

Biomarkers from the Tumor Microenvironment: Are they Useful?

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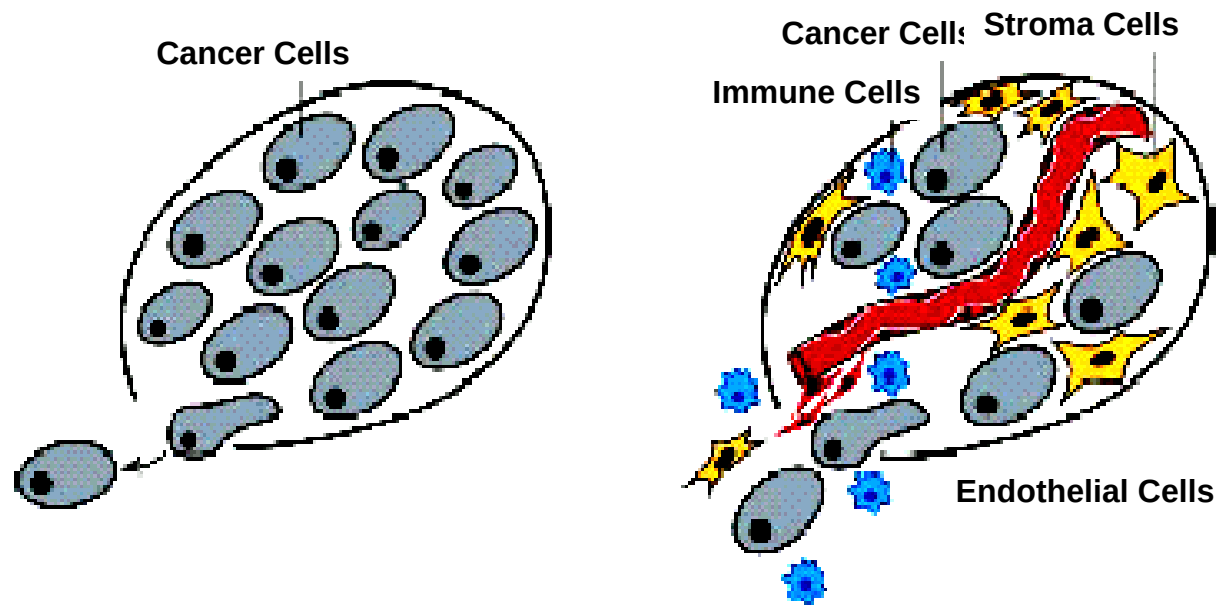
**Director, Gynecologic Malignancy Research Programs
University of Pennsylvania**



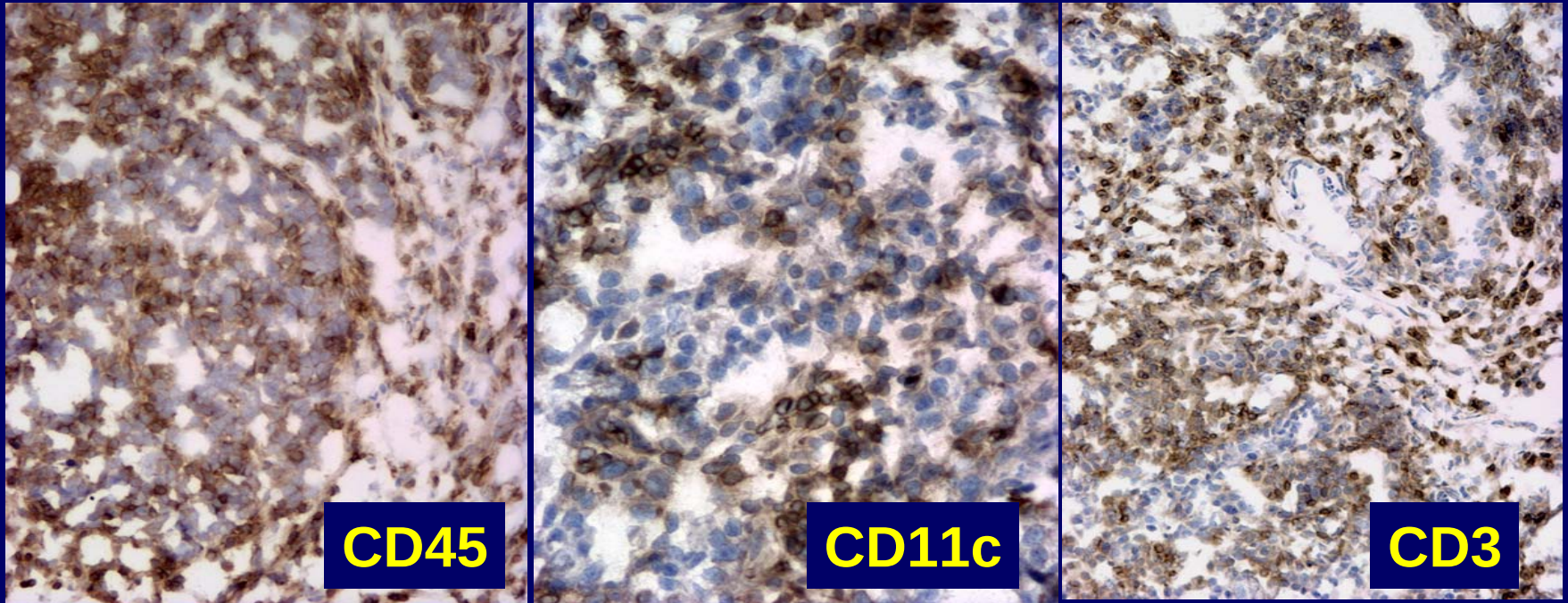
Biomarkers from the tumor microenvironment

- Tumor microenvironment events affect tumor outcome
- Tumor microenvironment events are identifiable through cellular or molecular markers
- Markers are mechanistically relevant
- Modulation of tumor microenvironment affects tumor outcome
- Modulation of tumor microenvironment can be traced through these markers

Tumor Microenvironment



Do Leukocytes Play a Role in Ovarian Cancer ?



