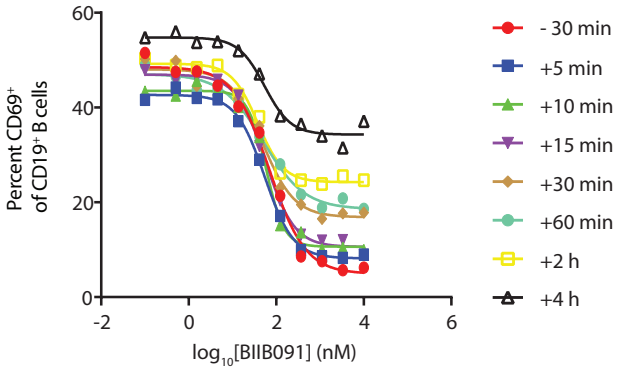
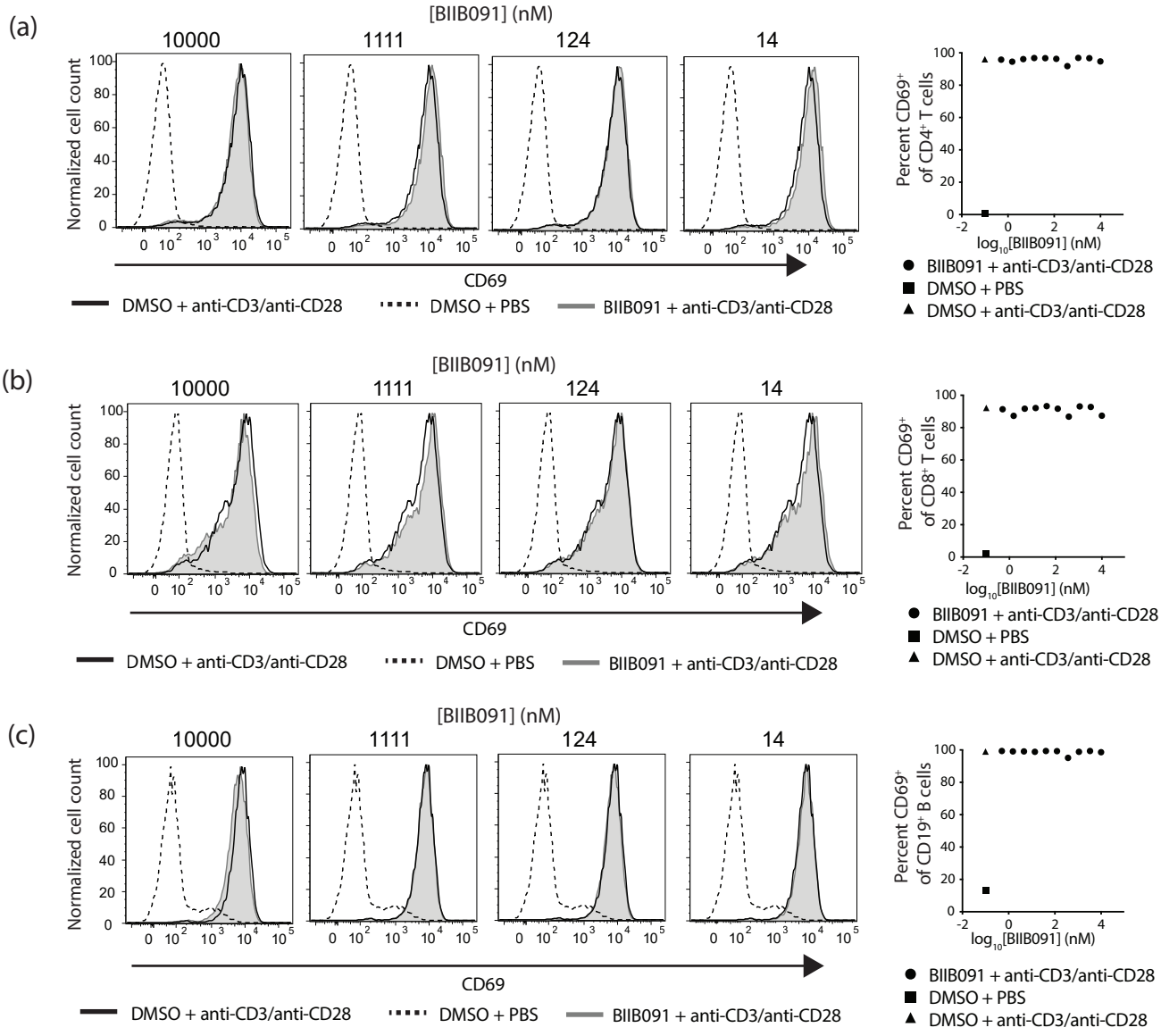
Supplementary figure 1



