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Society for Immunotherapy of Cancer

Radiation-Induced Viral Mimicry

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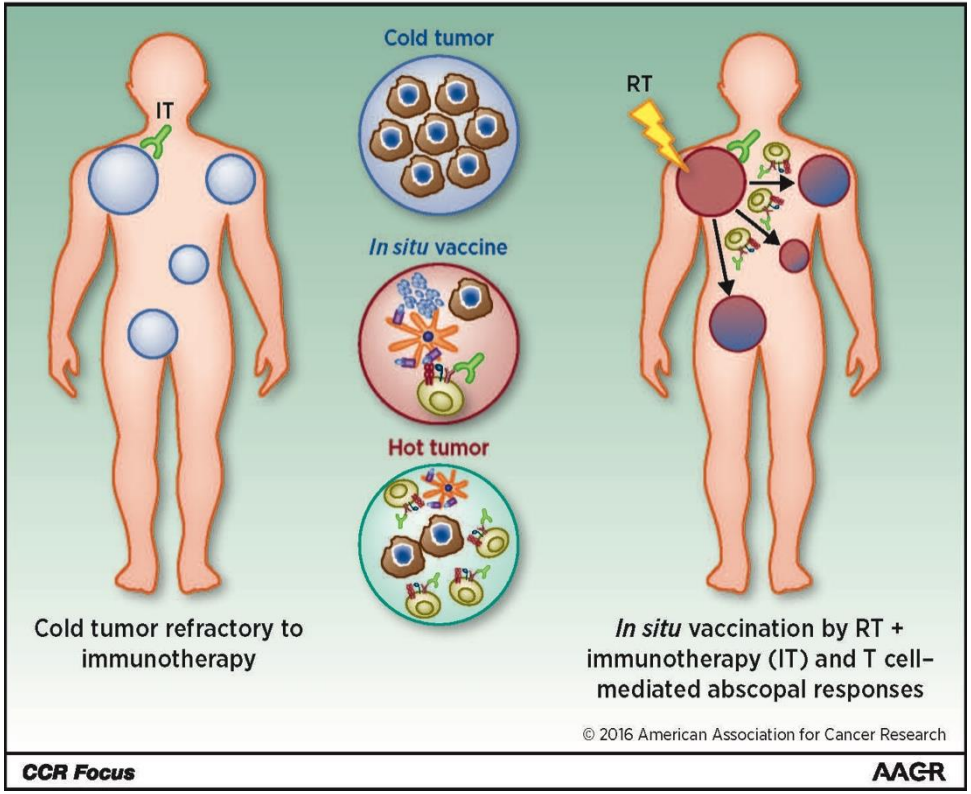
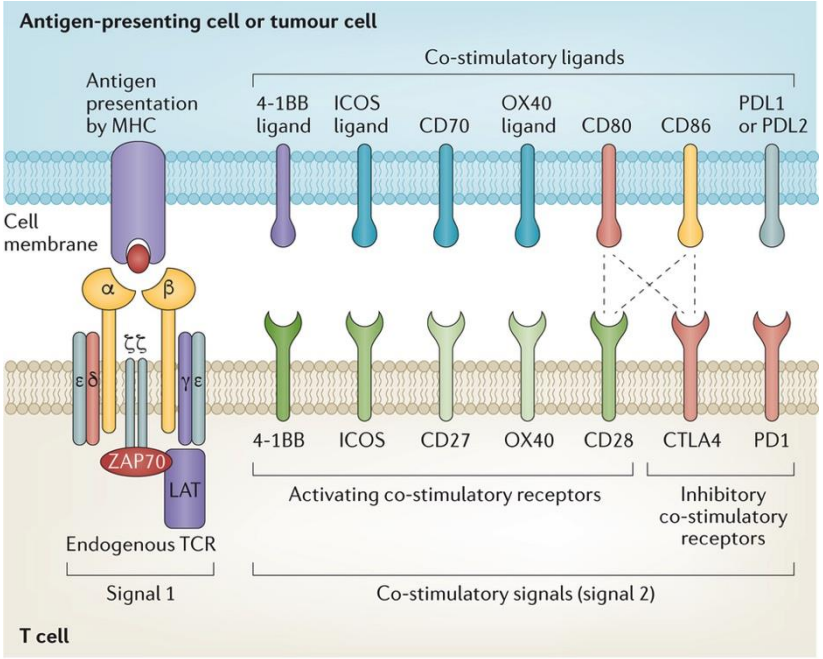
The role of radiotherapy in overcoming resistance to cancer immunotherapy





Nature Reviews | Cancer

T cell activation: Antigen + Adjuvant signals…and removing the brakes

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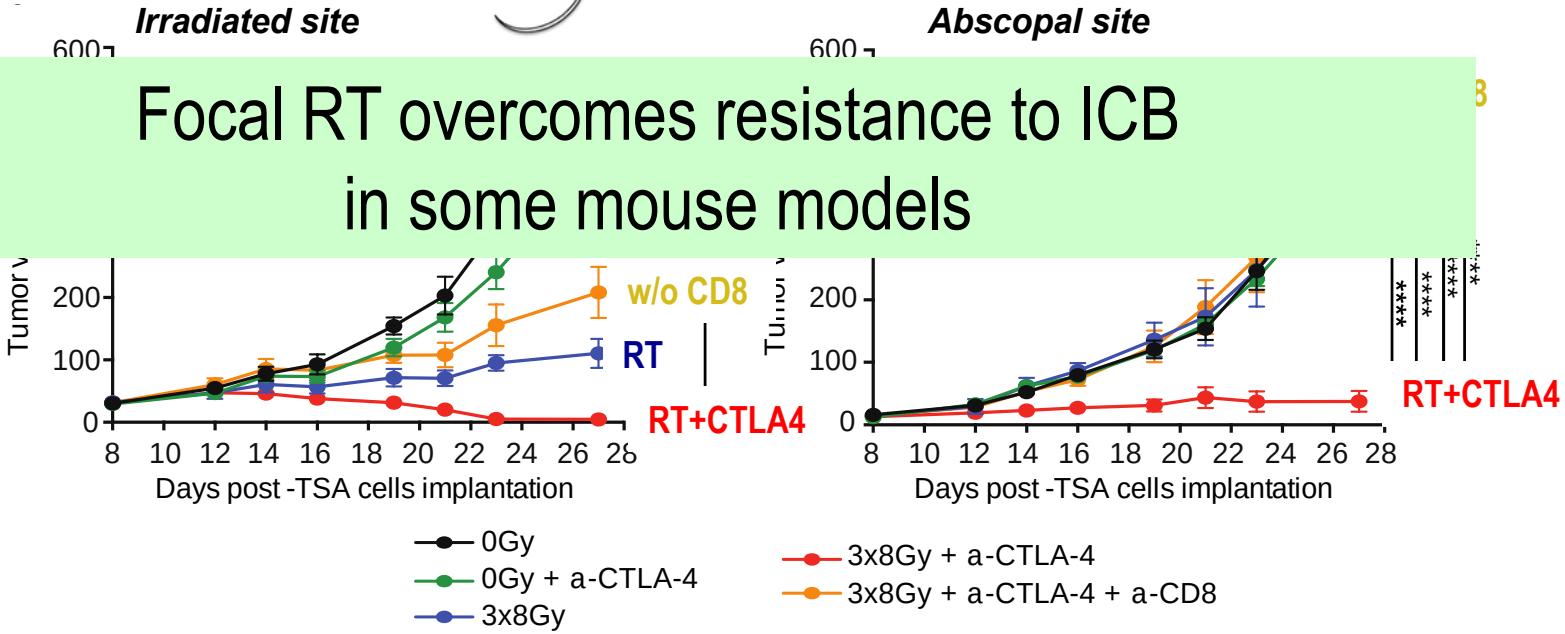
How radiation generates anti-tumor T cells?

