Society for Immunotherapy of Cancer

Is there a role for combining radiation therapy and immunotherapy?

Sandra Demaria, M.D.

Professor of Pathology and Radiation Oncology
Co-leader, Cancer Immunology Program of
NYU School of Medicine Cancer Institute

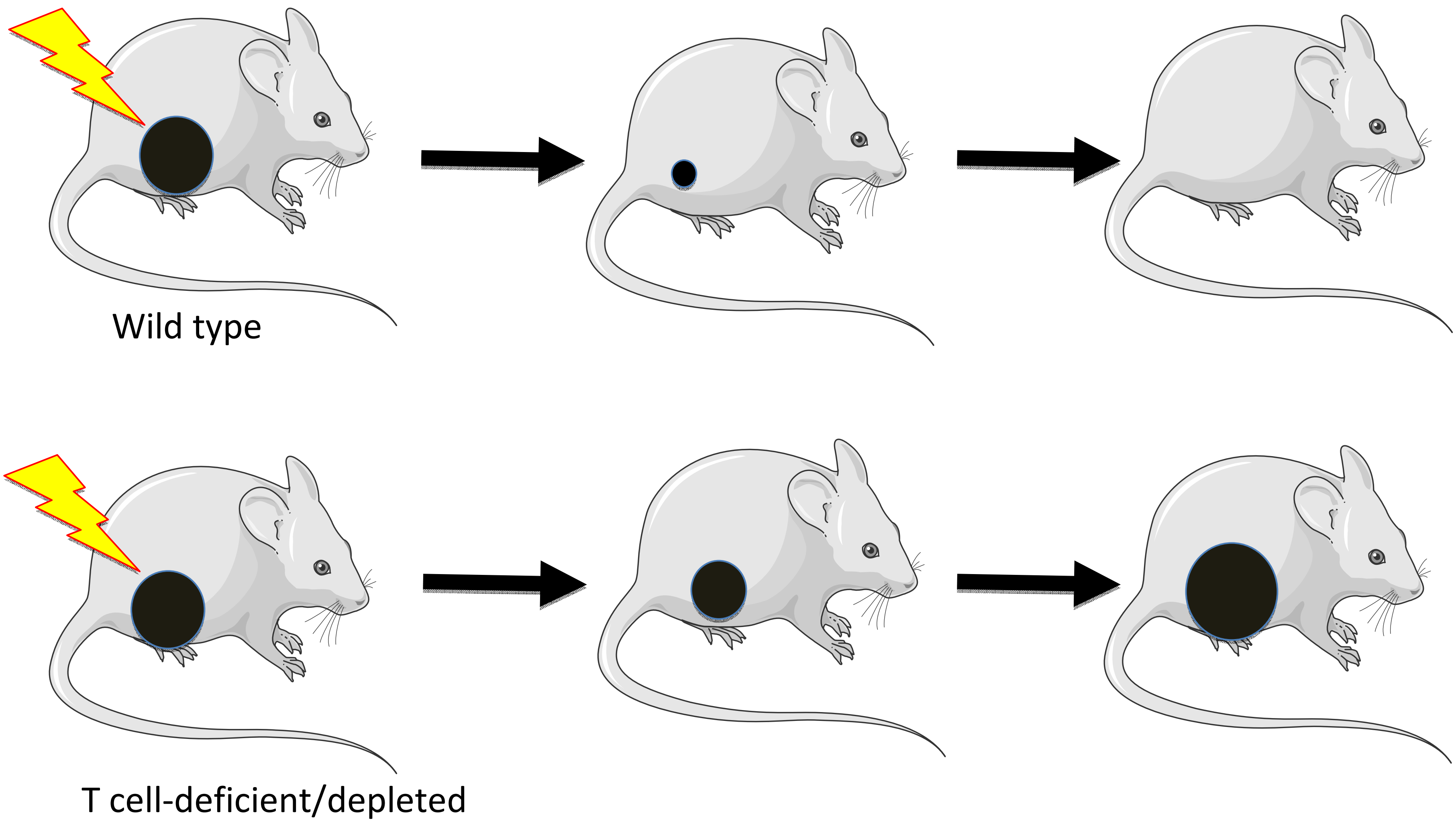
NYU School of Medicine
NYU LANGONE MEDICAL CENTER

No conflicts to disclose

Outline

- Evidence for a role of the immune system in response to ionizing radiation
- Radiation-induced tumor cell death
  - Apoptosis and necrosis
  - Mitotic catastrophe and senescence
  - Autophagy
  - Immunogenic Cell Death (ICD)
- Effects of radiation on the tumor microenvironment
  - Pro-inflammatory
  - Anti-inflammatory
- Combination of radiation and immunotherapy
  - Overview
  - Checkpoint receptor inhibitor (anti-CTLA-4)

Immunocompetence of the host affects the response to local radiotherapy



T cells contribute to the response to radiotherapy

FSA Tumor	TCD_{50} values	Metastases
Normal mice	**30.0Gy (28.5-32.4)**	**1%**
Immunosuppressed (6Gy)	**50.8Gy (47.6-54.3)**	**4%**
T cell deprived mice	**64.5Gy (62.0-67.1)**	**79%**

Stone et al., JNCI 63:1229, 1979

Evidence for induction of tumor-specific immune responses by radiation

IN MICE

Lugade et al., J Immunol 2005
B16-OVA model, induction of CD4 and CD8 T cells after irradiation with 15 Gy x 1 or 3 Gy x 5,

Lee et al, Blood 2009
B16-SIY model, induction of CD8 T cells after irradiation with 20 Gy x 1

Schaue et al., IJROBP 2012
B16-OVA, best induction of CD8 T cells with 7.5 Gy x 2

& MAN

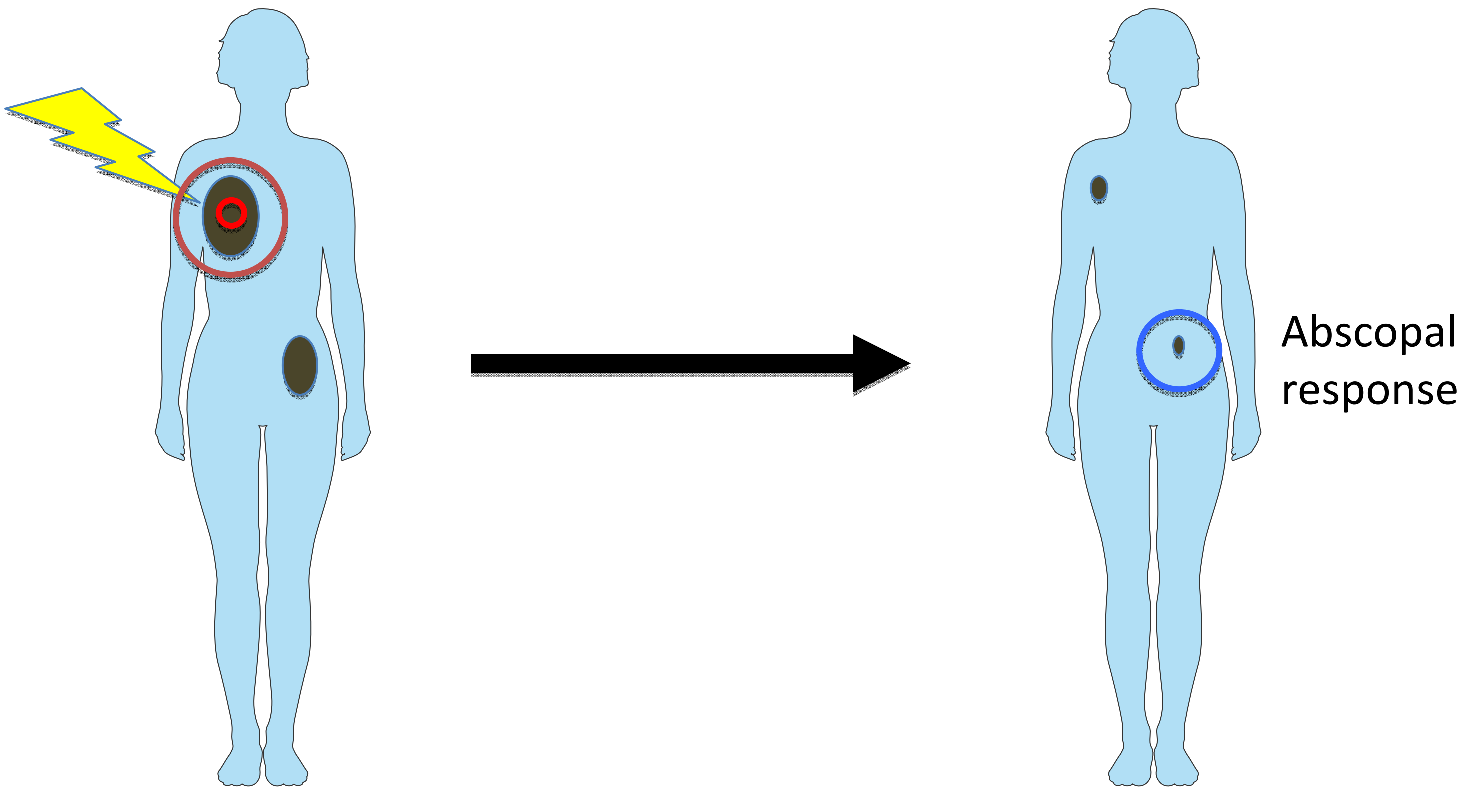
Nesslinger et al., Clin Cancer Res 2007
Tumor-specific antibodies in 14% of prostate cancer patients treated with EBRT and in 25% receiving brachytherapy

Schaue et al, Clin Cancer Res 2008
T cell responses to survivin in prostate and colorectal patients after radiotherapy

Abscopal effect

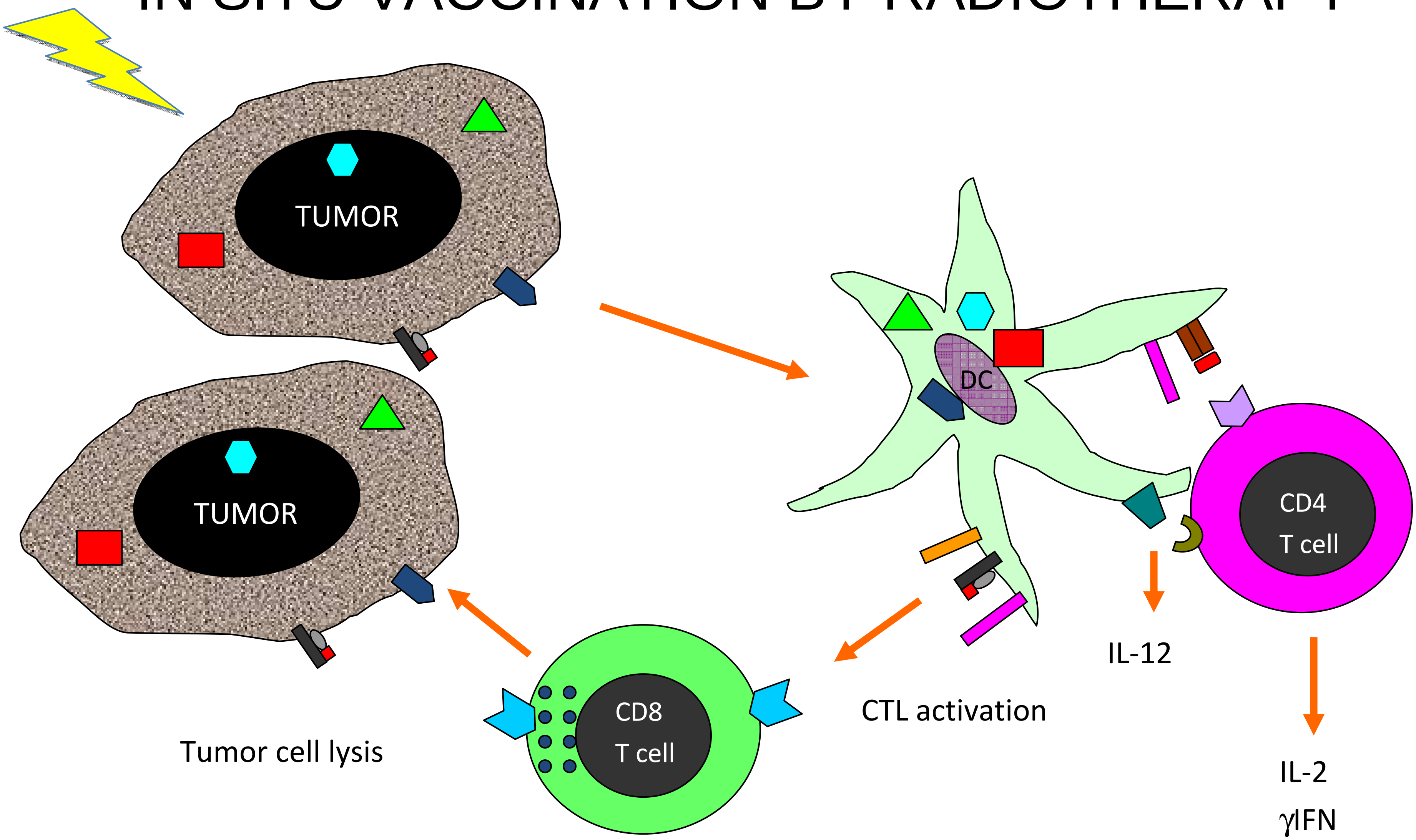
Effect of ionizing radiation on cancer outside the radiation field

