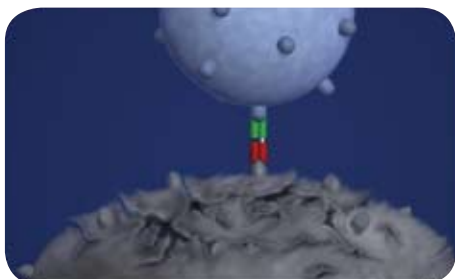
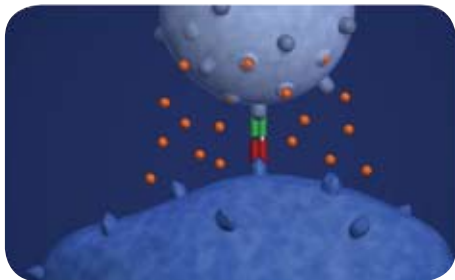
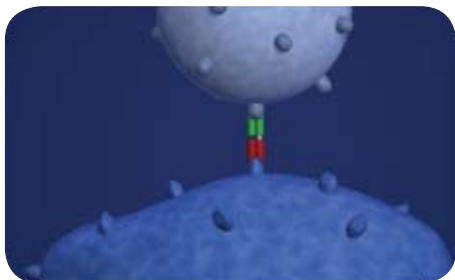
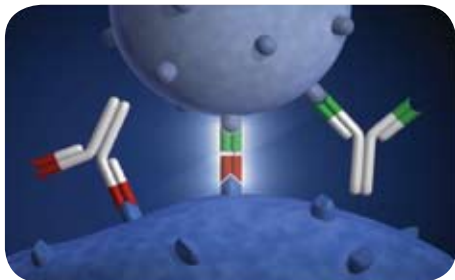




BiTE® Antibodies: A New Class of Tumor-Destroying Drugs

BiTE Antibodies: An Overview

Derived from antibodies, these drugs are unique in their ability to enable the body's killer T cells to recognize and attack their targets, while leaving normal cells unharmed. The current clinical focus of BiTE antibody therapy is to treat cancer. However, BiTE antibody technology may also have potential for treatment of inflammatory and autoimmune diseases.



BiTE ANTIBODIES: A UNIQUE TREATMENT

BiTE antibodies differ from other immune-based cancer treatments in several significant ways:

- BiTE antibodies enable a large population of the body's T cells to recognize tumor cells. As a result, T cells can attack and kill tumor cells using their regular killing mechanism.
- Two key features distinguish T cells from any other kind of immune cell in our body: their ability to serially kill and, while killing, to multiply. This way, an army of highly active T cells is formed right at the site where they encounter tumor cells.
- BiTE antibodies combine in one polypeptide chain the binding sites of two different antibodies – one of them specific for T cells, the other specific for target cells.
- BiTE antibodies are inert unless they transiently link a target cell with a T cell. The formed synapse will lyse the target cell and activate the T cell. In the absence of target cells, BiTE antibodies do not activate T cells.
- Unlike other T cell therapies such as anti-CTLA-4 antibodies, tumor vaccination approaches or T cell receptor gene transfer, BiTE antibodies activate T cells in a unique fashion. This does not require antigen presentation and most other elements of regular T cell recognition and, thus, has the potential to circumvent many immune evasion mechanisms of tumor cells that tend to limit existing T cell therapies.



BiTE® ANTIBODIES: FACTS

Research has shown that BiTE antibodies are:

- Very precise (are only active against targeted cells expressing the proper surface antigen)
- Extremely potent (induce destruction of target cells at concentrations 1,000-100,000 times lower than that required by conventional therapeutic antibodies)
- Cost-effective to produce (as a result of low drug quantity requirements)

Specificity

- One BiTE arm is specific for CD3, a component of the T cell receptor present on all T cells of the body
- The other BiTE arm is selected to bind an antigen of choice on the target cells

Mode of Action

- Specific elimination of pathogenic target cells by transiently recruiting and activating the body's killer T cells

Size

- 55 kDa (one third the size of a monoclonal antibody)

Manufacturing

- Produced as functional protein using eukaryotic cell culture system
- Common antibody manufacturing infrastructure
- Low costs of goods due to small amount of BiTE® required per treatment

Applicability

- Range of diseases, including cancer, autoimmune and inflammatory diseases

Clinical Proof of Concept

Interim data from an ongoing phase 1 study with blinatumomab (MT103/MEDI-538), a CD19-specific BiTE antibody targeting the CD19 antigen, provides proof-of-concept for the BiTE antibody technology. The drug candidate was evaluated in patients with relapsed, indolent non-Hodgkin's lymphoma (NHL).

