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An overview of the current status of engineered therapeutic monoclonal antibodies

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ABSTRACT:

Since the commercialization of the first therapeutic monoclonal antibody (mAb) product in 1986, this class of biopharmaceutical products have grown significantly. Due to the enhanced antigen binding and reduced cellular toxicity, they result in more efficacy in treatment of variety of diseases. The global sales of mAbs which was 95.1 b$ in 2017 have grown annually due to the dramatic increase in cancer and severe diseases rates and are estimated to reach 131.33 b$ by 2023, this represents a clear accelerating trend with more than 5.53% growth. In this review, we discuss some of these mAbs which have been approved by the FDA as well as others that are experiencing or being evaluated in clinical phases. Global sales of some monoclonal antibodies in 2016 are also considered, suggesting a significant increase in sales of mAbs over the years ahead.

Keywords: Monoclonal Antibody; Market; Phage display; ScFv Antibodies

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1. Introduction

Over the past 25 years, antibodies have become a major source of therapeutics for treatment of a wide spectrum of human diseases including cancers, infectious diseases, allergies, autoimmune diseases, and inflammations [1-3]. The ability of monoclonal antibodies (mAbs) to bind two antigens of the same type selectively with high affinity and elevated stability (in vitro and in vivo), signify them as suitable agents for therapeutic applications [4]. Compared to their polyclonal counterparts, mAbs are advantageous since they exhibit a much higher specificity and they are less susceptible to contaminations by pathogens [5, 6]. MAbs can also be conjugated to another therapeutic entities such as toxins or radioisotopes. The delivery of this entity to a target site can reduce potential side effects [7].

During the 1970s and 1980s, a series of technologies were developed which eventually converged to provide all of the technological and fundamental bases for the development of the therapeutic mAb industry. including the discovery of restriction enzymes [8], development of hybridoma technology [9] and site-directed mutagenesis [10-12]. In the 1980s, additional technologies and scientific discoveries were assisted to the development of recombinant antibodies such as phage display technology [13], Polymerase Chain Reaction (PCR) [14, 15], sequencing and characterization of human germline antibody genes [16], and expression of antibody genes in cell cultures [17, 18]. Since the first therapeutic mAb was approved by Food and Drug Administration (FDA) in 1986 for clinical use in the treatment of organ transplant rejection [19, 20], extraordinary development has been seen in this field (Table 1). The global monoclonal antibodies market was 95.1 Billion USD in 2017, nearly half of the biopharmaceutical market and it is estimated to reach 131.33 Billion USD by 2023 with a (Compound annual growth rate) CAGR of 5.53% during the period [18, 21] Figure 1 [22].

2. Structural and functional features of antibodies

Immunoglobulins (Igs) are exquisitely specific and naturally evolved molecules that recognize and eliminate foreign antigens. There are five classes of Igs: IgM, IgG, IgE, IgA, and IgD. From a biotechnology perspective, IgGs are the most important class of antibodies and exist both as soluble proteins and as membrane-bound receptors on the surface of B-lymphocytes. All of the immunoglobulins have a similar structure, consisting of two identical heavy chains (HCs) (MW~50 kDa) and two identical light chains (LCs) (MW~25 kDa). Each HC is attached to a LC via disulfide bonds, with additional disulfide bonds in the hinge region joining the two HCs together to complete the tetrameric structure (Figure 2). Both heavy and light chains of an immunoglobulin, are encoded by evolutionarily related members of a large multigene family. Functionally, each antibody can be consisted of two constant (Fc) region and an antigen-binding fragments (Fabs), which are connected via a flexible hinge region. The Fc portion of an antibody mediates effector functions, antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The human IgG1 is the most efficient structure in both CDC and ADCC, and therefore the most suitable for therapeutic applications against pathogens or tumor cells.

3. Therapeutic antibody formats in clinical use

3.1. Fully human mAbs

Monoclonal antibodies are produced in different formats including Murine (100% mouse protein), Chimeric (approximately 65% human and 35% mouse protein), Humanized (95% human and 5% mouse protein) and Fully human (100% human protein) (Figure 3) [23]. Human anti-mouse antibody or Human anti-murine antibody (HAMA) is an antibody found in humans that responds to different protein sequences(Igs) which found in mice [24]. This immunologic reaction is against both variable and constant domains in chimeric antibody [25, 26] Attaching the constant regions of a human antibody to the binding site domains of a murine antibody can't solve the problem of immune responses. Antibody humanization method is a process which used to reduce the content of murine residues in the variable domains by adding of the six (complementary determining regions) CDR loops from murine variable domains to human variable frameworks [27].

