Tumor Immunity

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Tumor *vs* Cancer

A **tumor**, also known as a **neoplasm**, (from Ancient Greek νεο-*neo-* "**new**" and πλάσμα *plasma* "formation, creation") is an abnormal mass of tissue which may be solid or fluid-filled.

A tumor does not mean cancer - tumors can be benign (**not cancerous**), pre-malignant (**pre-cancerous**), or malignant (**cancerous**).

In modern medicine, the term neoplasm means that it has formed a lump.

In the past, the term tumour was used differently, referring to a lump of any cause. Some neoplasms do not cause a lump (such as nevi, not progressive).

Tumor does not necessarily pose a health threat. Uncontrolled growth produces a tumor /neoplasm. A tumor that grows indefinitely and often spreads (metastasis) is called malignant--also called cancer.

A tumor that is not capable of indefinite growth:

Benign: does **not** kill host

Malignant: kills host

WHO classifies neoplasms into four main groups:

1. benign neoplasms
2. in situ neoplasms
3. malignant neoplasms (**cancer**）
4. neoplasms of uncertain or unknown behaviours

Tumor Antigens

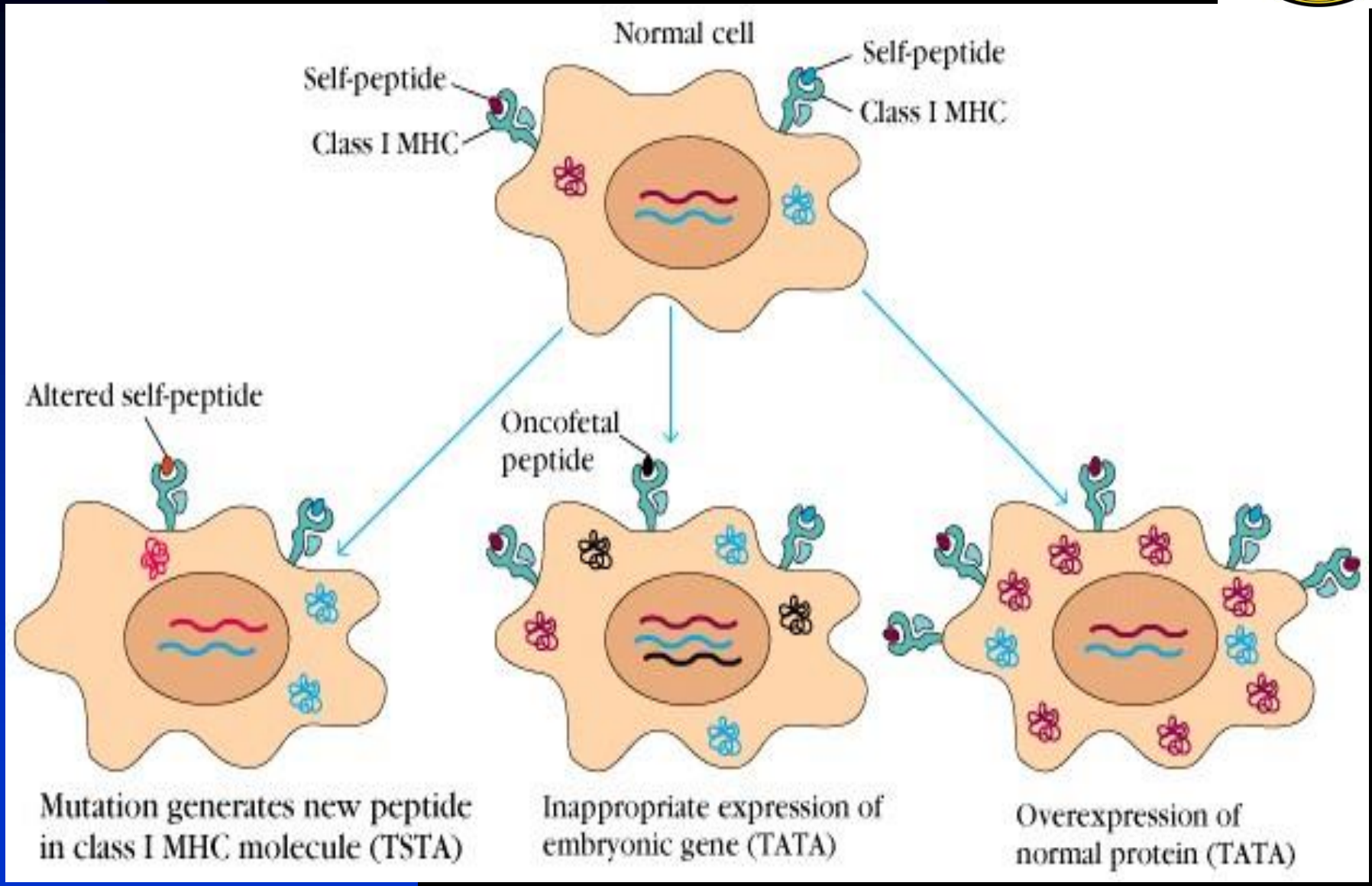


TABLE 22-4 SOME TUMOR ASSOCIATED-ANTIGENS UNDER EXAMINATION AS POTENTIAL TARGETS FOR MONOCLONAL ANTIBODY THERAPY

Tumor antigen	Tumor type	Target antigen
	Lymphoid cell-surface markers	
T-cell marker	T-cell leukemia/lymphoma	CD5
B-cell marker	B-cell lymphoma	CD20
Hematopoietic-cell marker	Acute myeloblastic leukemia	CD45
Anti-idiotype	B-cell lymphoma	Immunoglobulin
	Nonlymphoid tissue markers	
Cell Surface Antigens		
Carcinoembryonic antigen (CEA)	Colon cancer (some others)	Glycoprotein
MUC1	Breast cancer	Glyoprotein
Gangliosides such as GD2 and GD3	Neuroectodermal tumors	Glycolipids associated with neural tissue
Growth factor receptors		
Epidermal growth-factor receptor (EGFR)	Some lung, head, neck, and breast tumors	EGF-binding cell surface protein
HER2 (an EGF-like receptor)	Breast and ovarian tumors	Cell surface EGF-binding protein with homology to EGFR

SOURCE: Adapted from Scott and Welt, 1997, *Curr. Opin. Immunol.* **9**:717.

TABLE 22-5 TUMOR-ASSOCIATED AND TUMOR-SPECIFIC ANTIGEN PEPTIDES RECOGNIZED BY HUMAN T CELLS

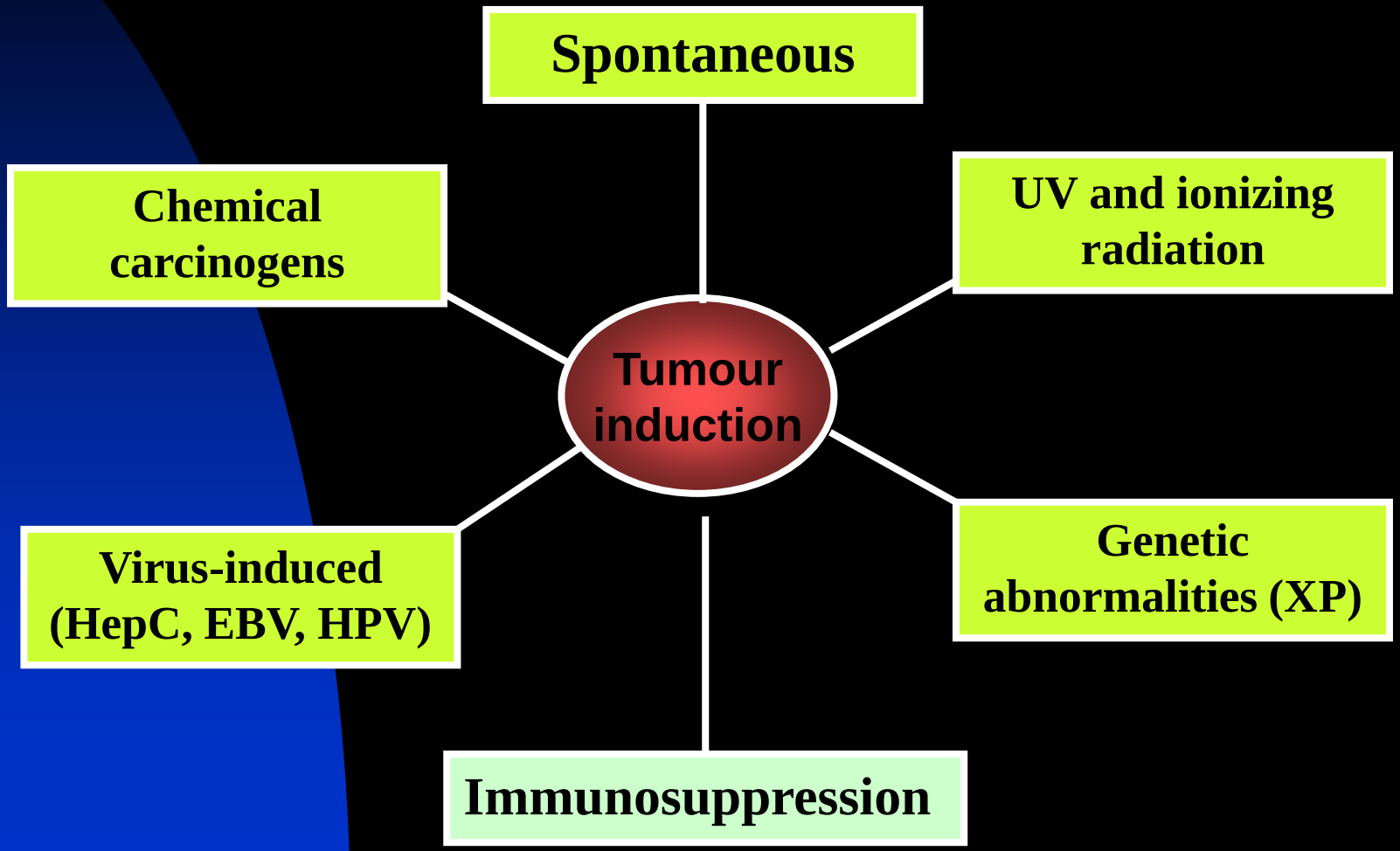
Human tumor	Protein	Peptide
Many melanomas, esophageal carcinomas, non small-cell lung carcinomas and hepatocellular carcinomas	MAGE-1	EADPTGHSY and SAYGEPRKL
Melanoma	Tyrosinase	MLLAVLYCL, YMNGTMSQV, YMDGTMSQV, and others
Colon cancer	Carcinoembryonic antigen (CEA)	YLSGANLNL
Breast and ovarian cancer	HER2/NEU	KIFGSLAFL
Head and neck squamous-cell carcinoma	Caspase 8	FPSDSWCYF
Chronic myeloid leukemia	*bcr-abl* fusion protein (product of a fusion of an Ig gene with the *abl* gene)	ATGFKQSSKALQRPVAS
Prostatic cancer	PSA	FLTPKKKLQCV and VISNDVCAQV

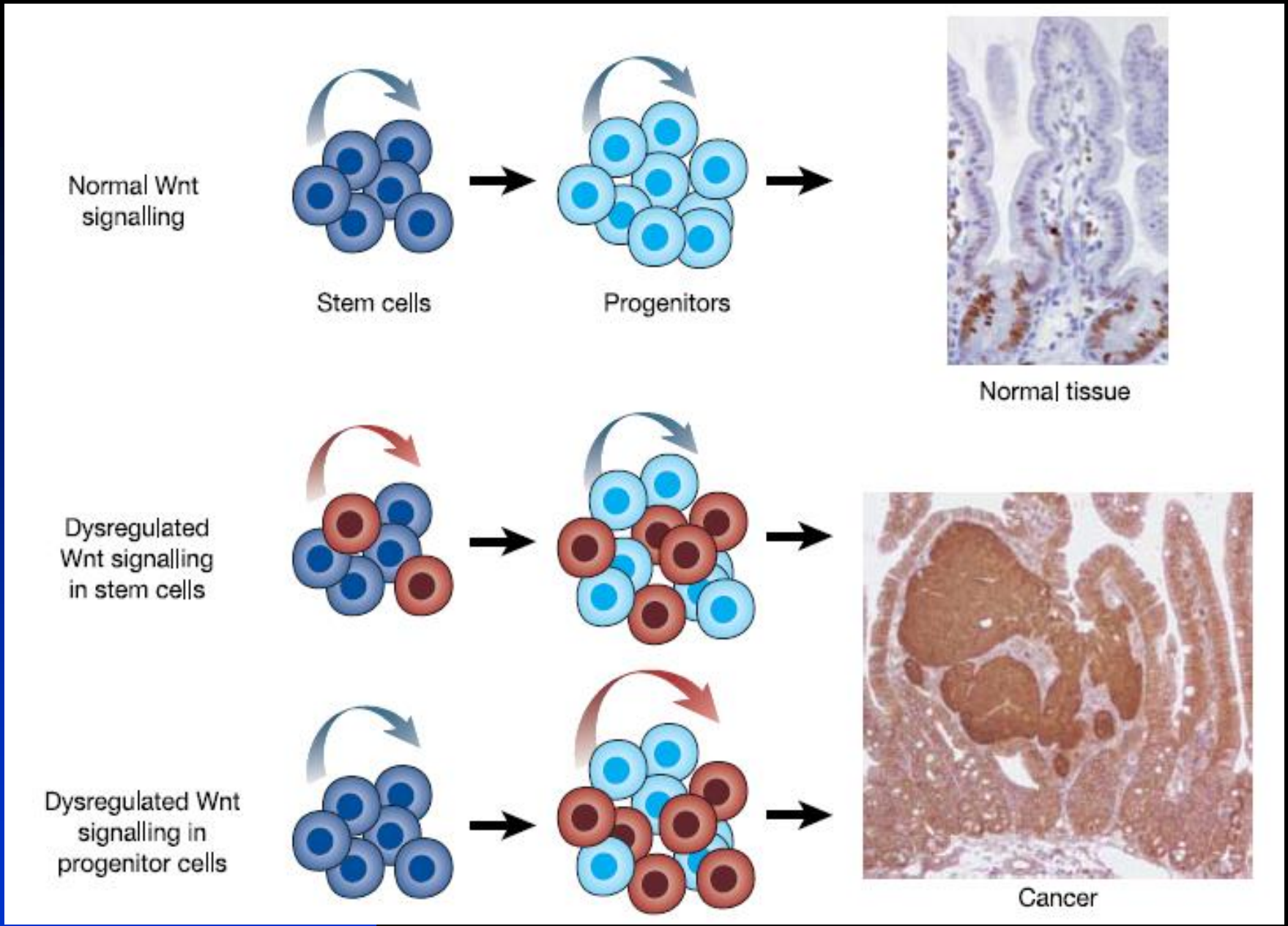
SOURCE: Adapted from B Van Den Eynde and P van der Bruggen, 1996, *Curr. Opin. Immunol.* **9**:684.

Cancer and the Immune System

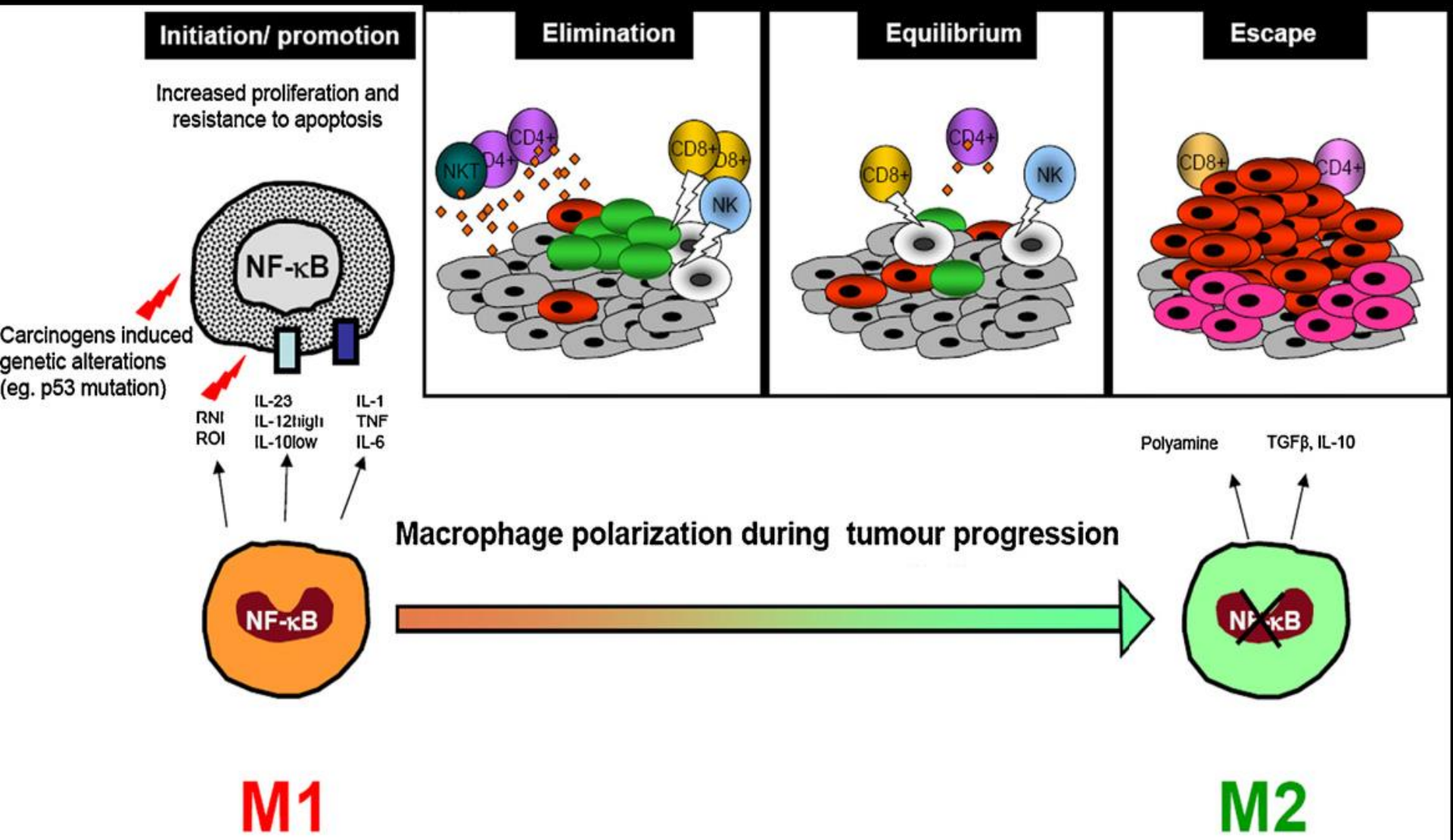
- **Is Cancer a disease caused by:**
  - **Genetic mutation or translocation or dysregulation?**
  - **Infectious agent?**
  - **Immune deficiency?**

Causative agents





Michael D, et al. Nature, 2005;5:275-84

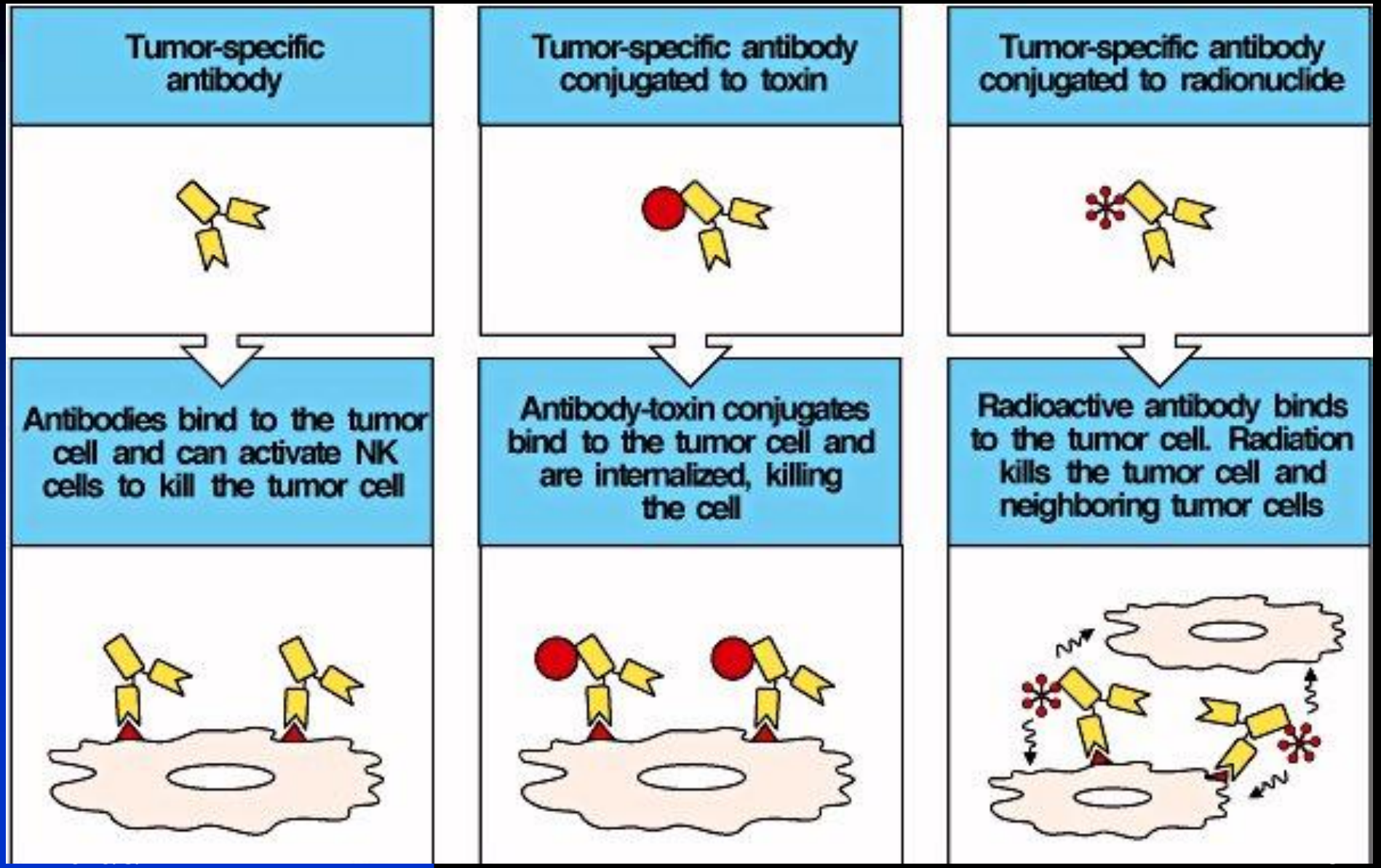


A. Sica et al. / Seminars in Cancer Biology xxx (2008)

Cancer Immunotherapy

- Manipulation of co-stimulatory signals.
- Enhancement of APC activity.
- Cytokine Therapy
  - Interferons
  - Tumor Necrosis Factor
- Lymphokine activated killer cells(**LAK** cells)
- Antibodies and immunotoxins.
- Cancer Vaccines

