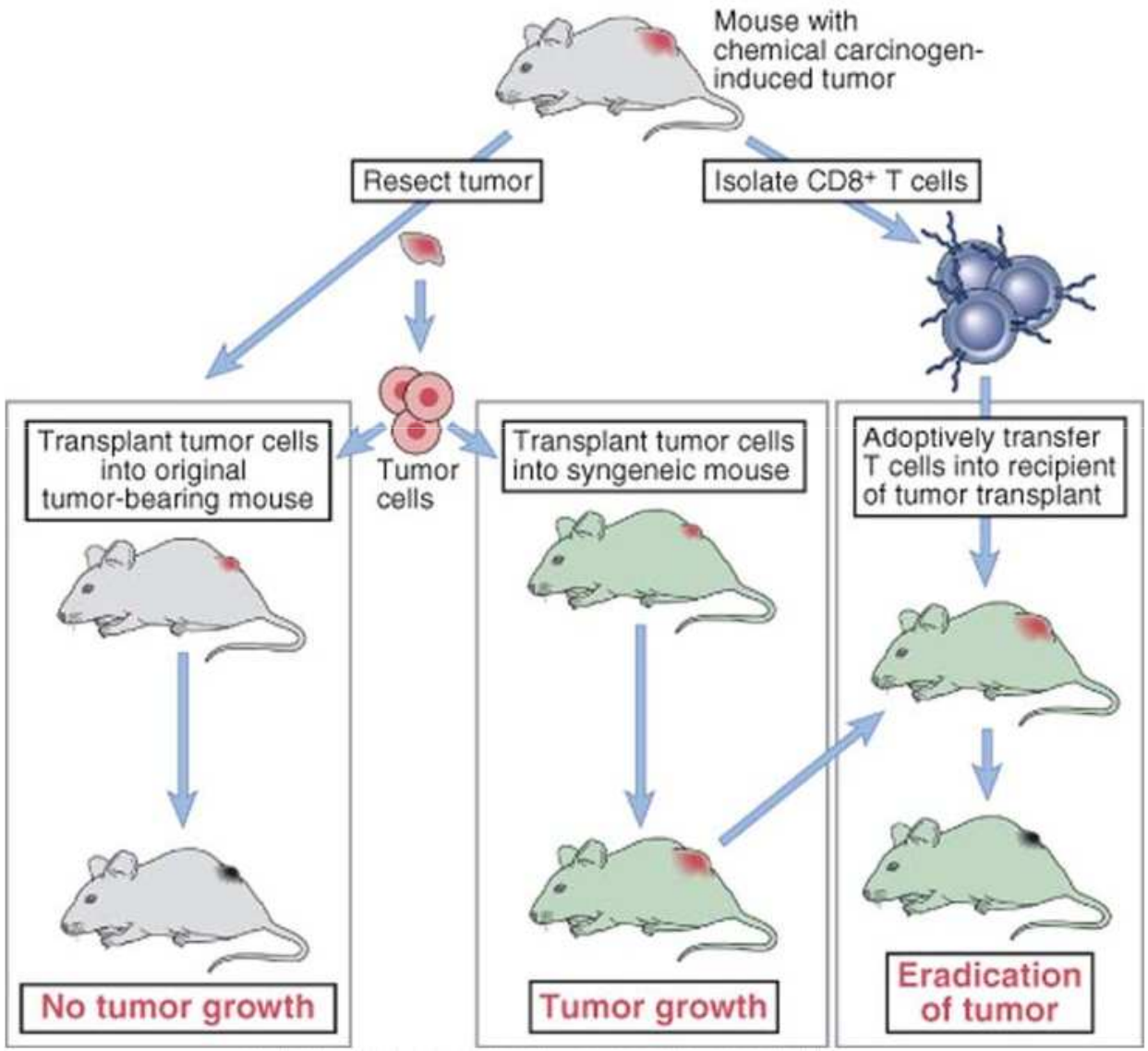
Immunity to tumors

Experimental evidence for tumor immunity



Tumor antigens

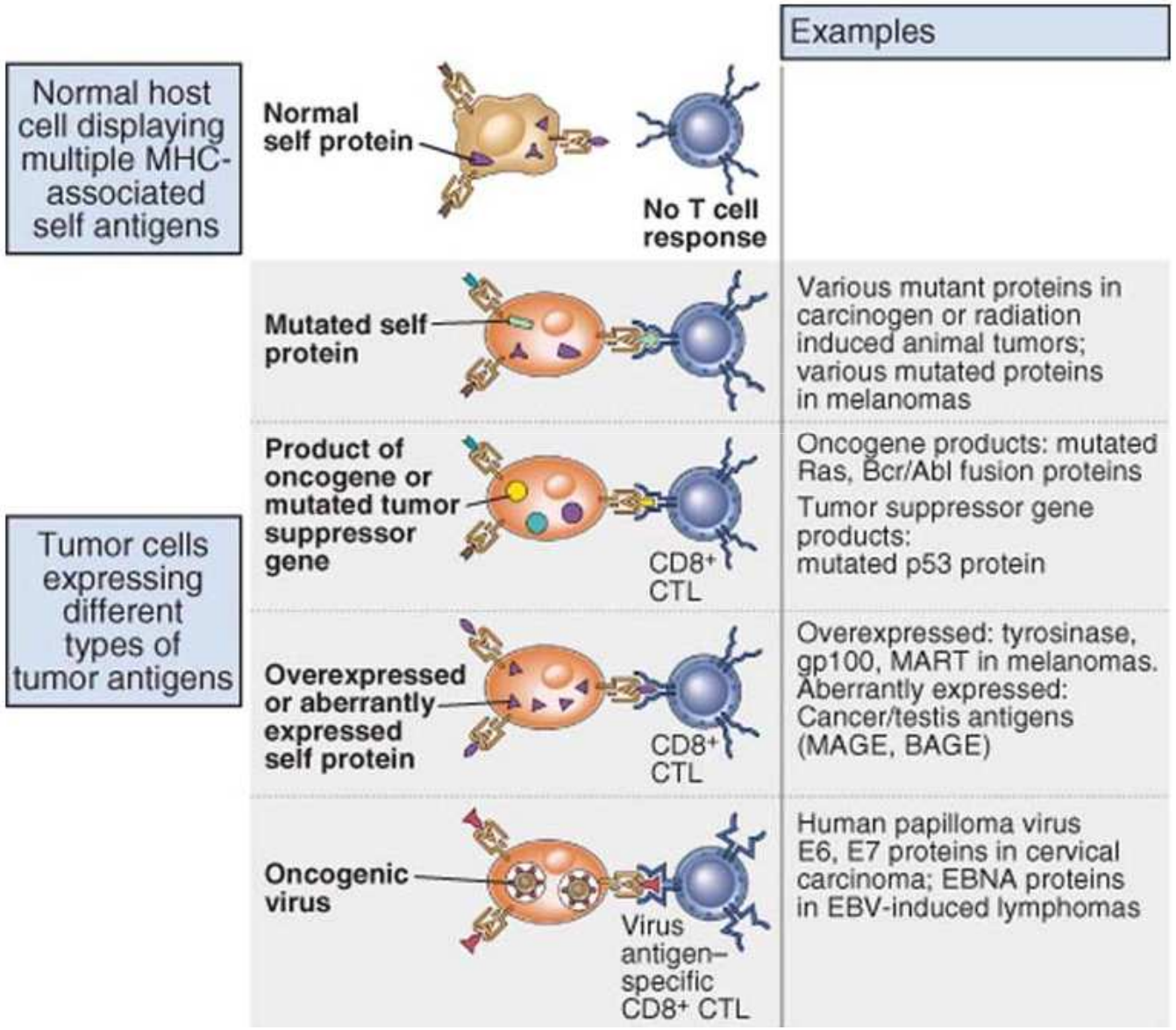
- tumor-specific antigens (TSA): products of mutated genes, can be recognized by both CD4 and CD8 T lymphocytes

