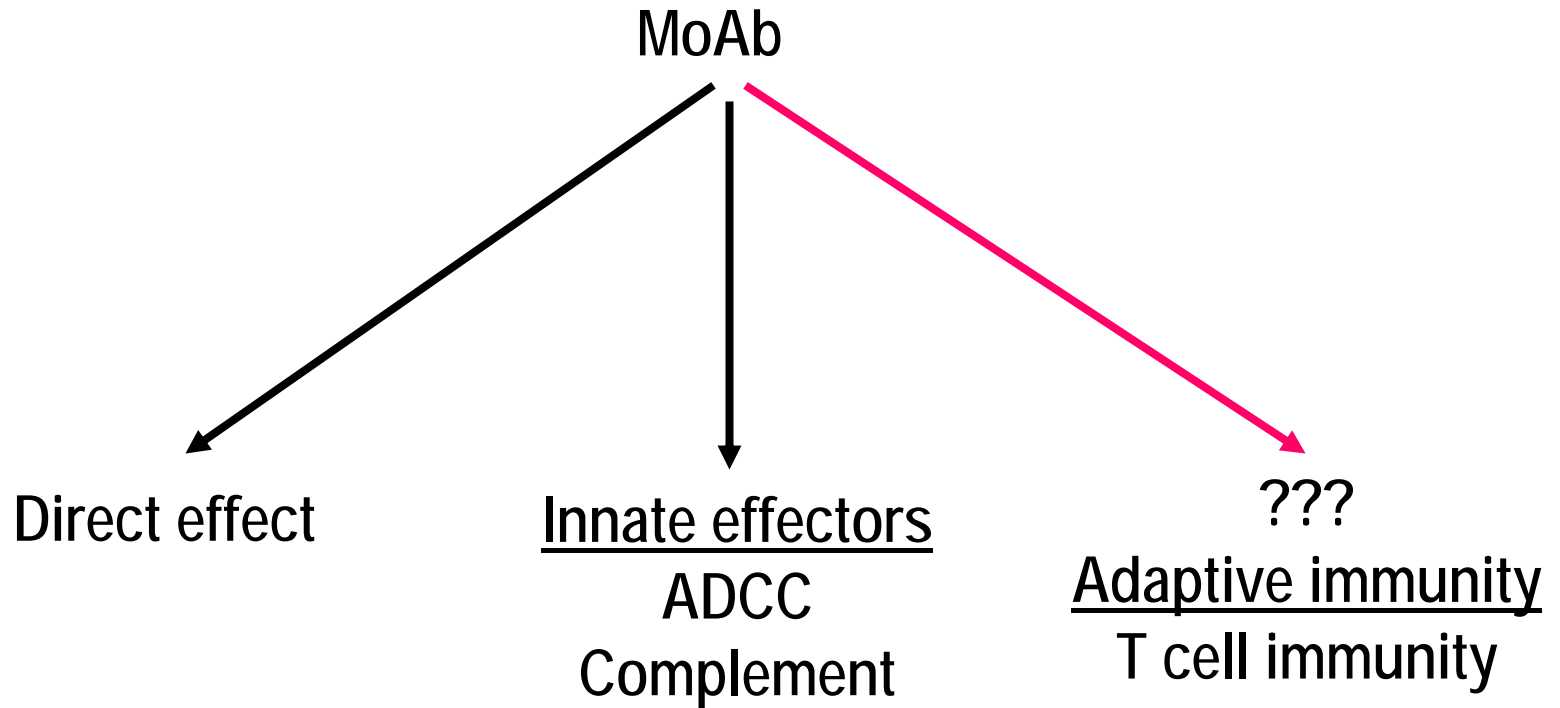


# Harnessing Antibodies To Stimulate Antigen-specific Immune Responses

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The Rockefeller University  
New York, NY

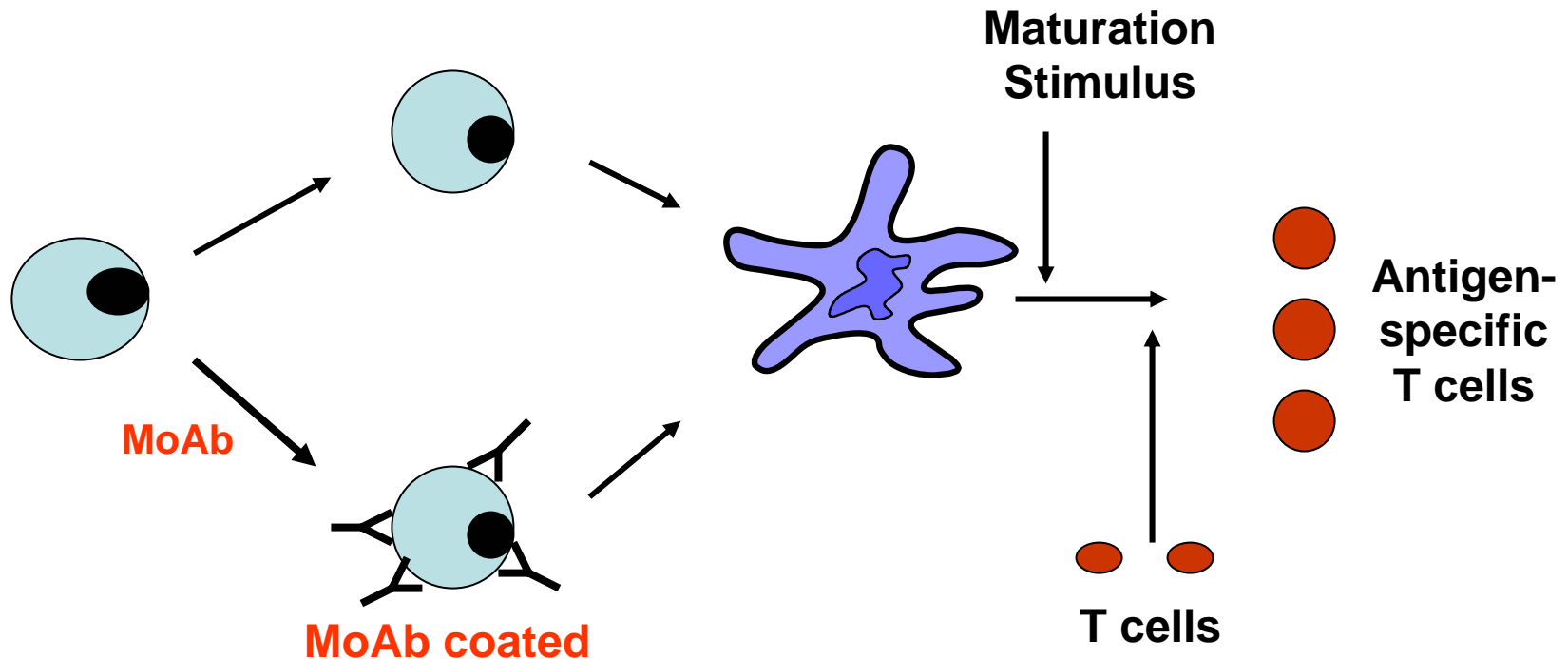
# Mechanisms of Anti-tumor Effects of MoAbs



