Is There a Role for Radiation Therapy and Immunotherapy?

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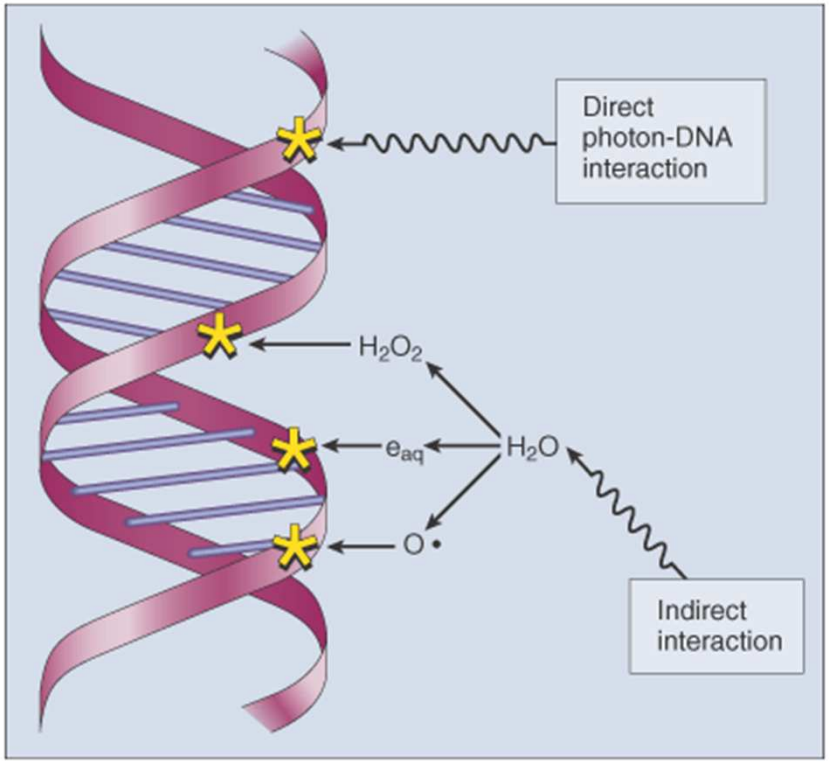
Outline

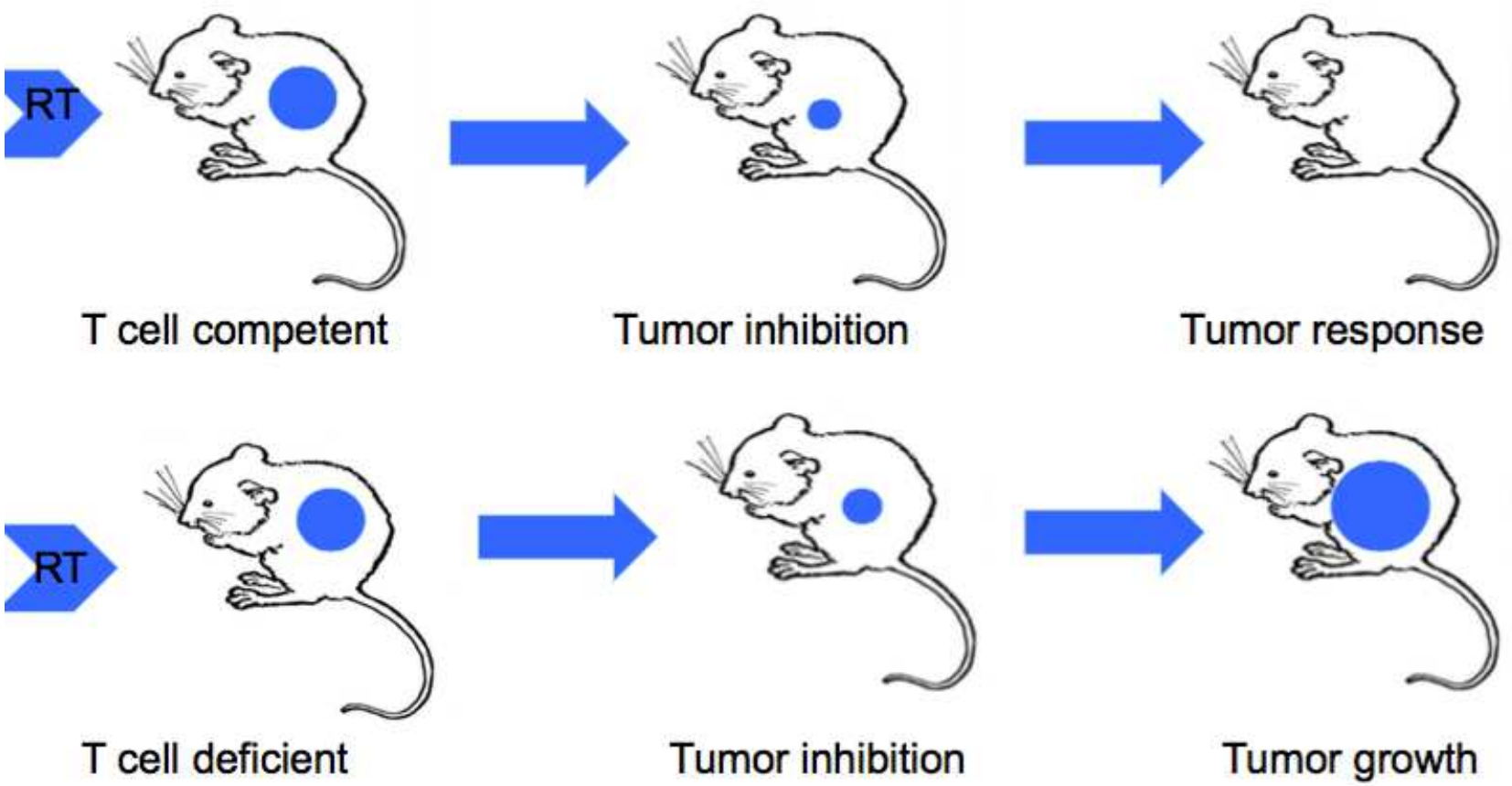
- Underlying immune mechanisms in radiation
- Effects of ionizing radiation on the immune system
- Radiation and Immunotherapy

