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UNIL | Université de Lausanne

Faculté de biologie  
et de médecine



Association Romande de Radioprotection

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**Journée thématique « Radiobiologie »**  
25.11.2022 à Lausanne, CHUV auditoire Auguste-Tissot

# Modulation de la réponse immunitaire en radiothérapie

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PhD student

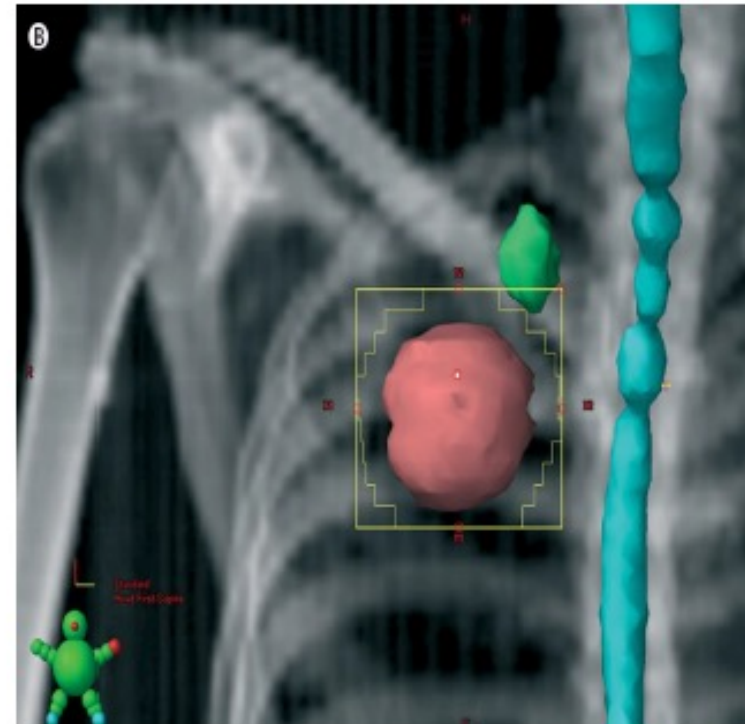
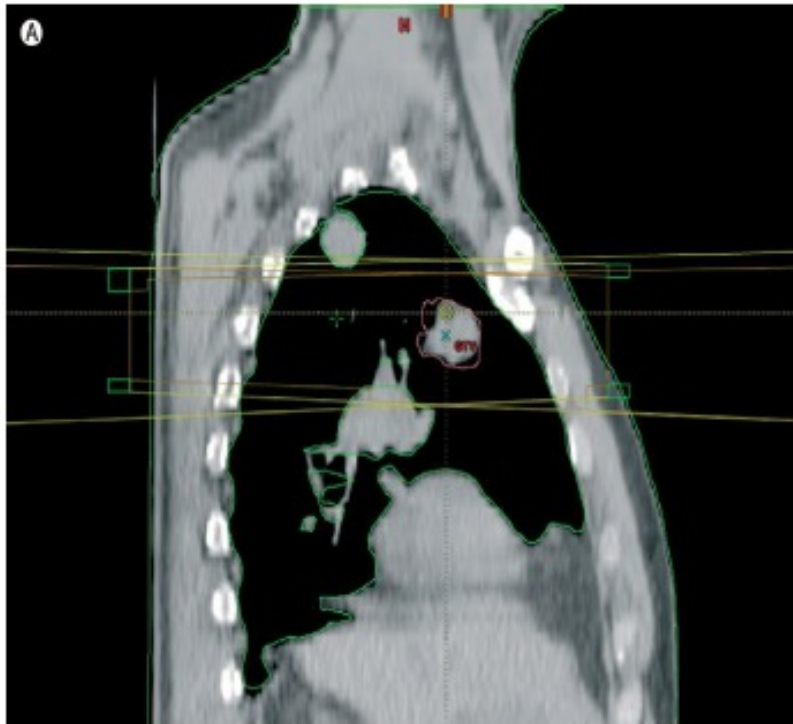
Prof. Pedro Romero, Thesis co-director  
Prof. Marie-Catherine Vozenin, Thesis co-director

# Systemic effects of local radiotherapy

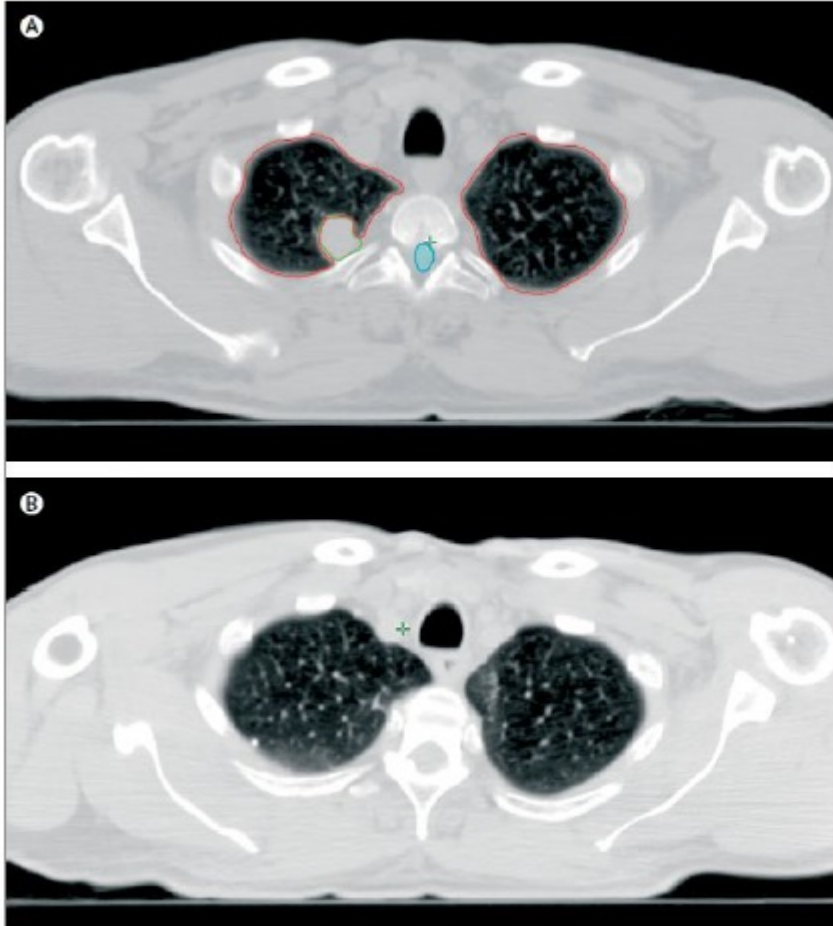
*Silvia C Formenti, Sandra Demaria*

Patient with thymic carcinoma

Two lung metastatic lesions, one irradiated, one not irradiated



# Systemic effects of local radiotherapy



Abscopal response in the unirradiated lesion

Ab = away from  
Scopus = the target

# Radiotherapy triggers immune mechanisms

Which processes resulted in the clinical response ?

Which components of the immune system may have engaged tumor targets ?

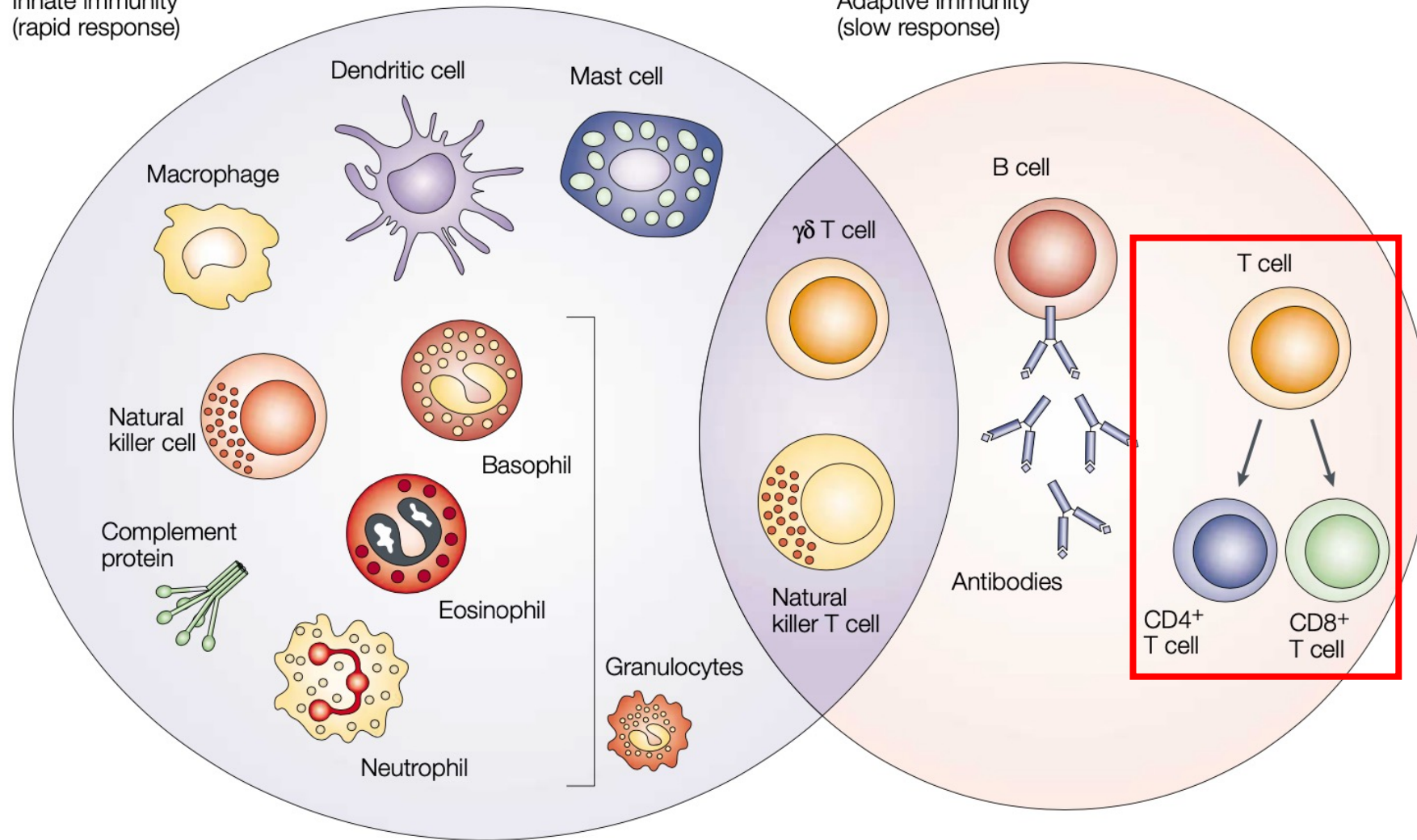
What is the role of RT in the local and systemic responses ?

