Vaccination thérapeutique en Oncologie

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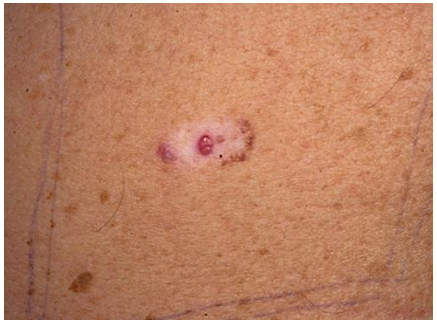
Plan

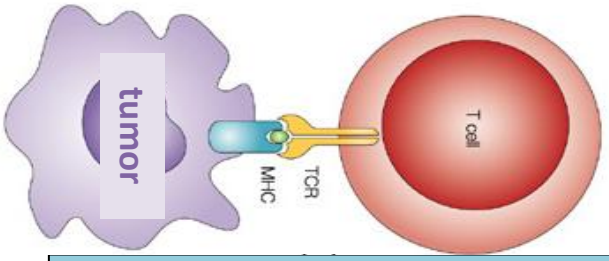
- Interaction cancer/host immune system
- Immunotherapy History
- Target identification
- Different types of Vaccines
- Adjuvants/Vaccine Delivery
- Response assessment to immune therapies
- Future : Overcoming microenvironment/T cell therapies
- Our experience : Glioma

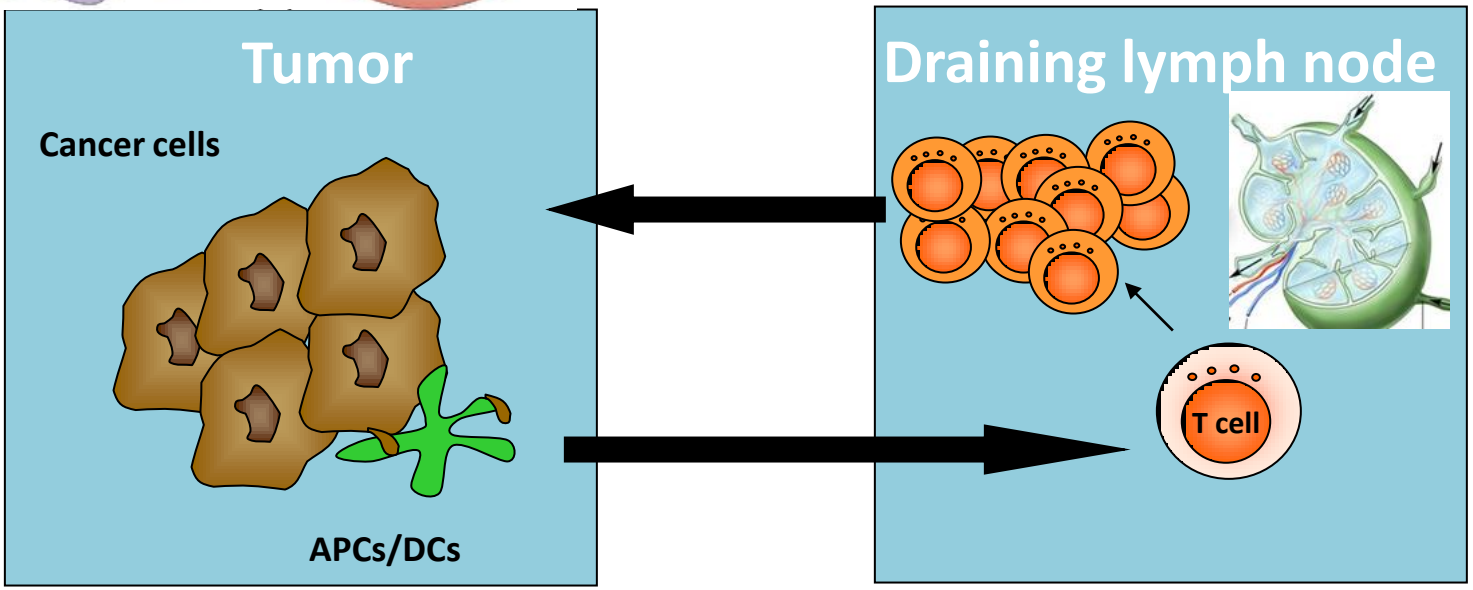
Using the immune system ?

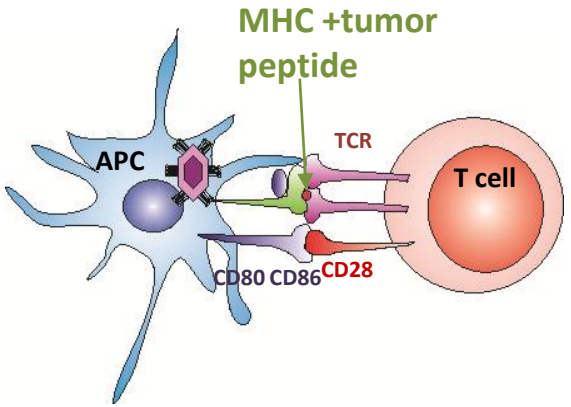
- Incidence of cancers is increased in
  - constitutive and acquired immunodeficiencies
- T cells may kill tumor cells
- T cells invade tumors
- intra-tumoral activated T cells is a
  - favorable prognostic factor for many cancers
- spontaneous regressions are mediated by T cells



Tumor immunity : how does it work ?







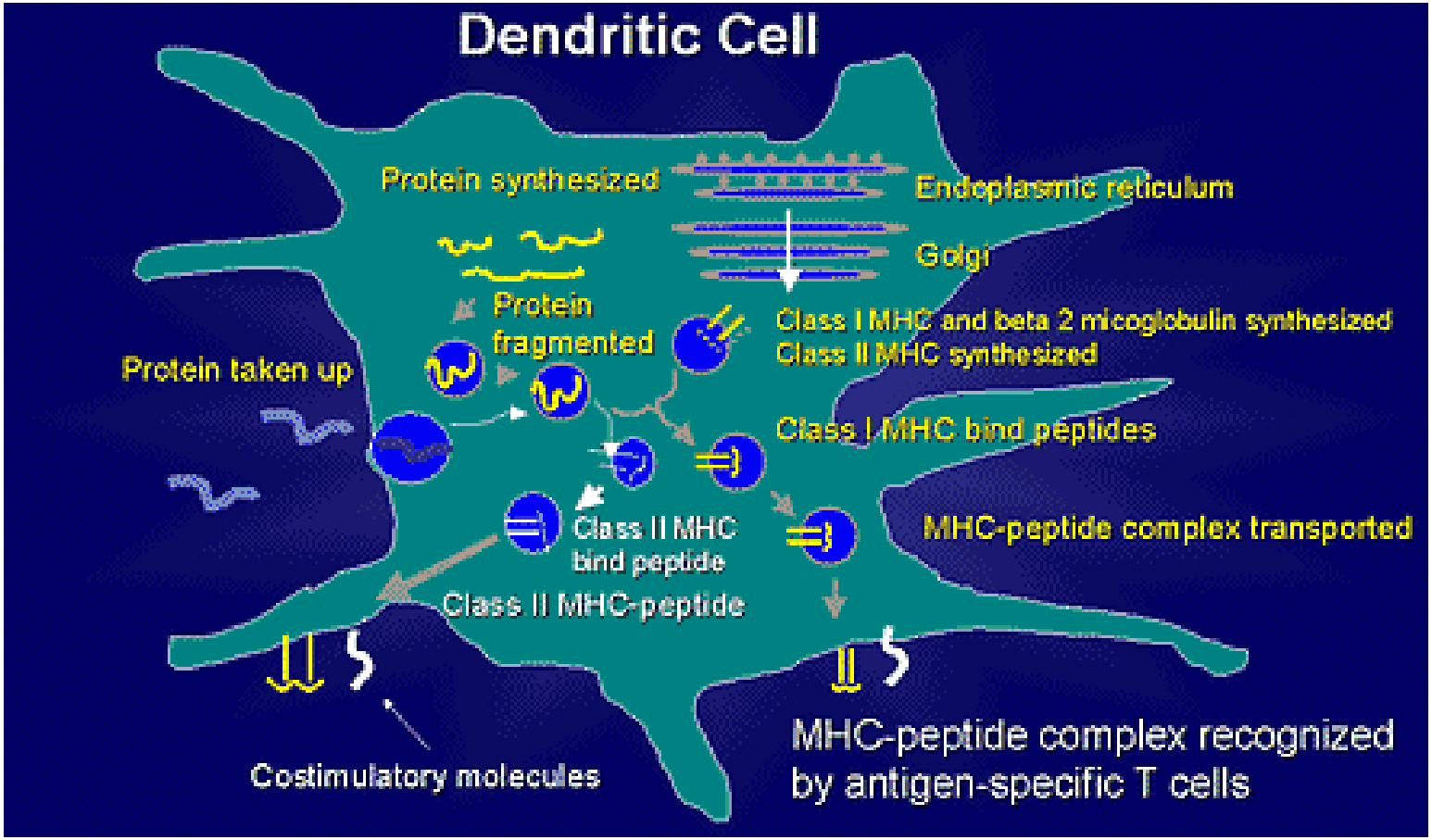
Biology of DCs

- most potent professional APCs
- sentinels at peripheral tissues

  uptake, process, and present pathogen to naive T lymphocytes at the lymphoid organs through MHC molecules
- bridge between innate and adaptive immunity

