FcγR Mediated Regulation of Adaptive Immunity: Implications for Antibody Therapies

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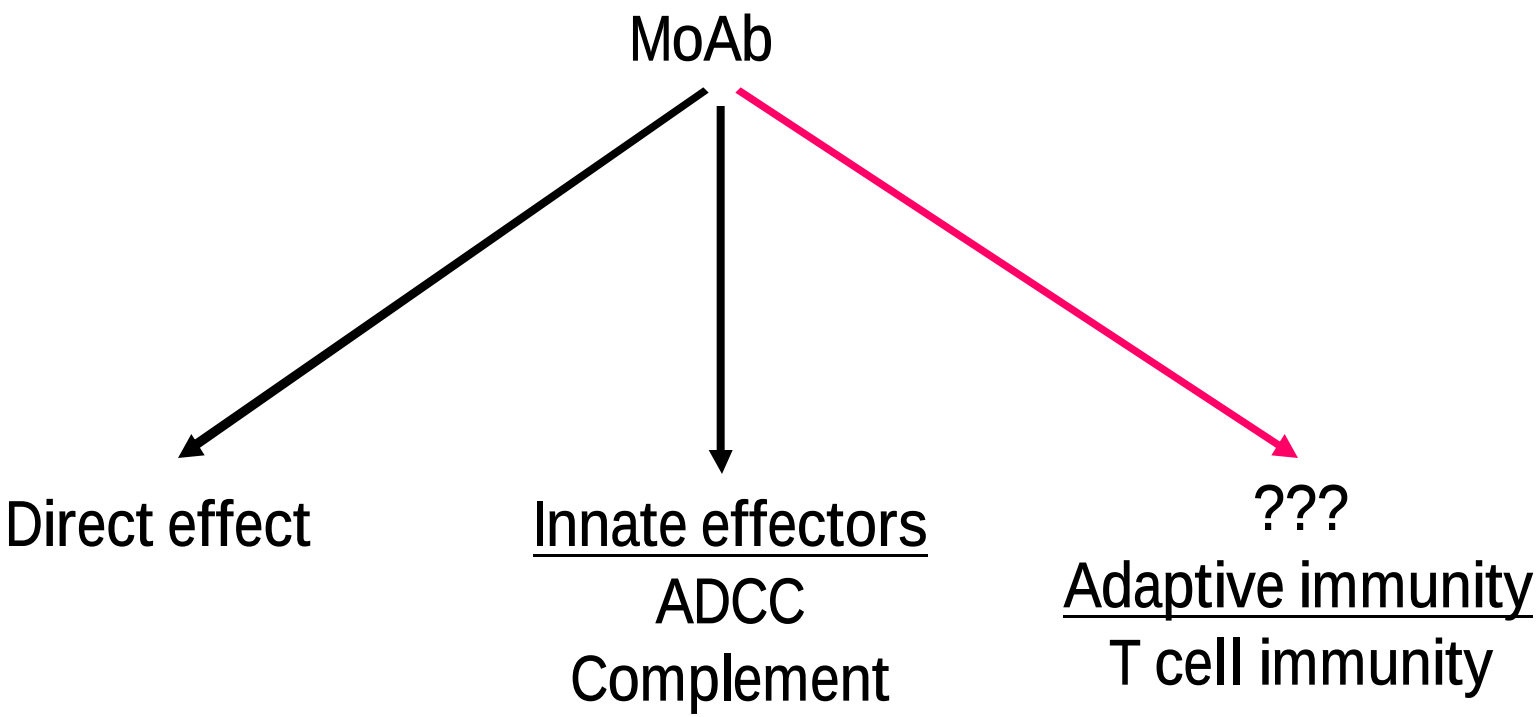
- mAb mediated enhancement of T cell immunity.
- Effect of activating / inhibitory FcγR balance on DC activation and T cell immunity.
- Induction of adaptive immunity in patients treated with mAb therapy

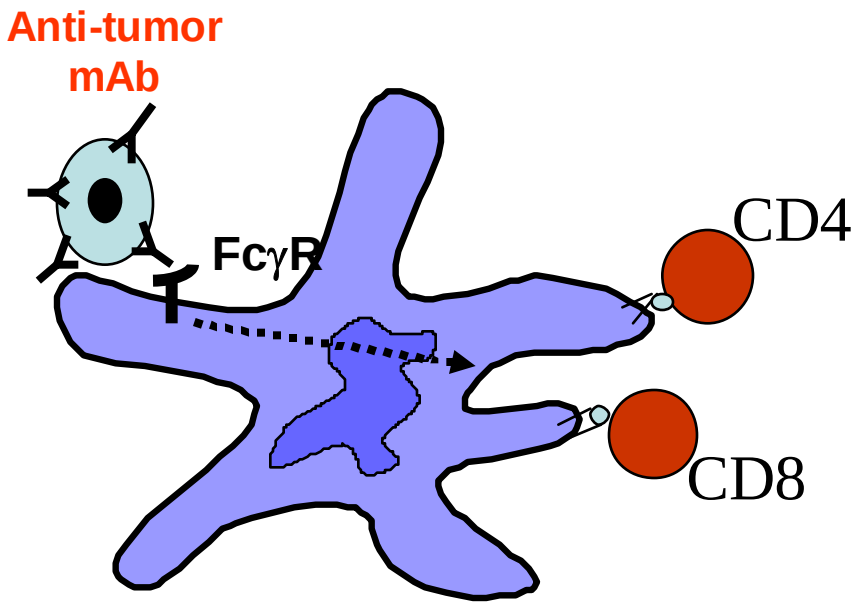
Mechanisms of Anti-tumor Effects of MoAbs