# Why Harness MoAbs to Elicit Adaptive Immunity

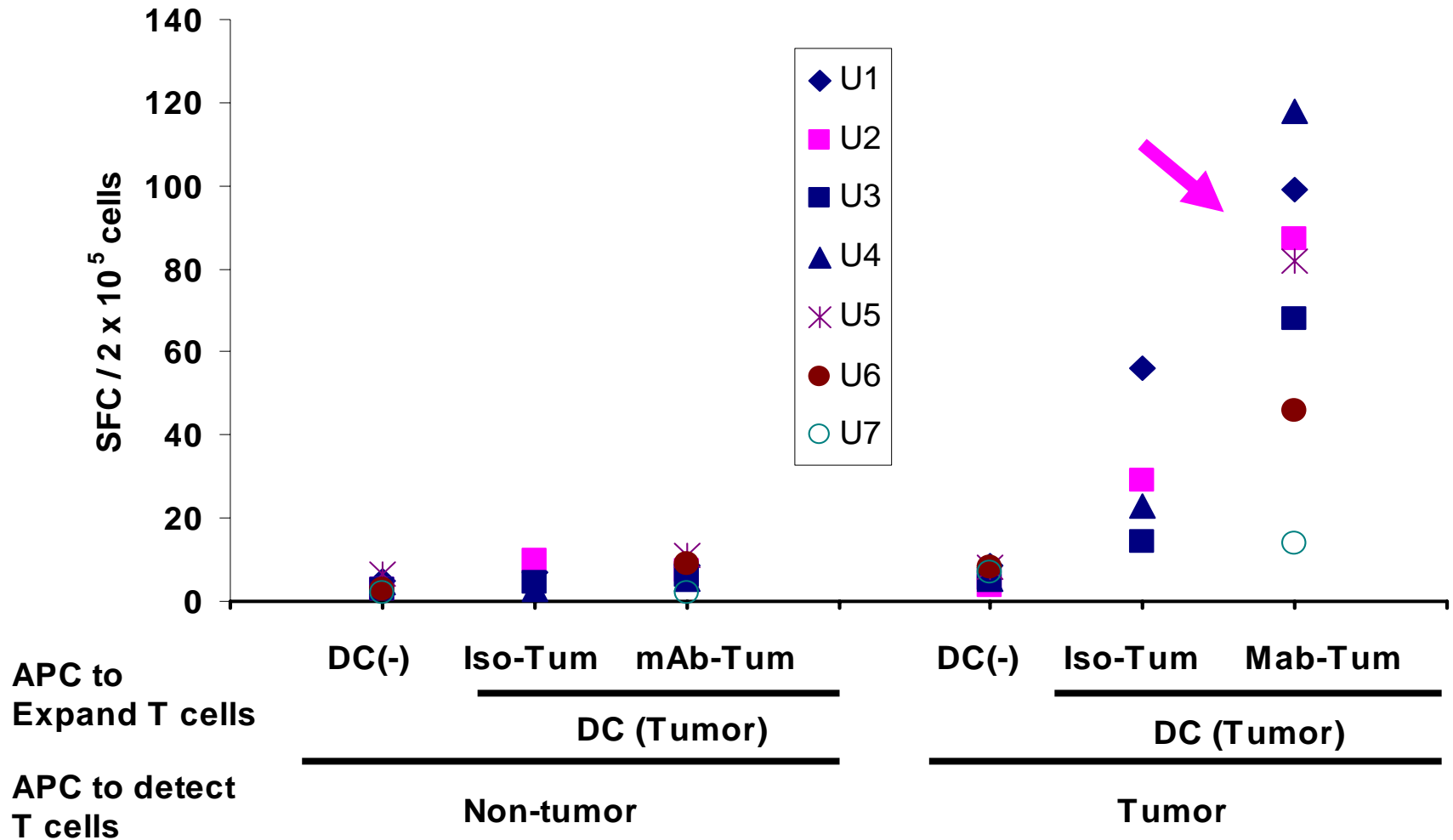
- May provide a mechanism for durable responses.
- Immunologic memory: booster effect with repeat administration.
- Targeting antigen negative tumor cells (epitope spread)

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



Fc $\gamma$ R dependent  
Not simply increased uptake

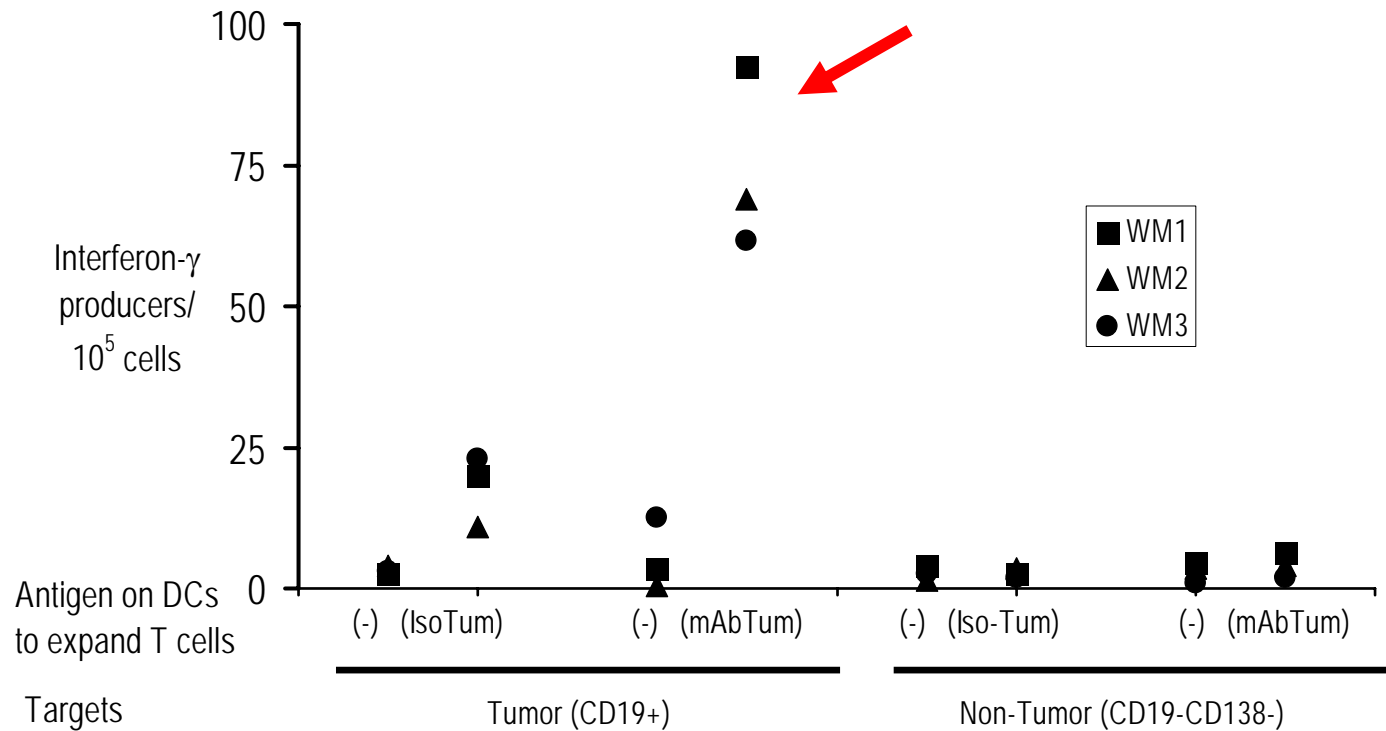
# Expansion of tumor reactive T cells in patients with progressive myeloma after stimulation with tumor cell loaded DCs



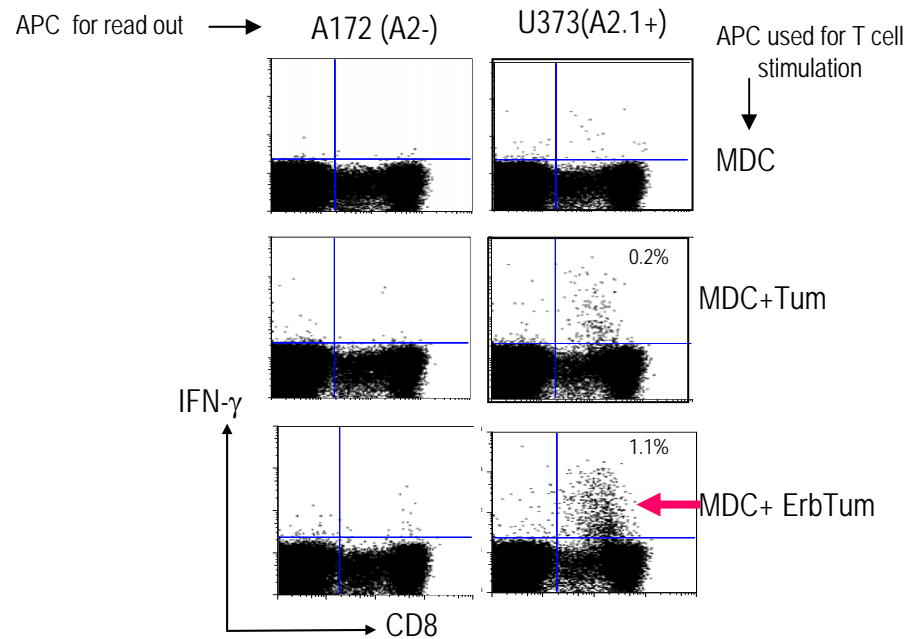
## Extending Fc $\gamma$ R targeting on DCs to clinical grade MoAbs

