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Anti-CD40L: biology and therapy in ITP

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Immune thrombocytopenic **purpura (ITP)** is an autoantibody-mediated disease. Platelet-reactive T cells have been found in the blood of patients with this disorder, with the major target antigen being platelet membrane glycoprotein IIb/IIIa (GPIIb-IIIa); autoreactive CD4⁺ T cells are found in lesser numbers in the blood of healthy controls. Kuwana, Ikeda, et al in a series of studies have demonstrated that B-cell production of antiplatelet antibody requires antigen-specific CD4⁺ T-cell help. Thus, T cells are related to the pathogenic process in chronic **ITP**.¹



CD40L (CD154, gp39), a transmembrane protein and member of the tumor necrosis factor (TNF) family, is expressed on activated CD4⁺ T cells, mast cells, basophils, eosinophils, natural killer (NK) cells, and activated platelets. CD40L is important for T-cell–dependent B-cell responses; a prominent function of CD40L, isotype switching, is demonstrated by the hyper-immunoglobulin M (IgM) syndrome in which CD40L is congenitally deficient. The interaction of CD40L-CD40 (on antigen-presenting cells such as dendritic cells) is essential for T-cell priming and the T-cell–dependent humoral immune response.² Therefore, interruption of the CD40-CD40L interaction with an anti-CD40L monoclonal antibody (mAb) has been considered to be a possible therapeutic strategy in human autoimmune disease, based upon the above information and on studies in animals.

In this issue, Kuwana and colleagues (page [1229](#)) report on a phase 1 study of anti-CD40L humanized mAb (IDEC-131/E6040) in patients with refractory **ITP** that allows them to link pathobiology with treatment effect. The investigators explored the in vivo effects of a cohort dose escalation (1 to 10 mg/kg) single infusion study of the effects of anti-CD40L mAb on 3 types of autoreactive T- and B-cell responses to GPIIb/IIIa at 3 time points (before treatment at day 0; after treatment at days 7 and 42) and compared them with the platelet responses. A platelet response was achieved only in 3 of the 5 patients treated at the highest dose (10 mg/kg), even though all 5 patients at this dose level had decreased numbers of B cells producing anti-GPIIb/IIIa antibodies by enzyme-linked immunospot (ELISPOT), reduced GPIIb/IIIa-induced T-

cell proliferation, and decreased anti-GPIIb/IIIa antibody in vitro. No platelet increases were seen at the 3 lower doses, even though patients treated at both the 5 and 10 mg/kg doses showed these autoimmune responses to be decreased. T-cell response to an irrelevant antigen (to which there was no ongoing stimulation) was not affected by anti-CD40L. The authors speculate that failure to achieve a platelet effect at 5 mg/kg, despite suppression of the autoimmune responses, may have been related to the shorter duration of the effect. It is also likely that extravascular effects (ie, in the spleen or other parts of the reticuloendothelial system) are critical and require a higher dose. In addition, there may be a heterogeneity in the pathophysiology of **ITP** since the responders and nonresponders at 10 mg/kg could not be distinguished on the basis of their in vitro responses.

As the authors indicate, there are 3 reports³⁻⁵ on clinical trials using another anti-CD40L mAb (hu5c8) in patients whose **ITP** was substantially more refractory than those included in this study (only 7 of 20 reported here had undergone splenectomy). From these reports and unpublished data (J. B. B., January 2004) for IDEC-131/E6040, it appears that 25% to 50% of patients with refractory **ITP** will have platelet responses to doses of 10 to 20 mg/kg of anti-CD40L administered every 2 to 4 weeks although the responses are rarely durable. These abstracts,³⁻⁵ together with the study reported here, suggest that CD40/CD40L blockade with IDEC-131/E6040 is a potentially effective therapy for refractory **ITP** through selective suppression of autoreactive T cells to platelet antigens.

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