Micromet: engaging immune cells for life

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Micromet is an emerging young German biotech company developing next-generation antibody-based pharmaceuticals. One of its drug formats is called the 'bi-specific T-cell engager' (BiTE™) that leverages the powerful cytotoxic activity of T cells for the elimination of pathogenic cells that cause cancer, inflammatory and autoimmune diseases.

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▼ In December 1998, Gert Riethmüller, Director of the Institute for Immunology at the University of Munich, Germany, achieved breakthrough results in the immunotherapy of cancer. In a clinical study, he and colleagues had shown for the first time that cancer patients at a particular stage of their disease could considerably benefit from a monoclonal antibody-based therapy [1,2].

Erich Felber, Micromet's Chief Executive Officer (who also studied at the Institute for Immunology), formed Micromet to capitalize on these scientific advances (see Box 1 for detail on Micromet's personnel). The first round of financing with international investors was completed in August 1996. In three further rounds, the company has accrued a total of €66 million from a variety of investors, including Atlas Venture, 3i, Schroder Venture, Abingworth, Advent Venture Partners, HBM BioVentures, The Wellcome Trust, International Biotechnology Trust (IBT) and funds advised by Medical Strategy.

Micromet has so far established a broad pipeline of drug candidates with two compounds in clinical trials: a human antibody for treatment of adenocarcinomas (MT201) and a new kind of bi-specific protein for the treatment of B-cell lymphoma (MT103). A further two bi-specific proteins are in preclinical development and several other compounds are at various stages of validation in research.

Adenocarcinomas

Micromet's MT201 is the only fully human antibody in clinical development against the well validated epithelial cell adhesion molecule (EpCAM) target, which is found expressed by most adenocarcinomas. MT201 has 95% homology of variable domains to human germline sequences because of its isolation from a human IgD-positive B cell repertoire. This should significantly reduce the immunogenicity of MT201 compared with humanized, chimeric and murine IgGs. Primate experiments have shown good tolerability of MT201 and a serum half-life of several weeks. MT201 is now in Phase I trials in hormone-refractory prostate cancer patients to determine the optimal biological dose. Prostate specific antigen (PSA) is being used as a surrogate marker for biological activity. Results so far suggest that MT201 is superior to the clinically validated, murine monoclonal antibody Panorex with respect to immunogenicity, serum half-life and cellular cytotoxicity mediated by human immune effector cells. Such IgG1 antibodies are thought to be well suited to the treatment of micrometastatic disease in which low tumour load, sufficient tumour penetration and long serum life of the antibody will contribute to a sustained tumour elimination with low side effects [3–6]. However, advanced cancer stages might require co-treatment of antibodies with chemotherapeutics that increase tumour permeability and reduce tumour cell load.

B-cell lymphoma

The technology underlying the company's therapeutics is BiTE™ (for bi-specific T cell engagers), which we believe is the first drug format to succeed in effectively and selectively engaging the large repertoire of T lymphocytes as cytotoxic effector cells for specific target cell elimination.

BiTE™ technology represents a miniature version of a bi-specific antibody (Fig. 1). BiTEs are

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Box 1. The Micromet team

Micromet has attracted a team of highly skilled individuals who bring together extensive experience and expertise in all aspects of drug development. Beyond Erich Felber, the Executive Board includes Gregor K. Mirow, Chief Financial Officer, previously Managing Director of the Rentschler Medical Drug Group; Patrick A. Baeuerle, Chief Scientific Officer, previously with Tularik, USA; and Christian Itin, Vice President of Corporate and Business Development, a co-founder of Zyomyx, USA. The total staff currently comprises 80 employees, 80% of whom are involved in research and development.

constructed by linking the binding domains of two antibodies with different specificity via short flexible peptides, and are expressed as a single polypeptide chain. BiTEs bind with one arm to a target cell and with their second arm to a T cell, whereupon they activate the T cell. This unique mode of action translates into a cytotoxic potency of BiTE molecules that is at least 10,000-fold higher than that of conventional human IgG1 antibodies. For instance, treatments with Rituxan® requires human doses of 5–10 mg kg^{-1}. However, in primates, BiTEs show a comparable biological activity at only 0.1 μg kg^{-1}, a difference of 50,000–100,000-fold. BiTE action is independent of major histocompatibility complex (MHC) class I and co-stimulatory molecule expression, specific T cell receptors and the addition of extra cytokines. Therefore, BiTEs can overcome many of the strategies tumour cells frequently employ to evade recognition and death by specific T cells. By this mechanism of action, solid tumour elimination is expected to proceed like an acute organ transplant rejection. An ongoing Phase I/II clinical trial with Micromet's first BiTE (MT103) is currently examining the safety of the compound and will be looking for initial suggestions of efficacy in humans. Patients suffering from refractory non-Hodgkin's lymphoma will be treated with total doses of up to 10 μg of MT103 that has shown safety and biological activity in a relevant primate model and essentially cured mice from B-cell lymphoma in a severe combined immunodeficiency disease (SCID) mouse model.

