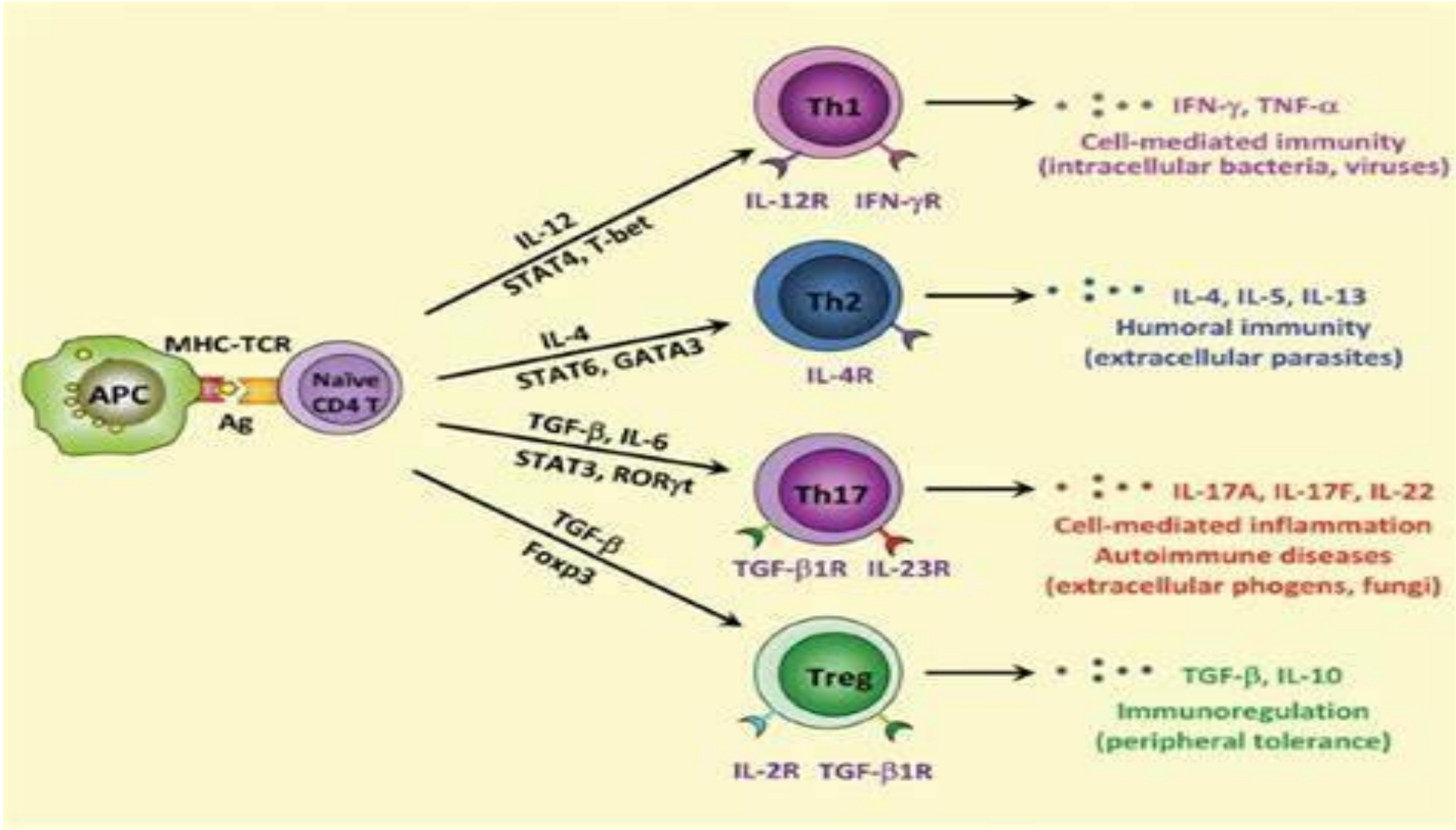
Integrative Immuno-Oncology

Lifetime cancer risk faced by any of us is a toss of a coin (50%)

Roles of cytokines in differentiation of T-cell subsets and CBC



Traditional arsenal of therapies in cancer treatment

Surgery

Limited by mechanism(s) of cancer spreading

Chemotherapy

Affects healthy tissues

Radiotherapy

Affects healthy tissues

Main theories in immuno-oncology :

Immunosurveillance, Immunoediting

1957

Cancer immunosurveillance

Lymphocytes act as sentinels in recognizing and eliminating continuously arising nascent transformed cells

F. M. Burnet

L. Thomas

Immunosurveillance component of
Cancer immunoediting

3 phases

Elimination

Potential cancer cells are created but they don't reach a clinical status because the immune system recognizes them and eliminates them.

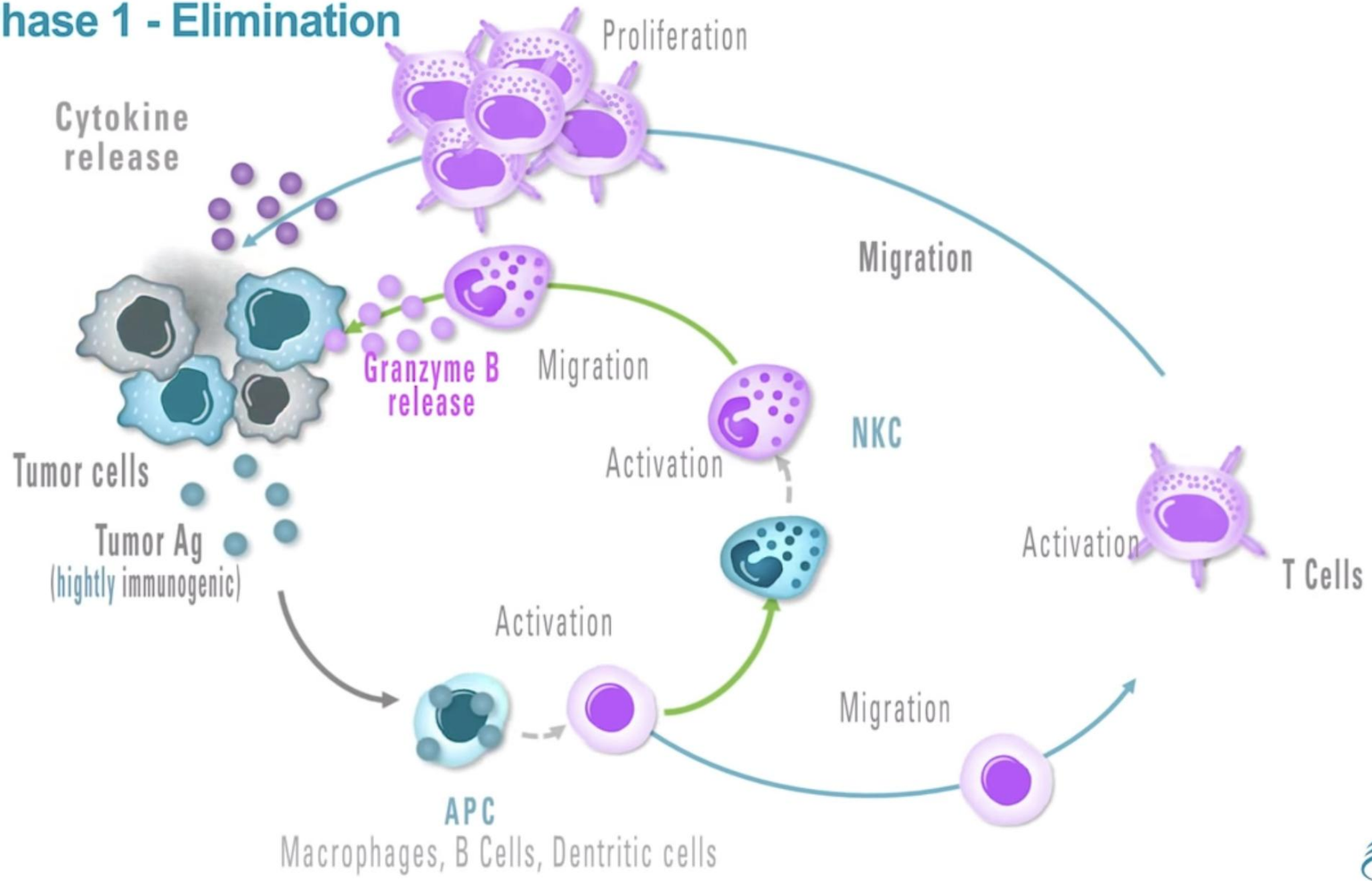
Equilibrium

A balance is reached and tumor cell proliferation equals the death cause by immunity. Cancer cells maintained chronically or immunologically sculpted to produce tumor variants.

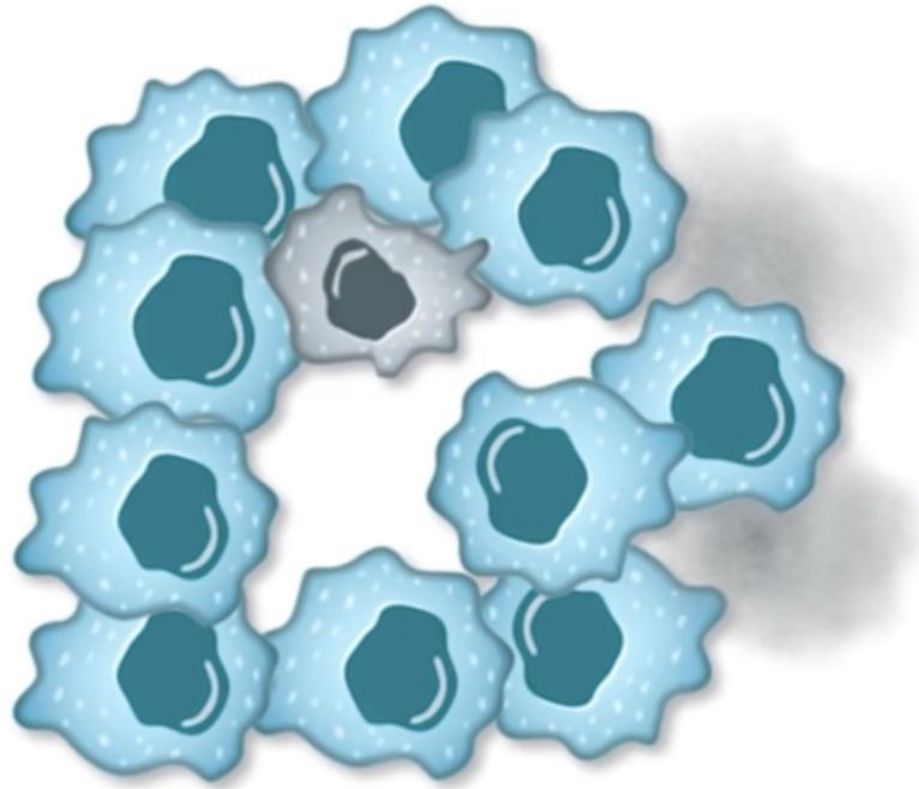
Escape

The tumor variants evade the immune system and become clinically detectable.

