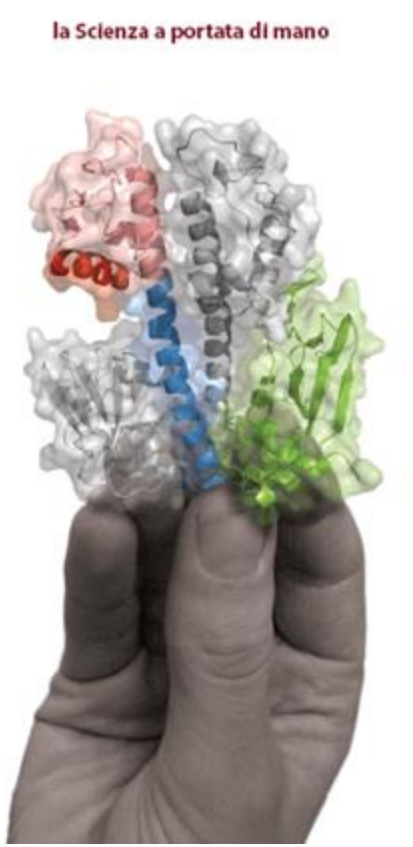
SAPIENZA
UNIVERSITÀ DI ROMA

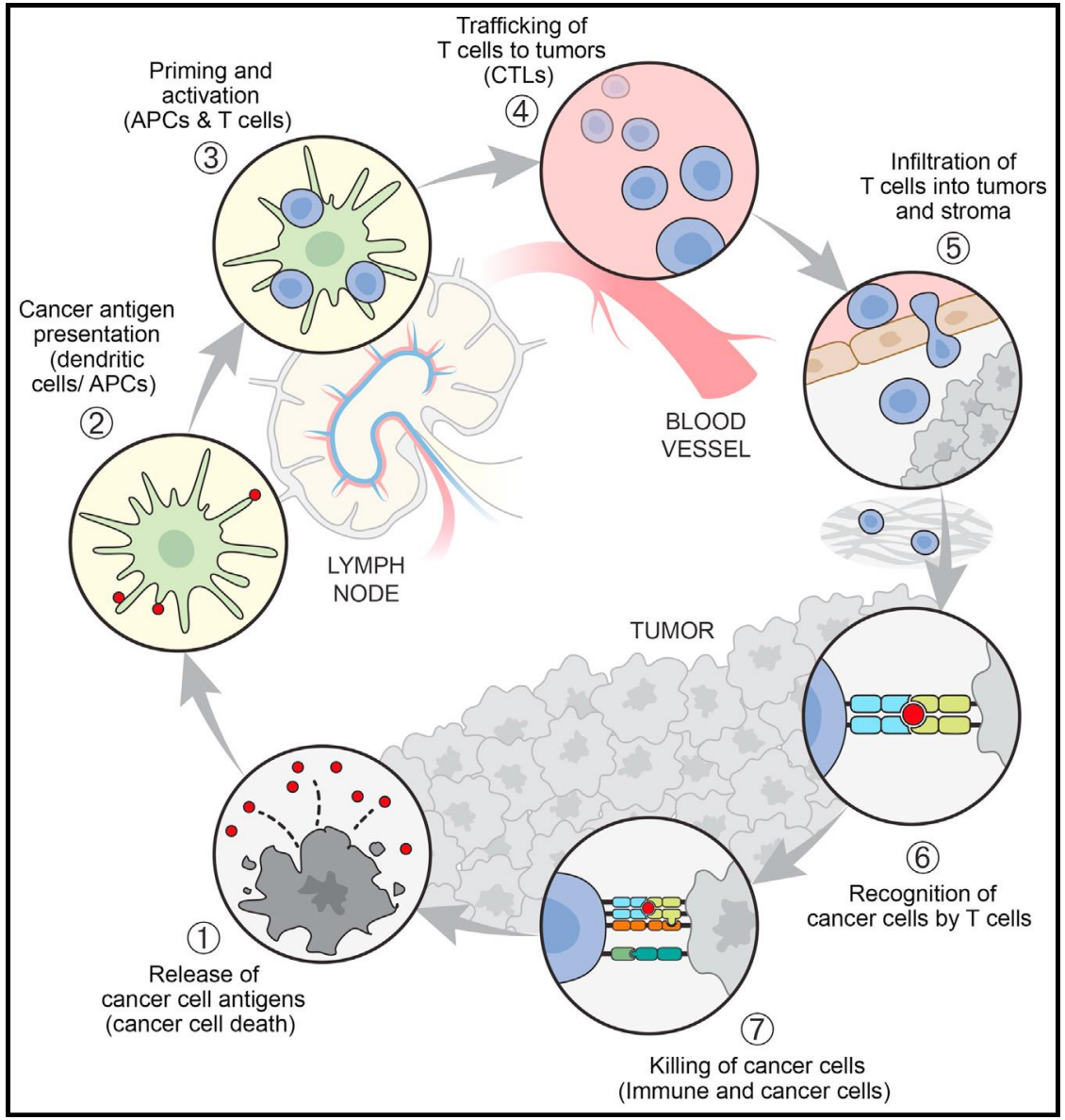


Comunicazione delle Scienze Biomediche

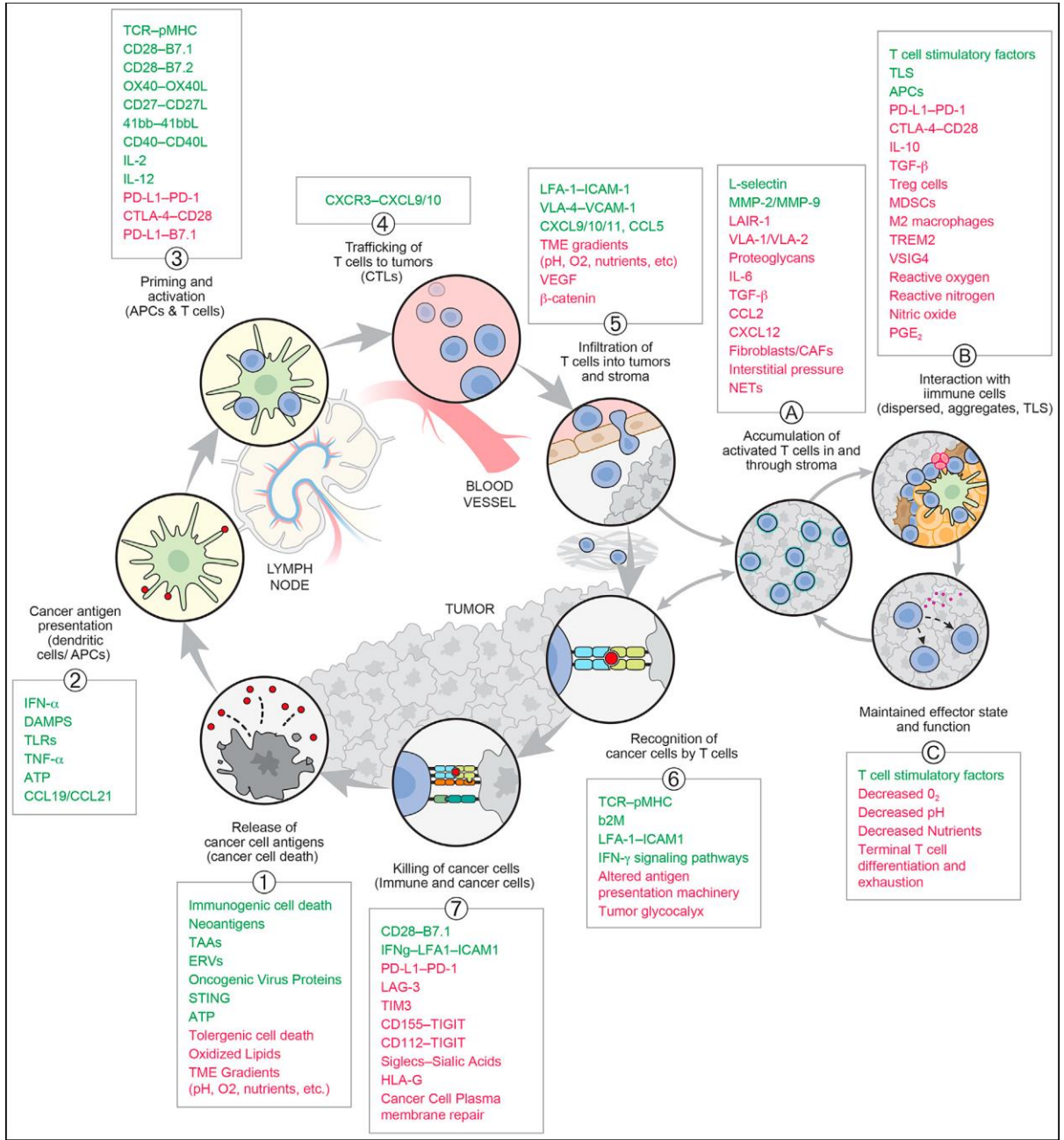
Prof.ssa Cristina Cerboni

Anno Accademico 2023-2024
"Immunità e tumori"

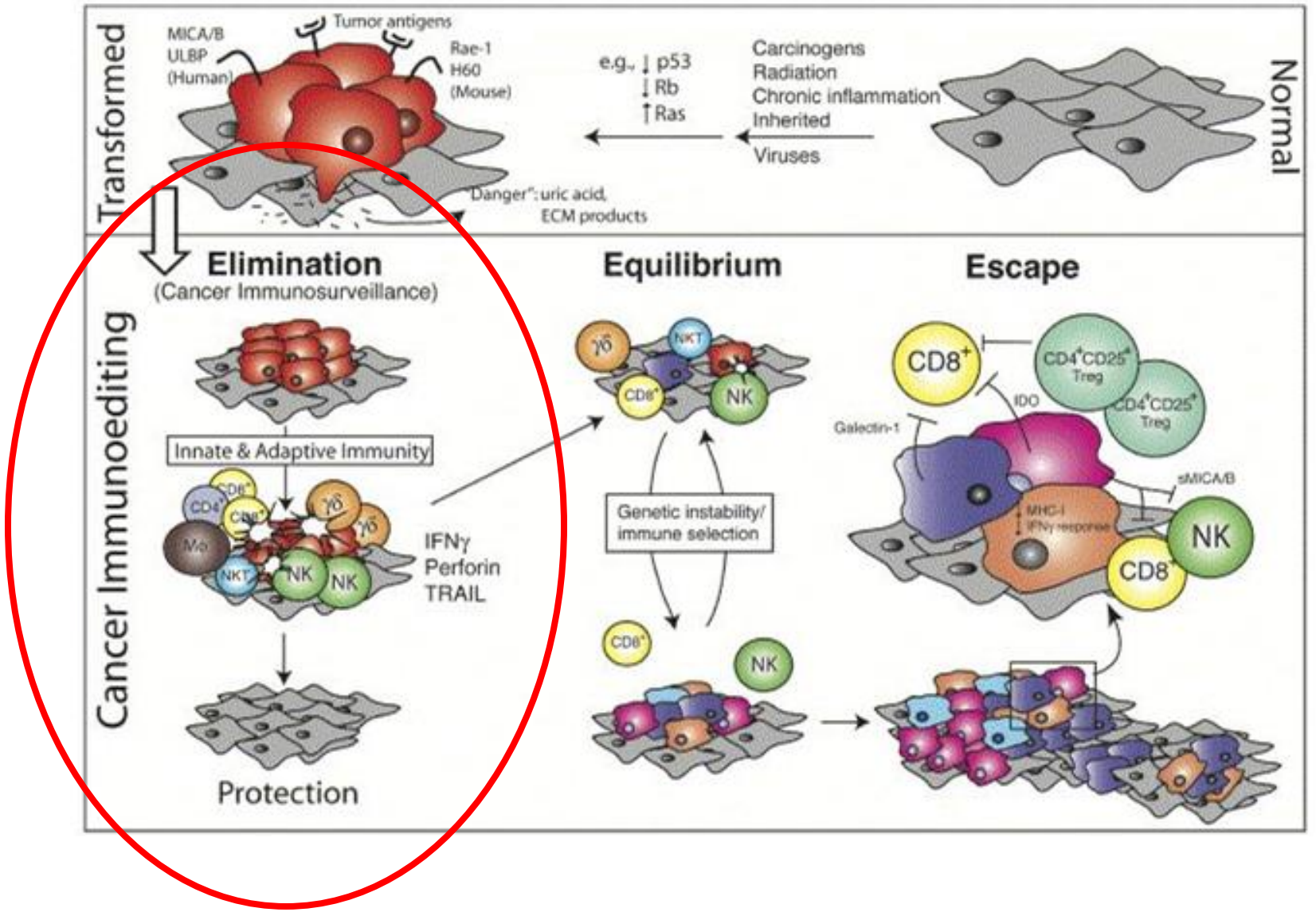
The Cancer-Immunity Cycle



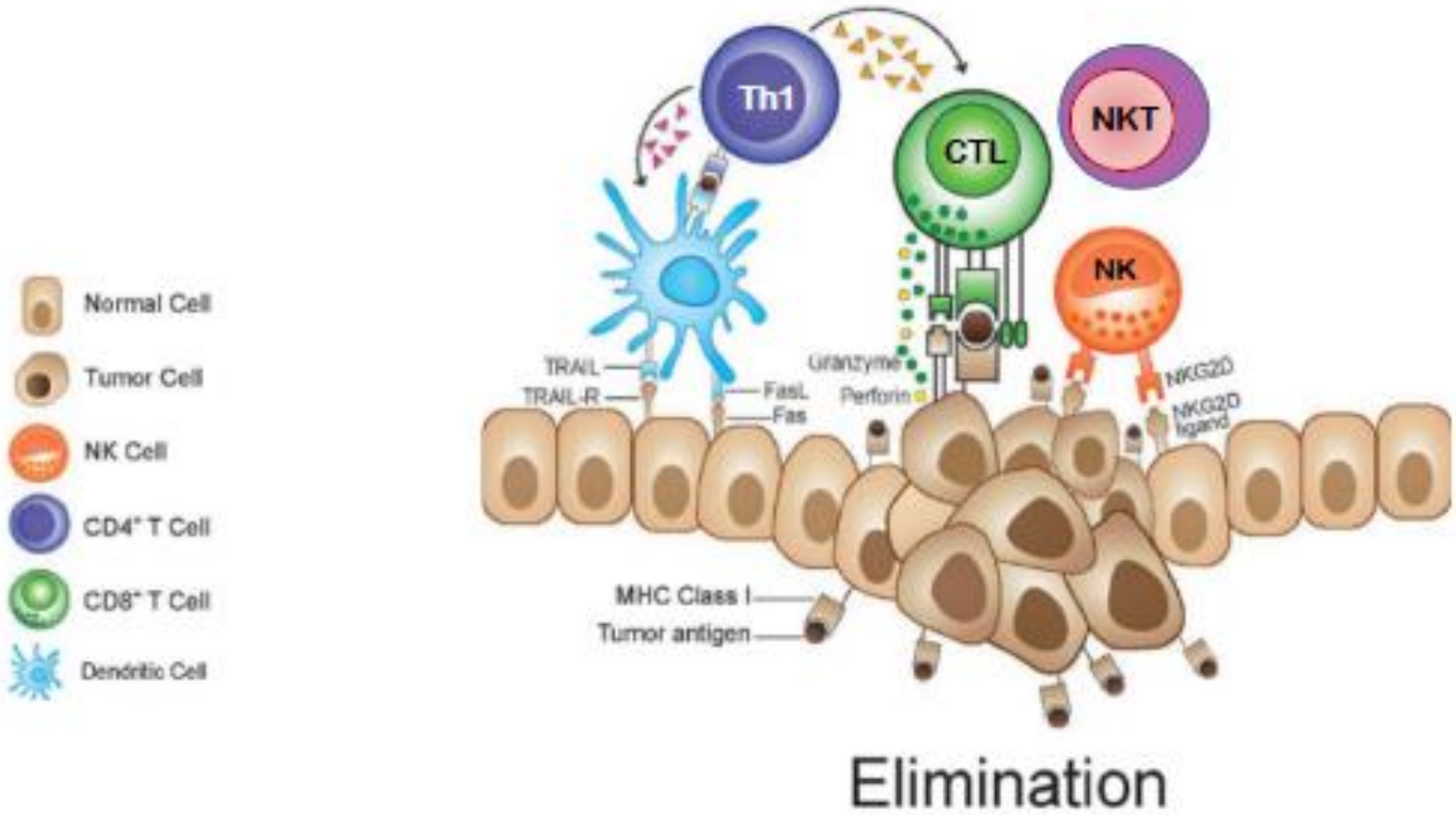
The cancer-immunity cycle with stimulatory and inhibitory factors



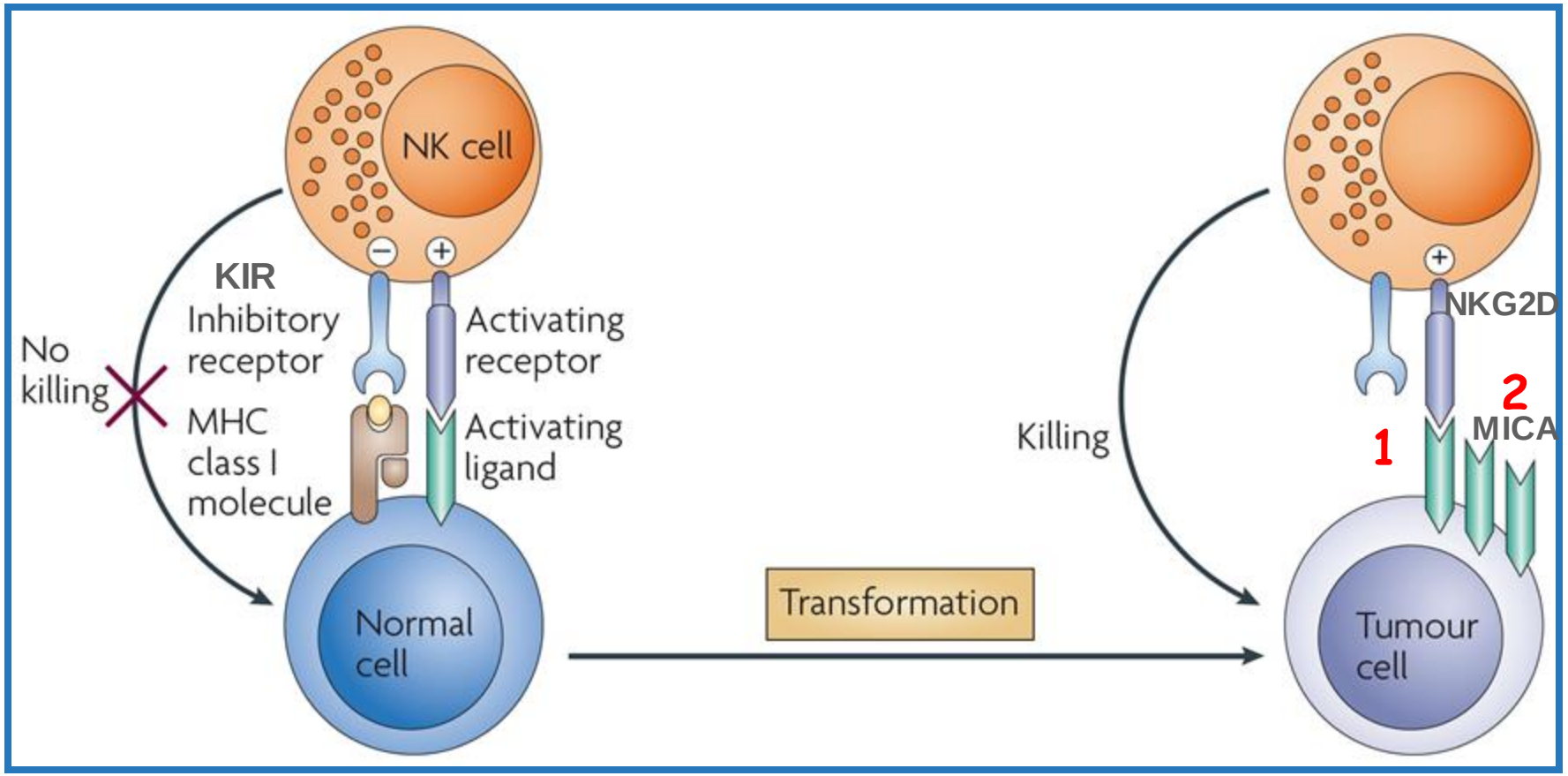
The immune system establishes a dynamic interaction with the tumour: cancer immunoediting



Dunn et al Immunity 2004

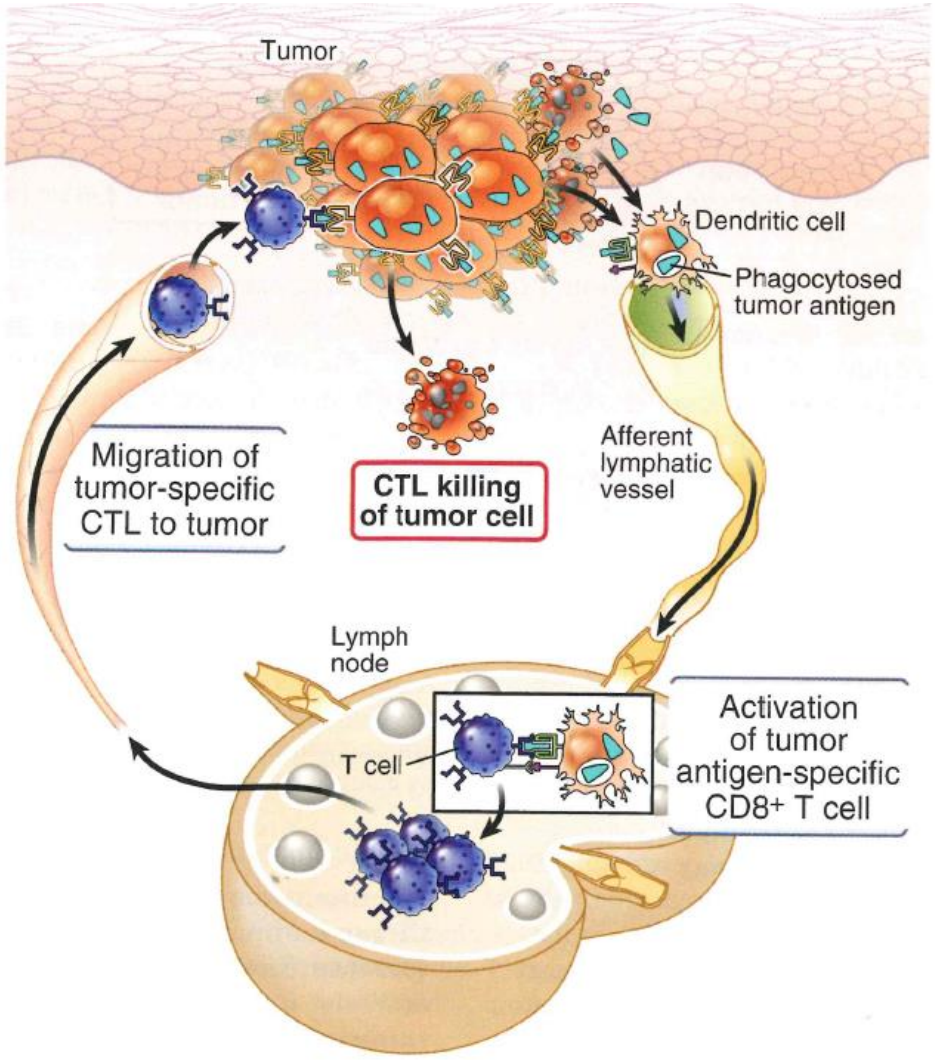

Normal Cell
Tumor Cell
NK Cell
CD4+ T Cell
CD8+ T Cell
Dendritic Cell
Th1
CTL
NKT
NK
TRAIL
TRAIL-R
FasL
Fas
Granzyme
Perforin
NKG2D
NKG2D ligand
MHC Class I
Tumor antigen
Elimination

Le cellule NK eliminano una cellula tumorale attraverso il *missing-self* (1) e l'*induced-self* (2)



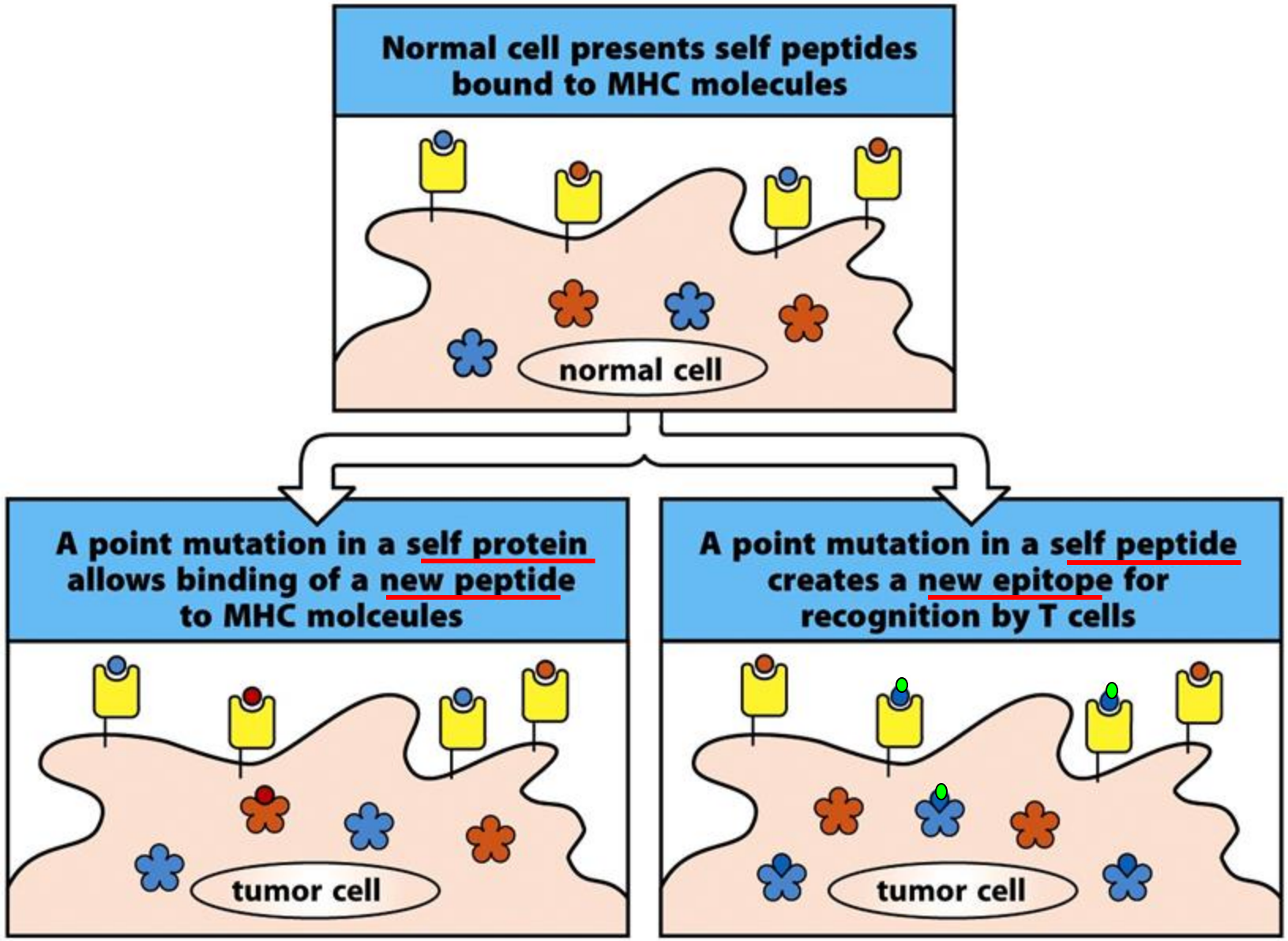
il *missing-self* (1) è la perdita di inibizione (MHC-I);
l'*induced-self* (2) è una "super-attivazione" (MICA, ULBPs)

The principal mechanism of immune protection against tumors is killing of tumor cells by CD8+ CTLs