<u>Antibody</u>	<u>Isotype</u>	<u>Target</u>	<u>Tumor</u>
Rituxan	IgG1	CD20	Lymphoma Macroglobulinemia
Cetuximab	IgG1	EGF-R	Epithelial tumors Glioma

# Generation of Anti-Lymphoma T Cells using Autologous Tumor Cells Coated With Anti-CD20 MoAb (Rituxan)

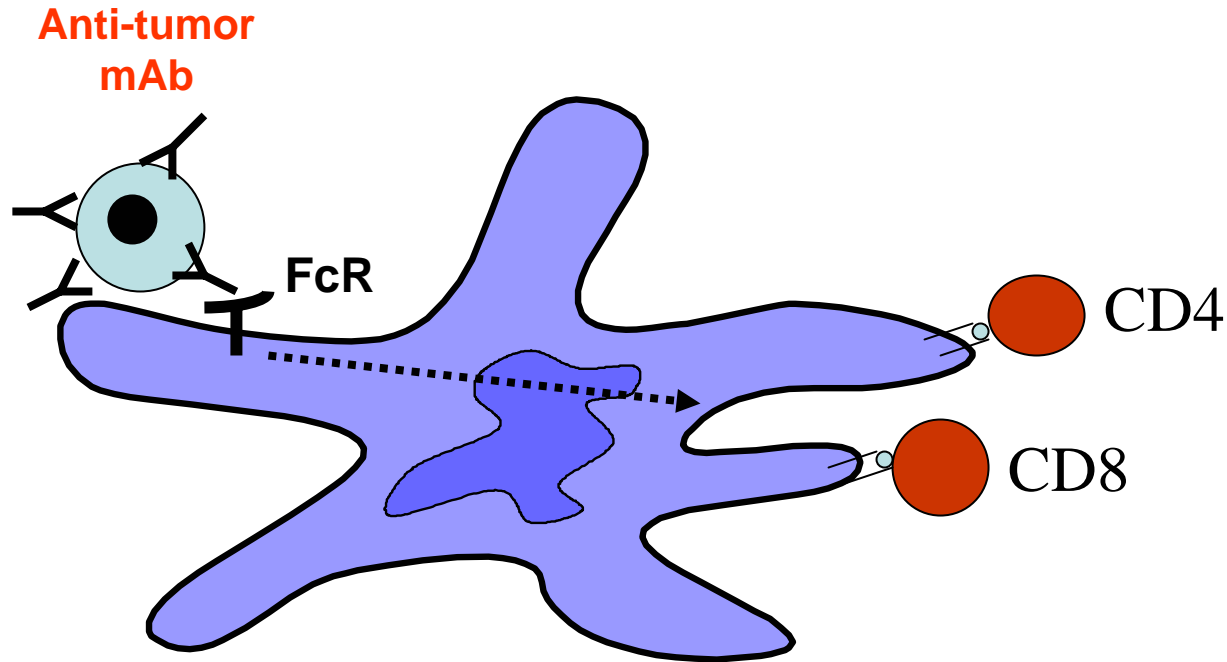


# Coating Human Glioma Cells With Anti-EGFR mAb Enhances The Induction Of Anti-Glioma Immunity

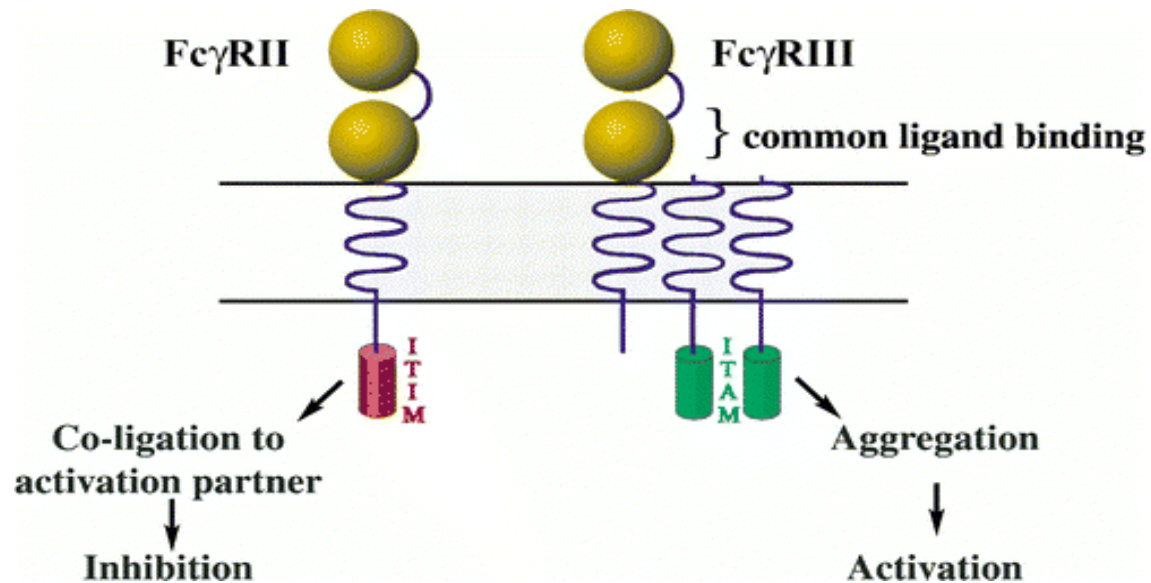




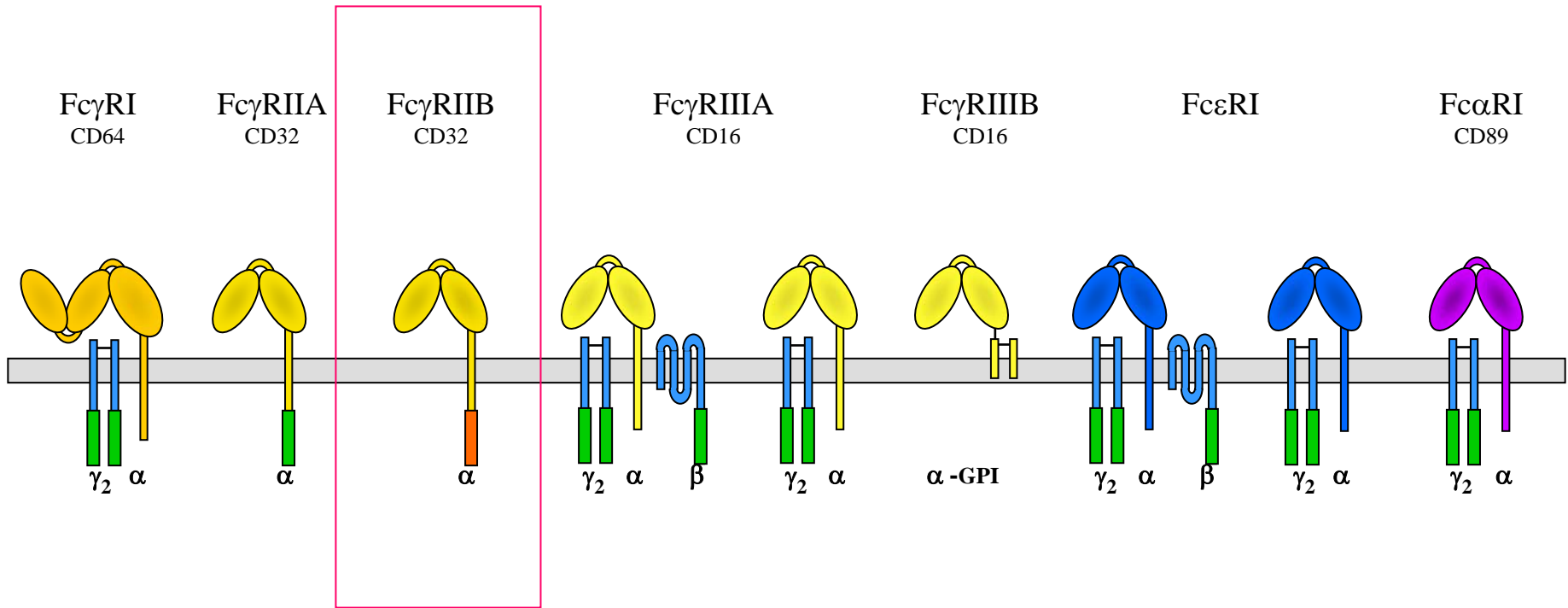
# Targeting tumor antigens to Fc $\gamma$ receptors on dendritic cells via anti-tumor mAb enhances anti-tumor immunity