- tumor-associated antigens (TAA): self proteins, normally expressed at undetectable levels, overexpressed in tumors - oncofetal antigens, normally expressed during fetal life (e.g. CEA, AFP)

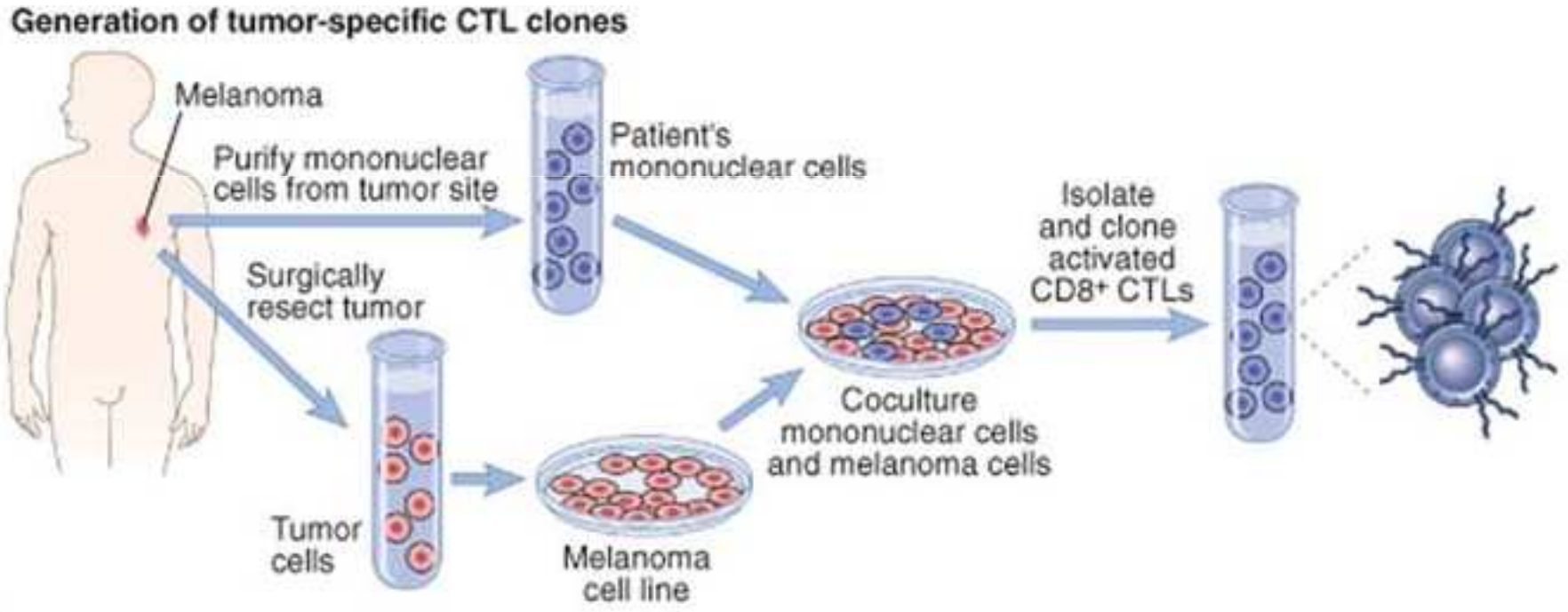
- viral proteins from oncogenic viruses

- overexpressed glycolipids (e.g. GM2, GD3)