Radiation and Inflammation: Teaching an Old Dog New Tricks



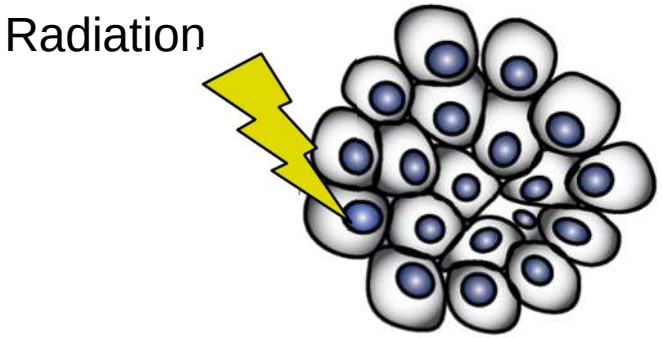
Traditional research in radiation has focused on cell intrinsic mechanisms: DNA damage, ROS production, tumor cell kill/survival

T cells are necessary for the full response to RT



Stone HB, Peters LJ JNCI 1979

Radiation leads to immunogenic cell death



Complement (C3, C5)
Surace, *Immunity* 2015

HMGB1
Apetoh, *Nat Med* 2007

ATP
Ghiringhelli, *Nat Med* 2009

Calreticulin
Obeid, *Nat Med 2007*

Hsp70
Gabai, *Oncogene* 2005

How does RT influence the anti-tumor immune response?

Immunogenic Cell Death

Outline

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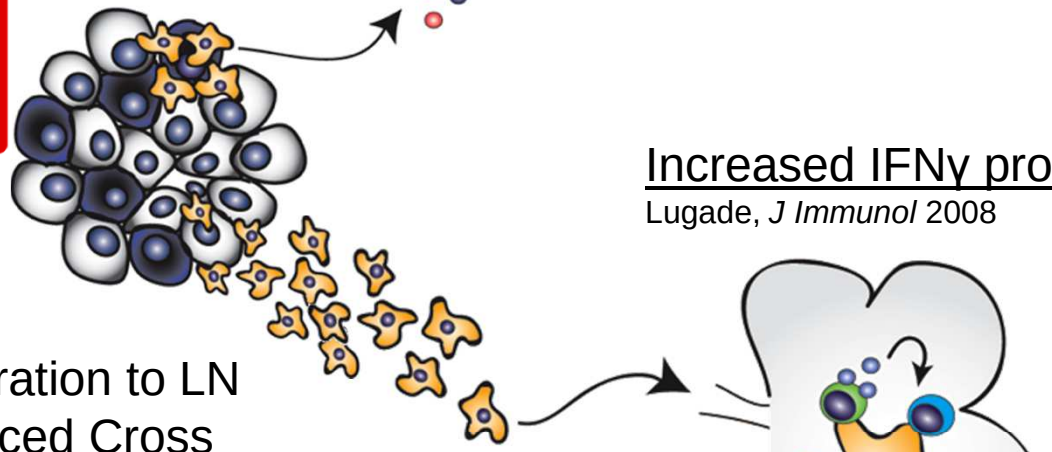
Radiation Enhances Multiple Inflammatory Pathways: *In Situ* Vaccination

