Does Antibody Therapy Induce Immune Responses ?

ISBTC Minisymposium 2006

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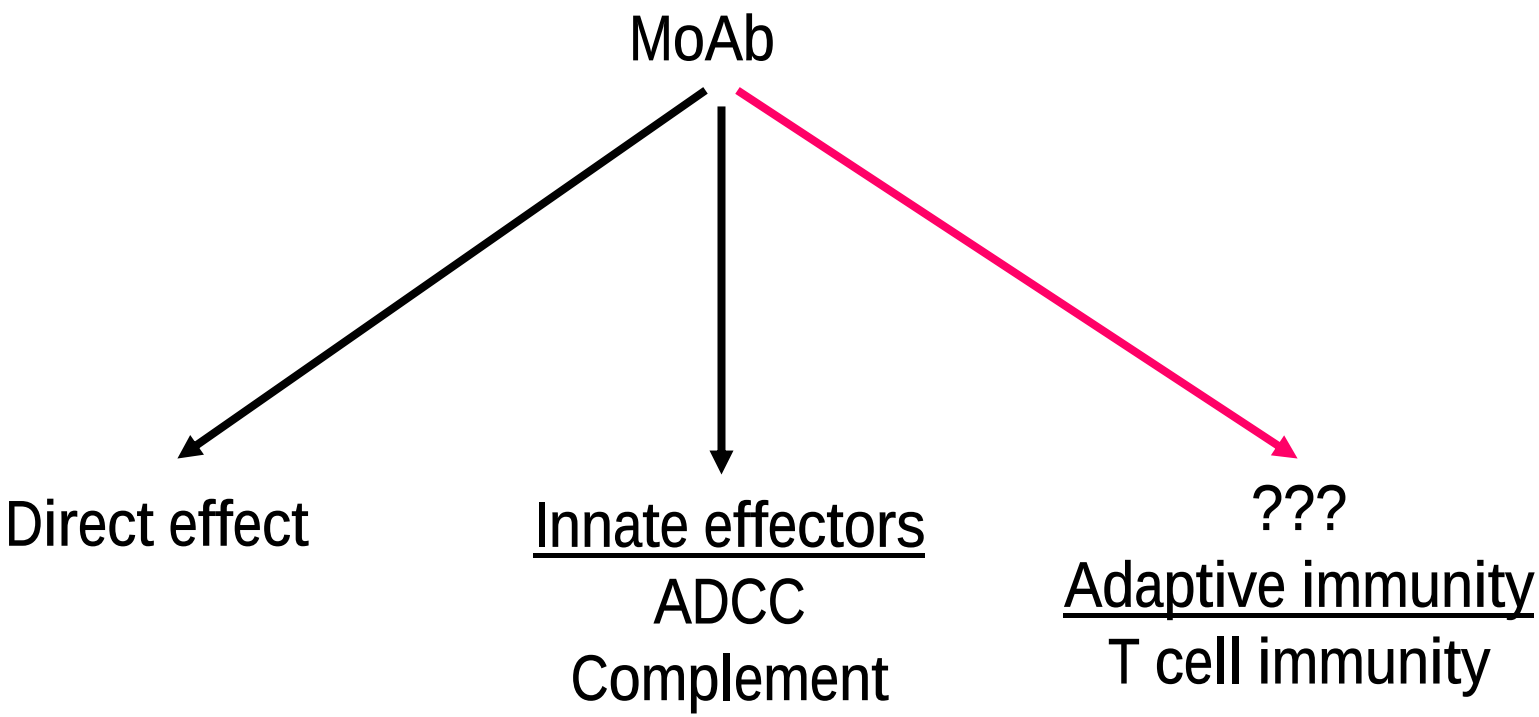
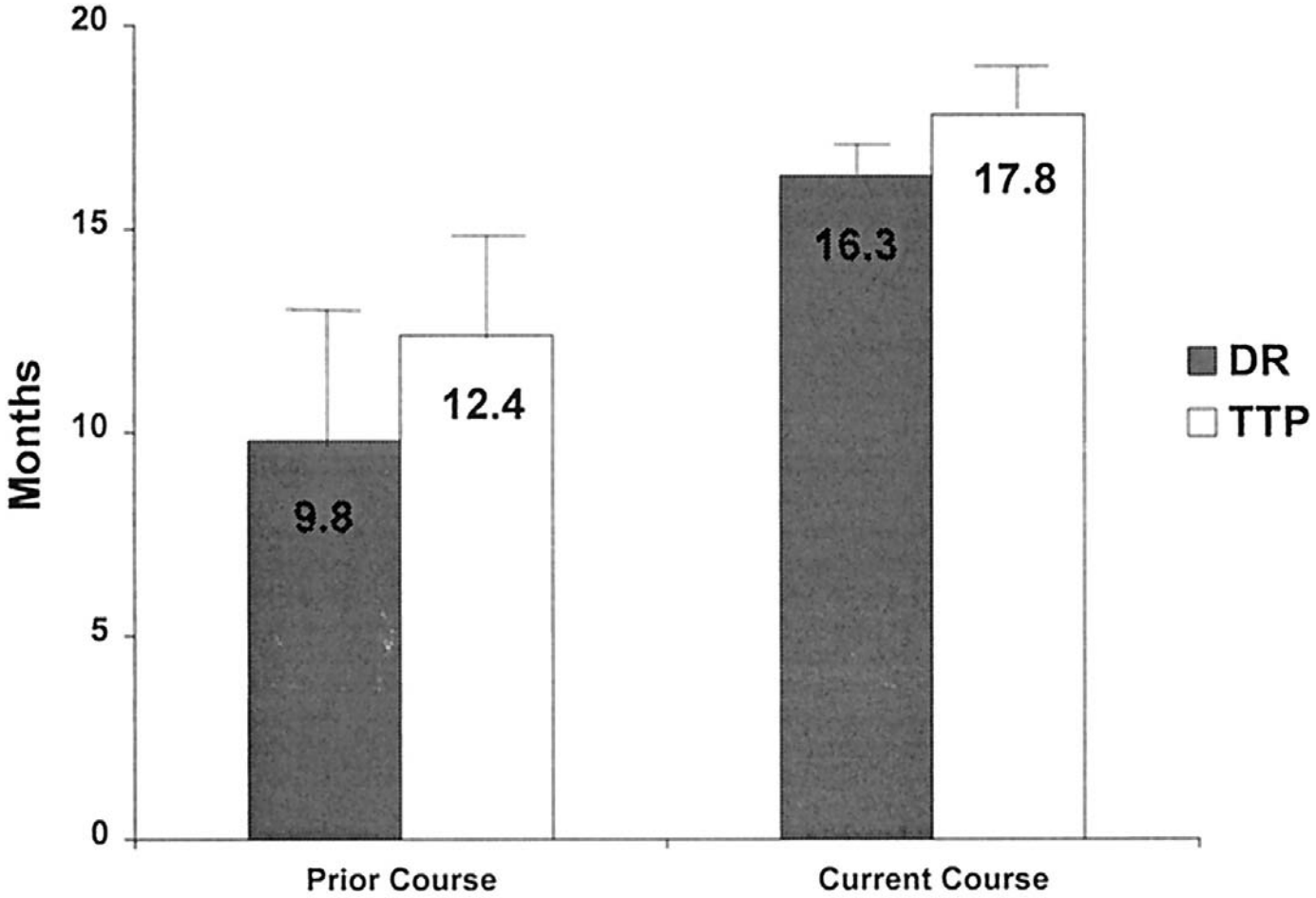
Mechanisms of Anti-tumor Effects of MoAbs



