan:2021 EMA Europe:2022
Romosozumab	Evenity	Sclerostin	Canonical antibody; Humanized	1.Male osteoporosis 2.Postmenopausal osteoporosis	PMDA Japan:2019 FDA US:2019 EMA Europe:2019
Efgartigimod alfa	Vyvgart	Neonatal Fc Receptor (FcRn)	Fc fragment; Human	1.Myasthenia gravis	EMA Europe:2019 FDA US:2021 PMDA Japan:2022
Camrelizumab	Airuika	Programmed cell death 1 (PD-1)	Canonical antibody; Humanized	1.Esophageal cancer 2.Non-small cell lung cancer 3.Hodgkin's lymphoma 4.Nasopharyngeal cancer 5.Liver cancer	NMPA China:2019

(continue)

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Polatuzumab vedotin	Polivy	CD79b	Antibody-drug conjugate; Humanized	1.Diffuse large B-cell lymphoma	FDA US:2019 EMA Europe:2020 PMDA Japan:2021
Luspatercept	Reblozyl	Transforming growth factor-beta (TGF-β)	Fc-Fusion protein	1.Beta-thalassemia 2.Myelodysplastic syndrome	FDA US:2019 EMA Europe:2020 NMPA China:2022
Rabimabs	Twinrab	Rabies virus glycoprotein (Rabies virus GP)	Canonical antibody; Rodent	1.Rabies virus infection	CDSCO India:2019
Netakimab	Efleira	Interleukin 17A (IL-17A)	Canonical antibody; Humanized	1.Plaque psoriasis 2.Ankylosing spondylitis 3.Psoriatic arthritis	Minzdrav Russia:2019
Inebilizumab	Uplizna	CD19	Canonical antibody; Humanized	1.Neuromyelitis optica	FDA US:2020 PMDA Japan:2021 NMPA China:2022 EMA Europe:2022
Teprotumumab	Tepezza	Insulin-like growth factor 1 receptor (IGF-1R)	Canonical antibody; Human	1.Graves' ophthalmopathy	FDA US:2020
Sacituzumab govitecan	Trodelvy	Tumor-associated calcium signal transducer 2 (TACSTD-2)	Antibody-drug conjugate; Humanized	1.Breast cancer 2.Urogenital cancer	FDA US:2020 EMA Europe:2021 NMPA China:2022
Atoltivimab + Odesivimab + Maftivimab	Inmazeb	Ebola virus Glycoprotein	Canonical antibody; Human	1.Ebola virus infection	FDA US:2020
Cetuximab sarotalocan	Akalux	Epidermal growth factor receptor (EGFR)	Antibody-drug conjugate; Chimeric	1.Head and neck cancer	PMDA Japan:2020
Isatuximab	Sarclisa	CD38	Canonical antibody; Chimeric	1.Multiple myeloma	FDA US:2020 EMA Europe:2020 PMDA Japan:2020
Belantamab mafodotin	Blenrep	B cell maturation antigen (BCMA)	Antibody-drug conjugate; Humanized	1.Multiple myeloma	FDA US:2020 EMA Europe:2020
Levilimab	Ilsira	Interleukin 6 receptor (IL-6R)	Canonical antibody; Human	1.Rheumatoid arthritis 2.Severe acute respiratory syndrome coronavirus 2	Minzdrav Russia:2020
Margetuximab	Margenza	Human epidermal growth factor receptor 2 (HER2)	Canonical antibody; Chimeric	1.Breast cancer	FDA US:2020
Satralizumab	Enspryng	Interleukin 6 receptor (IL-6R)	Canonical antibody; Humanized	1.Neuromyelitis optica	HC Canada:2020 PMDA Japan:2020 FDA US:2020 EMA Europe:2021 NMPA China:2021
Tafasitamab	Monjuvi	CD19	Canonical antibody; Humanized	1.Diffuse large B-cell lymphoma	FDA US:2020 EMA Europe:2021
Naxitamab	Danyelza	GD2 ganglioside (GD2)	Canonical antibody; Humanized	1.Neuroblastoma	FDA US:2020

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Ansuvimab	Ebanga	Ebola virus glycoprotein	Canonical antibody; Human	1.Ebola virus infection	FDA US:2020
Eptinezumab	Vyepti	Calcitonin gene-related peptide (CGRP)	Canonical antibody; Humanized	1.Migraine	FDA US:2020 EMA Europe:2022
Prolgolimab	Forteca	Programmed cell death 1 (PD-1)	Antibody-drug conjugate; Humanized	1.Melanoma	Minzdrav Russia:2020
Olokizumab	Artlegia	Interleukin 6 (IL-6)	Canonical antibody; Humanized	1.Rheumatoid arthritis 2.Severe acute respiratory syndrome coronavirus 2	Minzdrav Russia:2020
Penpulimab	Annike	Programmed cell death 1 (PD-1)	Canonical antibody; Humanized	1.Non-small cell lung cancer 2.Hodgkin's lymphoma 3.Nasopharyngeal cancer	NMPA China:2021
Dostarlimab	Jemperli	Programmed cell death 1 (PD-1)	Canonical antibody; Humanized	1.Endometrial cancer 2.Solid cancer	EMA Europe:2021 FDA US:2021
Evinacumab	Evkeeza	Angiopoietin-like protein 3 (ANGPTL3)	Canonical antibody; Human	1.Hyperlipoproteinemia Type IIa	FDA US:2021 EMA Europe:2021
Sugemalimab	Cejemly	Programmed cell death 1 ligand 1 (PD-L1)	Canonical antibody; Human	1.Non-small cell lung cancer	NMPA China:2021
Envafolimab	enweida	Programmed cell death 1 ligand 1 (PD-L1)	Fc-Fusion VHH; Humanized	1.Solid cancer	NMPA China:2021
Telitacicept	Taiai	B cell activating factor (BAFF), A proliferation-inducing ligand (APRIL)	Fc-Fusion protein	1.Systemic lupus erythematosus	NMPA China:2021
Regdanvimab	Regkirona	SARS-Cov-2 spike protein (SARS-Cov-2 S protein)	Canonical antibody; Human	1.Severe acute respiratory syndrome coronavirus 2	ANVISA Brazil:2021 EMA Europe:2021
Amubarvimab + Romlusevimab		SARS-Cov-2 spike protein (SARS-Cov-2 S protein)	Canonical antibody; Human	1.Severe acute respiratory syndrome coronavirus 2	NMPA China:2021
Amivantamab	Rybrevant	Epidermal growth factor receptor, C-Met (EGFR, cMet)	Bispecific antibody; Human	1.Non-small cell lung cancer	FDA US:2021
Zimberelimab	Yutuo	Programmed cell death 1 (PD-1)	Canonical antibody; Human	1.Hodgkin's lymphoma	NMPA China:2021
Bimekizumab	Bimzelx	Interleukin 17A, Interleukin 17F (IL-17A, IL-17F)	Canonical antibody; Humanized	1.Erythrodermic psoriasis 2.Plaque psoriasis 3.Generalized pustular psoriasis	EMA Europe:2021 PMDA Japan:2022
Loncastuximab tesirine	Lonca, Zynlonta	CD19	Antibody-drug conjugate; Chimeric	1.Diffuse large B-cell lymphoma	FDA US:2021
Tisotumab vedotin	Tivdak	Tissue factor (TF)	Antibody-drug conjugate; Human	1.Cervical cancer	FDA US:2021
Tralokinumab	Adtralza, Adbry	Interleukin 13 (IL-13)	Canonical antibody; Human	1.Atopic dermatitis	EMA Europe:2021 FDA US:2021

Table 1. Continued.

