The treatment or prevention of cancer by vaccines is vigorously sought. This approach is based on the qualitative and quantitative differences in antigenic repertoire between tumor cells and normal cells and the knowledge that the immune system can identify these differences. Many tumor associated antigens (TAAs) are recognized by Cytotoxic T Lymphocytes (CTL) as processed peptides bound to MHC class I. Using reverse immunology and a screening system based on DBx beta2Microglobulin double knockout mice, transgenic for a single-chain HLA-A2-beta2Microglobulin molecule (HHD mice), we have identified novel immunogenic and antigenic TAAs from breast, prostate, bladder and colon carcinomas. Specific CTL were derived by immunization of HHD mice with tumor peptide extracts loaded on antigen presenting cells and with HHD transfected human tumor cell lines. CTL induced against peptides from various tumors recognized tumor peptides more effectively than peptides extracted from normal tissues and also reacted with a series of peptides derived from overexpressed candidate proteins, identified by differential display methods (SAGE, Microarrays, SSH). Comparison of CTL derived from HHD mice to CTL induced from patient’s PBMC showed overlapping recognition of many candidate peptides. Peptide vaccines, derived from the breast carcinoma antigens MUC1 and BA46-1 and from the prostate antigens PAP, PSGR and STEAP induced CTL that lyse effectively human colon carcinoma cell lines. Analysis of colon carcinoma differentially expressed genes by SAGE, followed by screening for HLA-A2 binding peptides resulted in 500 candidate peptides for immunogenicity screening. We have identified 22 antigenic peptides of which 7 peptides were found to be immunogenic in HHD mice. Interestingly 3 of these peptides are derived from the same 1-8D IFN inducible protein.
xenografts retarded significantly tumor progression. The 1-8D gene was shown to be overexpressed in multiple colon carcinoma samples relative to normal colon tissue from the same patients. The 1-8D gene belongs to a three member family of interferon induced genes. 1-8D, 1-8U and 9-27 are linked on an 18Kb fragment of chromosome 11 and are highly homologous. The murine homologs of 1-8D and 1-8U genes are not tissue specific. Cell cycle analysis of murine 1-8D transfected cells exposed a possible role of these genes in cell growth regulation. The murine 1-8D gene was found to cause growth arrest of transiently transfected HEK293T cells. We also demonstrated that 1-8D stably transfected F10.9 melanoma cells have an increased fraction of apoptotic cells after starvation. Transformation assays in REF transfected with myc+ras in presence of 1-8D revealed a possible role of 1-8D gene as a cell growth inhibitor (figure 2). These observations suggest a putative role of the 1-8D gene as a cell growth inhibitor, Sequence comparison of the human 1-8D in pairs of tumor/normal colon samples revealed single nucleotides polymorphism, multiple mutations and 3 nucleotide in frame insertions in the tumor derived 1-8D gene. These observation suggest that the 1-8D may function as a classical tumor suppressor gene which is mutated in cancer.

Selected Publications

Acknowledgements:
Chair: The George F. Duckwitz Professor of Cancer Research
ISF, Minerva, ICRF, ICA, NOFAR
Horowitz foundation, David Lewis Charitable fund, Ornest family fund, Center for Scientific Excellence, Lombroso Foundation