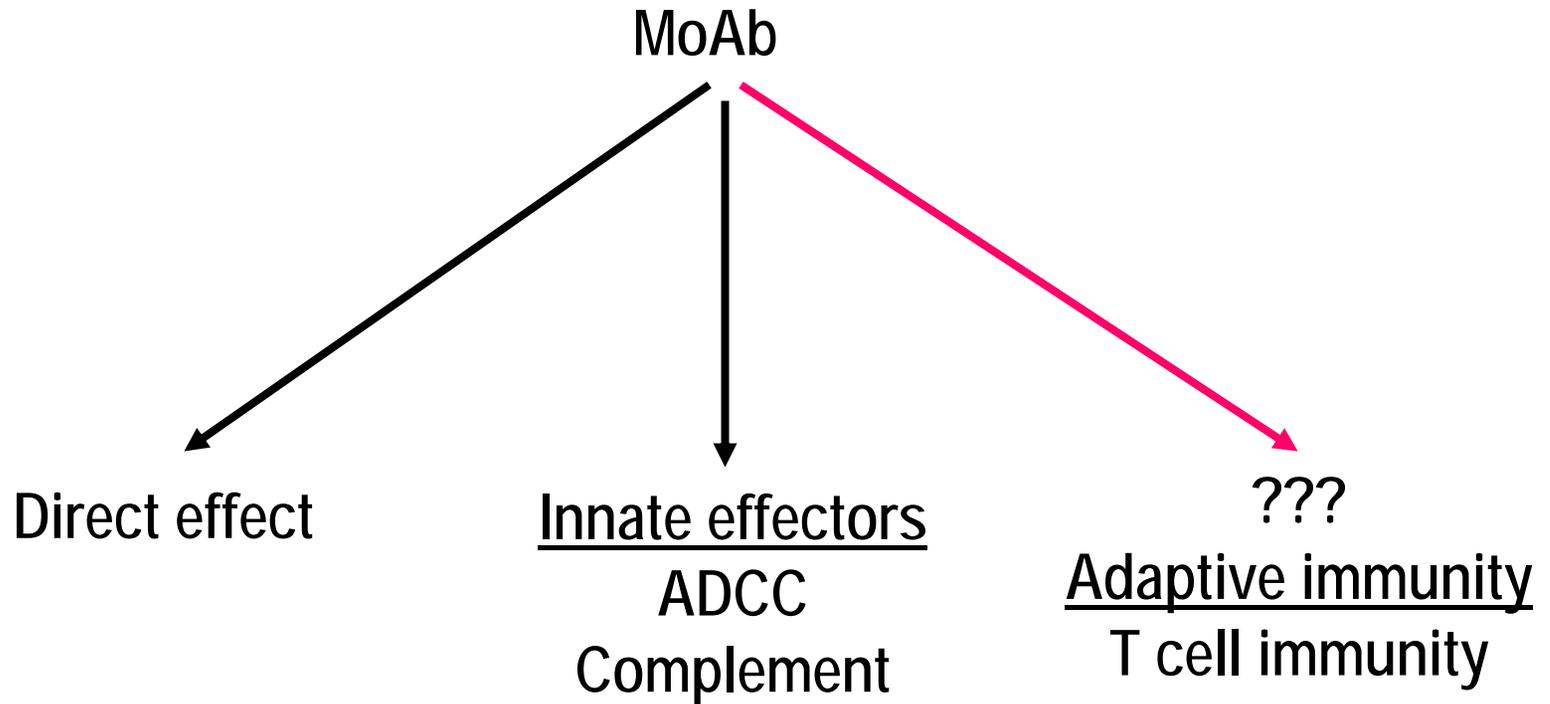


Harnessing Antibodies To Stimulate Antigen-specific Immune Responses

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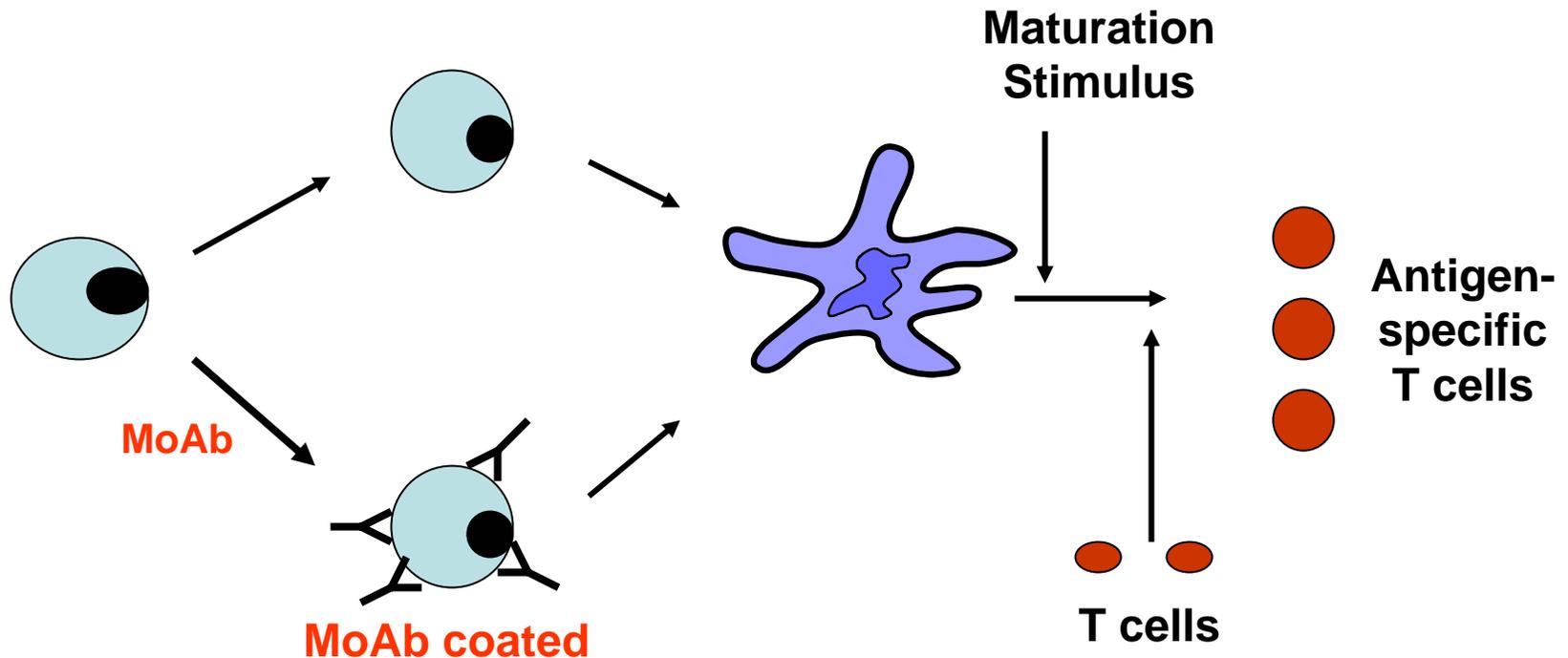
Mechanisms of Anti-tumor Effects of MoAbs



