SRF388, a first-in-class, fully human monoclonal antibody targeting IL-27, blocks the immunoregulatory effects of IL-27 in immune cells and demonstrates preclinical in vivo antitumor activity.

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Background
- IL-27 is a heterodimeric member of the IL-12/23 cytokine family that consists of two subunits: IL-27p28 and Epstein-Barr virus induced gene 3 (EBI3; Figure 1).
- IL-27 signals through a heterodimeric receptor composed of glycoprotein (gp130) and IL-27 receptor subunit alpha-27RA.
- IL-27 limits intensity and duration of T cell responses during infection and cancer.
- Effects mediated through STAT1 phosphorylation, inhibitory receptor expression, and cytokine production are pro-inflammatory cytokines.

SRF388 is a fully human IgG1 that binds to IL-27p28 and, in addition to binding to IL-27p28, neutralizes IL-27-induced STAT1 phosphorylation in human cell lines and primary T cells.

Ectopic Expression of hIL-27 Induces Inhibitory Receptor Expression in Mouse Immune Cells
- IL-27 Alters Immunoregulatory Receptor Expression on Human Immune Cells
  - IL-27 Inhibits Cytokine Production by Activated Human PBMC
  - SRF388 Screwing Strategy and Properties
  - SRF388 Inhibits IL-27-Induced Inhibition of Proinflammatory Cytokine Production Following PD-1 Blockade
  - SRF388 Inhibits Tumor Nodule Growth in the Disseminated B16 Model of Lung Metastases

Conclusions
- SRF388 is a novel, first-in-class antibody targeting IL-27 that is being developed to potentiate antitumor immune responses for cancers that rely on IL-27 mediated immune escape.
- SRF388 blocks IL-27/STAT1 pathways and, in addition, blocks IL-27-induced STAT1 phosphorylation in human cell lines and primary T cells.
- SRF388 inhibits IL-27-induced immunoregulatory receptor expression in primary human immune cells.
- SRF388 in vivo neutralizes pro-inflammatory cytokine production in response to PD-1 blockade—this effect is inhibited by SRF388.
- SRF388 inhibits growth of disseminated B16 lung tumors in vivo.