The Multikinase Inhibitor Sorafenib Reverses the Suppression of IL-12 and enhancement of IL-10 by PGE_2 in Murine Macrophages

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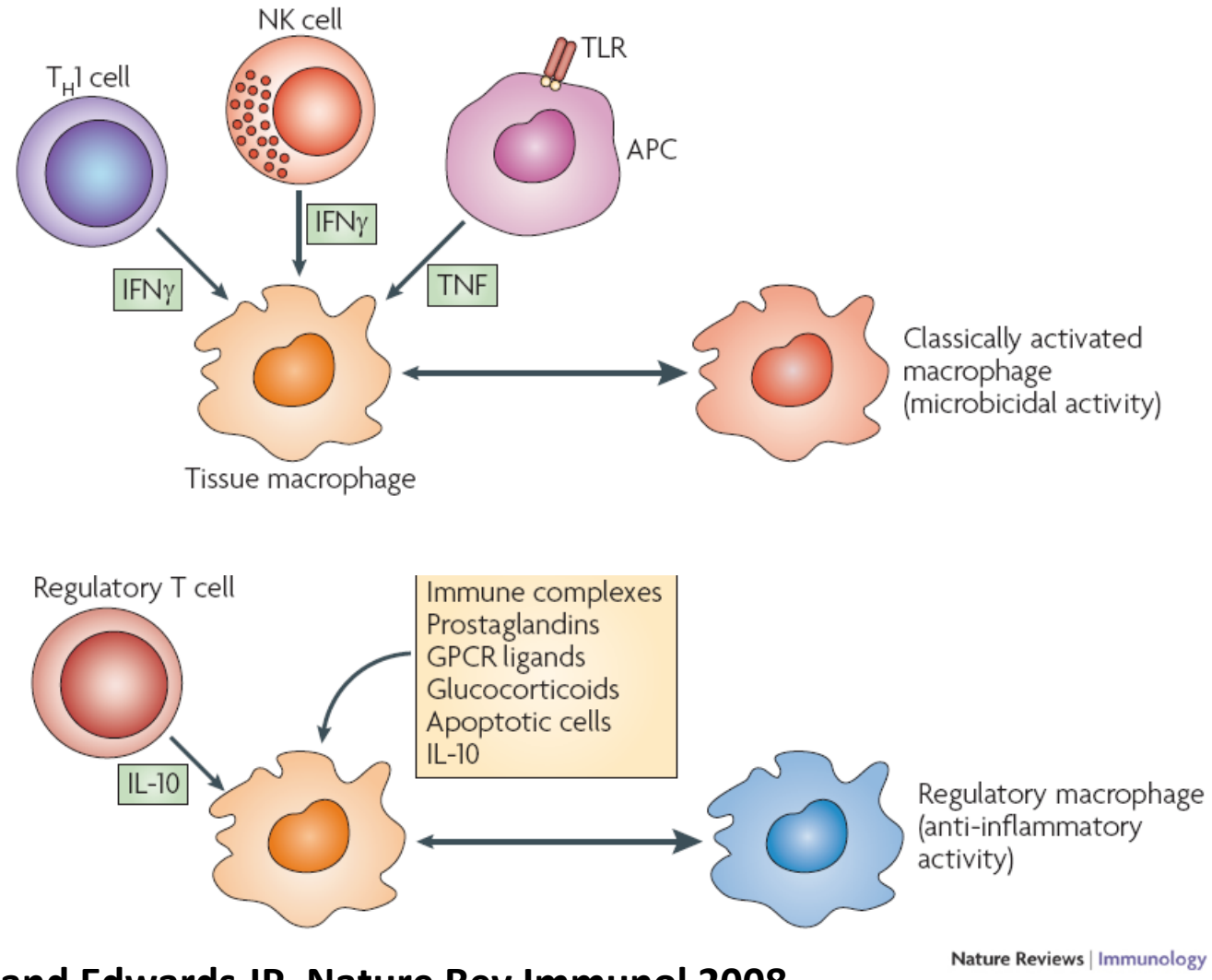
Conflict of Interest

Biosante: Under a licensing agreement between Biosante and the Johns Hopkins University, the University is entitled to milestone payments and royalty on sales of the vaccine product described in the presentation. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Genentech: Breast Cancer Advisory Board, Research Funding