Which agents can we test in combination with RT as a mean of maximizing antitumor immune response ?

# Innate versus adaptive immunity

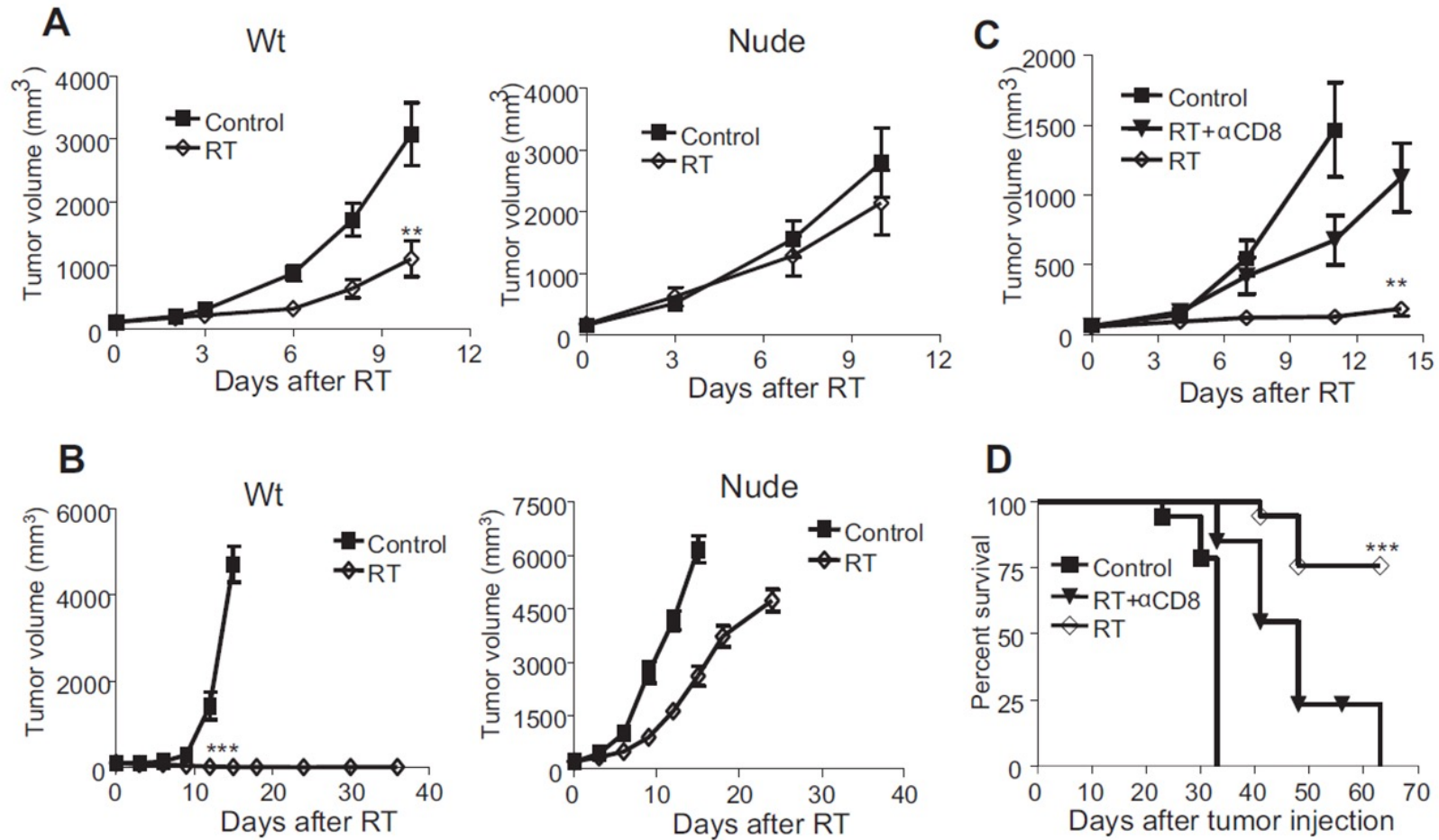
Innate immunity  
(rapid response)

Adaptive immunity  
(slow response)

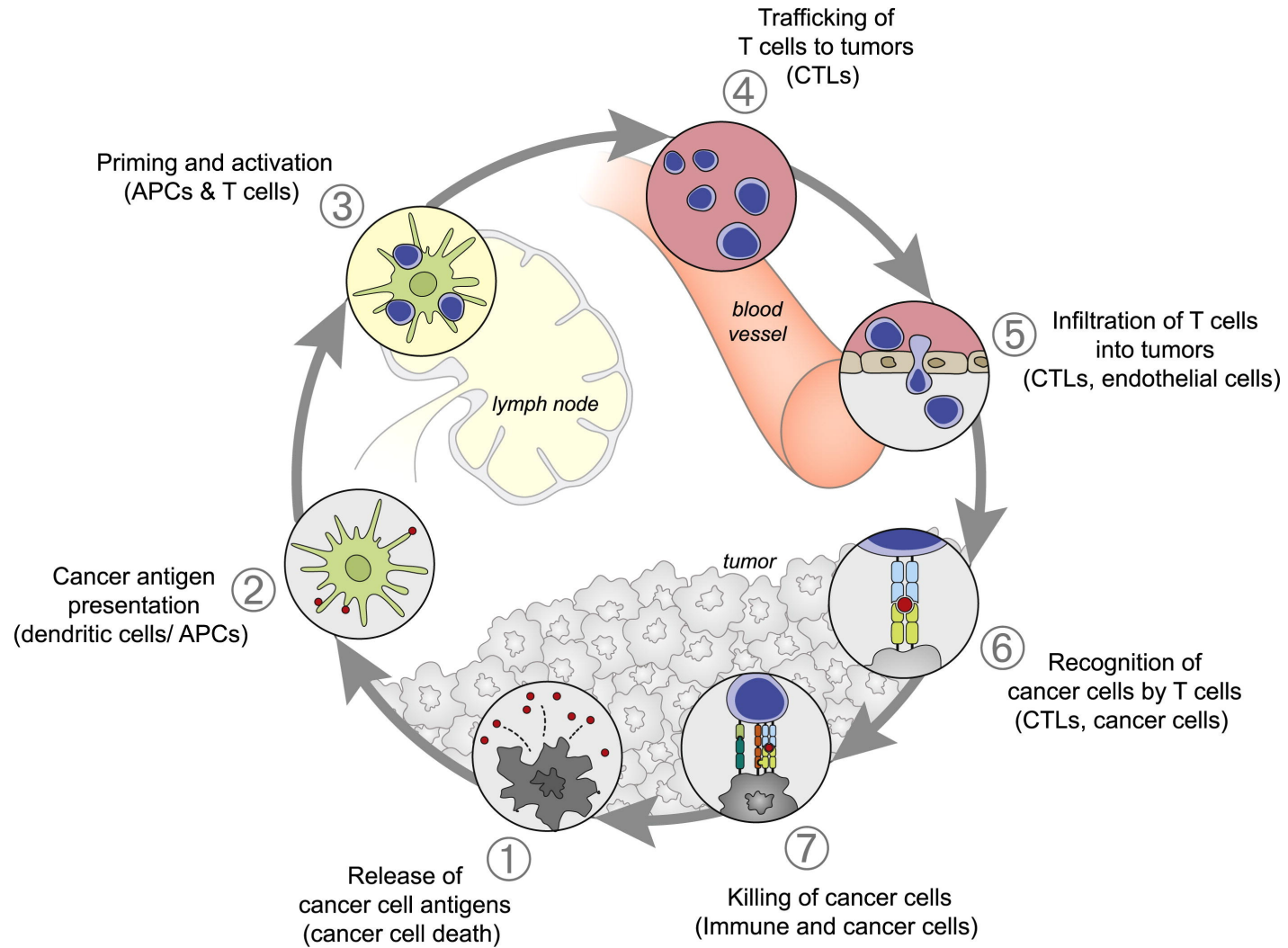


# Therapeutic effects of ablative radiation on local tumor require CD8<sup>+</sup> T cells: changing strategies for cancer treatment

