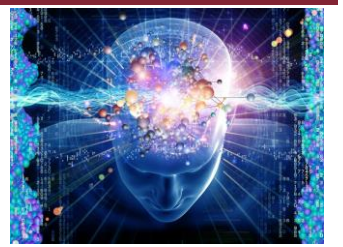
SAPIENZA
UNIVERSITÀ DI ROMA

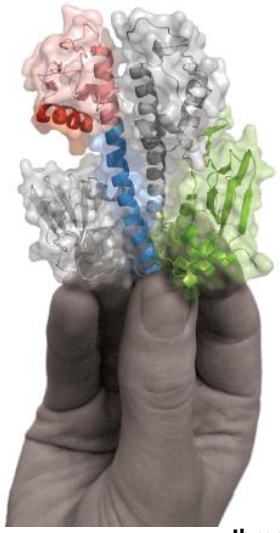
Comunicazione Scientifica Biomedico

la Scienza a portata di mano



Comunicazione delle Scienze Biomediche

Prof.ssa Cristina Cerboni

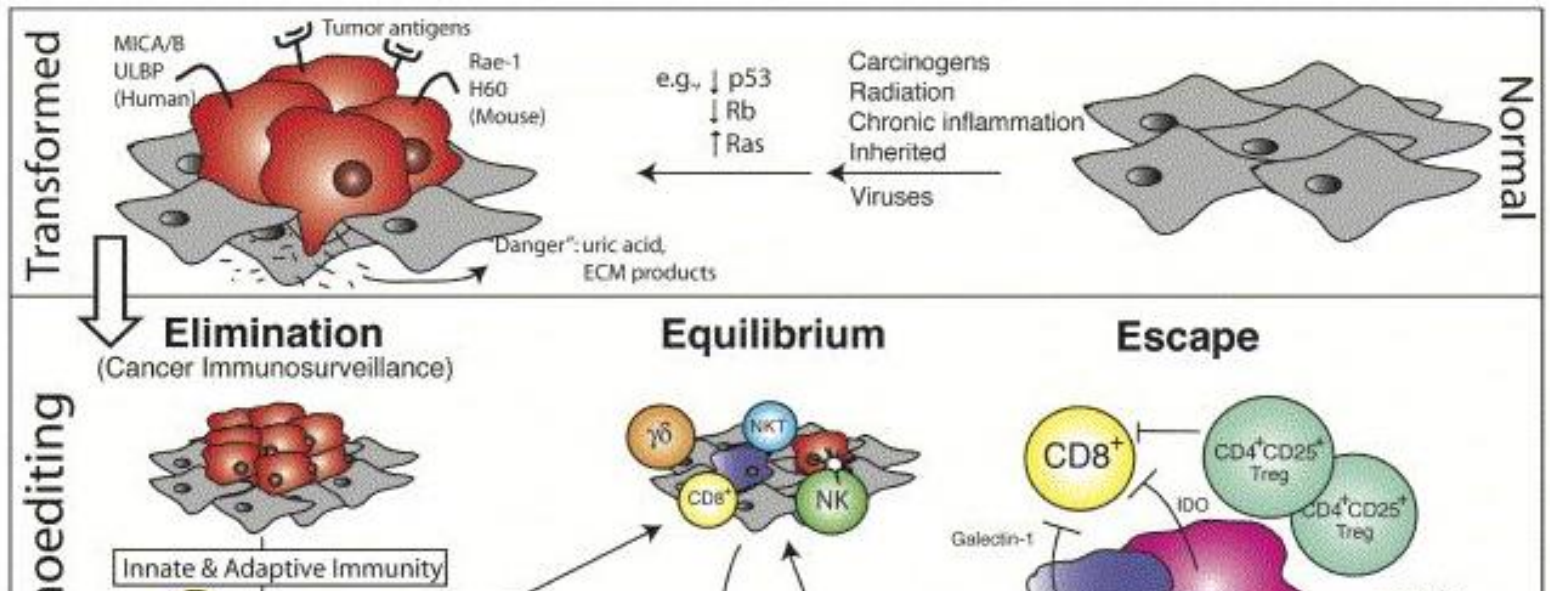


Immunoterapia dei tumori

Anno Accademico 2024-2025

Il materiale presente in questo documento viene distribuito solamente per uso interno ed esclusivamente a scopo didattico.

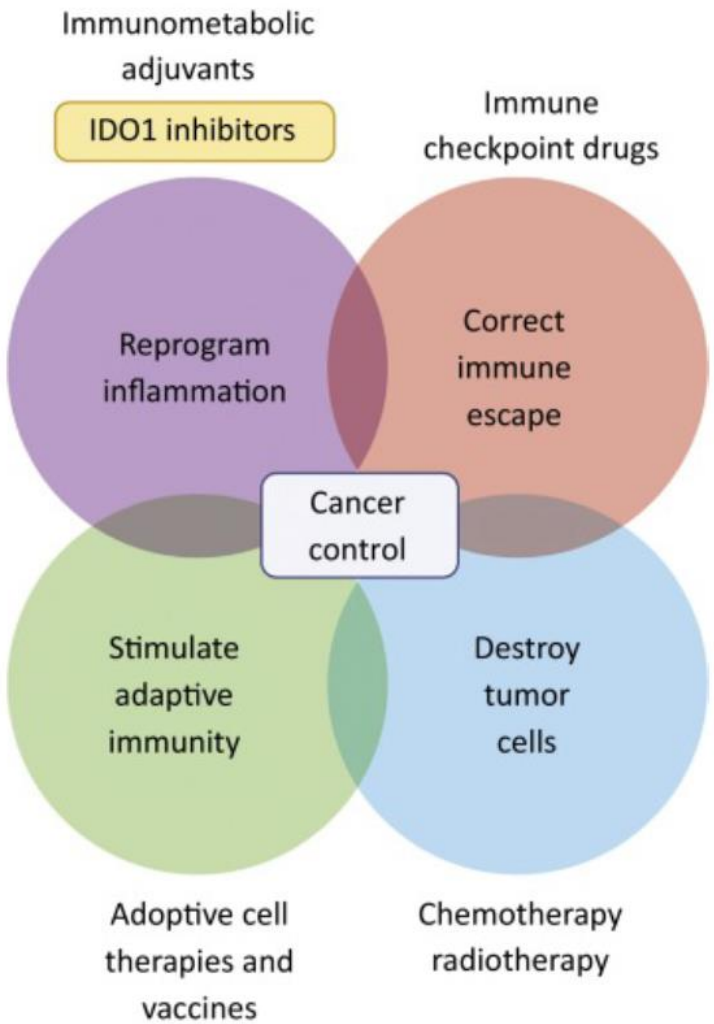
The immune system establishes a dynamic interaction with the tumour: cancer immunoediting



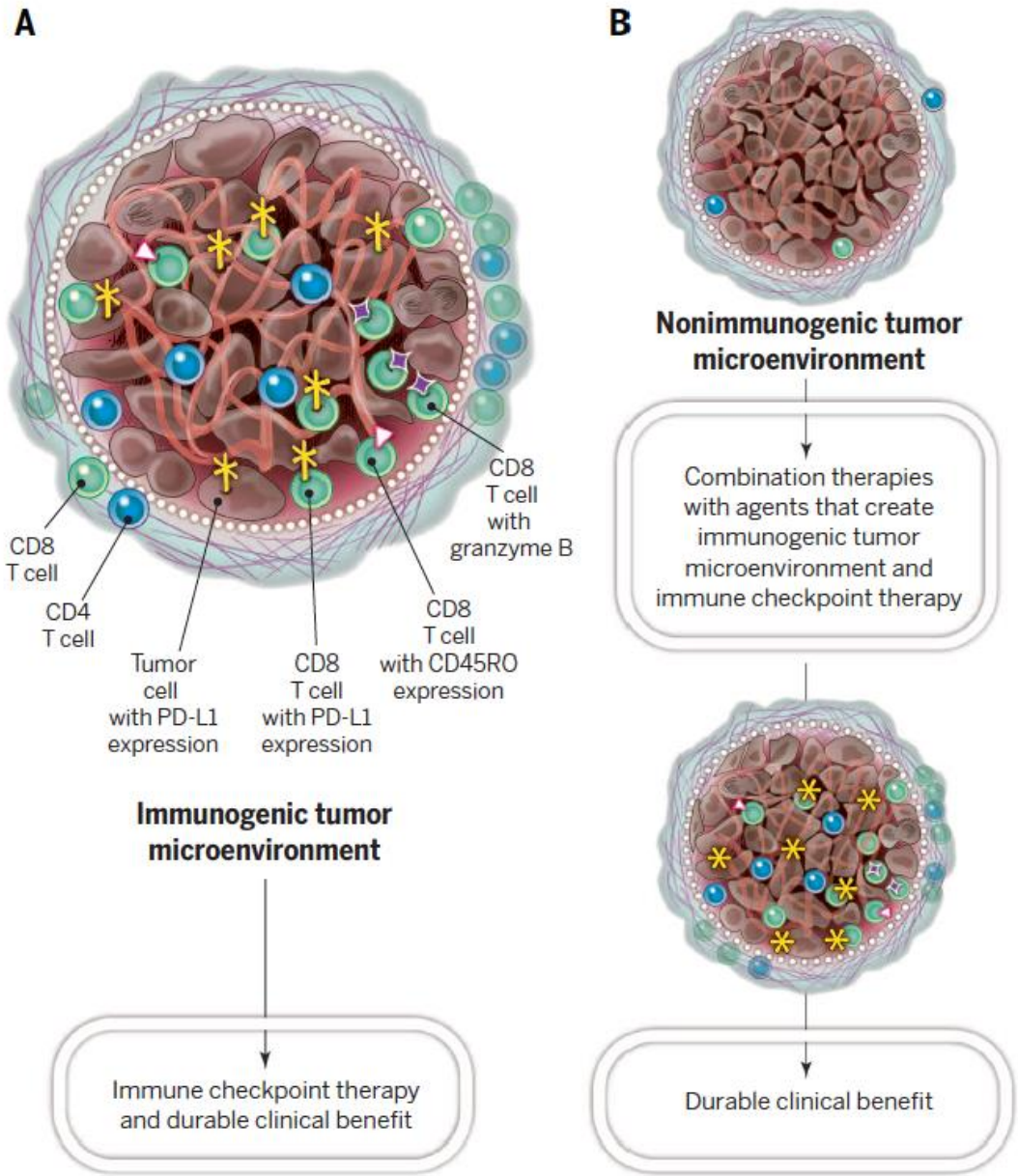
In an attempt to re-engage the immune system in its fight against cancer, cancer immunotherapy focuses on the development of agents that can activate the immune system to recognize and kill tumour cells.

Dunn et al Immunity 2004

Different approaches in cancer immunotherapy



Trasformare un tumore freddo in uno caldo



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

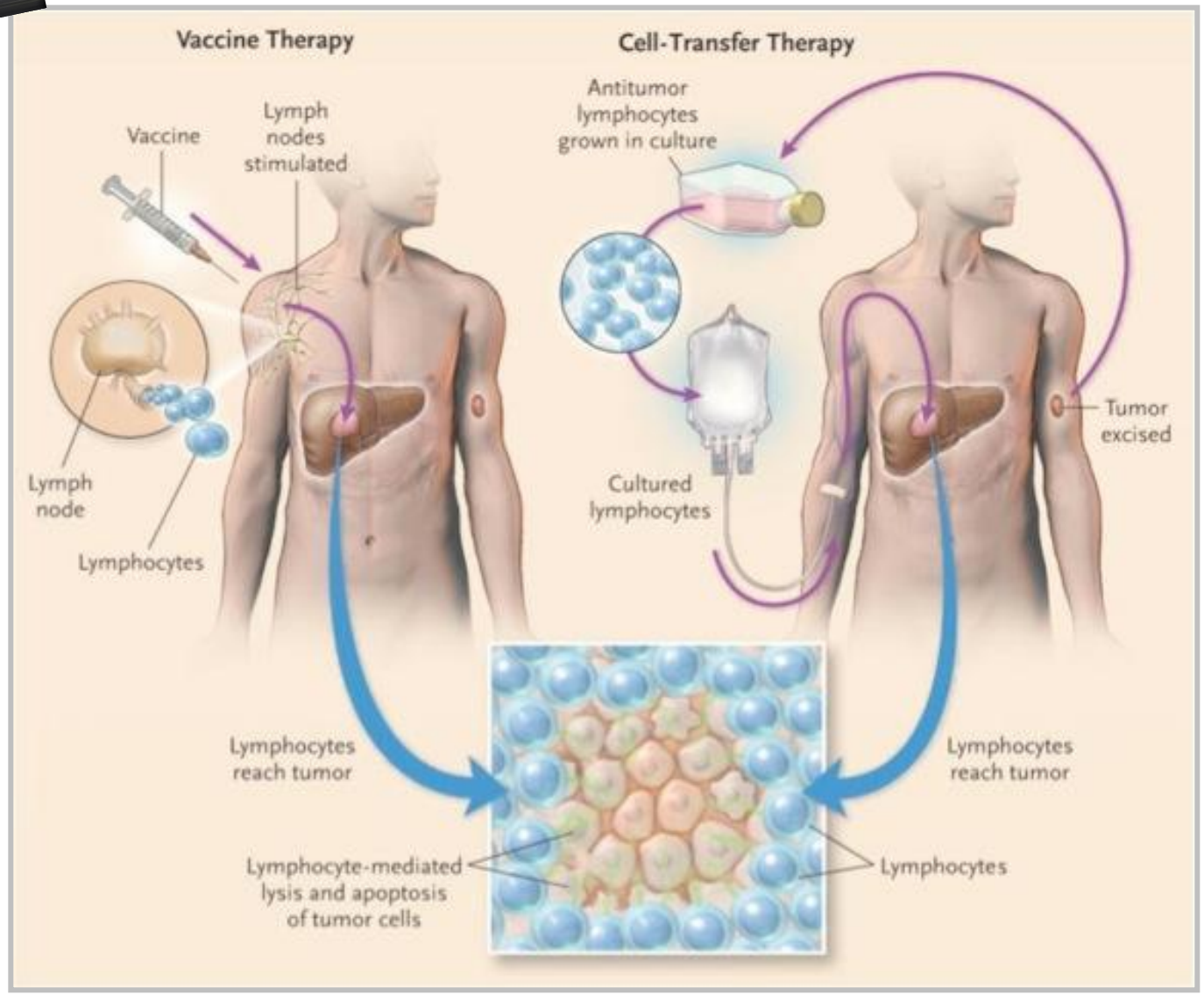
Escape

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

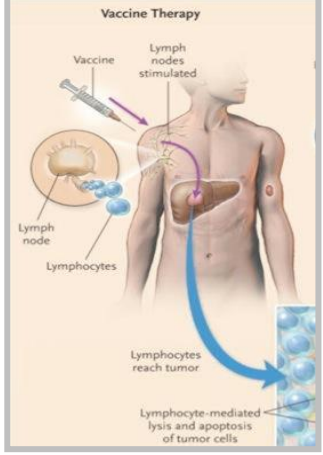


Rosenberg SA New England J Med 2004

ANTI-TUMOR IMMUNIZATION

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

Approcci sperimentali per i vaccini anti-tumore



1. Trovare antigeni tumore-specifici, da utilizzare per l'azione dei linfociti T CD8+ o di anticorpi.

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

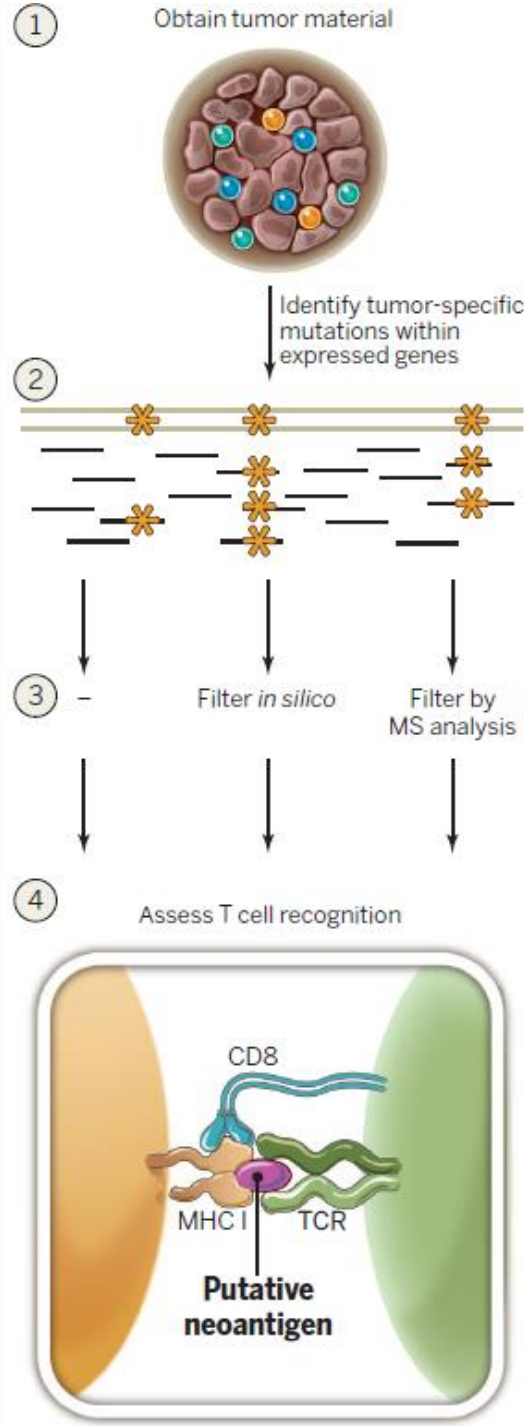
3. *"Dendritic cell loading"* con antigeni specifici o con cellule tumorali intere e stimolazione con adiuvanti specifici in sistemi di colture cellulari, prima del re-inoculo nel paziente.

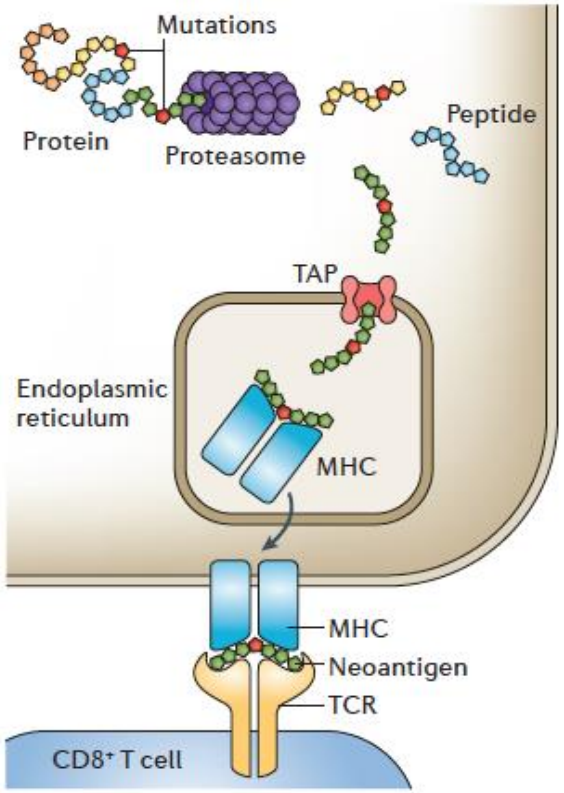
1+2+3

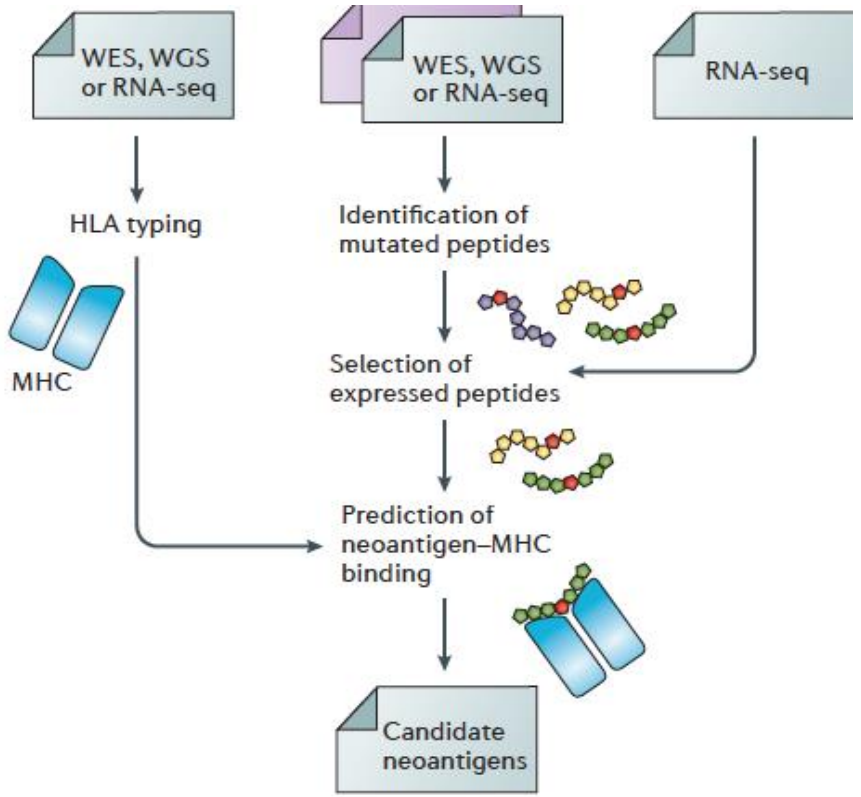
L’antigene tumorale “ideale” per la vaccinazione

- 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.

