Society for Immunotherapy of Cancer

Is there a role for radiation therapy and immunotherapy?

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The following relationships exist related to this presentation:

Honoraria/Advisory:

Sanofi US Services Inc.

Regeneron Pharmaceuticals, Inc

Outline

- Background: Evidence for a role of the immune system in response to ionizing radiation
- In situ vaccination by radiation-induced tumor cell death
- Overcoming T cell exclusion: Effects of radiation on the tumor microenvironment
- Exploiting radiation effects to improve response to immunotherapy

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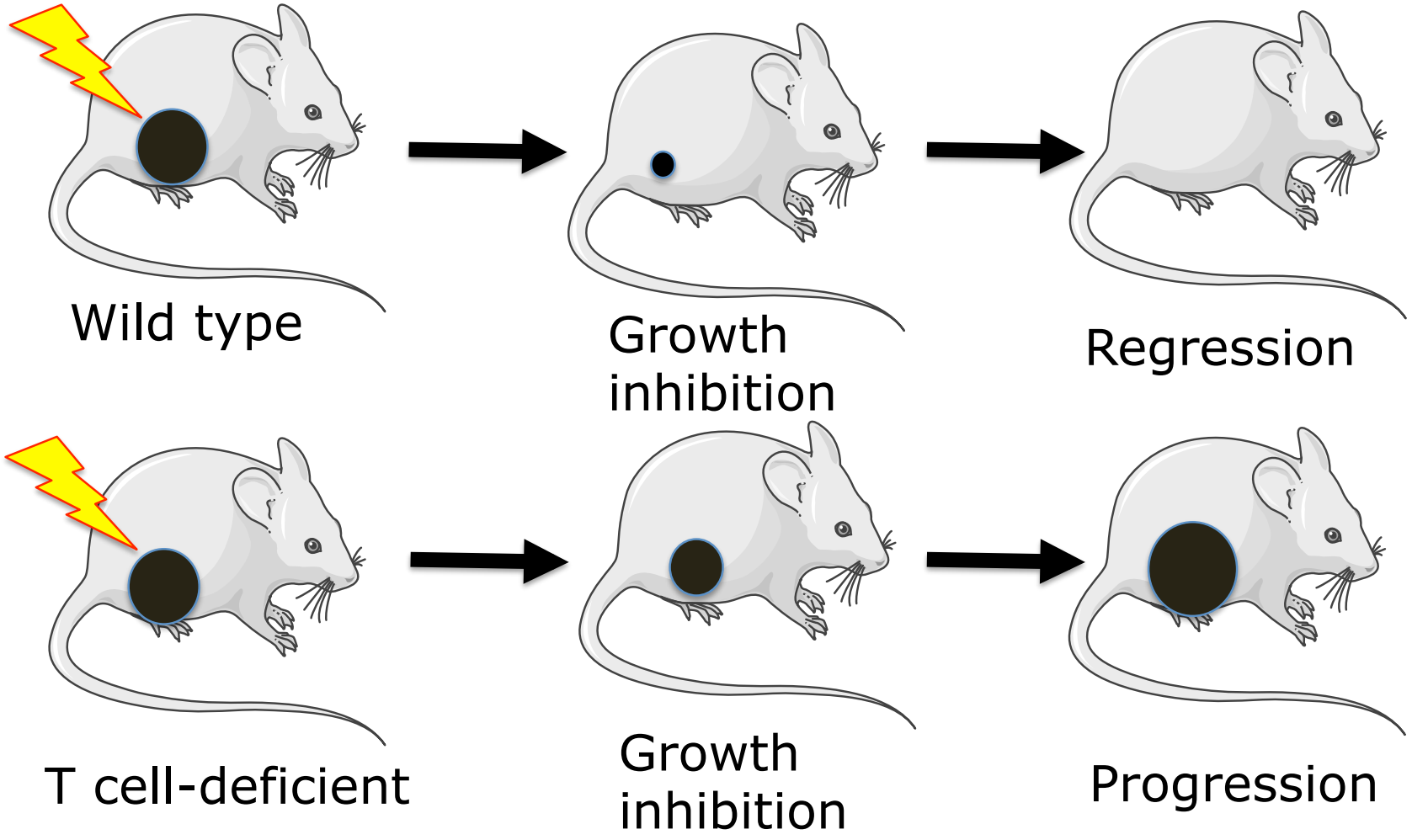
Immunocompetence of the host affects the response to local radiotherapy



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

Evidence for induction of tumor-specific immune responses by radiation

& HUMAN STUDIES

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

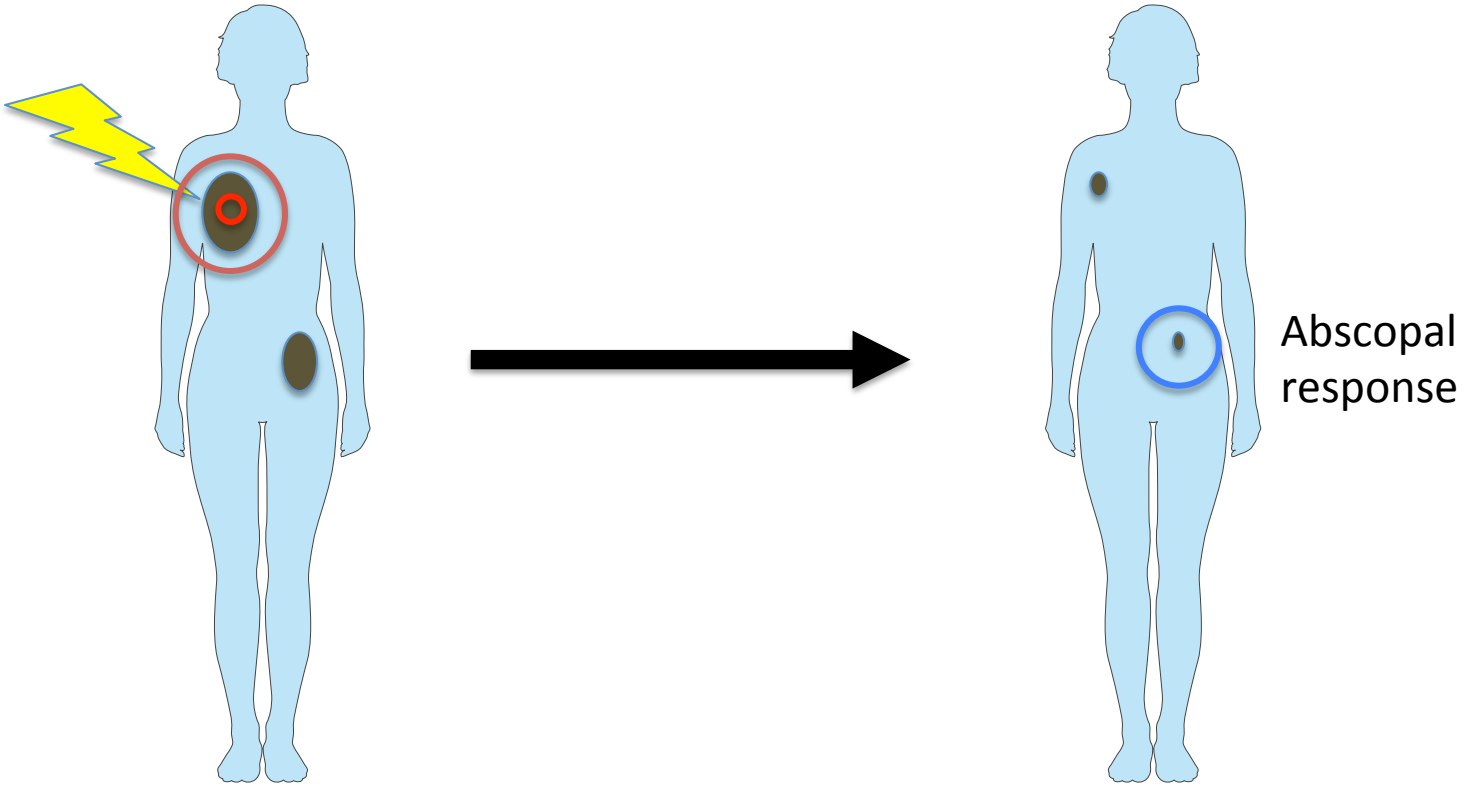
Schaue et al, Clin Cancer Res 2008
T cell responses to survivin in prostate and colorectal patients after radiotherapy

Teulings et al., *Br J Dermatol 2013*
T an B cell responses to MART-1 and gp100 in melanoma patient with complete durable regression after WBRT

Abscopal effect

Effect of ionizing radiation on cancer outside the radiation field

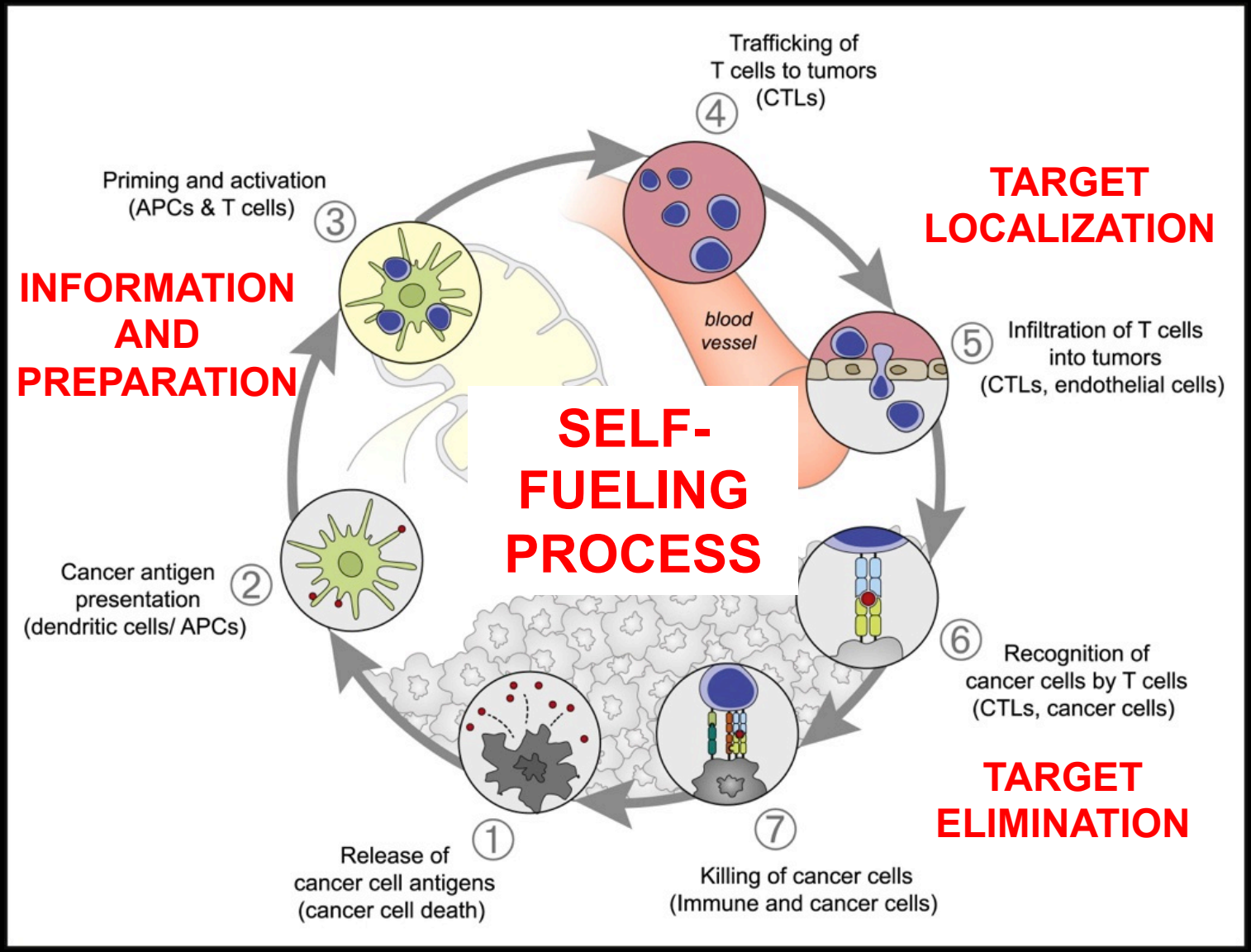
Latin *ab* (position away from) and *scopus* (mark or target)



