

Presenter Disclosure Information

Paulo C. Rodriguez, PhD

The following relationships exist related to this presentation:

No Conflict of Interest Relationships to Disclose

**Transgenic expression of Notch-1 intracellular domain
(N1IC) in CD8⁺ T cells: A potential therapy to
overcome suppression induced by tumors**

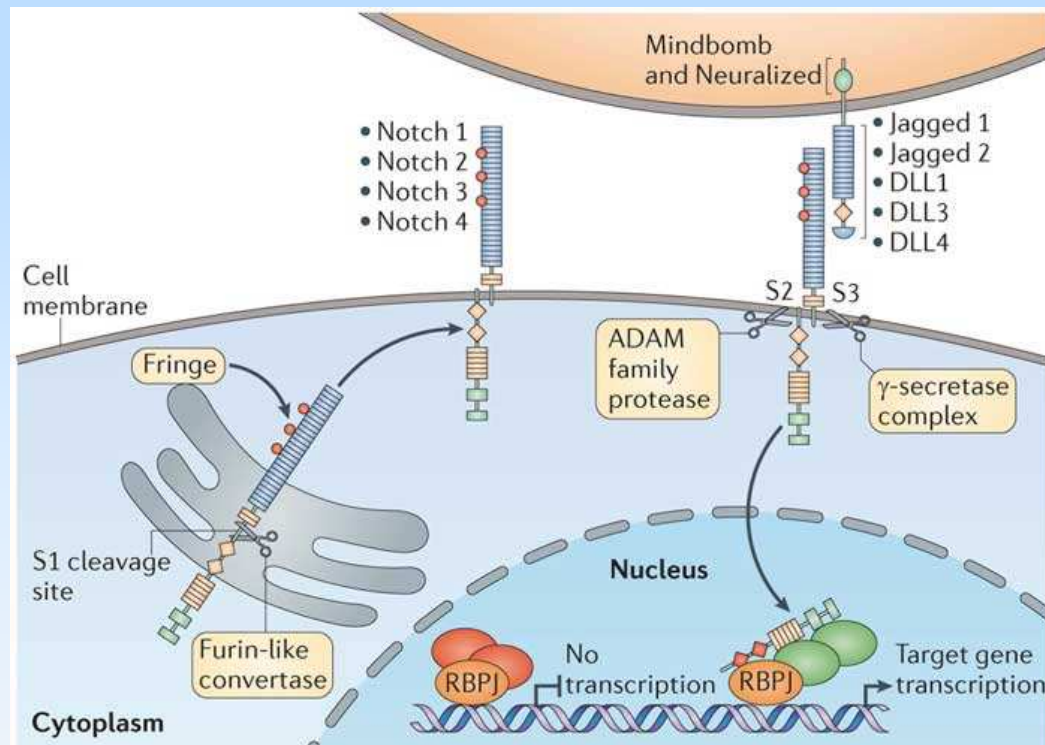
Poster #193

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Cell signaling through Notch receptors

-Notch signaling controls differentiation, proliferation, and apoptotic events in several tissues.

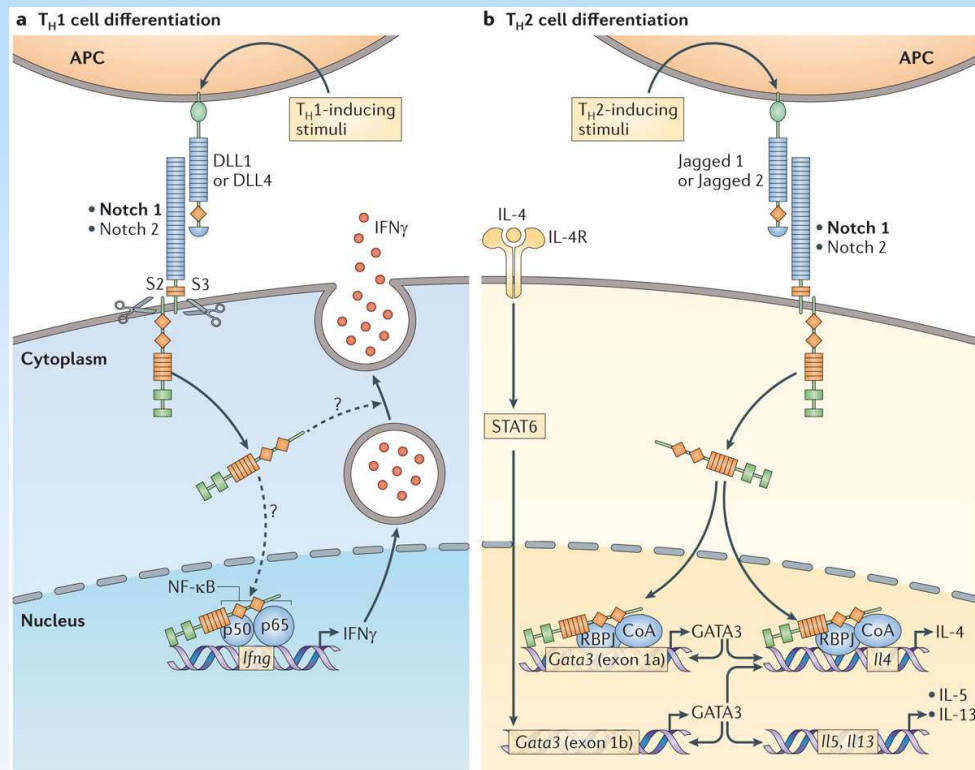


Radtke F et al. *Nature Reviews Immunology*. (2013)