Cancer exome-based identification of neoantigens





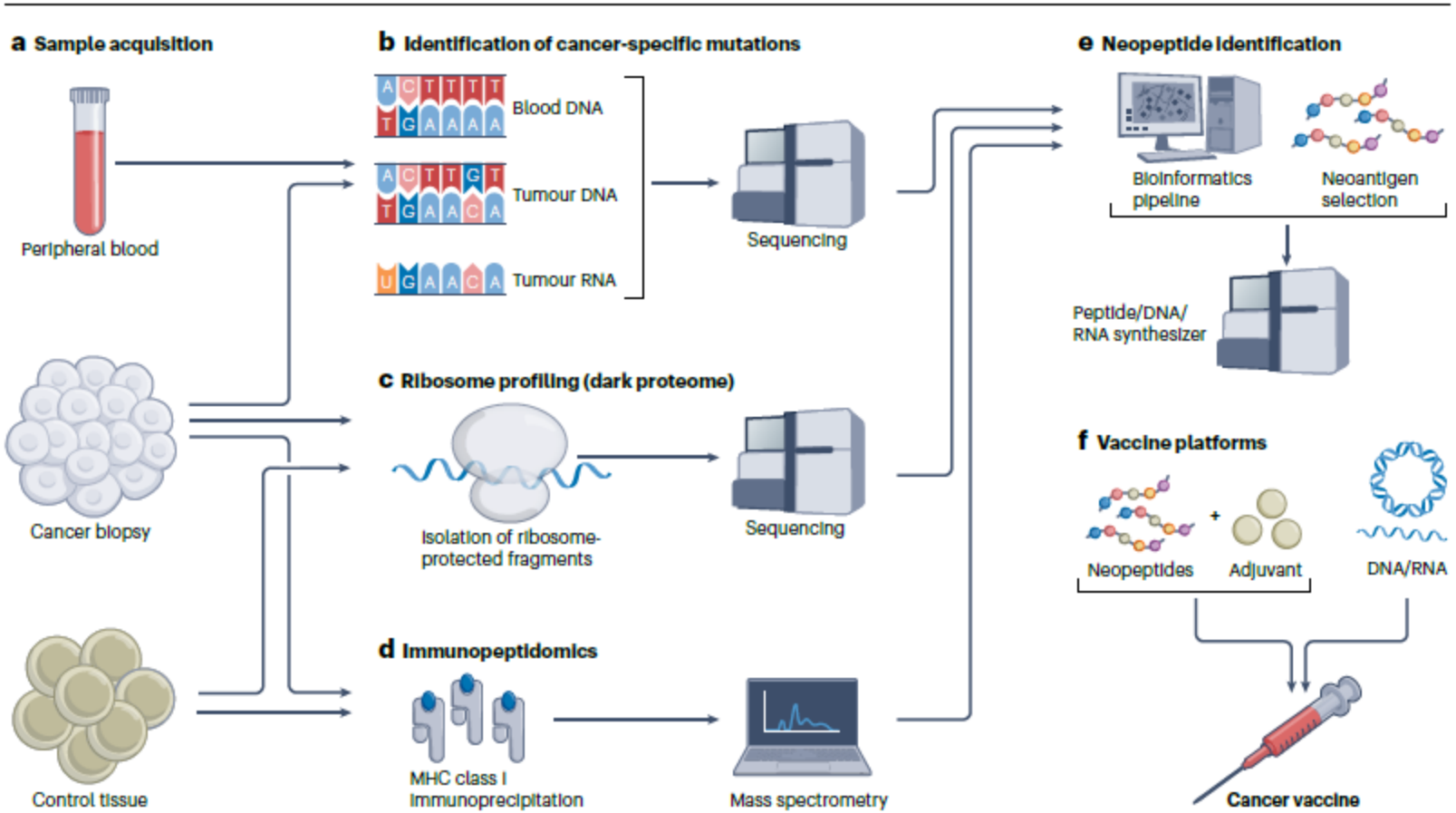


Cancer whole exome sequencing

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

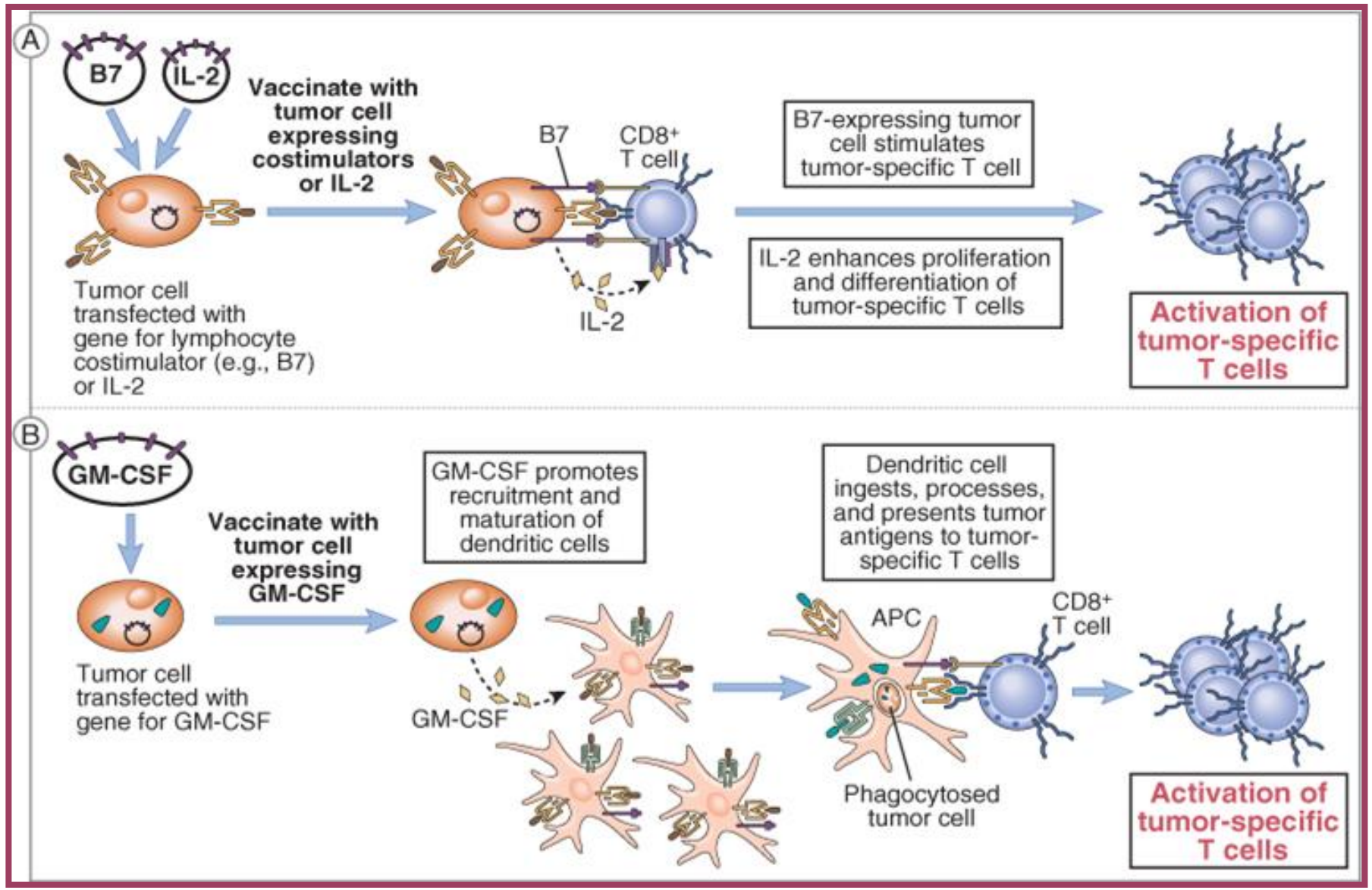
Neoantigens

Current approaches in neoantigen discovery and vaccine design

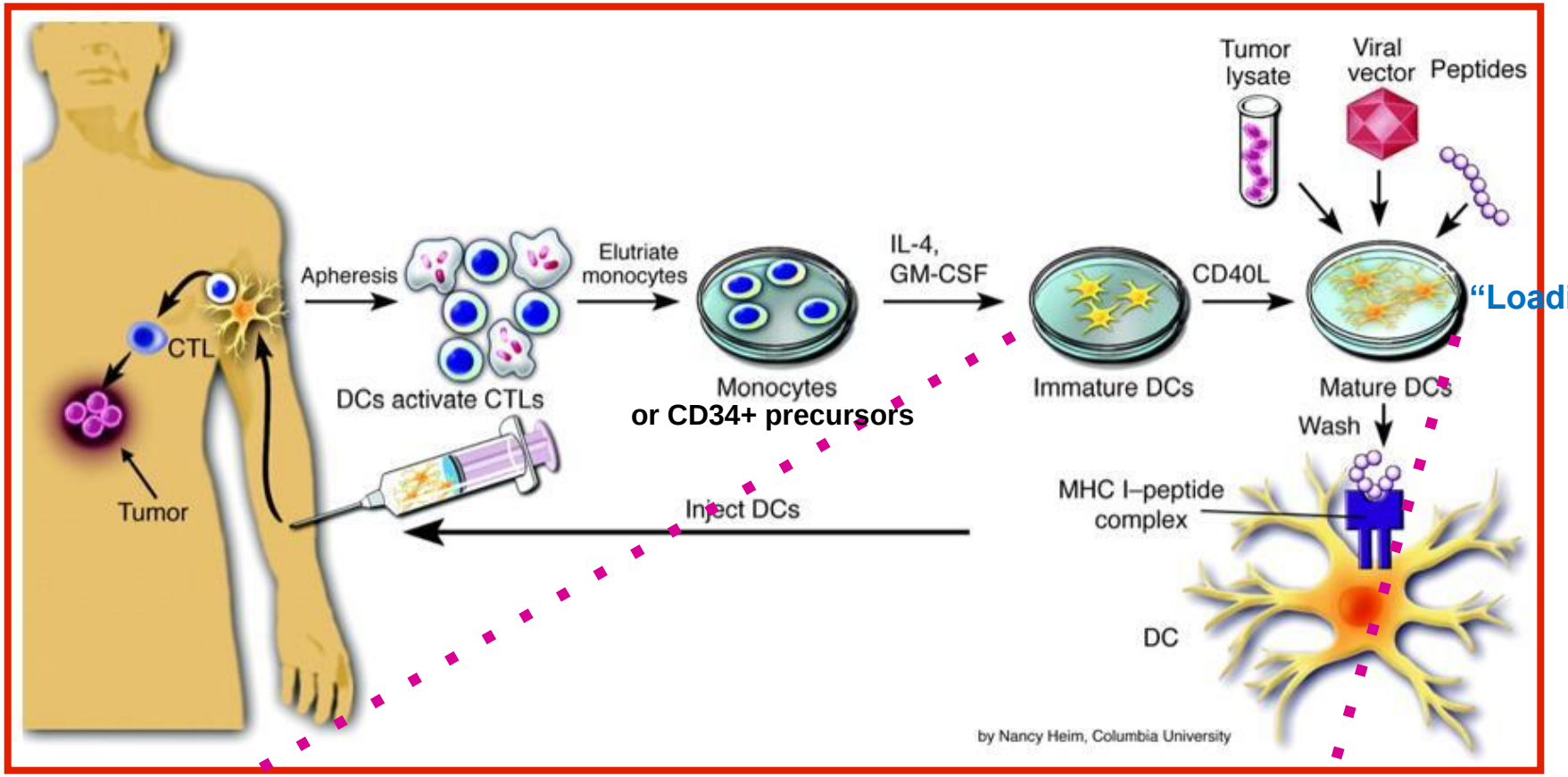


Katsikis Nat Rev Immunol 2023

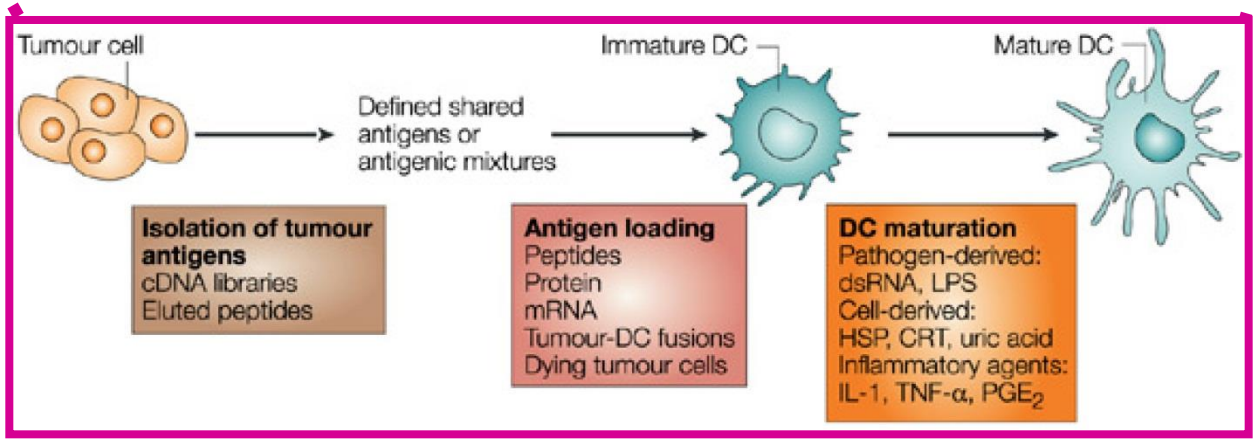
Manipolazioni genetiche per aumentare l'immunogenicità delle cellule tumorali



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



“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.

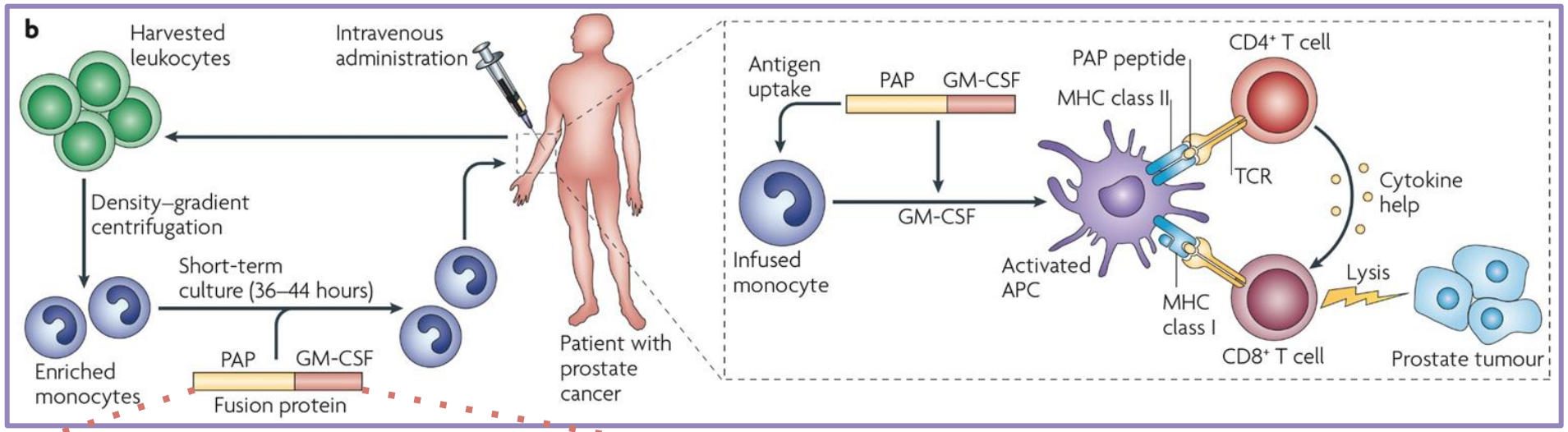
3. **Development of various immunomonitoring tools** to study the mechanisms underlying successful vaccination that will help to shape future vaccine design.

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

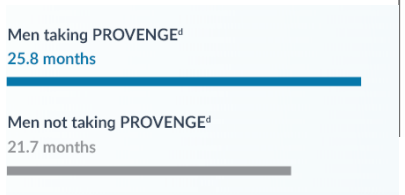
First U.S. «cancer vaccine» in 2010!

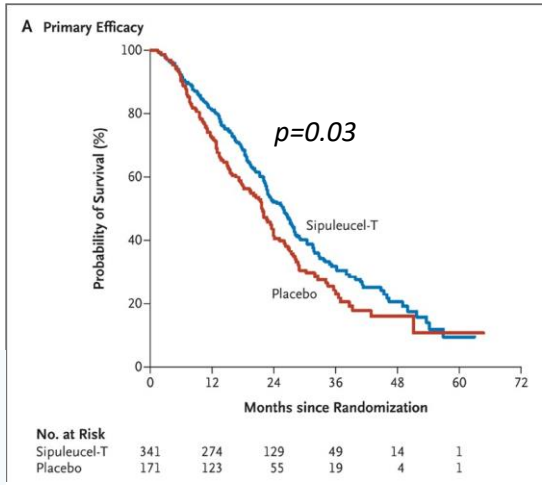
Sipuleucel-T (Provenge)

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

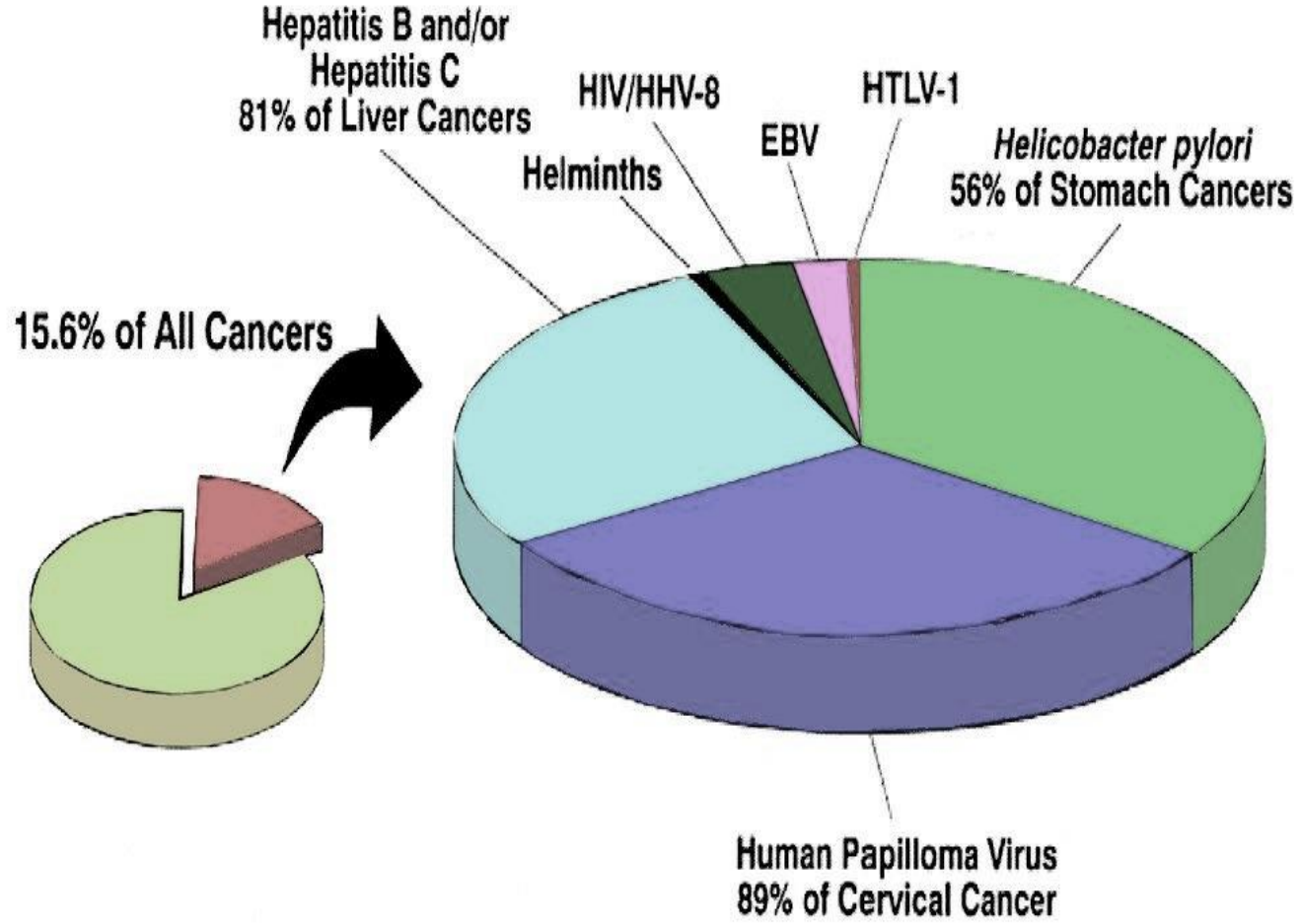
"The challenge now is to maximize the effectiveness of cancer vaccines such as Provenge by incorporating all we have learned in recent years about the immune response to cancer and cancer vaccine development, converting the four-month survival advantage of Provenge-vaccinated patients into prolonged-even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

A major breakthrough in anticancer therapy occurred in 2005 with the completion of a clinical trial involving 12167 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!!

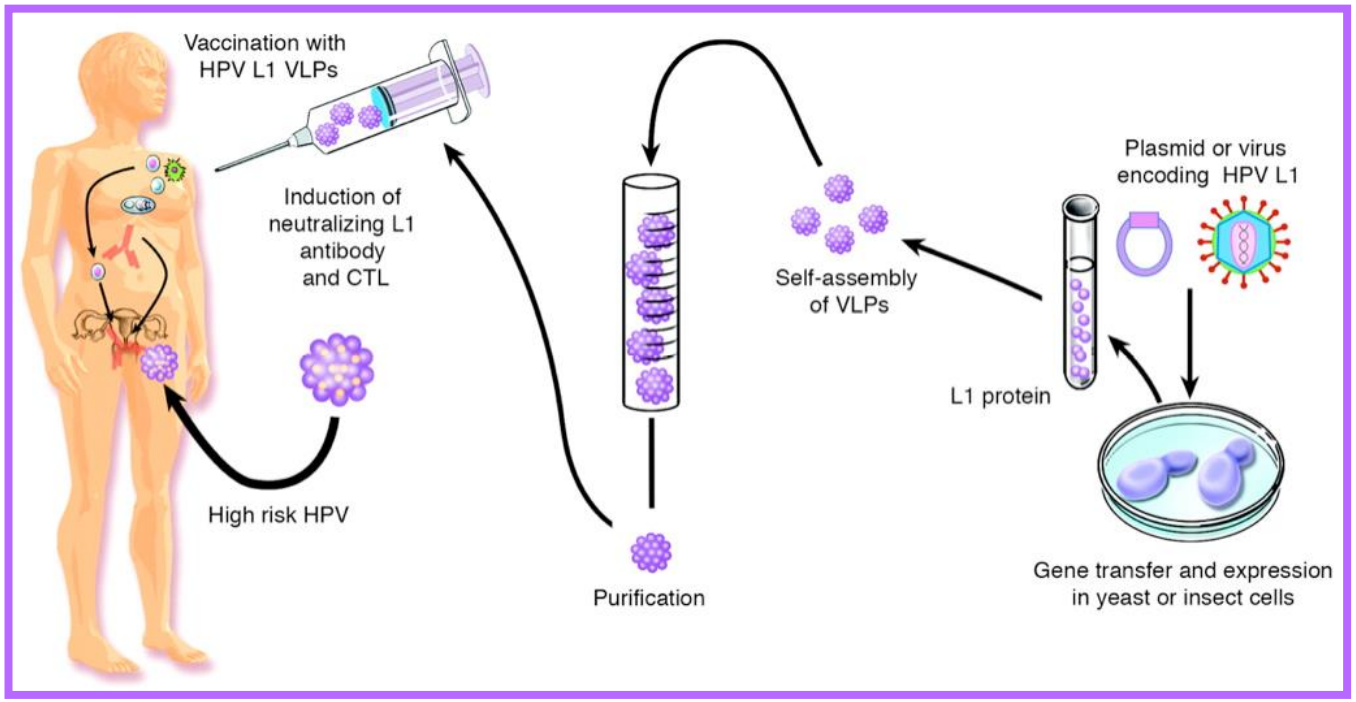
HPV vaccine consisting of L1 (capsid protein) Virus-Like Particles (VLP)

from HPV-16 and HPV-18

- HPV: virus a DNA responsabile di varie lesioni, comunemente note con il nome di condilomi, che si possono riscontrare a livello dell'apparato genitale femminile e maschile. Infezione a prevalente trasmissione sessuale.

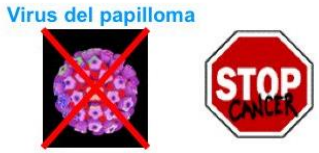
- Sono noti più di 20 ceppi virali alcuni dei quali, tra cui il ceppo 16 e 18, hanno un elevato potere trasformante *(*ceppi oncogeni o *high-risk).* Anche i ceppi 31, 33, 45, 52 e 58 hanno potere trasformante.

- I ceppi *high-risk* sono responsabili dell'85% dei tumori della cervice uterina (Fonte: AIFA/EMA)



(ad es., da HPV16 o HPV18)

I vaccini possono prevenire la trasformazione neoplastica indotta da virus



La ricerca che cura

Nel nostro Paese sono disponibili due vaccini:

•**Bivalente (CERVARIX):** somministrato solo alle femmine, contenente i sierotipi 16 e 18 (responsabili di oltre il 70% di tutti i tumori del collo dell'utero). Si inietta per via intramuscolare.

Proteina L1 del Papillomavirus1 umano di tipo 16 20 microgrammi
Proteina L1 del Papillomavirus1 umano di tipo 18 20 microgrammi

•**Quadrivalente (GARDASIL):** per maschi e femmine, contenente i sierotipi 6, 11 (responsabili di oltre il 90% dei condilomi ano-genitali), 16, 18. Si inietta per via intramuscolare.

Proteina L1 Tipo 6 di Papillomavirus Umano 20 microgrammi
Proteina L1 Tipo 11 di Papillomavirus Umano 40 microgrammi
Proteina L1 Tipo 16 di Papillomavirus Umano 40 microgrammi
Proteina L1 Tipo 18 di Papillomavirus Umano 20 microgrammi

Nonavalente (GARDASIL9):

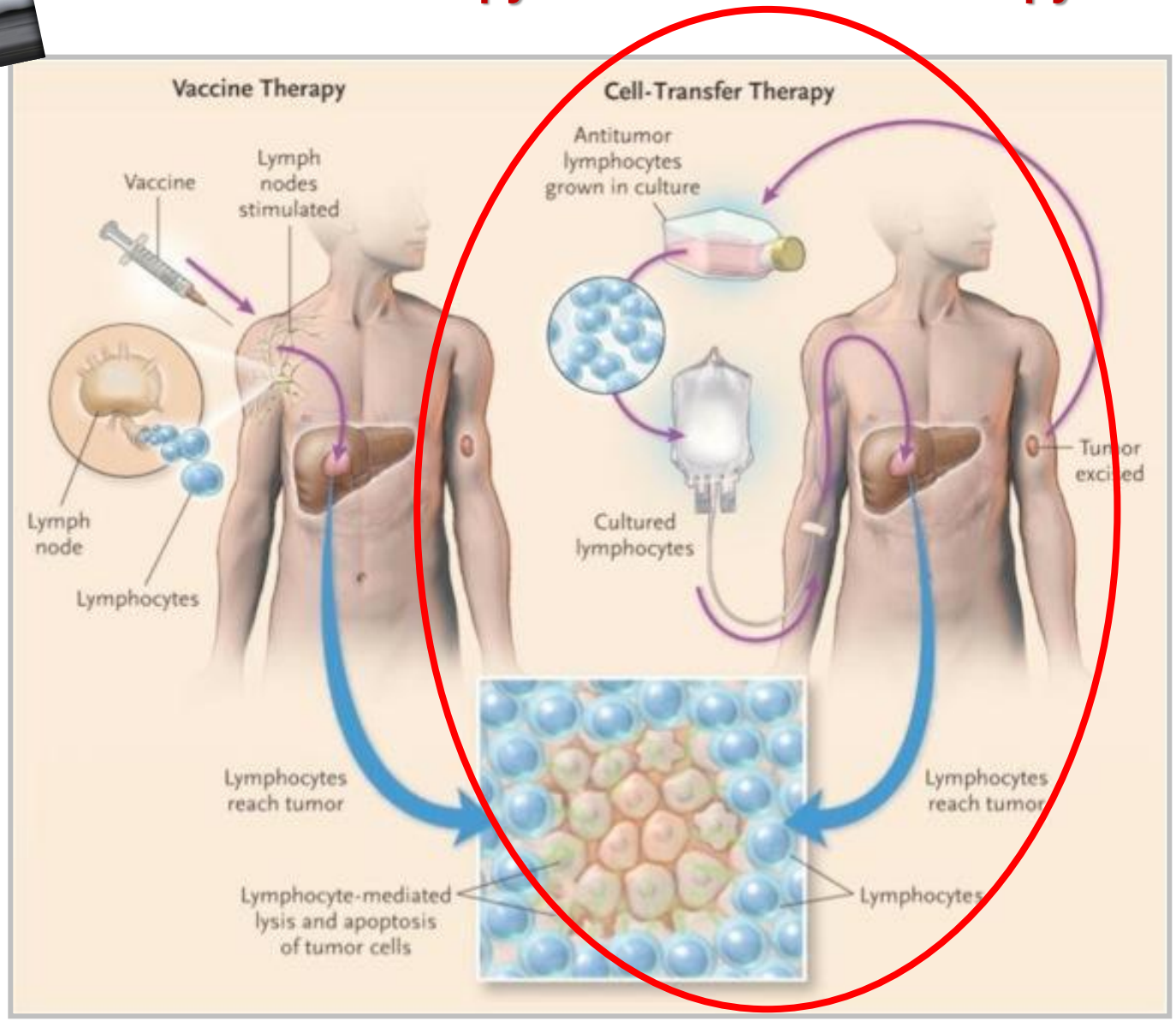
Proteina L1 Tipo 6 di Papillomavirus Umano 20 microgrammi
Proteina L1 Tipo 11 di Papillomavirus Umano 40 microgrammi
Proteina L1 Tipo 16 di Papillomavirus Umano 40 microgrammi
Proteina L1 Tipo 18 di Papillomavirus Umano 20 microgrammi
L1 HPV 31,33,45,52,58

