Radiotherapy Combined with immunotherapy Hope or Hype?

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Cancer and the Immune System– To REMEMBER

- All Cells in The Body Can Communicate with the Immune System
- Immune Cells patrol the body and are continuously exposed to the environmental insults
- Something goes wrong– Immune system can Detect it
- Cancer Cells acquire aberrant features which can be detected by many immune cells that then react.

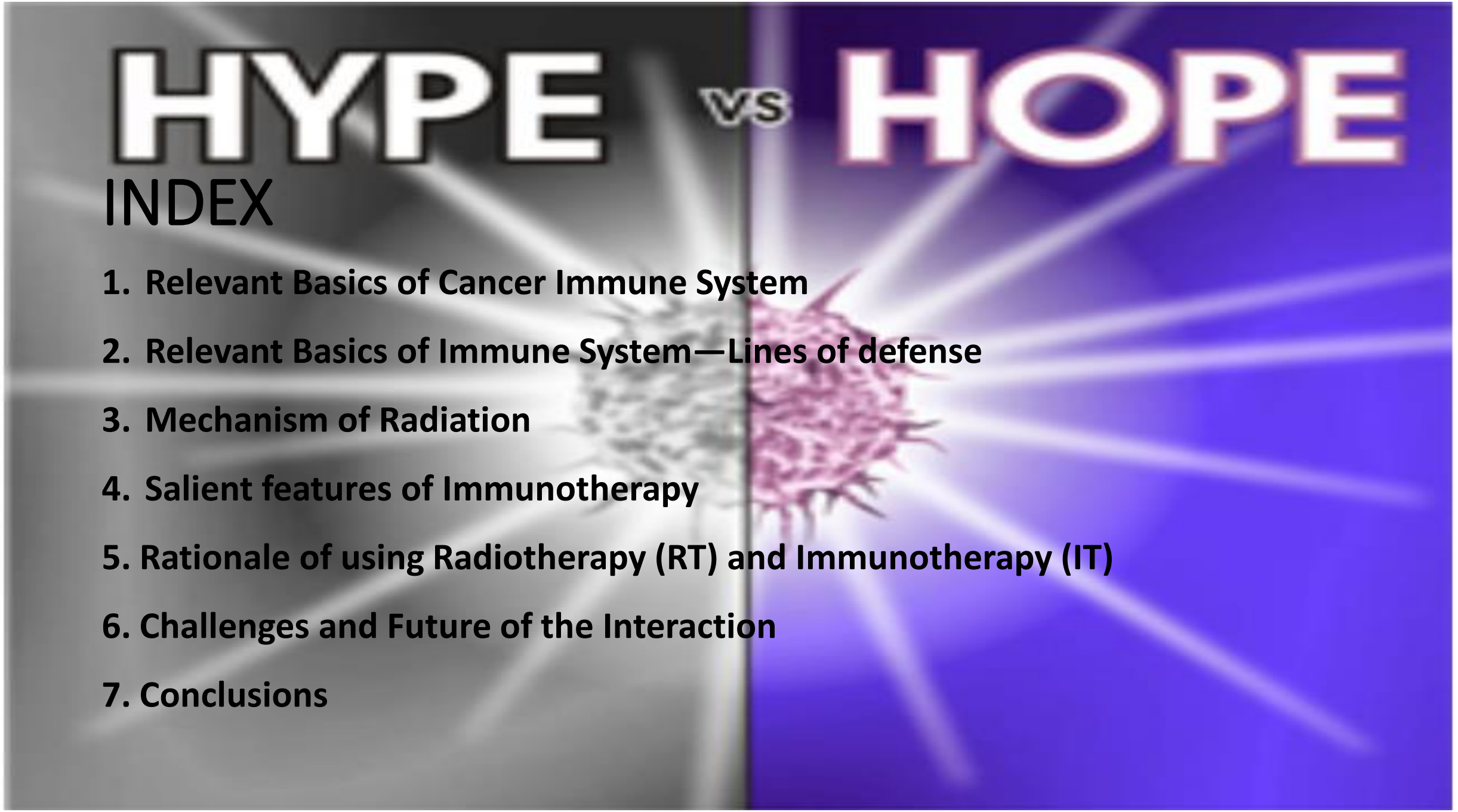
Janeways immunobiology

Background

- RT acts by direct tumour cytotoxicity and RT-induced DNA damage.
- RT is able to induce a local anti-tumour immune response, potentially leading to systemic anti- tumour immunity
- RT has both Immunomodulatory effects on the tumour microenvironment and also Immunosuppressive effects.

- Immune check point inhibitors (ICI) improve outcomes in many cancer types, but durable responses is rare

- **Immune effects of RT with ICI may potentially amplify anti-tumour immunity resulting in increased tumour responses.**



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What is Immunotherapy?

The NCI defines Immunotherapy as "***Treatment to boost or restore ability of immune system to fight cancer, infections and other disease***"

Tumour immunotherapy aims to augment the weak host immune response (active immunity) or to administer tumour specific antibodies or T cells, or form (passive immunity)

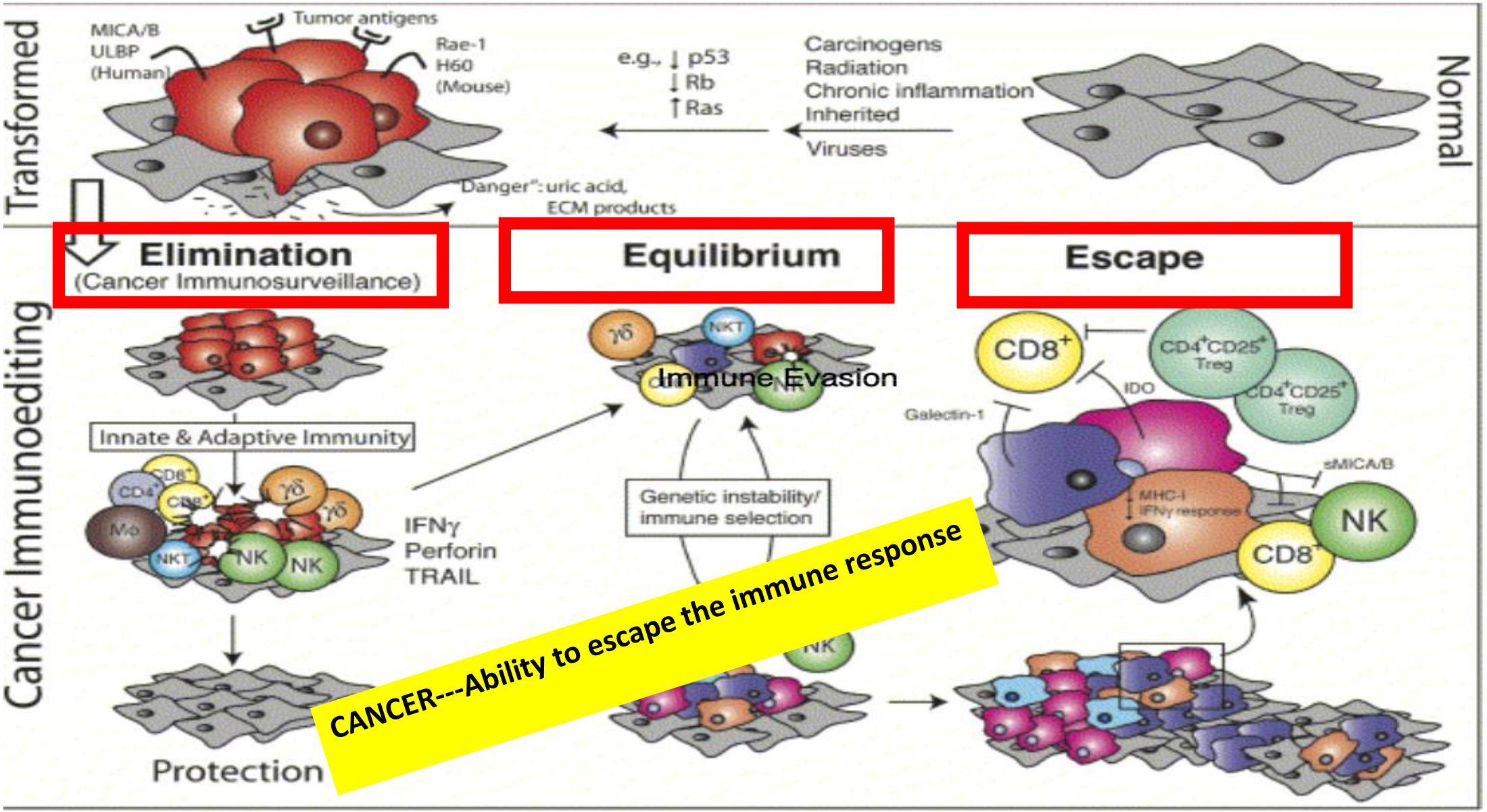
Evolution of Cancer--Tumor vs Host immune system

- **Immune elimination** --tumor cells are recognized and destroyed by the immune system
- **Immune equilibrium**,---- where tumor cells and immune system coexist.
- **Immune escape** --- Characterised by upregulated **inhibitory** ligands and **cytokines**, **reduced MHC class I** expression, and increased numbers of **myeloid-derived suppressor cells**