Gli antigeni tumorali

Gli antigeni tumorali possono derivare da proteine mutate…



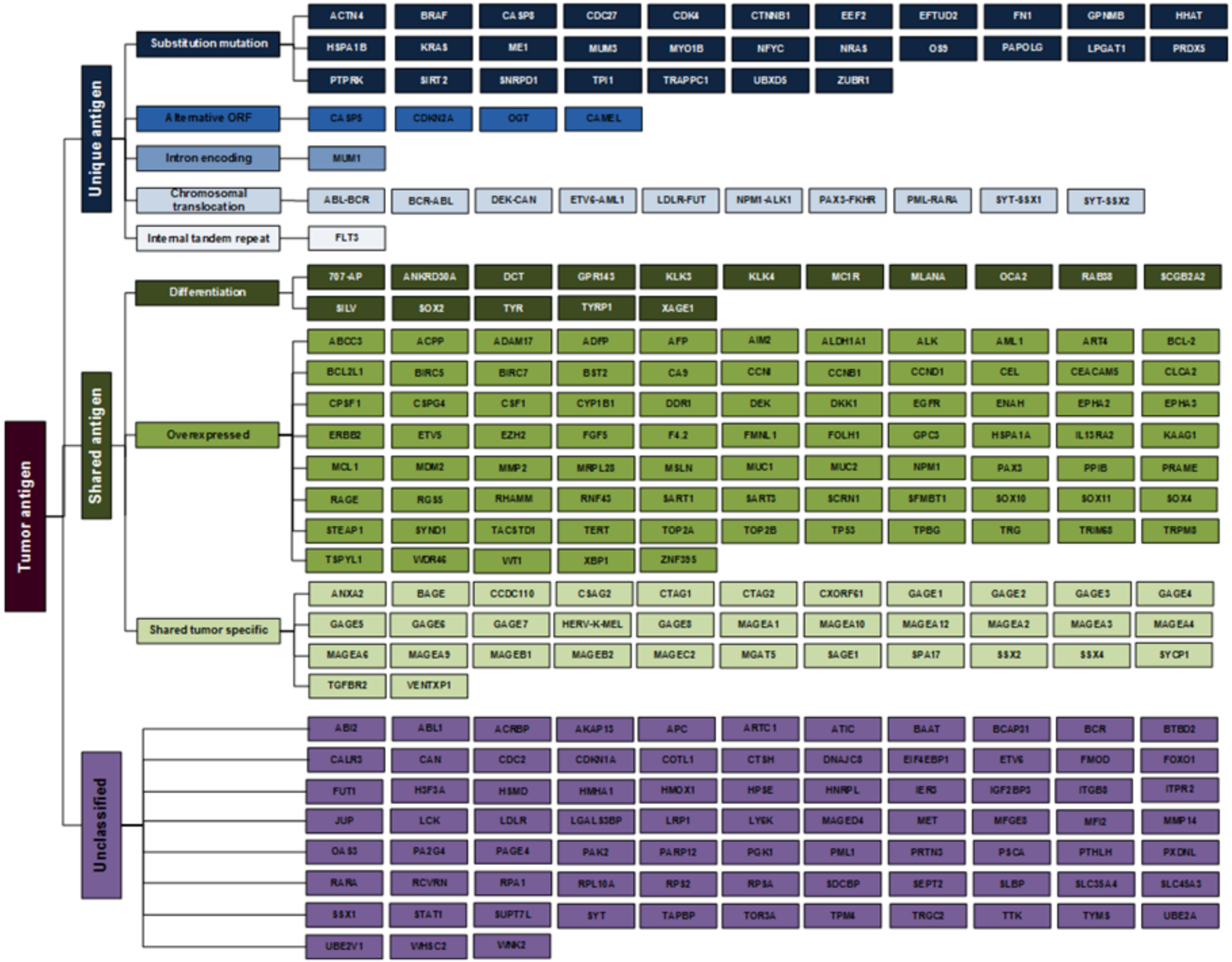
… ma anche da proteine non mutate

Antigen type	Description	Examples of antigen type
Tumour-specific antigens[8,9] TSA	• Completely absent from normal host cells • Arise in cancer cells from oncogenic viral proteins or nonsynonymous somatic mutations	• HPV oncoproteins E6 and E7 (HPV-associated cancers of the cervix, anus and oropharynx)[11,12] • Individual KRAS mutations (pancreatic, colon, lung and various other cancers)[10,19]
Tumour-associated antigens[9] TAA	• Low levels of expression on normal host cells • Disproportionately expressed on tumour cells • Often result from genetic amplification or post-translational modifications • Can be selectively expressed by the cell lineage from which the cancer evolved	• ERBB2 (some breast cancers and various other cancers)[158] • Mesothelin (pancreatic cancer and mesothelioma)[159–161] • CD19 on B cell malignancies[27,28]
Cancer/testis antigens[13,14] CTA	• Absent on normal adult cells, except in reproductive tissues (e.g. testes, fetal ovaries and trophoblasts) • Selectively expressed by various tumour types	• MAGE (various cancers)[162] • NY-ESO-1 antigen (various cancers)[163]

Yarchoan M et al. Nature Rev Cancer 2017

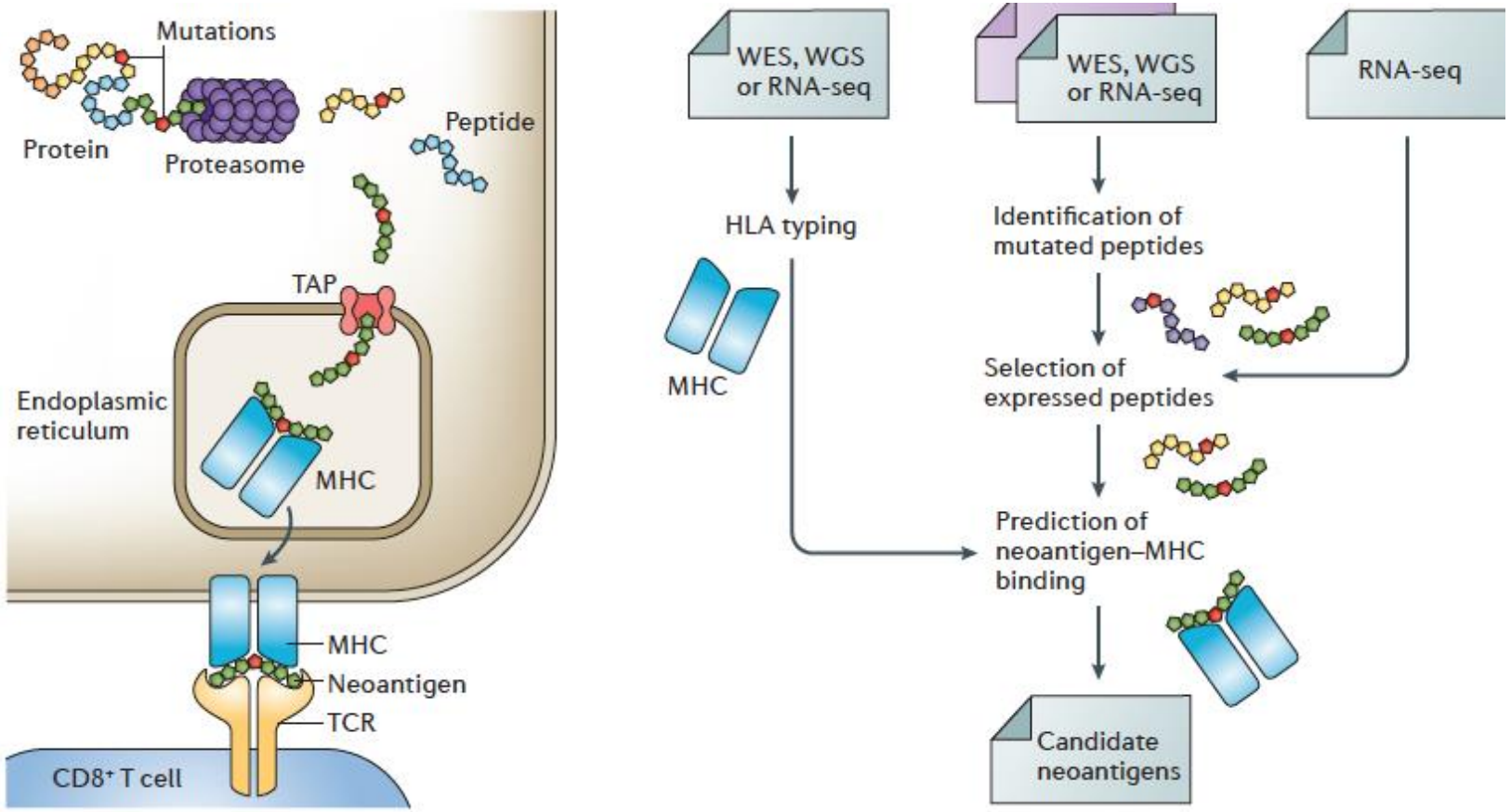
ANTIGENI TUMORALI UMANI

- **Prodotti di geni amplificati o mutati (HER-2/neu).**
- **Prodotti di oncogeni o geni onco-soppressori (Ras, Bcr-Abl, p53).**
- **Prodotti di virus oncogeni (E6 ed E7 del papilloma virus; EBNA-1 del virus di Epstein-Barr).**
- **Antigeni tumorali/testicolari: normalmente silenti nei tessuti normali (tranne testicolo e trofoblasto), ma espressi da molti tumori (MAGE).**
- **Antigeni oncofetali: espressi nei tessuti fetali in via di sviluppo e da molti tumori nell'adulto, ma non dai tessuti normali (CEA, AFP).**
- **Antigeni di differenziazione tissutale (tirosinasi dei melanociti, antigene prostatico specifico/PSA, CD10, CD20).**
- **Glicolipidi e glicoproteine alterate (MUC-1).**



TANTIGEN: Classification of tumor antigens

Developed by Bioinformatics Core at Cancer Vaccine Center, Dana-Farber Cancer Institute.

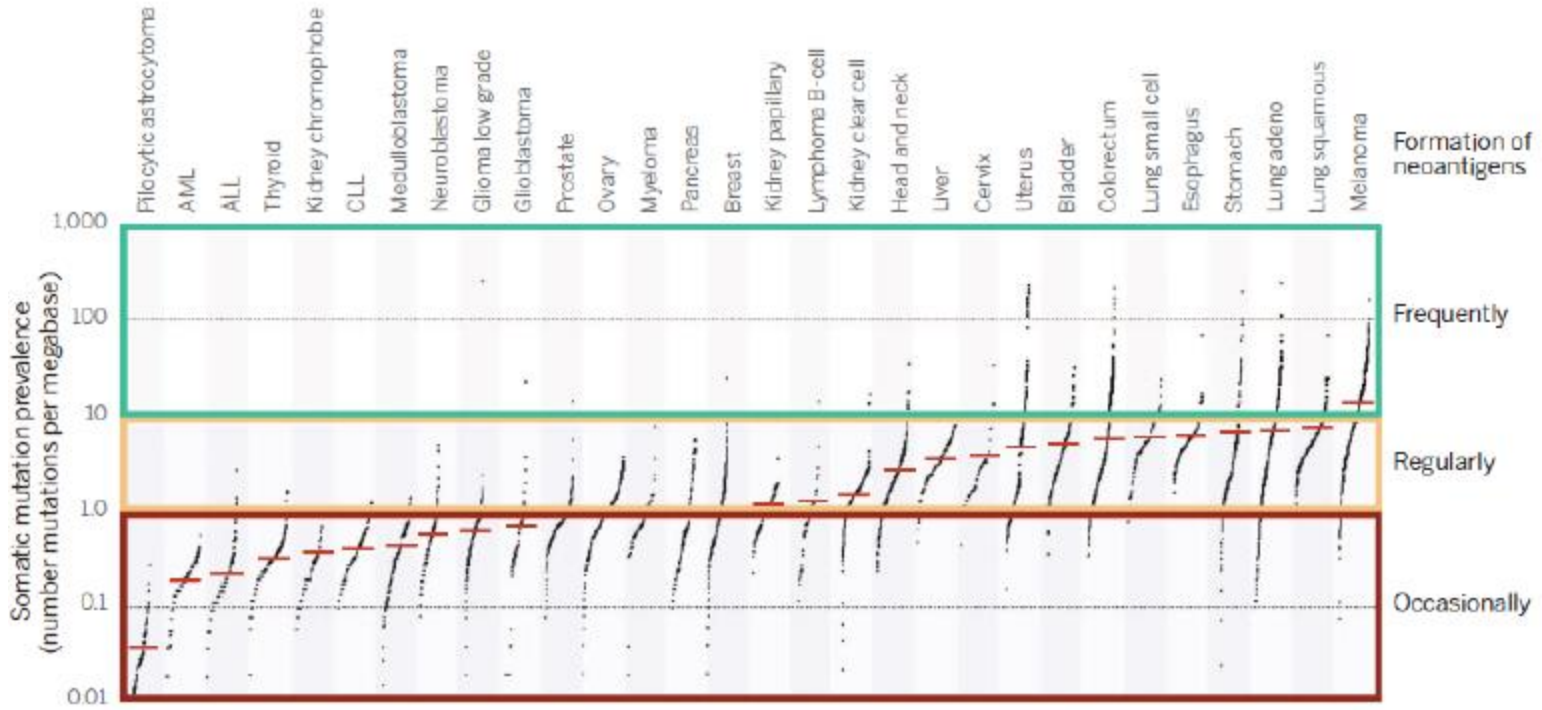


Cancer whole exome sequencing

- Driver mutations
- Passenger mutations
- Nonsynonimous mutations

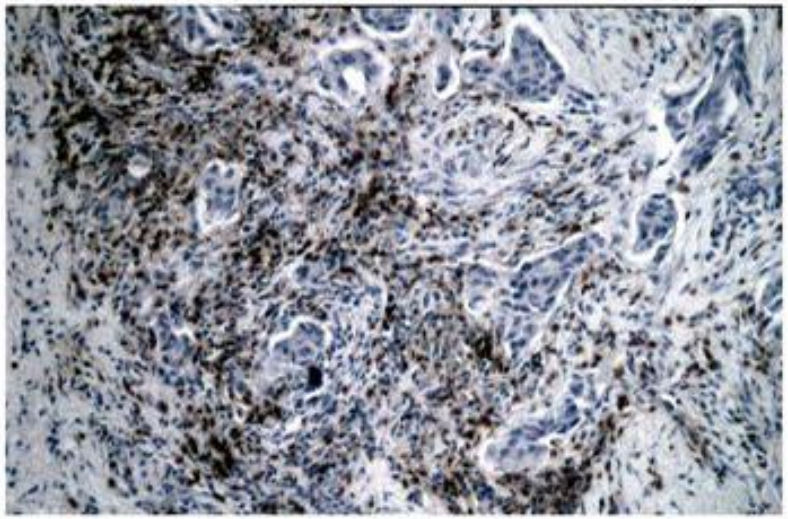
Neoantigens

Estimate of the neoantigen repertoire in human cancers

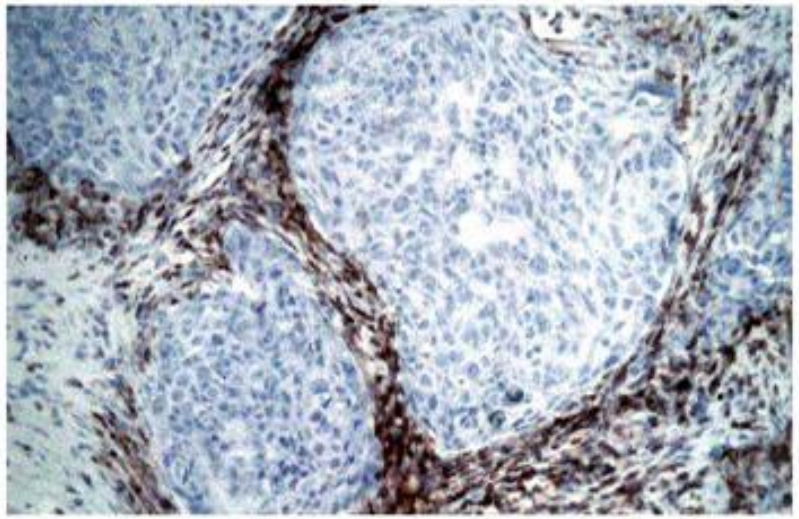


Schumacher TN and Schreiber RD, Science 2015

I linfociti T devono essere localizzati nel posto giusto!

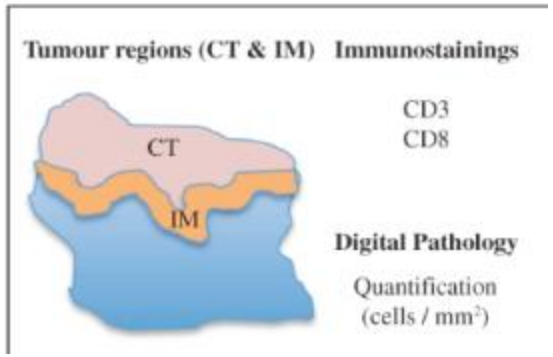


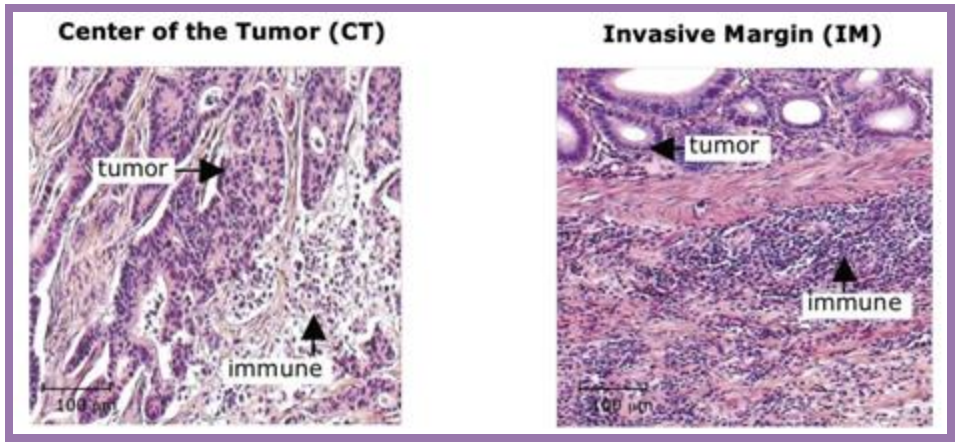
CD3+ INTRATUMORALI

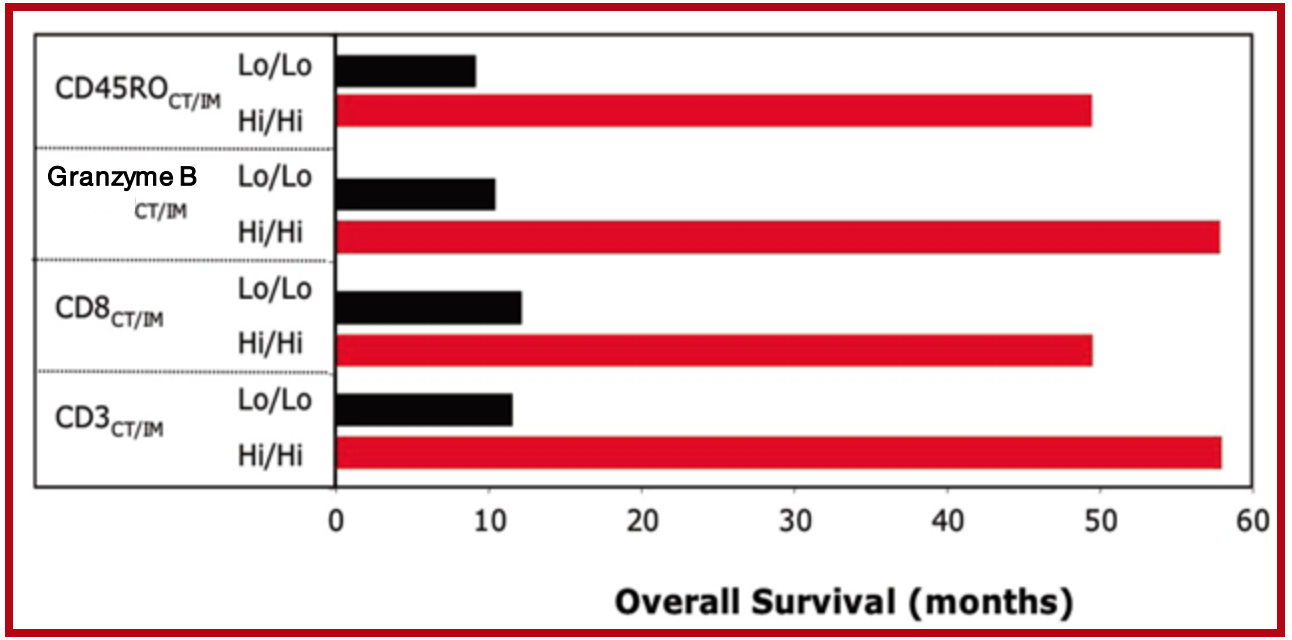


CD3+ PERITUMORALI

Tanti, di buona qualità e nel posto giusto: come la presenza dei linfociti T correla con una prognosi migliore nel cancro del colon-retto





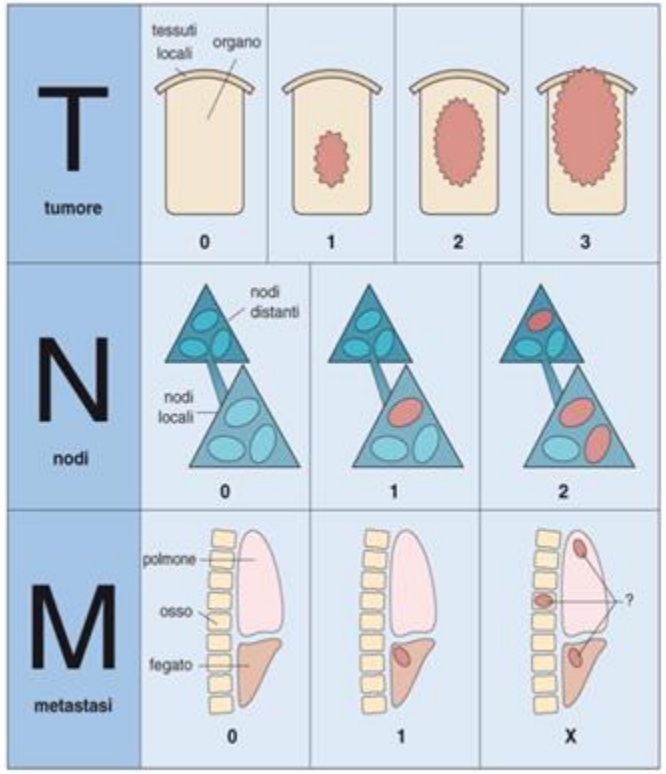


Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,[3*†] Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[1] Bernhard Mlecnik,[2] Christine Lagorce-Pagès,[3] Marie Tosolini,[1] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[5] Patrick Bruneval,[6] Paul-Henri Cugnenc,[5] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[1,7] Franck Pagès[1,7†]

29 SEPTEMBER 2006 VOL 313 SCIENCE www.sciencemag.org

Galon J et al, NEJM 2005 & Science 2006



Stadiazione e (staging)

A. Stevens, J. Lowe, I. Scott Patologia, terza edizione

T cells — **Memory**

TNM staging: a new view?

Tumor — **Lymph Node** — **Metastasis**

A new view in cancer staging?
T is for T cells and M is for Memory

4

immuno-score (IS)

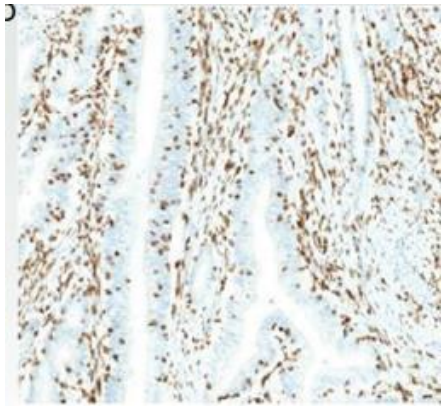
0

Low density
«Bad»

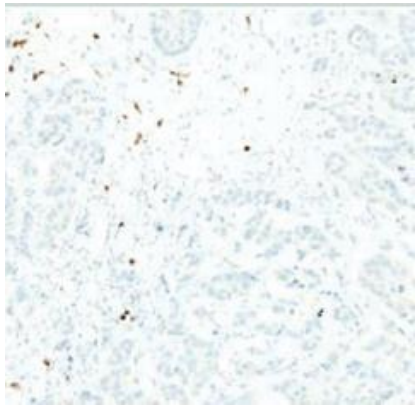
(tumori invasivi, metastasi)

High density
«Good»

(tumori in situ, o localizzati)



CD3 staining



CD3 staining

Immuno score: CD8+/CD45+RO+/GRZB+ in CT (center of the tumour) e IM (invasive margin)

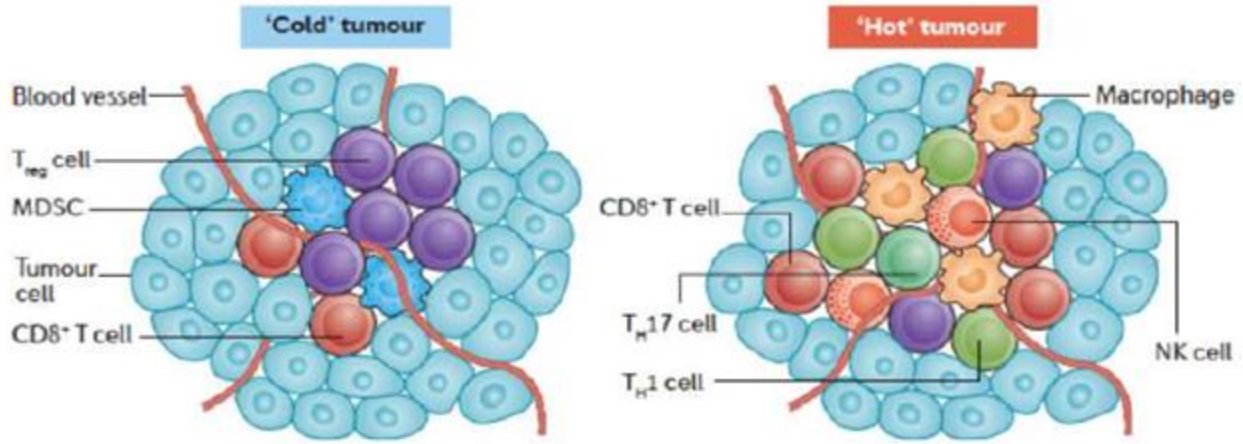
Capability of a tumor to correctly present immunogenic antigens has also been linked to the tumor's capacity to attract immune cells

Quantitation and distribution of immune cells within a tumor have been proposed as broad measurements of tumor immunogenicity, with three typical scenarios being recognized:

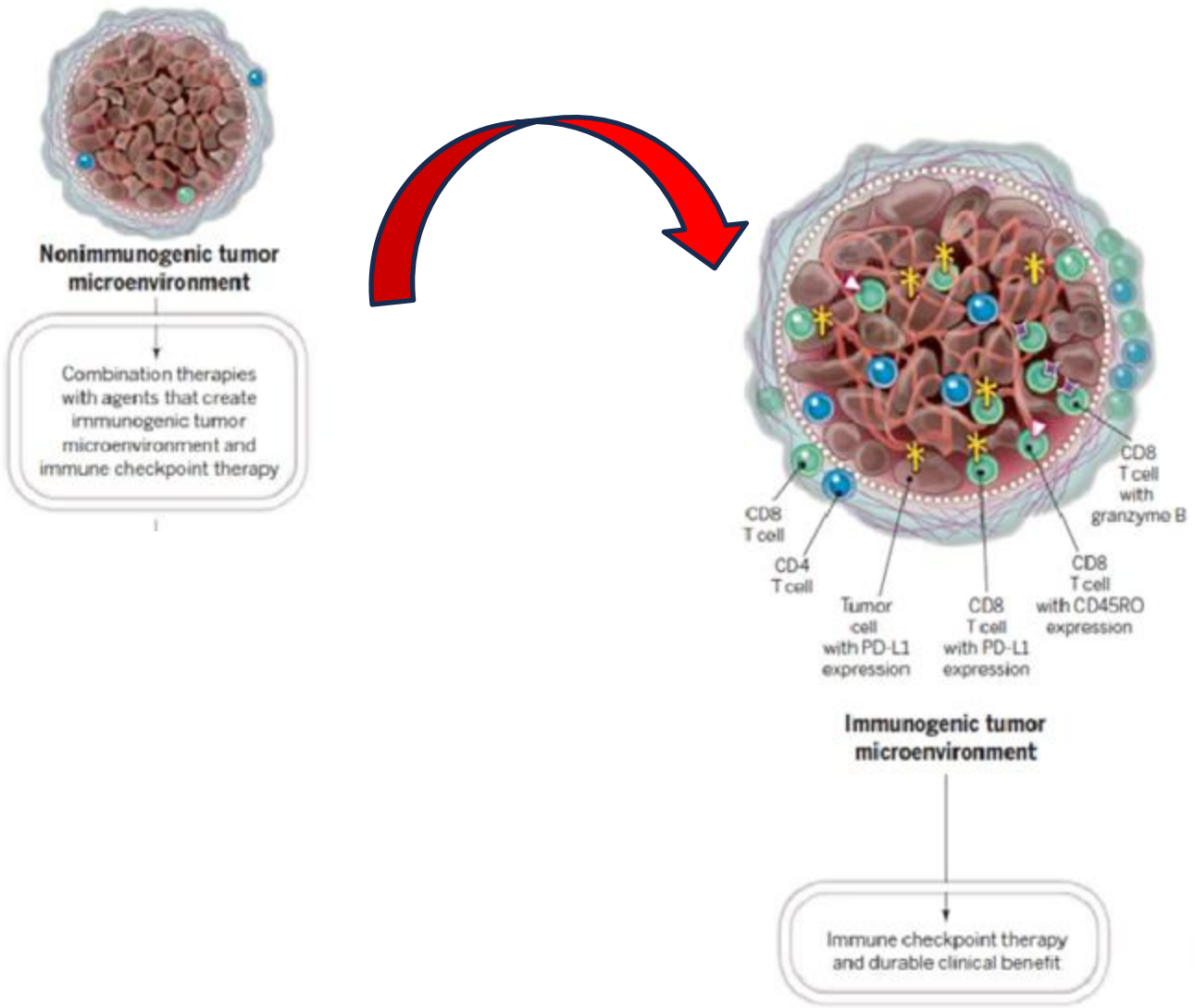
1- inflamed tumors (''hot'', immune infiltration),

