New strategies that target tumor microenvironment and generate local andsystemic immune protection

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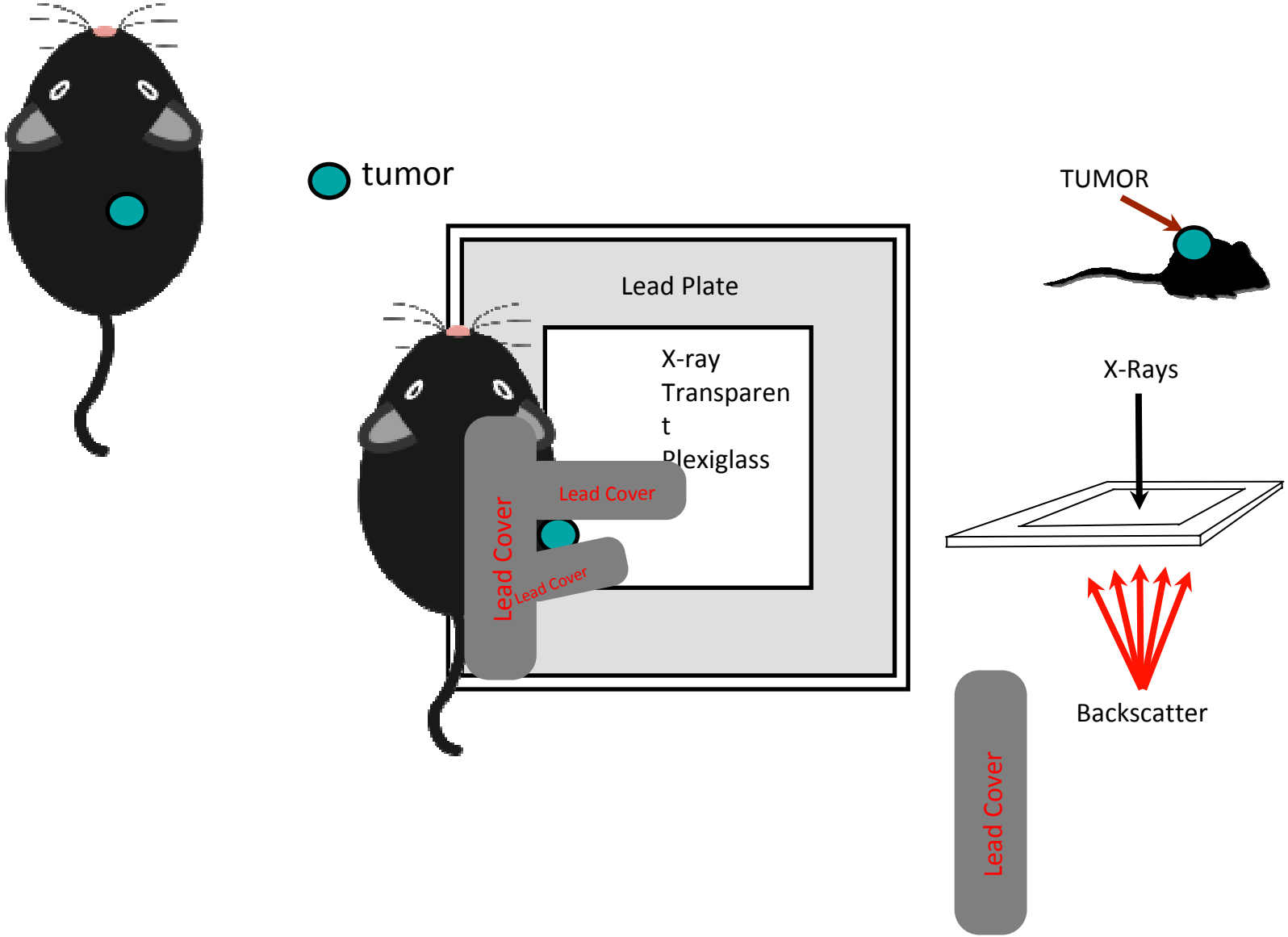
Major barriers in immunotherapy

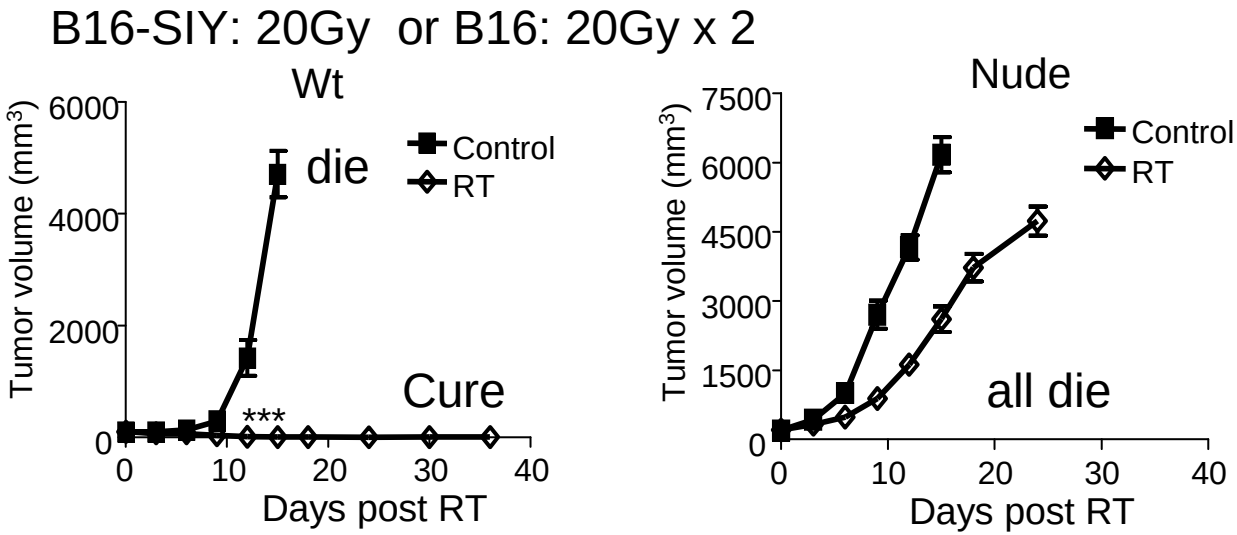
- Difficult to break tolerance
- Poor recruitment to tumor site
- Strong suppressive environment within the tumor site
- Fast growing tumor in mouse model
- Lack of defined antigens and adjuvant for CTL

Can we combine local RT, antibodies to tumor , selected chemo, hormones to alter tumor microenvironment that allow immunotherapy to optimize host immune response for tumor regression?

