

Antiangiogenesis - Immune Therapy Combinations

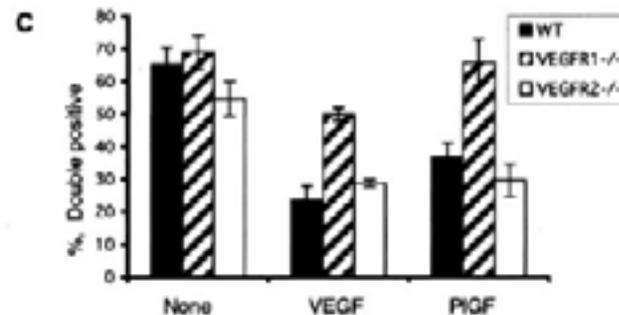
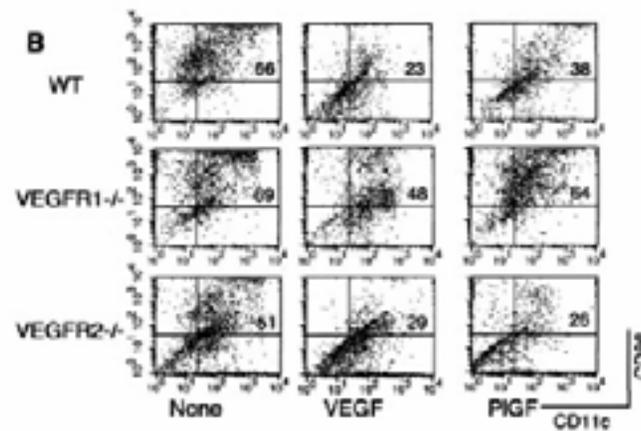
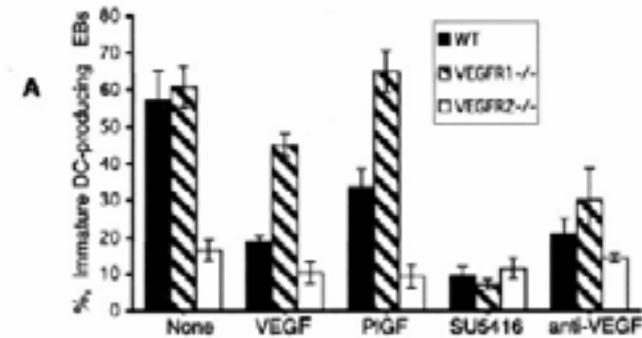
George Coukos, MD, PhD

Heinz Zwierzina, MD

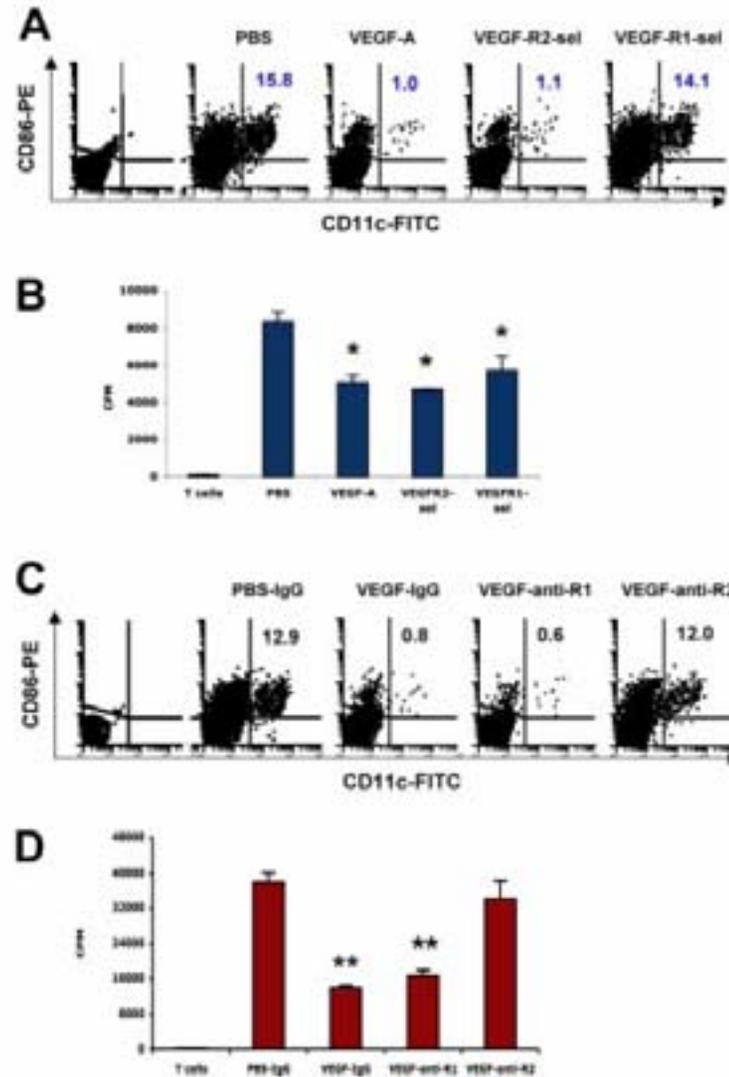
Overview

- Effect of VEGF on antitumor immune response
 - Antigen presentation
 - Effector mechanisms
 - Ying and yang and immunity and angiogenesis in tumors
- Effect of VEGF blockade on immune therapy
- Multifunctional tool opportunities

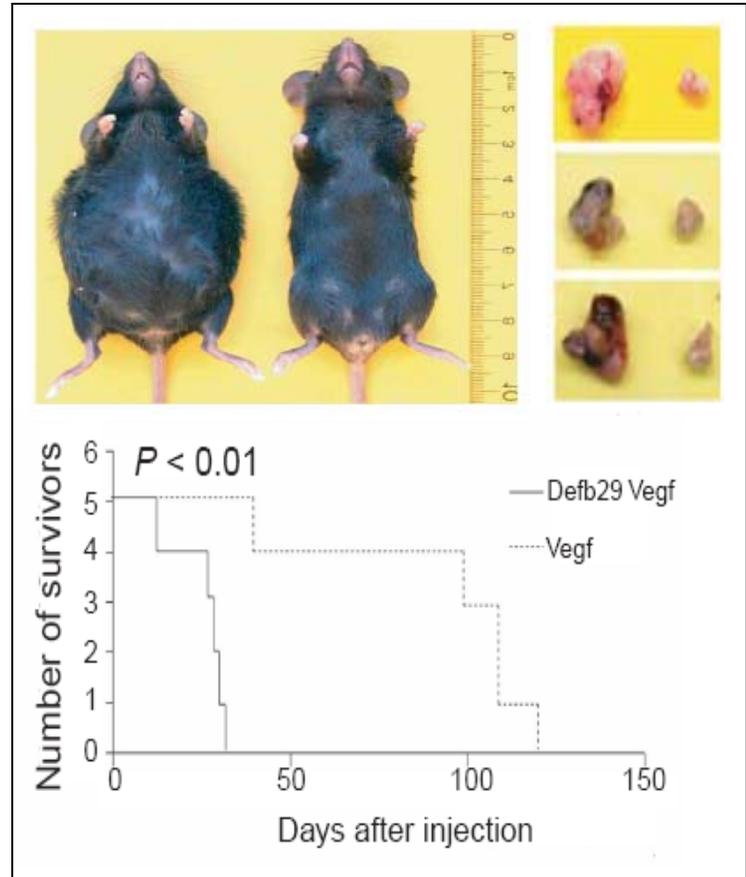
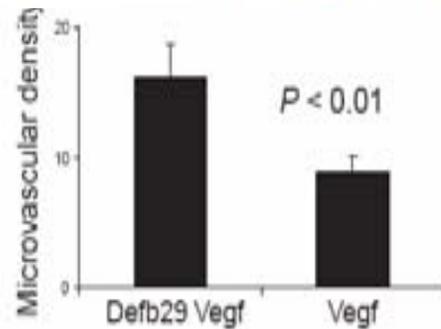
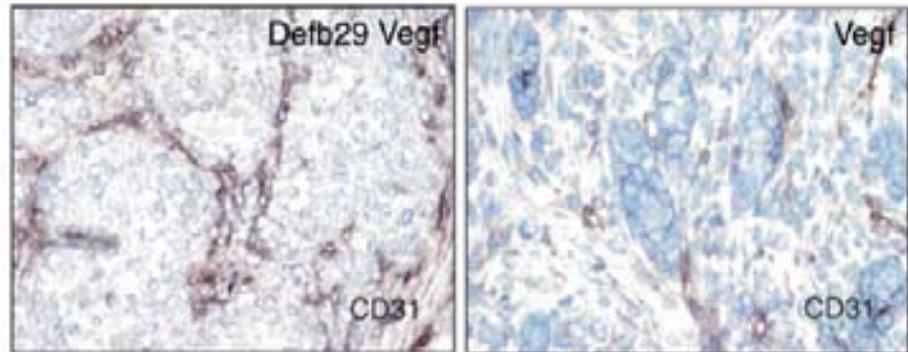
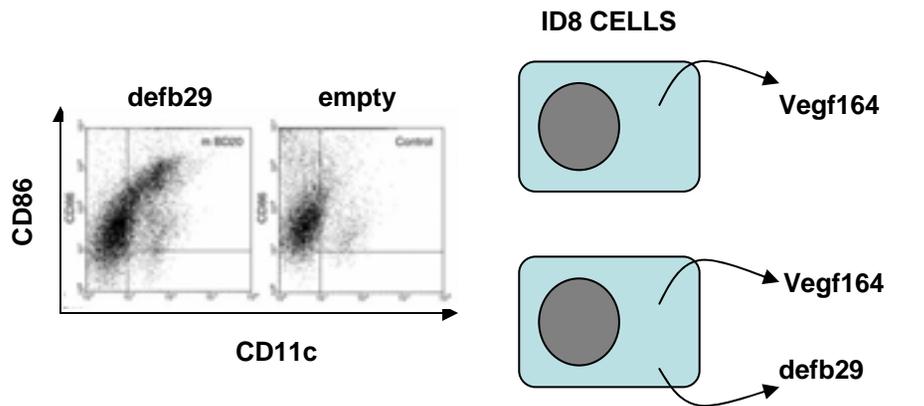
VEGF mediates immature DC development through VEGF-R2 and blocks DC maturation through VEGF-R1