Cancer Immunotherapy with tumor-specific antibody



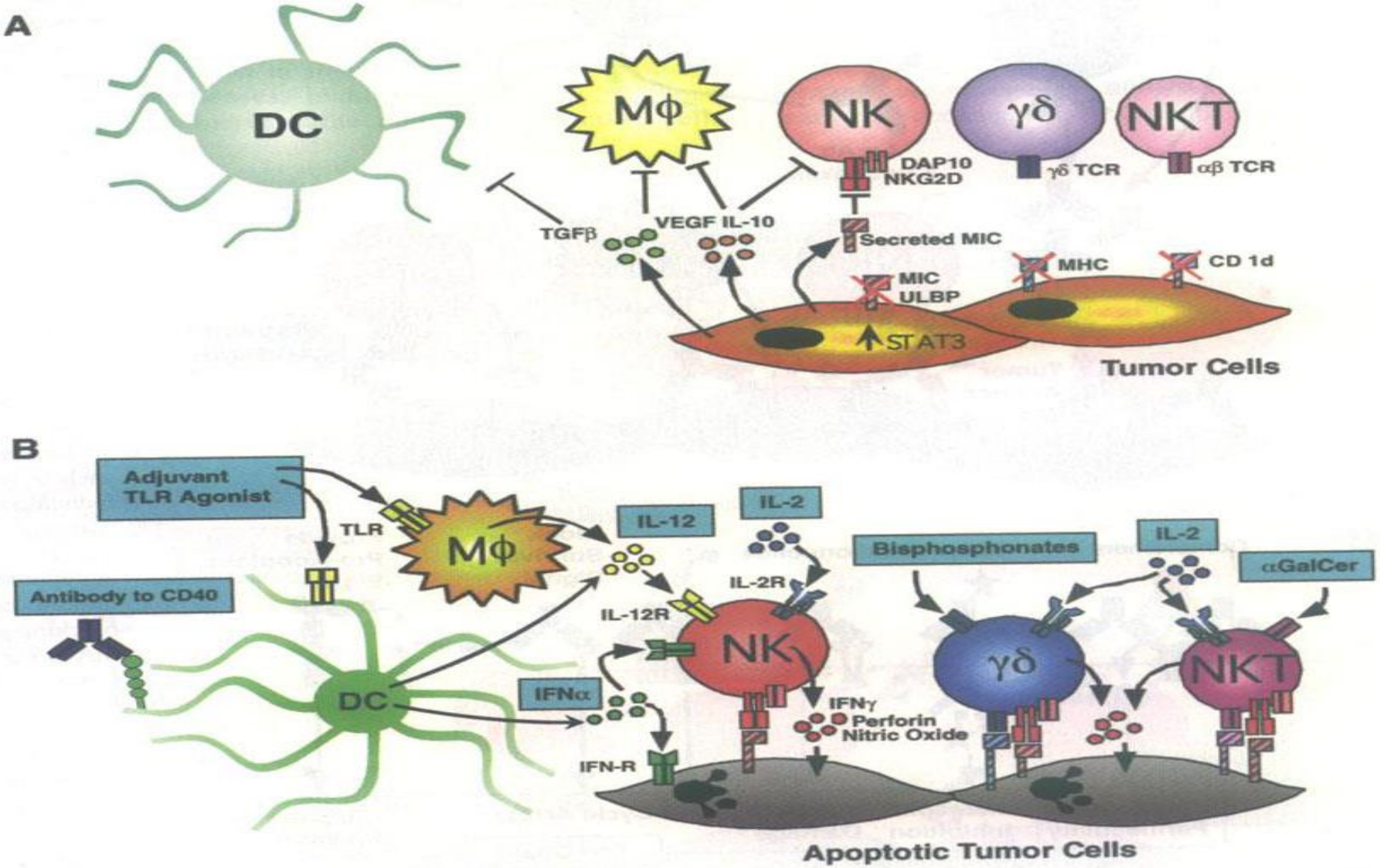


Fig. 1. Manipulating the innate immune response. (**A**) Tumor cells can avoid activating innate responses by producing inhibitory cytokines and down-regulating or secreting ligands for activating receptors. Mϕ, macrophage; TCR, T cell receptor. (**B**) Activation of innate responses can be enhanced by administering adjuvants, ligands for costimulatory proteins, cytokines, or drugs that directly trigger innate immune cells. αGalCer, α-galactosylceramide.

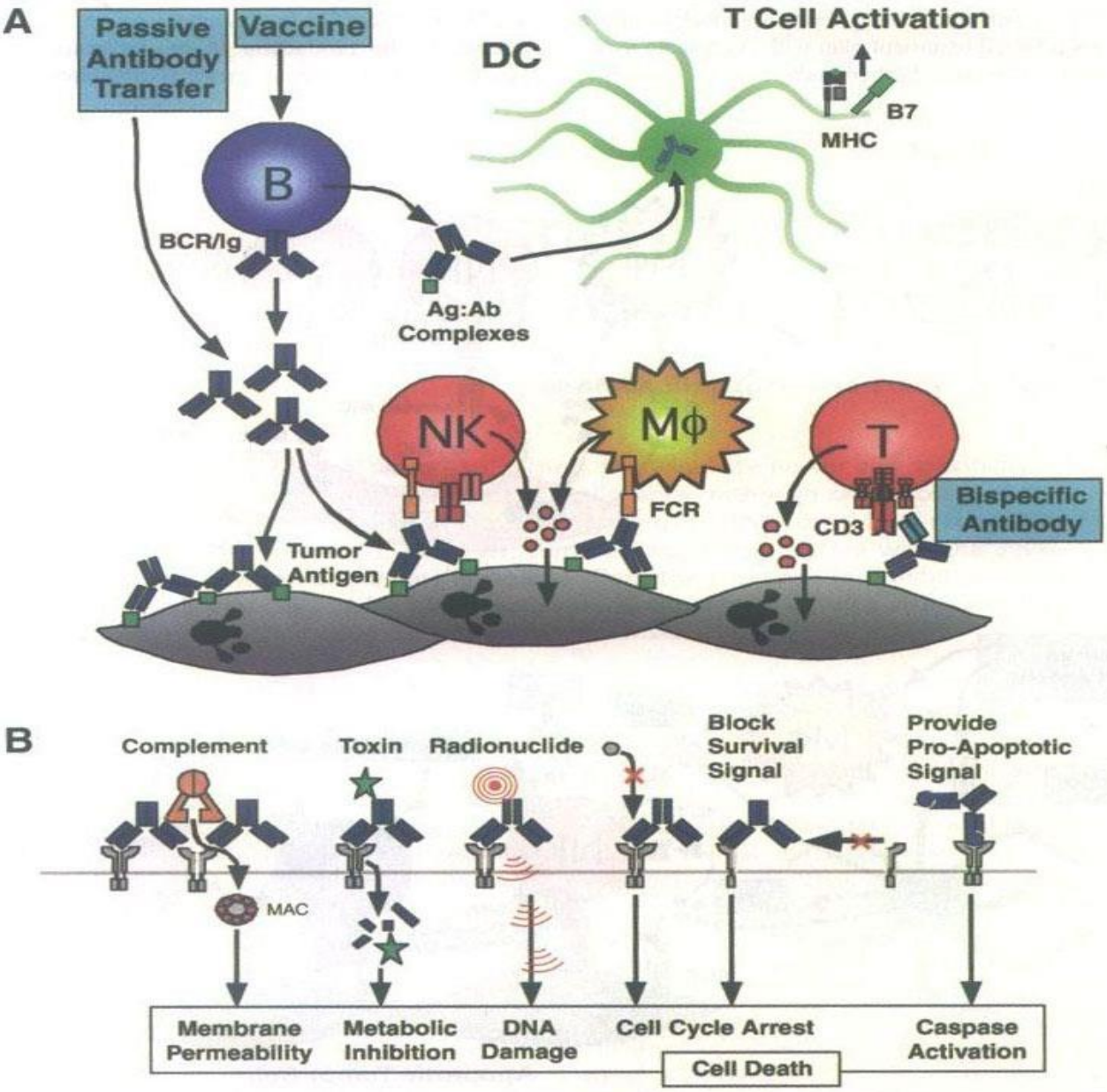


Fig. 2. Manipulating humoral immunity. **(A)** B cell responses can be augmented by vaccination with tumor antigens to induce antibodies that kill tumors or promote antigen presentation. Passively transferred mAbs or engineered bispecific antibodies can bind to tumors and activate effector cells. BCR/Ig, B cell receptor; Ag:Ab, antigen:antibody; MAC, membrane attack complex. **(B)** Modified and unmodified mAbs can kill tumor cells by many mechanisms independent of recruitment of effector cells.

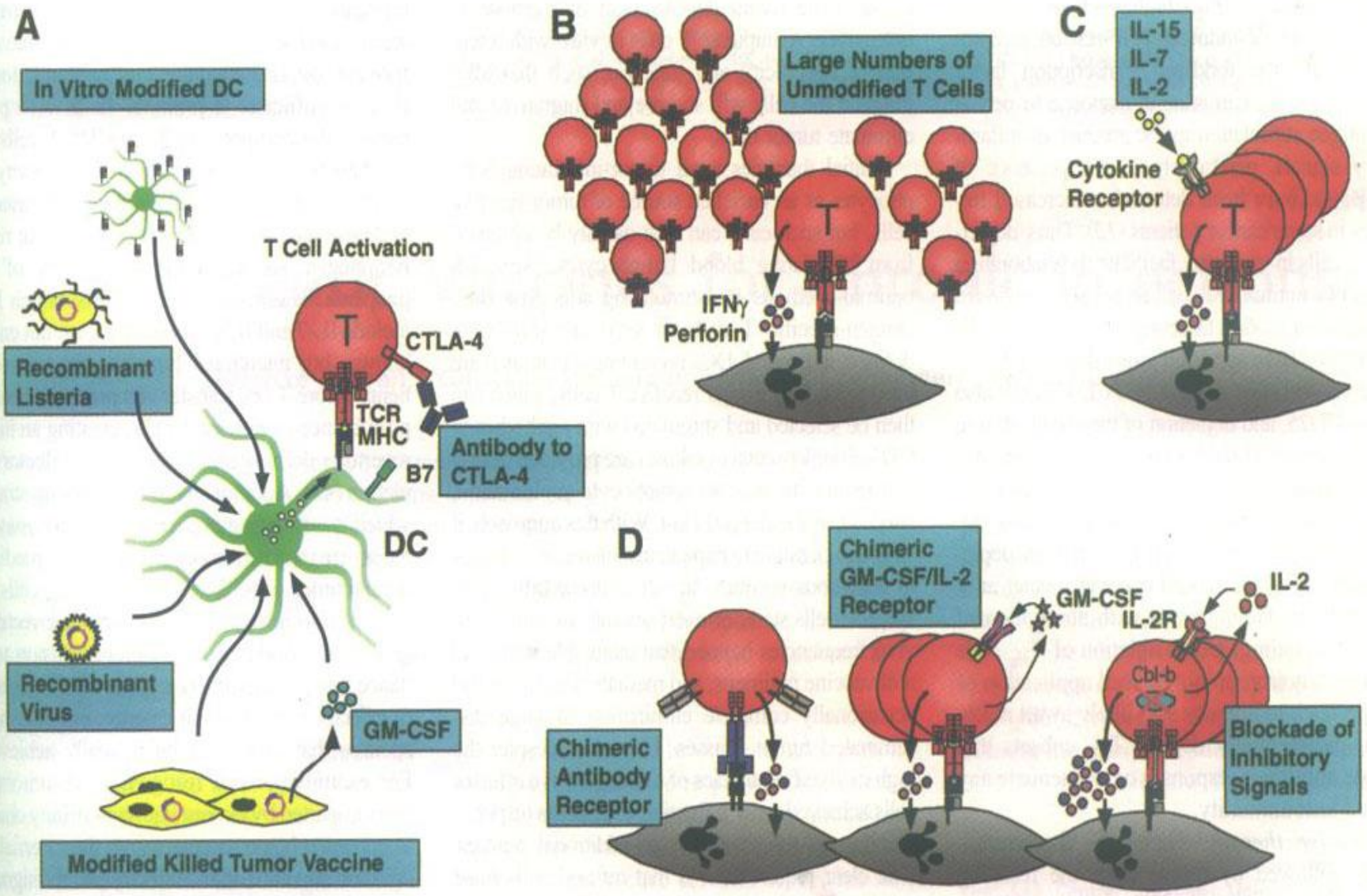
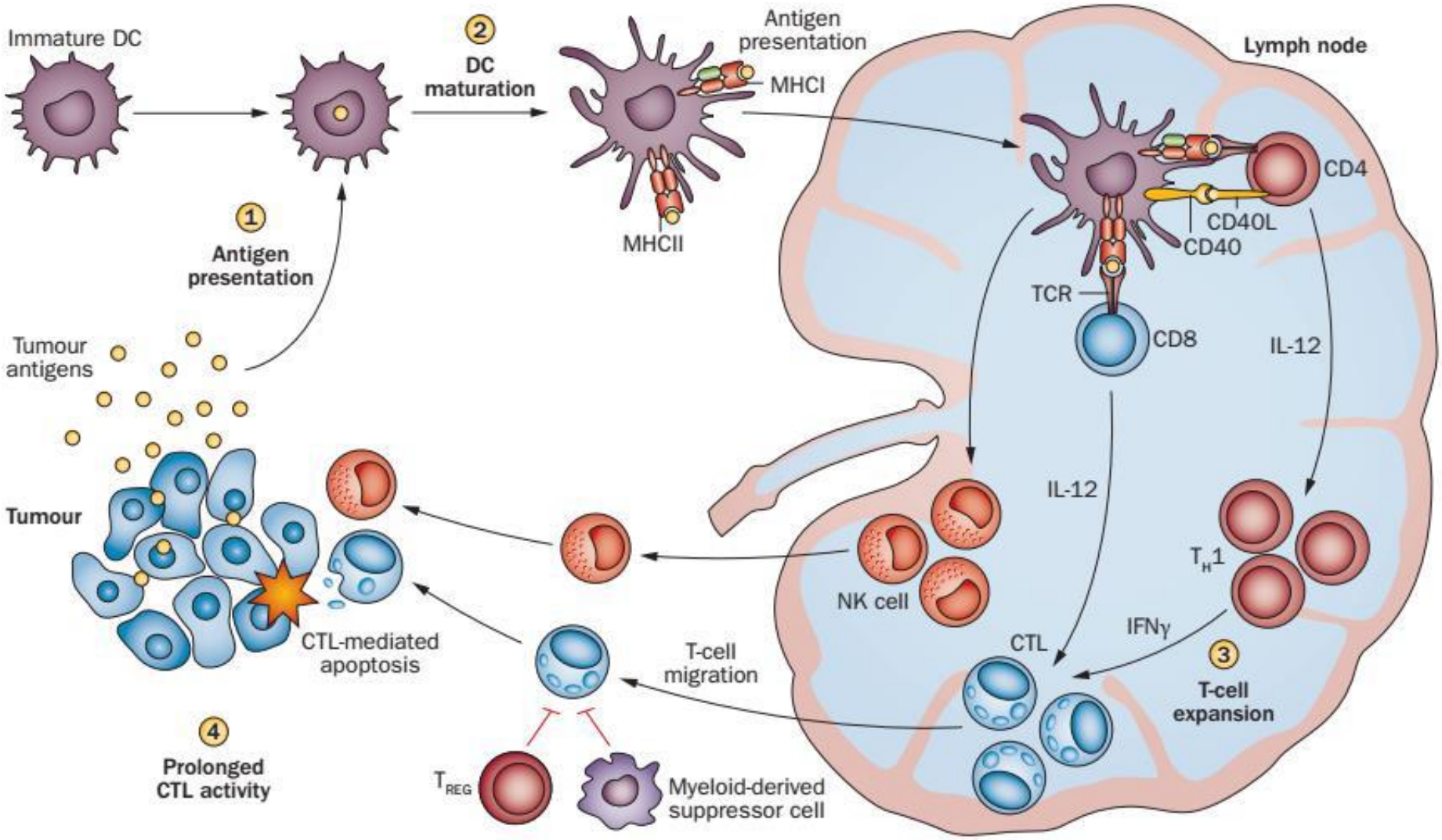


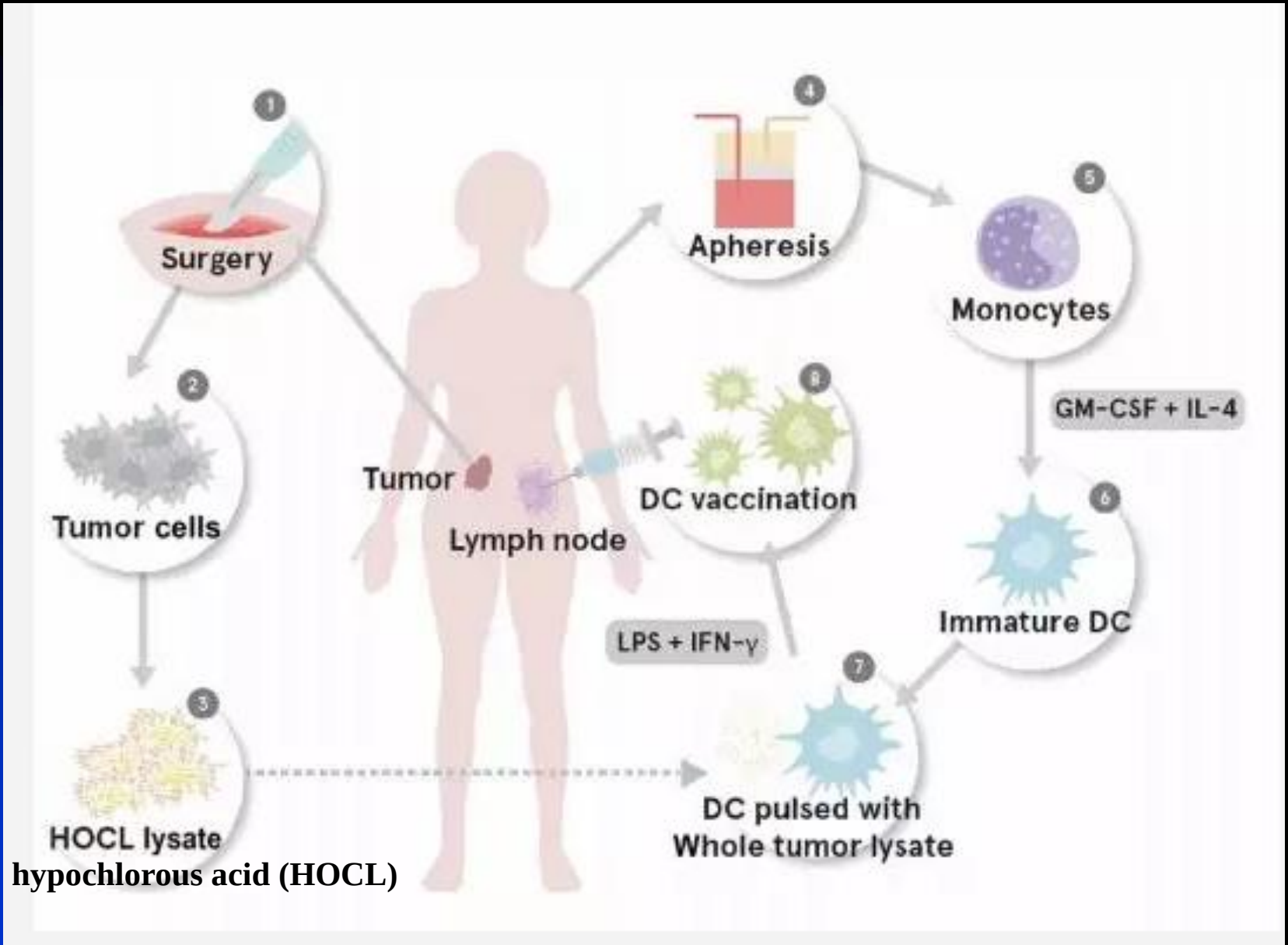
Fig. 3. Manipulating T cell immunity. T cell responses can be augmented by (**A**) stimulation with immunogenic vaccines, pro-inflammatory cytokines, or antibodies that block negative signals, (**B**) adoptive transfer of large numbers of tumor-reactive T cells generated in vitro, or (**C**) administration of cytokines. (**D**) T cells can be genetically modified before adoptive transfer to acquire novel receptors for tumor recognition or regulated autocrine proliferative signals, or to block inhibitory signals that limit T cell responses.