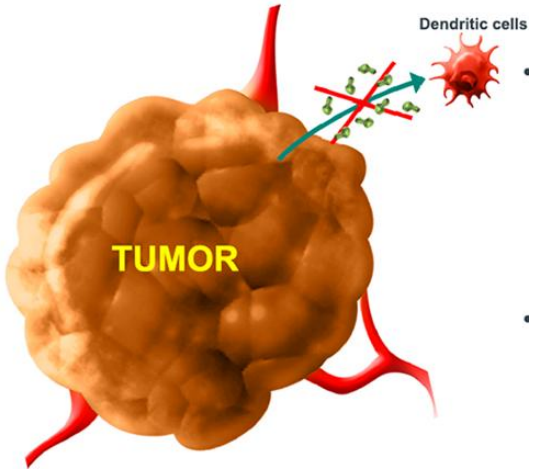
Ehrlich/Metchnikov

Ag Processing/Presentation

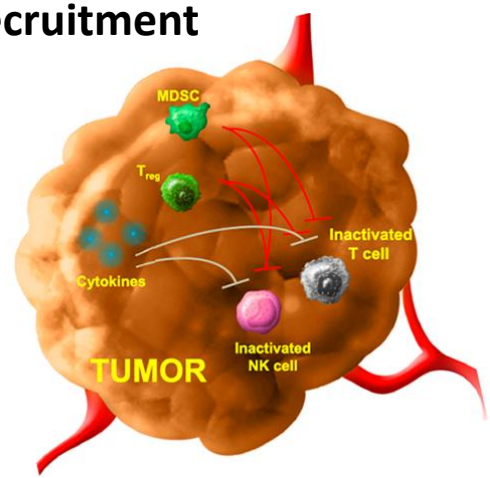


Immune evasion

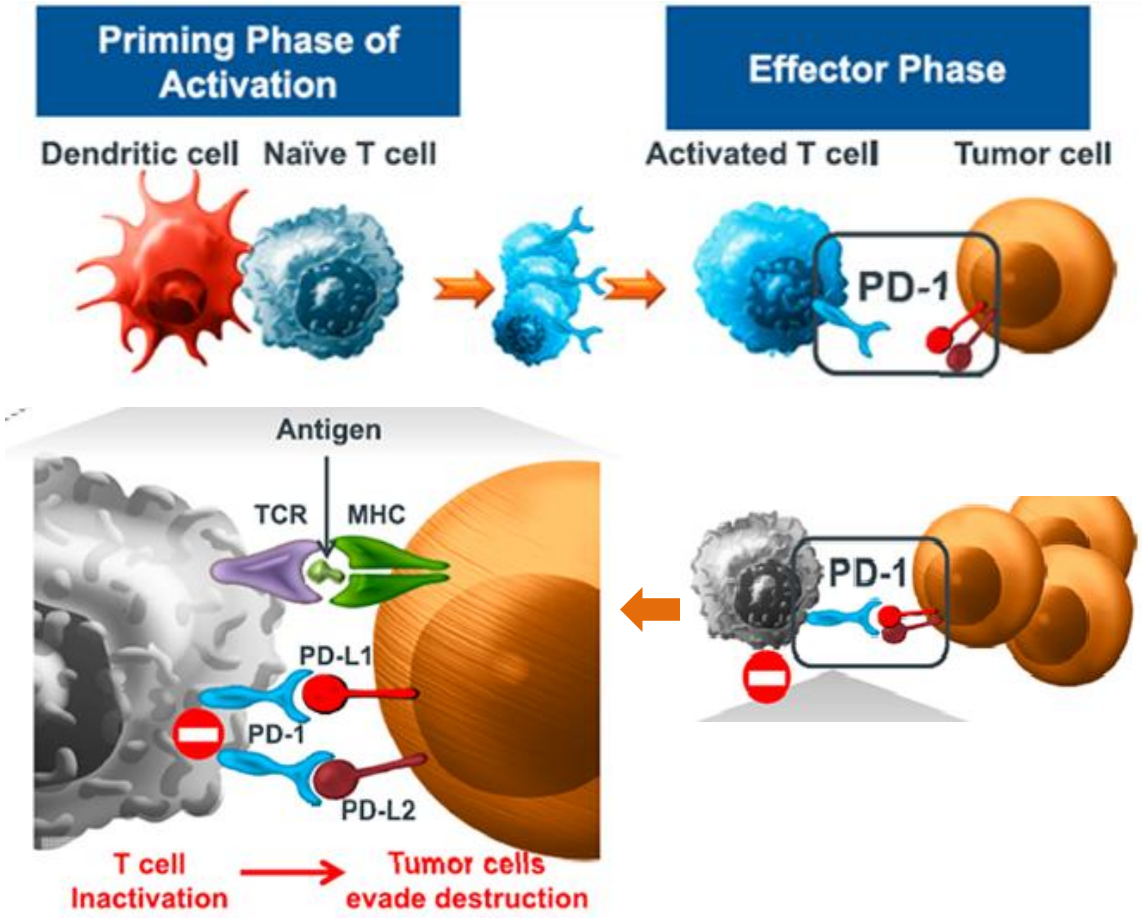
1. Loss of Ag expression



2. Immunosupp cell + cytokines recruitment



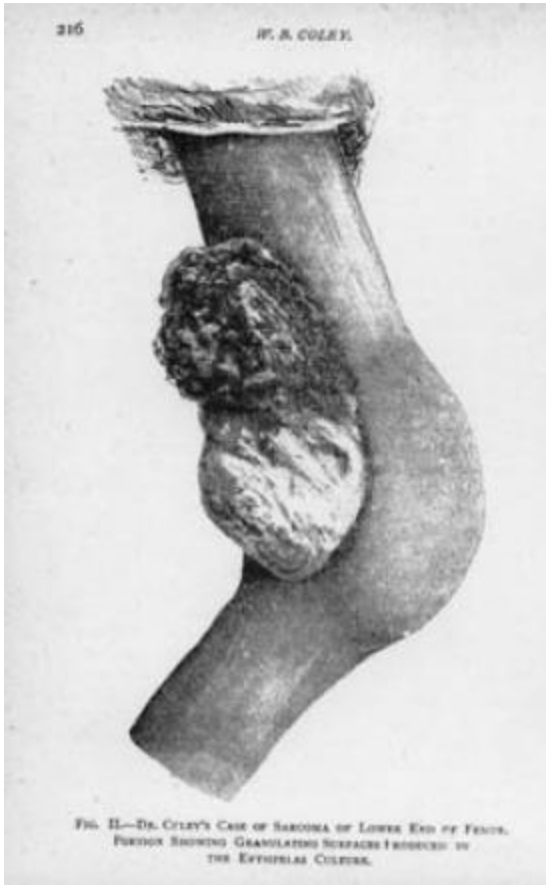
3. Exploiting PD1 immune checkpoint pathway



Hanahan D. Cell 2011

Coley's toxin

- 1891, Dr. W. Coley first attempt to stimulate the immune system
- intratumoral injections
- of inactivated Strepto. pyogenes
- and Serratia marcescens



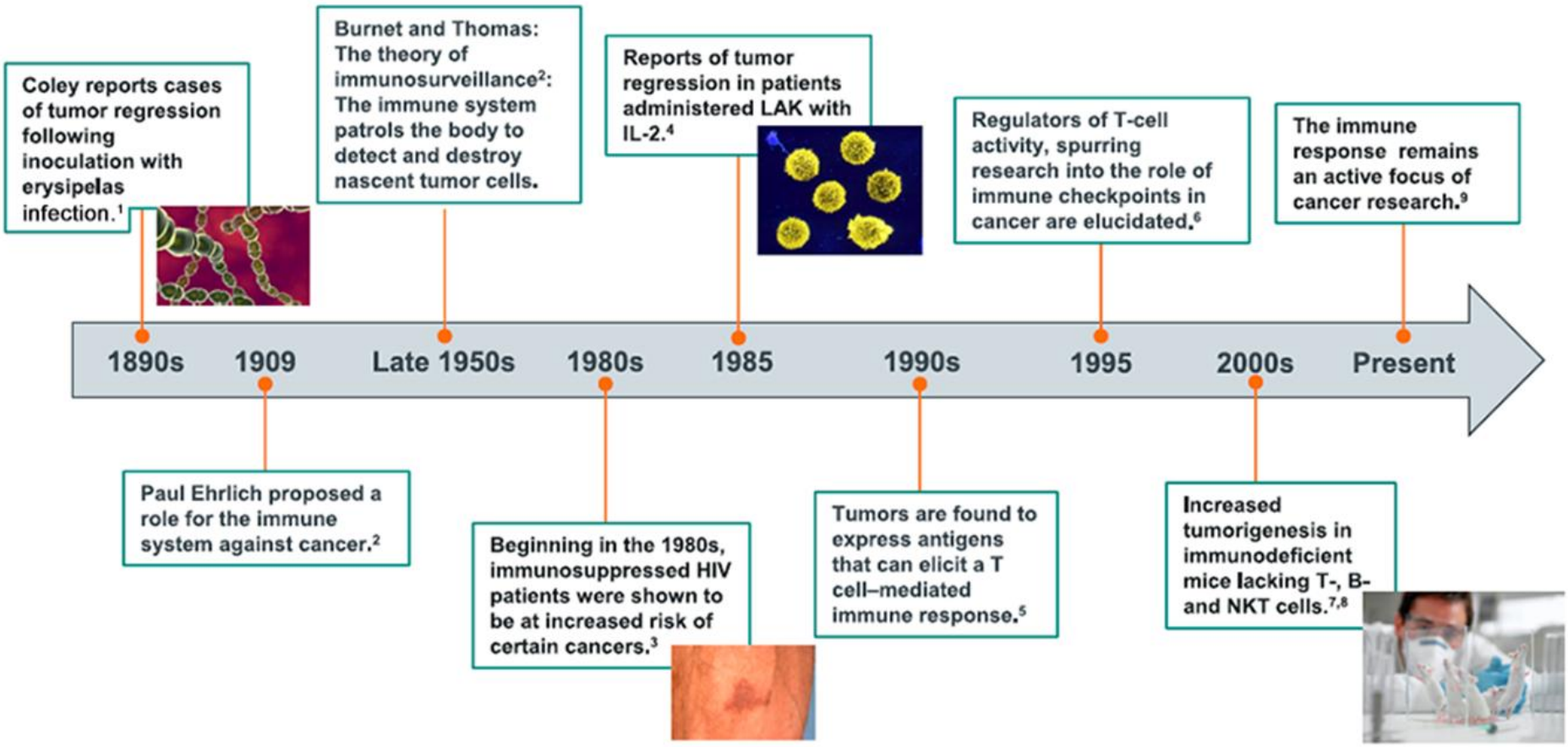
Coley WB. Contribution to the knowledge of sarcoma. Ann Surg 1891

