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Review Article

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Screening of Monoclonal Antibodies for Cancer Treatment

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Abstract

With the rapid development of cancer treatment using monoclonal antibodies (mAbs), the screening process of suitable biologics and indications attracts much attention. A general definition of 'screening' in the biopharmaceutical industry includes three aspects: the appropriate biologics for the specific cancers, the appropriate indications for the specific biologics and the promising biologic candidates from the pool at the pre-clinical drug discovery stage. Effective screening strategies in the biopharmaceutical industry are crucial to accelerate the drug commercialization process and select the effective biologics for patients. The current status of commercial mAbs and the global pharmaceutical market was briefly reviewed. The mechanism of commercial mAbs and the indications, as well as the current technologies for mAbs screening in the new drug discovery and cell line development stages were systematically reviewed, with an aim as a beneficial reference for screening high-quality mAbs, appropriate indications with efficient technologies.

Keywords

Screening; Cancer treatment; Biomarker; Monoclonal antibodies

Abbreviations

ADC: Antibody Drug Conjugate; BLA: Biologic License Application; CMC: Chemistry Manufacturing and Control; ELISA: Enzyme-Linked Immunosorbent Assay; FMAT: Fluorometric Microvolume Assay; FACS: Fluorescence-Activated Cell Sorting; MAb: Monoclonal Antibody; M-M: Michaelis-Menten; MWC: Monod-Wyman-Changeux; QbD: Quality by Design

Introduction

Cancer is the global leading cause of death [1]. It is featured as unregulated cell division and growth [2]. Caused by genic mutation or gene expression disorder, abnormal metabolism can be observed within cells [3]. While gene therapy is still away from well accepted by FDA, monoclonal antibodies (mAbs), as one of the major parts of biologics, are currently widely recognized drugs for conservative cancer treatment. The mAbs are antibodies made by identical cells, which are all derived from a unique parent immune cell [4,5]. The history of mAbs can be traced back to 1975 when recombinant DNA technology was applied to antibody design [6]. The first mAb approved by FDA was OKT3 in 1986 [7] though it took almost three decades to the current 'golden age' of cancer therapies using mAbs [8]. Currently, around one hundred commercial mAbs are available in the global market.

The biopharmaceutical industry is regarded, as a matter of fact, a high risk and high revenue industry. On average, it takes $1.2 to $4 billion and 10 to 12 years for a biologic candidate to be approved and enter the market from the discovery stage. From the risk point of view, less than 0.1 % of the biologic candidates before CMC stages are able to enter into Phase I. Among those biologics, 60 % fail to pass Phase Ⅱ, while there's another 50% failure risk at Phase Ⅲ the clinical stage. In addition, there are significantly higher risks at earlier new drug discovery stages. Thus, the efficient and successful screening of mAb candidates and corresponding indications is crucial. The word "screening" in the biopharmaceutical industry refers to three aspects:

Screening of drug or biologic candidates for specific diseases;

Screening the potential indications for specific drugs or biologics; and

Screening of promising drug or biologic candidates from the pool in the pre-clinical stage.

Undoubtedly, all the aspects are definitive for the destiny of one biologic candidate.

In this work, the current commercial mAbs and the recognized biomarkers were systematically reviewed. The principles, criteria, modeling and detection methods of biologics screening were presented and compared. This review aims at providing comprehensive screening information for cancer treatment, which is potentially beneficial for research institutes, pharmaceutical companies and patients.

Mechanism

It is known that one distinctive characteristics of cancer from other diseases is that immune cells have difficulties to distinguish tumor cells from normal cells [5]. Therefore, a process that can either assist the immune cells to identify the tumor cells, or stimulate the immune cells to be more active should exhibit potential for cancer treatment. MAbs, which are designed for distinguishing the biomarkers abnormally expressed on tumor cells or specifically expressed by immune cells, are recognized as promising biologics to annihilate tumor cells. Though the exact metabolic details of how mAbs work is awaiting better understanding, the general mechanism typically falls into two categories:

mAbs distinguish and bind the biomarkers abnormally expressed by the tumor cells, helping the immune cells to target these cells. For example, trastuzumab, which was designed to target the biomarkers HER2, is a representative commercial mAb for breast cancer.

