# Basic Mechanisms of Action in Immuno-Oncology


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# Disclosure

| *Company Name* | *Honoraria/ Expenses* | *Consulting/ Advisory Board* | *Contract Research* | *Funded Research* | *Royalties/ Patent* | *Stock Options* | *Ownership/ Equity Position* | *Employee* | *Other (please specify)* |
|---|---|---|---|---|---|---|---|---|---|
| Merck & Co., Inc | x | x | x | | | | | | Speakers' bureau |
| Roche | x | x | | x | | | | | Speakers' bureau |
| Sandoz | x | x | | x | | | | | |
| Tesaro | x | x | x | x | | | | | Speakers' bureau |
| Teva | x | x | | | | | | | Speakers' bureau |
| Heron Therapeutics | x | x | | | | | | | |
| BMS South Africa | x | x | x | X | | | | | Speakers' bureau |
| Novartis South Africa | x | x | x | | | | | | Speakers' bureau |
| Amgem South Africa | x | x | x | | | | | | Speakers' bureau |
| Bayer South Africa | x | x | x | | | | | | Speakers' bureau |
| Merck Serono S.Africa | x | x | | | | | | | |
| Astellas South Africa | x | x | | | | | | | Speakers' bureau |
| Sanofi Aventis S. Africa | x | x | | | | | | | |
| Astra Zeneca S. Africa | x | x | | | | | | | Speakers' bureau |
| Eli-Lilly South Africa | | | x | | | | | | |
| J & J South Africa | X | X | | | | | | | Speakers' bureau |

# Immune System Function and Immune Response

Identify and destroy foreign or abnormal cells in the body

## Innate Immunity

- Nonspecific
- First line of defense
- WBCs (natural killer cells, neutrophils)
- Activation of adaptive immunity

## Adaptive Immunity

- Specific target recognition
- Slower to develop
- Antibody or cell mediated
- Memory
  - Faster, stronger subsequent responses

Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

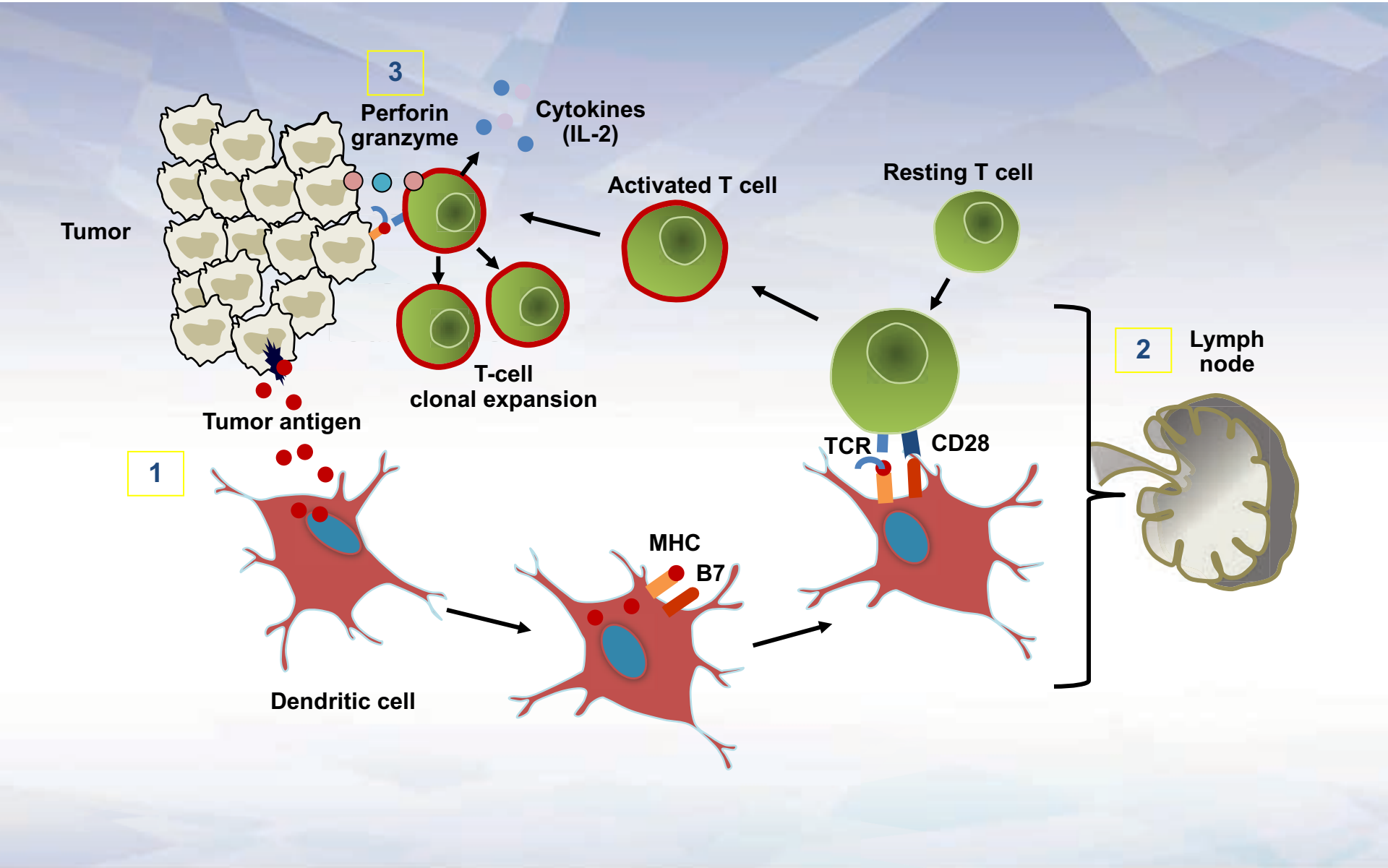
# Immuno-Therapy: Does it Work in Cancer? Paul Ehrlich's Immunosurveillance Concept

## 100+ years of progress

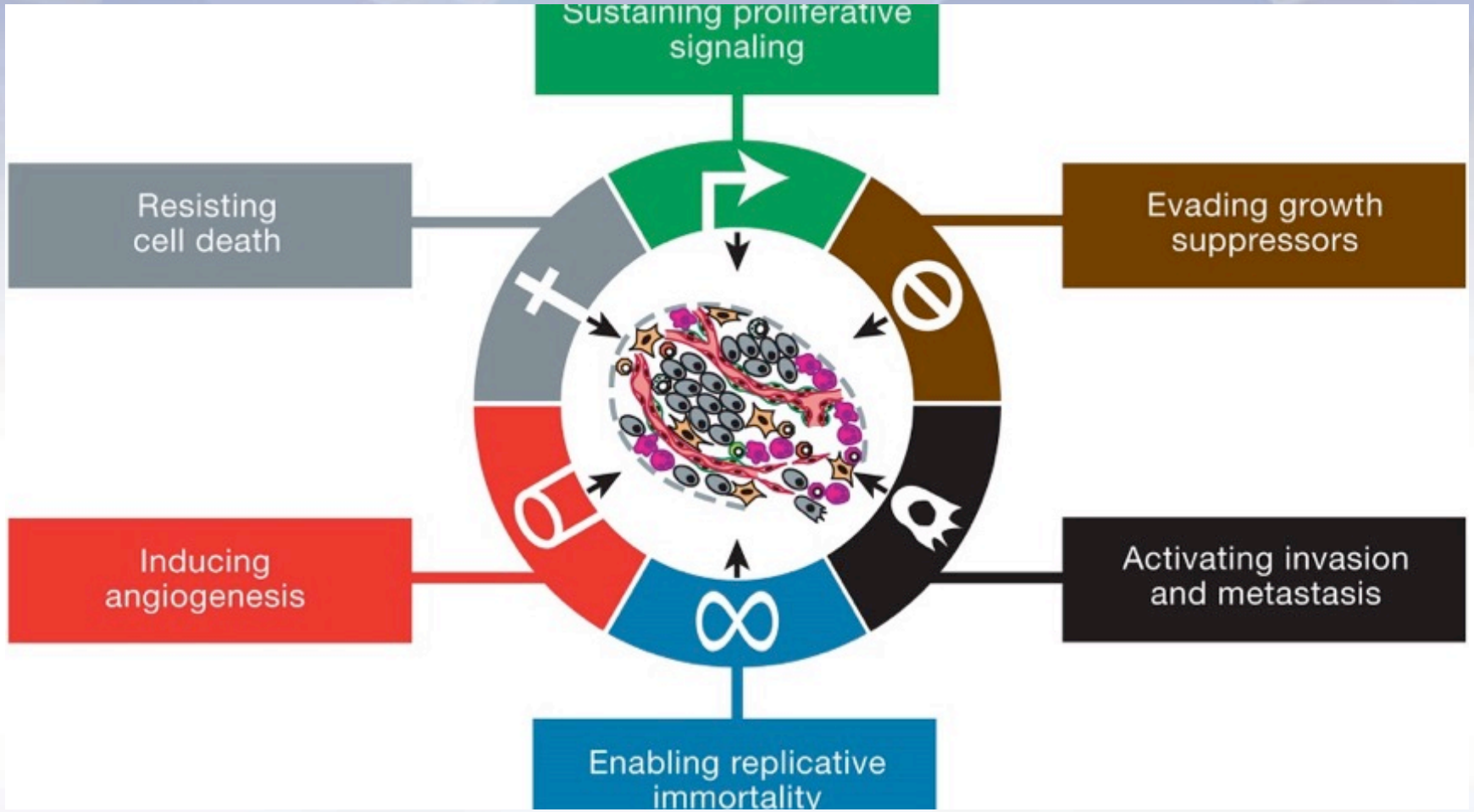
- Magic Bullet (Paul Ehrlich)
- Immunosurveillance (P Ehrlich 1909)

Paul Ehrlich

# Cell-Mediated Tumor Immunology: Overview

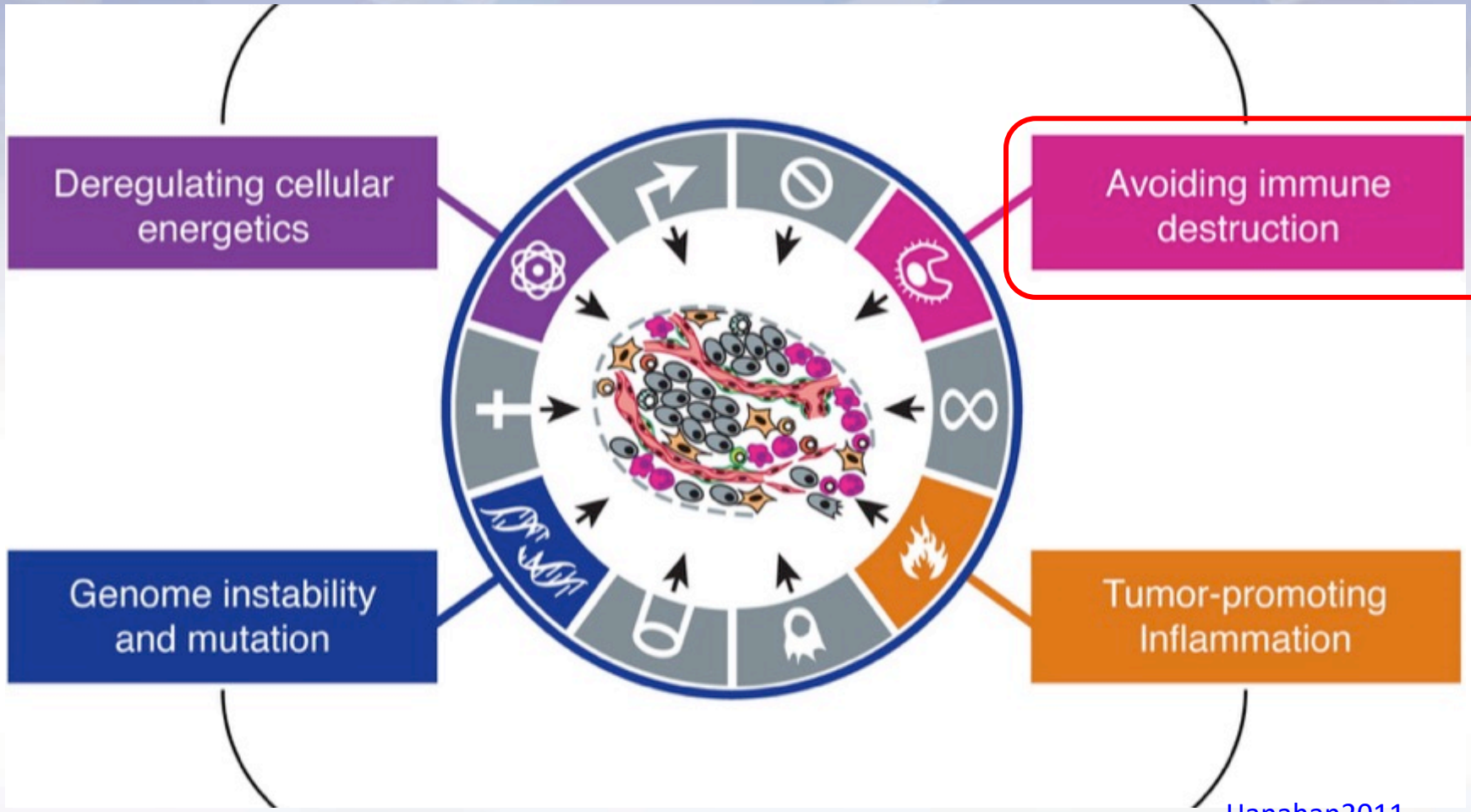


# Hallmarks of cancer




Hanahan2011

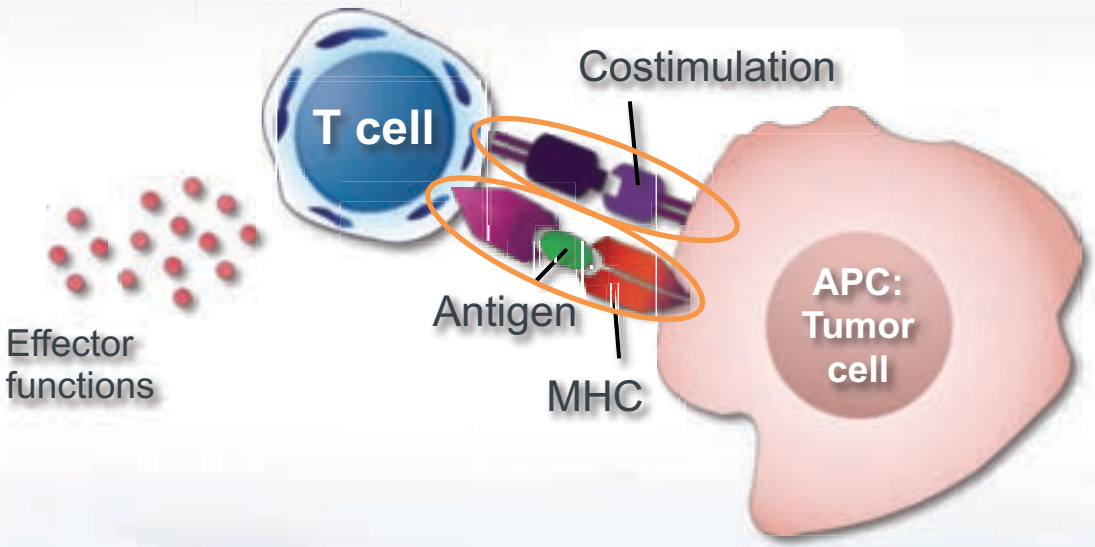
# Emerging hallmarks




Hanahan2011

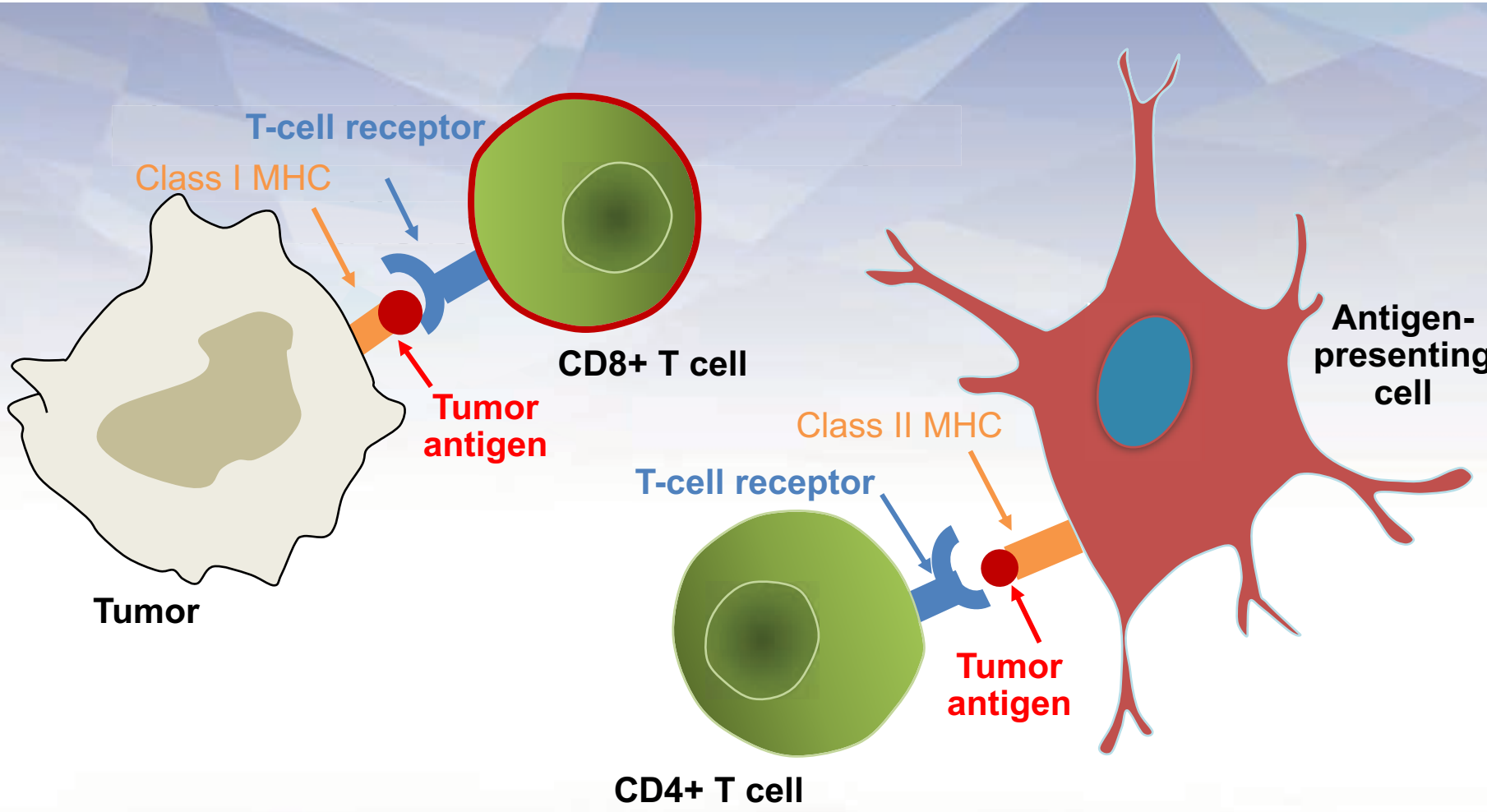
# Proper T-Cell Activation Requires 2 Signals[1]

- To be properly activated, a T cell MUST receive 2 signals[1]
  - Binding of an MHC-antigen complex to TCR
  - Binding of a second costimulatory signal
- This initiates intracellular signaling that activates the T cell, which can then kill infected or cancer cells or help support other immune functions[1,2]



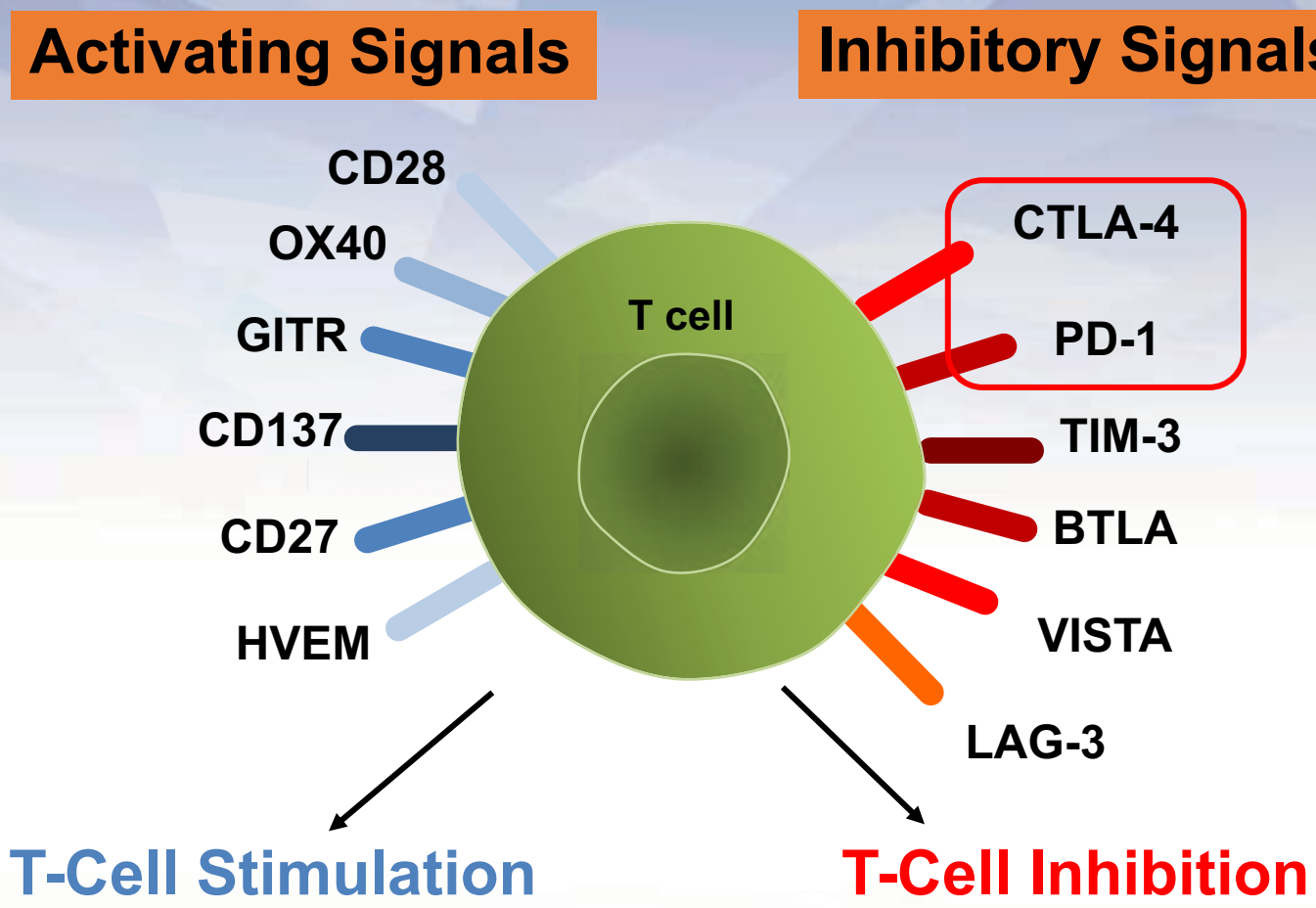

APC = antigen-presenting cell; MHC = major histocompatibility complex; TCR = T-cell receptor.