Why Harness MoAbs to Elicit Adaptive Immunity

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

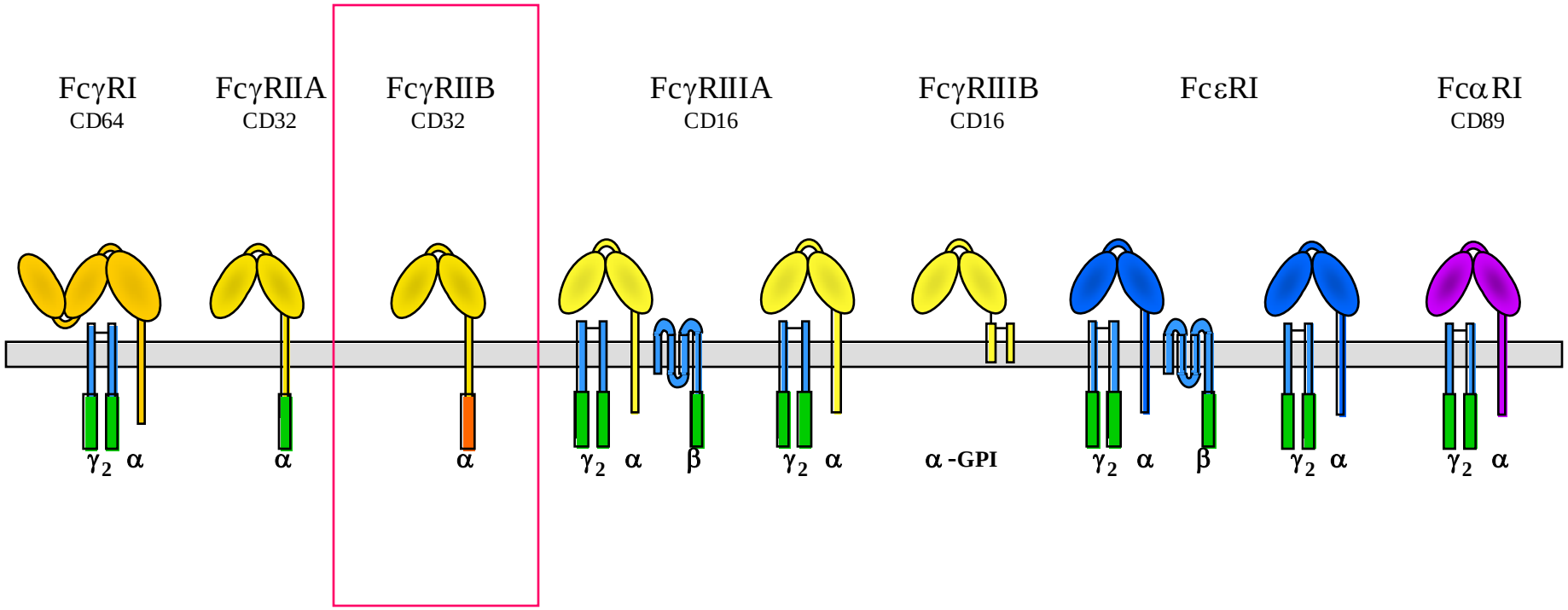
Targeting tumor antigens to Fcγ receptors of dendritic cells via anti-tumor monoclonal Ab enhances anti-tumor immunity



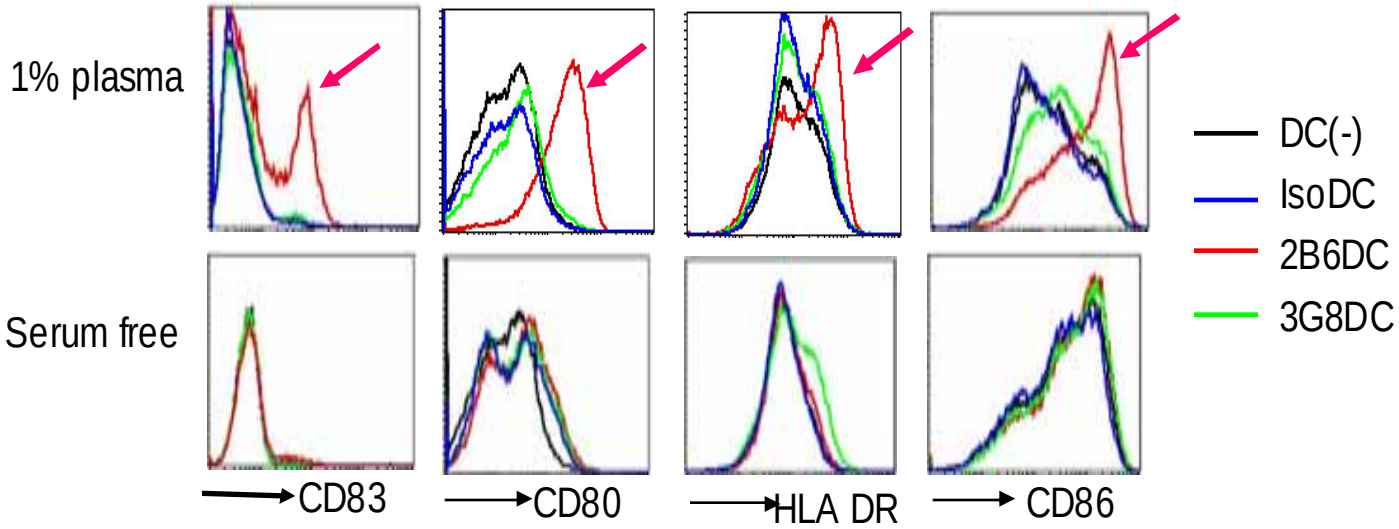
•The enhanced presentation requires presence of Fcγ receptors on DCs.