Latin *ab* (position away from) and *scopus* (mark or target)



Formenti & Demaria, Lancet Oncology 2009

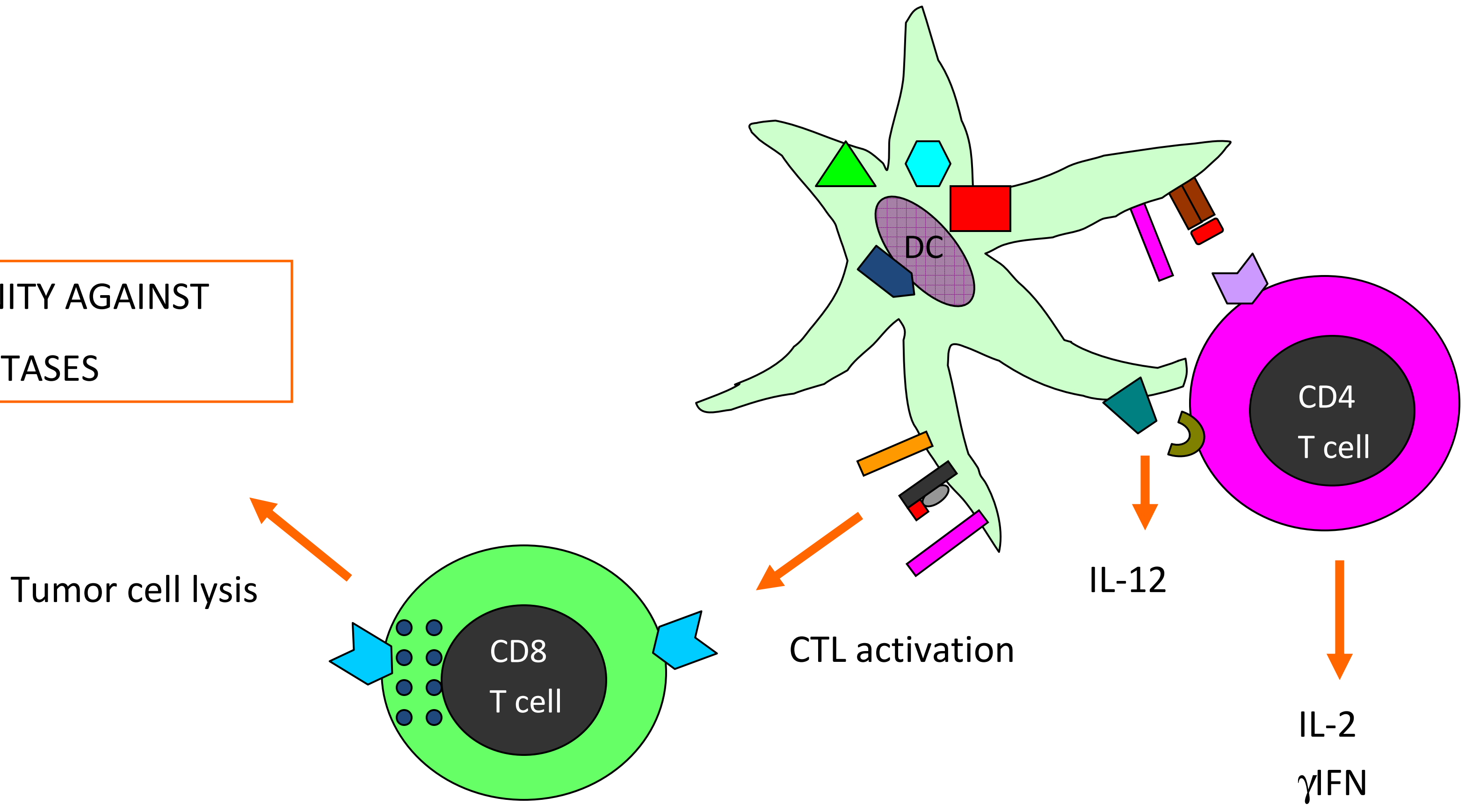
IN SITU VACCINATION BY RADIOTHERAPY



Demaria et al., IJROBP 2005
Formenti & Demaria, IJROBP 2012

IN SITU VACCINATION BY RADIOTHERAPY

IMMUNITY AGAINST METASTASES



Demaria et al., IJROBP 2005
Formenti & Demaria, IJROBP 2012

Radiation-induced tumor cell death

Radiation Damage → DNA, proteins, lipids

DIRECT energy deposition

INDIRECT free radicals (H_2O radiolysis)

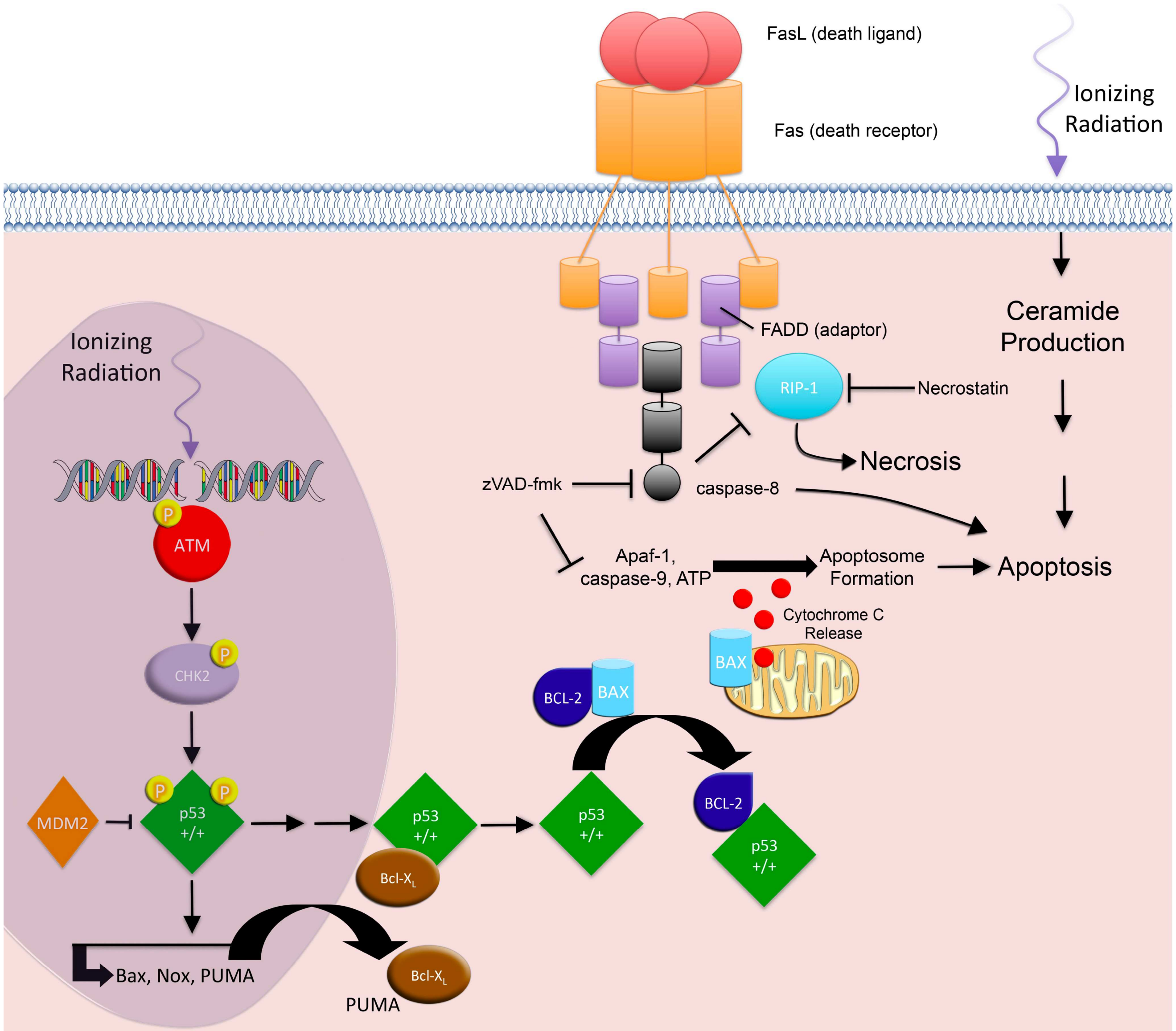
REPAIR

DEATH

Cell death type depends on:

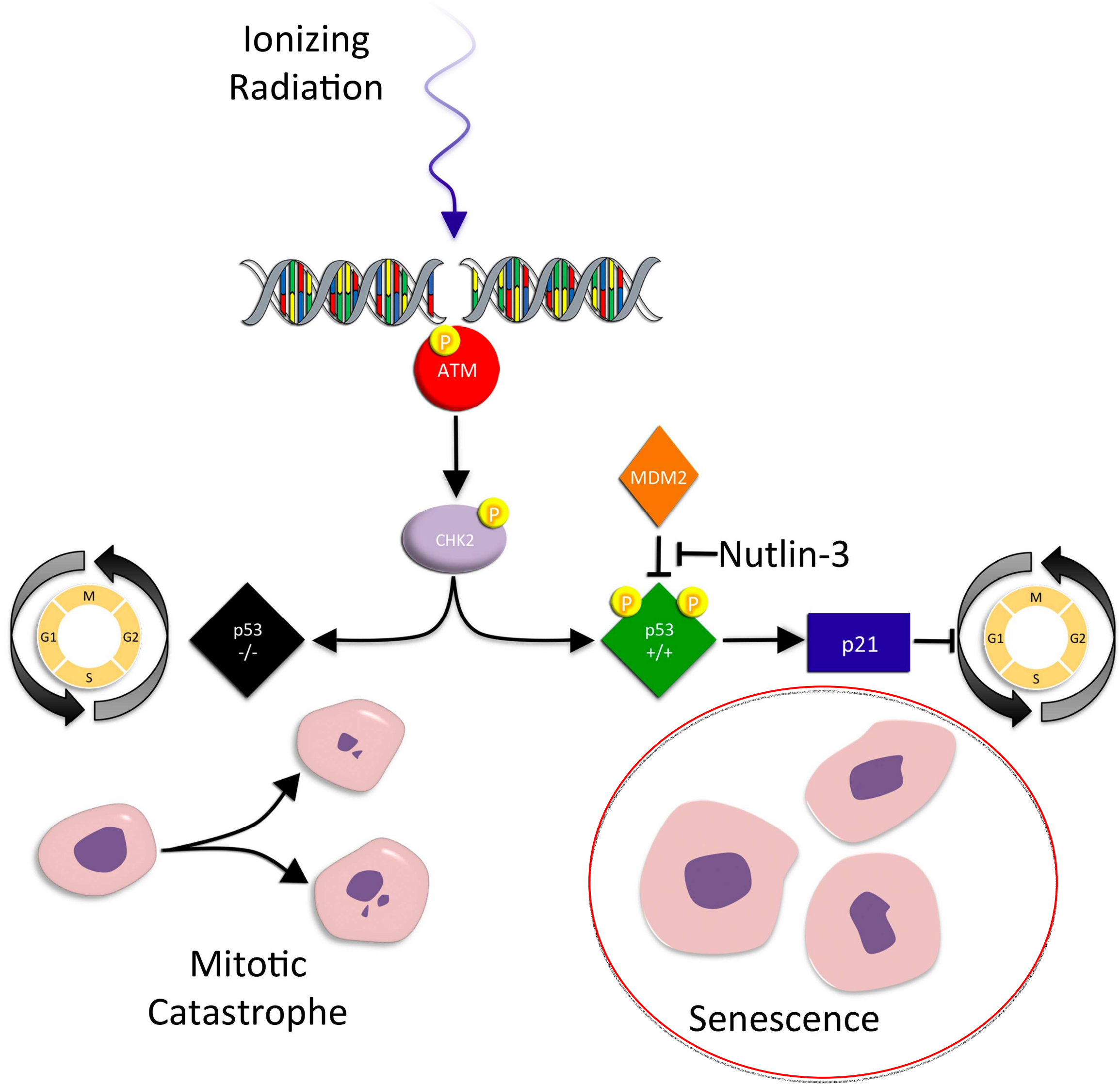
- intrinsic tumor cell characteristics (p53 status)
- radiation dose and quality (>8 Gy vascular death)
- oxygen tension
- DNA repair capacity
- redox status
- cell cycle phase