# T-Cell Response: First Signal



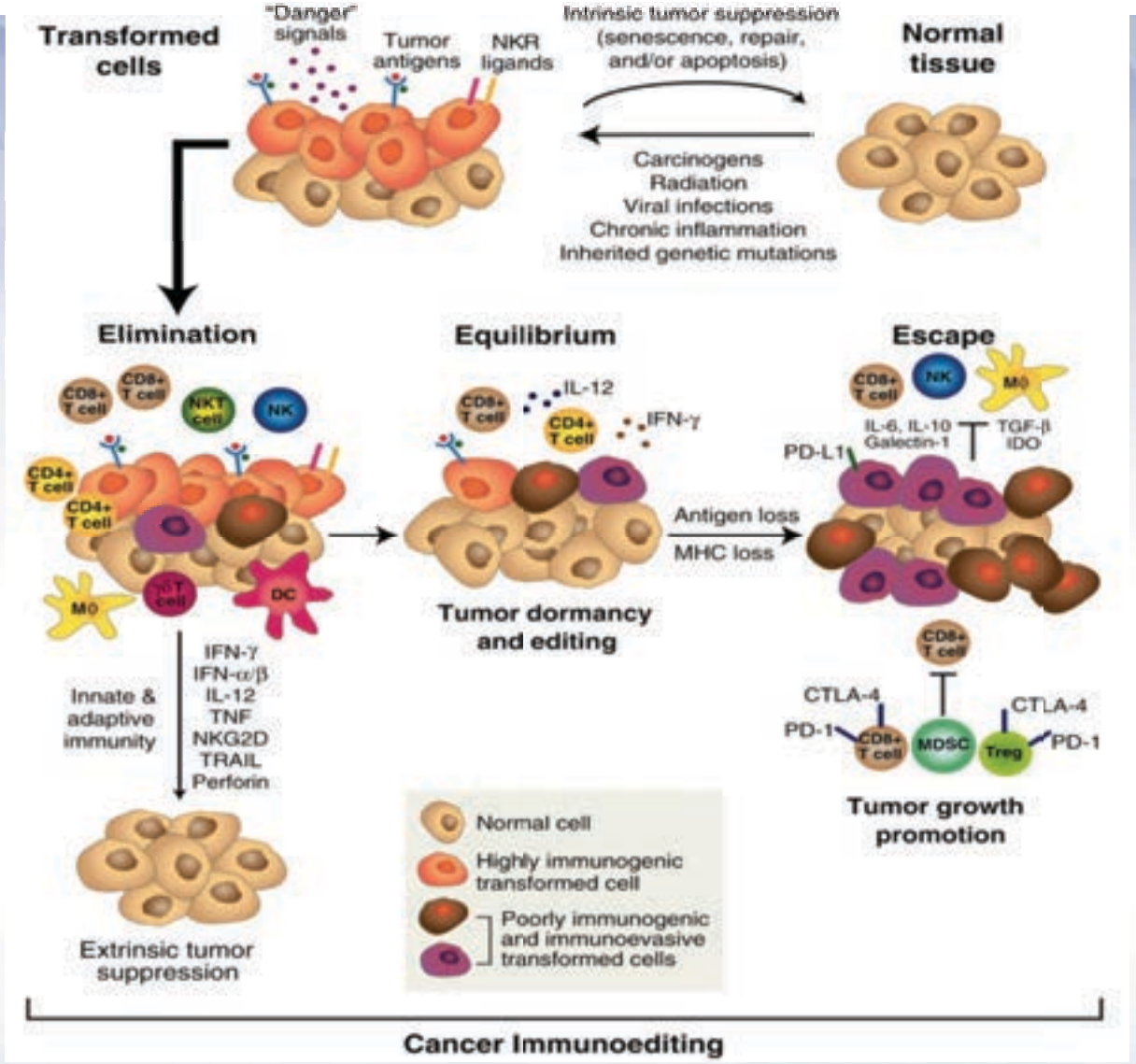

Adapted from Snyder A, et al. Curr Opin Genet Dev. 2015;30:7-16.

# T-Cell Response: Second Signal to Accelerate or Brake




Mellman I, et al. Nature. 2011;480:480-489.

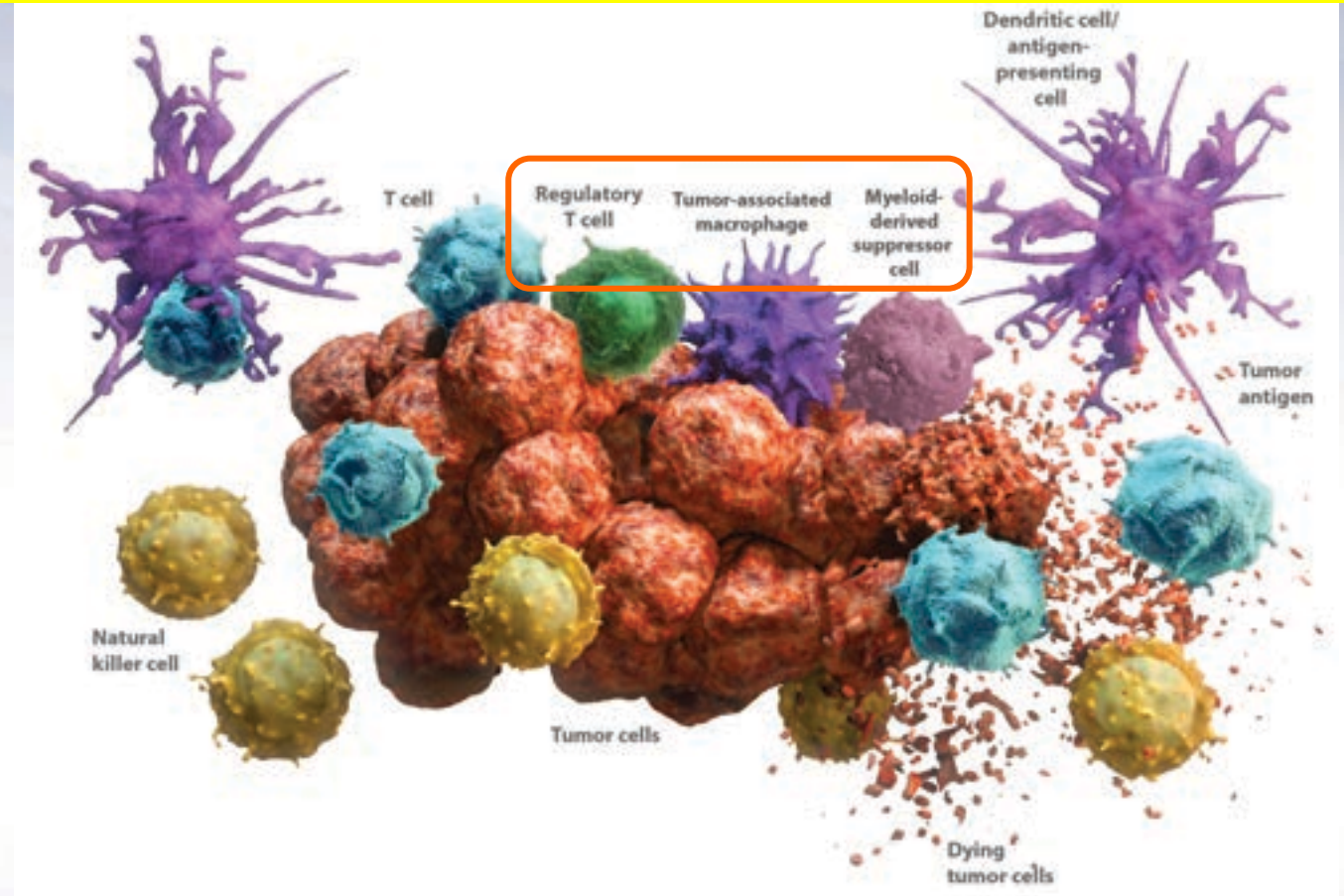
# Cancer Immunoediting




Robert D. Schreiber, Lloyd J. Old, Mark J. Smyth *Science* 25 Mar 2011: Vol. 331, Issue 6024, pp. 1565-1570

# Tumor microenvironment

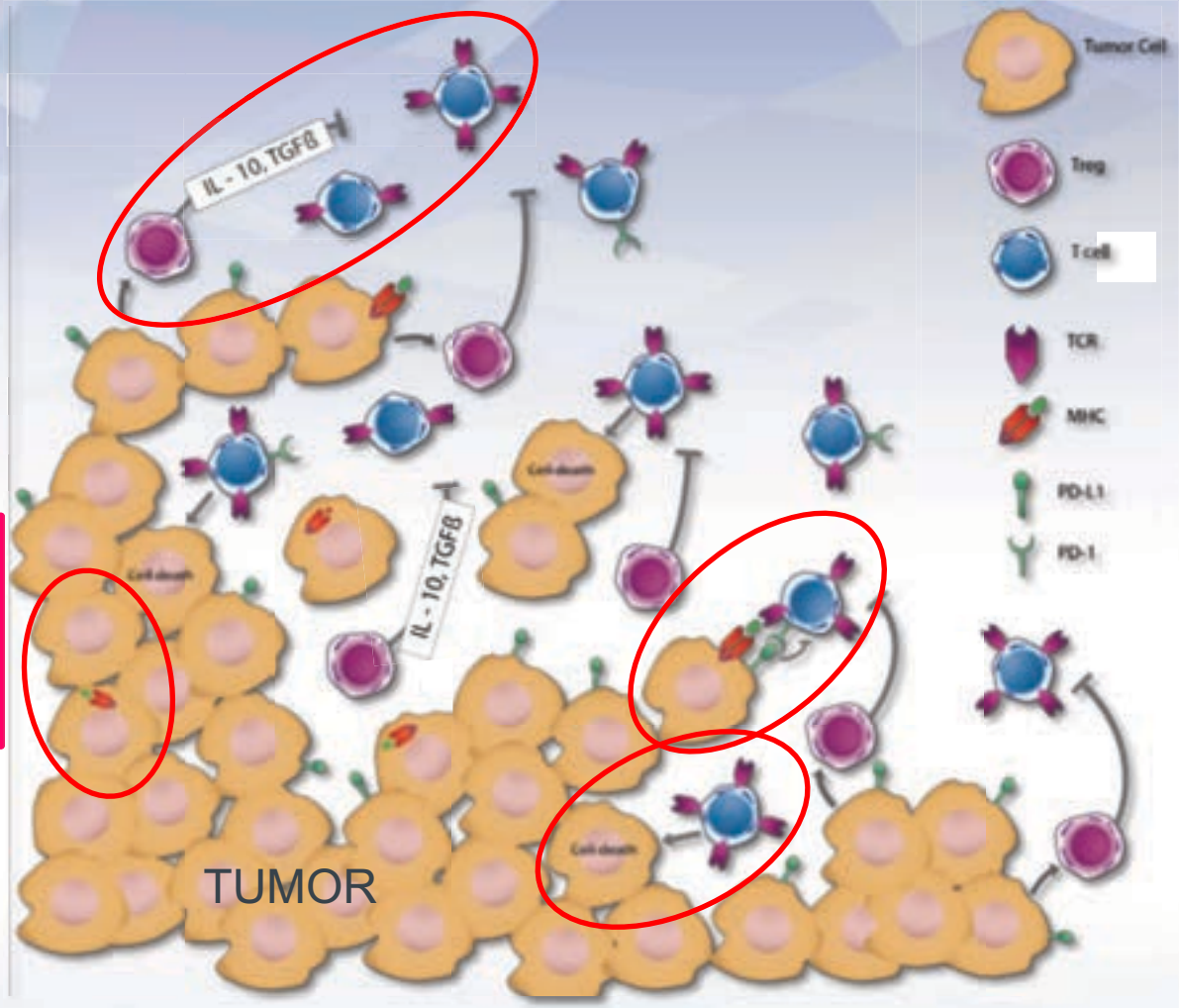
**The immune system is capable of recognizing and eliminating tumor cells in the tumor microenvironment. Innate and adaptive immunity act as a complementary network of self-defense against foreign threats.**




Tumors can use various mechanisms to escape detection and enable growth.

# Tumors Evade Immune Detection and Destruction[1]

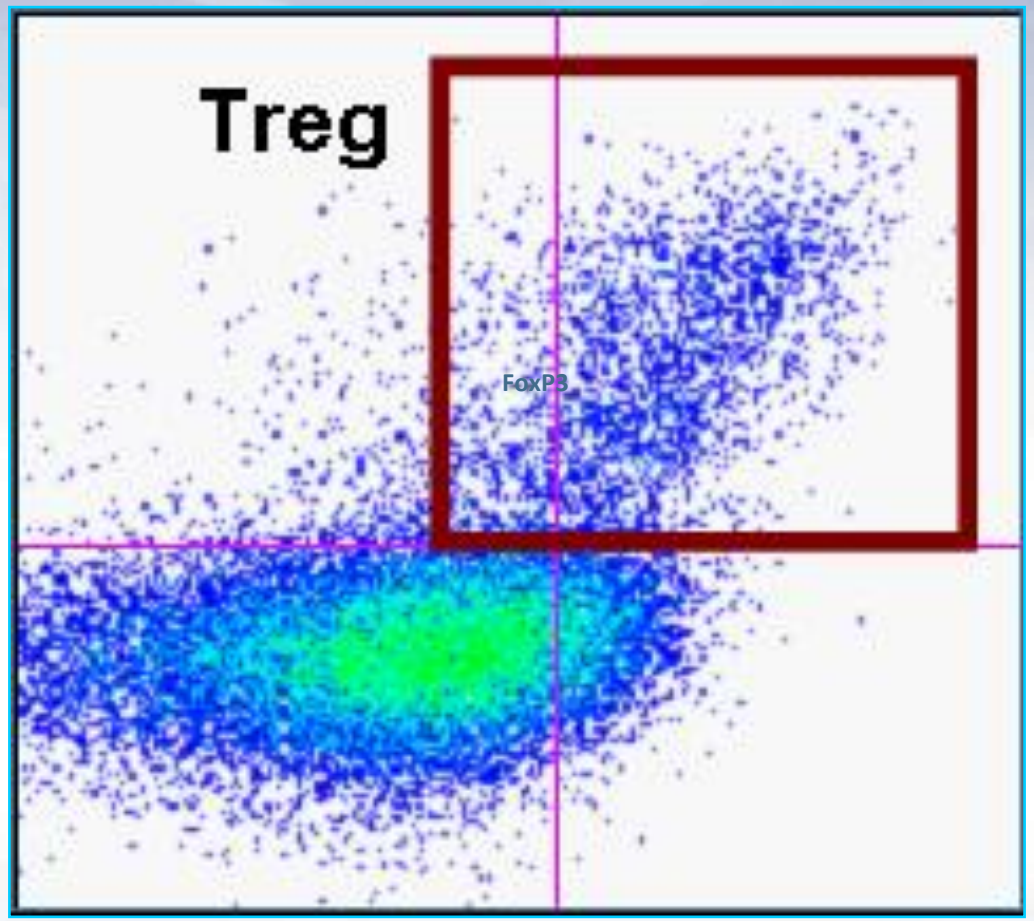
- The immune response to tumor cells can be evaded by a number of mechanisms:
  - Reduced antigen presentation[1]
  - Resistance to T-cell–mediated killing[1]
  - T-cell inhibition and anergy (eg, by upregulation of coinhibitory molecules, including PD-L1)[2]
  - Treg-mediated immunosuppression[1]



# Regulatory T cells


# Regulatory T cells

FoxP3




Flow cytometry plot gated on human CD4 T cells


# Regulatory T cells

- T-regs cells which have a role in regulating or suppressing other cells in the immune system
- T-regs control the immune response to self and foreign antigens and help prevent autoimmune disease.
- T-regs produced by a normal thymus are termed 'natural'
- T-regs formed by differentiation of naïve T cells outside the thymus, i.e. the periphery, or in cell culture are called 'adaptive'

# Regulatory T cells

- Natural T-reg are characterised as expressing both the CD4 T cell co-receptor and CD25, which is a component of the IL-2 receptor
- Tregs are thus CD4+ CD25+
- Expression of the nuclear transcription factor Forkhead box P3 (FoxP3) is the defining property which determines natural T-reg development and function

# Regulatory T cells

- FoxP3 is crucial for maintaining suppression of the immune system
- Naturally occurring mutations in the *FOXP3* gene can result in self-reactive lymphocytes that cause a rare but severe disease **IPEX** (**I**mmune Dysregulation, **P**olyendocrinopathy, **E**nteropathy, **X**-Linked) in humans

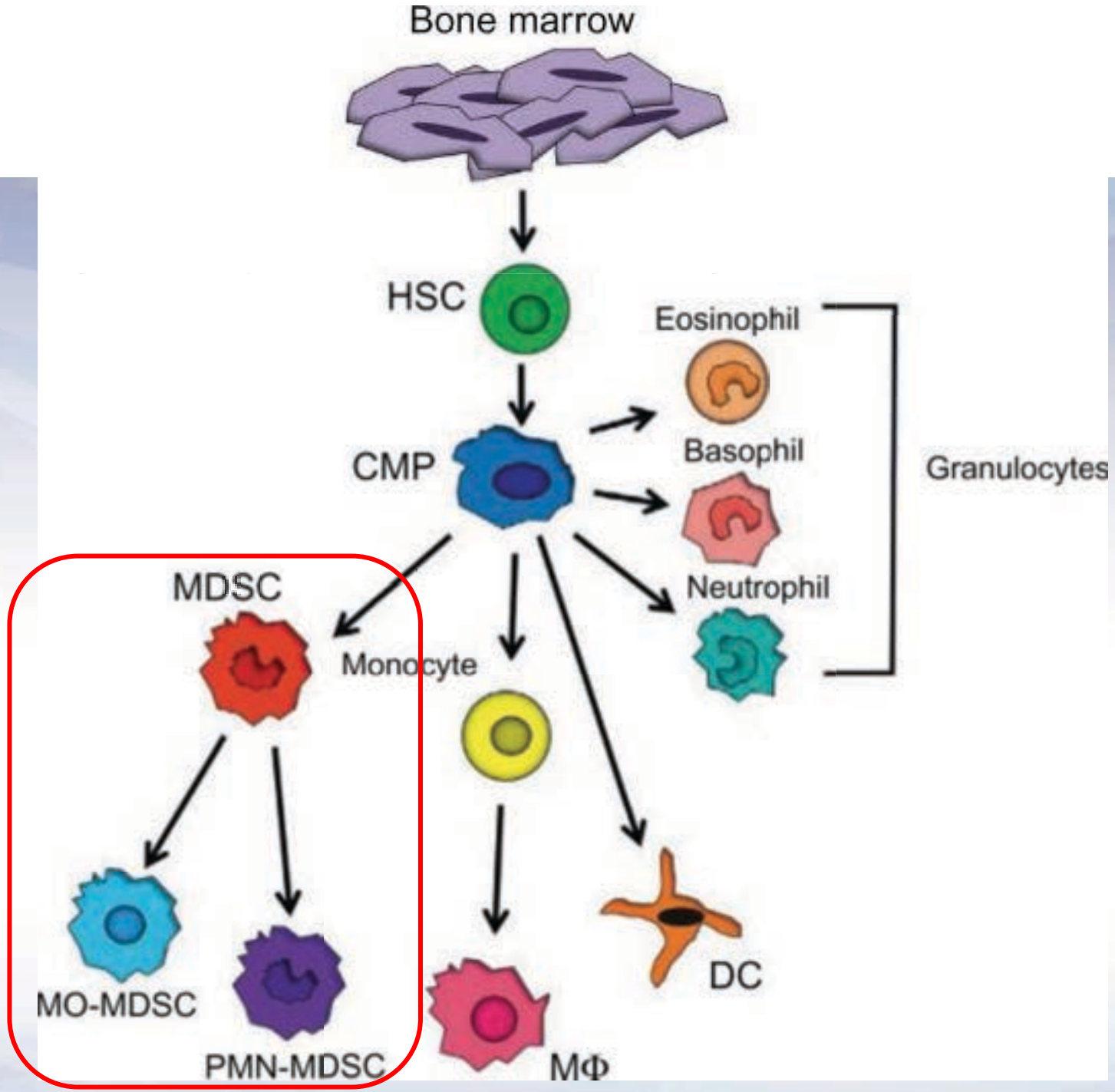
# MDSC
# Myeloid Derived Suppressor Cell

