

Acknowledgements

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STAT3: A target for many human cancers

50-100% Stat3 activation in

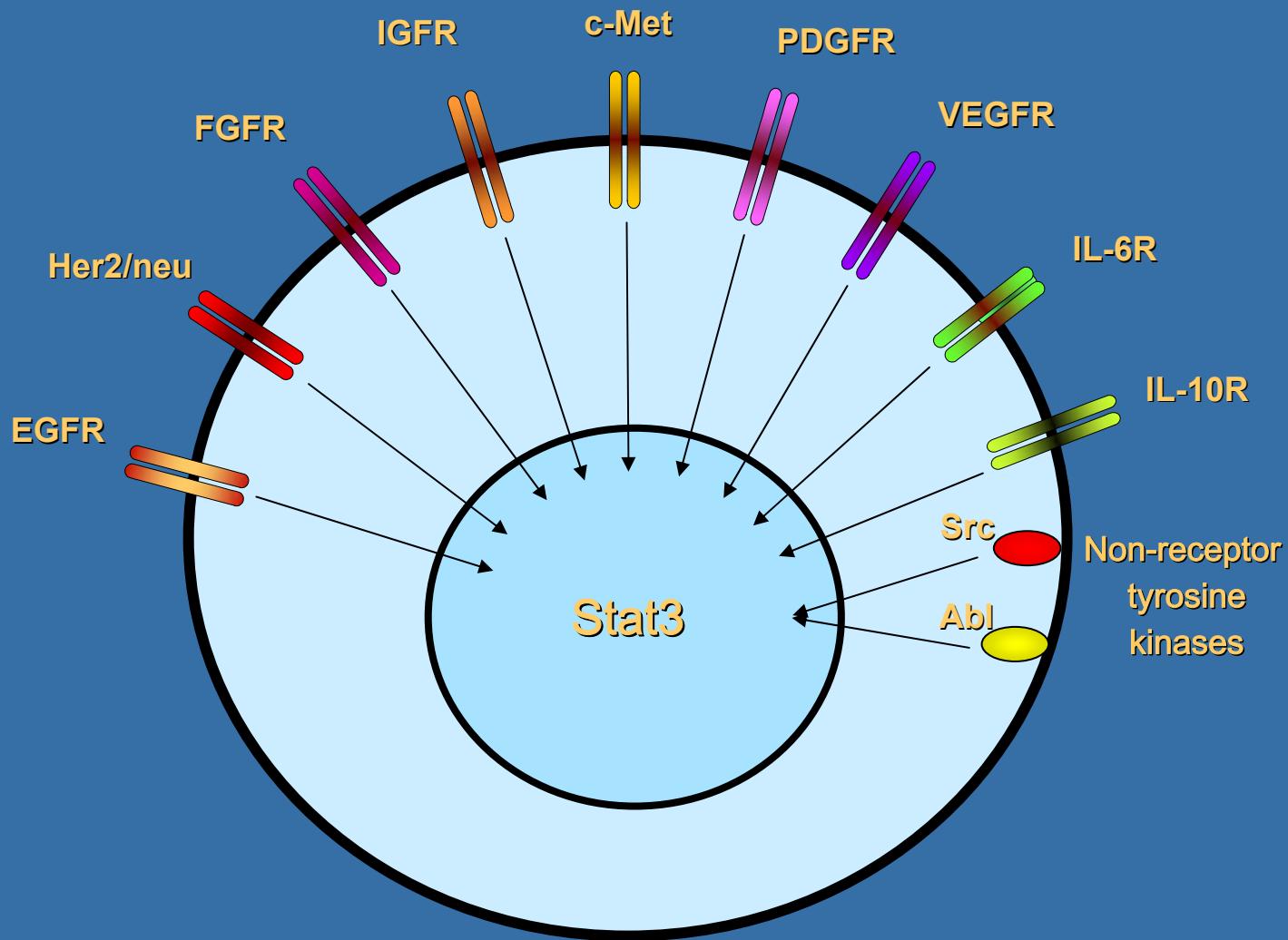
Solid Tumors

Prostate cancer	STAT3
Non-small Cell Lung cancer	STAT3
Breast cancer	STAT3, STAT5
Head and Neck cancer	STAT3
Melanoma	STAT3
Ovarian cancer	STAT3
Pancreatic cancer	STAT3
Glioma	STAT3
Stomach Cancer	STAT3
Cervical Cancer	STAT3

