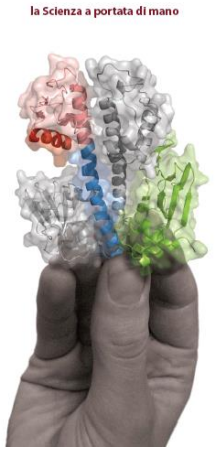
SAPIENZA
UNIVERSITÀ DI ROMA

Comunicazione delle Scienze Biomediche

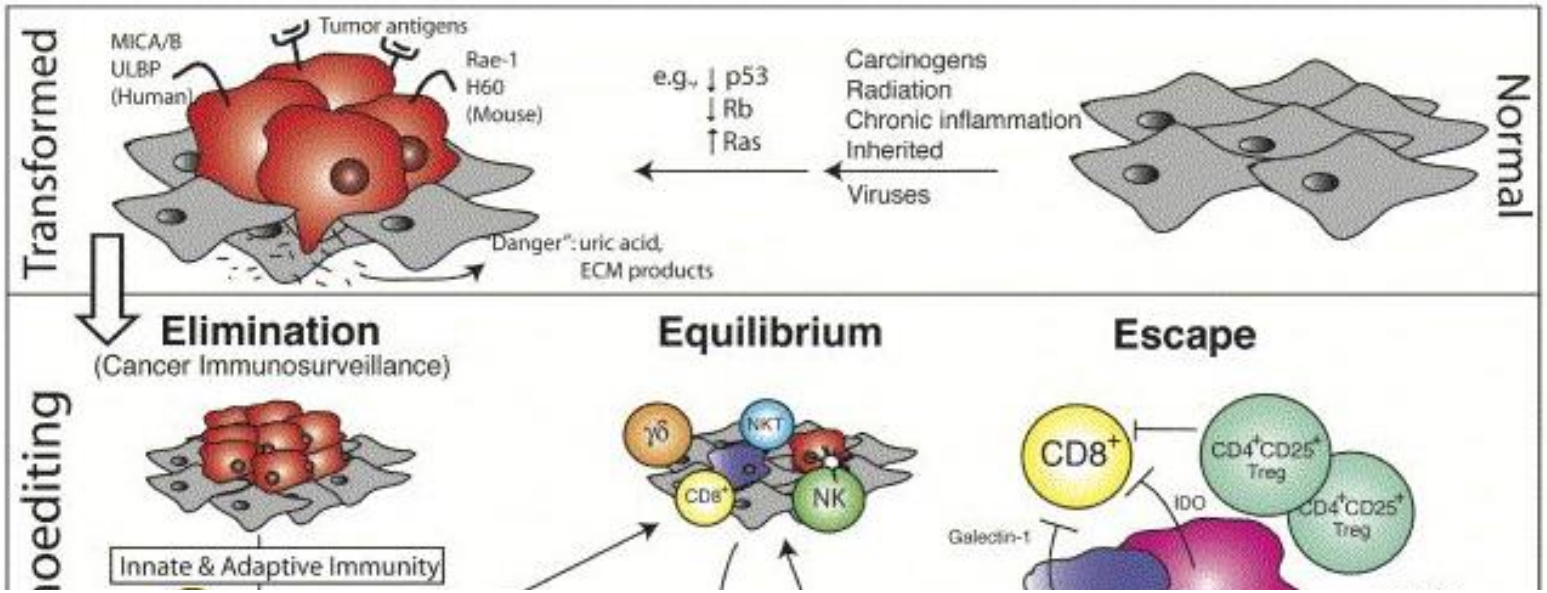
Prof.ssa Cristina Cerboni



Immunoterapia dei tumori

Anno Accademico 2025-2026

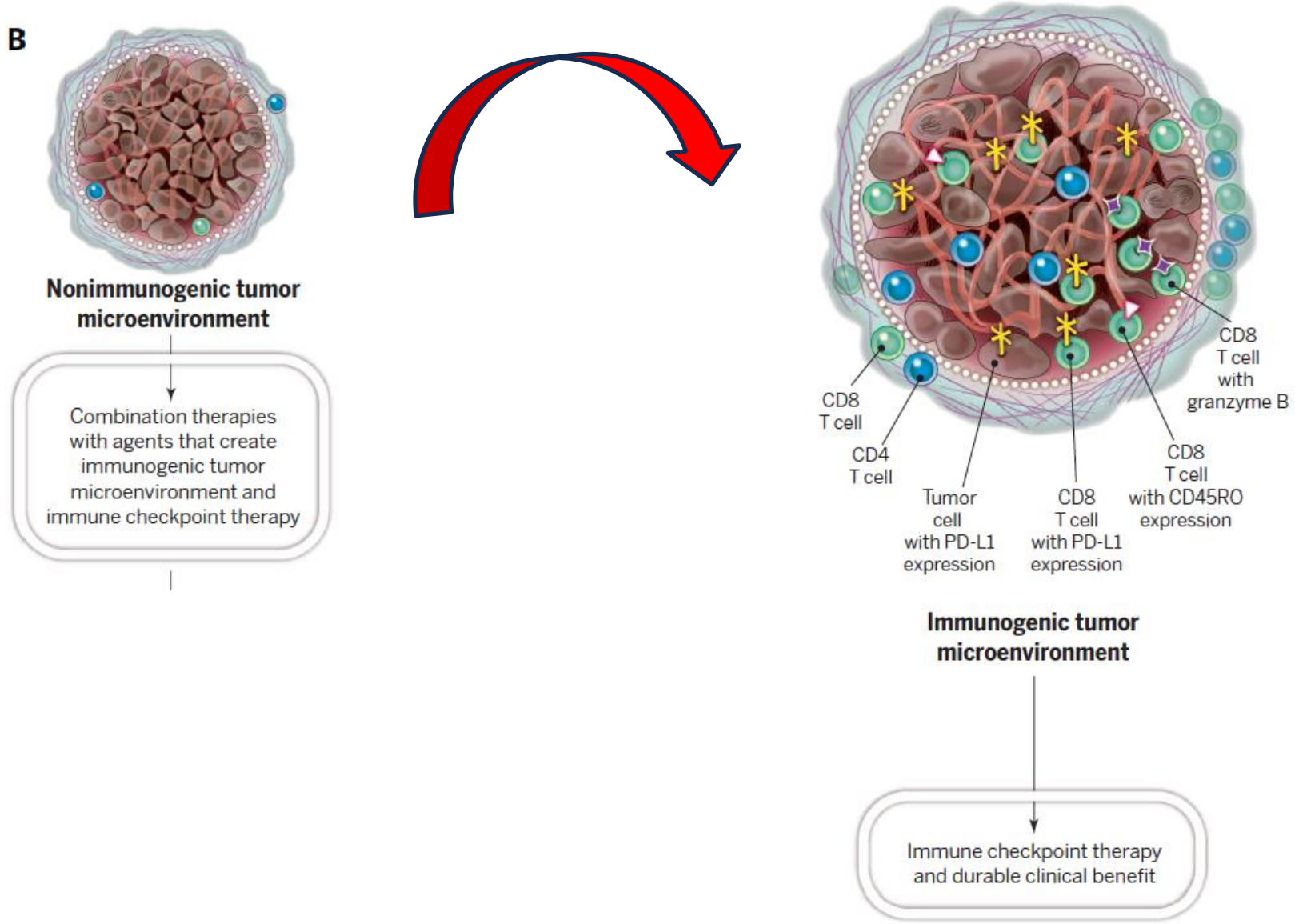
The immune system establishes a dynamic interaction with the tumour: cancer immunoediting



In an attempt to re-engage the immune system in its fight against cancer, cancer immunotherapy focuses on the development of agents that can activate the immune system to recognize and kill tumour cells.

Dunn et al Immunity 2004

Trasformare un tumore “freddo” in uno “caldo”



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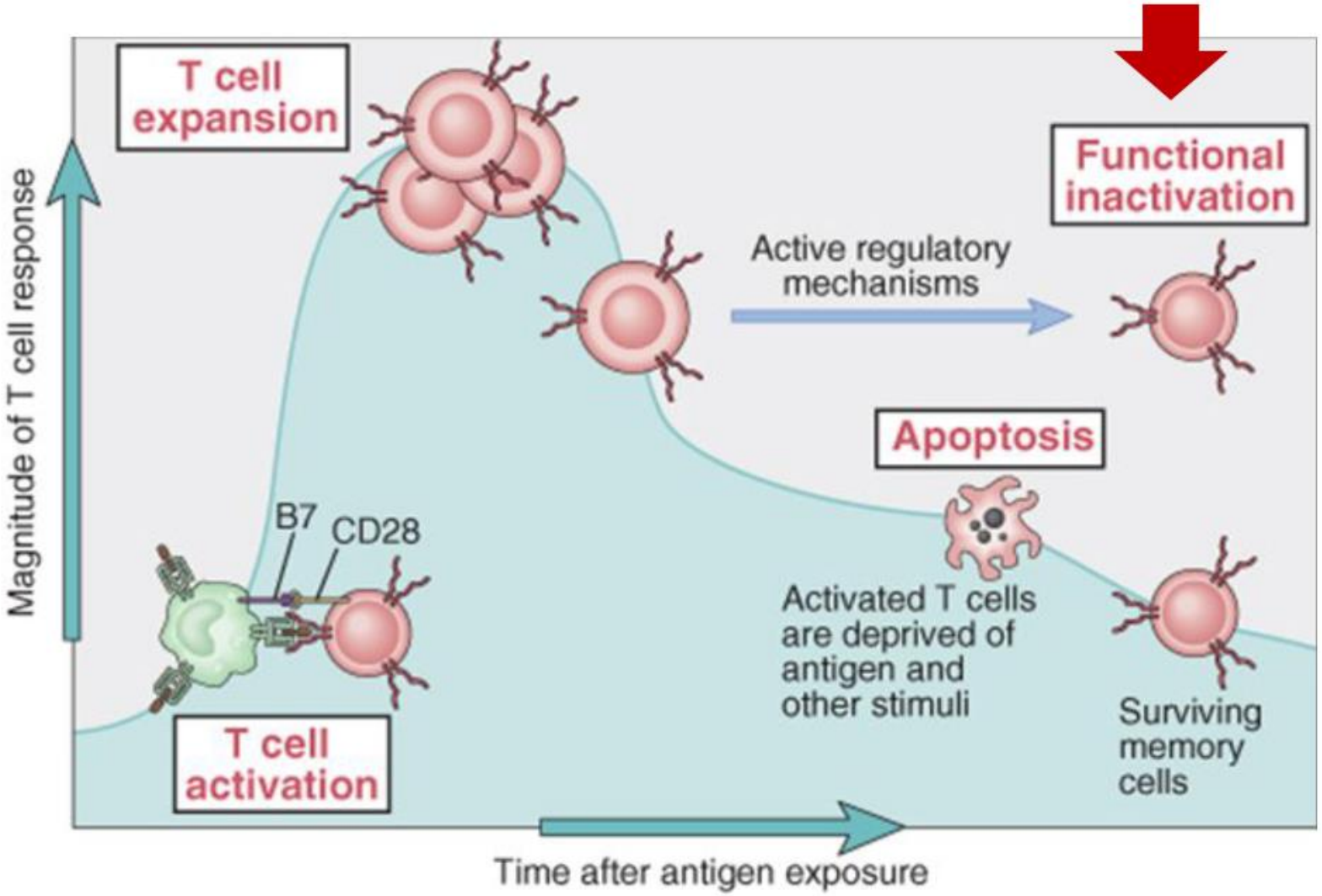
- Anticorpi monoclonali contro molecole inibitorie (anti-CTLA-4, anti-PD-1)

i checkpoint inhibitors!

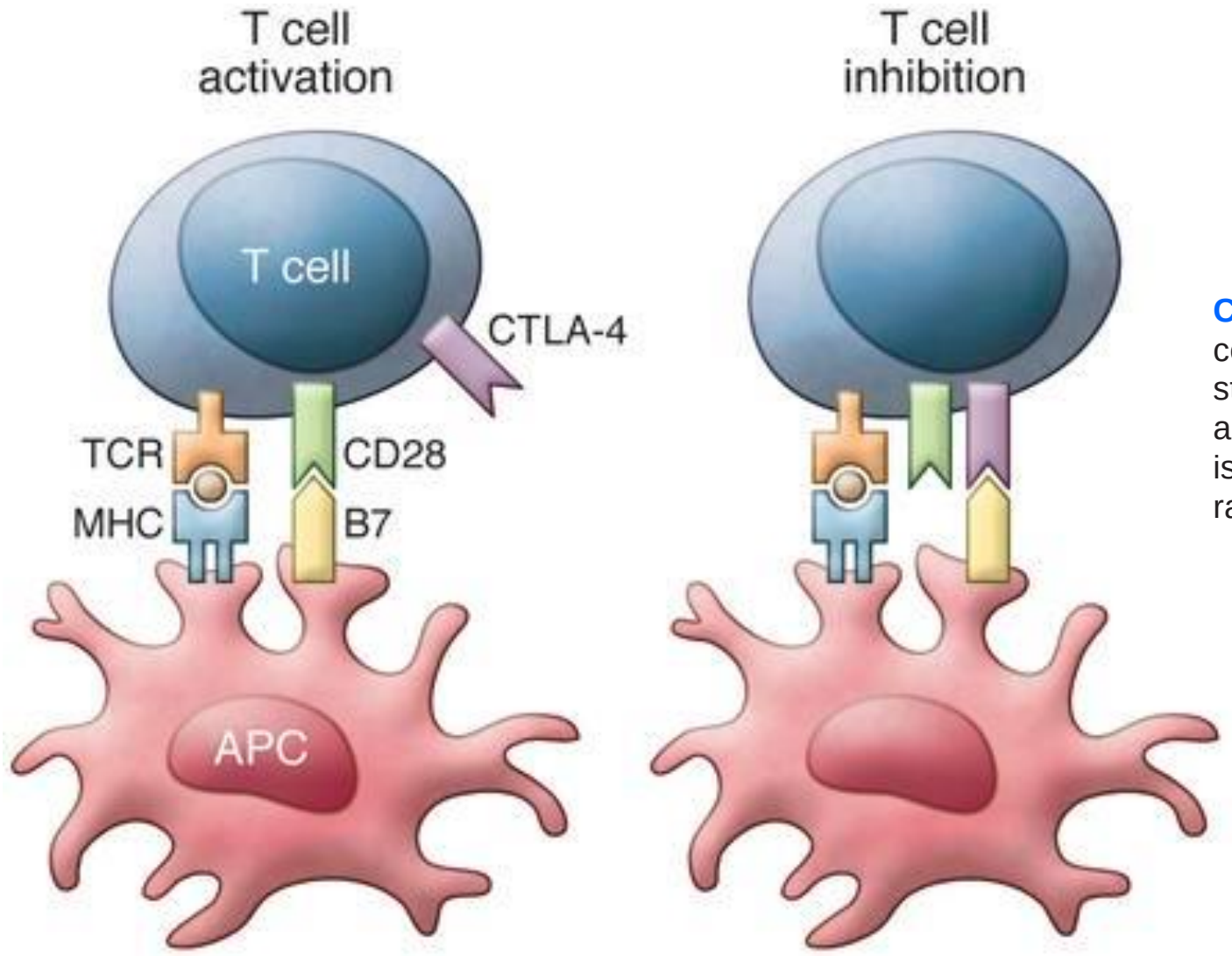
- Chemioterapia (es. ciclofosfamide)
- mAbs anti-CD25 (Treg)

Togliere i freni

Lo spegnimento della risposta immunitaria



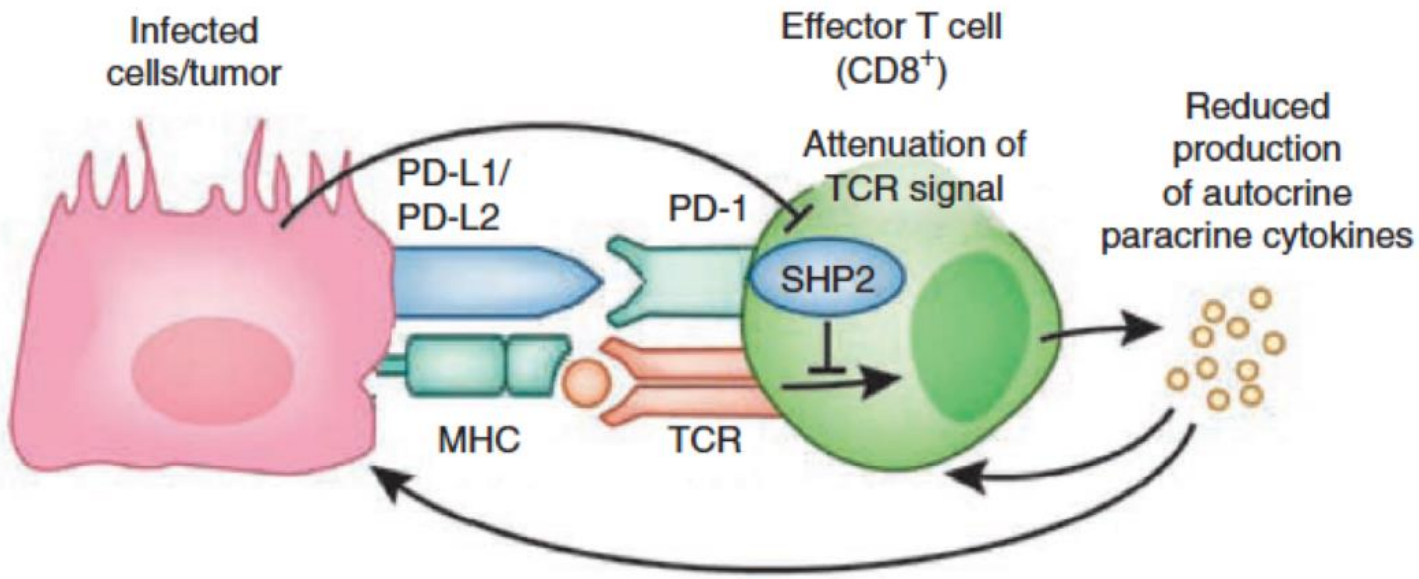
Lo spegnimento della risposta immunitaria: il recettore inibitorio CTLA-4



CTLA-4 is induced on activated T cells and binds to the same co-stimulatory ligands (B7.1 and B7.2) as CD28, but CTLA-4 engagement is inhibitory for T-cell activation, rather than enhancing

