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The effects of anti-BAFF monoclonal antibody in the HLA-A2 sensitized mouse model

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Introduction B-cell activating factor (BAFF) is a cytokine that plays a role in the survival, proliferation and differentiation of B-cells. The aim of this study is to develop an allosensitized mouse model using HLA.A2 transgenic mice, and to observe the effects of anti-BAFF monoclonal antibody (mAb) in this model.

Methods Wild-type C57BL/6 mice were sensitized with skin allografts from C57BL/6-Tg (HLA-A2.1)¹ Enge/J mice and were treated with intraperitoneal injections of anti-BAFF mAb (named Sandy-2) or control IgG1 antibody. Donor specific antibody (DSA) responses were observed by measuring anti-HLA.A2 antibodies in serum of the mice using the luminex assay. B-cell fractions in mice bone marrow and spleen were determined using flow cytometric analysis, and mRNA profiling was done using microarray analysis.

Results HLA.A2-specific IgG was reduced in mice injected with anti-BAFF mAb compared to the control group (Δ -15.8 \pm 6.7 vs. Δ 42.2 \pm 64.7, $p = 0.1$). BAFF blockade resulted in increased pre-pro and immature B-cell proportions in the bone marrow and decreased mature B-cells ($p < 0.05$ vs. control). In the spleen as well, an increase in the proportion of transitional B-cells was observed with a significant decrease in marginal and follicular B-cells ($p < 0.05$ vs. control). There was no significant difference in proportions of long lived plasma cells in the bone marrow and memory B-cells in the spleen. Microarray analysis results showed that, 19 genes were significantly up (>2 fold, $p < 0.05$) or down regulated (<2 fold, $p < 0.05$) in the BAFF blockade group. On further analysis using the CIBERSORT method, gene set enrichment results showed that the IL12 pathway, NO-IL12 pathway and CSK pathways were most significantly enriched (Nominal p -value < 0.05 , FDR $< 25\%$) in the BAFF blockade group.

Conclusion Anti-BAFF monoclonal antibody inhibited anti-HLA.A2 responses resulting in reduction of HLA.A2-specific IgG and significantly inhibited differentiation and maturation of B cells in both the bone marrow and spleen. Our data suggests that BAFF suppression may serve as a useful target in desensitization therapy.