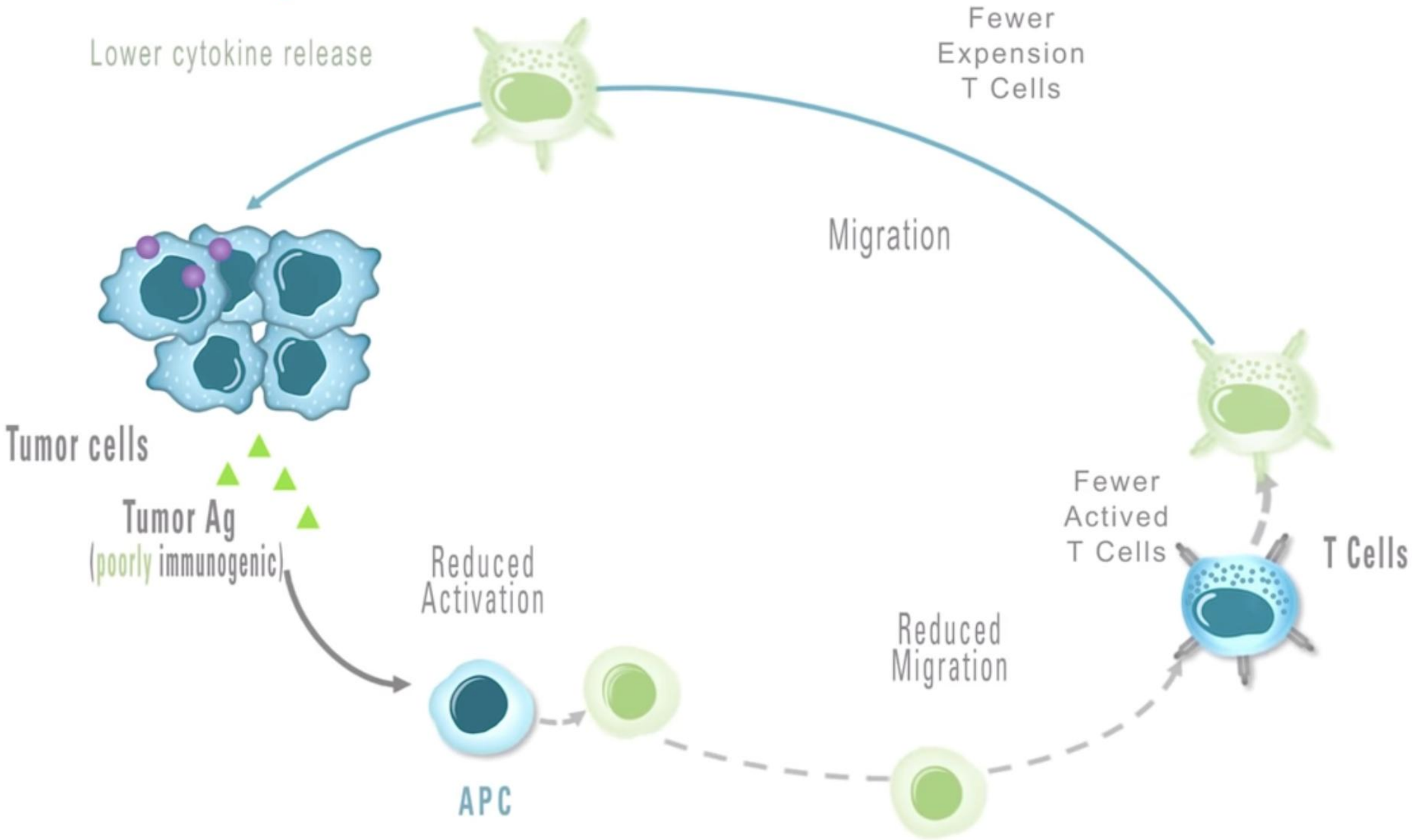
Phase 1 - Elimination



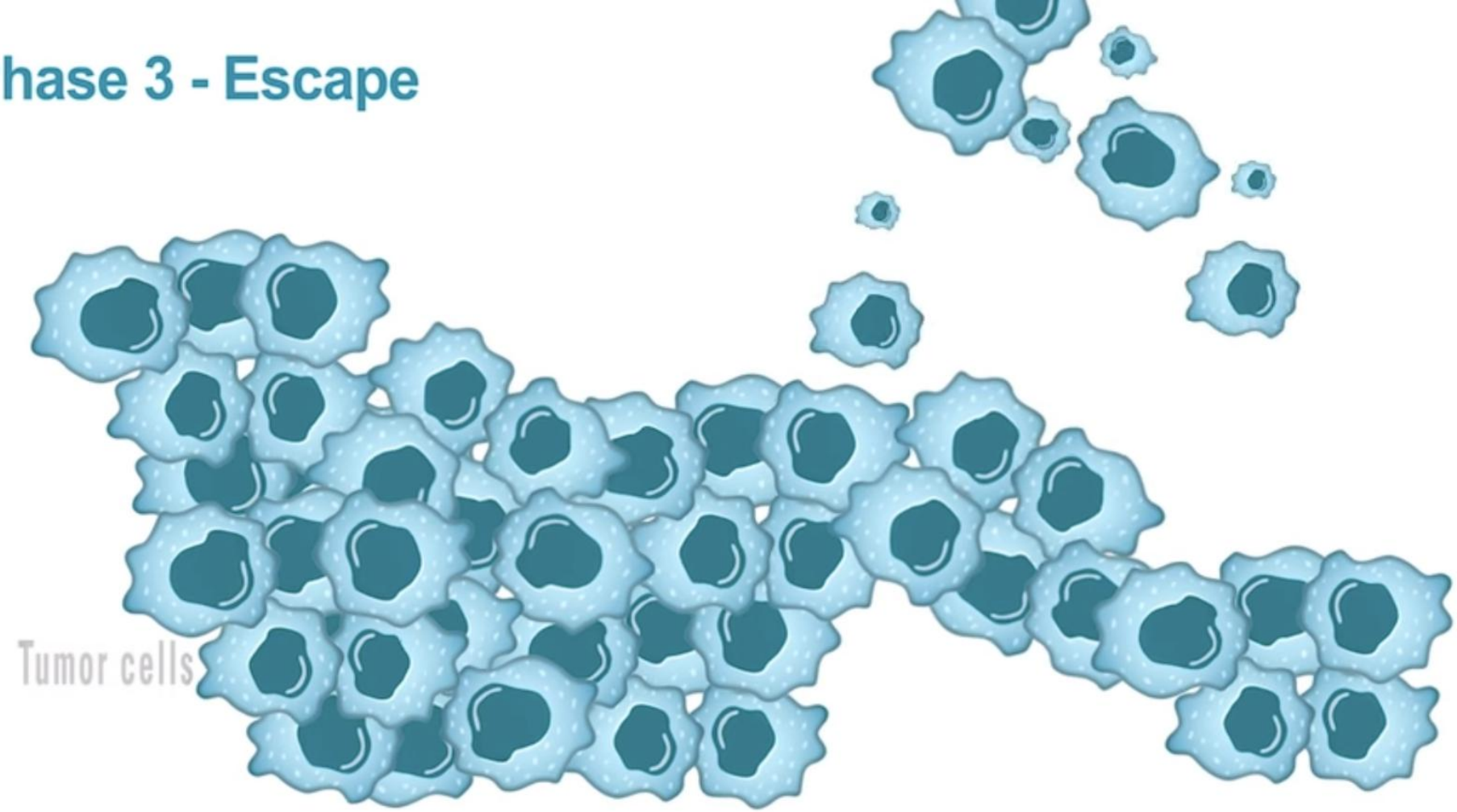
Phase 2 - Equilibrium



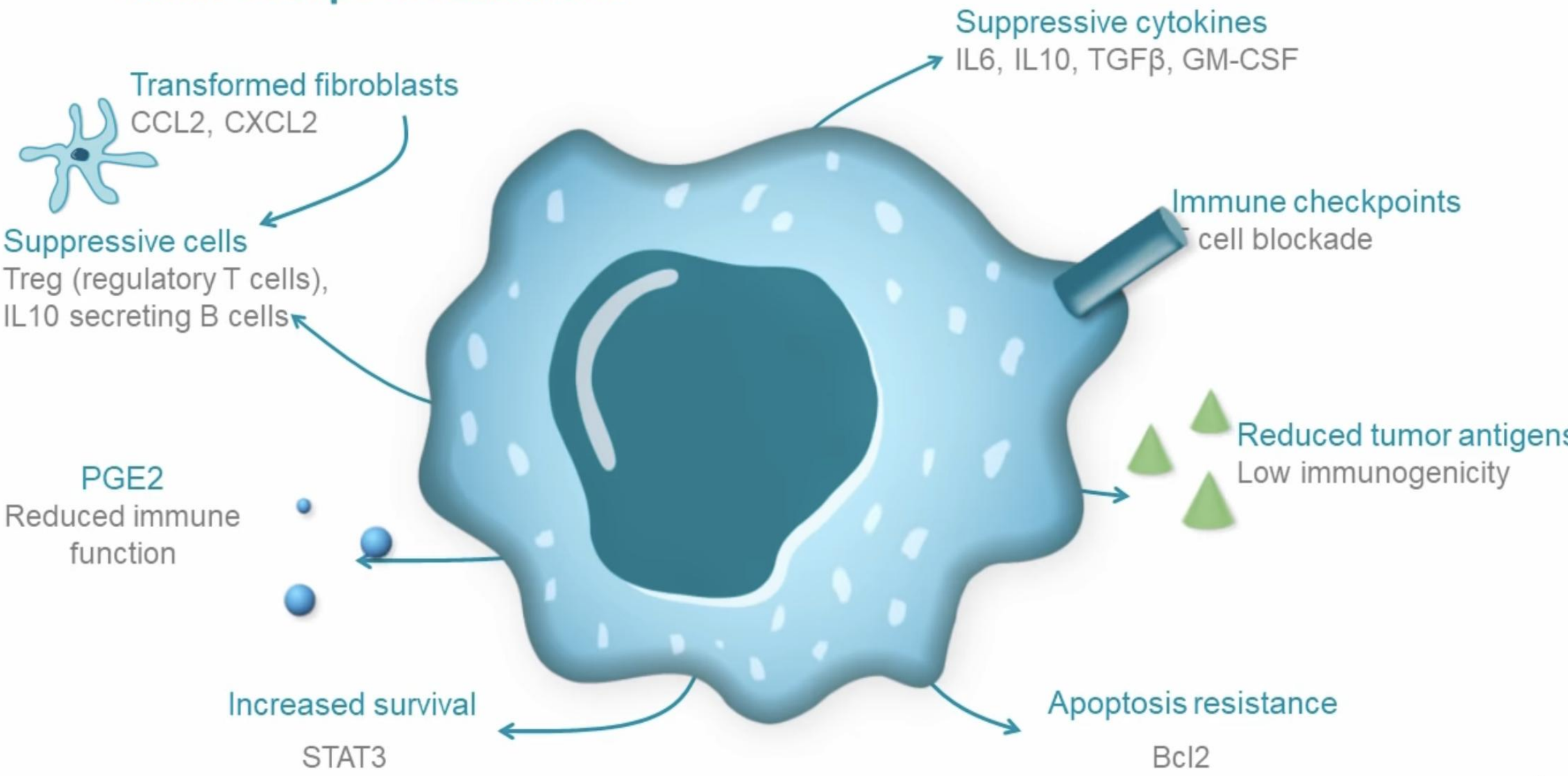
Phase 3 - Escape



Phase 3 - Escape

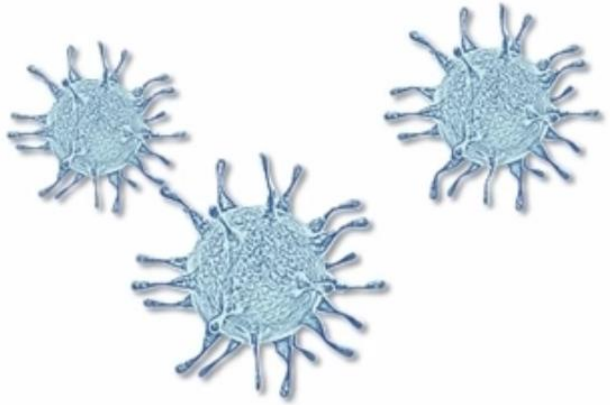


Tumor escape mechanisms



Immuno-therapy landscape

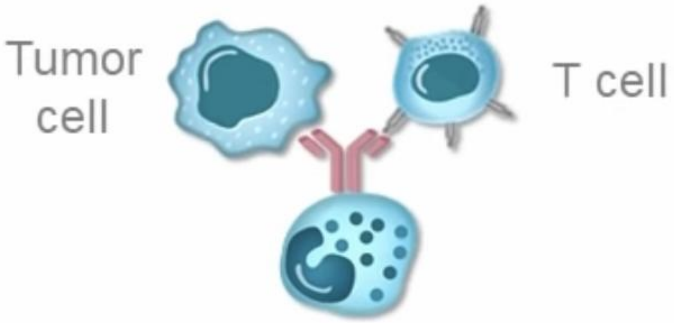
Anti-tumor mAbs



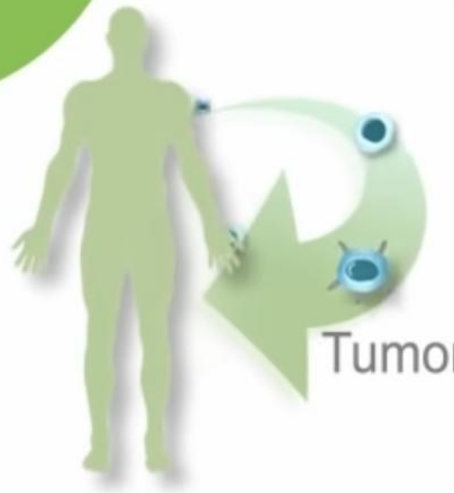
Oncolytic viruses

PASSIVE THERAPIES

Multi specific Abs



Cellular therapies



CAR-T

TCRs

Tumor Infiltrating Lymphocytes

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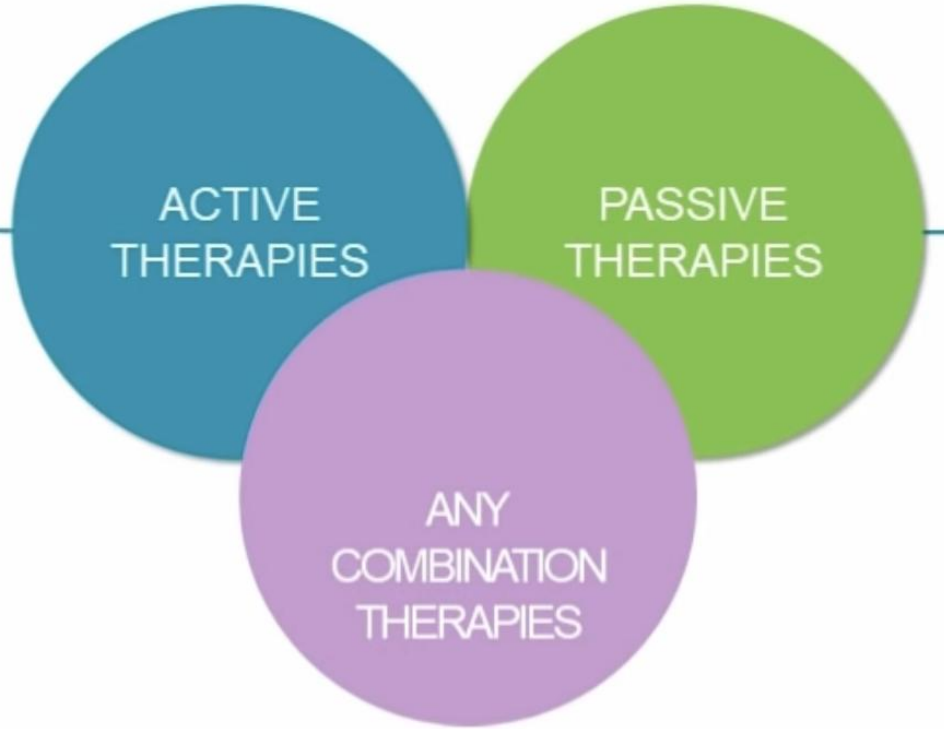
Immuno-therapy landscape

Anti-tumor mAbs

Multi specific Abs

Oncolytic viruses

Cellular therapies



Therapeutic vaccines

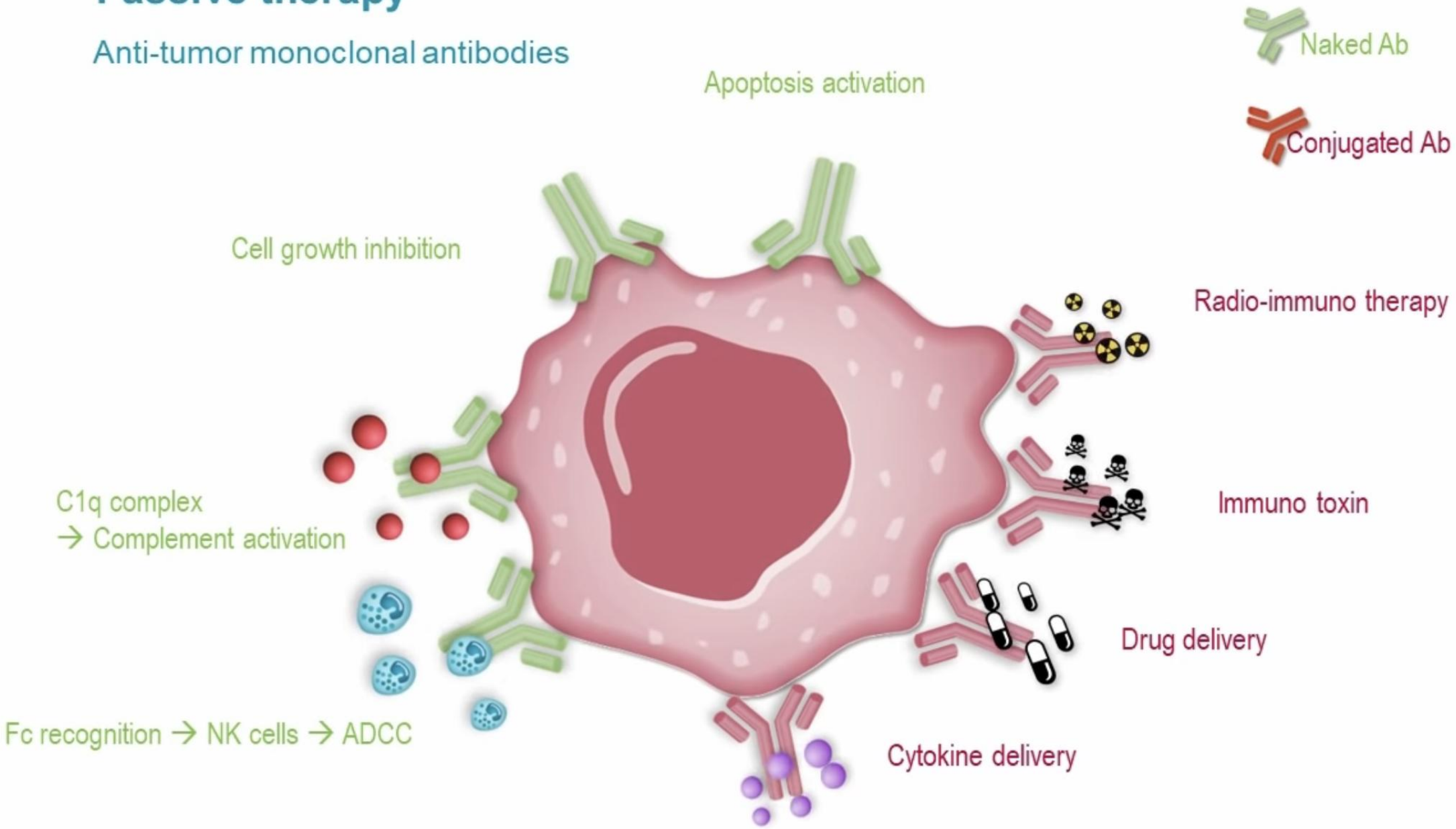
Cytokine treatments

IO therapies

cisbio

Passive therapy

Anti-tumor monoclonal antibodies



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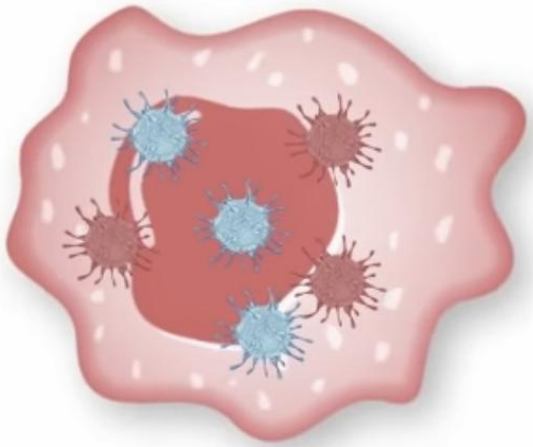
Passive therapy

Oncolytic viruses

Viral REPLICATION



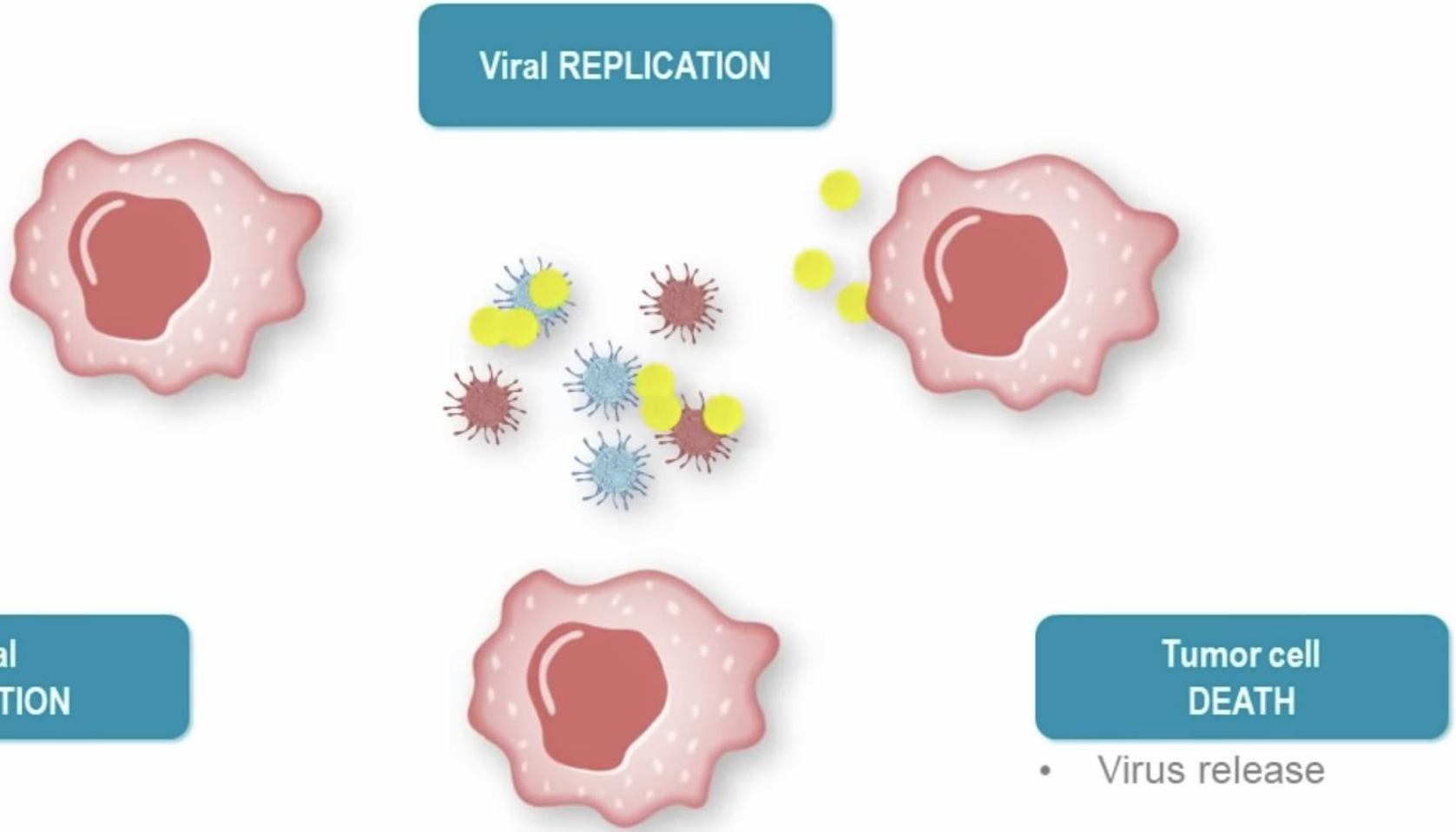
Viral INFECTION

Tumor cell DEATH

- Virus release

Passive therapy

Oncolytic viruses



- Virus release

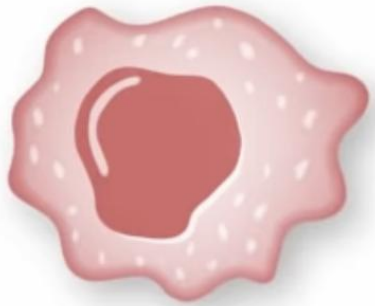
cisbio

Passive therapy

Oncolytic viruses

Viral REPLICATION

Viral INFECTION

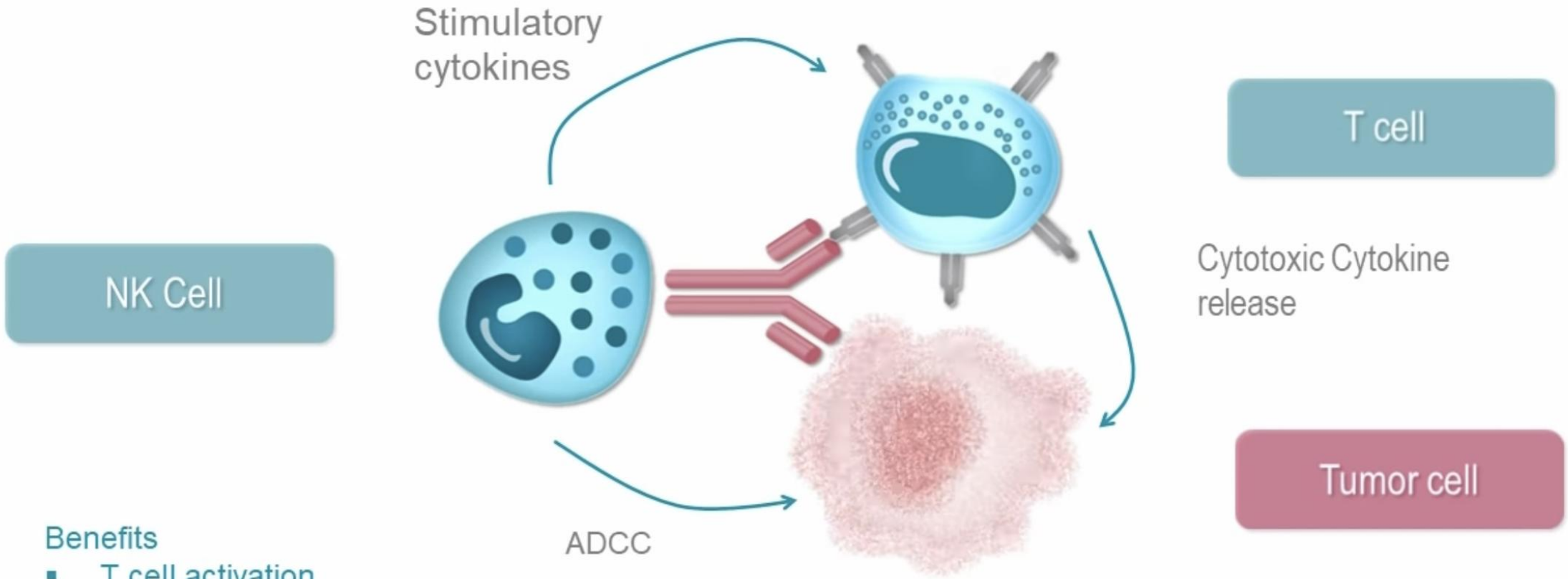


Tumor cell DEATH

- Virus release
- Cytokine release (e.g. GM-CSF)

