

### **Cell isolation and culture**

The splenocytes were isolated from the C57BL/6 (H-2b) mice. And then, B cells were purified using the Mouse CD19 Nanobeads (BioLegend, San Diego, CA, USA) according to the manufacturer's protocol. Purified B cells were seeded in RPMI 1640 (Gibco, Dublin, Ireland) containing 10% FCS, 100 U/mL penicillin. In the presence of IL-4, anti-CD40 antibody with FK228 or the vehicle, cells in 24-well plates at a density of  $3 \times 10^5$  cells/well at 37 °C under a saturated 5% CO<sub>2</sub> incubator. Cells and supernatants were collected for further detection. Cell proliferation rates were determined by Cell Counting Kit-8 (CCK-8) assays following the kit instructions. For the control group, purified B cells were cultured with the vehicle. The experimental groups (2, 5, 8 nM FK228) were cocultured for 48 h, following the kit instructions. Apoptosis was evaluated by flow cytometry (FCM) using an Annexin V-FITC Apoptosis Kit (BD Pharmingen, San Diego, CA, USA) according to the manufacturer's instructions.

### **Flow cytometric cross-matching assay**

Splenocytes were harvested and isolated from BALB/C (H-2D) mice. Suspended cells were counted, and 50,000 cells were transferred into flow tubes for staining. Serum samples collected at various time points from B6 were diluted 1:5 in 5 uL and added into the flow tube. The cells and sera were incubated at 20°C for 40 min and then washed and centrifuged. The pelleted cells were resuspended and stained with FITC-labeled anti-mouse IgM (BioLegend, San Diego, CA, USA) and PE-labeled anti-mouse IgG (BioLegend) for FACSCelesta (BD Biosciences, San Diego, CA, USA) detection. The mean fluorescence intensity was calculated.

### **Western blot analysis**

Forty micrograms of protein from each sample were resolved using sodium dodecyl sulfate polyacrylamide gel electrophoresis and subsequently transferred to a polyvinyl difluoride membrane at 300 mA for 2 h. The membrane was incubated with 5% blocking buffer (5% powdered skim milk in) at room temperature for 1 h. After blocking, the membrane was incubated with anti-acetyl-histone H2A-Lys4 (1:1000, Cell Signaling Technology, Danvers, MA, USA), anti-activation-induced deaminase (1:500, ELK Biotechnology, Hubei, China), anti-acetyl-histone H2A-Lys5 (1:1000, Cell Signaling Technology), anti-XBP1 (1:2000, Cell Signaling Technology), anti-acetyl-histone H3-Lys9 (1:1000, Cell Signaling Technology), anti-IRE1 $\alpha$  (1:1000, Abcam, Cambridge, UK), anti-BLIMP-1 (1:1000, Cell Signaling Technology), anti-acetyl-histone H3-Lys27 (1:1000, Cell Signaling Technology), anti-p-IRE1 $\alpha$  (1:500, Abcam), anti-acetyl-histone H3-Lys56 (1:1000, Cell Signaling Technology), anti-HDAC1 (1:1000, Cell Signaling Technology), anti-HDAC2 (1:2000, Abcam), and anti- $\beta$ -actin (1:10,000) at 4 °C overnight. The membrane was washed three times with TBST buffer and then incubated with HRP-conjugated goat anti-mouse secondary antibody (1:10000, ASPEN, Wuhan, China) at room temperature for 1 h. An enhanced chemiluminescence mixture was added to the membrane and chemiluminescence was detected using ChemiDoc XRS+ system (Bio-Rad, Hercules, CA, USA). Immunocomplexes were quantified by ImageJ software (NIH, Bethesda, MD, USA).