Antibody name	Brand name	Target	Antibody type	Approved indication	Approval
Tezepelumab	Tezspire	Thymic stromal lymphopoietin (TSLP)	Canonical antibody; Human	1.Asthma	FDA US:2021
Aducanumab	Aduhelm	Amyloid beta	Canonical antibody; Human	1.Alzheimer's disease	FDA US:2021
Disitamab vedotin	Aidixi	Human epidermal growth factor receptor 2 (HER2)	Antibody-drug conjugate; Humanized	1.Gastric cancer 2.Urothelial carcinoma	NMPA China:2021
Sotrovimab	Xevudy	SARS-Cov-2 spike protein (SARS-Cov-2 S protein)	Canonical antibody; Human	1.Severe acute respiratory syndrome coronavirus 2	PMDA Japan:2021 EMA Europe:2021
Pabinafusp alfa	Izcargo	Transferrin receptor protein 1 (TFR1)	Immunoconjugate; Humanized	1.Mucopolysaccharidosis II	PMDA Japan:2021
Anifrolumab	Saphnelo	Interferon alpha receptor 1 (IFNAR-1)	Canonical antibody; Human	1.Systemic lupus erythematosus	FDA US:2021 PMDA Japan:2021 EMA Europe:2022
Ormutivimab	Xunke	Rabies virus glycoprotein (Rabies virus GP)	Canonical antibody; Human	1.Rabies virus prophylaxis	NMPA China:2022
Faricimab	Vabysmo	Vascular endothelial growth factor A, Angiopoietin 2 (VEGF-A, ANG-2)	Bispecific antibody; Humanized	1.Diabetic macular edema 2.Wet age-related macular degeneration	FDA US:2022 PMDA Japan:2022
Sutimlimab	Enjaymo	Complement C1s (C1s)	Canonical antibody; Humanized	1.Autoimmune hemolytic anemia 2.Cold agglutinin disease	FDA US:2022
Mosunetuzumab	Lunsumio	CD3, CD20	Bispecific antibody; Humanized	1.Follicular lymphoma	EMA Europe:2022
Cadonilimab	Kaitanni	Cytotoxic T-lymphocyte antigen 4, Programmed Cell Death 1 (CTLA4, PD-1)	Bispecific antibody; Humanized	1.Cervical cancer	NMPA China:2022
Nemolizumab	Mitchga	Interleukin 31 receptor subunit alpha (IL-31RA)	Canonical antibody; Humanized	1.Atopic dermatitis	PMDA Japan:2022
Relatlimab + Nivolumab	Opdualag	Lymphocyte activation gene 3, Programmed cell death 1 (LAG-3, PD-1)	Canonical antibody; Human	1.Melanoma	FDA US:2022
Tixagevimab + Cilgavimab	Evusheld	SARS-Cov-2 spike protein (SARS-Cov-2 S protein)	Canonical antibody; Human	1.Severe acute respiratory syndrome coronavirus 2 prophylaxis	EMA Europe:2022
Serplulimab	Hansizhuang	Programmed cell death 1 (PD-1)	Canonical antibody; Humanized	1.Non-small cell lung cancer 2.Small cell lung cancer 3.Solid cancer	NMPA China:2022
Tebentafusp	Kimmtrak	CD3, Glycoprotein 100 (CD3, GP100)	Immunoconjugate; Humanized	1.Uveal melanoma	FDA US:2022 EMA Europe:2022

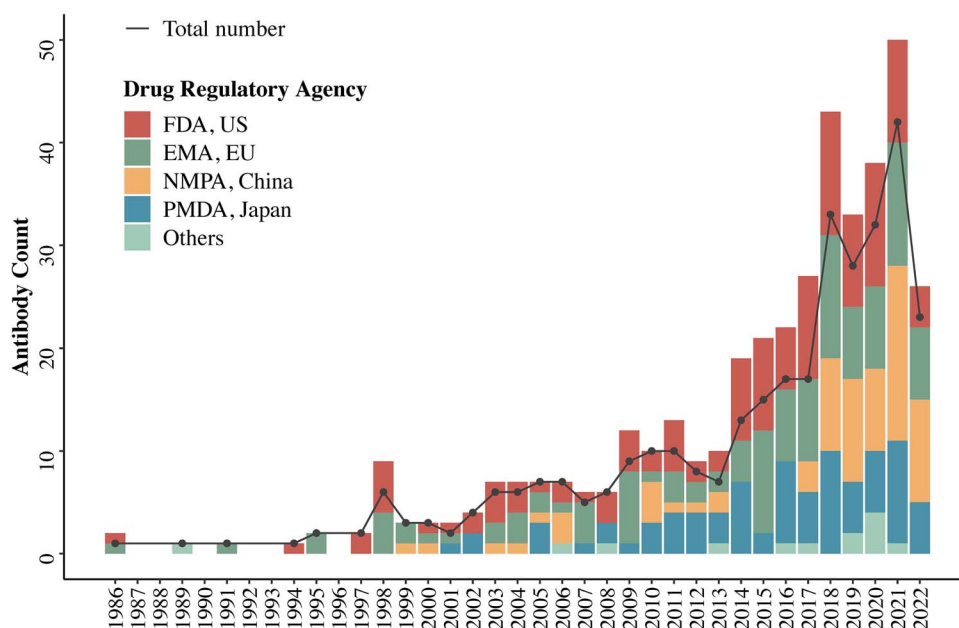*indicates the antibody therapy was withdrawn.

Figure 1. The number of antibody therapies approved by different regulatory agencies each year is based on the Umabs-DB data available as of 30 June 2022. Only the first approval is included for each regulatory agency. Biosimilar, diagnostic, and veterinary antibodies are not included, whereas withdrawn antibodies are included in the analysis.

of antibody therapies approved in China was <5 for each year. But since 2018, the annual approvals have increased to > 10, and even reached 18 in 2021. Although a total of 73 antibody therapies were approved by the NMPA in China for a wide range of indications, only 18 antibodies were developed by local companies. However, very recently, there was a first-in-class anti-PD-1/CTLA-4 bispecific antibody, Cadonilimab, approved by the NMPA for the treatment of metastatic cervical cancer [18]. Cadonilimab, the first bispecific antibody with dual immune checkpoint inhibition approved in the world, could signal a future increase in innovative antibody therapy development in China.

ANTIBODY DISCOVERY AND ENGINEERING IN APPROVED ANTIBODIES

In 1975, Georges Köhler and César Milstein established the hybridoma platform based on the fusion of murine B cell and myeloma cells, which enables the *in vitro* production of a large amount of pure mAbs [19]. Subsequently, chimeric antibodies formed by domain recombination, and then humanized antibodies, obtained primarily by complementary-determining region (CDR) grafting, have been enabled for mAb production [20]. Furthermore, fully human antibodies have been developed from phage display [21, 22], yeast display [23], mammalian cell display [24], transgenic animals [25, 26] and human blood samples [27, 28]. It is noted that the phage display developed antibodies are not naturally occurring human antibodies as their heavy chain and light chain sequences were not from the same B cells. More recently, glycoengineering has become a powerful tool to optimize the pharmacodynamic and pharmacokinetic properties of an antibody [29, 30]. For example, Fc core fucosylation has been shown to enhance

FcγRIIIa binding and antibody-dependent cellular cytotoxicity (ADCC) activity of antibodies [31]. Meanwhile, an antibody lacking core fucosylation (afucosylated) increased ADCC activity through highly increased IgG-Fc receptor IIIa (FcγRIIIa) affinity [32]. There are currently four approved afucosylated antibodies: Obinutuzumab, Mogamulizumab Benralizumab and Inebilizumab.

The total number of rodent antibody therapies is only 11, out of which four have been withdrawn. In 1986, the first antibody therapy based on this technique, OKT3, was a murine mAb against CD3 expressed on the T cell surface, acting as an immunosuppressor in organ transplant rejection [2, 33]. No more murine antibody therapies have been approved since Rabimabs, which was approved in India for the treatment of rabies in 2019 [34]. For those approved non-humanized antibodies, anti-CD3/EpCAM Catumaxomab is a mouse-rat hybrid bispecific antibody, first approved by the EMA for the treatment of gastric cancer in 2009. This was also the first bispecific antibody to gain regulatory approval despite being withdrawn due to commercial failure [35, 36]. Moxetumomab pasudotox is the only murine antibody-conjugate immunotoxin and was approved by the FDA in 2018 for the treatment of hairy cell leukemia (HCL) [37].