Apoptosis and necrosis



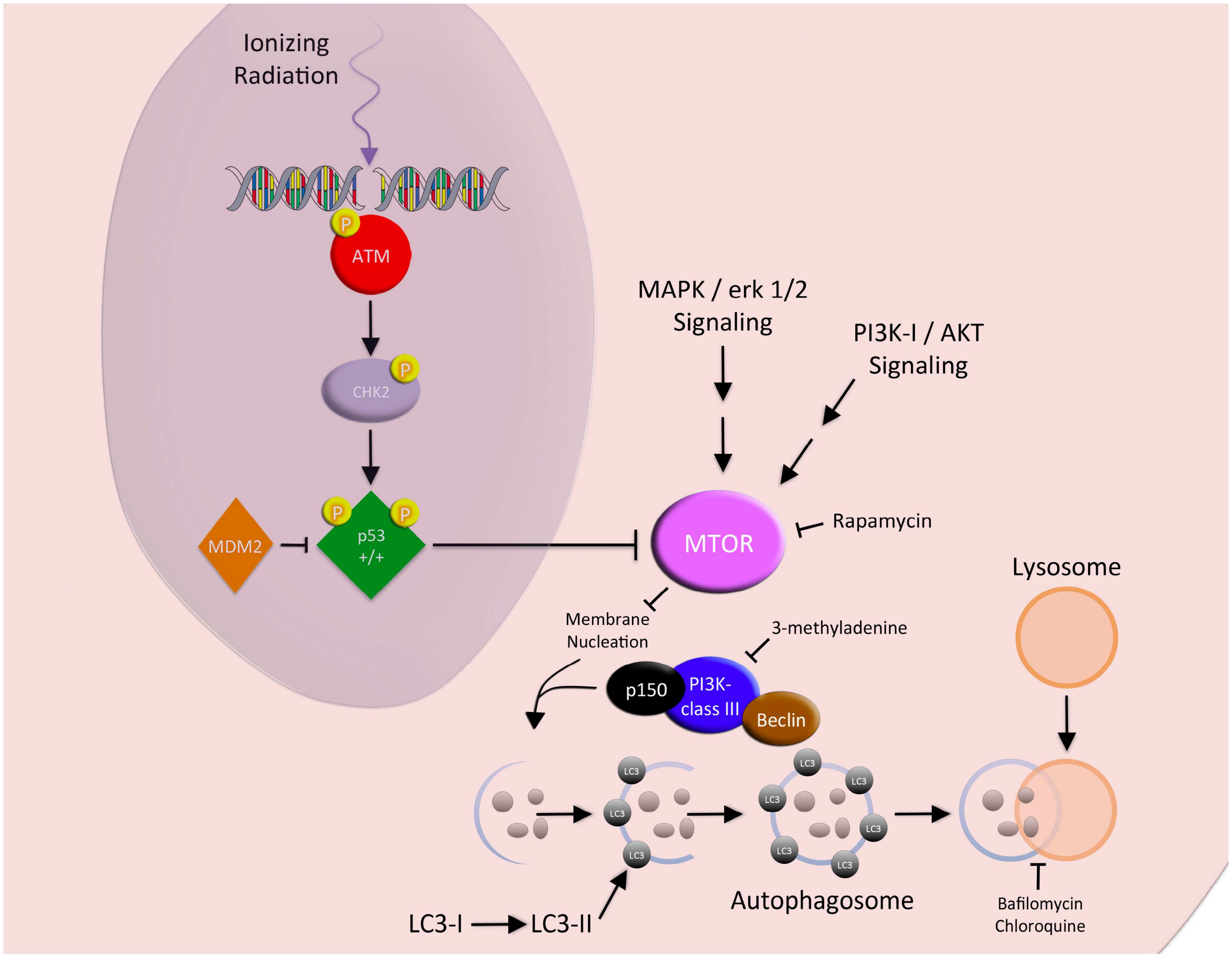
Golden et al, Front Oncol 2012 Aug 7;2:88. doi: 10.3389/fonc.2012.00088. eCollection 2012.

Mitotic catastrophe and senescence



Golden et al, Front Oncol 2012 Aug 7;2:88. doi: 10.3389/fonc.2012.00088. eCollection 2012.

Autophagy



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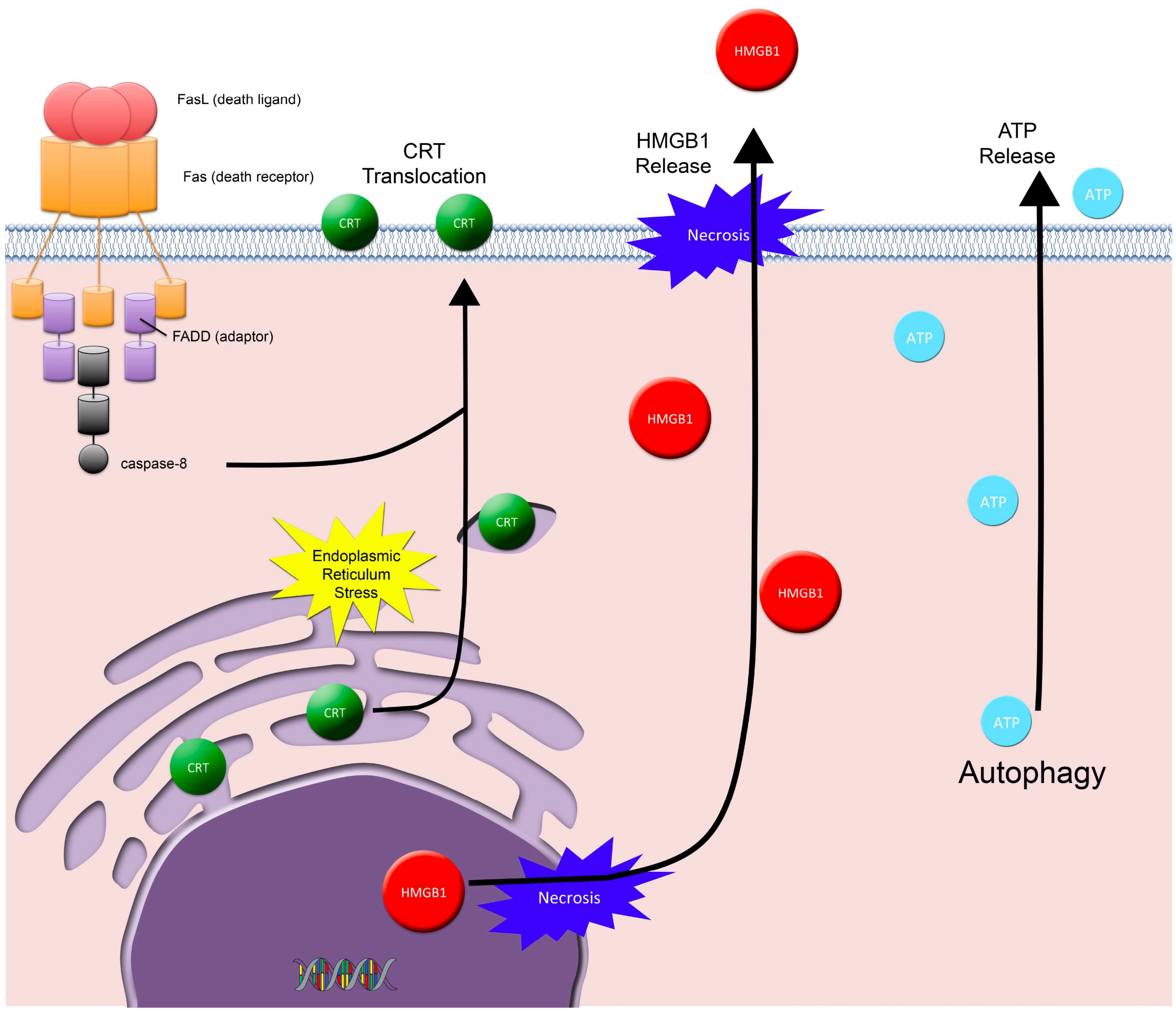
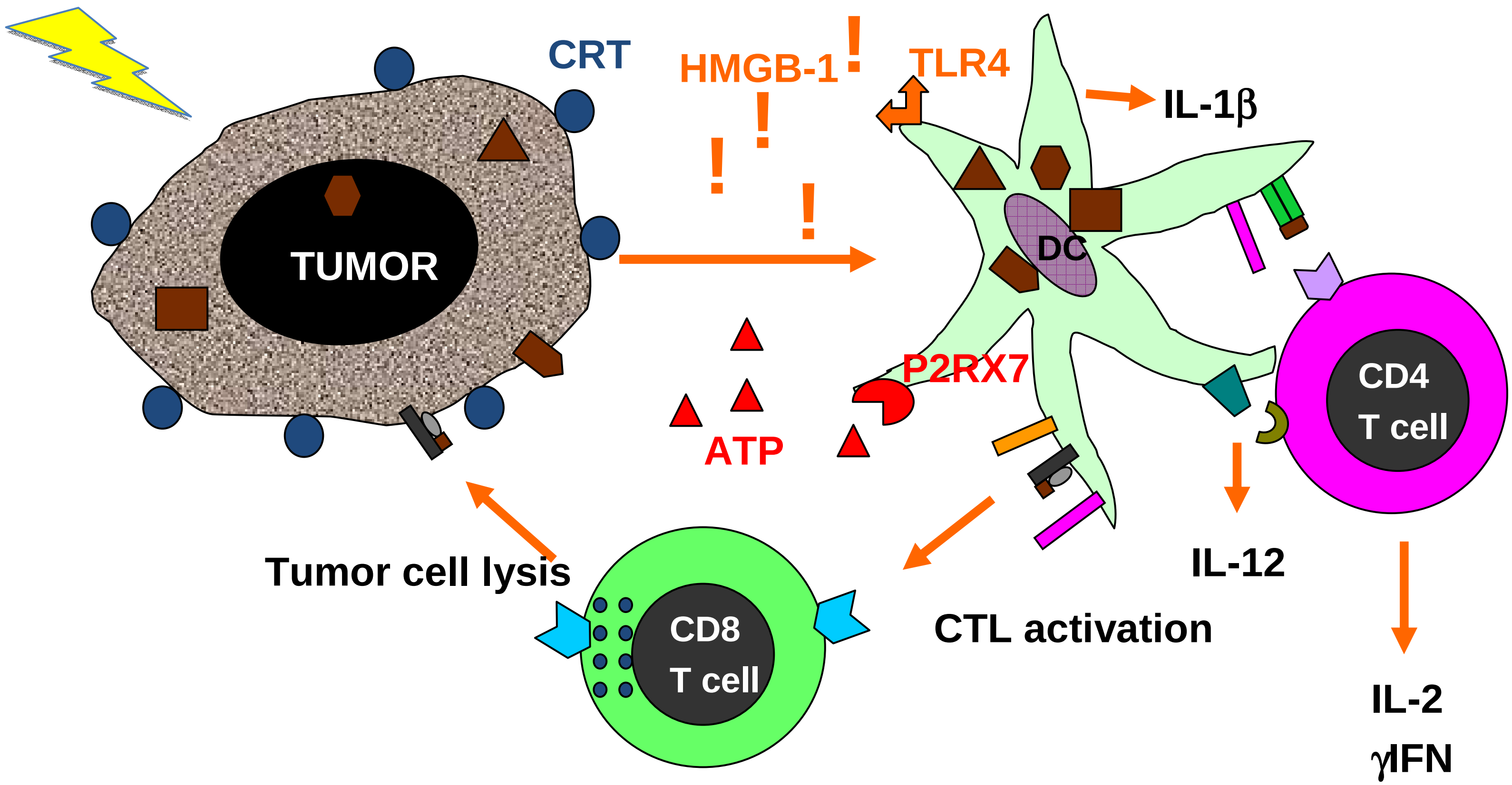
Immunogenic cell death (ICD)



Golden et al, Front Oncol 2012 Aug 7;2:88. doi: 10.3389/fonc.2012.00088. eCollection 2012.

