CANCER IMMUNOTHERAPY-OPPORTUNITIES AND BARRIERS

Darwinian selection and Newtonian physics wrapped up in systems biology

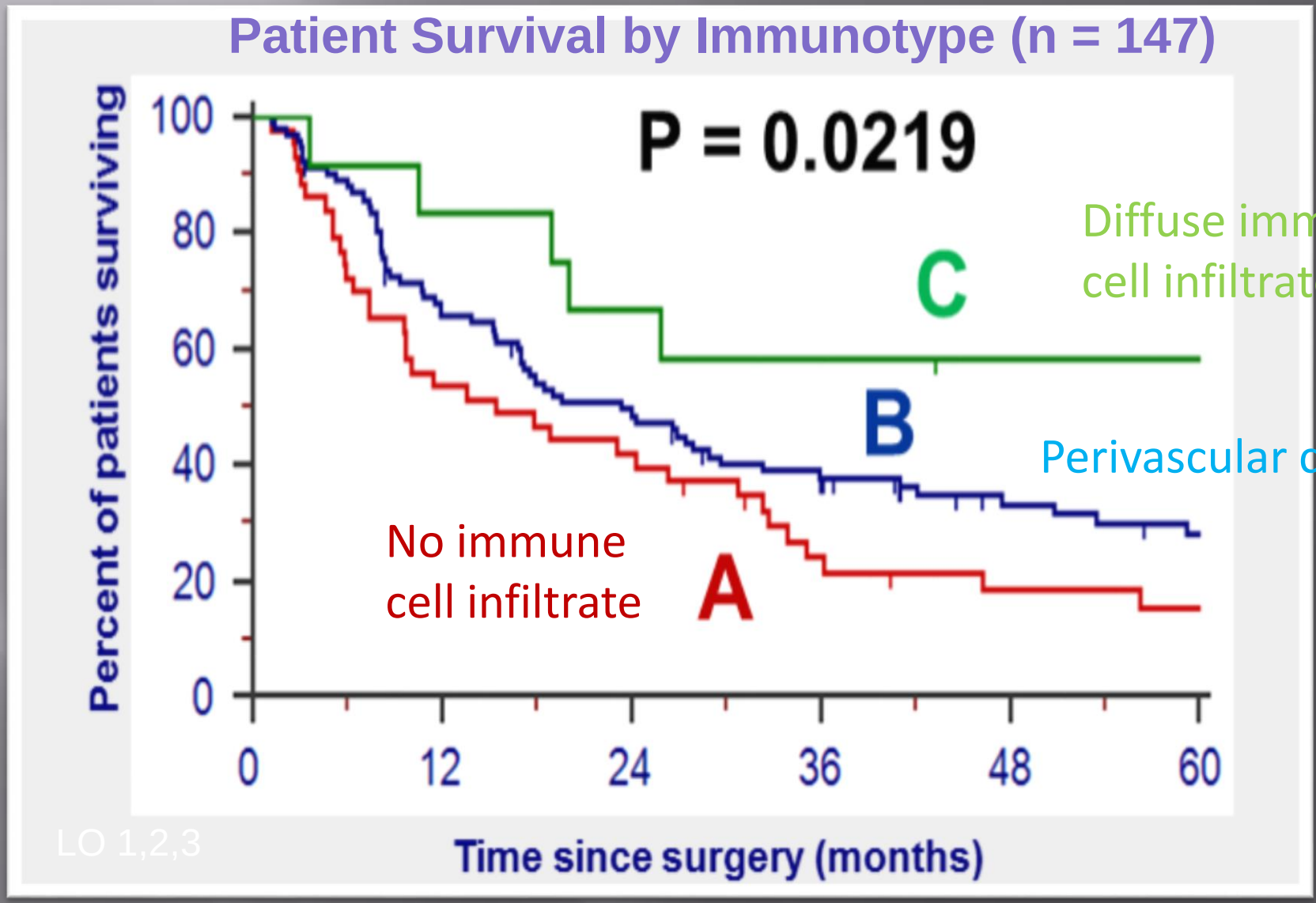
IMMUNOSURVEILLANCE

Immunosurveillance

- Concept published in 1957* by Macfarland Burnet (1960 Nobel Laureate for the theory of induced immune tolerance, leading to solid organ transplantation)
- Changes take place on the surface of cancer cells
- These changes can be used by immune cells to identify and eliminate neoplastic cells (similar to transplant rejection)
- ***Immunosurveillance = spontaneous host immune response to cancer***