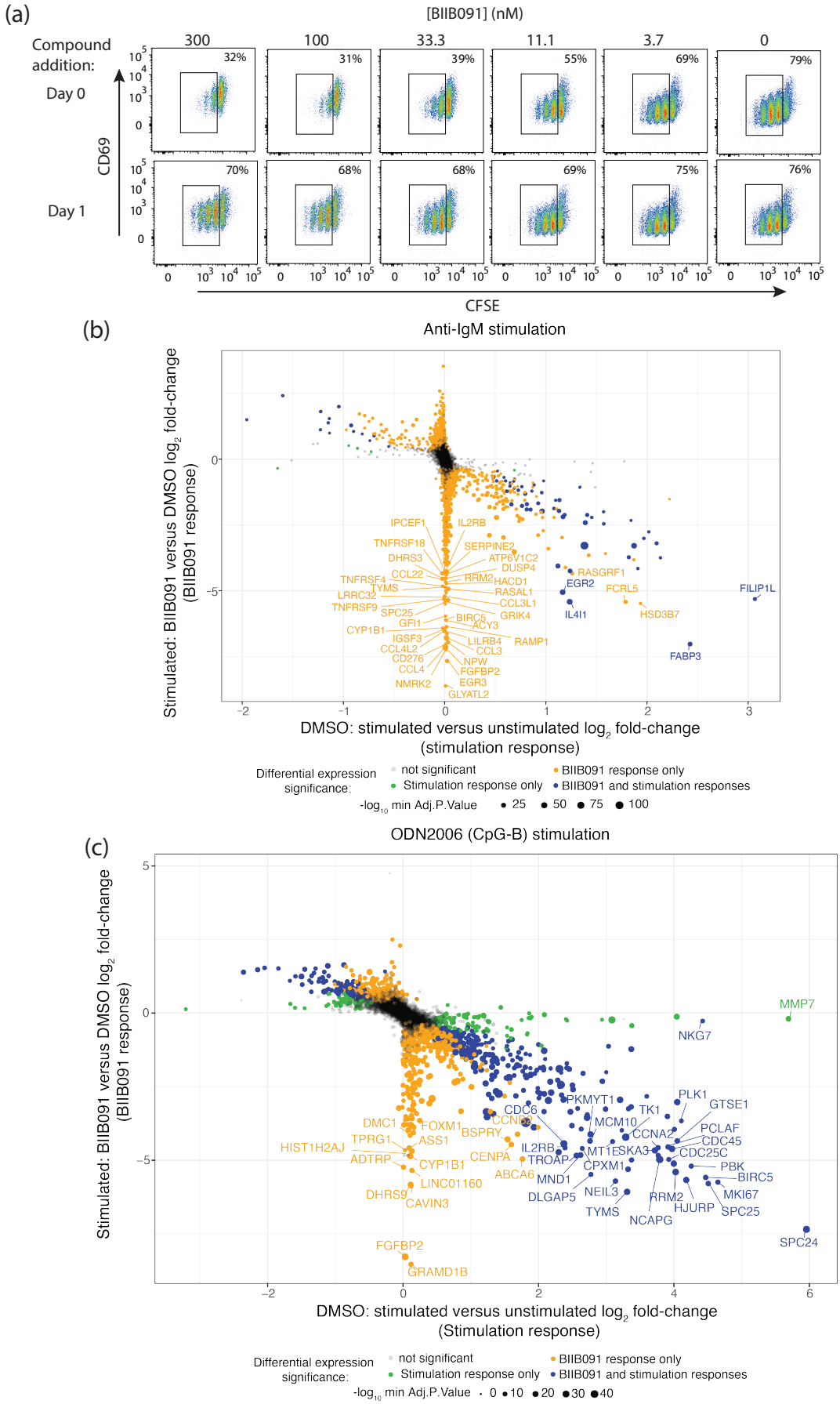
Supplementary figure 1. Inhibition of B cell activation by BIIB091 requires its presence at the time of or within a short time window following activation. Human whole blood was treated with titrating concentrations of BIIB091 30 min before or at the indicated time after stimulation with Dextran conjugated anti-human IgD antibody. Level of B cell activation was measured 16 hours post-stimulation by detection of CD69 by flow cytometry.

