Immune system role for traditional cancer therapies

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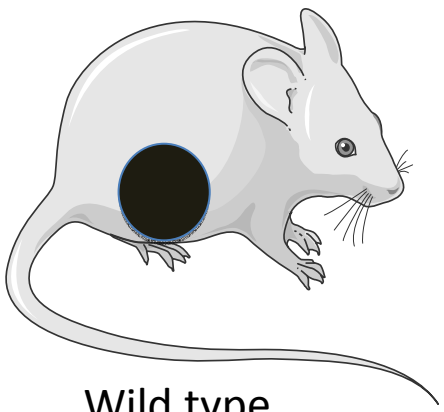
The following relationships exist related to this presentation:

Honoraria/Advisory: Bristol-Myer Squibb

Outline

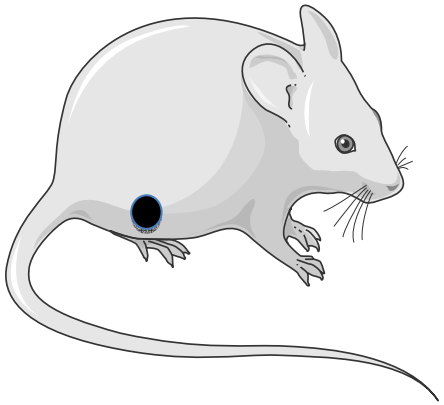
- Role of the immune system in the response to:
  - Chemotherapy
  - Radiotherapy
  - Targeted therapies
- Effects of cytocidal treatments on tumor-host interactions:
  - Immunogenic Cell Death
  - Direct effects on tumor cell phenotype/microenvironment
  - Off target effects on immune cells
- Combination of immunotherapy with standard treatments
  - Pre-clinical data
  - Clinical testing
  - Targeting Cancer Stem cells

Immunocompetence of the host affects the response to cytocidal treatments



Wild type

Antracyclines
Oxaliplatin
Radiotherapy
Imatinib
Anti-Her2 antibodies



T cell-deficient/depleted

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

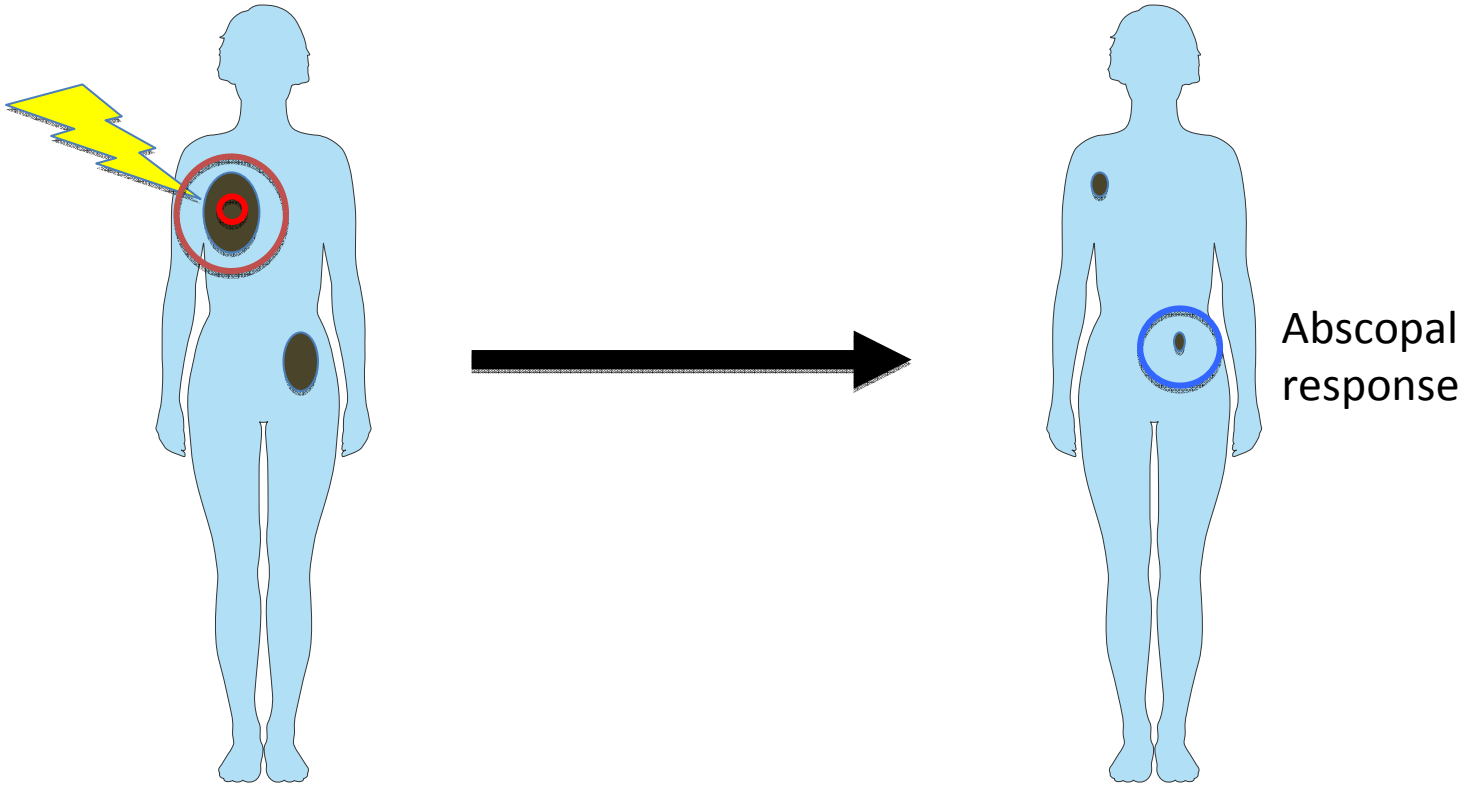
Nesslinger et al., Clin Cancer Res 2007
Tumor-specific antibodies in 14% of prostate cancer patients treated with EBRT and in 25% receiving brachytherapy