Why Harness MoAbs to Elicit Adaptive Immunity

- May provide a mechanism for durable responses.
- Immunologic memory: booster effect with repeat administration.
- Targeting antigen negative tumor cells (epitope spread)

Retreatment with Rituximab in Non-Hodgkin's Lymphoma



Davis, T. A. et al. J Clin Oncol; 18:3135-3143 2000

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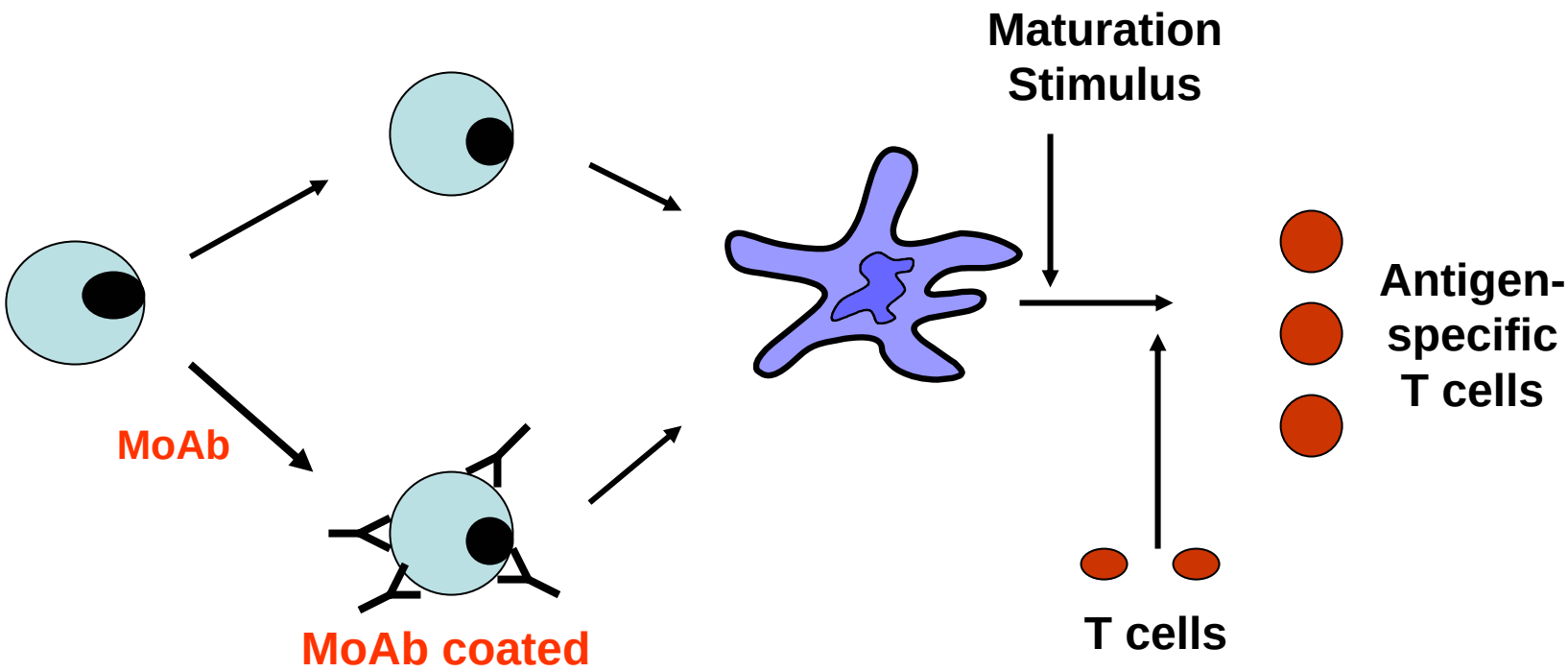
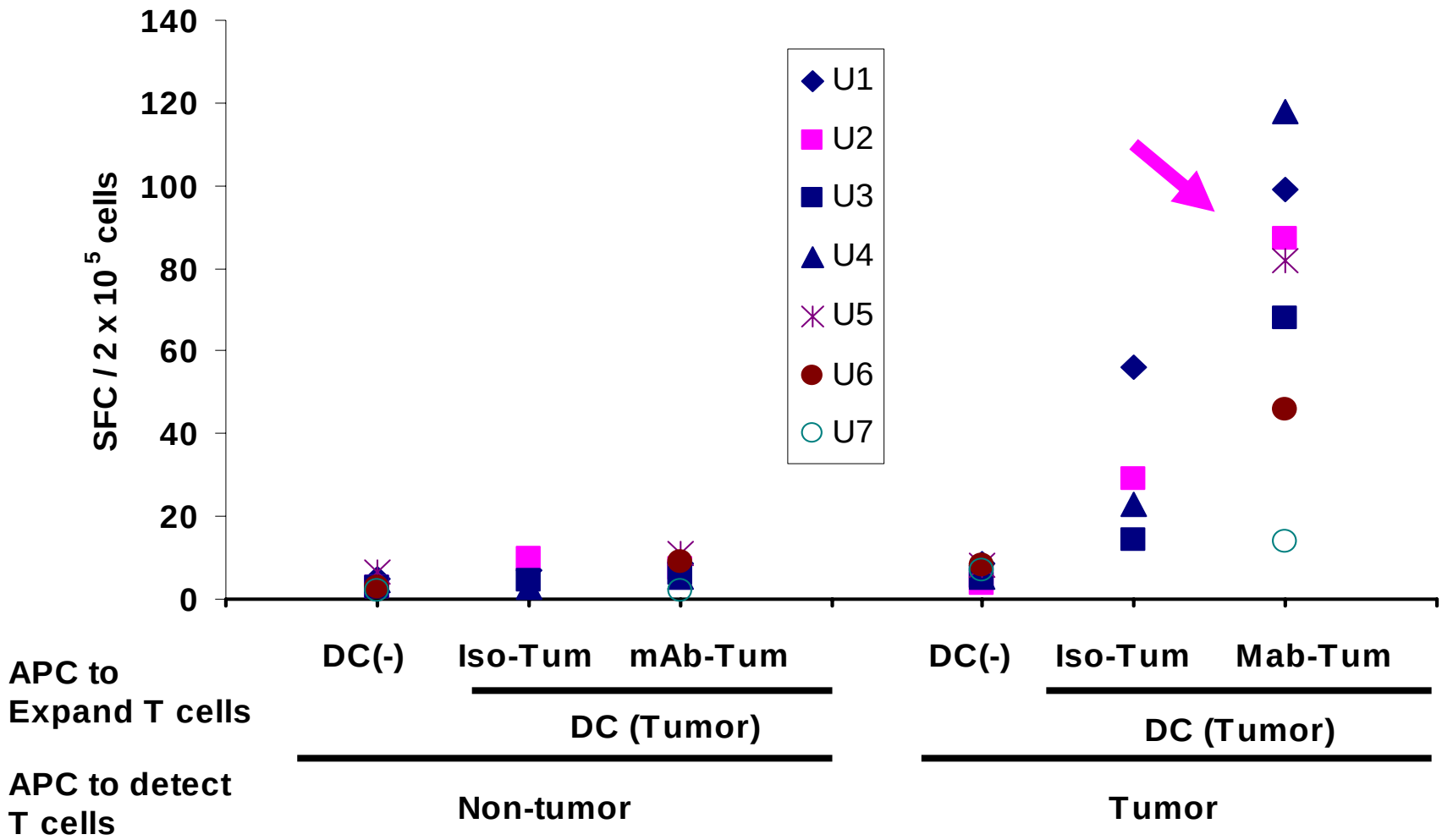
Opsonizing tumor cells with moAbs enhances dendritic cell mediated cross-presentation of cellular antigens