Passive therapy

Bi/Multi specific antibodies



Benefits

- T cell activation
- High cytotoxicity
- Binds to weak antigens
- Avoids treatment resistance

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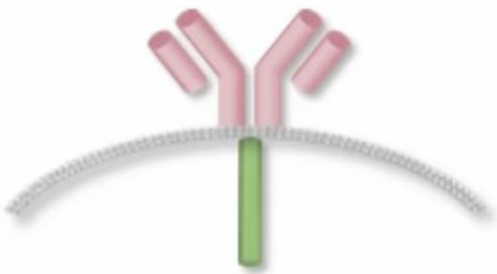
Passive therapy

Cellular therapies – CAR T cells

CAR-T

Chimeric Antigen Receptor T cell

Genetically engineered



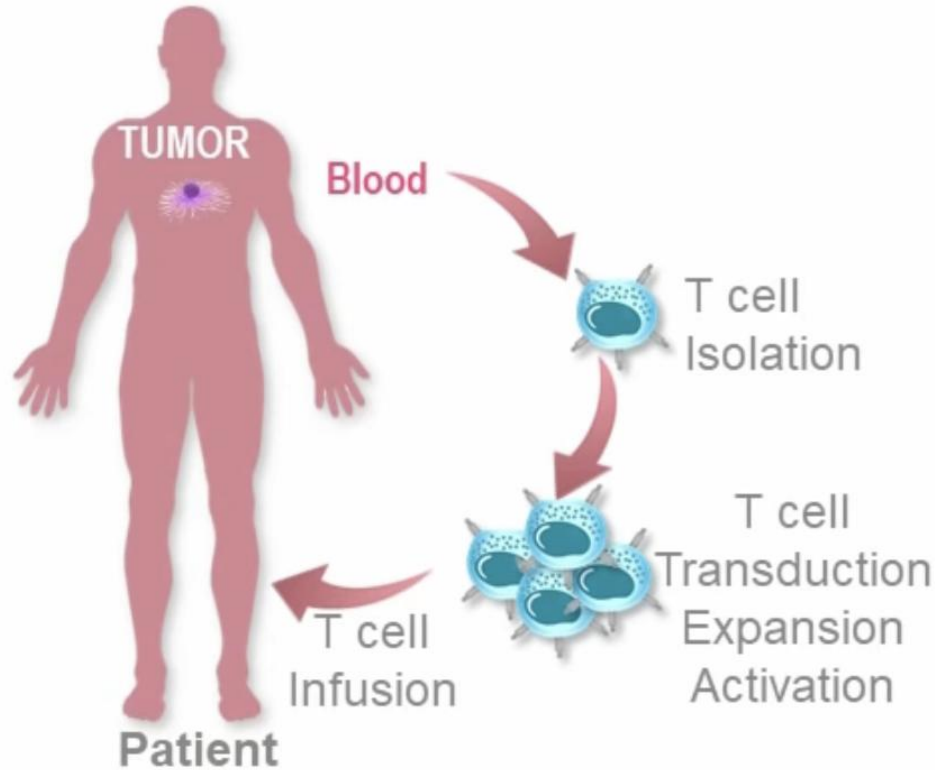
Full antigen recognition

TCR signaling

ZAP cascade activated

Cytokine release

Cell death



Patient specific treatment

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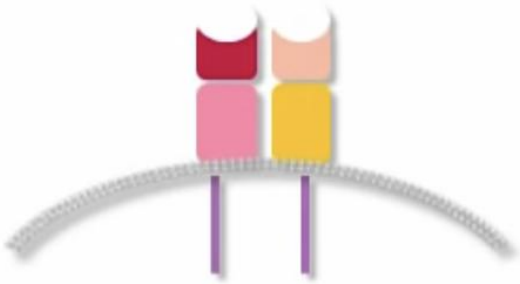
Passive therapy

Cellular therapy: TCR

TCR — T cell receptor

Extracellular
=
Engineered TCR



Intracellular
=
T cell receptor

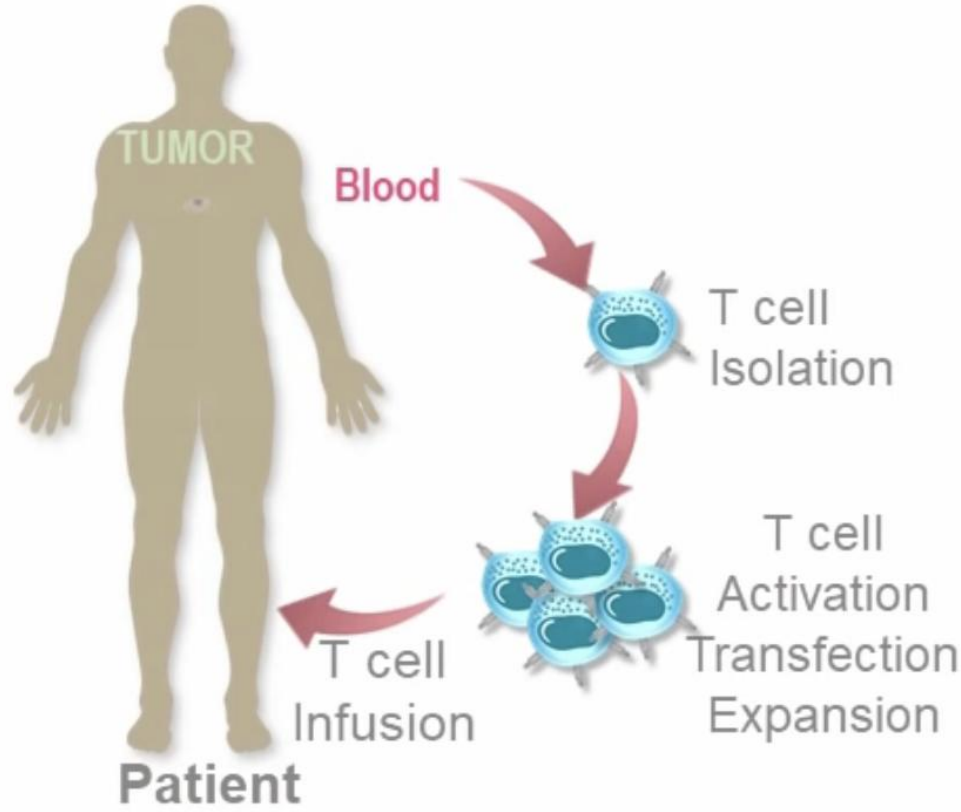
Better specificity

Cancer cell recognition

TCR signaling

Cell death

Genetically engineered



Personalized

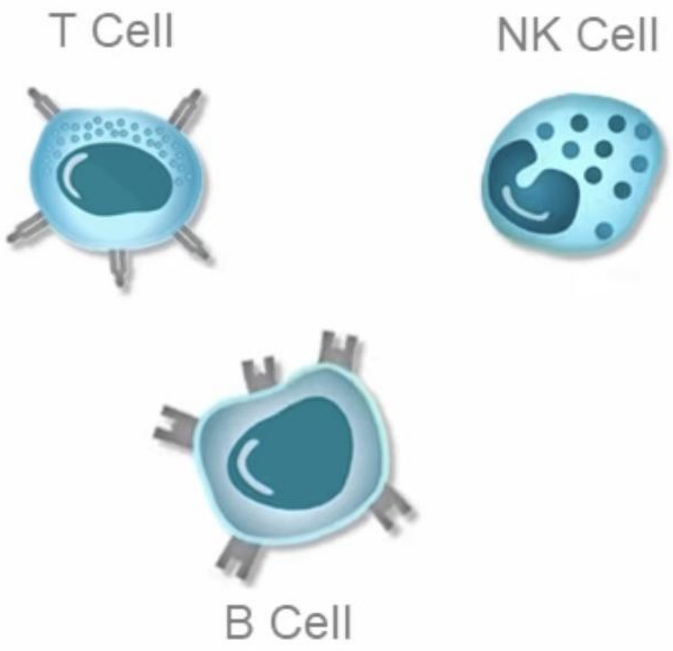
Passive therapy

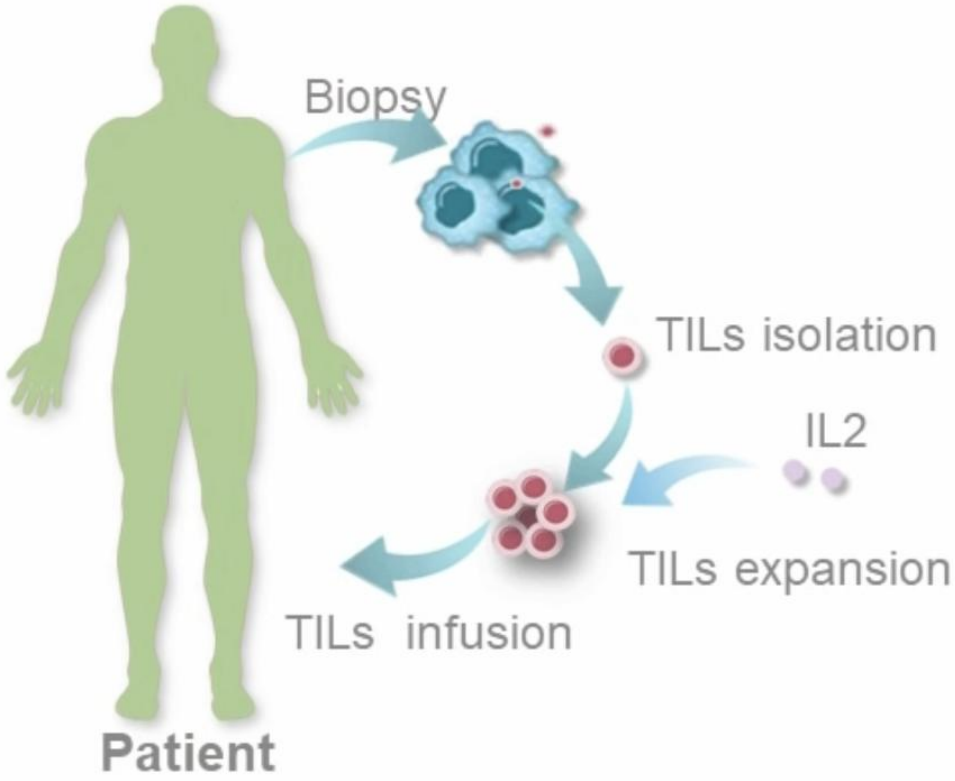
Cellular therapy: TILs

TILs

Tumor infiltrating lymphocytes

No cell engineering





Active therapy:

Cytokines

Cytokines

First & oldest treatment

FDA

IFNα

FDA

Natural Killer Cell
Activation

Tumor cell
Apoptosis

IL2

FDA

T cell
growth factor

Tumor cell
DEATH

GM-CSF

FDA

Immune system
Activation

Cytokine
perfusion

TUMOR

Patient

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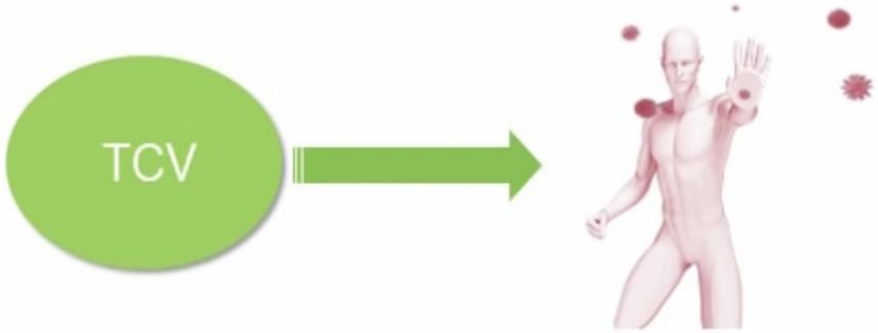
Active therapy:

Therapeutic Cancer Vaccines (TCV)

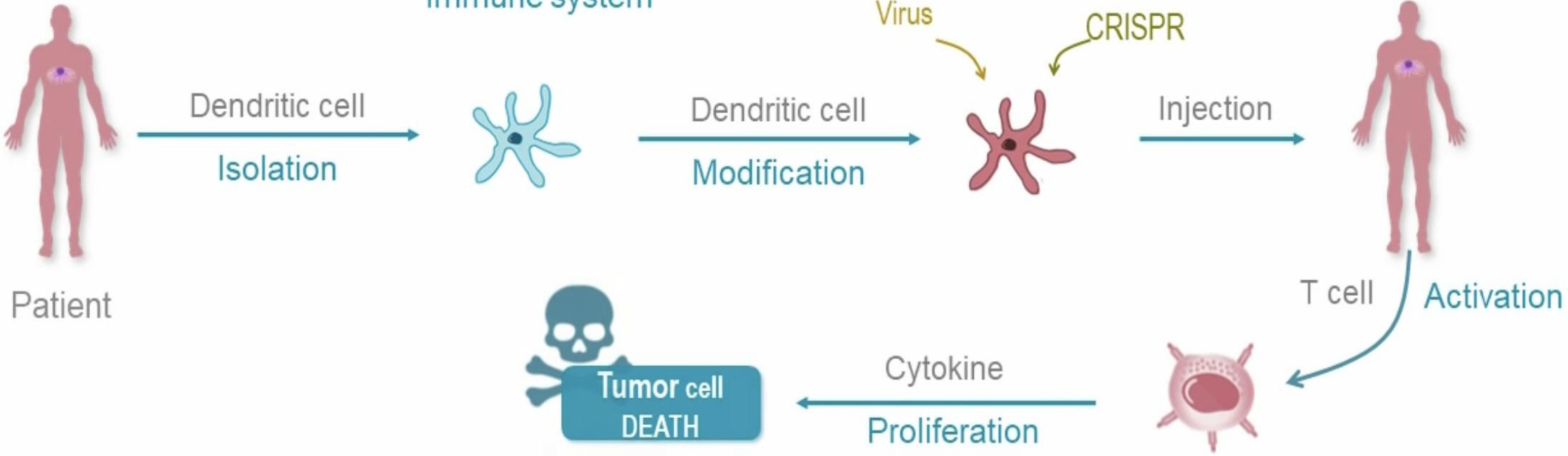


Sipuleucel-T for prostate cancer

FDA approved

Preventive

Therapeutic



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Active therapy:

Immune checkpoints

Ipilimumab {Yervoy)
CTLA-4 Inhibitor

Pembrolizumab (keytruda)
pd-1 inhibitor

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Active therapy:

Immune checkpoints

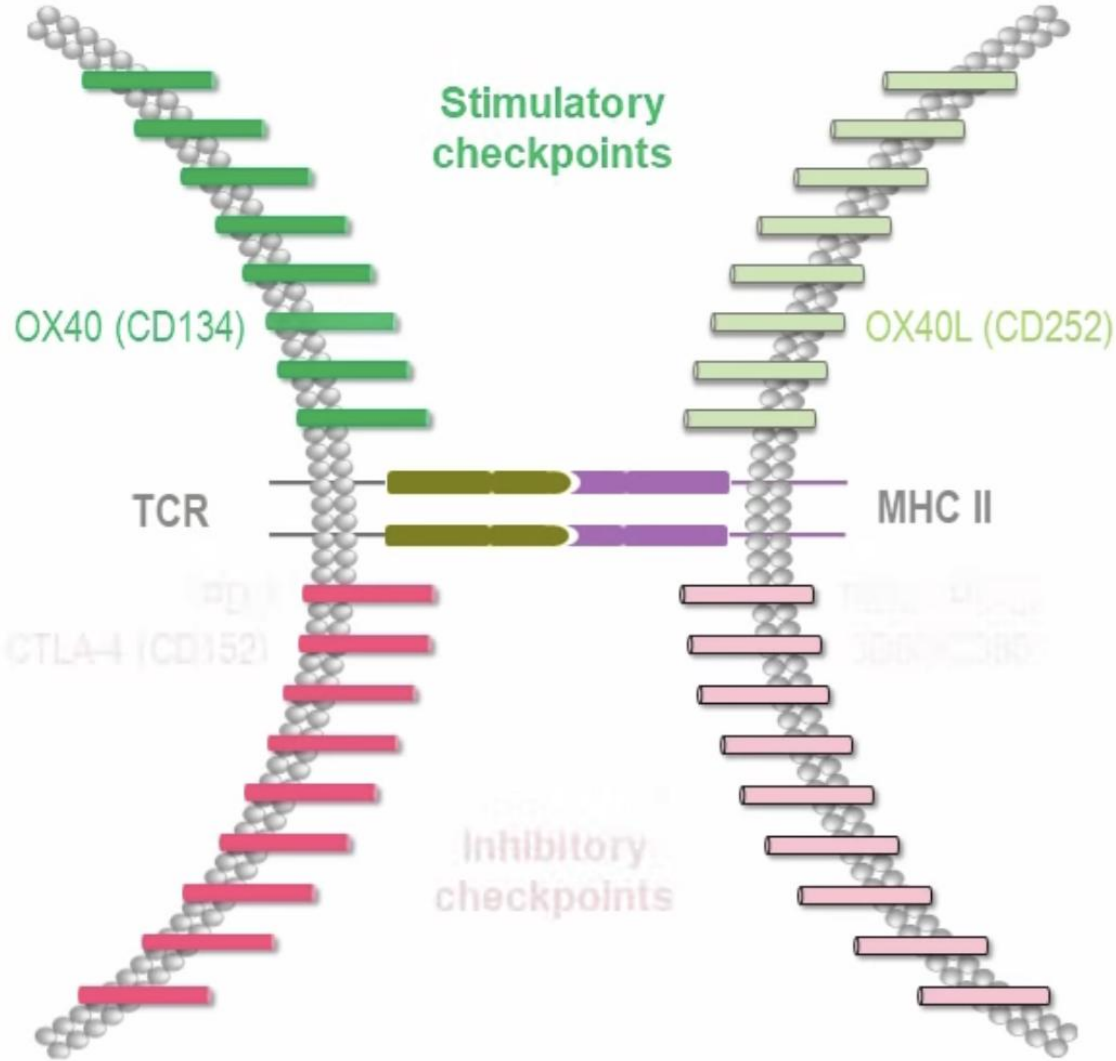
SIGNALING CASCADE ACTIVATED

ZAP cascade activated

T cell activation

Cytokine release (IL2-IFNγ)

Cell death



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Active therapy:

Immune checkpoints

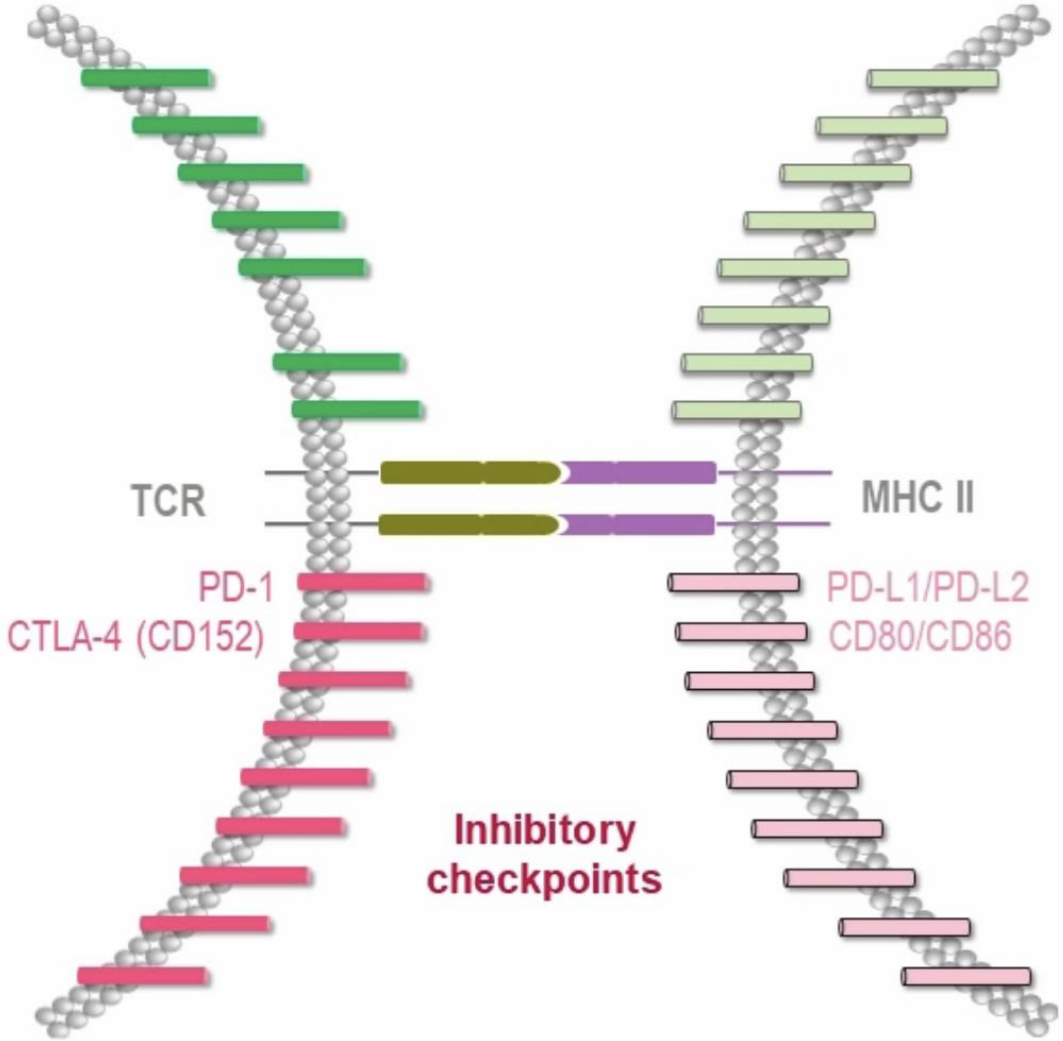
SIGNALING CASCADE INHIBITED

ZAP cascade activated

T cell activation

Cytokine release (IL2-IFNγ)

Cell death



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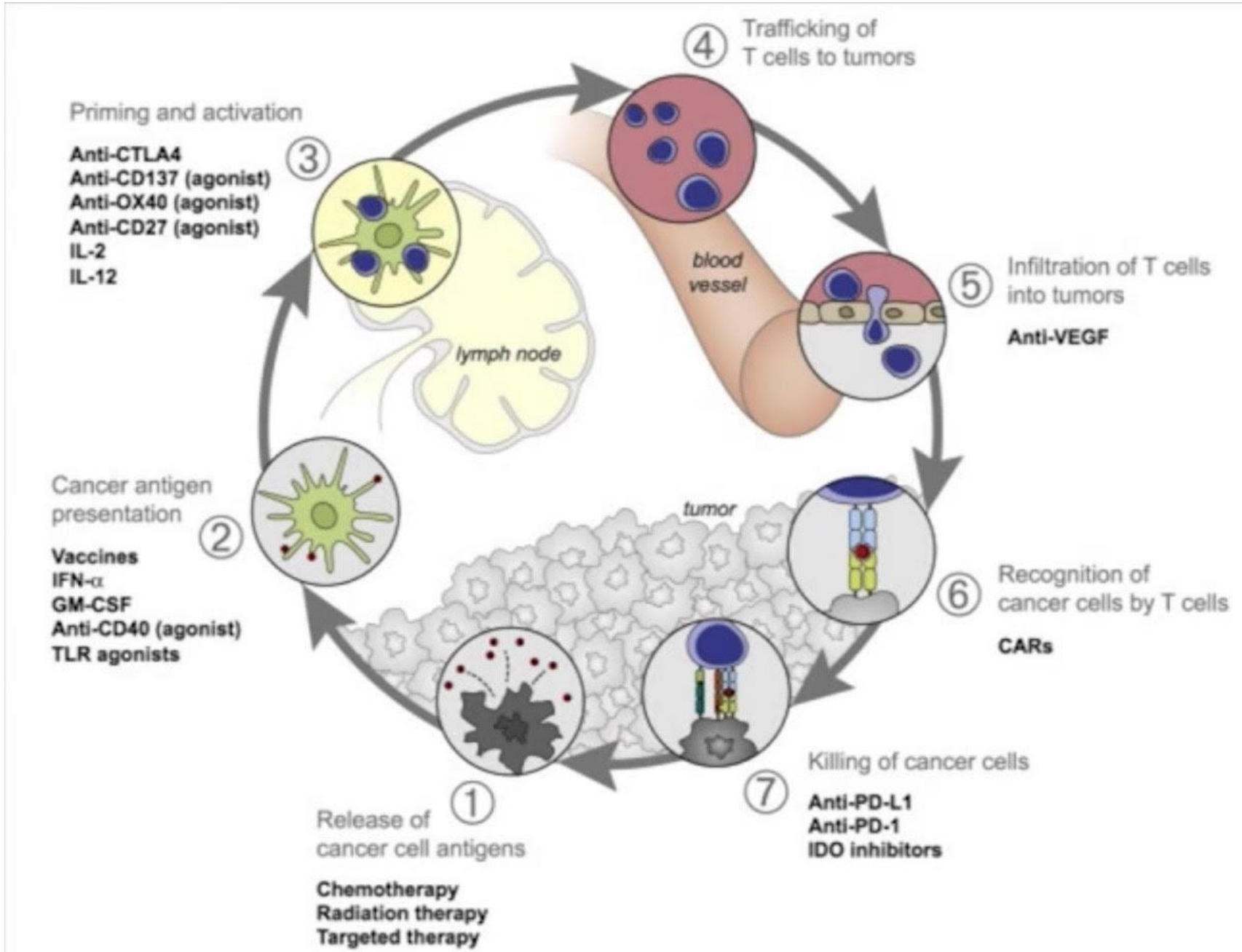
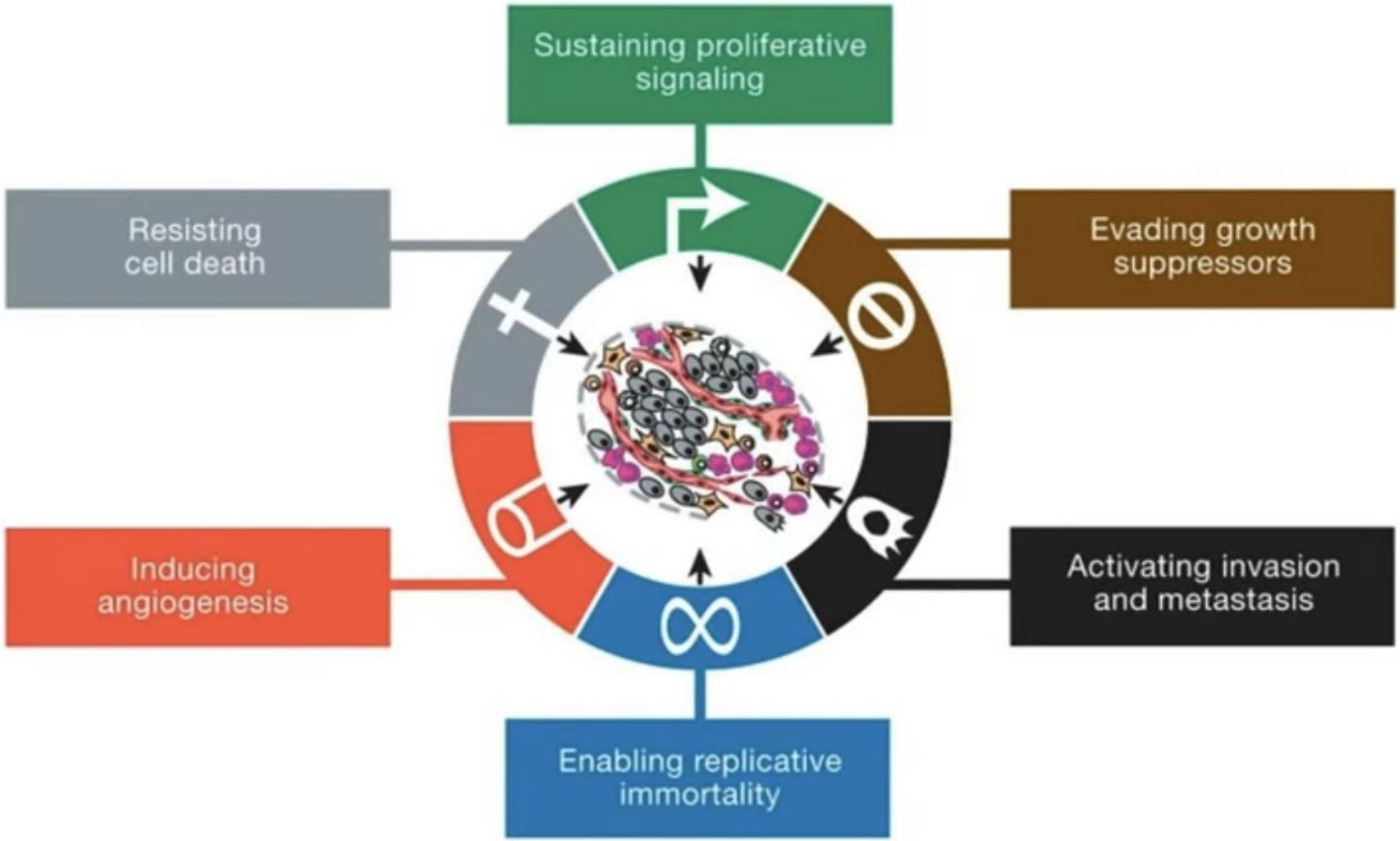

4 Trafficking of T cells to tumors
Priming and activation
Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12
3
blood vessel
5 Infiltration of T cells into tumors
Anti-VEGF
lymph node
tumor
Cancer antigen presentation
2
Vaccines
IFN-α
GM-CSF
Anti-CD40 (agonist)
TLR agonists
6 Recognition of cancer cells by T cells
CARs
7 Killing of cancer cells
Anti-PD-L1
Anti-PD-1
IDO inhibitors
1 Release of cancer cell antigens
Chemotherapy
Radiation therapy
Targeted therapy

Reactivating your immune system to fight cancer

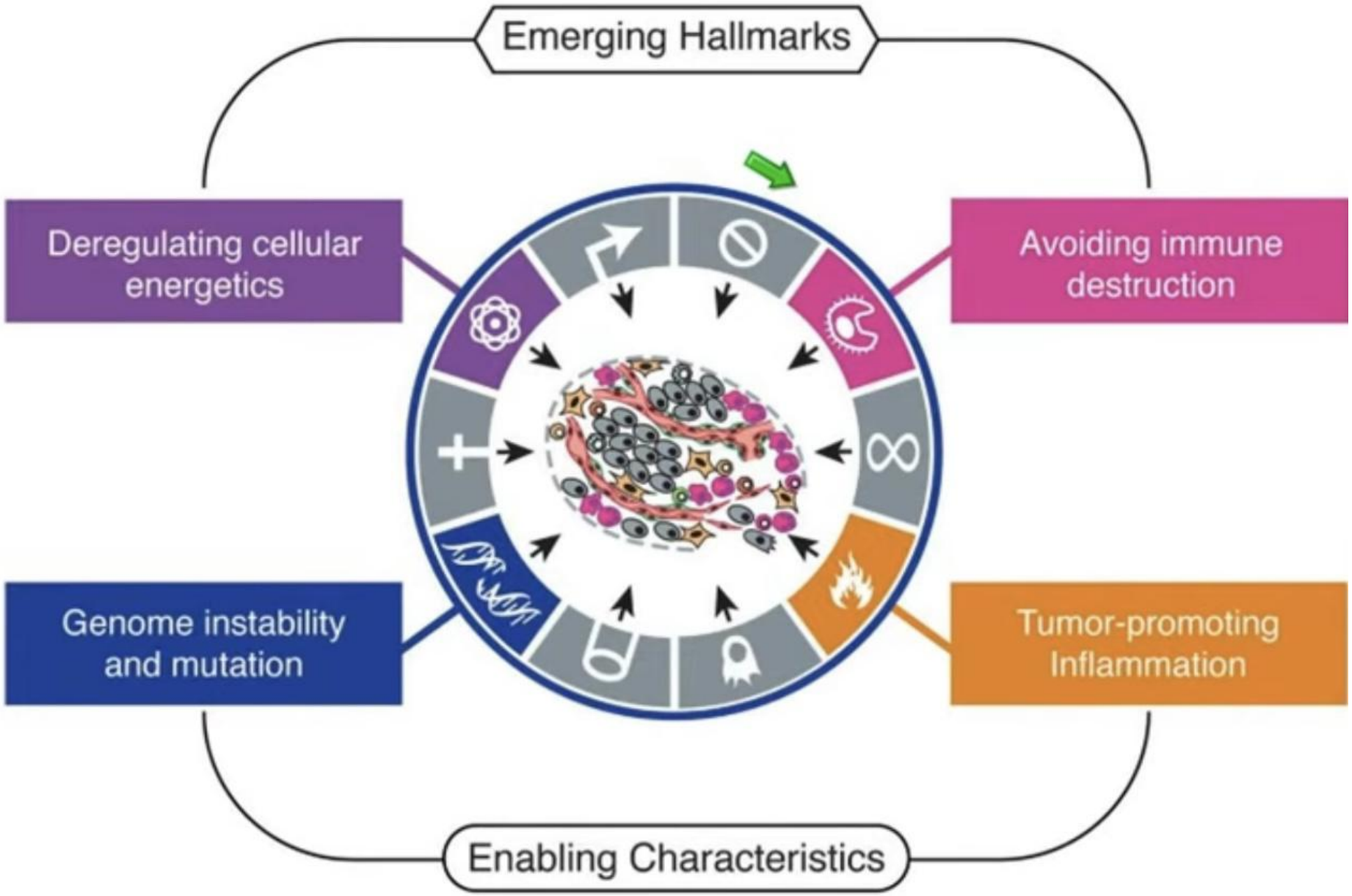
Overview

- Immune evasion as a hallmark of cancer
- Immune suppression in the Tumor Microenvironment
- Phosphatidylserine (PS) as an immune suppressive factor
- Antibody-mediated PS blockade activates the immune system

Hallmarks of Cancer, circa 2000

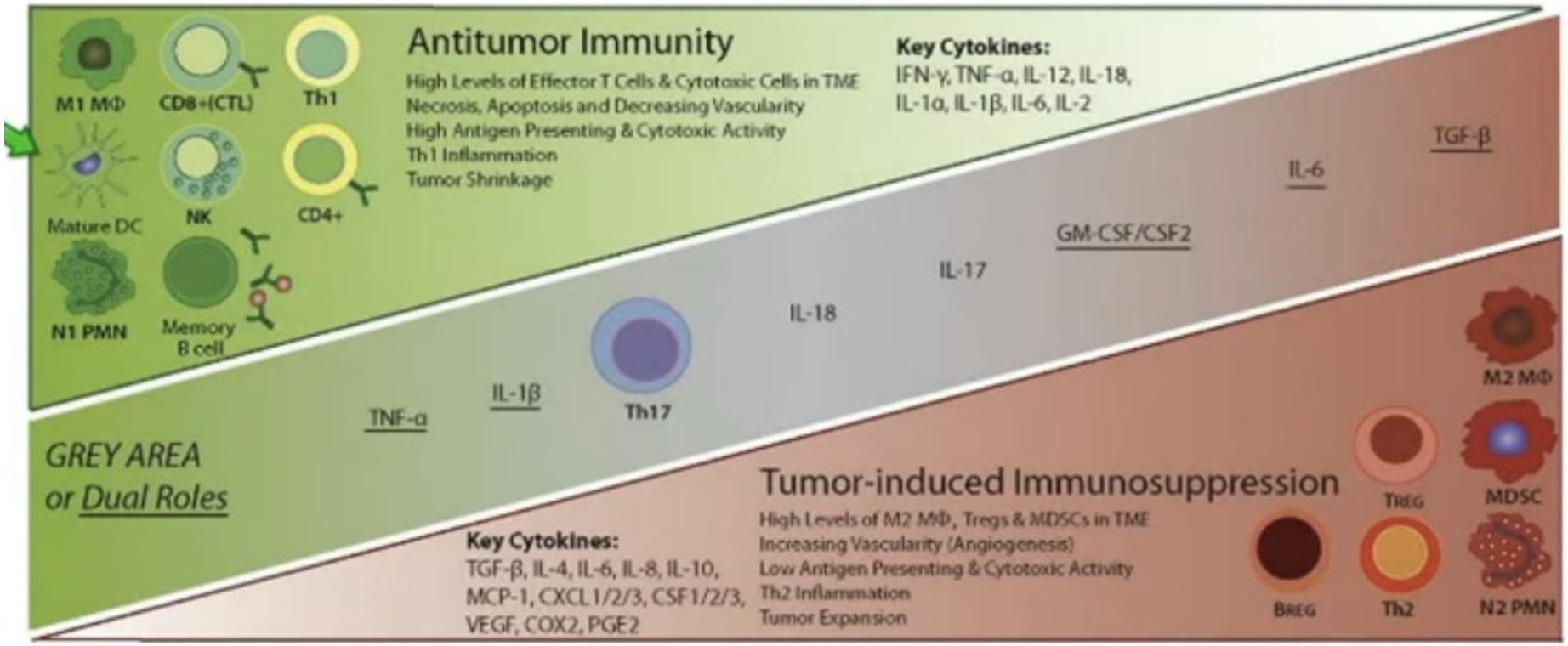


Douglas Hanahan, Robert A. Weinberg, **Hallmarks of Cancer: The Next Generation.** Cell, Volume 144, Issue 5, 2011, 646 – 674.
http://dx.doi.org/10.1016/j.cell.2011.02.013



Douglas Hanahan, Robert A. Weinberg, **Hallmarks of Cancer: The Next Generation.** Cell, Volume 144, Issue 5, 2011, 646 – 674.
http://dx.doi.org/10.1016/j.cell.2011.02.013

Immune evasion is a hallmark of cancer



Elimination

Net loss of tumor cell number
Net tumor volume shrinkage
Net loss of tumor vascularity

