

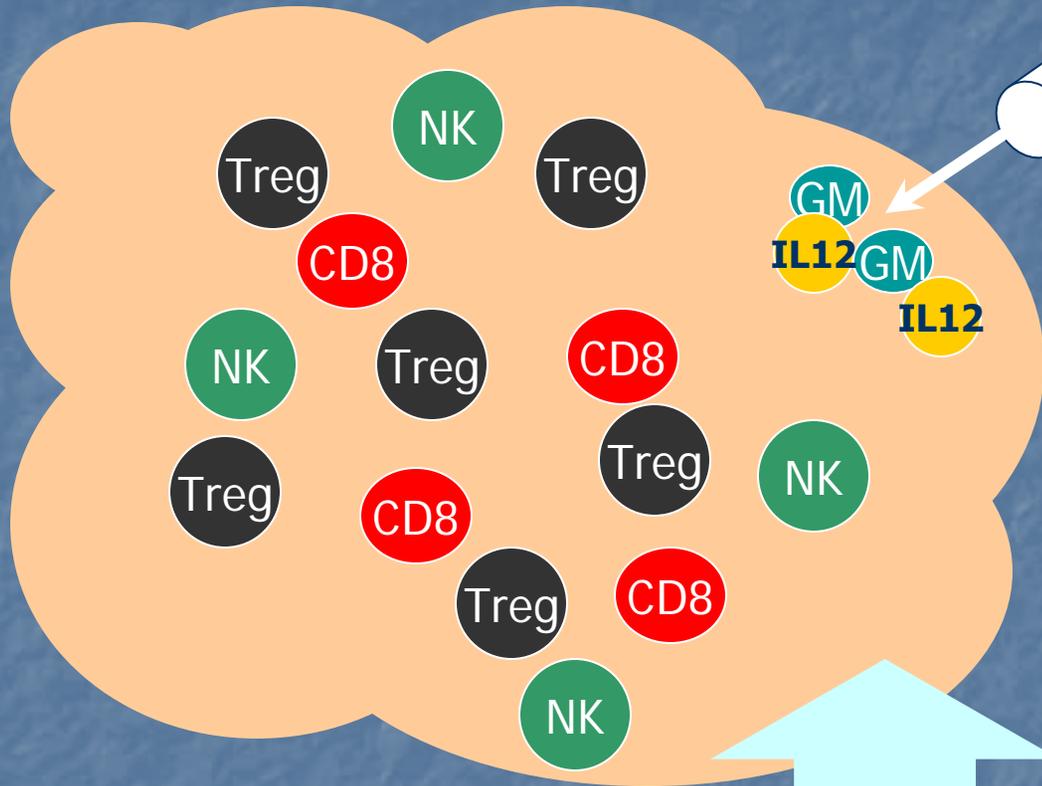
IFN-gamma is Central to Both Immunogenic and Tolerogenic Properties of Dendritic Cells After IL-12 and GM-CSF Microsphere Treatment

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Previous Data:

Tumor



GM-CSF and IL-12
Microsphere Rx

Tumor draining lymph node (TDLN)

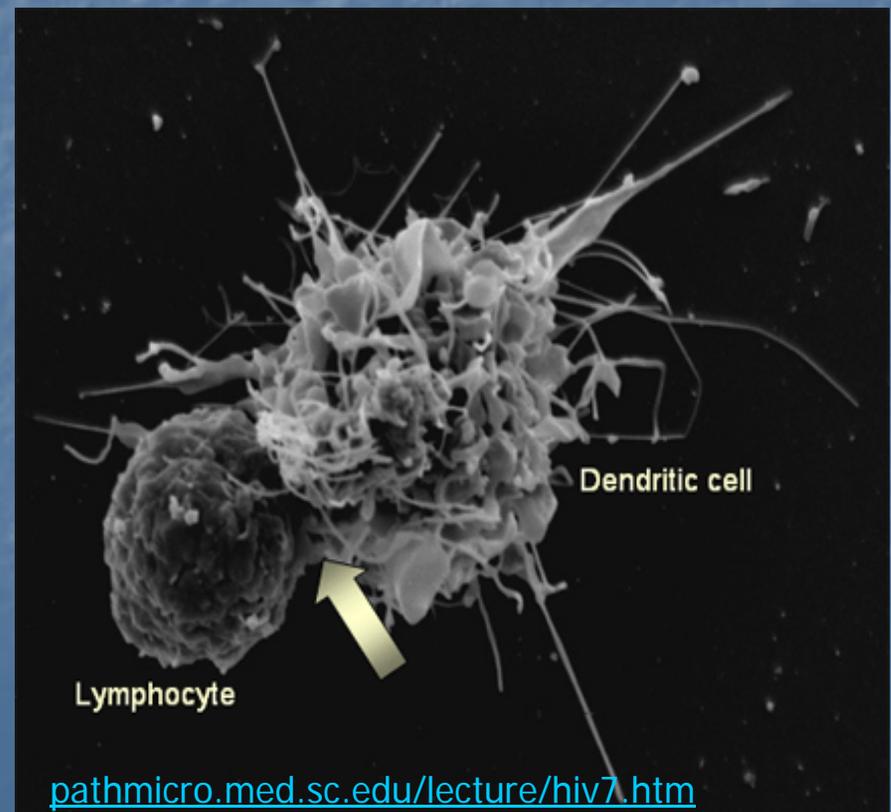


Activation of effector
memory Tregs and
CD8 Treg rebound
in the tumor

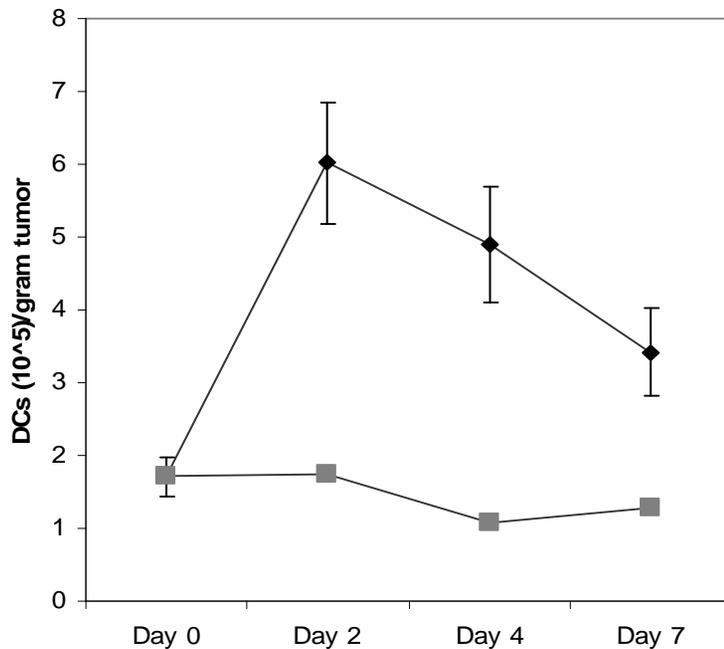
Background

- Dendritic Cells (DCs)
 - The most potent antigen presenting cell – master regulator of the immune response
 - Can prime in an immunogenic *OR* tolerogenic fashion

