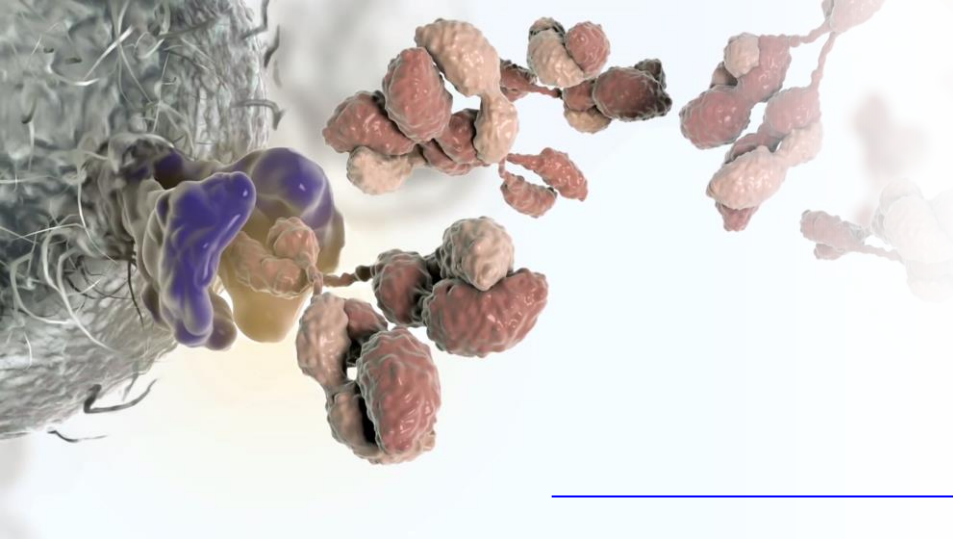




Immunothérapie oncologique : généralités

Anne-Sophie CHRETIEN

PharmD, PhD

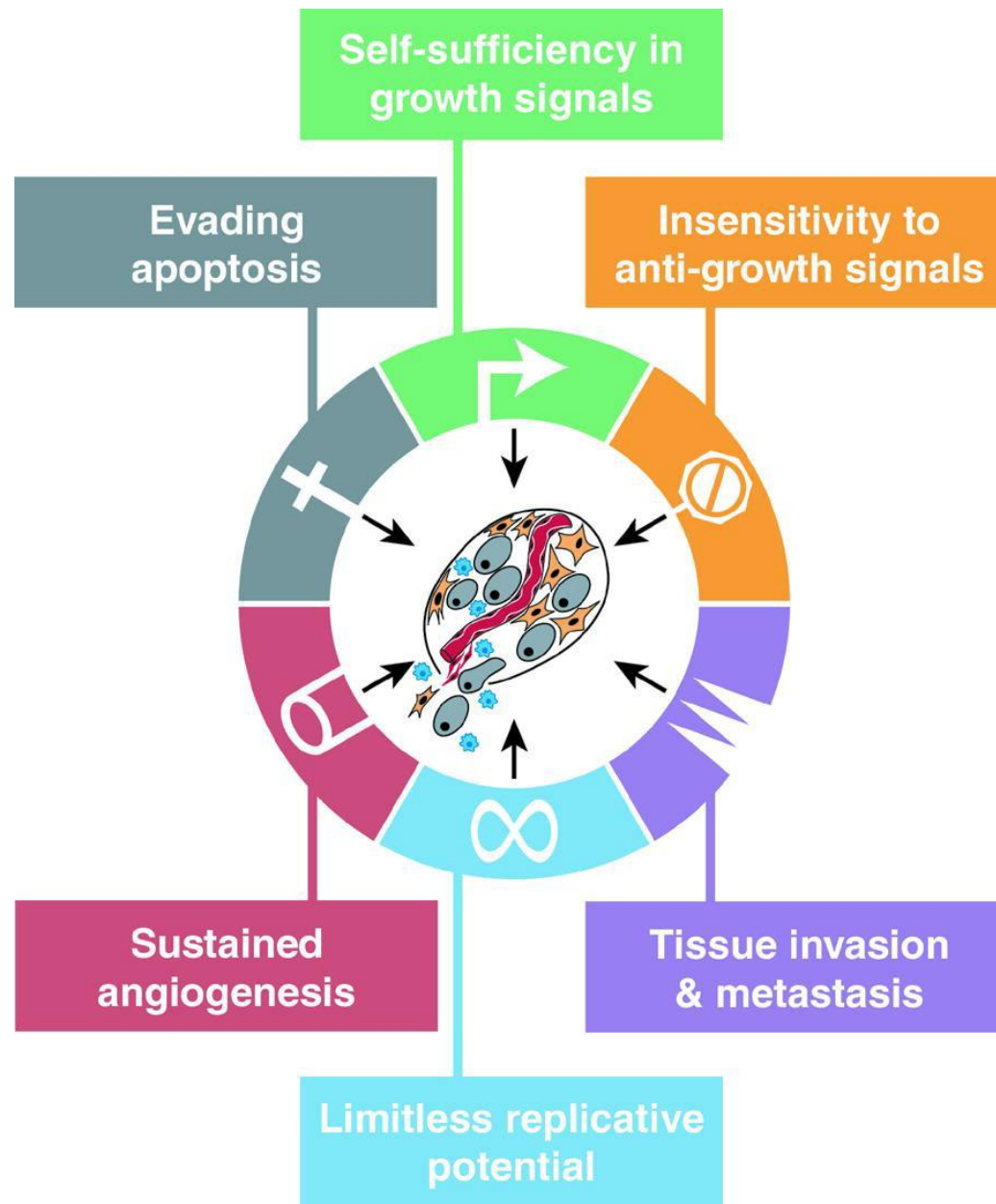
Equipe Immunité et Cancer – CRCM Inserm U1068