The immune cells are activated by mAbs to attack the tumor cells. Successful commercialized examples, such as nivolumab and pembrolizumab which target PD-1 and PD-L1 biomarkers; respectively, were designed based on such mechanism.

Owing to limited understanding of mammalian cell metabolism, limited biomarkers have been detected and only with parts of them have been used for mAbs design. Table 1 listed 43 recognized

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biomarkers that have been successfully used for commercial mAb design. Indications that exhibited abnormal expression of these biomarkers have been well studied. The one-to-one correspondence shown in the table aims to help narrow down the screening scope of the mAbs and indications, as well as predict the clinical results and control the quality of the designed protein therapeutics, which is in compliance with the Quality by Design (QbD) principles. This information may help biopharmaceutical industry to make decisions on biologics design at early discovery stage or on indication selection at clinical stages

Table 1: The recognized biomarkers for biologics and the approved indications.

Antigen Biomarkers	Indications	References
α-4 integrin	Multiple sclerosis	[39]
BLyS	Systemic lupus erythematosus	[40]
CCR4	Relapsed or refractory adult T-cell leukemia/lymphoma	[41]
CD3	Transplant rejection, organ	[42]
CD6	Psoriasis, Arthritis, rheumatoid	[43]
CD19	Precursor B-cell acute lymphoblastic leukemia	[44]
CD20	Relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and multiple sclerosis	[45]
CD30	Hodgkin lymphoma, and anaplastic large-cell lymphoma	[46,47]
CD38	Multiple myeloma	[48]
CD52	B-cell chronic lymphocytic leukemia	[49]
Clostridium difficile toxin B	Prevent recurrence of Clostridium difficile infection	[50]
Complement component 5	Paroxysmal nocturnal hemoglobinuria	[51]
CTLA-4	Metastatic melanoma	[52]
Dabigatran	Emergency reversal of anticoagulant dabigatran	[53]
EGFR	Metastatic colorectal carcinoma, and metastatic squamous non-small cell lung carcinoma	[54,55]
EpCAM	Malignant ascites, multiple cancers	[56]
F protein of RSV	Respiratory syncytial virus	[57]
Ganglionside P3	Multiple cancers	[58]
GD2	Pediatric high-risk neuroblastoma	[59]
GPIIb/IIIa	Percutaneous coronary intervention	[60]
HER2	Metastatic breast cancer	[61]
IgE	Moderate to severe persistent asthma	[62]
IL12	Plaque psoriasis	[63]
IL23	Psoriatic arthritis, plaque psoriasis, and crohn's disease	[63,64]
IL17A / IL17RA	Plaque psoriasis	[65]
IL1B	Cryopyrin-associated periodic syndrome	[66]
IL2R	Multiple sclerosis	[67]
IL2RA	Prophylaxis of acute organ rejection in renal transplant	[68]
IL4RA	Atopic dermatitis	[69]
IL5	Severe asthma	[70]
IL6	Multicentric Castleman's disease	[71]
IL6R	Rheumatoid arthritis, and systemic juvenile idiopathic arthritis	[72]
IL8	Psoriasis	[73]
integrin receptor	Ulcerative colitis, crohn's disease	[74]
PCSK9	Heterozygous familial hypercholesterolemia, and refractory hypercholesterolemia	[75]
PD-1	Metastatic melanoma, and metastatic squamous non-small cell lung carcinoma	[76-78]
PD-L1	Urothelial carcinoma, metastatic non-small cell lung cancer, and metastatic Merkel cell carcinoma	[79,80]
PDGFRA	Soft tissue sarcoma	[81]
Protective antigen of Bacillus anthracis / Anthrax toxin	Inhalational anthrax	[82]
PSMA	Diagnostic imaging agent in newly diagnosed prostate cancer or post-prostatectomy	[83]
RANKL	Postmenopausal women with osteoporosis	[84]
SLAMF7	Multiple myeloma	[85]
TNF	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, crohn's disease, ulcerative colitis, and plaque psoriasis	[86,87]
TNF α	Crohn's disease	[86]
VEGF	Metastatic colorectal cancer	[88,89]
VEGFR1	Wet age-related macular degeneration	[90]
VEGFR2	Wet age-related macular degeneration, and gastric cancer	[89,91]