*Burnet FM. Brit. Med. J. 1: 779. 1957

Survival is associated with the ability of T cells to infiltrate metastases



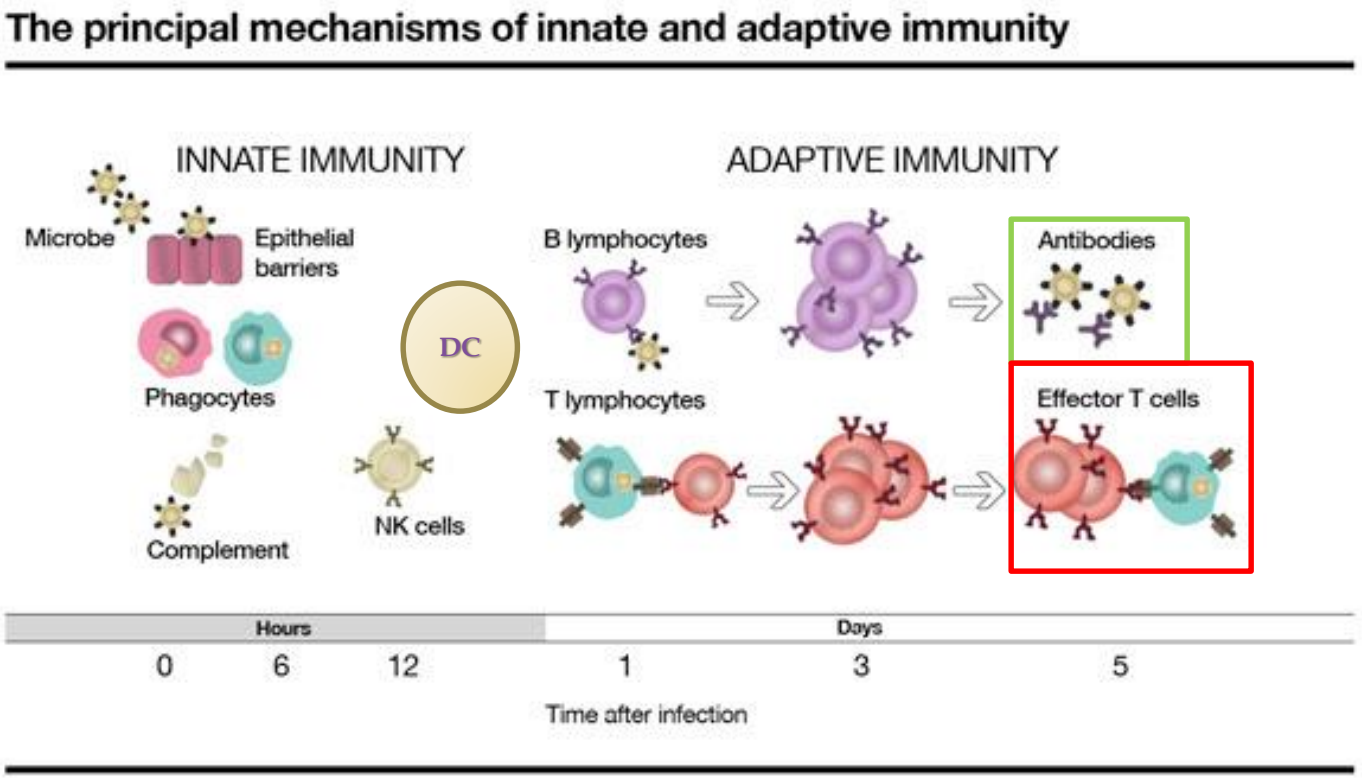
LO 1,2,3

Immunodeficiency States and Cancer Incidence

Cause of Immunodeficiency	Common tumor types	Virus involvement
Inherited	Lymphoma	EBV
Induced •organ transplant •HIV/AIDS	Kaposi's sarcoma	Human herpes B
	Cervical cancer	Human papilloma
	Liver cancer	Hepatitis B
Malaria	Burkitt's lymphoma	EBV
Autoimmunity	Lymphoma	EBV

INNATE AND ADAPTIVE IMMUNITY

Separate yet interlinking responsibilities



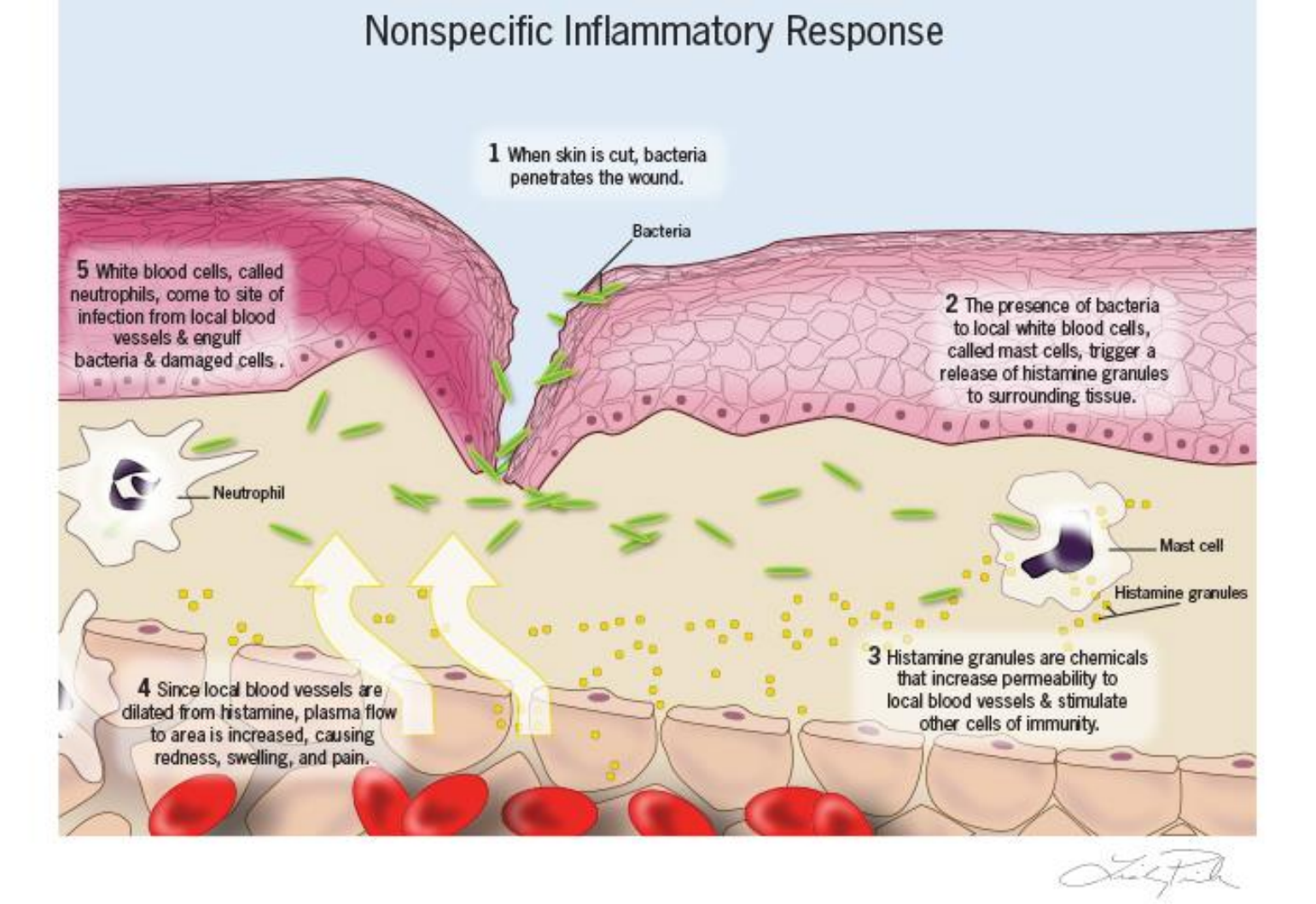
http://www.brianlischer.com/portfolio/ucsd-infographic/