Nature Reviews | Immunology

Regulation of T cell maturation and function by Notch signaling

- Notch signaling regulates T cell development/maturation.
- Notch plays a key role in the generation of Th1, Th2, Th17, and Treg.



Radtke F et al. *Nature Reviews Immunology*. (2013)

Nature Reviews | Immunology

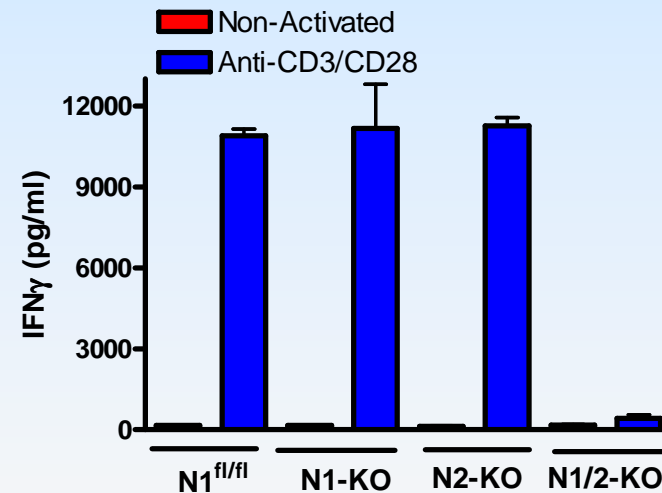
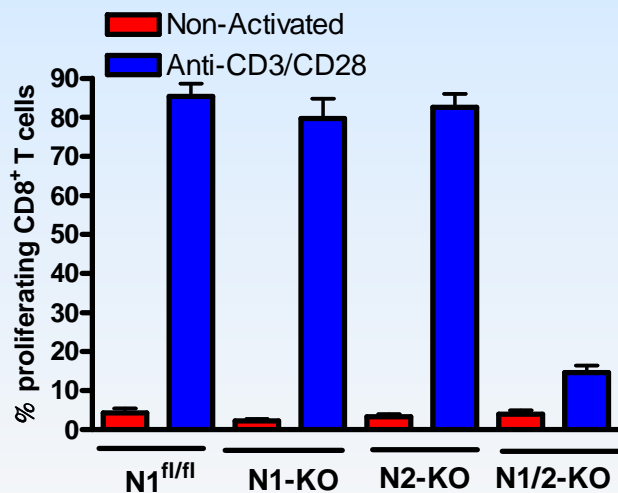
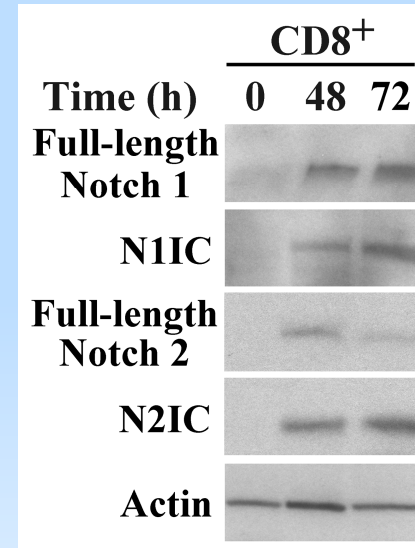
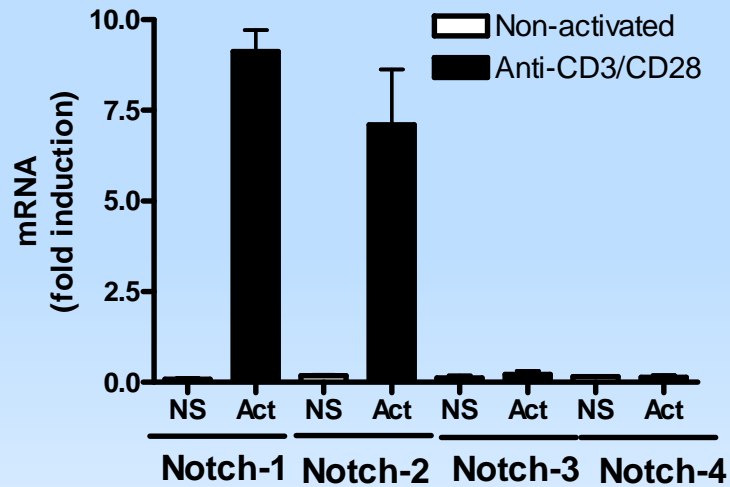
Effect of Notch in CD8⁺ T cell function

- Notch regulates function of CD8⁺ T cells:
 - * Gamma secretase inhibitors (GSI).
 - * Anti-sense Notch 1 mouse, Conditional KO Notch 2, Agonistic Antibodies against Notch 1 and 2.
 - * Fc-fused ligands (DLL1, DLL4), Expression DLL1/4 in DC's.
 - * DN-MAML and RBPJ KO.