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

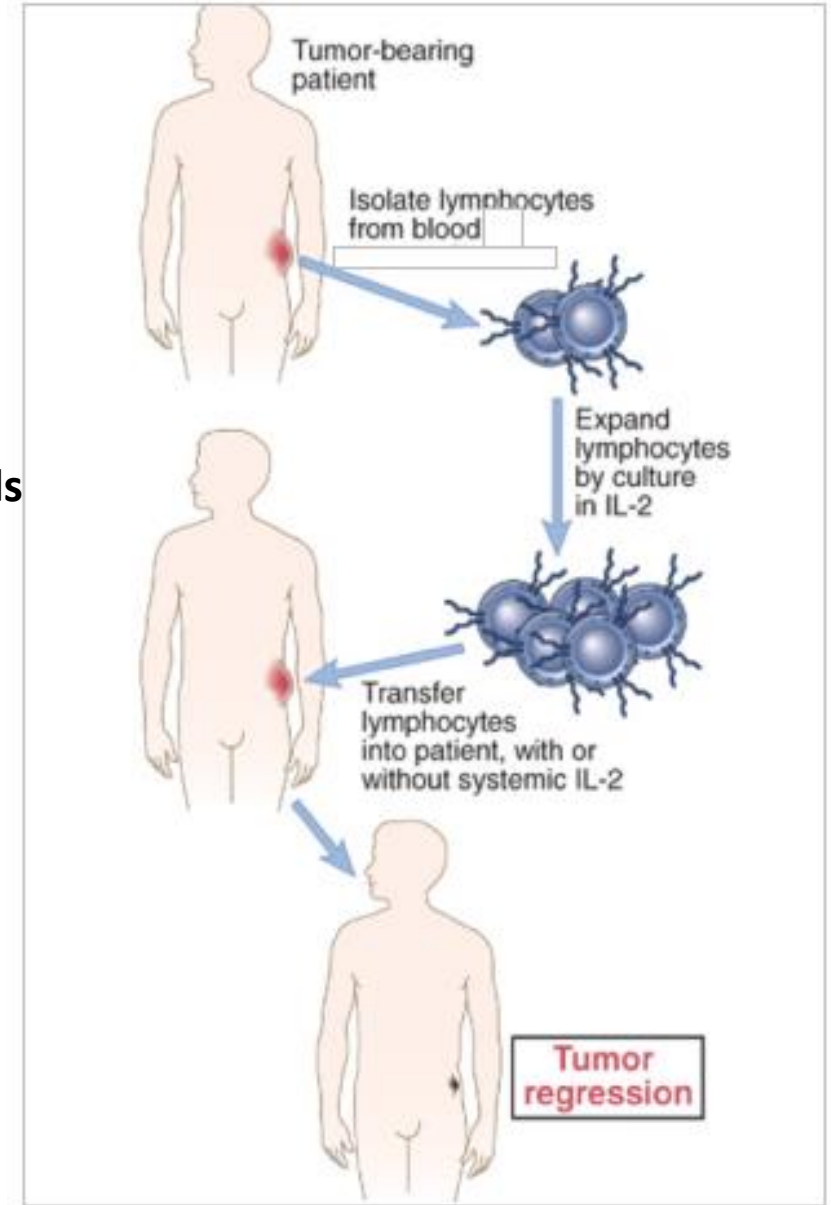


Rosenberg SA New England J Med 2004

ADOPTIVE CELL THERAPY

1985: Use of LAK cells plus IL-2 in cancer immunotherapy

LAK
Lymphokine-activated cells
mainly
IL-2 activated NK cells

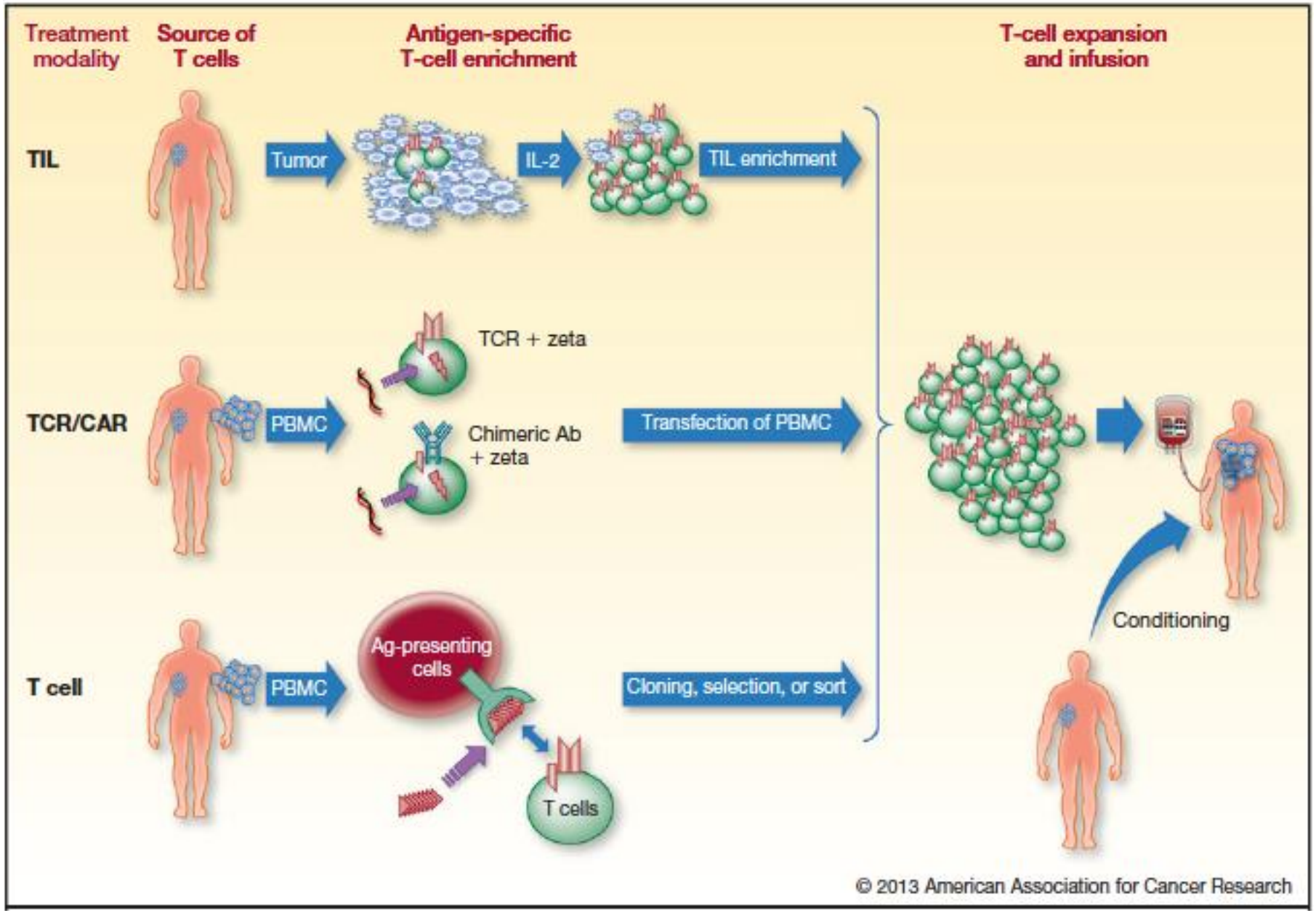


Diversi approcci per il trasferimento adottivo di linfociti T tumore-specifici

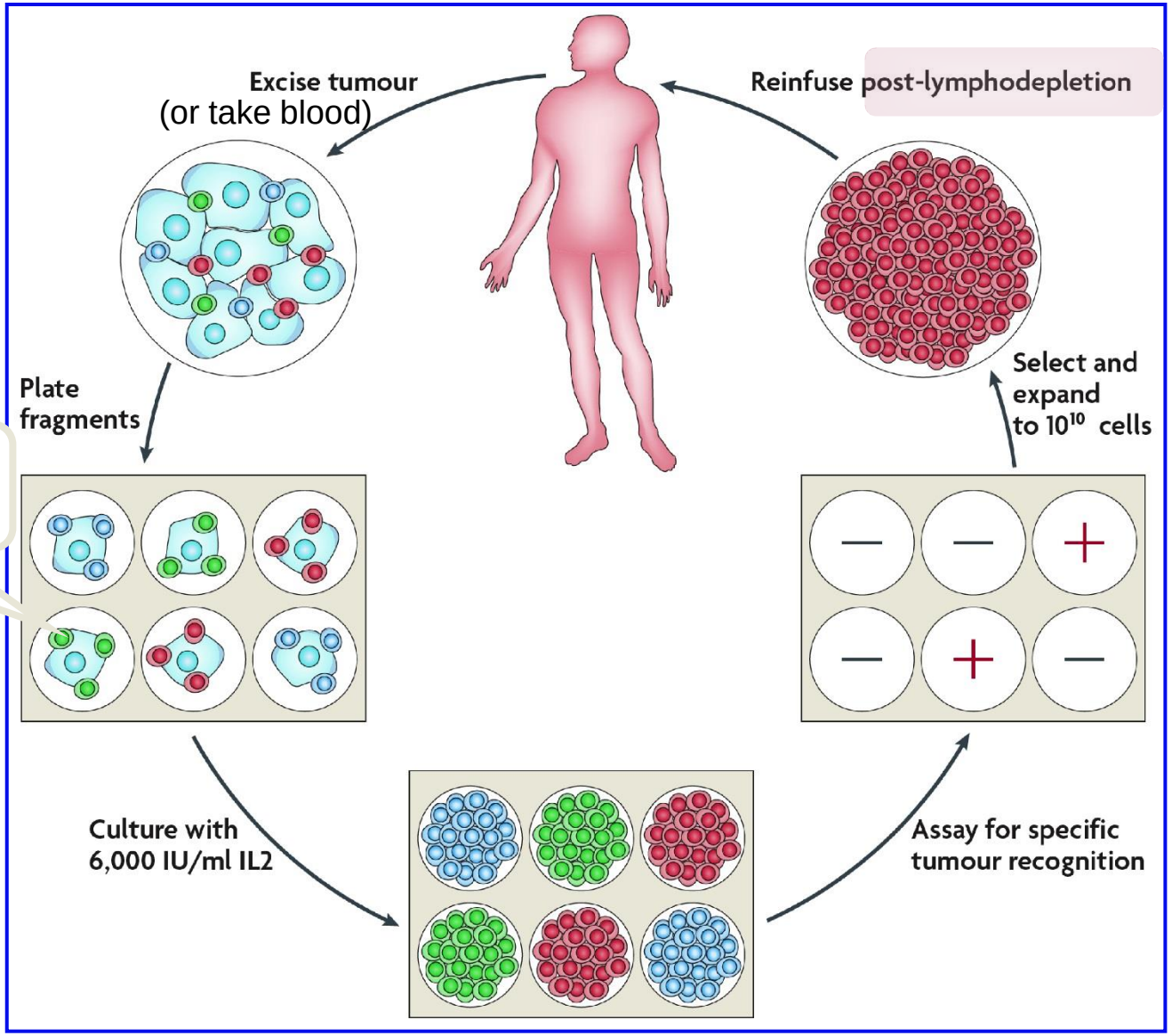
1

3-4

2



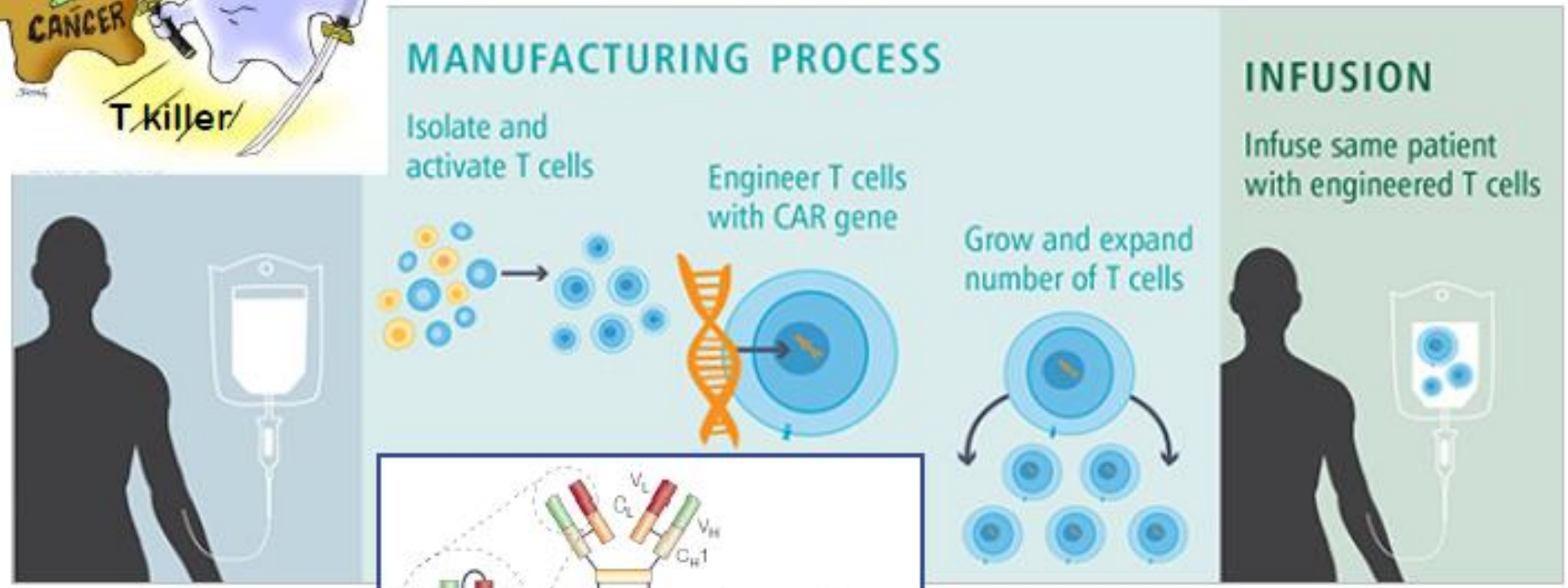
Trasferimento adottivo di linfociti T tumore-specifici

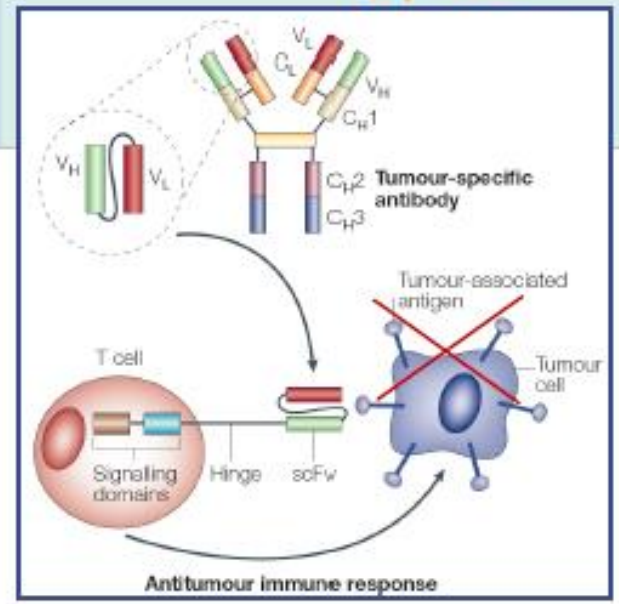


TIL: tumor-infiltrating lymphocytes

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.

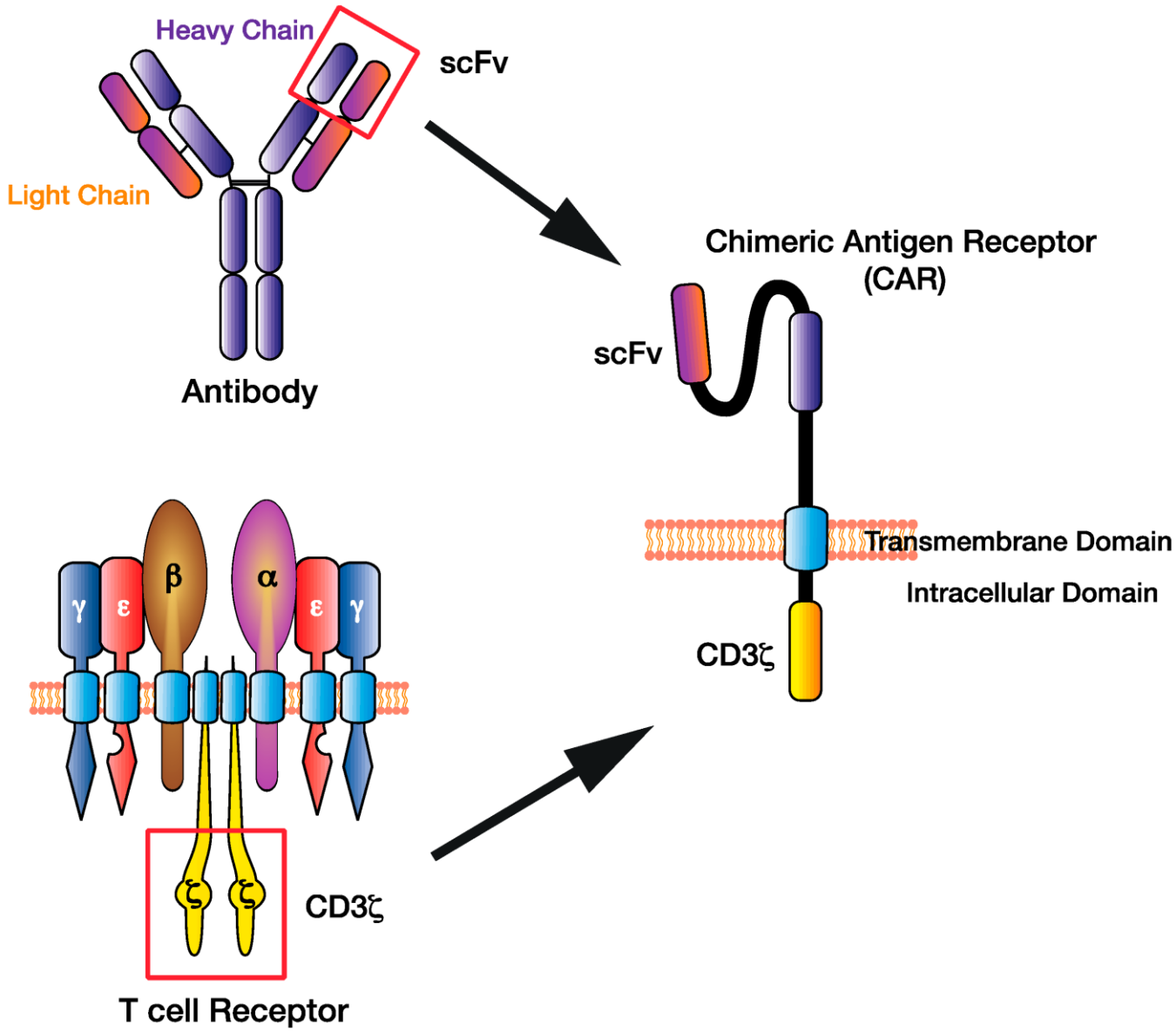
SUPERNATURAL T cells: genetic modifications of T cells for cancer therapy (T-CAR)





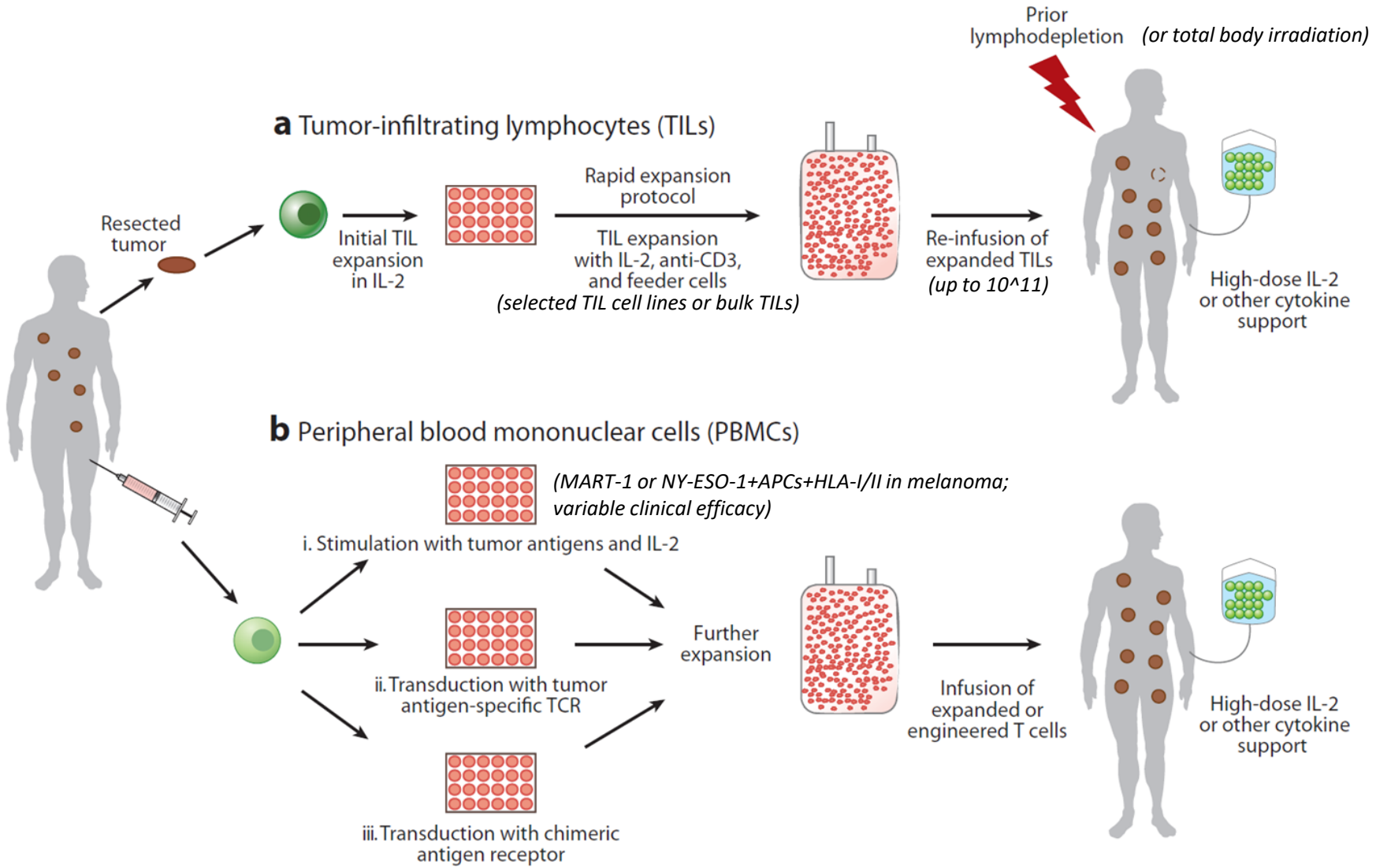
T-CAR (chimeric antigen receptor)

CAR
CHIMERIC ANTIGEN RECEPTOR



More info next week…

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



Lizee G Ann Rev 2013

ADOPTIVE NK CELL THERAPY

TABLE 1 Clinical studies of NK cells in cancer immunotherapy

Therapy	Stage	Disease	Interpretation
Adoptive transfer			
Autologous NK cells	Clinical trials	Haematologic malignancies	Safe but limited clinical efficacy
Allogeneic NK cells	Clinical trials	Haematologic malignancies	Promising data in AML but overcoming host immunity is a challenge
K562 NK-cell expansion	Clinical trial	AML	Easy to expand; safe; trials ongoing
iPSC-NK cells	Preclinical	Many cancers	Clonal starting cell lines; easy to expand; easy to genetically modify; unlimited capacity; off-the-shelf
CAR-NK cells	Clinical trial	B-cell malignancies	Use against a specific tumour antigen; many trials planned using this approach
Cytokines			
IL-2	FDA approved	Melanoma and kidney cancer	Repeated injections well tolerated but high treatment limited by vascular leak and limited efficacy
rhIL-15	Clinical trial	Many tumours	Activates NK cells without activating Treg cells; tested daily or five times per week
IL-15 complexes (ALT-803)	Clinical trial	Many tumours	Activates NK cells without activating Treg cells; can be given weekly and is safe; combination testing in progress
Depletion of Treg cells (IL2DT)	Clinical trial	AML	Improved efficacy of haploidentical NK-cell transfer; safe;
Induction of adaptive NK cells			
FATE-100 (GSK3 inhibitor)	Clinical trial	AML, ovarian cancer and other solid tumours	Enhances NK-cell killing; clinical testing in progress