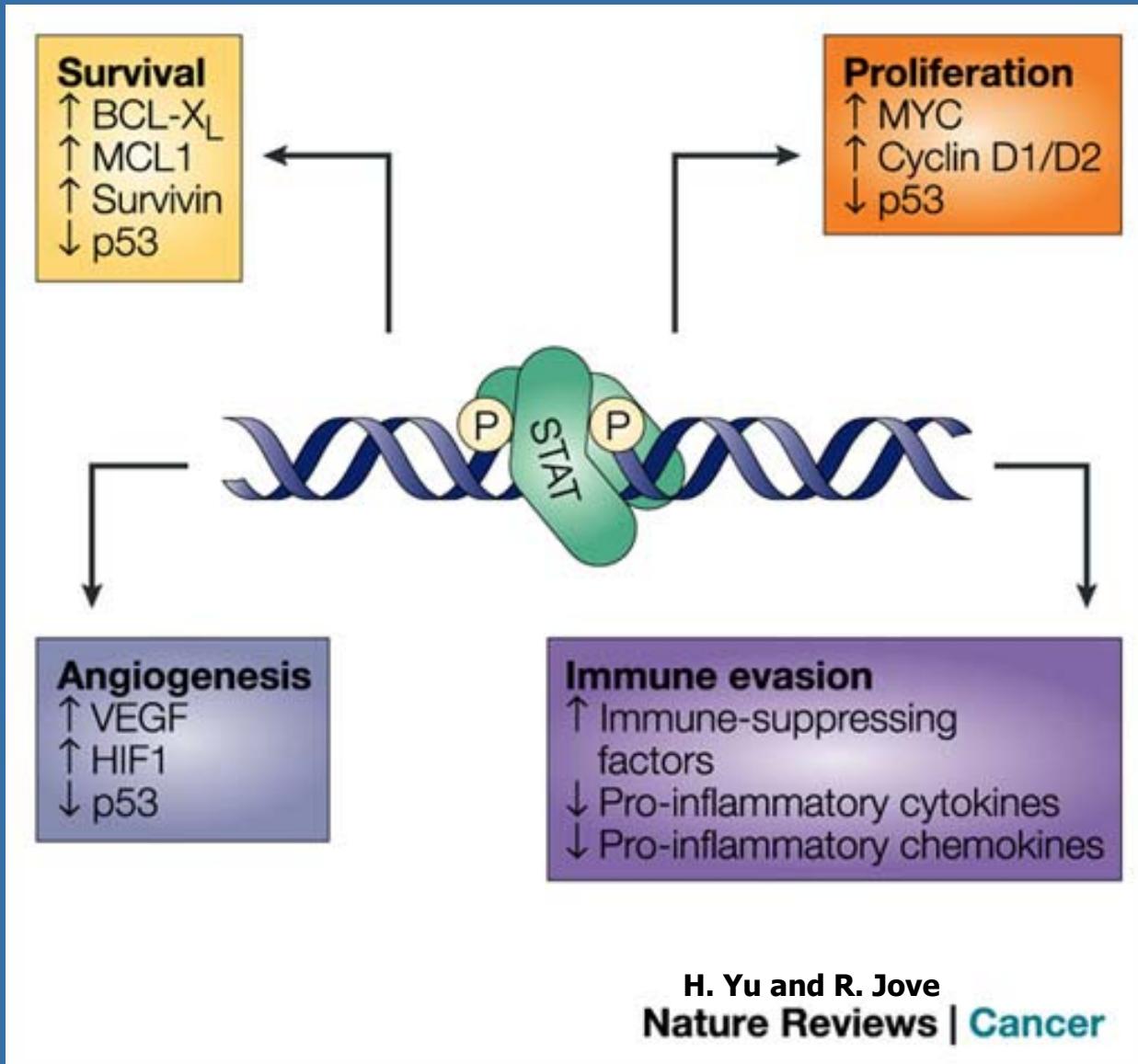
Blood Tumors

Multiple Myeloma	STAT3
Acute Myelogenous Leukemia (AML)	STAT3, STAT5
Chronic Myelogenous Leukemia (CML)	STAT5
Burkitt's Lymphoma	STAT3
Non-Hodgkins Lymphoma	STAT3
Cutaneous T cell Lymphoma	STAT3