Improved Targeting of X-rays



Local Ablative RT mediates tumor regression

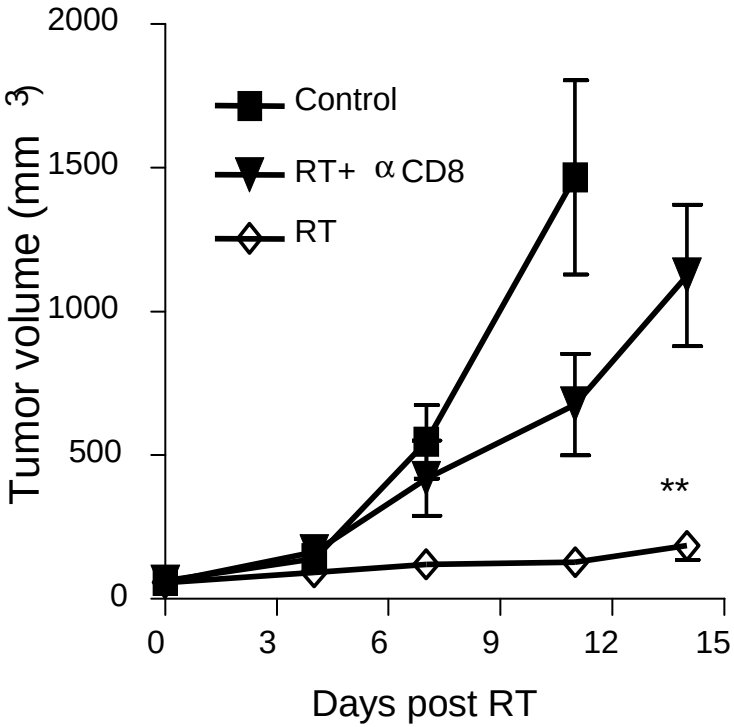


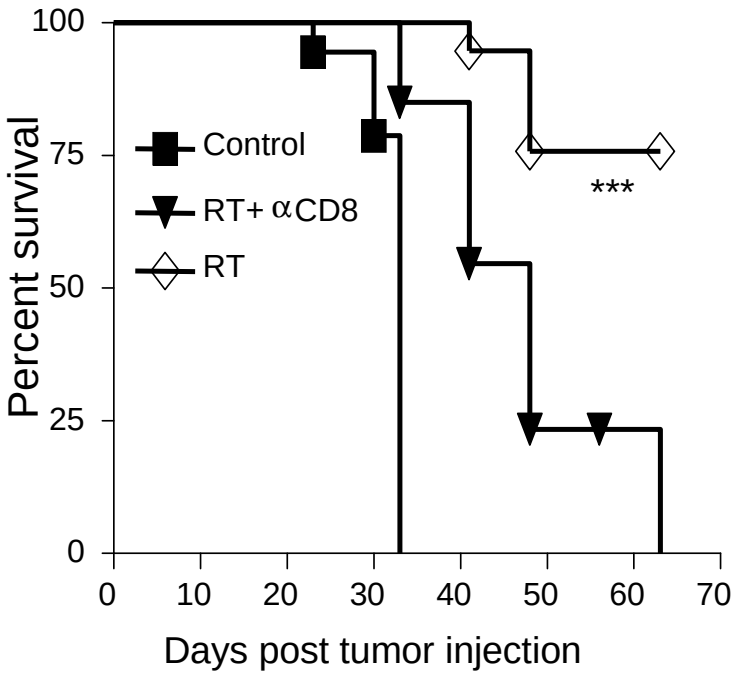
RT-mediated tumor regression depends on T cells
Traditional low dose and hyper-fractionated RT can not control tumor

Blood 2009, Cancer Res. 2011, JI 2013, JCI in press

Which immune cells controls tumor growth

B16→ RT on day 14: 15Gy x day 14, 15, ad 16

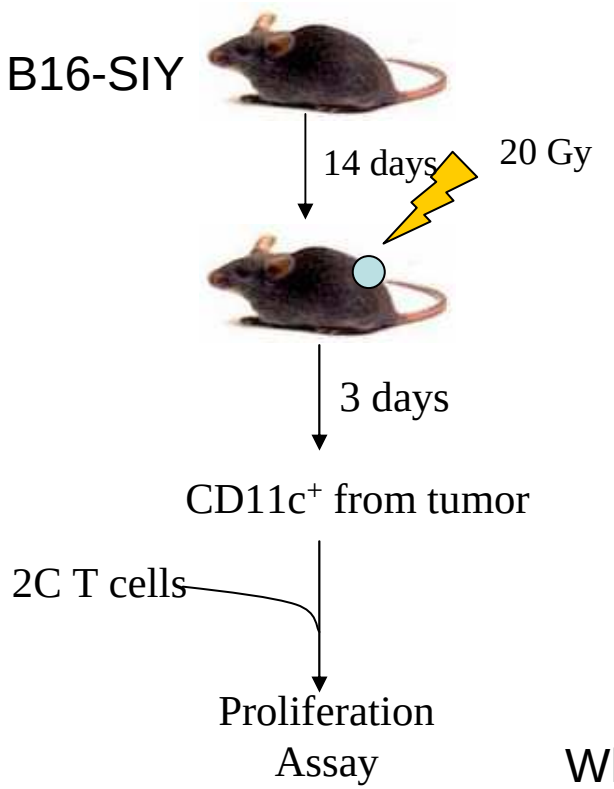


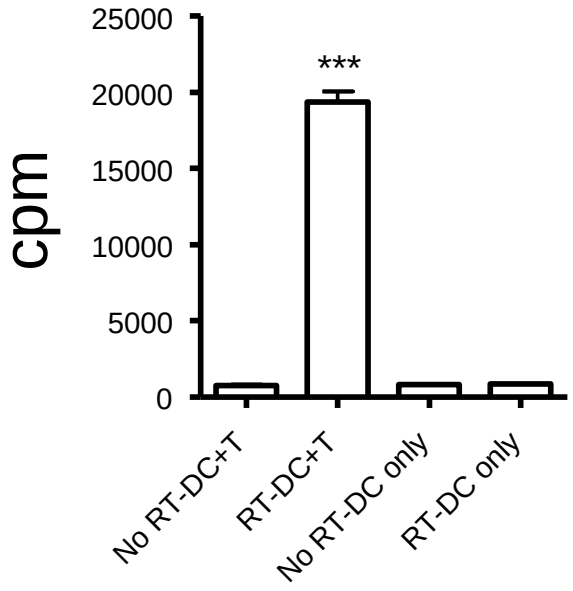


CD8+ T cells are required for therapeutic response to RT

Increase of PDL-1 induces resistance and allows relapse

can RT increase cross-priming of tumor Ag by intratumor DCs?



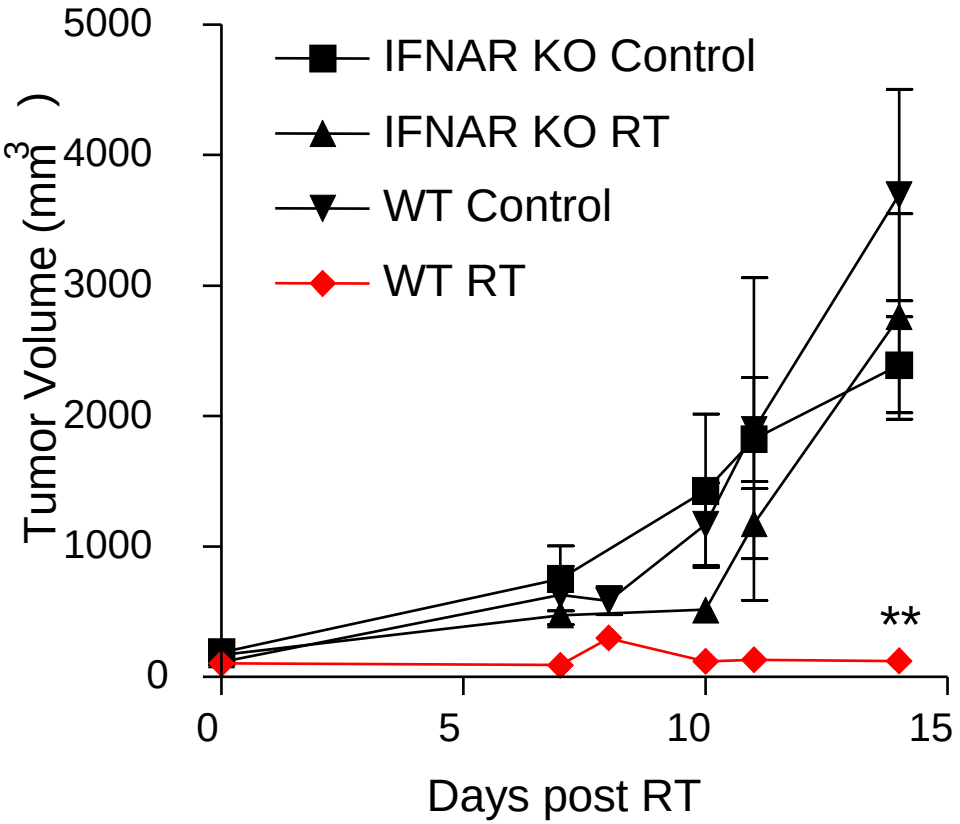


Which cytokines?

