Predictive Biomarkers for Tumor Immunotherapy: Are we ready for clinical implementation?

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Changing Paradigms in Cancer Treatment

Potential Uses of Biomarkers

- Adverse event monitoring
- Targets for drug discovery
  - Better systems for screening libraries
  - Providing “proof-of-principle” activity in pre-clinical setting
  - Help predict potential toxicity
- Clinical trial decision-making
  - Improved patient selection
  - Better selection of clinical endpoints
  - Reduce cost by optimizing dose selection

Requirements for Clinical Application of Biomarkers

- Must have a signaling characteristic
- Must be accurately measured
- Must be feasible to measure
- Must be validated

- Should be a commodity
- Should be cost-effective

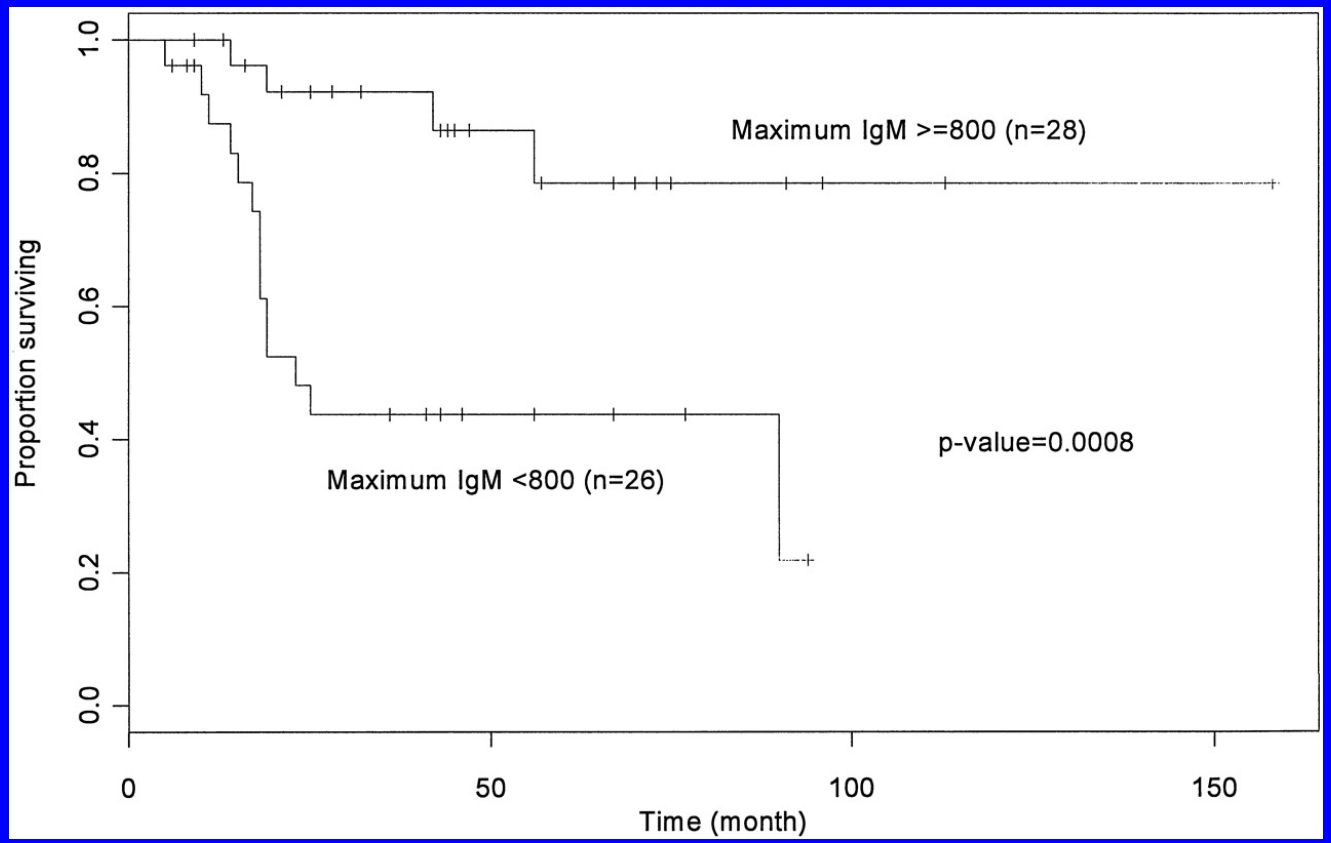
Biomarkers in Tumor Immunotherapy

- Soluble factors
  - Serum proteins
  - Circulating DNA and tumor cells
- Tumor factors
  - Receptor expression
  - Cellular infiltrates
- Patient factors
  - Humoral and cellular immune responses
  - Immune system polymorphisms
- Mathematical predictions

Tumor Immunotherapy Biomarkers

- To date, no biomarker has accurately predicted clinical response to tumor immunotherapy
- But, there are trends that have been noted…..

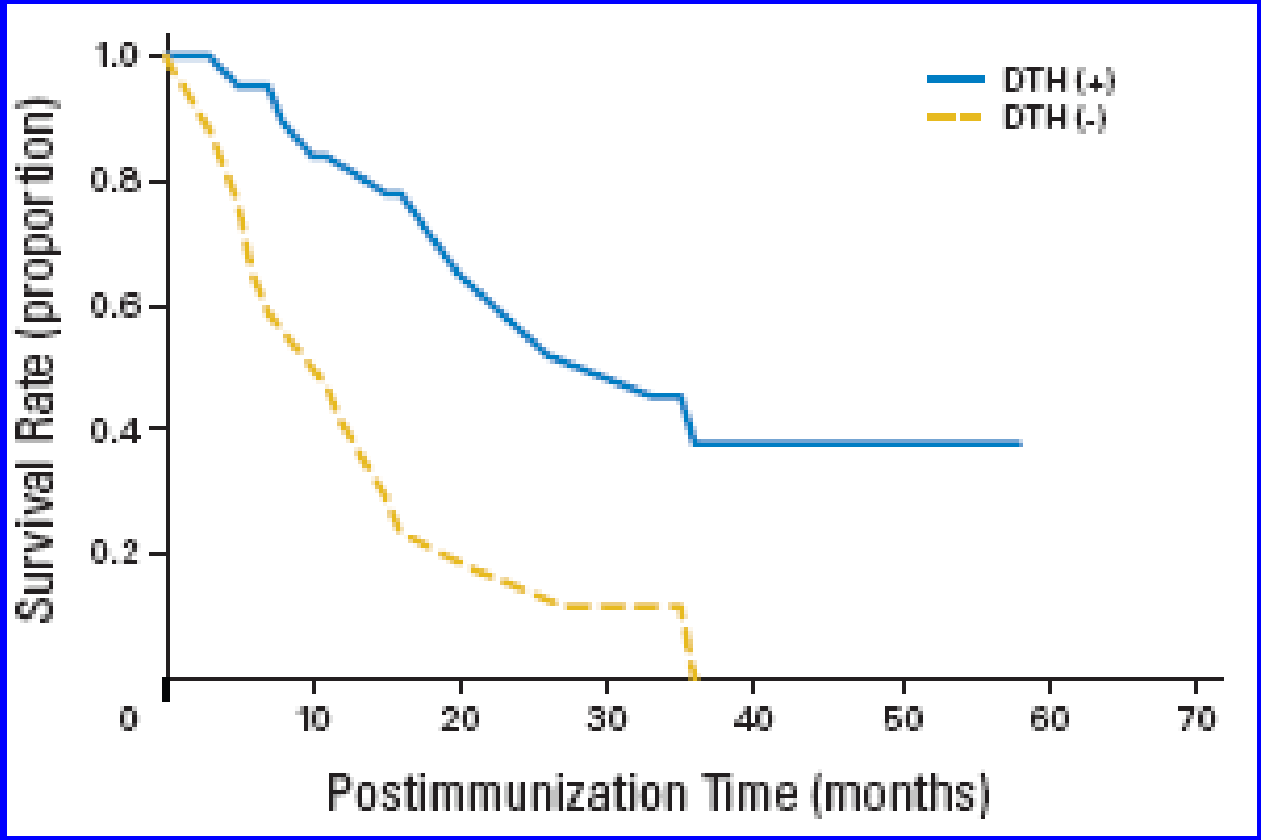
Correlation of clinical response and antibody titers