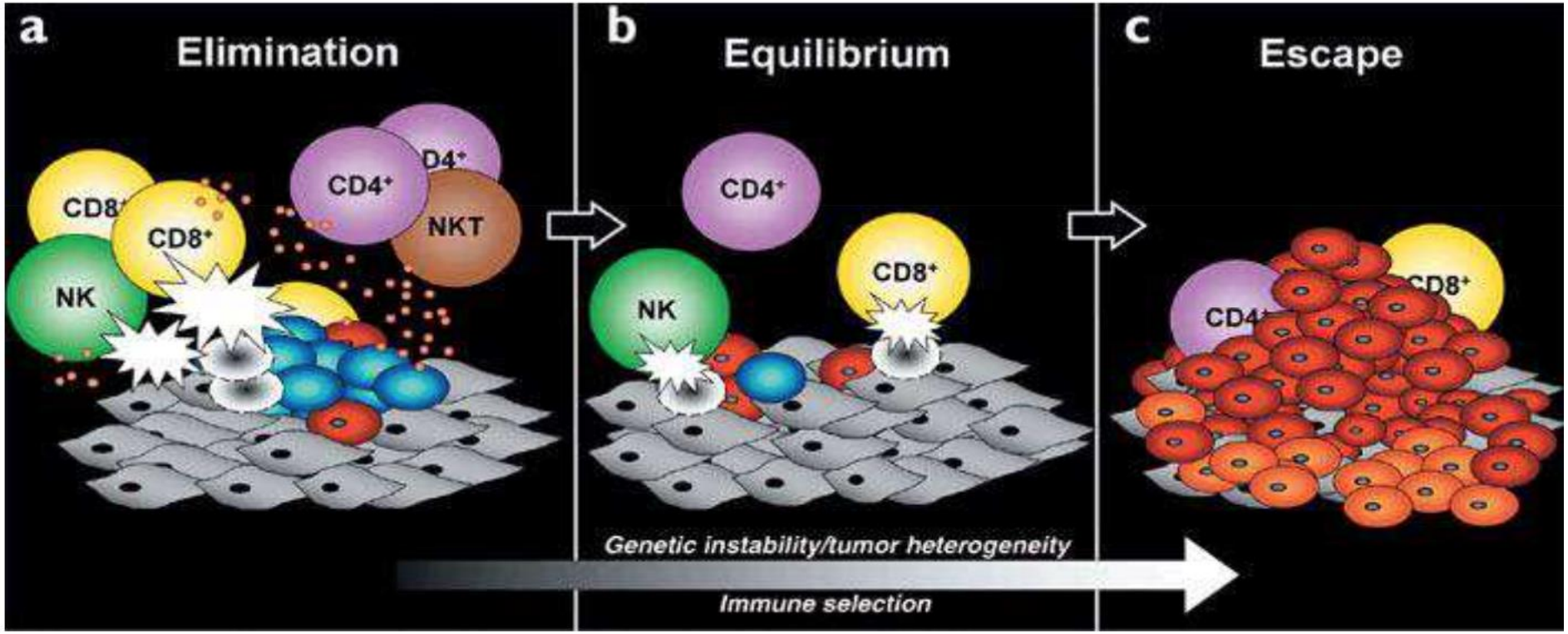
- ***CANCER---Ability to escape the immune response***

(Kalbasi et al., 2013)

Evolution of Cancer -Tumor and Host Immune system



Cancer and the Immune System: Evolving Cross-Talk



- **Cancer immune surveillance**:
  Immune system can recognize and destroy nascent transformed cells

- **Cancer Immunoediting**:
  Cancer cells acquire the ability to escape immune control before they develop into clinical cancer

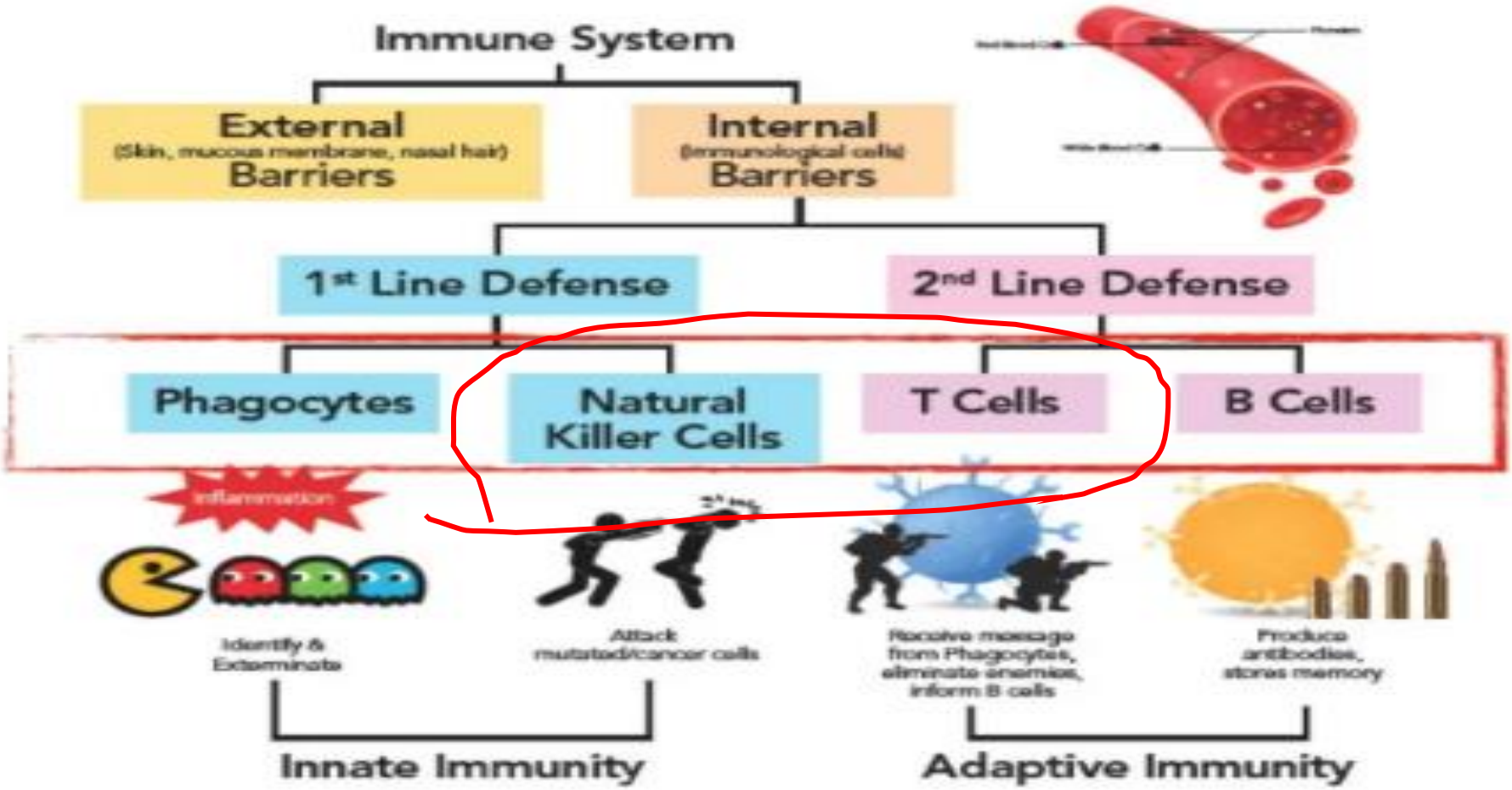
Cancer--------overall immunosuppressive environment

- Poor antigen presentation and
- Masks the tumor from immune surveillance and elimination

- Radiation may “unmask” the tumor, making it visible to both the innate and adaptive immune systems

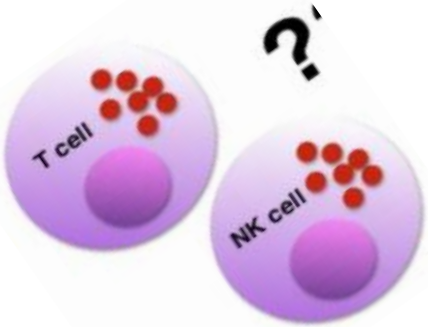
(Jiang et al., 2016).

The Immune System
Our Ultimate Line of Defence

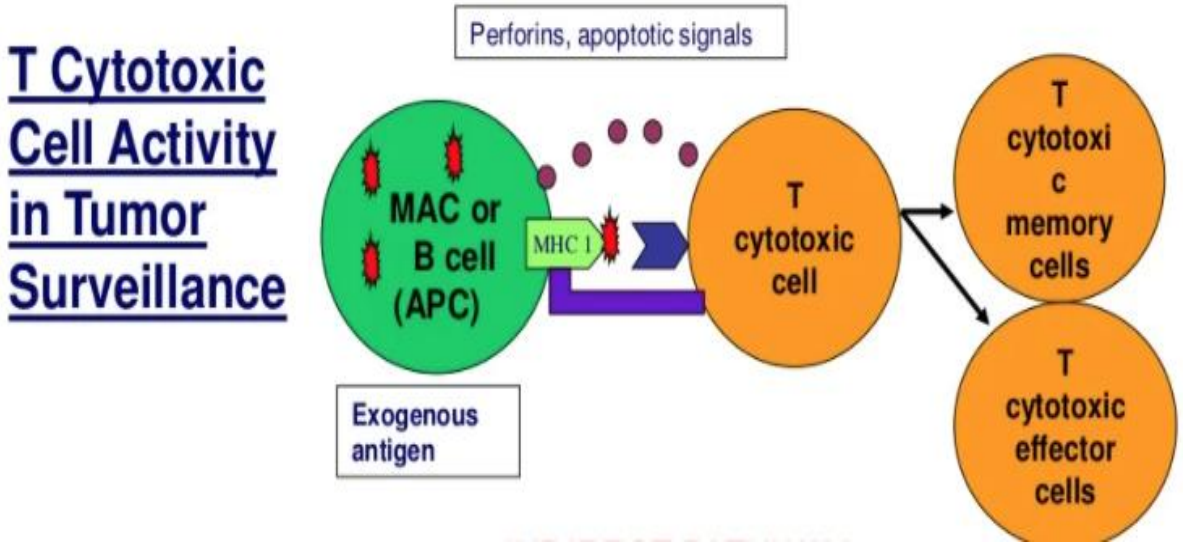


https://www.stemcellimmuneregenerative.com/what-is-the-immune-system

T and NK Cells

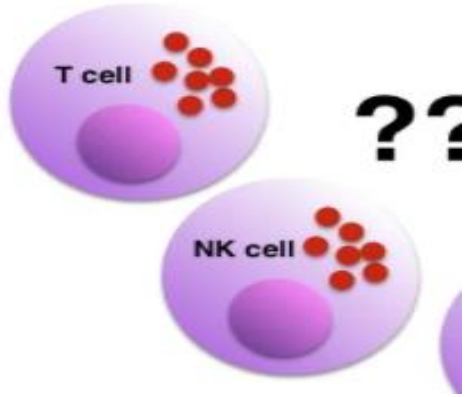


- Cytotoxic T cells (CTLs) CD8+ Cells--- Attach to Class I MHC- Peptide and destroy cancer cells by perforating the membrane with Enzymes or through apoptosis.