Why is cross-priming increased

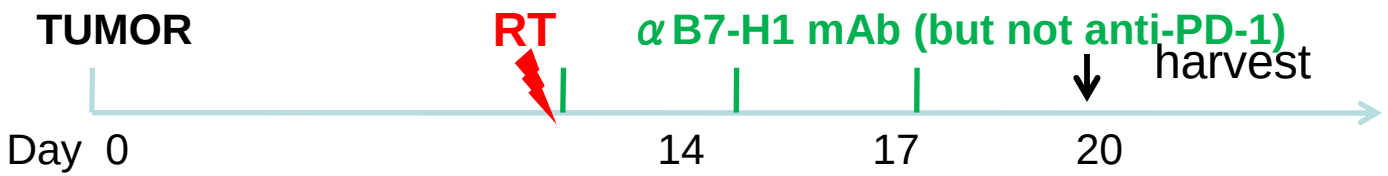
- It is known that IFNs can be induced by viral DNA for cross priming of CTL.
- Hypothesis: RT-induce DNA damage leads to excessive DNA fragments, like viral infection, which trigger IFNs that induce DC maturation and cross priming
- RT induces IFN inside tumor tissues

The therapeutic response to RT is dependent on type I IFNs



RT induced tumor regression depends on STING but not MyD88 and TRIF
While anti-Her2/neu uses MyD88.

RT and anti-PD-L1 reduces MDSC through CTL



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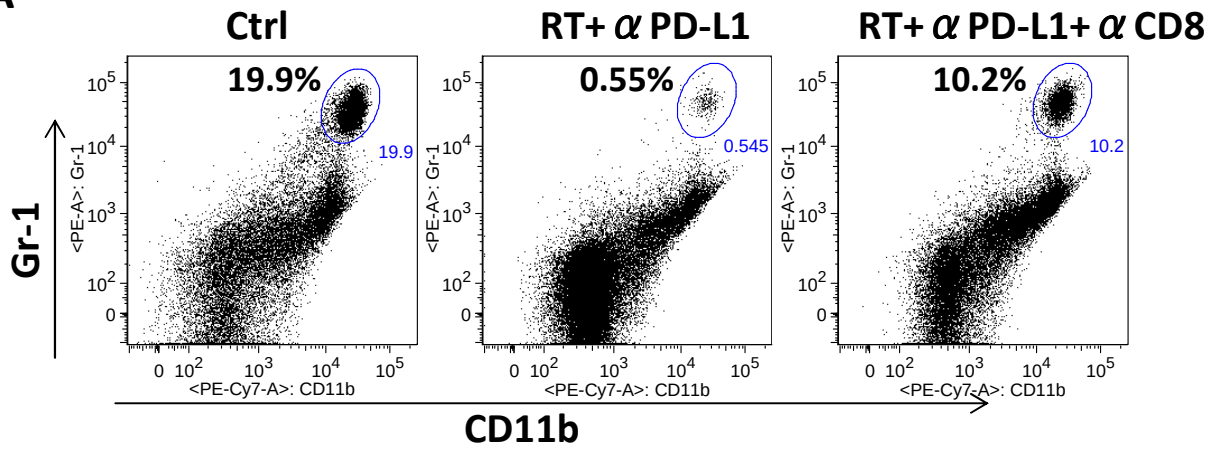

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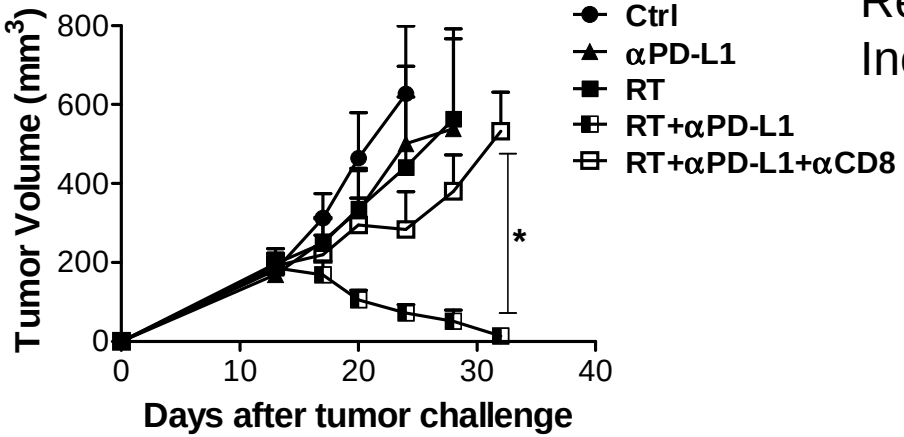
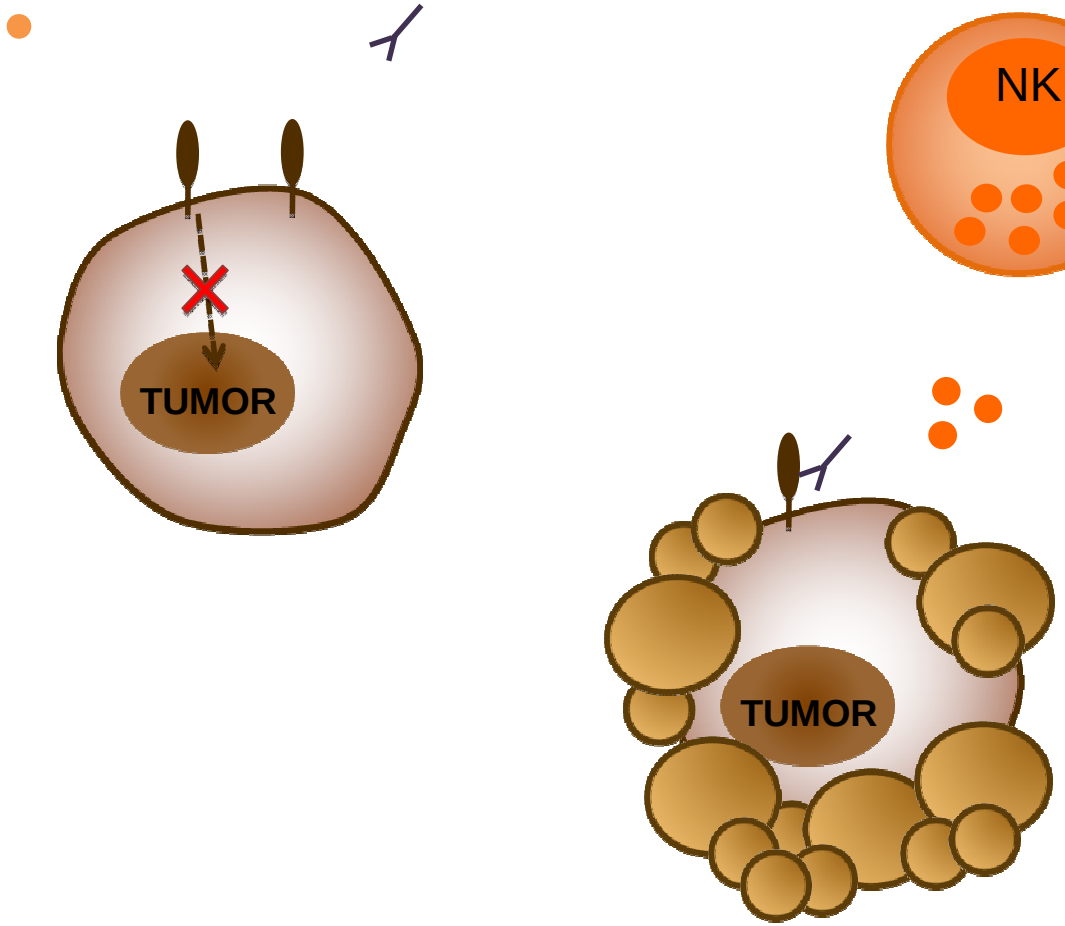


