Alligator Bioscience AB
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Raising the bar in immuno-oncology

Immuno-oncology (IO) has revolutionized cancer treatment but not for all. Alligator Bioscience is leveraging its antibody technology platform, including its novel RUBY bispecific platform to produce next-generation tumor-directed IO therapies with higher efficacies and lower toxicities.

Immuno-oncology, a concept that uses the body's own immune system to attack cancer, is fast becoming a standard of care, but only a small number of big pharma companies currently dominate the space. While their approaches have been successful, agile biotech companies such as Alligator Bioscience are using different tactics to develop effective next-generation cancer immunotherapies while minimizing the often severe side effects.

Alligator, based in Medicon Village in Lund, Sweden, began to focus on tumor-directed immuno-oncology in 2008. Alligator's pipeline has five monospecific and bispecific antibodies in clinical and preclinical development. "As early entrants into this field, we have the experience and expertise, backed by a strong scientific culture and in-depth immunology knowledge. We believe that we can create therapeutics that balance efficacy, safety, and tolerability by targeting the drug to the tumor. This gives us a competitive edge," said Per Norlén, CEO of Alligator.

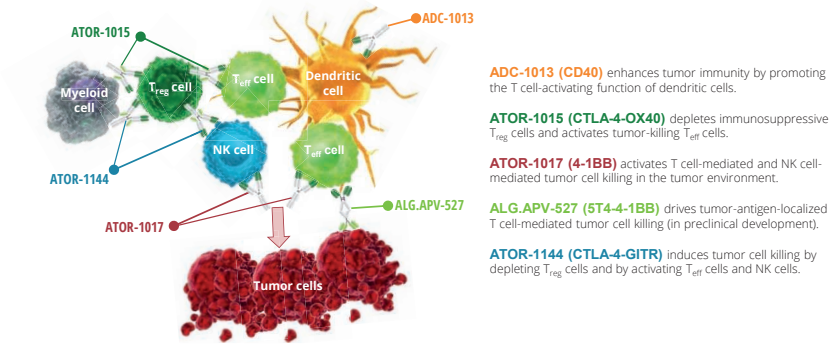

Fig. 1 | Alligator's drugs work on different nodes of the immune attack on cancer cells. CTLA-4, cytotoxic T lymphocyte-associated protein 4; GITR, glucocorticoid-induced tumor-necrosis-factor-receptor-related protein; NK cell, natural killer cell; T_{eff} cell, effector T cell; T_{reg} cell, regulatory T cell.

The technologies behind the pipeline

Alligator's pipeline is based on its proprietary technology platforms. ALLIGATOR-GOLD is a phage display library containing more than 60 billion unique antibody fragments (scFvs). FIND is a molecular evolution technology based on discoveries by company cofounder Carl Borrebaeck. FIND optimizes antibodies generated by ALLIGATOR-GOLD, in order to increase tumor retention, affinity, and potency, reduce antigenicity, and improve the ease of development and manufacturing.

Alligator launched RUBY, its latest platform, in early 2019. This generates immunoglobulin G-like bispecifics from any two antibodies, with excellent stability and manufacturability properties in shorter timelines.

"The addition of RUBY means that we have the technologies to generate virtually any bispecific or multispecific therapeutic antibody for immuno-oncology and other disease areas," said Peter Ellmark, VP of discovery at Alligator.

Another of Alligator's bispecific platform technologies is based around an inhibitor of the checkpoint receptor cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), optimized from the natural ligand CD86 using FIND. This inhibitor can be fused with any antibody, creating a stable, developable, and effective antibody-fusion protein. The approach was used to develop ATOR-1015 and ATOR-1144, the former targets CTLA-4 and OX40 while the latter targets CTLA-4 and glucocorticoid-induced tumor-necrosis-factor-receptor-related protein (GITR) (**Fig. 1**).

Alligator has in-house cell line, process and analytical development, and small-scale manufacturing capabilities, as well as experience in chemistry, manufacturing, and controls (CMC).

"Our capabilities mean that we can solve production challenges early on in development, which is critical when you are working with complex molecules," added Christina Furebring, senior VP of research.

Using bispecifics to target CTLA-4

Bristol-Myers Squibb's Yervoy (ipilimumab) is the first and, so far, the only CTLA-4-targeted monoclonal antibody to reach the market. It has shown impressive clinical efficacy in a proportion of patients, but the immunological side effects can be severe and even fatal. ATOR-1015, binds to both CTLA-4 and the costimulatory receptor OX40, which are highly expressed on tumor-infiltrating immune cells, potentially localizing the effect of the drug to the tumor. ATOR-1015 began a phase 1 clinical trial in December 2018.

"We are the first company to develop a CTLA-4–OX40 bispecific compound, and we should soon have clinical validation. Our technology platform could be used to rapidly create other bispecific CTLA-4 compounds, for example targeting CTLA-4 and PD-1 [programmed cell death 1] or PDL-1 [PD-1 ligand 1], and we are looking for partners," said Anu Balendran, VP of business development at Alligator.

Immuno-oncology compounds designed to overcome hurdles

4-1BB (also known as CD137) is a costimulatory target with potential in immuno-oncology, but safety and efficacy issues have made clinical development of 4-1BB antibodies challenging. Because the immunostimulating effect of Alligator's ATOR-1017, a 4-1BB antibody derived from the ALLIGATOR-GOLD library, is dependent on crosslinking by Fcγ receptors expressed on immune cells, its action should be strongest in tumors where immune cells are abundant. A clinical trial authorization (CTA) for ATOR-1017 is planned for submission in mid-2019.

ALG.APV-527 is a second-generation 4-1BB bispecific antibody. It targets 5T4, which will direct its activity to the tumor. The antibody is codeveloped with Aptevo Therapeutics and a CTA submission is planned for late 2019.

Strength in partnership

In 2015, Alligator outlicensed ADC-1013, which targets CD40, to Janssen Biotech in a deal worth up to $695 million, validating Alligator's science and business model. It is currently in phase 1 clinical development with Janssen.

While Alligator's aim is to develop its pipeline compounds to achieve proof of concept in humans and to subsequently find licensing or collaboration partners, its partnering model is opportunistic.

"We are currently in a fortunate position where several programs have delivered beyond expectations and will move into clinical development in 2019 and 2020. Therefore, we are open to partnering some of these programs at an earlier stage, including ATOR-1017. Given our strong technology platform and immunology expertise, we will also seek technology platform collaborations where we work with a partner to develop a molecule from scratch. We believe that our platforms could also have potential outside oncology," said Balendran.

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