Types of tumor antigens recognized by T cells



Identification of tumor antigens



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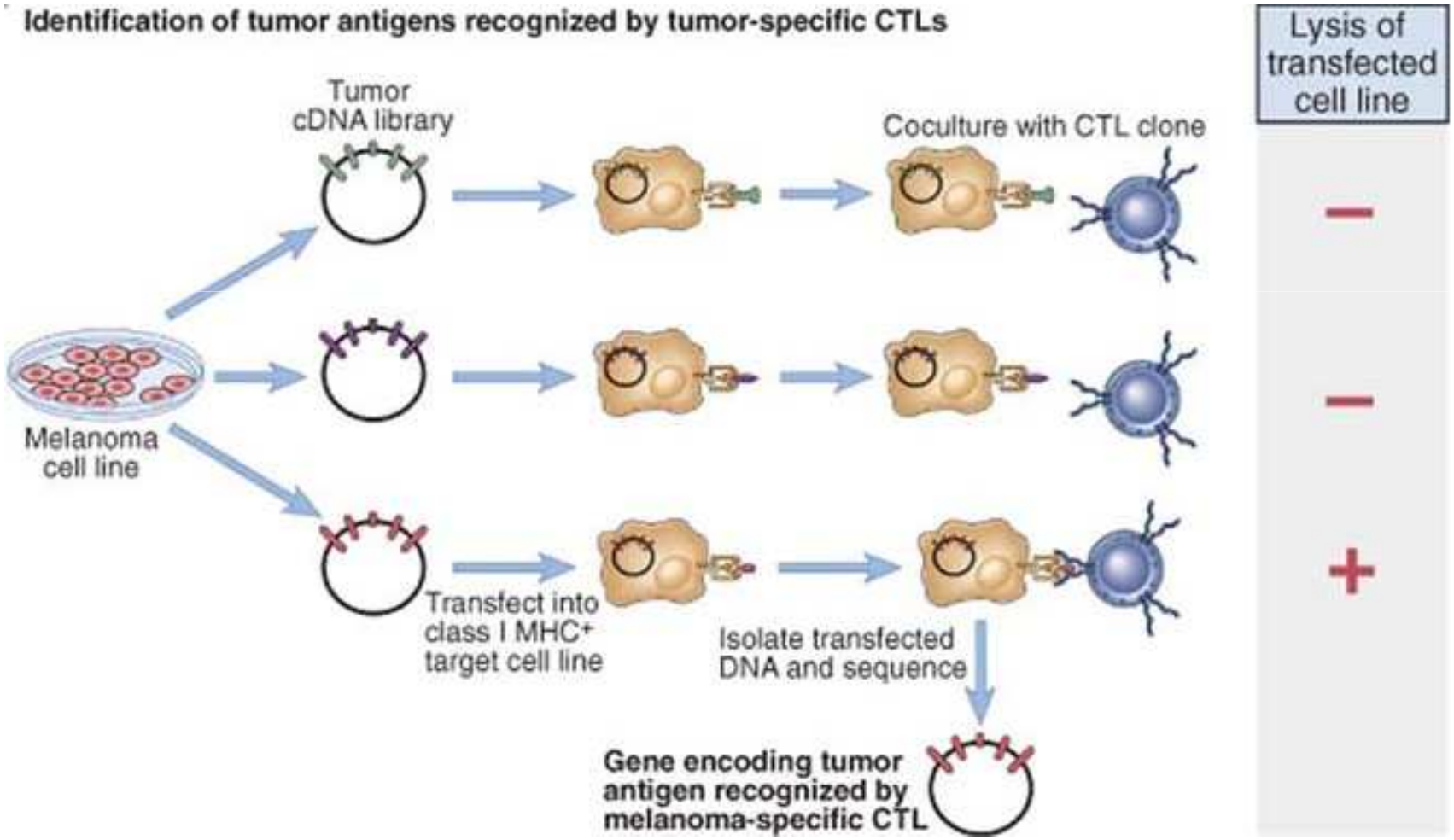


