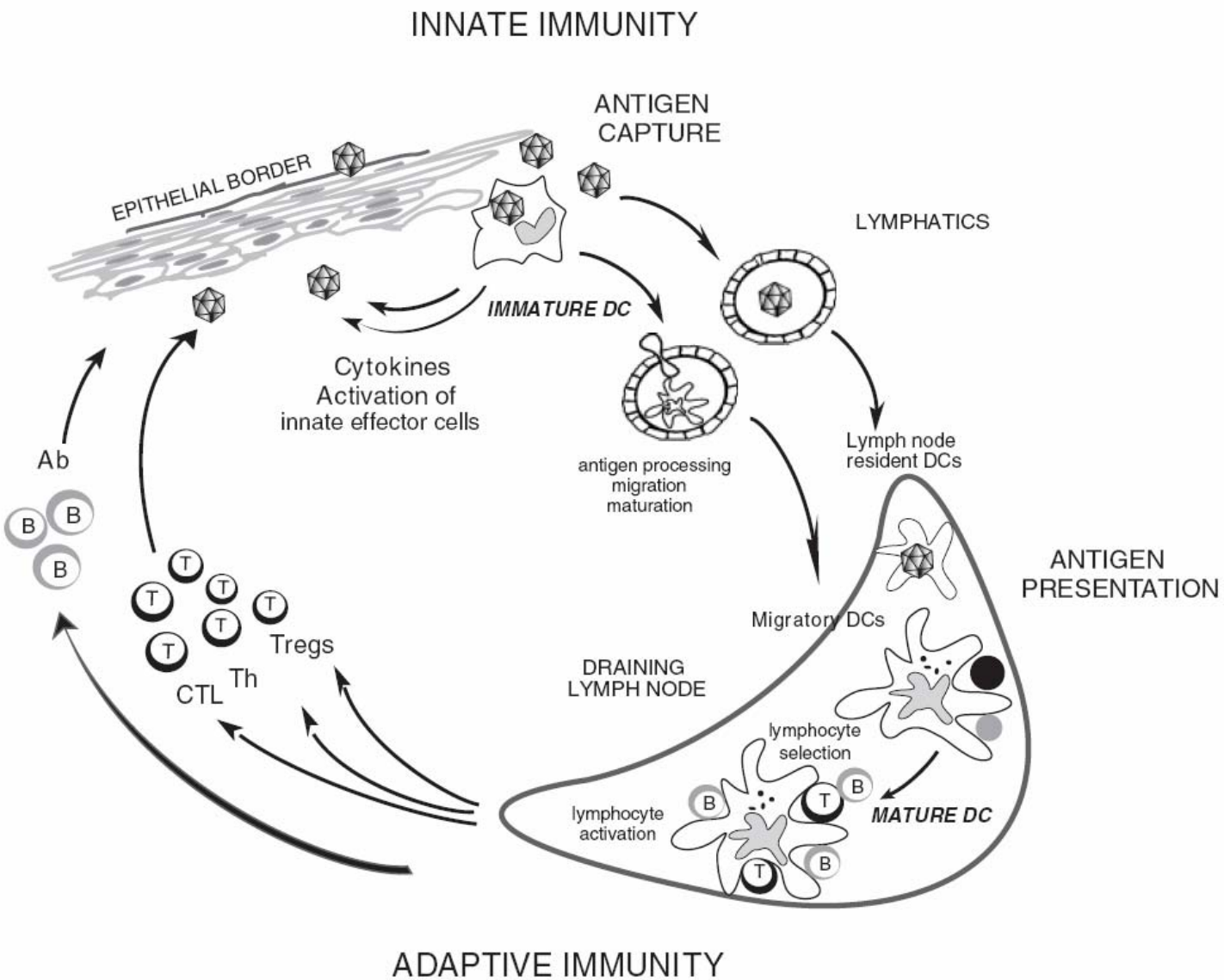
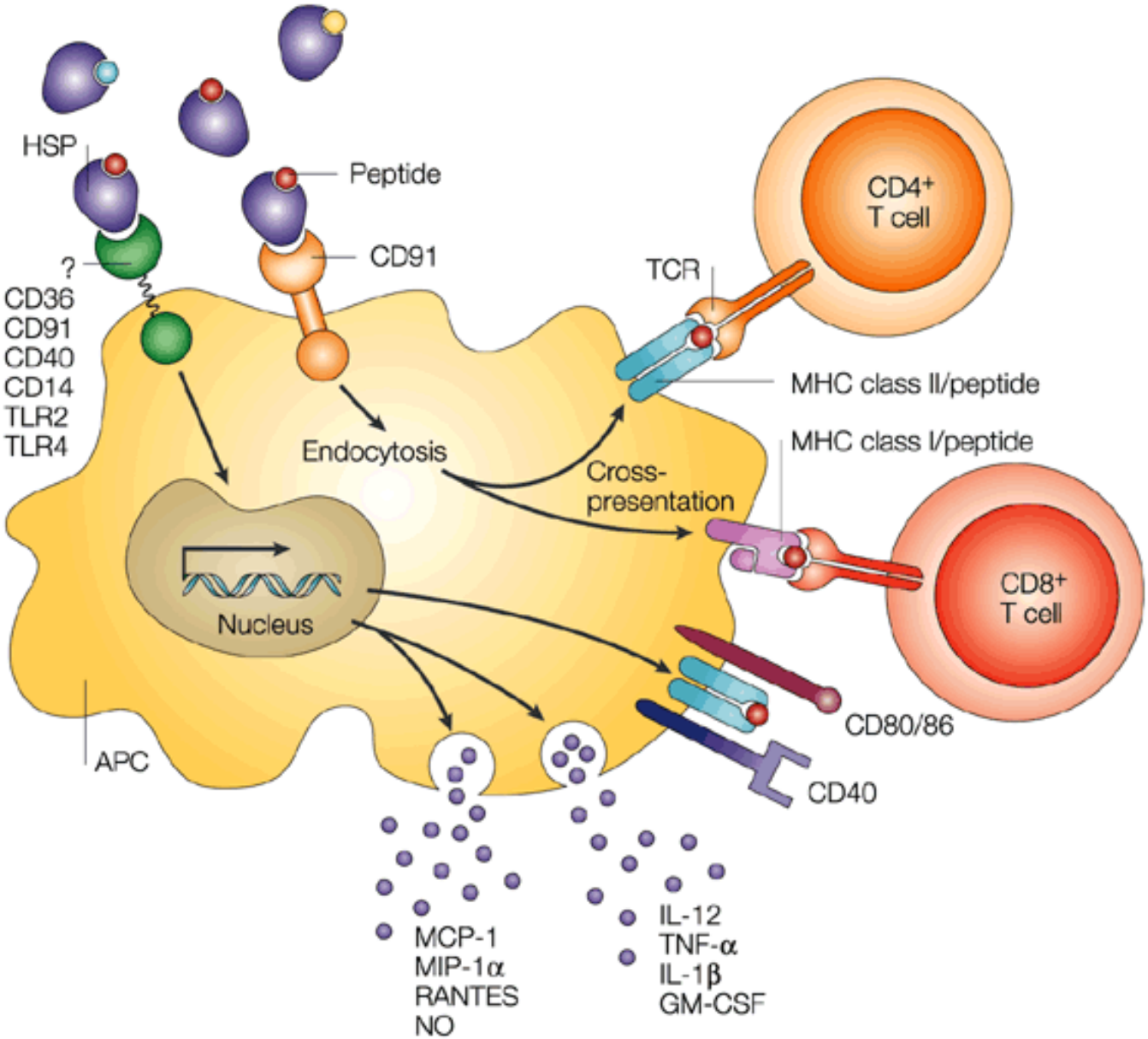
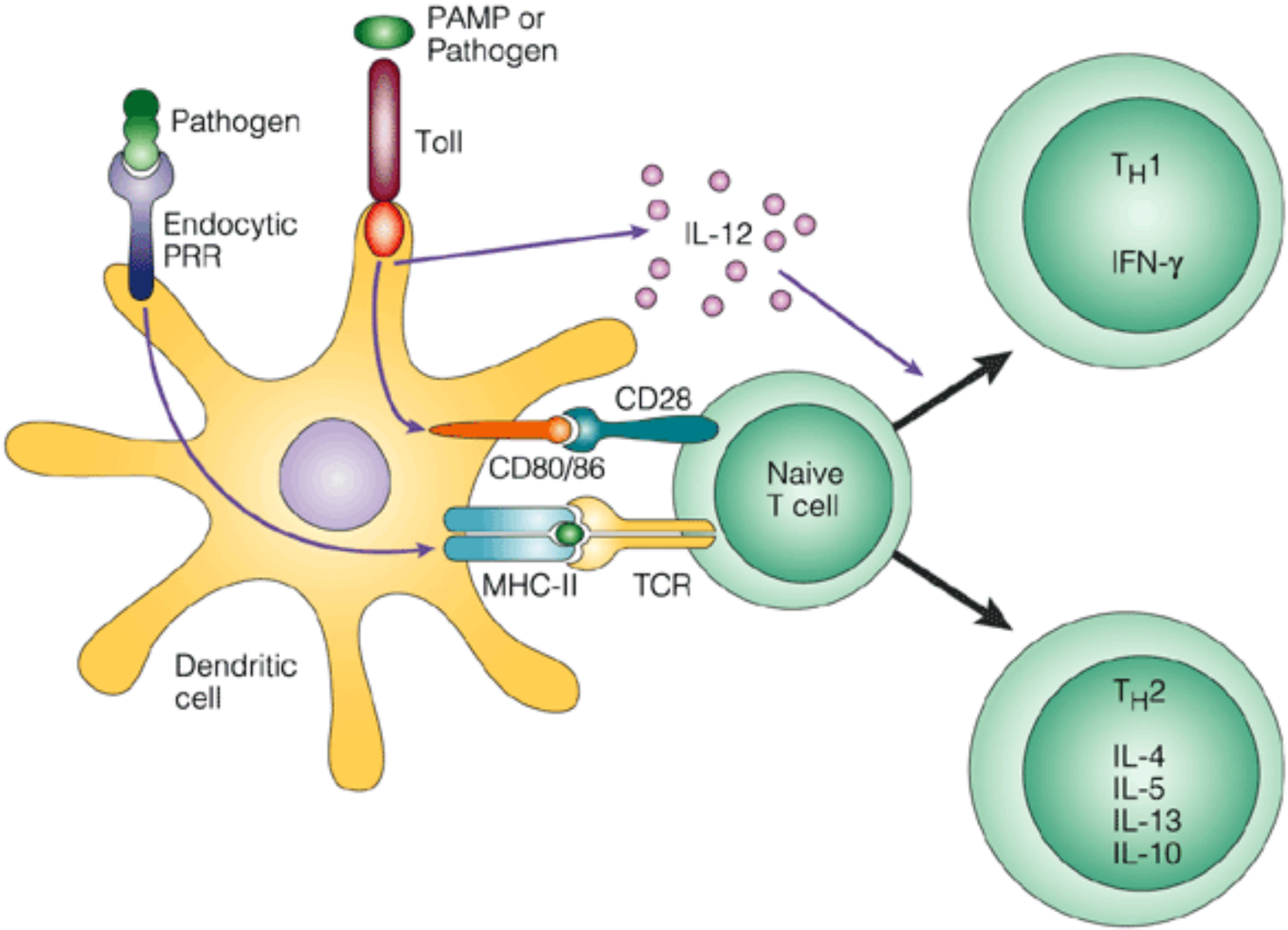
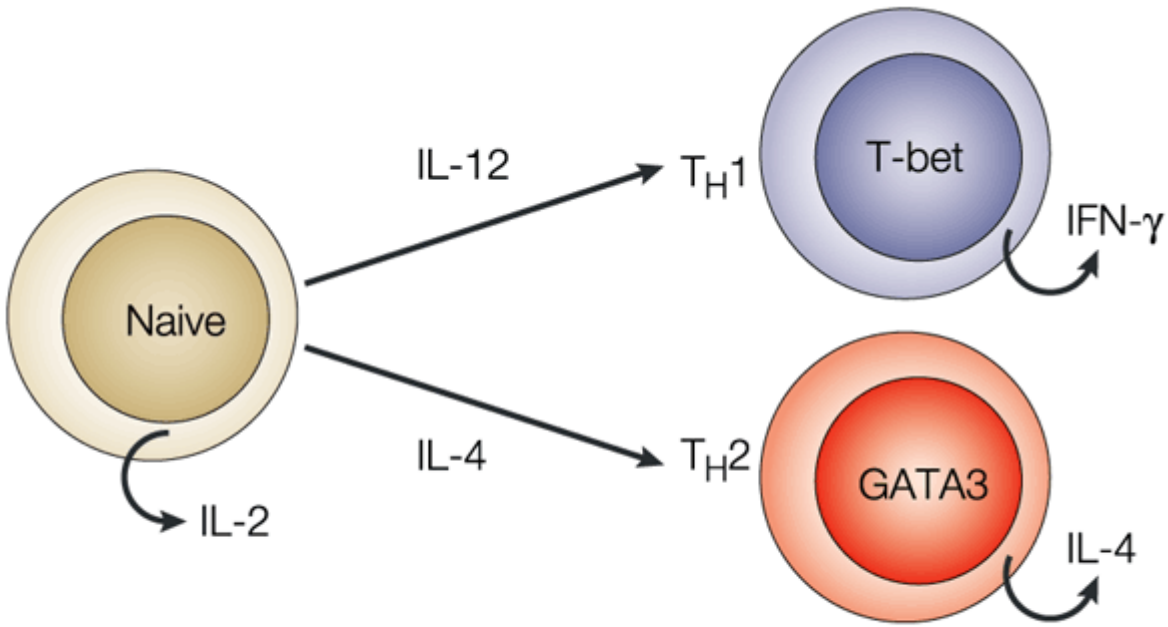
Cancer immunosurveillance and immunoediting in humans, ways to improve immunogenicity of tumor cells and to design better immunotherapy protocols

