

Long term memory against oncogene mutations following therapeutic peptide vaccination

*Gustav Gaudernack*, Section for Immunotherapy, Department of Immunology, Institute of Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital and Faculty of Medicine, University of Oslo

*K-Ras* mutations are frequently found in adenocarcinomas of the pancreas. Targeting the immune system specifically against mutant Ras may thus be of clinical importance. Results of earlier clinical studies indicated that synthetic peptide vaccines representing the individual mutations present in the tumour were able to elicit immune responses in the majority of the vaccinated patients, and that such immune responses were associated with prolonged survival. We have followed 23 Whipple operated patients with pancreatic adenocarcinoma for more than 10 years, with respect to long term survival and immunological memory. The patients previously participated in two phase I/II cancer vaccine trials. The vaccine was composed of long synthetic mutant ras peptides designed mainly to elicit T- helper response in combination with granulocyte-macrophage colony-stimulating factor. Out of 20 evaluable patients, 17 (85%) responded immunologically. Long term T-cell memory responses were measured in five, 5 year survivors. Surprisingly, three patients mounted a response up to nine years post vaccination against the single amino acid substitutions caused by the mutations. We have analyzed T cell responses in these long term survivors in detail, both at a polyclonal and clonal level. Both patients still mounted a vigorous Th response against the vaccines they had been given previously. Cytokine profiling on the long term survivors demonstrates high IFN $\gamma$ /IL10-ratios, favouring immunity over tolerance, and secretion of multiple chemokines likely to mobilize the innate and adaptive immune system. Interestingly, these pro-inflammatory cytokine profiles do not follow a Th1/Th2-delineation. Most IFN $\gamma^{\text{high}}$ /IL4 $^{\text{low}}$ /IL10 $^{\text{low}}$  cultures include high concentrations of hallmark Th2-cytokines IL-5 and IL-13. At a clonal level, this does not reflect a mixture of Th1- and Th2-clones, but applies to 19/20 T cell clones confirmed to be monoclonal through TCR clonotype mapping. The immune response was not simply reflecting the existence of a dominant T cell clone, since both fine specificity and HLA restriction studies revealed a surprisingly large variety of T cell specificities in these patients. This may have contributed to the survival of the patients.