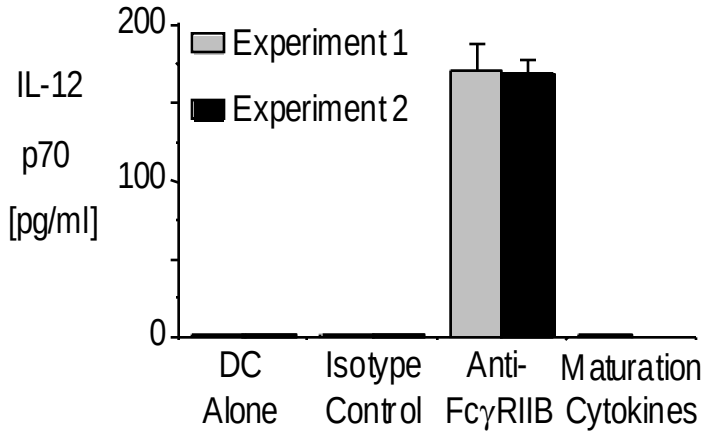
J Exp Med 195:125, 2002

Human Fcγ Receptors



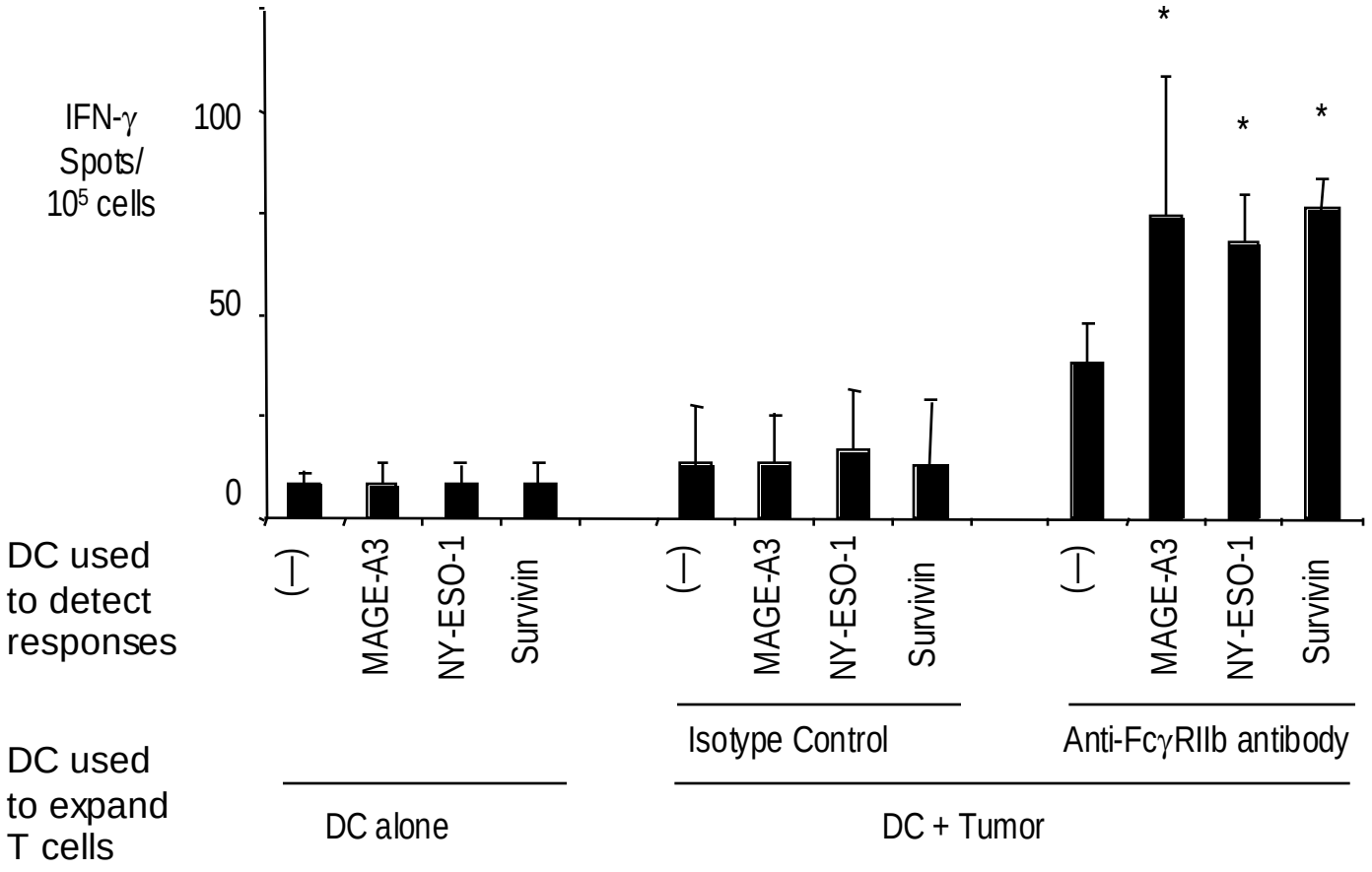
Selective blockade of inhibitory Fcγ receptor leads to DC maturation and induction of IL12p70 in the presence of normal human plasma



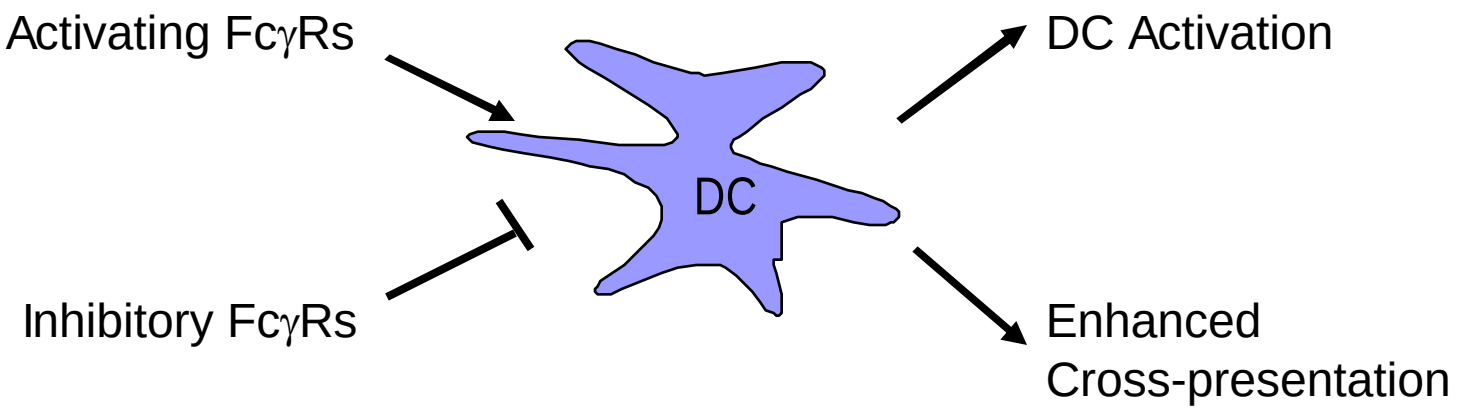


Dhodapkar et al. PNAS 2005

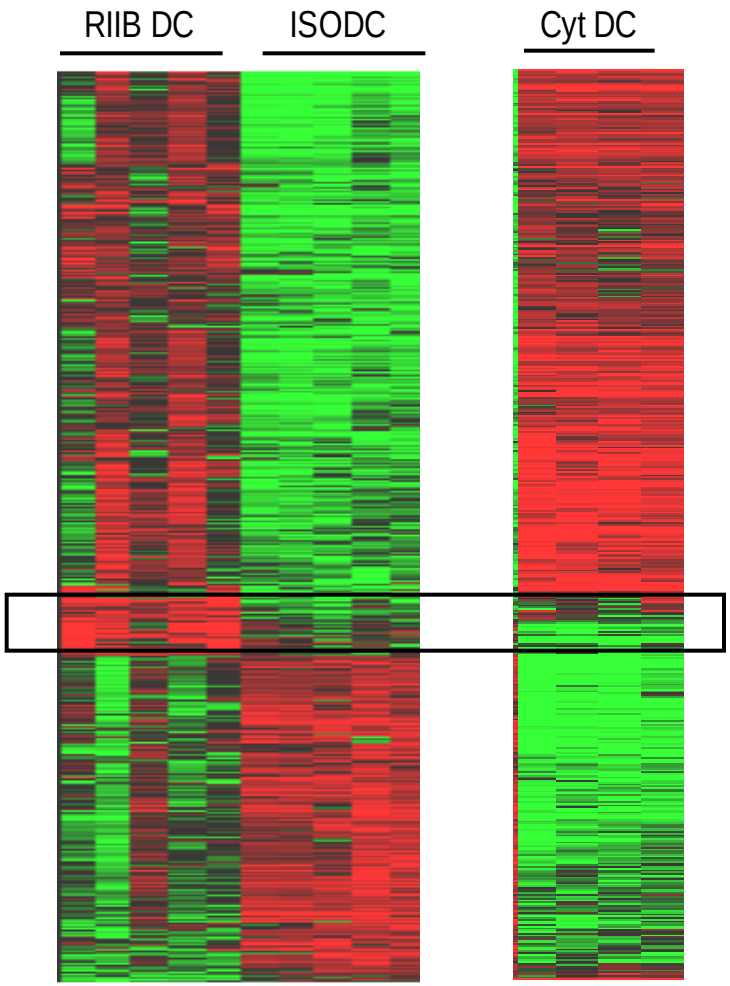
Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fcγ receptors on DCs