Cells involved in anti-tumor responses

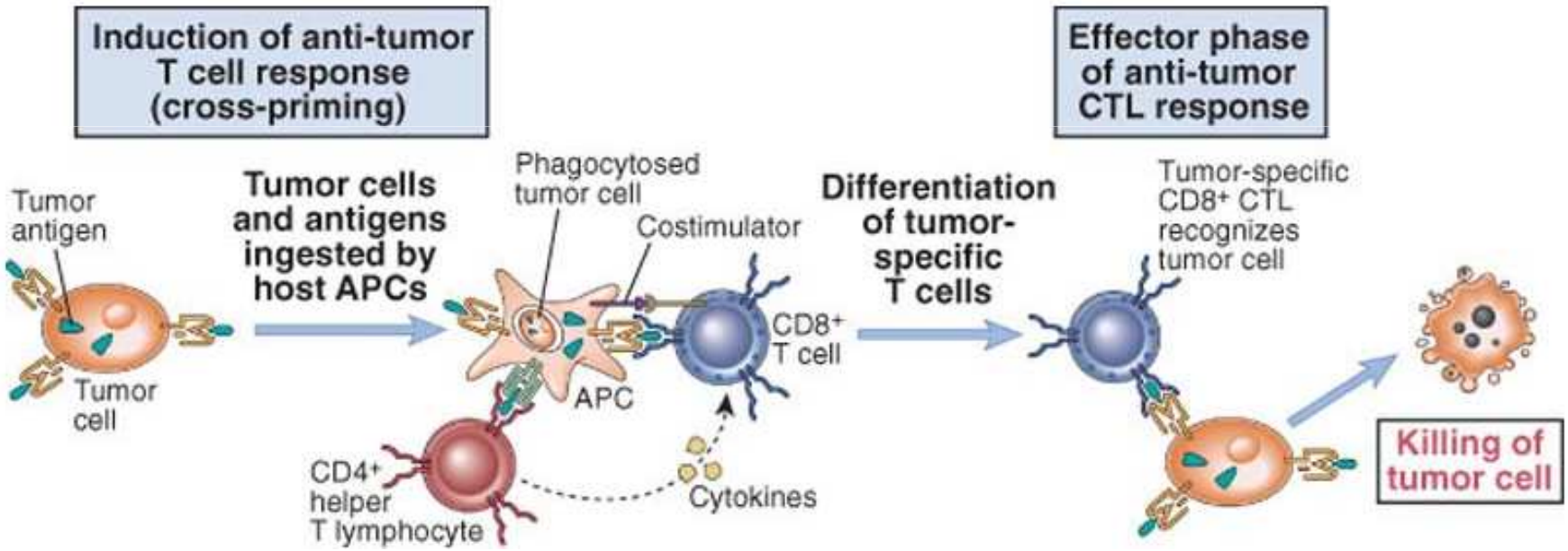
Innate immunity

- NK cells (low MHC, NKG2D→MICA, CD16, IL-2, IL-12→LAK)
- macrophages (IFNγ→TNF)

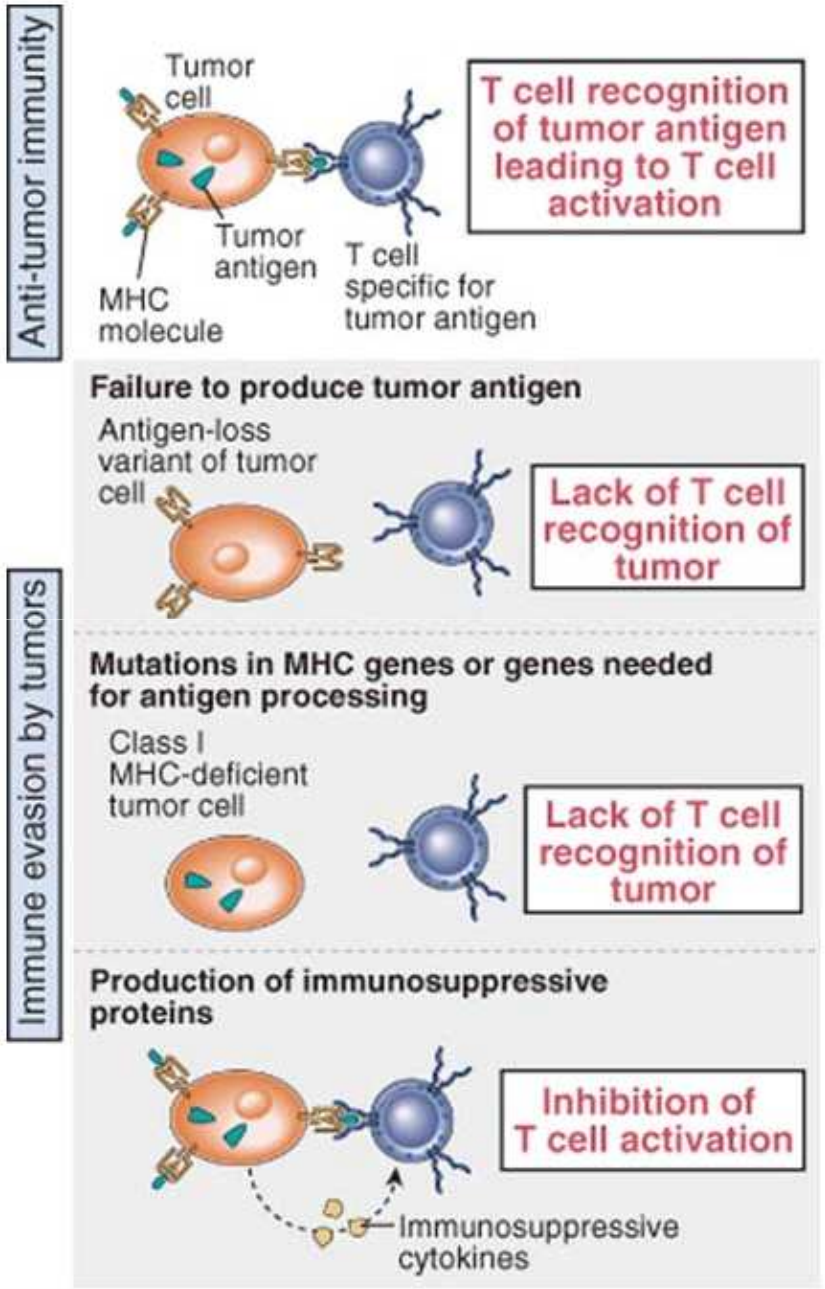
Adoptive immunity

- CTL (cross-priming)