Different qualities of innate and adaptive immunity

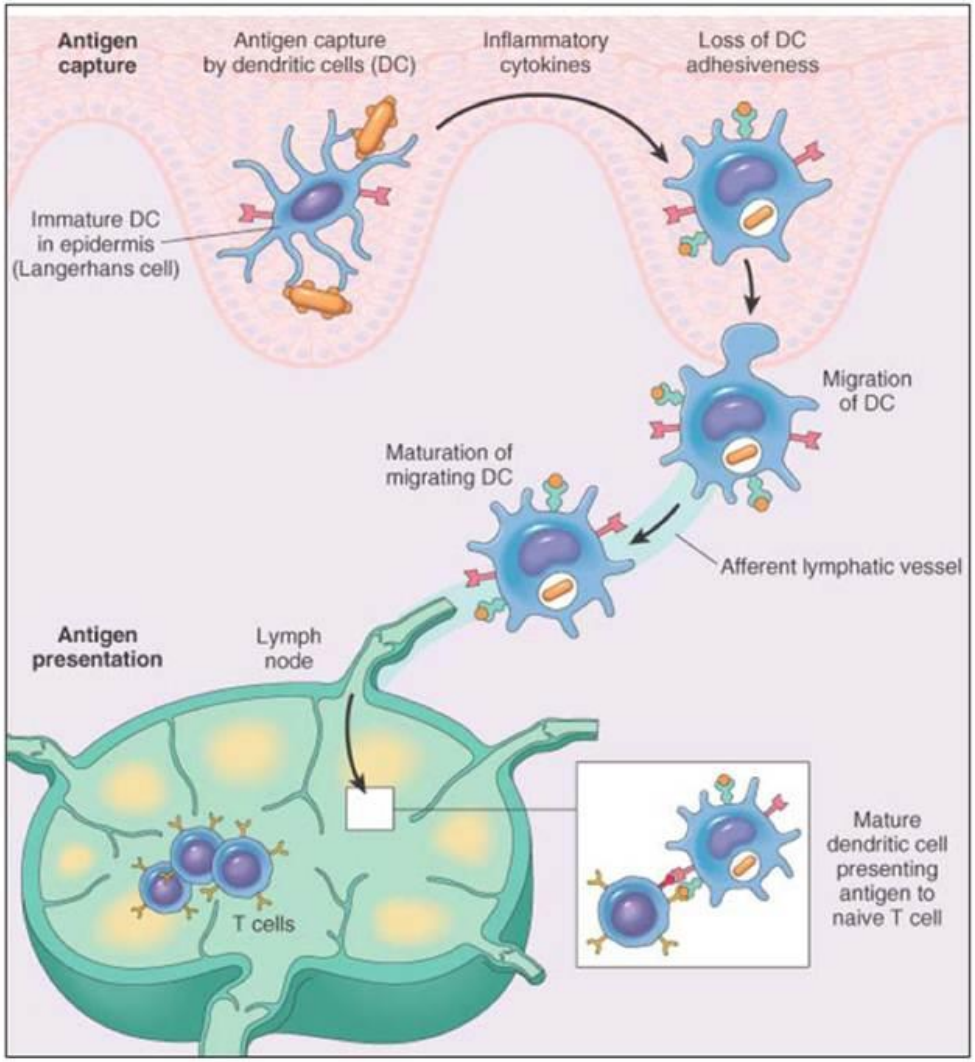
Innate *vs* adaptive immunity

	innate	adaptive
self / non-self discrimination	present, reaction is against foreign	present, reaction is against foreign
lag phase	absent, reponse is immediate	present, response takes at least a few days
specificity	limited, the same response is mounted to a wide variety of agents	high, the response is directed only to the agents that initiated it.
diversity	limited, hence limited specificity	extensive, and resulting in a wide range of antigen receptors.
memory	absent, subsequent exposures to agent generate the same response	present, subsequent exposures to the same agent induce amplified reponses