There are risks and disadvantages of murine mAbs or mAbs from other animals for human administration. For example, patients would produce a rapid immune response through generation of human anti-mouse antibody (HAMA) against the murine antibodies, which greatly shortens the serum half-life of the therapy [38]. In addition, the ability of the murine Fc region to elicit ADCC in patients is limited [39]. To overcome these problems of murine mAbs, several engineering techniques have been developed to make their sequence more similar to the

human antibody while maintaining binding affinity and specificity. The first technique developed was to create a chimeric antibody, which recombined the murine variable domains with a human constant region (Fig. 2A) [11, 40]. There are a total of 16 approved chimeric antibody therapies which are in multiple formats, including naked whole IgGs, fragments, and antibody drug conjugates (ADCs). The first murine antibody therapy, Abciximab [10, 11], was first approved in Cuba. A chimeric fragment antibody radiolabeled with Iodine 131, denoted as Iodine 131 Metuximab, was also approved by the NMPA in 2006 for the treatment of liver cancer [41]. In addition, in 2021, there was a chimeric ADC, loncastuximab tesirine, approved by the FDA for the treatment of large B-cell lymphoma. This indicates that the chimeric antibody is still popular for some applications [42].

Later, researchers set out to humanize an antibody mainly by grafting the CDR regions from mice into a human framework sequence [20]. After humanization, antibody therapies show much less immunogenicity but are often associated with loss of affinity. Therefore, a variety of methods have been innovated to restore and increase antibody affinity and specificity [43, 44]. As an important method of antibody engineering, 66 humanized antibodies from a diverse range of animals with multiple formats have been approved. The first humanized antibody therapy, anti-CD25 Daclizumab, was approved by the FDA in 1997 for the treatment of transplant rejection [45, 46]. Since then, humanized antibody therapies accounted for a high proportion of the approved antibody therapies each year (Fig. 2C).

In 1990, Gregory P. Winter introduced phage display of antibody fragments, in which exogenous human antibody genetic sequences can be incorporated into the filamentous bacteriophage genome and expressed on the phage surface for further specificity and affinity screening [21, 22]. Transgenic animals provided another powerful technique for the development of fully human antibodies, and was developed in 1994 by creating two transgenic mouse models that were genetically engineered to have human immunoglobulin genes, thus allowing the mice to express fully human antibodies after immunization [26]. In addition, the single B cell technique was developed to directly isolate antigen-specific B cells from human blood for the generation of human natural antibodies [47–49]. A total of 55 fully human antibody therapies have been approved so far. The first fully human antibody therapy, the IgM antibody Nebacumab, was approved in 1991 [13]. The first human whole IgG antibody therapy Adalimumab was approved by the FDA in 2002, which was developed by phage display to target against TNF-alpha for the treatment of rheumatic diseases [50]. The technique to isolate antigen-specific B cells directly from human blood has been successfully applied to discover antiviral antibodies [51, 52] such as REGN-EB3 targeting Ebola viral surface glycoprotein approved by the FDA in 2020 [53], and Evusheld targeting SARS-CoV-2 spike protein and first approved by the EMA in 2022 [54].

In addition, the recent advances in Next Generation Sequencing (NGS) make it a useful tool in rapid antibody discovery [55–57]. With the ever-progressing antibody discovery technologies, we believe there will likely be another wave of clinical trials and approvals for antibody therapies discovered from such innovative platforms.

Engineering of antibodies has evolved through a few stages whereby at first naked whole animal IgG antibodies were used directly as therapeutics, followed by recombination, humanization and affinity maturation. However, today we see more engineered antibody formats in a variety of shapes and sizes (Fig. 2B). We have categorized all approved antibody therapies into five classes: canonical antibody, fragment of antibody, ADC, bispecific antibody and other formats (Fig. 2C). Canonical antibodies have the whole antibody structure, consisting of two full-length heavy chains and two light chains. Of all approved antibodies, there are 115 canonical antibodies, 114 of which are IgGs and the other one is IgM (Nebacumab) [13]. Antibody fragments are composed of a few domains of the whole antibody structure but can act as therapies themselves. This format includes Fab fragments, single-chain variable fragments (scFvs), Fc fragments, and the variable regions of the camelid heavy chain of heavy-chain-only antibodies (VHH), which was fused with a human Fc fragment or with another VHH. There has been a total of eight fragment antibody therapies approved so far. The only scFv is the anti-vascular endothelial growth factor (VEGF)-A Brolucizumab for the treatment of wet age-related macular degeneration, approved by the FDA in 2019 [58]. Four Fab fragments have been approved so far, of which the first approved Fab fragment antibody therapy was Abciximab [10, 11]. There has also been one PEGylated Fab fragment, Certolizumab Pegol, approved in 2008 for the treatment of autoimmune-related diseases [59, 60]. ScFv is a small-sized antibody, which fuses only the variable regions of the heavy and light chain of the whole antibody, making it easier to penetrate the tissues [61–63]. The only Fc fragment antibody therapy, Efgartigimod alfa, was first approved by the FDA in 2021, targeting neonatal Fc Receptor (FcRn) for the treatment of myasthenia gravis [64]. There are two antibody therapies composed of VHH, Caplacizumab and Envafolimab, which were first approved by the EMA in 2018 and the NMPA in 2021, respectively. Caplacizumab is a bivalent single domain antibody with VHH–VHH format, whereas Envafolimab is a VHH-Fc fusion.

