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Mini Review

The emergence of AntibodyPlus: the future trend of antibody-based therapeutics

Yong Zhu[1,*], Shawn Shouye Wang[2,3], Zhaohui Sunny Zhou[4,5] and Mitchell Ho[6,7]

[1]Consultant for Biopharma Companies, Anaheim, CA 92808, USA , [2]Chinese Antibody Society, 955 Massachusetts Ave, #276, Cambridge, MA 02139, USA , [3]CMC Management, WuXi Biologics, 1 Cedarbrook Drive, Cranbury, NJ 08512, USA , [4]Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115-5000, USA , [5] Barnett Institute for Chemical and Biological Analysis, Northeastern University, Boston, MA 02115-5000, USA , [6]Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA , and [7]Antibody Engineering Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

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ABSTRACT

To date, close to 100 canonical monoclonal antibody drugs have been approved by the FDA; furthermore, a number of antibody-derived therapeutics in nontraditional formats have reached late development stages and the market, and many more are being evaluated in early-stage development. To better reflect this trend and to set up a framework for forward thinking, we herein introduce the concept of AntibodyPlus, embracing any therapeutics with an antibody component. AntibodyPlus therapeutics contain effector modules, in the form of small molecules, nucleic acids, proteins or even cells, to enhance their therapeutic activities against cancer, virus infection and other diseases. In this short review, we discuss historic perspective and current status of therapeutic antibody development, and the scope and categories of AntibodyPlus therapeutics along with their advantages, applications and challenges. We also present several examples that highlight their design principles, potentials and future trends.

Statement of Significance: Statement of Significance: With more nontraditional antibody-based or antibody-containing therapeutics emerging from late-stage development into the market, we herein formally introduce the all-embracing concept of AntibodyPlus and discussed its scope, advantages and applications, setting up a foundation for further discussion in the field and to inspire more innovative strategies in developing antibody therapeutics.

KEYWORDS: Antibody therapeutics; noncanonical antibody; hybrid modality; antibody conjugates; antibody-Plus

In April 2021, the FDA approved the 100th monoclonal antibody drug—the anti-PD-1 drug dostarlimab from GSK for the treatment of endometrial cancer [1]. This is an important milestone—it took us 35 years to go from 1 to 100, dramatically expanding our arsenal for many difficult-to-treat diseases. As of 31 March 2022, the number of antibody-based drugs approved by the FDA has reached 111, or 117 if cell-based therapeutics with an antibody component such as chimeric antigen receptor (CAR) are also included in the list [2] (Fig. 1).

As observed from the historical trend, most of the antibody drugs approved in the early days are canonical or based on full-length IgG. In recent years, more and more therapeutic antibodies are of nontraditional formats: single-domain antibody fragments such as nanobody (e.g., V_H, V_HH, V_{NAR}) and single-chain fragment variable

*To whom correspondence should be addressed. Yong Zhu, Consultant for biopharma companies, Anaheim, CA 92808, USA. Email: yong.zhu@gmail.com