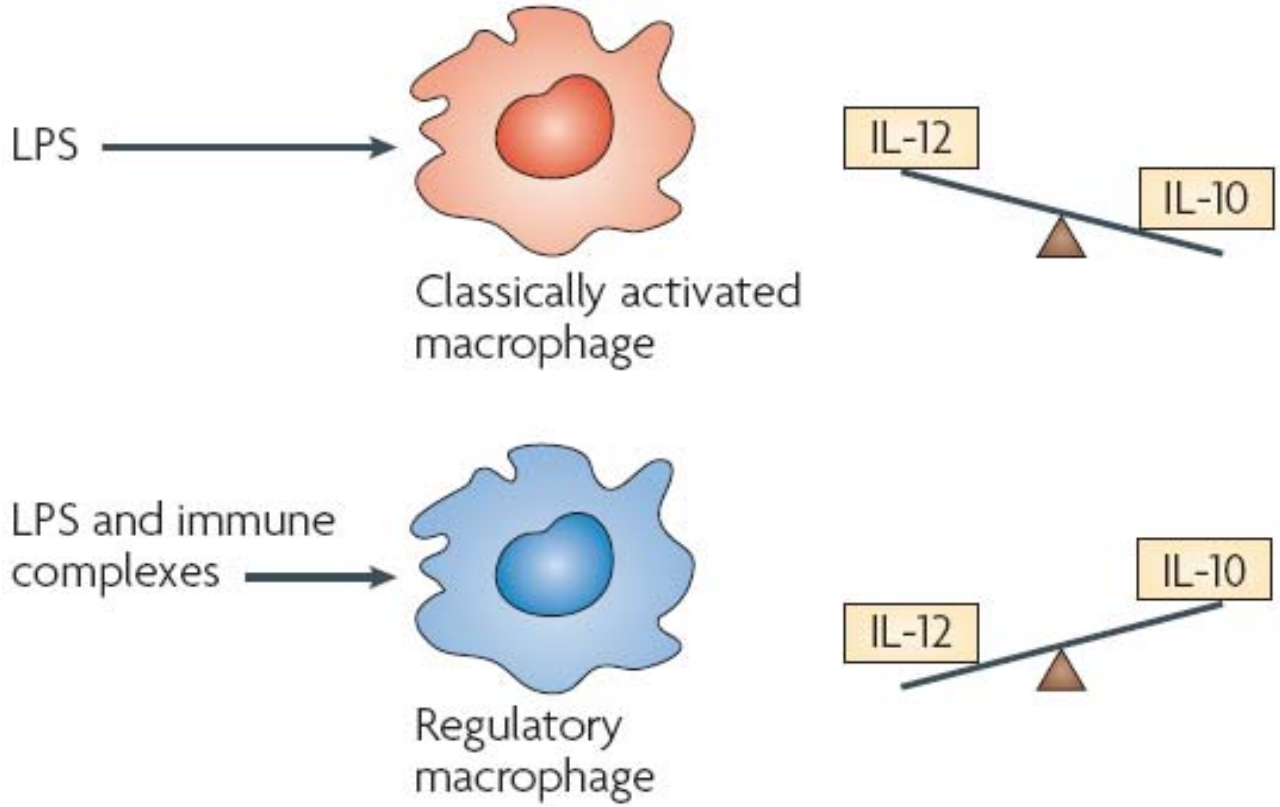
Roche: Xeloda Advisory Board

Sculpting Immunity By Cross-Talk Between Immune Cells and Macrophages



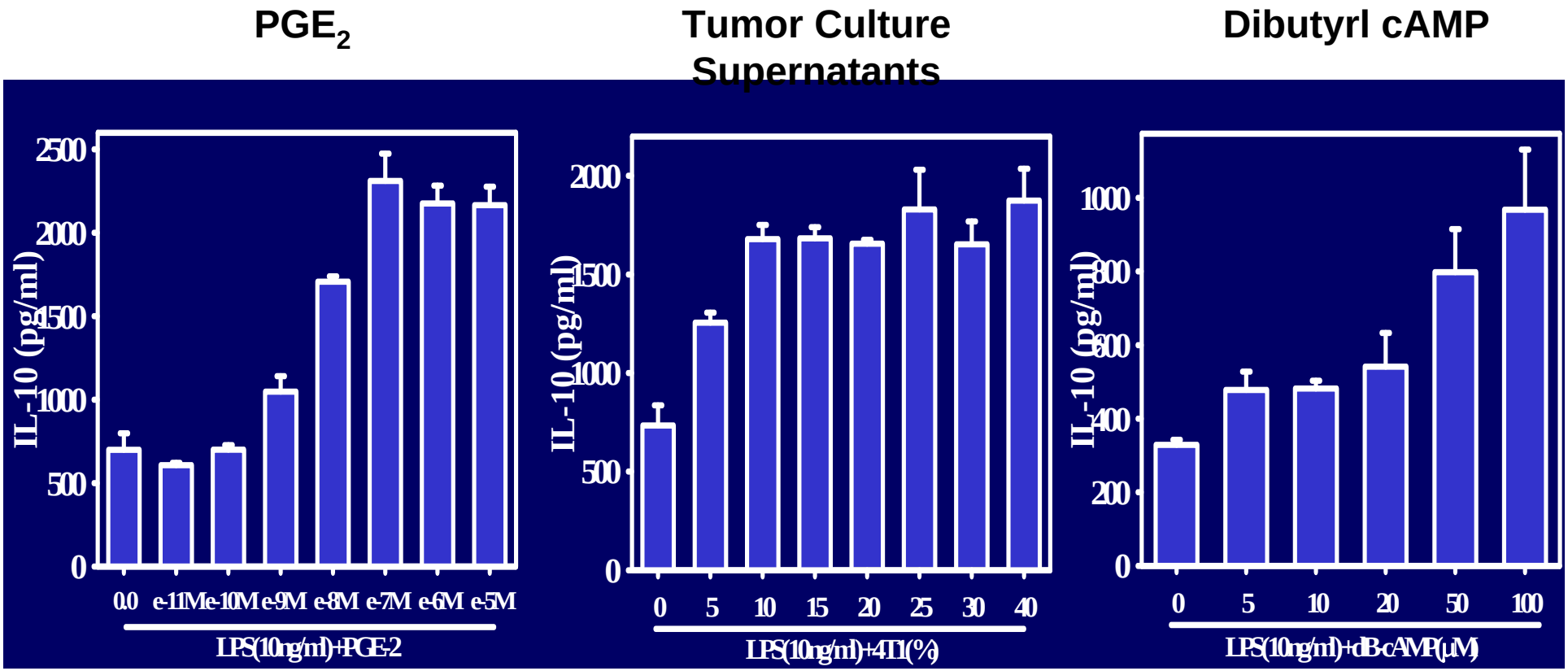
Mosser DM and Edwards JP, Nature Rev Immunol 2008