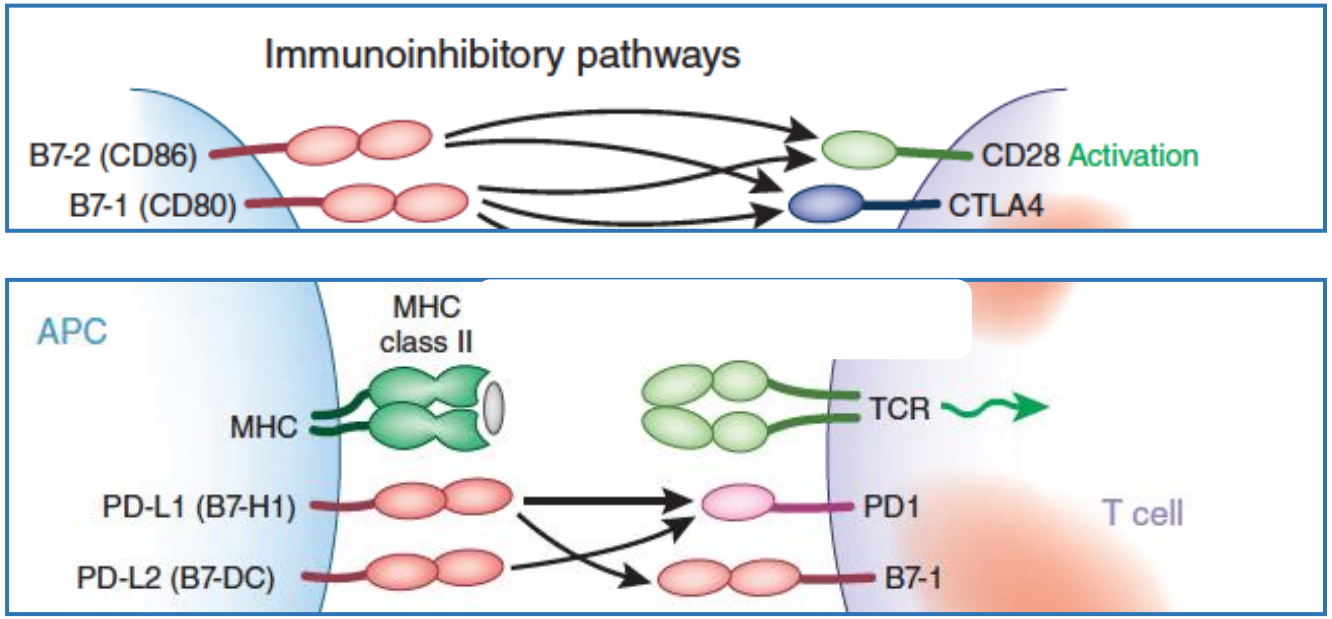
CTLA-4 has a higher affinity for its B7 ligands than does CD28

Lo spegnimento della risposta immunitaria: il recettore inibitorio PD-1 e i suoi ligandi (PD-L1, PD-L2)



Okazaki T et al Nature Immunol 2013

I linfociti T «exhausted» possono esprimere diversi recettori inibitori…



Adapted from Freeman GJ & Sharpe AH Nature Immunol 2012

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

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

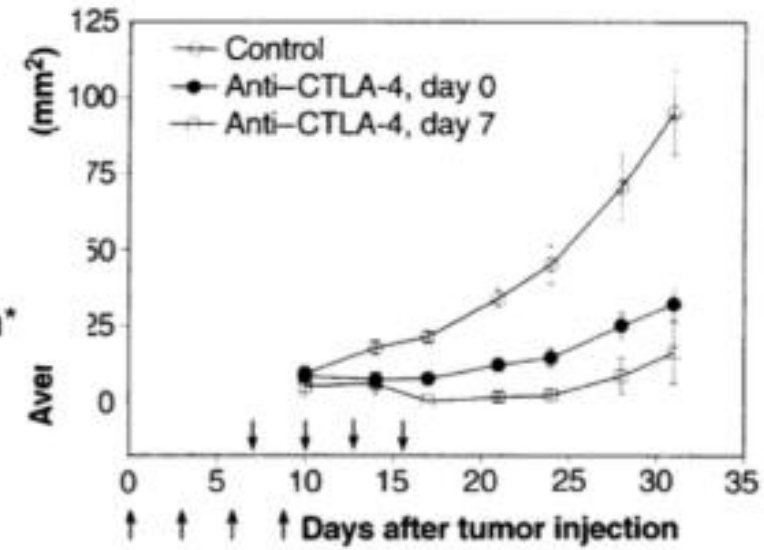
Prof. Allison discovered another important immunosuppressive molecule: cytotoxic T-lymphocyte antigen-4 (CTLA-4)

Immunocheckpoint blockade therapy

Enhancement of Antitumor Immunity by CTLA-4 Blockade

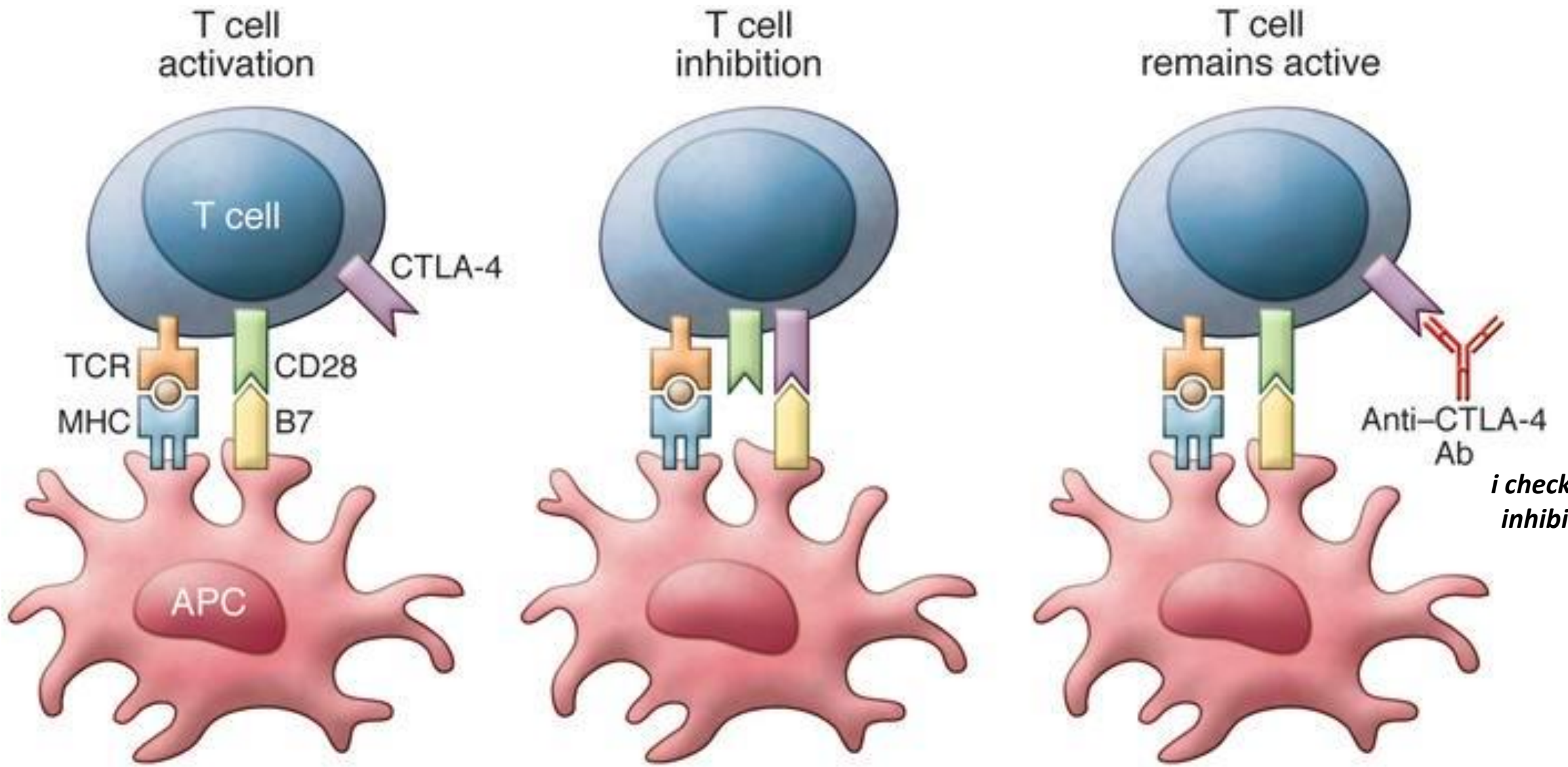
Dana R. Leach, Matthew F. Krummel, James P. Allison*

SCIENCE • VOL. 271 • 22 MARCH 1996



Releasing the brakes against cancer

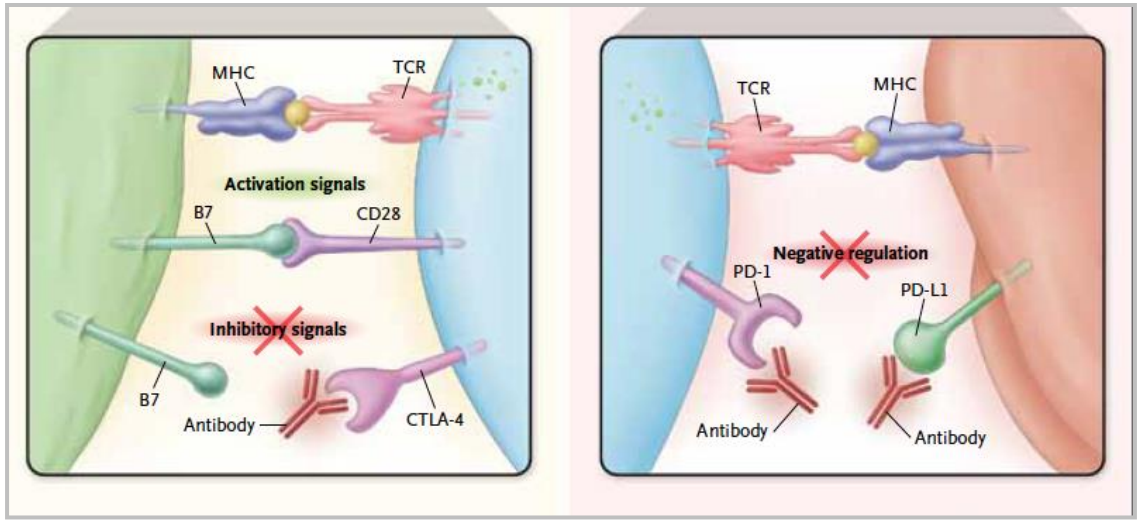
i checkpoint inhibitors!



i checkpoint inhibitors!

Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy

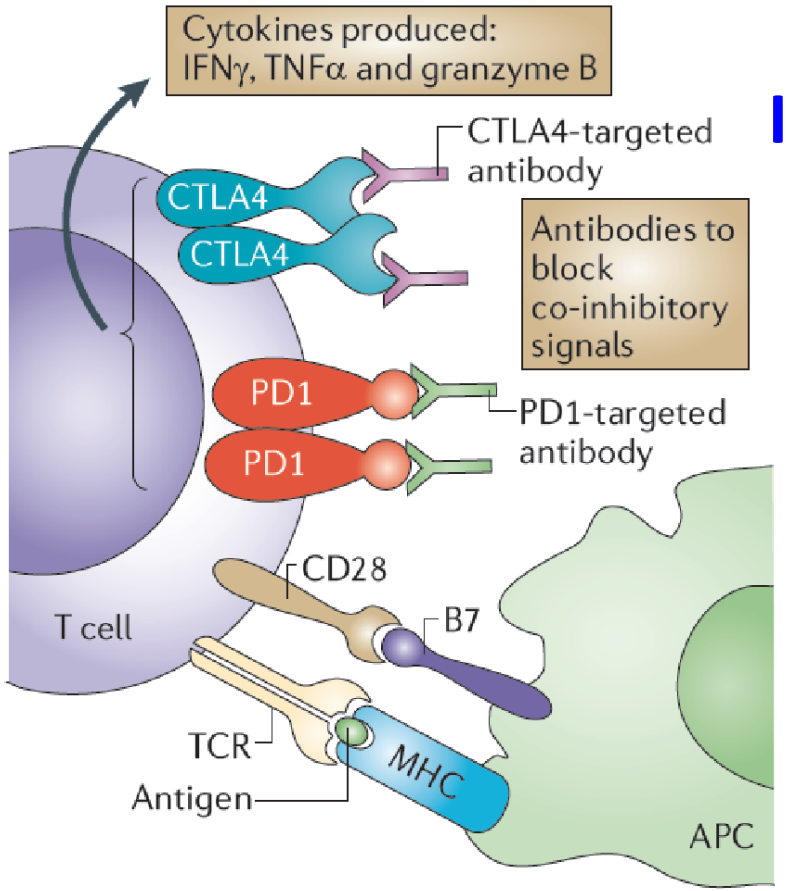
Nei linfonodi **Nel tessuto**



Ribas A N Engl J Med 2012

Togliere i freni….

Gli inibitori dei checkpoint immunitari (immunocheckpoint inhibitors, ICI)

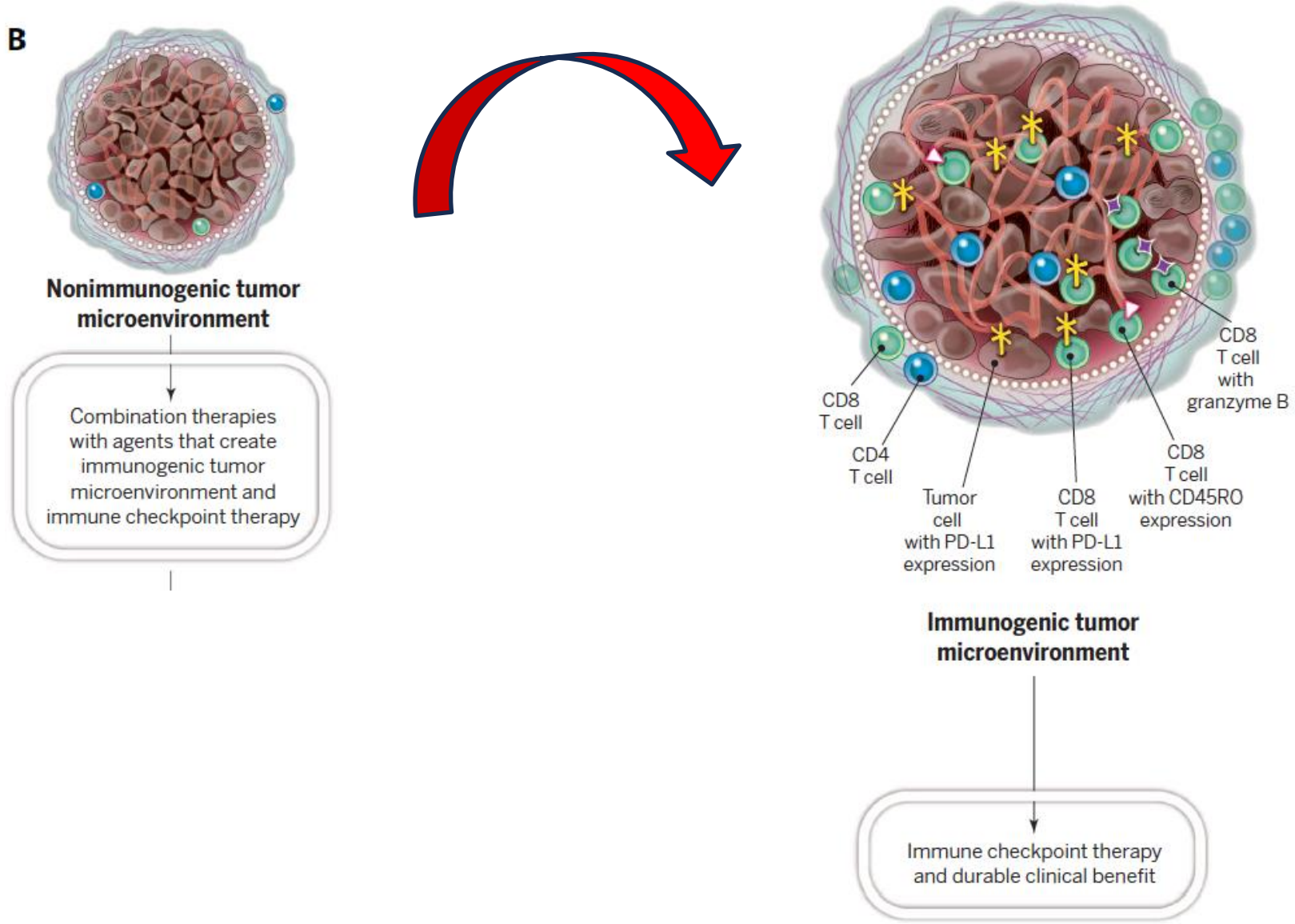


Ipilimumab (anti-CTLA-4)

Nivolumab (anti-PD1)

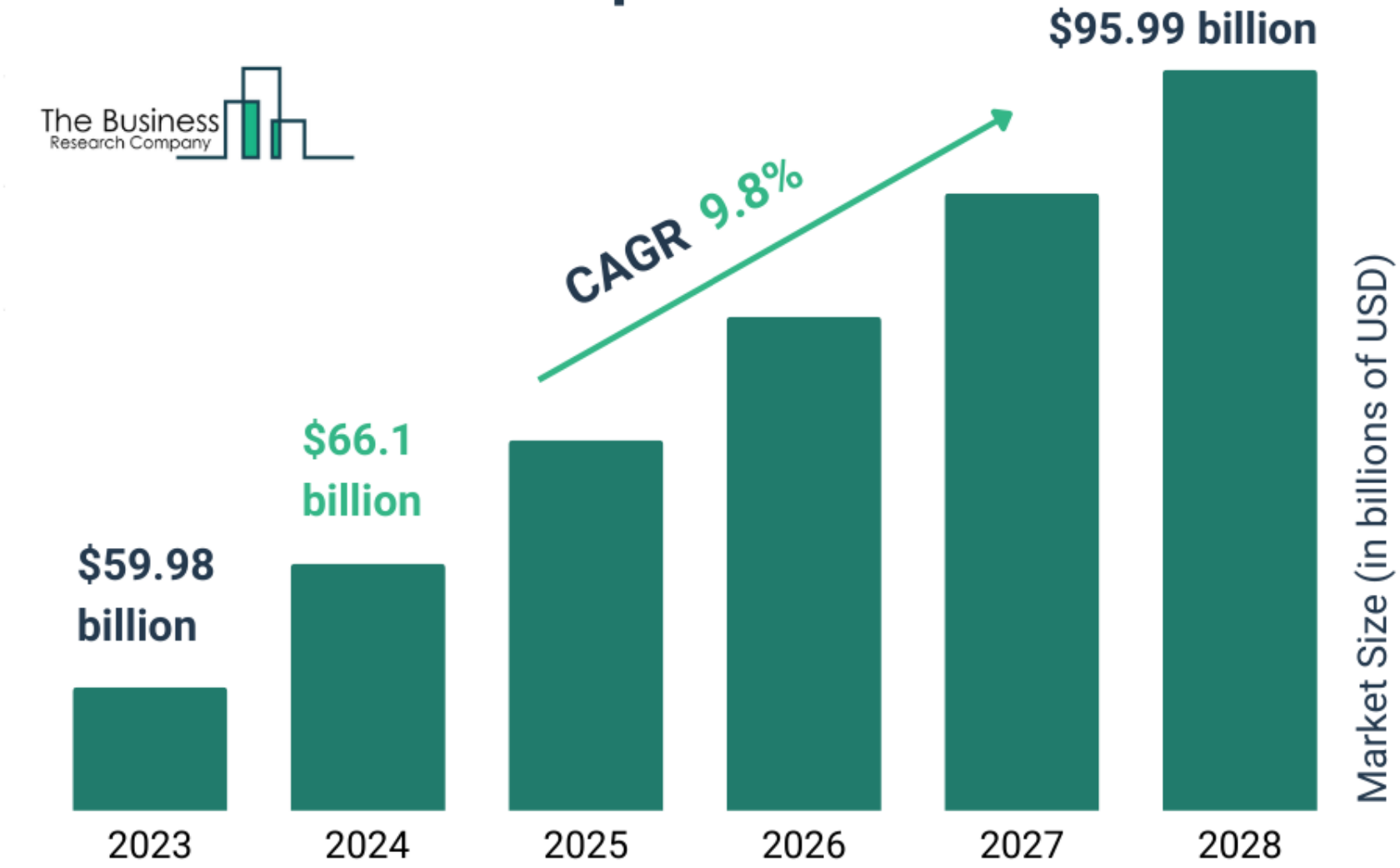
Metastatic melanoma
FDA 2011 Ipilimumab
FDA 2014 Nivolumab