Cross-priming of anti-tumor T cells

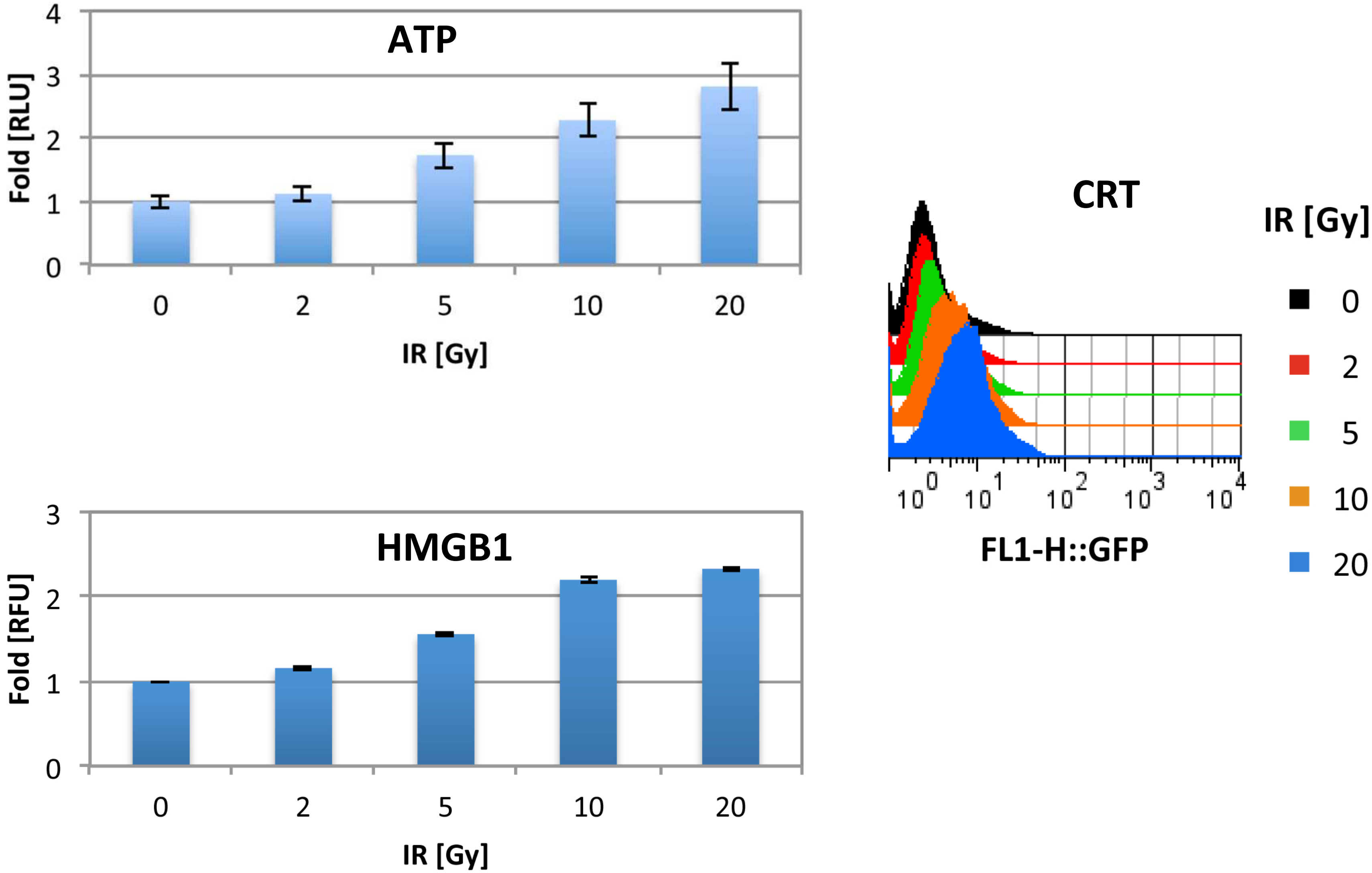


CRT, the "eat me" signal calreticulin translocates to cell surface (Obeid et al., Nat Med 2007, 13:54-61; Cell Death Differ 2007, 14:1848)

HMGB-1, a damage associated molecular pattern (DAMP) binds to TLR4 to promote cross-presentation of tumor-derived antigens (Apetoh et al., Nat Med 2007, 13:1050)

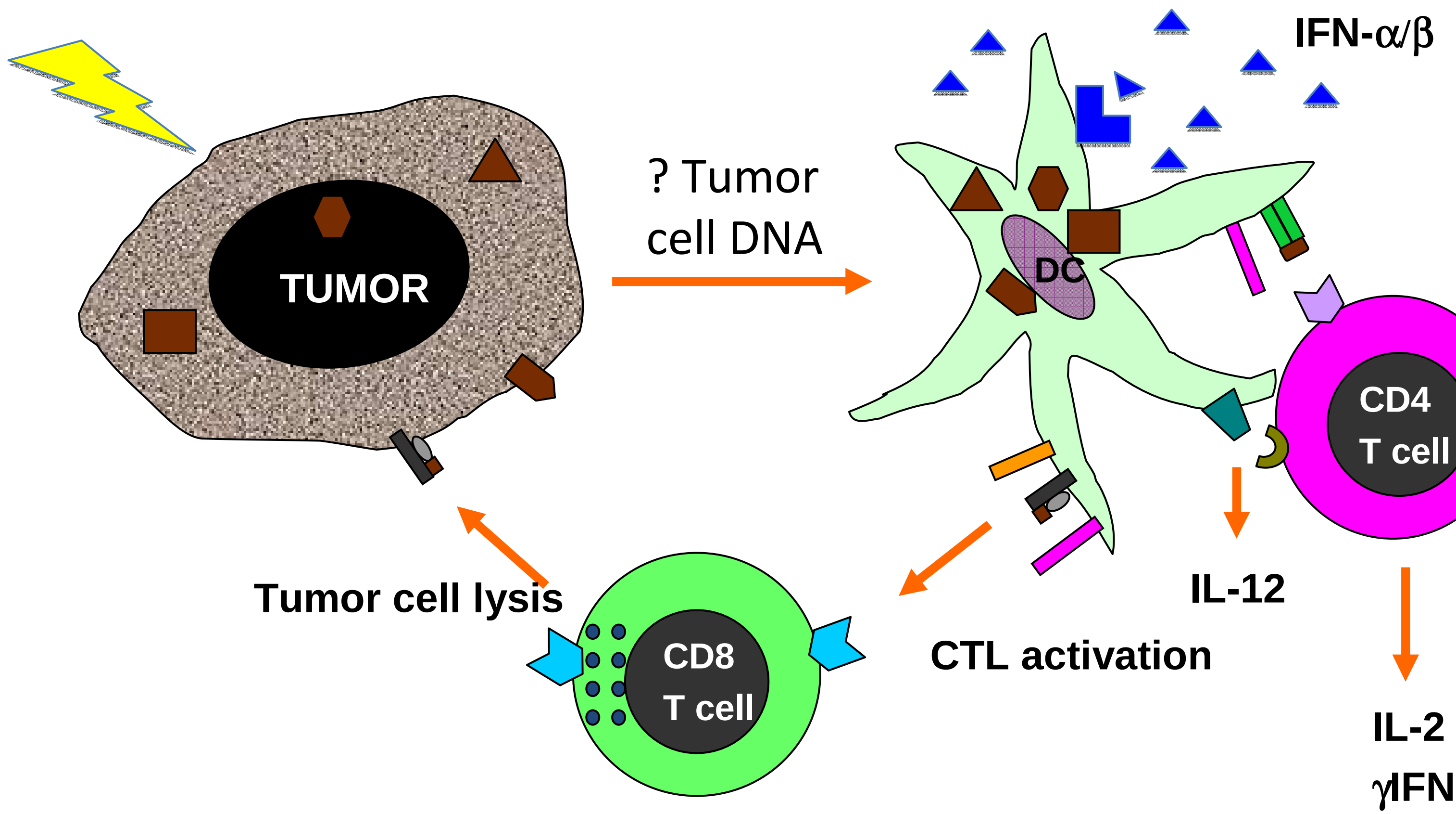
ATP released by dying cells binds to P2RX7 purigergic receptor leading to inflammasome activation and IL-1β production (Ghiringhelli et al., Nat Med 2009, 15:1170)

Immunogenic cell death (ICD)



Golden et al, OncoImmunology 3:4, e28518; January 1, 2014; © 2014 Landes Bioscience.

Cross-priming of anti-tumor T cells



IFN type I is produced by DC infiltrating irradiated tumors (Burnette et al., Cancer Res 2011; 71(7); 2488–96)

Effects of radiation on the tumor microenvironment

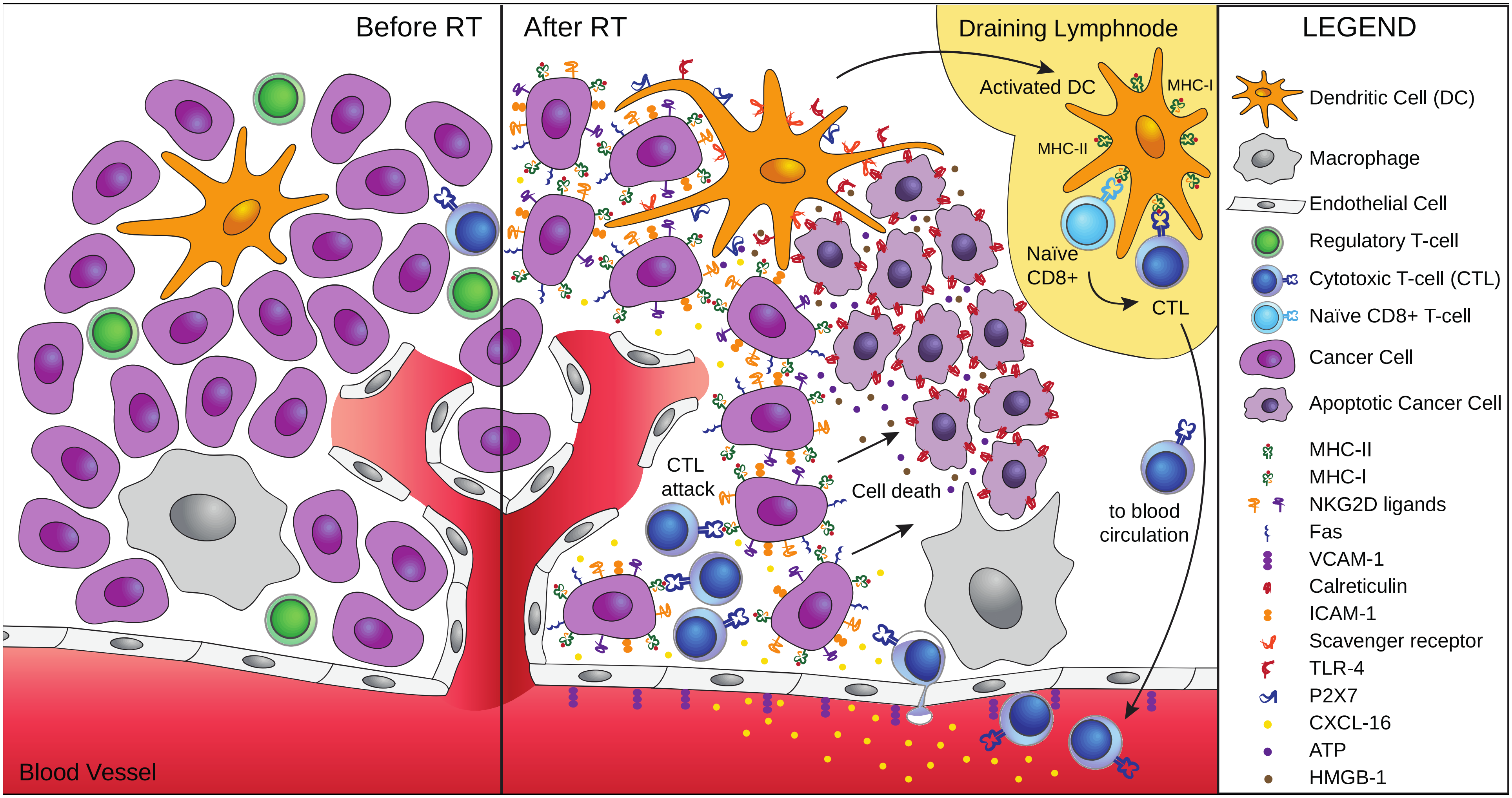
Increased expression by irradiated tumor/stromal cells of:

MHC class I molecules
Stress-induced ligand (NKG2D ligands)
ICAM-1, VCAM
Co-stimulatory molecules (CD80, CD86)
Death Receptors (Fas/CD95)
Tumor antigens (e.g., CEA, MUC-1)
Chemokines (e.g, CXCL16, CXCL10, CXCL9)
Cytokines (e.g., IL-1β, TNFα, IFN type I)
Hsp70

Increased DC and T cell recruitment and infiltration
Increased interactions between effector T cells and tumor cells
Increased tumor cell killing

Formenti & Demaria, J Natl Cancer Inst 2013 Feb 20;105(4):256-65

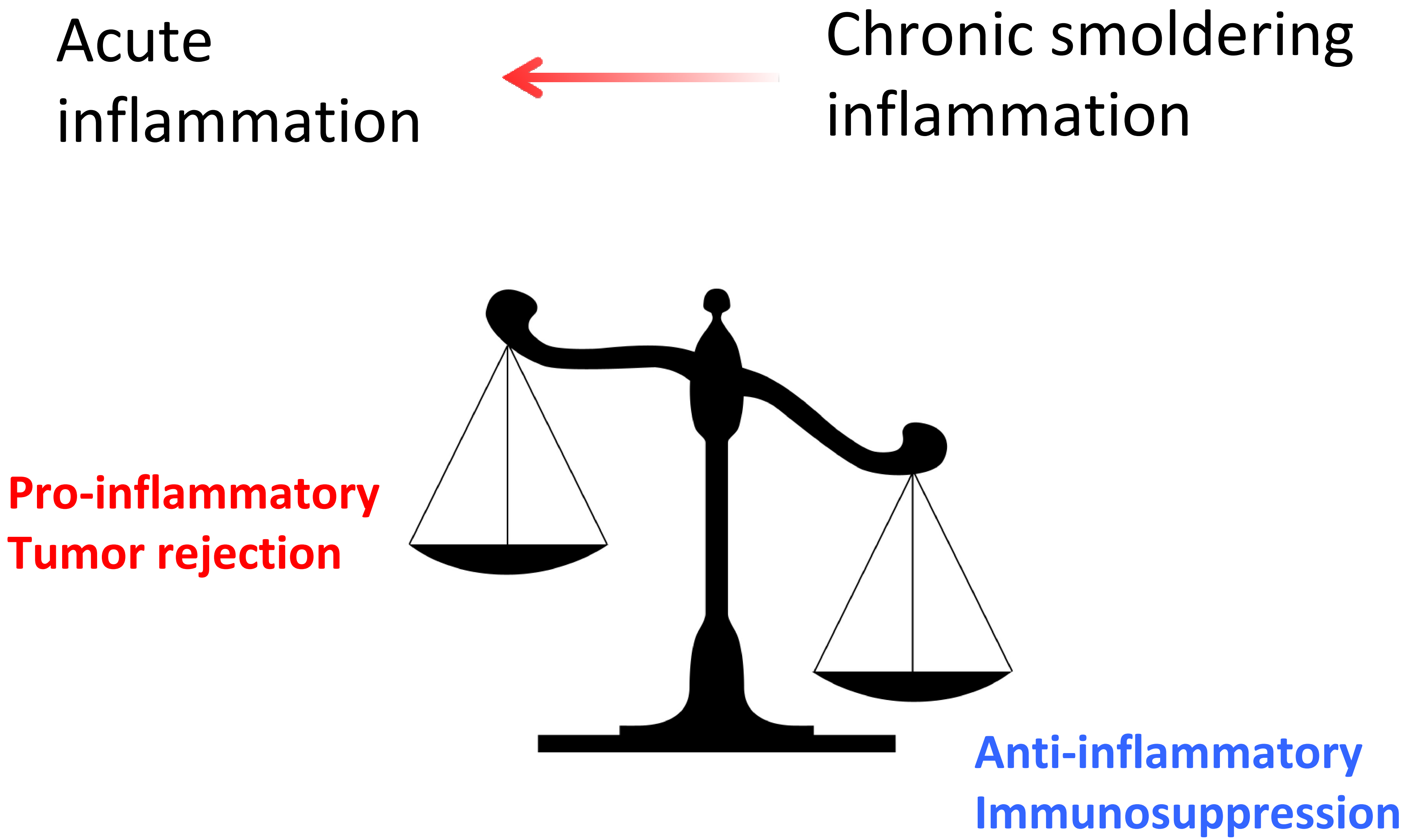
Radiotherapy converts the tumor into an immunogenic hub

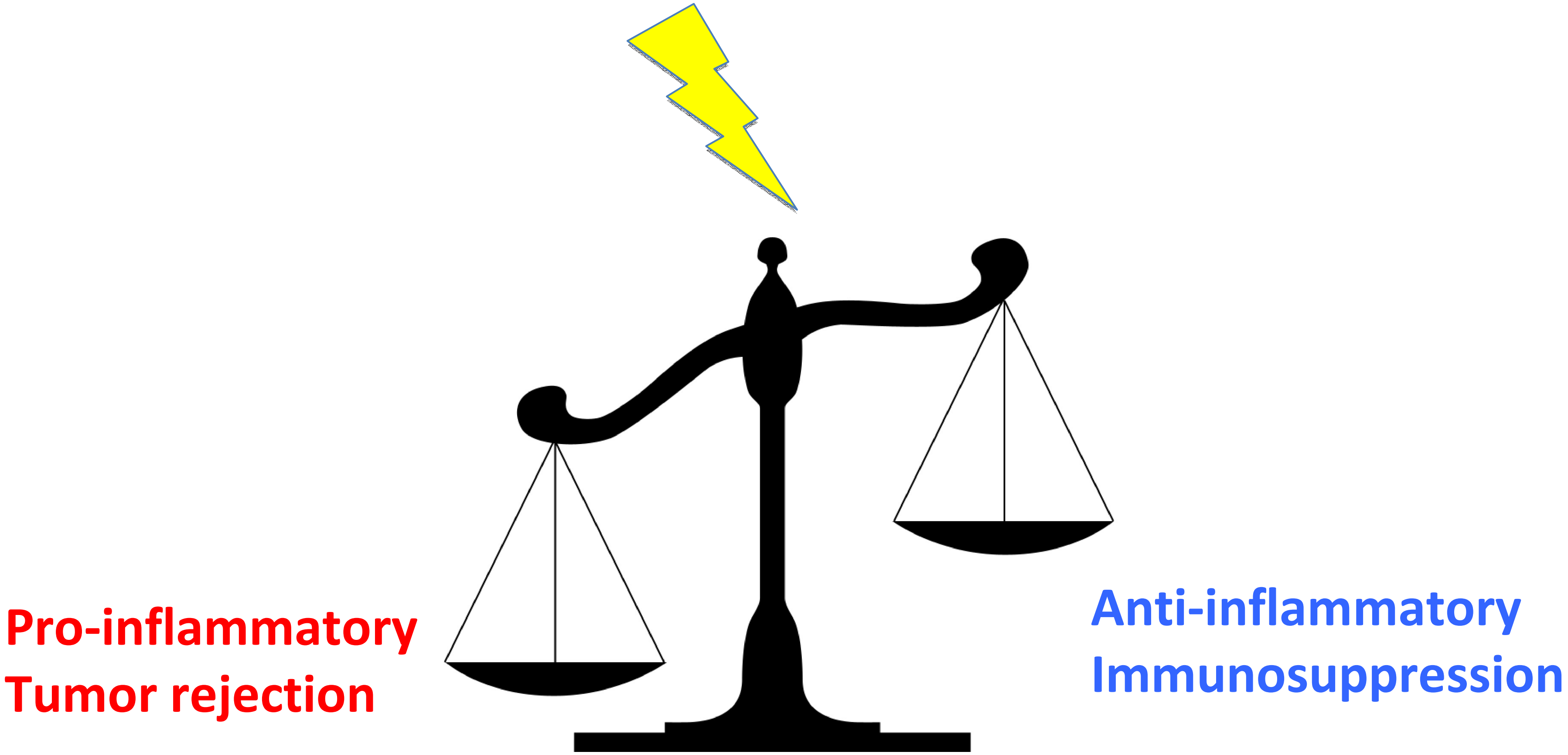


Demaria & Formenti, Front Oncol 2012;2:95. doi: 10.3389/fonc.2012.00095

Effects of radiation that can hinder the development of anti-tumor immunity

- Induction of Treg cells (*Schaue et al., Front Oncol 2012*)
- Activation of TGFβ (*Barcellos-Hoff et al., J Clin Invest 1994)*
- Up-regulation of PDL-1 (*Deng et al., J Clin Invest 2014)*
- Induction of pro-tumorigenic M2 macrophages (*Tsai et al., IJROBP 2007)*
- Induction/activation of STAT-3, Bcl-XL, VEGF (*Ho et al., Cancer Sci 2010; Kargiotis et al., J Neurooncol 2010*)


Acute inflammation
Chronic smoldering inflammation
Pro-inflammatory
Tumor rejection
Anti-inflammatory
Immunosuppression



? Radiation dose and fractionation

Combination of radiation and immunotherapy

Effective cancer immunotherapy

<u>IMPROVING PRIMING</u>

- APC defects (decreased co-stimulation) Flt3-L, GM-CSF, TLR agonists, exogenous DC
- Active immune suppression (e.g., TGFβ, IL-10, IDO) TGFβ neutralizing mAb
- Tolerance to TAA Immune checkpoint blockade
- Vaccination GVAX, TRICOM

<u>IMPROVING EFFECTOR PHASE</u>

- Barriers to *homing* of activated T cells to tumors T Cell Therapy
- Barriers to *function* of activated T cells within tumors CD137 costimulation
  OX40 costimulation

Pre-clinical combinations of RT and immunotherapy

Increasing APC	Flt3-Ligand	Chakravarty et al, Cancer Res 1999 Demaria et al. IJROBP 2004
	Exogenous DC	Nikitina et al., Int J Cancer 2001 Teitz-Tennenbaum et al, Cancer Res 2003 Kim et al., Int J Cancer 2004
Increasing danger signals	TLR9 agonists	Milas et al., Cancer Res 2004 Mason et al., Clin Cancer Res 2005 Zhang et al., PlosOne 2012
	TLR7 agonists	Dewan et al., Clin Cancer Res 2012 Dovedi et al., Blood 2013

Pre-clinical combinations of RT and immunotherapy

Improving T cell co-stimulation	Anti-CD137 mAb	Shi et al., Anticancer Res 2006
		Newcomb et al., Radiat Res 2010
	Anti-OX40 mAb	Gough et al., J. Immunother 2010
Blocking immune checkpoints	Anti-CTLA-4 mAb	Demaria et al., Clin Cancer Res 2005
		Dewan et al., Clin Cancer Res 2009
	Anti-PD-1 mAb	Verbrugge et al., Cancer Res 2012
		Zeng et al., IJROBP 2013
	Anti-PDL-1 mAb	Deng et al., J Clin Invest 2014

Pre-clinical combinations of RT and immunotherapy

Priming anti-tumor T cells	Vaccinia and avipox CEA vaccines	Chakraborty et al., Cancer Res 2004
	GM-CSF tumor cell vaccine (GVAX)	Newcomb et al., Clin Cancer Res 2006
Adoptive T cell transfer	Effector CD8 T cells	Chakraborty et al., J Immunol 2003 Reits et al., J Exp Med 2006
	CD8 and CD4 T cells	Klug et al., Cancer Cell 2013

Clinical Translation

DC administration

Hepatocellular carcinoma: DC i.t. 2 days after one dose radiation: partial response in 2/14 patients *(Chi et al., J Immunother 2005)*

Sarcoma: DC i.t. during multi-fraction neoadjuvant radiation: tumor-specific immune responses in 9/17 patients *(Finkelstein et al., IJROBP 2012)*

Vaccination

Prostate carcinoma: Poxviral vaccine expressing PSA with standard multi fraction radiation starting vaccination before radiation: PSA-specific T cell in 13/17 patients plus evidence of antigenic cascade *(Gulley et al., Clin Cancer Res 2005)*

Clinical Translation

<u>TLR9 agonists</u>

Lymphoma: phase I/II study 2 Gy x 2 plus i.t. synthetic CpG. Abscopal responses in 27% with one complete response, three partial responses, and eight patients with stable disease *(Brody et al., JCO 2009)*

Second trial performed in Mycosis fungoides *(Kim et al., Blood. 2012).*

<u>TLR7 agonists</u>

Breast cancer with cutaneous metastases: phase I/II study 6 Gy x 5 topical imiquimod (NCT01421017).