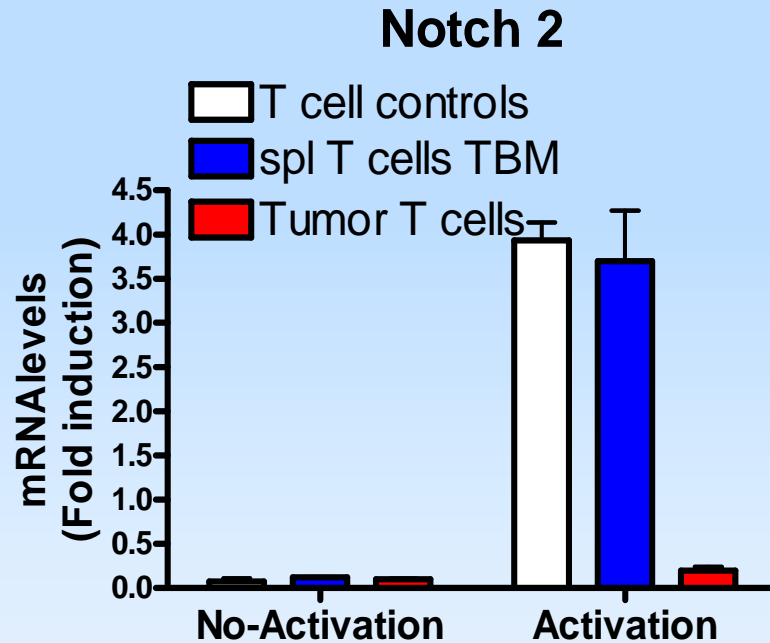
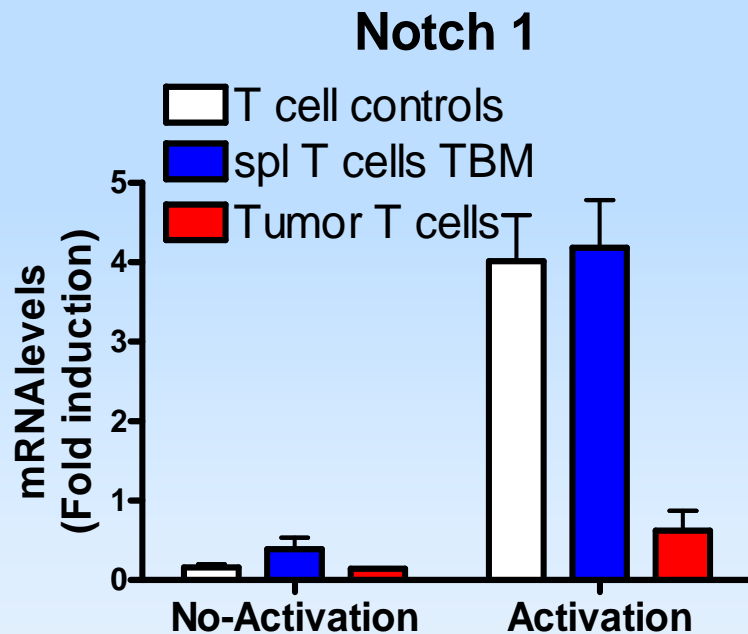
Gap of knowledge

- The role of Notch signaling in the suppression of T cell responses in tumor-bearing hosts.
- Effect of the rescue of T cell-Notch signaling in anti-tumor T cell responses (Adoptive cellular immunotherapy).

CD8⁺ T cell activation induces the expression of Notch 1 and Notch 2



Decreased expression of Notch 1-2 in tumor-infiltrating CD8⁺ T cells



Generation of conditional N1IC transgenic mice in activated antigen-specific CD8⁺ T cell