Initiation of Local Inflammation

Increased cytokines:
IL-1, TNFα, Type I Interferons
Hallahan, *PNAS* 1995; Deng, *Immunity* 2014

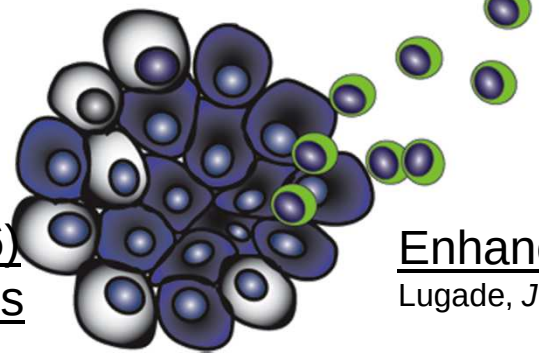


Increased IFNγ production
Lugade, *J Immunol* 2008

DC Migration to LN
Enhanced Cross Presentation
Reits, *J Exp Med* 2006

Antigen Presentation

Tumor Destruction



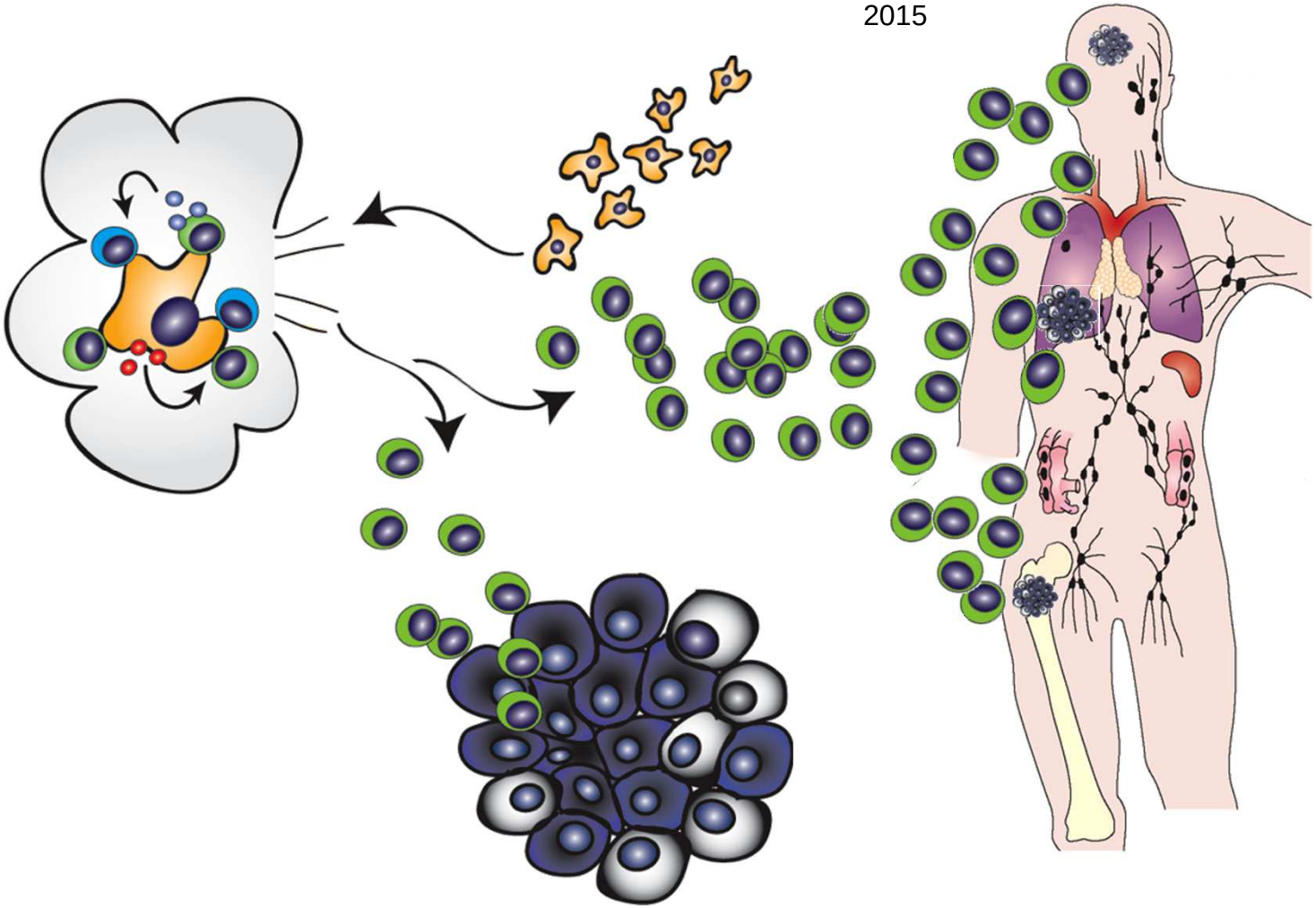
Increased chemokine (CXCL16) production to attract CD8+ CTLs
Matsumura, *J Immunol* 2012