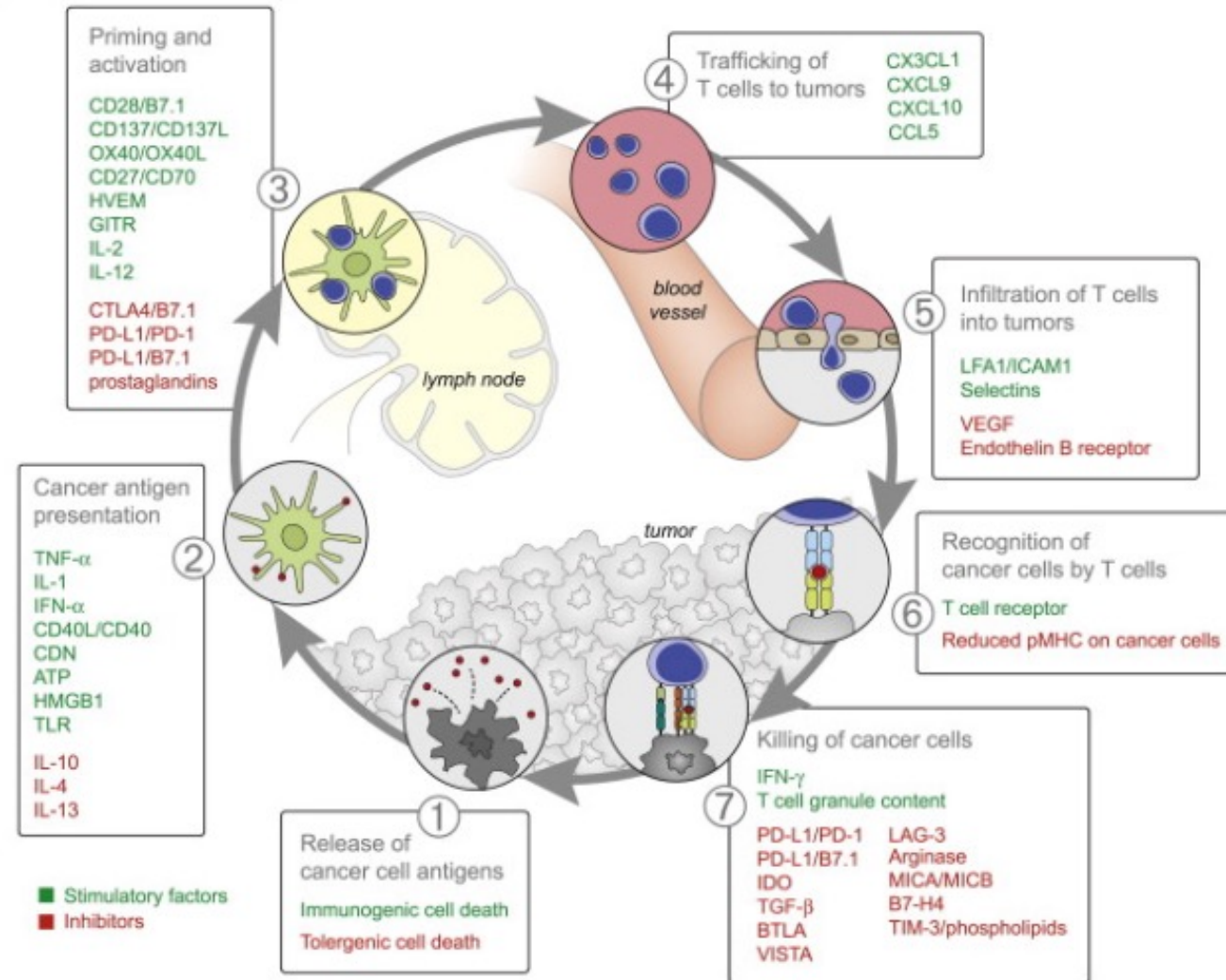
\*Youjin Lee,<sup>1</sup> \*Sogyong L. Auh,<sup>1</sup> Yugang Wang,<sup>1</sup> Byron Burnette,<sup>1</sup> Yang Wang,<sup>1</sup> Yuru Meng,<sup>2</sup> Michael Beckett,<sup>2</sup> Rohit Sharma,<sup>3</sup> Robert Chin,<sup>1</sup> Tony Tu,<sup>1</sup> Ralph R. Weichselbaum,<sup>2</sup> and Yang-Xin Fu<sup>1</sup>



# The Cancer-Immunity Cycle



# Stimulatory and inhibitory factors in the Cancer-Immunity Cycle

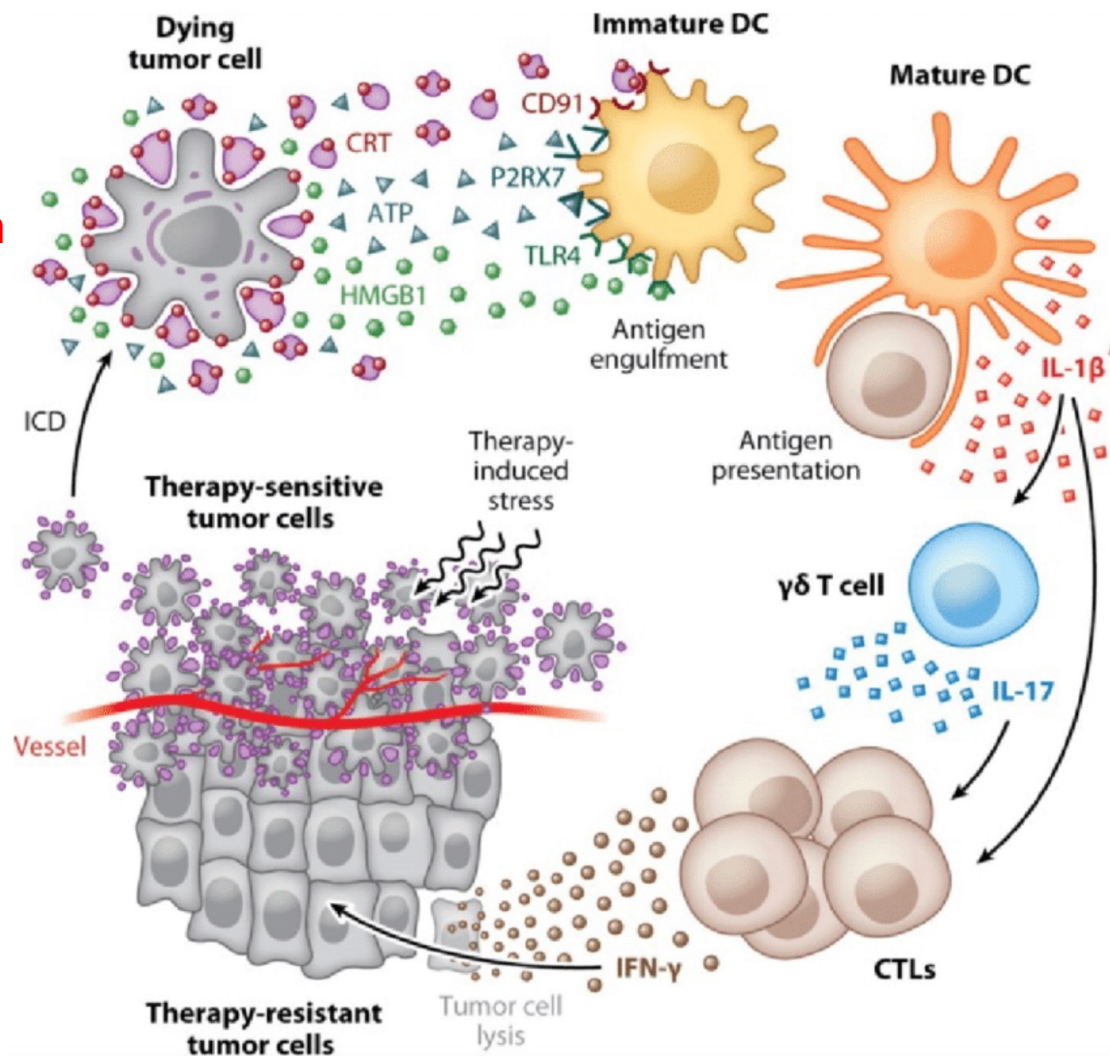




# Release of cancer cell antigens



Immunogenic cell death  
Novel antigen generation

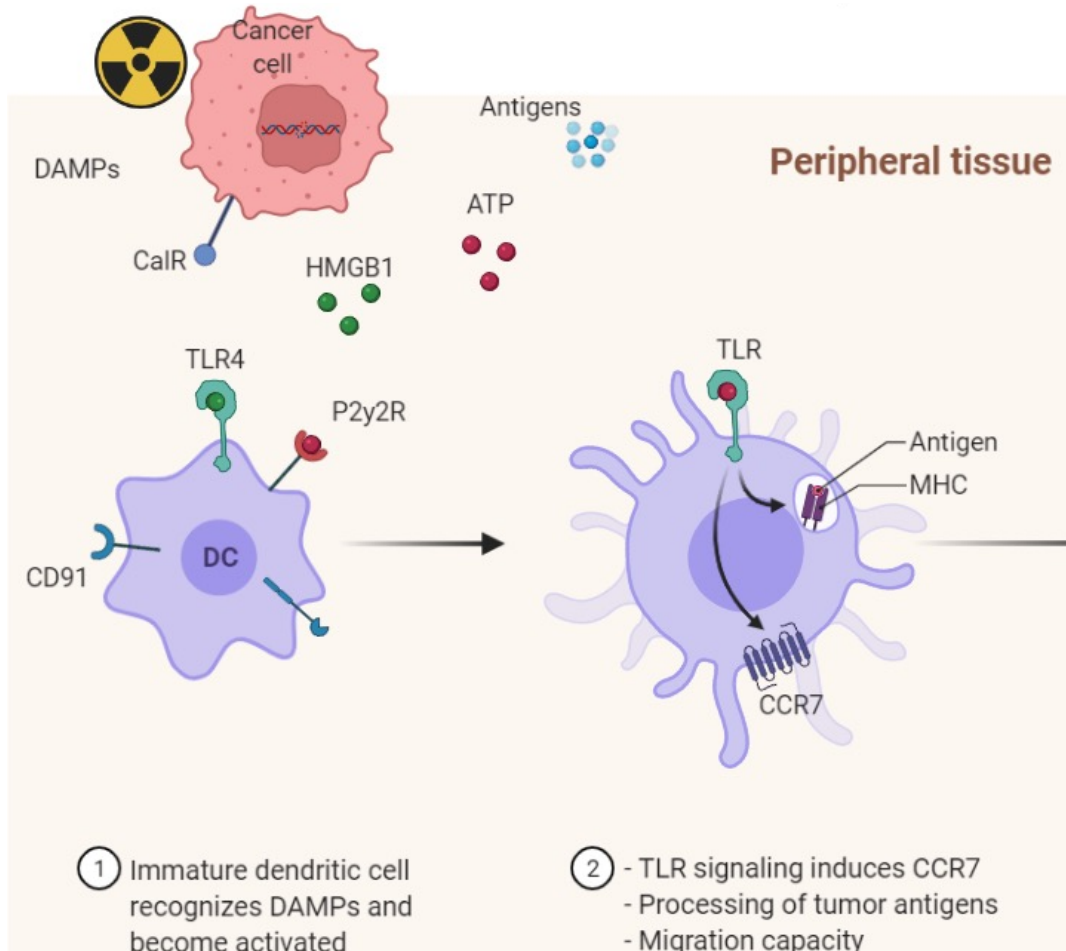
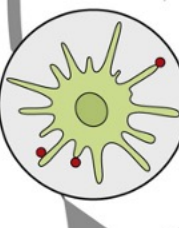