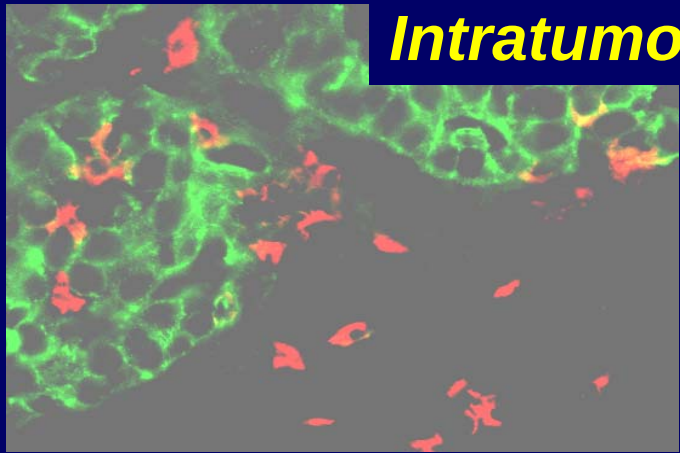
Cellular Biomarkers

Intratumoral T cells

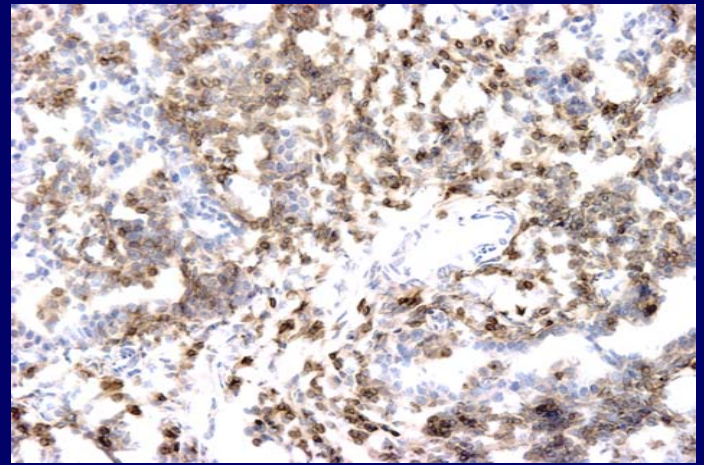
T regulatory cells

Vascular leukocytes

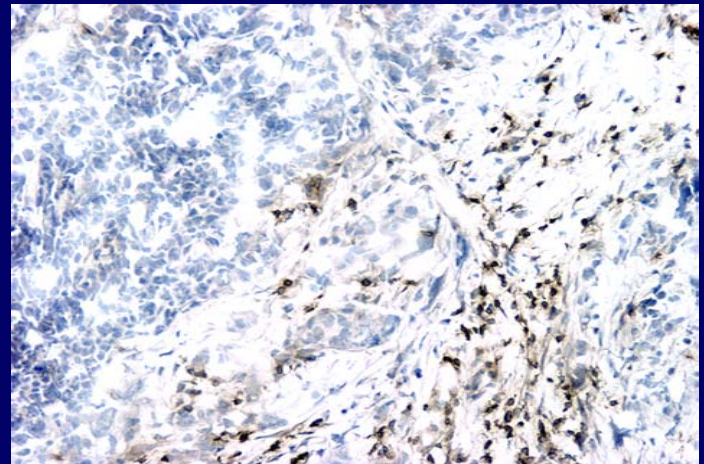
Intratumoral T cells



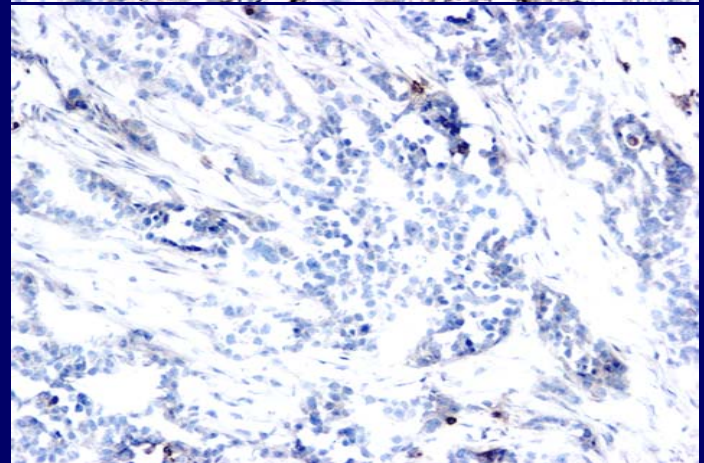
54.8%



38.7%



6.5%

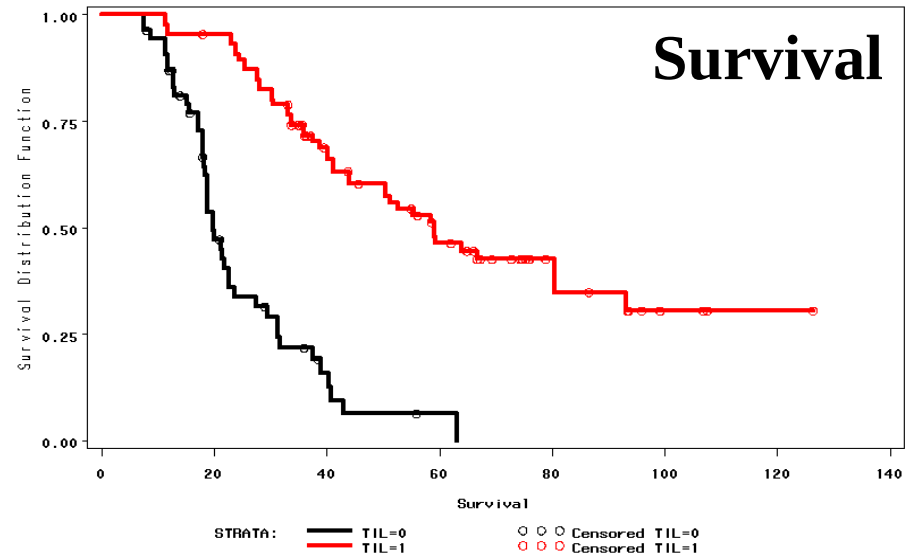
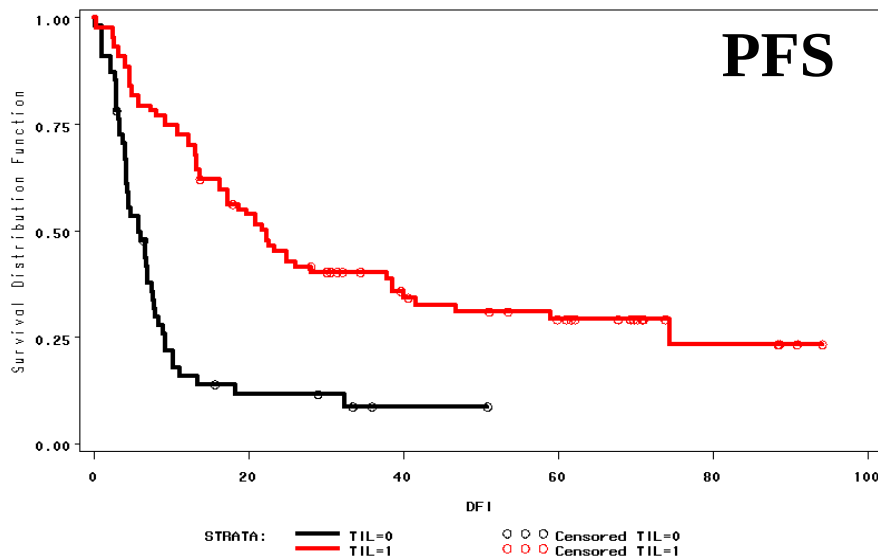


CD3⁺

N=174

Zhang et al., *NEJM* 2003