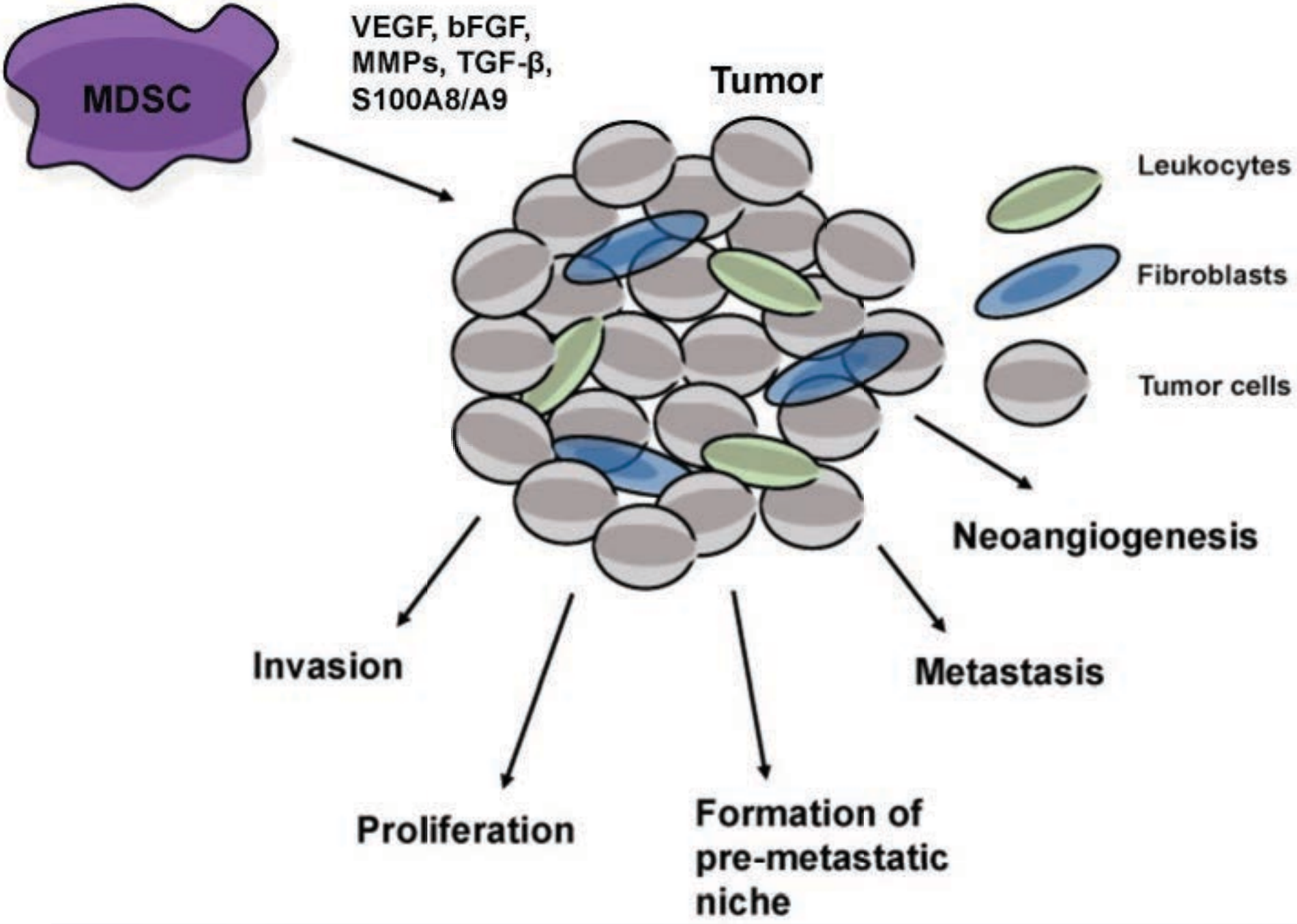

# MDSC

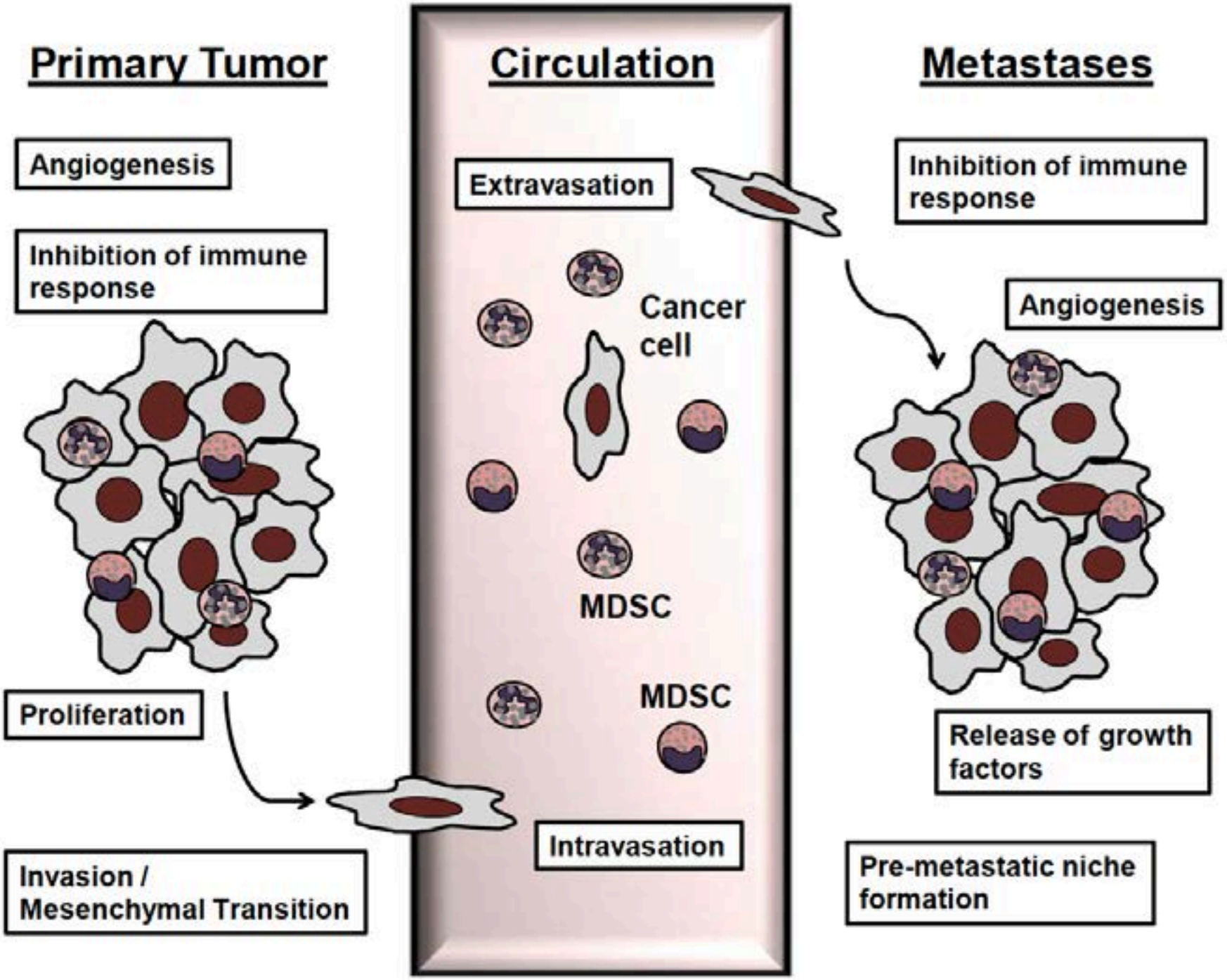
- MDSCs expand in pathological situations such as chronic infections and cancer
- Cancer is associated with altered hematopoiesis and development of MDSC

# MDSC

- MDSCs infiltrate tumors
- Inhibition of  T cells and NK cells immune
- MDSCs also accelerate angiogenesis, tumor progression and metastasis through the expression of cytokines and factors such as TGF-beta and IL10
- MDSC works on L-arginine metabolism & ROS


Bone marrow
HSC
Eosinophil
Basophil
CMP
Granulocytes
Neutrophil
MDSC
Monocyte
MO-MDSC
PMN-MDSC
MΦ
DC


MDSC
VEGF, bFGF,
MMPs, TGF-β,
S100A8/A9
Tumor
Leukocytes
Fibroblasts
Tumor cells
Neoangiogenesis
Invasion
Proliferation
Formation of
pre-metastatic
niche
Metastasis

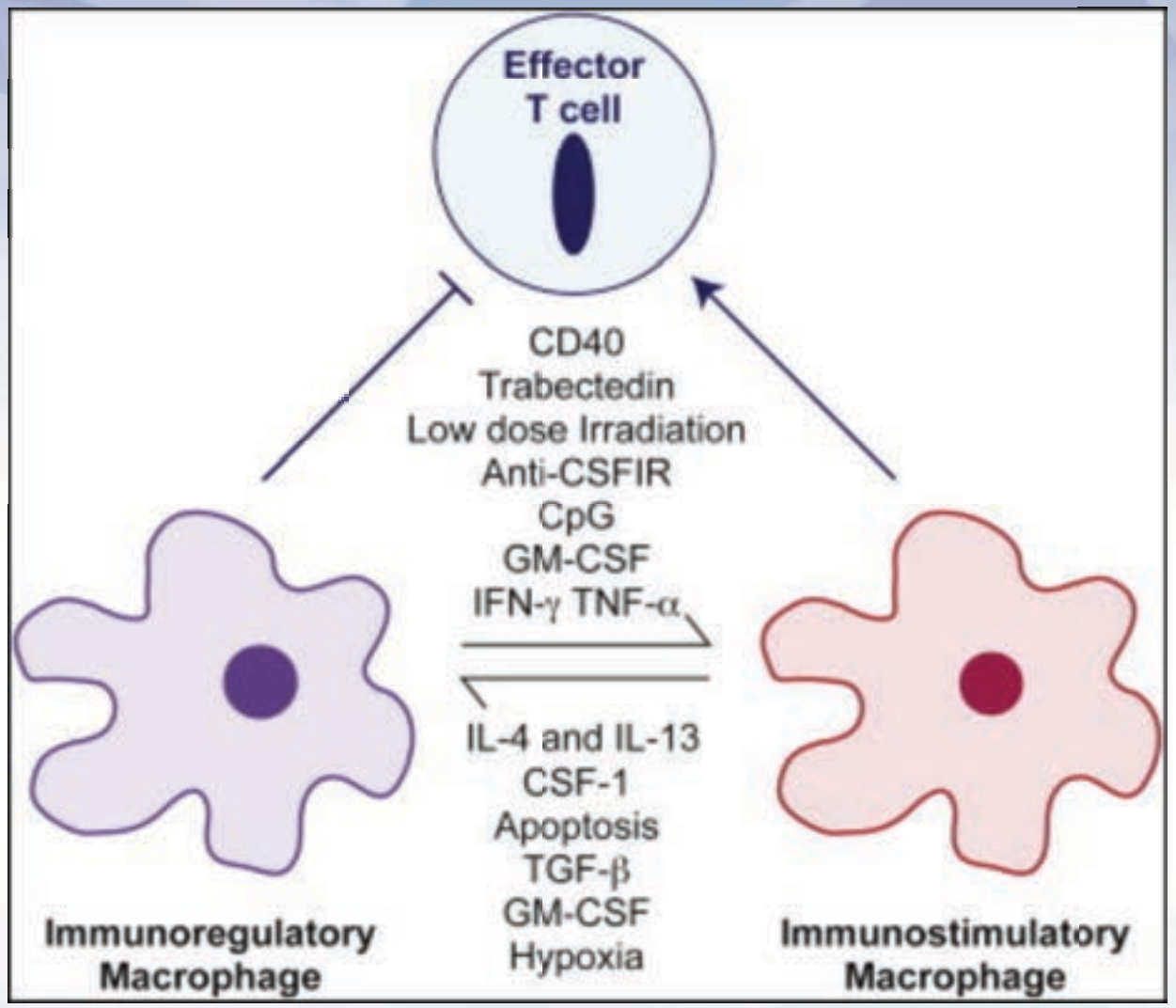

Primary Tumor
Circulation
Metastases
Angiogenesis
Inhibition of immune response
Proliferation
Invasion / Mesenchymal Transition
Extravasation
Cancer cell
MDSC
MDSC
Intravasation
Inhibition of immune response
Angiogenesis
Release of growth factors
Pre-metastatic niche formation

# TAM
# Tumor-associated macrophages

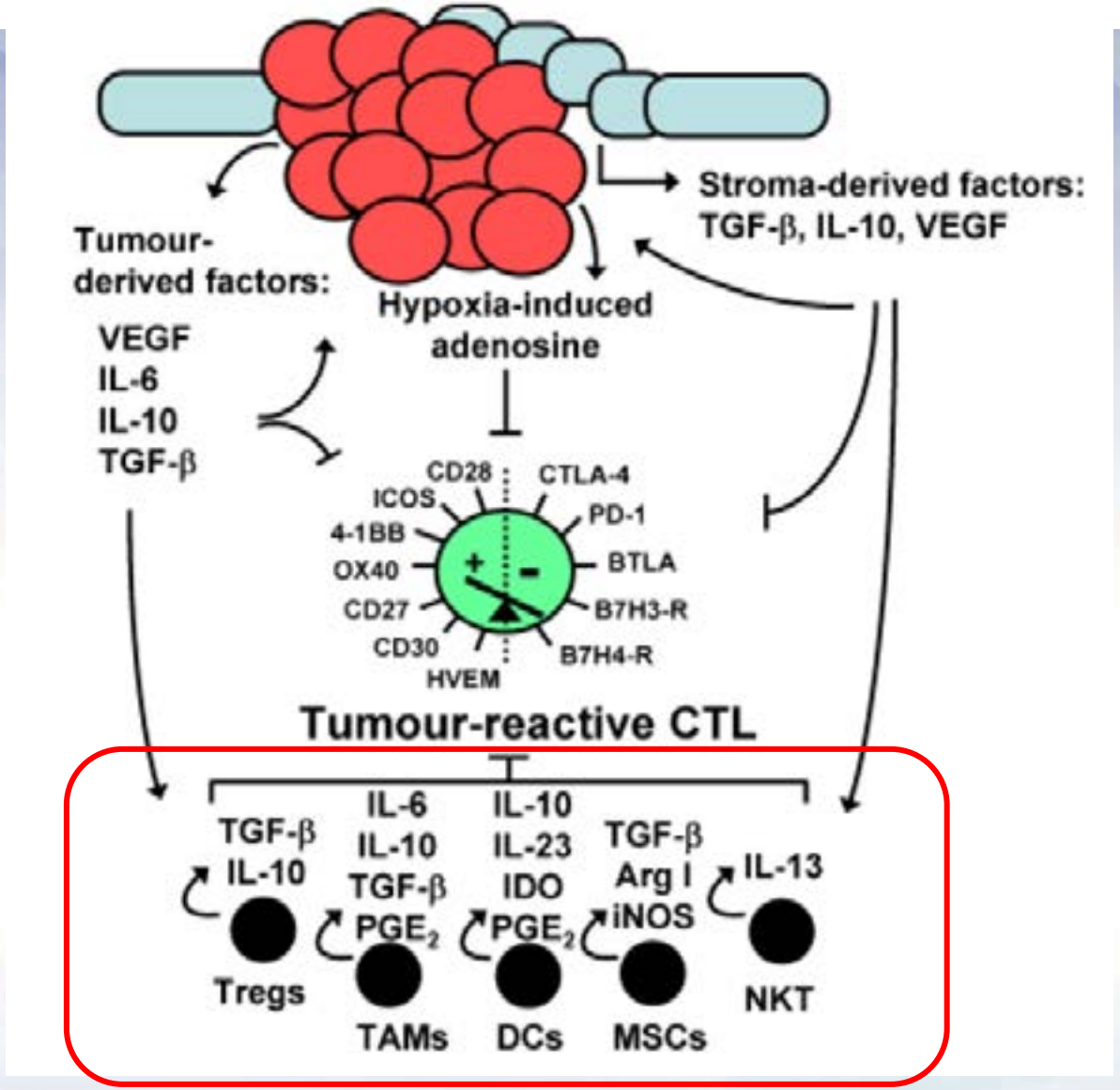

# Tumor-associated macrophages

- (**TAMs**) are a group of cells that originate mainly from the peri-tumoral tissue or bone marrow
- Two main types: M1 and M2
- Infiltrating M1 TAMs present in the early stages of tumorigenesis
- Secrete pro-inflammatory cytokines and in turn inhibit tumor growth
- M2 TAMs are predominant in the late stage of tumor formation
- It remains unclear when M1 TAMs are transformed to M2 TAMs
- Tumor hypoxia is currently thought to be associated with such a shift

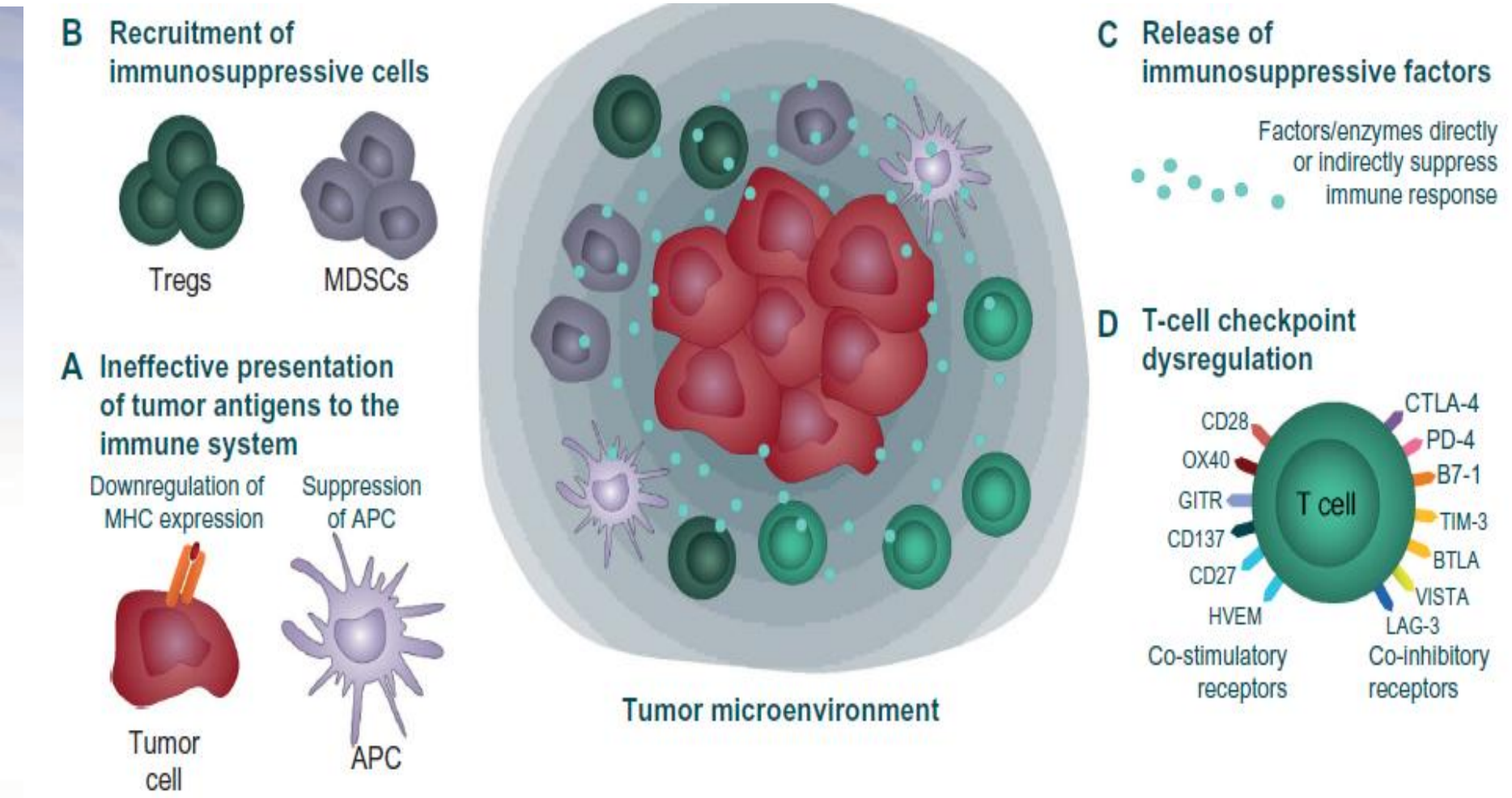
# Tumor-associated macrophages



# Factors inhibiting anti-tumor immune response



# HOW CAN TUMORS EVADE THE IMMUNE RESPONSE




APC = antigen-presenting cells; BTLA = B- and T-lymphocyte attenuator; CD = cluster of differentiation; CTLA-4 = cytotoxic T-lymphocyte–associated protein-4; GITR = glucocorticoid induced tumor necrosis factor-related protein; HVEM = herpes virus entry mediator; LAG-3 = lymphocyte-activation gene 3; MDSC = myeloid-derived suppressor cell; MHC = major histocompatibility complex; PD-4 = programmed death receptor-4; TIM-3 = T-cell immunoglobulin domain and mucin domain-3; Tregs = regulatory T cells; VISTA = V-domain immunoglobulin-containing suppressor of T-cell activation.