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Design Technologies Selection

Unlike small molecule drugs that can directly enter the cells and interrupt the metabolism with poor capacity of discernment, mAbs are mild and impact indirectly on the metabolic pathways with good targeting ability on tumor cells. To improve the efficacy as well as avoid patent dispute, several advanced design technologies have been applied to improve mAb performance. The characteristics of different biologic design technologies are briefly summarized in Table 2, which were further discussed as follows:

Antibody drug conjugate

Antibody drug conjugate (ADC) technology is one improvement strategy, which allows small molecules conjugated on an antibody molecule [9]. Via the excellent targeting ability of the protein therapeutics, the small molecule is able to directly interrupt the metabolic pathways of tumor cells with significantly improved capacity of discernment [10]. Nevertheless, challenges that ADC faces in manufacturing include:

Unstable expression level due to the variety of the link structure, especially, when the link consists of unnatural amino acids.

Low downstream yield due to the added purification steps after the conjugation of the small molecule drug to the protein molecule.

Bi-specific

Bi-specific antibody technology is another option for better biologics design. It allows one biologic molecule to recognize two biomarkers simultaneously. Theoretically, the combination of the two biomarkers should fall into one of the three types: both on tumor cells, both on immune cells and one on tumor cell and one on immune cell. Nevertheless, the third design is the major preference in the industry. By this design, the immune cells can be effectively activated, then rapidly and adequately attack the tumor cells *in situ* [11]. This makes the protein therapeutics exhibit synergistic effect compared to using two or more independent mAbs. This technology has the potential to enhance the efficacy while reducing the biologics dosage and side effects. However, bi-specific molecules also have their drawbacks in manufacturing, such as:

Low expression level during cell culture due to the high risks of chain mispairing and protein aggregation

Low downstream separation efficiency because of the similar physicochemical properties of the mis-pairing molecules.

Combined medication

Combined medication technology is an alternative choice to improve the efficacy. The joint usage of two or more biologics or biologics with small molecule drugs has the potential to exhibit synergistic effect on tumor cells, because different biologics and/or drugs may impact on different metabolic pathways. This technology provides one strategy to screen new indications for existing mAbs avoiding huge investment for new drug design and application. This strategy, however, has some disadvantages for commercialization, including:

Significantly high cost in manufacturing, factory operation, storage and supply chain management for different products/molecules;

Difficulties in maintaining acceptable stability of different biologics and/or drugs if in one formulation;

Inconvenience and high cost in drug delivery if different formulations were used for different biologics/drugs.

Commercial mAbs

With increasing attention focused on mAbs, large amounts of investment have been attracted into the biopharmaceutical industry aiming at biologics commercialization. The study of the current commercial mAbs can benefit the biopharmaceutical industry, especially those start-up companies focusing on biosimilars, to rapidly follow up the recent trends and successfully screen the promising molecules. Figure 1 lists the top 10 best-selling mAbs in 2016 and their global annual sales in the recent three years. The data were obtained from the annual reports of these enterprises. Little ranking change was observed in Figure 1, except Opdivo was regarded as a dark-horse in the recent years due to the excellent performance of this anti-PD-1 mAb. Humira, Remicade and Rituxan kept the top three best-selling for the recent three years (Figure 1), bringing considerable revenue to Abbvie, Johnson & Johnson and Roche, respectively. In 2016, the total sales of these 10 mAbs were $ 61.2 billion, which is almost 70% of the whole global antibody market. The global oligopolistic market landscape may not be broken in the next few years due to limited number of validated biomarkers and long period of time for one biologic product to be commercialized. A list of biomarkers with corresponding commercial mAbs and patent holders were shown in Table 3. The mAbs and patent information was filtered manually from an open source tool called 'Citeline Service' before July 16th, 2017. Most of the biosimilars currently in research were designed based on these listed mAbs. This table also includes the major biomarkers for ADC and bi-specific antibodies, which is a trend for biologic design in the next few years.