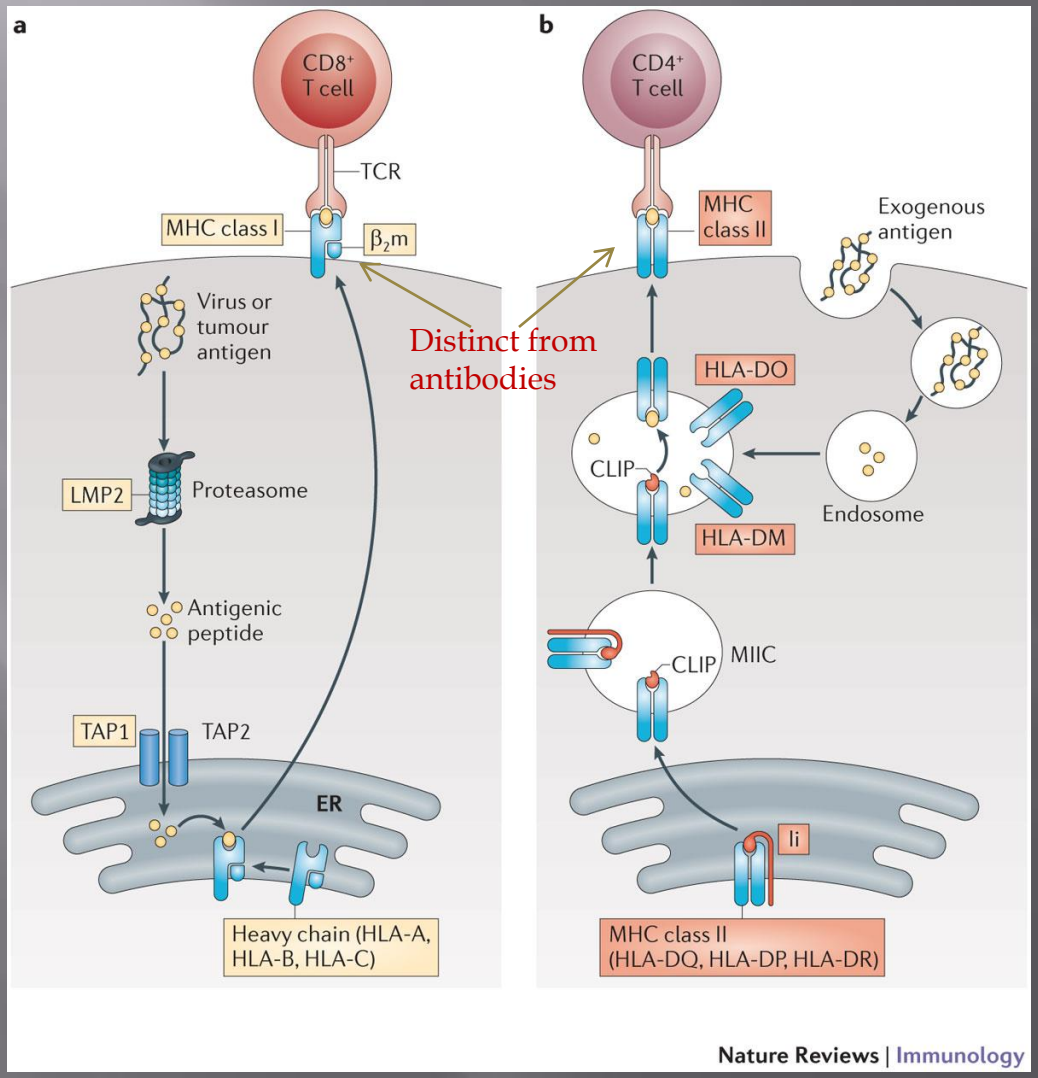
Acute Innate sensing of pathogen components activates inflammatory pathway and cellular recruitment



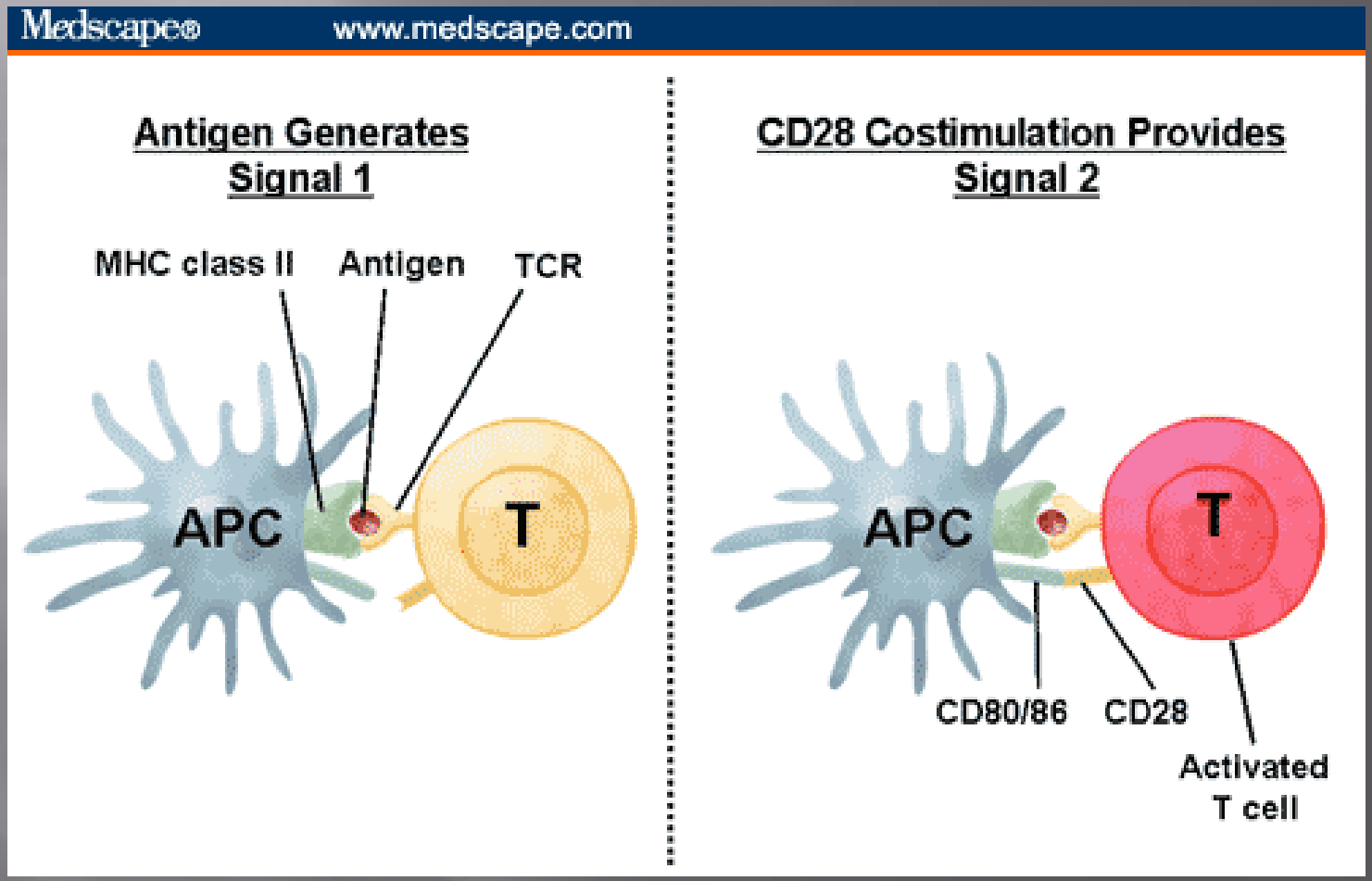
Sensing innate signals mobilizes DC to the lymph node



