

Is There a Role for Radiation Therapy and Immunotherapy?

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Disclosures

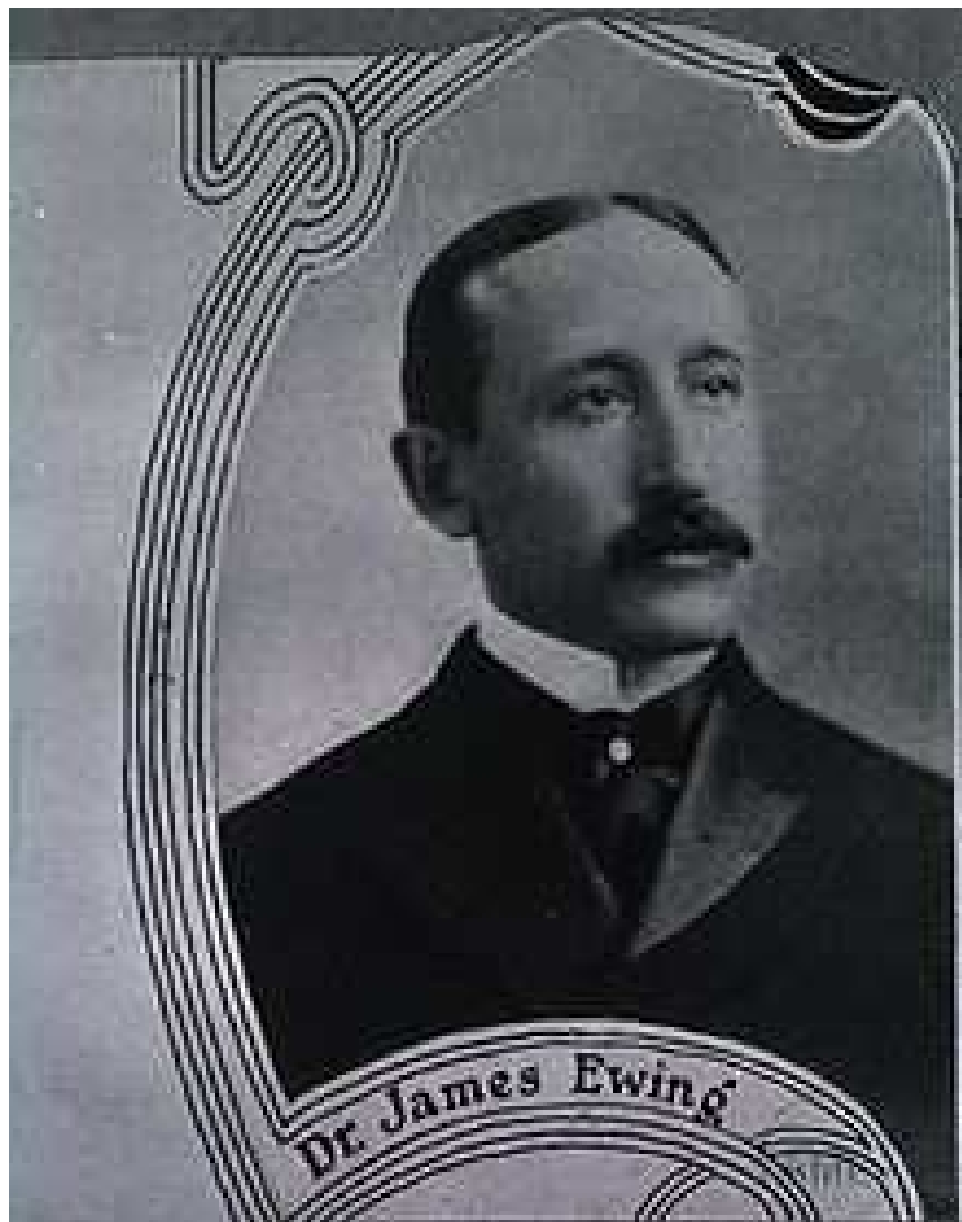
- ◆ Consulting Fees:
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Dr. William B. Coley



