PNAS

Supporting Information for:

IL-15 synergizes with CD40 agonist antibodies to induce durable immunity against bladder cancer

Jeffrey L. Wong[1,2,7], Patrick Smith[1], Juan Angulo-Lozano[1], Daniel Ranti[3,4], Bernard H. Bochner[5], John P. Sfakianos[6], Amir Horowitz[3,4], Jeffrey V. Ravetch[1*], David A. Knorr[1,2*]

Affiliations
[1]Laboratory of Molecular Genetics and Immunology, Rockefeller University, New York, NY
[2]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[3]The Marc and Jennifer Lipschultz Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[4]Department of Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[5]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY
[6]Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY
[7]Current address: Genentech, Inc., South San Francisco, CA, USA

*Correspondence:

David Knorr dknorr@rockefeller.edu
Jeffrey Ravetch ravetch@rockefeller.edu

This PDF file includes:

Figures S1 to S3

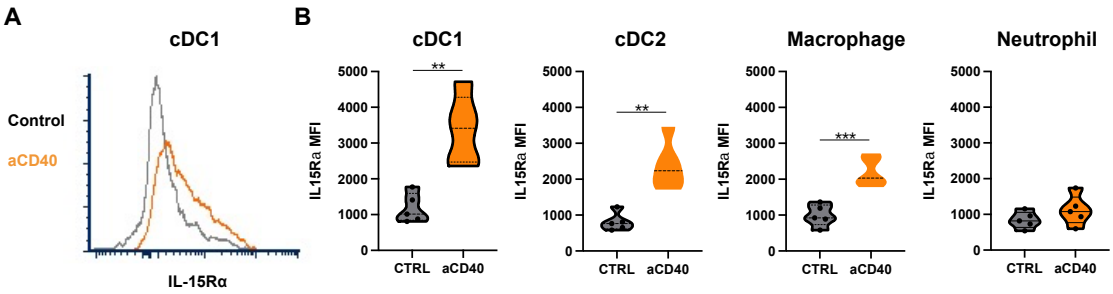

Fig. S1. CD40 agonism induces IL-15Rα upregulation on dendritic cells in the UPPL1541 bladder tumor microenvironment. Mice bearing orthotopic UPPL1541 bladder tumors were treated intravesically with anti-CD40 antibody or isotype-matched control antibody on days 6 and 9 post-tumor implantation. (*A*) Representative histogram and (*B*) quantification across mice of IL-15Rα mean fluorescence intensity on type-1 conventional DCs (cDC1; defined as F4/80$^-$Ly-6G$^-$ CD11c$^+$MHCII$^+$XCR1$^+$), type-2 conventional DCs (cDC2; defined as F4/80$^-$Ly-6G$^-$ CD11c$^+$MHCII$^+$SIRPα$^+$), macrophages (defined as CD11b$^+$F4/80$^+$Ly-6G$^-$), and neutrophils (defined as CD11b$^+$Ly-6G$^+$) in the bladder microenvironment as assessed by flow cytometry at day 12 post-tumor implantation (n = 5 mice per group). **$p < 0.01$, ***$p < 0.001$.

