Pathogenesis of solid tumors

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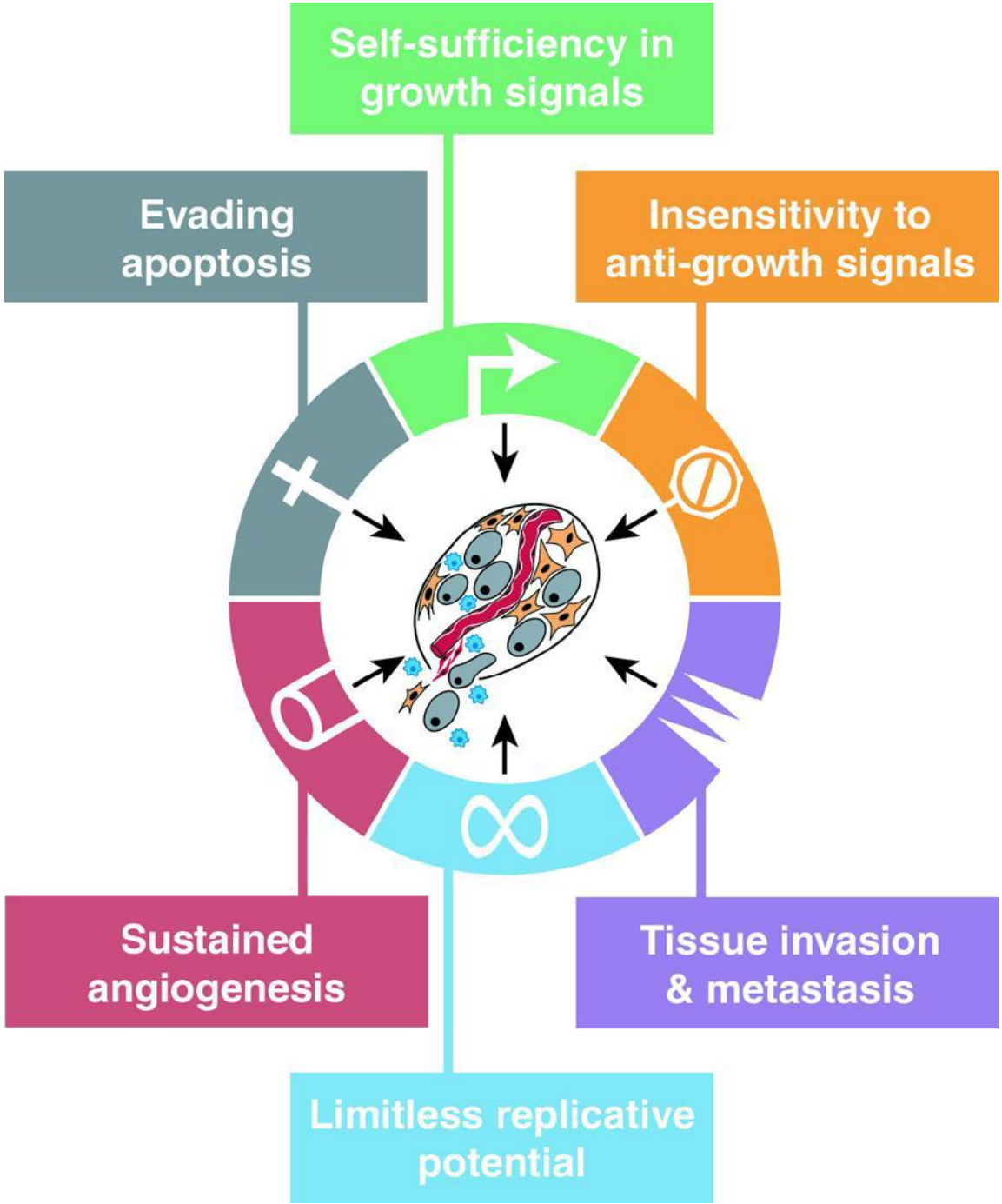
If you think we are going to discuss…

- Asbestos…mesothelioma
- Ultraviolet light…melanoma
- HPV…cervical carcinoma
- HHV8…Kaposi sarcoma
- Smoking…lung, urothelial carcinomas…
- **You are wrong!**

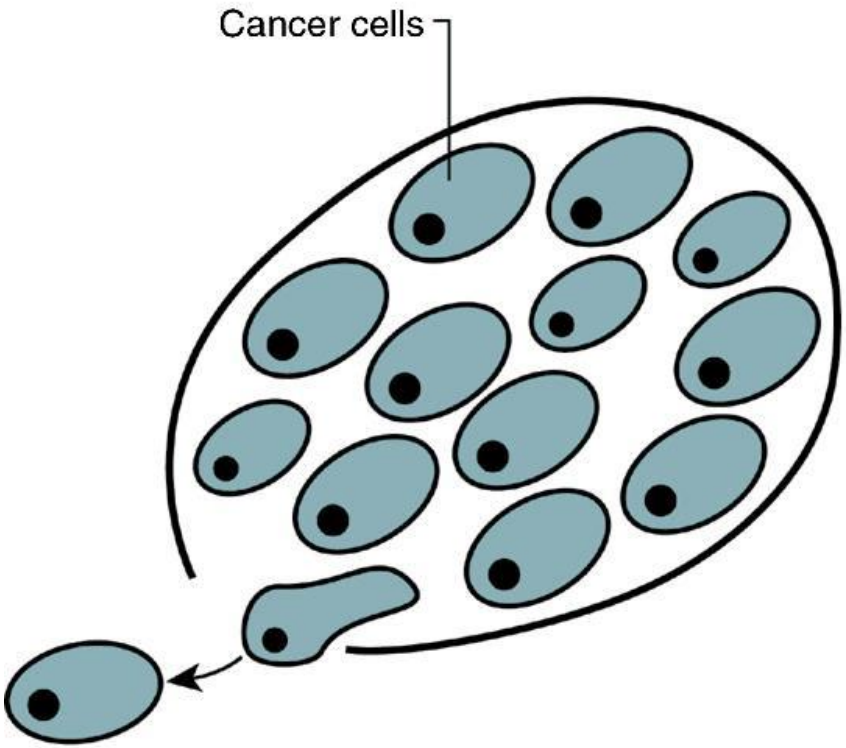
The hallmarks of cancer"

(Hanahan D. and Weinberg R.A. **2000**, *Cell* 100: 57-70)

