B6-hBAFF

Strain Name: B6/JGpt-Tg(hBAFF)35/Gpt
Strain Type: Tg
Strain Number: T036794
Background: ： C57BL/6JGpt

Description

The B cell activating factor (BAFF) is a B cell survival factor that supports autoreactive B cells' survival and prevents their deletion. Excess BAFF can increase autoreactive B cells, driving autoimmunity(1). BAFF is commonly overexpressed in Systemic Lupus Erythematosus (SLE) and is strongly involved in the pathogenesis of the disease(2). Mice with BAFF deficiency results in the lack of mature B cells, whereas mice that overproduce BAFF have high numbers of mature B cells and antibodies, including autoantibodies, and develop an autoimmune disease similar to SLE in humans(3). BAFF has been shown to be the pivotal target in autoimmunity disease(4).

GemPharmatech used the gene editing technology to generated transgenic mice with overexpression of human BAFF (B6-hBAFF), which displayed significantly high IgG, IgA and IgM compared with wild-type mice, and the antibody levels in the transgenic mice gradually increased with age. The B6-hBAFF mice secrete a high level of anti-DNA autoantibodies, along with an increased ratio of B cells/CD45+ in the spleen and lymph node compared with wild-type mice, indicating over reactive B cells. Proteinuria started at 6 weeks of age with an increase of protein/creatinine in B6-hBAFF mice. This is accompanied with infiltration of inflammatory leukocytes cells in the kidney at 15 weeks of age, suggesting a local kidney inflammation. Taken together, the B6-hBAFF mice developed autoimmune manifestations with overreactive B cells, providing a valuable tool for the efficacy study of drugs targeting B cells in autoimmune disease therapy.