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

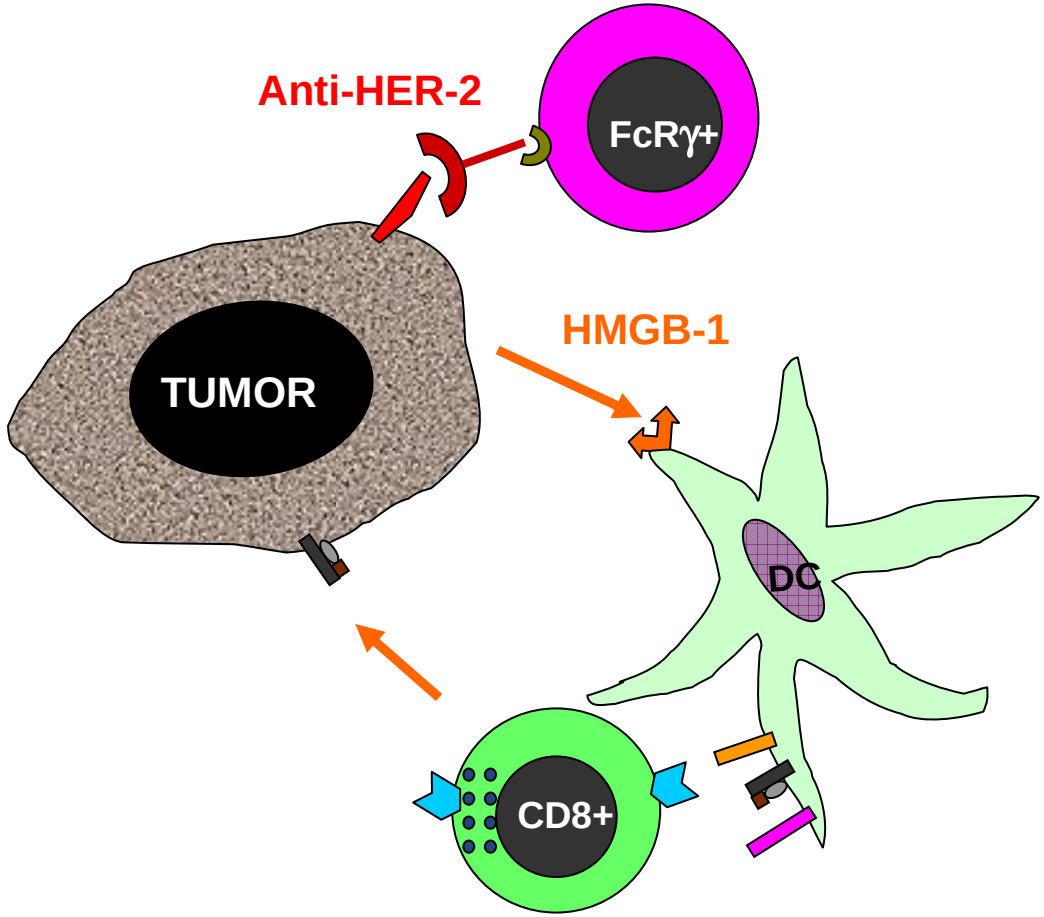
Latin *ab* (position away from) and *scopus* (mark or target)



Role of T cells in response to targeted therapy

Anti-HER2/neu antibody therapy causes the release of danger signals such as HMGB-1, triggers MyD88-dependent activation of DC, and generates CD8+ anti-tumor T cells.

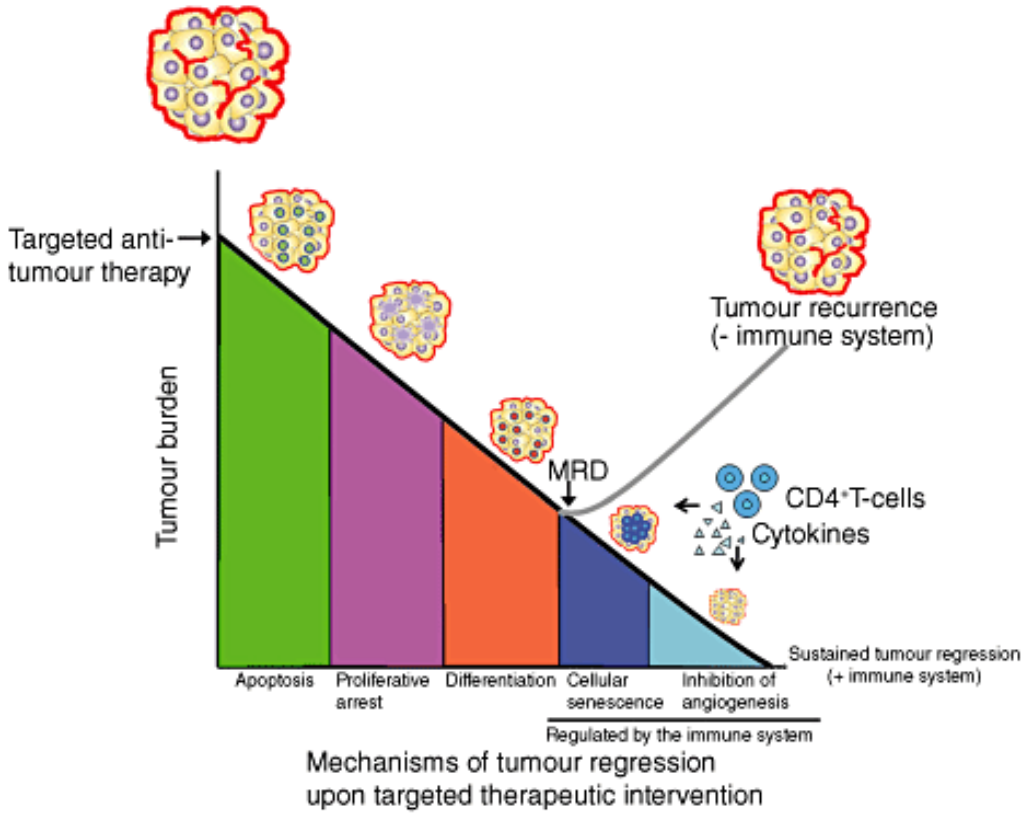
Park et al., Cancer Cell, 18 (2010), pp. 160–170



Role of T cells in oncogene addiction

CD4+ T cells are required for sustained tumor regression upon inactivation of the MYC or BCR-ABL oncogenes in mouse models of T cell acute lymphoblastic lymphoma and pro-B cell leukemia, respectively

Rakhra et al., Cancer Cell. 2010 Nov 16;18(5):485-98.