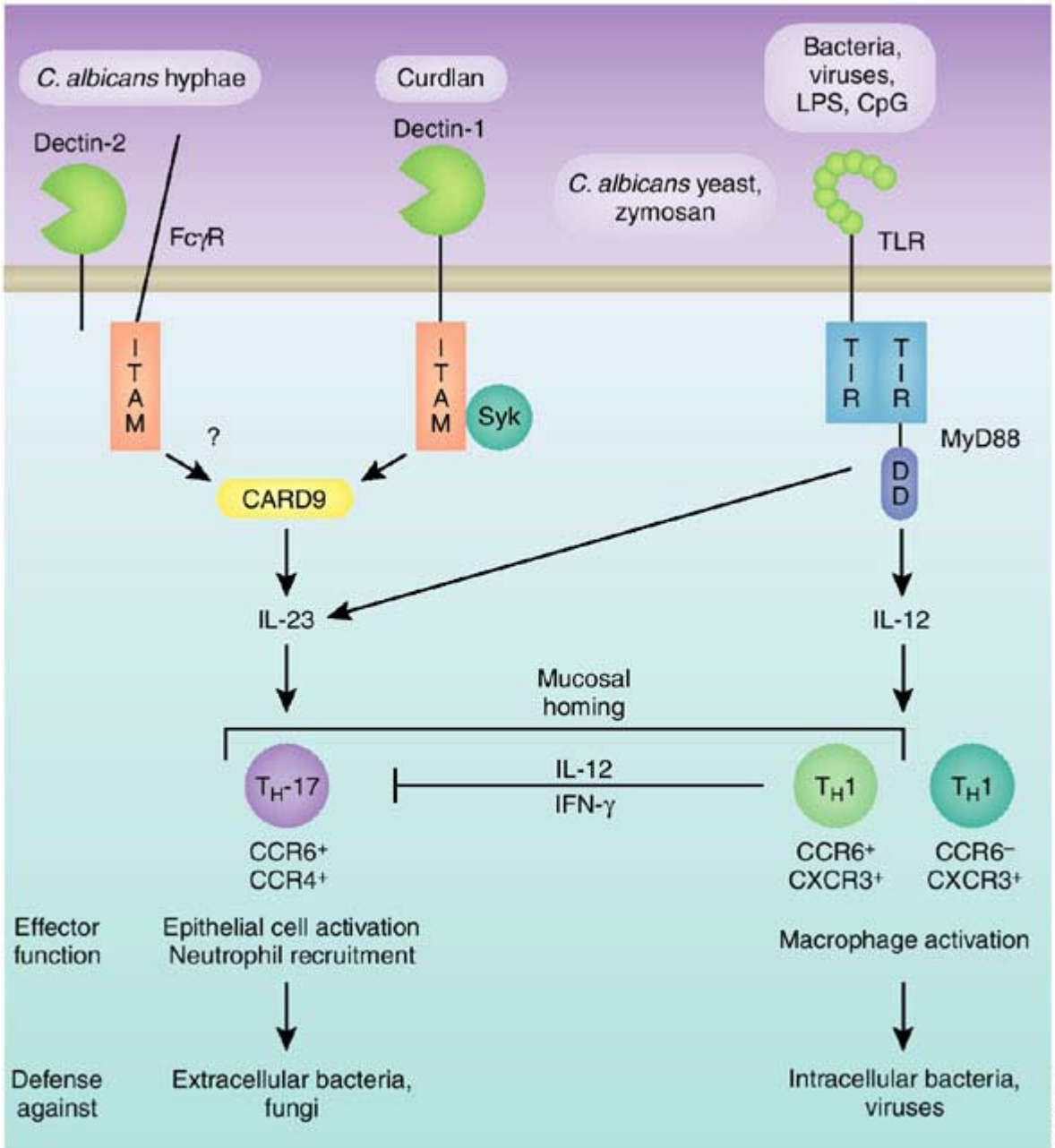

INNATE IMMUNITY
ANTIGEN CAPTURE
EPITHELIAL BORDER
LYMPHATICS
IMMATURE DC
Cytokines
Activation of
innate effector cells
antigen processing
migration
maturation
Lymph node
resident DCs
Ab
B
B
B
T
T
T
T
T
T
Tregs
Th
CTL
DRAINING
LYMPH NODE
Migratory DCs
ANTIGEN
PRESENTATION
lymphocyte
selection
lymphocyte
activation
B
T
B
T
B
MATURE DC
ADAPTIVE IMMUNITY


HSP
Peptide
?
CD91
CD36
CD91
CD40
CD14
TLR2
TLR4
CD4+
T cell
TCR
MHC class II/peptide
MHC class I/peptide
Endocytosis
Cross-
presentation
Nucleus
CD8+
T cell
CD80/86
CD40
APC
MCP-1
MIP-1α
RANTES
NO
IL-12
TNF-α
IL-1β
GM-CSF


PAMP or
Pathogen
Pathogen
Toll
Endocytic
PRR
IL-12
T_H1
IFN-γ
CD28
CD80/86
Naive
T cell
MHC-II
TCR
Dendritic
cell
T_H2
IL-4
IL-5
IL-13
IL-10

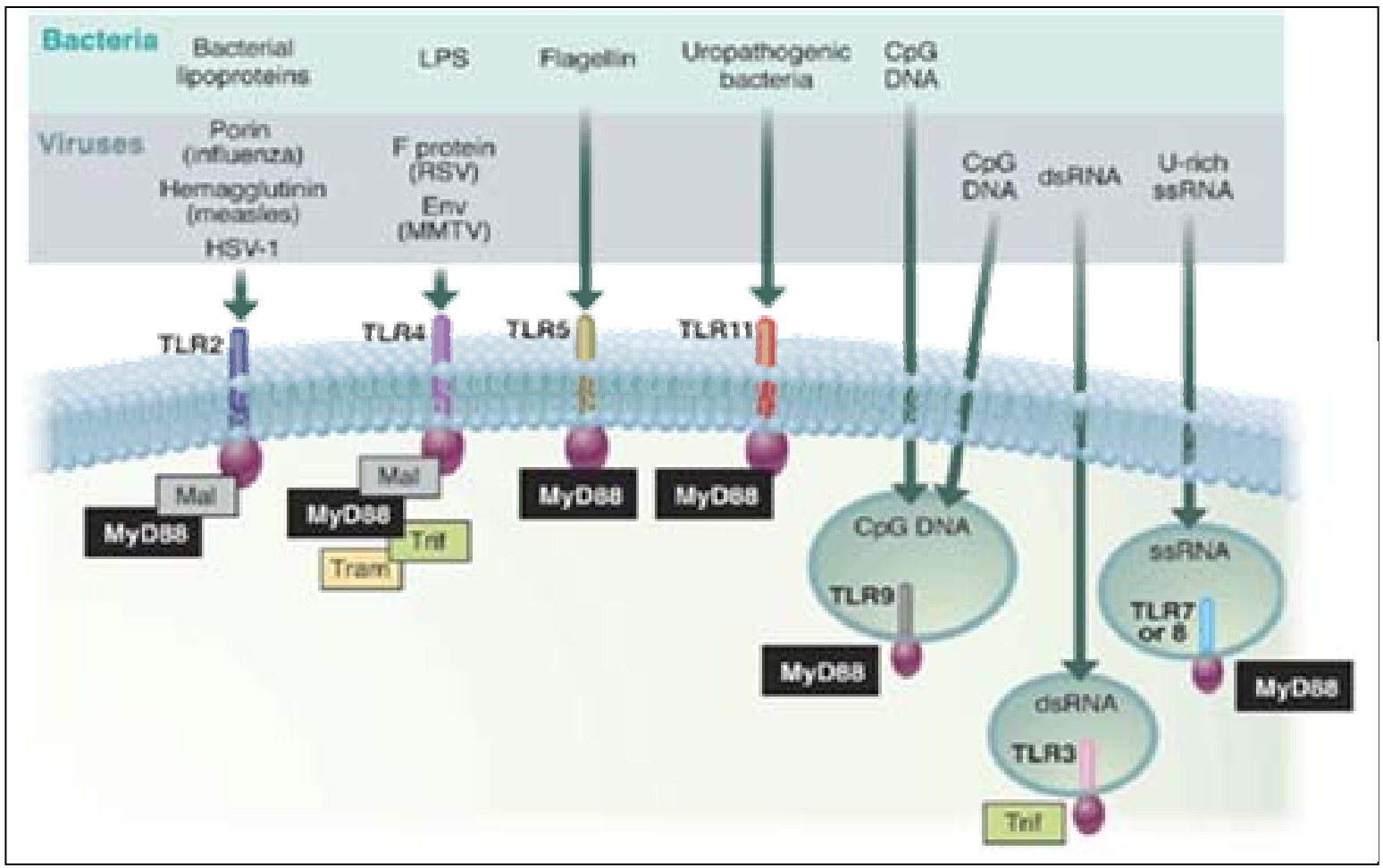


Nature Reviews | Immunology


C. albicans hyphae
Curdlan
Bacteria, viruses, LPS, CpG
Dectin-2
Dectin-1
C. albicans yeast, zymosan
FcγR
TLR
ITAM
ITAM
Syk
?
TIR
TIR
MyD88
DD
CARD9
IL-23
IL-12
Mucosal homing
TH-17
IL-12
IFN-γ
TH1
TH1
CCR6+ CCR4+
CCR6+ CXCR3+
CCR6− CXCR3+
Effector function
Epithelial cell activation Neutrophil recruitment
Macrophage activation
Defense against
Extracellular bacteria, fungi
Intracellular bacteria, viruses
Kim Caesar

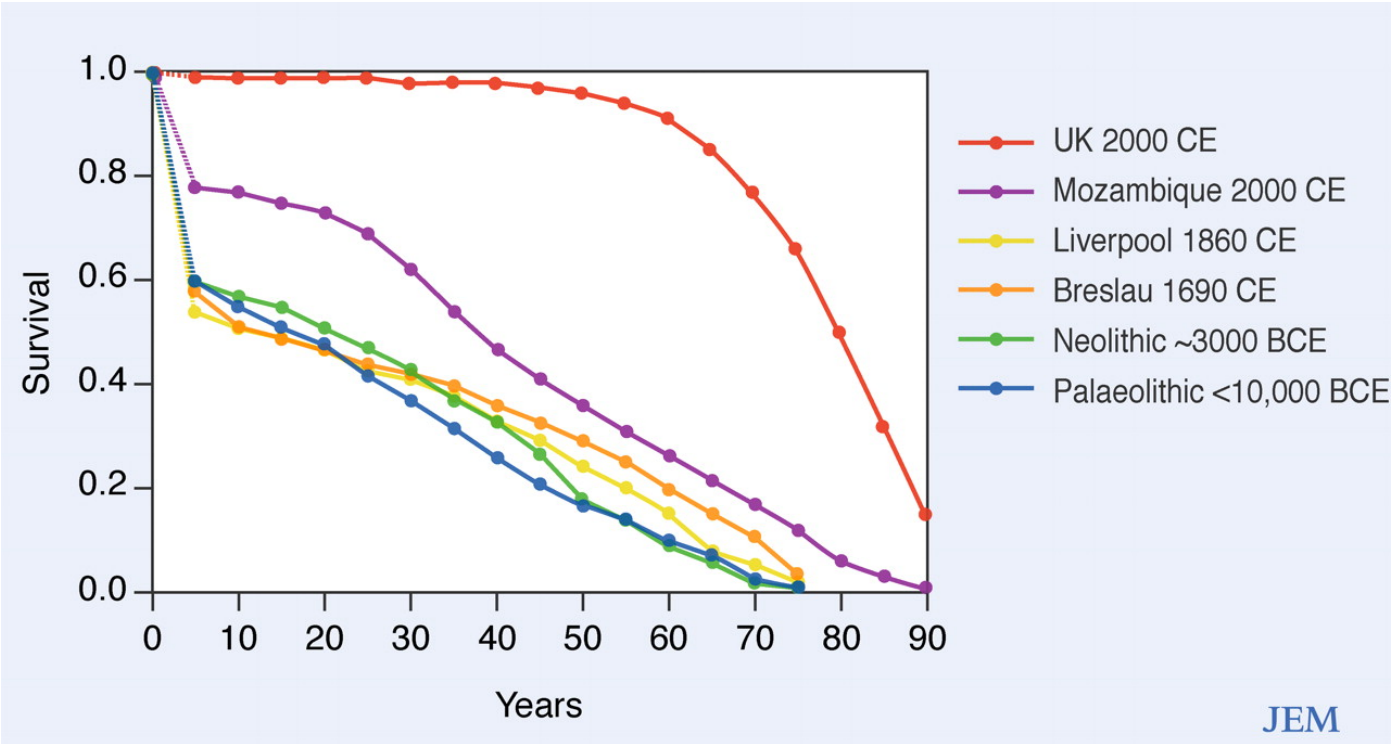
Toll-like receptory

- Transmembránové receptory I. typu
- extracelulární doména bohatá na leucin
- intracelulární Toll/IL-1 receptor (TIR) doména



Receptor	Ligand	Origin of ligand	Ref
TLR1	Triacyl lipopeptides	Bacteria and mycobacteria	
	Soluble factors	*Neisseria meningitidis*	
TLR2	Lipoprotein/lipopeptides	Various pathogens	
	Peptidoglycan	Gram-positive bacteria	
	Lipoteichoic acid	Gram-positive bacteria	
	Lipoarabinomannan	Mycobacteria	
	Phenol-soluble modulin	*Staphylococcus epidermidis*	
	Glycoinositolphospholipids	*Trypanosoma cruzi*	
	Glycolipids	*Treponema maltophilum*	
	Porins	*Neisseria*	
	Atypical lipopolysaccharide	*Leptospira interrogans*	
	Atypical lipopolysaccharide	*Porphyromonas gingivalis*	
	Zymosan	Fungi	
	Heat-shock protein 70*	Host	
TLR3	Double-stranded RNA	Viruses	
TLR4	Lipopolysaccharide	Gram-negative bacteria	
	Taxol	Plants	
	Fusion protein	Respiratory syncytial virus	
	Envelope protein	Mouse mammary-tumour virus	
	Heat-shock protein 60*	*Chlamydia pneumoniae*	
	Heat-shock protein 70*	Host	
	Type III repeat extra domain A of fibronectin*	Host	
	Oligosaccharides of hyaluronic acid*	Host	
	Polysaccharide fragments of heparan sulphate*	Host	
	Fibrinogen*	Host	
TLR5	Flagellin	Bacteria	
TLR6	Diacyl lipopeptides	*Mycoplasma*	
	Lipoteichoic acid	Gram-positive bacteria	
	Zymosan	Fungi	
TLR7	Imidazoquinoline	Synthetic compounds	
	Loxoribine	Synthetic compounds	
	Bropirimine	Synthetic compounds	
	Single-stranded RNA	Viruses	
TLR8	Imidazoquinoline	Synthetic compounds	
	Single-stranded RNA	Viruses	
TLR9	CpG-containing DNA	Bacteria and viruses	
TLR10	N.D.	N.D.	
TLR11	N.D.	Uropathogenic bacteria	