Strategy

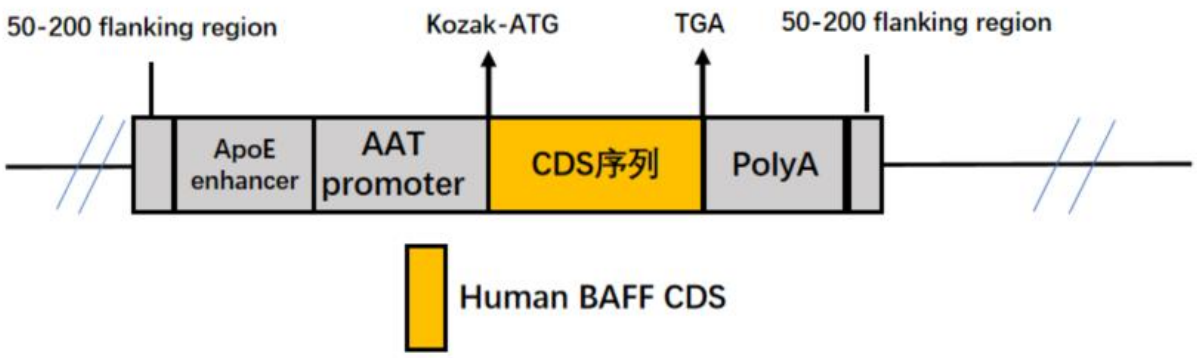


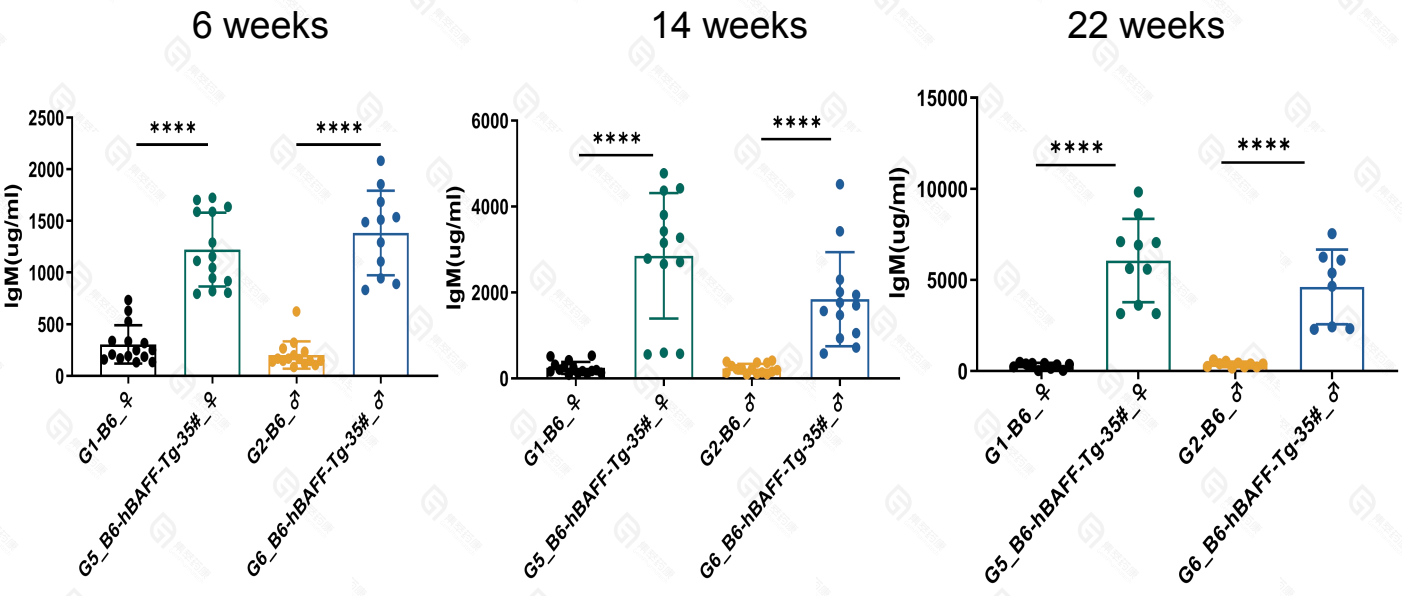
Fig 1. Schematic diagram of BAFF humanization strategy on B6-hBAFF mice.