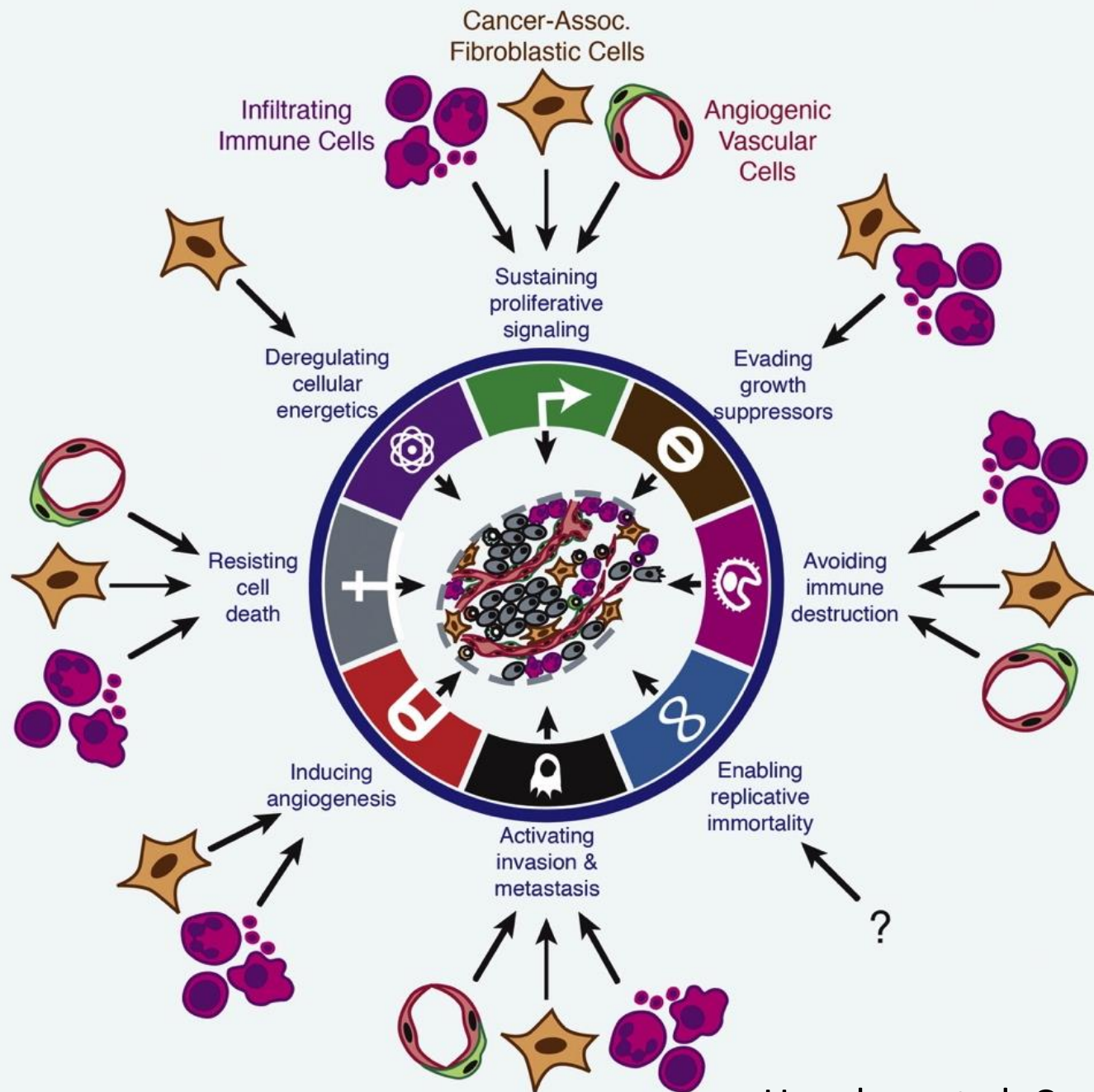
Service d'Immunomonitoring

Institut Paoli Calmettes, Marseille

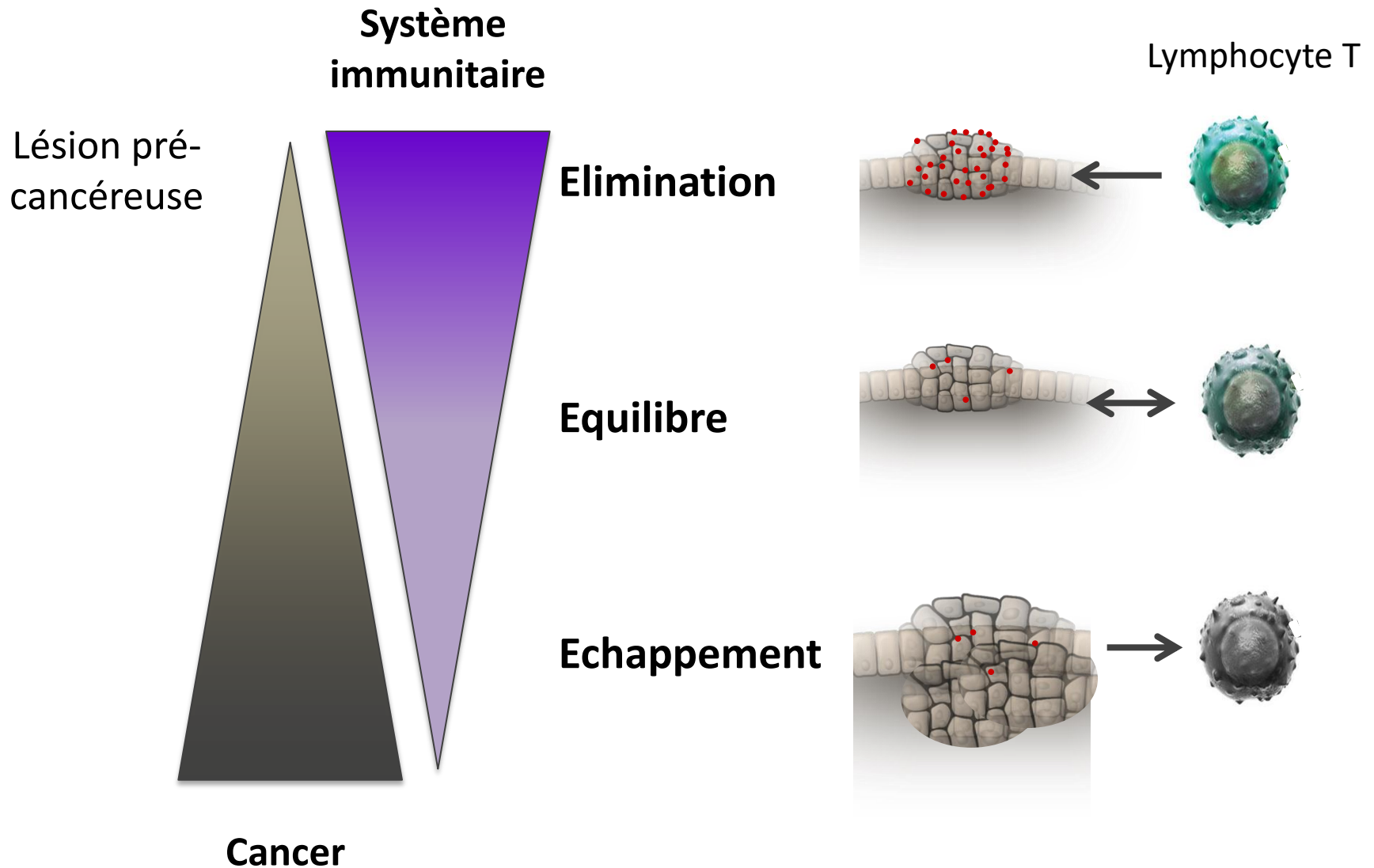
Pr. Daniel Olive

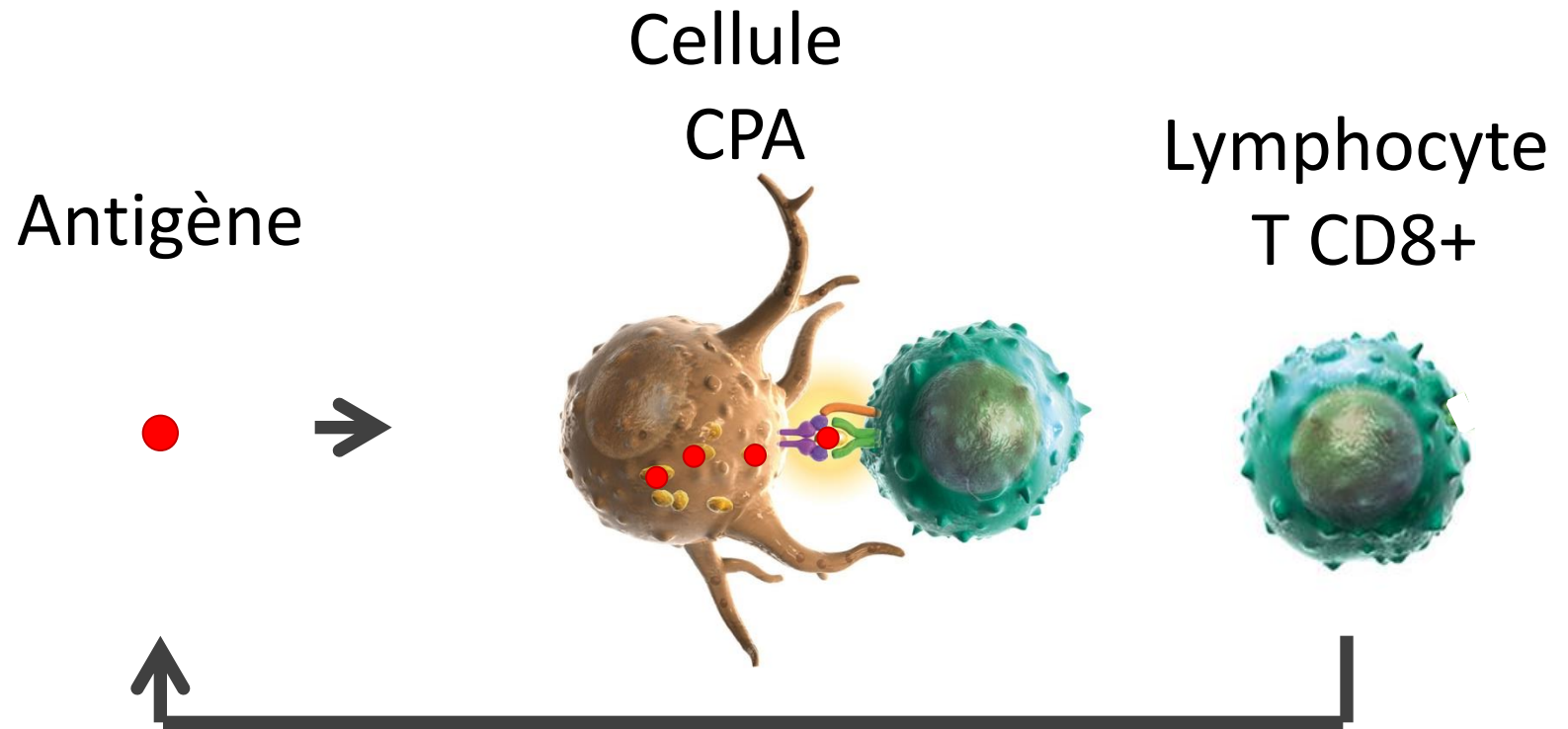
SFPO 2018 11 20





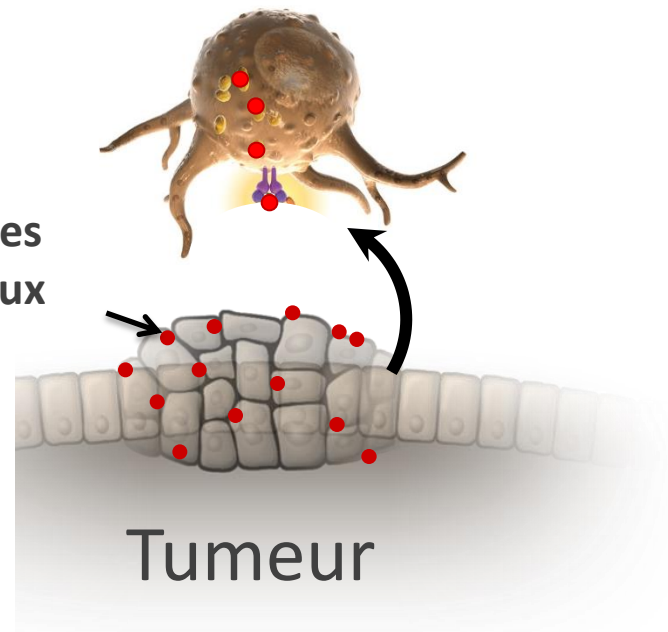
Immunosurveillance: les 3 E

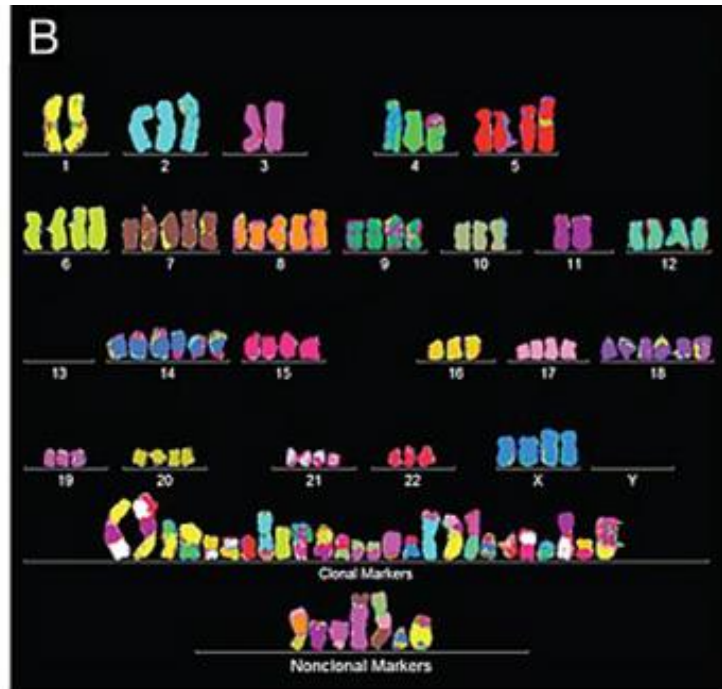
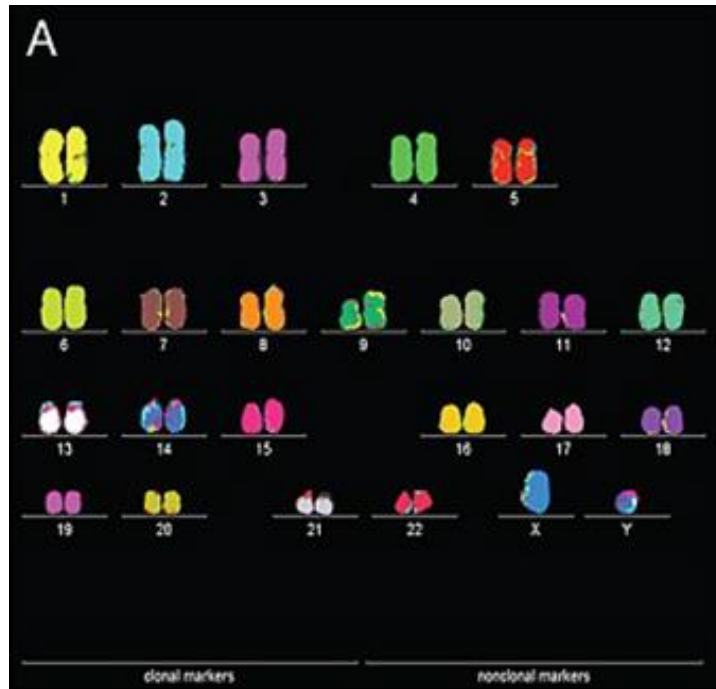




Destruction

**Antigènes
tumoraux**





Cellule normale (gauche) et cellule tumorale (droite) - FISH

Présentation
antigénique



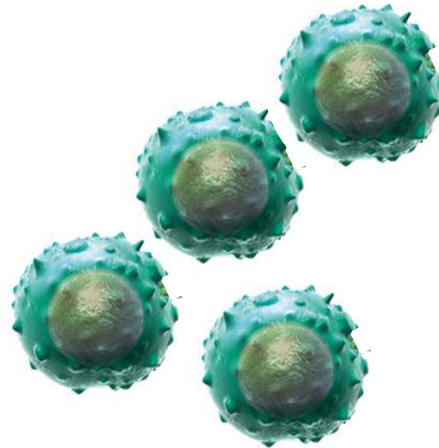
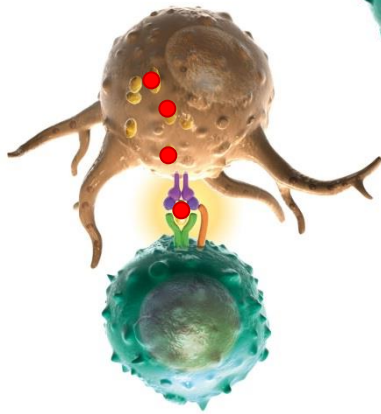
Prolifération



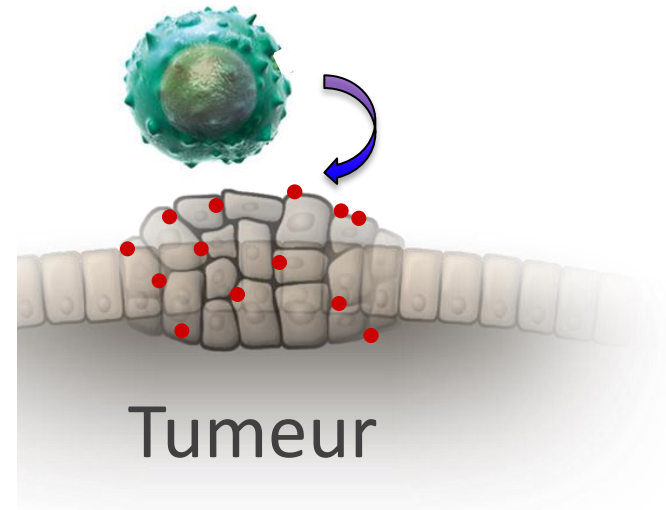
Activation

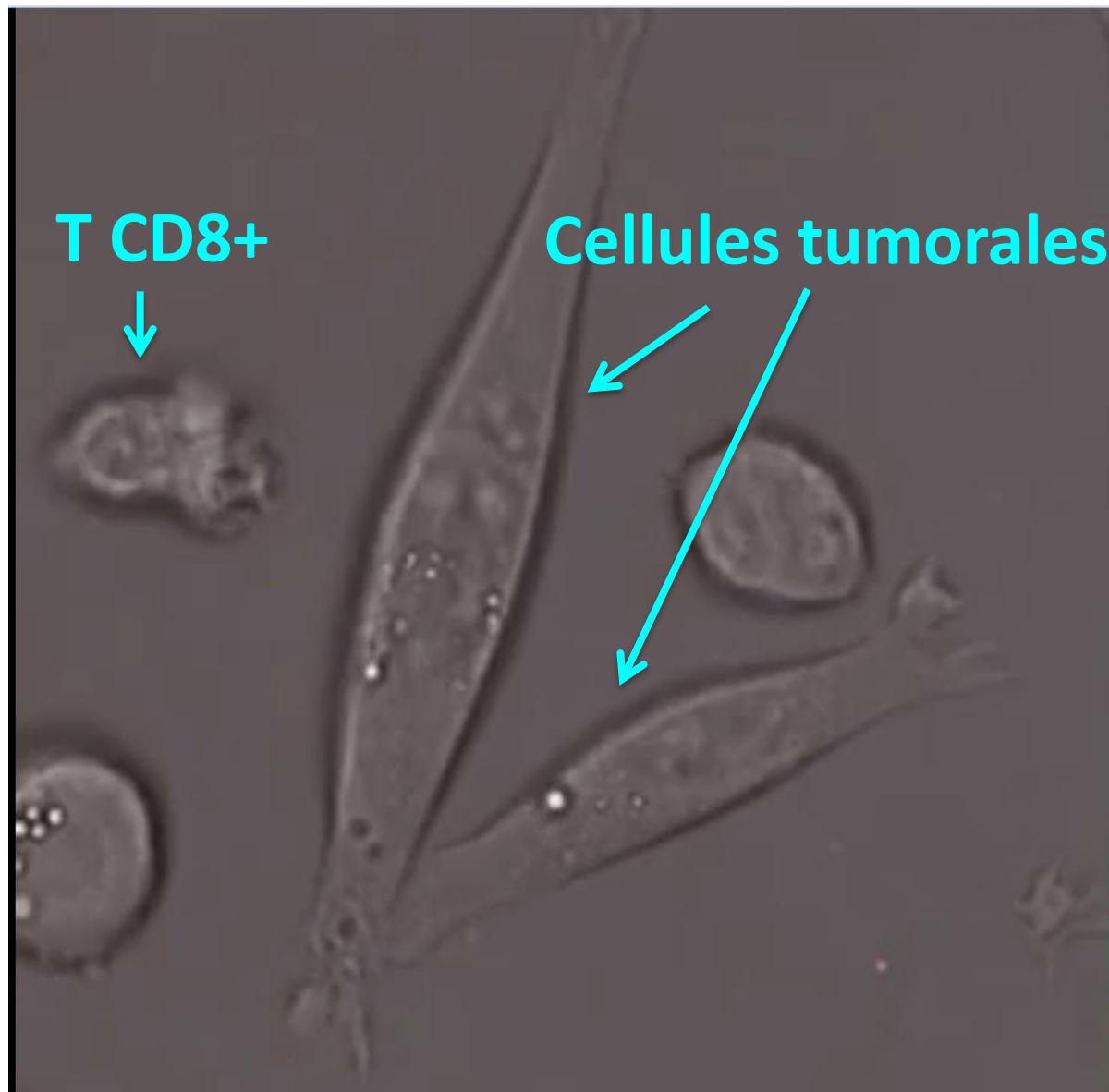
Cellule
CPA

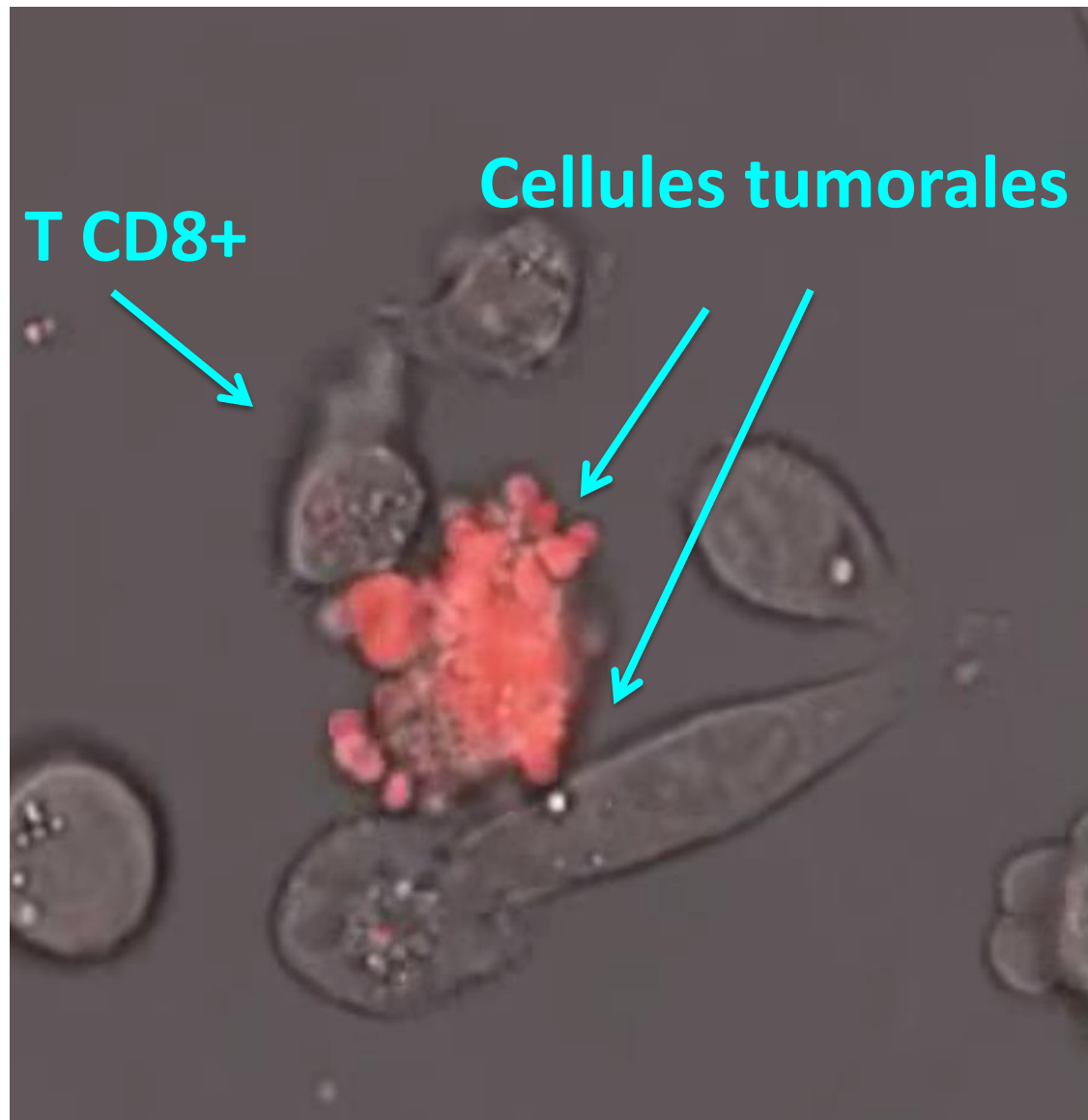
T CD8+



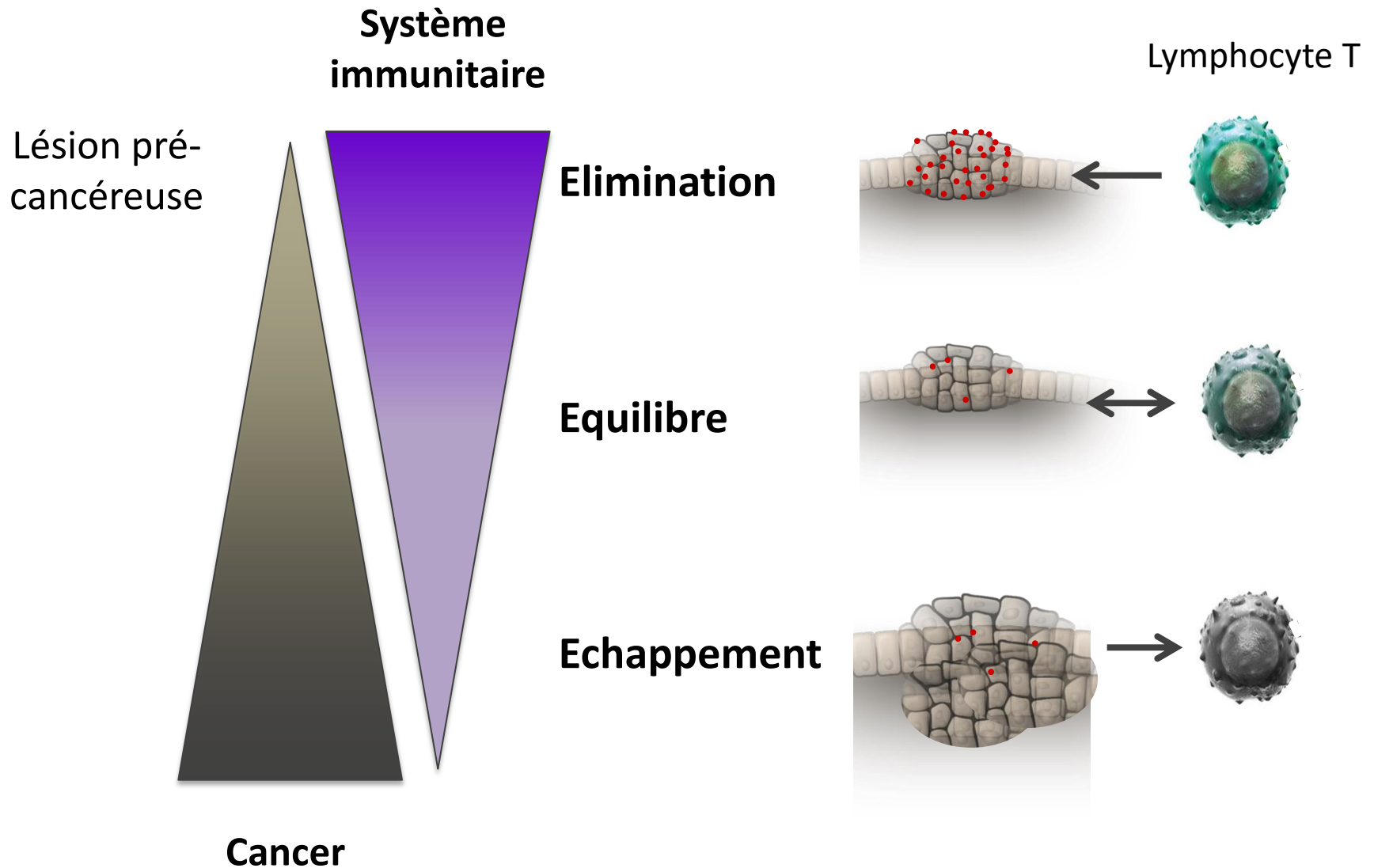
Perforine
Granzyme
➤ Destruction







Immunosurveillance: les 3 E



Phase d'équilibre

Perte antigènes tumoraux

Modifications balance cytokinique

TGF β , IL10, PGE2

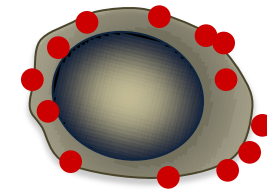
cellule tumorale + stroma

Défaillance système présentation antigénique

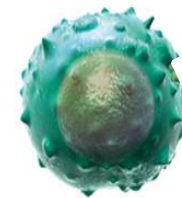
Perte du CMH

Perte d'expression des molécules de la famille B7

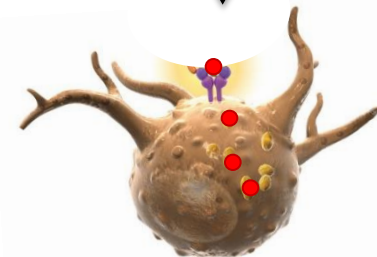
→ T avec un signal activateur sans co-stimulation
deviennent anergiques.



Cellule
tumorale



T CD8+



Cellule
CPA

Phase d'équilibre

Perte antigènes tumoraux

Modifications balance cytokinique

TGF β , IL10, PGE2

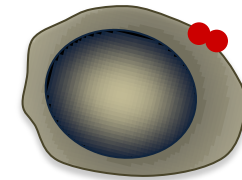
cellule tumorale + stroma

Défaillance système présentation antigénique

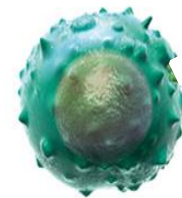
Perte du CMH

Perte d'expression des molécules de la famille B7

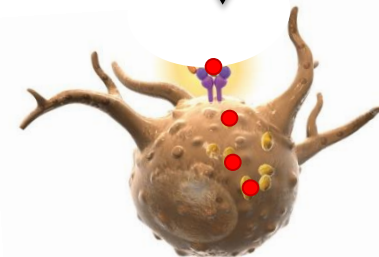
→ T avec un signal activateur sans co-stimulation
deviennent anergiques.