VEGF impairs DC maturation mainly through VEGF-R2

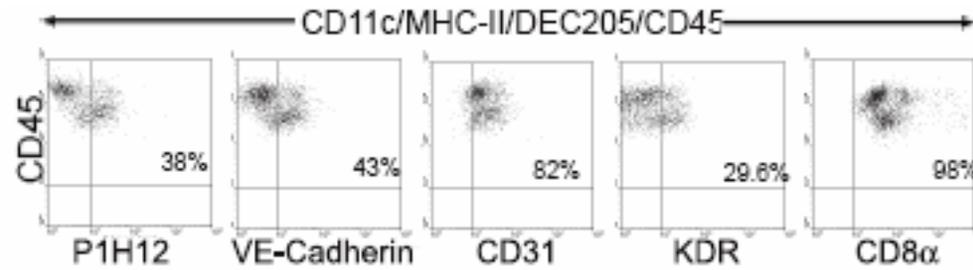
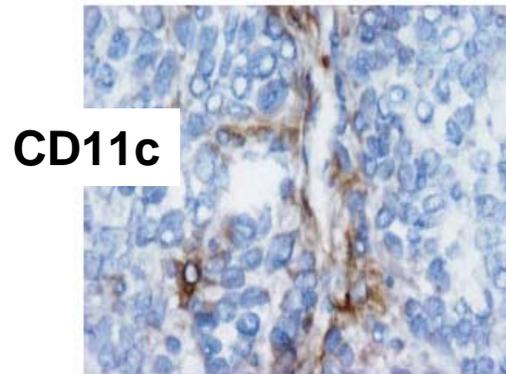


VEGF collaborates with beta-defensin to induce vascular leukocytes

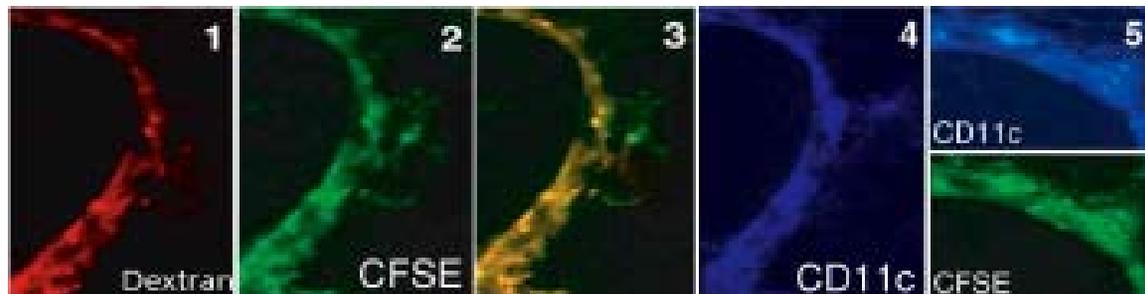


Conejo-Garcia et al., *Nature Med.* 2004

Discovery of mouse vascular DCs

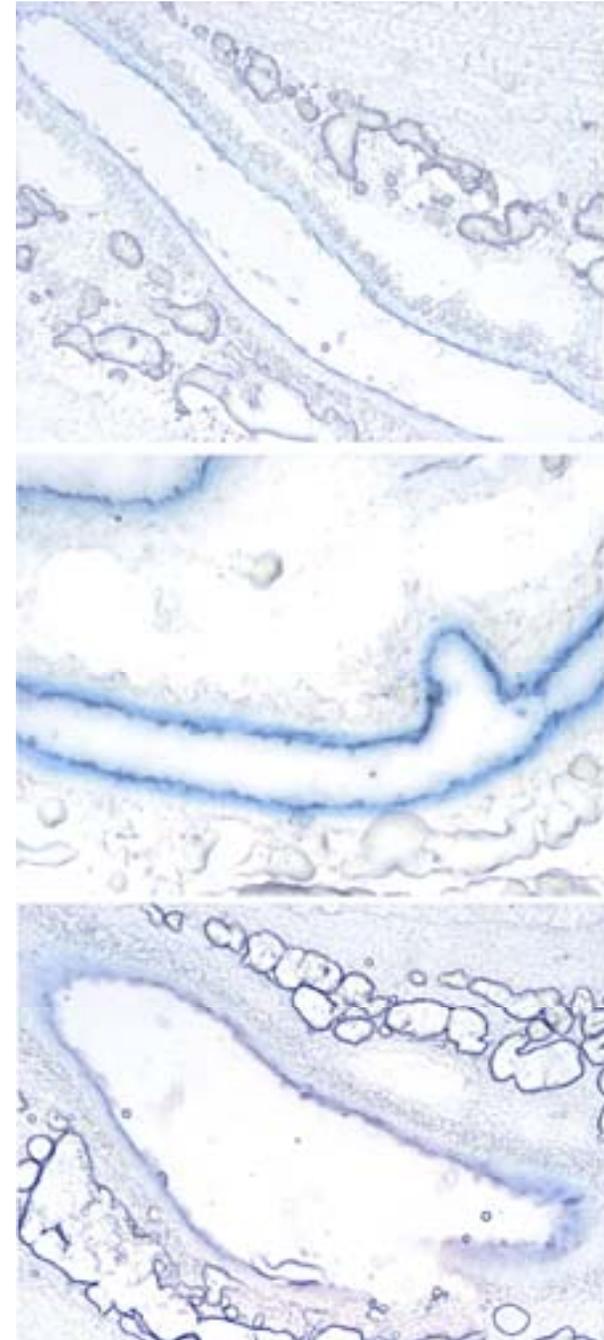
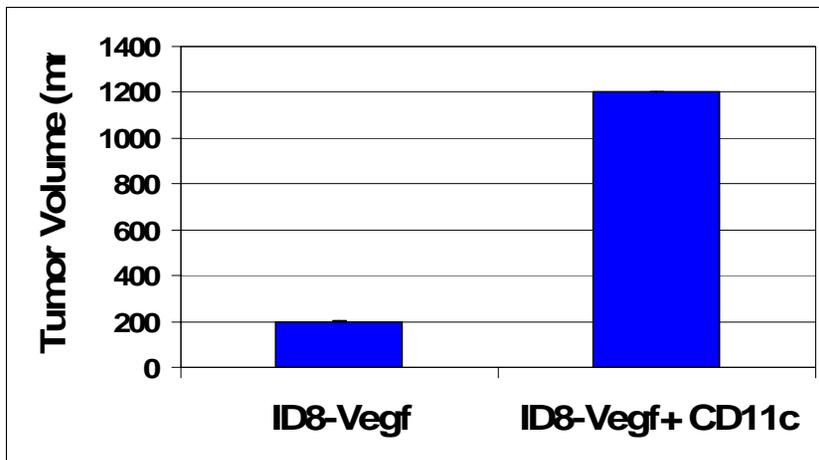
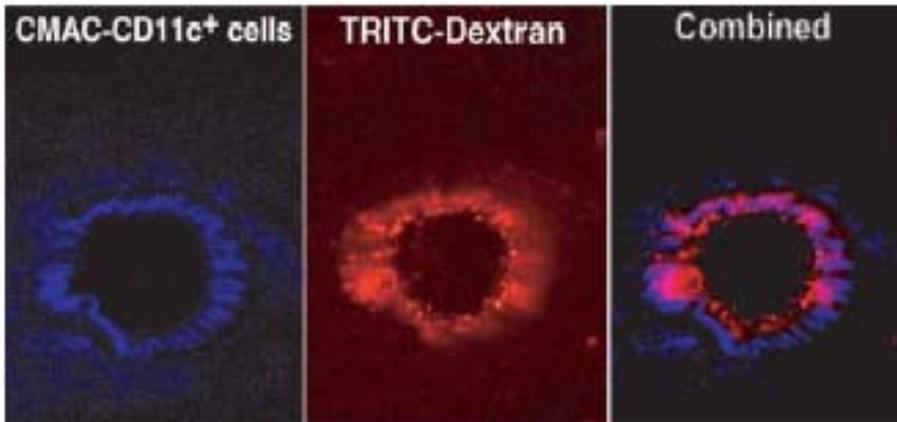