1. Davies M. *Cancer Manag Res.* 2014;6:63–75.

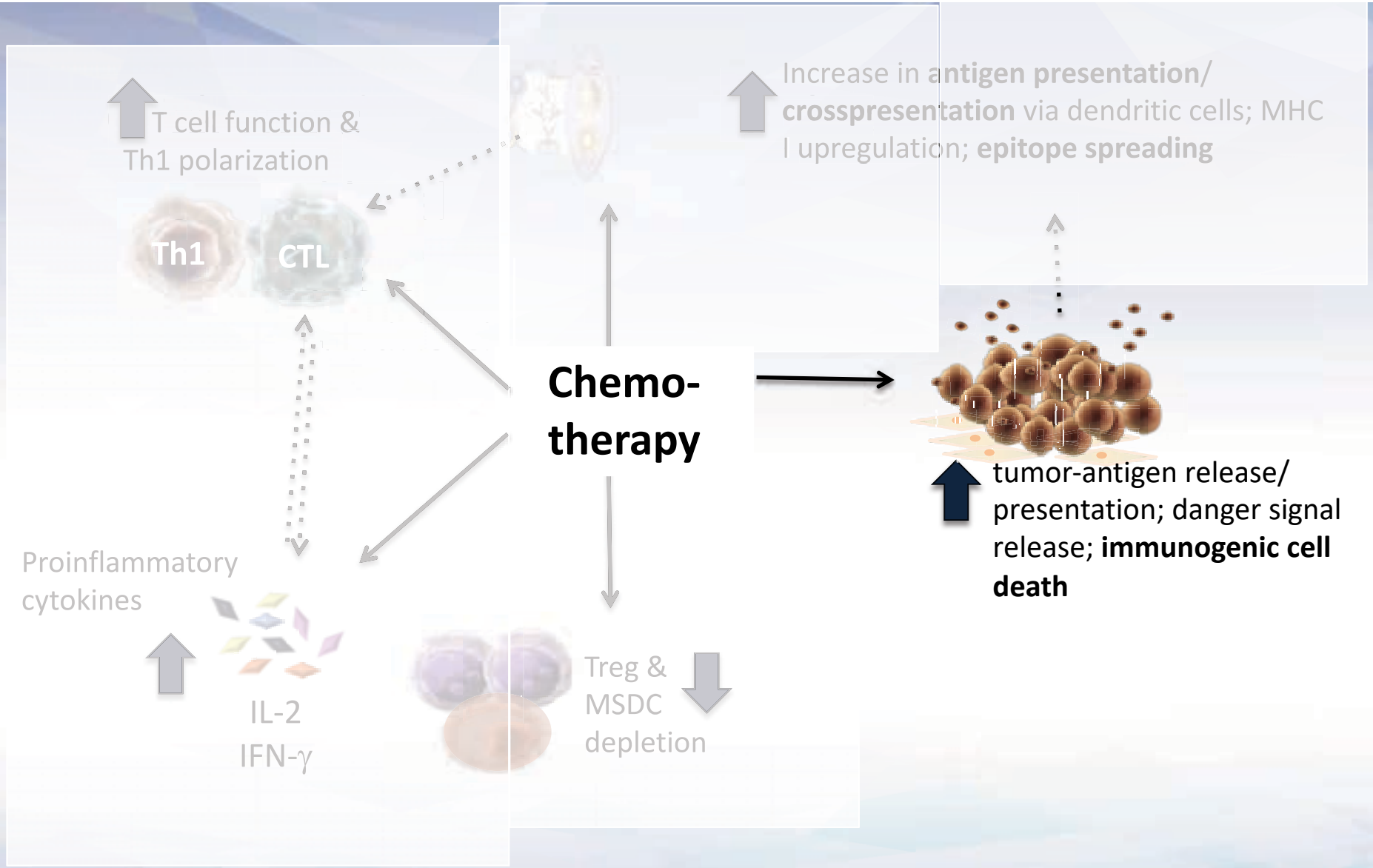
# Immune response and chemotherapy


# Immune response and chemotherapy

| Drug | Effect on immune system |
|---|---|
| Taxanes | • Enhances T cell and NK cell function<br>• Increases recruitment of TIL<br>• Increase efficacy of immuno-stimulatory agents |
| Doxorubicin | • Induces immunogenic cell death<br>• Increases proliferation of CD8 T cells<br>• Stimulates antigen presentation by DCs<br>• Stimulates MCP1 and M6PR |
| Cyclophosphamide | • Induces immunogenic cell death<br>• Suppresses Treg inhibitory functions and restores the proliferative capacity of effector T cells and NK cell cytotoxicity |
| Gemcitabine | • Reduces the number of myeloid suppressor cells<br>• Increases the antitumor activity of CD8(+) T cells and activated NK cells |
| Oxaliplatin | • Induces immunogenic cell death<br>• Increases MHC I complex<br>• Inhibits PD-L2 |

Kono et al. Cell Death and Disease 2013

# Chemotherapy: Pleiotropic stimulatory effects on the immune system



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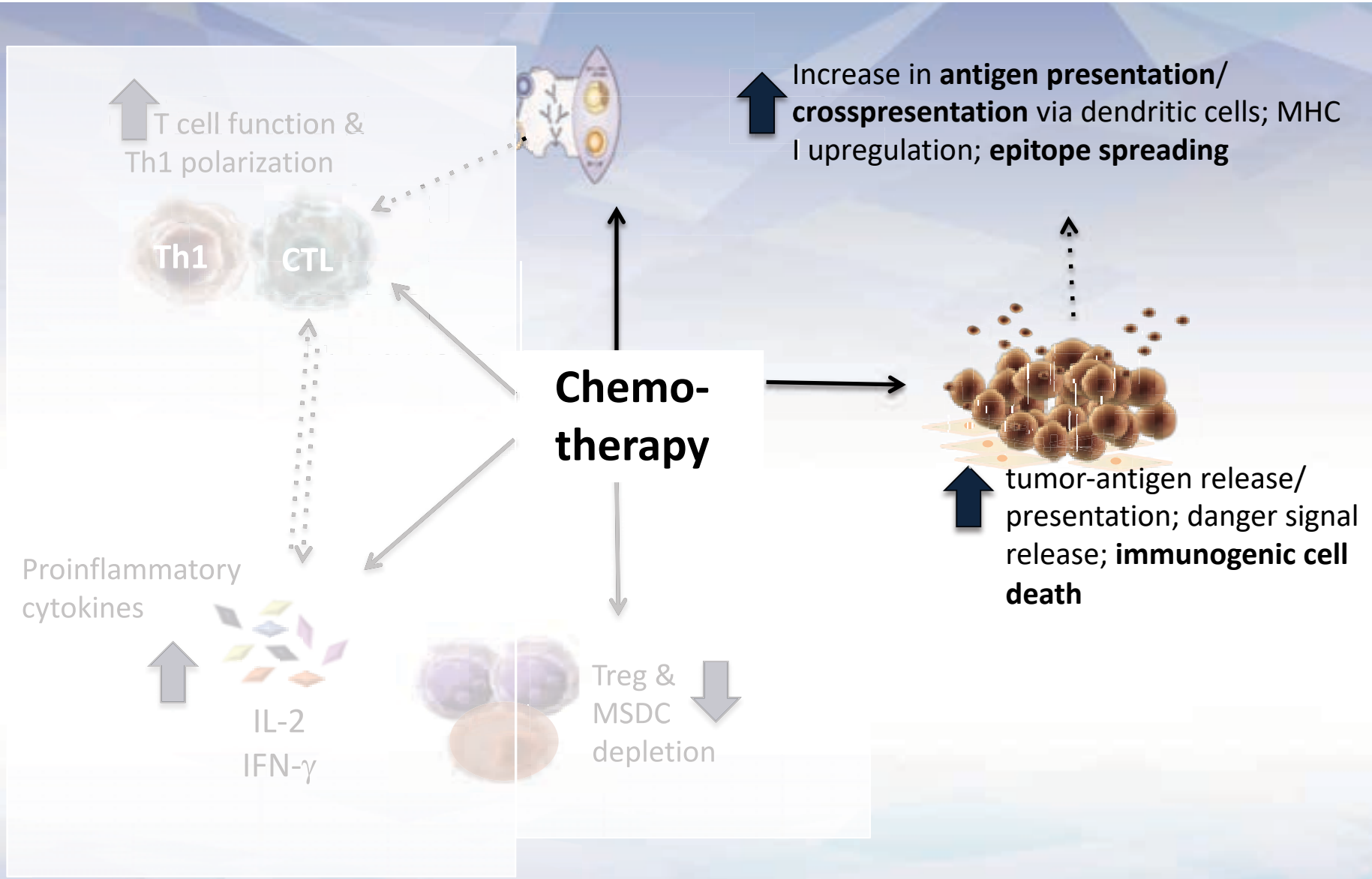

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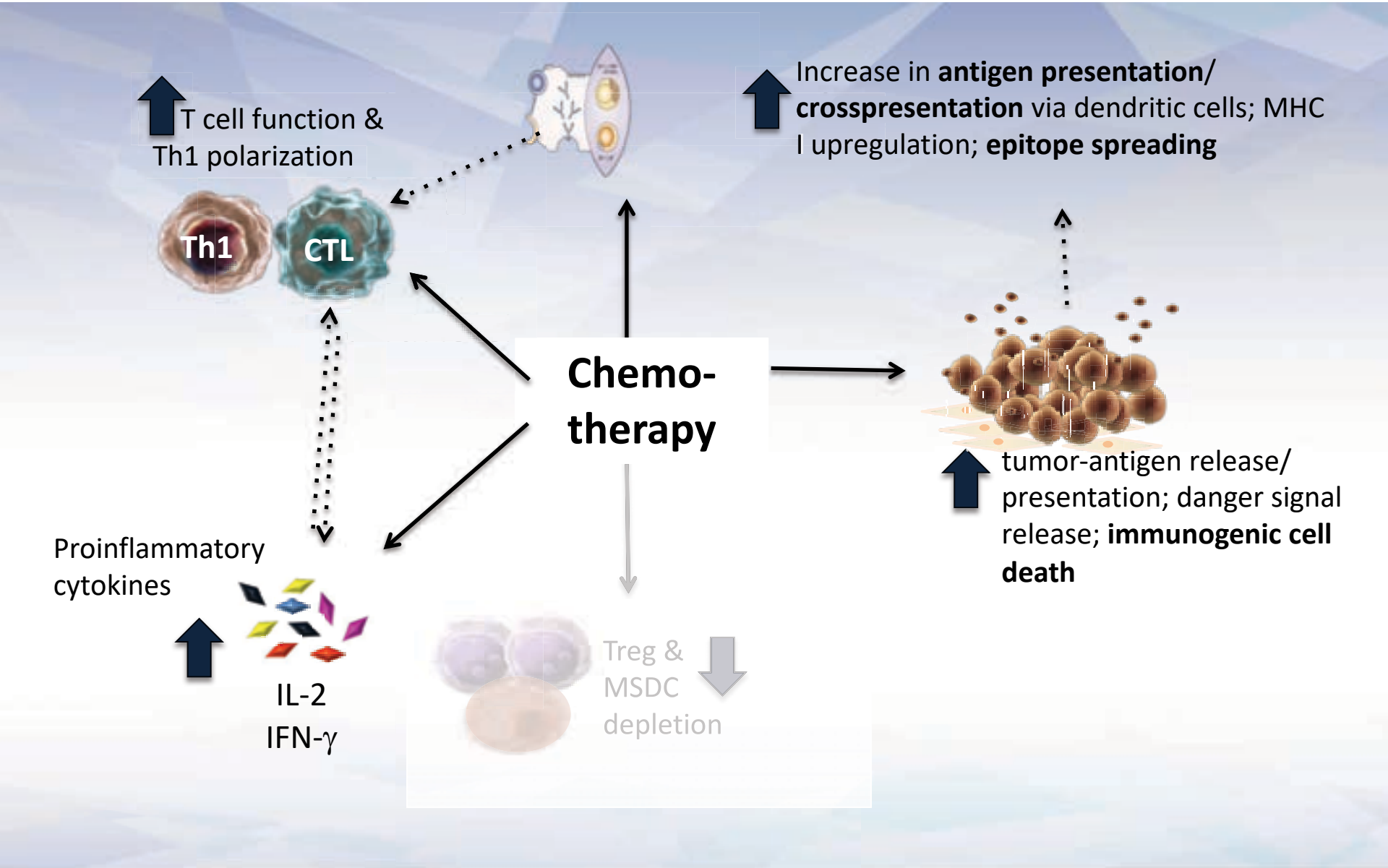

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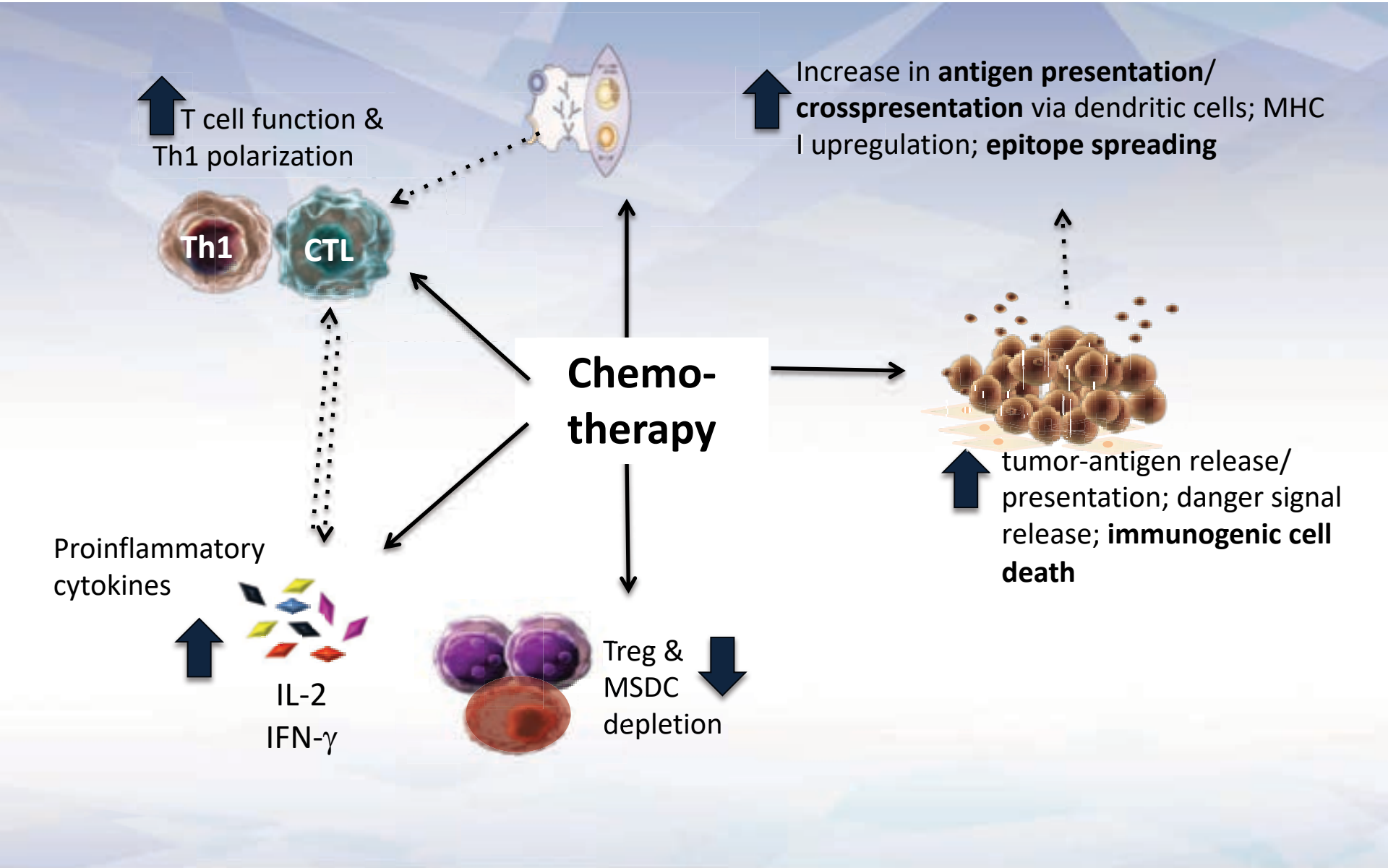


# Immunogenic Cell Death


# ICD

- Agents inducing ICD are targeting endoplasmic reticulum (ER), leading to ER stress and production of reactive oxygen species (ROS)
- Both ER stress and ROS production are key players of intracellular signaling pathways that govern ICD
- ICD is characterized by secretion of damage-associated molecular patterns (DAMPS)

# ICD – DAMPs

## Calreticulin & Heat-Shock Proteins

- Calreticulin (CRT) "eat me" signal
- Normally in the lumen of endoplasmic reticulum (ER)

- Heat-shock proteins (HSPs), HSP70 and HSP90
- On the cell surface HSPs have an immunostimulatory effect
- HSP Interact with antigen-presenting cell (APC) surface receptors like CD91 and CD40
- Facilitate cross-presentation of antigens derived from tumour cells on MHC class I molecule, which than leads to the CD8+ T cell response

# ICD – DAMPS
## High Motility Group B1 (HMGB1)

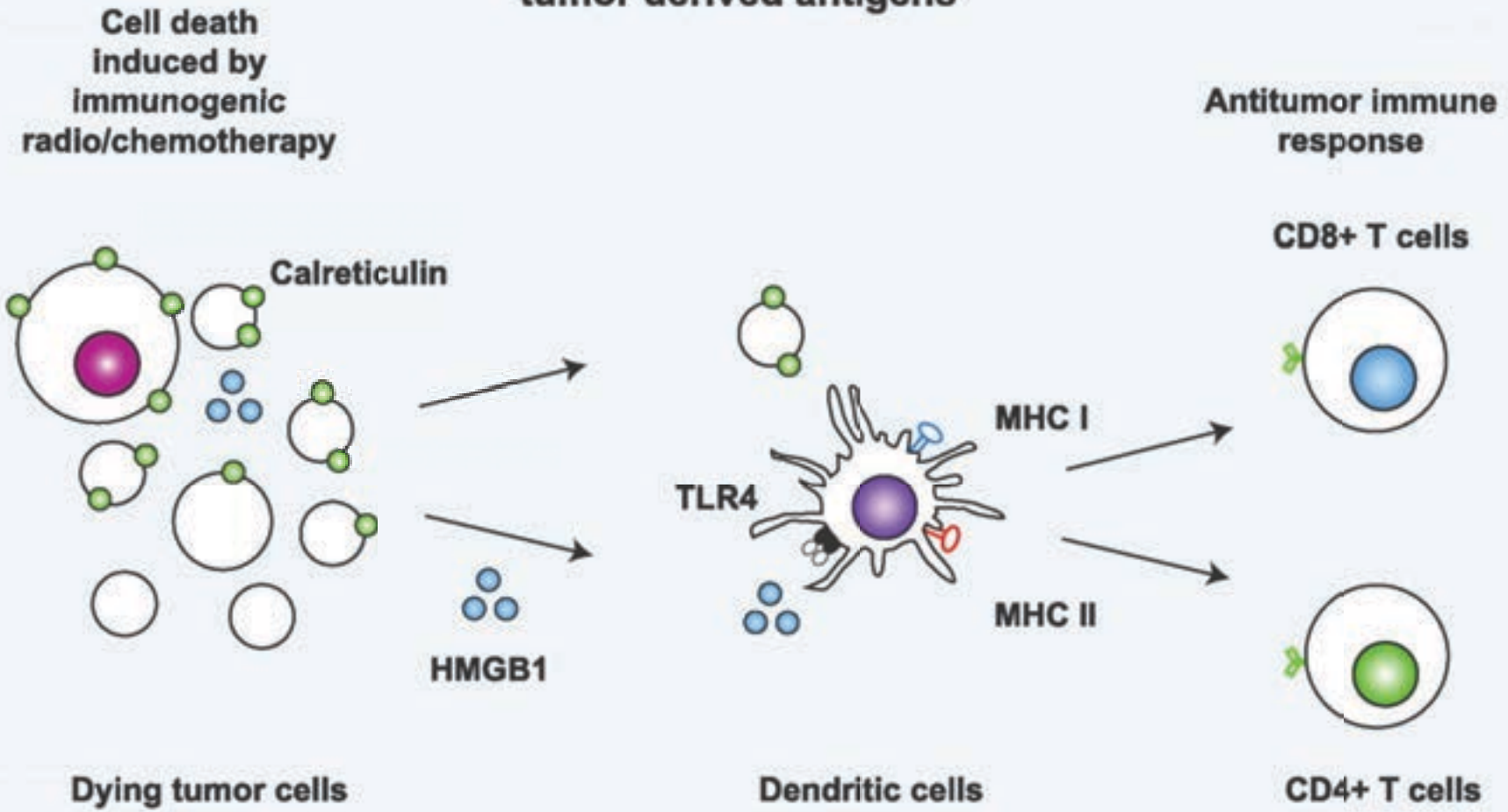
- Late apoptotic marker and its release to the extracellular space seems to be required for the optimal release and presentation of tumor antigens to dendritic cells

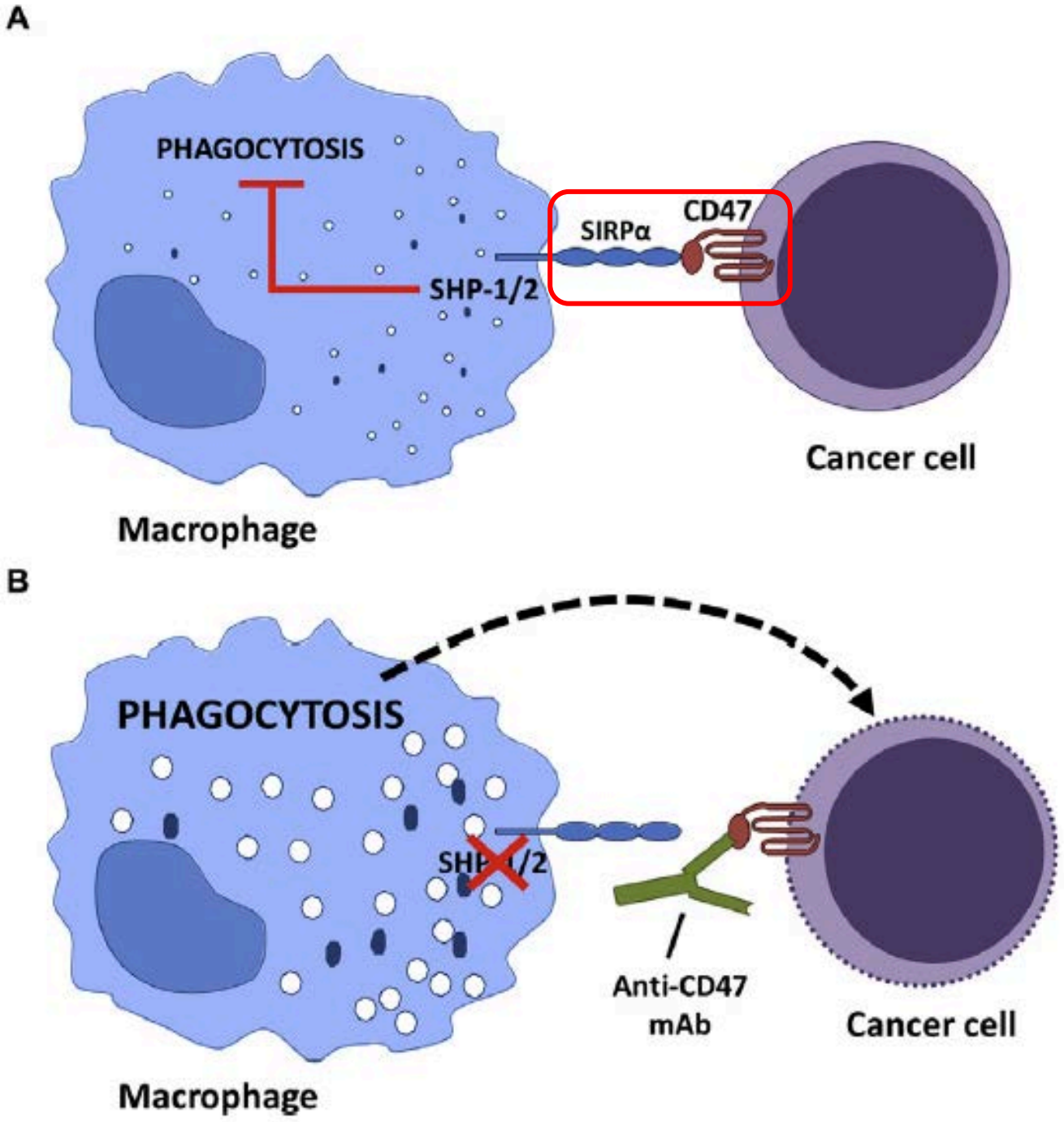
- It binds to several pattern recognition receptors (PRRs) such as Toll-like receptor (TLR) 2 and 4, which are expressed on APCs