2- immune excluded tumors (presence of T cells at the tumor margins but not in the tumor core)

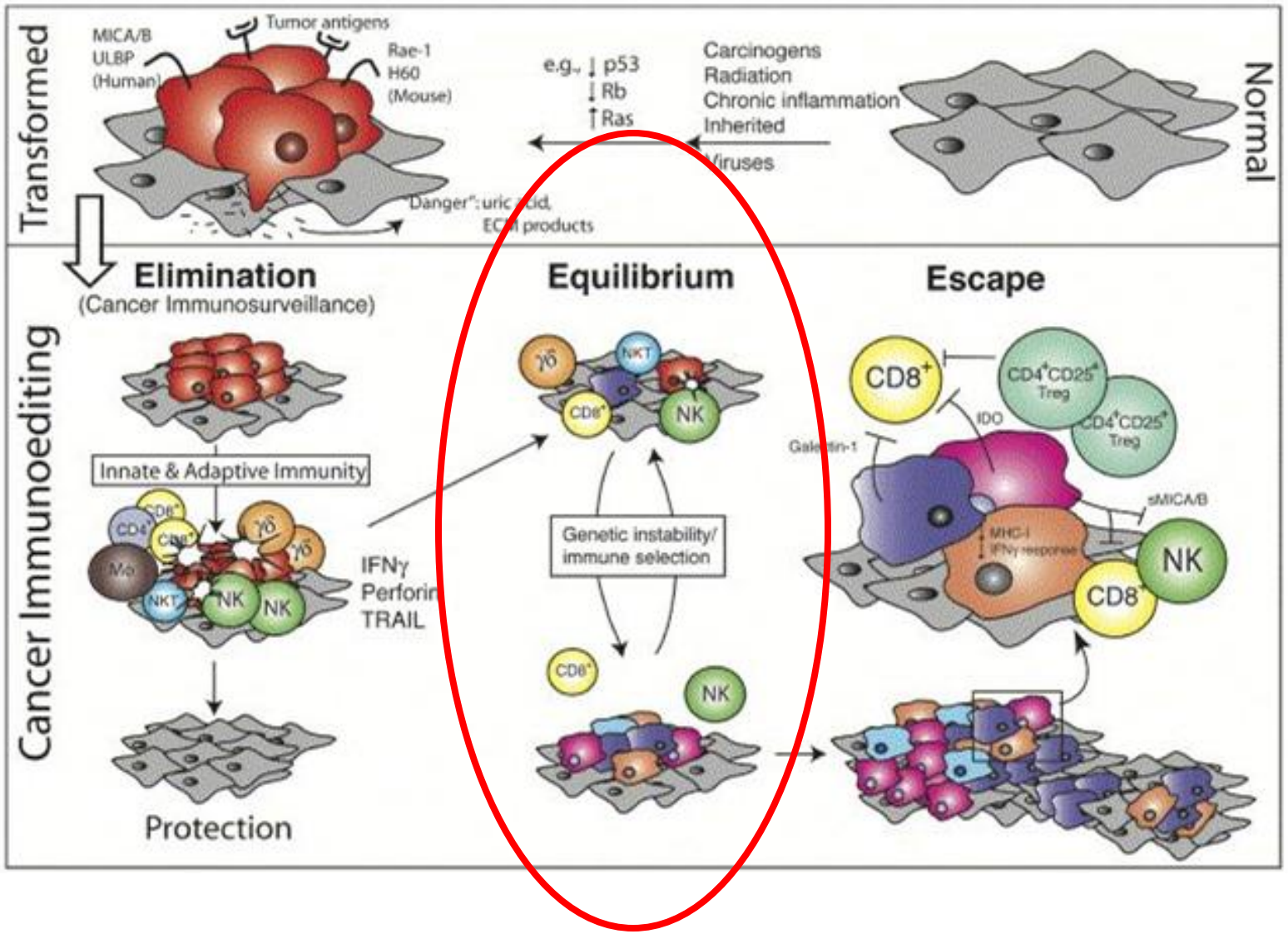
3- Immune desert tumors (''cold'', no immune infiltration)



Trasformare un tumore “freddo” in uno “caldo”



The immune system establishes a dynamic interaction with the tumour: cancer immunoediting

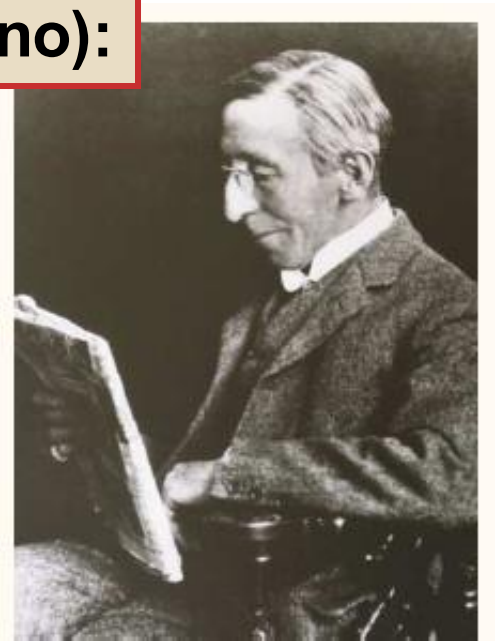


Dunn et al Immunity 2004

Il processo di formazione delle metastasi

1889 Stephen Paget
L'ipotesi "Seed and Soil" (Il seme e il terreno):

Le metastasi si sviluppano solo se il seme e il terreno sono compatibili!



In his paper, Paget analyzes 735 fatal cases of breast cancer, complete with autopsy, as well as many other cancer cases from the literature and argues that the distribution of metastases cannot be due to chance, concluding that although "the best work in pathology of cancer is done by those who… are studying the nature of the seed…" [the cancer cell], but the "observations of the properties of the soil" [the secondary organ] "may also be useful"...

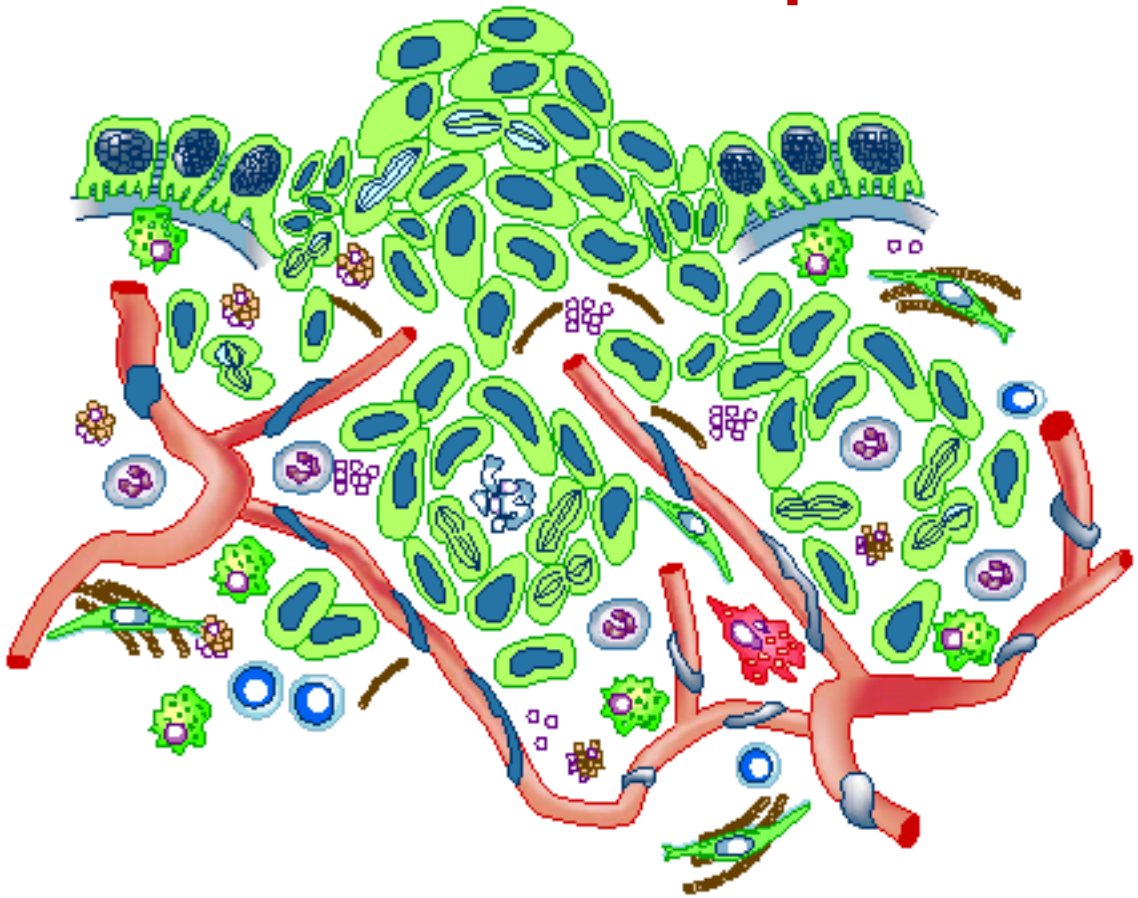
The Lancet, 1889

"When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil."

Seed and Soil

I semi vanno in tutte le direzioni, ma cresceranno solo quelli che cadranno dove il terreno gli è congeniale

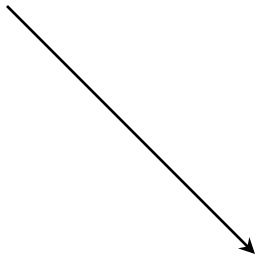
… Il terreno…
Il microambiente è importante!



Il microambiente tumorale è un protagonista indispensabile del processo neoplastico, poiché favorisce la proliferazione, la sopravvivenza e la migrazione delle cellule tumorali.

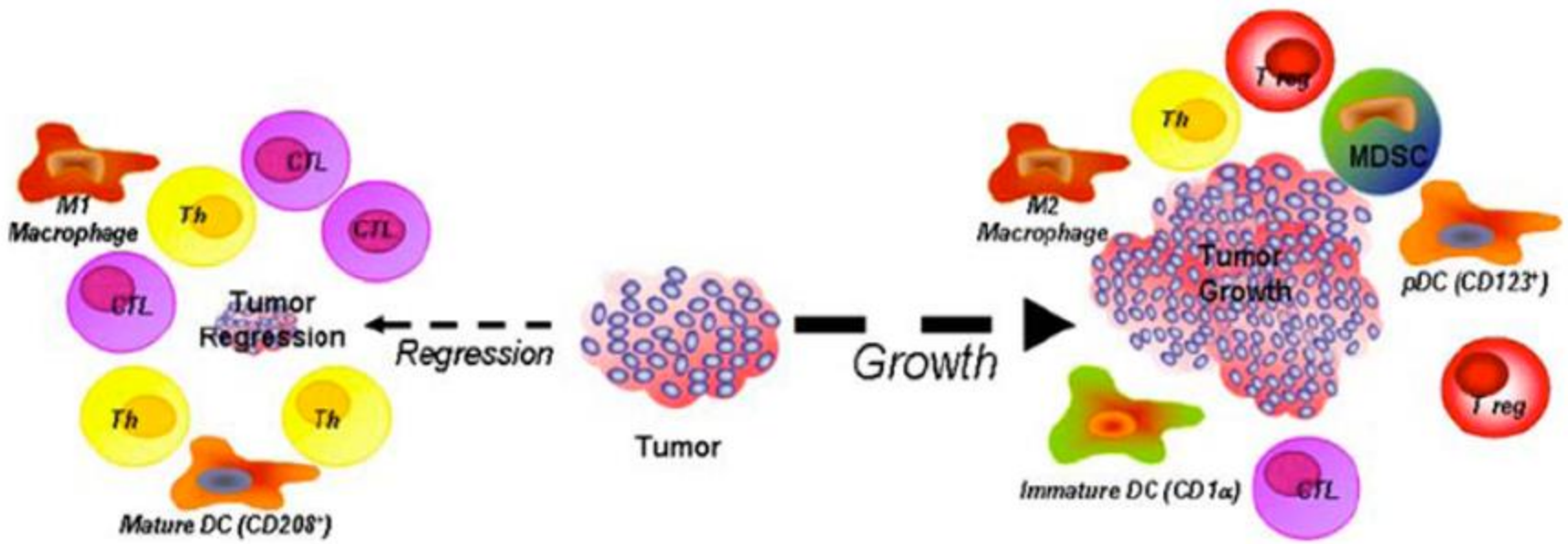
Coussens LM and Werb Z Nature 2002

Although cancer is described as a disease of genetic mutations, it is clear the important, but multifaceted role of the host.



Infiammazione e cancro

Il sistema immunitario è come “un’arma a doppio taglio”



THE IMMUNE SYSTEM IS A “DOUBLE-EDGED SWORD”

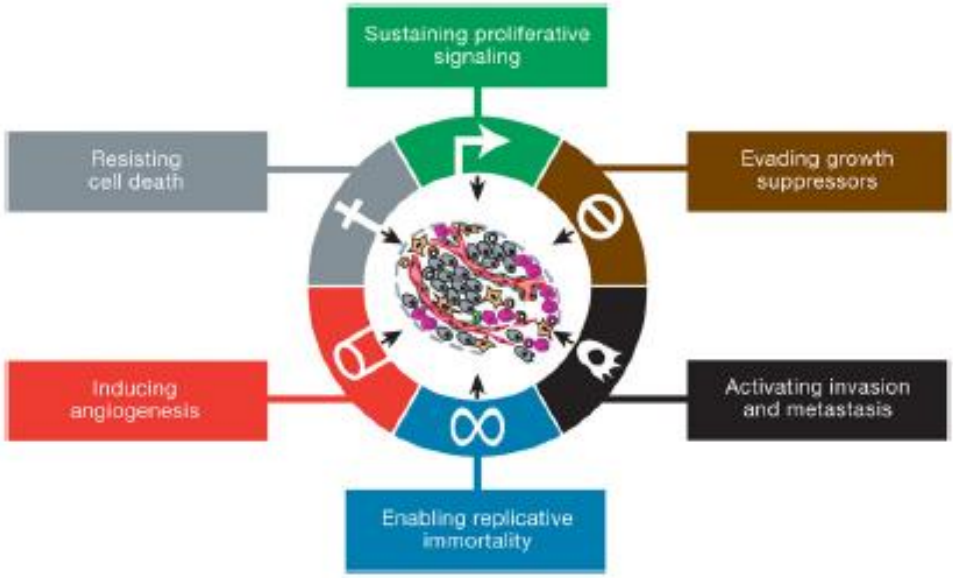
- It can destroy tumor cells, and yet paradoxically also promote and sustains cancer.

- The complexity of the immune system-cancer relationship depends on tumor cellular origin, mode of transformation, anatomic location, stromal response, cytokine production profile, inherent immunogenicity….etc.

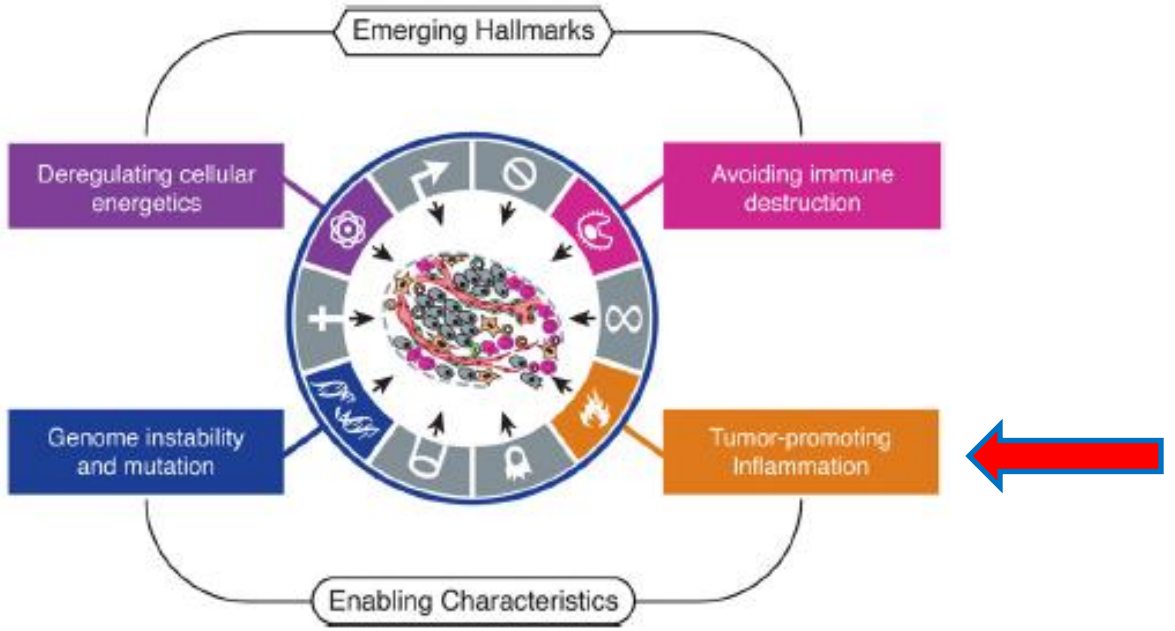
Talmadge JE et al, Cancer Metastasis Rev 2007

Le proprietà di un tumore

2001



2011



10 anni dopo emergono nuove proprietà…

The Hallmarks of Cancer
Hanahan D and Weinberg RA, Cell 2011

Infiammazione e cancro: evidenze a favore

Virchow, 1863

- **Le malattie infiammatorie dell'intestino (colite ulcerosa, malattia di Crohn) sono associate ad un alto rischio di cancro del colon-retto. Individui con la colite ulcerosa hanno un rischio dieci volte maggiore di sviluppare un cancro del colon-retto, rispetto al rischio calcolato per il resto della popolazione.**

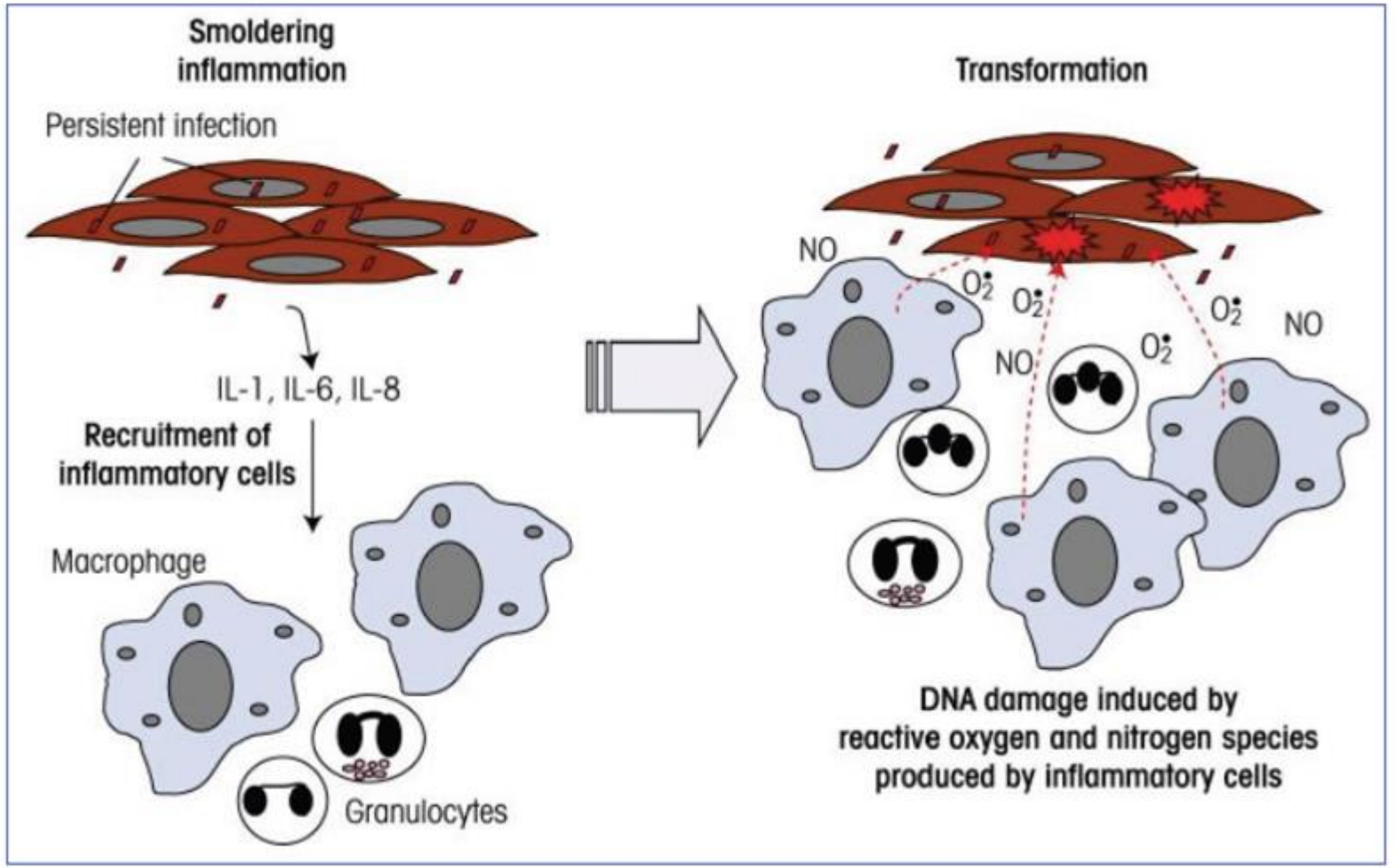
- **L'esposizione cronica a sostanze irritanti che causano un'infiammazione dei bronchi (es., sigarette, asbesto, silice) è associata ad un elevato rischio di cancro del polmone.**

- **L'esposizione eccessiva ai raggi UV aumenta il rischio di melanoma.**

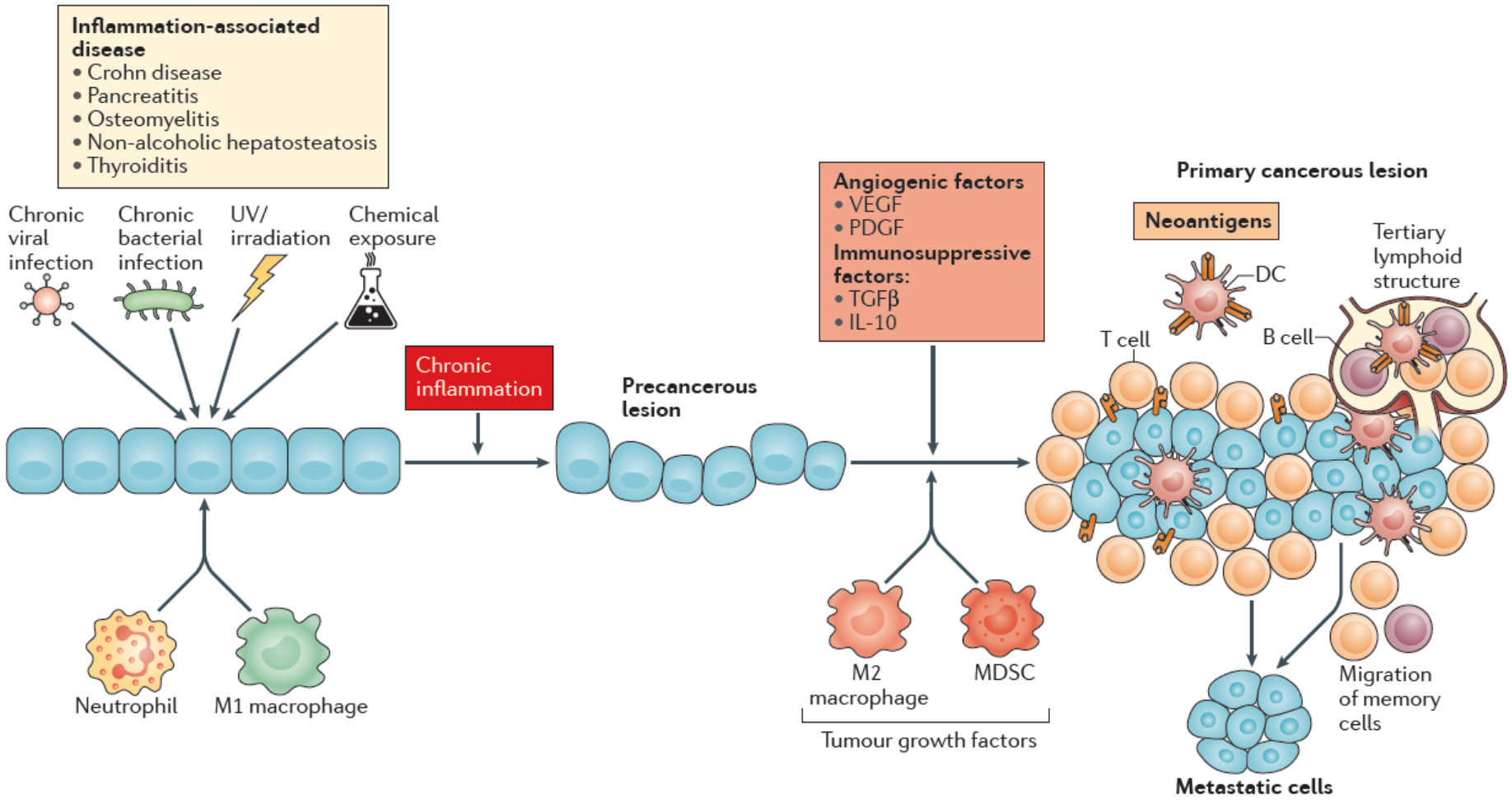
- **Molti tumori sono correlati ad una esposizione cronica ai patogeni (es., cancro dello stomaco ed *Helicobacter pylori;* epatocarcinoma e HCV; cancro della cervice e HPV).**

Inductor	Inflammation	Cancer
Gut pathogens	Inflammatory bowel disease	Colorectal cancer
Tobacco smoke	Bronchitis	Bronchial lung cancer
Helicobacter pylori	Gastritis	Gastric cancer
Human papilloma virus	Cervicitis	Cervical cancer
Hepatitic B/C virus	Hepatitis	Hepatocellular carcinoma
Bacteria, gall bladder stones	Cholecystitis	Gall bladder cancer
Tobacco, genetics, alcohol	Pancreatitis	Pancreatic cancer
Epstein-Barr virus	Mononucleosis	Burkitt's lymphoma
Ultraviolet light	Sunburn	Melanoma
Asbestos fibers	Asbestosis	Mesothelioma
Gram-uropathogens	Schistosomiasis (Bilharzia)	Bladder cancer
Gastric acid, alcohol, tobacco	Esophagitis	Esophageal adenocarcinoma

Chronic inflammation can promote malignant transformation



Key elements of cancer-related inflammation



Fridman et al. Nat. Rev Clin Onc 2017

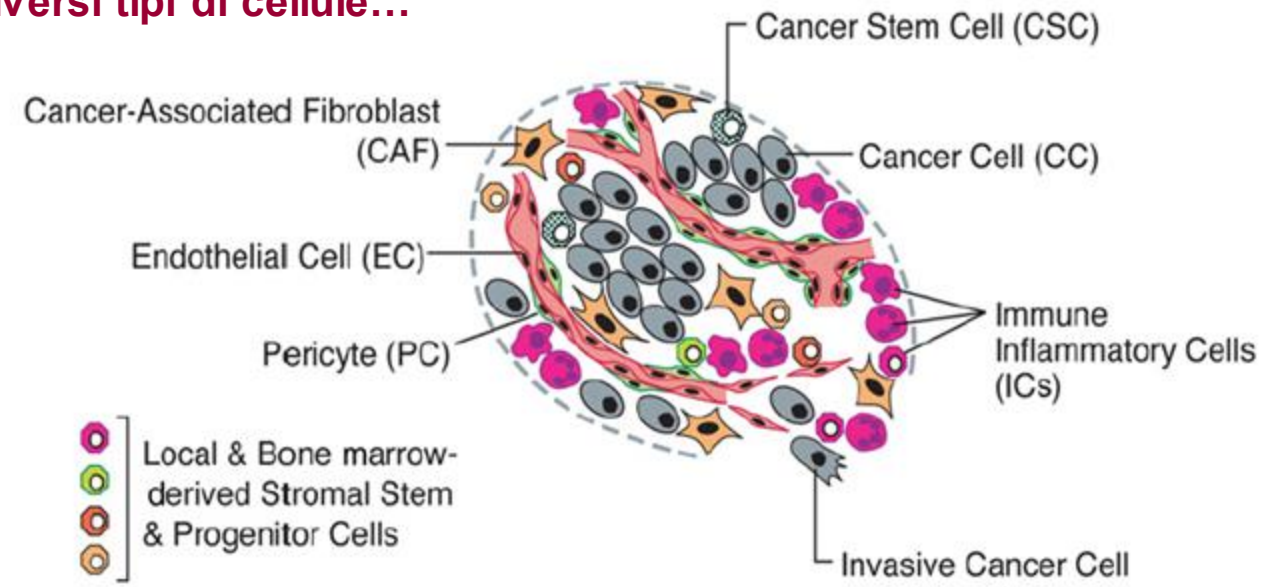
Quali sono le cellule infiammatorie nel microambiente tumorale che favoriscono lo sviluppo e la progressione tumorale?

