

In vivo efficacy of anti-CD40 antibody for human B- cell lineage hematological malignancies. Iqbal S. Grewal, Ph.D., Dept. Immunology, Genentech Inc., S. San Francisco, USA.

CD40 is a cell surface molecule expressed on antigen-presenting cells, such as B cells, dendritic cells, monocytes and macrophages. The discovery of high CD40 expression on hematological lymphomas has raised interest in the potential for using CD40 as a tumor antibody target for anti-cancer therapy. Our analysis of primary human tumor specimens including samples from NHL, MM, and CLL patients by immunohistochemical staining indicates high expression of CD40 on these tissues. A murine anti-human CD40 monoclonal antibody (SGN-14) and a fully humanized form of this antibody, PRO64553, were evaluated for their in vitro and in vivo anti-tumor properties. These antibodies are weakly agonistic to primary B cells and send a growth inhibitory signal to CD40 expressing neoplastic cells, and induce apoptosis in several B cell lymphoma cell lines. PRO64553 also mediates antibody dependent cytotoxicity (ADCC) of B cell lymphoma cell lines in vitro. Administration of anti-CD40 antibody alone or in combination with Rituxan to tumor-bearing mice in murine xenograft models of Non-Hodgkins lymphoma and multiple myeloma showed (1) significant inhibition of tumor growth; (2) partial, and in some cases complete, tumor shrinkage; (3) delayed, and in some cases undetectable, tumor progression; and (4) significant prolongation of survival of recipient mice. These studies demonstrate that anti-CD40 antibody alone, or in combination with Rituxan, has substantial anti-tumor activity. The ability of anti-CD40 antibody to induce apoptosis and inhibit growth of a wide variety of B cell driven cancer cell lines, while having little effect on normal cells, suggests that this molecule may be useful for cancer therapy.