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L'immunité du cancéreux : un nouveau paradigme

Laurence Buisseret, MD, PhD
Institut Jules Bordet
Université Libre de Bruxelles (ULB)

Immunité, cancer et soins intensifs
RENCONTRE EVELINE MARKIEWICZ - 19ème ÉDITION
URGENCES ET COMPLICATIONS SÉVÈRES CHEZ LE PATIENT CANCÉREUX
17 Novembre 2018

Plan de la présentation

- ◆ Immunité et cancer
- ◆ L'immunothérapie contre le cancer
- ◆ La réponse immune anti-tumorale
- ◆ Perspectives pour l'immunothérapie

L'immunité du cancéreux: un nouveau paradigme

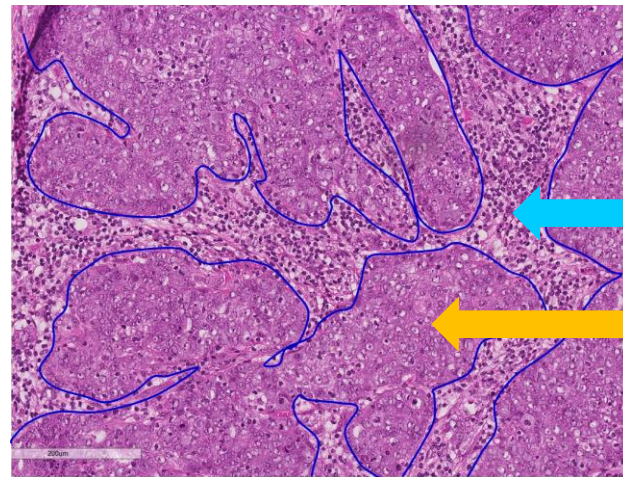
IMMUNITÉ & CANCER

L'immunité du patient cancéreux

- ◆ Le système immunitaire reconnaît et réagit contre le cancer
- ◆ La réponse immune anti-tumorale est contrôlée par des mécanismes de régulation et tolérance
- ◆ Certaines réponses inflammatoires peuvent promouvoir la progression du cancer
- ◆ Une meilleure compréhension de ces mécanismes a permis le développement de l'immunothérapie

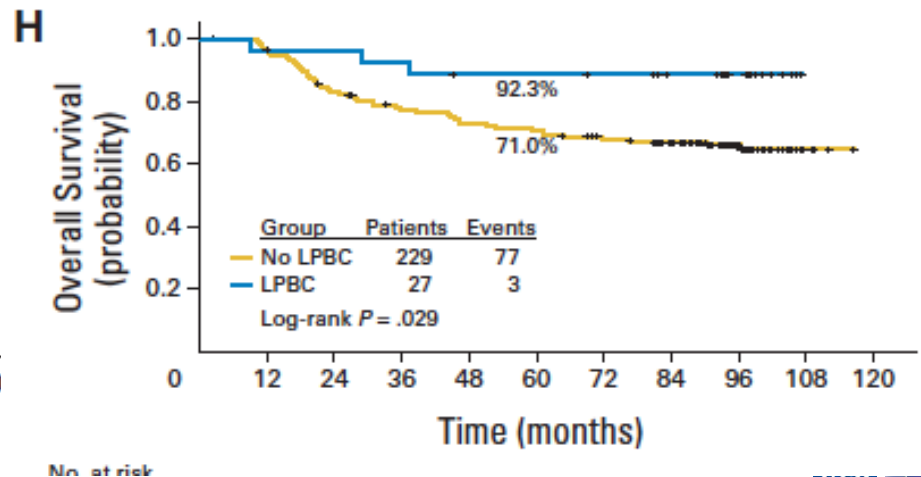
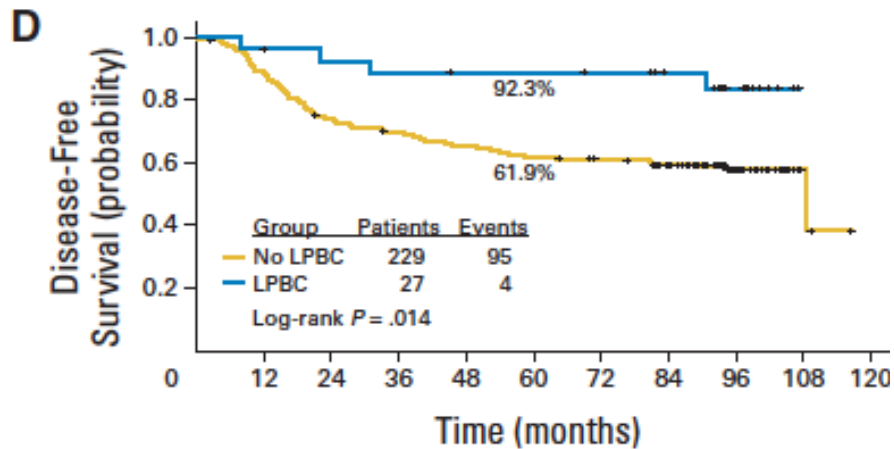
Immuno-oncologie

- ◆ Importance des lymphocytes infiltrant les tumeurs



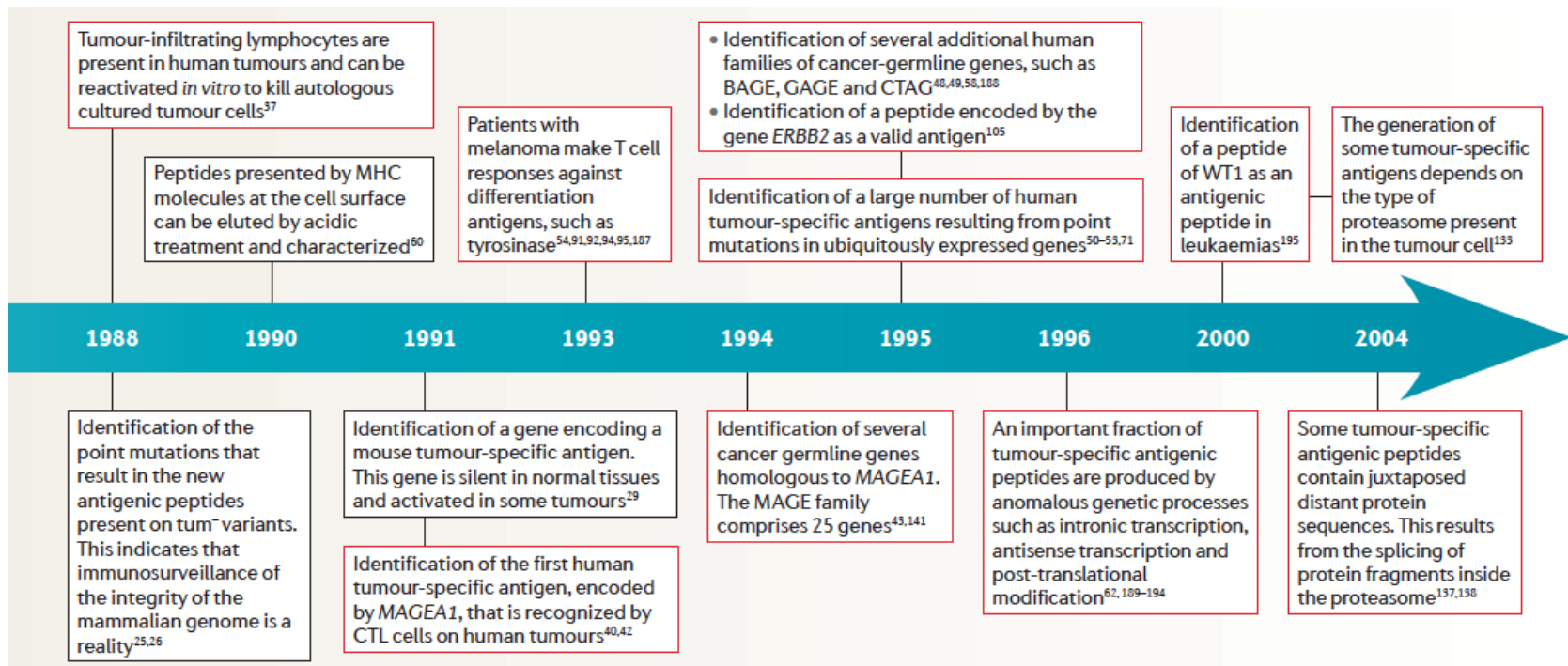
Stromal TIL %: area occupied by mononuclear inflammatory cells over total stromal area.

Intratumoral TIL %: area occupied by mononuclear inflammatory cells over total tumor cell area.



