Presenter Disclosure Information

Mary L. Disis

The following relationships exist which may related to this presentation:

VentiRx, Consultant
Hemispherex, Grant Funding
Glaxo Smith Kline, Grant Funding
University of Washington, Patent Holder
Epigenomics, Stockholder

Immunologic Biomarkers as Correlates for Clinical Response

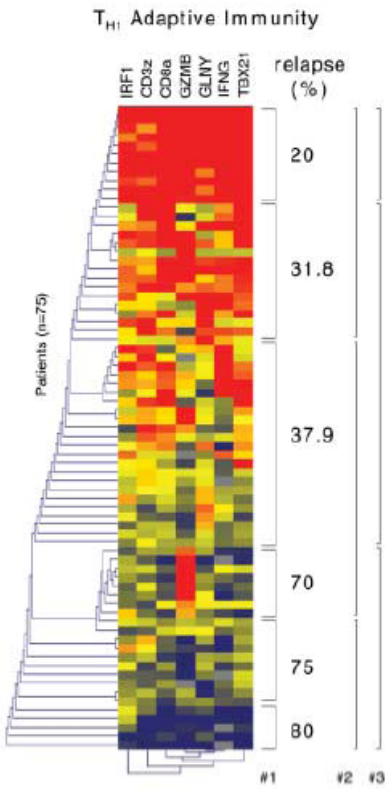
I. Population based studies of endogenous immunity