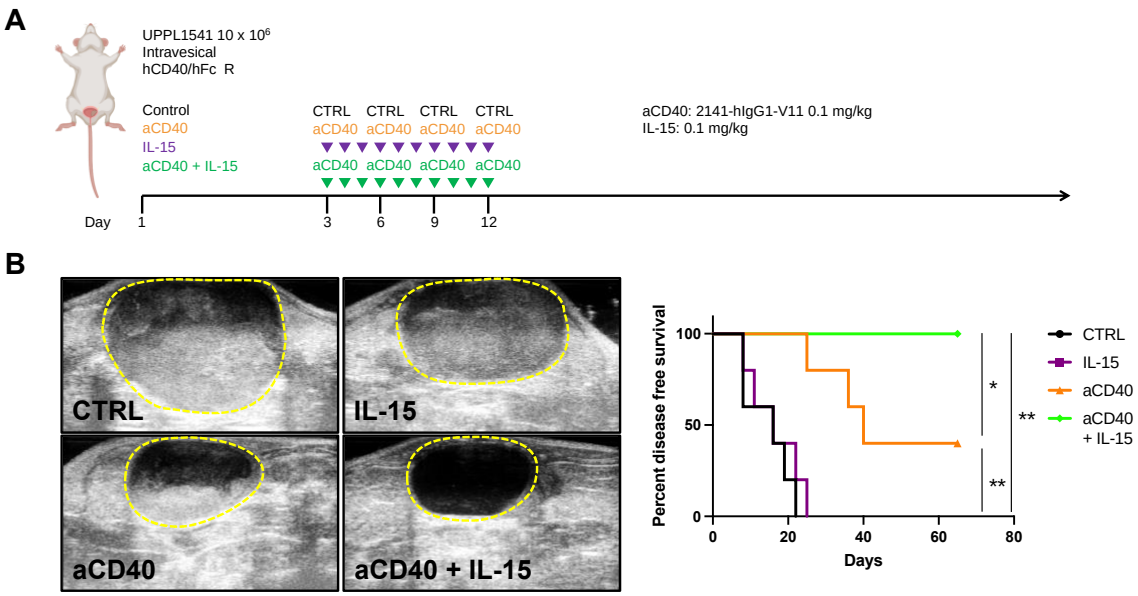

Fig. S2. Combination of Fc-optimized anti-CD40 agonist antibody 2141-V11 and IL-15 enhances anti-tumor activity against UPPL1541 tumors. (*A*) Schematic of the treatment of humanized hCD40/hFcyR mice bearing orthotopic UPPL1541 bladder tumors with anti-CD40 antibody 2141-V11 and/or IL-15 or control (isotype-matched control antibody and/or vehicle). (*B*) Representative bladder ultrasound imaging (left) at day 45 post-tumor implantation and disease-free survival (right) of mice treated as outlined in A. *$p < 0.05$, **$p < 0.01$.

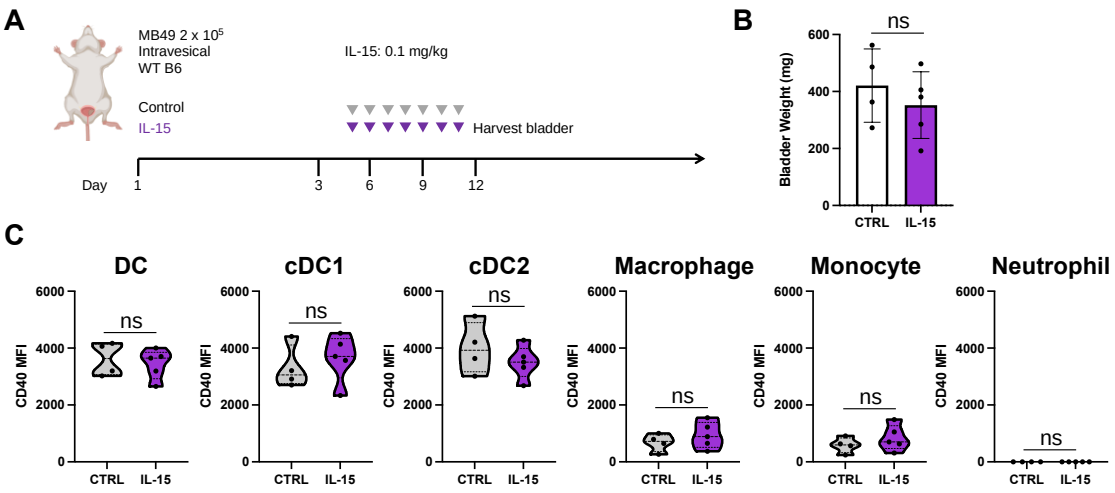

Fig. S3. IL-15 therapy does not modulate myeloid CD40 expression. (*A*) Schematic of the treatment of mice bearing orthotopic MB49 bladder tumors with IL-15 or vehicle control. (*B*) Bladder weights across mice at day 12 post-tumor implantation (n = 4-5 mice per group; bars represent SD). (*C*) CD40 mean fluorescence intensity across mice on total dendritic cells (DC; defined as F4/80$^-$Ly-6G$^-$CD11c$^+$MHCII$^+$), type-1 conventional DCs (cDC1; defined as F4/80$^-$Ly-6G$^-$CD11c$^+$MHCII$^+$XCR1$^+$), type-2 conventional DCs (cDC2; defined as F4/80$^-$Ly-6G$^-$CD11c$^+$MHCII$^+$SIRPα^+), macrophages (defined as CD11b$^+$F4/80$^+$Ly-6G$^-$), monocytes (defined as CD11b^{hi}Ly6G$^-$), and neutrophils (defined as CD11b$^+$Ly-6G$^+$) in the bladder microenvironment as assessed by flow cytometry at day 12 post-tumor implantation (n = 4-5 mice per group). ns = not significant.