Matrigel



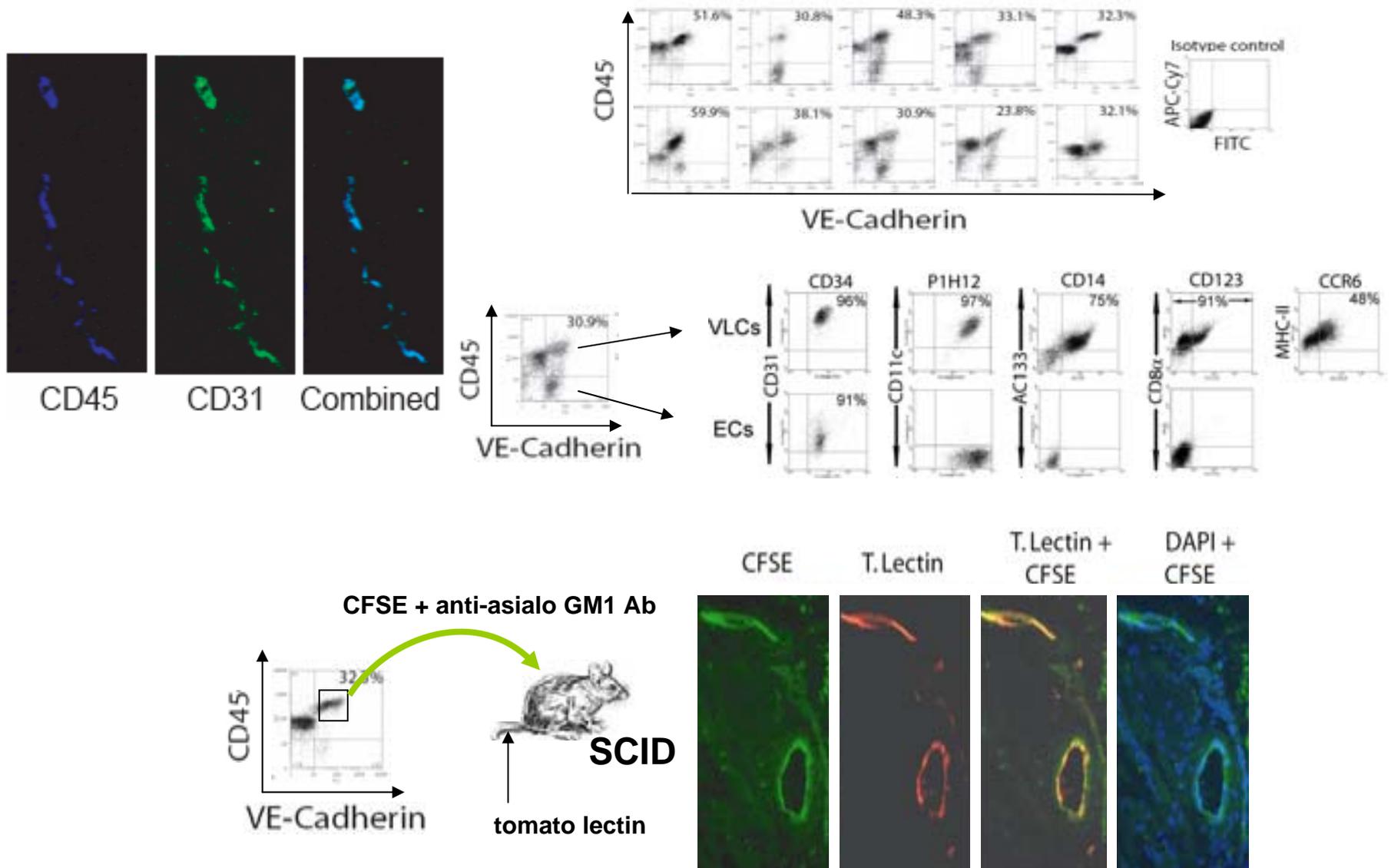
Conejo-Garcia et al., *Nature Med.* 2004