Equilibrium

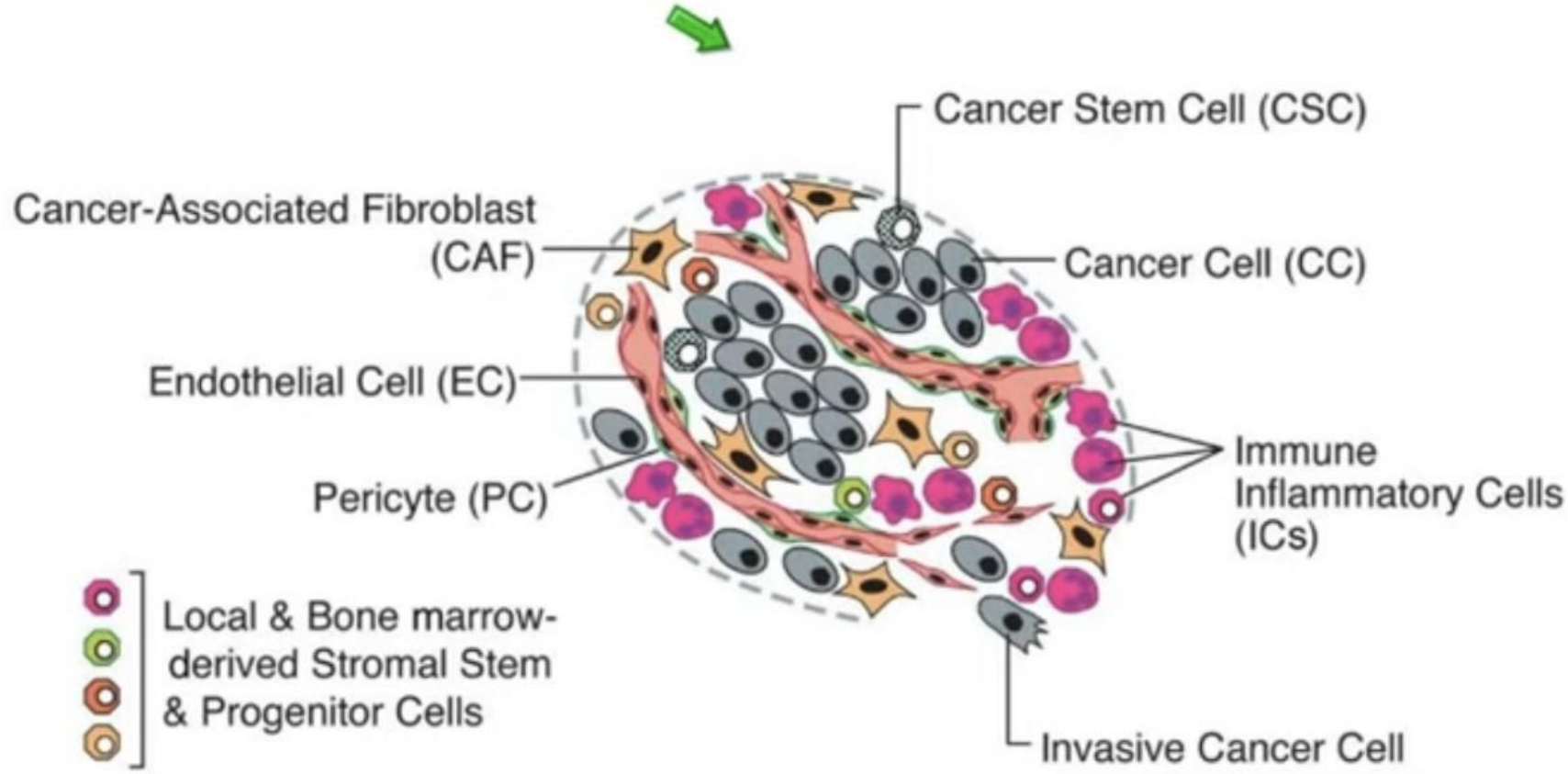
Little change in tumor cell number
Little change in tumor volume
Little change in tumor vascularity

Escape

Net gain of tumor cell number
Net gain in tumor volume
Net increase in tumor vascularity

Brett Burkholder, et al., **Tumor-induced perturbations of cytokines and immune cell networks.** Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, Volume 1845, Issue 2, 2014, 182 - 201

Tumor microenvironment (TME)



Douglas Hanahan, Robert A. Weinberg, **Hallmarks of Cancer: The Next Generation.** Cell, Volume 144, Issue 5, 2011, 646 – 674.
http://dx.doi.org/10.1016/j.cell.2011.02.013

Tumor microenvironment (TME) cont.

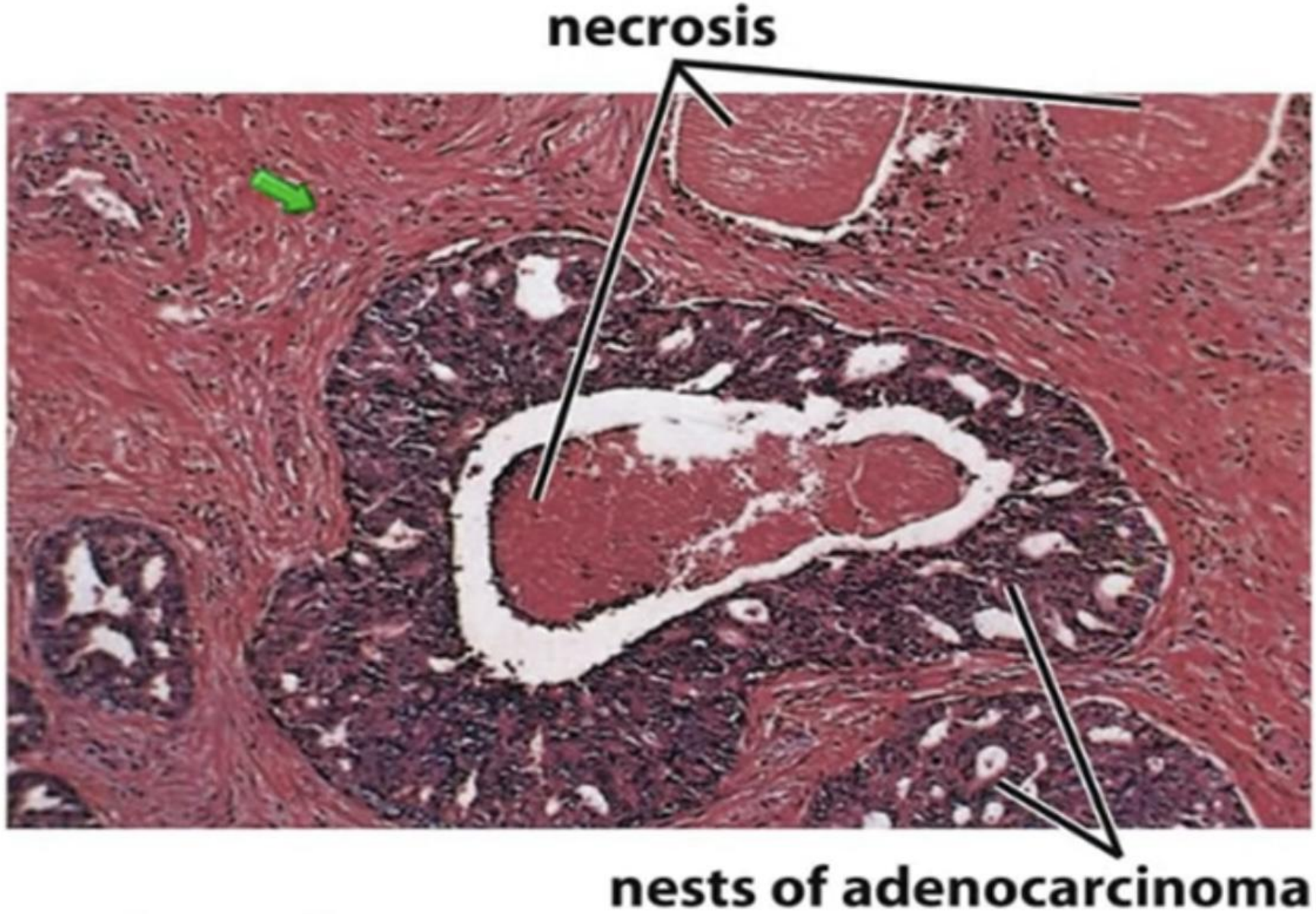
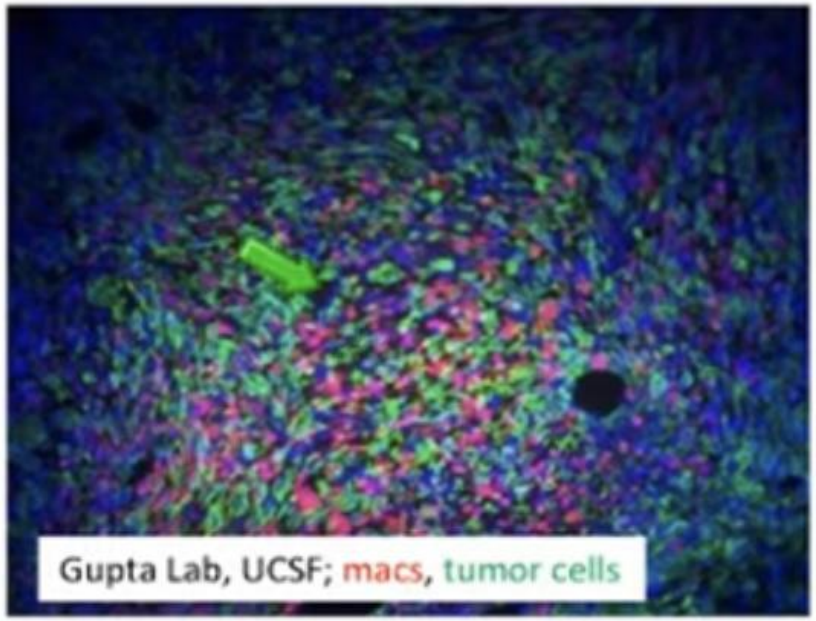
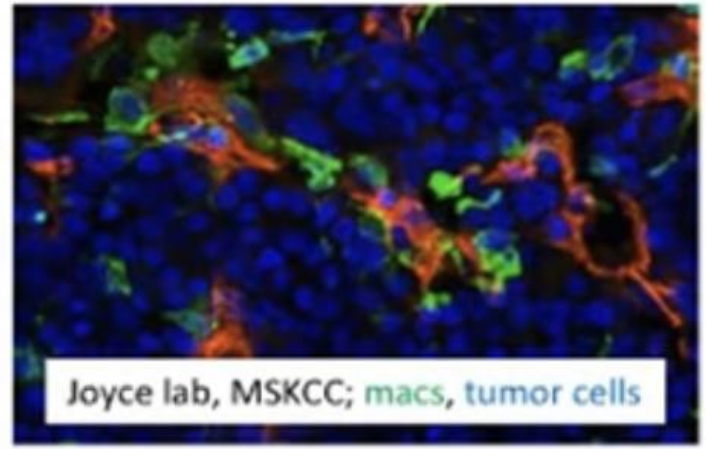
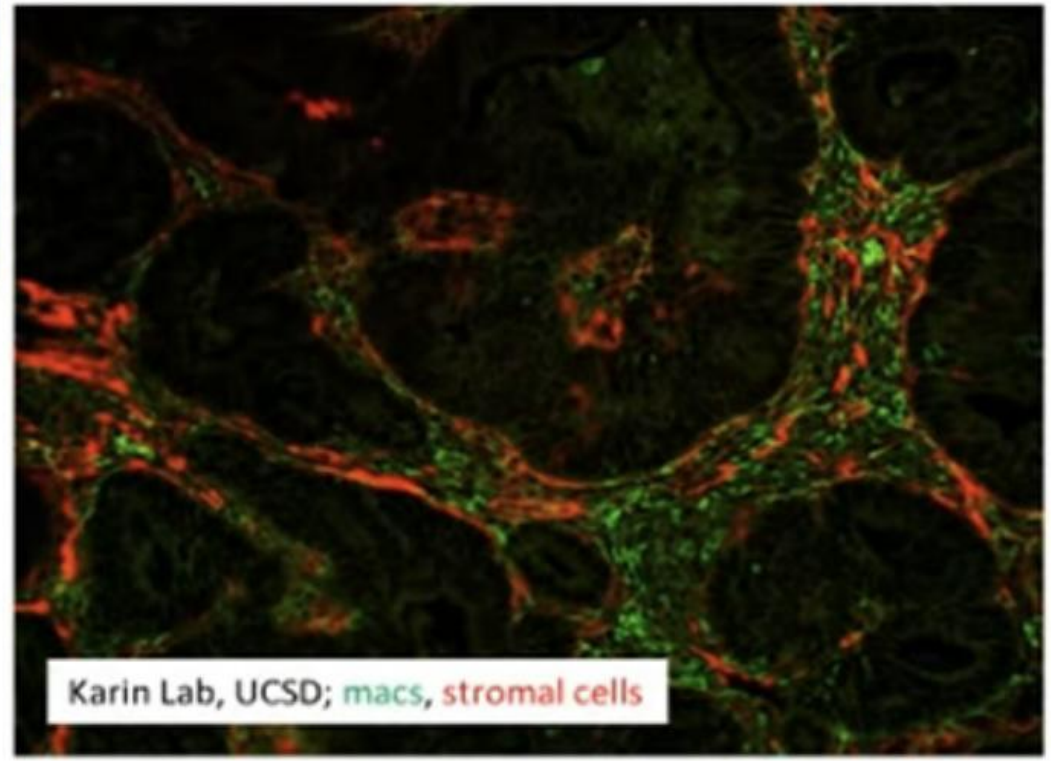


Figure 13.28 *The Biology of Cancer* (© Garland Science 2007)

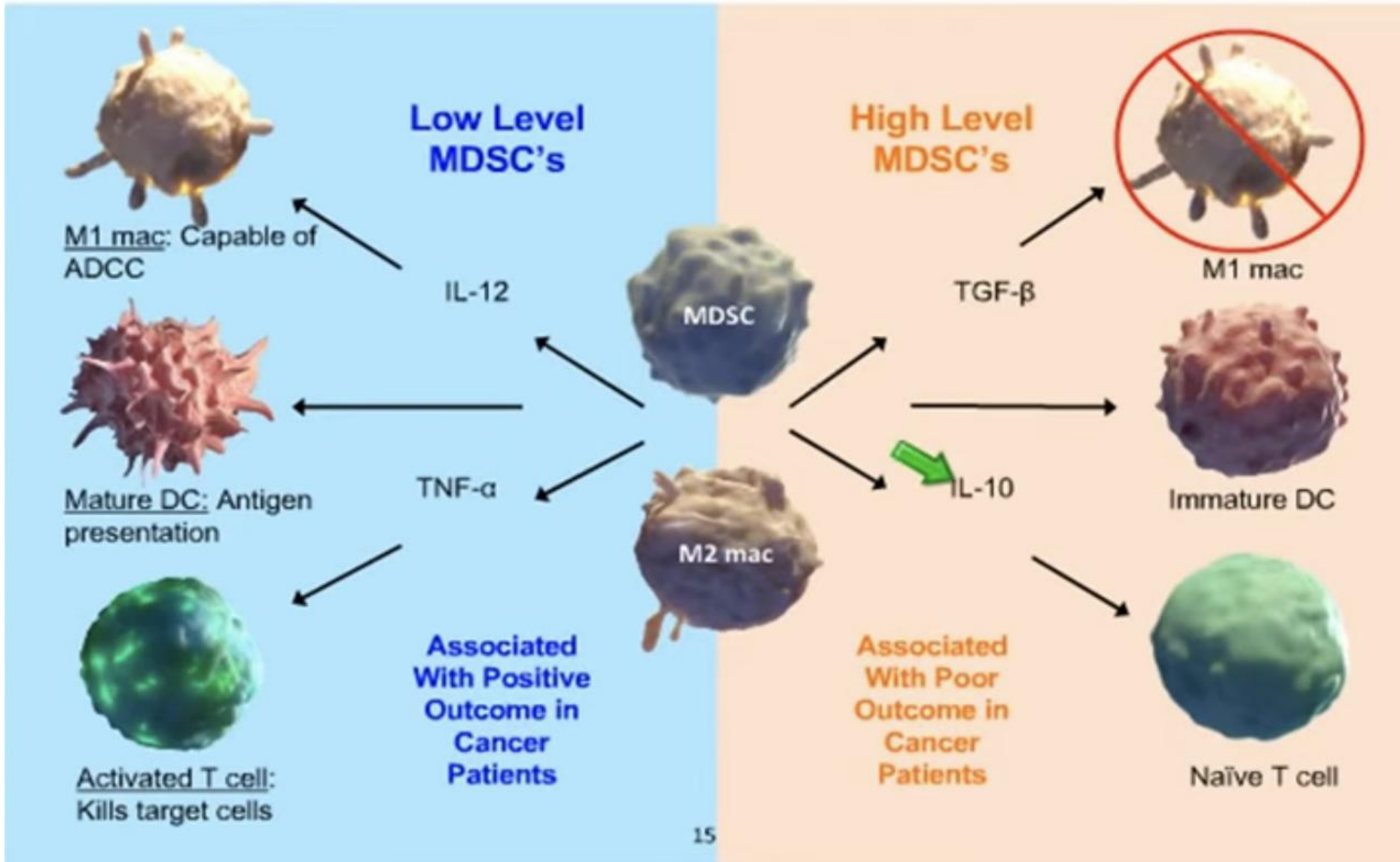
Macrophages in the TME







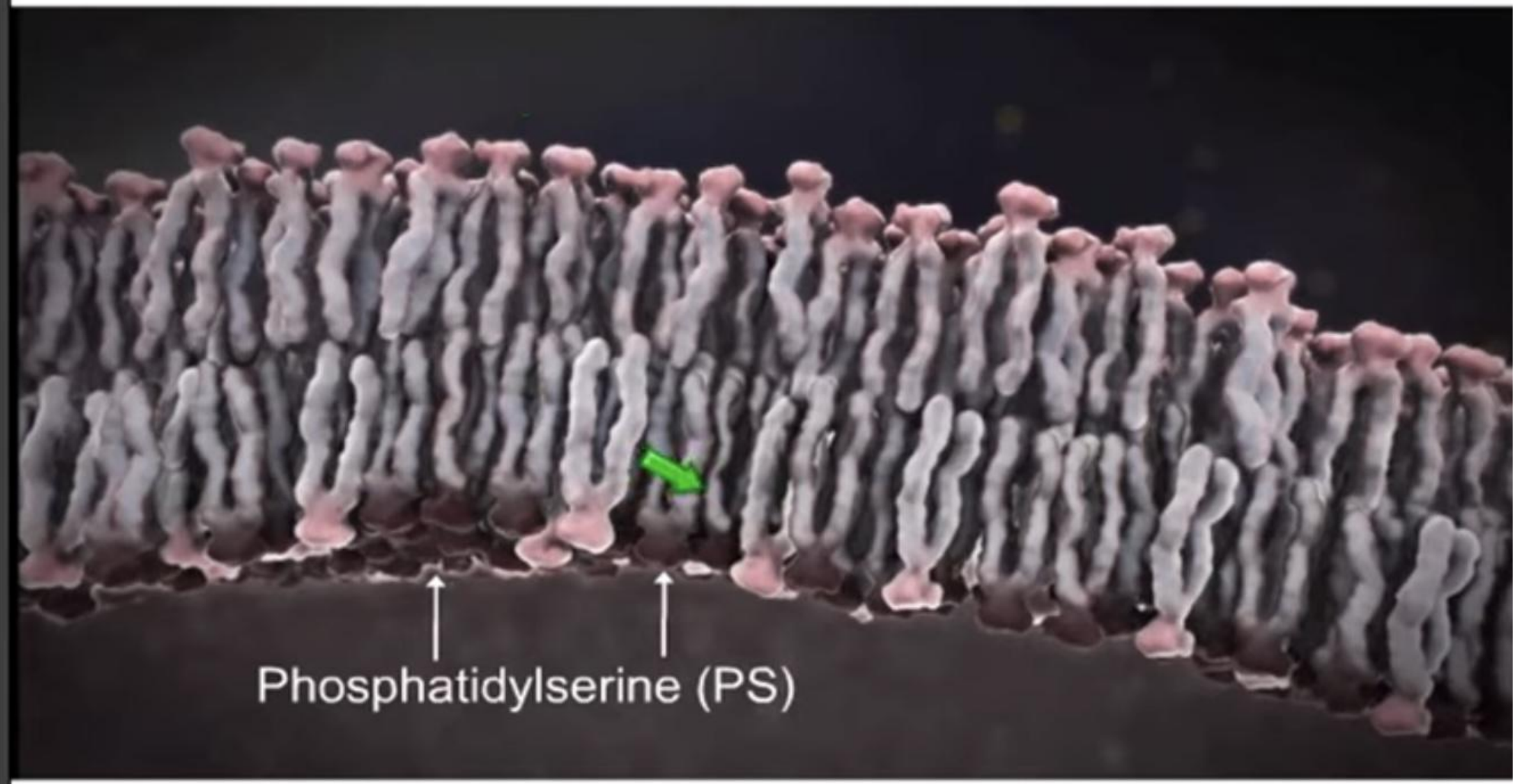
Immunotherapy Primer: MDSCs and M2 Macrophages are Key Gatekeepers in Determining Immune Response to Tumors