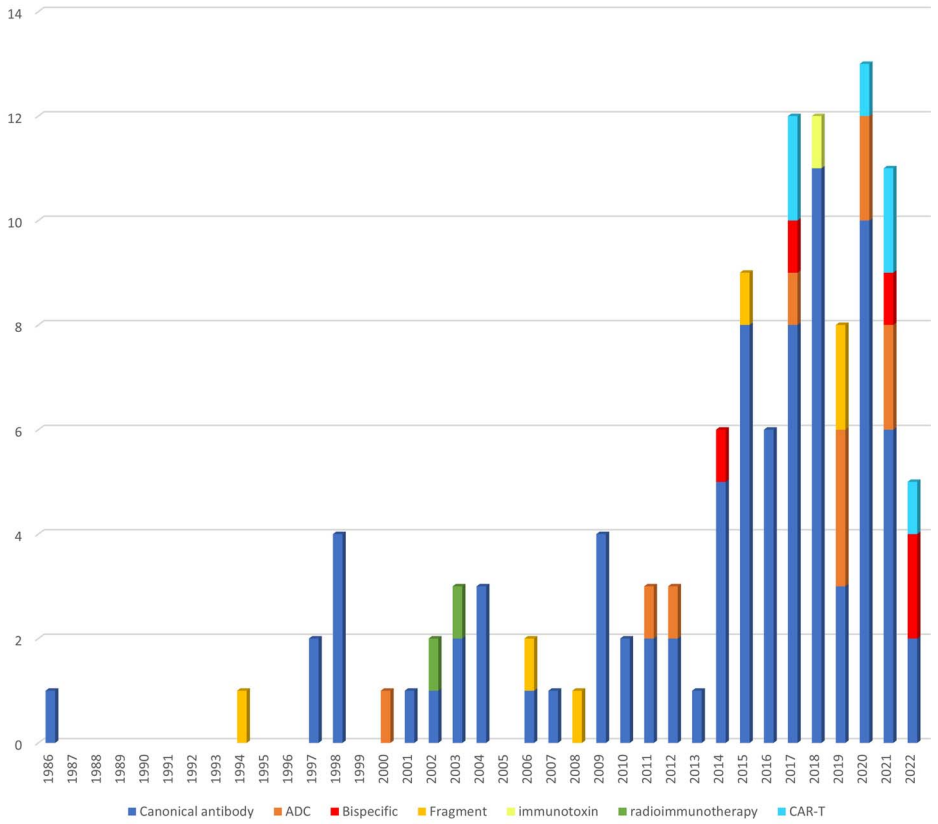

Figure 1. Antibody or antibody-containing therapeutics approved by the FDA as of 31 March 2022.

(scFv), antibody-drug conjugates (ADC), bispecific antibodies (bsAbs), etc.

To better reflect this trend and to set up a framework for forward thinking, we would like to introduce the concept of AntibodyPlus, an all-embracing term that describes any therapeutics that contain an antibody component, in the format of protein or nucleic acid (antibody encoded and delivered in mRNA or DNA). In this perspective, we will discuss the scope and categories of AntibodyPlus therapeutics, their potential advantages and applications, and some examples that highlight their design principles, potentials and future trends.

SCOPE AND CATEGORIES

In AntibodyPlus, "antibody" is broadly defined to include full-length antibody, antibody fragment, nanobody (e.g., V_H, V_HH and V_{NAR}), Fc region or any protein binding modules. The other components or modules in this hybrid modality could be small molecules, proteins/peptides, glycopeptides, nucleic acids, nanoparticles, cells or any combination among them. Based on the type of these accompanying modules, AntibodyPlus therapeutics can be divided into several categories: Ab+ complex system, Ab+ nucleic acid, Ab+ small molecule, Ab+ protein/peptide and Ab+ glycopeptide. Each category can be further divided into several subcategories depending on the subtypes or mechanisms of the accompanying modules (Fig. 2 and Table 1).

We notice that the scope of "Antibody" in AntibodyPlus is broader than that of monoclonal antibody (mAb) in the WHO international nonproprietary names (INN) nomenclature scheme [18]. In addition to "any substances that contain an immunoglobulin variable domain that binds to a defined target," AntibodyPlus also include Fc conjugated drugs, Fc fusion proteins and antibody-directed cellular therapies.

Various AntibodyPlus therapeutics may be created primarily through either biologic fusion of antibody with peptides, proteins and/or function domains or chemical conjugation of antibody with other modules, e.g., small molecule drugs (ADCs), PEGs, nucleotides, radionuclide, steroids, proteolysis-targeting chimeras (PROTACs), etc. A variety of conjugation technologies have been developed, among which are novel site-specific protein conjugation technologies that have contributed to the rapid development of ADCs in the past decade. Three promising site-specific bioconjugation techniques were recently reviewed [19].

The scope of AntibodyPlus may be even broader. For example, although not shown in Fig. 2, it may contain therapeutic antibodies encoded and delivered in the format of mRNA or DNA.