Previous attempts to harness the broad repertoire of cytotoxic T cells via bi-specific antibody therapeutics have encountered severe limitations as indicated by an extensive literature search. These included toxic side effects in clinical trials, low efficacy in T cell activation, the need for co-stimulatory signals and a considerable excess of T cells relative to pathogenic cells and also difficulties with expression and purification. Micromet solved these problems by combining the right format (single-chain bi-specific) with an engineered T-cell-specific antibody.

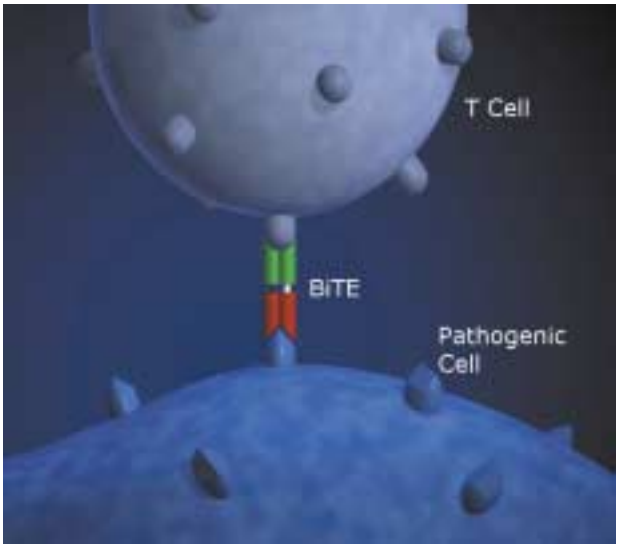

Figure 1. BiTE™ technology represents a miniature version of a bi-specific antibody. BiTEs are constructed by linking the binding domains of two antibodies with different specificity via short flexible peptides, and are expressed as a single polypeptide chain. BiTEs bind with one arm to a target cell and with their second arm to a T cell, whereupon they activate the T cell. This unique mode of action translates into a cytotoxic potency of BiTE molecules that is at least 10,000-fold higher than that of conventional human IgG1 antibodies.

Micromet has consolidated the BiTE technology into a product development platform. In addition to the molecular design and optimization, this includes process development, manufacturing and preclinical and clinical development. Micromet currently has 22 granted patents, giving it a dominant position in the underlying field of single-chain antibody technology and BiTE technology, as well as freedom to operate for BiTE products.

Future projects

The therapeutic mechanism of BiTE drugs is broadly applicable and forms the basis for continuous expansion of Micromet's drug pipeline. Micromet has a primary focus on cancer, inflammation and autoimmune diseases. The company pursues several parallel approaches to secure access to suitable therapeutic targets and antibodies. These include: (1) focussed internal research programs to discover new targets; (2) evaluation of public domain targets; (3) licensing of targets or respective antibodies from academic or industry partners; and (4) co-development of BiTE molecules based on partner-owned targets and antibodies.

Product candidates are developed by Micromet to first proof of therapeutic efficacy in humans. Micromet then seeks partnerships to complete clinical development and then market

products worldwide. To leverage its BiTE platform, the company is prepared to offer one or two BiTE access programs for the co-development of BiTE drugs with partner-derived proprietary targets or antibodies during 2002.

The efficacy and safety of Micromet's drug candidates in the clinic is the key measure of the company's success. In 2002, Micromet will deliver first data from clinical Phase I/II studies in humans (MT103 and MT201), is preparing Phase II studies, and will select further compounds to enter preclinical and clinical development. Micromet will further expand internal resources as well as the network of academic, clinical and industrial partnerships to drive the progress of its therapeutic projects. The team will continue to grow to an estimated 120 employees by 2003. In summer 2002 Micromet will move into a new, dedicated life-science facility, which is currently being built south-west of central Munich. Micromet has signed a tenancy agreement for more than 6,000 m^2 with options for stepwise expansion in subsequent years.

References

1 Riethmüller, G. *et al.* (1998) Monoclonal antibody therapy for resected Dukes' C colorectal cancer: seven-year outcome of a multicenter randomized trial. *J. Clin. Oncol.* 16, 1788–1794

2 Riethmüller, G. *et al.* (1994) Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. *Lancet* 343, 1177–1183

3 Riethmüller, G. *et al.* (1993) Monoclonal antibodies in cancer therapy. *Curr. Opin. Immunol.* 5, 732–739

4 Lindemann, F. *et al.* (1992) Prognostic significance of micrometastatic tumour cells in bone marrow of colorectal cancer patients. *Lancet* 340, 685–689

5 Funke, I. *et al.* (1989) Targeting monoclonal antibodies to micrometastatic cells in colon and breast cancer patients. In *Human Tumor Antigens and Specific Tumor Therapy* (Metzger, R. and Mitchell, M., eds), pp. 199–208, Alan Liss Publishers

6 Braun, S. *et al.* (1999) Monoclonal antibody therapy with edrecolomab in breast cancer patients: monitoring of elimination of disseminated cytokeratin-positive tumor cells in bone marrow. *Clin. Cancer Res.* 5, 3999–4004