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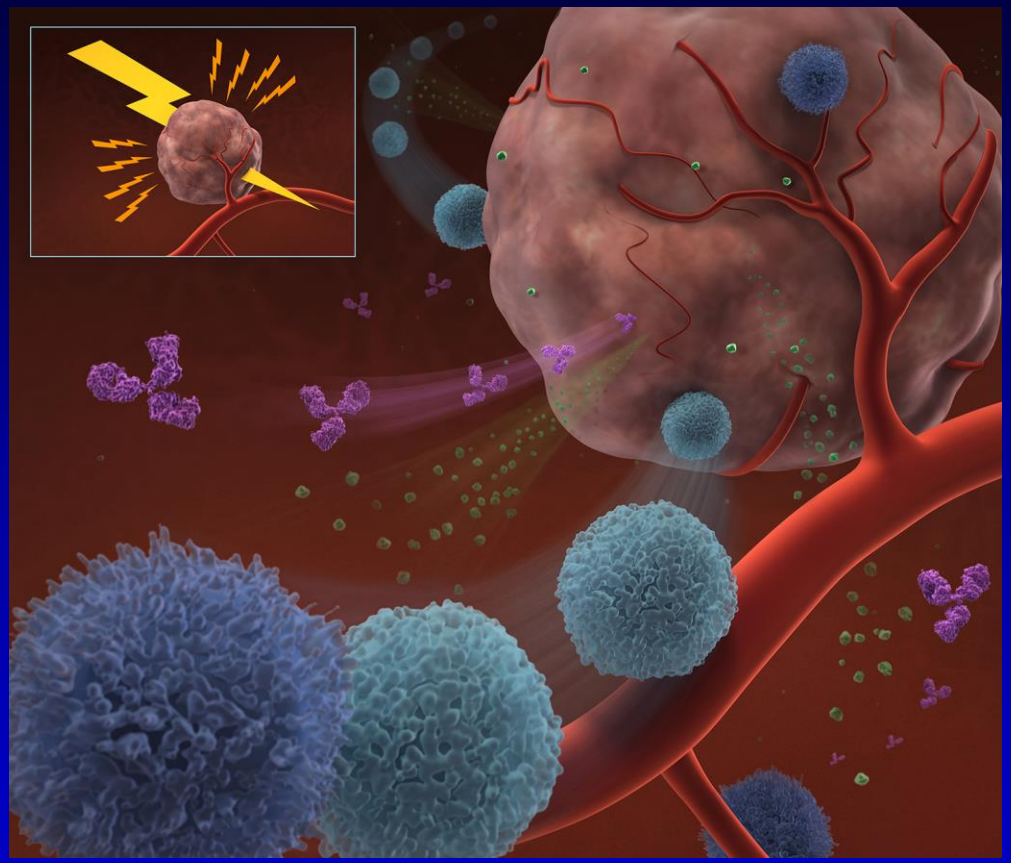
The symbiosis of science of radiation biology with immunology: Impact on basic and translational research



Mansoor M. Ahmed Ph.D.
Radiation Research Program
NCI, NIH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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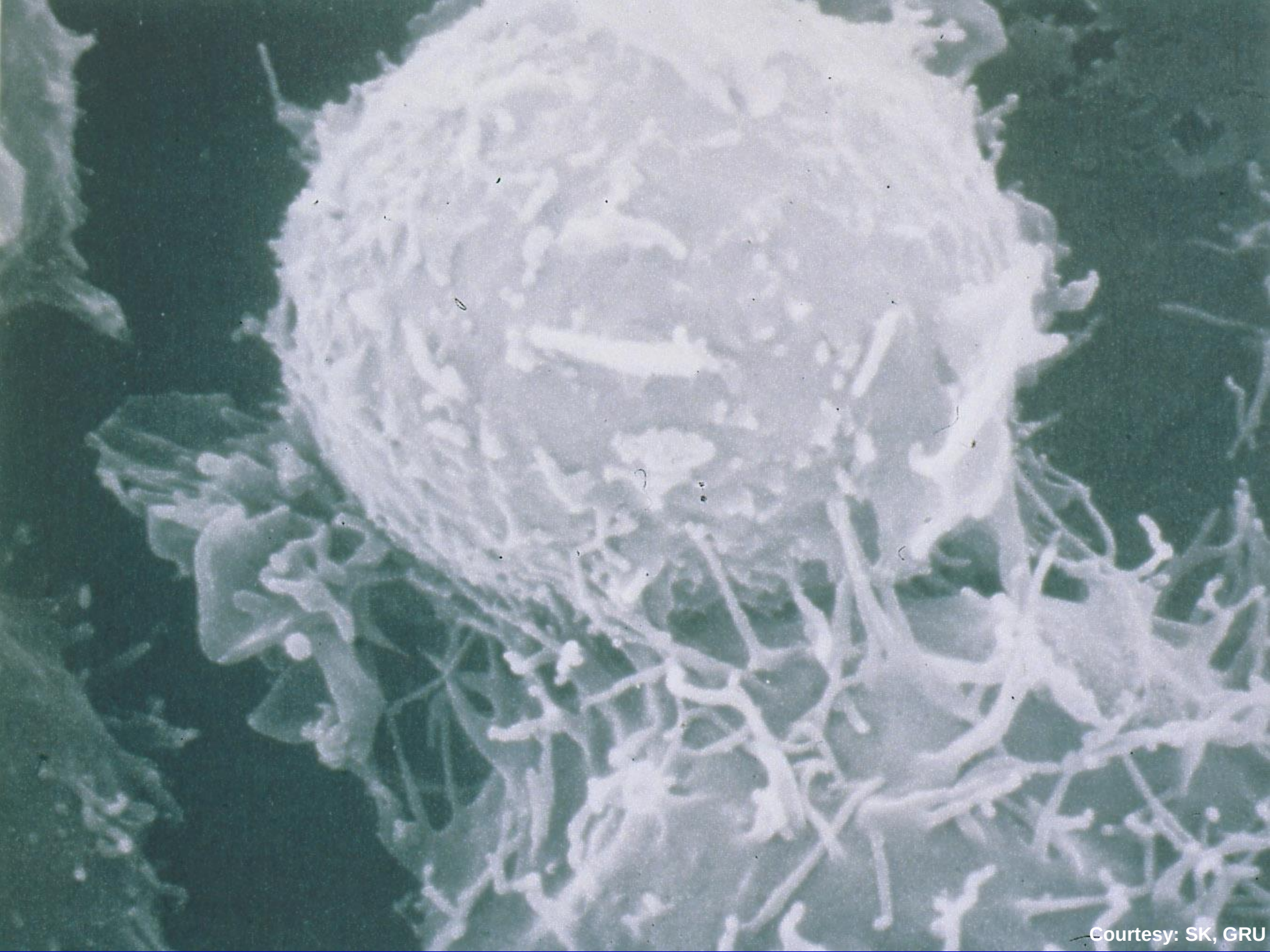

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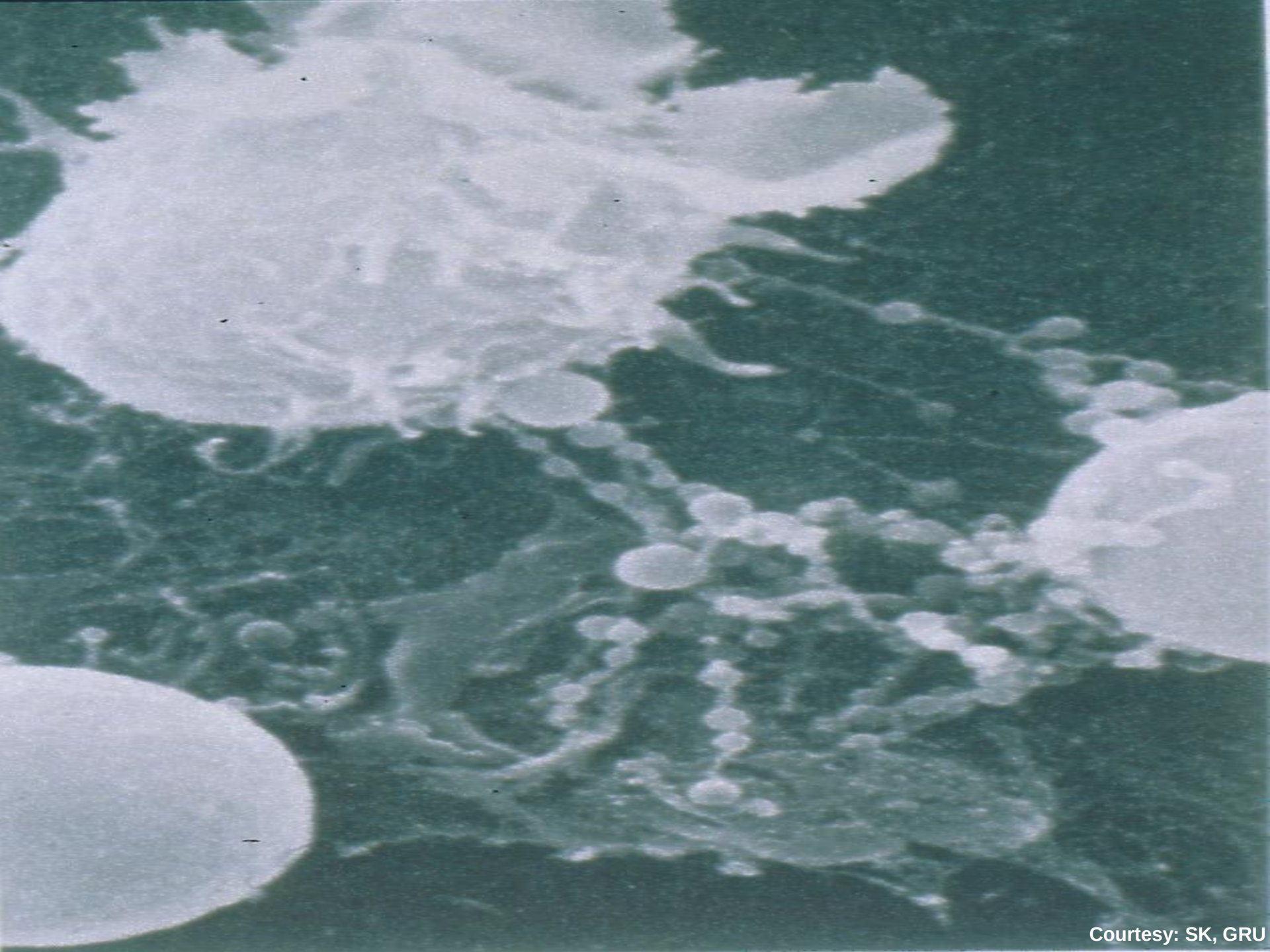