Enhanced CD8+ T cell production
Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012

Radiation can also induce distant effects: "The Abscopal Effect"

Systemic Anti-tumor Immunity

Demaria, *IJROBP* 2004; Sharabi, *Cancer Immunol Res* 2015

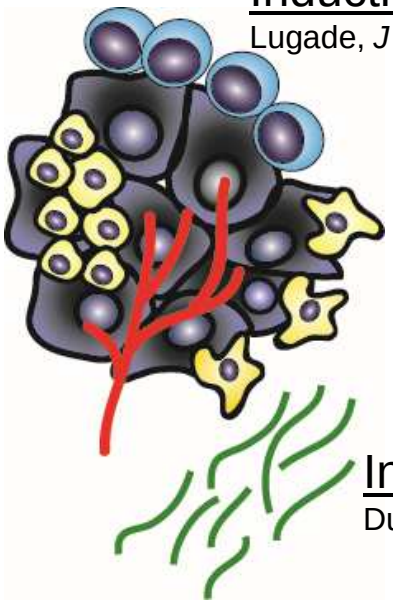


…But radiation can also be anti-inflammatory

Resolution of Immune Response (Repair)

Induction of regulatory T cells
Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012

Upregulation of PD-L1
Zheng *IJROBP* 2013



Increased TGFβ production
Du *IJROBP* 2015

Like any immune response, and perhaps even more so, the immune system works to control RT-induced inflammation

Summary

- Radiation produces a targeted *in situ* vaccination by triggering immunogenic cell death leading to anti-tumor immune response

- However, tumor-mediated suppression and radiation-induced suppression act to limit the extent of the RT-induced immune response

Key Question

How do we enhance the immune response induced by radiation?

1. Augment the anti-tumor immune response induced by RT

2. Prevent the innate tumor and radiation-induced suppression of the anti-tumor immune response

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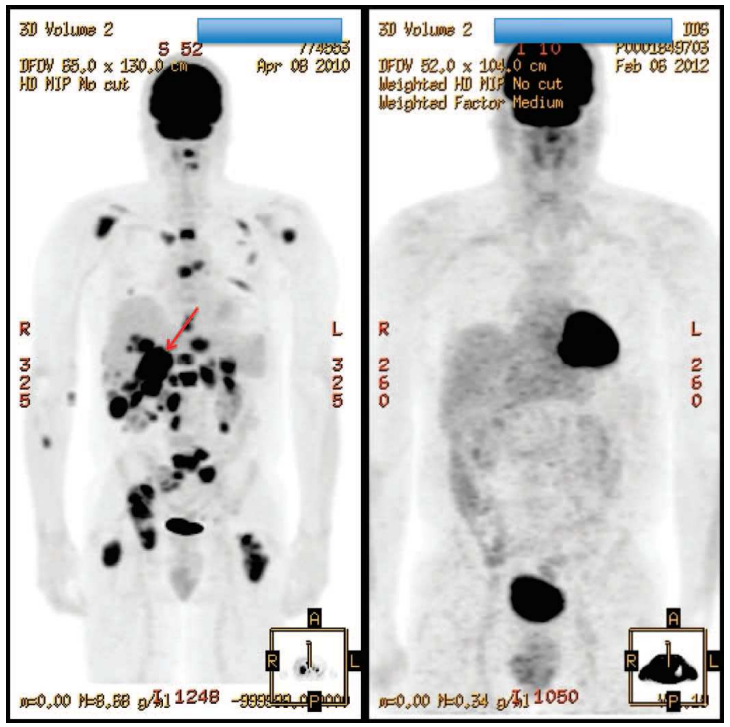
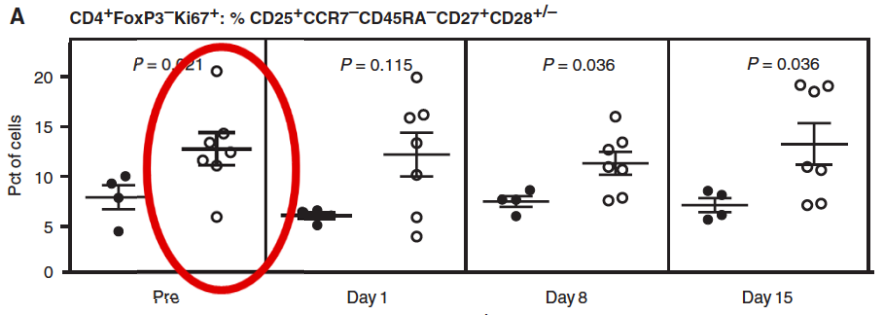
Augmenting the immune response: Pre-clinical data