II. Clinical trials of cancer immunotherapy

III. Identifying unifying themes

Effective anti-tumor immunity: T cell response

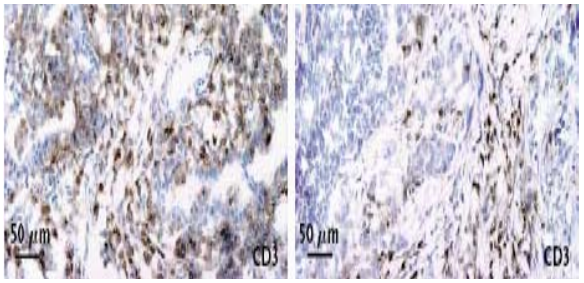
Type I T cells

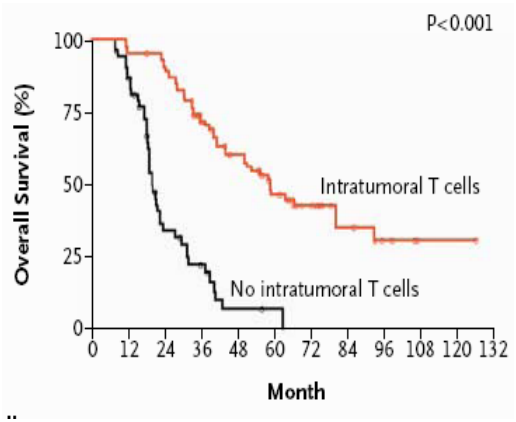


- Colorectal cancer
- Inverse correlation of gene expression and relapse

Galon et al, Science, 2006

High density of T-cells penetrating tumor

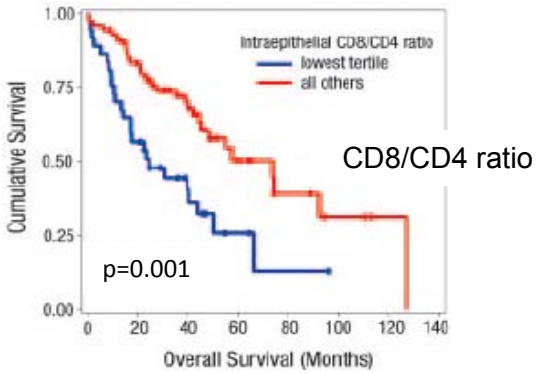


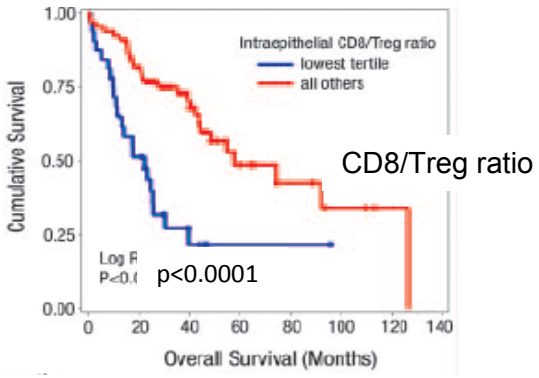


- Ovarian cancer
- MVA: Intratumoral T cells independent predictor survival

Zhang et al, NEJM, 2003

Infiltrating $CD8^+$ T cells



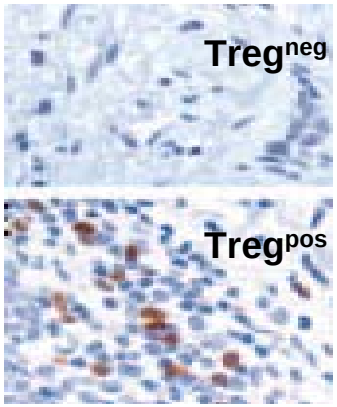


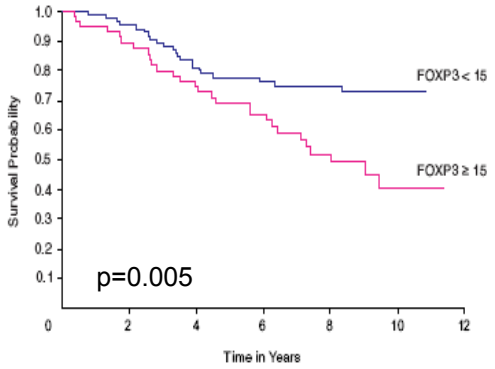
- Ovarian cancer
- MVA: $CD8^+$ and $CD8^+/CD4^+$ ratio (FOXP3): independent predictor survival

Sato et al, PNAS, 2005

Effective anti-tumor immunity: Tumor environment

Modulation of self-regulation

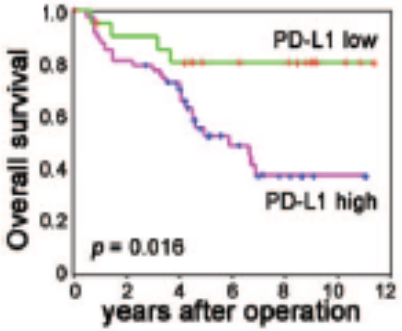


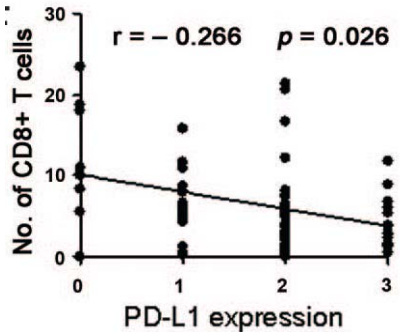


- Breast cancer
- MVA: Density of Treg^{+} in ER^{+} tumors predictor of survival

Bates et al, JCO, 2006

Modulation of tumor specific immune evasion

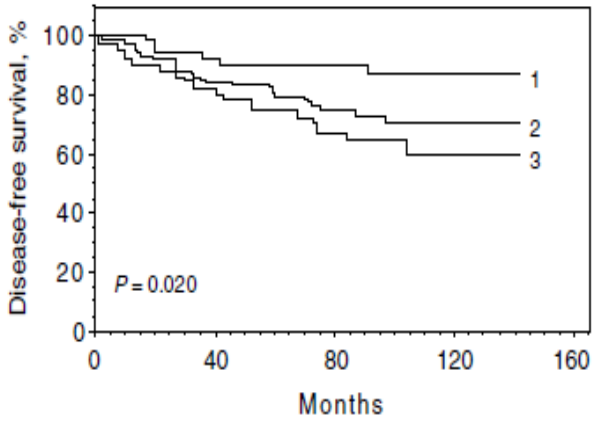




- Ovarian cancer
- MVA: High PD-L1= poor prognosis and DFS
- Inverse associationCD8&PDL-1

Hamanishi et al PNAS, 2007

Modulation of the tumor microenvironment



Patients at risk

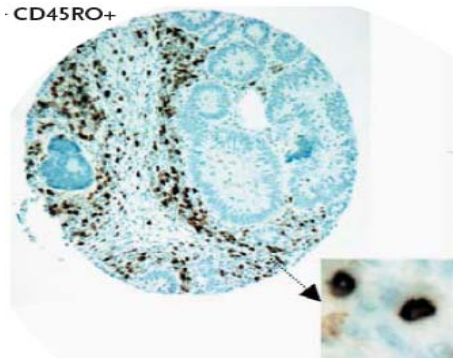
<42 pg TGFβ1 mg^{-1} protein
42–148 pg TGFβ1 mg^{-1} protein
≥148 pg TGFβ1 mg^{-1} protein

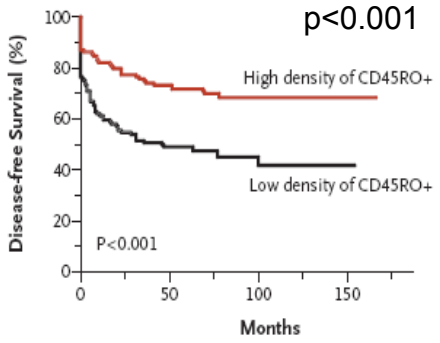
- Breast cancer
- TGFß-1 protein level in tumors
- MVA: TGFß-1 was an independent predictor of survival