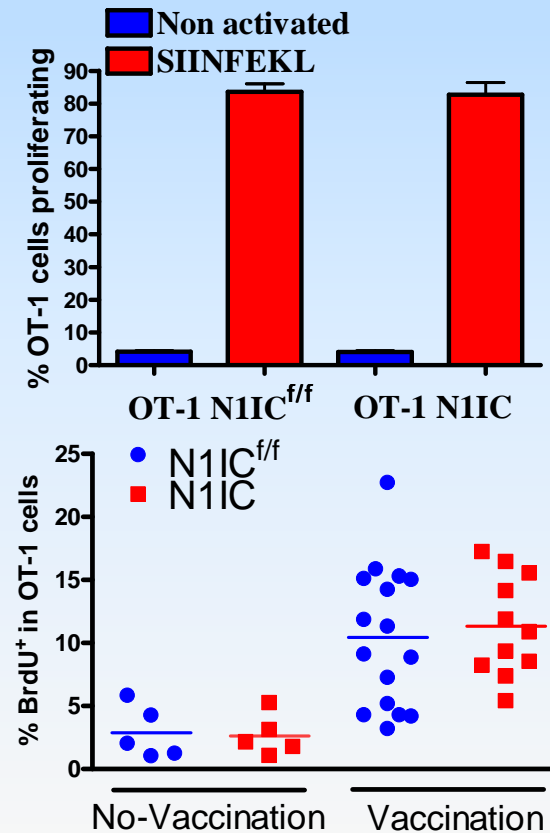
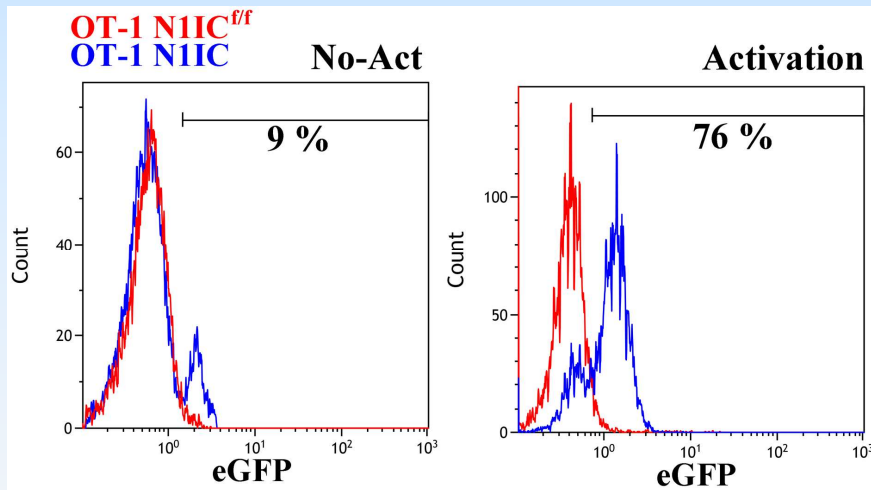
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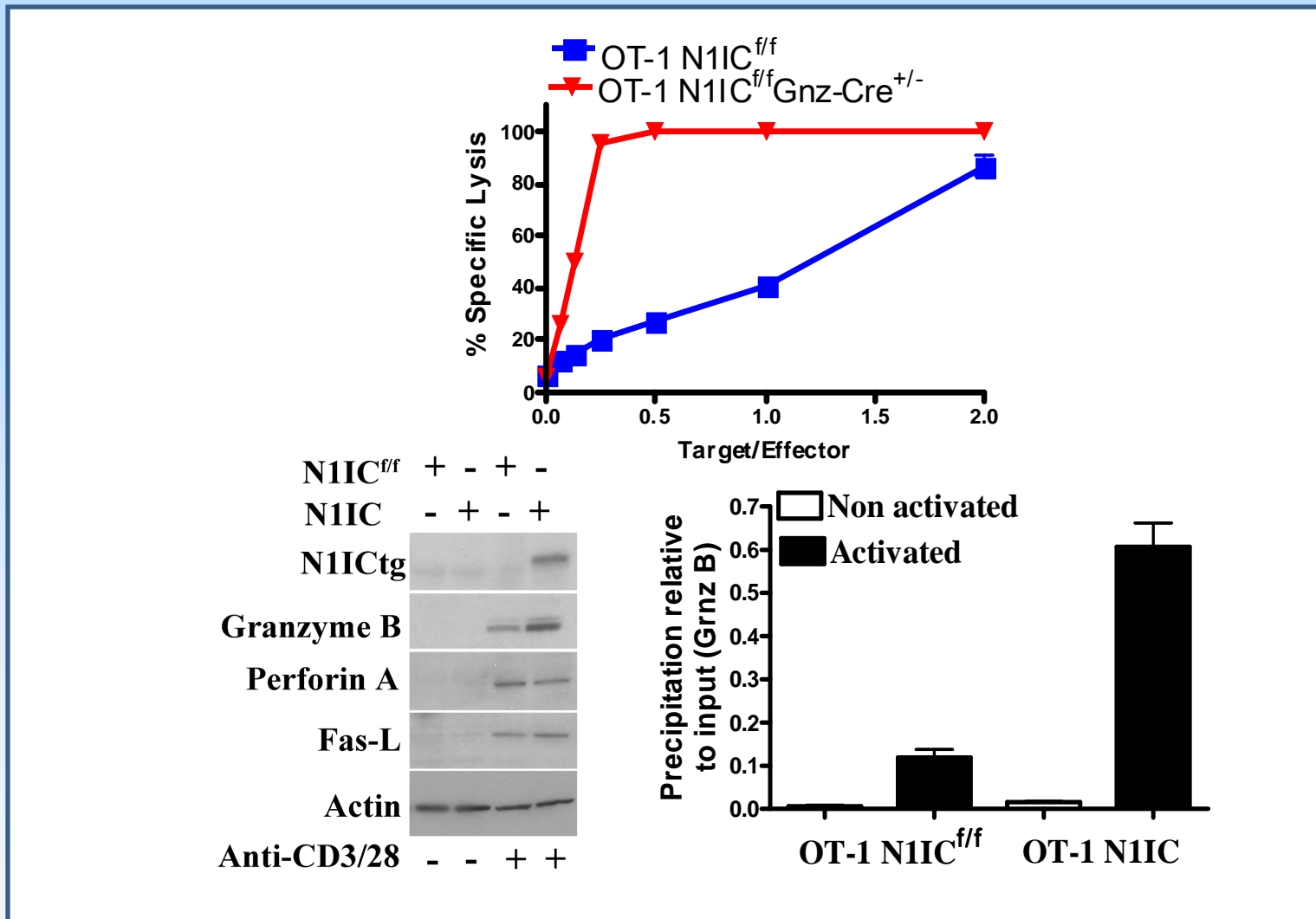