- By ***increasing*** the immune response, multiple groups have shown that immunotherapy can enhance the radiation-induced anti-tumor immune response. Some examples from murine models showing improved efficacy with RT include:
  - **Adjuvants** – CpG (TLR9 agonist), Imiquimod (TLR7 agonist)
  - **Cytokines** – IL-2, IL-12, GM-CSF, Flt-3L
  - **T cell Costimulation** – OX-40L Ab, 4-1BBL Ab, ICOSL Ab
  - **Antigen Presentation** – DC vaccines, Viral vaccines

Augmenting the immune response: Clinical examples





- IL-2 and RT (Sueng SK *Sci Transl Med* 2012)
  - IL-2 is a cytokine necessary for growth, proliferation and differentiation of both CD4+ and CD8+ T-cells
  - IL-2 + SBRT (20 Gy x 1,2 or 3 fractions) in metastatic RCC/melanoma showed a CR in 8/12 pts
  - Higher frequency of proliferating CD4+ T cells with an early activated memory phenotype in responders

Augmenting the immune response: Clinical examples

- DC Vaccination and RT (Finkelstein *Immunotherapy* 2012)
  - High risk prostate cancer pts tx with ADT +EBRT 45Gy+ DC injections into prostate
  - Autologous DCs were cultured in vitro and reintroduced directly into the prostate
  - Serial bx show tumor cell apoptosis and prostate specific CD8+ T cells in the peripheral blood, but limited increase in

Table 3. Quantitation of therapy-related changes and apoptosis among visible tumor cells within the biopsy and CD4⁺ or CD8⁺ infiltrates among 22 evaluable specimens.

Time point	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
	CD4	*CD8*	*CD4*	*CD8*	*CD4*	*CD8*	*CD4*	*CD8*	*CD4*	*CD8*
Baseline biopsy	1+	1+	1+	1+	1+	1+	1+	1+	0	1+
At fraction 5	1+	1+	1+	1+	1+	1+	0	1+	0	1+
At fraction 15	1+	1+	1+	1+	0	0	ND	ND	0	1+
At fraction 25	1+	1+	0	1+	1+	1+	ND	ND	1+	1+
>3 months later	1+	1+	0	0	1+	1+	ND	ND	ND	ND

CD4, CD8 infiltrates: 0/1+/2+/3+.
ND: No data.

Preventing tumor immune suppression: Pre-clinical data

- ***Preventing inhibition*** of the immune response has also been shown not only to enhance RT, but also potentiate a systemic response
  - Checkpoint inhibitors – Anti-CTLA-4, Anti-PD-1/PD-L1
    - CTLA-4 blockade is synergistic with RT to produce an abscopal response in breast and colon cancer models
    - Specific doses are critical: 8 Gy x 3 is more effective than 20 Gy x 1 or 6 Gy x 5 (Dewan MZ, CCR 2009) in mouse models with anti-CTLA-4 therapy
  - TGF-βinhibition