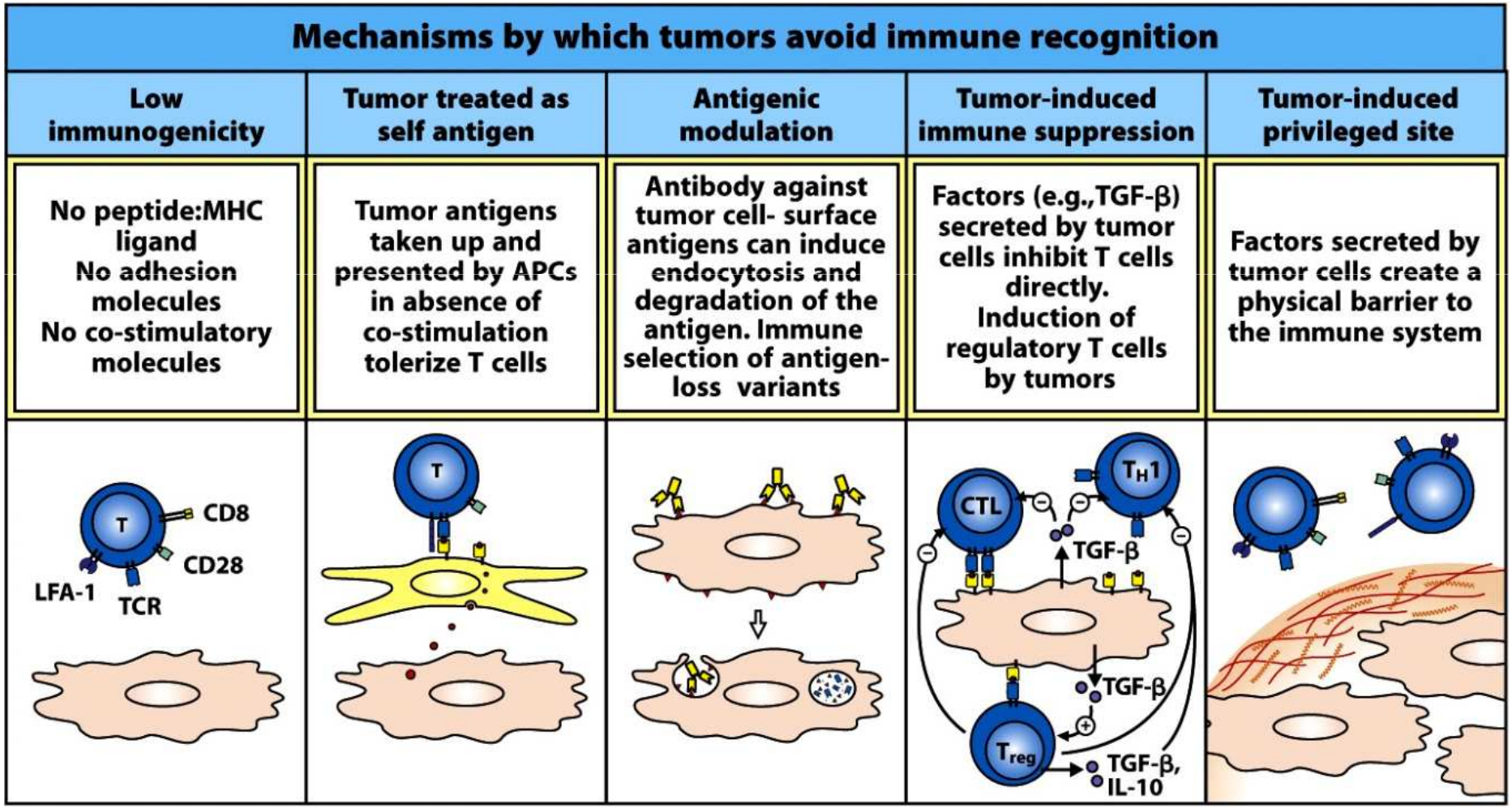
Induction of tumor-specific CTLs



Tumor escape

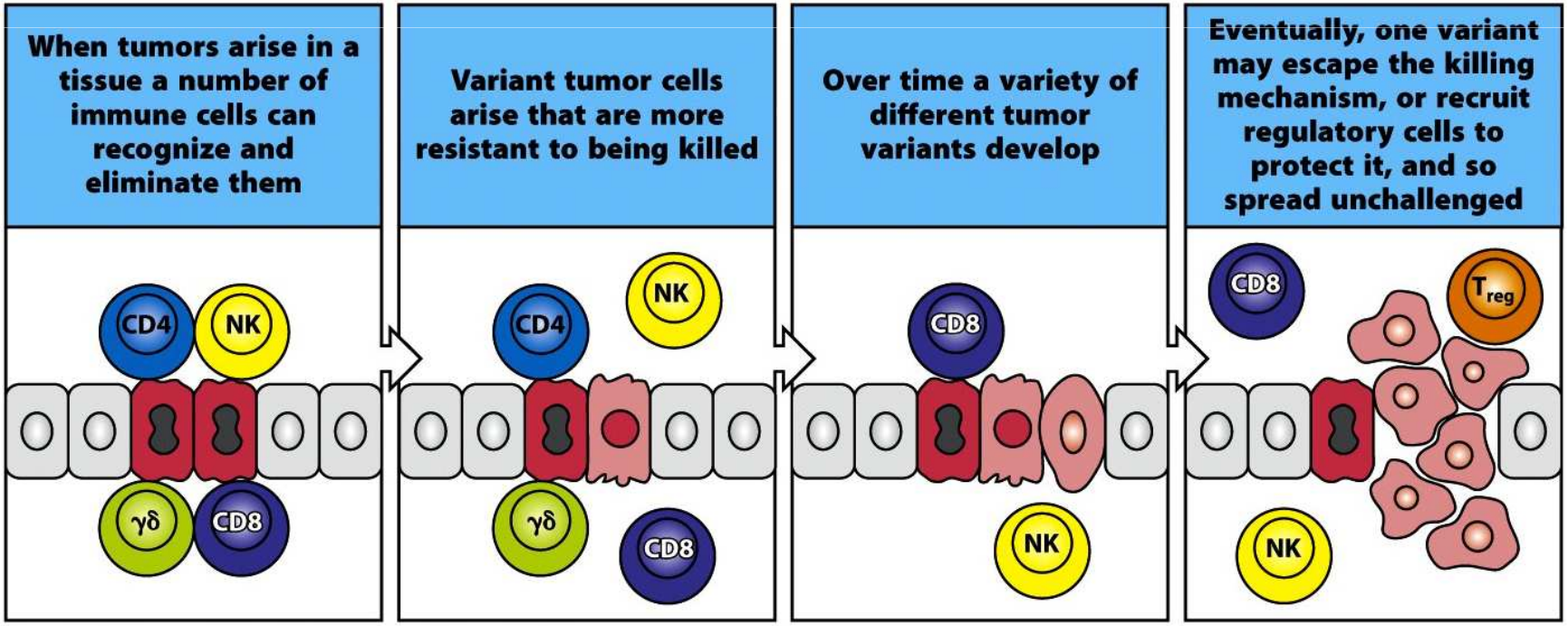


Tumor escape

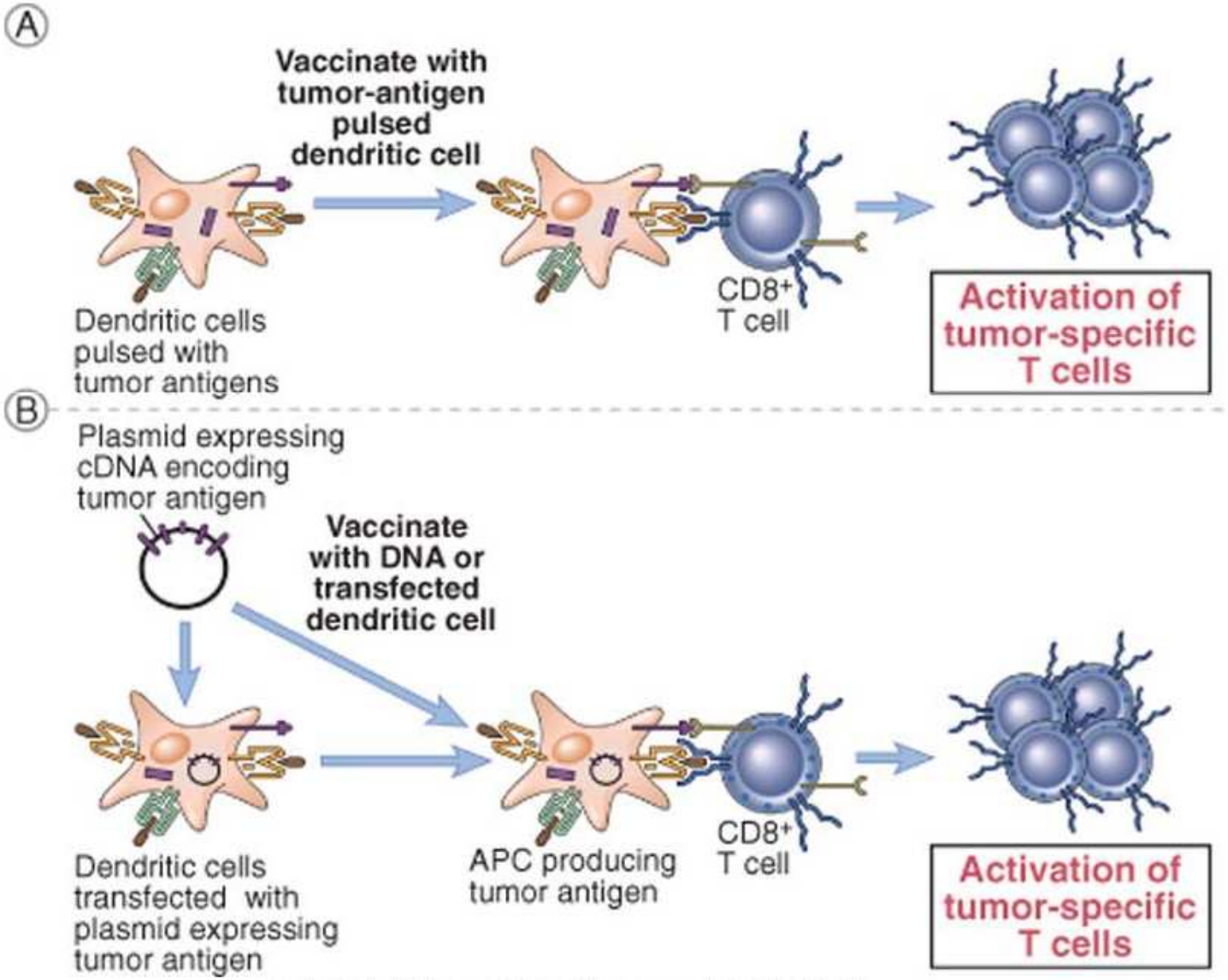


Tumor escape, tumor editing

- tumor antigens can induce tolerance (absence of co-stimulation)
- production of TGFβ → activation of Treg → IL-10, suppression
- antigen loss→ no recognition
- MHC loss→ no recognition
- FasL expression→killing of attacking CTL
- blockade of the apoptotic machinery