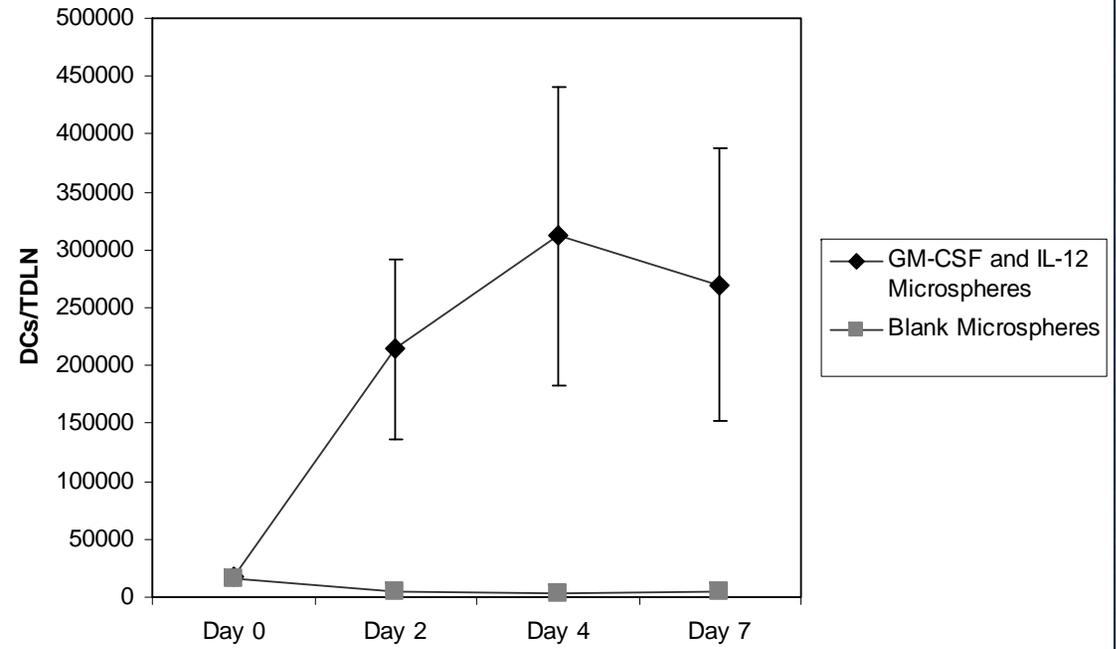
How does GM-CSF and IL-12 microsphere treatment affect DCs?



DC numbers increase in tumor and tumor draining lymph nodes after treatment



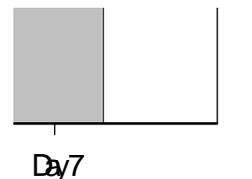
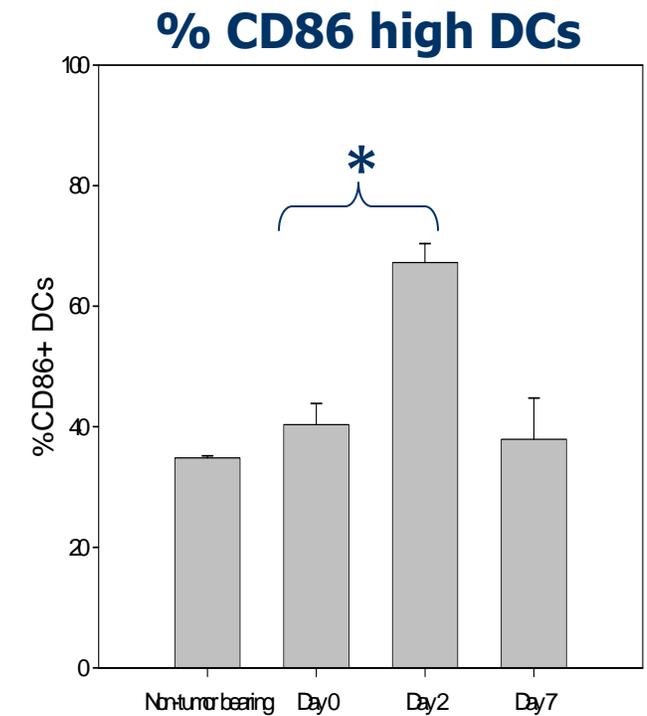
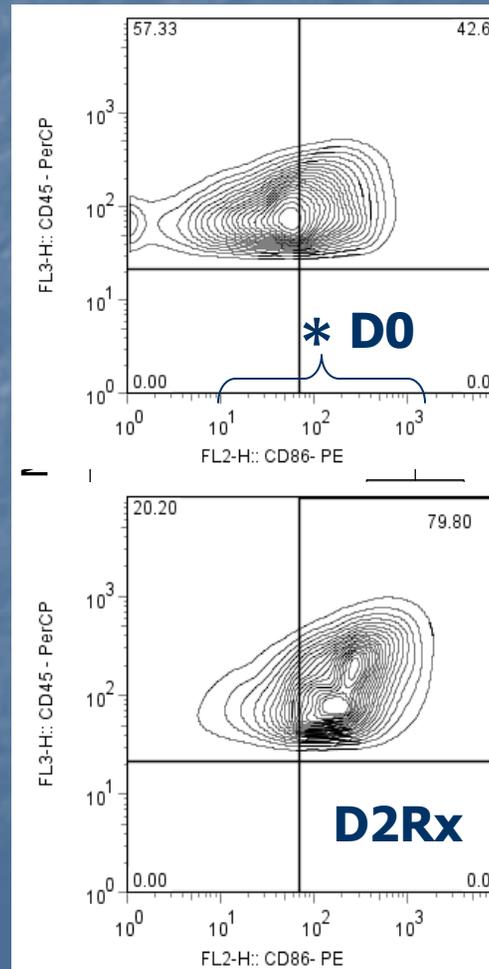
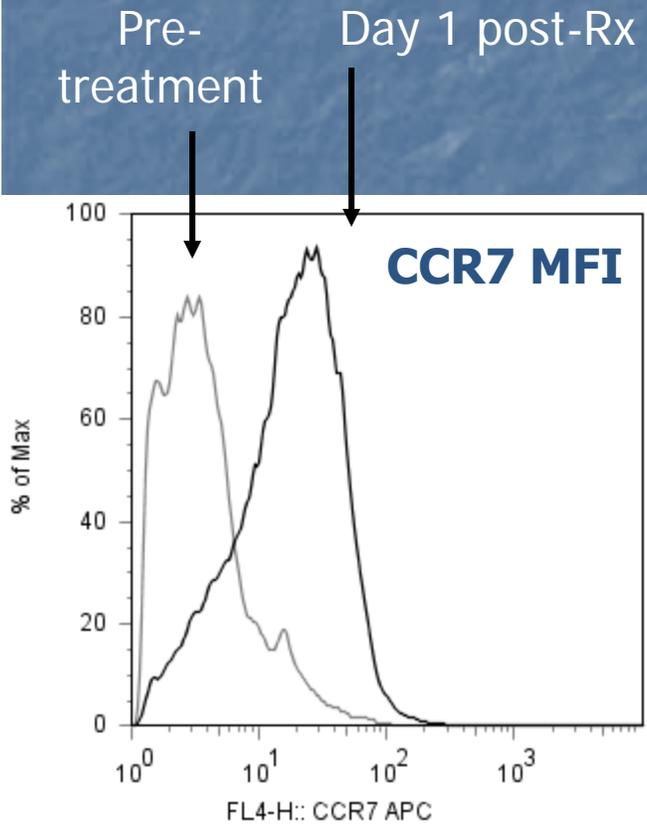
Absolute DC numbers in the tumor