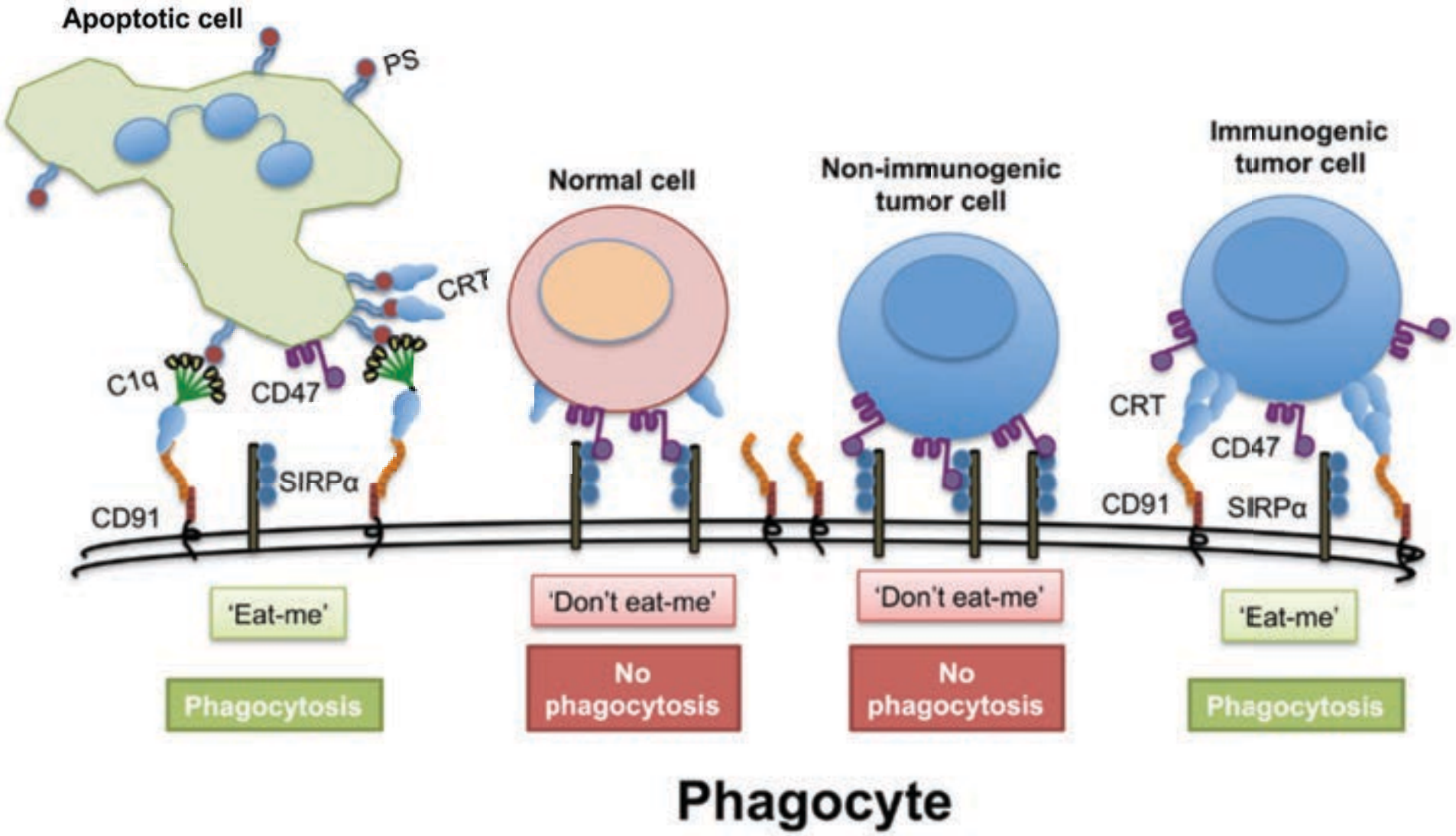
# ICD – DAMPS
# ATP

- ATP released during ICD
- Functions as a "find-me" signal for monocytes at the site of apoptosis

# Crosspresentation of tumor derived antigens

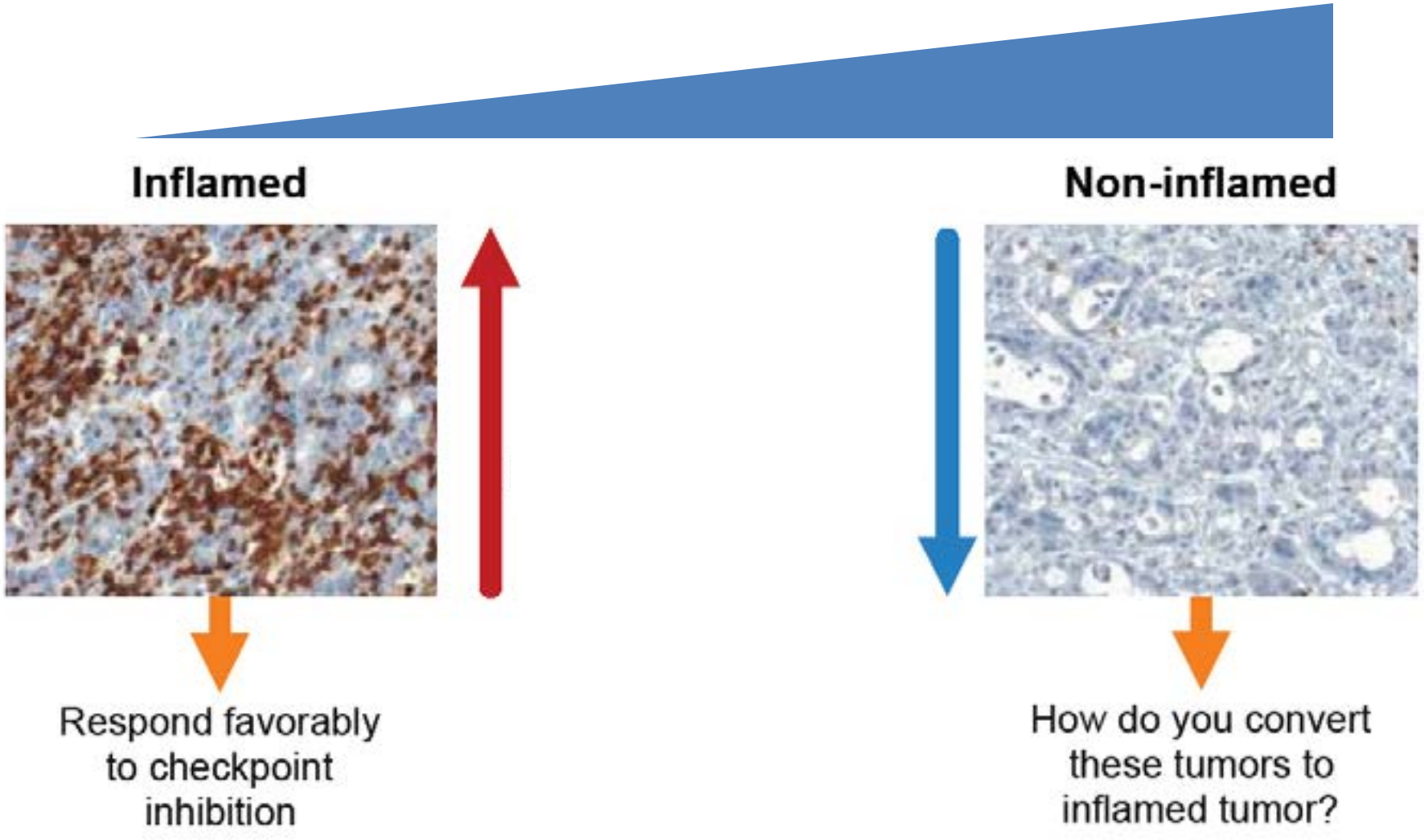



A
PHAGOCYTOSIS
SHP-1/2
SIRPα
CD47
Cancer cell
Macrophage
B
PHAGOCYTOSIS
Anti-CD47
mAb
Cancer cell
Macrophage

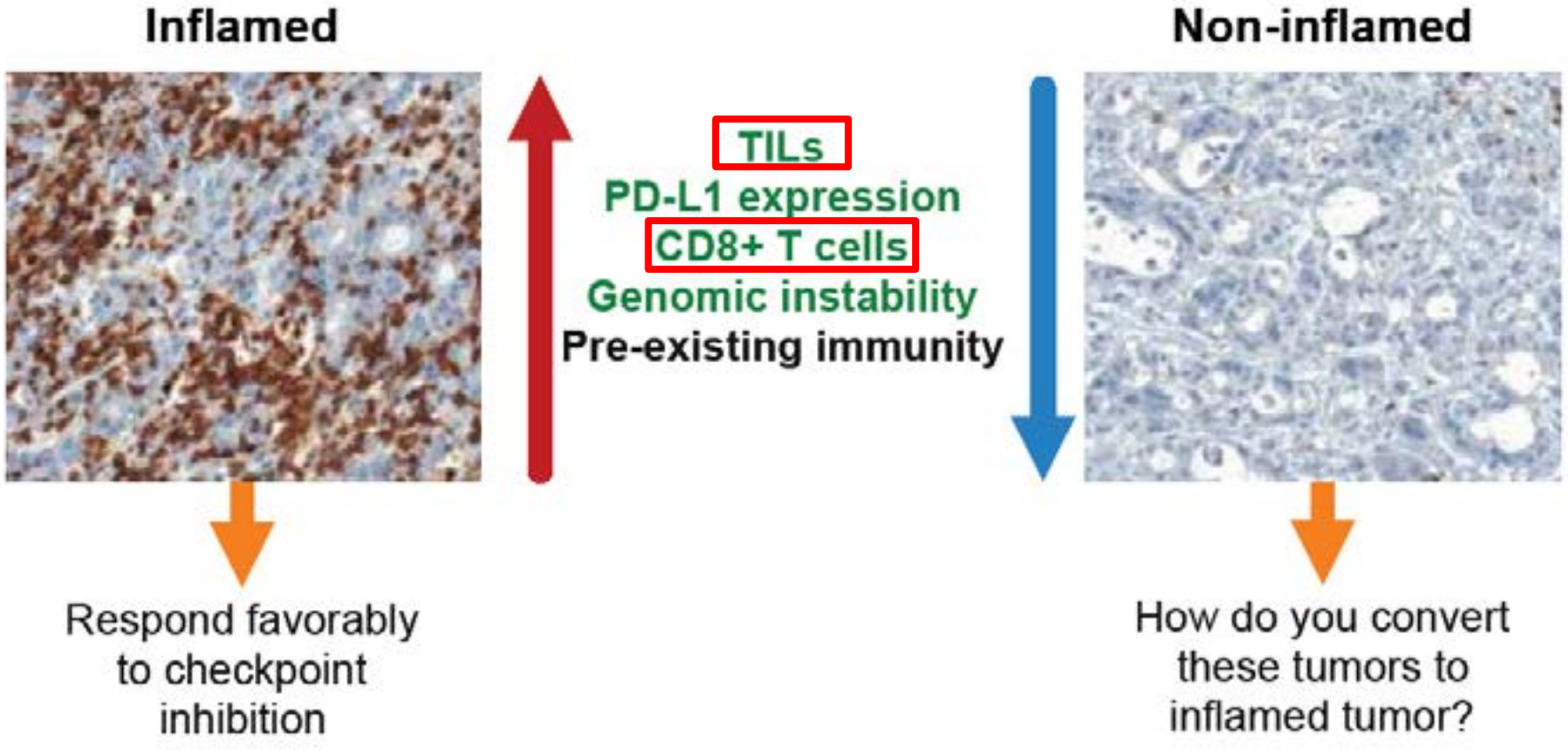

Apoptotic cell
PS
CRT
C1q
CD47
SIRPα
CD91
'Eat-me'
Phagocytosis
Normal cell
'Don't eat-me'
No phagocytosis
Non-immunogenic tumor cell
'Don't eat-me'
No phagocytosis
Immunogenic tumor cell
CRT
CD47
CD91
SIRPα
'Eat-me'
Phagocytosis
Phagocyte

# Immunogenic vs. Non-immunogenic Tumors

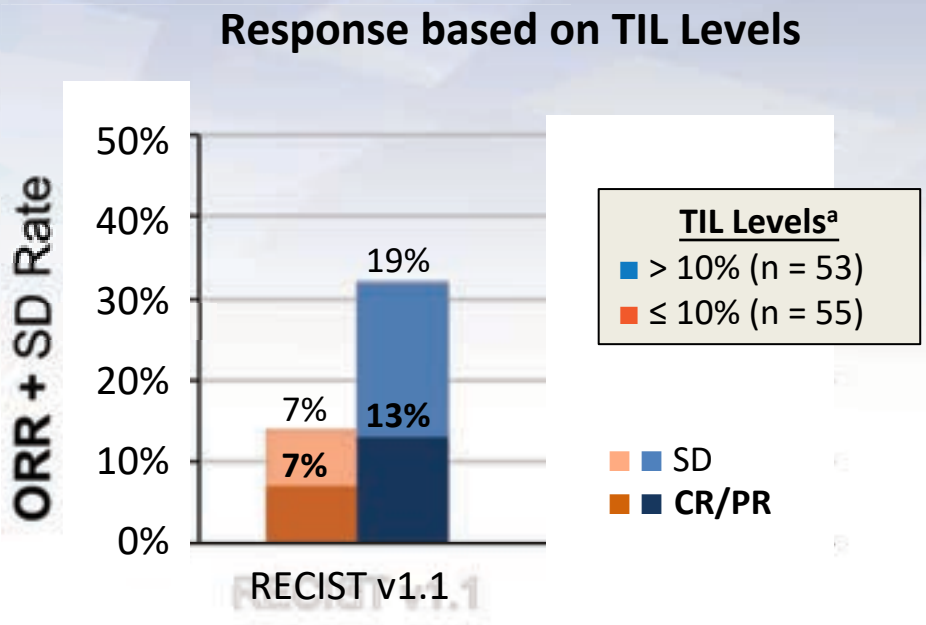

# Immunogenic vs. Non-immunogenic Tumors



# Immunogenic vs. Non-immunogenic Tumors

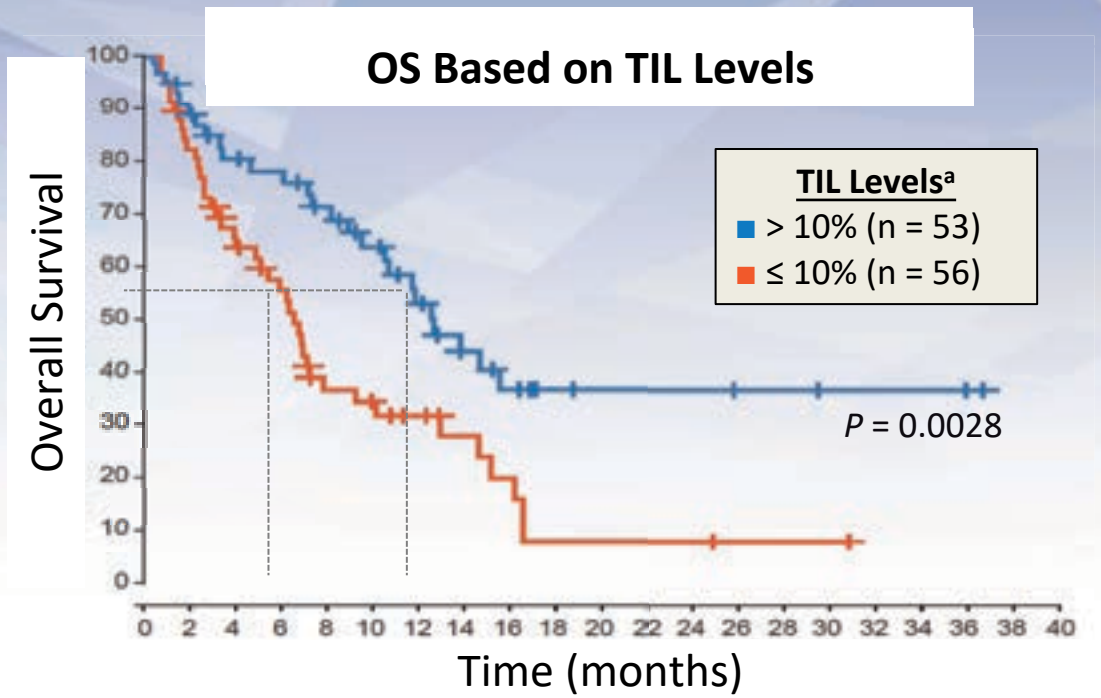


# Biomarker Analysis: Tumor-Infiltrating Lymphocytes




Schmid P, et al. AACR 2017 Phase Ia Atezolizumab in TNBC

# Biomarker Analysis: Tumor-Infiltrating Lymphocytes

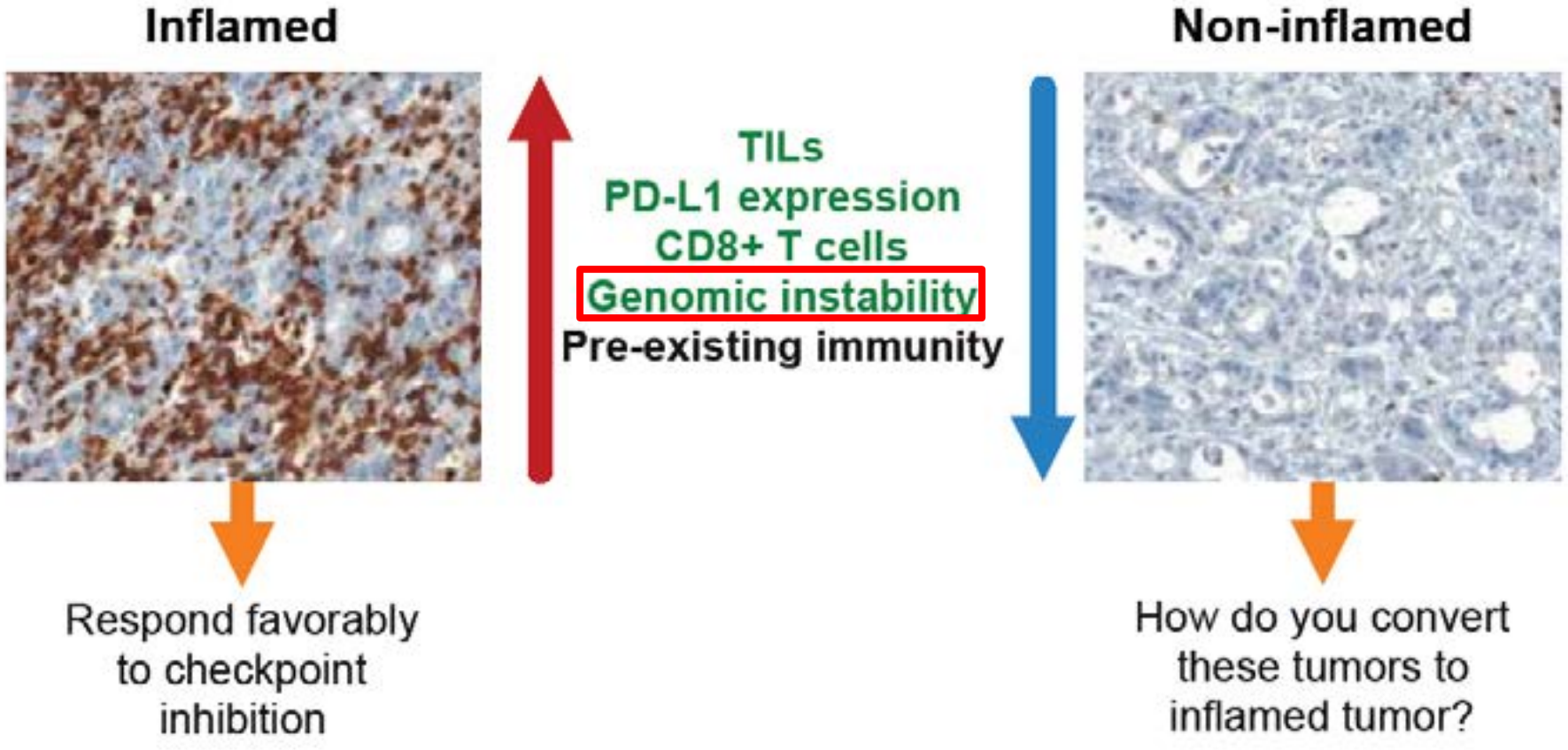



| | ≤ 10% TILs (n = 53) | > 10% TILs (n = 56) |
|---|---|---|
| **mOS (95% CI)** | 6.6 mo (4.9, 10.2) | 12.6 mo (10.5, NA) |

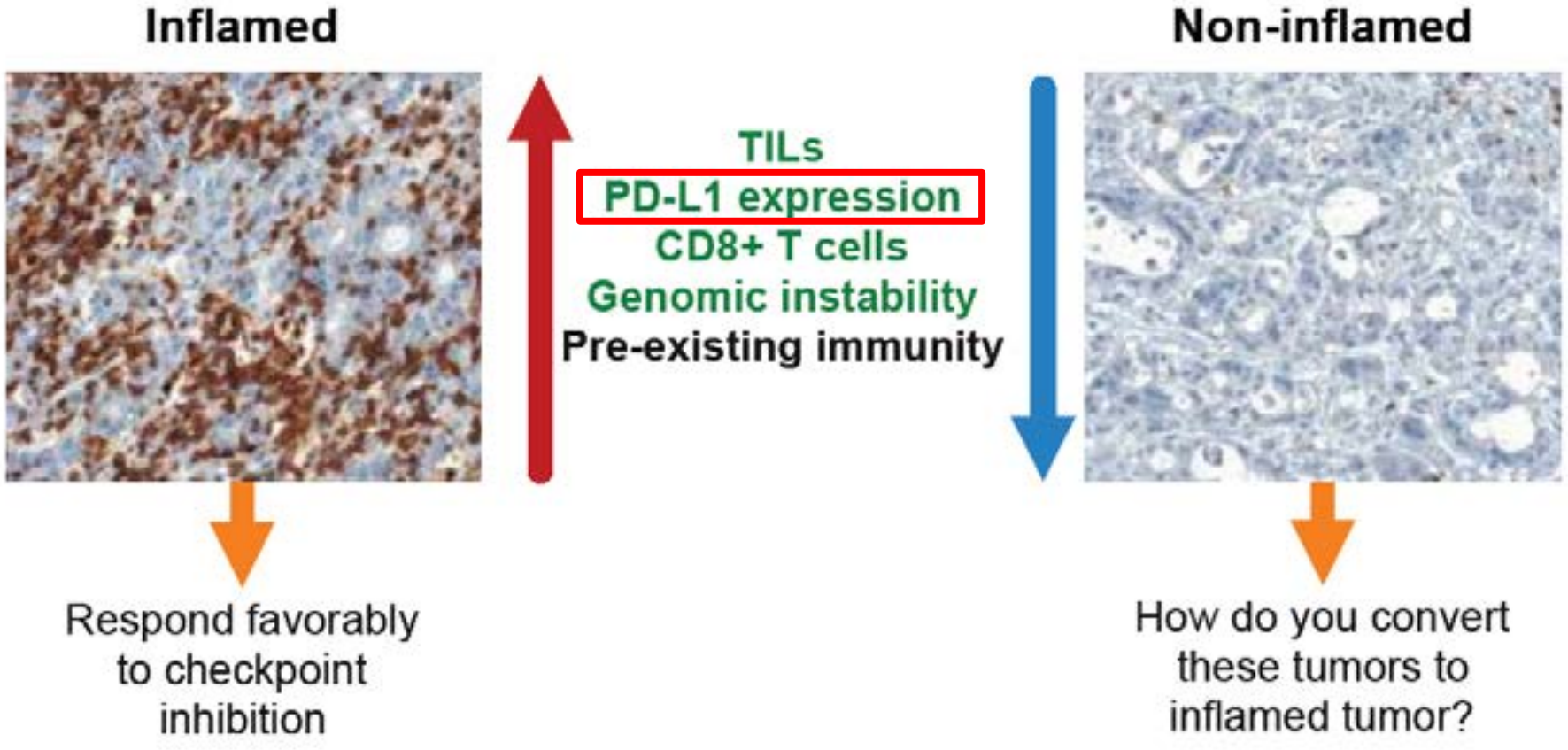
- Higher ORR and longer OS were seen with higher baseline TIL (CD8) infiltration