Impact of TILs on Outcome in Ovarian Cancer Stage III/IV – All patients (n=174)



— + TILs
— - TILs

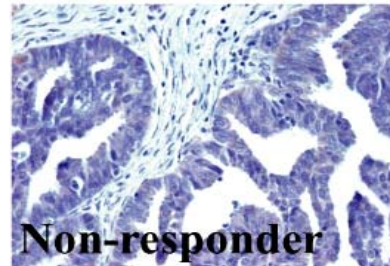
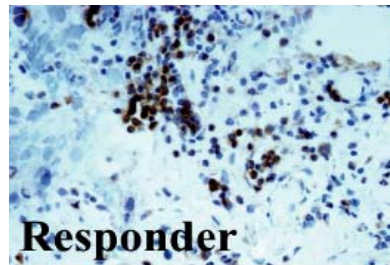
N=174

Zhang et al., *NEJM* 2003

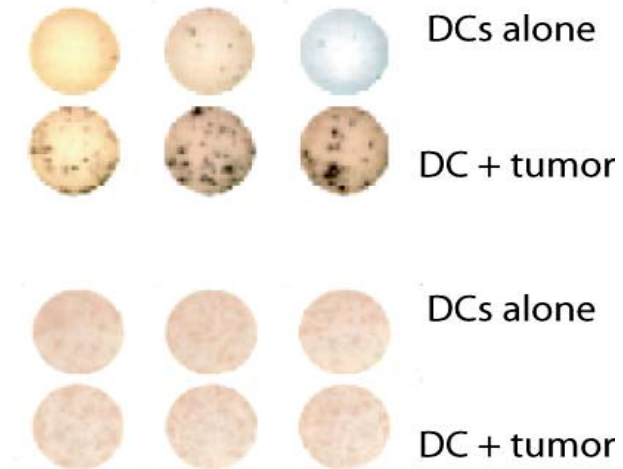
TILs correlate with tumor-reactive PBLs

Patient No.	ELISPOT	TILs
OV22	+	+
OV23	-/+	+
OV24	--	--
OV26	--	--
OV27	+	+
OV28	--	--
OV29	+	+
OV31	+	--
OV32	+	+
OV34	--	--

