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Bispecific antibodies and novel immune cell targets for immuno-oncology

ABL Bio's immuno-oncology programs are addressing the limitations of current checkpoint inhibitors by developing bispecific antibodies and the next generation of checkpoint inhibitors.

ABL Bio is a biotechnology research company focused on the development of antibody-based therapeutics for oncology and neurodegenerative diseases through an open innovation model. Founded in South Korea in 2016, the company is building a pipeline of promising technologies and novel drugs in collaboration with research and development (R&D) partners, and is out-licensing assets to commercialization partners.

The growing R&D pipelines at ABL Bio are based on two platform technologies. One pipeline is built around antibody–drug conjugate (ADC) technology, of which the most advanced asset, ABL202, is being codeveloped in partnership with LegoChem Biosciences. Other pipelines are using the structural advantages of bispecific antibodies (BsAbs), which are designed to bind to two different targets. ABL Bio's most advanced asset from all its pipelines, ABL001, is a BsAb that targets vascular endothelial growth factor and delta-like ligand 4 (DLL4). It is currently being tested in a phase 1 clinical trial, and is the first BsAb to enter a clinical study in South Korea. Another of ABL Bio's advanced BsAb assets is ABL301, a first-in-class BsAb in development for Parkinson disease, which combines a novel drug targeting the formation of α-synuclein aggregates with enhanced penetration of the blood–brain barrier.

ABL Bio is also using its BsAb technology to advance a number of immuno-oncology programs, alongside developing novel immune cell targets with the potential to become next-generation checkpoint inhibitors.

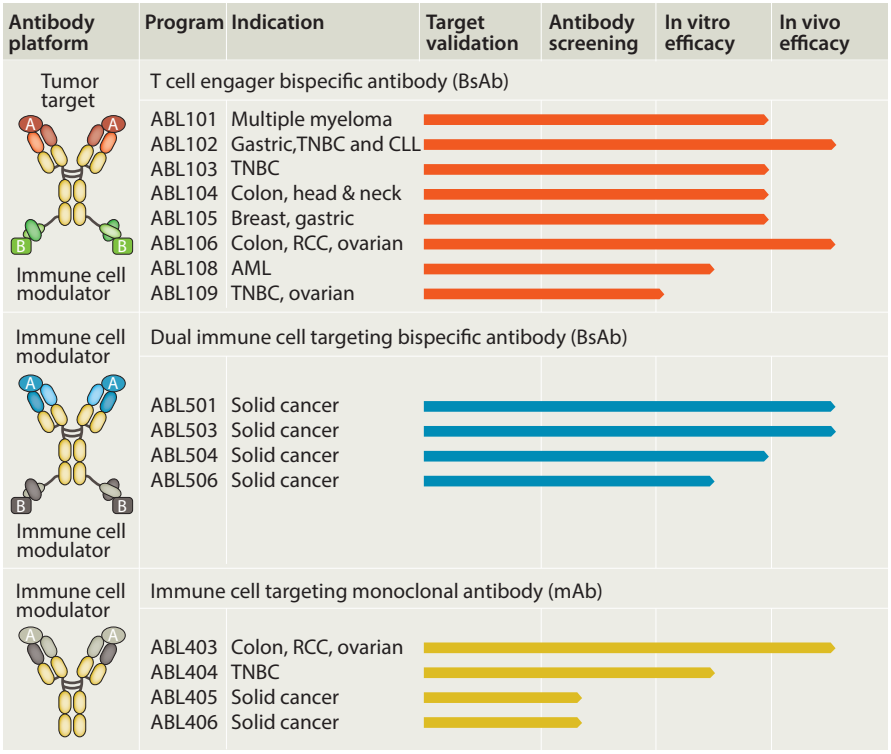

Fig. 1 | ABL Bio's immuno-oncology pipeline has programs focused on three different antibody platforms. T cell engager bispecific antibodies (BsAbs) are designed to activate immune cells in the tumor microenvironment only. Dual immune cell-targeting BsAbs aim to increase the response rates and antitumor activity, while novel immune cell-targeting monoclonal antibodies (mAbs) are designed to overcome the resistance and relapse observed with PD-1/PD-L1 (programmed cell death 1/programmed cell death ligand 1) therapy. AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Immuno-oncology strategy

Immune checkpoint inhibitors have created a new paradigm for cancer treatment but they have some limitations, including immune-related adverse events and poor responses in a proportion of treated patients. Numerous clinical trials of combination treatments using checkpoint inhibitors are now underway as pharmaceutical companies seek ways to improve the response rates.