ADCs are composed of a monoclonal antibody chemically linked to a small molecule drug as a payload. There have been 14 ADCs approved so far. Meanwhile, bispecifics are engineered antibodies or antibody fragments designed to combine two or more different antigen-binding domains in an integrated structure. There have been seven bispecific antibodies approved to date. The structures of bispecific antibodies include the heterodimeric bispecific antibody (Catumaxomab, Emicizumab, Amivantamab, Faricimab, Mosunetuzumab), scFv-based bispecific antibody such as bispecific T-cell engager (BiTE) (Blinatumomab), and IgG-scFv-based tetravalent (Cadonilimab). As for other special formats of antibody therapies, we have classified them into the "others" group, which includes antibody-conjugate immunotoxin (with a bacterial toxin, moxetumomab pasudotox), radiolabeled antibodies (Iodine 131 derlotuximab biotin, Iodine 131 Tositumomab), radiolabeled Fab fragments (Iodine 131 Metuximab), Fc-fusion proteins, an scFv fused with a TCR (Tebentafusp), and an antibody fused with an enzyme (Pabinafusp alfa).
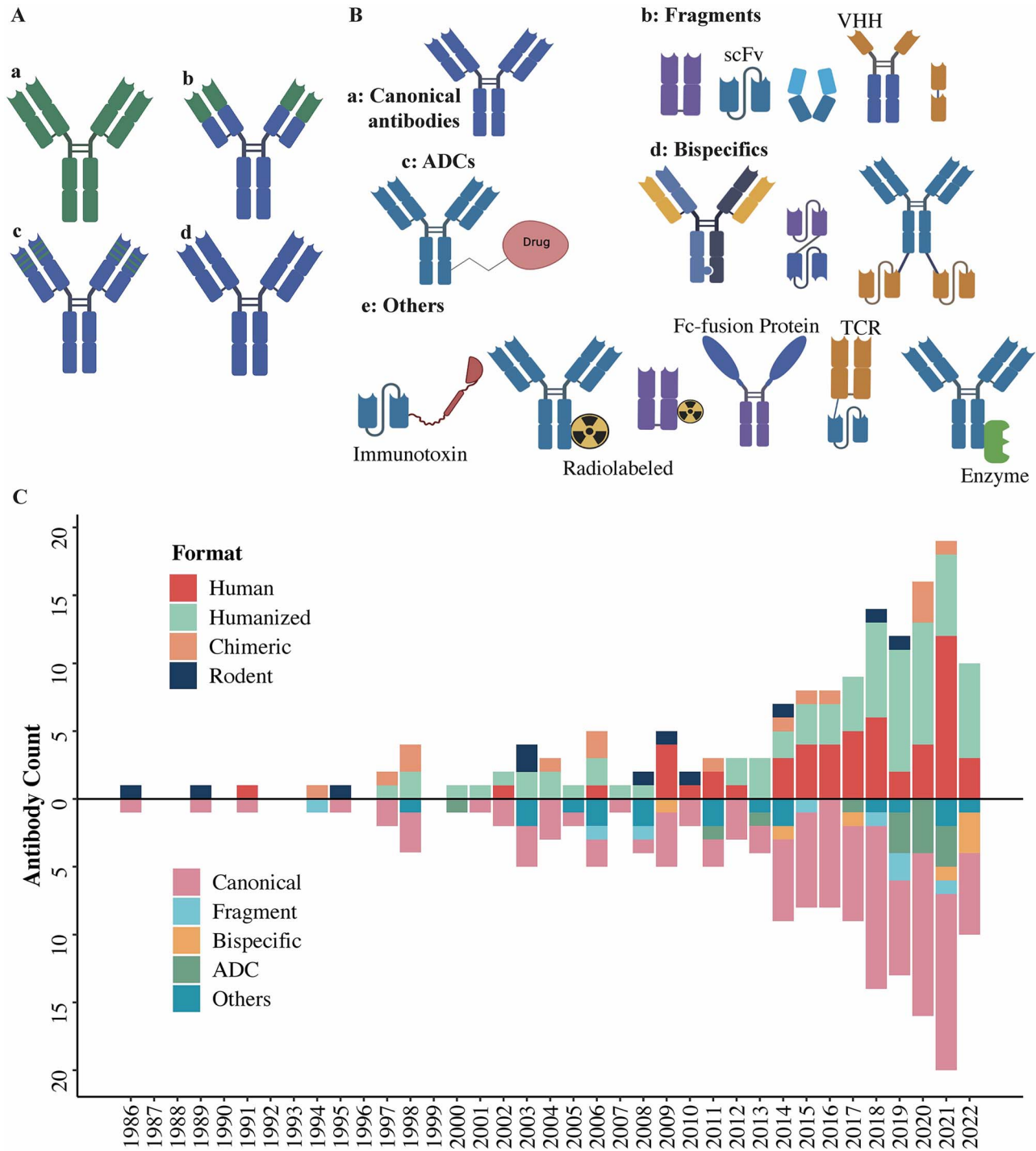
Figure 2. Antibody discovery and engineering for approved antibodies. A: Antibody therapies of different degree of humanization: a: the non-human antibody; b: the chimeric antibody, where the variable region (green region) is from a non-human animal, and the other domains (blue region) are from human; c: humanized antibody, where only the hypervariable region fragment is non-human; d: full human antibody. B: Different engineering formats of approved antibody therapies: a. canonical antibodies; b. fragments: including Fab fragment, single-chain variable fragment (scFv), Fc fragment, the variable regions of camelid heavy-chain-only antibodies (VHH) fused with human Fc fragment or with another VHH; c. antibody drug conjugates (ADCs): monoclonal antibody conjugate with cytotoxic small molecule drug payloads; d. bispecifics: including heterodimeric bispecific antibody, scFv–scFV bispecific antibody such as bispecific T-cell engager (BiTE) and IgG-scFv-based tetravalent; e. others: including antibody-conjugate immunotoxin, radiolabeled canonical antibody, radiolabeled Fab fragment, Fc-fusion protein, a scFv fused with a soluble T-cell receptor (TCR), and an IgG fused with an enzyme. C: The number of different formats of antibody therapies for the year that they were first approved (Fc-fusion proteins are not included).

LANDSCAPES OF TARGETS AND INDICATIONS OF APPROVED ANTIBODY THERAPIES

There are several effects when an antibody binds to its targets, including blocking of a ligand, blocking receptor dimerization, mediating receptor internalization, antibody-dependent cellular phagocytosis, ADCC, and complement-dependent cytotoxicity [65].

Validation of a therapeutic target takes considerable research input, rendering the number of targets for clinical development very limited. There are 91 targets involved in the 162 approved antibody therapies. Some targets have been extensively studied, such as PD-1, CD3, CD20, EGFR, VEGF, and HER2, such that a large proportion of approved antibody therapies have been based on these targets, which are all cancer and immune-related disease targets [66–70]. It is notable that CD3 is used as a target for T cell-dependent bispecific antibodies, rather than as a direct tumor target for cancer treatment. Furthermore, other targets emerged recently such as the SARS-CoV-2 spike protein for SARS-CoV-2 infections since the Covid-19 pandemic (antibody therapy Regdanvimab, Amubarvimab + Romlusevimab cocktail, Sotrovimab, and Evusheld) and the CGRP for CNS diseases (antibody Fremanezumab, Galcanezumab, and Eptinezumab) (Fig. 3A).

For approved antibody therapies, 112 have been developed against 30 targets, and the remaining 61 targets are associated with the 63 antibody therapies. Of those antibody therapies against the 30 targets, seven are bispecific antibodies, one is a combination therapy (Relatlimab + Nivolumab), two are canonical antibodies (Ustekinumab and Bimekizumab), two are Fc-Fusion proteins (Abatacept and Belatacept) and one is an immunoconjugate (Tebentafusp) developed against two targets (thus counted twice), resulting in significant research and market competition on these popular targets. The most popular 20 targets are mainly applied to the treatment of cancers (PD-1/PD-L1, CD20 [71, 72], VEGF [69], EGFR [67, 73], HER2 [70], CD3 [74], CD19 [75], CD22 [76], GD2 [77]), immune-related diseases (TNF-alpha [59], IL-6R [78], IL-23 [79], IL-17A [80], IL-1 [81]), infectious diseases (SARS-CoV-2 spike protein [82], Rabies virus GP [83]), CNS diseases (CGRP [5]), and hematological disease (C5 [84], Factor IX [85]). Approval agencies of these antibodies and their targets are also presented showing different healthcare demands in these countries or regions (Fig. 3B).

Choices of therapeutic targets have progressed over time. Among the top 20 targets, there are some "new" targets (PD-1/PD-L1, CD19, SARS-CoV-2 spike protein, CGPR, Rabies virus GP, and IL-6R) with antibodies approved only after 2011. In contrast, the target TNF-alpha has no antibodies approved after 2010, showing that it has been thoroughly developed and left no market space. In 2018, the Nobel Prize for Physiology or Medicine was awarded to the discovery of the immune checkpoint PD-1, which acts as a "brake" for activated T cells in the tumor microenvironment and is considered to be a key target for the treatment of many cancers [86]. With the global pandemics of COVID-19, there came an emerging focus on the discovery of neutralizing antibodies for the prevention or treatment of respiratory syndromes from COVID-19, for which a total of four antibody therapies have been approved so far.

With respect to the indications of the approved antibodies, we have categorized seven classes based on their pathology. It can be easily interpreted that nearly half (42.6%) of the antibody therapies are for cancers, 37% for immune-related diseases, 11% for infectious diseases, and 7.4% for hematological diseases, whereas antibodies for other indications only account for < 3% (Fig. 3C). Likewise, interests on indications have changed over time. Cancers have always been the largest indication for antibody therapies, enabled by the extensive characterization of several key therapeutic targets, as discussed before. The first antibody therapy for the treatment of cancer, Rituximab, was a chimeric IgG1 mAb targeting CD20 and was approved for non-Hodgkin's lymphoma in 1997 by the FDA [87, 88]. Rituximab worked well in the clinic as a chimeric antibody, as it caused prompt and nearly complete depletion of peripheral B cells, which alleviated the immunogenic concern introduced by the administration of a chimeric antibody. Antibody therapies have revolutionized the treatment of immune-related diseases due to their efficacy, specificity, speed of onset, and tolerability. It should be noted that CNS diseases have been an emerging therapeutic area for antibody therapies since 2016, in which antibodies could lead to some breakthrough treatments (Fig. 3D).