Schmid P, et al. AACR 2017 Phase Ia Atezolizumab in TNBC

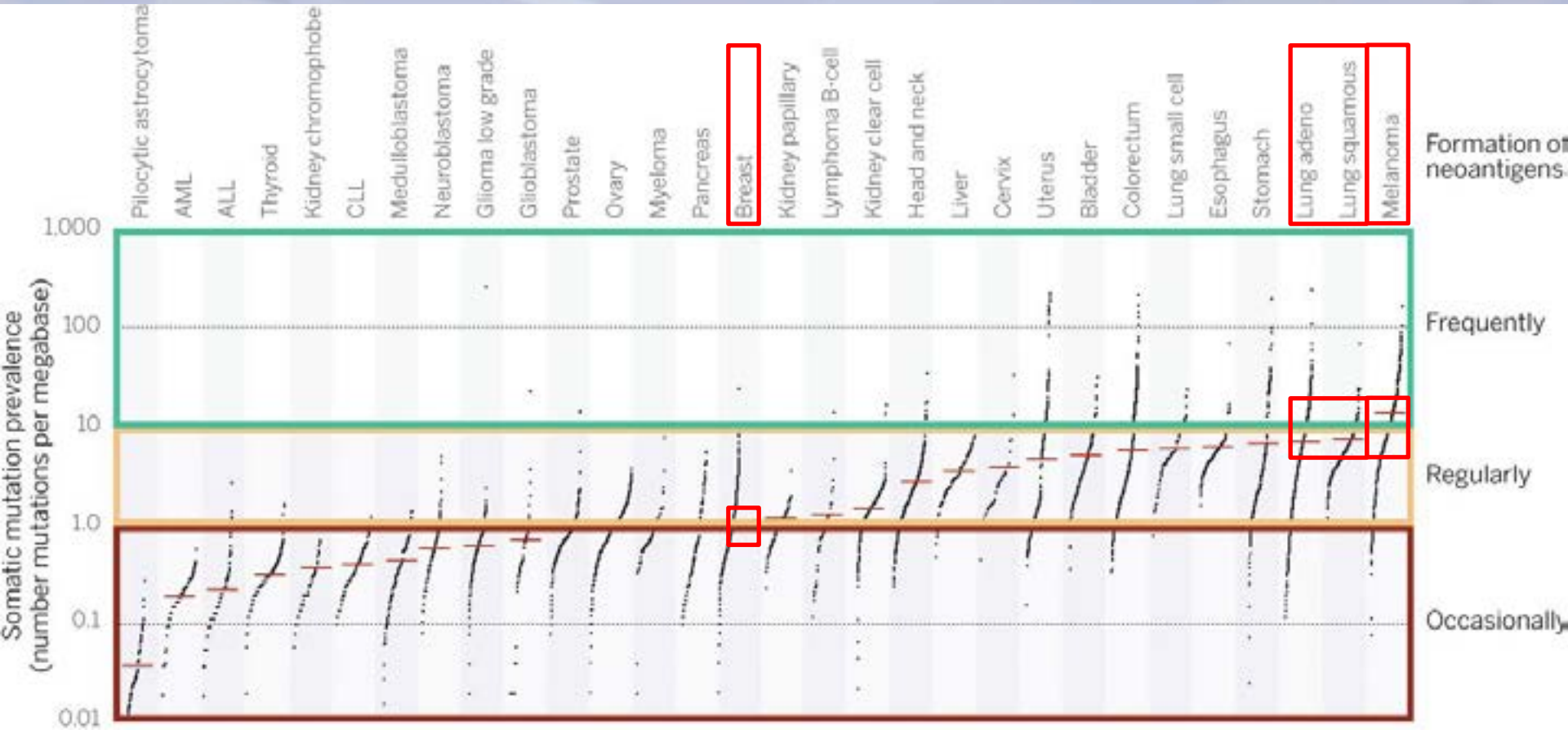
# Immunogenic vs. Non-immunogenic Tumors



# Immunogenic vs. Non-immunogenic Tumors

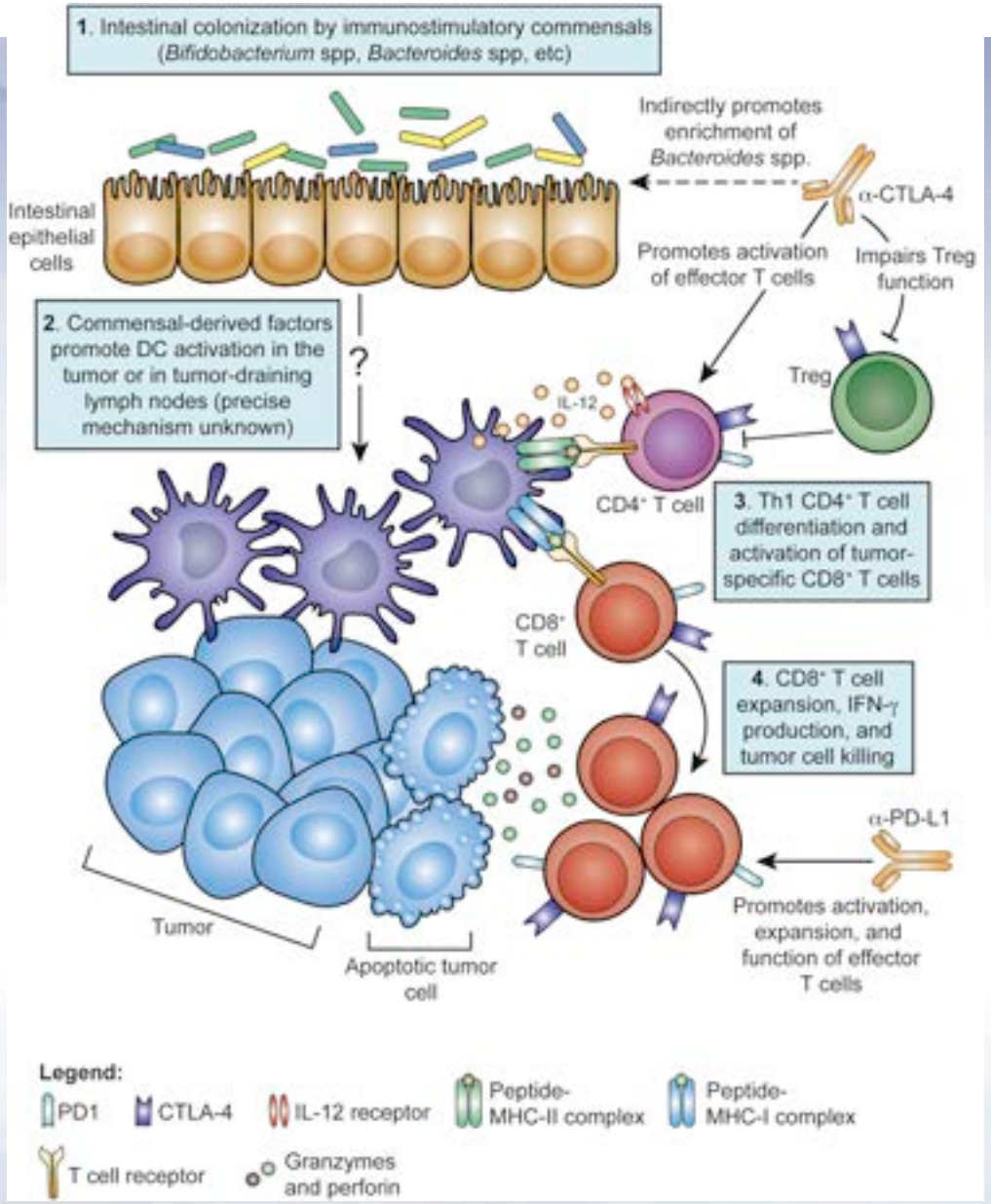


# Immunogenic vs. Non-immunogenic Tumors




Alexandrov et al., 2013

# MICROBIOME


1. Intestinal colonization by immunostimulatory commensals (*Bifidobacterium* spp, *Bacteroides* spp, etc)
Indirectly promotes enrichment of *Bacteroides* spp.
α-CTLA-4
Intestinal epithelial cells
Promotes activation of effector T cells
Impairs Treg function
2. Commensal-derived factors promote DC activation in the tumor or in tumor-draining lymph nodes (precise mechanism unknown)
?
Treg
IL-12
CD4⁺ T cell
3. Th1 CD4⁺ T cell differentiation and activation of tumor-specific CD8⁺ T cells
CD8⁺ T cell
4. CD8⁺ T cell expansion, IFN-γ production, and tumor cell killing
α-PD-L1
Promotes activation, expansion, and function of effector T cells
Tumor
Apoptotic tumor cell
Legend:
PD1
CTLA-4
IL-12 receptor
Peptide-MHC-II complex
Peptide-MHC-I complex
T cell receptor
Granzymes and perforin

# Conclusion

- Major advances in the understanding of the immune system in cancer
- Major advances in immunotherapy in cancer treatment
- Additional work is needed
- Long term remissions & possible cures



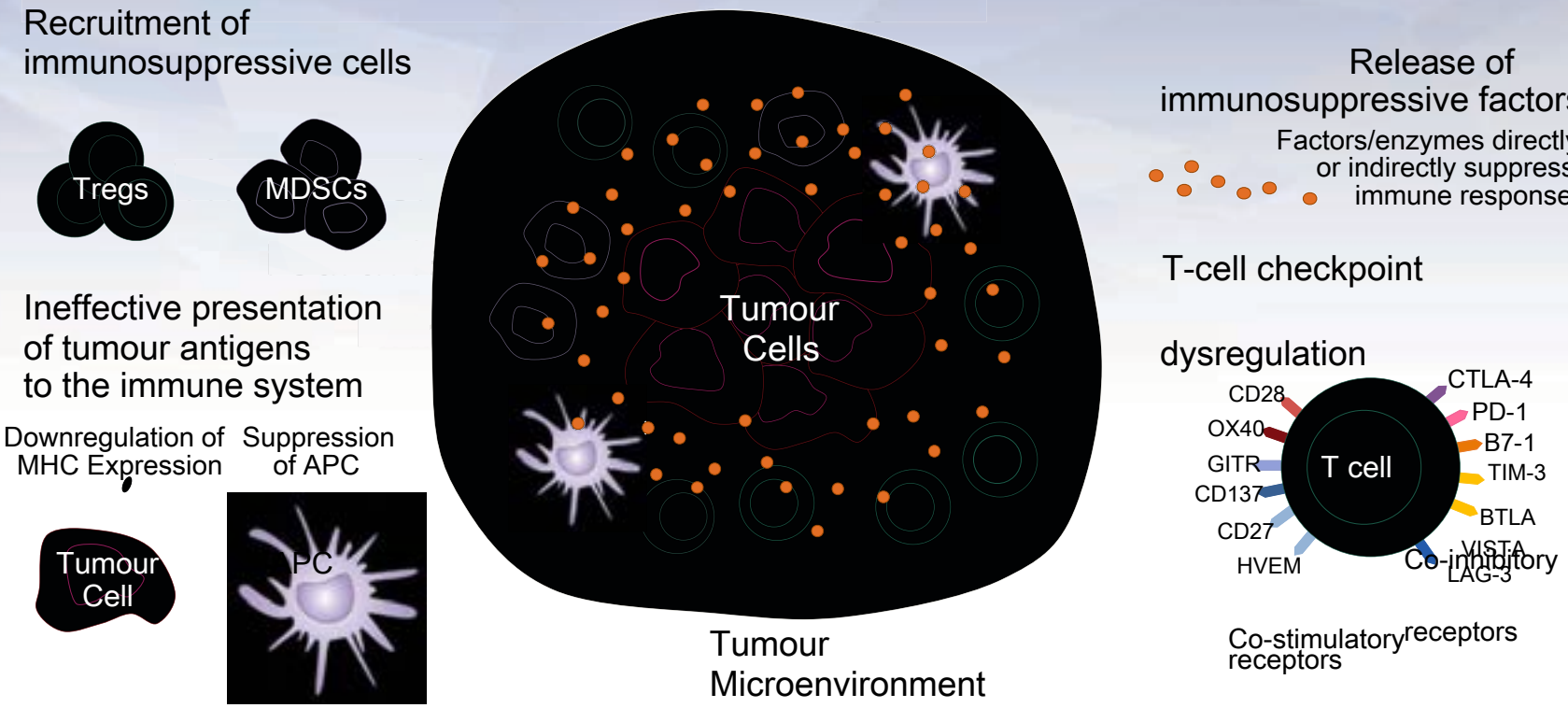
JOBURG

# Thank You


2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

# Immune Escape in Cancer

Many tumours escape the immune response by creating an immunosuppressive microenvironment that prevents an effective antitumour response[1,2]




The mechanisms tumours use to escape the immune system provide a range of potential therapeutic targets for cancer

APC=antigen-presenting cell; MDSC=myeloid-derived suppressor cell; MHC=major histocompatibility complex; Treg=regulatory T cell.

1. Bremnes RM et al. J Thorac Oncol. 2011;6:824-833. 2. Jadus MR et al. Clin Dev Immunol. 2012:160724.

# Combining immune pathways to refine response

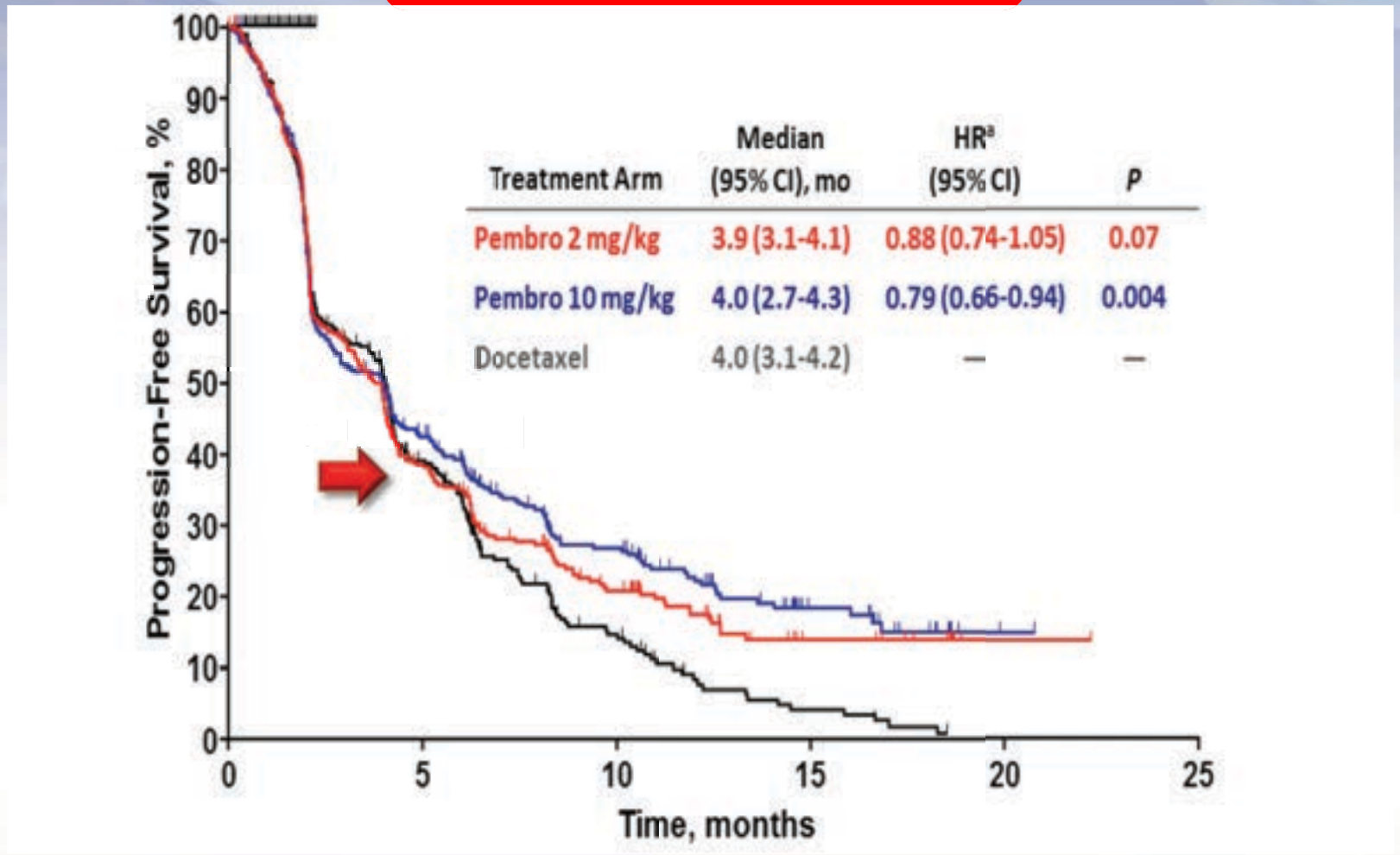
- Immune balance is maintained through the combination of activating and inhibitory signaling pathways.[8,9] Signaling pathways can work **in combination** to **directly** or **indirectly** modulate the activity of effector cells such as cytotoxic T cells and NK cells.

Immune pathways that involve molecules found on the surface of effector cells can **directly** inhibit or activate their antitumor activity.[77-79]

Inhibitory signals from other immune-related pathways can **indirectly** augment immune suppression.[25]

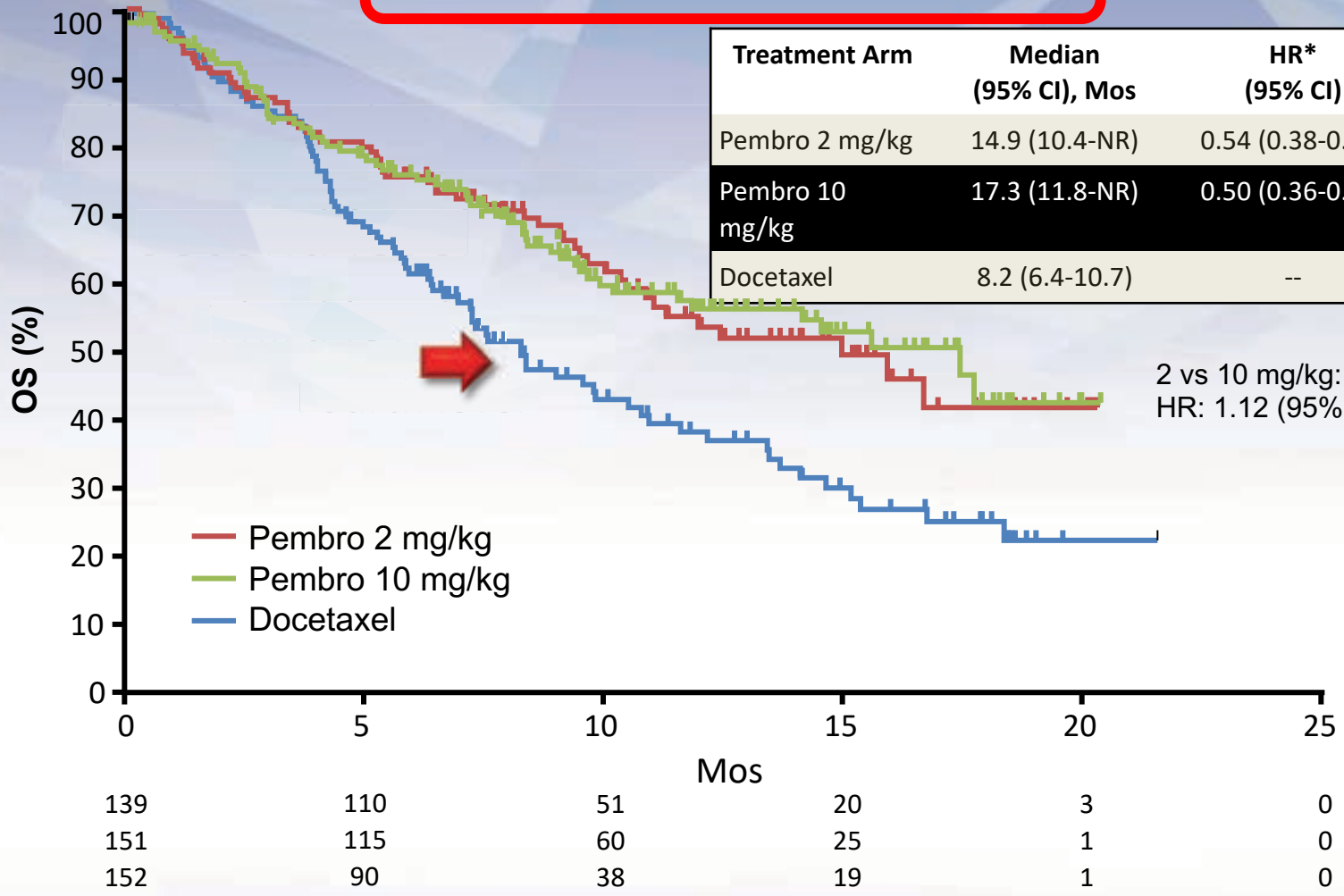
**Modulation of two immune pathways can more effectively activate immune activity compared with either pathway alone, as suggested by preclinical data.[80-83]**

# KEYNOTE-010: OS for PD-L1 TPS ≥ 1% Stratum



# KEYNOTE-010: OS for PD-L1 TPS ≥ 50% Stratum

| Treatment Arm | Median (95% CI), Mos | HR* (95% CI) | *P* Value |
|---|---|---|---|
| Pembro 2 mg/kg | 14.9 (10.4-NR) | 0.54 (0.38-0.77) | .0002 |
| Pembro 10 mg/kg | 17.3 (11.8-NR) | 0.50 (0.36-0.70) | < .0001 |
| Docetaxel | 8.2 (6.4-10.7) | -- | -- |