<u>High dose IL-2</u>

Melanoma and RCC (phase I): SBRT followed by high dose IL-2. Response rate of 66% was observed, higher than historical comparisons. Patients who responded showed a higher effector memory T cell phenotype (*Seung et al.*, *Sci Transl Med. 2012*).

Phase II randomized study of SBRT (20 Gy) and high-dose IL-2 versus IL-2 alone in patients with metastatic melanoma is ongoing (NCT01416831).

Phase II in metastatic RCC (NCT01896271).

Clinical Translation

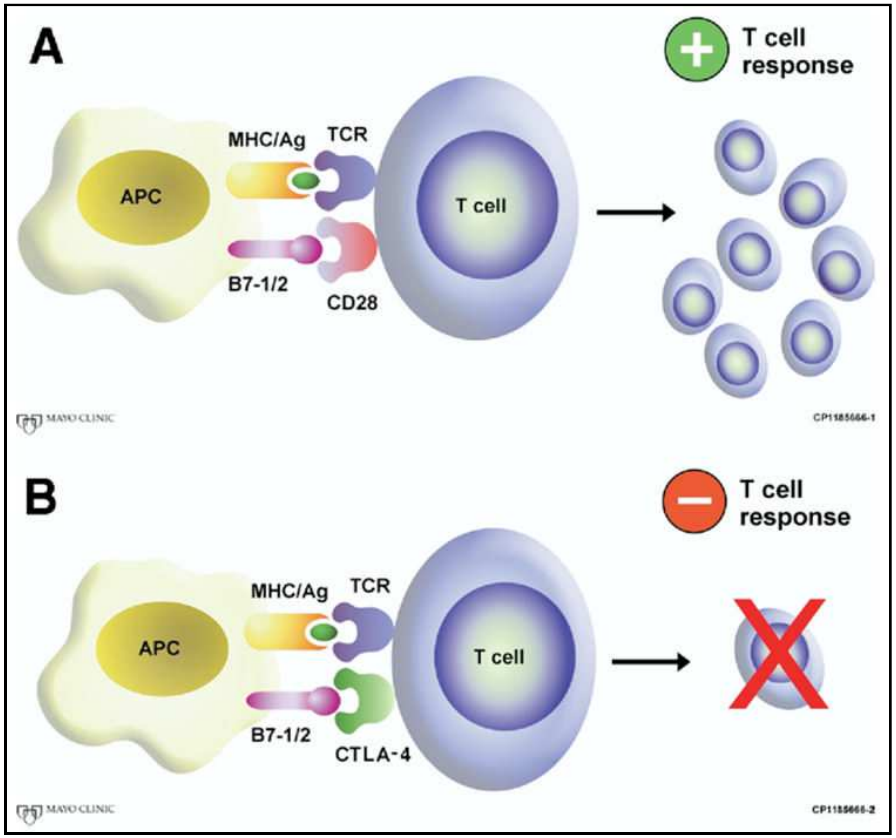
Anti-CTLA-4 (Ipilimumab)
Metastatic melanoma: Case report of a patient with progressive disease on Ipilimumab who showed a dramatic abscopal effect after radiotherapy (9.5 Gy x 3) to one site, accompanied by immunological changes (*Postow et al., NEJM 2012*).

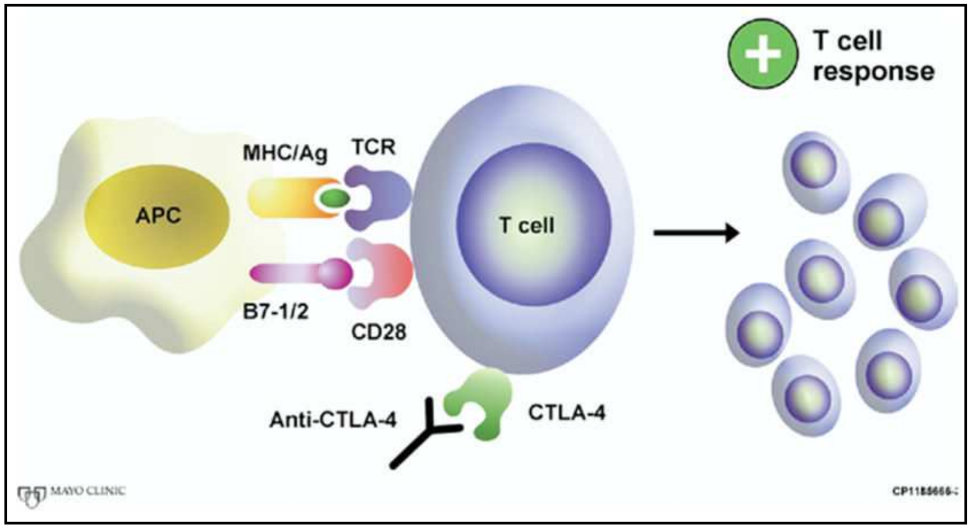
Data are supported by pre-clinical data demonstrating that tumors unresponsive to anti-CTLA-4 show abscopal responses when one site is irradiated (*Dewan et al., Clin Cancer Res 2009*)

Currently >20 trials testing combination of radiotherapy and Ipilimumab are underway.

Synergy of radiation and anti-CTLA-4 mAb: a complex interaction

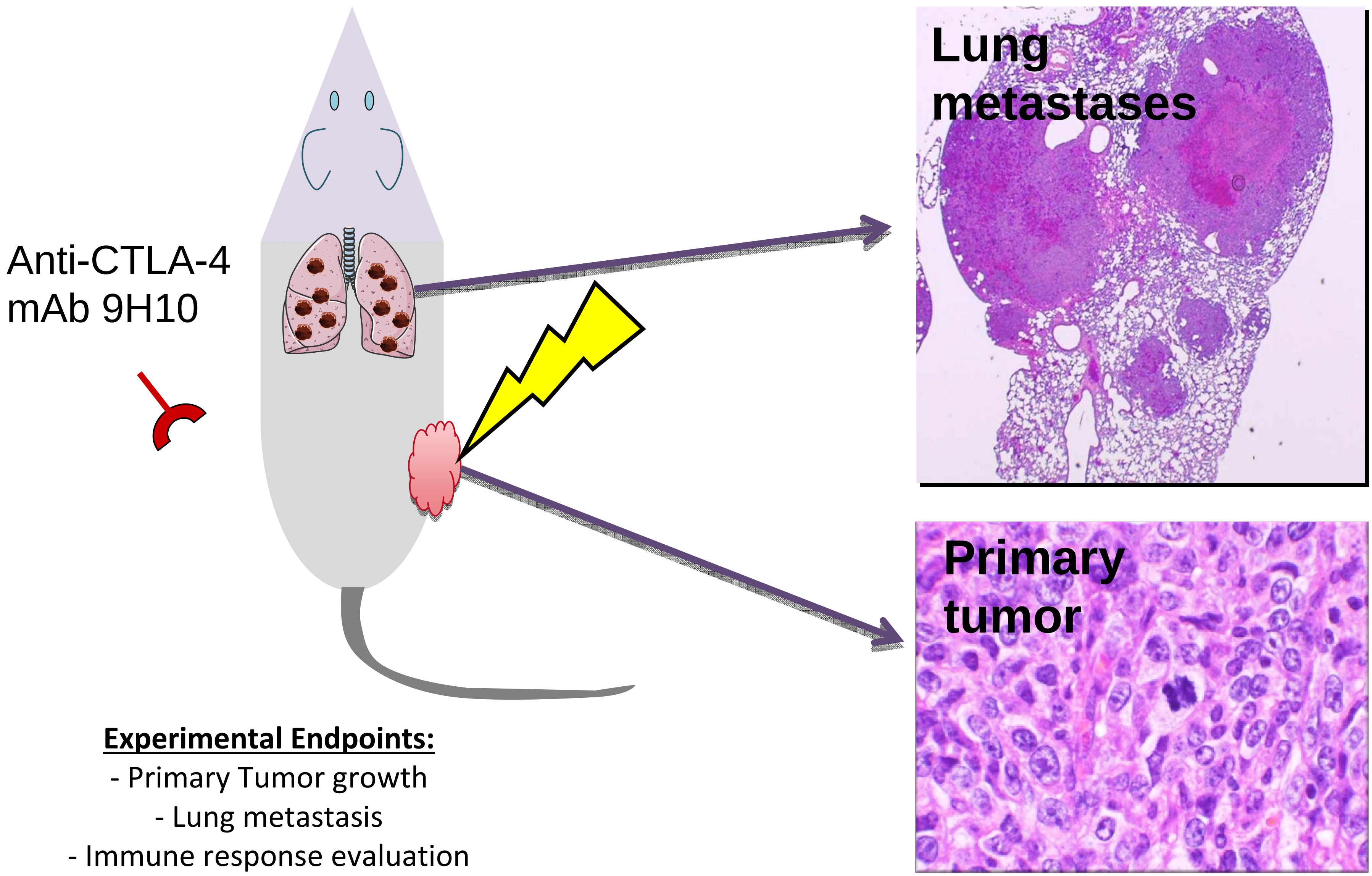
CTLA-4 is a master regulator of T cell activation





Thompson RH et al. *Urol Oncol.* 2006:24:442-7

4T1 mouse model of metastatic breast cancer



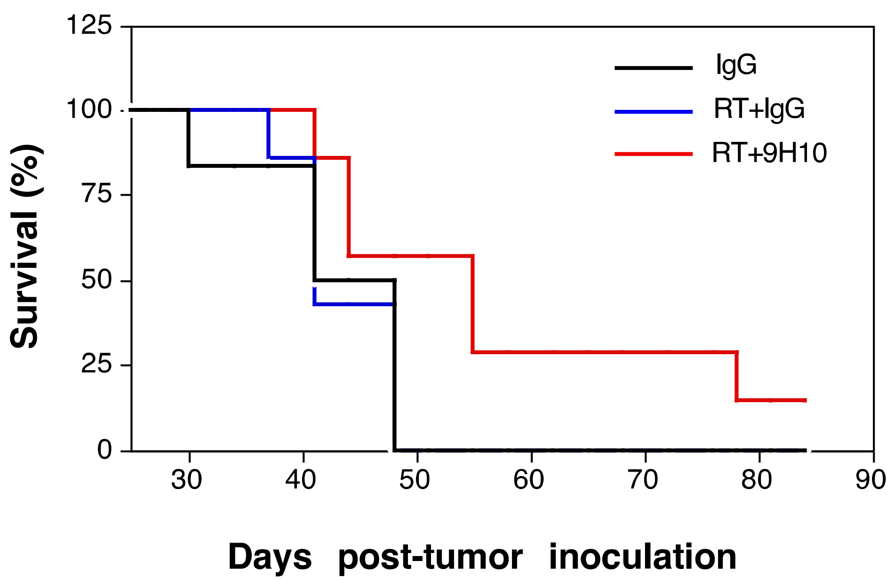
Experimental Endpoints:

- Primary Tumor growth
- Lung metastasis
- Immune response evaluation

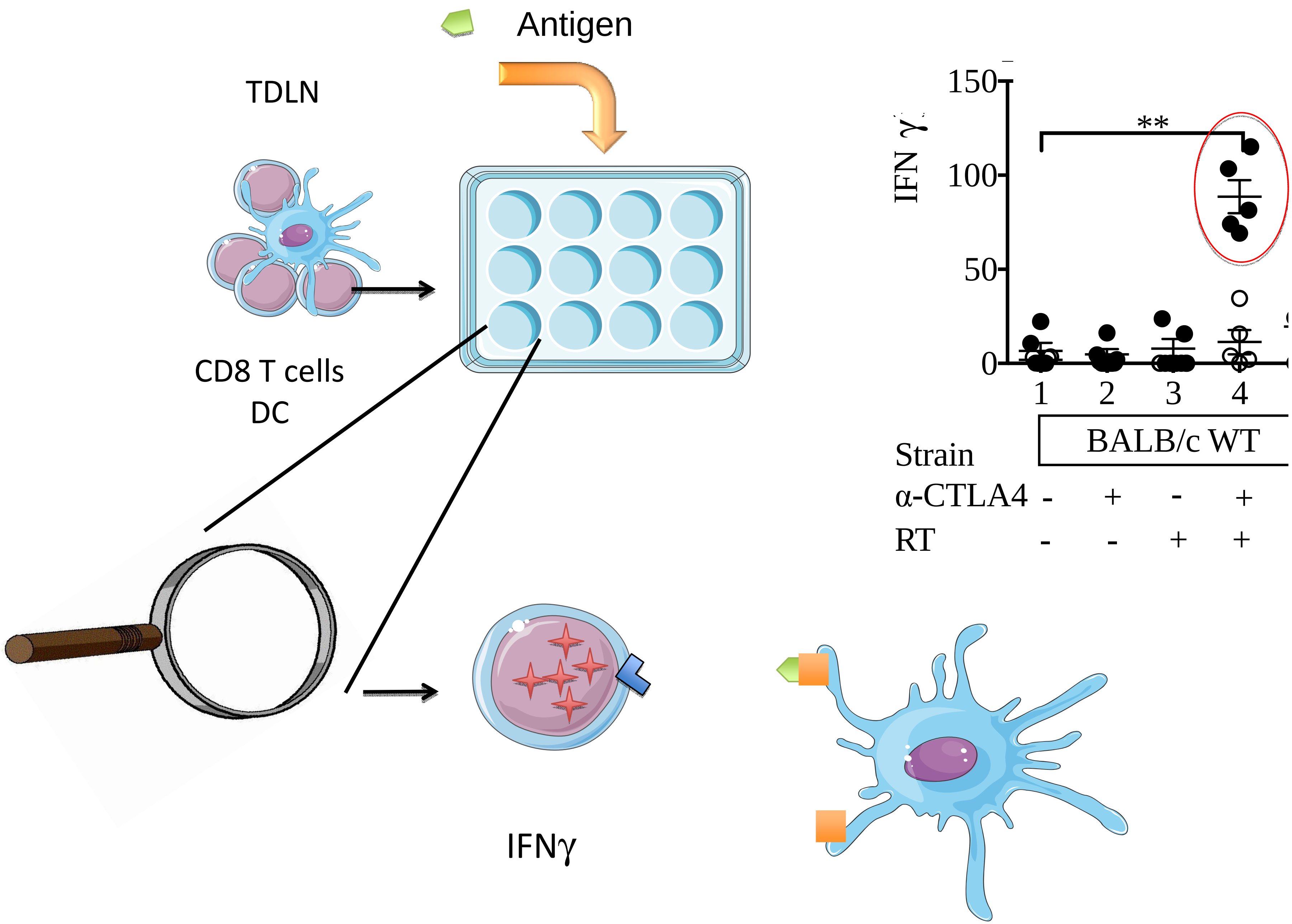
Immune-Mediated Inhibition of Metastases after Treatment with Local Radiation and CTLA-4 Blockade in a Mouse Model of Breast Cancer

Sandra Demaria,[1] Noriko Kawashima,[1] Anne Marie Yang,[1] Mary Louise Devitt,[2] James S. Babb,[3] James P. Allison,[4] and Silvia C. Formenti[2]

Departments of [1]Pathology, [2]Radiation Oncology, and [3]Radiology, New York University School of Medicine, New York, New York; and [4]Howard Hughes Medical Institute, University of California at Berkeley, Berkeley, California

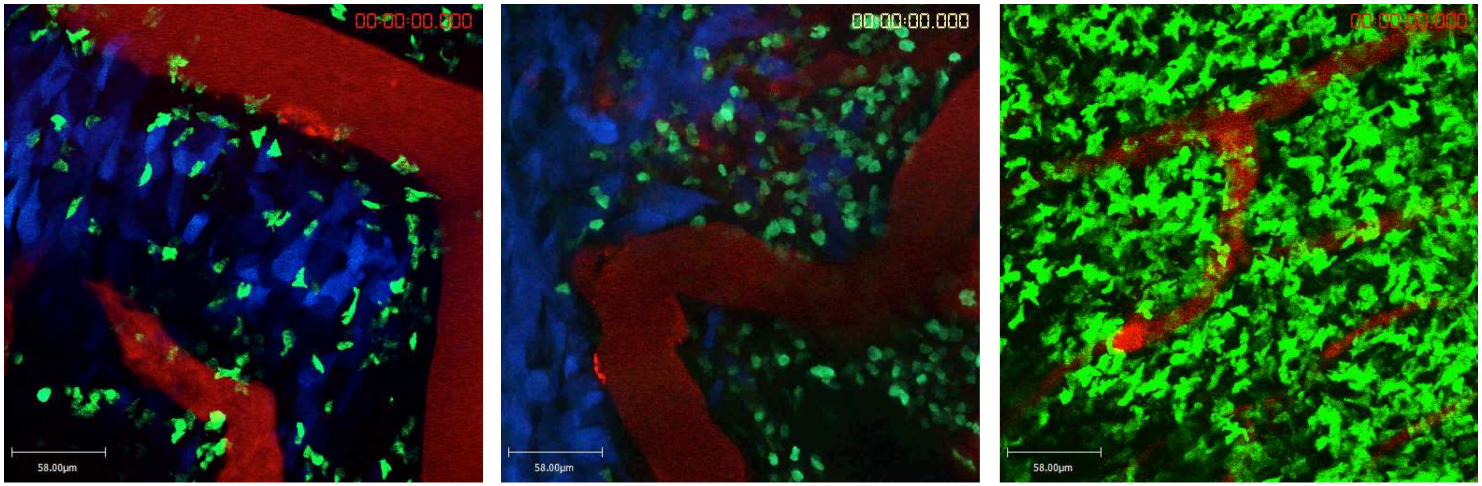


Anti-tumor CD8$^+$ T cells priming



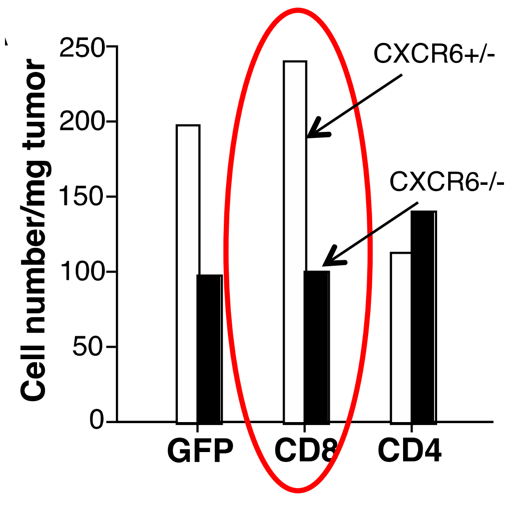
CD8$^+$ T cells recruitment and tumor infiltration

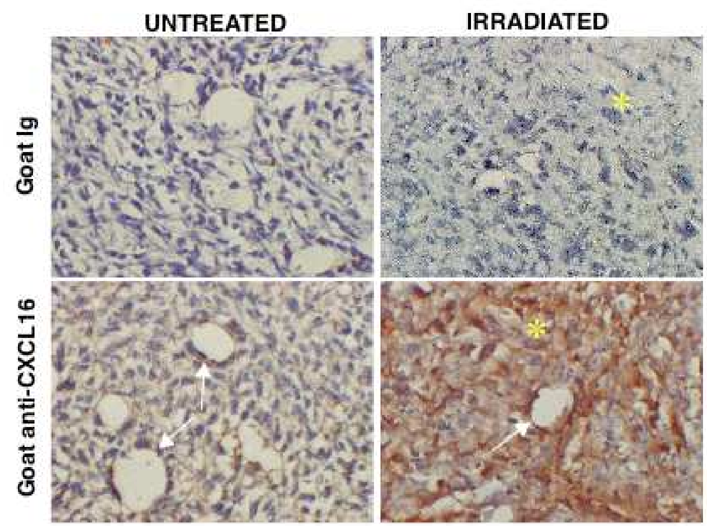
RT **Anti-CTLA-4** **RT + Anti-CTLA-4**



Blood vessels
T cells
Tumor cells

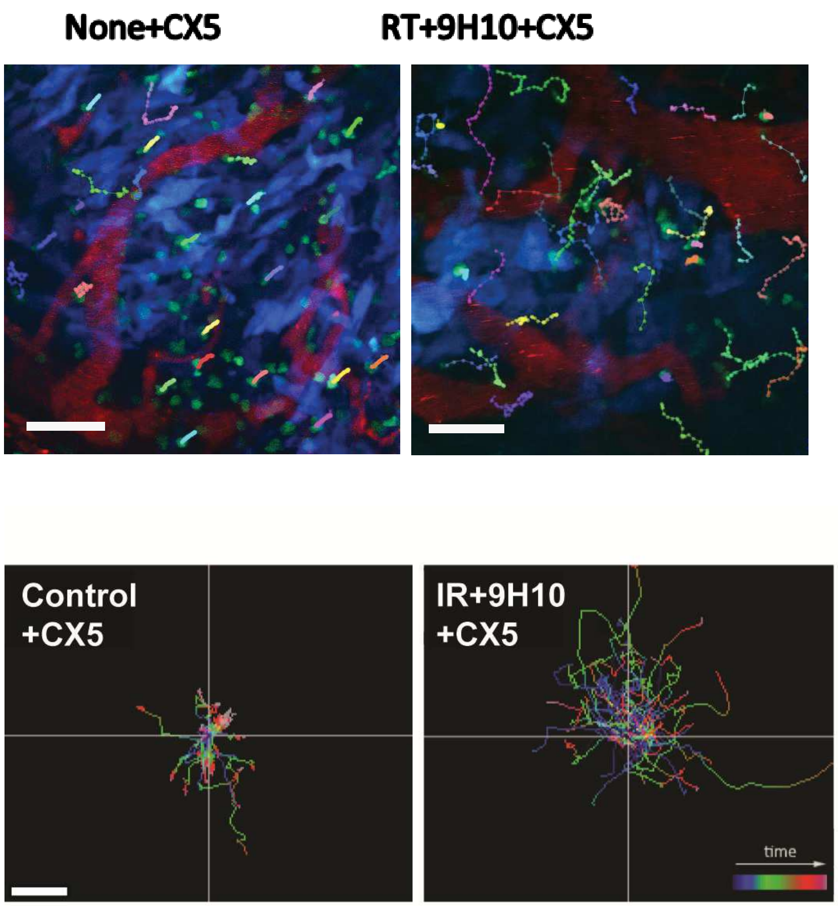
Ruocco et al., *J Clin Invest* 122:3718-30 2012