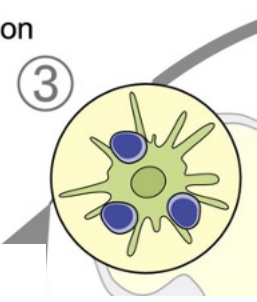
1  
Release of cancer cell antigens (cancer cell death)

Exposure of calreticulin, secretion of ATP, release of HMGB1  
Recruitment of DCs into tumor bed, optimal antigen presentation to T cells

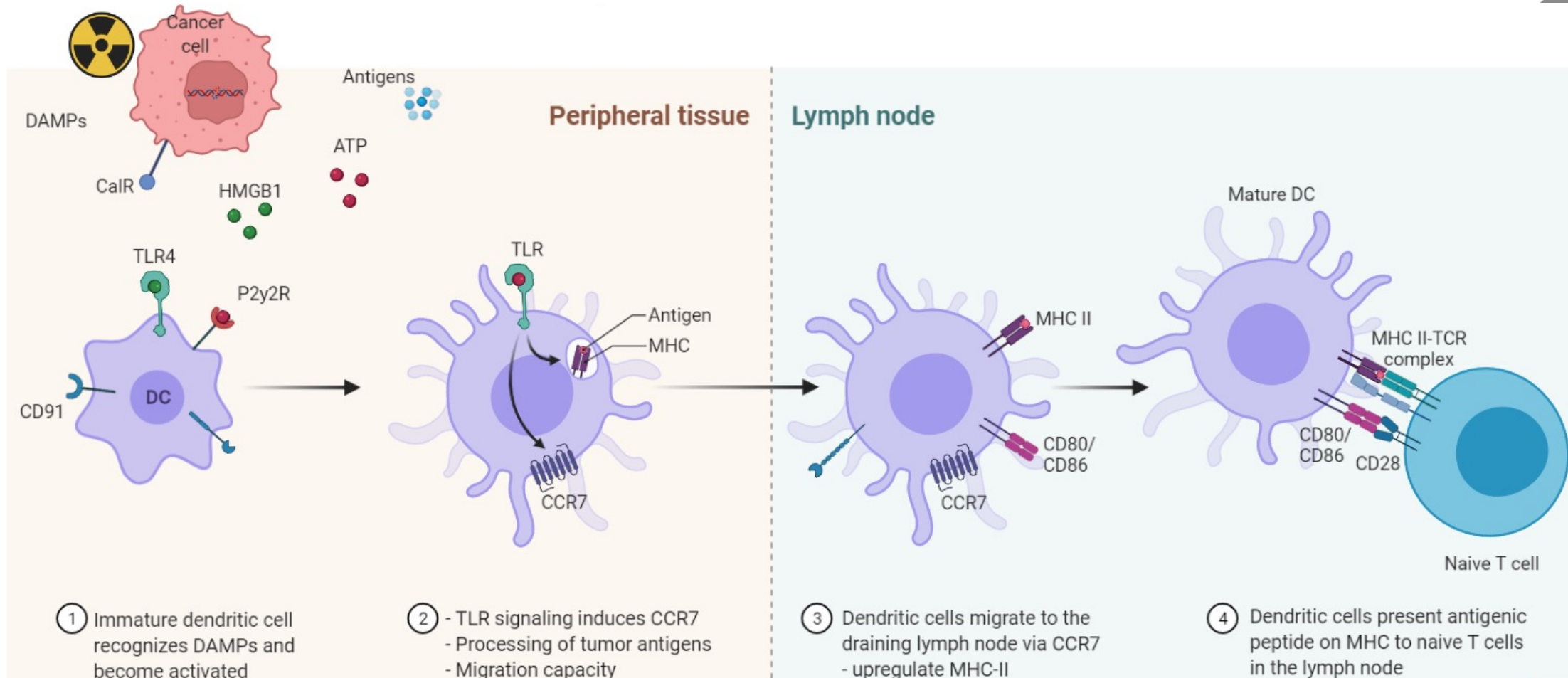
# Cancer antigen presentation

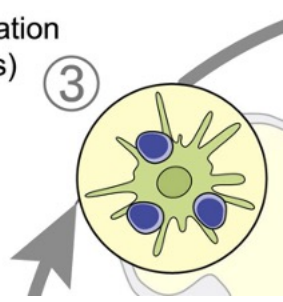
Cancer antigen presentation  
(dendritic cells/ APCs) ②