Why Harness MoAbs to Elicit Adaptive Immunity

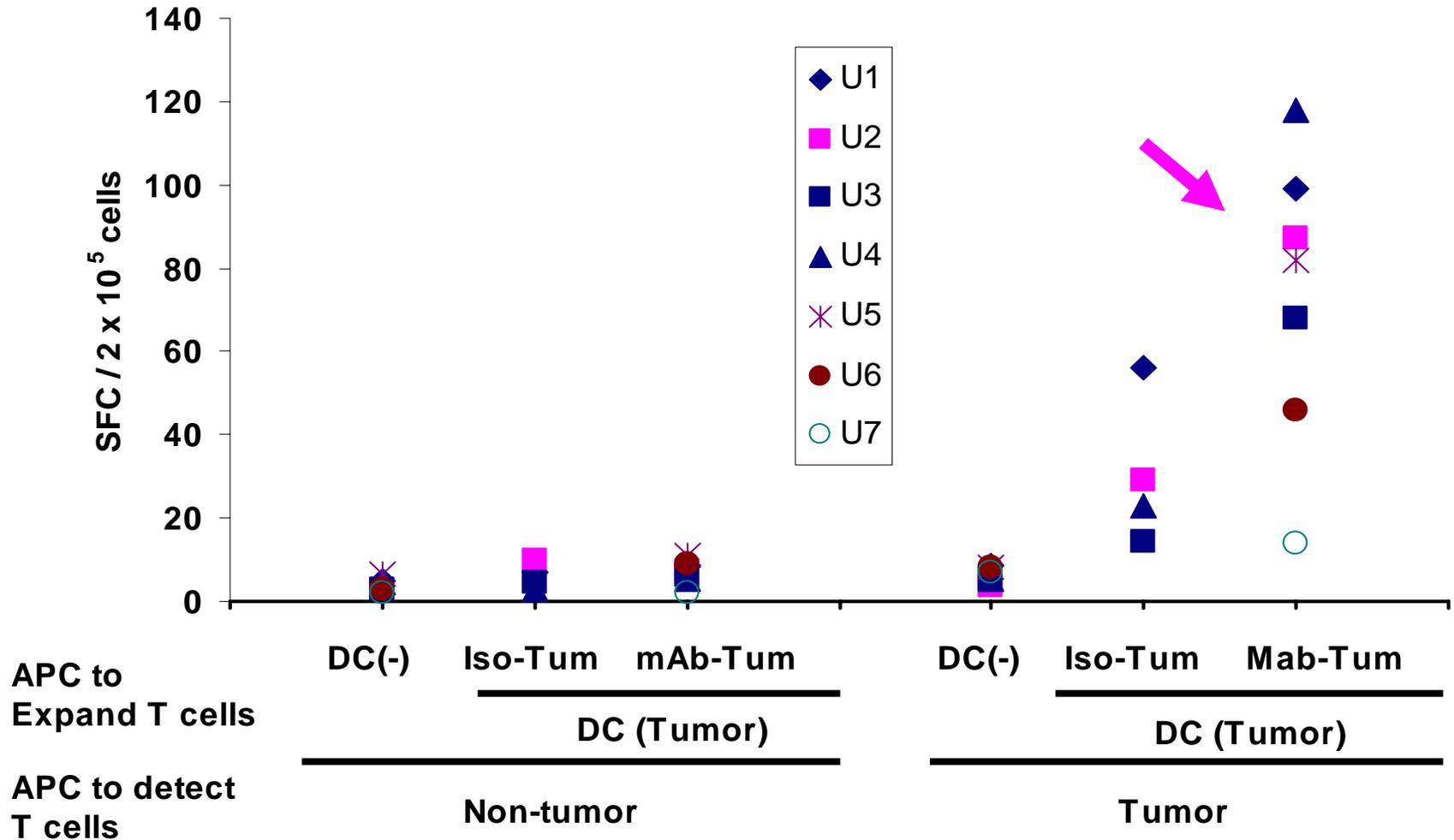
- May provide a mechanism for durable responses.
- Immunologic memory: booster effect with repeat administration.
- Targeting antigen negative tumor cells (epitope spread)

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



Fc γ R dependent
Not simply increased uptake

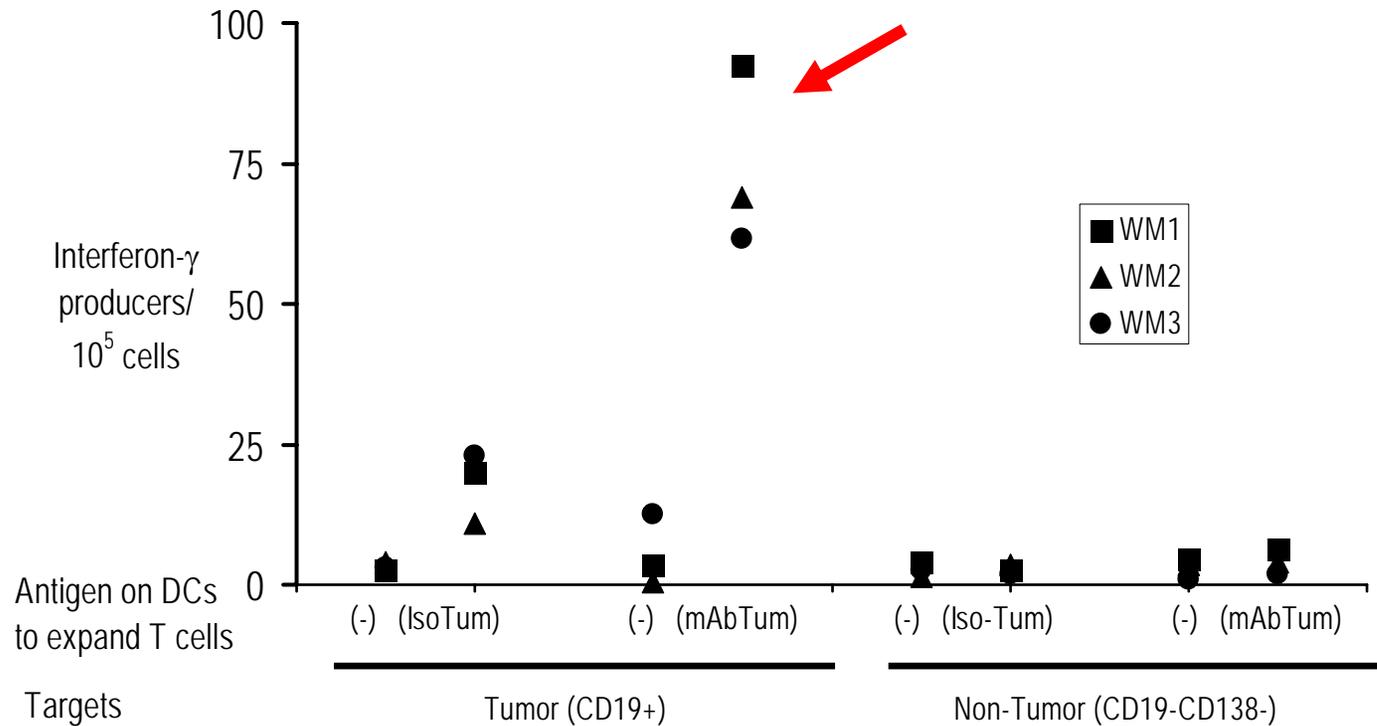
Expansion of tumor reactive T cells in patients with progressive myeloma after stimulation with tumor cell loaded DCs