Steps in the development of a cellular immune response against tumour-associated antigen.

Melero I, et al. Nat Rev Clin Oncol. 2014;11:509-24.

Scheme of DC vaccine production and administration



Tanyi JL, et al. Sci Transl Med. 2018 ;10(436)

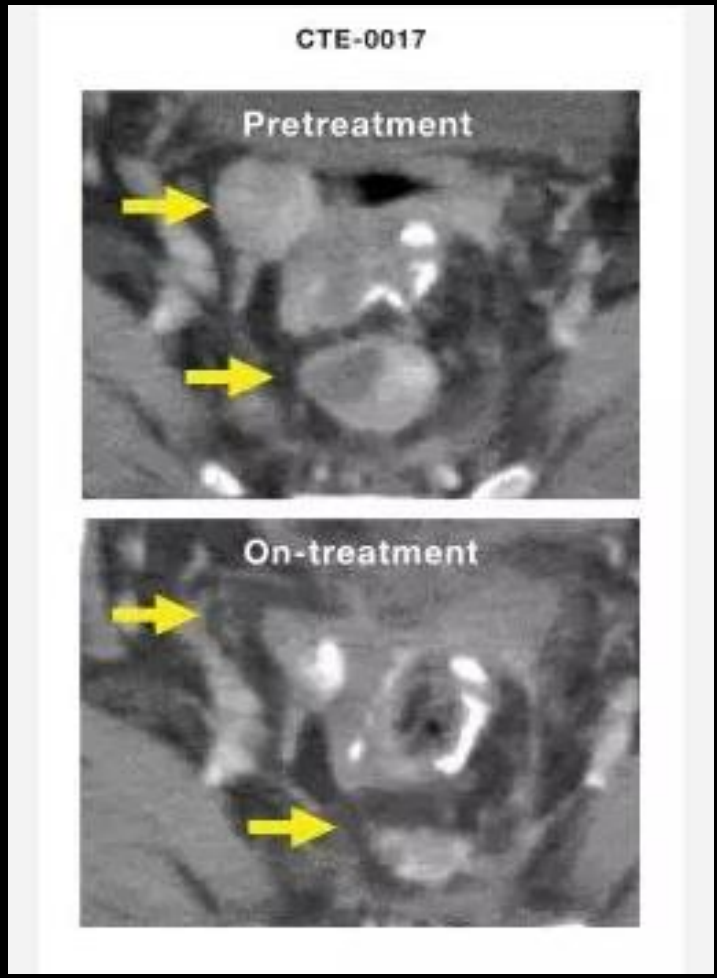
We conducted a pilot clinical trial testing a personalized vaccine generated by autologous dendritic cells (DCs) pulsed with oxidized autologous whole-tumor cell lysate (OCDC), which was injected intranodally in platinum-treated, immunotherapy-naïve, recurrent ovarian cancer patients. OCDC was administered alone (cohort 1, *n* = 5), in combination with bevacizumab (cohort 2, *n* = 10), or bevacizumab plus low-dose intravenous cyclophosphamide (cohort 3, *n* = 10) until disease progression or vaccine exhaustion.

A total of 392 vaccine doses were administered without serious adverse events. Vaccination induced T cell responses to autologous tumor antigen, which were associated with significantly prolonged survival.

Vaccination also amplified T cell responses against mutated neoepitopes derived from nonsynonymous somatic tumor mutations, and this included

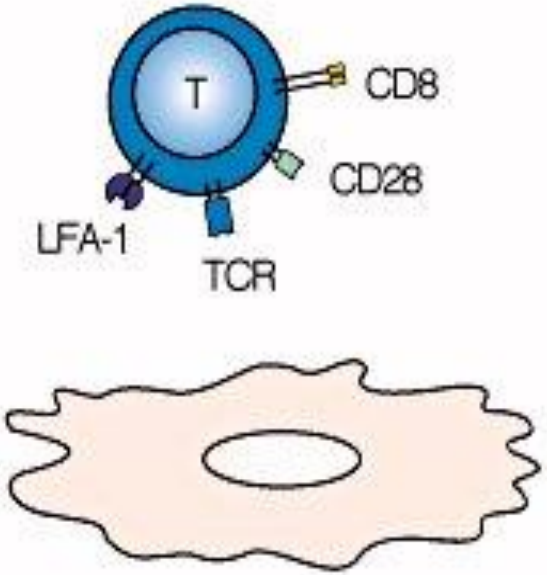
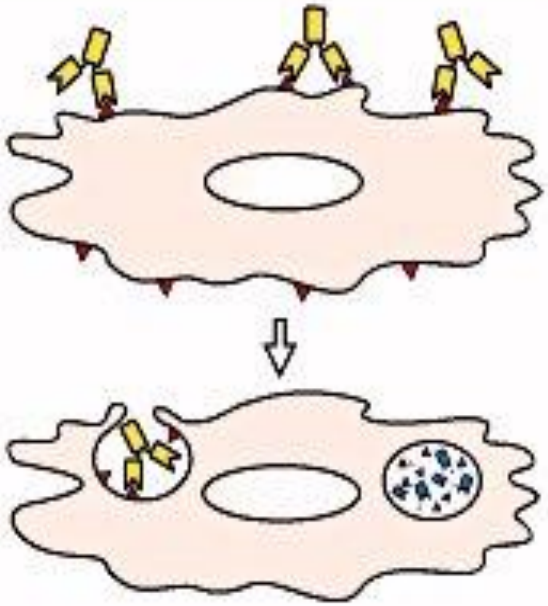
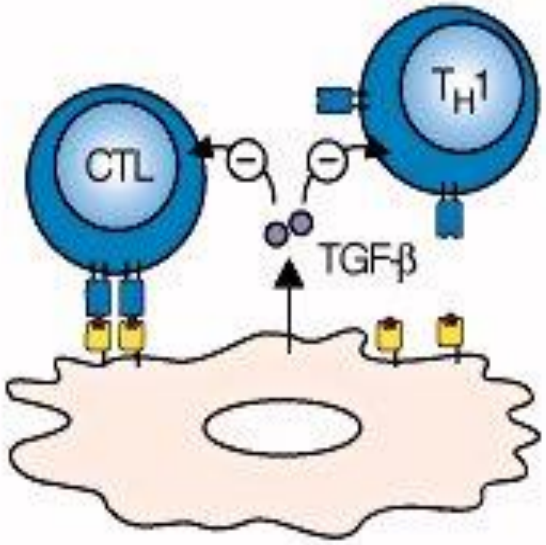
Tanyi JL, et al. Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. **Sci Transl Med. 2018 ;10(436)**

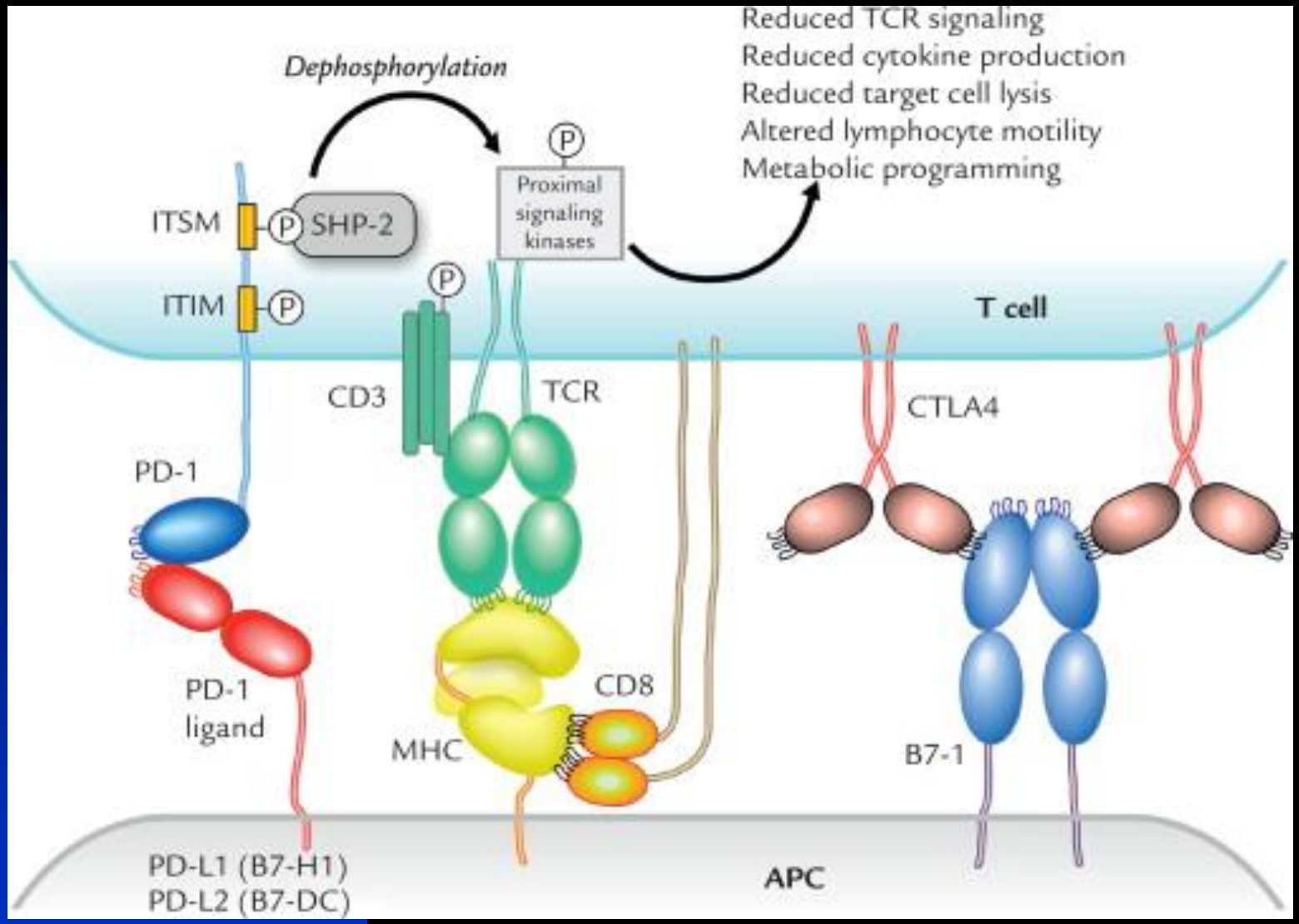
priming of T cells against previously unrecognized neoepitopes, as well as novel T cell clones of markedly higher avidity against previously recognized neoepitopes. We conclude that the use of oxidized whole-tumor lysate DC vaccine is safe and effective in eliciting a broad antitumor immunity, including private neoantigens, and warrants further clinical testing.



Tanyi JL, et al._Sci Transl Med. 2018 ;10(436)

Mechanisms whereby tumors escape immune recognition

Low immunogenicity	Antigenic modulation	Tumor-induced immune suppression
No peptide:MHC ligand No adhesion molecules No co-stimulatory molecules	Antibody to tumor cell-surface antigens may induce endocytosis and degradation of the antigen. Immune selection of antigen-loss variants	Factors (eg TGF-β) secreted by tumor cells inhibit T cells directly
		



The interaction of PD-1 and PD-L1 reduces T-lymphocyte function.

ITIM = immunoreceptor tyrosine-based inhibitory motif; ITSM = immunoreceptor tyrosine-based switch motif; P = phosphoryation site; PD = programmed cell death protein; SHP = Src homology 2 domain–containing phosphatase.

Clin Ther. 2015;37:764-82.

NATURE REVIEWS IMMUNOLOGYVOLUME 6 2006 457-463

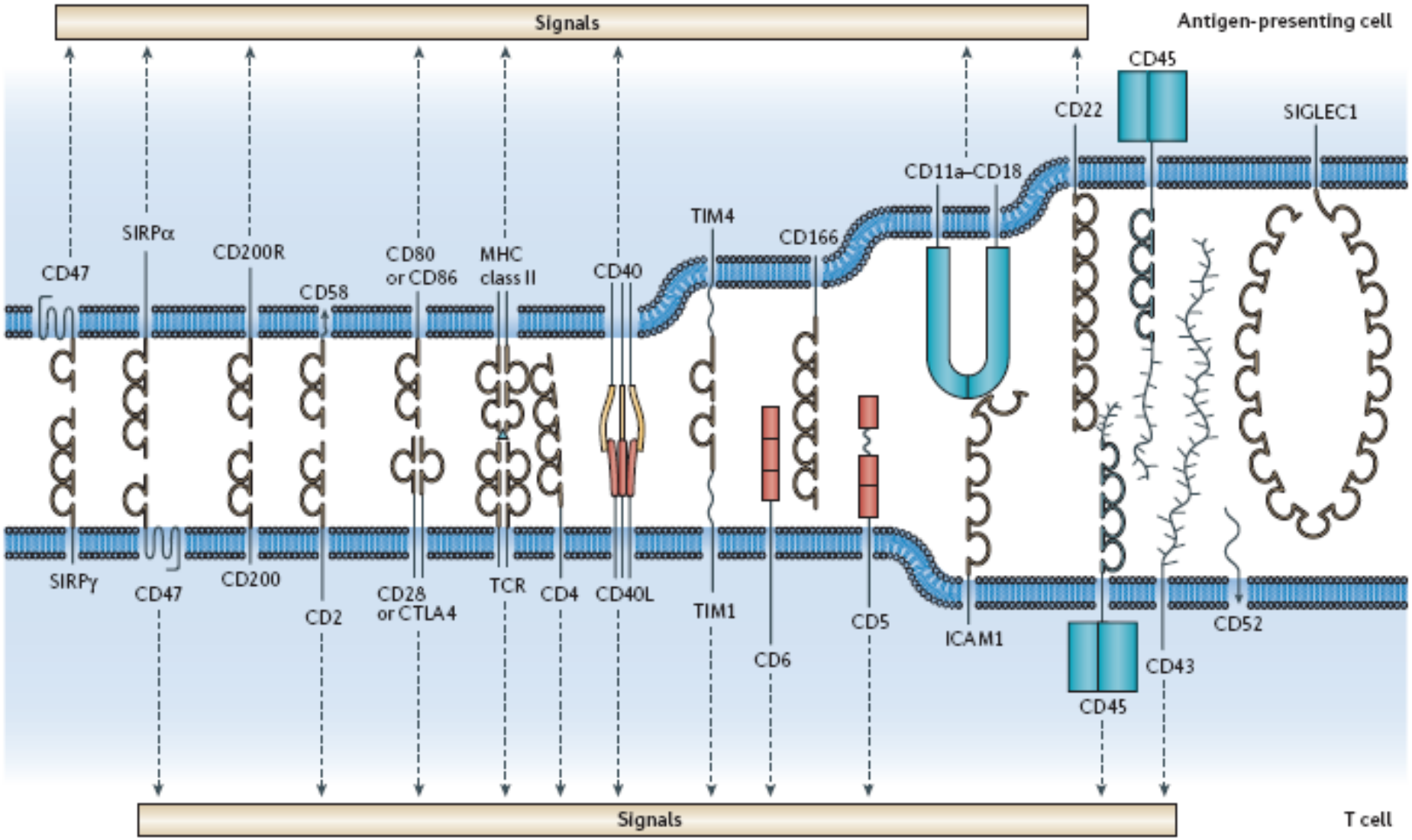
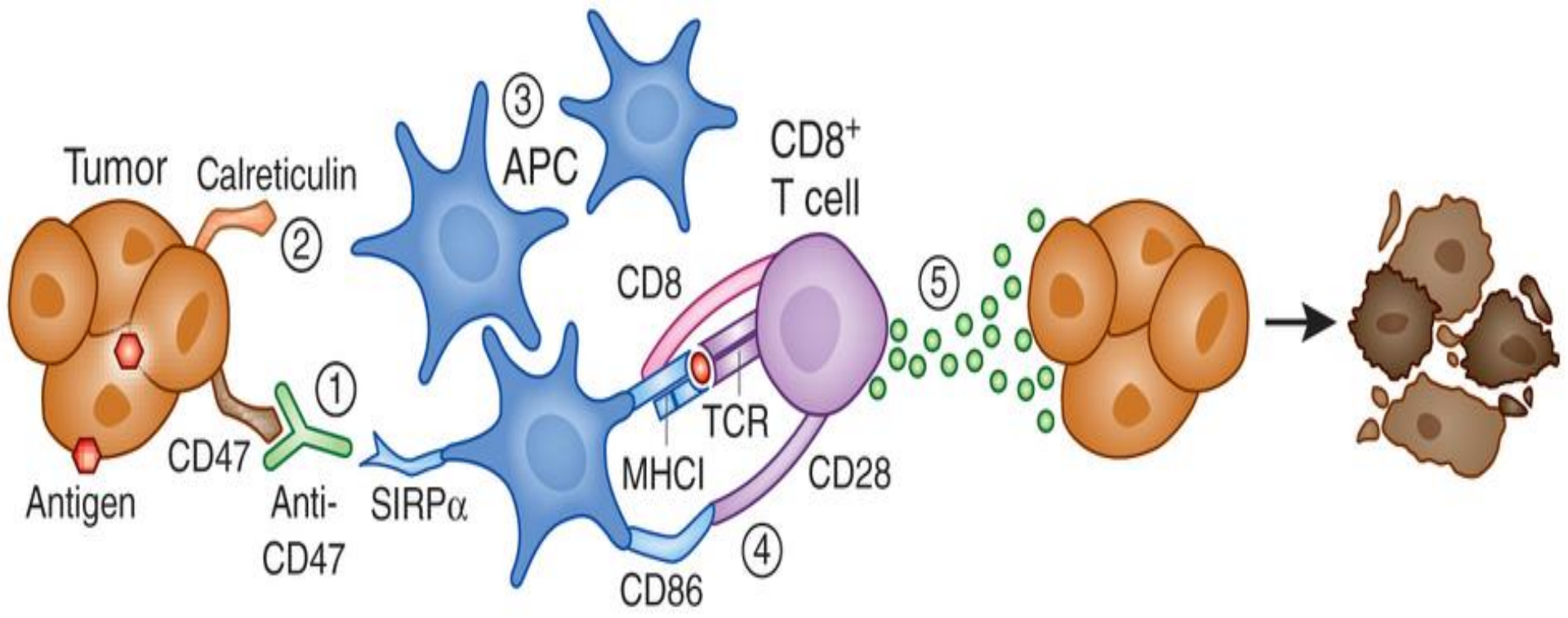


Figure 2 | **The topology of interactions between an antigen-presenting cell and a T cell.** Some of the interactions between plasma-membrane proteins on a T cell and an antigen-presenting cell are shown. The molecules are drawn to their relative approximate sizes based on electron microscopy and X-ray crystallography data, together with predictions from domain organization[45,46]. CD40L, CD40 ligand; CD200R, CD200 receptor; CTLA4, cytotoxic T-lymphocyte antigen 4; ICAM, intercellular adhesion molecule; SIGLEC1, sialic-acid-binding immunoglobulin-like lectin; SIRP, signal-regulatory protein; TCR, T-cell receptor; TIM, T-cell immunoglobulin domain and mucin domain.



Xiaojuan Liu, et.al. **CD47 blockade triggers T cell-mediated destruction of immunogenic tumors** Nat med.2015;21(10):1209-15.

Vonderheide RH. CD47 blockade as another immune checkpoint therapy for cancer Nat Med. 2015 ;21(10):1122-3.