Applications

1. Efficacy evaluation of human BAFF blockades
2. Safety study of Anti-hBAFF antibody
3. Research on autoimmune diseases

Supporting Data

1. Analysis of antibody expression



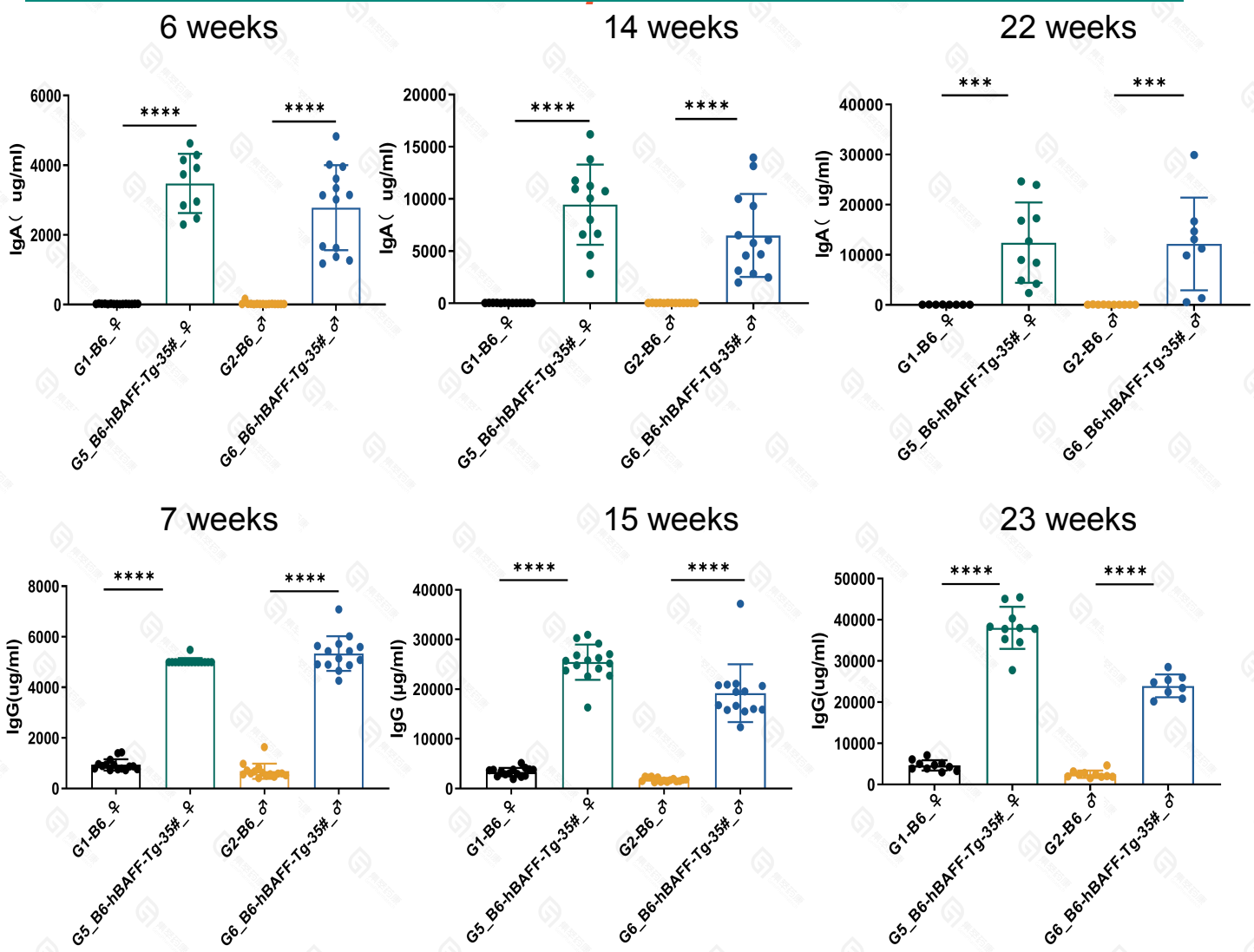


Fig.2 The antibody levels in B6-hBAFF humanized mice

Overexpression of human BAFF led to significantly increased IgG, IgA, and IgM levels since 6 weeks of age compared with wild-type mice, which continued to increase gradually as the transgenic mice aged. Data were presented as Mean ± SEM, *p<0.05, **p<0.01 , ***p<0.001, **** p<0.0001