- Macrofagi associati al tumore (TAM)
- Cellule dendritiche (DC)
- Mastociti
- Neutrofili
- Eosinofili

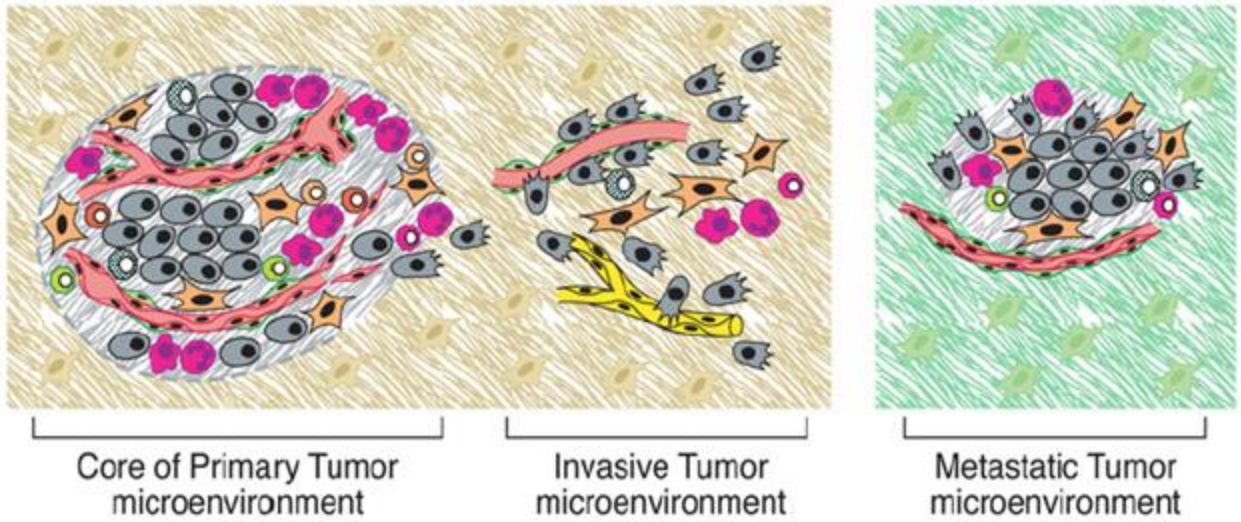
Cosa fanno?

- Inibiscono la risposta anti-tumorale.
- Promuovono la proliferazione cellulare, la deposizione dello stroma, l'angiogenesi.
- Inducono o aumentano il danno al DNA.

Un tumore è costituito da diversi tipi di cellule…



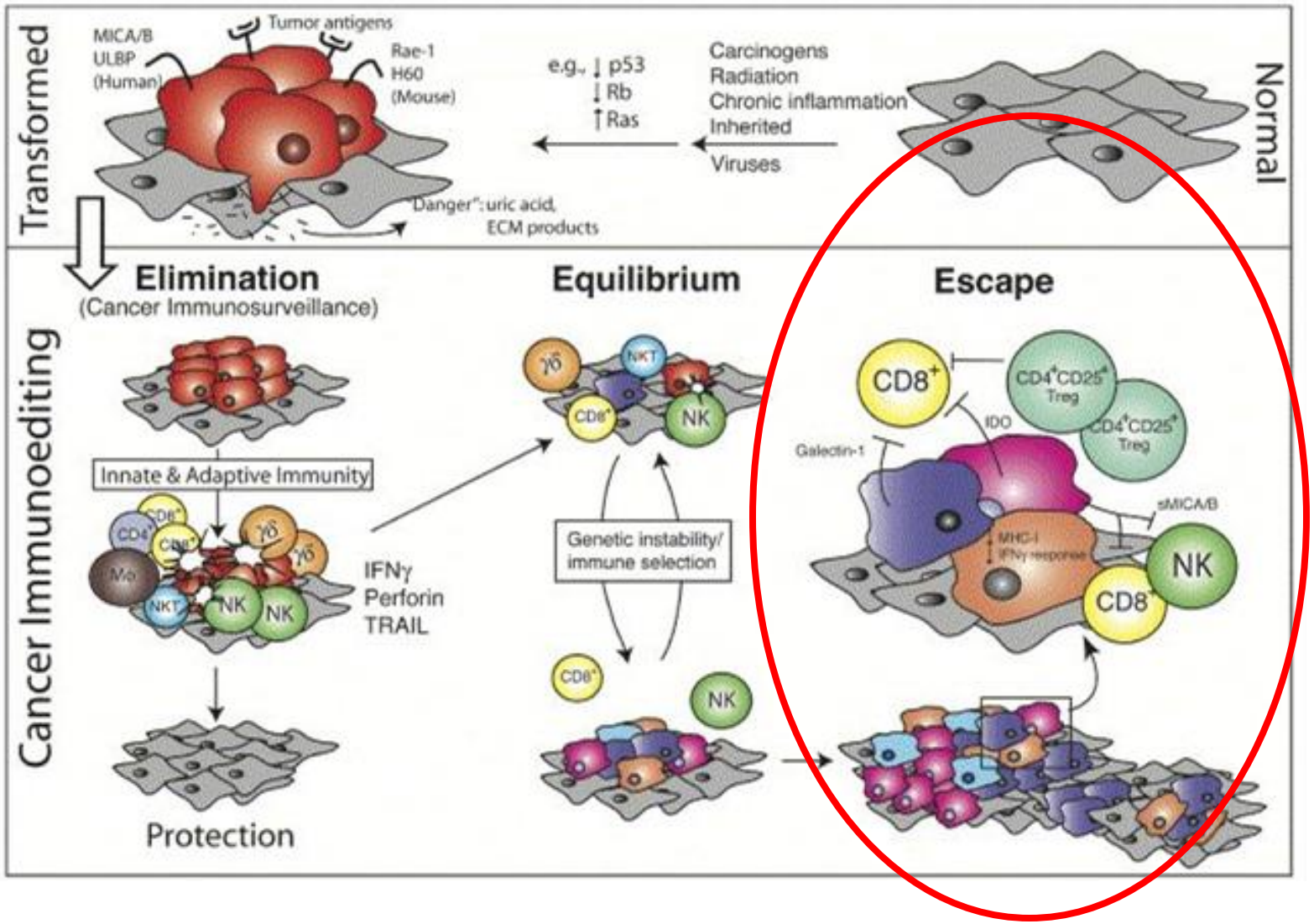
tumor-promoting & tumor-killing



…e da diversi microambienti

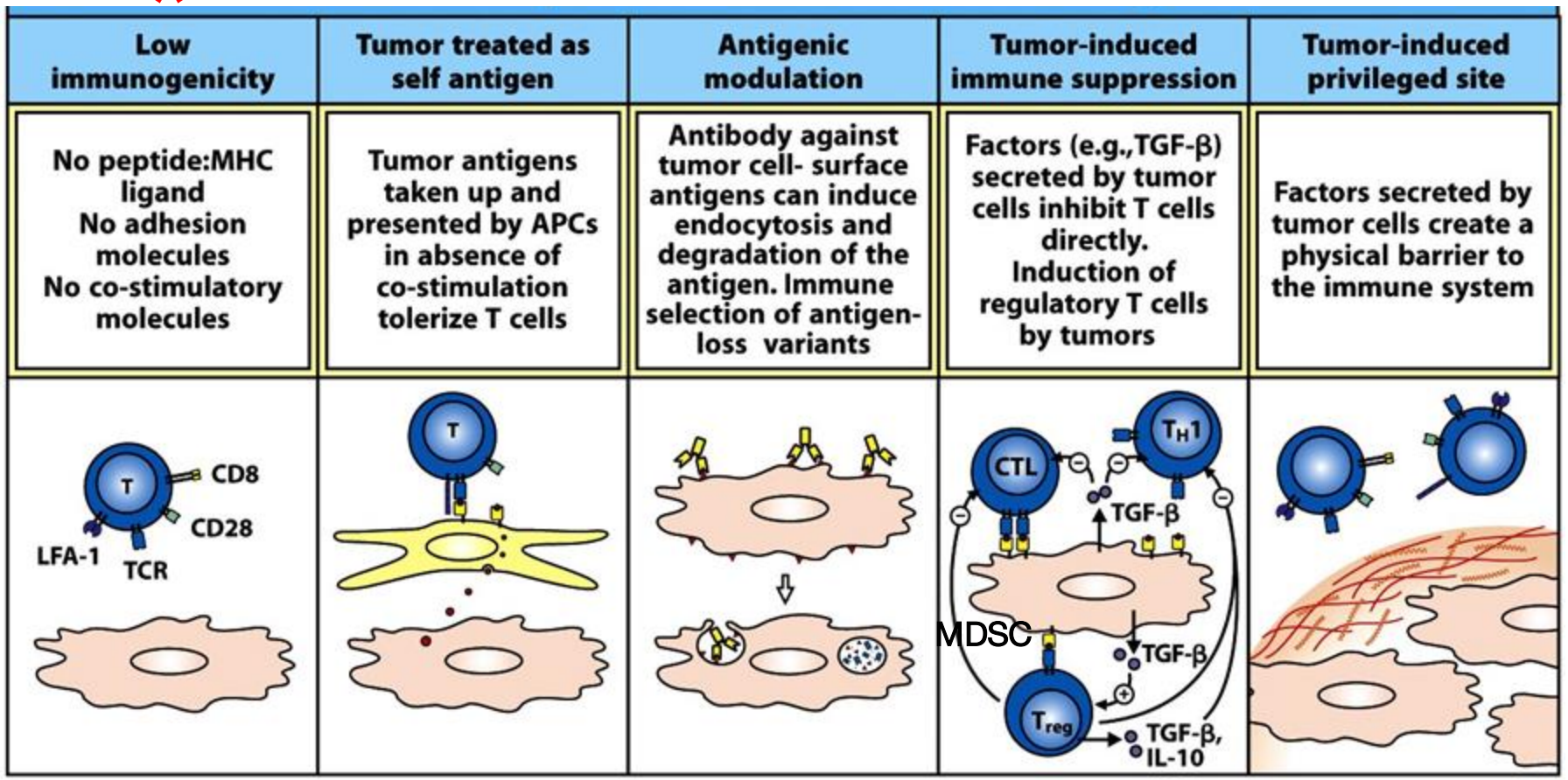
Hanahan and Weinberg, Cell 2010

The immune system establishes a dynamic interaction with the tumour: cancer immunoediting



Dunn et al Immunity 2004

Alcuni meccanismi con cui i tumori sfuggono al riconoscimento da parte del sistema immunitario



MDSC: Myeloid-Derived Suppressor Cells

Class I HLA down-modulation as a tumor evasion strategy against CTL recognition

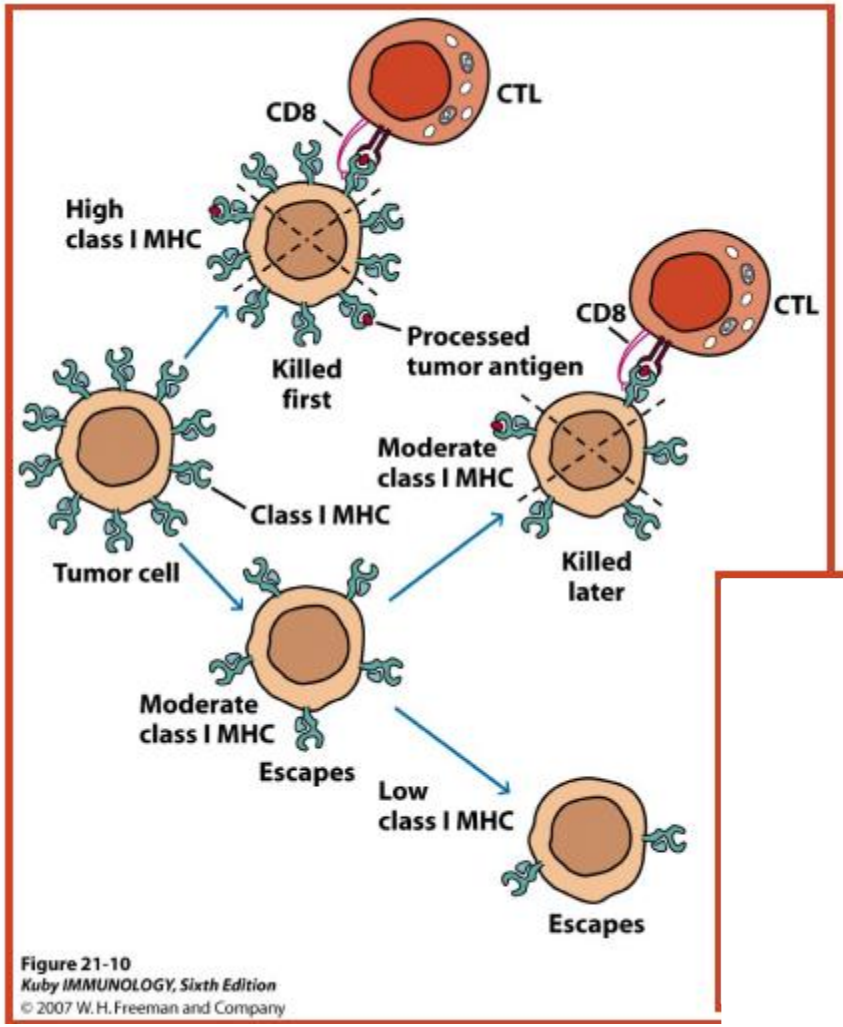
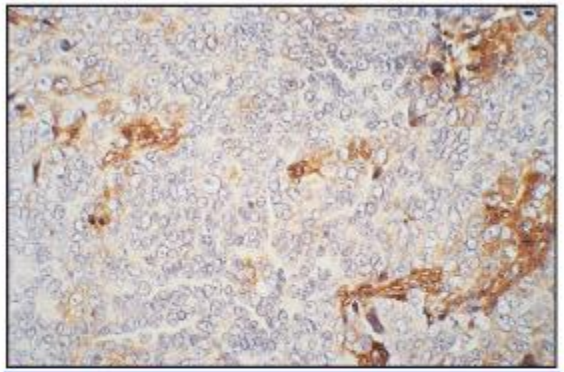


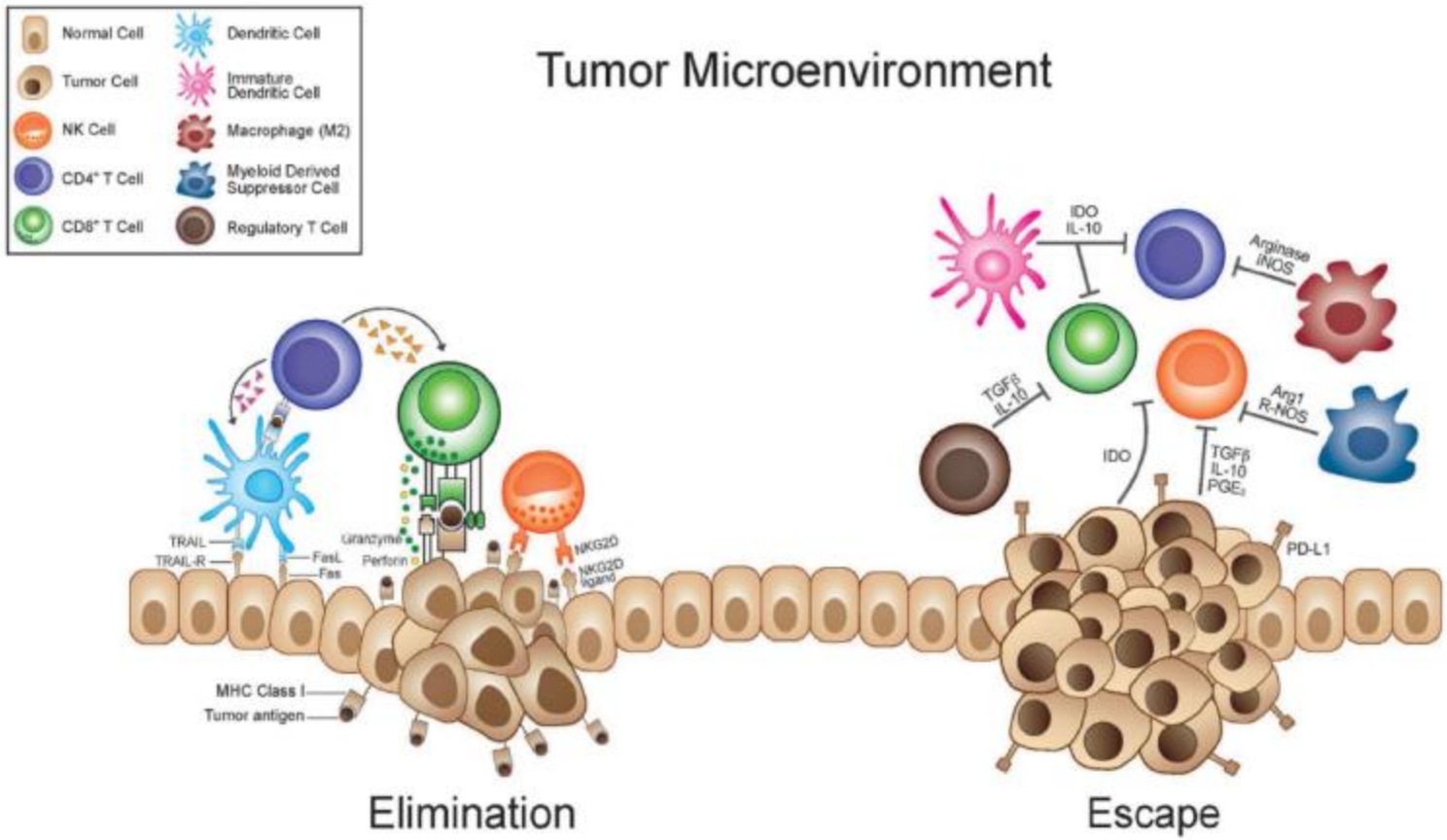
Figure 21-10
Kuby IMMUNOLOGY, Sixth Edition



HLA-I- prostate cancer, with HLA-I+ stroma and infiltrating cells

Frequency (%) of HLA-I altered phenotypes in invasive tumors

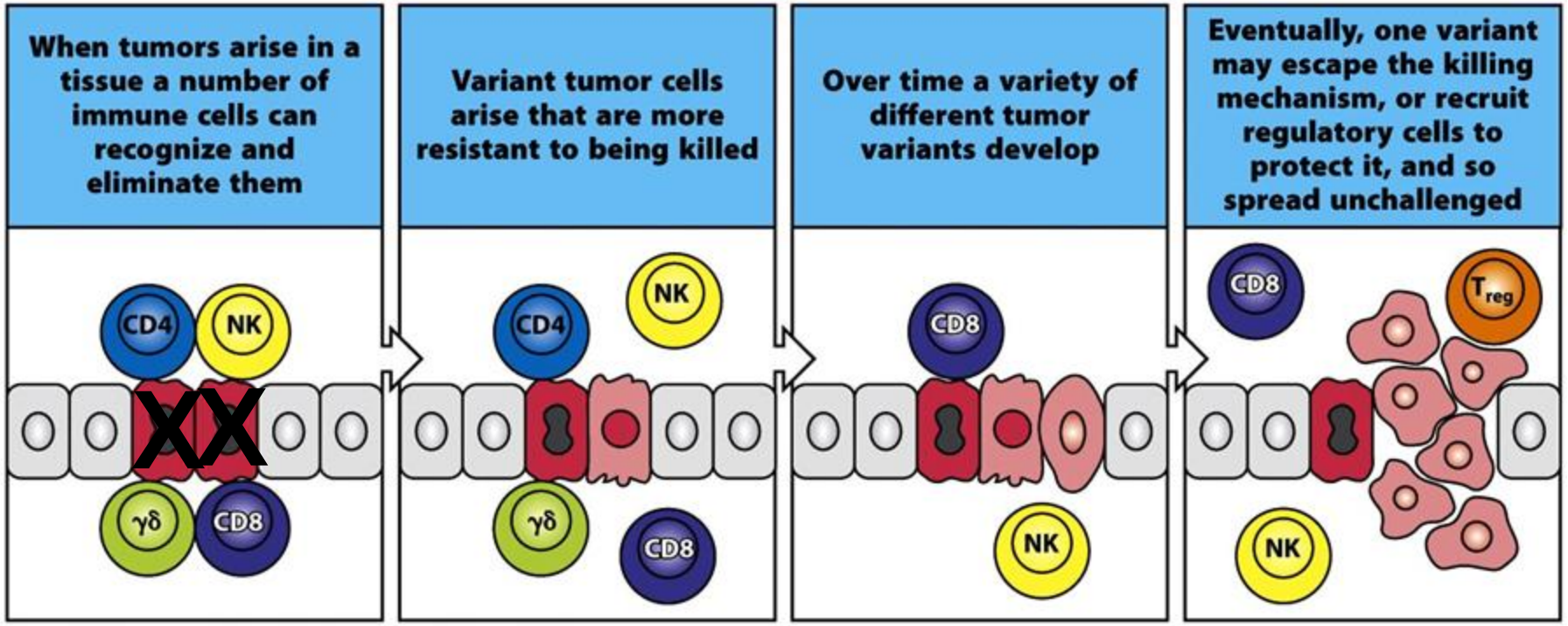
Escape



Monjazeb et al. Front Oncol 2013

"Immunoediting" del tumore: le 3 E

Eliminazione | Equilibrio | Evasione



Immunoterapia dei tumori

Immunoterapia dei tumori

Elimination

Attivazione dell'immunità innata e adattativa

- Vaccinazione con antigeni tumorali
- Anticorpi monoclonali che attivano molecole co-stimolatorie (OX40, 4-1BB, CD40, ecc.)
- Trattamento con citochine (es., IFN-α, IL-2)
- Aumento della presentazione dell'antigene (es., TLRs, DCs)
- Trasferimento adottivo di linfociti T tumore-specifici

Premere sull'acceleratore

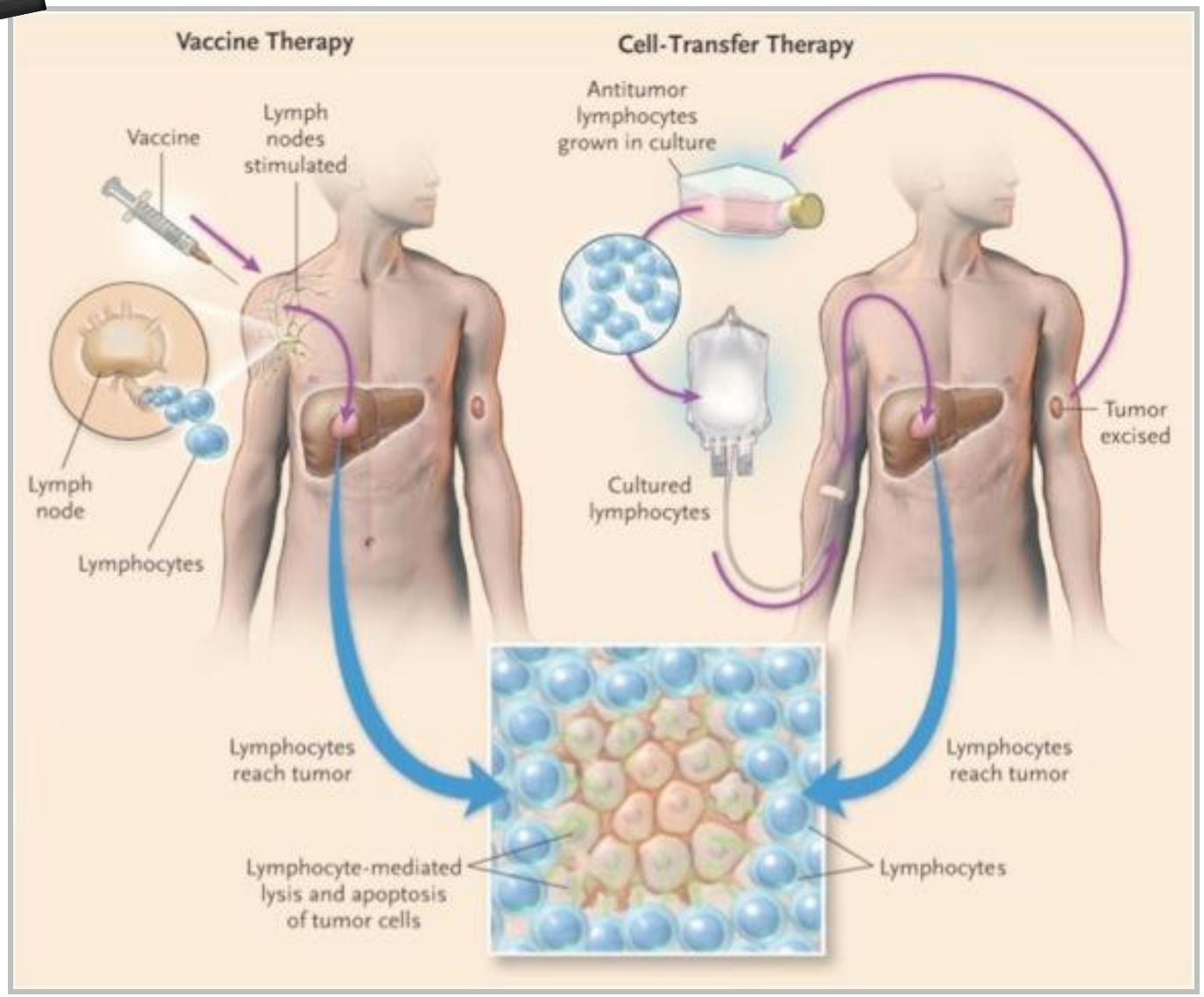
Escape

Neutralizzazione dei meccanismi di inibizione e di soppressione

- Chemioterapia/Radioterapia
- Anticorpi monoclonali contro molecole inibitorie (anti-CTLA-4, anti-PD-1)
- mAbs anti-CD25 (cellule T regolatorie)

Togliere i freni

Two main approaches to cancer immunotherapy: vaccine therapy and cell-transfer therapy



Rosenberg SA New England J Med 2004

Approcci sperimentali per i vaccini anti-tumore

1. Trovare antigeni tumore-specifici, da utilizzare per l'azione dei CD8+ CTLs o di anticorpi.

2. Rendere i tumori più immunogenici, unendoli ad adiuvanti o facendogli esprimere citochine o molecole costimolatorie.

3. "Dendritic cell loading" con antigeni specifici o con cellule tumorali intere e stimolazione con adiuvanti specifici in sistemi di colture cellulari, prima del re-inoculo nel paziente.