Trasformare un tumore “freddo” in uno “caldo”




Immune Checkpoint Inhibitors Market, By Type, 2021 – 2032 (USD Billion)
35.3
40.9
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
PD-1
PD-L1
CTLA-4
Other types
Source: www.gminsights.com

Cancer Monoclonal Antibodies Global Market Report 2024



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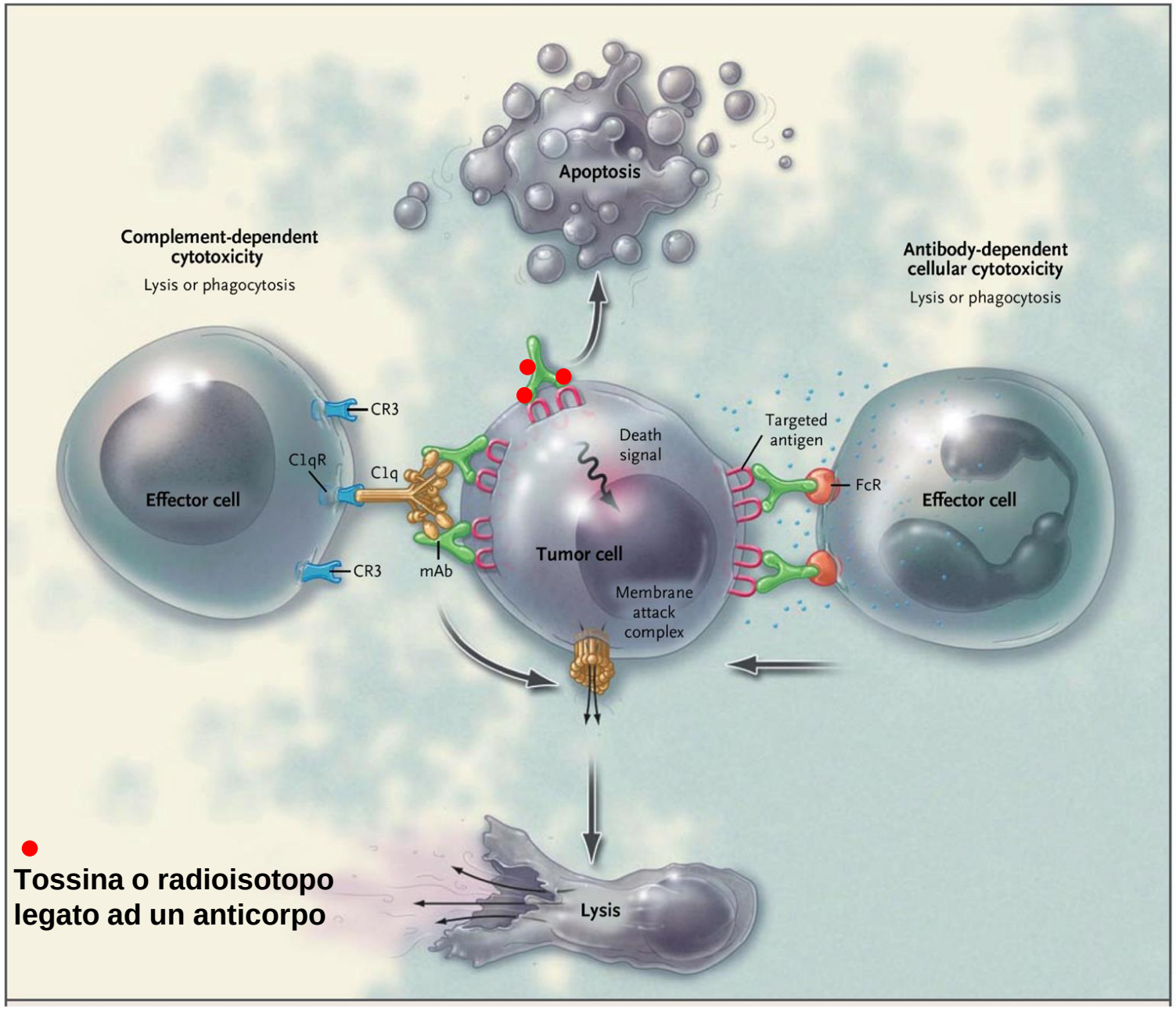
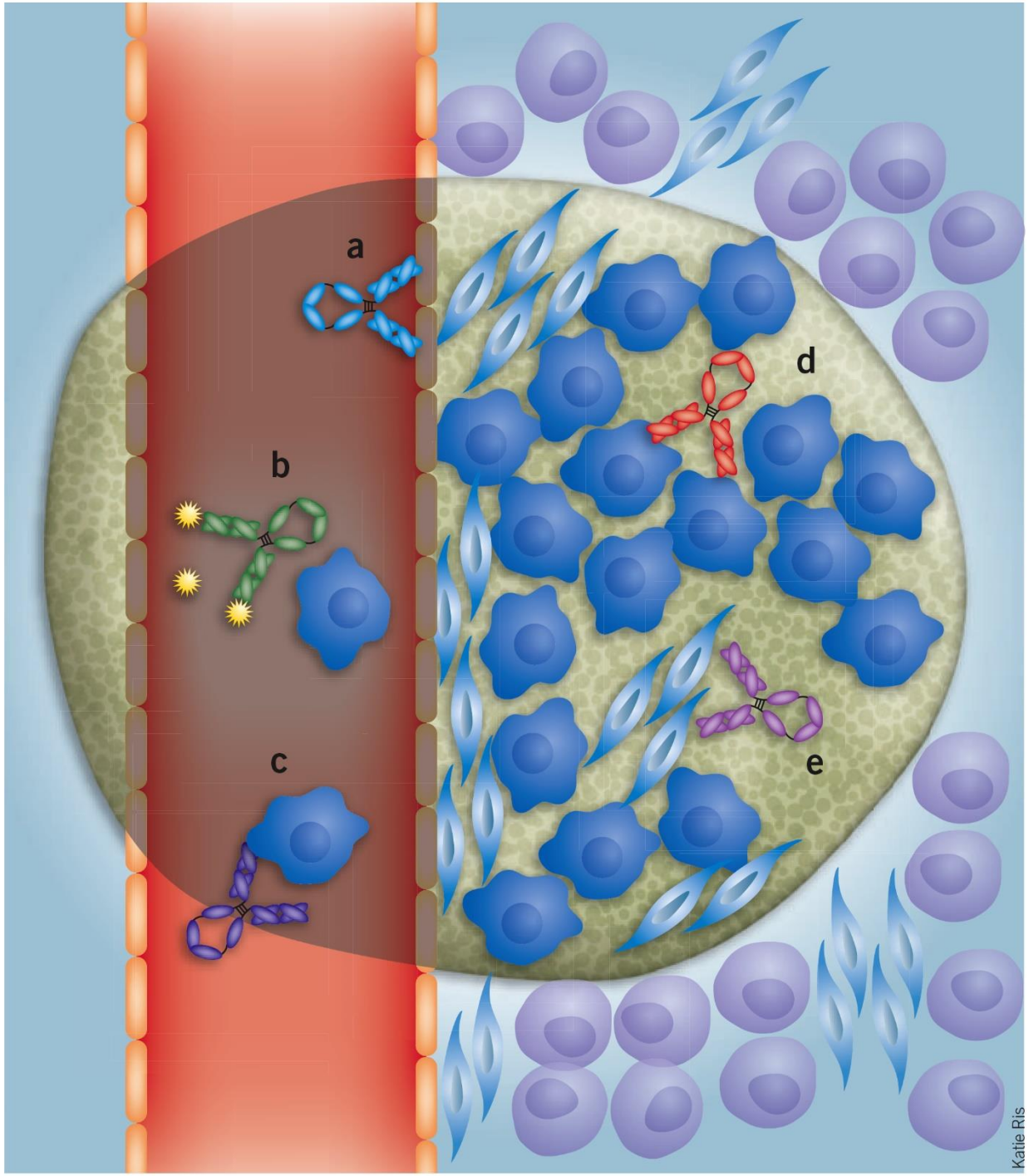
Togliere i freni

Immunoterapia mediata dagli anticorpi monoclonali: meccanismi d'azione





Potential targets for antibody therapy of cancer

a) Tumor-associated blood vessel

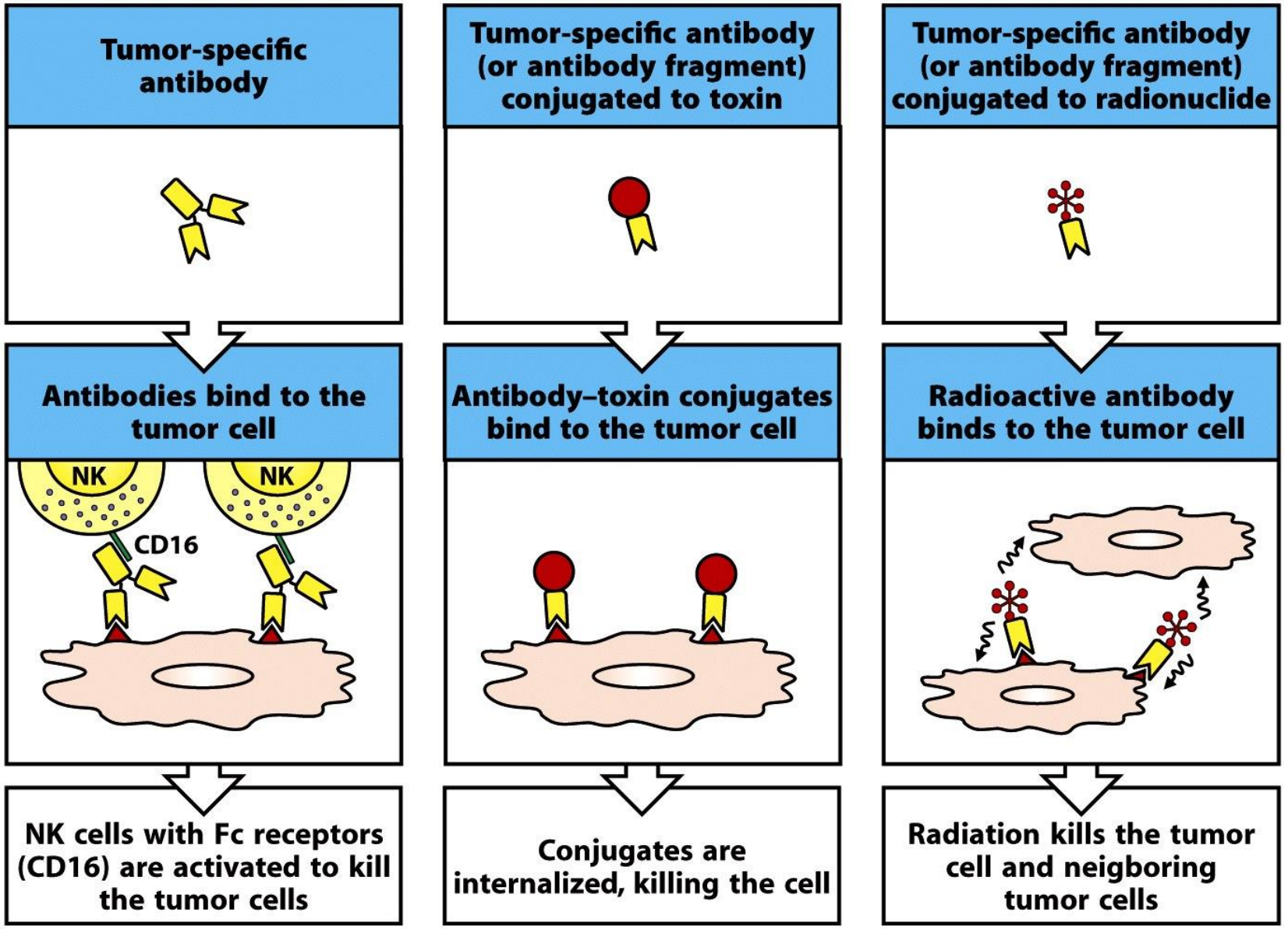
b) Vascular growth factors (i.e. VEGF)

c) Diffuse malignant cells

d) Tumor cells in a solid tumor

e) Tumor-associated stroma

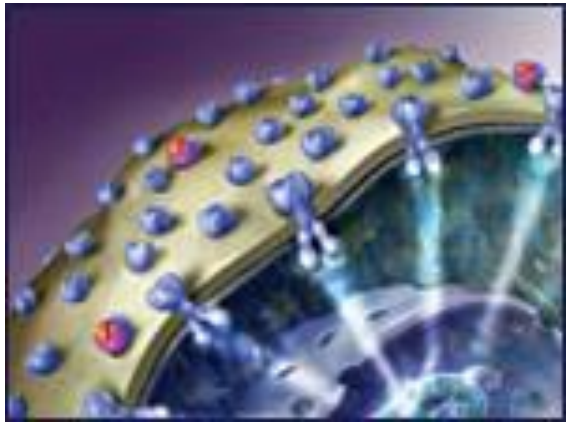
MoAb-MEDIATED IMMUNOTHERAPY



Anticorpi monoclonali approvati dalla FDA per l'uso clinico in oncologia negli USA

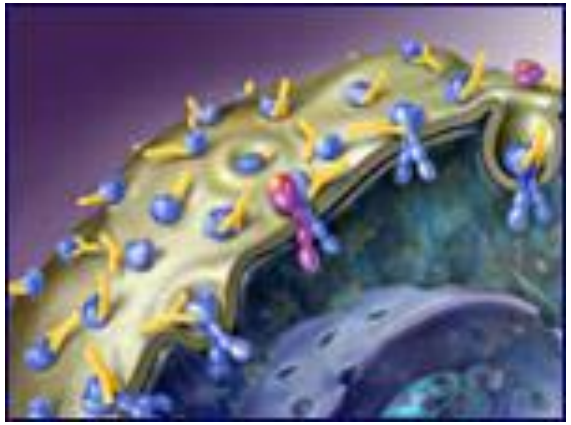
Target	*Drug*	*Clinical use*
Epidermal growth factor receptor	Necitumumab	Squamous non-small-cell lung cancer
	Cetuximab	Colorectal, head and neck cancer
	Panitumumab	Colorectal cancer
	Nimotuzumab	Squamous cell carcinoma, glioma
VEGF	Bevacizumab	Anti-angiogenic therapy
CD19-dircted CD3 T cell engager	Blinatumomab	Acute lymphoblastic leukemia
		Diffuse Large B cell Lymphoma
CD20	Ibritumomab	Non-Hodgkin's lymphoma
	Rituximab	Non-Hodgkin's lymphoma
	Tositumomab	Non-Hodgkin's lymphoma
	Ofatumumab	Chronic lymphocyte leukemia and multiple sclerosis
	Obinutuzumab	Chronic lymphocytic leukemia (in combination with chlorambucil
CD33 (myeloid cell surface antigen on leukemia cells)	Gemtuzumab	Acute myeloid leukemia
CD38	Daratumumab	Multiple myeloma
CD52	Alemtuzumab	Chronic lymphocytic leukemia
HER2/neu receptor	Trastuzumab	Breast cancer
PD-1	Pembrolizumab	Cervical cancer
		Head and neck squamous cell carcinoma
	Nivolumab	Renal cell cancer
		Hodgkin's lymphoma
		Squamous cell carcinoma of the head and neck
PD-L1	Avelumab	Merkel cell carcinoma
		Non-small cell lung cancer
	Durvalumab	Urothelial cancers
		Unresectable stage III non-small cell lung cancer
	Atezolizumab	In combination with carboplatin and etoposide for treatment of small cell lung cancer,
		In combination with cobimetinib and vemurafenib for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.
SLAM F7	Elotuzumab	Multiple myeloma (used in combination with lenalidomide and dexamethasone)
GD2	Dinutuximab	Neuroblastoma in pediatric patients
CTLA-4	Ipilimumab	Melanoma

