Graduiertenkolleg 1172/FIRST

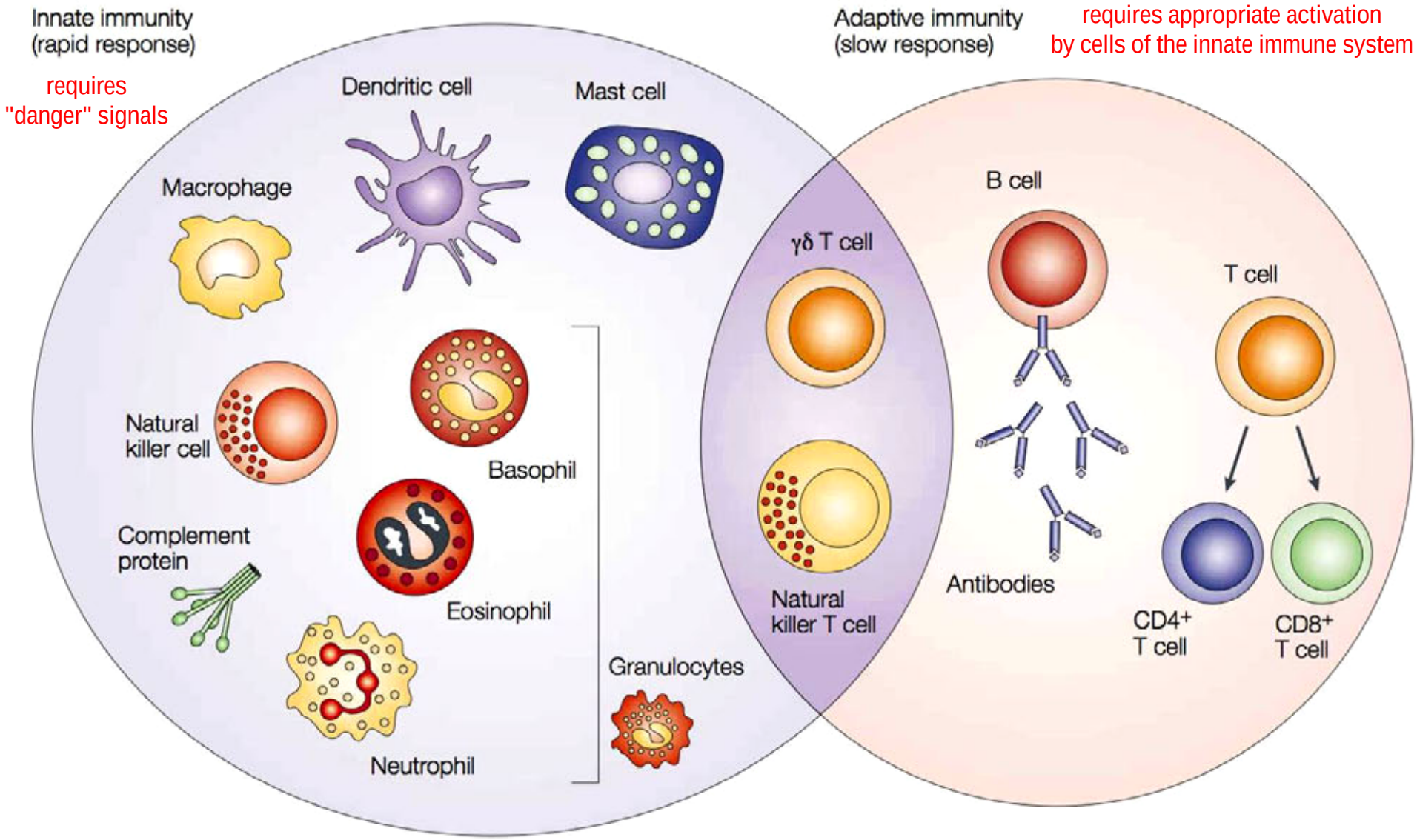
Tumor Biology

Cancer Immunology and Immunotherapy

May 9, 2011

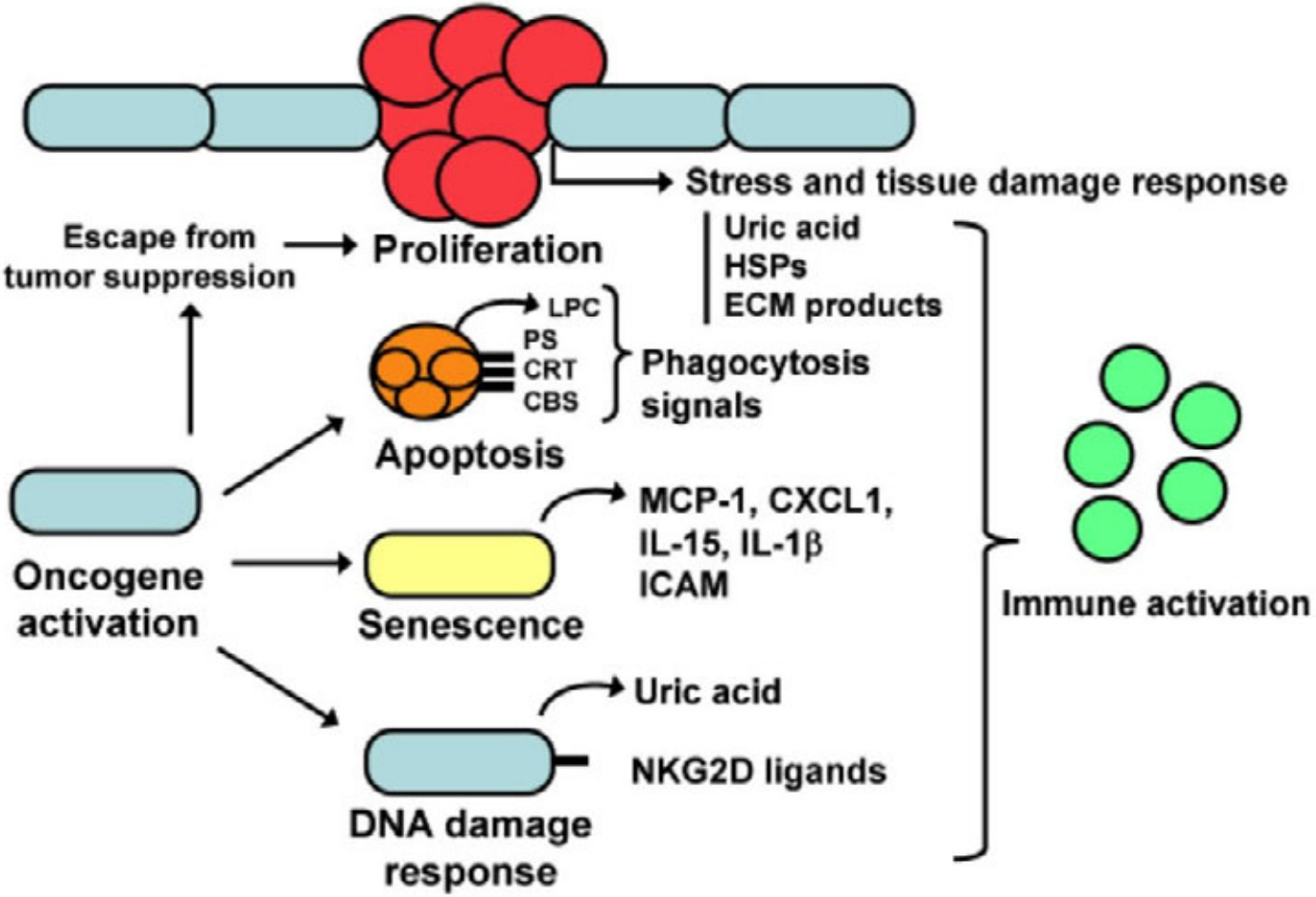
Winfried Wels

Innate and adaptive immunity



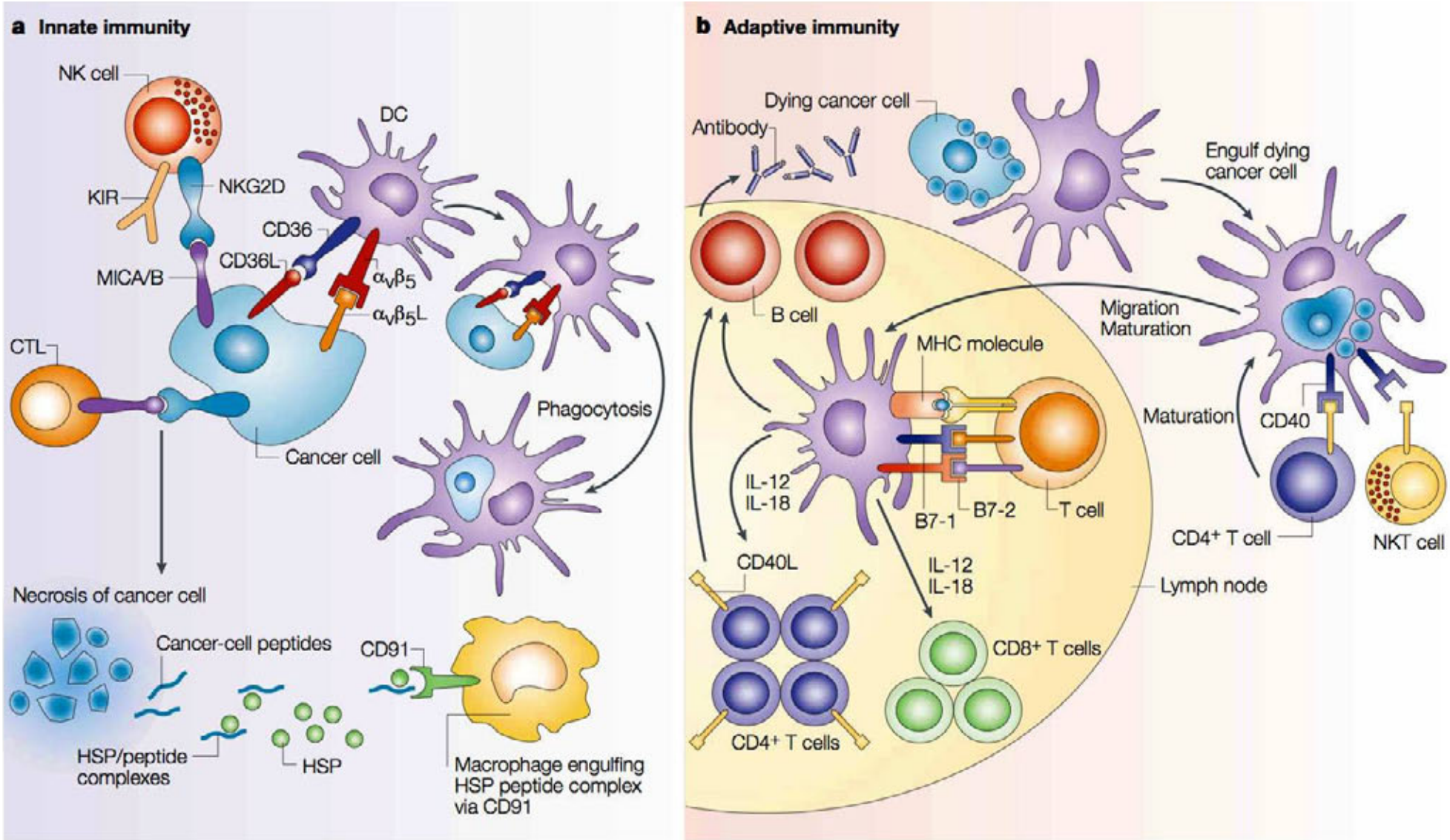
Dranoff, 2004

Danger signals linking oncogenesis and immunosurveillance



Stagg et al., 2007

Anti-tumor effector arms of the immune response

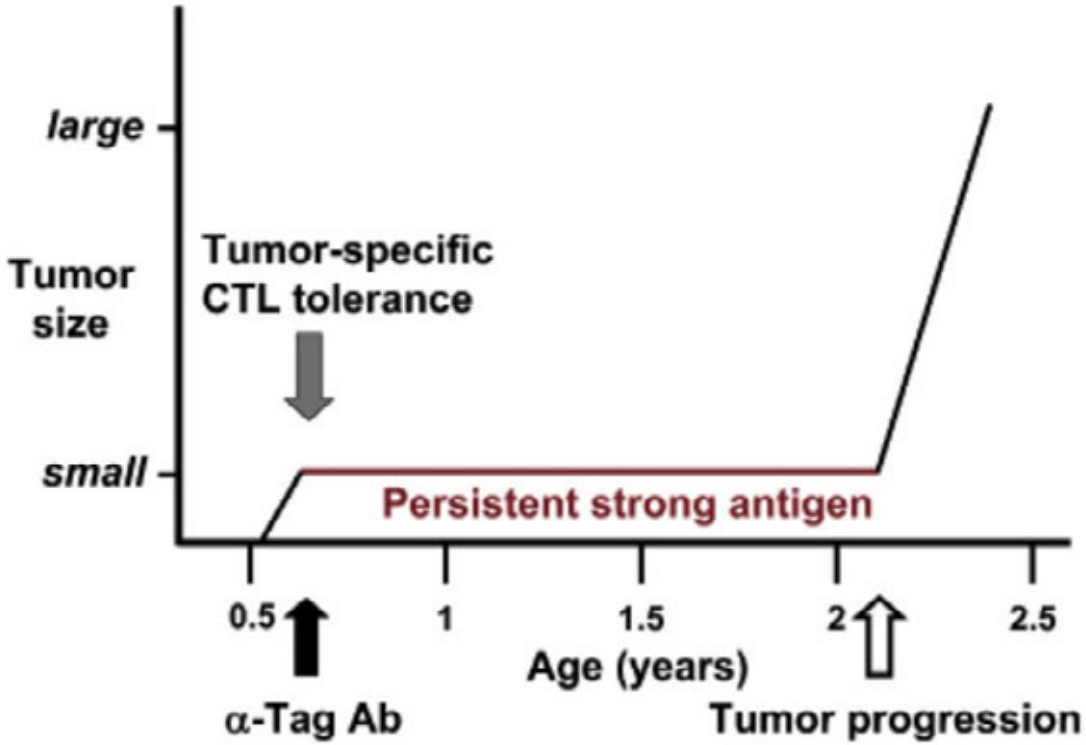


Dranoff, 2004

Tumor-specific tolerance in mouse models for sporadic cancer

LoxP-Tag mice

(spontaneous expression of highly immunogenic SV40 small and large T-Ag in single cells)



Willimsky & Blankenstein, 2007

The basic problem

Tumors carry many mutations and it is now clear that most if not all tumors express neo-antigens against which the host has a capacity to react in order to eliminate the tumor (*immunosurveillance*).

However, the immune system seems to slow, but not prevent, tumor progression, due to the selection of poorly immunogenic and immune-resistant malignant cells that favor tumor immune tolerance (*immunoediting*).