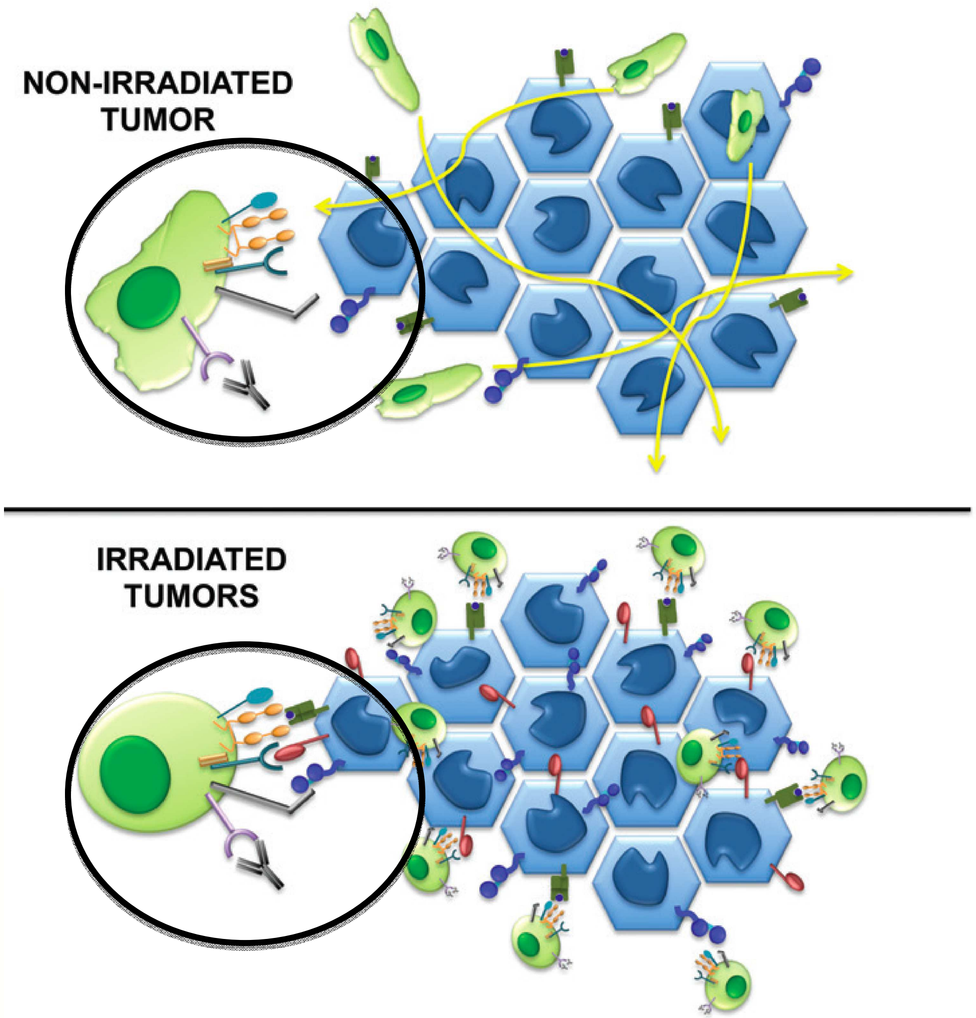


Matsumura *et al., J Immunol* 181:3099-3107 *2008*

Formation of immune synapse between CD8^{+} T cells and tumor cells



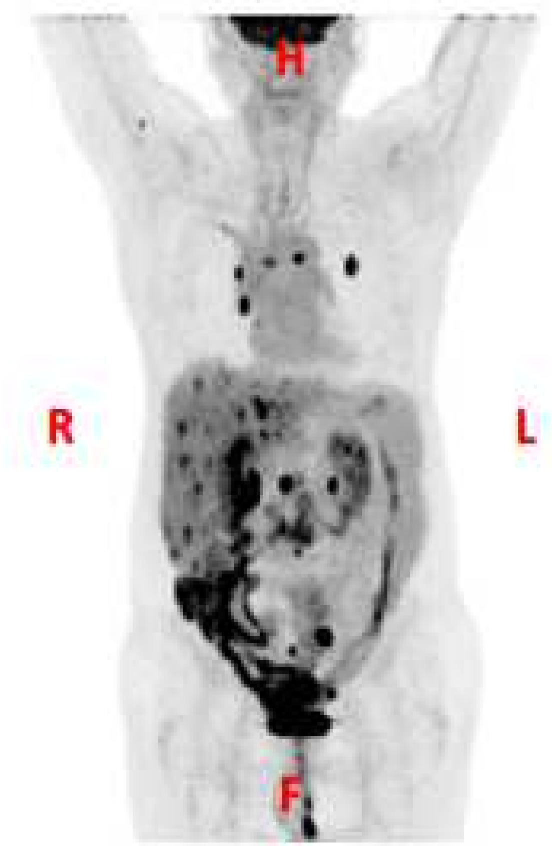
Ruocco et al., *J Clin Invest* 122:3718-30 2012



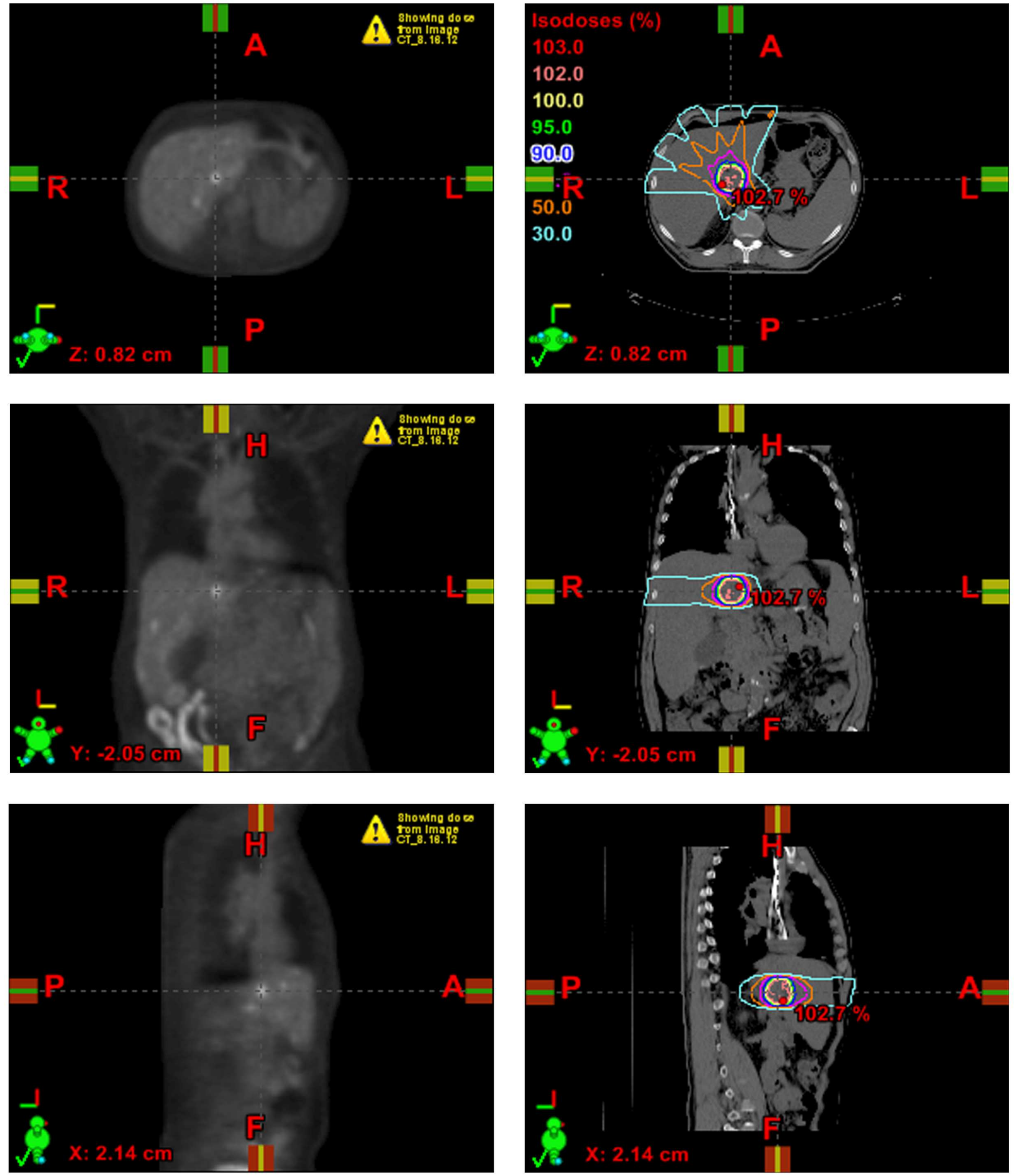
Demaria et al., OncoImmunology 2:3, e23127 2013

Patient with Metastatic NSCLC

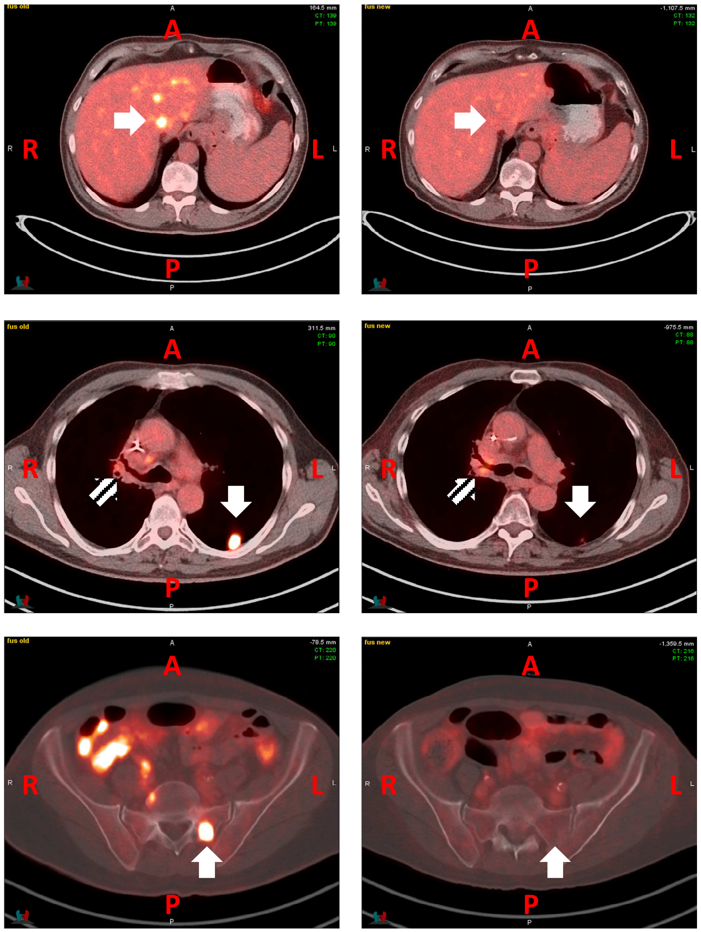
Progressing after 3 lines of chemo and chest RT: Multiple lung, bone and liver metastasis



RT to one liver met
6 Gy X 5 (TD 30 GY)
Ipilimumab, 3 mg/Kg, after first RT
q3 weeks, X 4 cycles

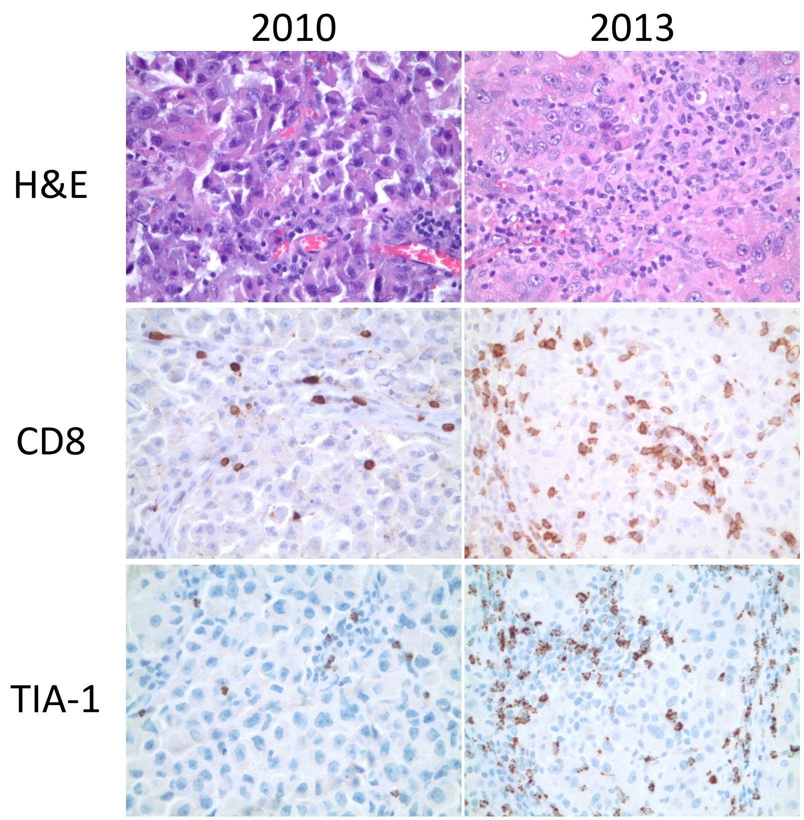


Abscopal response in a NSCLC patient treated with local RT and Ipilimumab



August 2012 PET/CT

January 2013 PET/CT



Golden *et al., Cancer Immunology Res.* 2013

CONCLUSIONS

- RT can promote the priming and effector phase of anti-tumor immune responses and may be able to **convert a T-cell poor into T-cell inflammed tumor**
- RT can be successfully combined with different immunotherapy strategies
- The optimal doses and regimens of RT and sequencing with immunotherapy remain to be defined and may depend on the immunotherapy used
- There is at least some evidence that RT can induce anti-tumor immune responses in patients
- Several trials testing combinations of RT and immunotherapy are ongoing