Re-activated CTL kills Ag+ cells
Including MDSC and tumor

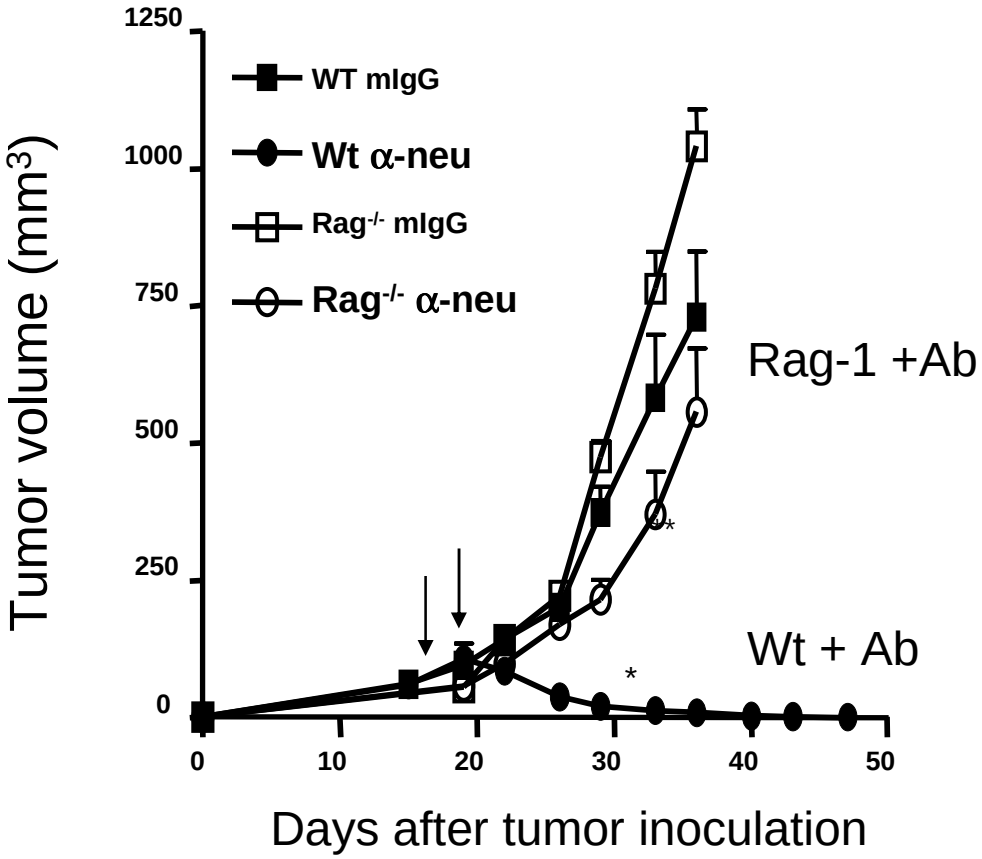
anti-HER2/neu antibody reduces tumor burden: how?

Oncogenic blockade

FcR mediated kill?



Tumor model that depends on oncogenic signals and FcR dependent in immunocompetent host

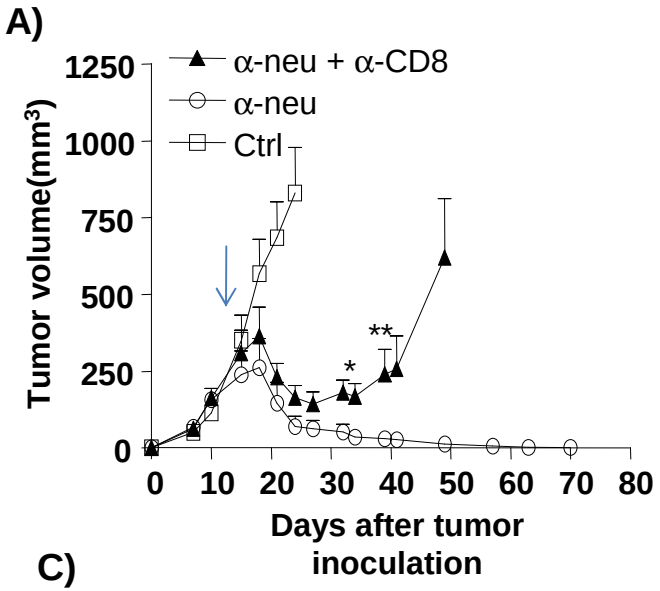


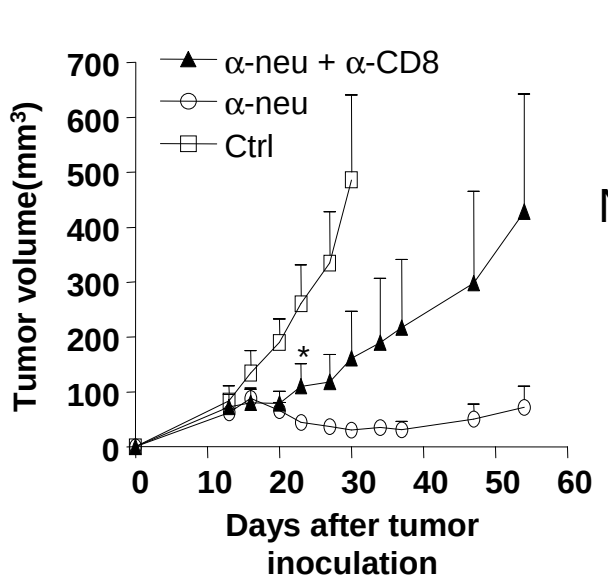
TUBO derived from MMTV-Rat neu Tg FcR and NK dep.

Are T cells essential for Ab-mediated tumor regression?

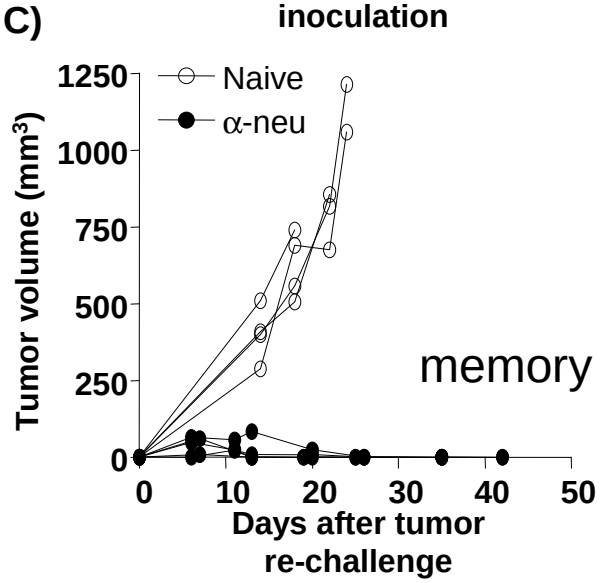
Cancer Cell, 2010

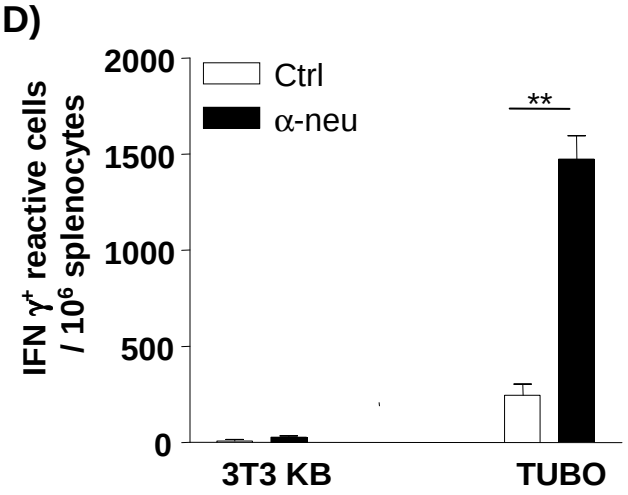
Ab-mediated tumor regression is CD8 dependent: wt and Tg mice