- Helper T cells----CD4+ cells—React to Class II MHC, secrete Cytokines

T and NK Cells



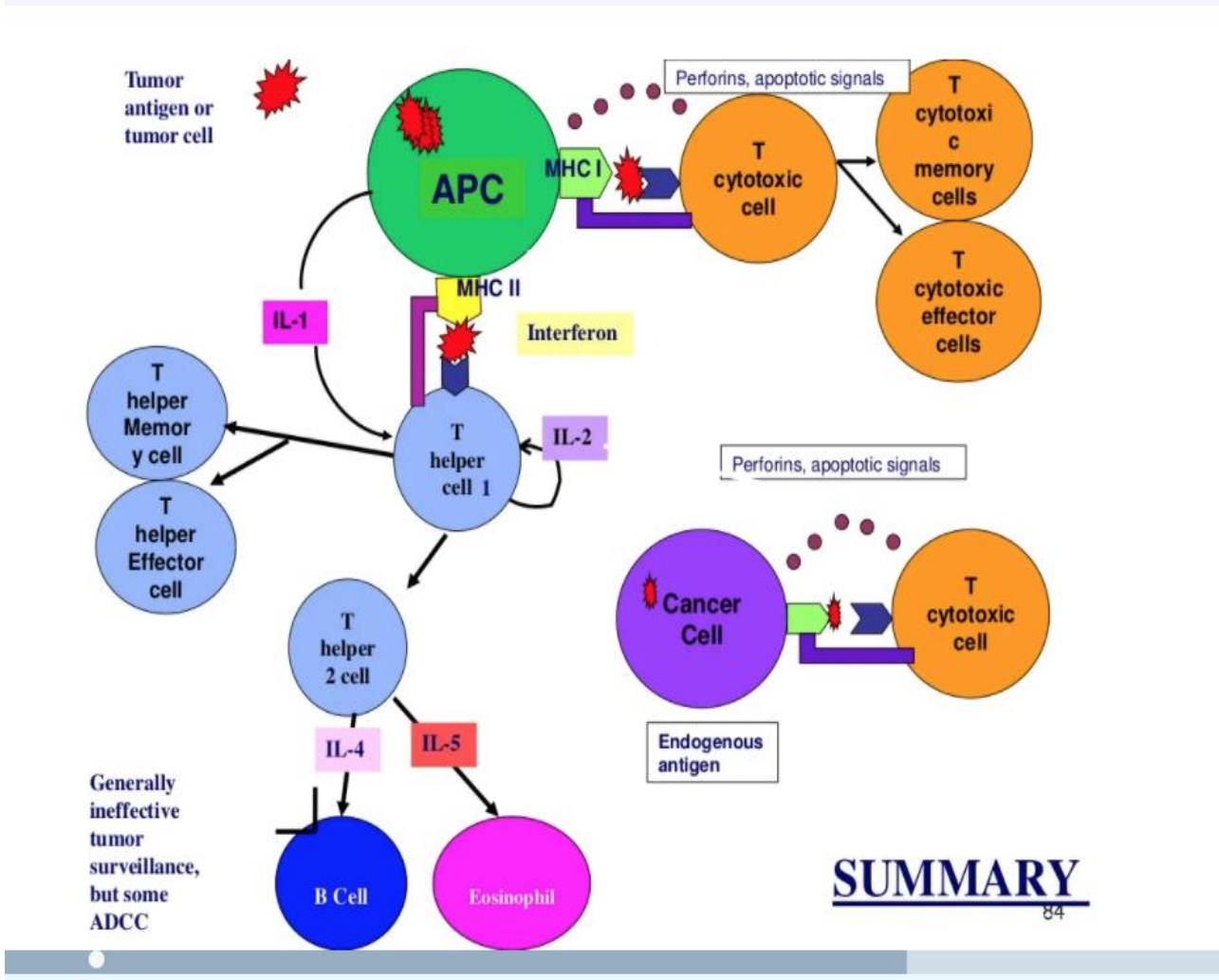
- NK Cells– Lymphocytes, that destroy tumour cells without prior sensitization

- Tumours that do not express MHC Class I Ag, cannot be recognized by T cells

- Such Tumours can Trigger NK cells since NK cells are inhibited by MHC Class I molecules

T cell Activation and Tumour suppression

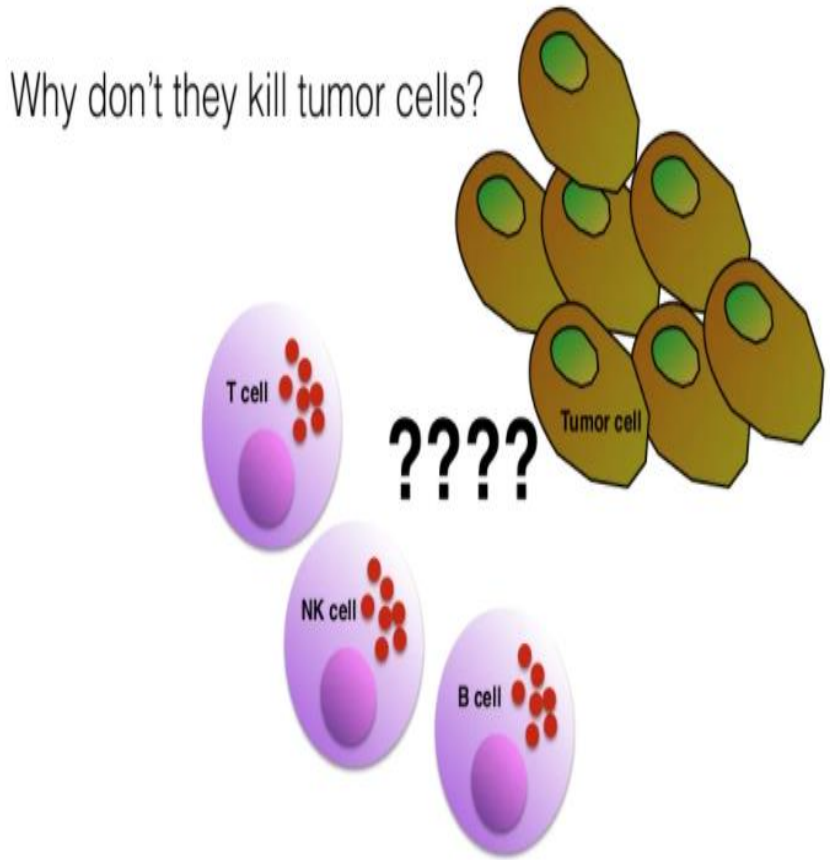
- APC process and engulf the tumor cells /foreign antigens
- Bind to Major histocompatibility complexes (MHC) molecules on APC surface.
- MHC molecules present the processed antigens to the T cells
- T cells interact with the complex and are then activated
- Release cytokines that kills cancer cells and release other immune cells



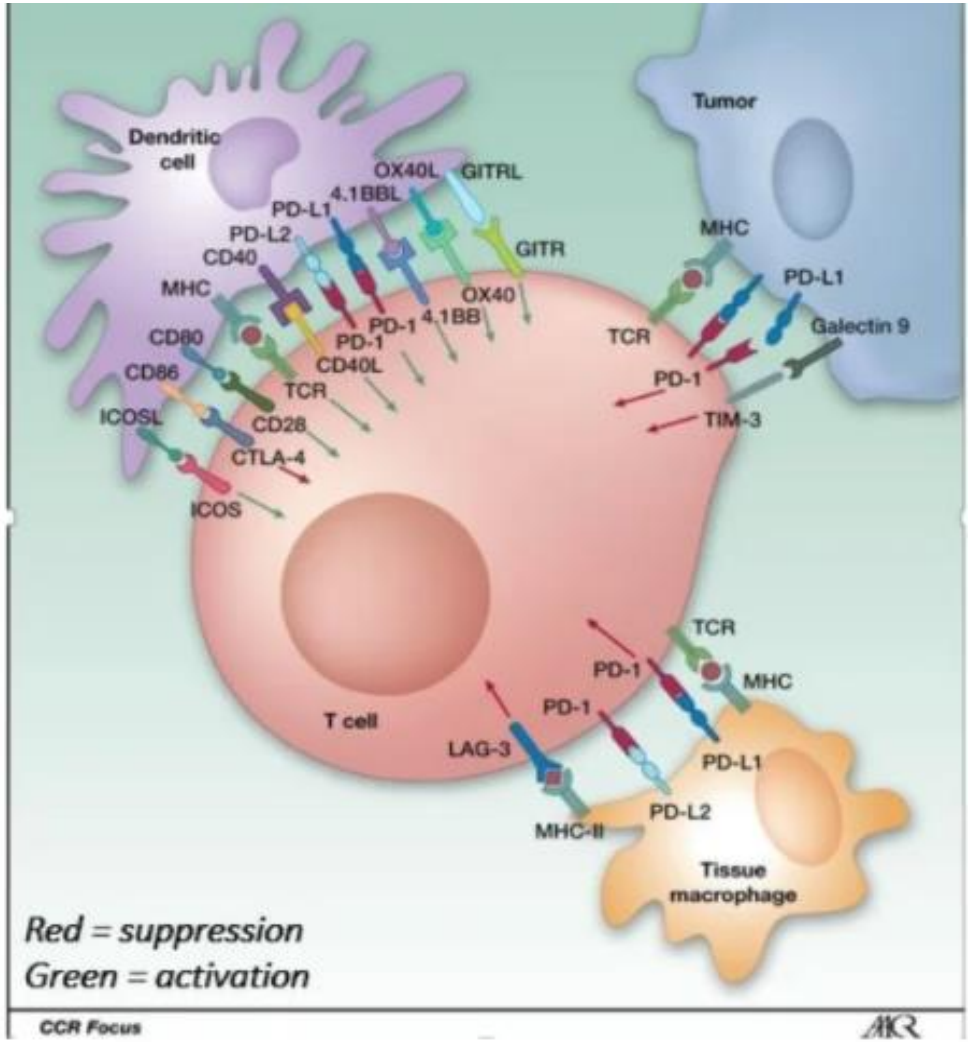
SUMMERY OF TUMOUR AND IMMUNE RESPONSE

- Line of Defense–

- **Phagocytes, T cells, NK Cells, B Cells**
- T and NK cells Specifically kill Tumour Cells
- Activated Macrophages kill tumour by production of reactive O2 metabolites or secretion of TNF
- T cells, NK cells and Macrophages collaborate because interferons-y (a cytokine secreted by T cells and NK cells) is a potent activator of macrophages
- Dendritic Cells are Ag presenting cells present in skin, LNs etc



- Activation of Immune cells including T cells is regulated by **POSITIVE** and **NEGATIVE** Signals
- **BALANCE** between them is important for auto immunity
- **Tumors** may exploit the **negative** signals provided by the the INHIBITORY CHECK POINT RECEPTORS to escape the Immune Response



