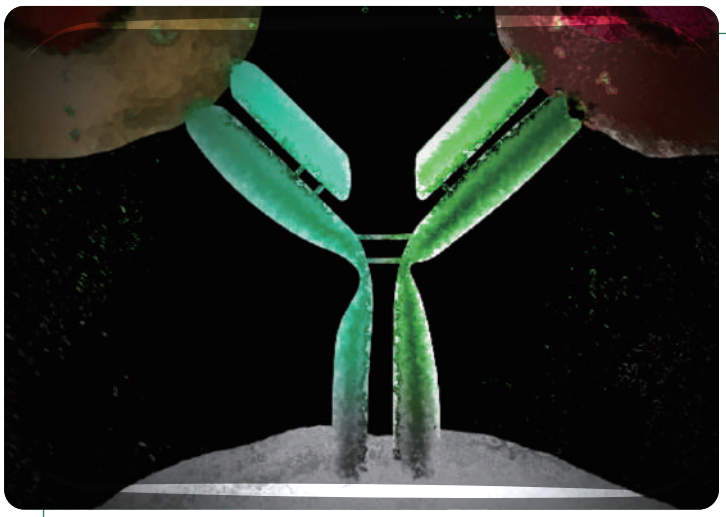

The New Era of Bispecific Antibodies for Cancer Immunotherapy

Emerging bispecific antibodies and their targets in cancer immunotherapy in the discovery, development, preclinical, and clinical stages

Monoclonal antibodies have revolutionized cancer therapy since their introduction as therapeutics in the field. To enhance the specificity and potency of antibodies, bispecific antibodies (bsAbs) are emerging, with the ability to bind two different antigens or two different epitopes on the same antigen. More than 85% of bsAbs in clinical trials are cancer therapeutics.

As of 2022, 6 bsAbs had been approved by EMA and/or FDA in cancer immunotherapy (Table 1), including the first approved bsAb, Catumaxomab, which was withdrawn from the European Union market in 2017, and 3 bsAbs approved for marketing in 2022. By the end of 2023, marketing application submissions for 5 bsAbs in late-stage clinical studies may occur. With more than 600 bsAbs currently under investigation, the industry is projected to grow to more than $30 billion in the next five years. Therefore, big pharmaceutical companies have increasing overall interest in exploring and investing in this promising immunotherapy.

Table 1. BsAbs approved by EMA and/or FDA in cancer immunotherapy

BsAbs Name	Brand Name	Company	Target 1	Target 2	Mechanism of Action	Indications	Approved by	First Approval
Catumaxomab	Removab	Neovii	CD3 (T cell)	EpCAM (cancer cell)	Recruitment and activation of T cells	Malignant ascites	EMA	Apr 2009 (withdrawn in Jun 2017)
Blinatumomab	Blincyto	Amgen	CD3 (T cell)	CD19 (cancer cell)	Recruitment and activation of T cells	B-cell precursor acute lymphoblastic leukemia (ALL)	EMA and FDA	Dec 2014
Amivantamab	Rybrevant	Janssen	EGFR (cancer cell)	c-MET (cancer cell)	Blocking of dual signal pathways	Non-small cell lung cancer (NSCLC)	EMA and FDA	May 2021
Tebentafusp	Kimmtrak	Immunocore	CD3 (T cell)	gp100 (cancer cell)	Recruitment and activation of T cells	Unresectable or metastatic uveal melanoma	EMA and FDA	Jan 2022
Mosunetuzumab	Lunsumio	Roche	CD3 (T cell)	CD20 (cancer cell)	Recruitment and activation of T cells	Relapsed or refractory follicular lymphoma	EMA and FDA	Jun 2022
Teclistamab	Tecvayli	Janssen	CD3 (T cell)	BCMA (cancer cell)	Recruitment and activation of T cells	Relapsed or refractory multiple myeloma	EMA and FDA	Aug 2022

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Mechanisms of Action of BsAbs and Emerging Targets

There are different categories of bsAbs based on their mechanisms of action (MoAs). A large number of bsAbs have been designed to bridge tumor cells and T cells, which simultaneously bind to a tumor-associated antigen (TAA) expressed on tumor cells and CD3 on T cells, redirecting the cytotoxic activity of effector T cells to specifically eliminate tumor cells (Figure 1). The TAAs targeted by the approved cell-bridging bsAbs involve EpCAM, CD19, gp100, CD20, and BCMA. Besides the already approved bsAbs, the TAAs of cell-bridging bsAbs that are currently being tested in clinical trials include CD123, CD33, CD37, CD38, CLEC12A, and FLT-3 for hematologic malignancies, and CEA, HER2, PSMA, PMEL, B7H3, GPA33, and GPC3 for solid tumors. In addition to T cells, NK cells can also be the effector in cell-bridging bsAbs. CD16 on NK cells is often used as the target for this category of bsAbs. For example, bsAbs targeting CD30×CD16 are now undergoing evaluation in clinical trials for hematologic malignancies.