mAbs Screening Methods

Screening criteria

After the designing of the mAbs based on the mechanisms discussed above, there could still be thousands of candidates available. This will be followed by two major screening processes to obtain best performed antigen-specific antibodies from the pool, which are:

Table 2: Different biologic design technologies with their characteristics.

Design Technology	Characteristics			
	Manufacturing Cost	Expression (g/L)	Purification Recovery (%)	Efficacy
Conventional	*	2-10	60-80	Normal
ADC	**	0.4-5	50-70	Small and Large Molecule
Bi-specific	**	0.5-3	<20	Tumor and Immune Cells (Synergistic)
Combined Medication	***	Depends	Depends	Synergistic Effect

Note: The number of '*' indicates the cost of manufacturing and factory operation. More '*' means higher cost

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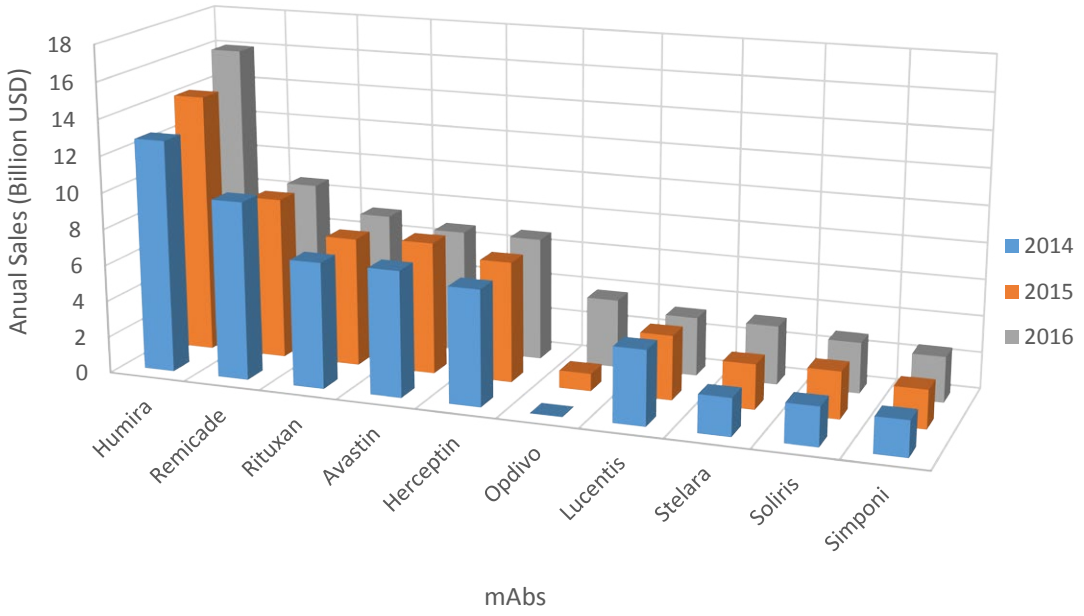

Figure 1: Top 10 best-selling mAbs in 2016 and their global annual sales in the recent three years. Different colors refer to the selling data in different years.

Table 3: Commercial biologics and the corresponding antigen biomarkers, patent holders and the biologic license application (BLA) approved dates.