Antigen acquired in the periphery by DC is processed and presented on MHC molecueles to T cells in the lymph node

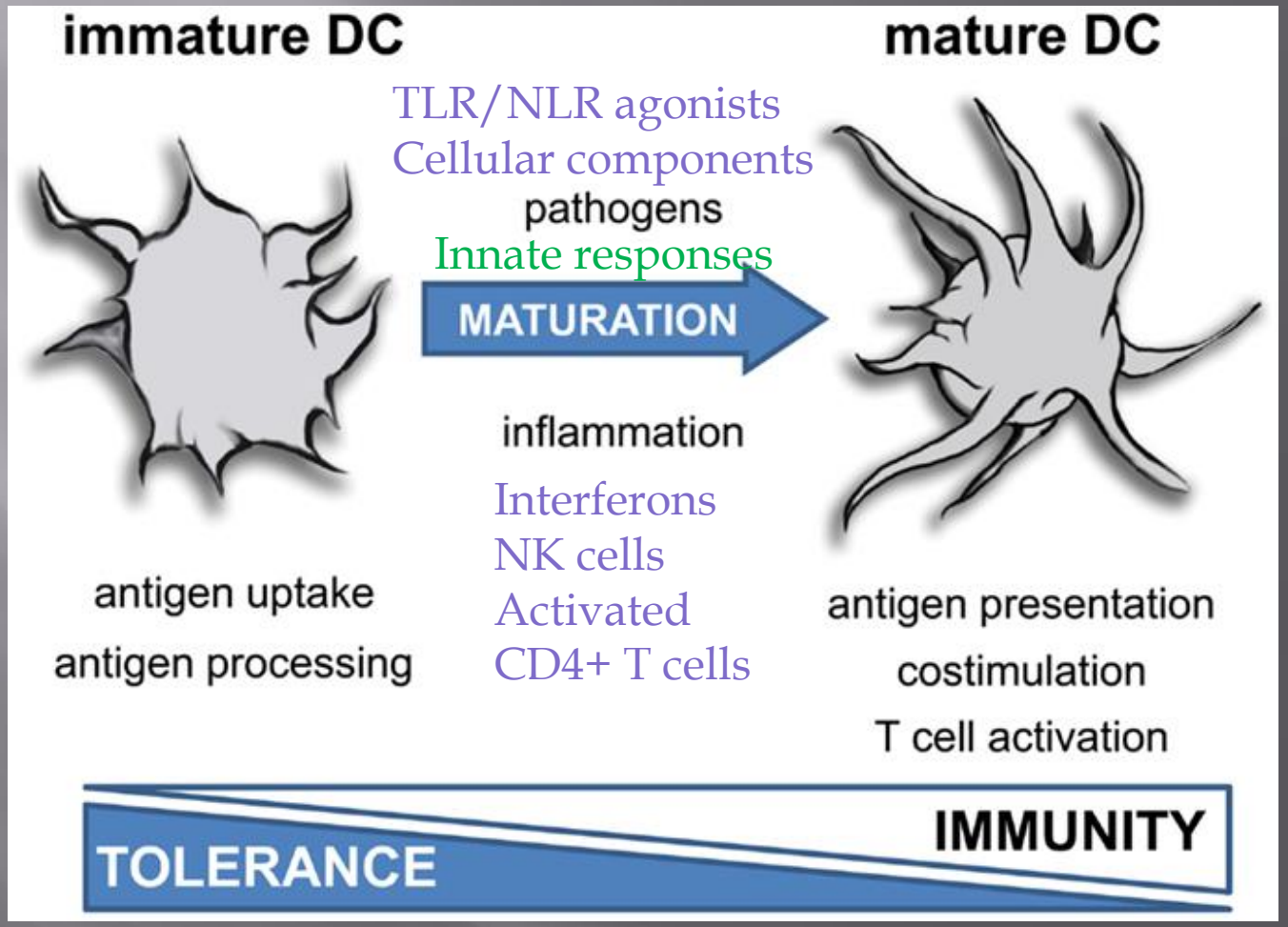


Antigen presentation, in the appropriate context, leads to the activation of T cells