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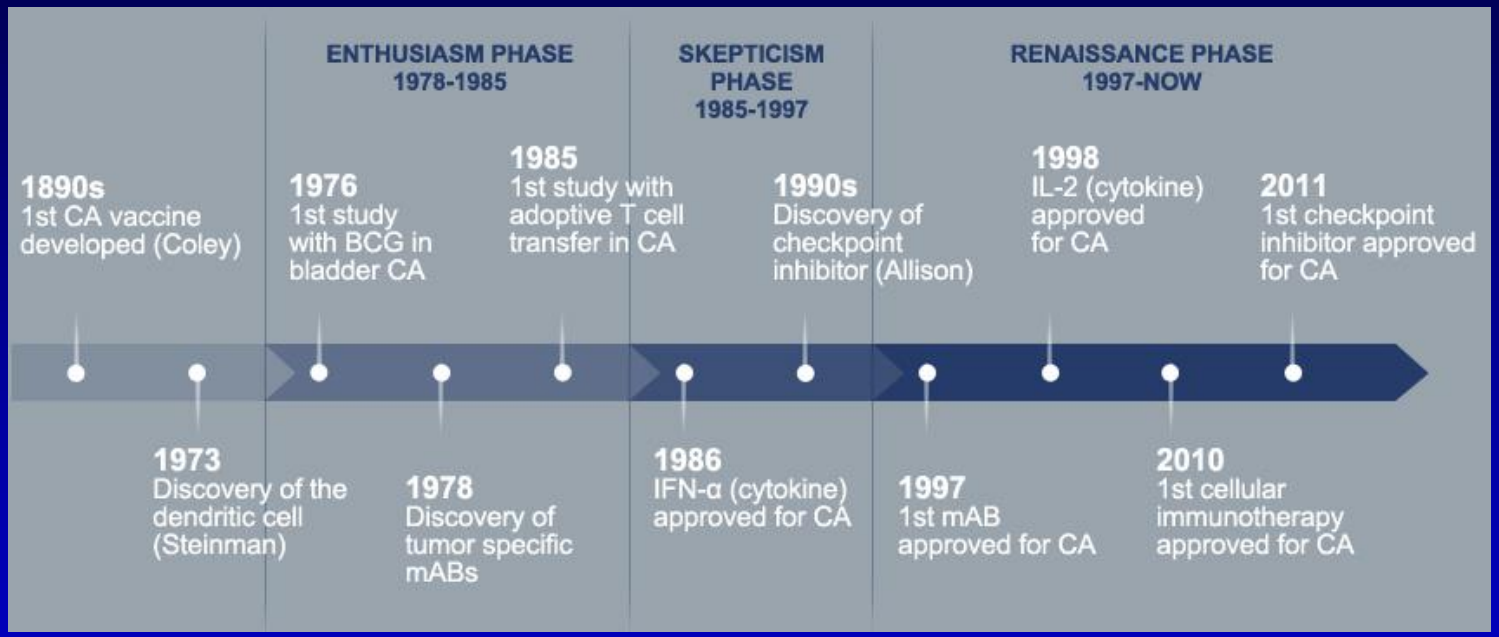
Cancer Immunotherapy Development



2014/2015

Approval of 2 anti-PD-1 antibodies for advanced melanoma and lung cancer

http://www.fightcancerwithimmunotherapy.com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T cells on the attack
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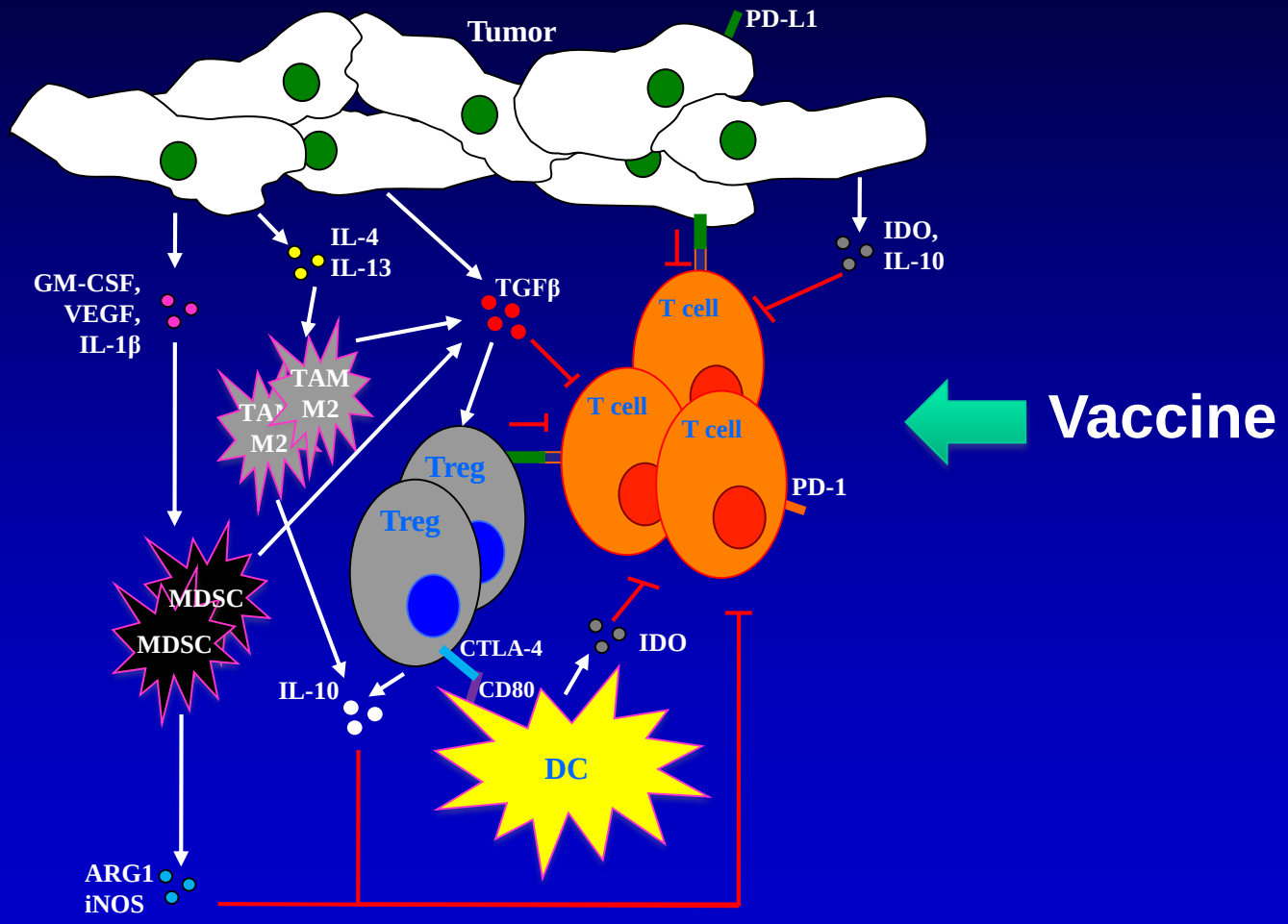
*Yes, it's now possible—thanks to new cancer dream teams that are delivering better results faster

Tumor-Immune Interaction



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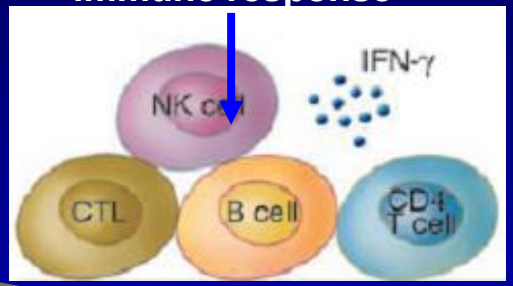
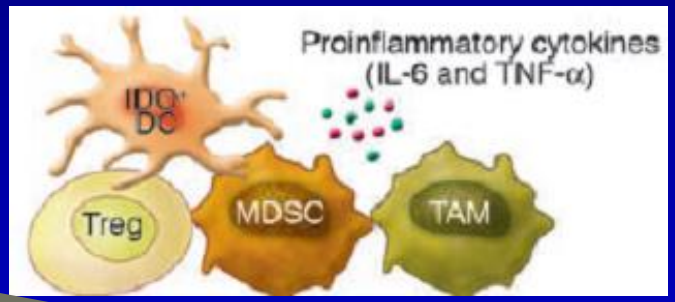
Effective Therapeutic immune-balance