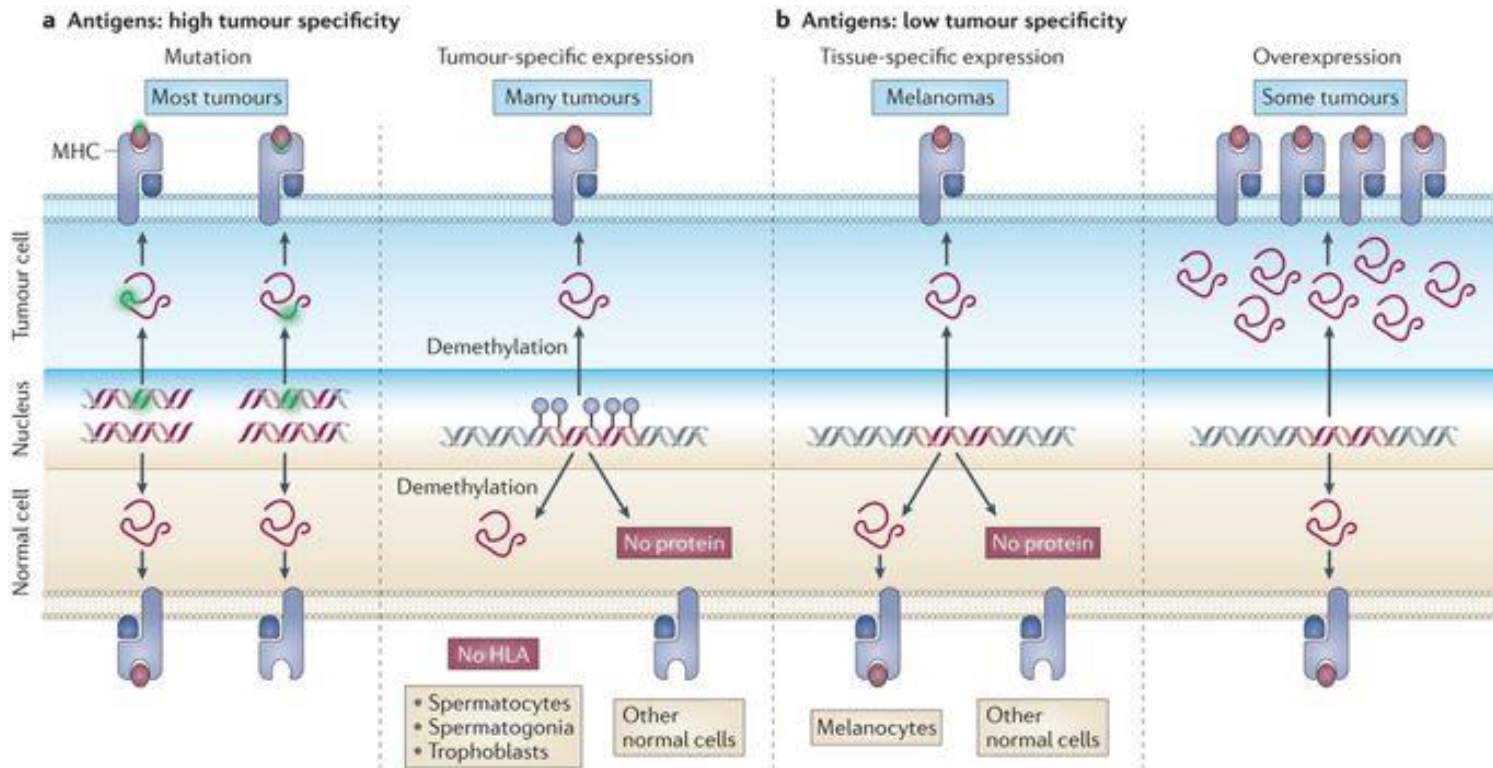
Immuno-oncologie

- ◆ Les lymphocytes T reconnaissent différents antigènes tumoraux



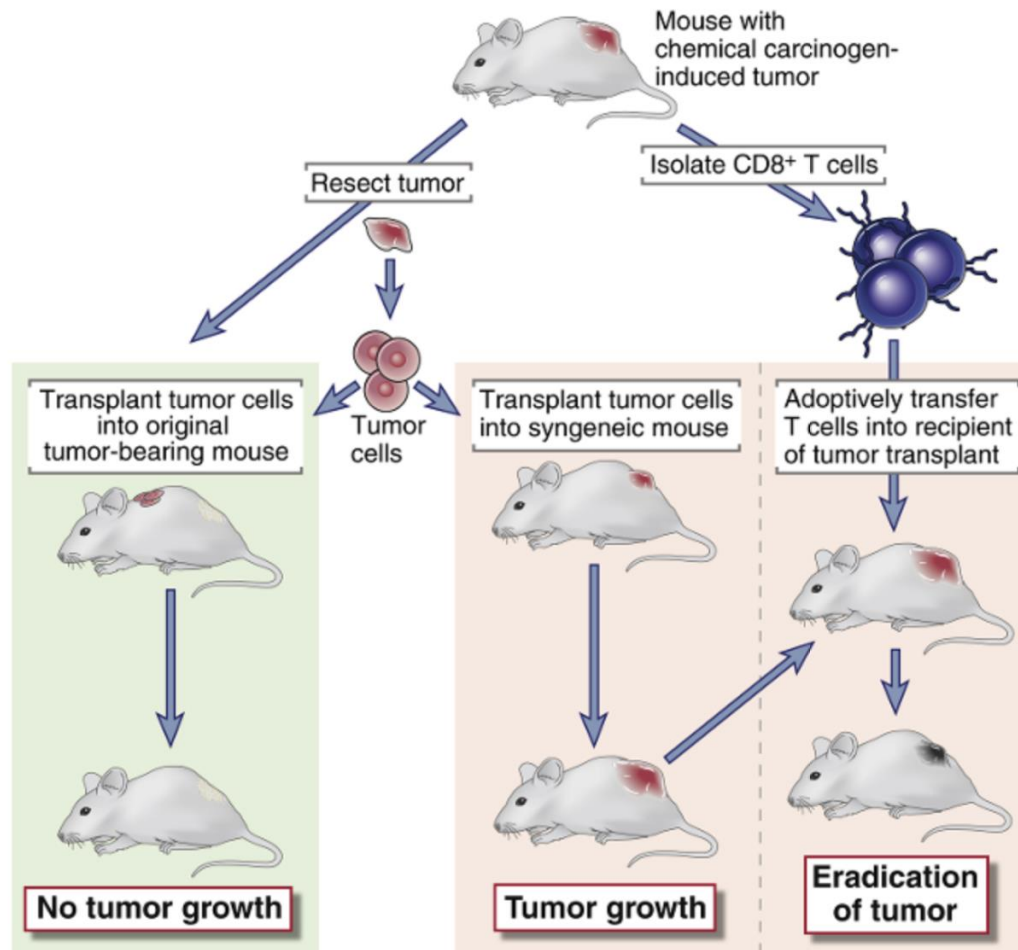
Immuno-oncologie

- Les lymphocytes T reconnaissent différents antigènes tumoraux

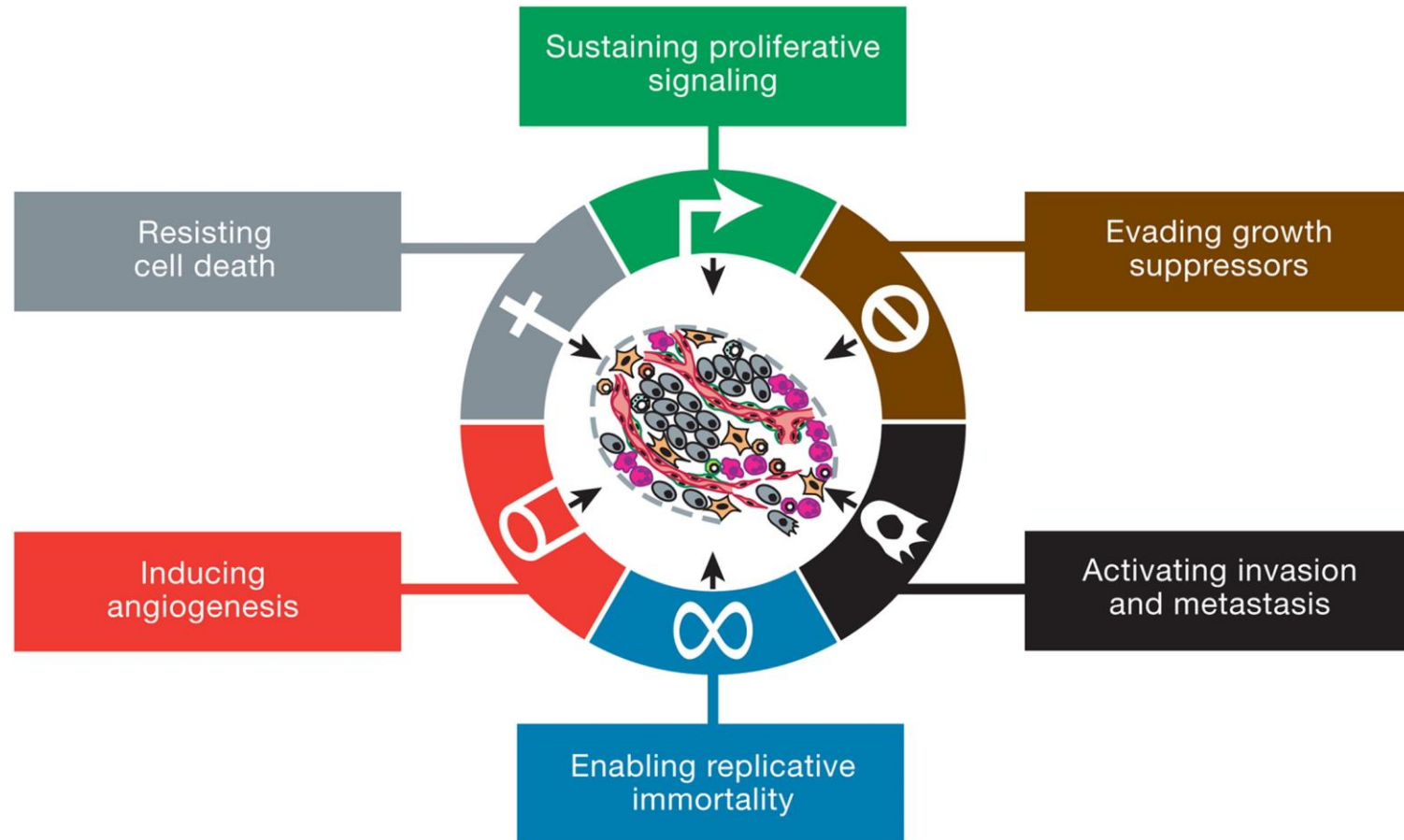


Immuno-oncologie

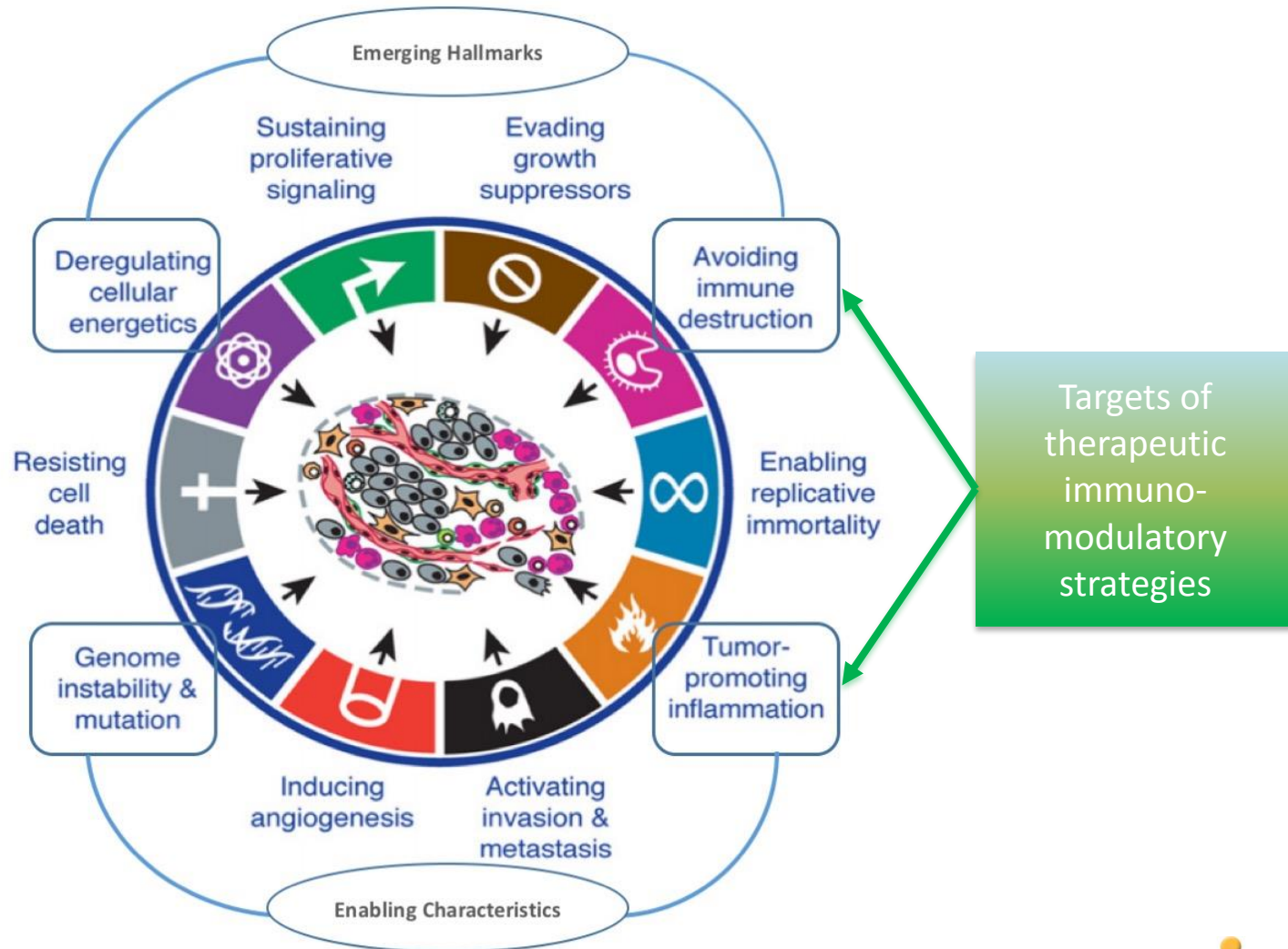
- ◆ Lymphocytes T anti-tumoraux



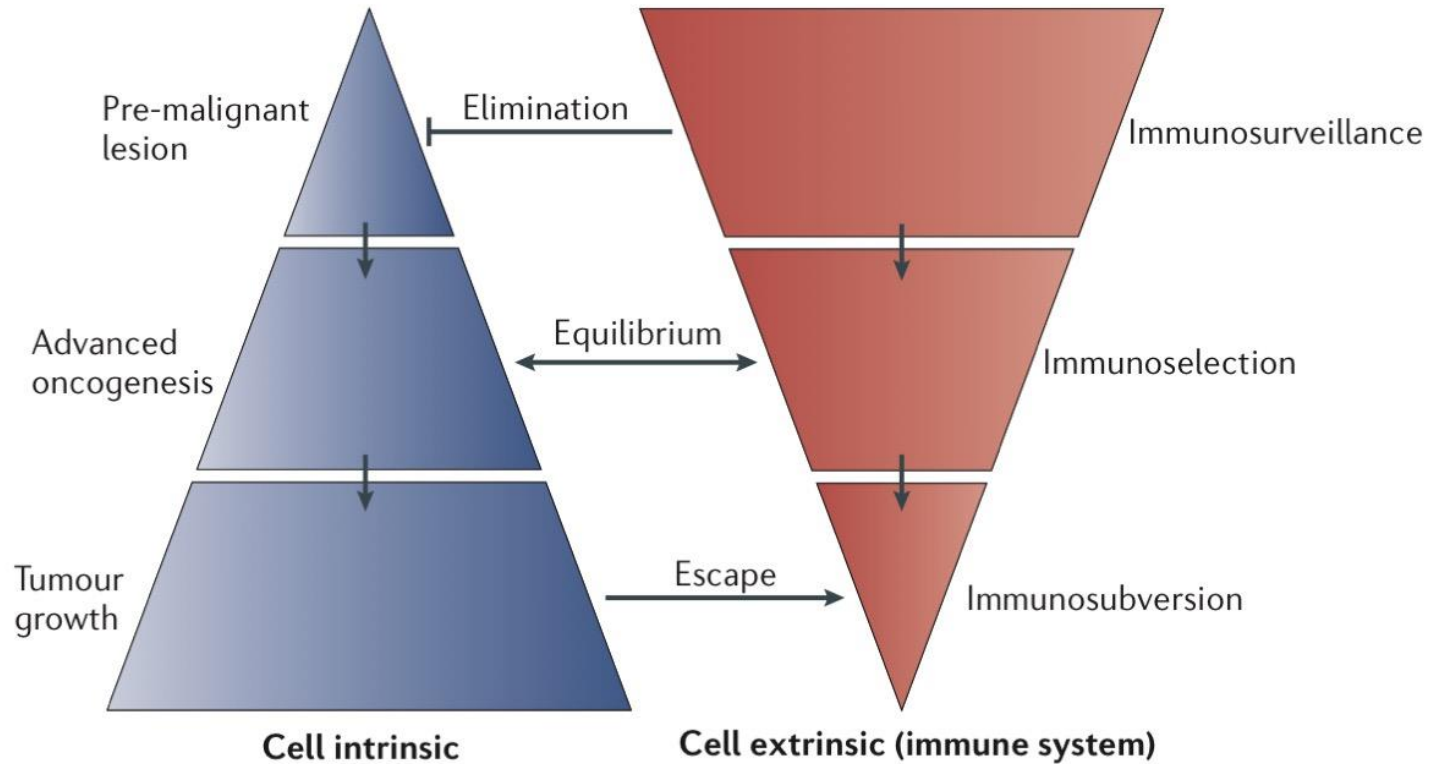
Caractéristiques des cellules cancéreuses



Caractéristiques des cellules cancéreuses

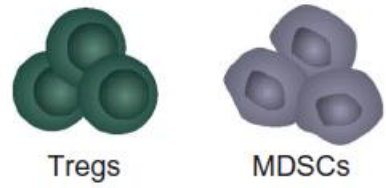


Le concept d'immunosurveillance

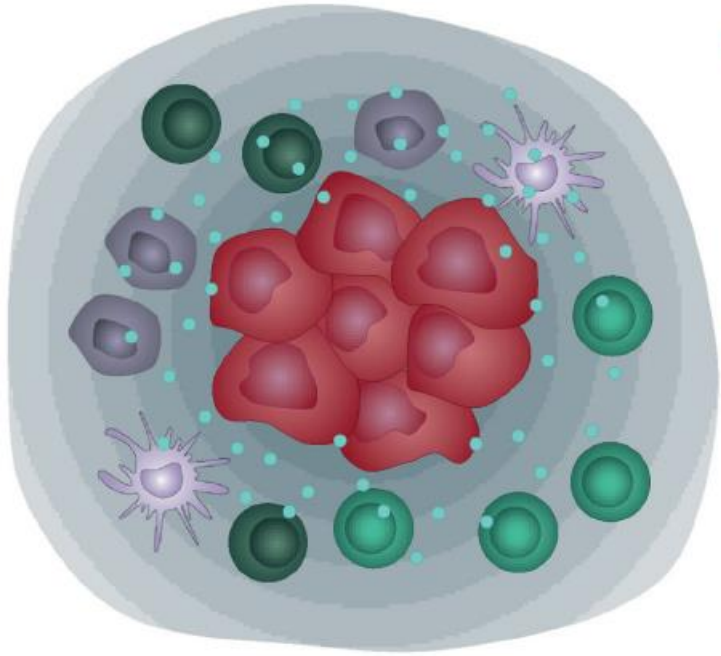
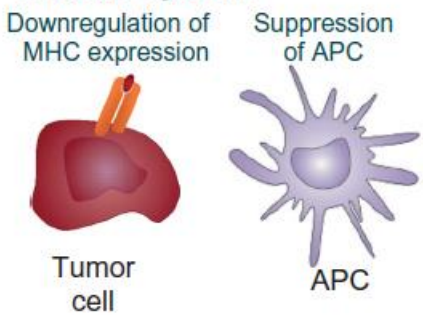


Echappement à la réponse immune anti-tumorale

B Recruitment of immunosuppressive cells



A Ineffective presentation of tumor antigens to the immune system

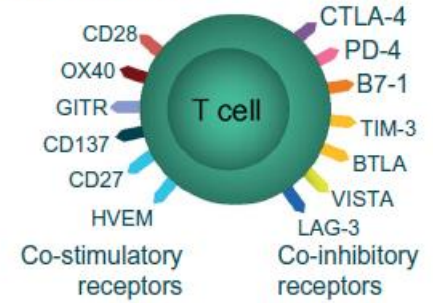


Tumor microenvironment

C Release of immunosuppressive factors



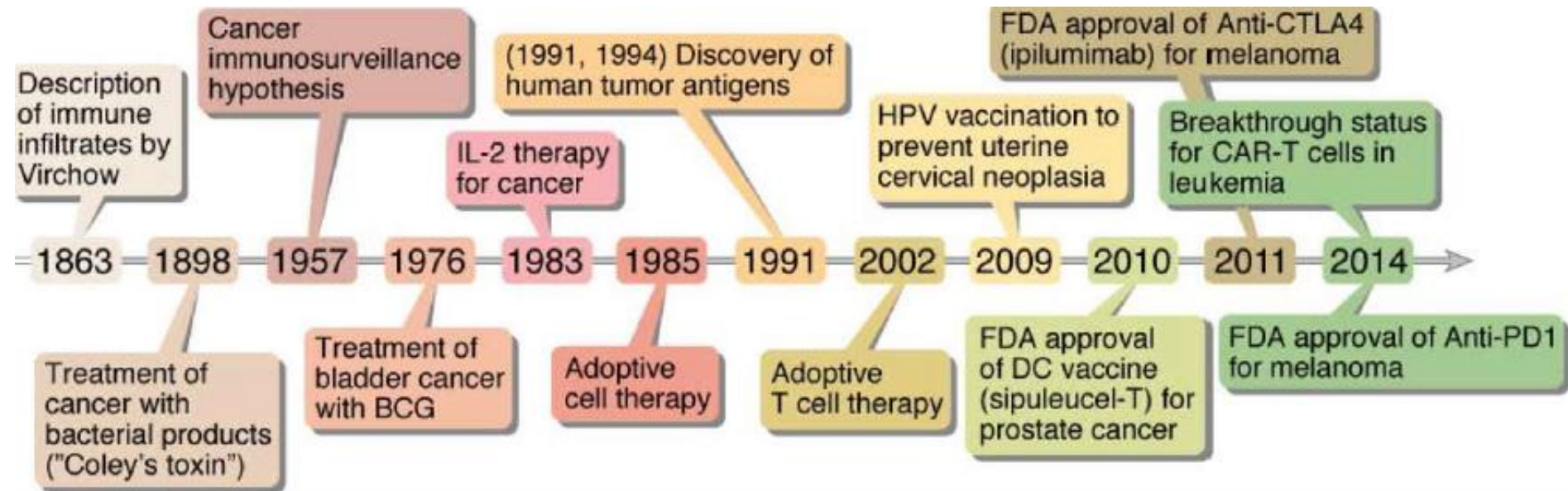
D T-cell checkpoint dysregulation



L'immunité du cancéreux: un nouveau paradigme

L'IMMUNOTHÉRAPIE CONTRE LE CANCER

Développement de l'immunothérapie



From infection to immunotherapy



FIG. II.—DR. COLEY'S CASE OF SARCOMA OF LOWER END OF FEMUR. PORTION SHOWING GRANULATING SURFACES PRODUCED BY THE ERYSIPELAS CULTURE.