Mortality curves at various periods of human history



Improvement of hygiene, beginning in the mid–19th century (preventing the transmission of infection)

Introduction of vaccines, beginning in the late 19th century (preventing disease in infected individuals)

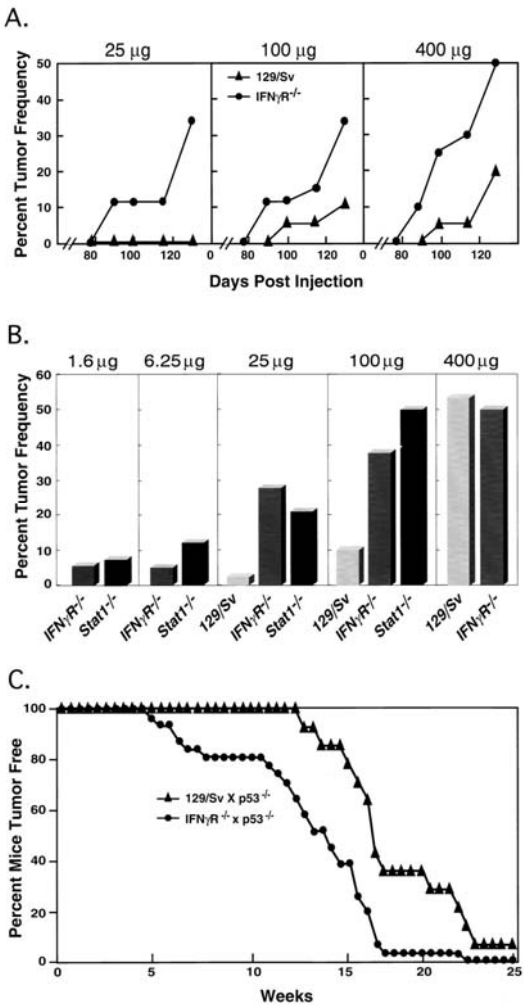
Development of anti-infectious drugs, beginning in the early 20th century (preventing death in patients with clinical disease).

Casanova, J.-L. et al. J. Exp. Med. 2005;202:197-201

JEM

1957- formulation of the cancer immunosurveillance hypothesis proposed by Thomas and Burnet:
“sentinel thymus dependent cells of the body constantly surveyed host tissues for nascent transformed cells”

Role of IFNg in protection against cancer



Kaplan, Daniel H. et al. (1998) Proc. Natl. Acad. Sci. USA 95, 7556-7561

Mouse immunodeficiency	Immune status	Tumour susceptibility relative to wild-type mice	Refs
Rag1$^{-/-}$ or *Rag2*$^{-/-}$	Lacks T cells, B cells and NKT cells	↑ MCA-induced sarcomas ↑ Spontaneous intestinal neoplasias	6,27
Rag2$^{-/-}$*Stat1*$^{-/-}$	Lacks T cells, B cells and NKT cells; insensitive to IFNα, IFNβ and IFNγ	↑ MCA-induced sarcomas ↑ Spontaneous intestinal and mammary neoplasias	6
SCID BALB/c	Lacks T cells, B cells and NKT cells	↑ MCA-induced sarcomas	27
Tcrb$^{-/-}$	Lacks αβ T cells	↑ MCA-induced sarcomas	100
Tcrd$^{-/-}$	Lacks γδ T cells	↑ MCA-induced sarcomas ↑ DMBA- plus TPA-induced skin tumours	100
Tcrb$^{-/-}$*Tcrd*$^{-/-}$	Lacks αβ T cells and γδ T cells	↑ DMBA- plus TPA-induced skin tumours	101
Jα281 TCR gene-segment deficiency	Lacks NKT-cell subset	↑ MCA-induced sarcomas	19,27,102
Lmp2$^{-/-}$	Lacks LMP2 subunit	↑ Spontaneous uterine neoplasms	103
Asialo-GM1-specific antibody treatment	Lacks NK cells, monocytes and macrophages	↑ MCA-induced sarcomas	27,102
NK1.1-specific antibody treatment	Lacks NK cells and NKT cells	↑ MCA-induced sarcomas	27,102
Thy1-specific antibody treatment	Lacks T cells	↑ MCA-induced sarcomas	27,102
Immunization with self antigen	Increased regulatory T-cell activity	↓ Latency of MCA-induced sarcomas	104
Stat1$^{-/-}$	Insensitive to IFNα, IFNβ and IFNγ	↑ MCA-induced sarcomas Wider tumour range in *Stat1*$^{-/-}$*Tp53*$^{-/-}$ mice	6,18
Ifngr1$^{-/-}$	Insensitive to IFNγ	↑ MCA-induced sarcomas Wider tumour range in *Ifngr1*$^{-/-}$*Tp53*$^{-/-}$ mice	6,18
Ifnar1$^{-/-}$	Insensitive to IFNα and IFNβ	↑ MCA-induced sarcomas	9
Ifng$^{-/-}$	Lacks IFNγ	↑ MCA-induced sarcomas C57BL/6 mice: ↑ Spontaneous disseminated lymphomas; ↓ latency of *tax*-transgene-induced leukaemia BALB/c: ↑ Spontaneous lung adenocarcinomas	19,20,105
Gmcsf$^{-/-}$*Ifng*$^{-/-}$	Lacks GM-CSF and IFNγ	↑ Spontaneous lymphomas ↑ Non-lymphoid solid cancers	21
Pfp$^{-/-}$*Ifng*$^{-/-}$	Lacks perforin and IFNγ	↑ MCA-induced sarcomas ↑ Spontaneous disseminated lymphomas	19,20
Pfp$^{-/-}$*b2m*$^{-/-}$	Lacks perforin, MHC class I molecules and CD8$^+$ T cells	↑ Spontaneous disseminated lymphomas	106
Pfp$^{-/-}$	Lacks perforin	↑ MCA-induced sarcomas ↑ Spontaneous lymphomas ↑ Spontaneous lymphomas and sarcomas in *Pfp*$^{-/-}$*Tp53*$^{+/-}$ mice	19,102,107
Trail$^{-/-}$	Lacks TRAIL	↑ MCA-induced sarcomas ↑ Spontaneous lymphomas ↑ Spontaneous lymphomas and sarcomas in *Trail*$^{-/-}$*Tp53*$^{+/-}$ mice	108,109
TRAIL-specific antibody treatment	Blockade of TRAIL	↑ MCA-induced sarcomas ↑ Spontaneous lymphomas and sarcomas	10
NKG2D-specific antibody treatment	Blockade of NKG2D	↑ MCA-induced sarcomas	39
Il12a$^{-/-}$	Lacks IL-12	↑ DMBA- plus TPA-induced papillomas	68
Il23a$^{-/-}$	Lacks IL-23	↓ DMBA- plus TPA-induced papillomas	68
Il12b$^{-/-}$	Lacks IL-12 and IL-23	↑ MCA-induced sarcomas ↓ DMBA- plus TPA-induced papillomas	40,68
IL-12 treatment	Exogenous IL-12	↓ MCA-induced sarcomas	26
α-GalCer treatment	Exogenous NKT-cell activation	↓ MCA-induced sarcomas	110
Tnf$^{-/-}$	Lacks TNF	↓ DMBA- plus TPA-induced papillomas	69
Conditional *Socs1*$^{-/-}$	SOCS1 expressed only by T cells and B cells	↑ Spontaneous colitis-associated colorectal adenocarcinomas	70
Conditional *Socs1*$^{-/-}$ plus IFNγ-specific antibody treatment	SOCS1 expressed only by T cells and B cells; IFNγ depletion	↓ Spontaneous colitis-associated colorectal adenocarcinomas	70

b2m, β_2-microglobulin; DMBA, 7,12-dimethylbenz(a)anthracene; α-GalCer, α-galactosylceramide; GM1, a ganglioside; *Gmcsf*, granulocyte/macrophage colony-stimulating factor; *Ifnar1*, type I IFN receptor 1; *Ifn*, interferon; *Ifngr1*, IFNγ receptor 1; *Il*, interleukin; Jα281, joining gene segment Jα281 of TCRα; *Lmp2*, low-molecular-mass protein 2; MCA, 3-methylcholanthrene; NK, natural killer; NK1.1, NK-cell-associated antigen 1.1; NKG2D, NK group 2, member D; NKT, natural killer T; *Pfp*, perforin; *Rag*, recombination-activating gene; SCID, severe combined immunodeficient; *Socs1*, suppressor of cytokine signalling 1; *Stat1*, signal transducer and activator of transcription 1; *Tcr*, T-cell receptor; *Tnf*, tumour-necrosis factor; TPA, 12-*O*-tetradecanoyl phorbol 13-acetate; *Tp53*, tumour-suppressor protein p53; *Trail*, TNF-related apoptosis-inducing ligand.

Dunn *et al. Nature Reviews Immunology* **6**, 836–848 (November 2006) | doi:10.1038/nri1961

nature REVIEWS IMMUNOLOGY

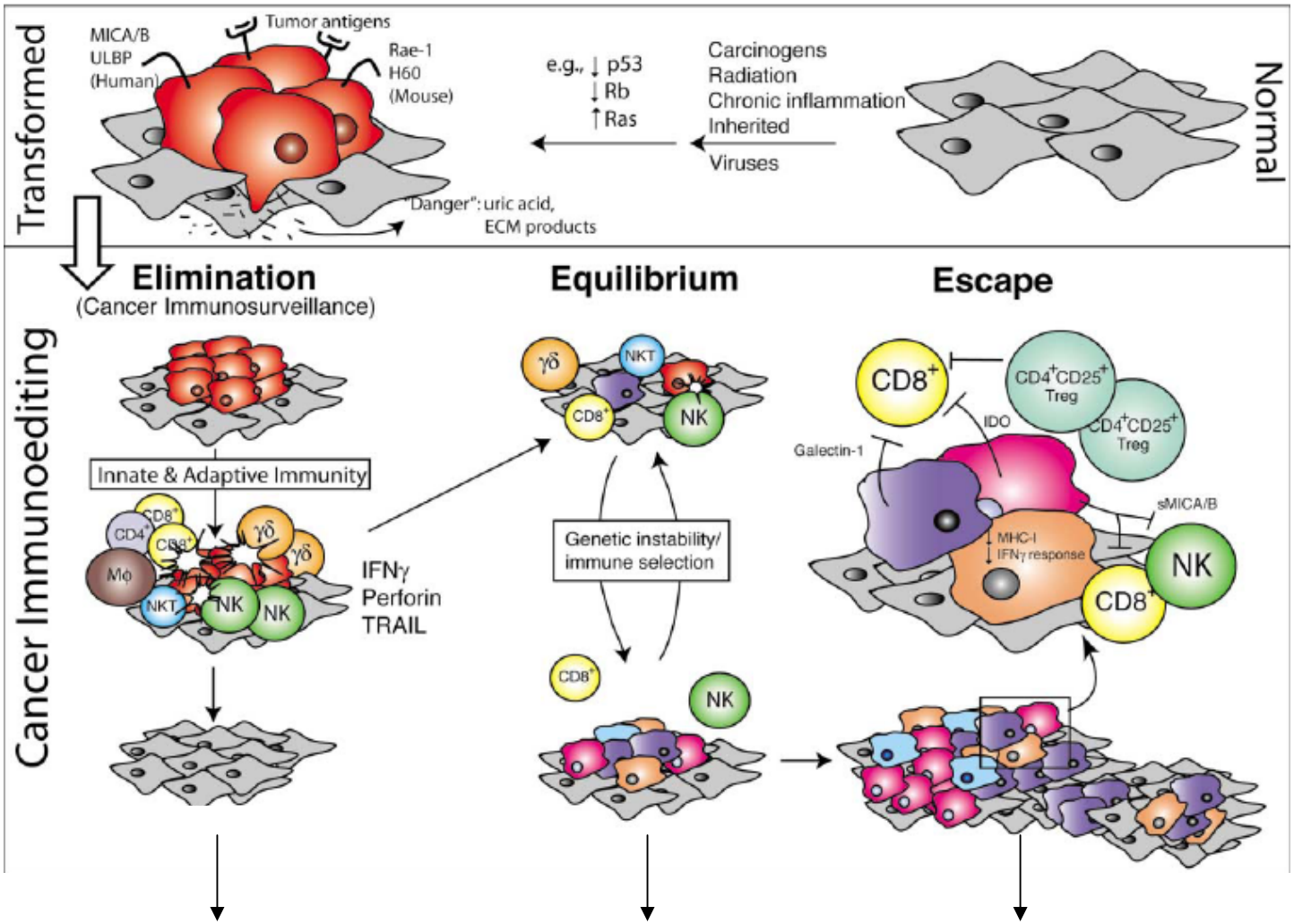
Cancer immunosurveillance and immunoediting hypothesis

- immune system is capable of early recognition and elimination of cell in the process of malignant transformation

- mediated by various components of the immune system (T-cells, NKT cells, NK cells)