One way in which ABL Bio is addressing the current limitations is to develop the next generation of checkpoint inhibitors. Another is to develop BsAbs, which offer potential advantages compared with combination therapies. BsAbs could provide superior potency, as one antibody can bind to two different targets, along with improved safety via low levels of off-target binding. BsAb therapies can also be more cost-effective compared with combination therapy as only one molecule is developed.

ABL Bio is using these two approaches to advance a number of programs in its immuno-oncology pipeline, which are focusing on three different antibody platforms: T cell engager BsAbs, dual immune cell-targeting BsAbs and novel immune cell-targeting monoclonal antibodies (mAbs) (**Fig. 1**).

T cell engager bispecific antibody

ABL Bio's T cell engager BsAbs are designed to minimize systemic adverse events with immunotherapy by activating immune cells in the tumor microenvironment (TME) only. This is achieved by combining an immune cell modulator with a tumor target.

For example, one program is developing a BsAb with binding sites for tumor-associated antigen (TAA) and 4-1BB (also known as CD137), an inducible costimulatory molecule found on a number of cell types, including T cells. No T cell costimulation occurs when there is no tumor cell present, where only the 4-1BB binding site is occupied, as 4-1BB requires clustering to deliver an activation signal. In the TME, however, the BsAb also binds to TAA, leading to 4-1BB clustering. Only in this case are T cells activated, resulting in the killing of tumor cells (**Fig. 2**).

In vitro functional assays, which use peripheral blood mononuclear cells, have confirmed that ABL106, the lead anti-4-1BB antibody candidate characterized as an undisclosed TAA (ABL106T)×4-1BB BsAb format, acts on the tumor target specifically. Interferon (IFN)-γ production, a measure of T cell activity, was observed with the ABL106T cell engager BsAb, while baseline levels only of IFN-γ production were observed with either the anti-ABL106T mAb or anti-4-1BB mAb alone.

ABL106 has also been tested in an in vivo preclinical study using an MC38 colon cancer model that expresses ABL106T. ABL106 showed strong, target-specific inhibition of tumor growth. Liver toxicity was observed with anti-4-1BB mAb but not with the ABL106T×4-1BB BsAb format.

Another in vivo study used transgenic mice in which the mouse immune checkpoint modulators were replaced with their human counterparts. ABL106 showed strong antitumor effects. Only minimal antitumor effects were seen with either the anti-ABL106T mAb or the anti-4-1BB mAb alone.

There are eight T cell engager programs in the immuno-oncology pipeline with candidates in development to treat various solid and hematologic cancers. Two programs are being codeveloped with a Korean pharmaceutical company (including ABL106), and two with US-based TRIGR Therapeutics.

Dual immune cell-targeting bispecific antibody

A second strategy aims to increase the response rate or improve antitumor activity by combining binding sites for programmed cell death ligand 1 (PD-L1) and an immune checkpoint modulator in a single BsAb, blocking inhibition signals or triggering an activation signal and blocking an inhibition signal. There are four programs developing candidates for solid tumors in collaboration with I-Mab Biopharma in China.

For example, the effects of a candidate dual immune cell-targeting BsAb on T cell activation (measured by interleukin (IL)-2 production) have been tested in vitro. The ABL501 dual immune cell-targeting BsAb has binding sites for PD-L1 and an undisclosed immune checkpoint modulator, ABL501T. Minimal effects were seen when mAbs against either immune checkpoint modulator were used alone. However, the response improved when they were used together, and was significantly higher when PD-L1 and ABL501T binding sites were combined as a BsAb. An in vivo study that used the transgenic mouse model with human immune checkpoint modulators has also shown that the BsAb achieved a superior antitumor effect compared with the mAbs.

> **These results show that ABL403 works as a novel immune checkpoint inhibitor**

ABL503 is another candidate BsAb with binding sites for PD-L1 and an undisclosed immune checkpoint modulator, ABL503T. In an in vivo study using the transgenic model, an antitumor effect was seen with the anti-PD-L1 mAb or anti-ABL503T mAb alone. A superior antitumor effect was observed when the mice were treated with anti-PD-L1 and anti-ABL503T mAbs in combination, and the best antitumor effect was seen with the ABL503 BsAb.

Novel immune cell-targeting monoclonal antibody

ABL Bio's third immuno-oncology strategy focuses on novel immune cell-targeting mAbs, which could become the next generation of immune checkpoint inhibitors. The aim is to overcome the resistance and relapse observed with PD-1/PD-L1 therapy by developing mAbs that bind to novel immune cell modulators.