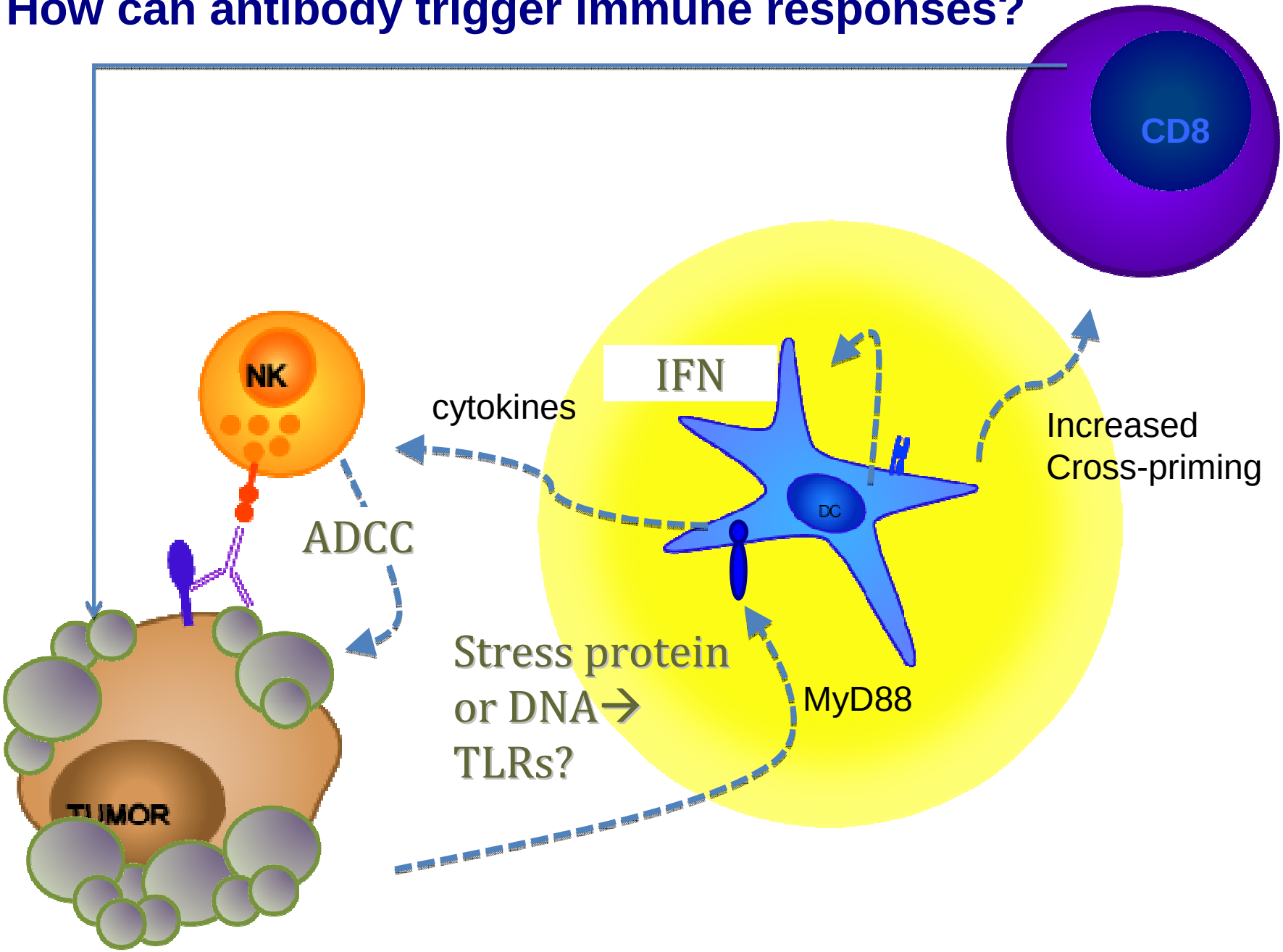
Neu Tg mice





Cancer Cell, 2010, MT, 2013, CCR 2013

How can antibody trigger immune responses?



Type I interferons are induced and necessary during antibody-mediated tumor regression.

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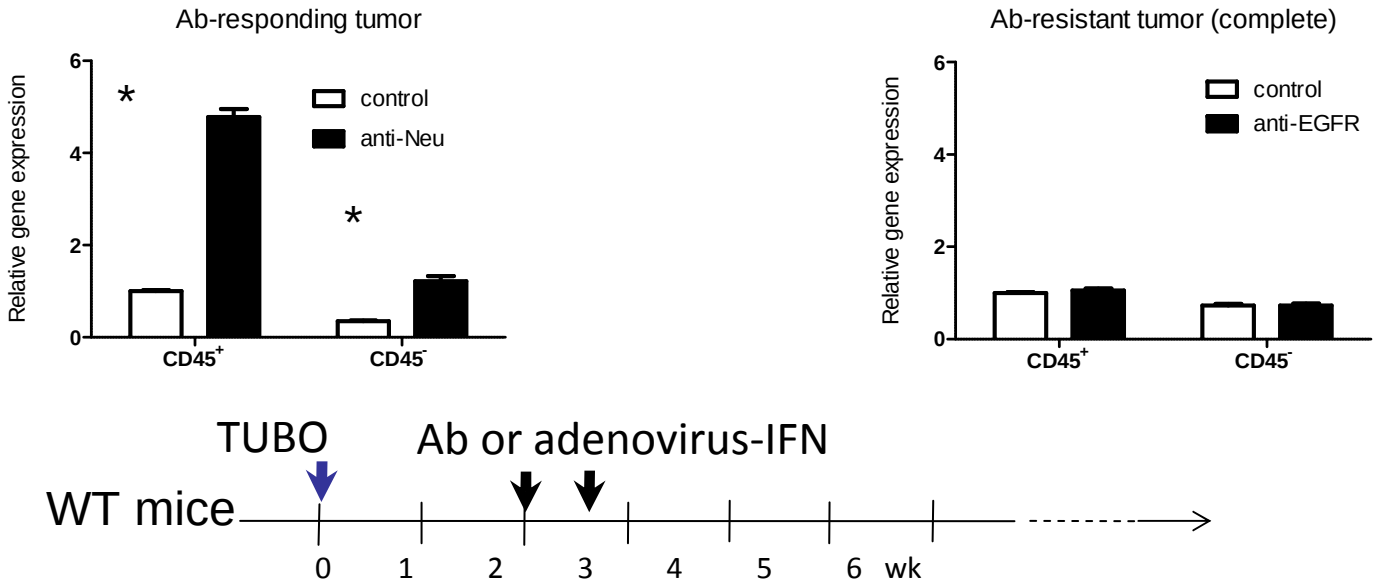