CD8 T cells generated by RT+anti-CTLA4 act locally and systemically

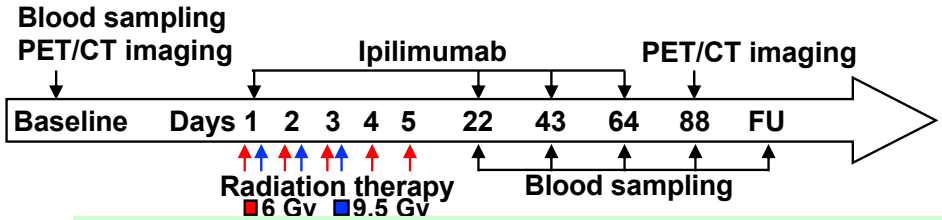
Anti-CTLA4
(9H10)

Focal RT overcomes resistance to ICB
in some mouse models



Vanpouille-Box et al., Nature Communications, June 2017

Abscopal response to RT+anti-CTLA-4 (NCT 02221739)

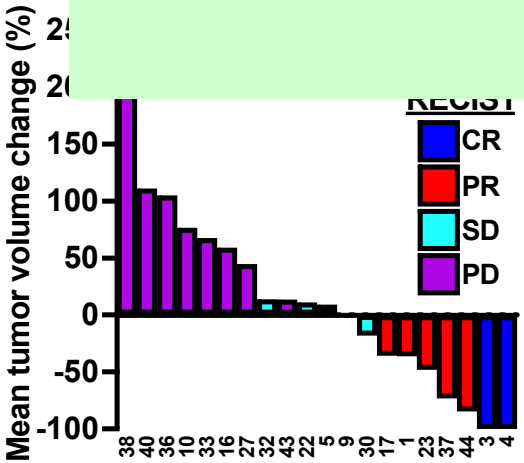


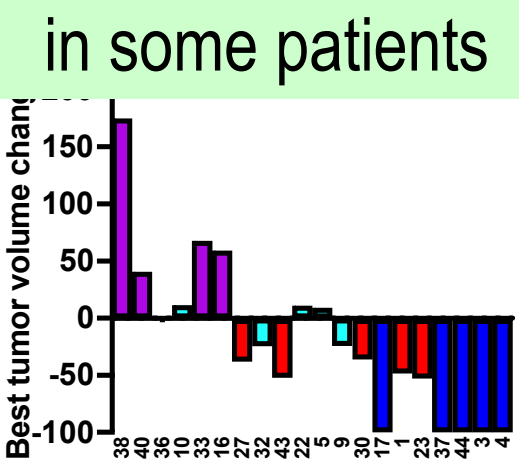
39 metastatic chemo-refractory NSCLC enrolled patients

22/39 patients completed treatment;

21/22 patients were evaluable

Focal RT overcomes resistance to ICB in some patients





CR = 2

PR = 5

SD = 5

PD = 28

Total pts = 39

Formenti, et al., Nature Medicine 2018

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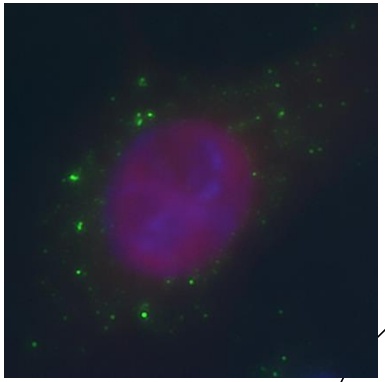
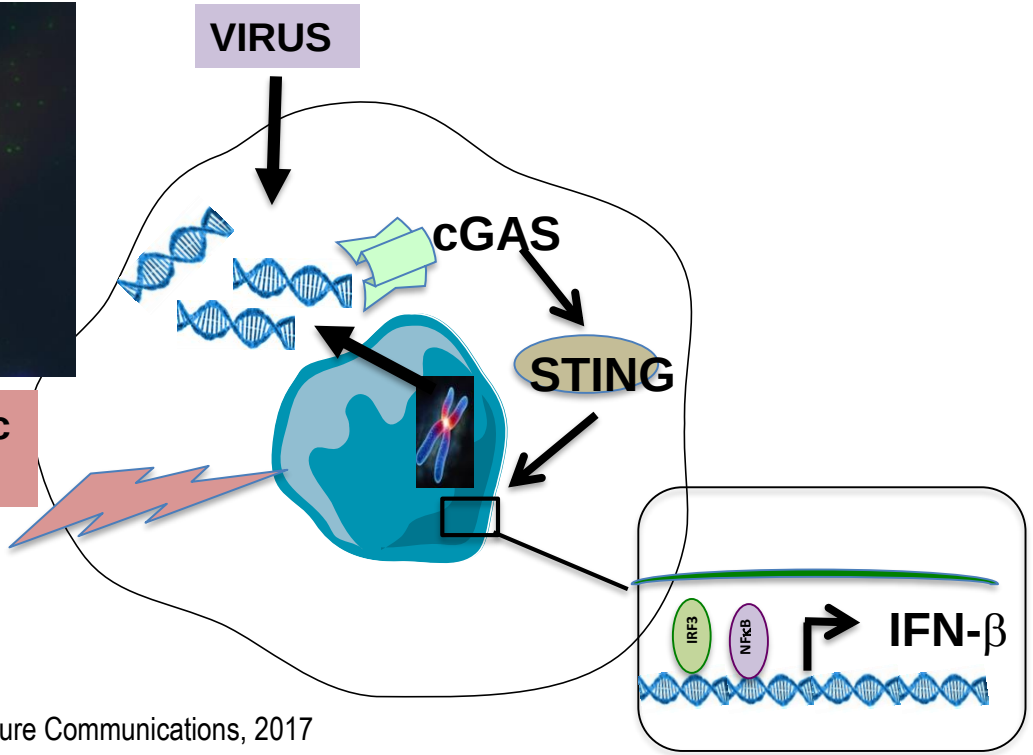
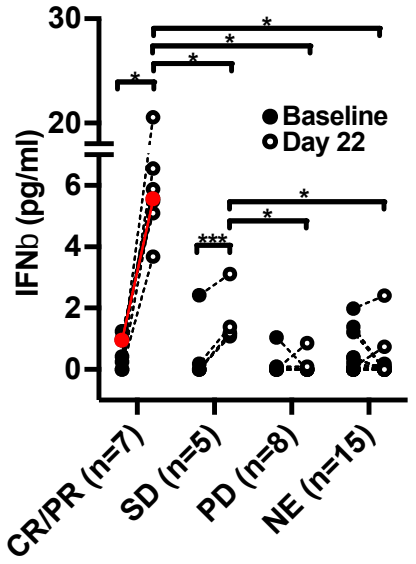
Radiation therapy activates a viral defense response pathway