Lately, human mAbs are more developed than other chimeric or humanized antibodies. Although humanization process is often successful, it is difficult, time-consuming and superseded by the rapid, direct isolation of fully human antibodies from phage display libraries or transgenic mice. The first fully human mAb, Adalimumab, which developed via phage display technology, was approved in 2002 by the FDA and marketed under trade name Humira® (Table 1). Two of transgenic mouse antibodies, panitumumab (manufactured by Amgen and marketed as Vectibix) and ustekinumab (manufactured by Janssen Biotech and marketed as Stelara), have now been approved for human therapeutic use, and over 160 additional similar antibodies are now in human clinical trials (Tabs, http://tabs.craic.com/, accessed May 2018).

Although, mAbs have become an important therapeutic option, they often present severe drawbacks when they are using of full mAbs in patient's therapy. So, researchers has determined recombinant antibody engineering techniques to develop new therapeutic mAb formats with the same activity as the whole size to escape these disadvantages [28]. New approaches, such as phage display [29, 30], are utilized to develop new therapeutically efficient antibody domains or fragments. Examples include Fab, single chain fragment variable (scFv), diabodies, domain antibodies (dAbs), bispecific antibodies, and intrabodies. These molecules suggest numerous therapeutic advantages, such as fast tissue penetration due to their small size and the capability to take on the exact tertiary structure [31].

3.2. The antigen binding fragments (Fabs)

The Fab fragment antibody with a molecular weight of 50 kDa, is monovalent, just containing a single antigen-binding site. So far, Fabs are the most successful antibody fragments categories. they account for over 49% of the fragments in active clinical development. Four antibody fragments, e.g. ReoPro™ (Abciximab); Lucentis™ (Ranibizumab); Cimzia® (Certolizumab pegol) and Verluma™ [(Technetium (^{99m}Tc) nofetumomab merpentan] have been approved by FDA for clot prevention, Macular degeneration, severe Crohn disease and diagnosis of lung cancer, respectively. Currently, there are many companies developing different Fabs to treat various diseases (Table 2). As of the end of May 2018, there are 16 ongoing industry-sponsored clinical trials and one of the trails is in phase III (Tabs, http://tabs.craic.com/, accessed May 2018).

3.3. Single chain variable Fragments (scFvs)

ScFv is a single chain monoclonal antibody, which has variable regions of light and heavy chains, jointed by flexible linker sequences, usually multiple glycines. In recent years, phage display of nonimmune, human naïve scFv antibody repertoires has proven to be an important tool for generating highly specific antibodies [8]. Blinatumomab is a CD19/CD3 bispecific antibody that is the first bispecific T-cell engager (BiTE) which approved by the U.S [32]. So far, about 65 scFvs are in clinical evaluation stage (Table 3) and two of them, Brolucizumab (anti-VEGF-A) and Pexelizumab (anti component 5) are in phase III clinical trials, although many more are still in preclinical development (Tabs, http://tabs.craic.com/, accessed May 2018).

3.3.1. Blinatumomab

Blinatumomab (Blincyto®) is a bispecific T-cell antibody against CD19. This antibody combines two binding sites, T-cell-specific CD3 and B-cell-specific CD19 which are brought in close proximity. Blinatumomab works by connecting these two cell types and activating the T-cell to apply cytotoxic activity on the target cell. Due to its short half-life, this antibody needs continuous intravenous infusion and thereforthe need for continuous exposure to the drug to exert sufficient efficacy, and lessenetoxicity. The drug was approved by FDA in 2014 to the treatment of acute lymphoblastic leukemia (ALL).

3.4. "Min¬iaturize" full-sized mAbs

The new category of the antibody fragment is called the "Miniaturize" full-sized mAbs. Among the best examples of mAb, miniaturization are the small modular immunopharmaceuticals (SMIPs) from Trubion Pharmaceuticals. It only consists of one VL, one VH antigen binding domain and one constant "effectors" domain. The main difference between scFvs and SMIP is that the latter retains the immune effector function. So far, the SMIPs only account for 4% of the clinical pipeline.
The most SMIPs advanced development project is TRU-015, an anti-CD20 developed in collaboration with Wyeth, having progressed to Phase II for RA. Earlier attempts in systemic lupus erythematosus (SLE) and B cell lymphomas were ultimately discontinued. Trubion and Facet Biotechnology are collaborating in the development of phase II project Otlertuzumab (formerly known as TRU-016), which is a CD37-specific single-chain, homodimeric therapeutic protein, for the treatment of CLL and other lymphoid neoplasias [33]. Wyeth has licensed the anti-CD20 SMIP SBI-087 for the treatment of autoimmune diseases, like as RA, SLE and possibly MS, although these projects remain in the earliest stages of clinical trials [34] (Table 4).