COMPANIES/ORGANIZATIONS

Scrutinizing the companies with at least one approved antibody, there are a total of 82 companies. The number of companies that have had their antibody therapies first approved by the FDA is 33. For the EMA, it is 15 companies, for the NMPA it is 17, for the PDMA it is 7, and for other agencies it is 10 (Fig. 4A and Table 1). The number of companies suggests that the US is in a leading position in antibody therapy as it also dominates the research and clinical development in the field. For the companies in the FDA group, most approvals occurred between 2016 and 2020, which is similar to the first approvals by the EMA, PMDA, and agencies in the other group. However, the year 2021 saw a peak (8 companies) in the number of companies that had first approvals by the NMPA (Fig. 4A). This suggests an enormous scale of research funding and capital was put into the field over the past decade in China.

For the top 10 companies with the greatest number of approved antibodies, their product portfolio shows different R&D focuses of therapeutic areas (Fig. 4B and Supplementary Table 1) such as cancer, immune-related disease, infectious disease, hematological disease, and CNS disease. GSK, BMS, Amgen, and Eli Lilly show a stronger historical interest in cancer antibody therapies as they possess 5, 4, 3, and 3 approvals, respectively. In comparison, they possess 2, 2, 2, and 1 approvals in immune-related diseases, which are their second largest therapeutic field. Johnson & Johnson, AstraZeneca and Novartis show higher achievement in immune-related disease antibody therapies, as they possess 6, 3 and 3 approvals, which outnumber their approvals in cancer. Roche, Sanofi and
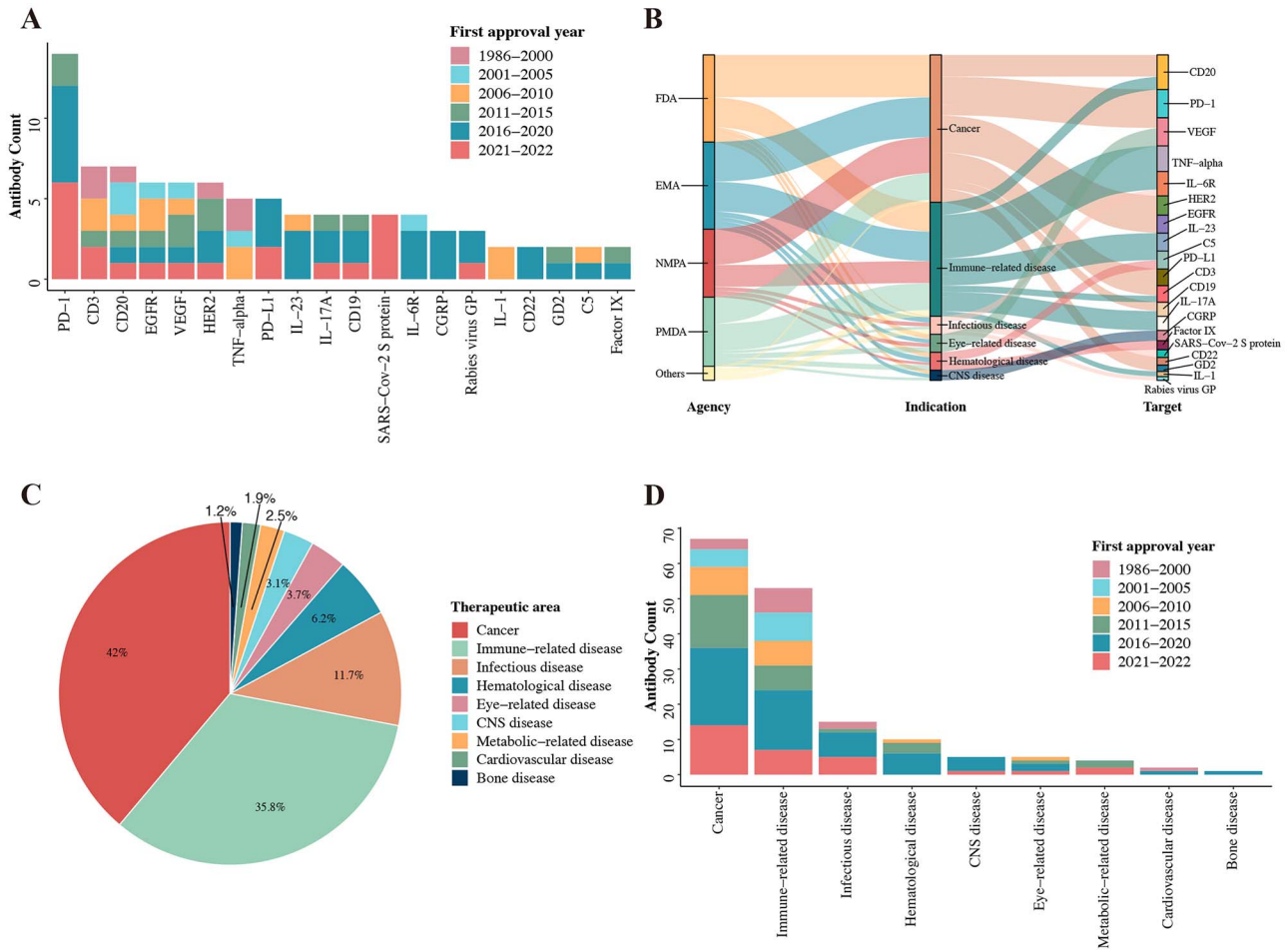
Figure 3. The landscape of targets and indications of approved antibody therapies based on the Umabs-DB data are available as of 30 June 2022. A: Statistics of the top 20 approved antibody targets by their first approval year; B: Top 20 targets and their related indications approved by different agencies; C: The proportion of different therapeutic areas of approved antibody therapies; D: Approval antibodies over indications and year of approval.
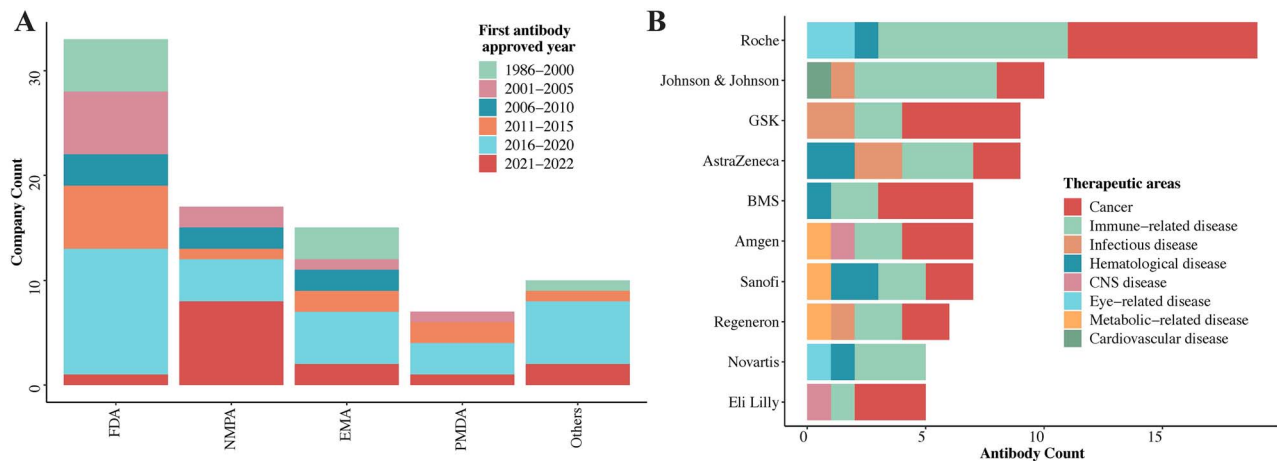

Figure 4. A. Companies with their first approval by different regulatory agencies (the MHRA from the UK is included in the Others group). B. Top 10 companies ranking by the number of approved antibody therapies.

Regeneron show a balanced output in antibody therapy for cancer (8, 2, and 2 approvals) and immune-related disease (8, 2 and 2 approvals). Hematological disorder has been more explored by AstraZeneca and Sanofi (2 and 2 approvals). Similarly, antibody therapy of infectious disease is characteristic to GSK and AstraZeneca (2 and

2 approvals), whereas therapy of eye-related diseases has only successfully been developed by Roche and Novartis (2 and 1 approvals).