Formenti & Demaria, Lancet Oncology 2009

The Cancer-Immunity Cycle

(Chen and Mellman, Immunity 2013)



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Radiation-induced tumor cell death

Radiation Damage → DNA, proteins, lipids

DIRECT energy deposition

INDIRECT free radicals (H_2O radiolysis)

REPAIR

DEATH

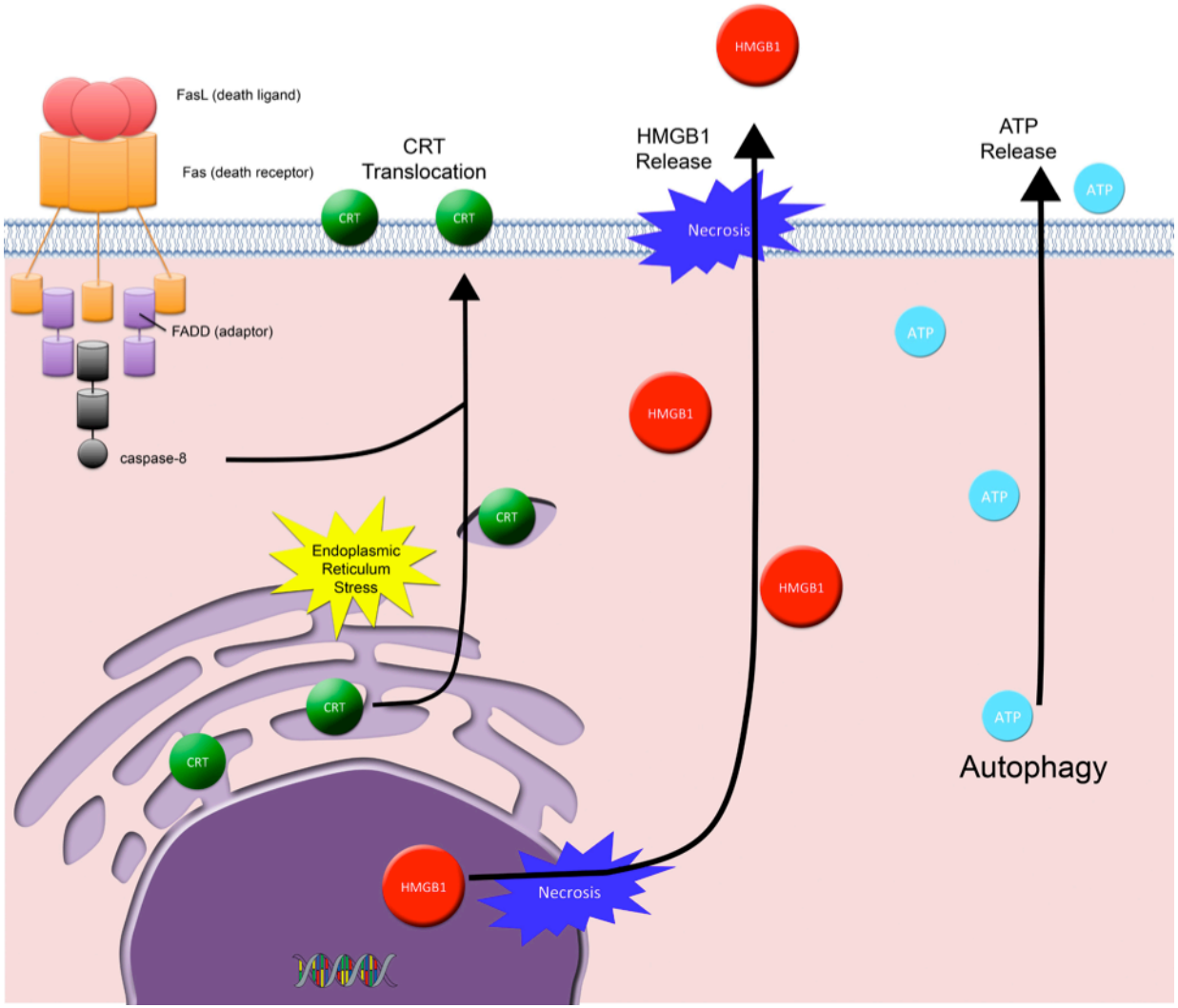
Cell death type depends on:

- intrinsic tumor cell characteristics (p53 status)
- radiation dose and fractionation
- oxygen tension
- DNA repair capacity
- redox status
- cell cycle phase

- APOPTOSIS
- NECROSIS
- MITOTIC CATASTROPHE
- SENESCENCE
- AUTOPHAGY

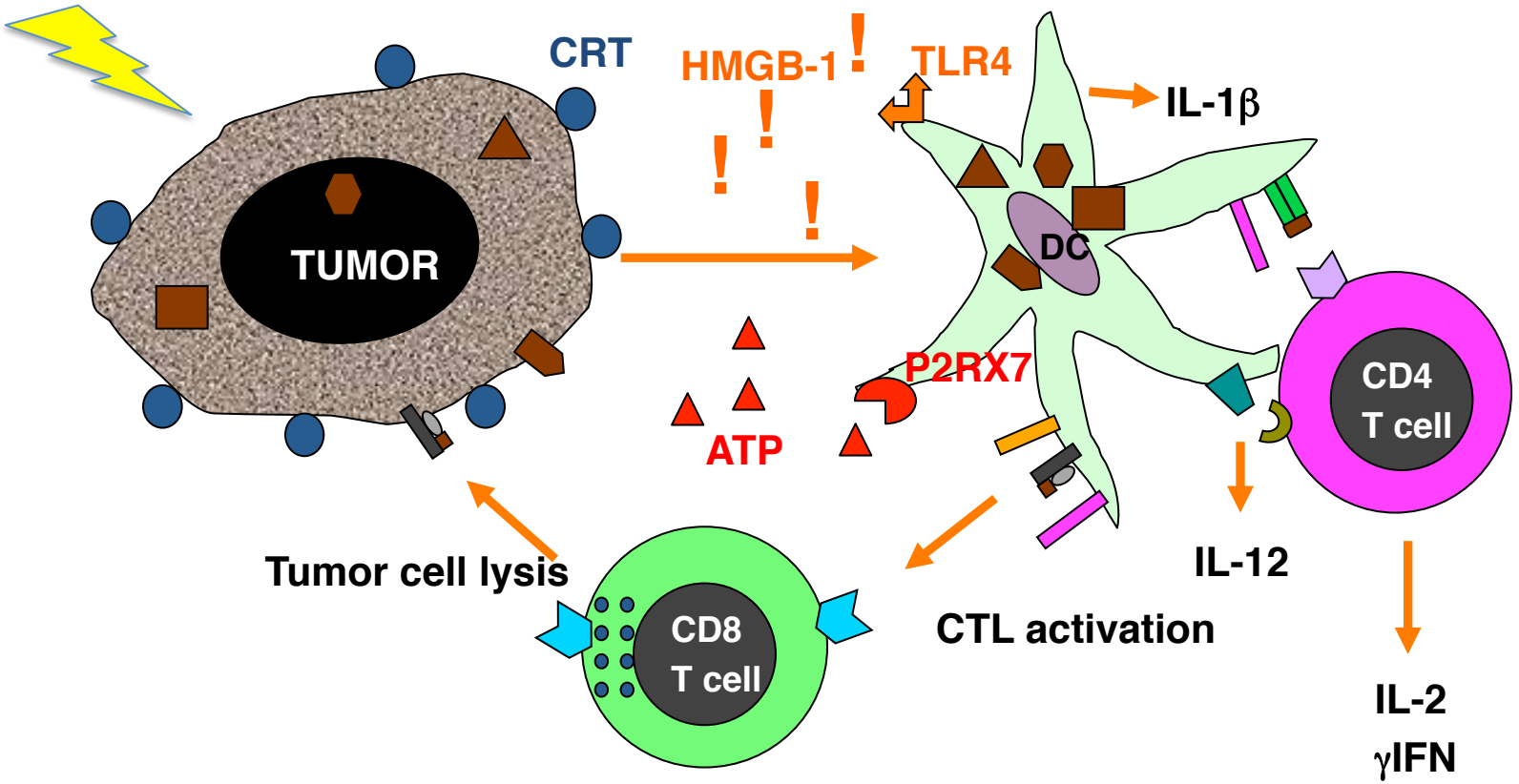
✧ **IMMUNOGENIC CELL DEATH**

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

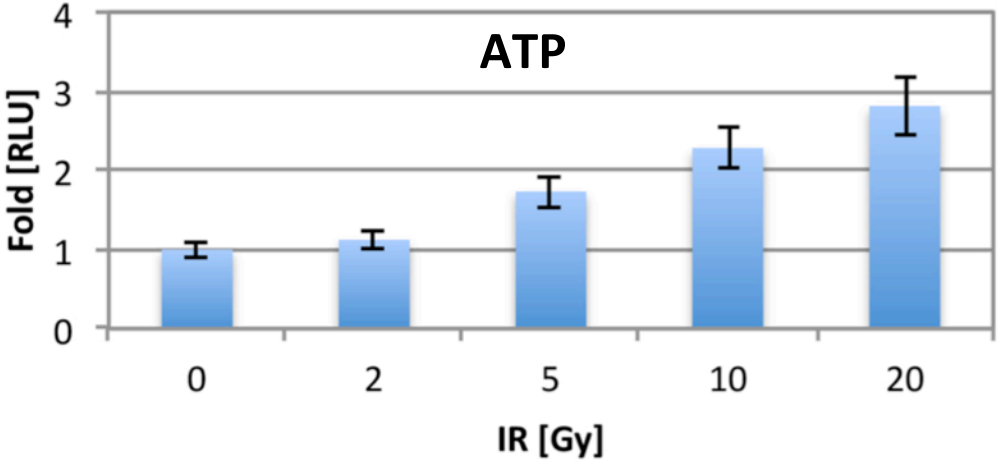


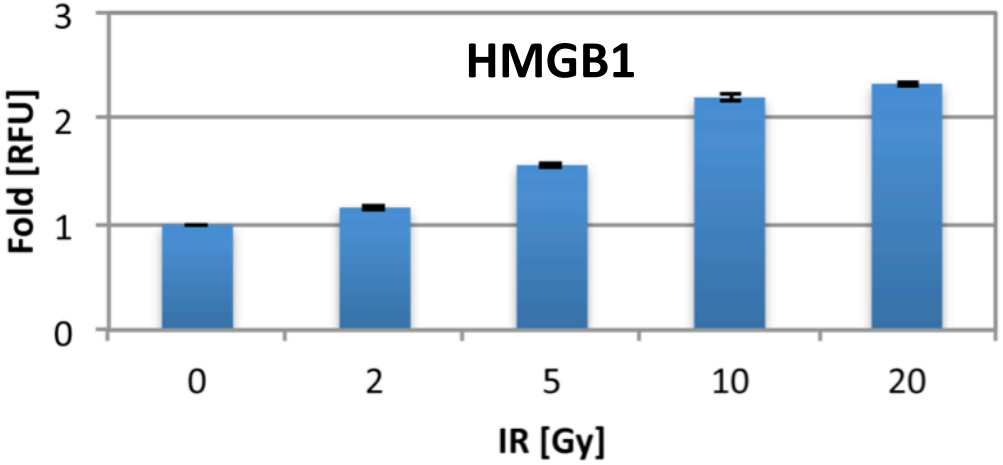
CRT, the "eat me" signal calreticulin translocates to cell surface (Obeid et al., Nat Med 2007, 13:54-61; Cell Death Differ 2007, 14:1848)