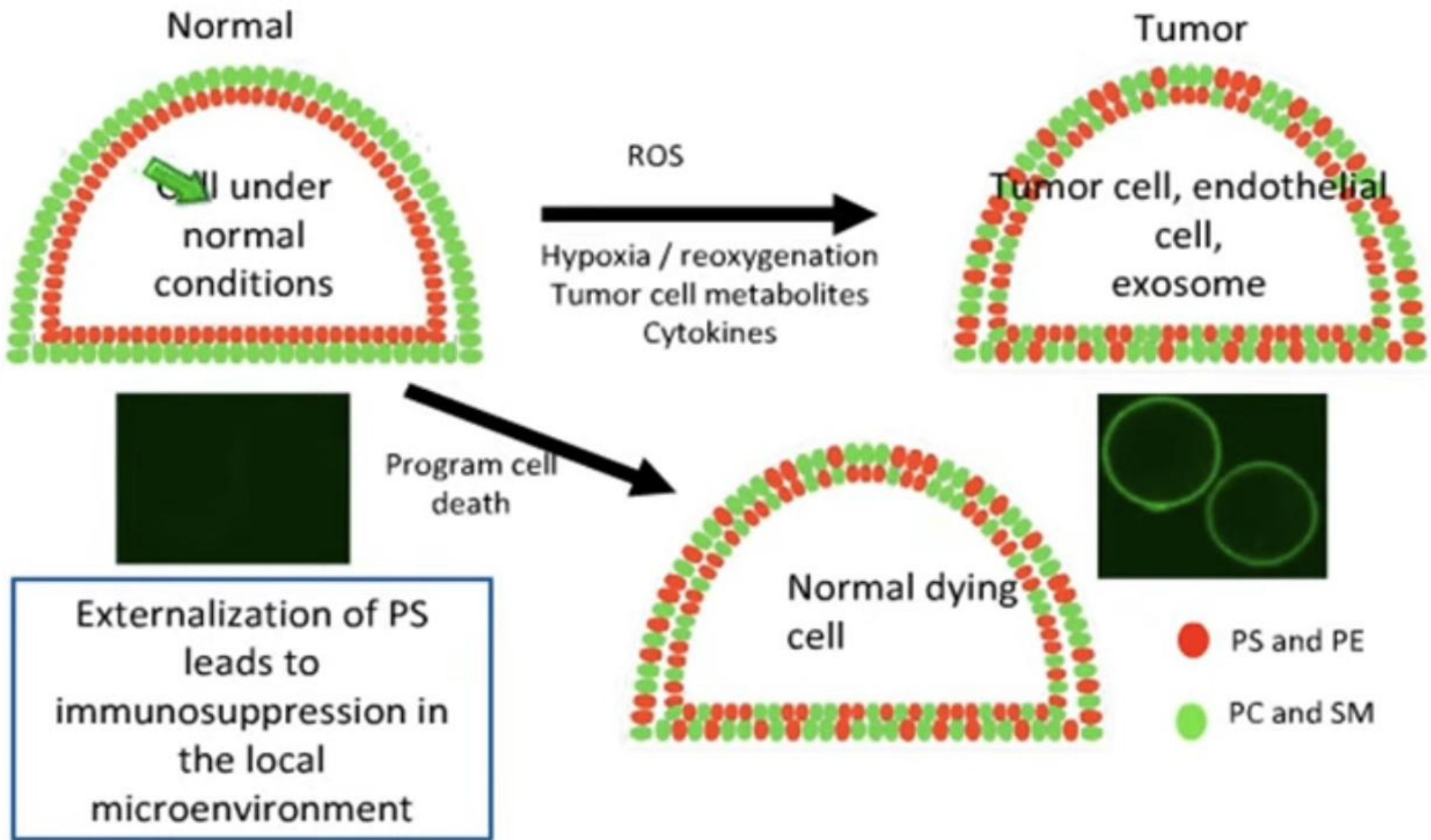
Key Messages

- Phosphatidylserine (PS) is exposed on the external surface of cells and vesicles in the tumor microenvironment
- PS exposure is immunosuppressive
- PS signaling is an immune check point that is upstream of PD-1/L1, CTLA-4 and IL-2 signaling
- Antibody-mediated inhibition of PS results in immune activation and durable anti-tumor responses

Healthy Cell Plasma Membrane: PS on Interior Leaflet

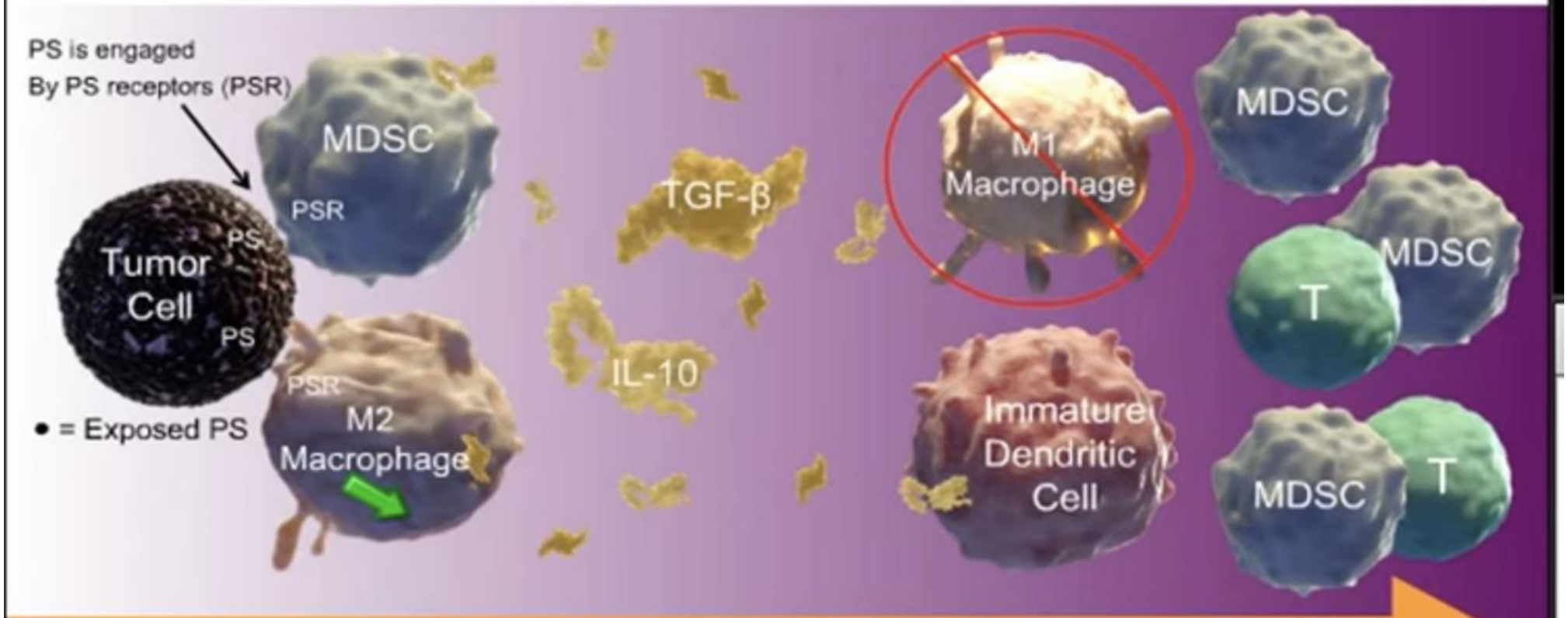


Exposure of Phosphatidylserine (PS) on the surface of cells



PS Signaling suppresses immune surveillance

Exposed PS in the tumor environment provides a fundamental upstream immunosuppressive signal



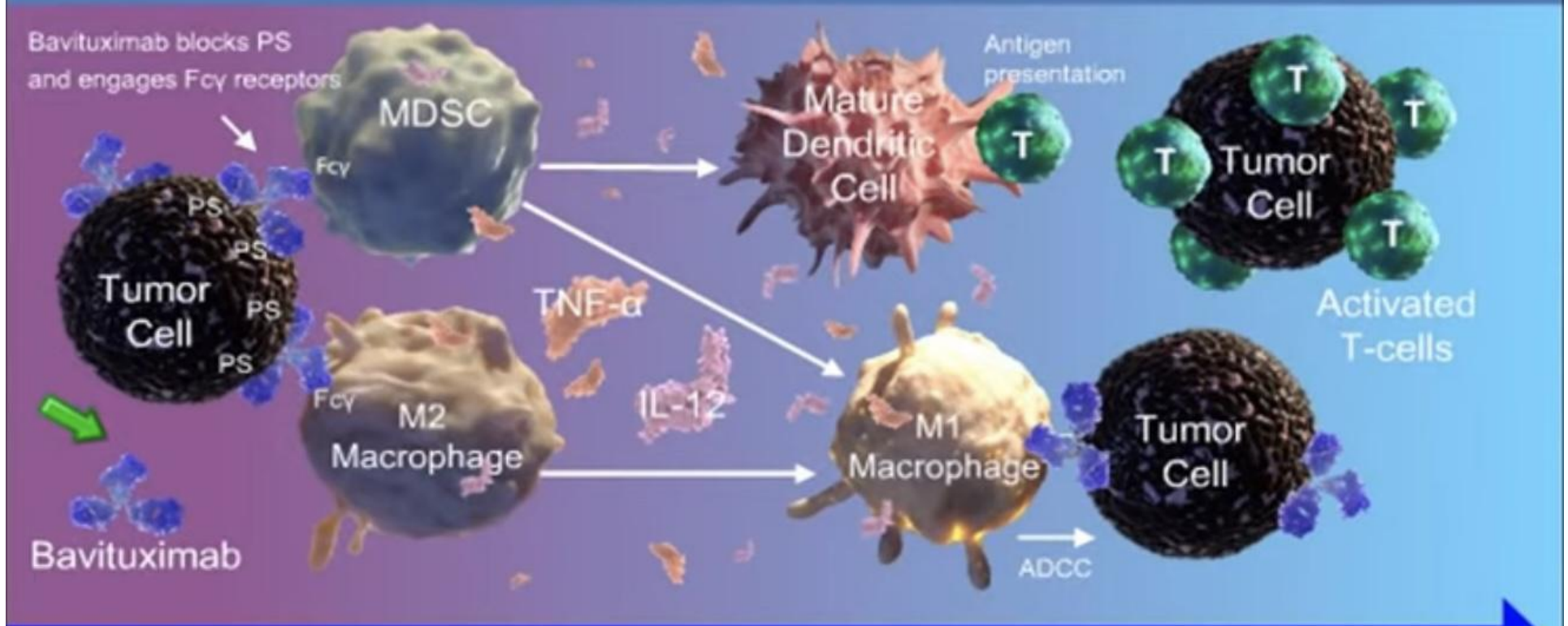
1. PS Signaling
2. Immune System Signaling
3. Immune Suppression

- PS exposed on tumor is a checkpoint that inhibits tumor immune response
- PS is engaged through PS receptors

- PS signaling causes increased anti-inflammatory cytokine expression

- MDSCs accumulate
- DCs fail to mature
- T-cells remain naïve
- M1 Macrophages fail to develop

Bavituximab blocks PS immune suppression and activates a robust immune response



1. Bavituximab Treatment

- Effector cells engage bavi-coated PS through Fcγ receptors
- Overrides upstream PS-mediated immunosuppressive signal

2. Upstream Immune Activation

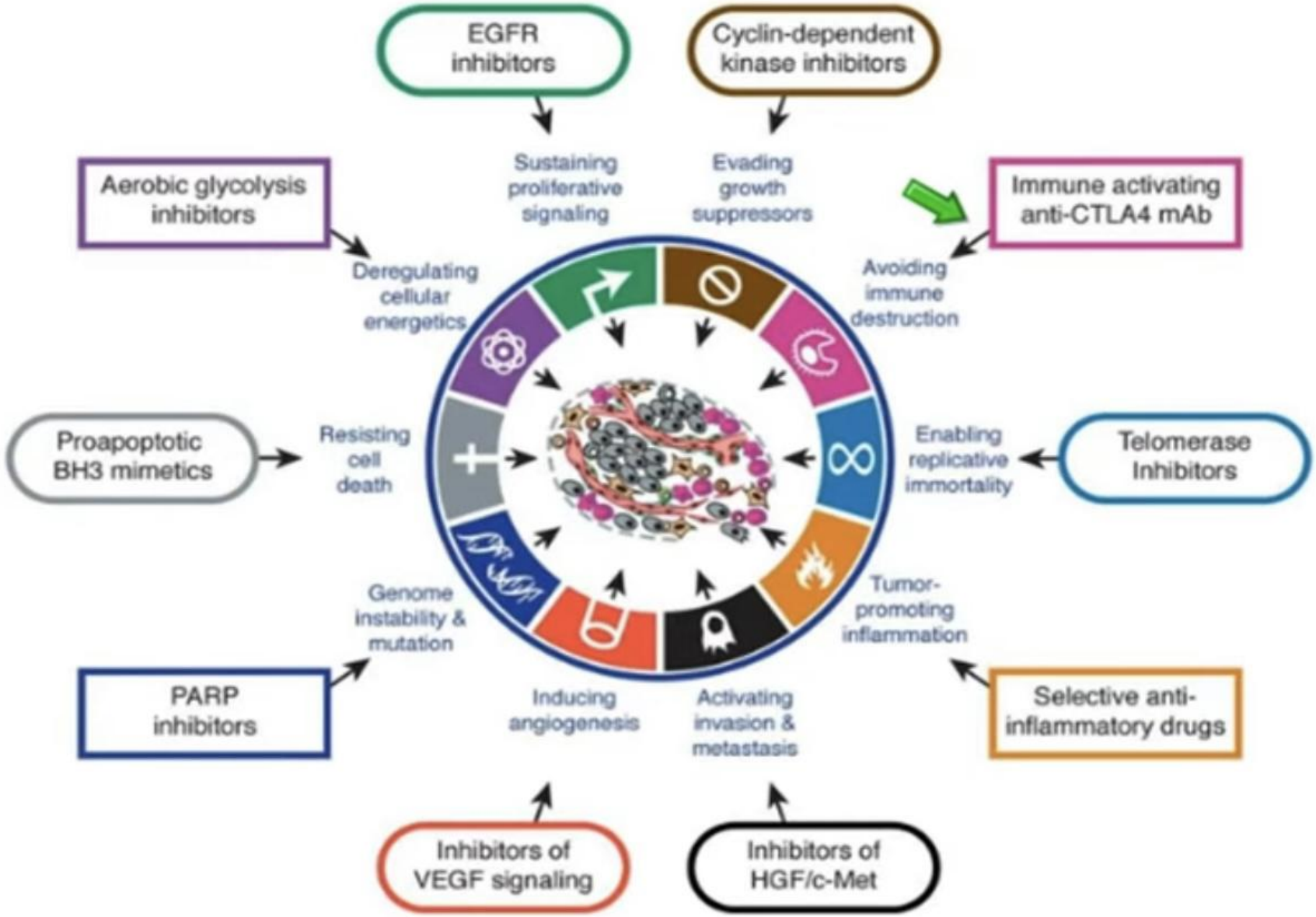
- Inflammatory cytokines
  - Tumor necrosis factor-alpha (TNF-α)
  - Interleuken-12
- MDSC differentiation
- M2 to M1 macrophage polarization
- DC maturation

3. Sustained Immune Response

- M1 macrophages kill cells via antibody-dependent cellular cytotoxicity (ADCC)
- Mature dendritic cells present tumor antigens to T-cells
- Tumor-specific cytotoxic T-cells

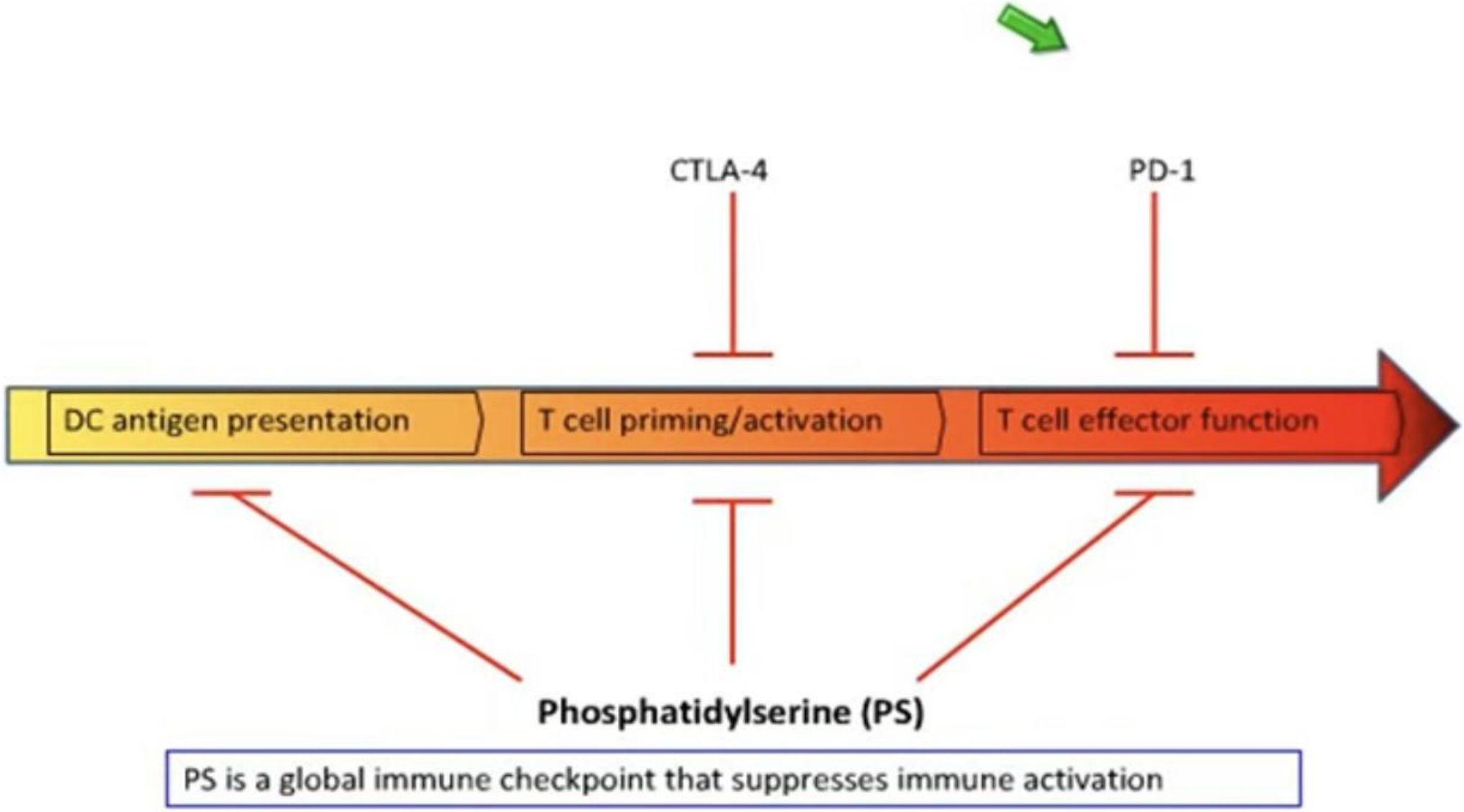
PS is a global immune checkpoint

- Suppresses dendritic cell functions
- Polarizes macrophage towards M2
- Induces the production of immunosuppressive cytokines, such as TGF-β and IL-10
- Inhibits the production of immunostimulatory cytokines, such as IL-12, TNFα
- Promotes T cell tolerance