CAR-T, CAR-NK and other engineered cells with recombinant cell surface receptors are assigned to the category of Ab+ complex system. This category also includes antibody-coated nanoparticles, liposomes and extracellular vesicles [7], all of which may carry diverse effectors,

Table 1. The categories and subcategories of AntibodyPlus therapeutics

Category	Subcategory	Examples	Sponsor	Status	Antibody properties	Therapeutic payload	Target tissue/cell	Indication	Reference
Ab+ Complex system	CAR-T	Tisagenlecleucel	Novartis	Market	CD19-targeted CAR	T cells	B cells	B-cell acute lymphoblastic leukemia	[3]
	CAR-NK	FT596	Fate therapeutics	Phase 1	CD19-targeted CAR	NK cells	B cells	B-cell lymphoma	[4]
	CAR-MA	CT-0508	Carisma therapeutics	Phase 1	HER2-targeted CAR	Macrophage	Tumor	Cancer	[5]
	LNP	Caveolae-targeted LNP	AstraZeneca	Discovery	PV1-targeted Fab	mRNA	Lungs	To be determined	[6]
	EV	Neutrophil-derived EVs	Queen Mary University of London	animal studies	ROS-CII-targeted mAb	Viral IL-10 and/or anti-TNF	Arthritic joint	Rheumatoid arthritis	[7]
Ab+ Nucleic acid	siRNA	AOC 1001	Avidity Biosciences	Phase 1/2	TfR1-Targeted mAb	DMPK siRNA	Muscle	DM1	[8]
	ASO	DYNE-101	Dyne	Phase 1 in 2022	TfR1-Targeted Fab	DMPK ASO	Muscle	DM1	[8]
	saRNA	None							
	ADAR-oligos	None							
	miRNA, anti-miRNA and antago-miRNA	None							
Ab+ Small molecule	ADC	Trastuzumab deruxtecan	Daiichi-Sankyo/ AstraZeneca	Market	HER2-targeted mAb (trastuzumab)	Deruxtecan	HER2+ tumor cells	Cancer	[9]
	Targeted drug	BDC-1001	Bolt Biotherapeutics	Phase 1/2	HER2-targeted mAb (trastuzumab)	TLR7/8 agonists	HER2+ tumor cells	Cancer	[10]
	Radiopharmaceuticals	Tositumomab-I131	GSK	Market/discontinued	CD20-targeted mAb	Iodine-131	B cells	Non-Hodgkin Lymphoma	[11]
	PROTAC	Trastuzumab-PROTAC conjugate	Imperial College London/GSK	Cell studies	HER2-targeted mAb (trastuzumab)	Protac targeting BRD4	HER2+ tumor cells	Cancer	[12]
Ab+ Protein/peptide	bsAb/msAb	Emicizumab	Roche	Market	Bispecific Ab binding to factor IX and X	n/a	Blood	Hemophilia A	[13]
	cytokine	PD1-IL2v	Roche	Phase 1	PD-1-targeted mAb	IL2 variant	T cells	Cancer	[14]
	enzyme	DNL310	Denali Therapeutics	Phase 1/2	TfR1 binding Fc	Enzyme replacement	Brain	Hunter syndrome	[15]
	toxin	Moxetumomab pasudotox	AstraZeneca	Market	CD22-targeted Fv	Pseudomonas exotoxin A fragment	B cells	Hairy cell leukemia	[16]
Ab+ gp	LYTAC	Anti-PD-L1-M6Pn LYTAC	Lycia Therapeutics	Discovery	PD-L1-targeted mAb	M6PR ligands	Tumor	Cancer	[17]