Induction of immune response

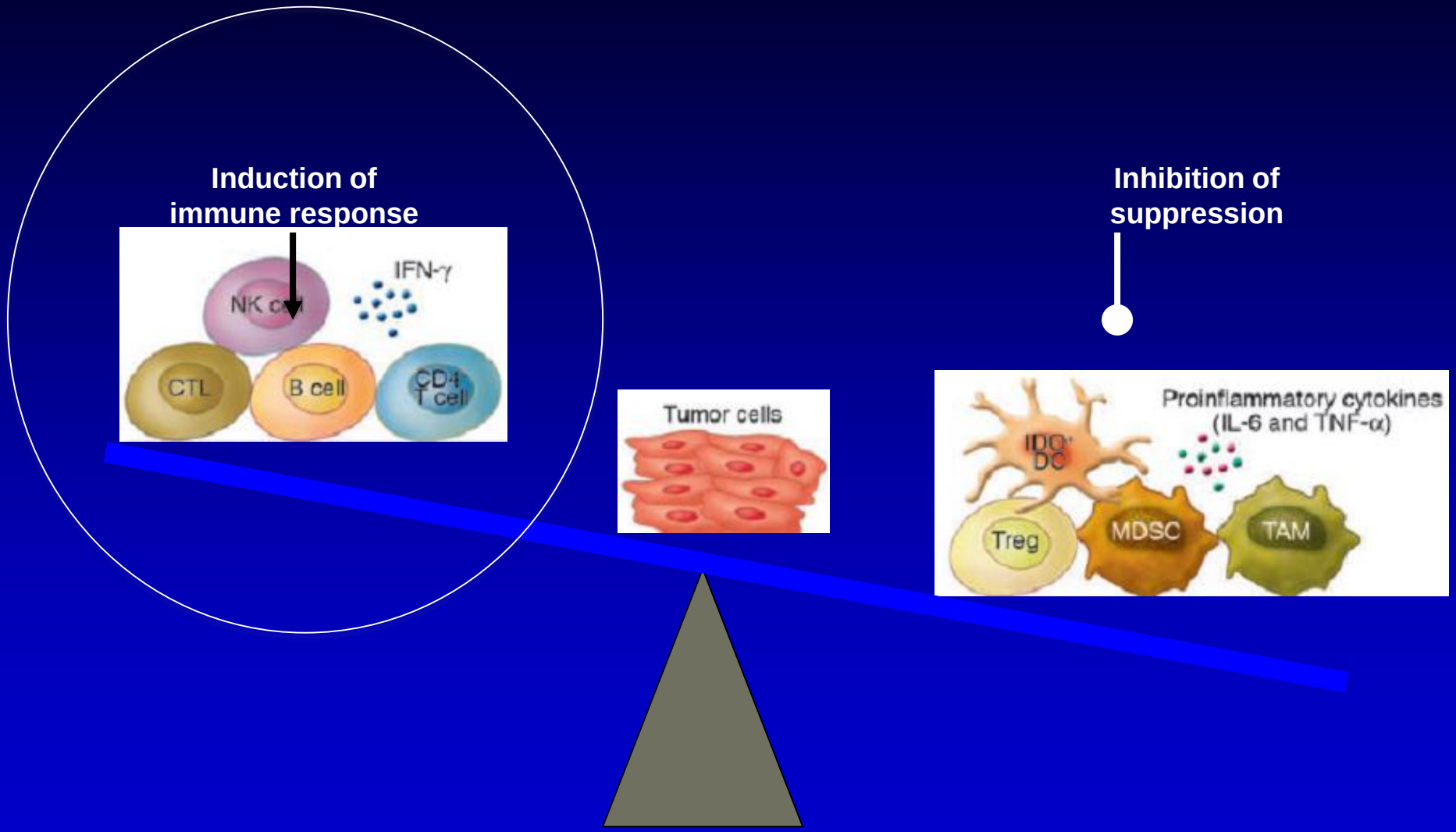


Inhibition of suppression

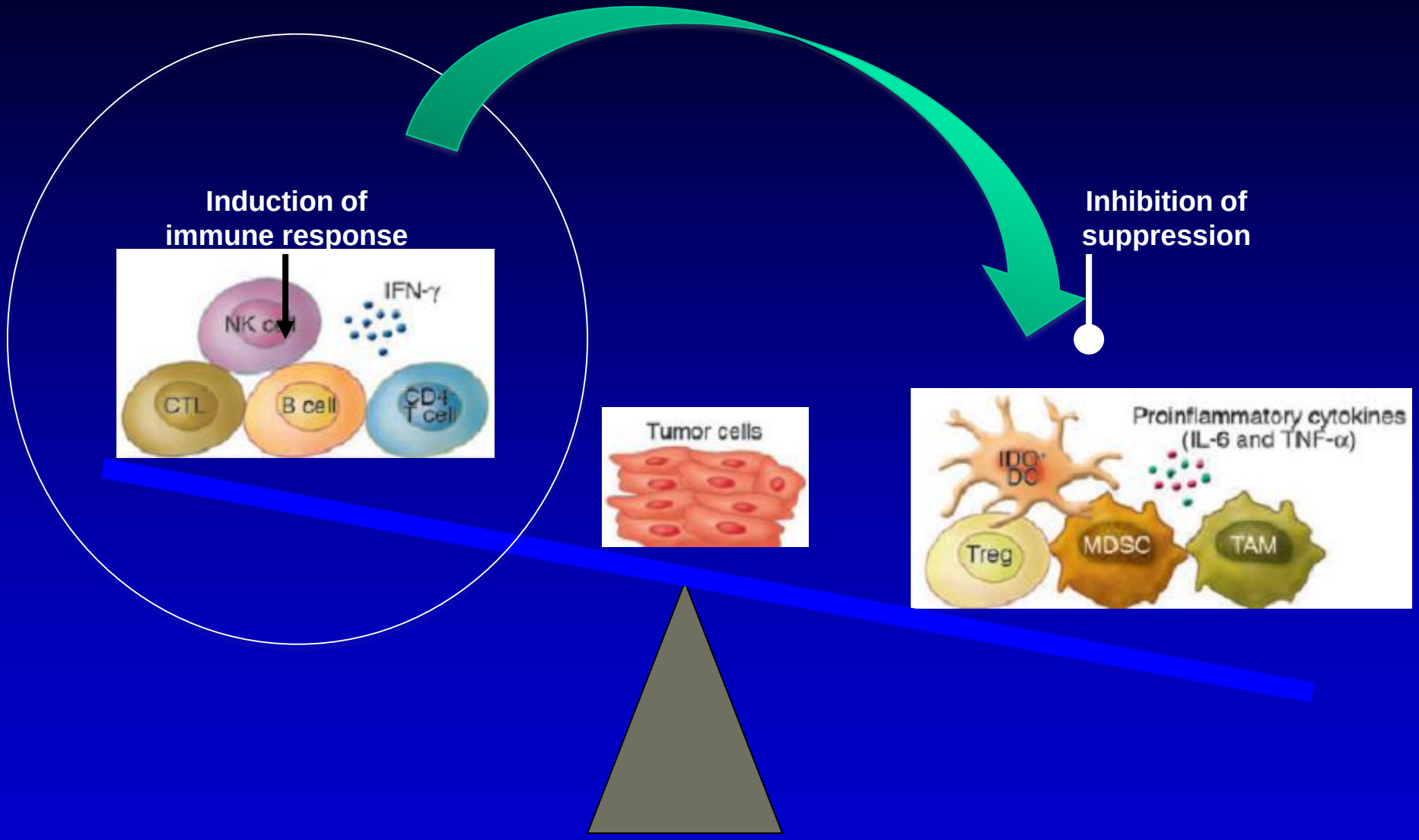


Courtesy: SK, GRU

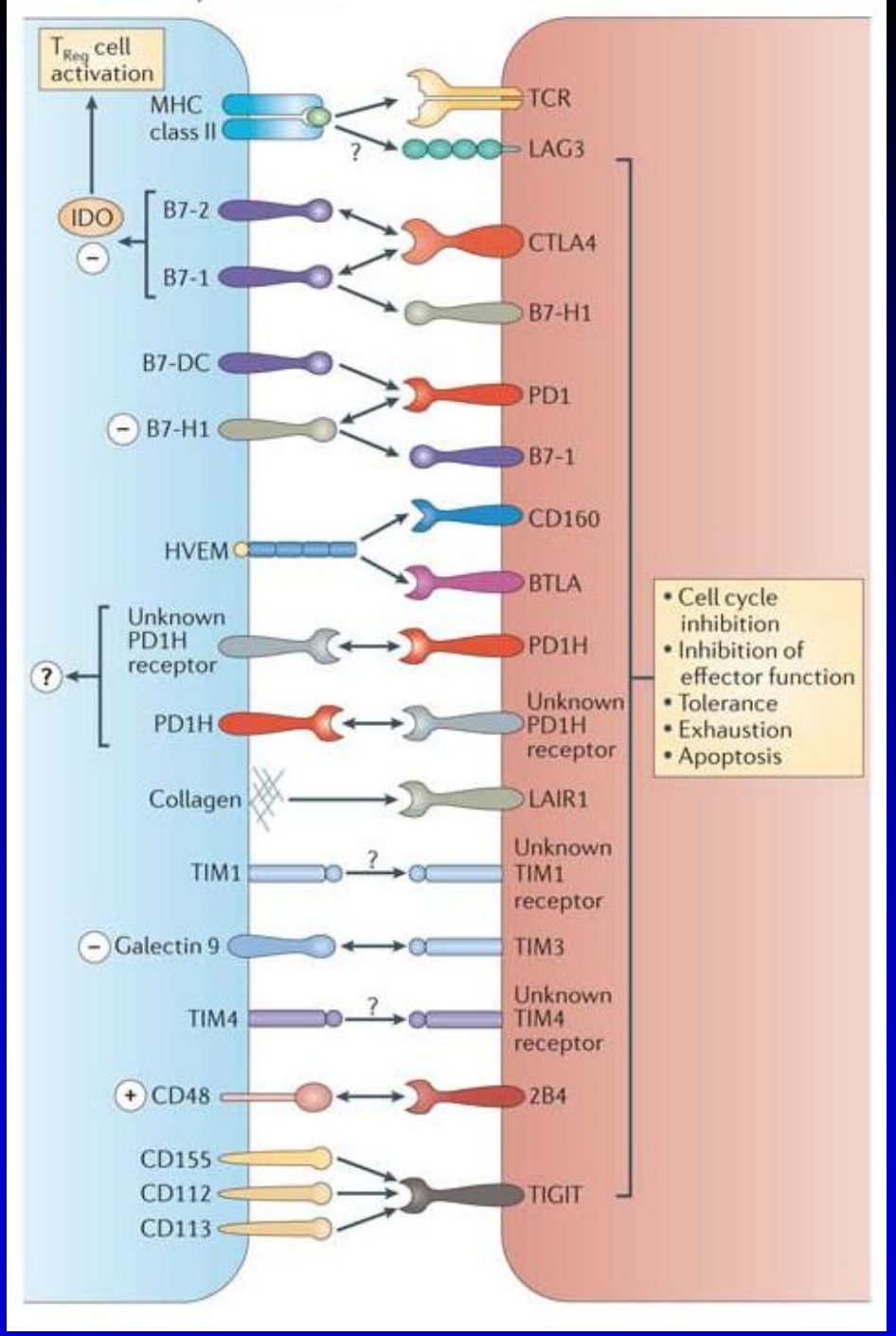
Effective Therapeutic immune-balance



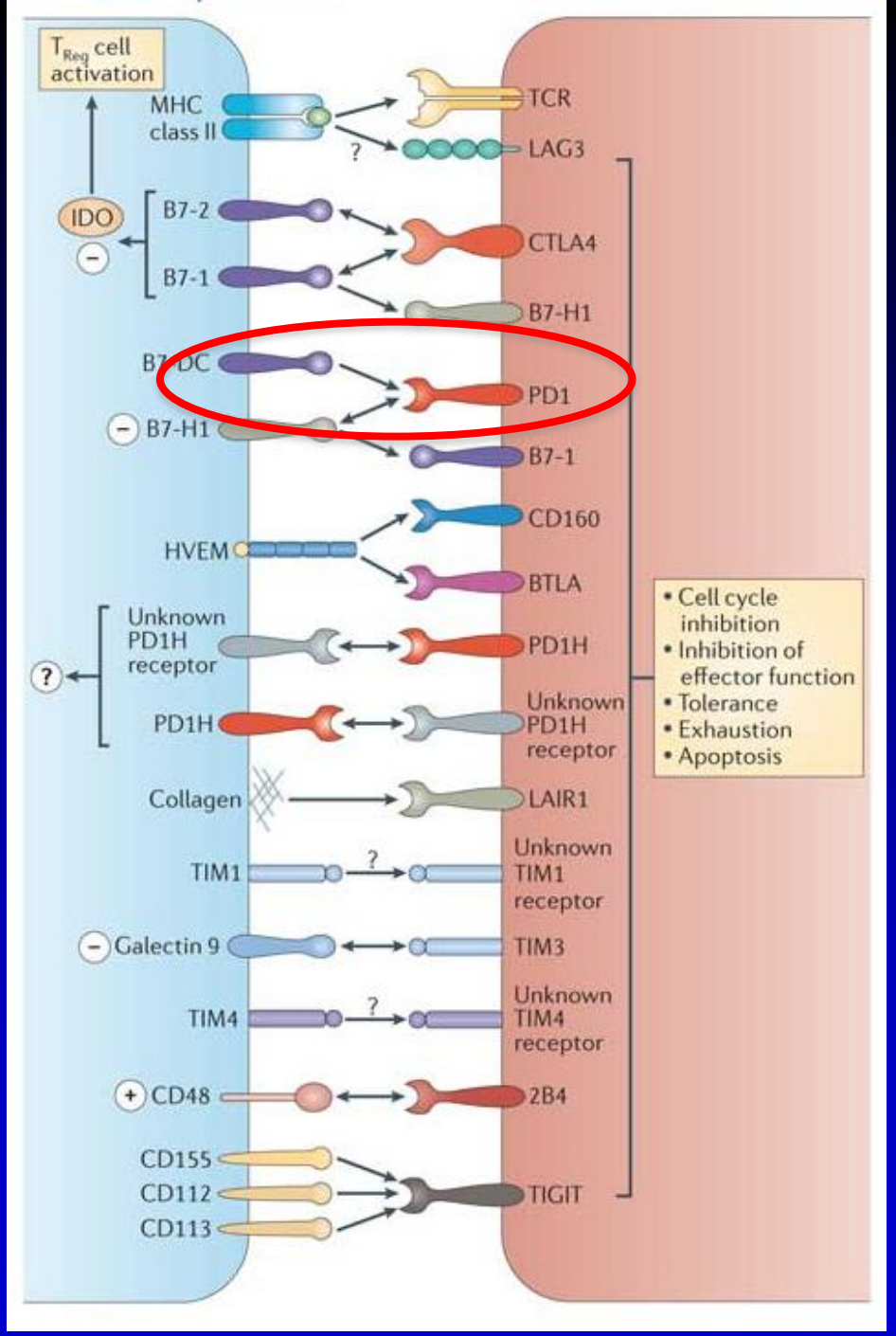
Effective Therapeutic immune-balance



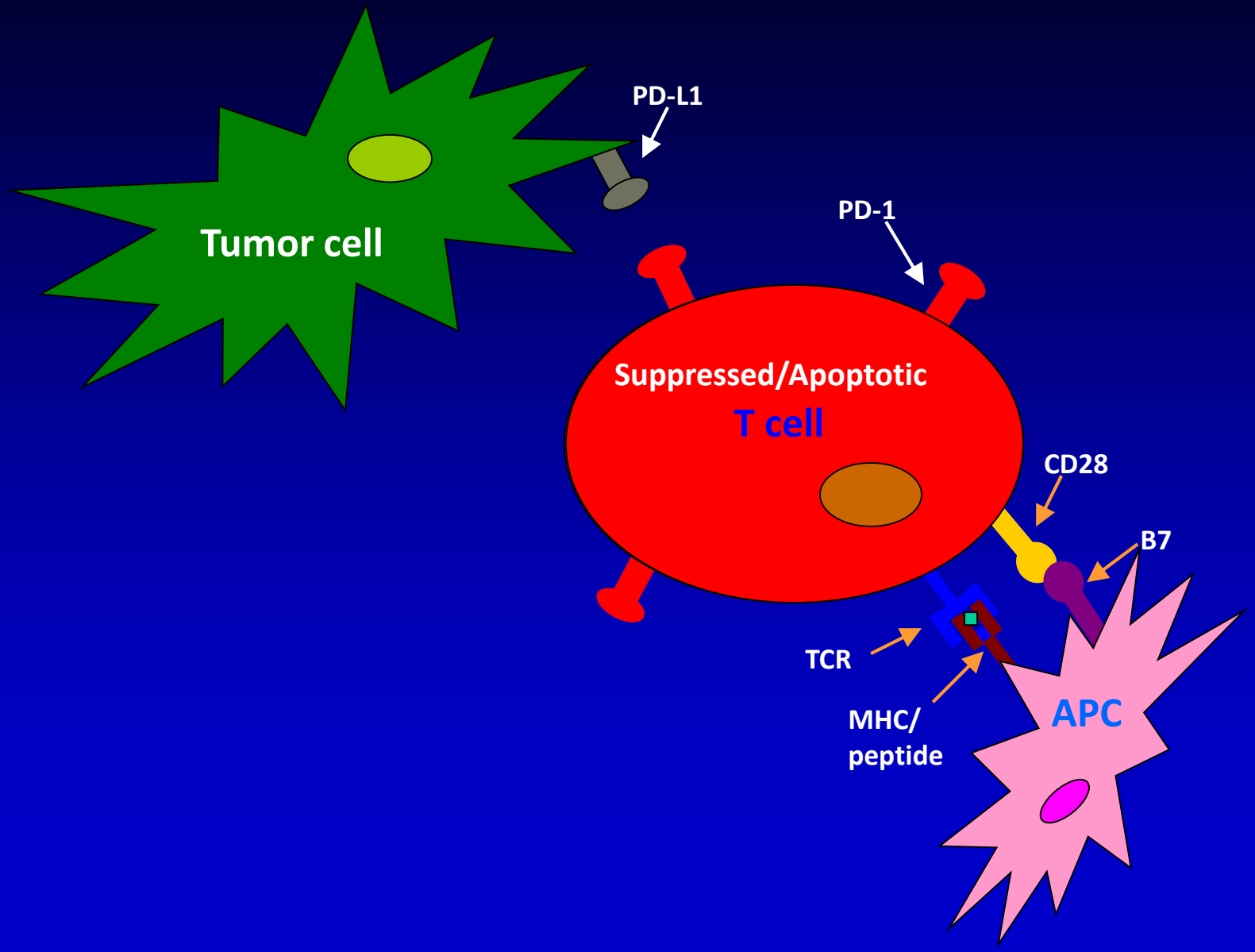
Co-inhibitory Molecules



Co-inhibitory Molecules

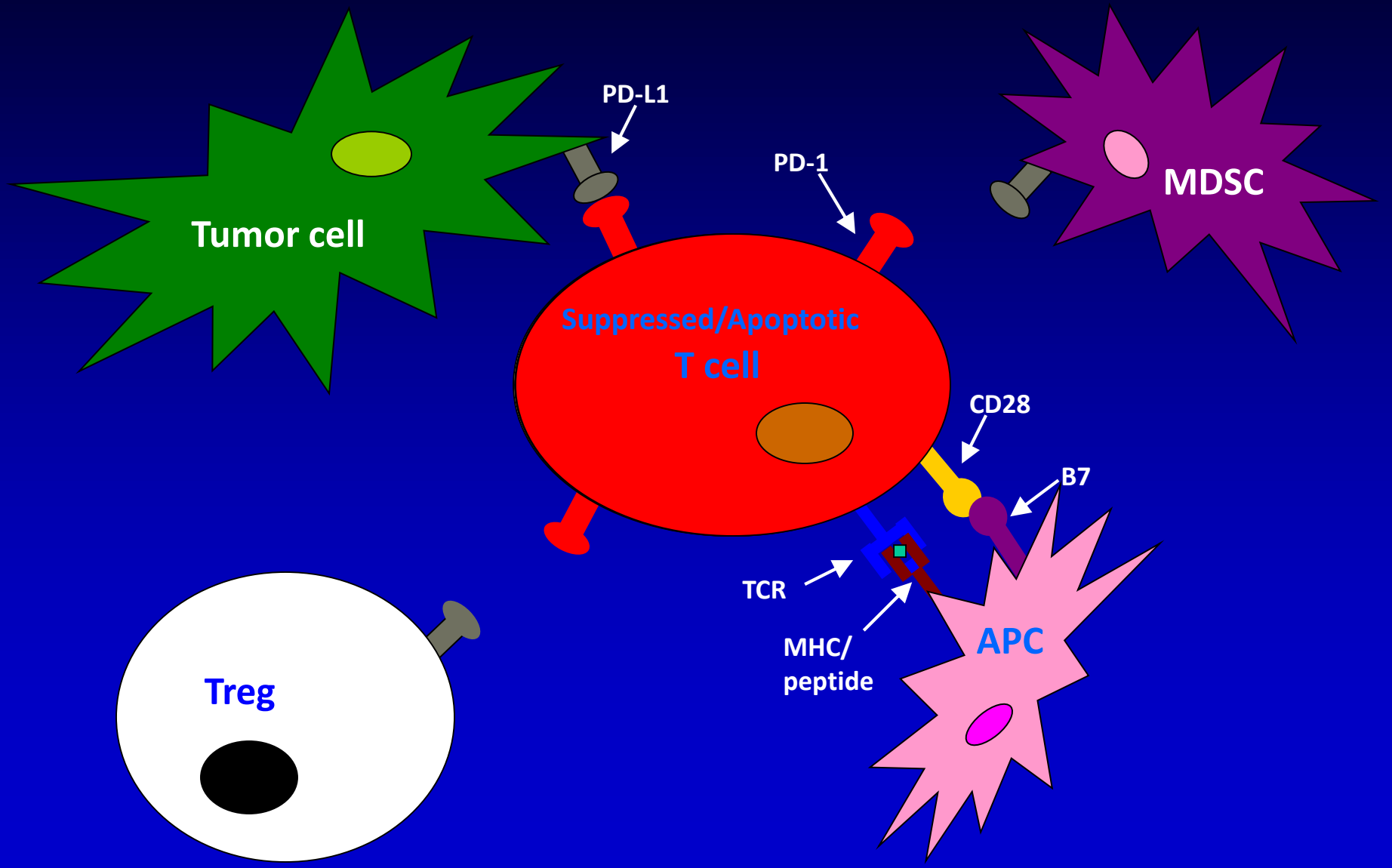


PD-1/PD-L1 Engagement Suppresses Effector T-cells



Courtesy: SK, GRU

PD-1/PD-L1 Engagement Suppresses Effector T cells



PD-1/PD-L1 Engagement Suppresses Effector T cells

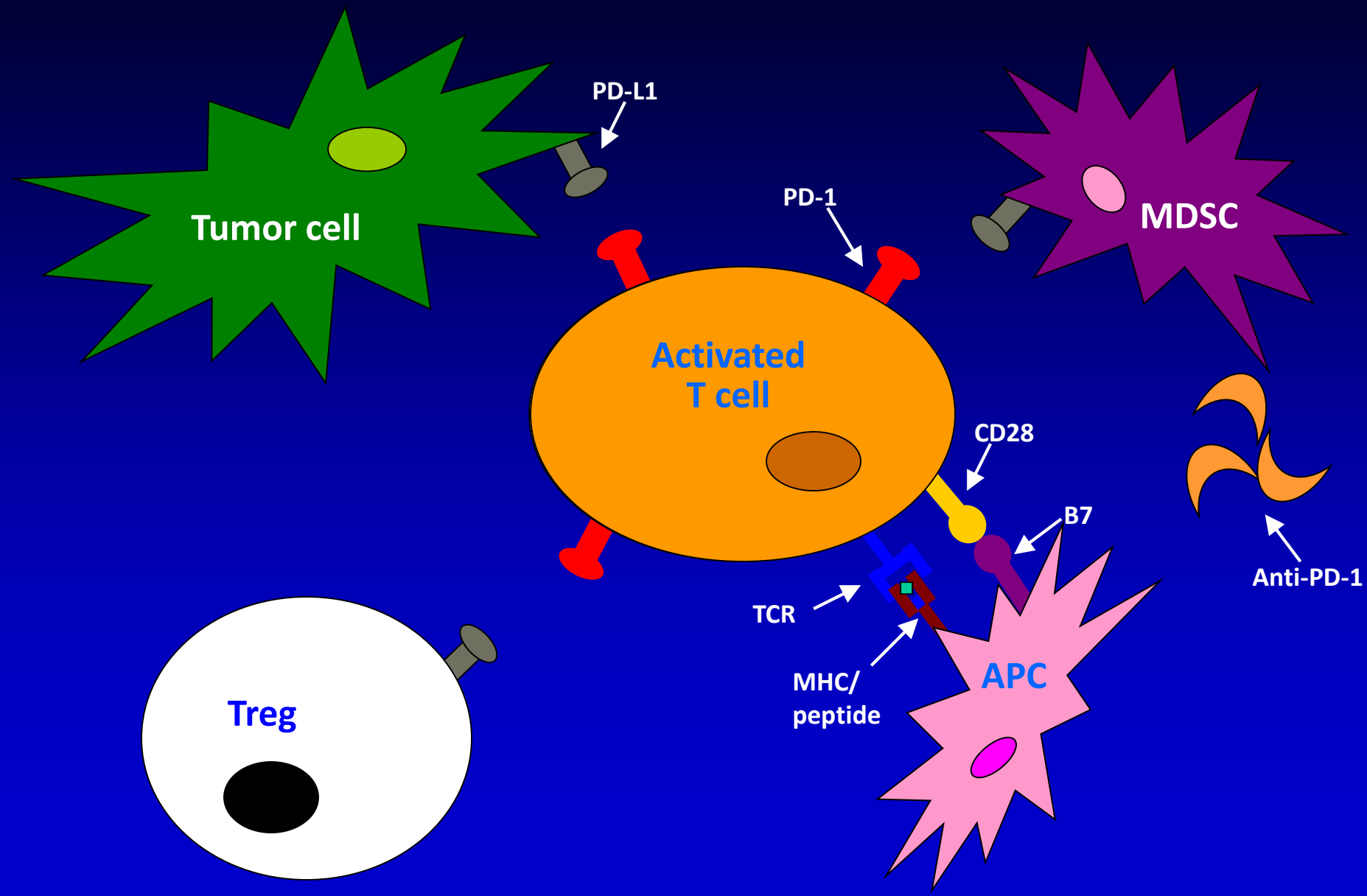


Table 1. Final Rankings of Agents with High Potential for Use in Treating Cancer

Rank*	Agent	Agent Category
1	IL-15	T-Cell Growth Factor