1+2+3

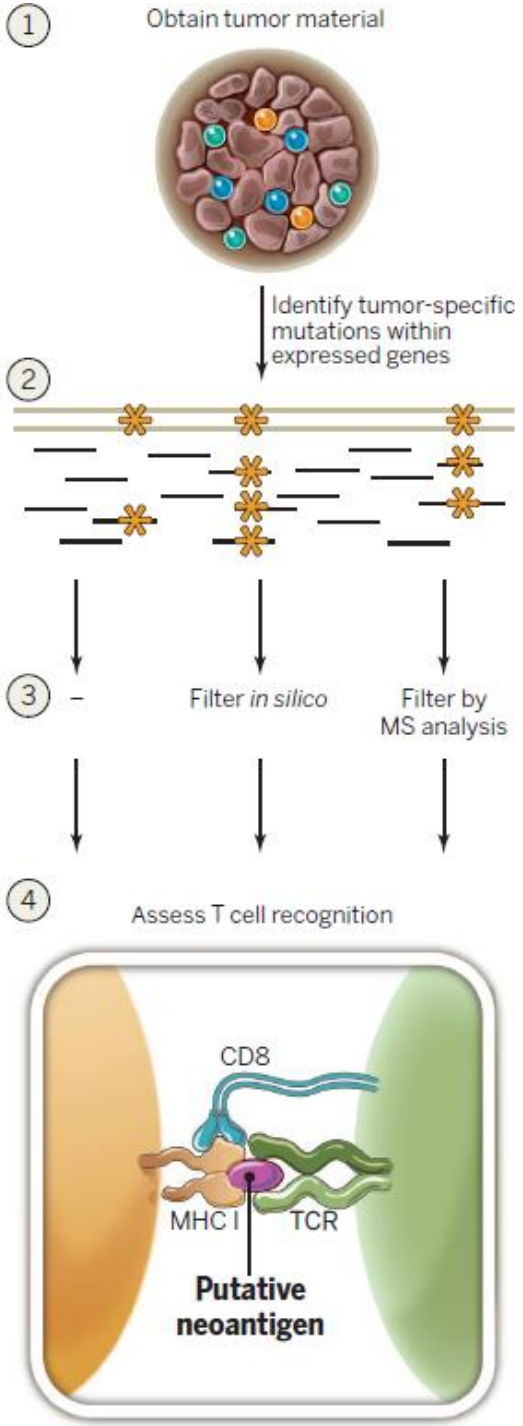
Therapeutic vaccines: Augmentation of anti-tumor immune response

L'antigene tumorale "ideale" per la vaccinazione

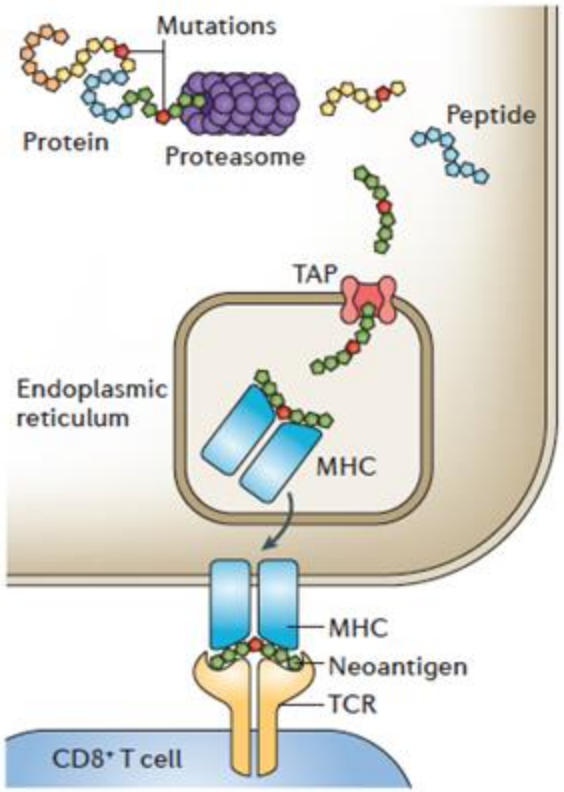
- E' altamente espresso in un ampio numero di tumori.
- E' espresso durante le prime fasi della trasformazione neoplastica.
- Gioca un ruolo fondamentale nella trasformazione neoplastica.
- E' dotato di più peptidi immunogenici che possono essere presentati da alleli HLA diversi.
- I suoi peptidi immunogenici sono generati dalla processazione nella cellula tumorale.
- E' riconosciuto da un vasto repertorio di cellule T in grado di generare delle risposte efficaci.

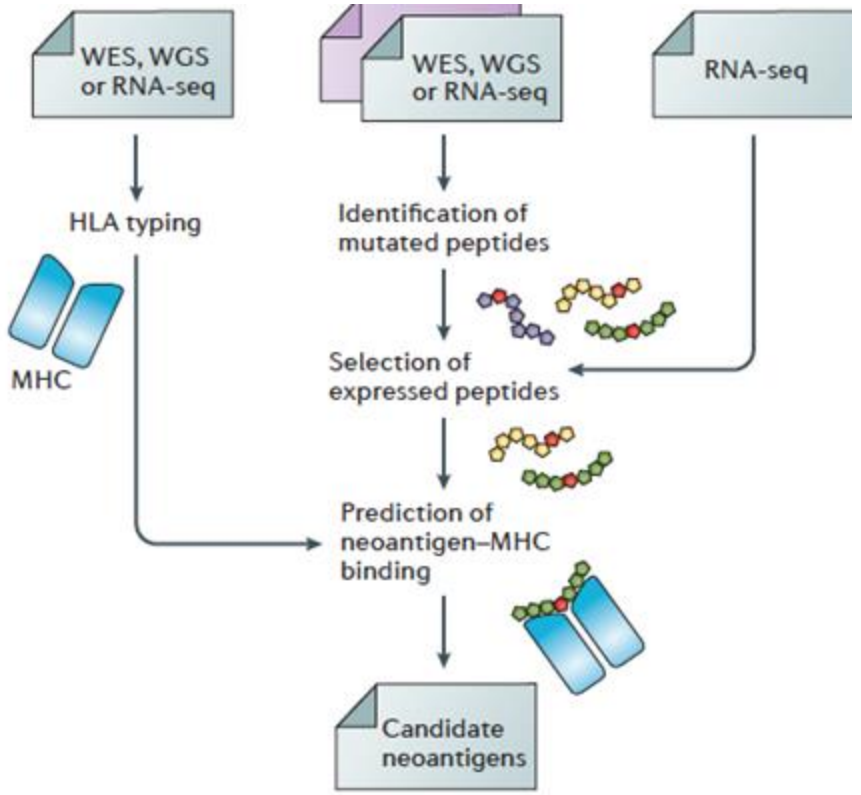
1. Trovare antigeni tumore-specifici

Cancer exome-based identification of neoantigens



1. Trovare antigeni tumore-specifici



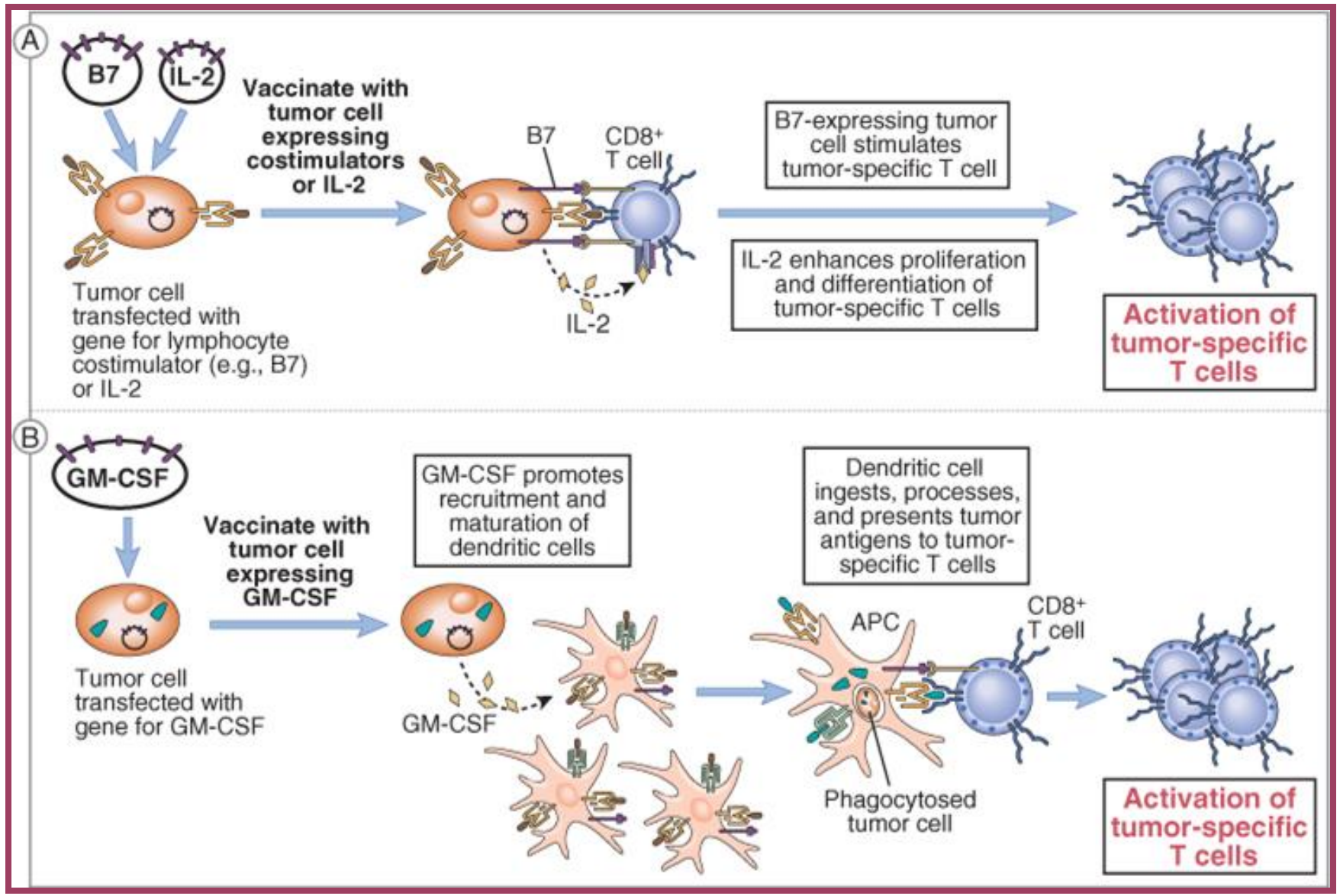


Cancer whole exome sequencing

- **Driver mutations**
- **Passenger mutations**
- **Nonsynonimous mutations**

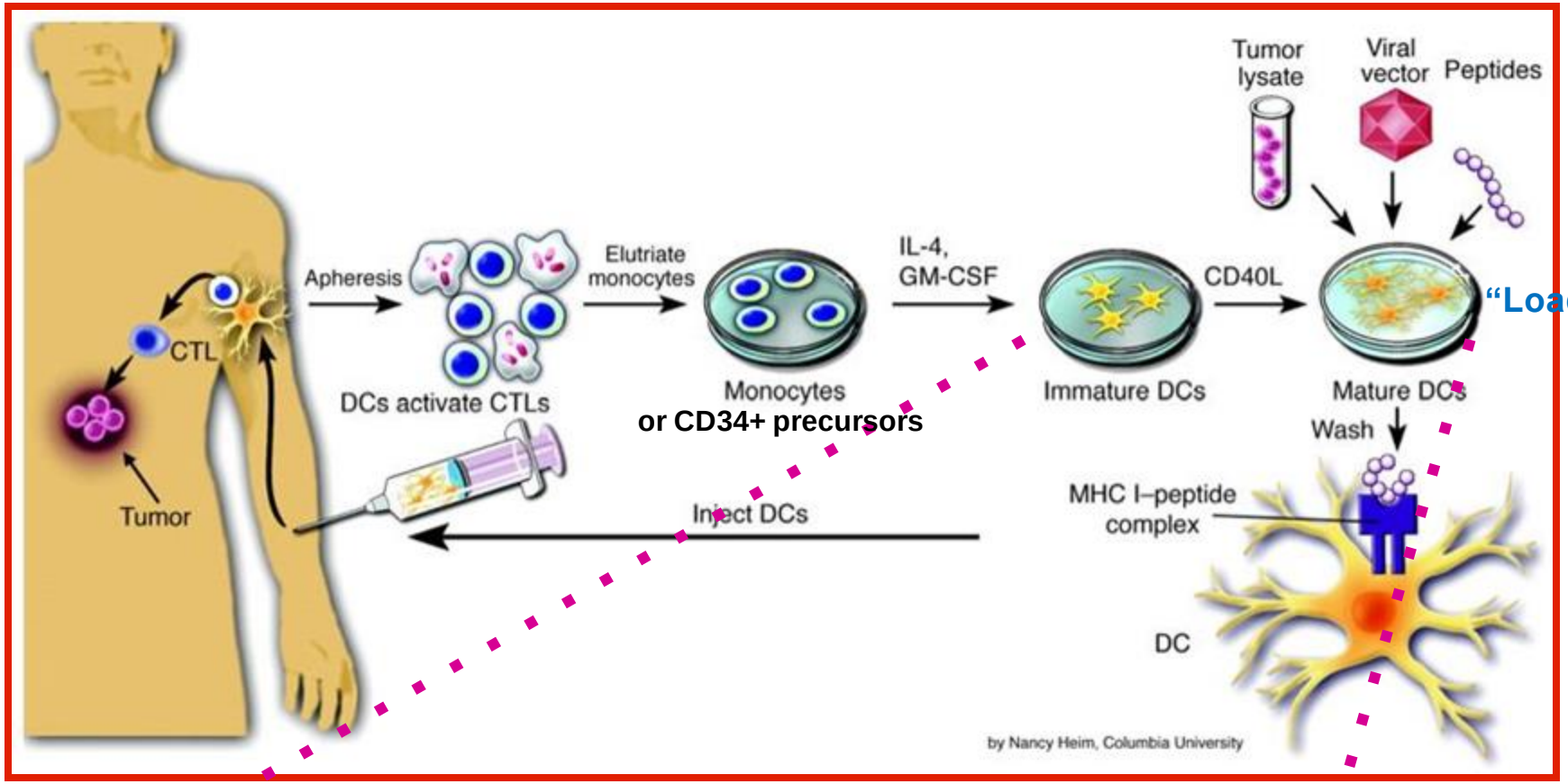
Neoantigens

Manipolazioni genetiche per aumentare l'immunogenicità delle cellule tumorali

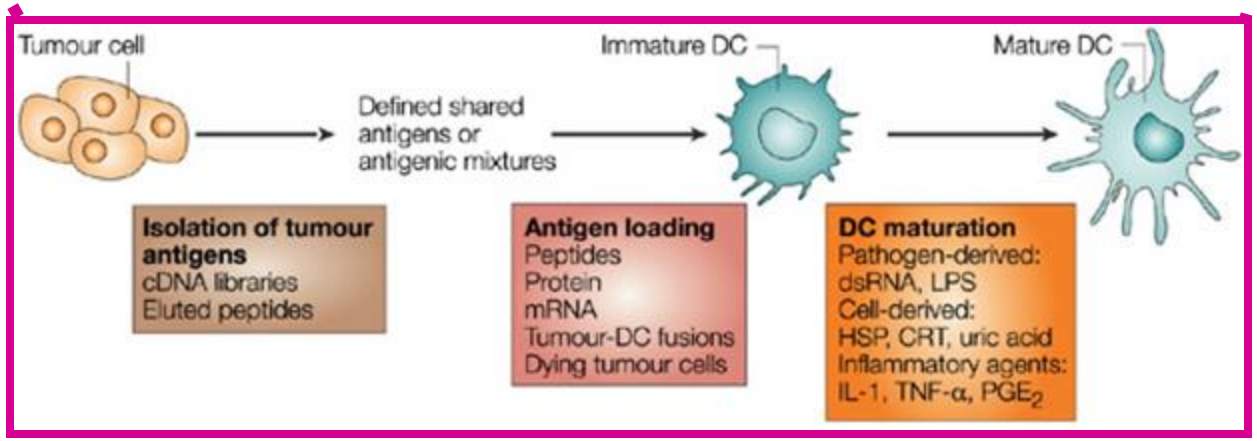


3. DC loading

Generazione di vaccini basati sulle cellule dendritiche (DC) anti-tumore



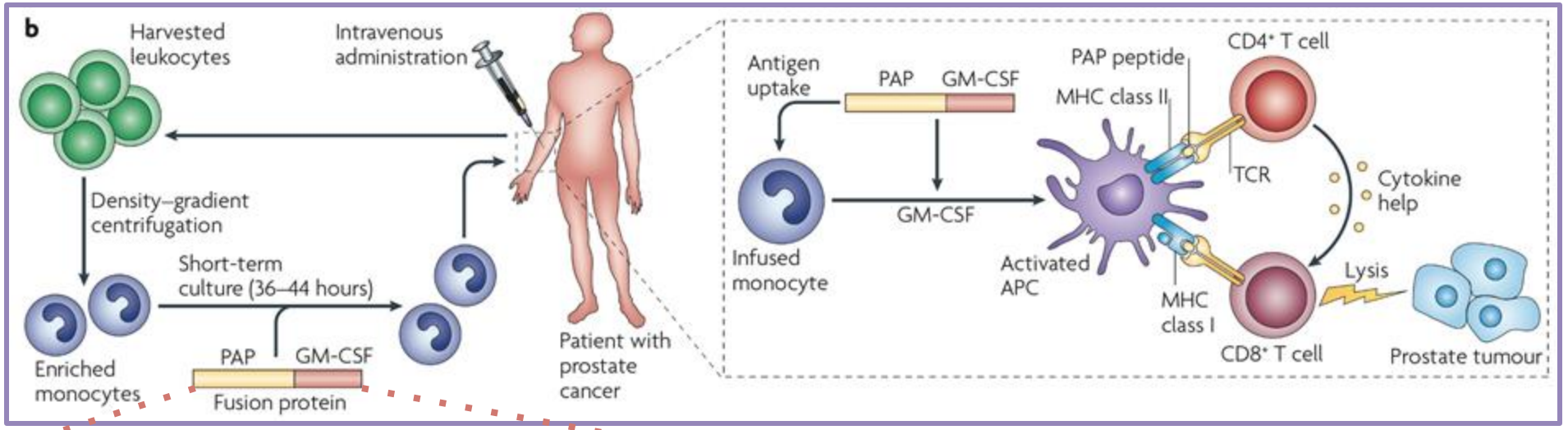
"Loading"



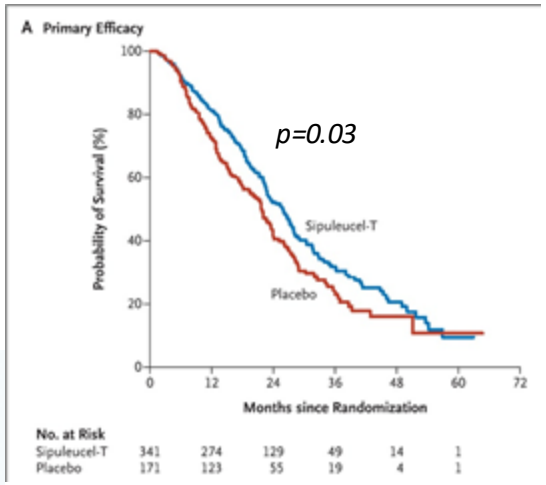
First U.S. "cancer vaccine"!

Sipuleucel-T (Provenge)

Autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic and hormone refractory prostate cancer

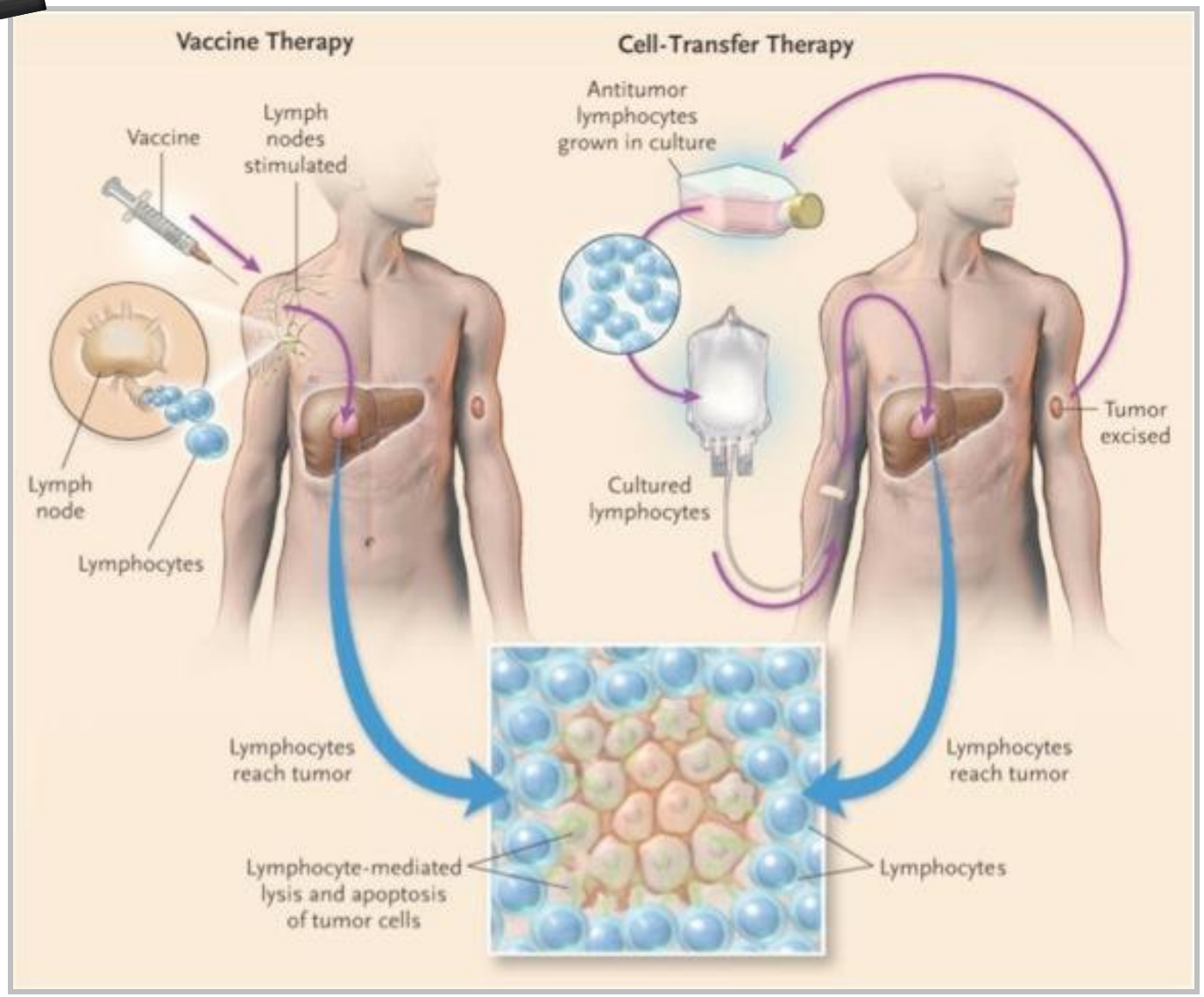


PAP-GM-CSF consists of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF)



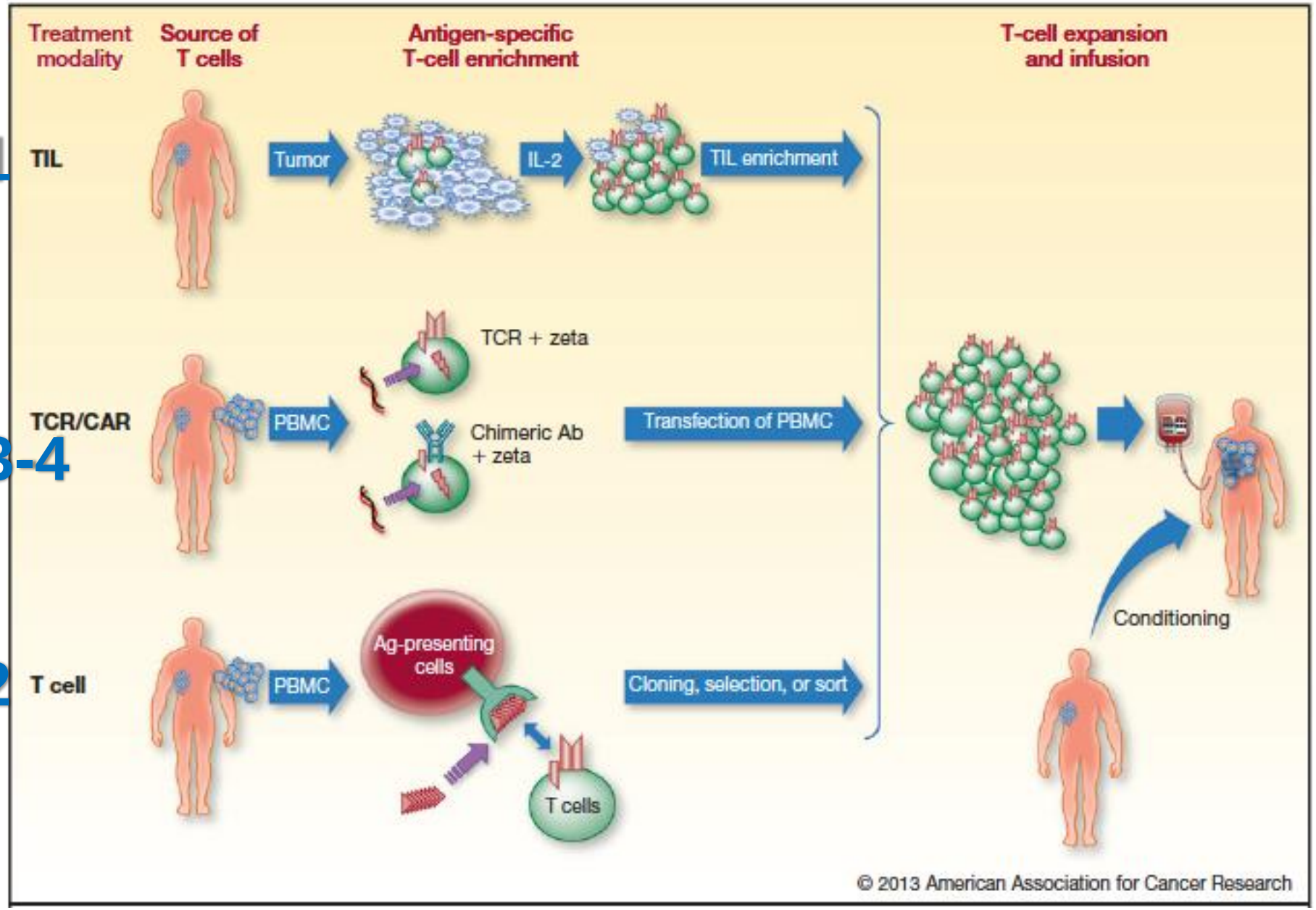
Kantoff, N Engl J Med 2010

Two main approaches to cancer immunotherapy: vaccine therapy and cell-transfer therapy