Vascular DCs enhance tumor vascularization and growth

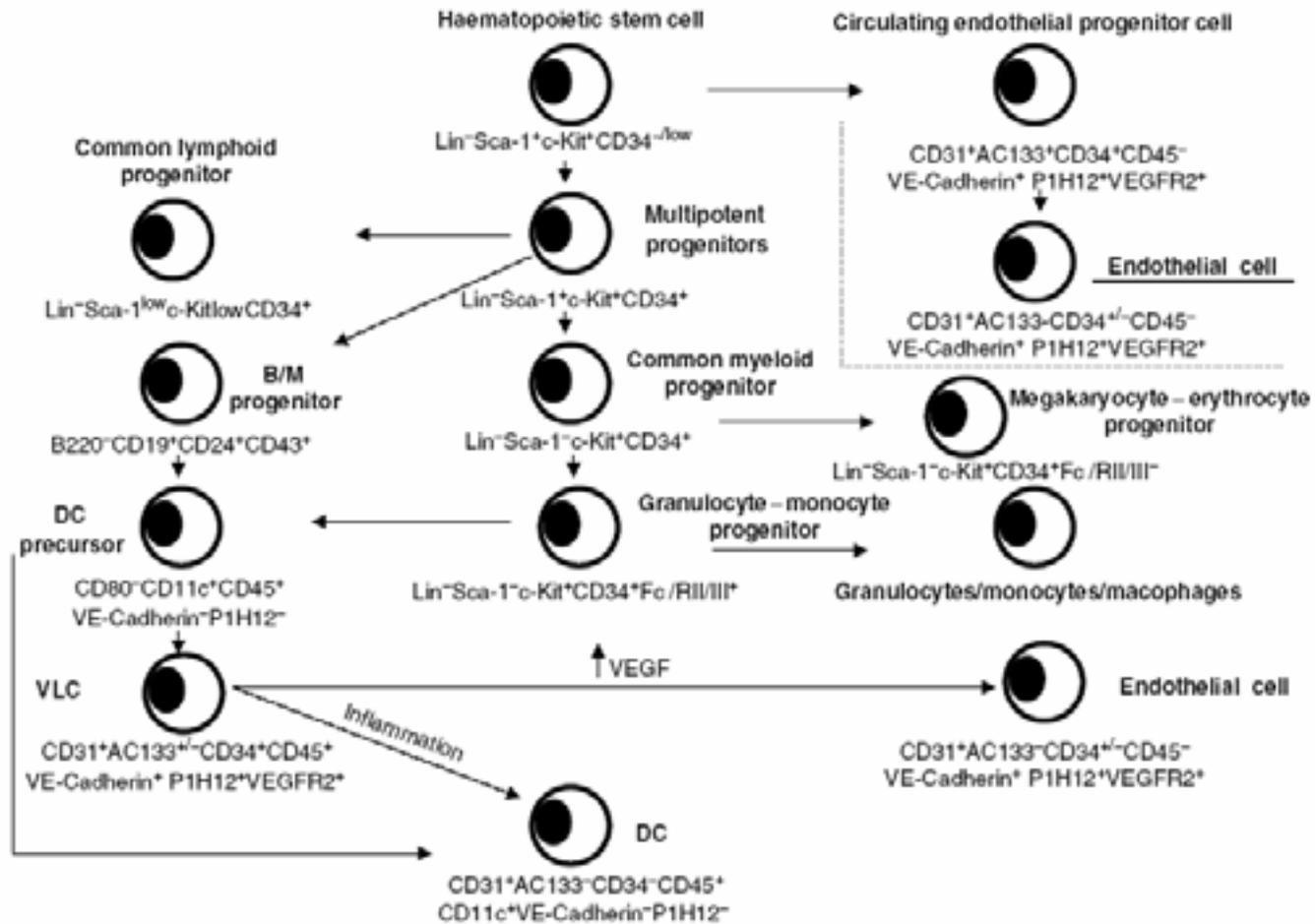


Conejo-Garcia et al., *Nat Med* 2004

Discovery of Human Vascular DCs

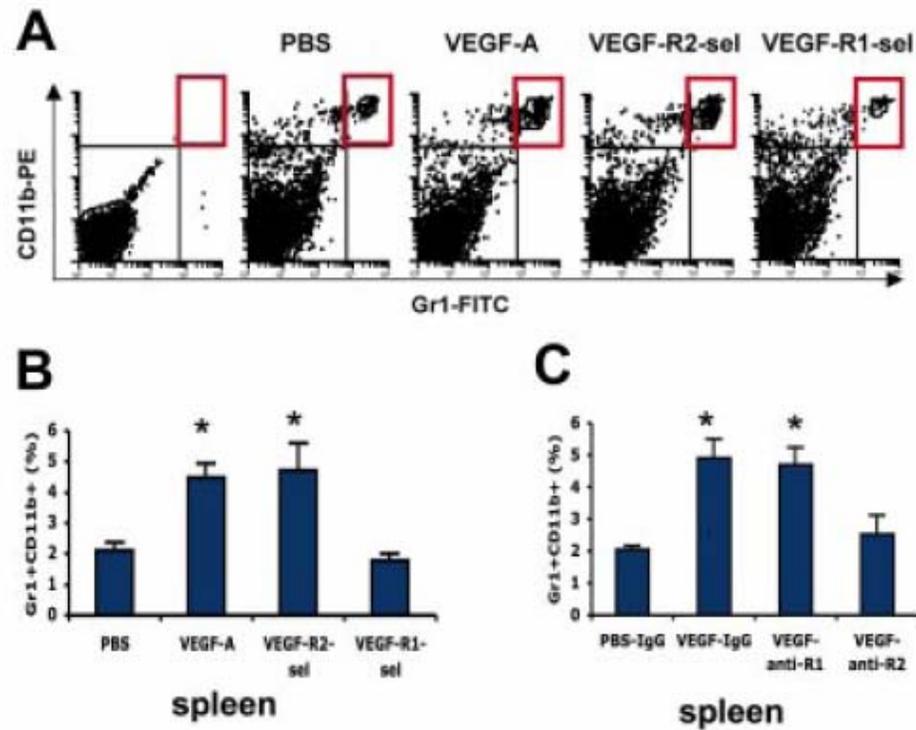


Transdifferentiation of DC precursors into endothelial-like vascular leukocytes



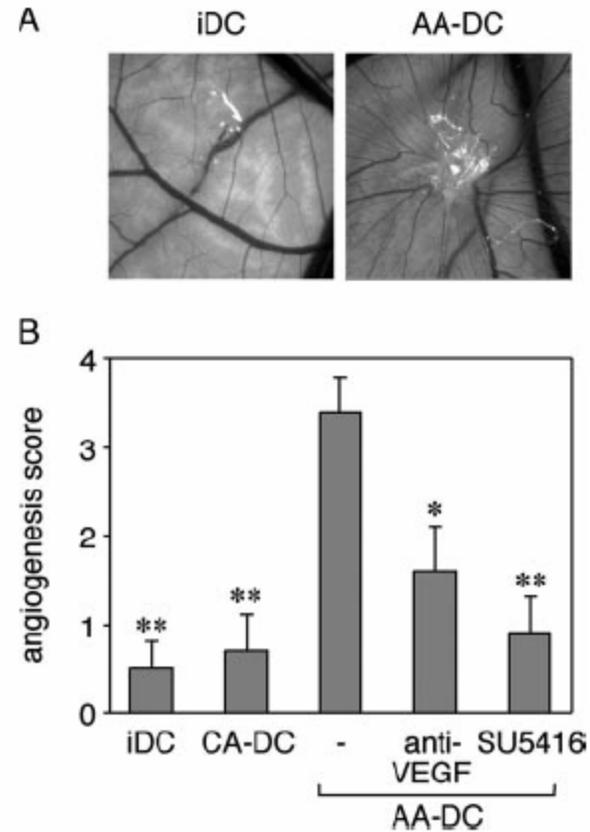
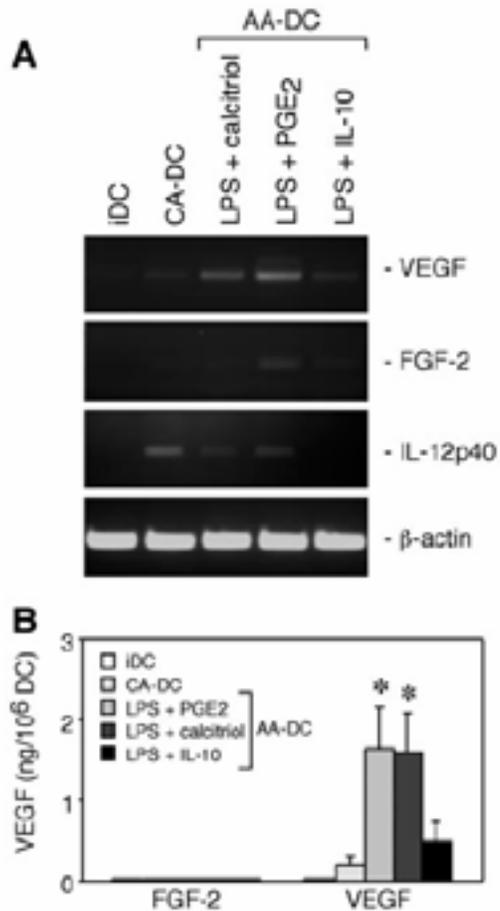
Coukos et al, BJC 2007

VEGF induces MDSCs through VEGF-R2



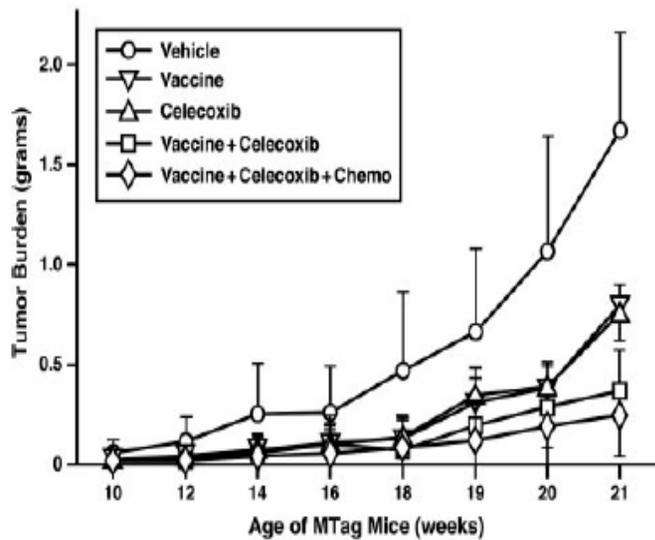
Huang et al, Blood, 2007

Alternatively activated DC produce VEGF and promote angiogenesis



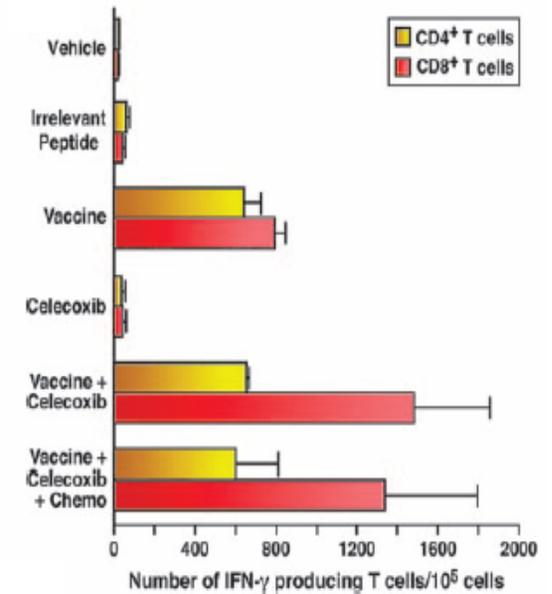
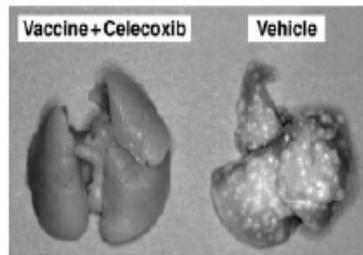
Riboldi et al, J Immunol 2005

COX-2 suppression enhances the efficacy of vaccination



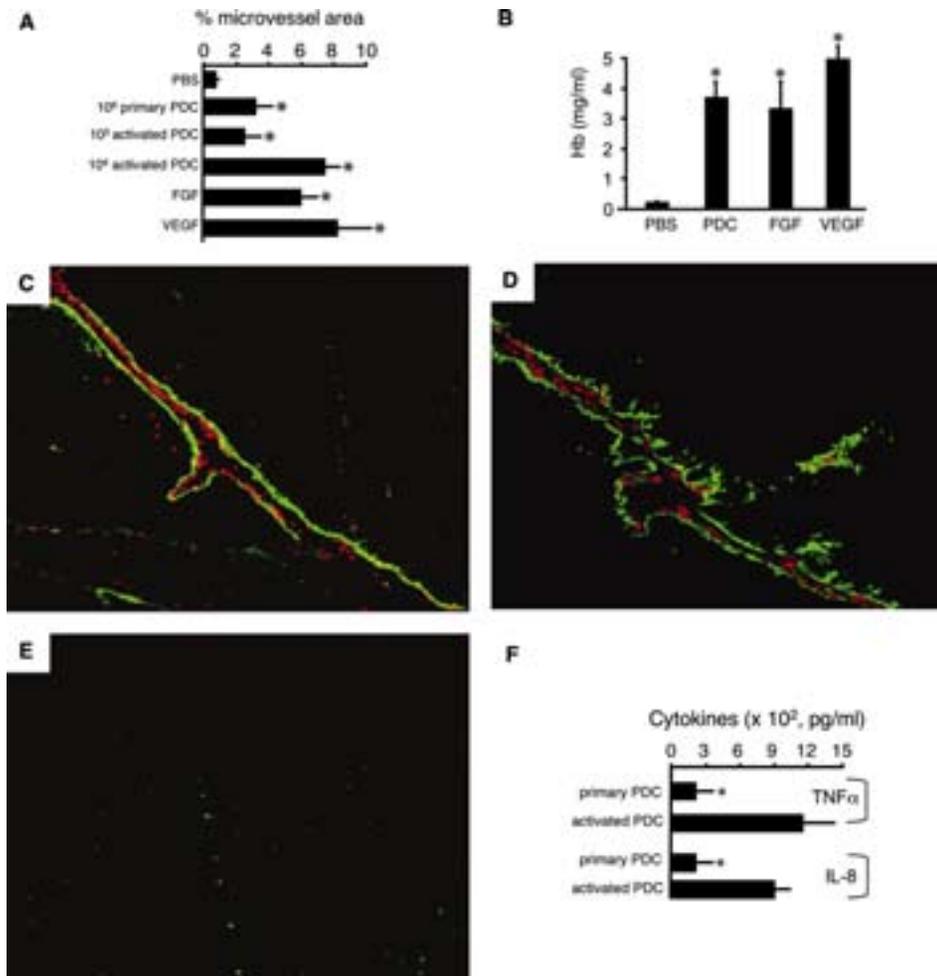
Number of Mice with Lung Metastases

Vehicle	4/10
Vaccine	3/10
Celecoxib	1/10
Vaccine + Celecoxib	0/10
Vaccine + Celecoxib + Chemo	0/10

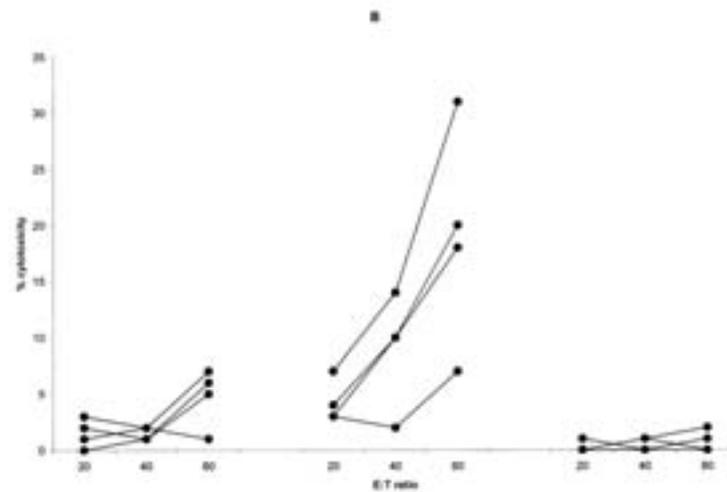
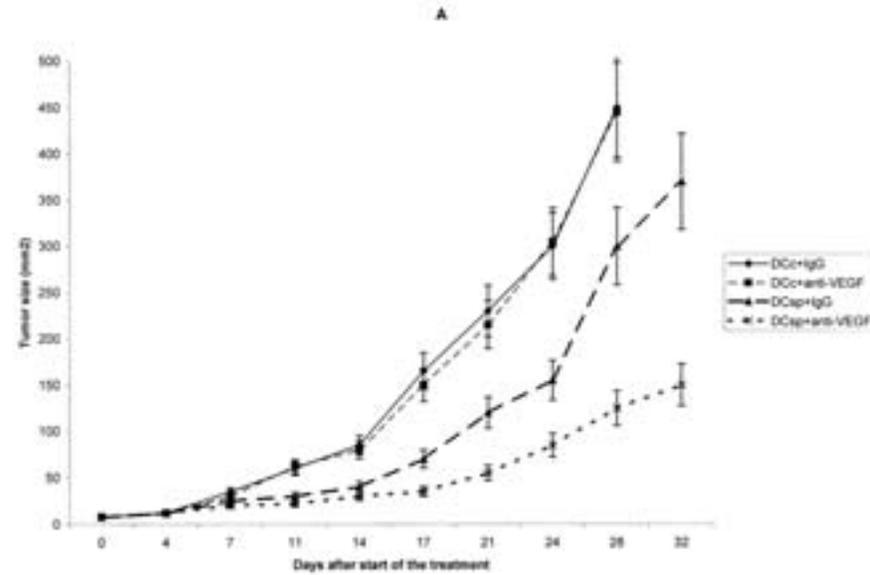