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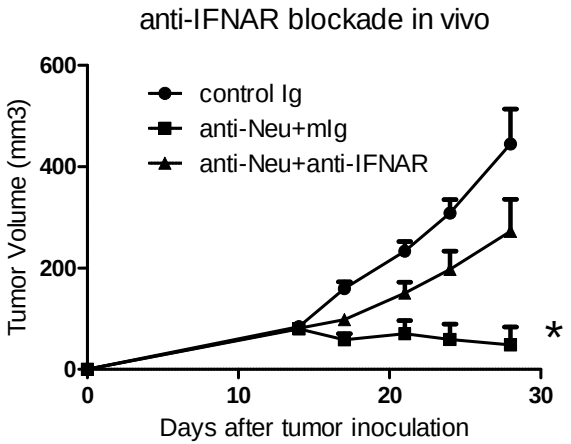
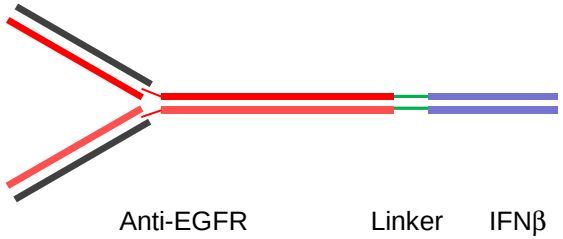
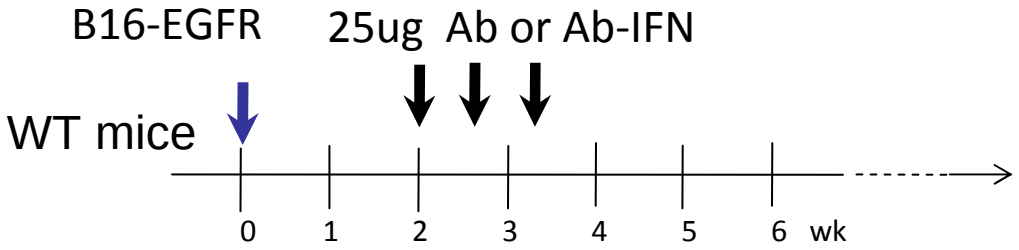


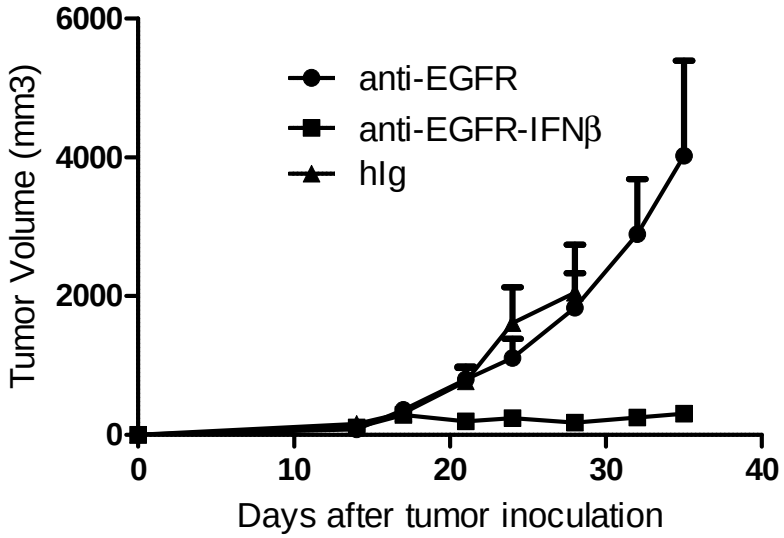
Ab can induce IFN for tumor regression but antibody can not induce IFN in Ab-resistant tumor
Could exogenous IFN be potent for targeting tumor?

How to target tumor with IFN: armed Ab with IFN for Ab-resistant tumor





Mouse Ab-resistant B16-EGFR tumor (complete)



Anti-EGFR-IFNb is effective for controlling Ab resistant tumor

Anti-EGFR-IFNb could induce anti-tumor CTL responses through increase of cross-priming

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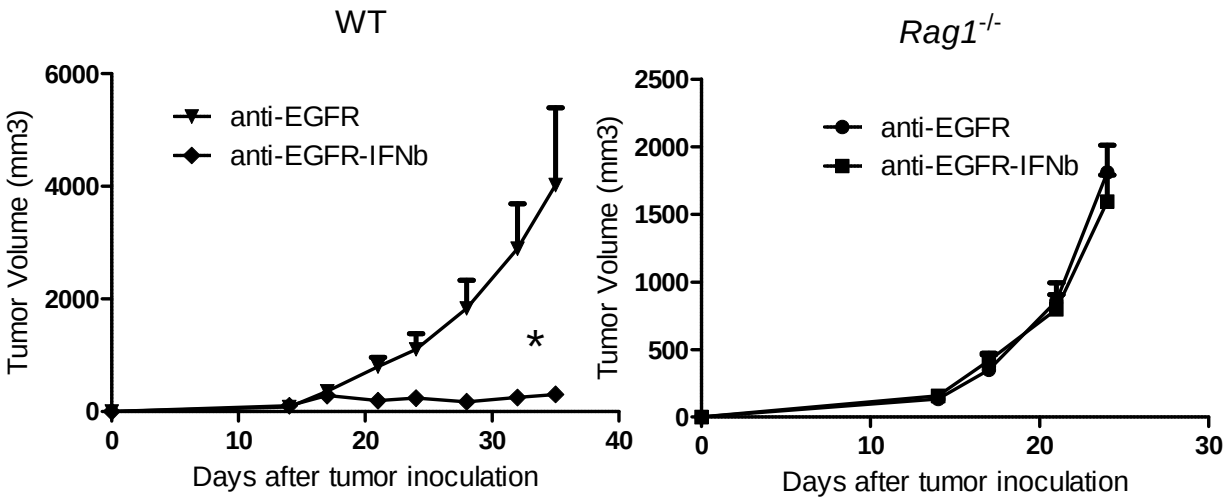

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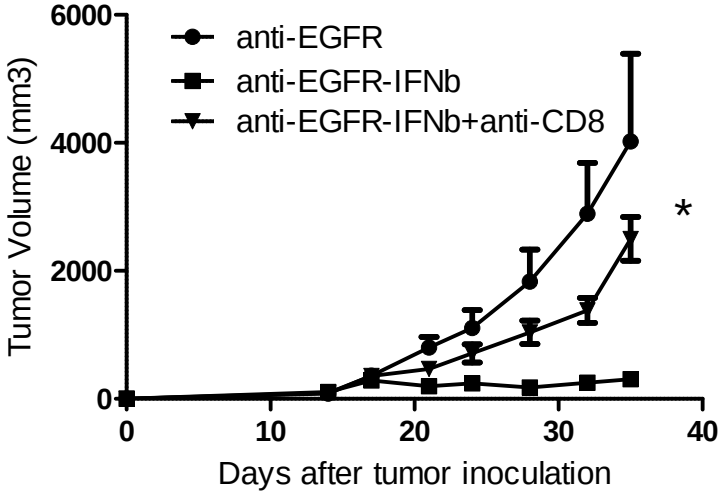