Induced pluripotent stem cell

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

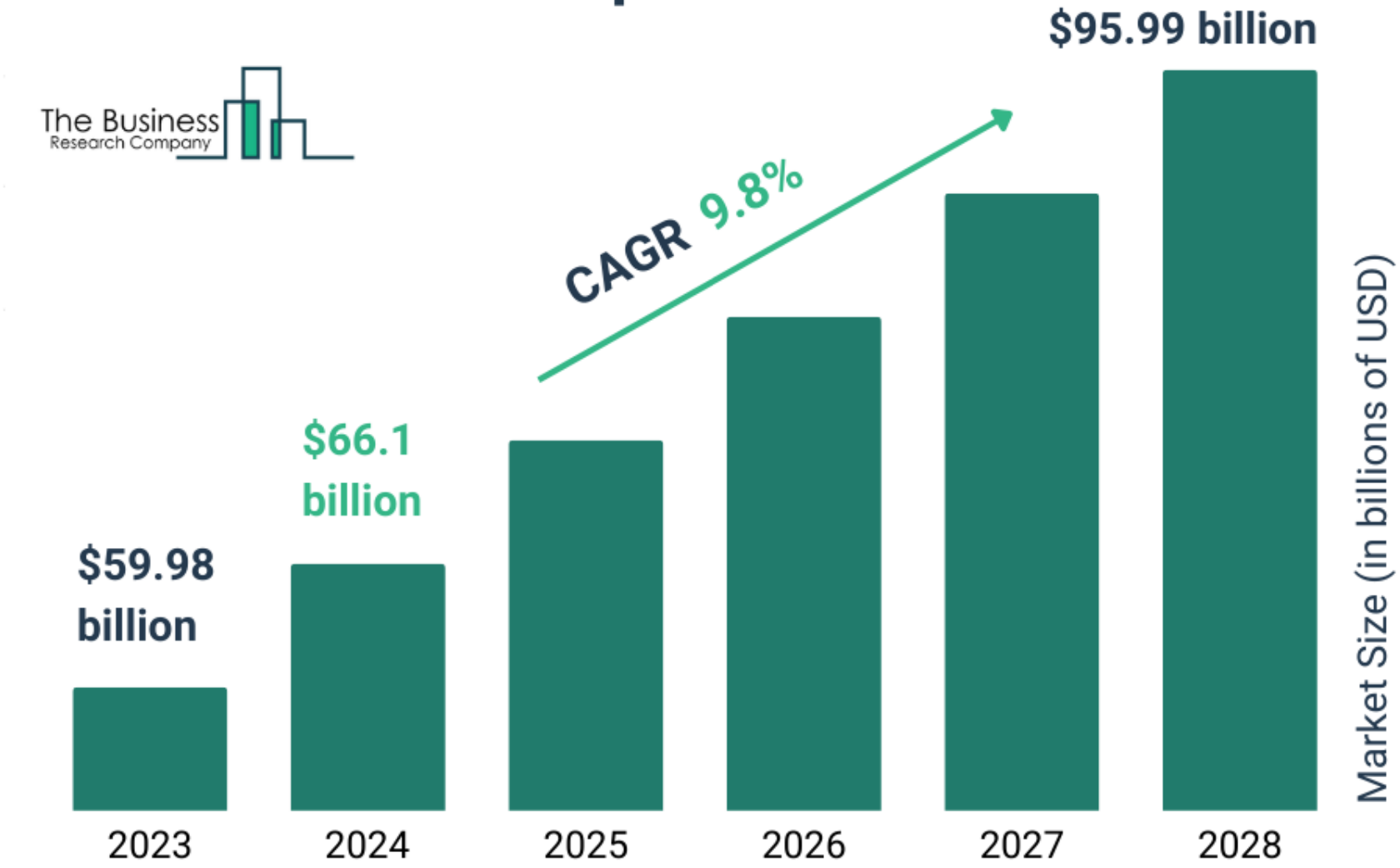
Escape

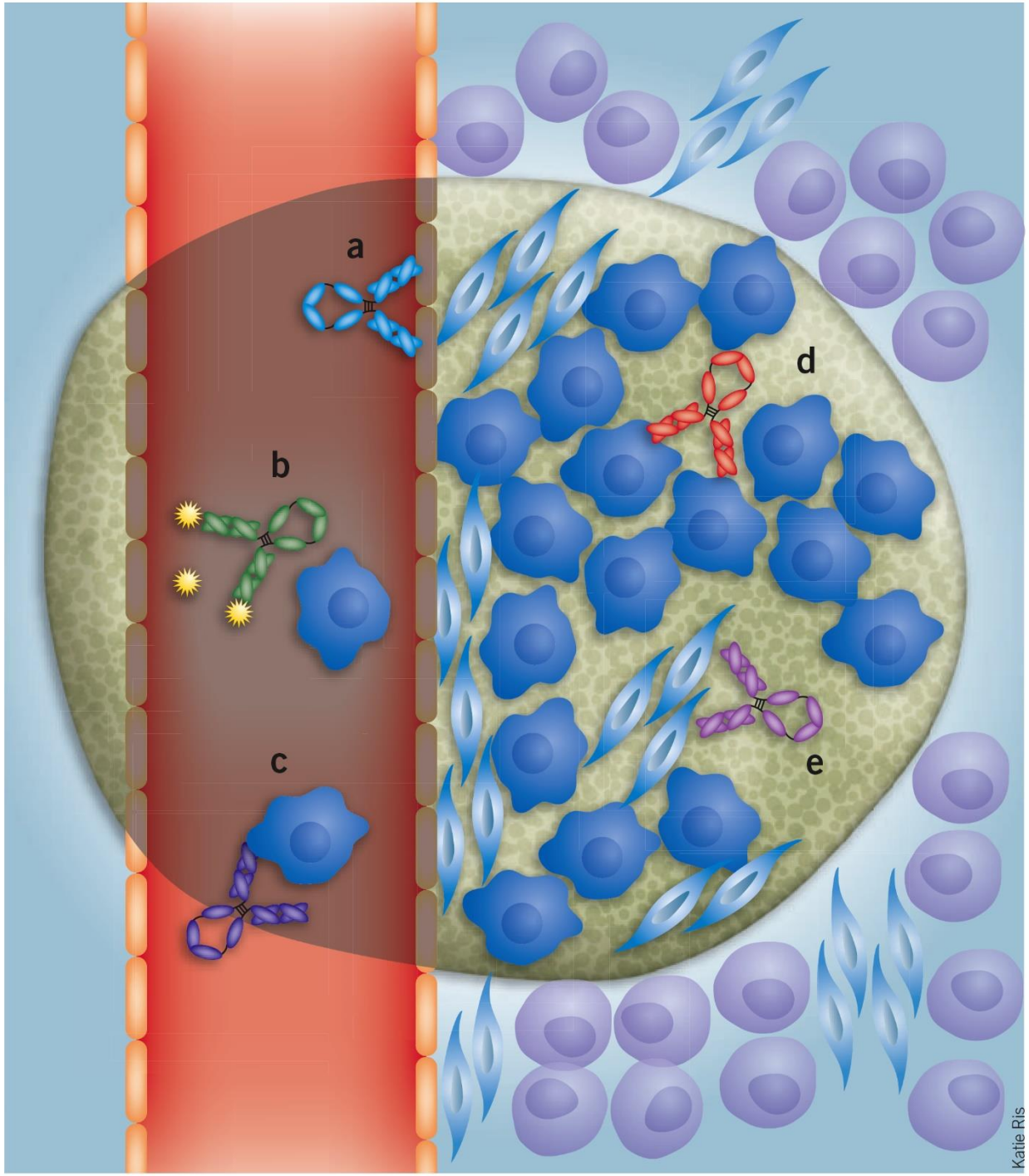
Neutralizzazione dei meccanismi di inibizione e di soppressione

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

Togliere i freni

Cancer Monoclonal Antibodies Global Market Report 2024





Potential targets for antibody therapy of cancer

a) Tumor-associated blood vessel

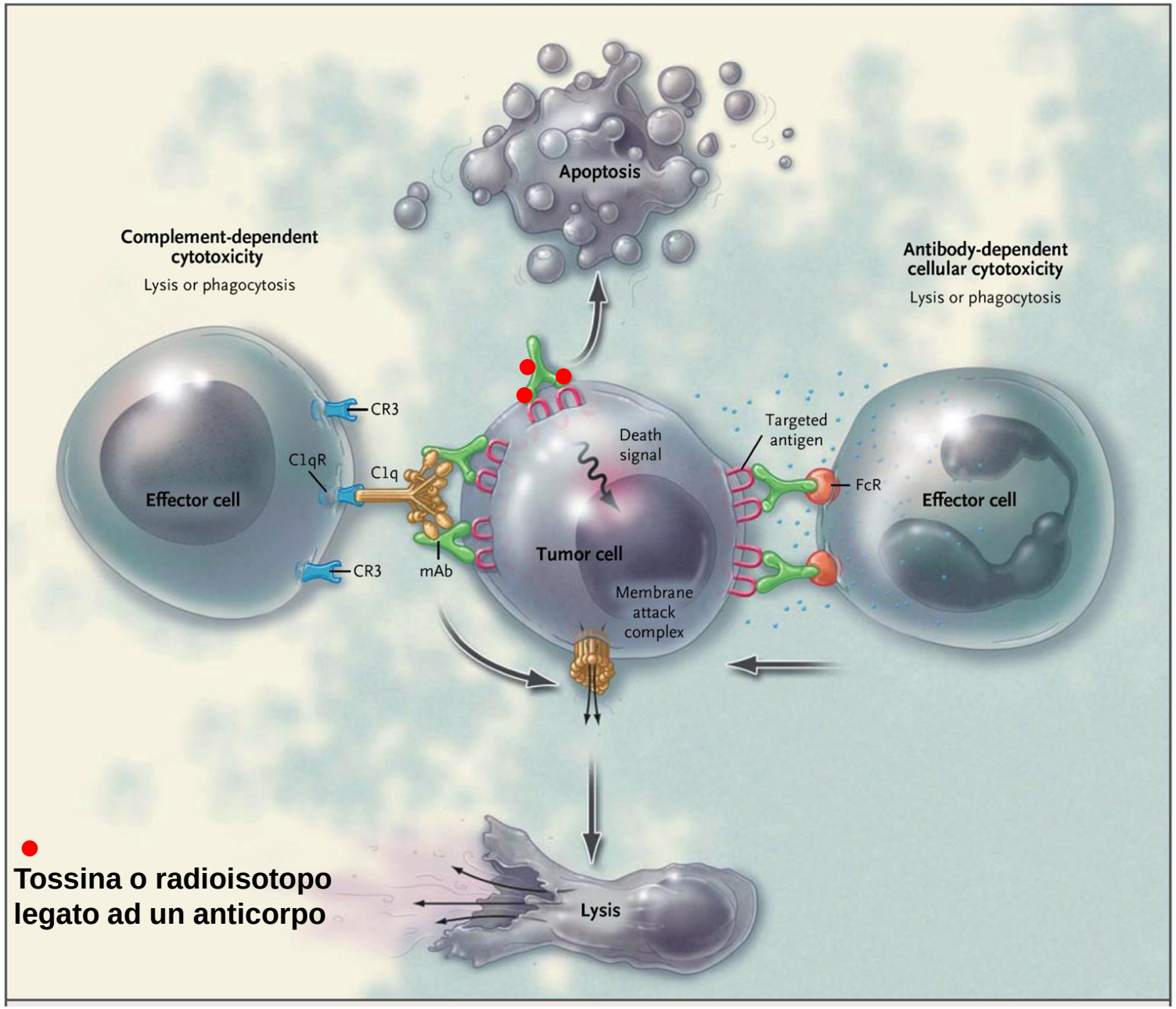
b) Vascular growth factors (i.e. VEGF)

c) Diffuse malignant cells

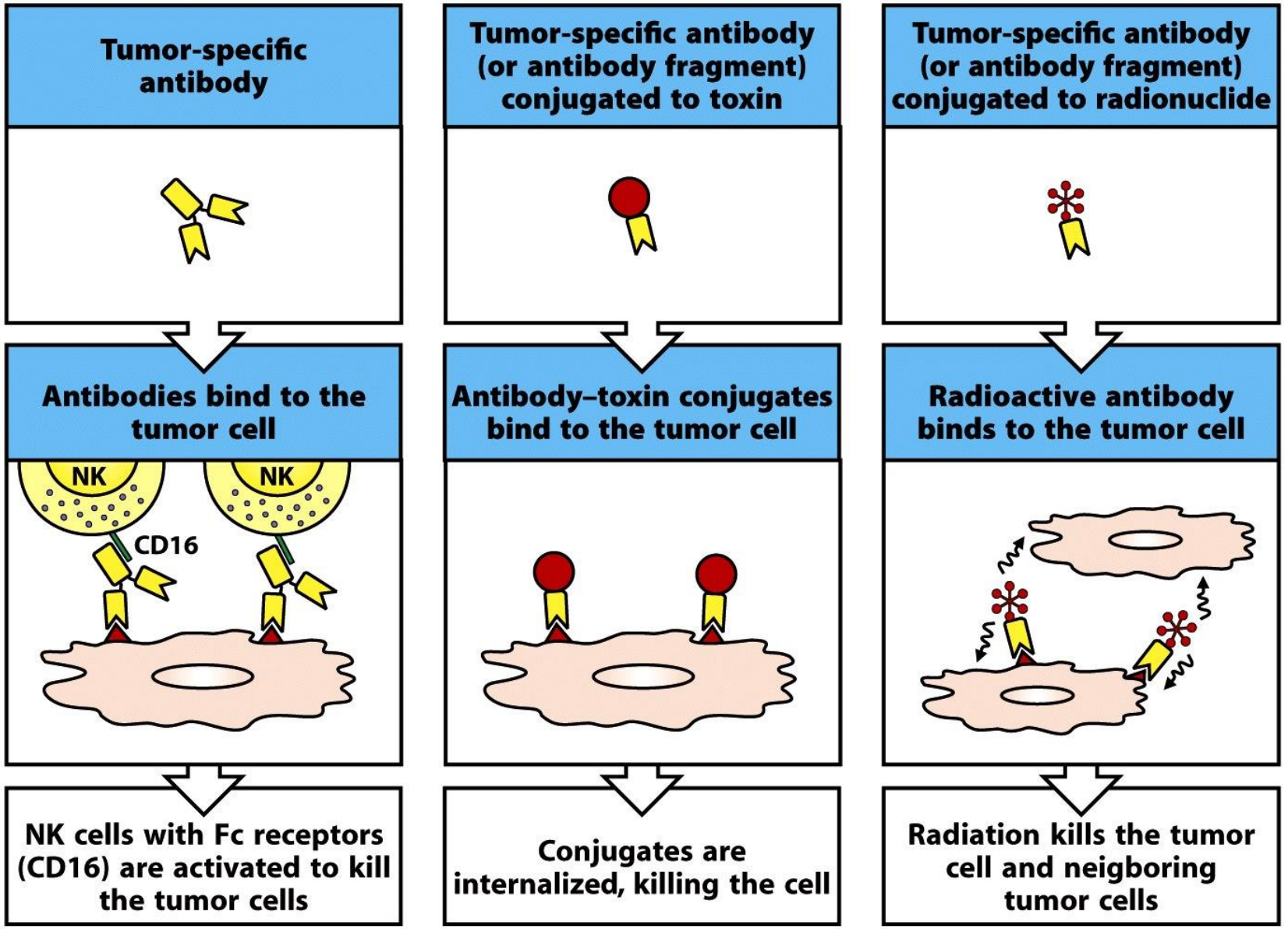
d) Tumor cells in a solid tumor

e) Tumor-associated stroma

Immunoterapia mediata dagli anticorpi monoclonali: meccanismi d'azione



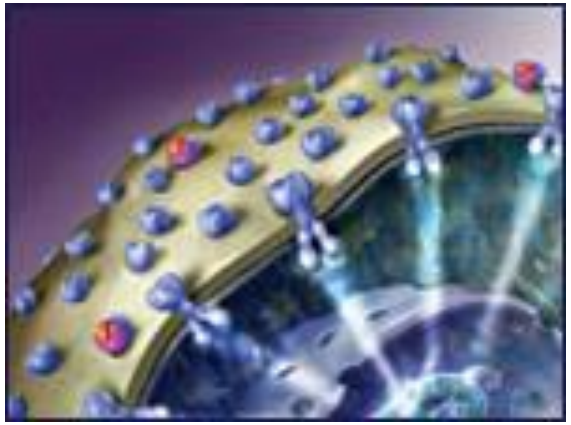
Monoclonal antibody (mAb)-mediated immunotherapy



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

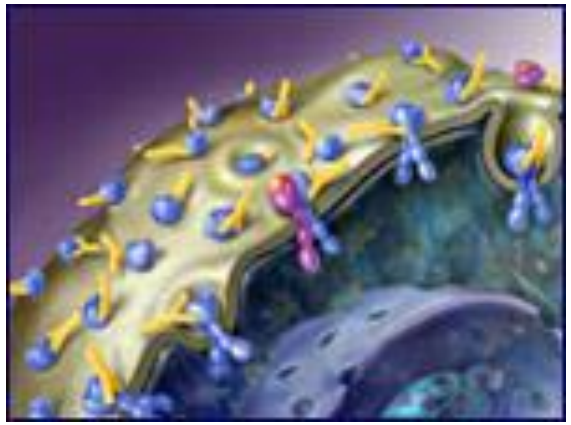
Target	*Drug*	*Clinical use*
Epidermal growth factor receptor	Necitumumab	Squamous non-small-cell lung cancer
	Cetuximab	Colorectal, head and neck cancer
	Panitumumab	Colorectal cancer
	Nimotuzumab	Squamous cell carcinoma, glioma
VEGF	Bevacizumab	Anti-angiogenic therapy
CD19-dircted CD3 T cell engager	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

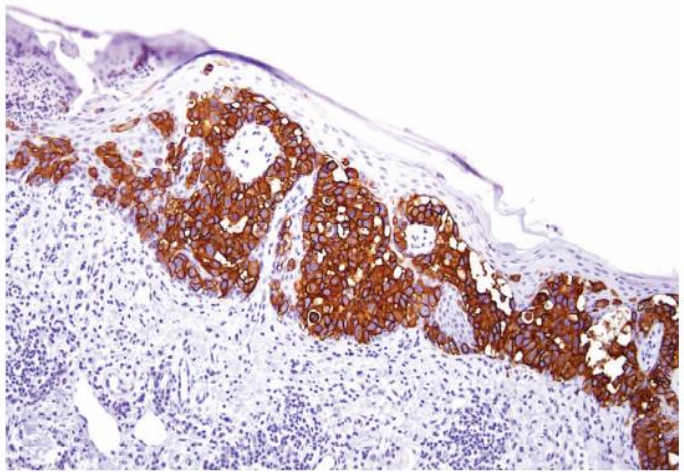
DALLA MOLECOLA ALLA CLINICA: Her2/Neu

- **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.**

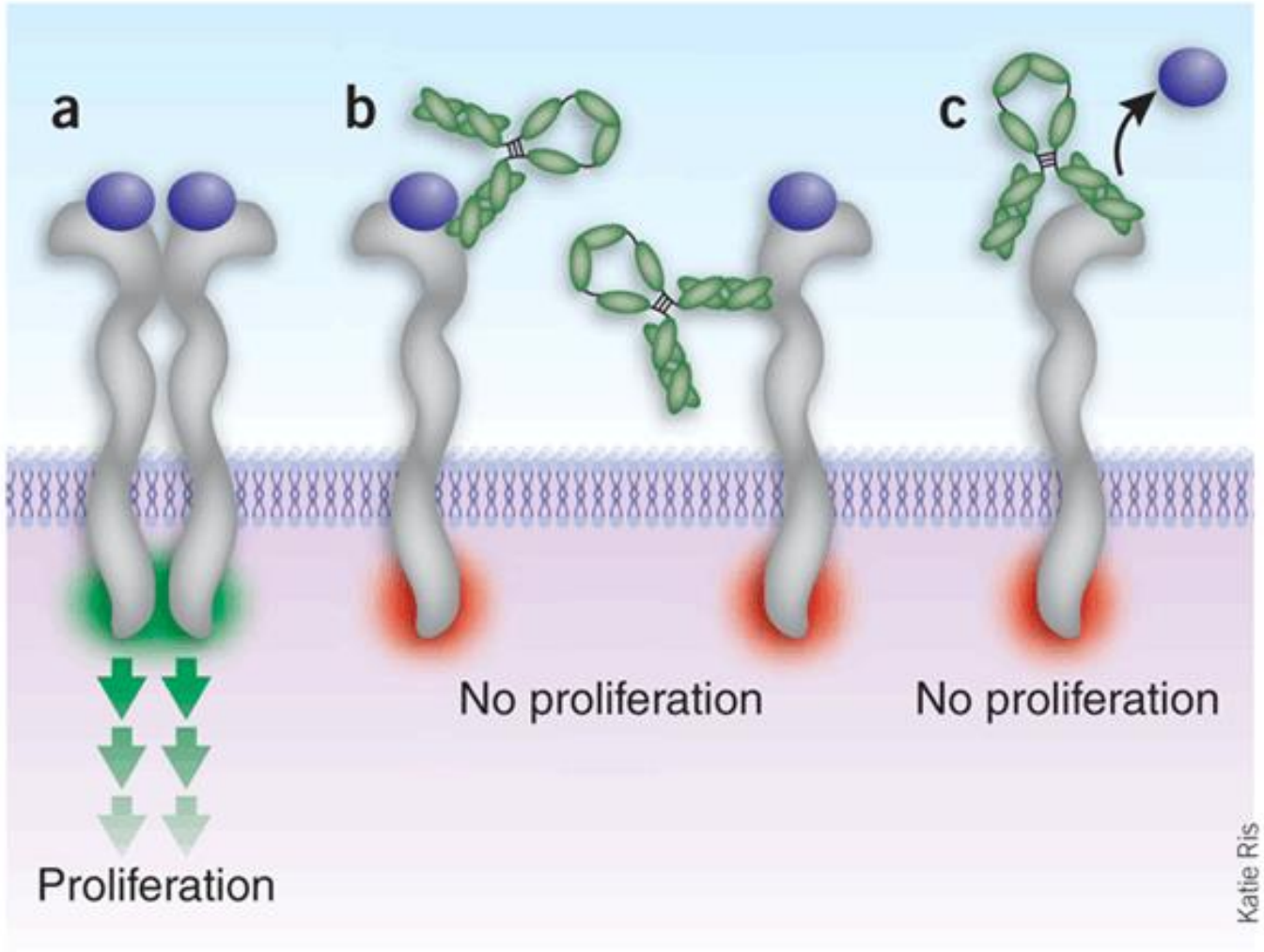
- **Inibizione di Her2 per trattare il carcinoma della mammella:**

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)



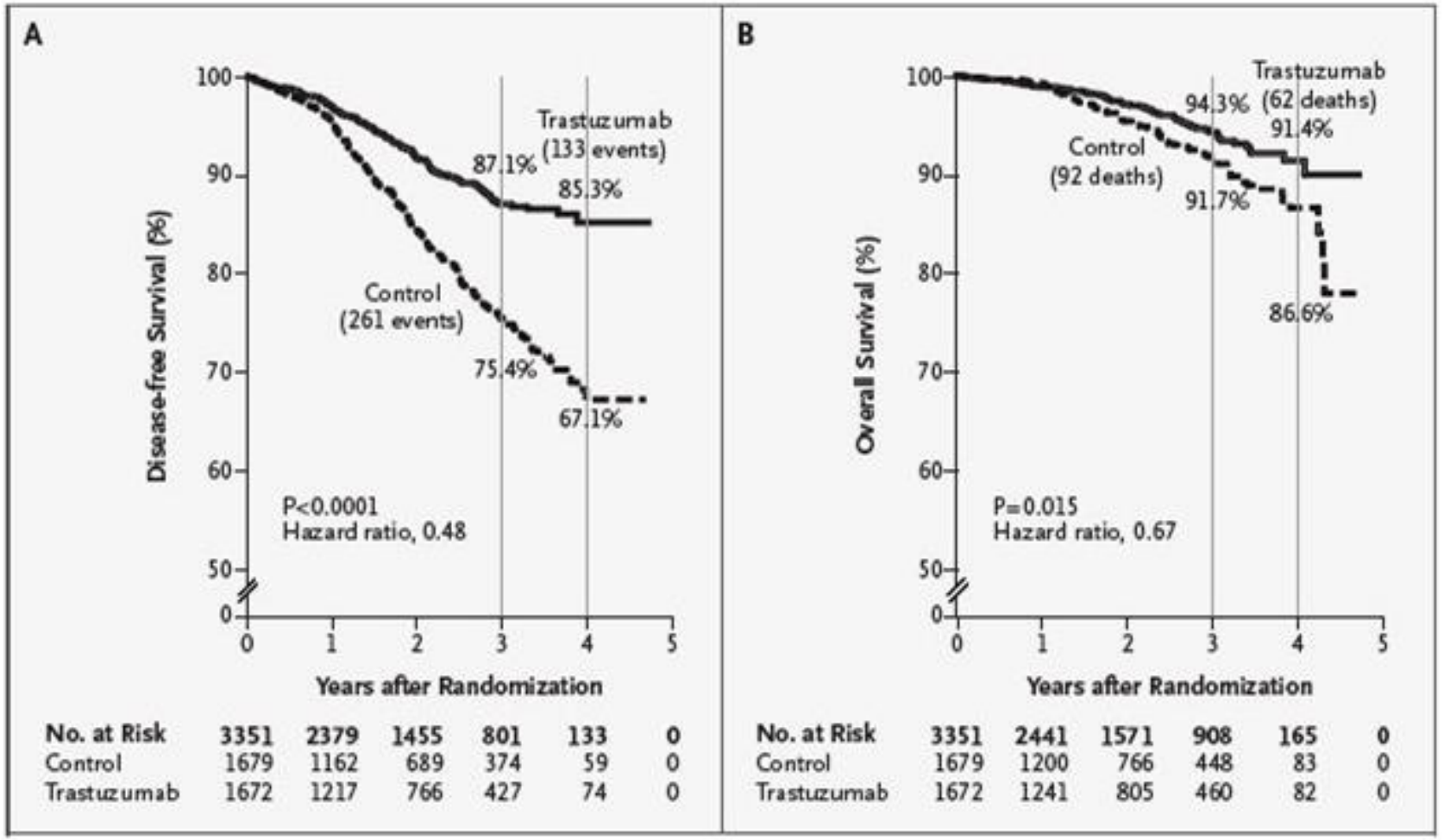
HER-2–positive invasive ductal carcinoma