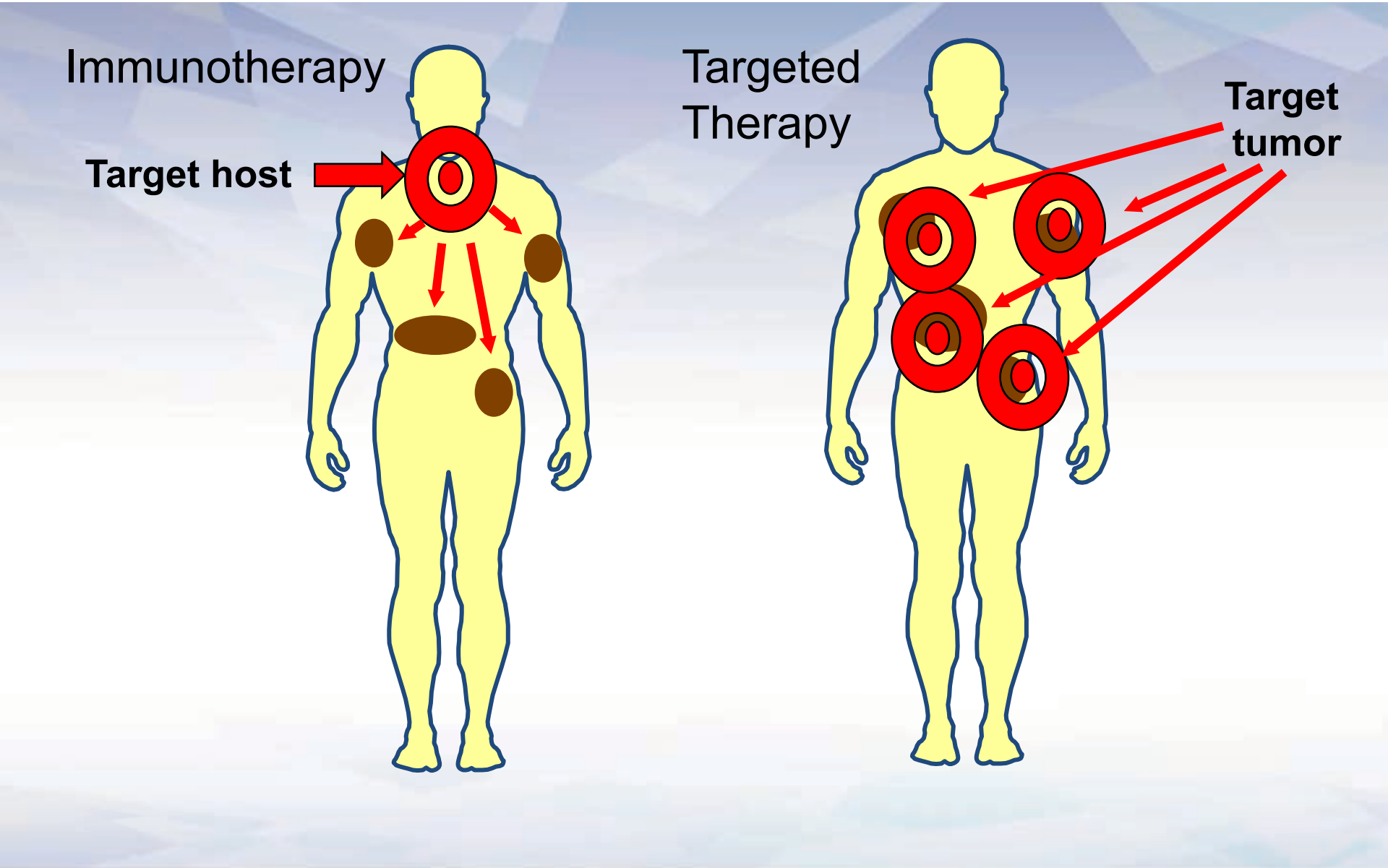



2 vs 10 mg/kg:
HR: 1.12 (95% CI: 0.77-1.62)

*Comparison of pembrolizumab vs docetaxel.

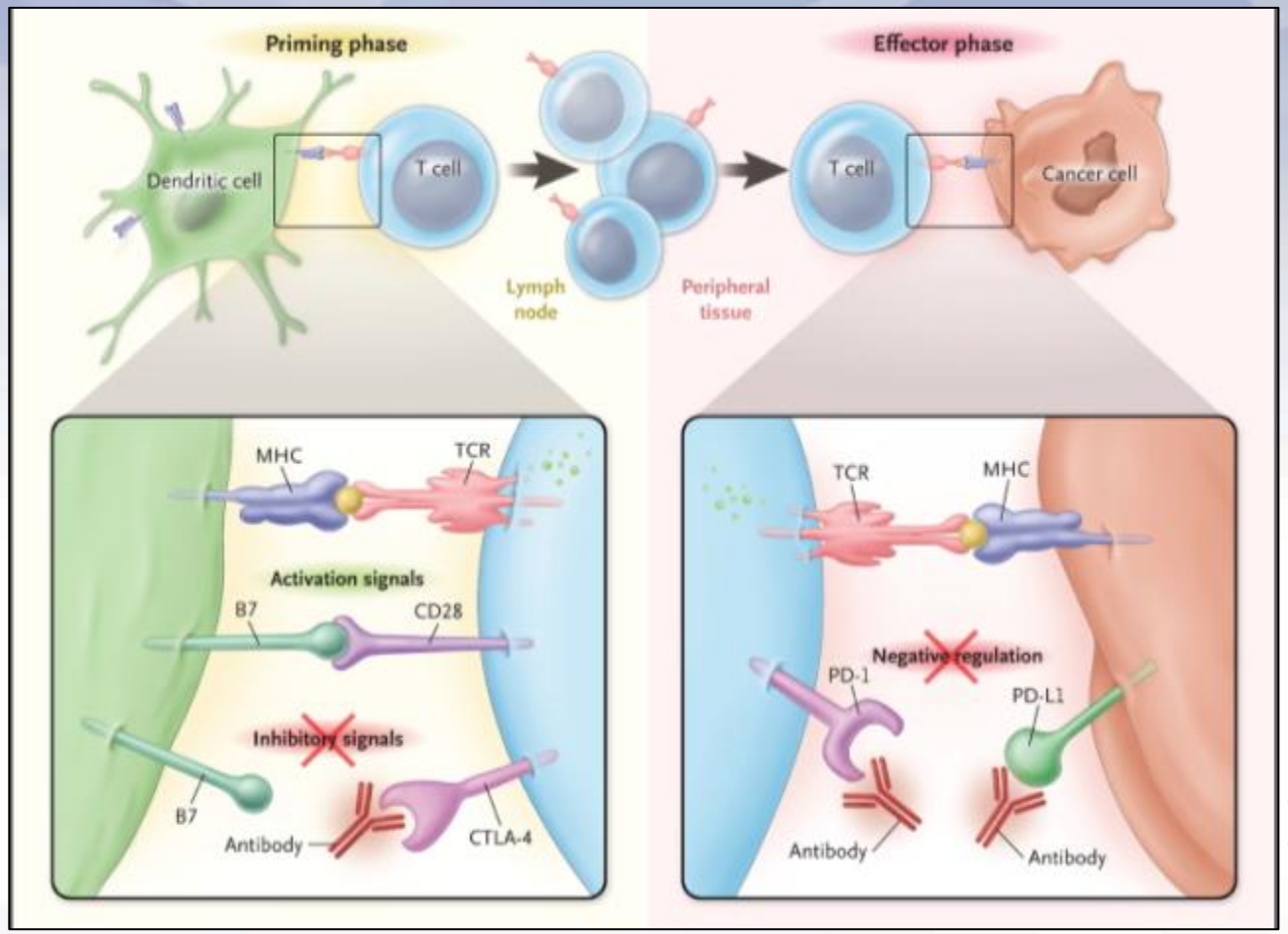
Herbst R, et al. Lancet. 2015;[Epub ahead of print].

# Two Paradigms for Advancing the Therapy of Metastatic Melanoma



# CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

CTLA-4 mAbs:
Ipilimumab
Tremelimumab




PD-1 mAbs:
Nivolumab
Pembrolizumab

PD-L1 mAbs:
Atezolizumab
Avelumab
Durvalumab

# HOW CAN TUMORS EVADE THE IMMUNE RESPONSE

# Empowering the immune system: innate and adaptive immunity

## Innate immune response

The first line of defense, it identifies and attacks tumor cells without antigen specificity.[1,4-6] **Natural killer (NK) cells** are the main effector cells of innate immunity.

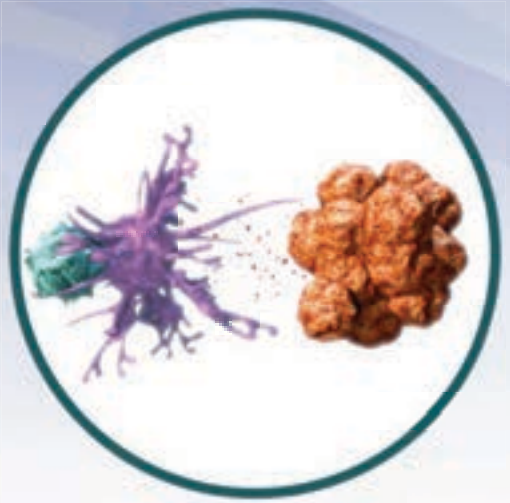
## Adaptive immune response

A durable response that attacks tumor antigens.[1,6] Once activated, it can be sustained through a memory response.[7] **Cytotoxic T cells** are the main effector cells of adaptive immunity.

The antitumor activity of NK cells and cytotoxic T cells is regulated through a network of **activating** and **inhibitory** signaling pathways:[8-10]

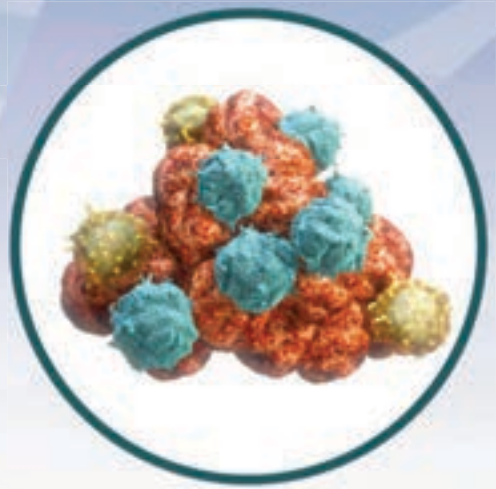
**⊕ ACTIVATING**
**Stimulating pathways trigger immune responses**

**⊖ INHIBITORY**
**Pathways that counterbalance immune activation such as checkpoints**



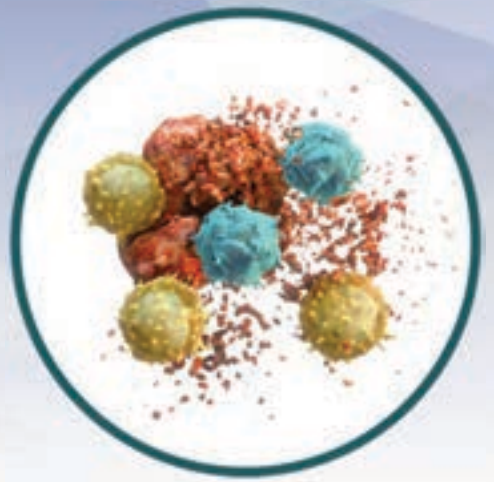
## Presentation

The innate immune system rapidly identifies and attacks tumor cells. Tumor cell death releases tumor antigens, which can activate the cytotoxic T cells of the adaptive immune system.[6,15]



## Infiltration

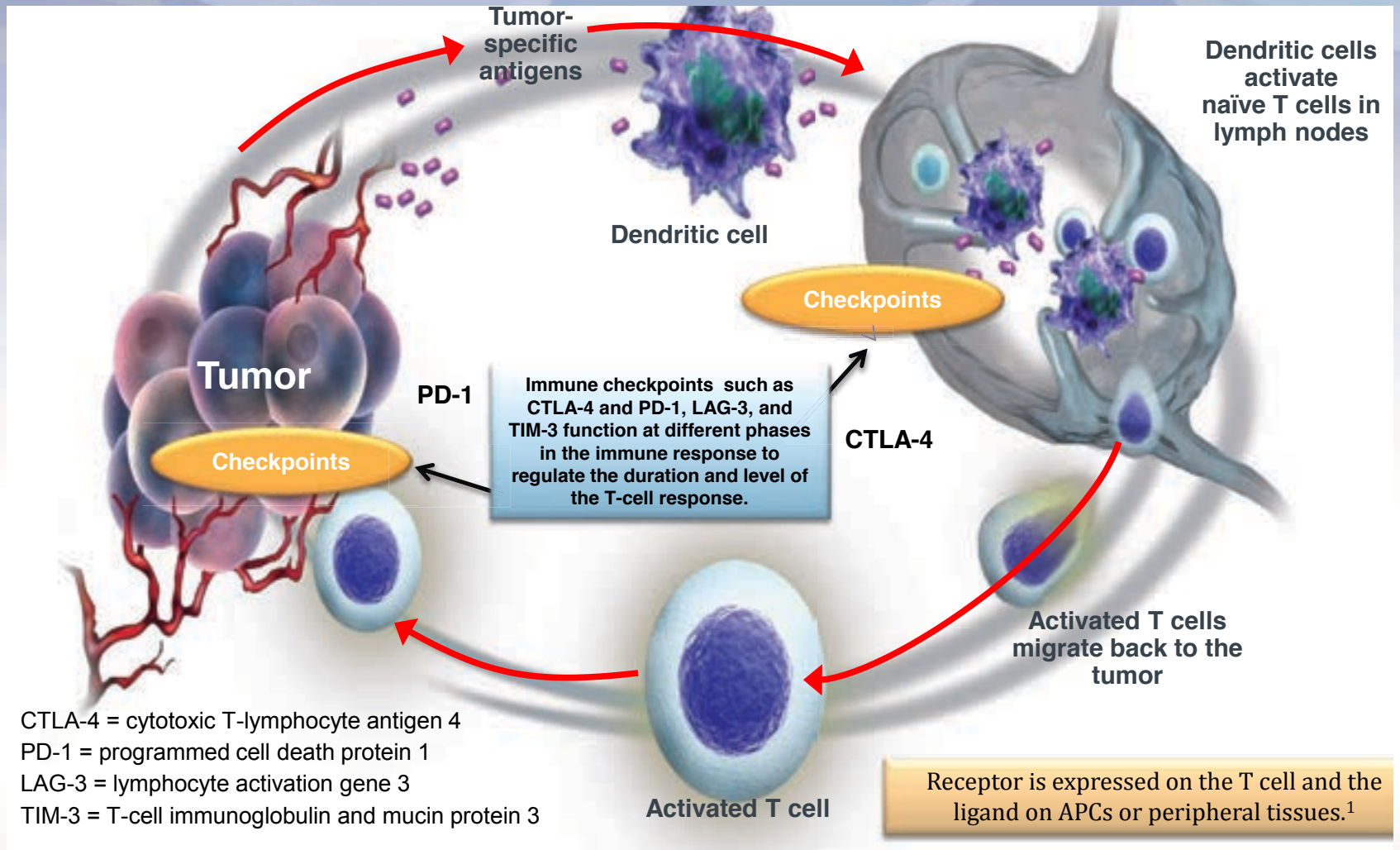
Tumor antigens and other factors attract immune cells to the tumor site, where they invade and attack.[15]



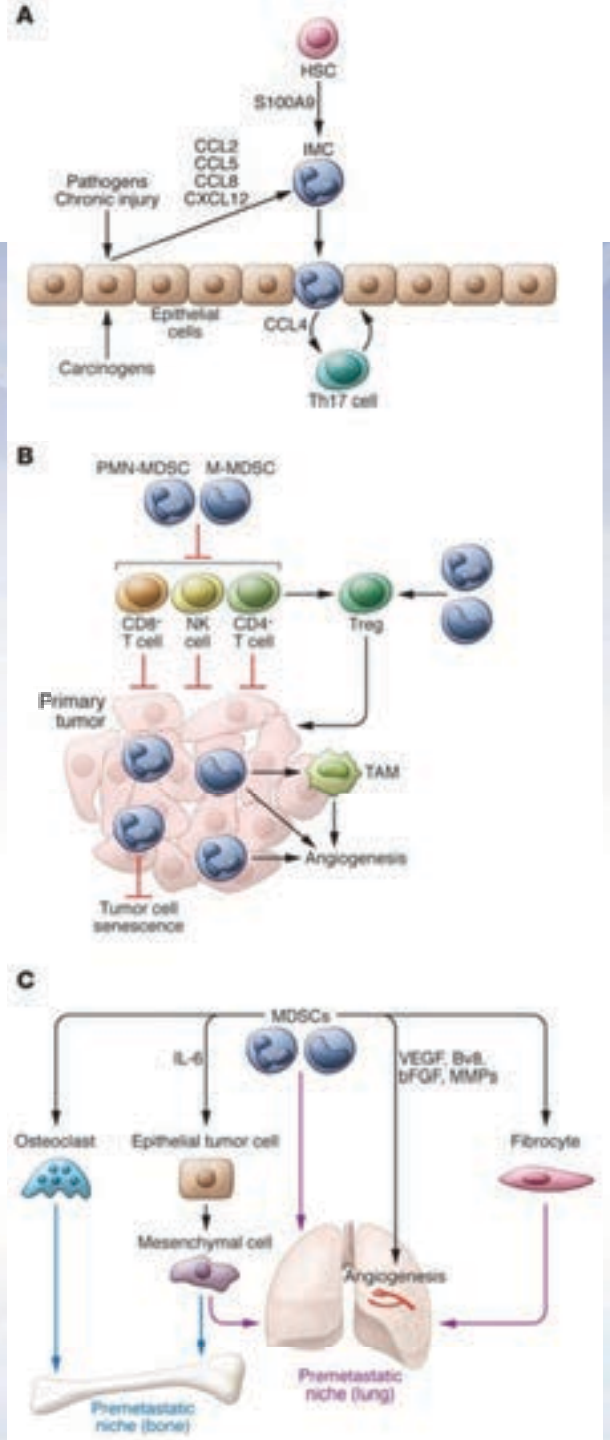
## Elimination

Activated cytotoxic T cells recognize tumor cells as the source of the antigen and targe them for elimination.[15]

# Immuno-surveillance[1-3]

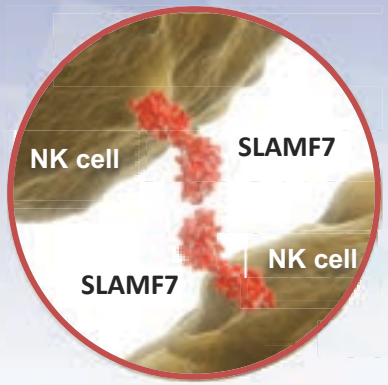



1. May KF Jr et al. In: Prendergast GC, Jaffee EM, eds. Cancer Immunotherapy: Immune Suppression and Tumor Growth. 2nd ed. Amsterdam, Netherlands; Elsevier: 2013:111–113. 2. Mellman I et al. Nature. 2011;480:480-489. 3. Pardoll DM. Nat Rev Cancer. 2012;12:252–264.


A
HSC
S100A9
IMC
CCL2
CCL5
CCL8
CXCL12
Pathogens
Chronic injury
Epithelial cells
CCL4
Carcinogens
Th17 cell
B
PMN-MDSC
M-MDSC
CD8+ T cell
NK cell
CD4+ T cell
Treg
Primary tumor
TAM
Angiogenesis
Tumor cell senescence
C
MDSCs
IL-6
VEGF, Bv8, bFGF, MMPs
Osteoclast
Epithelial tumor cell
Fibrocyte
Mesenchymal cell
Angiogenesis
Premetastatic niche (lung)
Premetastatic niche (bone)

# Pathways that modulate the innate immune response (1/2)

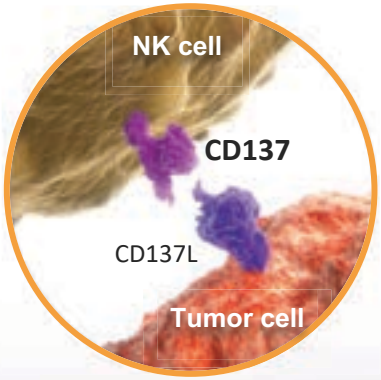
Current research is investigating the following pathways to understand how they can be modulated to restore the **innate immune response**'s ability to fight cancer:




activating

**SLAMF7** is an activating receptor on the surface of NK cells and other immune cells.[11] When engaged, SLAMF7 activates NK cells, the rapid responders of the immune system and the body's first line of defense against cancer.[5,12]

Continuous activation of NK cells through pathways like SLAMF7 may initiate the development of long-term immunity.[4,13]



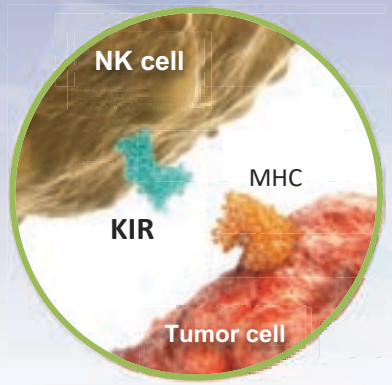

activating

**CD137** is an activating receptor on the surface of NK cells and T cells that can stimulate them to reproduce and generate antitumor activity.[14,15] In animal models, CD137 also plays a critical role on T cells in the development of immune memory and the creation of a durable immune response.[16]

**Preclinical data** suggests that activation of CD137 can stimulate NK-cell and cytotoxic T-cell activity and generate a lasting memory response.[17,18]

# Pathways that modulate the innate immune response (2/2)

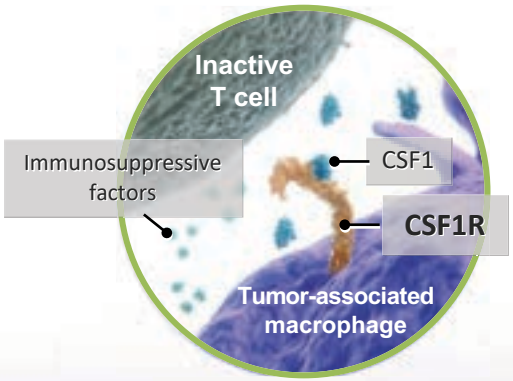
Current research is investigating the following pathways to understand how they can be modulated to restore the **innate immune response**'s ability to fight cancer:




inhibitory

**KIR** is an immune checkpoint receptor on the surface of NK cells that acts to stop NK cells from killing normal cells.[19] Tumor cells can use the KIR pathway to disguise themselves as normal cells and escape detection by NK cells.[20]