Coley's toxin

- Despite effectiveness, skepticism by scientific community
- modern science has shown that Coley's principles were correct
- BCG similar to Coley's toxin : still being used intravesically for superficial bladder cancer

Lamm, D. L. et al. , NEJM 1991

History


Coley reports cases of tumor regression following inoculation with erysipelas infection.[1]
Burnet and Thomas: The theory of immunosurveillance[2]: The immune system patrols the body to detect and destroy nascent tumor cells.
Reports of tumor regression in patients administered LAK with IL-2.[4]
Regulators of T-cell activity, spurring research into the role of immune checkpoints in cancer are elucidated.[6]
The immune response remains an active focus of cancer research.[9]
1890s
1909
Late 1950s
1980s
1985
1990s
1995
2000s
Present
Paul Ehrlich proposed a role for the immune system against cancer.[2]
Beginning in the 1980s, immunosuppressed HIV patients were shown to be at increased risk of certain cancers.[3]
Tumors are found to express antigens that can elicit a T cell–mediated immune response.[5]
Increased tumorigenesis in immunodeficient mice lacking T-, B- and NKT cells.[7,8]

U.S. Food and Drug Administration (FDA)

- approved two prophylactic vaccines :

  For HBV (cause of liver cancer)

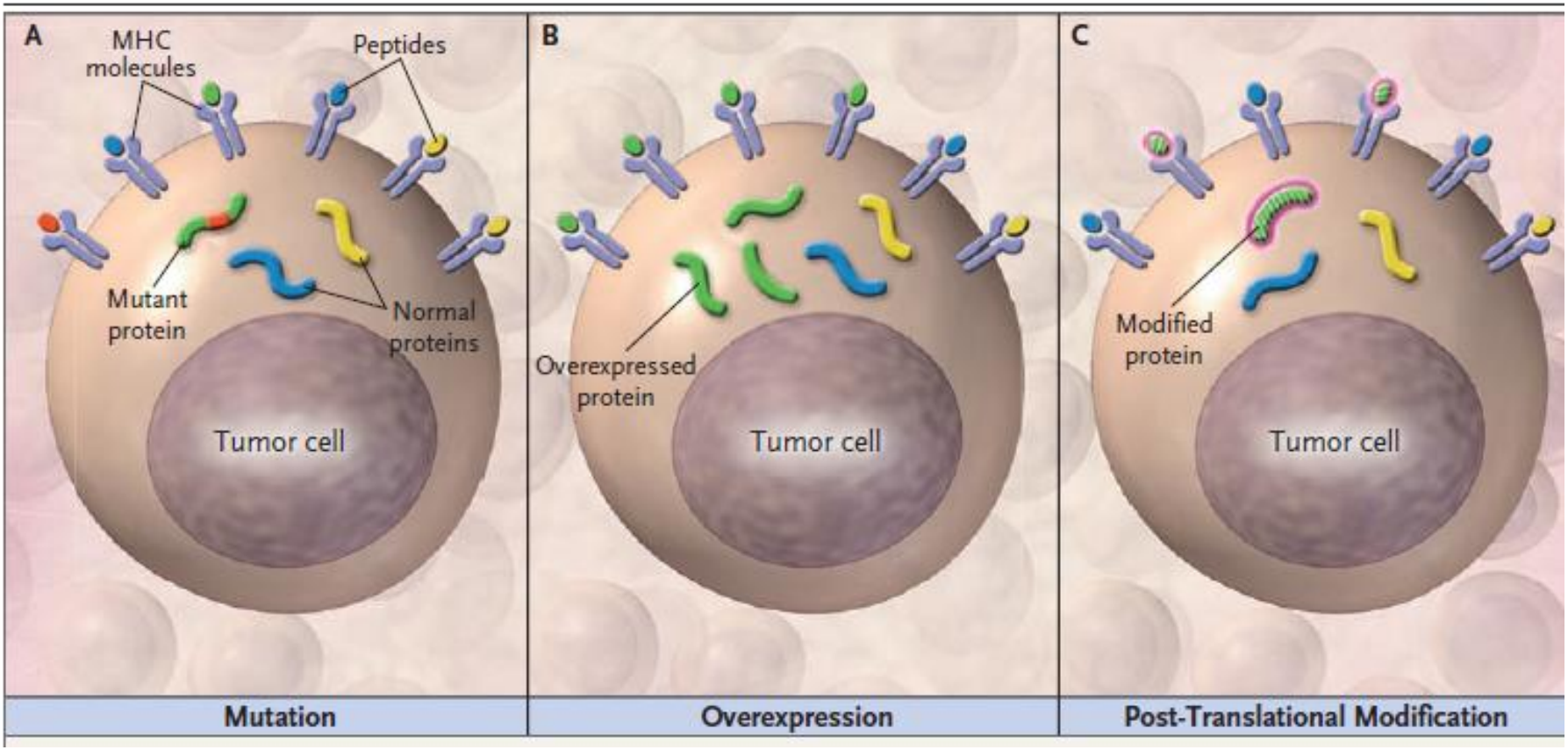
  For HPV (70% of cervical cancers)

- One therapeutic vaccine :

  Sipuleucel-T (1), prostate cancer patients

(1)Kantoff P.W. et al. NEJM 2010

Targets ?



Three Ways for Self Antigens to Become Tumor Antigens

Finn et al. 2008 NEJM

Immune strategies

- Active immunotherapy

  Priming of lymphocytes by stimulation of dendritic cells with Ags

- Adoptive immunotherapy:

  Passive administration of lymphocytes, ater amplification/activation

Therapeutic cancer vaccine : definition

- Vaccin therapeutic, not prophylactic
- Aim : activate various immune effector mechanisms to :

  specifically attack and destroy cancer cells

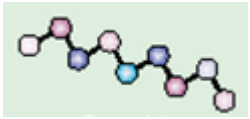
  and spare normal cells.

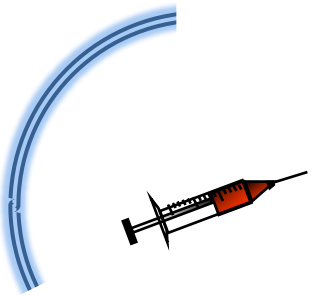
  Alter tumor microenvironment

Therapeutic vaccines

1. synthetic peptides

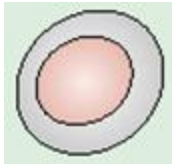
- **single peptide (EFGRvIII)**
- **multiple peptides (EphA2, IL-13Rα2, YKL-40, gp100; HSPPC-96, …)**





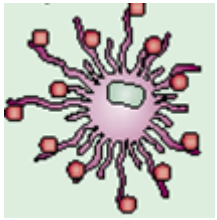
3. Cell based

- **DC vaccines**
- **Autologuous tumor cells**
- **Allogeneic tumor cells**



2. Genetic vaccines

- **DNA/RNA**
- **Viral vaccines**



Cell vaccines

Autologous tumor cell vaccines

- entire spectrum of tumor-associated antigens (TAAs)
- may be modified to confer higher immunostimulatory characteristics.

Allogeneic tumor cell vaccines

- contain 2 or 3 established human tumor cell lines
- overcome many limitations of autologous tumor cell vaccine

Standardized/large-scale vaccine production

Easy manipulation for expression of immunostimulatory molecules

Cost effectiveness.

Allogeneic tumor cell vaccines

- Canvaxin™ : 3 melanoma lines combined with BCG as an adjuvant
- belagenpumatucel-L : 4 NSCLC lines + TGF-b2

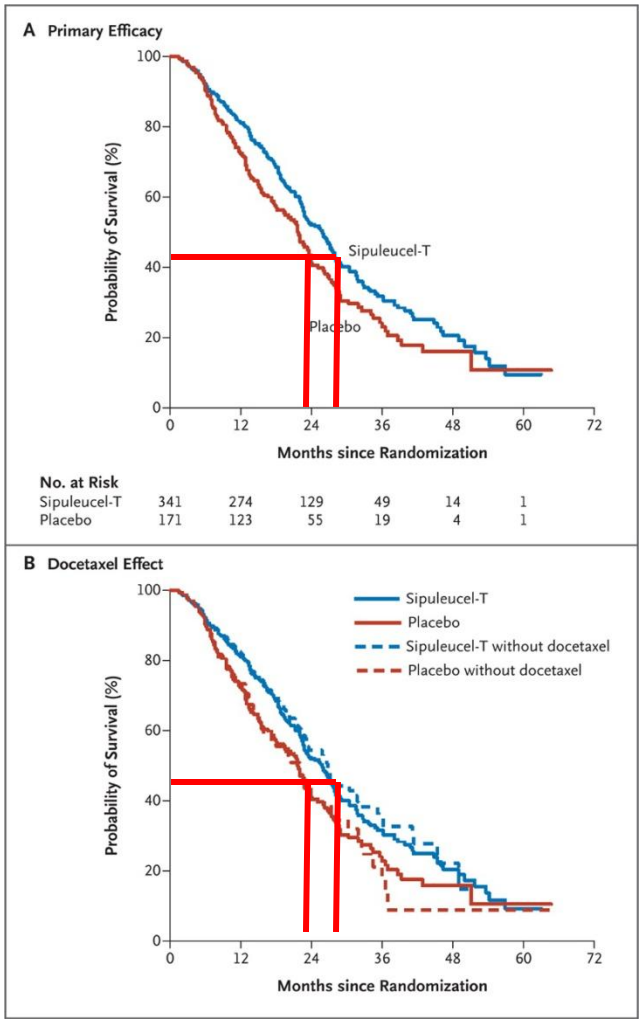
DC vaccines

Sipuleucel T Provenge

APCs from PBMCs
Incubated with PAP
fused to GM-CSF.