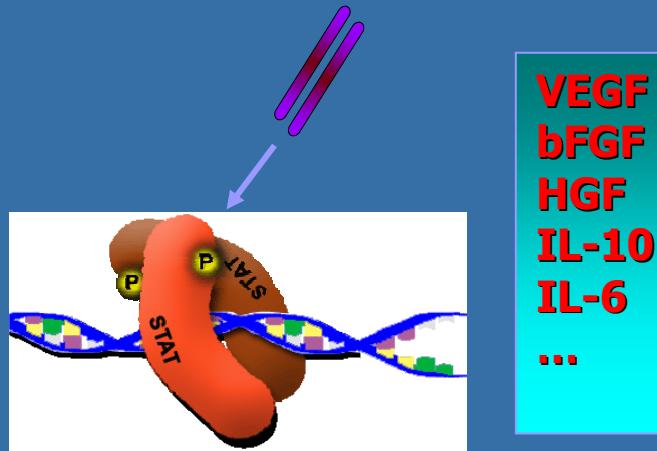
Importance of Stat3 in Cancer Therapy



Multiple roles of STAT activation in tumor cells



Role of Stat3 in Oncogenesis and the Tumor Microenvironment



Proliferation and survival

↑ Myc
↑ Cyclin D1/D2
↑ BCL-X_L ↓ p53
↑ MCL-1 ↓ Stat1
↑ Survivin ↓ IFNs

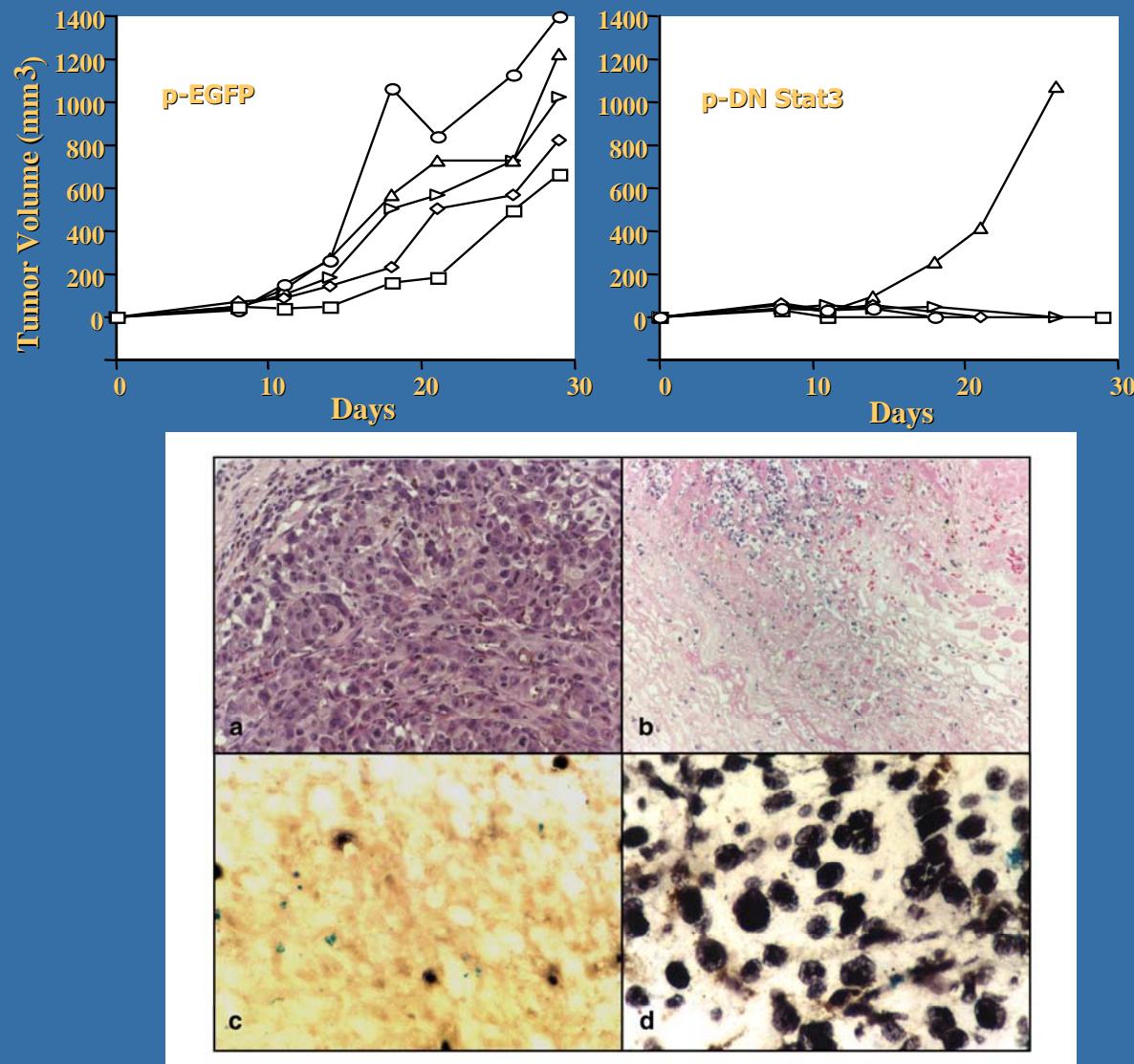
Angiogenesis

↑ bFGF ↓ IFNγ
↑ HGF ↓ IL-12
↑ VEGF ↓ IP-10
↑ HIF-1 ↓ Stat1
↑ MMP-2 ↓ IFNβ
↑ MMP-9 ↓ p53

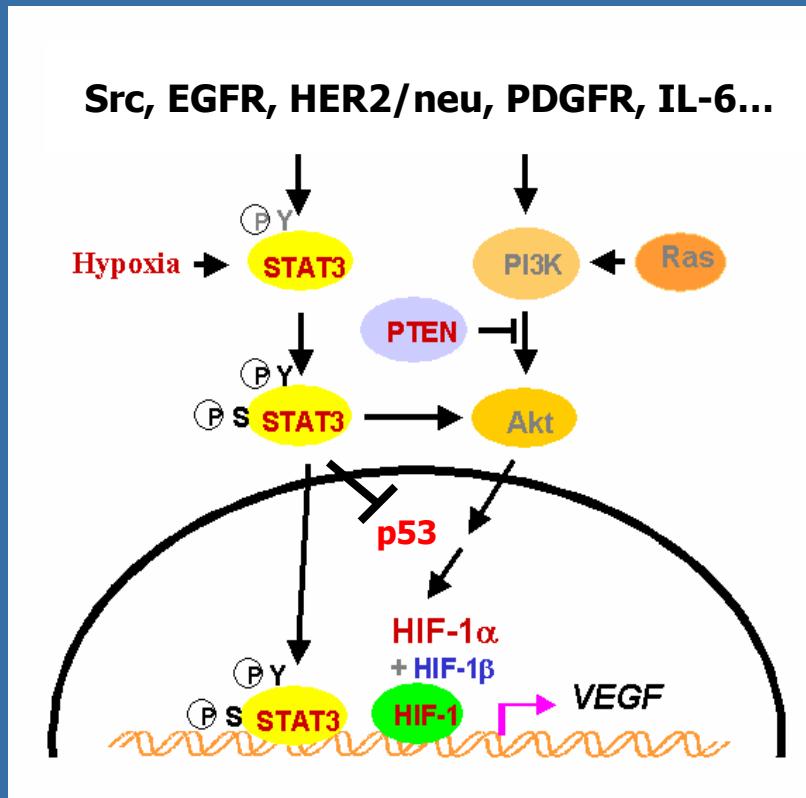
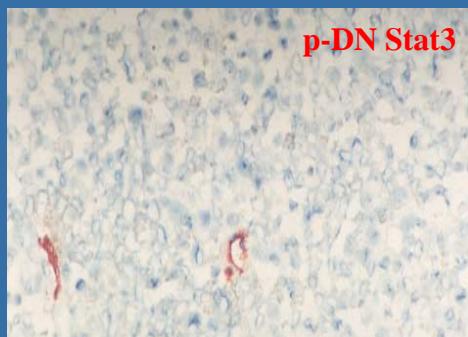
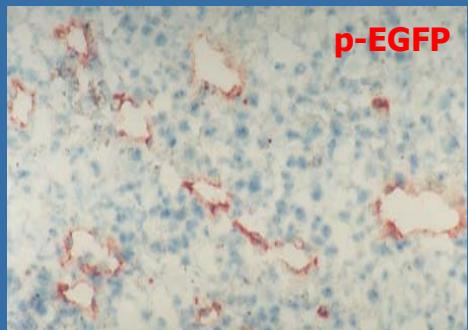
Immunosuppression

↓ IFNβ
↓ IFNγ
↑ IL-10 ↓ IL-12
↑ TGFβ ↓ TNFα
↑ VEGF ↓ IP-10
↑ IL-6 ↓ RANTES
↑ Foxp3 ↓ MHC II
 ↓ CD80
 ↓ CD86
 ↓ Stat1

Gene Therapy with a DN Stat3 Involves “Bystander Effects”