2	Anti-Programmed Death-1 (PD1)and/or anti–B7-H1 (PD1 Ligand)	**T-Cell Checkpoint Blockade Inhibitor
3	IL-12	Vaccine Adjuvant
4	Anti-CD40 and/or CD40L	Antigen Presenting Cell Stimulator
5	IL-7	T-Cell Growth Factor
6	CpG	Vaccine Adjuvant
7	1-Methyl Tryptophan	Enzyme Inhibitor
8	Anti-CD137 (anti–4-1BB)	T-Cell Stimulator
9	Anti–TGF-beta	Signaling Inhibitor
10	Anti–IL-10 Receptor or Anti–IL-10	Suppression Inhibitor
11	Flt3L	Dendritic Cell Growth Factor/ Vaccine Adjuvant
12	Anti-Glucocorticoid-Induced TNF Receptor (GITR)	T-cell Stimulator
13	CCL21 Adenovirus	T-Cell Attracting Chemokine
14	Monophosphoryl Lipid A (MPL)	Vaccine Adjuvant
15	Poly I:C and/or Poly ICLC	Vaccine Adjuvant
16	Anti-OX40	T-Cell Stimulator
17	Anti–B7-H4	T-Cell Checkpoint Blockade Inhibitor
18	Resiquimod and/or 852A	Vaccine Adjuvant
19	LIGHT and/or LIGHT vector	T-Cell Stimulator
20	Anti–Lymphocyte Activation Gene-3 (LAG-3)	T-Cell Checkpoint Blockade Inhibitor

Combinational Immunotherapy

- Vaccines
- Immune Modulators
  - Immune Agonists
    - Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
    - Co-stimulatory molecules (OX-40, GITR, 4-1BB)
  - Immune inhibitors
    - Check point inhibitors (CTLA4, PD1/PDL1, LAG3, TIM3, iDO)
    - Inhibitory cytokines/factors (IL-10, TGFβ)
- Standard Therapy
  - Chemotherapy
  - Radiation Therapy
- Small Molecules
- Chimeric Antigen ReceptorS

Immune modulation by ionized irradiation

Z. Tochner and S. Slavin*

Departments of Radiation Therapy and Clinical Oncology and *Bone Marrow Transplantation and Cancer Immunobiologicy Research Laboratory, Hadassah University Hospital, Jerusalem, Israel