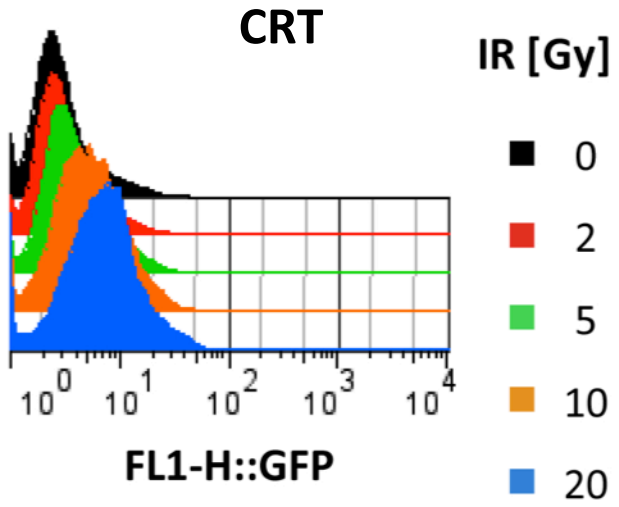
HMGB-1, a damage associated molecular pattern (DAMP) binds to TLR4 to promote cross-presentation of tumor-derived antigens (Apetoh et al., Nat Med 2007, 13:1050)

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)

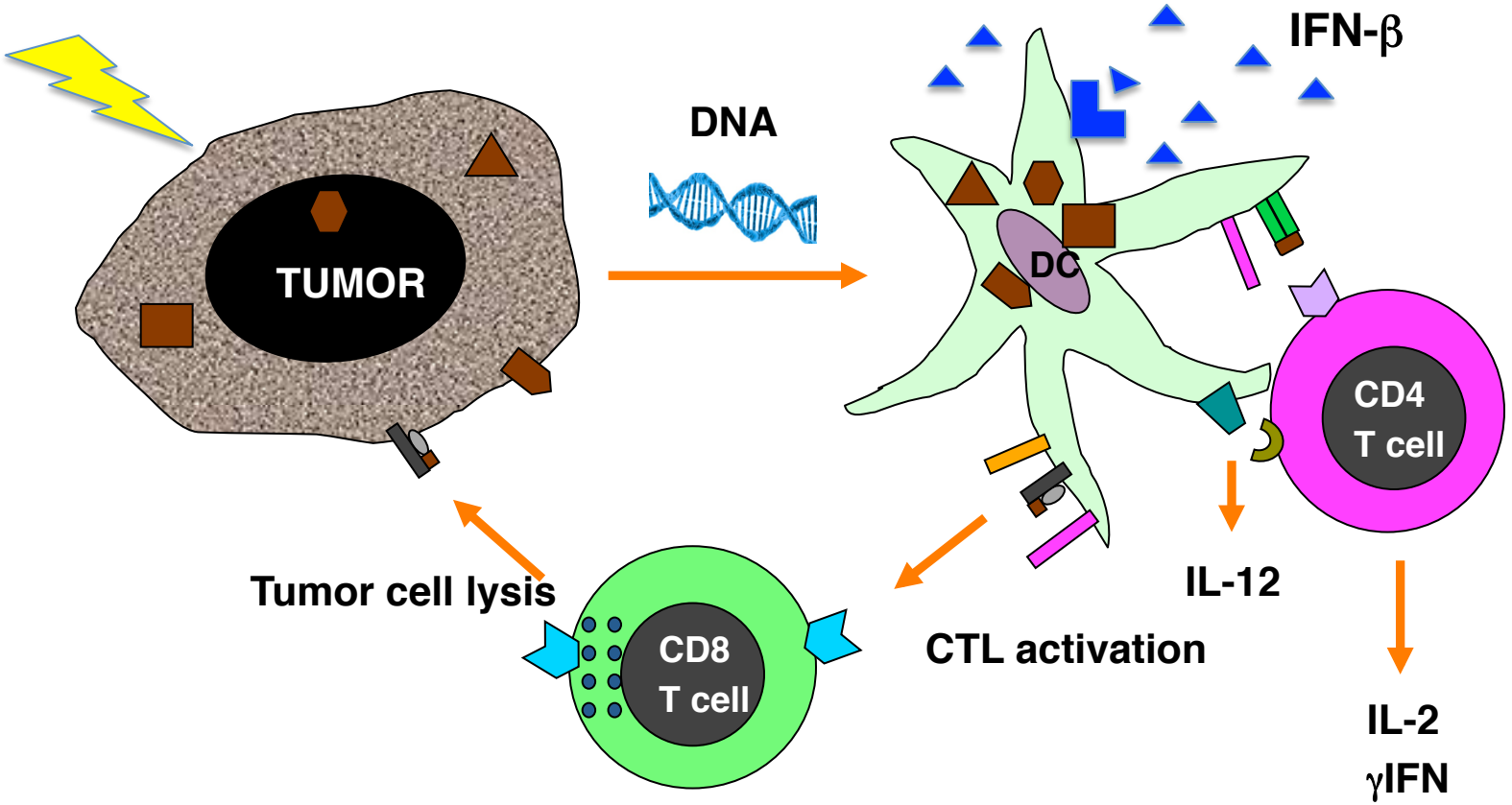






Golden et al, OncoImmunology 3:4, e28518; January 1, 2014

Cross-priming of anti-tumor T cells

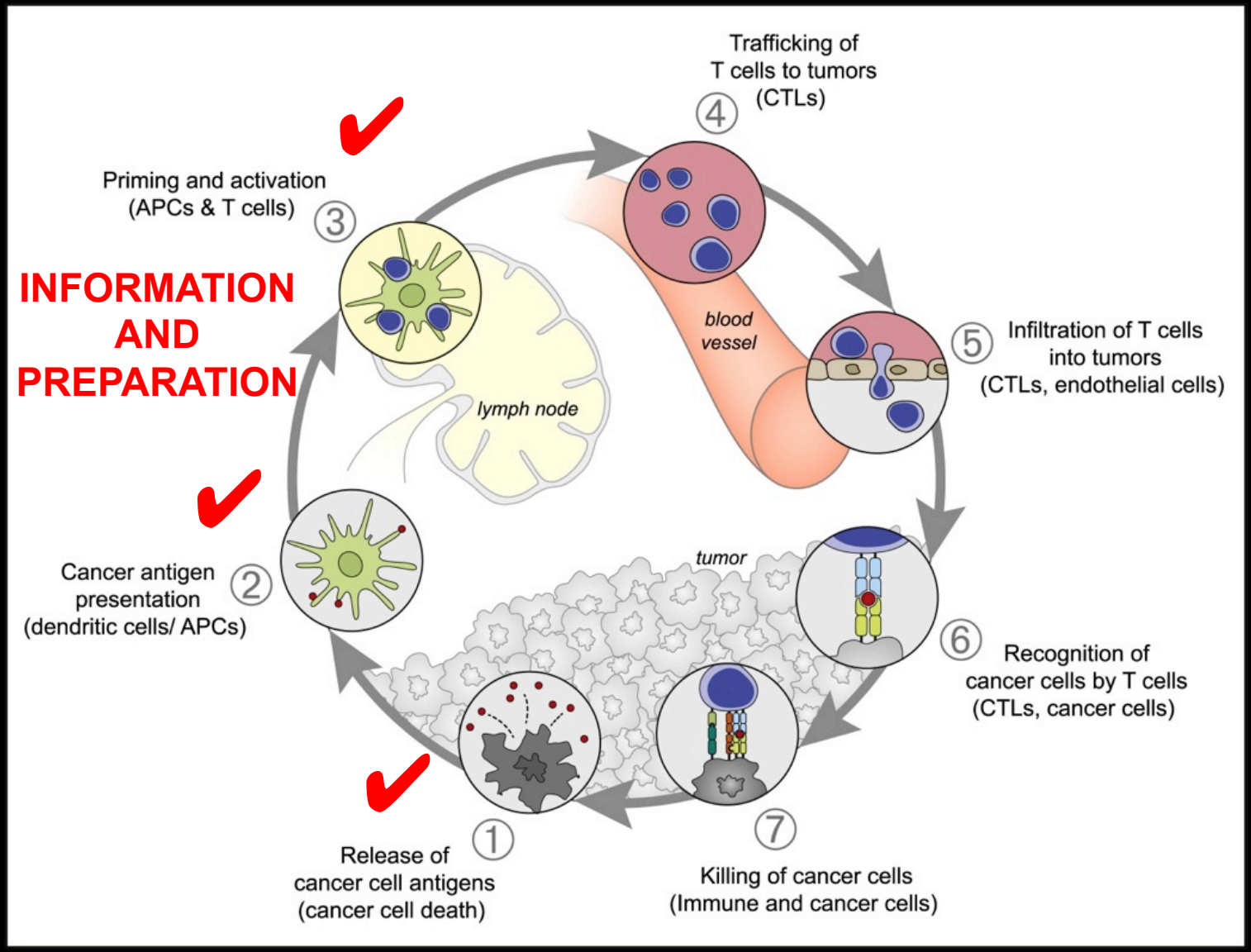


IFN type I is produced by DC infiltrating irradiated tumors (Burnette et al., Cancer Res 2011; 71(7); 2488–96)

STING-dependent cytosolic DNA sensing by in irradiated tumors (Deng et al., Immunity 2014; 41; 843)

The Cancer-Immunity Cycle

(Chen and Mellman, Immunity 2013)



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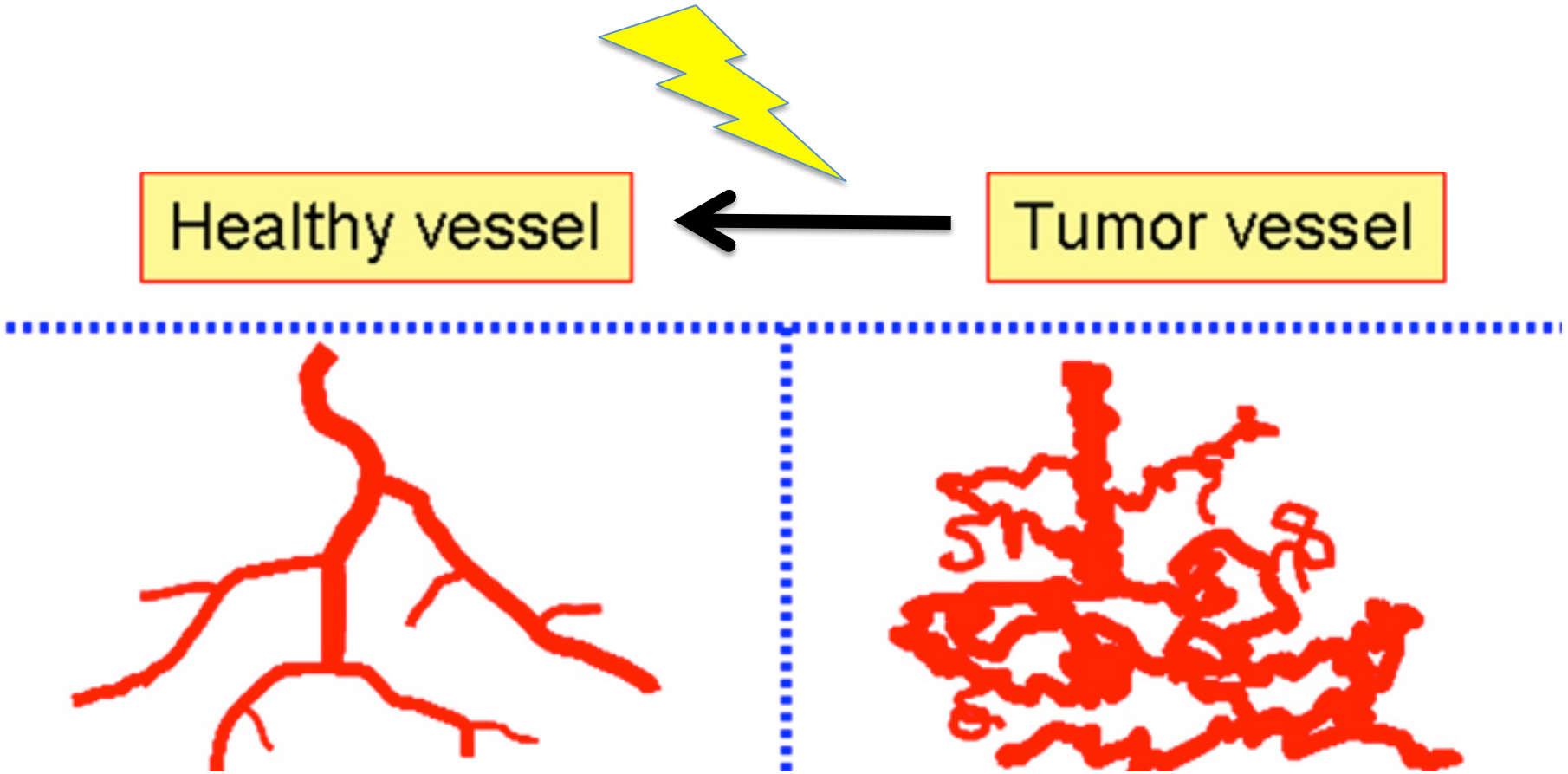
Vascular barrier: radiation-induced vascular normalization