Antigen Biomarkers	Biologics	Patent Holders	BLA Approved
α-4 integrin	Tysabri	Biogen Idec	11/23/2004
BLyS	Benlysta	Human Genome Sciences	03/09/2011
CCR4	Poteligeo	Amgen	03/30/2012, Japan
CD6	Alzumab	Center of Molecular Immunology	01/07/2013, India
CD19	Blincyto	Amgen	12/03/2014
CD20	Zevalin	Spectrum Pharmaceuticals	02/19/2002
	Gazyva	Genentech	11/01/2013
	Ocrevus		03/28/2017
	Rituxan		10/26/2009
	Arzerra	Glaxo Grp	11/26/1997
CD30	Adcentris	Seattle Genetics	09/19/2011
CD38	Darzalex	Janssen Biotech	11/16/2015
CD52	Campath	Genzyme	05/07/2001
	Lemtrada		
Clostridium difficile toxin B	Zinplava	Merck	10/21/2016
Complement component 5	Soliris	Alexion	03/16/2007
CTLA-4	Yervoy	Bristol-Myers Squibb	03/25/2011
dabigatran	Praxbind	Boehringer Ingelheim	10/16/2015
EGFR	Erbitux	ImClone Systems	02/12/2004
	Portrazza	Eli Lilly	11/24/2015
	Vectibix	Amgen	09/27/2006
	BIOMAB EGFR	Biocon	11/12/2007, India
	Theraloc	Oncoscience	11/12/2003, EMEA
	CIMAher	Center of Molecular Immunology	11/18/1994, Cuba
CD3	Ior-t3[a]	Center of Molecular Immunology	05/15/1996, Cuba
EpCAM	Removab	Fresenius, Swedish Orphan Biovitrum, Neovii Biotech	01/27/2011, EMEA
F protein of RSV	Synagis	Med-Immune	06/19/1998
Ganglionside P3	Vaxira	Recombio, Laboratorio Elea, Innogene Kalbiotech	12/31/2012, Cuba
GD2	Unituxin	United Therapeutics	03/10/2015
GPIIb/IIIa	ReoPro	Centocor	12/22/1994

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HER2	Kadcyla	Genentech	02/22/2013
	Perjeta		06/08/2012
	Herceptin		09/25/1998
IgE	Xolair		06/20/2003
IL12 IL23	Stelara	Centocor	09/25/2009
		Janssen Biotech	09/23/2016
IL17A	Taltz	Eli Lilly	03/22/2016
	Cosentyx	Novartis	01/21/2015
IL17RA	Siliq	Valeant	02/15/2017
IL1B	Ilaris	Novartis	06/17/2009
IL2R	Zinbryta	Biogen	05/27/2016
IL2RA	Simulect	Novartis	05/12/1998
	Zenapax	Roche	12/10/1997
IL4RA	Dupixent	Regeneron	03/28/2017
IL5	Nucala	GlaxoSmithKline	11/04/2015
	Cinqair	Teva	03/23/2016
IL6	Sylvant	Janssen Biotech	04/23/2014
IL6R	Actemra	Genentech	01/08/2010
			10/21/2013
	Kevzara	Sanofi	02/01/2017, Canada
IL8	ABCream[a]	Yes Biotech	07/13/2004, China
Integrin receptor	Entyvio	Takeda	05/20/2014
PCSK9	Praluent	Sanofi Aventis	07/24/2015
	Repatha	Amgen	08/27/2015
PD-1	Opdivo	Bristol-Myers Squibb	12/22/2014
			03/04/2015
	Keytruda	Merck	09/04/2014
PD-L1	Tecentriq	Genentech	05/18/2016
			10/18/2016
	Bavencio	EMD Serono	03/23/2017
	Imfinzi	AstraZeneca	05/01/2017
PDGFRA	Lartruvo	Eli Lilly	10/19/2016
Protective antigen of *Bacillus anthracis*	Raxibacumab	Human Genome Sciences	12/24/2012
Protective antigen of the Anthrax toxin	Anthem	Elusys Therapeutics	03/18/2016
PSMA	ProstaScint	Cytogen	10/28/1996
RANKL	Prolia	Amgen	06/01/2010
	Xgeva		
SLAMF7	Empliciti	Bristol-Myers Squibb	11/30/2015
TNF	Humira	Abbvie	12/31/2002
	Amjevita	Amgen	09/23/2016
	Cimzia	UCB (company)	04/22/2008
	Simponi	Centocor	04/24/2009
	Simponi Aria	Janssen Biotech	07/18/2013
	Renflexis	Samsung Bioepis	04/21/2017
	Inflectra	Celltrion Healthcare	04/05/2016
TNFα	Remicade	Centocor	08/24/1998
VEGF	Avastin	Genentech	02/26/2004
VEGFR1	Lucentis		06/30/2006
VEGFR2	Cyramza	Eli Lilly	04/21/2014