Current Opinion in Immunology 1988, **1**:261–268

Radiation can

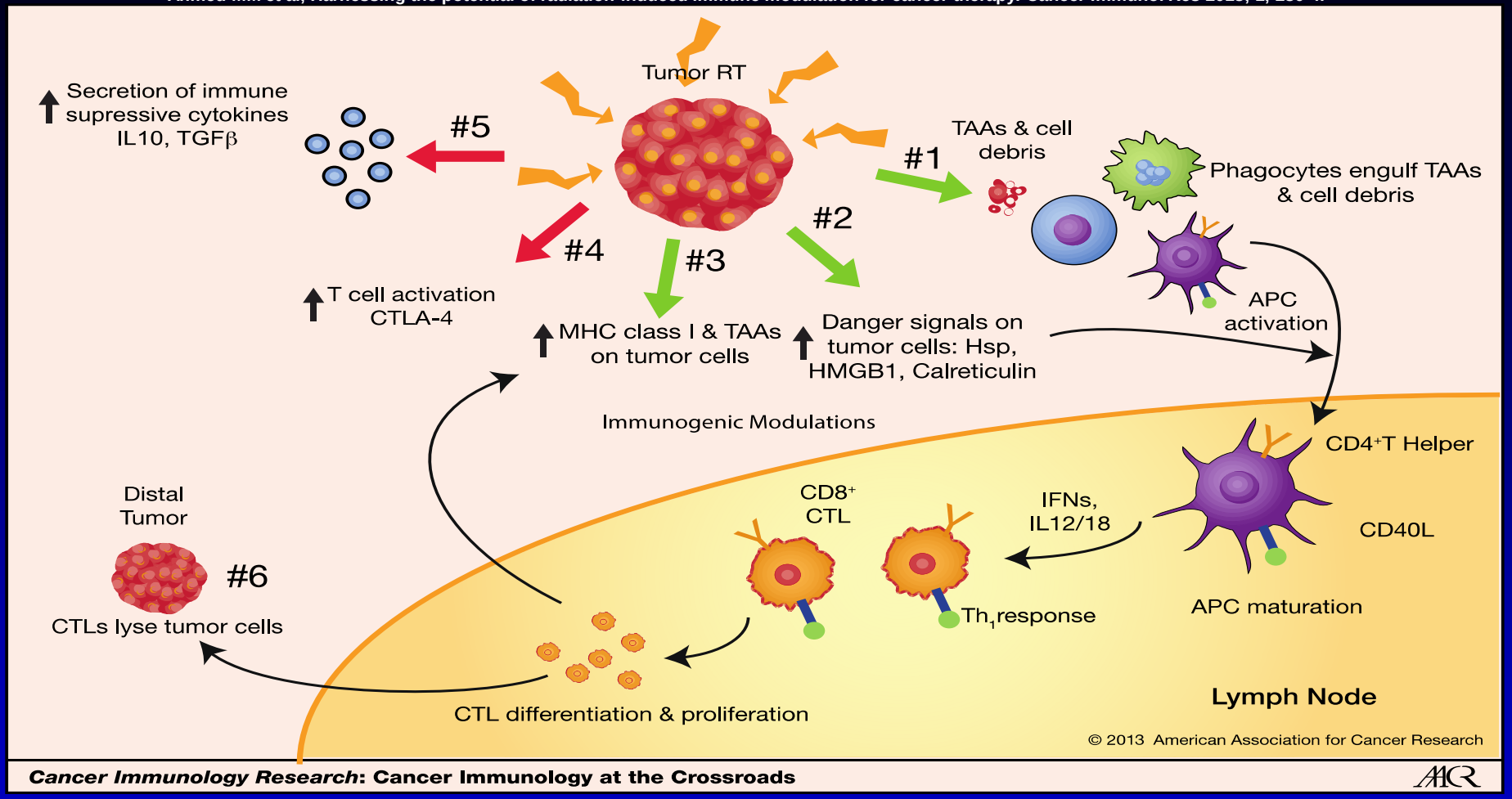
- Impact both innate and adaptive immunity
- Provide a source of robust tumor antigens
- Induce cytokines that can help to alter the profile and function of immune infiltrates
- Remodels the stromal and angiogenic compartments of the tumor microenvironment

More importantly

Surviving tumor cells after radiation therapy are more sensitive to immune-mediated killing

A Schematic view of RT-induced immune modulations

Ahmed MM et al, Harnessing the potential of radiation-induced immune modulation for cancer therapy. Cancer Immunol Res 2013; 1, 280-4.



Cancer Immunology Research: Cancer Immunology at the Crossroads

AACR

#1: Tumor-associated antigens (TAAs) are released by irradiated dying cancer cells. TAAs and cell debris are engulfed in the tumor microenvironment by phagocytes such as macrophages, neutrophils, and dendritic cells for antigen processing and presentation.

#2: RT-induced cell death releases danger signals including heat-shock protein (Hsp), HMGB1, and calreticulin (eat-me signal for phagocytes).

#3: RT induces increased expression of tumor antigens and MHC class I molecules on tumor cells.

#4: RT-induced T cell activation increases expression of negative stimulatory molecules such as CTLA-4.

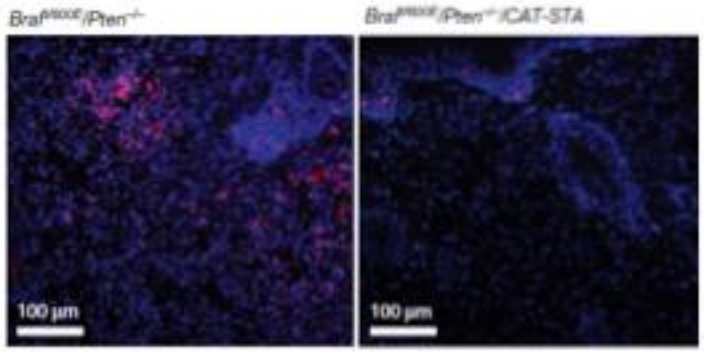
#5: Certain radiation doses may increase tumor production/secretion of immunosuppressive cytokines such as IL-10 and TGF-b.

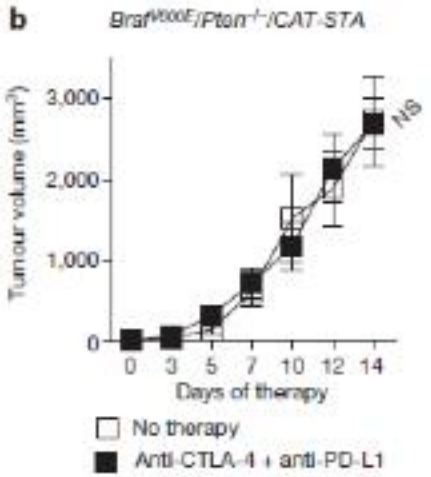
#6: Activated APCs migrate to the draining lymph node, further mature upon encountering T helper cells, release interferons (IFNs) and IL-12/18 to stimulate Th_1 responses that support the differentiation and proliferation of antigen-specific CTLs. Activated antigen-specific CTLs traffic systematically from the draining lymph node to infiltrate and lyse primary and distal tumors.

Rationale for Combining Radiation with PD-L1 and CTLA-4 Inhibition

- **Targeted radiation can have immune stimulating effects**
  - Potential mechanisms: immune co-stimulation, recognition of tumor antigens / epitope spreading, increased MHC class I expression, interferon secretion, natural killer cell activity, tumor infiltrating lymphocytes.
- **Preclinical data and case reports demonstrate synergy between targeted radiation and CTLA-4 and/or PD-1 inhibition**
  - Radiation combined with dual checkpoint blockade (CTLA-4 and PD-1) led to 60-80% response rates across multiple preclinical models with non overlapping mechanisms of action (Saint-Victor et al. Nature 2015)
  - Radiation combined with checkpoint blockade can lead to "abscopal" responses out of the radiation field (Postow et al. NEJM 2012)
- **The optimal radiation dose / fractionation scheme to combine with checkpoint blockade is unknown**

Exclusion of Tumor Infiltrating T-cells is a mechanism of resistance to dual checkpoint blockade

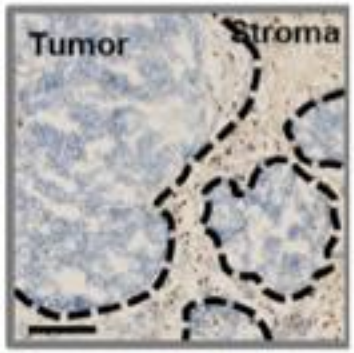




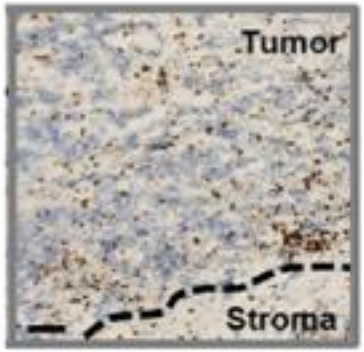
Spranger, Bao, Gajewski - Nature 2015

RT can increase Tumor Infiltrating T-cells

non-irradiated

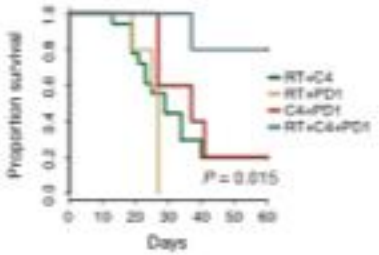


irradiated

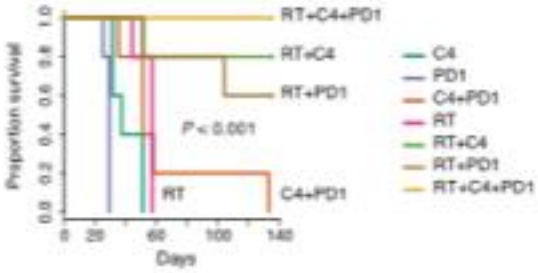


Klug et al.- Cancer Cell 2013

RT can improve response to dual checkpoint blockade



Two-way comparison	Log-rank P value
C4 vs. RT+C4	< 0.001
RT+C4 vs. RT+C4+PDL1	0.017
C4+PDL1 vs. RT+C4+PDL1	0.003
RT+C4 vs. RT+C4+PD1	0.022
C4+PD1 vs. RT+C4+PD1	0.064