Ab, antibody; ADAR, adenosine deaminase acting on RNA; ADC, antibody drug conjugate; ASO, antisense oligonucleotide; bsAb, bispecific antibody; CAR, chimeric antigen receptor; DM1, myotonic dystrophy type 1; EV, extracellular vesicles; Fab, fragment antigen-binding; LNP, lipid nanoparticle; LYTAC, lysosome-targeting chimera; M6PR, mannose-6-phosphate receptor; MA, macrophage cells; mAb, monoclonal antibody; miRNA, microRNA; msAb, multispecific antibody; NK, natural killer cells; PROTAC, proteolysis-targeting chimera; siRNA, small interfering RNA; saRNA, small activating RNA; TfR1, transferrin receptor 1

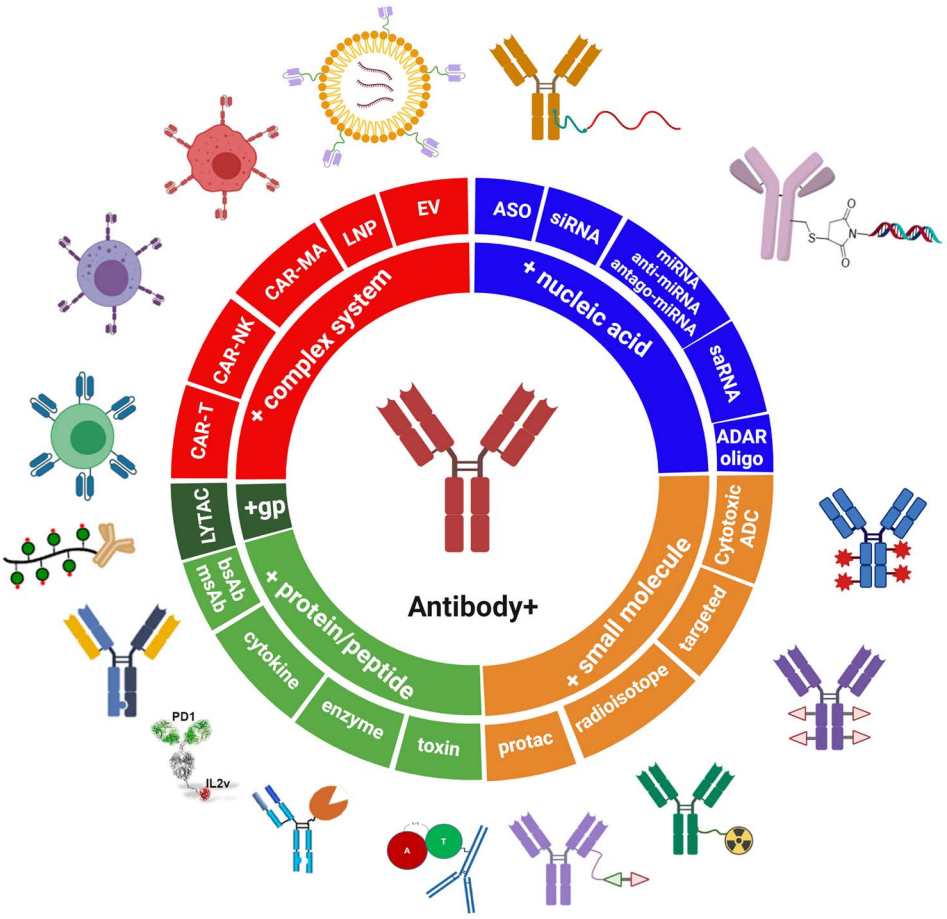

Figure 2. The categories and subcategories of AntibodyPlus therapeutics. ADAR, adenosine deaminase acting on RNA; ADC, antibody drug conjugate; ASO, antisense oligonucleotide; bsAb, bispecific antibody; EV, extracellular vesicles; CAR, chimeric antigen receptor; GP, glycopeptide; LNP, lipid nanoparticle; LYTAC, lysosome-targeting chimera; MA, macrophage cells; msAb, multispecific antibody; miRNA, microRNA; NK, natural killer cells; PROTAC, proteolysis-targeting chimera; siRNA, small interfering RNA; saRNA, small activating RNA. Created with BioRender.com.

including mRNA, miRNA/siRNA, DNA or CRISPR system (CAS-sgRNA). For example, lipid nanoparticle (LNP)-encapsulated mRNA therapeutics can be specifically delivered to lung tissue if LNP is conjugated to an antibody that binds to plasmalemma vesicle-associated protein (PV1) [6]. In delivering RNA/DNA, some Ab+ complex systems serve the same purpose as Ab+ nucleic acid, which mainly refers to therapeutics with nucleic acids directly conjugated to antibodies.