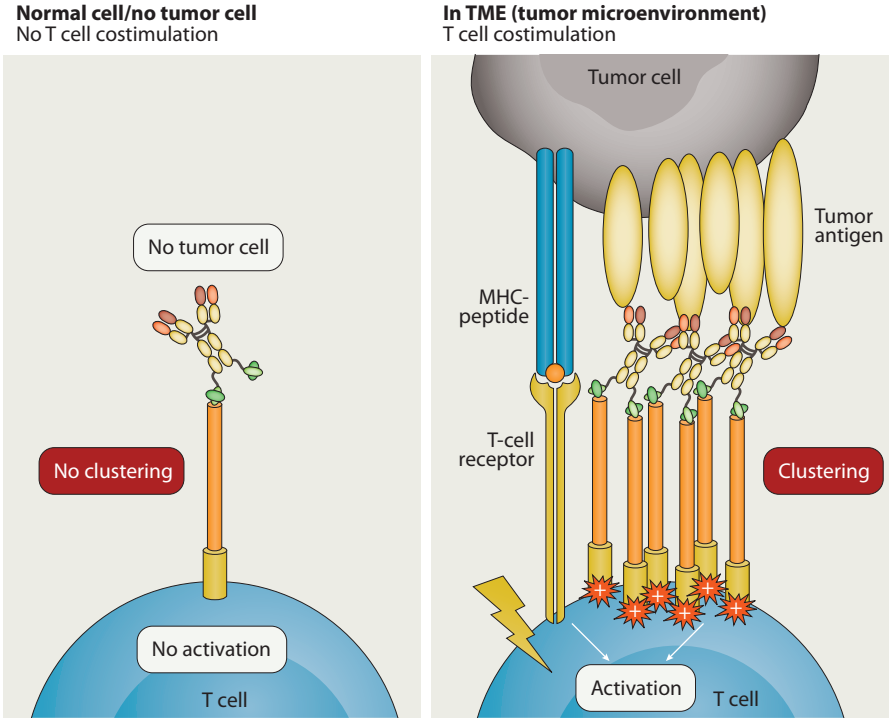

Fig. 2 | T cell engager BsAbs are designed to activate immune cells in the TME only. T cell engager bispecific antibodies (BsAbs) bind to tumor associated antigen (TAA) and 4-1BB. In the tumor microenvironment (TME), the BsAb binds to TAA and 4-1BB; this leads to 4-1BB clustering, which is required to deliver an activation signal to the T cell. When there is no tumor cell present, the TAA binding site is unoccupied, so 4-1BB clustering does not occur and T cells are not activated. MHC, major histocompatibility complex.

There are four programs developing candidates for various solid tumors. The most advanced candidate is ABL403, which is being developed for solid tumors including colon cancer, renal cell carcinoma and ovarian cancer. ABL403 blocks the interaction between an undisclosed target (ABL403T) expressed on antigen-presenting cells and its counterpart on T cells; removal of this inhibitory signal leads to reactivation of T cells.

In vitro functional assays have shown that IFN-γ secretion increased in the presence of ABL403T and ABL403 (indicating T cell activity) compared with ABL403T alone. ABL403T alone interacted with its counterpart on T cells, leading to a reduction in T cell activity. Superior T cell activation, in terms of IFN-γ production, was seen when ABL403 was tested in combination with the following immune-regulating antibodies: anti-4-1BB (urelumab), anti-PD-1 (pembrolizumab) and anti-PD-L1 (atezolizumab).

In an in vivo CT26 mouse colon cancer model, the combination of ABL403 with a known immune checkpoint inhibitor (anti-PD-1) resulted in greater inhibition of tumor growth and improved survival compared with anti-PD-1 alone. The effect of ABL403 in combination with anti-PD-1 on tumor-infiltrating lymphocytes (TILs) was compared with ABL403 and anti-PD-1 alone. The combination group showed the best effect, with lower proliferative capacity of regulatory T cells and enhanced functionality of CD8 TILs.

These results show that ABL403 works as a novel immune checkpoint inhibitor. The data suggest that ABL403 could also be used in combination with existing checkpoint inhibitors to increase response rates.

Partnering opportunities

ABL Bio is developing its immuno-oncology pipeline in collaboration with a number of Korean and global biotechnology companies and research institutes. For example, ABL Bio and TRIGR Therapeutics recently announced a global oncology collaboration for next-generation therapeutic antibodies. Under the terms of the agreement, TRIGR Therapeutics paid ABL Bio a $4.3 million upfront fee to license global rights (except for South Korea) to five antibodies currently under development by ABL Bio. ABL Bio will also receive success-based payments of approximately $550 million in total plus royalties. As the company continues to grow, ABL Bio is looking to expand its network of partnerships, including future out-licensing opportunities.

The CEO and leadership team at ABL Bio are all US-educated with global pharmaceutical company or research institute experience, and the company has grown to more than 40 employees, including 12 PhD scientists, since it was founded. In just 2.5 years, ABL Bio has been successful in raising $93 million in series A, B and C funding, and is now working toward an initial public offering at the end of 2018.

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