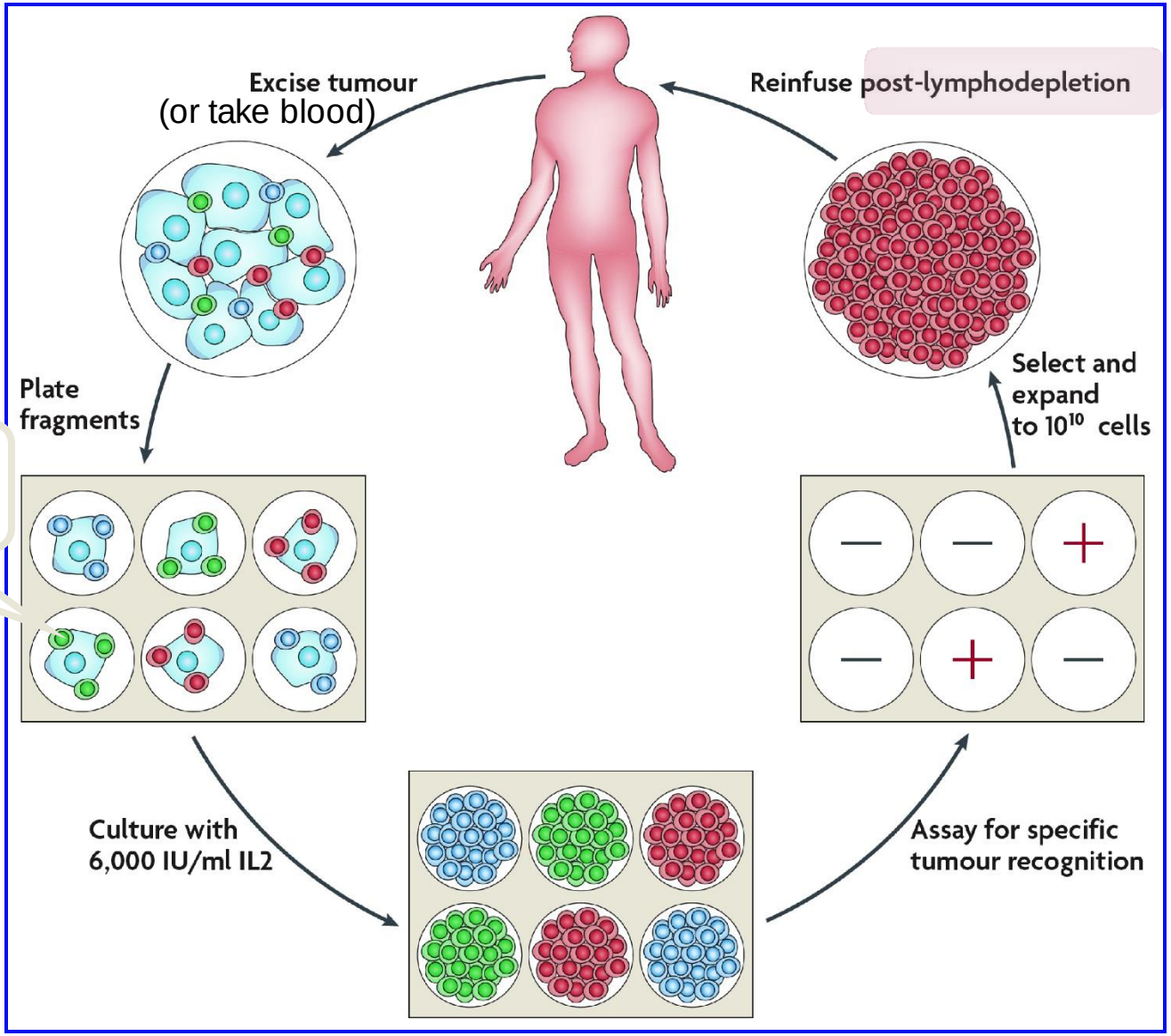
Rosenberg SA New England J Med 2004

Diversi approcci per il trasferimento adottivo di linfociti T tumore-specifici



1-2 Trasferimento adottivo di linfociti T tumore-specifici

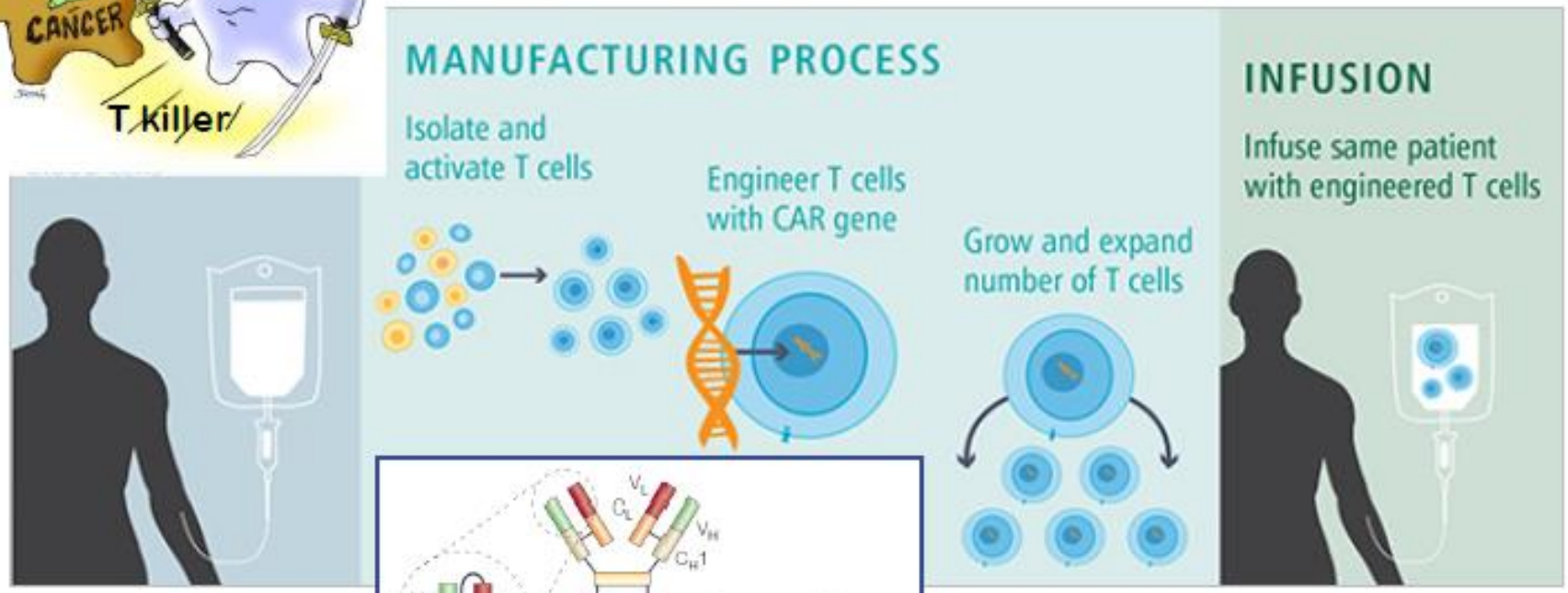
TIL: tumor-infiltrating lymphocytes

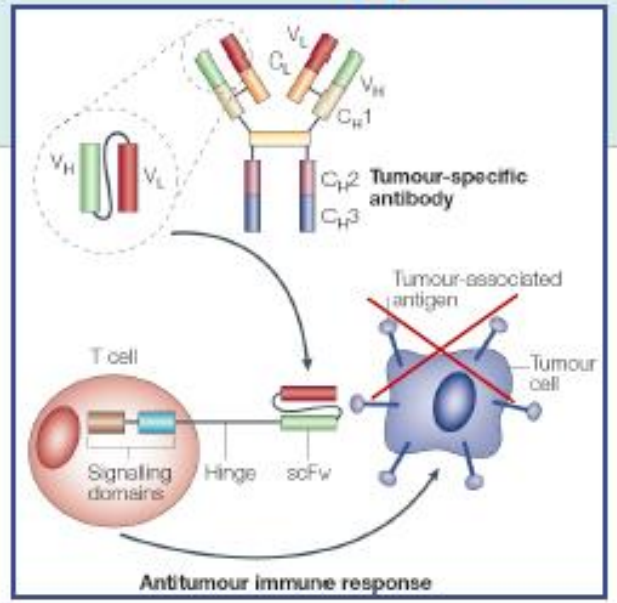


Rapid expansion of T cells (1,000- to 5,000-fold, sometimes with infusion of IL-2), achieving 10-100 billion cells for adoptive transfer.

3-4

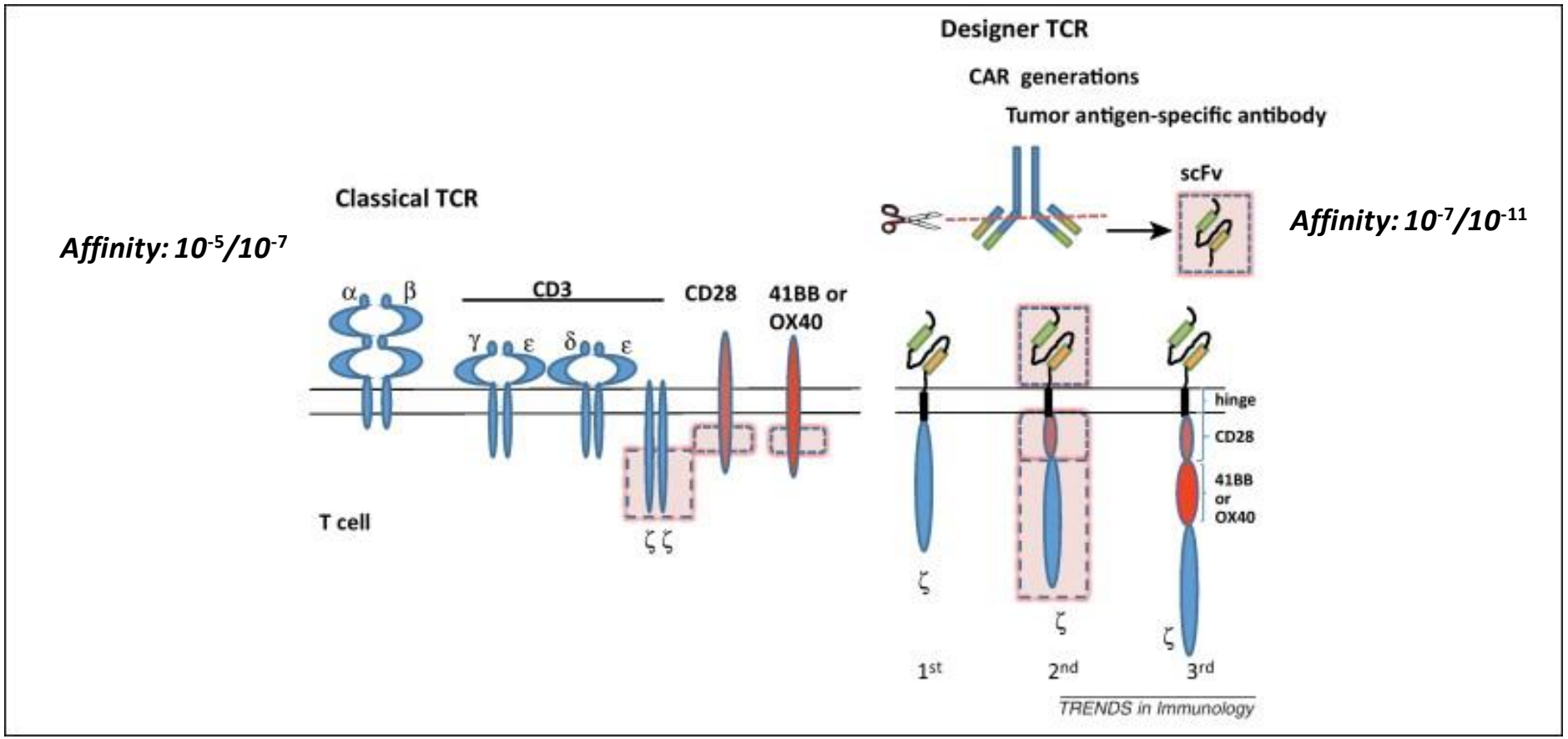
SUPERNATURAL T cells: genetic modifications of T cells for cancer therapy (T-CAR)





T-CAR (chimeric antigen receptor)

3-4 Chimeric Antigen Receptor (CAR) engineering

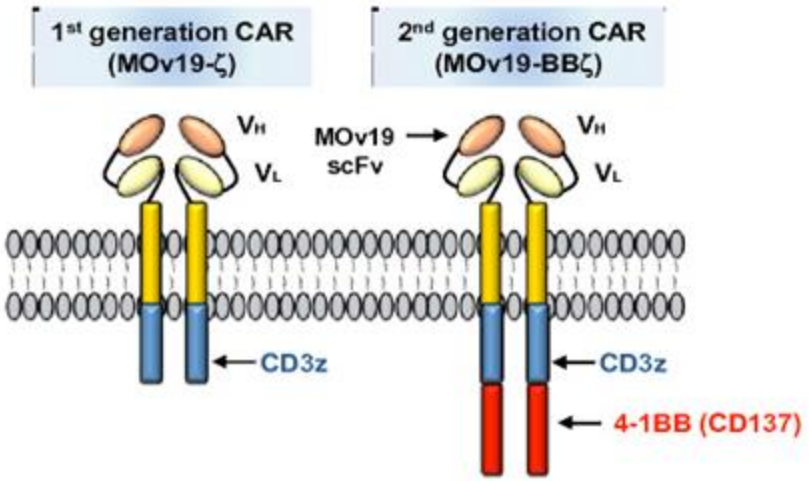


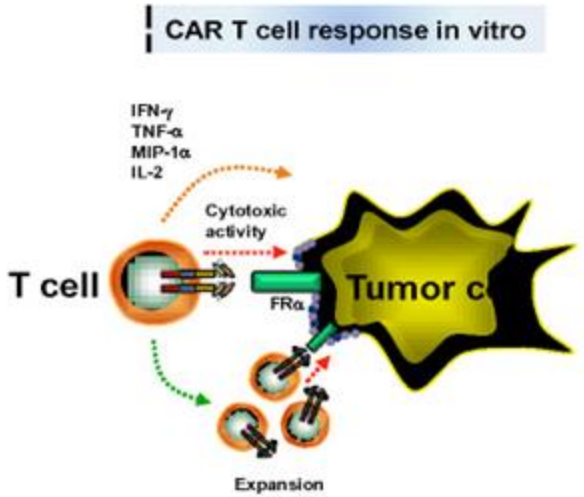
scFv: single-chain variable fragments

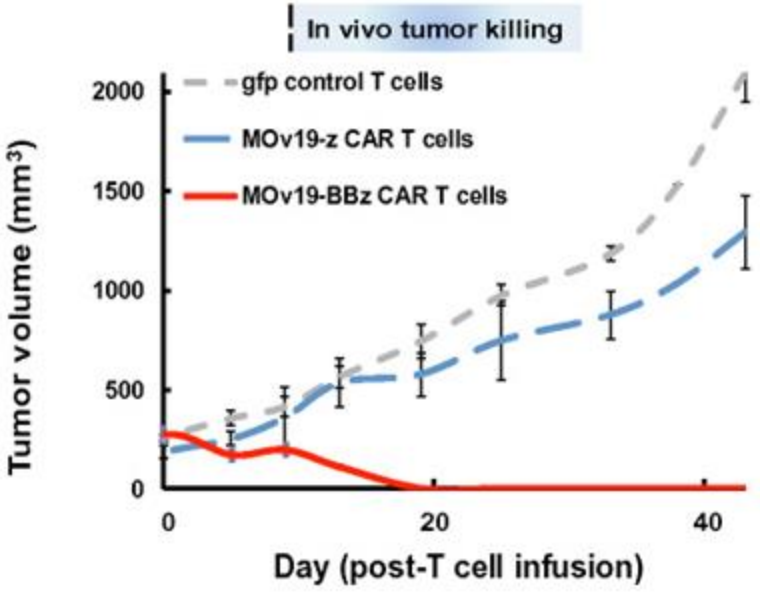
Gao J, Trends Immunol, 2013

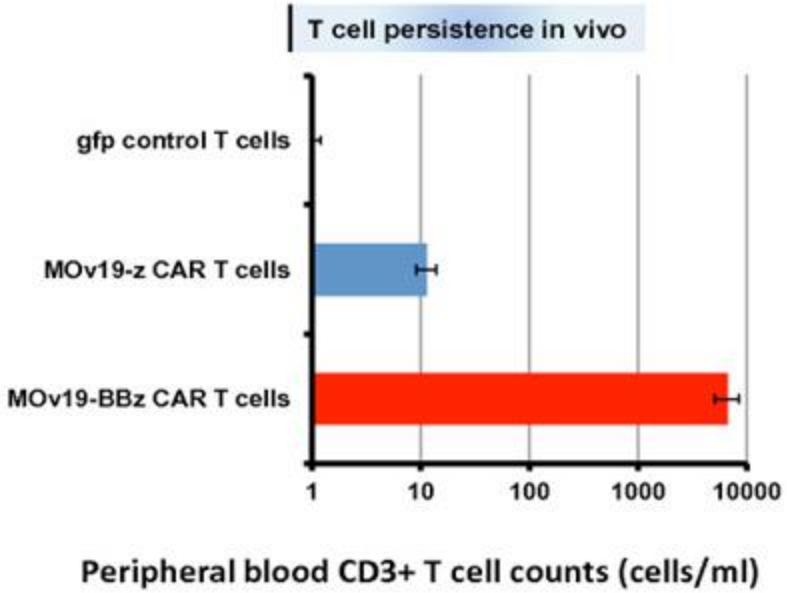
3-4

Preclinical results for CAR T cell therapy



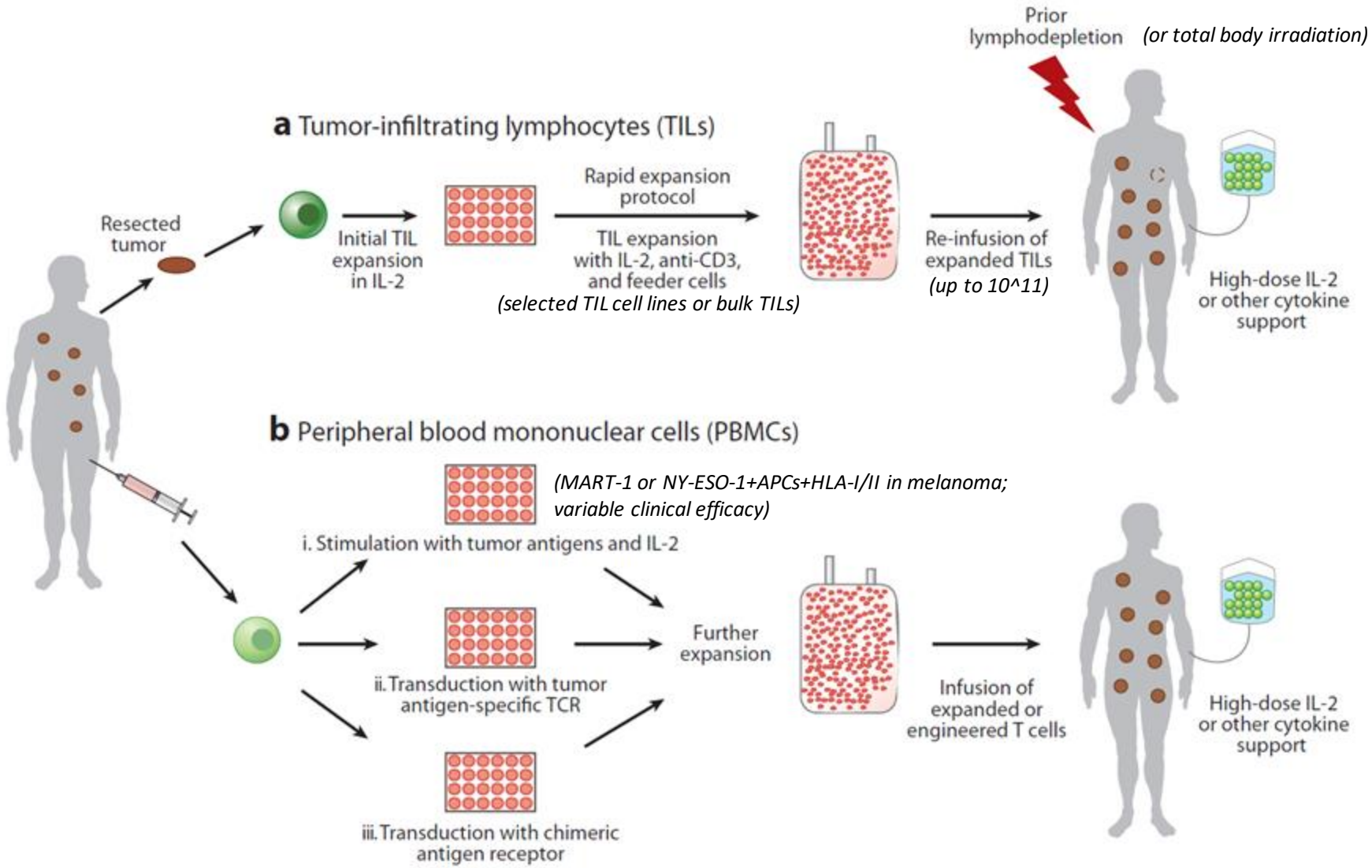




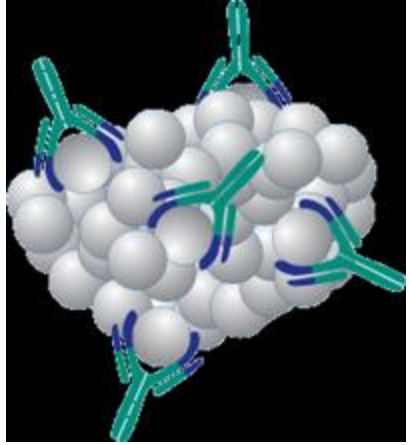


1-2-3-4

Diversi approcci per il trasferimento adottivo di linfociti T tumore-specifici per il melanoma metastatico



Lizee G Ann Rev 2013



Elimination

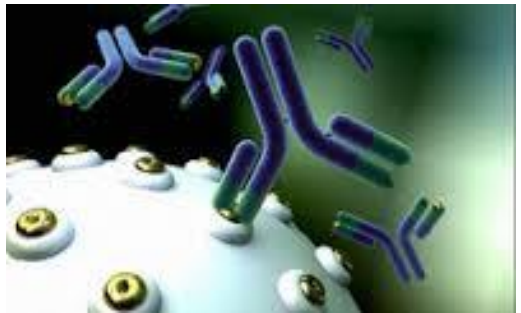
Escape

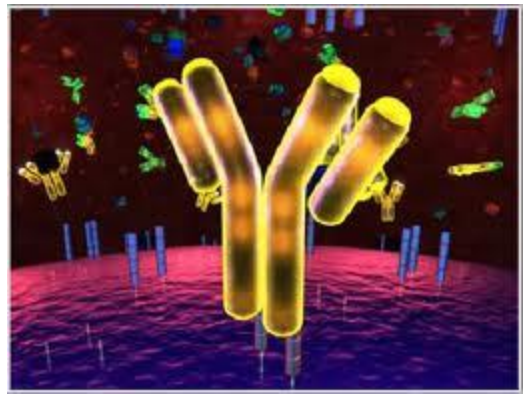
Gli anticorpi monoclonali:

come sfruttare un prodotto del sistema immunitario nella terapia contro il cancro

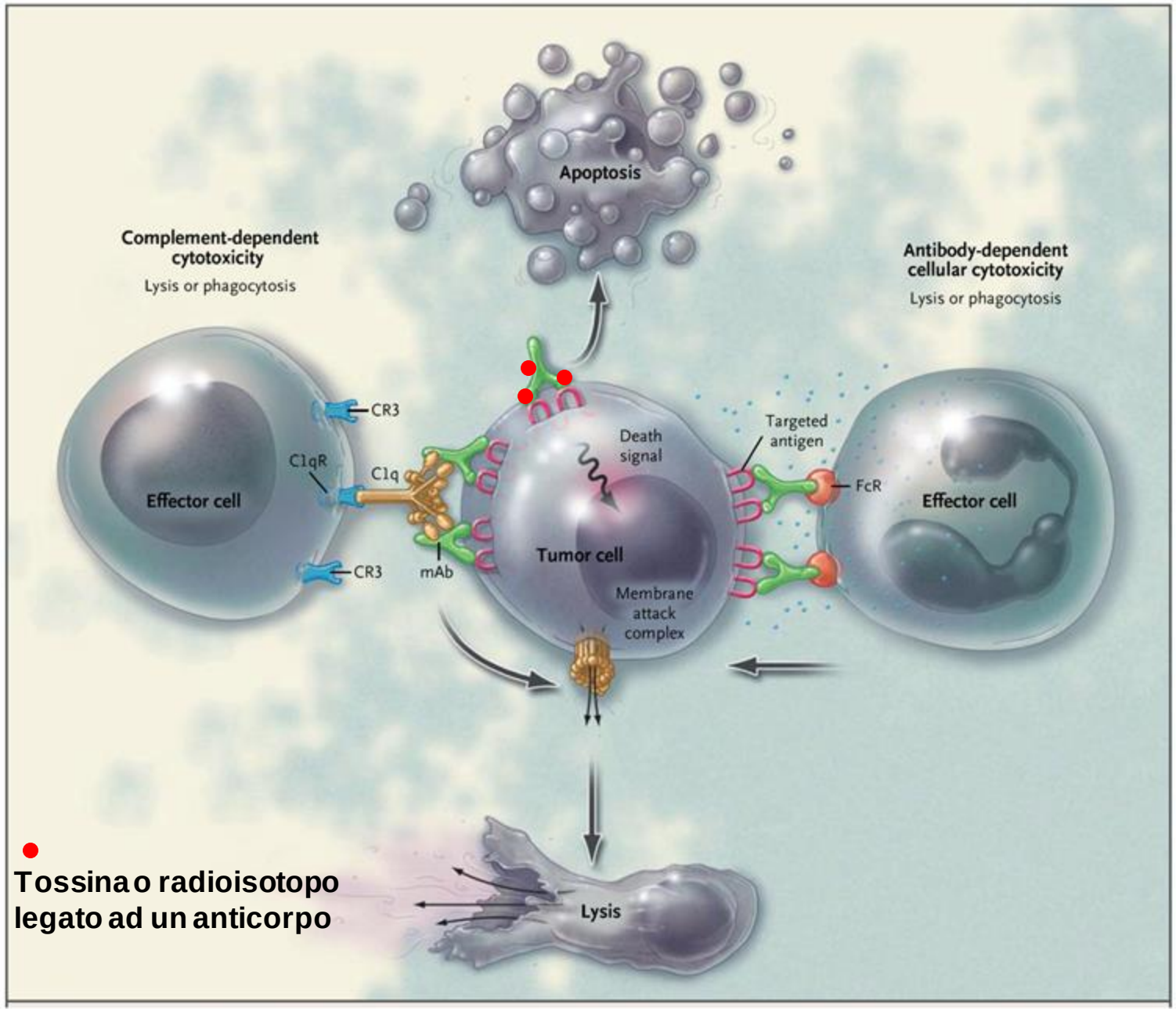
contro un antigene tumorale
o una molecola espressa dalla cellula neoplastica

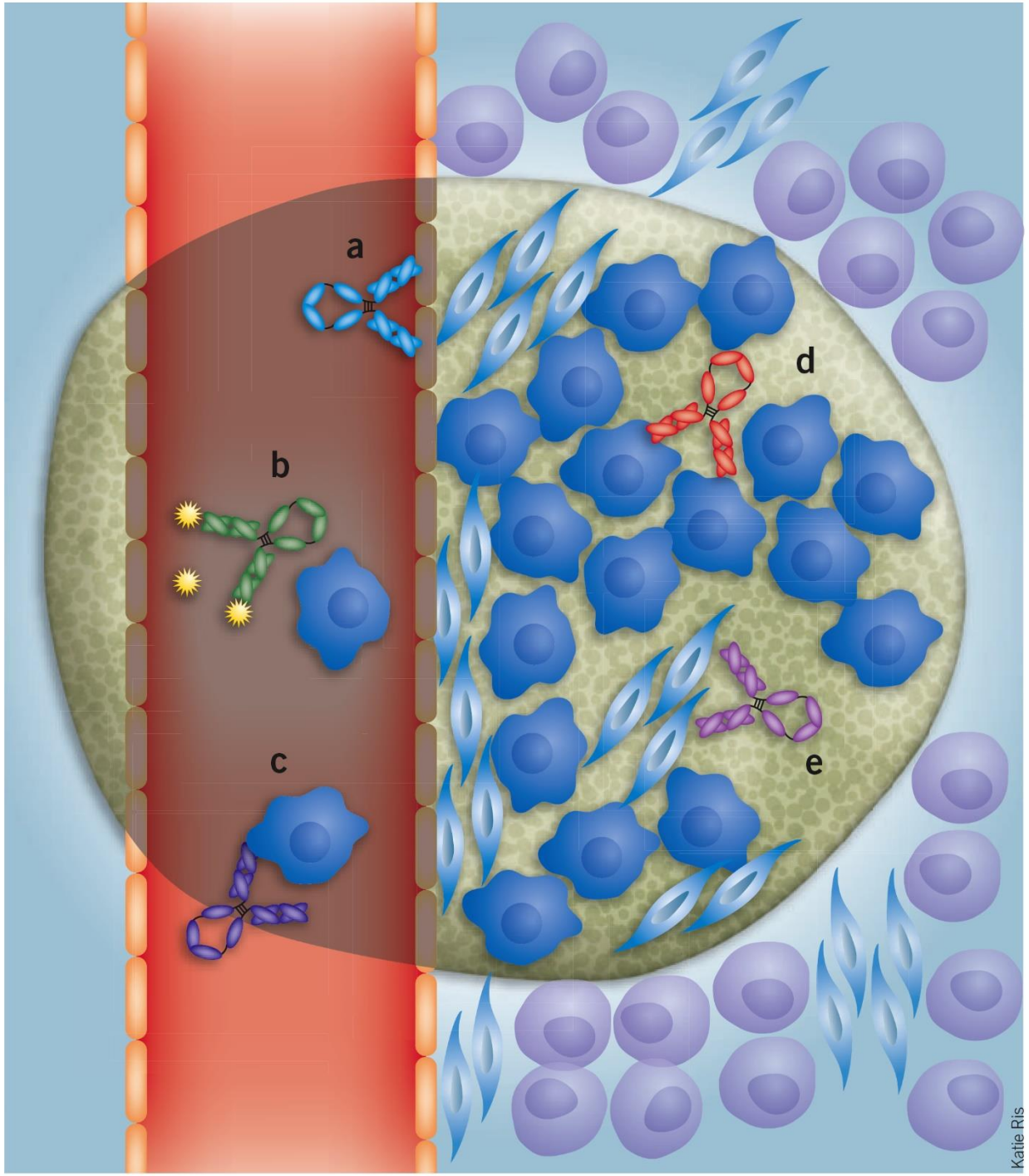
contro una molecola espressa dai linfociti T