CONCLUSION AND PERSPECTIVE

Antibody therapies have become the leading treatment for a range of human diseases. More than 160 antibody therapies have been approved in the world, but this is just a start. The emerging discovery technologies play an important role in speeding up R&D that will make more antibody candidates available for clinical development. Several antibody discovery technologies are widely applicable today, including hybridoma, *in vitro* display (phage display, yeast display and mammalian cell display, etc.) and single B cell technology. During the COVID-19 pandemic, several neutralizing antibodies that were discovered by characterizing single B cells in patients' blood have been approved. Bamlanivimab (LY-CoV555) was the first antibody receiving FDA emergency use authorization to treat COVID-19 infection [89]. It only took a few months to complete the early discovery of neutralizing antibodies by the combination of single B cells characterization, NGS, and a machine learning algorithm. Furthermore, NGS, bioinformatics, and artificial intelligence are advancing antibody discovery to find and generate new antibody molecules that have better pharmacological properties. We believe further advancements in the fields of NGS, bioinformatics, and data-driven technology will continue to accelerate antibody discovery. Antibody discovery advancement and the discovery of new antibody targets will also combine to benefit the development of new antibody therapies.

The past decade has witnessed that the immunotherapeutic PD-1/PD-L1 blockade revolutionized the treatment of many types of cancer. The success of anti-PD-1/PD-L1 antibodies catalyzed the development of cancer immunotherapy. So far, the global regulatory authority has approved 12 antibodies targeting PD-1 (Pembrolizumab, Nivolumab, Sintilimab, Cemiplimab, Toripalimab, Tislelizumab, Camrelizumab, Prolgolimab, Penpulimab, Dostarlimab, Zimberelimab, and Serplulimab) and five antibodies targeting PD-L1 (Atezolizumab, Durvalumab, Avelumab, Sugemalimab, and Envafolimab). In addition, a bispecific antibody targeting CTLA-4 and PD-1 (Cadonilimab) and a two-antibody cocktail targeting LAG-3 and PD-1 (Relatlimab + Nivolumab) were approved this year. However, among the immune checkpoint antibodies, only anti-CTLA-4 and anti-LAG-3 antibodies have shown promising efficacy in combination with anti-PD-1/PD-L1 antibodies; it may help overcome the limitations seen in prior treatments. Apart from PD-1/PD-L1 antibodies, the limited efficacy of the immune checkpoint antibodies encouraged the discovery of novel targets for cancer immunotherapy.

Over the past four decades, there has been a significant change in the spectrum of antibody modalities. Traditional modalities of antibody therapies are protein-based molecules including canonical antibodies, ADCs, bispecific antibodies, and antibody fragments. Recently, the Chinese Antibody Society (CAS) introduced a new concept of AntibodyPlus™ for future antibody therapies. The AntibodyPlus™ therapies contain an antibody component and/or other modalities in medicine such as cell and mRNA expressing antibody therapies. There is no doubt that CAR-T cell therapy is getting more attention in such AntibodyPlus™ therapies. The FDA has already approved five CAR-T cell therapies (Abecma [90], Breyanzi [91], Kymriah [92], Tecartus [93], and Yescarta [94]) to treat hematological malignancies. With the novel strategies introduced to enhance the efficacy of CAR-T cell therapies, we will see a breakthrough for the treatment of solid tumors soon. In addition, one more interesting modality of antibody therapies is mRNA-encoded antibodies. The mRNA-encoded antibody circumvents the problems of complex production and purification processes, aberrant post-translational modifications inherent in protein-based antibodies. In addition, a mixture of mRNA sequences can simplify the manufacturing of antibody cocktails [95, 96]. The potential of mRNA-based antibody therapies is one of the most attractive aspects of next-generation antibody therapies.

In spite of these advancements, antibody therapies are still one of the fastest growing therapeutic forms in the world. This is achieved by consistent investment in R&D and the maturation of emerging markets. The global antibody therapy industry and its market will be substantially larger in the future.

FUNDING STATEMENT

None.

CONFLICT OF INTEREST STATEMENT

Xiaochen Lyu, Qichao Zhao and Hongyu Zhang are current employees of Zhanyuan Therapeutics ltd., and Bo Liu is a current employee of Umabs Therapeutics Inc. Hongyu Zhang holds the position of Assistant Editor for Antibody Therapeutics and is blinded from reviewing or making decisions for the manuscript.

ETHICS AND CONSENT STATEMENT

The consent is not required.

ANIMAL ETHICS STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

All relevant data are available in Umabs Antibody Therapies Database (Umabs-DB, https://umabs.com).

REFERENCES

1. NCI dictionary of Cancer Terms. In: *National Cancer Institute*. 2 Feb 2011 [cited 1 Jul 2022]. Available: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/antibody-therapy
2. Van Wauwe, JP, De Mey, JR, Goossens, JG. OKT3: a monoclonal anti-human T lymphocyte antibody with potent mitogenic properties. *J Immunol* 1980; **124**: 2708–13.

3. Reichert, JM, Valge-Archer, VE. Development trends for monoclonal antibody cancer therapeutics. *Nat Rev Drug Discov* 2007; **6**: 349–56.

4. Mullard, A. FDA approves 100th monoclonal antibody product. *Nat Rev Drug Discov* 2021; **20**: 491–5.

5. Edvinsson, L, Haanes, KA, Warfvinge, K *et al.* CGRP as the target of new migraine therapies - successful translation from bench to clinic. *Nat Rev Neurol* 2018; **14**: 338–50.

6. Edvinsson, L. The CGRP pathway in migraine as a viable target for therapies. *Headache* 2018; **58**: 33–47.

7. Ugalmugale, S, Swain, R. Antibody Therapy Market Size by Type, by End-Use, Industry Analysis Report, Regional Outlook, Growth Potential, COVID-19 Impact Analysis, Price Trends, Competitive Market Share & Forecast, 2022–2028. Global Market Insights Inc.; 2022 Feb. [cited 26 Jun 2022] Available: https://www.gminsights.com/industry-analysis/antibody-therapy-market

8. Ecker, DM, Jones, SD, Levine, HL. The therapeutic monoclonal antibody market. *MAbs* 2015; **7**: 9–14.

9. *UmabsDB - the antibody therapies database*. [cited 26 Jun 2022]. Available: https://umabs.com/

10. Kastrati, A, Mehilli, J, Schühlen, H *et al.* A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004; **350**: 232–8.

11. Foster, W, Markham, A. Abciximab: an updated review of its use in ischaemic heart disease. *Drugs* 1998; **56**: 629.

12. Reichert, JM. Marketed therapeutic antibodies compendium. *MAbs* 2012; **4**: 413–5.

13. Derkx, B, Wittes, J, Mc Closkey, R *et al.* Randomized, placebo-controlled trial of HA-1A, a human monoclonal antibody to endotoxin, in children with meningococcal septic shock. *Clin Infect Dis* 1999; 28 770–7. https://doi.org/10.1086/515184

14. Braun, S, Hepp, F, Kentenich, CR *et al.* Monoclonal antibody therapy with edrecolomab in breast cancer patients: monitoring of elimination of disseminated cytokeratin-positive tumor cells in bone marrow. *Clin Cancer Res* 1999; **5**: 3999–4004.

15. Hu, Y, Turner, MJ, Shields, J *et al.* Investigation of the mechanism of action of alemtuzumab in a human CD52 transgenic mouse model. *Immunology* 2009; **128**: 260–70.

16. Venkiteshwaran, A. Tocilizumab. *MAbs* 2009; **1**: 432–8.

17. Amador-Perez, RB. Immunologic monitoring of renal allografted patients treated with the IOR-T3 (anti-CD3) monoclonal antibody. Effects on CD markers and its Inmunologia. [cited 9 Jul 2022]. Available: https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=4020664

18. Akeso, Inc. Akeso's Cadonilimab (PD-1/CTLA-4), the First Dual Immune Checkpoint Inhibitor To Treat Cancer, Approved For Marketing in China. *In: PR Newswire [Internet]. 29 Jun 2022 [cited 9 Jul 2022]. Available:* https://www.prnewswire.com/news-releases/akesos-cadonilimab-pd-1ctla-4-the-first-dual-immune-checkpoint-inhibitor-to-treat-cancer-approved-for-marketing-in-china-301577866.html

19. Kohler, G. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975; **256**: 495–7. https://ci.nii.ac.jp/naid/10021259092/

20. Jones, PT, Dear, PH, Foote, J *et al.* Replacing the complementarity-determining regions in a human antibody with those from a mouse. *Nature* 1986; **321**: 522–5.