Supplementary figure 2



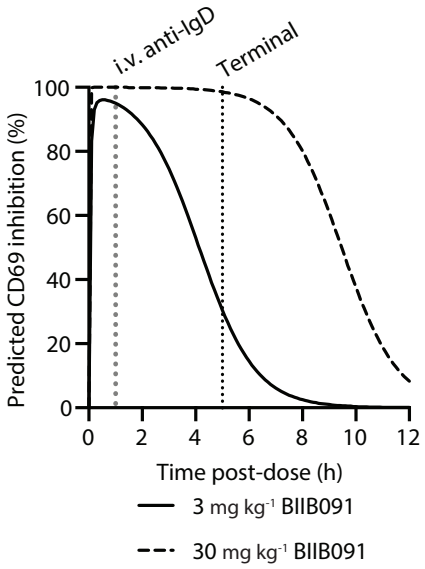
Supplementary figure 2. BIIB091 does not inhibit T cell activation nor antigen-independent B cell activation. (a-c) Histogram overlays of CD69 expression on $CD4^+$ T cells (a), $CD8^+$ T cells (b), and $CD19^+$ B cells (c) from human PBMCs treated with DMSO or titrating concentrations of BIIB091 and stimulated with PBS or plate-bound anti-human CD3 and soluble anti-human CD28 antibodies (left). The percentage of $CD4^+$ T cells (a), $CD8^+$ T cells (b) and $CD19^+$ B cells (c) expressing CD69 was plotted versus the concentration of BIIB091 (right).

Supplementary figure 3



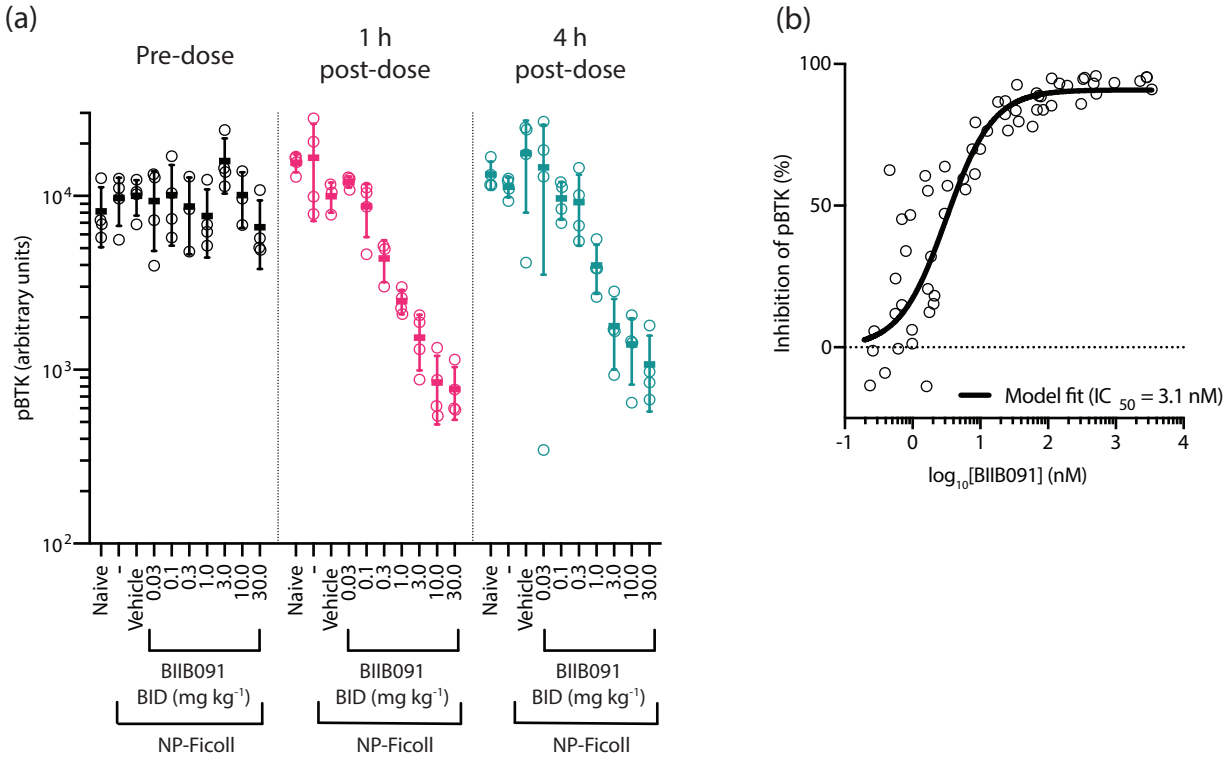
Supplementary figure 3. BIIB091 blocks human B cell activation and associated transcriptional programs. (a) CFSE-labeled human B cells stimulated with anti-IgM/CD40L/IL-21 in the presence of titrating concentrations of BIIB091 added at the time of stimulation or 1 day after. Level of B cell proliferation was analyzed on Day 5. Data representative of 2 independent experiments; (b, c) Log2 fold-change x fold-change plots of differentially expressed genes (FDR < 0.05; fold-change > |1.2|) observed when comparing human B cells treated with DMSO or 100 nM BIIB091 and stimulated in vitro with anti-IgM (b) or CpG ODN 2006 (c).