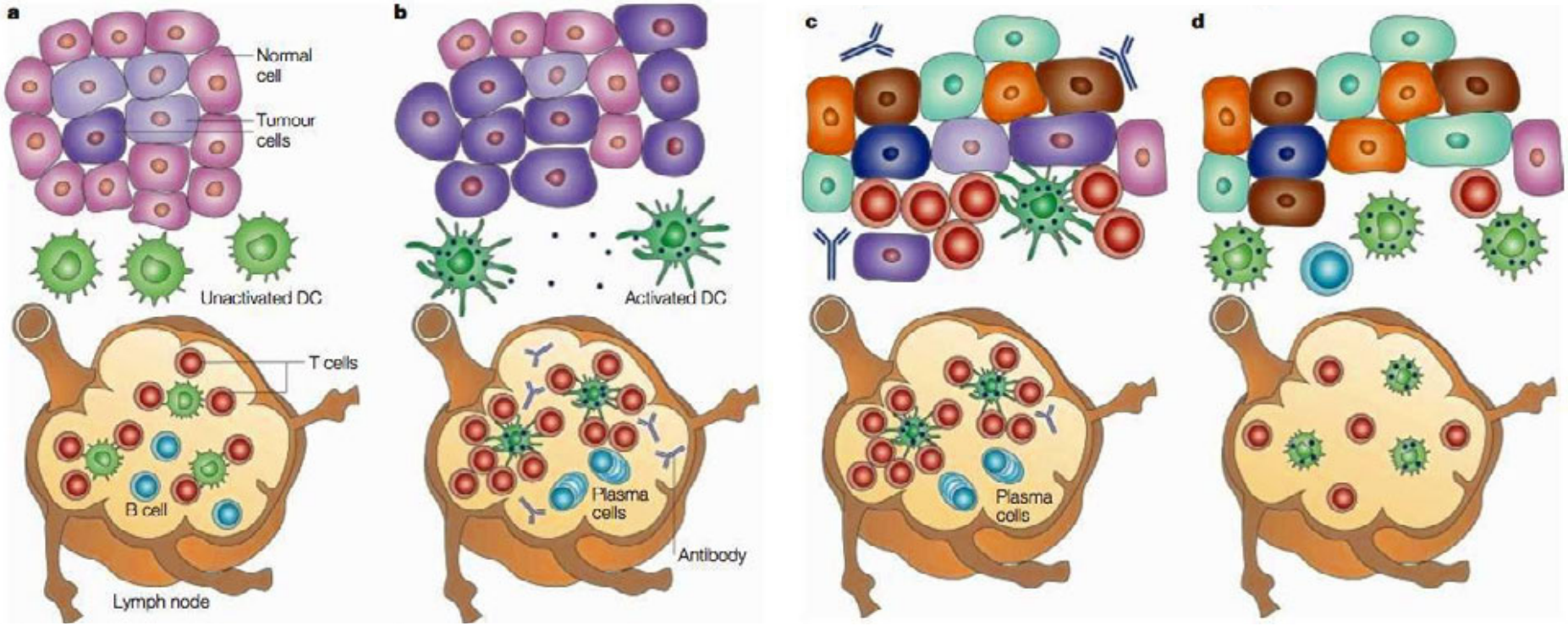
Evolution and fate of anti-tumor immune responses

Small tumor:
the immune system
remains ignorant

Damage to normal
tissues alerts
the immune system

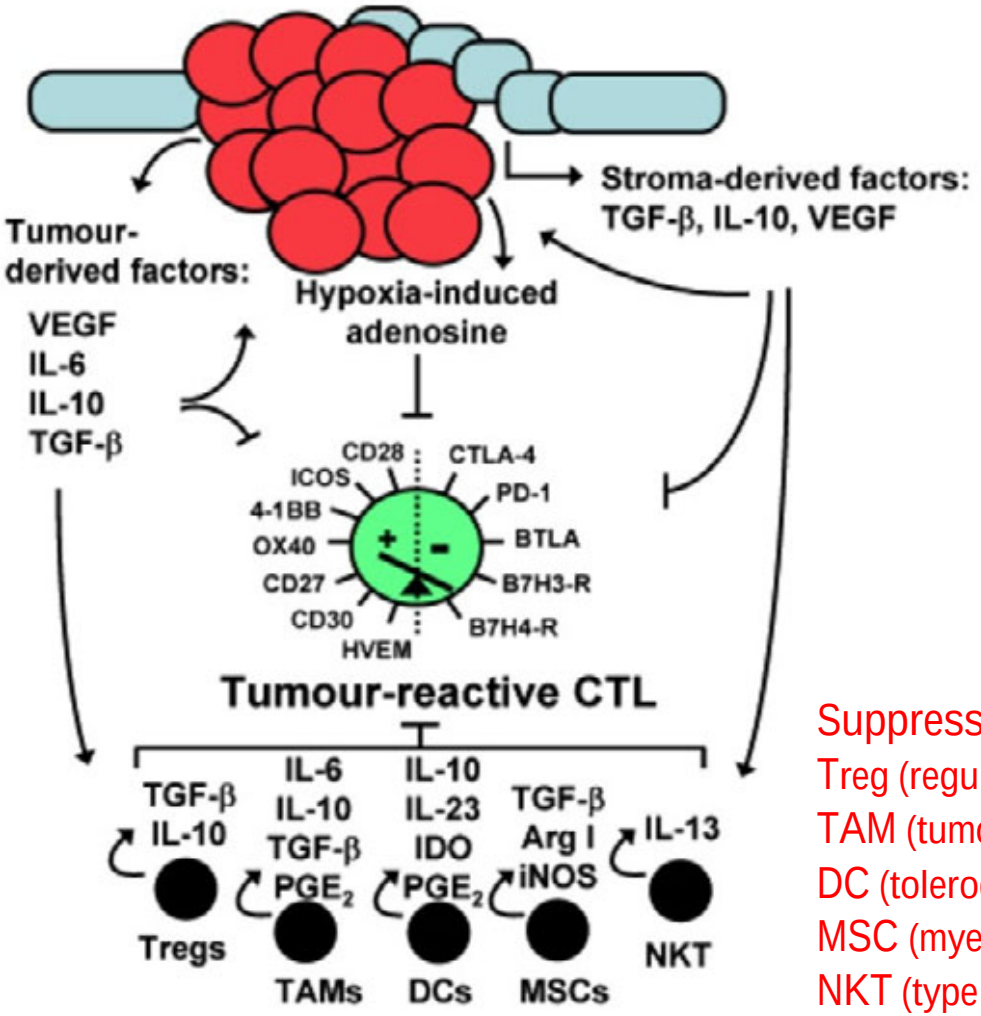
Tumor-specific T cells,
antibodies and DCs
reach the tumor but fail
due to tumor heterogeneity

The tumor has evaded
the initial immune response
and actively suppresses
local and systemic immunity



Finn, 2003

Mechanisms of tumor-mediated immune evasion



Tissue damage reponse

Suppressors:

Treg (regulatory T cells)

TAM (tumor-associated macrophage)

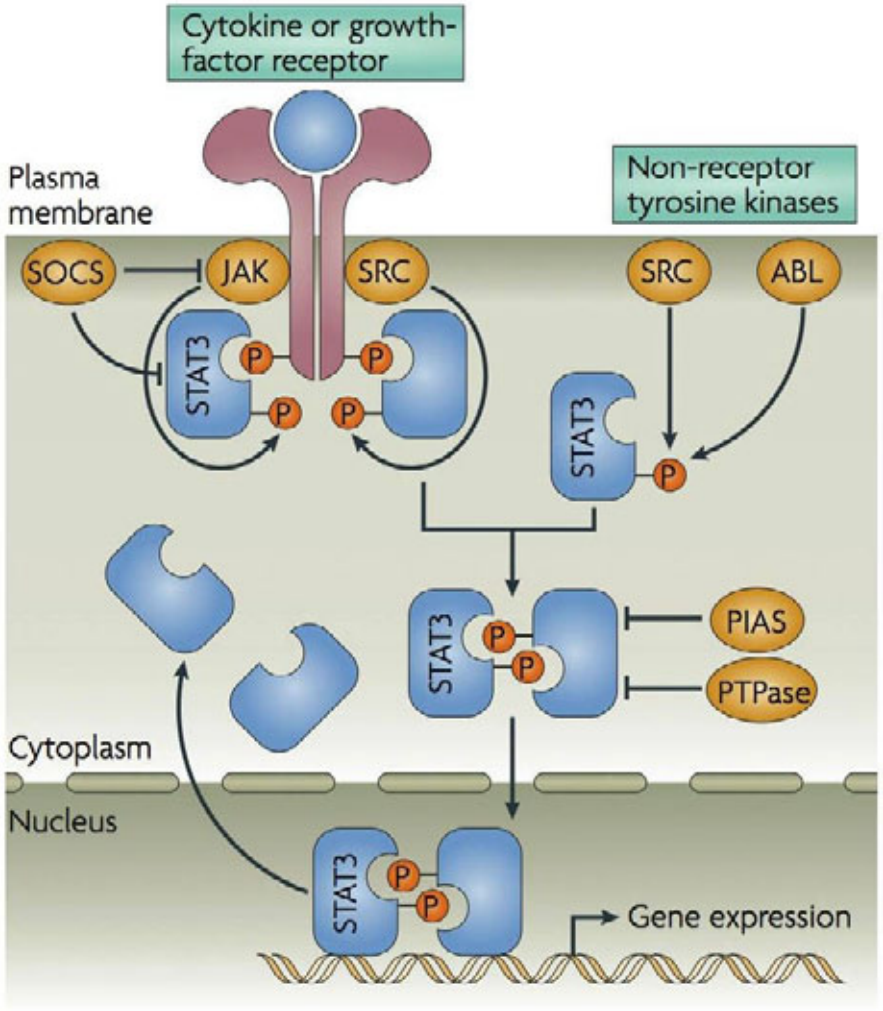
DC (tolerogenic/immature dendritic cells)

MSC (myeloid-derived suppressor cell)

NKT (type II natural killer T cells)

Stagg et al., 2007

STAT3 promotes oncogenesis and immune evasion



STAT3 regulated genes

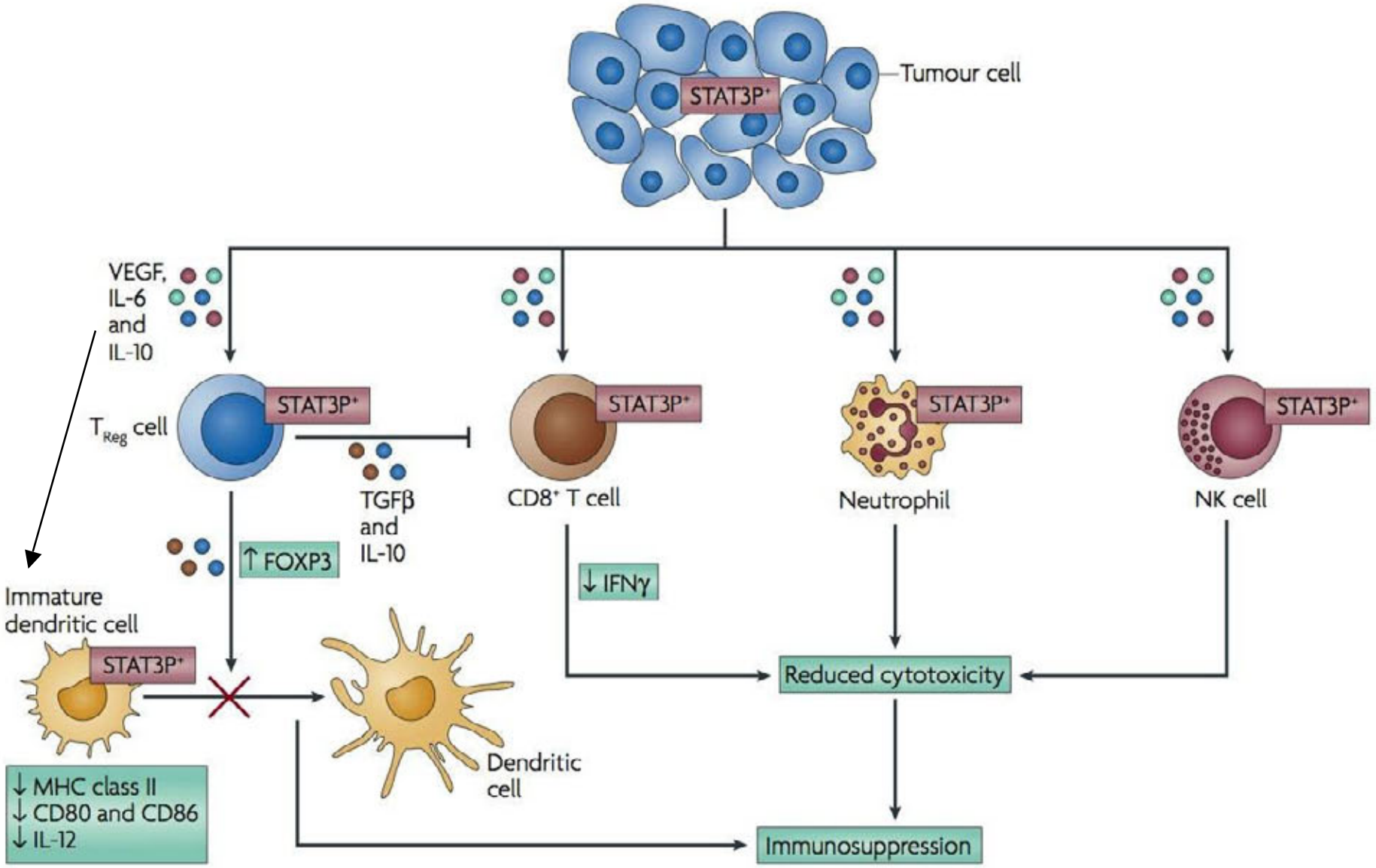
Proliferation and survival	↑MYC
	↑Cyclin D1/D
	↑BCL-X_L
	↑MCL1
	↑Survivin
	↓p53

Angiogenesis	↑VEGF
	↑HGF
	↑bFGF
	↑HIF1α
	↑MMP2
	↑MMP9
	↓IL-12
	↓IFNβ
	↓IFNγ
	↓CXCL10
	↓p53
	↓AKT

Immunosuppression	↑IL-6
	↑IL-10
	↑TGFβ
	↑VEGF
	↓IFNβ
	↓IFNγ
	↓IL-12
	↓TNF
	↓CXCL10
	↓CCL5
	↓MHC class II
	↓CD80
	↓CD86

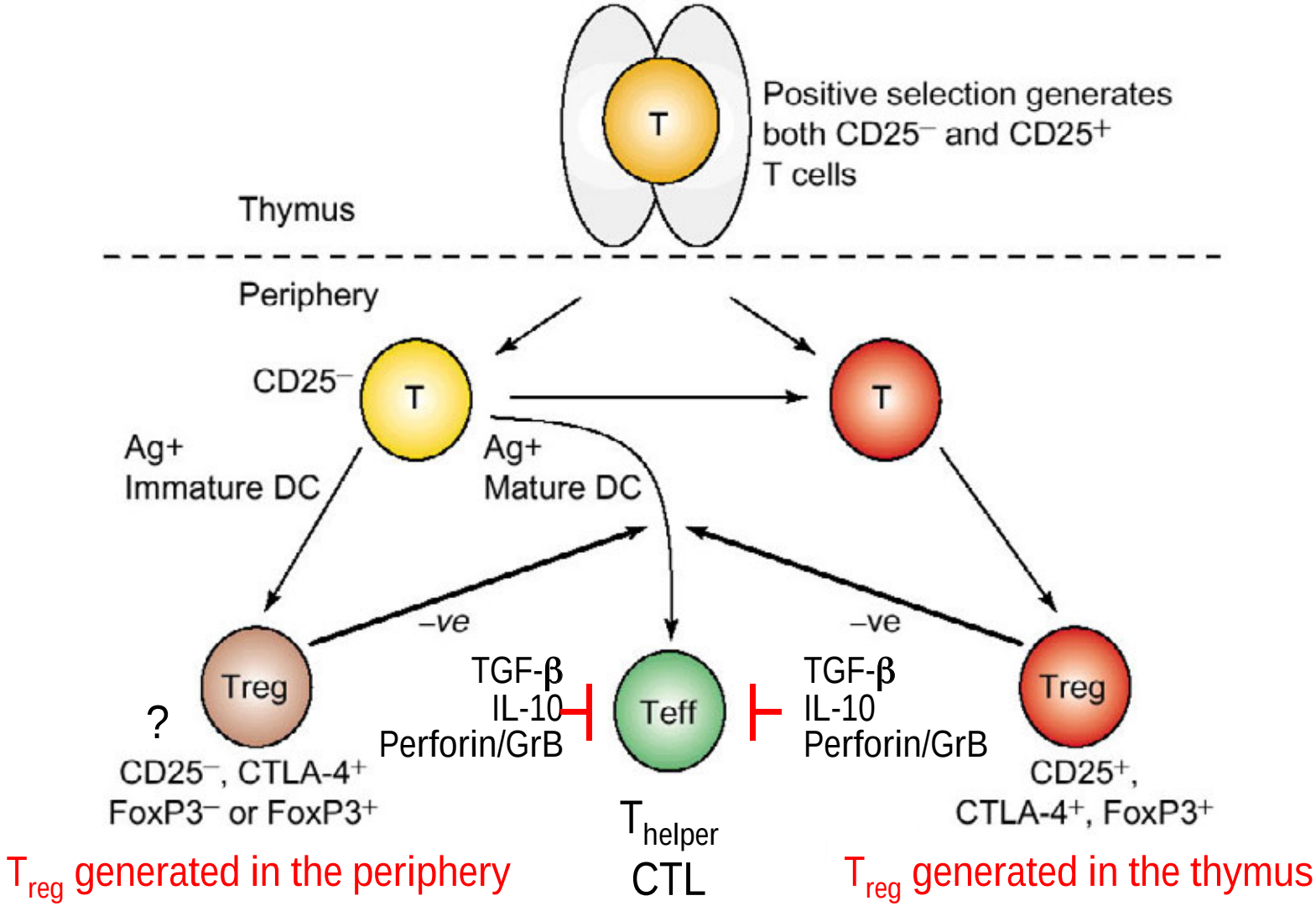
Yu et al., 2007

STAT3 signaling mediates communication between tumor and immune cells, and facilitates immunosuppression