Basu et al, J Immunol 2006

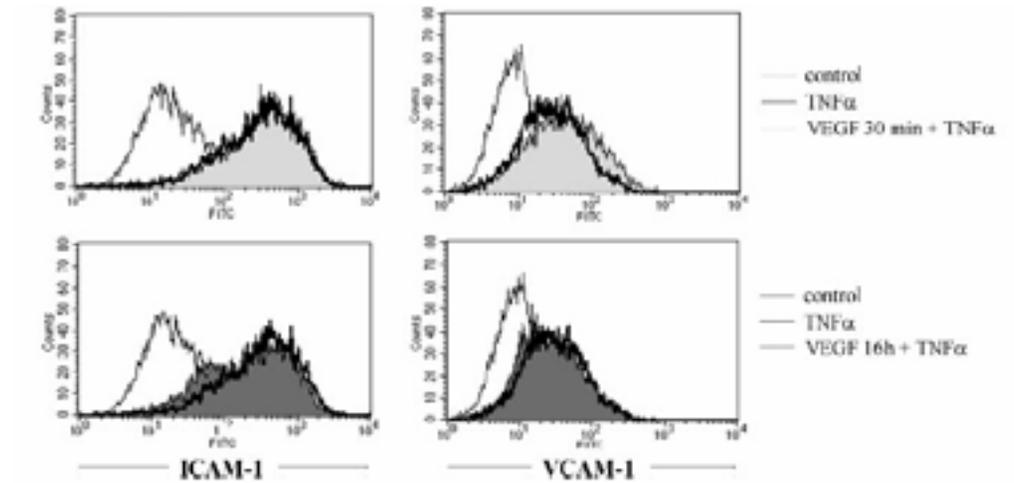
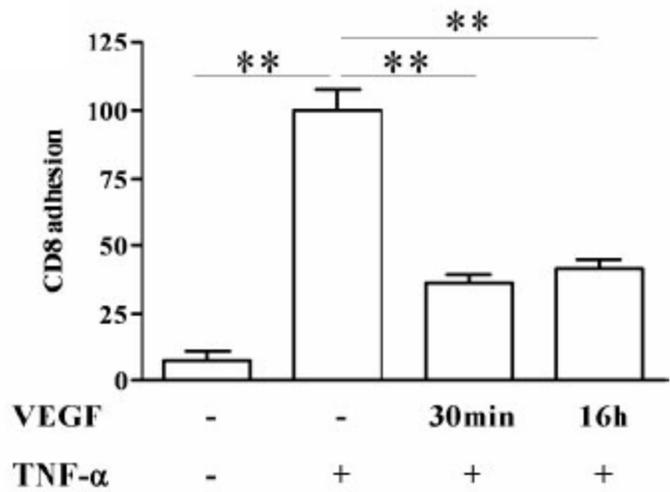
Plasmacytoid DC produce VEGF and promote angiogenesis



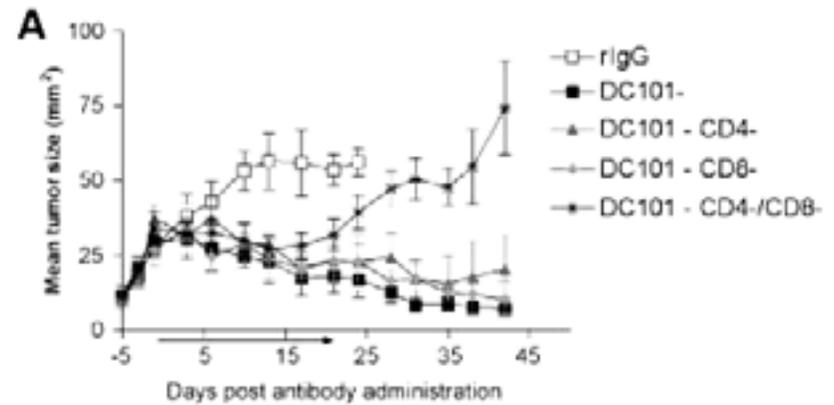
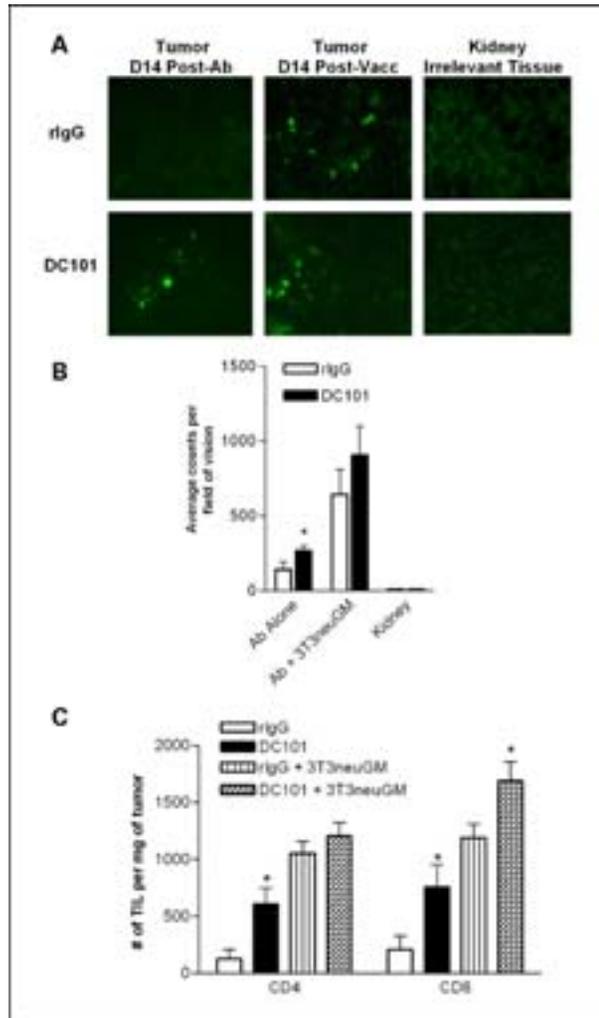
VEGF blockade improves vaccine therapy



VEGF blocks T cell adhesion on endothelium

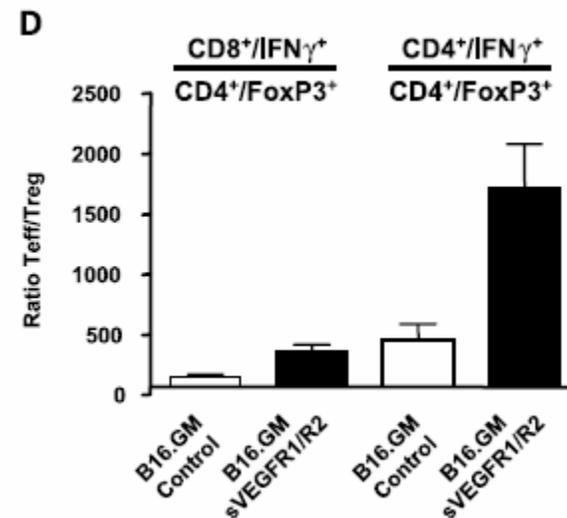
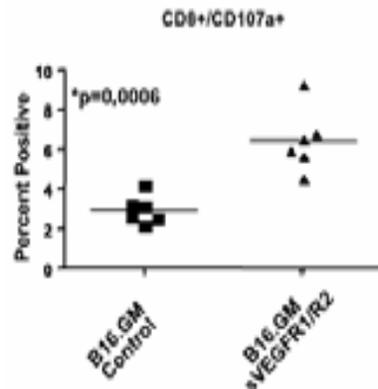
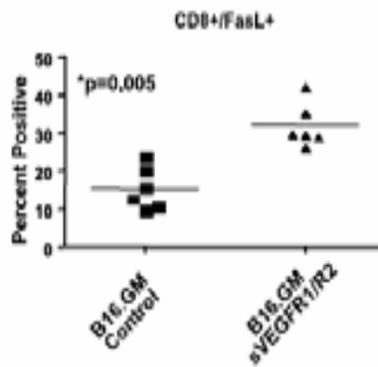
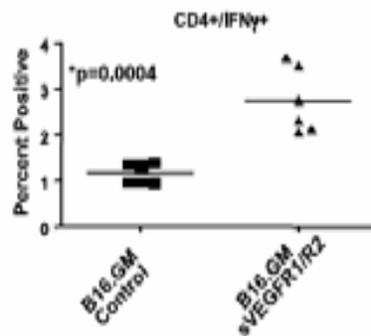
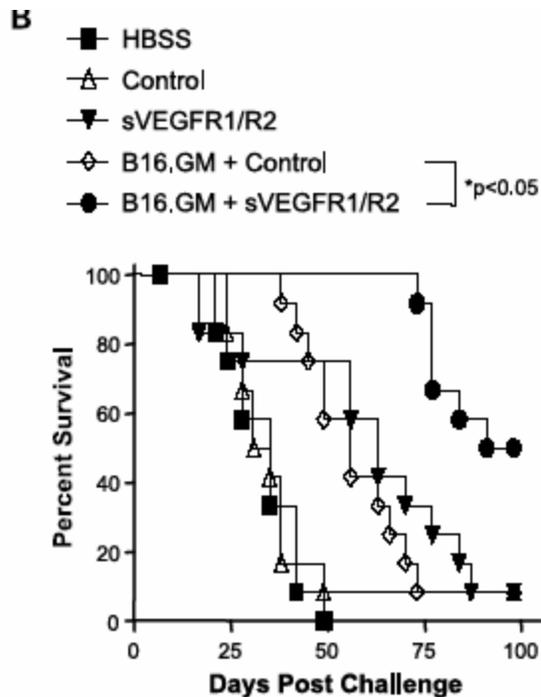