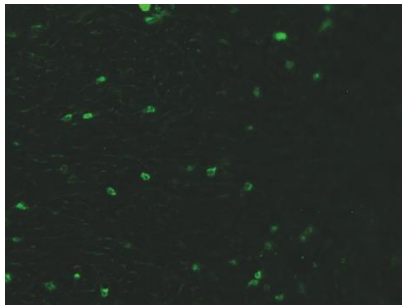


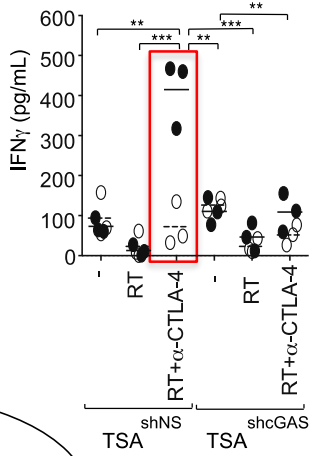


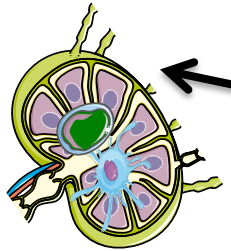


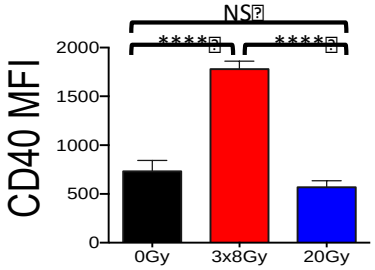
Formenti et al., Nature Medicine 2018

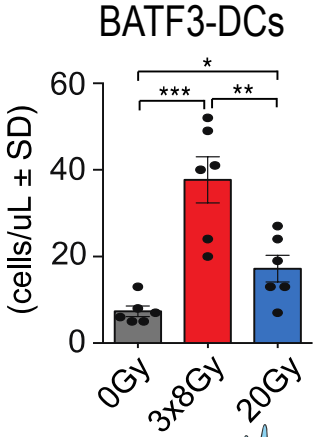
Vanpouille-Box et al., Nature Communications, 2017
Harding et al, Nature 2017, Mackenzie et al., Nature 2017
Deng et al, Immunity 2014

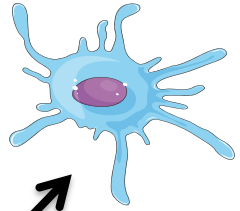


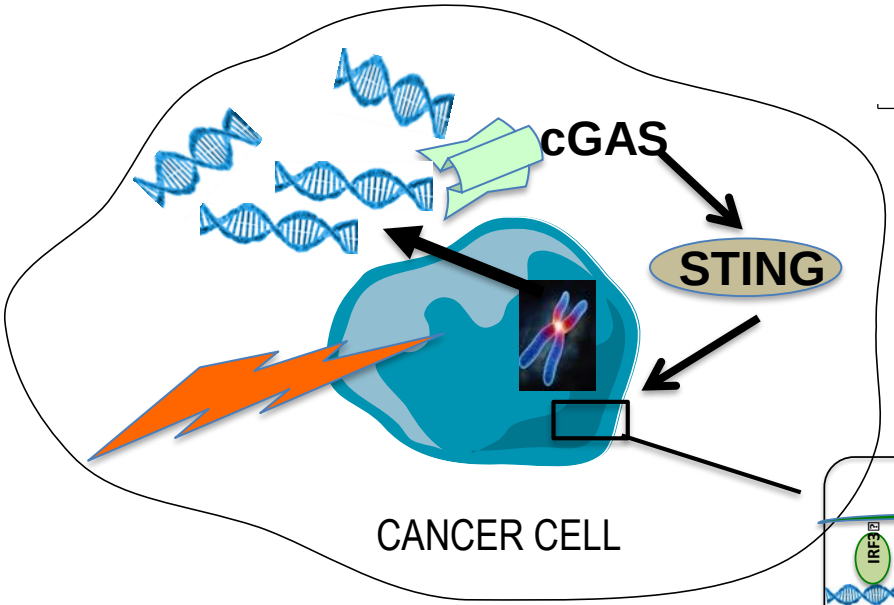


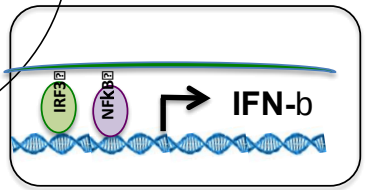


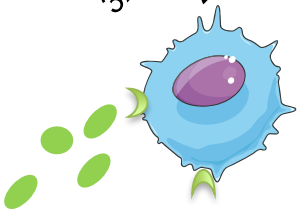












Vanpouille-Box et al., *Nature Communications*, 2017

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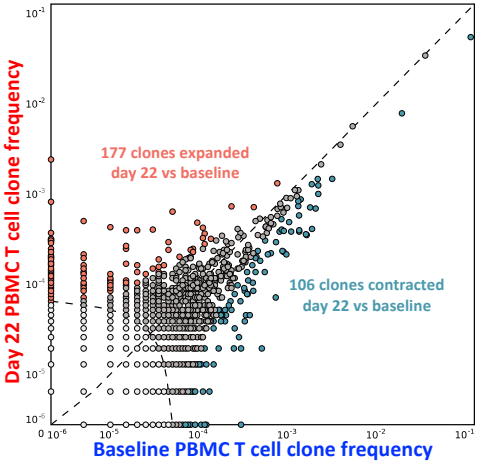
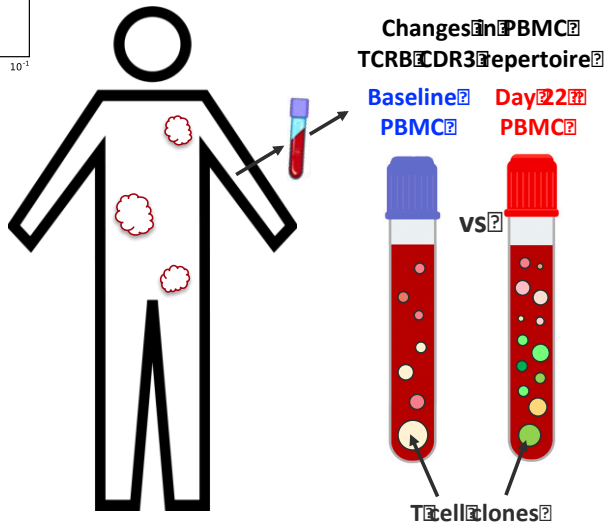
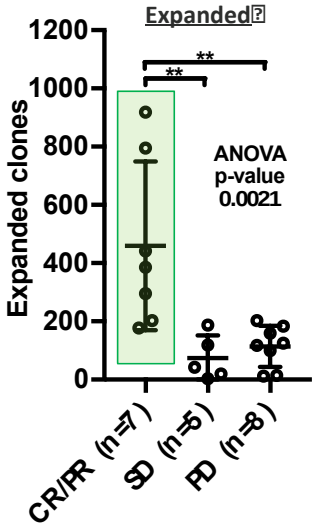
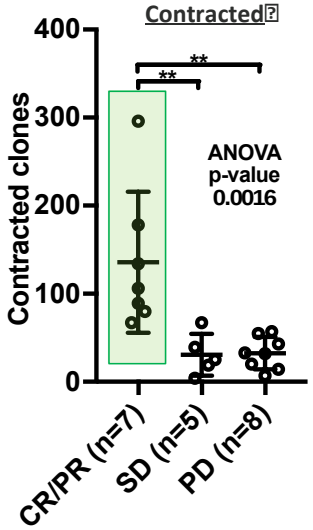
Large dynamic changes in TCR repertoire between baseline and day 22 for responders