Cellule
tumorale



T CD8+



Cellule
CPA

Phase d'équilibre

Perte antigènes tumoraux

Modifications balance cytokinique

TGF β , IL10, PGE2

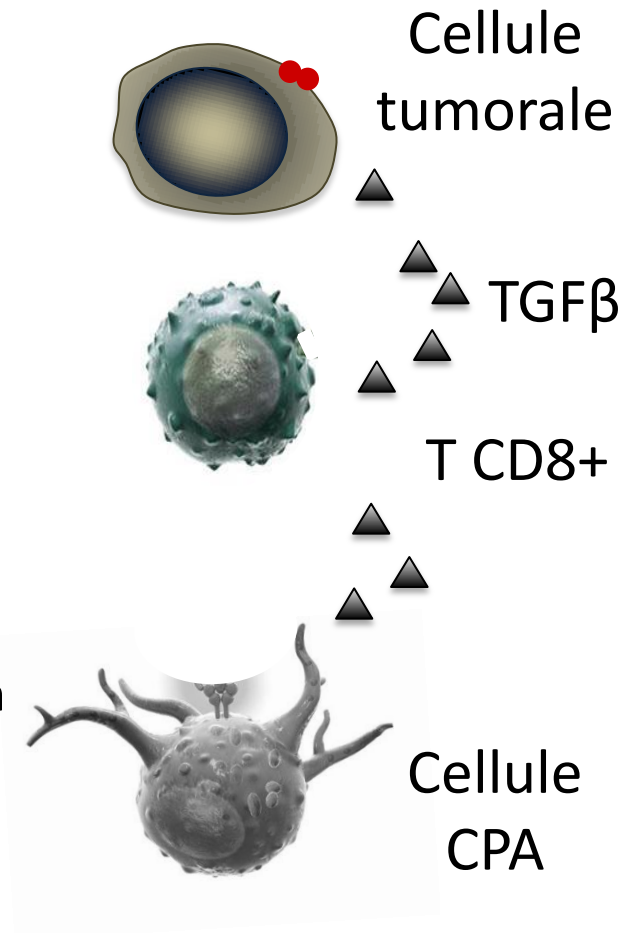
cellule tumorale + stroma

Défaillance système présentation antigénique

Perte du CMH

Perte d'expression des molécules de la famille B7

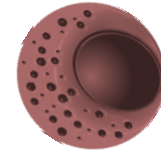
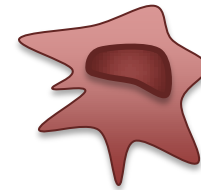
→ T avec un signal activateur sans co-stimulation
deviennent anergiques.



Phase d'échappement

MDSC

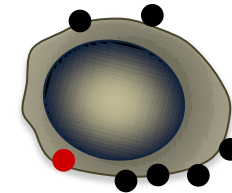
T régulateurs



Accumulation cellules immuno-suppressives

Acquisition ligands immunosuppresseurs

Détournement immune checkpoint

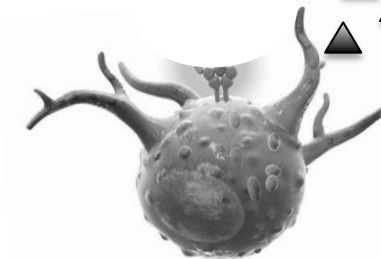


Cellule tumorale



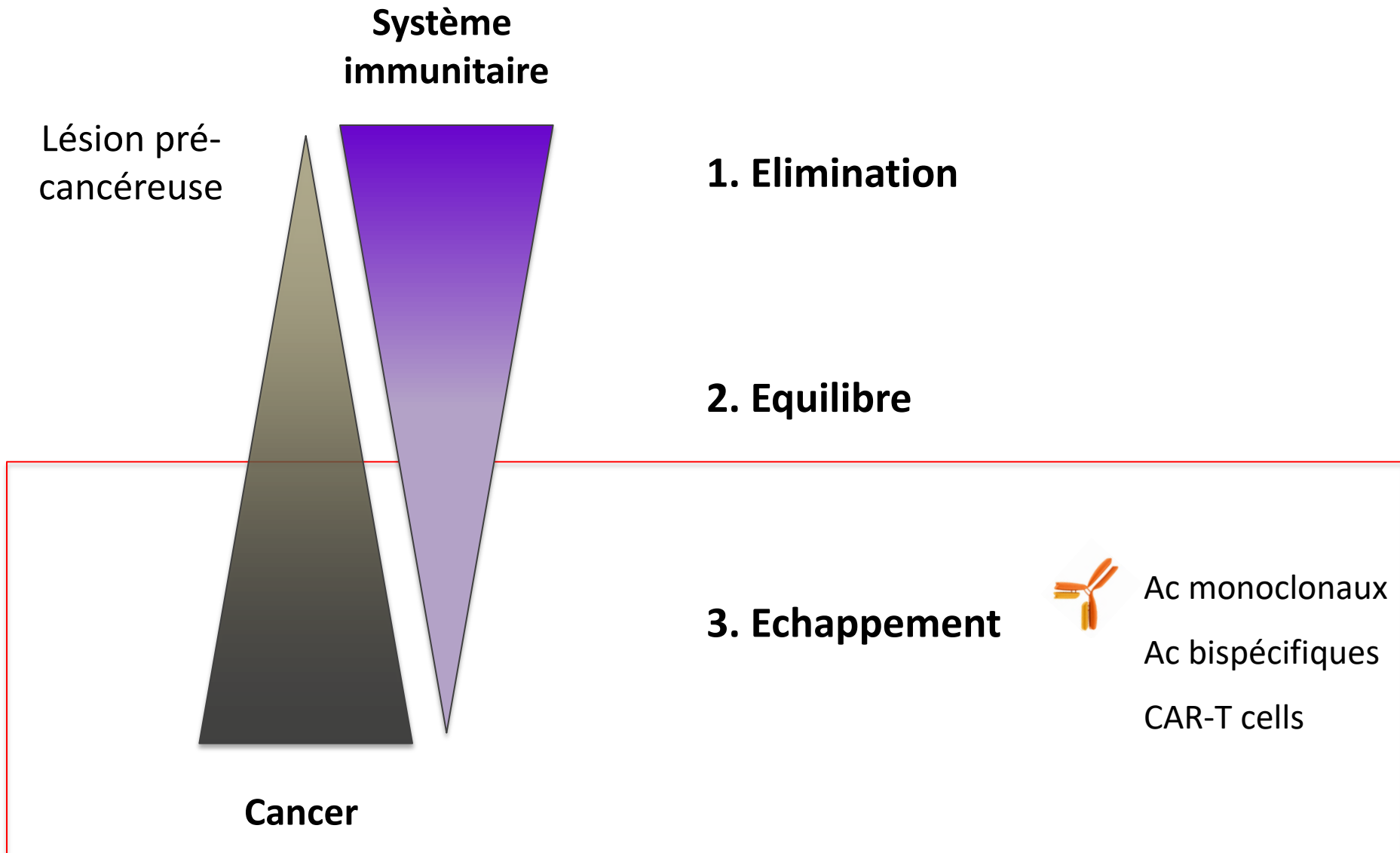
TGF β

T CD8+



Cellule CPA

Immunosurveillance: les 3 E





William Coley

AMERICAN JOURNAL OF THE MEDICAL SCIENCES.

MAY, 1893.

THE TREATMENT OF MALIGNANT TUMORS BY REPEATED
INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF
TEN ORIGINAL CASES.¹

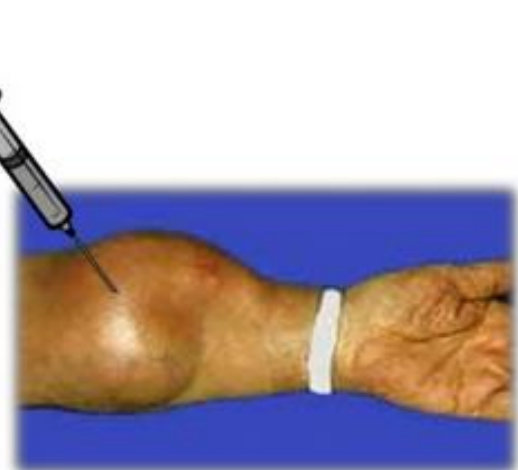
By WILLIAM B. COLEY, M.D.,
ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED; INSTRUCTOR IN SURGERY
IN THE POST-GRADUATE MEDICAL SCHOOL, NEW YORK.

"...on May 2, 1891,
I inoculated a case of sarcoma"

"At the end of two
weeks, the tumor had
disappeared"



Streptococcus pyogenes



Drugs and vaccines regulating immune responses in cancer patients

■ 1985 ex vivo expanded LAK and TILs for melanoma patients

LAK: Lymphokine-activated killer cells

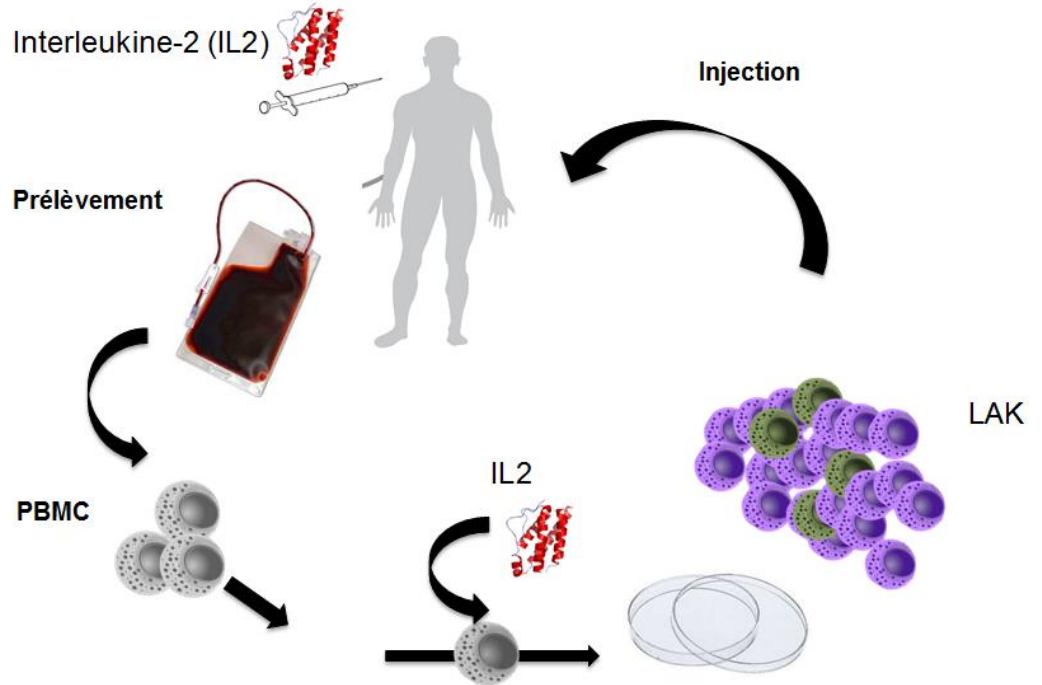
TILs: Tumor Infiltrating Lymphocytes

Ex vivo expansion of NK and T cells

IL2 stimulation

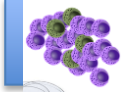
Mice models of metastatic sarcoma

Clinical trial (N=25 patients)



1985

LAK



Drugs and vaccines regulating immune responses in cancer patients

■ 1985 ex vivo expanded LAK and TILs for melanoma patients

25 patients cancer métastatique en échec de ttt standard :

→ plusieurs milliards de cellules après expansion ex vivo + injections IL2 forte dose.

11 réponses objectives ($\geq$ 50% volume)

1 réponse complète pendant 10 mois

Réponse partielle chez 9 patients.

Effet non durable.

Effets secondaire résolutifs à l'arrêt ttt : oedèmes sévères notamment oedèmes pulmonaires

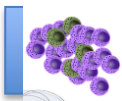
Etudes suivantes avec résultats contradictoires mélanome et rein

IL2 seule : essais cliniques démontrent efficacité modérée

1985

LAK

Rosenberg NEJM 1985



Drugs and vaccines regulating immune responses in cancer patients

■ 1985 ex vivo expanded LAK and TILs for melanoma patients

2011 NCI (Rosenberg)

N=93 patients mélanomes métastatiques réfractaires

3 régimes de conditionnement testés: cyclophosphamide fludarabine

+/-irradiation corporelle totale à 2 et 12 Gy.

Taux de réponse globale entre 50% et 70%

21 % de réponses complètes (RC).

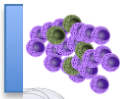
19 des 20 RC maintenues à dix ans

Résultats confirmés en 2012 par le MD Anderson et Moffitt Cancer Center

1985

LAK

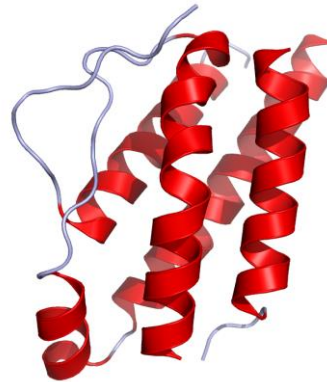
Rosenberg ClinCancer Res 2011



Drugs and vaccines regulating immune responses in cancer patients

- 1992 Interleukin 2 in metastatic renal cell cancer for expansion of CD8 and NK cells.

At a preclinical stage complex of IL2 and anti-IL2 (SAB6, MAB602)



1985

LAK



1992

IL2



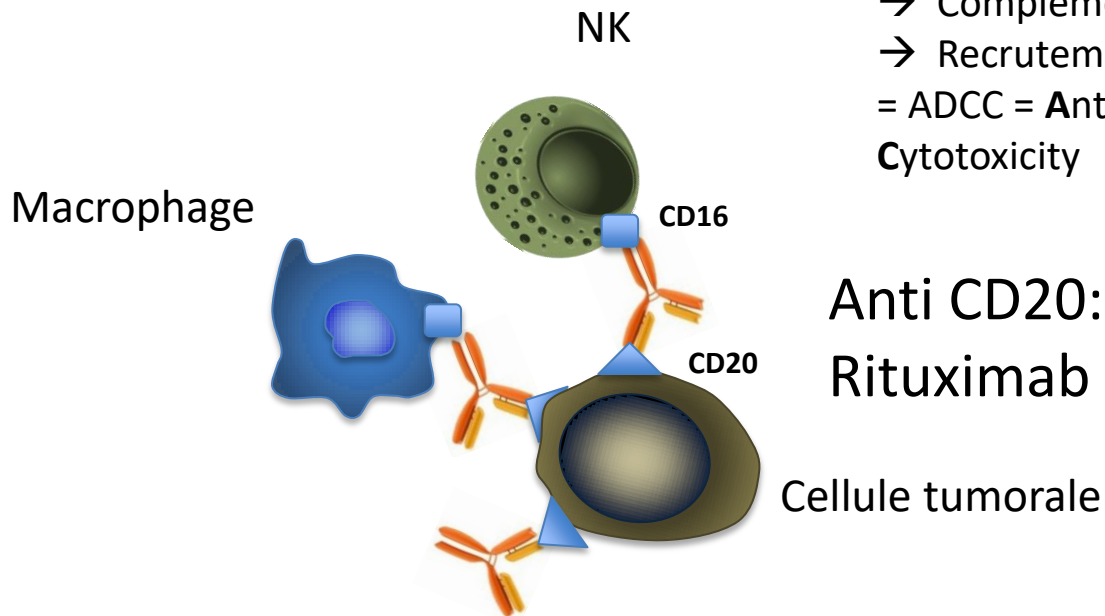
Boyman et al Science 2006



Drugs and vaccines regulating immune responses in cancer patients

- 1997 anti-CD20 (rituximab) for non hodgkin lymphoma and CLL; then anti-HER2 (trastuzumab, Herceptin[®]) and others

→ Activité directe: apoptose
→ Complément
→ Recrutement et activation NK macrophages
= ADCC = **A**ntibody-**D**ependent **C**ell-mediated Cytotoxicity

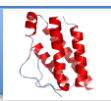
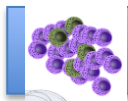


Adapté de Craig A. Portell & Anjali S. Advani Leukemia & Lymphoma 2014

1985
LAK

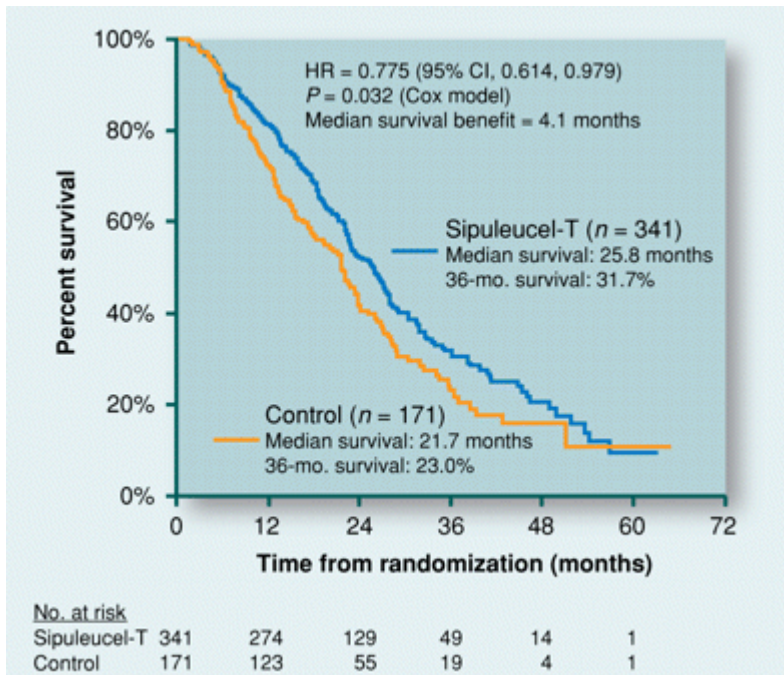
1992
IL2

1997
Anti-CD20



Drugs and vaccines regulating immune responses in cancer patients

- **PROVENGE® (sipuleucel-T) (1st DA Approved cancer vaccine, 2010)**



Cheever et al Clin Cancer Res 2011

- Autologous cellular immunotherapy
- Patients with metastatic castration-resistant prostate cancer
- Target antigen: PAP (prostate acid phosphatase)
- Fusion protein: recombinant PAP+GM-CSF

