Mini Review

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

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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: 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., VH, VH, VNAR) and single-chain fragment variable

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

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, radionuclides, 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 | Target 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 Cancer                  | [4]         |
|                         | CAR-MA                       | CT-0508                         | Carisma Therapeutics          | Phase 1          | HER2-targeted CAR                            | Macrophage          | Tumor                          | [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        | TIR1-Targeted mAb                           | DMPK siRNA          | Muscle                        | DM1                     | [8]       |
|                         | ASO                          | DYNE-101                        | Dyne                           | Phase 1 in 2022  | TIR1-Targeted Fab                            | DMPK ASO            | Muscle                        | DM1                     | [8]       |
|                         | saRNA                        | None                            | None                           | None             | None                                         | None                | None                          | None                   | None      |
|                         | ADAR-oligos                  | None                            | None                           | None             | None                                         | None                | None                          | None                   | None      |
| Ab+ Small molecule      | ADC                          | Trastuzumab deruxtecan          | Daiichi-Sankyo/                | Market           | HER2-targeted mAb (trastuzumab)              | Deruxtecan          | HER2+ tumor cells                | Cancer                | [9]       |
|                         | Targeted drug                | Bolt Biotherapeutics            | AstraZeneca                    | Phase 1/2        | HER2-targeted mAb (trastuzumab)              | TLR7/8 agonists     | HER2+ tumor cells                | Cancer                | [10]      |
|                         | Radiopharmaceuticals         | Tositumomab-I131                | GSK                            | Market/discontinued Cell studies             | HER2-targeted mAb (trastuzumab) | Iodine-131 | B cells                       | Non-Hodgkin Lymphoma Cancer | [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 enzyme              | PD1-IL2v                        | Roche                          | Phase 1          | PD-1-targeted mAb                            | IL2 variant         | T cells                       | Cancer                | [14]      |
|                         |                              | DNL310                          | Denali Therapeutics            | Phase 1/2        | TIR1 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                  | 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; TIR1, 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 therapies 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 TIR1-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 tetraaetic 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 consequence 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 Antibody-Plus 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/c 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 CONSENT STATEMENT**

No patient consent is required for this mini review.

**ANIMAL USE STATEMENT**

No animal was used for this mini review.

**REFERENCES**

1. Mullard, A. FDA approves 100th monoclonal antibody product. *Nat Rev Drug Discov* 2021; 20: 491–5.
2. The Antibody Society. Therapeutic monoclonal antibodies approved or in review in the EU or US. [https://www.antibodysociety.org/resourc es/approved-antibodies/](https://www.antibodysociety.org/resources/approved-antibodies/) (31 March 2022, last accessed).
3. O’Leary, MC, Lu, X, Huang, Y et al. FDA approval summary: tiageneclecucel for treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. *Clin Cancer Res* 2019; 25: 1142–6.

4. Goodridge, JP, Mahmood, S, Zhu, H et al. FT596: translation of first-of-kind multi-antigen targeted off-the-shelf CAR-NK cell with engineered persistence for the treatment of B cell malignancies. *Blood* 2019; 134: 301.

5. Gabrusiewicz, K, Anderson, N, Lu, X et al. Abstract B65: CT-0508, a novel CAR macrophage product directed against HER2, promotes a proinflammatory tumor microenvironment. *Cancer Immunol Res* 2020; 8: B65–5.

6. Li, Q, Chan, C, Peterson, N et al. Engineering Caveola-targeted lipid nanoparticles to deliver mRNAs to the lungs. *ACS Chem Biol* 2020; 15: 830–6.

7. Topping, LM, Thomas, BL, Rhys, HI et al. Targeting extracellular vesicles to the arthritic joint using a damaged cartilage-specific antibody. *Front Immunol* 2020; 11: 10.

8. Mullard, A. Antibody-oligomucleotide conjugates enter the clinic. *Nat Rev Drug Discov* 2022; 21: 6–8.

9. Modi, S, Saura, C, Yamashita, T et al. Trastuzumab Deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2019; 382: 610–21.

10. Sharma, M, Dumbrava, EI, Carvajal, R et al. 401 phase 1/2 study of novel HER2-targeting, TLR7/8 immune-stimulating antibody conjugate (ISAC) BDC-1001 with or without immune checkpoint inhibitor in patients with advanced HER2-expressing solid tumors. *J Immunother Cancer* 2020; 8: A244–4.

11. Horning, SJ, Younes, A, Jain, V et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol* 2005; 23: 712–9.

12. Maneiro, MA, Forte, N, Shchepinova, MM et al. Antibody-PROTAC conjugates enable HER2-dependent targeted protein degradation of BRD4. *ACS Chem Biol* 2020; 15: 1306–12.

13. Blair, HA. Emicizumab: a review in haemophilia a. *Br J Pharmacol* 2020; 178: 581–90.

14. Umana, P. Abstract ND03: PD1-IL2v: a next generation, PD-1-targeted cytokine. *Cancer Res* 2021; 81: ND03–3.

15. Kariolis, MS, Wells, RC, Getz, JA et al. Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys. *Sci Transl Med* 2020; 12: eaay1359.

16. Kreitman, RJ, Pastan, I. Antibody fusion proteins: anti-CD22 recombinant immunotoxins monomucleotid passudotox. *Clin Cancer Res* 2011; 17: 6398–405.