Examples of antibody-mediated signaling inhibition



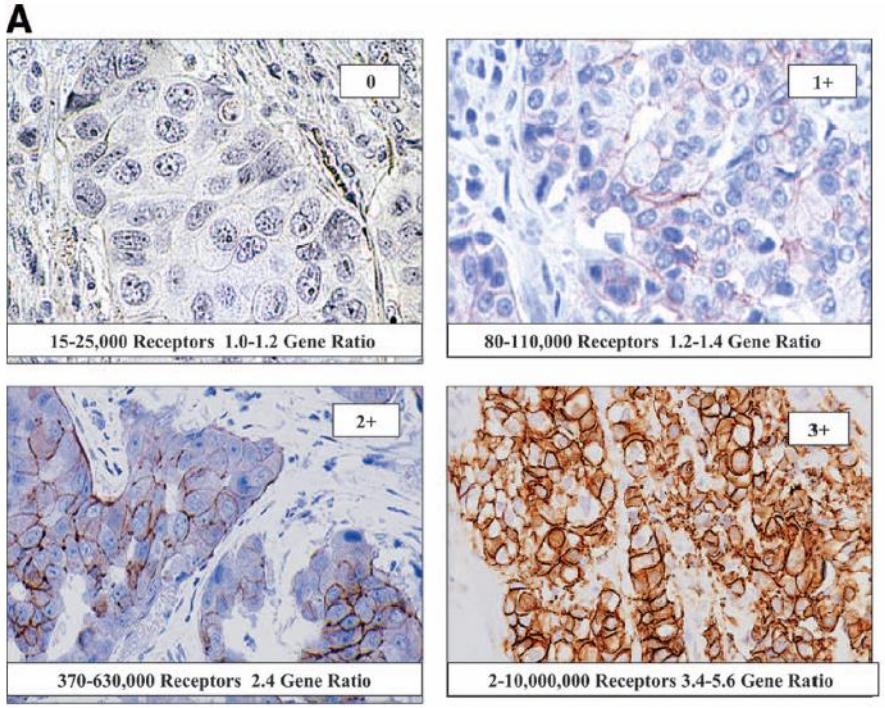
Adams & Weiner Nature Biotechnology 2005

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



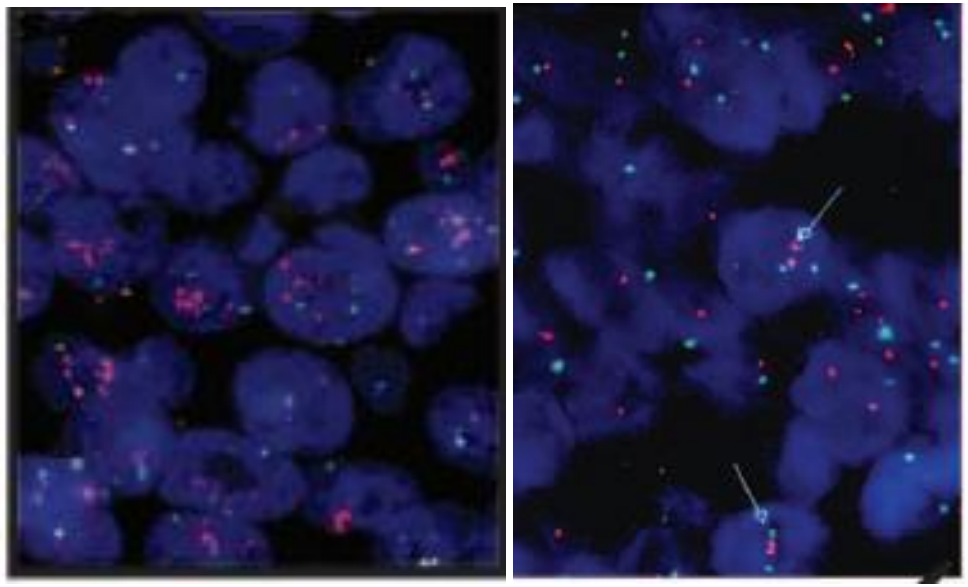
Score (USA):
0-1+: negative
2+: equivocal
3+: positive

Trastuzumab is not good for everyone…

Gene copy number:

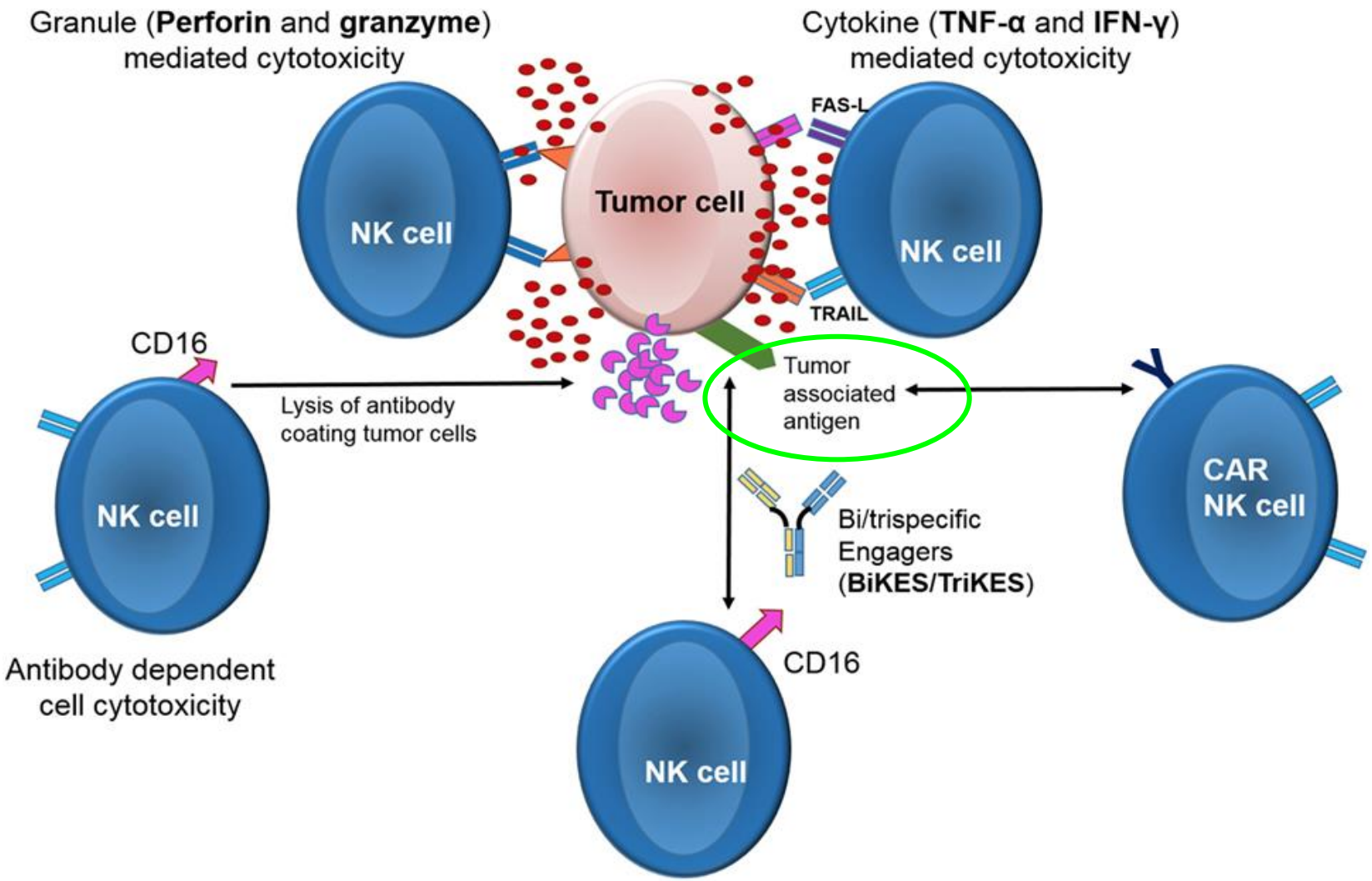
=4 (amplified)

=1.9 (not amplified)



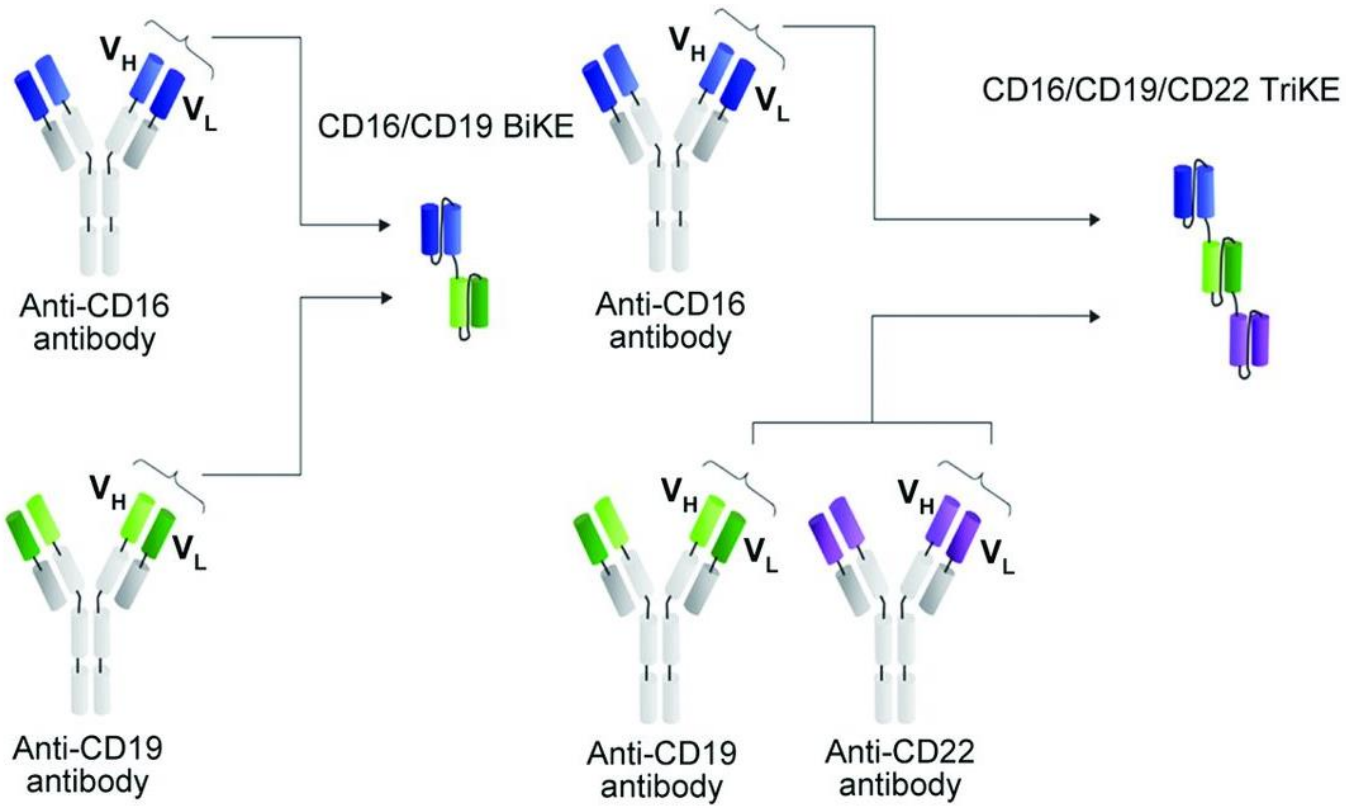
Pink: Her2 gene
Green: centromere (chr 17)

STRATEGIES TO ENHANCE ADCC FOR Ab-BASED NK CELL THERAPIES



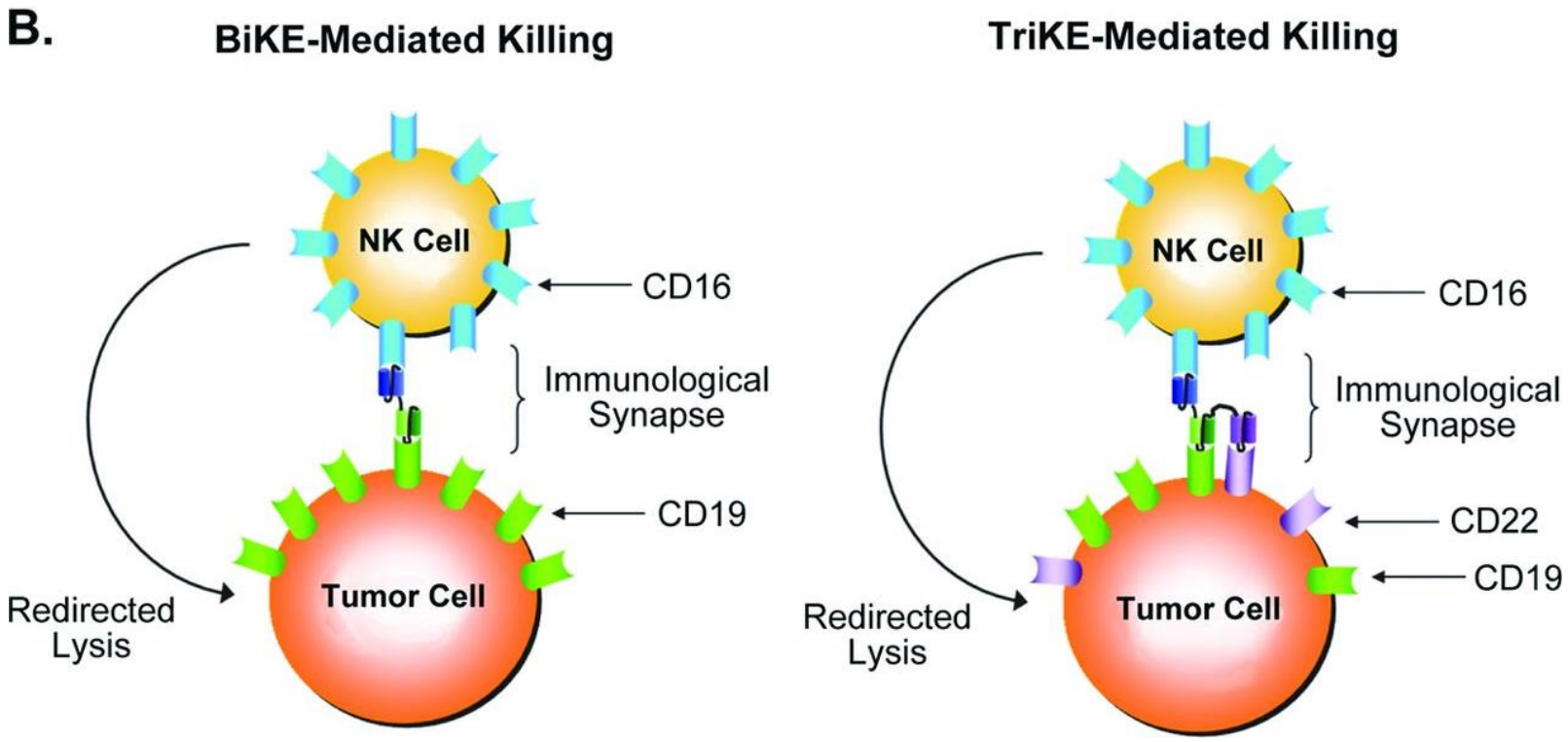
Mehta R.S. et al., Front Immunol 2018

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



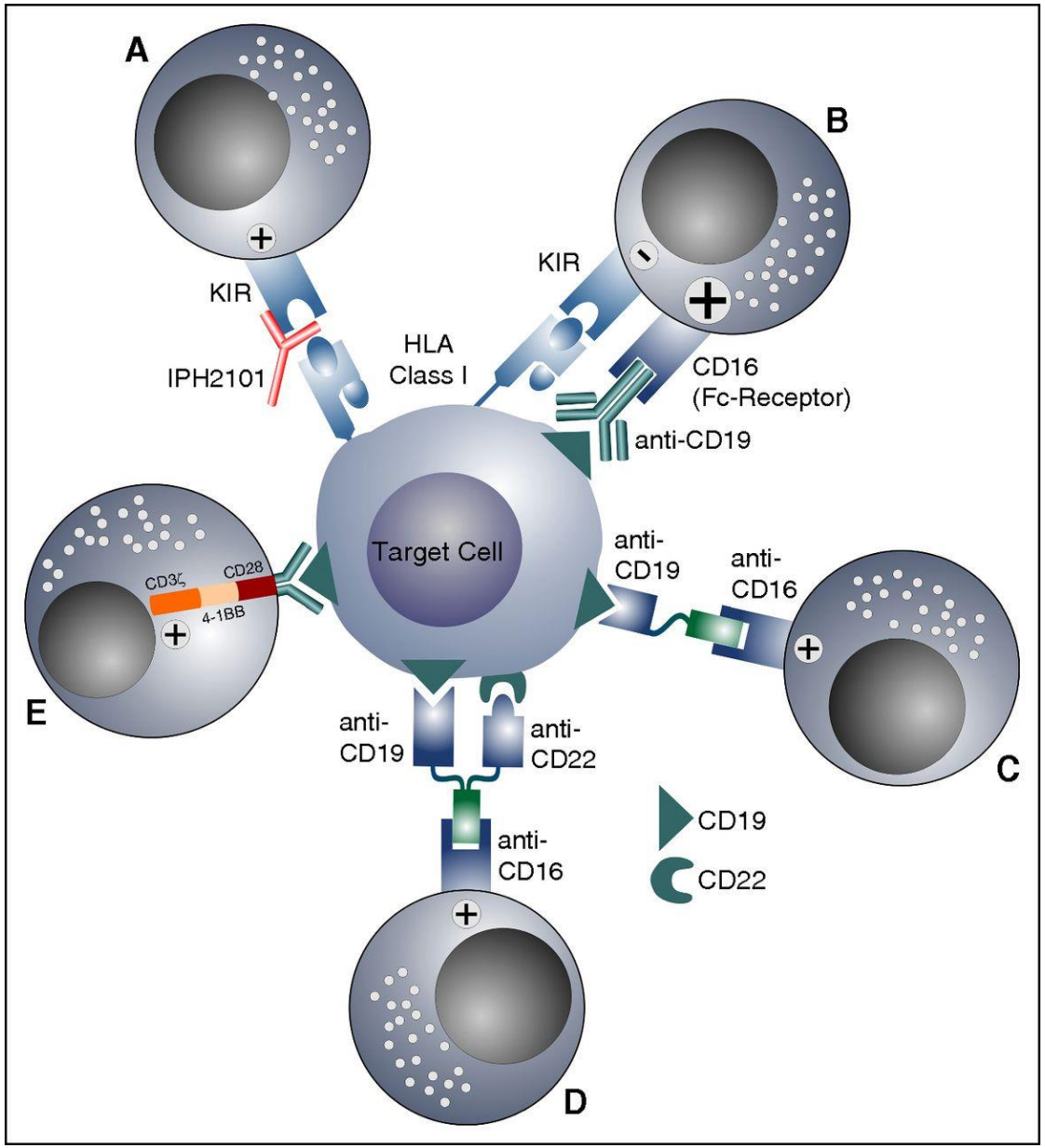
Jeffrey S. Miller Hematology 2013

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



Jeffrey S. Miller Hematology 2013

Tumor-targeted antibody strategies to enhance NK cell activity



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

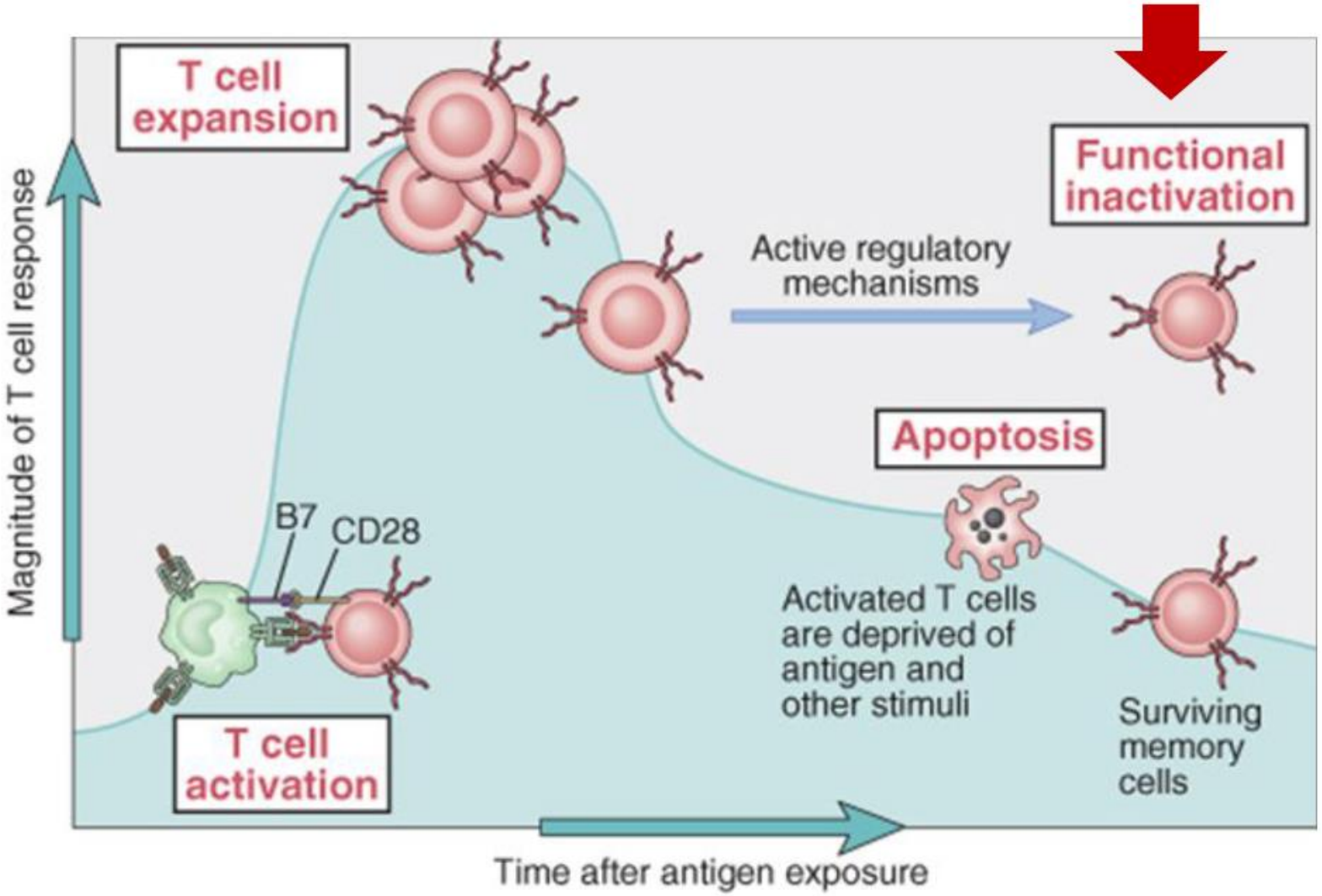
Escape

Neutralizzazione dei meccanismi di inibizione e di soppressione

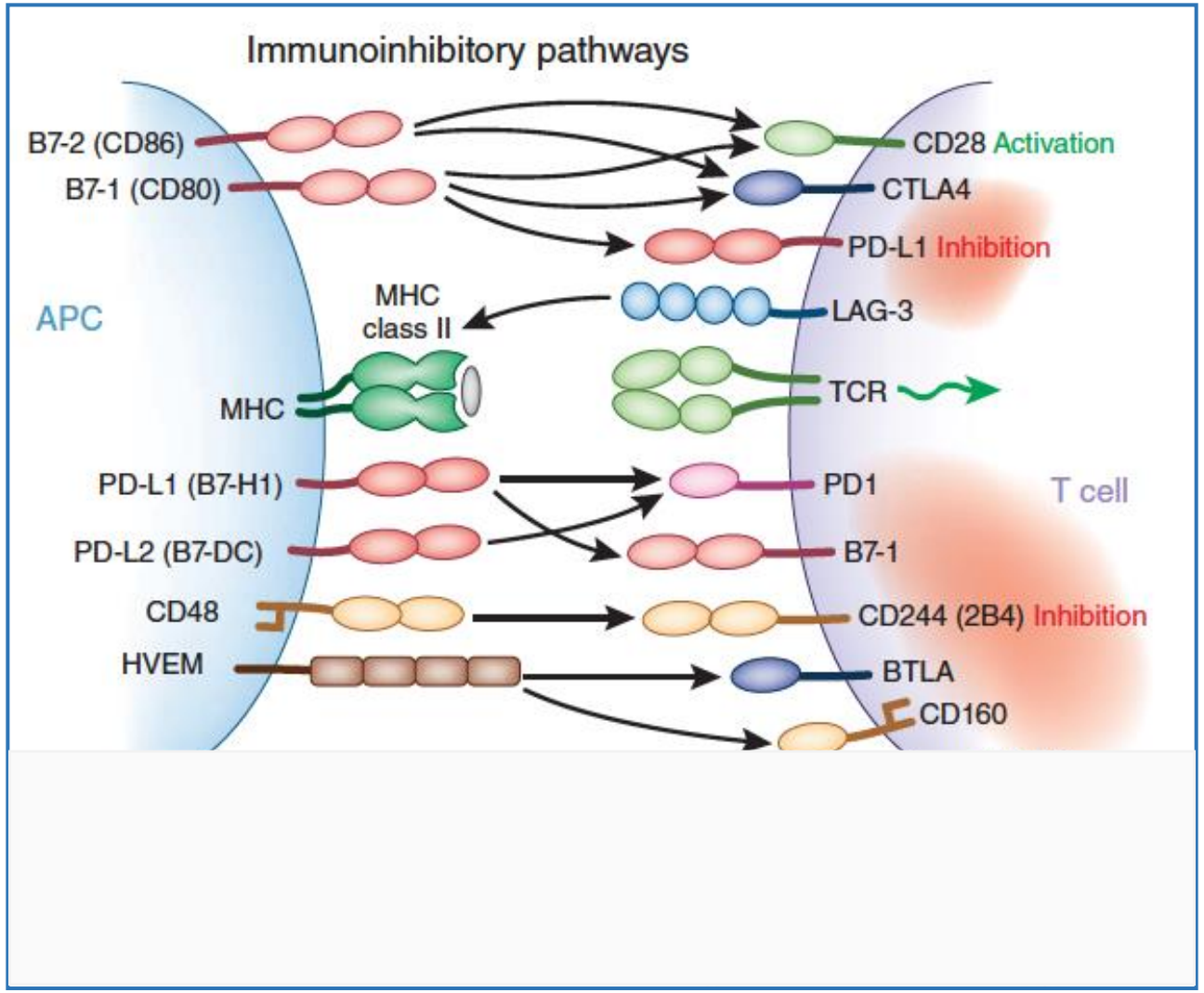
- Anticorpi monoclonali contro molecole inibitorie (anti-CTLA-4, anti-PD-1)
- Chemioterapia (es. ciclofosfamide)
- mAbs anti-CD25 (Treg)

Togliere i freni

Lo spegnimento della risposta immunitaria



Exhausted T cells can express multiple inhibitory receptors

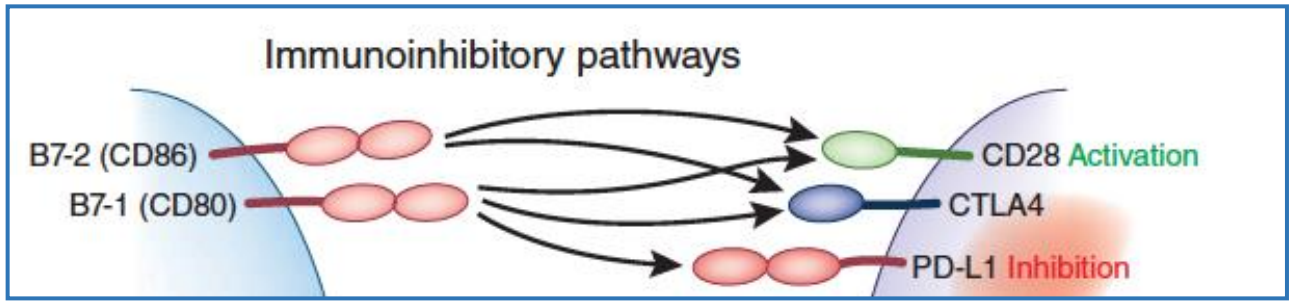


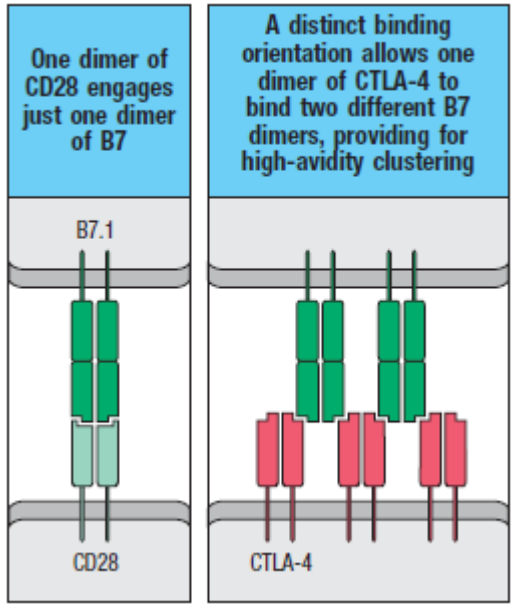
Freeman GJ & Sharpe AH Nature Immunol 2012

CTLA-4 has higher affinity than CD28 for B7 and engages it in a multivalent orientation

CTLA-4 is induced on activated T cells and binds to the same ligands (B7.1/B7.2, CD80/CD86) as CD28, the most important costimulatory molecule of T cells.