3-years survival: 31.7% vs 23%

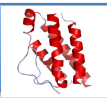
1985

LAK



1992

IL2



1997

Anti-CD20



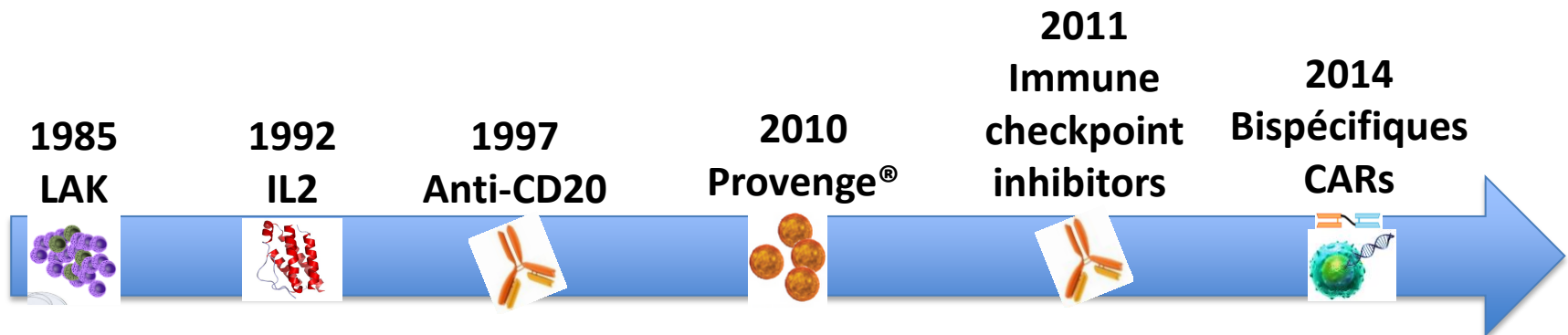
2010

Provenge®



Drugs and vaccines regulating immune responses in cancer patients

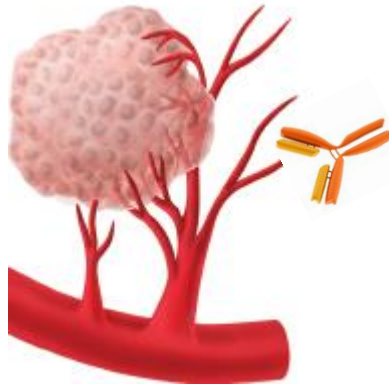
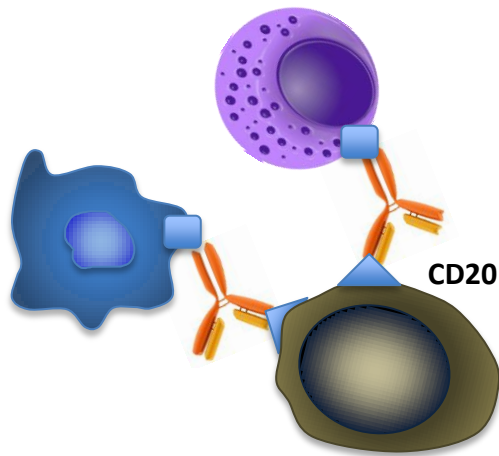
- mAbs against cosignaling molecules (2002 then 2010) anti-CTLA-4 FDA approved 2011, anti-PD1 FDA approved 2014 melanoma followed by NSCLCC, H&N, urothelial, HL...
- Bispecific mAbs (blinatumomab FDA approved 2014 Amgen)
- CARs (FDA approved 2014, Novartis, Juno Therapeutics, KITE)



Anticorps thérapeutiques en cancérologie

Changement de paradigme

- Ciblage cellule tumorale
- Ciblage micro-environnement tumoral
- Immunostimulation





P. Golstein
Brunet et al Nature 1987

Immune checkpoints

CTLA4

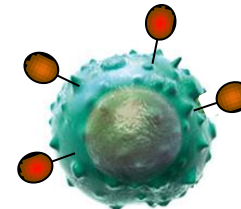
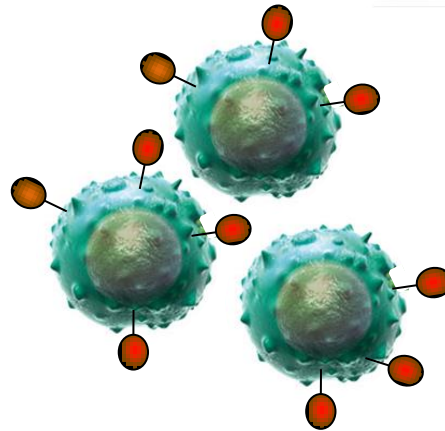


PD1



Tasuku Honjo
Ishida et al EMBO 1992

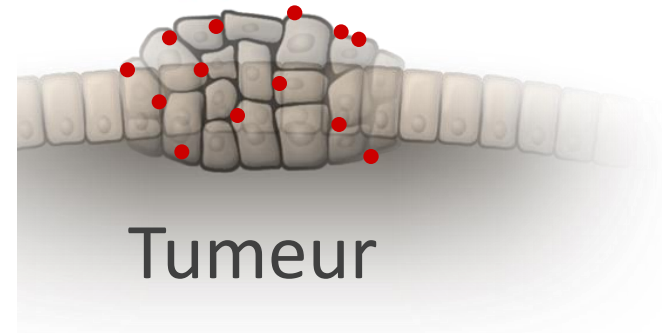
James Allison
Leach et al Science 1996



Cellule
CPA



T CD8+



Tumeur



P. Golstein
Brunet et al Nature 1987



Tasuku Honjo
Ishida et al EMBO 1992

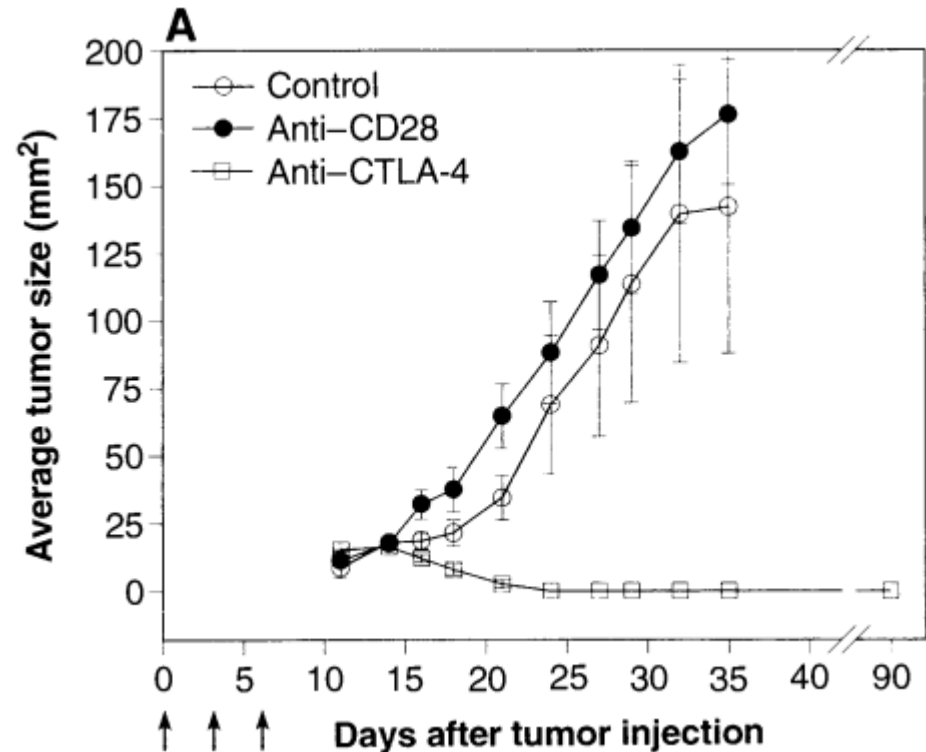
James Allison
Leach et al Science 1996

Immune checkpoints

CTLA4



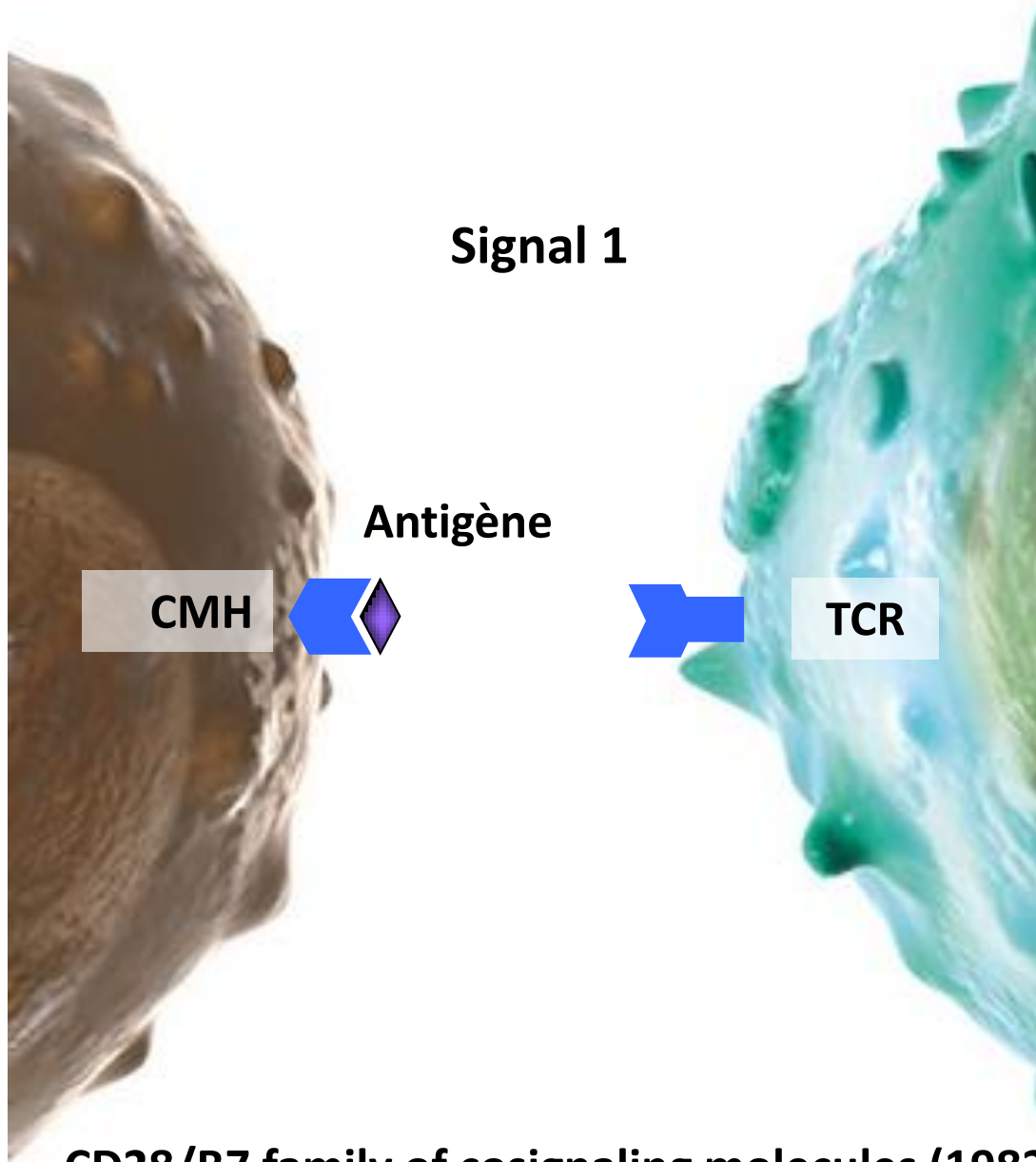
PD1



Leach et al Science 1996

Régulation de l'immunité adaptative par la cosignalisation

Cellule
présentatrice
d'antigène

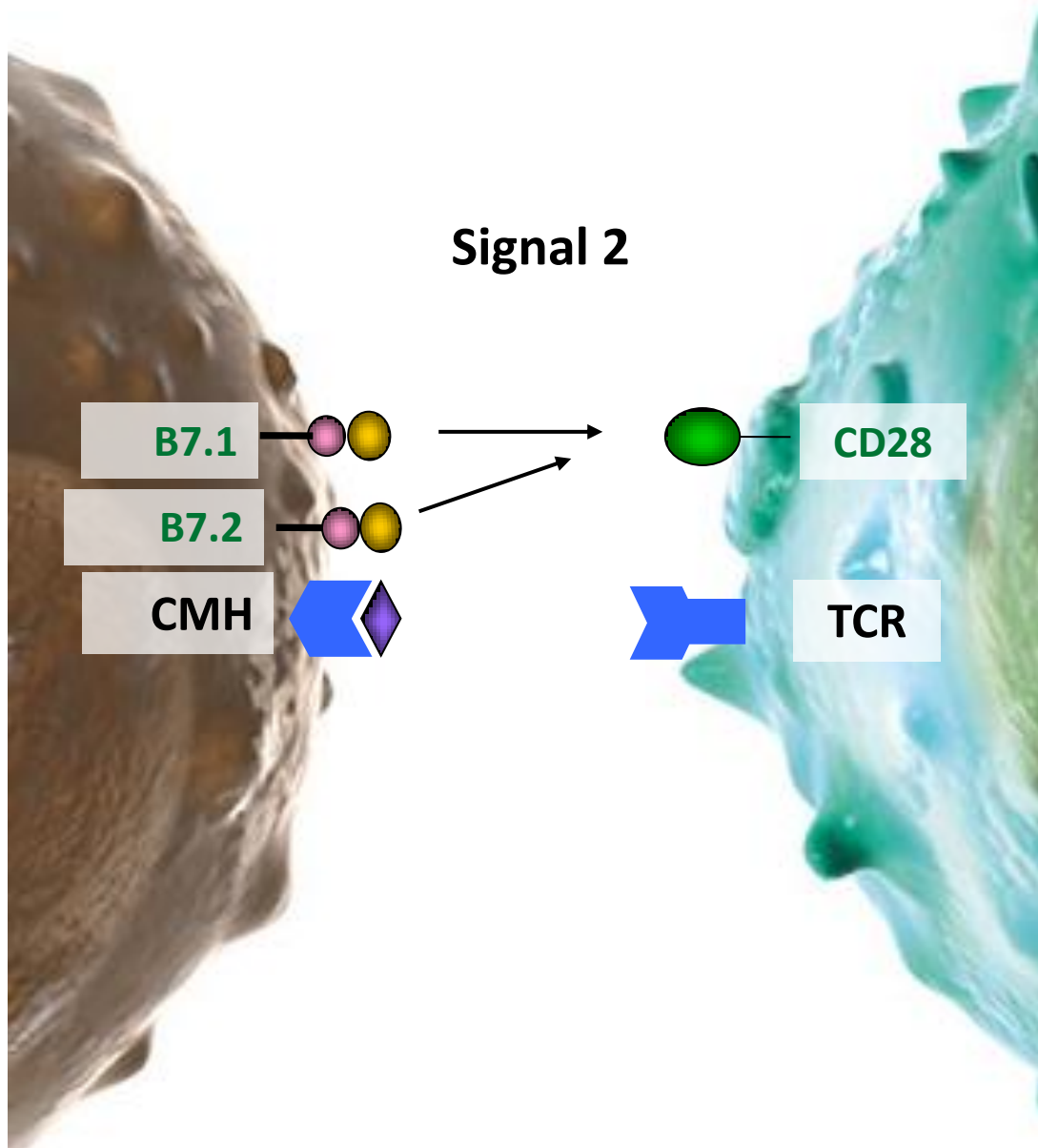


Lymphocyte
T

CD28/B7 family of cosignaling molecules (1982)

Présentation antigénique et costimulation par CD28

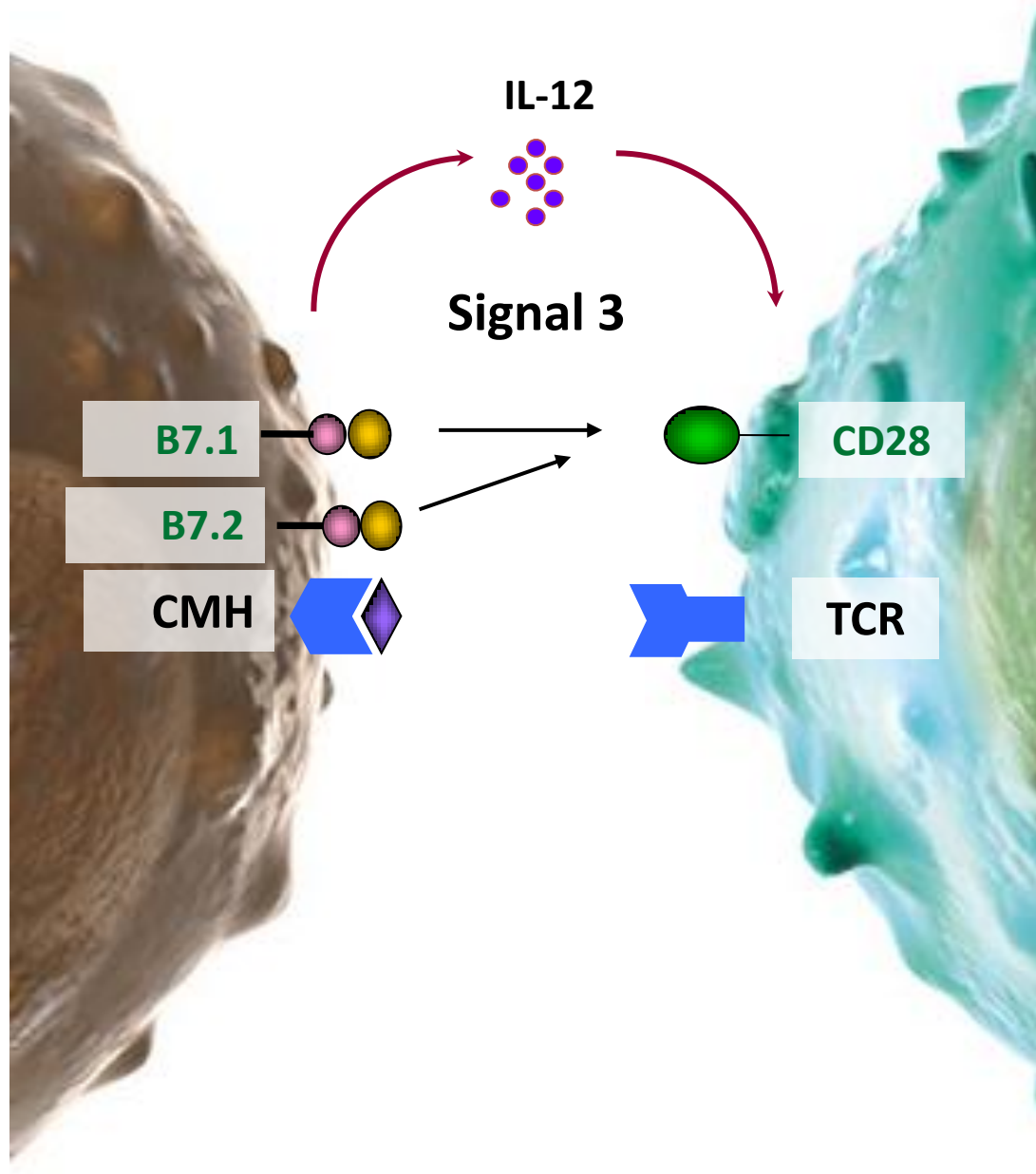
Cellule
présentatrice
d'antigène



CD28/B7 family of cosignaling molecules (between 1982 and 1990)