The Ab+ small molecule category is rapidly expanding and has gone beyond the conventional antibody-drug conjugates (ADCs). One exciting subcategory emerged is Ab+ PROTAC drugs, which enable target protein degradation in cells expressing specific antigens [12,20,21]. A PROTAC may be a more suitable ADC payload than the cytotoxic agents, since it benefits from potent catalytic degradation activity driven by serial target engagement from a low dose of compound [12].

A similar new exciting technology is lysosome-targeting chimaeras, or LYTACs, consisting of an antibody fused to chemically synthesized glycopeptide ligands that are agonists of cell-surface lysosome-shuttling receptor such as the cation-independent mannose-6-phosphate receptor (CI-M6PR) [17]. LYTACs can be used to specifically degrade extracellular and membrane-associated proteins, potentially providing a precise and complementary weapon against cancer, autoimmune disorders and other diseases. Because its effector is glycopeptide, different from the other types of effector molecules, LYTAC was assigned to a stand-alone category (Ab-gp).

Ab+ protein/peptide may be the category that is the most active in development effort—more than 100 different bispecific antibodies (bsAbs) and multispecific antibodies (msAbs), which constitute a special subcategory of Ab+ protein/peptide, are currently being evaluated in clinical studies [22]. Besides bsAb/msAb, this category also includes Ab+ cytokine, Ab+ enzyme and Ab+ protein toxin.

The maturity of different AntibodyPlus technologies varies greatly. Some AntibodyPlus classes, such as ADC and bsAbs, already have multiple commercialized products. Some classes, such as Antibody+ small activating RNA (saRNA), only exists in concept for now.

It is difficult to generalize which subcategories are more suitable for certain disease areas. As seen from the examples in Table 1, cancer is still the dominant disease targeted by AntibodyPlus drugs. In fact, many subcategories, such

as CAR-T, ADC and Ab+ radioisotope, were created for cancer. However, the drug candidates from one category, Ab+ nucleic acid, are mainly targeted at genetic diseases, at least initially. We expect that AntibodyPlus will be applied in more diverse disease areas, such as immunologic diseases, infectious diseases, metabolic diseases and central nervous system (CNS) diseases.

Please note that the scope and categorization of AntibodyPlus therapeutics are dynamic. The current classification may not be perfect. For example, differentiating peptides from glycopeptides and/or small molecules may be difficult sometimes. Some subcategories can be defined and divided differently, such as antibody-glycopeptide for the LYTAC technology. Thus, the scope and categorization of AntibodyPlus will need continuous refinement down the road. In addition, with more new formats emerging, Fig. 2 and Table 1 need to be further updated on a regular basis. Instead of attempting to precisely define the scope and the subcategories, we focus herein on therapeutic applications and the underlying concepts, and particularly their interconnectivity and overlap, as our ultimate goal is to stimulate, connect and expand the community.

ADVANTAGES AND APPLICATIONS

The reason why antibodies have become the lynchpin in multi-modality drugs is that they have six major advantages:

1. They can bind to the target molecule with high specificity and high or tailored affinity.
2. Full-length antibodies have a relatively long half-life and confined biodistribution in human bodies. Moreover, the half-life and biodistribution can be tuned via protein engineering [23].
3. Full-length antibodies can communicate with the immune system, mainly via their Fc effector functions.
4. Humanized or fully human antibodies have low immunogenicity *in vivo*.
5. Compared with small molecule drugs, the development time of monoclonal antibody drugs is relative short and more straightforward. Today for some antibody drug programs, from target to IND only takes 1 to 2 years [24].
6. Compared with small molecule drugs, antibody drugs have higher success rate in reaching the market [25,26].