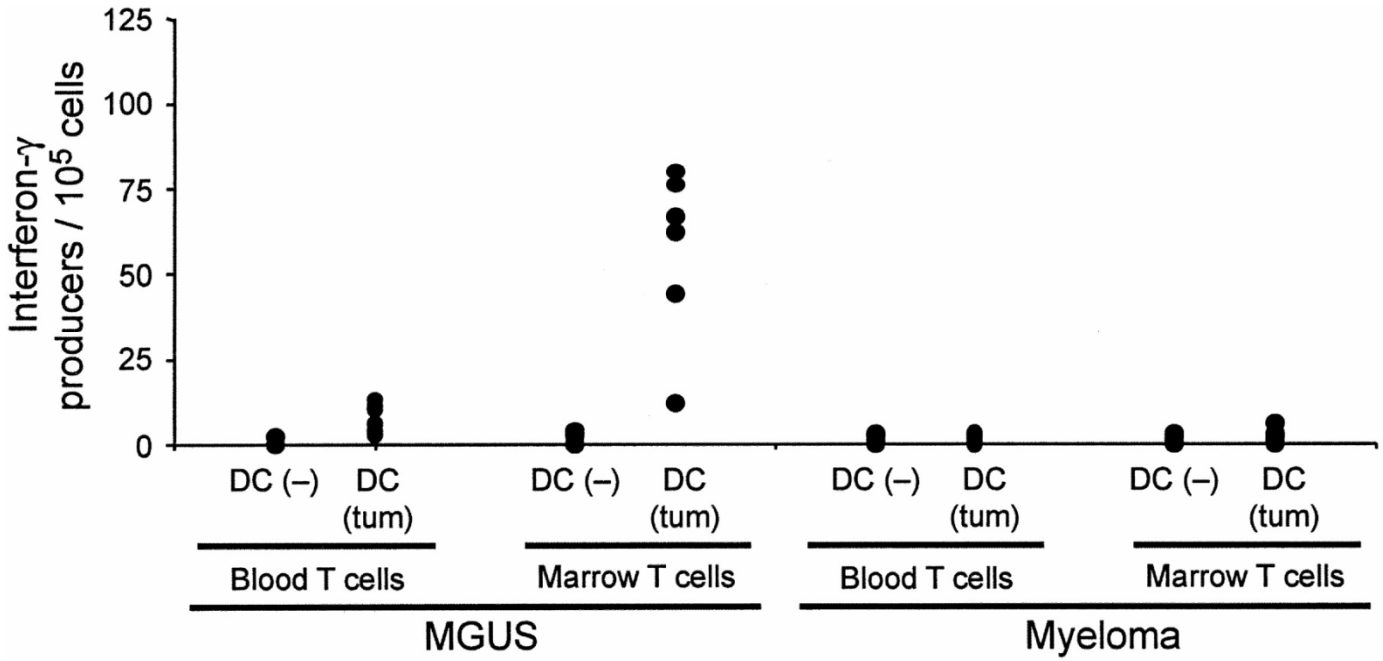
- scarce evidence for its existence in humans

Cancer immunosurveillance and immunoediting hypothesis



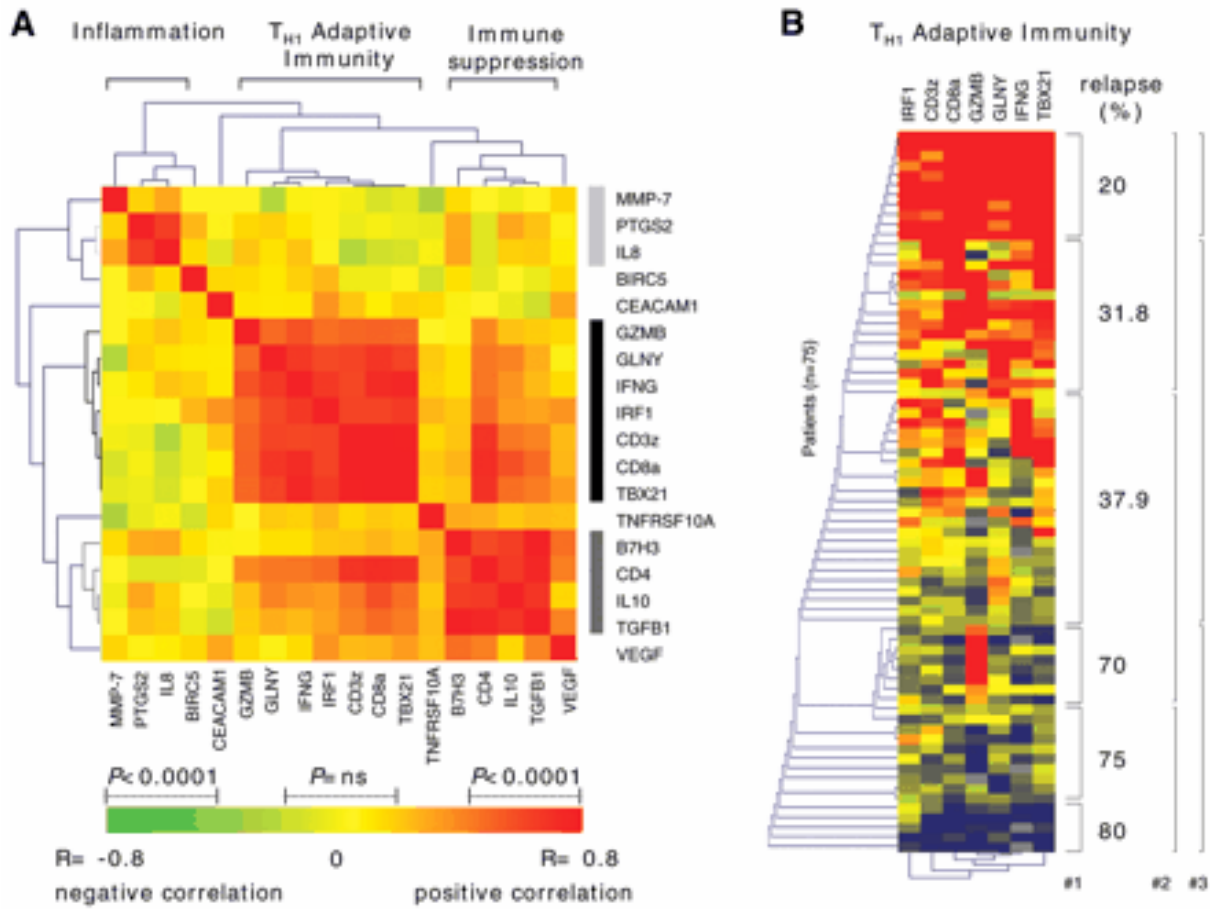
GP Dunn, Immunity, 2004

Tumor cell specific enrichment of IFNγ producing T cells in the bone marrow of patients with MGUS

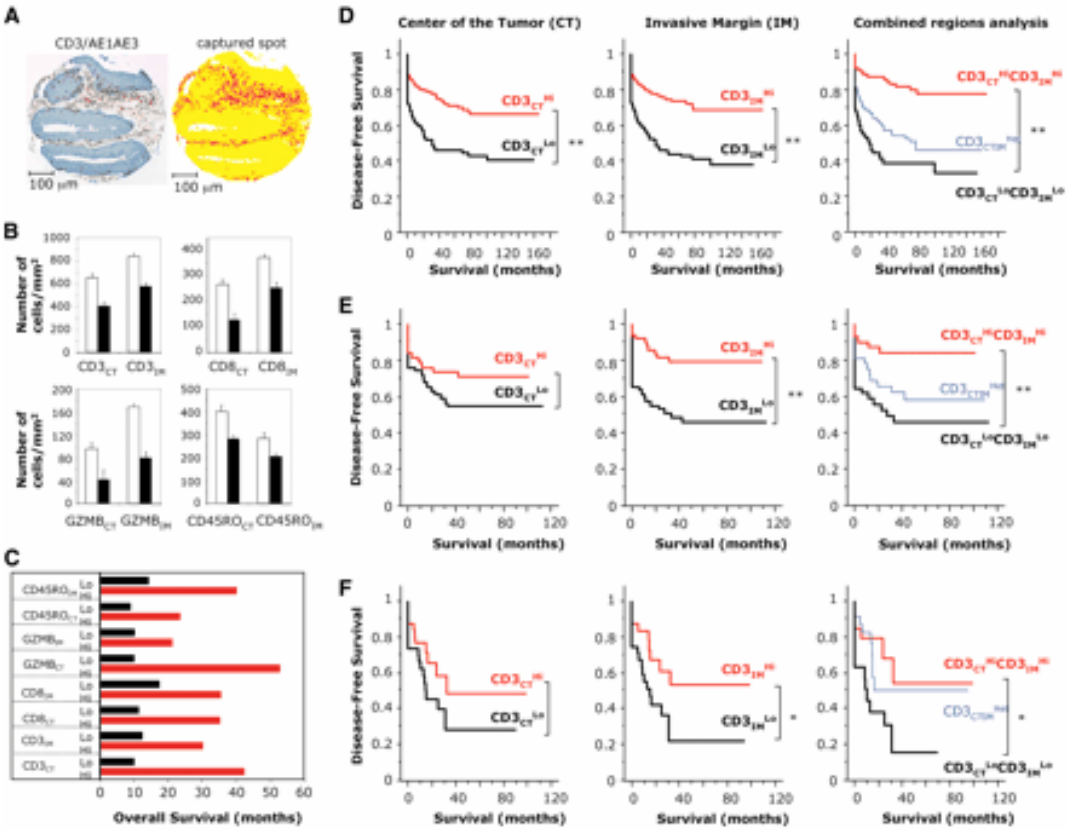


Dhodapkar M., JEM, 2003

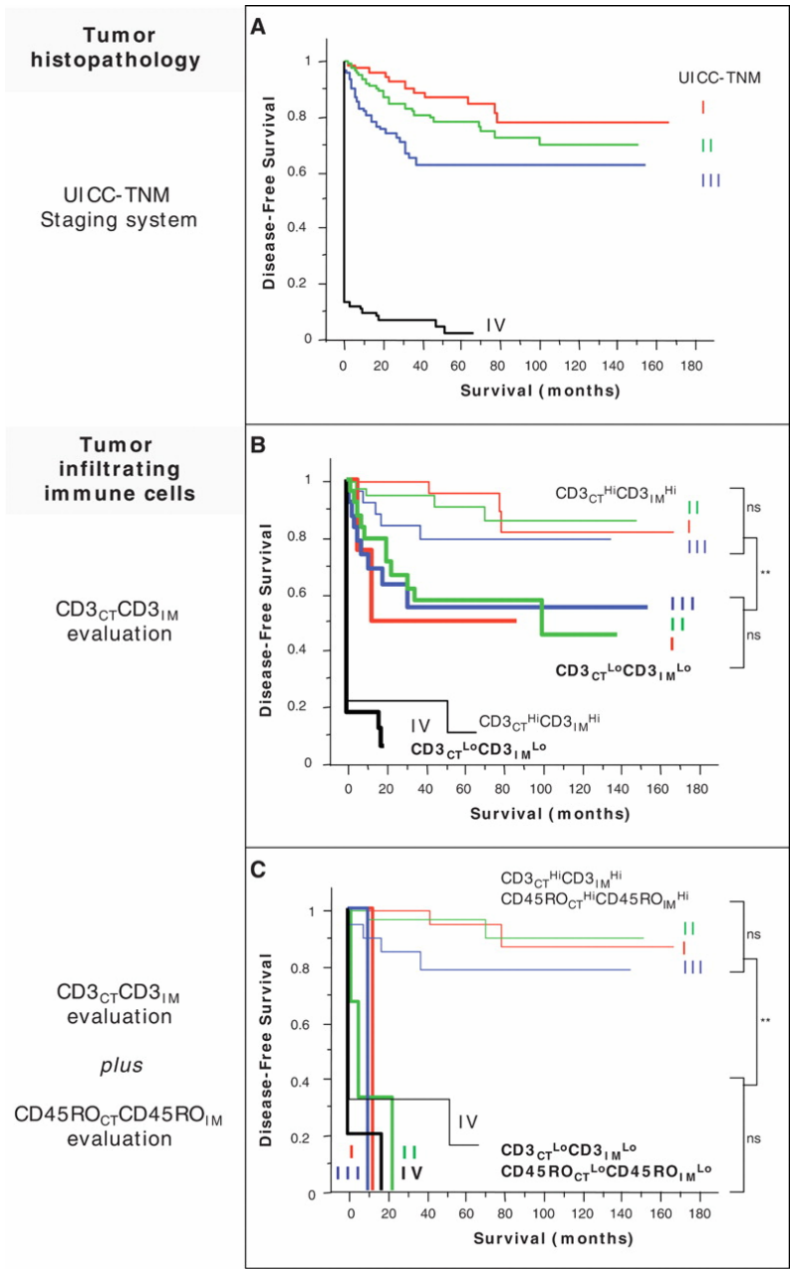
Infiltration of tumor tissue by T cells predicts better prognosis in colon cancer