Klug et al., Cancer Cell 2013

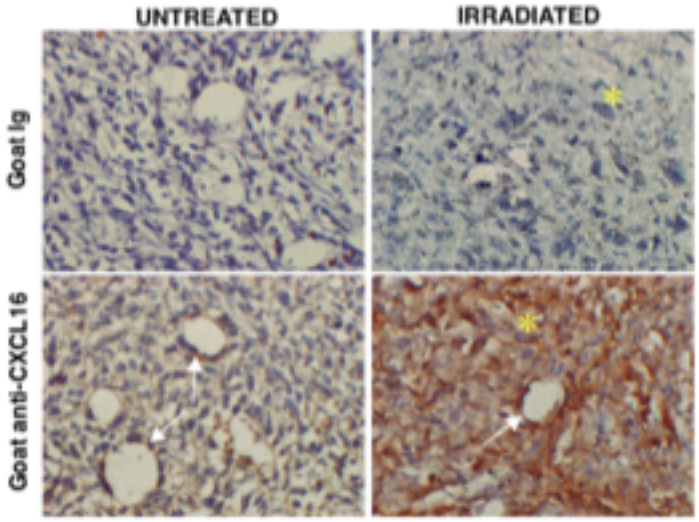
Increased expression by irradiated tumor and stromal cells of:

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

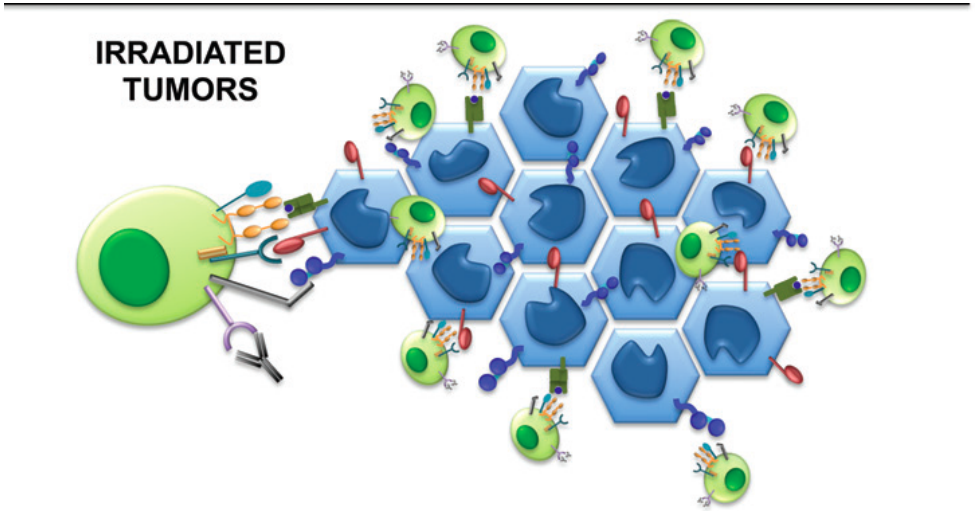
Increased T cell recruitment and infiltration
Increased interactions between effector T cells and tumor cells
Increased tumor cell killing

Formenti & Demaria, J Natl Cancer Inst 2013

Induction of CXCL16 and NKG2D ligands in the tumor by RT is required for tumor rejection by CD8 T cells

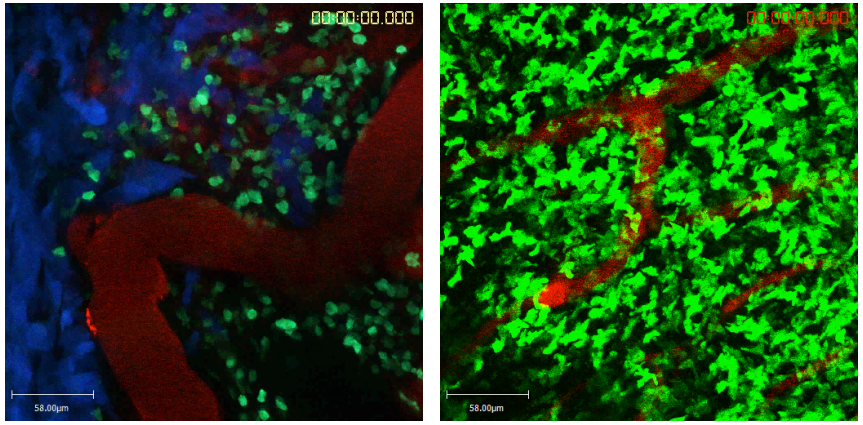


Matsumura *et al., J Immunol 2008*



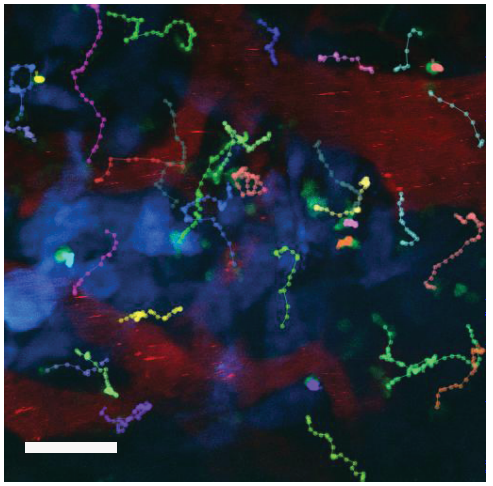
Demaria et al., OncoImmunology 2:3, e23127 2013

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



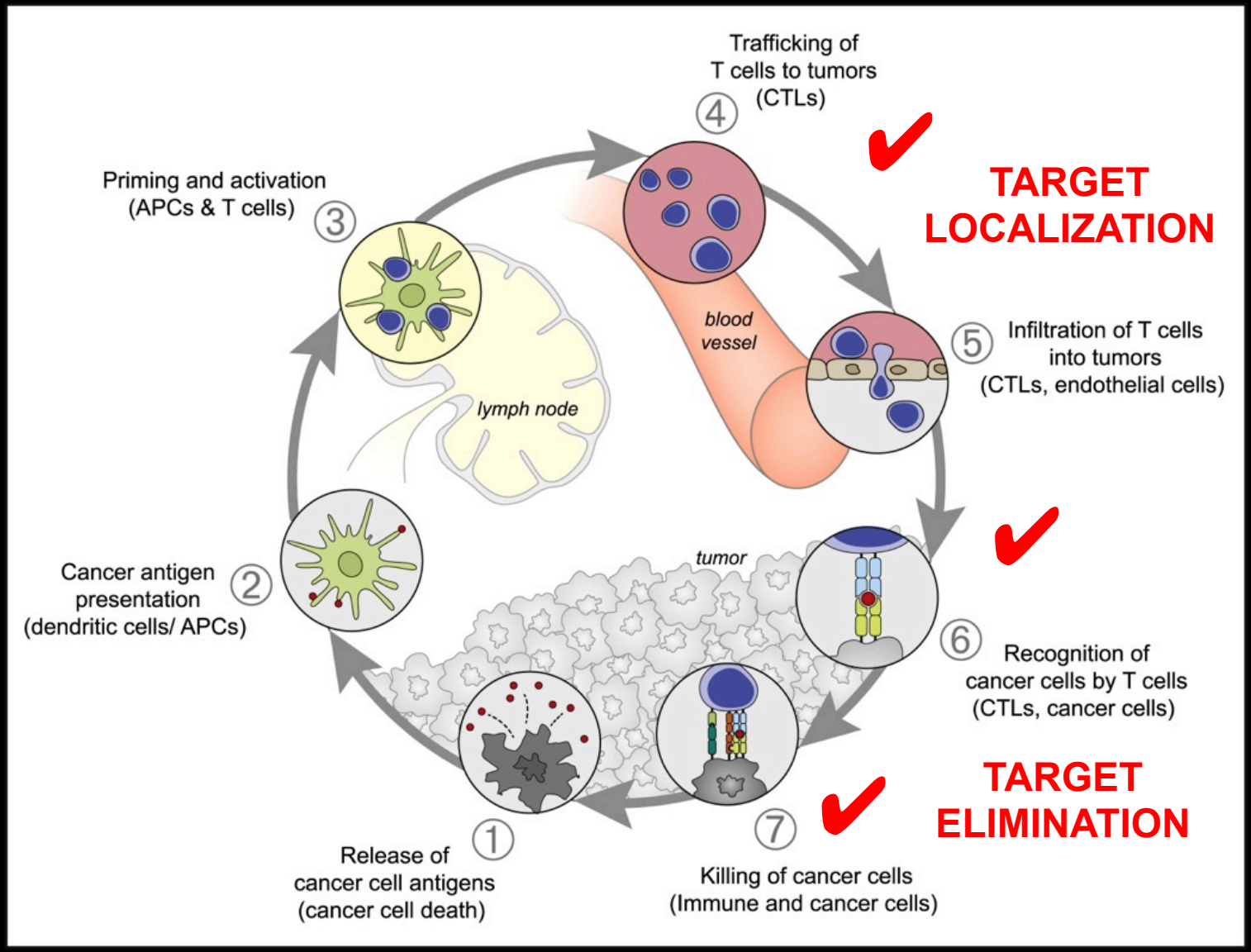
Ruocco et al., *J Clin Invest* 122:3718-30 2012

Blood vessels
T cells
Tumor cells



The Cancer-Immunity Cycle

(Chen and Mellman, Immunity 2013)



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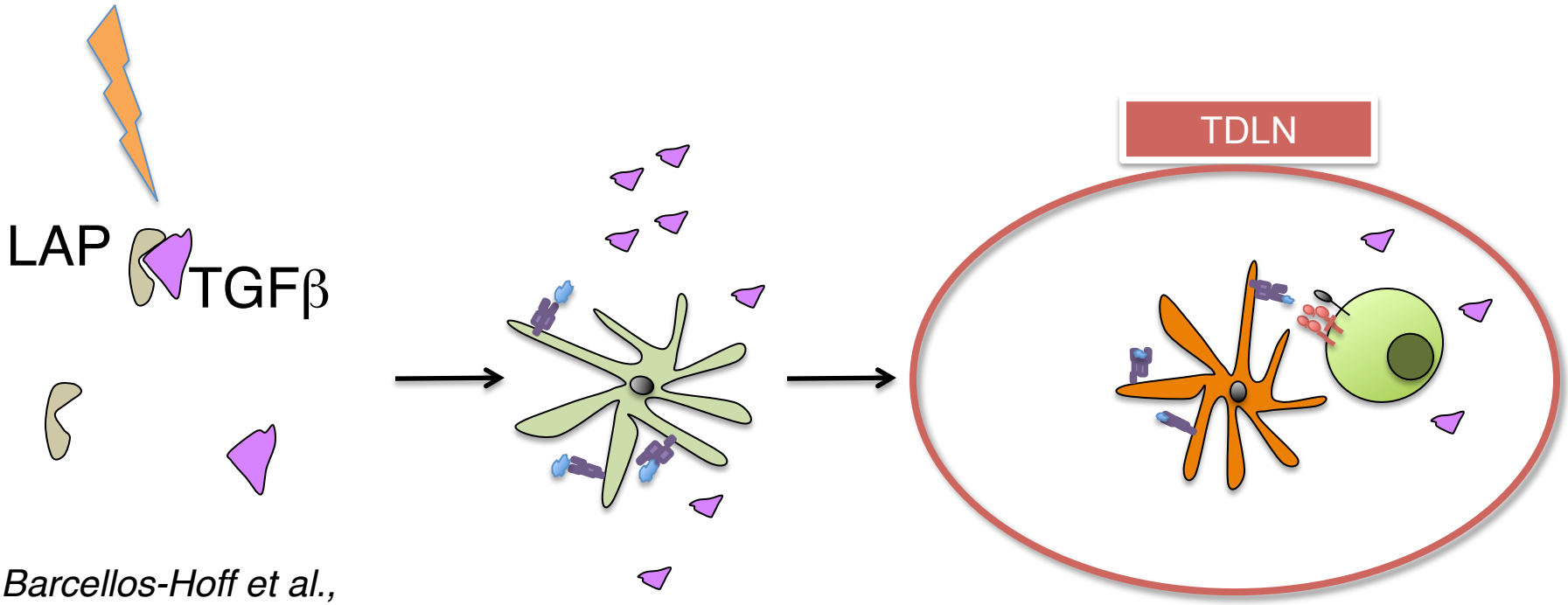
Effects of radiation that can hinder the development of anti-tumor immunity