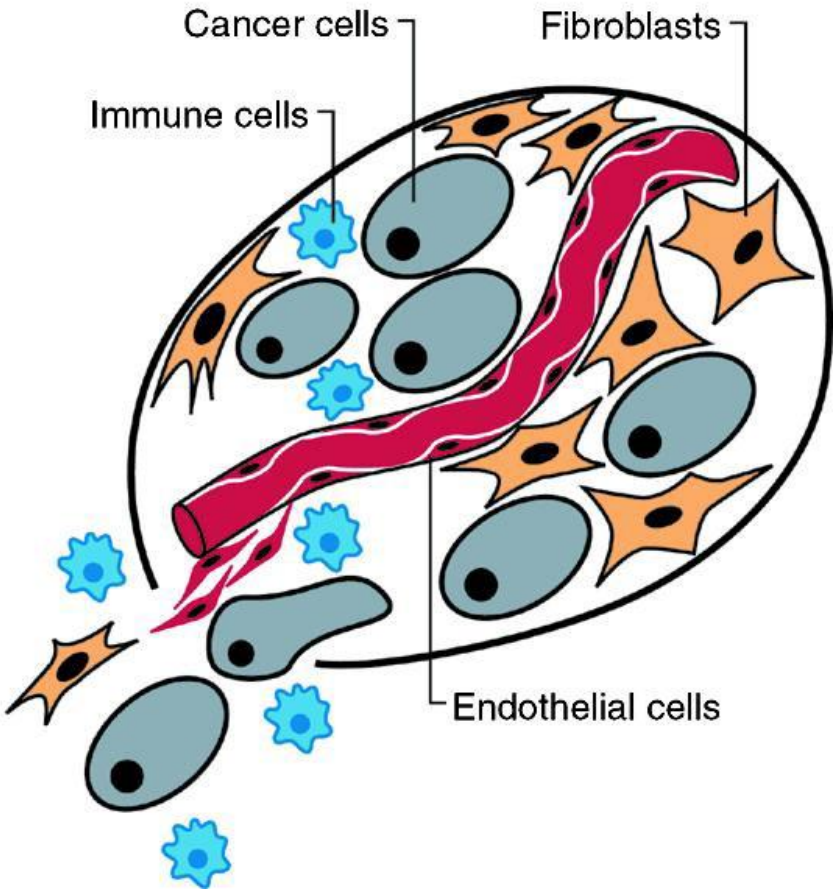

Self-sufficiency in growth signals
Evading apoptosis
Insensitivity to anti-growth signals
Sustained angiogenesis
Tissue invasion & metastasis
Limitless replicative potential

- **Self-Sufficiency in Growth Signals:** normal cells require mitogenic growth signals before they can move from a quiescent state into an active proliferative state. Cancer cells not.
- **Insensitivity to Antigrowth Signals:** within a normal tissue, multiple antiproliferative signals operate to maintain cellular quiescence and tissue homeostasis
- **Evading Apoptosis**
- **Limitless Replicative Potential**

The Reductionist View



A Heterotypic Cell Biology

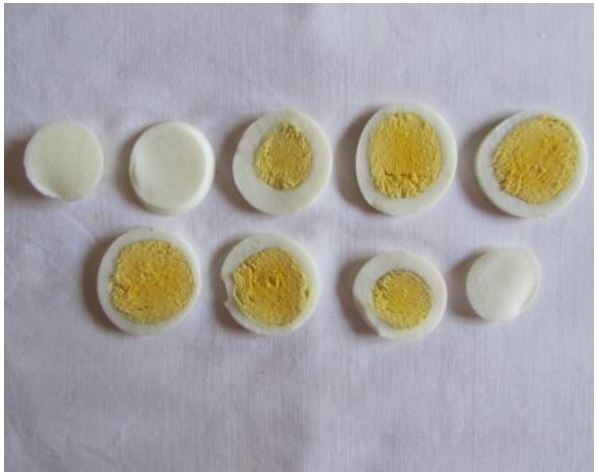


- "…a reductionist focus … has produced ***an extraordinary body of knowledge***…new important new inroads will come from regarding tumors as ***complex tissues*** …mutant cancer cells **have conscripted** and **subverted normal cell types to serve** as ***active collaborators*** in ***their neoplastic agenda***….these **supporting coconspirators** will prove **critical to** understanding cancer pathogenesis and to **the development** of **novel**, effective **therapies.**"