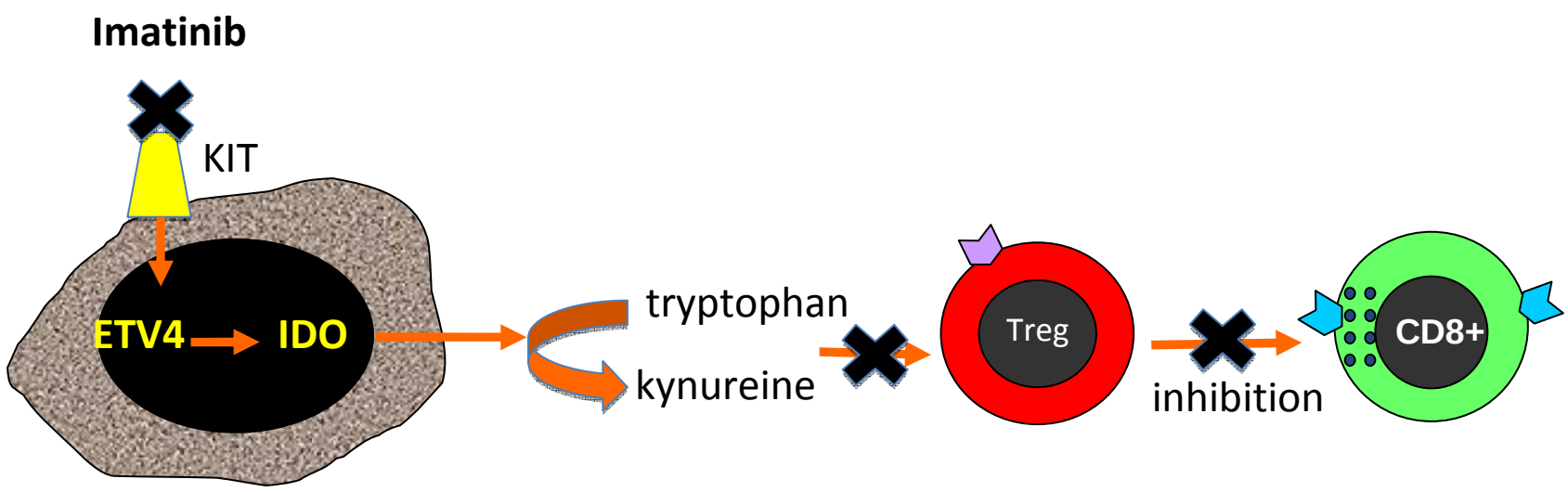
Mechanisms of tumour regression upon targeted therapeutic intervention

Clinical & Experimental Immunology
Volume 167, Issue 2, pages 188-194, 11 JAN 2012 DOI: 10.1111/j.1365-2249.2011.04514.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2249.2011.04514.x/full#f2

Role of T cells in oncogene addiction

In a mouse model of spontaneous GIST Imatinib therapy activated CD8+ T cells and induced regulatory T cell (Treg) apoptosis within the tumor by reducing tumor-cell expression of the immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO). In human GIST specimens the T cell profile correlated with imatinib sensitivity and IDO expression.

Balachandran et al., Nature Medicine, 17 (2011), pp. 1094-1101



- Effects of cytocidal treatments on the tumor-host interactions:

- Immunogenic Cell Death

Antracyclines, oxaliplatin, cyclophosphamide, radiotherapy

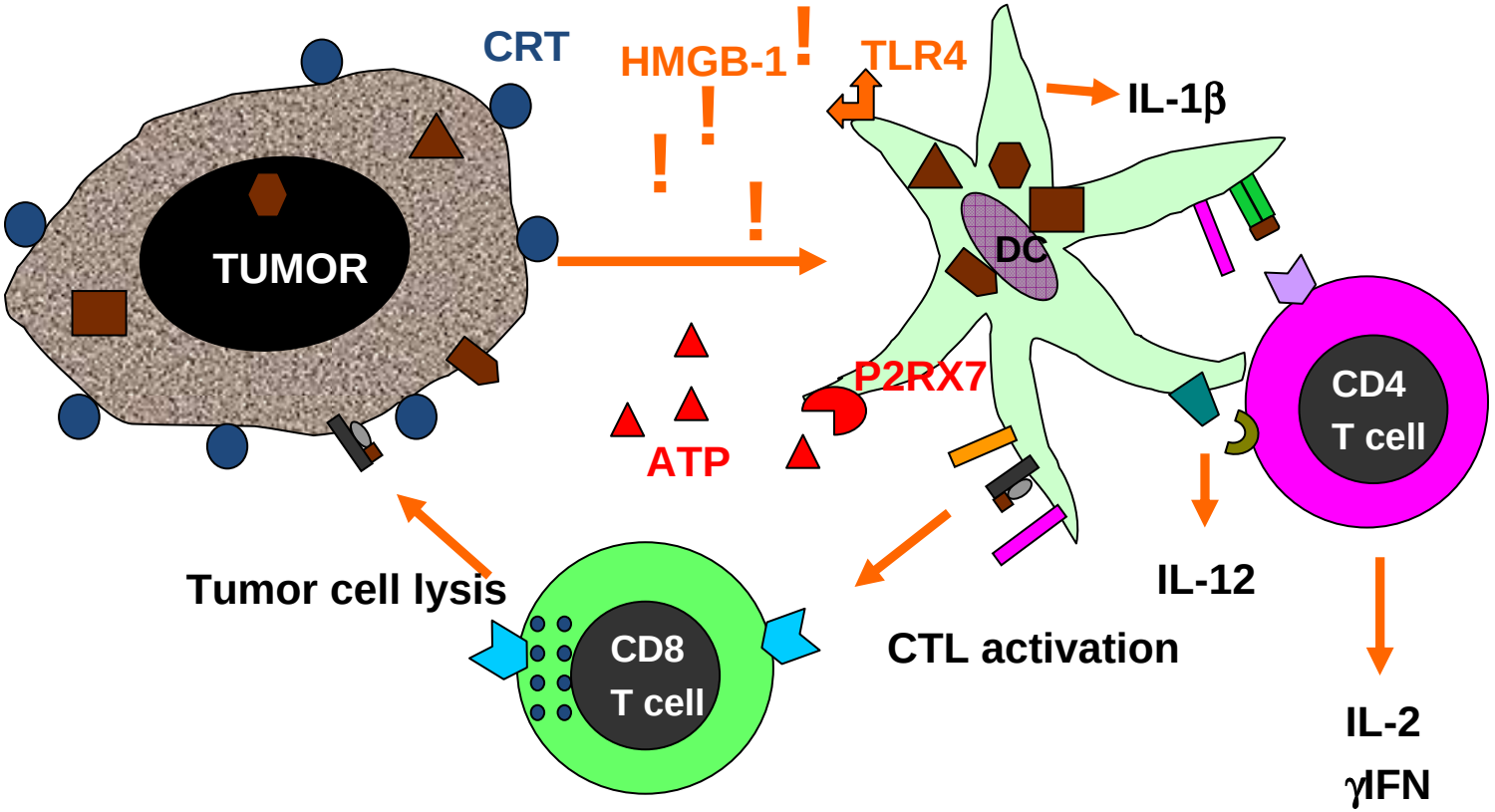
- Direct effects on tumor cell phenotype/microenvironment