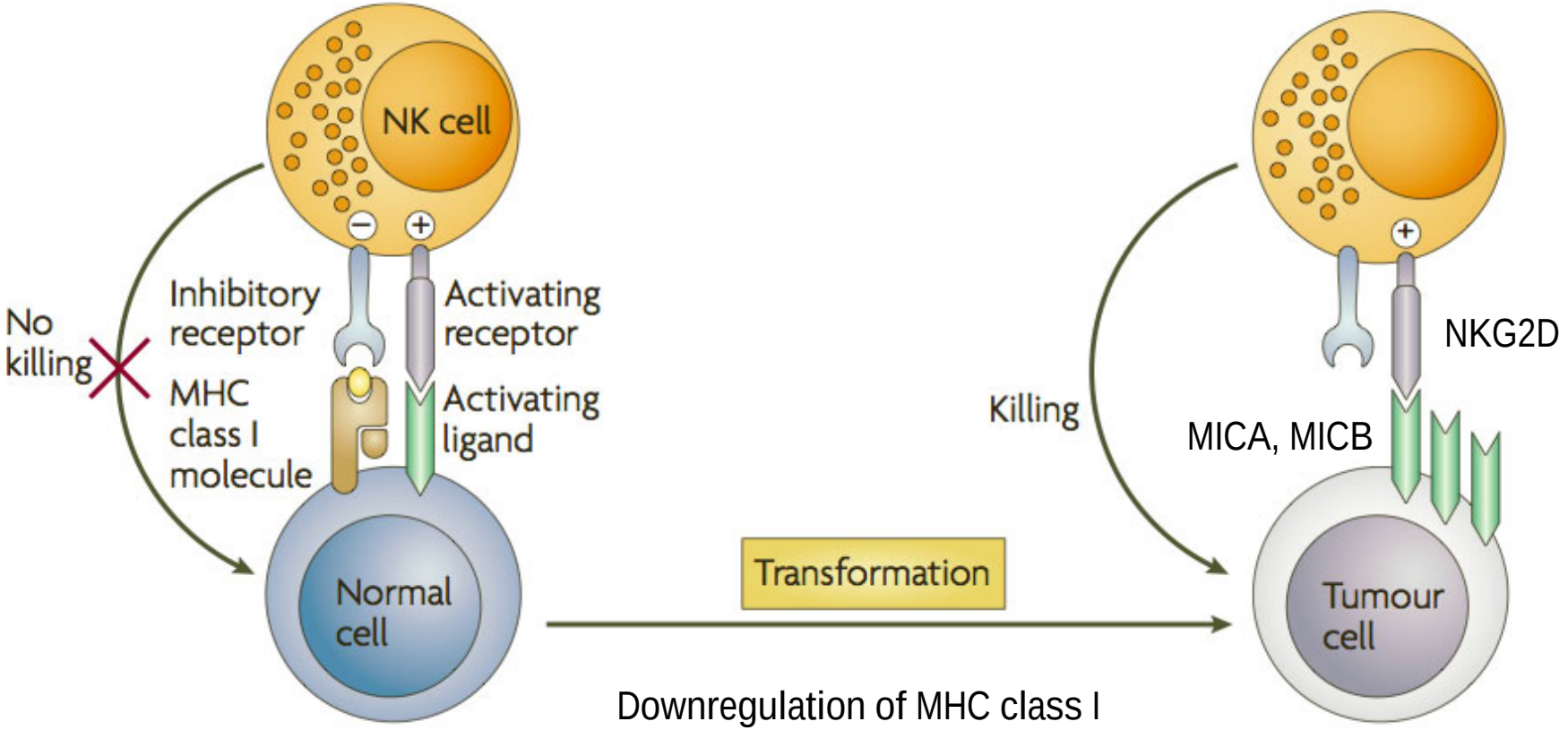
Yu et al., 2007

CD4+ regulatory T cells (Treg)



Wraith et al., 2004

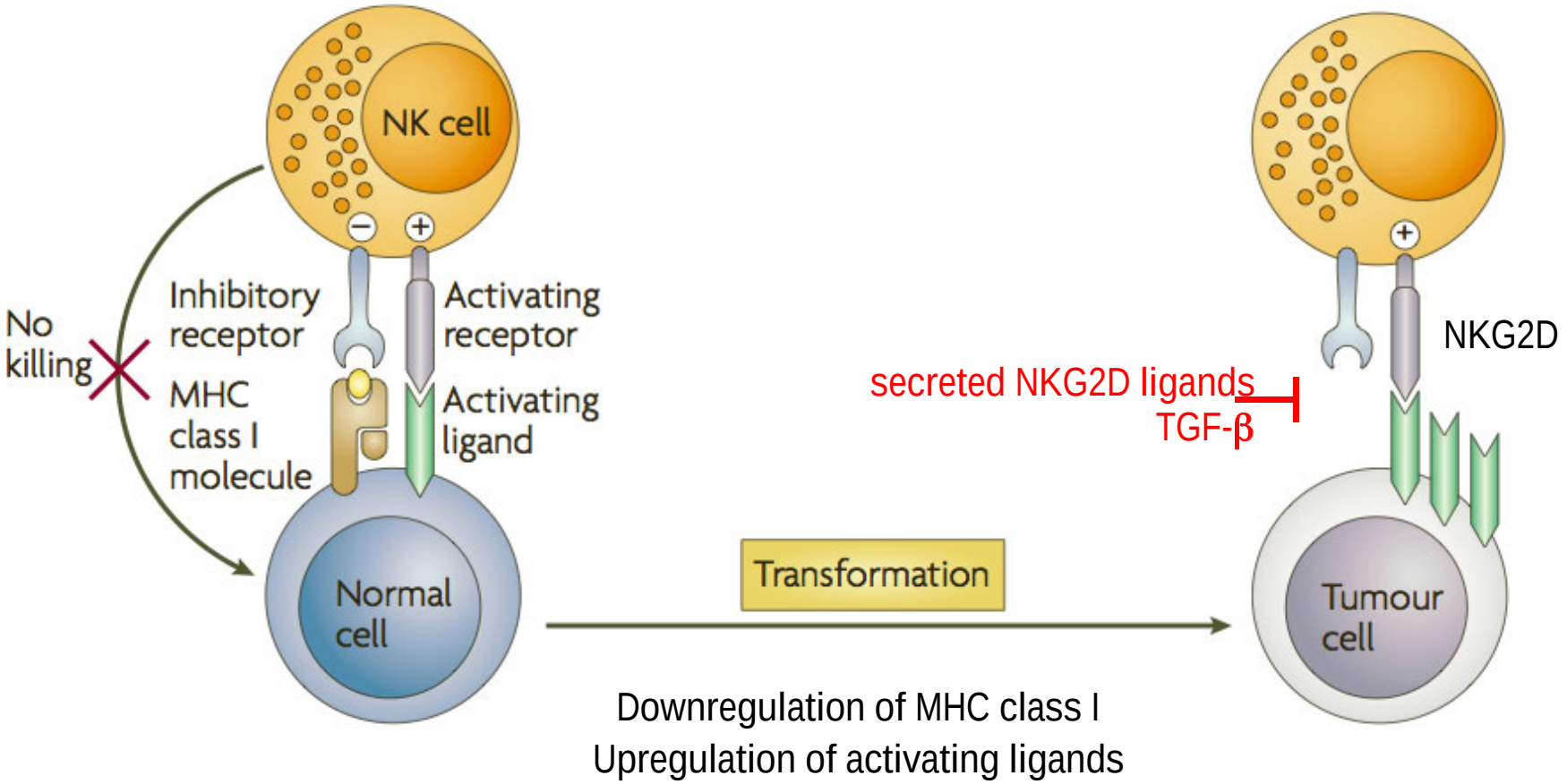
Missing-self recognition of tumor cells



Downregulation of MHC class I
Upregulation of activating ligands

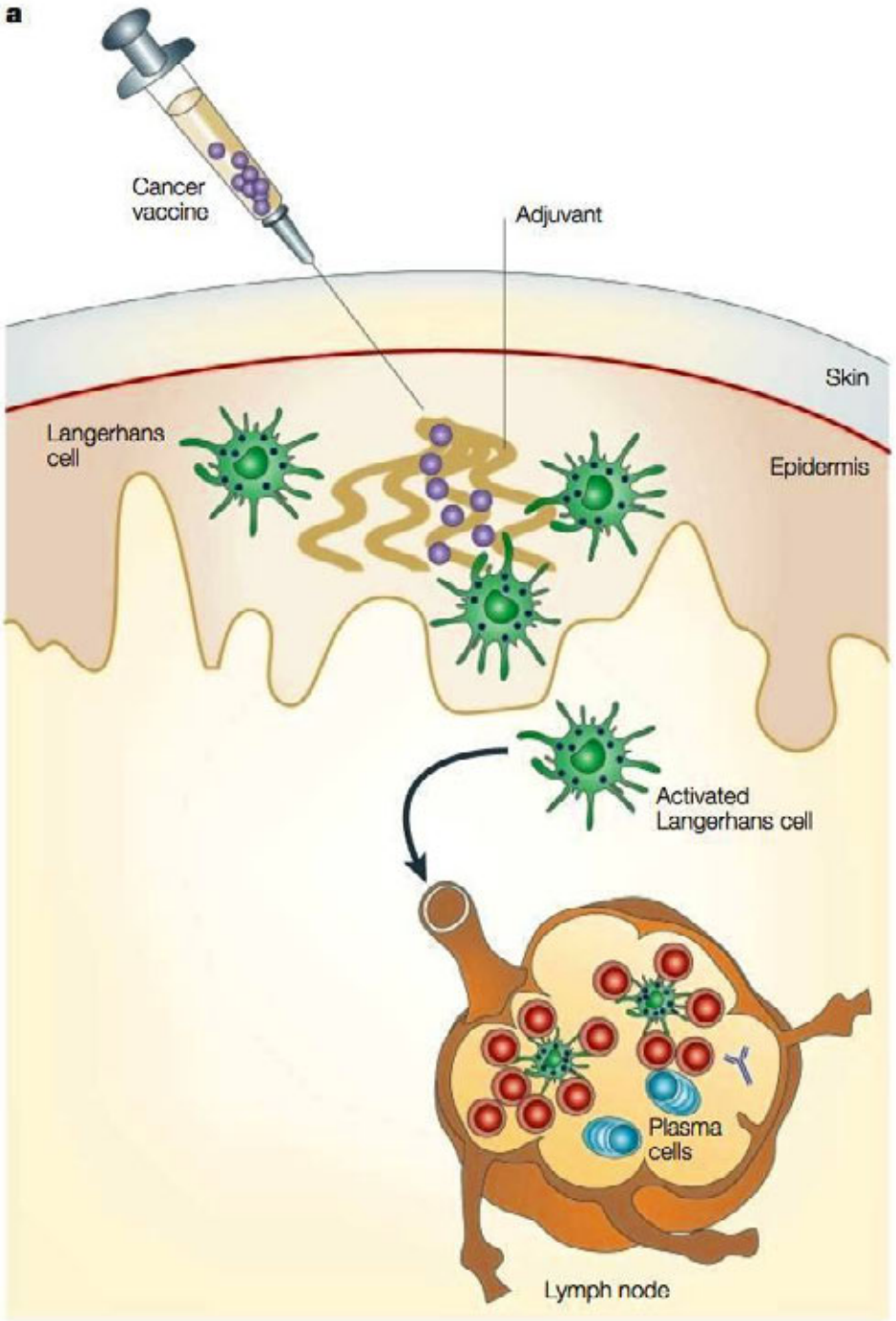
Ljunggren et al., 2007

Missing-self recognition of tumor cells



Ljunggren et al., 2007

Therapeutic vaccination as cancer therapy



Finn, 2003

Tumor antigens

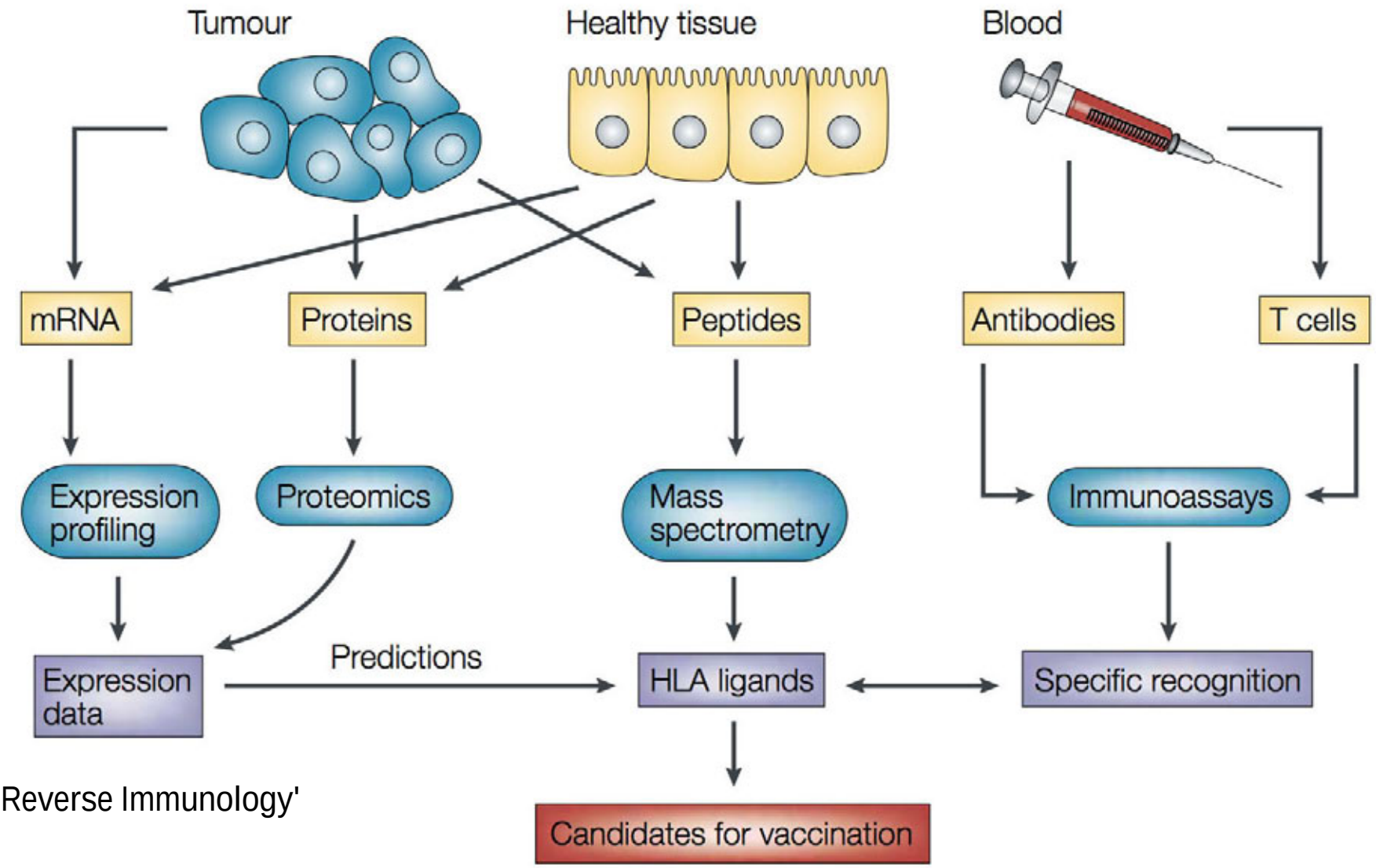
Tumor-specific antigens (TSAs)

Neo-antigens expressed by radiation- or chemical carcinogen-induced tumors due to mutations; idiotype expressed by B-cell malignancies; developmental antigens re-expressed by the tumor (oncofetal antigens); viral antigens.

Tumor-associated antigens (TAAs)

Differentiation antigens; antigens expressed in immunoprivileged tissues (cancer-testis/cancer-germline antigens); overexpressed 'self' antigens.

Identification of tumor antigens



'Reverse Immunology'

Stevanovic, 2002

Tumor antigens

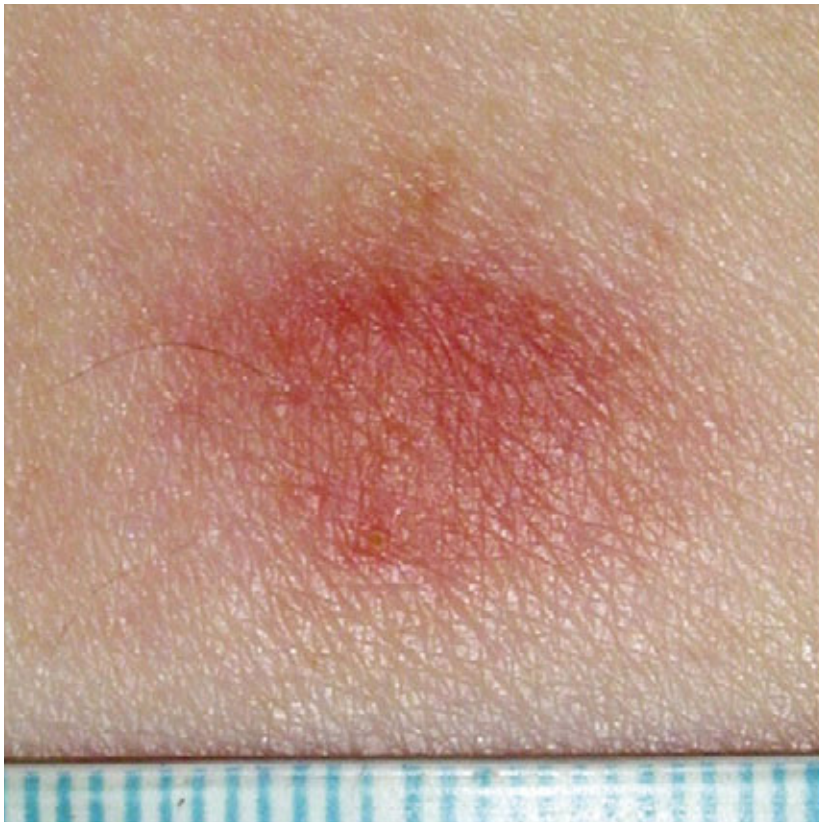
Human cancer antigens recognized by T lymphocytes.

