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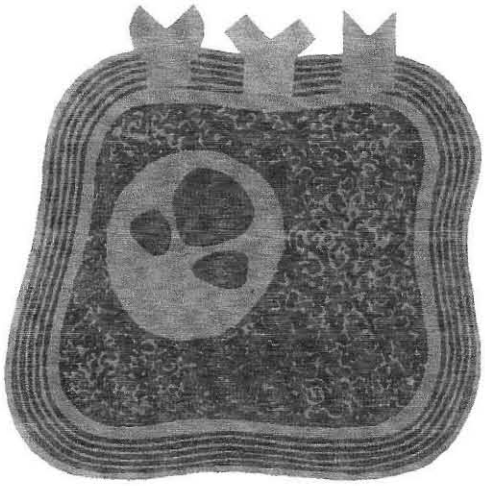

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DNA VACCINE STRATEGY AGAINST CHRONIC B-CELL LYMPHOMA: ANTI-IDIOTYPIC CDR3 VACCINATION AND CYTOKINE CO-EXPRESSION

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B-cell lymphomas express tumor-specific immunoglobulin, the variable regions of which [idiotype (Id)] can be regarded as tumor-specific antigens and targets for vaccine immunotherapy. Promising results have been obtained in clinical studies of Id vaccination using Id proteins or naked DNA Id vaccines. Several reports have indicated that the immunodominant epitopes of the clone-specific Ig lie mainly in the CDR3. Our group has recently demonstrated the possibility of using the short peptide encompassing the CDR3 of immunoglobulin heavy chain (VH-CDR3) as a target for eliciting a tumor specific immune response via DNA-based vaccination. DNA immunization of outbred mice with different patient-derived VH-CDR3 peptides elicited antibodies able to recognize native antigens on individual patient's tumor cells. In the present study, we evaluated the humoral and cellular immune response recruited by VL-CDR3-directed DNA vaccines using the murine 38C13 B-cell lymphoma tumor as a model system. The nucleic acid sequence of the idiotypic IgM (38C-Id) light chain was analyzed and the region corresponding to the CDR3 sequence was chosen for the production of a synthetic mini-gene. A high-level expression bicistronic plasmid DNA vaccine was designed to express both the short VL-CDR3 and the mouse IL-2 sequences. IL-2 was chosen as immunomodulating cytokine to enhance T cell-mediated immune response, to improve antigen-specific T cell proliferation, differentiation and Ig secretion of antigen-activated B cells. Vaccination of syngenic C3H/HeN mice with the described plasmid DNA vaccine was found to generate an immune response to the 38C13 tumor, inducing both specific circulating antibodies and specific cytotoxic T-cell (CTL) activity. This study indicates that a novel CDR3-based DNA vaccine can be used and improved to develop a protective vaccine against B-cell lymphoma by optimization of vaccine dose, route of administration, vector design and prime-boost strategy.