Stat3 Is Critical for Tumor Angiogenesis

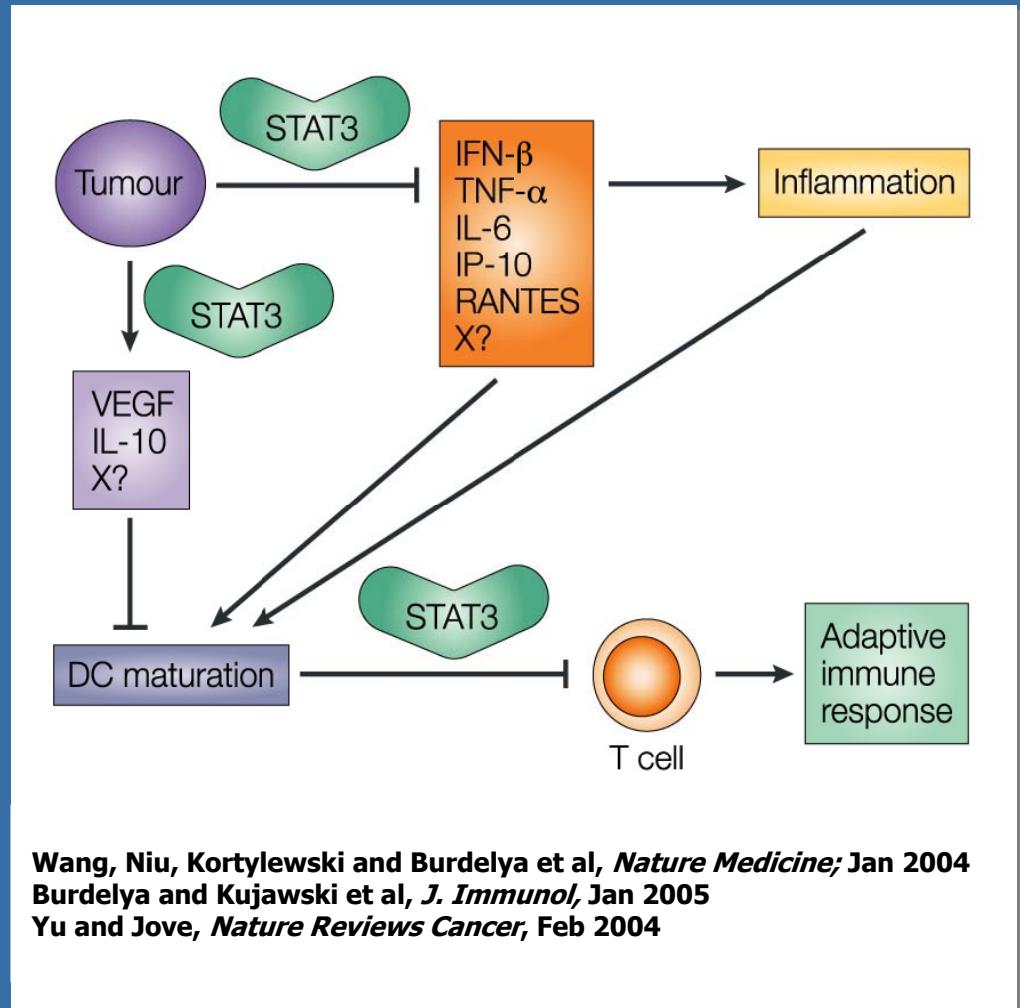
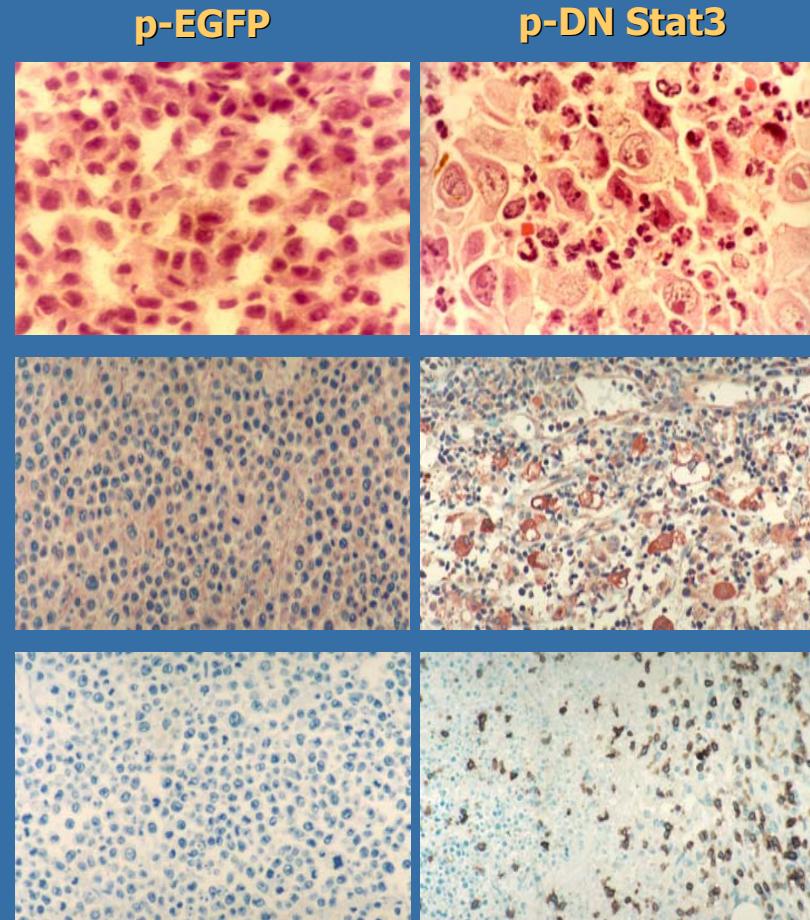


Niu et al, *Oncogene*, 21:2000-2008, 2002

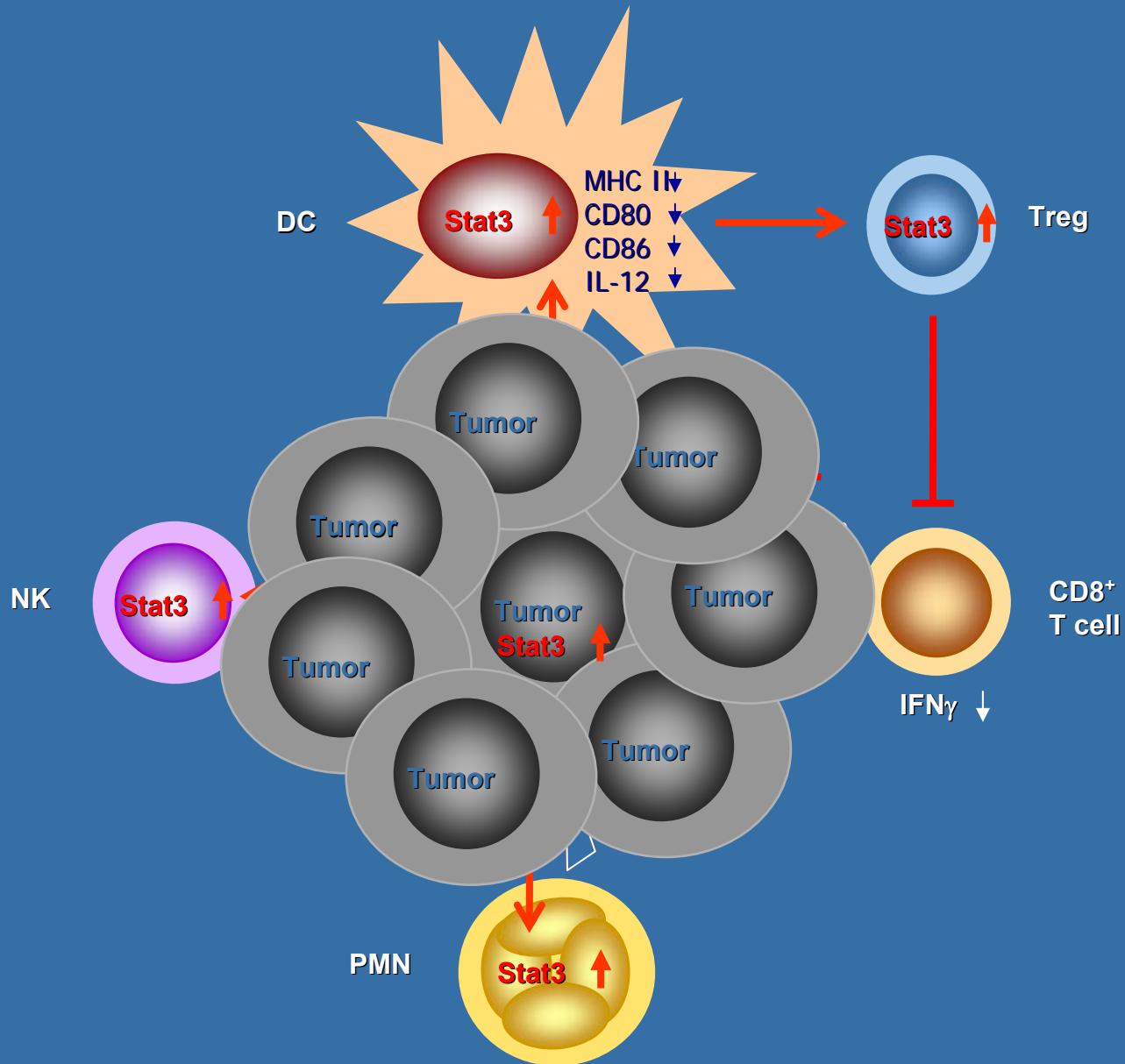
Xu et al, *Oncogene*, 25:5552-5560, 2005