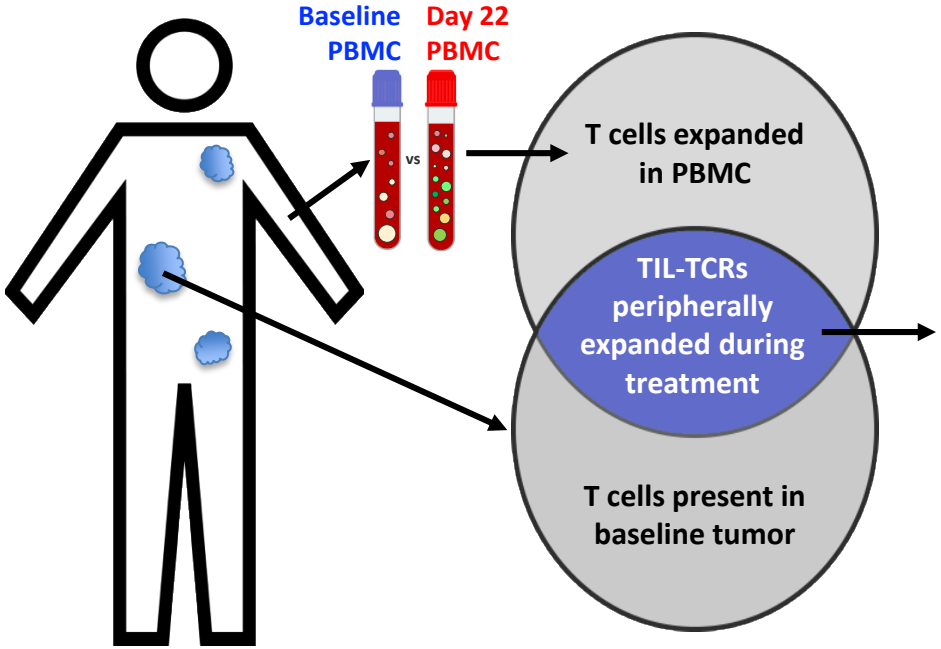




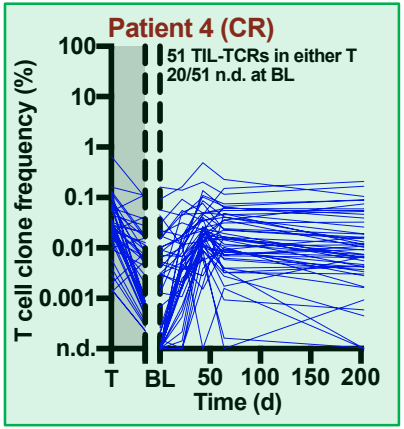


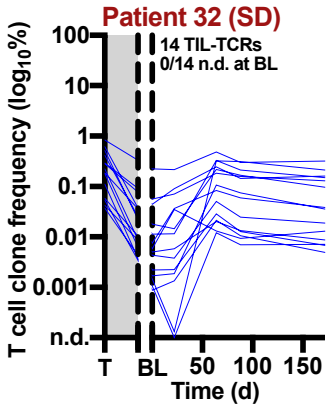
Formenti et al., Nature Medicine 2018

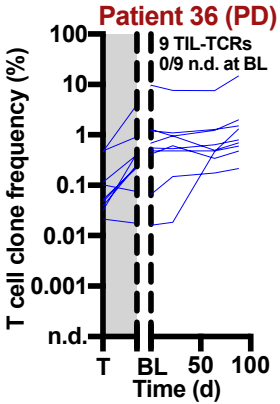
Expansion of tumor-derived T cell clones in blood of complete responder

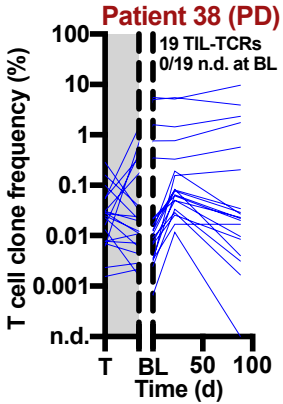


Frequency of TIL-TCRs expanding in PBMC









T = tumor
BL = baseline

Formenti, Rudqvist, et al., Nature Medicine 2018

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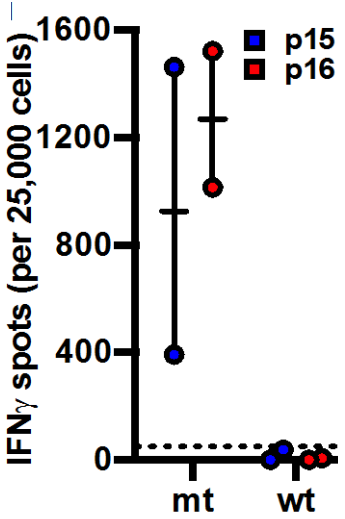
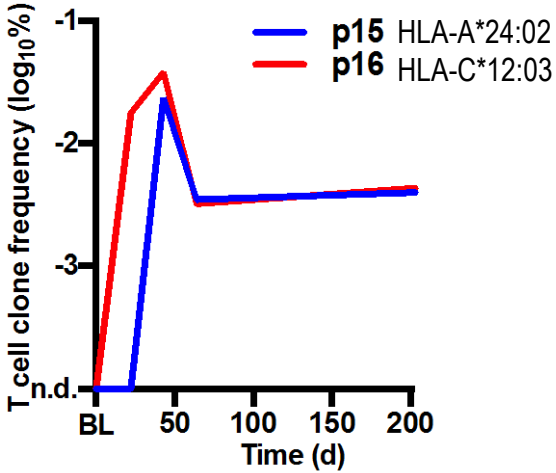
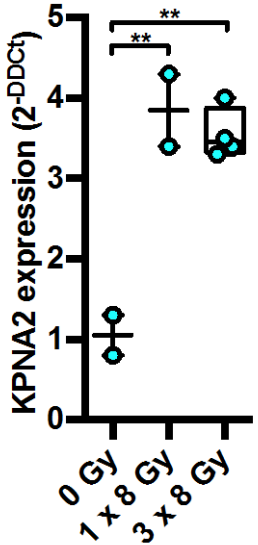
CD8 T cells present in the post-treatment blood of CR recognize an immunogenic mutation in KPNA2 (karyopherin A2)





p15 ***not*** detected in pre-tx tumor
p16 detected in pre-tx tumor

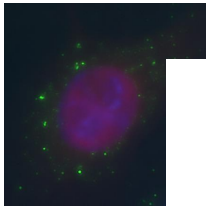
NSCLC PDTX



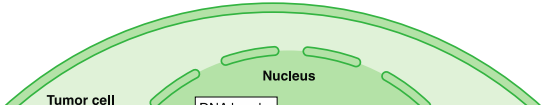
RT **enhances the expression** of an immunogencic mutation

Formenti, et al., Nature Medicine 2018

Viral mimicry and *in situ* vaccination by focal RT



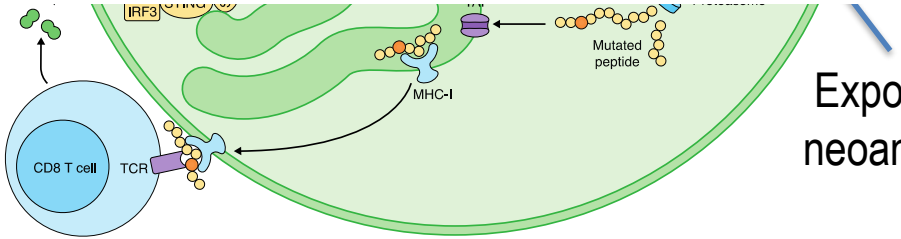
Productior
endogeno
adjuvants



Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy

Eric A. Reits,[1] James W. Hodge,[2] Carla A. Herberts,[1] Tom A. Groothuis,[1] Mala Chakraborty,[2] Elizabeth K. Wansley,[2] Kevin Camphausen,[3] Rosalie M. Luiten,[1] Arnold H. de Ru,[4] Joost Neijssen,[1] Alexander Griekspoor,[1] Elly Mesman,[1] Frank A. Verreck,[4] Hergen Spits,[1] Jeffrey Schlom,[2] Peter van Veelen,[4] and Jacques J. Neefjes[1]