Présentation antigénique et costimulation par CD28

Cellule
présentatrice
d'antigène

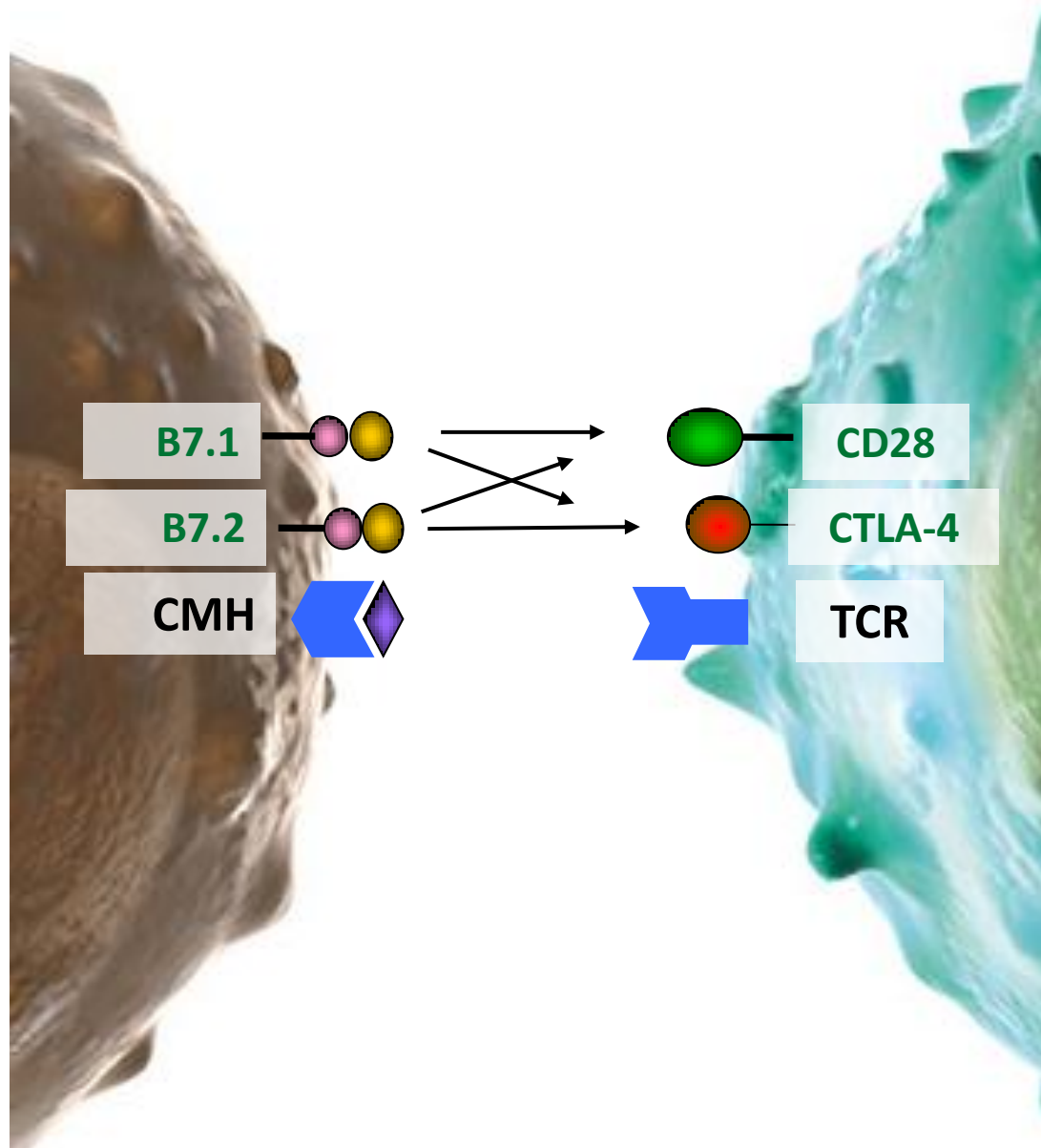


+ Lymphocyte
T

+ B7/CD28

Le signal 2 peut être modifié par voies de cosignalisation supplémentaires

Cellule
présentatrice
d'antigène



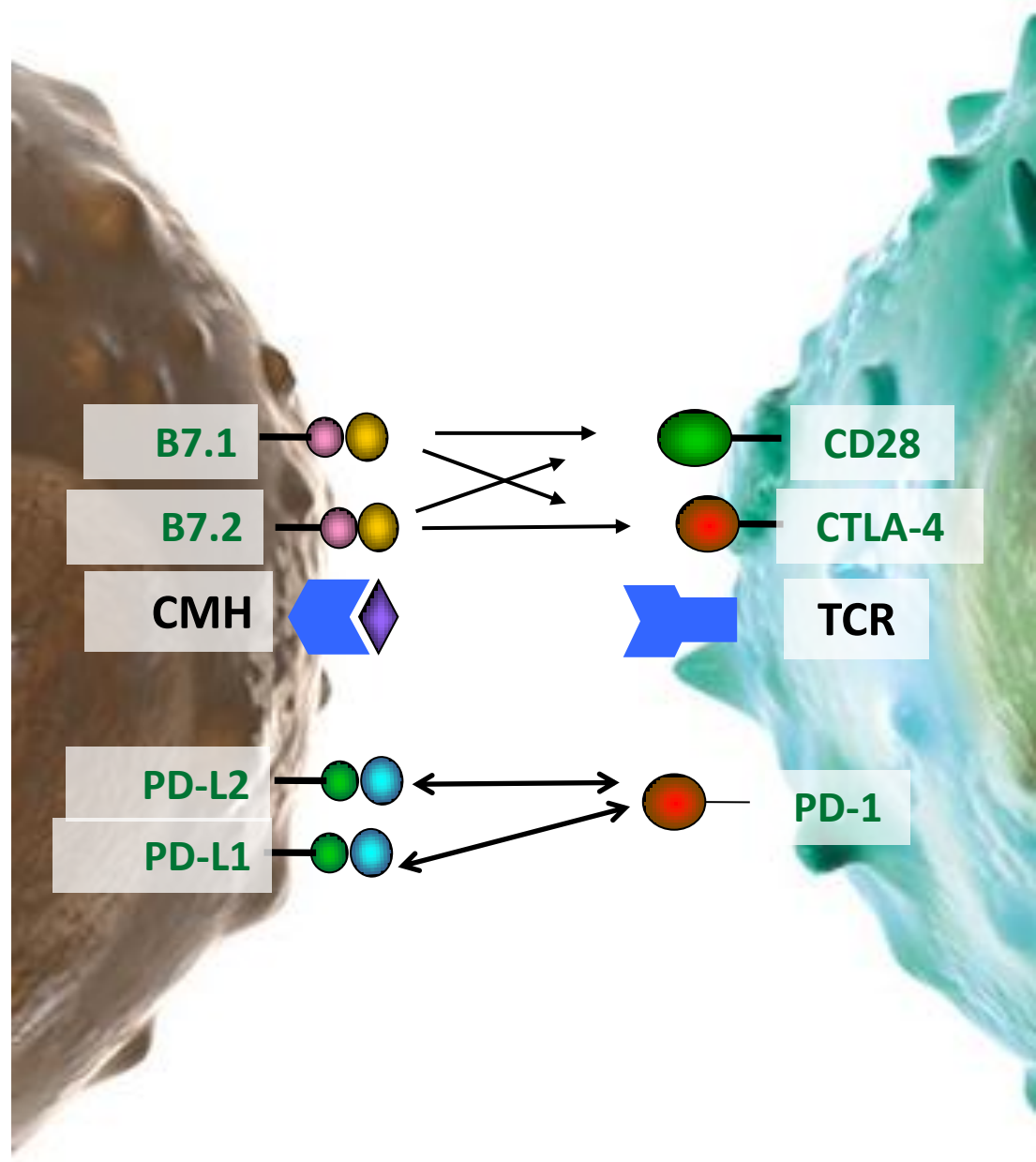
+ Lymphocyte
- T

+
B7/CD28

CD28/B7 family of cosignaling molecules (after 1991)

Le signal 2 peut être modifié par voies de cosignalisation supplémentaires

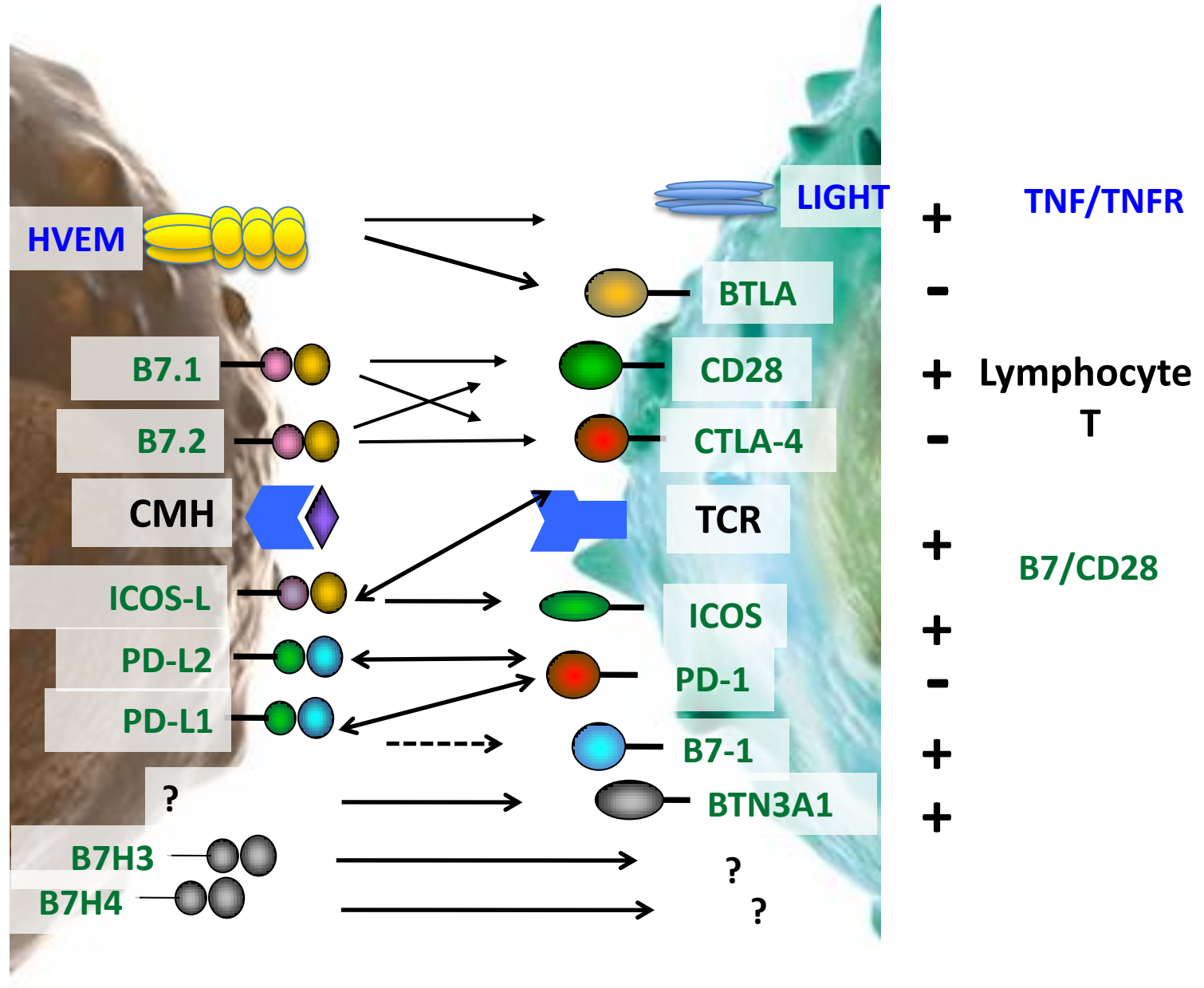
Cellule
présentatrice
d'antigène



+ Lymphocyte
- T
+ B7/CD28
- PD-1

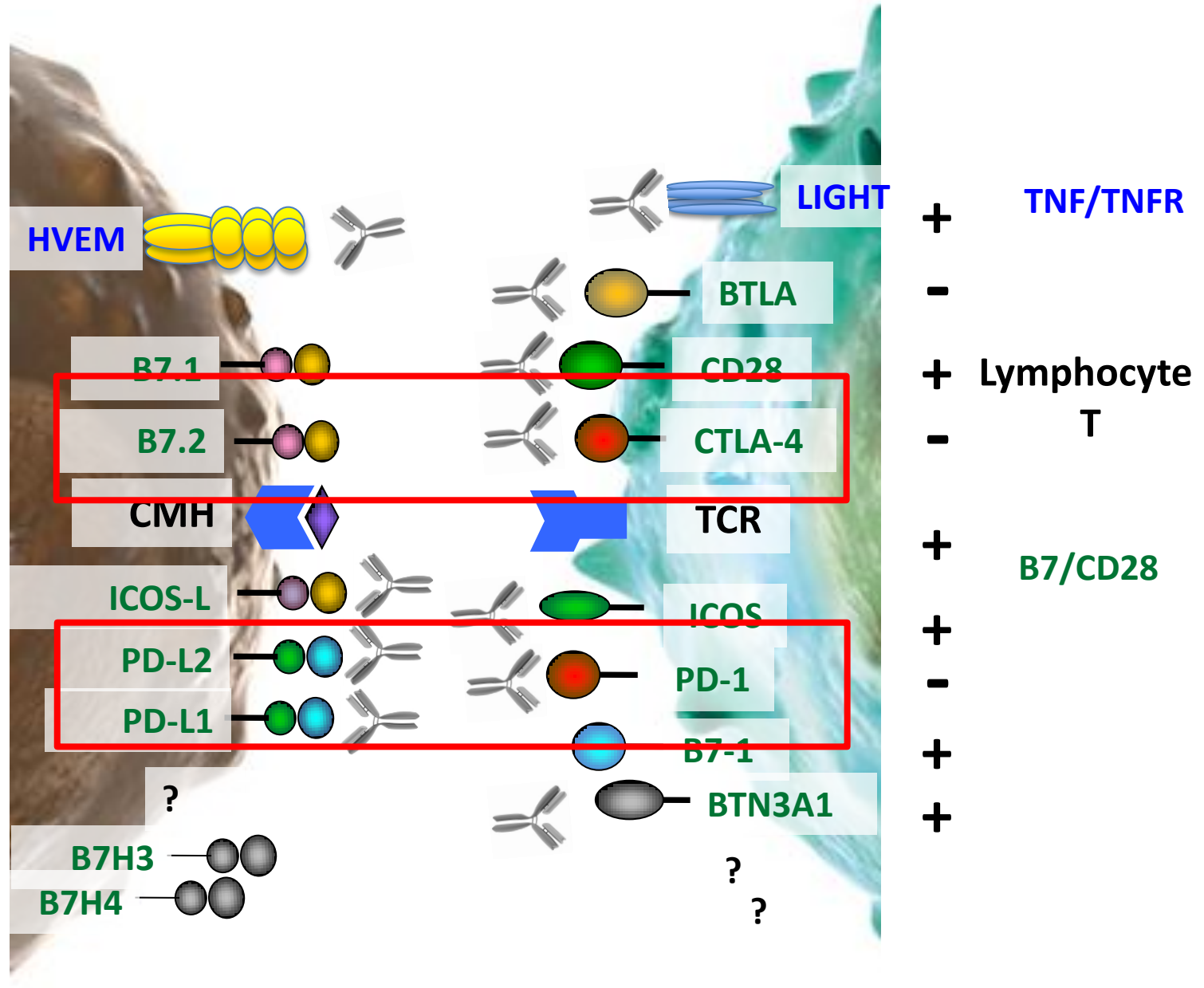
Le signal 2 peut être modifié par voies de cosignalisation supplémentaires

Cellule
présentatrice
d'antigène



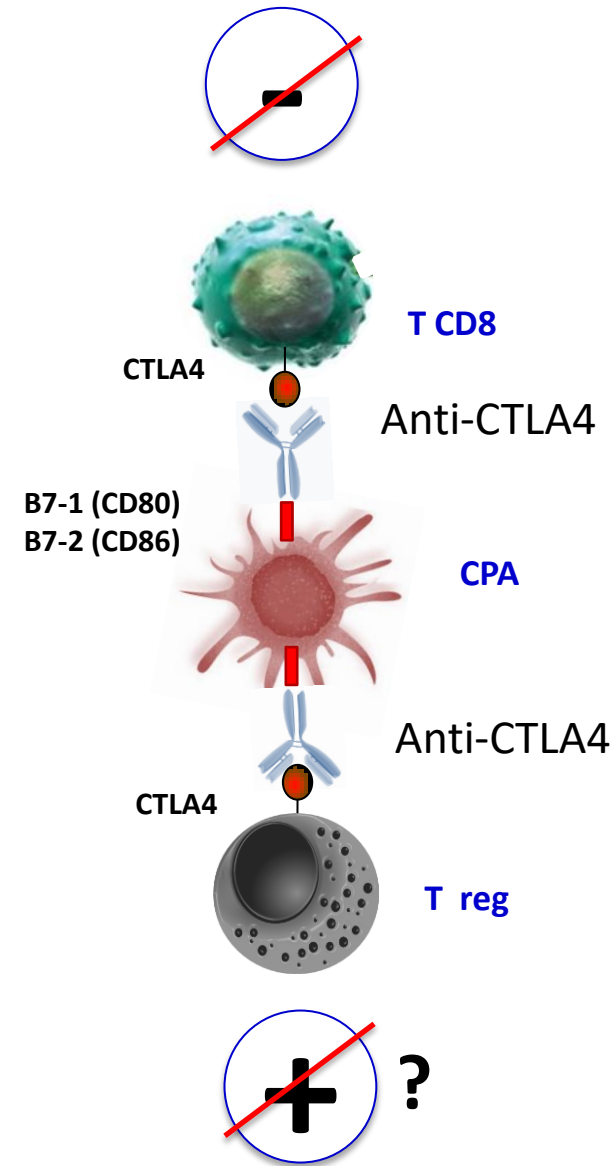
Modulation de l'activation T par inhibiteurs de checkpoints