Immunoterapia mediata dagli anticorpi monoclonali: meccanismi d'azione





Potential targets for antibody therapy of cancer

a) Tumor-associated blood vessel

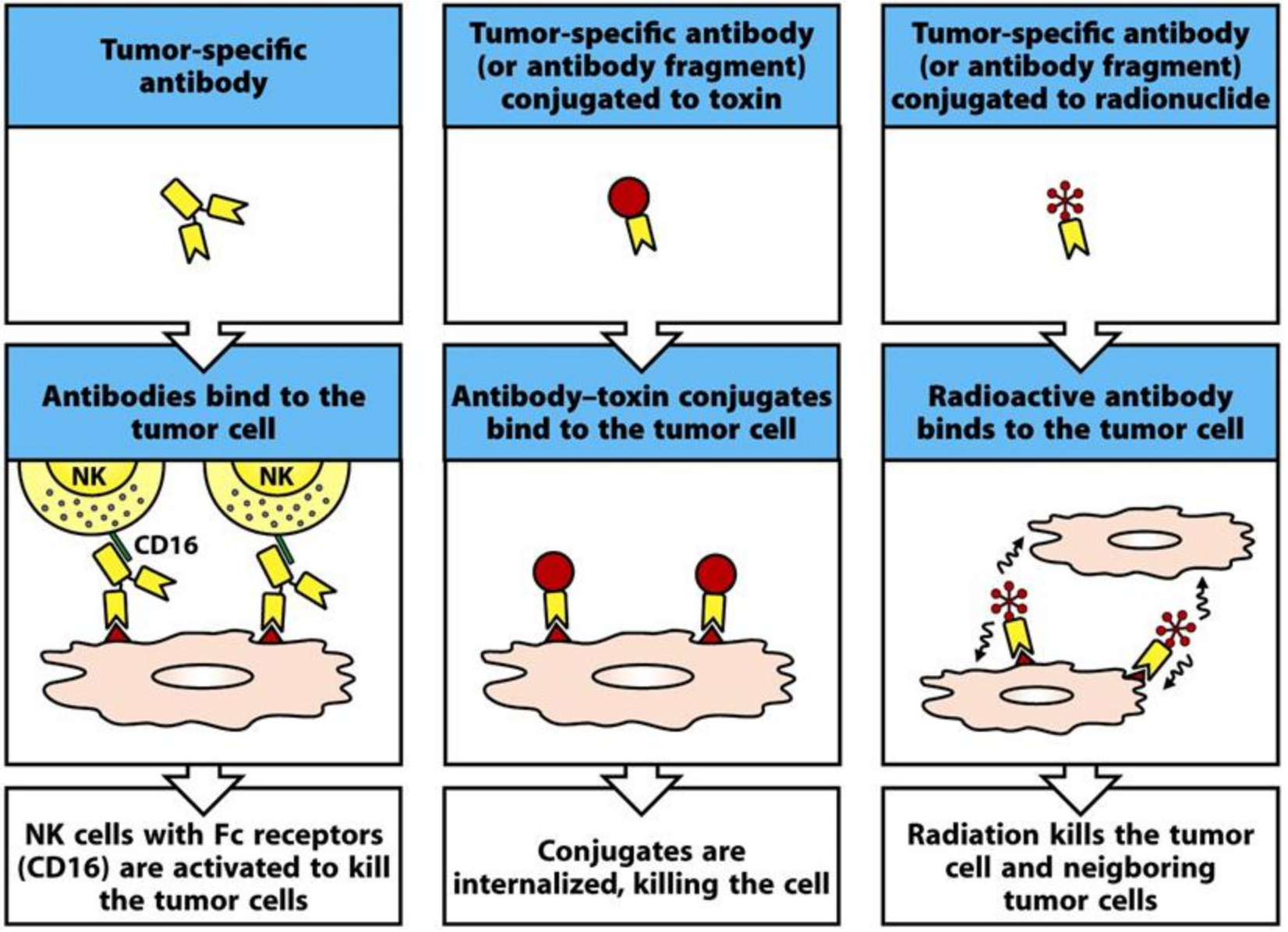
b) Vascular growth factors (i.e. VEGF)

c) Diffuse malignant cells

d) Tumor cells in a solid tumor

e) Tumor-associated stroma

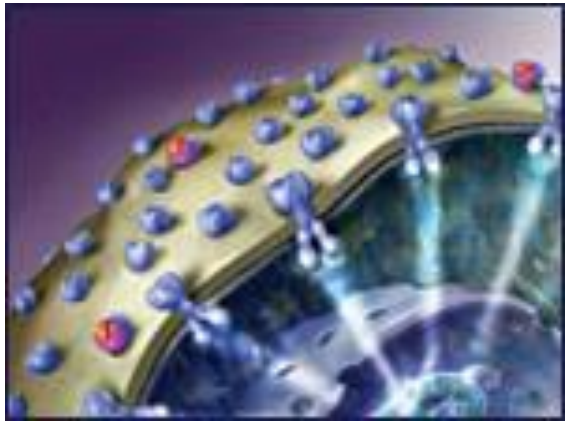
MoAb-MEDIATED IMMUNOTHERAPY



Anticorpi monoclonali approvati per l'uso clinico in oncologia

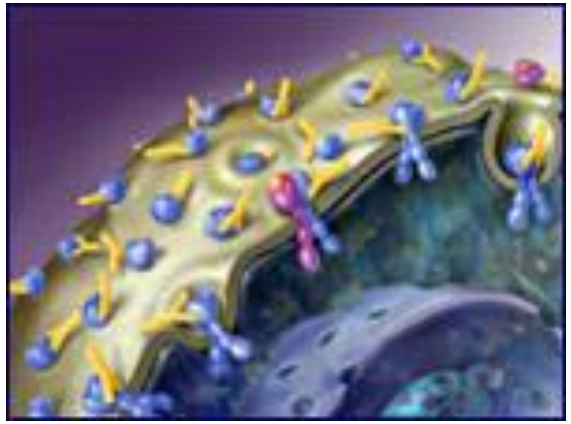
Generic name (trade name)	Origin	Isotype and format	Target	Indication	Year approved by FDA
Unconjugated mAbs					
Trastuzumab (Herceptin)	Humanized	Human IgG1	HER2/*neu*	Breast cancer	1998
Rituximab (Rituxan)	Murine-human chimeric	Human IgG1	CD20	Lymphoma	1997
Cetuximab (Erbitux)	Murine-human chimeric	Human IgG1	EGF receptor	Colorectal cancer	2004
Bevacizumab (Avastin)	Murine-human chimeric	Human IgG1	VEGF	Colorectal, lung cancers	2004
Alemtuzumab (Campath-1H)	Humanized	Human IgG1	CD52	Chronic lymphocytic leukemia	2001
Immunoconjugates					
Ibritumomab tiuxetan (Zevalin) together with rituximab	Murine	^{90}Y-radiolabeled murine IgG1	CD20	Lymphoma	2002
Tositumomab and ^{131}I tositumomab (Bexxar)	Murine	^{131}I-radioabeled murine IgG2a	CD20	Lymphoma	2003
Gemtuzumab (Myelotarg)	Human (drug derived from streptomycete)	Human IgG4 conjugated to calicheamicin	CD33	Acute myelogenous leukemia	2000

Trastuzumab
[un anticorpo diretto contro l'human epidermal growth factor receptor 2 (HER-2)] [nome commerciale HERCEPTIN]: storia di un successo



HER-2 iperespresso

HERCEPTIN



HERCEPTIN blocca HER-2

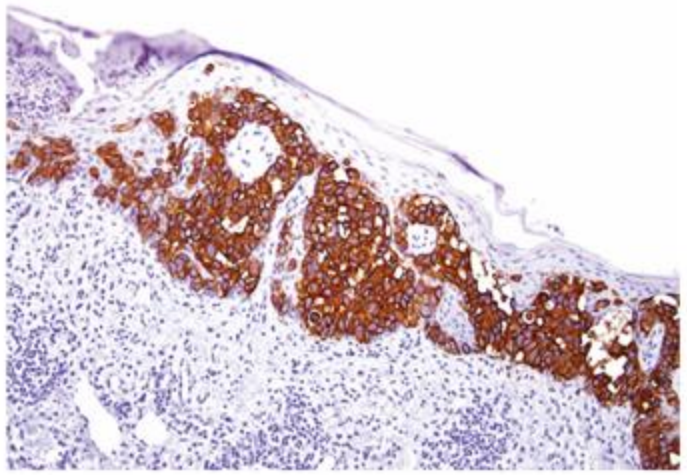
DALLA MOLECOLA ALLA CLINICA: Her2/Neu

- **Her2 è over-espresso nel 30% dei carcinomi mammari e questo correla con il grado di aggressività del tumore (*staging* e *grading* più avanzati).**

- **Rappresenta un utile mezzo per identificare quelle pazienti che potrebbero beneficiare della terapia con anticorpi anti-Her2.**

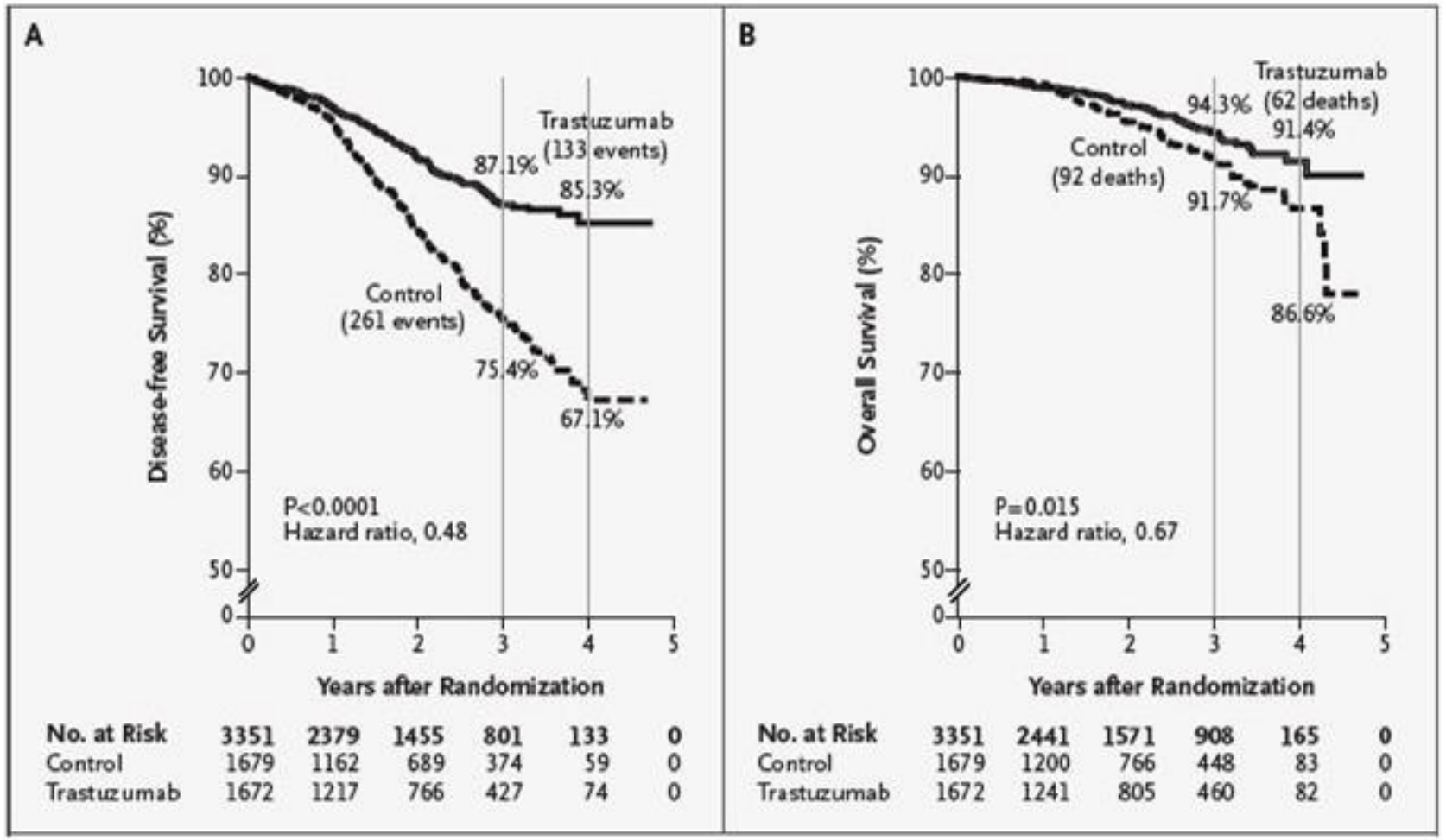
- **Inibizione di Her2 per trattare il carcinoma della mammella:**

L'uso dell'anticorpo monoclonale anti-Her2 TRASTUZUMAB (un mAb umanizzato) porta all'arresto del ciclo cellulare (effetto anti-proliferativo diretto o interferenza con il legame dell'EGF al recettore)



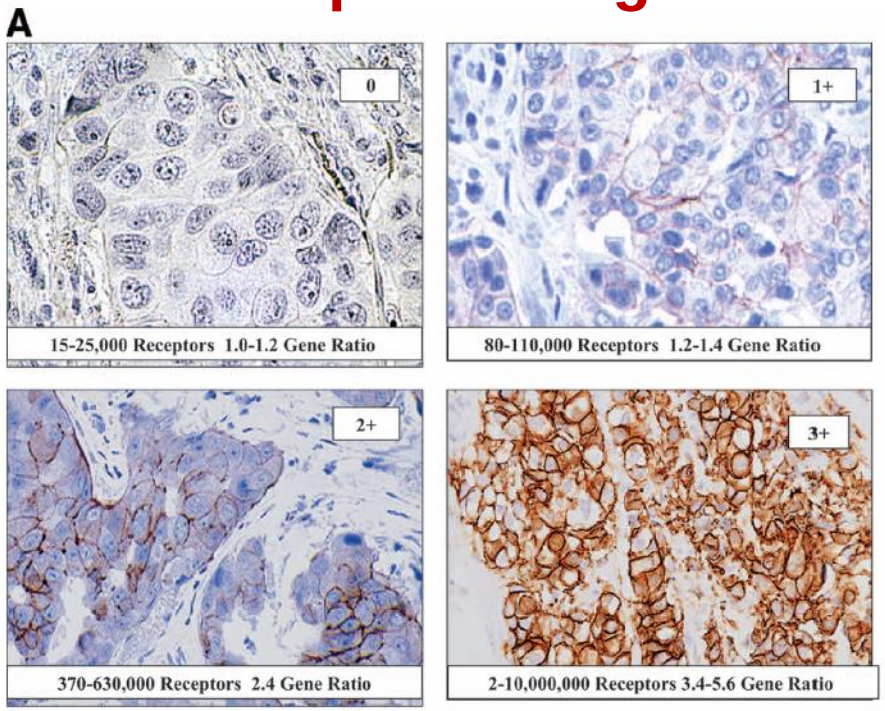
HER-2–positive invasive ductal carcinoma

Trastuzumab: the first success



Dati su 1694 donne (NEJM) hanno dimostrato un allungamento significativo della sopravvivenza dopo trattamento con chemioterapia seguita da Herceptin

Human epidermal growth factor receptor (HER)-2 testing



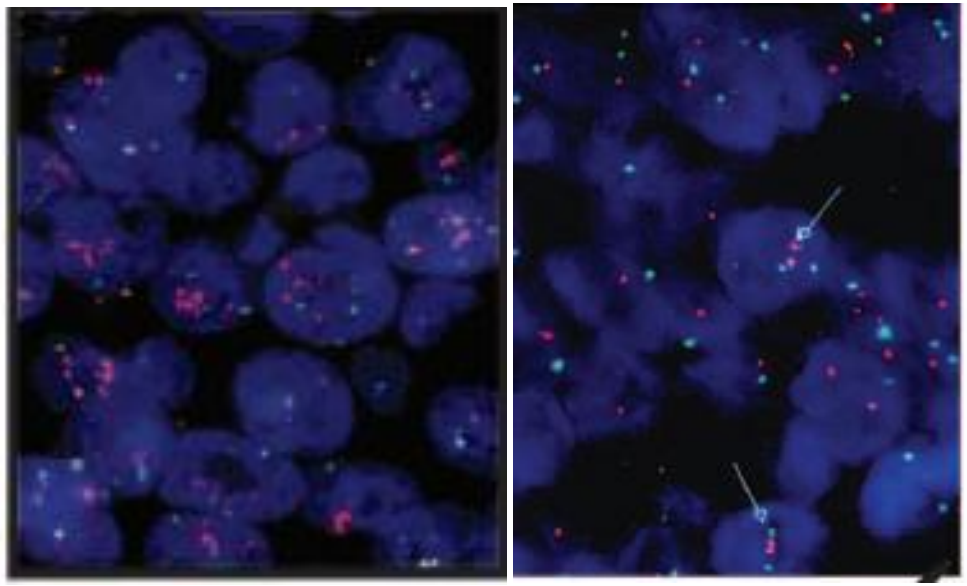
Score (USA):
0-1+: negative
2+: equivocal
3+: positive

Trastuzumab is not good for everyone…

Gene copy number:

=4 (amplified)

=1.9 (not amplified)



Pink: Her2 gene
Green: centromere (chr 17)

Immunoterapia dei tumori

Elimination

Attivazione dell'immunità innata e adattativa

- Vaccinazione con antigeni tumorali
- Anticorpi monoclonali che attivano molecole co-stimolatorie (OX40, 4-1BB, CD40, ecc.)
- Trattamento con citochine (es., IFN-α, IL-2)
- Aumento della presentazione dell'antigene (es., TLRs, DCs)
- Trasferimento adottivo di linfociti T tumore-specifici

Premere sull'acceleratore

Escape

Neutralizzazione dei meccanismi di inibizione e di soppressione

- Anticorpi monoclonali contro molecole inibitorie (anti-CTLA-4, anti-PD-1)
- Chemioterapia (es. ciclofosfamide)
- mAbs anti-CD25 (Treg)

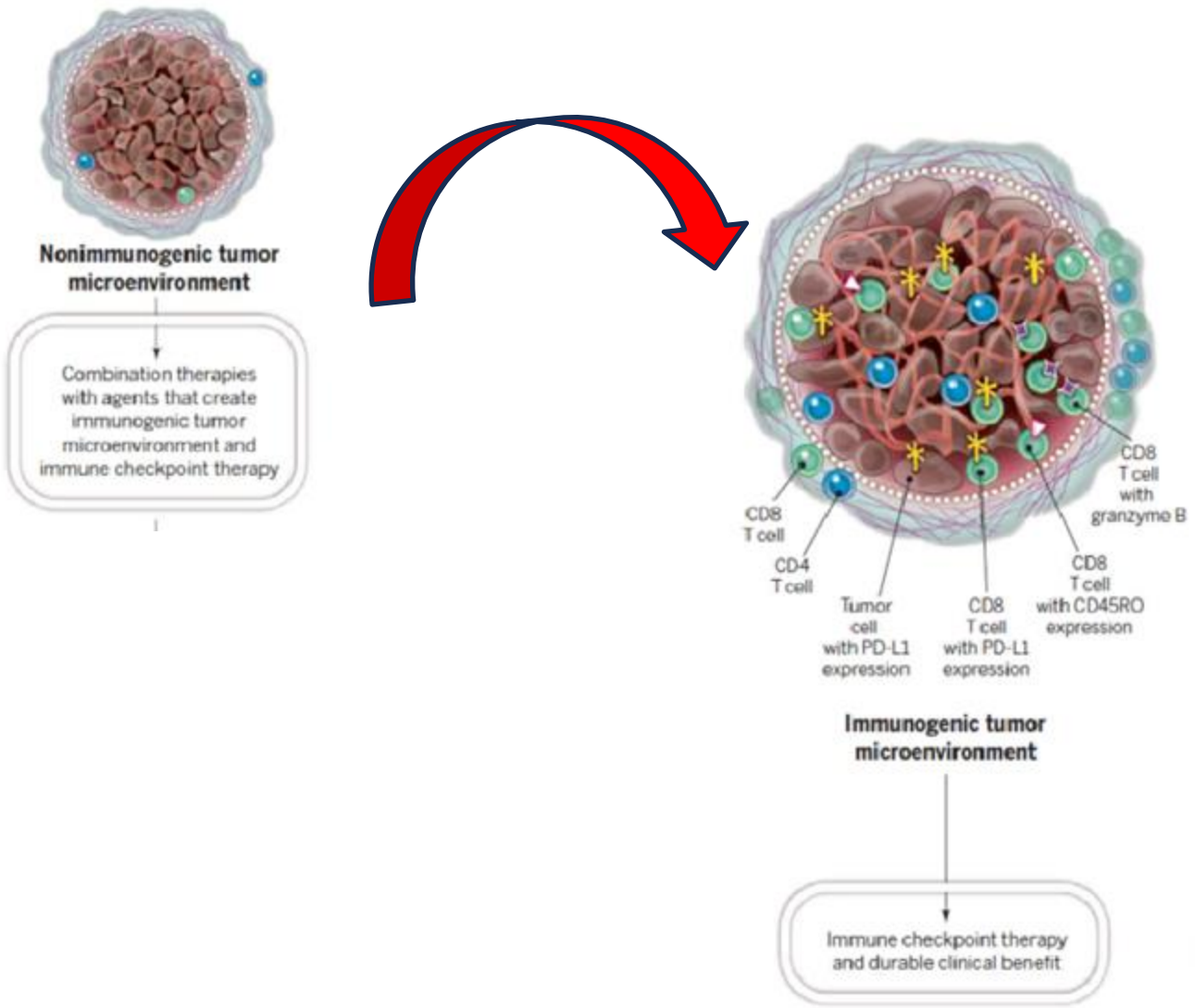
Togliere i freni

2018 Nobel Prize in Physiology and Medicine was awarded to Tasuku Honjo and James Allison for their discoveries in cancer immunology.

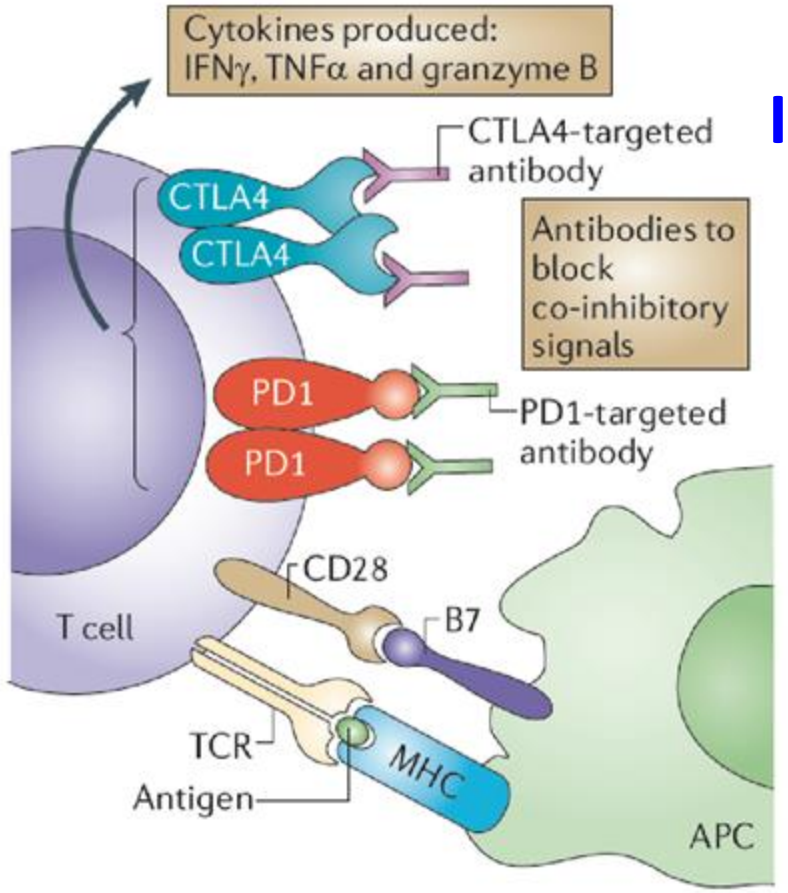
Professor Honjo was awarded due to his discovery of the programmed death molecule-1 (PD-1) on T cells.

Professor Allison discovered another important immunosuppressive molecule: cytotoxic T-lymphocyte antigen-4 (CTLA-4)

Trasformare un tumore “freddo” in uno “caldo”



Togliere i freni….