VEGF blockade induces antitumor immune response, increases T cell homing and improves vaccine therapy

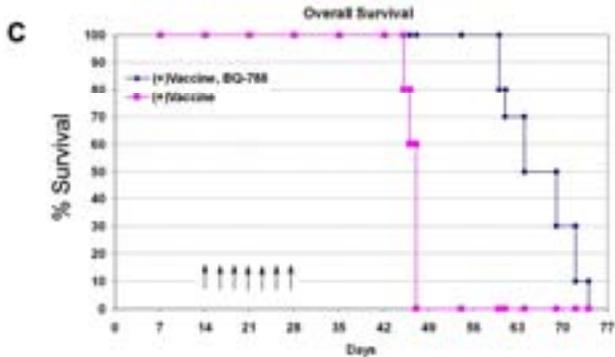
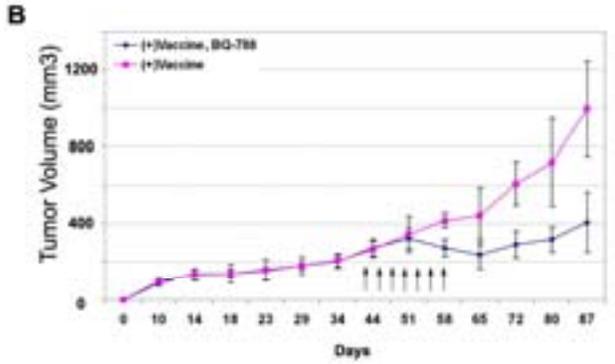
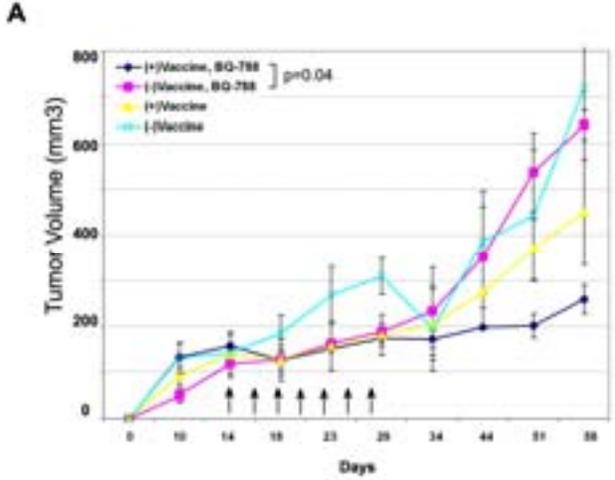
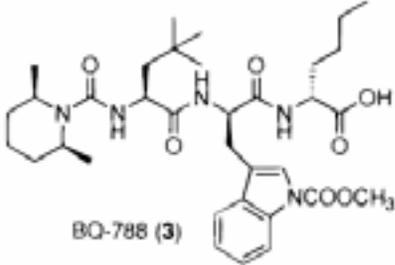
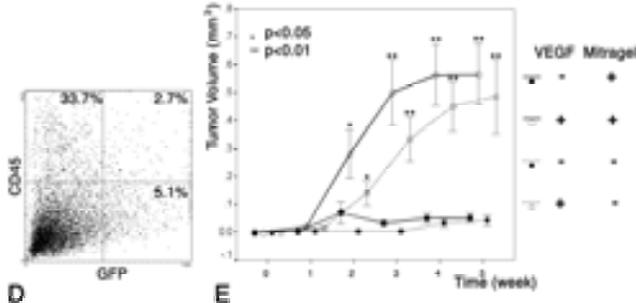
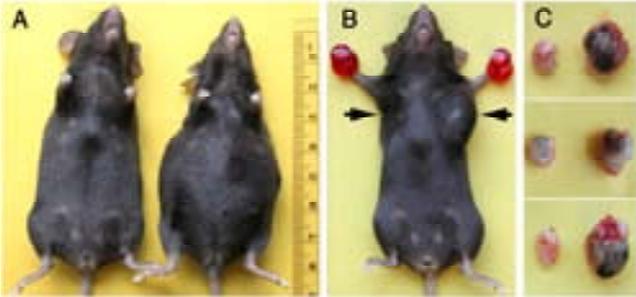


Manning et al, Clin Ca Res, 2007

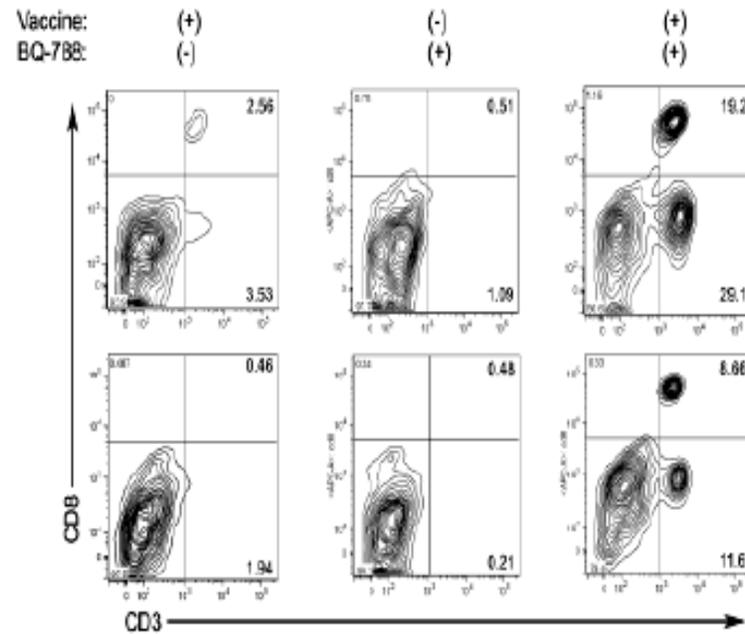
VEGF-R1 and R2 blockade improves immune therapy and reduces Treg