Cellule
présentatrice
d'antigène



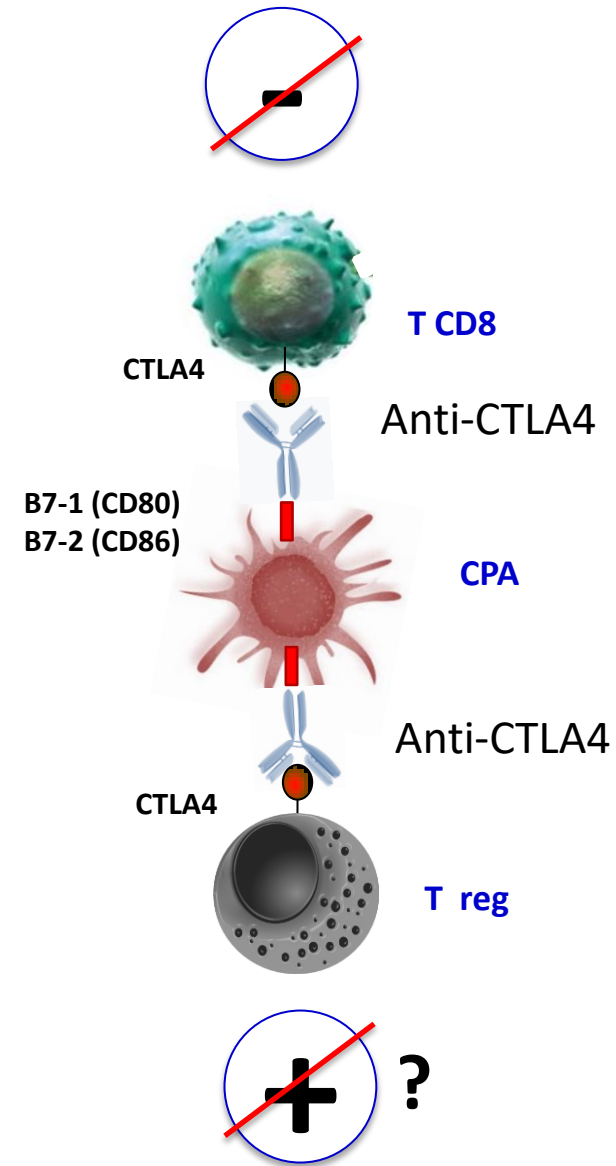
Anti-CTLA-4

- Clonage: nouveau membre IgSF Brunet et al. , 1987;
- Function et ligand (Linsley et al., 1991; Walunas et al., 1994);
- Preuve de concept chez l'animal (Leach et al, 1996)
- Mécanisme: Inhibition des signaux négatifs et déplétion Tregs + autres...
 - Tremelimumab (IgG2), Ipilimumab (IgG1)

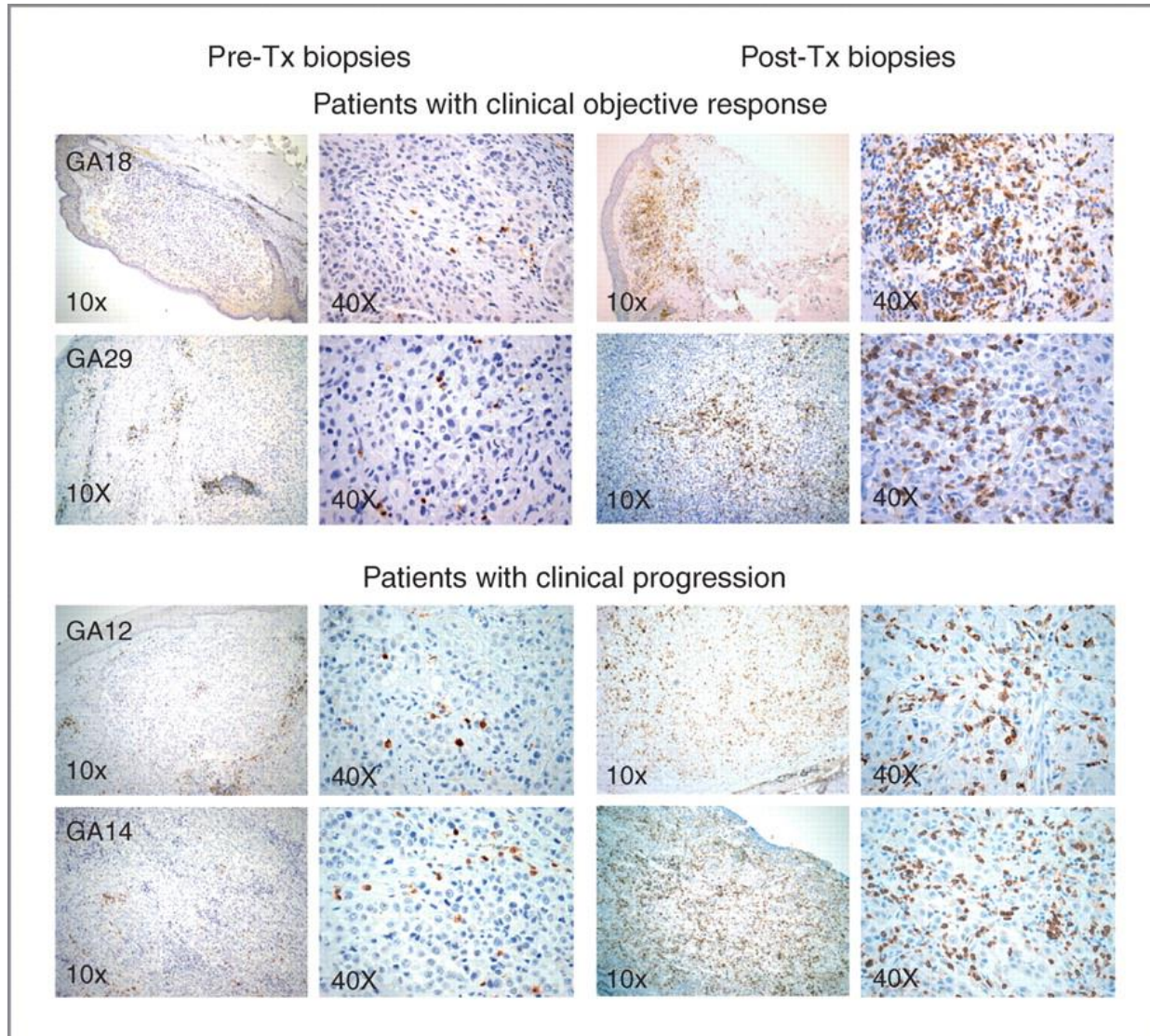


Anti-CTLA-4

- Activité clinique mélanome non résecable stades III et IV (Hodi et al., NEJM, 2010)
- Activité : mélanome, prostate, rein, vessie, ovaires et poumon
- Elargissement du répertoire T (Robert et al., 2014)
- Induit infiltration tumorale par cellules immunes (Huang et al., 2011)
- AMM mélanome métastatique réfractaire (2011)
étendue aux patients non traités (2014)



Infiltration CD8+ avant et après traitement par tremelimumab (anti-CTLA4) chez 4 patients représentatifs (IHC)

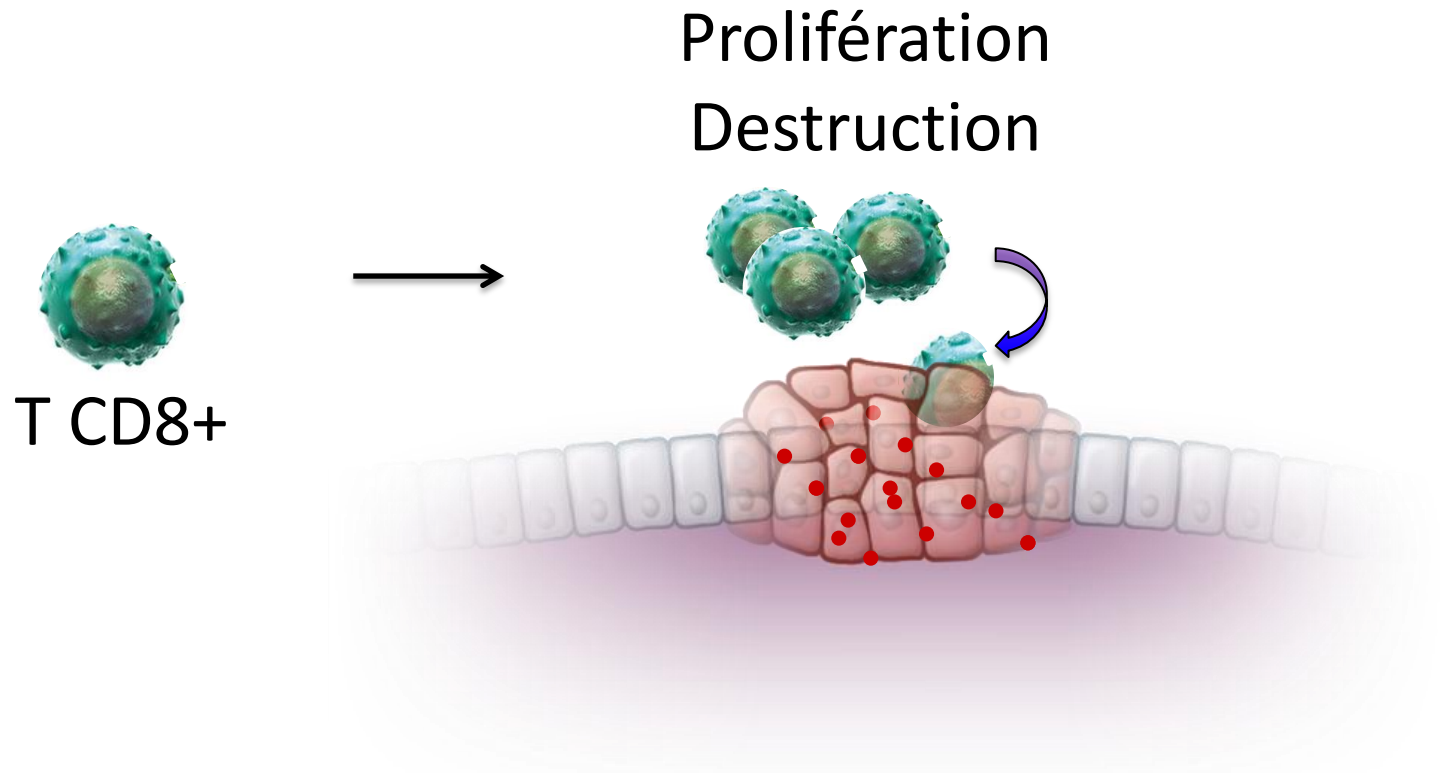


Anti-CTLA-4: Ipilimumab

Diagnostic



Anti-CTLA-4: Ipilimumab



Anti-CTLA-4: Ipilimumab

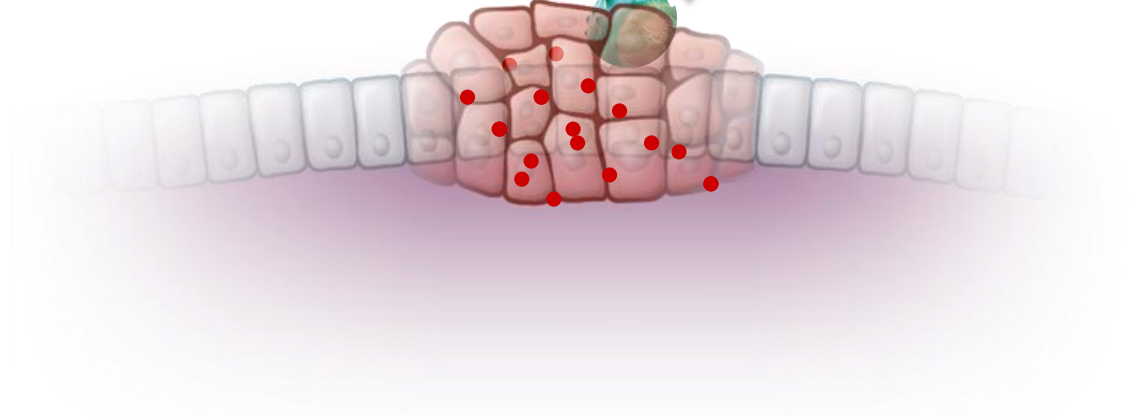
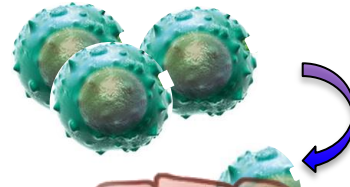
CTLA4



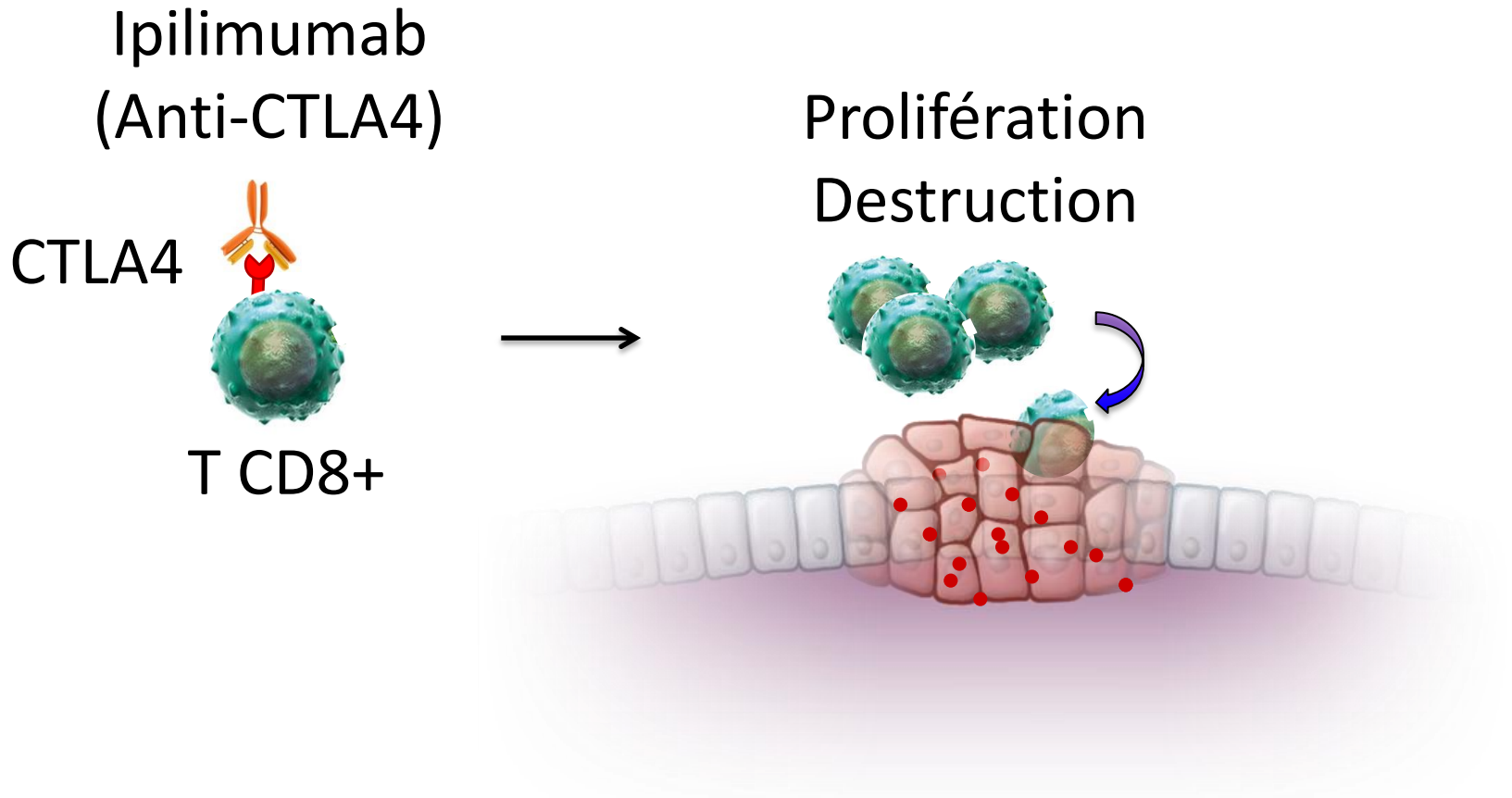
T CD8+



Prolifération
Destruction

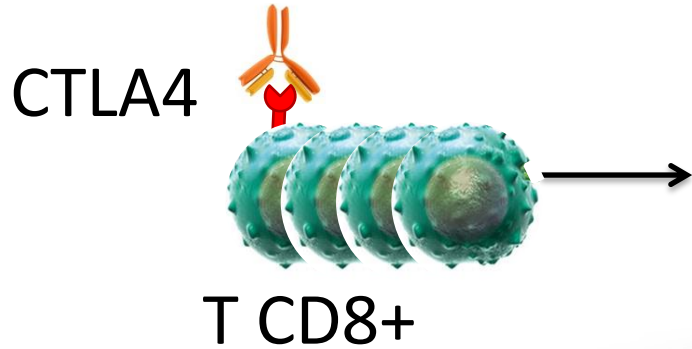


Anti-CTLA-4: Ipilimumab

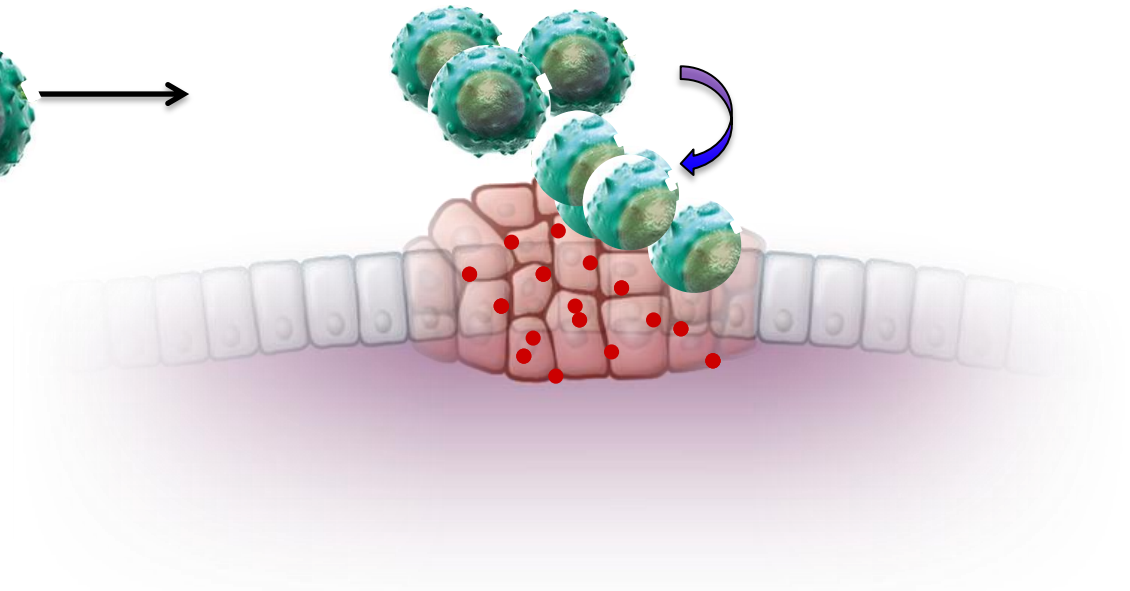


Anti-CTLA-4: Ipilimumab

Ipilimumab
(Anti-CTLA4)