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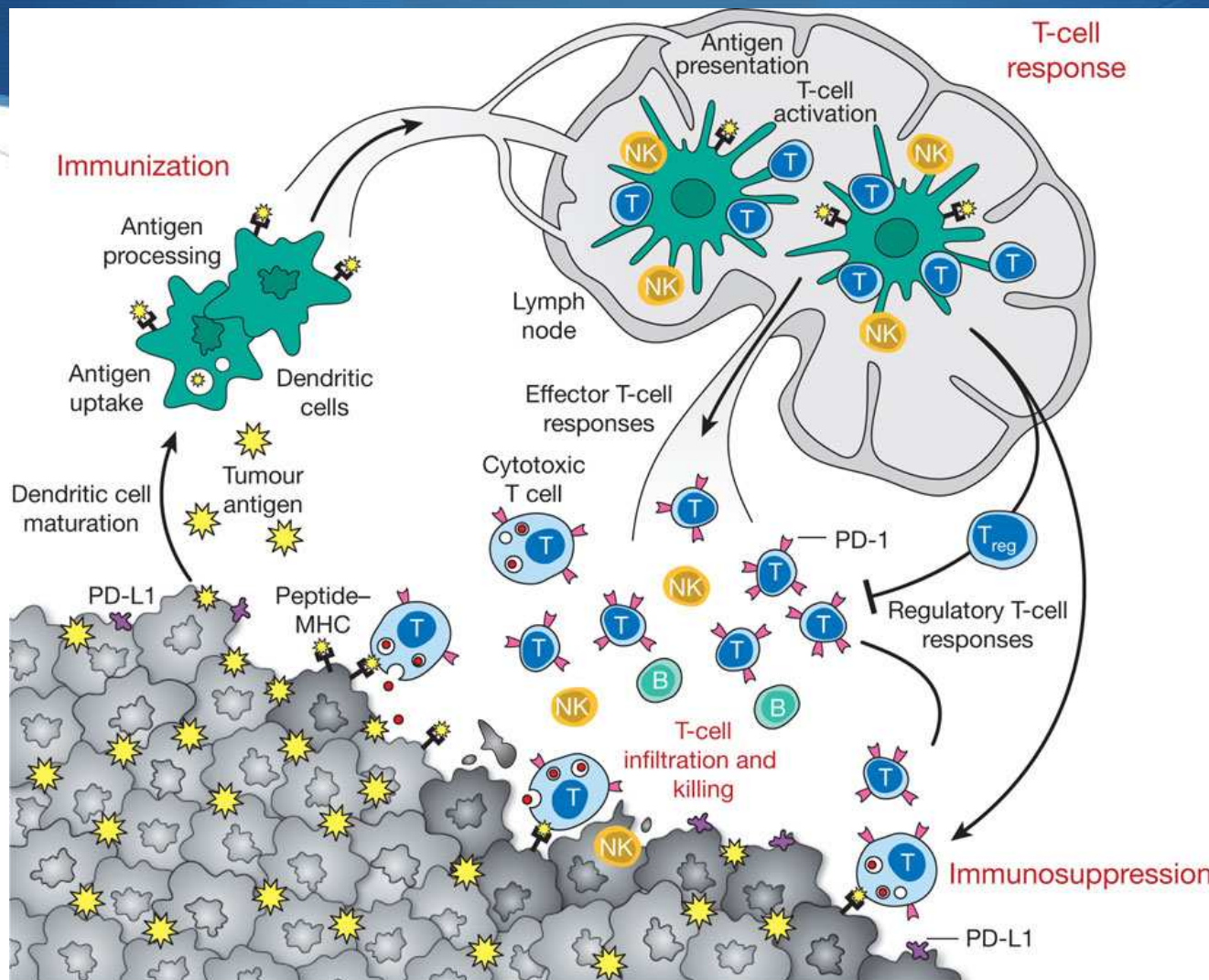


Dr. James Ewing

Outline

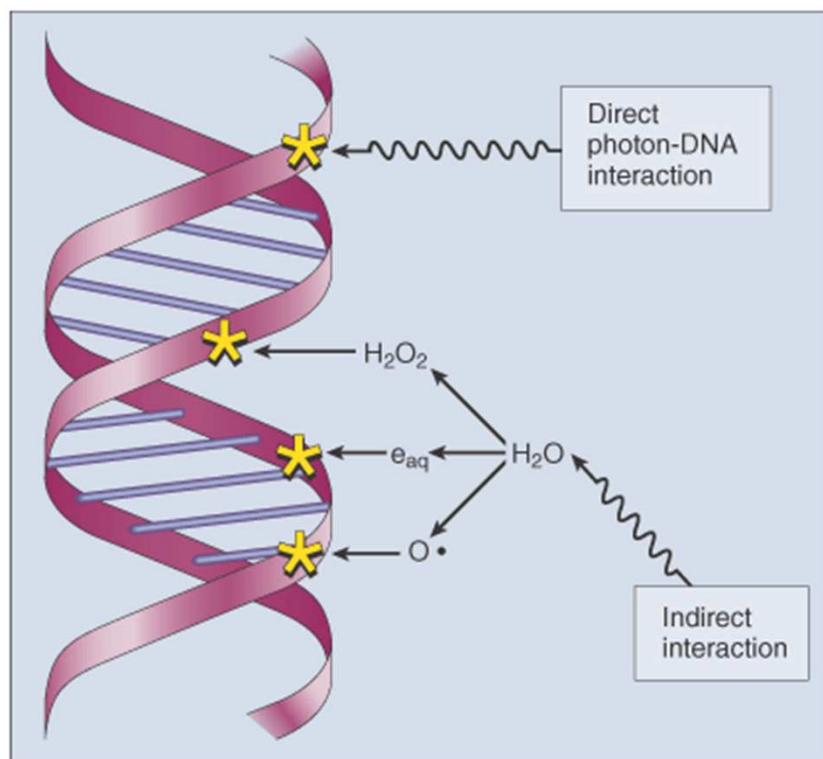
- Underlying immune mechanisms in radiation
- Effects of ionizing radiation on the immune system
- Radiation and Immunotherapy