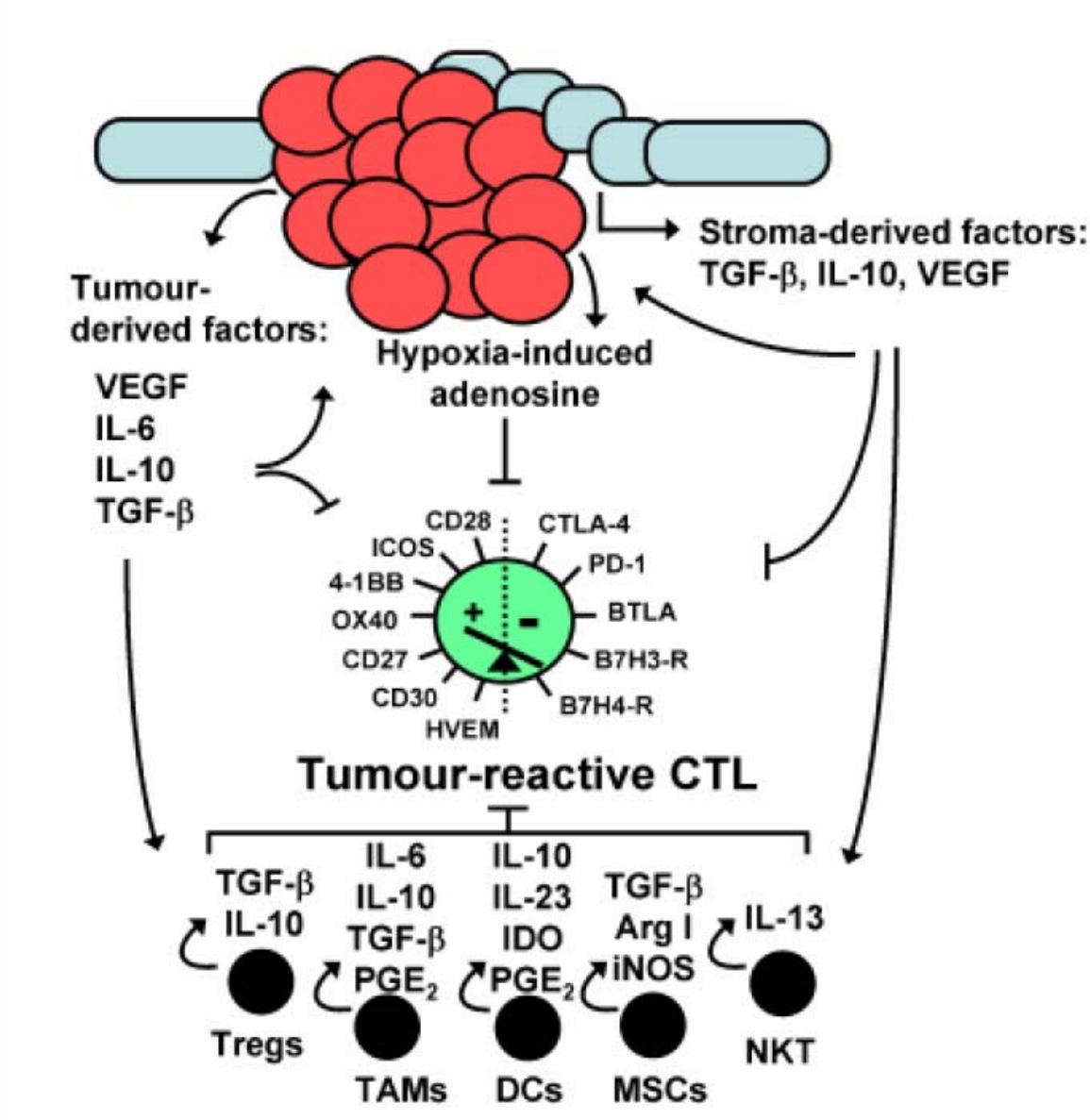
Infiltration of tumor tissue by T cells predicts better prognosis in colon cancer

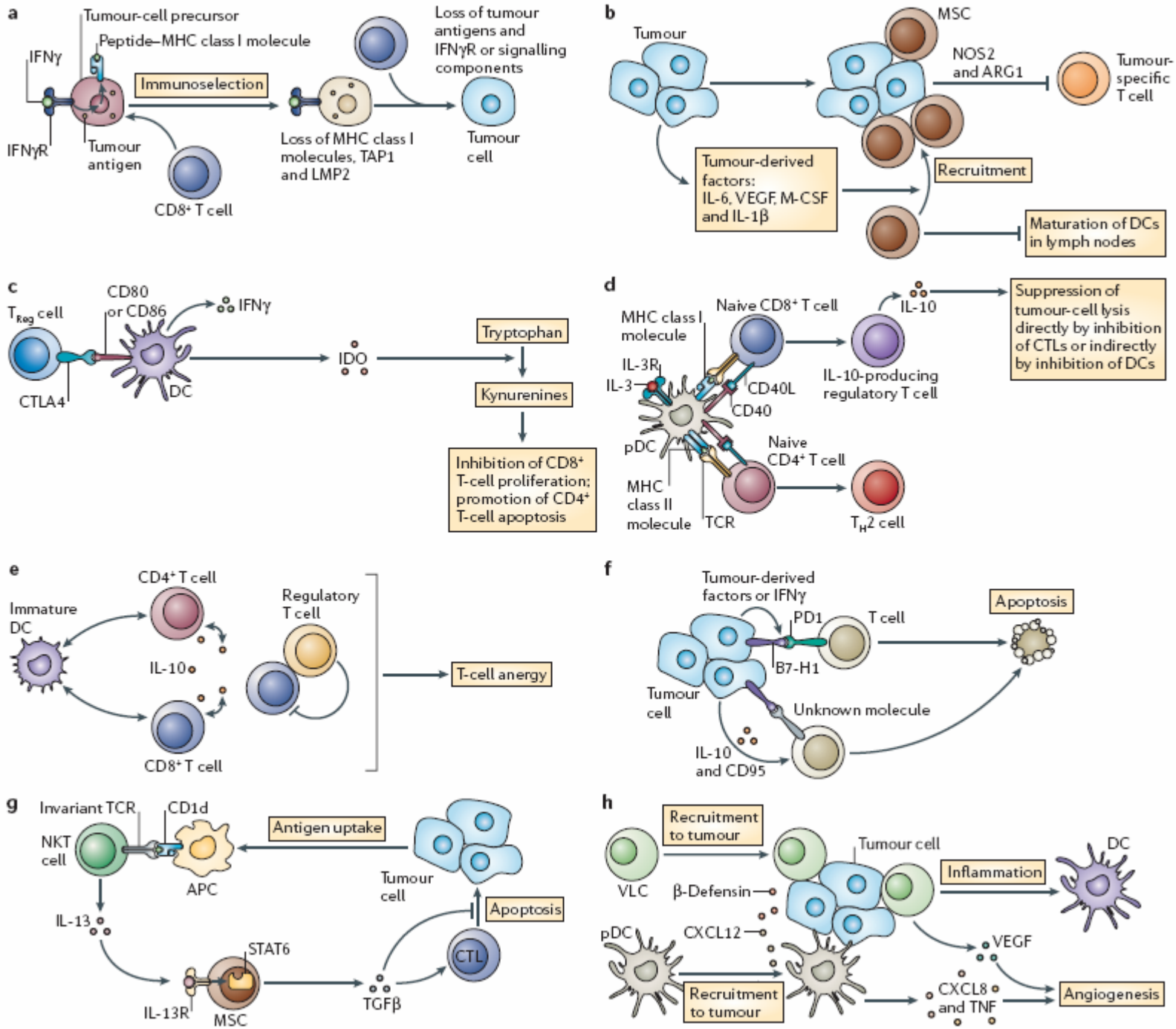


Infiltration of tumor tissue by T cells predicts better prognosis in colon cancer

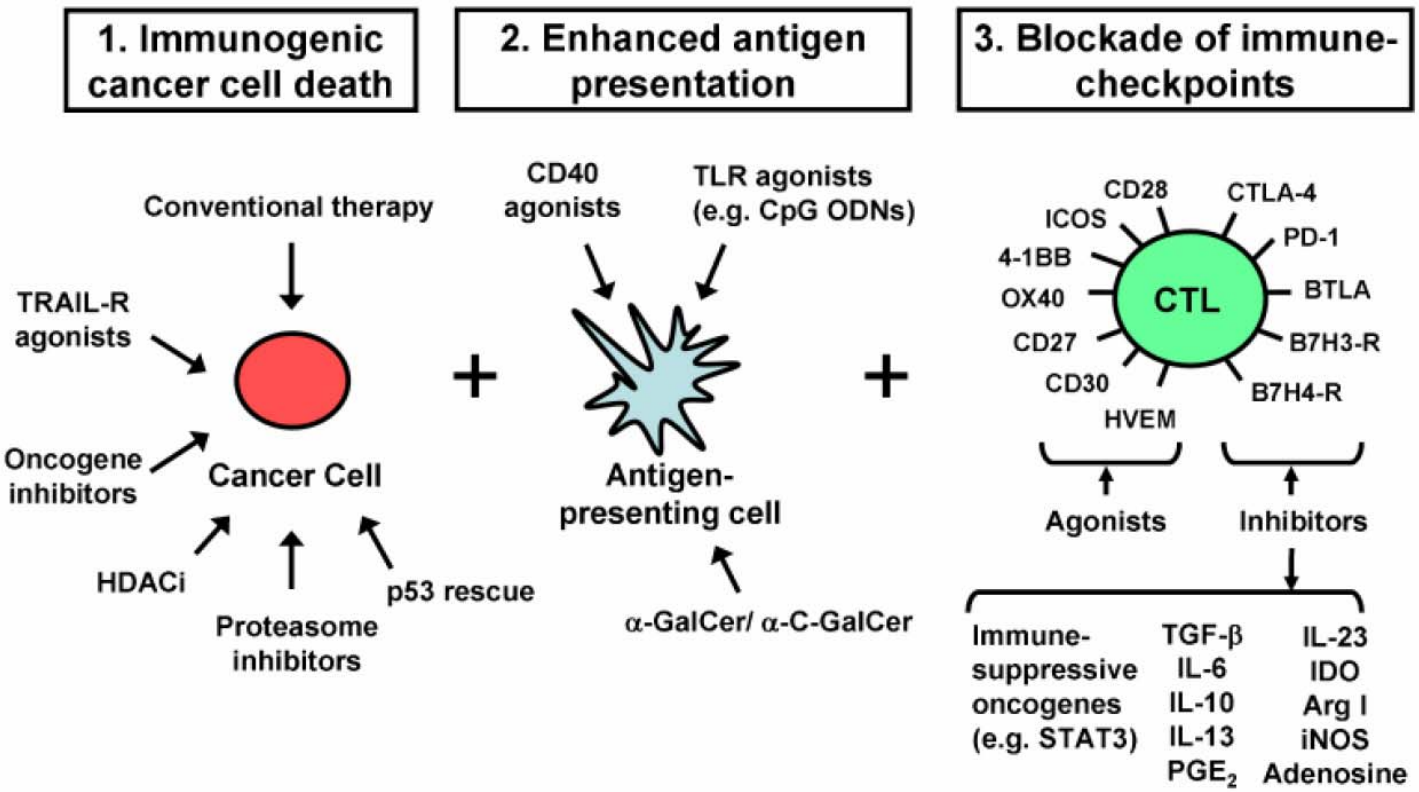


Factors inhibiting anti-tumor immune response

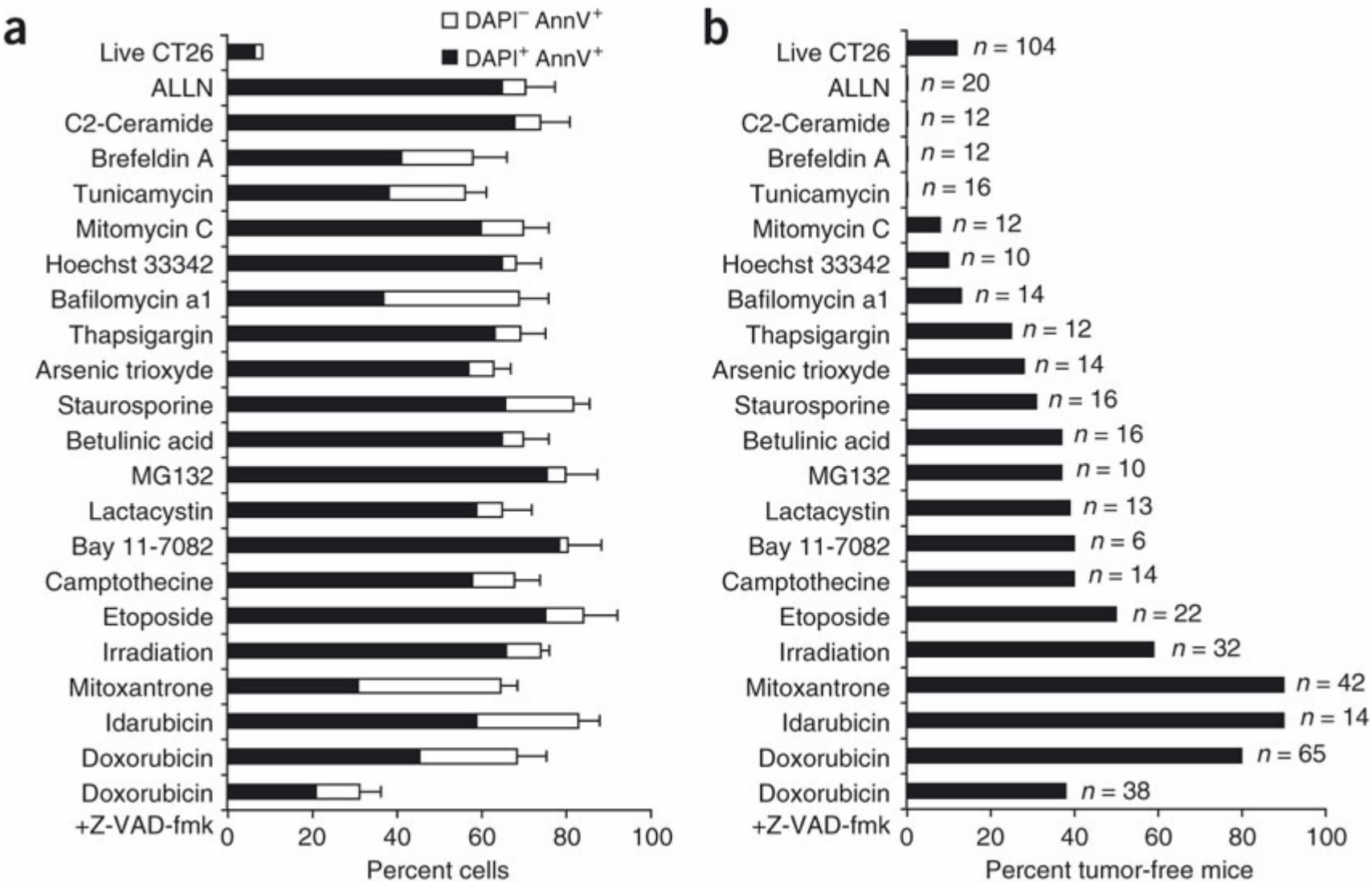



a
Tumour-cell precursor
Peptide–MHC class I molecule
IFNγ
IFNγR
Tumour antigen
Immunoselection
Loss of MHC class I molecules, TAP1 and LMP2
Loss of tumour antigens and IFNγR or signalling components
Tumour cell
CD8+ T cell
b
Tumour
MSC
NOS2 and ARG1
Tumour-specific T cell
Tumour-derived factors: IL-6, VEGF, M-CSF and IL-1β
Recruitment
Maturation of DCs in lymph nodes
c
TReg cell
CD80 or CD86
IFNγ
CTLA4
DC
IDO
Tryptophan
Kynurenines
Inhibition of CD8+ T-cell proliferation; promotion of CD4+ T-cell apoptosis
d
MHC class I molecule
Naive CD8+ T cell
IL-10
Suppression of tumour-cell lysis directly by inhibition of CTLs or indirectly by inhibition of DCs
IL-3R
IL-3
CD40L
CD40
IL-10-producing regulatory T cell
pDC
Naive CD4+ T cell
MHC class II molecule
TCR
TH2 cell
e
CD4+ T cell
Immature DC
Regulatory T cell
IL-10
T-cell anergy
CD8+ T cell
f
Tumour-derived factors or IFNγ
PD1
T cell
Apoptosis
B7-H1
Tumour cell
Unknown molecule
IL-10 and CD95
g
Invariant TCR
CD1d
NKT cell
APC
Antigen uptake
Tumour cell
Apoptosis
IL-13
STAT6
CTL
IL-13R
MSC
TGFβ
h
Recruitment to tumour
Tumour cell
DC
Inflammation
VLC
β-Defensin
CXCL12
pDC
VEGF
Recruitment to tumour
CXCL8 and TNF
Angiogenesis