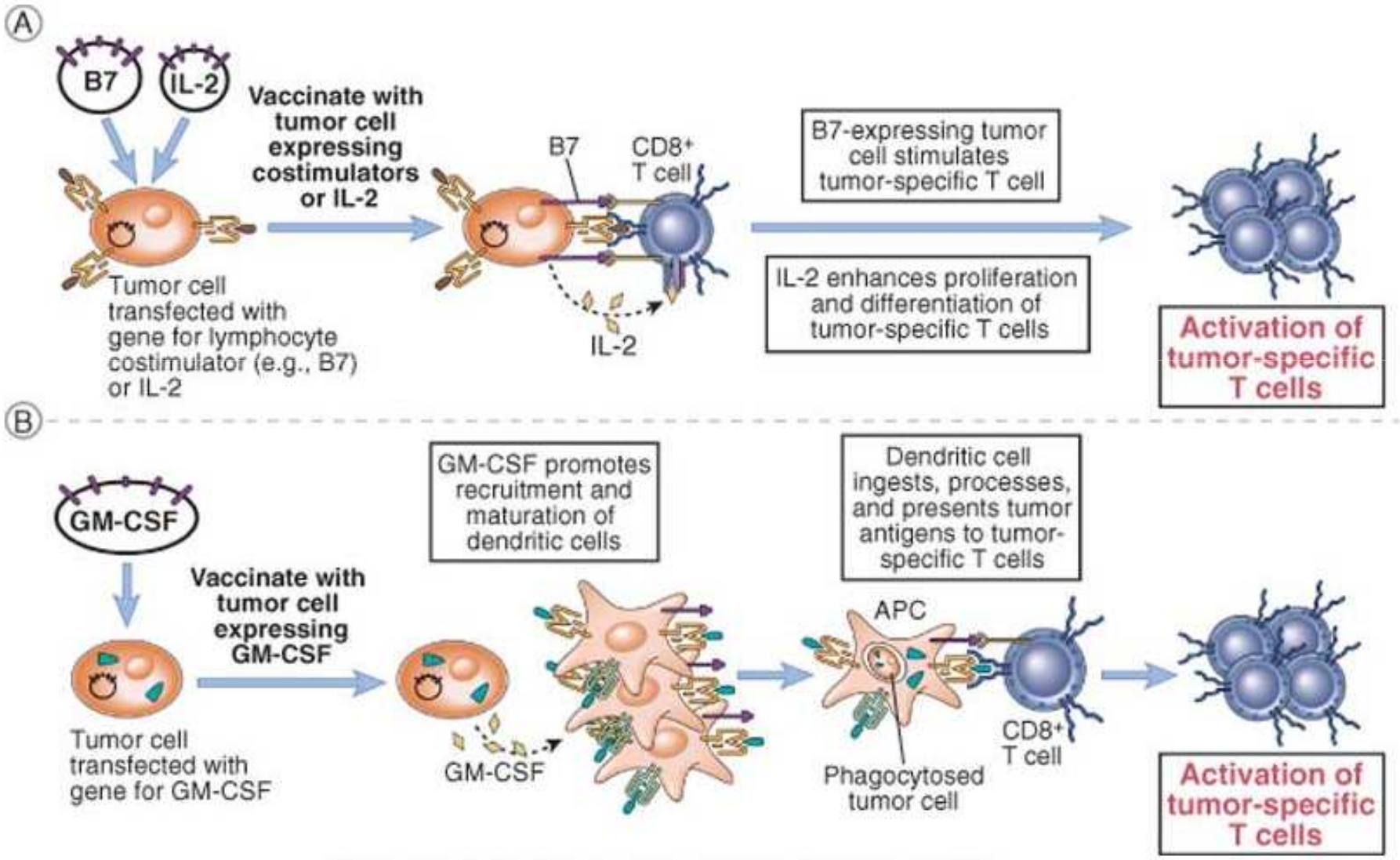
Tumor antigens as vaccines



Tumor antigens as vaccines

Type of vaccine	Vaccine preparation	Animal models	Clinical trials
Killed tumor vaccine	Killed tumor cells + adjuvants	Melanoma, colon cancer, others	Melanoma, colon cancer
Tumor cell lysates + adjuvants	Sarcoma	Melanoma	
Purified tumor antigens	Melanoma antigens	Melanoma	Melanoma
Heat shock proteins	Various	Melanoma, renal cancer, sarcoma	
Professional APC-based vaccines	Dendritic cells pulsed with tumor antigens	Melanoma, B cell lymphoma, sarcoma	Melanoma, non-Hodgkin's lymphoma, prostate cancer, others
	Dendritic cells transfected with genes encoding tumor antigens	Melanoma, colon cancer	Various carcinomas
Cytokine- and costimulator-enhanced vaccines	Tumor cells transfected with cytokine or B7 genes	Renal cancer, sarcoma, B cell leukemia, lung cancer	Melanoma, sarcoma, others
APCs transfected with cytokine genes and pulsed with tumor antigens		Melanoma, renal cancer, others	
DNA vaccines	Immunization with plasmids encoding tumor antigens	Melanoma	Melanoma
Viral vectors	Adenovirus, vaccinia virus encoding tumor antigen ± cytokines	Melanoma, sarcoma	Melanoma