$P < 0.045$

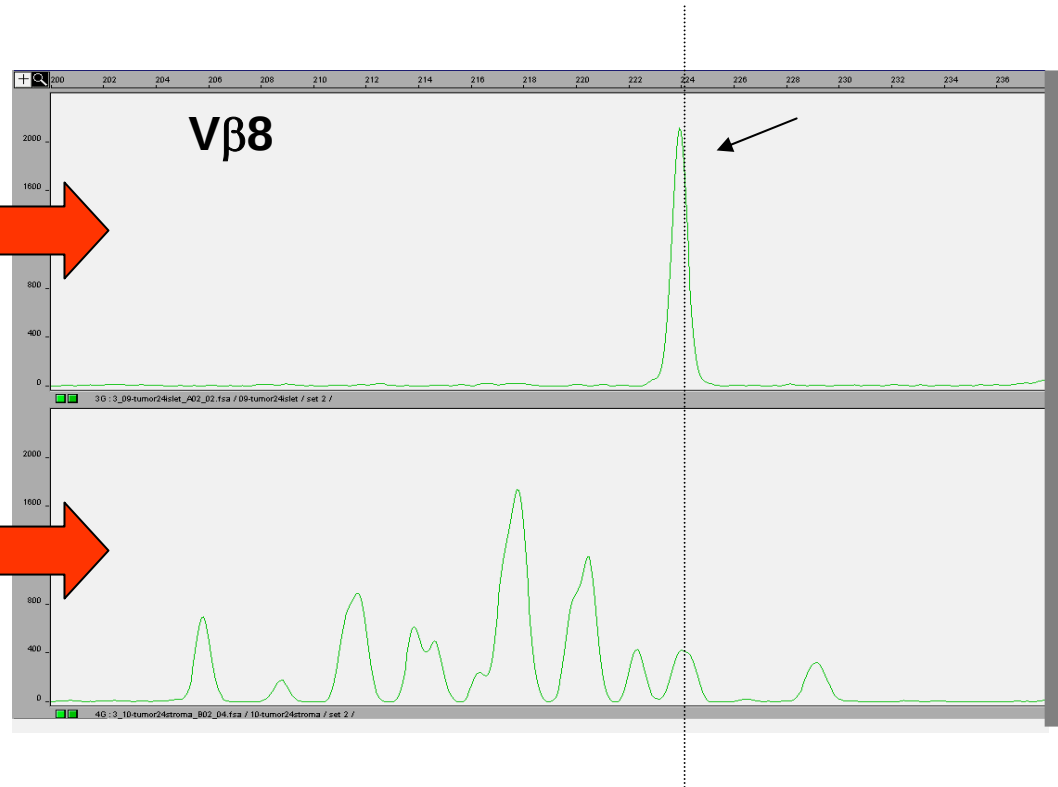
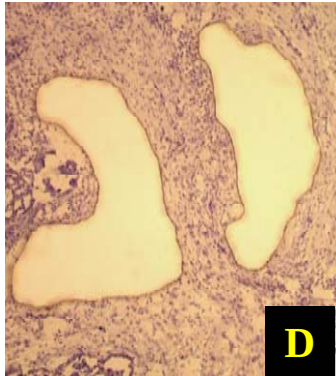
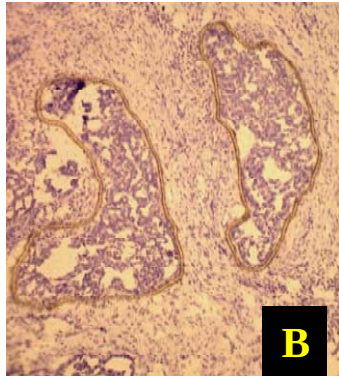
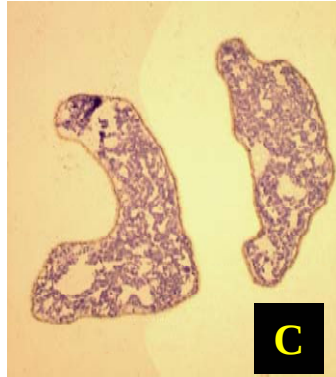
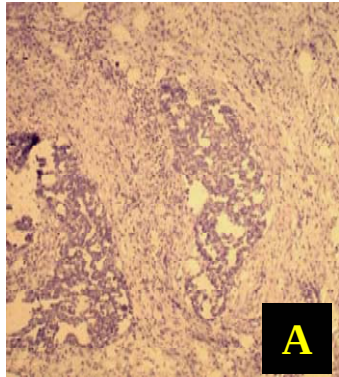


