Fig. S1

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The dual SYK/JAK inhibitor PRT062070 (Cerdulatinib) demonstrates efficacy in models of autoimmunity and B cell cancer

Greg Coffey, Andreas Betz, Francis DeGuzman, Yvonne Pak, Mayuko Inagaki, Dale C Baker, Stanley J Hollenbach, Anjali Pandey, and Uma Sinha

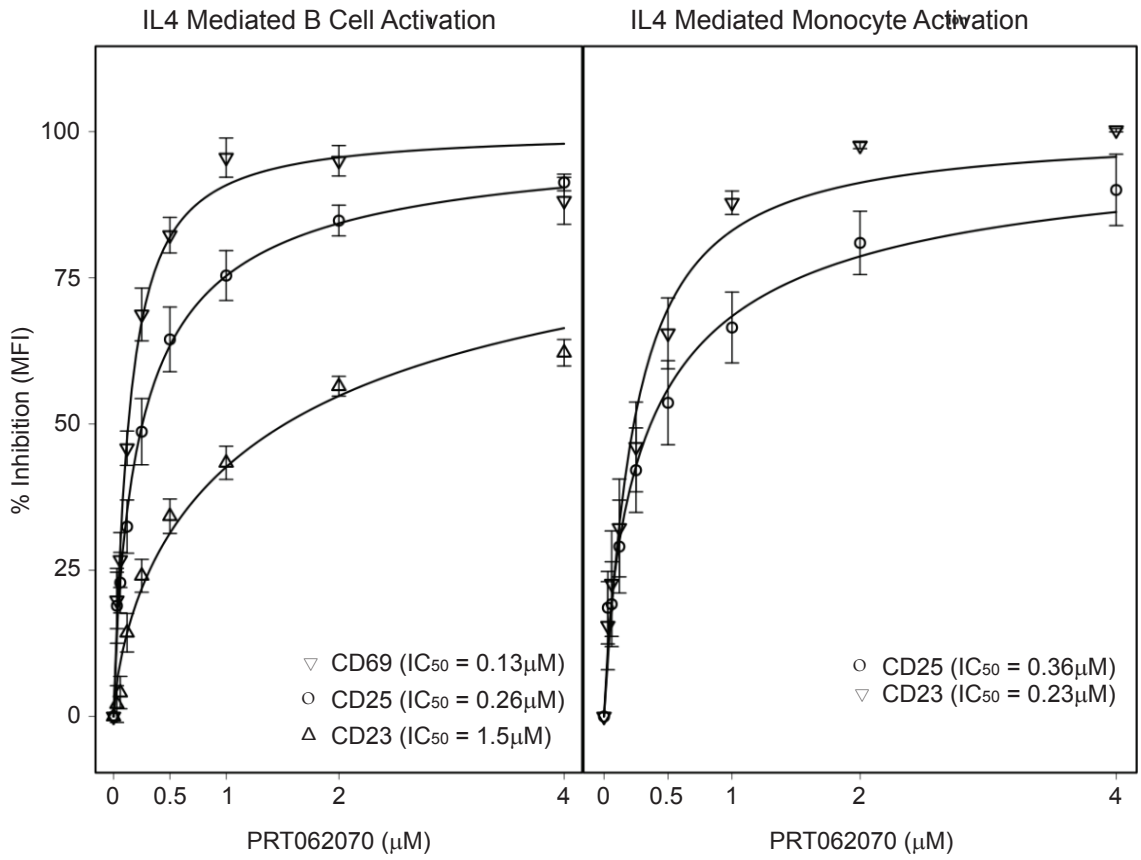

Fig. S1: Inhibition of IL4-induced cellular activation in human whole blood by PRT062070. Whole blood from healthy donors (n=4) was stimulated overnight with IL4 to induce cellular activation in the presense of various concentrations of PRT062070, as shown on the x-axis. Percent inhibition of the various activation markers (CD69, CD25, and CD23) are presented on the y-axis. Activation responses in B cells are shown in the left panel, and responses in monocytes are shown in the right panel. The IC_{50} for each measure of cellular activation is presented on the graph.

