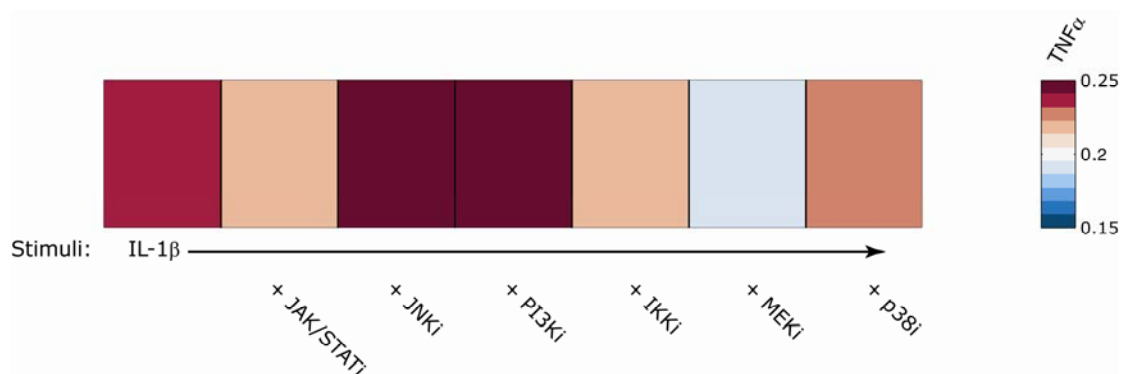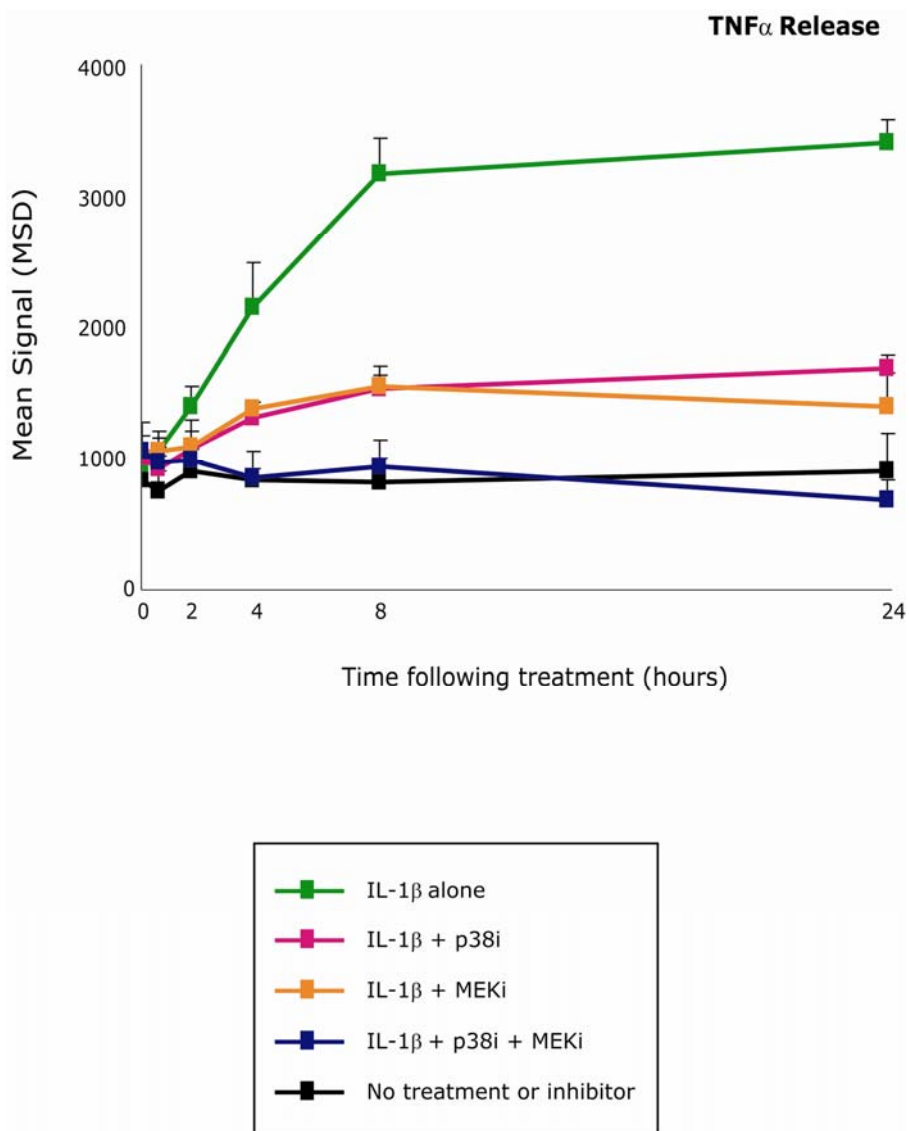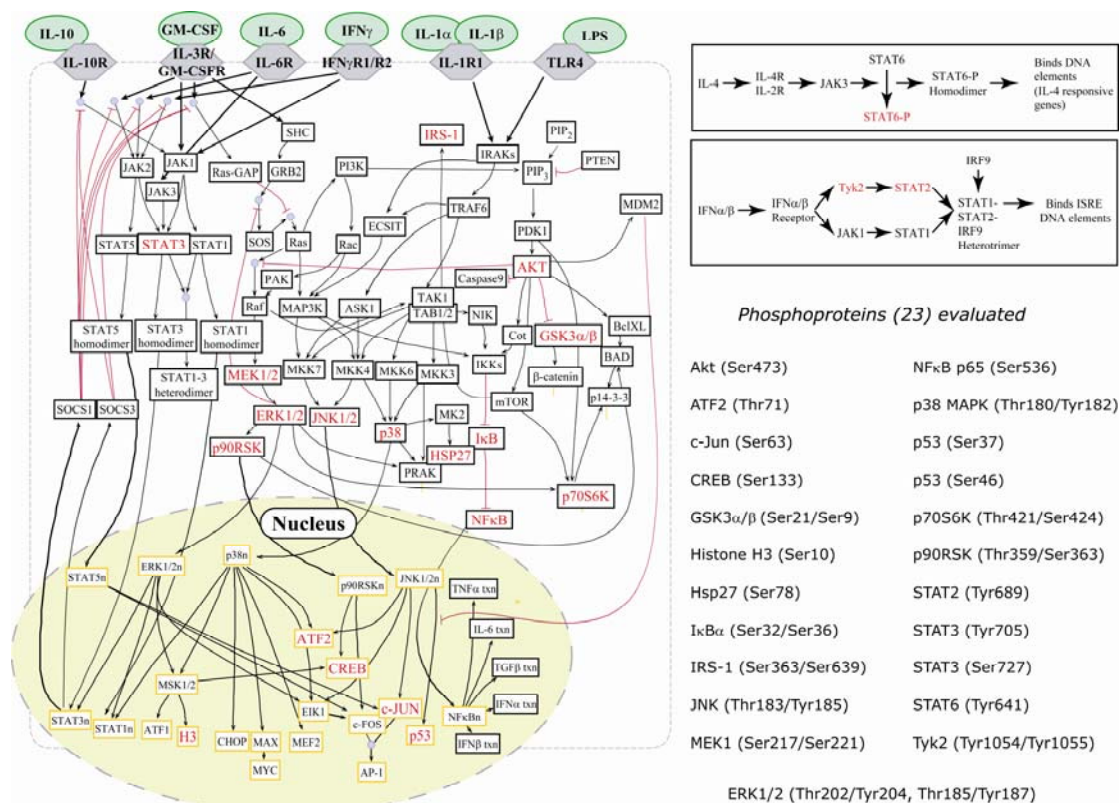# Supplementary Figures
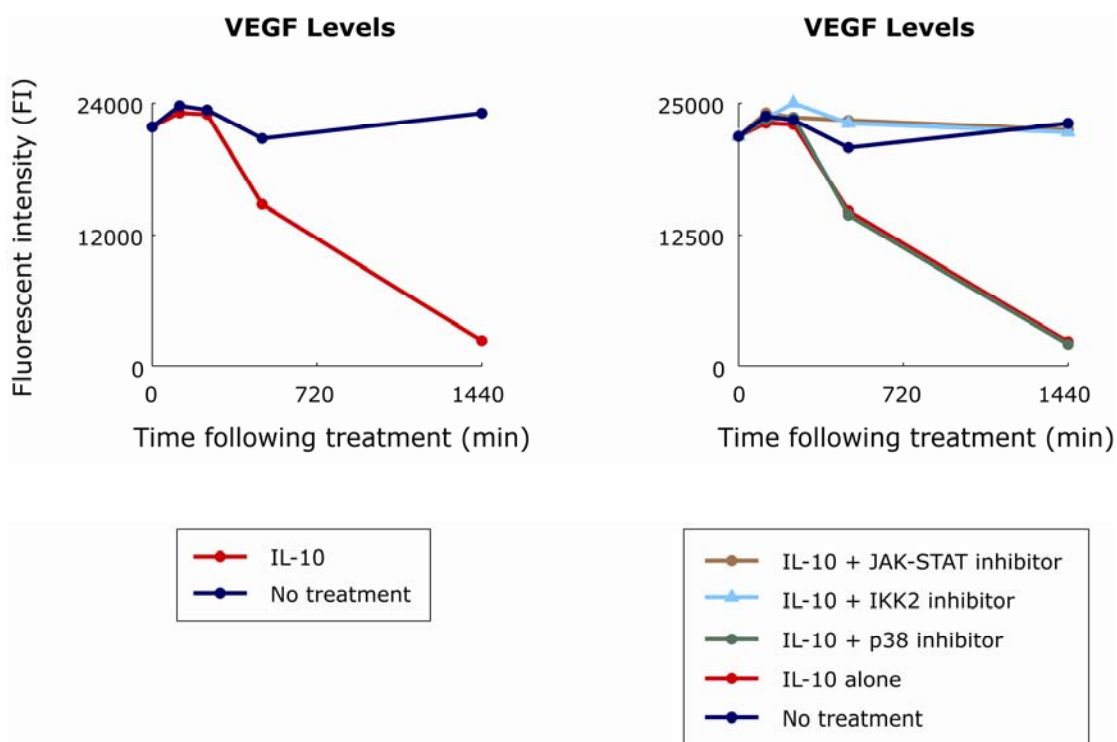

Supplementary Figure 1. *Inhibitor effects with IL-1β treatment.* TNFα levels in supernatant following stimulation with IL-1β in combination with the indicated inhibitors. Data is normalized relative to IL-1β treatment with no inhibitor.

Supplementary Figure 2. *Timecourse data with p38i and MEKi co-treatment.* U937 cells were treated with IL-1β alone (green line), IL-1β + p38 inhibitor (pink line), IL-1β + MEK inhibitor (orange line), or IL-1β + p38 inhibitor and MEK inhibitor simultaneously (purple line). No cytokine or inhibitor serves as a control (black line). Remaining details are as in Figure 4A.

Supplementary Figure 3: *Canonical Pathway diagram for measured phosphoprotein species.* Red text indicates phosphoproteins evaluated in this study. Green spheres indicate ligands. Red lines indicate inhibitory connections. Boxes on top right depict connections not readily integrated with main diagram, but with target proteins which were evaluated. Specific phosphorylation sites targeted with BioPlex antibodies are indicated on right

Supplementary Figure 4: *Effects of IL-10 and Inhibitors on VEGF. (Left)* U937 cells were treated with IL-10 (red line) or media (blue line; No treatment) for the indicated periods of time, supernatants recovered and VEGF levels determined using a BioPlex/xMAP assay. *(Right)* U937 cells were treated with IL-10 alone (red line), or in combination with a JAK/STAT inhibitor (brown line), an IKK2 inhibitor (light blue line) or a p38 MAPK inhibitor (green line). No IL-10 or inhibitor served as a control (No treatment; dark blue line). Inhibitors were added to cells 30 minutes prior to addition of IL-10 at each timepoint. Supernatants were recovered and VEGF levels determined using a BioPlex/xMAP assay.