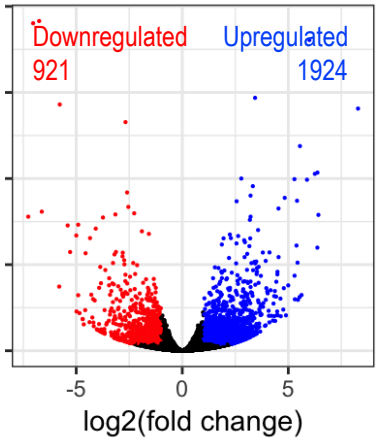
JEM 2006



Exposure of neoantigens

Lhuillier et al., Genome Medicine, 2019

RNA Seq data of NSCLC PDX



Rudqvist & Demaria, unpublished results

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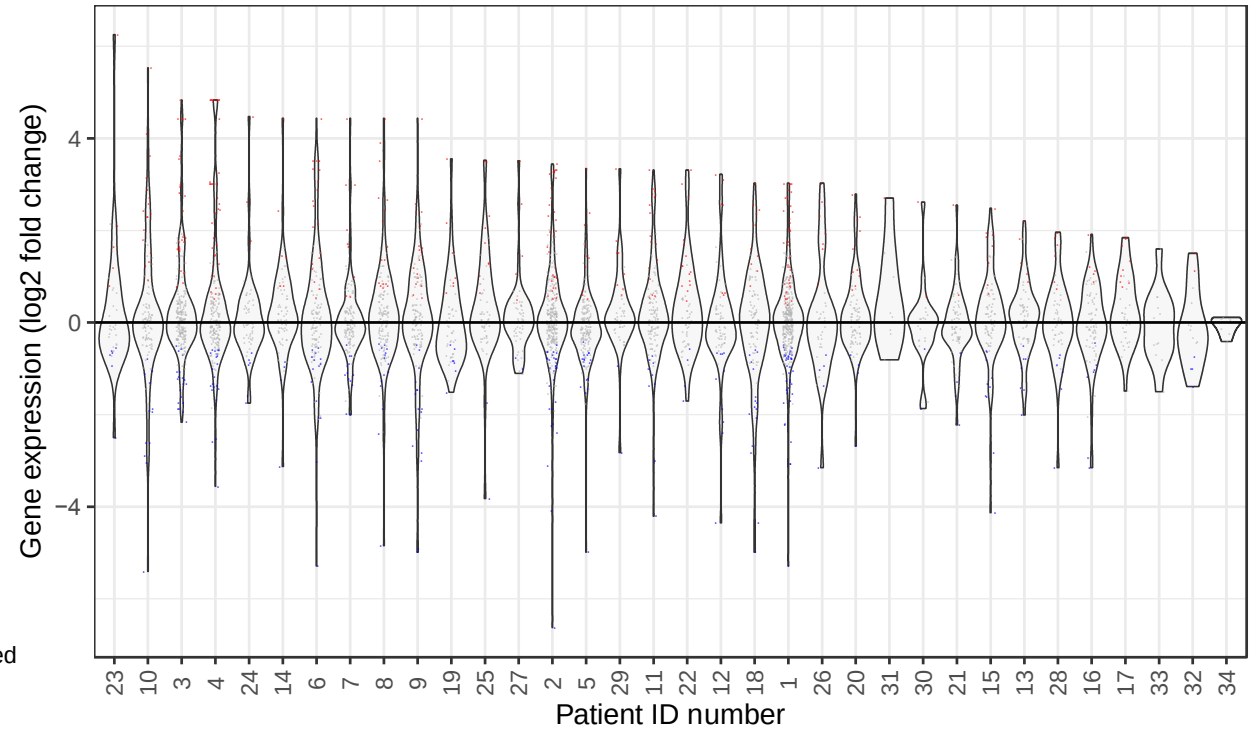
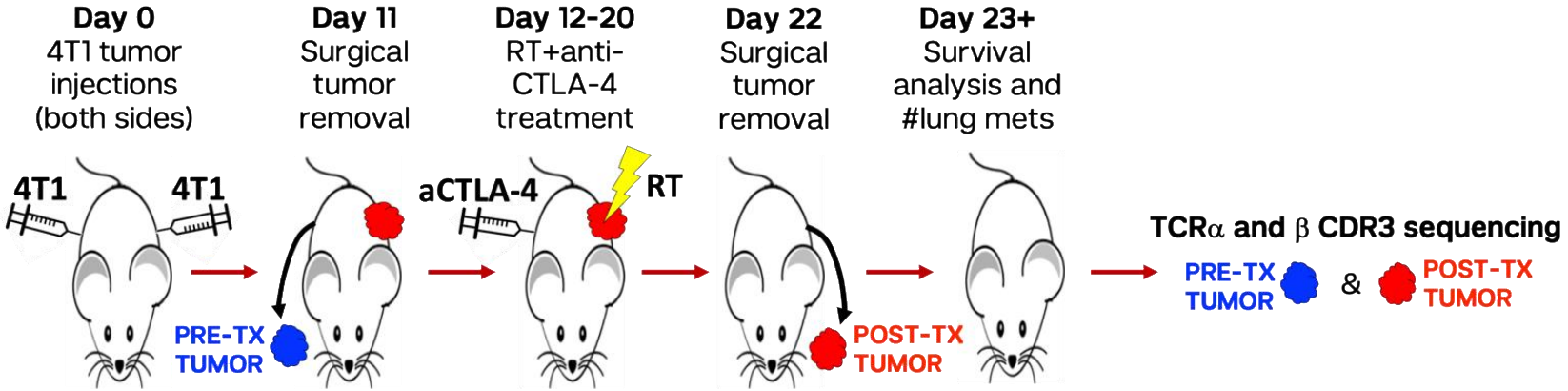
Antigenic mutations in NSCLC could be modulated by RT

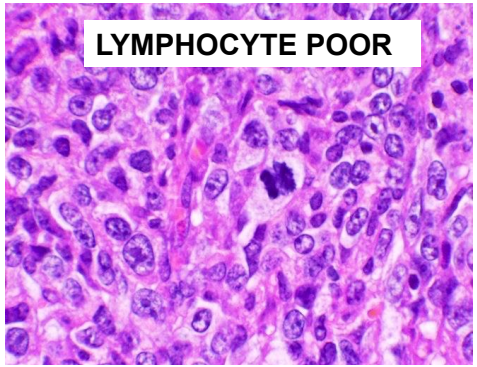
Immunogenic mutations as defined in: Rizvi et al., Science (2015)



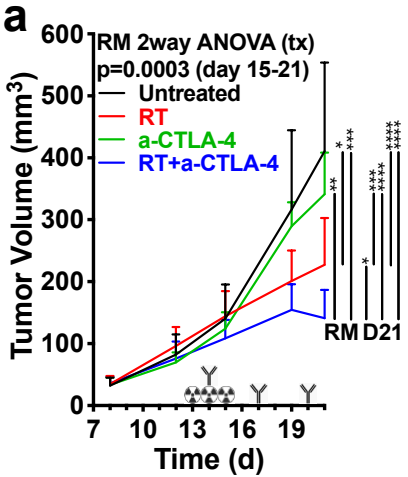
Rudqvist & Demaria, unpublished

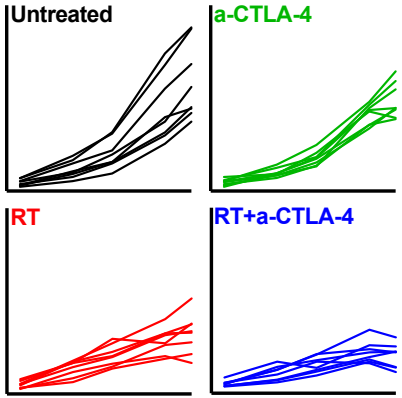
A deep dive into T cells activated in irradiated tumors