2. Analysis of anti-dsDNA level

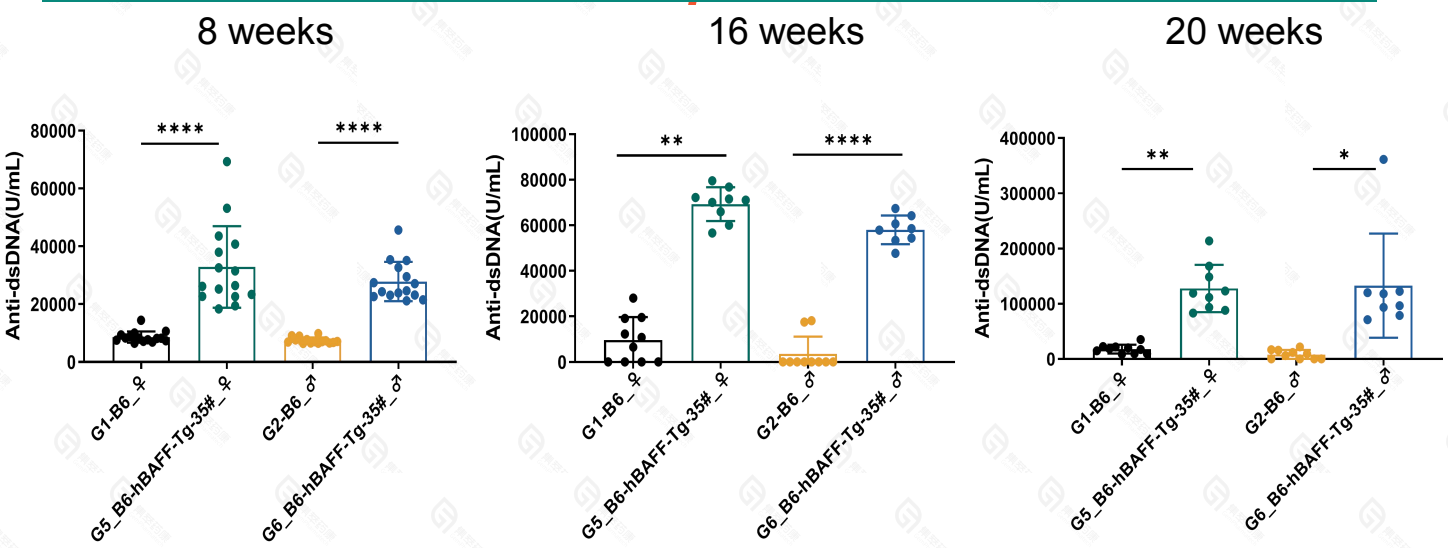
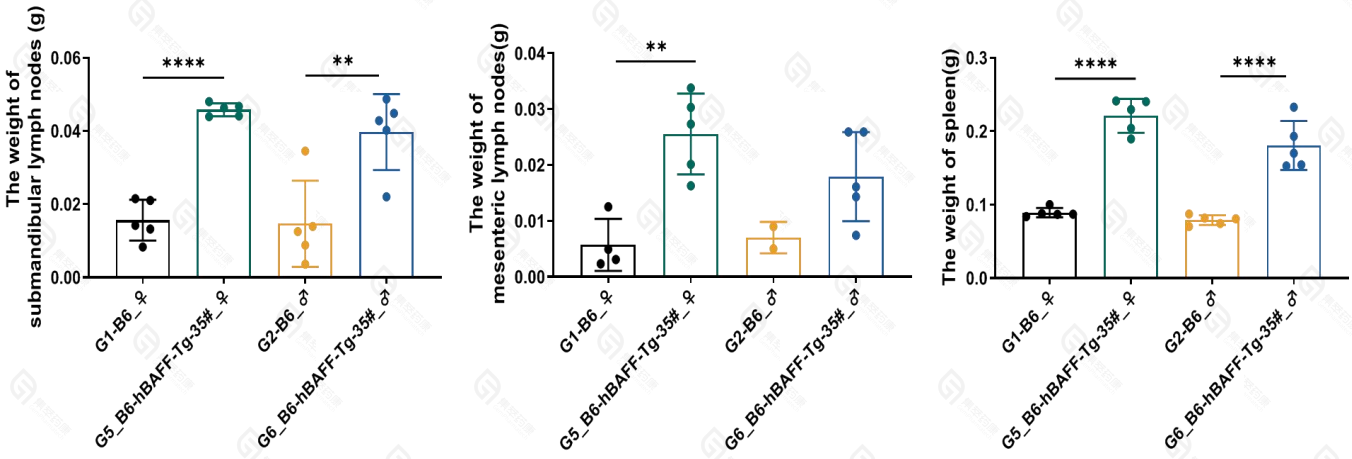


Fig.3 Detection of anti-dsDNA level in B6-hBAFF mice

The B6-hBAFF mice secreted a high level of anti-DNA autoantibodies compared with wild-type mice . Data were presented as Mean ± SEM, *p<0.05, **p<0.01 , ***p<0.001, **** p<0.0001