3.5. Nanobodies

Nanobodies are a novel class of recombinant antigen-specific, single-domain, variable fragments of the naturally-occurring heavy chain only antibodies. Some preferred advantage of these fragments are minimal size, great stability, reversible refolding and prominent solubility in aqueous solutions and ability to exactly identify unique epitopes with subnanomolar affinity, have been combined to make them a valuable class of biomolecules for research and many medical diagnostic and therapeutic applications [35, 36] (Table 5).

3.6. Antibody-drug conjugates

Antibody-drug conjugates (ADCs) are becoming a progressively significant sub-class of antibody-related therapeutics. Two ADCs, brentuximab vedotin (Adcetris®) and adotrastuzumab emtansine (Kadcyla®), were recently approved for marketing both by the FDA and the EMA [37].
The approval accomplishments of these two ADCs might only be the first two of (potentially) many to come. As of the end of May 2018, there are more than 60 novels ADCs currently being investigated in clinical trials for treatments of a variety of tumors. Nearly 70% of the 60 ADCs entered the clinical study in the past three years [38] (Table 6).

3.7. Antibody-Radionuclide Conjugates

This approach based on the use of monoclonal antibodies as delivery carriers for radionuclides, such as Tositumomab- $I^{131}$and Ibritumomabtiuxetan, leading to obtain better imaging and therapy of cancer, which demonstrates the unique theranostic (therapy+diagnostic) potential of radioimmunoconjugates. At first, a cancer patient would receive a diagnostic dose of a radio immuno conjugates compatible with imaging procedures. If acceptable antibody localization of disease is achieved, the therapeutic dose of the same antibody labeled with a radio nuclide capable of inducing curative effects will be injected [39, 40] (Table 7).

3.8. Immunotoxins

Immunotoxins (ITs) such as Gemtuzumab ozogamicins are chimeric proteins consist of an antibody linked to a toxin [41]. The antibody confers specificity, whereas the toxin confers cytotoxicity. ITs have been used in both mice and humans to eliminate tumor cells, autoimmune diseases, and virus-infected cells [42, 43].

3.9. Antibody-Radionuclide Conjugates

Immunostimulatory mAbs is defined as mediators that increase ongoing immune reactions. Utilizing mAbs to stimulate the immune response against tumor cells is a novel indirect mode of action, achieved by either blocking inhibitory 'immune checkpoint' receptors such as Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4), or triggering activating receptors such as 4-1BB or CD40 [44]. Some of these antibodies such as ipilimumab and tremelimumab have already entered clinical trials [45, 46].

4. Novel technologies in production of fully human mAbs

4.1. Transgenic Mice

In 1985, the possibility of generation of transgenic mice producing human antibodies (humanized mice) was suggested. Transgenic mice in which the native immunoglobulin repertoire has been replaced with human V-genes in the murine chromosome have been generated [47-49]. The desired antigen can be injected to

the transgenic mice, and the resulting antibody genes are recovered by selection technologies [50]. Vectibix® was the first fully human antibody developed using Abgenix Xeno Mouse™ technology and marketed in 2006 [51].

4.2. Phage display technology

Phage display involves the introduction of foreign peptide sequences into the genome of the phage leading to presentation and "display" of large peptide libraries on the surface of phage as a fusion product to coat proteins. These statues provide means for selection of proteins and antibodies with specific binding ability against almost any target. This technology was initially introduced by George Smith in 1985 [13]. The starting point is usually an antibody library which comprises a population of clones. The bacteriophages are the main vehicle for presenting large peptides and protein libraries on their surface which are normally screened through biopanning process within a couple of weeks [13]. After usually three rounds of selection, the population is enriched for a high percentage of antibody fragments specific for the target antigen. The main benefit of phage display is a physical linkage between phenotype and genotype. This implies that selection of bacteriophage harboring a fused single binding molecule to phage coat proteins, enables us to isolate and identify its cognate genome by sequencing the encoding genome after amplification [30, 52]. Currently, more than 60 phage display derived antibody and peptides are in late-stage clinical trials or approved [53] (Table 8).