Because of these advantages, antibody components have the potential to endow molecules unfit as stand-alone drugs with drug-like profiles. Specifically, they can perform the following functions in an AntibodyPlus format:

Enabling targeted delivery

A drug, whether its modality is small molecule, nucleic acid or protein, is safer and more effective if delivered only to target cell compartments, cells or tissues. Antibody can be used as a guide or a carrier for the payload to achieve that end.

The most validated example is ADC. An ADC's antibody module binds to a tumor-specific antigen (TSA) or a tumor associated antigen (TAA), delivering the conjugated cytotoxic drug specifically into tumor cells. For example, trastuzumab deruxtecan, an ADC drug first approved by the FDA in 2019, was developed to specifically deliver the topoisomerase I inhibitor deruxtecan to HER2 expressing tumor cells via its trastuzumab module [9].

Ab-toxin under the Ab+ protein/peptide category is another example of targeted delivery. Moxetumomab pasudotox, an scFv-toxin fusion protein (called immunotoxins) targeting CD22, was approved for B-cell leukemia [16] and more immunotoxins are being developed for treating solid tumors [27–29].

The lack of an effective targeted delivery to specific tissues other than liver via systemic administration has always been an obstacle to the development of oligonucleotide therapeutics [30]. The use of antibodies as delivery vehicles will help expand the reach of ASO, siRNA or miRNA beyond liver. Encouraging data have been obtained in cell and animal experiments (for review, [31]). The first antibody+ siRNA drug has entered clinical trials—AOC 1001, a TfR1-targeted mAb conjugated to DMPK siRNA, is being evaluated among adult patients with myotonic dystrophy type 1 (DM1) [8].

AntibodyPlus drugs can selectively enter not only certain types of cells, but also specific organs or tissues. For example, anti-transferrin receptor (anti-TfR1) has been used in a series of antibody-enzyme conjugated drugs that break through the blood–brain barrier for treating central nervous system diseases caused by enzyme deficiency [15].

Improving the therapeutic index (TI)

AntibodyPlus format improves the safety of the payload drug by confining their effects to specific cells or tissues and limiting their undesired toxicities. For example, some small-molecule compounds such as calicheamicins, auristatins and maytansinoids are too toxic to be used as stand-alone chemotherapeutic drugs, but they become effective treatments in hematological and solid tumors after being conjugated to antibodies. Another example is the anti-PD1-IL2v in the antibody-cytokine fusion format, which avoids the toxicity caused by systemic administration of IL-2, especially capillary leak syndrome, as shown in preclinical data [14]. In another example of Ab+ cytokine, IL-12 carried by antibody targeting tumor neovasculature increases IL-12's therapeutic index by more than 20× in mouse models [32].

Creating obligate effects

Some AntibodyPlus drugs can generate new functions or obligate effects that cannot be achieved by simply co-administering the two parent molecules. This is more common for bispecific antibodies, such as T-cell-redirecting bispecific antibodies [33]. Administering two parent antibodies alone or in combination does not bridge tumor cells and T cells, which can only be accomplished by a bispecific T-cell engager antibody. In another example, emicizumab, a bsAb binding to both factor IXa and X,

mimics the function of activated factor VIII and has been approved in several countries for bleeding prophylaxis in patients with haemophilia A [13]. Combination of two monospecific antibodies targeting FIXa or FX cannot fulfill such bridging function.

Improving the PK profile

The half-lives of antibody drugs in plasma are usually 10–20 days, much longer than those of small molecule drugs. The half-lives can be even further extended by introducing mutations to the FcRn binding sites on the IgG Fc. The long half-life of antibody offers stability to the payload, endowing "nondrug-like" compounds with "drug like" PK profiles. For example, oligonucleotides are easily degraded *in vivo.* However, their stability is improved when conjugated to antibodies, with half-lives in plasma extended from 1.9 days to 5.7 days [34]. Conversely, shorter or tailored half-lives can be achieved via Fc engineering [23].

