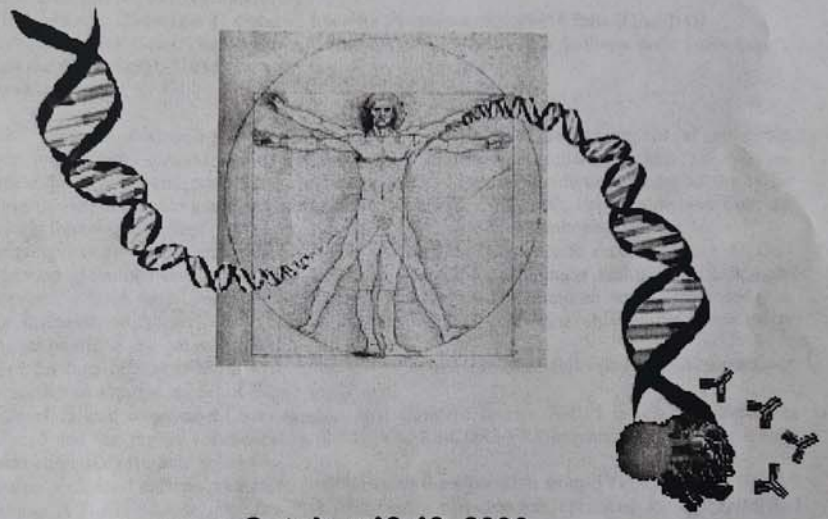
International Workshop on Strategies and Perspectives for Effective Cancer Vaccines



October 12-13, 2006
Polaris, The Science and Technology Park of Sardinia

NIBIT
Network Italiano di Bioterapia dei Tumori

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DNA VACCINATION IN B-CELL LYMPHOMA

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B-cell lymphomas express tumor-specific immunoglobulin, the variable regions of which (Id determinants) are tumor-specific antigens and therefore are suitable targets for vaccine immunotherapy. Several reports have indicated that the immunodominant epitopes of the Ig lie within the hypervariable complementary-determining regions (CDRs). Peptides derived from the flanking framework regions (FRs) may also express cytotoxic T-cell epitopes.

Our group has previously tested the possibility of using the short peptide encompassing the CDR3 of immunoglobulin heavy chain (V_H-CDR3) as a target for eliciting a tumor specific immune response via DNA-based vaccination. We demonstrated that DNA immunization of outbred mice with different patient-derived V_H-CDR3 peptides elicited antibodies able to recognize native antigens on individual patient's tumor cells.

These findings prompted us to investigate the antitumor response following CDR3-based DNA vaccination in a mouse model of B-cell lymphoma.

The nucleic acid sequence of the idiotypic IgM from the murine 38C13 B-cell lymphoma was analyzed and the region corresponding to the V_L-FR3-CDR3-FR4-sequence was chosen for the construction of a synthetic minigene.

We also performed epitope prediction analysis using the algortithm from SYFPEITHI and BIMAS database. A 8-mer peptide from the V_H-CDR3 region was selected, enhanced for further MHC I presentation, and used for the production of a distinct mini-gene.

A pathogen-derived sequence from tetanus toxin (TT) was fused to the tumor antigen to enhance the immunogenicity of the corresponding vaccine. The high-level expression bicistronic plasmid pRC110, designed to express the tumor antigen and the mouse IL-2 as immunomodulating cytokine, was improved by inclusion of a DNA nuclear targeting sequence (NTS) and was delivered by *in vivo* electroporation.

Vaccination of syngenic C3H/HeN mice with CDR3-targeted DNA vaccines protects vaccinated mice against a lethal tumor challenge and generates an immune response to the 38C13 tumor, inducing specific circulating antibodies. Preliminary results indicate that vaccination with the DNA fusion vaccines described in this study improved survival rates when delivered after the onset of tumor growth, suggesting a potential therapeutic application of these vaccines for the treatment of B-cell lymphoma.