FcγR dependent
Not simply increased uptake

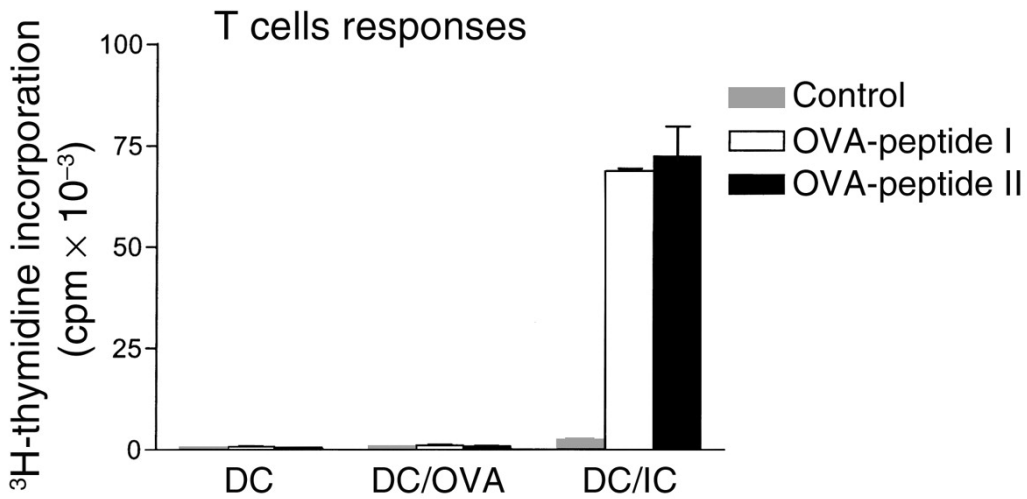
Dhodapkar et al. J Exp Med 195:125, 2002

Expansion of tumor reactive T cells in patients with progressive myeloma after stimulation with tumor cell loaded DCs