Balance of Activating / Inhibitory FcγRs As A Checkpoint for Regulating Ag Presentation



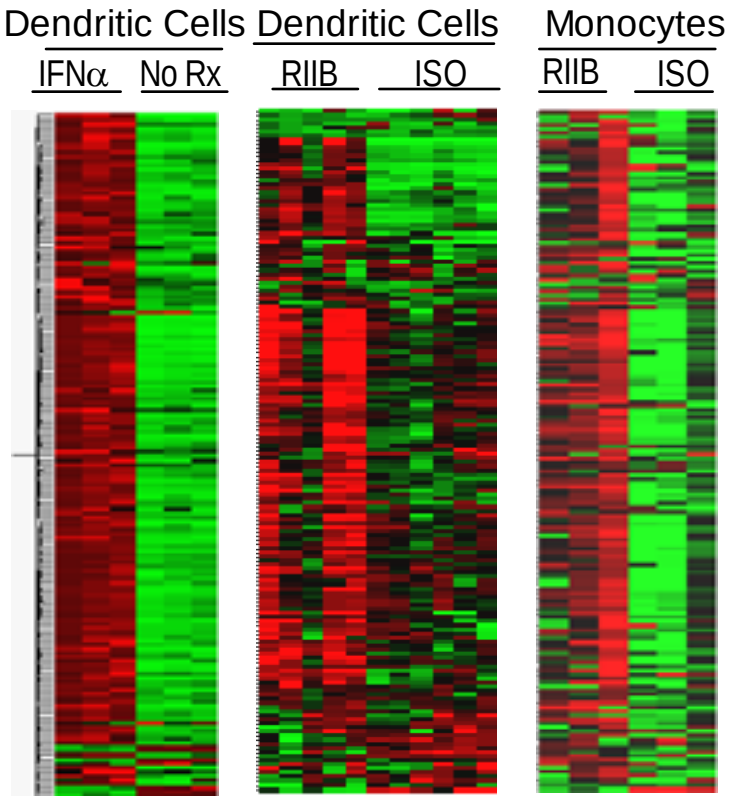
Selective Blockade Of Inhibitory FcγRIIB On Human DCs Leads To A Distinct Gene Expression Profile

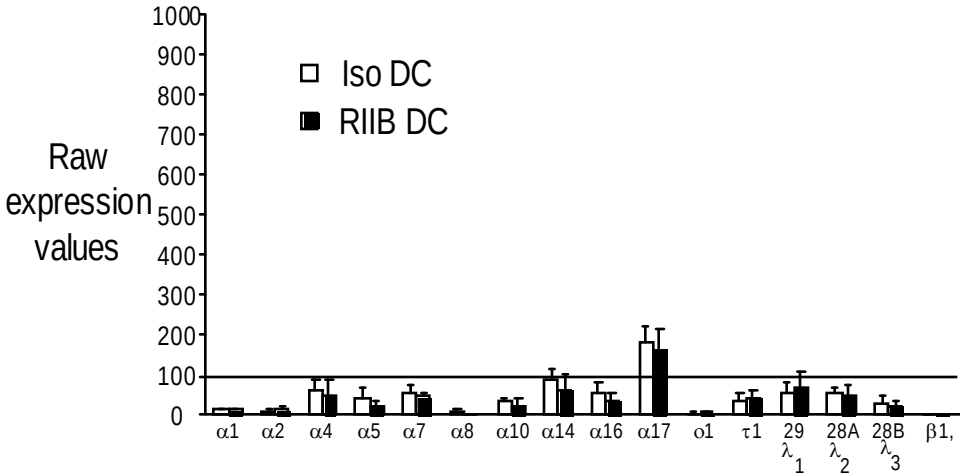


- Inflammation associated cytokines / chemokines
- FcR / complement related genes

- Type I IFN response genes

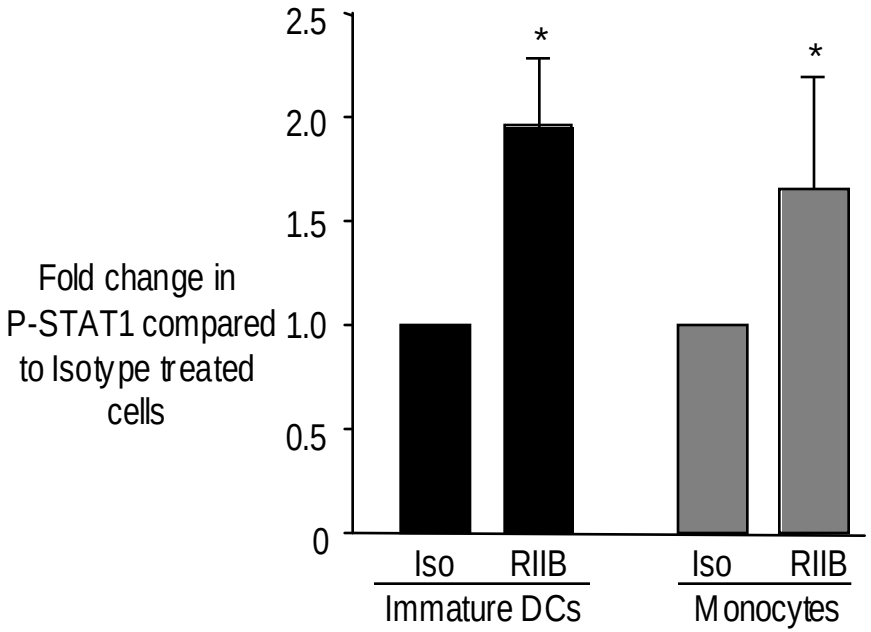
Selective blockade of inhibitory FcγRs on human DCs and monocytes leads to the Induction of type I IFN responses genes

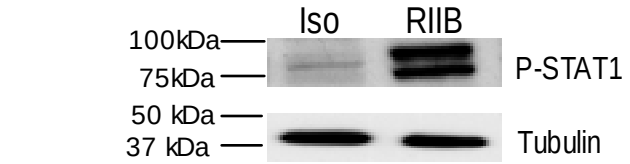


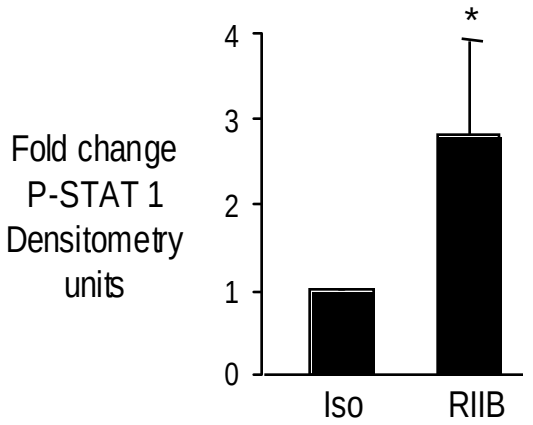


…but no increase in expression of type I interferons themselves !!! (including α, β, ω, τ, IFN28A, IFN28B, IFN29).