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed
Toxins Makes One Disease
Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15
Years and Treated 430 Cases—
Probably 150 Sure Cures.



Just how this influence is exerted is at present undetermined. The theories that have the greatest support are (1), that the erysipelas coccus has a *direct destructive action* upon the cell elements of the new growth; (2), that the *high temperature* alone is sufficient to destroy the cells of lower vitality causing a fatty degeneration followed by subsequent re-absorption; (3), that *sarcoma and carcinoma are both of bacterial origin* and the erysipelas germ has a direct antagonistic effect upon the cancer bacillus.

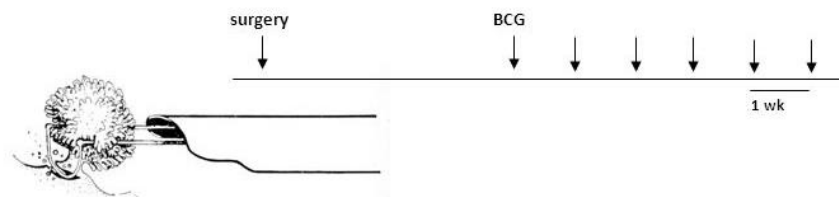
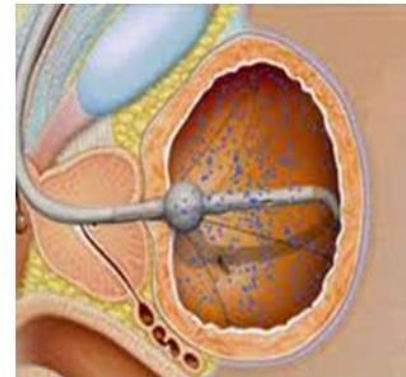
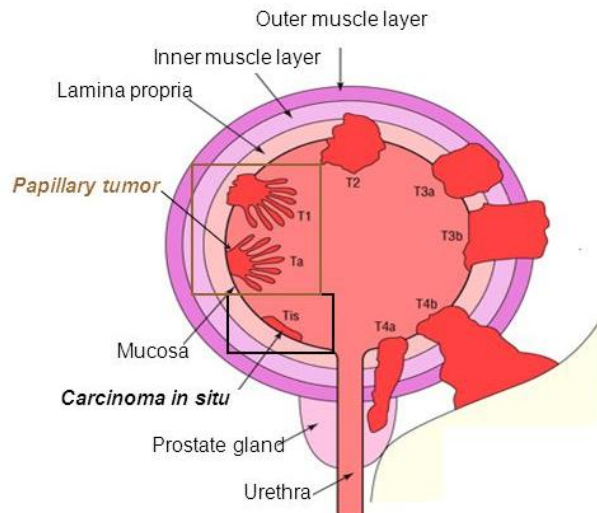
From infection to immunotherapy

INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

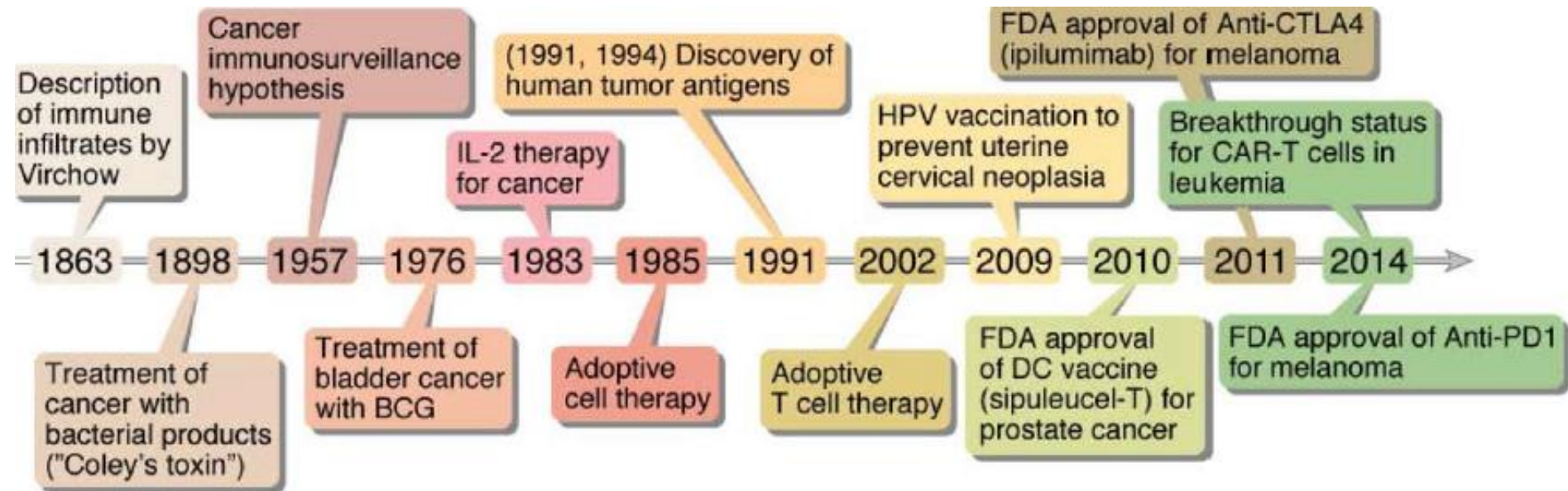
A. MORALES,* D. EIDINGER AND A. W. BRUCE

From the Departments of Urology, and Microbiology and Immunology, Queen's University, Kingston, Ontario, Canada

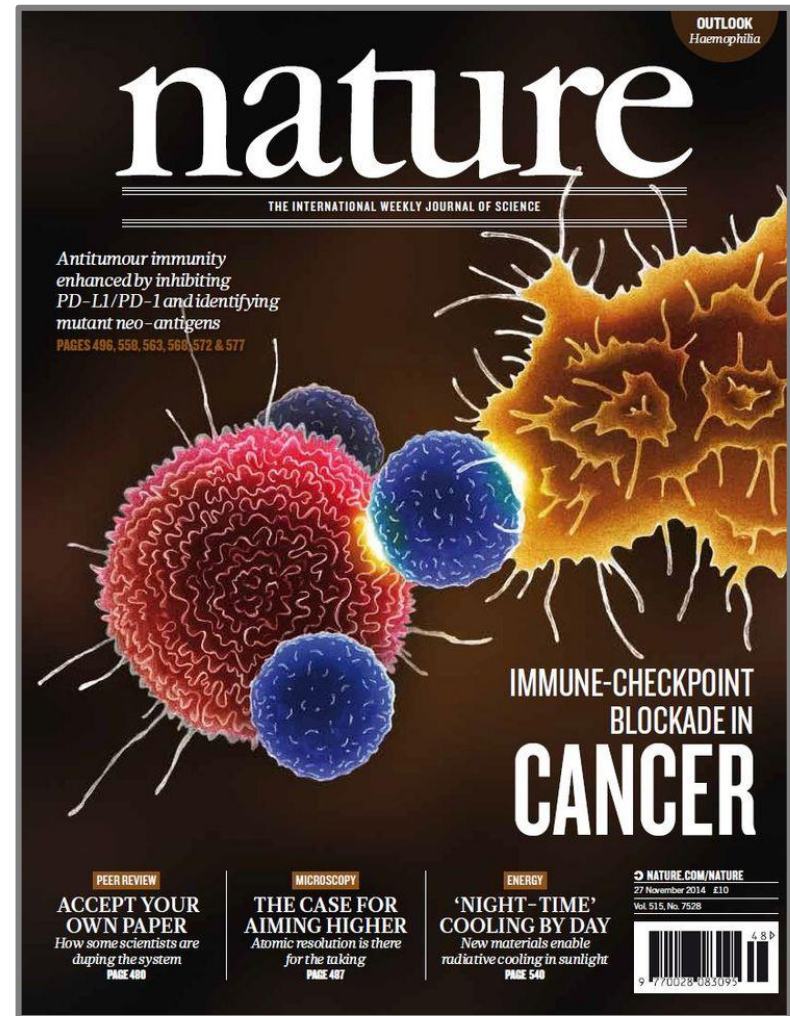
(Reprinted from J Urol, 116: 180-183, 1976)



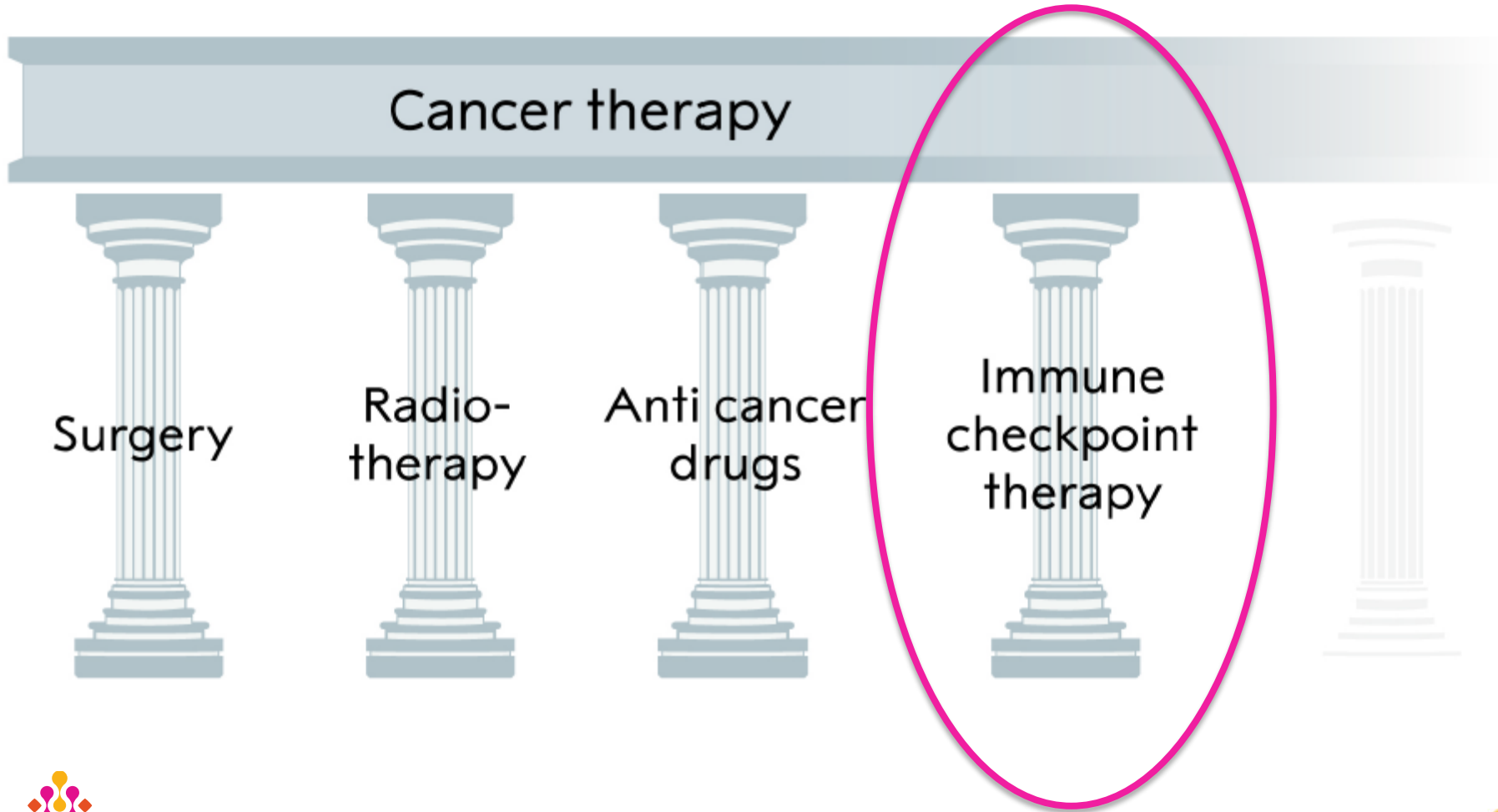
Développement de l'immunothérapie



Immunothérapie contre le cancer



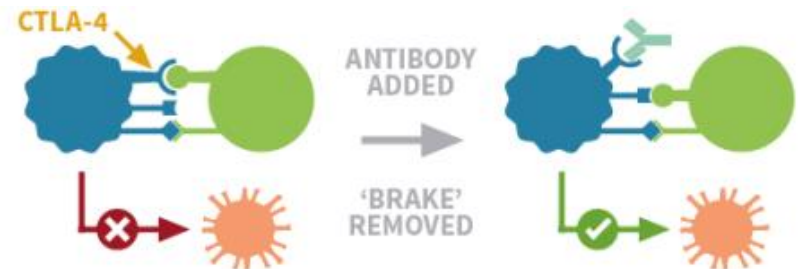
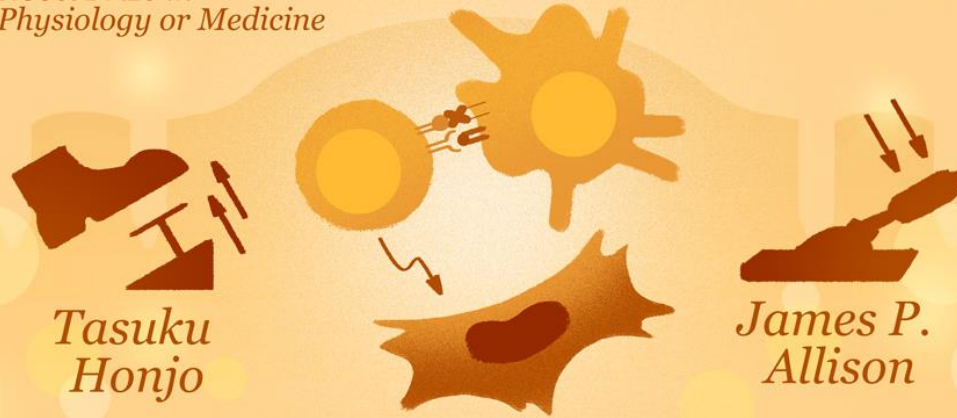
Immunothérapie contre le cancer



Inhibiteurs de point de contrôle

2018

Nobel Prize in
Physiology or Medicine



Honjo discovered another brake protein, PD-1. It operates by a different mechanism, but also arrests the immune response. Treatment with antibodies releases the brake. This has been effective against different cancers, including metastatic cancer, previously considered untreatable.