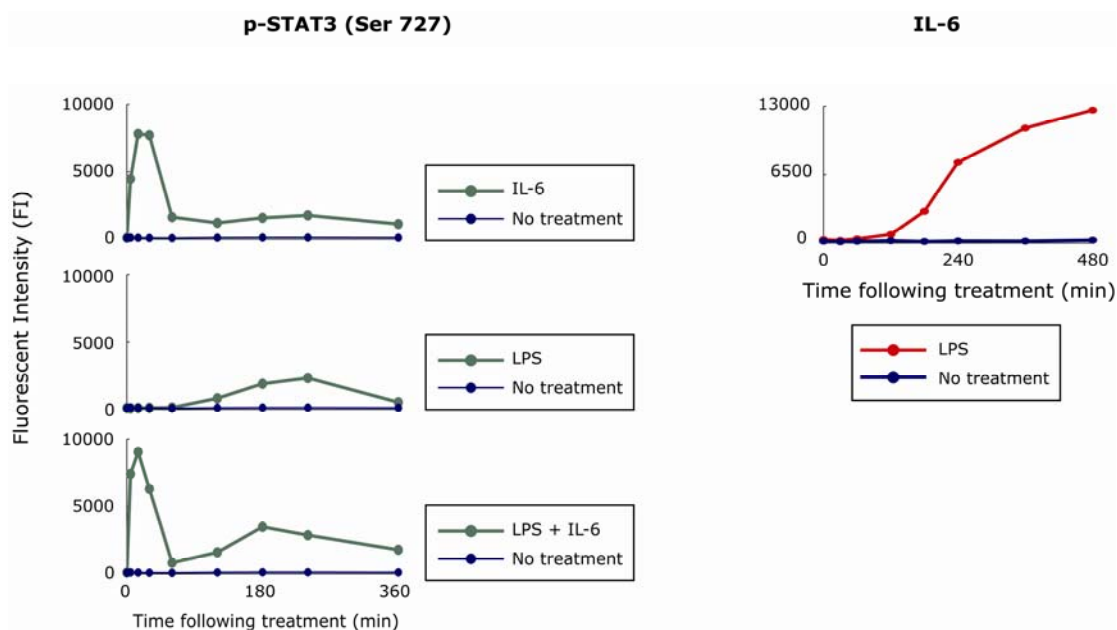
Supplementary Figure 5: *Autocrine/paracrine activities.* U937 cells were treated with IL-6 (top left), LPS (middle left), LPS + IL-6 (bottom left) or media (No treatment; all) for the indicated periods of time. Cell lysates were prepared from each timepoint and p-STAT3 (Ser727) levels determined (BioPlex/xMAP phosphoprotein assay). *(Right)* U937 cells were treated with LPS (red line) or media (blue line; No treatment) for the indicated periods of time. Supernatants were recovered and IL-6 levels determined (BioPlex/xMAP cytokine assay).

Cells treated with IL-6 demonstrate a significant increase in p-STAT3 within 5-30 minutes, while those treated with LPS alone produce a more modest p-STAT3 signal starting at 2 hours. Treatment with LPS + IL-6 results in two peaks, one at 5-30 and another at 2 hours, representing the combined effects of both stimuli. Analysis of cytokines released from the cells treated with LPS reveals a significant increase in IL-6 starting at 2 hours, which presumably binds to the same or nearby cells resulting in the second observed peak of p-STAT3 shortly thereafter.

A.