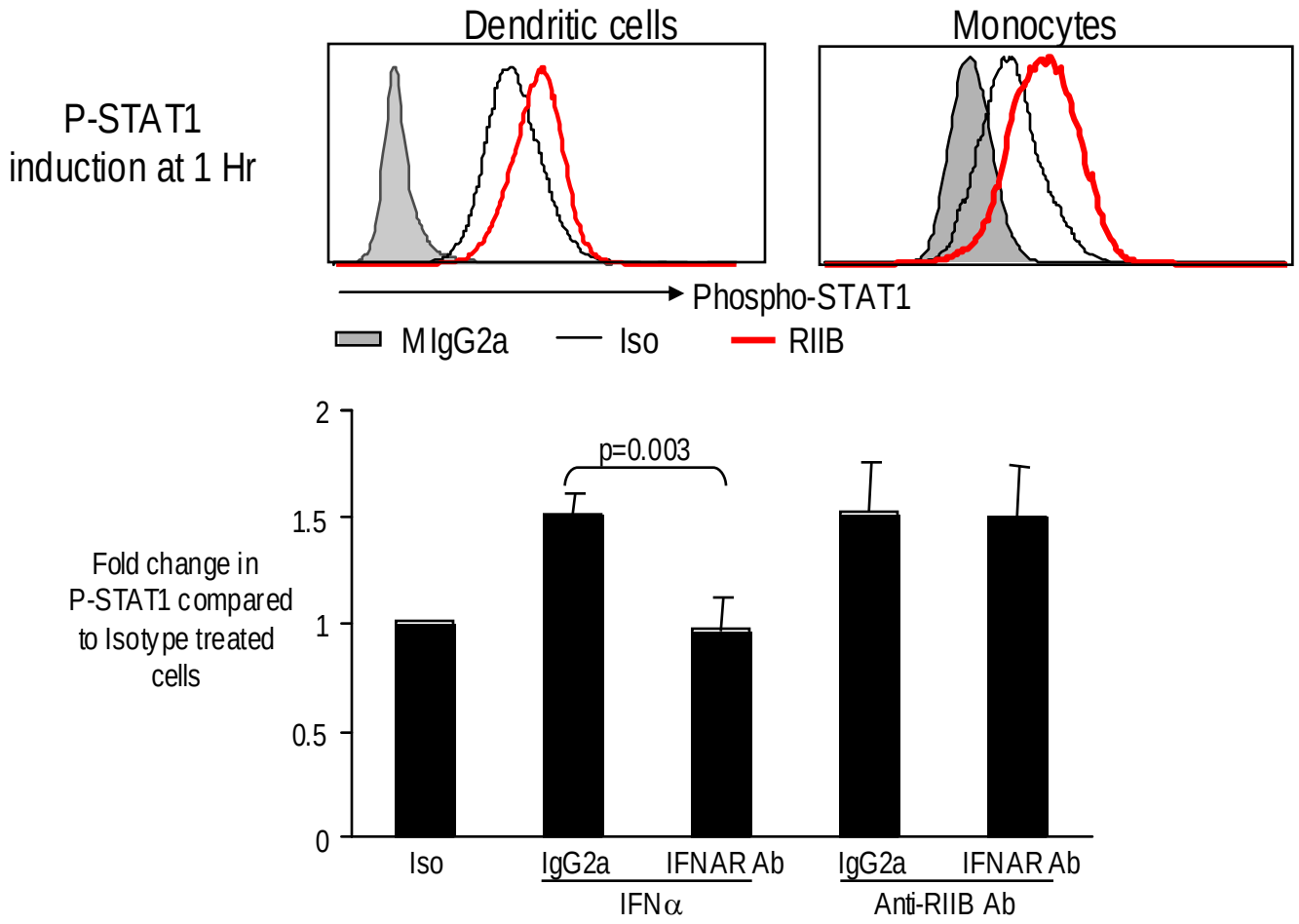
Blocking the inhibitory Fc receptor on DCs leads to induction of Phospho-STAT1





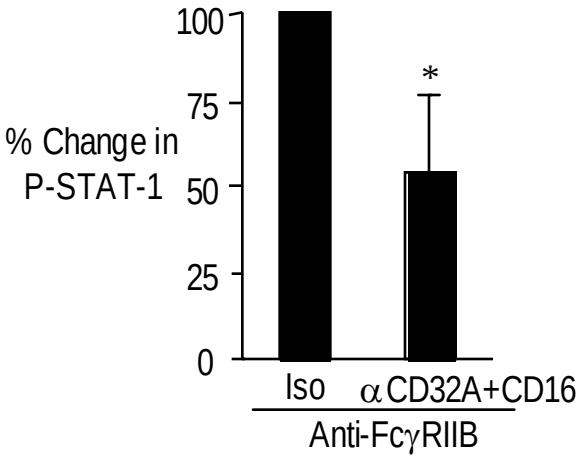


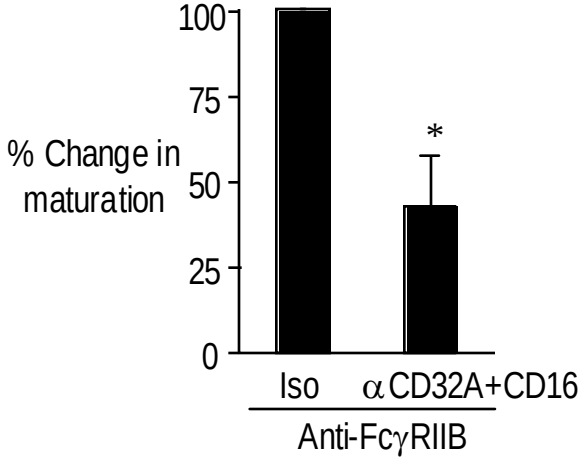
FcγR mediated induction of P-STAT1 is rapid and not blocked by anti-IFN Abs

