Cancer Cell International

Oral presentation

Open Access

HLA DR-directed bispecific single-chain Fv antibodies for lymphoma therapy

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from Association for Immunotherapy of Cancer: Cancer Immunotherapy – 2nd Annual Meeting
Mainz, Germany, 6–7 May 2004

Published: 1 July 2004

Received: 28 April 2004

Cancer Cell International 2004, **4**(Suppl 1):S4

This article is available from: http://www.cancerci.com/content/4/S1/S4

Fc receptors are important for the clinical efficacy of therapeutic antibodies. Bispecific antibodies (BsAb) are immunoglobulin-conjugates with two different binding specifities, targeting tumor antigens and effector cell trigger molecules. BsAb, produced by chemical coupling of one antibody against a tumor cell surface antigen with another against a Fc receptor, mediate effective interactions between effector and target cells.

Here, genetically coupled bispecific single chain Fv (bsscFv) were produced – as they easily enable further modifications of the molecule – directed against one of the effector cell antigens FcαRI (CD89) or FcγRIII (CD16) and against HLA class II or Lym-2. Lym-2 represents a variant form of the HLA-DR antigen and is highly expressed on the surface of malignant B cells, but only at low levels on normal cells. HLA class II and Lym-2 are both known as effective targets for effector cell-mediated lysis of malignant human B-lymphoid cells. CD89 is an interesting trigger molecule for BsAb therapy, as it recruits neutrophils as effector cells, which have tumor cytolytic potential against a broad spectrum of tumor cells and are the most abundant circulating blood leukocytes. Antibodies against CD16 have already shown biological activity *in vitro* and in tumor patients by recruting NK cells. The two component scFv were fused via a flexible 20aa linker. ScFv fragments were generated by producing phage display libraries from corresponding hybridomas, and screening the libraries with antigen-positive cells. Recombinant scFv against HLA class II, Lym-2, CD89 and CD16 were thus obtained from the hybridomas F3.3, Lym-2, A77 and 3G8 respectively. Functional bsscFv were expressed and secreted by insect cells and were purified via Nickel chelate chromatography. Purified BsAb reacted with HLA class II or Lym-2-positive target cells and one of the effector cell antigens, CD89 or CD16, respectivly. In ADCC experiments all constructs mediated specific lysis of HLA class II or Lym-2-positive malignant human B-lymphoid cell lines with human MNC or PMN as effector cells. The [CD89 x HLA class II] and the [CD16 x HLA class II] bsscFv also mediated significant lysis of primary cells from patients with B-cell chronic lymphocytic leukaemia (B-CLL). In conclusion, these recombinant bsscFv may allow the specific recruitment of effector cells for an improved therapy in B-lymphoid malignancies.