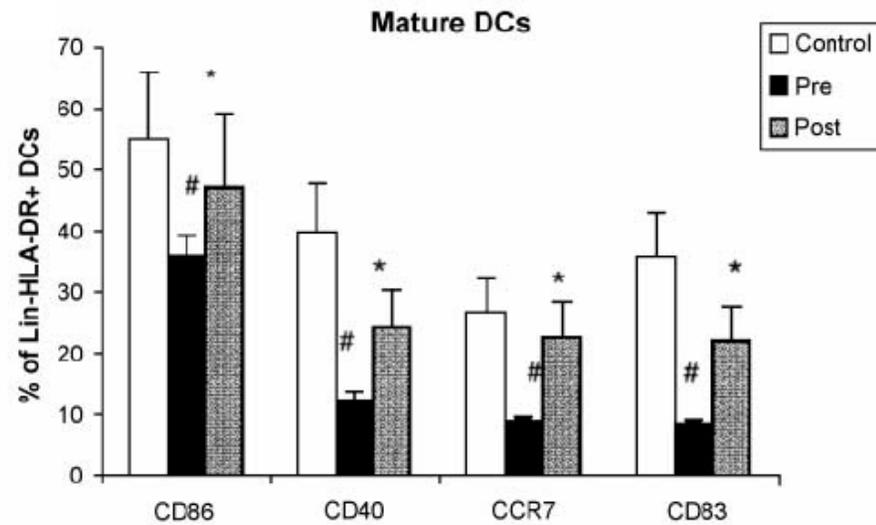
ET_BR blockade enhances tumor vaccine



ET_BR blockade enhances tumor vaccine by increasing T cell homing to tumor



VEGF blockade improves DC maturation in patients with solid tumors



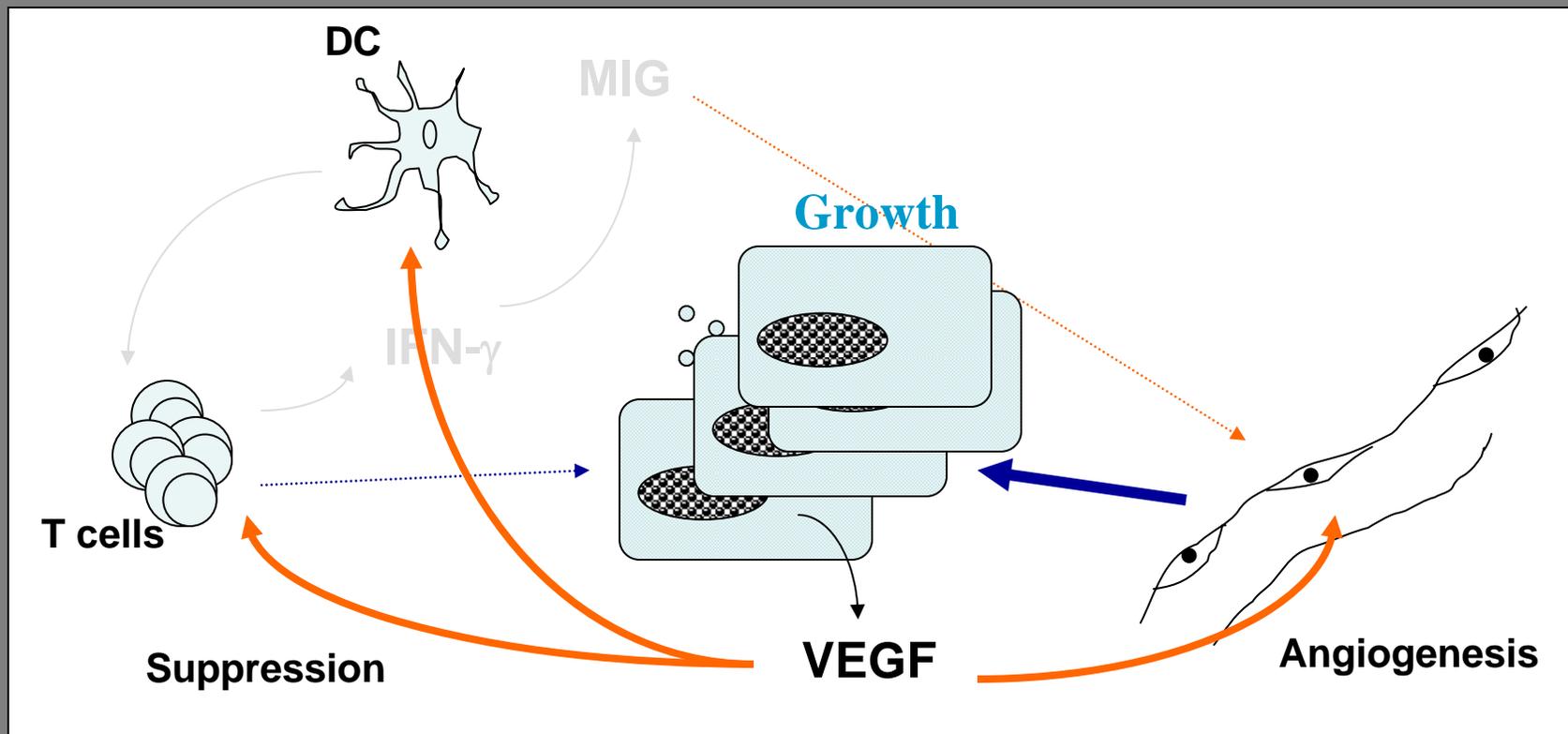
Fricke et al, Clin Ca Res, 2007

Vaccine + VEGF blockade moves to the clinic

- Sipuleucel-T (APC loaded with recombinant prostatic acid phosphatase/GM-CSF fusion protein) i.v. on weeks 0, 2, and 4 + bevacizumab 10 mg/kg i.v. on Weeks 0, 2, 4, and every 2 weeks thereafter until toxicity or disease progression in androgen-dependent prostate cancer patients who had received prior definitive therapy with nonmetastatic, recurrent disease as manifested by a rising PSA.
- 22 patients treated, 3 patients responded with PSA ↓ >25%, 1 patient with PSA ↓ >50%.

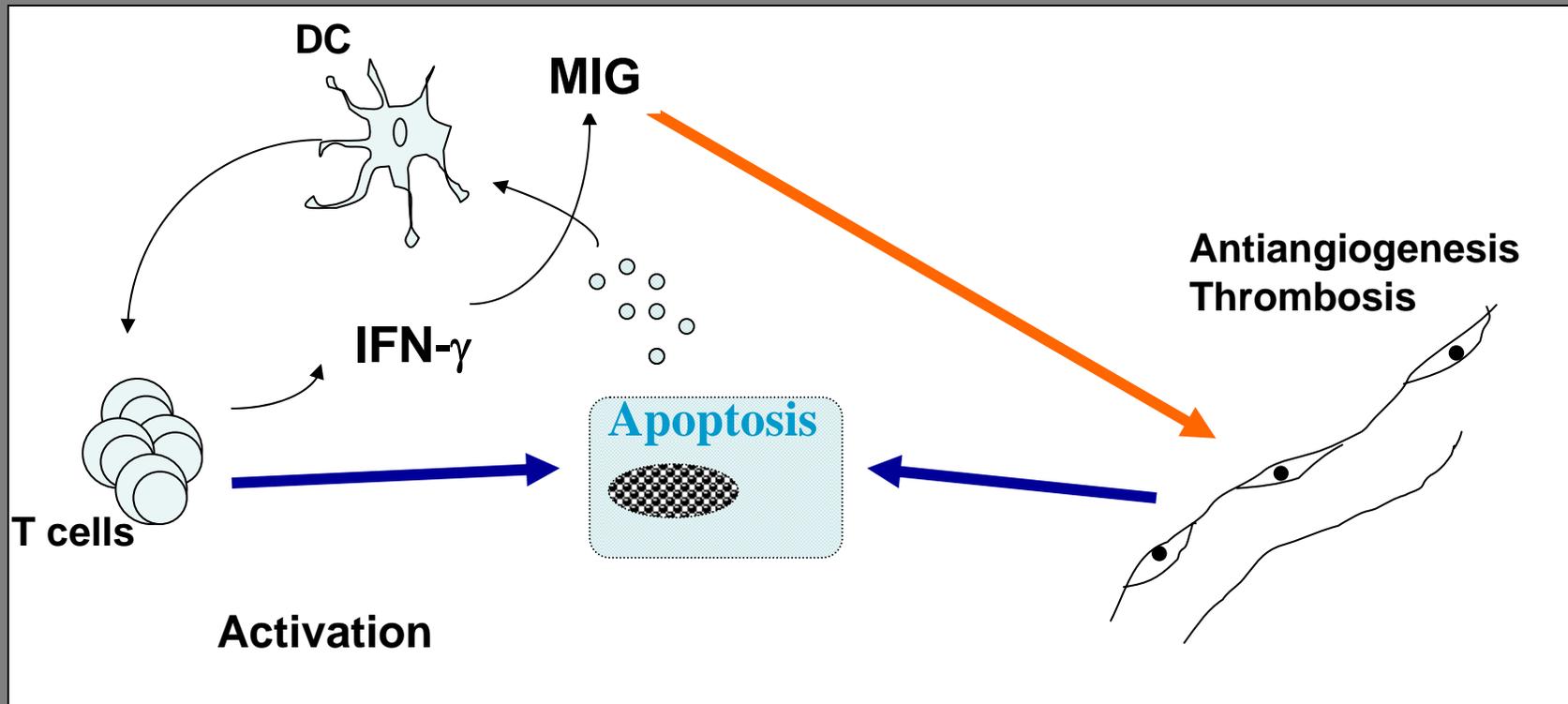
Integrative Model of Immune Response and VEGF Interactions

Predominance of angiogenesis

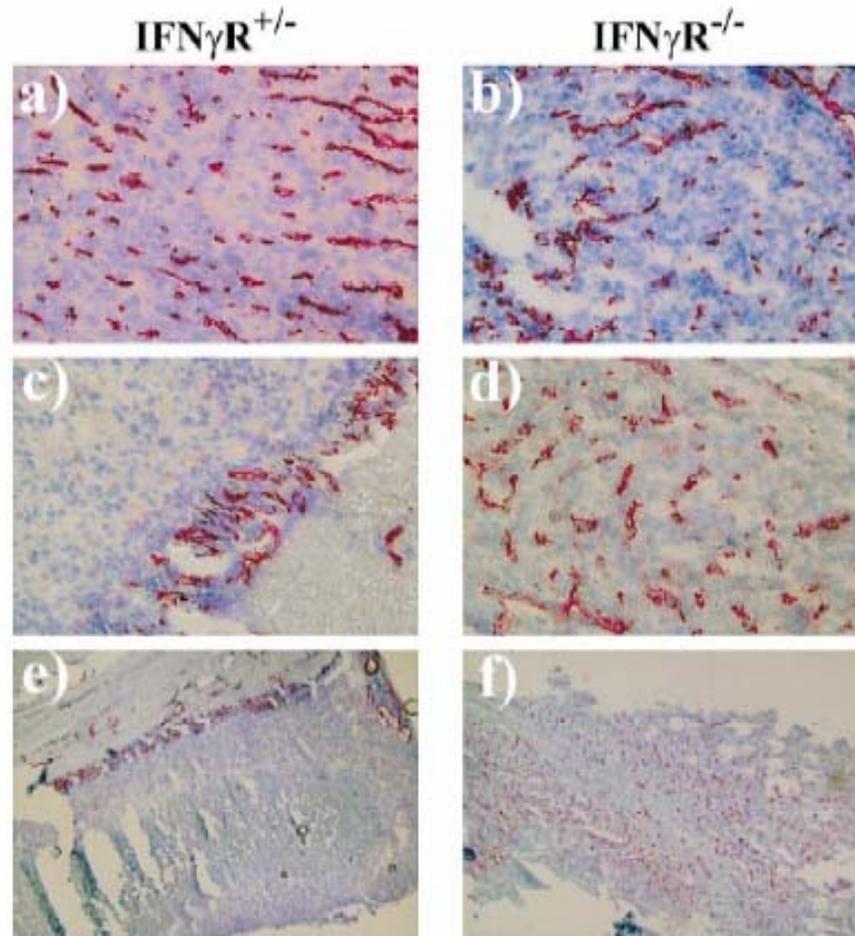
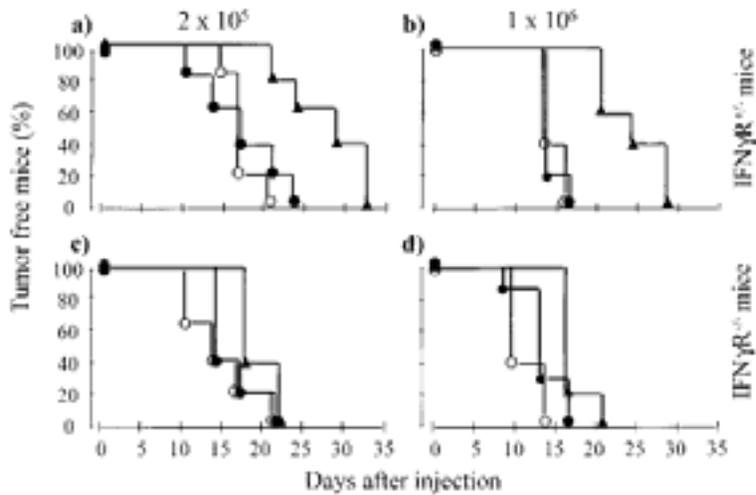