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

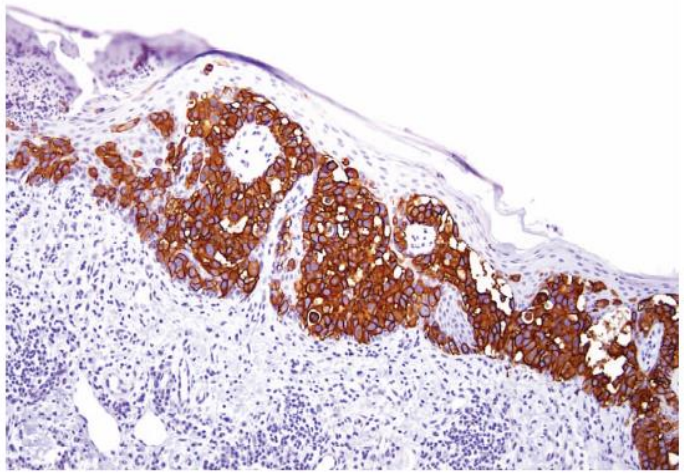
DALLA MOLECOLA ALLA CLINICA: Her2/Neu

- **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.**

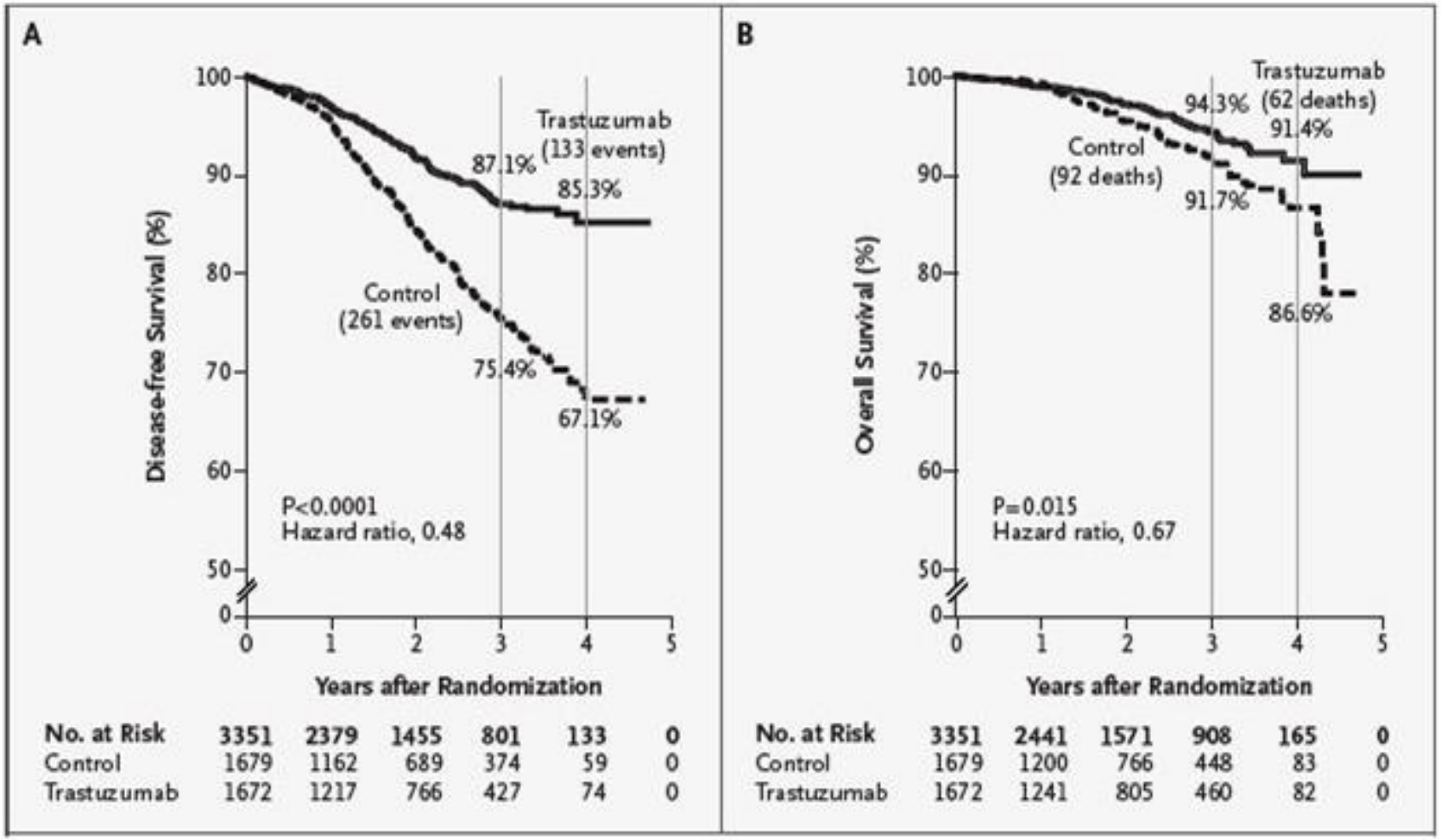
- **Inibizione di Her2 per trattare il carcinoma della mammella:**

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)



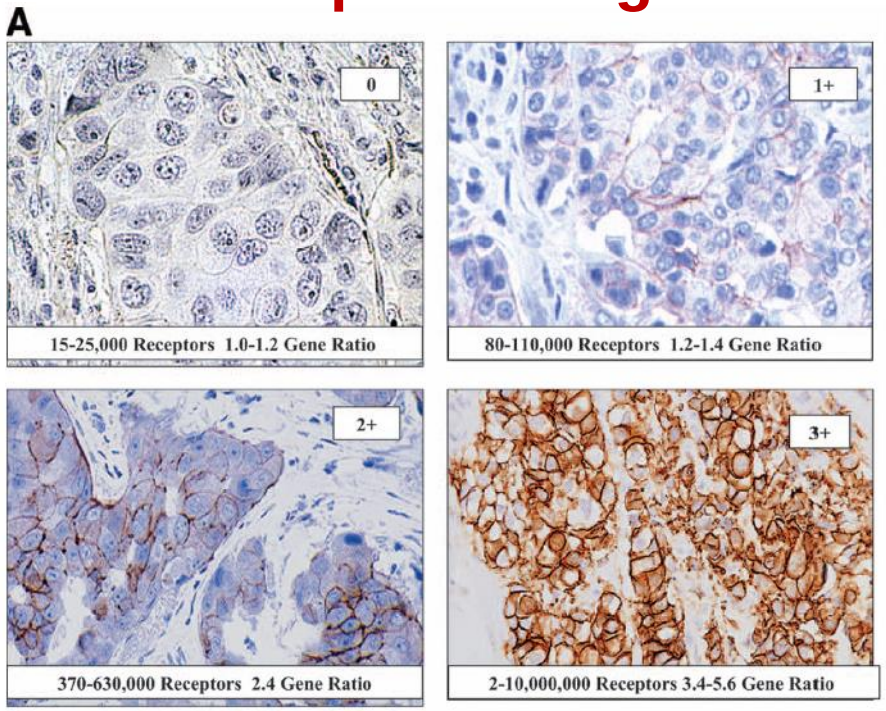
HER-2–positive invasive ductal carcinoma

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



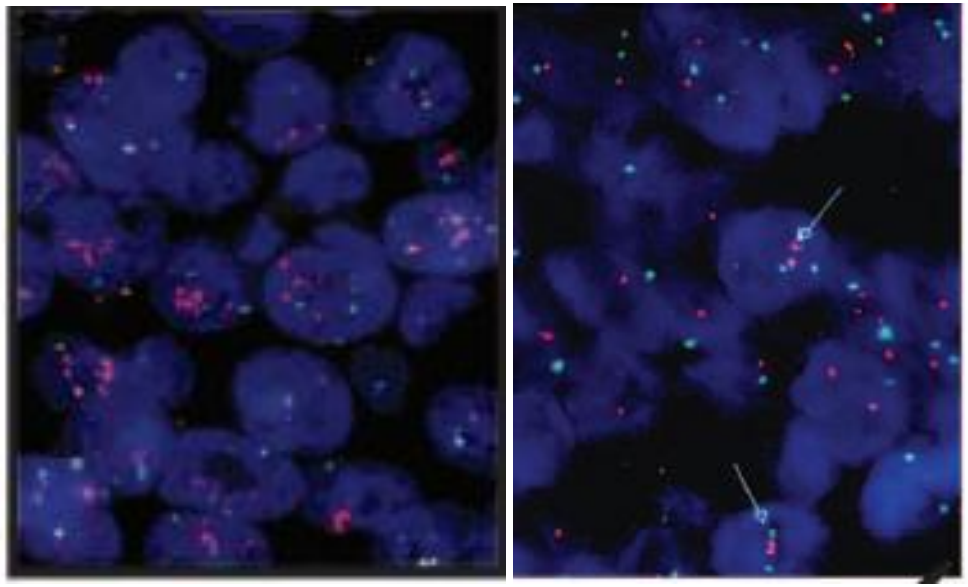
Score (USA):
0-1+: negative
2+: equivocal
3+: positive

Trastuzumab is not good for everyone…

Gene copy number:

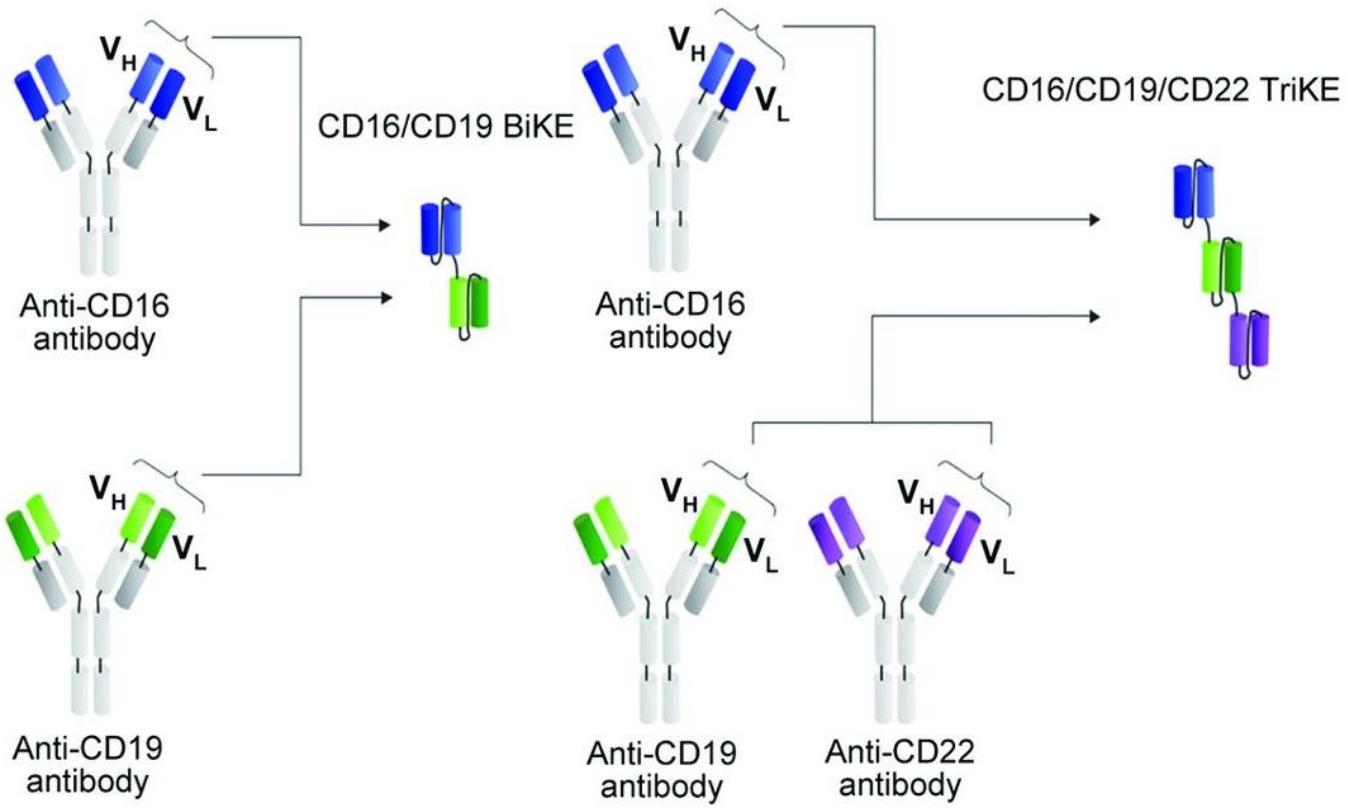
=4 (amplified)

=1.9 (not amplified)



Pink: Her2 gene
Green: centromere (chr 17)

BiKE- and TriKE-mediated NK cell targeting to tumor-associated antigens



Jeffrey S. Miller Hematology 2013

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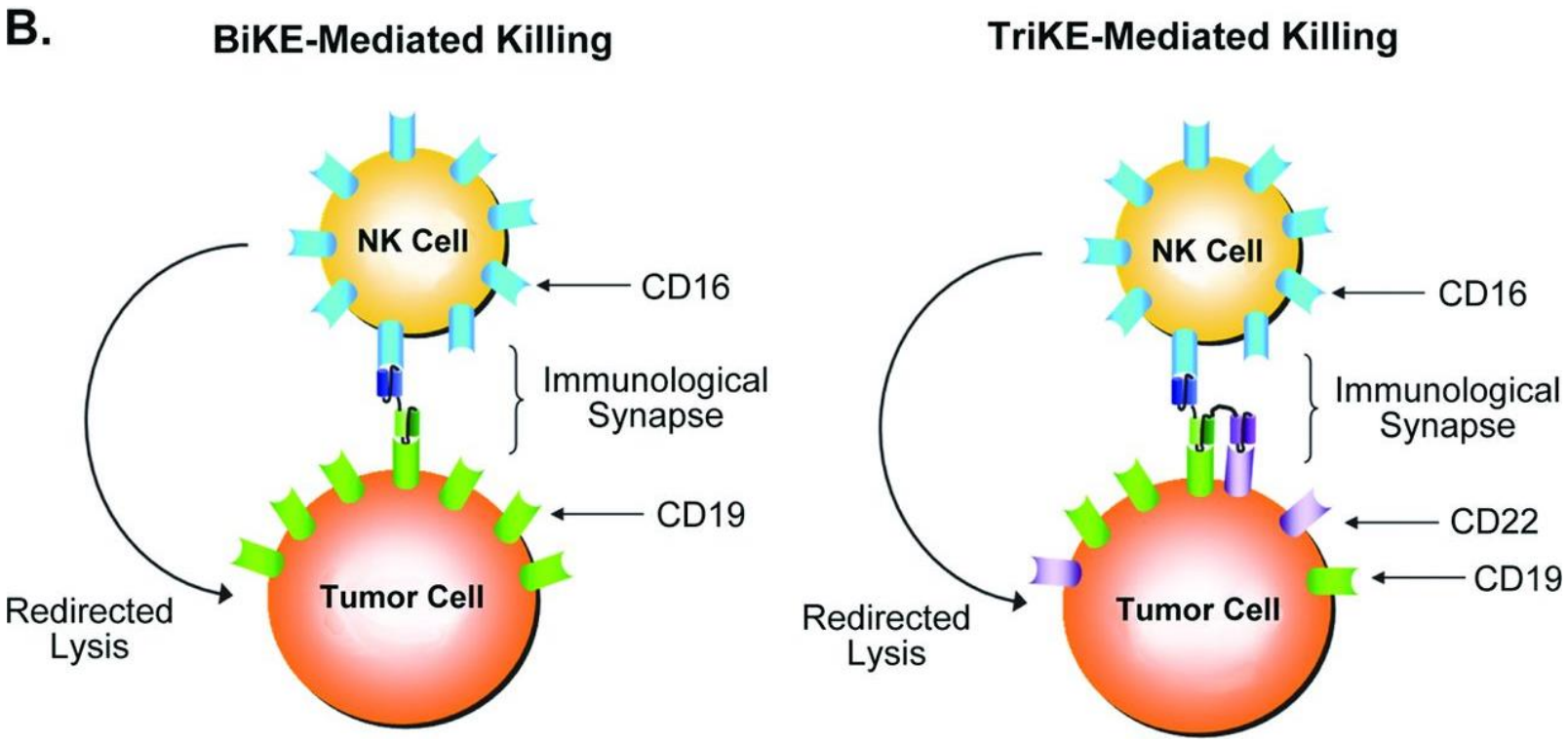

Jeffrey S. Miller Hematology 2013

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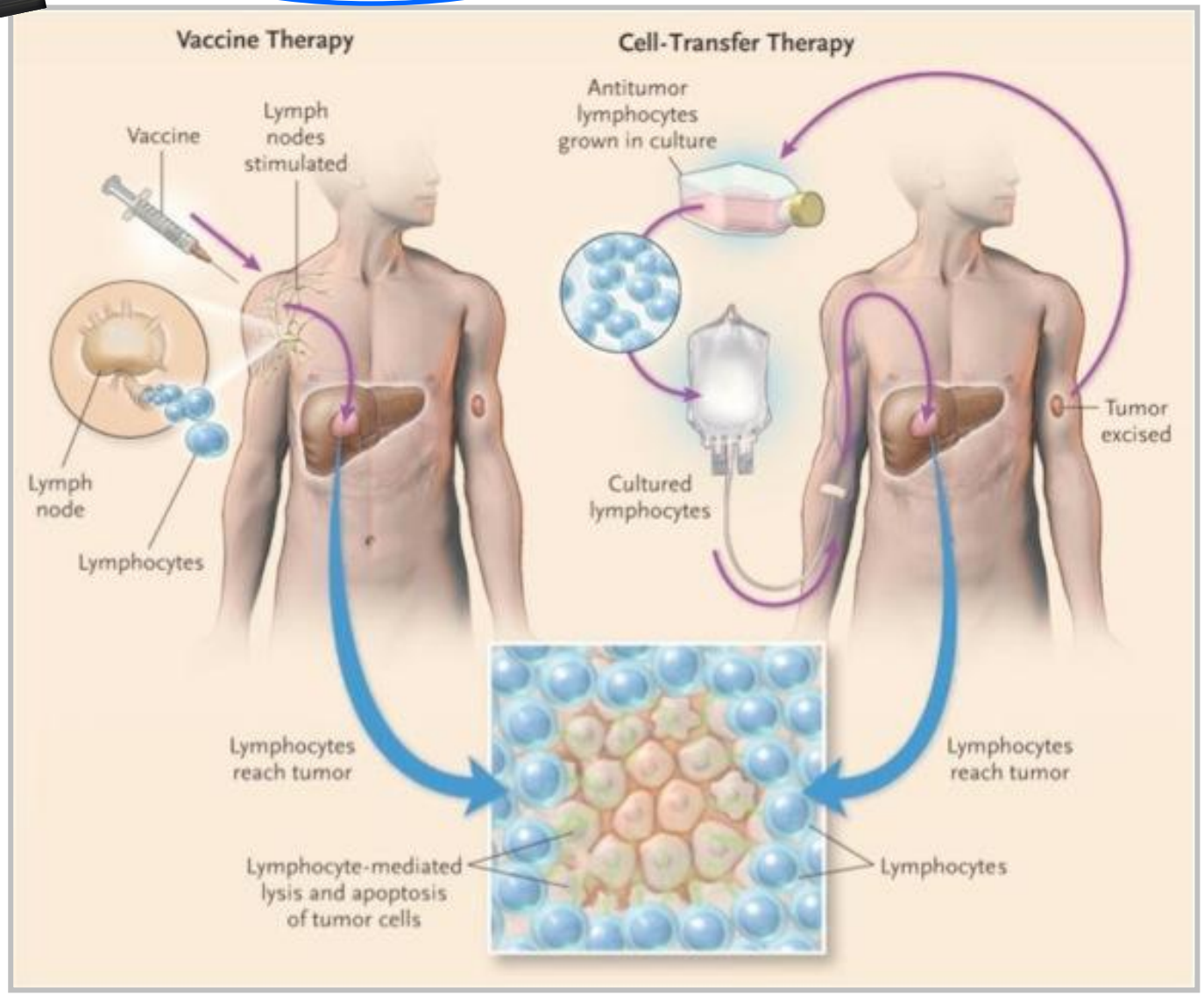
Togliere i freni

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



Rosenberg SA New England J Med 2004

ANTI-TUMOUR IMMUNIZATION

- **Therapeutic vaccines:** **Augmentation of anti-tumour immune response**
- **Prophylactic vaccines:** **Prevention of tumour transformation**