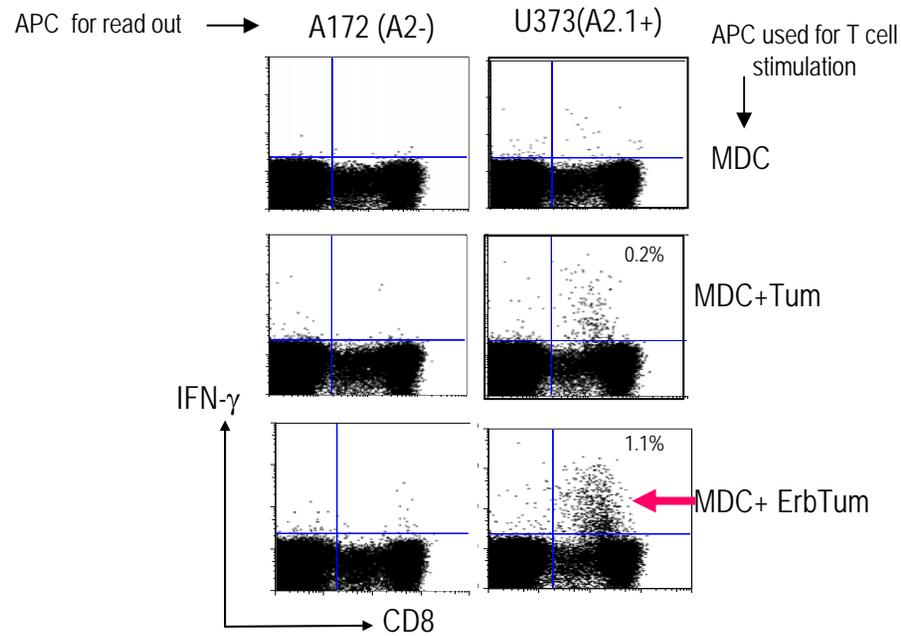
Extending Fc γ R targeting on DCs to clinical grade MoAbs

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

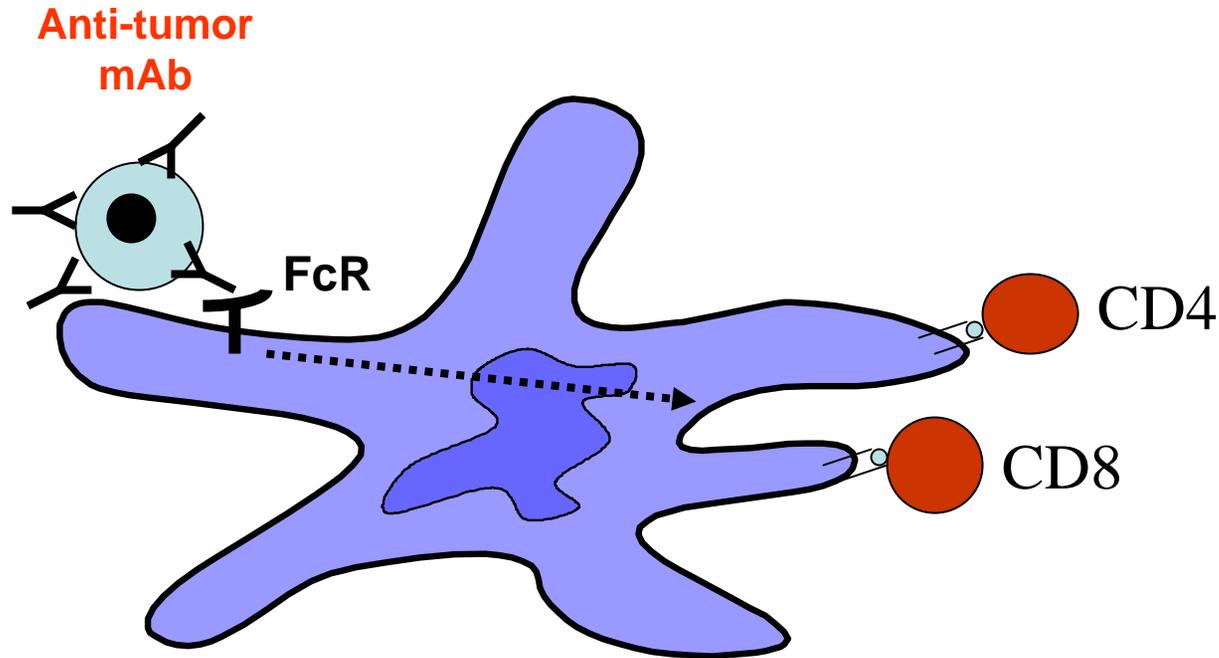
Generation of Anti-Lymphoma T Cells using Autologous Tumor Cells Coated With Anti-CD20 MoAb (Rituxan)



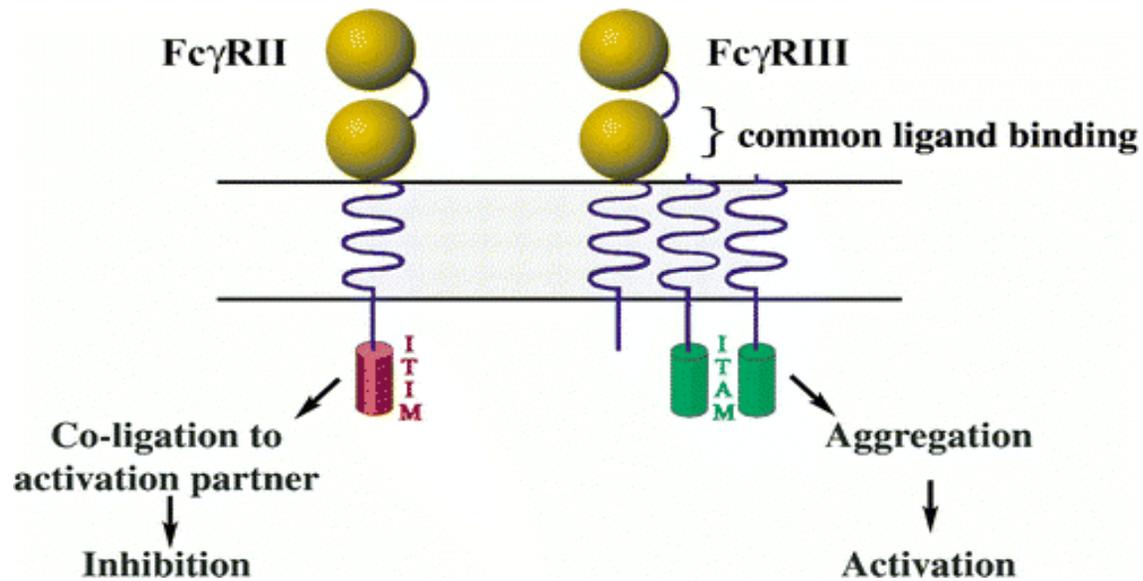
Coating Human Glioma Cells With Anti-EGFR mAb Enhances The Induction Of Anti-Glioma Immunity