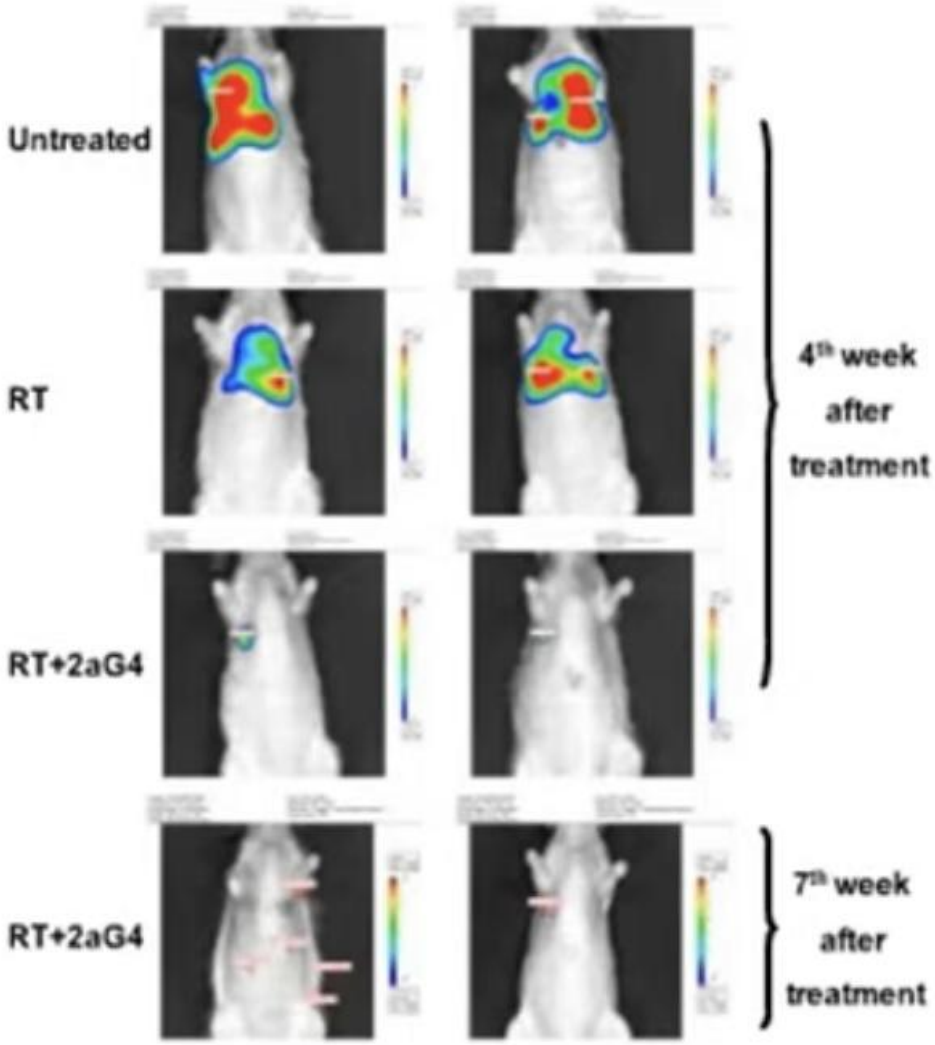


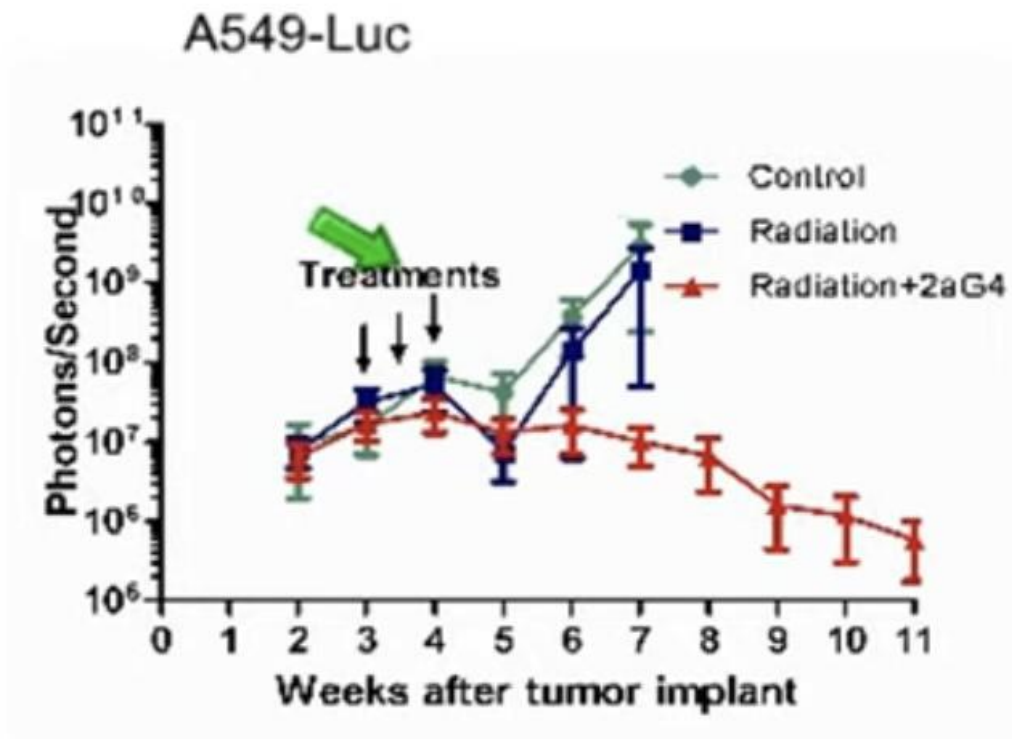
Douglas Hanahan, Robert A. Weinberg, **Hallmarks of Cancer: The Next Generation.** Cell, Volume 144, Issue 5, 2011, 646 – 674.
http://dx.doi.org/10.1016/j.cell.2011.02.013

Tumors exploit multiple immune suppressive mechanisms



Regression of Radioresistant NSCLC by Treatment with PS-targeting Antibody + Intense Radiotherapy



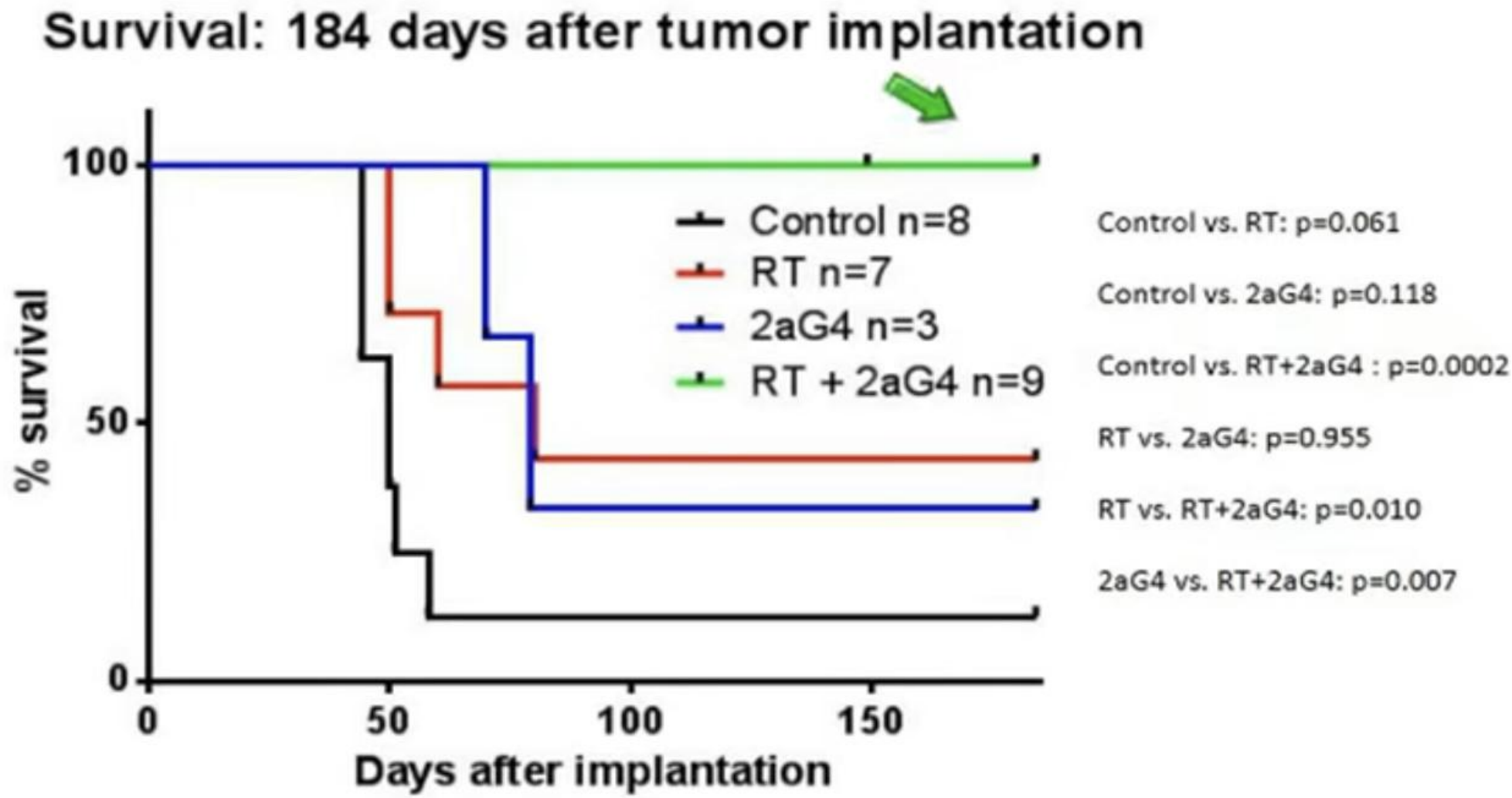


RT = 3 x 12 Gy

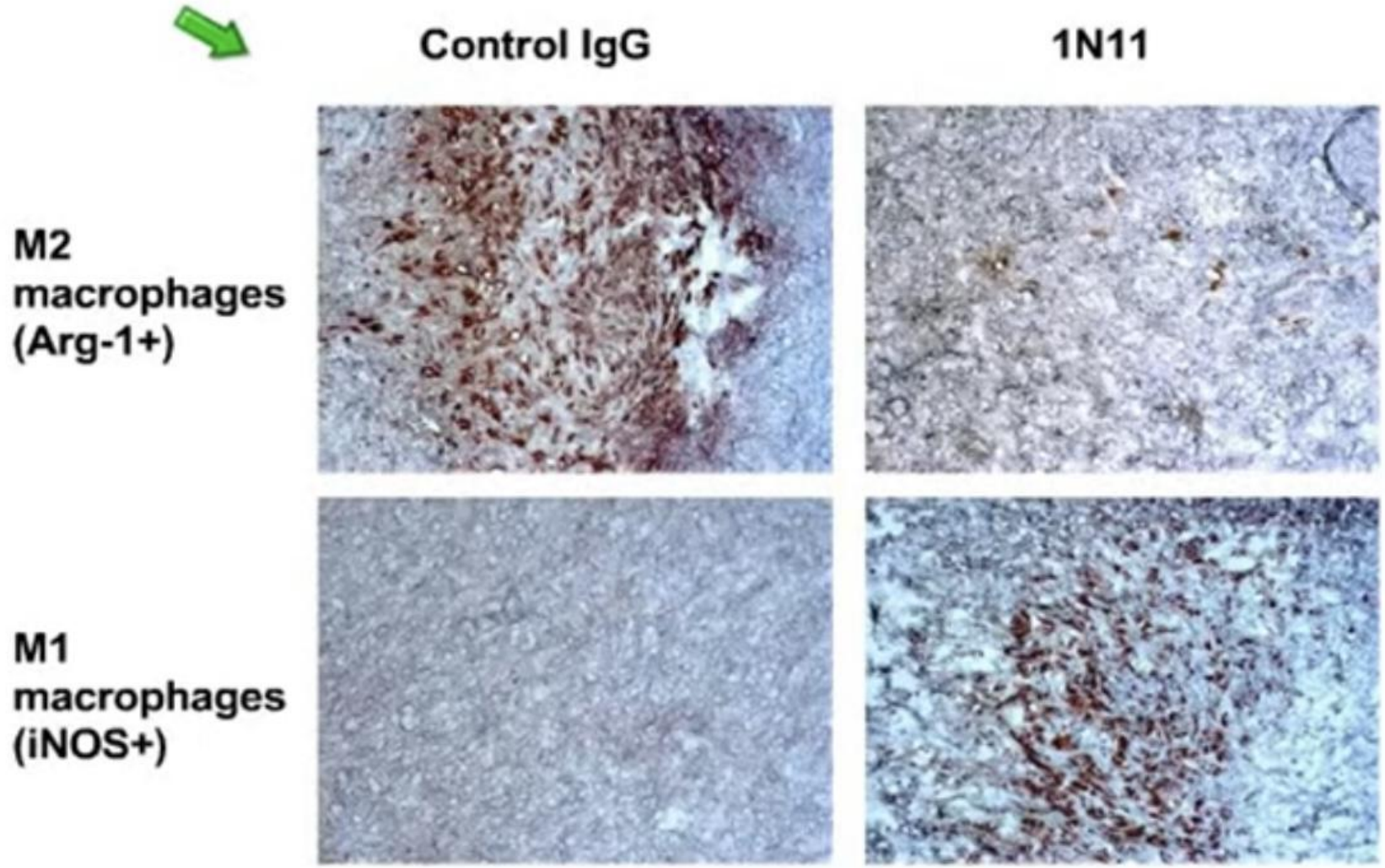
Three of six rats had no detectable tumor!

Thorpe lab, UT Southwestern

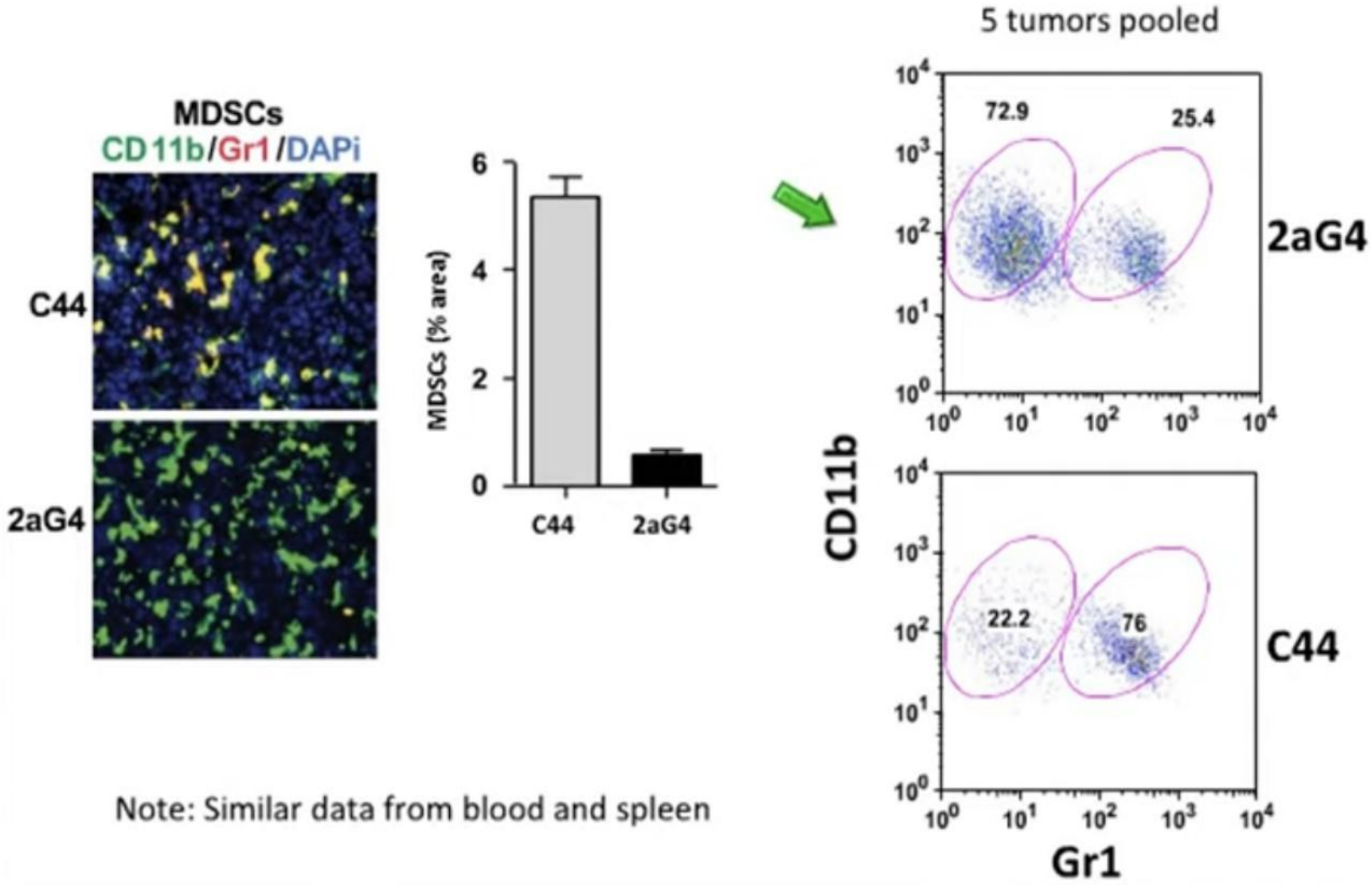
Current Results: Prelim data, combining SBRT with 2aG4 in Orthotopic A549 Rat Lung Model



PS-Targeting antibody causes tumor macrophages to switch from M2 to M1



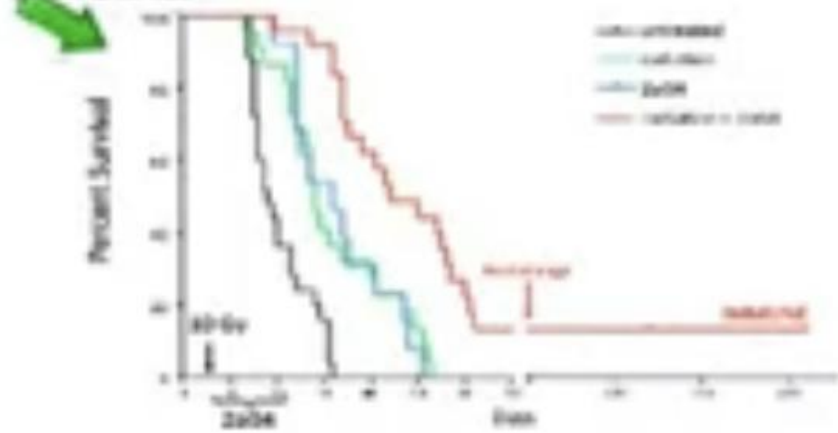
PS blockade reduces tumor-infiltrating MDSCs



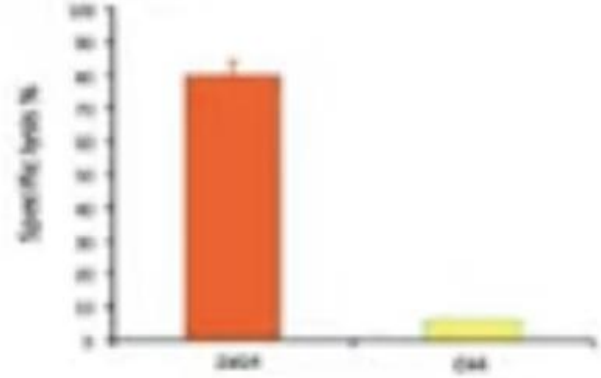
Note: Similar data from blood and spleen