Dhodapkar et al. PNAS 99: 13009, 2002

Enhanced T cell Immunity after Immune Complex Mediated Antigen Presentation



Rafiq, K. et al. J. Clin. Invest. 2002;110:71-79

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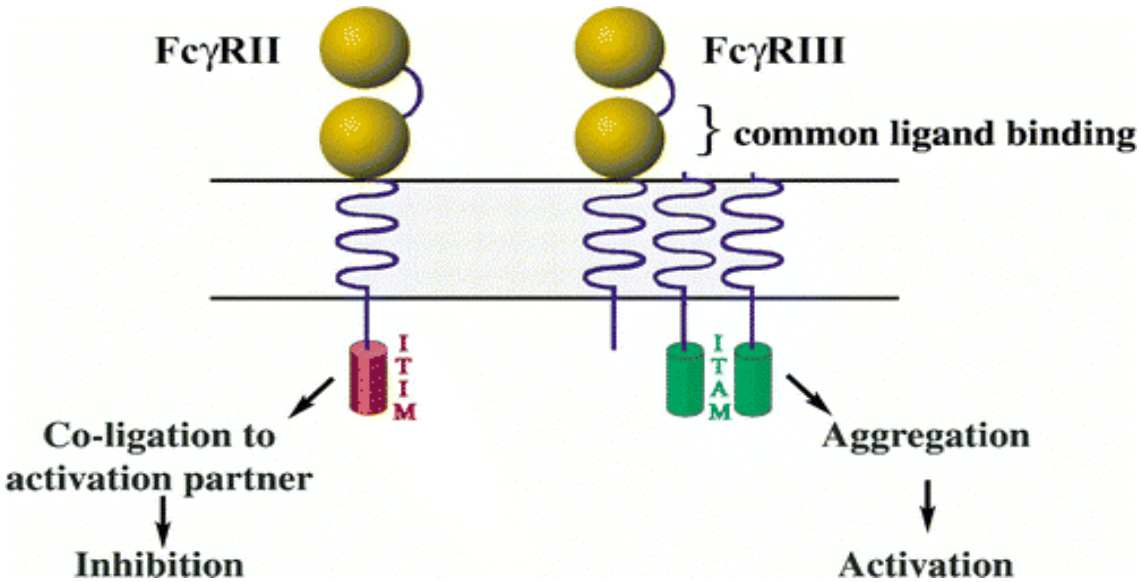
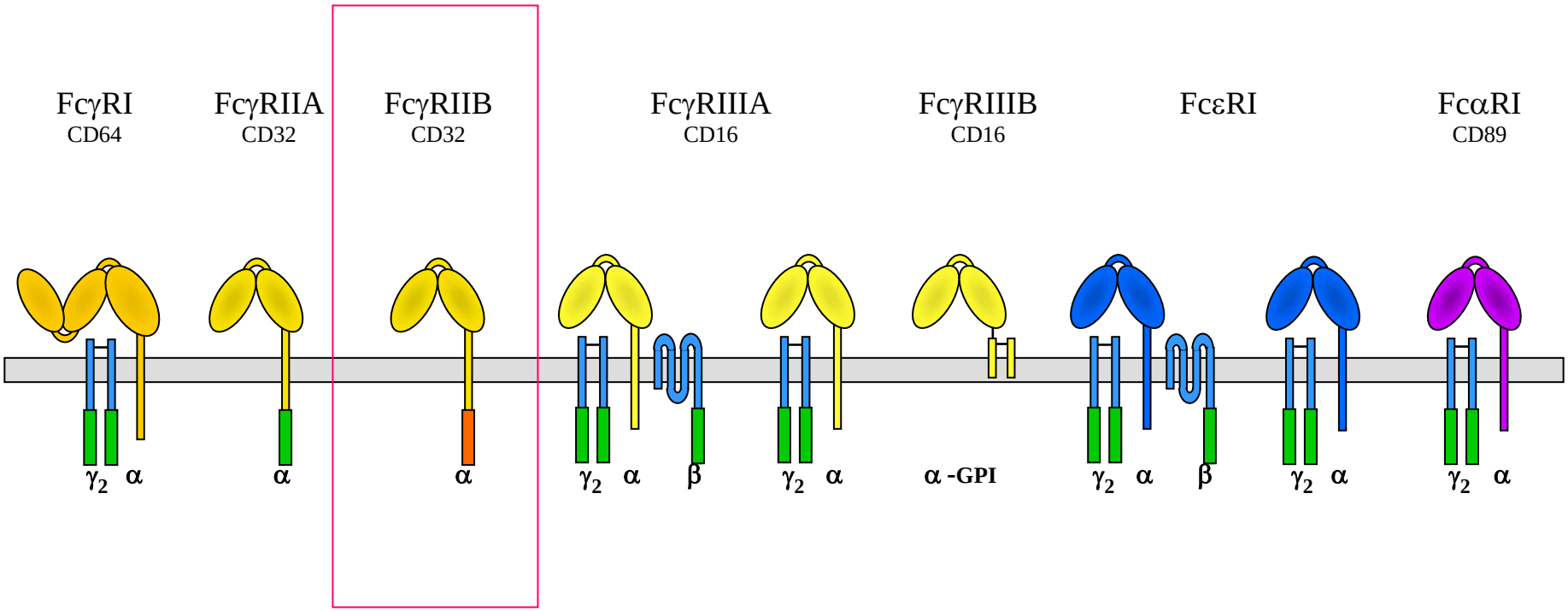
Fc receptor system as a balance of activating and inhibitory receptors