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

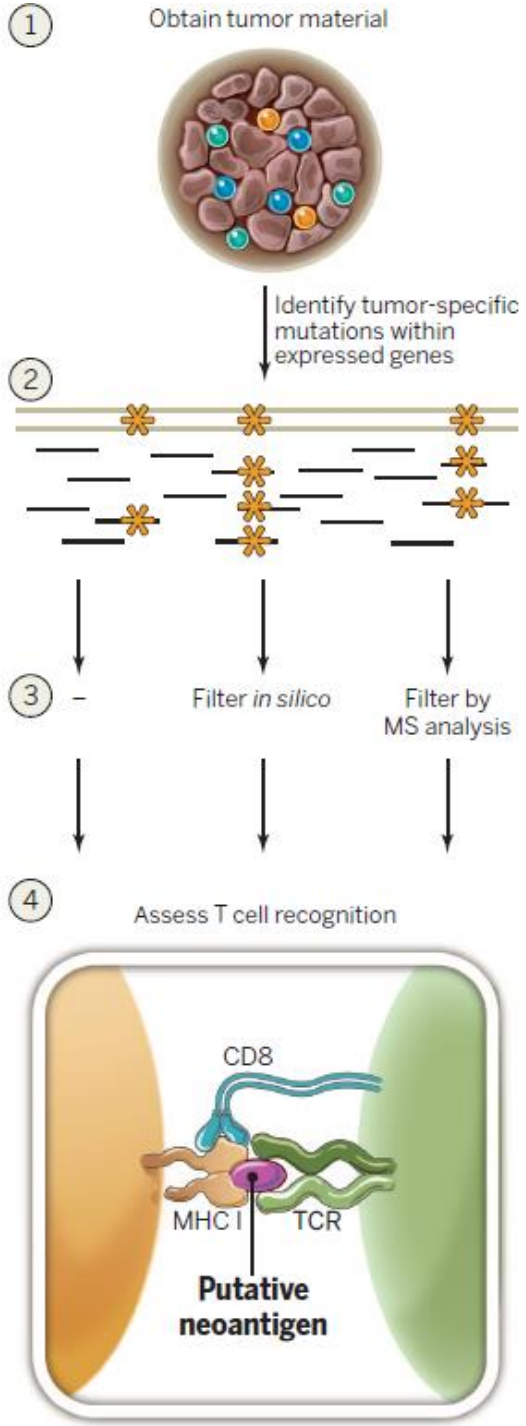
Therapeutic vaccines: Augmentation of anti-tumor immune response

L’antigene tumorale “ideale” per la vaccinazione

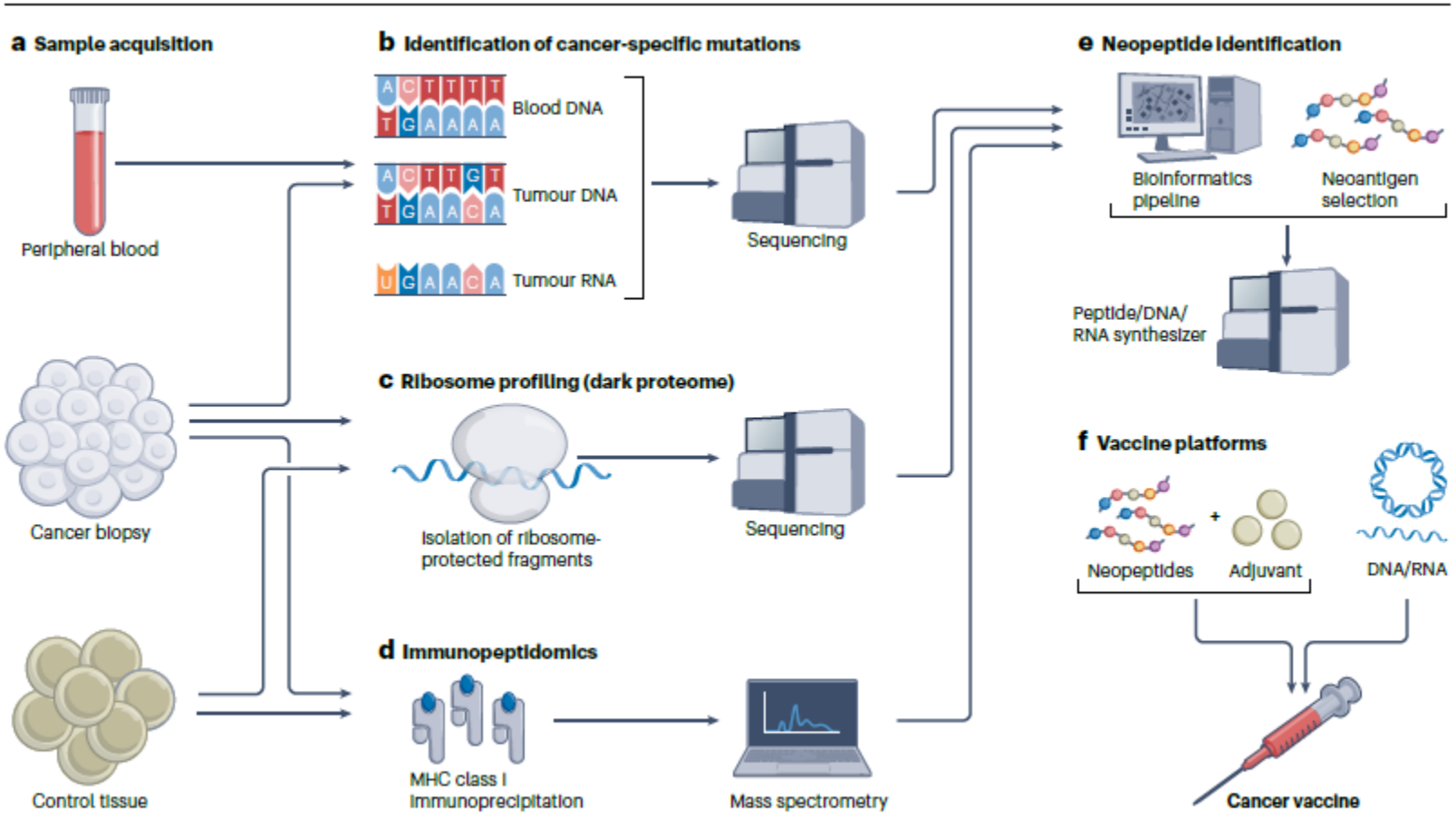
- E’ altamente espresso in un ampio numero di tumori.
- E’ espresso durante le prime fasi della trasformazione neoplastica.
- Gioca un ruolo fondamentale nella trasformazione neoplastica.
- E’ dotato di più peptidi immunogenici che possono essere presentati da alleli HLA diversi.
- I suoi peptidi immunogenici 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

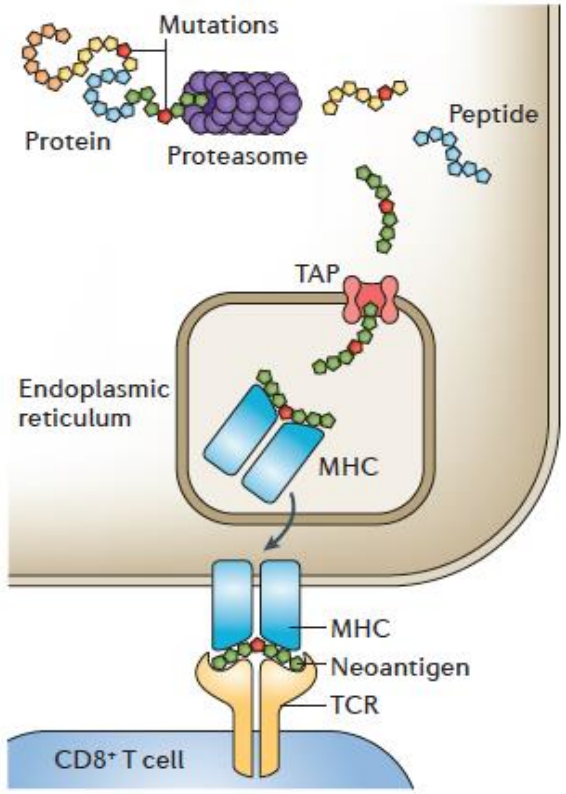


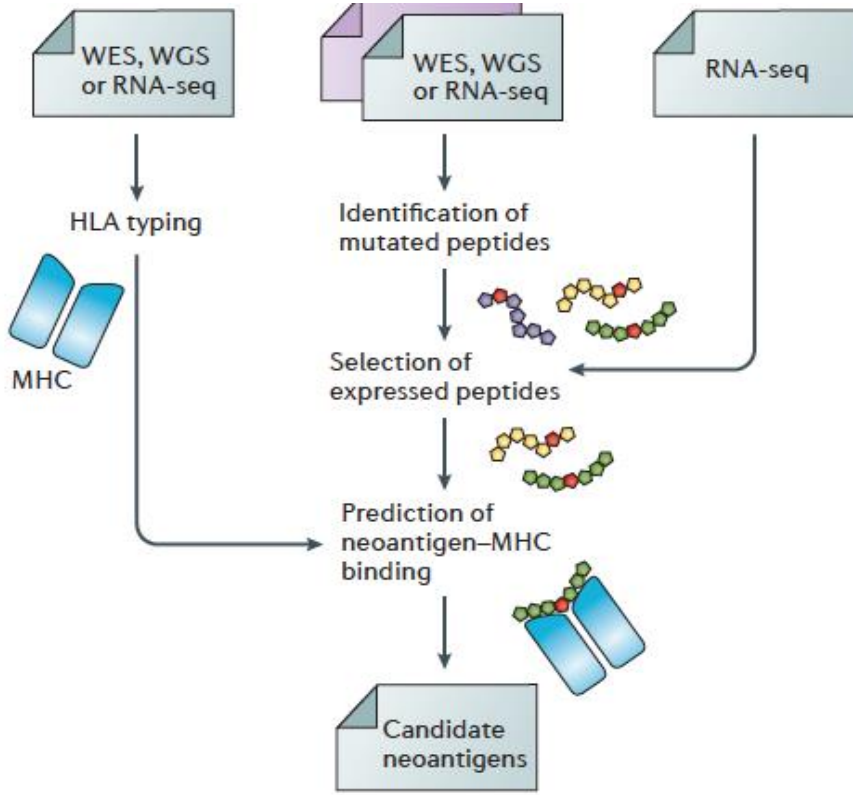
Current approaches in neoantigen discovery and vaccine design



Katsikis Nat Rev Immunol 2023

1. Trovare antigeni tumore-specifici



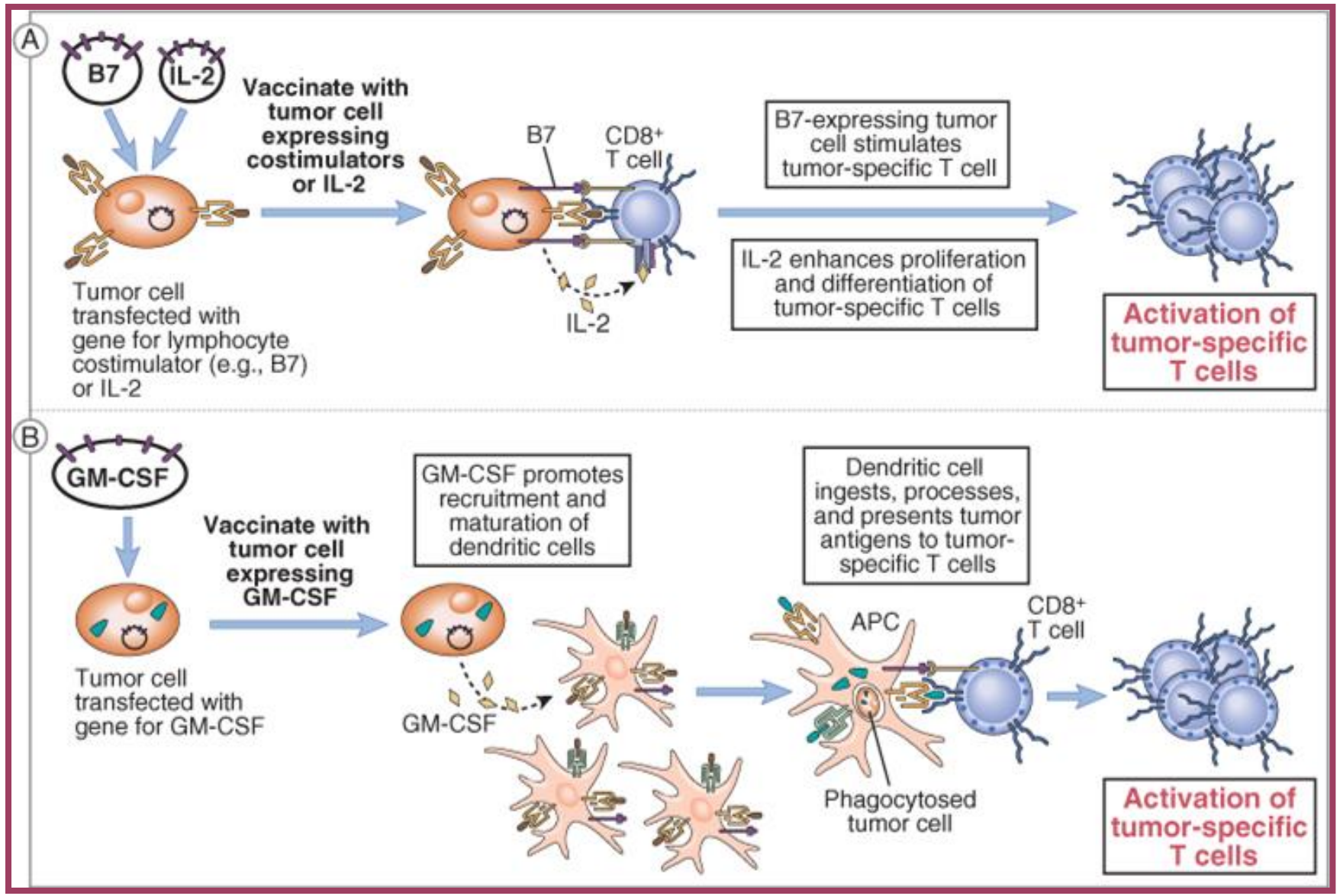


Cancer whole exome sequencing

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

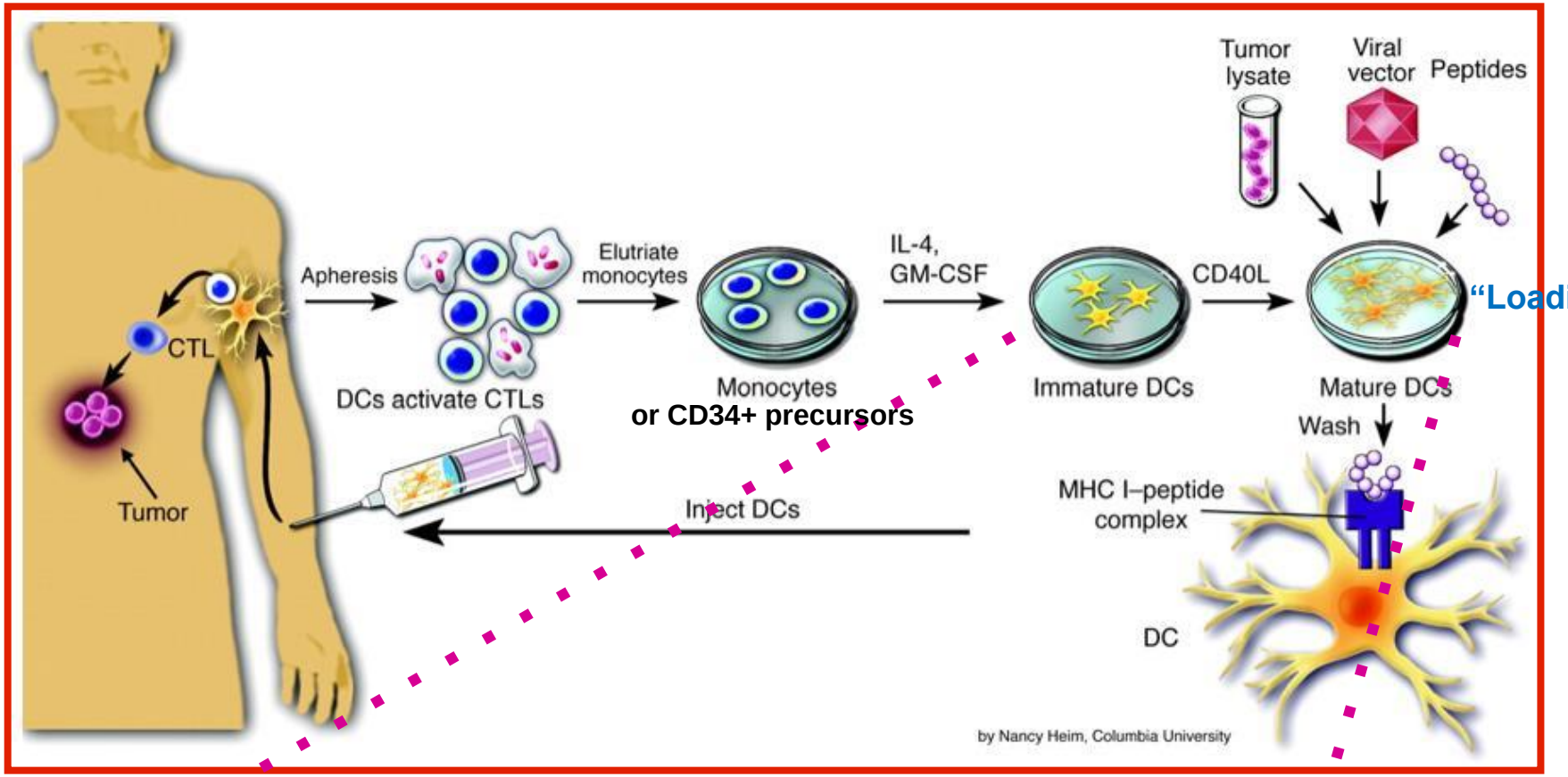
Neoantigens

Manipolazioni genetiche per aumentare l'immunogenicità delle cellule tumorali

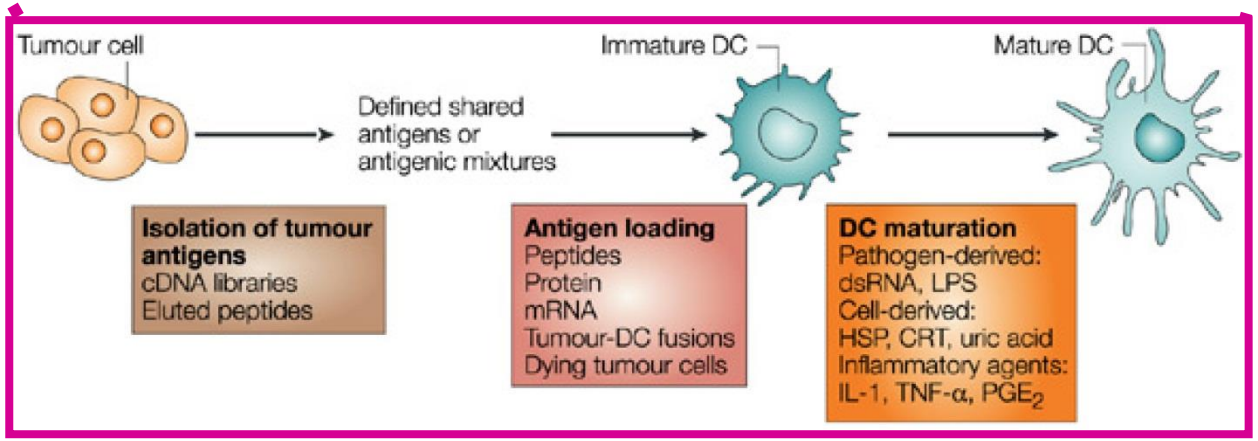


3. DC loading

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



"Loading"



Generation of anti-tumor DC vaccines

1. **The therapy is safe and well tolerated**, side effects are constrained to **induration of the skin at the injection site and a mild fever**.