# Fc receptor system as a balance of activating and inhibitory receptors



# Human Fc Receptors

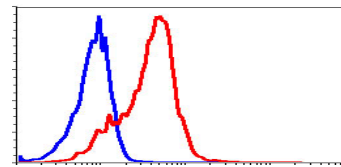
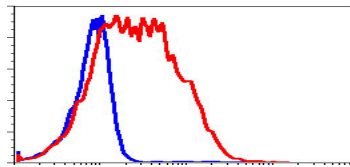


# Hypothesis

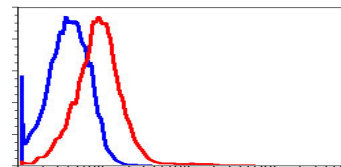
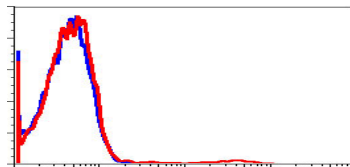
Selective blockade of inhibitory Fc $\gamma$  receptors using new antibodies that selectively bind these receptors will enhance DC function and presentation of tumor antigens by human DCs.

## Expression of Fc $\gamma$ RII receptors on myeloid and plasmacytoid DCs

Myeloid DCs  
Lin<sup>-</sup>, HLA DR<sup>+</sup>, CD11c<sup>+</sup>



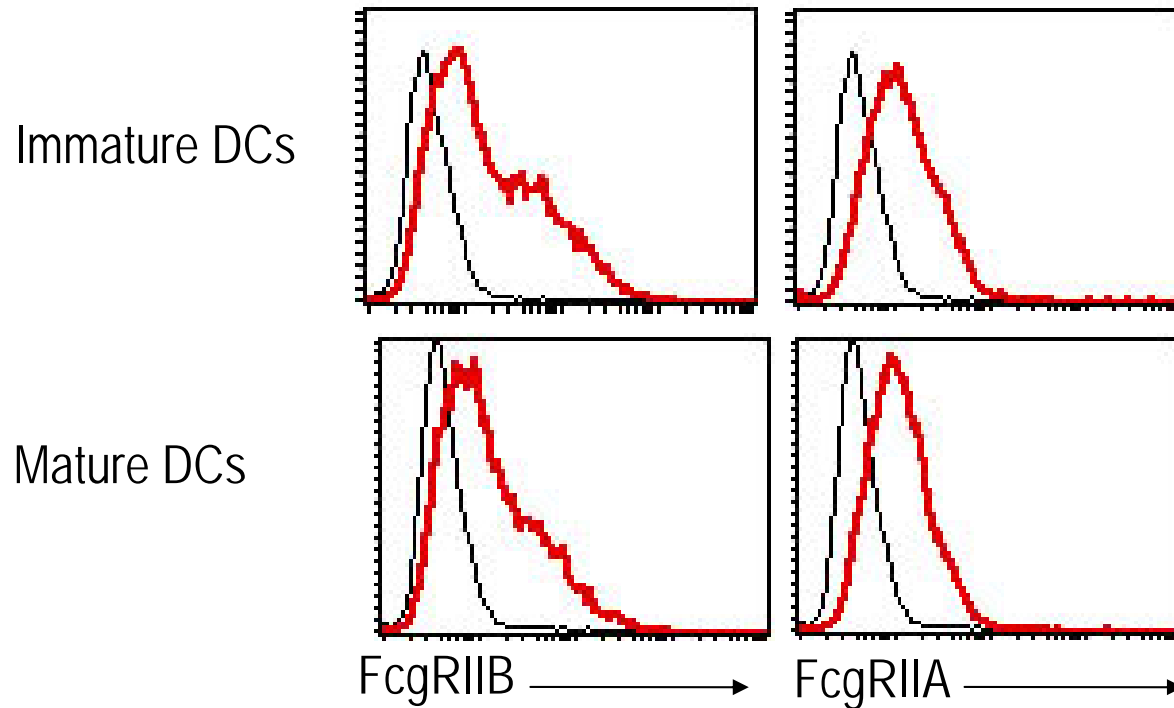
Plasmacytoid DCs  
Lin<sup>-</sup>, HLA-DR<sup>+</sup>, CD123<sup>+</sup>