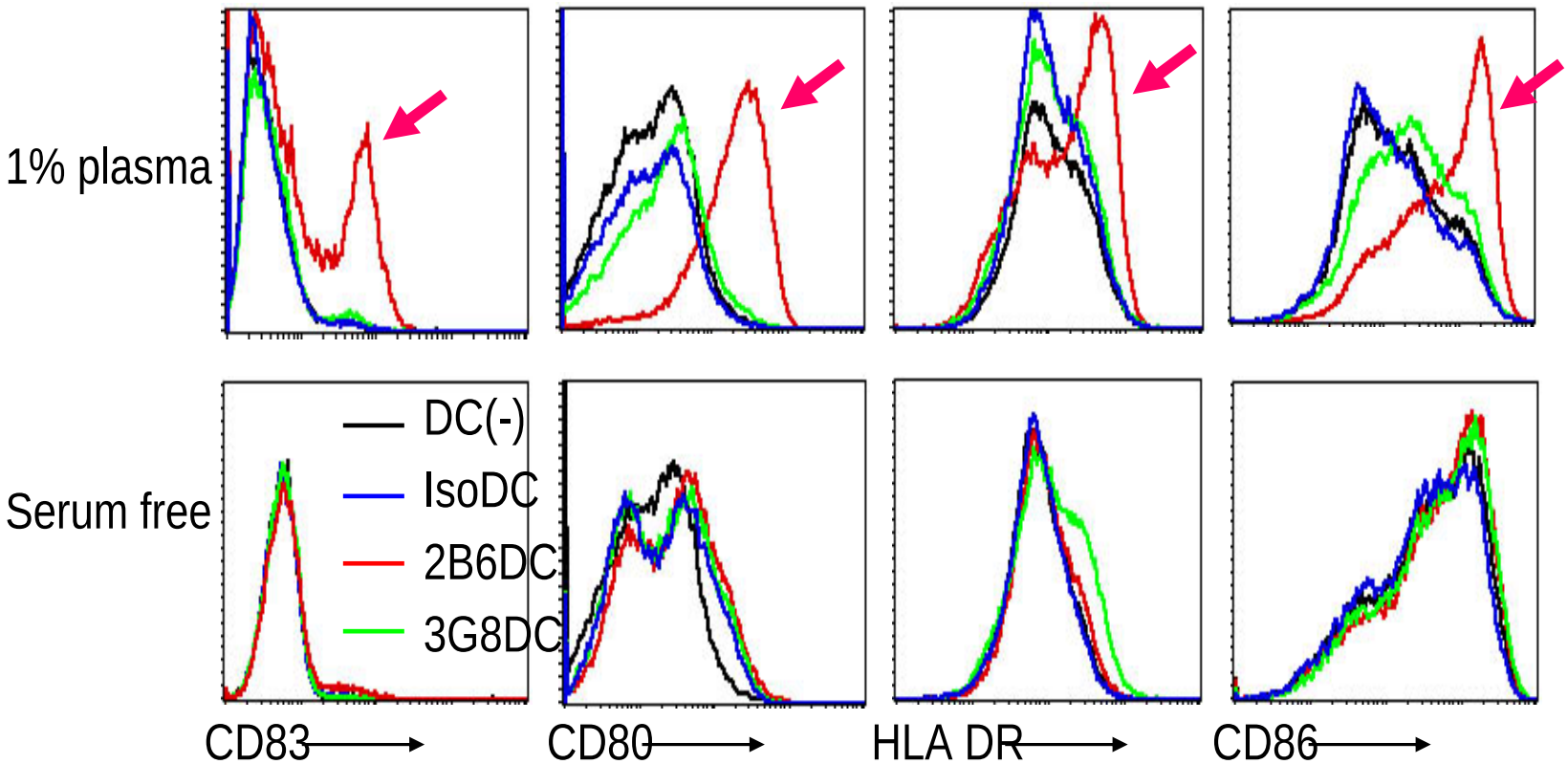


Ravetch JR. Ann Rev Imm 2001

Human Fc Receptors

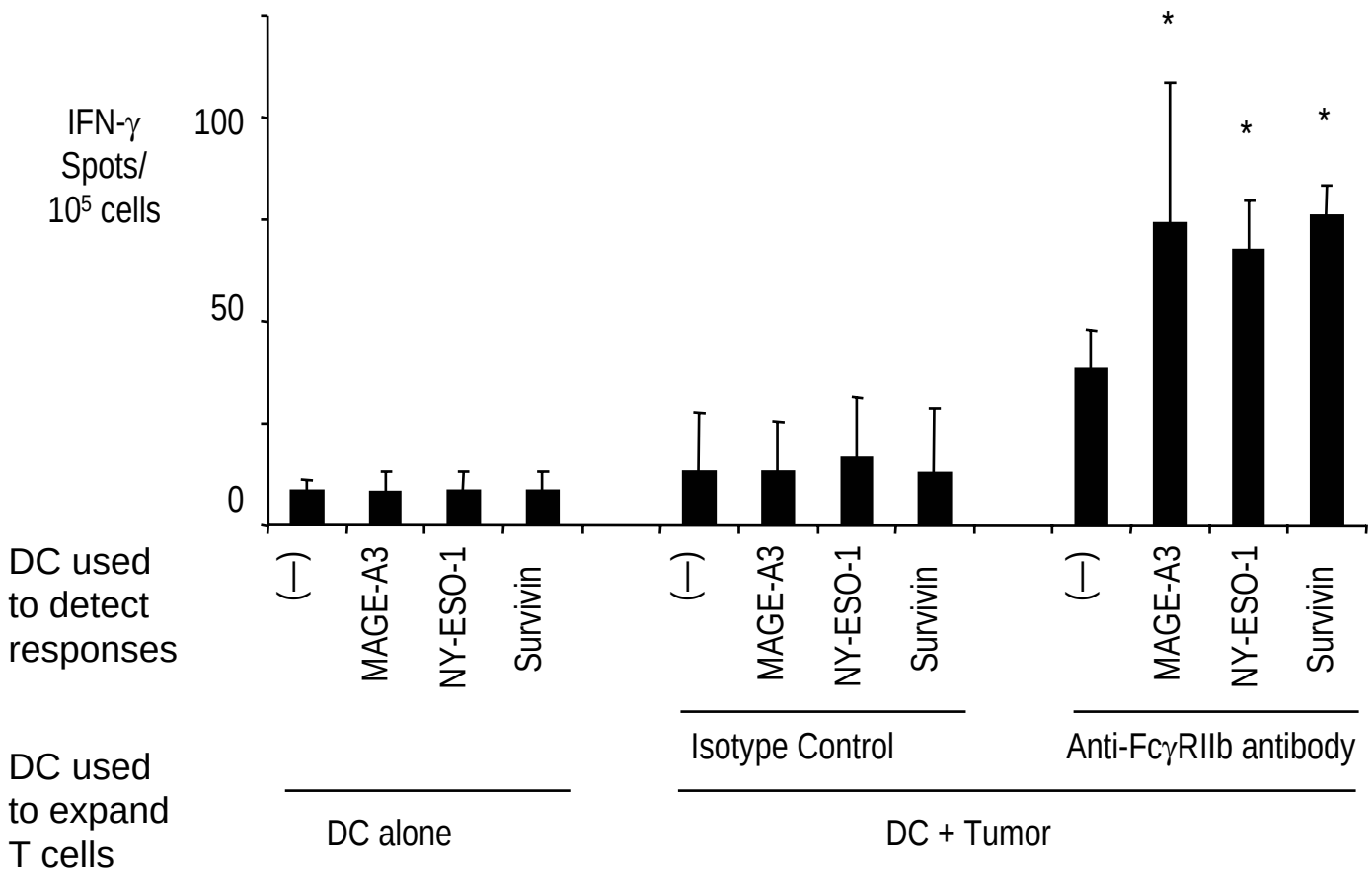


Selective blockade of inhibitory Fcγ receptor leads to DC maturation in the presence of normal human plasma



Dhodapkar et al. PNAS 2005

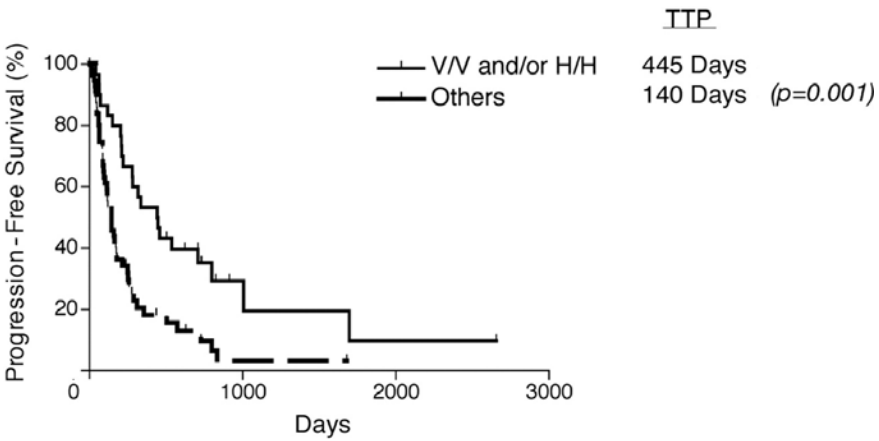
Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fcγ receptors on human DCs