Enhancing Immunogenicity of Tumors

CK genes (IL-2,IL-12, IL-21,GM-CSF), membrane surface molecular genes (B7,MHC,GPI)

A. immunization i.m with GM-CSF recombinant B. immunization i.m with blank plasmid

C. immunization s.c with blank plasmid D. immunization s.c with GM-CSF recombinant

Fig.1 Anti-tumor effect was enhanced by immunization with GM-CSF recombinant.
After Balb/c mice were inoculated with 5×10^5 SP2/0 cells 12 days , tumor-bearing mice were immunized i.m (A) or s.c(D) with GM-CSF recombinant or blank plasmid(B) and(C)

IL-21 Elicits Pleiotropic Immune Modulation

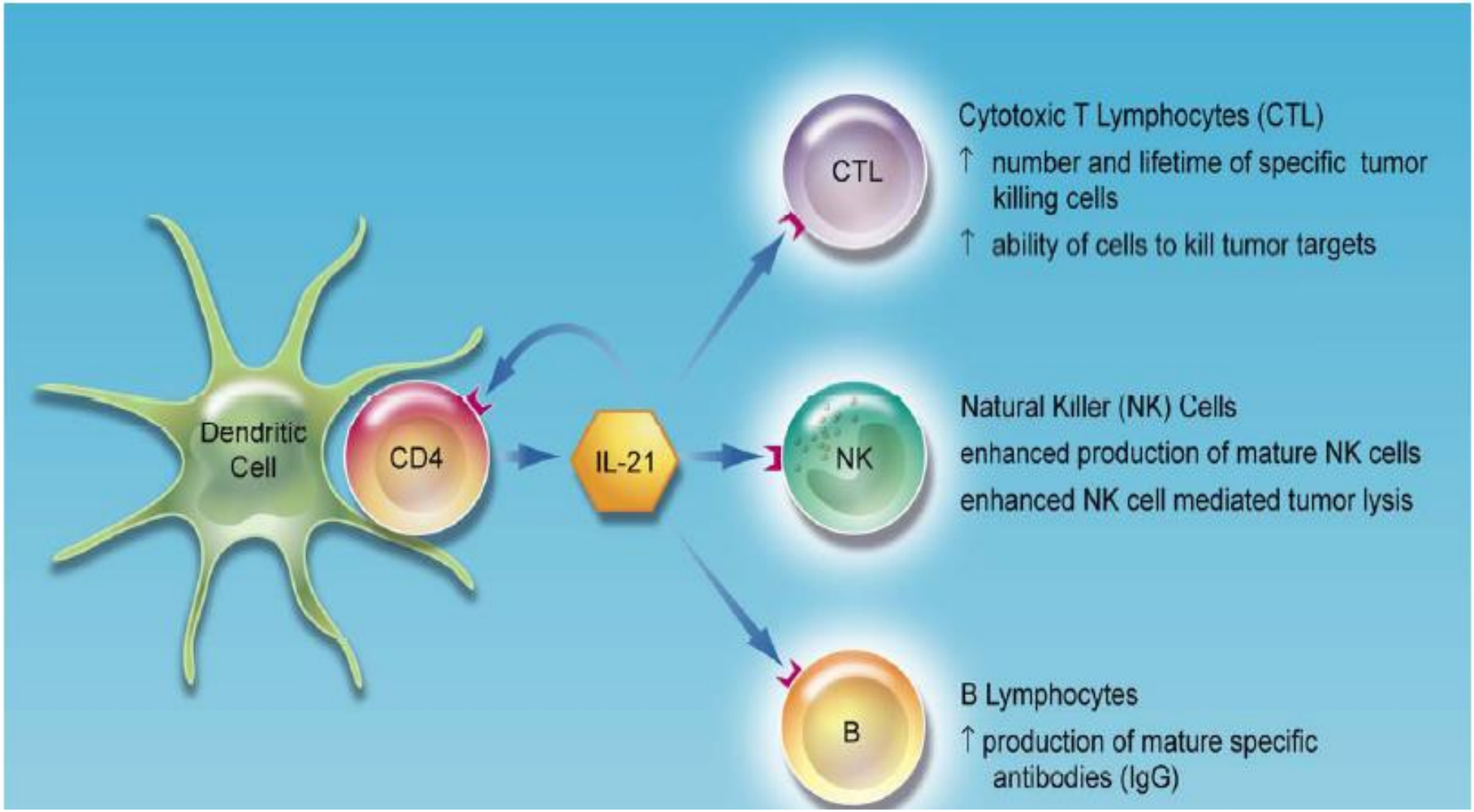
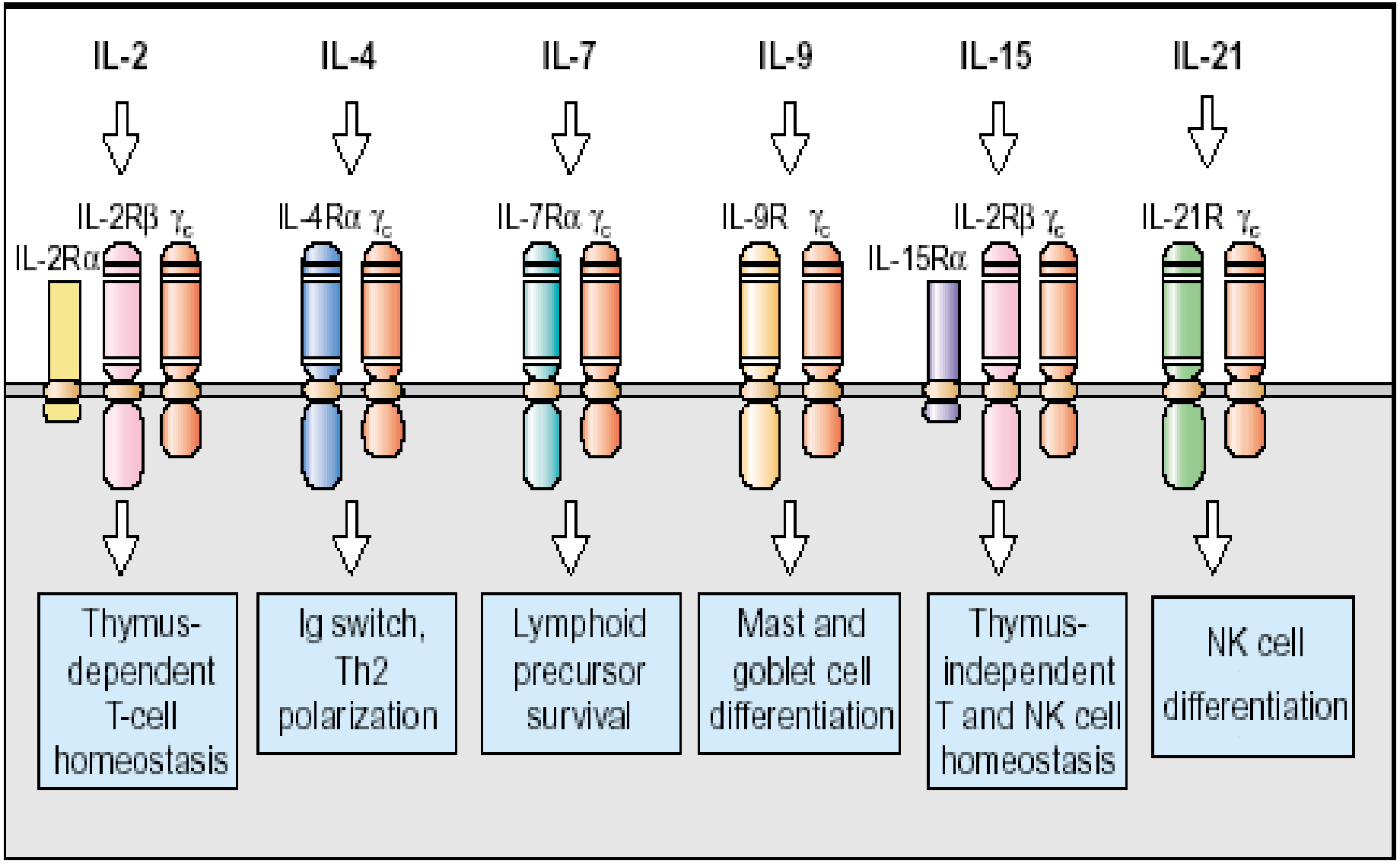


Figure 1

γc-dependent cytokines network



pawnking@sina.com

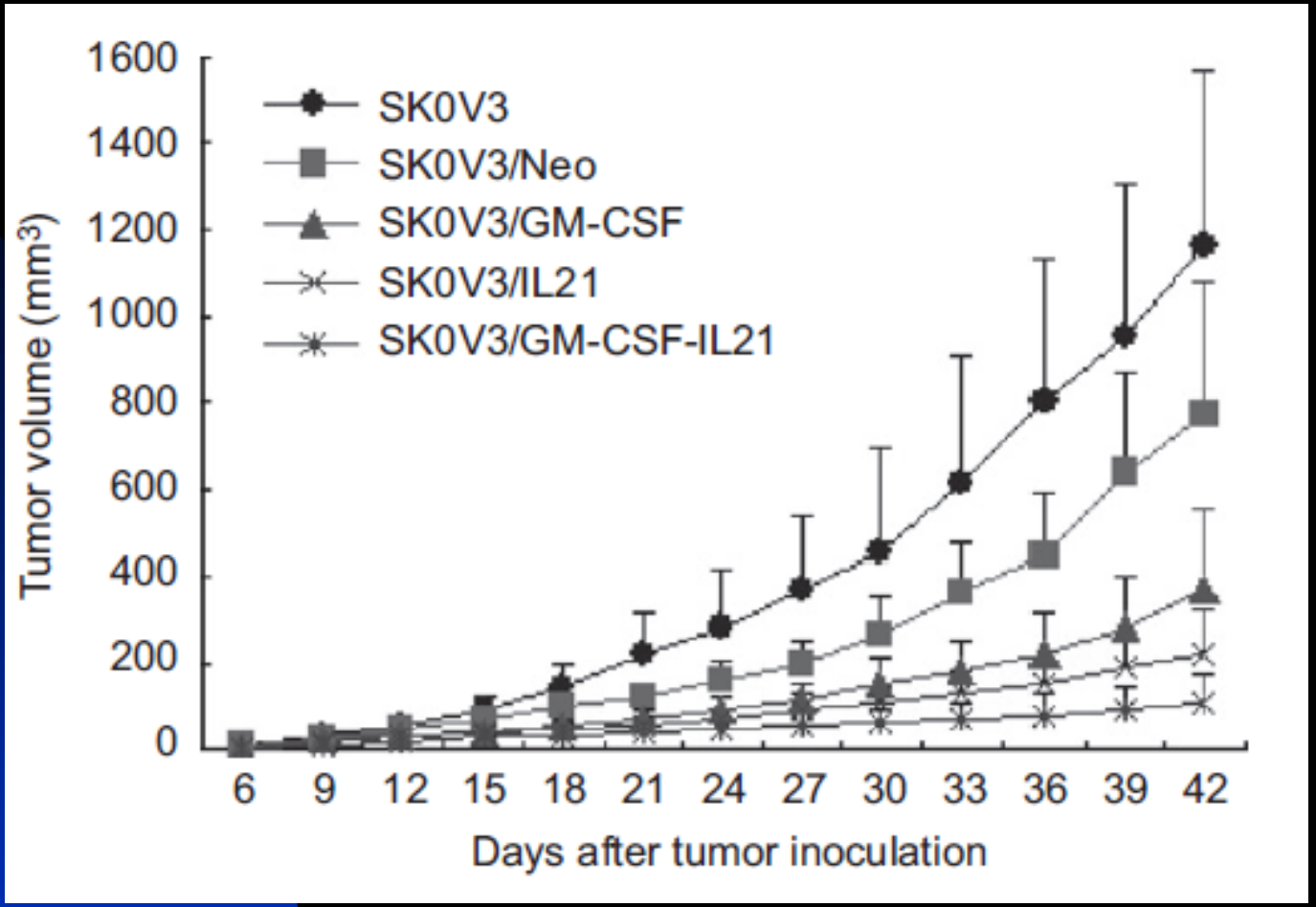
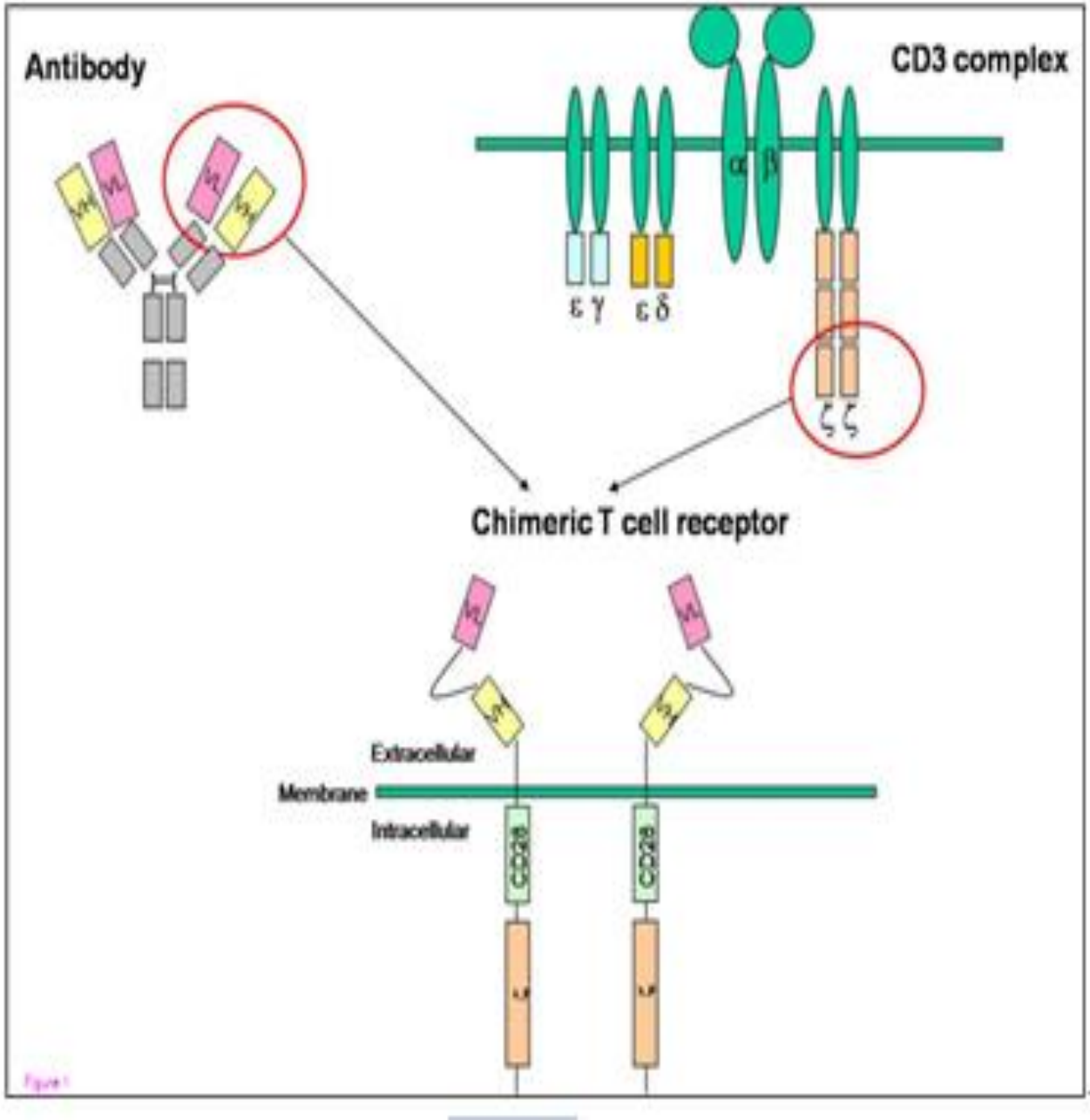


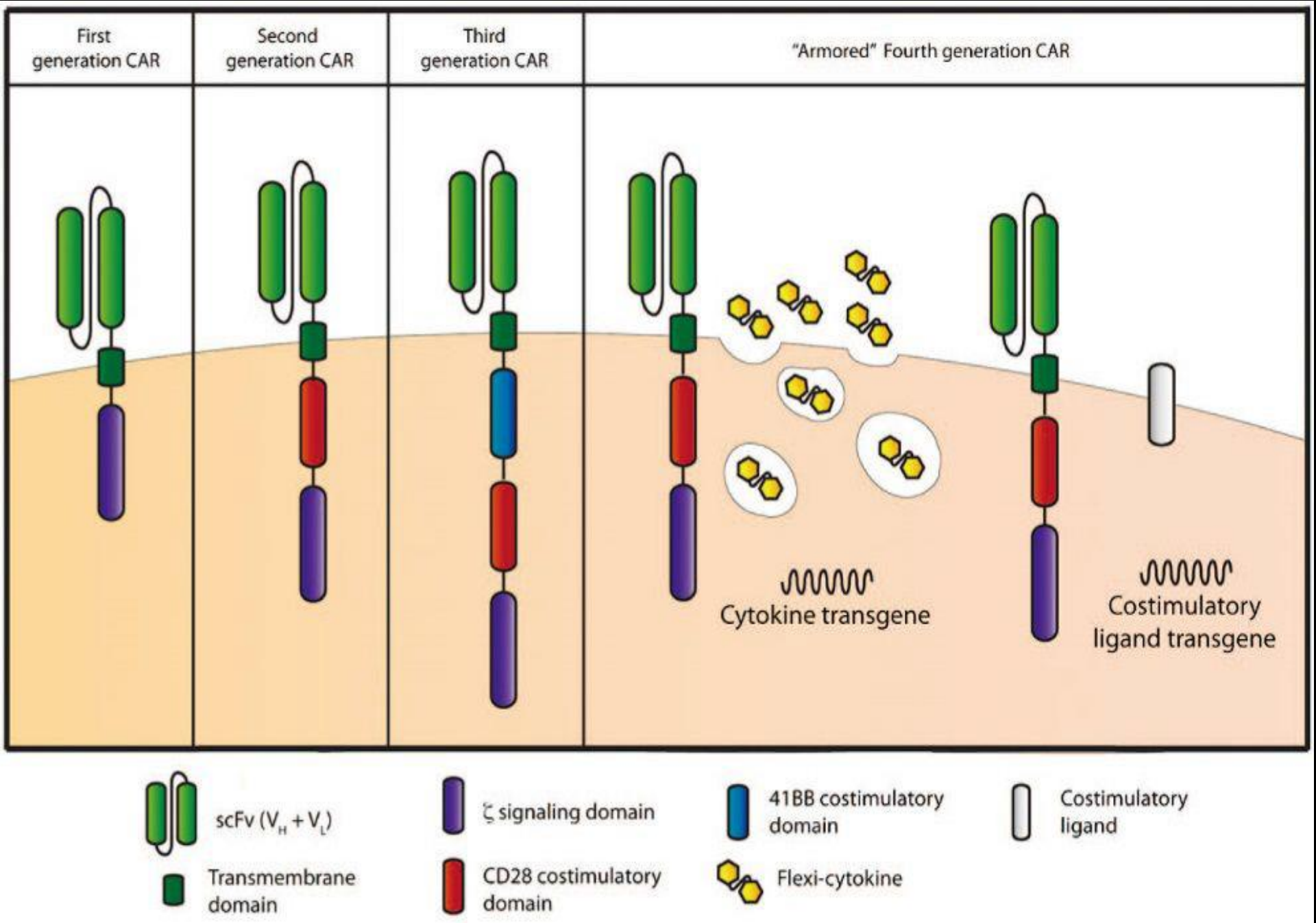
Fig. 4. Antitumor effect induced by the SKOV3 cells secreting IL-21 and GM-CSF cytokines in the null mice.

Jun D, Yongfang W, et al.
Immunobiology. 2009

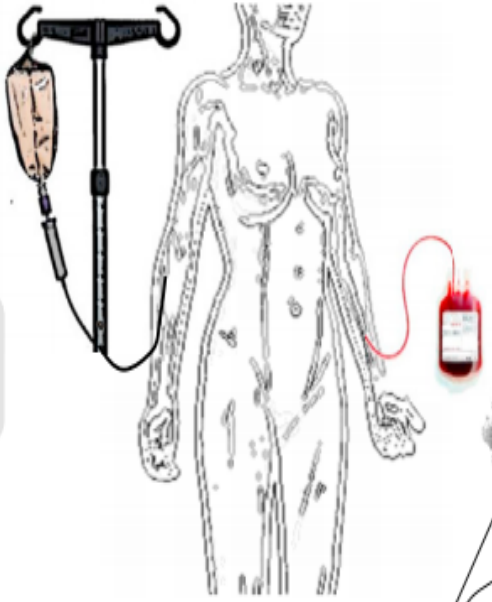
CAR-T(chimeric antigen receptor T cells)

CAR-T：将能识别某种肿瘤抗原的抗体的抗原结合部与CD3-ζ链或FcεRIγ的胞内部分在体外偶联为一个能表达嵌合蛋白基因，再转导进入患者的T细胞，使其表达**CAR**。患者的T细胞被“重编码”后，生成大量肿瘤特异性的**CAR-T**细胞。



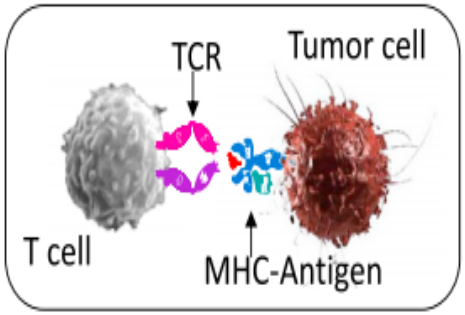

First generation CAR
Second generation CAR
Third generation CAR
"Armored" Fourth generation CAR
Cytokine transgene
Costimulatory ligand transgene
scFv ($V_H + V_L$)
Transmembrane domain
ζ signaling domain
CD28 costimulatory domain
41BB costimulatory domain
Flexi-cytokine
Costimulatory ligand

5. Close monitoring of tolerability, tumor kinetics and immune surveillance: rationale to combine with other therapies (e.g.: IMIDs or checkpoint inhibitors)



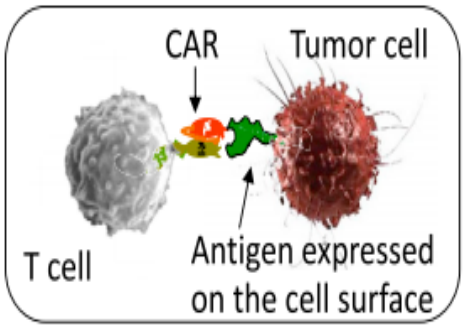
1. Isolation of T cells from blood

2. Gene modification of T cells to express CARs or TCRs with viral/non viral vectors



T cell receptor (TCR) α and β chains

3. Ex vivo T cell expansion



Chimeric Antigen receptor (CAR)