4.1-month
improvement
in median survival

modest antitumor efficacy
Labor intensive



Kantoff PW et al. N Engl J Med 2010

Modification of DCs to improve vaccine potency

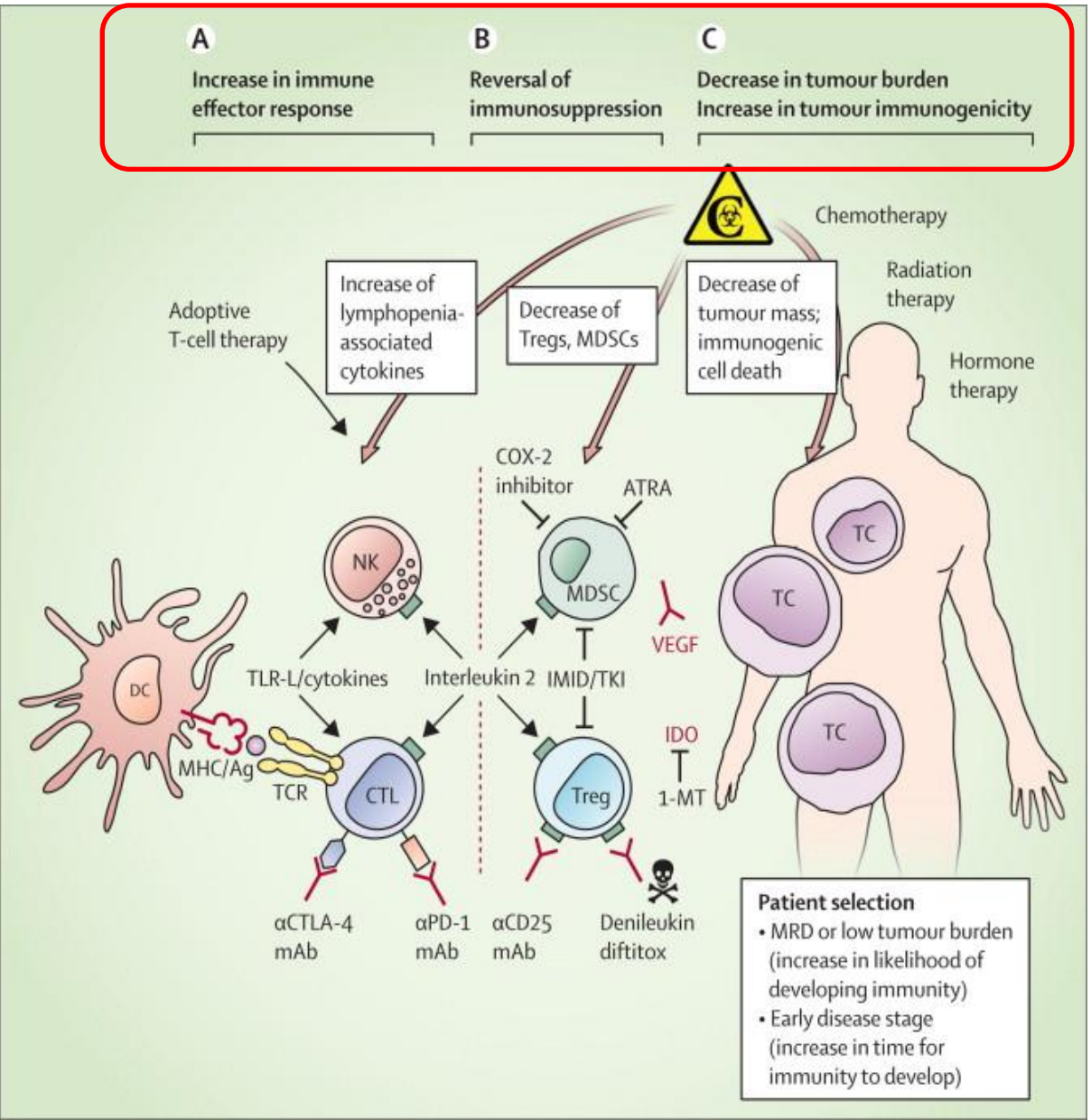
- Stimulation with costimulatory molecules

CD40, CD70, GITRL, 4-1BBL (CD137L), and OX40L

- proinflammatory factors

IL-12p70, IL-2, IL-18, CCR7,and CXCL10, also enhances DC functions

Combination strategies for DC vaccines



Anguille S. et al. Lancet Oncol 2014

Clinical use of DCs for cancer therapy

	Dendritic cell product	Control group	Status	ClinicalTrials.gov identifier
Melanoma	Autologous monocyte-derived DCs pulsed with melanoma peptides Autologous DCs mixed with irradiated autologous tumour cells suspended in GM-CSF (melapuldencel-T)	Dacarbazine Autologous PBMCs suspended in GM-CSF	Completed Not yet recruiting	NA[5] NCT01875653
Prostate	Autologous APCs (including DCs) loaded with PAP/GM-CSF (sipuleucel-T)	Autologous APCs	Completed	NCT00005947 NCT00065442 NCT00779402 NCT01133704
Brain (GBM)	Autologous DCs pulsed with autologous tumour lysate (DC-VAX-L)	Autologous PBMCs	Recruiting	NCT00045968
Renal	Autologous DCs electroporated with autologous tumour mRNA and CD40L mRNA, in combination with sunitinib (AGS-003)	Sunitinib	Recruiting	NCT01582672

Excludes one study in prostate cancer that was withdrawn before enrolment (NCT00043212) and three studies with phase 2/3 design (NCT01759810, NCT01782274, and NCT01782287). DCs=dendritic cells. GM-CSF=granulocyte macrophage colony-stimulating factor. PBMCs=peripheral blood mononuclear cells. APCs=antigen-presenting cells. PAP/GM-CSF=chimeric antigen consisting of the prostate tumour antigen prostatic acid phosphatase (PAP) linked to GM-CSF. GBM=glioblastoma multiforme. NA=not available.

Table 1: **Overview of completed and ongoing randomised phase 3 clinical trials of dendritic cell-based cancer immunotherapy, by cancer type**

Anguille S. et al. Lancet Oncol2014

Conclusion DC vaccines

- Very potent tool to induce immune response
- variable that may affect the function in clinical trials :

Ag loading strategy

maturation status

route and frequency of administration

Adjuvants

Genetic vaccines

DNA/RNA Vaccines

Viral vaccines

Genetic vaccines

Ex vivo transfection of somatic cells

- myocytes, keratinocytes or DCs
- with viral or plasmid DNA vectors carrying the expression cassettes

- Those cells infiltrate muscle or skin as a part of the inflammatory response to vaccination
- Results in subsequent cross-priming or direct Ag presentation.
- easy delivery and activation of various arms of immunity

Aurisicchio & Ciliberto, 2012

DNA vaccines

- bacterial plasmids
- constructed as a shuttle to deliver and express TAA

- bacterial DNA itself acts as PAMPs to stimulate TLRs

Barber, 2011; Beutler et al., 2006; Spies et al., 2003, Liu 2011

RNA Vaccines

- mRNA from autologous tumor tissues

- Diff with DNA vaccines :
- Total RNA vaccine (various TAA) : reduce the possibility of tumor escape
- Less side effects or autoimmune diseases due to rapid degradation and clearance

Carralot et al., 2005; Scheel et al., 2005; Wolff et al., 1990

Viral vaccines

- viral vectors :

low disease-causing potential

low intrinsic immunogenicity

engineered to encode TAAs +/- immunomodulating molecules.

Peptide vaccines

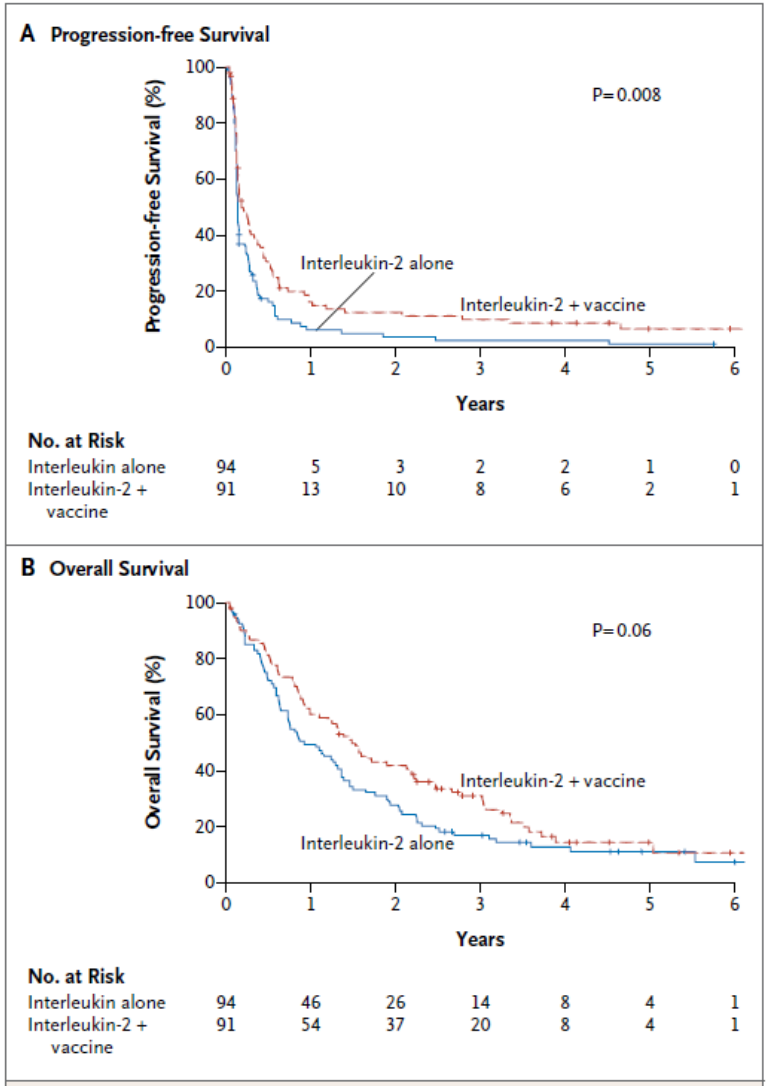
Peptide vaccines

- MAGE-1 is the first gene reported to

encode a human TAA recognized by T cells

- target only one epitope or a multiple epitopes of the TAA
- able to induce antigen-specific T-cell responses
- Disappointing clinical outcomes