CD3

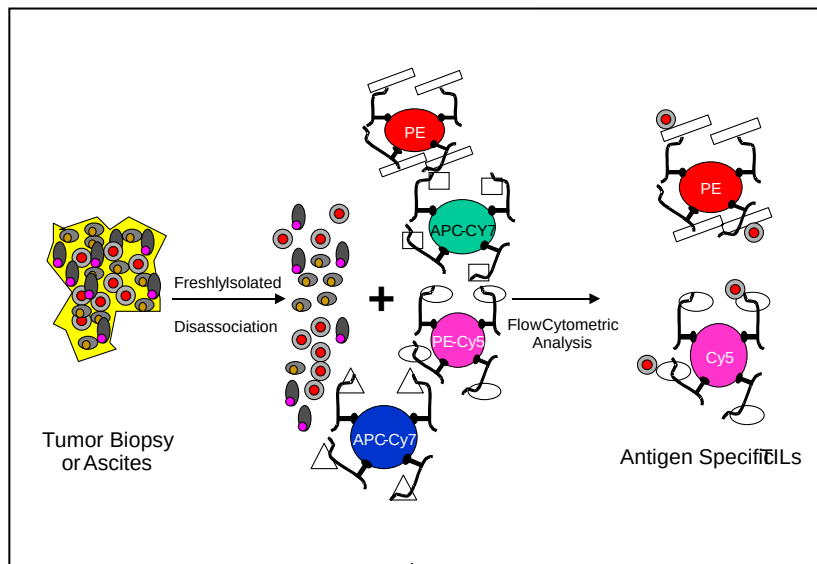
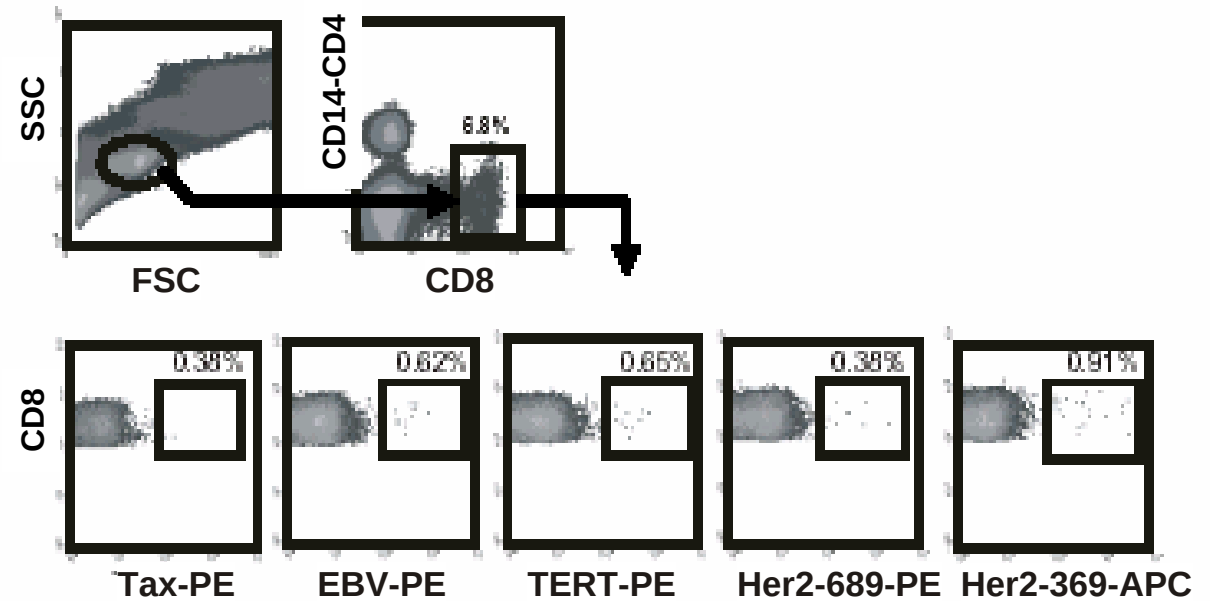


ELISPOT

Intratumoral T cells exhibit oligoclonal expansion



TILs Recognize TAAs in Ovarian Cancer

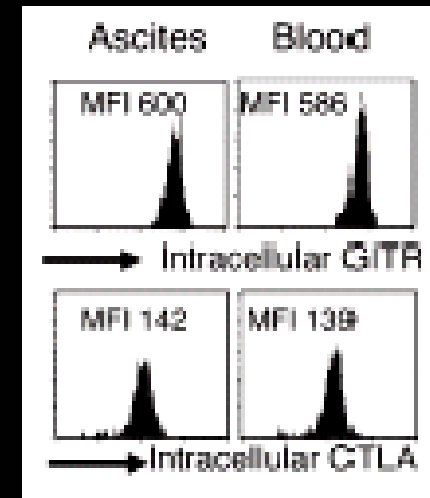
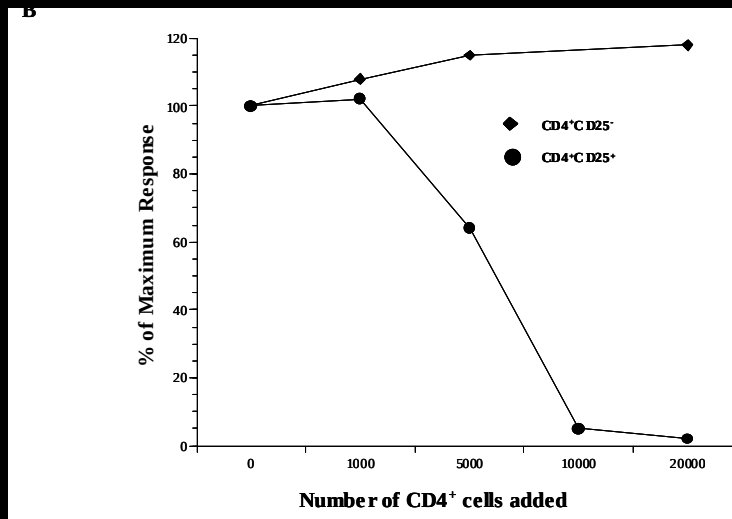
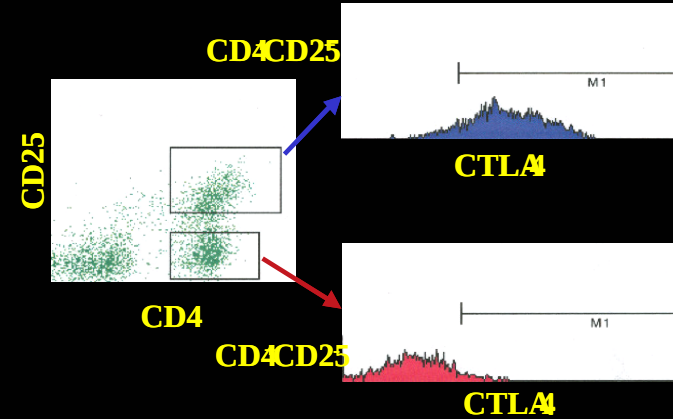
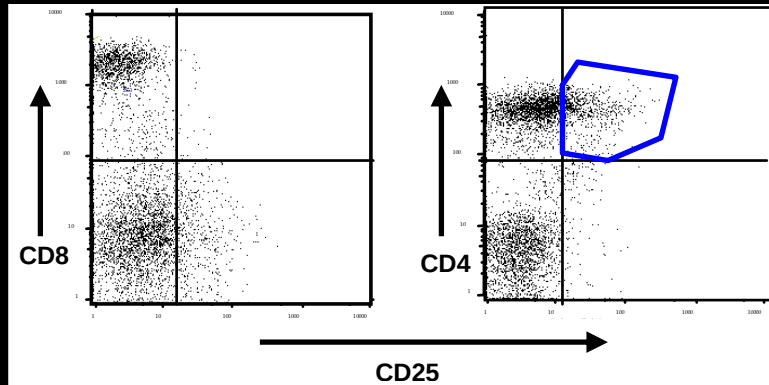