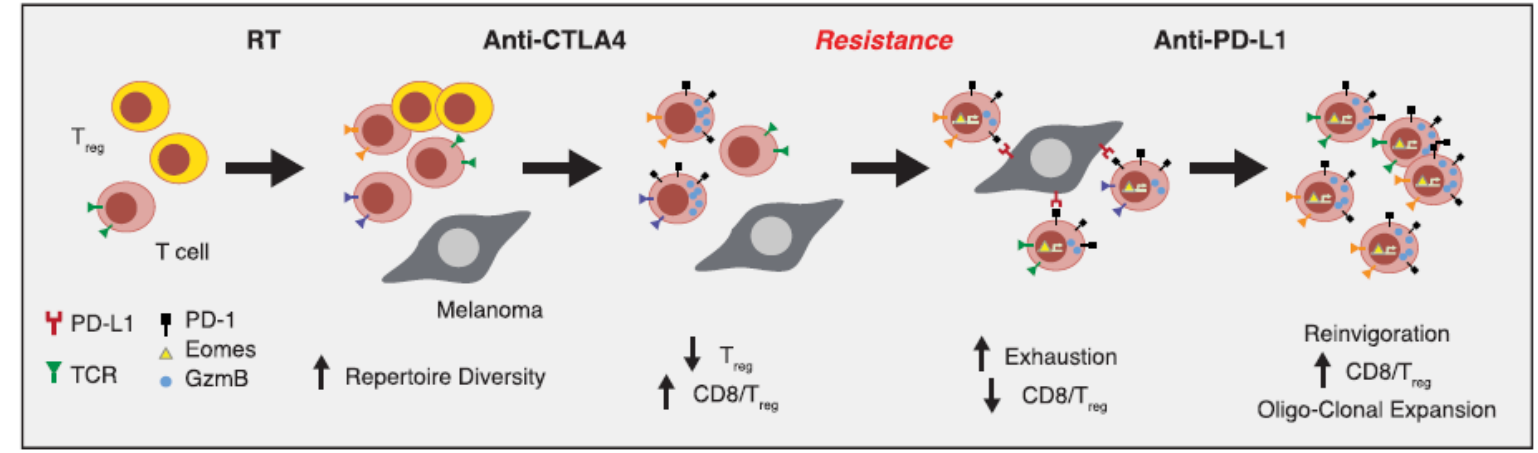
Saint-Victor et al. Nature 2015

LETTER

doi:10.1038/nature14292

Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Christina Twyman-Saint Victor[1,2]*, Andrew J. Rech[2]*, Amit Maity[3,4], Ramesh Rengan[3,4]†, Kristen E. Pauken[5,6], Erietta Stelekati[5,6], Joseph L. Benci[2,3], Bihui Xu[2,3], Hannah Dada[2,3], Pamela M. Odorizzi[5,6], Ramin S. Herati[1,6], Kathleen D. Mansfield[5,6], Dana Patsch[3], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Hemant Ishwaran[7], Rosemarie Mick[4,8], Daniel A. Pryma[4,9], Xiaowei Xu[4,10], Michael D. Feldman[4,10], Tara C. Gangadhar[1,4], Stephen M. Hahn[3,4]†, E. John Wherry[4,5,6]§, Robert H. Vonderheide[1,2,4,6]§ & Andy J. Minn[2,3,4,6]§



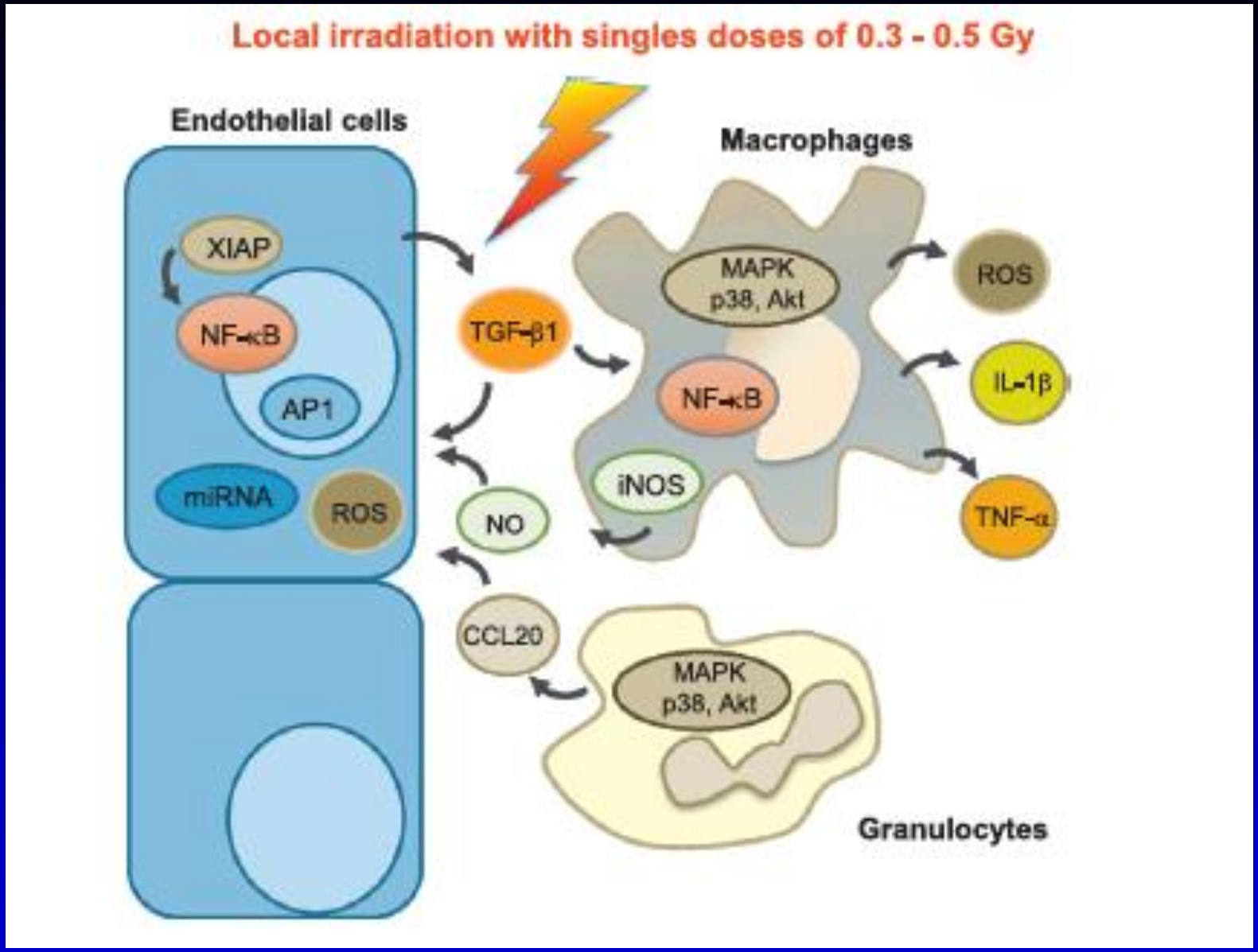
Approximately 20 Ongoing Trials Using PD-1 Pathway Inhibitors and Radiation Therapy

Histology	Stage	Agent	Type of RT
NSCLC	Metastatic	Pembrolizumab	SBRT
SCLC	Limited or extensive	Pembrolizumab	Conformal
H&N, RCC, Urothelial, Melanoma, SCLC	Metastatic	Pembrolizumab	Conformal
Glioma	Recurrent	Pembrolizumab+ Bevacizumab	SRT
Colorectal	Metastatic	Pembrolizumab	Unspecified
NSCLC	Metastatic	Pembrolizumab	SBRT
H&N	Localized	Pembrolizumab	Fractionated
Pancreatic cancer, Melanoma, NSCLC, breast	Metastatic	Pembrolizumab	Unspecified
Melanoma, NSCLC	Metastatic	Pembrolizumab	6 Gy x5 or 3 Gy x10

Histology	Stage	Agent	Type of RT
Pancreatic cancer	Locally advanced	Pembrolizumab+ Capecitabine	Fractionated
Breast	Oligometastatic	Pembrolizumab	SBRT
H&N	Locally recurrent	Pembrolizumab	Fractionated, BID
Pancreatic cancer	Unresectable	MEDI4736	Fractionated
GBM	Upfront	MEDI4736	Fractionated
NSCLC	IIIA/IIIB	Nivolumab	Fractionated
Multiple histologies	Metastatic	REGN2810	SBRT
NSCLC	Metastatic	MPDL3280	SBRT
NSCLC	Metastatic	MPDL3280	SBRT
Colon	Metastatic	AMP224	Unspecified

- **Only 1 trial testing the combination of radiation PD-1 and CTLA-4 blockade in unresectable pancreatic cancer**

- **Few trials testing RT parameters in combination with checkpoint blockade**
  - **One trials testing low-dose ultrafractionated radiation (<1 Gy per fraction) with PD-L1.**
    - **Low-dose radiation was an effective inducer of tumor infiltrating T-cells in mouse models (Klug et al. Cancer Cell 2013)**
    - **Low-dose RT allows exploration of synergistic effects on local control**
  - **Only one trial explicitly evaluating RT dose (40 patients, 5 histology, multiple timings), not using combined checkpoint blockade**