Strategies to enhance anti-tumor immune response



Cell surface calreticulin expression is a marker of immunogenic cell death



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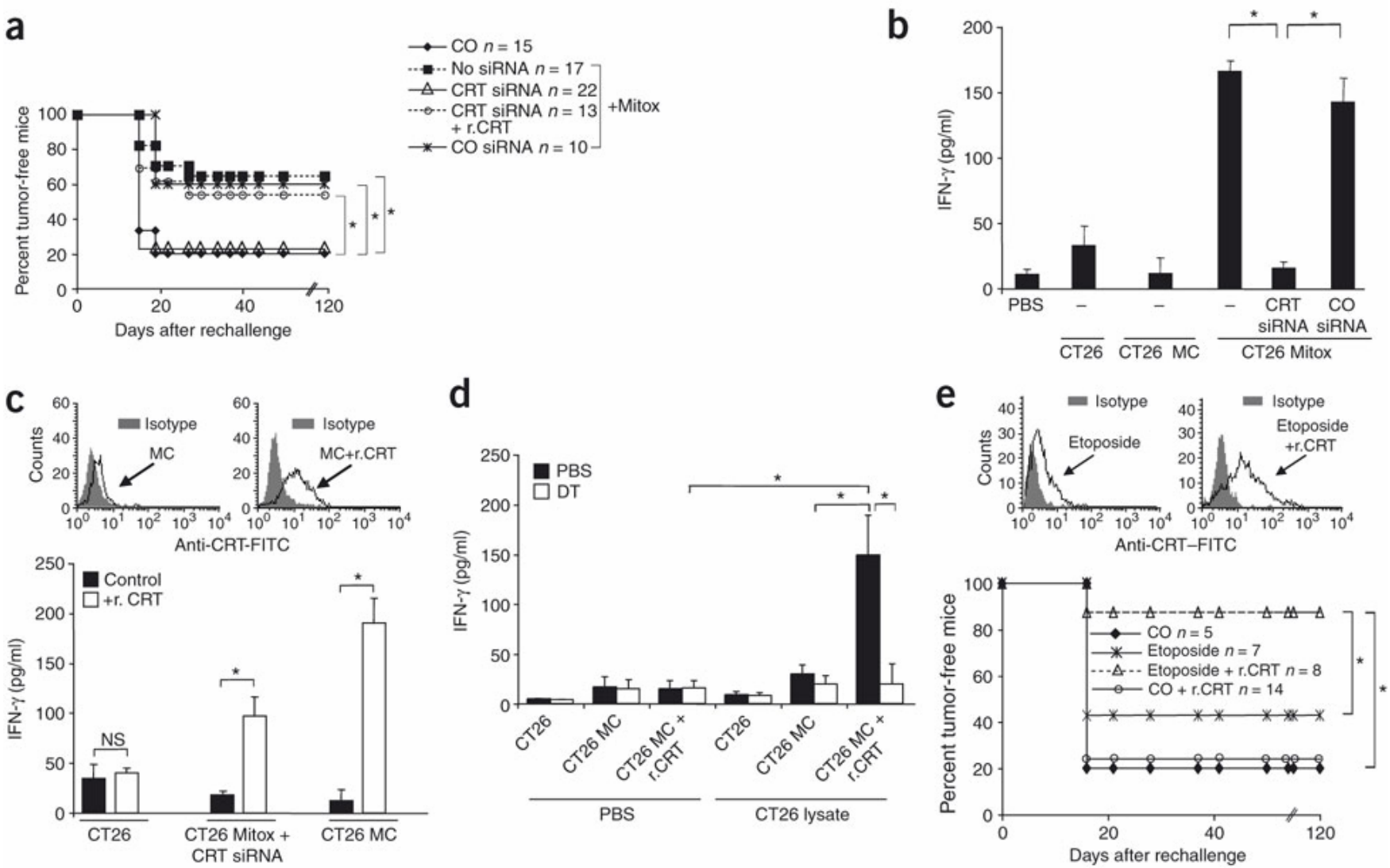
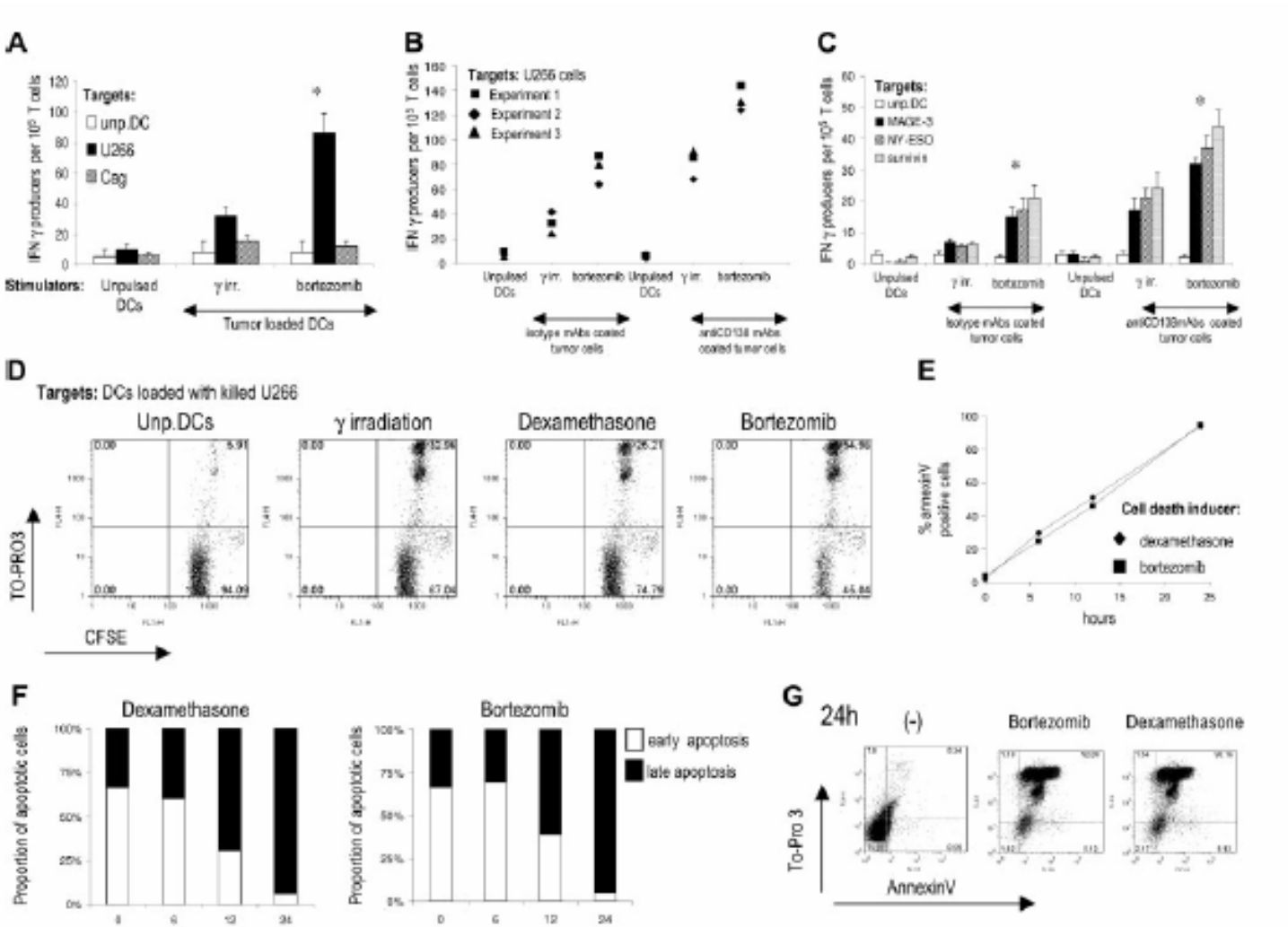
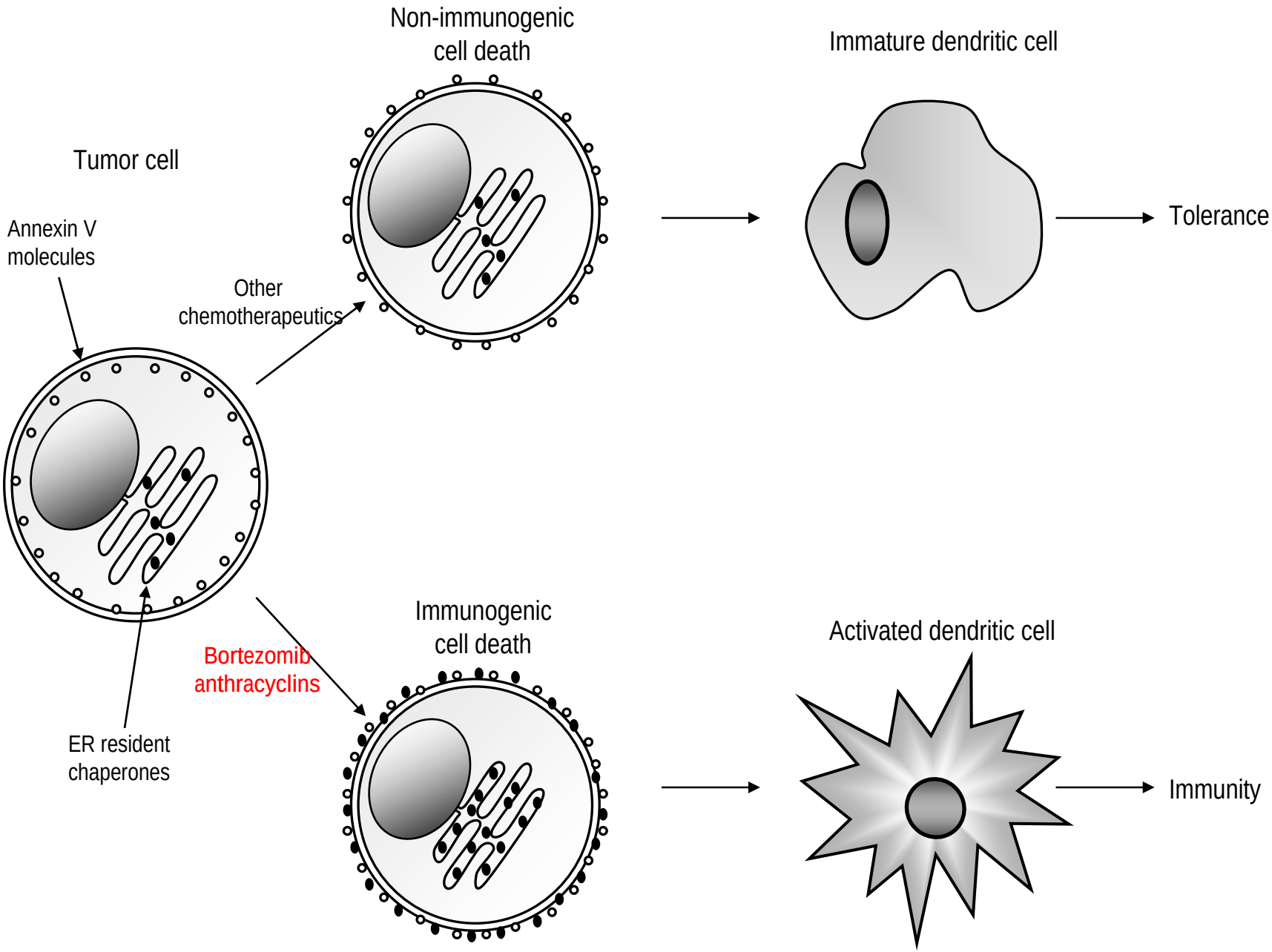