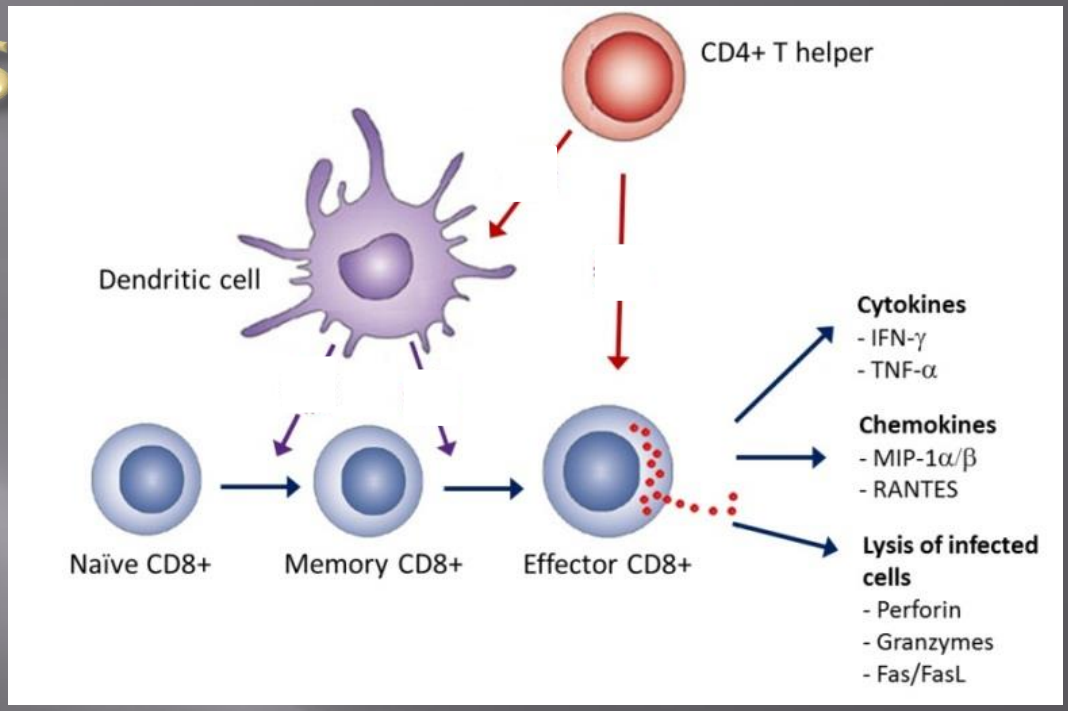
http://images.medscape.com/pi/editorial/journalcme/2004/3709/art-emery.fig3.gif

Diverse inflammatory signals lead to the maturation of DC with promotes T cell immunity over tolerance

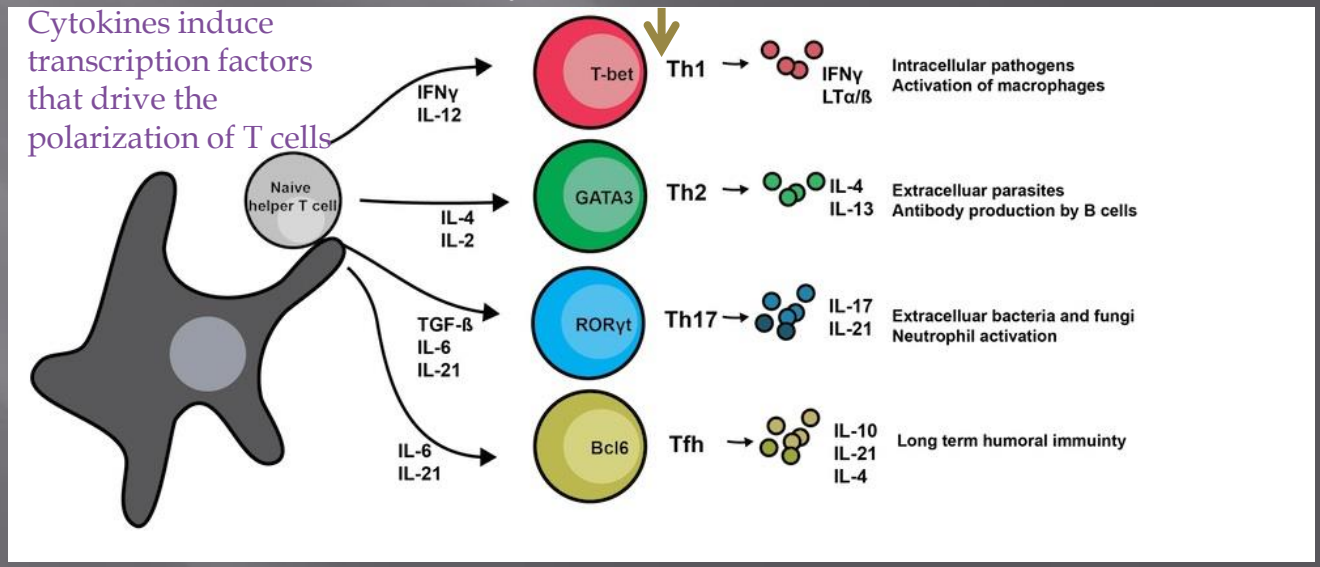


Effector T cells

- T cells expand and differentiate in response to extrinsic factors often derived from inflammation.
- They traffic to sites of infection following chemokine trails, and extravaste using adhesion molecules.
- They perform their effector functions upon TCR engagement in the periphery; killing cells and secreting cytokines.