Cancer–testis antigens	MAGE-3, BAGE, GAGE, NY-ESO-1
Melanocyte differentiation antigens	Melan-A/MART-1, tyrosinase, gp100
Point mutations	β-Catenin, MUM-1, CDK-4, p53, ras
Overexpressed 'self' antigens	Her-2/neu, p53, MUC-1
Viral antigens	HPV, HBV, HCV, EBV

EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papilloma virus.

Jäger et al., 2002

Cancer vaccines can induce specific immune responses ...



A DTH reaction induced after intradermal injection of 100 µg of the HLA-A2-restricted NY-ESO-1 peptide p157–165 (SLLMWITQC)

Jäger et al., 2002

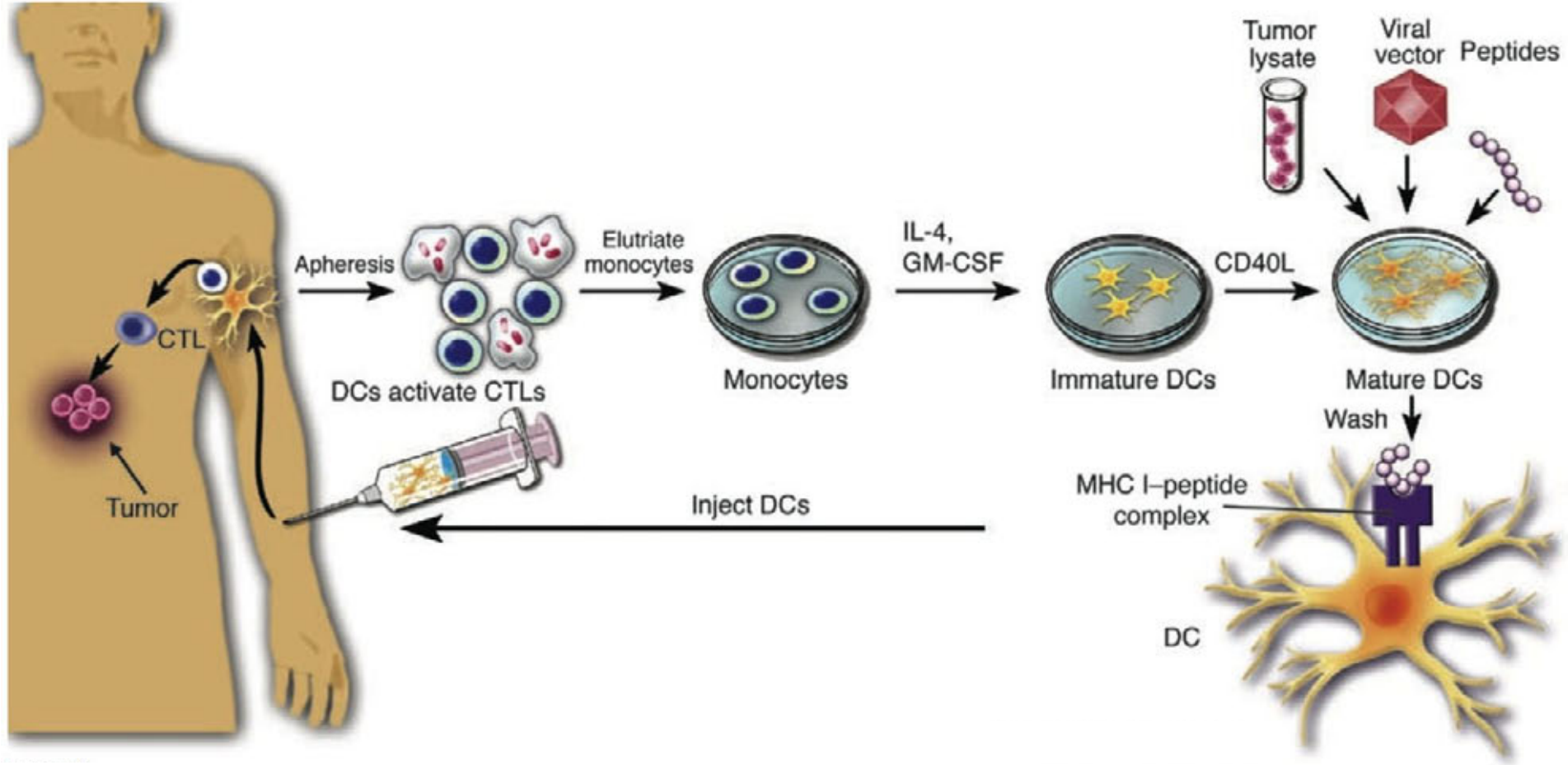
... but most often fail to induce tumor regression

Table 1 | **Clinical outcomes of cancer vaccines in patients with melanoma**

Vaccine	Total patients	Responding patients	Response rate (%)	References
Peptide vaccines	410	11	2.7	12,144,145
Viral vectors	160	3	1.9	12
Tumour cells	43	2	4.6	146,147
Dendritic cells	116	11	9.5	12,57,58,62,65,148

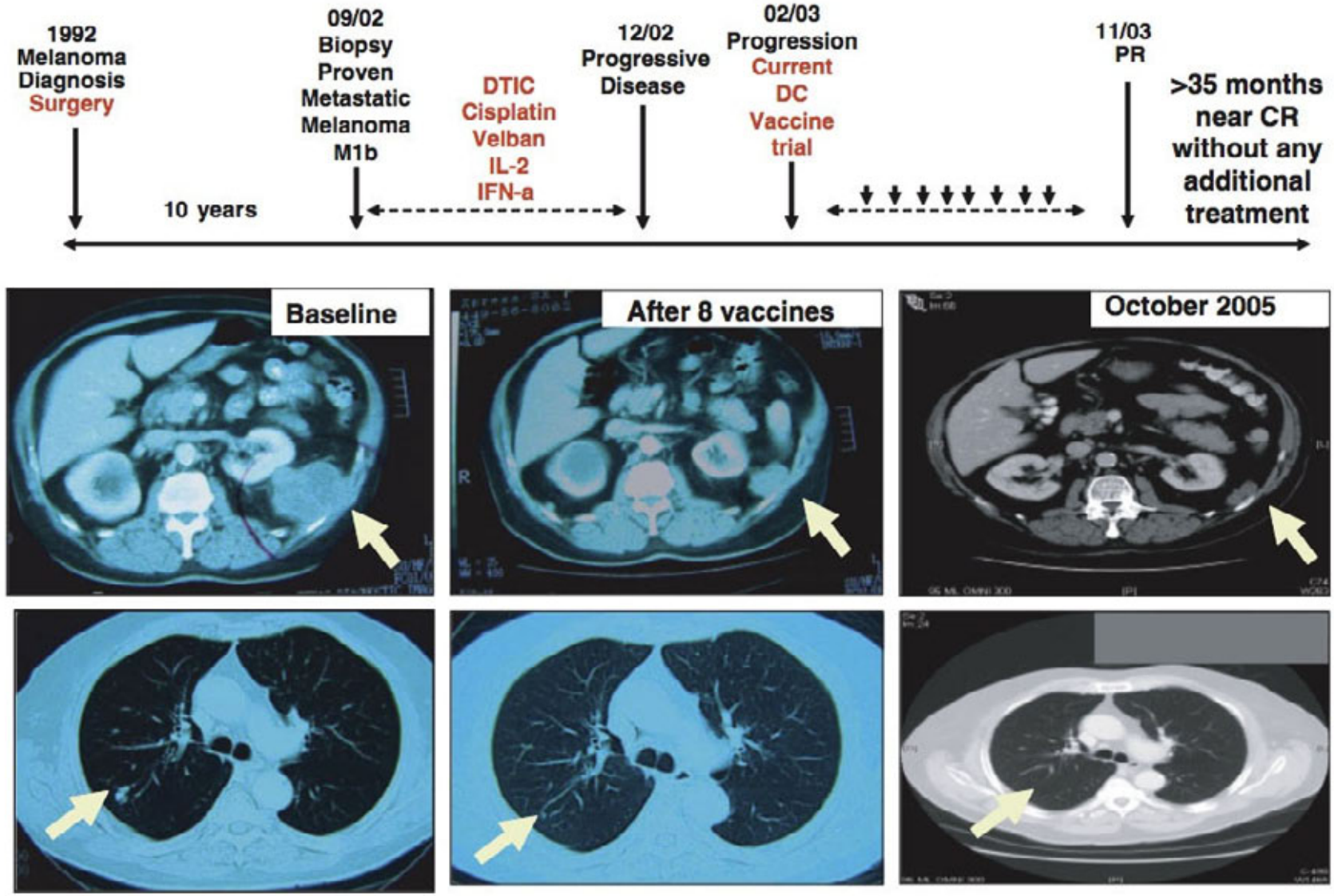
Banchereau & Palucka, 2005

Generation of DC vaccines



Berzofsky et al., 2004

Durable tumor regression in response to vaccination with DCs loaded with killed allogeneic melanoma cells

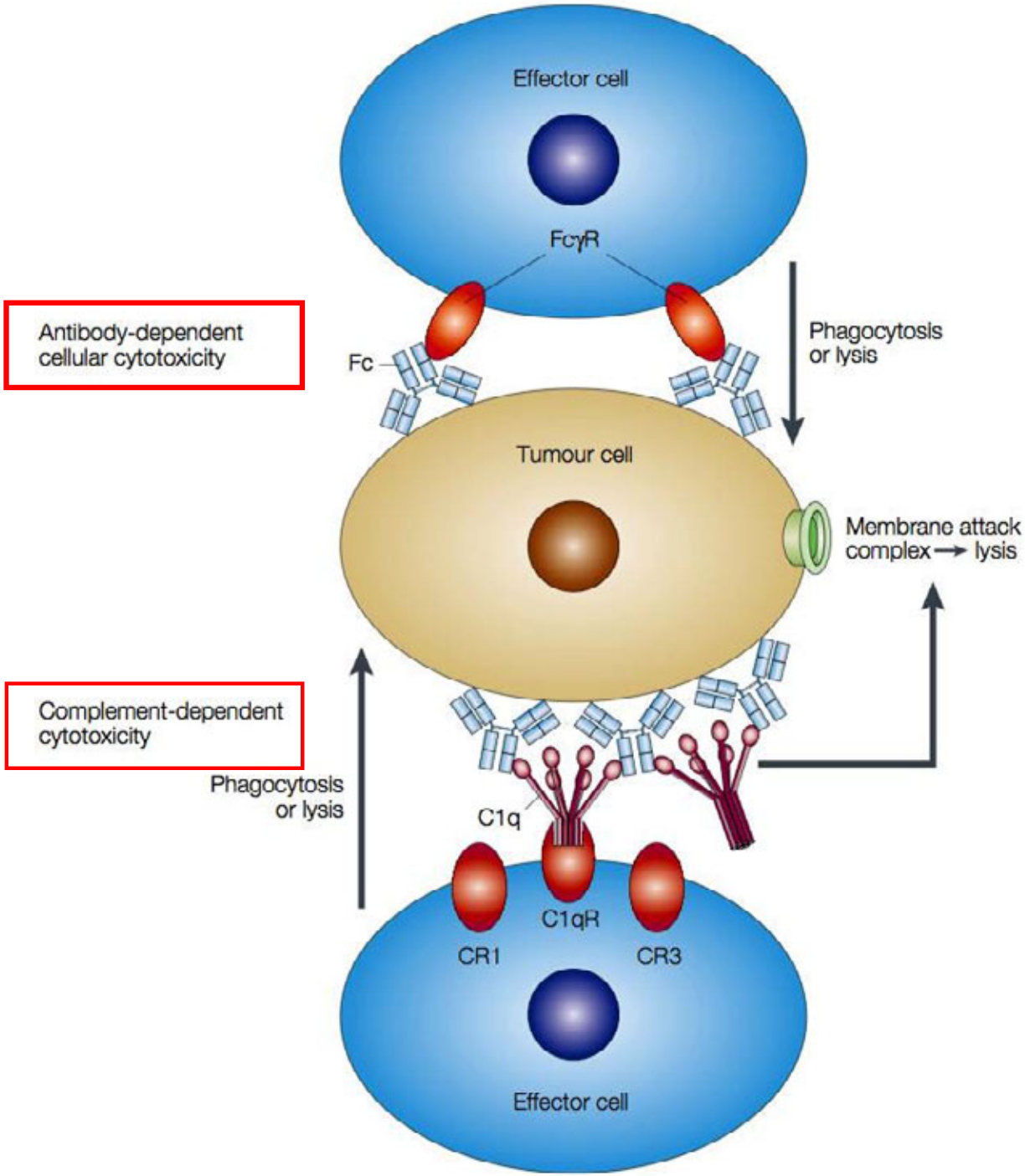


Palucka et al., 2007

Increasing the effectiveness of cancer immunotherapy: Enhancing the 'Enhancers'

Tumor antigens	Mode of delivery; combination with adjuvants
Dendritic cells	Proper activation/differentiation; stimulation of CD40 and/or Toll-like receptors
T cells	Adoptive cell therapy
NK cells	Activation of ADCC; adoptive cell therapy
Effector cytokines	IL-2, IL-12, IL-15, IFN-α

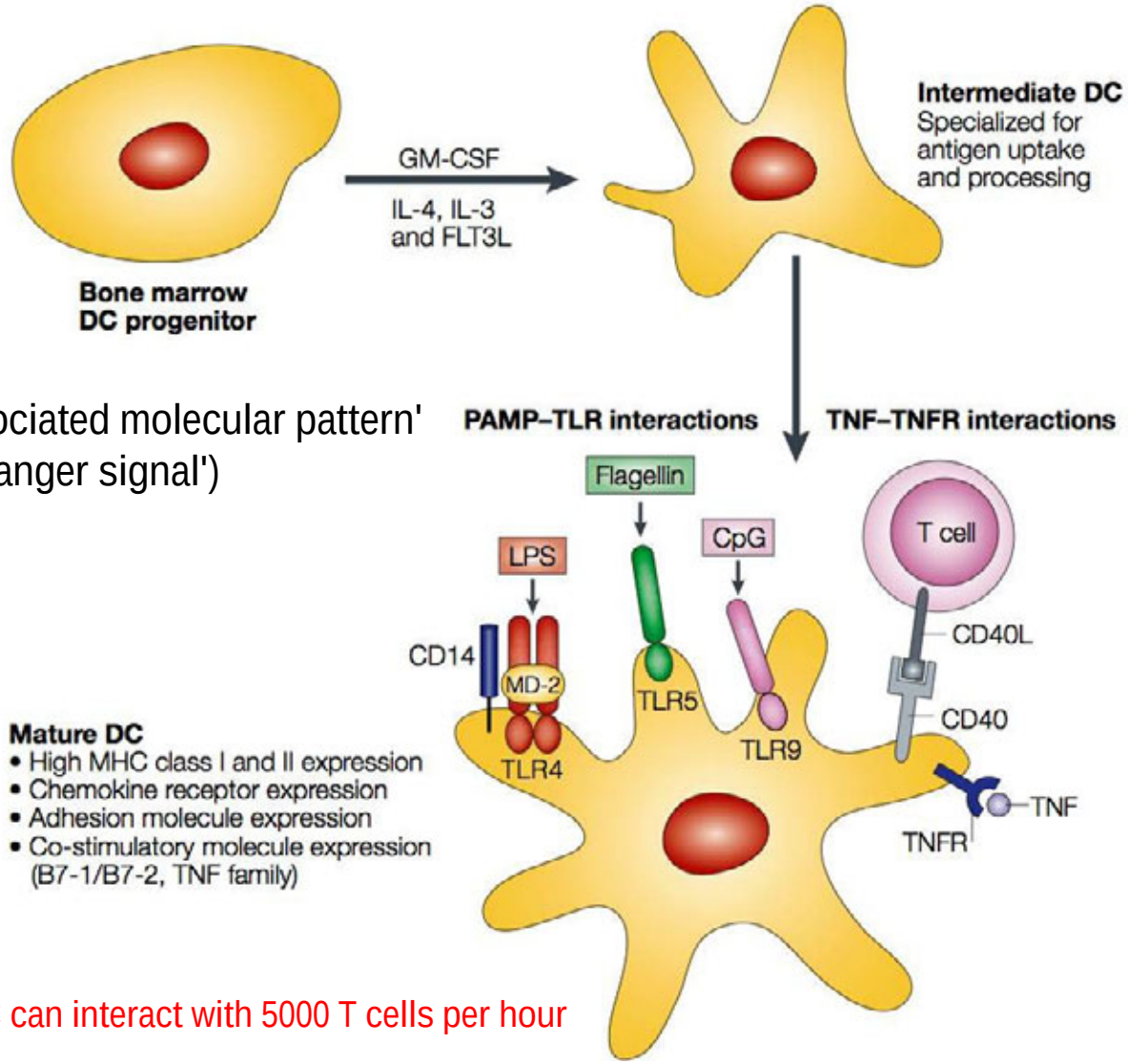
Antibody-dependent effector mechanisms



Cancer immunotherapy with monoclonal antibodies

Antibody	Type	Target	Cancer
Rituxan (rituximab)	ch IgG1	CD20	non-Hodgkin's lymphoma FDA approval 1997
Herceptin (trastuzumab)	hu IgG1	ErbB2/HER2	breast cancer FDA approval 1998
Erbitux (cetuximab)	ch IgG1	EGFR	colorectal cancer FDA approval 2004
Avastin (bevacizumab)	hu IgG1	VEGF	colorectal cancer FDA approval 2005