Bob Vonderheide

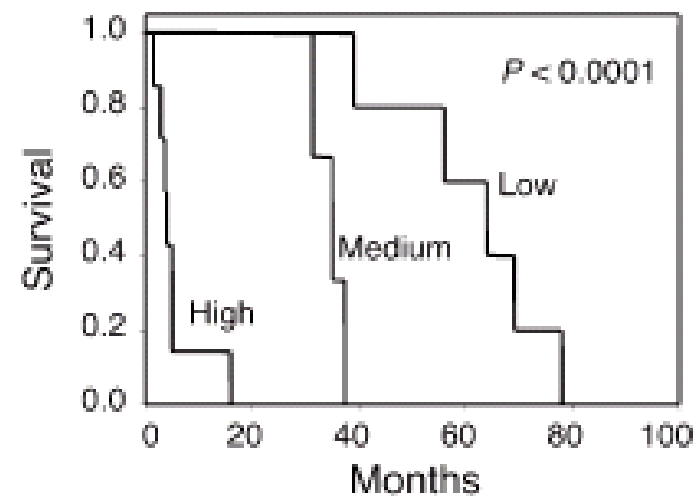
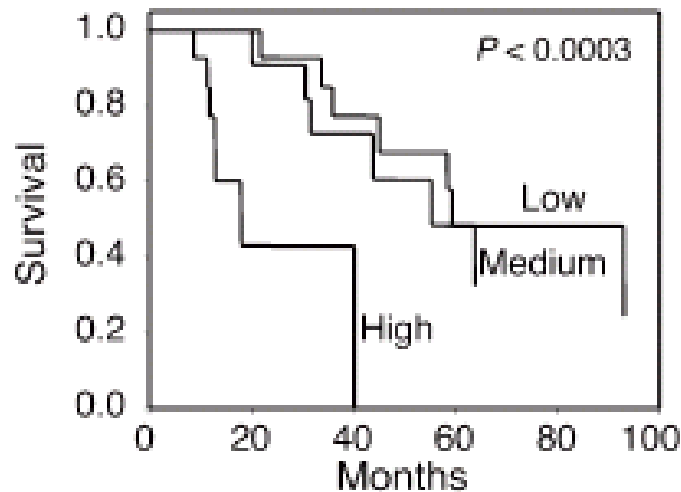
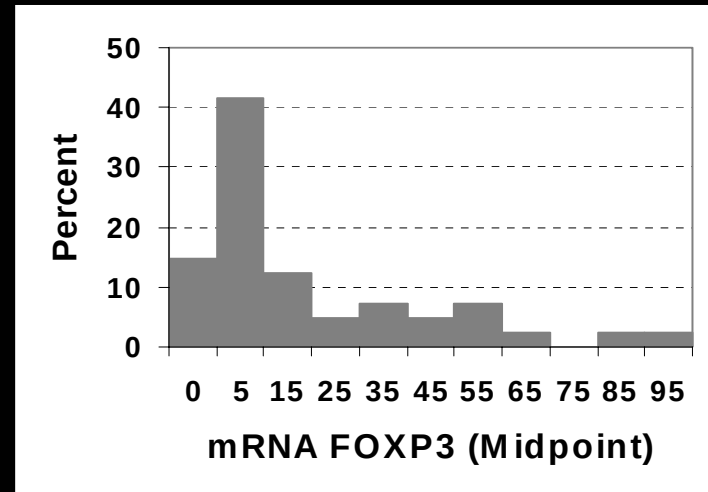
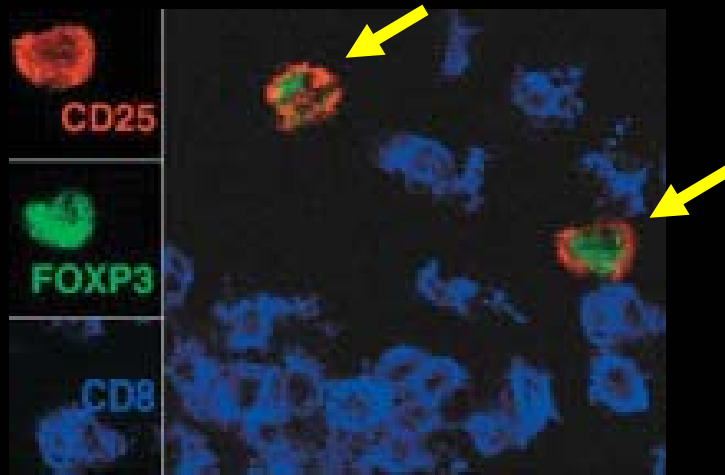
Proposed Biomarkers for Tumor Immune Surveillance

- Intratumoral CD8⁺ T cells
- IFN- γ , MIG, IP-10
- pLCK, pZap-70
- NKG2D ligands