Reciprocal Cytokine Balance of Classically-Activated and Regulatory Macrophages



Mosser DM and Edwards JP, Nature Rev Immunol 2008

ERK Activation Promotes the Generation of IL-10-secreting Macrophages



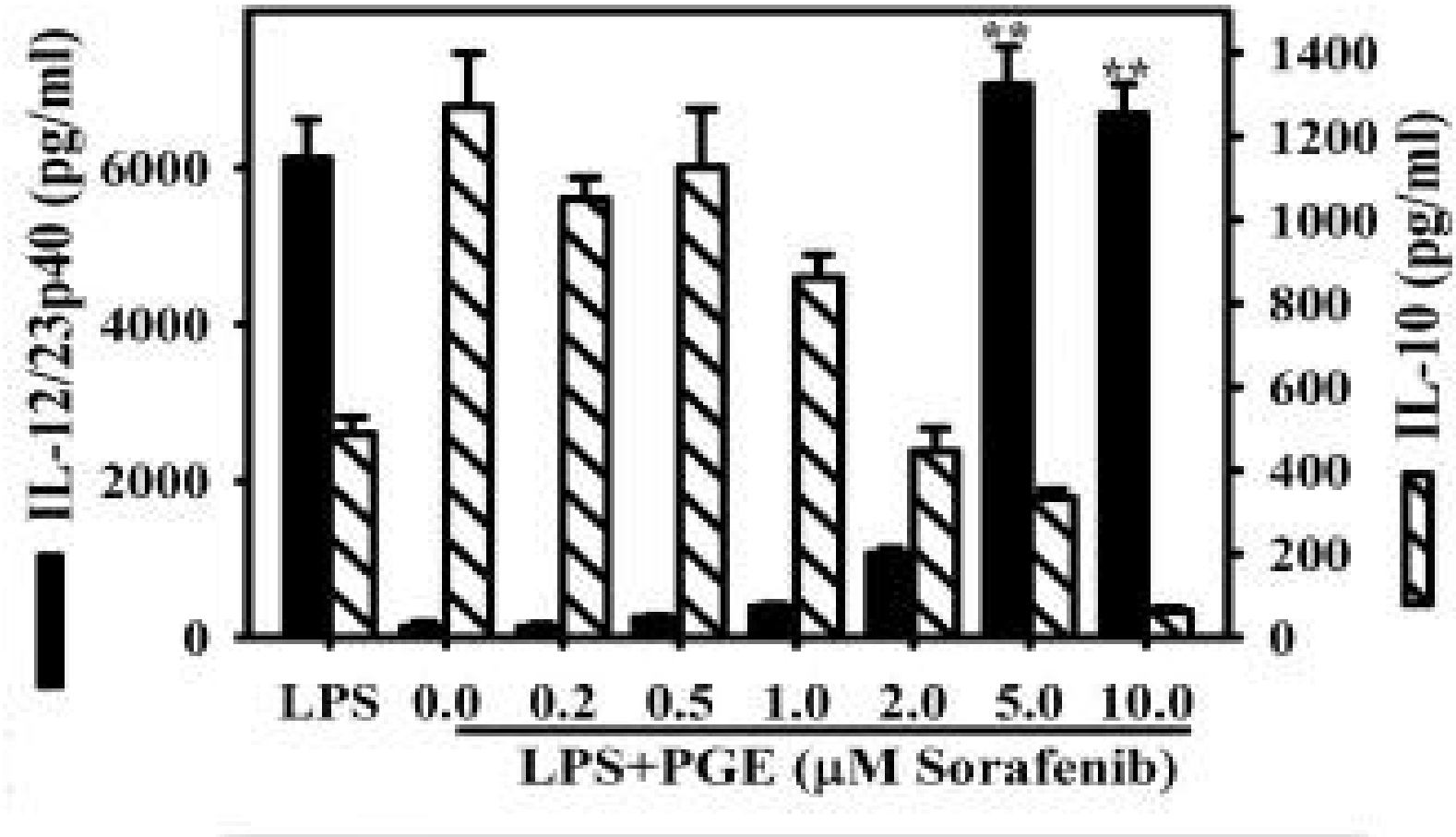
Edwards JP, unpublished data

Sorafenib: A Modulator of Macrophage Cytokine Balance?

- multikinase inhibitor originally designed to inhibit RAF/MEK/ERK pathways
- approved for the treament of renal cell carcinoma and hepatocellular carcinoma
- negatively regulates tumor growth, cell proliferation, and angiogenesis
- conditions of strong ERK activation promote the evolution of IL-10-secreting regulatory macrophages
- regulatory macrophage phenotype (IL-10 secretion) can be reversed by ERK inhibitors
- regulatory macrophages and tumor-associated macrophages (TAM) are similar in their IL-10 secretion