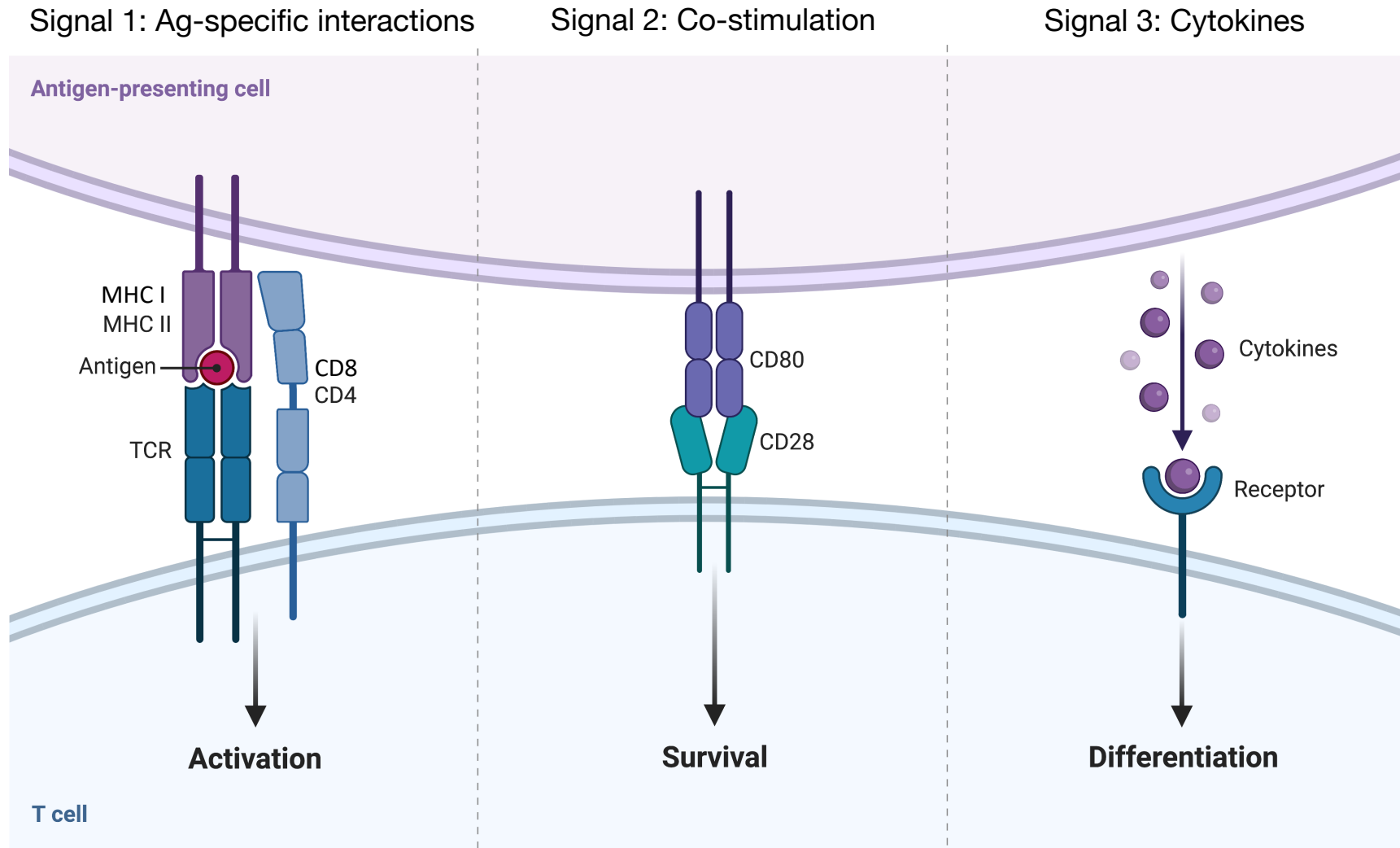


# Priming and activation





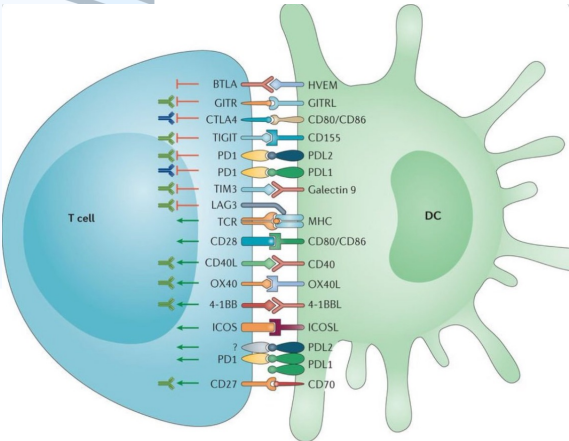
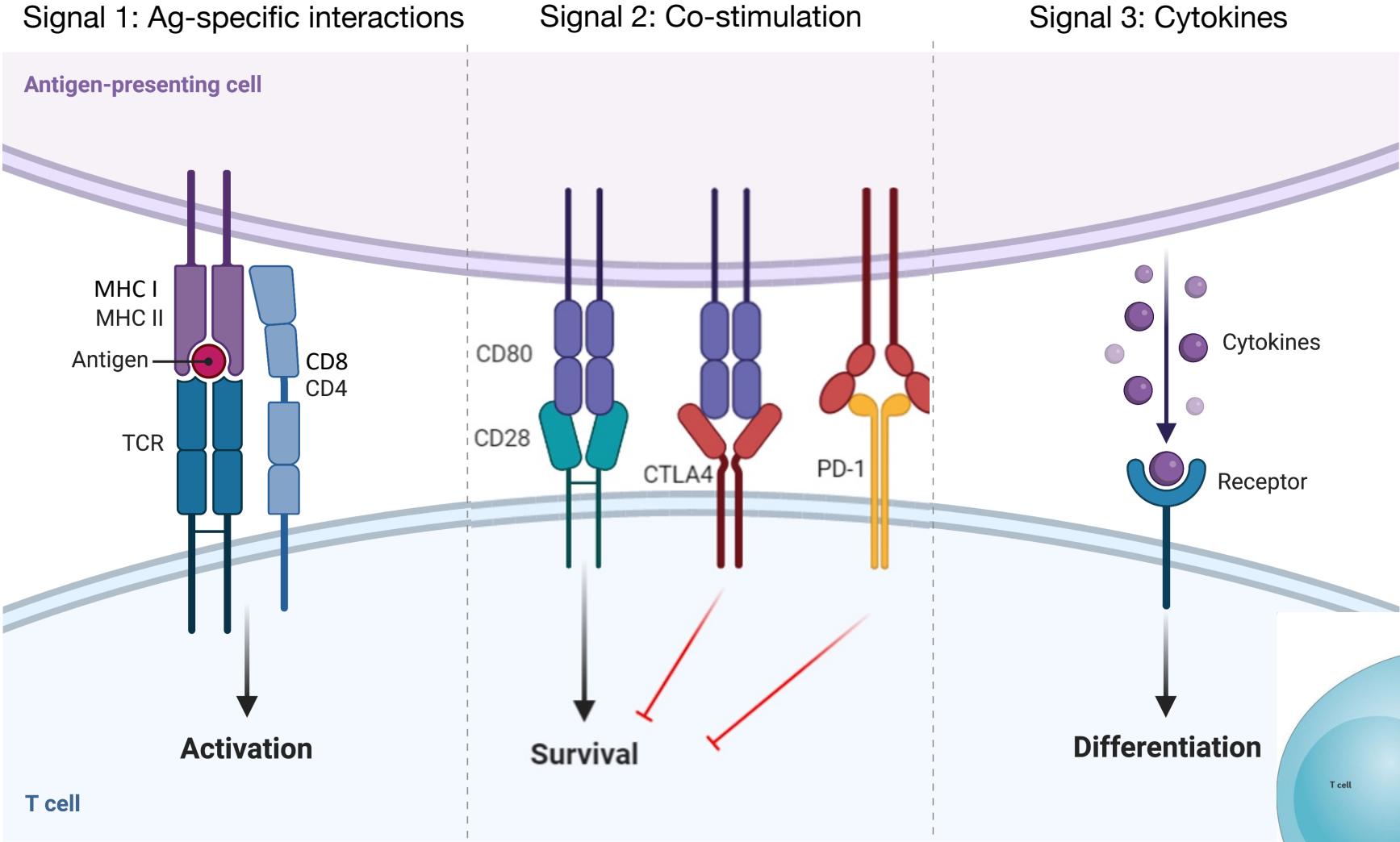
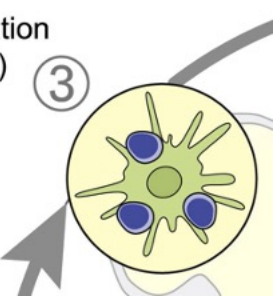
# Priming and activation



# Priming and activation

Priming and activation  
(APCs & T cells)

3



# T cell trafficking and infiltration

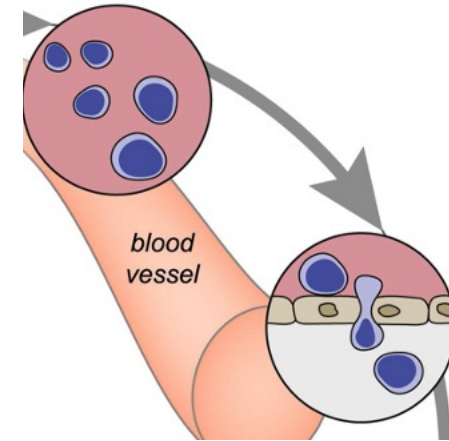


Adhesion molecule up-regulation

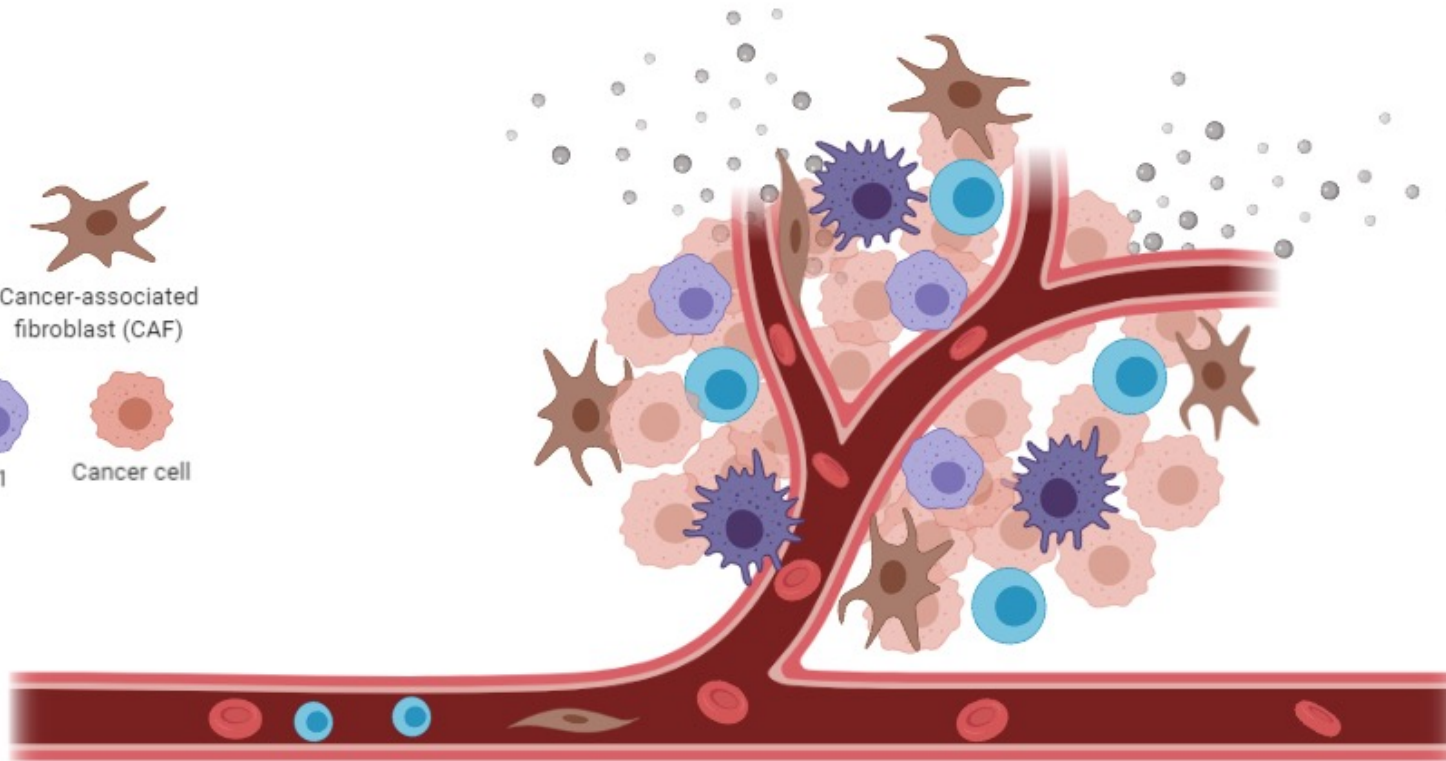
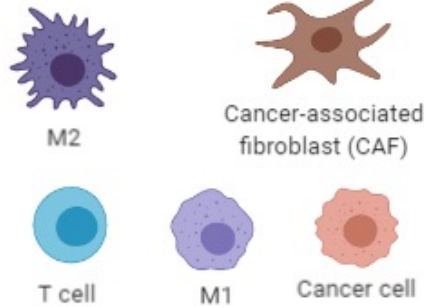
Vascular structure modulation