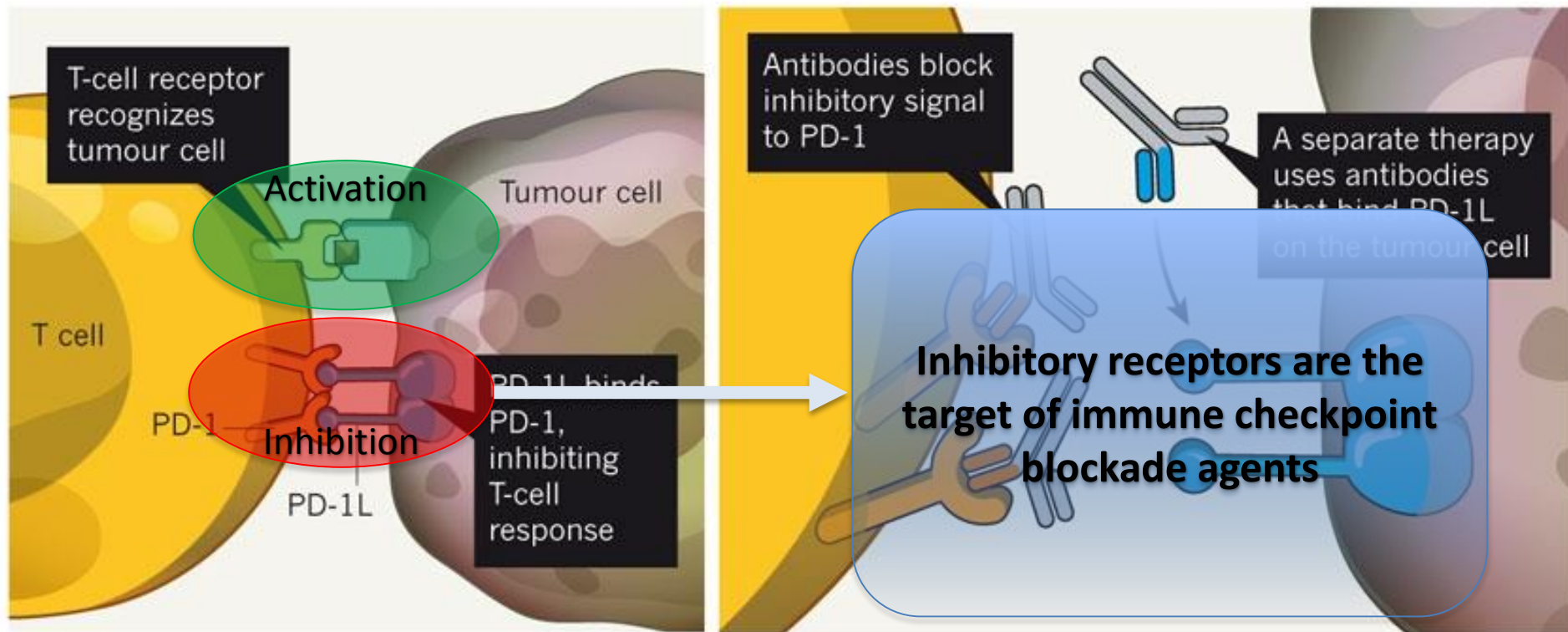
Allison studied the T cell brake protein CTLA-4. He developed an antibody that could bind to CTLA-4 and block its function, allowing the immune system to attack cancer cells. The antibodies successfully cured mice with cancer, and later human trials were also successful.

KEY ● T cell ● antigen presenting cell ● cancer cell ● 'brake' protein ● antibody

Immunothérapie contre le cancer

WAKING UP THE BODY'S DEFENCES

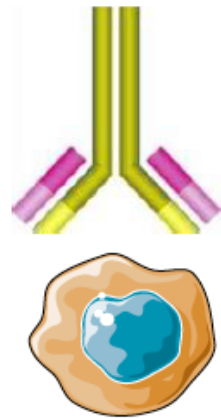
Tumour cells can inhibit the body's immune response by binding to proteins, such as PD-1, on the surface of T cells. Antibody therapies that block this binding reactivate the immune response.



Immunothérapie contre le cancer

Paradigm Shift in Cancer Therapy

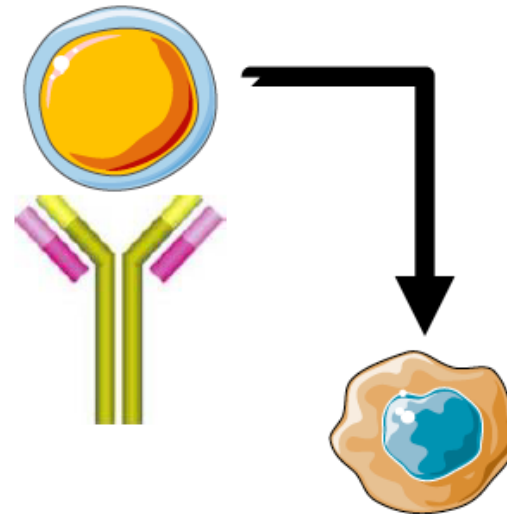
**Historical Paradigm:
Targeting Tumor Cells**



Tumor Cell

**New Paradigm:
Targeting Immune Cells**

Lymphocyte

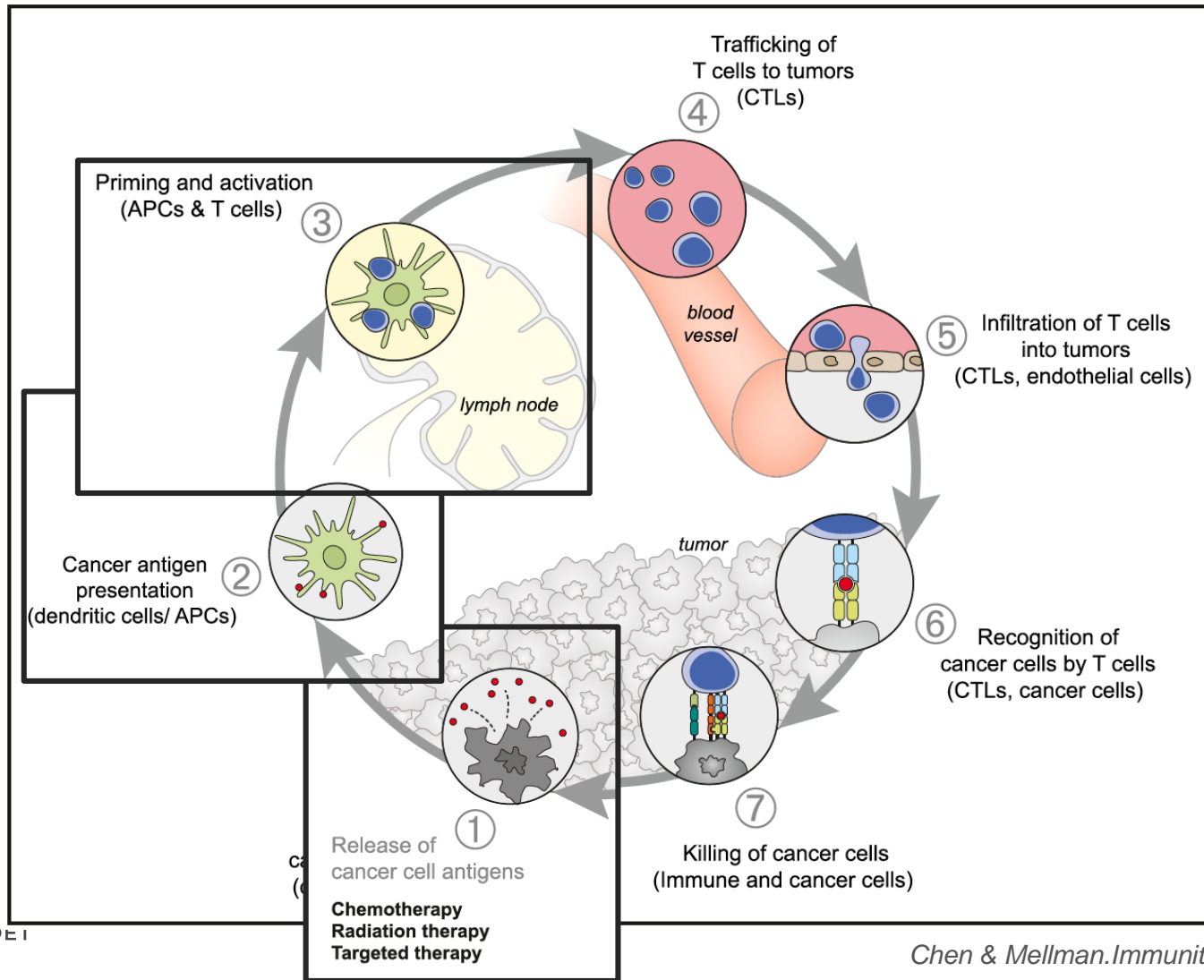


L'immunité du cancéreux: un nouveau paradigme

LA RÉPONSE IMMUNE ANTI-TUMORALE

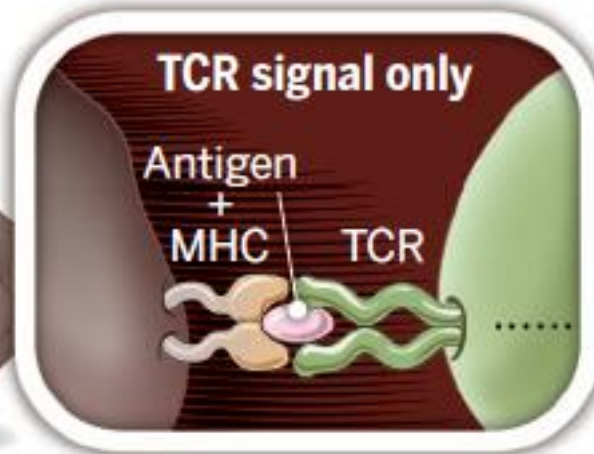
La réponse immune anti-tumorale

The cancer immunity cycle

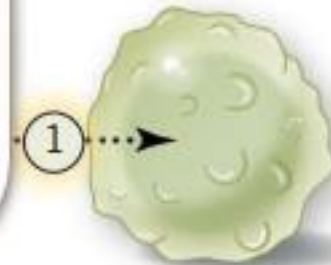


Activation des lymphocytes T

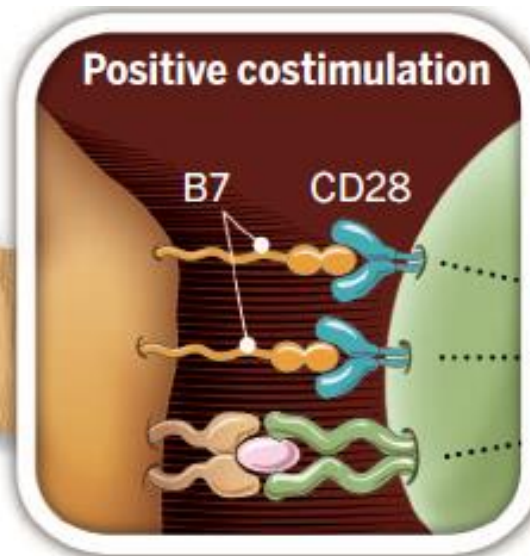
Tumor or epithelial cells



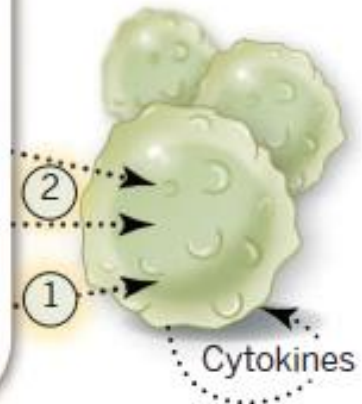
No T cell proliferation



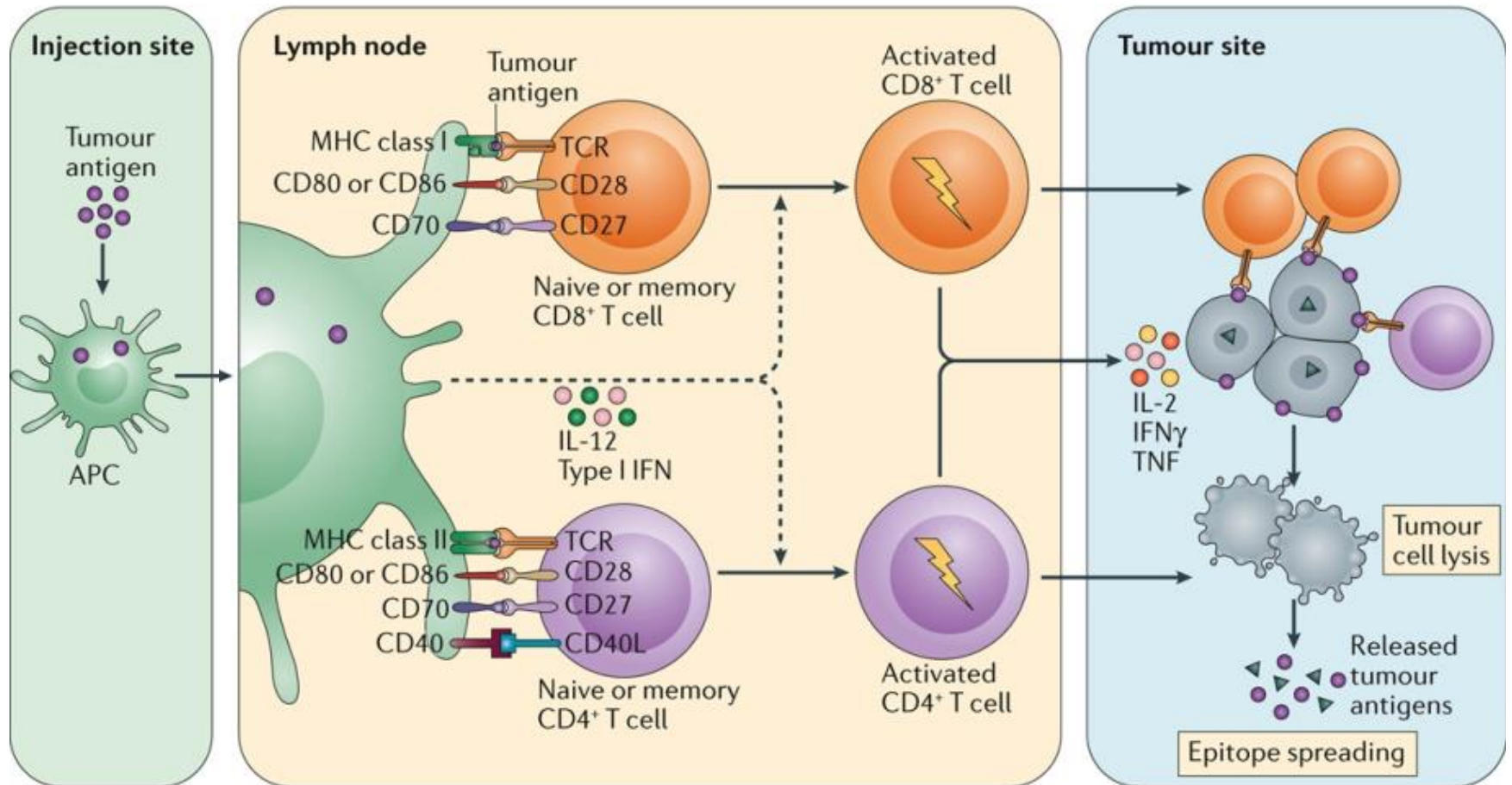
APC's
(dendritic cells,
macrophages)