Preventing tumor immune suppression: Clinical data

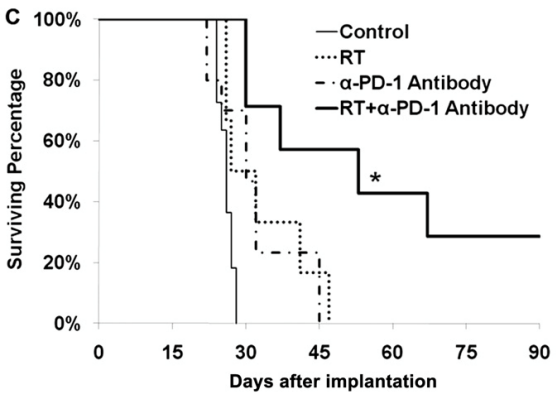
- Ipilimumab CTLA-4 inhibition allows increased proliferation and function of activated T-cells, including tumor-specific CTLs
  - Several retrospective studies showed improved survival treating brain mets with SRS and ipilimumab with limited toxicity except at the highest doses of RT[1]
  - Multiple phase I/II trials are currently enrolling testing the safety and efficacy of RT + Ipilimumab

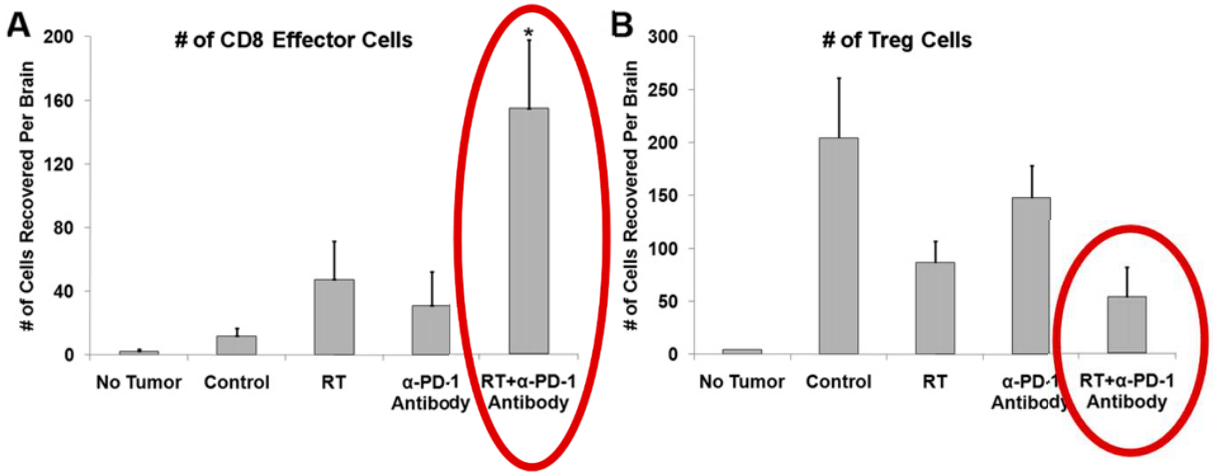
[1]Barker and Postow. *IJROBP* 2014

Preventing tumor immune suppression: Pre-clinical data

Zeng J, *IJROBP* 2013

- Glioma model
- RT+antiPD-1 tx increased survival and tumor infiltration by cytotoxic T cells (CD8+/interferon-γ+/tumor necrosis factor-α+) and decreased regulatory T cells (CD4+/FOXP3)