Vaccine; CancerVax

Chung et al. JCO 2003

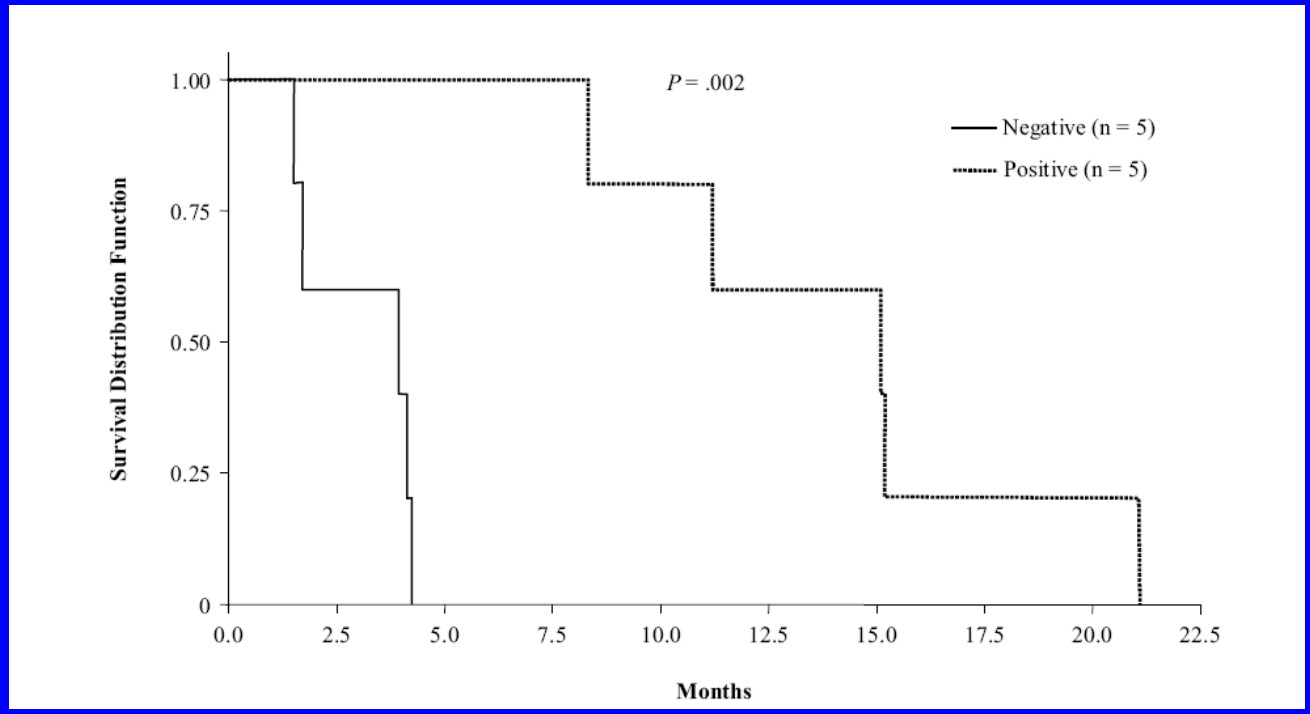
Correlation of clinical response and CD4+ T cell response



Vaccine:
Allogeneic tumor cell-pulsed DC

Lopez et al. JCO 2009

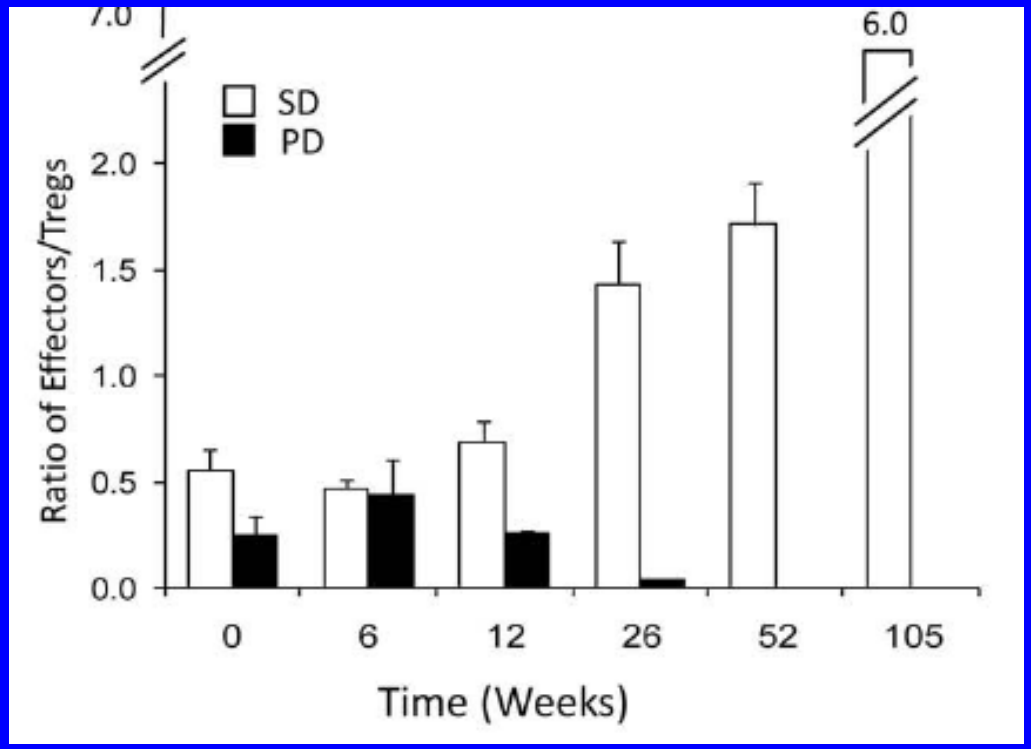
Correlation of clinical response and CD8+ T cell response