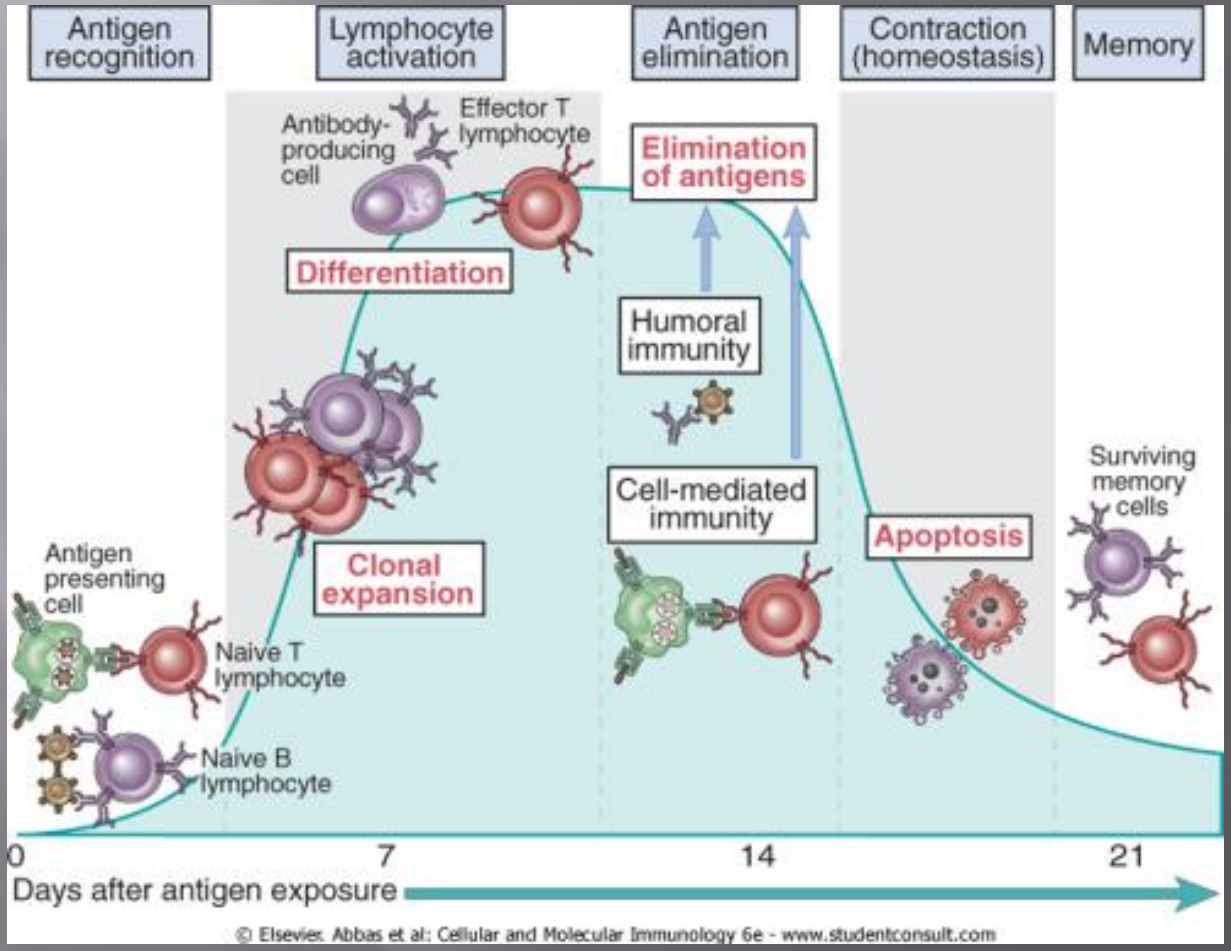


Types of helper T cell



http://ansel.ucsf.edu/mirnaintcells

Phases of a T cell response



II. Barriers to tumor immunity

-T cell activation

-The healing wound hypothesis

-Extrinsic regulators of immune function

-Intrinsic regulators of immune function

Weaknesses in tumor specific immunity that constrain responses

Extrinsic regulators

- Regulatory T cells (Treg)
- Myeloid derived suppressor cells (MDSC)
- Tumor associated macrophages (M2)

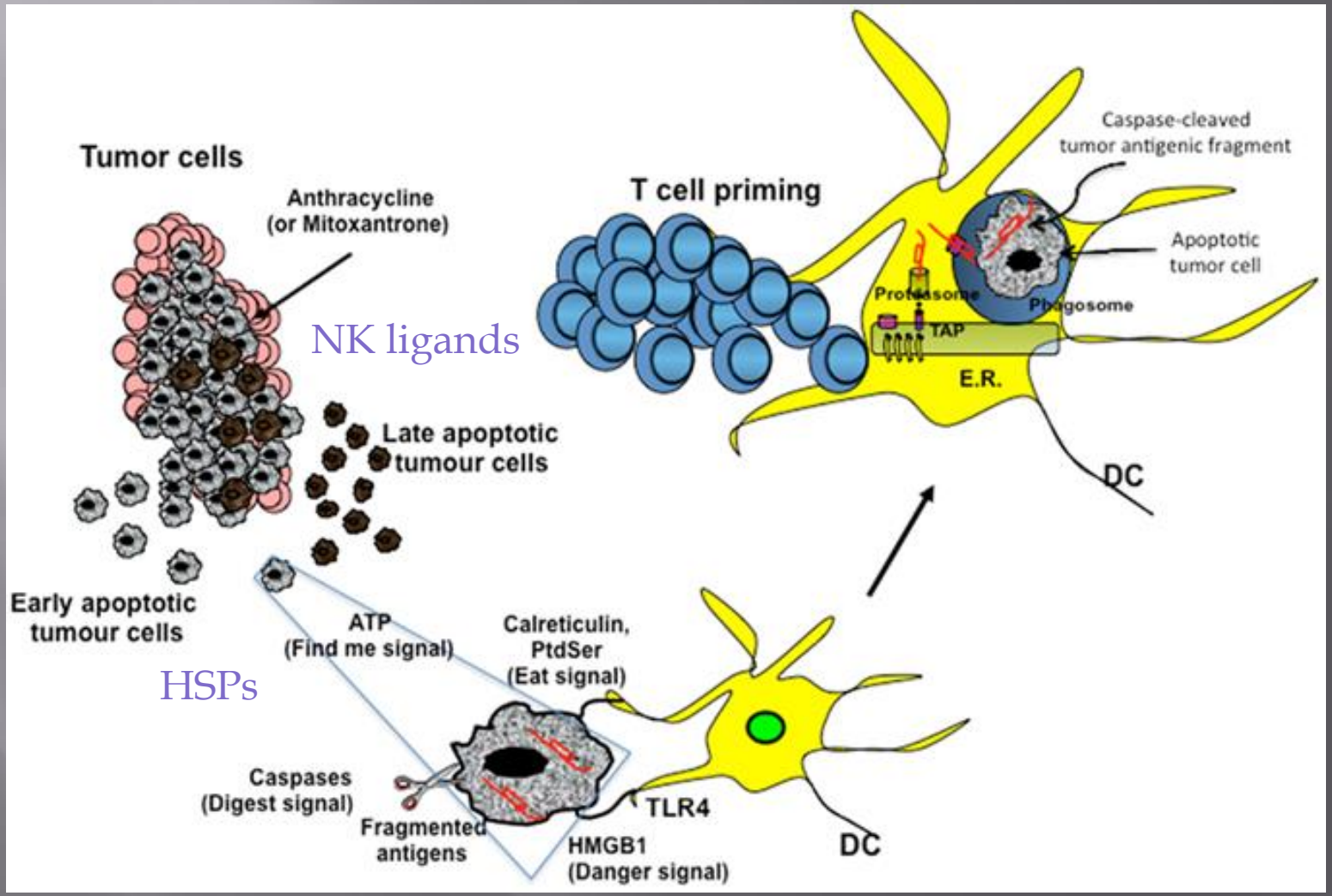
Tumor-derived regulators

- Antigen loss
- Antigen processing defect
- Inhibitory molecule expression
- Suppressive cytokine secretion
- Vasculature