Phase III trial



gp100 peptide vaccine and interleukin-2 in advanced melanoma

this was the first phase III trial to demonstrate a clinical benefit for a peptide vaccine in melanoma

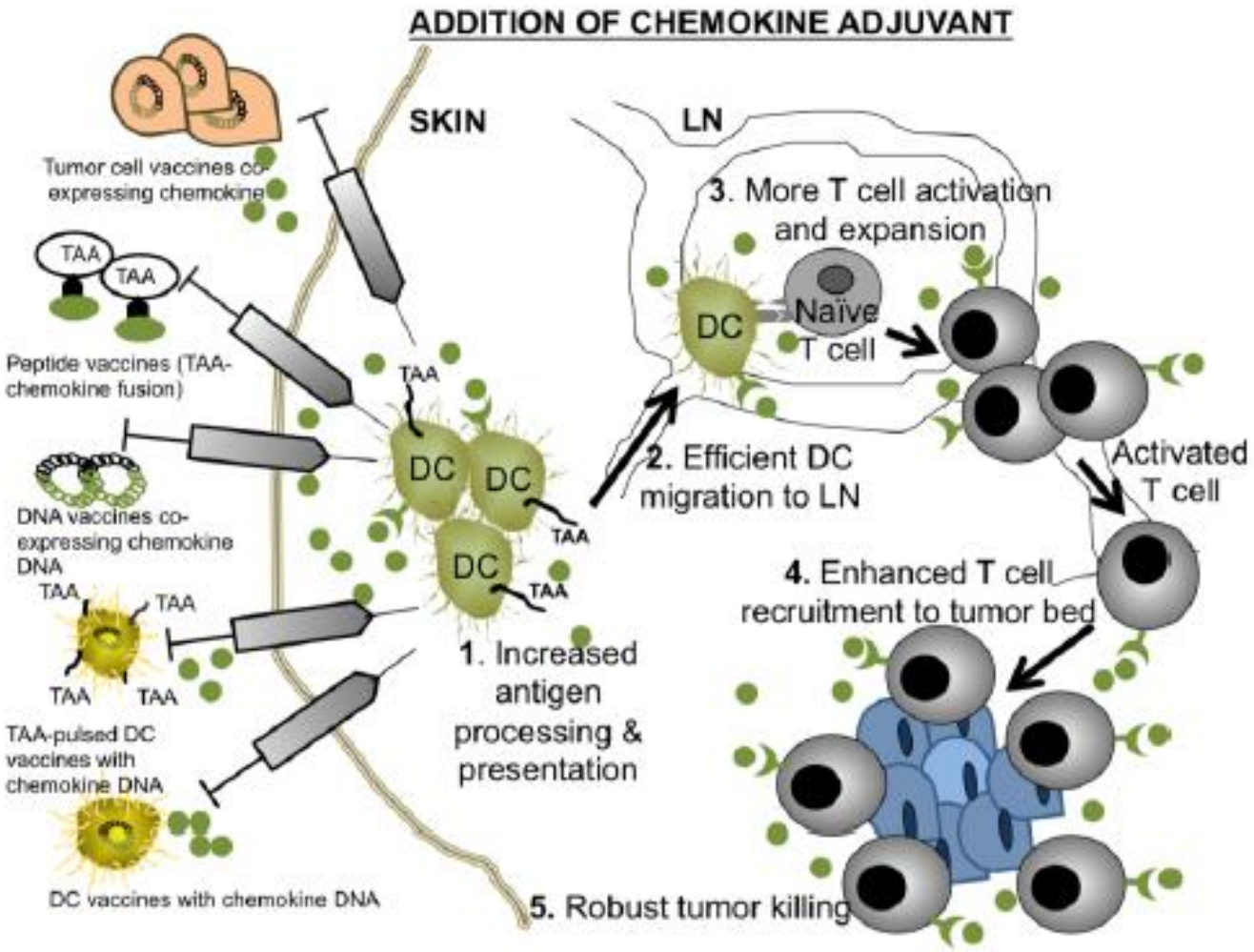
Schwartzentruber, D. J., et al. (2011) N Eng J Med, 364, 2119–2127.

Adjuvants

- TAAs are poorly immunogenic in nature
- pioneering work of Charles Janeway
- adaptive immune responses are preceded by innate immunity receptors triggered by microbial components : PAMPs
- via TLRs on DCs, engages innate and adaptive immunity

Janeway, C. A., Jr. (1992). Immunology Today

Adjuvants



Bobanga I et al., Vaccine 2013

Immunomonitoring of response

- In vivo

T cell infiltration of tumor

Autoimmunity

Dth

- In vitro

ELISA or ELISPOT for cytokine release

Intracellular cytokine

T cell proliferation

Peptide MHC tetramer

Cytotoxic T cell function

CTL plas frequency

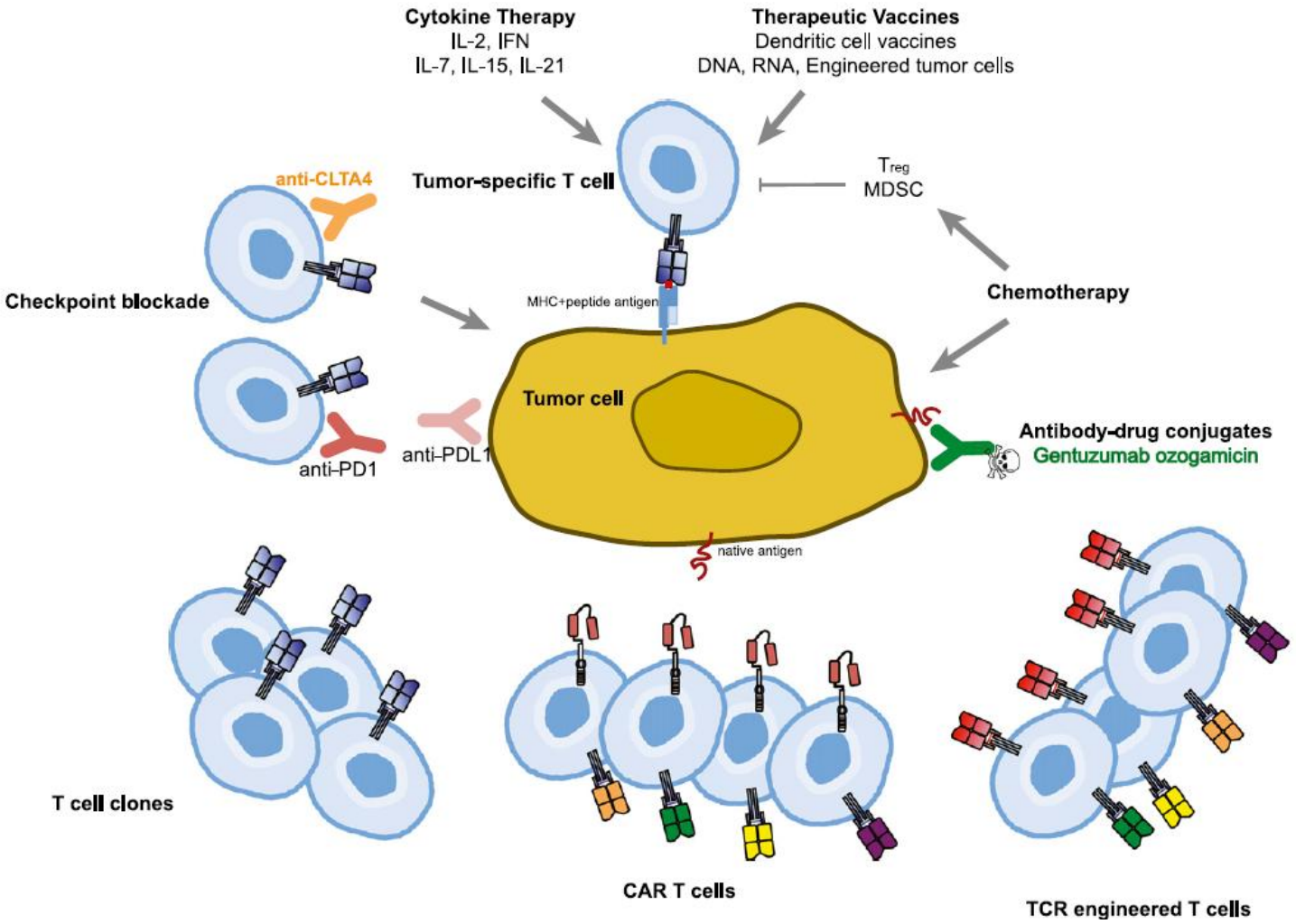
Response assessment

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Comparison between WHO criteria and IrRC