Dendritic-cell differentiation and activation

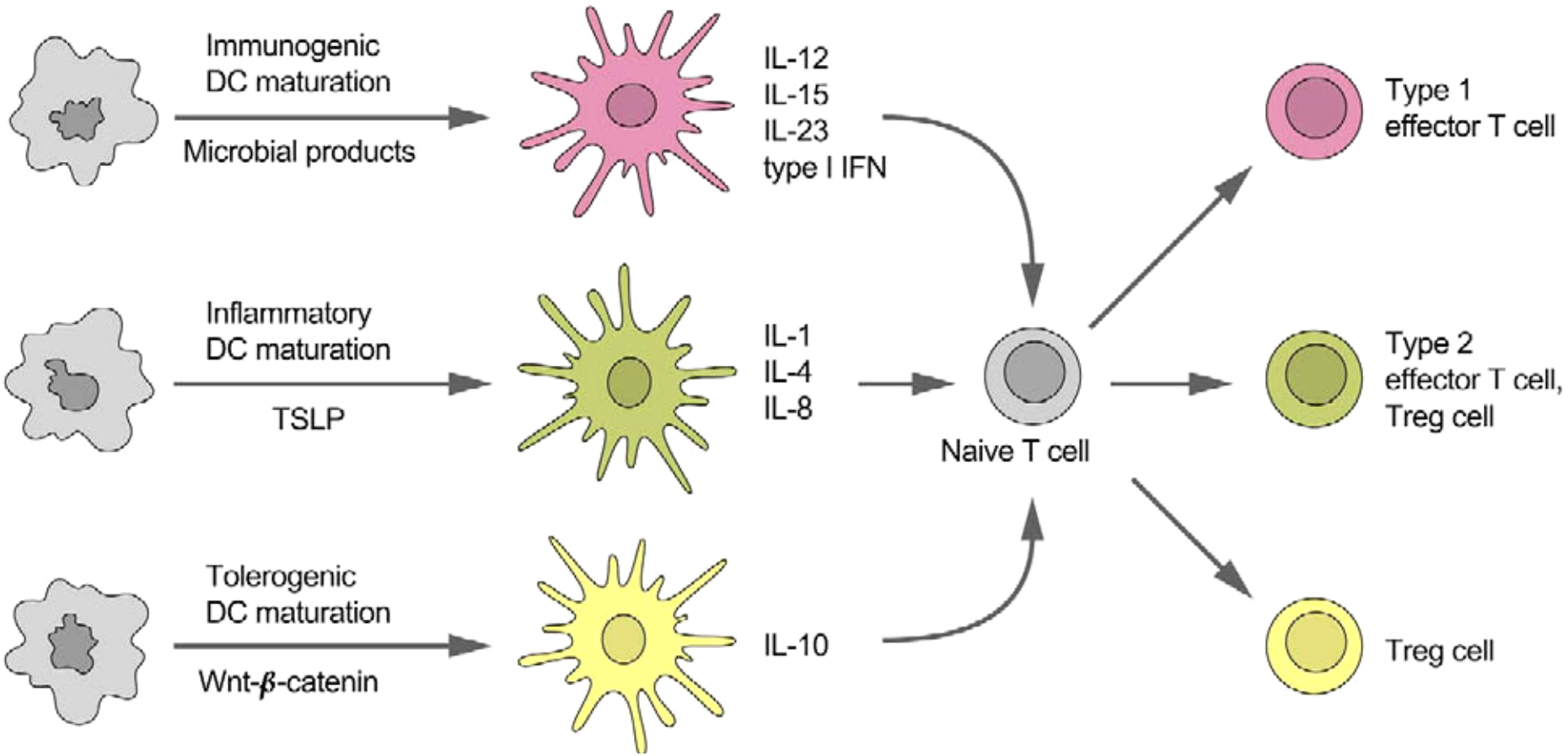


'Pathogen-associated molecular pattern'
('danger signal')