T cell proliferation

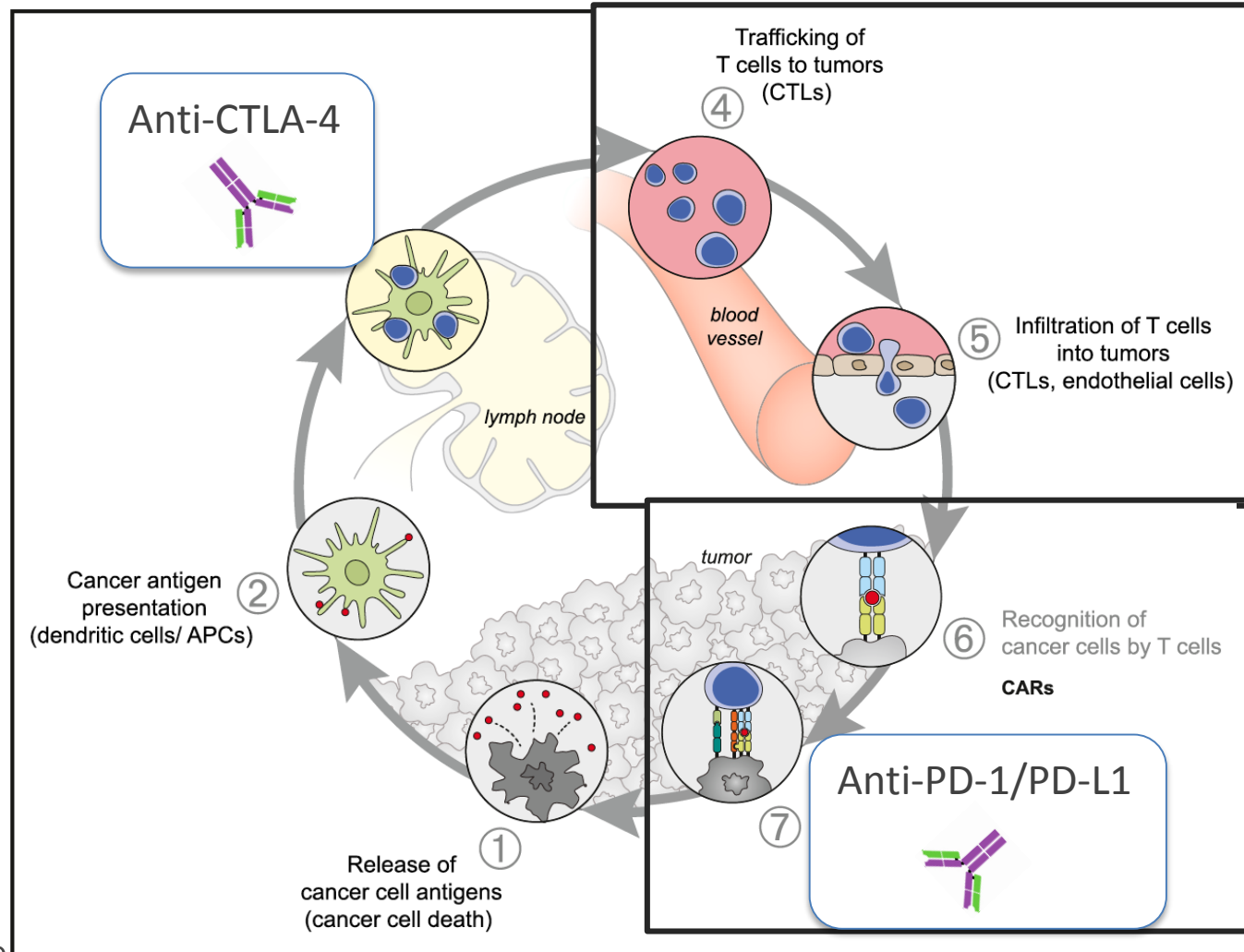


Activation des lymphocytes T

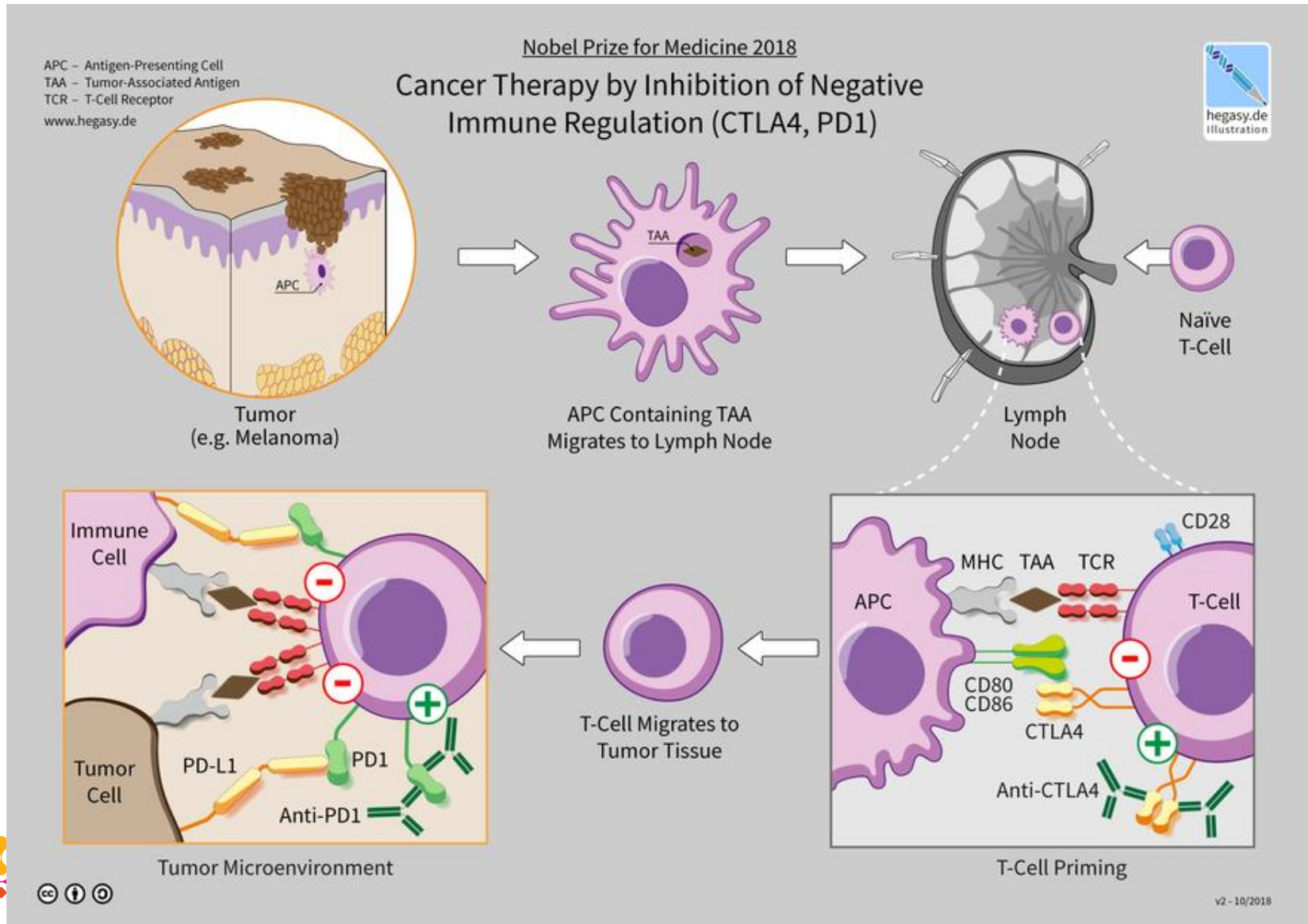


La réponse immune anti-tumorale

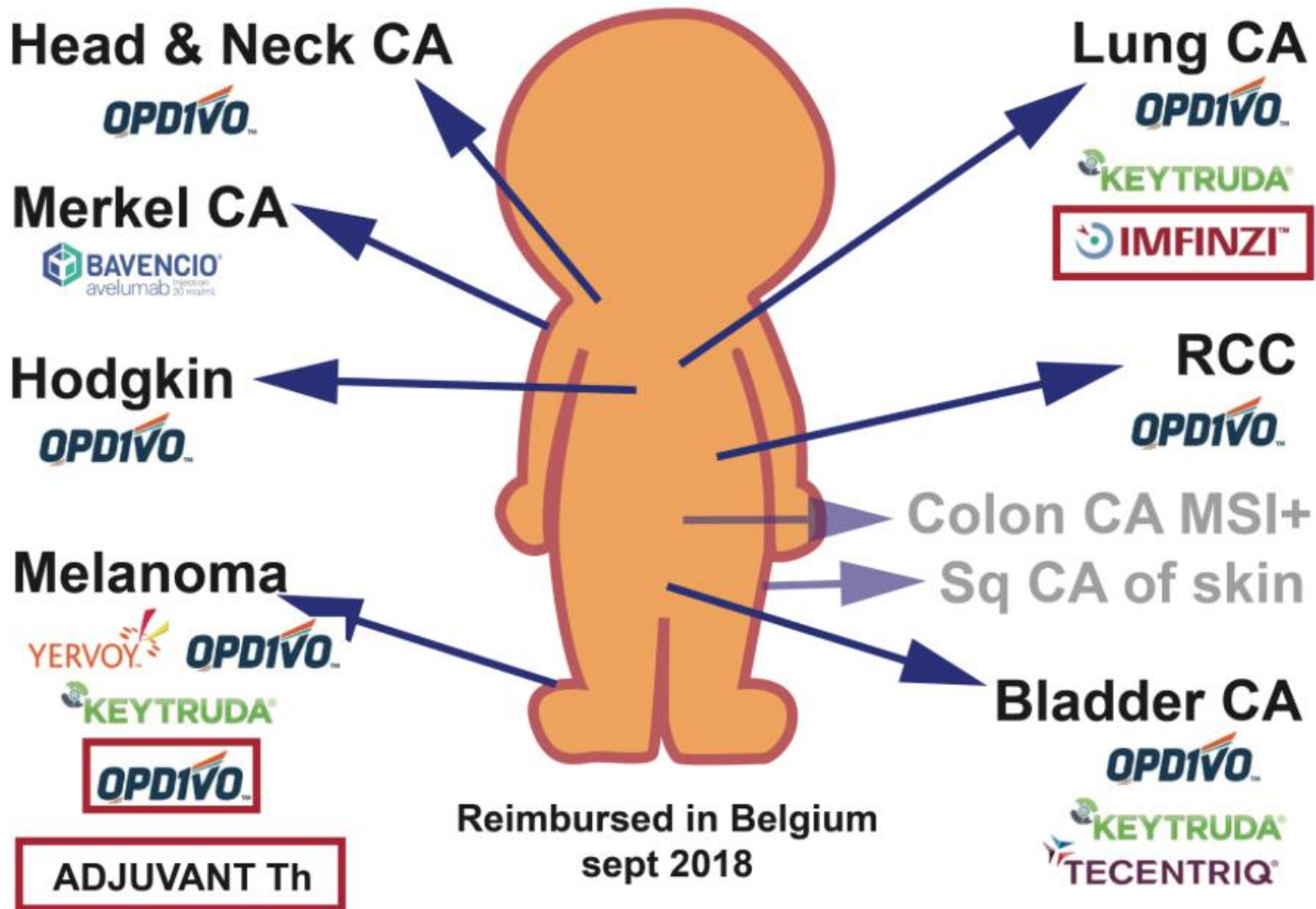
The cancer immunity cycle



Inhibiteurs de point de contrôle immunitaire



Immunothérapie en Belgique



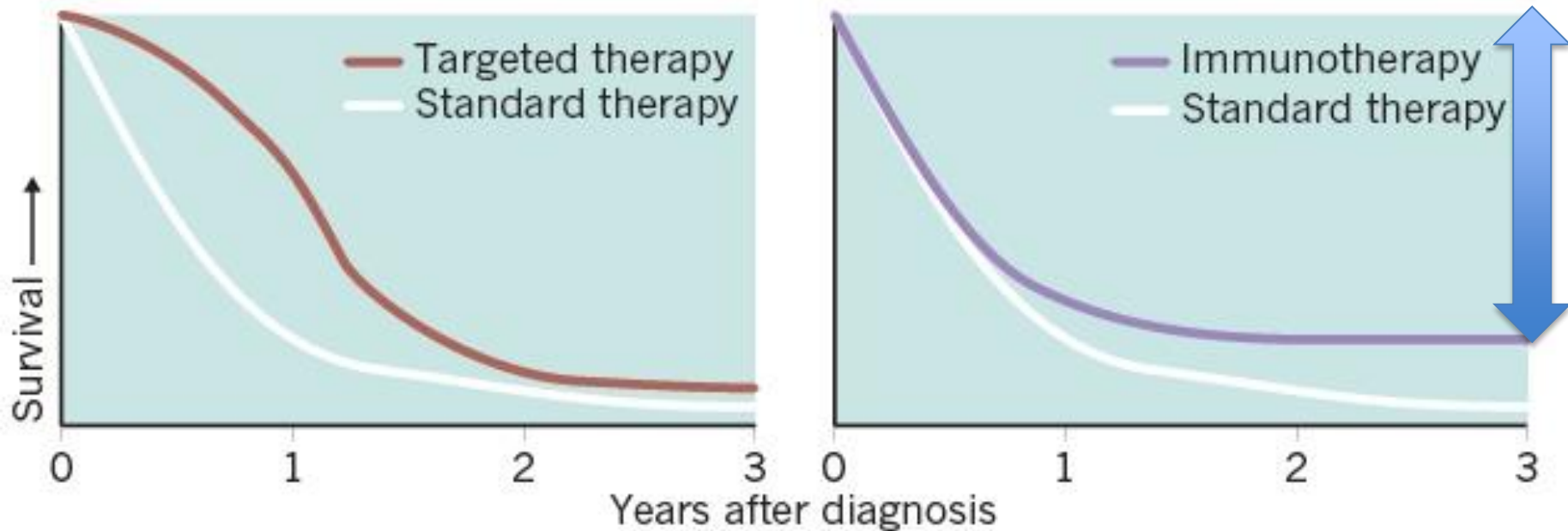
L'immunité du cancéreux: un nouveau paradigme