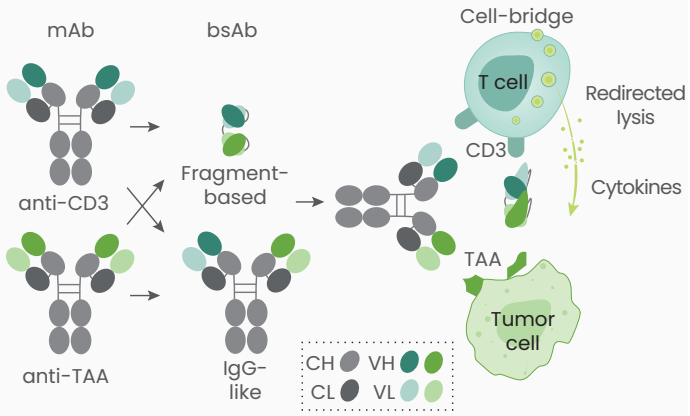

Figure 1. Schematic diagram of bsAbs bridging tumor cells and T cells

BsAbs that block two mutually related signaling pathways by targeting two epitopes on tumor cells or in the tumor microenvironment are also widely investigated. The antigen pairs include EGFR×c-MET, VEGF×Ang-2, VEGF×DLL4, IGF-1×IGF-2, HER2×HER3, and HER2×HER2. In May 2021, FDA granted approval to Janssen's Amivantamab (Rybrevant) targeting EGFR×c-MET for non-small cell lung cancer (NSCLC) treatment.

BsAbs blocking immune checkpoints, such as PD-L1×CTLA-4, PD-1×LAG3, and PD-L1×TIGIT, are another category tested in clinical trials. Immune checkpoints have an inhibitory effect on the activity of immune cells. BsAbs targeting two immune checkpoints simultaneously are mostly investigated for treating solid tumors and potentially improve the efficacy of checkpoint inhibition compared to monotherapy. In June 2022, Akeso's Cadonilimab (开坦尼®), a PD-1×CTLA-4 blocker, was approved in China for the treatment of relapsed or metastatic cervical cancer. It is the first approved dual immune checkpoint inhibitor bsAb. BsAbs of immune checkpoints combined with TAAs have also been developed, such as PD1×HER2 and PD1×VEGF. Moreover, bsAbs co-targeting immune checkpoints and T-cell-costimulatory molecules, such as PD-L1×4-1BB (CD137) and CTLA-4×OX40 (CD134), are under development.

BsAbs and Targets Beyond Cancer

Following the success in oncology, bsAbs are being pursued for the treatment of other diseases, including autoimmune disorders, infections, neurologic diseases, ophthalmic disorders, and rare diseases. Since FDA approval of Roche's Emicizumab (Hemlibra) for hemophilia A in 2017, which acts on coagulation factor IXa (FIXa)×FX, new avenues for the application of bsAbs in other diseases have been unlocked. In January 2022, FDA approved Genentech's Faricimab (Vabysmo), which targets VEGF×Ang-2, to treat wet ADM and DME.

Then, in September 2022, Taisho Pharmaceutical's Ozoralizumab (Nanozora), a humanized trivalent NANOBODY® compound consisting of two anti-TNFα NANOBODIES® and one anti-HSA NANOBODY®, was approved in Japan for the treatment of rheumatoid arthritis (RA). In the autoimmune disease field, some of the targets of bsAbs in development include CD32B, CD79B, TNF, IL-17A, IL-4, IL-13, IL-1α, IL-1β, and IL-17F.

The rapid success of bsAbs in cancer and noncancer programs has garnered abundant attention and investment to further this field of therapeutics. With the current ongoing research in the discovery, preclinical, and clinical stages, bsAb therapy holds a very promising future and brings hope to patients suffering from these different diseases that may not have many treatment options.

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Supporting Bispecific Antibody Development at Sino Biological

As a global leader in recombinant technology, Sino Biological is at the forefront of the bioreagents and contract research services industries. Sino Biological has developed a large variety of extremely high-quality recombinant proteins and antibodies to support the research and therapeutic development of bispecific antibody targets in immunotherapy and other diseases. Featured products include high-purity and high-activity proteins for CD3, CD16a, CD38, CD278/ICOS, CTLA-4, HER2, HER3, c-MET, VEGFR2, DLL4, TIGIT, 4-1BB, and much more well-established and emerging targets.

Sino Biological also provides fast and efficient bispecific antibody production service on the basis of its extensive expertise and experience in mammalian cell expression and proprietary technology platforms that are specifically optimized. Starting from the antibody sequence, Sino Biological can deliver multiple bsAb formats, such as BiTE, Diabody, CrossMab, and DVD-IgG. Numerous bsAb projects have been completed with greater than 90% overall success rates, and yields of 250 mg/L or more have been achieved.

To accelerate multispecific antibody development and clinical research, Sino Biological offers complete solutions, including antibody development and optimization, druggability assessment, animal model evaluation, and process development. The comprehensive reagents and CRO services cover various phases of the multispecific development process from lead discovery to clinical studies.

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