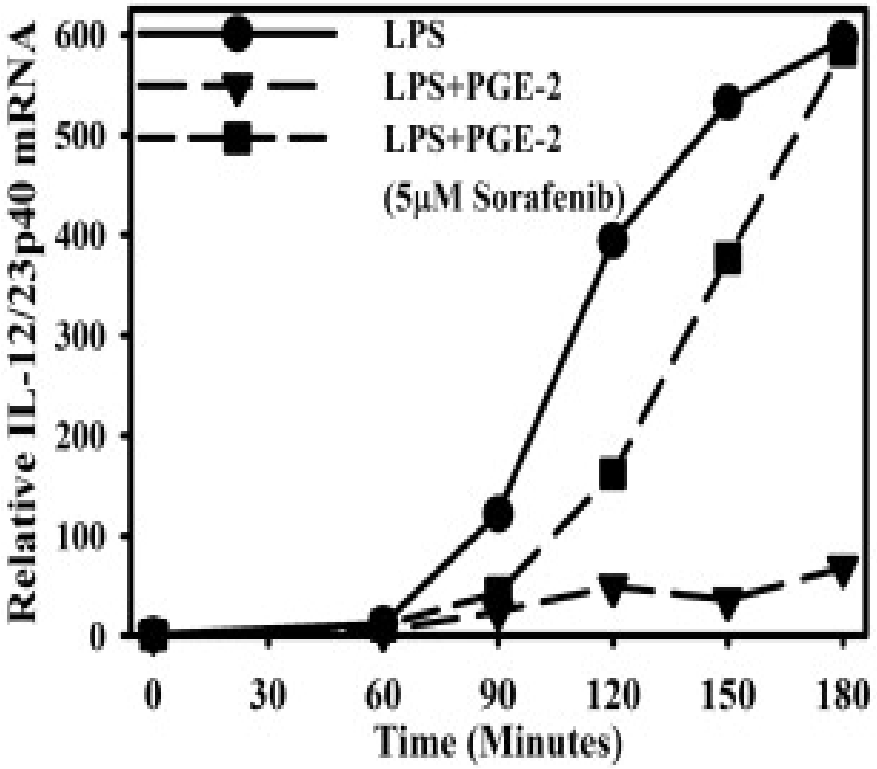
Could sorafenib reverse the regulatory phenotype of macrophages, and restore pro-inflammatory IL-12 secretion?

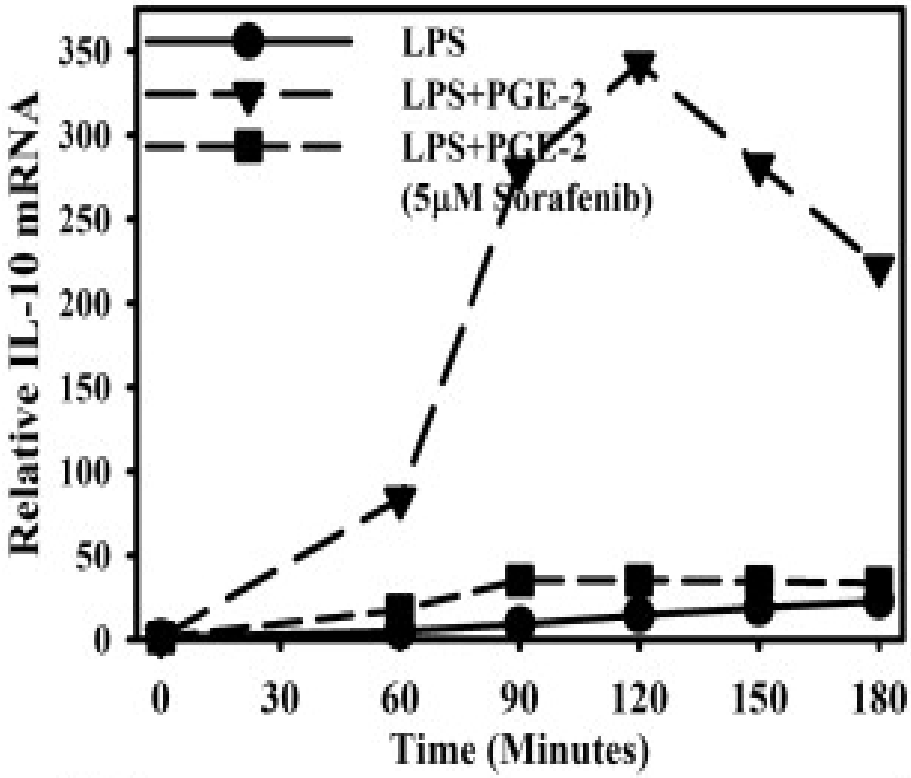
Sorafenib Reverses PGE_2-mediated Suppression of LPS-induced IL-12 Production



Edwards JP and Emens LA, Int Immunopharm 2010

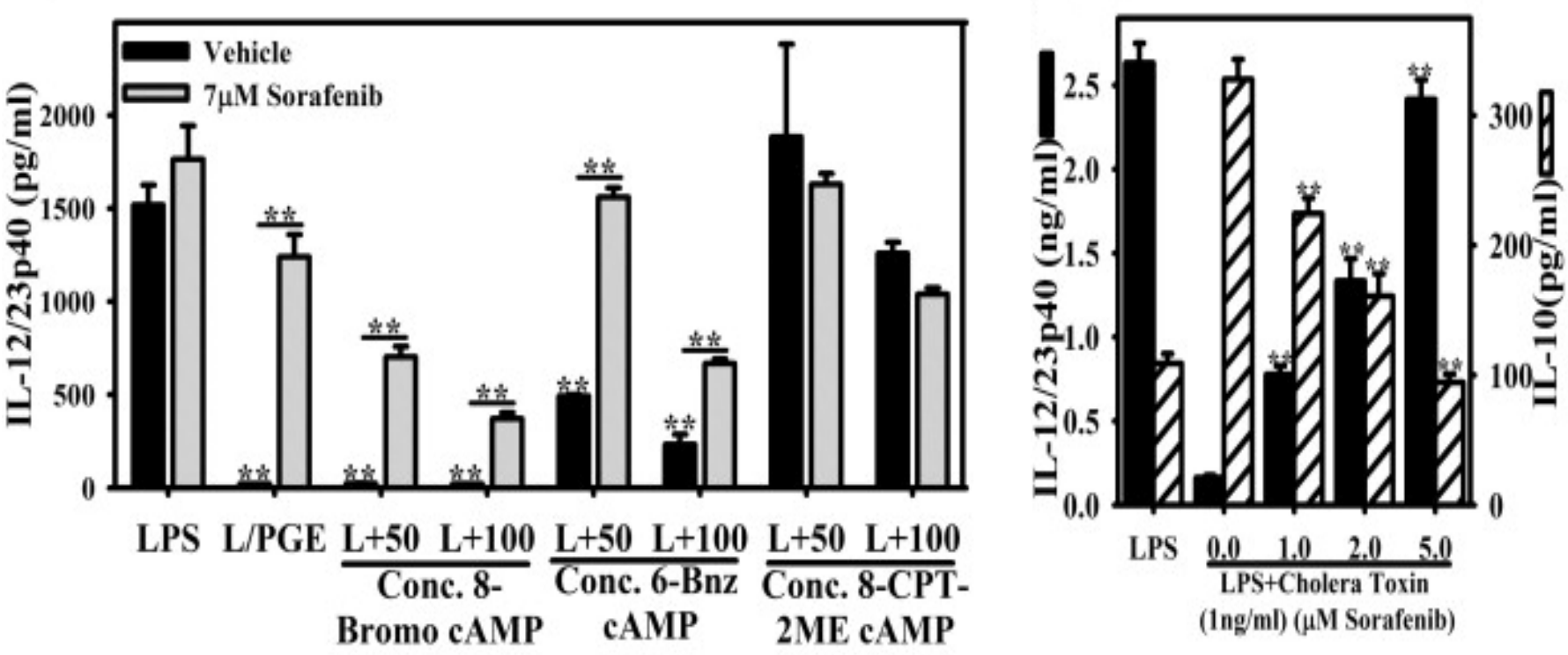
Sorafenib Reverses PGE2-mediated Suppression of LPS-induced IL-12 Production