PERSPECTIVES POUR L'IMMUNOTHERAPIE

Perspectives

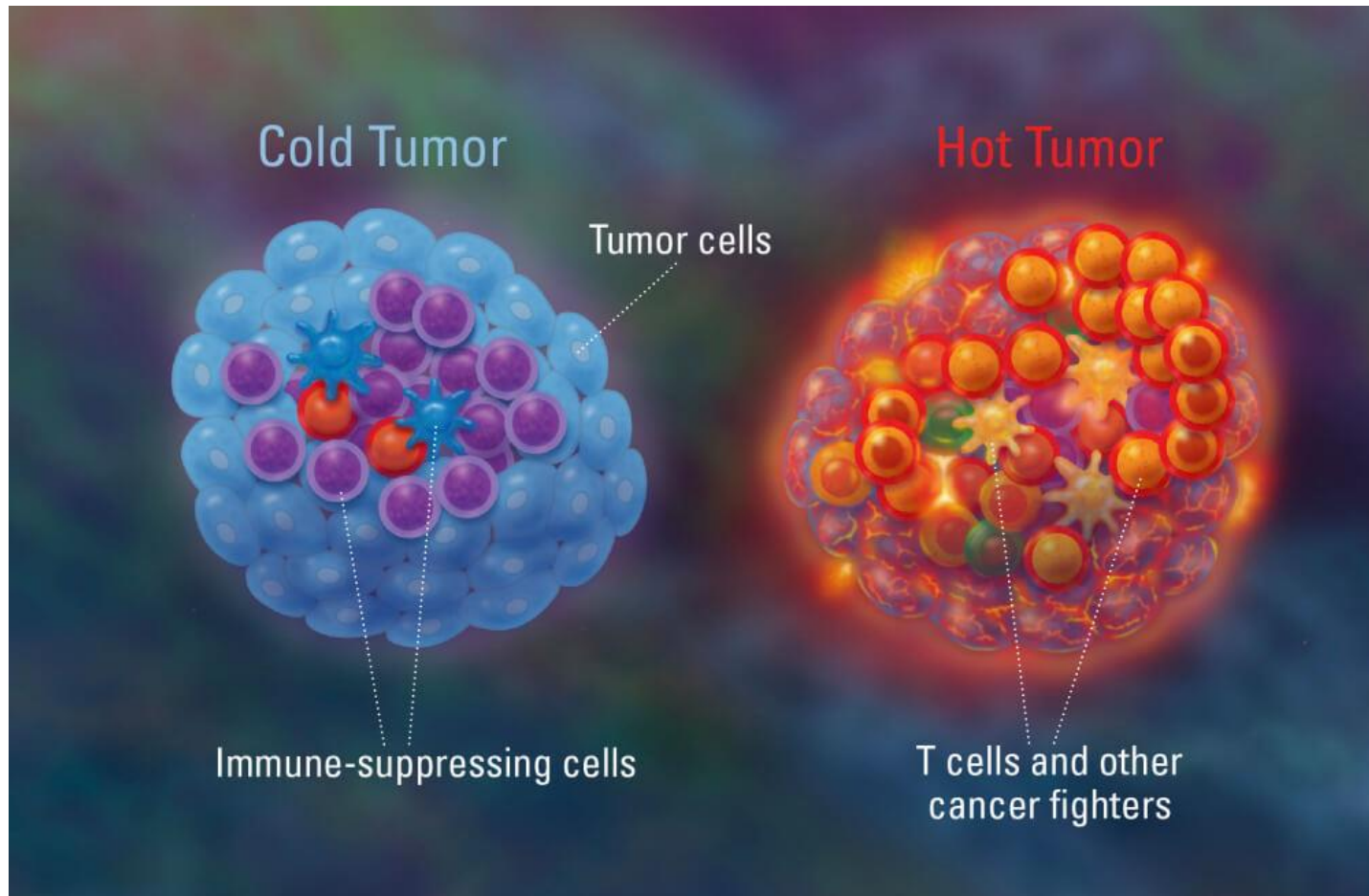
DESPERATELY SEEKING SURVIVAL

Patients generally respond well to targeted therapies (left), which are directed at specific mutations in a cancer, but only for a short time. Checkpoint immunotherapies (right) do not help as many people, but those they do help tend to live longer. Oncologists are trying to get the best out of both strategies by combining the drugs.



©nature

Le concept des tumeurs “chaudes” et “froides”



COLD and HOT tumors

Cold Tumors

- No pre-existing immunity
- No tumor immune infiltrates
 - Immunosuppressive cells
 - No PD-L1 expression
- No immune recognition

Cancers considered as “cold”
Glioblastoma, pancreatic, ovarian,
prostate cancer

Hot Tumors

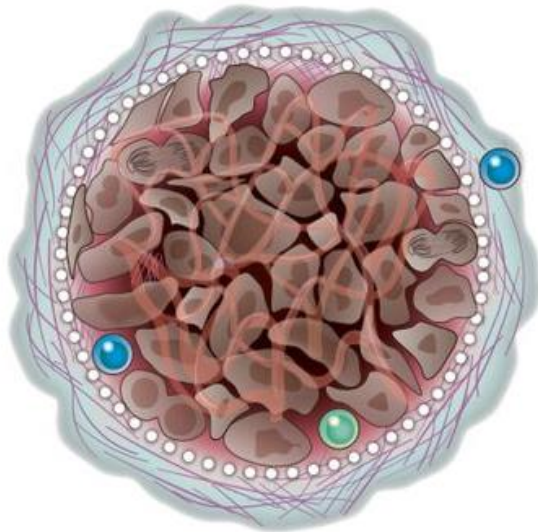
- Pre-existing immunity
- Tumor immune infiltrates
 - PD-1/PD-L1 expression
- Immunogenic neoantigens

Cancers considered as “hot”
Bladder cancers, head & neck cancer,
kidney cancer, melanoma and lung
cancer

SENSITIVE TO ICB

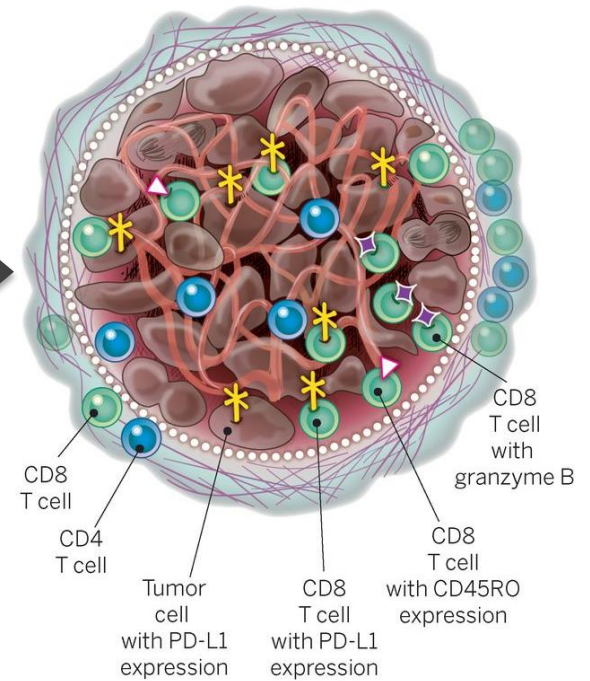
Convertir les tumeurs “froides” en “chaudes”?

Non immunogenic tumor microenvironment

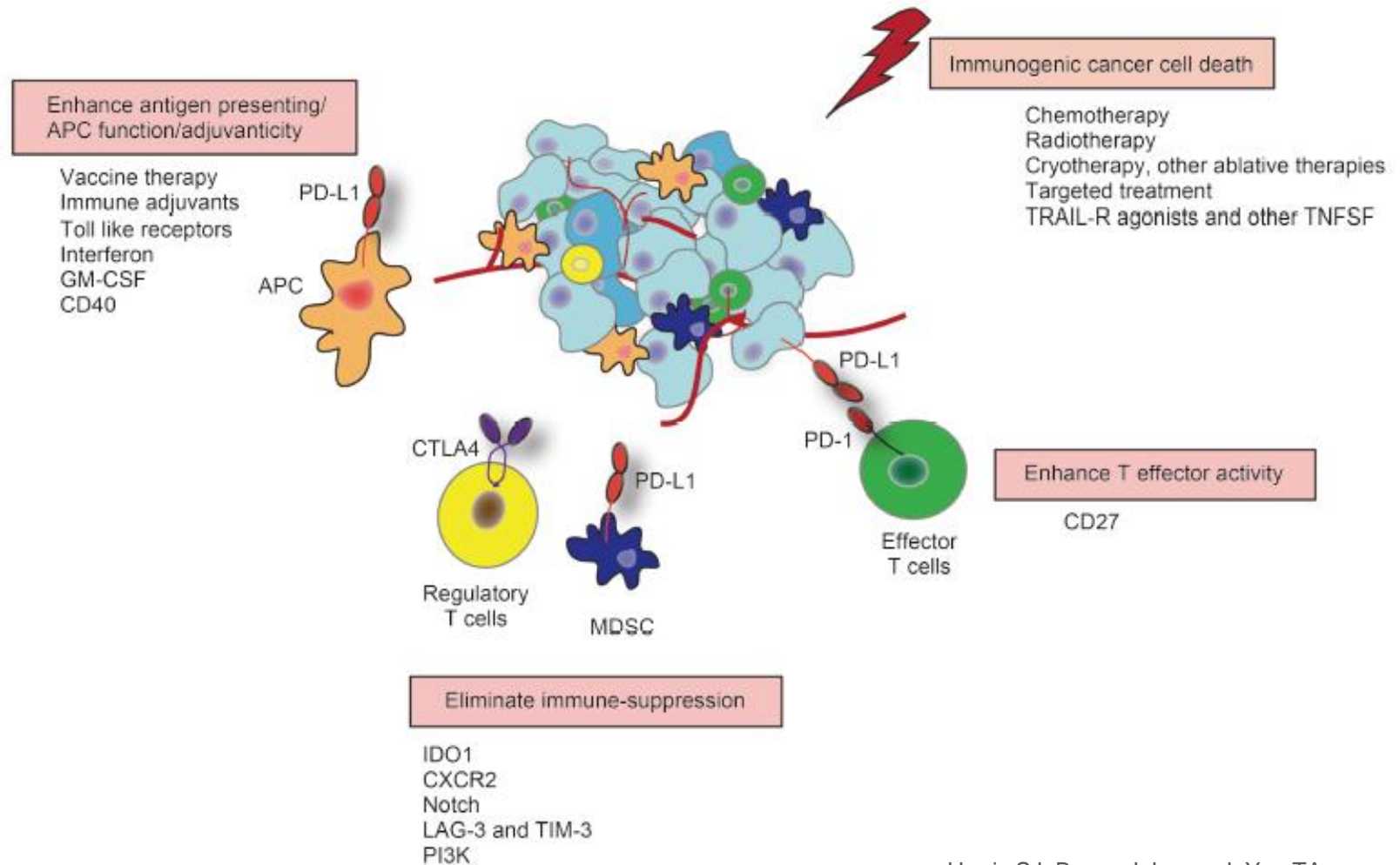


Combination therapies
with agents that create
immunogenic tumor
microenvironment

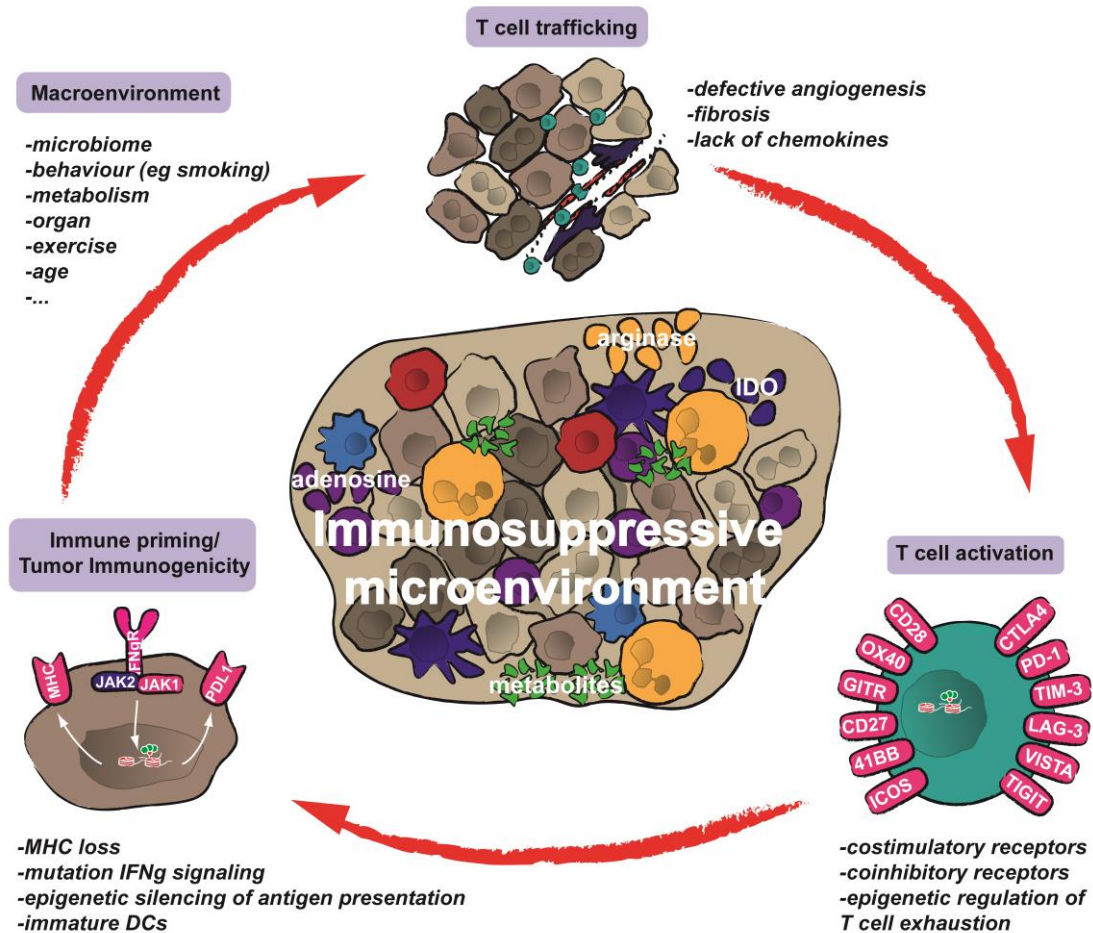
Immunogenic tumor microenvironment



Enhancing immunotherapy: The race to make “Cold” tumors “Hot”