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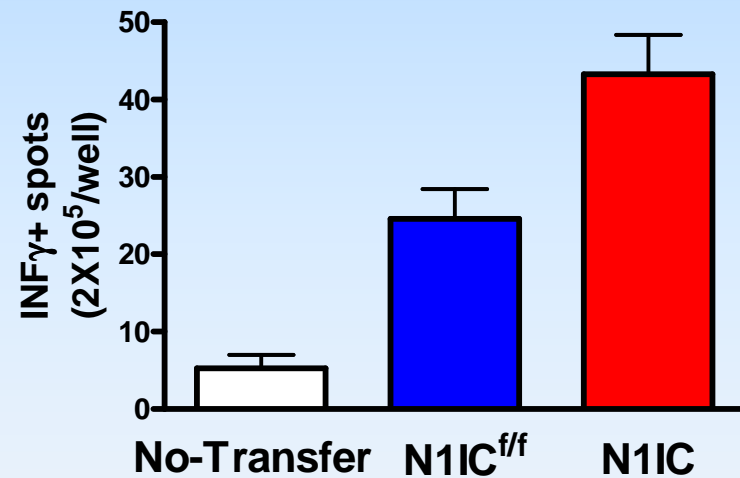
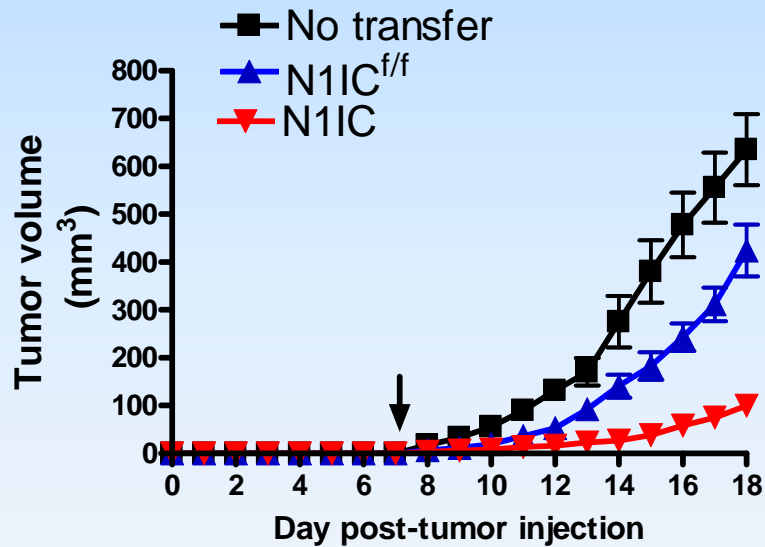
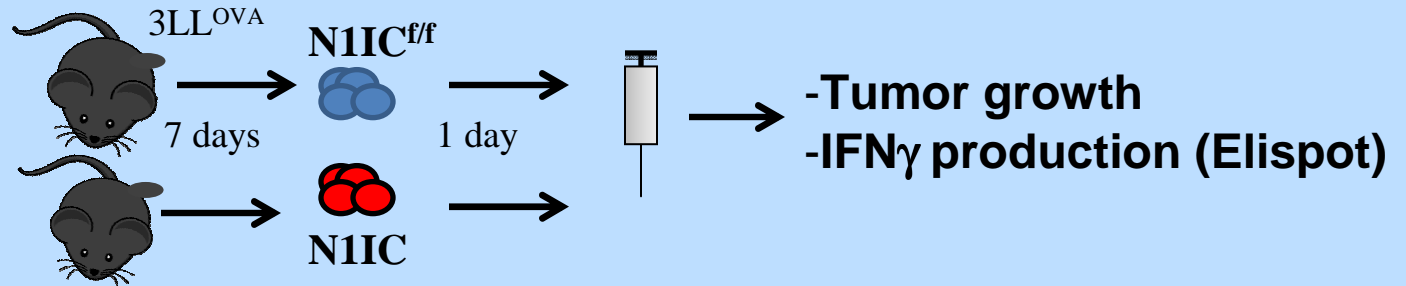
Melton D. PNAS. 9; 100:1490