Vaccine:
V/F-CEA-MUC1-TRICOM

Kaufman et al. J Transl Med 2007

Correlation of clinical response and Tregs



Vaccine:
MVA-5T4

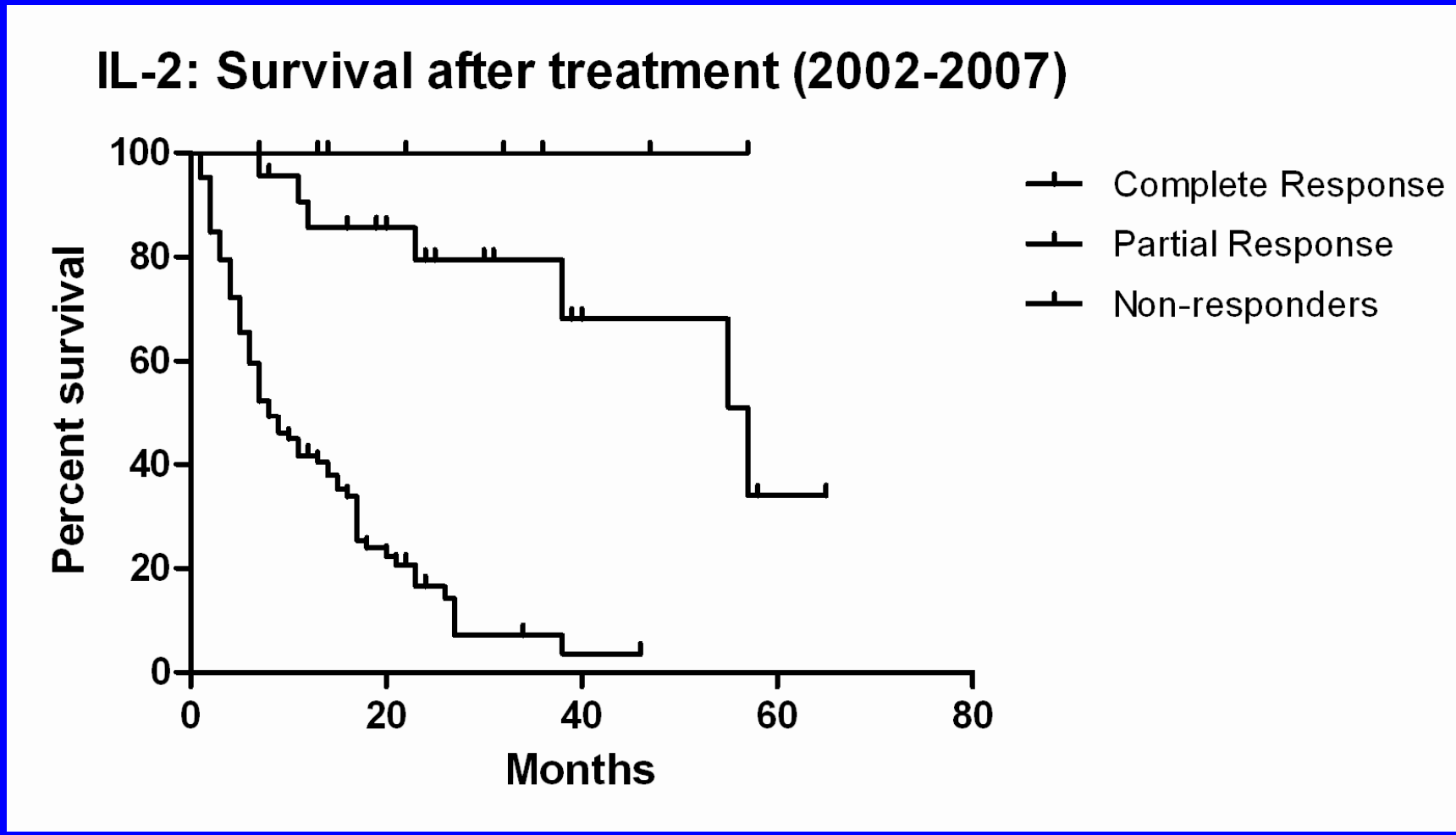
Kaufman et al. J Transl Med 2009

Issues with current biomarkers

- Small sample sizes
- Limited extension to larger phase clinical studies
- Lack of acceptance by industry
- Expensive
- Largely retrospective (and unplanned) analyses

Can biomarkers be selected for prospective evaluation?

Overall Survival of IL-2 Patients



Interleukin-2 Immunotherapy

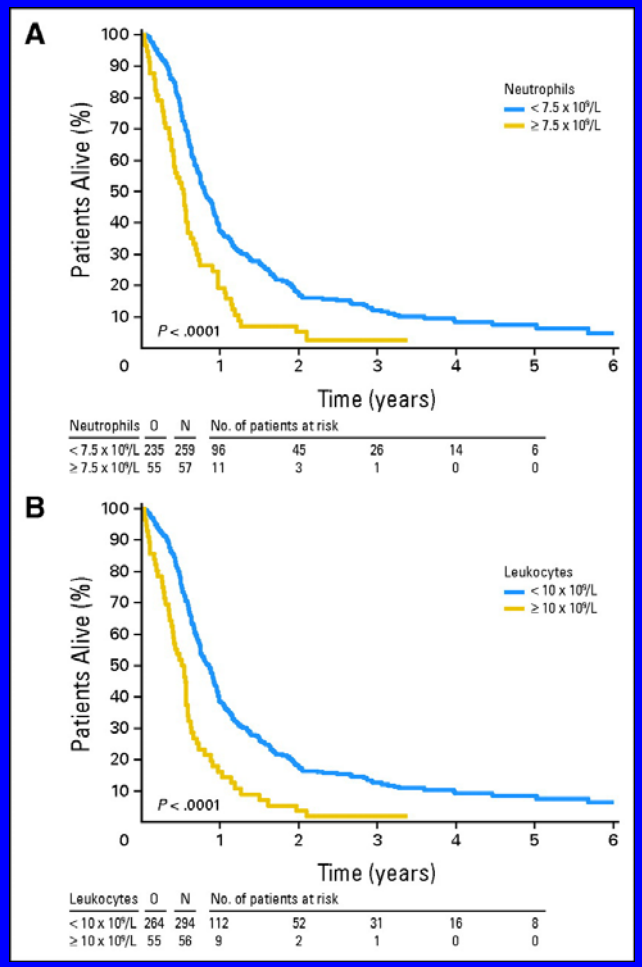
- How does IL-2 mediate anti-tumor effects?
- Why does IL-2 induce anti-tumor responses in only 17%?
- Can we improve the number of patients who will respond to treatment?
- Is there a biomarker that can predict response to IL-2 treatment?