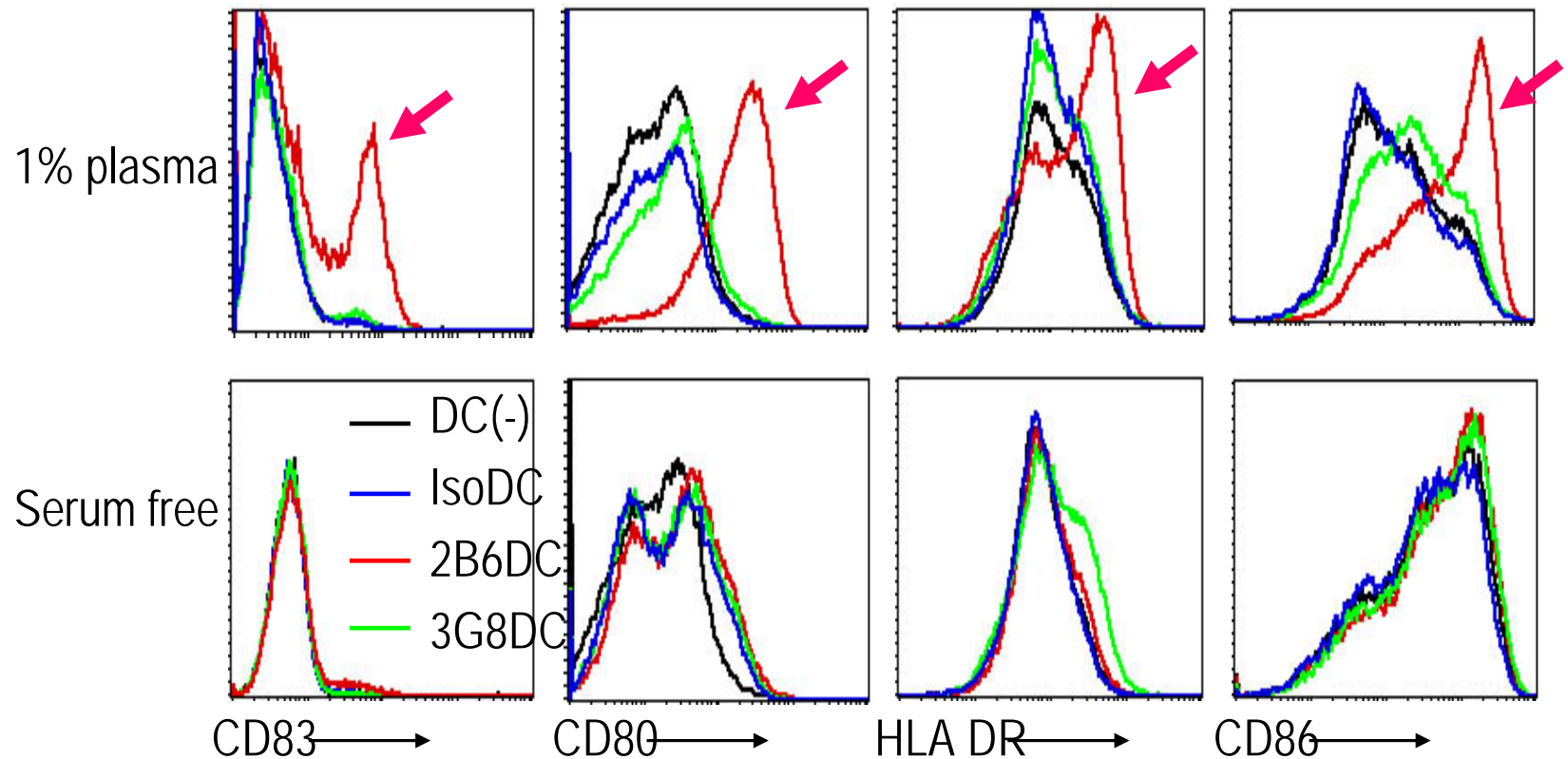
→ Fc $\gamma$ RIIB

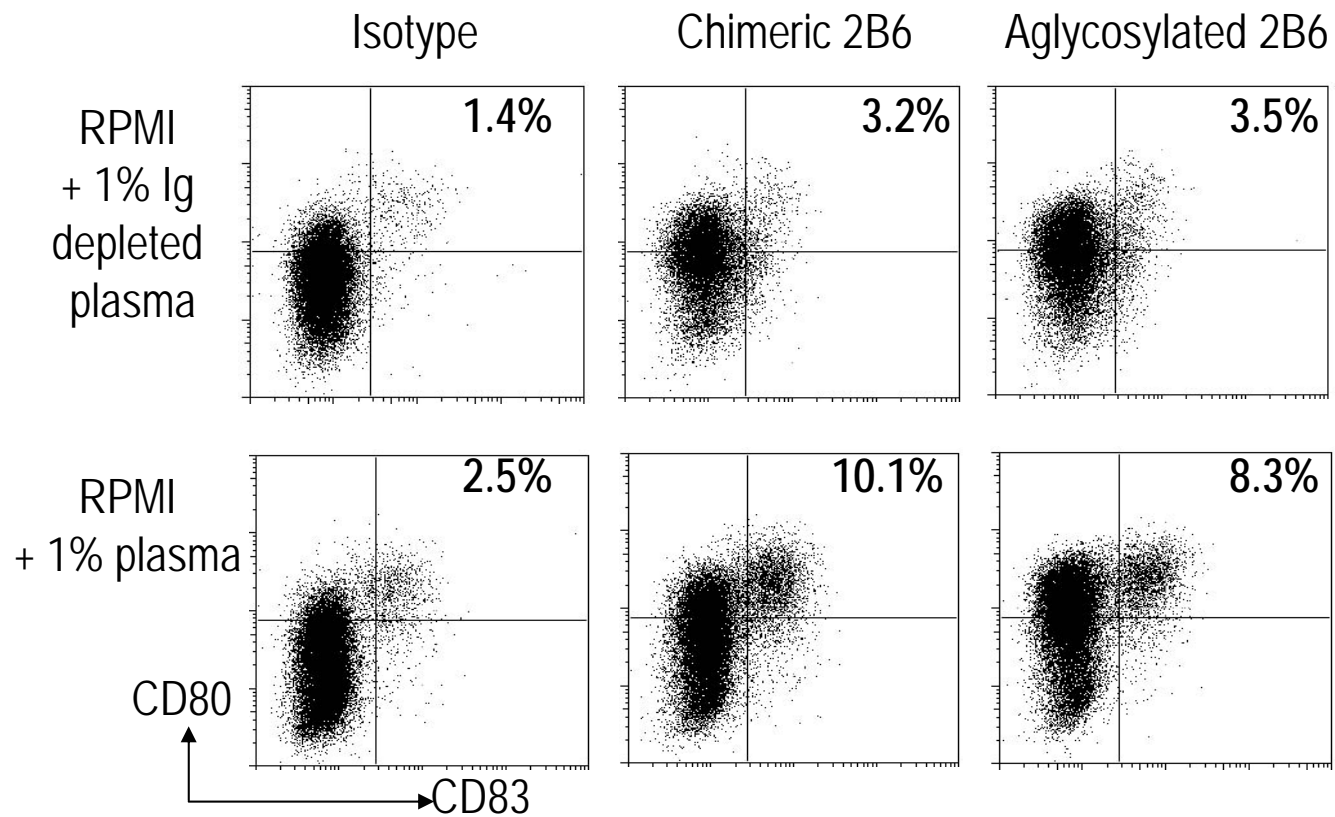
→ Fc $\gamma$ RIIA

# Both Immature and Mature Monocyte Derived DCs Express Both Activating and Inhibitory forms of Fc $\gamma$ RII



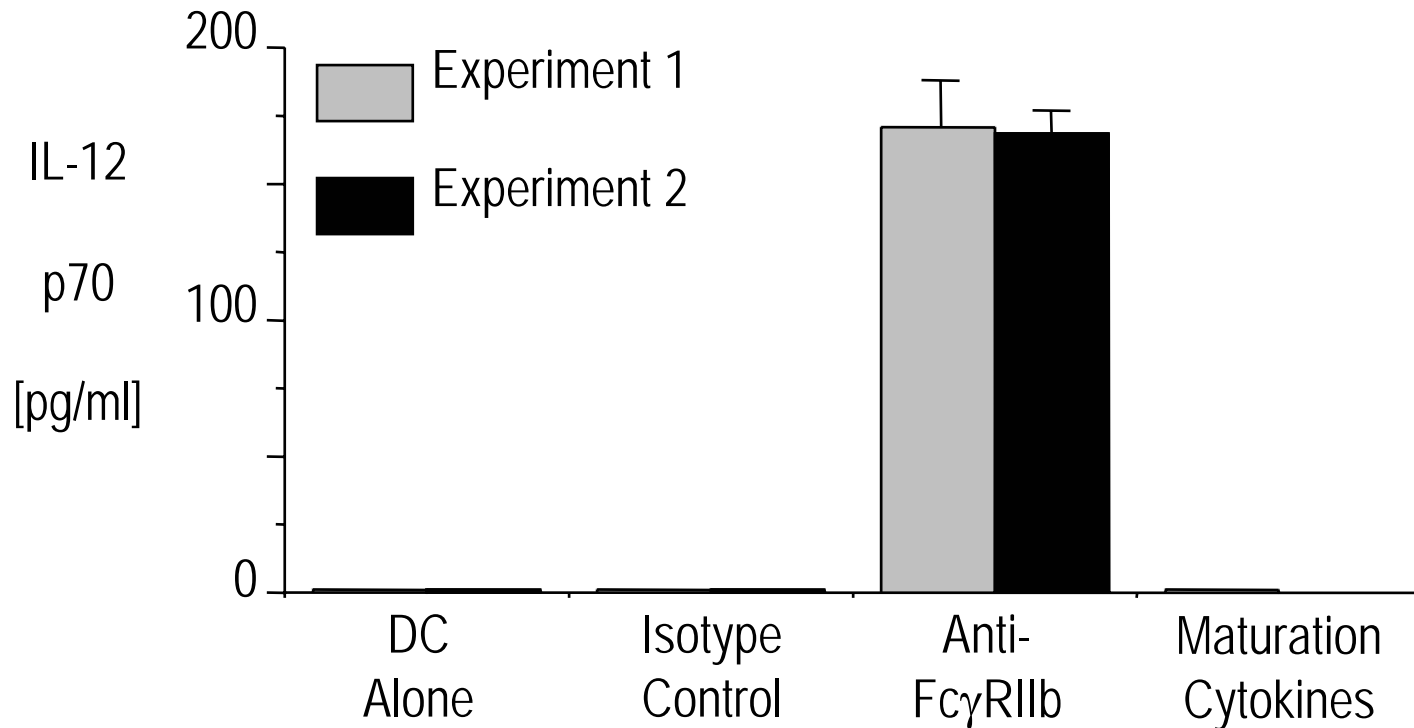
# Selective blockade of inhibitory Fcγ receptor leads to DC maturation in the presence of normal human plasma