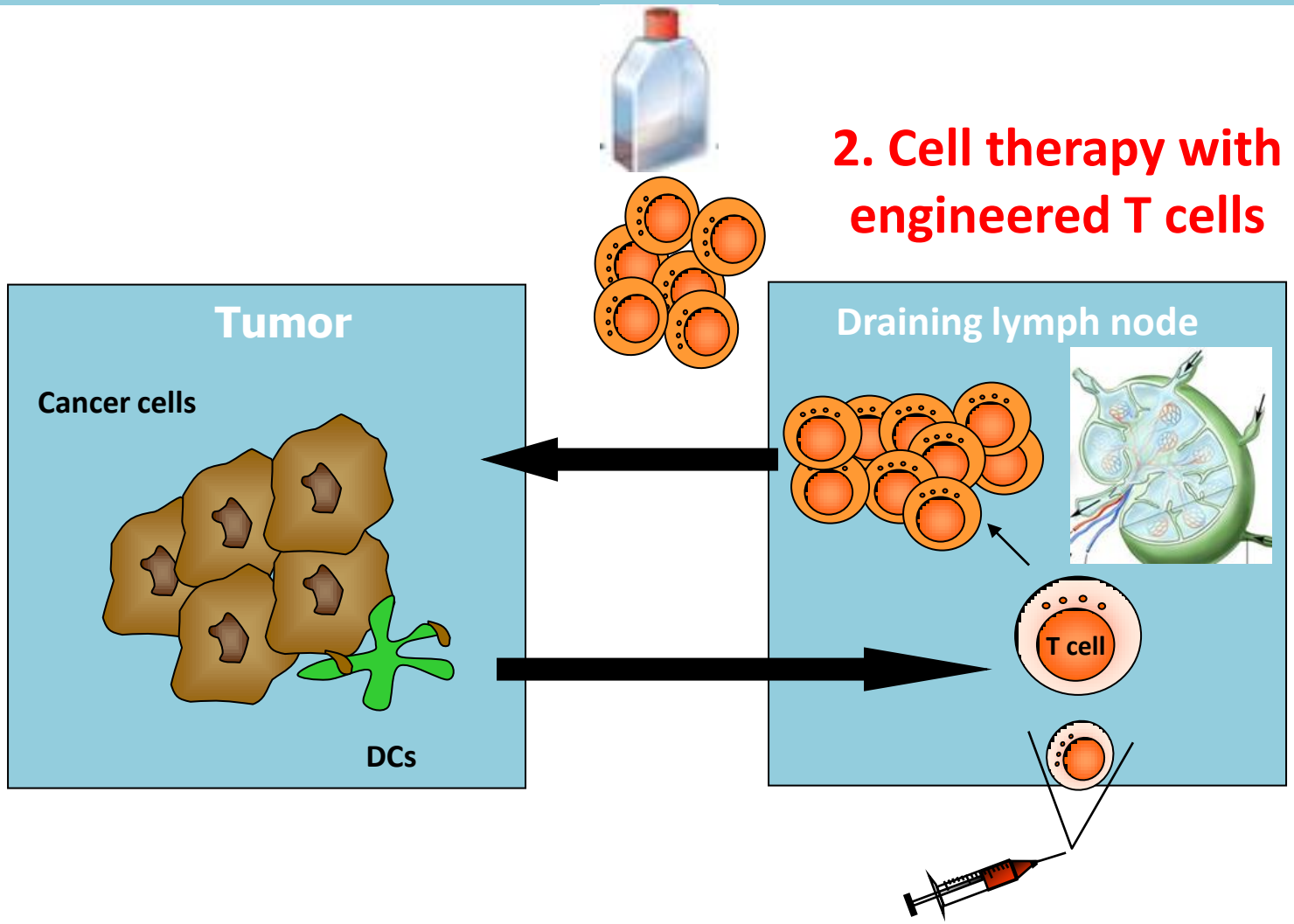
Wolchok J. et al., Clin Cancer Res 2009

Therapeutic approaches to overcome immune tolerance

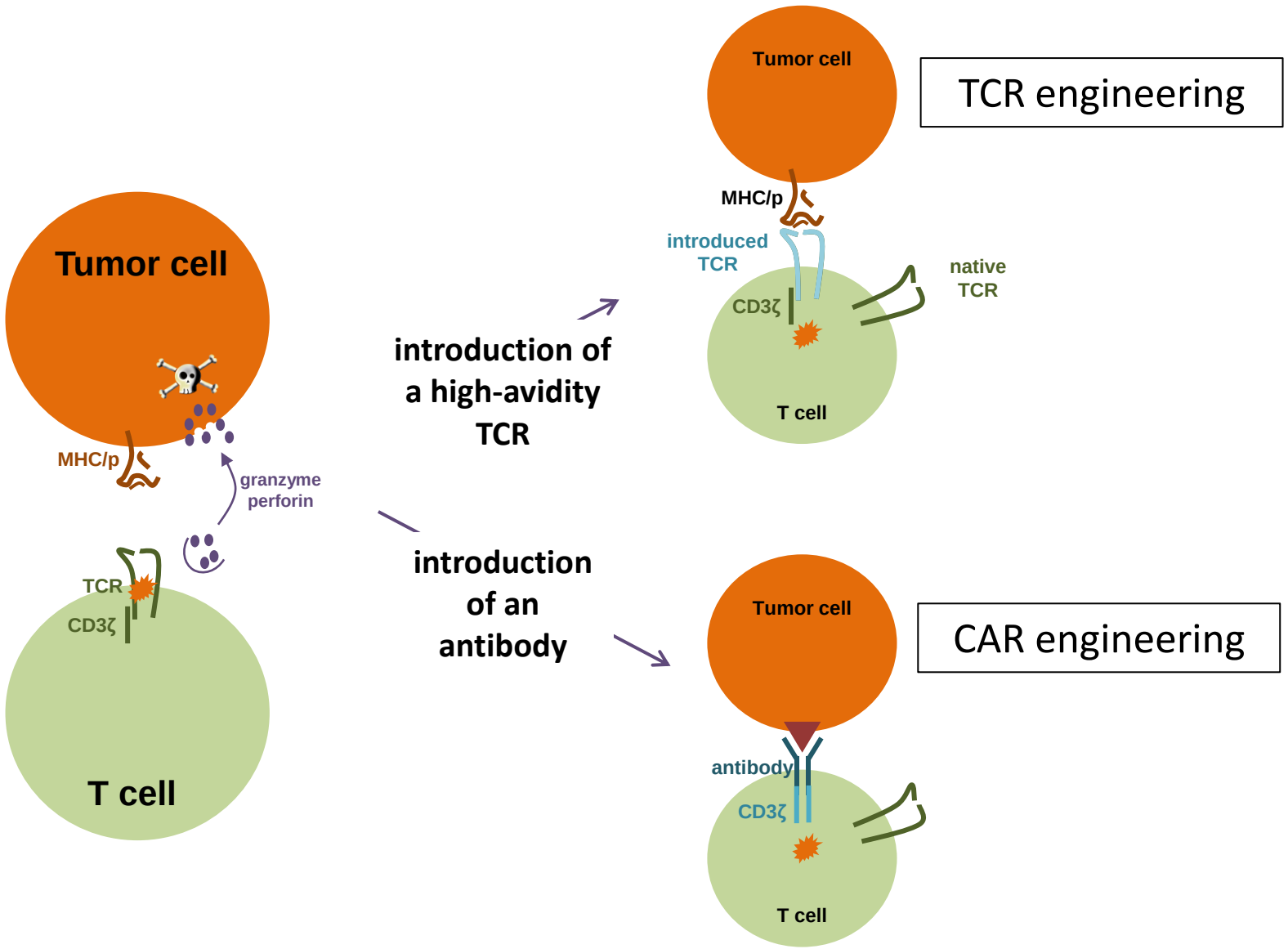


Maus M.V. et al. Blood 2014

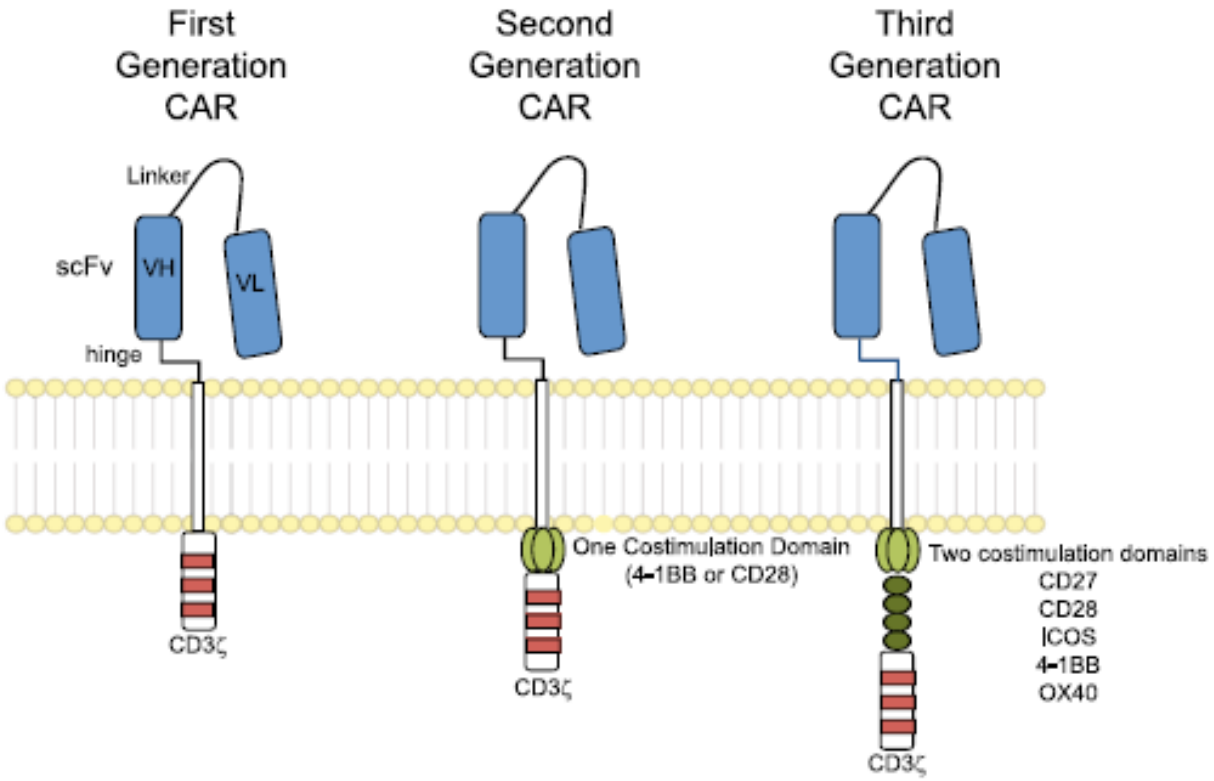
T cell therapy



TCR and CAR T cell engineering

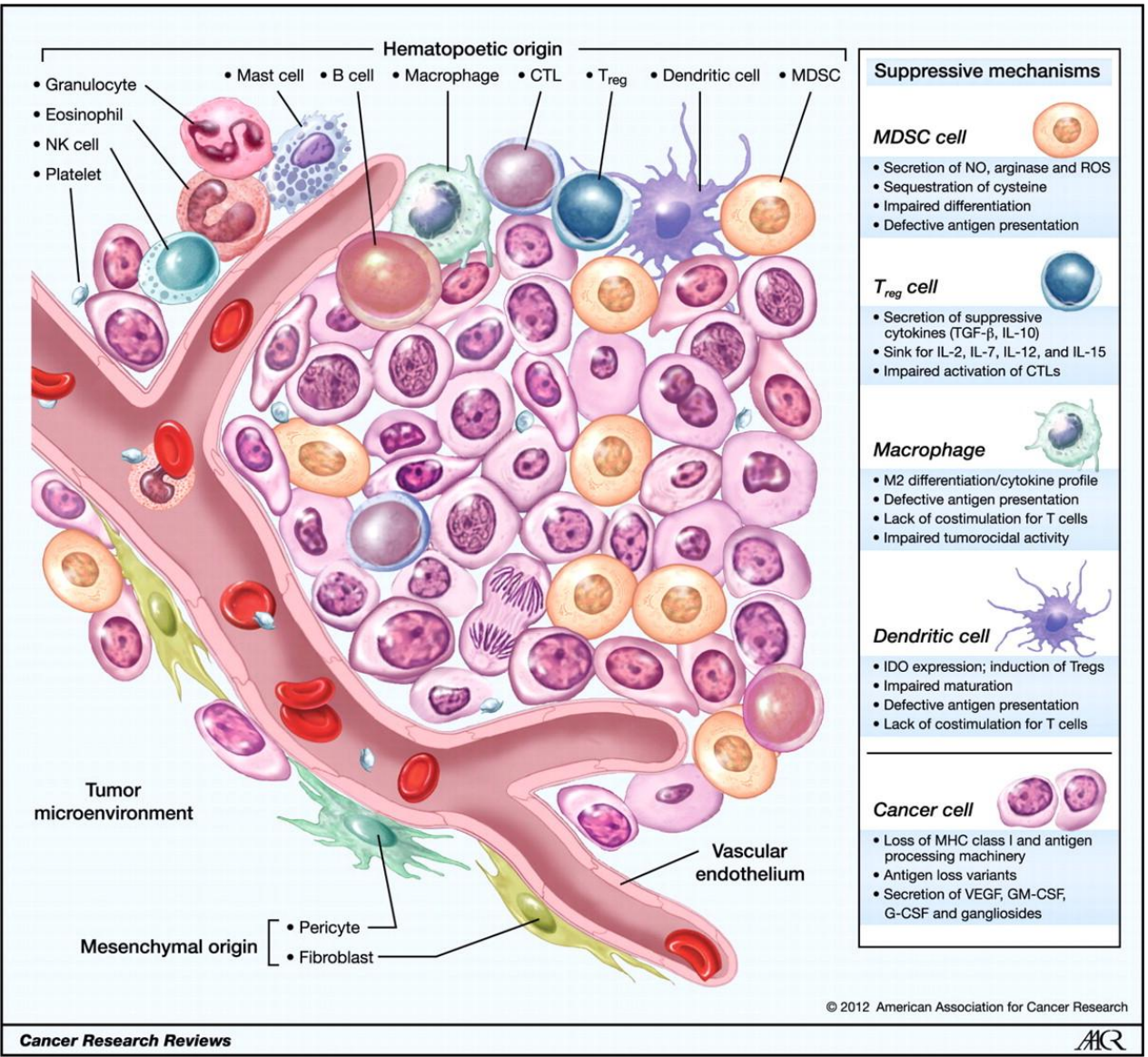


Chimeric Ag Receptor