Molecular biology methods vs. histo(patho)logy in whole tissue examination

Molecular biology

Histo(patho)logy

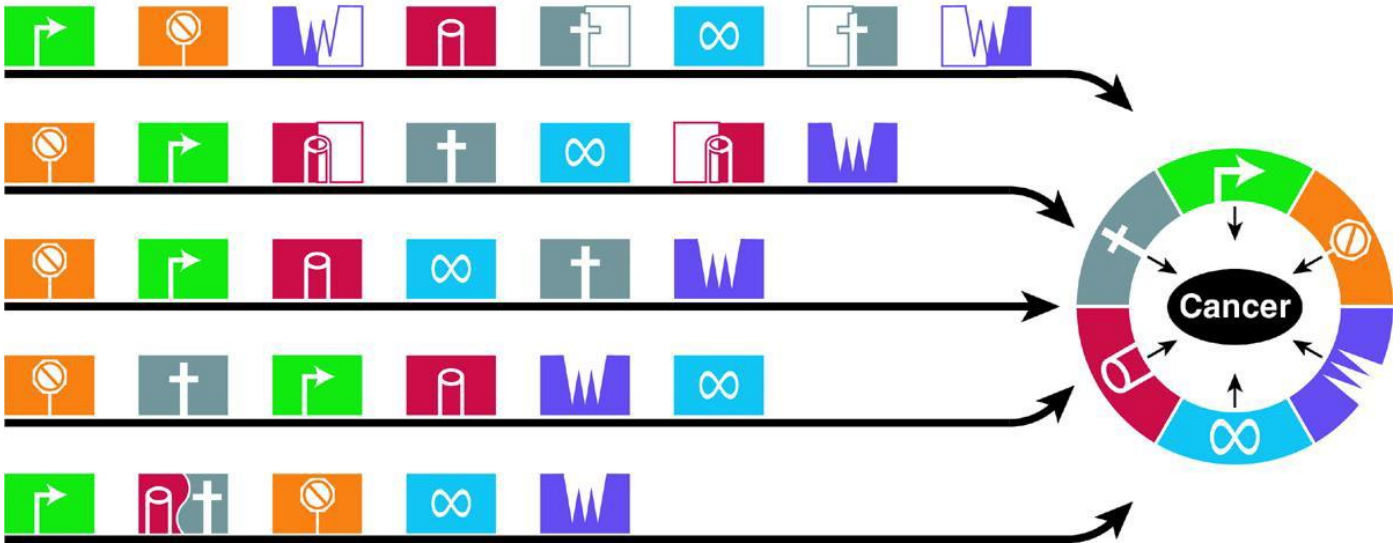


- **Sustained Angiogenesis**
- **Tissue Invasion and Metastasis**

A

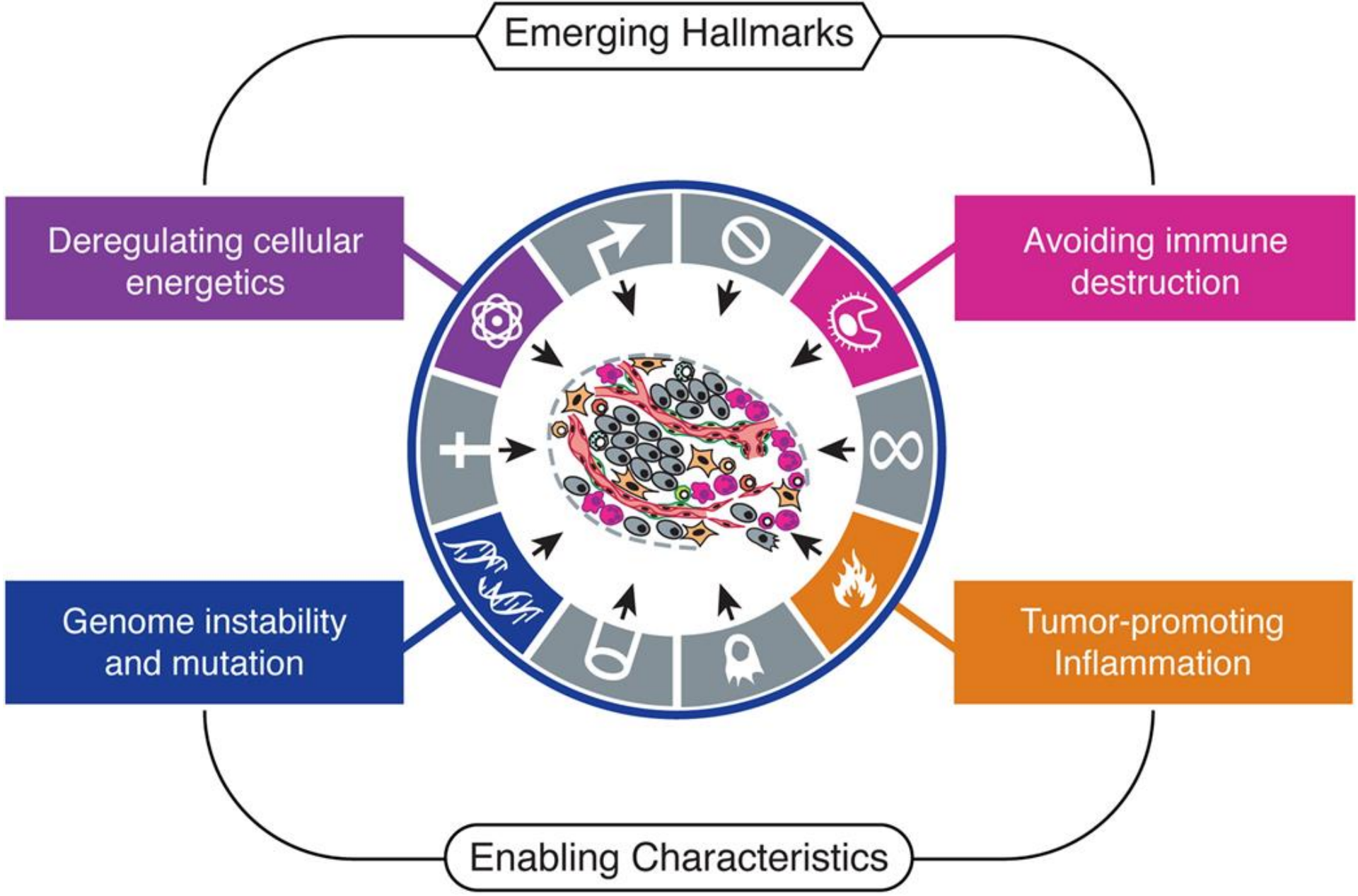
Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