$CD4^+CD25^+$ Treg



Regulatory CD4⁺CD25⁺ T Cells in Ovarian Cancer

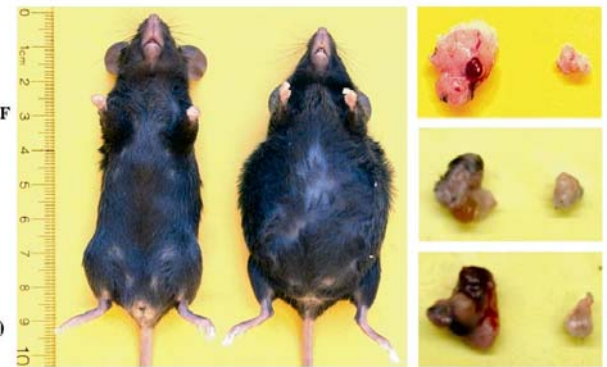
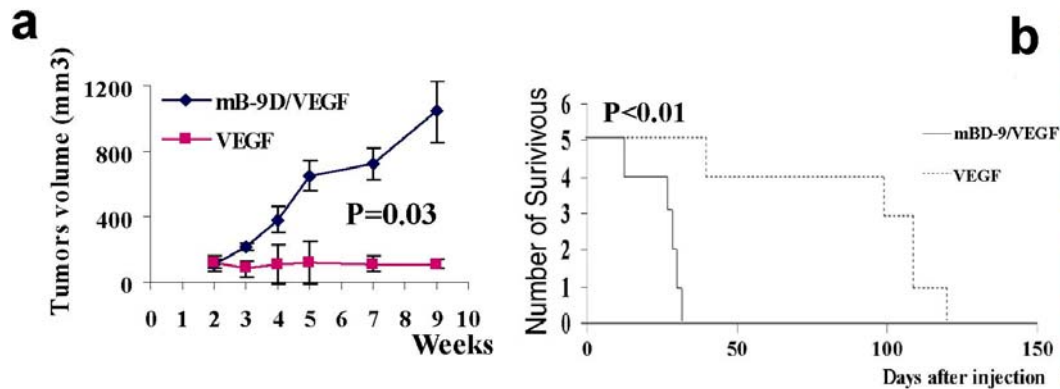
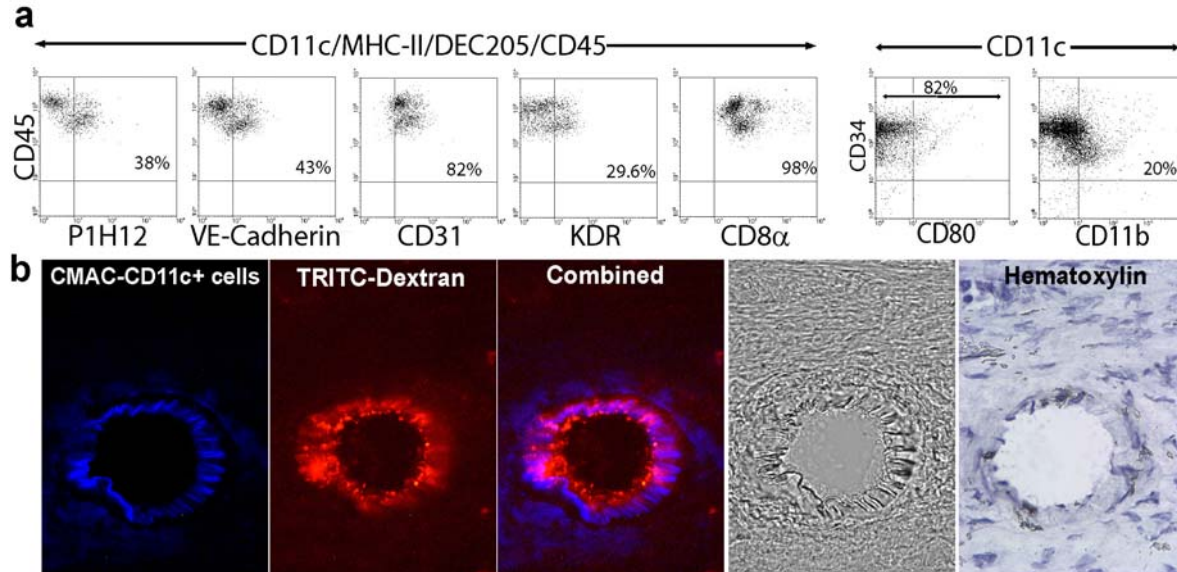