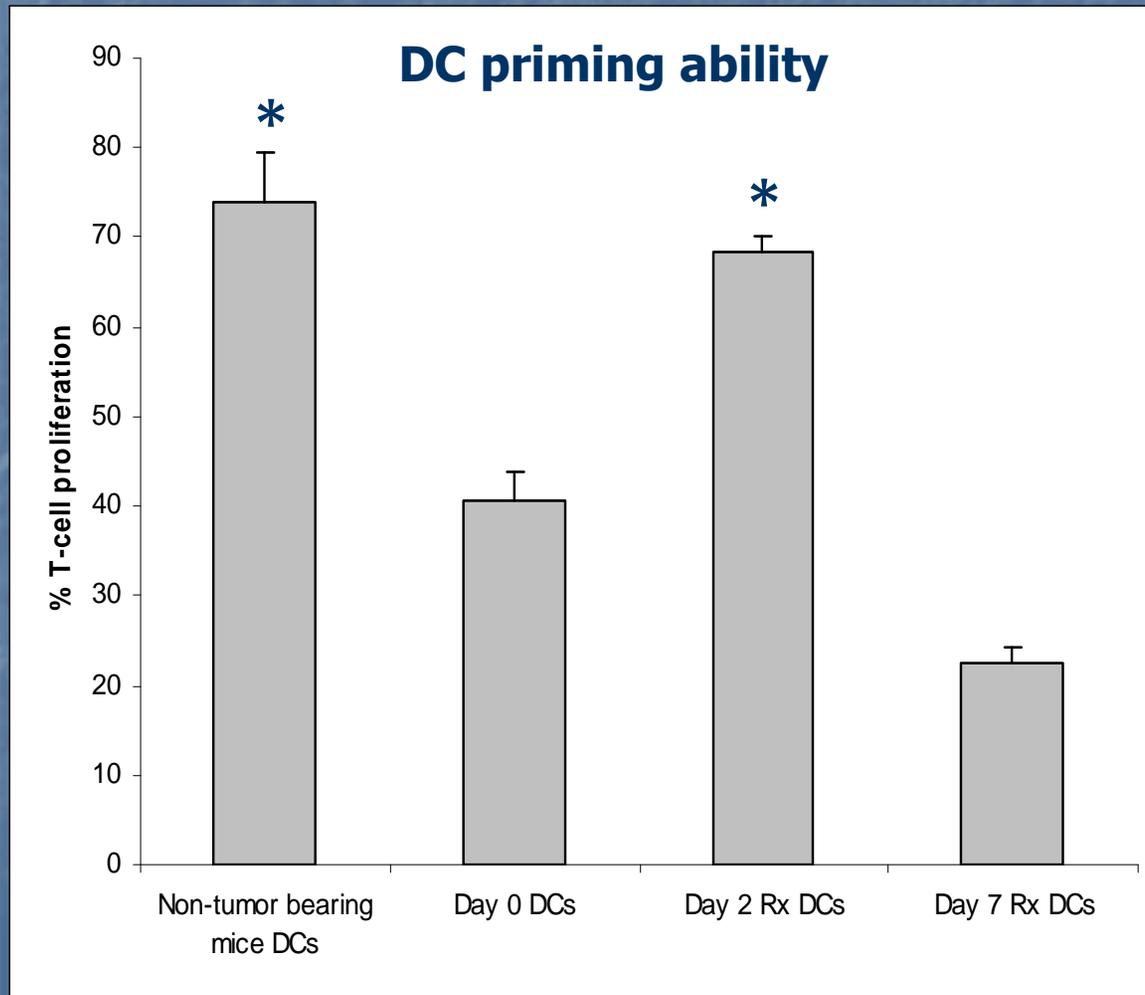
Absolute DC numbers in the TDLN post-Rx

DCs post-treatment upregulate CCR7 and CD86

Gated on CD45+, CD11c+, MHCII+ (DCs)



DCs become immunogenic after treatment, followed by tolerogenicity

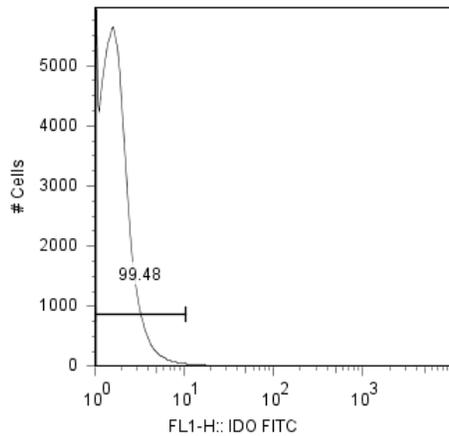


What is the cause of the poor DC priming ability by Day 7 post-treatment?