Ipilimumab (anti-CTLA-4)

Nivolumab (anti-PD1)

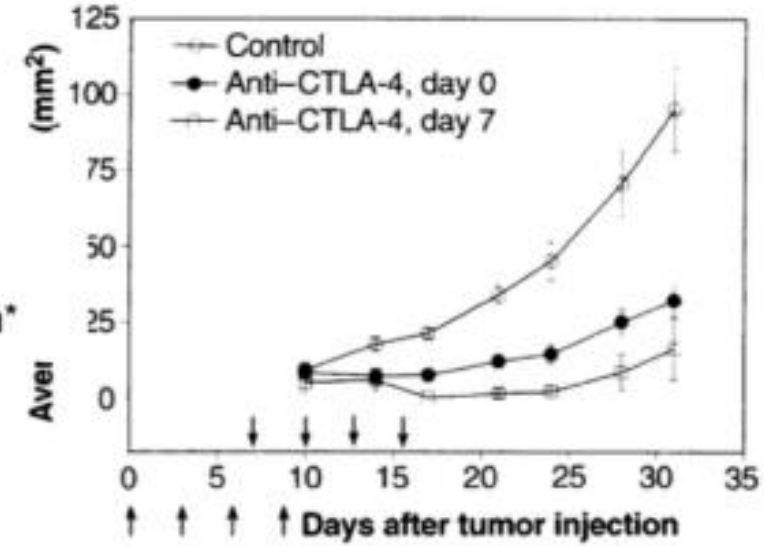
Metastatic melanoma
FDA 2011 Ipilimumab
FDA 2014 Nivolumab

Immunocheckpoint blockade therapy

Enhancement of Antitumor Immunity by CTLA-4 Blockade

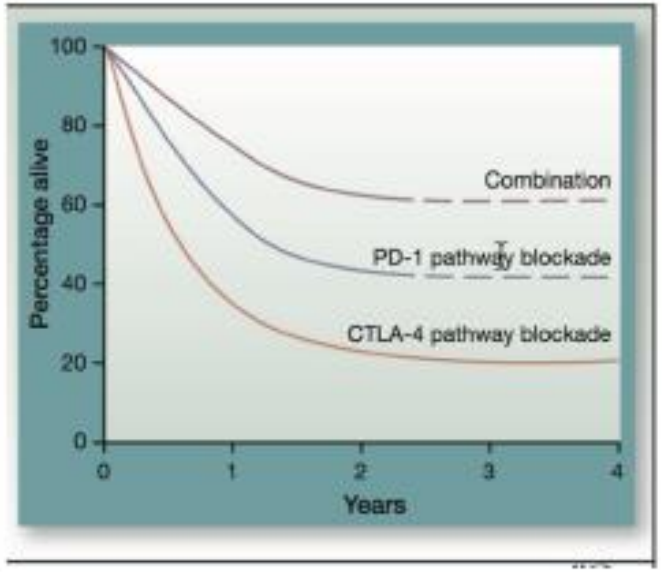
Dana R. Leach, Matthew F. Krummel, James P. Allison*

SCIENCE • VOL. 271 • 22 MARCH 1996

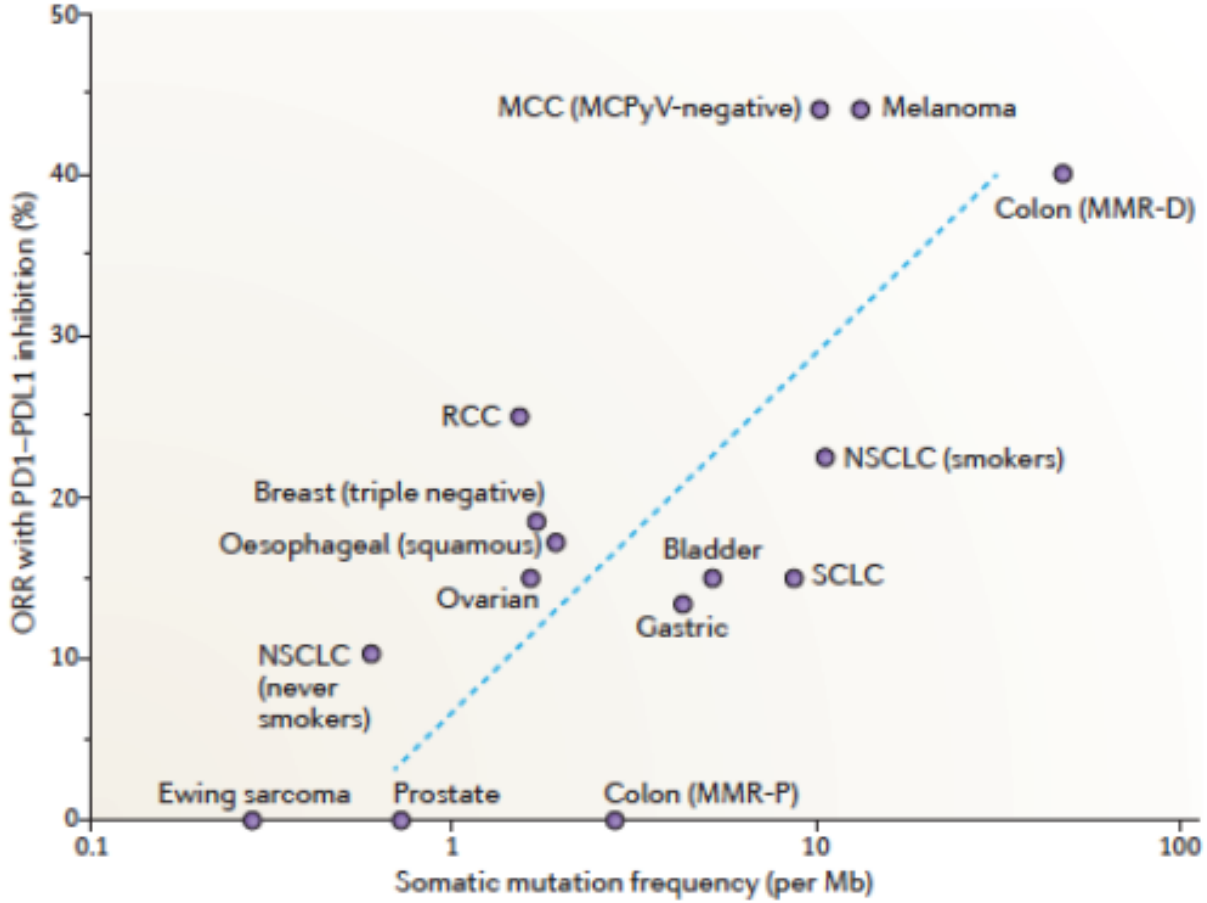


...ategies for overcoming tumor immune evasion mechanisms and examples of agents in clinical development (12)

Treatment strategy	Examples of agents in clinical development
Reversing the inhibition of adaptive immunity (blocking T-cell checkpoint pathways)	
• Inhibiting the CTLA-4 checkpoint molecule[a]	Ipilimumab: approved for melanoma Tremelimumab: phase II for malignant mesothelioma, HCC, melanoma
• Inhibiting the interaction between PD-1 checkpoint and its ligands[a]	Nivolumab (anti–PD-1): phase III for melanoma, NSCLC, RCC Pembrolizumab (MK-3475; anti–PD-1): phase III for NSCLC, melanoma MPDL3280A (RG7446; anti–PD-L1): phase III for NSCLC Pidilizumab (CT-011; anti–PD-1): phase II for FL, prostate, pancreatic, melanoma AMP-514 (MEDI0680; anti–PD-1): phase I for solid tumors MEDI4736 (anti–PD-L1): phase I for solid tumors AMP-224 (recombinant PD-L-Fc fusion protein): phase I for solid tumors rHIgM12B7 (anti–PD-L2): phase I for melanoma
• Inhibiting the LAG-3 checkpoint molecule	IMP321: phase I for breast, RCC; phase II for melanoma BMS-986016: phase I for solid tumors
• Inhibiting the TIM-3 checkpoint	No agent undergoing clinical evaluation

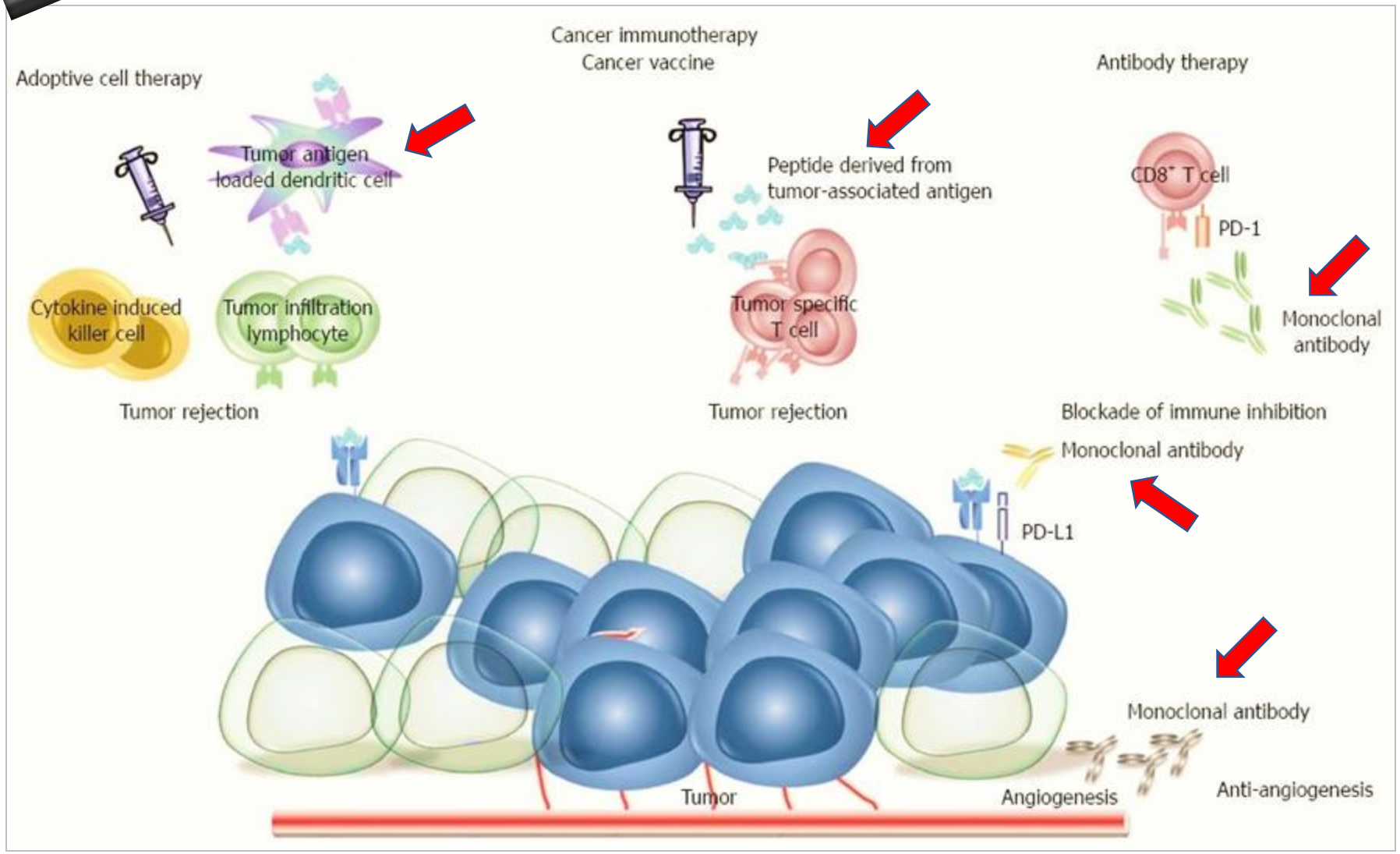


Correlation of tumor somatic mutation frequency with objective response rates to immune checkpoint blockade



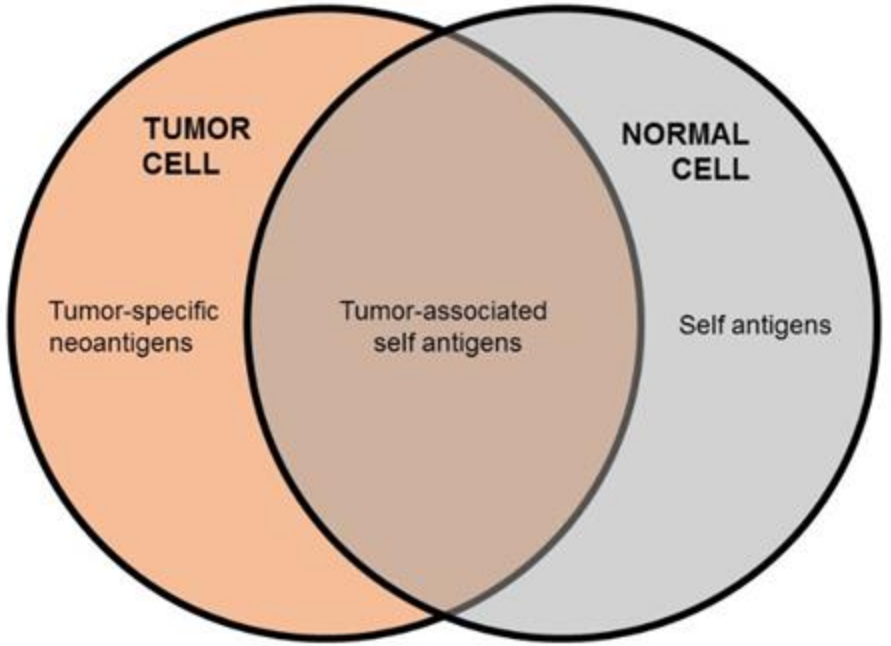
Premere sull'acceleratore e togliere i freni:

la terapia che unisce i vaccini anti-tumorali con gli inibitori degli «immuno checkpoint»



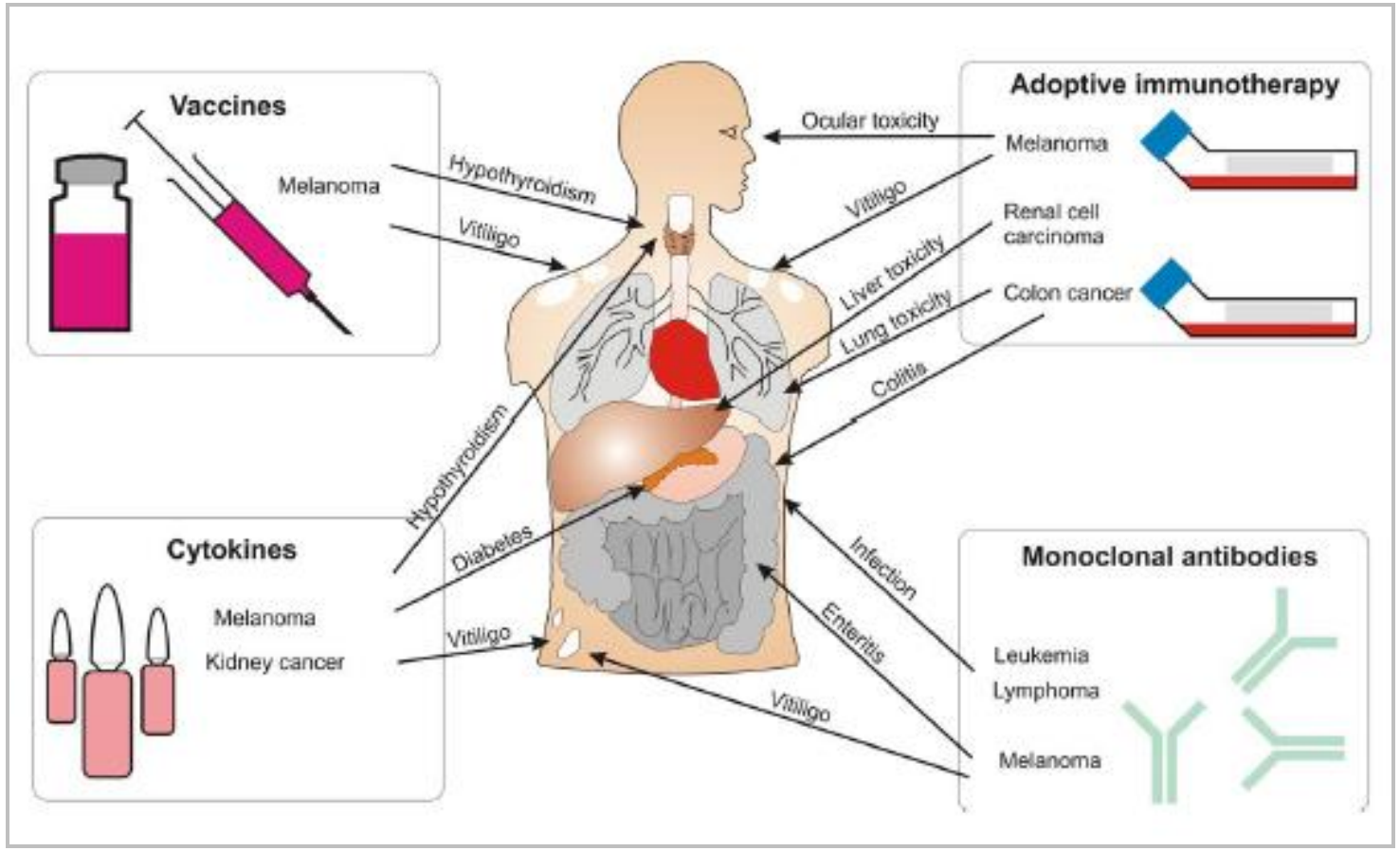
ATTENZIONE!

Tumours represent a dilemma to *"self-non self"* dichotomy: the link between tumor immunity and autoimmunity



The tumor represents an immunoprivileged self entity, based on the observation that malignant cells could employ self tolerance mechanisms more efficiently than their normal counterparts to avoid autoimmune responses.

Immune toxicity associated with immunotherapy of cancer



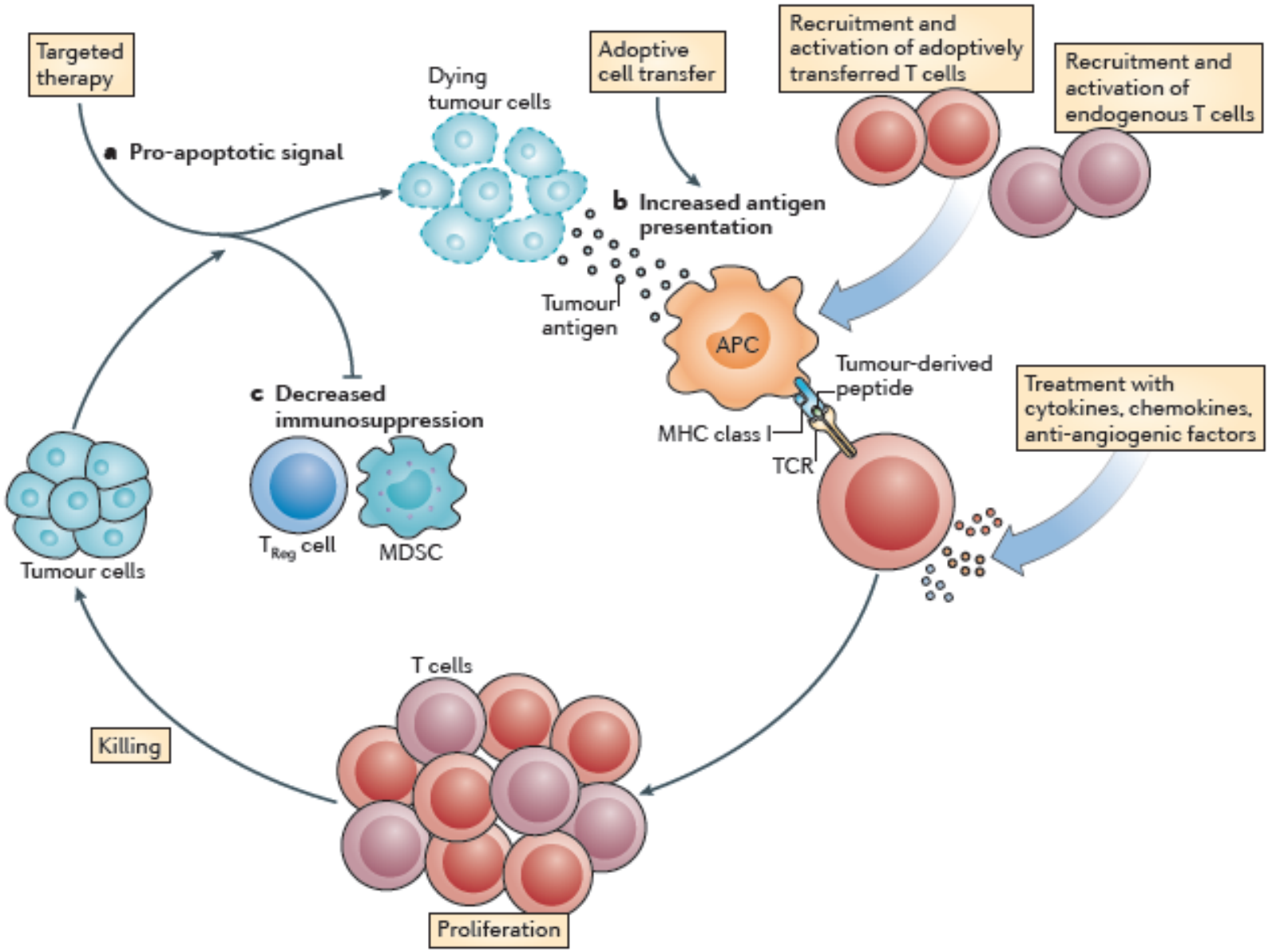
Clinical benefits of anti-cancer immunotherapy are often paralleled by robust autoimmune reactions, suggesting that tumor cells, no matter how malignant they are, remain for the most part self entities.

The challenge of the future cancer immunotherapy research will be a better understanding of the link between tumor immunity and autoimmunity

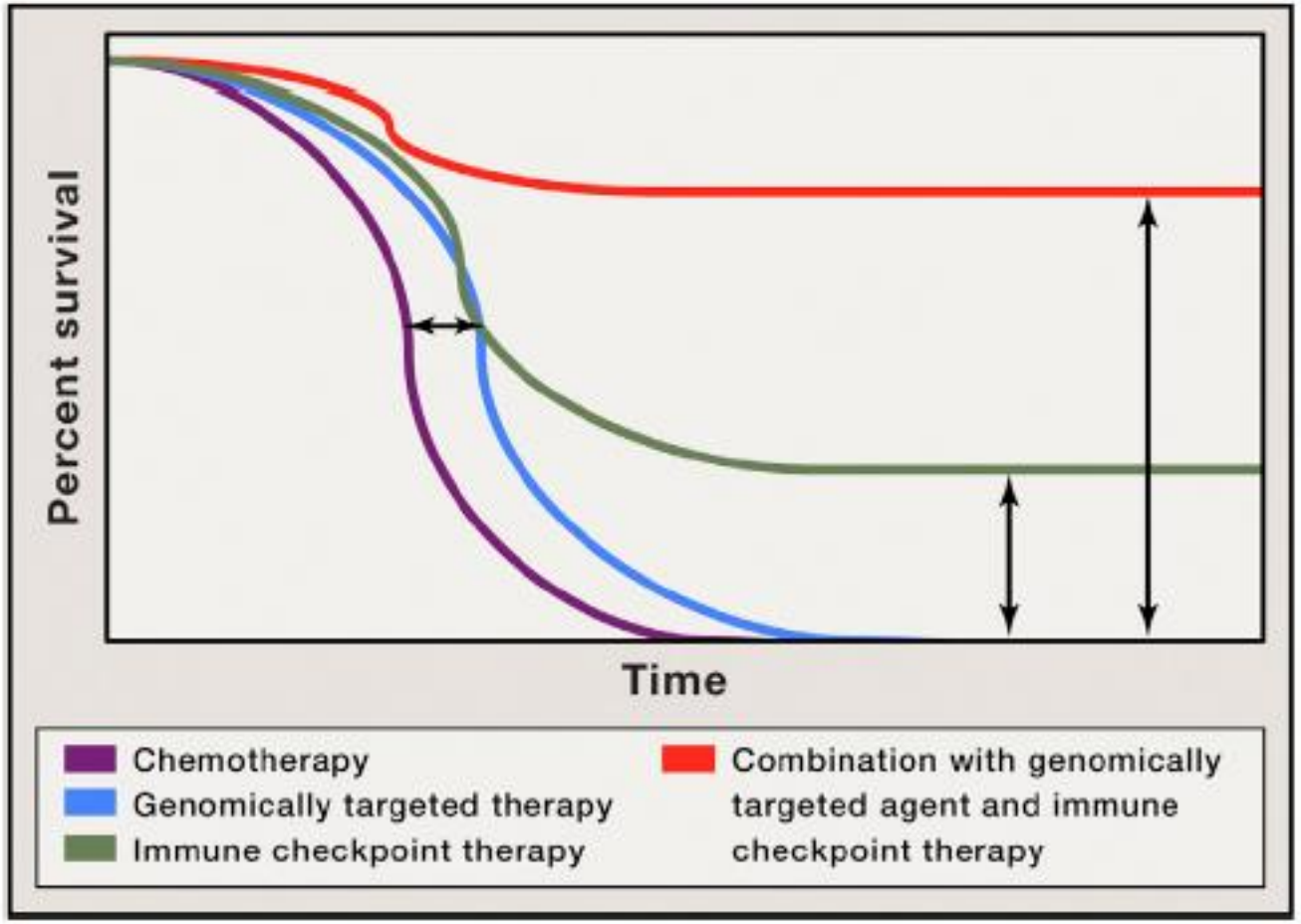
To avoid

Jumping from the frying pan into the fire

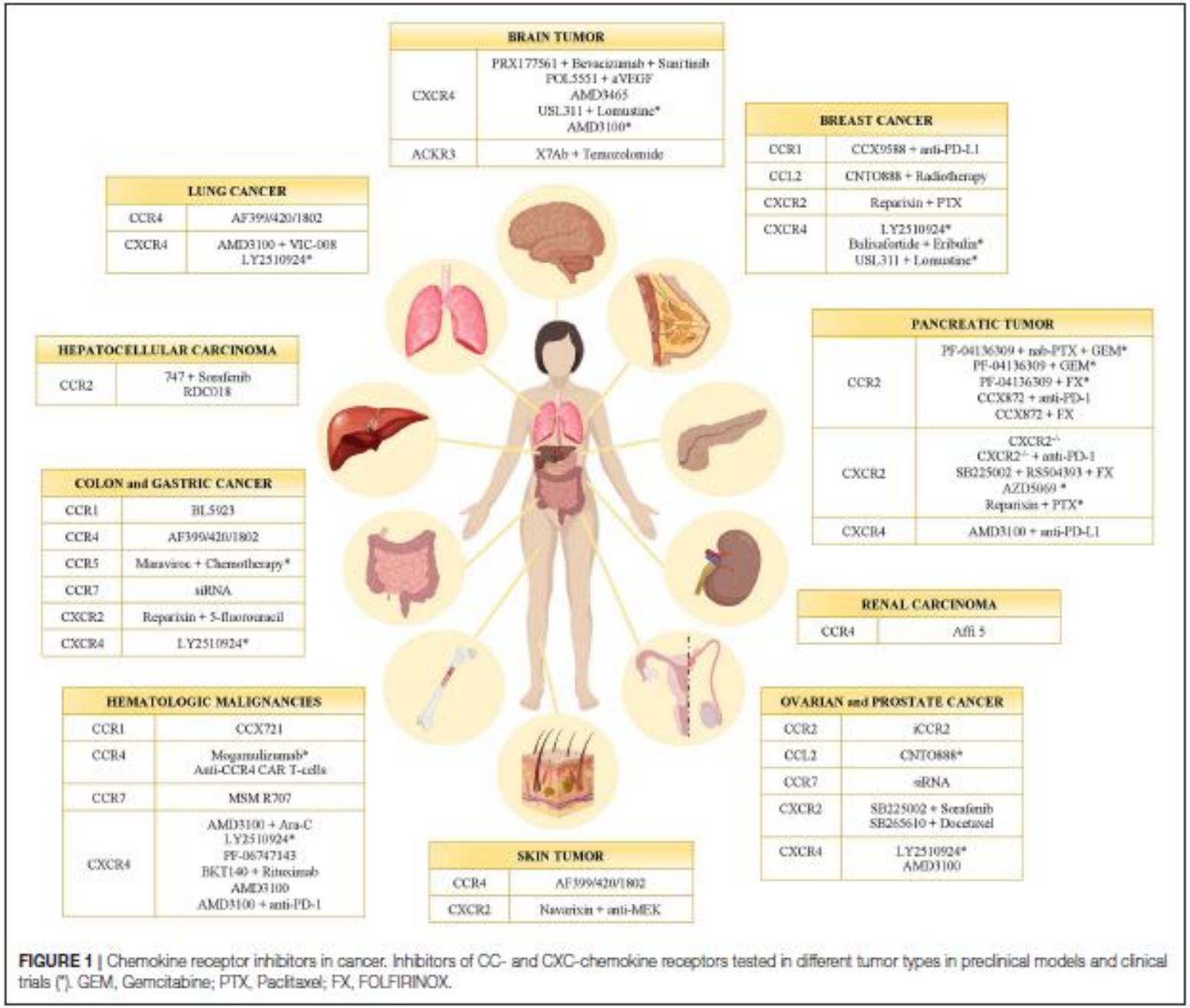
Combining targeted therapies with adoptive cell transfer-based immunotherapy



Improved overall survival as a result of combination therapy



Chemokine receptor as targets for therapy



BRAIN TUMOR	
CXCR4	PRX177561 + Bevacizumab + Sunitinib PCL5551 + aVEGF AMD3465 USL311 + Lomustine* AMD3100*
ACKR3	X7Ab + Temozolomide

LUNG CANCER	
CCR4	AF399/420/1802
CXCR4	AMD3100 + VIC-008 LY2510924*

BREAST CANCER	
CCR1	CCX9588 + anti-PD-L1
CCL2	CNTO888 + Radiotherapy
CXCR2	Reparixin + PTX
CXCR4	LY2510924* Balixafortide + Eribulin* USL311 + Lomustine*

HEPATOCELLULAR CARCINOMA	
CCR2	747 + Sorafenib RDC018

PANCREATIC TUMOR	
CCR2	PF-04136309 + nab-PTX + GEM* PF-04136309 + GEM* PF-04136309 + FX* CCX872 + anti-PD-1 CCX872 + FX
CXCR2	CXCR2$^{-/-}$ CXCR2$^{-/-}$ + anti-PD-1 SB225002 + RS504393 + FX AZD5069 * Reparixin + PTX*
CXCR4	AMD3100 + anti-PD-L1

COLON and GASTRIC CANCER	
CCR1	BL5923
CCR4	AF399/420/1802
CCR5	Maraviroc + Chemotherapy*
CCR7	siRNA
CXCR2	Reparixin + 5-fluorouracil
CXCR4	LY2510924*

RENAL CARCINOMA	
CCR4	Affi 5

HEMATOLOGIC MALIGNANCIES	
CCR1	CCX721
CCR4	Mogamulizumab* Anti-CCR4 CAR T-cells
CCR7	MSM R707
CXCR4	AMD3100 + Ara-C LY2510924* PF-06747143 BKT140 + Rituximab AMD3100 AMD3100 + anti-PD-1

OVARIAN and PROSTATE CANCER	
CCR2	iCCR2
CCL2	CNTO888*
CCR7	siRNA
CXCR2	SB225002 + Sorafenib SB265610 + Docetaxel
CXCR4	LY2510924* AMD3100

SKIN TUMOR	
CCR4	AF399/420/1802
CXCR2	Navarixin + anti-MEK

FIGURE 1 | Chemokine receptor inhibitors in cancer. Inhibitors of CC- and CXC-chemokine receptors tested in different tumor types in preclinical models and clinical trials (*). GEM, Gemcitabine; PTX, Paclitaxel; FX, FOLFIRINOX.

Mollica Front imm 2019

Combinare vecchie e nuove terapie può essere la strategia vincente!

immunoterapia

radioterapia

chemioterapia

chirurgia