21. McCafferty, J, Griffiths, AD, Winter, G *et al.* Phage antibodies: filamentous phage displaying antibody variable domains. *Nature* 1990; **348**: 552–4.

22. Smith, GP. Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface. *Science* 1985; **228**: 1315–7.

23. Xu, Y, Roach, W, Sun, T *et al.* Addressing polyspecificity of antibodies selected from an in vitro yeast presentation system: a FACS-based, high-throughput selection and analytical tool. *Protein Eng Des Sel* 2013; **26**: 663–70.

24. Beerli, RR, Bauer, M, Buser, RB *et al.* Isolation of human monoclonal antibodies by mammalian cell display. *Proc Natl Acad Sci U S A* 2008; **105**: 14336–41.

25. Lonberg, N, Taylor, LD, Harding, FA *et al.* Antigen-specific human antibodies from mice comprising four distinct genetic modifications. *Nature* 1994; **368**: 856–9.

26. Mendez, MJ, Green, LL, Corvalan, JR *et al.* Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nat Genet* 1997; **15**: 146–56.

27. Küppers, R, Zhao, M, Hansmann, ML *et al.* Tracing B cell development in human germinal centres by molecular analysis of single cells picked from histological sections. *EMBO J* 1993; **12**: 4955–67.

28. Smith, K, Garman, L, Wrammert, J *et al.* Rapid generation of fully human monoclonal antibodies specific to a vaccinating antigen. *Nat Protoc* 2009; **4**: 372–84.

29. Li, S, AJ, MC, Gardner, RA *et al.* Glycoengineering of therapeutic antibodies with small molecule inhibitors. *Antibodies (Basel)* 2021; **10**: 44. https://doi.org/10.3390/antib10040044.

30. Mastrangeli, R, Palinsky, W, Bierau, H. Glycoengineered antibodies: towards the next-generation of immunotherapeutics. *Glycobiology* 2019; **29**: 199–210.

31. Pereira, NA, Chan, KF, Lin, PC *et al.* The "less-is-more" in therapeutic antibodies: afucosylated anti-cancer antibodies with enhanced antibody-dependent cellular cytotoxicity. *MAbs* 2018; **10**: 693–711.

32. Dammen-Brower, K, Epler, P, Zhu, S *et al.* Strategies for glycoengineering therapeutic proteins. *Front Chem* 2022; **10**: 863118.

33. A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. *N Engl J Med* 1985; **313**: 337–42.

34. Kaplon, H, Muralidharan, M, Schneider, Z *et al.* Antibodies to watch in 2020. *MAbs* 2020; **12**: 1703531.

35. Linke, R, Klein, A, Seimetz, D. Catumaxomab: clinical development and future directions. *MAbs* 2010; **2**: 129–36.

36. digiONE, Coder. *Neovii completes marketing authorisation withdrawal of Removab® in EU*. [cited 9 Jul 2022]. Available: https://neovii.com/neovii-completes-marketing-authorisation-withdrawal-of-removab-in-the-european-union/

37. Center for Drug Evaluation, Research. *FDA approves moxetumomab pasudotox-tdfk for hairy cell leukemia*. In: U.S. Food and Drug Administration. [cited 9 Jul 2022]. Available: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-moxetumomab-pasudotox-tdfk-hairy-cell-leukemia

38. Legouffe, E, Liautard, J, Gaillard, JP *et al.* Human anti-mouse antibody response to the injection of murine monoclonal antibodies against IL-6. *Clin Exp Immunol* 1994; **98**: 323–9.

39. van der Horst, HJ, Nijhof, IS, Mutis, T *et al.* Fc-engineered antibodies with enhanced fc-effector function for the treatment of B-cell malignancies. *Cancer* 2020; **12**: 3041. https://doi.org/https://doi.org/10.3390/cancers12103041.

40. Morrison, SL, Johnson, MJ, Herzenberg, LA *et al.* Chimeric human antibody molecules: mouse antigen-binding domains with human constant region domains. *Proc Natl Acad Sci U S A* 1984; **81**: 6851–5.

41. Chen, Z-N, Mi, L, Xu, J *et al.* Targeting radioimmunotherapy of hepatocellular carcinoma with iodine (131I) metuximab injection: clinical phase I/II trials. *Int J Radiat Oncol Biol Phys* 2006; **65**: 435–44.

42. Caimi, PF, Ai, W, Alderuccio, JP *et al.* Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2021; **22**: 790–800.

43. Safdari, Y, Farajnia, S, Asgharzadeh, M *et al.* Antibody humanization methods – a review and update. *Biotechnol Genet Eng Rev* 2013; 175–86. https://doi.org/10.1080/02648725.2013.801235.

44. Kuramochi, T, Igawa, T, Tsunoda, H *et al.* Humanization and simultaneous optimization of monoclonal antibody. *Methods Mol Biol* 2019; 1060: 213–30. https://doi.org/10.1007/978-1-4939-8958-4_9.

45. Fisher. *Genetically Engineered Drug Approved for Kidney Transplants*. NY Times. [cited 9 Jul 2022]. Available: https://repository.library.georgetown.edu/handle/10822/532092

46. Bell, J, Colaneri, J. Zenapax: transplant's first humanized monoclonal antibody. *ANNA J* 1998; **25**: 429–30.

47. Lopez, C, Roizman, B. The Herpesviruses: Immunobiology and Prophylaxis of Human Herpesvirus Infections. Berlin, German. Springer Science & Business Media; 2012. Editors: Carlos Lopez, Ryoichi Mori, Bernard Roizman, Richard J. Whitley.

48. Traggiai, E, Becker, S, Subbarao, K *et al.* An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. *Nat Med* 2004; **10**: 871–5.

49. Bonsignori, M, Hwang, K-K, Chen, X *et al.* Analysis of a clonal lineage of HIV-1 envelope V2/V3 conformational epitope-specific broadly neutralizing antibodies and their inferred unmutated common ancestors. *J Virol* 2011; **85**: 9998–10009.

50. Frenzel, A, Schirrmann, T, Hust, M. Phage display-derived human antibodies in clinical development and therapy. *MAbs* 2016; **8**: 1177–94.

51. Woda, M, Friberg, H, Currier, JR *et al.* Dynamics of dengue virus (DENV)-specific B cells in the response to DENV serotype 1 infections, using flow cytometry with labeled virions. *J Infect Dis* 2016; **214**: 1001–9.

52. Cox, KS, Tang, A, Chen, Z *et al.* Rapid isolation of dengue-neutralizingantibodies from single cell-sorted human antigen-specific memory B-cellcultures. MAbs 2016; 8:129–40. https://doi.org/10.1080/19420862.2015.1109757.

53. Markham, A. REGN-EB3: first approval. *Drugs* 2021; **81**: 175–8.

54. Benotmane, I, Velay, A, Thaunant, O *et al.* Pre-exposure prophylaxis with Evusheld™ elicits limited neutralizing activity against the omicron variant in kidney transplant patients. *bioRxiv.* 2022. https://doi.org/https://doi.org/10.1101/2022.03.21.22272669.

55. Goldstein, LD, Chen, Y-JJ, Wu, J *et al.* Massively parallel single-cell B-cell receptor sequencing enables rapid discovery of diverse antigen-reactive antibodies. *Commun Biol* 2019; **2**: 304.

56. Mathew, NR, Jayanthan, JK, Smirnov, IV *et al.* Single-cell BCR and transcriptome analysis after influenza infection reveals spatiotemporal dynamics of antigen-specific B cells. *Cell Rep* 2021; **35**: 109286.

57. Cao, Y, Su, B, Guo, X *et al.* Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells. *Cell* 2020; **182**: 73–84.e16. https://doi.org/10.1016/j.cell.2020.05.025.