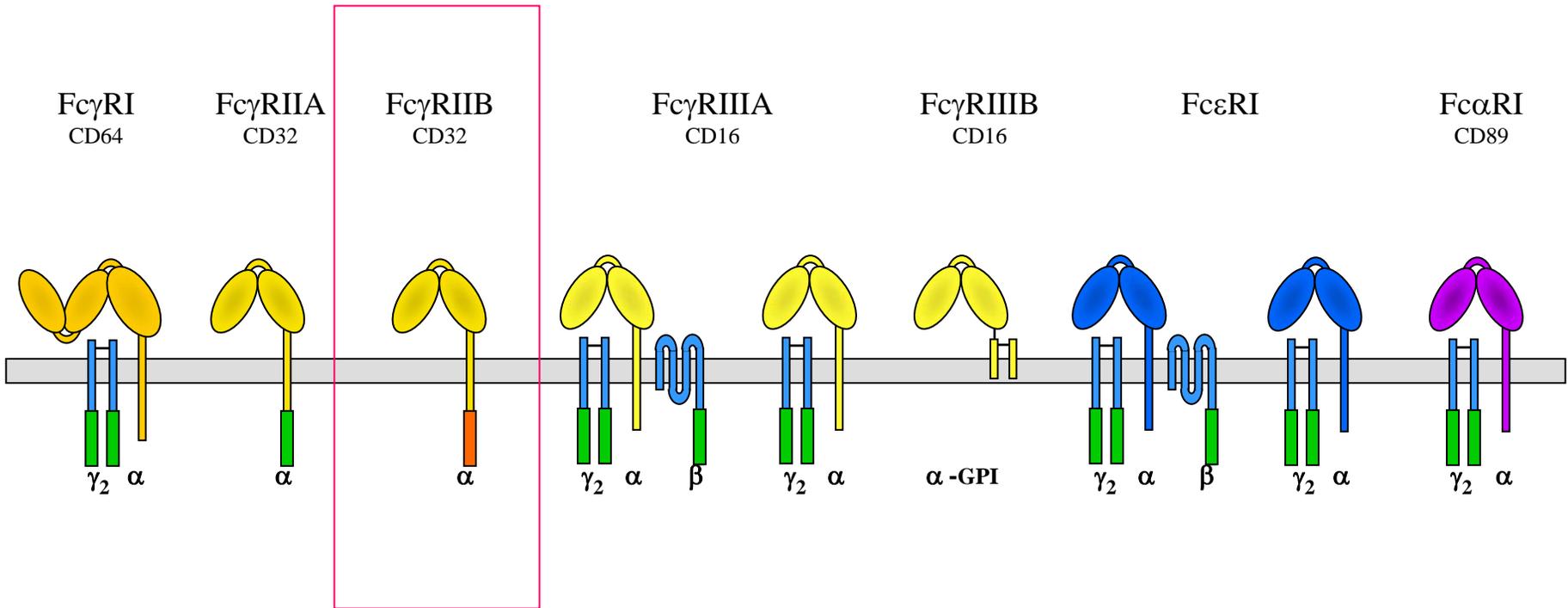
Targeting tumor antigens to Fc γ receptors on dendritic cells via anti-tumor mAb enhances anti-tumor immunity



Fc receptor system as a balance of activating and inhibitory receptors



Human Fc Receptors

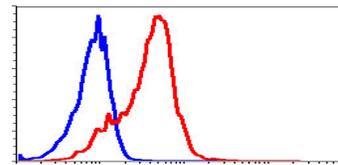
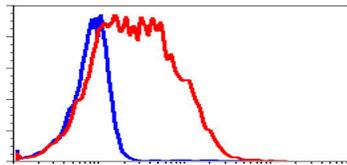


Hypothesis

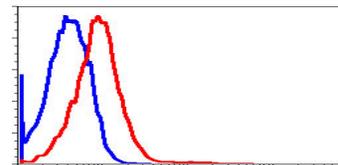
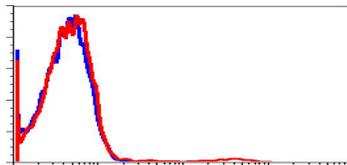
Selective blockade of inhibitory Fc γ receptors using new antibodies that selectively bind these receptors will enhance DC function and presentation of tumor antigens by human DCs.