5. Conclusion

Antibody based drugs proved to play an important role in the treatment of numerous human diseases over the past three decades. A large number of engineered antibodies in clinical development demonstrate the value of this type of therapeutic antibodies. With the use of advanced and novel technologies like phage display for mAb production, their dominance as the major class of biopharmaceutical products will continue.

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Conflict of interest

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Table 1: Blockbuster therapeutic mAbs.

Group	2016 sales bln $	Trade Name	Generic Name	Target	App.Year	Indication
Anti-TNF-α	**35.98**	Humira	Adalimumab	TNF-α	2002	Autoimmune diseases (ankylosing spondylitis, juvenile RA, psoriasis, psoriatic arthritis, RA)
		Enbrel	Etanercept		1998	
		Remicade	Infliximab		1998	
		Revlimid	Lenalidomide		2017	
Anti-Cancer	**35.44**	Rituxan	Rituximab	CD20	1997	NHL
		Herceptin	Trastuzumab	HER2	1998	Breast cancer
		Avastin	Bevacizumab	VEGF	2004	Colorectal cancer
		Erbitux	Cetuximab	EGFR	2004	Colorectal cancer
		Keytruda	Pembrolizumab	PD-1	2014	Melanoma
		Yervoy	Ipilimumab	CTLA-4	2011	Melanoma
		Opdivo	Nivolumab	PD-1	2014	Melanoma
		Ibrance	Palbociclib	CDK-4,CDK5	2017	Breast cancer (HRpositive,HER2negetive)
		Imbruvica	Ibrutinib	BTK	2013	Chronic lymphocytic leukemia, Mantle cell lymphoma
		Perjeta	Pertuzumab	HER2	2012	Breast Cancer
		Xolair	Omalizumab	IgE	2003	Asthma
		Orencia	Abatacept	CD80/CD86	2005	RA
		Soliris	Ecolizumab	Com. C5	2007	PNH
		Stelara	Ustekinumab	IL-12/IL-23	2013	Psoriatic arthritis
		Tysabri	Natalizumab	alpha-4 integrin	2006	MS
Ophthalmic	**6.58**	Lucentis	Ranibizumab	VEGF	2006	Wet AMD
		Eylea	Aflibercept	VEGF	2011	Wet AMD
Antiviral	**1.40**	Synagis	Palivizumab	RSV	1998	RSV

Abbreviations: RA, rheumatoid arthritis; RSV, respiratory syncytial virus; NHL, non-Hodgkin's lymphoma; TNF, tumor necrosis factor; PNH, paroxysmal nocturnal hemoglobinuria; AMD, age-related macular degeneration; HR, Hormone Receptor. (pharmalive, http//::pharmalive.com/ accessed June 2018), (pmlive, http//::pmlive.com/ accessed June 2018)

