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Merus

Battling cancer with bispecific antibodies

Merus is using its Biclonics technology platform to generate differentiated therapeutics in the form of full-length human IgG bispecific antibodies designed to recruit the immune system to eliminate cancer cells.

Bispecific antibodies, which bind simultaneously to two different antigens, can attack tumors via novel mechanisms of action that cannot be evoked with combinations of conventional monoclonal antibodies (mAbs). Through careful functional screening, it is possible to identify bispecific antibodies that convey greater potency and selectivity compared with combinations of two mAbs. "The bispecific format itself is the basis of much more potent and selective drugs, while potentially diminishing toxicity," said Ton Logtenberg, founder and CEO of Merus.

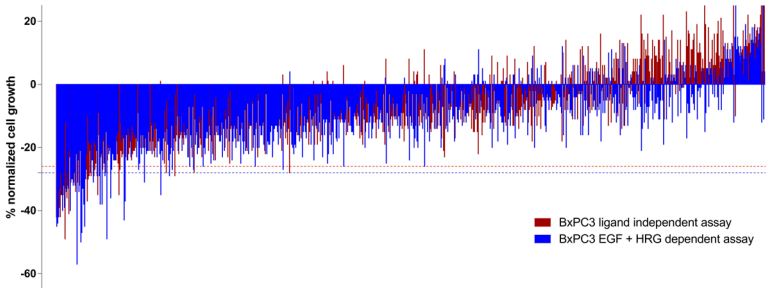
Headquartered in Utrecht, the Netherlands, Merus is a clinical-stage immuno-oncology company developing innovative bispecific antibody therapeutics (Biclonics). One approach engages T cells to kill tumor cells by combining high-affinity binding to a tumor-associated antigen with low-affinity binding to CD3 on the T cell membrane. Another uses a target with high expression on tumor cells, such as HER2, for high-affinity binding with one arm. "With the other arm, one can zoom in and block a molecule such as HER3 that is expressed at a considerably lower level," said Logtenberg. "Such a 'dock and block' mechanism mediated by bispecific antibodies makes targets expressed at a low level actually druggable."

At the same time, bispecific antibodies reduce the likelihood of unintended effects on healthy cells that express only one of the two targets, because the monovalent binding by one arm of the bispecific antibody alone has no functional consequences. For example, Merus has shown in studies in cynomolgus monkeys that a Biclonics with one EGFR-specific arm does not cause toxicities in the skin—unlike EGFR-targeting mAbs such as Erbitux (cetuximab)—due to monovalent low-affinity binding to EGFR, which is ubiquitously expressed by skin cells.

Biclonics technology platform

Merus uses a suite of proprietary technologies to generate its Biclonics bispecific antibodies, which have a full-length IgG format that retains the favorable features associated with conventional mAbs, such as a long half-life, low immunogenicity, and use of the standard process for mAb manufacturing.

The proprietary transgenic mouse MeMo is used to generate large panels of diverse and high-quality human antibodies characterized by a common light chain. Merus overcomes the potential for mispairing during the generation of bispecific antibodies by combining common light chain antigen-binding fragment (Fab) regions with CH3 electrostatic engineering in the crystallizable fragment (Fc) region to efficiently drive the formation of the heterodimer. The full-length IgG format also enables further modification of the Fc region for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) or to prevent binding to Fc-γ receptors on immune cells.



Unbiased functional screen of 750 different Biclonics. These are composed of diverse EGFR and HER3 specific Fabs in proliferation inhibition assays, with (blue) or without (red) the ligands EGF and Heregulin.

High-throughput functional screening is carried out in semi-automated cell-based functional assays to identify product leads with differentiated modes of action. "Functional screening is a critical element of our preclinical research effort," said Logtenberg. "We have found that it is necessary to screen large numbers of bispecific antibodies in order to find just a handful of potent molecules with differentiated modes of action."

Differentiated pipeline

The lead bispecific antibody candidate in Merus's clinical-stage pipeline is MCLA-128, which is designed to block HER3/heregulin dependent tumor growth and survival as well as enhance immune-mediated killing of tumors. MCLA-128 employs a 'dock and block' mechanism to effectively block oncogenic signaling through the HER2:HER3 heterodimer even under high heregulin concentrations. In addition, MCLA-128 is engineered for enhanced ADCC in order to recruit and activate immune effector cells to directly kill the tumor. Preclinical *in vivo* data show that MCLA-128 is more effective at inhibiting the growth of cell lines resistant to HER2-targeted therapies than Herceptin (trastuzumab) plus Perjeta (pertuzumab). A phase 1/2 clinical trial is ongoing in patients with HER2-expressing solid tumors, including metastatic breast, gastric, ovarian, and endometrial cancer.

MCLA-117 is a T cell engager designed to retarget T cells via CLEC12A—a first-in-class target expressed by acute myeloid leukemia (AML) blast and stem cells with restricted expression in normal hematopoietic cells. An *ex vivo* preclinical study that used AML samples showed that MCLA-117 caused T cell activation and expansion, and efficient killing of large numbers of tumor cells by low numbers of T cells in bone marrow samples from people with AML. A phase 1/2 clinical trial in people with AML is ongoing.

Merus also has a pipeline of proprietary bispecific antibody candidates in preclinical development, including MCLA-158, which targets the Wnt signaling pathway receptor LGR5 and EGFR. "This is an unusual combination, but we learned from our functional screens that Biclonics with this particular target combination are very effective at inducing apoptosis of tumor stem cells," said Logtenberg. Preclinical studies show that MCLA-158 is more potent than EGFR-targeting mAbs such as Erbitux, and eliminates tumor stem cells effectively *in vitro* and *in vivo*.

Research into various combinations of coinhibitory and/or costimulatory targets for immunomodulation is also being conducted. The aim is to find bispecific antibodies that induce a more potent reactivation of tumor-specific T cells, or that improve targeting to the tumor microenvironment with a lower risk of toxicity.

Alongside its R&D program, Merus recently entered into a research collaboration with Incyte Corporation focused on research into and development of bispecific antibodies, utilizing the Biclonics technology platform. It also has an ongoing research partnership with Ono Pharmaceutical, as well as partnerships with a number of academic institutions.

"We have a very robust platform for generating high-quality bispecific antibodies, and we are open to partnering with academic institutions and other industry partners," said CBO Hui Liu. "Our ability to do high-throughput functional screening enables us to explore interesting areas of biology by quickly generating bispecific antibodies to different target pairs and, with the right functional assays, helps us to identify the best targets to go after."

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