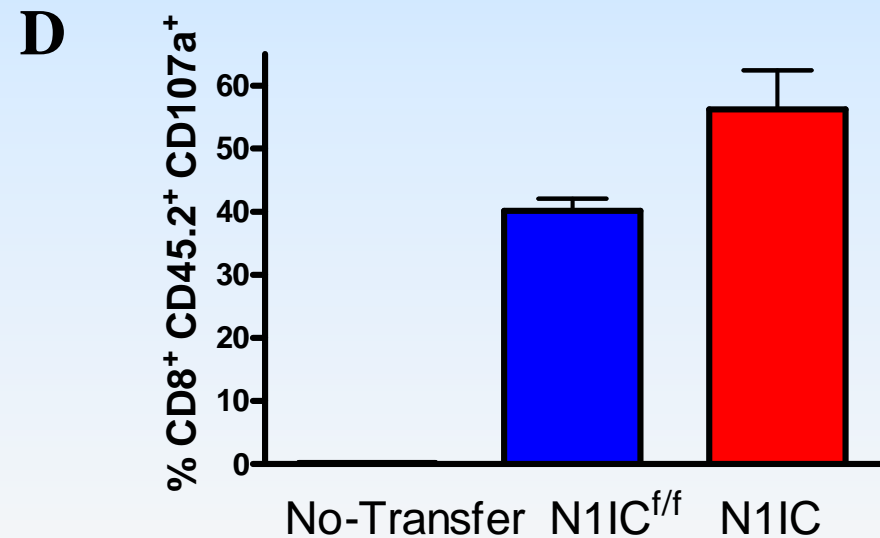
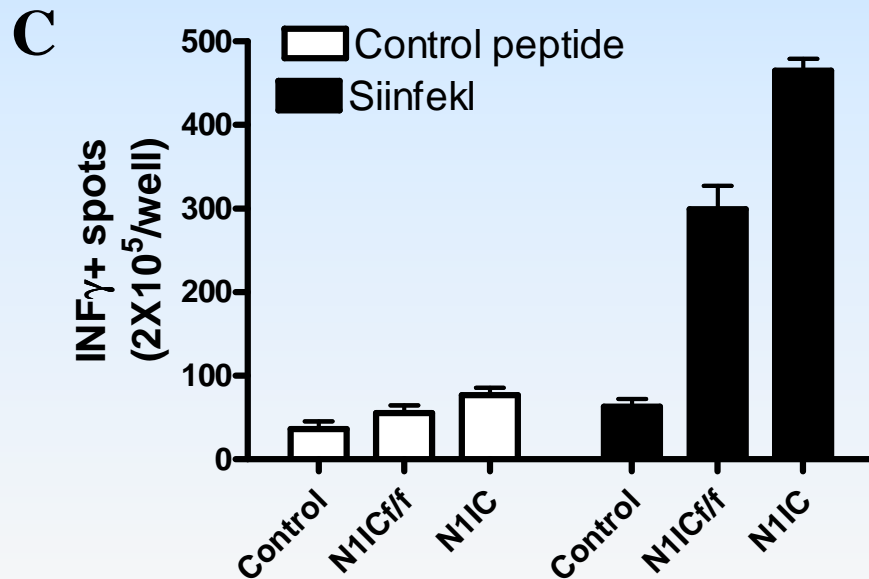
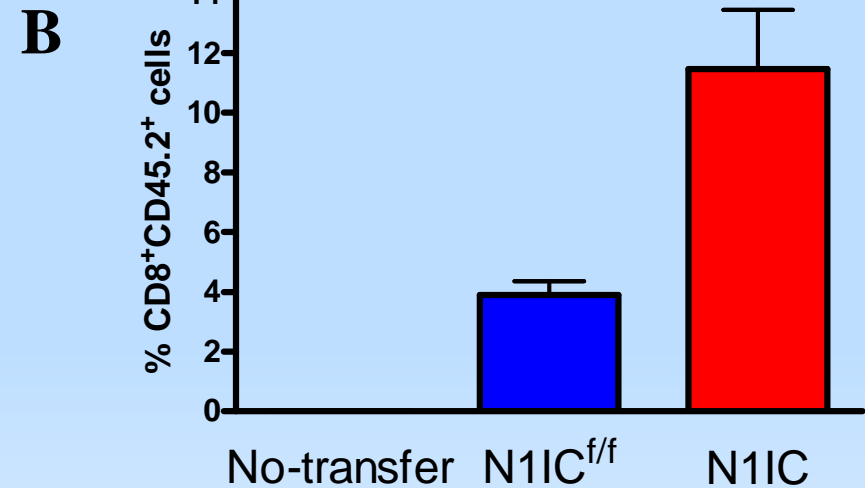
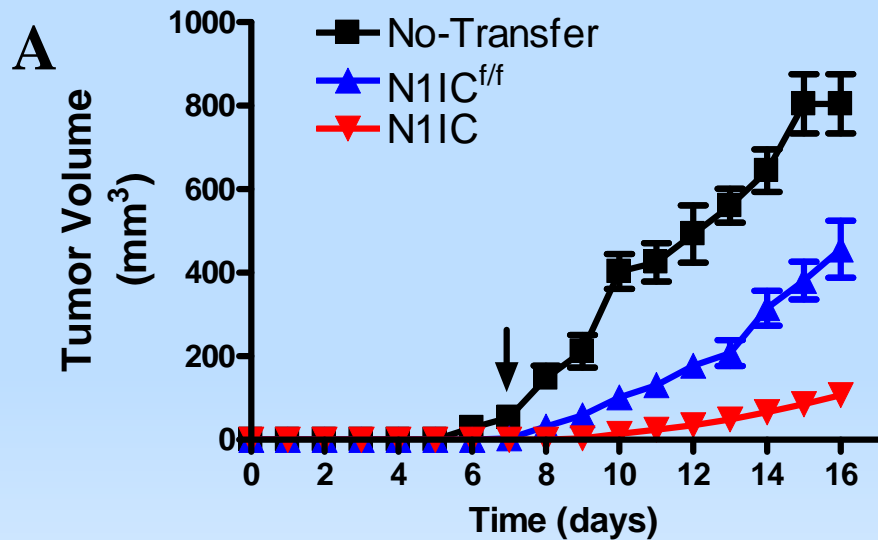
N1IC endogenously promotes CD8⁺ T cell cytotoxicity



