Turning T cells against tumors

A small human study shows promise for an approach harnessing the immune system to treat non-Hodgkin's lymphoma. Ralf Bargou *et al.*[1] infused 38 subjects who had relapsed after convetional therapies with an antibody construct called a bispecific T cell engager (BiTE). This construct—which was directed to a molecule expressed on tumor cells, CD19—transiently tethers resting T cells to tumor cells and can lead to T cell activation and tumor cell destruction. The construct caused tumor regression in eleven subjects total and in all seven subjects treated at the highest dose.

> "The real test of this technology is whether it proves effective against tumors other than indolent lymphoma —NH"

Michel Sadelain :

The approach taken in this study is a hybrid between antibody-based and cell-based therapies: the CD19-specific small antibody fragments do not cause tumor cell lysis in and of themselves but are designed to recruit endogenous effector T cells. The specificity and magnitude of the induced *in vivo* T cell activation determine the outcome. The recombinant protein resulted in an impressive overall response rate, but also elicited some significant, albeit reversible, side effects such as tremor and convulsions. Restricting the effects of the treatment to the targeted tumor cells will be a battleground for all emerging powerful immunotherapies—including genetically engineered T lymphocytes targeting CD19, at least six of which will be tested in upcoming clinical trials, and antibodies against CD19 and other targets.

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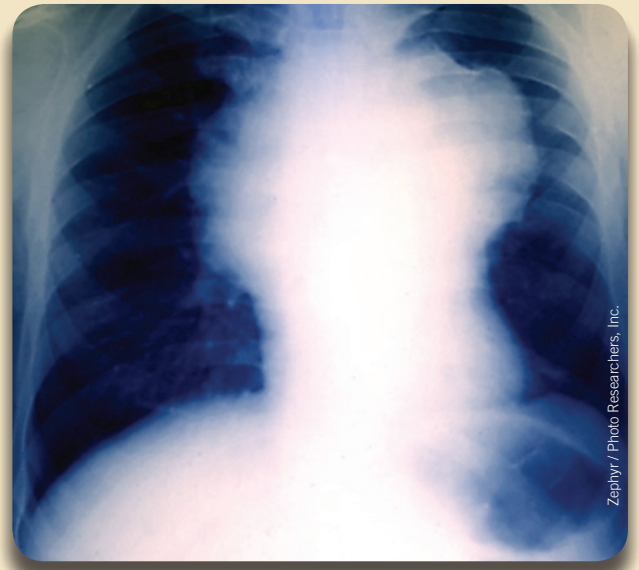

Swollen lymph node (white mass) in center of chest of individual afflicted with non-Hodgkin's lymphoma. Heart (white) at lower center.

Larry W. Kwak:

Human lymphoid tumor cells are known to be sensitive to direct or indirect killing by antibodies, including rituximab, but the BiTE antibody showed much more potent clinical antitumor responses. The findings also dovetail with other immunotherapy studies showing direct lysis of autologous lymphoma cells by T cells—including vaccines that elicit tumor antigen–specific T cells in people pretreated with rituximab to deplete B cells[2]. To nail down the mechanism, future studies of this and other BiTE constructs will need to show functional killing of tumor cells by T cells and the presence of activated T cells in the tumor bed.

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COMPETING INTERESTS STATEMENT
The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

Nick Haining:

Bargou *et al.*[1] appear to have overcome two major obstacles in cancer immunotherapy: making patients' own T cells recognize their tumors and generating T cells of the right sort in sufficient numbers to eradicate bulk disease. Because the BiTE antibody activates essentially all T cells, the latter problem becomes redundant. Widespread activation of the T cell compartment probably explains the remarkable potency of the drug, but also suggests that the balance between efficacy and toxicity will be precarious. But the real test of this technology is whether it proves effective against tumors other than indolent lymphoma, a disease known to be sensitive to immunotherapy with antibodies or allogeneic bone marrow transplant.

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1. Bargou, R. *et al.* Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science* **321**, 974–977 (2008).
2. Neelapu, S.S. *et al.* Vaccine-induced tumor-specific immunity despite severe B-cell depletion in mantle cell lymphoma. *Nat. Med.* **11**, 986–991 (2005).