Predictors of Response to IL-2 Therapy

Predictor	Reference
Performance status	Fyfe et al. JCO 1995
Number of organs involved*	Besana et al. Eur J Cancer 1994
Bone metastasis*	Rosenberg et al. JCO 1989
Thrombocytopenia	Royal et al. J Immunother 2003
Thyroid dysfunction	Atkins et al. NEJM 1988
Rebound lymphocytosis	West et al. NEJM 1987
Erythropoietin production	Janik et al. JCO 2002
Increased TNF-α and IL-1	McDermott et al. Sem Oncol 2006
Prior nephrectomy**	Figlin et al. Cancer J Sci Am 1997

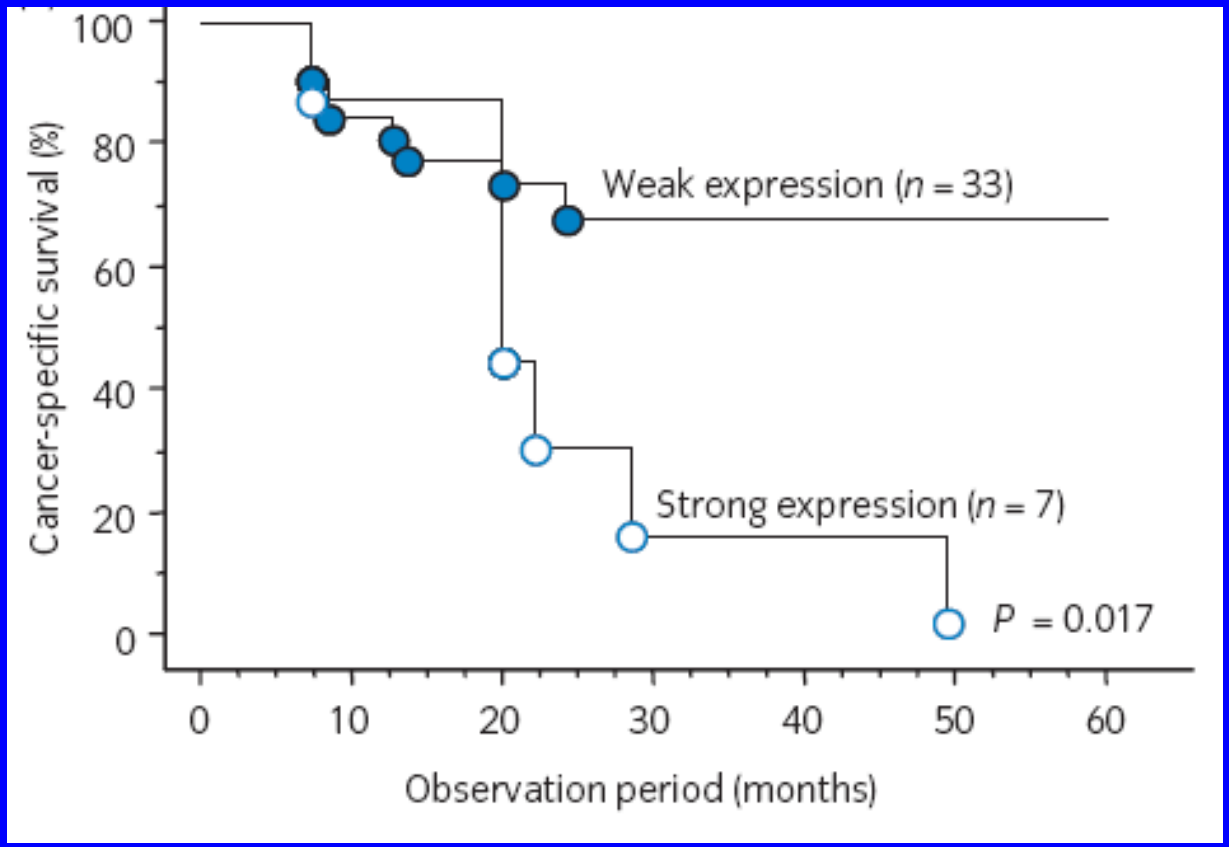
*Subsequently challenged
** Renal cell only

Pre-treatment leukocytes and neutrophils predict response to IL-2-based immunotherapy



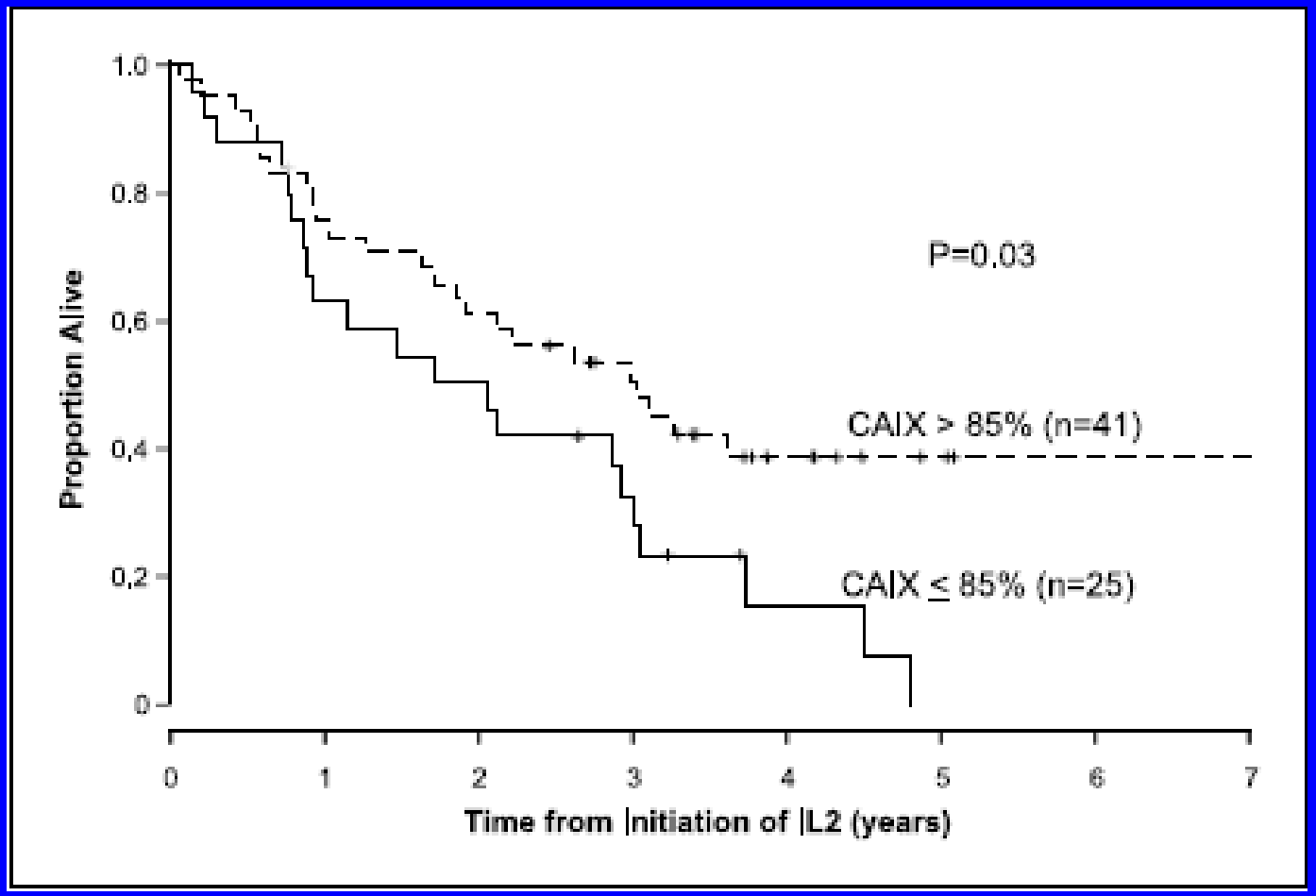
Schmidt H et al. JCO 2007;25:1562-1569

Expression of Ki-67 negatively correlates with survival following interferon-α and low-dose IL-2 in renal cell carcinoma