Expression of FcγRII receptors on myeloid and plasmacytoid DCs

Myeloid DCs
Lin⁻, HLA DR⁺, CD11c⁺



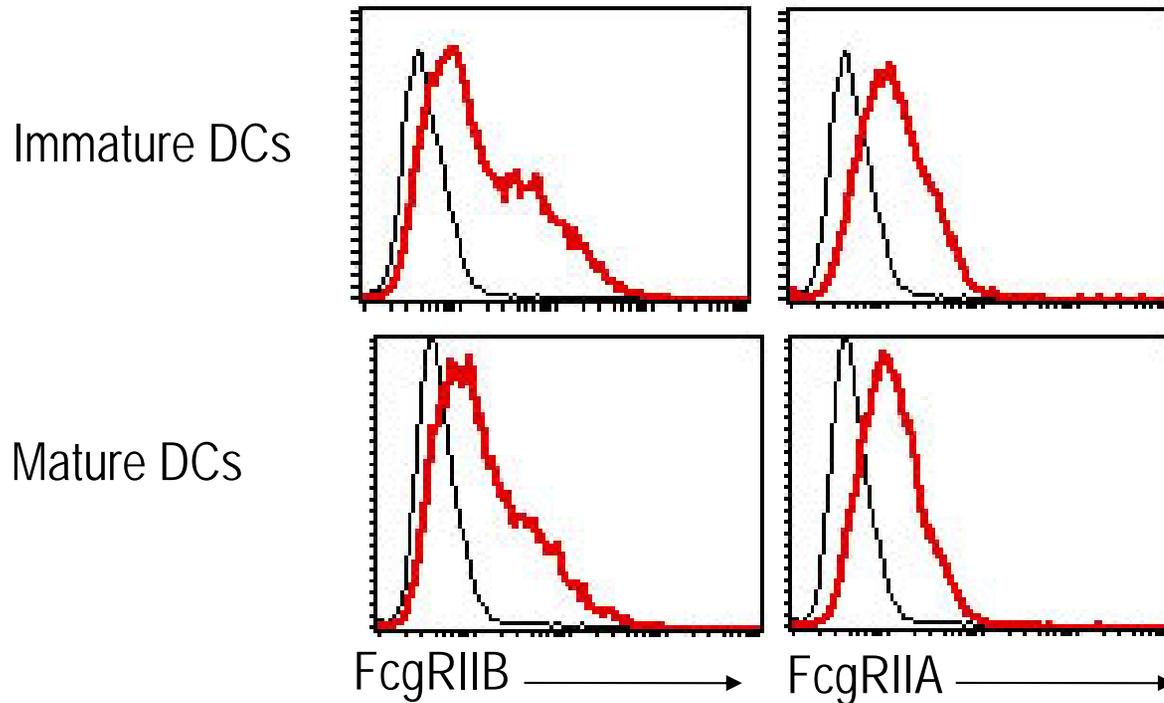
Plasmacytoid DCs
Lin⁻, HLA-DR⁺, CD123⁺



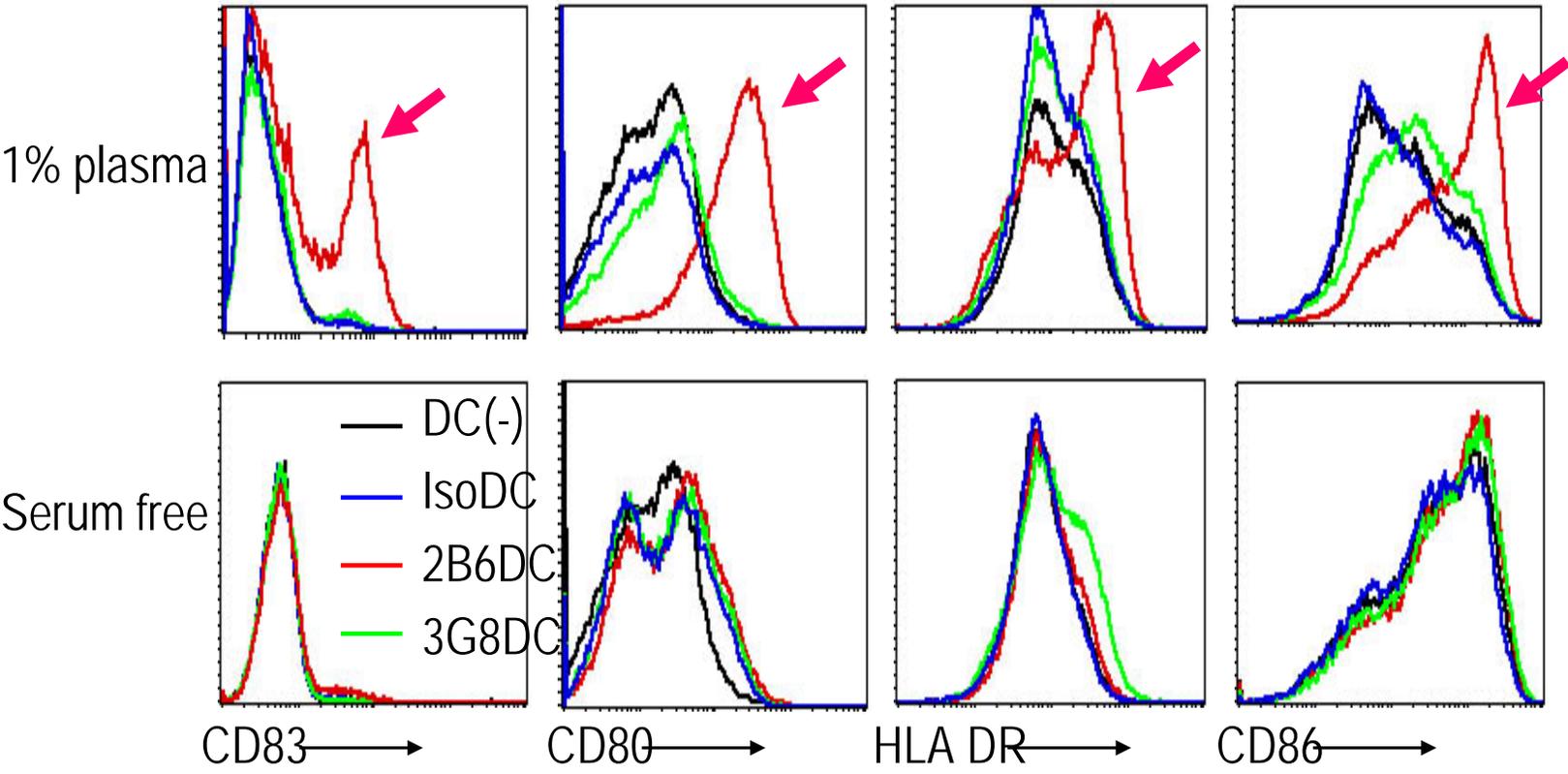
→ FcγRIIB

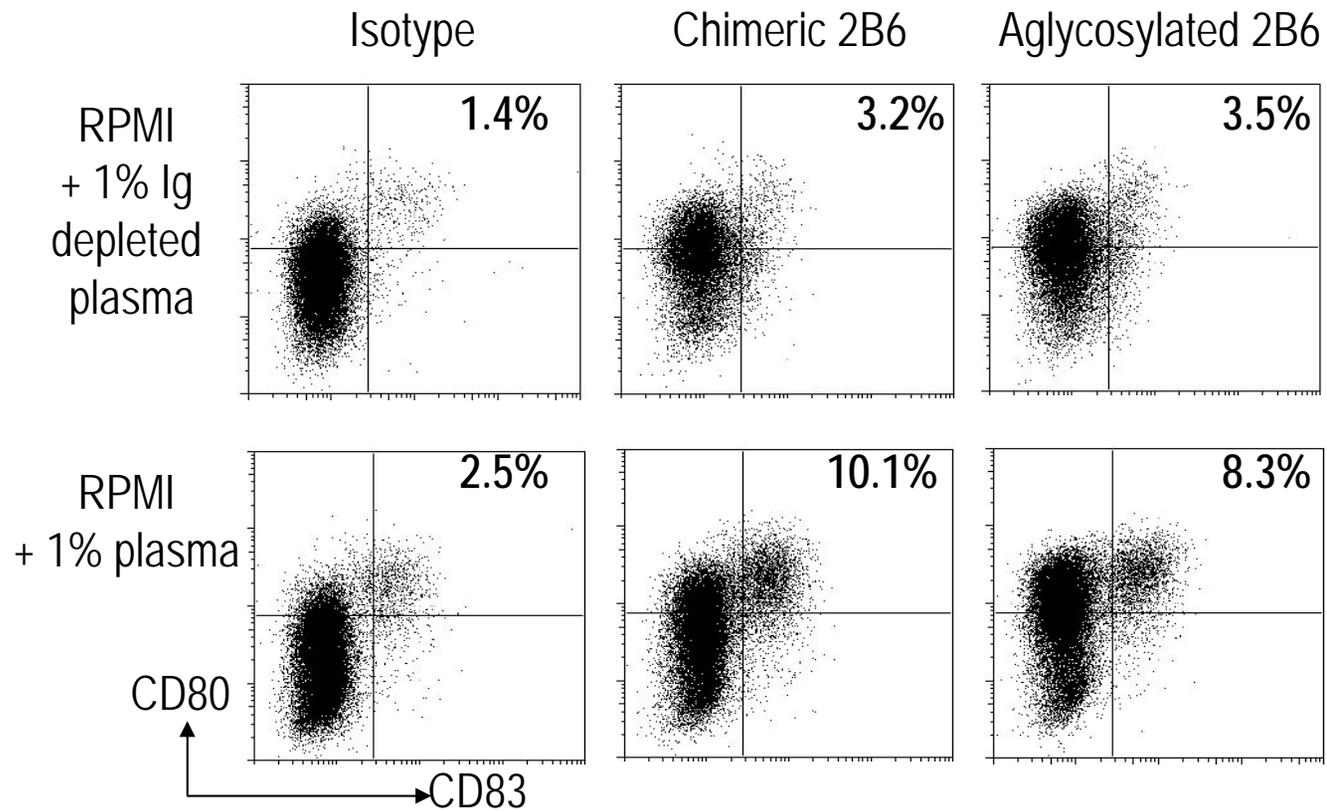
→ FcγRIIA

Both Immature and Mature Monocyte Derived DCs Express Both Activating and Inhibitory forms of Fc γ RII

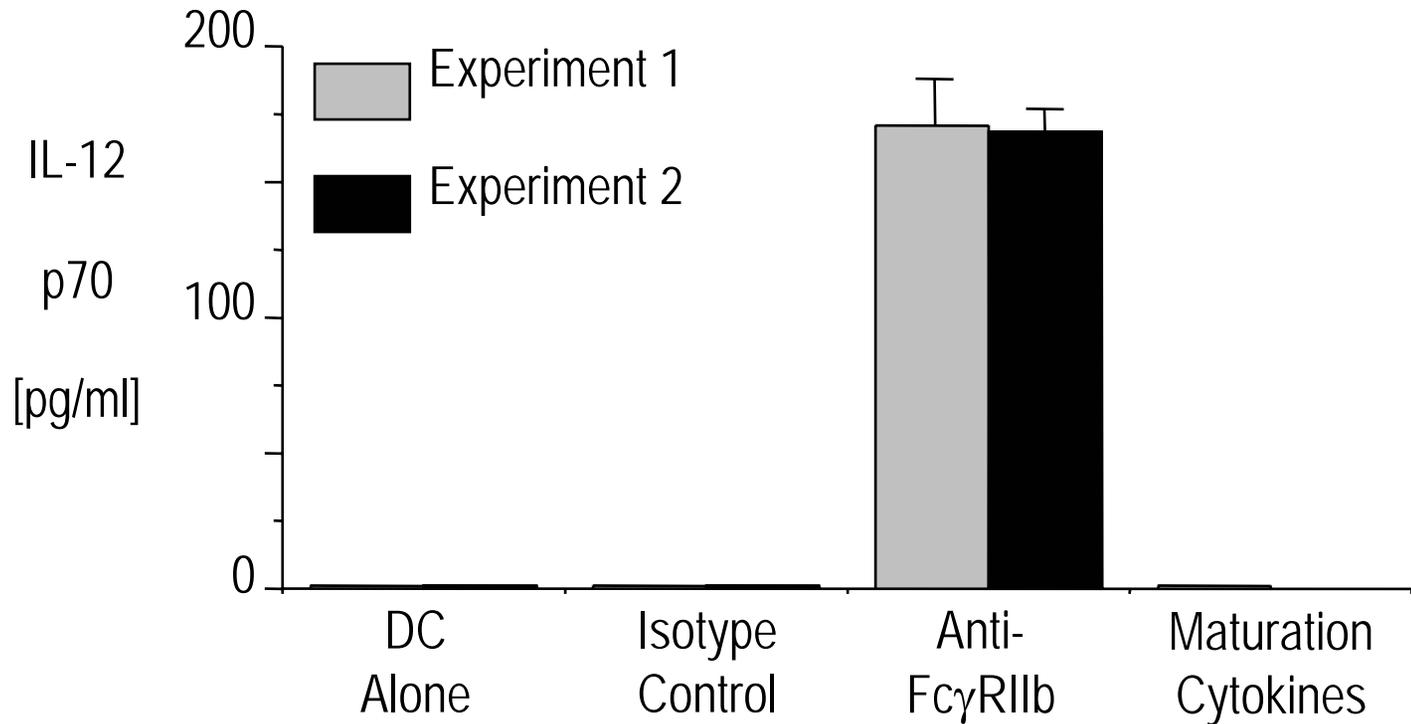


Selective blockade of inhibitory Fcγ receptor leads to DC maturation in the presence of normal human plasma