Fig. S2

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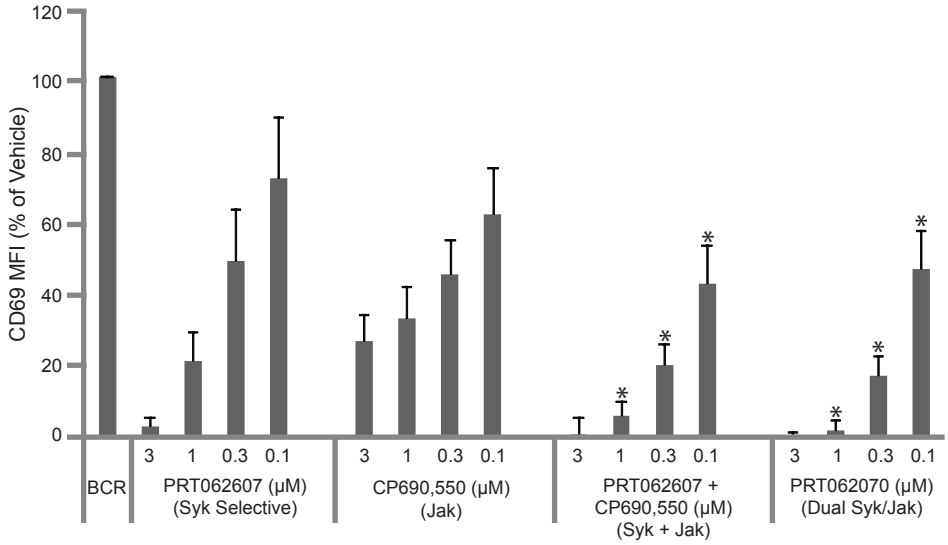

Fig. S2: PRT062070 potency against BCR-mediated B cell function is mimicked by combined SYK and JAK selective inhibition. BCR-induced CD69 up-regulation was evaluated in human whole blood in the presence of SYK selective (PRT062607), JAK selective (CP690,550), combined SYK and JAK selective (PRT062607 + CP690,550) and dual SYK/JAK (PRT062070) inhibitors. CD69 MFI normalized to percent of vehicle control is plotted on the y-axis (mean ± SEM). The asterisks represent significant differences when compared to selective inhibition of SYK or JAK alone ($P < 0.05$).

Fig. S3

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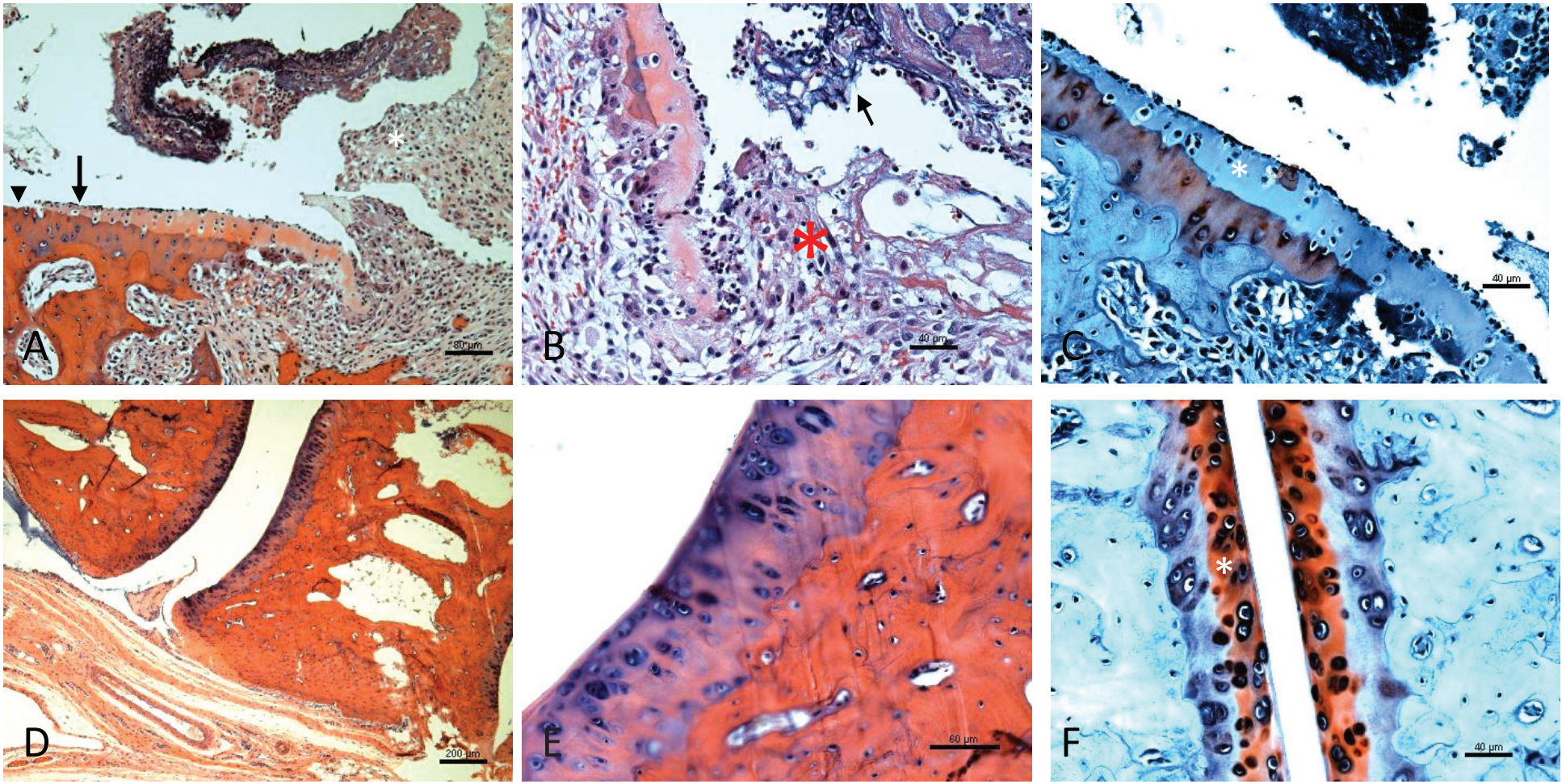