Niu et al, *Mol Cell Biology*, 25, 7432-7440, 2005

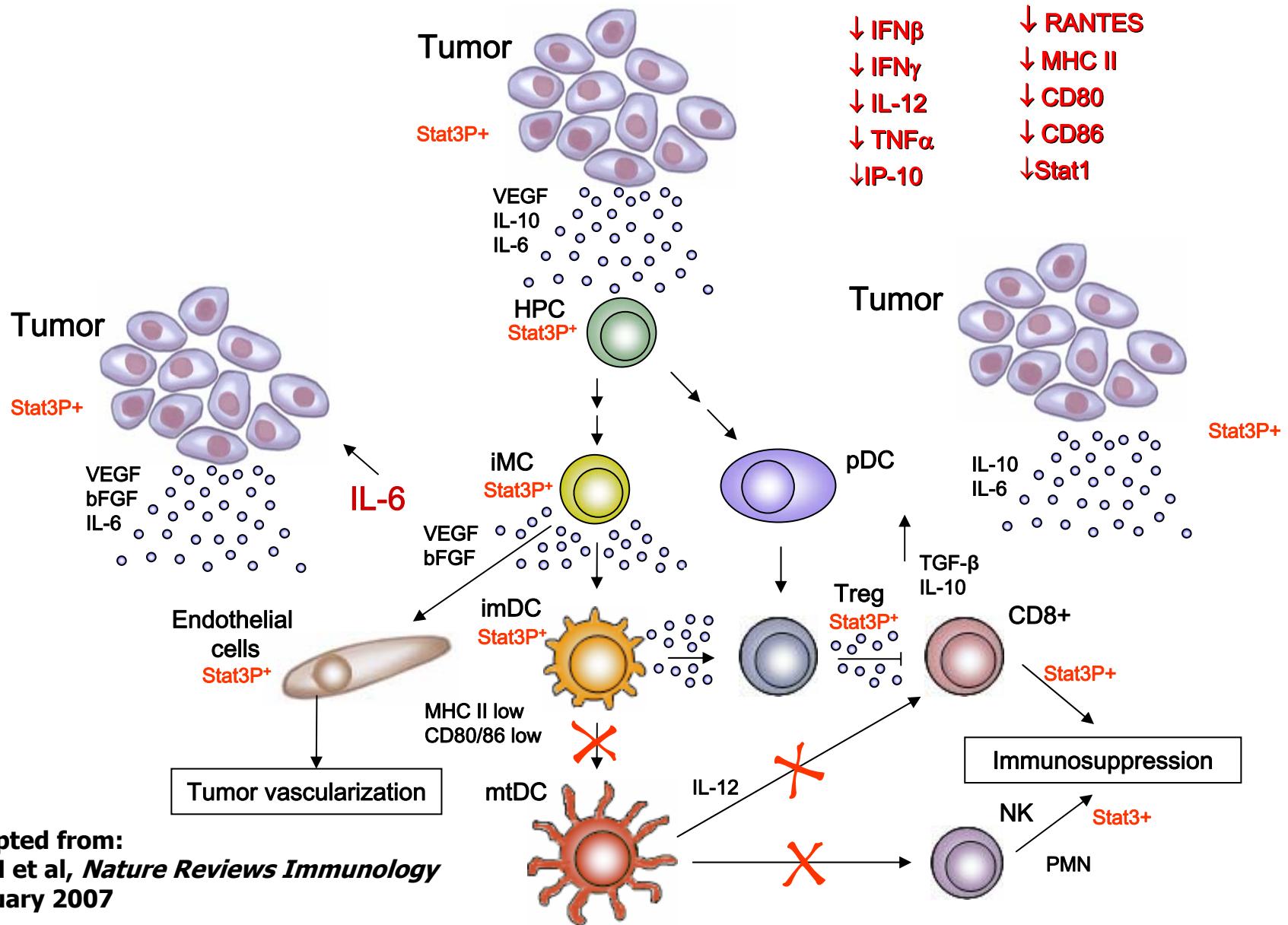
Critical Role of Tumor Stat3 Activity in Immune Evasion



Stat3 Activity in Immune Cells Mediates Immune Suppression



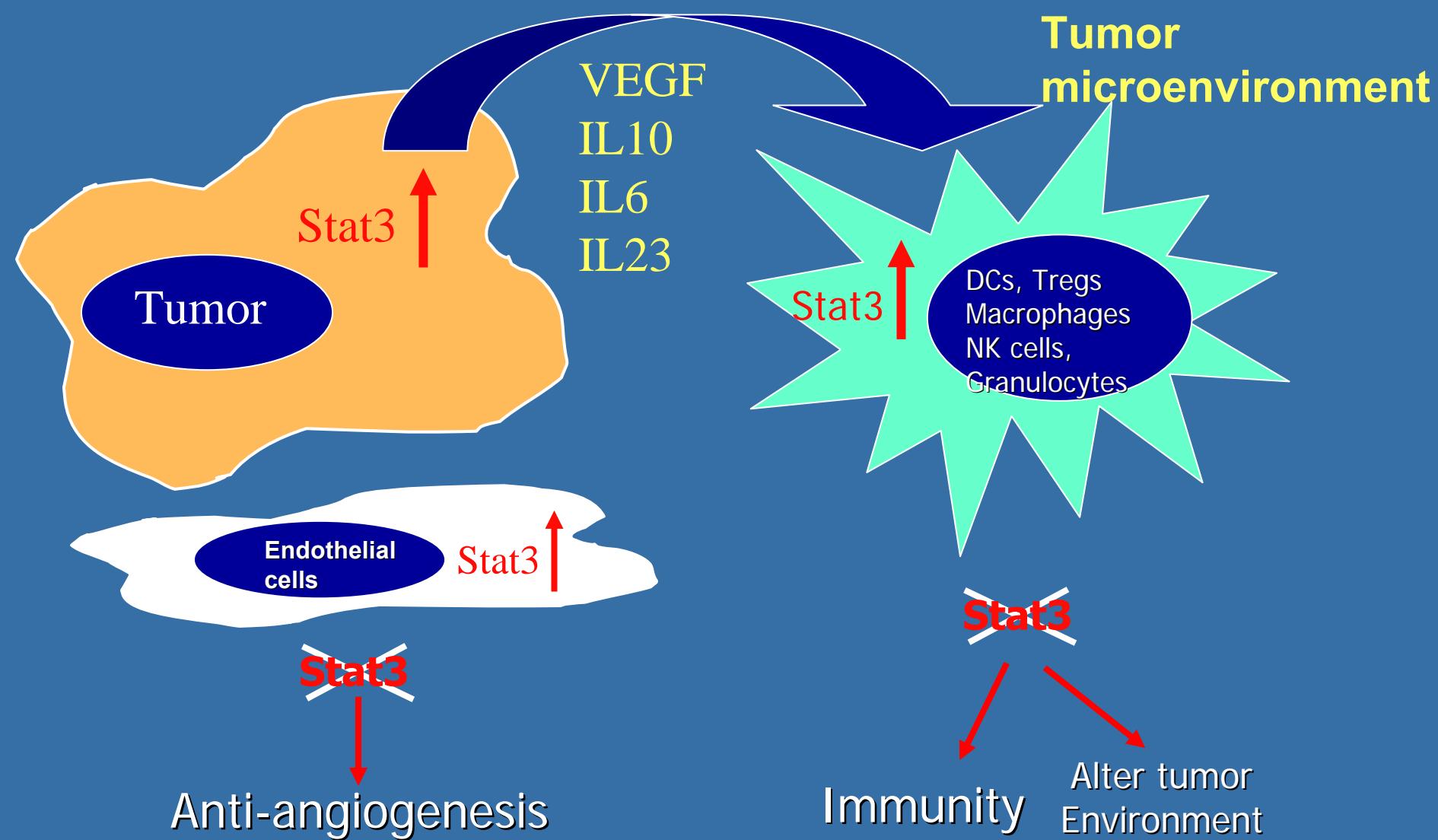
Stat3 mediates the crosstalk between tumor and immune cells:



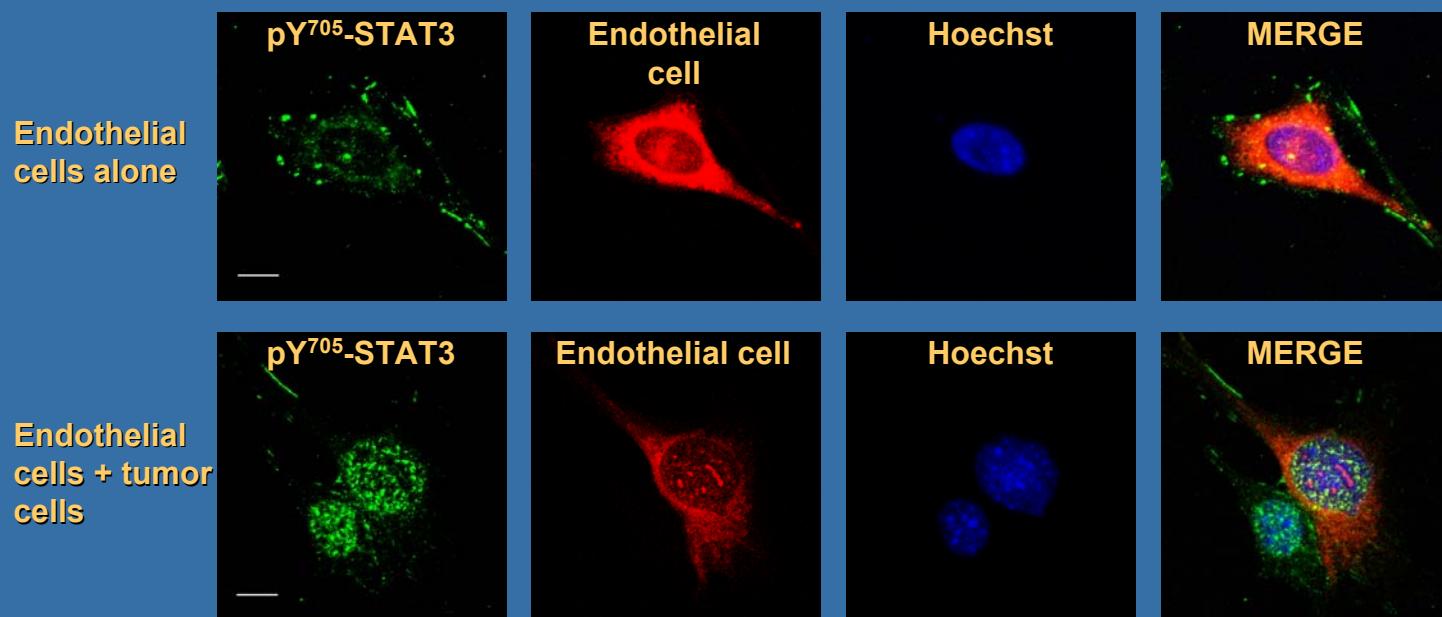
Adapted from:

Yu H et al, *Nature Reviews Immunology*
January 2007

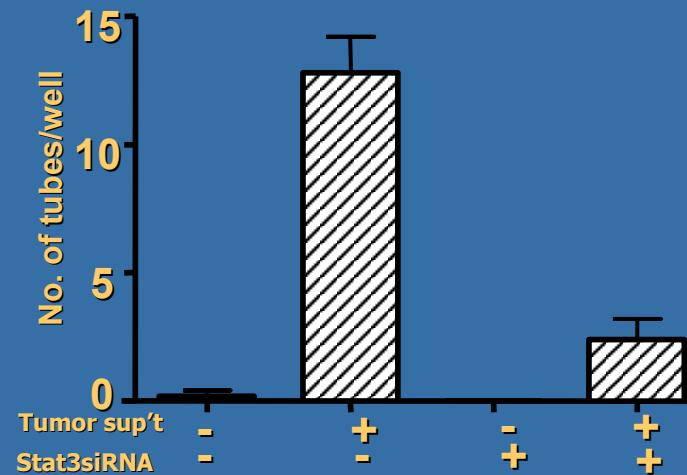
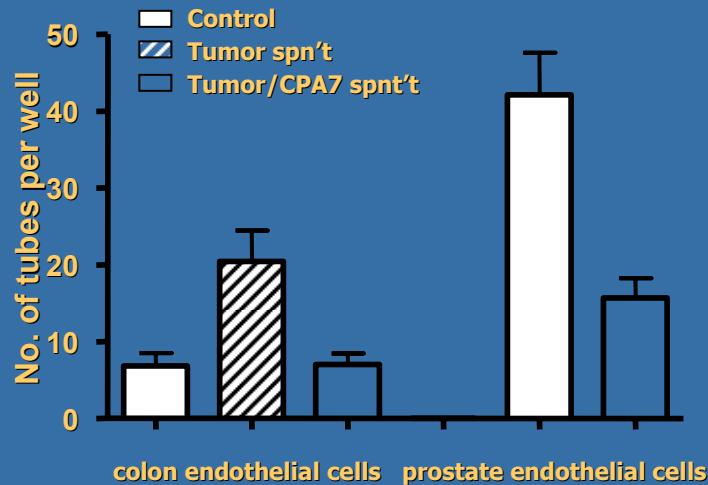
Stat3 targeting: beyond tumor cells