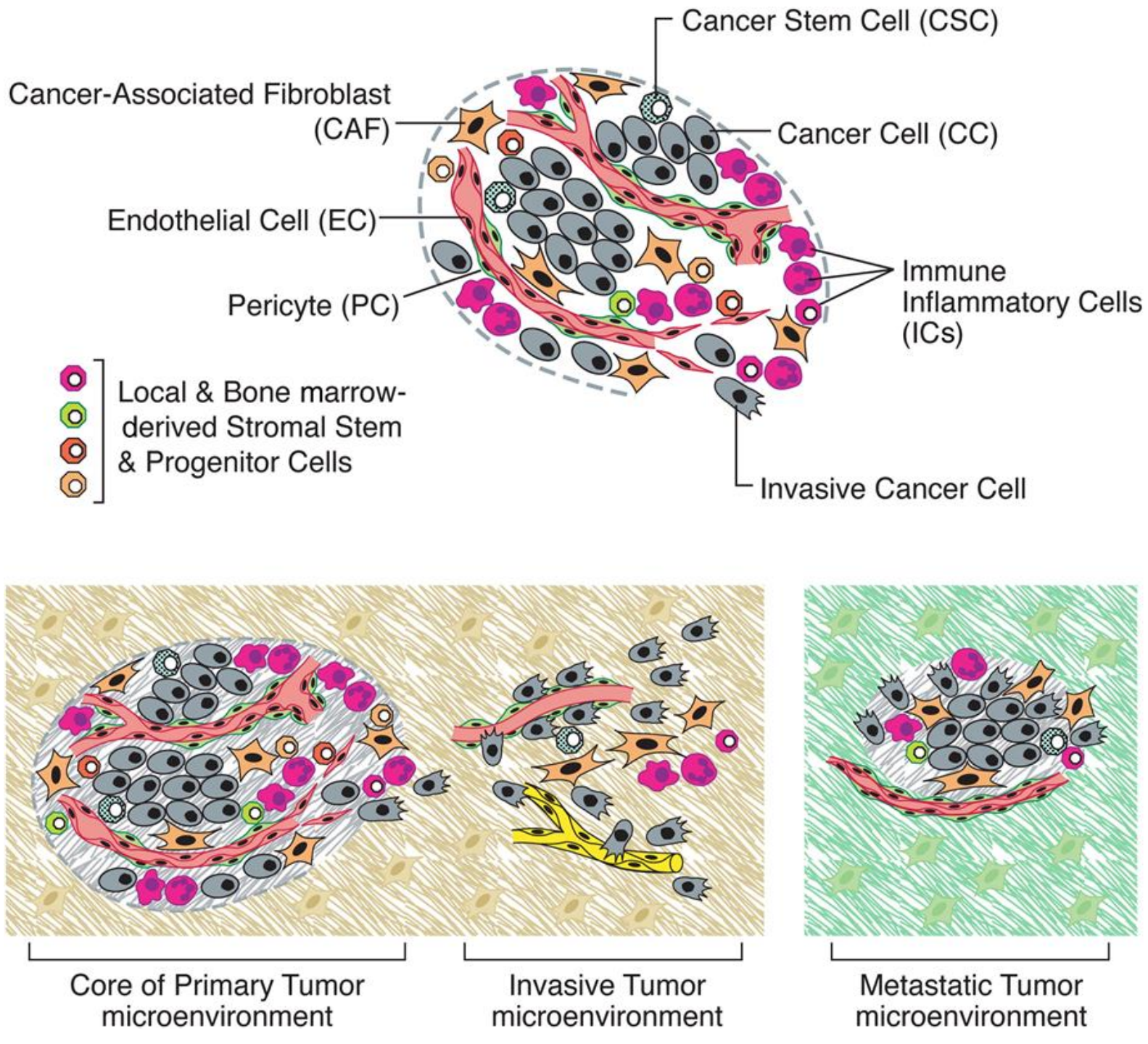
B

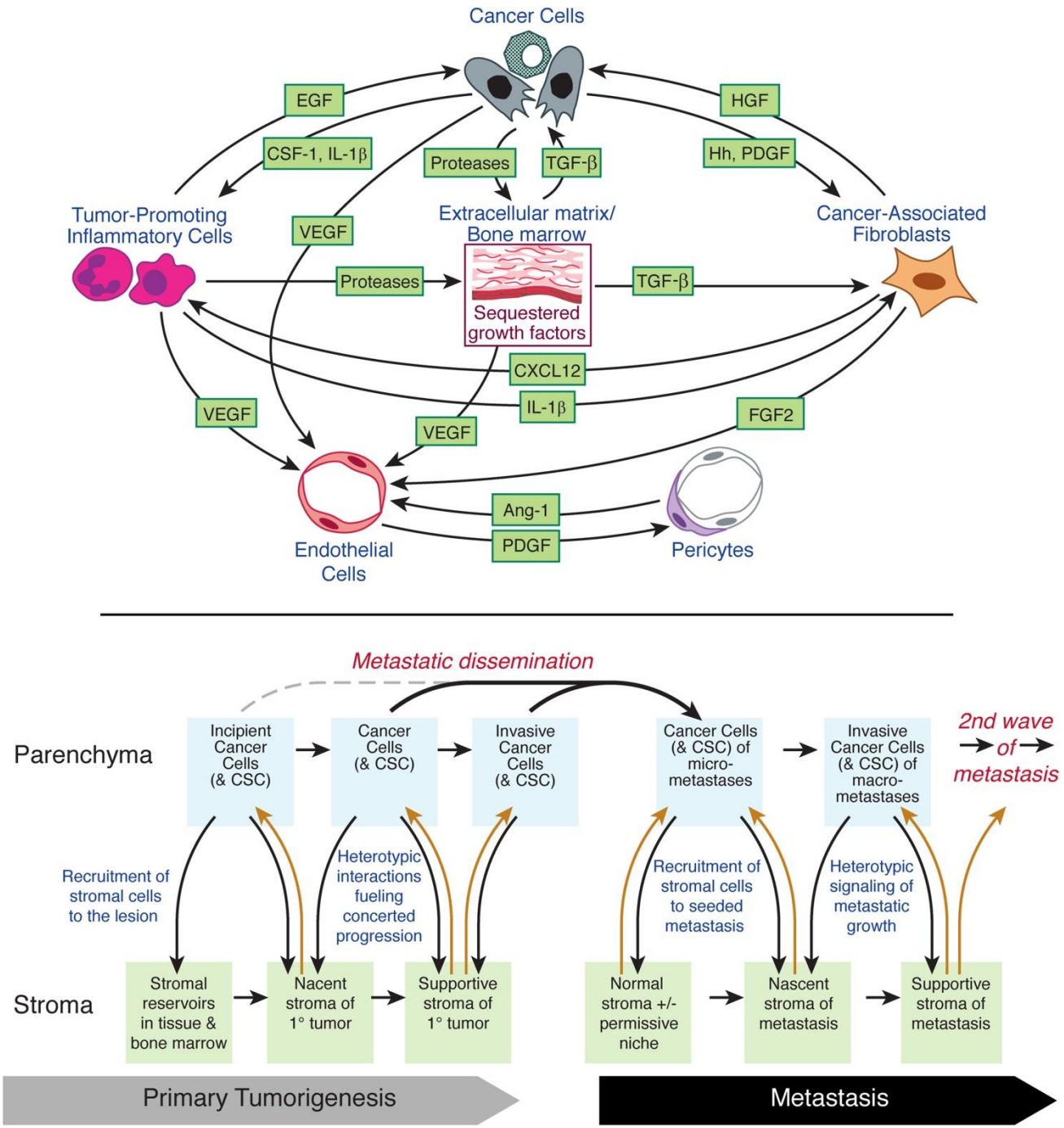


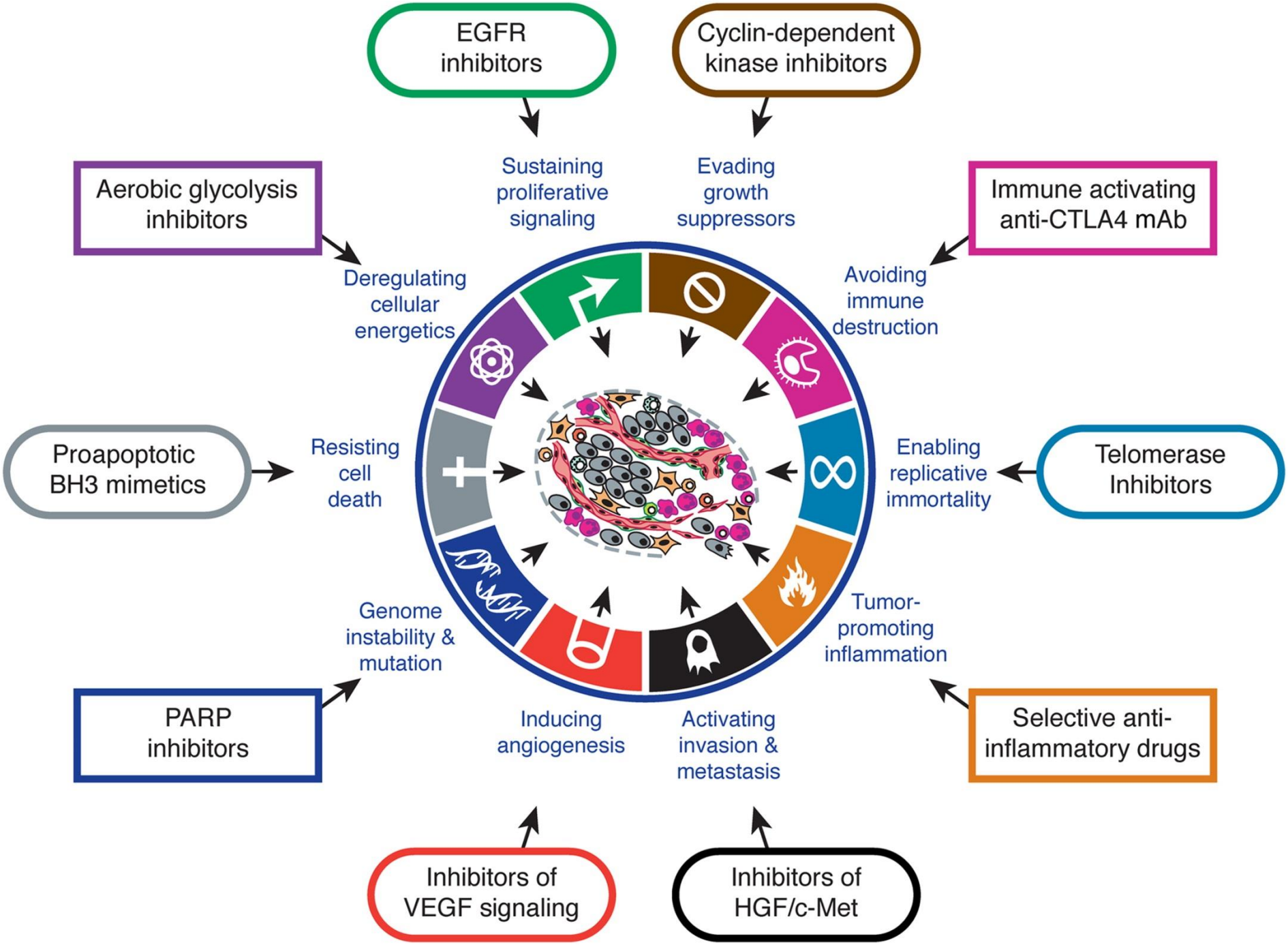
Hallmarks of Cancer: The Next Generation

(Hanahan D. and Weinberg R.A. **2011**, *Cell* 144: 646-674)


Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics


Cancer Stem Cell (CSC)
Cancer-Associated Fibroblast (CAF)
Cancer Cell (CC)
Endothelial Cell (EC)
Pericyte (PC)
Immune Inflammatory Cells (ICs)
Local & Bone marrow-derived Stromal Stem & Progenitor Cells
Invasive Cancer Cell
Core of Primary Tumor microenvironment
Invasive Tumor microenvironment
Metastatic Tumor microenvironment


