Cancer Cell International

Oral presentation

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Therapeutic efficacy of RAGE-1 and MAGE-9 peptide specific cytotoxic T cell clones in renal cell carcinoma

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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):S13

This article is available from: http://www.cancerci.com/content/4/S1/S13

Renal cell carcinoma (RCC) are supposed to be immunogenic and several clinical trials of immunotherapy using tumor-lysate pulsed dendritic cells have been performed. We here report on the generation and therapeutic efficacy of RAGE-1 and MAGE-9 peptide specific cytotoxic T cell clones.

RAGE-1 and MAGE-9 are expressed on 61% and 40% of RCC. Six MAGE-9 and 14 RAGE-1 derived peptides were found to be immunogenic in the context of the HLA-A2.1 MHC complex. CTL were generated by co-culture with peptide pulsed dendritic cells (DC) or peptide pulsed CD40-activated B cells. The latter are as efficient in antigen presentation as DC, but have the advantage of being easier to generate in great quantitities and to display functional activity for a prolonged period of time. Therefore, they are well suited for the generation of CTL clones to be used in adoptive transfer. Three MAGE-9 and RAGE-1 specific CTL clones were generated. The clones were strictly peptide-specific and displayed high cytotoxic activity not only against peptide-loaded T2 cells, but also against HLA-A2.1-positive RCC lines that naturally expressed MAGE-9, RAGE-1 or both. The *in vivo* efficacy of these MAGE-9 and RAGE-1 peptide specific CTL clones is currently being evaluated in human RCC-bearing SCID, which received after intraperitoneal RCC injection repeated applications of the CTL clones at weekly intervals. So far, the majority of control mice became moribund, but only one mouse receiving a MAGE-9 and a RAGE-1 specific CTL developed a tumor, that had retained MHC class I as well as MAGE-9 and RAGE-1 expression. CTL recovered from these mice at 2 and 3 weeks after the last T cell transfer revealed that CTL had retained their specificity and cytotoxic activity was only slightly reduced.

Thus, B cells appear well suited as antigen presenting cells for the generation of large quantities tumor peptide specific CTL as required for adoptive transfer and cancer testis antigens may well provide suitable target for immunotherapy of RCC.