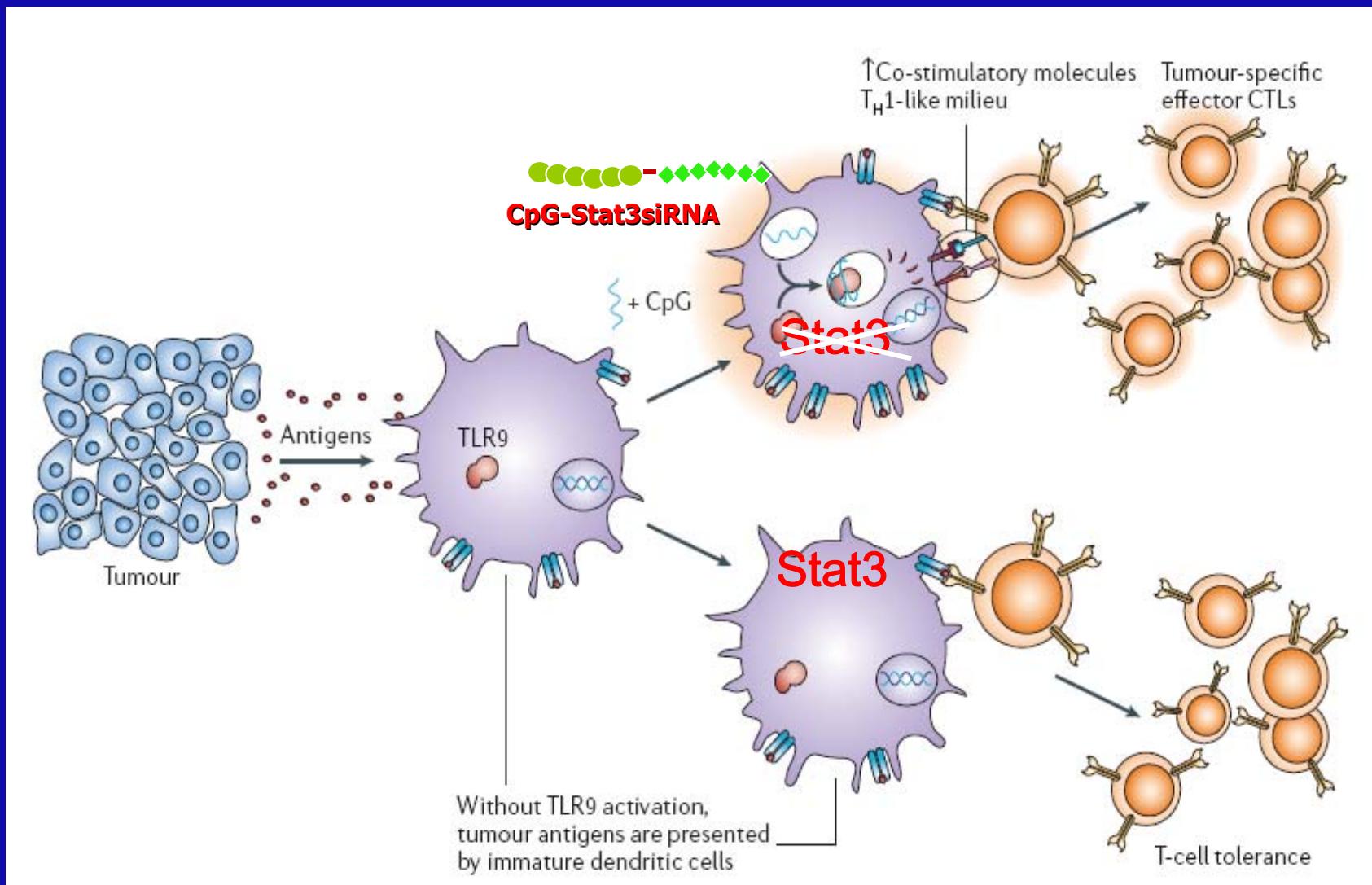
Crosstalk between tumor cells and endothelial cells: role of Stat3



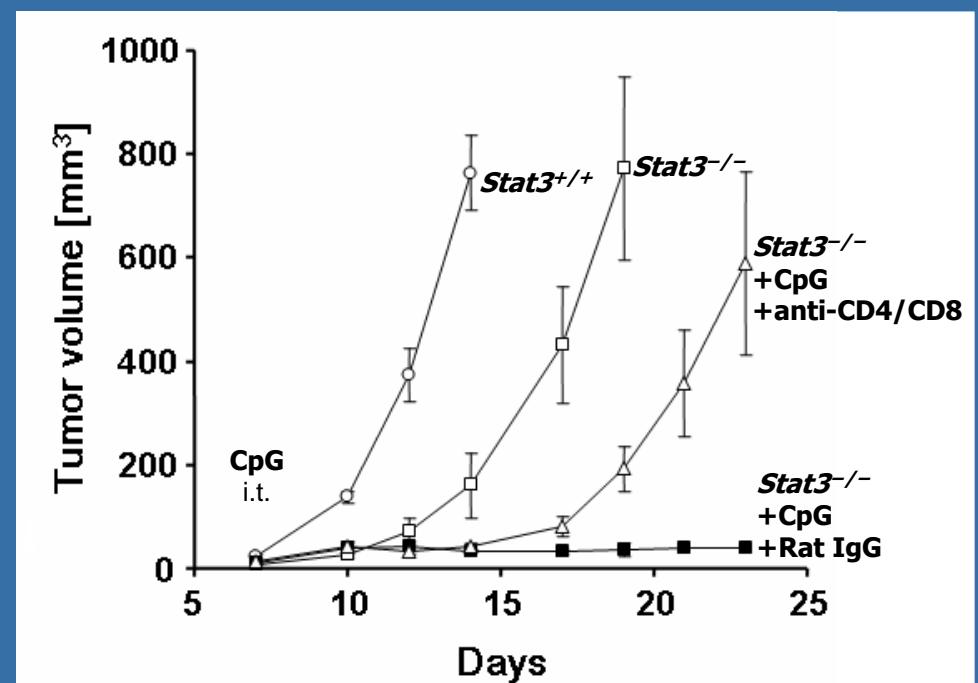
Crosstalk between tumor cells and endothelial cells: role of Stat3



CpG-Stat3siRNA: Targeted delivery, DC activator and Stat3 inhibitor into a single agent