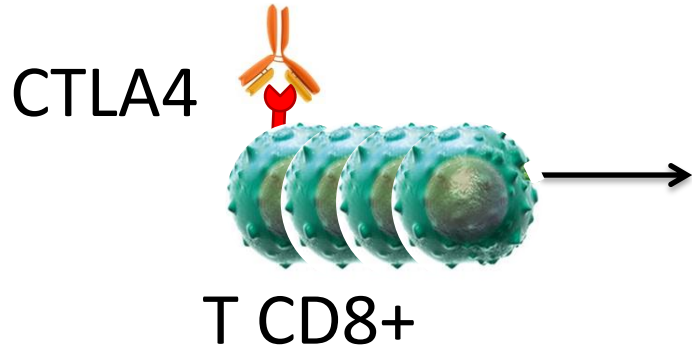


Prolifération Destruction

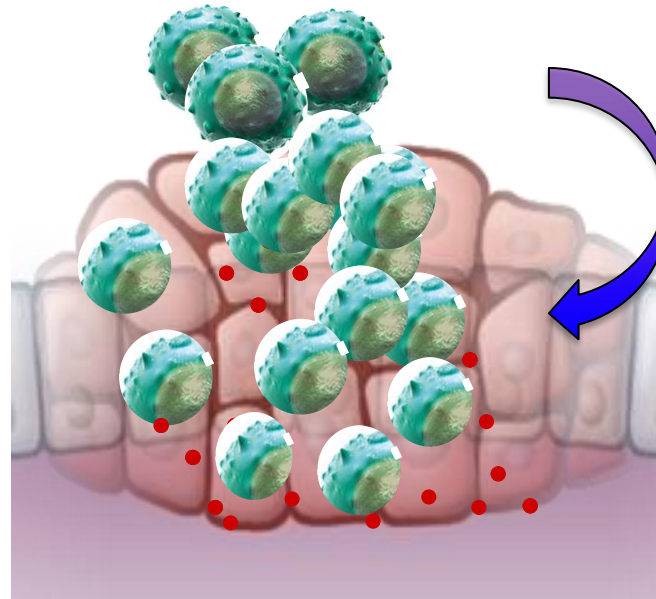


Anti-CTLA-4: Ipilimumab

Ipilimumab
(Anti-CTLA4)



Prolifération
Destruction



Diagnostic



**Semaine 12:
Pseudo-progression**



Diagnostic



**Semaine 12:
Pseudo-progression**



Semaine 16



Semaine 108

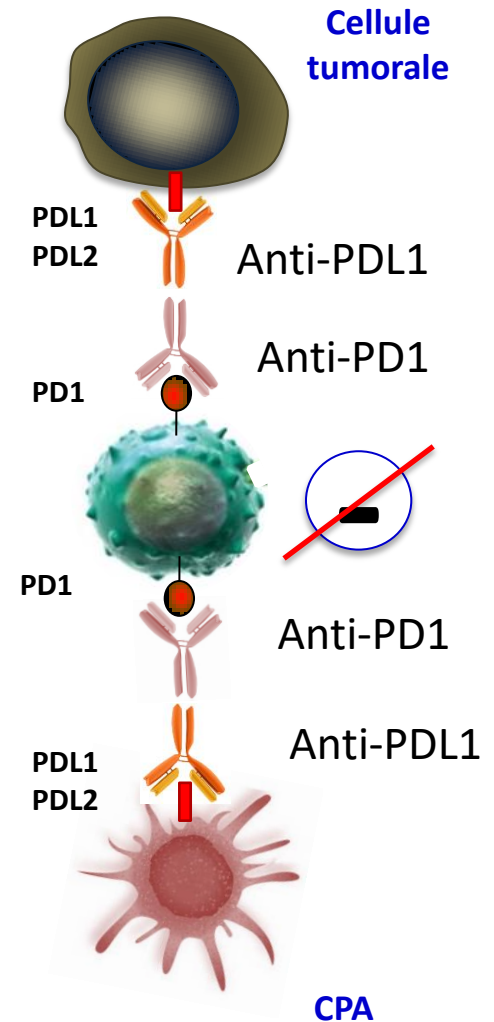


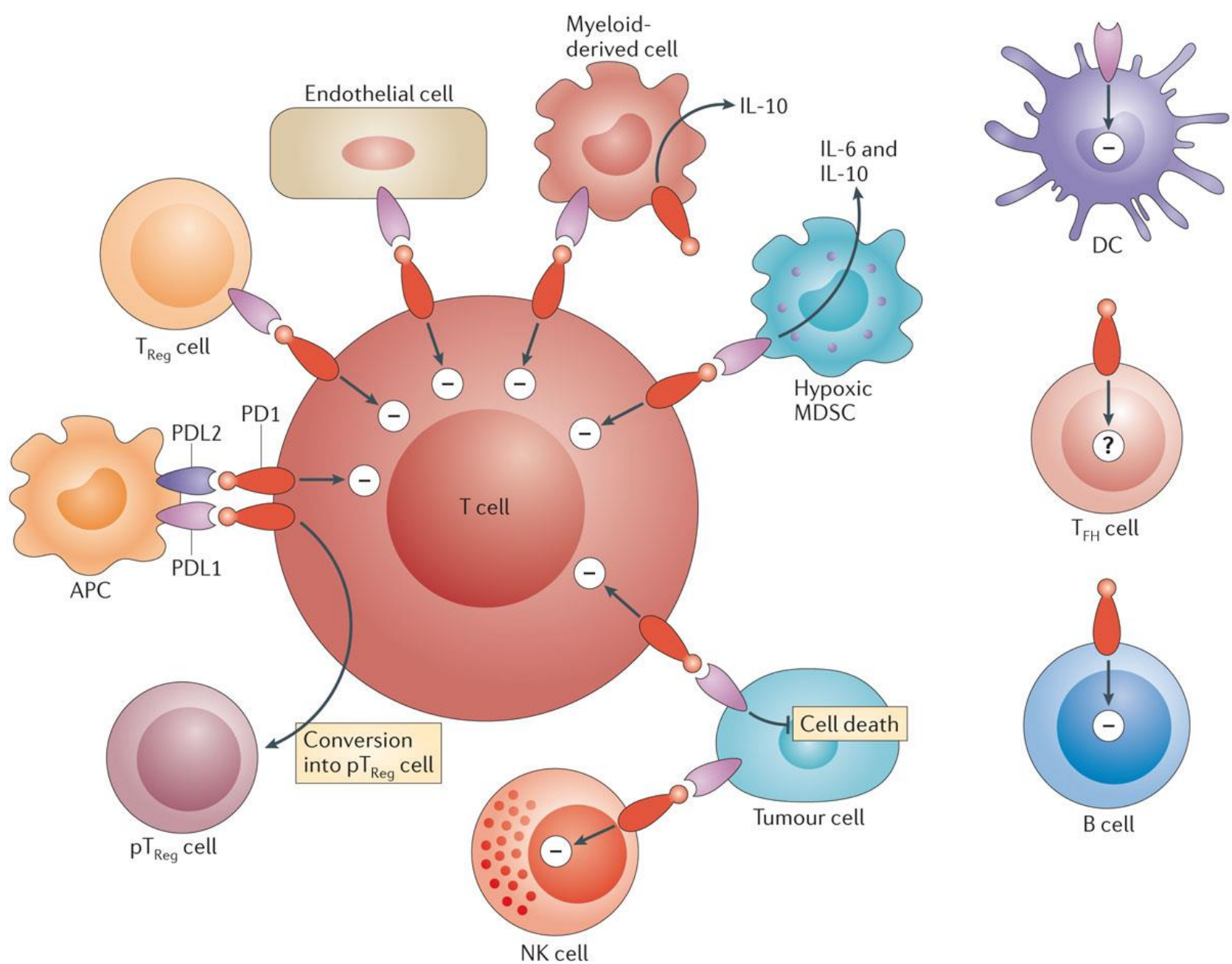
PD-1 / PDL-L1

- Clonage Ishida 1992; molécule de co-signalisation Nishimura 1999; Importance en cancérologie Dong Nat Med 2002
- Molécules de co-signalisation
 - 2 ligands : PDL-1 et PDL-2
 - Impliquées dans la tolérance
- Utilisés en cancérologie: inhibition de signaux négatifs
- Essais de phases I à III en cours
 - *Berger Clin. Can. Res. 2008, Brahmer JCO, 2010, Topalian NEJM 2012, including combo Hamid NEJM, 2013: lymphomas, NSCLC, melanoma, RCC. Brhamer et al. J. Clin. Oncol. 2012, Rosenberg Lancet 2016, Fehrenbacher Lancet 2016.*

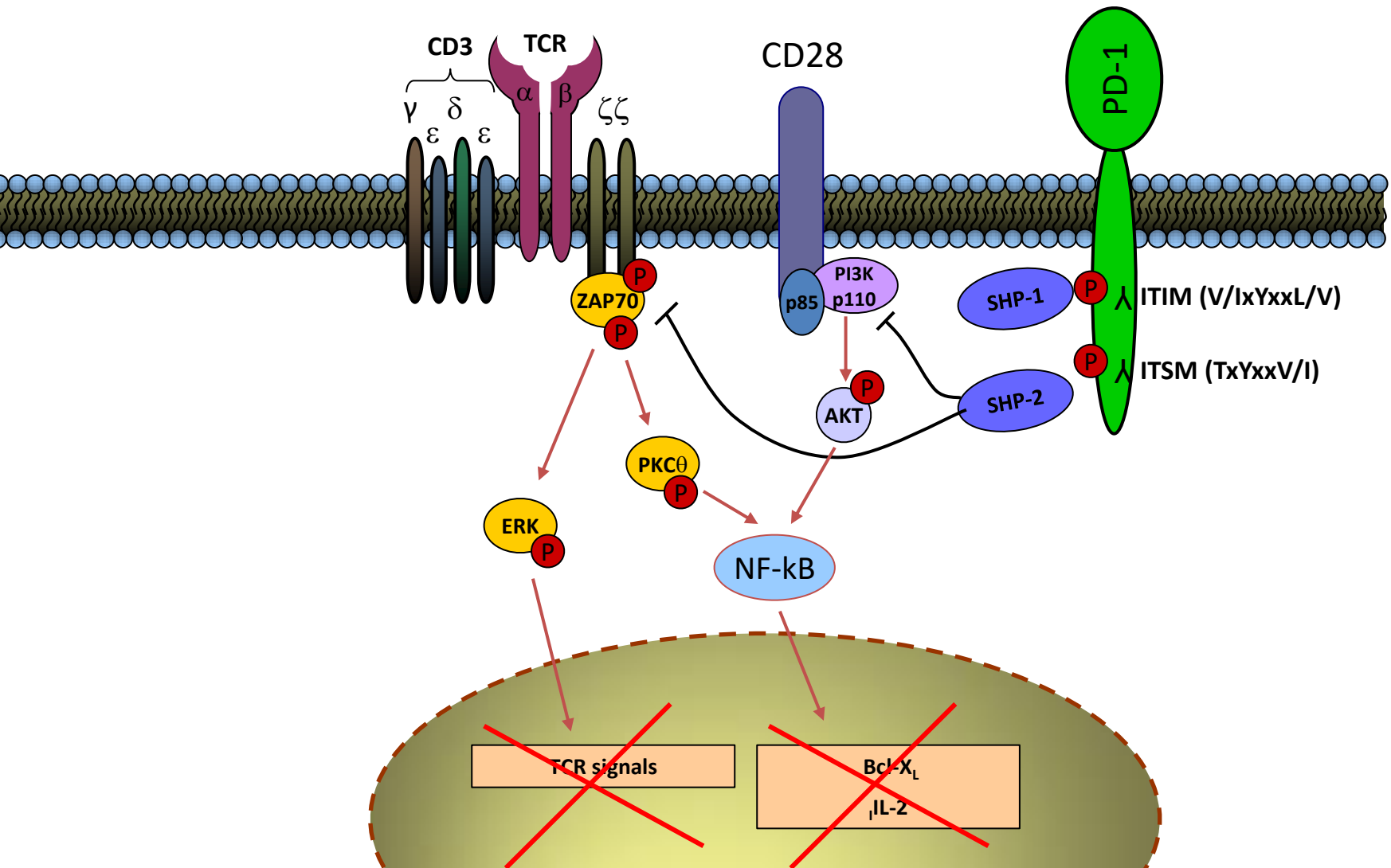
Anticorps anti-PD1: Nivolumab, Pembrolizumab

Anticorps anti-PDL1: Avelumab, Atezolizumab, Durvalumab

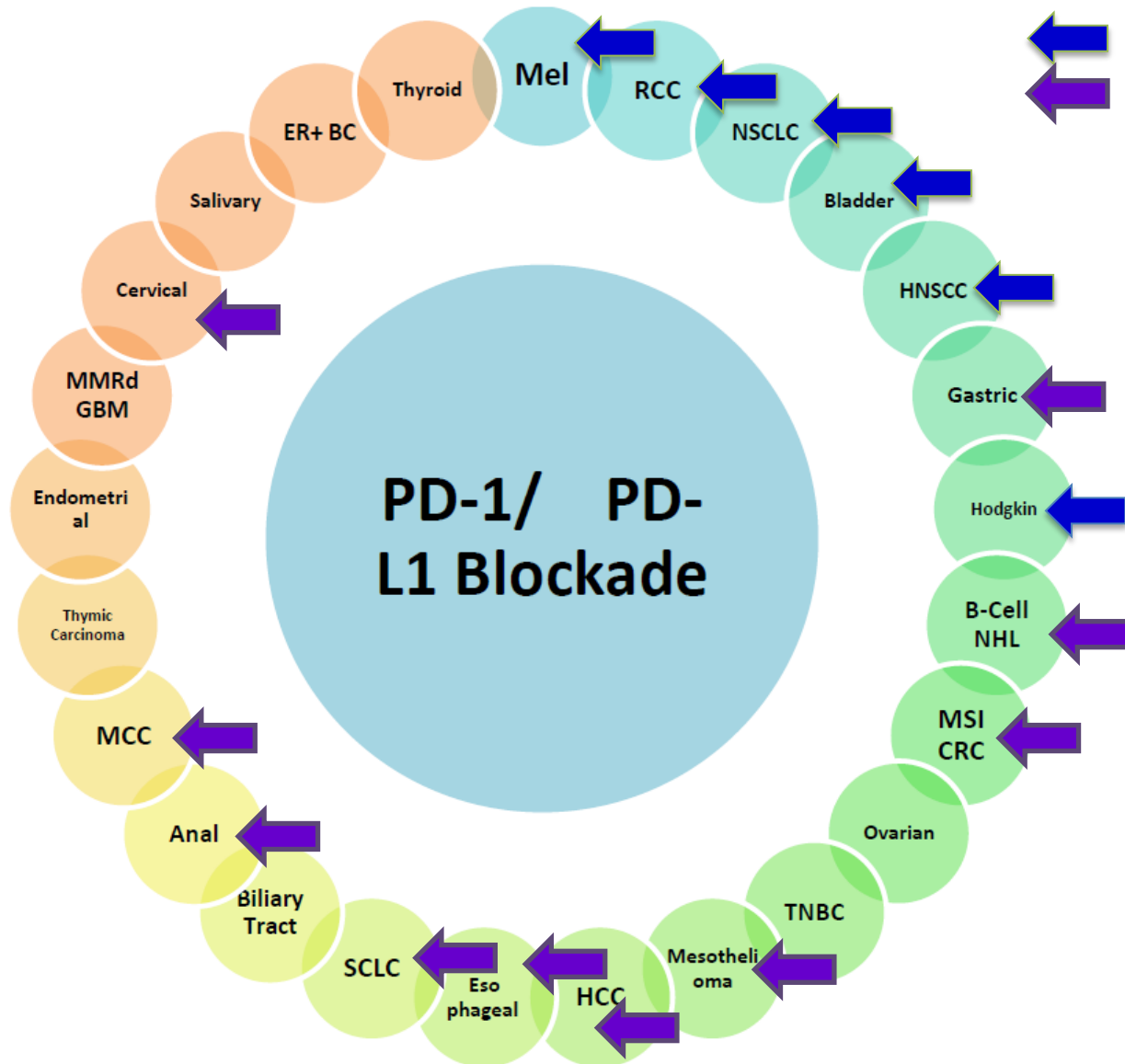




Inhibitory function of PD-1



Très large spectre d'activité



Toxicité checkpoint inhibiteurs

Anti-CTLA4:

Dermatologiques, **gastrointestinaux, endocrinopathies** (axe HH)

→ Corticothérapie

Anti-PD1:

Généralement grade 1/2; 7 à 12% grade 3/4

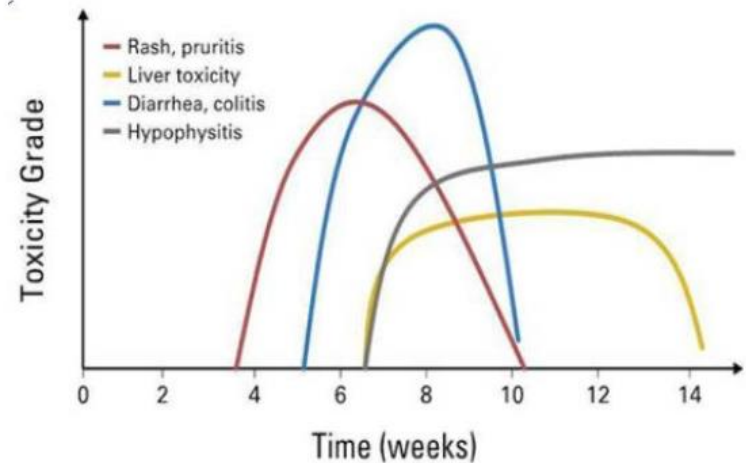
Asthénie, anorexie, rash, **colite/diarrhée**,

nausées, **endocrinopathies**,

pneumopathies interstitielles (2-3%),

néphropathies interstitielles (3%)