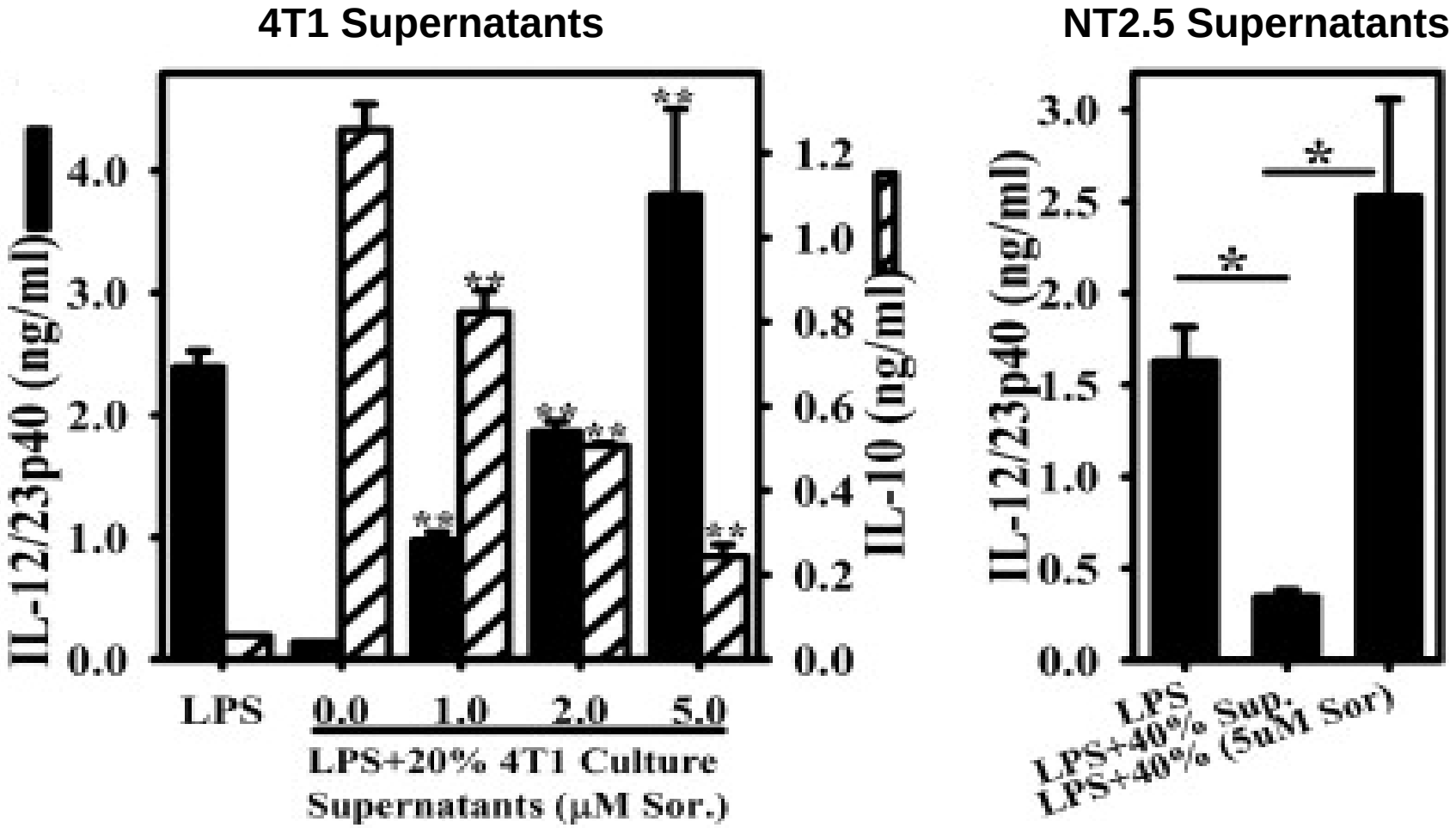
Edwards JP and Emens LA, Int Immunopharm 2010