Tumor cells as vaccines and immunostimulators



Cytokine-transfected tumor cells as immunotherapy

Cytokine	Tumor rejection in animals	Inflammatory infiltrate	Immunity against parental tumor (animal models)	Clinical trials
Interleukin-2	Yes; mediated by T cells	Lymphocytes, neutrophils	In some cases of renal cancer, melanoma	Renal cancer, melanoma
Interleukin-4	Yes	Eosinophils, macrophages	No long-lasting immunity in human trials	Melanoma, renal cancer
Interferon-γ	Variable	Macrophages, other cells	Sometimes	
TNF	Variable	Neutrophils and lymphocytes	No	
GM-CSF	Yes	Macrophages, other cells	Yes (long-lived T cell immunity)	Renal cancer
Interleukin-3	Sometimes	Macrophages, other cells	Sometimes	

Systemic anti-tumor cytokine therapy

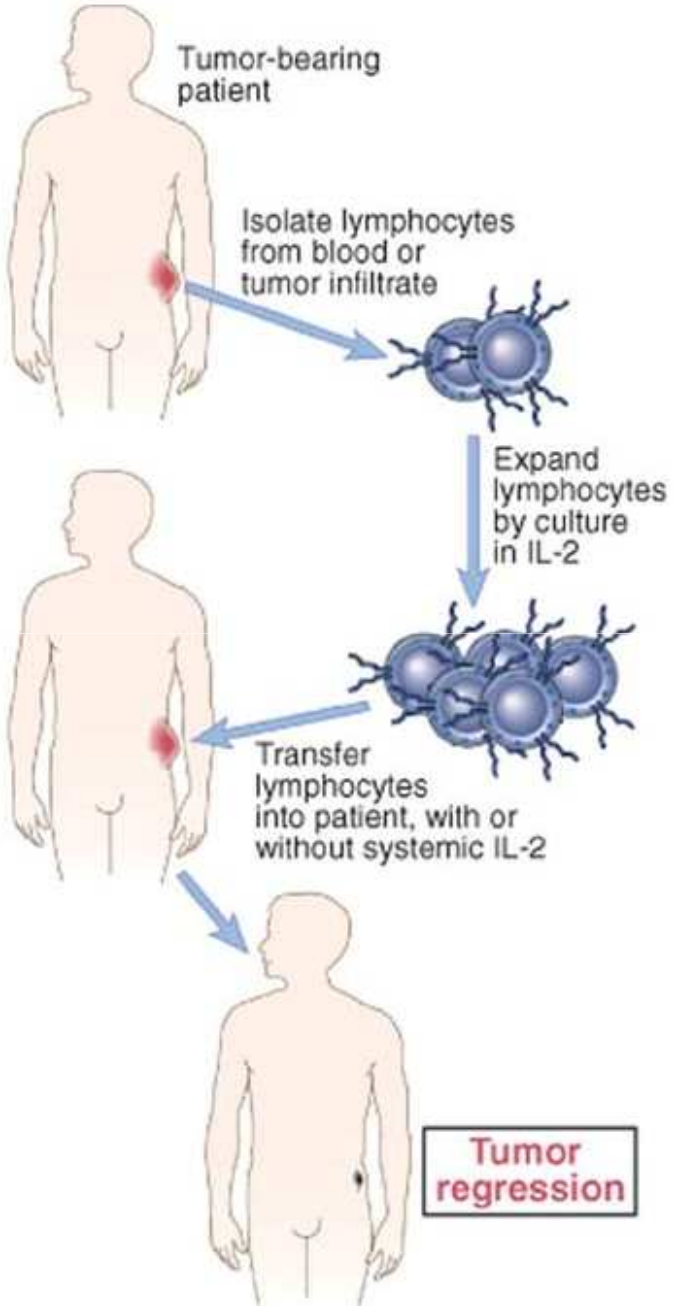
Cytokine	Tumor rejection in animals	Clinical trials	Toxicity
Interleukin-2	Yes	Melanoma, renal cancer, colon cancer; limited success (<15% response rate)	Vascular leak, shock, pulmonary edema
Interferon-α	No	Approved for melanoma	Fever, fatigue
TNF	Only with local administration	Sarcoma, melanoma (isolated limb perfusion)	Septic shock syndrome
Interleukin-12	Variable	Toxicity trials (phase I) in melanoma, others	Abnormal liver function
GM-CSF	No	In routine use to promote bone marrow recovery	Bone pain

FDA-approved anti-tumor mAbs for therapy

Specificity of antibody	Form of antibody used	Clinical trials
Her-2/Neu	Humanized mouse monoclonal	Breast cancer (approved for clinical use)
CD20 (B cell marker)	Humanized mouse monoclonal	B cell lymphoma
CD10	Humanized mouse monoclonal, immunotoxin	B cell lymphoma; in routine use to purge bone marrow of residual tumor cells
CEA	Humanized mouse monoclonal	Gastrointestinal cancers, lung cancer
CA-125	Mouse monoclonal	Ovarian cancer
GD3 ganglioside	Humanized mouse monoclonal	Melanoma

Adoptive cellular therapy

LAK (lymphokine-activated killers)



LAK