Desruisseau et al, Br J Ca, 2006

Effective anti-tumor immunity: Functional persistence

Maintenance of memory

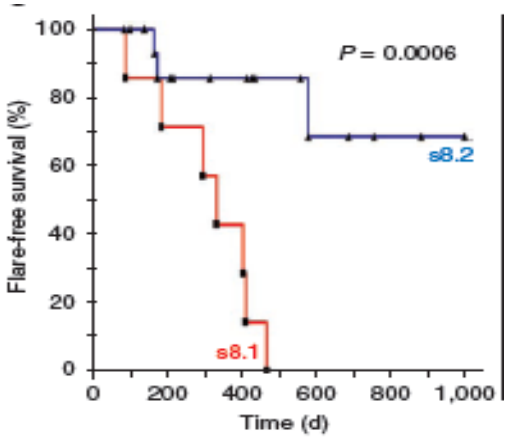


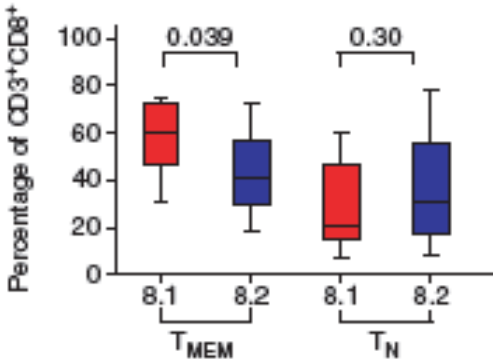


- Colorectal cancer
- MVA: Memory T cells CD45RO$^+$ independent predictor survival

Pages et al, NEJM, 2005

Tissue destructive function





- Autoimmune disease
- Peripheral blood signature of CD8+ memory (common to 3 diseases)
- Predicts disease flairs, poor survival

McKinney et al, Nat Med, 2010

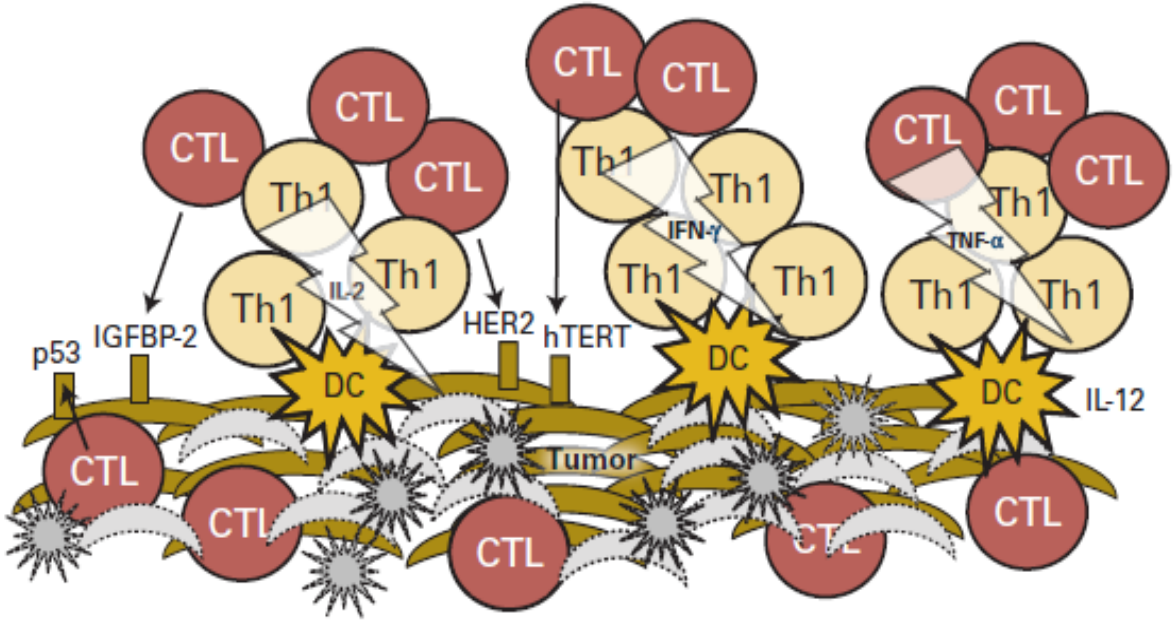
Immunologic biomarkers of clinical response after vaccine and T cell therapy

- Ag specific Th1 (HPV) correlates to VIN resolution, p=0.02, after HPV peptide vaccine, *Kenter et al NEJM 2009*