2. **Importance of the quality of DCs,** especially their migratory capacity and ability to induce potent T-cell responses. Notably, only a small percentage of the DCs injected in current trials actually migrate from the injection site into the draining lymph node to present the antigen to T cells. This might be due to suboptimal maturation protocols, and could be enhanced by **preconditioning DCs** with pro-inflammatory cytokines or Toll-like receptor agonists.

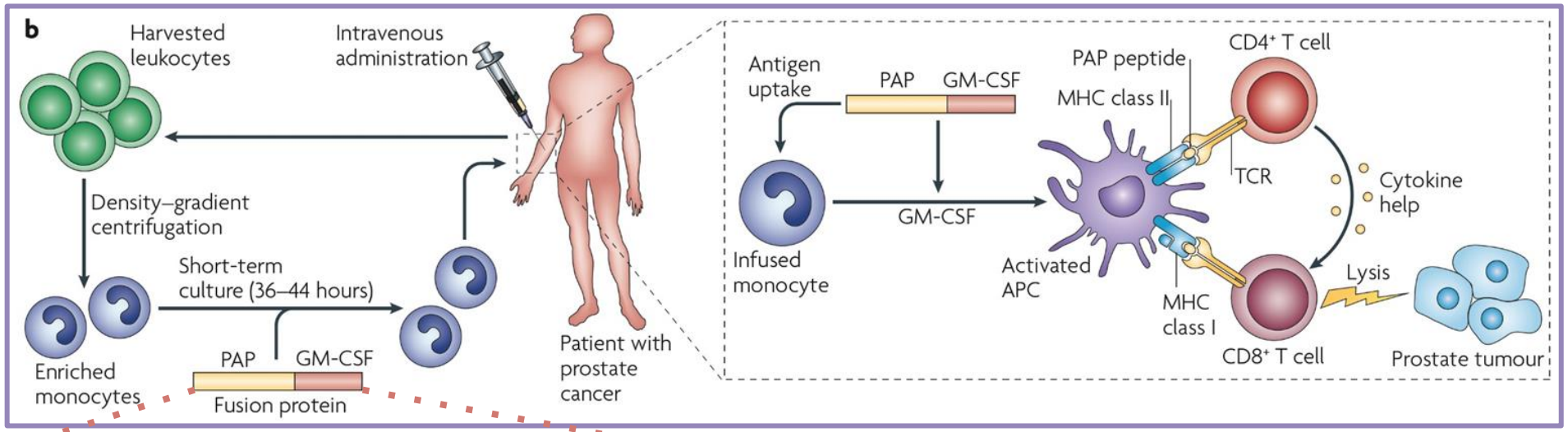
3. **Development of various immunomonitoring tools** to study the mechanisms underlying successful vaccination that will help to shape future vaccine design.

4. **DC vaccination** can induce immunological responses in many of the patients.

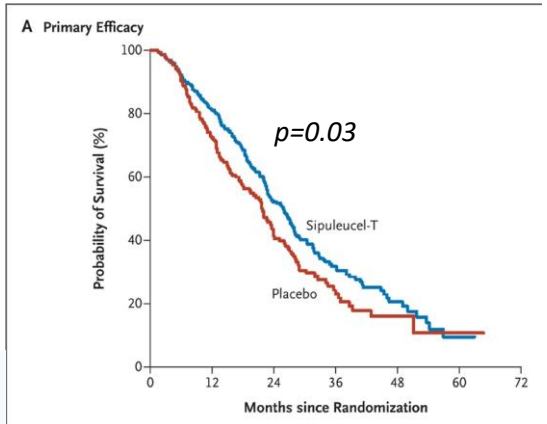
First U.S. "cancer vaccine"!

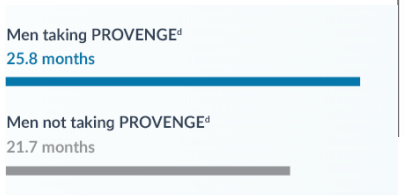
Sipuleucel-T (Provenge)

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

First FDA Approval of therapeutic Cancer Vaccine

A Milestone Victory for Field of Cancer Immunotherapy

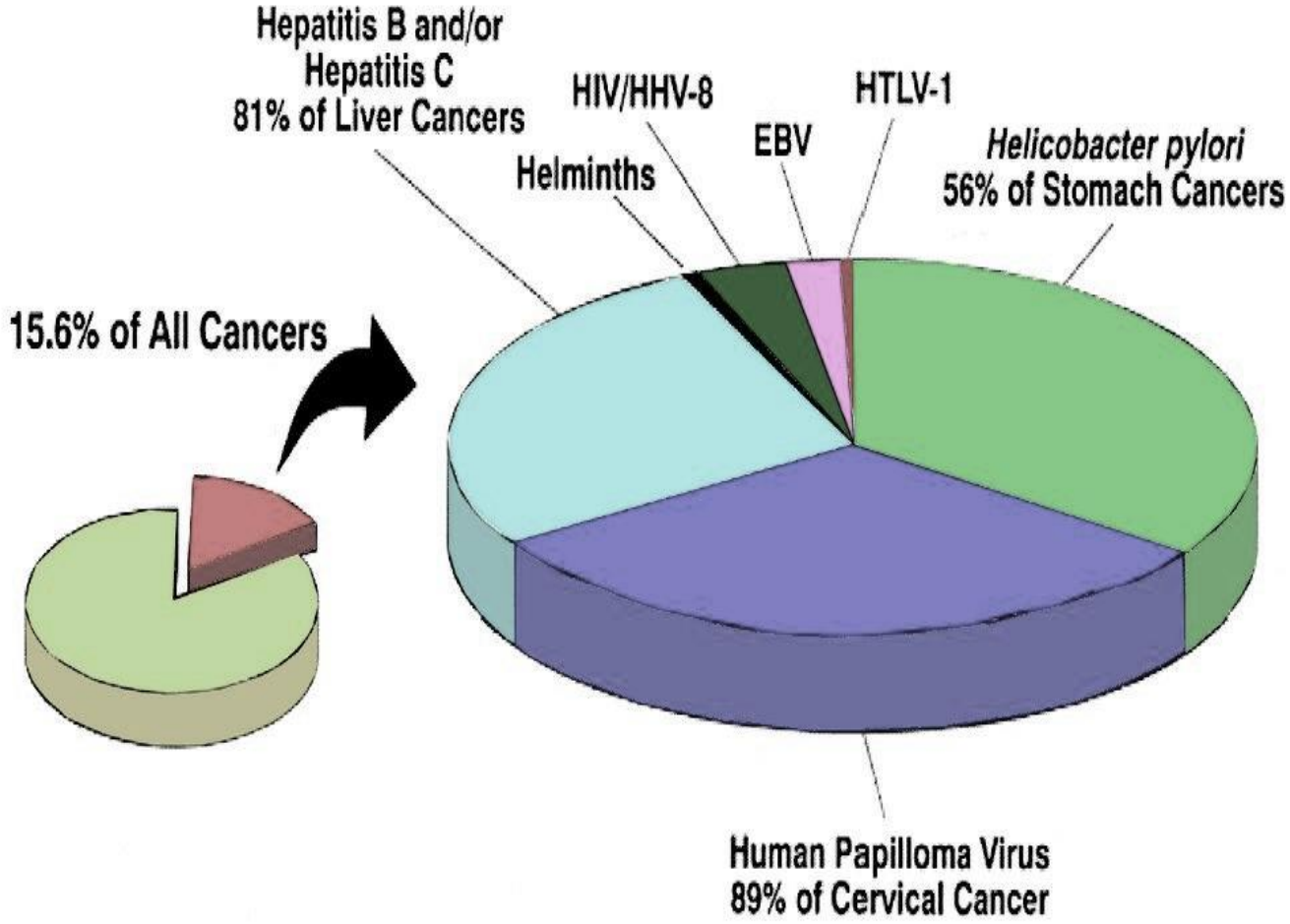
“The challenge now is to maximize the effectiveness of cancer vaccines such as Provenge by incorporating all we have learned in recent years about the immune response to cancer and cancer vaccine development, converting the four-month survival advantage of Provenge-vaccinated patients into prolonged-even lifelong-control of the disease”

National Cancer Institute
at the National Institutes of Health

ANTI-TUMOR IMMUNIZATION

- **Therapeutic vaccines:** Augmentation of anti-tumor immune response
- **Prophylactic vaccines:** Prevention of tumor transformation

Infectious causes of cancer



Fauci AS, 2001

PROPHYLACTIC VACCINATION - PREVENTION OF NEOPLASTIC TRANSFORMATION BY VACCINES

- **Identification of infectious agents as THE cause (viruses and bacteria)**

- **Biology of preneoplastic lesions: definition of lesions with high risk of transformation**

- **Identification of novel molecular targets expressed in the pre-neoplastic lesions and recognized by the immune system**

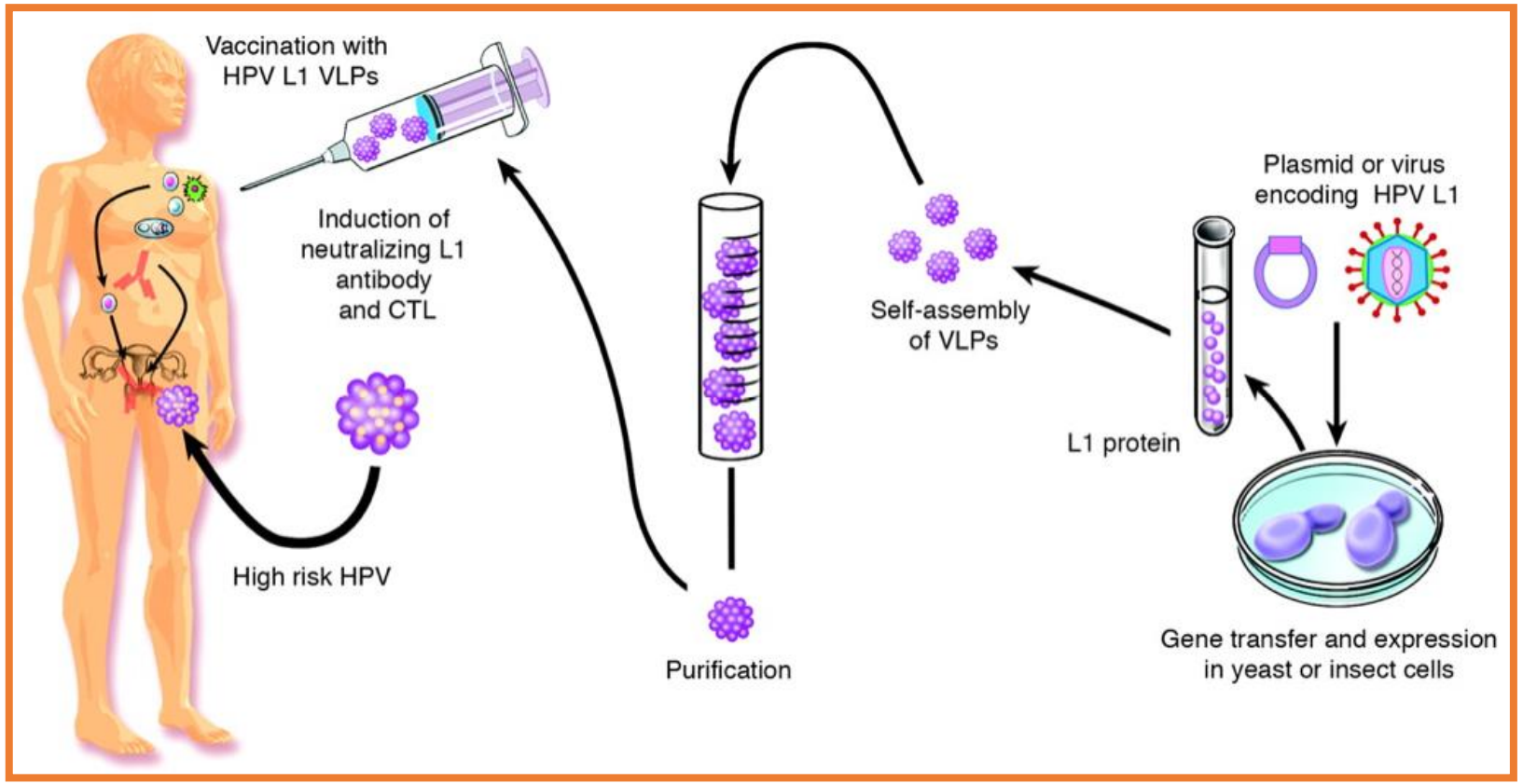
Many cancers are associated with viral infections, and vaccines that prevent these infections can reduce cancer risk.

A major breakthrough in anticancer therapy occurred in 2005 with the completion of a clinical trial involving 12,167 women that tested a vaccine **against human papilloma virus (HPV**). This trial showed that a recombinant vaccine against HPV was 100% effective in preventing cervical (uterine cervix) cancer caused by two key HPV strains**, HPV-16 and HPV-18**, which are associated with 70% of cervical cancers. The vaccine most likely prevents infection of cervical epithelium by HPV through the induction of anti-HPV antibodies.

It is a prophlylactic vaccine!!

HPV vaccine consisting of L1 (capsid protein) Virus-Like Particles (VLP)

HPV: DNA virus responsible for various lesions, commonly known as warts, that can be found at the level of the female and male genital apparatus.
More than 20 viral strains are known, some of which, including the strain 16 and 18, with high transforming power.



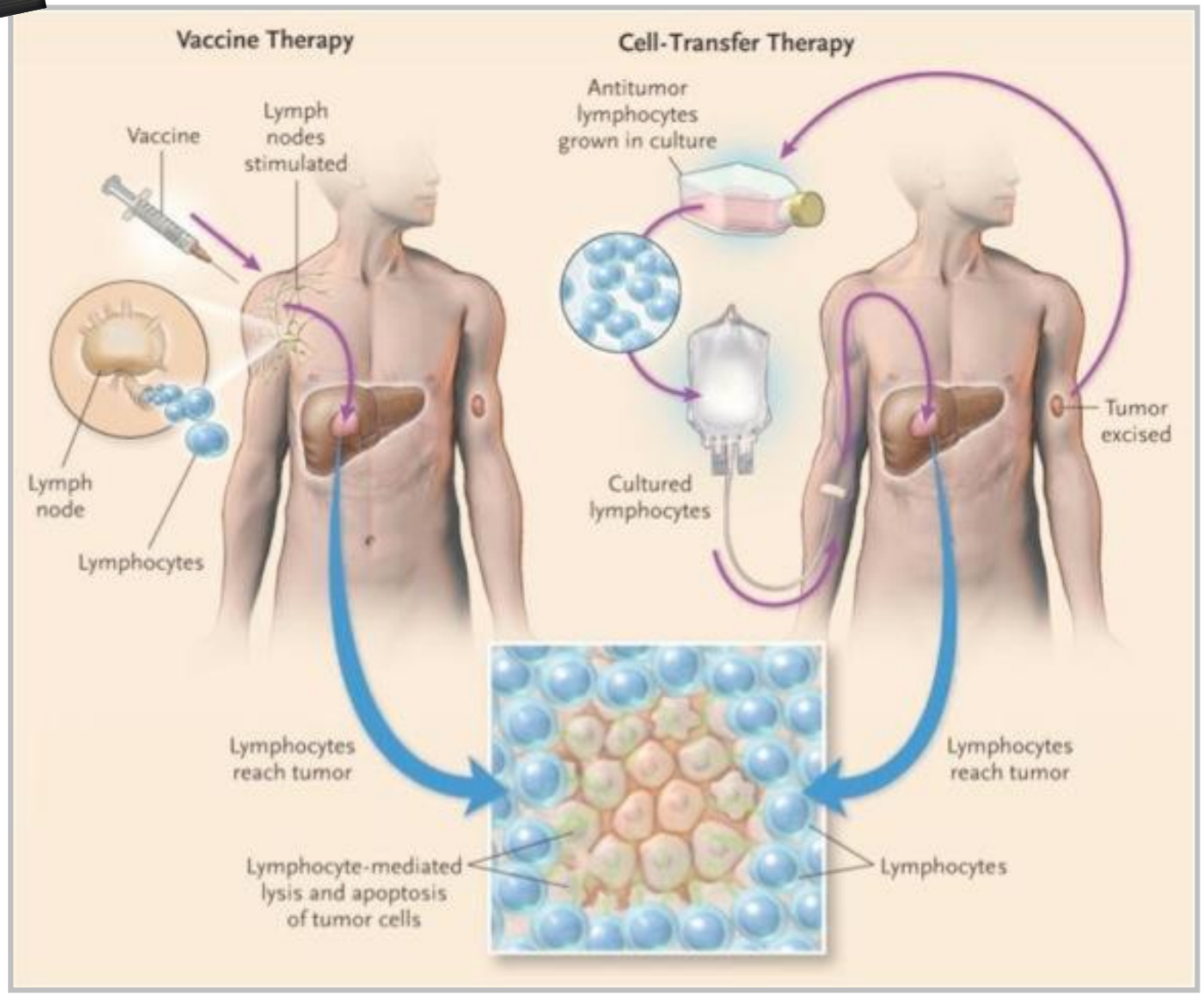
Adesso c'è un vaccino 9-valente

Cancer immunoprevention

Proposed antigens for preventative cancer vaccines in the setting of premalignant disease