Bortezomib induces immunogenic cell death in myeloma cells





Špíšek, R., Cell cycle, 2007

Signals of immunogenic cell death

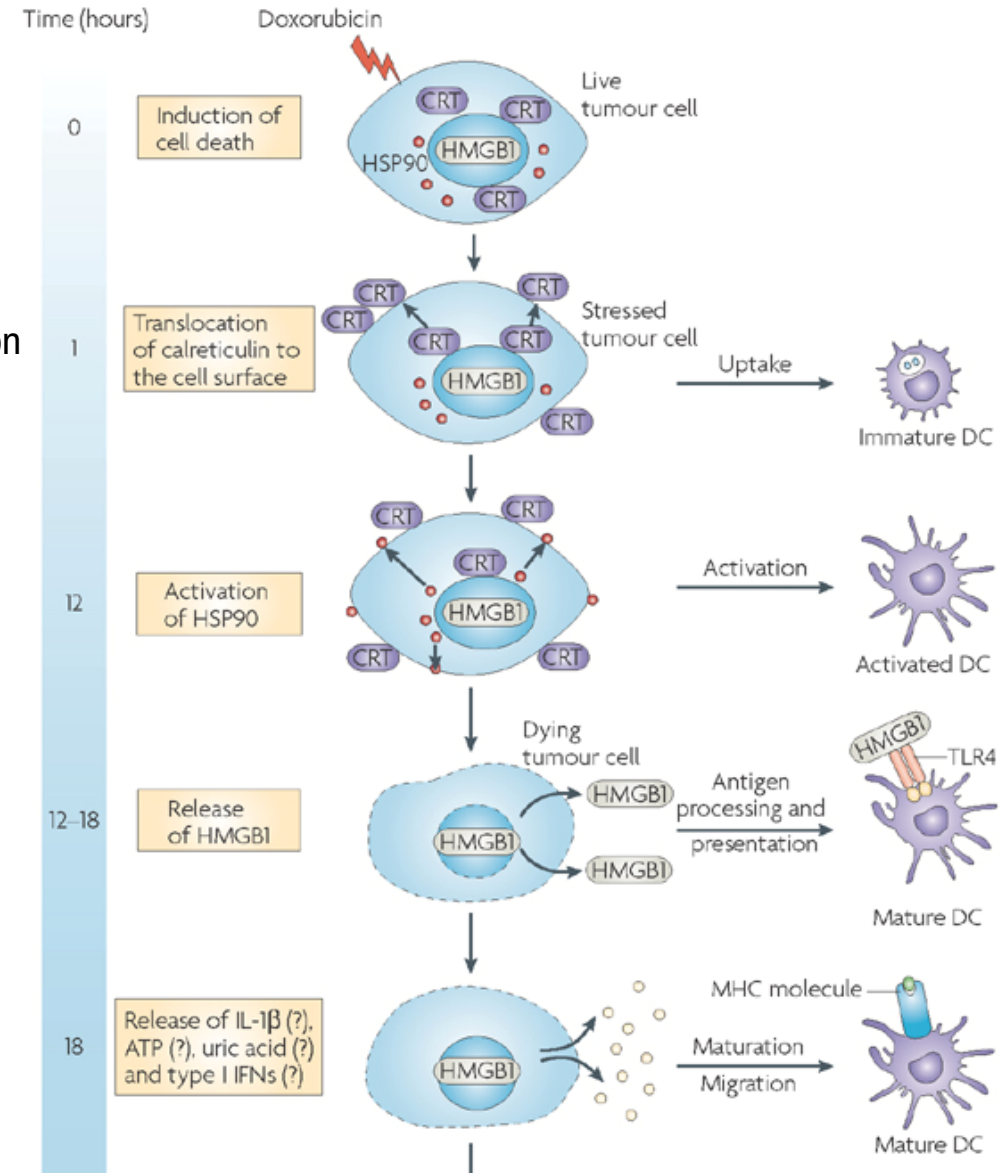
Cell death induction

Calreticulin translocation

HSP90 translocation

HMGB1 release

Uric acid, ATP



Principal of immunotherapy

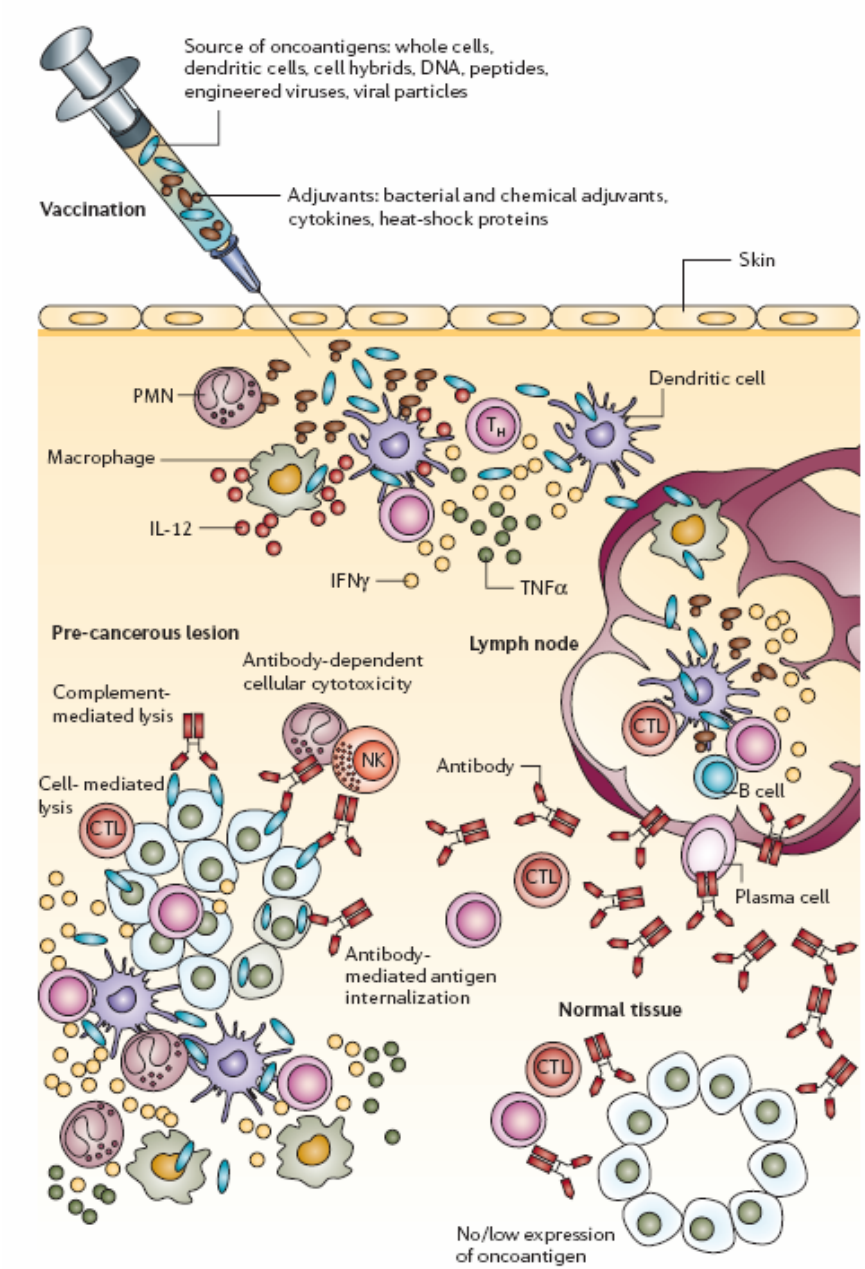
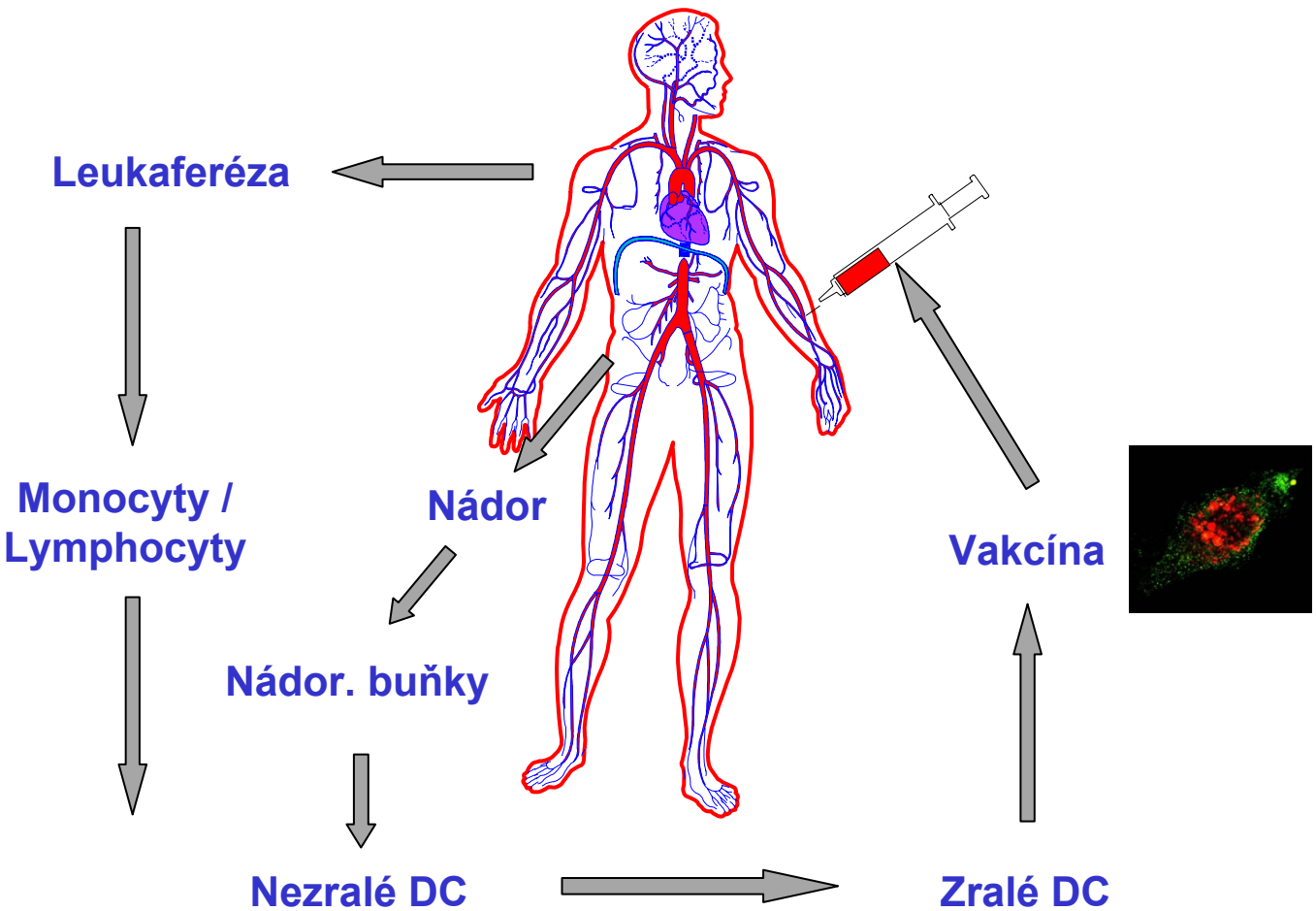
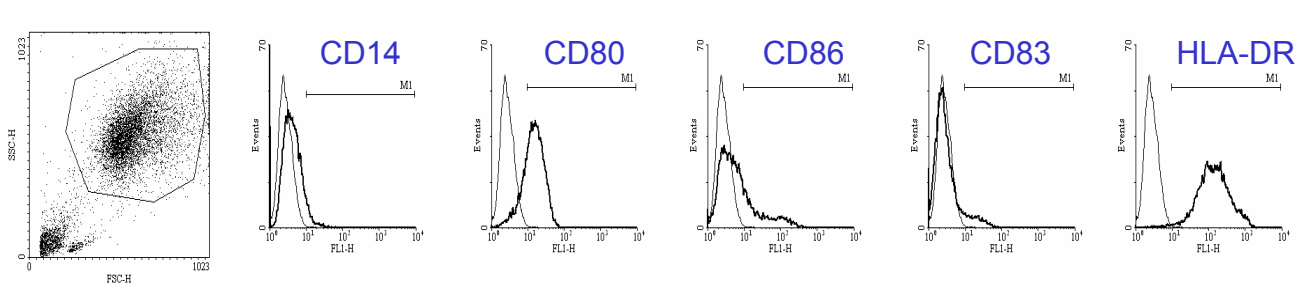


Schéma protokolu protinádorové imunoterapie

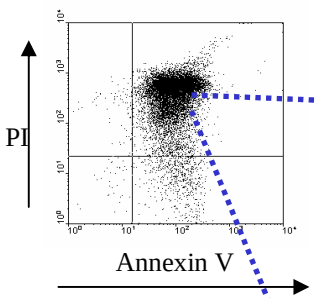


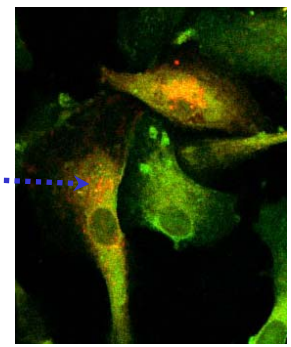
Indukce nádorově specifických T lymfocytů na modelu akutní myeloidní leukér