3. Immune cell subpopulations analysis



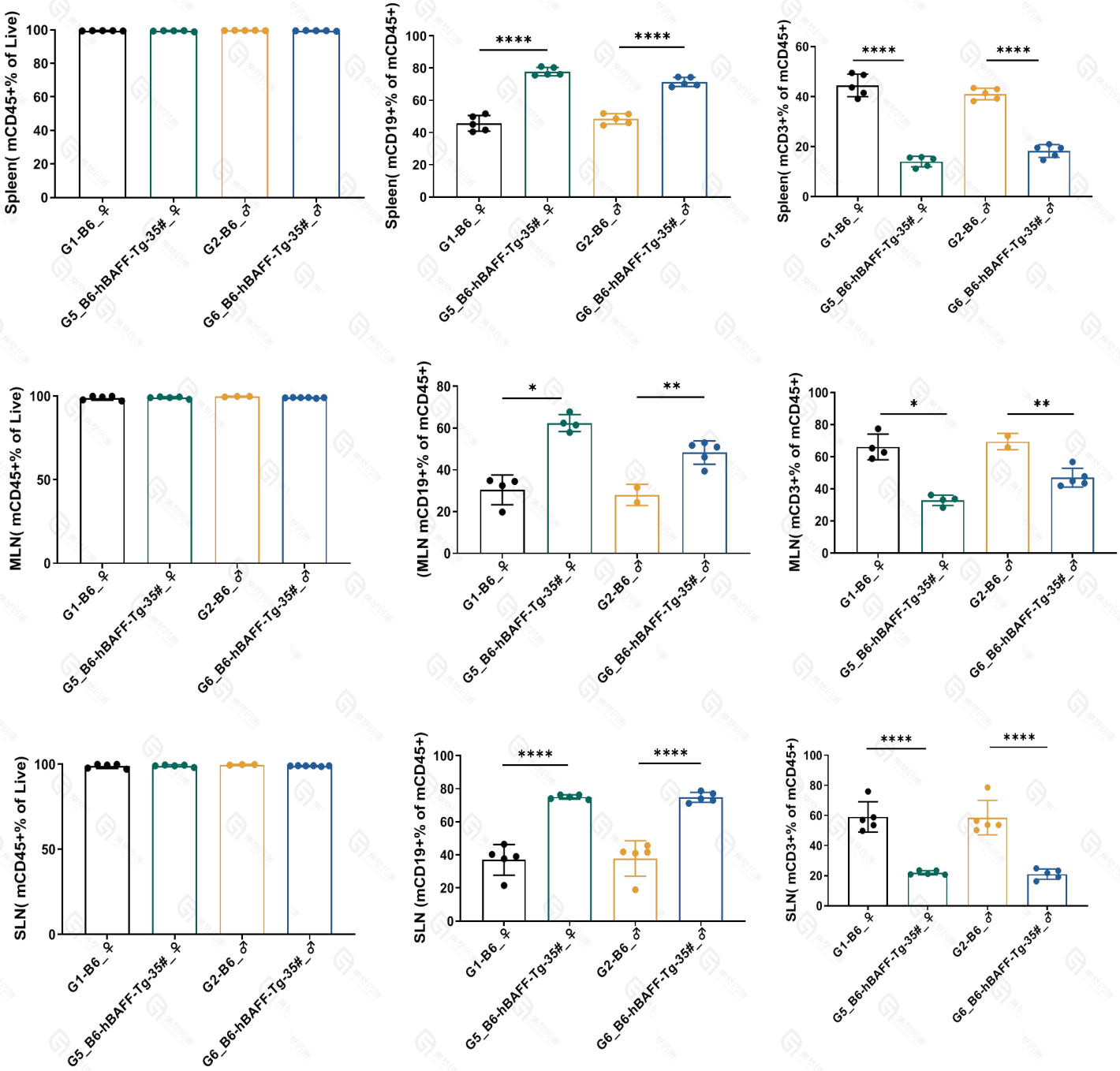


Fig.3 Analysis of immune cell subpopulations in spleen and lymph node

The weight of spleen and lymph node in B6-hBAFF mice was significantly increased compared with wild-type mice at 15 weeks of age.An increased ratio of B cells/CD45+ in the spleen and lymph node compared with wild-type mice was also observed ,indicating overreactive B cells. MLN,mesenteric lymph nodes;SLN,submandibular lymph nodes. Data were presented as Mean ± SEM, *p<0.05, **p<0.01 , ***p<0.001, **** p<0.0001

