Supplemental Figure 1 **Btk**flox Btkflox/Cre-ERT2 **Btk**null CD11b+ CD11b+ CD11b+ cDCs cDCs cDCs CD11c Macrophages Macrophages Macrophages Ly6G B Btk excision: Btk excision: Btk excision: **Macrophages** Neutrophils cDCs Cre-ERT2 BTK+ BTK+ Btkflox/Cre-ERT2 **Btk**null Secondary alone Btk excision: Macrophages Btk excision: cDCs % BTK positive % BTK positive

Supplemental Figure 1. Inducible knockdown of Btk in $Btk^{flox}/Cre-ER^{T2}$ is stably achieved in splenic innate cells. (A) Representative flow plots for Btk^{flox} (left), $Btk^{flox}/Cre-ER^{T2}$ (middle) and Btk^{null} (right) showing splenic macrophages (CD11b+CD11c+A/80+), neutrophils (CD11b+CD11c-Ly6G+), and conventional dendritic cells (cDCs) (CD11b+CD11c+), five days after tamoxifen injections. Cells are pregated as single live cells. (B, top) Representative histograms of macrophage (left), neutrophil (middle) and cDC (right) Btk expression five days after treatment. Shown are a representative Btk^{flox} (black, solid), $Cre-ER^{T2}$ (black, dashed), $Btk^{flox}/Cre-ER^{T2}$ (red), Btk^{null} (blue), and isotype control (gray). (B, bottom) Percent Btk positive macrophages (left) and cDCs (right). Shown in white are Btk^{flox} (solid, n=18), and $Cre-ER^{T2}$ (diagonal pattern, n=8), in light gray $Btk^{flox}/Cre-ER^{T2}$ vehicle controls (horizontal pattern, n=3), in gray $Btk^{flox}/Cre-ER^{T2}$ after five days (solid, n=12), two weeks (diagonal pattern, n=5), or five weeks (horizontal pattern, n=3) and in black, Btk^{null} (n=13). ***p<0.001 as calculated by one-way ANOVA compared to Btk^{flox} .

		$Btk^{ m flox}$	$Btk^{flox}/Cre-ER^{T2}$ 5 day	$Btk^{flox}/Cre-ER^{T2}$ 5 week	$Btk^{ m null}$
1:10	$\mathit{Btk}^{\mathrm{flox}}$	X	NS	NS	< 0.001
	$Btk^{flox}/Cre-ER^{T2}$ 5 day	X	X	NS	< 0.001
	$Btk^{flox}/Cre-ER^{T2}$ 5 week	X	X	X	0.0012
1:20	$Btk^{ m flox}$	X	NS	NS	< 0.001
	$Btk^{flox}/Cre-ER^{T2}$ 5 day	X	X	NS	0.0031
	$Btk^{flox}/Cre-ER^{T2}$ 5 week	X	X	X	0.0073
1:50	$Btk^{ m flox}$	X	NS	NS	0.0215
	$Btk^{flox}/Cre-ER^{T2}$ 5 day	X	X	NS	NS
	$Btk^{flox}/Cre-ER^{T2}$ 5 week	X	X	X	NS

Supplemental Table 1: Statistics for Figure 6.