Inhibitory Receptors Regulate Immune Cell Activation

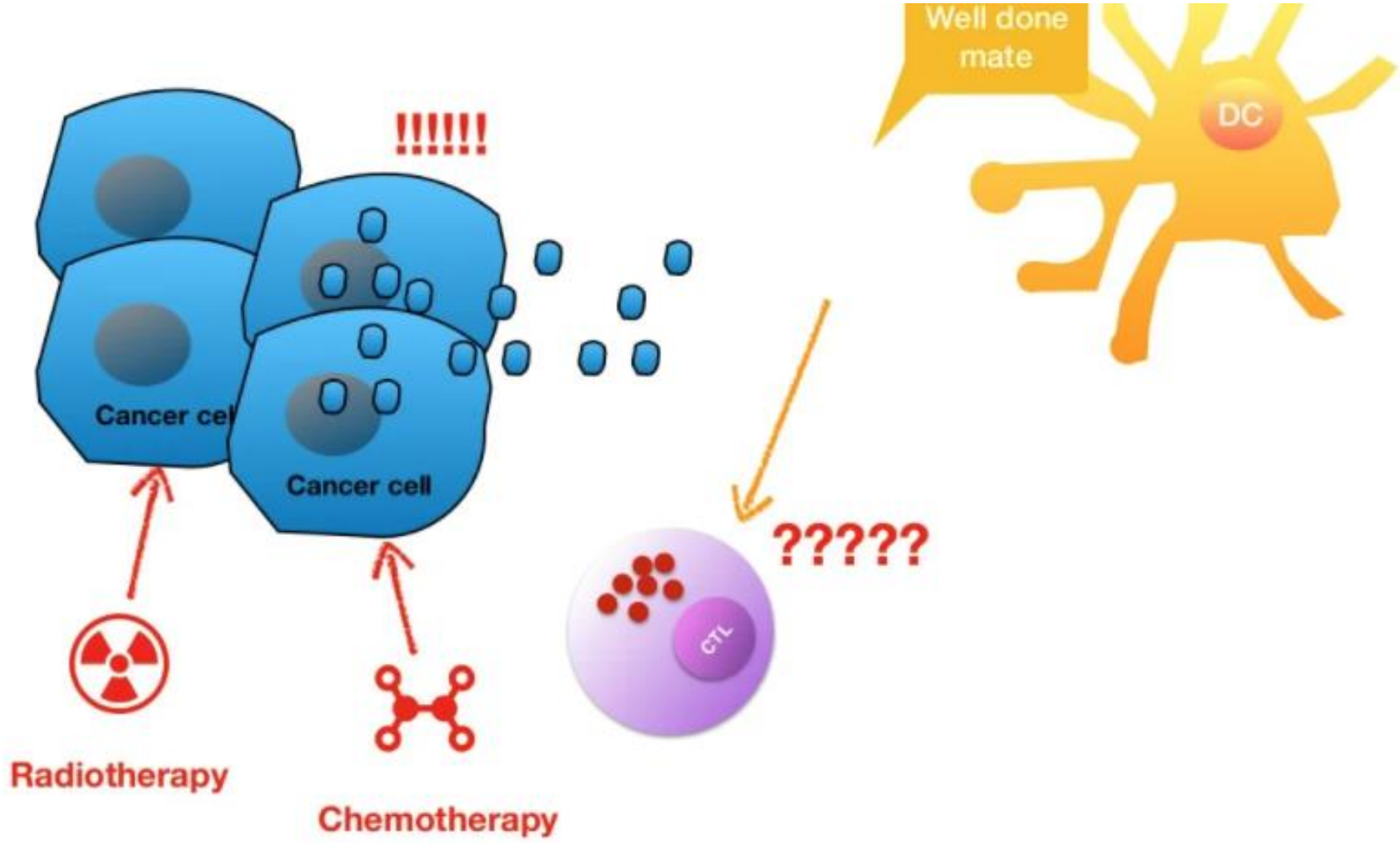
Inhibitory receptors regulate immune cell activation

- T cells and NK cells Kill Tumour Cells
- These are Inhibited by Check point Receptors
- HENCE Check Point Blockade removes Breaks from The immune system

and reactivate Immune cells against Cancer

The 2018 Nobel Prize for Physiology was awarded to James Allison and Tasuku Honjo for this discovery that-
there was a negative immune regulatory system that could itself be inhibited through PD-1 and PD-L1 modulation

Traditional Cancer Treatments Activate Immune System



MECHANISTIC RATIONALE OF RADIATION

Radiation affects both tumor cells and surrounding stromal cells.

- **DNA DAMAGE MEDIATED---Local Effect**

makes tumor-specific antigens visible to immune surveillance and promotes the priming and activation of cytotoxic T cells.

- **Modifies Tumor Stromal Microenvironments (TME)—Systemic Effect**

facilitate the recruitment and infiltration of immune cells.

Wang Y, (2018) Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Front. Pharmacol. 9:185. doi: 10.3389/fphar.2018.00185

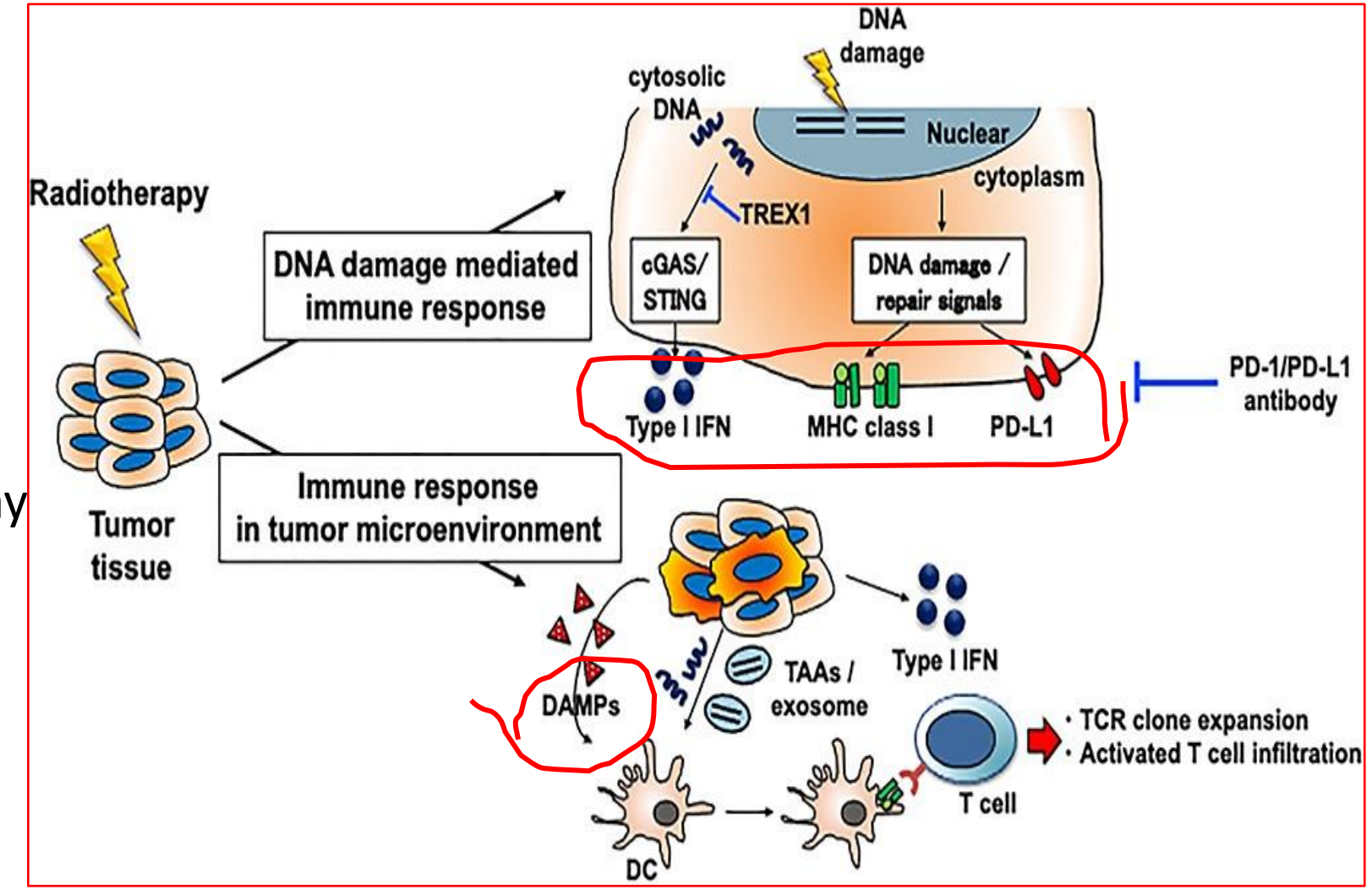
MECHANISTIC RATIONALE OF RADIATION

- **DNA DAMAGE MEDIATED**
- **Local Effect**

✓ Increases Antigen Visibility

✓ Activates cGAS-STING Pathway

- **Modifies Tumor Stromal Microenvironments (TME)**
- **Systemic Effect**



Jpn J Clin Oncol, Volume 51, Issue 4, April 2021, Pages 513–522, https://doi.org/10.1093/jjco/hyaa268

MECHANISTIC RATIONALE OF RADIATION

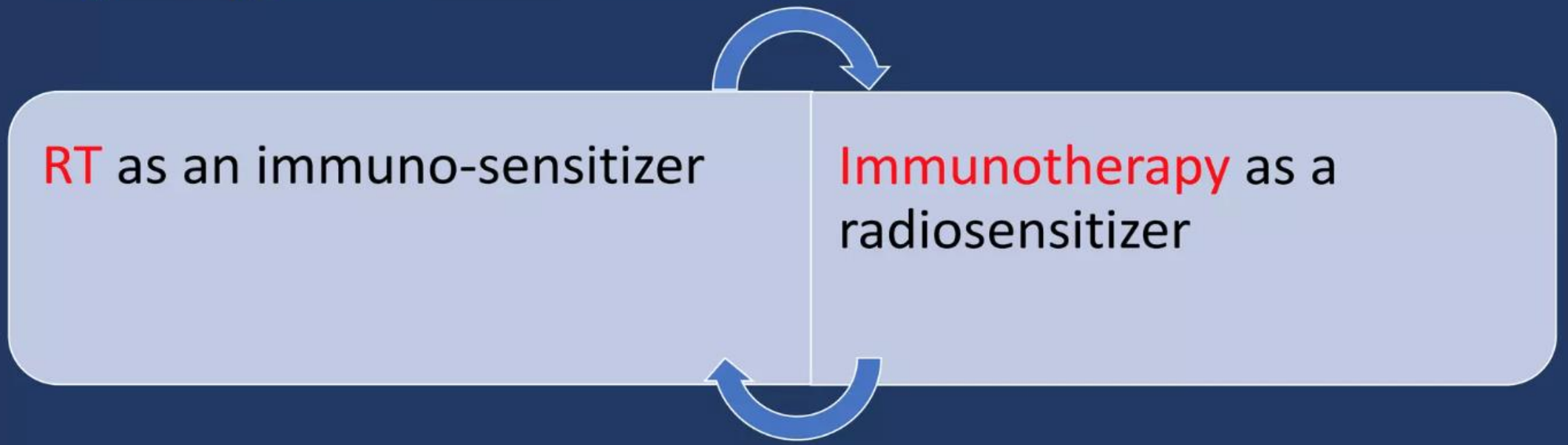
- DNA damage generate Tumour and **neoantigen** and trigger the immune surveillance
- Upregulates expression of **MHC-I** on the tumor surface & better presentation of tumor-specific peptides
- Clearance of damaged tumor cells by the antigen-presenting cells, -- promoting priming of T cells.