a single DC can interact with 5000 T cells per hour

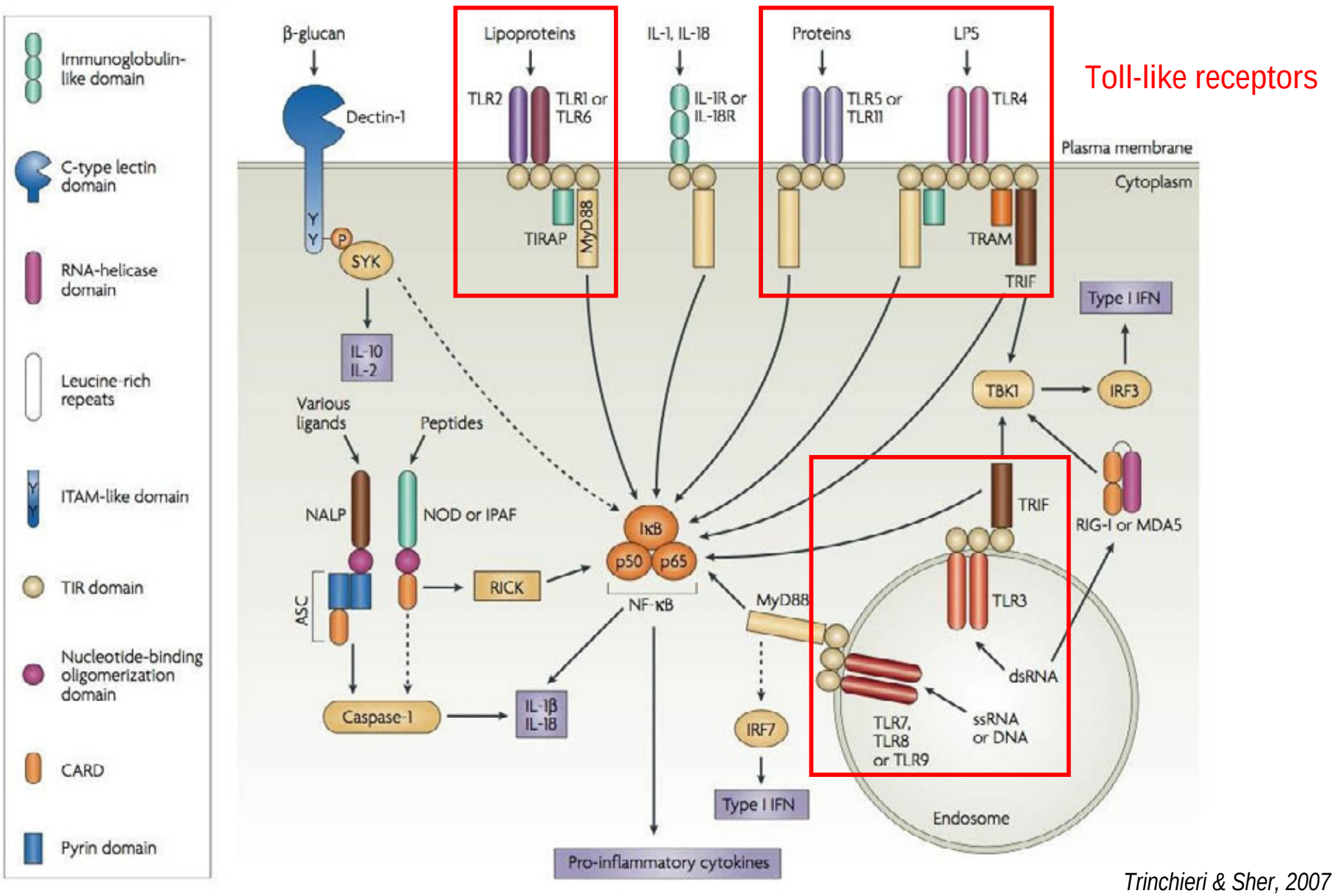
Pardoll, 2002

Different mechanisms of DC maturation



Palucka et al., 2010

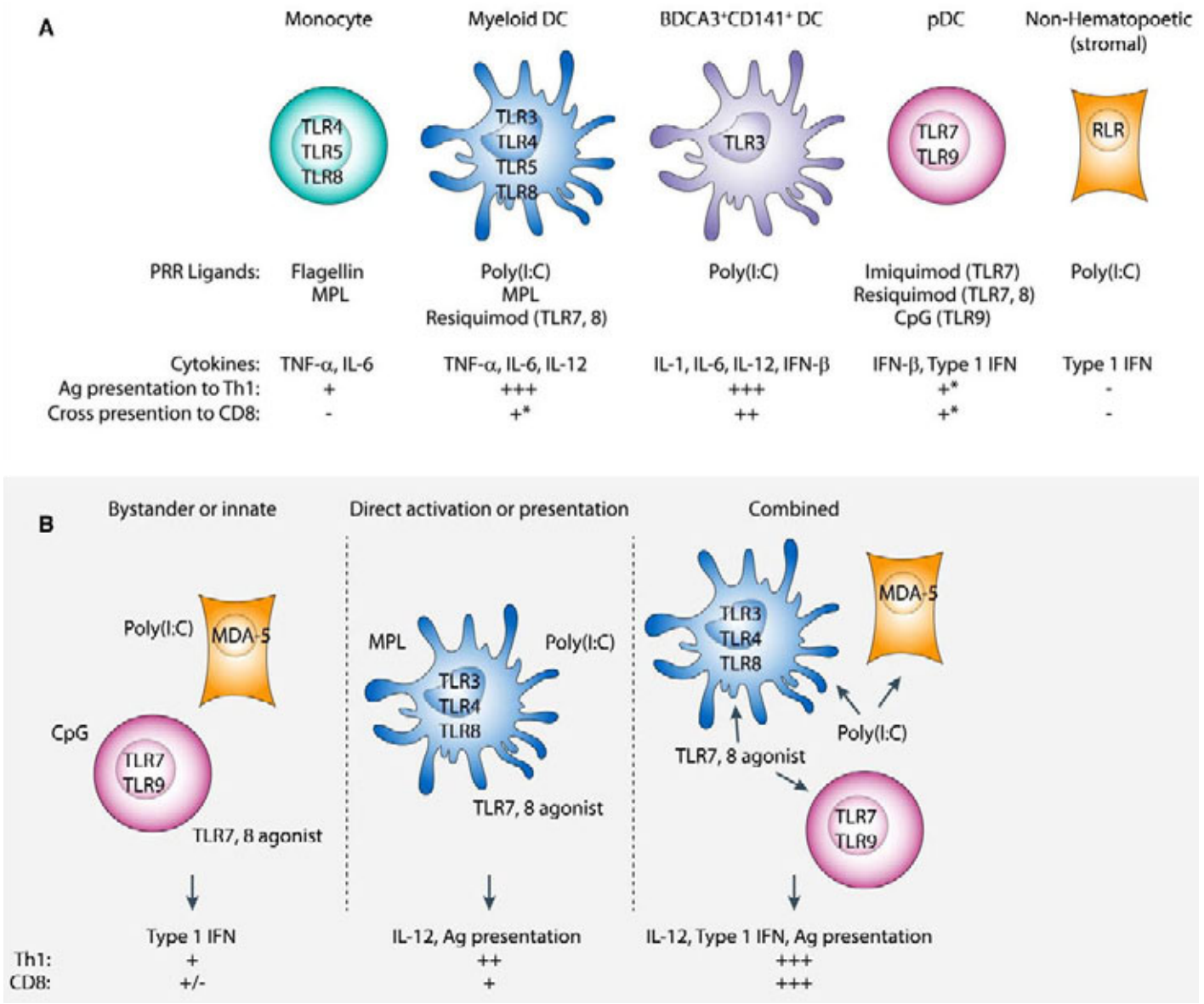
Pattern-recognition receptors



Toll-like receptors

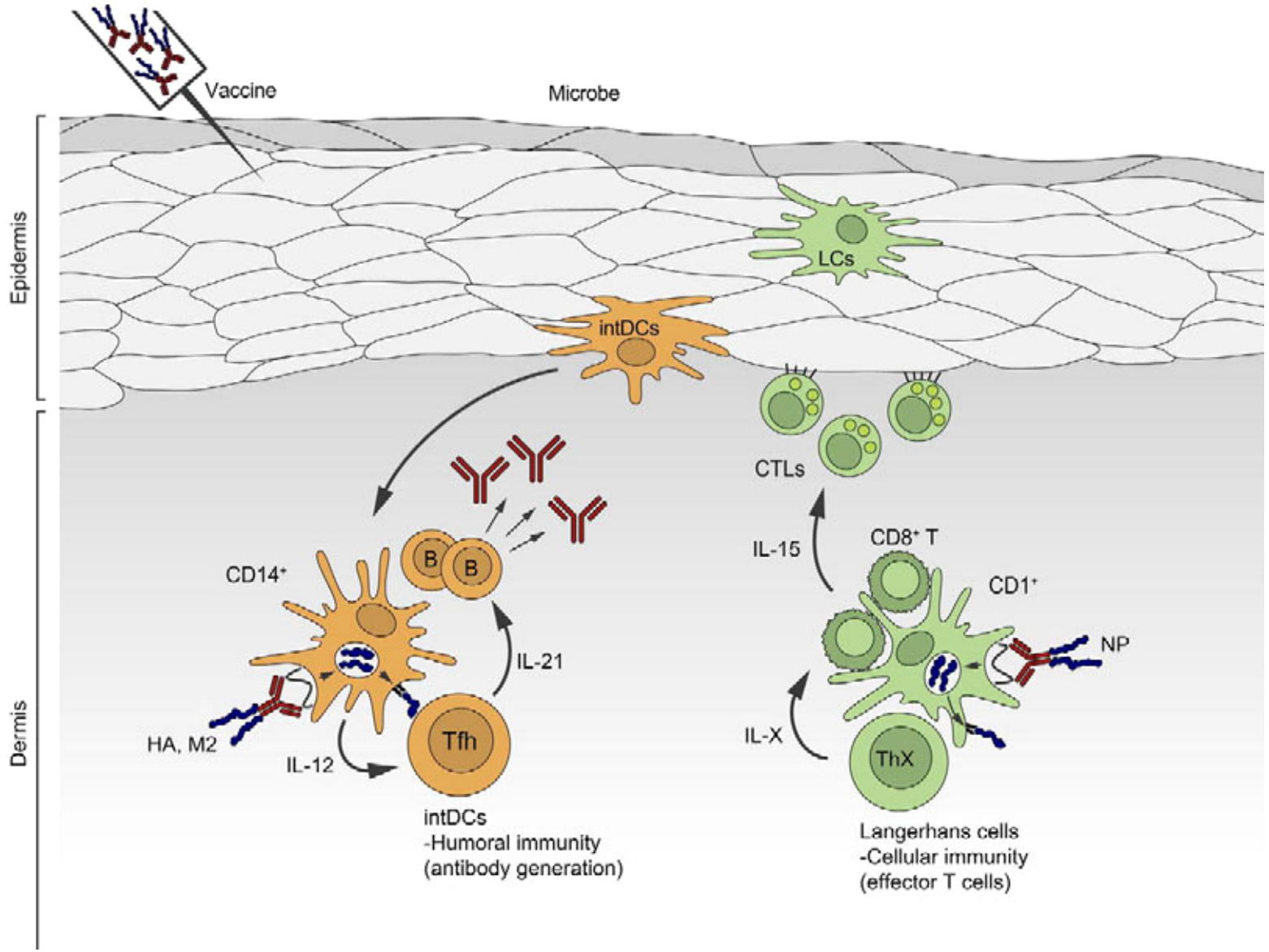
Trinchieri & Sher, 2007

Direct and indirect effects of PRR ligands

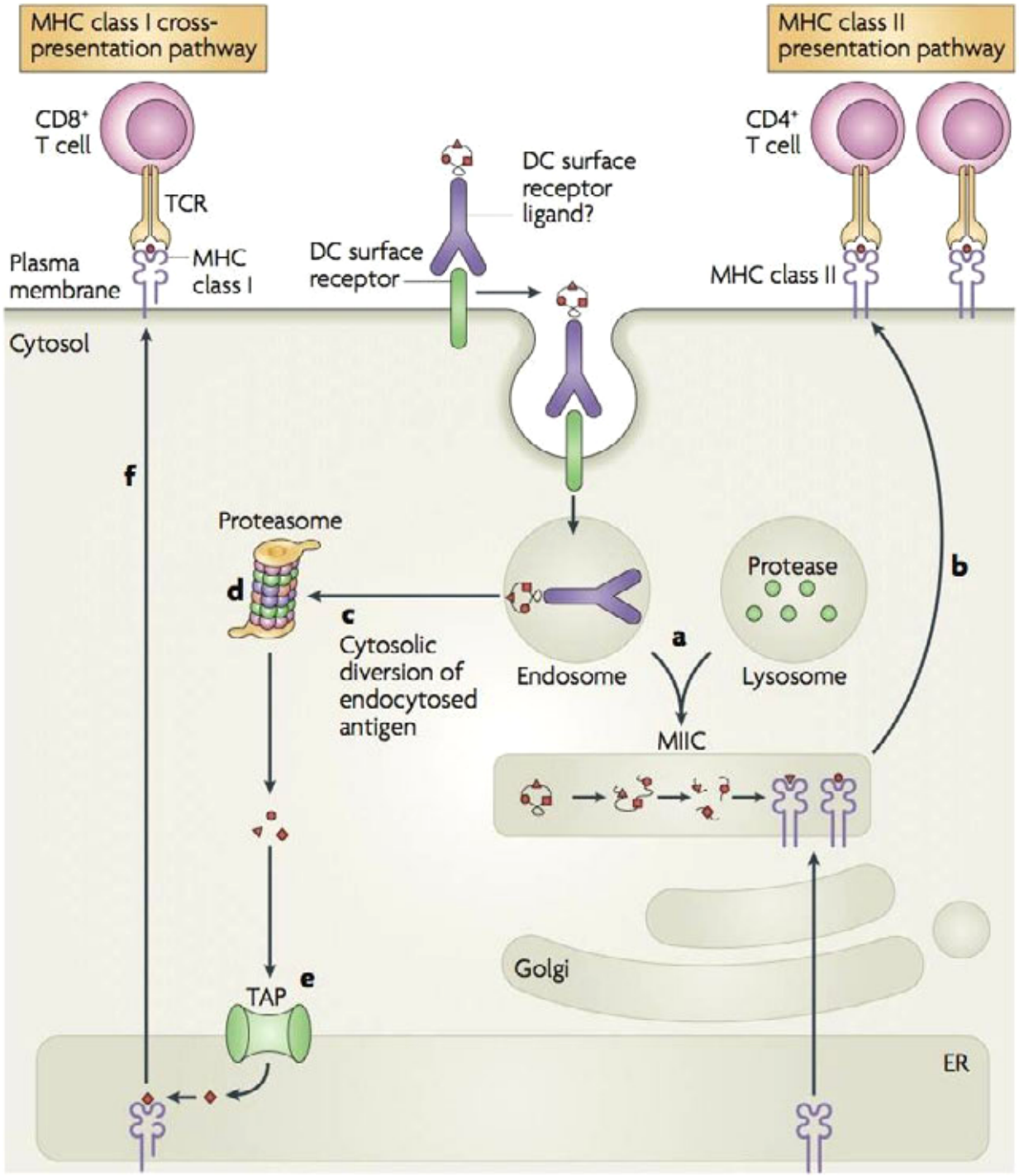


Coffman et al., 2010

Targeting vaccines to different DC subsets



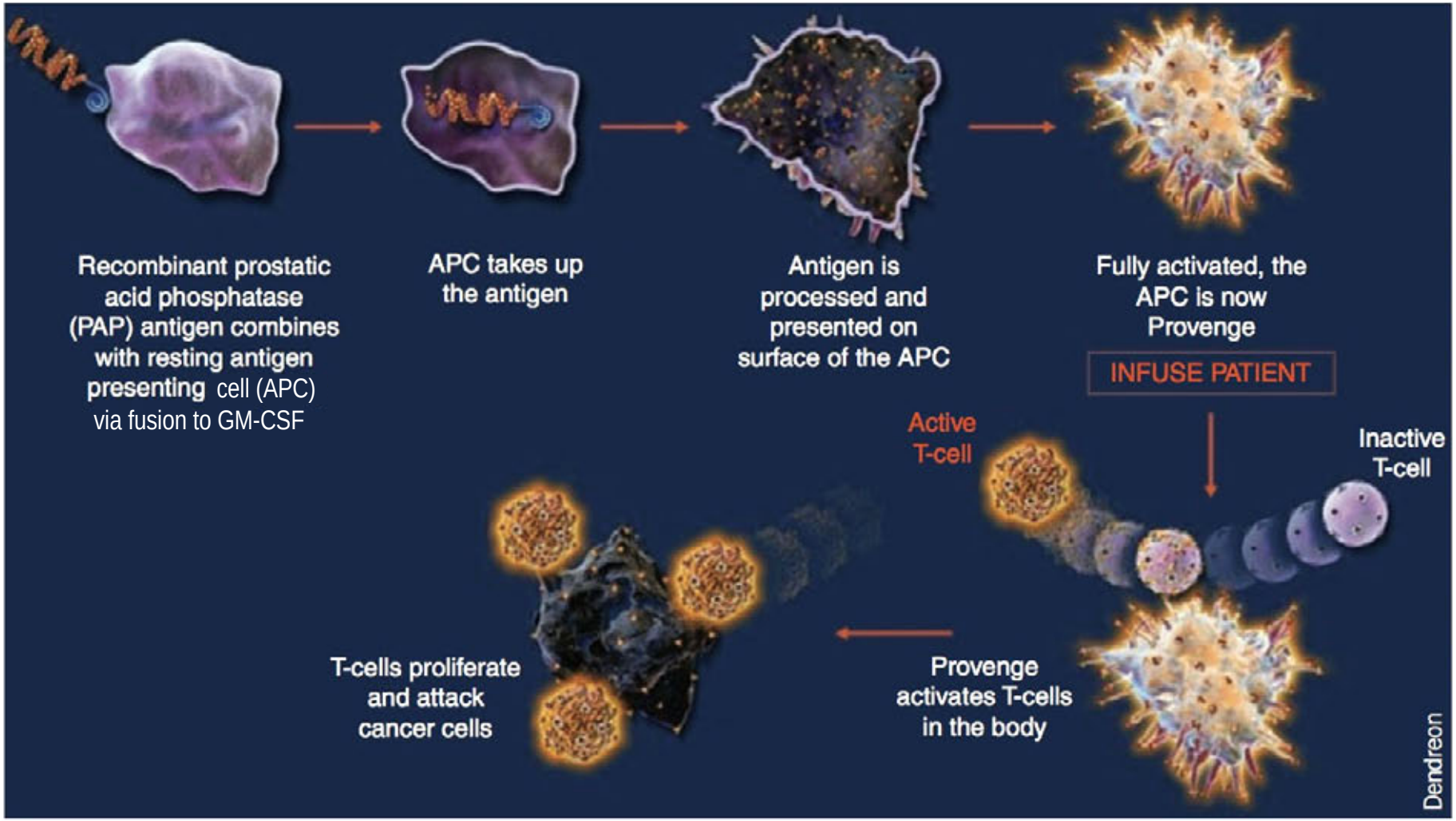
Palucka et al., 2010



Tacken et al., 2007

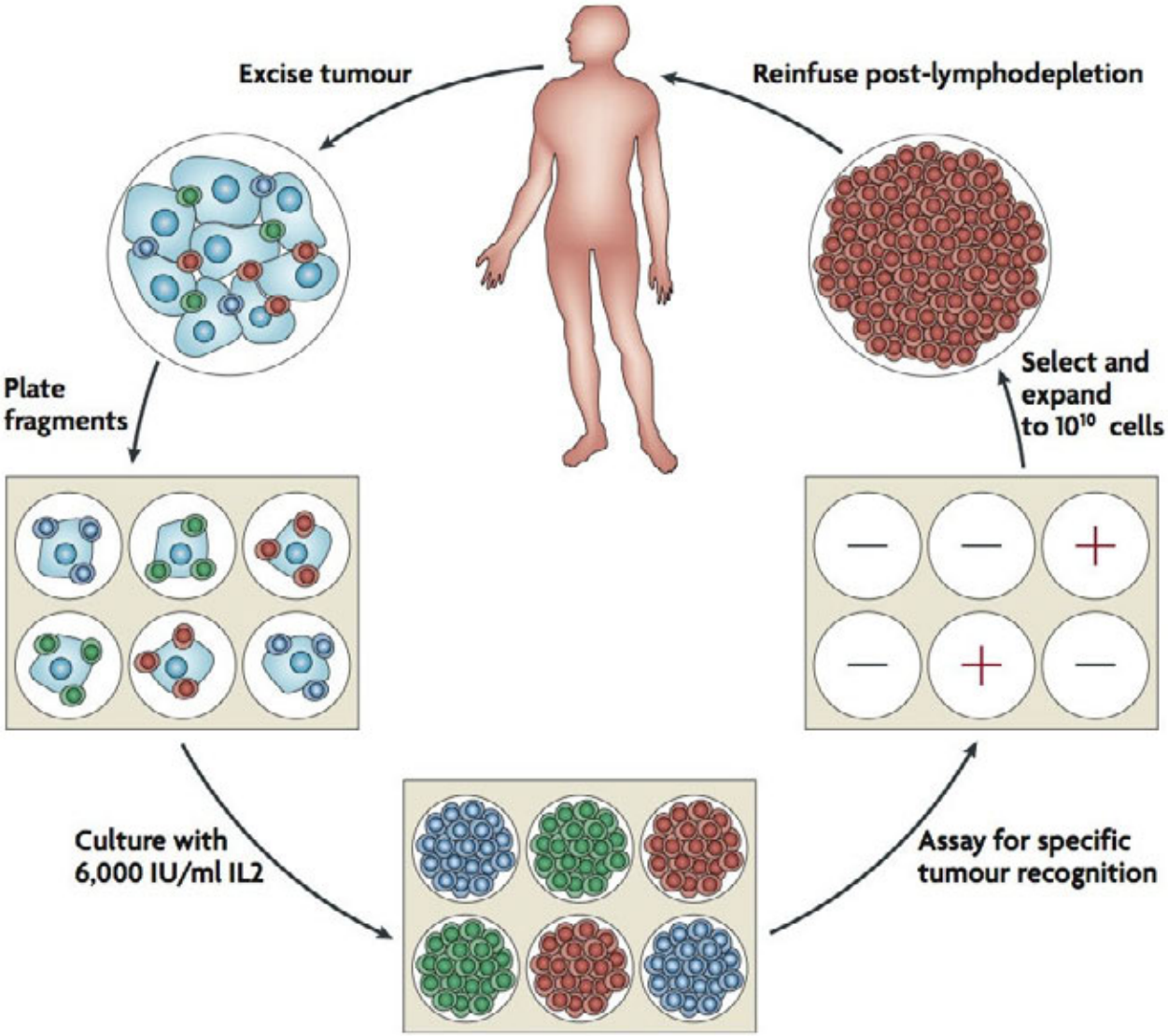
Fate of antigens targeted to DC surface receptors

The prostate cancer vaccine sipuleucel-T (Provenge)



DeFrancesco, 2010

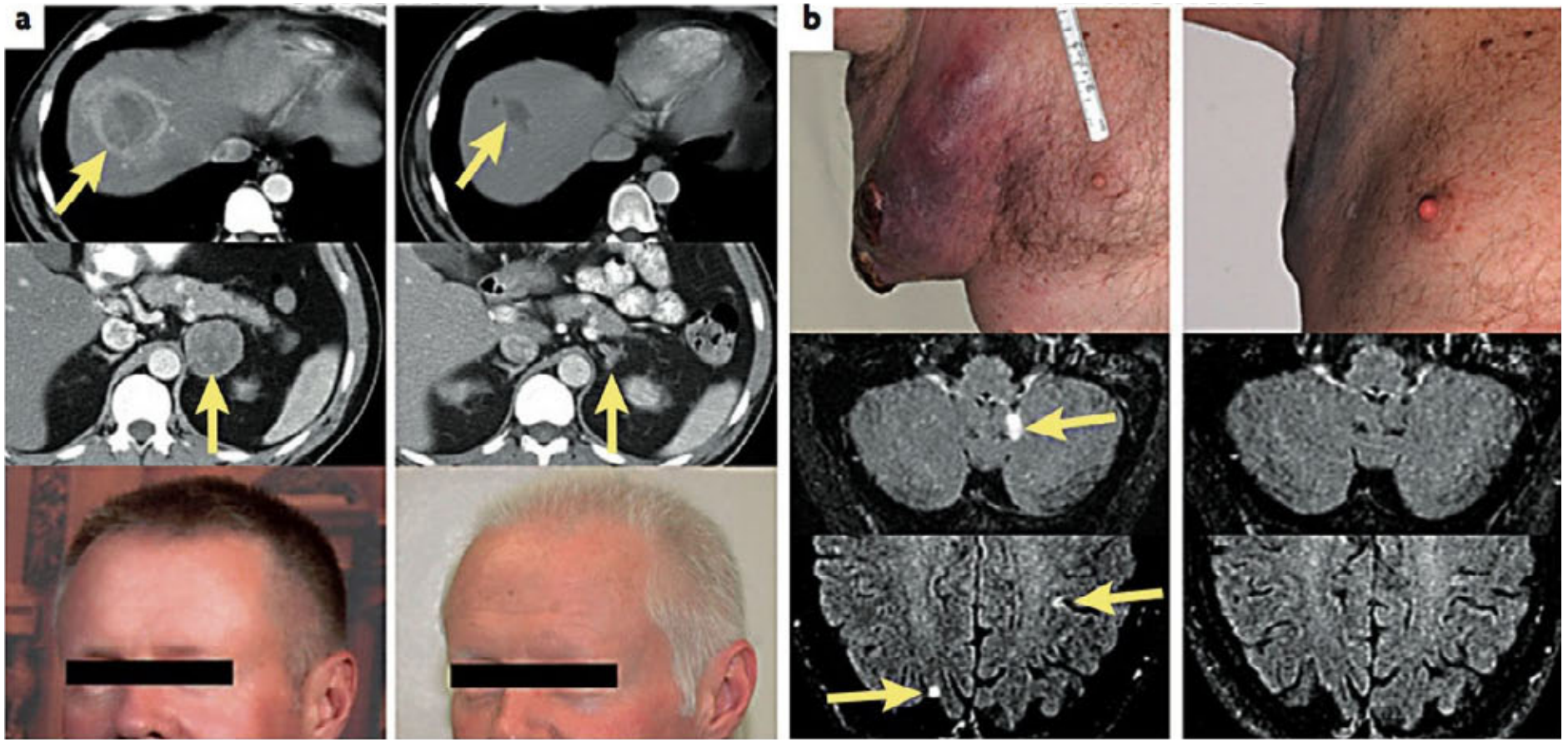
Generation of tumor-specific T cells for adoptive cell therapy



IL-2
anti-CD3

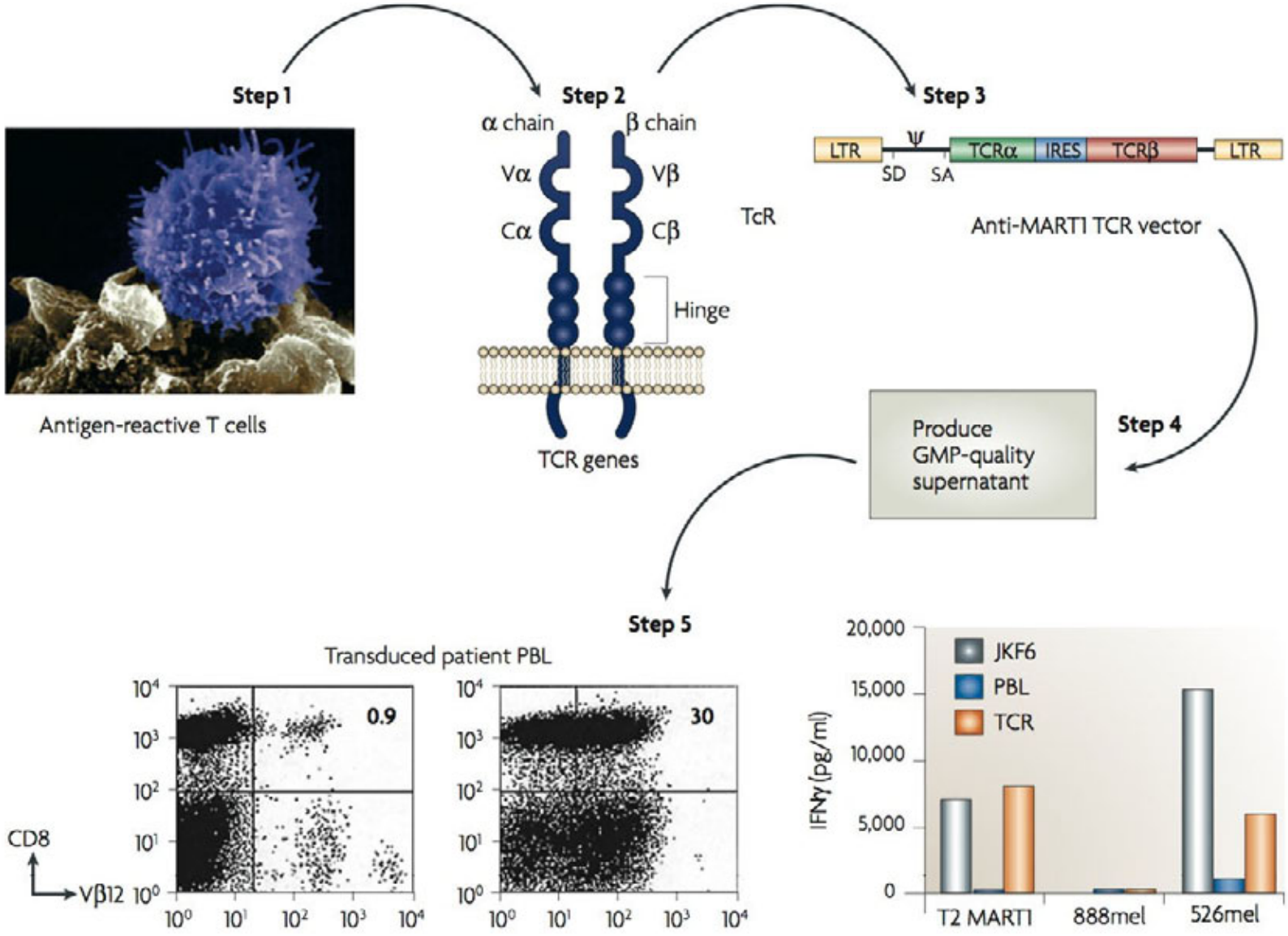
Rosenberg et al., 2008

Objective tumor regression in melanoma patients after ACT following lymphodepleting conditioning