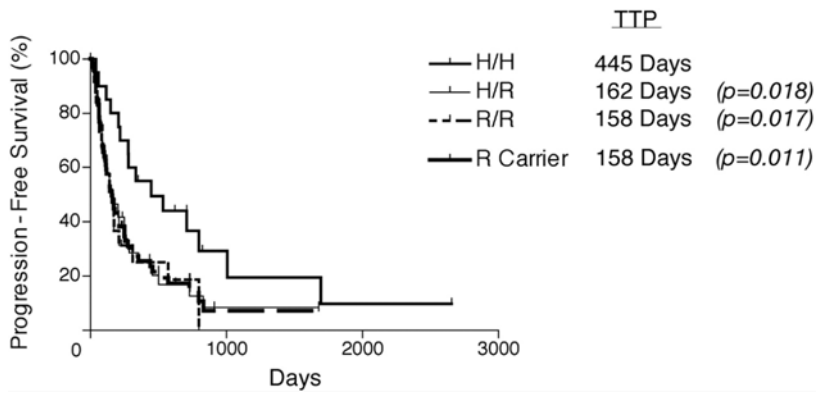
Dhodapkar et al, PNAS 2005

Effect of activating FcγR polymorphisms on survival of Rituxan treated patients

FcγRIIIa



FcγRIIa



Weng, W.-K. et al. J Clin Oncol; 21:3940-3947 2003

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Preliminary Evidence for Induction of T cell immunity In Patients Treated With Anti-tumor mAbs