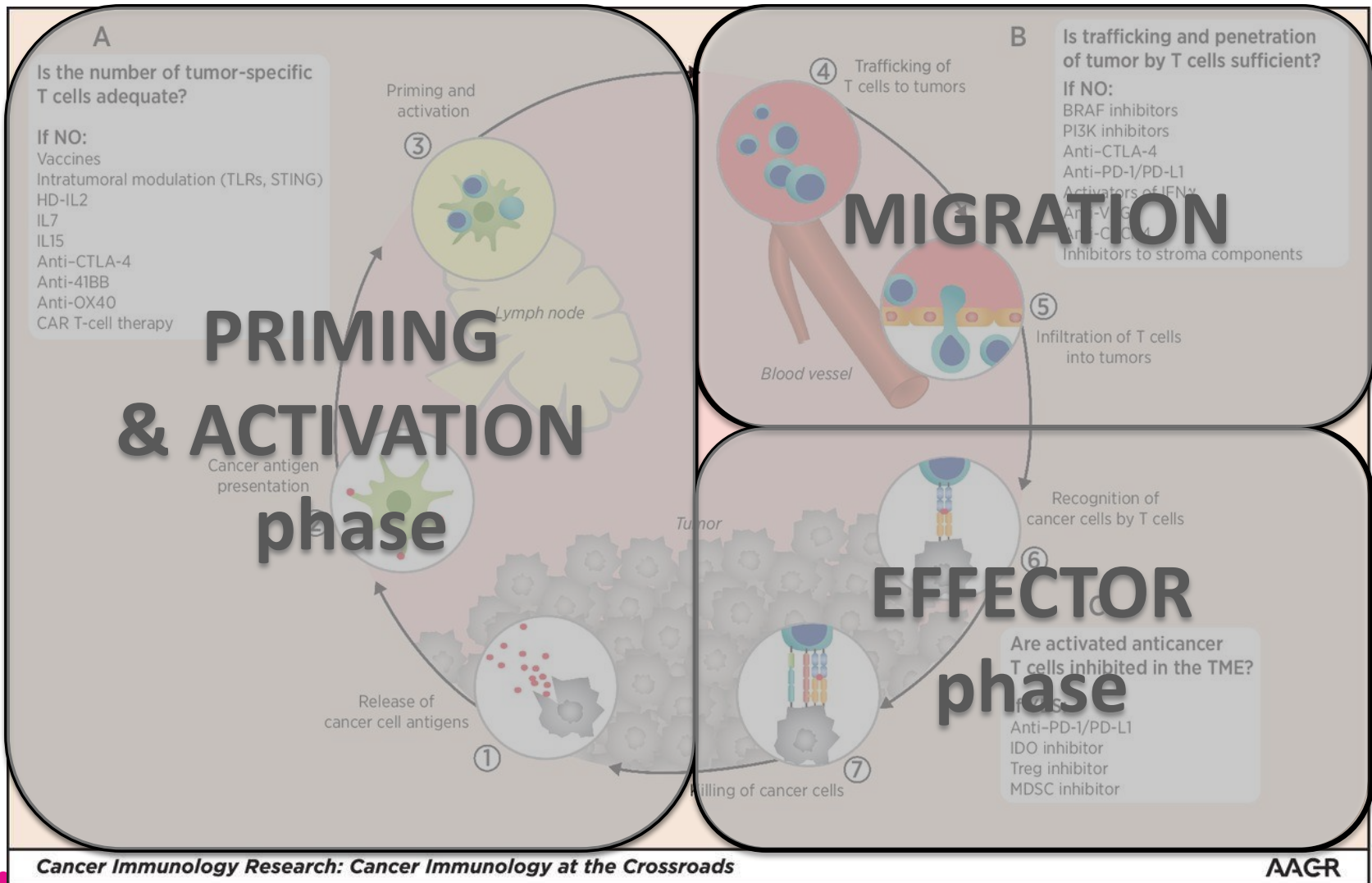


Combinaisons synergiques

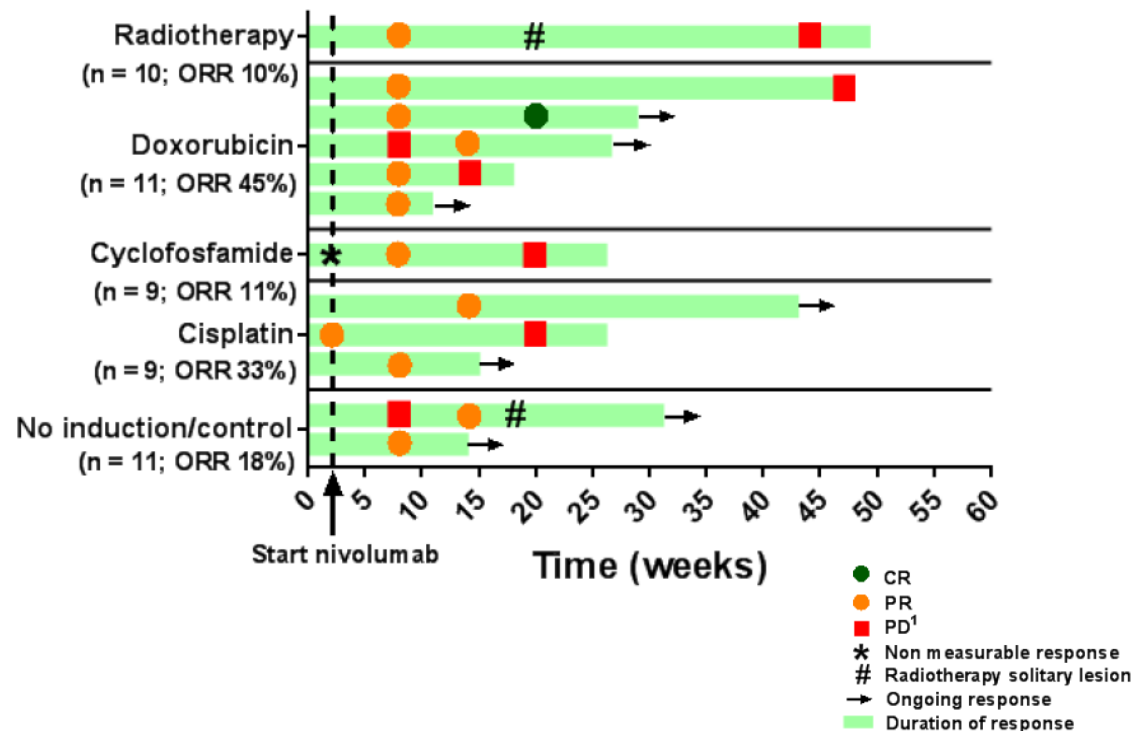
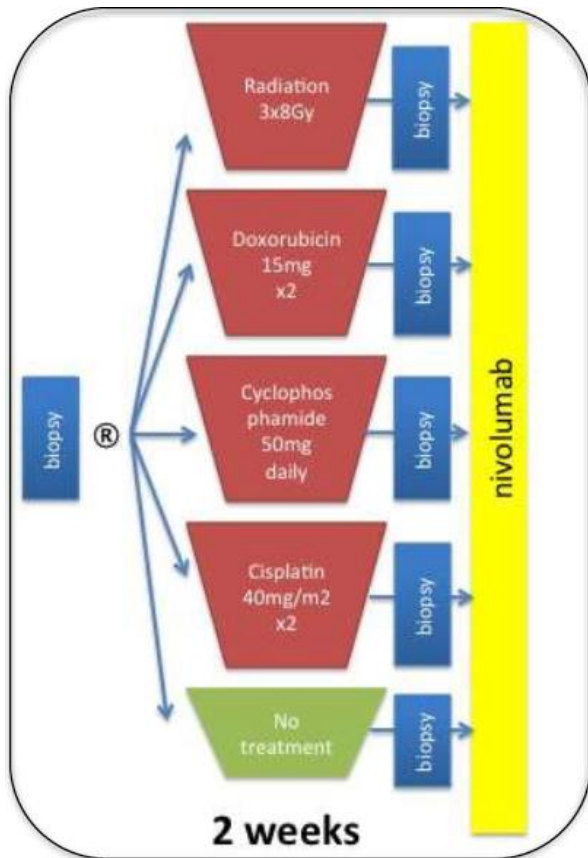


→ enhancing the potential of the immune system in cancer

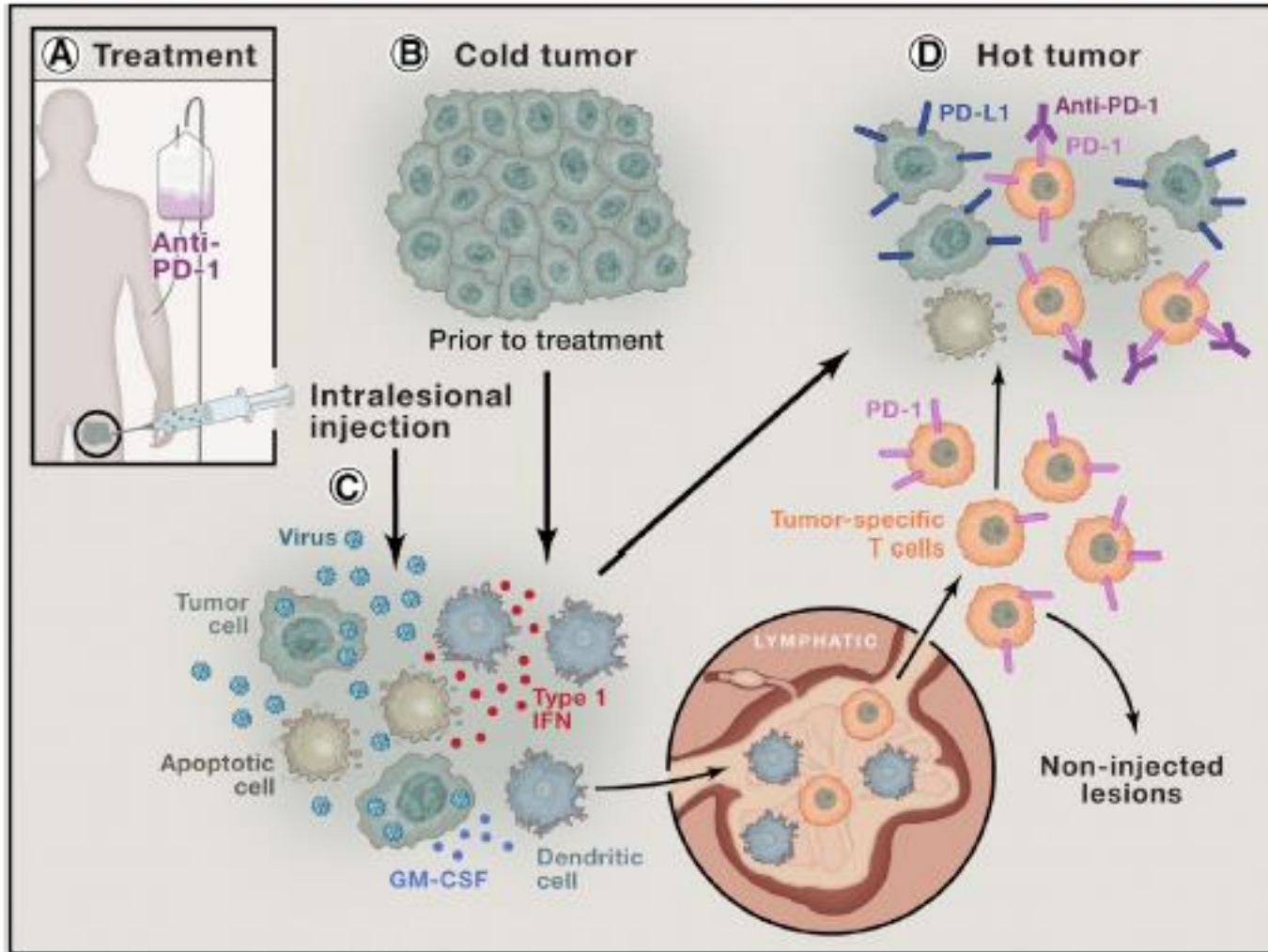
Combinaisons synergiques



Nivolumab after induction treatment in metastatic TNBC- TONIC trial

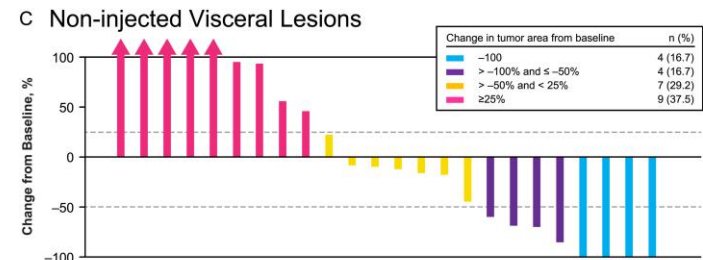
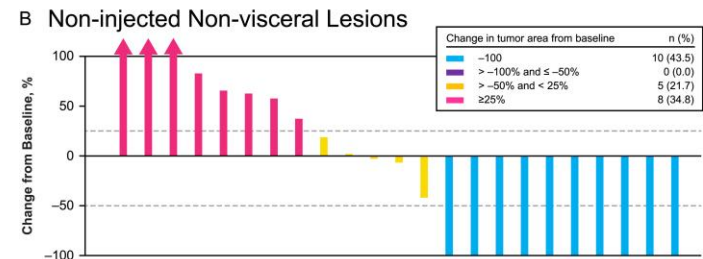
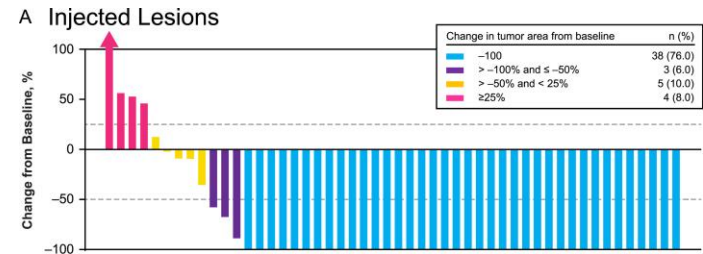
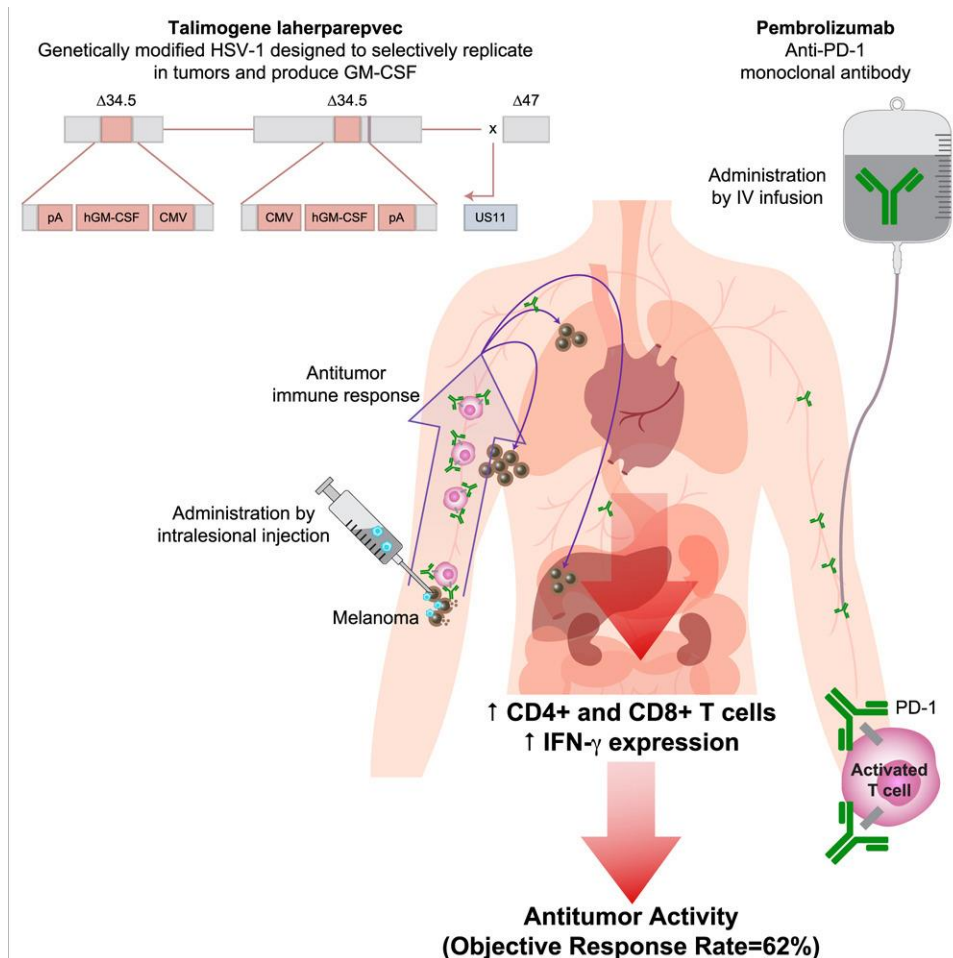