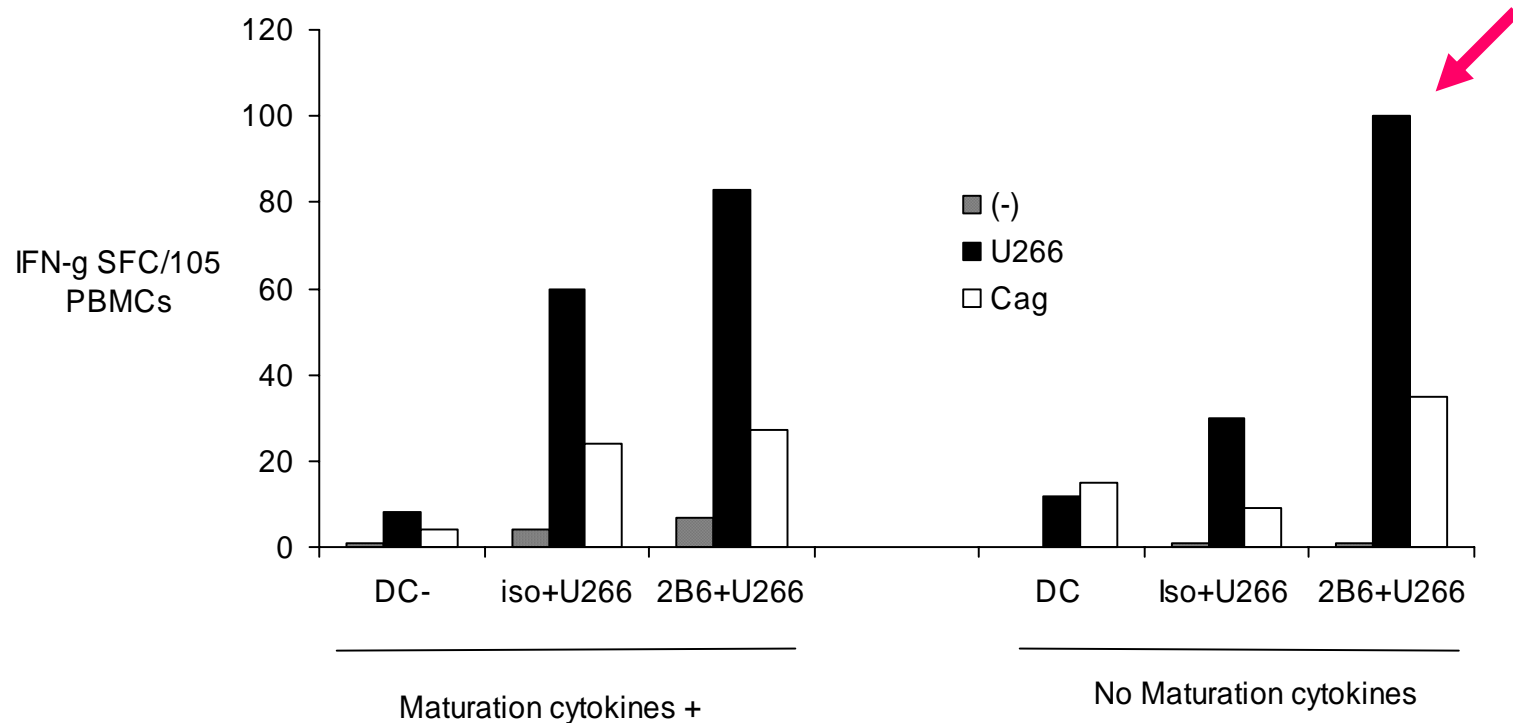




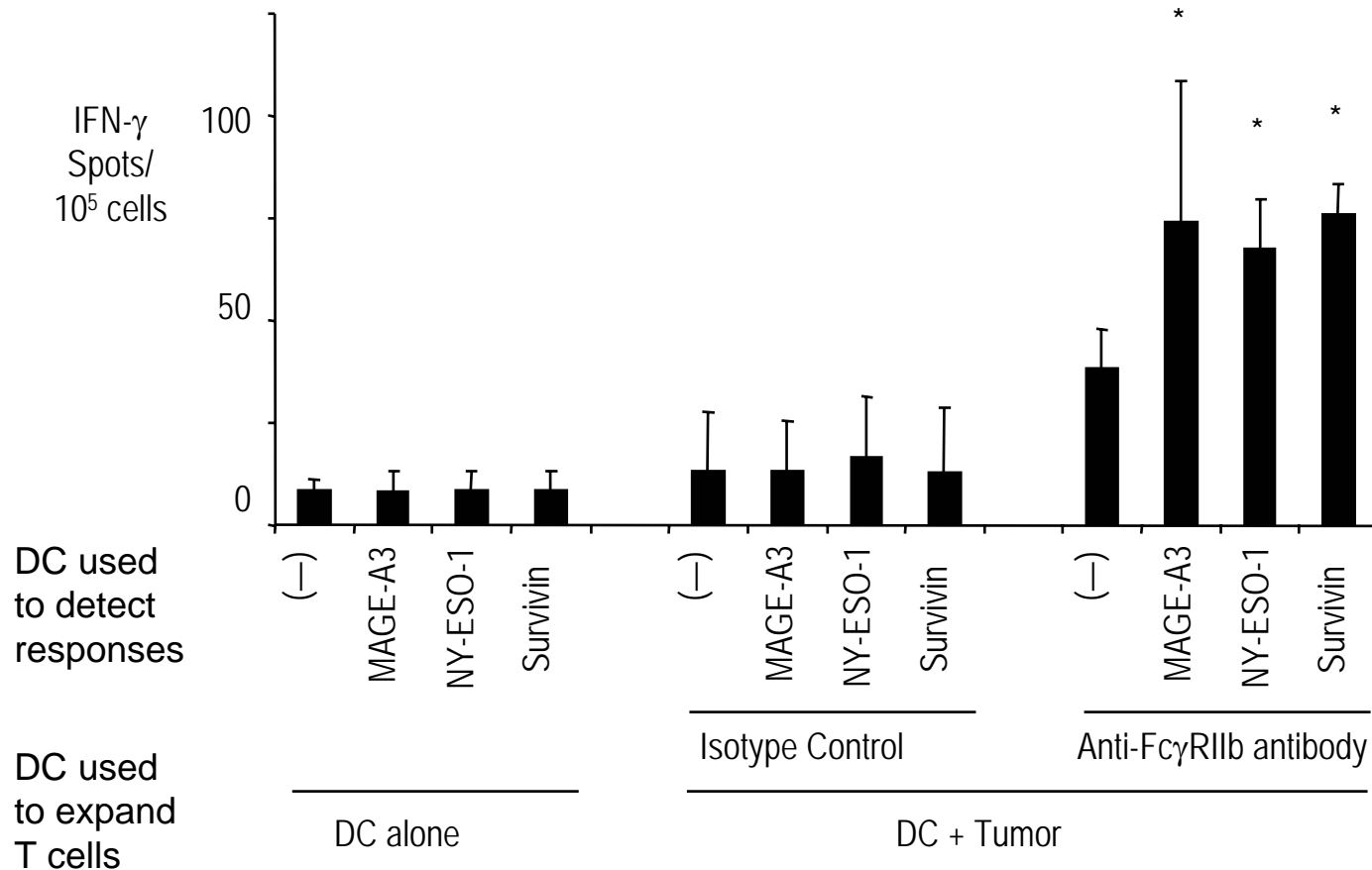
# Selective blockade of inhibitory Fc $\gamma$ receptor on purified DCs Leads to Induction of IL-12p70 production