Antitumor Immune Response



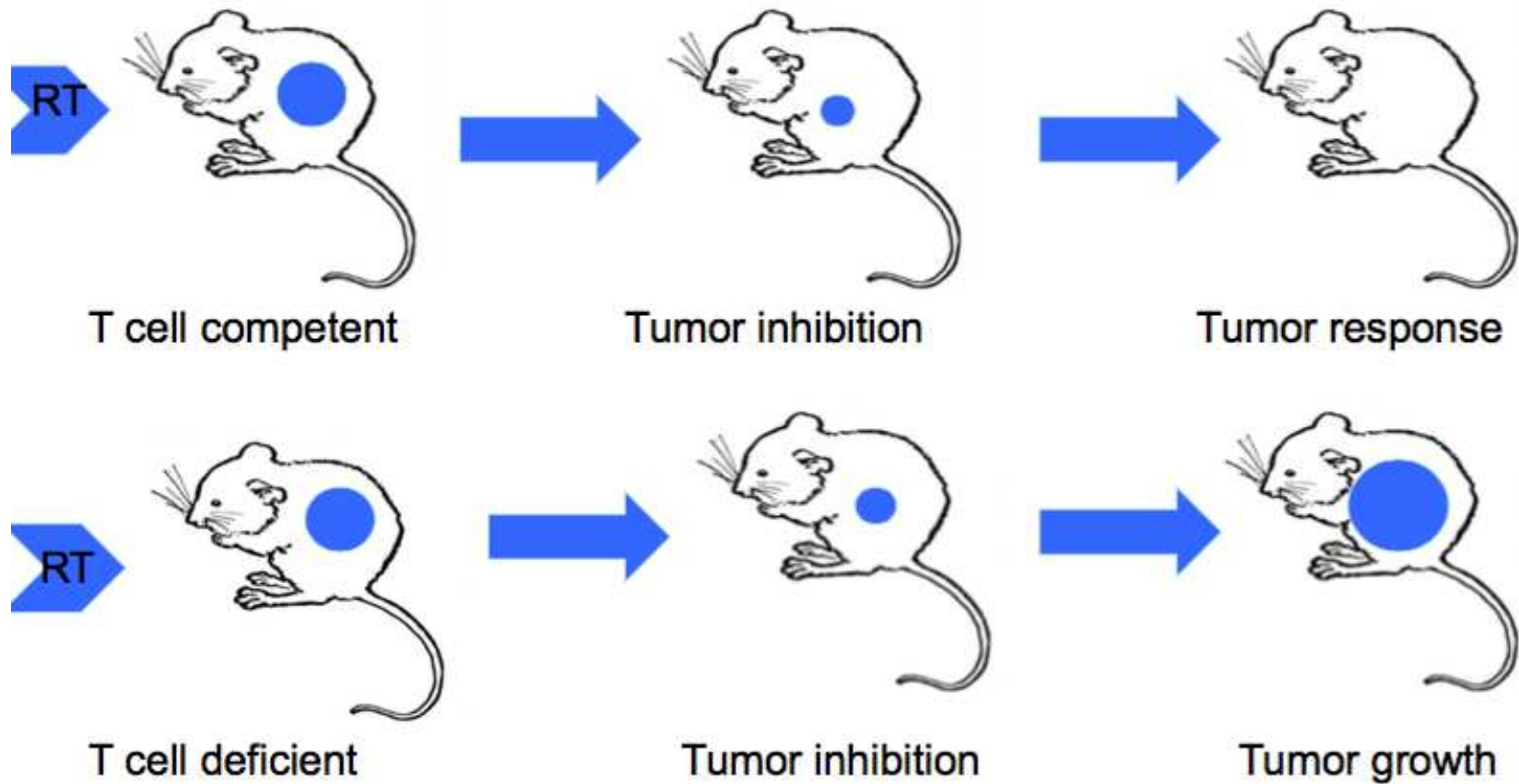
Mellman et al. *Nature* 2011

Radiation and Inflammation: Teaching an Old Dog New Tricks

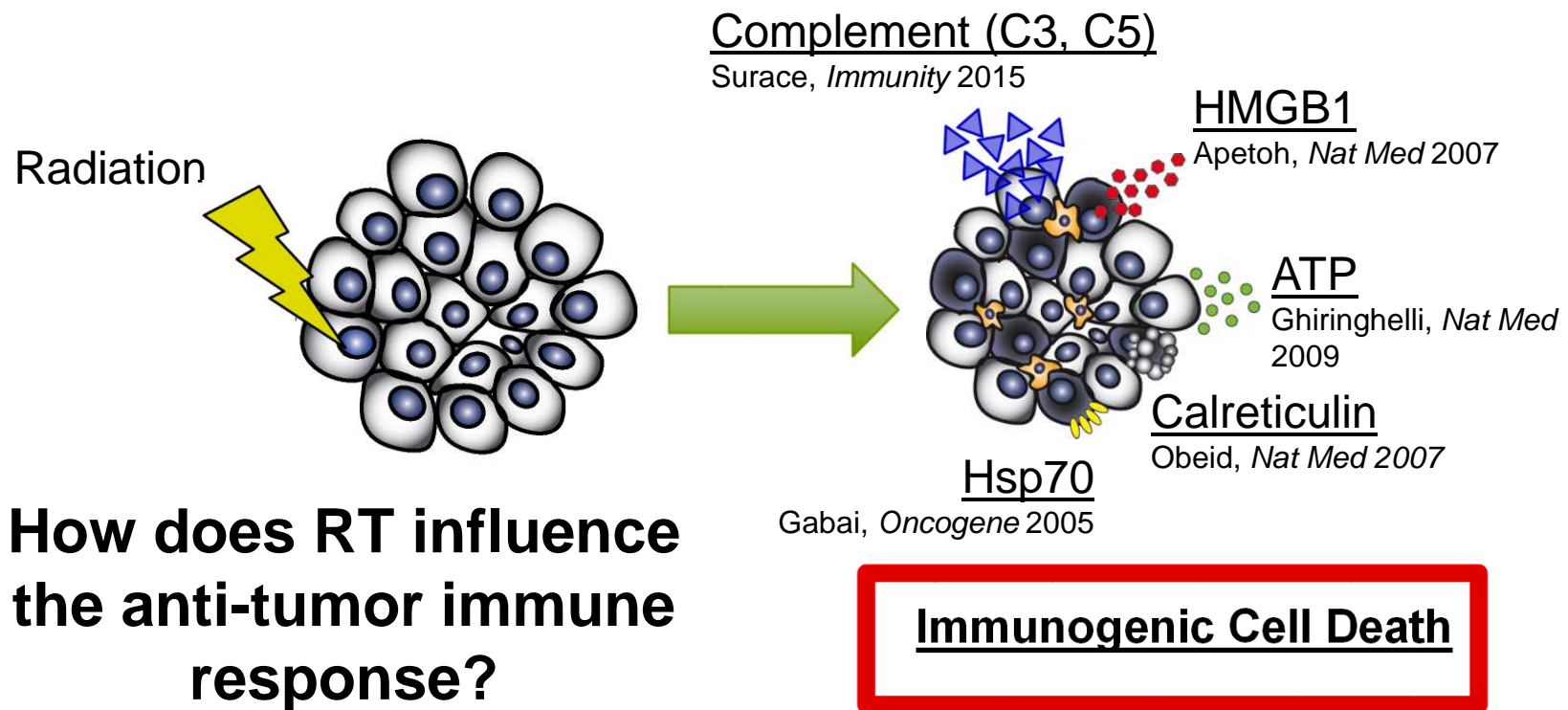


Traditional research in radiation has focused on cell intrinsic mechanisms: DNA damage, ROS production, tumor cell kill/survival

T cells are necessary for the full response to RT



Radiation leads to immunogenic cell death



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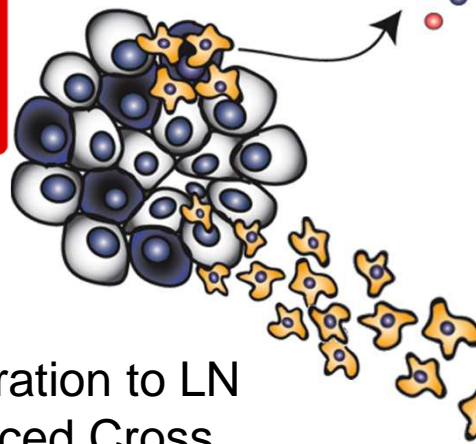
Radiation Enhances Multiple Inflammatory Pathways: *In Situ* Vaccination