- Induction of Treg cells (*Schaue et al., Front Oncol 2012*)
- Activation of TGFβ (*Barcellos-Hoff et al., J Clin Invest 1994)*
- Up-regulation of PD-L1 (*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*)

RT-induced negative regulators

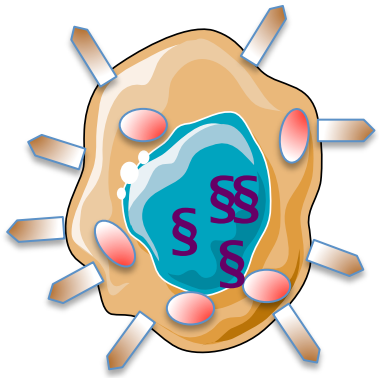


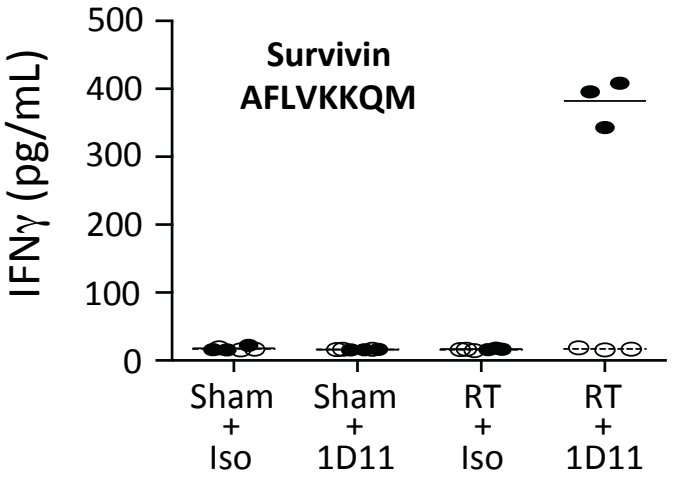
(*Barcellos-Hoff et al., J Clin Invest 1994*)

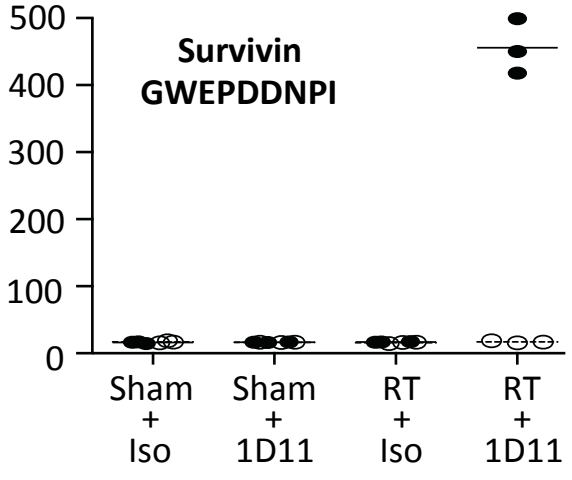
Inhibition of DC activation

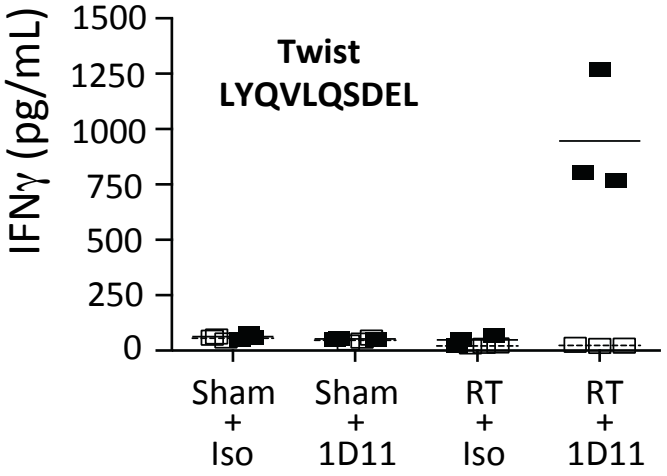
Inhibition of T cell effector function

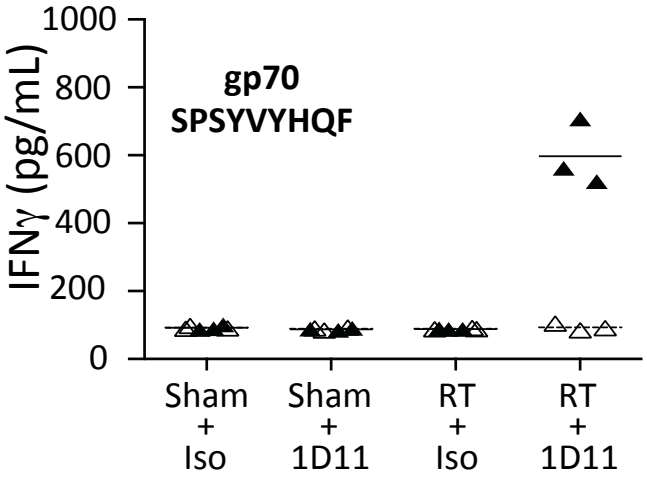
TGFβ neutralization is required for RT-induced tumor-specific T cell priming







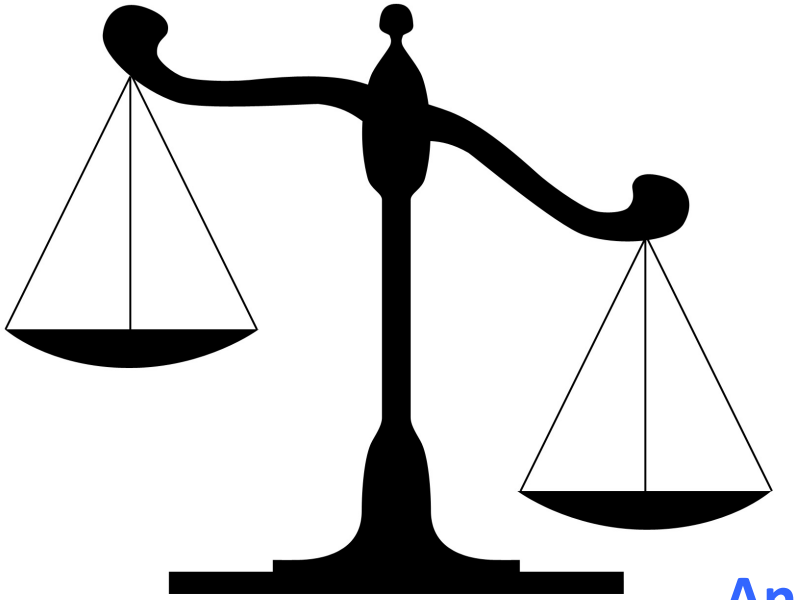




Vanpouille-Box et al., Cancer Res 2015

Acute inflammation

Immunosuppression



Pro-inflammatory
Tumor rejection

Anti-inflammatory
Immunosuppression

Pro-inflammatory
Tumor rejection

Anti-inflammatory
Immunosuppression

? Radiation dose and fractionation

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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

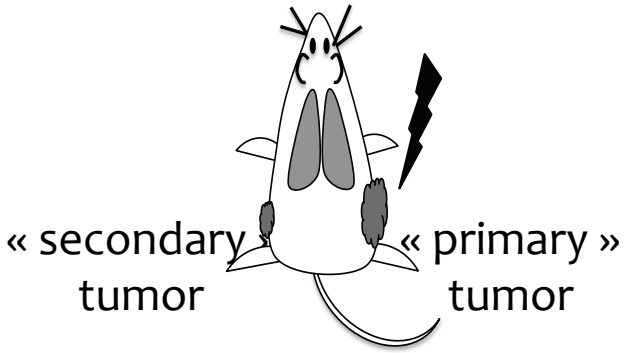
Pre-clinical combinations of RT and immunotherapy

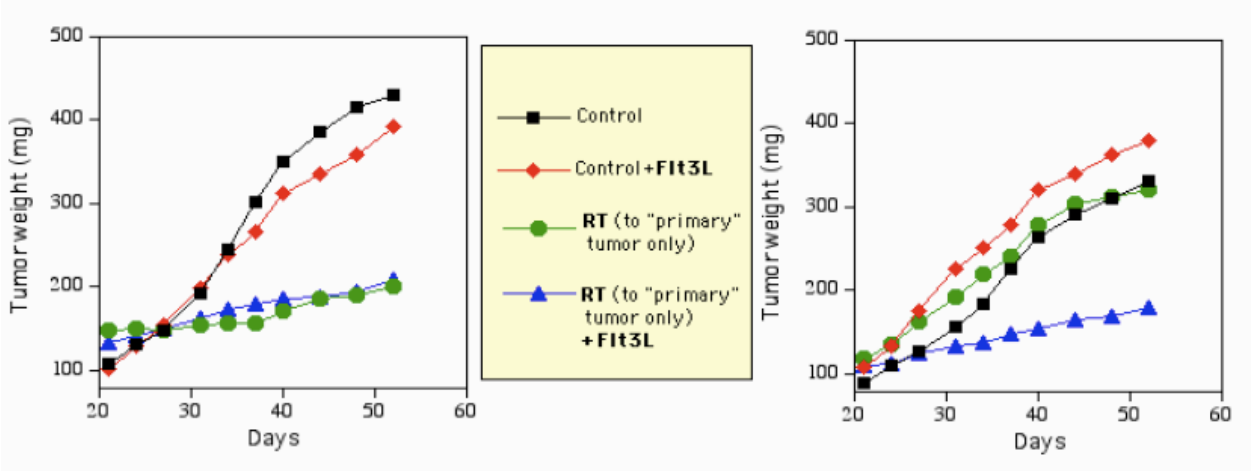
Improving T cell co-stimulation	Anti-CD137 mAb	Shi et al., Anticancer Res 2006 Newcomb et al., Radiat Res 2010
	Anti-OX40 mAb	Gough et al., J. Immunother 2010
Blocking immune checkpoints	Anti-CTLA-4 mAb	Demaria et al., Clin Cancer Res 2005 Dewan et al., Clin Cancer Res 2009
	Anti-PD-1 mAb	Verbrugge et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

Pre-clinical combinations of RT and immunotherapy

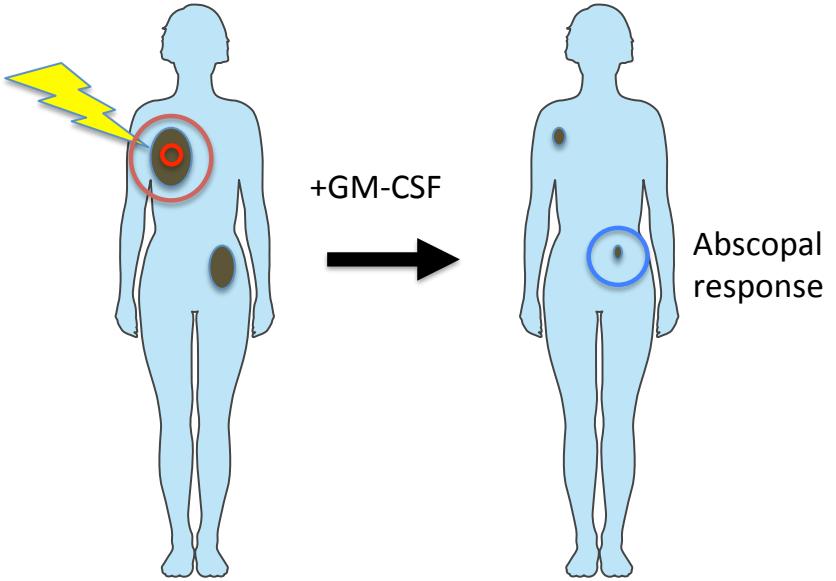
Priming anti-tumor T cells	Vaccinia and avipox CEA vaccines	Chakraborty et al., Cancer Res 2004
	GM-CSF tumor cell vaccine (GVAX)	Newcomb et al., Clin Cancer Res 2006
Adoptive T cell transfer	Effector CD8 T cells	Chakraborty et al., J Immunol 2003 Reits et al., J Exp Med 2006
	CD8 and CD4 T cells	Klug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