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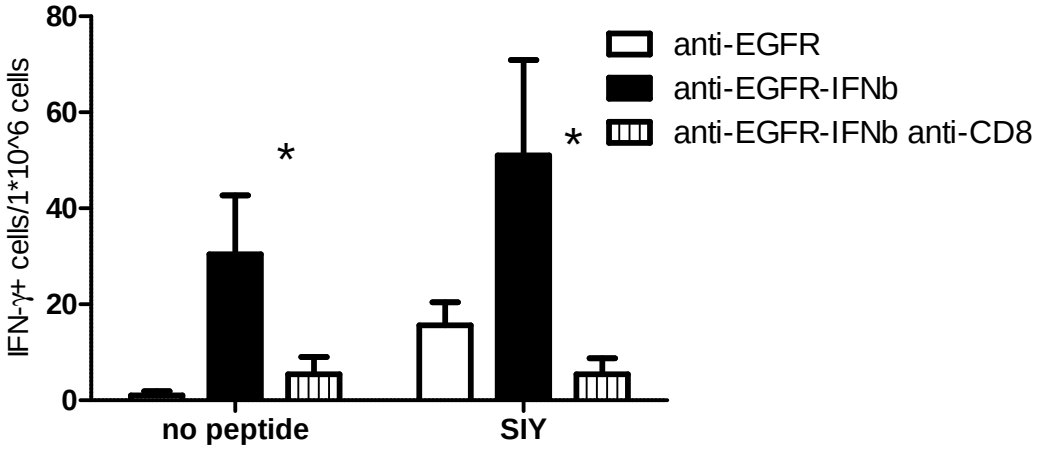
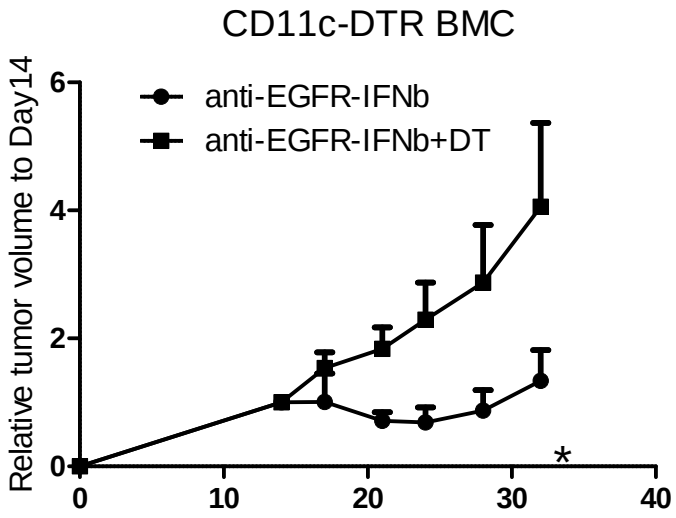
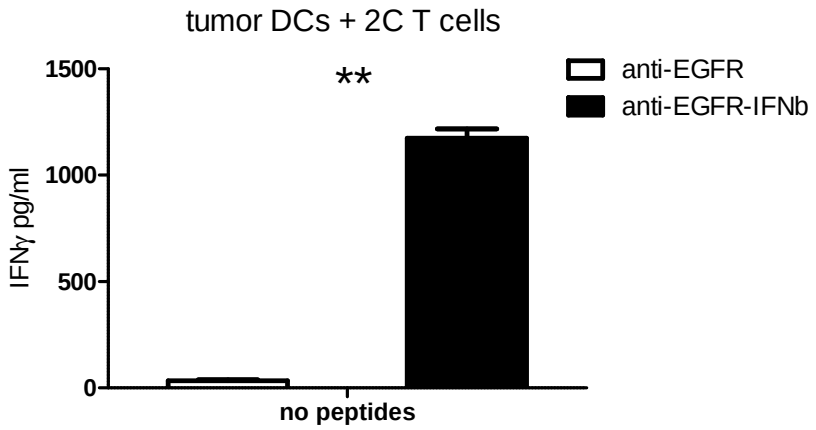
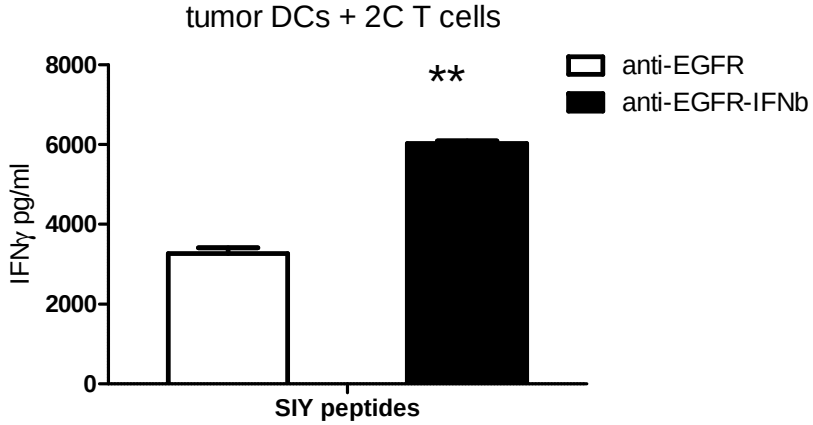


Targeting tumor with Ab-IFNb depend on DC and increase the cross-presentation



Cross-priming: DC from tumor





DCs were the major cell type responding to the anti-EGFR-IFNβ treatment

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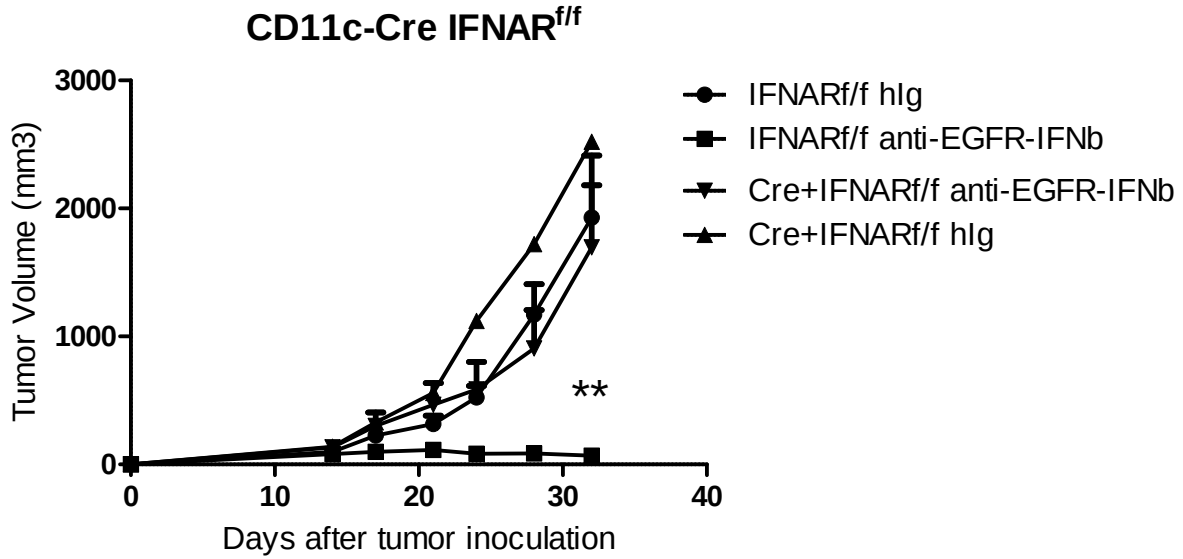