Radiotherapy, Platinum-drugs, Paclitaxel, Cyclophosphamide

- Off target effects on immune cells

Many conventional and targeted therapeutics

Immunogenic cell death



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)

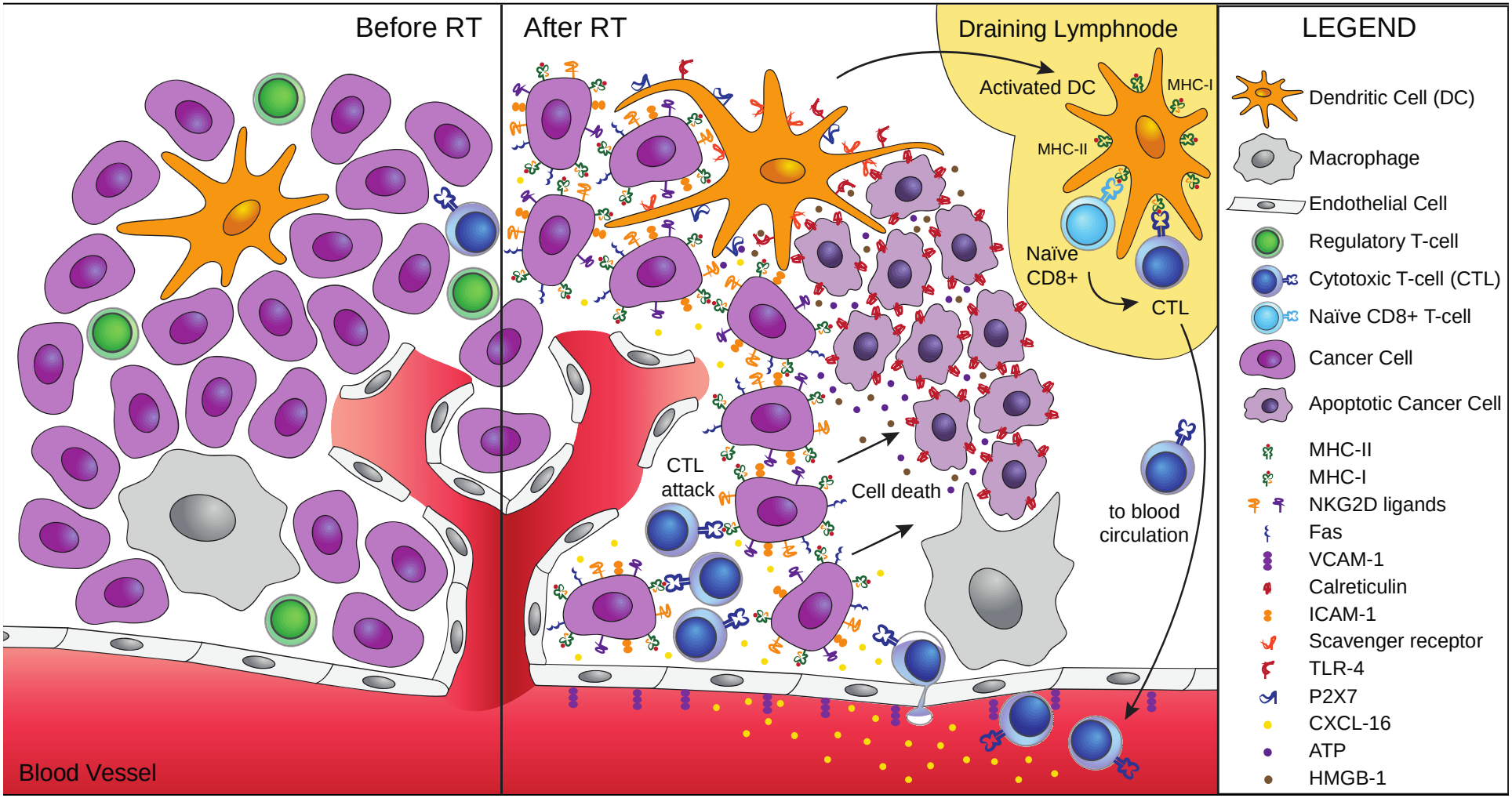
ATP released by dying cells binds to P2RX7 purigergic receptor leading to inflammasome activation and IL-1β production (Ghiringhelli et al., Nat Med 2009, 15:1170)

Evidence for a possible role of treatment-induced ICD in patients

Breast cancer patients with a Tlr4 Asp299Gly polymorphism that impairs binding to HMGB-1 showed reduced time to progression after treatment with anthracyclines and radiotherapy (log-rank test, $P = 0.03$).
(Apetoh et al., Nat Med 2007, 13:1050)