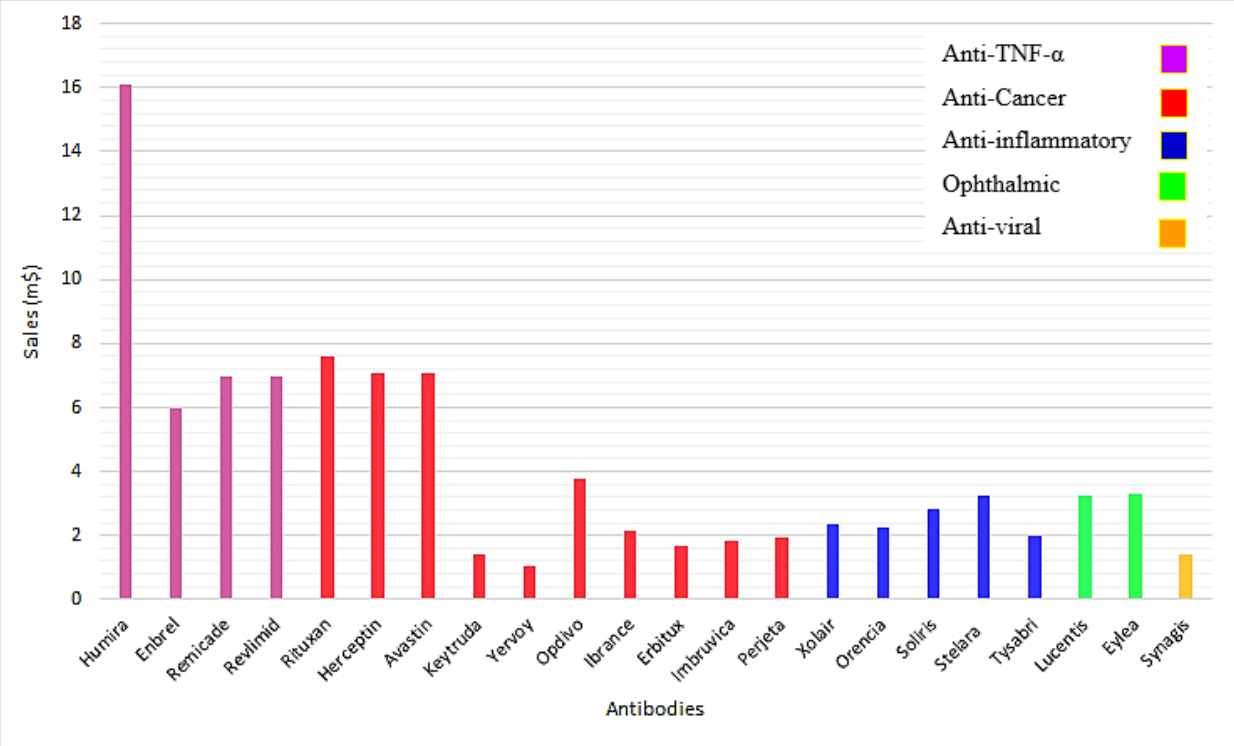

Figure 1. Comparison of marketed mAbs sales in 2016.

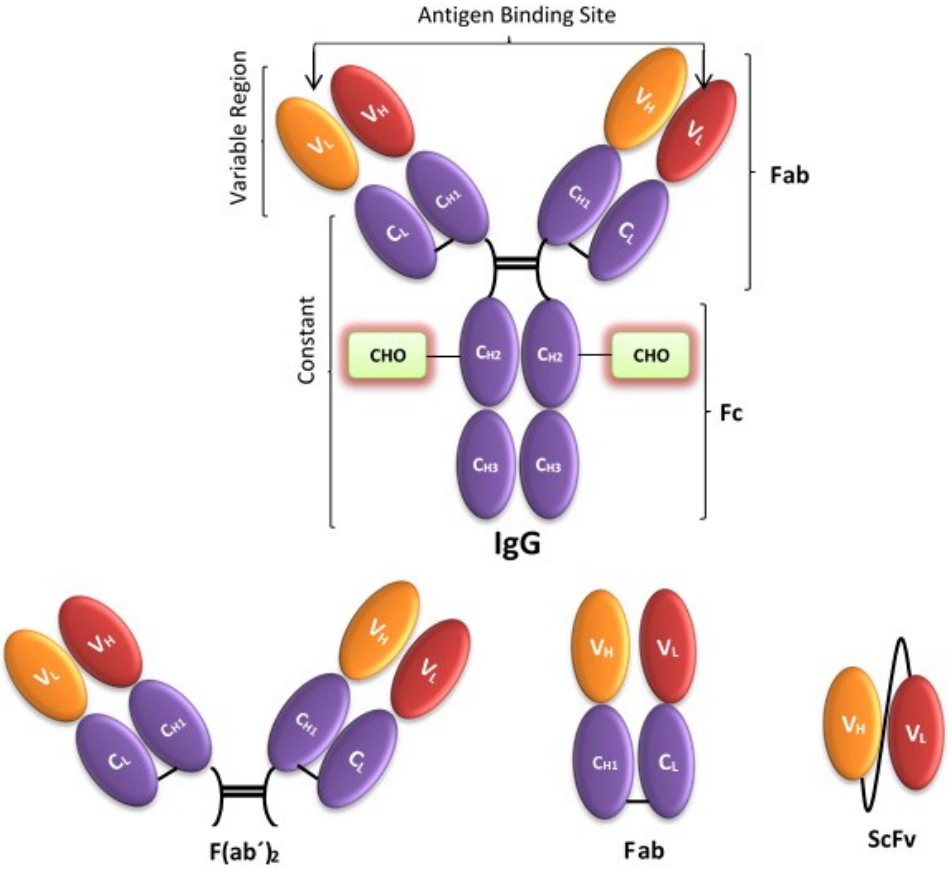

Figure2. Structures of a full-size antibody and antibody fragments. Nomenclature and structural features of antibody fragments Fc, Fab, F(ab′)$_2$, and scFv compared to a full size immunoglobulin (IgG). Recombinant antibodies (rAbs) are shown as monovalent as well as bivalent and bispecific scFvs, combined with linkers where required.