F. Rödel et al. / Cancer Letters 356 (2015) 105–113

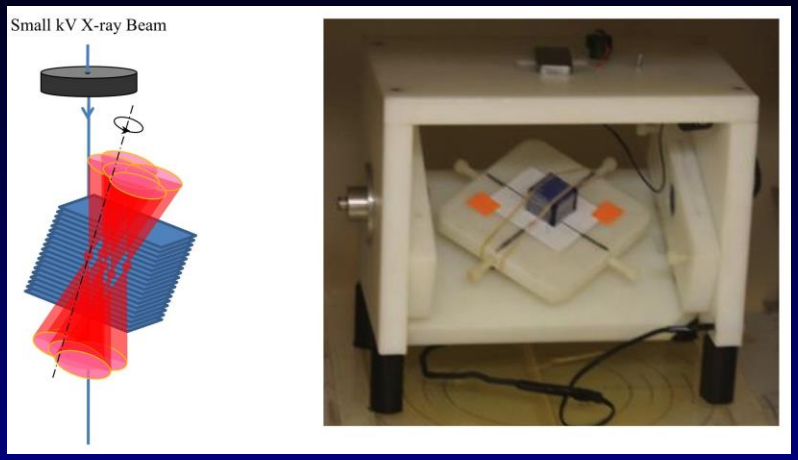
Challenges

Immune-modulation of tumor microenvironment and tumor cells by radiation

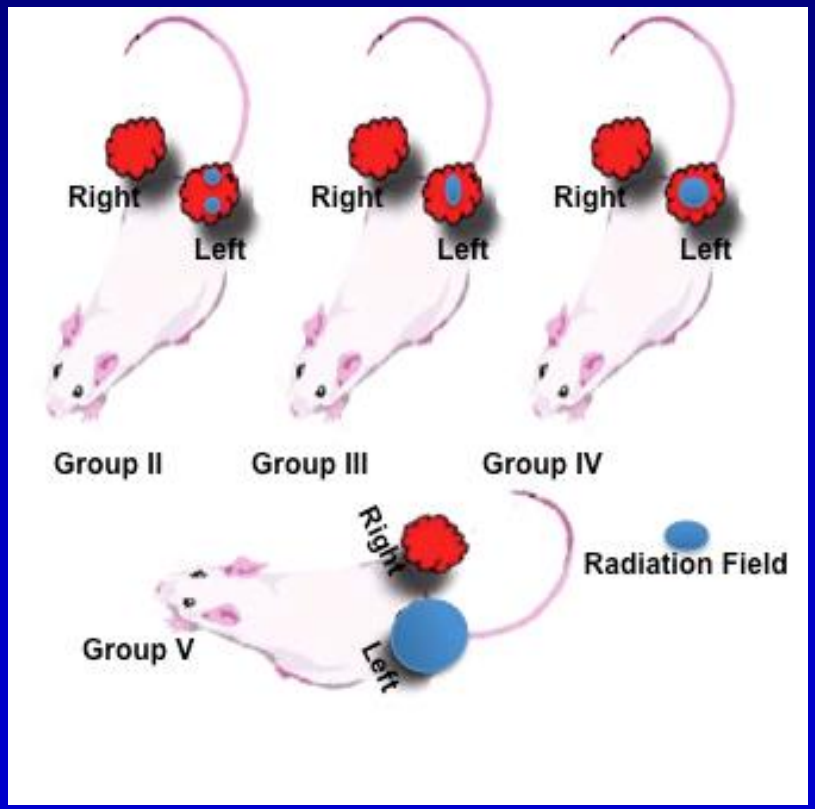
- **Quality of radiation (high versus low-LET), dose, size, fractionation (low-dose versus high-dose fractionation) and dose-rate (high-dose rate versus low-dose rate), and schedule (hypofractionation versus multifractionation**

- **Irradiation of complete tumor volume or partial volume adequate for effective modulation of tumor immune microenvironment**
  - ⊙ **Gross tumor volume (GTV) or GTV plus LN**

Partial volume radiation : Lattice Radiotherapy



Kanagavelu, S., Gupta, S., Wu, X., Philip, S., Wattenberg, M. W., Hodge, J. W., Couto, M. D., Chung, K. D. and Ahmed, M. M. In Vivo Effects of Lattice Radiation Therapy on Local and Distant Lung Cancer: Potential Role of Immunomodulation. Radiat. Res. 182, 149–162 (2014).



Partial tumor volume (20-50%) irradiation caused:

- **Distal tumor growth delay**
- **IFNg and Th1 up and Th2 down**
- **Increased CD3+ infiltration**

Challenges

Immune-modulation of tumor microenvironment and tumor cells by radiation

- **Quality of radiation (high versus low-LET), dose, size, fractionation (low-dose versus high-dose fractionation) and dose-rate (high-dose rate versus low-dose rate), and schedule (hypofractionation versus multifractionation**

- **Irradiation of complete tumor volume or partial volume adequate for effective modulation of tumor immune microenvironment**
  - **Gross tumor volume (GTV) or GTV plus LN**
  - **Evoking it by irradiating normal tissue**

[CANCER RESEARCH 63, 1990–1993, April 15, 2003]

Radiation Abscopal Antitumor Effect Is Mediated through p53[1]

Kevin Camphausen,[2] Marsha A. Moses, Cynthia Ménard, Mary Sproull, Wolf-Dietrich Beecken, Judah Folkman, and Michael S. O'Reilly

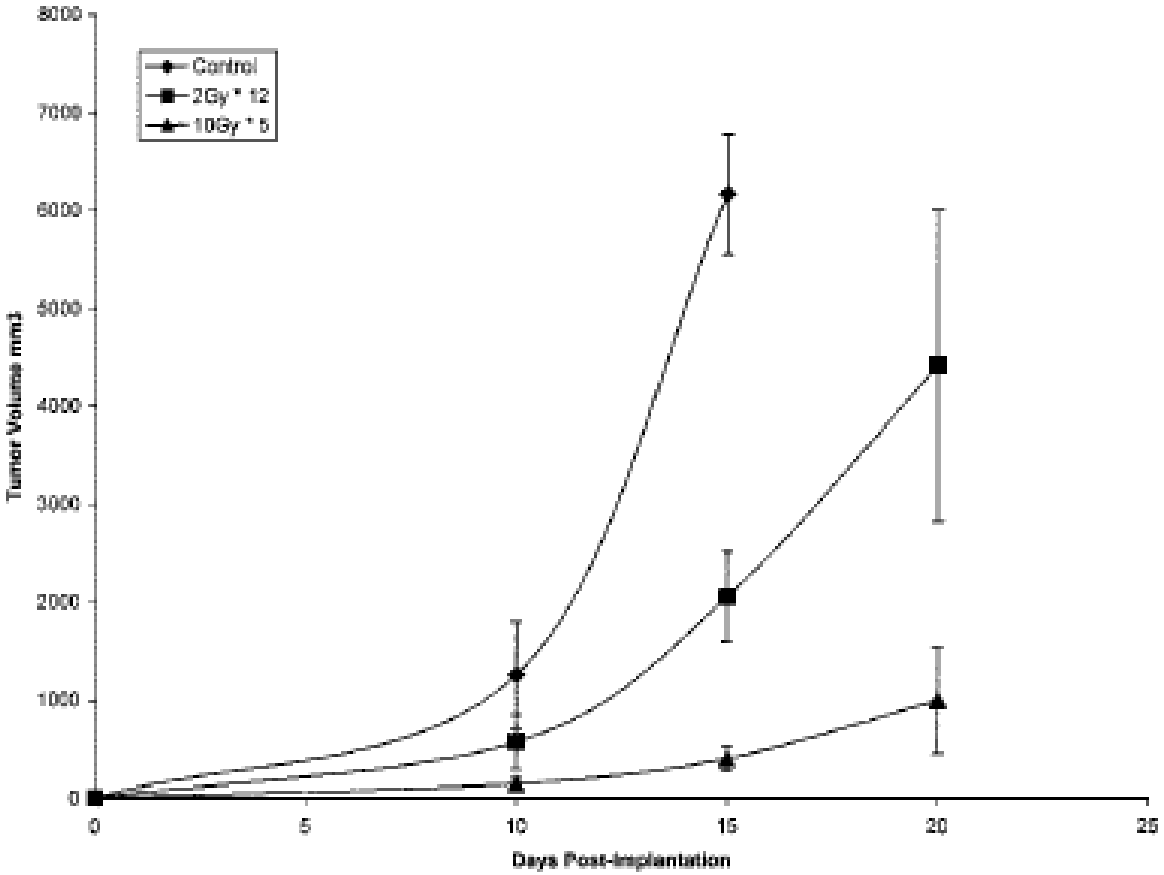


Fig. 1. The radiation abscopal effect is dose dependent. Five mice in each treatment group, 10 Gy * 5, and 2 Gy * 12, were irradiated, and the tumor was measured in each group, as well as the sham-irradiated group, and plotted *versus* days postimplantation. At 15 days, the abscopal effect is dose dependent.

Challenges

Immune-modulation of tumor microenvironment and tumor cells by radiation

- **Quality of radiation (high versus low-LET), dose, size, fractionation (low-dose versus high-dose fractionation) and dose-rate (high-dose rate versus low-dose rate), and schedule (hypofractionation versus multifractionation**

- **Irradiation of complete tumor volume or partial volume adequate for effective modulation of tumor immune microenvironment**
  - **Gross tumor volume (GTV) or GTV plus LN**
  - **Evoking it by irradiating normal tissue**

- **HLA class I loss or low TCR diversity or checkpoint expression or TILs.**

- **Balance between radio-induction of immune suppressive cytokines and radio-induction of immune activating cytokines**

Challenges

Effective combinations of radiation and immunotherapy

- **Relevant pre-clinical models (NSG-PDX, GEMMs and canine) or from clinical trials (reverse translational)**

- **Radiation effect on normal tissues and its impact on the efficacy of radiation + checkpoint blockade therapy**
  - **Efficacy area versus safety area**
  - **Use of traditional endpoints for safety and efficacy**

- **Significant challenges in the selection of opportune biomarkers of immunogenicity when radiation is combined with immunotherapy**

Thanks