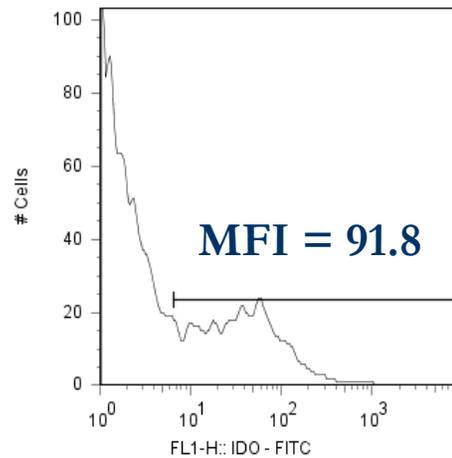
IDO is upregulated in DCs post-treatment

Intracellular Staining for IDO

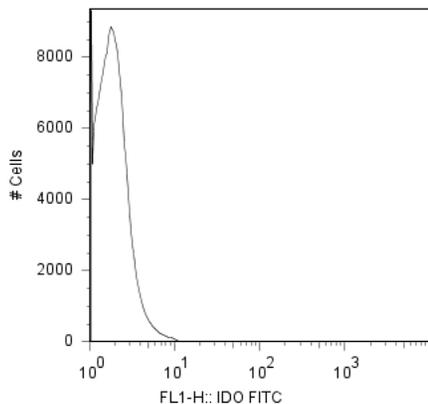
Primary antibody with isotype control secondary antibody:



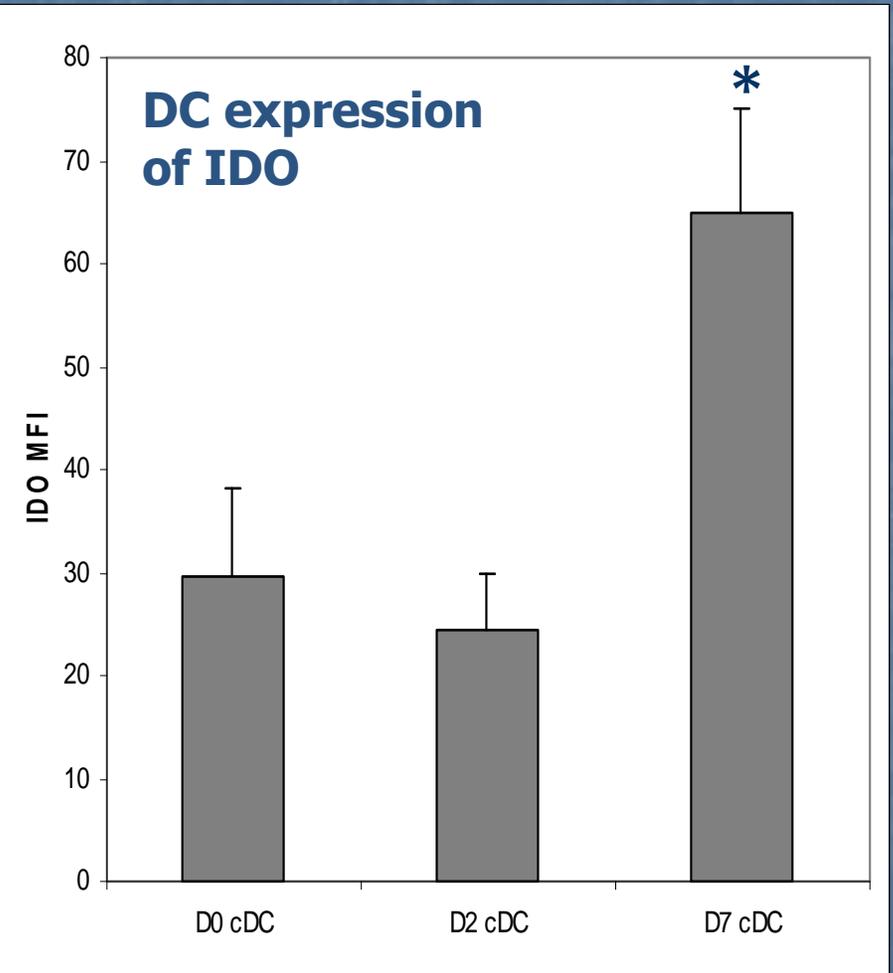
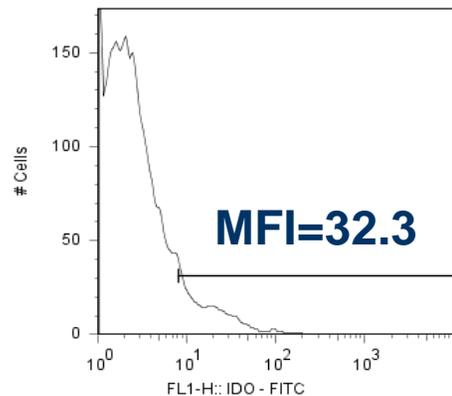
Intracellular IDO staining of D7Rx TDLN sample:



Isotype control primary antibody with secondary antibody:

