Recombinant Antibodies (D0500)

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Experimental Cancer Therapy with Recombinant Antibodies

To isolate human antibodies against targets on tumor cells, we have made large human antibody libraries either by amplifying the antibody gene repertoire from lymphocytes or by gene synthesis using randomised sequences for the antigen binding domains. The binding domains of several mouse monoclonal antibodies against tumor markers and surface molecules on effector cells of the immune system have also been cloned and expressed in bacteria. The antibody binding domains are being used to construct bispecific antibodies in so-called diabody and tandem diabody formats as well as for the construction of immune toxins and tumor vaccines.

Generation and screening of a large antibody library


In cooperation with: Dr. Peter Terneß, Dr. Martin Welschof und Christian Kleist (Institute of Immunology, University of Heidelberg).

We have amplified the antibody gene repertoire from the lymphocytes of a large number of donors and succeeded in generating a library of more than 10^9 independent clones. We were able to isolate antibodies to a wide variety of antigens including small haptenes, peptides and proteins from this library.

Diabodies and tandem diabodies for lysing tumor cells

S. Kipriyanov, M. Arndt, F. Le Gall, M. Little

In cooperation with: Prof. Michael Pfreundschuh (Univ. Klinik Homburg); Dr. Gerd Moldenhauer, Dr. Gudrun Strauss, Dr. Jochen Schumacher, Dr. Claus-Wilhelm von der Lieth, Dr. E. Ronald Matys (DKFZ).

We have made bispecific antibodies in a so-called diabody format. They consist of two molecules: one comprises a heavy chain variable domain of specificity A linked by a short linker to a light chain variable domain of specificity B; the other comprises a heavy chain variable domain of specificity B linked by a short linker to a light chain variable domain of specificity A. The two molecules dimerise to form a bivalent bispecific molecule. A more advanced tetravalent molecule was made by combining the latter four variable domains in a single chain construct that dimerises with itself to form a tandem diabody. These molecules were particularly effective for coupling effector cells such as cytotoxic T cells and natural killer cells with targeted tumor cells for their destruction. We were able, for example, to achieve a complete cure of a Burkitts lymphoma in an animal model system using a tandem diabody for recruiting cytotoxic T cells together with T cell costimulation.

Development of tumor vaccines


In cooperation with: Dr. Ulrich Moebius, University Heidelberg; Dr. Gerd Moldenhauer, Prof. Volker Schirmacher, DKFZ

To increase the immunogenicity of tumor cells, we have used retroviral expression vectors to introduce genes coding for immune stimulatory anti CD3 and anti CD28 single chain antibodies fused to a membrane binding domain into a human melanoma cell line. After a two step incubation of peripheral blood lymphocytes with a mixture of cells that presented one or other of the two antibodies, we succeeded in inducing a specific T cell response against the unmodified tumor cells. Instead of using retroviral vectors, we are also developing bispecific antibodies which com-
prize immune stimulatory antibodies linked to a second an-
tibody that binds to a cell surface antigen. For example, in
one procedure, the targeted antigen is a viral coat protein
expressed after infection with Newcastle’s Disease Virus.
In a quite different approach, we have used mRNA iso-
lated from bladder tumor cells to elicit a specific T cell re-
sponse by using dendritic cells to present antigens.

**Targeting and lysing thromboses with recombinant antibodies**

M. Zeve-Welschof, S. Kipriyanov, M Little

In cooperation with: Prof. Dr. Christof Bode, Dr. Karl-Heinz Peter
und Justin Gruber (Ludolf Krehl Klinik, Univ. Heidelberg)

In a cooperation with the group of Prof. Dr. Bode, a fusion
protein was created comprising a single chain antibody
against fibrin linked by a peptide to hirudin. A factor Xa
cleavage site was positioned just in front of the N-terminus
of hirudin which facilitates the release of hirudin at the site
of the blood clot. This construct was able to efficiently lyse
an artificially produced blood clot.

Grants: BMBF (1 scientist), Mildred Scheel Stiftung (1 scientist),
EU (1 scientist).

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