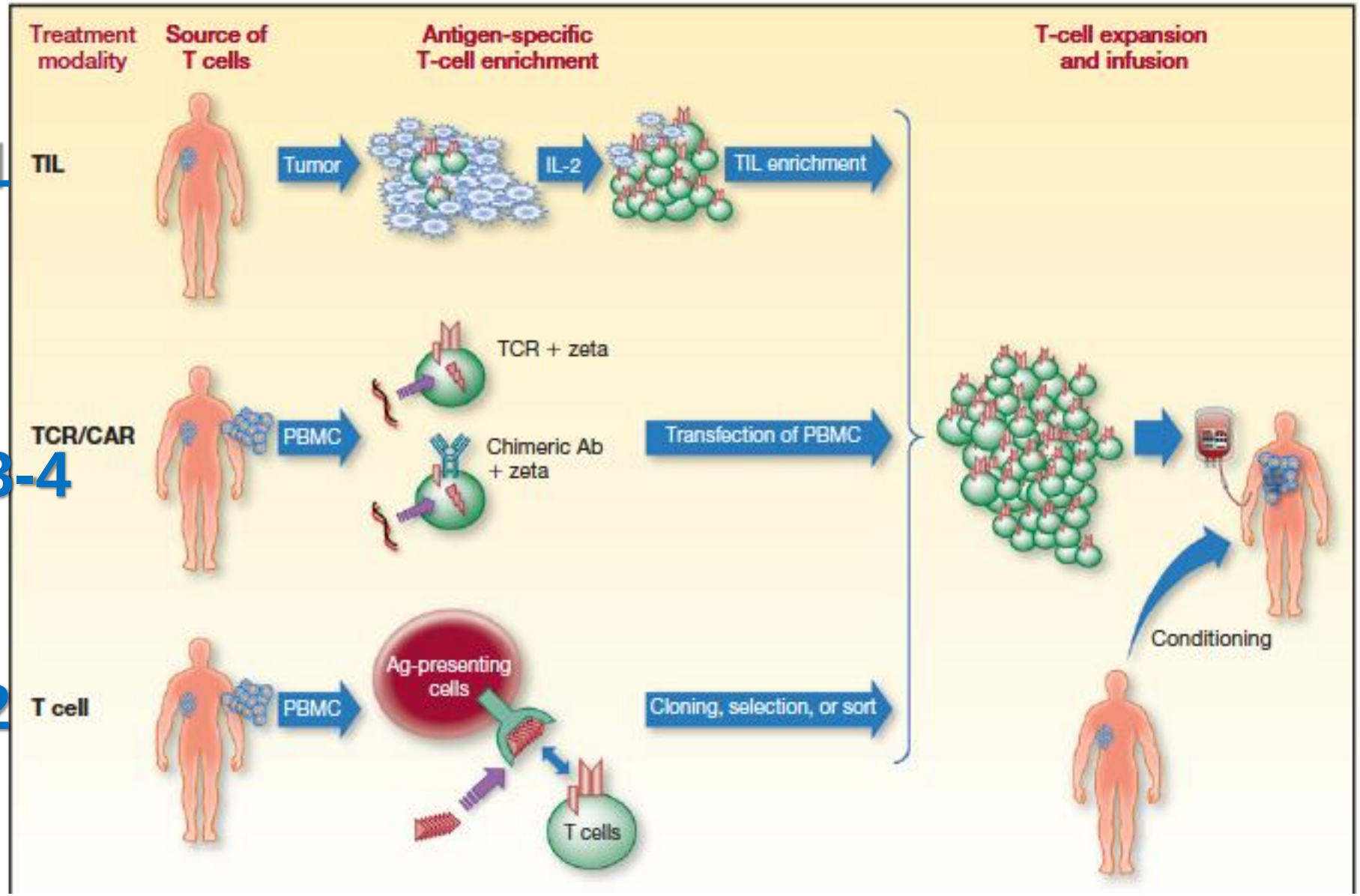
Candidate antigens	Premalignant lesions (cancer type)
HPV16	Cervical intraepithelial neoplasia (CIN) (cervical)
E6 and E7	Vulvar intraepithelial neoplasia (vulvar)
Cancer testis (CT) antigens	Ductal carcinoma in situ (breast)
MAGE-A1-A4, NYESO-1, GAGE	Squamous dysplasia of the head and neck (SCCHN)
	Esophageal squamous carcinoma in situ (esophageal)
Her-2/neu	Ductal carcinoma in situ (breast)
	Colon adenomas (colorectal)
MUC1	Pancreatic intraepithelial neoplasia (PanIn) (pancreatic)
	Intraductal papillary mucinous neoplasms (IPMN) (pancreatic)
	Berrett's Esophagus (esophageal)
	Adenomatous polyps (colon)
	Monoclonal gammopathy of undetermined significance (MGUS) and Asymptomatic multiple myeloma (AMM) (multiple myeloma)
	Bronchial preneoplasia (lung)
Mesothelin	Pancreatic intraepithelial neoplasia (PanIn) (pancreatic)
	Intraductal papillary mucinous neoplasms (IPMN) (pancreatic)
Cyclin B1	Bronchial preneoplasia (lung)
	Squamous dysplasia of the head and neck (SCCHN)
	Ductal carcinoma in situ (breast)
	Preneoplastic PSA negative stage (prostate)
SOX-2	Monoclonal gammopathy of undetermined significance (MGUS) and Asymptomatic multiple myeloma (AMM) (multiple myeloma)
EGFR	Bronchial preneoplasia (lung)

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



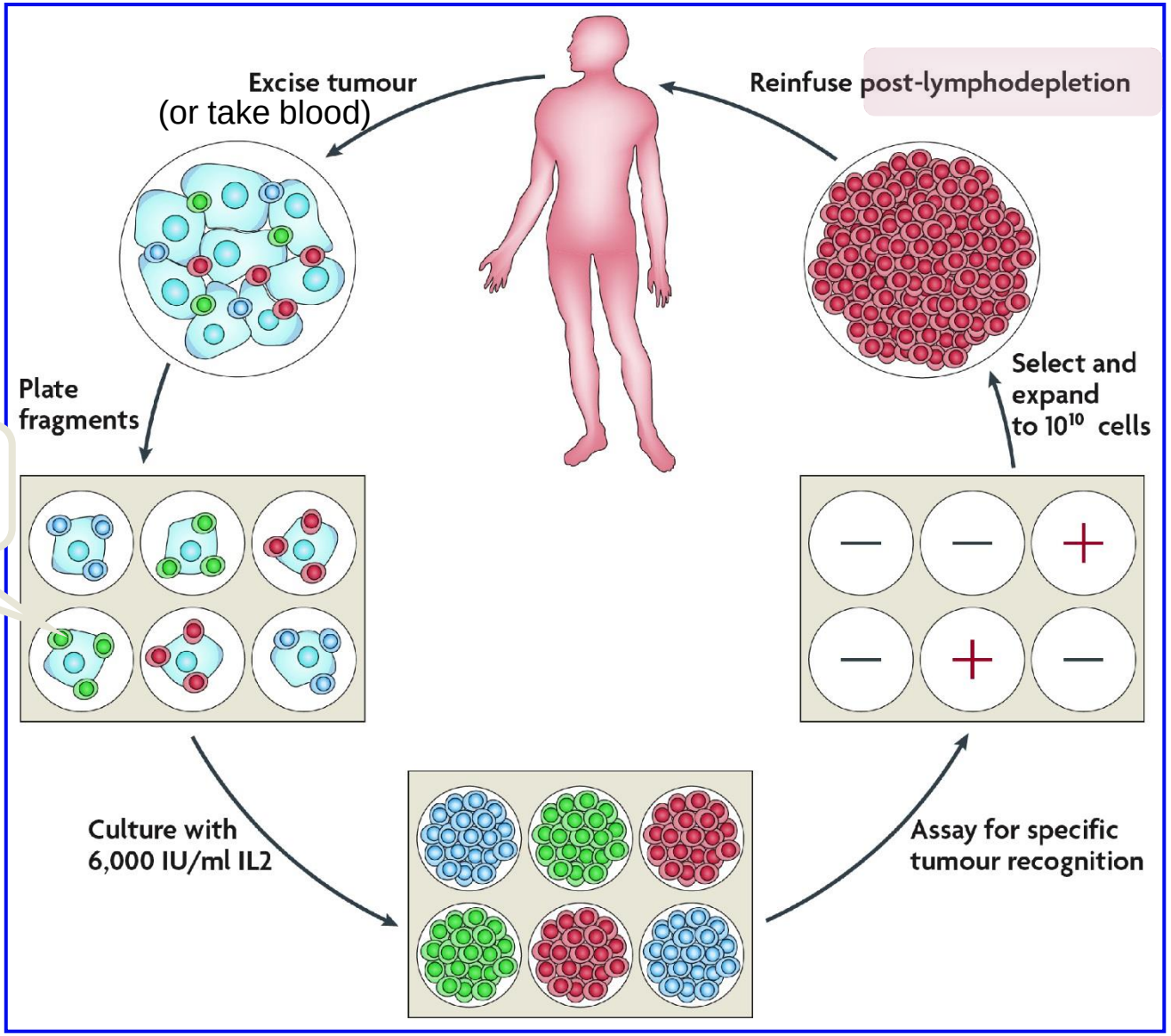
Rosenberg SA New England J Med 2004

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



1-2 Trasferimento adottivo di linfociti T tumore-specifici

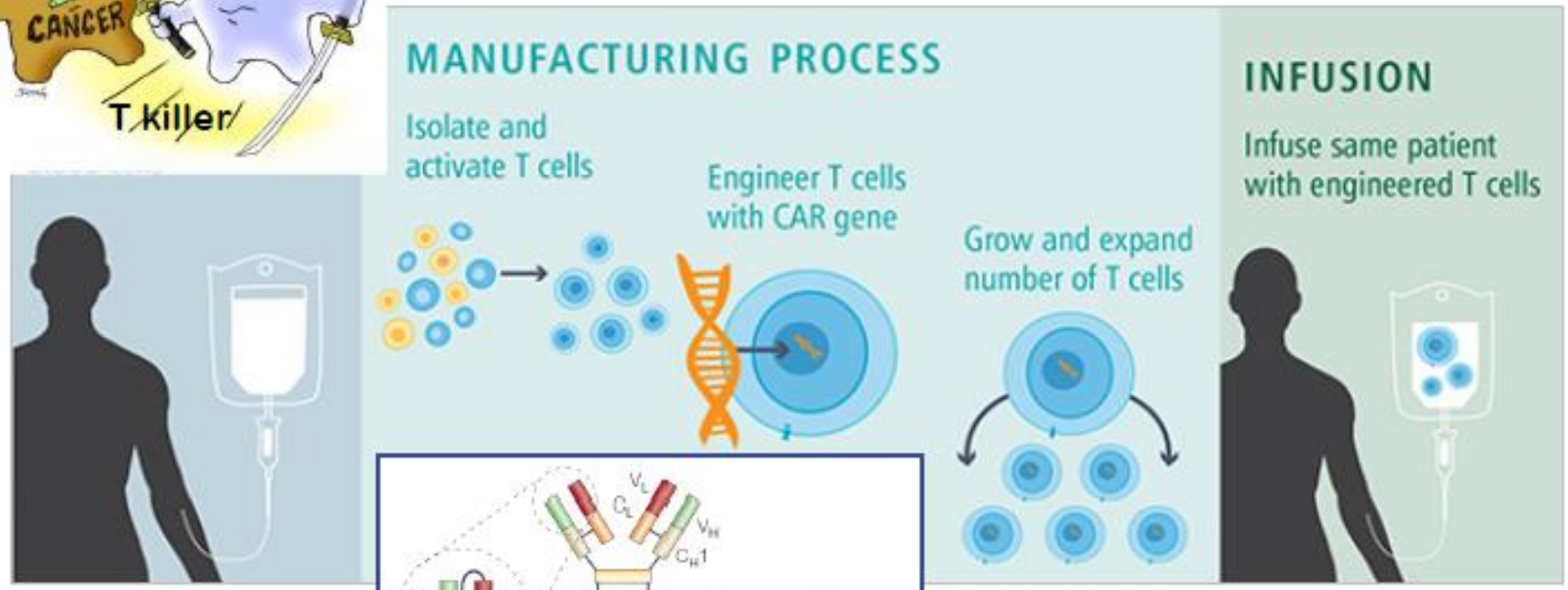
TIL: tumor-infiltrating lymphocytes

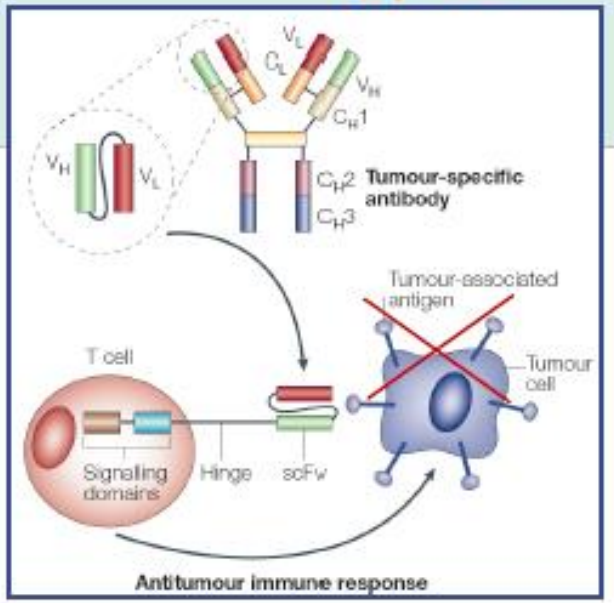


Rapid expansion of T cells (1,000- to 5,000-fold, sometimes with infusion of IL-2), achieving 10-100 billion cells for adoptive transfer.

3-4

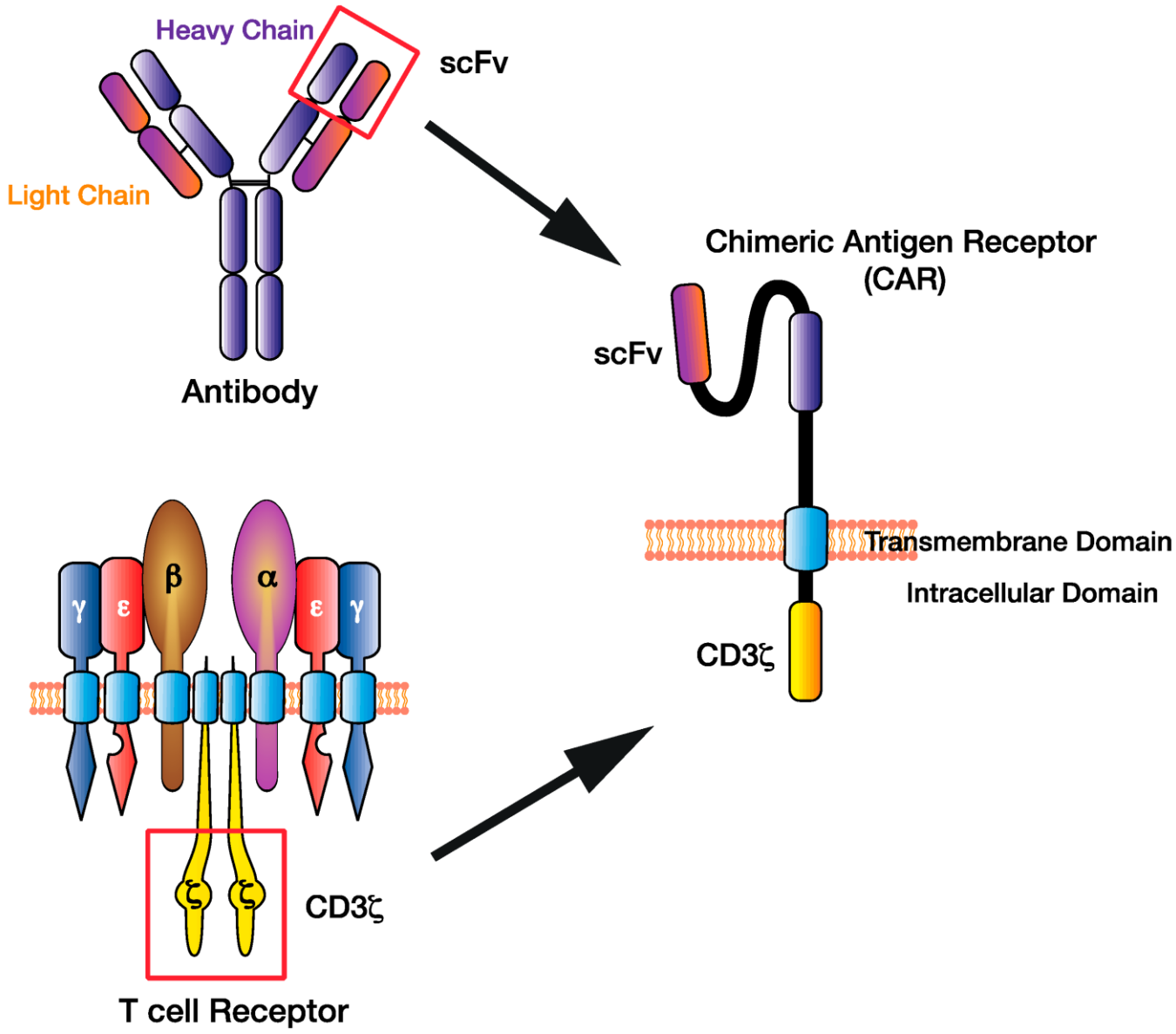
SUPERNATURAL T cells: genetic modifications of T cells for cancer therapy (T-CAR)

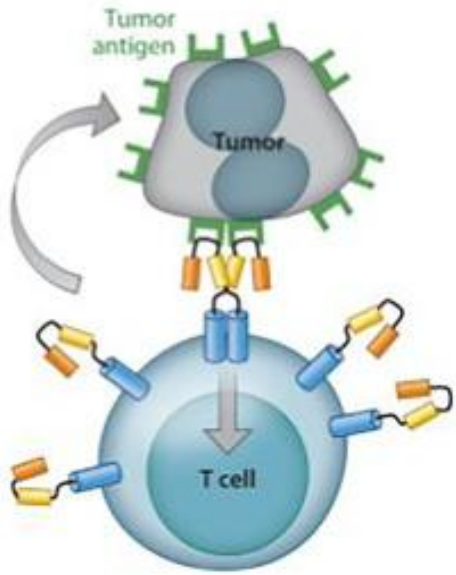




T-CAR (chimeric antigen receptor)