Initiation of Local Inflammation

Increased cytokines:

IL-1, TNF α , Type I Interferons

Hallahan, *PNAS* 1995; Deng, *Immunity* 2014

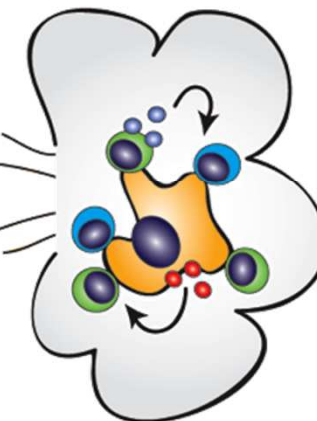


DC Migration to LN
Enhanced Cross
Presentation

Reits, *J Exp Med* 2006

Increased IFN γ production

Lugade, *J Immunol* 2008

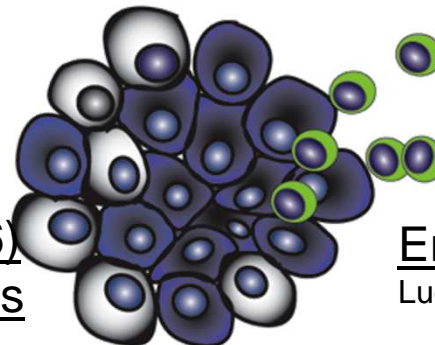


Antigen Presentation

Tumor Destruction

Increased chemokine (CXCL16)
production to attract CD8+ CTLs

Matsumura, *J Immunol* 2012



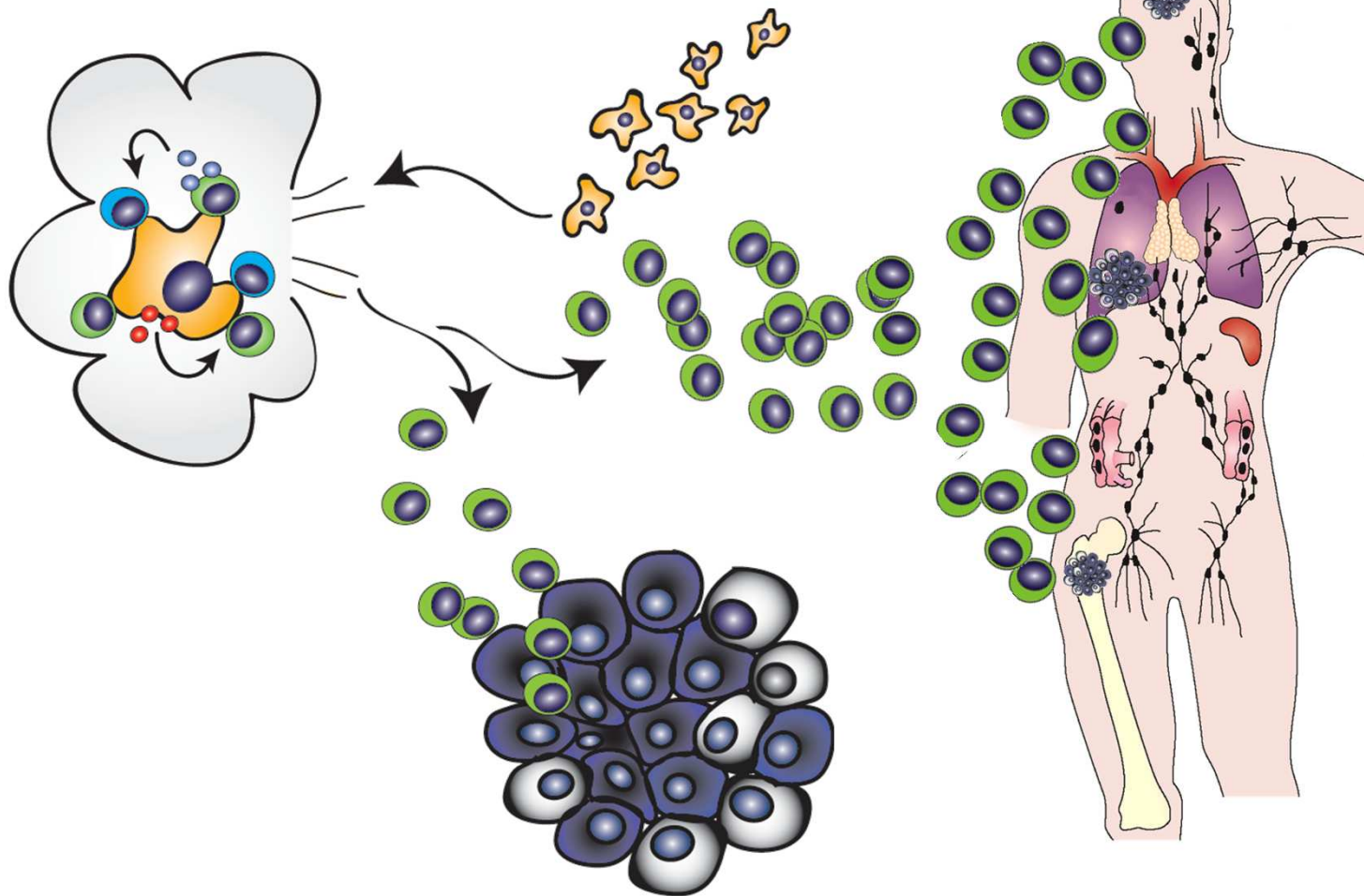
Enhanced CD8+ T cell production

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

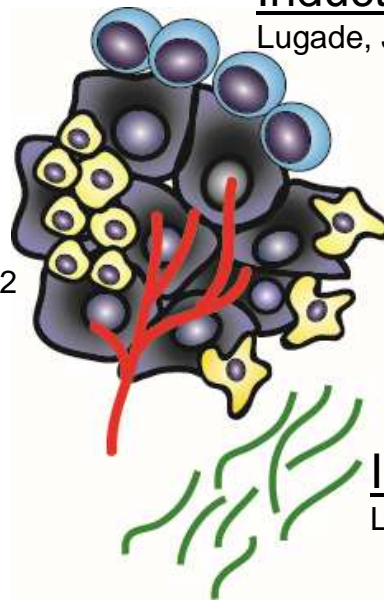
**Resolution of
Immune Response
(Repair)**

Upregulation of PD-L1

Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012

Induction of regulatory T cells

Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012



Increased TGF β production

Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012

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

Outline

- Underlying immune mechanisms in radiation
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- Radiation and Immunotherapy

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)¹
 - Cytokines – IL-2, IL-12, GM-CSF, Flt-3L²
 - T cell Costimulation – OX-40L Ab, 4-1BBL Ab, ICOSL Ab³
 - Antigen Presentation – DC vaccines, Viral vaccines⁴

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-L1¹
 - CTLA-4 blockade is synergistic with RT to produce an abscopal response in breast and colon cancer models
 - CTLA-4 blockade + PD-L1 blockade + RT triplet therapy demonstrates increased efficacy to either doublet combination alone.
 - 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- β inhibition²

Preventing tumor immune suppression: Pre-clinical data

PD-1 blockade + RT

- Sharabi A et al, *Cancer Immunol Research* 2015 (melanoma)
 - RT and anti-PD-1 immunotherapy altered the ratio of CD4 to CD8 T cells and decreased percentages of CD4 Tregs and absolute increases in CD8 T-cell populations
- Zeng J, *IJROBP* 2013 (glioma): 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: Clinical data