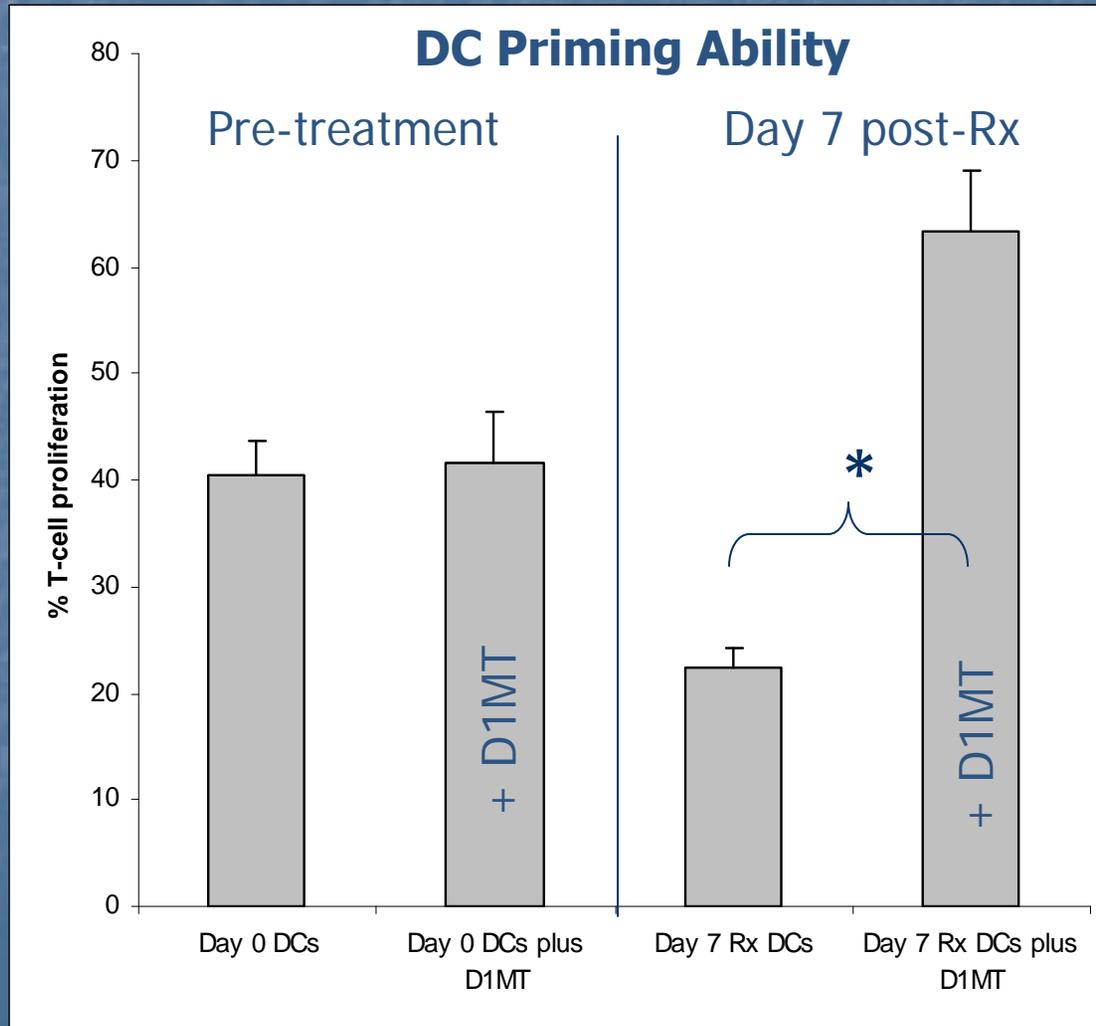


Intracellular IDO staining of untreated TDLN sample:

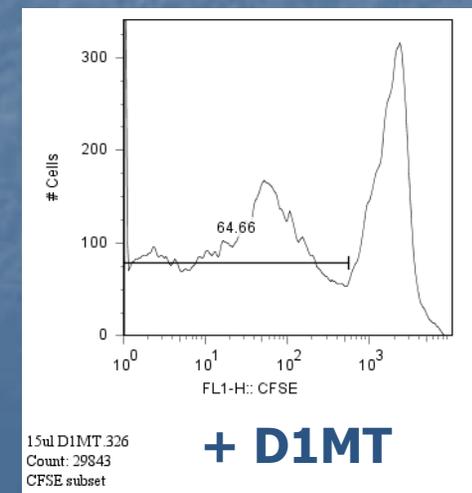
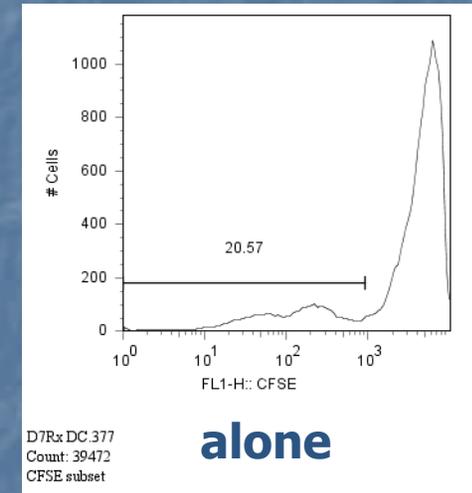