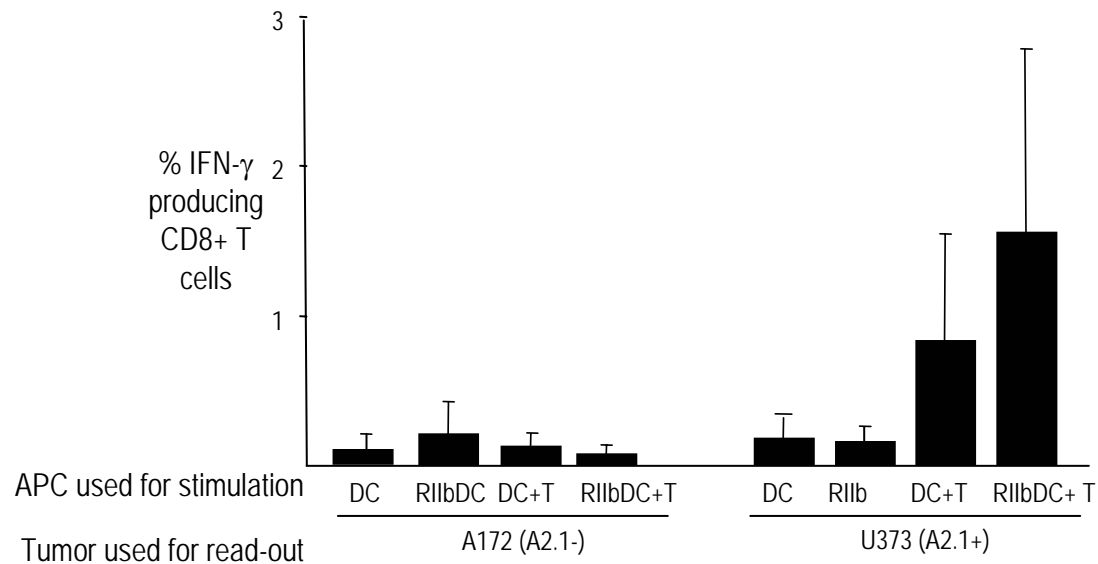
# Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fc $\gamma$ receptors on Human DCs



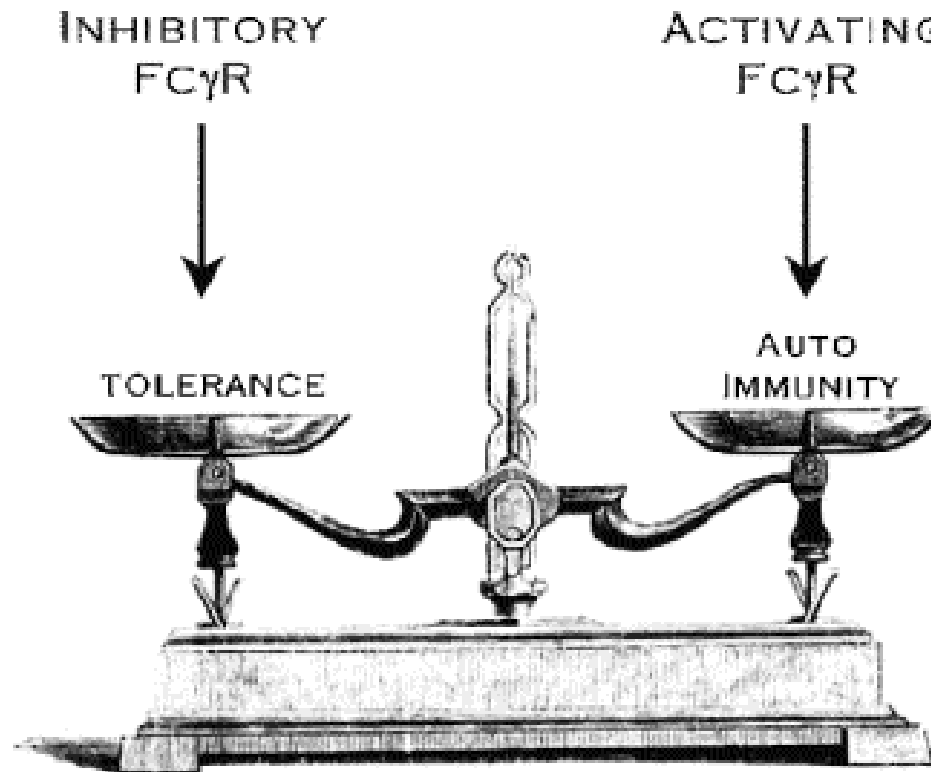
# Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fcγ receptors on DCs



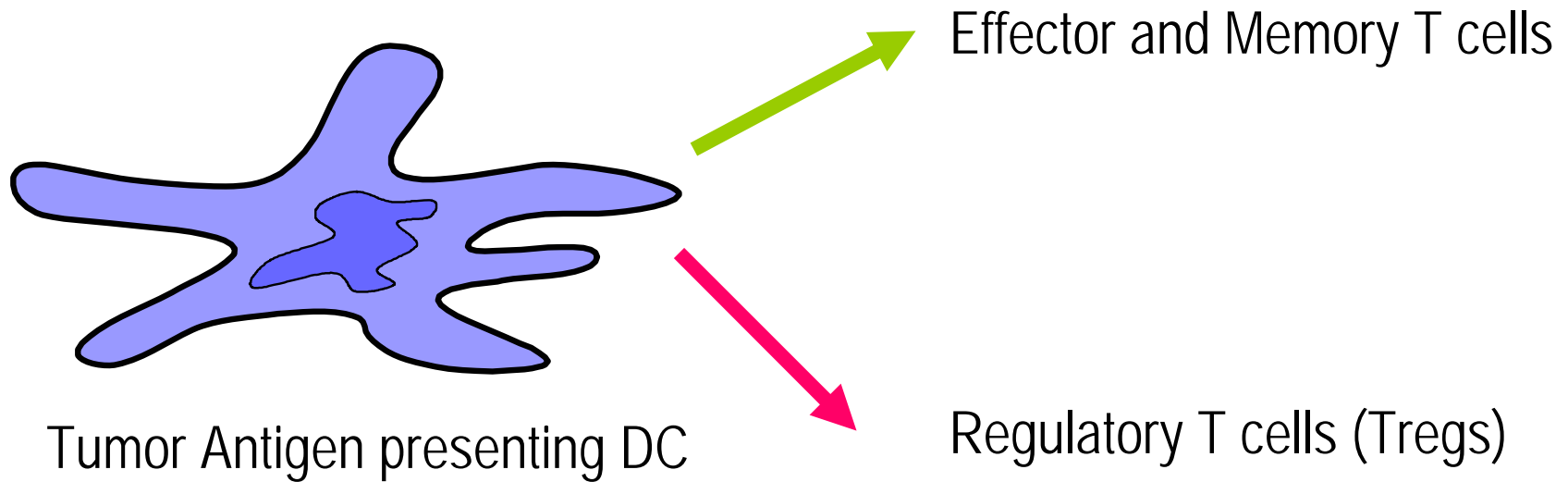
# Blockade of Fc $\gamma$ RIIB leads to induction of anti-glioma immunity without the need for exogenous maturation stimulus