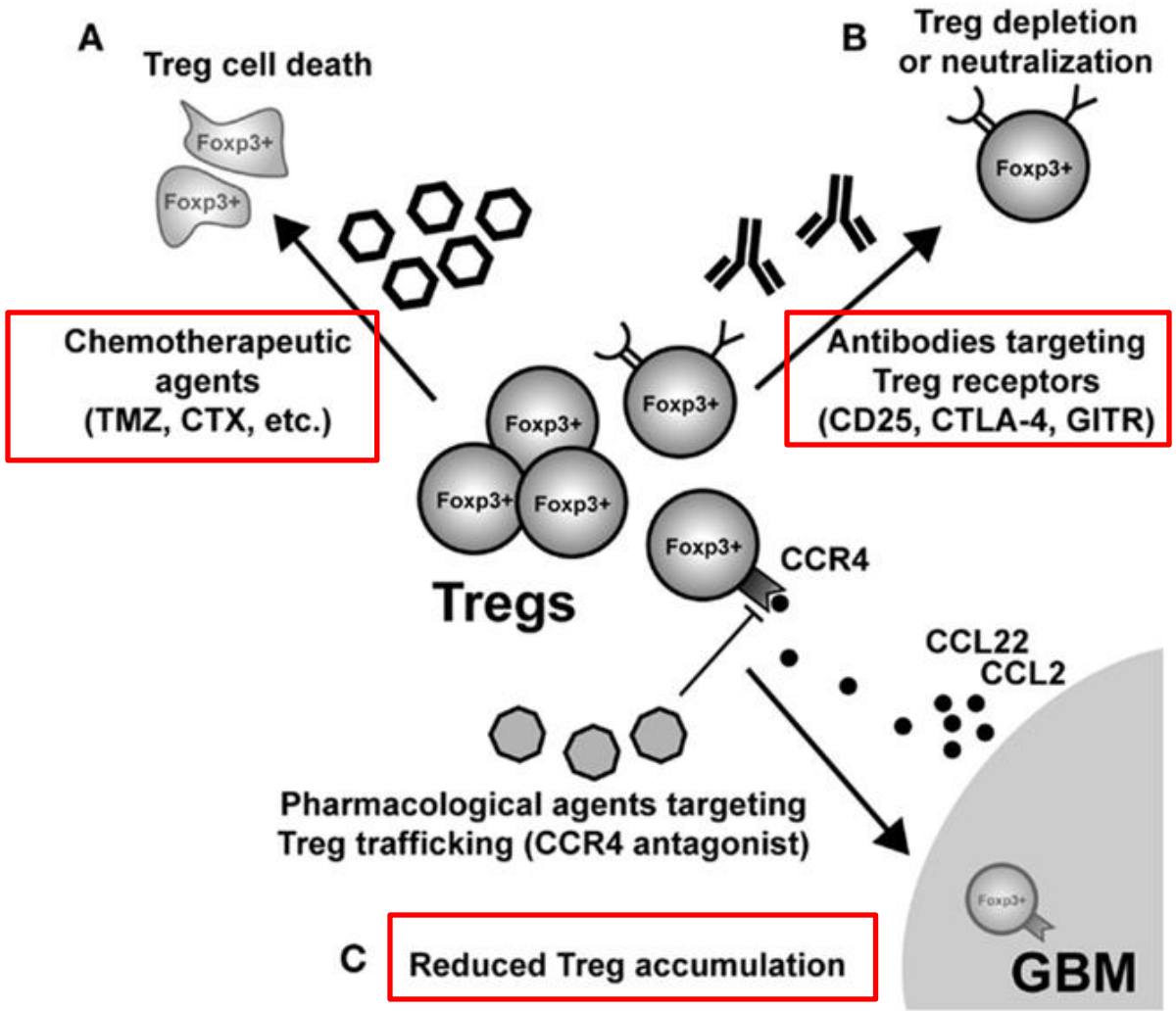
June, C. H. Principles of adoptive T cell cancer therapy. *J. Clin. Invest.* 2007

Tumor microenvironment



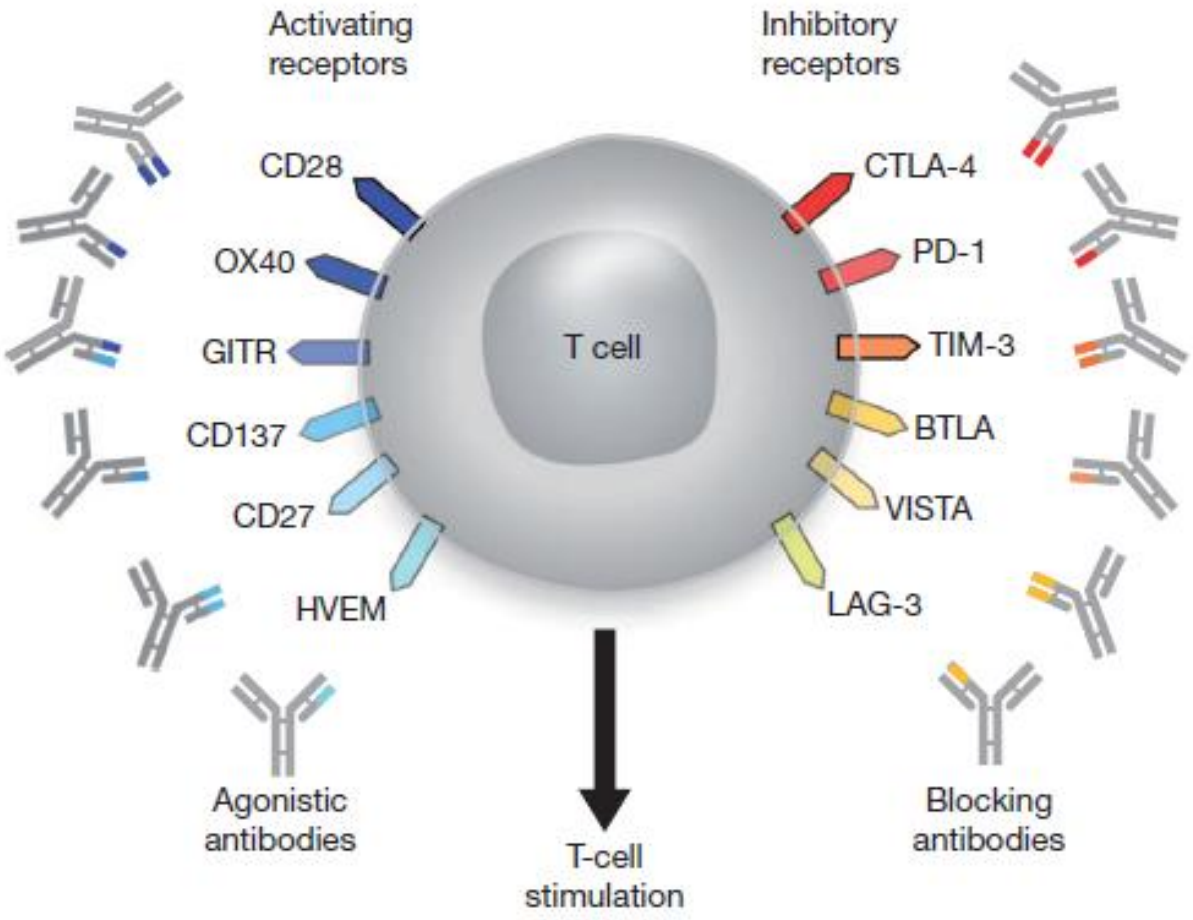
Restifo N. et al. Cancer Res 2012

Reshaping tumor Microenvironment



Front Immunol. 2013 May 15;4:116

T cell targets for immunoregulatory antibody therapy.