IDO mediates post-treatment DC tolerogenicity

Addition of D1MT restores priming ability to D7Rx DC, but not pre-treatment DCs



Day 7 post-Rx
DC Priming

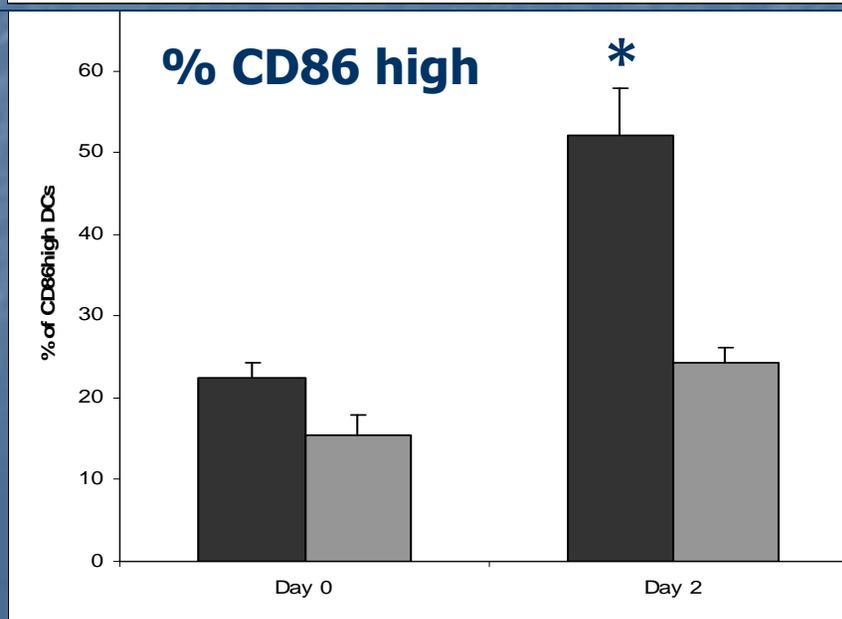
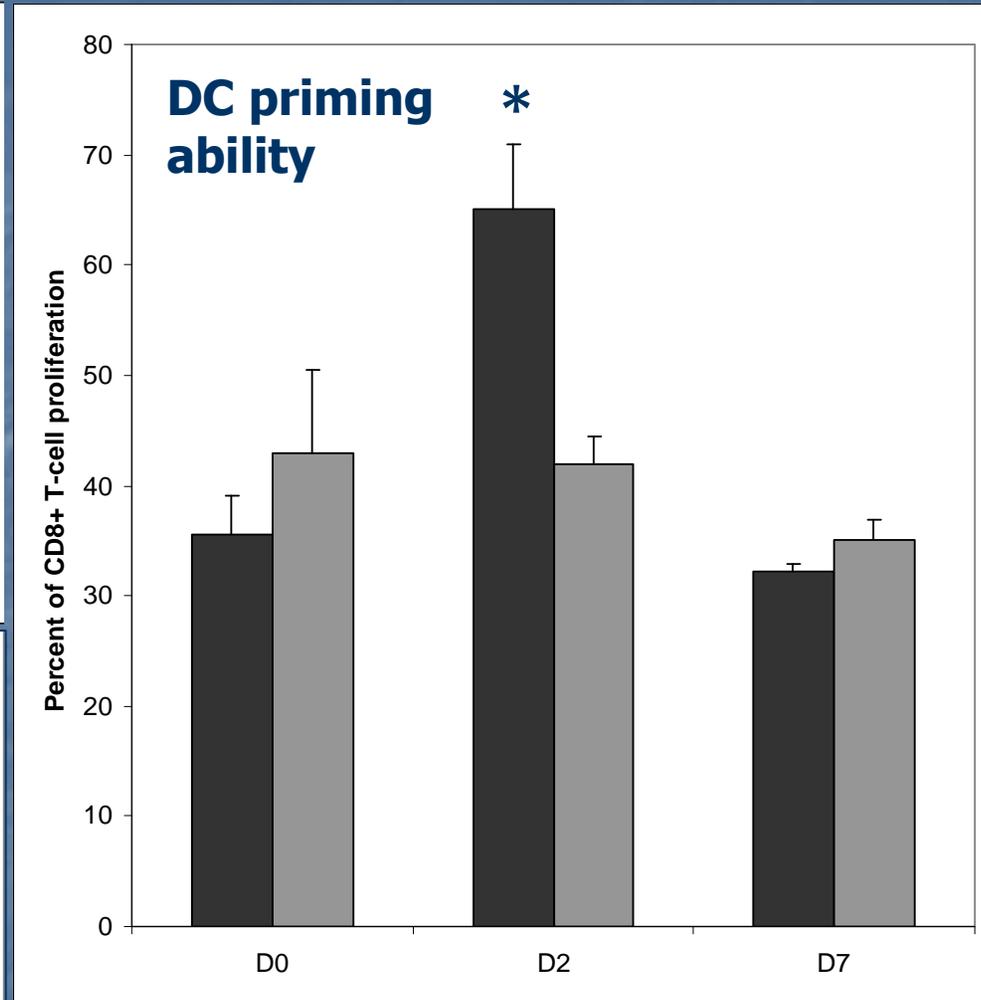
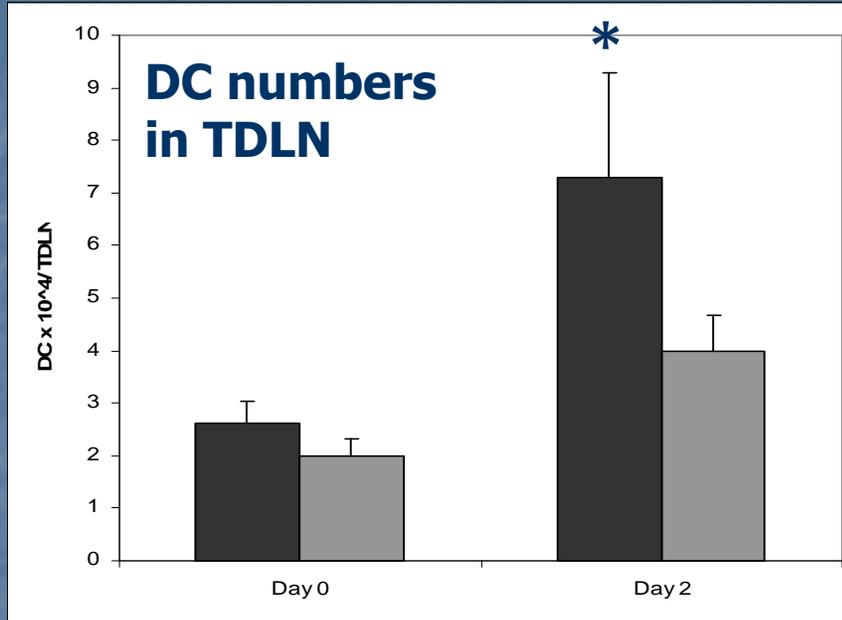


Requires IFN-gamma

- Effector memory CD8+ T-cell activation
- Reduction in T-reg numbers
- NK cell activation
- *De novo* CD8+ T-cell priming in TDLN

Is IFN-gamma required for treatment mediated effects on DCs?