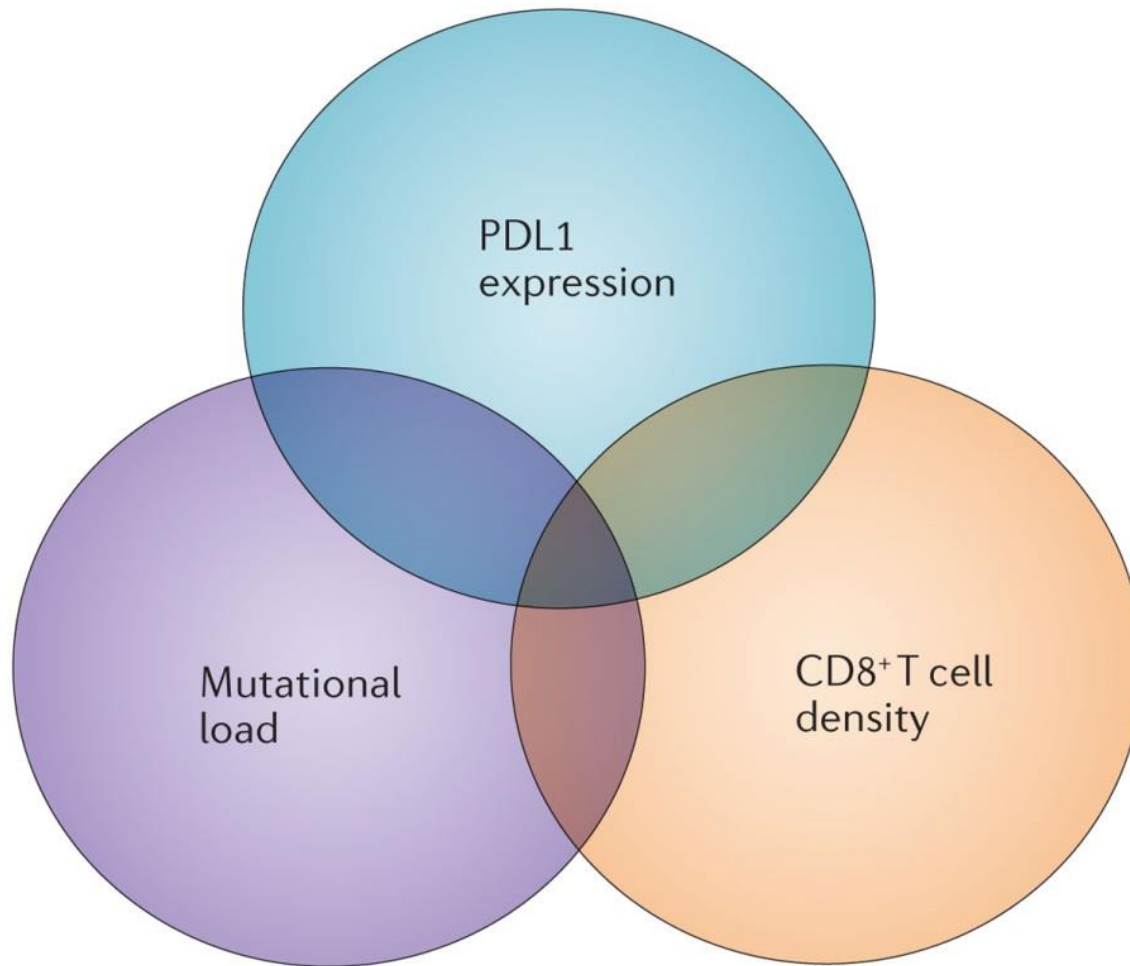
→ Corticothérapie



Questions et enjeux actuels associés à ces traitements

- **Développement de biomarqueurs** prédictifs de réponse aux traitements
- **Classification des patients** pour développer des algorithmes de décision thérapeutiques pour un patient ou un groupe de patients donné
- Immunomonitoring des réponses aux immunothérapies pour le **suivi de l'efficacité des traitements**
- Mise en évidence précoce de leurs **toxicités**
- Déterminer les **combinaisons** optimales et les **schémas de traitement**

Biomarqueurs prédictifs de la réponse thérapeutique aux inhibiteurs de checkpoints.



Nature Reviews | **Cancer**

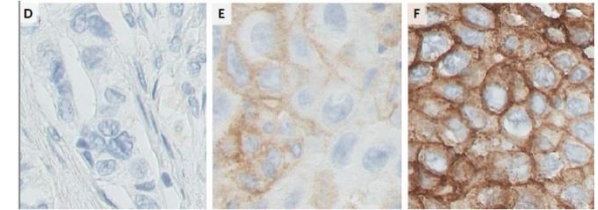
Topalian et al., Nature Reviews Cancer 2016

Expression tumorale de PDL1

NSCLC: détection de PDL1 par IHC

% cellules tumorales PDL1+

Variable continue à discrétiser → seuils

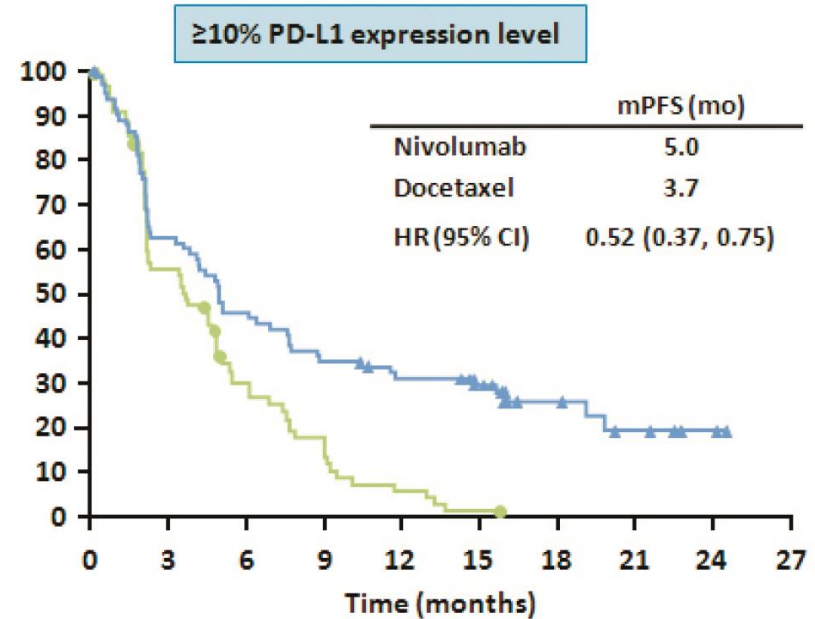
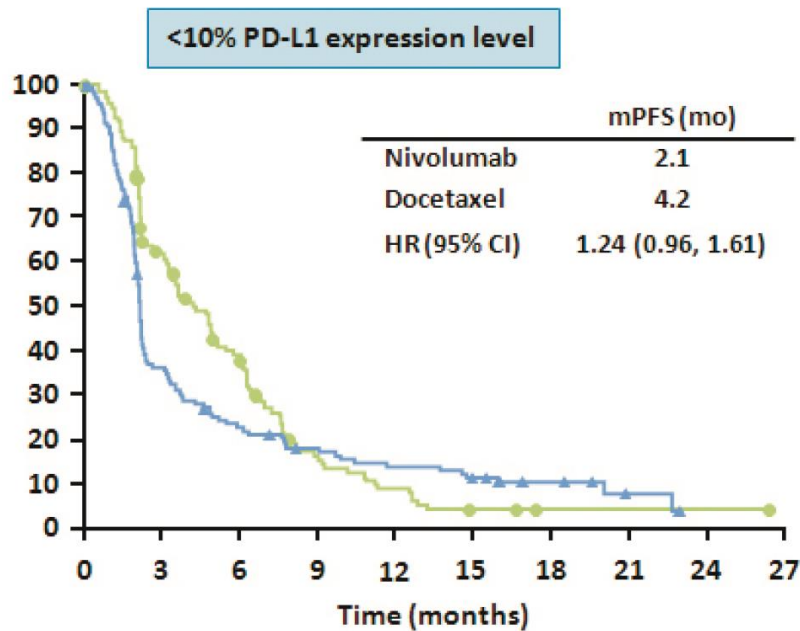


Checkmate 057: Nivolumab vs docetaxel in Non squamous non small cell lung cancer:

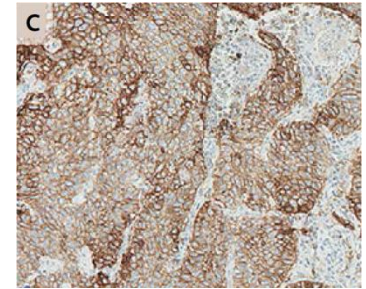
OS associated with PDL1 expression

Phase III

N=582



Expression tumorale de PDL1: les limites



Garon NEJM 2015

Disponibilité tissus tumoral

Définition de seuils

Stabilité expression PDL1 dans le temps

Immunothérapie: $\nearrow$ ou $\searrow$ expression PDL1

Radiothérapie $\nearrow$ PDL1

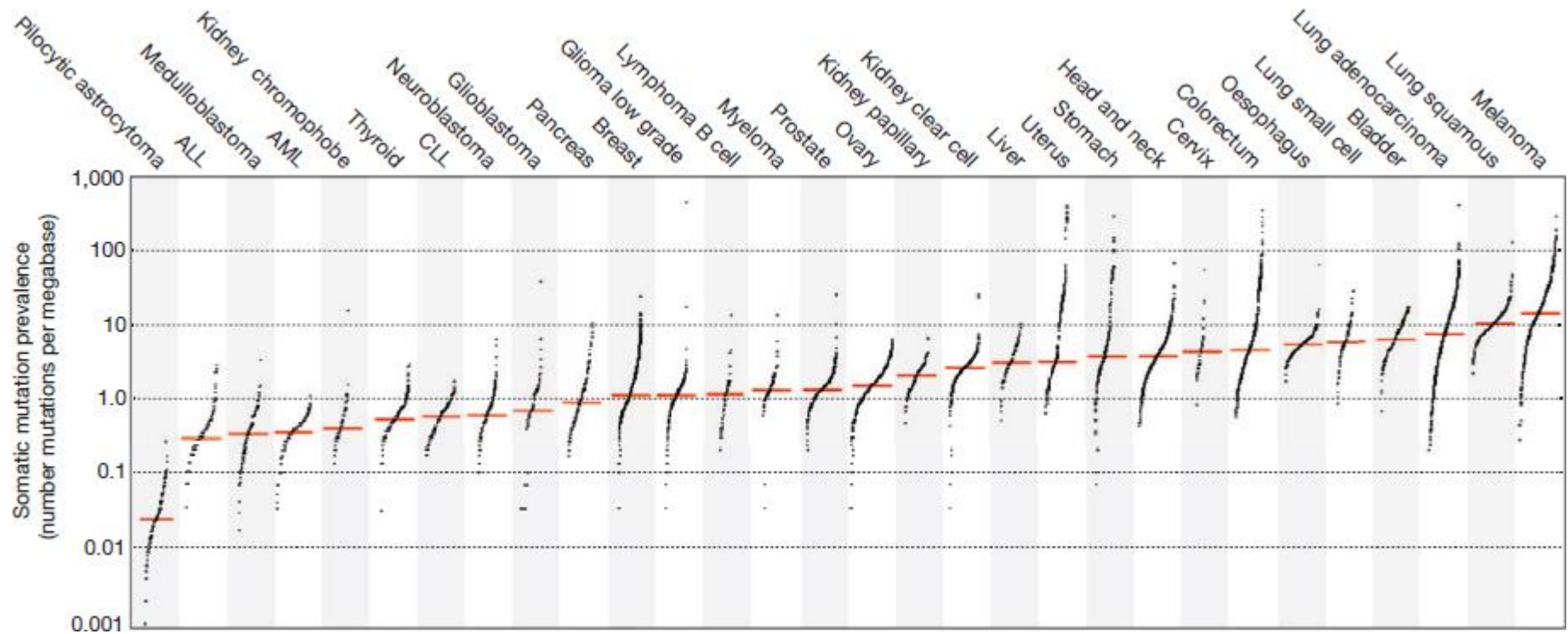
Stade (méta vs non méta)

Multiples tests (Dako, Ventana) : discordances (Sica et al JAMA Oncol 2017)

Hétérogénéité des tissus $\rightarrow$ biopsie

Expliquerait les réponses sous anti-PD1/PDL1 chez patients PDL1-

Charge mutationnelle

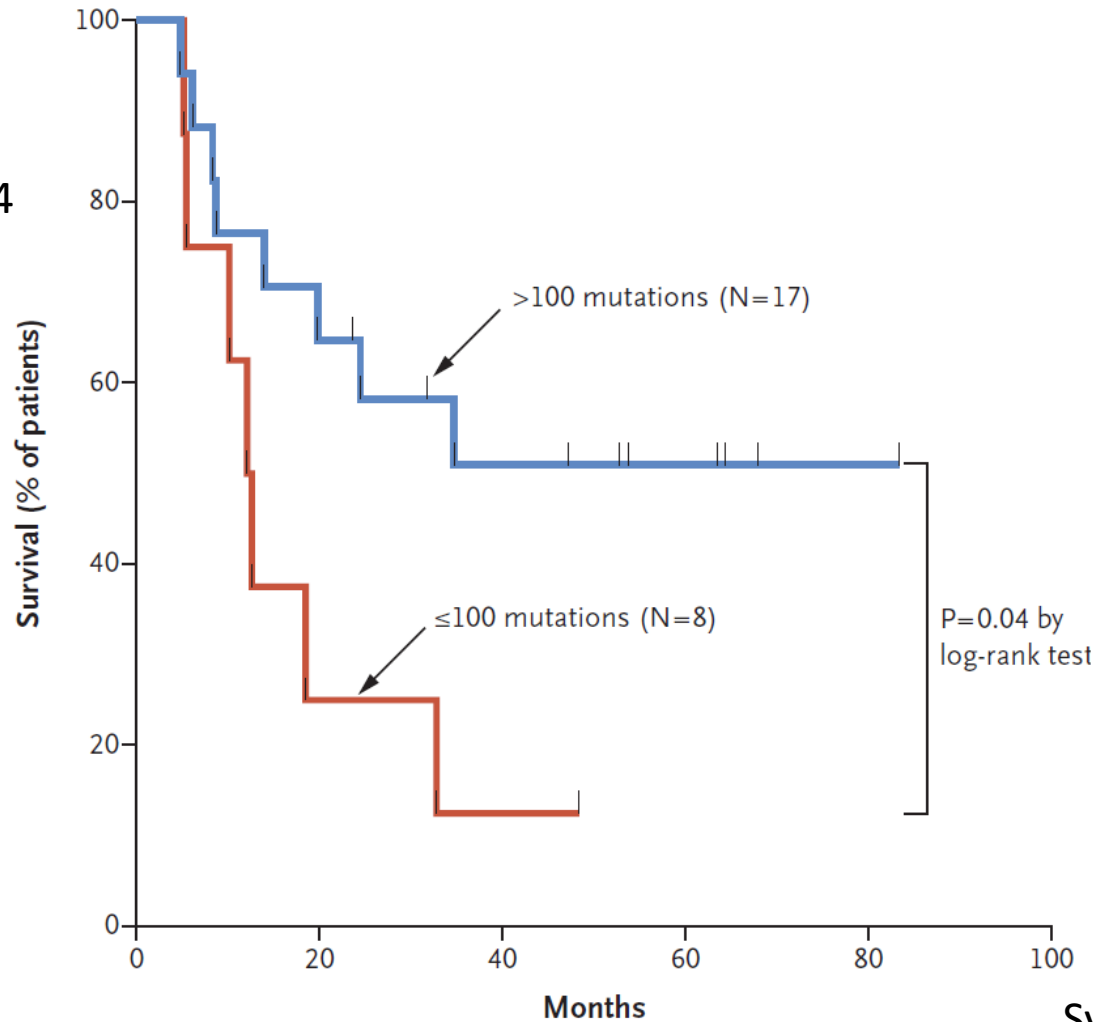


Neoantigens in cancer immunotherapy
Schumacher and Schreiber Science 2015

Charge mutationnelle

B Survival in Discovery Set

N= 64 patients
Metastatic melanoma
Treatment: Anti-CTLA4



Synder NEJM 2014

Neoantigens in cancer immunotherapy
Schumacher and Schreiber Science 2015

Take-home message

La plupart des cancers sont immunogènes

Les tumeurs humaines expriment des antigènes tumoraux

Antigènes reconnus par le système immunitaire

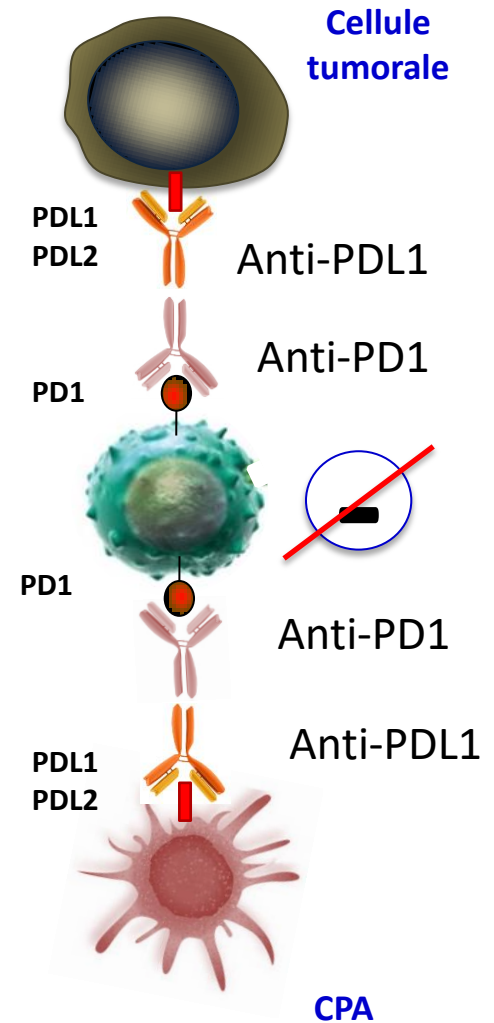
→ base des essais de vaccination anti-tumorale

Phénomènes de tolérance/échappement à l'immunité innée et adaptative

Stimulation possible de ce système: levée des mécanismes d'inhibition

→ Inhibiteurs d'immune checkpoints: anti-CTLA4, anti-PD1, anti-PDL1

→ Induction de la co-stimulation: CD40, 41BB, ICOS



**Aix Marseille Université, CRCM, Cancer
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