**Preclinical data** suggests that blockade of inhibitory KIRs can help restore NK cell-mediated immune activity.[21,22]



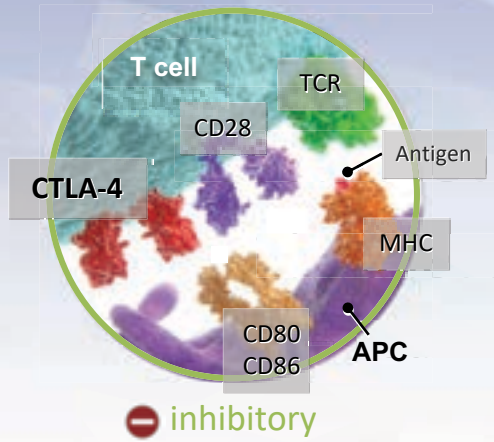

inhibitory

**CSF1R** is a receptor on the surface of macrophages and other cells of the myeloid lineage.[23] In the tumor microenvironment, some macrophages evolve from antitumor to protumor in their activity.[24] Protumor, or tumor-associated macrophages (TAMs) can drive immunosuppression and support tumor growth.[24] Mouse models have shown that tumor cells use CSF1 to target CSF1R on macrophages, stimulating the development and survival of TAMs.[25]

**Preclinical data** suggests that blockade of CSF1R can result in depletion of TAMs and improved T-cell responses.[26,27]

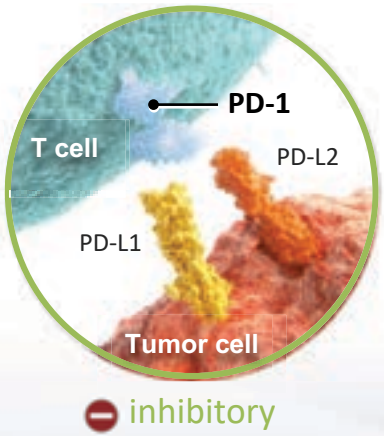
# Pathways that modulate the adaptive immune response (1/4)

Current research is investigating the following pathways to understand how they can be modulated to restore the **adaptive immune response**'s ability to fight cancer:




**CTLA-4** is an immune checkpoint receptor on T cells that plays a key role in preventing T-cell overactivation.[28-31] Tumor cells use the CTLA-4 pathway to suppress initiation of an immune response, resulting in decreased T-cell activation and ability to proliferate into memory T cells.[32,33] CTLA-4 signaling diminishes the ability of memory T cells to sustain a response, damaging a key element of durable immunity.[34]

**Preclinical data** suggests that treatment with antibodies specific for CTLA-4 can restore an immune response through increased survival of memory T cells and depletion of regulatory T cells.[35-38]

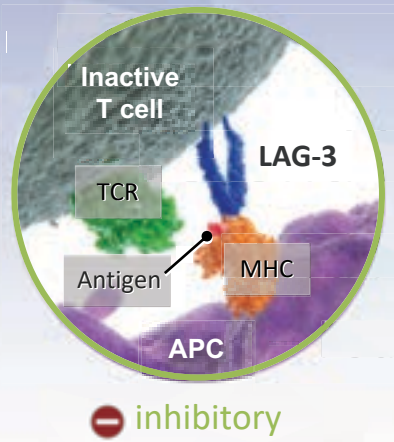



**PD-1** is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.[39-41] Tumor-infiltrating T cells across solid tumors and hematologic malignancies display evidence of exhaustion, including upregulation of PD-1.[42]

**Preclinical data** suggests that PD-1 blockade reinvigorates exhausted T cells and restores their cytotoxic immune function.[40] Inhibiting both PD-1 ligands (PD-L1 and PD-L2) may be more effective at reversing T-cell exhaustion than inhibiting PD-L1 alone.[43]

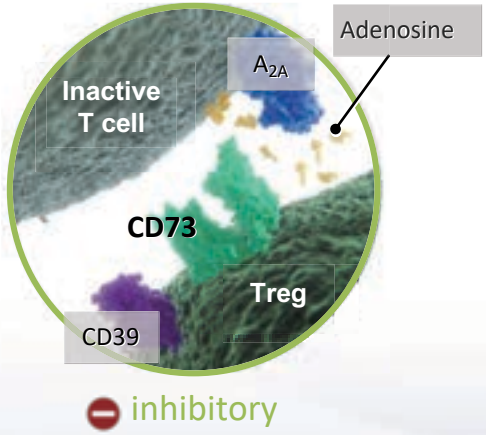
# Pathways that modulate the adaptive immune response (2/4)

Current research is investigating the following pathways to understand how they can be modulated to restore the **adaptive immune response**'s ability to fight cancer:




**LAG-3** is an immune checkpoint receptor on the surface of both activated cytotoxic and regulatory T cells (Tregs).[44,45] When bound to the antigen-MHC complex, LAG-3 can negatively regulate T-cell proliferation and the development of lasting memory T cells.[46] Repeated exposure to tumor antigen causes an increase in the presence and activity of LAG-3, leading to T-cell exhaustion.[47,48]

**Preclinical data** suggests that inactivation of LAG-3 allows T cells to regain cytotoxic function.[49]

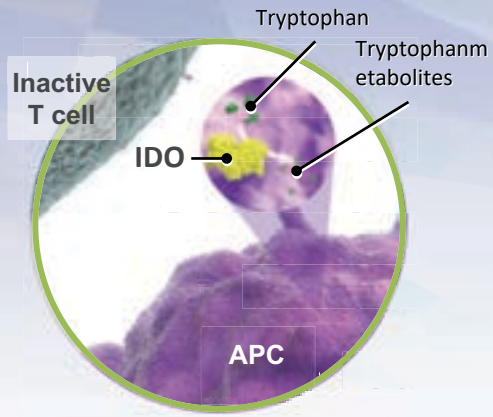



**CD73** is a cell-surface enzyme on Tregs. CD73 is a critical checkpoint in the production of adenosine, which has been demonstrated to be a powerfully immunosuppressive molecule in cellular studies.[50] Tumor cells exploit this pathway by expressing CD73 and releasing adenosine into the tumor microenvironment.[51-53]

**Preclinical data** suggests that inhibition of CD73 activity can stimulate T-cell activity.[54]

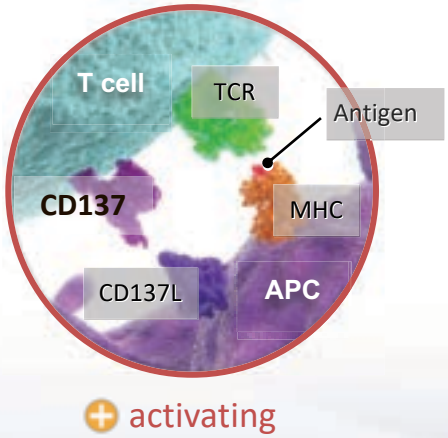
# Pathways that modulate the adaptive immune response (3/4)

Current research is investigating the following pathways to understand how they can be modulated to restore the **adaptive immune response**'s ability to fight cancer:




**IDO** is an intracellular enzyme that initiates the breakdown of tryptophan, an amino acid that is essential for T-cell survival.[55-57] Tumor cells can upregulate IDO activity in order to suppress T-cell antitumor function.[58,59]

**Preclinical data** suggests that blockade of IDO can restore cytotoxic T-cell function.[60,61]

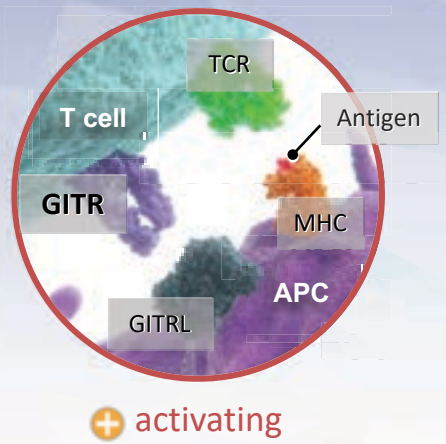



**CD137** is an activating receptor on the surface of NK cells and T cells that can stimulate them to reproduce and generate antitumor activity.[14,15] CD137 also plays a critical role on T cells in the development of immune memory and the creation of a durable immune response, in animal models.[16]

**Preclinical data** suggests that activation of CD137 can stimulate NK-cell and cytotoxic T-cell activity and generate a lasting memory response.[17,18]

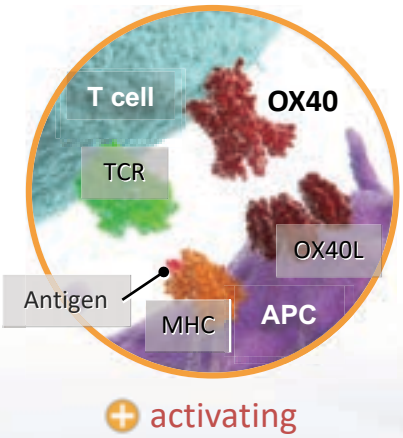
# Pathways that modulate the adaptive immune response (4/4)

Current research is investigating the following pathways to understand how they can be modulated to restore the **adaptive immune response**'s ability to fight cancer:




**GITR** is an activating receptor on the surface of T cells and other immune cells that helps to enhance cell reproduction and generate antitumor activity.[62-64] GITR signaling can also block the suppressive abilities of regulatory T cells (Tregs), further enhancing cytotoxic T-cell function.[65]

**Preclinical data** suggests that activation of GITR signaling can help enhance immunity through the activation of cytotoxic T cells and inhibition of Treg activity.[66]

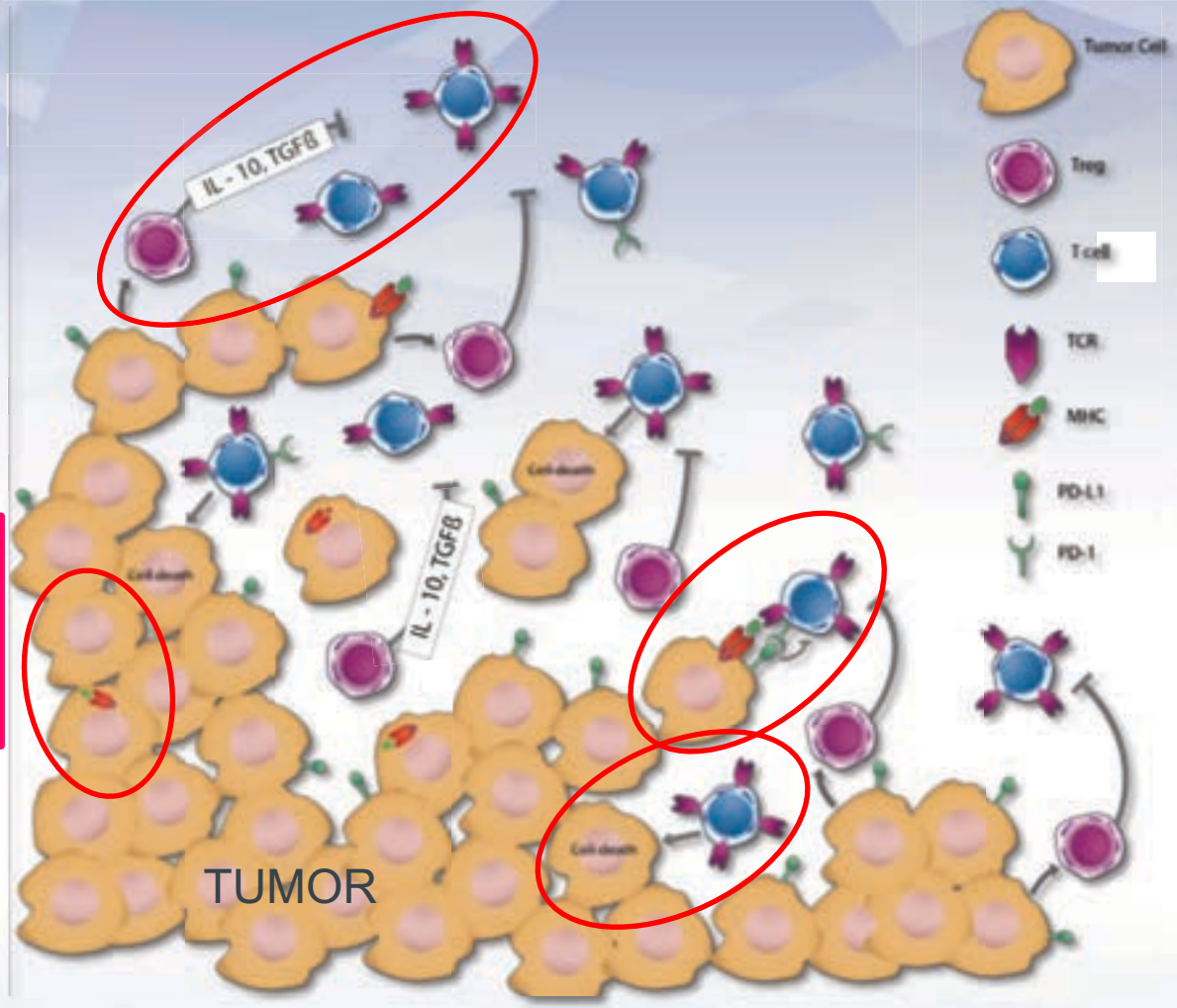


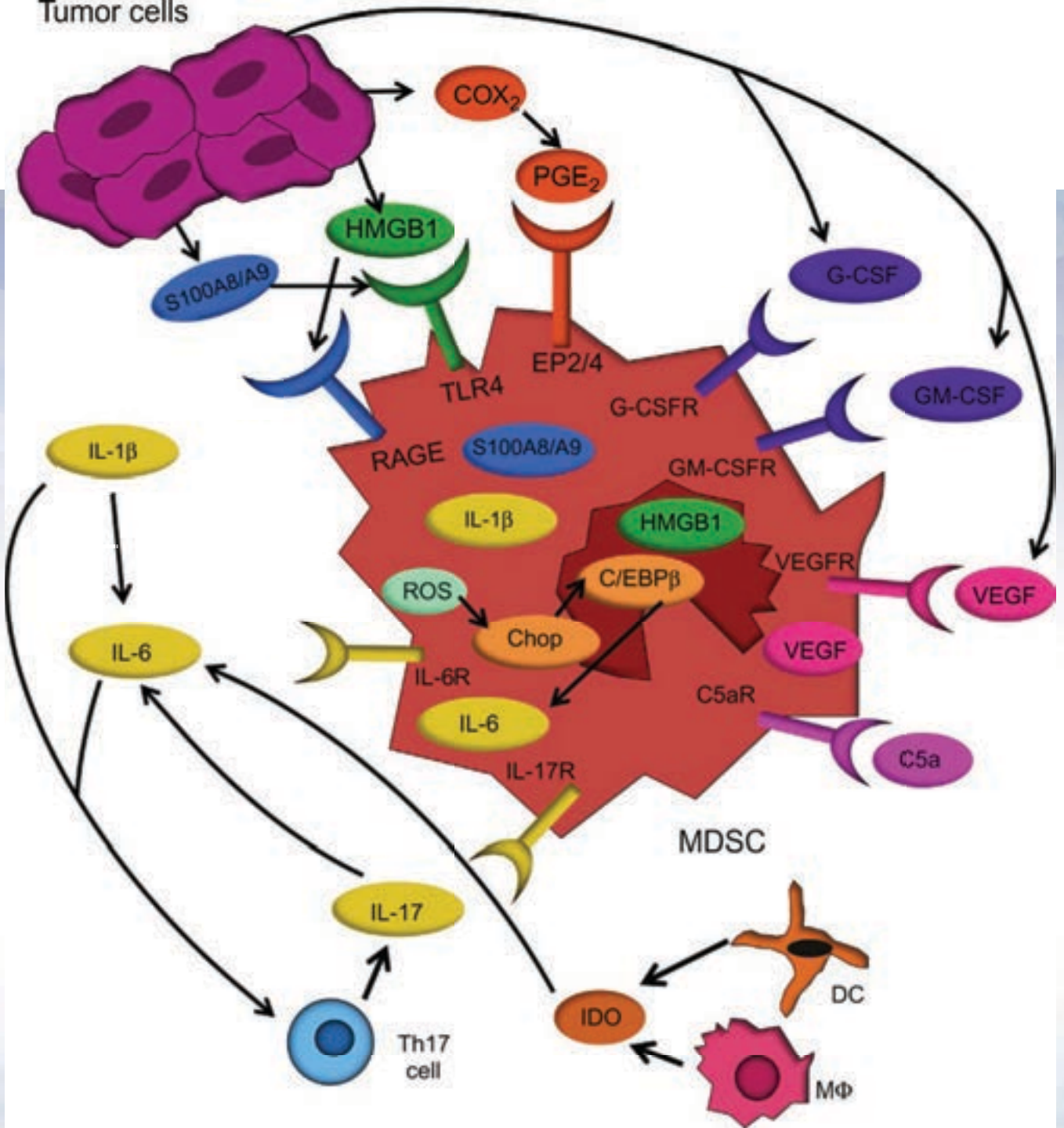

**OX40** is an activating receptor on the surface of activated cytotoxic T cells and Tregs.[67-69] OX40 plays a dual role in the immune response, both activating and amplifying T-cell responses. This dual effect helps create a tumor microenvironment that is more favorable to antitumor response.[70-73]

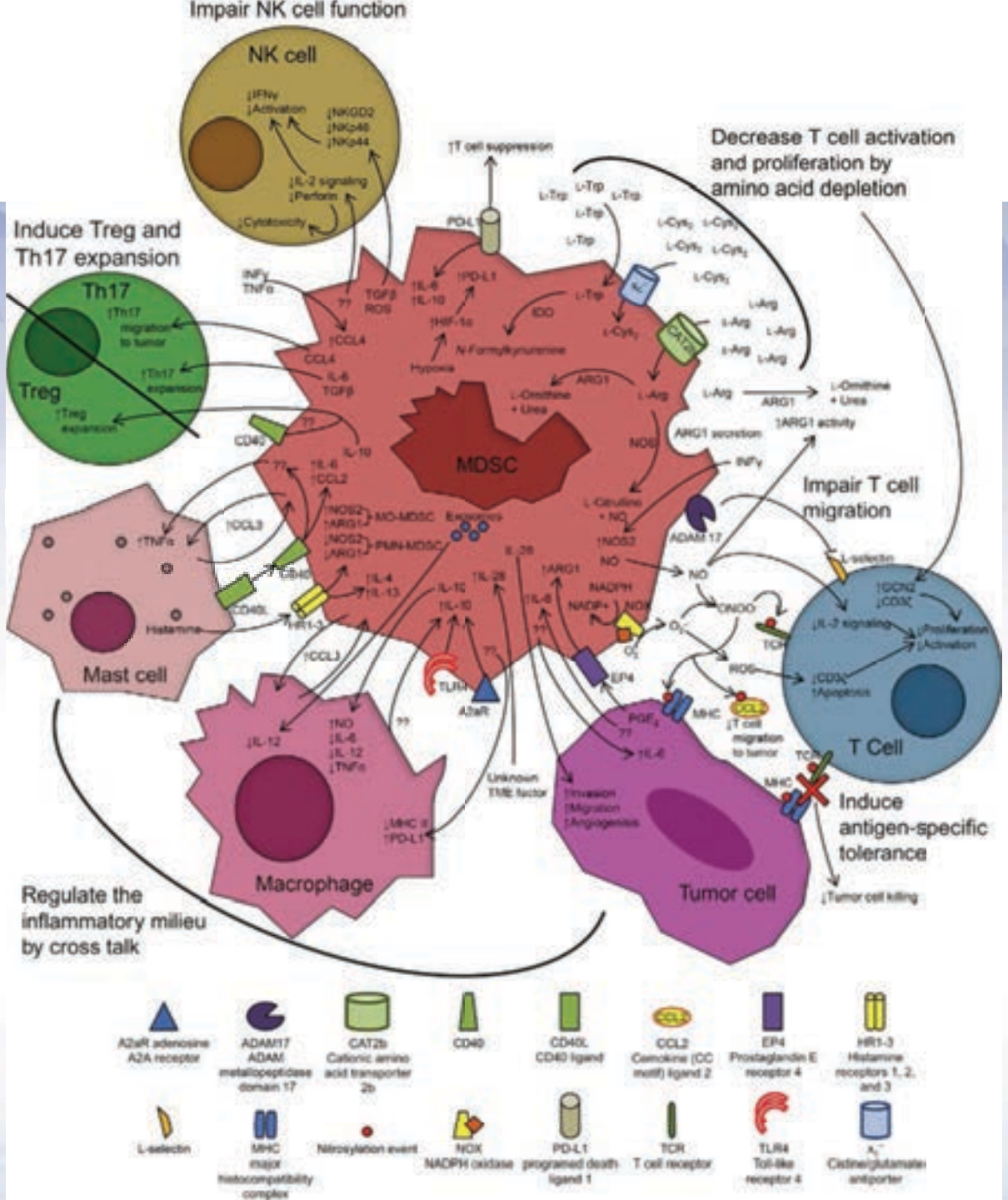
**Preclinical data** suggests that OX40 increases the number and activity of cytotoxic T cells and curtails the immunosuppressive impact of Tregs.[74-76]

# Tumors Evade Immune Detection and Destruction[1]

- The immune response to tumor cells can be evaded by a number of mechanisms:
  - Reduced antigen presentation[1]
  - Resistance to T-cell–mediated killing[1]
  - T-cell inhibition and anergy (eg, by upregulation of coinhibitory molecules, including PD-L1)[2]
  - Treg-mediated immunosuppression[1]




Tumor cells
COX2
PGE2
HMGB1
S100A8/A9
G-CSF
EP2/4
TLR4
G-CSFR
GM-CSF
RAGE
S100A8/A9
GM-CSFR
IL-1β
IL-1β
HMGB1
VEGFR
ROS
C/EBPβ
VEGF
IL-6
Chop
VEGF
IL-6R
C5aR
IL-6
C5a
IL-17R
MDSC
IL-17
DC
IDO
Th17 cell
MΦ


Impair NK cell function
NK cell
Induce Treg and Th17 expansion
Th17
Treg
Decrease T cell activation and proliferation by amino acid depletion
MDSC
Mast cell
Macrophage
Tumor cell
T Cell
Impair T cell migration
Induce antigen-specific tolerance
Regulate the inflammatory milieu by cross talk
A2aR adenosine A2A receptor
ADAM17 ADAM metallopeptidase domain 17
CAT2b Cationic amino acid transporter 2b
CD40
CD40L CD40 ligand
CCL2 Cytokine (CC motif) ligand 2
EP4 Prostaglandin E receptor 4
HR1-3 Histamine receptors 1, 2, and 3
L-selectin
MHC major histocompatibility complex
Nitrosylation event
NOX NADPH oxidase
PD-L1 programed death ligand 1
TCR T cell receptor
TLR4 Toll-like receptor 4