Rosenberg et al., 2008

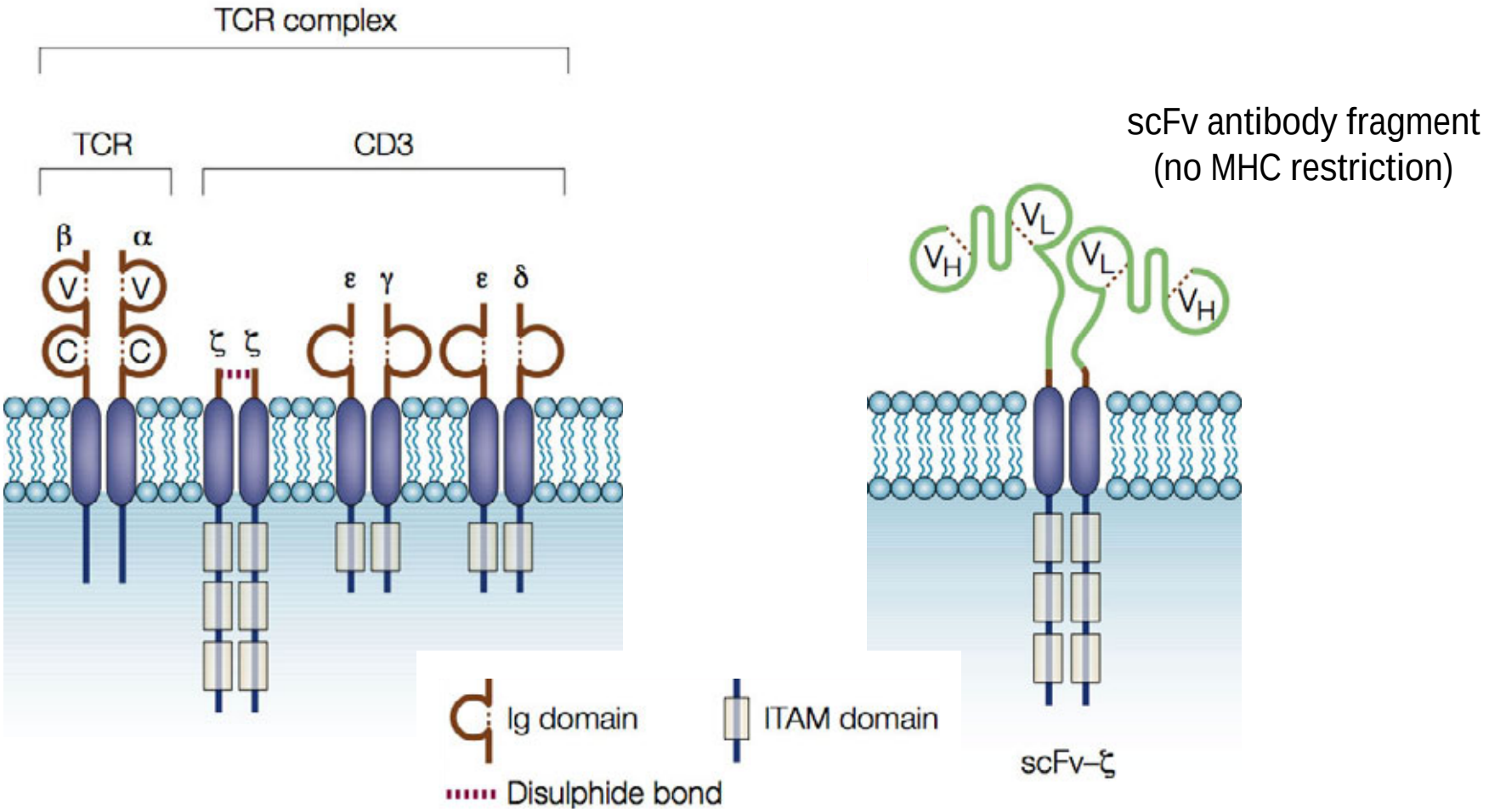
Enhancing specificity and activity of T cells for adoptive therapy



Rosenberg et al., 2008

Enhancing specificity and activity of T cells for adoptive therapy

Ectopic expression of defined MHC-restricted, tumor-specific T-cell receptors, or chimeric antigen receptors utilizing antibody fragments for tumor cell recognition

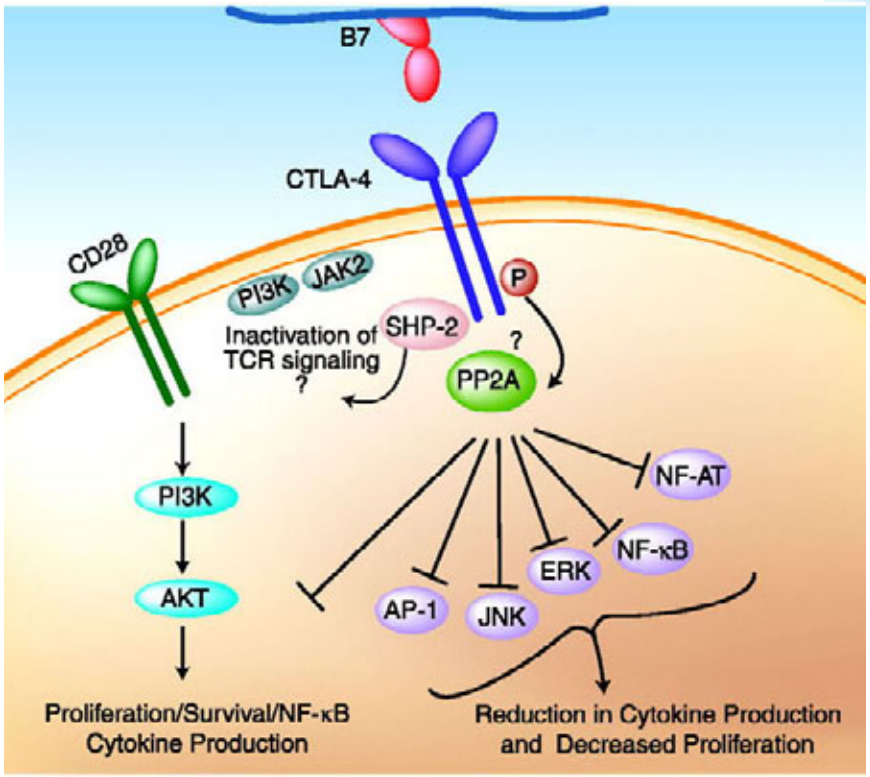


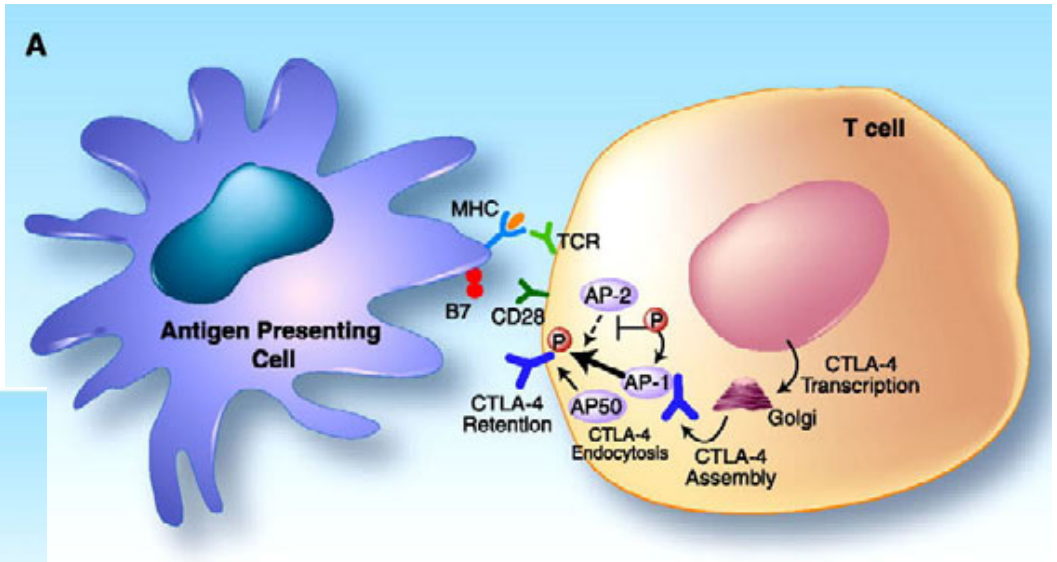
Sadelain et al., 2002

Increasing the effectiveness of cancer immunotherapy: Inhibiting the 'Inhibitors'

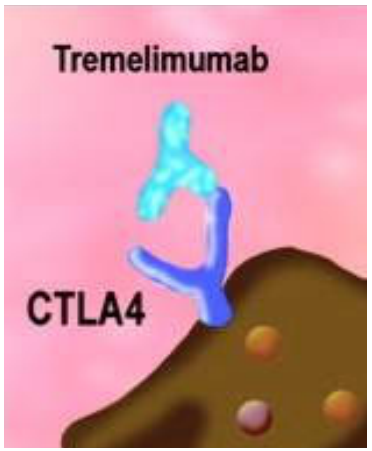
Treg	Low dose cyclophosphamide; anti-CD4; anti-CD25; recombinant toxins
CTLA-4; PD1	Blocking antibodies
Suppressive cytokines and growth factors	Blocking antibodies; STAT3 inhibitors
Suppressive DCs	Blocking suppressive pathways (IDO); STAT3 inhibitors
Immunodominant/ self-antigens	Fostering antigen release by targeting the stroma

CTLA-4 negatively regulates T-cell activity





Blocking anti-CTLA-4 antibody



Hodi, 2007

Treatment of melanoma patients with anti-CTLA-4 antibody

Clinical Responses and Immune-Related Adverse Events (irAEs) in Trials of Ipilimumab and Tremelimumab Melanoma

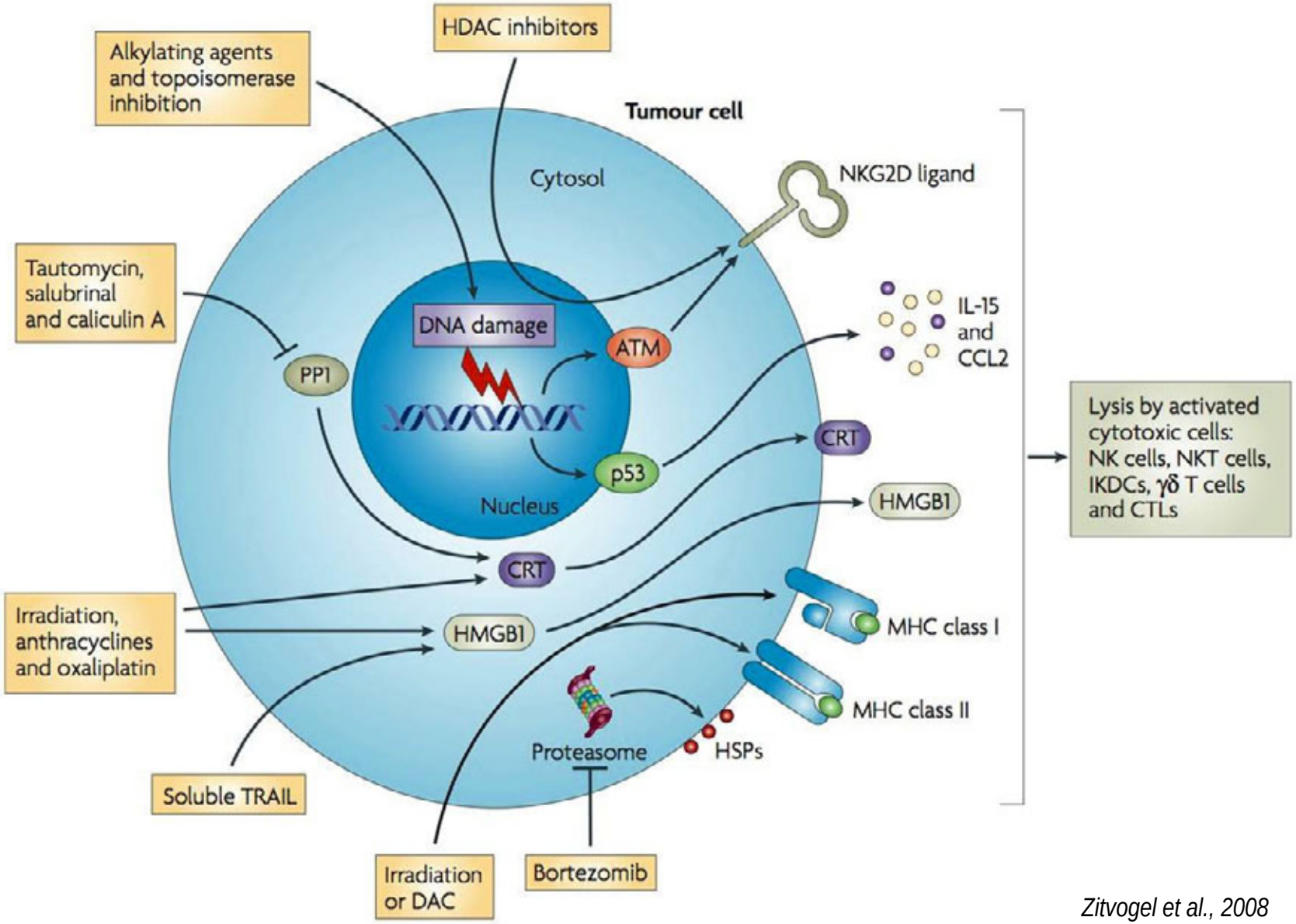
Regimen	% CR (No.)	% PR (No.)	% SD (No.)	Most common grade 3/4 or serious irAEs
Tremelimumab, first/ pretreated/adjuvant	5.9 (2 of 34)	5.9 (2 of 34)	11.8 (4 of 34)	Dermatitis*, diarrhea*
Tremelimumab, pretreated	3.3 (3 of 90)	4.4 (4 of 90)	28.9 (26 of 90)	Diarrhea
Ipilimumab, first-line	0	5.4 (2 of 37)	10.8 (4 of 37)	N/A
Ipilimumab+DTIC, first-linc	5.7 (2 of 35)	11.4 (4 of 35)	11.4 (4 of 35)	
Ipilimumab+vaccine, pretreated	3.6 (2 of 56)	8.9 (5 of 56)	N/A	Colitis, dermatitis
Ipilimumab+vaccine, pretreated	14.3 (2 of 14)	7.1 (1 of 14)	0	Dermatitis, colitis/enterocolitis
Ipilimumab+IL-2	8.3 (3 of 36)	13.9 (5 of 36)	N/A	Enterocolitis

CR indicates complete response; PR, partial response; SD, stable disease; IL-2, interleukin-2; DTIC, dacarbazine; N/A, neither available nor reported.

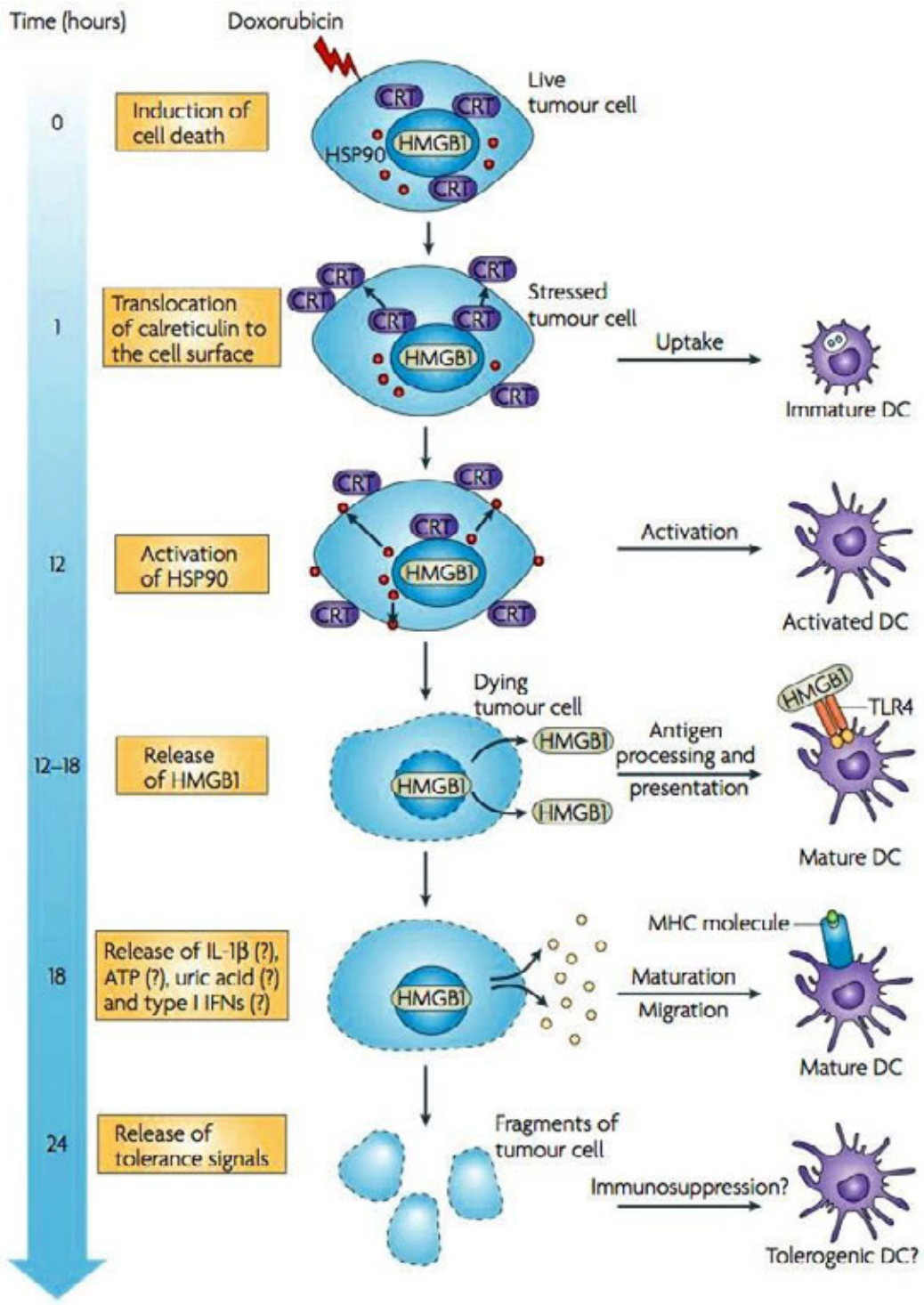
* Dose-limiting toxicity.