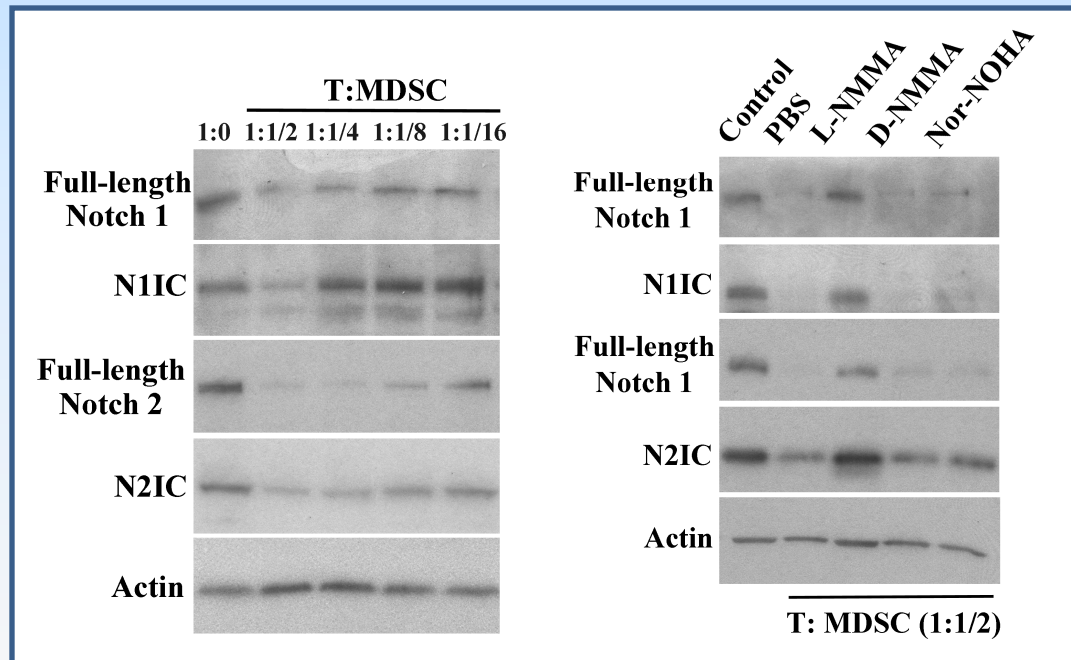
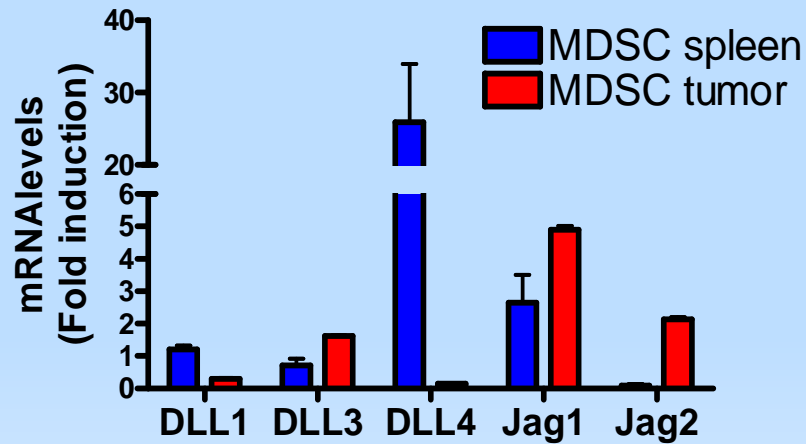
Transgenic N1IC increases anti-tumor efficacy of antigen-specific CD8⁺ T cells