4. Proteinuria analysis

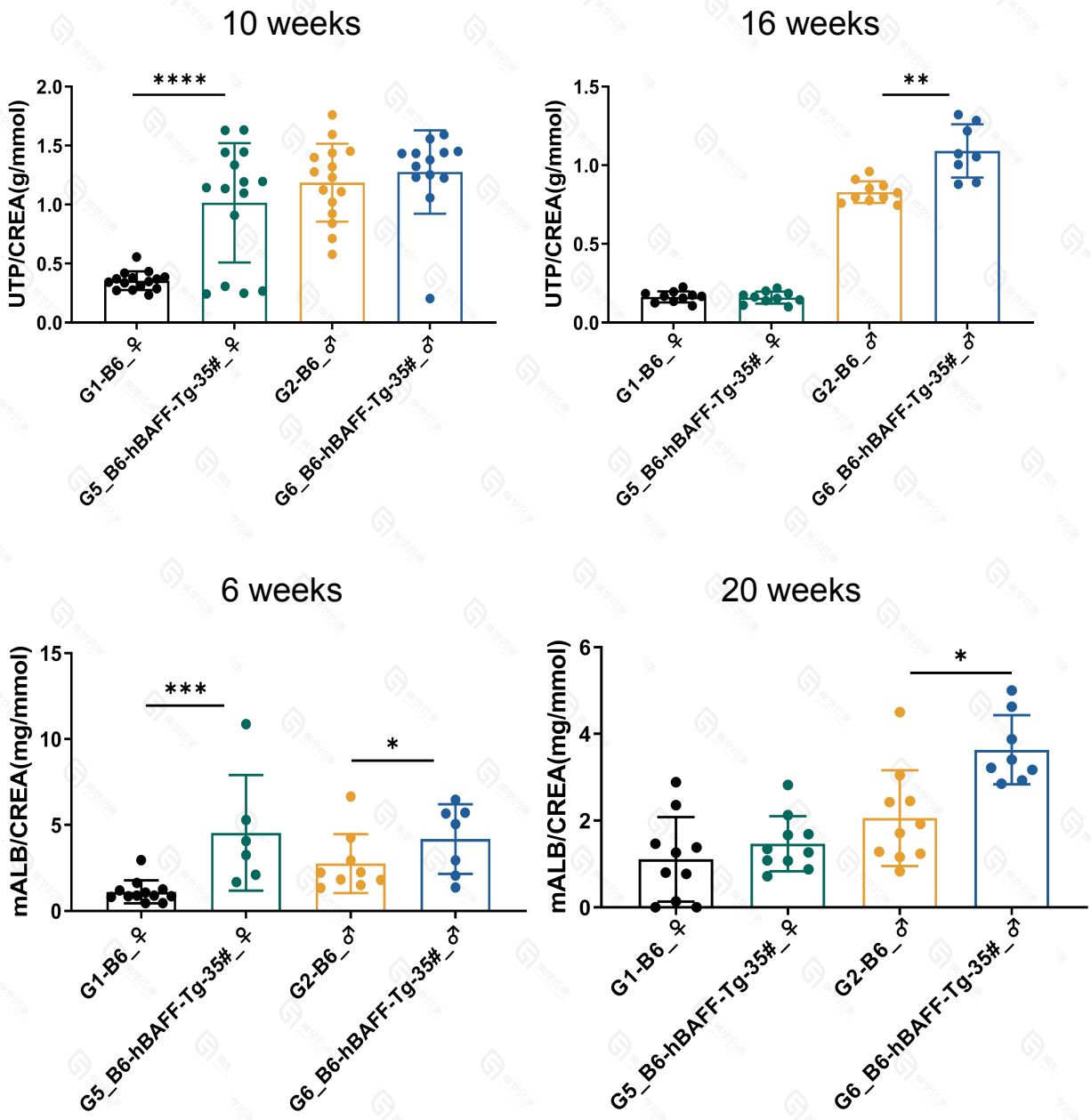


Fig 4. Proteinuria analysis

Proteinuria was observed in B6-hBAFF mice as indicated by increased UTP/CREA and mALB/CREA ratio. UTP, urine total protein; mALB, mouse albumin; CREA, creatinine. Data were presented as Mean ± SEM, *p<0.05, **p<0.01 ,***p<0.001,****p<0.0001

References

1. Schwarting A, Relle M, Meineck M, Föhr B, Triantafyllias K, Weinmann A, Roth W, Weinmann-Menke J. Renal tubular epithelial cell-derived BAFF expression mediates kidney damage and correlates with activity of proliferative lupus nephritis in mouse and men. Lupus. 2018 Feb;27(2):243-256
2. Steri M, et al. Overexpression of the Cytokine BAFF and Autoimmunity Risk. N Engl J Med. 2017 Apr 27;376(17):1615-1626.
3. Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, Tschopp J, Browning JL. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med. 1999 Dec 6;190(11):1697-710.
4. Stohl W. Inhibition of B cell activating factor (BAFF) in the management of systemic lupus erythematosus (SLE). Expert Rev Clin Immunol. 2017 Jun;13(6):623-633. doi: 10.1080/1744666X.2017.1291343. Epub 2017 Feb 15. PMID: 28164726