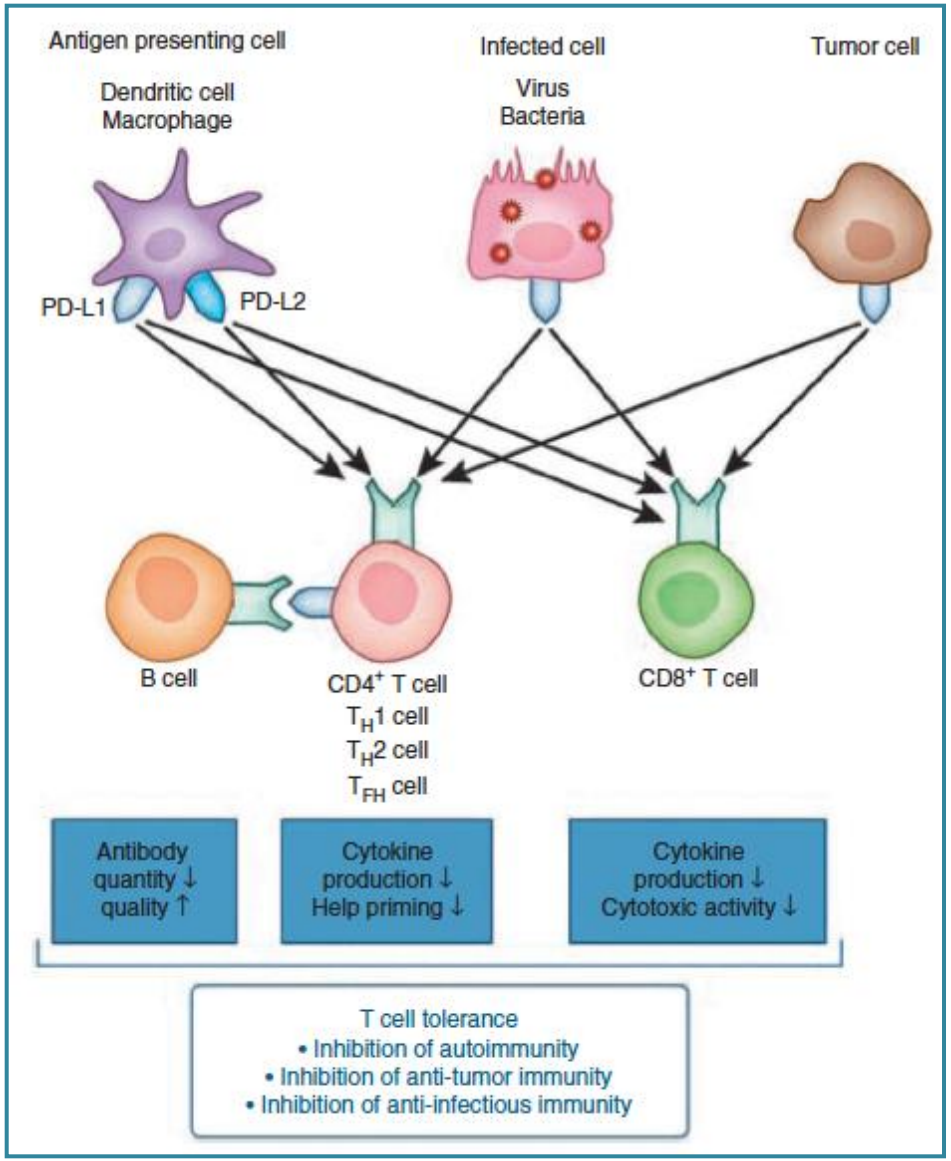
However, CTLA-4 engagement is inhibitory for T-cell activation, rather than activatory.





CTLA-4 has a higher affinity for its B7 ligands than does CD28, and, apparently of importance for its inhibitory function, it aggregates multiple B7 molecules

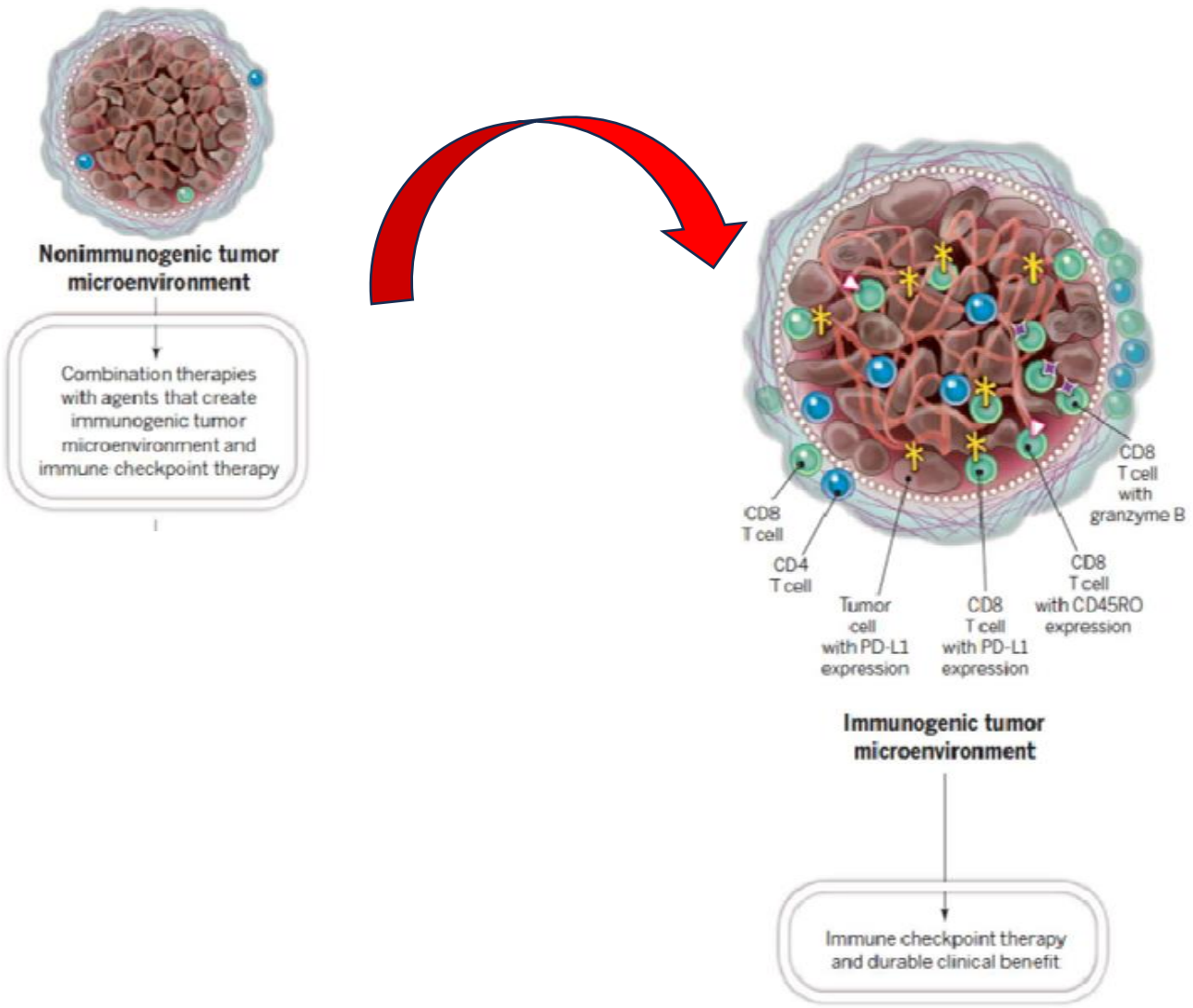
Biological importance of PD-1 immunoinhibition



Okazaki T et al Nature Immunol 2013

Releasing the brakes against cancer

Trasformare un tumore “freddo” in uno “caldo”



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.

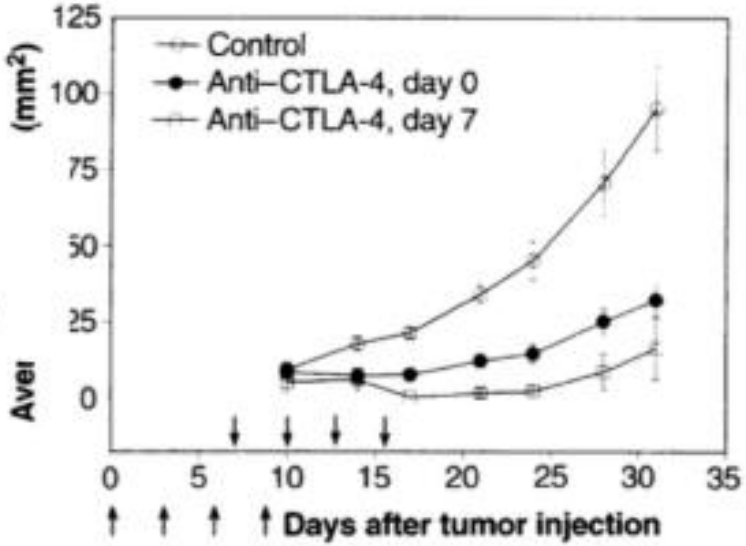
Prof. Allison discovered another important immunosuppressive molecule: cytotoxic T-lymphocyte antigen-4 (CTLA-4)

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



tegies 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

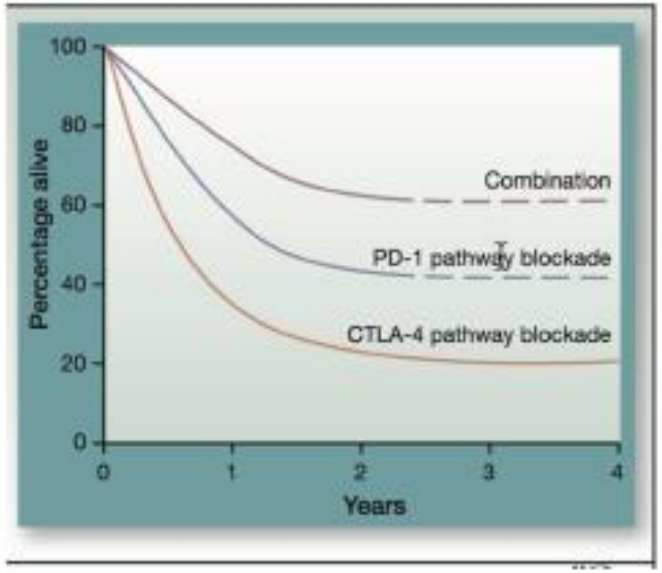
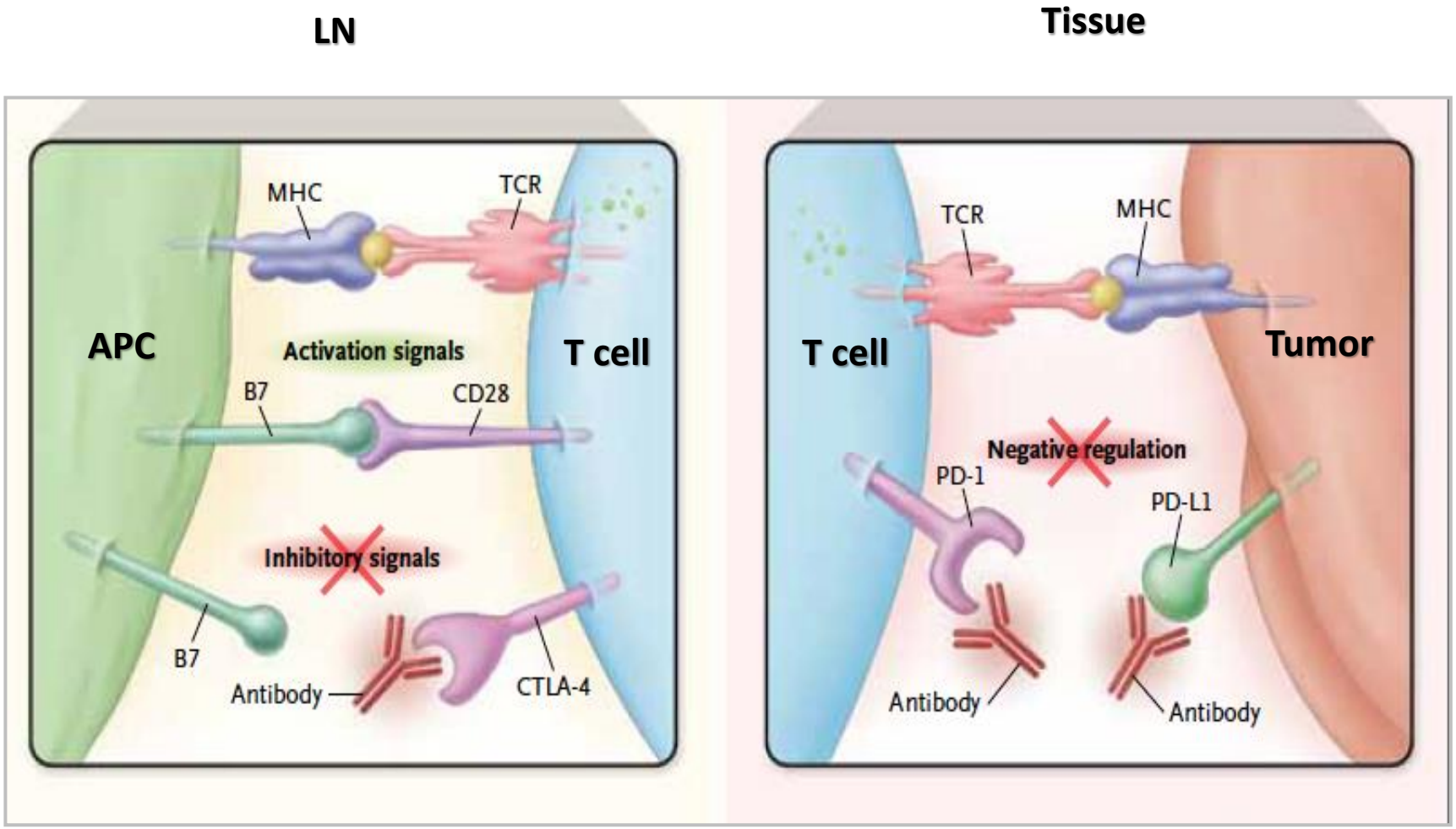


Table 2 | **Antibodies targeting molcules expressed by immune cells**

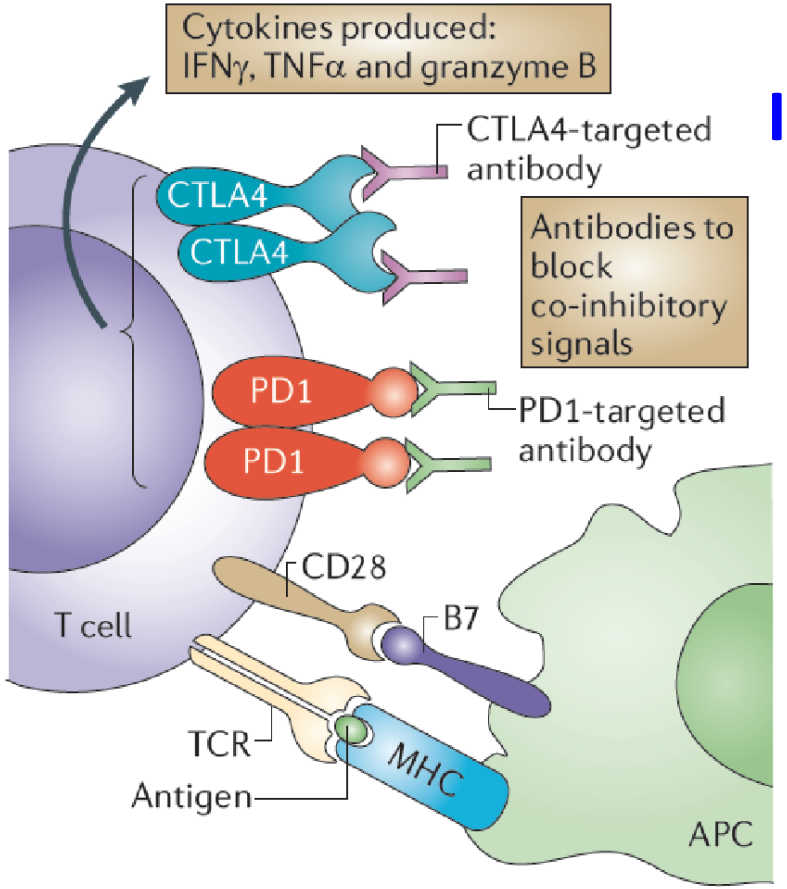
Target	Generic antibody name (trade name; sponsoring companies)	Target expression	Target function	Agonist or antagonist	Effect of antibody treatment in preclinical studies
CD40	Dacetuzumab (SGN-40; Seattle Genetics) and CP-870893 (Pfizer)	DCs, B cells, monocytes and macrophages	Promotes DC maturation, germinal center formation, Ig-isotype switching and affinity maturation	Agonist	Apoptosis in some tumours and increased number of tumour-specific $CD8^+$ T cells[33]
CTLA4	Tremelimumab (CP-675,206; Pfizer) and ipilimumab (MDX-010; Bristol-Myers Squibb/Medarex)	Activated T cells	Inhibition of T cell proliferation	Antagonist	Tumour rejection, protection from rechallenge[36]; enhanced tumour-specific T cell responses[37]
OX40	OX86	Activated mouse T cells	T cell proliferation and maintenance of memory T cells	Agonist	Increase in antigen-specific $CD8^+$ T cells at the tumour site; fewer MDSCs and T_{Reg} cells and decreased levels of TGFβ; enhanced tumour rejection[114]
PD1	CT-011 (Cure Tech)	Activated lymphocytes	Negative regulator of lymphocyte proliferation and cytokine production	Antagonist	Maintenance and expansion of tumour specific memory T cells populations and NK cell activation[115]
CD137	BMS-663513 (Bristol-Myers Squibb)[116]	Activated T cells, T_{Reg} cells, NK cells, NKT cells, DCs, neutrophils and monocytes[117]	Promotes expansion of T cell populations, $CD8^+$ T cell survival, NK cells proliferation and IFNγ production	Agonist	Regression of established tumours, expansion and maintenance of $CD8^+$ T cells[117]
CD25	Daclizumab (Zenapax; Roche)	Activated T cells	IL-2Rα chain. Promotes T cell proliferation; highly expressed by T_{Reg} cells	Antagonist	Transient depletion of $CD4^+CD25^+FOXP3^+$ T_{Reg} cells[48]; enhanced tumour regression and increased number of effector T cells[118]

Blockade of PD-1 or CTLA-4 signaling in tumor immunotherapy



Ribas A N Engl J Med 2012

Togliere i freni….

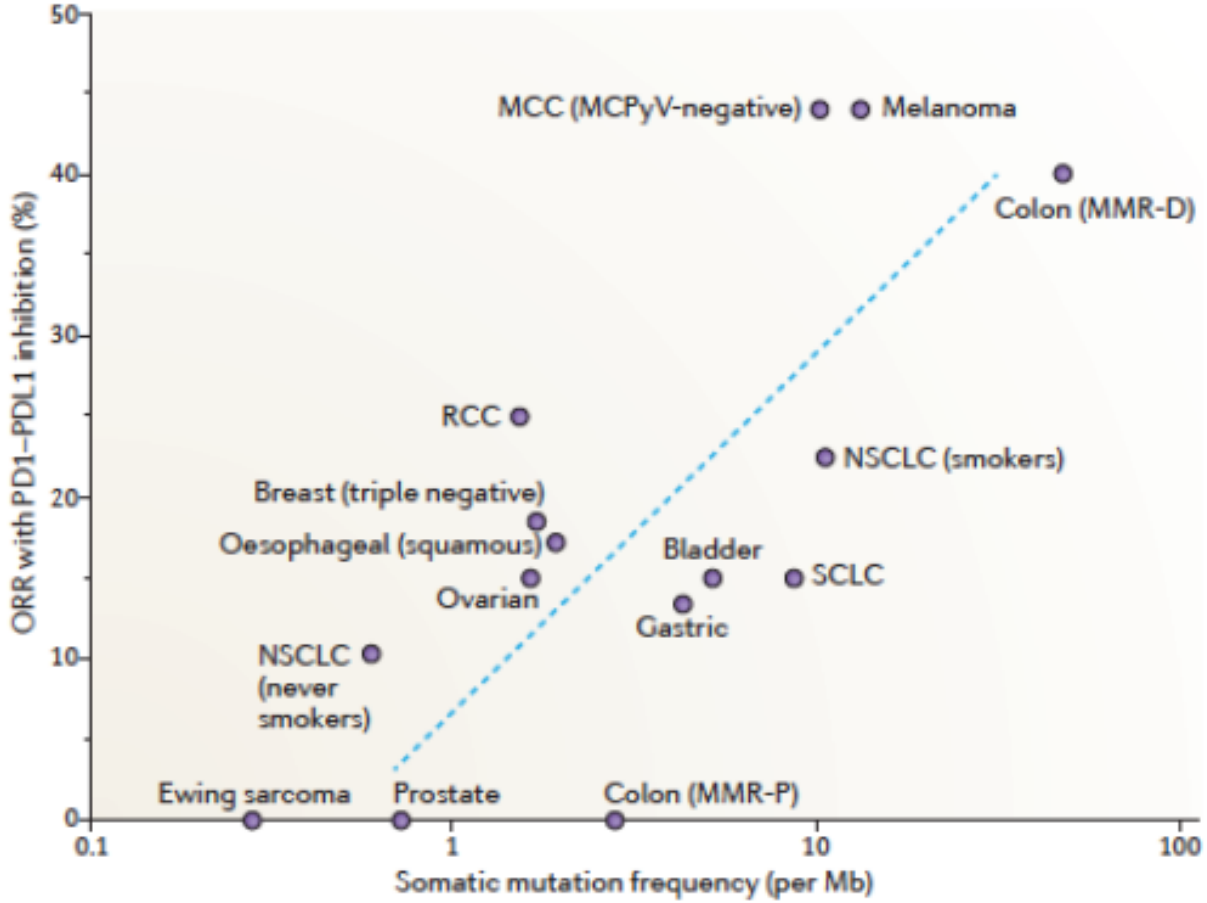


Ipilimumab (anti-CTLA-4)

Nivolumab (anti-PD1)

Metastatic melanoma
FDA 2011 Ipilimumab
FDA 2014 Nivolumab

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

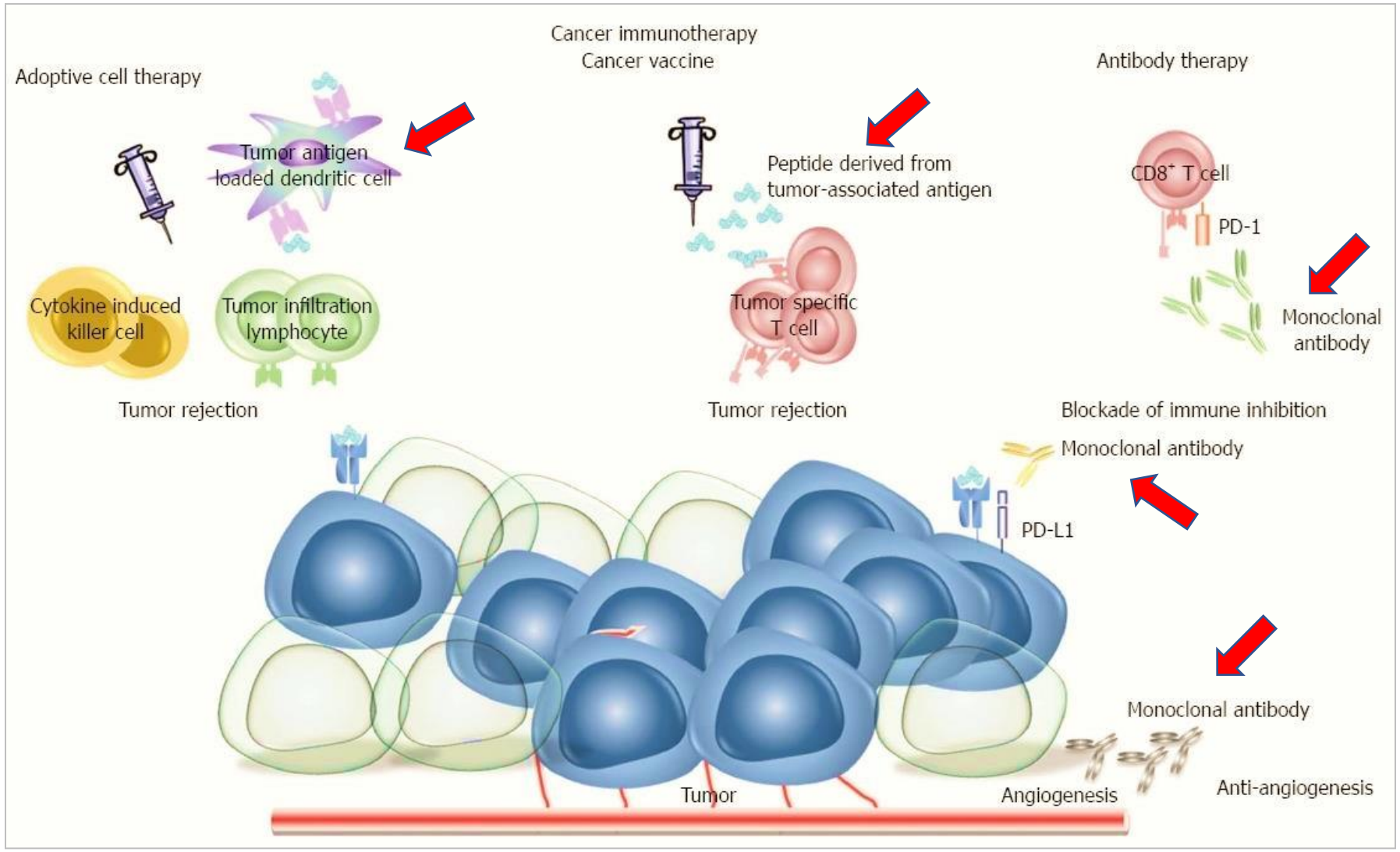


Despite these encouraging results, **efficacy of ICIs is not consistent across indications**, and the percentage of responders is far from optimal. Several mechanisms could be at play underlying these differential clinical activities.