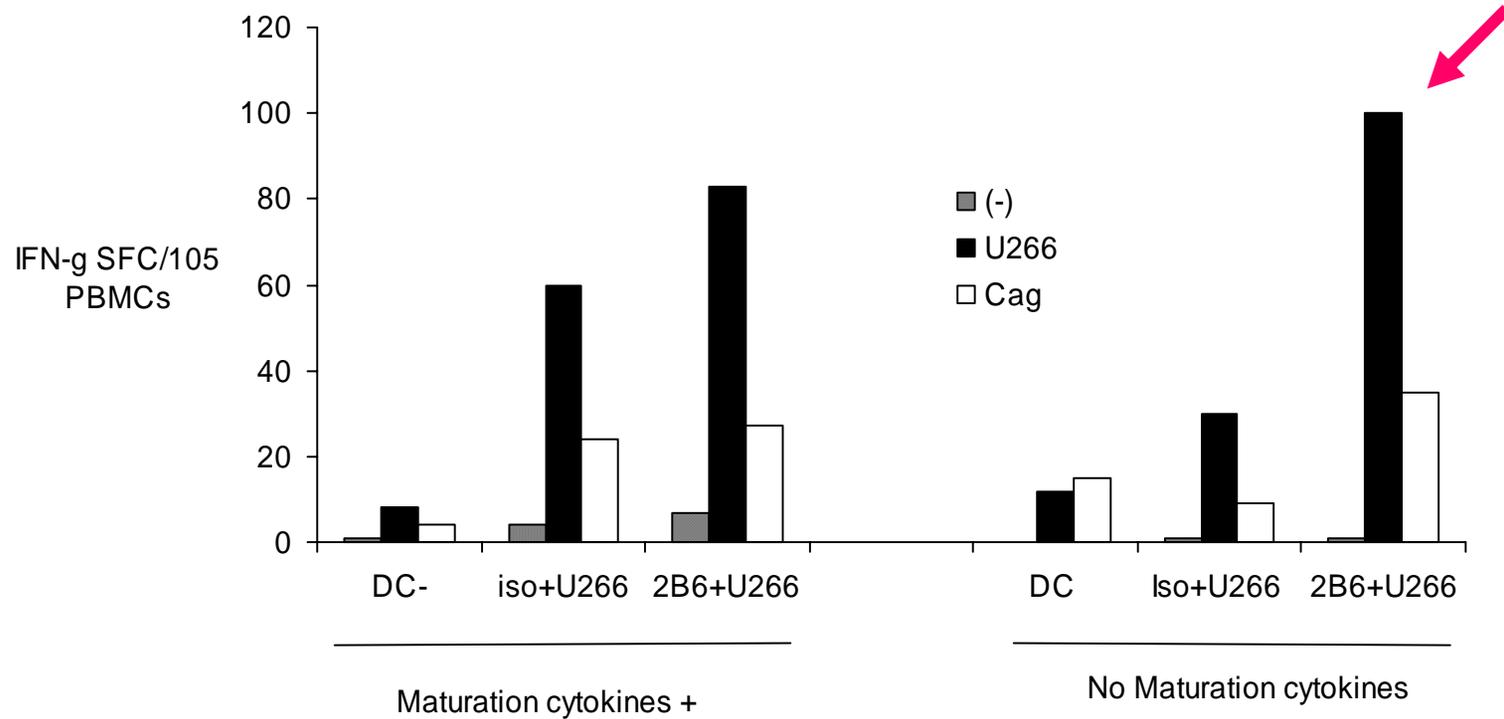




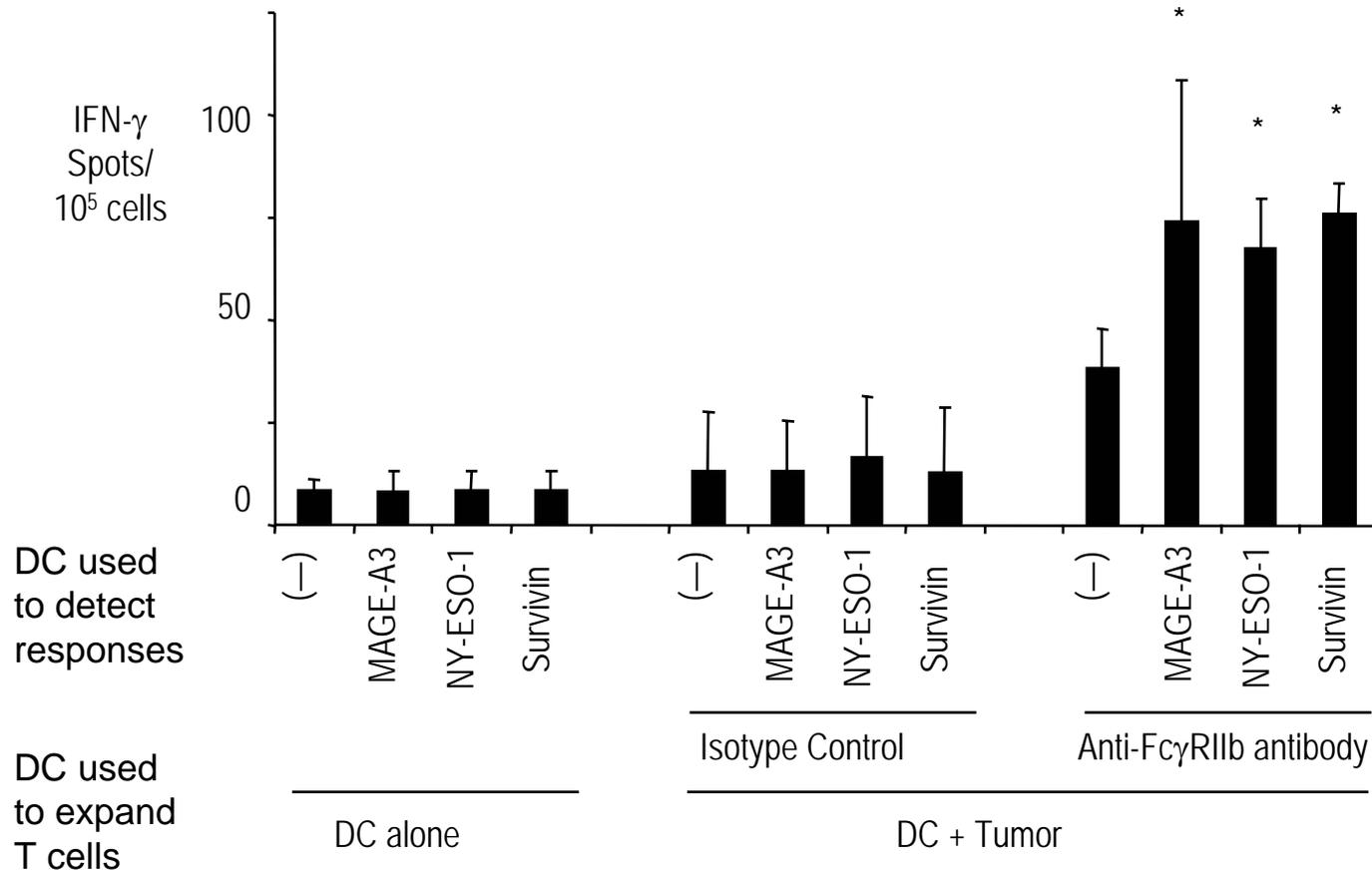
Selective blockade of inhibitory Fc γ receptor on purified DCs Leads to Induction of IL-12p70 production