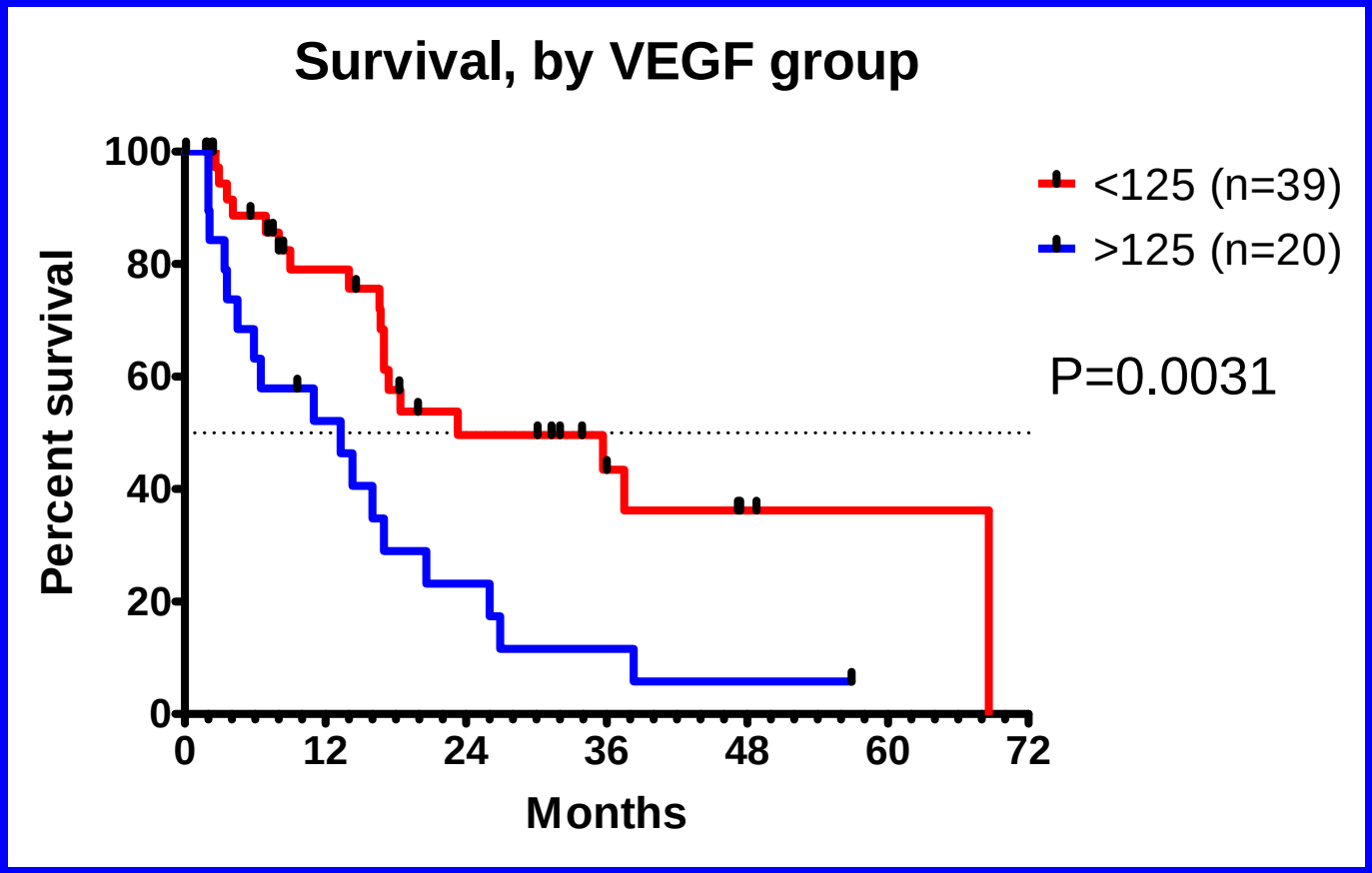
Miyake et al. Int J Urol 2009

High CA-IX levels predict response to IL-2 in renal cell carcinoma



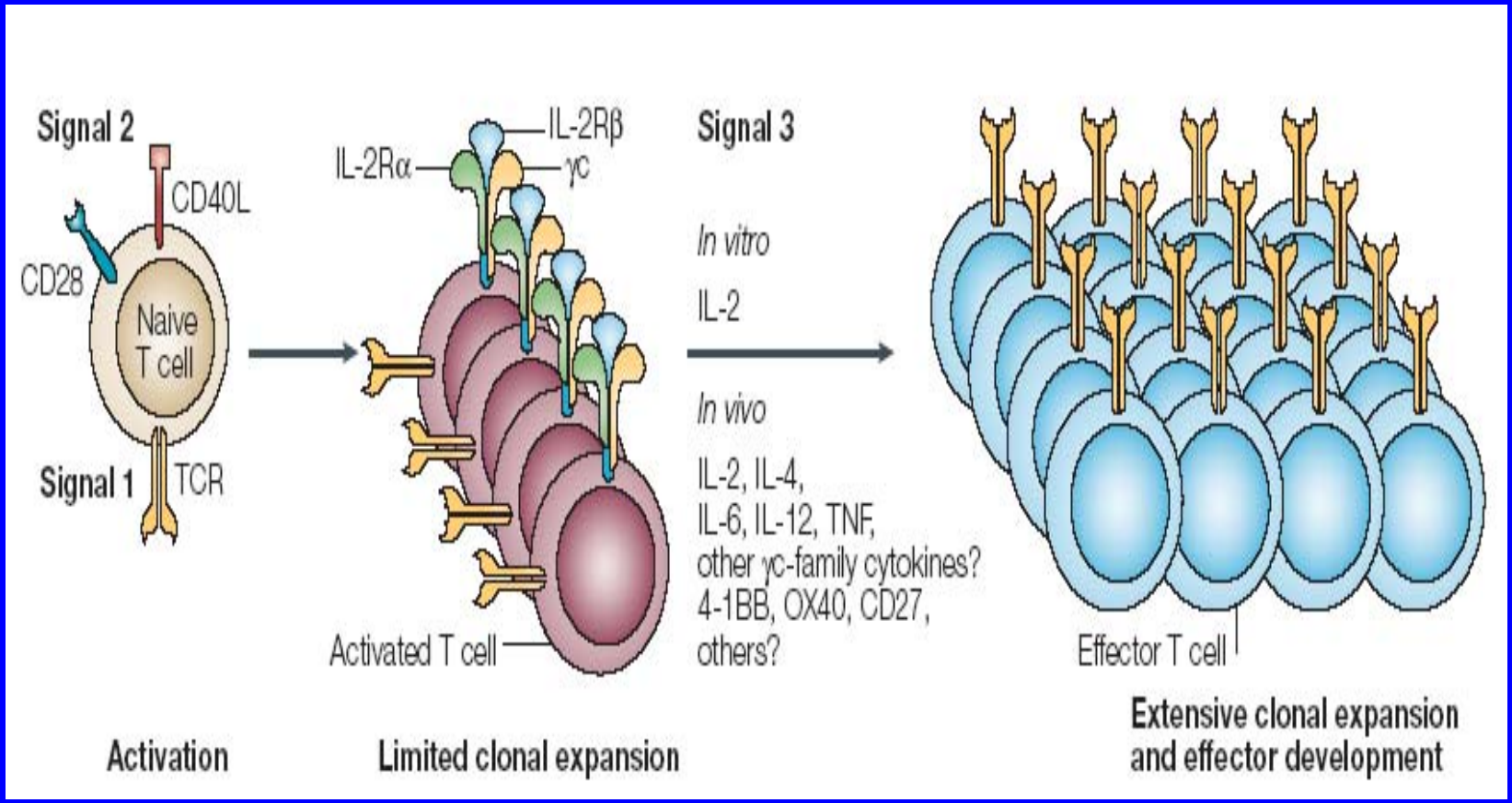
Atkins et al. Clin Cancer Res 2005