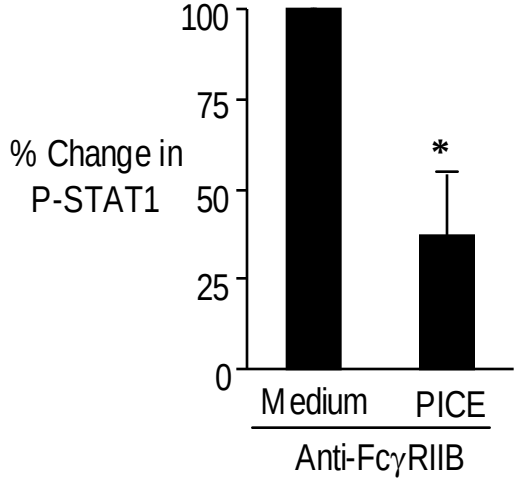


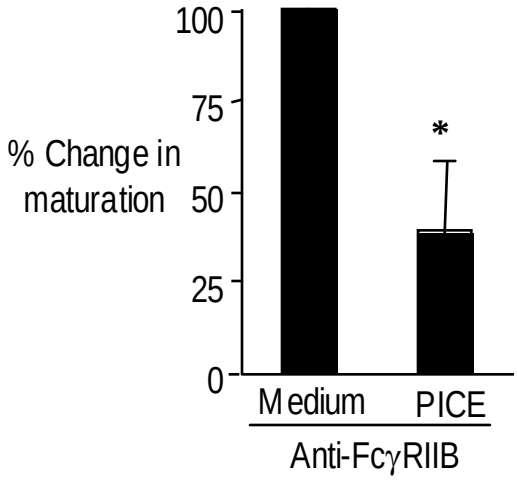
Similar result with anti-IFNα and anti-IFNγ antibody

Suppression of FcγR mediated induction of P-STAT1 by blockade of activating FcγRs and Syk inhibition

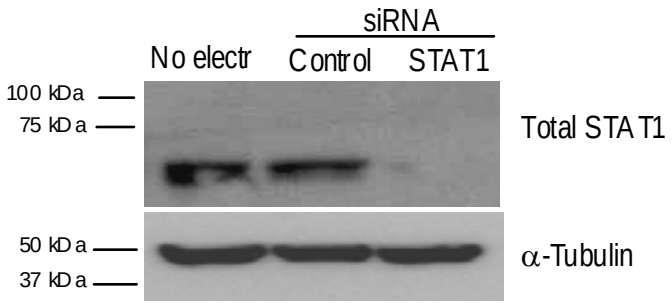


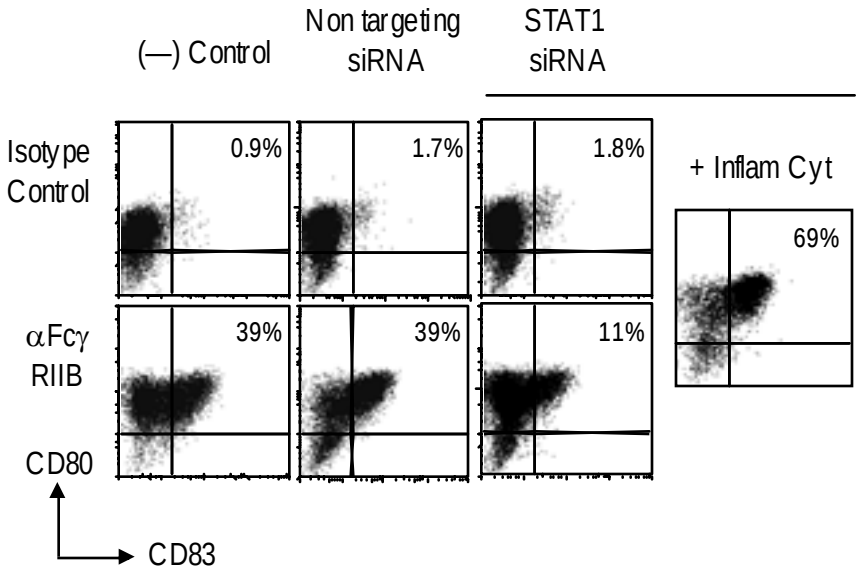






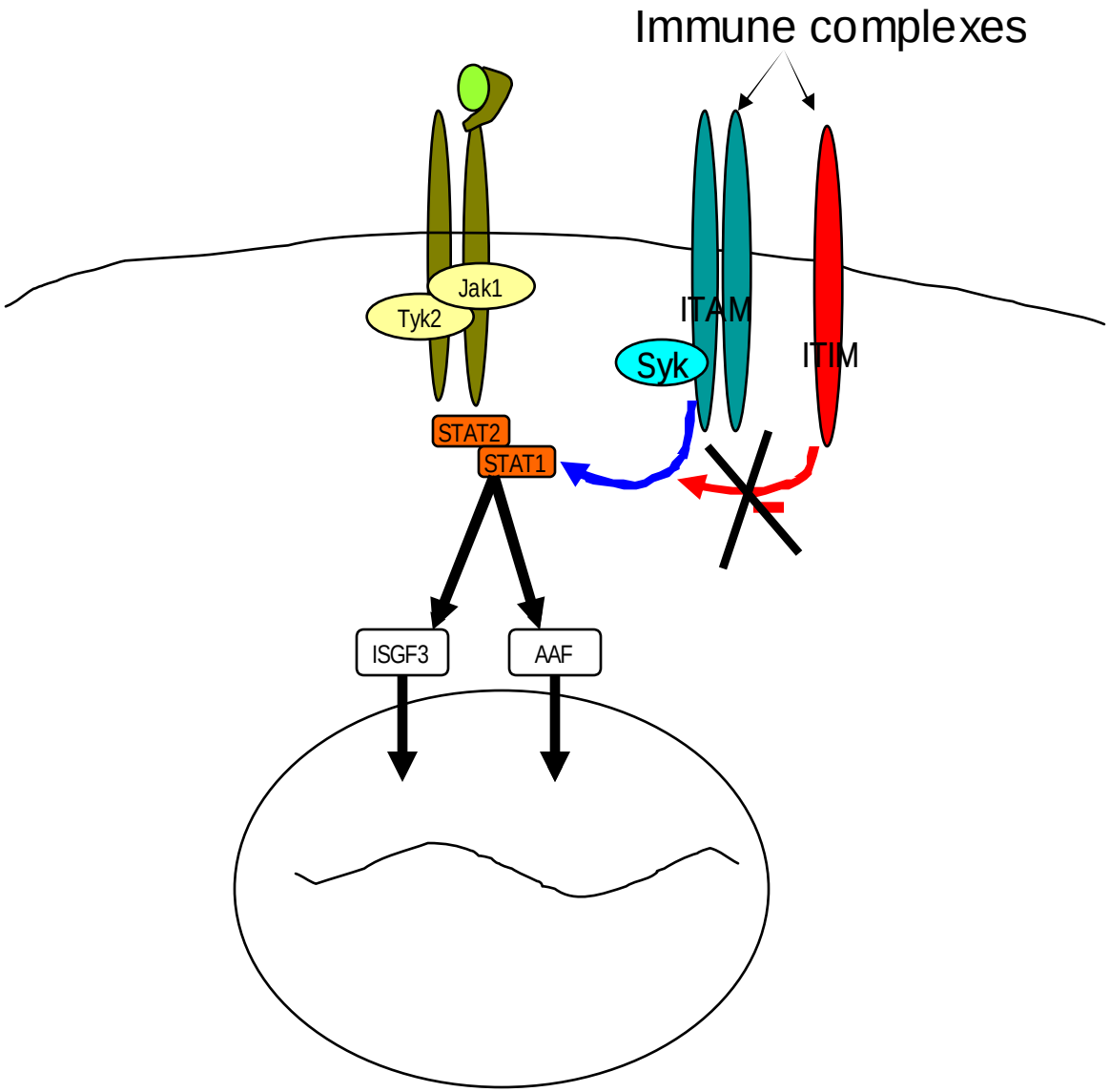
Knockdown of STAT1 inhibits FcγR mediated DC maturation