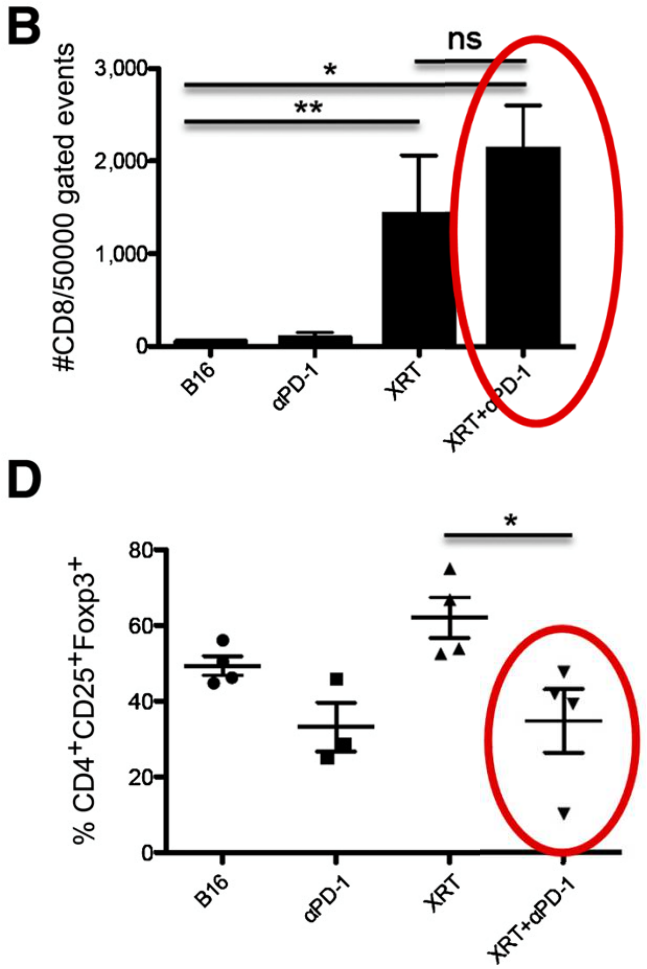


Preventing tumor immune suppression: Pre-clinical data

PD-1 blockade + RT

Sharabi A et al, *Cancer Immunol Research* 2015

- Melanoma tumor model
- RT and anti–PD-1 immunotherapy decreased percentages of CD4 Tregs while RT increased CD8 T-cell populations



Summary for RT + Immunotherapy

- Given that RT is already immunogenic, combinations of RT and various immunotherapies showed enhanced anti-tumor immunity, but limited data showing clinical efficacy

- RT+ immunotherapy in pre-clinical and clinical studies show:
  - Enhanced cross-priming and stimulation of tumor-specific CTLs
  - Specific fractionation schemes seem to enhance the immunogenicity of RT
  - Neutralizing the immunosuppressive effects of the tumor microenvironment can lead to enhanced responses locally and systemically

Radiation and the “Abscopal Effect”

- Irradiation of a tumor causes response at distant metastatic site
- Probably mediated by the immune system
- Although RT can cause cross-priming of CTLs, the effect of RT elsewhere may be weak
- With the addition of immunotherapies, this rare effect may be more reproducible

The NEW ENGLAND JOURNAL of MEDICINE

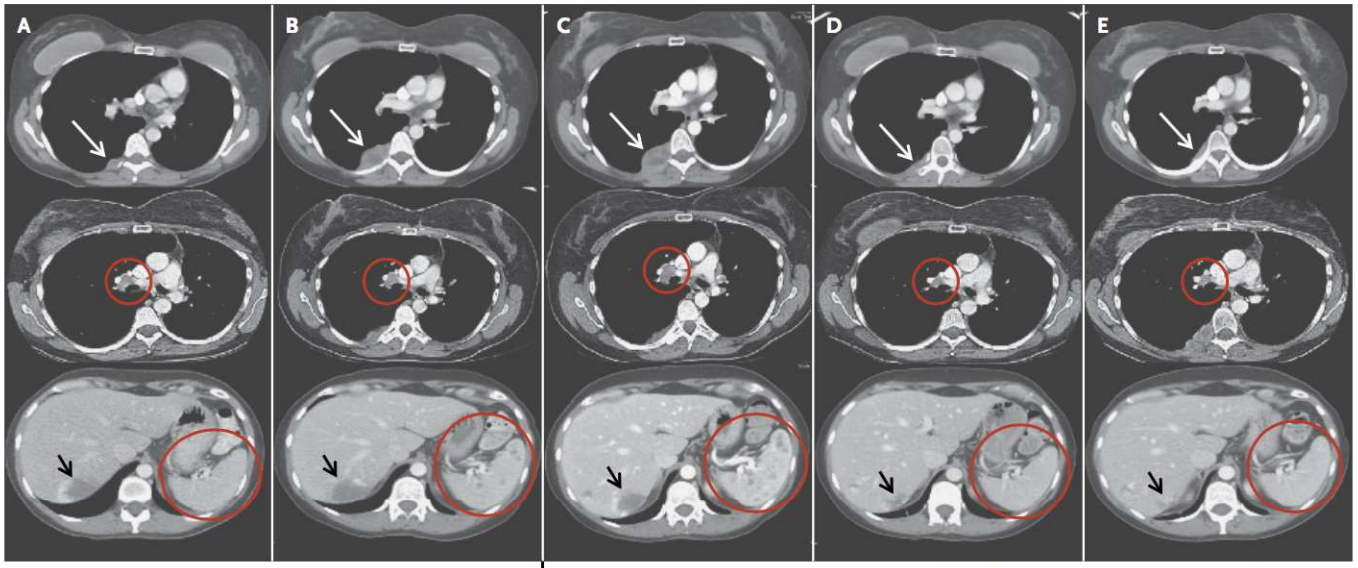
BRIEF REPORT

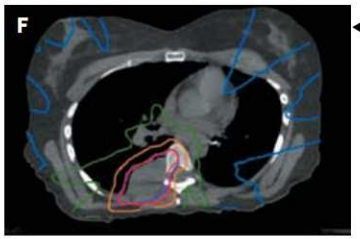
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