Efficacy of ICIs requires a preexisting strong immune infiltrate and generation or rescue of an effective antitumor immune response. Of note, this parallels the prognostic importance of the Immunoscore.

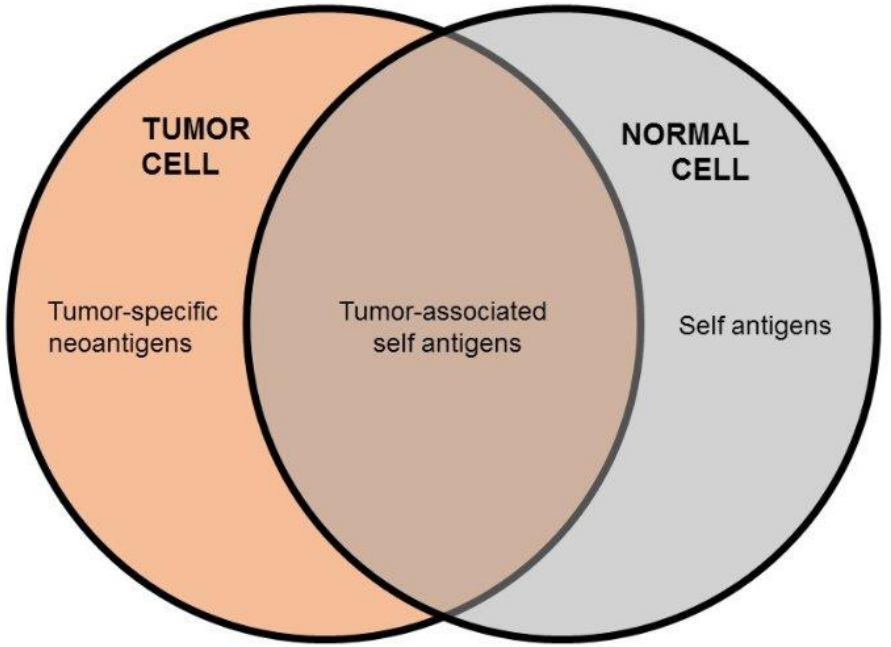
Premere sull'acceleratore e togliere i freni:

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

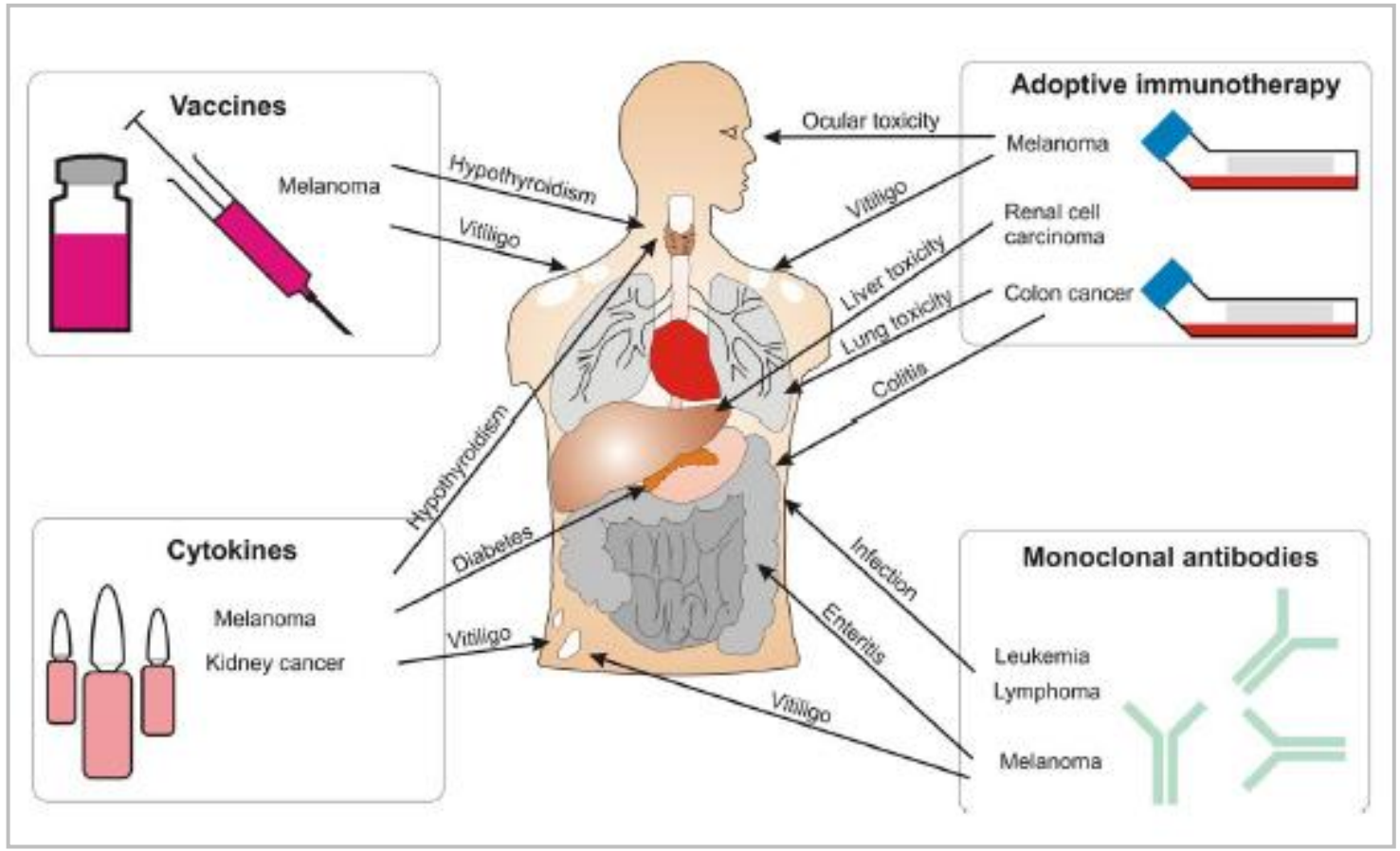


ATTENZIONE!

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

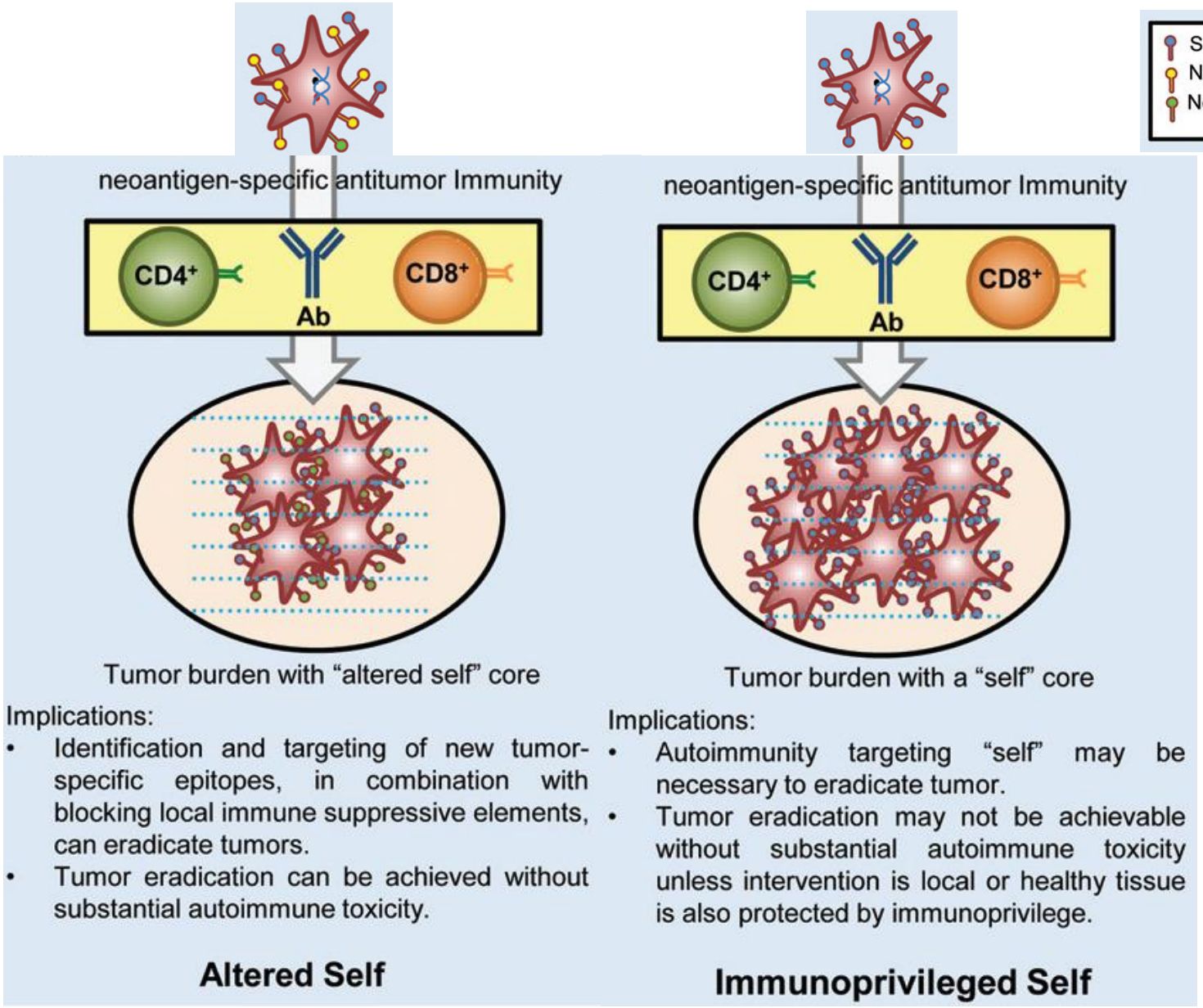


Immune toxicity associated with immunotherapy of cancer



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.

Quanto un tumore può essere considerato «self»?



I tumori attivano meccanismi di tolleranza molto più efficacemente dei tessuti normali, riflettendo uno stato «immunoprivilegiato».

Risposte autoimmuni potenti possono eradicare il tumore, ma l'effetto «collaterale» della distruzione dei tessuti sani si è rivelato difficile da aggirare.

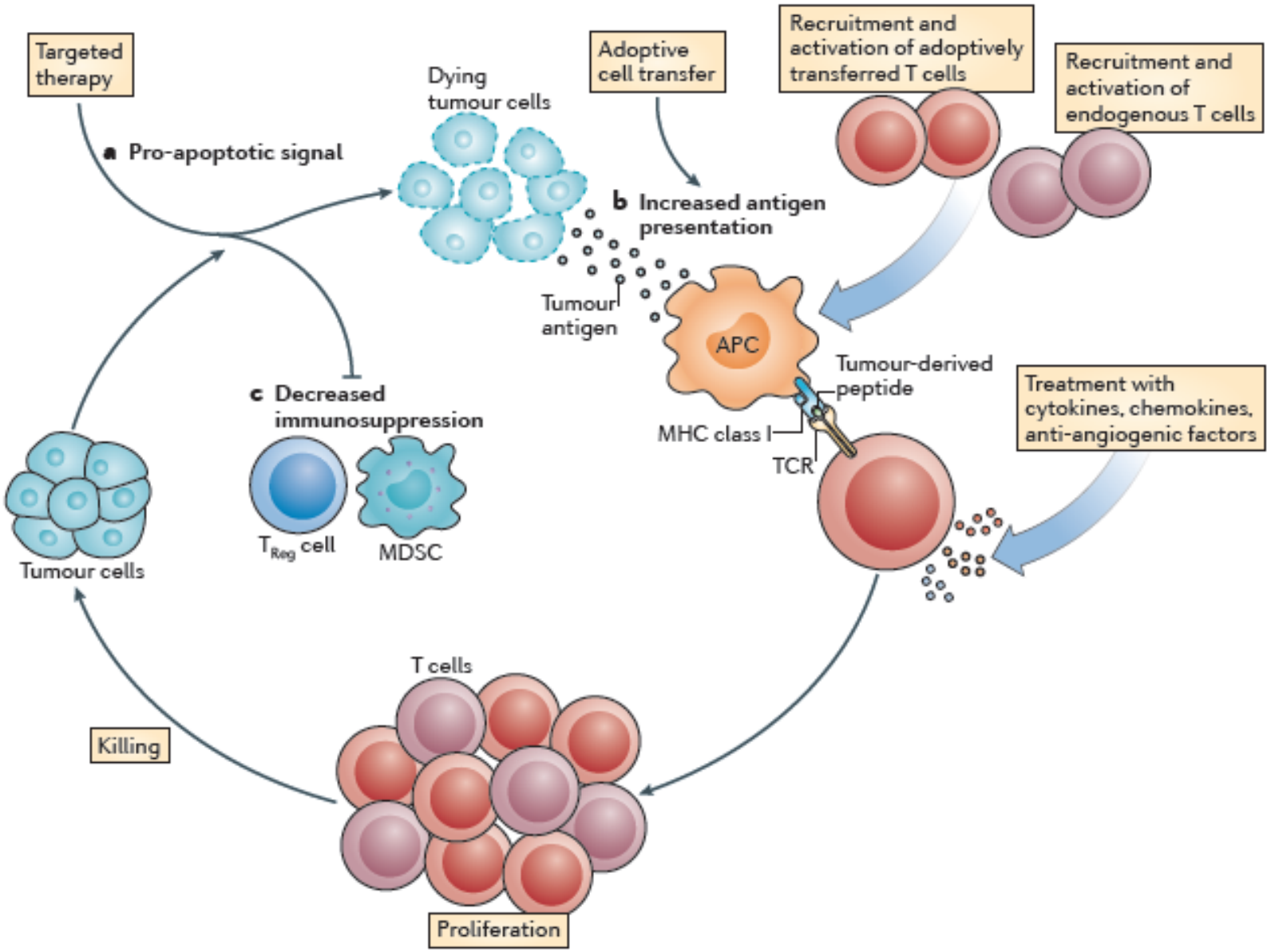
Miska J et al, Oncoimmunology 2013

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

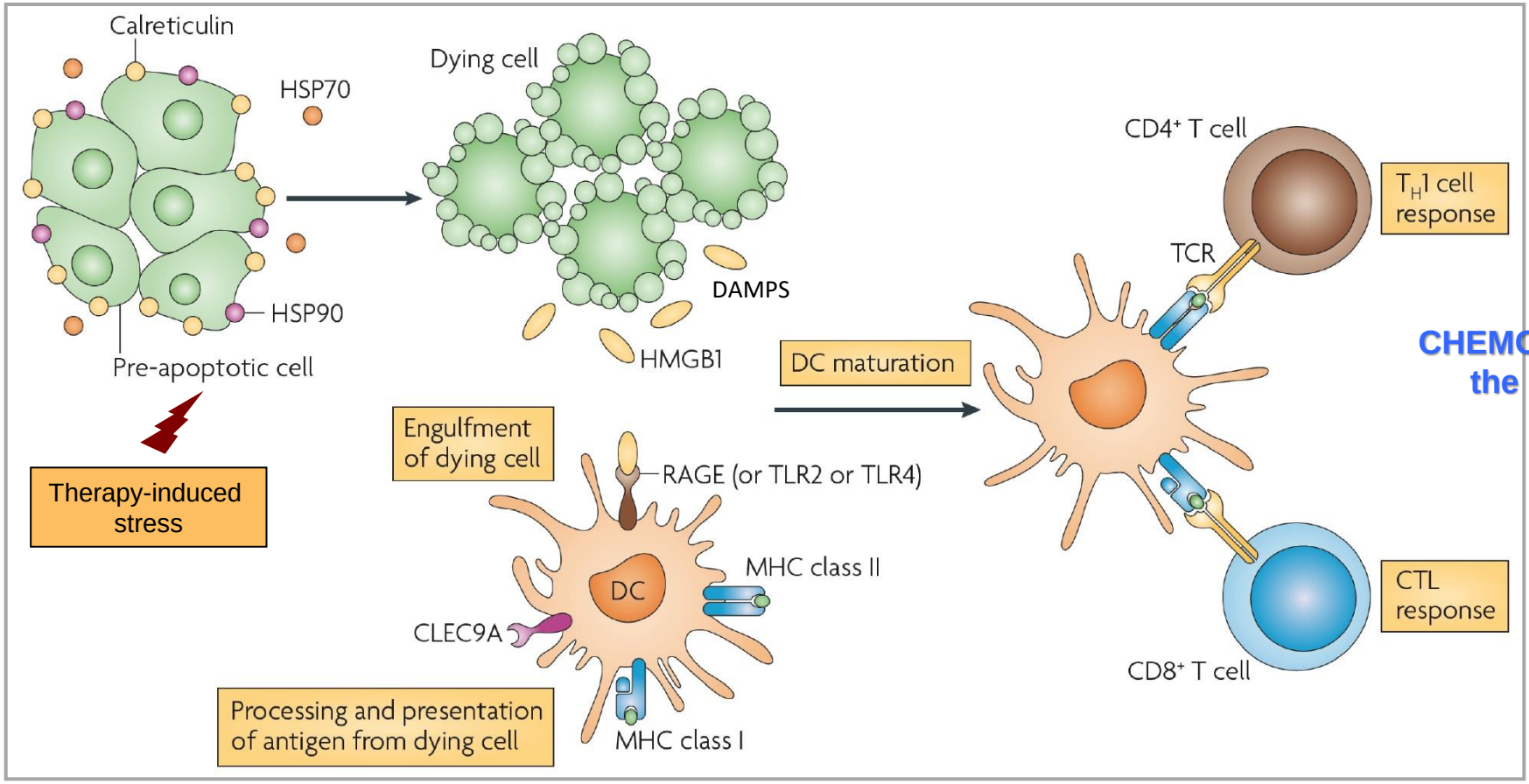
To avoid

Jumping from the frying pan into the fire

Combining targeted therapies with adoptive cell transfer-based immunotherapy



Radio/chemotherapy induces tumor immunogenic cell death



CHEMOIMMUNOTHERAPY: the NEW in the OLD!

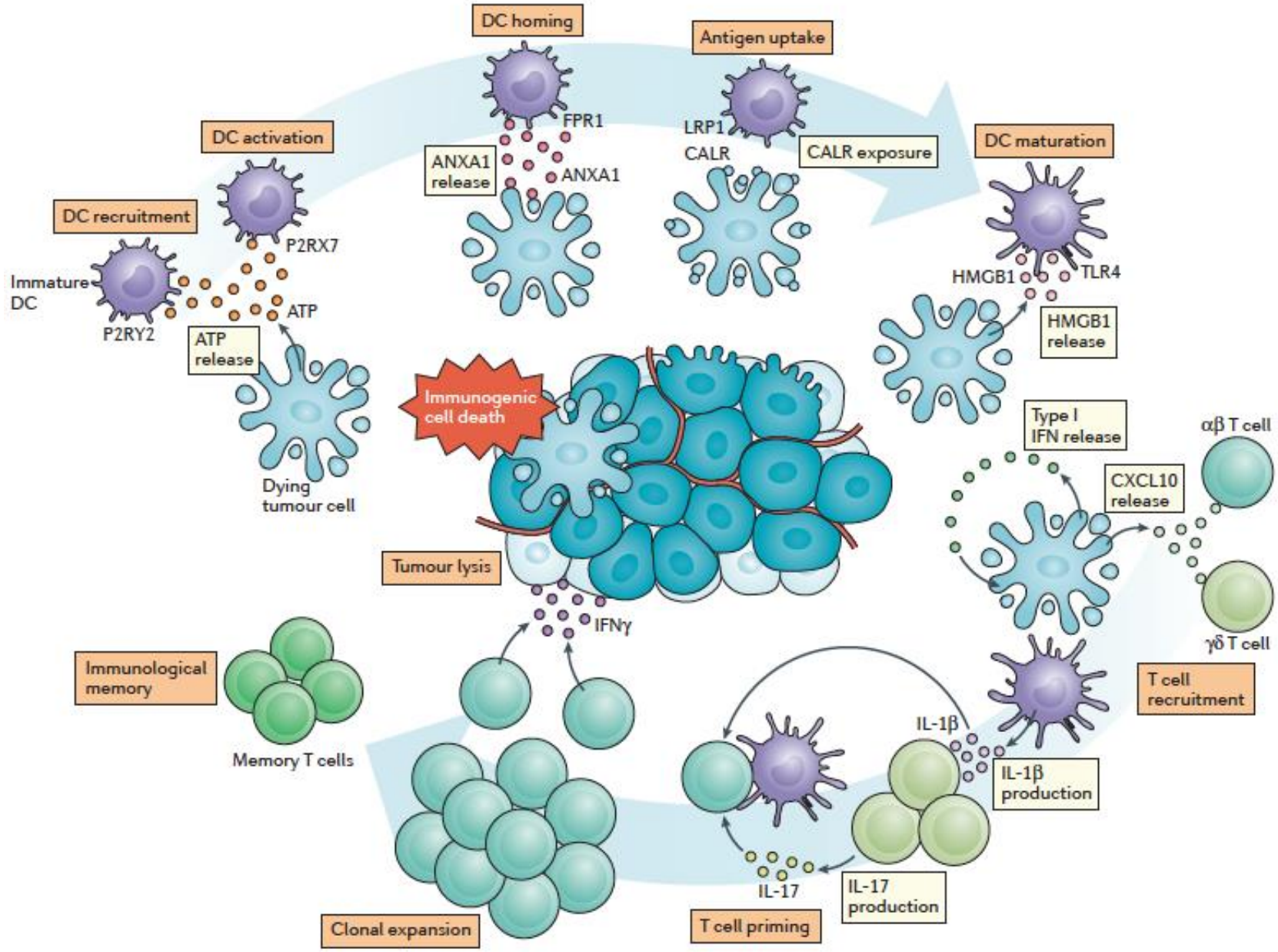
Some characteristics of immunogenic cell death:

Surface-exposed molecules, as well as soluble products from dying cells, affect the function of DCs in several ways, by binding to specific receptors or to PRR