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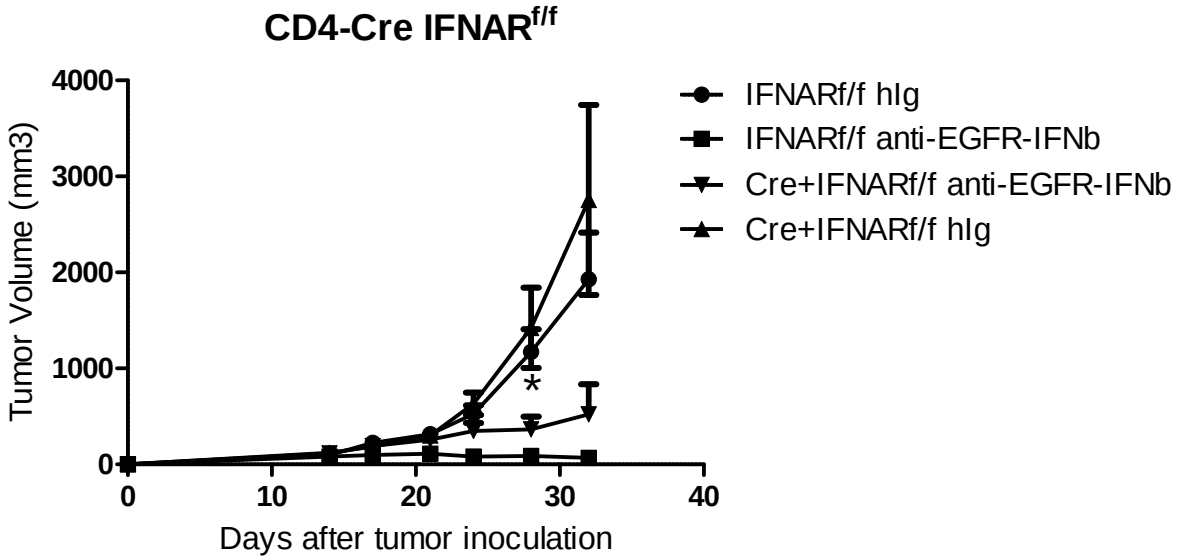
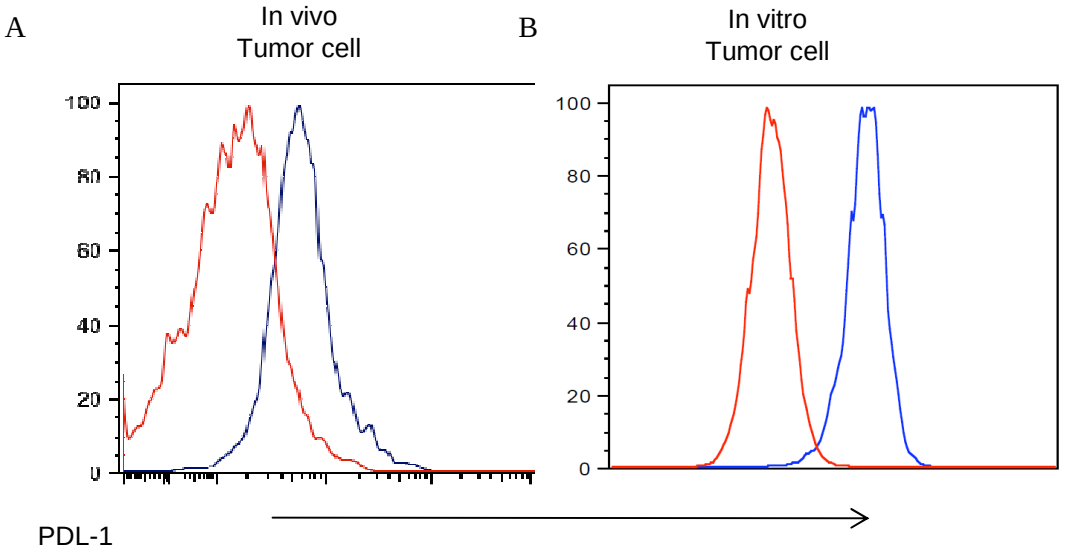
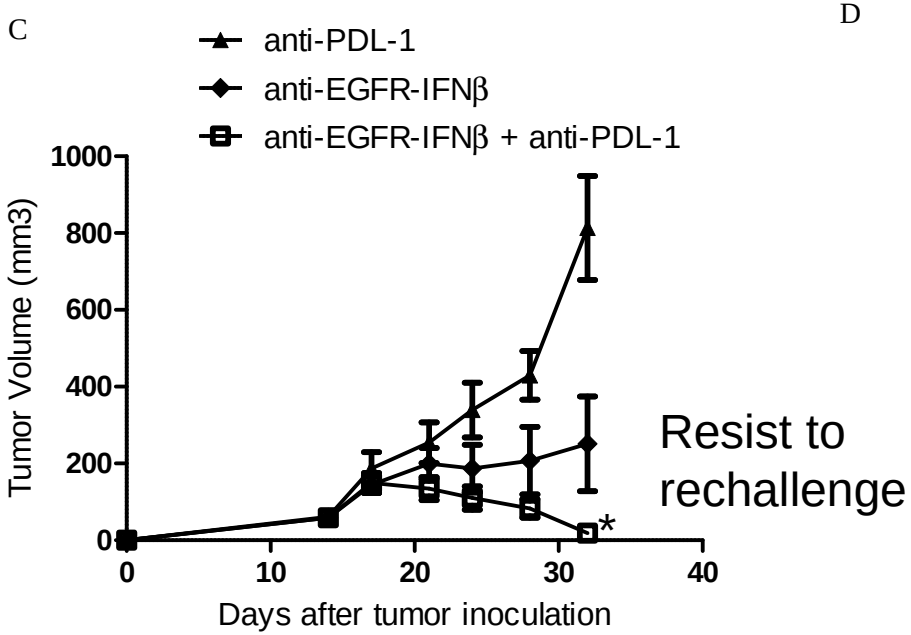
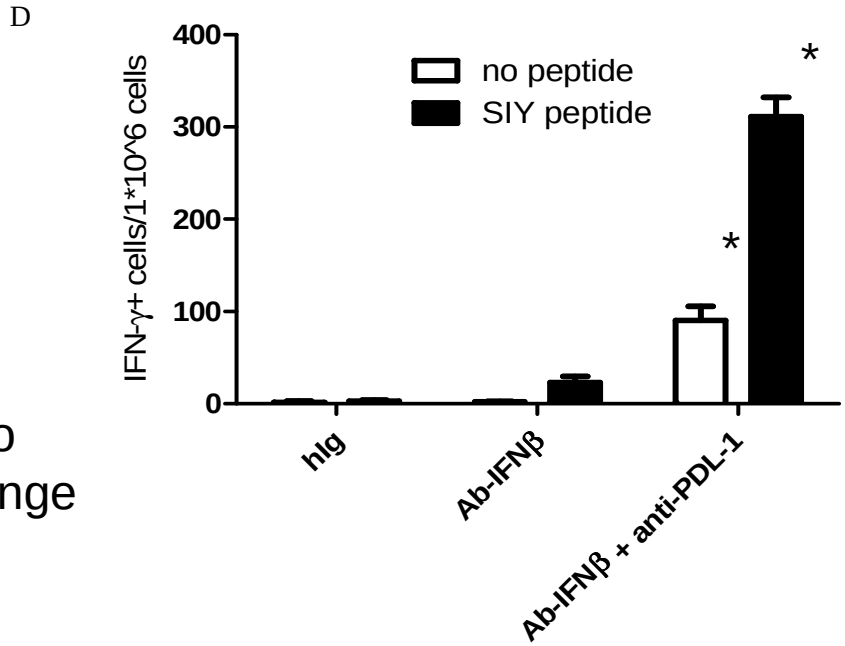


Antagonizing PDL-1 expression induced by AB-IFNβ achieved tumor-free outcome.







Why is anti-tumor effect by antibody diminished when tumor is further progressed?

- Ab dose is too low
- Ab fails to penetrate inside tumor
- Tumor grows more rapidly
- Increased tumor induced tolerance
- Suppressive cells are increased: which one?

Acknowledgements

HER2/neu

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Mark Greene