Note: "α" refers that it is the generic name of the biologics instead of the commercial name

If the BLA was not approved by FDA, the biologics was specified with its approved location or organization

Binding screening including specificity [12] and affinity [13]

Functional screening including cell growth, proliferation, apoptosis, endothelial tube formation, etc. [14]

While the functional assays are based on different disease models, the binding screening assays are universal in biopharmaceutical industry.

Specificity is the ability of the antibody binding to its cognate antigen and not to other targets. Affinity is the characteristic of antibody-antigen binding strength. These two criteria are crucial to ensure the efficacy, while good specificity can minimize the side-effects and good affinity is well preferred to reduce the drug dosage.

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Functional activities are often the most significant characteristics of an antibody, including ability to deliver a toxin, antagonist activity, partial and full agonist activity, etc. These activities are often related to the protein allostery via the antigen-antibody specific binding [15,16].

Screening models

To quantitatively evaluate the above criteria, kinetic modeling strategies are usually applied [17]. Known models include Michaelis–Menten (M-M) model [18], Hill Equation [19-22], different types of Binding Models [23-25], Morpheein Model, Monod–Wyman–Changeux (MWC) model [26], Mechanistic kinetic description strategy [27] and empirical models derived from software such as JMP [28]. Nevertheless, different models have their advantages and drawbacks and none is appropriate in all situations.

M-M Equation has been the preferred modeling strategy in many enzyme kinetic studies due to its convenience for calculation [20,29]. M-M equation is only applicable for single domain enzymes or non-interactive oligomeric enzymes. However, most of the enzymes involved in metabolism are oligomeric. By introducing the Hill Coefficient, better simulation results can usually be generated than those using the M-M Equation [30]. However, kinetic parameters lose their mechanistic information due to the forcible introduction of the empirical Hill Coefficient. This shortcoming makes the Hill Equation more appropriate for empirical data manipulation in industry instead of mechanism research.

The Binding Models are extensions of the M-M and Hill Equations when there are more than two, typically three, molecules involved in one reaction. They were derived based on the ordered/random molecule collision process and the second order elementary reaction mechanism [31]. These models considered multiple reaction processes simultaneously. In addition, the substrate-enzyme binding during the subsequent coenzyme and substrate binding processes for oligomeric enzymes with more than two active subunits can be important [24,31].

Morpheein Model, MWC model and Mechanistic kinetic description strategy are three modeling methods to mechanistically illustrate the molecular kinetic process by taking the interactive nature of one molecule with substrate and/or inhibitors into consideration [27,32]. More parameters are involved in the modeling which typically requires much more experimental data to support. Thus, these time- and cost-consuming methods are not the first choice in most commercial activities.