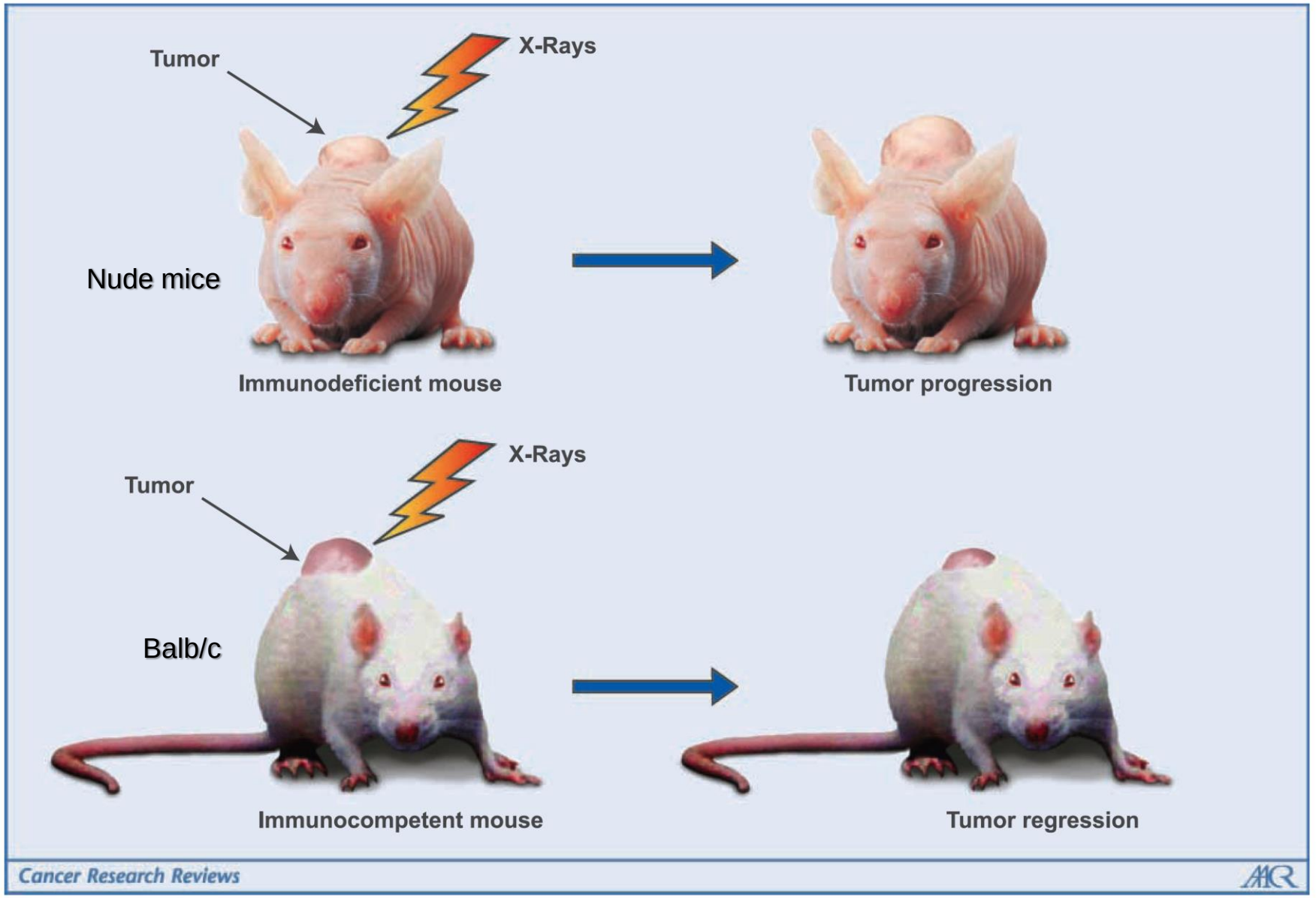
RAGE (receptor for advanced glycosylation end products

C-type lectin domain family 9, member A

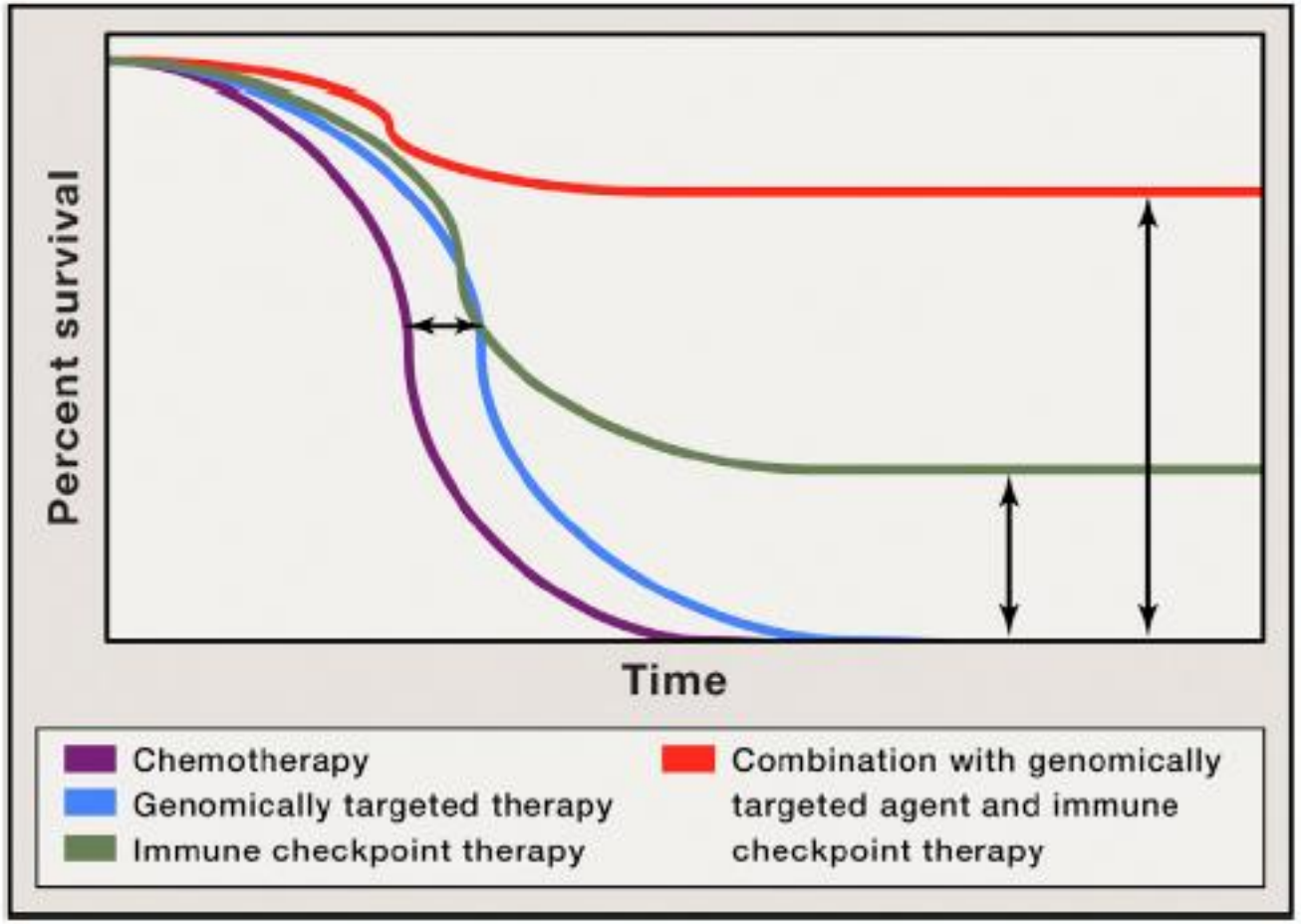
Mechanisms of chemotherapy-driven immunogenic cell death (ICD)



Contribution of the immune system to the success of anti-tumour conventional therapy



Improved overall survival as a result of combination therapy



Combinare vecchie e nuove terapie può essere la strategia vincente!

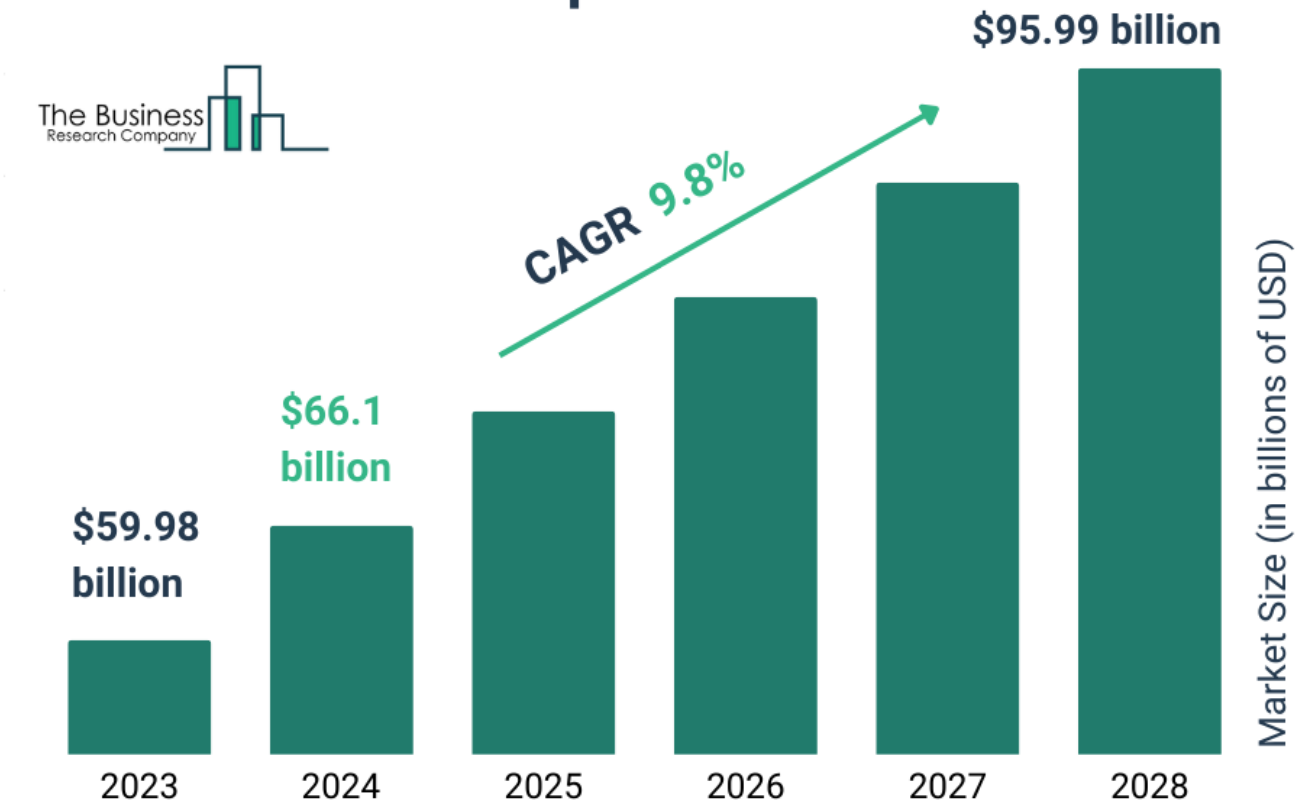
immunoterapia

radioterapia

chemioterapia

chirurgia

Cancer Monoclonal Antibodies Global Market Report 2024

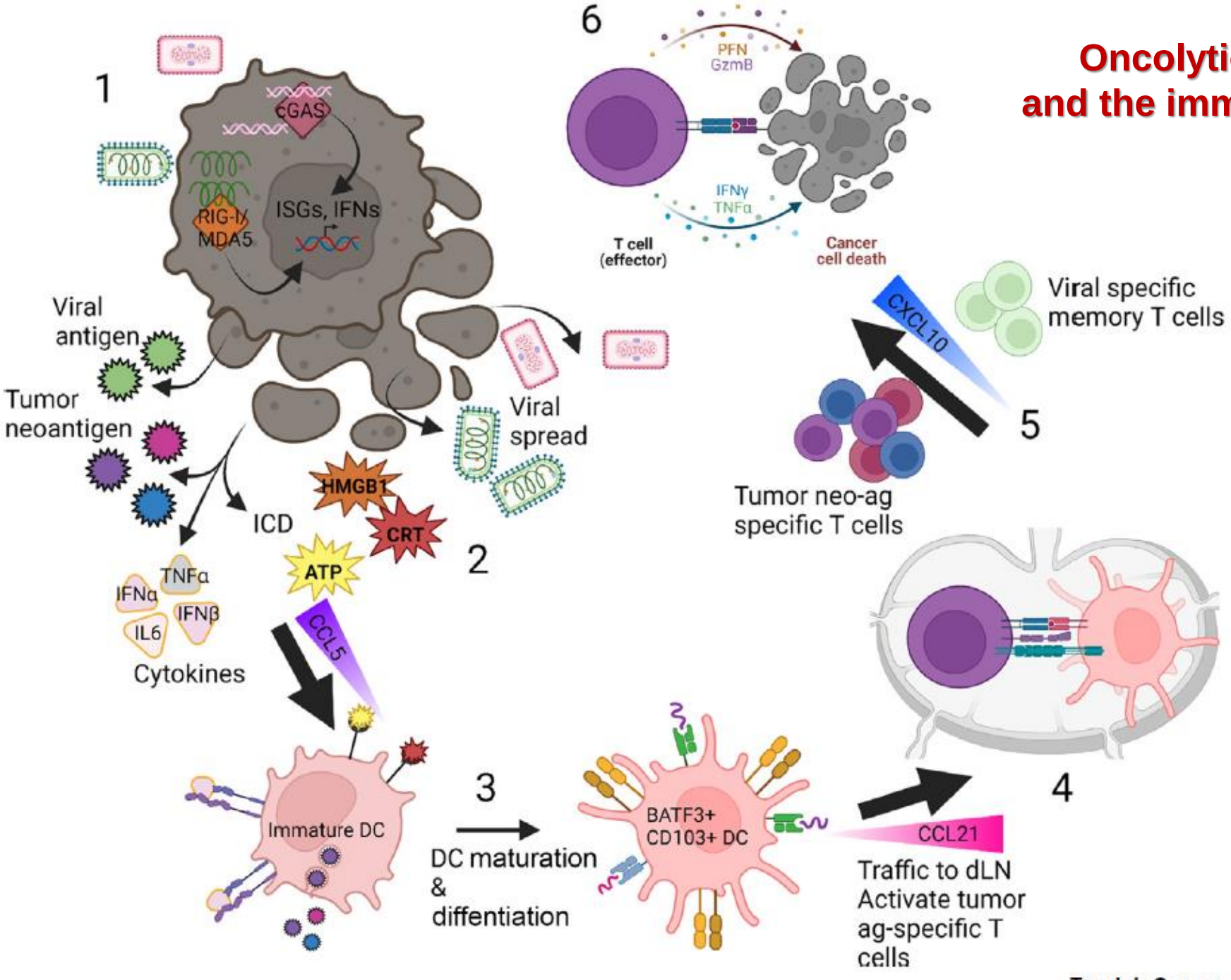


10 MOST PROMISING CANCER DRUGS NOT YET APPROVED SOLID TUMORS

OncoDaily 2024 Edition

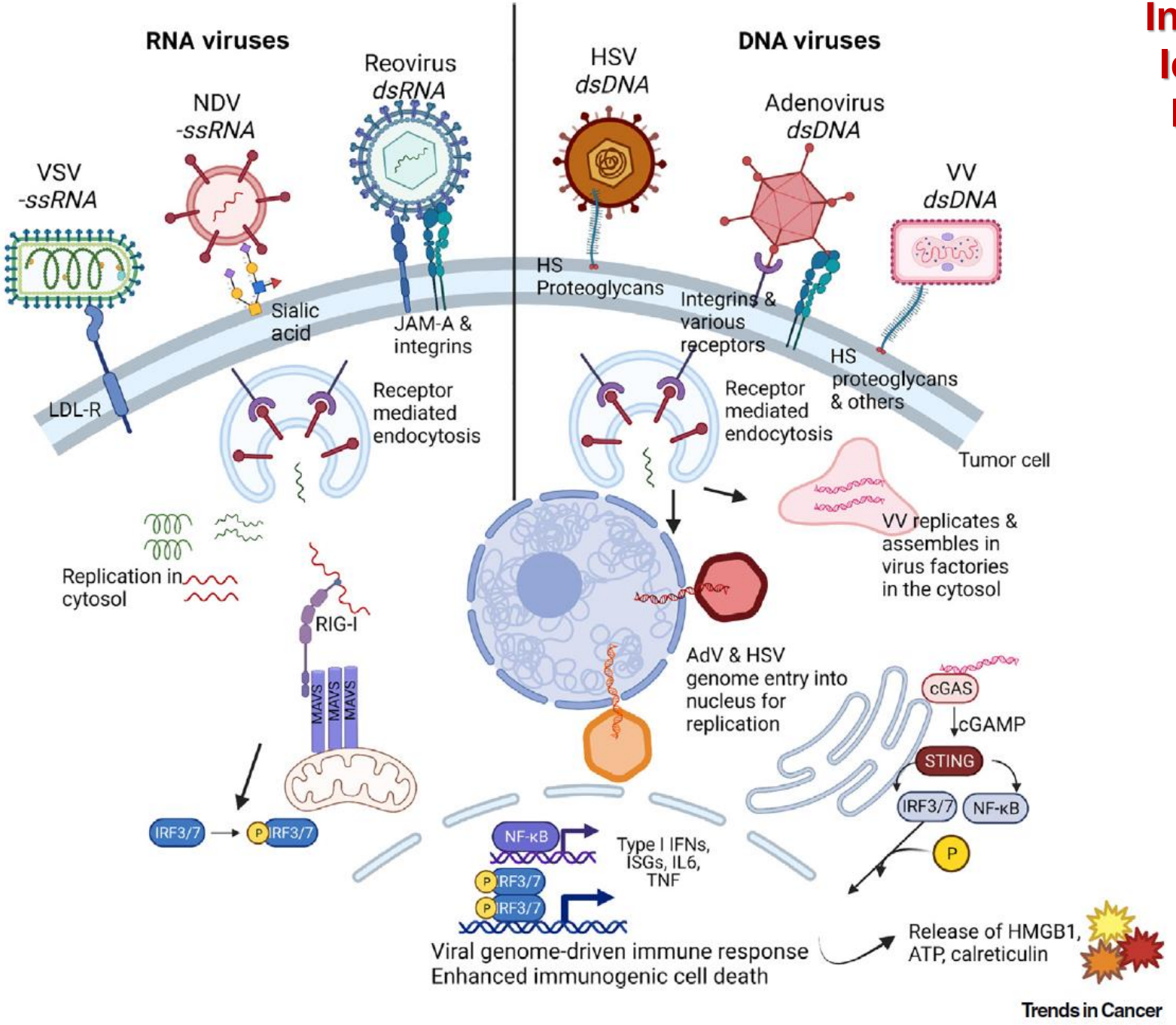
DRUG	Company	Indication
Datopotamab Deruxtecan (Dato-DXd)	Daiichi-Sankyo AstraZeneca	NSCLC Breast cancer
Botensilimab	agenus	Colorectal cancer Sarcomas Other solid tumors
Sunvozertinib	Dizal Pharma AstraZeneca	NSCLC with EGFR exon 20 insertion mutations
Zolbetuximab	astellas	GEJ cancer
Glecirasib	Jacobio	NSCLC Pancreatic cancer Other cancers with the KRAS G12C mutation
Rinatabart Sesutecan	ProfoundBio	Ovarian cancer Endometrial cancer Breast cancer NSCLC Mesothelioma
Tiragolumab	Genentech	Lung cancer Esophageal cancer Cervical cancer Other solid tumors
Bemarituzumab	AMGEN	Gastric cancer GEJ cancer Bladder cancer Other solid tumors with FGFR2b overexpression
Zenocutuzumab	Merus	NSCLC with NRG1 fusions Pancreatic cancer with NRG1 fusions Other solid tumors with NRG1 fusions
mRNA-4157/V940	MERCK moderna	Melanoma Potentially other solid tumors

Oncolytic viruses and the immune system



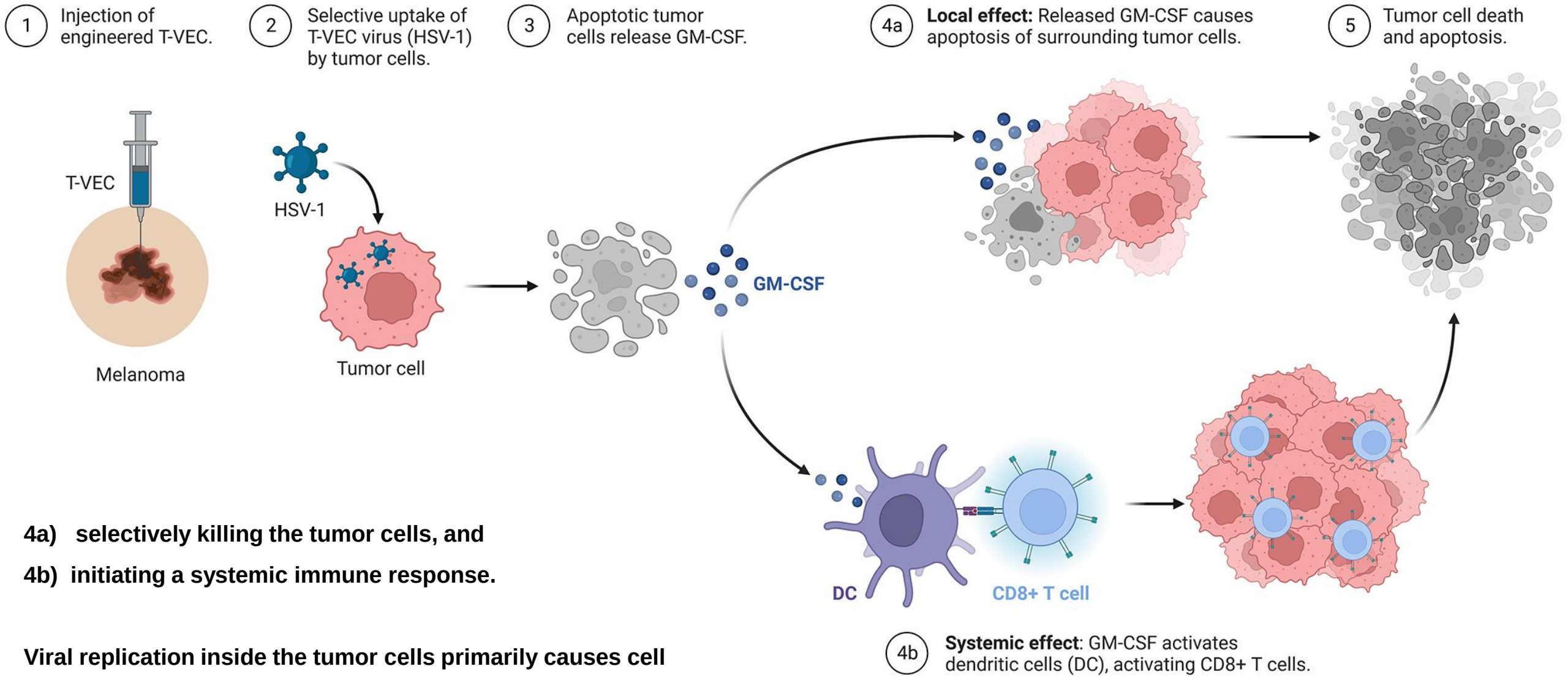
Trends in Cancer

Innate sensing of OVs leads to induction of ISGs and cytokines



DePeaux K., Trends in Cancer 2024

OVs cause tumor lysis by two mechanisms



4a) selectively killing the tumor cells, and

4b) initiating a systemic immune response.

Viral replication inside the tumor cells primarily causes cell death. It is mediated by cell receptor targeting and disruption in the host cell defense mechanism.

Reddy R, J Neurosurgery 2024

TABLE 4. Oncolytic viral therapy in phase III–IV clinical trials

OV & Delivery Method	Type of Tumor	Clinical Trial Phase	Outcome Measures	Status	Location
Intralesional talimogene laherparepvec (herpesvirus) vs PV-10	Melanoma	III	PFS, CRR, DCR, OS, adverse events	Terminated (inadequate rate of enrollment)	St. Luke's University, USA
Intravesical CG0070 (AdV)	Bladder cancer	III	CRR, DCR, progression rate to muscle invasion, complete response survival	Terminated (change in study design)	CG Oncology Inc, USA
Intralesional pexastimogene devacirepvec (poxvirus)	Hepatocellular carcinoma	III	ORR	Completed	SillaJen Inc, South Korea
Intravenous Reolysin (ReoV)	Squamous cell carcinoma of head & neck	III	OS, PFS, objective response	Completed	Oncolytics Biotech, USA & United Kingdom
Intravesical CG0070 (AdV)	Bladder cancer	III	CRR, DOR, PFS, TTP, adverse events	Recruiting	CG Oncology Inc, USA
Intraperitoneal olvimulogene nanivacirepvec (poxvirus)	Ovarian cancer	III	PFS, adverse events, DOR, ORR, OS	Not yet recruiting	Advent Health, USA
Intralesional talimogene laherparepvec (herpesvirus)	Melanoma	III	Adverse events, ORR, DRR	Completed	BioVex Limited, USA
Intralesional talimogene laherparepvec (herpesvirus) vs GM-CSF	Melanoma	III	DRR, OS, ORR, duration of response, response onset, TTF, response interval	Completed	BioVex Limited, USA
Intralesional recombinant human AdV type 5	Hepatocellular carcinoma	IV	ORR, DCR, PFS, 1-yr survival, adverse events	Active, not actively recruiting	First Affiliated Hospital Xi'an Jiaotong University, China
Intralesional recombinant human AdV type 5	Intrahepatic cholangiocarcinoma	IV	PFS, 1-year survival, ORR, DCR	Not yet recruiting	Beijing Tsinghua Chang Gung Hospital, China

CRR = complete response rate; DCR = disease control rate; DOR = duration of response; DRR = durable response rate; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure; TTP = time to progression.