- cGAS/STING pathway induces **IFN-I & dendritic cell** migration and cross-priming of T cells,--- required for the antitumor effect of radiotherapy

- Induce systemic increase in **T cell-mediated** inhibition of untreated distant tumors (abscopal effect)

(Reits et al., 2006)
(Demaria et al., 2004).

Synergistic relationship



Synergy 1 : RT works as **in-situ vaccine** to enhance immune control of distant disease (Ab-scopal effect)

Synergy 2 : RT induces changes in the TME, allowing **for immune-mediated clearance of residual local disease**

in situ vaccine”

- Irradiation triggers immunogenic cell death (ICD) by inducing DNA damage
- Subsequent release of damage-associated molecular patterns (DAMPs) from tumour cells,
- Turns tumour cells into an “in situ vaccine”
- **DAMP signals** enhance the function of DCs.
- **Calreticulin** is translocated to the surface of dying cells , promoting phagocytosis
- The cGas/STING cascade is negatively regulated by protective DNA damage **response (DDR) pathways**.

Rationale For Combination of RT and IT

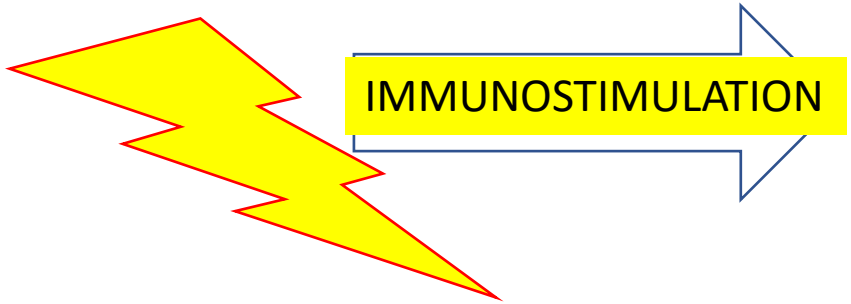
IMMUNOSUPRESSION

IMMUNOSTIMULATION

ABSCOPAL EFFECT

Wang Y, (2018) Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Front. Pharmacol. 9:185. doi: 10.3389/fphar.2018.00185

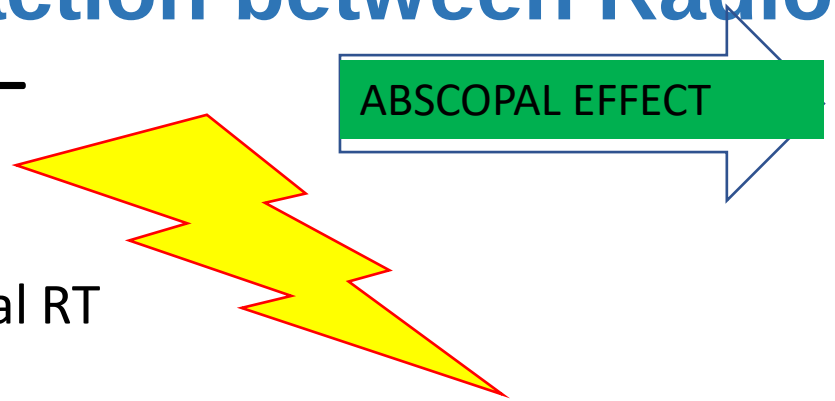
Interaction between Radiotherapy (RT) & Immunotherapy (IT). —



- Radiation affects both tumor cells and surrounding stromal cells.
- **Local effects** result from direct damage to cancer cells exposes tumor-specific antigens, causing cell death from triggering activation of CD8+ T cells
- **Systemic immune response** triggered by radiation-induced micro environmental changes facilitating recruitment and infiltration of immune cells.

(Lee et al., 2009).
(Jiang et al., 2016).

Interaction between Radiotherapy (RT) & Immunotherapy (IT). —



1953– R H Mole

Ab— Position away from
Scopos---A target for shooting at

Local RT

↓

Induces a systemic increase in antigen recognition

↓

Cell death and release of immunogenic factors

↓

Release of endogenous Damage Associated Molecular factors (calreticulin,HMGB1,ATP)

↓

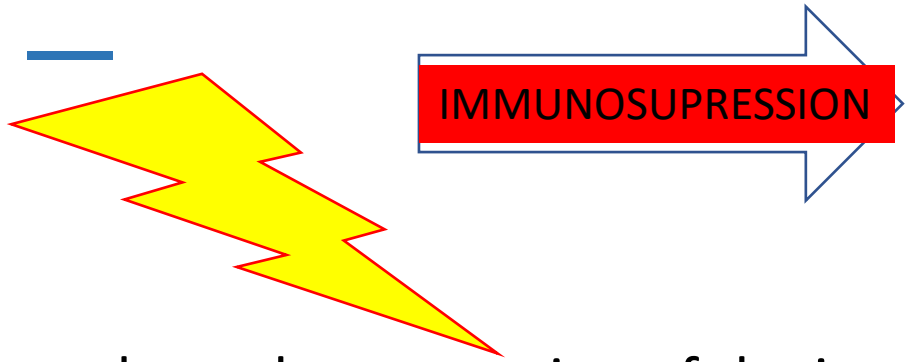
Triggers Dendritic Cells---improved Ag presentation to T cells

↓

Tumour specific T cell Response (Anti tumour response) outside field of RT

(Demaria et al., 2004).

Interaction between Radiotherapy (RT) & Immunotherapy (IT). —



- RT upregulates the expression of the immune checkpoint **PD-L1** limiting the activation of tumour T cells.

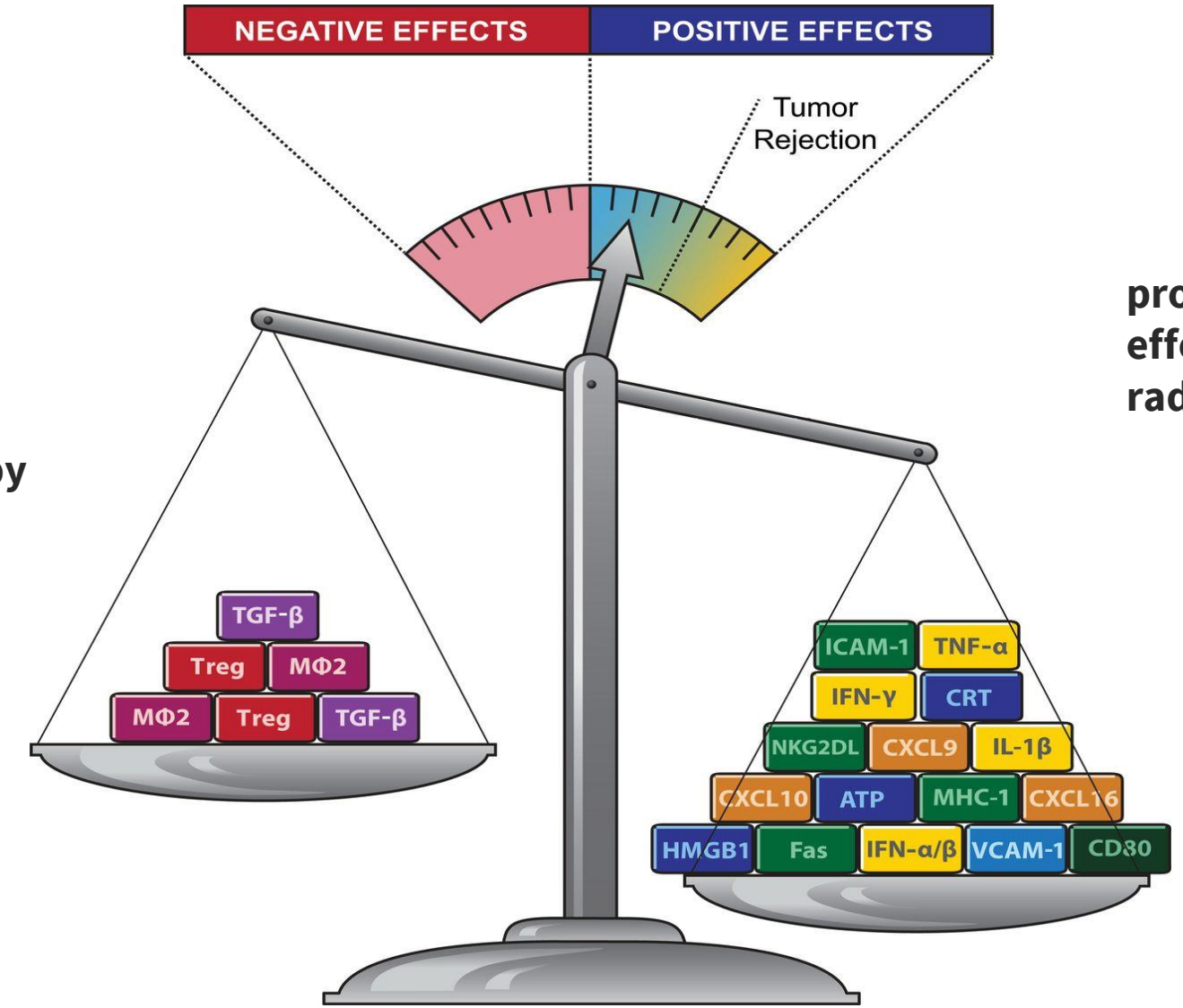
- RT enhance release of immunosuppressive cytokines such as transforming growth factor beta **(TGF-b)** in the tumour environment.