Sorafenib Reverses IL-12 Suppression by cAMP Analogs and Cholera Toxin



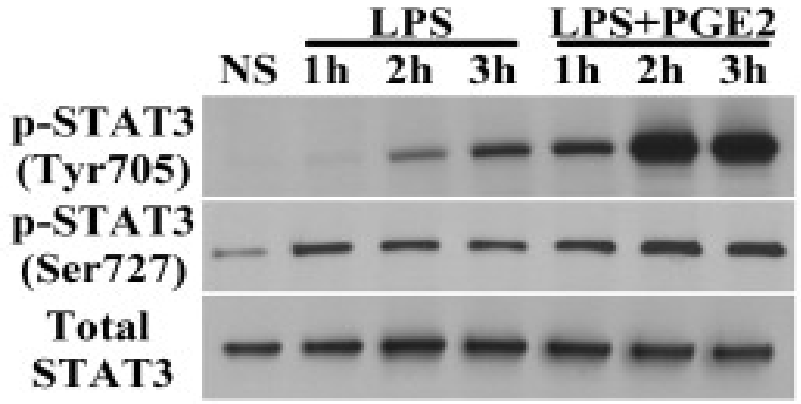
Edwards JP and Emens LA, Int Immunopharm 2010

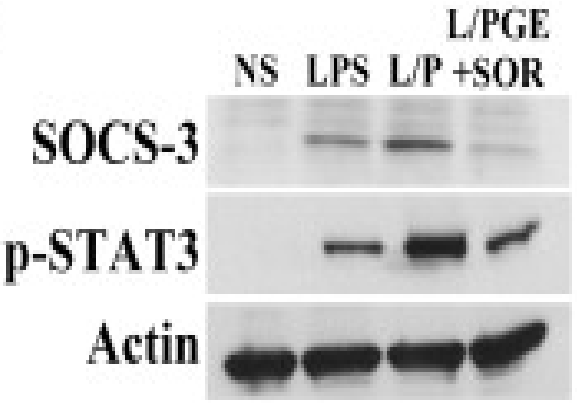
Sorafenib Reverses IL-12 Suppression by Breast Tumor Cell Supernatants

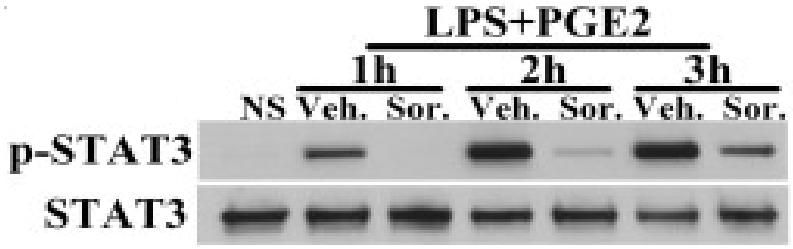


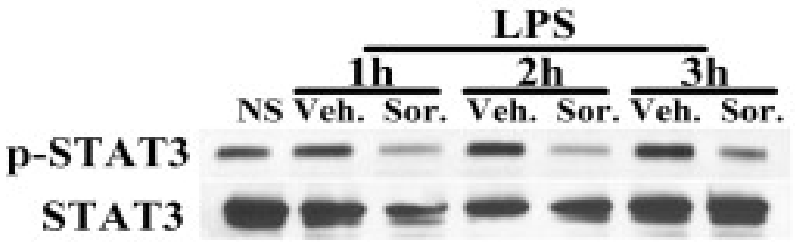
Edwards JP and Emens LA, Int Immunopharm 2010

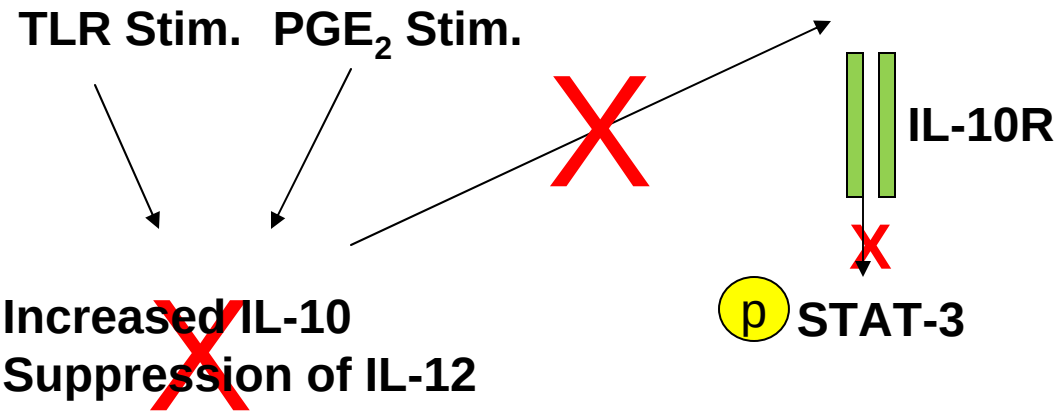
Sorafenib Reverses IL-10-mediated Activation of STAT-3 and Expression of SOCS-3