- All seven patients treated to date at 0.06 mg/m² per day achieved complete or partial responses.
- Based on the search and destroy mechanism of T cells, BiTE antibodies can lead to the elimination of lymphoma cells from infiltrated organs like the bone marrow. Cancer cells that reside in the bone marrow are the source of cancer re-growth and are rather difficult to eradicate. In the ongoing phase 1 trial, eight out of nine patients treated with blinatumomab had bone marrow improvement and five of these patients had complete bone marrow clearance from cancer cells.

These data were presented at the 10th International Conference on Malignant Lymphomas (ICML) in Lugano, Switzerland in June 2008.

Product Platform

- Micromet has consolidated the BiTE antibody technology into an integrated product development platform and controls all stages of drug development: from engineering and production of a new BiTE antibody to characterizing its pharmacology, developing assays, setting up animal models, and bringing BiTE antibodies into clinical trials
- MT110, a pan-carcinoma solid tumor BiTE antibody, is in a phase 1 clinical trial in patients with lung or gastrointestinal cancer
- Three additional BiTE antibodies, targeting CD33, CEA and MCSP, respectively, are in preclinical development
- Various BiTE antibodies are currently in research showing that BiTE antibody technology can be used against a wide variety of target antigens as are used by monoclonal antibody therapies

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Reviews:

- BiTE: A new class of antibodies that recruit T cells
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- Bispecific antibody constructs with unique anti-tumor activity
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- Therapeutic window of an EpCAM/CD3-bispecific BiTE antibody in mice is determined by a subpopulation of EpCAM-expressing lymphocytes that is absent in humans
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- Therapeutic window of muS110, a single-chain antibody construct bispecific for murine EpCAM and murine CD3.
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- Strictly target cell dependent activation of T cells by bispecific single-chain antibody constructs of the BiTE class
Brischwein, K et al. *J Immunother* 8: 798-807 (2007)
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- EpCAM (CD326) finding its role in cancer
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- Potent inhibition of local and disseminated tumor growth in immunocompetent mice by a bispecific single-chain antibody construct specific for murine CD3
Schlereth, B. et al. *Cancer Immunol Immunother*. 55: 785-796 (2006)
- MT110: A novel bispecific single-chain antibody construct with high efficacy in eradicating solid tumors
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- T cell activation and B cell depletion in chimpanzees by an anti-CD19/anti-CD3 single-chain bispecific antibody construct
Schlereth, B. et al. *Cancer Immunol. Immunother*. 55:503-14 (2006)
- Induction of regular cytolytic T cell synapses by bispecific single-chain antibody constructs
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- Serial killing of tumor cells by cytotoxic T cells activated through a bispecific single-chain antibody construct
Hoffmann, P. et al. *Intl. J. Cancer* 115: 98-104 (2005)
- Eradication of tumors from a human colon cancer cell line and primary ovarian cancer metastases in immunodeficient mice by a single-chain Ep-CAM-/CD3-bispecific antibody construct
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- Efficient elimination of chronic lymphocytic B cells by autologous T cells with a bispecific CD19xCD3 single-chain antibody
Löffler, A. et al. *Leukemia*. 17: 900-909 (2003)
- Efficient tumor cell lysis by autologous, tumor-resident T lymphocytes in primary ovarian cancer samples by an Ep-CAM-/CD3-bispecific antibody
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- Extremely potent, rapid and co stimulation-independent cytotoxic T cell response against B lymphoma cells catalyzed by a single-chain bispecific antibody
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Bargou et al., *10th International Conference on Malignant Lymphomas*, June 4-7, 2008, Lugano, Switzerland
- Anti-CD19 BiTE Antibody MT103 (MEDI-538) Induces Dose-dependent Objective Complete and Partial Responses in Relapsed Non-Hodgkin Lymphoma (NHL) Patients. Update from Ongoing Phase 1 Study MT103-104
Bargou et al., *49th Annual Meeting of the American Society of Hematology*, December 8-11, 2007, Atlanta, Georgia
- MT103 (anti-CD19 x anti-CD3-BiTE) induces B cell depletion, clearance of bone marrow infiltration and clinical responses in heavily pre-treated NHL patients: first data from dose-escalation study MT103-104
Bargou et al., *11th Congress of the European Hematology Association*, June 15 – 18, 2006, Amsterdam
- T Cell Responses during Long-Term Continuous Infusion of MT103 (MEDI-538; Anti-CD19 BiTE) in Patients with Relapsed B-NHL: Data from Dose-Escalation Study MT103-104
Klinger et al., *48th Annual Meeting of the American Society of Hematology*, December 9 – 12, 2006, Orlando, Florida
- The MT103 BiTE (MEDI-538) Induces Clinical Responses in Heavily Pre-Treated NHL Patients: Update from the Ongoing Phase I Study MT103-104
Bargou et al., *48th Annual Meeting of the American Society of Hematology*, December 9 – 12, 2006, Orlando, Florida