Cancer Cells
EGF
HGF
CSF-1, IL-1β
Proteases
TGF-β
Hh, PDGF
Tumor-Promoting Inflammatory Cells
VEGF
Extracellular matrix/ Bone marrow
Cancer-Associated Fibroblasts
Proteases
Sequestered growth factors
TGF-β
CXCL12
IL-1β
VEGF
VEGF
FGF2
Ang-1
PDGF
Endothelial Cells
Pericytes
Metastatic dissemination
Parenchyma
Incipient Cancer Cells (& CSC)
Cancer Cells (& CSC)
Invasive Cancer Cells (& CSC)
Cancer Cells (& CSC) of micro-metastases
Invasive Cancer Cells (& CSC) of macro-metastases
2nd wave of metastasis
Recruitment of stromal cells to the lesion
Heterotypic interactions fueling concerted progression
Recruitment of stromal cells to seeded metastasis
Heterotypic signaling of metastatic growth
Stroma
Stromal reservoirs in tissue & bone marrow
Nacent stroma of 1° tumor
Supportive stroma of 1° tumor
Normal stroma +/- permissive niche
Nascent stroma of metastasis
Supportive stroma of metastasis
Primary Tumorigenesis
Metastasis

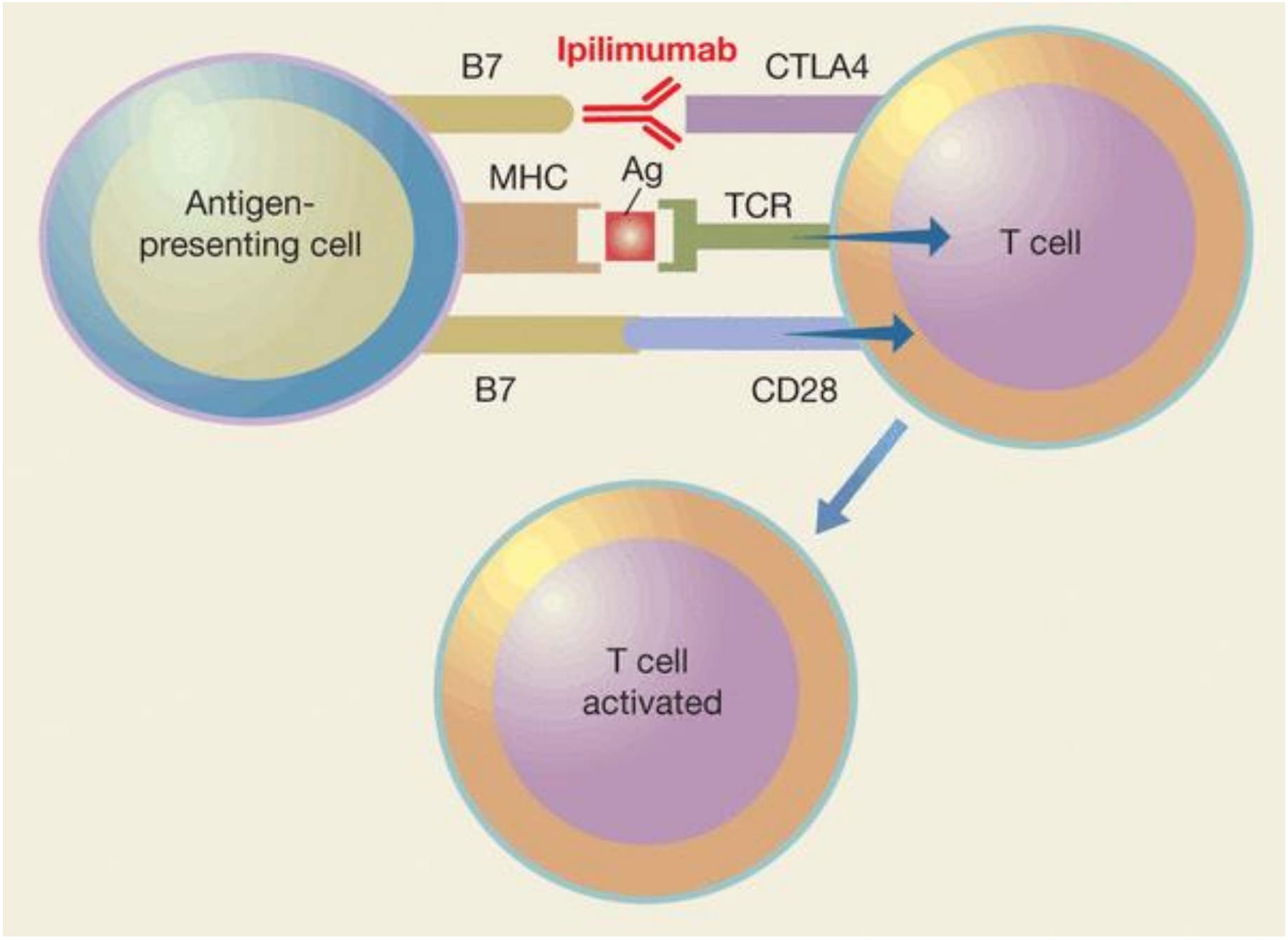

EGFR inhibitors
Cyclin-dependent kinase inhibitors
Aerobic glycolysis inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