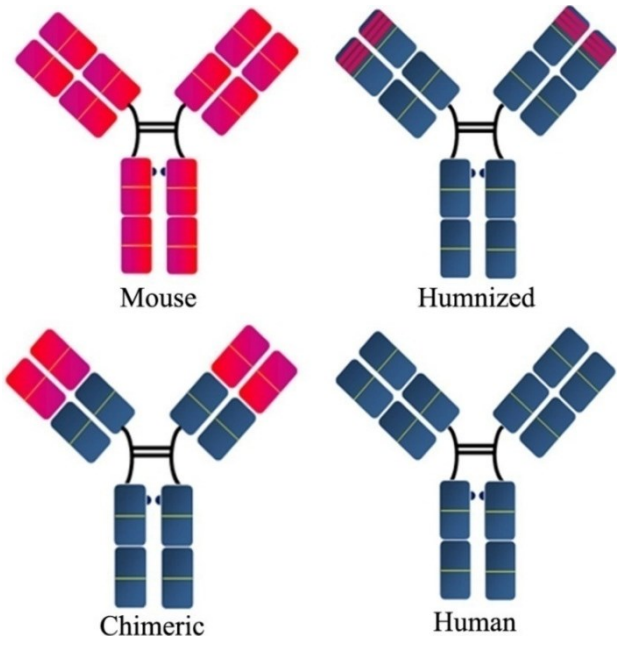

Figure 3. Antibody engineering for humanization.

Table 2. Therapeutic Fab fragments

Phase	Name	Antigen	Company	Number of clinical trials
Approved	Ranibizumab	VEGF-A	, NovartisGenentech	302
	Certolizumab Pegol	TNF-alpha	, Celltech, Dermira, UCB, XomaAstellas	90
	Abciximab	Integrin αIIbβ3	, Isu Abxis, LillyCentocor Ortho	62
	Nofetumomab Merpentan	EpCAM	, NeoRxBoehringer	
Phase III	Onartuzumab	cMet	Genentech	9
	Lampalizumab	Complement Factor D	Genentech	7
Phase II	Dapirolizumab Pegol	CD40L	, UCBBiogen	3
	Alacizumab Pegol	VEGFR-2	UCB	1
Phase I	Citatuzumab Bogatox	EpCAM	, ViventiaUniv. Zurich	1

(Tabs, http://tabs.craic.com/, accessed May 2018).

Table 3. Therapeutic scFv fragments

Phase	Name	Antigen	Company	Number of clinical trial
Approved	Blinatumomab	CD-19, CD-3	Amgen, Medimmun, MicrometAG	38
Phase III	Brolucizumab	VEGF-A	, ESBATech, NovartisDelenex	7
	Pexelizumab	C5	Alexion	3
Phase II	Moxetumomab Pasudotox	CD22	Medimmune	15
	Vobarilizumab	IL-6R	, AblynxAbbvie	6
	Esba 1622	TNFα	ESBATech	2
	Sloan-Kettering Patent Anti-B7H3	B7-H3	Sloan-Kettering	3
	Oportuzumab Monatox	EpCAM	Viventia	3
Phase I/II	Efungumab	HSP90	NeuTec, Novartis	3
	Radretumab	Fibronectin	Bayer, Philogen	1
Phase I	Cirmtuzumab	ROR 1	U.California	3
	Duke D2C7	EGFR	Duke U.	1

(Tabs, http://tabs.craic.com/, accessed May 2018)

Table 4. Therapeutic SMIPs

Phase	Name	Antigen	Company	Number of clinical trials
Phase II	SBI-087	CD-20	Pfizre, Trubion	4
	Otlertuzumab	CD-37	Aptevo, Emergent, Facet, Trubion	4

Table 5. Therapeutic nanobodies

Phase	Name	Antigen	Company	Number of clinical trials
Phase III	Caplacizumab	vWF	Ablynx	4
Phase II	ALX-0761	, IL-17FIL-17	, Merck SeronoAblynx	2
	ALX-0681	vWF	Ablynx	1
Phase I	ALX-0171	RSV	Ablynx	3
	PF-05230905	TNF-alpha	, PfizerAblynx	1
	ALX-0651	CXCR4	Ablynx	1
	TAS266	DR5	, NovartisAblynx	1
	KN035	PD-1	Alphamab	1
	ALX-0141	RANKL	, EddingpharmAblynx	
	BI 1034020	Amyloid beta	, BoehringerAblynx	

(Tabs, http://tabs.craic.com/, accessed May 2018).