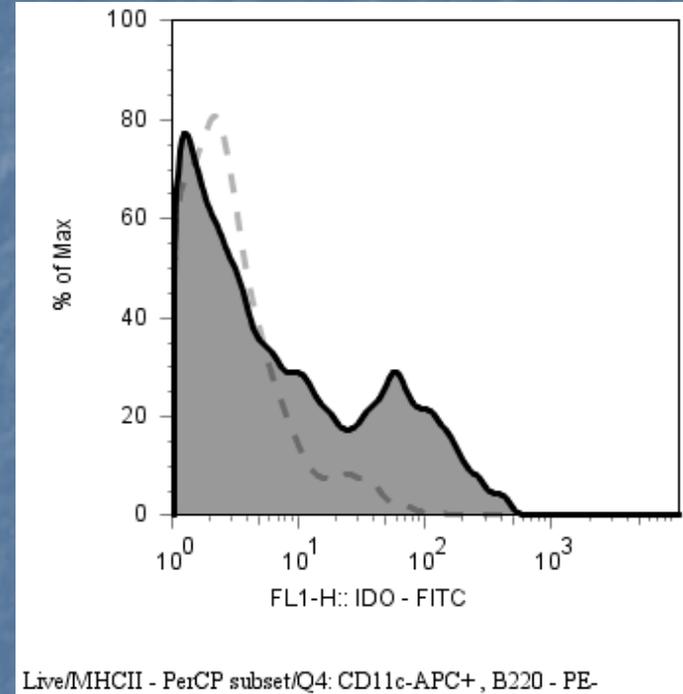
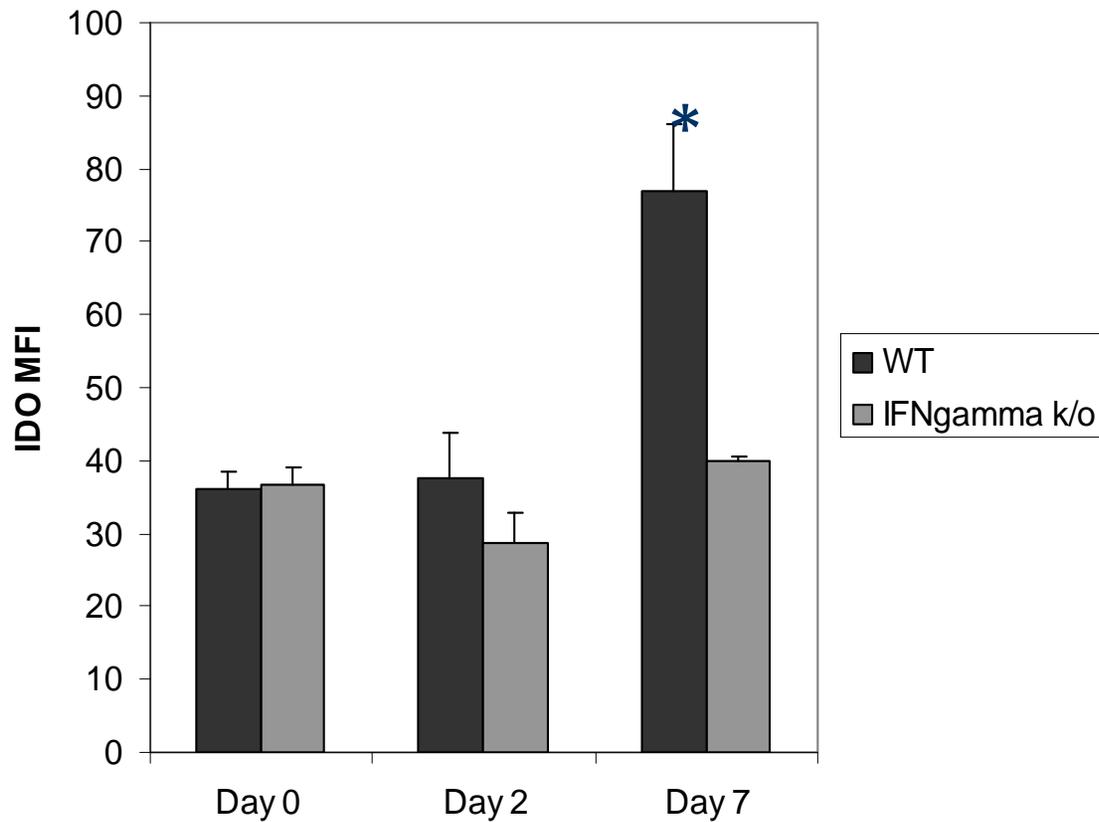
IFN-gamma drives DC immunogenicity



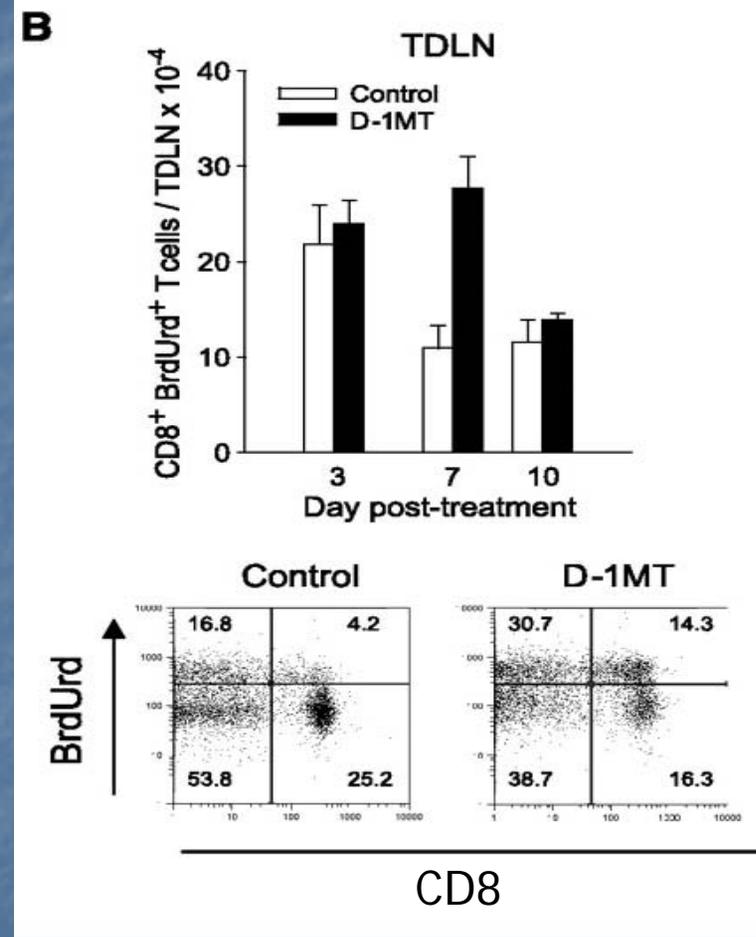
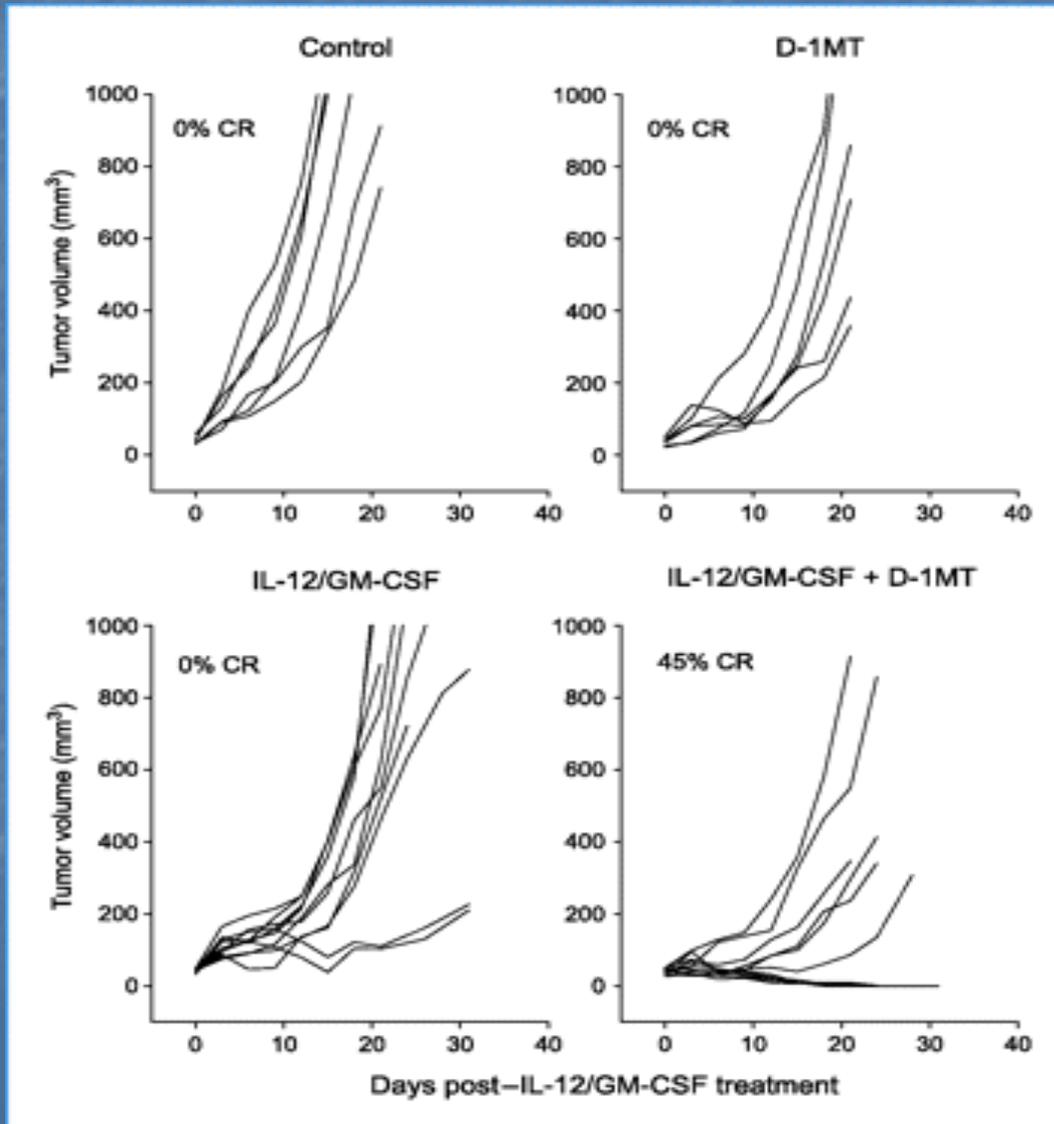
■ = WT
■ = IFN-gamma k/o