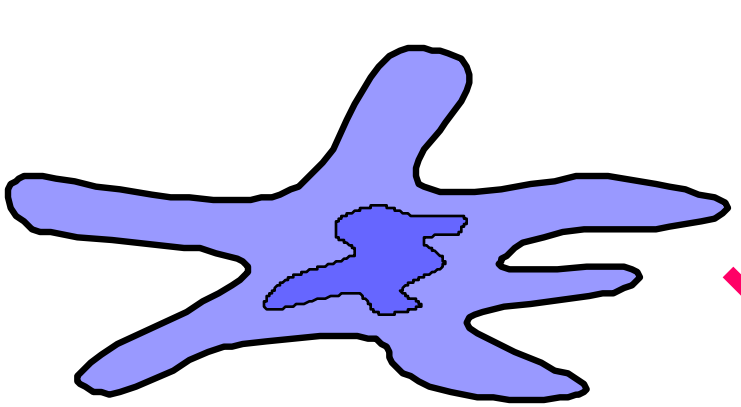


Dhodapkar et al, J Exp Med 2007

Linking FcγR signaling to IFN pathway



Balance Of Effector Versus Tregs As A Determinant Of Vaccine Efficacy

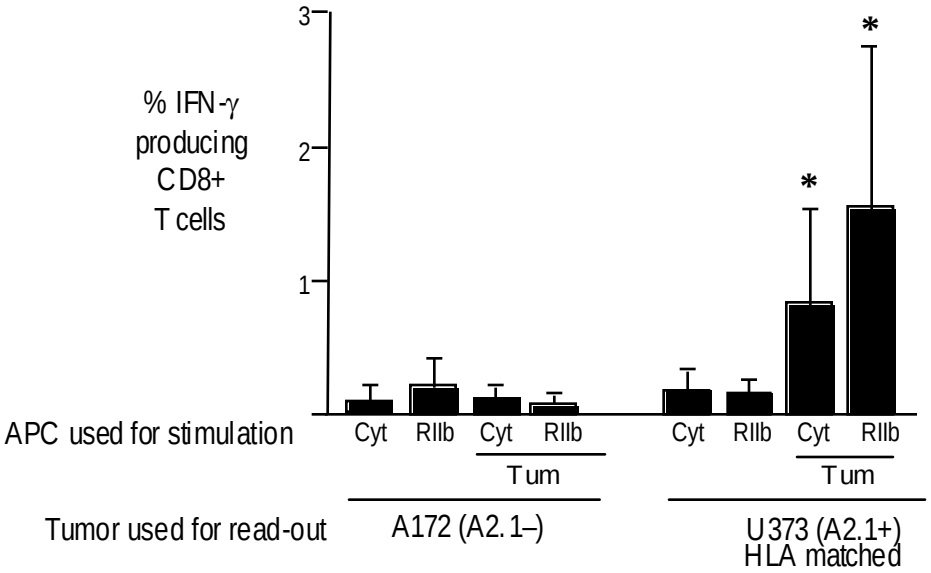


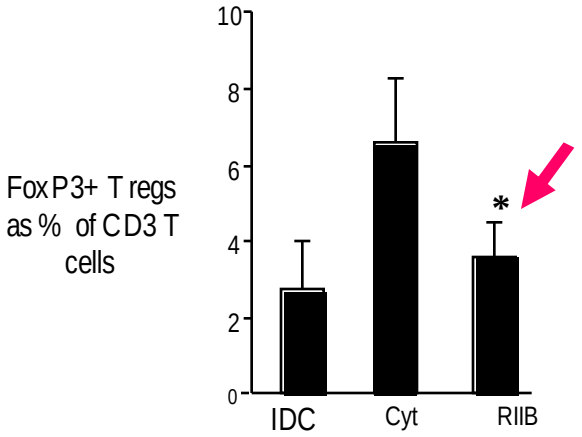
Tumor Antigen presenting DC

Effector and Memory T cells

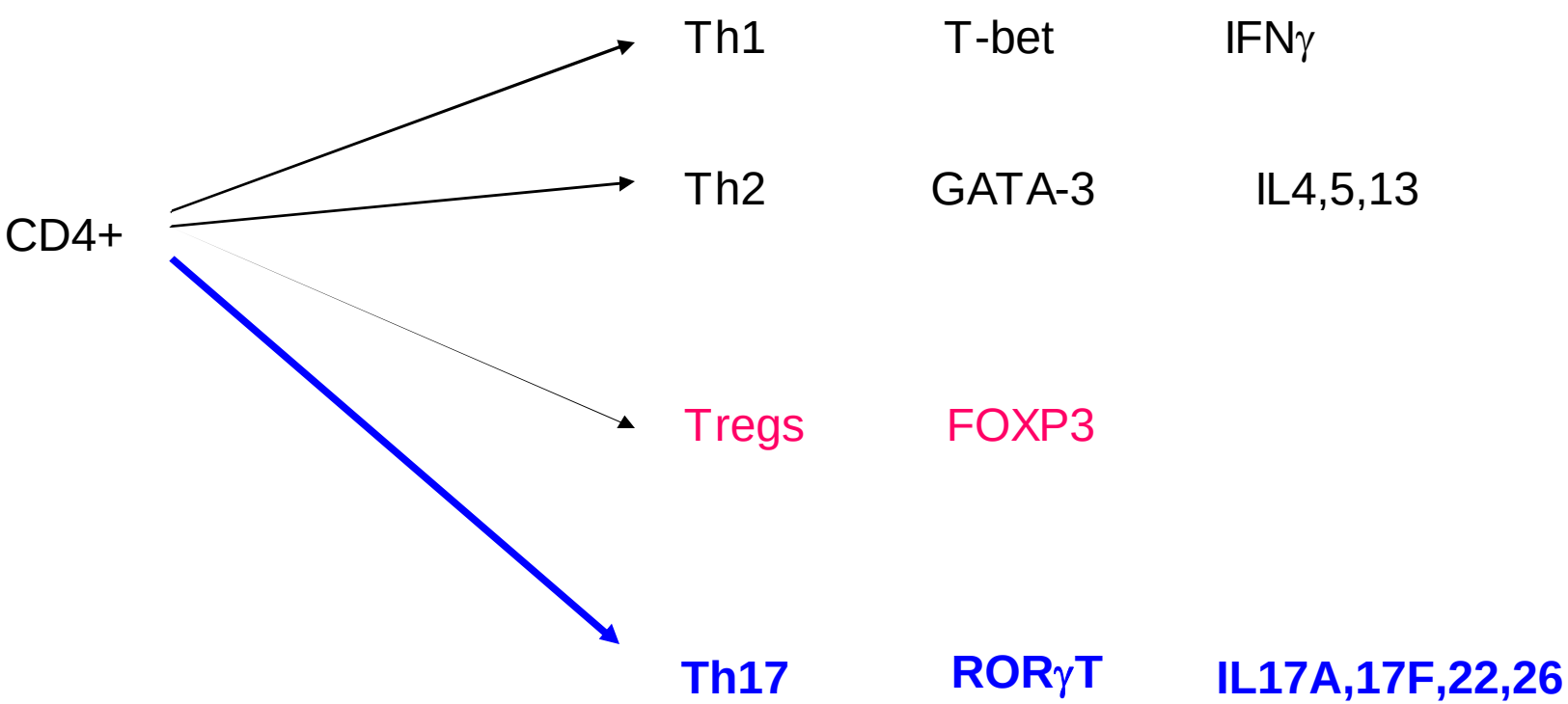
Regulatory T cells (Tregs)