A loss-function polymorphism that affects $P2RX_7$ (Glu496Ala, rs3751143) had a significant negative prognostic impact on metastatic disease-free survival (log-rank test; $P = 0.02$) in breast cancer patients treated with anthracyclines
(Ghiringhelli et al., Nat Med 2009, 15:1170)

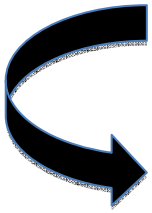
Effects of radiotherapy on tumor cell phenotype and tumor microenvironment



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

Increased expression by irradiated tumor cells of:

MHC class I molecules
Stress-induced ligand (NKG2D ligands)
ICAM-1
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)



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

Immunosuppressive factors are also induced by radiation, e.g., TGFβ
Outcome will depend on the pre-existing tumor microenvironment and balance of pro-inflammatory and immunosuppressive factors induced

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

Modulation of tumor cell phenotype by chemotherapy:

Carboplatin, Cisplatin, Oxaliplatin: inhibit PDL-2 expression
Gemcitabine, Oxaliplatin, Cyclophosphamide: increase MHC-I expression
Cisplatin, Doxorubicin, Paclitaxel: increase permeability to granzyme B

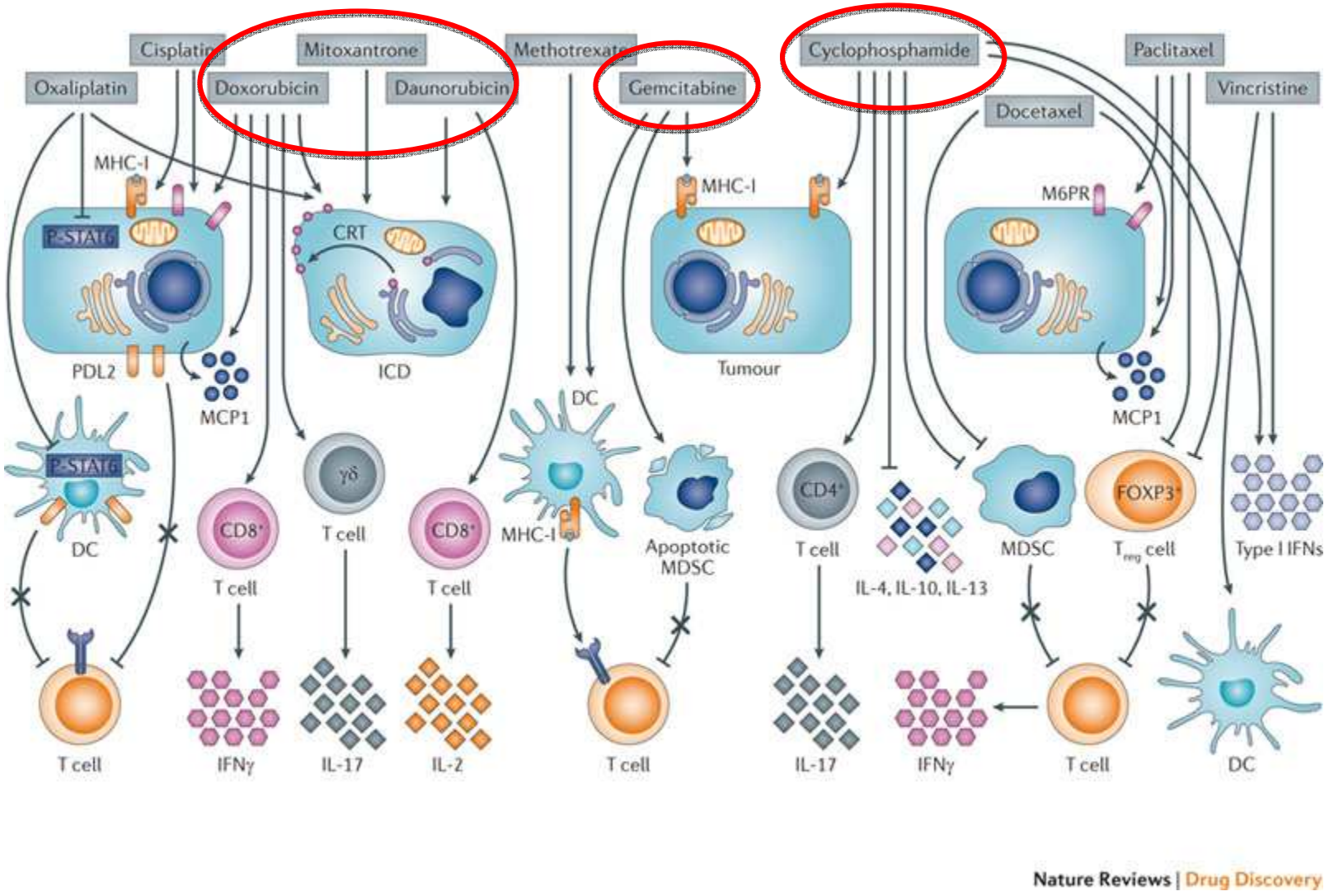
Improved recognition and killing by effector T cells

Immunosuppressive factors are also induced (e.g., MCP-1 induced by Doxorubicin, Docetaxel, Paclitaxel drives immunosuppressive environment)

Dose and schedule of administration determine the immunosuppressive versus pro-immunogenic effects (e.g., Cyclophosphamide at high dose is immunosuppressive versus metronomic administration promotes anti-tumor immunity)

Galluzzi et al., Nat Rev Drug Discov. 2012 Feb 3;11(3):215-33.

Effects of conventional chemotherapy drugs on immune cells



Galluzzi et al., Nat Rev Drug Discov. 2012 Feb 3;11(3):215-33.