VEGF predicts survival following IL-2 treatment



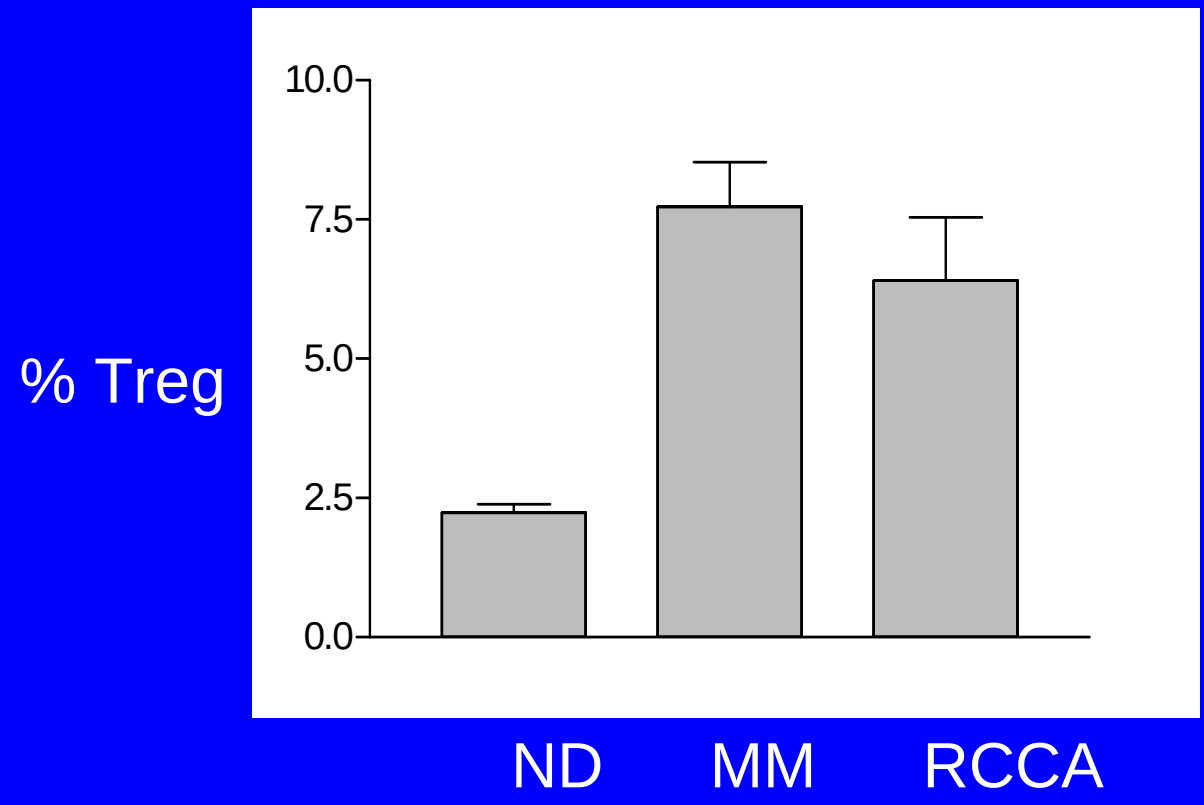
Sabatino et al. J Clin Oncol 2009

Clonal T cell expansion



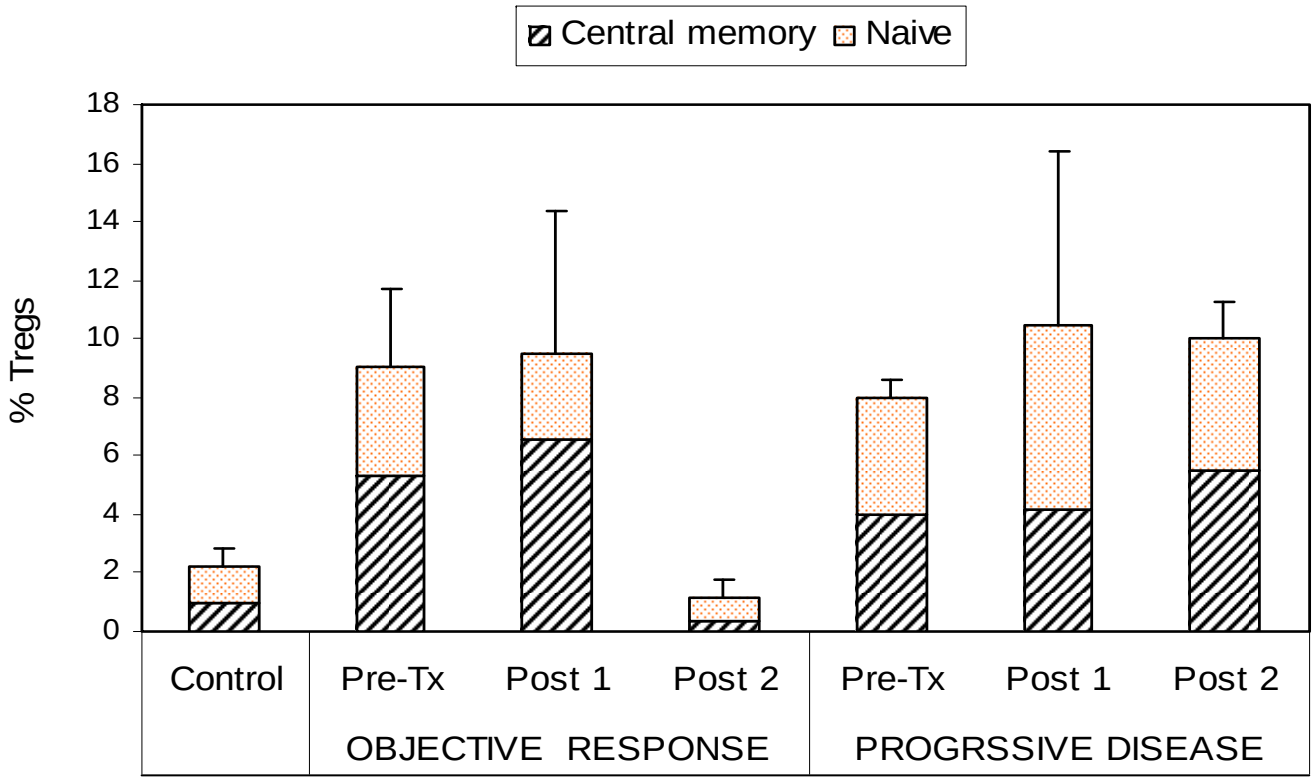
Malek and Bayer, Nature Rev Immunol 2004