Intra-tumoral cancer immunity priming



Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy

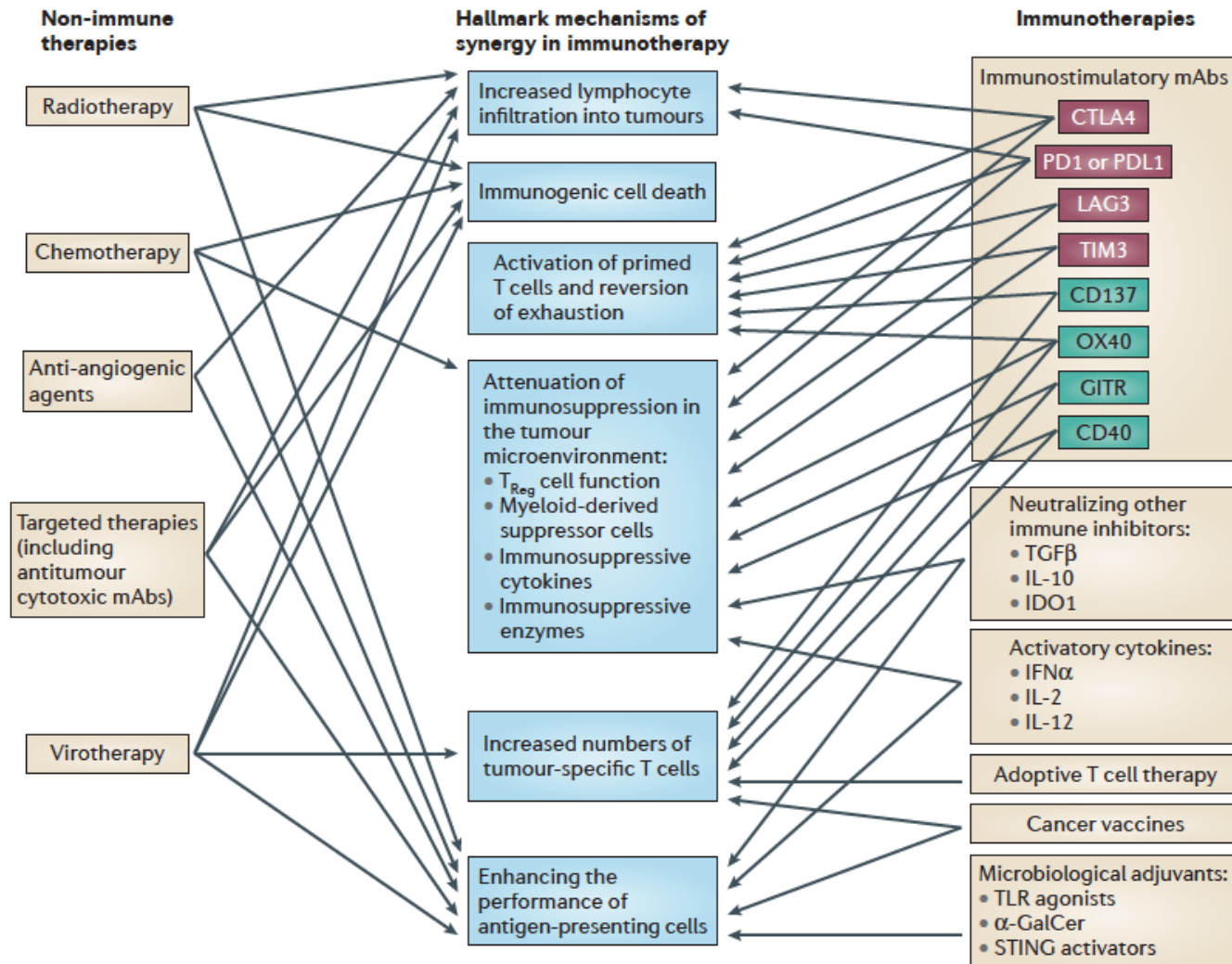
Antoni Ribas, Reinhard Dummer, Igor Puzanov, Ari VanderWalde, Robert H.I. Andtbacka, Olivier Michielin, Anthony J. Olszanski, Josep Malvehy, Jonathan Cebon, Eugenio Fernandez, John M. Kirkwood, Thomas F. Gajewski, Lisa Chen, Kevin S. Gorski, Abraham A. Anderson, Scott J. Diede, Michael E. Lassman, Jennifer Gansert, F. Stephen Hodi, Georgina V. Long



Includes index or new measurable lesion.
Evaluable indicates at least 2 assessments with bi-dimensional measurements.
Safety analysis set includes all subjects who received at least 1 dose of talimogene laherparepvec or pembrolizumab.

Immunothérapies: combinaisons synergiques

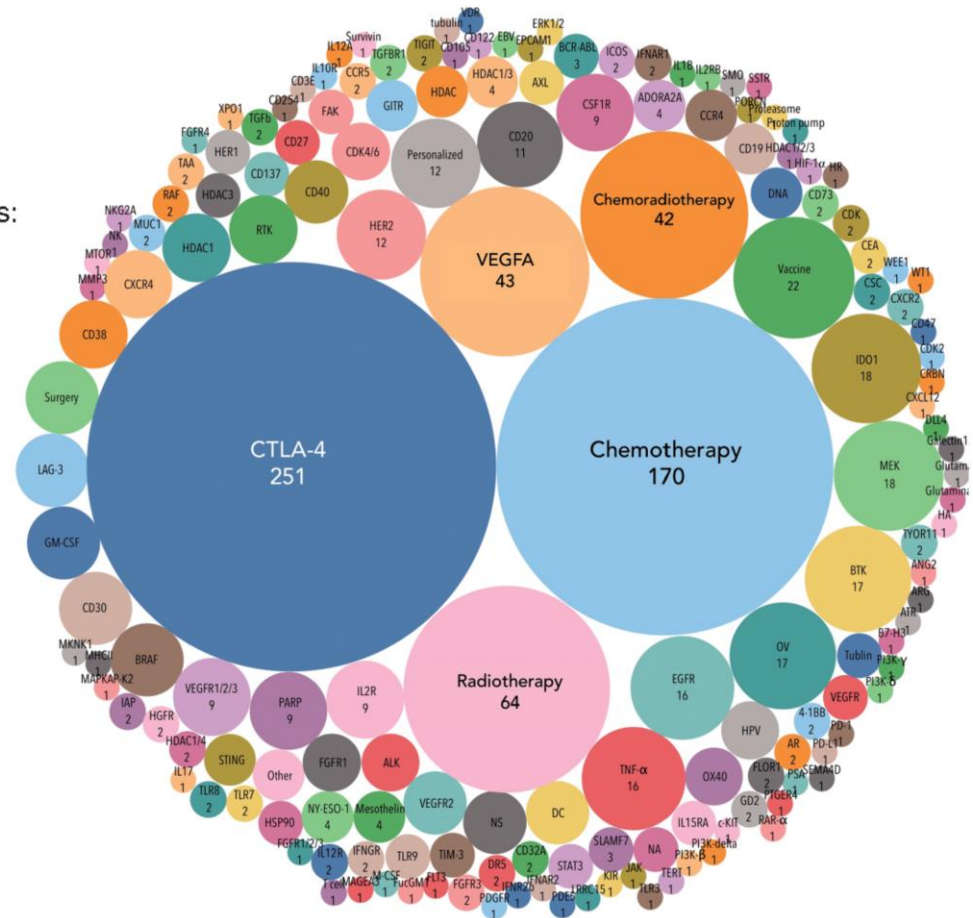
Synergistic effects of combined immunotherapies



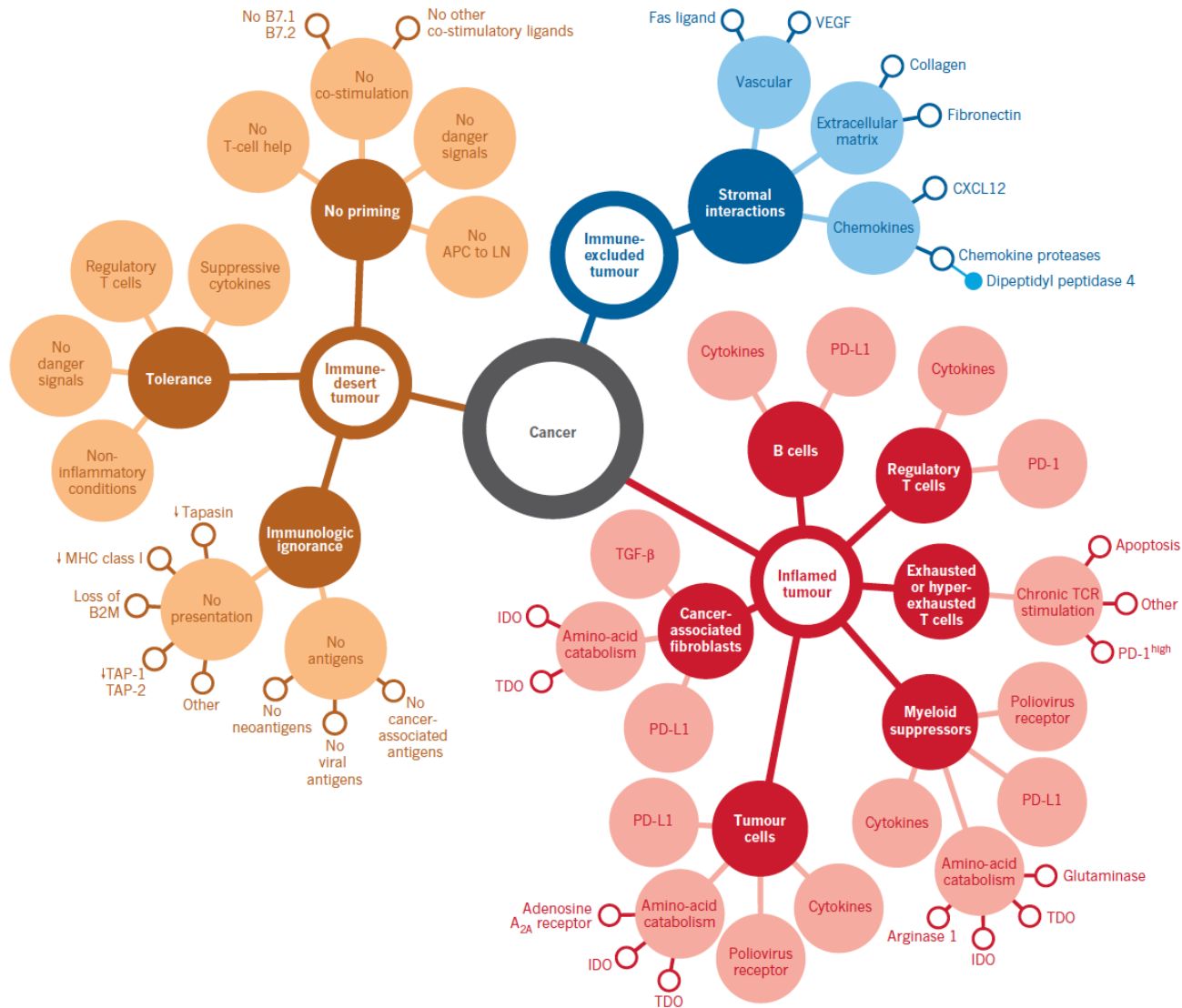
Immunothérapies: combinaisons synergiques

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42

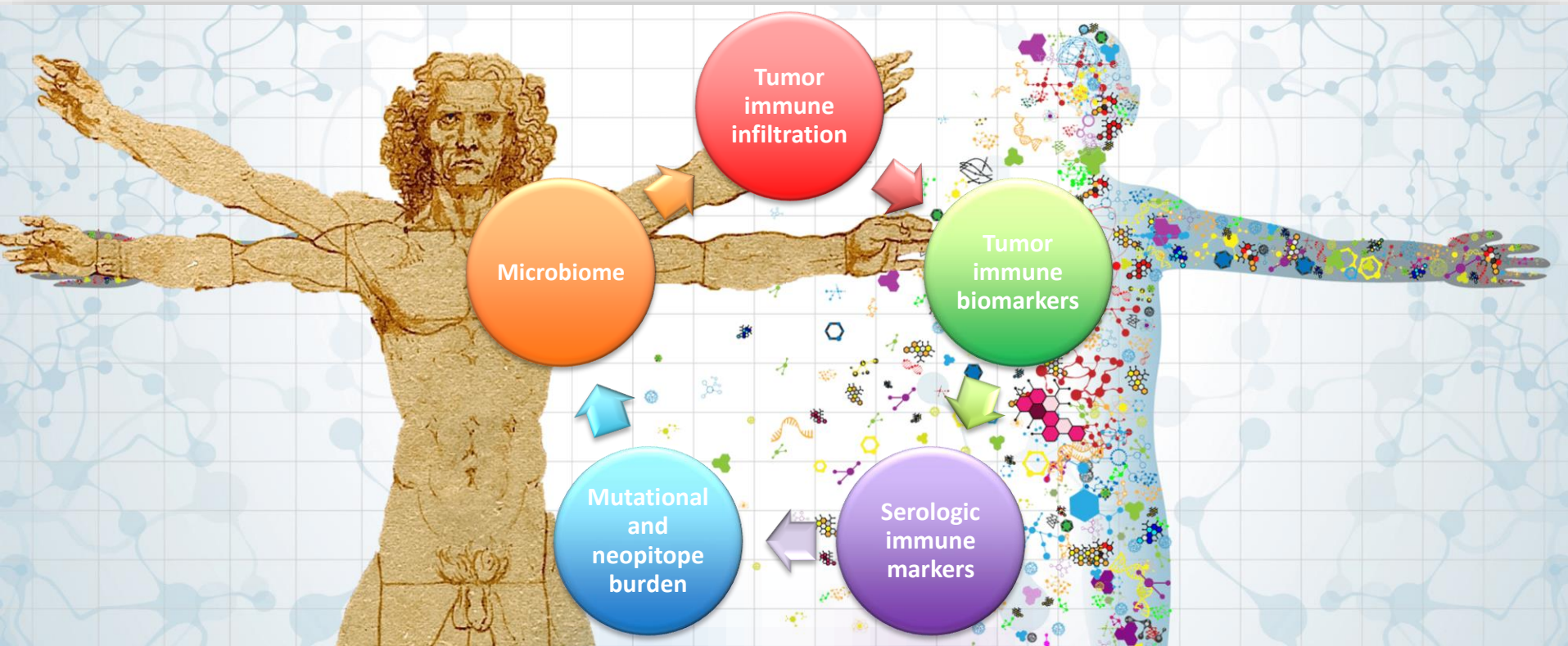


Perspectives : cancer-immune phenotypes



Perspectives

- ◆ Immune precision medicine to guide therapy



Merci pour votre attention