Modulation of tumor cell phenotype by targeted agents:

Erlotinib, Cetuximab: increase MHC-I expression

Imatinib: decreases IDO

Modulation of immune cell function by targeted agents:

Imatinib: inhibit STA3 and STA5 signaling, decreasing Treg frequency and function, promotes DC-mediated NK cell activation

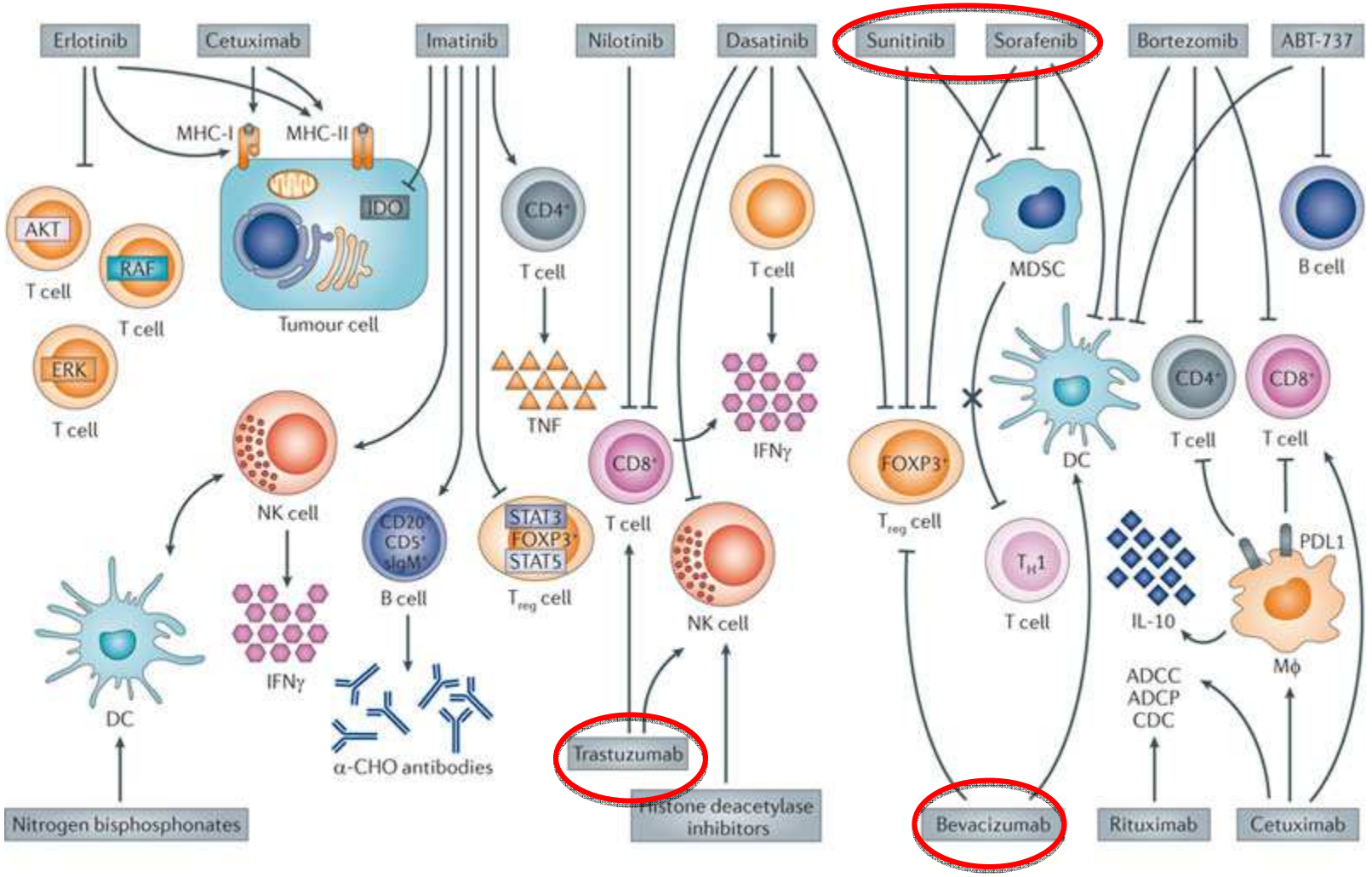
Erlotinib, Dasatininb: inhibit T cell functions

Sunitinin and Sorafenib: inhibit Treg and MDSC

Cetuximab: NK-mediated ADCC, stimulation of CD8 T cells by DC

Galluzzi et al., Nat Rev Drug Discov. 2012 Feb 3;11(3):215-33.

Effects of targeted therapeutics on immune cells



Galluzzi et al., Nat Rev Drug Discov. 2012 Feb 3;11(3):215-33.

- Combination of immunotherapy with standard treatments

- Radiotherapy
- Chemotherapy
- Targeted treatments
- An opportunity to eliminate Cancer Stem Cells

Table 1. Combinations of immunotherapy and local radiotherapy tested in pre-clinical tumor models*

Immunotherapy	Schedule of administration	Main radiation effect	Main mechanism of tumor inhibition	Reference(s)
Flt3-Ligand	Post-radiation	Release of tumor antigens	Induction of anti-tumor T cells	Chakravarty et al, Cancer Res 1999 Demaria et al. IJROBP 2004
Exogenous DC s.c. or i.v.	Post-radiation	Recruitment of DC and release of tumor antigens	Induction of anti-tumor T cells	Nikitina et al., Int J Cancer 2001
Exogenous DC i.t.	Post-radiation	Release of tumor antigens	Induction of anti-tumor T cells	Teitz-Tennenbaum et al, Cancer Res 2003 Kim et al., Int J Cancer 2004
CpG s.c. peri-tumorally and i.t.	Pre- and post-radiation	Release of tumor antigens	Induction of anti-tumor T cells	Milas et al., Cancer Res 2004 Mason et al., Clin Cancer Res 2005
Synthetic modified TLR-9 agonist, s.c.	Concomitant with and post-radiation	Release of tumor antigens	Recruitment and activation of NKDC	Zhang et al., PlosOne 2012
ECI301 (CCL3 variant) i.v.	Post-radiation	Release of tumor antigens	Induction of anti-tumor T cells	Shiraishi et al., ClinCancer Res 2008
Anti-CTLA-4 antibody, i.p.	Post-radiation	Release of tumor antigens	Induction of anti-tumor T cells.	Demaria et al., Clin Cancer Res 2005 Dewan et al., Clin Cancer Res 2009
		Induction of CXCL16 release	Improved recruitment of $CCXR6^{+}$ effector CD8 T cells	Matsumura et al., J Immunol 2008
		Induction of NKG2D ligand expression on tumor cells	Stable interaction between $NKG2D^{+}$ effector CD8 T and tumor cells	Ruocco et al., J Clin Invest 2012