Nezralé DC, den 5



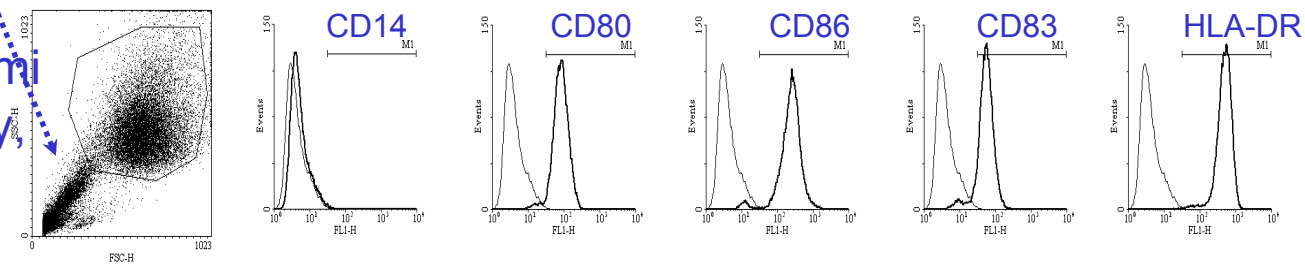
Tumor Ag: UV irradiated AML blasts





Ag-pulsing + maturation

DC pulzované mrtvými leukemickými blasty, den 7



Špíšek, Cancer Research, 2002

Jednotka buněčné imunoterapie UK, 2.LF, FN Motol- 2007

Povolení SÚKL pro přípravu vakcín na bázi dendritických buněk- 2008

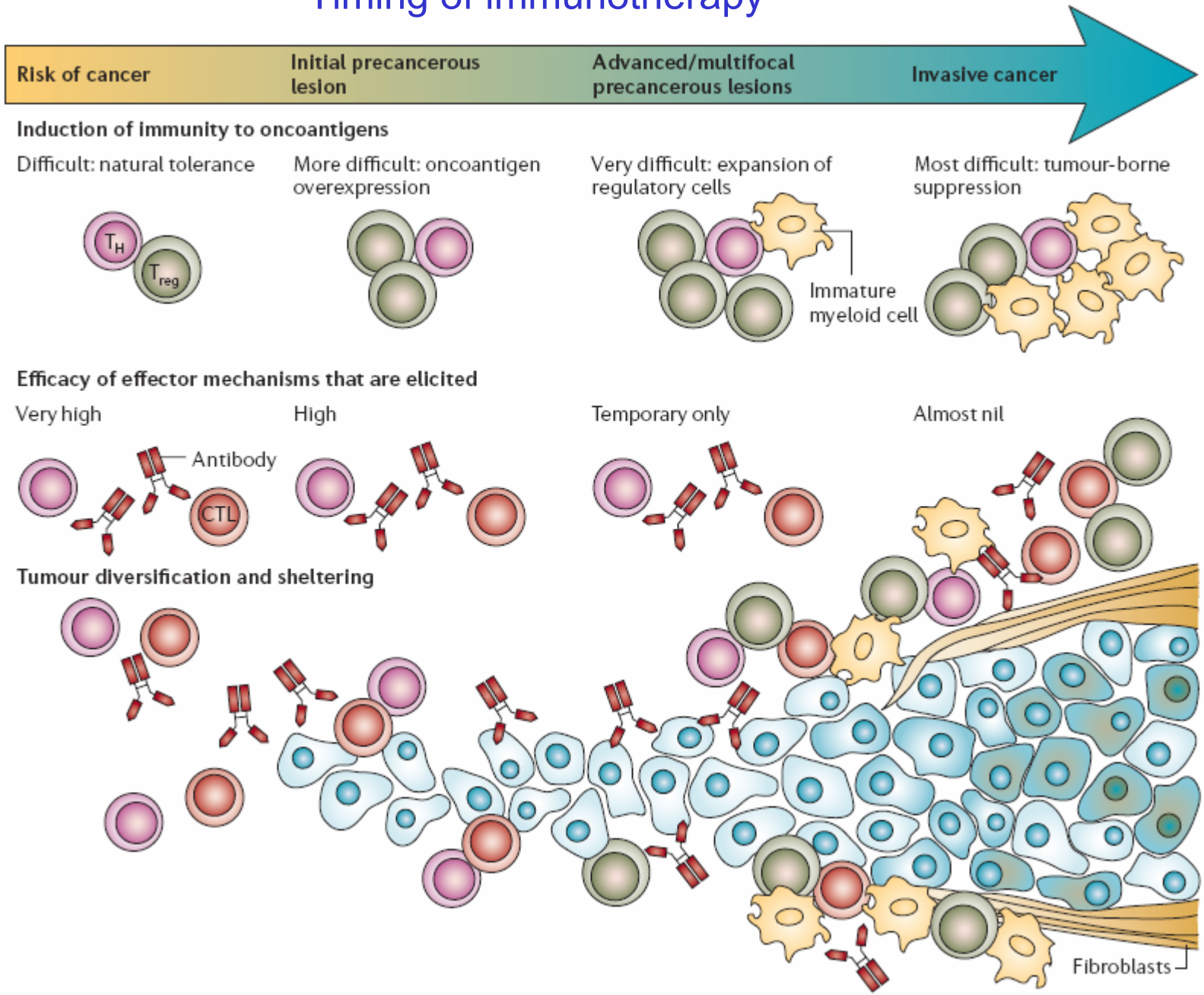
SÚKL
Státní ústav pro kontrolu léčiv
Šrobárova 48, 100 41 Praha 10
tel.: +420 272 185 111
fax: +420 271 732 377
e-mail: posta@sukl.cz
web: www.sukl.cz

certifikát sp.zn./ certificate Ref.No: 21442/4/INS/07

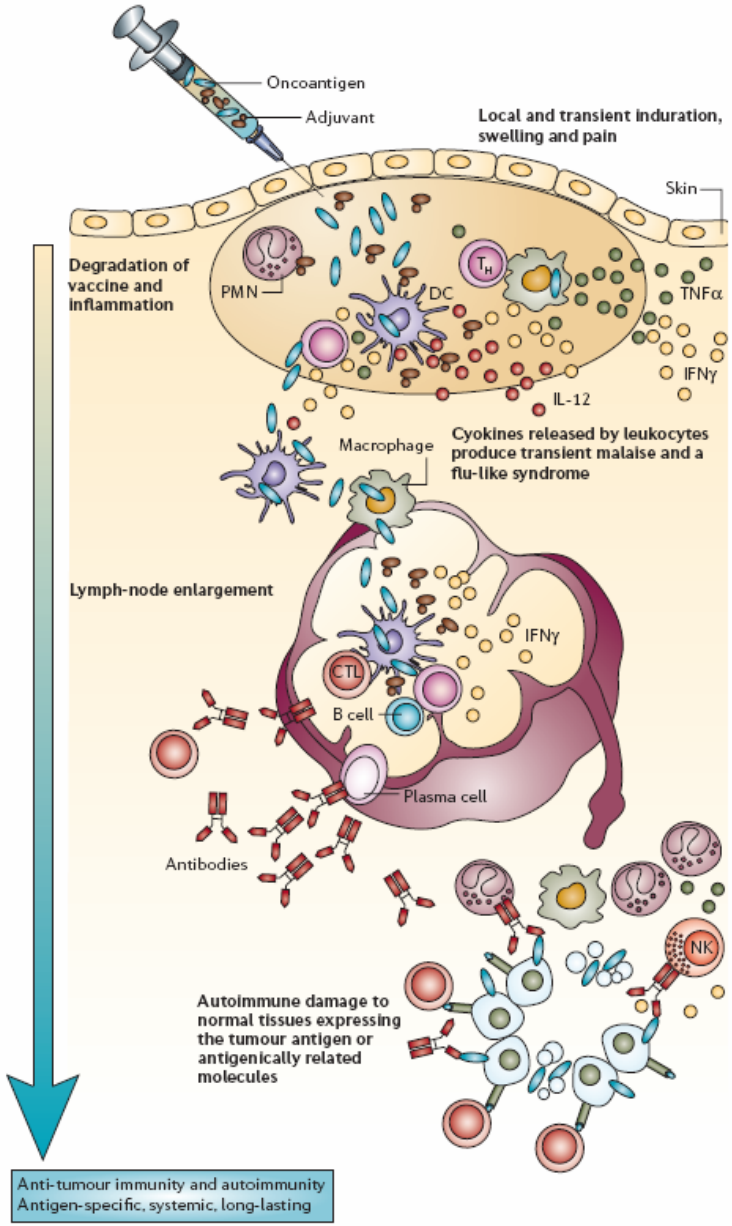
CERTIFIKÁT SVP PRO VÝROBCE
Část 1

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER
Part 1

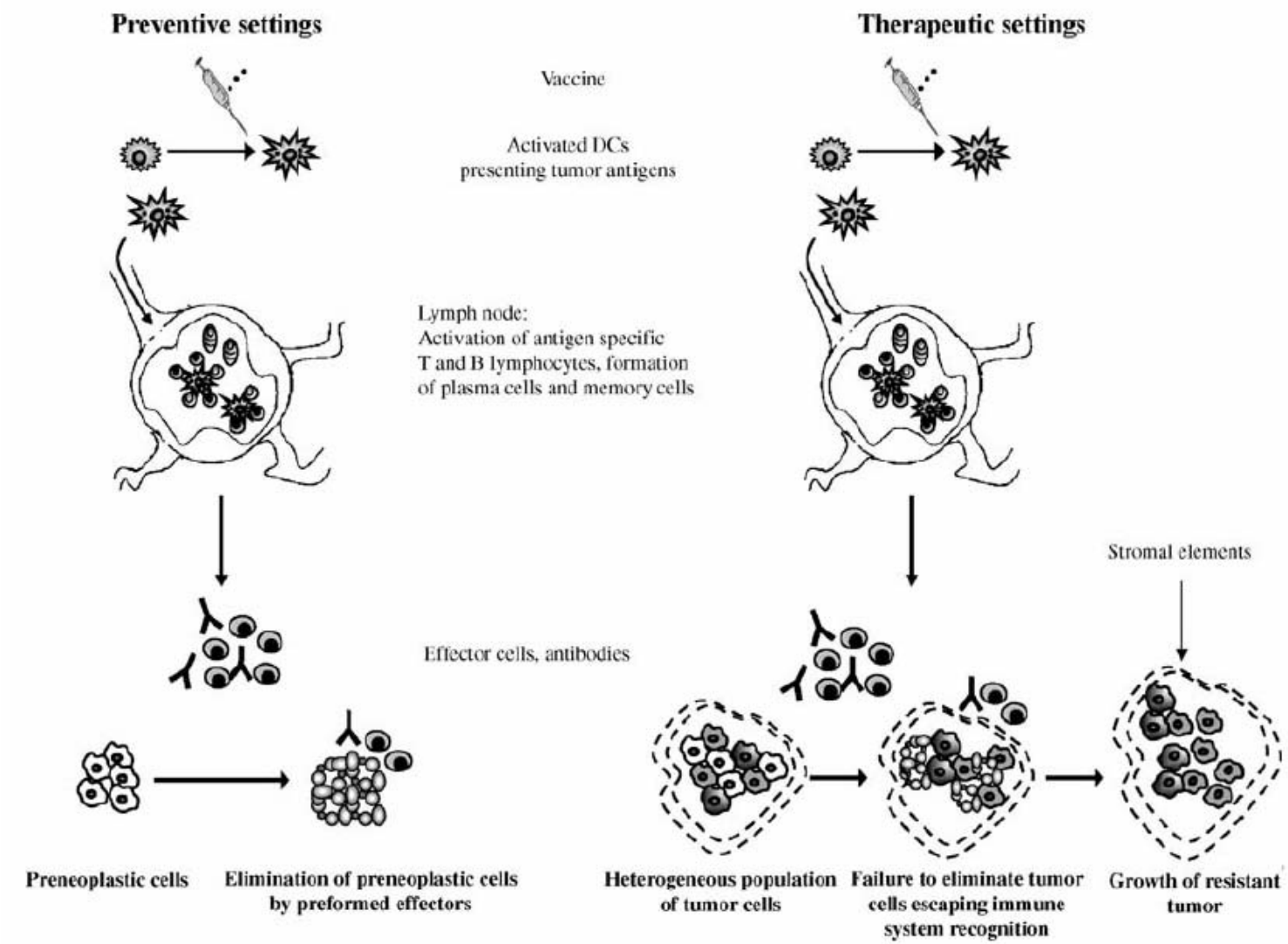
Timing of immunotherapy



Adverse effects of immunotherapy



Timing of immunotherapy



Target populations

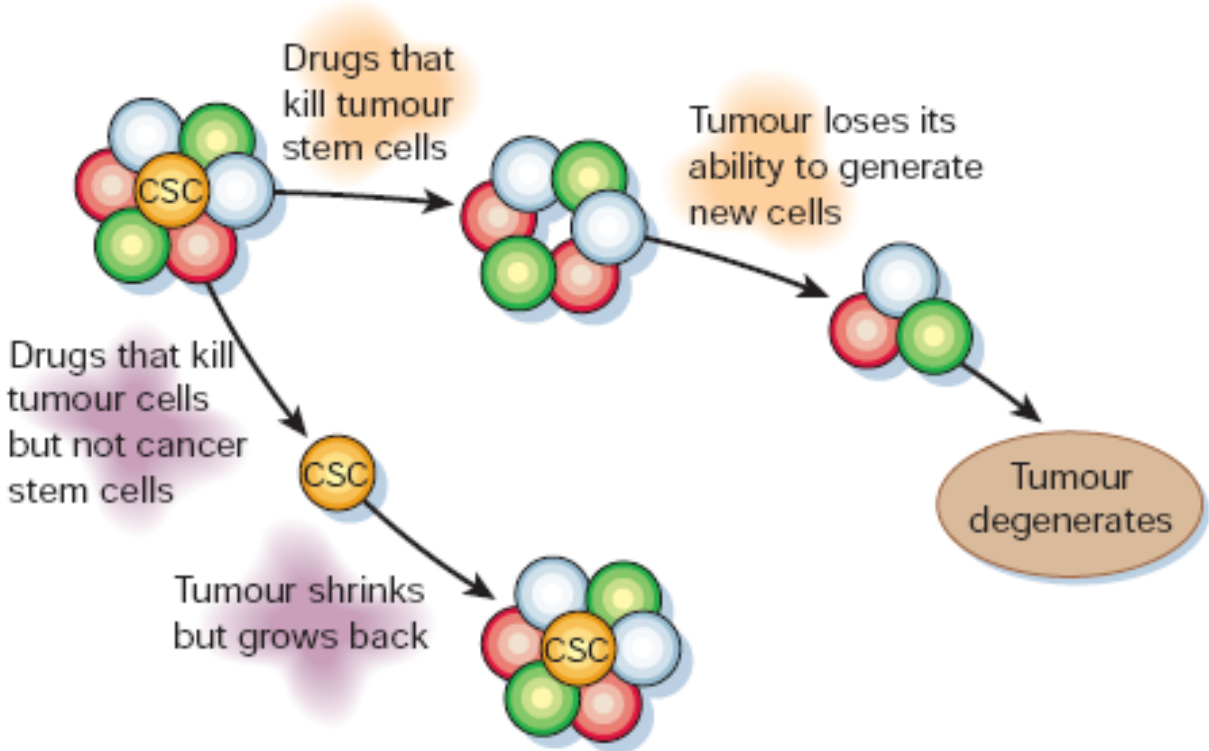
Primary prevention- individuals at risk of cancer development, hereditary cancer syndromes (e.g. families with hereditary colorectal cancer, or women with BRCA mutations) where specific mutations can be detected and the increased risk for cancer is well established.

Secondary prevention- is feasible in patients with preneoplastic lesions, wherein preventive anti-tumor vaccination should prevent progression to malignant tumors. Examples of the latter are patients with colon polyps, oral leukoplakia, and cervical intraepithelial neoplasia, or monoclonal gammopathy of unknown significance.

Tertiary prevention- Many tumors can be eradicated or substantially reduced by current treatment modalities. Cancer vaccines could be used as a form of adjuvant therapy designed to elicit and boost antitumor immunity in patients with minimal residual disease.

Targeting of tumor clonogenic progenitors

- Important therapeutic implications
  - if treatment does not eliminate cancer stem cells, tumor regenerates once the treatment stops



Reya, Nature, 2001