Increased pro-inflammatory cytokines

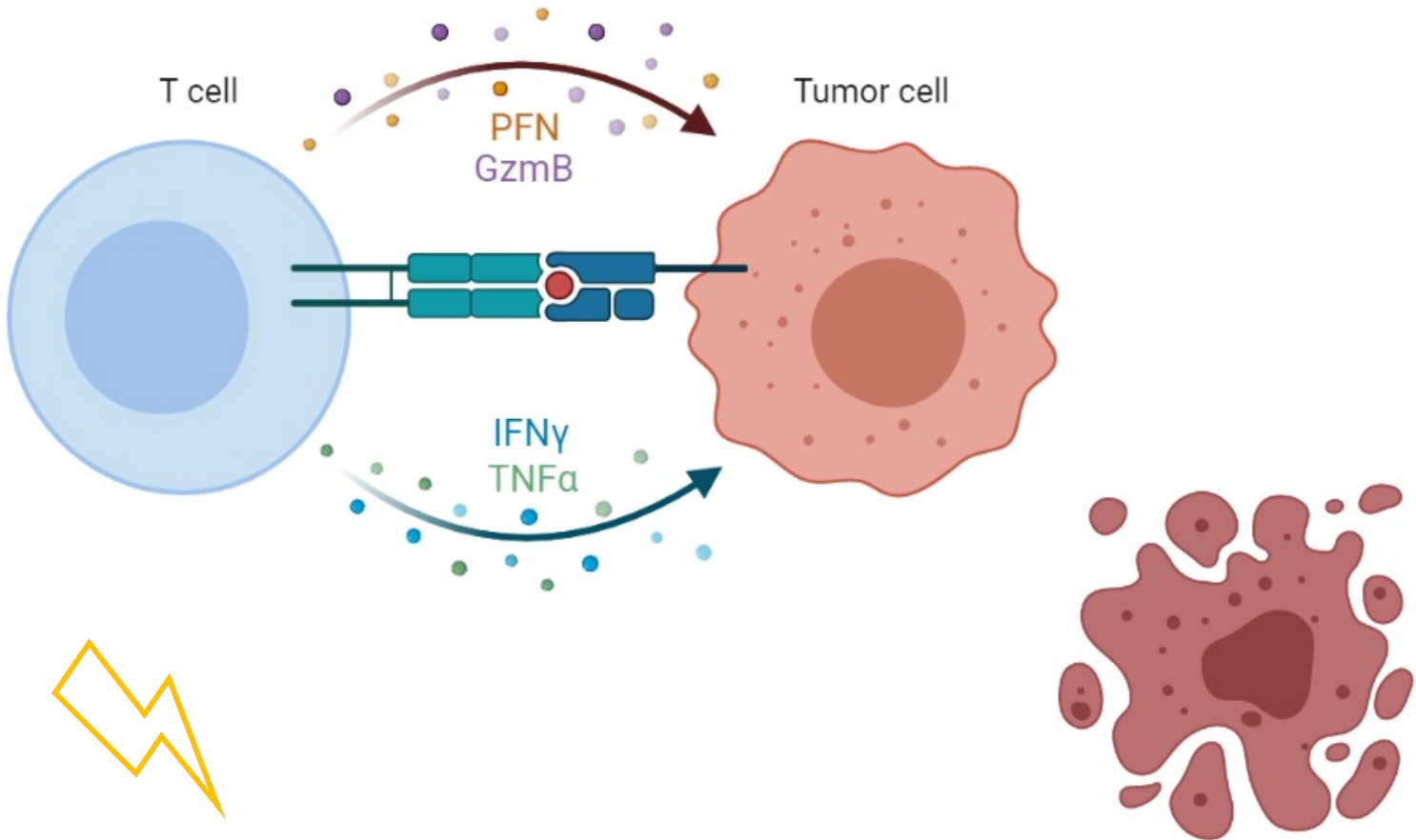
Trafficking of T cells to tumors (CTLs) ④



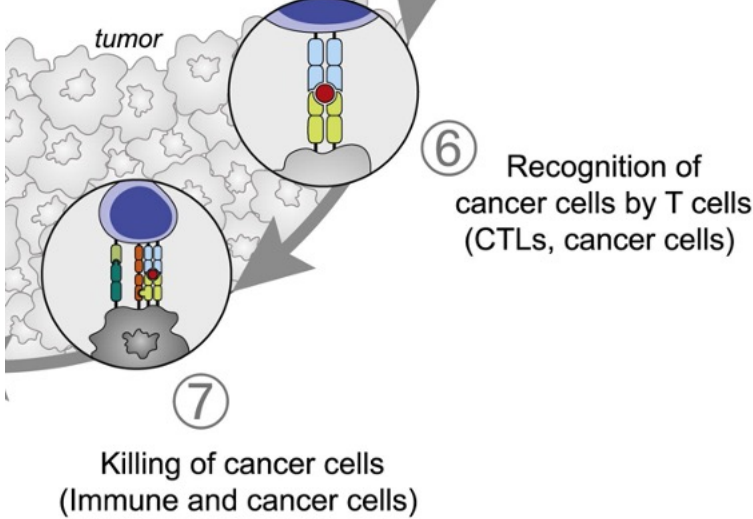
⑤ Infiltration of T cells into tumors (CTLs, endothelial cells)