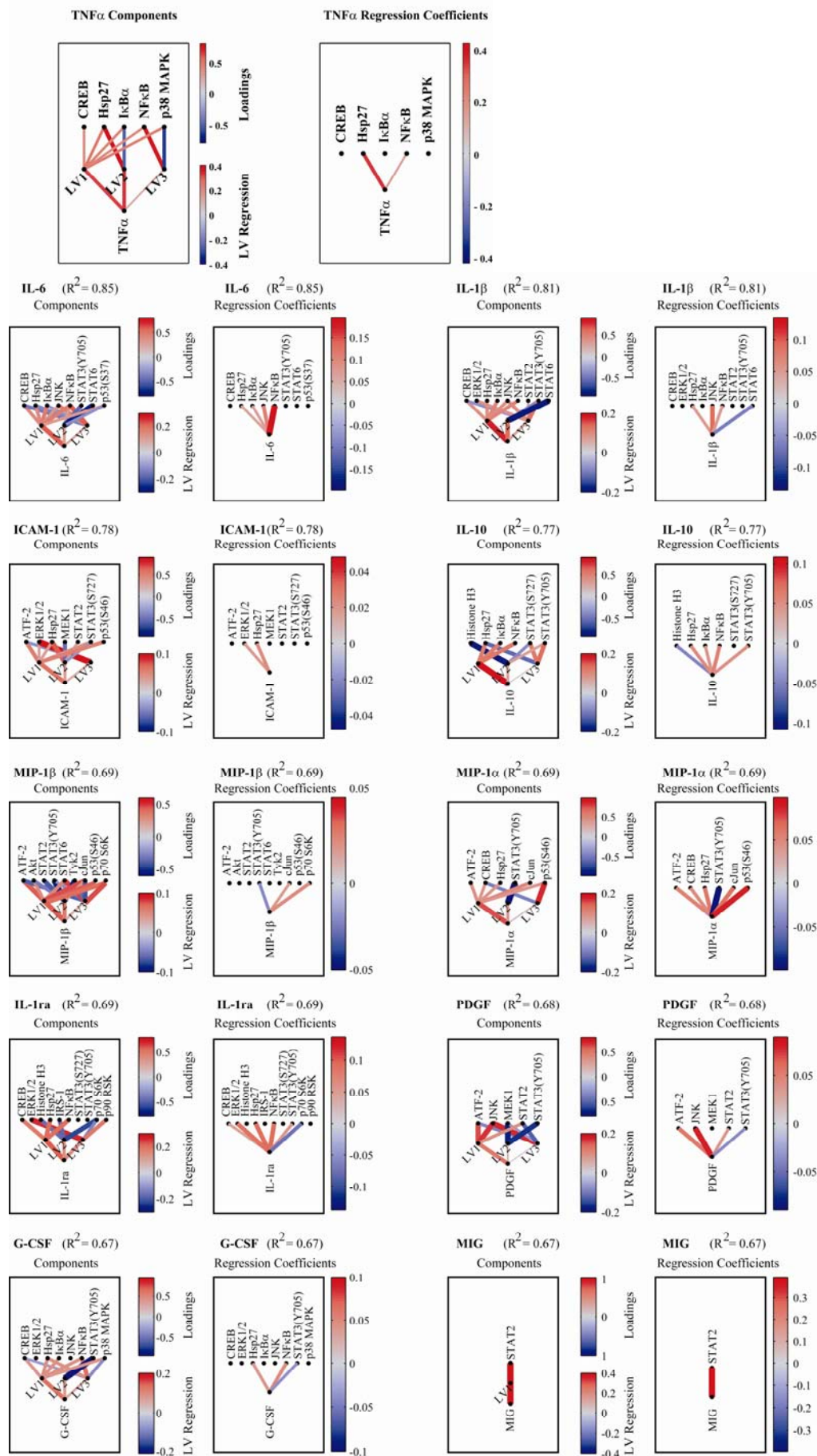
Supplementary Figure 6: *Phosphoprotein-cytokine regression coefficient maps*. The complete phosphoprotein and cytokine dataset, including all inhibitor treatments, was used to generate PLSR models to connect phosphoprotein signals with cytokine production, as described in *Methods*. *(A)* The components of the PLSR model for TNFα, including the most significant loadings connecting phosphoproteins to latent variables (LVs) and the regression coefficients connecting LVs to TNFα. *(B)* The complete phosphoprotein and cytokine dataset, including all inhibitor treatments, was used to generate PLSR models to connect phosphoprotein signals with cytokine production, as described in *Methods*. The most significant loadings and regression coefficients are shown for all cytokines with PLSR models having $R^2 > 0.66$. The loadings and coefficients are drawn as lines, with the color and line thickness indicating the strength of the relationship. Positive values are colored red and negative values colored blue, as indicated by the colorbars.