  HPV specific T cells/FOXP3 ratio, *Welters et al PNAS, 2010*
- Ag specific T1 correlates with survival, p=0.05, after peptide vaccine for melanoma, *Kirkwood et al, Clin Ca Res, 2009*
- Ag specific T1 (PSA) trended to survival benefit, p=0.06, after poxviral vaccine for prostate Ca, *Gulley et al CII, 2010*
- Ag specific Th1 (HER2) trended to survival benefit, p=0.08, in breast Ca, *Disis et al JCO, 2009*
- DTH response correlates to survival, p=0.001 (↓ FOXP3) after allogeneic lysate DC vaccine for melanoma, *Lopez et al, JCO, 2009*
- T cell persistence after adoptive T cell therapy, *Zhou, J Immunother, 2005*

Small studies, no independent predictors

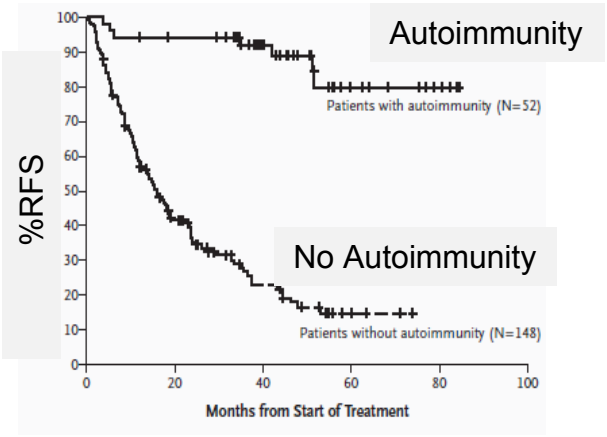
Unifying theme: Type I immunity facilitates cross-priming

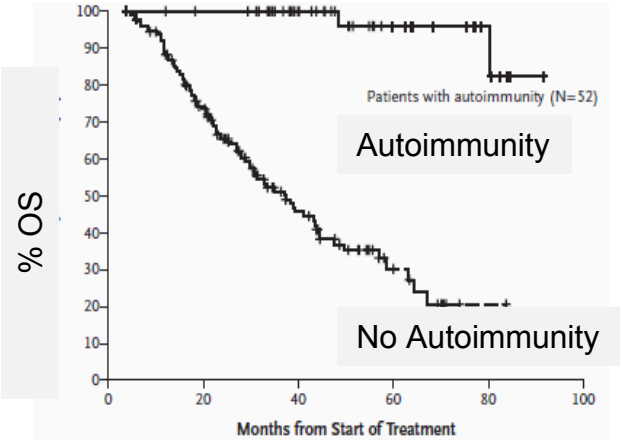


- Determinant or epitope spreading correlates with clinical response/survival,

Butterfield et al, Clin Ca Res, 2003, Salazar et al ASCO, 2009

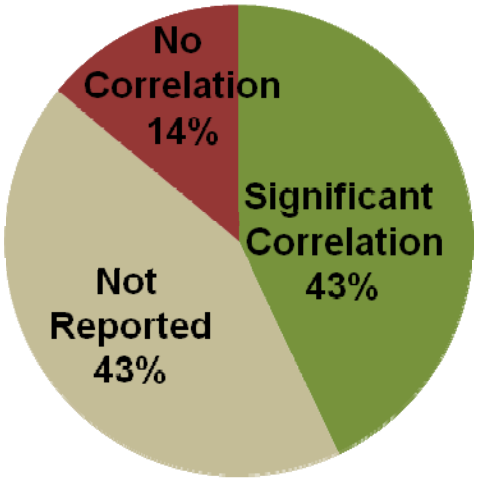
Autoimmunity is the ultimate endpoint of effective cross-priming





- Melanoma treated with IFN-α2b
- Autoimmunity: serologic+clinical
- MVA: independent predictor of RFS and OS, p<0.001

Gogas et al, NEJM, 2006



- Phase I and II of ipilumumab (n=7, >750 pts)
- Clinical autoimmunity
- Enterocolitis predictive in MM (p=0.007) or RC (p=0.016),

Beck et al, JCO, 2006

Weber, CII, 2009

Autoimmune parameters

	95% CI	P_2
TSH		
Normal	1.16-4.54	.01
Abnormal		
FT4		
Normal	1.24-4.60	.0049
Abnormal		
Vitiligo		
Present	2.29-8.14	$< 10^{-6}$
Absent		

	Vitiligo	
	No.	%
Responders	28/58	48.3
Nonresponders	56/316	17.7

- 374 patients with MM
- HD IL-2
- Abn. Thyroid fxn, p<0.01/vitilgo, p<0.0001 associated with response

Phan et al, JCO, 2001

Immunologic Biomarkers as Correlates for Clinical Response

- Candidate immunologic biomarkers have been identified that show correlation to clinical outcome
- Larger studies are needed to demonstrate stronger associations
- Current common candidates focus only on treatment induced immune response
- Impact of therapy on tumor microenvironment may best predict maintenance of the induced immune response
- Newer approaches which integrate measurement of effectors and environmental impact need to be fully assessed