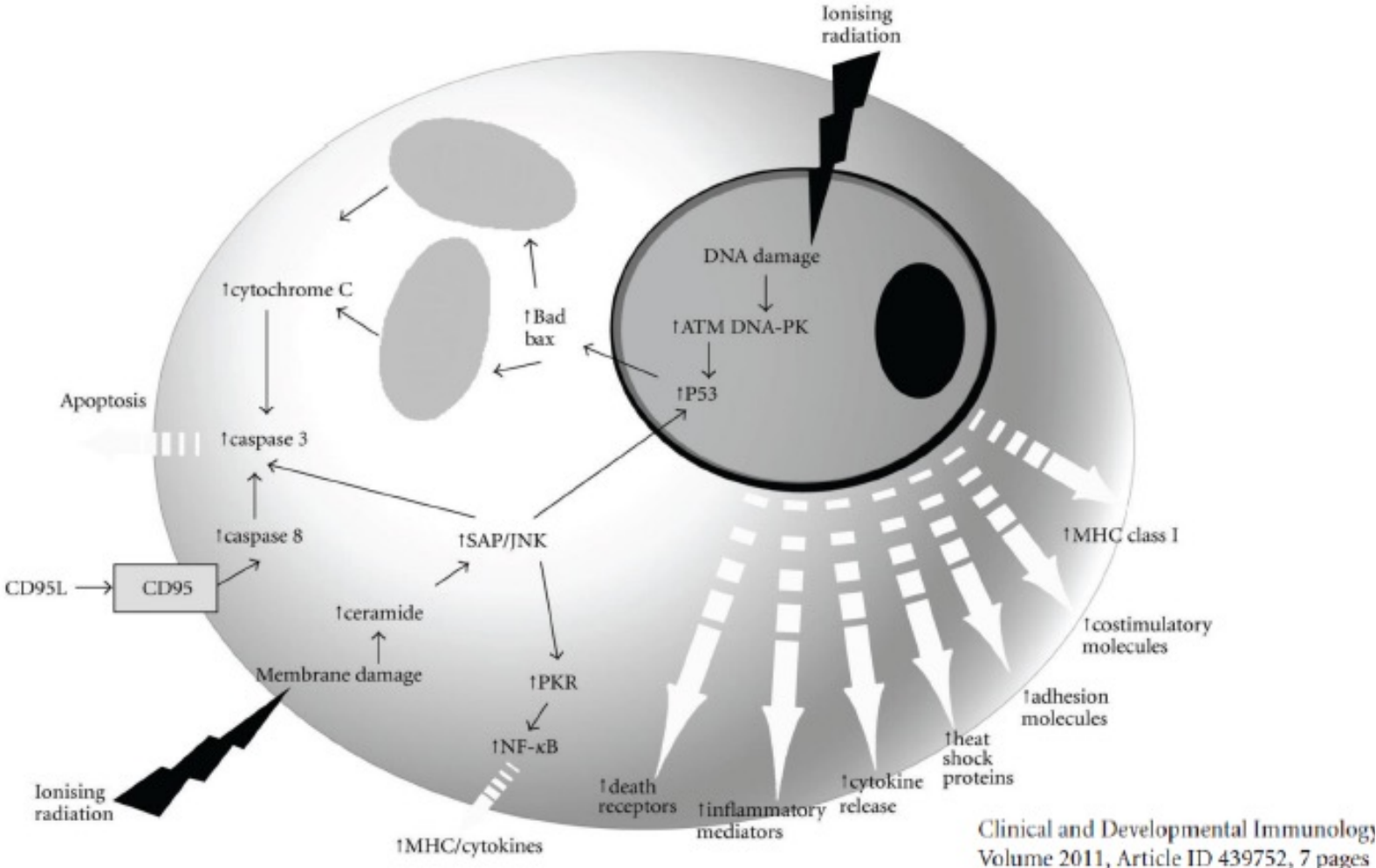
# Cancer cell killing



NK cells more potent

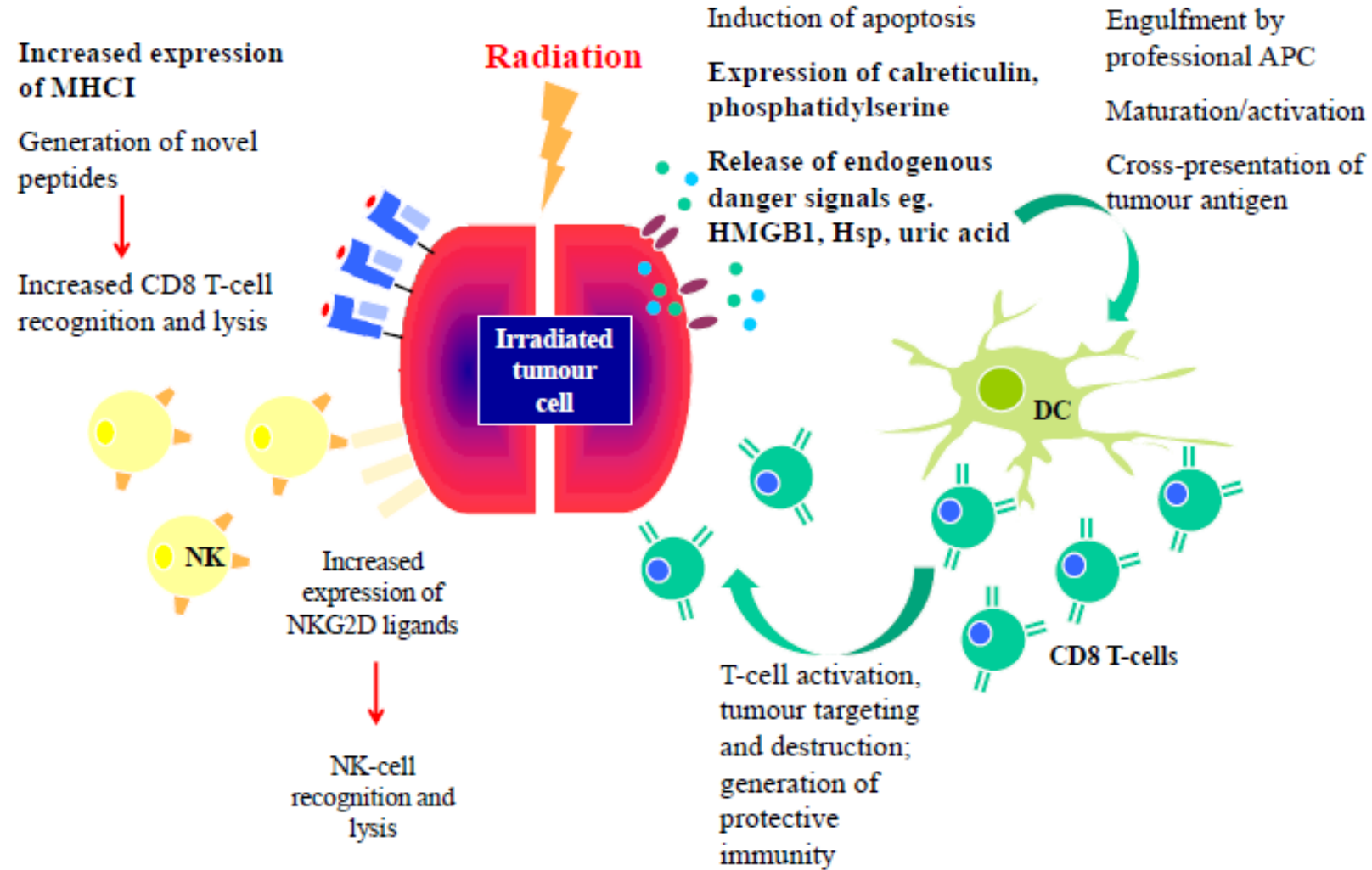


# Immunological effect of RT on tumor cells

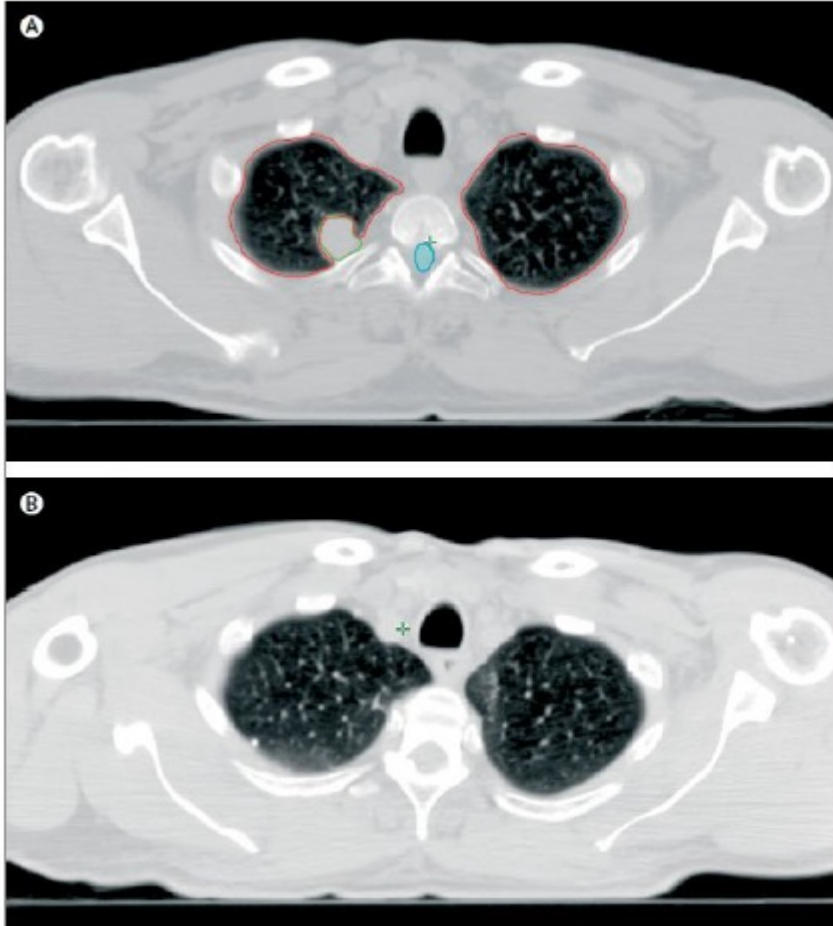




# *In situ* vaccination induced by RT



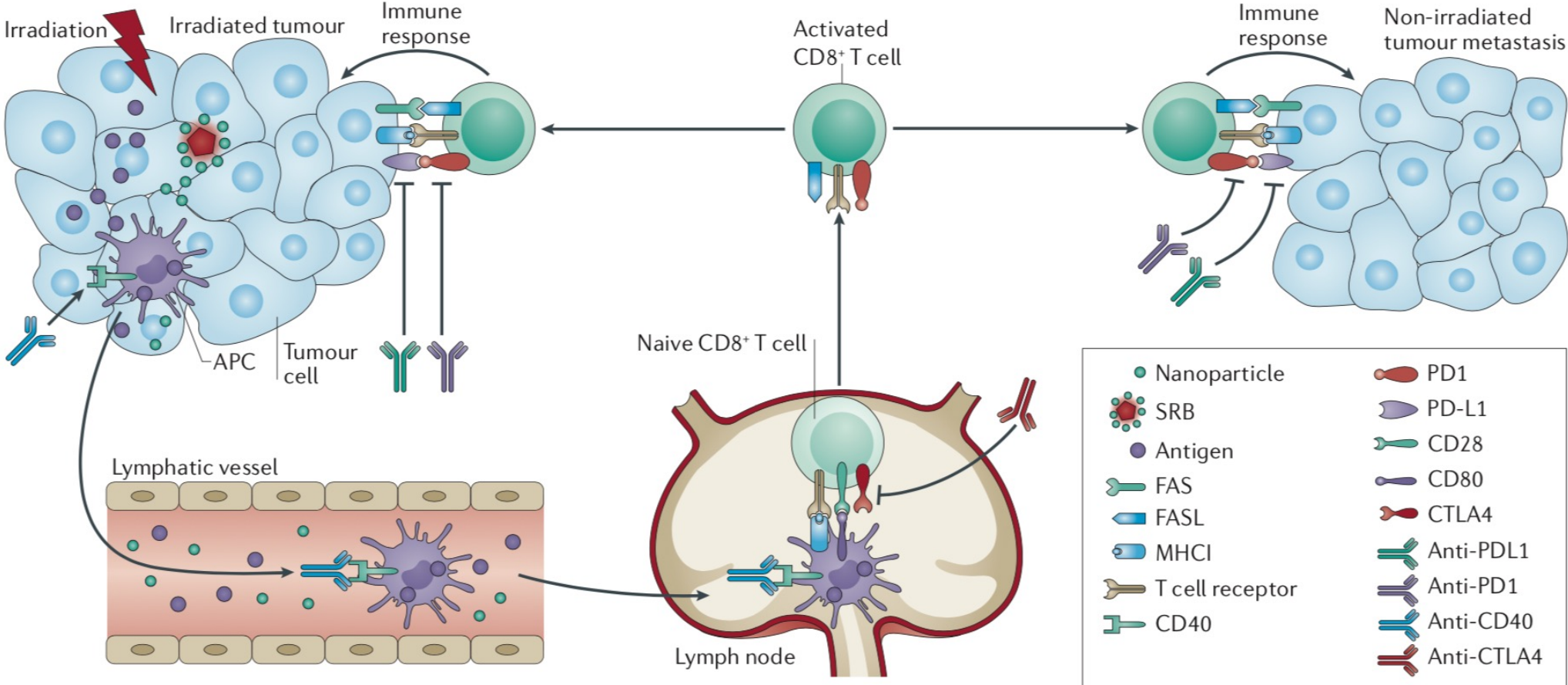
# Systemic effects of local radiotherapy



Abscopal response in the unirradiated lesion

Ab = away from  
Scopus = the target

# Mechanism of the abscopal effect



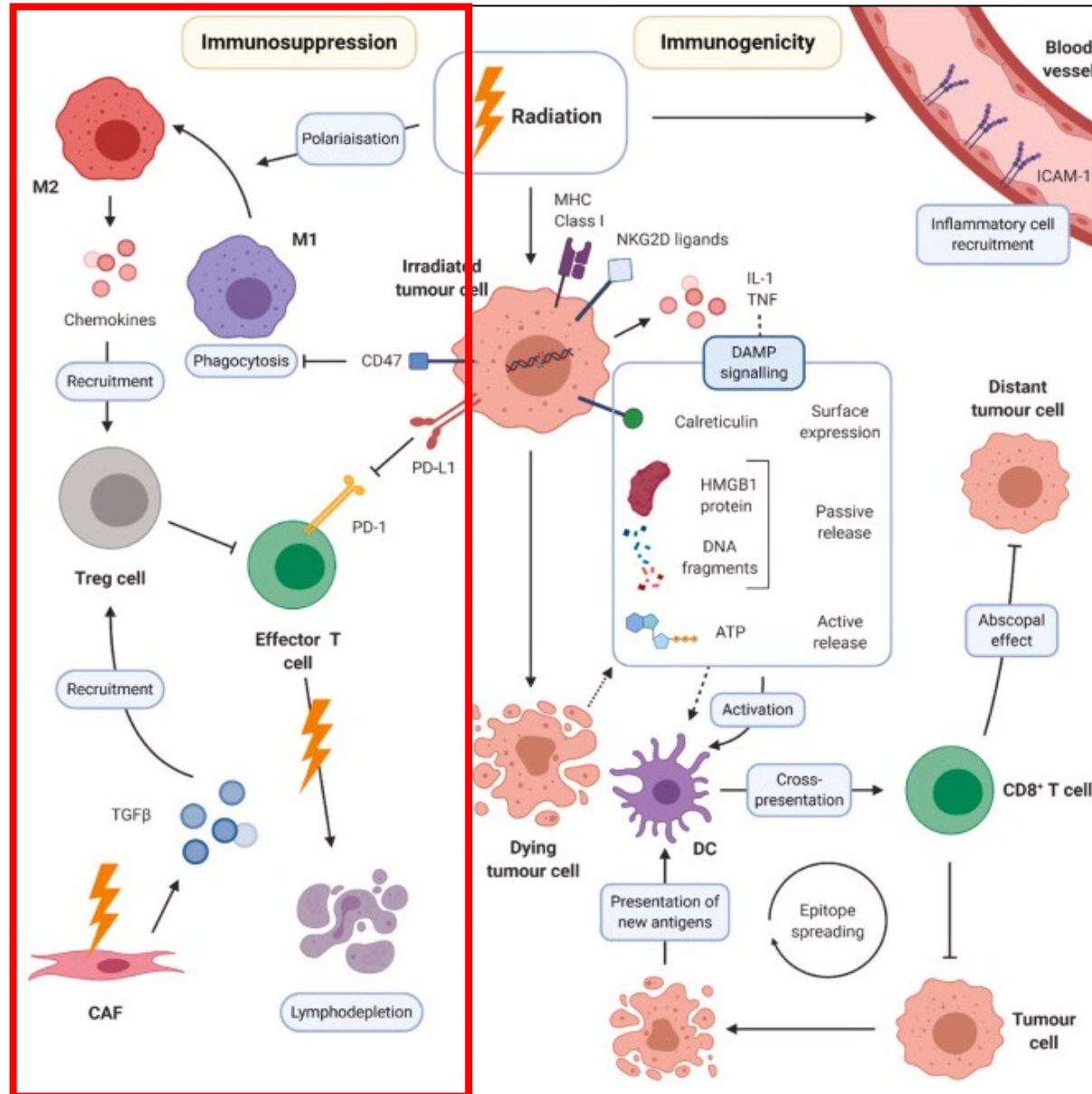
# RT is able to modulate innate immunity