Table 6. Therapeutic ADCs

Phase	Name	Antigen	Company	Number of clinical trial
Approved	Brentuximab Vedotin	CD-30	Millennium, seattle Genetics	113
	Gemutuzumab Ozogamicin	CD-33	PDL, Pfizer, wyeth	55
	Inotuzumab Ozogamicin	CD-22	Pfizer, UCB, wyeth	28
	Trastuzumab Emtansine	HER2/neu	Genentech, Immunogen, PDL, Roche	27
Phase III	Trastuzumab Deruxtucan	HER2/neu	Daiichi Sankyo	9
	Mirvetuximab Soravtansine	FRA	ImmunoGen	6
	Enfortumab Vedotin	Nectin-4	Agensys, Astellas, Seattle Genetics	6
	Vadastuximab Talirine	CD-33	Seattle Genetics	5
	Depatuxizumab Mafodotin	EGFR	Abbvie, seattle Genetics	5
	Syd985	HER2/neu	Synthon	2

(Tabs, http://tabs.craic.com/, accessed May 2018).

Table 7. Therapeutic radiolabeled antibodies

phase	Name	Antigen	Company	Number of clinical trial
Approved	Ibritumomab tiuxetan	CD-20	Biogen, CTI Biopharma, spectrum	81
	Tositumomab	CD-20	GSK	28
	Capromab pendetide	PSMA	Cytogen, EUSA	2
	Votumumab	CTAA16.88	Organon Technika	
Phase III	Clivatuzumumab tetraxetan	MUC1	Immunomedics	5

(Tabs, http://tabs.craic.com/, accessed May 2018).

Table 8. Therapeutic Phage display derived antibodies

Name	Target	Company	Phase
Avelumab (Bavencio®)	PD-L1	Merck serone, Pfizer	Approved (2017)
Guselkumab (Tremfya®)	IL-23p19	Centocore ortho	Approved (2017)
Necitumumab (Portrazza®)	EGFR	ImClone	Approved (2015)
Adalimumab (Humira®)	TNF-α	Abbott	Approved (2002)
Belimumab (Benlysta®)	BAFF	GSK, HGS	Approved (2011)
Ramucirumab (Cyramza®)	VEGFR-2	Imclone	Approved (2014)
Gantenerumab	Amyloid-β	Morphosys, Roche	3
Ganitumab	IGF-1R	Amgen	
Gevokizumab	IL-1β	XOMA	
Beriakinumab	IL-12	Abbott, CAT	
Tralokinumab	IL-13	AstraZeneca, Medimmune	
AMG386	Angiopoietin2	Amgen	
MED18968	IL-1R1	Medimmune	2
CDX-3379	HER3	Bulldog pharma, Celldex, Kolltan	
Otilimab	GM-CSF	GSK, Morphosys	
Opicinumab	LINGO-1	biogen	
Cixutumumab	IGF-1R	Imclone	
Seribantumab	HER3	Merrimack, Sanofi	
Anetumab Ravtansine	Mesothelin	Bayer, Immunogen, Morphosys	
Fresolimumab	TGF-β	CAT, Genzyme	
Mapatumumab	TRAIL-R1	HGS	
Guselkumab	IL-23	Centocor Ortho, Morphosys	
Drozitumab	DR5	Genentech	
Namilumab	GM-CSF	Micromet, Nycomed, Takeda	
Duligotuzumab	EGFR, HER3	Genentech, Roche	
Carlumab	MCP-1	Centocor Ortho, J&J, Morphosys	
Mavrilimumab	GM-CSF2RA	CAT, CSL, Medimmune	
BIIb033	LINGO-1	Biogen Idec	
BHQ880	DKK-1	Morphosys, Novartis	
BI-505	ICAM-1	BioInvent	
Orticumab	oxLDL	BioInvent, Genentech	
NI-0801	IP-10	NovImmune	
Adecatumumab	EpCAM	Merck Serono, Micromet	