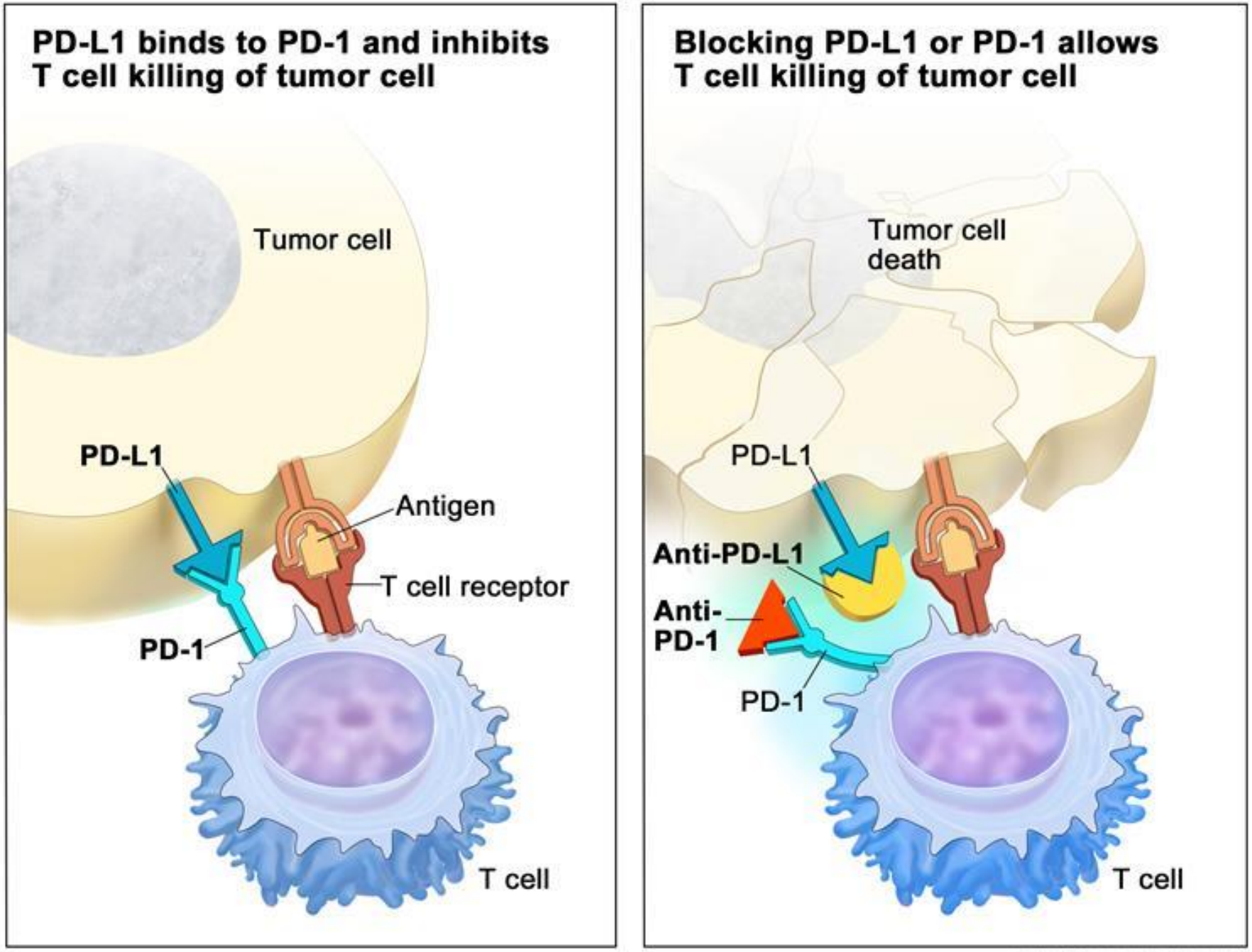
Milestones of anticancer therapy

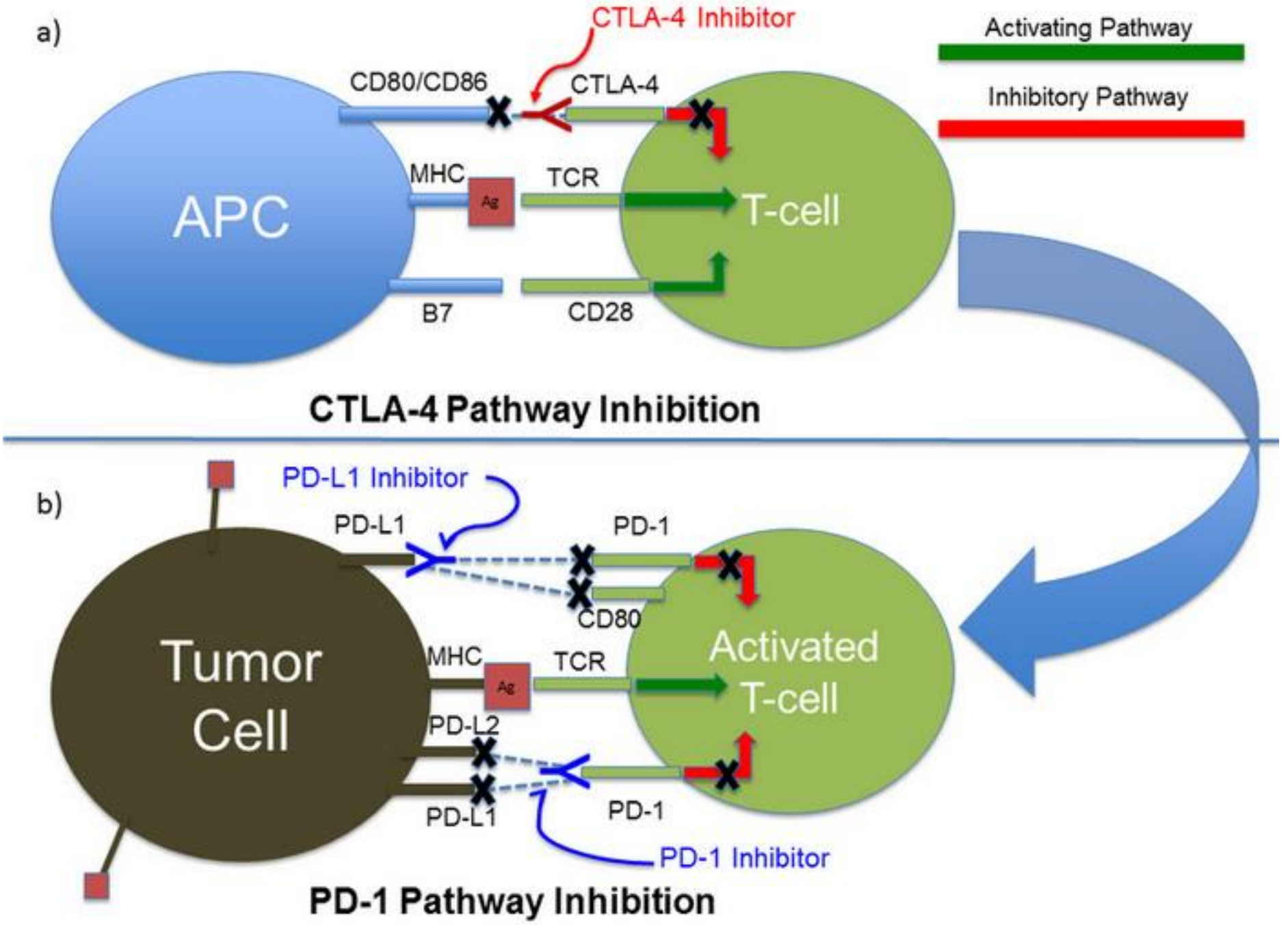
- Ionizing radiation
- Chemotherapy
- Immunotherapy (vaccines, **blockade of immune checkpoints**

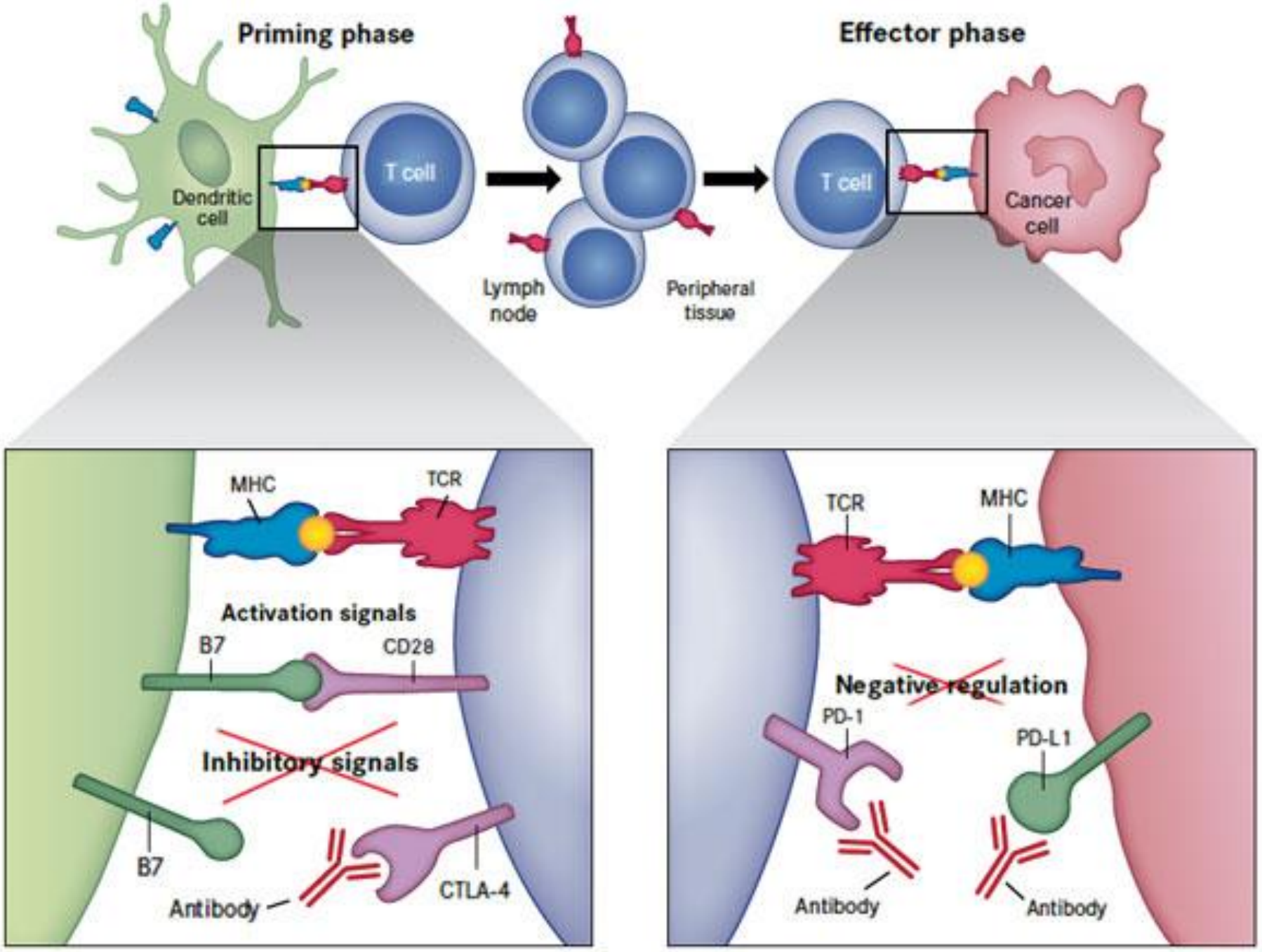
Immune checkpoints (negative feedback in immune reactions)