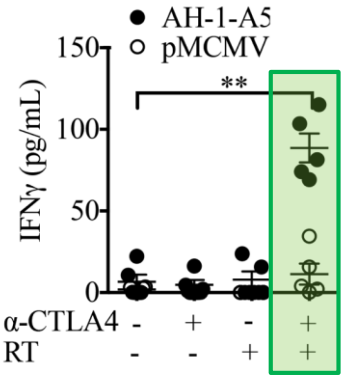




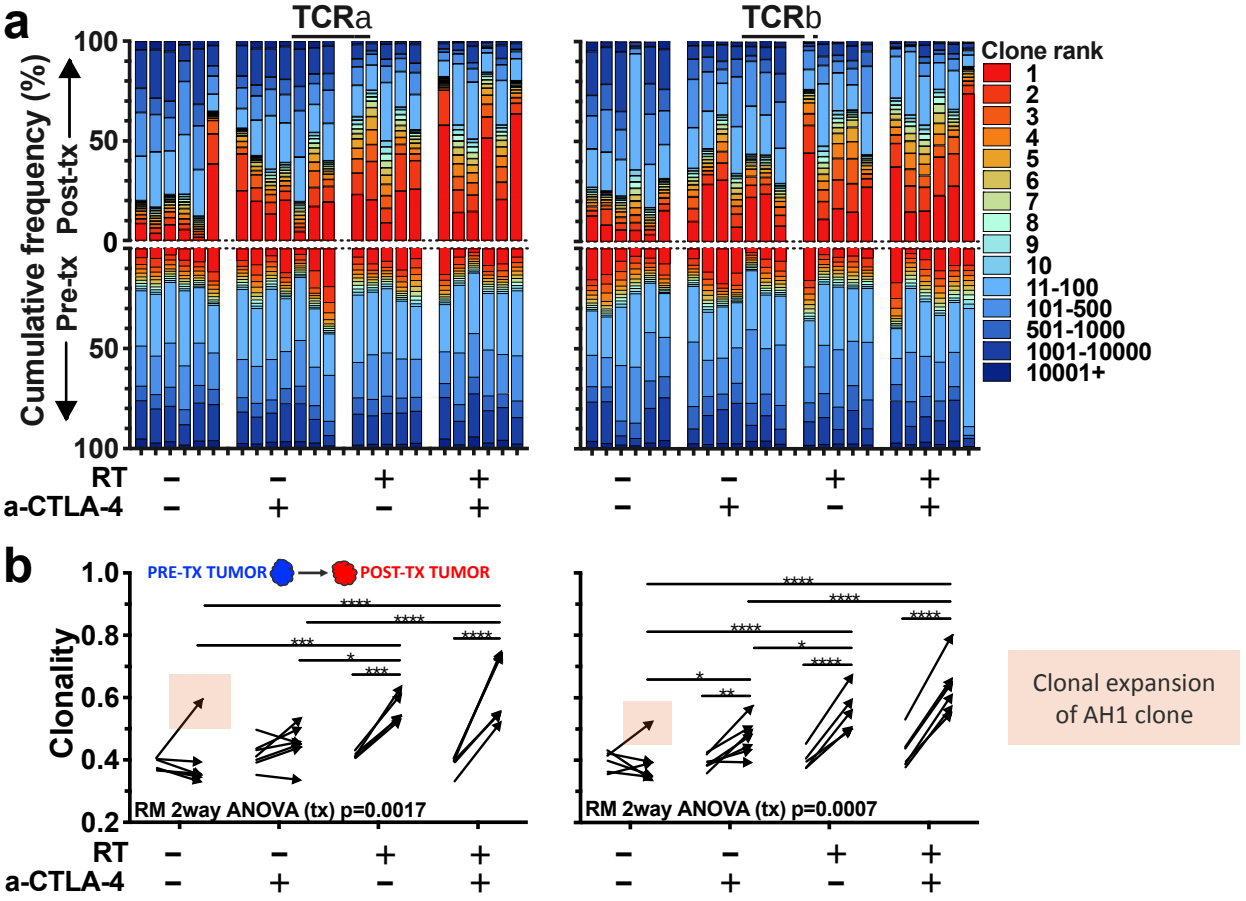
4T1: 309 NSV







Increased clonality of TCR repertoire is driven primarily by RT

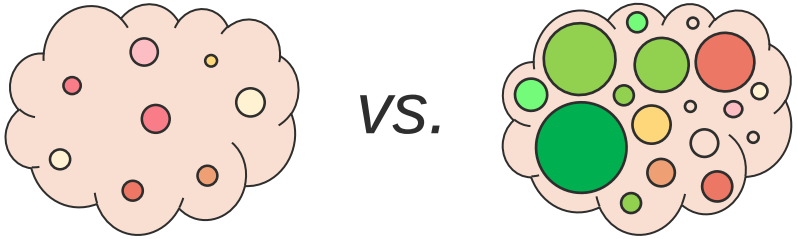


Clonal expansion of AH1 clone

Rudqvist et al., *unpublished data*

Increased divergence of TCR repertoire is driven primarily by RT

- **Jensen-Shannon divergence *(JSD)*** =
  = difference between pre-tx and post-tx TCR repertoires
  If *JSD* ⇧, then similarity⇩

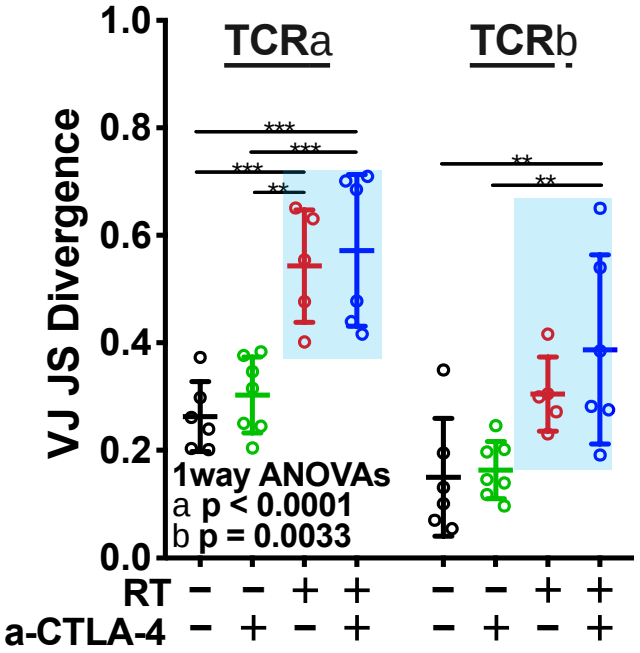


Pre-tx tumor TCR repertoire

Post-tx tumor TCR repertoire

,

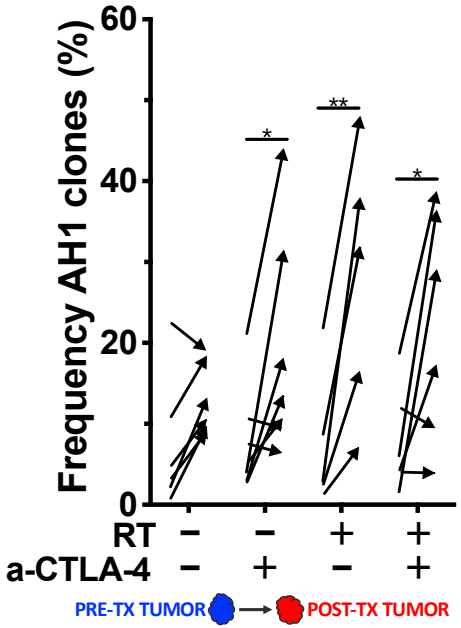
where *KLD* (Kullback-Liebler divergence) =