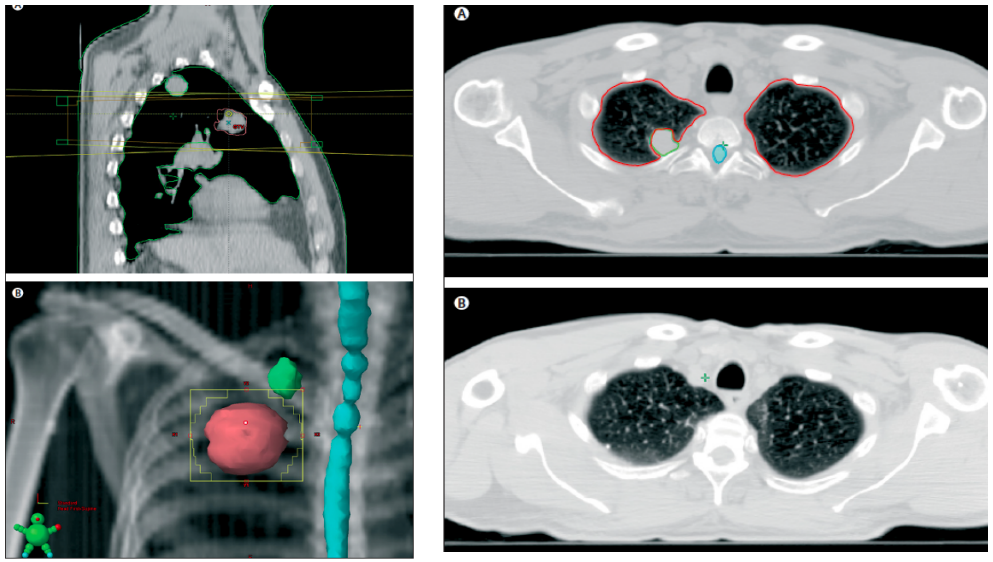
DC growth factors in combination with RT induce abscopal effects in mice and patients





Demaria et al., *Int J Radiation Oncology Biol Phys 2004*





Golden et al., *Lancet Oncology 2015, In press*

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)*

TLR9 agonists

Lymphoma: phase I/II study 2 Gy x 2 plus i.t. synthetic CpG. Abscopal responses in 27% with 1 complete response, 3 partial responses, and 8 patients with stable disease *(Brody et al., JCO 2009)*

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

TLR7 agonists

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

High dose IL-2

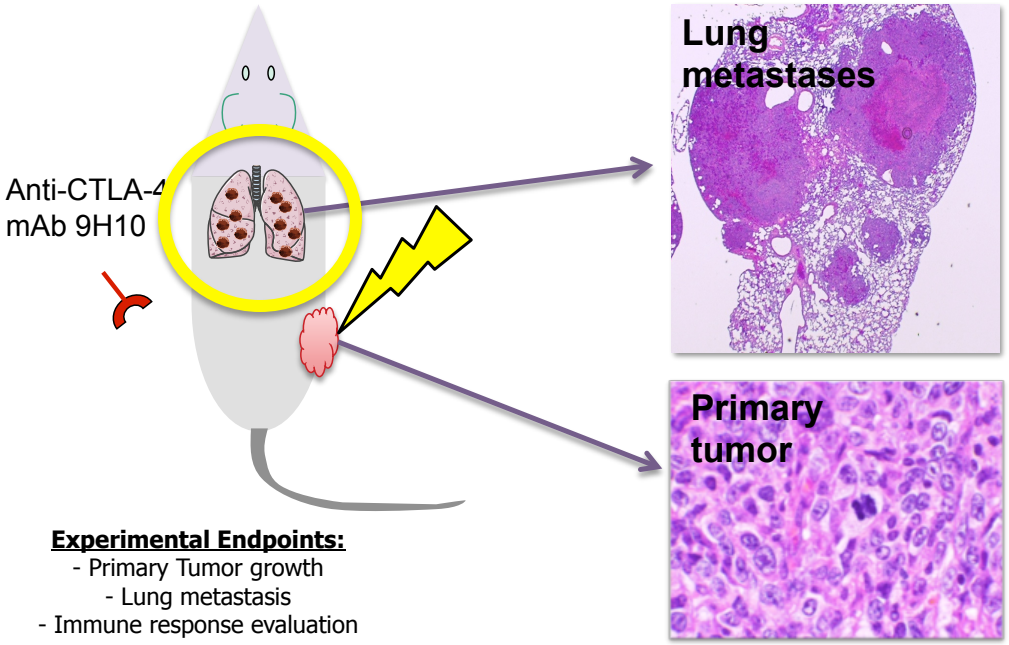
Melanoma and RCC (phase I): SBRT followed by high dose IL-2. Response rate of 66%. Patients who responded showed increase in effector memory T cells (*Seung et al., Sci Transl Med. 2012*).

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).

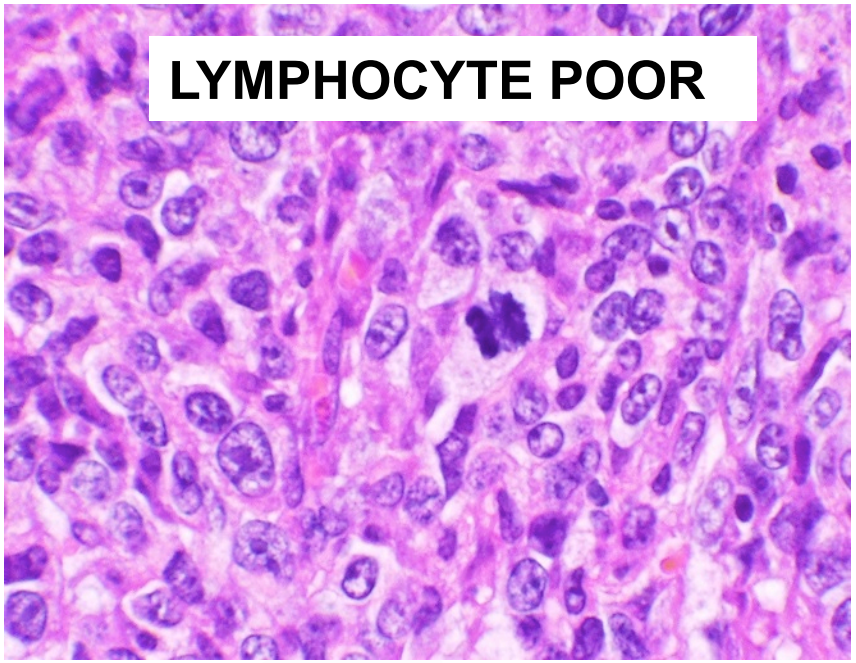
Phase II in metastatic RCC (NCT01896271).

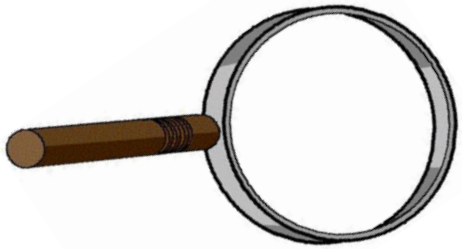
Mouse model of anti-CTLA-4-refractory cancer

4T1 mouse model of metastatic breast cancer

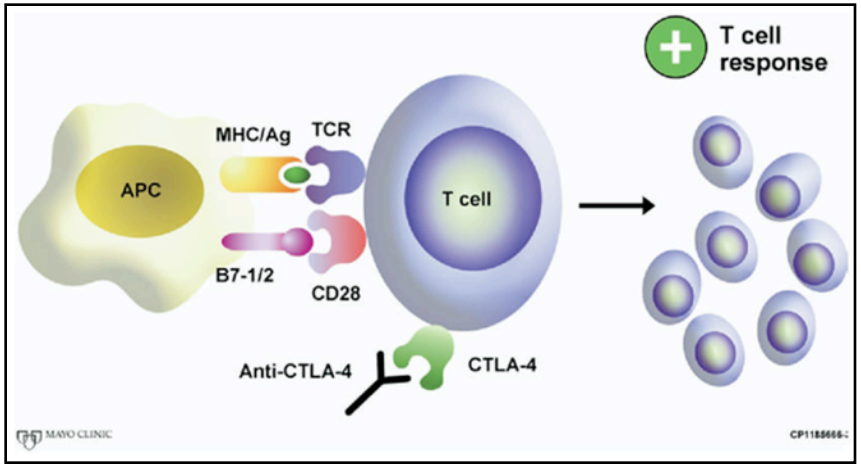


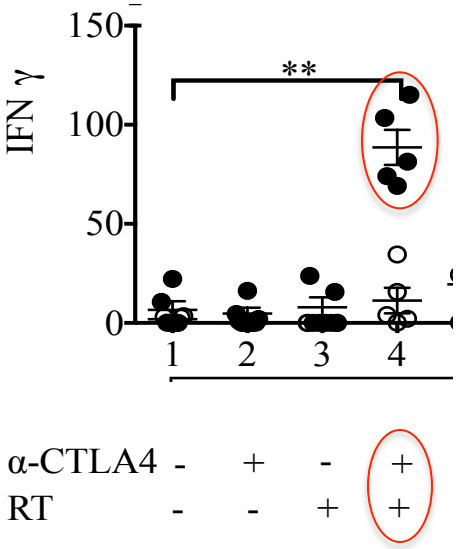
Experimental Endpoints:
- Primary Tumor growth
- Lung metastasis
- Immune response evaluation