RT induces complement activation

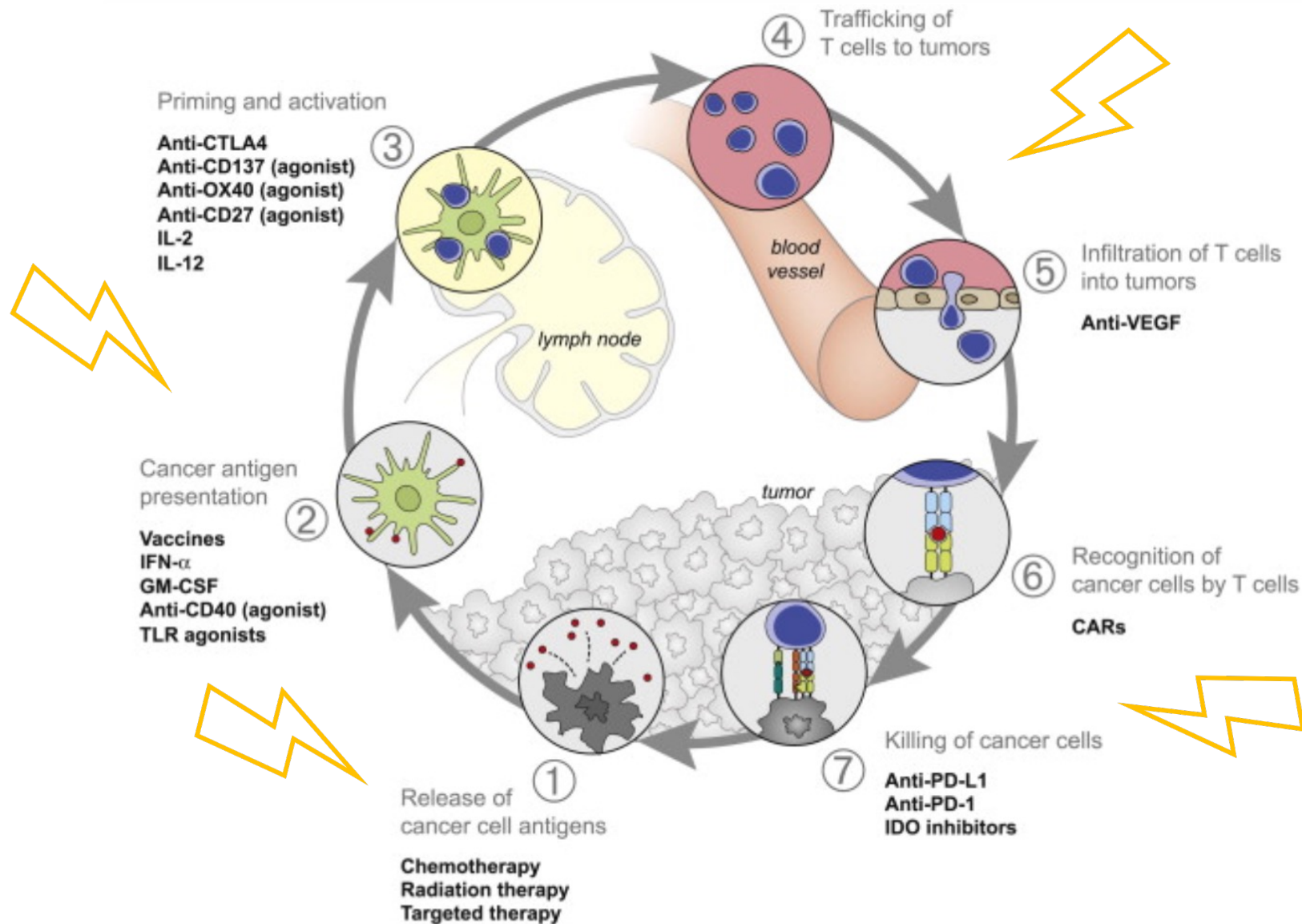
RT induces macrophages polarisation in a dose dependent manner

RT induces neutrophils differentiation and aging

# Radiotherapy also drives immunosuppression



# RT/IT: partnership to ameliorate anti-tumor immune response



# Conclusions

RT- induced abscopal effect are immune-mediated

Adaptive immune response are central to the phenomenon

Innate immune response are also important

Novel immunomodulatory agents have the potential to maximise RT-induced anti-tumor immune response

# Acknowledgements

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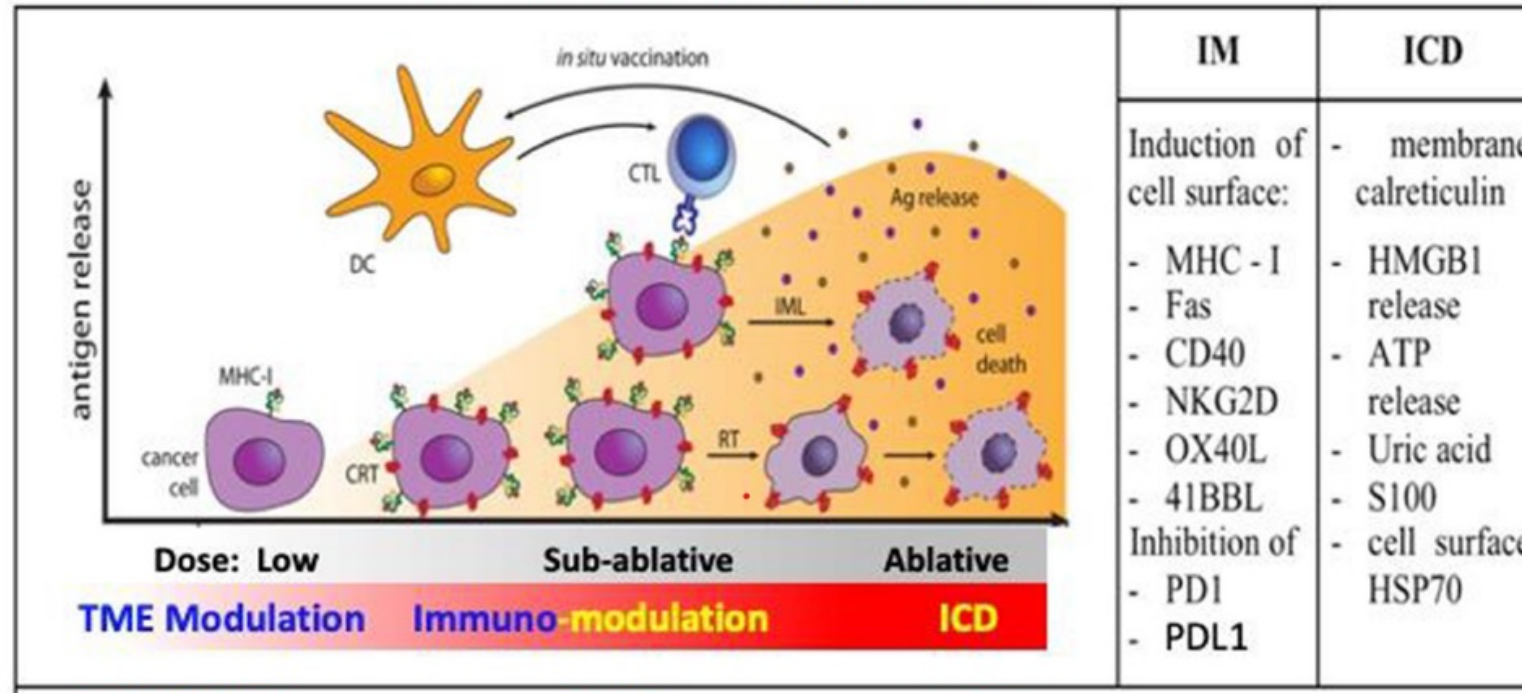
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# RT as an immunomodulatory drug



## TMEM-RT

Tumor microenvironment modulating RT  
~ 0.5 Gy x 4

- Local cytokine production
- Increases vascular access
- Surface expression of stress marker
- May augment NK cell activation

## ImRT SBRT

Immunomodulatory RT  
~ 8 Gy x 3  
~ 6 Gy x 5

- Similar effect induced by standard fractionation
- *In situ* vaccination
- IFN type I response
- increased MHC- I

## IART SRS / SABR

Immunoablative RT  
~ 34 Gy x 1  
~ 18 Gy x 3  
~ 10 Gy x 5

- Cell death
- High vascular damage
- Deplete radioresistant immunosuppressive cells in TME
- Increases M2 Mo
- Increases fibrosis
- Immune/inflammatory suppressive path ?

# Effect of RT on various components of TME