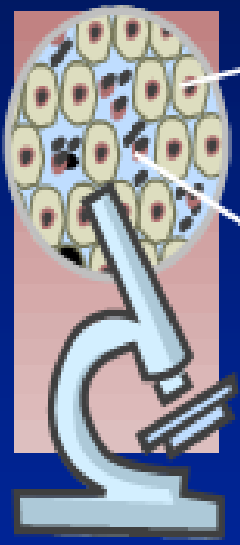
Fig 1. Gene Modification of Peripheral Blood Lymphocytes CAR T cells expressing on their surface a single-chain including the variable region of a monoclonal antibody (scFv) specific for a surface tumor antigen linked in tandem to the CD3z chain of the TCR complex and the endodomain of costimulatory molecules are not restricted by the HLA of the patient. Genetically modified TCR T cells express ab TCRs incorporated with an epitope that recognizes a tumor antigen. The therapeutic potential of TCR T cells depends on their affinity and avidity for the tumor derived T cell epitope. Several strategies have been developed to generate TCR with increased affinity for tumor antigens, most of them for HLA-A*0201 restriction (expressed in almost 50% of Caucasians). It is important to note that a TCR with supra-physiologic affinity might have an increased risk to damage normal tissues that physiologically express the same target antigen even at a negligible level (on-target toxicity) or cross-react with an unrelated protein (off-target toxicity)

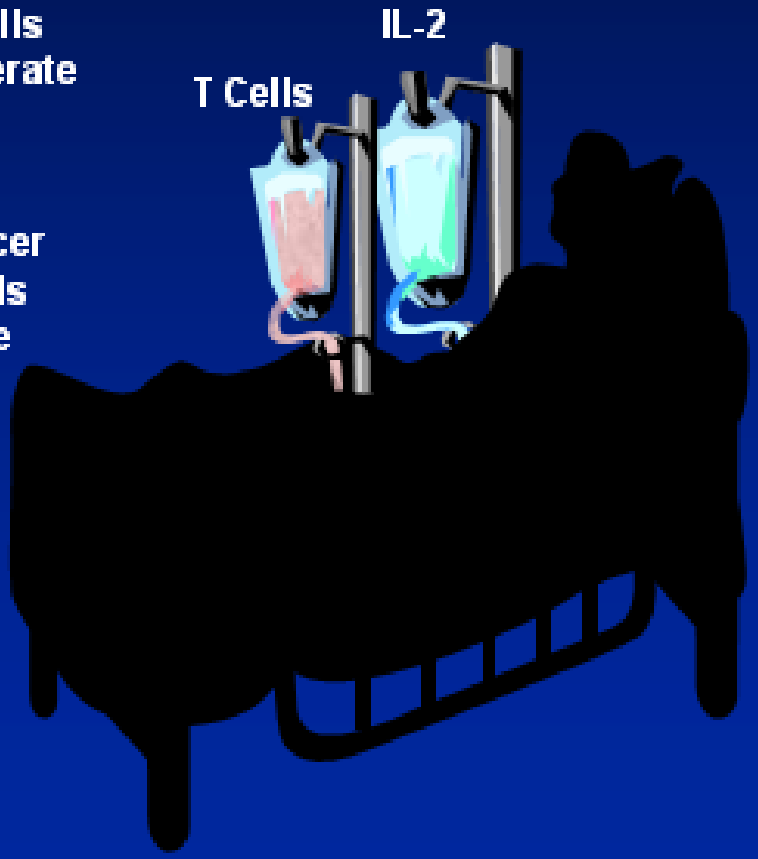
Jesus F. San Miguel,et al. Cancer Cell, 2015, 28: 281-283

Adoptive Cell Therapy (ACT) with Antigen Specific T-cells

Surgical Removal of Cancer Nodule

Single Cell Suspension Incubated with IL-2, anti-CD3





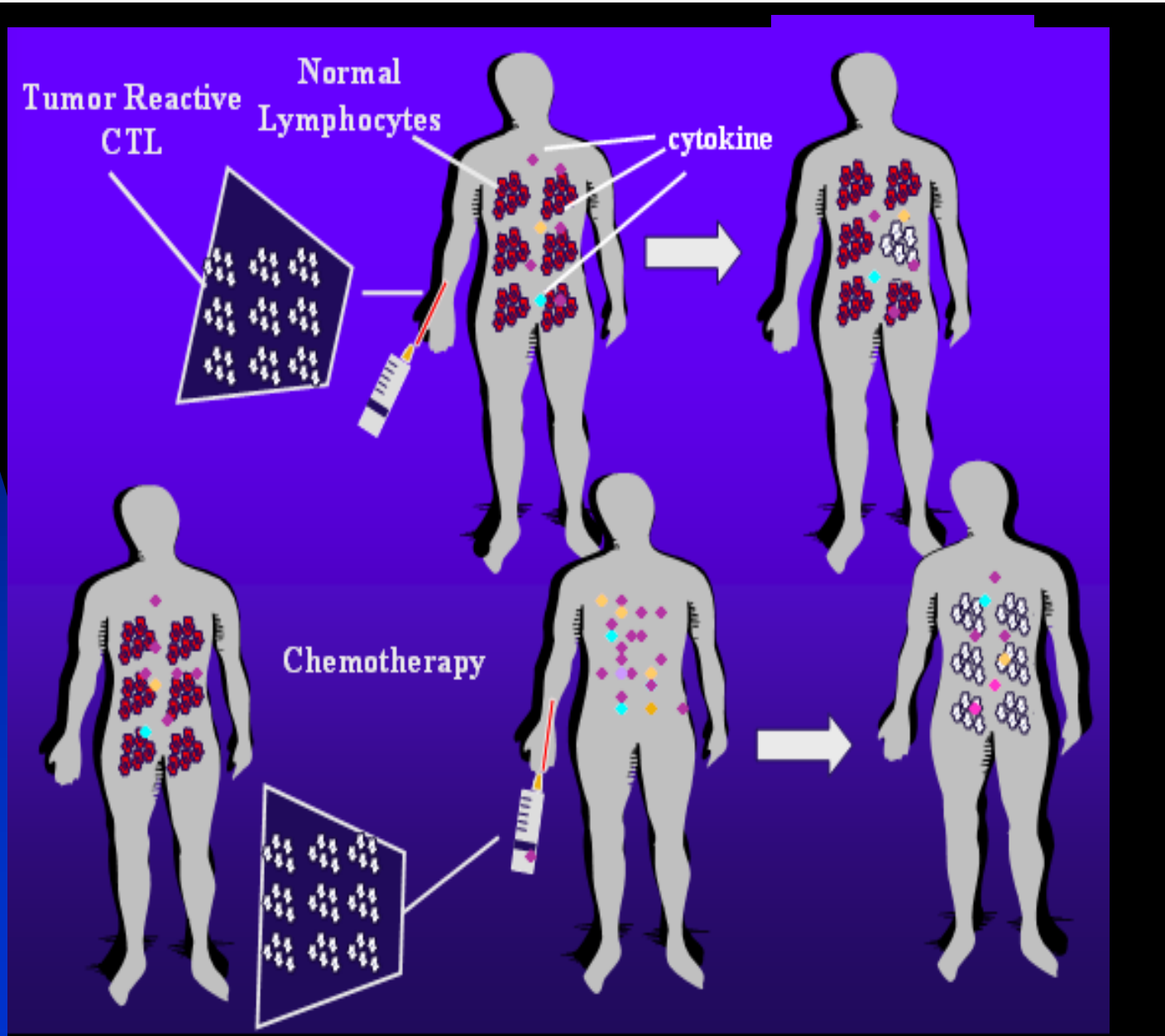
lymphopenia induced proliferation

Mechanism:

Make "Space"

"Cytokine sink"

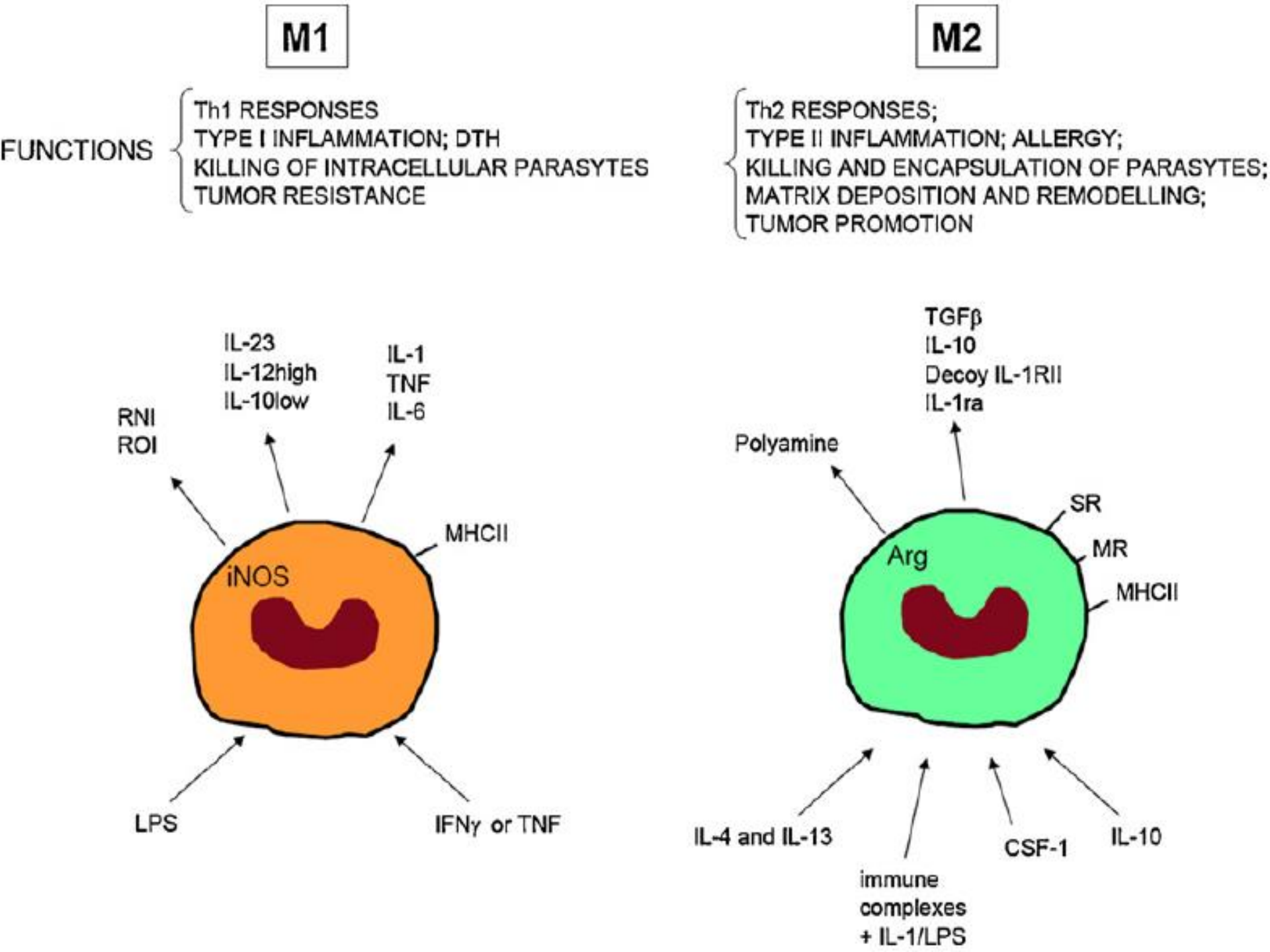
Eliminating Regulatory Cells

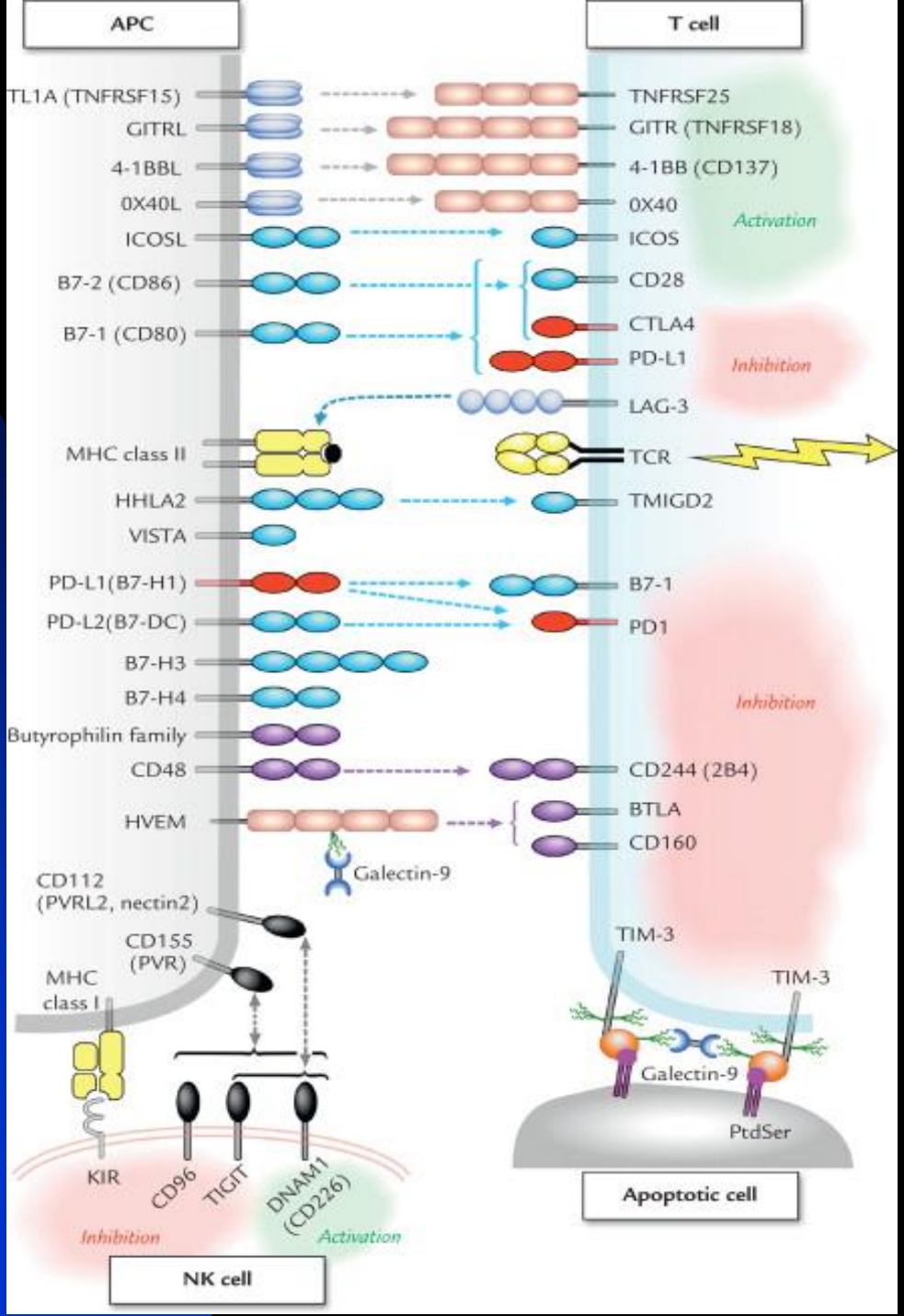


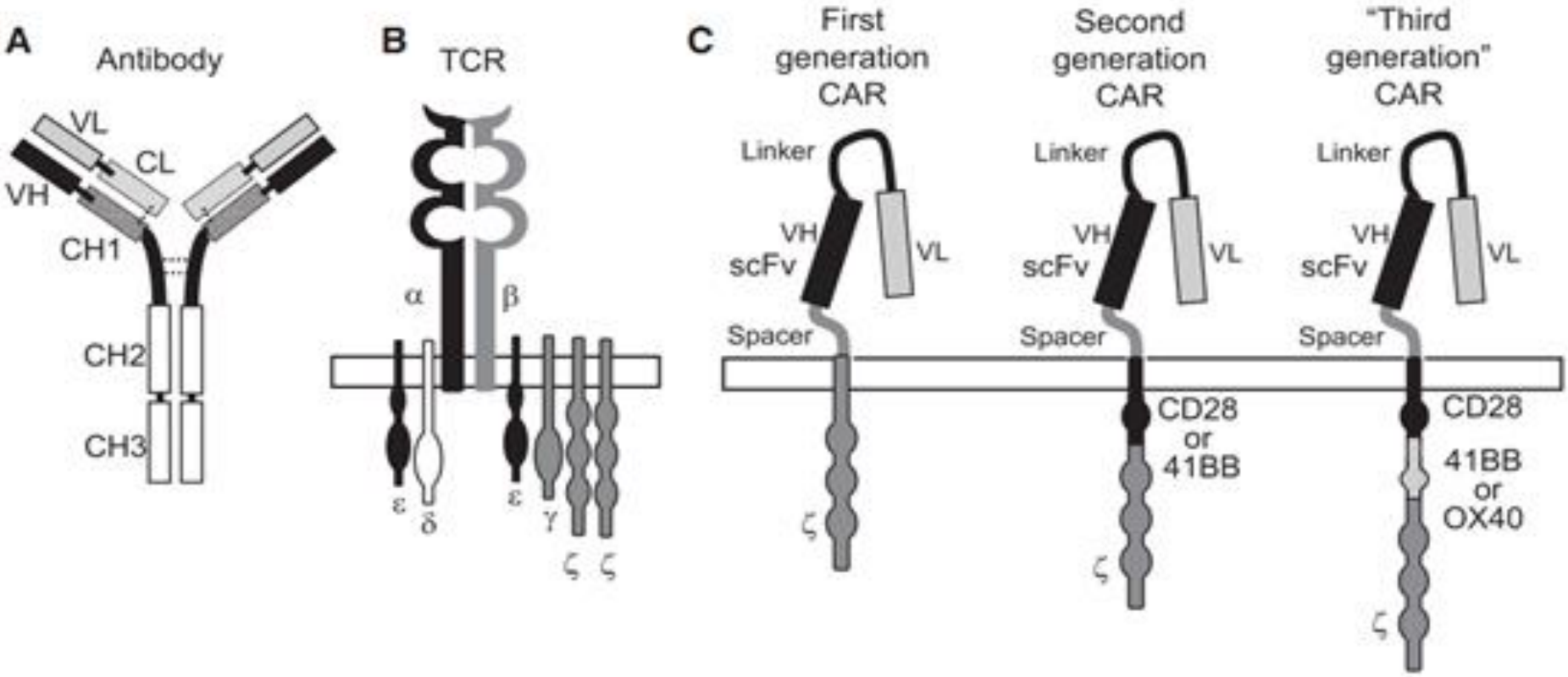
Summary

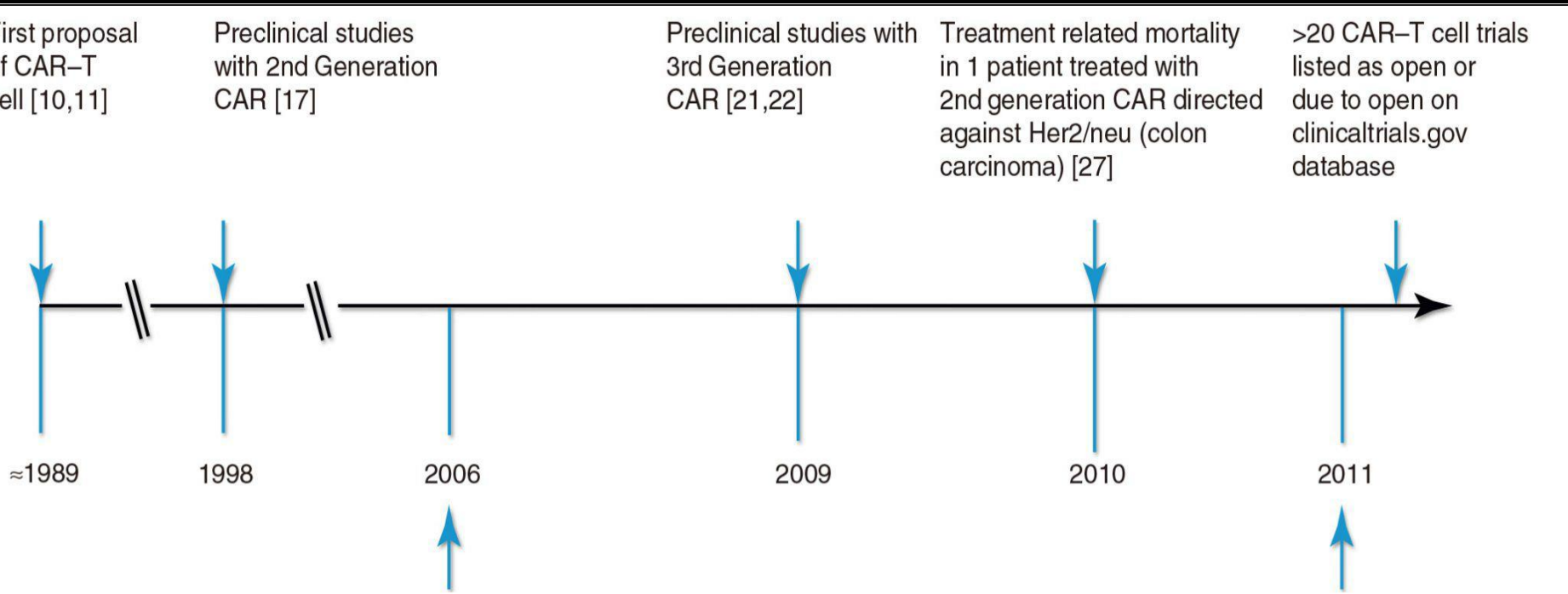
- 1. Cancer reflects failure of immune system.
- 2. There is a still a long way to go in cancer
- immunotherapy.

You may continue to further study the contains after the page.