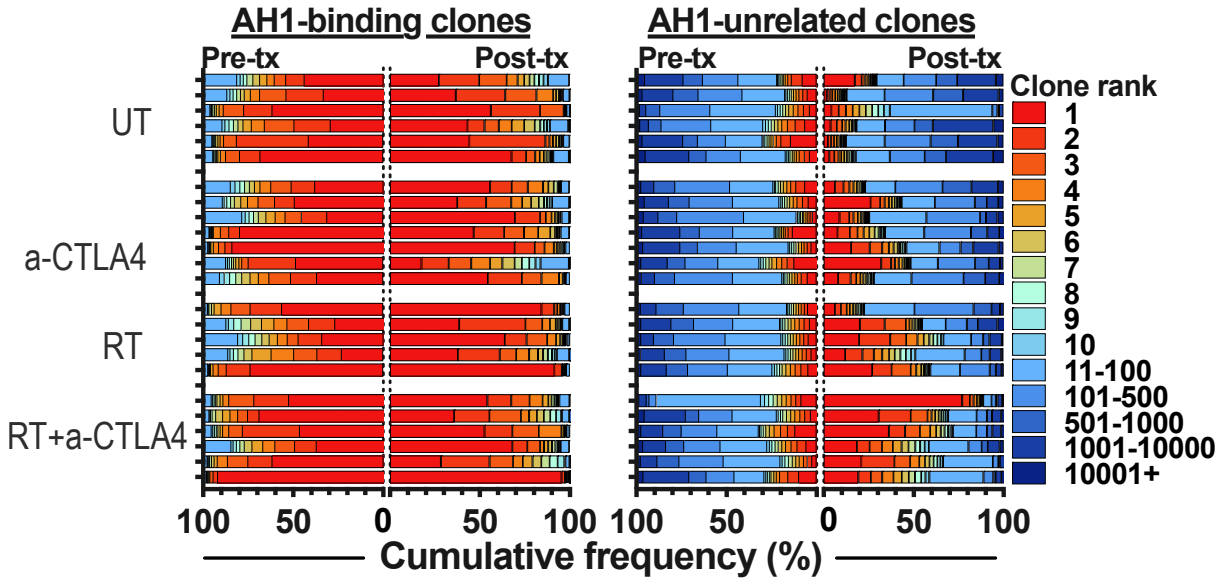
Rudqvist et al., *unpublished data*

The AH1 repertoire is expanded but increase in clonality comes from AH1-unrelated clones