Supplementary figure 4



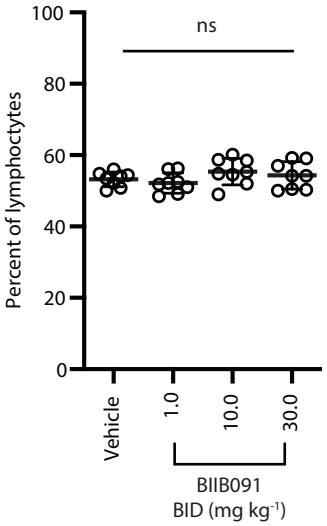
Supplementary figure 4. BIIB091 PK/PD modeling of predicted CD69 inhibition levels in mice. Standard hill equation was used to project CD69 inhibition over the dosing interval for single oral doses of 3 and 30 mg kg^{-1} BIIB091 in mouse using the in vitro mouse whole blood CD69 IC_{50} of 57 nM as a surrogate biomarker of B cell activation. Timepoints for the injection of the anti-IgD antibodies (i.v. anti-IgD) relative to dosing and terminal animal euthanasia (Terminal) for analysis of CD69 and transcriptomic changes (See Figure 6a, b) are indicated by dashed lines.

Supplementary figure 5



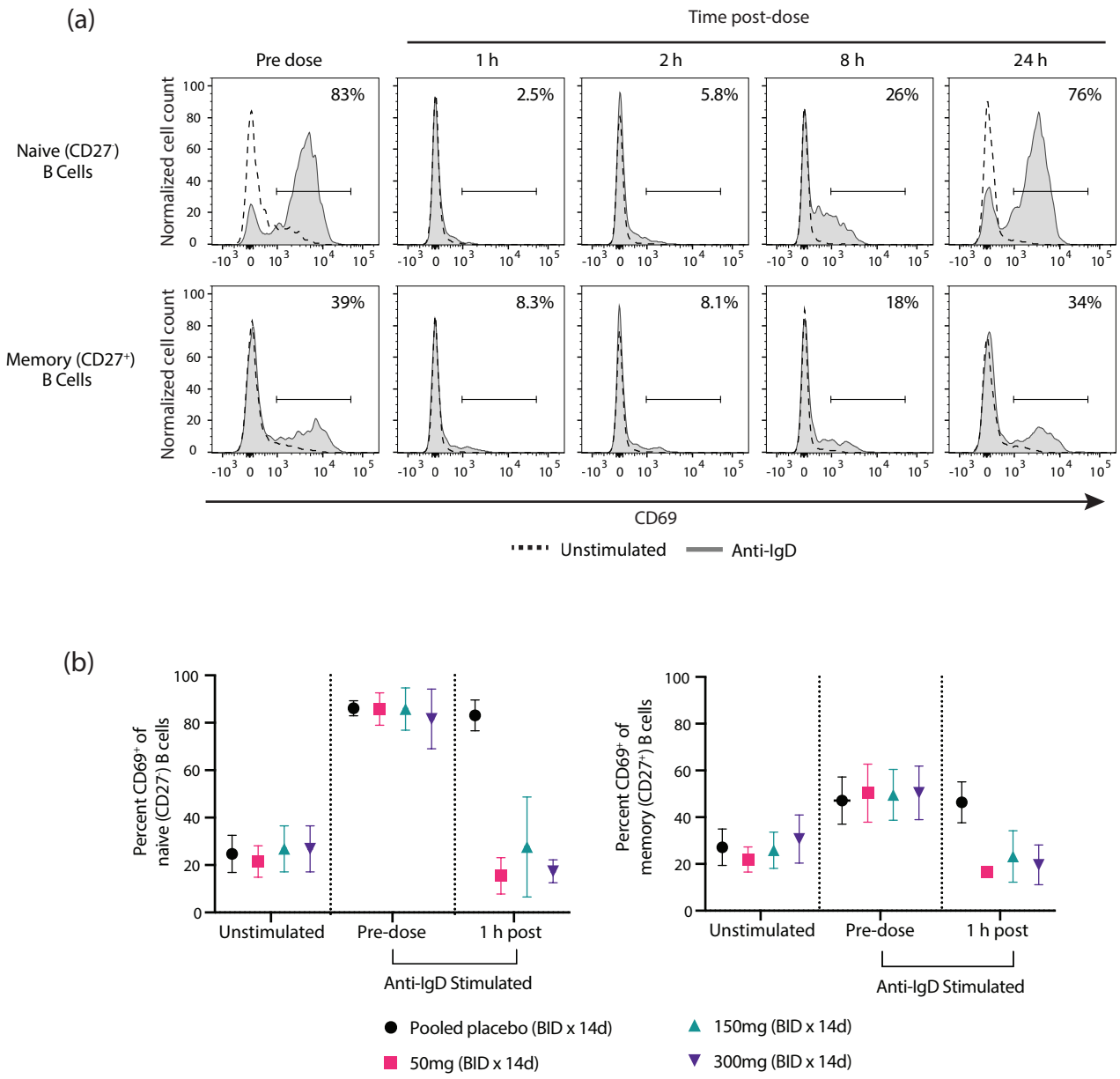
Supplementary figure 5. BIIB091 inhibits phosphorylation of BTK in vivo. (a) Levels of phosphorylated BTK (pBTK) measured in whole blood collected from mice of the indicated dose level groups and at the specified time points from the TI2 immunization experiment (See Figure 6d). n = 4 mice/arm. (b) PK/PD relationship depicting percent inhibition of BTK phosphorylation against plasma concentrations of BIIB091.

Supplementary figure 6



Supplementary figure 6. In vivo treatment with BIIB091 does not alter B cell survival. Dotplot showing the frequency of B cells ($CD3^-$ $CD19^+$ $B220^+$) in spleens of mice dosed BID with vehicle or BIIB091 for 8 days (See Figure 6e, f).

Supplementary figure 7



Supplementary figure 7. BIIB091 inhibits CD69 expression on naïve and unswitched memory B cells. (a) Representative histogram overlays of CD69 expression on naïve ($CD27^-$) and memory ($CD27^+$) B cells from whole blood of a healthy individual receiving a single dose (50 mg) of BIIB091 and stimulated ex vivo with anti-human IgD. (b) Quantification of the frequency (mean ± SD) of $CD69^+$ cells among unstimulated and anti-IgD stimulated naïve ($CD27^-$) and memory ($CD27^+$) B cells from whole blood of healthy individuals dosed with BIIB091 or placebo. BID = twice daily; h = hour(s); d = days