M1
FUNCTIONS
Th1 RESPONSES
TYPE I INFLAMMATION; DTH
KILLING OF INTRACELLULAR PARASYTES
TUMOR RESISTANCE
M2
Th2 RESPONSES;
TYPE II INFLAMMATION; ALLERGY;
KILLING AND ENCAPSULATION OF PARASYTES;
MATRIX DEPOSITION AND REMODELLING;
TUMOR PROMOTION
IL-23
IL-12high
IL-10low
IL-1
TNF
IL-6
RNI
ROI
MHCII
iNOS
LPS
IFNγ or TNF
TGFβ
IL-10
Decoy IL-1RII
IL-1ra
Polyamine
SR
MR
MHCII
Arg
IL-4 and IL-13
immune
complexes
+ IL-1/LPS
CSF-1
IL-10


APC
T cell
TL1A (TNFRSF15)
TNFRSF25
GITRL
GITR (TNFRSF18)
4-1BBL
4-1BB (CD137)
0X40L
0X40
Activation
ICOSL
ICOS
B7-2 (CD86)
CD28
B7-1 (CD80)
CTLA4
PD-L1
Inhibition
LAG-3
MHC class II
TCR
HHLA2
TMIGD2
VISTA
PD-L1(B7-H1)
B7-1
PD-L2(B7-DC)
PD1
B7-H3
B7-H4
Inhibition
Butyrophilin family
CD48
CD244 (2B4)
HVEM
BTLA
CD160
Galectin-9
CD112
(PVRL2, nectin2)
CD155
(PVR)
TIM-3
MHC
class I
TIM-3
Galectin-9
PtdSer
KIR
CD96
TIGIT
DNAM1
(CD226)
Inhibition
Activation
Apoptotic cell
NK cell


A
Antibody
VL
CL
VH
CH1
CH2
CH3
B
TCR
α
β
ε
δ
ε
γ
ζ ζ
C
First generation CAR
Second generation CAR
"Third generation" CAR
Linker
VH
scFv
VL
Spacer
CD28
or
41BB
41BB
or
OX40
ζ



TRENDS in Molecular Medicine

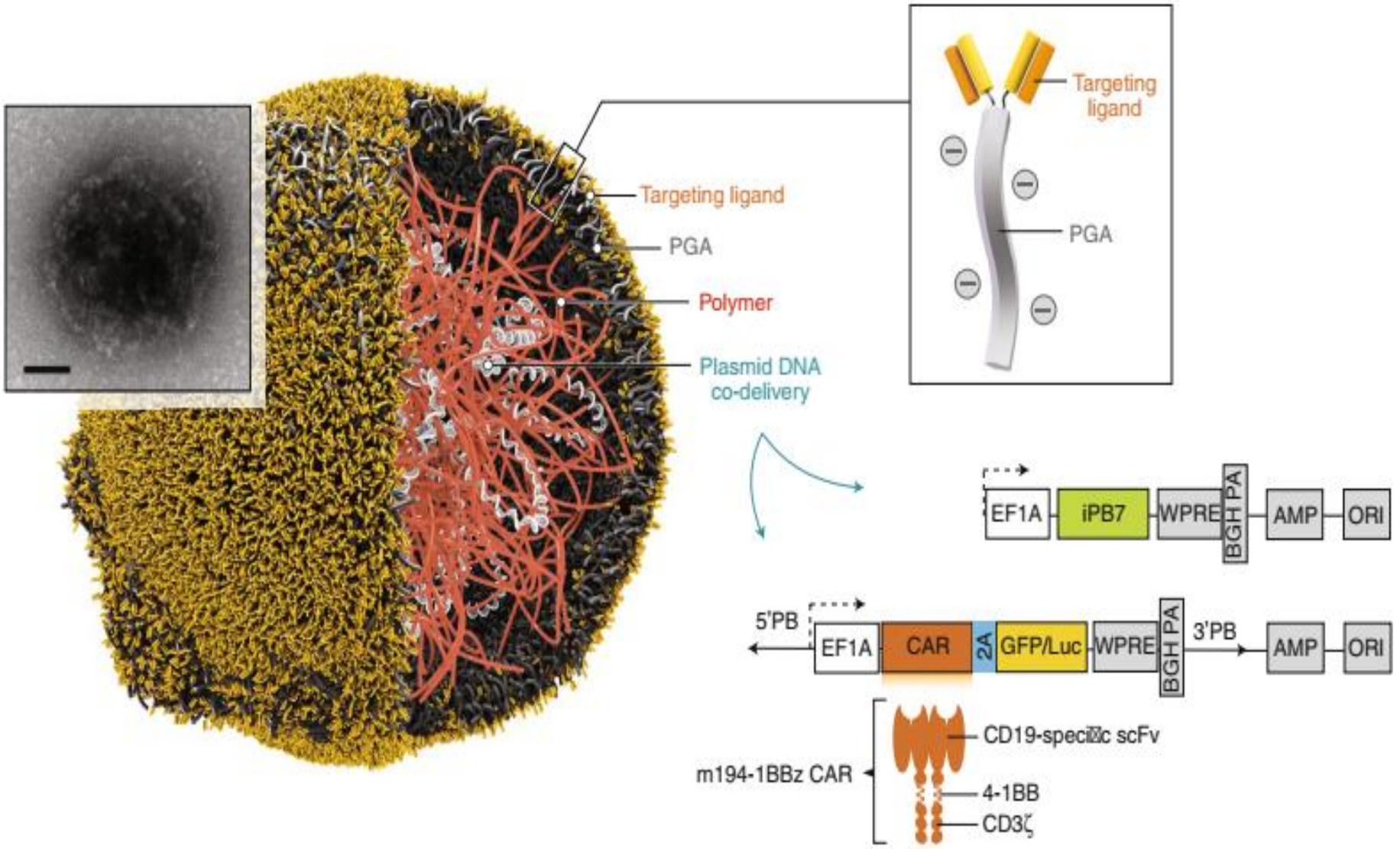
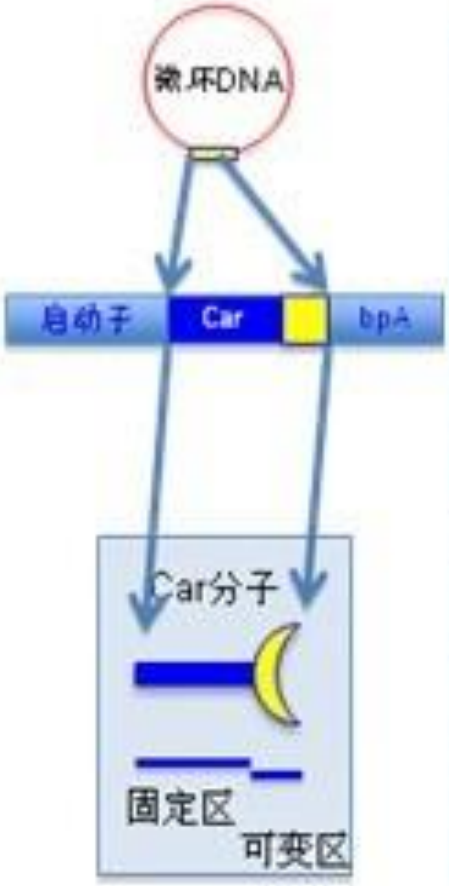
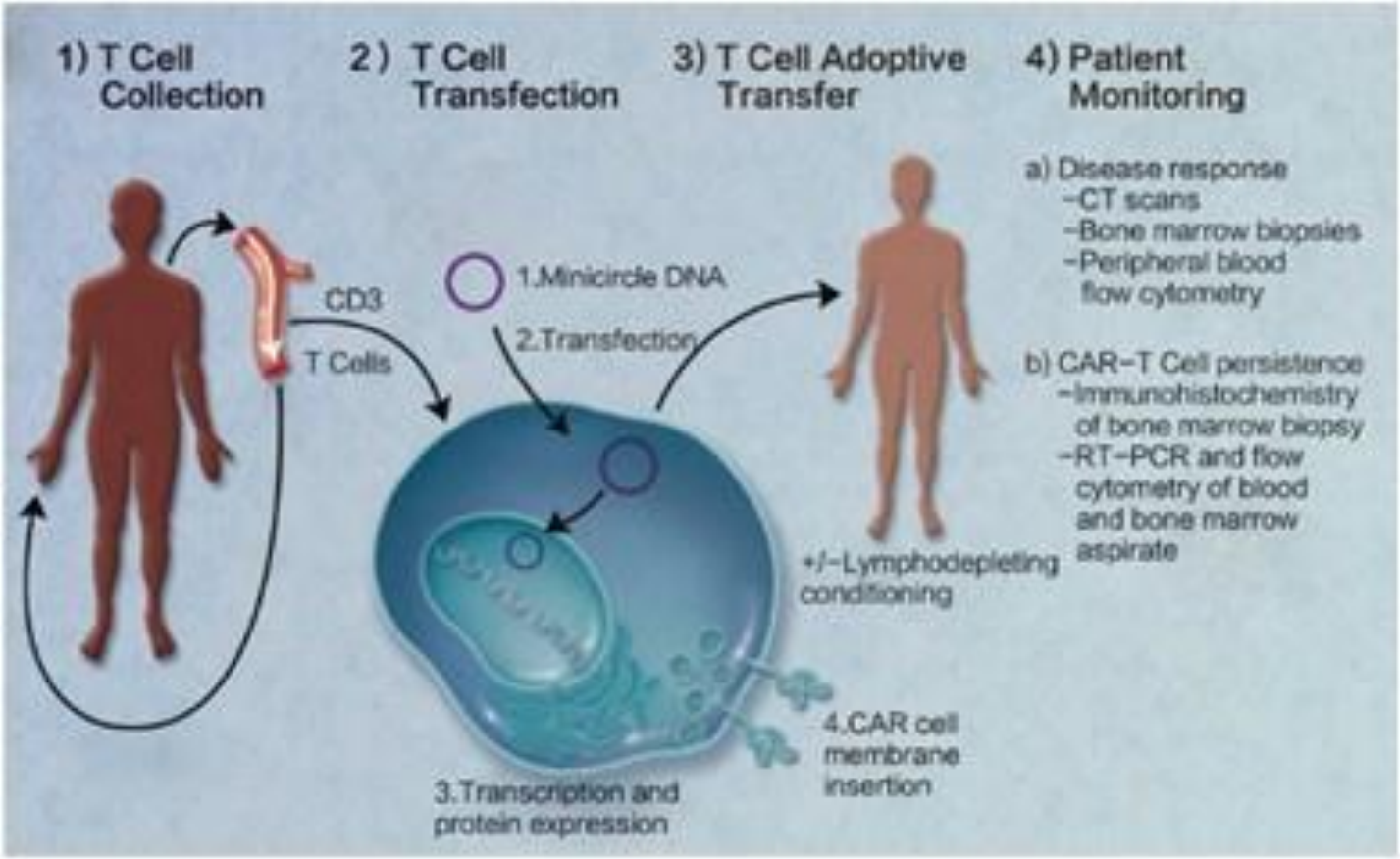


Fig. 5 | Targeted delivery of CAR genes to peripheral T lymphocytes in situ. Plasmid DNA encoding a CAR, a microtubule-associated sequence, a nuclear-localization signal peptide and poly(beta-amino ester) polymer make up the scaffold of the nanoparticle, which is covered with PGA-tailed anti-CD3ζ f(ab')2 via electrostatic interactions. The two plasmids encode an all-murine 194-1BBz CAR and the hyperactive iPB7 transposase. Scale bar, 100 nm. EF1A, eukaryotic translation elongation factor 1 alpha 1; BGH PA, bovine growth hormone polyadenylation signal; AMP, ampicillin resistance gene; ORI, origin of replication. Figure reproduced from ref. [113], Springer Nature Ltd.





左：微环 DNA 示意图

右：CAR-T 细胞治疗流程

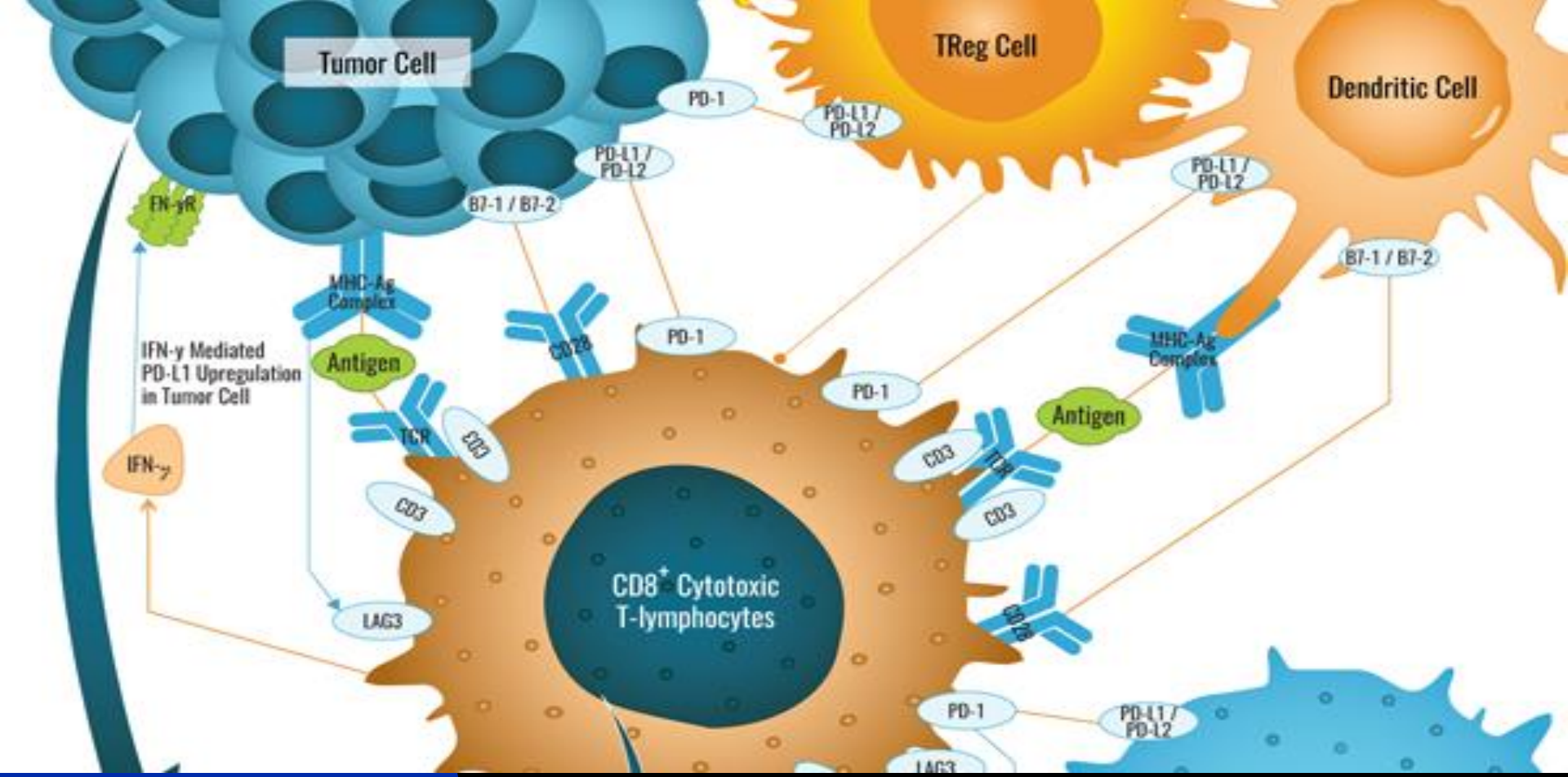
基于微环**DNA(MC)**技术的**MC-CAR-T**细胞治疗技术。微环**DNA**是世界上最好的基因载体，与现有的基于病毒载体的技术相比，具有转染率高、基因表达持久的优点、同时具有非病毒载体毒性低、免疫反应低，携带基因不整合至宿主细胞基因组等优点。

nature medicine

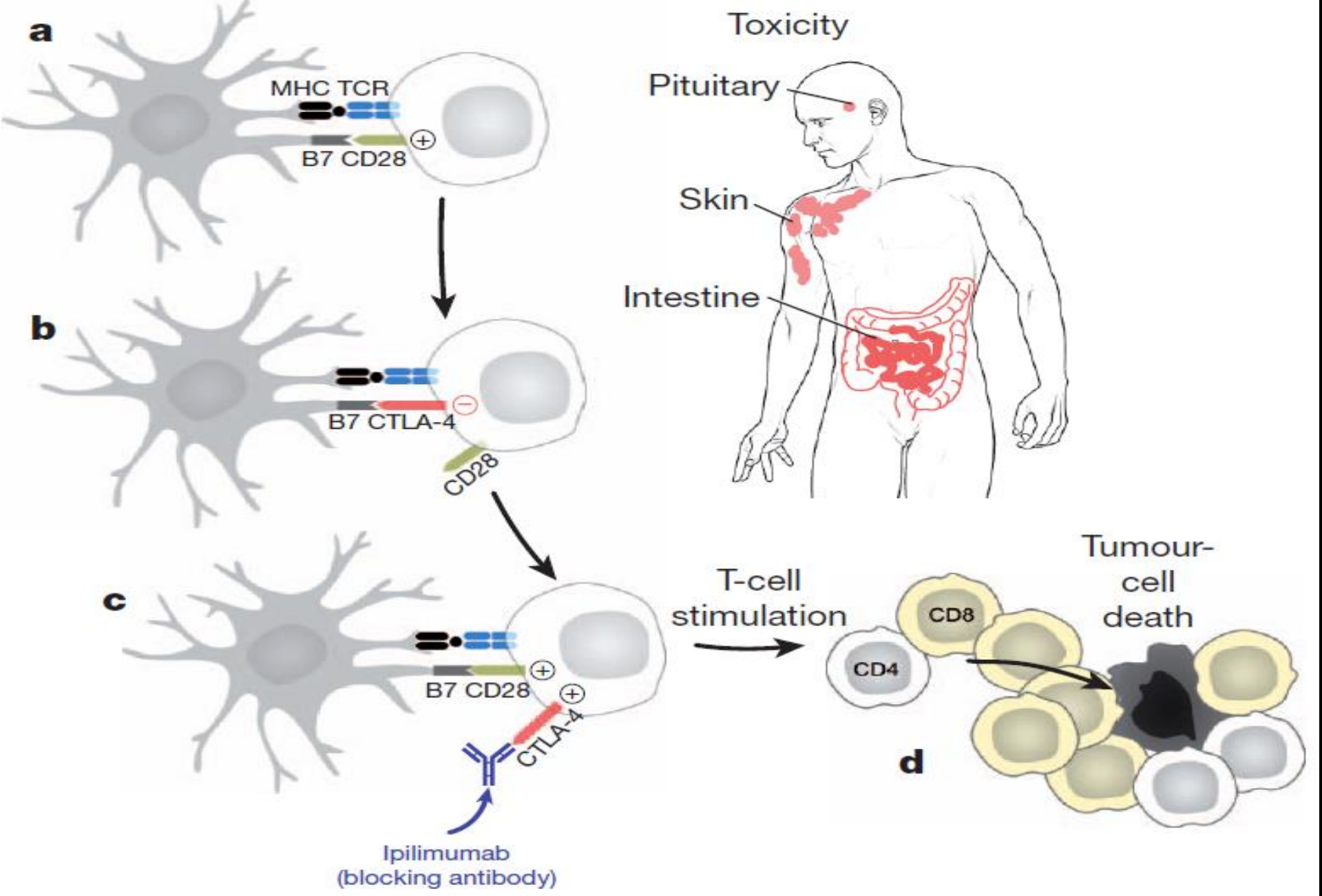
BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-018-0201-9

Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell



PD-1/PD-L1 Pathway in Cancer: In normal conditions, mutated antigens from tumor cells will lead to the activation of T cells that bind to and trigger apoptosis in target cancer cells. On the surface of T cells are PD-1 (programmed cell death-1) receptors whose ligands include PD-L1 and PD-L2. Together, PD-1 and PD-L1/PD-L2 are involved with inhibiting T cell response so that the immune response is only initiated when necessary, avoiding chronic autoimmune inflammation. However, tumor cells have utilized the PD-1/PD-L1 pathway to resist anticancer immune responses by producing abnormally high levels of PD-L1. When the PD-L1 ligands bind to the PD-1 receptors on T cells, the T cells become deactivated and anti-tumor activity is obstructed.