Integrative Model of Immune Response and VEGF Interactions

Predominance of antitumor immune response



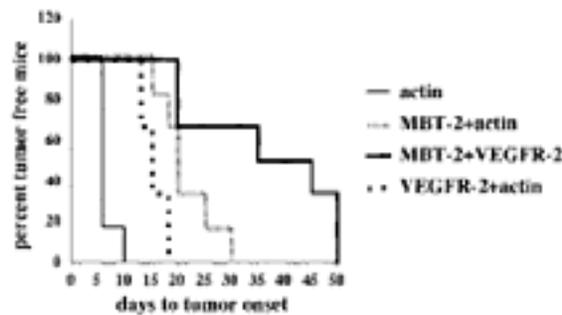
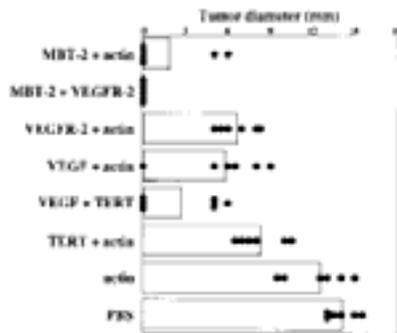
Successful tumor immunotherapy suppresses tumor vascularization



Multifunctional tool opportunities

- Angiogenesis-targeting immunotherapy
- Thalidomide and analogs (antiangiogenic/anti-inflammatory and Th1 costimulatory)
- ET_BR inhibitors
- STAT3 inhibitors ?
- COX-2 inhibitors ?
- Sorafenib ?
- Sunitimib ?

Vaccination against tumor and angiogenesis targets produces synergism

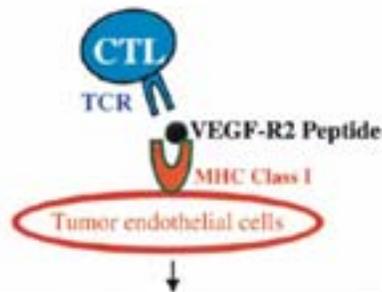


Nair et al, Blood 2003

Angiogenesis/Vascular Targets

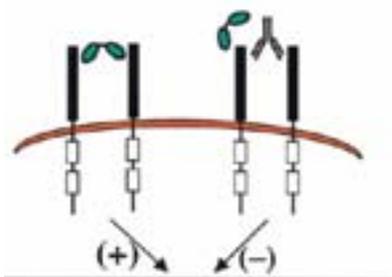
- Mixed endothelial cells
- VEGF
- VEGF-R2
- VEGF-R1
- FGF-2
- FGF-R1
- Tie-2
- Endoglin (CD105)
- Integrin β 3
- Calreticulin

CTL-mediated lysis of tumor endothelial cells



Direct lysis of tumor vessels

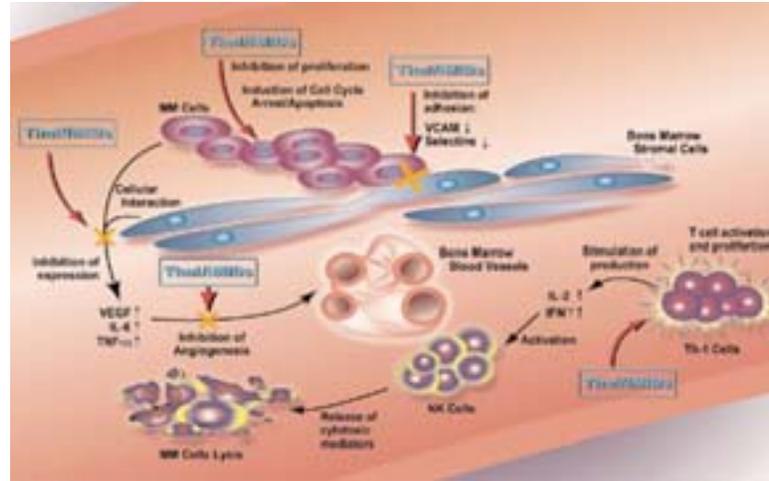
Blockade of VEGF:VEGF-R2 signaling by neutralizing antibody



Signals for survival, proliferation and migration of endothelial cells

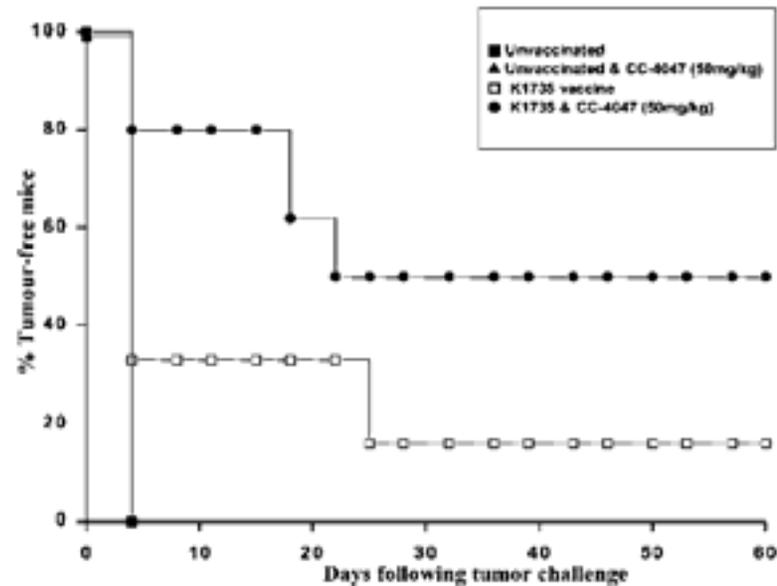
Rafii, Cancer Cell 2002

Thalidomide and analogs



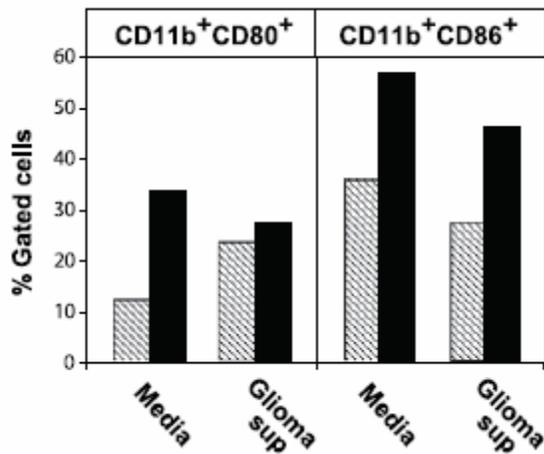
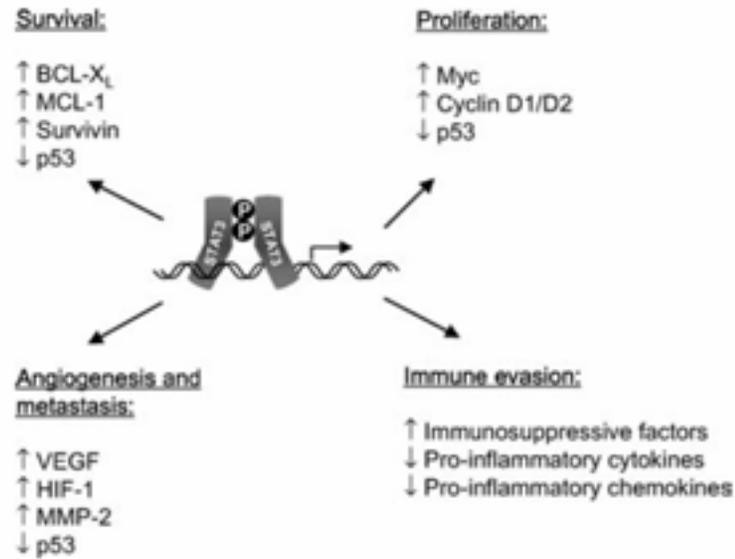
Thd and IMiDs:

- Inhibit TNF- α , IL-1 β , 6, 12, and GM-CSF
- Costimulate primary human T lymphocytes inducing proliferation, Th1 polarization, cytokine production, and cytotoxic activity.

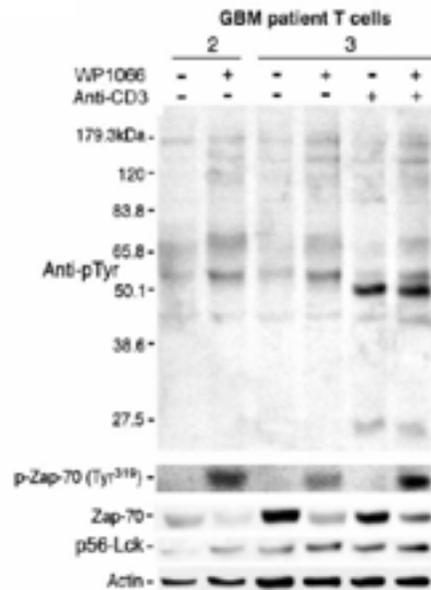


Dredge et al, J Immunol 2002

STAT3 Inhibition



▨ Unstimulated
 ■ WP1066



Conclusions

- Tumor VEGF suppresses antitumor immune response
- Immune tolerance may increase, while immune activation may suppress tumor angiogenesis
- VEGF blockade enhances immune therapy
- Novel targets are available for therapy (ET_BR)
- Novel functions discovered for existing drugs generate opportunities for combinatorial biologic therapy with multifunctional tools