mAb	Investigator
Rituxan (Anti-CD20)	Wong & Levy
2B1 (HER2-neu-RIII bispecific)	Weiner et al.
Anti-MUC1	DeBono et al.

INDUCTION OF ADAPTIVE ANTI-HER2/*neu* IMMUNE RESPONSES BY ANTIBODY THERAPY

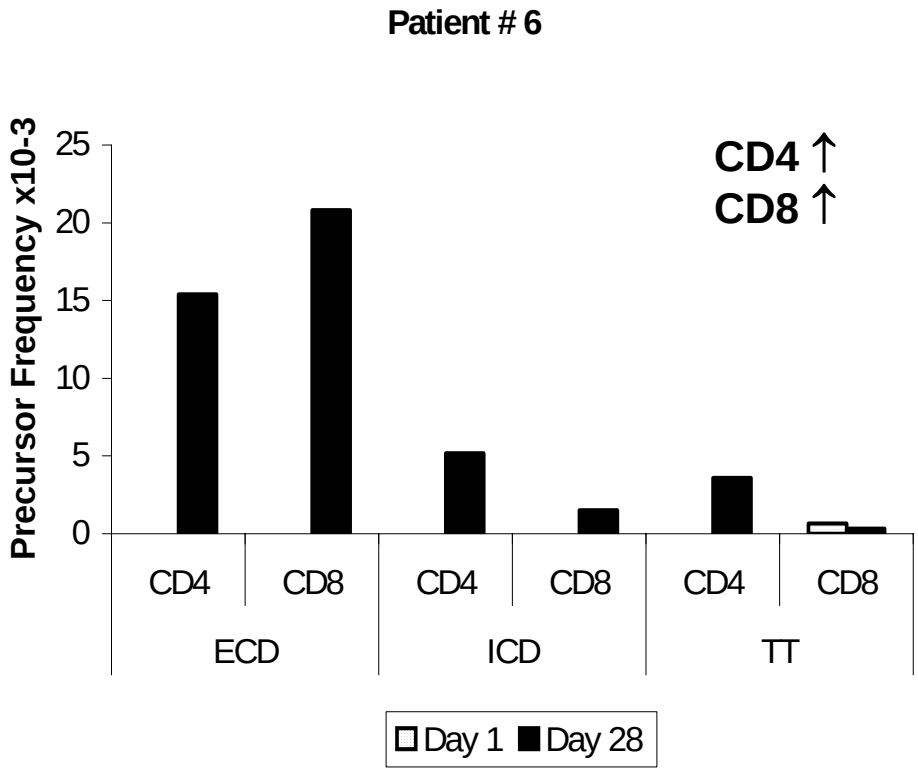
Phase IB/II Trial of 2B1 Antibody in HER2/neu (+) Breast Cancer

ECOG Trial E3194

Alpaugh, Borghaei, Clark,. Weiner

2B1 Treatment-induced T-Cell Responses

Anti-HER2/neu x anti-FcγRIII bispecific antibody treatment is associated with the induction of host immune responses against HER2/neu in a manner that suggests antigen presentation



Intracellular cytokine flow cytometry analysis of antibody therapy-induced anti-HER2/neu CD4 and CD8 T cell responses

Induction of T cell immunity after injection of anti-MUC1 mAb

Dose level	# Pts with MUC1 sp T cell responses
2 mg	3/5 patients
4 mg	2/4 patients

deBono JS et al. Ann Oncol 2004

Induction of T cell immunity by mAbs: Some questions

- Nature of T cell response
  - How frequent, antigenic targets, effector function, tissues.
- Underlying biology
  - What is special about FcR mediated signals and cross-presentation
- Variables that impact induction
  - Host related (e.g. FcR polymorphism)
  - mAb related (e.g. Fc engineering, target antigen)
- Clinical Significance / opportunities
  - Impact on durability of responses, immune escape.
  - Combination with other vaccines.

Conclusion

- Anti-tumor mAbs can lead to the induction of adaptive immunity against cancer.

- Harnessing the ability of these mAbs to elicit adaptive immunity may enhance the anti-tumor effects of mAbs in the clinic.

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