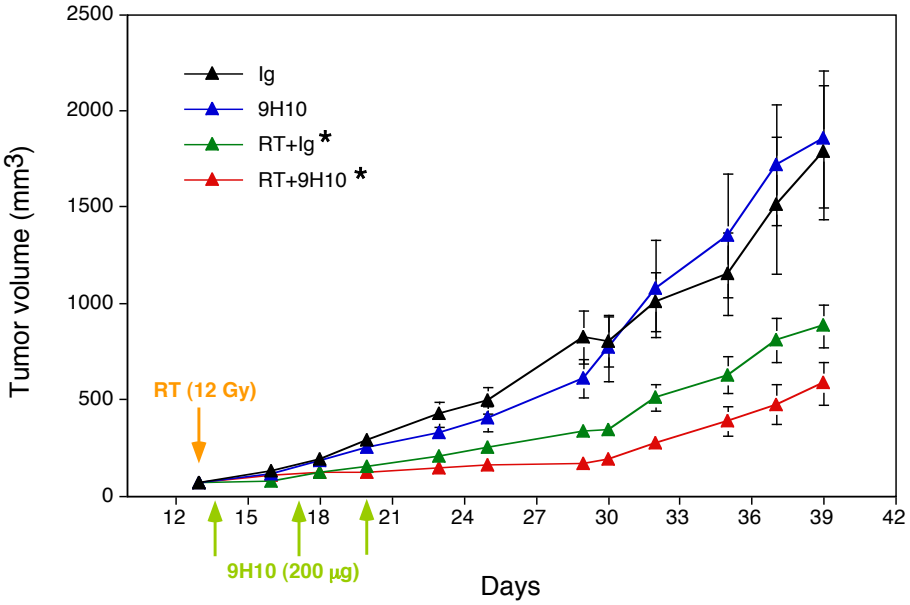


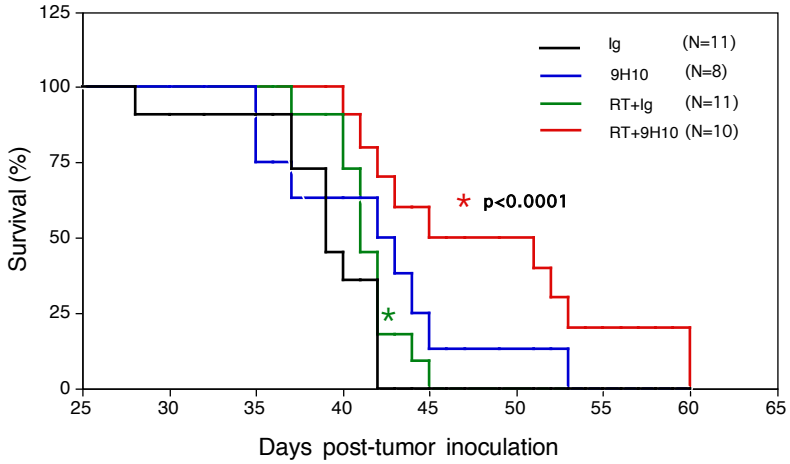


Radiotherapy synergizes with CTLA-4 blockade



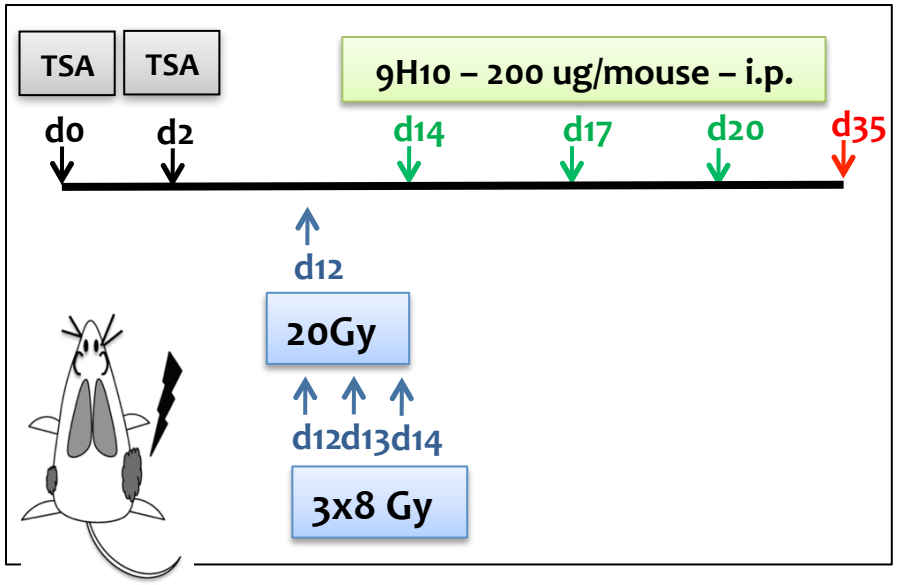


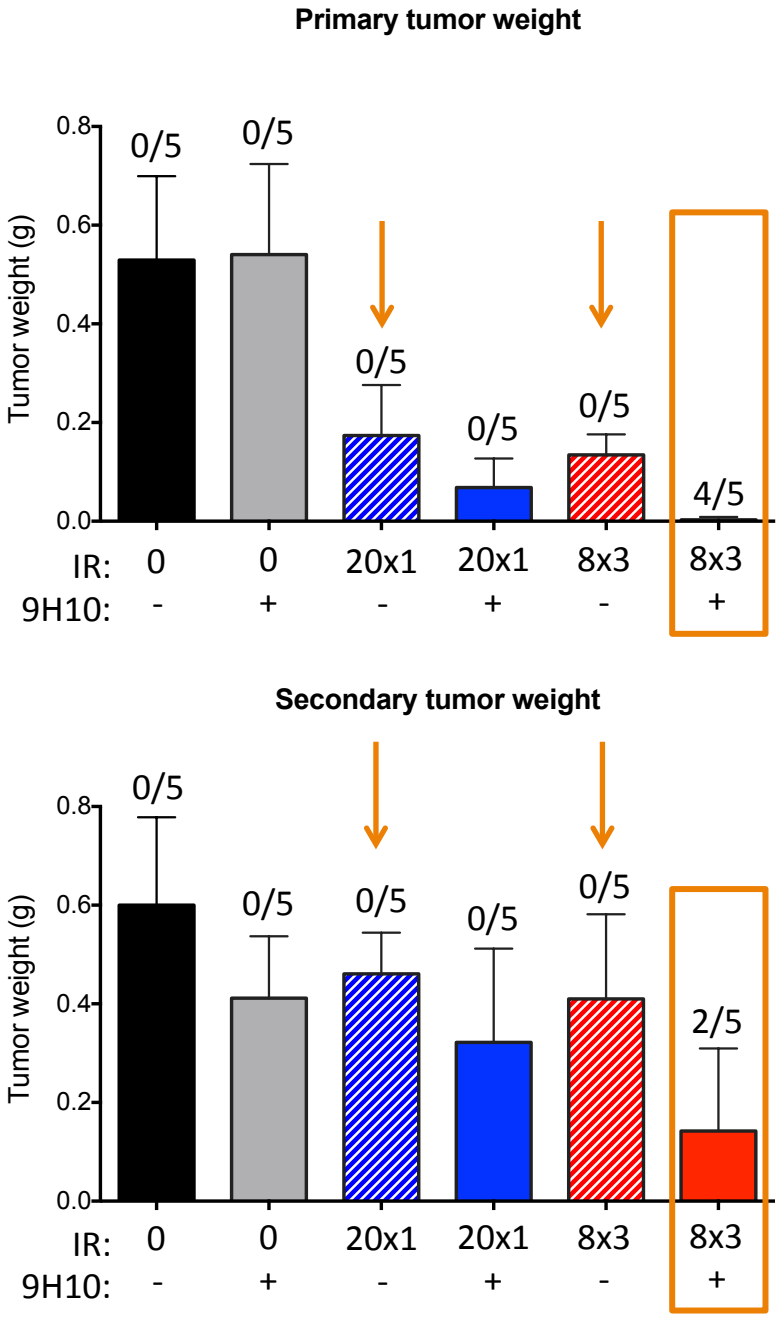




Demaria et al., Clin Cancer Res 2005

Fractionated but not single dose RT elicits an abscopal response in combination with anti-CTLA-4





Dewan et al. ***Clin Cancer Res****. 2009; 15:5379-88.*

Anti-CTLA-4 (Ipilimumab)

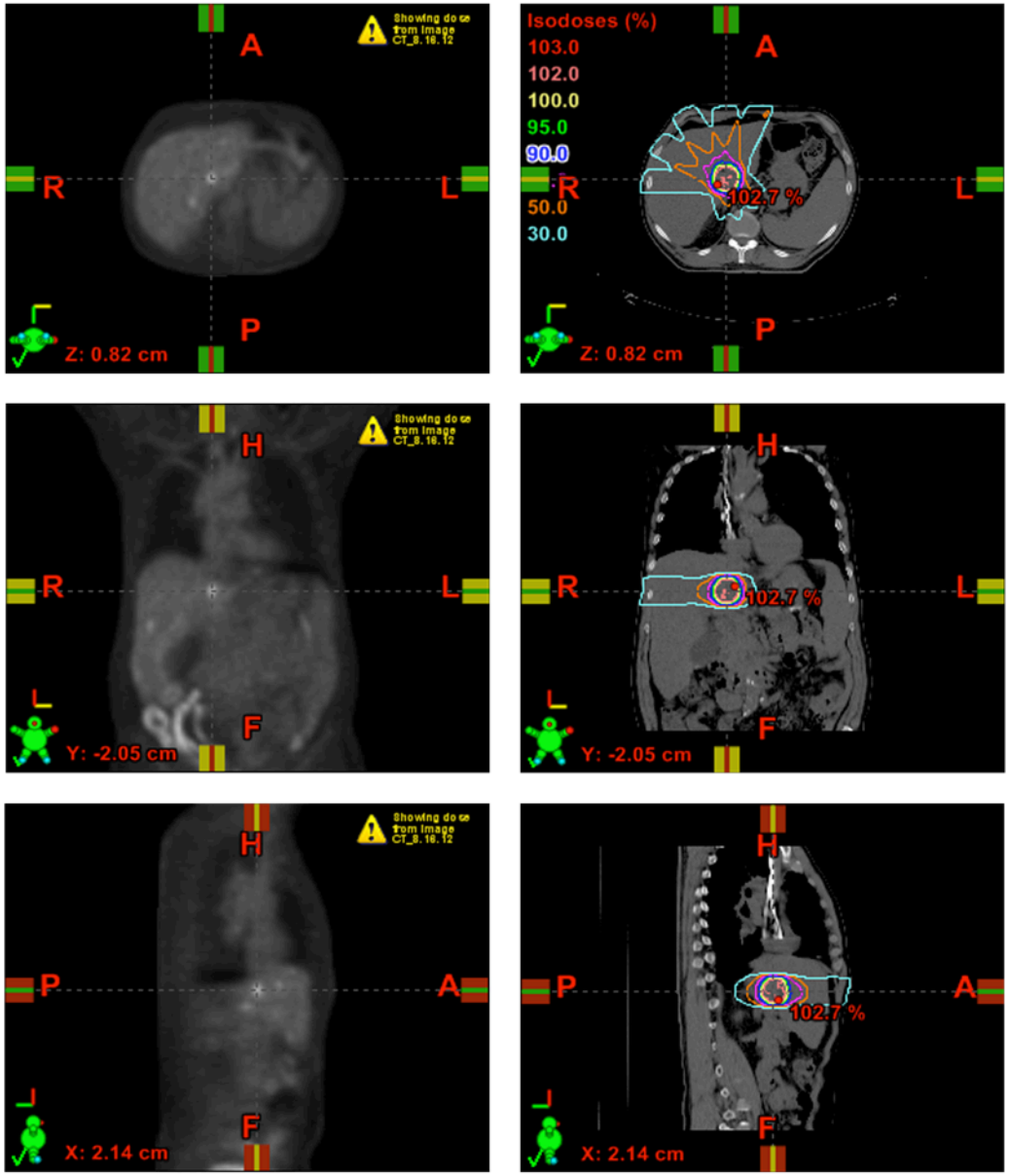
Metastatic melanoma: Case report of a patient with progressive disease on Ipilimumab who showed a dramatic abscopal response after radiotherapy (9.5 Gy x 3) to one paraspinal mass, accompanied by immunological changes (*Postow et al., NEJM 2012*).