17. Banik, SM, Pedram, KM, Wisnovsky, S et al. Lysosome-targeting chimaeras for degradation of extracellular proteins. *Nature* 2020; 584: 291–7.

18. Balocco, R, Koch, SDSG, Thorpe, R et al. New INN nomenclature for monoclonal antibodies. *The Lancet* 2022; 399: 24.

19. Lieser, RM, Yur, D, Sullivan, MO et al. Site-specific biocoujugation approaches for enhanced delivery of protein therapeutics and protein drug carriers. *Bioconjug Chem* 2020; 31: 2272–82.

20. Pillow, TH, Adhikari, P, Blake, RA et al. Antibody conjugation of a chimeric BET degrader enables in vivo activity. *ChemMedChem* 2020; 15: 17–25.

21. Dragach, PS, Adhikari, P, Blake, RA et al. Antibody-mediated delivery of chimeric protein degraders which target estrogen receptor alpha (ERα). *Bioorg Med Chem Lett* 2020; 30: 126907.

22. Nie, S, Wang, Z, Moscoso-Castro, M et al. Biology drives the discovery of bispecific antibodies as innovative therapeutics. *Antibody Therapeutics* 2020; 3: 18–62.

23. Saunders, KO. Conceptual approaches to modulating antibody effector functions and circulation half-life. *Front Immunol* 2019; 10: 1296.

24. Kelley, B. Developing therapeutic monoclonal antibodies at pandemic pace. *Nat Biotechnol* 2020; 38: 540–5.

25. Smietana, K, Siatkowski, M, Moller, M. Trends in clinical success rates. *Nat Rev Drug Discov* 2016; 15: 379–80.

26. Hughes, JP, Rees, S, Kalindjian, SB et al. Principles of early drug discovery. *Br J Pharmacol* 2011; 162: 1239–49.

27. Fleming, BD, Urban, DJ, Hall, MD et al. Engineered anti-GPC3 immunotoxin, HN3-ABD-T20, produces regression in mouse liver cancer xenografts through prolonged serum retention. *Hepatology* 2020; 71: 1696–711.

28. Gao, W, Tang, Z, Zhang, YF et al. Immunotoxin targeting glypican-3 regresses liver cancer via dual inhibition of Wnt signalling and protein synthesis. *Nat Commun* 2015; 6: 6536.

29. Li, N, Fu, H, Hewitt, SM et al. Therapeutically targeting glypican-2 via single-domain antibody-based chimeric antigen receptors and immunotoxins in neuroblastoma. *Proc Natl Acad Sci U S A* 2017; 114: E6623–31.

30. Roberts, TC, Langer, R, Wood, MJA. Advances in oligomucleotide drug delivery. *Nat Rev Drug Discov* 2020; 19: 673–94.

31. Dugal-Tessier, J, Thirumalairajan, S, Jain, N. Antibody-oligomucleotide conjugates: a twist to antibody-drug conjugates. *J Clin Med* 2021; 10: 838.

32. Halin, C, Rondini, S, Nilsson, V et al. Enhancement of the antitumor activity of interleukin-12 by targeted delivery to neovasculature. *Nat Biotechnol* 2002; 20: 264–9.

33. Labrijn, AF, Jannaert, ML, Reichert, JM et al. Bispecific antibodies: a mechanistic review of the pipeline. *Nat Rev Drug Discov* 2019; 18: 585–608.

34. Dovgan, J, Ehkirch, A, Lehot, V et al. On the use of DNA as a linker in antibody-drug conjugates: synthesis, stability and in vitro potency. *Sci Rep* 2020; 10: 7691.

35. Döhrmann, S, Almaguer, A, Dedeic, N et al. 162. CD377, a novel antiviral fc-conjugate, demonstrates potent viral burden reduction against influenza a (H1N1) in mouse and ferret models. *Open Forum Infect Dis* 2020; 7: S210–1.

36. Minutolo, NG, Hollander, EE, Powell, DJ. The emergence of universal immune receptor T cell therapy for cancer. *Front Oncol* 2019; 9: 176.

37. Santich, BH, Cheal, SM, Ahmed, M et al. A self-assembling and Disassembling (SADA) bispecific antibody (BsAb) platform for curative two-step pretargeted radioimmunotherapy. *Clin Cancer Res* 2021; 27: 532–41.

38. Dakhel, S, Ongaro, T, Gouyou, B et al. Targeted enhancement of the therapeutic window of L19-TNF by transient and selective inhibition of RIPK1-signaling cascade. *Oncotarget* 2019; 10: 6678–90.

39. Endo, Y, Mohan, N, Dokmanovic, M et al. Mechanisms contributing to ado-trastuzumab emtansine-induced toxicities: a gateway to better understanding of ADC-associated toxicities. *Antib Ther* 2021; 4: 55–9.

40. Cunningham, O, Scott, M, Zhou, ZS et al. Polyelectivity and polyspecificity in therapeutic antibody development: risk factors for failure in preclinical and clinical development campaigns. *MAbs* 2021; 13: 1999195.

41. Mohan, N, Jiang, J, Dokmanovic, M et al. Trastuzumab-mediated cardiotoxicity: current understanding, challenges, and frontiers. *Antib Ther 2018*; 1: 13–7.

42. Sadiki, A, Vaidya, SR, Abdollahi, M et al. Site-specific conjugation of native antibody. *Antibody Therapeutics* 2020; 3: 271–84.