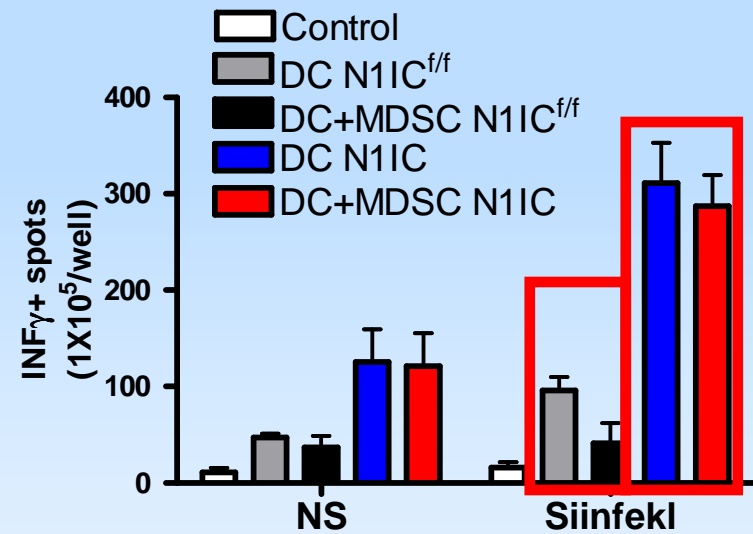
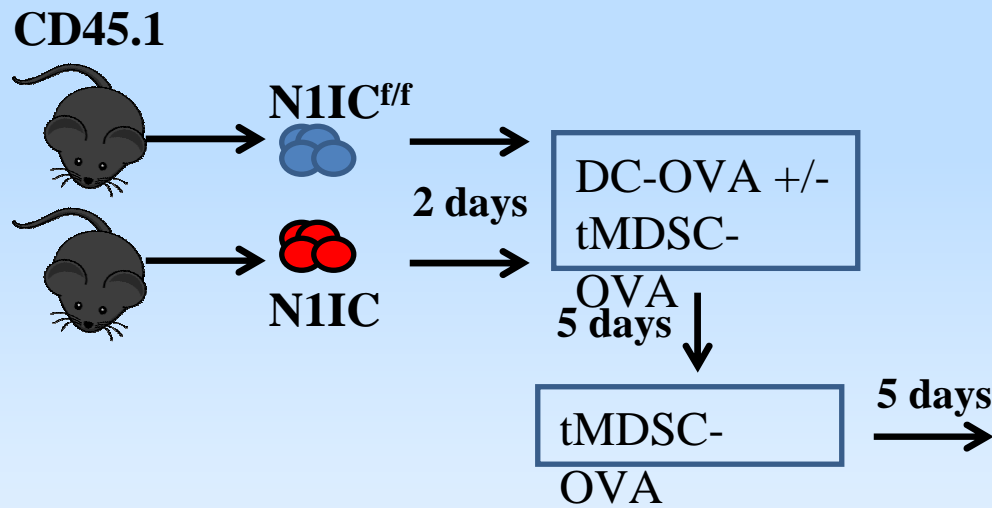
Transgenic N1IC increases anti-tumor effect of pre-activated antigen-specific CD8⁺ T cells



MDSC inhibited T cell-Notch 1-2 expression through a Nitric Oxide-dependent mechanism



Transgenic N1IC renders antigen-specific T cells resistant to MDSC



Conclusions

- Notch 1 and Notch 2 play a key role in CD8⁺ T cell function.
- Expression of N1IC increases anti-tumor capacity of CD8⁺ T cells, through endogenous promotion of effector mediators (Granzyme B and IFN γ).
- Rescue of Notch 1 signaling in CD8⁺ T cells increases adoptive cellular immunotherapy.
- N1IC CD8⁺ T cells are resistant to the suppressive effect of tumor-infiltrating MDSC.

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