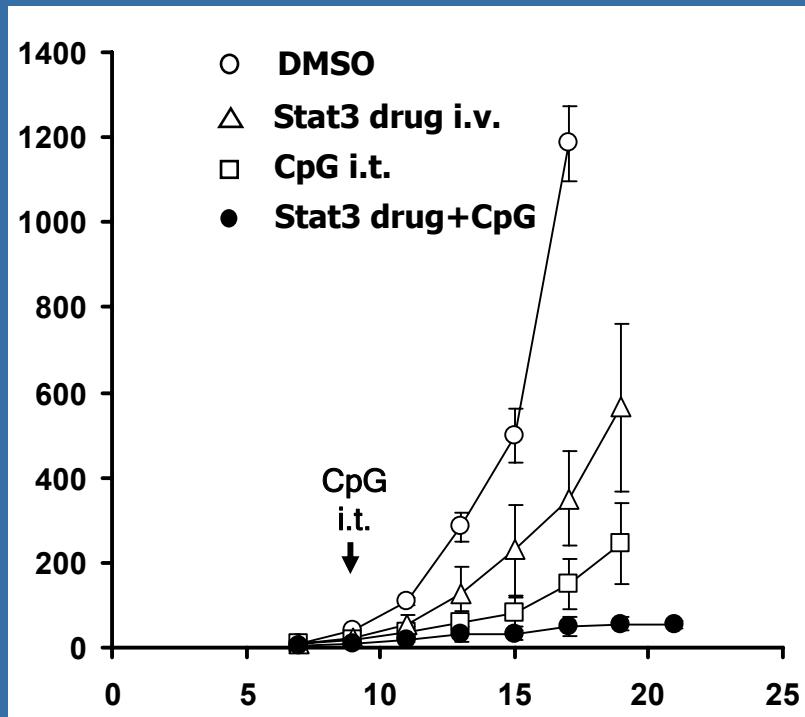
Genetic ablation of Stat3 in immune cells: drastic improvement of immunotherapy



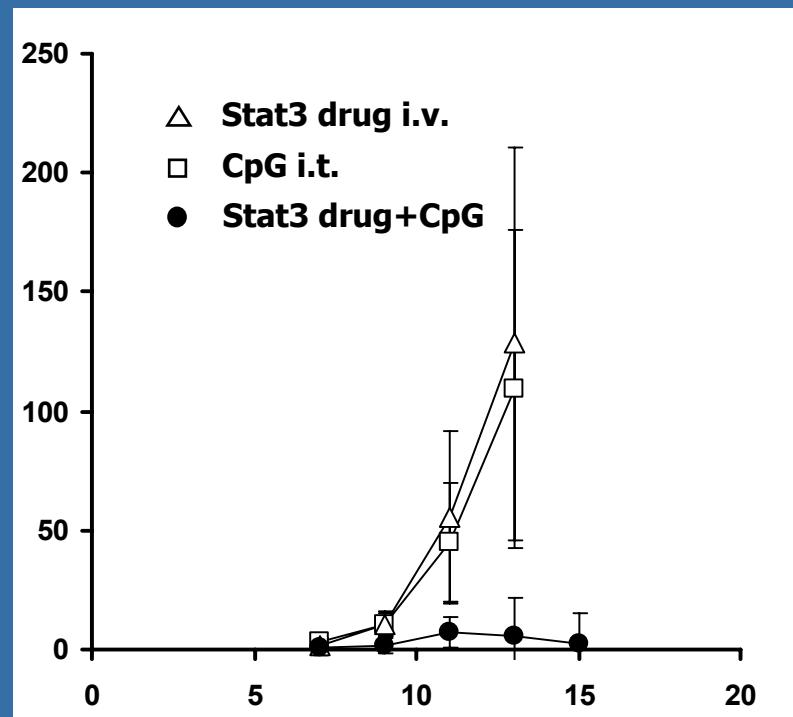
Enhancing CpG antitumor immunity by a small-molecule Stat3 inhibitor

B16 tumor

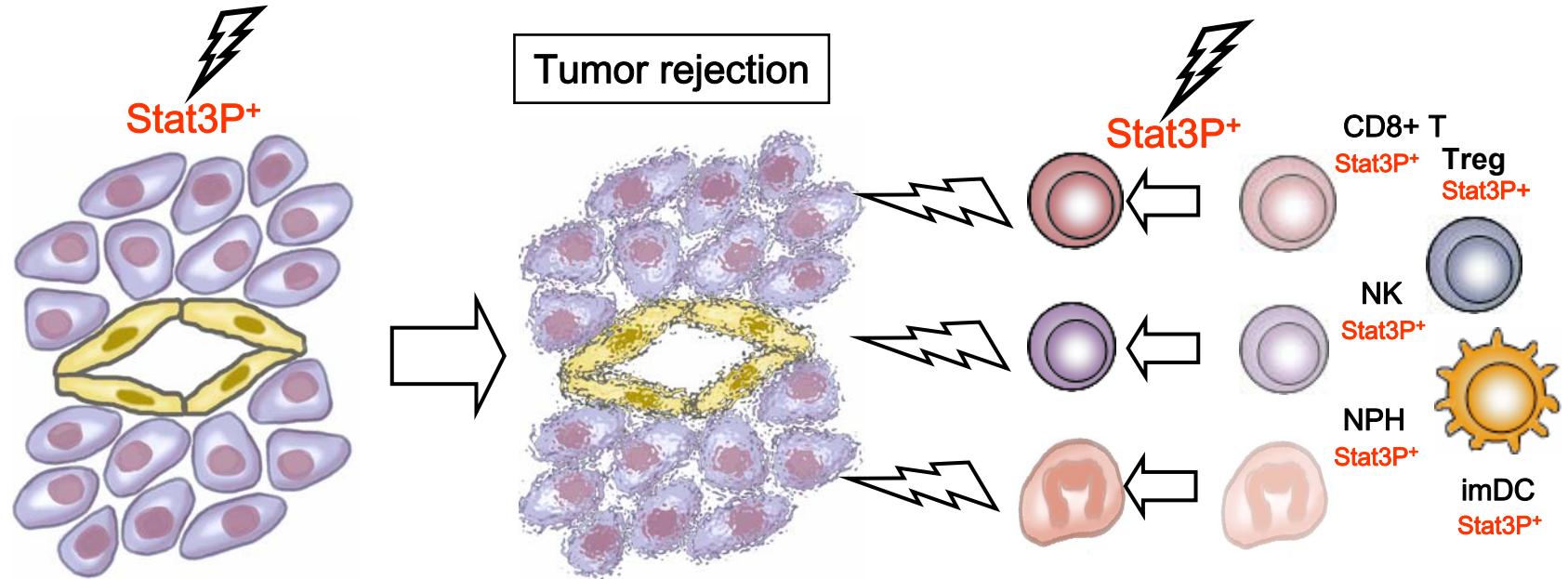
Primary tumor site



Secondary tumor site



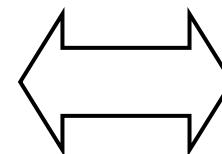
Targeting Stat3 for Cancer Therapy



NF- κ B
PI3K/Akt
Tyrosine kinases
MAPK
Cox2
....
Anti-angiogenesis

Immune inhibitors

CTLA-4
B7-H1
B7-H4
IDO
PD-1
SOCS1
IL-10
TGF- β
COX2



Immune activators

Dendritic cell vaccines
Modified tumor cell vaccines
Engineered T cells
CpG ODNs
LIGHT
Tumor-associated antigens
(Peptides)
Cytokine or chemokine administration