Anti-CD137 antibody, i.v or i.p.	Post-radiation	Release of tumor antigens and/or MHC class I induction on tumor cells	Induction of anti-tumor T cells.	Shi et al., Anticancer Res 2006 Newcopmb et al., Radiat Res 2010
Anti-CD137 and anti-PD-1 antibodies, i.p.	Concomitant with and post-radiation	Release of tumor antigens	Induction of anti-tumor T cells	Verbrugge et al., Cancer Res 2012
Adoptive T cell transfer	Post-radiation	Induction of Fas/CD95 on tumor cells Upregulation of MHC class I on tumor cells	Improved killing of tumor cells by adoptively transferred effector CD8 T cells	Chakraborty et al., J Immunol 2003 Reits et al., J Exp Med 2006
Vaccinia and avipox recombinants expressing CEA and T-cell costimulatory molecules	Pre- and post-radiation	Induction of Fas/CD95 on tumor cells	Improved killing of tumor cells by vaccine-induced T cells, induction of antigenic cascade	Chakraborty et al., Cancer Res 2004
Autologous tumor cell vaccine expressing GM-CSF	Post-radiation	Upregulation of MHC class I on tumor cells	Improved killing of tumor cells by vaccine-induced T cells	Newcomb et al., Clin Cancer Res 2006

* CEA = carcinoembryonic antigen; CpG = C-G enriched, synthetic oligodeoxynucleotide ; CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; DC = dendritic cells; GM-CSF = granulocyte-macrophage colony-stimulating factor; i.p. = intraperitoneally; i.t. = intratumorally; i.v. = intravenously; MHC = major histocompatibility complex; NKDC = natural killer dendritic cells; PD-1 = programmed death-1; s.c. = subcutaneously; TLR = Toll-like receptor.

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

TLR9 agonists

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.

High dose IL-2

Melanoma and renal cell carcinoma (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 and high-dose IL-2 versus IL-2 alone in patients with metastatic melanoma is ongoing.

Clinical Translation

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 8 trials testing combination of radiotherapy and Ipilimumab are underway.

Combination of immunotherapy with conventional chemotherapy

Vaccination (whole cell vaccine secreting GM-CSF):
Cyclophosphamide, doxorubicin and paclitaxel improved breast cancer vaccine response in Her-2/neu tolerized mice *(Machielis et al., Cancer Res 2001*).
Drug dose and sequencing critical.

Cyclophosphamide at low dose improved vaccine response in an autochthonous prostate cancer model (*Wada et al., Cancer Res 2009*).

Translation: allogeneic GM-CSF secreting breast cancer vaccine given to metastatic breast cancer patients. HER2-specific antibody responses were enhanced by 200 mg/m^2 CY and 35 mg/m^2 DOX, but higher CY doses suppressed immunity. (Emens et al., *J Clin Oncol 2009*)

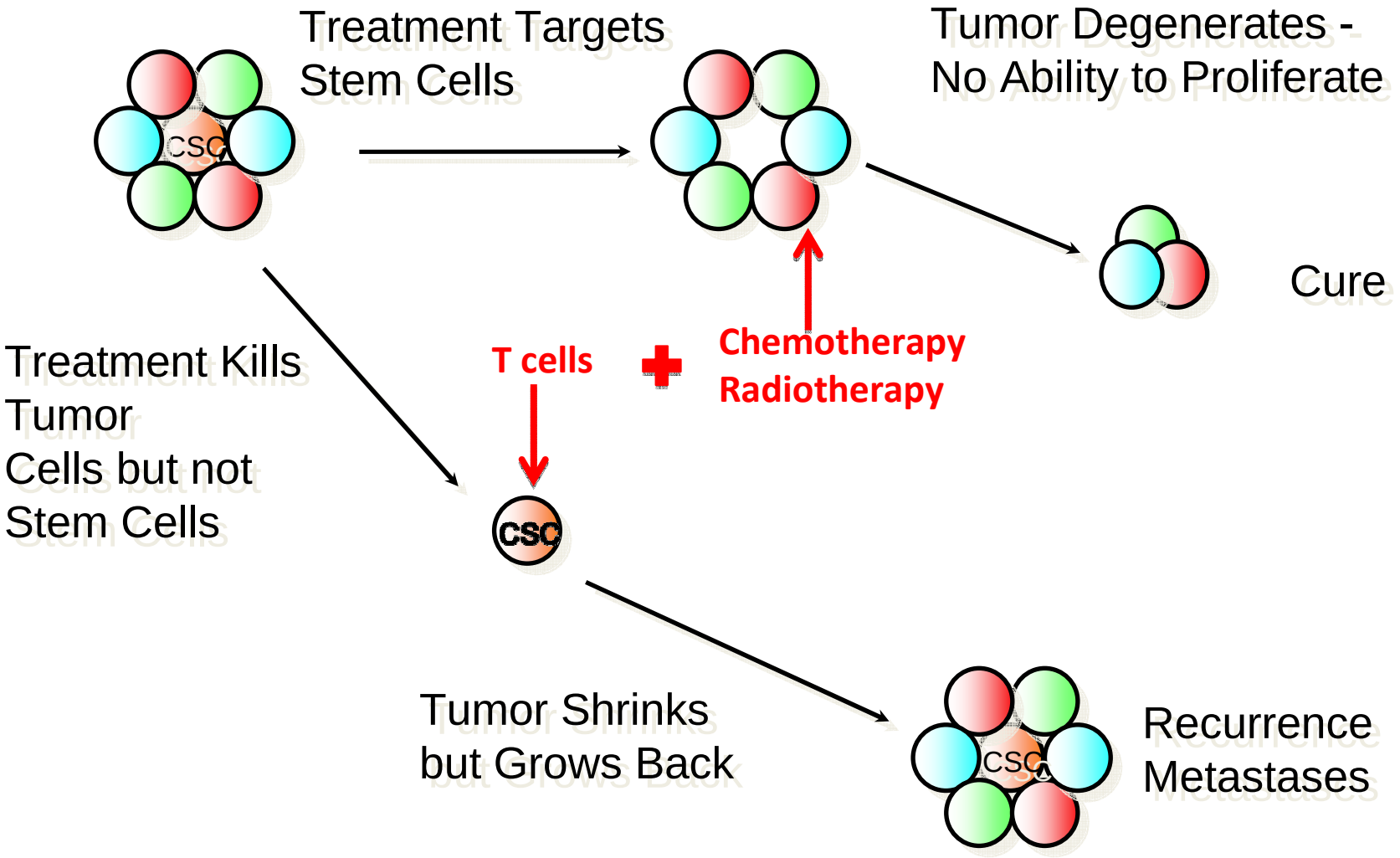
Combination of immunotherapy with targeted agents