Ira Mellman et al. Nature 2011

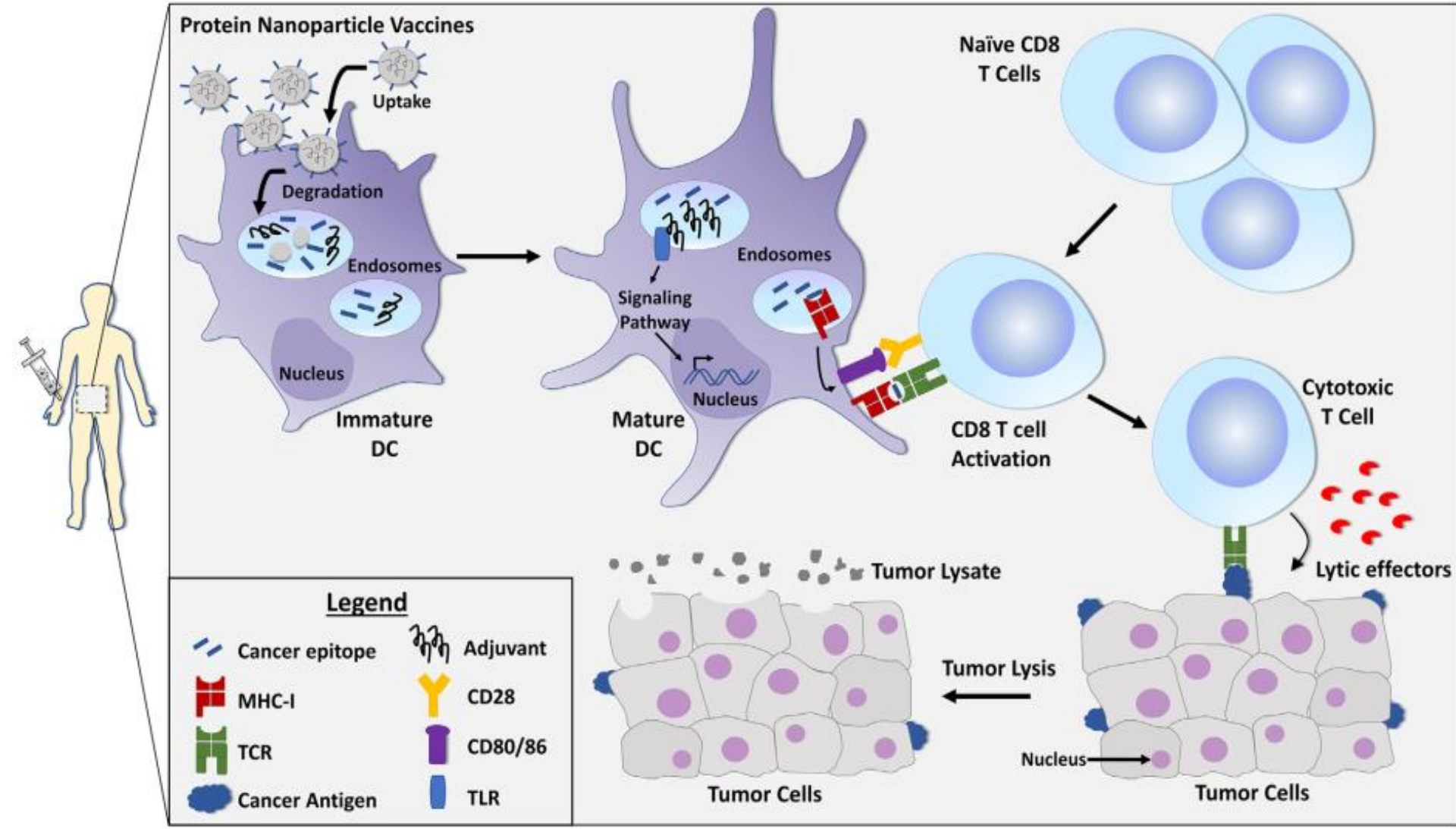
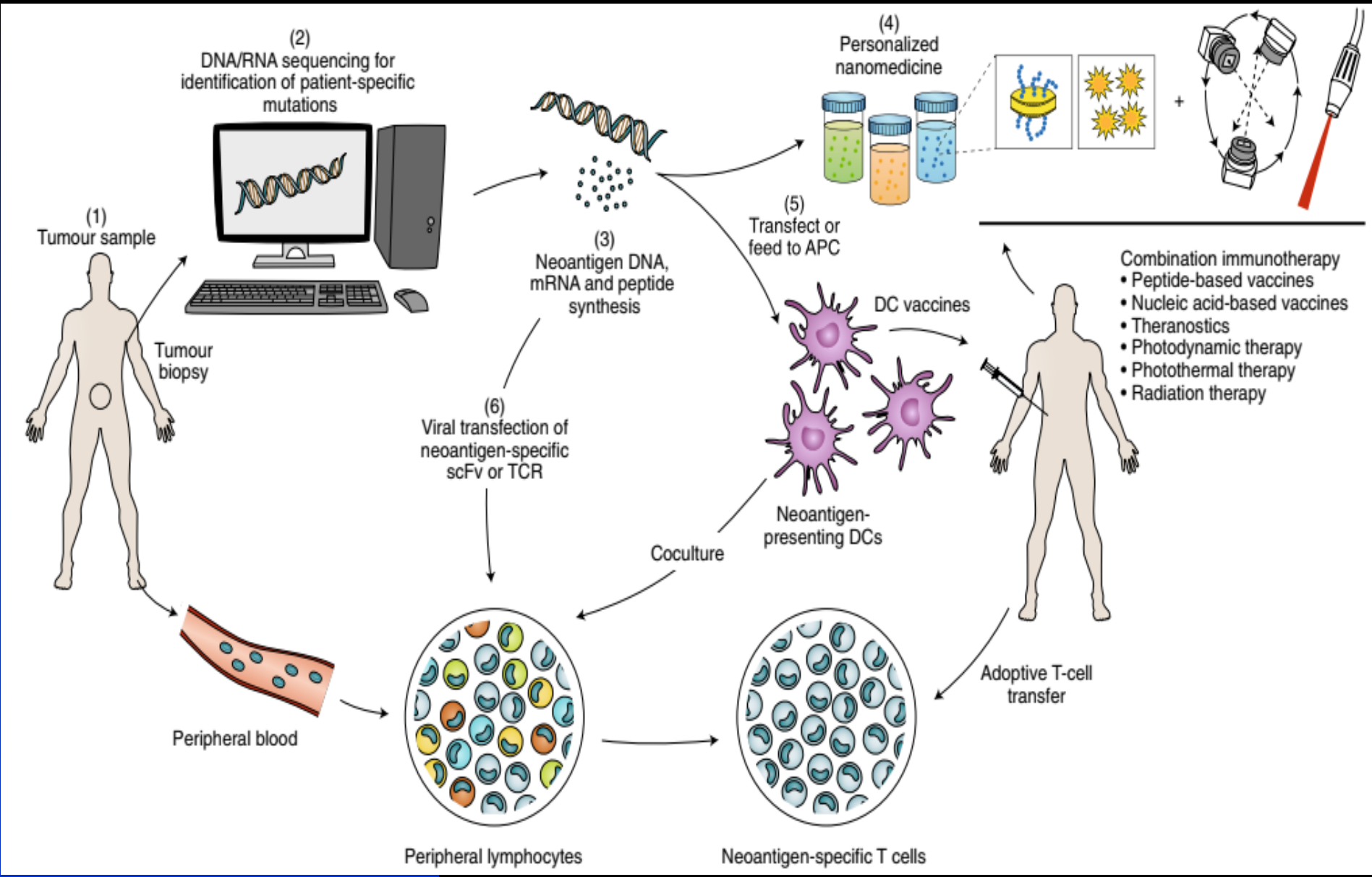


Figure 1. Common mechanism of tumor cell elimination. Protein nanoparticle (NP) cancer vaccines that are injected can accumulate in the LNs and spleen. Immature DCs residing in these tissues internalize and degrade the NPs and process the associated antigens and adjuvants for potential danger signals. If DCs are activated through an adjuvant-TLR interaction, they present the antigens to the T cells in the context of MHC-I molecules for specific and longer-term T cell responses (cross-presentation). Upon T cell activation and recognition of tumor-associated antigens on cancer cells, T cells secrete lytic effectors (such as perforin), leading to tumor lysis and elimination. Abbreviations in the figure include: MHC-I (major histocompatibility complex, class I), TCR (T-cell receptor), CD28 (cluster of differentiation 28, costimulatory molecule), CD80/86 (cluster of differentiation 80/86, costimulatory molecules), TLR (Toll-like receptor).

Neek M, et al Nanomedicine. 2019

Engineering approaches for personalized immunotherapy



Scheetz L, et al. Nat Biomed Eng 2019

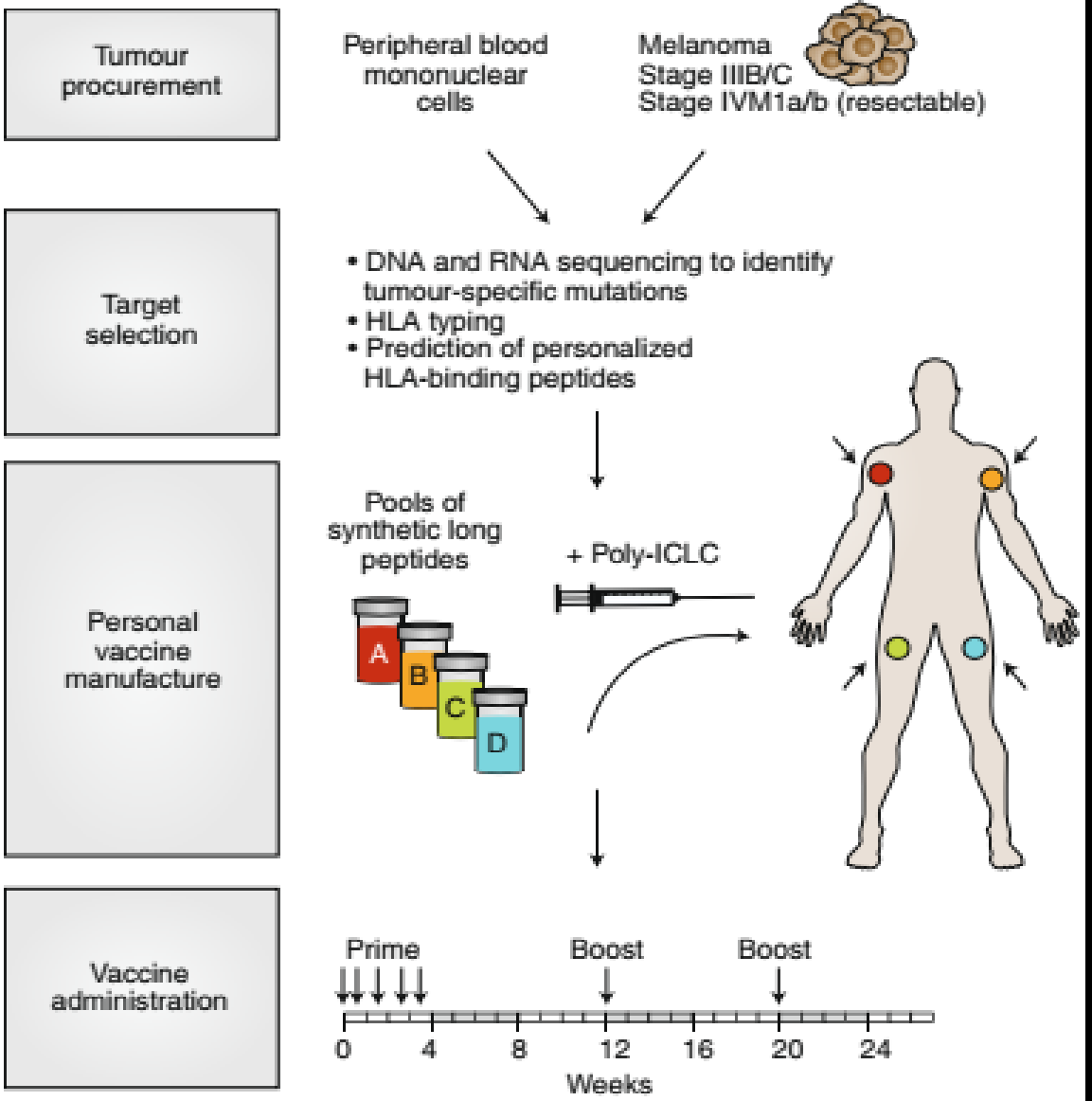
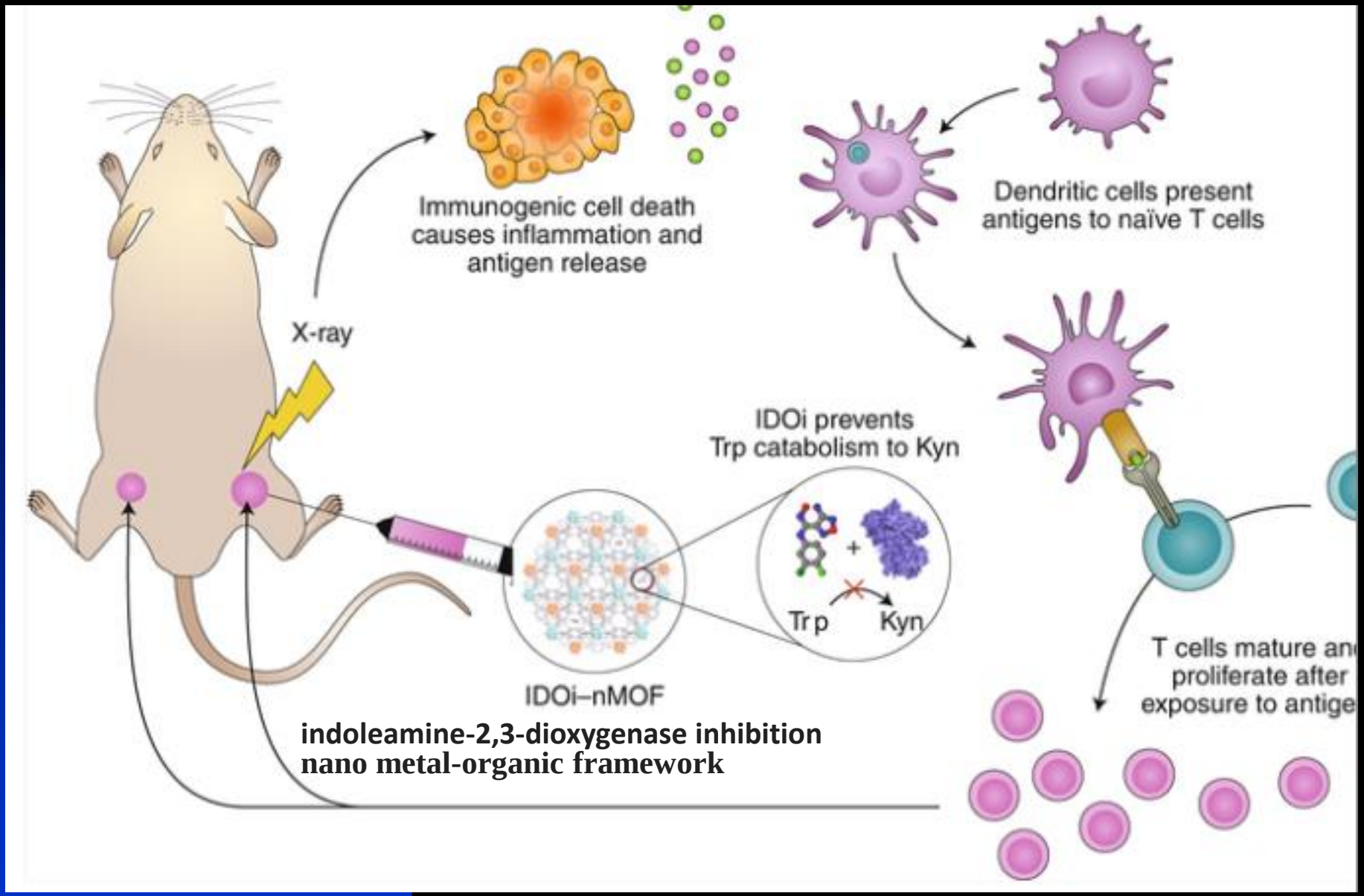


Fig. 2 | Preparation process for a personalized vaccine. Matched tumour-cell and normal-cell DNA from peripheral blood mononuclear cells and resected tumours are compared by whole-exome sequencing to detect mutations. Candidate neoantigen peptides are selected, synthesized and used for therapeutic vaccination in corresponding patients with poly-ICLC adjuvant. HLA, human leukocyte antigen. Figure reproduced from ref. [27], Springer Nature Ltd.

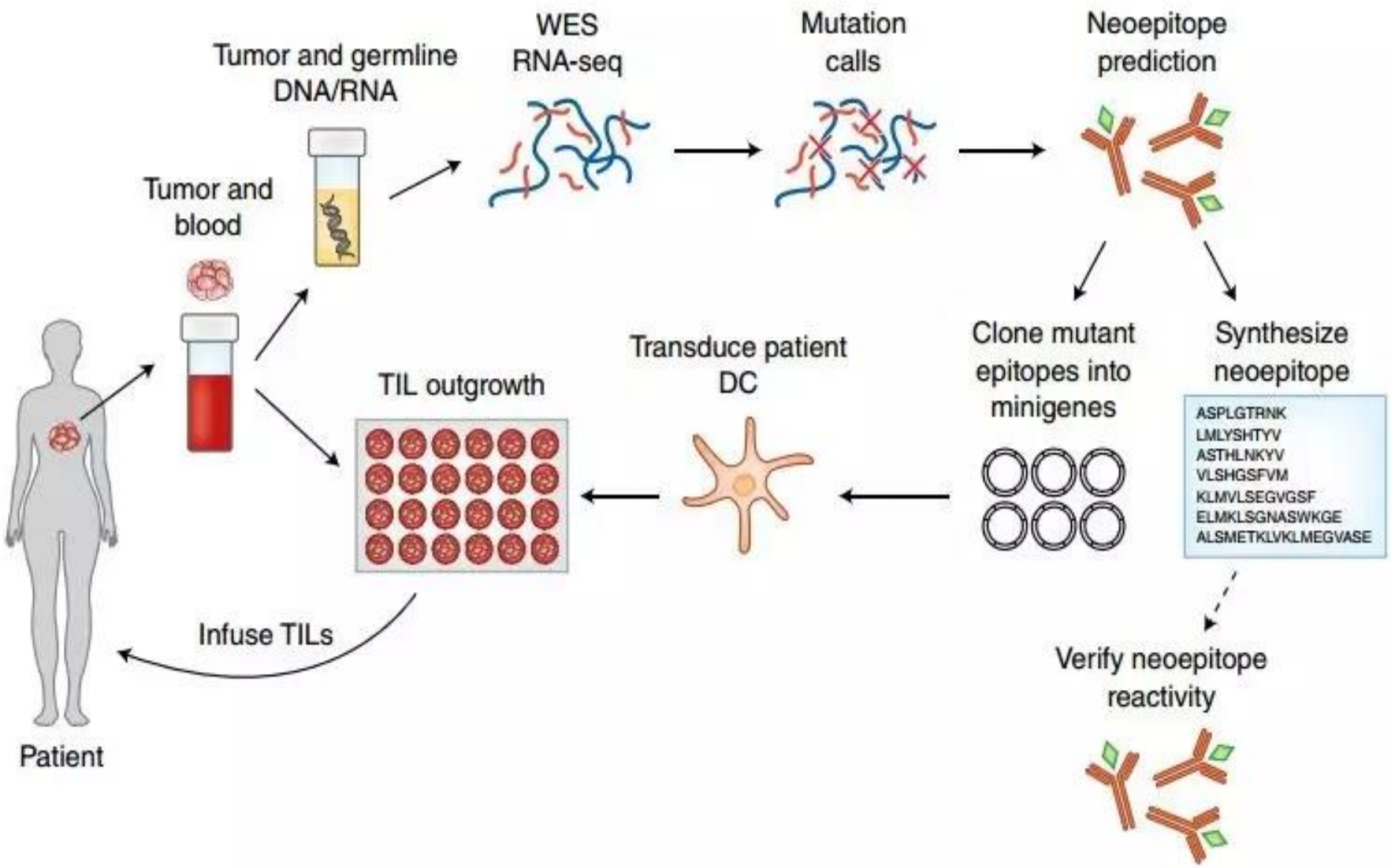
Poly-ICLC: poly-L-lysine and carboxymethyl cellulose

Scheetz L, et al.
Nat Biomed Eng 2019



Trp:tyrosinase-related protein

Scheetz L, et al. Nat Biomed Eng 2019


Tumor and germline DNA/RNA
WES RNA-seq
Mutation calls
Neoepitope prediction
Tumor and blood
Clone mutant epitopes into minigenes
Synthesize neoepitope
ASPLGTRNK
LMLYSHTYV
ASTHLNKYV
VLSHGSFVM
KLMVLSEGVGSF
ELMKLSGNASWKGE
ALSMETKLVKLMEGVASE
Transduce patient DC
TIL outgrowth
Infuse TILs
Verify neoepitope reactivity
Patient