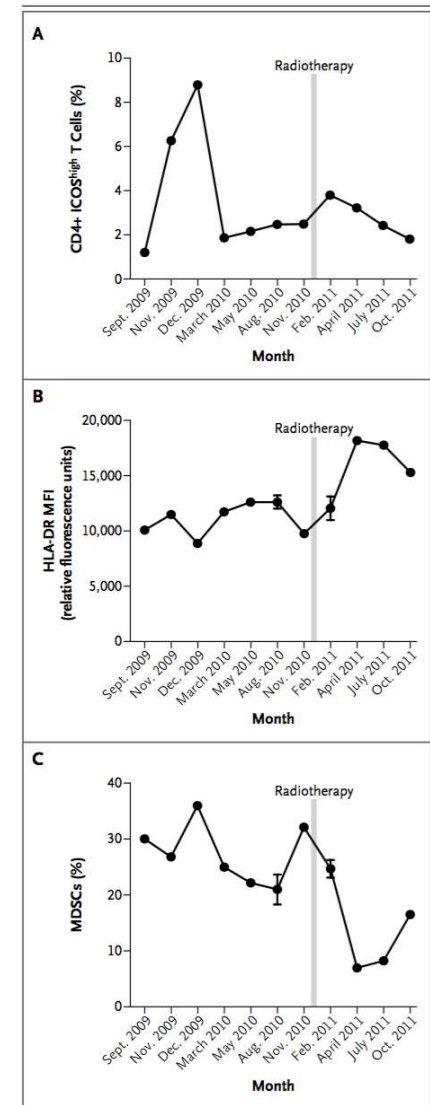
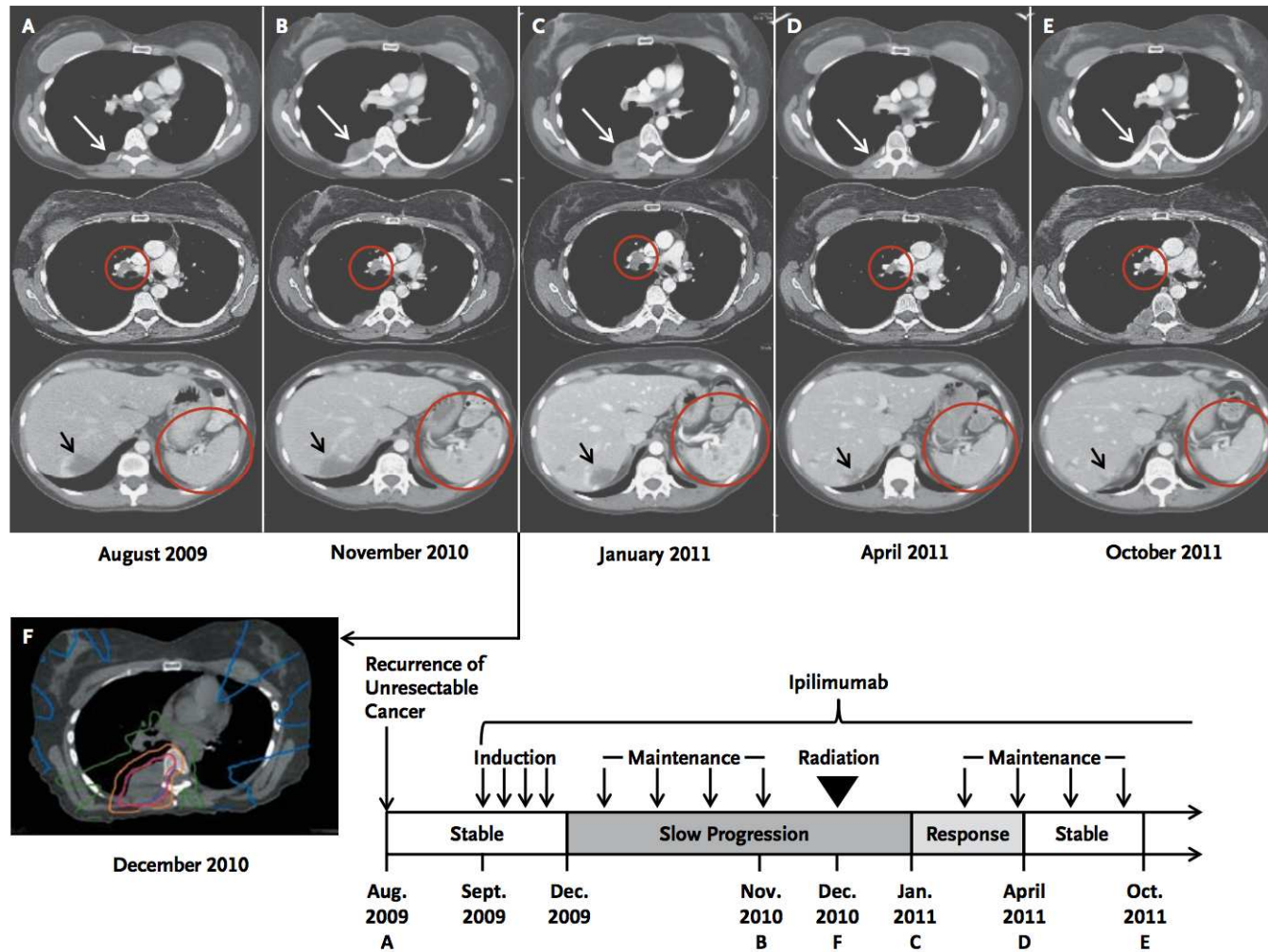
Ipilimumab CTLA-4 inhibition allows increased proliferation and function of activated T-cells, including tumor-specific CTLs

- Several retrospective studies showed safety combining ipilimumab and radiotherapy^{1,2}