O'Day et al., 2007

Linking tumor-cell stress and effector-cell killing



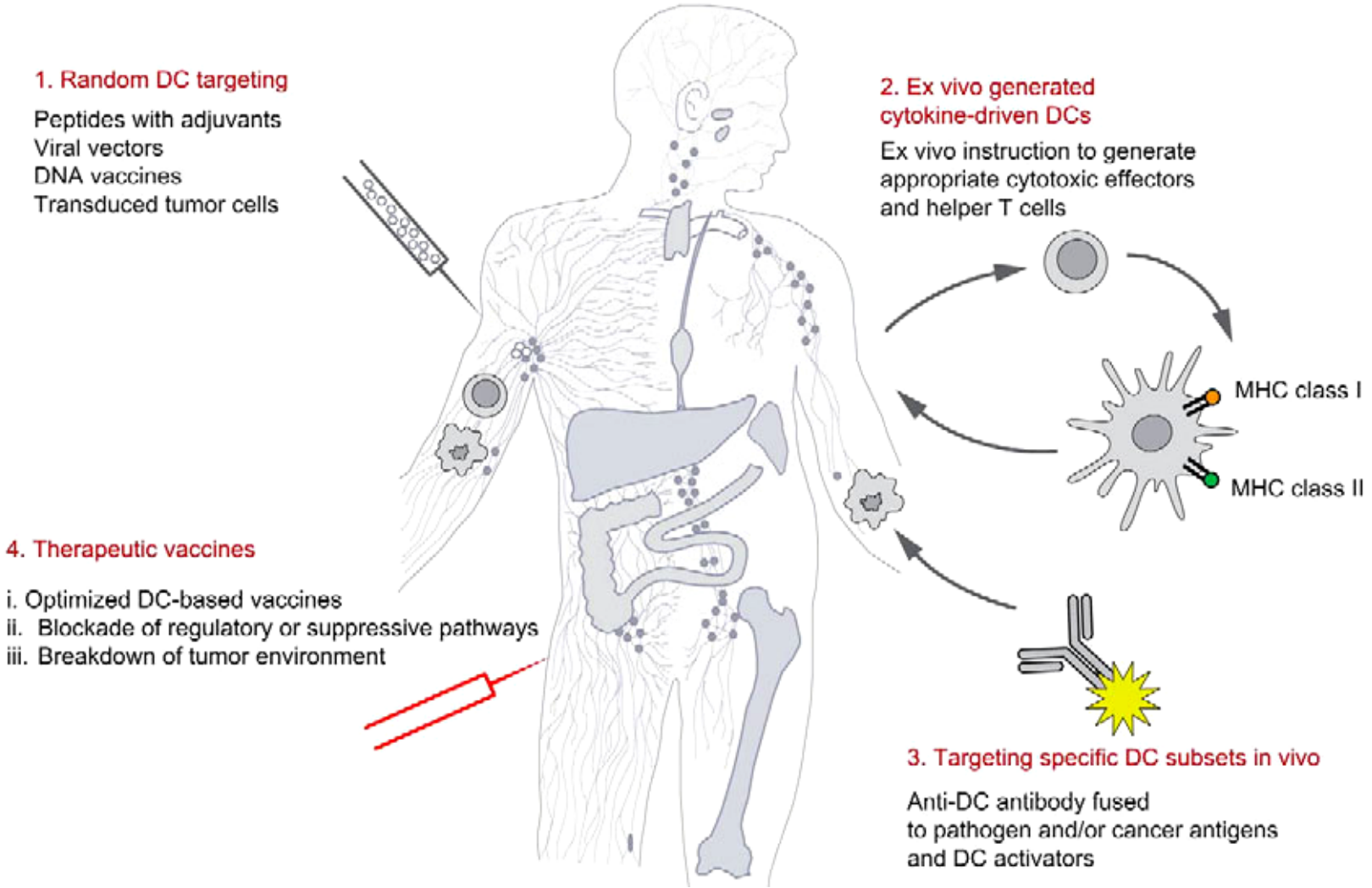
Zitvogel et al., 2008



Zitvogel et al., 2008

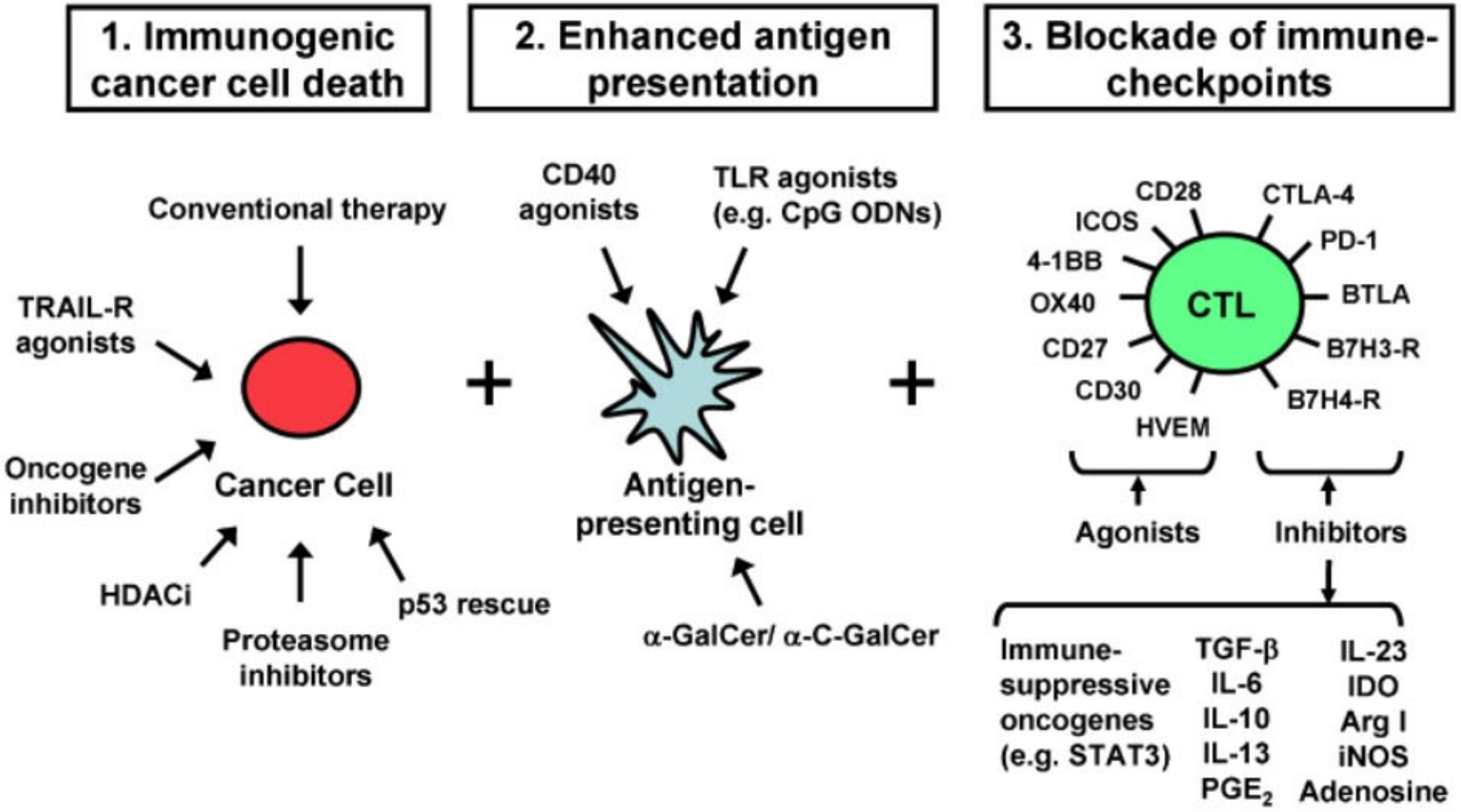
Tumor-cell stress and activation of APCs

Approaches to DC-based therapeutic vaccination



Palucka et al., 2010

An integrated approach will be required to achieve clinically relevant anti-tumor immune responses



Stagg et al., 2007

Additional Tables

Ligand recognition by Toll-like receptors

TLR	Microbial ligands	Endogenous ligands
TLR1/TLR2	Triacyl lipopeptide (Pam3CSK4)	n.d.
TLR2/TLR6	Diacyl lipopeptides (Pam2CSK4); lipoteichoic acid; zymosan; porins; MALP2; bacterial peptidoglycan; lipoarabinomannan	HSP-60,-70,-96; HMGB1
TLR3	dsRNA	mRNA
TLR4	LPS; mannan; phospholipids; envelope proteins (MMTV, RSV)	HSP-22,-60,-70,-96; fibrinogen; HMGB1; hyaluronan fragments; fibronectin (extra domain A); minimally modified low-density lipoprotein; surfactant protein A
TLR5	Flagellin	n.d.
TLR7	ssRNA (viral)	ssRNA (immune complexes)
TLR8	ssRNA (viral)	ssRNA (immune complexes)
TLR9	DNA (bacterial/viral)	DNA (immune complexes)
TLR10	Unknown	n.d.

Kanzler et al., 2007

Vaccine adjuvants in experimental and clinical use

Table 1. Triggering of the Innate and Adaptive Components of the Immune System by Major Adjuvants

Adjuvant	Major Immunostimulatory Component(s)	Innate Receptors or Pathway Activated	Principal Immune Responses Stimulated
Licensed Adjuvants			
Alum	aluminum salts	NLRP3 inflammasome (?)	Ab, Th2 (+ Th1 in humans)
MF59 and AS03	squalene-in-water emulsions	tissue inflammation (no receptors defined)	Ab, Th1 + Th2
AS04	MPL plus alum	TLR4 and inflammasome (?)	Ab, Th1
Adjuvants in Widespread Experimental Use or in Late Stage Clinical Development			
Poly-IC (also Poly-ICLC)	synthetic derivatives of dsRNA	TLR3, MDA5	Ab, Th1, $CD8^+$ T cells
MPL and formulations (AS01, AS02)	MPL and QS-21	TLR4 (MPL), ? (QS21)	Ab, Th1
Flagellin, flagellin-Ag fusion proteins	Flagellin from *S. typhimurium*	TLR5	Ab, Th1 + Th2
Imiquimods	imidazoquinoline derivatives	TLR7, TLR8 or both	Ab, Th1, $CD8^+$ T cells (when conjugated)
CpG oligodeoxynuceotides and formulations (IC31, QB10)	synthetic phophorothioate-linked DNA oligonucleotides with optimized CpG motifs	TLR9	Ab, Th1, $CD8^+$ T cells (when conjugated)
CAF01	trehalose dimycolate (cord factor)	Mincle	Ab, Th1, Th17
ISCOMS and ISCOMATRIX	saponins	mechanism undefined	Ab, Th1+ Th2, $CD8^+$ T cells
IFA (and Montanide formulations)	mineral or paraffin oil + surfactant	mechanism undefined	Ab, Th1 + Th2
CFA	IFA + peptidoglycan, trehalose dimycolate	NLR, inflammasome, Mincle, TLR?	Ab, Th1, Th17

The principal immune response stimulated is based on results from human and mouse studies, although it may be limited to one species in some cases. Where indicated, conjugation of TLR ligand to antigen is necessary to obtain significant $CD8^+$ T cell responses.

Coffman et al., 2010

Targeting DC surface receptors

Targeted receptor	Receptor family	Expression by human cells	Co-stimulation required for induction of CTL response	Refs
Mannose receptor	CLR	iDCs (low on mDCs), monocytes, macrophages, subsets of endothelial cells, retinal pigment epithelium, kidney mesangial cells, tracheal smooth muscle cells	Yes	11–13, 67
CD205	CLR	mDCs (low on iDCs), thymic epithelial cells, monocytes, B cells, NK cells, T cells	Yes	17–20, 23,34
DC-SIGN	CLR	iDCs (low on mDCs), macrophages, megakaryocytes	Unknown‡	30,112
LOX1	CLR	iDCs, macrophages, fibroblasts, smooth muscle cells, endothelial cells	No	61
Dectin-1	CLR	iDCs (low on mDCs), monocytes, macrophages, neutrophils, eosinophils, B cells, subpopulation of T cells	Unknown§	40
FcγRI	FcR	DCs, monocytes, macrophages, activated neutrophils	Unknown‡	113
FcγRIIa	FcR	DCs, monocytes, macrophages, neutrophils, eosinophils, platelets	Unknown‡	114
FcγRIII	FcR	DCs, NK cells, macrophages, neutrophils, stimulated eosinophils	Unknown‡	115
FcγR	FcR	mDCs (low on iDCs), monocytes, macrophages, neutrophils, eosinophils	Unknown‡	116
CD11c–CD18	Integrin	DCs, monocytes, macrophages, granulocytes, NK cells, activated B cells, certain CTLs	Yes	21
MACI	Integrin	DCs, monocytes, macrophages, granulocytes, NK cells, subsets of T and B cells	No‖	117–120
CD40	TNF-receptor superfamily	DCs, B cells, macrophages, endothelial cells, keratinocytes, fibroblasts, $CD34^+$ haematopoietic cell progenitors, thymic epithelial cells	No	60,90
Siglec-H	Siglec	No human orthologue identified	Yes	108

*Summary of dendritic cell (DC) surface receptors that have been used for the targeting of antigens to DCs. Unfortunately, the expression of most receptors is not restricted to DCs. The table shows the expression pattern of the receptors in human cells. In addition, it indicates whether antigen targeting to the receptor required co-stimulation for induction of CTL responses in mouse studies. ‡No specific *in vivo* targeting studies have been performed, or only humoral responses were assessed. §Conditions without maturation stimuli were not studied. ‖MAC1 was targeted with antigen conjugated to the N-terminal catalytic domain of adenylate cyclase toxin from *Bordetella pertussis*. CLR, C-type lectin receptor; CTL, cytotoxic T lymphocyte; DC-SIGN, DC-specific intercellular adhesion molecule 3 (ICAM3)-grabbing non-integrin; FCR, FC receptor; iDC, immature DC; LOX1, lectin-type oxidized low-density lipoprotein receptor 1; MAC1, macrophage receptor 1; mDC, mature DC; NK, natural killer; Siglec, sialic-acid-binding immunoglobulin-like lectin, TNF, tumour-necrosis factor.

Tacken et al., 2007

Selected cancer vaccines in phase 3 clinical trials

Company (location)	Product description	Indication
Antigenics (Lexington, Massachusetts)	HSPPC-96 Oncophage: heat-shock protein vaccine isolated from patient tumor cells	Melanoma Glioma Renal cell carcinoma
BioVest International (Tampa, Florida)	Biovaxid: patient-specific immunoglobulin idiotype vaccine conjugated to the immunogenic protein KLH	Non-Hodgkin's lymphoma
Genitope (Fremont, California)	Patient-specific immunoglobulin idiotype-KLH conjugate	Non-Hodgkin's lymphoma
GlaxoSmithKline (Brentford, UK)	MAGE: liposomally packaged tumor-specific antigen	Melanoma Lung cancer
Northwest Biotherapeutics (Bethesda, Maryland)	DCVax: patient-derived dendritic cells loaded with cancer proteins or lysates	Prostate cancer Brain cancer
NovaRX (San Diego)	Lucanix: four cell lines carrying antisense oligos against transforming growth factor	Lung cancer
Oncothyreon (Seattle)	Stimuvax: liposomal vaccine with a synthetic peptide derived from tumor-specific antigen MUC-1	Lung cancer
Oxford Biomedica (Oxford, UK)	TroVax: pox viral vector carrying tumor-associated antigen 5T4	Renal cell carcinoma

DeFrancesco, 2010