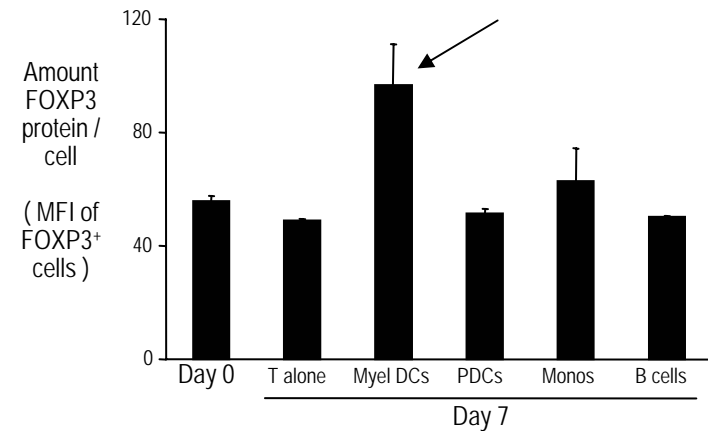
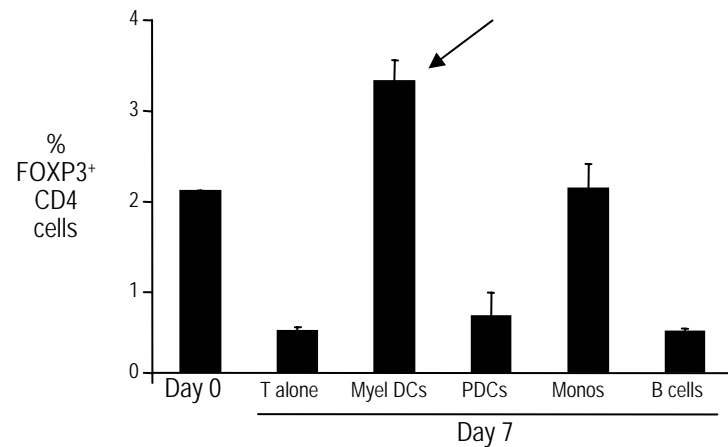
# DC Function Is Modulated by a Balance Between Activating and Inhibitory Fc Receptors



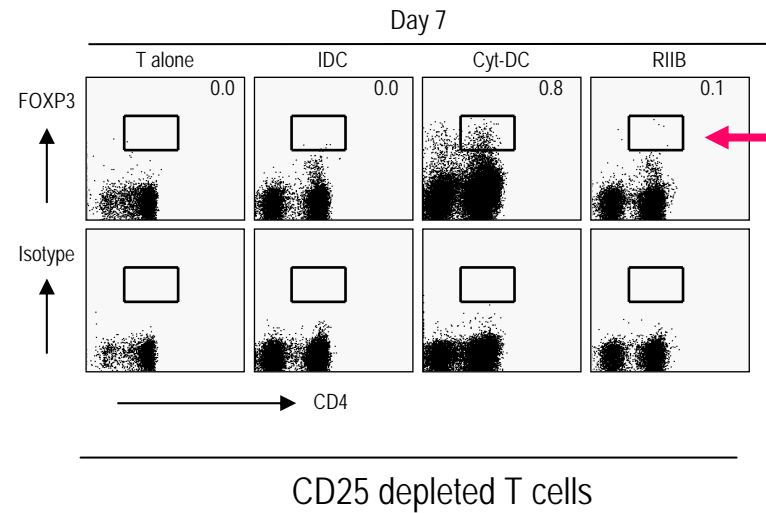
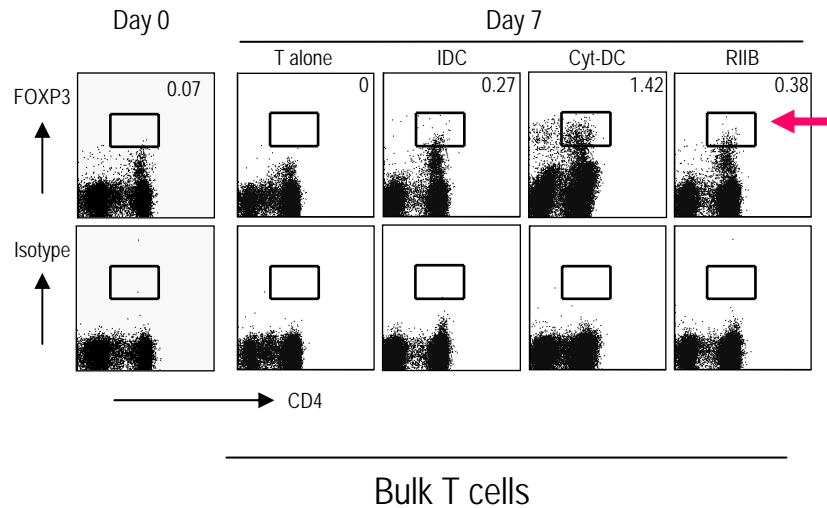
# Balance Of Effector Versus Tregs As A Determinant Of Vaccine Efficacy



# Efficiency of DCs for expansion of Human FOXP3+ Tregs

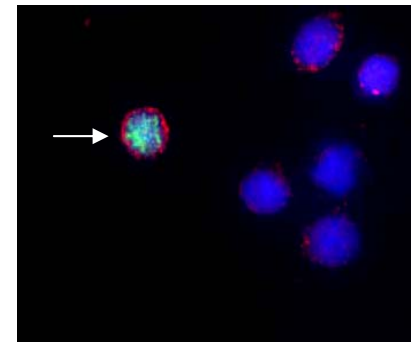
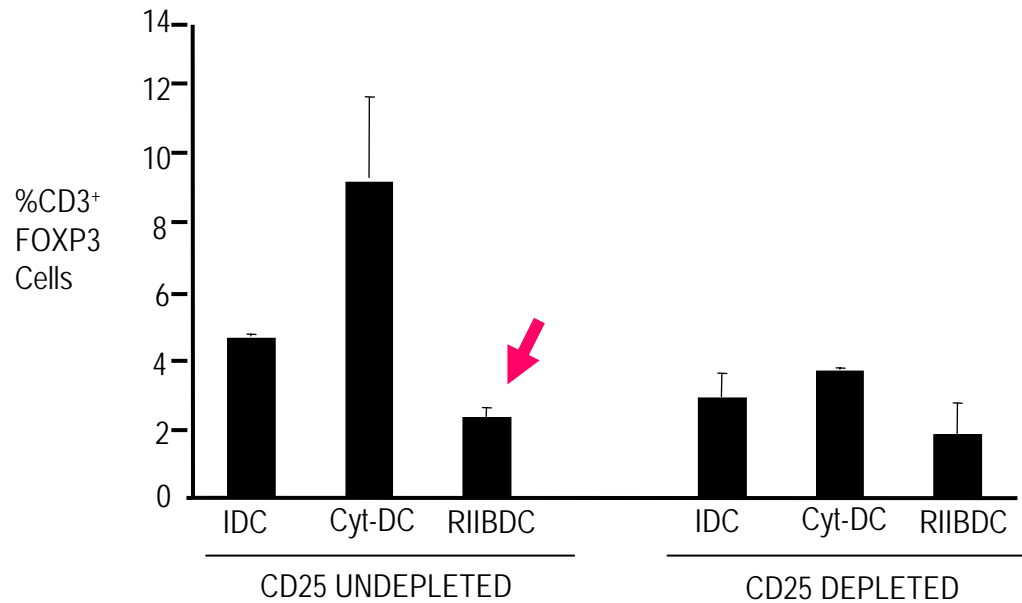


# Effect Of FcR Mediated DC Maturation On The Ability of DCs To Induce FOXP3+ Tregs





# Expansion of FOXP3<sup>+</sup> Tregs after stimulation with tumor loaded DCs



# Conclusions

- Selective engagement of activating FcRs leads to DC maturation and boosts the generation of anti-tumor immunity by human DCs
  - More anti-tumor effector T cells
  - Fewer concurrent FoxP3+ Tregs.
- Alteration of activating / inhibitory FcR balance may impact the ability of DCs to induce adaptive immunity in vivo in mAb treated patients
  - FcR polymorphisms
  - Fc engineering
- Further studies are needed to directly characterize the nature of T cell response in patients treated with anti-tumor MoAbs, and understand the mechanism of Fc $\gamma$ R mediated enhancement of dendritic cell function.

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