N Engl J Med Volume 366(10):925-931 March 8, 2012

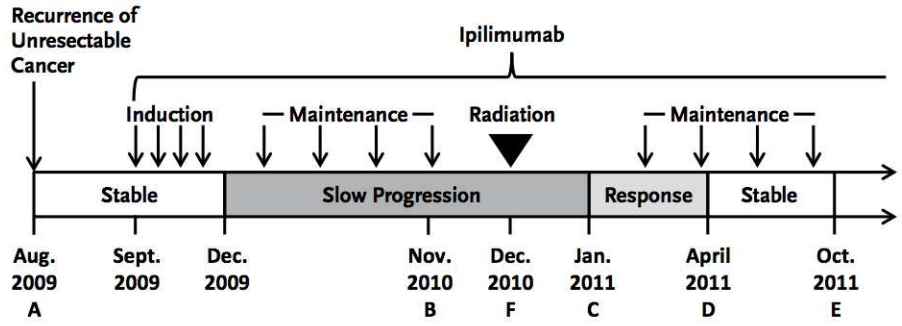
RT/Ipi can induce distant immune-mediated tumor regression

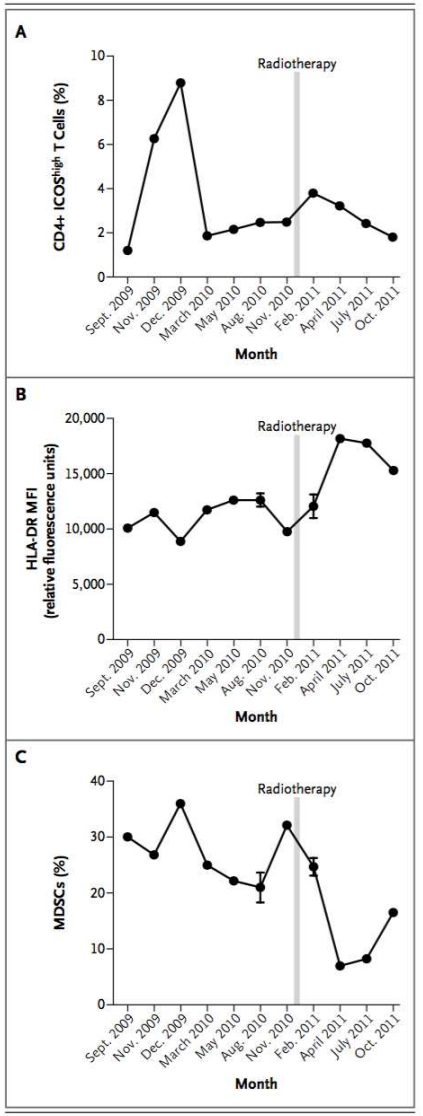




December 2010

**9.5 Gy *
3 fractions**





Many ongoing RT and immune trials are currently enrolling

- Over 35 trials are currently open throughout the nation studying combinations of RT and immunotherapy

- Current efforts are directed mainly at combining RT with the following immunotherapies in most cancer subsites:
  - Vaccines (Viral, Dendritic Cells)
  - Checkpoint inhibitors (CTLA-4, PD-1, PD-L1)

Conclusions

- RT generates anti-tumor immunity that impacts both local and, more rarely, distant disease:
  - Creates an **in-situ vaccine**
  - Positively impacts many aspects of the immune response
  - However, also triggers strong compensatory immune suppression

Conclusions

- Combinations of RT with immunotherapy have been shown in pre-clinical and early studies to be synergistic with the most promising combinations thus far being with checkpoint inhibitors
- ***Recommendations***
  - **Short course, high-dose RT** (ex 7-10 Gy x 5 fractions or 8 Gy x 3 fractions) in combination with checkpoint blockade appears to be the most efficacious regimen though data is very limited
  - Consider enrolling patients on trials