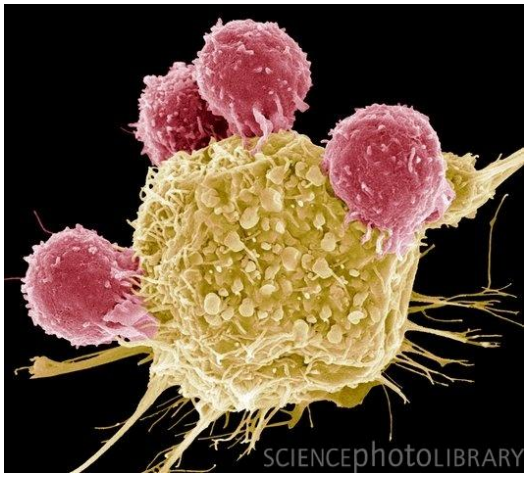


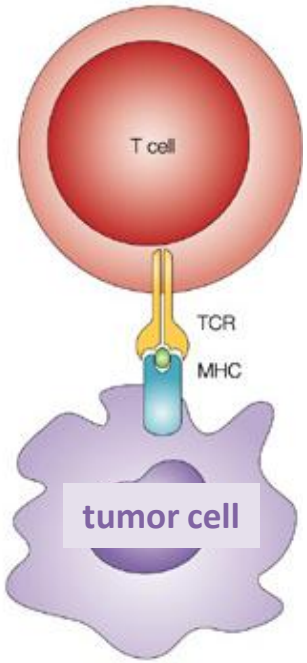
Mellman I. et al. Nature 2011

Our experience

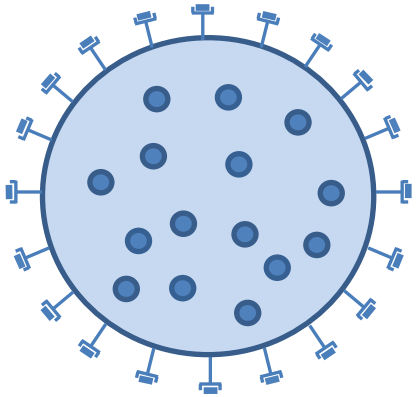
The wish list for glioma antigens

- Antigen expressed by glioma in vivo
- Presented as MHC-peptides complexes and recognized by CD8 T cells
- Wide expression in tumors and by many patients
- Little or no expression on normal tissue

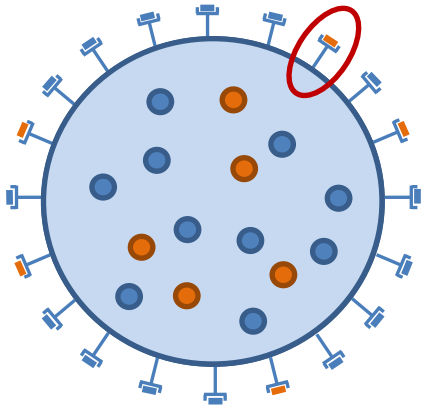




Normal

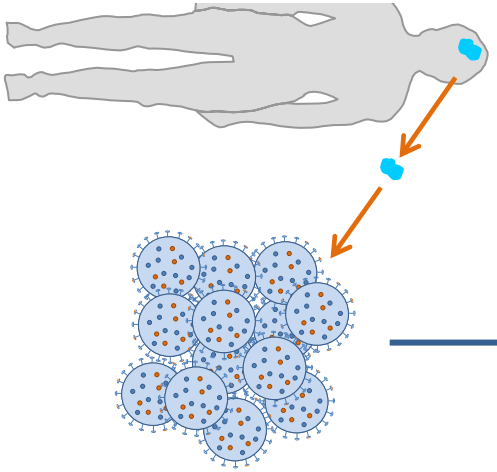


tum



Identification of glioma-associated antigens

32 HLA-A2⁺ patients



tumor

MHC/peptide

peptides

sequencing

GLFVTARIL
ELVRQATIG
AAGIGILTV
GIFGTLAVL
RTAGIWYVL
TAARIGLVI
ALFVTARIL

immatics biotechnologies GmbH
Tubingen, Germany

immatics

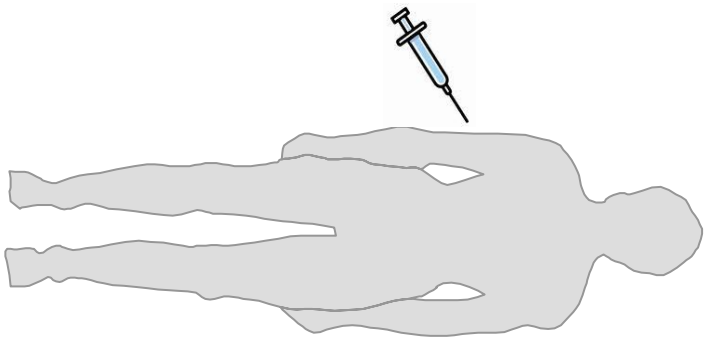
3686 HLA-A2-restricted peptides

selection process

- proteins over-expressed in glioma
- absent/low expression in healthy tissues
- function associated with tumorigenesis
- immunogenic

Peptide	Source protein
$BCA_{478-486}$	BCAN (Brevican)
CHI_{10-18}	CHI3L2 (Chitinase 3-like 2)
CSP_{21-29}	CSPG4 (Chondroitin sulfate proteoglycan 4)
$FABP7_{118-126}$	FABP7 (Fatty acid binding protein 7, brain)
$IGF2BP3_{552-560}$	IGF2BP3 (Insulin-like growth factor 2 mRNA binding protein 3)
$NLGN4X_{131-139}$	NLGN4X (Neuroligin 4, X-linked)
$NRCAM_{692-700}$	NRCAM (Neuronal cell adhesion molecule)
$PTP_{195-203}$ $PTP_{1347-1355}$	PTPRZ1 (Protein tyrosine phosphatase, receptor-type, Z polypeptide 1)
TNC_{3-11}	TNC (Tenascin C)

Phase I/II clinical trials in GBM patient with the IMA950 vaccine



UK	USA	Geneva
45 patients	25 patients	16 patients
GM-CSF	GM-CSF	Poly-ICLC (TLR3 agonist)
	cyclophosphamide	
	imiquimod (TLR7/8 agonist)	

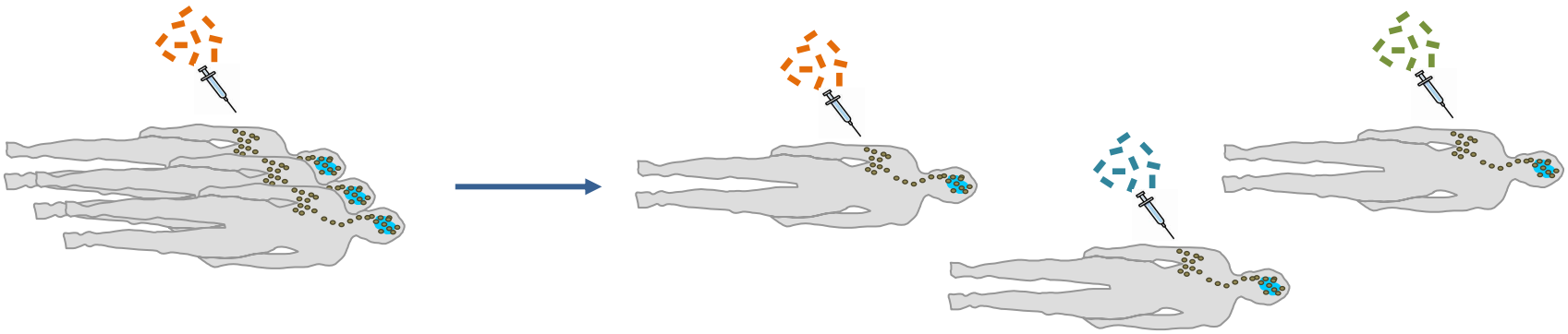
Personalized glioma vaccines

GAPVAC
The Glioma Actively Personalized VAccine Consortium

immatics

BIONTECH

GAPVAC
Glioma actively personalized vaccine consortium



Step 1: overexpressed antigens

- peptides are eluted from the patient's tumor
- peptides are compared to a pool of pre-defined peptides known to be presented by GBM tumors
- the patient is vaccinated with these peptides

Step 2: mutated antigens

- tumor is sequenced
- mutated peptides are identified
- the patients is vaccinated with mutated peptides

PI: W. Wick, Heidelberg
Co-PI: PY. Dietrich, Geneva

N = 20 pts (7 centers)
Combination with adjuvant TMZ chemotherapy

SEVENTH FRAMEWORK PROGRAMME

Conclusion

- Feasibility and toxicity already proven
- Efficacy only in a minority of patients
- Less immune editing when multiple peptide approach
- Importance of chosing the right set of peptides
- HLA restriction is limiting factor
- T cell therapy seems to overcome vaccine hurdles