The frequency of $CD4^{+}CD25^{hi}$ T cells are elevated in patients with MM and RCCA



Cesana et al. JCO 2005

Tregs decrease to normal levels after the cycle 2 in objective responders



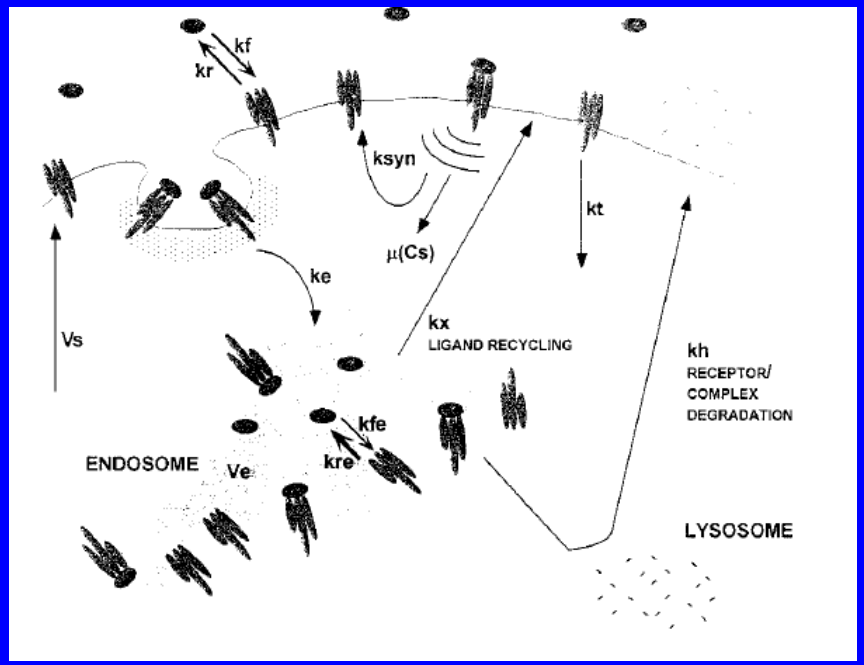
Cesana et al. JCO 2005

The change in Treg frequency is associated with clinical response

	Mean change in Treg frequency			
Time	***PD***	***PR***	***CR***	***P-value****
Pre-Tx – Post 1	2.05%	1.52%	0.19%	0.826
Pre-Tx – Post 2	5.09%	2.37%	-7.85%	0.004

Cesana et al. JCO 2005

Computational Modeling of IL-2



$$\frac{dR_s}{dt} = -k_f \cdot L[t] \cdot R_S[t] + (k_r + k_{syn}) \cdot C_s[t] - k_t \cdot R_S[t] + V_S \quad (1)$$

$$\frac{dC_s}{dt} = k_f \cdot L[t] \cdot R_S[t] - (k_r + k_e) \cdot C_s[t] \quad (2)$$

$$\frac{dR_i}{dt} = -k_{fe} \cdot L_i[t] \cdot R_i[t] + k_{re} \cdot C_i[t] + k_t \cdot R_S[t] - k_h \cdot R_i[t] \quad (3)$$

$$\frac{dC_i}{dt} = k_{fe} \cdot L_i[t] \cdot R_i[t] - (k_{re} + k_h) \cdot C_i[t] + k_e C_s[t] \quad (4)$$

$$\frac{dL_i}{dt} = \frac{(-k_{fe} \cdot L_i[t] \cdot R_i[t] + k_{re} \cdot C_i[t])}{(V_e \cdot N_A)} - k_x \cdot L_i[t] \quad (5)$$

$$\frac{dL_d}{dt} = k_h \cdot C_i[t] \quad (6)$$

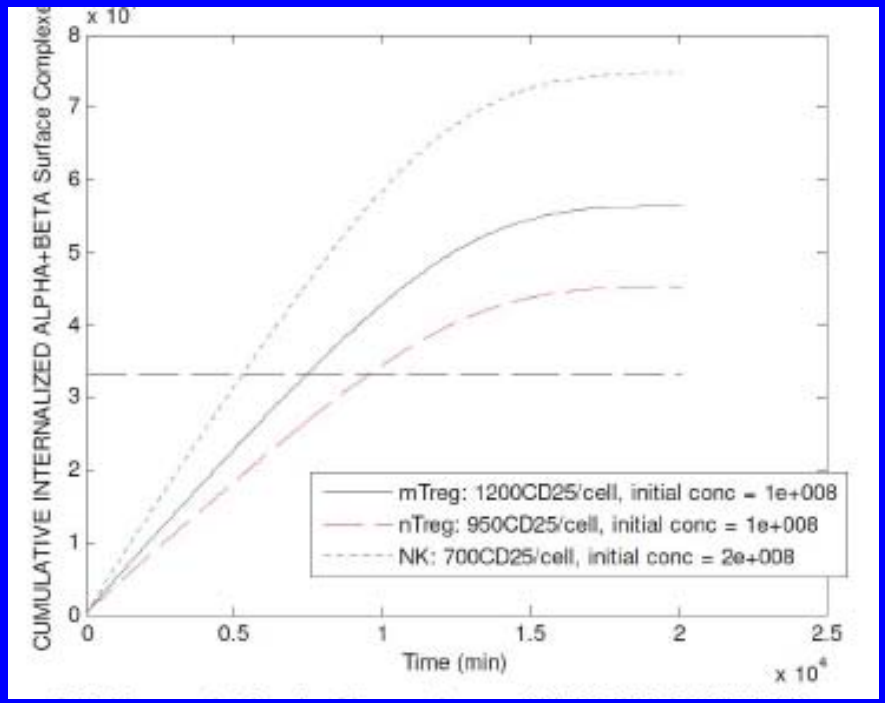
$$\frac{dL}{dt} = \frac{(-k_f \cdot L[t] \cdot R_S[t] + k_r \cdot C_s[t] + k_x \cdot L_i[t] \cdot V_e \cdot N_A) \cdot Y[t]}{(N_A)} \quad (7)$$

$$\frac{dY}{dt} = \mathrm{Max}\left\{\left[\frac{600 \cdot C_s(t)}{250 + C_s(t)}\right] - 200{,}0\right\} \times 10^3 \quad (8)$$