Phase III randomized trial in prostate cancer (8Gy x 1 to bone metastasis +/- Ipi) with no significant difference in OS but benefit of Ipi in subgroup with good prognostic features (*Kwon et al., Lancet Oncol 2014*)

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

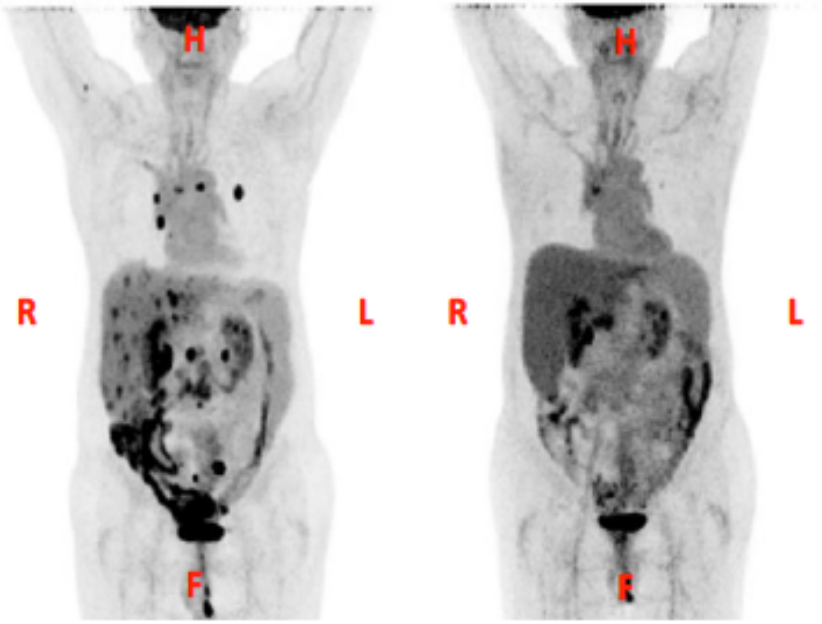
Patient with Metastatic NSCLC

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

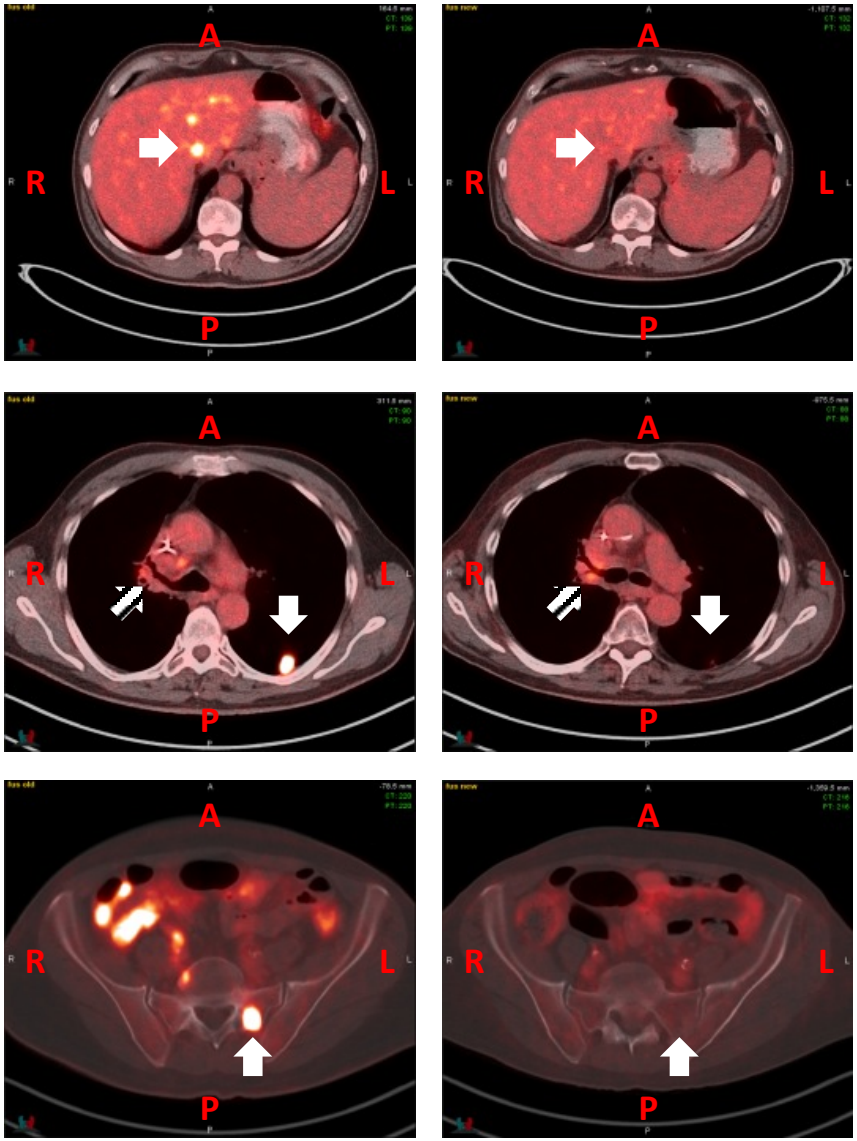


RT to one liver met
6 Gy X 5 (TD 30 GY)
Ipilimumab, 3 mg/Kg, after first RT
q3 weeks, X 4 cycles

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

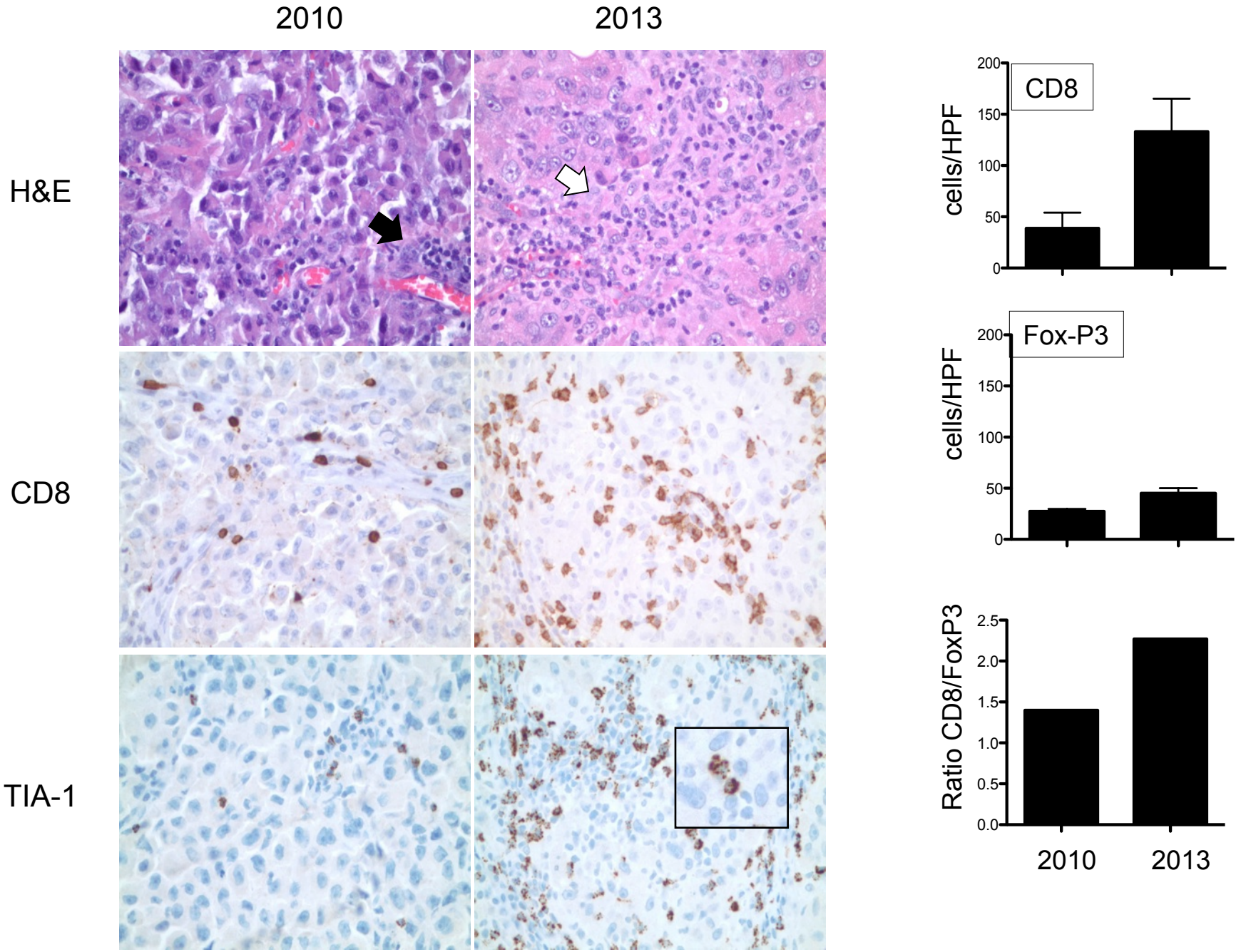


August 2012 PET/CT January 2013 PET/CT

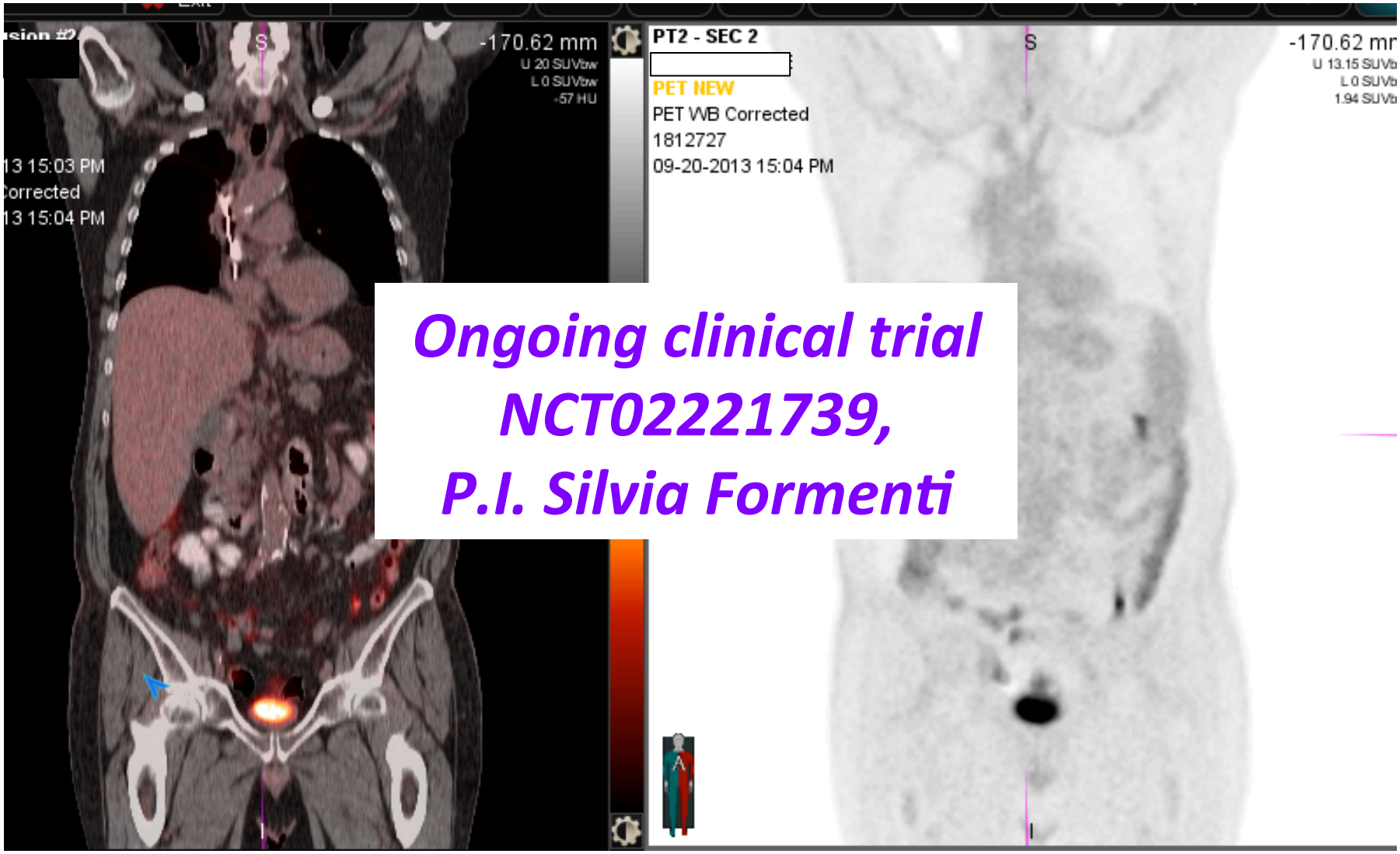


August 2012 PET/CT January 2013 PET/CT

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


2010
2013
H&E
CD8
TIA-1
CD8
cells/HPF
200
150
100
50
0
Fox-P3
cells/HPF
200
150
100
50
0
Ratio CD8/FoxP3
2.5
2.0
1.5
1.0
0.5
0.0
2010
2013

Clinical and radiological CR at one year: currently NED at >2 years



Lessons and Take Home Messages

- RT has positive effects at all steps of anti-tumor immune response
- Radiotherapy is a suitable partner for combination with multiple immunotherapies
- Several trials testing combinations of RT and immunotherapy are ongoing

Open Questions

- Dose and fractionation matter
- Tumor type/histology
- Sequencing of RT and immunotherapy
- Location of metastasis irradiated (e.g., visceral vs bone)