Ipilimumab:
In combination with dacarbazine in metastatic melanoma patients improved survival compared with dacarbazine alone but there was no additonal benefit of drug (*Robert et al., NEJM 2011*).

Anti-CTLA-4 in combination with imatinib in mouse GIST model was synergistic (*Balachandran et al., Nature Medicine 2011*)

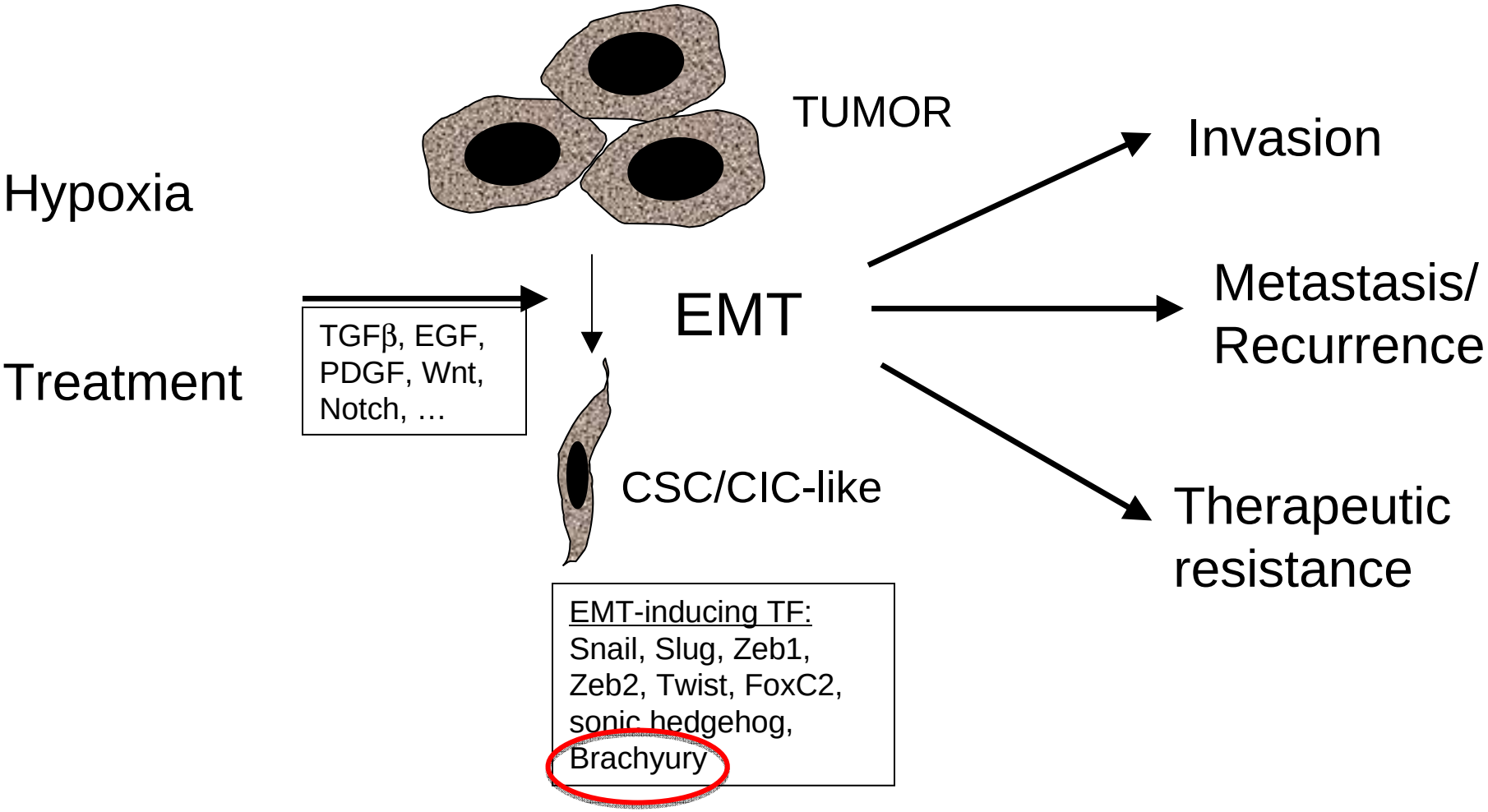
BRAF inhibitors in metastatic melanoma patients increased T cell infiltration in tumors. Magnitude of CD8 T cell infiltration correlated with tumor response (*Wilmott et al., Clin Cancer Res 2012*).
Phase I/II trial testing vemurafenib and Ipilimumab ongoing.

CSC/CIC and treatment



Modified after Reya et al, Nature: 414,105-11 , 2001

Epithelial to Mesenchymal Transition



T cell responses to antigens expressed by CIC/CSC

EMT TF Brachyury is a T cell antigen (Palena et al., Clin Cancer Res 2007)

CSC marker Aldehyde dehydrogenase (ALDH) is a T cell antigen (Visus et al., Clin Cancer Res 2011)

Cancer Testes Antigens were found to be highly and frequently expressed in cancer stem cells compared with differentiated glioma cells (Yawata et al., Mol Carcinog 2010)

HER2 was shown to be selectively expressed in and regulate self-renewal of the CSC population in estrogen receptor-positive, HER2 luminal breast cancers (Ithimakin et al., Cancer Res 2013)

Questions?