Complementing the function of payload

CD377 (or its improved version, CD388), an experimental drug to treat and prevent influenza, comprises zanamivir conjugated to IgG1 Fc. Zanamivir is a neuraminidase inhibitor and prevents the release of influenza virus from infected cells. The Fc module further enhances zanamivir's antiviral function, recruiting macrophages, NK cells or other components of the immune system to help kill viruses [35]. In addition, incorporating the Fc module also extend the circulatory half-life of zanamivir (Function 4 as discussed above).

TUNABILITY AND PROGRAMMABILITY

Developing and manufacturing AntibodyPlus drugs is more complex and challenging than single-modality drugs. But gains in functionality, flexibility and tunability more than compensate for the increased burden in fulfilling development and regulatory requirements. Specificity, affinity, circulatory half-life and effector functions can all be fine-tuned when constructing the drug candidate to achieve desirable therapeutic profiles. Moreover, the most distinguished advantage of AntibodyPlus drugs is the potential for *in vivo* tunability. Here are a few examples of AntibodyPlus therapeutics that demonstrate tunability:

Switchable CAR-T

CAR-T has been established as an effective treatment for some types of blood cancer. However, it has some limitations, including tendency to cause cytokine release syndrome (CRS) and neurotoxicity, and inability to overcome resistance generated by antigen escape. To overcome these limitations, researchers have been developing a more flexible technology based on CAR-T—universal immune receptor T cell therapy or switchable CAR-T for cancer [36]. Autologous or allogenous T cells are engineered to express CARs that bind to a tag, instead of specific tumor antigen. After infusing patients with such T cells, anti-tumor activities can be initiated and controlled by administering a bispecific molecule that binds to both TAAs on tumor cells and CARs of these engineered T cells. The bispecific molecule act as an adapter bridging the target tumor cells and T cells with universal immune receptors. By substituting different binders for different TAAs in the adaptor molecule, the system can be used to target tumor cells with heterogenous or switched antigens. Furthermore, the activities and toxicities of switchable CAR-T can be quantitatively and temporally controlled by adjusting the dosing scheme of the adapter molecules.

SADA-PRIT radioimmunotherapy

Conventional radioimmunotherapy, such as tositumomab-iodine-131, has anti-tumor activity, but unfortunately also incur significant systemic radioactivity exposure. A new radioimmunotherapy approach is safer and more effective by combining two technologies: Self-Assembling and DisAssembling (SADA) bispecific antibodies and Pretargeted RadioImmunoTherapy (PRIT) [37]. Briefly, animals were first administered with a cold dose of bispecific antibody to prelocalize at the tumor. Each BsAb comprises one scFv targeting at a TAA, one scFv targeting at the chelator S-2-(4-aminobenzyl)-1,4,7,10-tetraazacyclododecane tetraacetic acid (DOTA), and one tetramerization tag. In mouse studies, such SADA-BsAbs self-assembled into stable tetramers (220 KD) that bound tumors with high avidity, with unbound molecules disassembled into monomers (55 KD) that were rapidly cleared through renal filtration. Then DOTA-caged radioisotopes were consequentially administered into animals. Most of chelated radioisotopes were sequestered by tetramer SADA-BsAbs that had been enriched in tumors. These tumor-bound radioisotopes were effective in ablating tumors. Remaining unbound radioisotopes were quickly cleared from the body without significant toxicities to the bone marrow, kidneys or liver. This two-step SADA-PRIT is flexible because of its modular design: the DOTA caged payload can be alpha-emitting or beta-emitting isotopes or other cytotoxic agents.