Table 4 presented a summary of the above models with their typical mathematic formula and applicable scopes. In the current biopharmaceutical researches, M-M Model and Hill Equation are the favored modeling strategies for biologics screening, due to their simplicity. While Morpheein Model, MWC Model and Mechanistic kinetic description strategy are able to well describe the kinetic properties of the molecular interactions, if the kinetic mechanism is critical to understand the biologics. Different types of Binding Models can be applied for multiple molecules involved reactions, such as bi-specific antibody involved reactions. Different strategies are selectively used based on the study purposes and research limitations.

Binding screening assays

Enzyme-linked Immunosorbent assay (ELISA) is one of the most popular platform technologies to identify antigen-antibody complex and both qualitatively and quantitatively evaluate the binding strength. The basic principle of ELISA based on radioimmunoassay techniques dates back top 1941 [33] and the exact method was created in 1971 [34]. Currently, it is a major detection method for biologics screening, because it is simple, quick, sensitive, specific and high-throughput [35]. Another screening technology is surface Plasmon resonance (SPR) biosensor [36]. As a gold standard for real-time and label-free monitoring technology of bimolecular interactions,

Table 4: Reported kinetic modeling strategies for molecular interaction study.

Type	Formula	Parameter number	Applicable Scope	References
M-M Model	$r = \frac{kES}{K+S}$	2	non-interactive oligomeric or mono- molecular interactions	[18,23]
Hill Equation	$r = \frac{kES^{n_{Hill}}}{K+S^{n_{Hill}}}$	3	Data manipulation for all molecular interactions	[22,92]
MWC model	$r = ES\left(\frac{\frac{k_T}{k_R K_R}\left(1+\frac{S}{K_R}\right)^{n-1} + \frac{\alpha K_e}{K_R}\left(1+\frac{\alpha S}{K_R}\right)^{n-1}}{\left(1+\frac{S}{K_R}\right)^{n} + K_e\left(1+\alpha\frac{S}{K_R}\right)^{n}}\right)$	5	Oligomeric molecular interactions	[32,93]
Morpheein Model	$r = \frac{k_1 f_1 ES}{K_1+S} + \frac{k_2(1-f_1)ES}{K_2+S}$ s	5	Oligomeric molecular interactions	[94]
Random Binding Model	$r = \frac{kEAB}{K_A K_B + K_A B + K_B A + AB}$	3	Three molecule involved interactions	[25,95]
Ordered Binding Model	$r = \frac{kEAB}{K_A K_B + K_B A + AB}$	3	Three molecule involved interactions	[25,96]
Mechanistic Kinetic Description	$r = \frac{4kE[S]}{K}\frac{1-\beta+\beta\left(1+\frac{[S]}{\alpha K}\right)^{n-1}}{1-\alpha+\alpha\left(1+\frac{[S]}{\alpha K}\right)^{n}}$	5	Oligomeric molecular interactions	[27,94]

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it is able to determine the thermodynamic and kinetic properties of specific molecular interactions [37].

While ELISA and SPR are the common techniques for extracellular or cell-free antigen-antibody binding detection, fluorometric micro volume assay (FMAT) and fluorescence-activated cell sorting (FACS) are well-developed methods for on-cell or native binding screening [38]. The working principle based on antibodies binding to the antigen expressed on cell surface and the immunoglobulin constant region of the antibodies is detected by a fluorescently conjugated secondary antibody. As a high-throughput cell-based assay in the hybridoma screening, FMAT and FACS based technologies has significantly improved the screening efficiency and success probability.

Conclusion

Though cancers are not incurable disease due to the rapid technology development, they are still a leading threat for human health. In this paper, the recent trends and technologies of mAb development are comprehensively reviewed. The information of biomarkers, indications, commercial mAbs and the pattern status were systematically reviewed, which is beneficial for biopharmaceutical industry, research institutes and patients to make decisions. This review aims at providing a comprehensive understanding of the biomarker, indication and mAb screening strategies, which may promote further advancements in new drug discovery, novel indications of exiting drugs, as well as joint usage of mAbs and other cancer treatment methods.

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Declaration of Interest

The authors declare no financial or commercial conflict of interest.

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