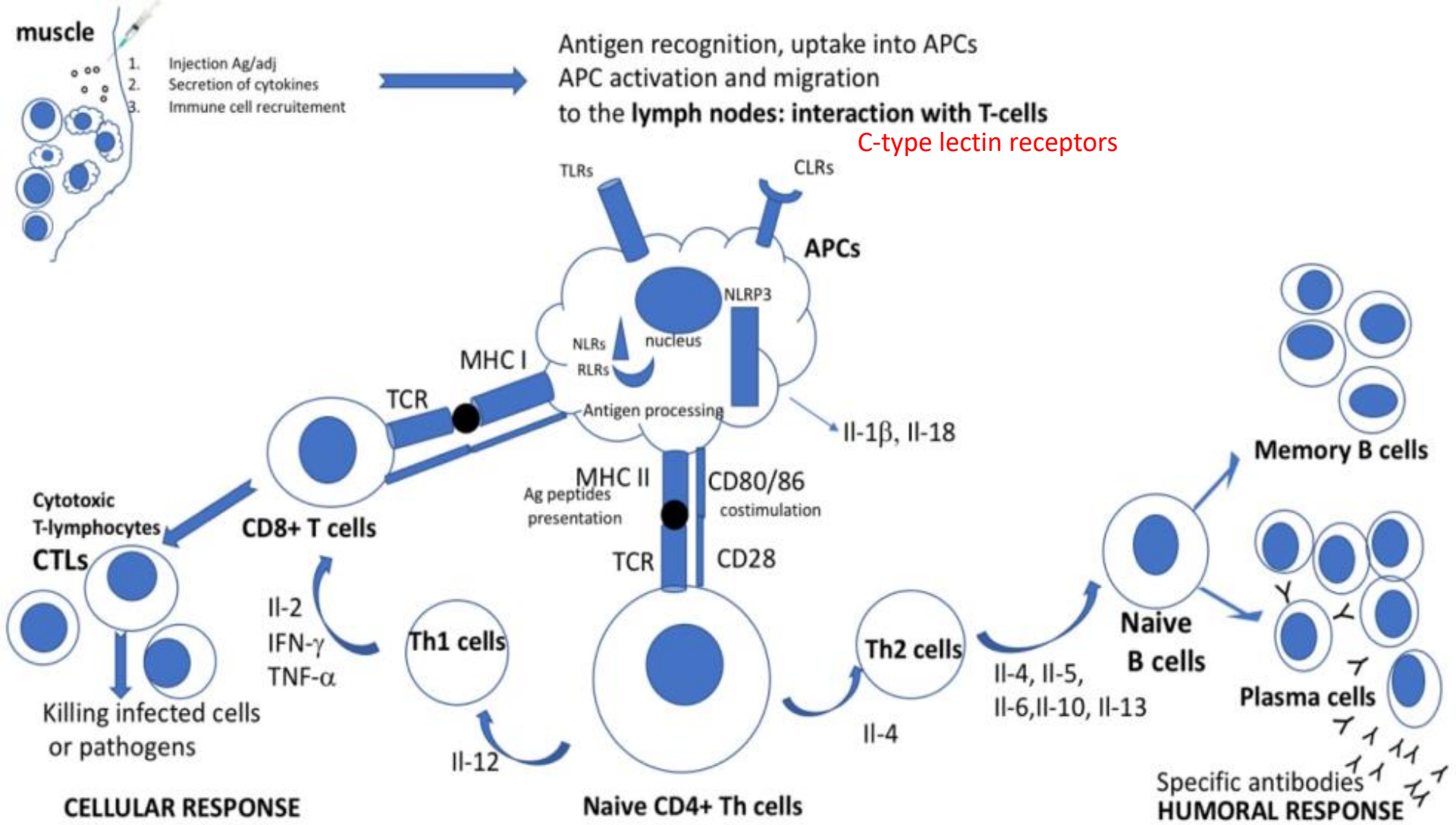
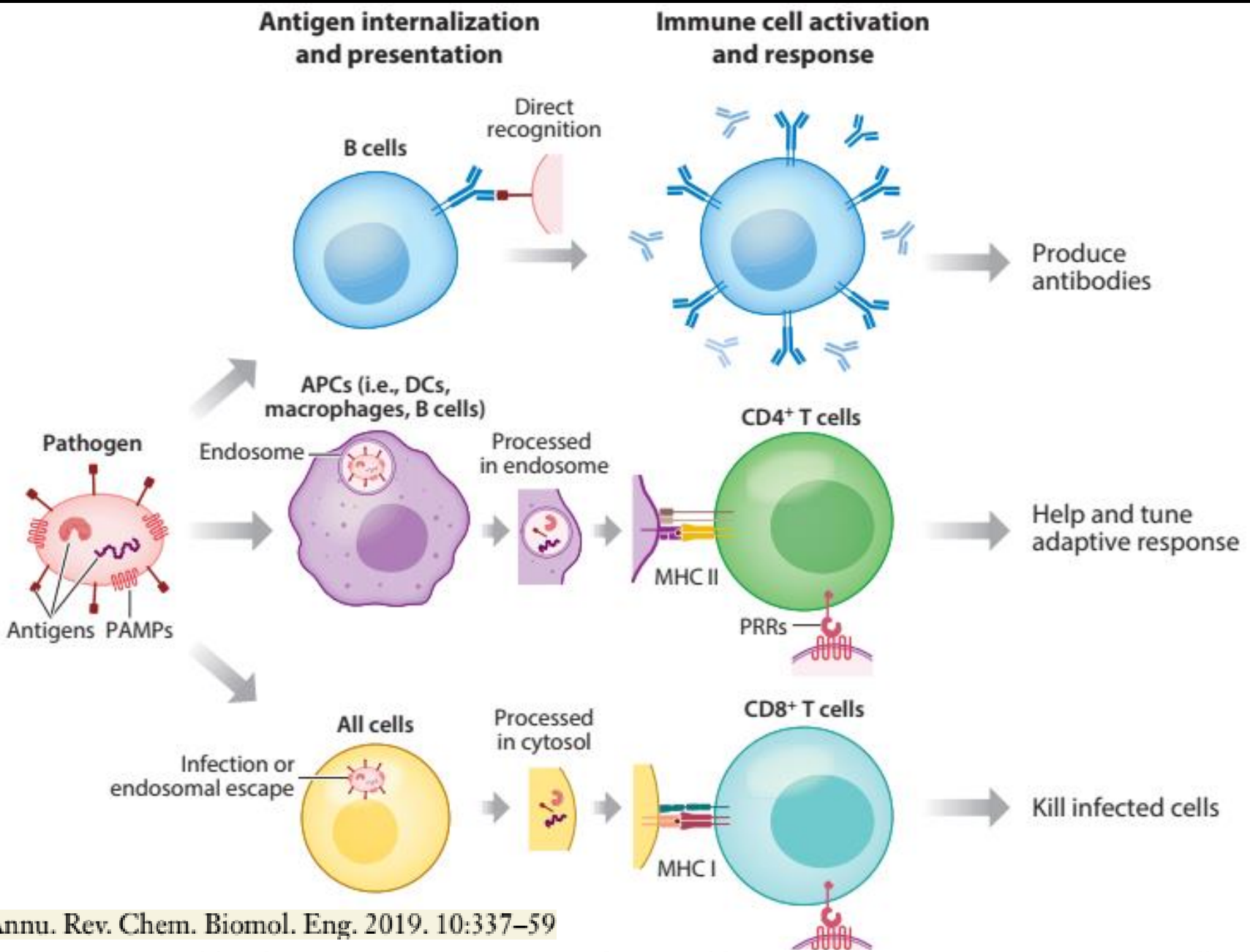


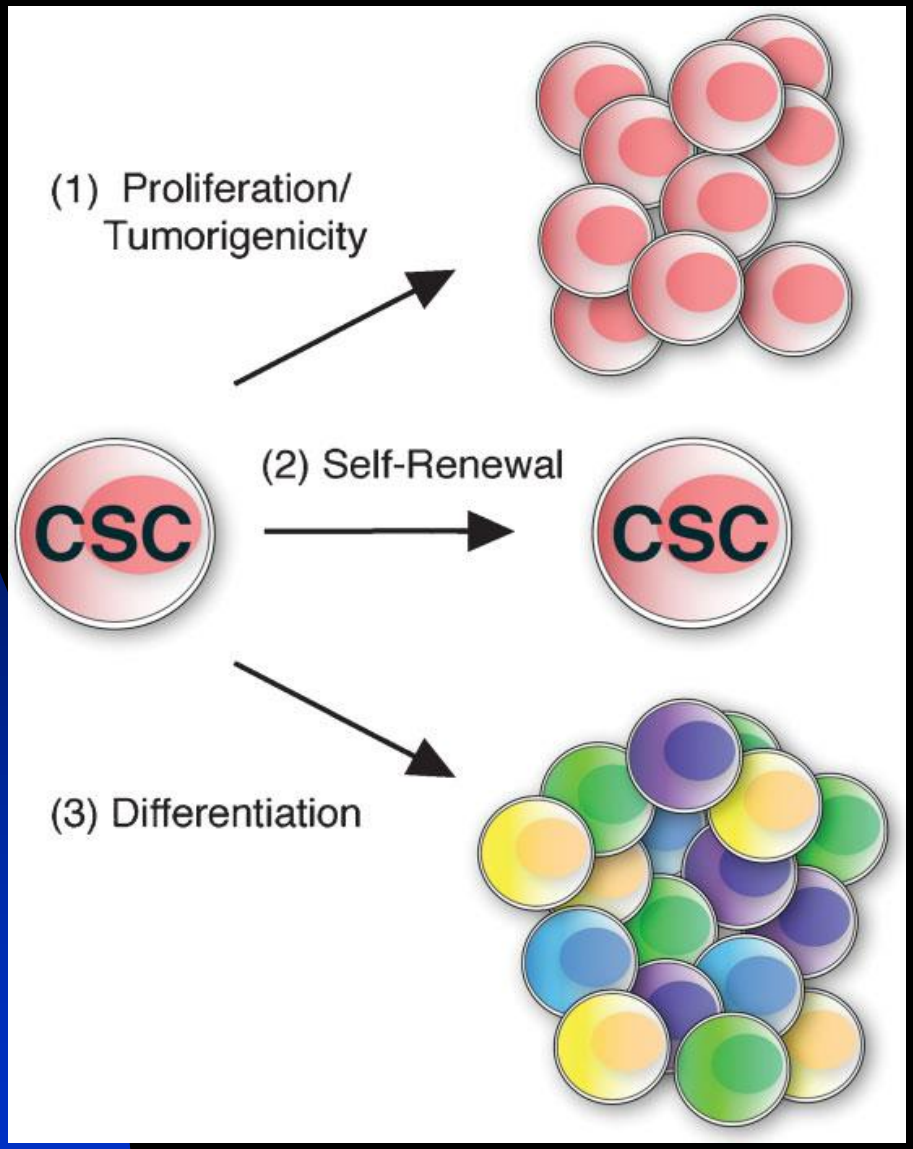
Fig. 1. Schematic representation of the mechanism of action of an adjuvanted vaccine (adapted from Awate et al., 2013; Reed et al., 2013; Lacaille-Dubois and Wagner, 2017).

Marie-Aleth Lacaille-Dubois, Phytomedicine, https://doi.org/10.1016/j.phymed.2019.152905



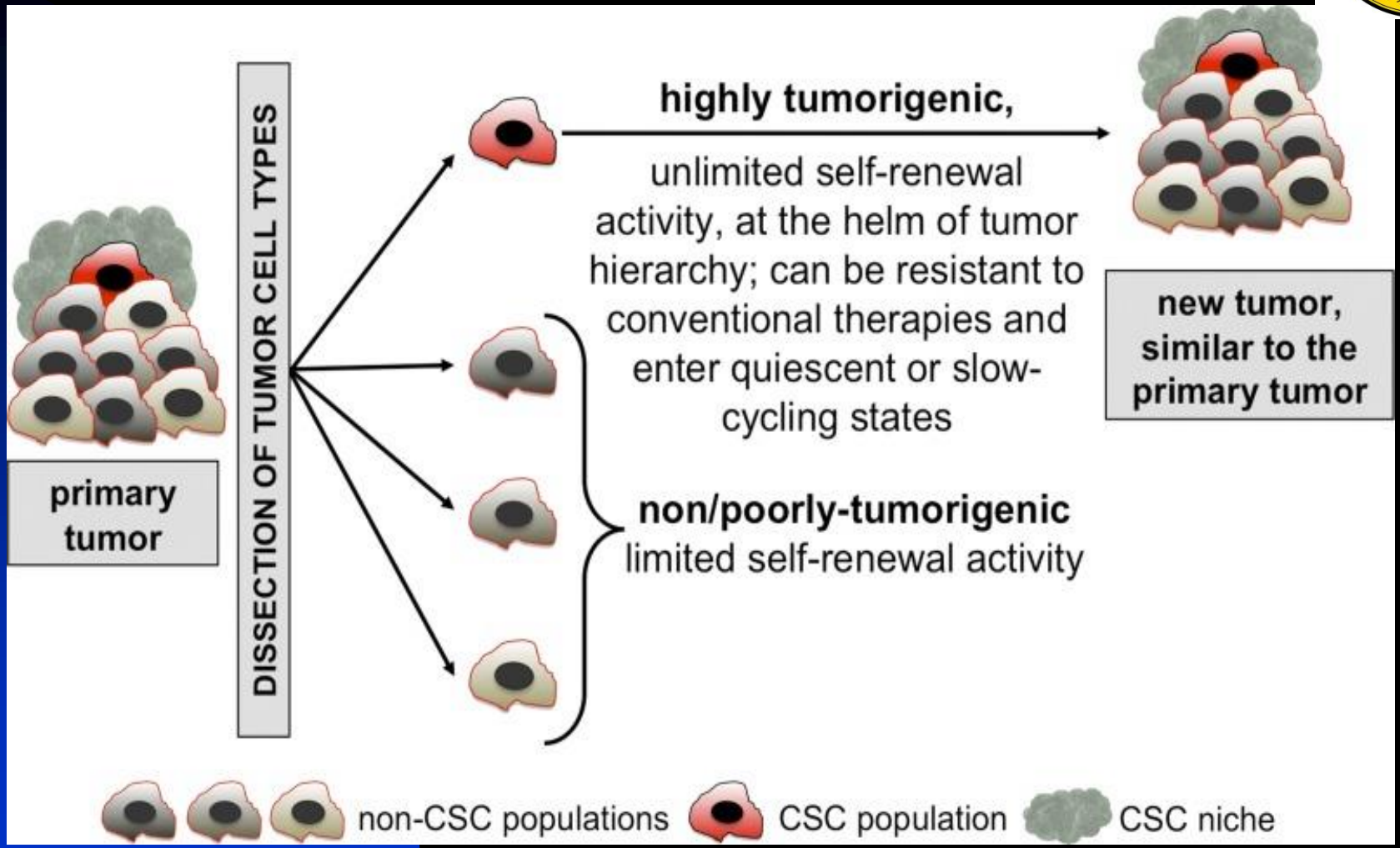
Annu. Rev. Chem. Biomol. Eng. 2019. 10:337–59

Summary of possible adaptive immune response pathways. Abbreviations: APC, antigen presenting cell; DC, dendritic cell; MHC, major histocompatibility complex; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor.



The cardinal features of CSC.

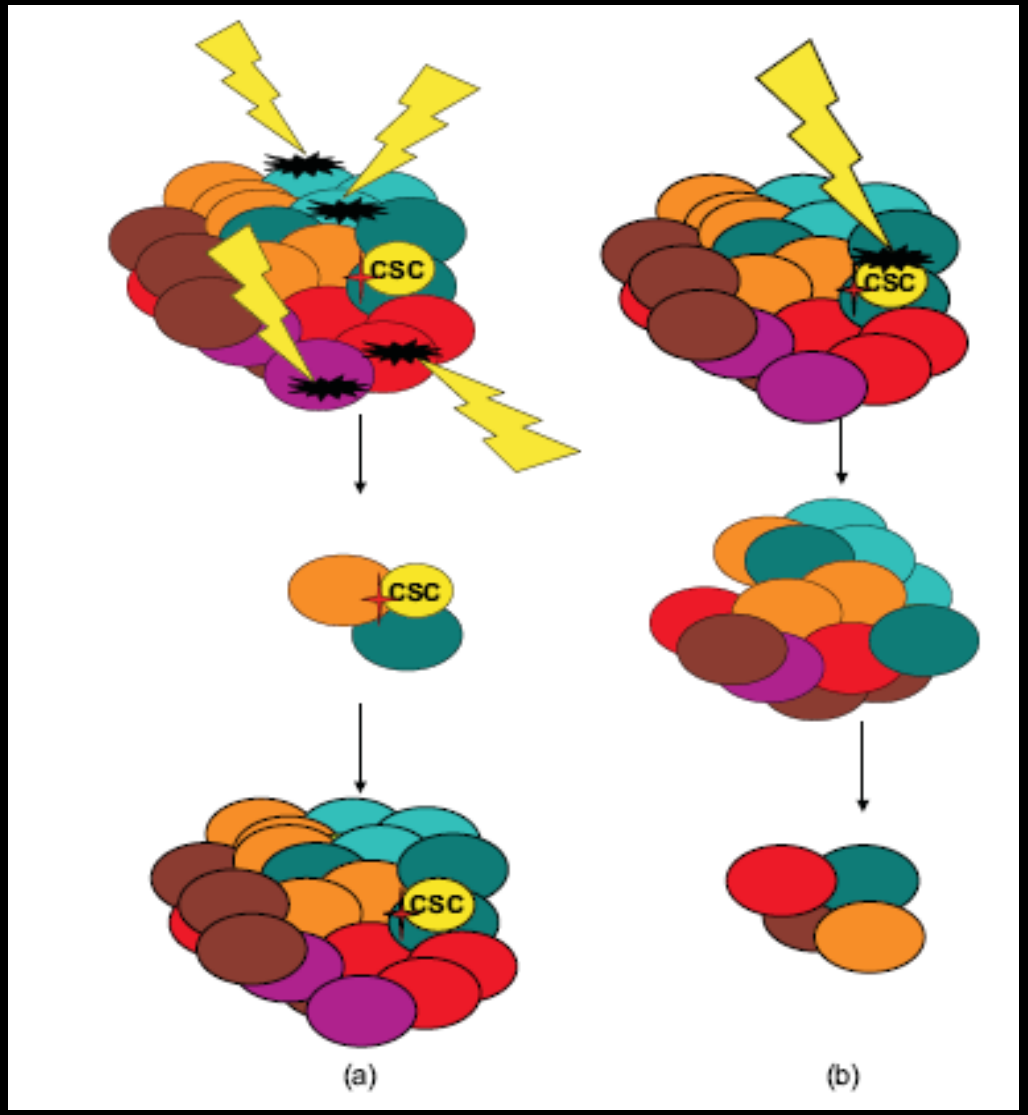
Schatton T. 2009 BioEssays



The classical "cancer stem cell" (CSC) concept.

J Cell Biol 2012; 198 (3): 281–293

How to targeted Therapy of CSCs?

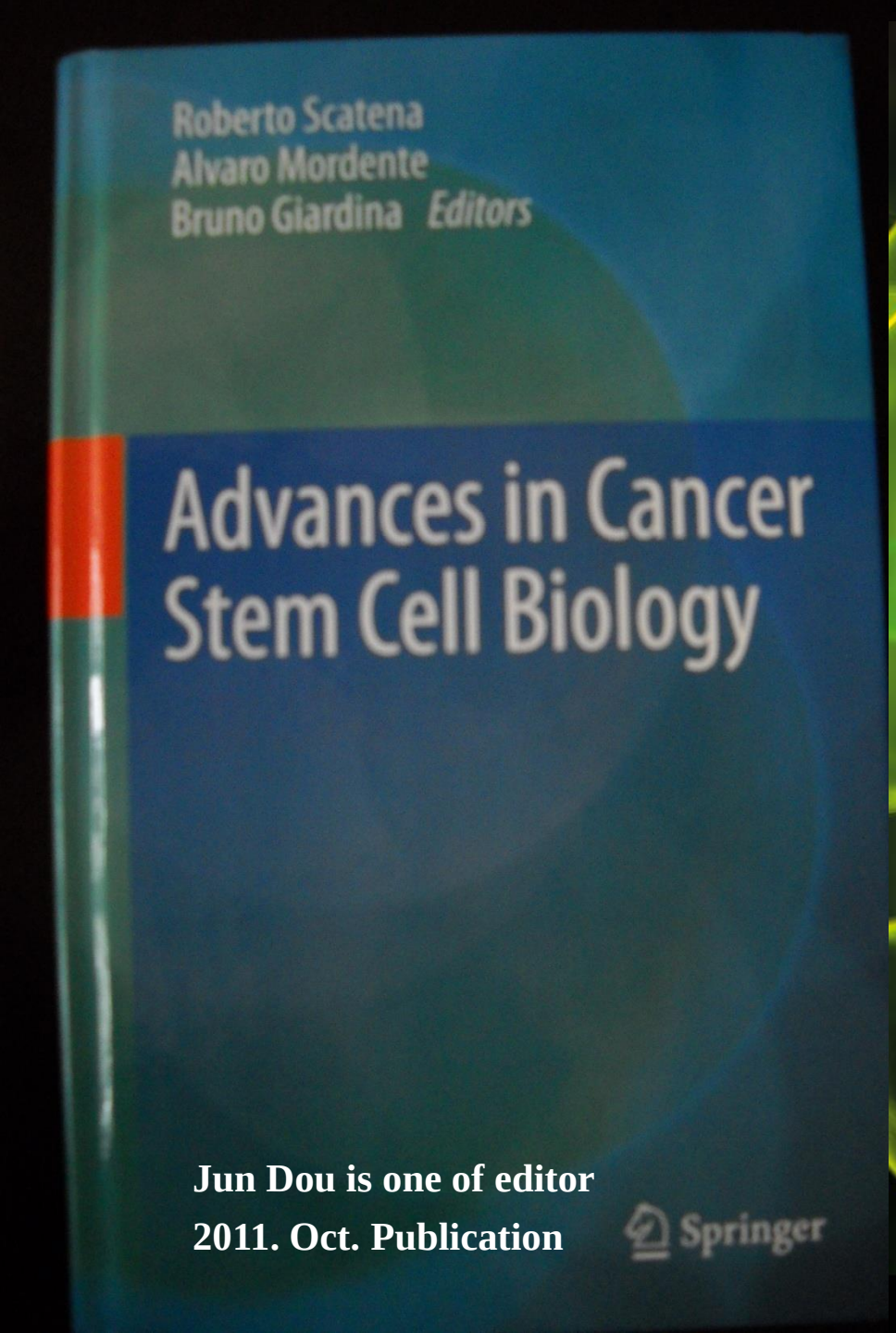


Targeted therapeutic strategy for cancer stem cells.

(a) Conventional therapy (b) Novel cancer therapy CSCs.

J. Gil et al. | J App Genet 49(2), 2008, pp. 193–199

ISBN: 9787564117269 2009.7出版



Jun Dou is one of editor

2011. Oct. Publication

Jun Dou is one of editor

2011. July Publication

Concepts:

1. TAA and TSA
2. CAR-T, CSC/TSC
3. Tumor immunological escape
4. Cancer immunotherapy
5. Immune checkpoint blockade

Questions:

1. In what ways do tumor cells different antigenically from normal cells? Please explain how tumor cells may be destroyed by the immune system!
2. If tumor cells can be destroyed by the immune system, how does cancer develop? What does immune cells and molecules involve?