IFN-gamma drives DC regulation via IDO

IDO Upregulation in DCs requires IFNgamma

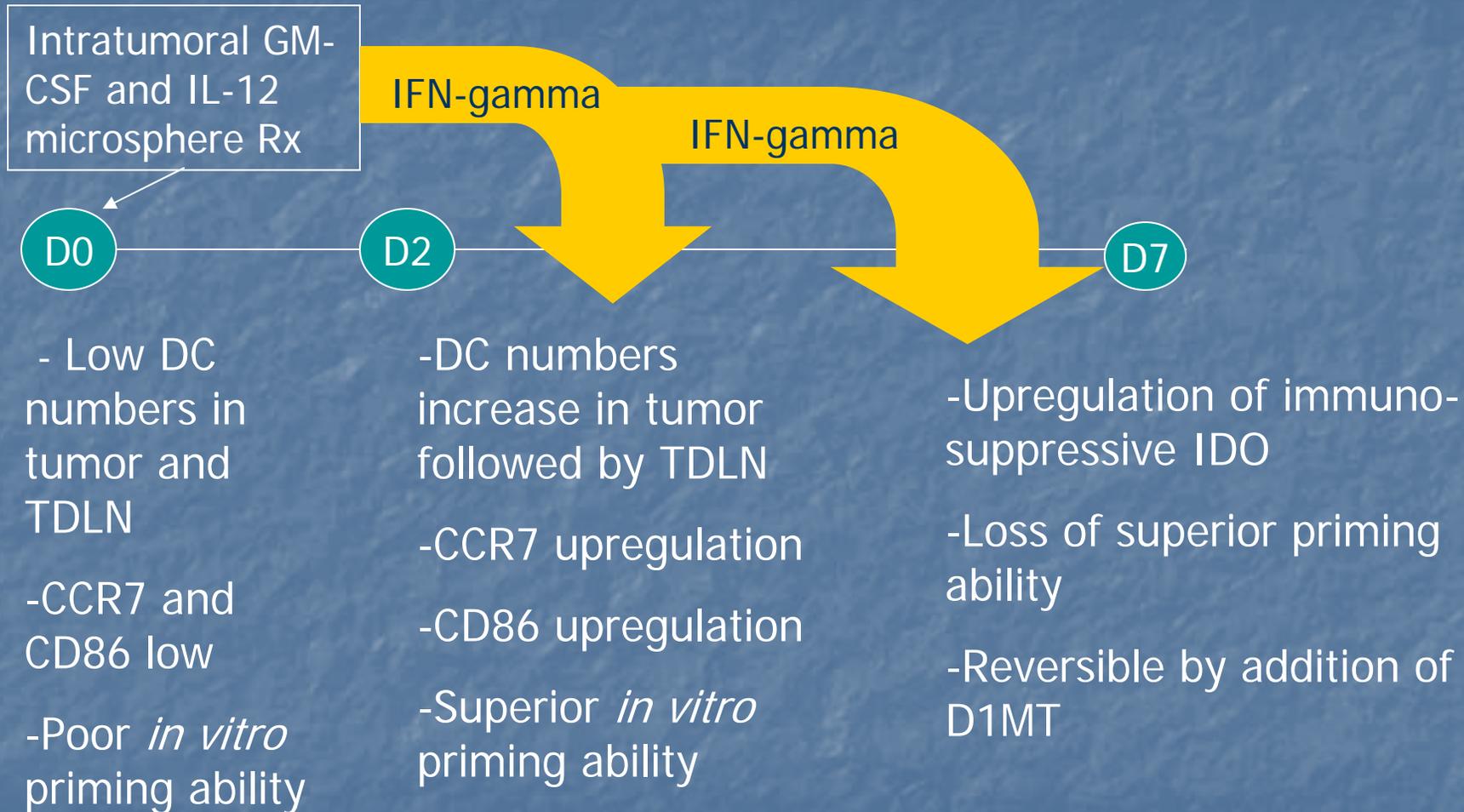


Addition of D1MT to microsphere treatment results in complete regression of tumors



Central Role of IFN γ -Indoleamine 2,3-Dioxygenase Axis in Regulation of Interleukin-12-Mediated Antitumor Immunity. Tao Gu et al. *Cancer Res.* 70(1) 129-38.

Summary:



Acknowledgements