- Priming, central phase: **CTLA-4** (Cytotoxic T Lymphocyte Associated Protein 4)
- Effector, peripheral phase: **PD-1** (Programmed Death receptor)

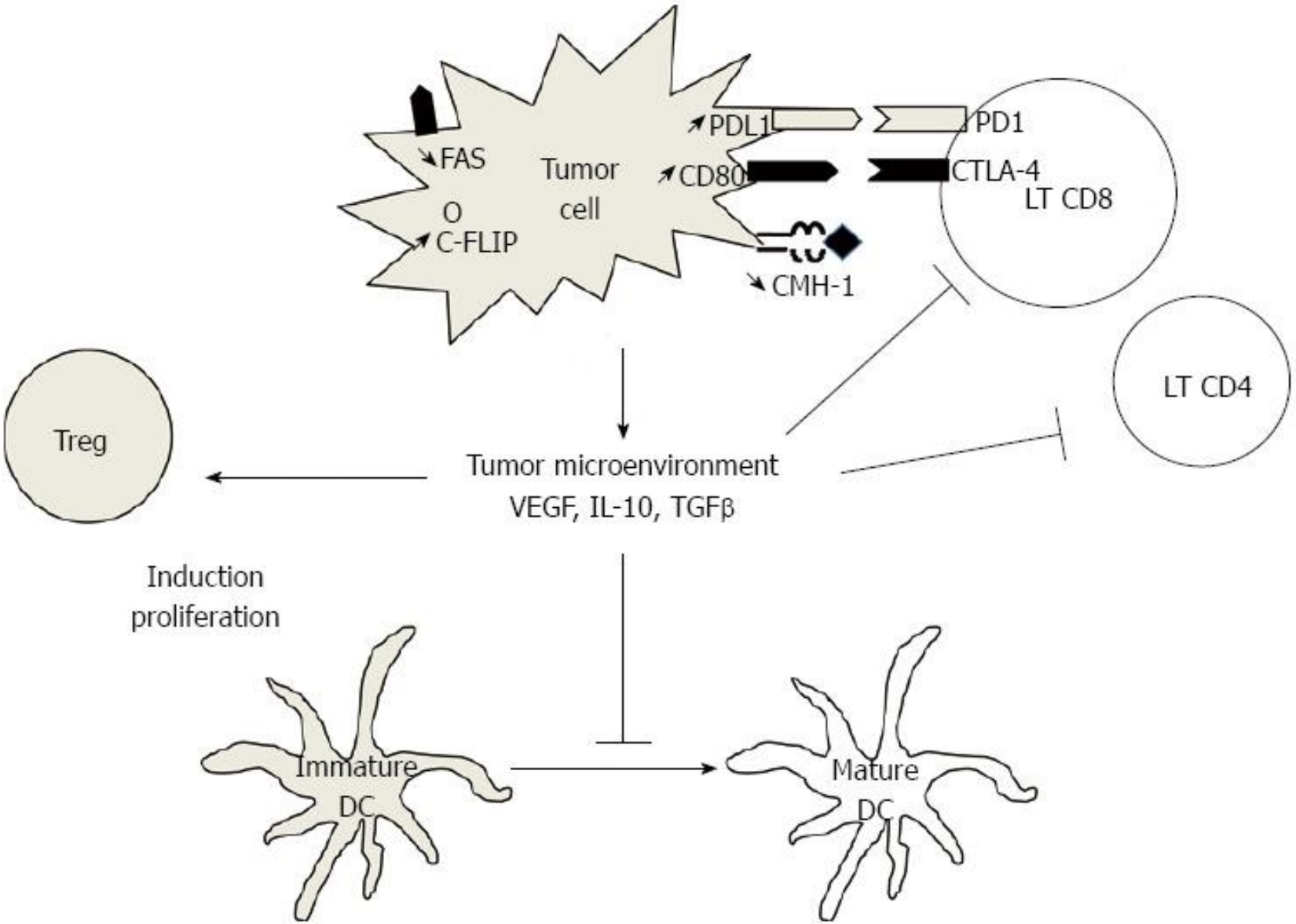

Ipilimumab
B7
CTLA4
MHC
Ag
TCR
Antigen-
presenting cell
T cell
B7
CD28
T cell
activated