Proposed Biomarkers for Tolerance

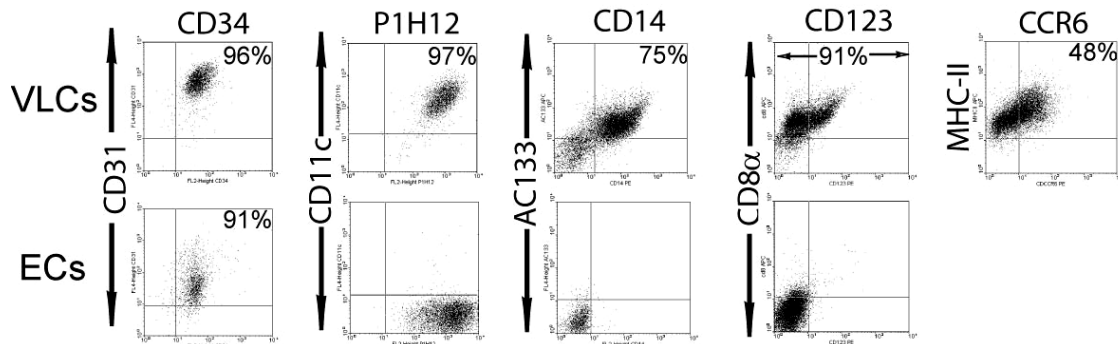
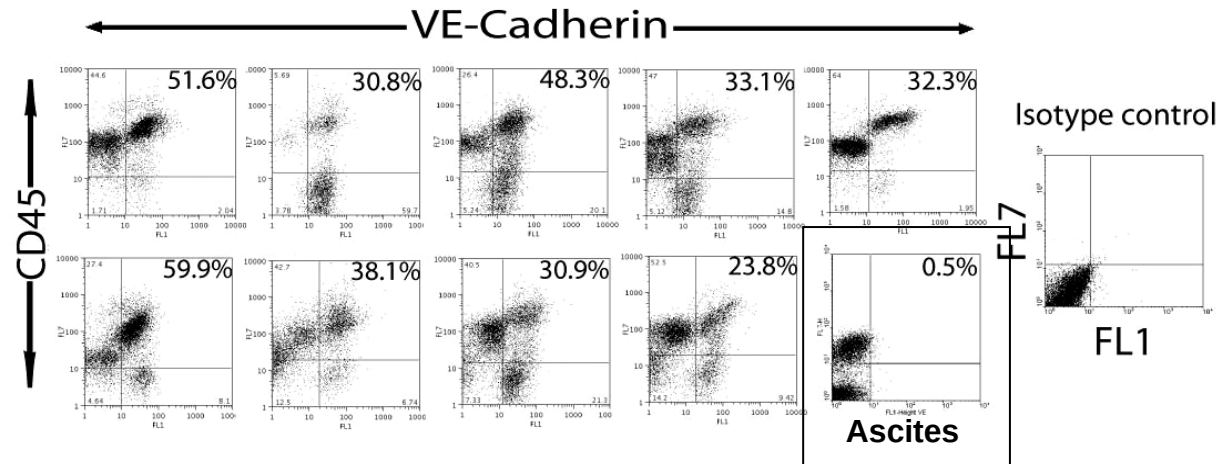
- CD4⁺CD25⁺ T cells
- foxP3
- GITR, CTLA-4
- Neuropilin-1
- IL-10, TGF- β
- PD-1

Vascular Leukocytes

CD11c⁺ cells with
DC / endothelial phenotype and
vasculogenic competence



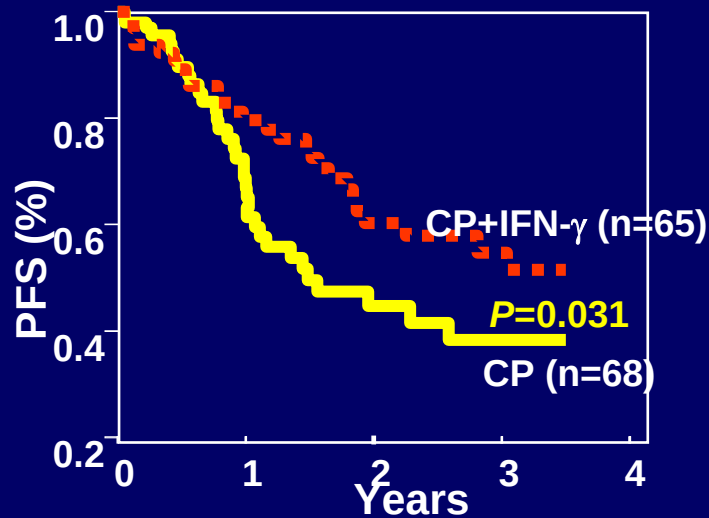
Endothelial cells and vascular leukocytes coexist in human ovarian cancer



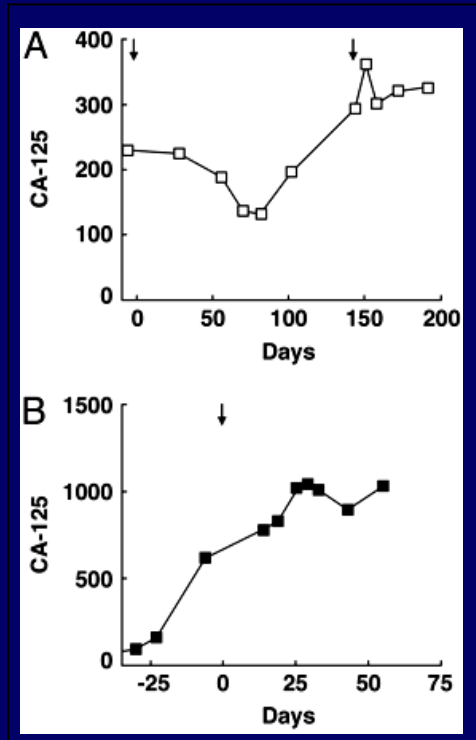
Proposed Biomarkers for Angiogenesis

- CD45⁺CD11c⁺VE-cadherin⁺ cells
- VEGF-A

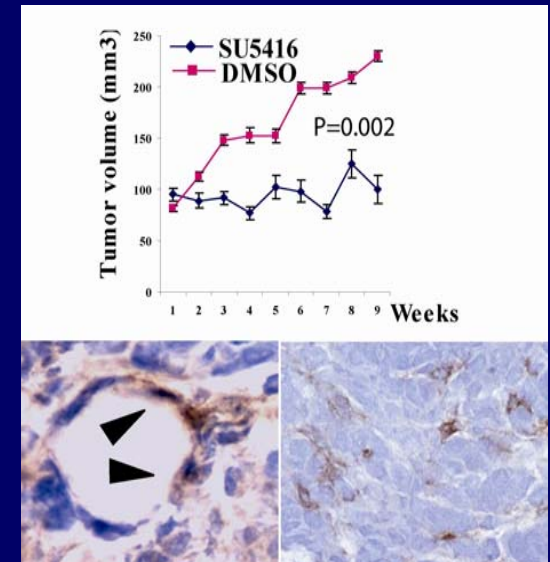
Activity of Biological Therapy in Ovarian Cancer



Windbichler GH, et al. *Br J Cancer*. 2000



Hodi et al., *PNAS* 2003



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

Acknowledgements

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