FcγR matured DCs induce T effectors with less induction of FoxP3 Tregs





Functional Diversity of T cell Response



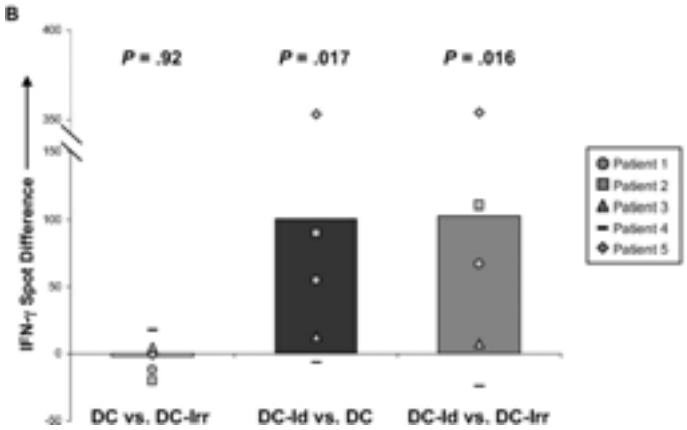
Expression of cytokines/chemokines in response to treatment with 2B6Ab (RIIBDC), isotype control antibody (IsoDC) IgG1 and inflammatory cytokines (CC-DC).

	IsoDC	RIIBDC	CC-DC	RIIBDCvs IsoDC	RIIBDC vs CC-DC
IL-1a	57.19 (29.4)	**699.5(184.4)**	87.6(80.8)	**0.0002**	**0.0005**
IL-1b	11(15.6)	**668.9(780)**	NE	**0.071**	NE
IL-2	10.2(4.1)	14.3 (4.7)	21.9(14)	0.120	0.170
IL-3	102.2(16.2)	176 (56.5)	137.6(35.5)	0.023	0.147
IL-5	0(0)	0.0	0(0)	0.000	0.000
IL-6	229.6(142.6)	**7941.8(4116.4)**	NE	**0.005**	NE
IL-7	0.1 (0.2)	27(3.8)	16.4(12.7)	0.000	0.080
IL-8	628.1(408.1)	**10000(0)**	5727(4992.1)	0.000	**0.069**
IL-10	22.5(2.8)	**1200.9(987.5)**	108.6(111.5)	**0.027**	**0.035**
IL-12p40	40.5(28.4)	**4713.3(5019.4)**	3191(4483.3)	**0.056**	0.333
IL-12p70	15.9(16.6)	**148.2(148.5)**	29(20.1)	**0.064**	**0.082**
IL-13	8.9(3.4)	28.9 (21.1)	39.7(47.2)	0.055	0.345
IL-15	3.8(7.7)	0.9 (1.8)	0(0)	0.242	0.178
IFNg	116.5(8.8)	**264.2(61.1)**	198.3(81.6)	**0.002**	0.122
TNFa	5.3(6.3)	**1059.8(911.3)**	NE	**0.030**	NE
Eotaxin	15.5(19.2)	35(11)	43.1(14.5)	0.065	0.204
MCP1	1173.1(1074)	2776.34(2655.6)	1314.8(1908.4)	0.153	0.203
Rantes	27.8(16.5)	**1531(682)**	264.8(356.3)	**0.002**	**0.008**
MIP1α	710.6(351.3)	**9746.9(388)**	3067.8(2733.7)	**< 0.0002**	**0.001**
IP10	395.3(185.4)	**8629.8(2364.7)**	637.9(664.9)	**0.0002**	**0.0003**
IFNa	10.2(9.9)	10.3(12.5)	28.9(15.6)	0.493	0.056

Does Antibody Therapy Lead To The Induction
Of Anti-tumor Adaptive Immunity In Vivo In Humans ?

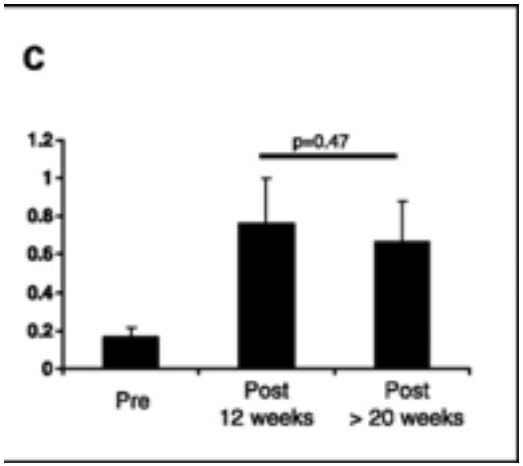
Induction of Adaptive Immunity After mAb Therapy of Cancer

Rituximab



Id specific T cell responses

Trastuzumab



Anti-HER-2/neu Igλ responses

Taylor C et al. Clin Cancer Res 2007;13:5133-5143
Hilchey, S. P. et al. Blood 2009;113:3809-3812

Conclusions

- Selective engagement of activating FcγRs leads to a distinct form of DC maturation and boosts the generation of anti-tumor immunity by human DCs
  - More anti-tumor effector T cells
  - Fewer FoxP3+ Tregs.
  - ? Increased CD8+ IL17 producing T cells

- Early evidence for induction of adaptive immunity in patients treated with anti-tumor mAbs
  - Enriched in the tumor bed.
  - Both CD4 and CD8+ T cells

- Alteration of activating / inhibitory FcγR balance may impact the ability of DCs to induce adaptive immunity in vivo in mAb treated patients
  - FcγR polymorphisms / Fc engineering

- Antibody mediated activation of tumor specific T cell responses provides an opportunity to further optimize their effects.

Acknowledgment

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