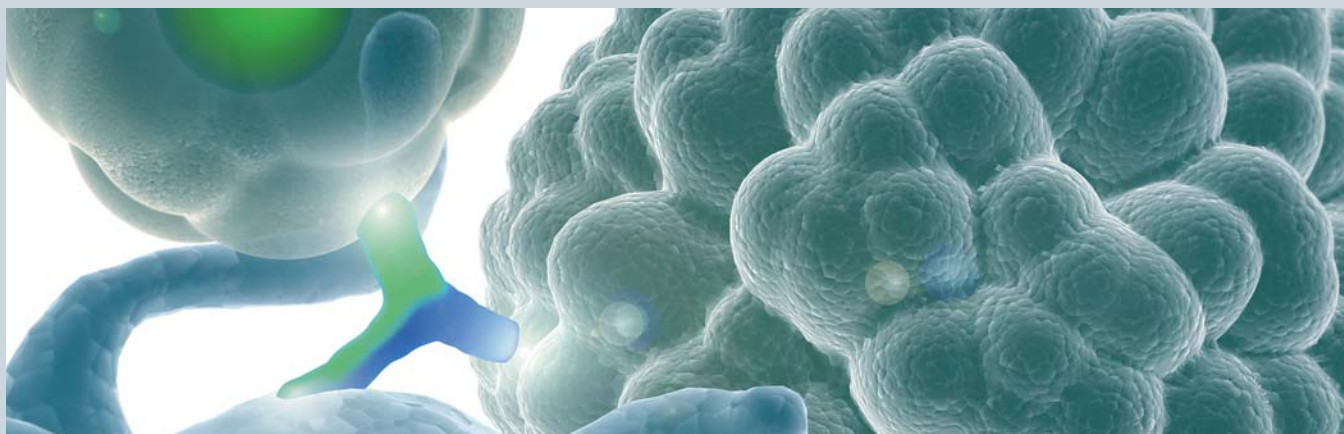


Triomab[®] Antibodies: Trifunctional Design to Fight Cancer

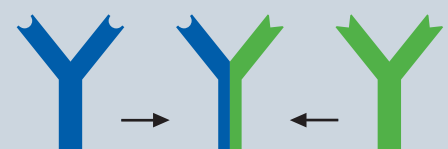


The human immune system is usually quite effective at identifying and eliminating abnormal cells. Cancer cells, however, can form tumors and spread throughout the body as they develop a range of strategies to escape the immune system's control mechanisms.

It has therefore been a long-standing vision of physicians and scientists to develop a treatment that can put the immune system back on track. TRION has achieved this goal with its trifunctional Triomab[®] antibodies. Removab[®] (catumaxomab), the most advanced Triomab[®] candidate, received EU market approval in 2009 and is the first bispecific, trifunctional antibody on the market worldwide.

Design: Made up of two halves

Trifunctional antibodies (Triomab[®]) combine the halves of two distinct full-size antibodies, a tumor-specific mouse antibody and a T cell specific rat antibody, in one molecule. Triomab[®] antibodies therefore have two different specific binding sites, while traditional antibodies have two identical specific binding sites.



Tumor-specific antibody (mouse) Trifunctional Triomab[®] antibody (hybrid) T cell-specific antibody (rat)

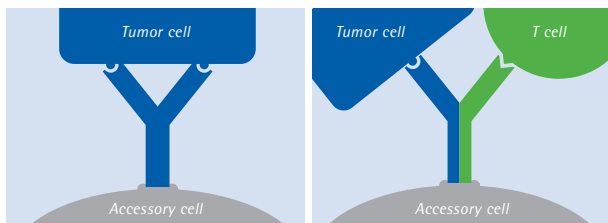
Only the combination of two antibody species (rat and mouse) enabled TRION to overcome production problems encountered by many other types of bispecific antibodies and to establish a pharmaceutical production process¹. With their GMP approved in-house production facilities, TRION is able to supply the world market.

Mode of action: Three binding sites, multiple effects

Thanks to their trifunctional design, Triomab[®] antibodies can simultaneously bind to a tumor cell, a T cell and, via its Fc region, to an accessory cell of the innate immune system. The resulting tri-cell complex triggers several immune defense cascades at the same time:

- T cells, being the most potent killer cells of the human body, induce highly effective tumor cell lysis and apoptosis of tumor cells. In addition, they trigger the typical necrotic processes of tumor cell killing (rounding, swelling, disrupting).
- Accessory cells such as monocytes, macrophages and natural killer cells eliminate tumor cells by, for example, phagocytosis or apoptosis. Moreover, they release cytokines which further stimulate T cell activity.
- Dendritic cells can induce long-lasting immunity against cancer by processing and subsequently presenting tumor cell debris to the immune system.