- RT induce STING and type I interferon activation, recruits **myeloid-derived suppressor cells** to the irradiated tumor through the CCR2 pathway

(Dahmani and Delisle, 2018). (Liang et al., 2017)
M. Mondini et al.
Combination of radiotherapy and immunotherapy

Balance Between Proimmunogenic And Immunosuppressive Effects Of Radiotherapy

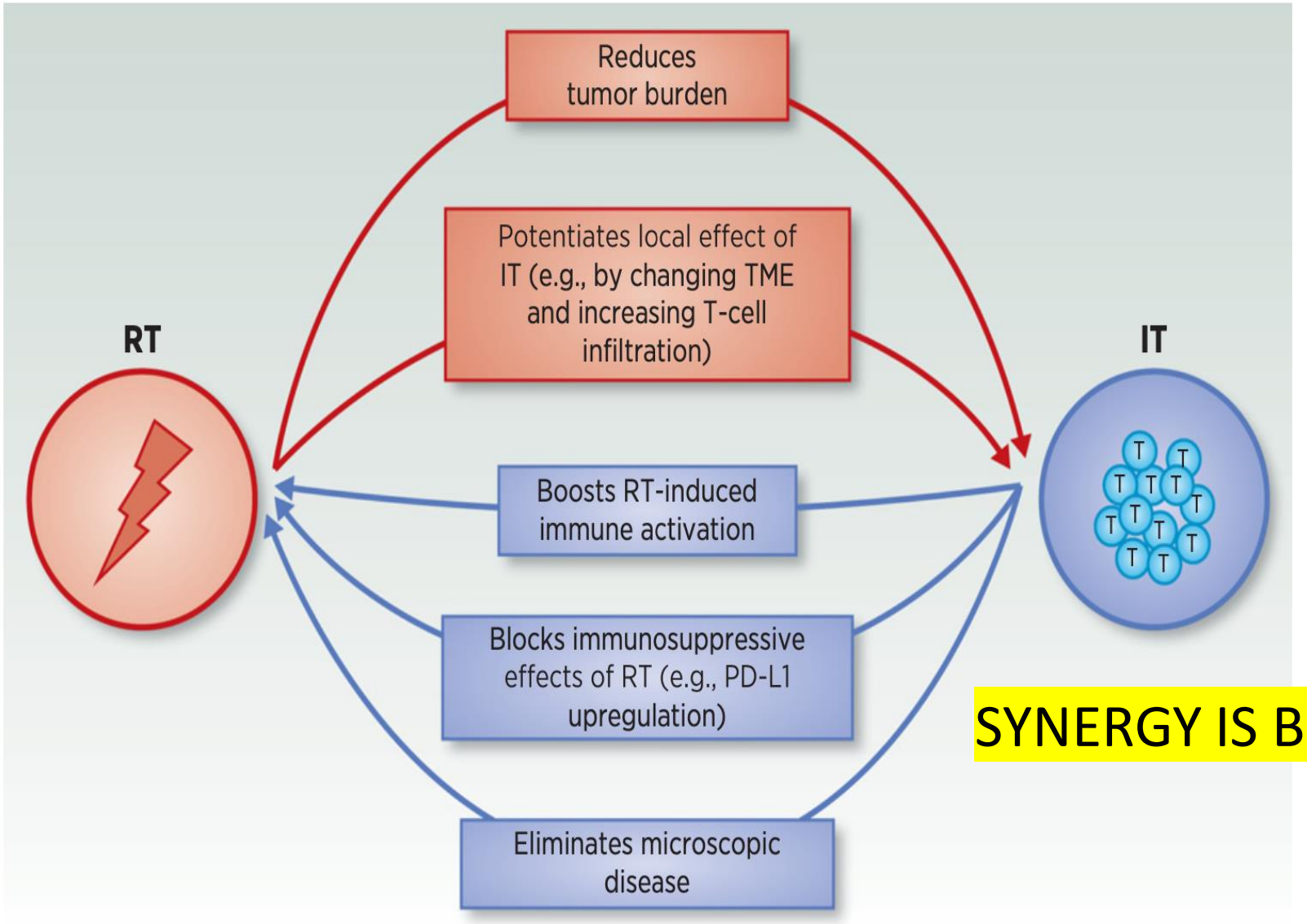
immunosuppressive effects of radiotherapy



proimmunogenic effects of radiotherapy

J Natl Cancer Inst, Volume 105, Issue 4, 20 February 2013, Pages 256–265, https://doi.org/10.1093/jnci/djs629

Interaction between Radiotherapy (RT) & Immunotherapy (IT).



Red arrows -- RT help IT to greater tumor control;

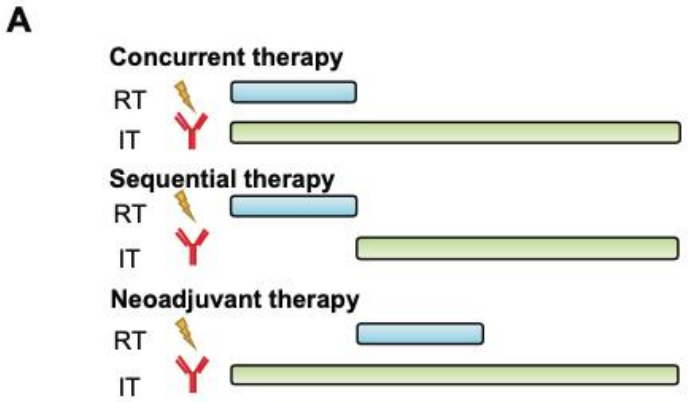
Blue arrows -- IT help RT .

TME, tumor microenvironment.

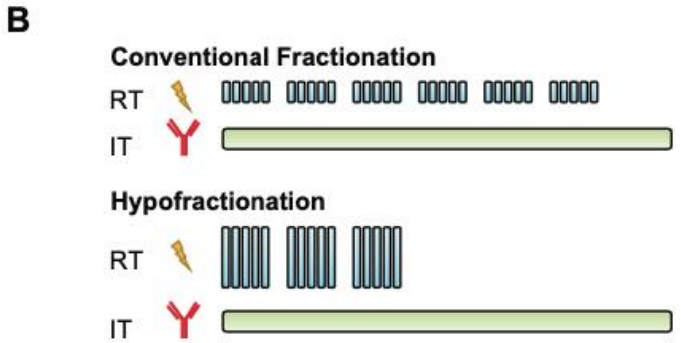
SYNERGY IS BIDIRECTIONAL

Clin Cancer Res; 26(12) June 15, 2020

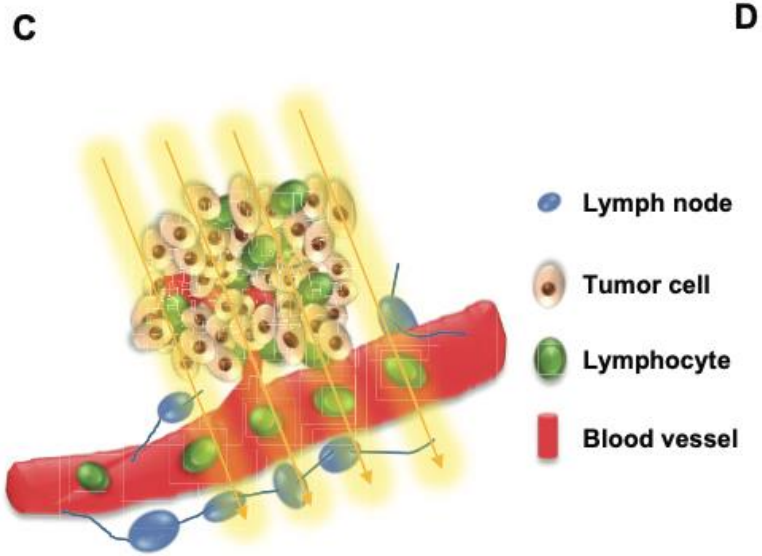
Challenges in Radiation and Immunotherapy



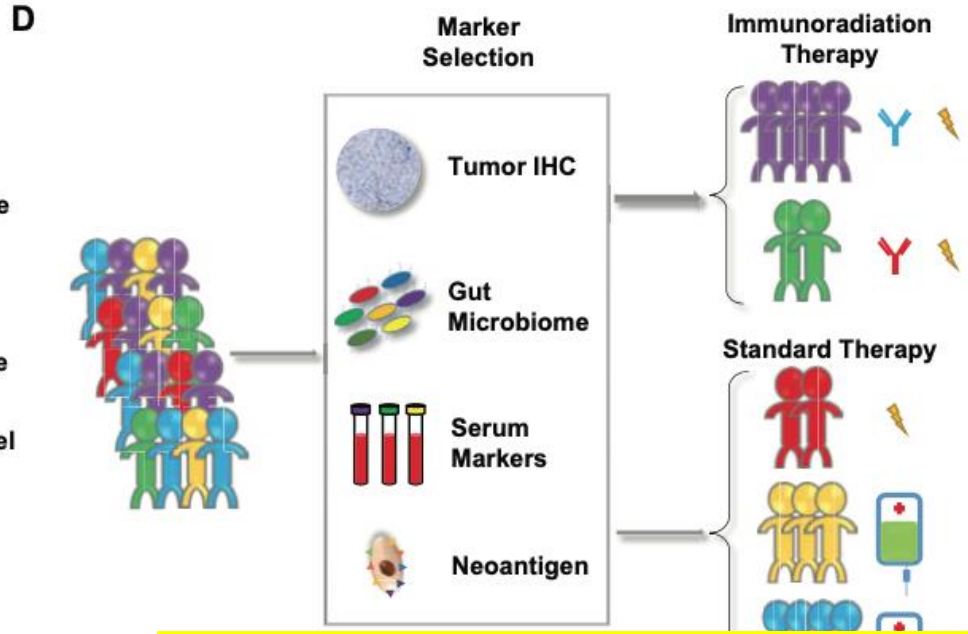
Optimization of treatment timing:



Optimization of radiation dosing:

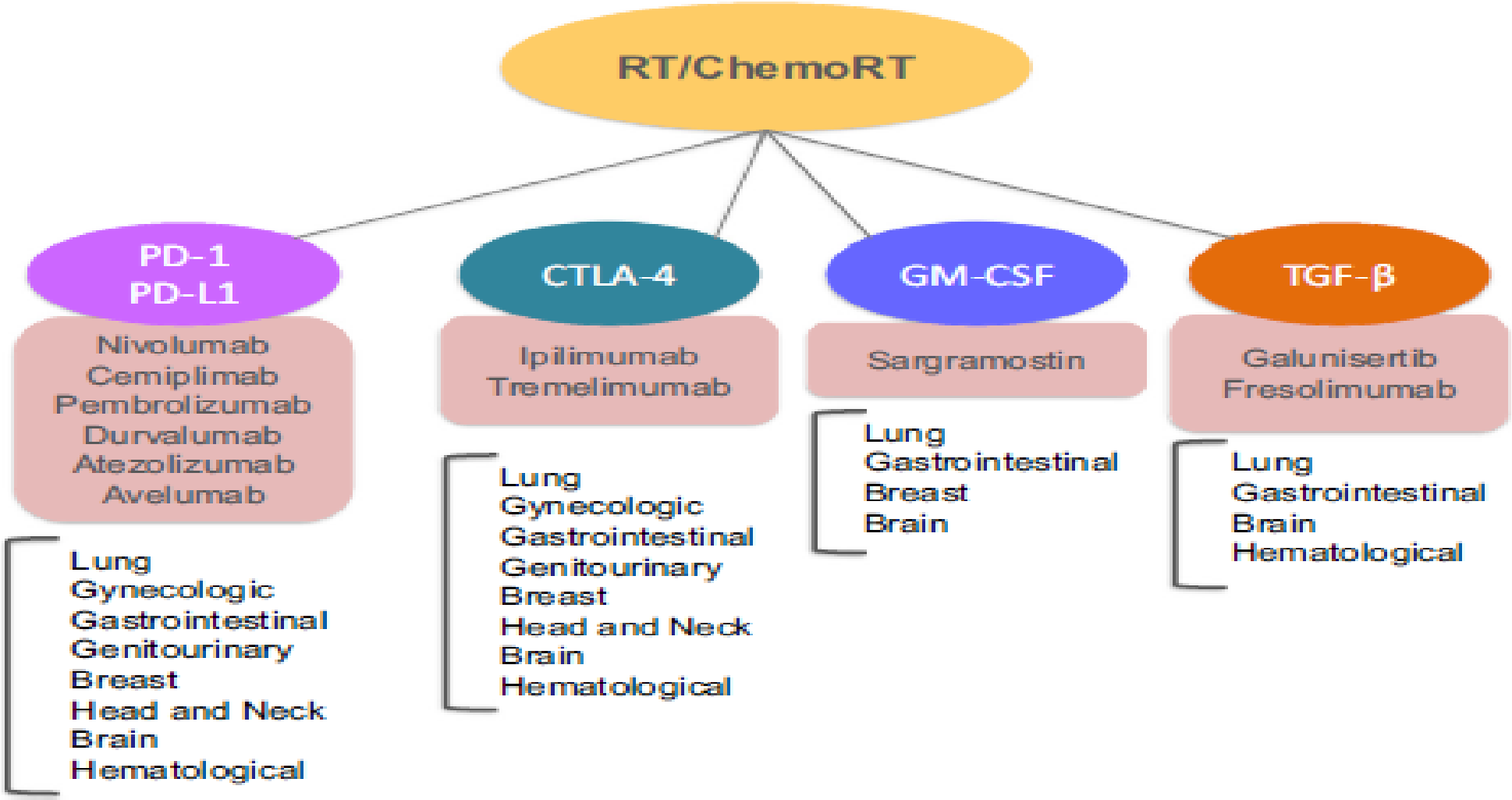


Reduction of the radiation-induced toxicity of circulating and tumor-infiltrated lymphocytes.



Selection of immunoradiation therapy or standard therapy for patients based on predictive biomarkers.

Immunomodulators used combination with radiotherapy/ chemoradiotherapy.



Combination Of Radiotherapy & Immune Therapeutics

- **Anti-CTLA4** (Cytotoxic T Lymphocyte Associated Protein 4) with RT ----among the first
- **Immune checkpoint inhibitors (ICI)** with RT can unleash the potential of the T-cell compartment
- **Anti-PD-1/PD-L1- PDL1** expression is increased after RT, (Shevtsov et al.,2019).
- **Additional immunomodulators** being tested -- anti- TIM-3 or anti-LAG-3.
- **CoStimulatory** molecules of T cell –Anti OX-40 or CD-40.
- **Modulation of TME** , such as targeting TGF-b, chemo-attractive axes such as that of CCL2/CCR2.
- **Increasing antigen presentation** as agonists of Toll-like receptors or at boosting the RT-induced interferon response using modulators of the cGAS/STING pathway

Optimizing the Timing of Radiotherapy and Immunotherapy

- Aim – Maximum synergistic effects
- Trials suggest that optimal timing is tumor-type and immunotherapy-specific.
- Anti-CTLA4 work most effectively when given before radiation
- Anti-OX40 was more effective when given 1 day after the radiation (Young et al., 2016).
- Concurrent immunotherapy with Anti-PDL1 and Anti-CTLA4 given within 4 weeks of stereotactic radiosurgery led to improved response of brain lesions relative to treatments that were separated by more than 4 weeks (Qian et al.,2016).

KEYNOTE-001 trial (NCT01295827)

- The secondary analysis of the showed the NSCLC patients who received radiotherapy before pembrolizumab (anti-PD1) had better OS and PFS compared with those who did not receive radiotherapy (Shaverdian et al., 2017),
- Suggested radiation may enhance the efficacy of immunotherapy.

PACIFIC trial (Antonia et al., 2017)

- Phase III randomized trial
- Role of the PDL1 antibody durvalumab vs. placebo as consolidation therapy after chemoradiation for stage III non-small cell lung cancer (NSCLC)
- Substantial improvement in PFS with durvalumab (16.8 months vs. 5.6 months with placebo), with similar side effects
- Starting durvalumab **within 14 days** after completing chemoradiotherapy appeared to have greater PFS efficacy than if durvalumab were started after 14 days.

Dose, Fractionation, Volume Of Radiation

Dose and fractions of RT play critical role in immunomodulation of TME.

FRACTIONATION induces expansion of unique immune populations, --

- Standard fractionation INCREASES a **Myeloid response**

- Hypofractionation increase a **Lymphoid response** –

  (more favorable to adaptive antitumor immunity)

- Extreme HYPOFRACTIONATION (20–30 Gy in 1 fraction) ----

  Induce DNA exonuclease **Trex1** to stop cGAS-STING pathway activation, and blocks immunogenicity

(Vanpouille-Box et al., 2017; Ye and Formenti, 2017).
A promising new combination. J Immunother Cancer 2019;7:160.

Dose, fractionation, volume of radiation

- Unclear whether single high-doses or fractionated low-doses would better complement ICIs
- High-doses of 12–16 Gy/ single fraction induce protective DDR pathways within the tumour → **hinder T-cell response**.
- Lower doses shown to optimally induce the production of **IFNβ required for DC activation**

- Both High-dose RT (12 or 20 Gy) and fractionated low doses, **increase PD-L1** expression on tumour cells, → anti-PD1 treatment induce successful tumour control

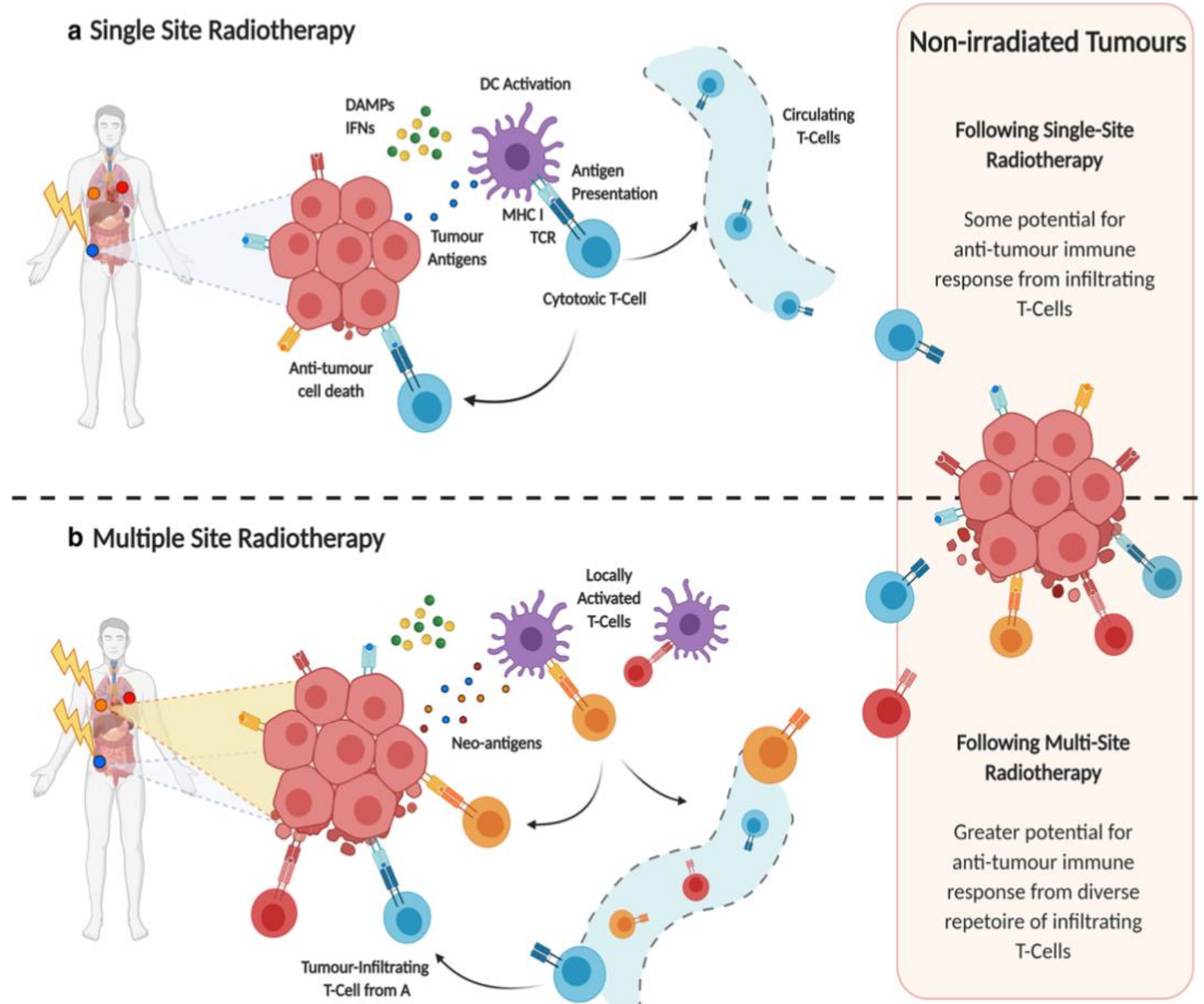
RT Single or Multiple sites?