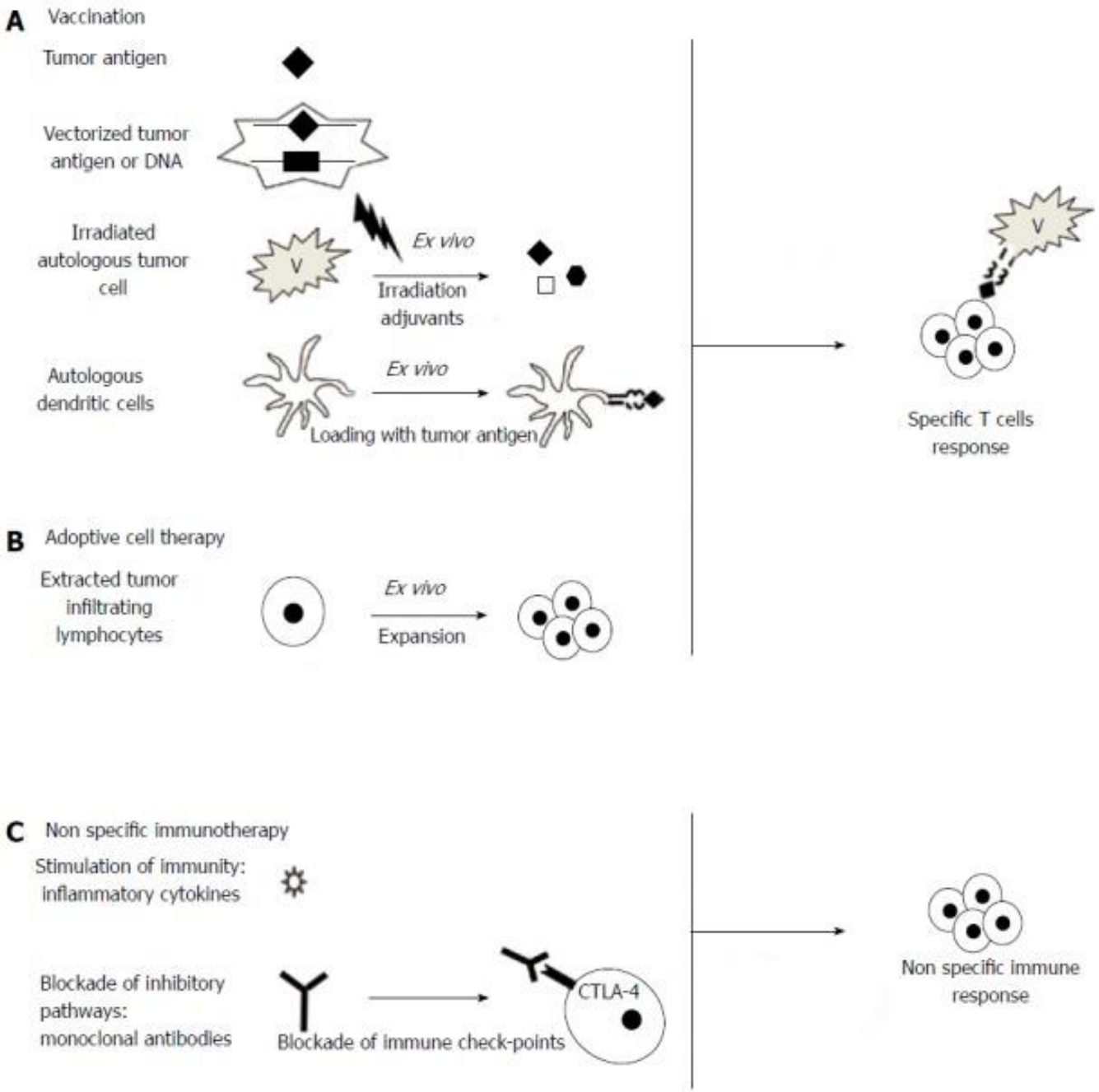



a)
CTLA-4 Inhibitor
Activating Pathway
Inhibitory Pathway
CD80/CD86
CTLA-4
APC
MHC
Ag
TCR
T-cell
B7
CD28
CTLA-4 Pathway Inhibition
b)
PD-L1 Inhibitor
PD-L1
PD-1
CD80
Tumor Cell
MHC
Ag
TCR
Activated T-cell
PD-L2
PD-L1
PD-1
PD-1 Inhibitor
PD-1 Pathway Inhibition


Priming phase
Effector phase
T cell
Dendritic cell
Lymph node
Peripheral tissue
T cell
Cancer cell
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
Antibody
CTLA-4
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

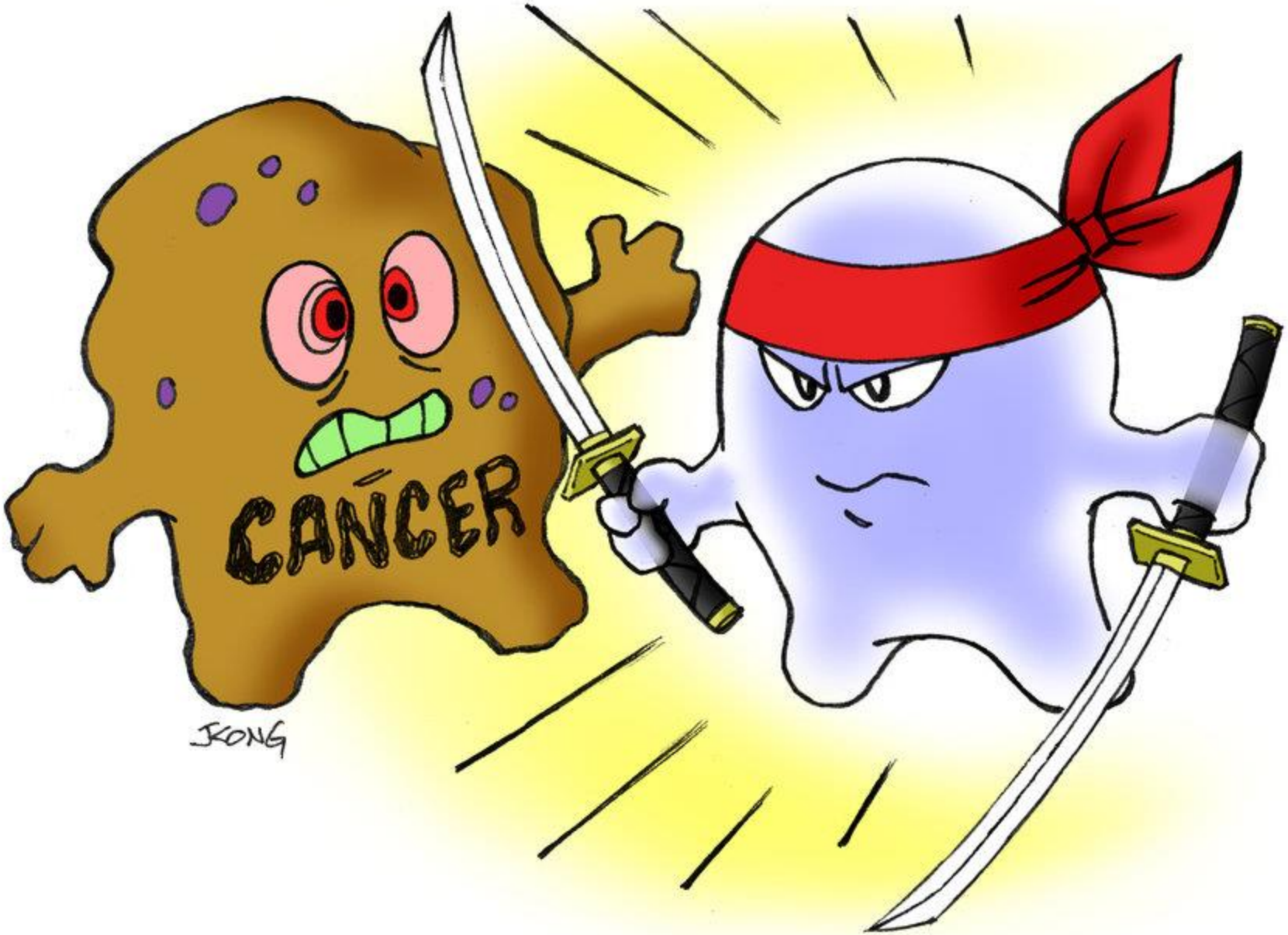
S. Pernot, World J Gastroenterol 2014




A
Vaccination
Tumor antigen
Vectorized tumor antigen or DNA
Irradiated autologous tumor cell
Ex vivo
Irradiation adjuvants
Autologous dendritic cells
Ex vivo
Loading with tumor antigen
Specific T cells response
B
Adoptive cell therapy
Extracted tumor infiltrating lymphocytes
Ex vivo
Expansion
C
Non specific immunotherapy
Stimulation of immunity: inflammatory cytokines
Blockade of inhibitory pathways: monoclonal antibodies
CTLA-4
Blockade of immune check-points
Non specific immune response

- CTLA-4: ipilimumab…
- PD-L1: nivolumab…

- Cave: so far financial toxicity (even in the most developed countries)


CANCER
JKONG