This unique mode of action makes Triomab[®] antibodies at least 1,000-fold more effective in destroying cancer cells than conventional monospecific antibodies. Whereas these are applied in doses of milligrams or grams, Triomab[®] antibodies work in the range of micrograms and can thus be produced in much smaller facilities.

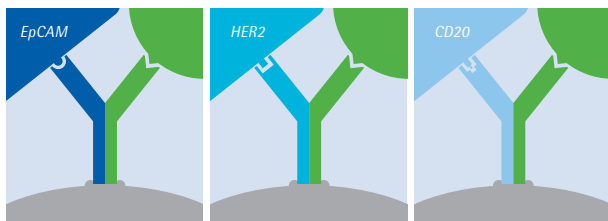


Conventional antibodies can only recruit accessory cells

Trifunctional antibodies can additionally recruit the particularly potent T cells

Platform: Modular approach

Triomab® is a powerful product development platform: By exchanging the tumor-specific arm, trifunctional antibodies can easily be tailored to various indications. So far, Triomab antibodies® have been generated against EpCAM, HER2 and CD20. Using the Triomab® technology, any traditional antibody on the market could be transformed into a trifunctional format with improved anti-tumor efficacy against tumor cells.



Target: EpCAM

Target: Her2

Target: CD20

Advantages: New quality in cancer therapy

In total, Triomab® compounds have a number of advantages over conventional antibodies. Triomab® molecules:

- Specifically and simultaneously activate multiple immune defense mechanisms against cancer cells.
- Efficiently induce the elimination of tumor cells by activating accessory cells (as conventional antibodies do) and T cells (as conventional antibodies cannot do).
- Can trigger a long-term immune response, similar to that conferred by vaccination.
- Are up to 1,000-fold more effective than conventional antibodies.
- Can be produced in comparatively small facilities using a straight-forward process.
- Can easily be adapted to other cancer indications via exchange of the tumor-associated antigen.

Triomab® Pipeline

Several Triomab® antibodies are currently under development. While the three most advanced candidates are being co-developed with Fresenius Biotech, TRION holds full commercial rights for all other compounds.

- Removab® (catumaxomab) targeting EpCAM is marketed in the EU for the intraperitoneal treatment of malignant ascites in patients with EpCAM-positive carcinomas. Phase II studies for the treatment of ovarian and gastric cancer are ongoing.
- Rexomun® (ertumaxomab) targeting HER2 is in Phase II trials for the treatment of metastatic breast cancer.
- Lymphomun™ (FBTA05) targeting CD20 is in development for the treatment of B cell lymphoma.
- Further candidates are in preclinical development, among others Ektomun™ for the treatment of melanoma.

Triomab® Data

Triomab® antibodies and their mode of action have been investigated extensively in vitro and in vivo, and in a range of clinical studies, involving more than 500 patients. TRION has demonstrated that Triomab® antibodies:

- Potently trigger multiple immune reactions.
- Activate both T lymphocytes and accessory cells to produce immunomodulating cytokines (IL-1beta, IL-2, IL-6, IL-12, TNF alpha, interferon gamma, GM-CSF, and DC-CK1).²
- Induce the typical necrotic processes of tumor cell killing as well as phagocytosis.^{3,4}
- Elicit a lasting immune response.⁵

The clinical trials, conducted in cooperation with Fresenius Biotech, have shown that Triomab® antibodies:

- Are safe and well tolerated in clinical trials.^{6,8}
- Show clinical activity at dose levels 1,000-fold lower than those of conventional antibodies.^{6,7,8}
- Showed anti-tumor response in 5 out of 15 evaluable patients in a Phase I trial in metastatic breast cancer patients.⁶
- Completely reversed leukocyte/tumor cell ratio in a Phase I/II trial in malignant ascites, so that 22 of 23 patients were ascites-free at the end of treatment.^{8,9}
- Achieved significantly longer puncture-free time (77 days under Triomab® treatment as compared to 13 days in untreated control group; $p < 0.0001$) and prolonged puncture-free survival (46 versus 11 days; $p < 0.0001$), in a Phase II/III trial involving 258 patients with malignant ascites.¹⁰

Based on these results, Removab® (catumaxomab) received EU market approval for the intraperitoneal treatment of malignant ascites in patients with EpCAM-positive carcinomas.

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