Fig. S3: PRT062070 protects rats from tissue damage in the CIA model. Panels A-F are H&E stained (A,B,D, and E) or Safranin O stained (C and F) sections of tissue from rats immunized with collagen and subsequently orally treated with either vehicle (A-C) or 5mg/kg PRT062070. A) There is cartilage thinning (arrow) and loss of cartilage (arrowhead). B) The joints also had infiltrates of neutrophils and macrophages tangled in figrin (arrow) in the stroma surrounding the joint (red asterisks) and free in the lumen (arrow).C) The surface hyaline cartilage had decreased affinity for safranin O (C, white asterisks) with cartilage only staining with the blue counter-stain rather than red as in normal cartilage (F, white asterisks). D) Normal appearing joint structure in rat dosed 5mg/kg PRT062070. E) Cartilage is normal in rat dosed 5mg/kg PRT062070, and stains normally with Safranin O (F).

Fig. S4

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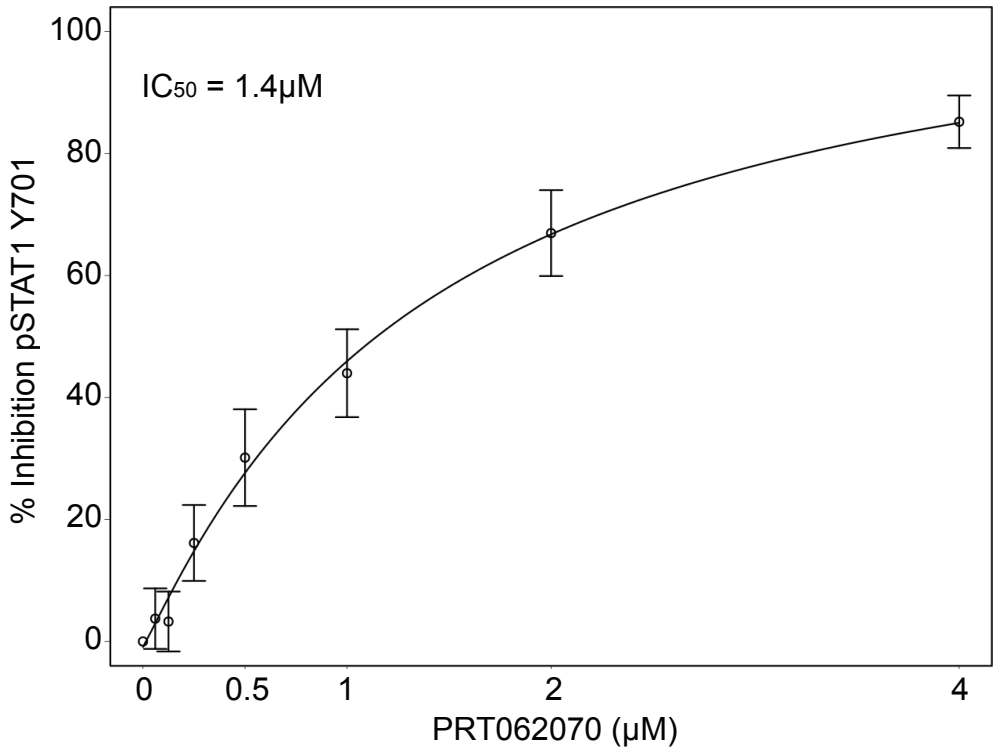

Fig. S4: Inhibition of IL6 signaling by PRT062070 in rat whole blood. Concentration-response curve following stimulation of rat whole blood with IL6 (n=4) in the presense of the indicated concentrations of PRT062070 (x-axis). Percent inhibition of STAT1 Y701 phosphorylation in T cells is depicted on the y-axis. The observed IC_{50} of 1.4μM is shown on the graph.