Cancer Cell International

CANCER CELL INTERNATIONAL

BioMed Central

Oral presentation

Open Access

Genetically modified natural killer cells specifically recognizing the tumor-associated antigens ErbB2/HER2 and EpCAM

C Uherek*[1], T Müller[1], T Tonn[1,2], B Uherek[1], H-G Klingemann[3] and WS Wels[1]

Address: [1]Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus, Frankfurt/Main, Germany, [2]Institute for Transfusion Medicine and Immunohematology RCBDS, Frankfurt/Main, Germany and [3]Section of Bone Marrow Transplant and Cell Therapy, RUSH Medical Center, Chicago, IL, USA

Email: C Uherek* - uherek@em.uni-frankfurt.de

* Corresponding author

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):S7

This article is available from: http://www.cancerci.com/content/4/S1/S7

The continuously growing natural killer (NK) cell line NK-92 is highly cytotoxic against malignant cells of various origin without affecting normal human cells. Based on this selectivity, the potential of NK-92 cells for adoptive therapy is currently being investigated in phase I clinical studies. To further enhance the antitumoral activity of NK-92 cells and expand the range of tumor entities suitable for NK-92-based therapies, here by transduction with retroviral vectors we have generated genetically modified NK-92 cells expressing chimeric antigen receptors specific either for the tumor-associated ErbB2 (HER2/neu) antigen or the human Epithelial Cell Adhesion Molecule (Ep-CAM). Both antigens are overexpressed by many tumors of epithelial origin. The chimeric antigen receptors consist of either the ErbB2 specific scFv(FRP5) antibody fragment or the Ep-CAM specific scFv(MOC31), a flexible hinge region derived from CD8, and transmembrane and intracellular regions of the CD3 zeta chain.

Transduced NK-92-scFv(FRP5)-zeta or NK-92-scFv(MOC31)-zeta cells express high levels of the fusion proteins on the cell surface as determined by FACS analysis. In europium release assays no difference in cytotoxic activity of NK-92 and transduced NK-92 cells towards ErbB2 or Ep-CAM negative targets was found. However, even at low effector to target ratios transduced NK-92 cells specifically and efficiently lysed established ErbB2 or Ep-CAM expressing tumor cells that were completely resistant to cytolytic activity of parental NK-92 cells. Similarly, ErbB2-positive primary breast cancer cells isolated from pleural effusions of patients with recurrent disease were selectively killed by NK-92-scFv(FRP5)-zeta. In an *in vivo* model in immunodeficient mice treatment with retargeted NK-92-scFv(FRP5)-zeta, but not parental NK-92 cells resulted in markedly delayed growth of ErbB2 transformed cancer cells.

These results demonstrate that efficient retargeting of NK-92 cytotoxicity can be achieved, and might allow the generation of potent cell-based therapeutics for the treatment of ErbB2 and Ep-CAM expressing malignancies. This therapeutic approach might be applicable for a large variety of different cancers where suitable cell surface antigens have been identified.