58. Dugel, PU, Koh, A, Ogura, Y *et al.* HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of Brolucizumab for Neovascular age-related macular degeneration. *Ophthalmology* 2020; **127**: 72–84.

59. Esposito, E, Cuzzocrea, S. TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma. *Curr Med Chem* 2009; **16**: 3152–67.

60. Goel, N, Stephens, S. Certolizumab pegol. *MAbs* 2010; **2**: 137–47.

61. Brolucizumab. In: *Drugs.com.* [cited 18 Jul 2022]. Available: https://www.drugs.com/monograph/brolucizumab.html

62. Huston, JS, Levinson, D, Mudgett-Hunter, M *et al.* Protein engineering of antibody binding sites: recovery of specific activity in an anti-digoxin single-chain Fv analogue produced in Escherichia coli. *Proc Natl Acad Sci U S A* 1988; **85**: 5879–83.

63. Ahmad, ZA, Yeap, SK, Ali, AM *et al.* scFv antibody: principles and clinical application. *Clin Dev Immunol* 2012; **2012**: 980250.

64. Efgartigimod alfa (Vyvgart) for myasthenia gravis. *Med Lett Drugs Ther* 2022; **64**: 62–3.

65. Strohl, WR, Strohl, LM (eds). 8 - Monoclonal antibody targets and mechanisms of action. In: William R. Strohl and Lila M. Strohl. (eds), *Therapeutic Antibody Engineering*. Sawston, Cambridge. Woodhead Publishing, 2012, 163–595.

66. Beers, SA, Chan, CHT, French, RR *et al.* CD20 as a target for therapeutic type I and II monoclonal antibodies. *Semin Hematol* 2010; **47**: 107–14.

67. Paez, D, Paré, L, Espinosa, I *et al.* Immunoglobulin G fragment C receptor polymorphisms and KRAS mutations: are they useful biomarkers of clinical outcome in advanced colorectal cancer treated with anti-EGFR-based therapy? *Cancer Sci* 2010; **101**: 2048–53.

68. Kuhn, C, Weiner, HL. Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside. *Immunotherapy* 2016; **8**: 889–906.

69. Ferrara, N, Mass, RD, Campa, C *et al.* Targeting VEGF-A to treat cancer and age-related macular degeneration. *Annu Rev Med* 2007; **58**: 491–504.

70. Zwick E, Wallasch C, Ullrich A. HER2/neu: a target forbreast cancer therapy. Breast Disease 2000; **11**: 7–18.

71. Alduaij, W, Illidge, TM. The future of anti-CD20 monoclonal antibodies: are we making progress? *Blood* 2011; **117**: 2993–3001.

72. Alduaij, W, Ivanov, A, Honeychurch, J *et al.* Novel type II anti-CD20 monoclonal antibody (GA101) evokes homotypic adhesion and actin-dependent, lysosome-mediated cell death in B-cell malignancies. *Blood* 2011; **117**: 4519–29.

73. Patel, D, Guo, X, Ng, S *et al.* IgG isotype, glycosylation, and EGFR expression determine the induction of antibody-dependent cellular cytotoxicity in vitro by cetuximab. *Hum Antibodies* 2010; **19**: 89–99.

74. Adams, AB, Ford, M, Larsen, CP. *Transplantation immunobiology and immunosuppression. Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice* 20th ed Philadelphia, PA: Elsevier. 2017. Editor: Robertson-Poth.

75. Zalevsky, J, Leung, IWL, Karki, S *et al.* The impact of fc engineering on an anti-CD19 antibody: increased Fcγ receptor affinity enhances B-cell clearing in nonhuman primates. *Blood* 2009; **113**: 3735–43.

76. Sullivan-Chang, L, O'Donnell, RT, Tuscano, JM. Targeting CD22 in B-cell malignancies: current status and clinical outlook. *BioDrugs* 2013; **27**: 293–304.

77. Fleurence, J, Fougeray, S, Bahri, M *et al.* Targeting O-acetyl-GD2 ganglioside for cancer immunotherapy. *J Immunol Res* 2017; **2017**: 1–16.

78. Yousefi, H, Momeny, M, Ghaffari, SH *et al.* IL-6/IL-6R pathway is a therapeutic target in chemoresistant ovarian cancer. *Tumori* 2019; **105**: 84–91.

79. Tang, C, Chen, S, Qian, H *et al.* Interleukin-23: as a drug target for autoimmune inflammatory diseases. *Immunology* 2012; **135**: 112–24.

80. Kellner, H. Targeting interleukin-17 in patients with active rheumatoid arthritis: rationale and clinical potential. *Ther Adv Musculoskelet Dis* 2013; **5**: 141–52.

81. Klein, AL, Imazio, M, Cremer, P *et al.* Phase 3 trial of Interleukin-1 trap Rilonacept in recurrent pericarditis. *N Engl J Med* 2021; **384**: 31–41.

82. Huang, Y, Yang, C, Xu, X-F *et al.* Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacol Sin* 2020; **41**: 1141–9.

83. Kramer, RA, Marissen, WE, Goudsmit, J *et al.* The human antibody repertoire specific for rabies virus glycoprotein as selected from immune libraries. *Eur J Immunol* 2005; **35**: 2131–45.

84. Hawksworth, OA, Li, XX, Coulthard, LG *et al.* New concepts on the therapeutic control of complement anaphylatoxin receptors. *Mol Immunol* 2017; **89**: 36–43.

85. Orlova, NA, Kovnir, SV, Vorobiev, II *et al.* Coagulation factor IX for hemophilia B therapy. *Acta Naturae* 2012; **4**: 62–73.

86. Tumeh, PC, Harview, CL, Yearley, JH *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014; **515**: 568–71.

87. Maloney, DG, Grillo-López, AJ, White, CA *et al.* IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood* 1997; **90**: 2188–95.

88. Maloney, DG, Grillo-López, AJ, Bodkin, DJ *et al.* IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *J Clin Oncol* 1997; **15**: 3266–74.

89. Gottlieb, RL, Nirula, A, Chen, P *et al.* Effect of Bamlanivimab as monotherapy or in combination with Etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA* 2021; **325**: 632–44.

90. Wire, B. US Food and Drug Administration approves Bristol Myers Squibb's and Bluebird Bio's Abecma (idecabtagene vicleucel), the first anti-Bcma car T cell therapy for . . . . Abecma is a first-in-class BCMA-directed personalized. 2021. [cited 18 Jul 2022]. Available: https://www.myelomacanada.ca/pixms/uploads/serve/ckeditor/032621_abecma_fda_approval_release.pdf

91. Center for Biologics Evaluation, Research. BREYANZI (lisocabtagene maraleucel). In: U.S. Food and Drug Administration [Internet]. FDA; [cited 16 Sep 2022]. Available: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel

92. Philippidis, A. *Kymriah, First CAR-T Cancer Immunotherapy Approved by FDA.* 2017. [cited 18 Jul 2022]. Available: https://www.liebertpub.com/doi/pdf/10.1089/clinomi.04.05.09

93. Center for Biologics Evaluation, Research. TECARTUS (brexucabtagene autoleucel). In: U.S. Food and Drug Administration [Internet]. FDA; [cited 16 Sep 2022]. Available: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel

94. Fala, L. *Yescarta (axicabtagene ciloleucel) second CAR T-cell therapy approved for patients with certain types of large B-cell lymphoma*. 2018 [cited 14 Jul 2022]. Available: https://jons-online.com/browse-by-topic/fda-approvals-news-updates/1829-yescarta-axicabtagene-ciloleucel-second-car-t-cell-therapy-approved-for-patients-with-certain-types-of-large-b-cell-lymphoma

95. Deal, CE, Carfi, A, Plante, OJ. Advancements in mRNA encoded antibodies for passive immunotherapy. *Vaccine* 2021; **9**: 108. https://doi.org/10.3390/vaccines9020108.

96. Van Hoecke, L, Roose, K. How mRNA therapeutics are entering the monoclonal antibody field. *J Transl Med* 2019; **17**: 54.