PS blockade facilitates induction of tumor-specific cytotoxic T-cells

Generation of antitumor T-cell immunity in syngeneic F98 glioma in rat[1]

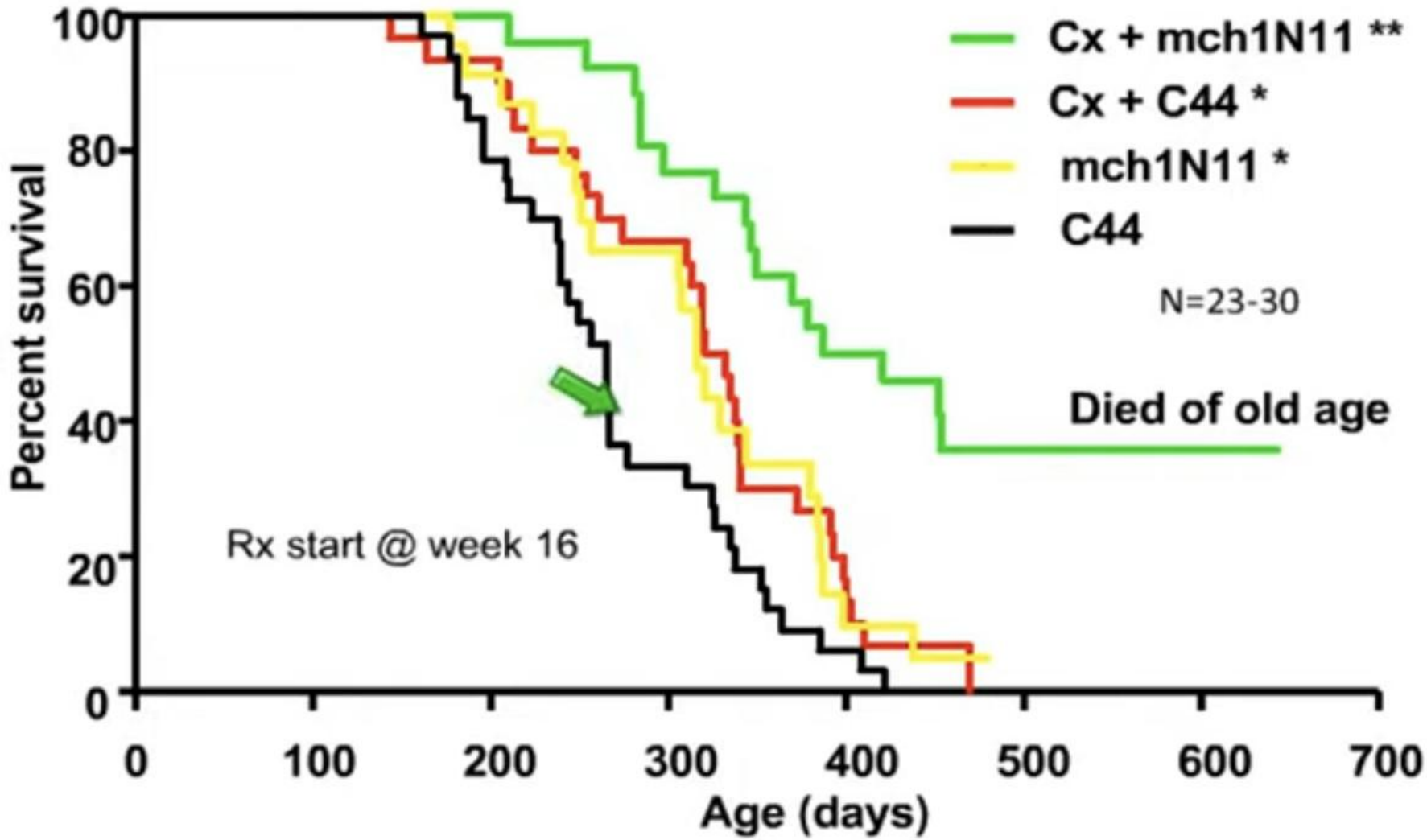


Cytotoxic T-cell Generation[1]



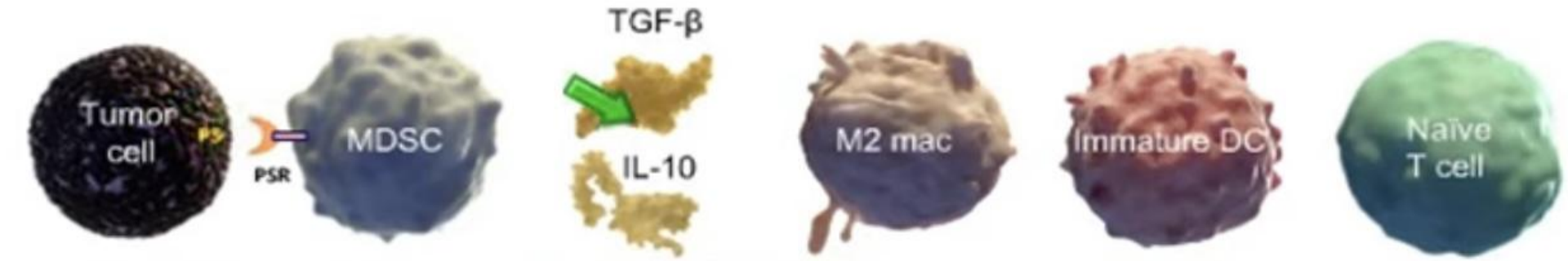
1. Ito et al., Antiphosphatidylserine Antibody Combined with Irradiation Eliminates Tumor Blood Vessels and Induces Tumor Immunity in a Rat Model of Glioblastoma. Clin Cancer Res. 2009;15:6875-6885.

Cure of transgenic model of prostate cancer (TRAMP) mice



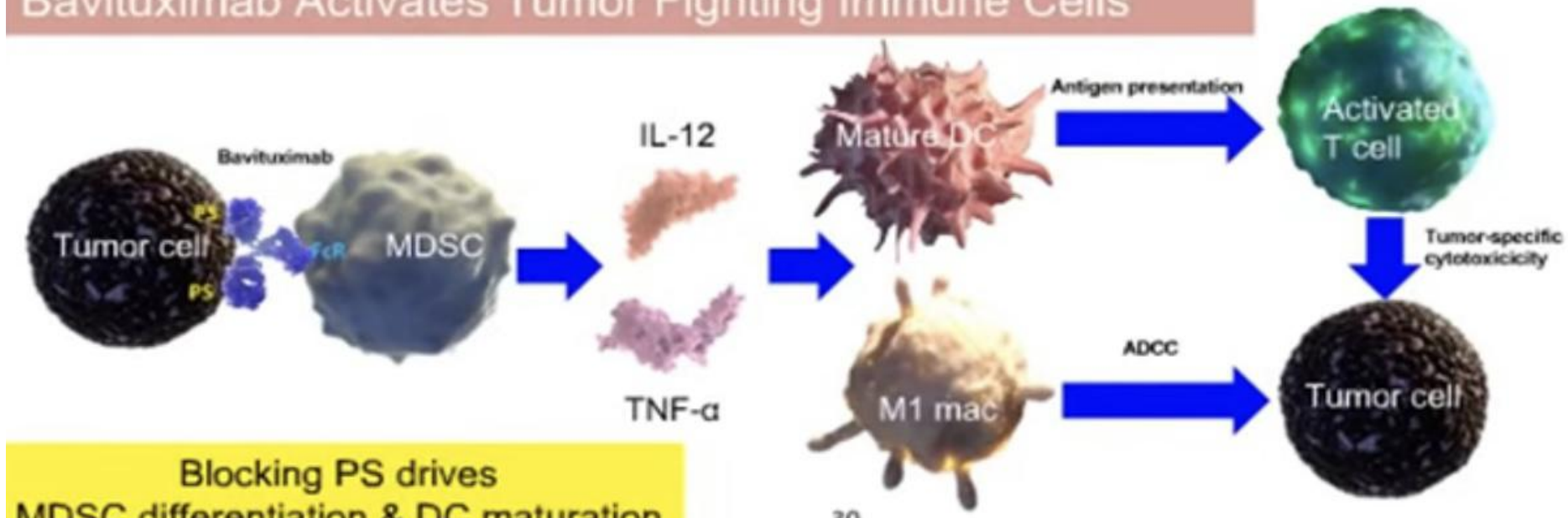
1. AACR 2012 Annual Meeting: Yin et al. & Keystone 2014 Huang et al

Summary: Bavituximab activates tumor immunity



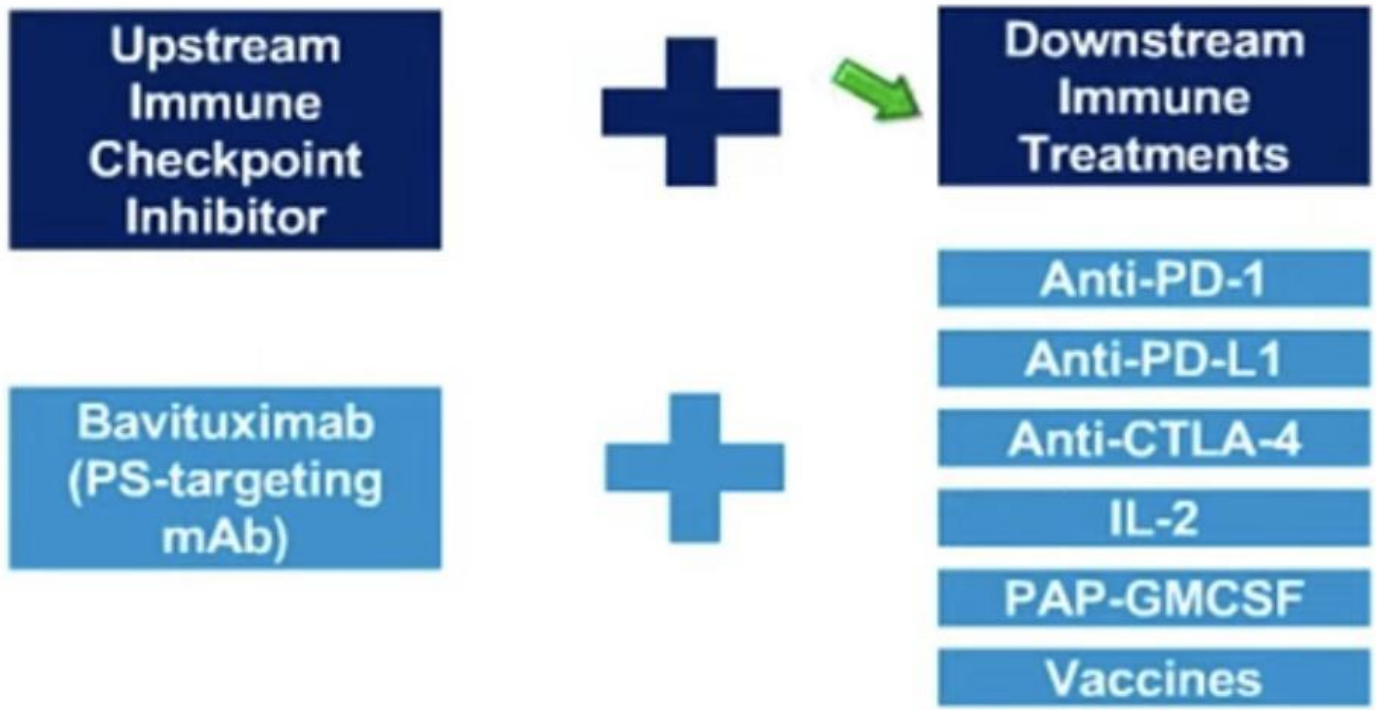
PS in Tumor Environment Causes Immune Suppression

Bavituximab Activates Tumor Fighting Immune Cells

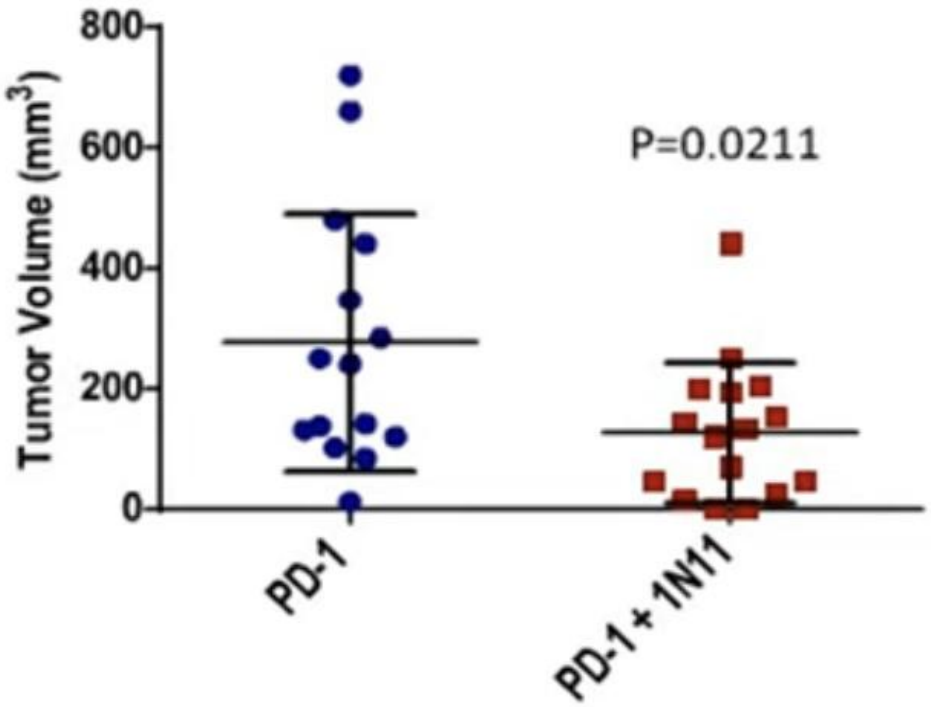


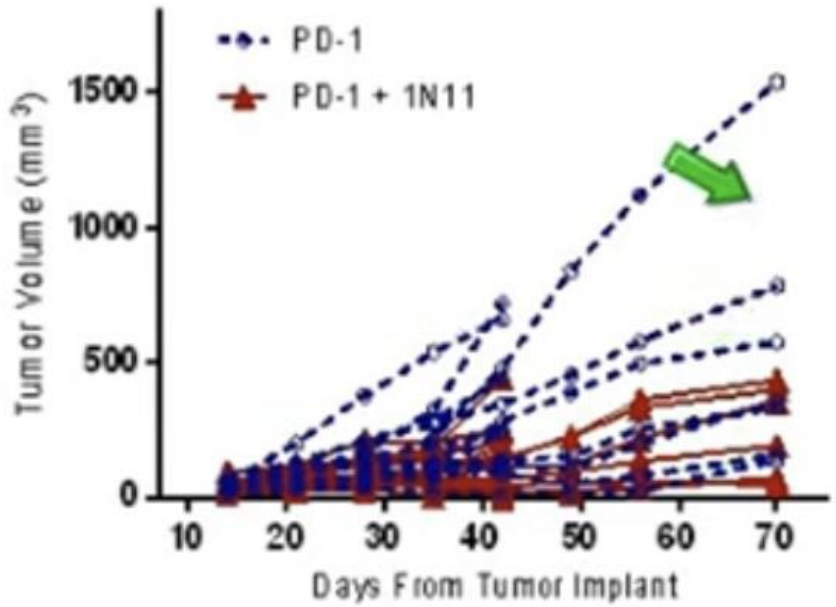
Blocking PS drives
MDSC differentiation & DC maturation

MOA supports multiple opportunities with other immunotherapies



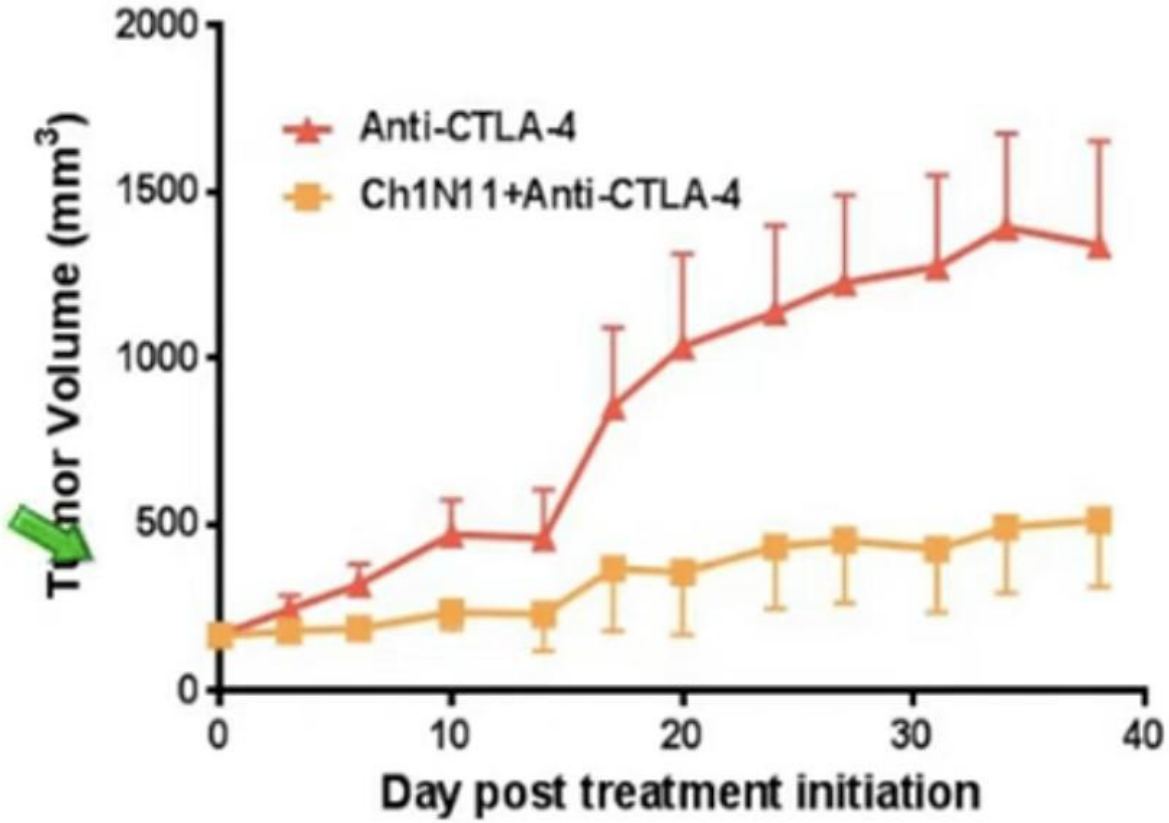
mch1N11 enhances the efficacy of anti-PD1 in K1735 melanoma





Anti-PD1 + mch1N11 induced IFNγ and IL-2 from splenic T-cells and an induction of CD8+ T cells in the spleen

mch1N11 enhances the efficacy of anti-CTLA-4 in K1735 melanoma



- Mean ± SEM; N=10/group; T-test, P = 0.004, sig
- Tumors ≥ 2000mm^3 are carried forward

Key Messages - Summary

- Phosphatidylserine (PS) is externalized in the tumor microenvironment and is a major immunosuppressive signal
- PS is a global immune checkpoint
- Antibody-mediated blockade of PS signaling breaks immune tolerance reactivating innate and adaptive immunity and results in durable anti-tumor responses in multiple pre-clinical models
- Combination pre-clinical studies with other immune checkpoint inhibitors are underway and early phase clinical studies are planned