Expansion of AH1-binding clones

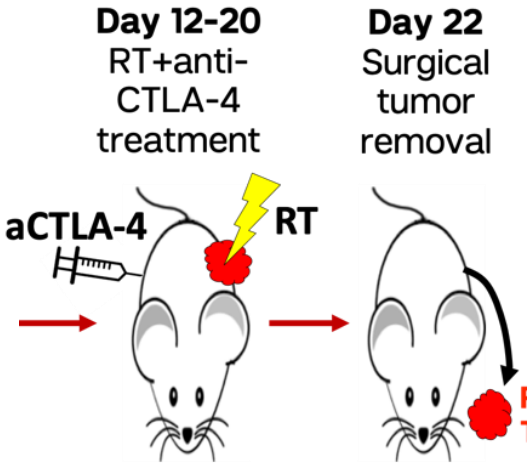


Clonality increase only in the AH1-unrelated compartment



Rudqvist et al., *unpublished data*

Phenotyping of T cells infiltrating the 4T1 model using scRNA-sequencing

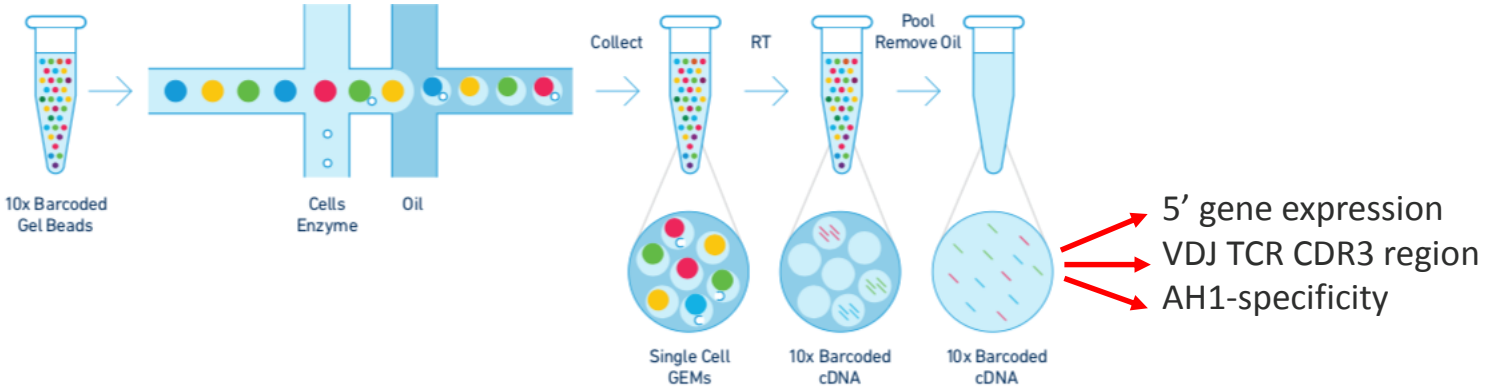


POST-T TUMOR

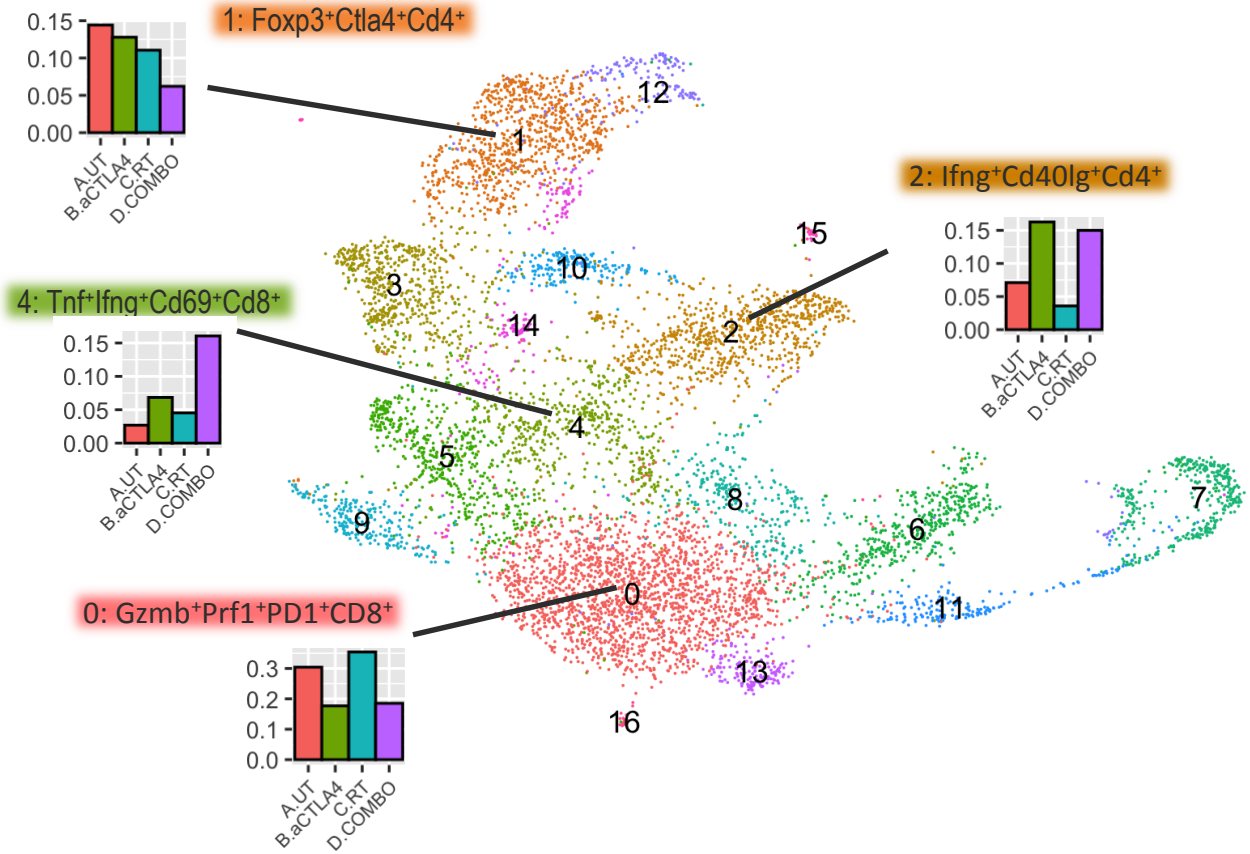
Sorting of CD3+ T cells

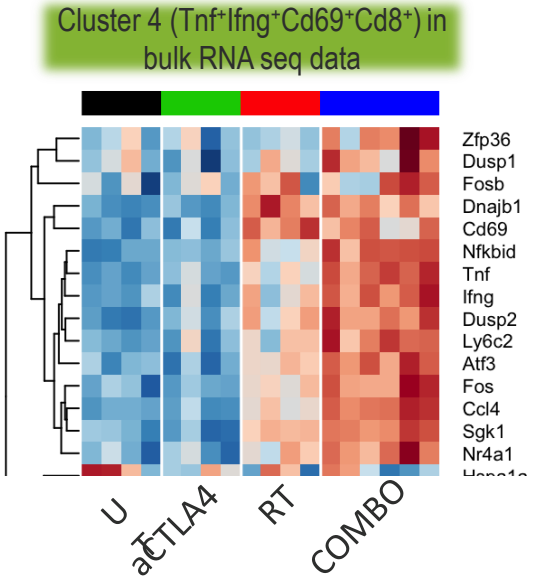
10X Single cell sequencing

- 5’ gene expression
- VDJ TCR CDR3 region
- AH1-specificity



Ifnγ/Tnfα producing CD8 T cells are selectively expanded by RT+a-CTLA-4



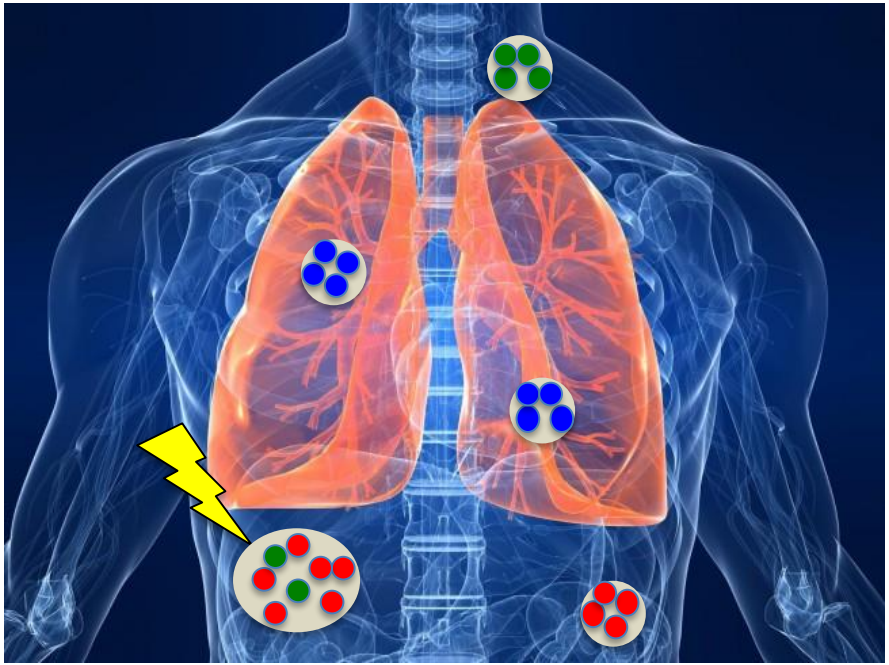


Rudqvist et al., *unpublished data*

Take Home message

- The DNA damage response elicited by radiation activates canonical viral defense pathways via cytosolic DNA
- The radiation-induced transcriptome “exposes” immunogenic mutations to the immune system
- Radiation promotes a diversification and expansion of the TIL TCR repertoire
- A subset of polyfunctional CD8 T cells is expanded only in tumors of mice treated with RT+anti-CTLA-4

Barriers: Tumor heterogeneity and resistance to T cells



Antigenic diversity= multi-site "vaccination"

Downregulation of cGAS/STING

Loss of MHC/b2m/IFNγR

Immunize and then treat resistant lesions!

RADIATION & IMMUNITY PROGRAM

Weill Cornell Medicine

Sandra Demaria
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Sheila Spada
Maud Charpentier
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Yasmeen Sarfraz
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Julie Diamond

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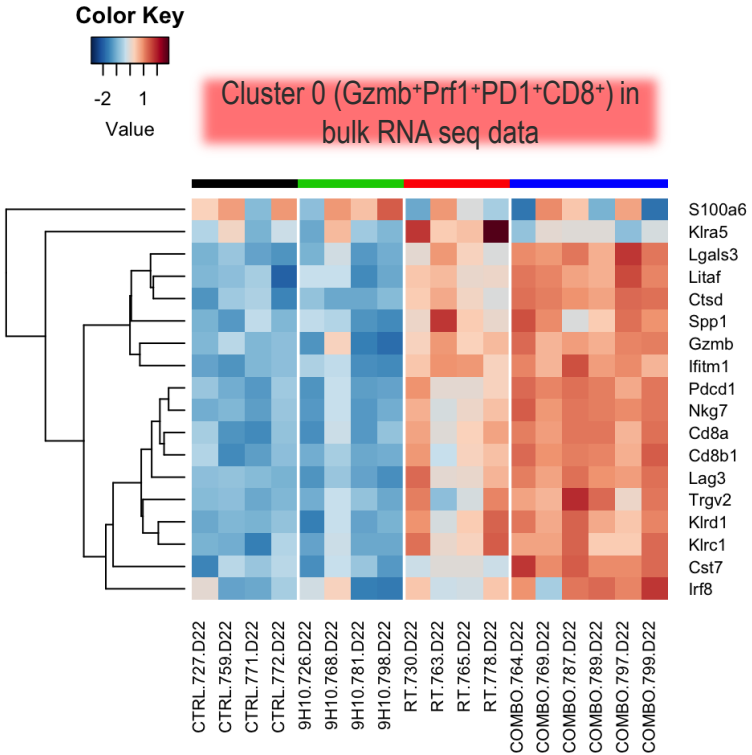
BCRF
DOD BCRP


Color Key
-2
1
Value
Cluster 0 (Gzmb+Prf1+PD1+CD8+) in bulk RNA seq data
S100a6
Klra5
Lgals3
Litaf
Ctsd
Spp1
Gzmb
Ifitm1
Pdcd1
Nkg7
Cd8a
Cd8b1
Lag3
Trgv2
Klrd1
Klrc1
Cst7
Irf8
CTRL.727.D22
CTRL.759.D22
CTRL.771.D22
CTRL.772.D22
9H10.726.D22
9H10.768.D22
9H10.781.D22
9H10.798.D22
RT.730.D22
RT.763.D22
RT.765.D22
RT.778.D22
COMBO.764.D22
COMBO.769.D22
COMBO.787.D22
COMBO.789.D22
COMBO.797.D22
COMBO.799.D22