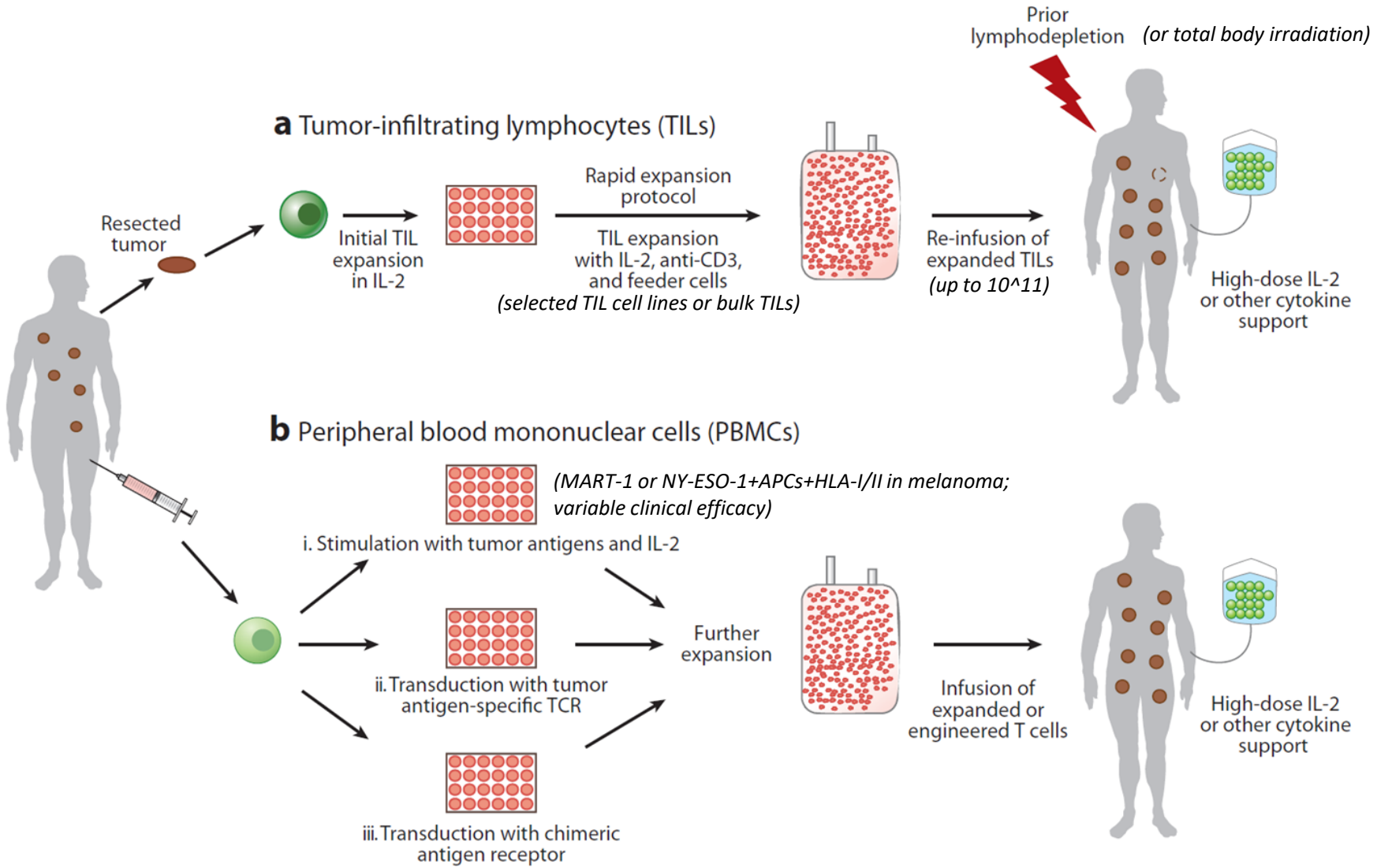
CAR
CHIMERIC ANTIGEN RECEPTOR





1-2-3-4

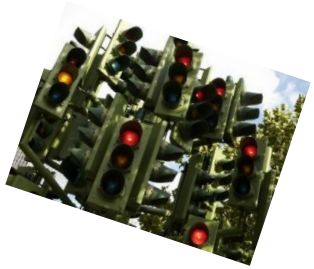
Diversi approcci per il trasferimento adottivo di linfociti T tumore-specifici per il melanoma metastatico

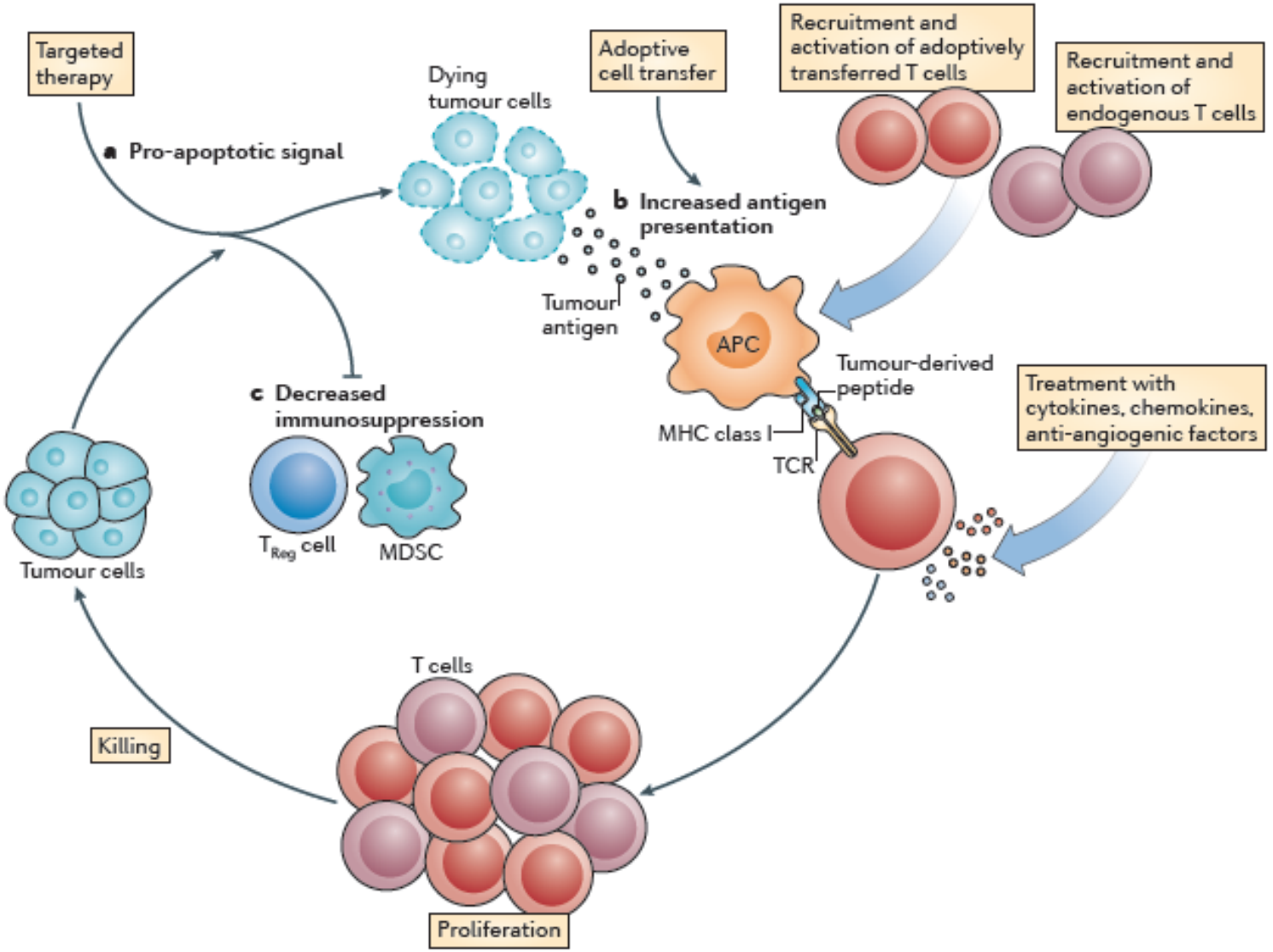


Lizee G Ann Rev 2013

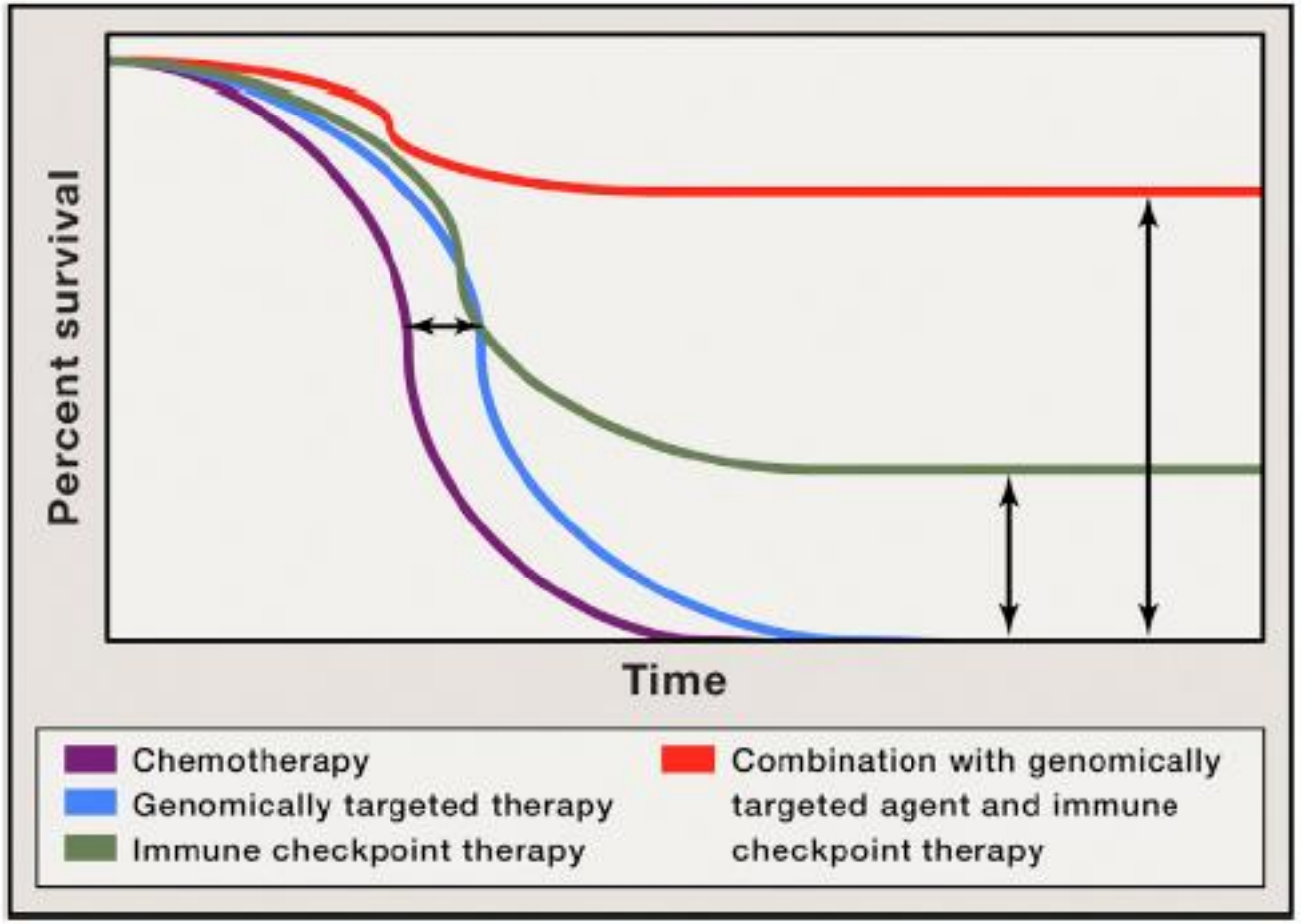
Premere sull'acceleratore e togliere i freni:

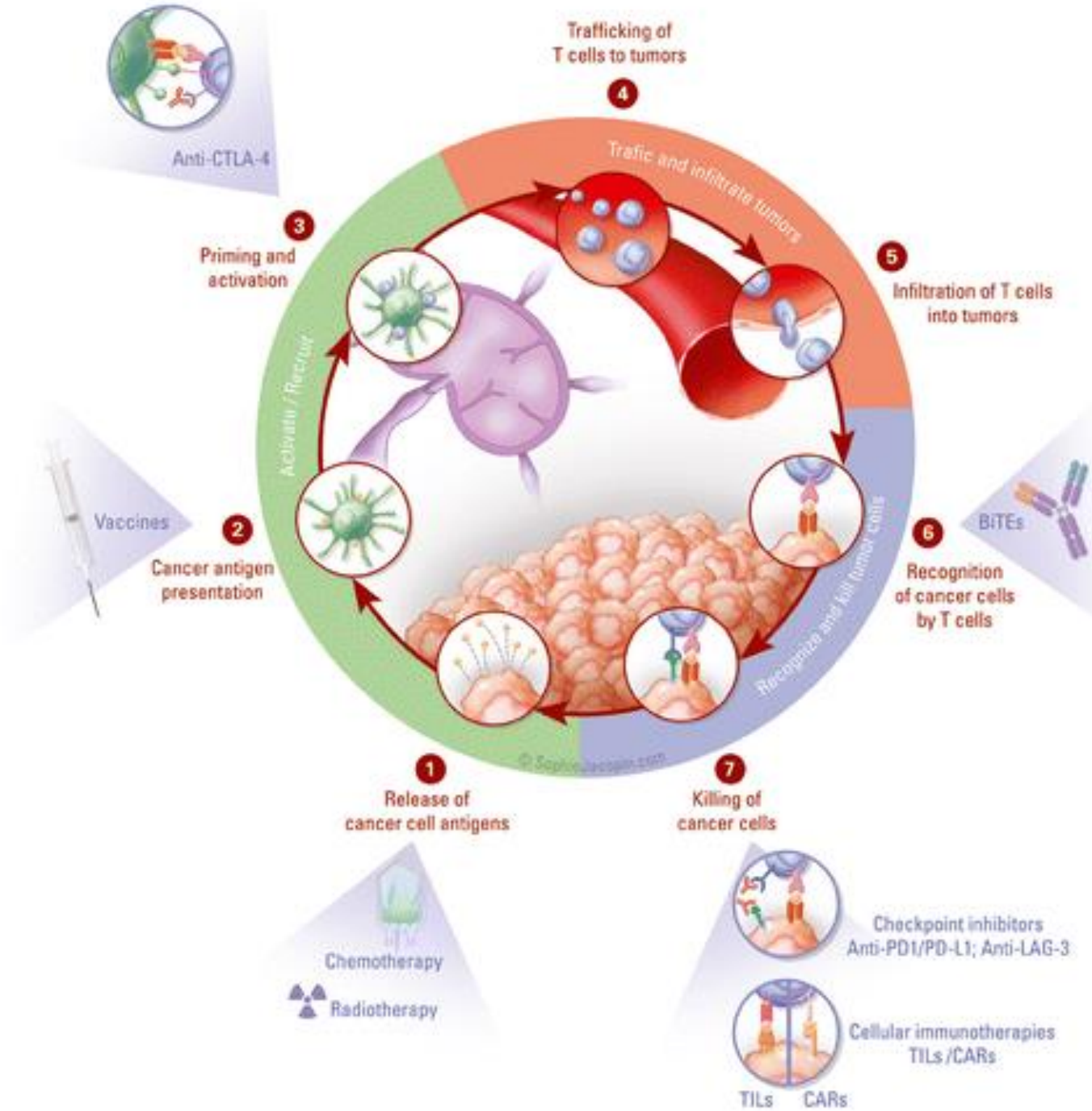
la terapia che unisce i vaccini anti-tumorali con gli inibitori degli «immuno checkpoint»





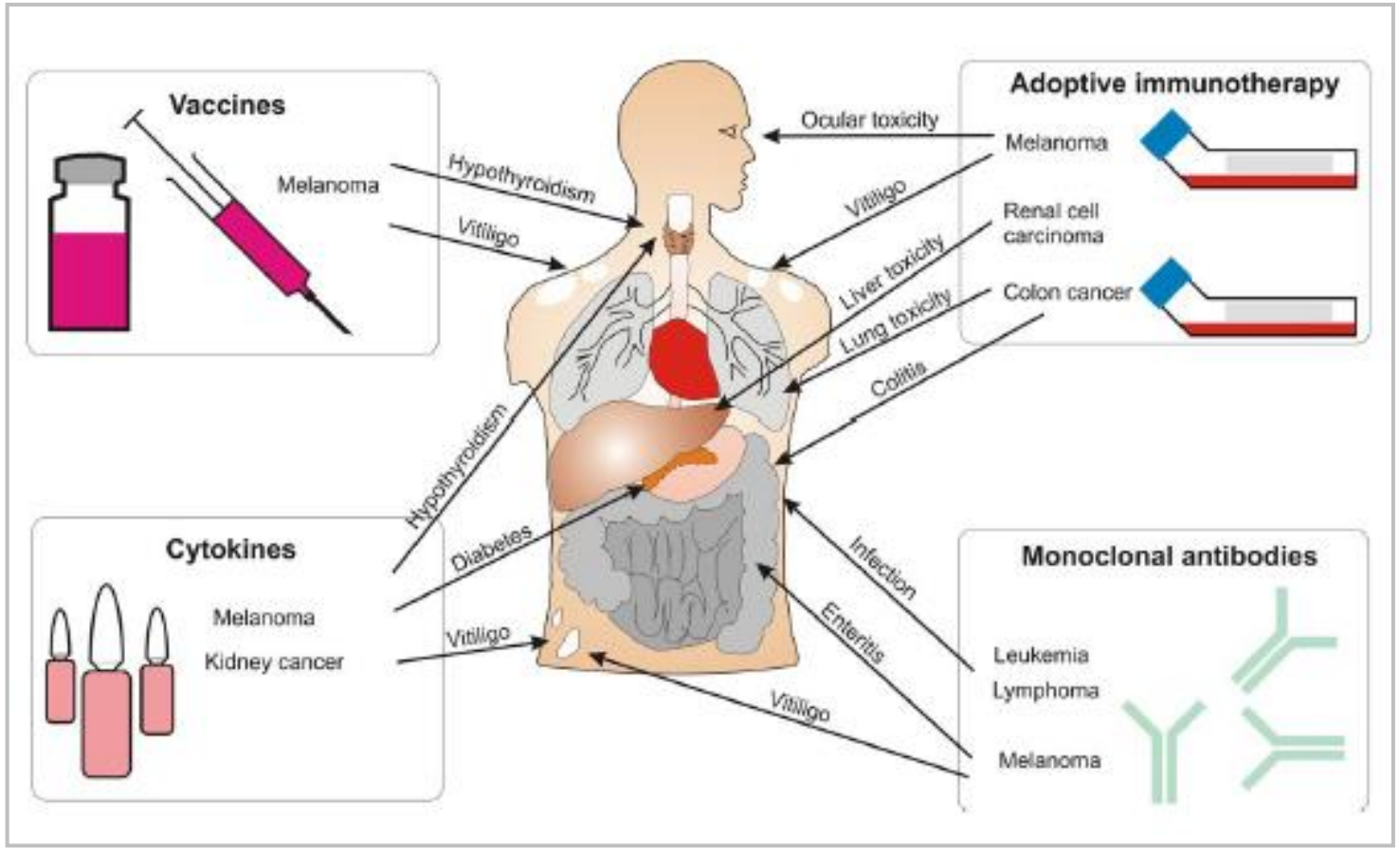
Improved overall survival as a result of combination therapy




Anti-CTLA-4
Trafficking of
T cells to tumors
4
Trafic and infiltrate tumors
3
Priming and
activation
5
Infiltration of T cells
into tumors
Activate / Recruit
Vaccines
2
Cancer antigen
presentation
BiTEs
6
Recognition
of cancer cells
by T cells
Recognize and kill tumor cells
1
Release of
cancer cell antigens
7
Killing of
cancer cells
Chemotherapy
Radiotherapy
Checkpoint inhibitors
Anti-PD1/PD-L1; Anti-LAG-3
Cellular immunotherapies
TILs /CARs
TILs
CARs

ATTENZIONE!

Immune toxicity associated with immunotherapy of cancer



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

Combinare vecchie e nuove terapie può essere la strategia vincente!

immunoterapia

radioterapia

chemioterapia

chirurgia