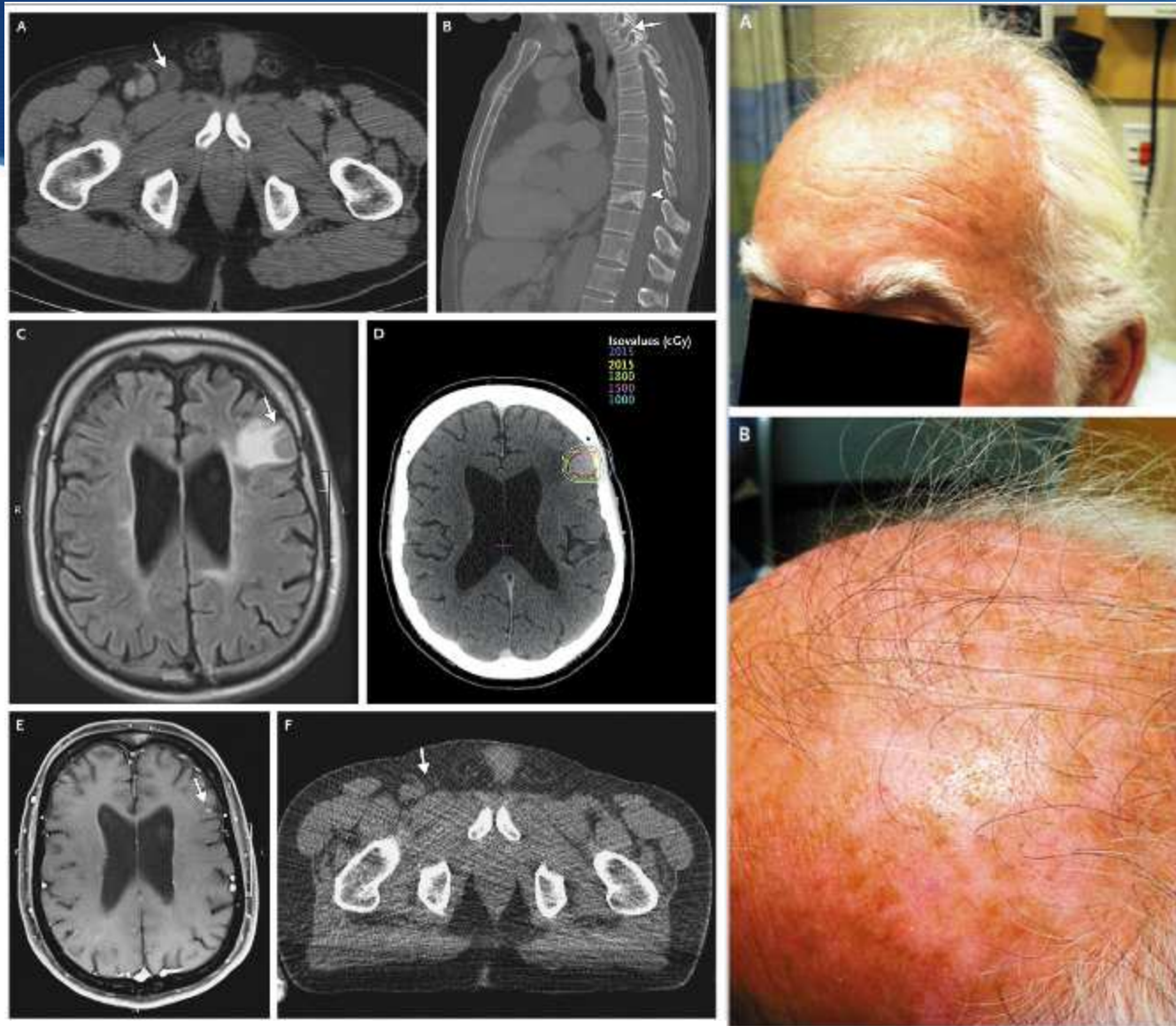
¹Barker and Postow. *IJROBP* 2014

²Barker, Postow, Khan et al. *Cancer Immunol Res* 2013

RT/Ipi can induce distant immune-mediated tumor regression



Clinical examples of the abscopal effect



Vitiligo and
response after 11
months

Doing well 1.5
years after SRS

Sullivan et al. *NEJM* 2013

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 T-cells to become antigen-specific CD4+ and CD8+ T cells
 - RT+IL-2 increased inflammatory cytokine production and upregulation of MHC-I and B7.1
 - IL-2 +SBRT in metastatic RCC/melanoma showed a CR in 8/12 pts
 - Higher frequency of proliferating CD4+ T cells with and early activated memory phenotype in responders
- 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 increase in tumor- infiltrating CD8+ T-cells and prostate specific CD8+ T cells in the peripheral blood

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

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

Conclusions

- Preclinical data for immunogenicity of RT
- Preclinical data for enhancing efficacy of checkpoint blockade with RT
- Clinical anecdotes
- Whether RT and immunotherapy are synergistic in a clinical context remains unknown and subject to ongoing prospective trials