Intracellular corks

In some cases, the difference in PK between AntibodyPlus drugs and small molecule drugs can be exploited to dynamically control the efficacy and toxicity of treatment. The technology of "intracellular corks" is based on such scheme [38]. The utilities of tumor necrosis factor (TNF) as a stand-alone cancer therapy are limited because of its substantial toxicity. To overcome that limitation, drug candidate L19-TNF can specifically deliver TNF into tumors. In this fusion protein, TNF is linked to a targeting module, the L19 antibody, which binds to the alternatively spliced EDB domain of fibronectin, a pan-tumoral antigen. However, antibody-fused TNFs may still cause toxicities including a drop in blood pressure, flu-like symptoms, nausea and vomiting, especially at early time points after intravenous administration, when its concentration in circulation is highest. To suppress such temporary toxicity, a small molecule drug, such as receptor-interacting

protein kinase 1 (RIPK1) inhibitor GSK963, may be pre-administered to turn down TNF signaling in the L19-TNF distribution phase and thus function as an intracellular cork. After L19-TNF is localized to tumors, the small molecular drugs are cleared from the body, allowing TNF to exert its anti-tumor function.

CHALLENGES AND POTENTIAL ISSUES

Naturally, the hybrid nature of AntibodyPlus therapeutics, such as with the addition of the effector modules, may lead to new challenges and potential issues/complications. For instance, Wu *et al*. have examined the antibody-independent mechanism of toxicity for ADC (ado-trastuzumab emtansine or T-DM1), demonstrating binding to a different cell surface target by the payload contributes to the toxicity [39]. The additional binding of the effector modules, and moreover, the synergetic binding with the antibody (avidity), may alter both binding specificity and selectivity [40,41]. To reduce potential safety issues for ADC or other types of AntibodyPlus therapeutics, more research needs to be done to study their off-target binding and toxicity, and additional assays, such as screening for polyspecificity, need to be developed and employed at discovery stages.

CONCLUSIONS

Antibody drugs have become the most prominent drug class in the past three decades. Their success has been built on our expanding insights from immunology, cell biology, molecular biology, protein structure and engineering, protein chemistry and bioconjugation [42], and other disciplines, and our collected efforts in pushing the boundary in drug development. In the process, researchers and scientists also realize that some diseases, like cancer, are far more complicated than we initially thought. Fighting such complicated and difficult diseases often calls on more sophisticated drug format and modalities. The emergence of AntibodyPlus drugs reflects such trend.

AntibodyPlus drugs build on the advantages of antibodies, including high specificity, long half-life, low immunogenicity, and engagement with the immune system, and further create extra benefits such as obligate functions, improved TI and flexibility. The development of AntibodyPlus drugs requires more extensive cross-disciplinary collaborations and demands deep knowledge from diverse fields including biology, chemistry, physics and mathematics. In coming decades, we expect to see a growing number of therapeutic innovations coming out of the AntibodyPlus landscape, ultimately improving clinical outcomes and raising standards of care for many difficult diseases.

AUTHORS' CONTRIBUTIONS

Yong Zhu drafted the manuscript and designed the AntibodyPlus cartoon. Shawn Shouye Wang proposed the prototype of AntibodyPlus concept and revised the manuscript. Zhaohui Sunny Zhou and Mitchell Ho provided feedbacks to the AntibodyPlus concept, and revised and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Dr. Yong Zhu is a member of the Chinese Antibody Society (CAS). Dr. Shawn Shouye Wang is an employee and shareholders of WuXi Biologics. Shawn Shouye Wang was the founding president of CAS and has been serving as a member of the Board of Directors for CAS. *Antibody Therapeutics* is the official journal of Chinese Antibody Society. Prof. Mitchell Ho has also been serving as a member of the Board of Directors for CAS and is also the Editor-in-Chief of *Antibody Therapeutics.* Prof. Zhaohui Sunny Zhou is a co-founder and equity holder of NIRa Biosciences, and a member of editorial board of *Antibody Therapeutics.* All the authors are blinded from reviewing or making decisions on the manuscript.

DATA AND MATERIALS AVAILABILITY

No extra data beyond the scope of this article are available.

ETHICS AND CONCENT STATEMENT

No patient consent is required for this mini review.

ANIMAL USE STATEMENT

No animal was used for this mini review.

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