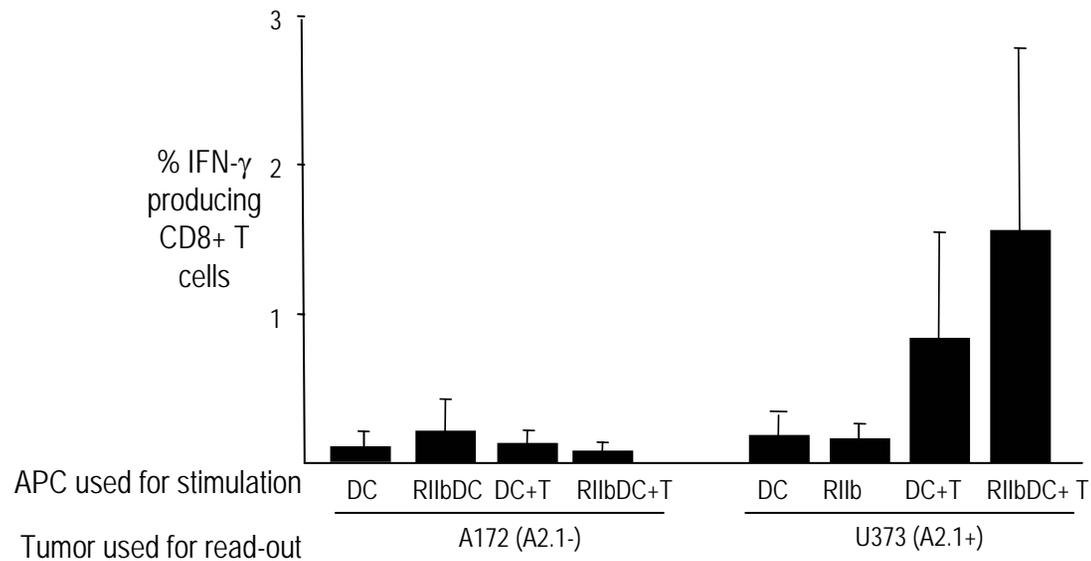
Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fcγ receptors on Human DCs



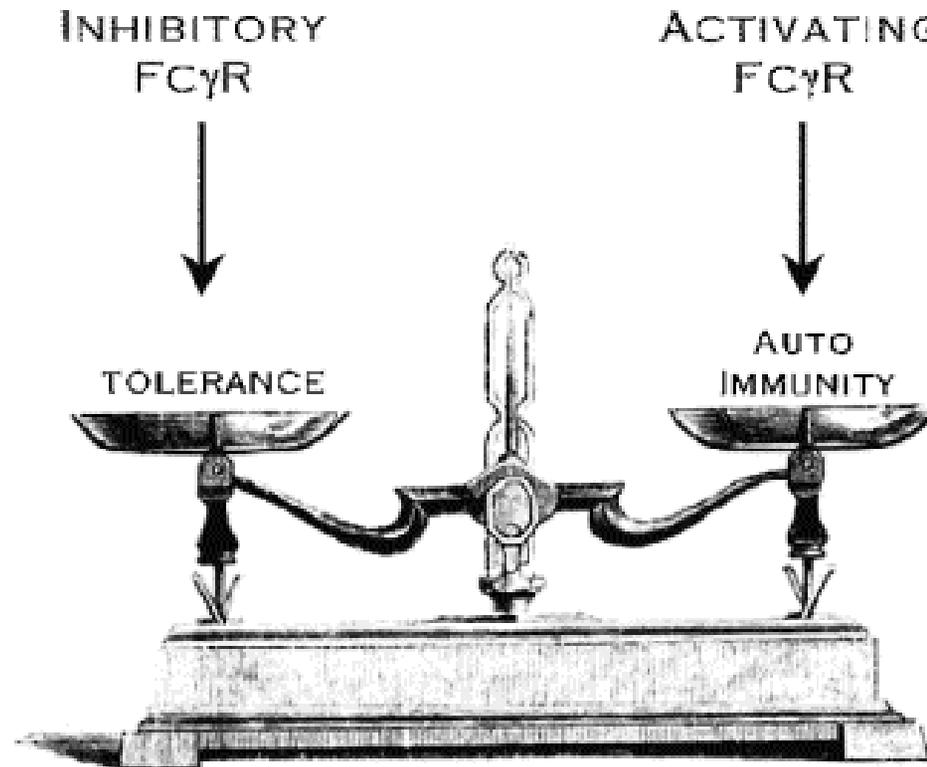
Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fc γ receptors on DCs



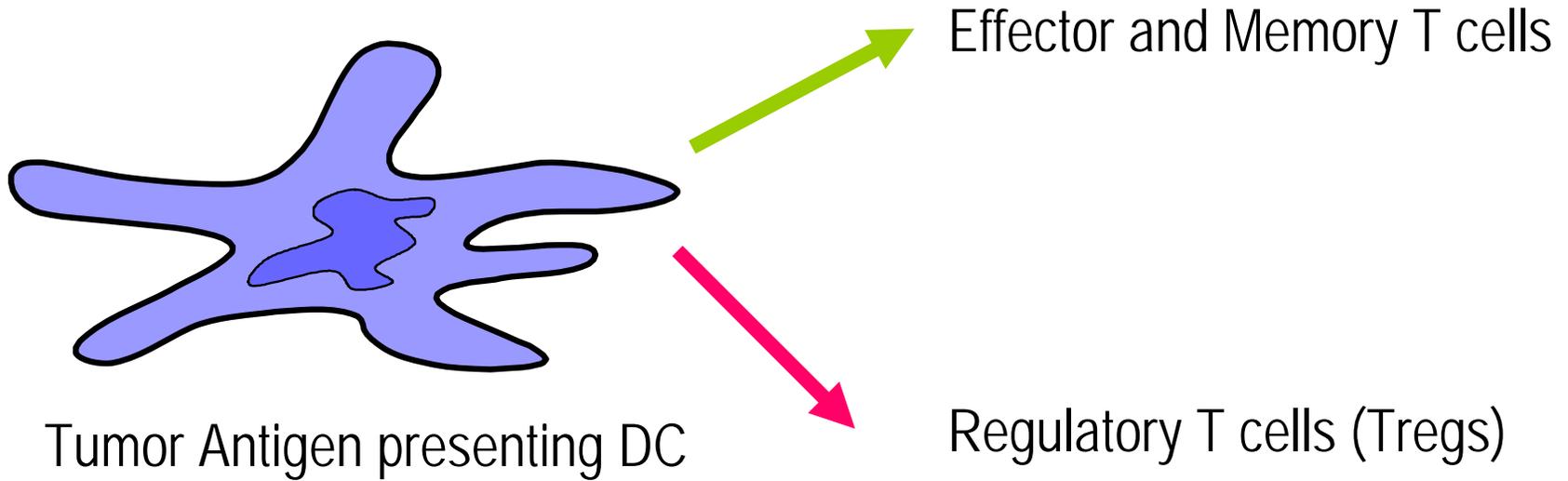
Blockade of Fc γ RIIB leads to induction of anti-glioma immunity without the need for exogenous maturation stimulus