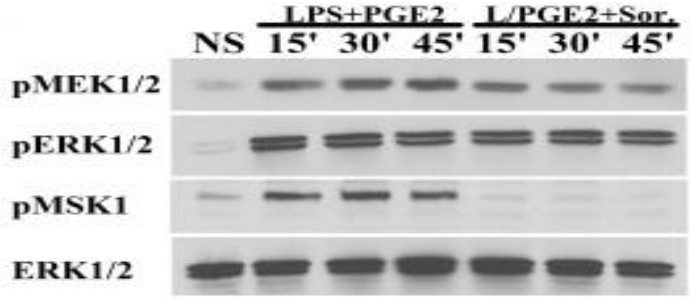


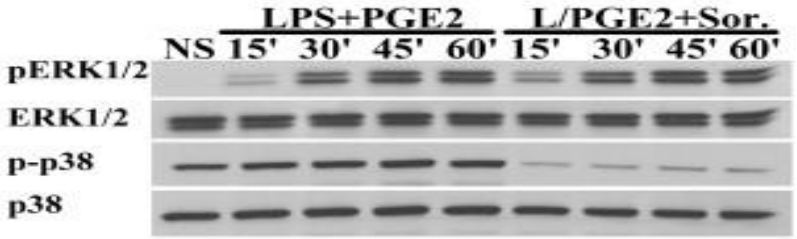


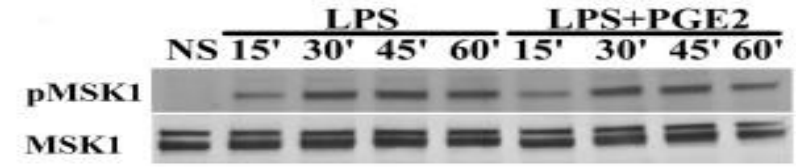


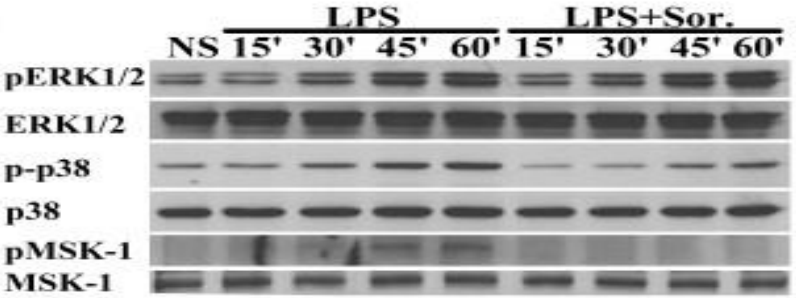


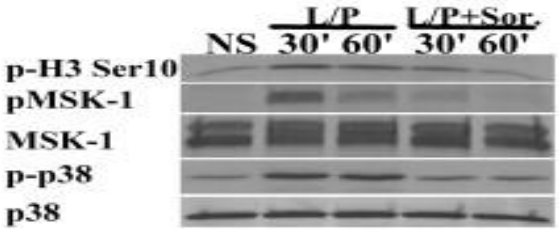
Edwards JP and Emens LA, Int Immunopharm 2010



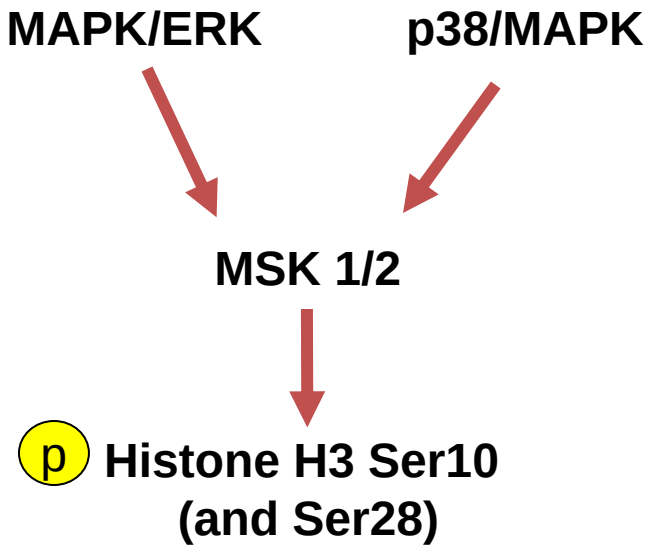








Sorafenib Modulates MAPK Signaling in Macrophages



The kinases MSK1 and MSK2 act as negative regulators of Toll-like receptor signaling

Olga Ananieva[1], Joanne Darragh[1], Claus Johansen[2], Julia M Carr[1], Joanne McIlrath[1], Jin Mo Park[3], Andrew Wingate[1], Claire E Monk[1], Rachel Toth[1], Susana G Santos[1], Lars Iversen[2] & J Simon C Arthur[1]

nature immunology

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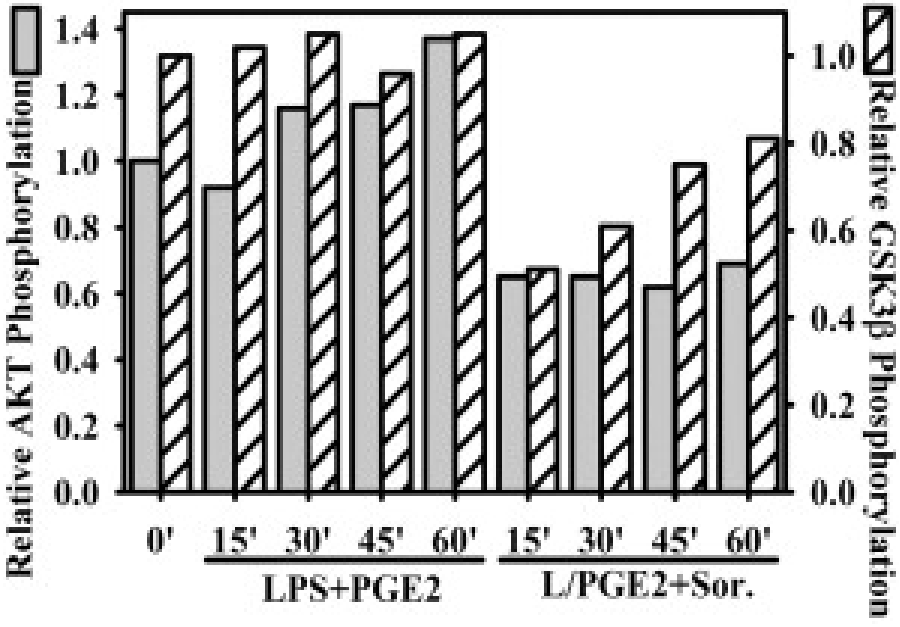
Sorafenib Partially Inhibits AKT Activation and GSK3-β Phosphorylation