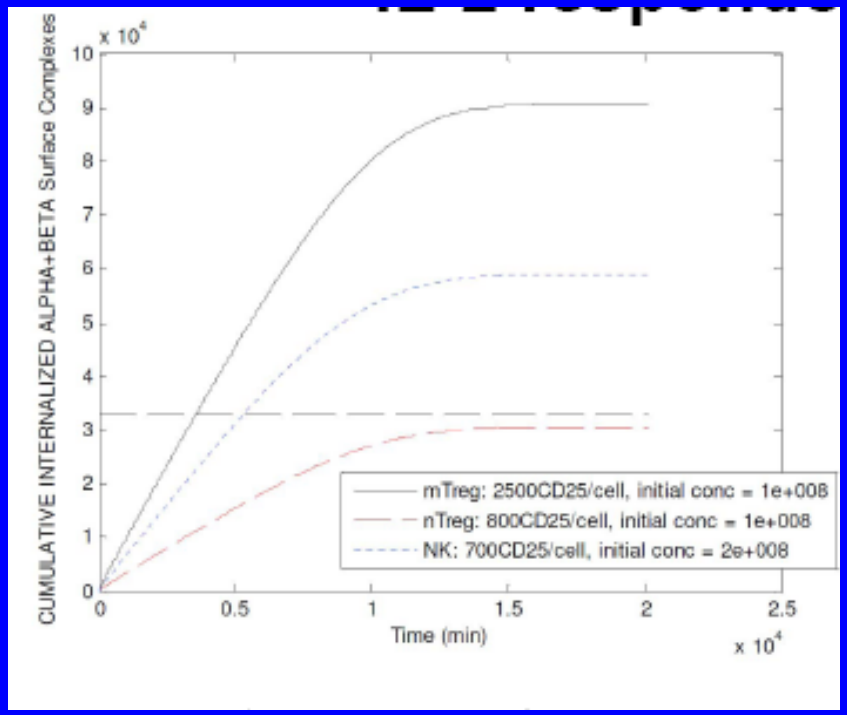
Fallon and Lauffenberger Biotechn Progr 2000

Hypothesis: IL-2 will preferentially affect nTregs at different doses

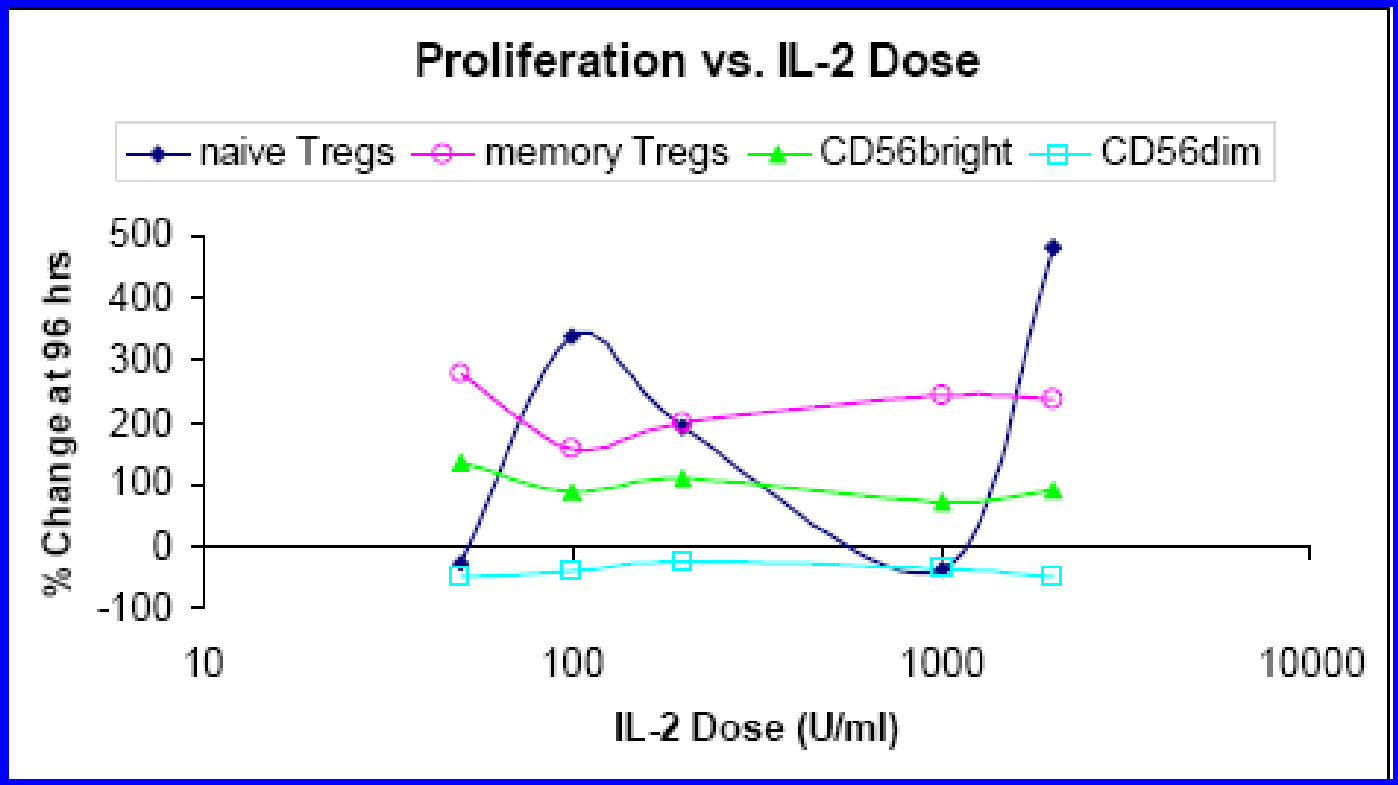
IL-2 100 U/ml



IL-2 1000 U/ml



Experimental: IL-2 preferentially affects naïve Tregs in a dose-dependent manner



Are we ready for clinical implementation?

- Yes - for inclusion of putative biomarkers in clinical trial design
- Yes- for further validation in larger sample sizes
- Should be a high priority for academia, industry and government

Acknowledgements

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