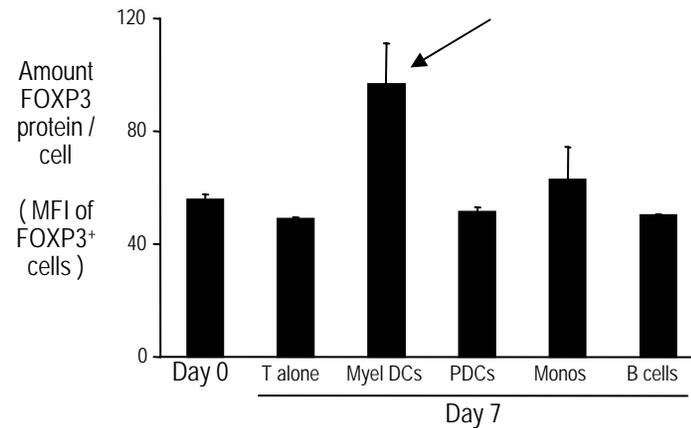
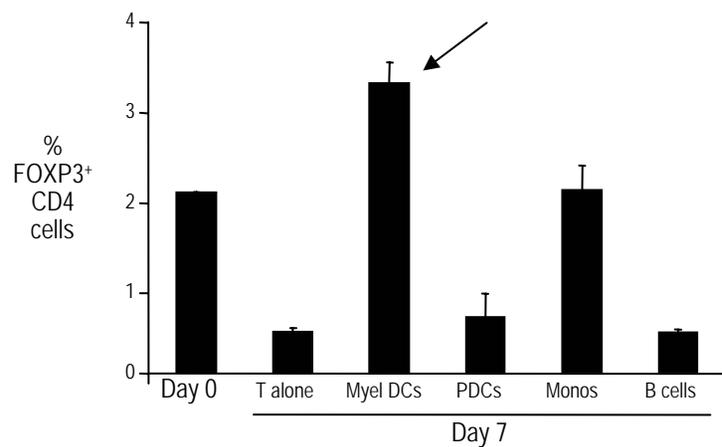
DC Function Is Modulated by a Balance Between Activating and Inhibitory Fc Receptors



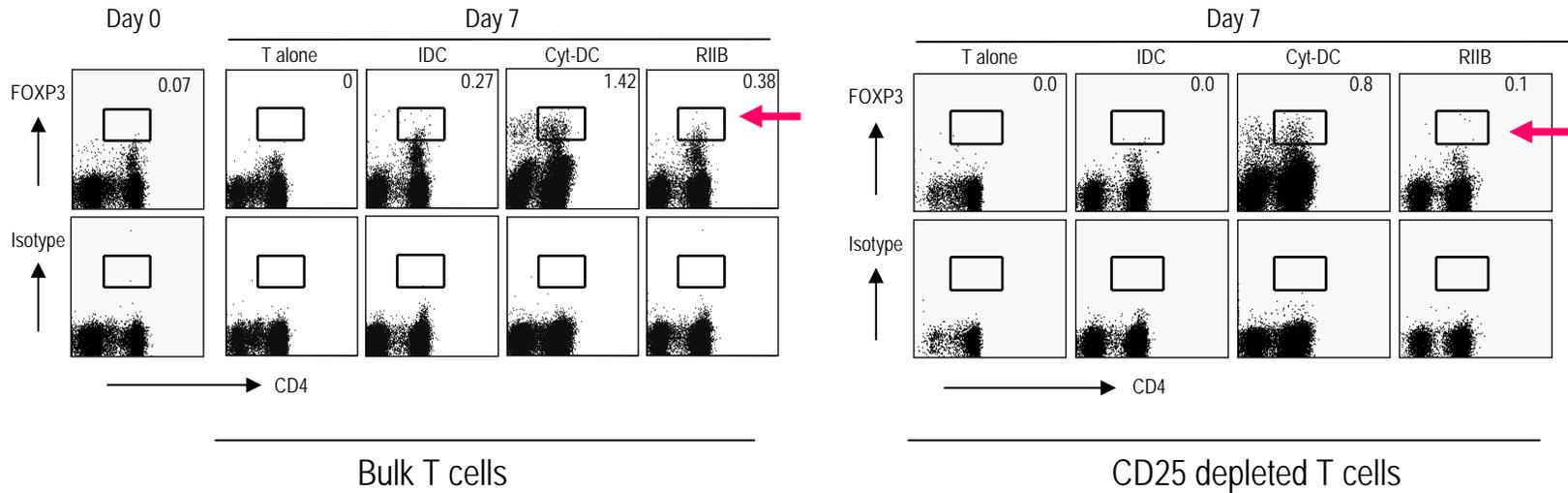
Balance Of Effector Versus Tregs As A Determinant Of Vaccine Efficacy



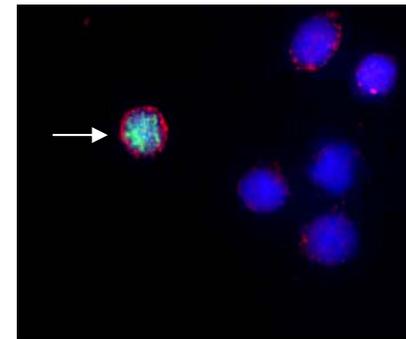
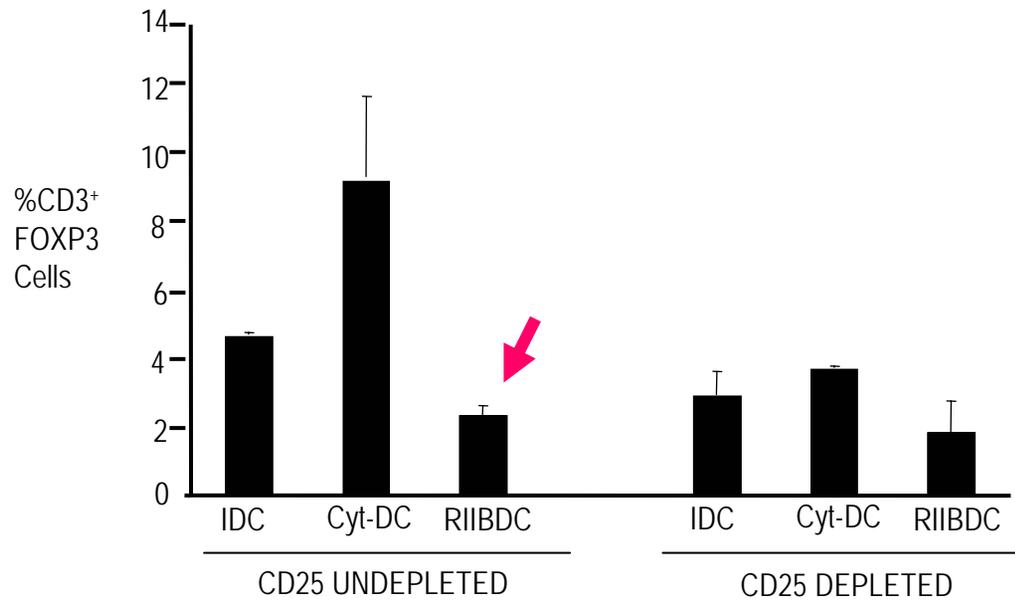
Efficiency of DCs for expansion of Human FOXP3+ Tregs



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



Expansion of FOXP3+ 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 γ R mediated enhancement of dendritic cell function.

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