GSK3-β

↓

Promotes Inflammatory Cytokine Production

AKT

↓

p GSK3-β

↓

Suppresses Inflammatory Cytokine Production

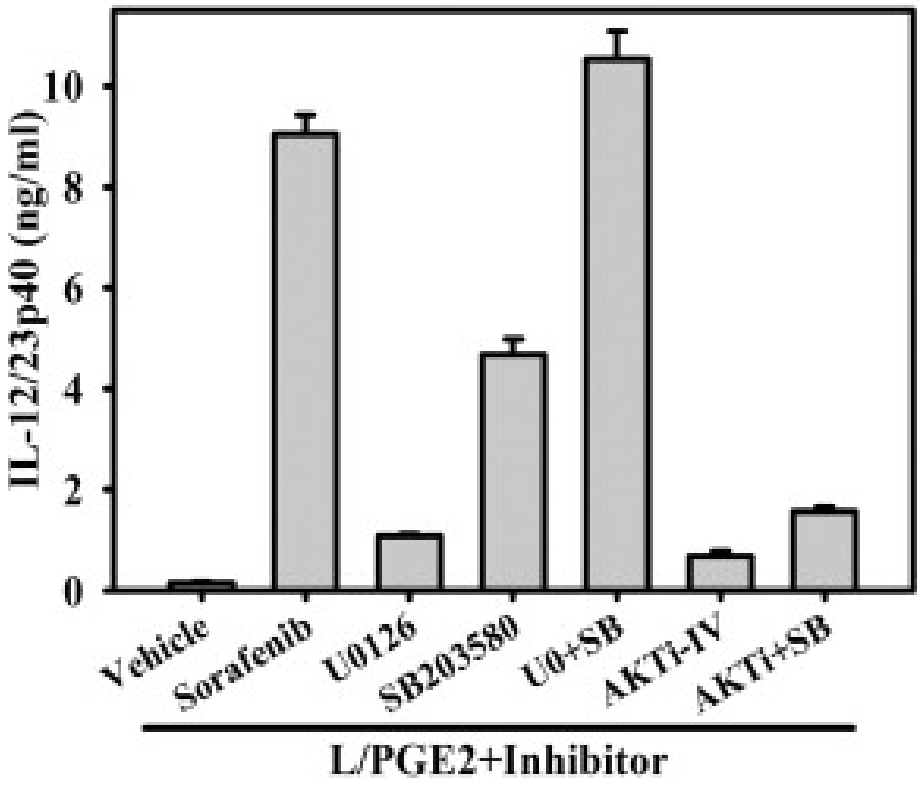
Toll-like receptor–mediated cytokine production is differentially regulated by glycogen synthase kinase 3

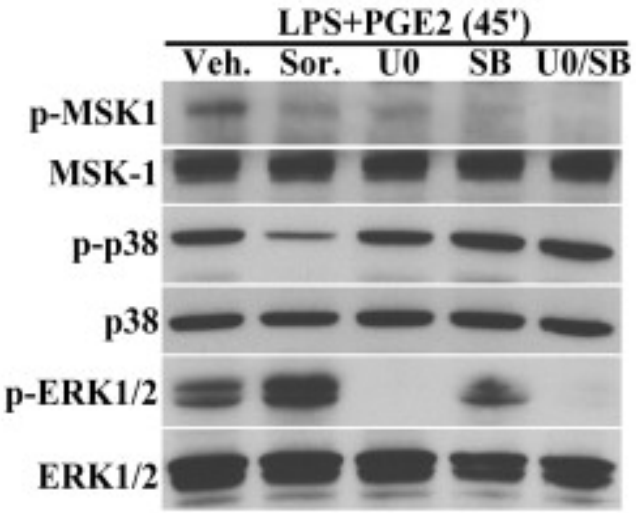
Michael Martin[1], Kunal Rehani[2], Richard S Jope[3] & Suzanne M Michalek[2]

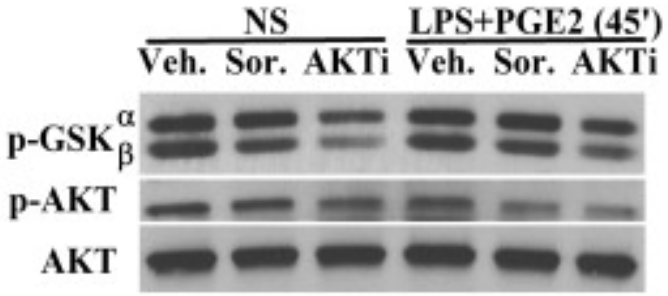
nature immunology

Edwards JP and Emens LA, Int Immunopharm 2010

Similar Downstream Effects of Sorafenib and MAPK Inhibition







Inhibitors: U0126—MEK1/2
SB203580—p38
AKT IV--AKT

Edwards JP and Emens LA, Int Immunopharm 2010

Conclusions

In murine macrophages, Sorafenib

- **reverses the shift in IL-10/IL-12 balance induced by PGE_2**
- **inhibits PGE_2-induced IL-10 secretion, indirectly preventing STAT3 activation**
- **inhibits p38 MAPK activation, thereby preventing MSK1 activation**
- **impacts the cytokine profile of macrophages by an ERK-independent mechanism**

Further investigation of the impact of Sorafenib on tumor-associated macrophages, and it's potential role in combination immunotherapy, is ongoing.

Acknowledgements

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