- Unclear
- **IFNγ**, is found at greater levels within the irradiated tumour than at secondary sites,
- **IFNγ** mediates T-cell survival post RT,  targeting multiple tumour sites could increase immune responses
- Multi-site irradiation may improve therapeutic outcomes by reducing disease burden and also by increasing RT-induced immune stimulation.

- Increasing **RT target volume** to reduce disease burden and increase immune infiltration may therefore enhance the efficacy of IO agents

Nat Commun. 2019;10(1):3959.

RT Single or Multiple sites?



RT delivered to multiple sites may increase the quantity and diversity of migrating T-cells, enhancing the potential for systemic immune responses at non-irradiated sites

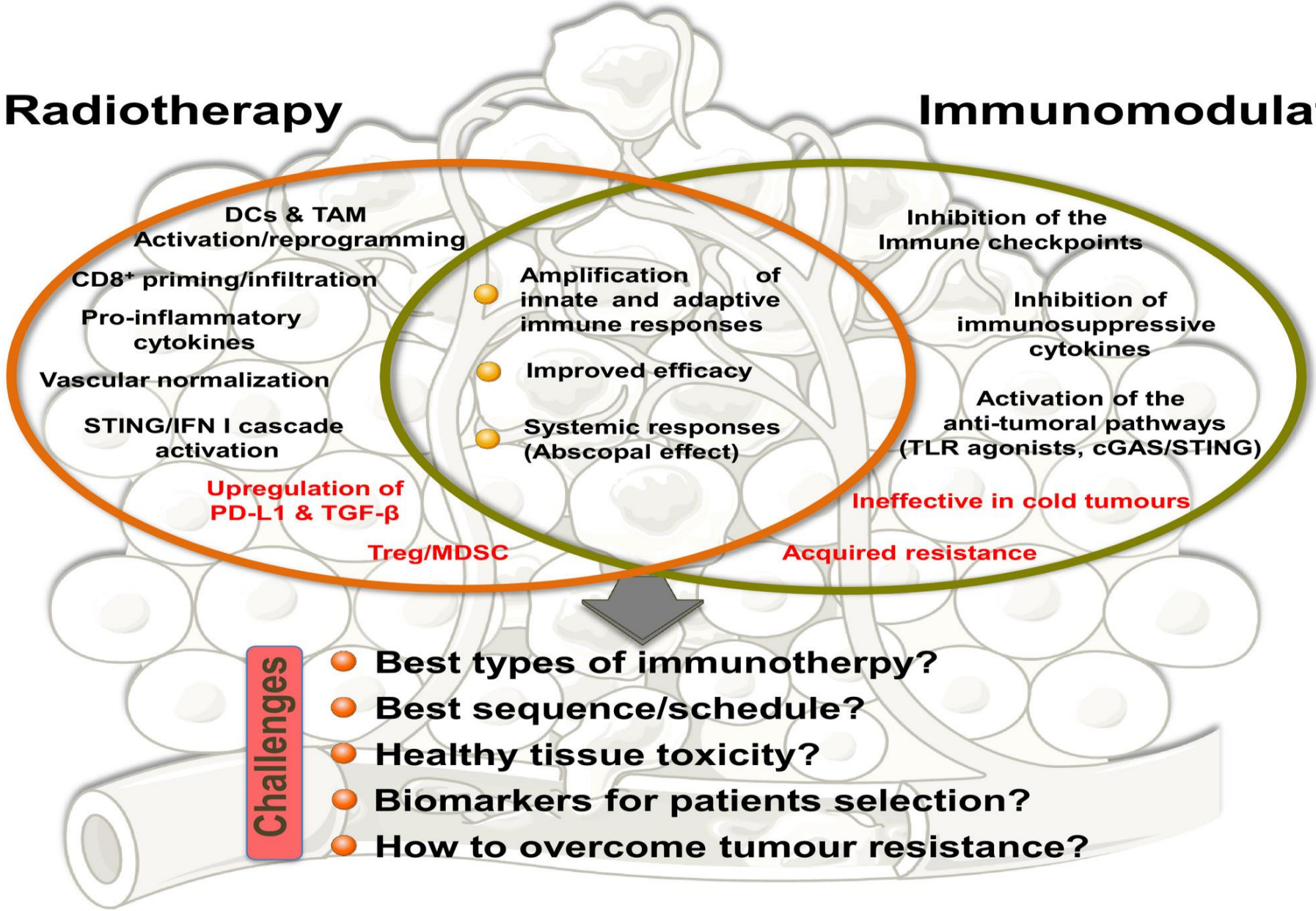
Immunoradiotherapy and normal tissue toxicity

- Some of the non-tumor-specific antigens might prime auto-reactive T cells which will attack and damage normal tissues.

- Recent retrospective studies indicate the adverse events were increased when immunotherapies were combined with EGFR-TKI for NSCLC

(Tang et al., 2018)
(Oshima et al., 2018

Radiotherapy–immunotherapy – perspectives and challenges



Molecular Oncology, Volume: 14, Issue: 7, Pages: 1529-1537, First published: 28 February 2020, DOI: (10.1002/1878-0261.12658)

Conclusion

- RT acts by cytotoxic DNA damage with Tumour cell kill
- RT induces ‘immunogenic cell death’ (ICD), a type of cell death that promotes a T- cell-mediated immune response against antigens derived from dying cells
- Radiation synergize with immunotherapy via several mechanisms, such as

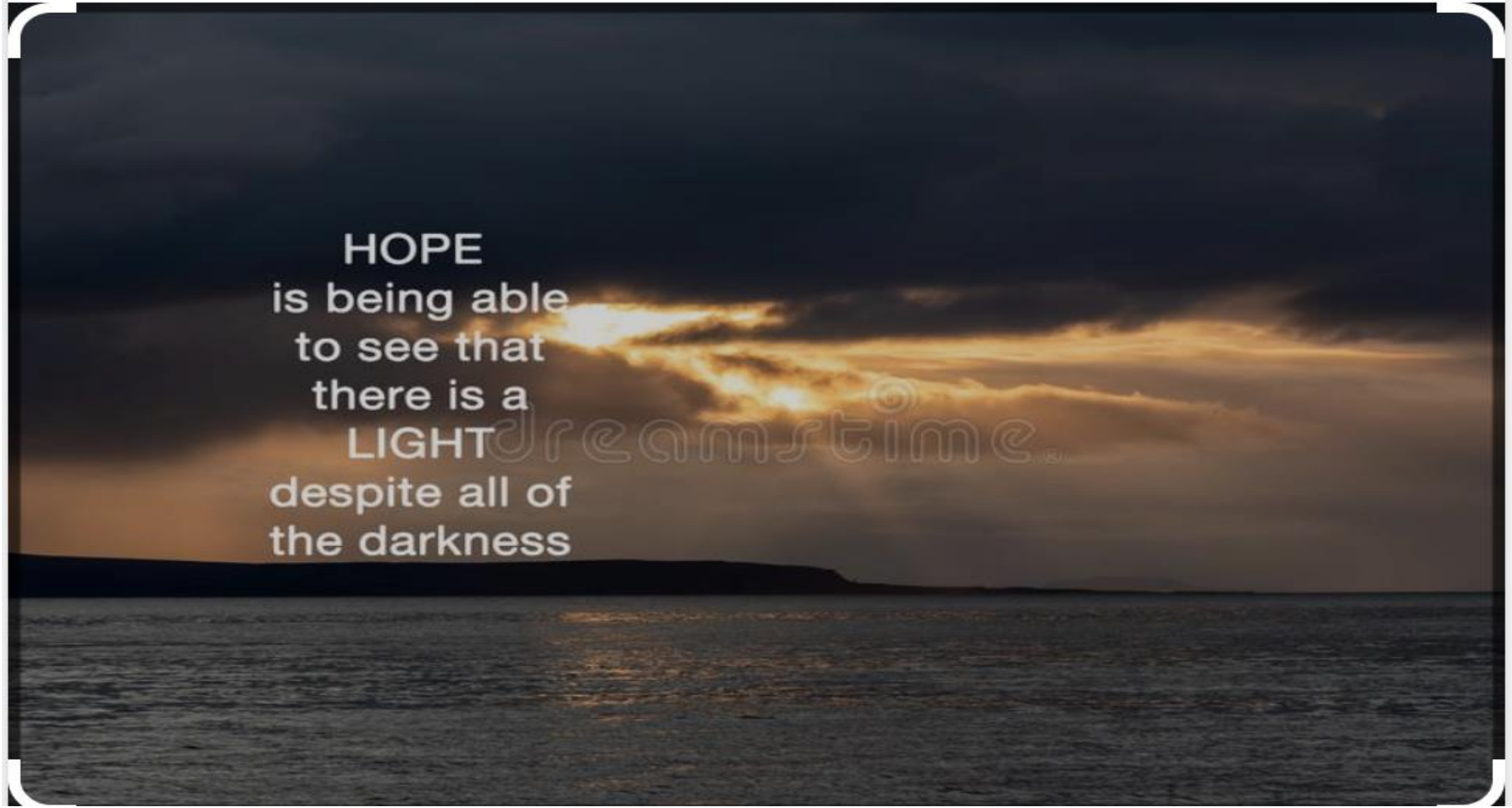
  increasing the visibility of tumor antigens,

  activating the cGAS-STING pathway, and

  modulating the tumor microenvironment.
- RT can assist IT by enhancing immune activation both systemically and locally
- IT can enhance the immune response induced by local RT.
- **Future Directions-**-Optimizing the Timing and dose of Radiotherapy and Immunotherapy

FUTURE DIRECTIONS

- Optimizing the Timing of Radiotherapy and Immunotherapy
- Optimizing the Dose of Radiotherapy: Conventional or Hypofractionation
- Minimizing the Direct Effects of Radiation on T Cells
- Because most immunotherapies depend on functioning T cells, lymphopenia is likely to undermine immunotherapy efficacy.
- Identifying Biomarkers to Predict Responders to Combination Therapy
- COULD IMMUNOTHERAPY BE A RADIATION SENSITIZER?


HOPE
is being able
to see that
there is a
LIGHT
despite all of
the darkness

THANK YOU

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