Intrinsic regulators

- Tolerance; weak TCR
- Anergy: weak activation (DAMPs/PAMPS)
- Inhibitory molecules
- cAMP

Activation of T cell responses to tumors

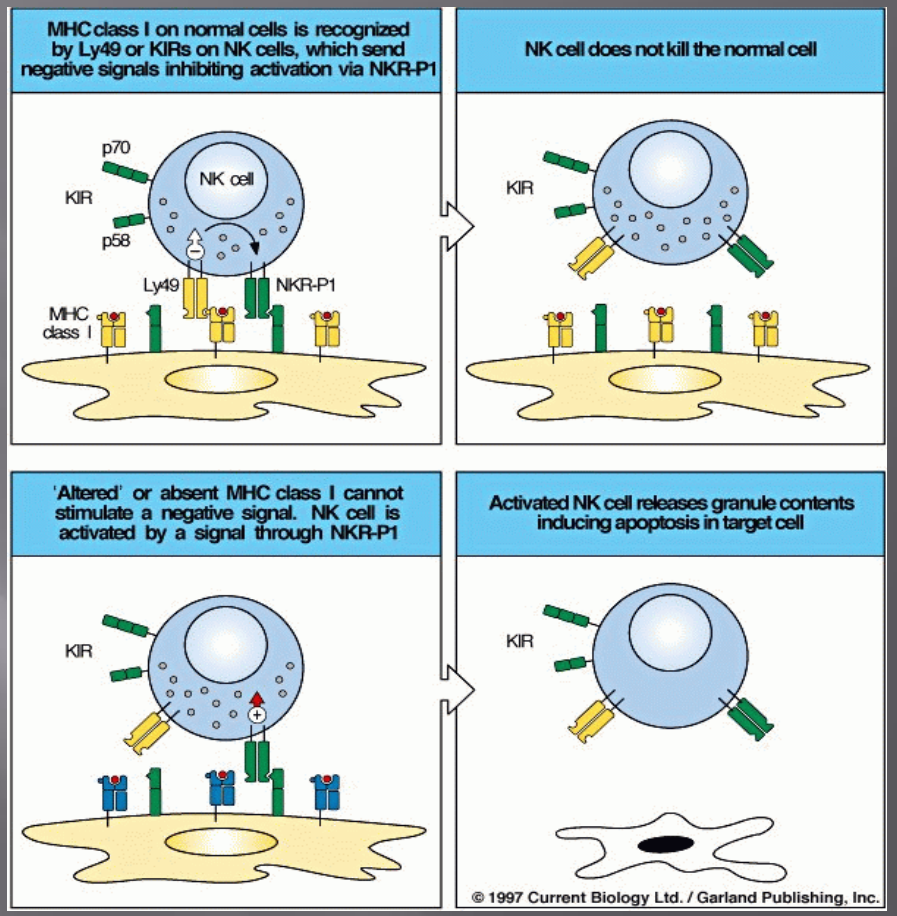


Front. Immunol. **4**:503. doi: 10.3389/fimmu.2013.00503

Recognition of transformed cells by Natural Killer

1) Missing self: mutation-induced alteration/loss in MHC molecules is sensed by NK cells

2) Stress-induced expression of NK-ligands also can make them a target for NK mediated lysis



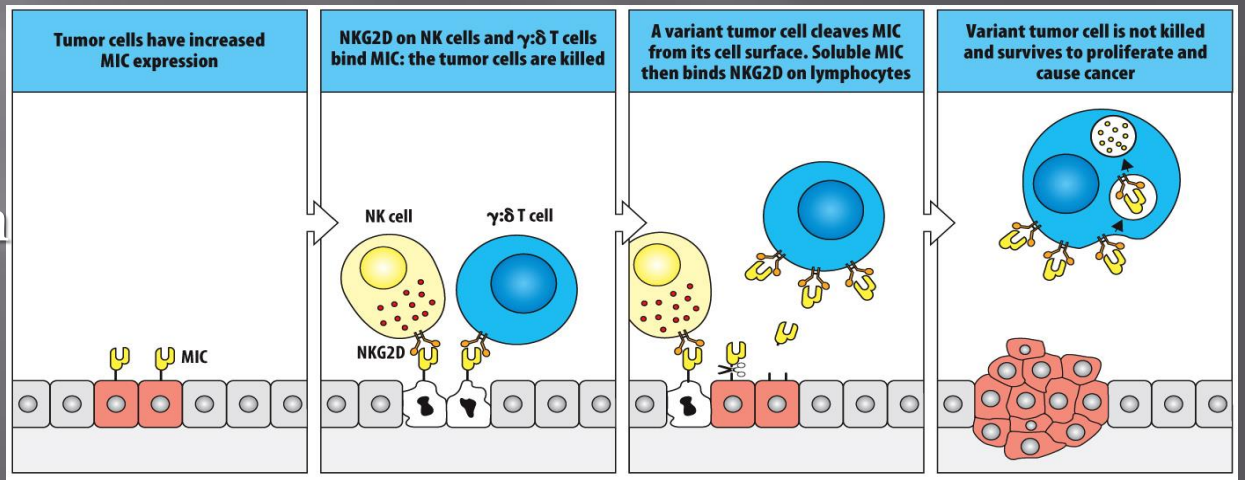
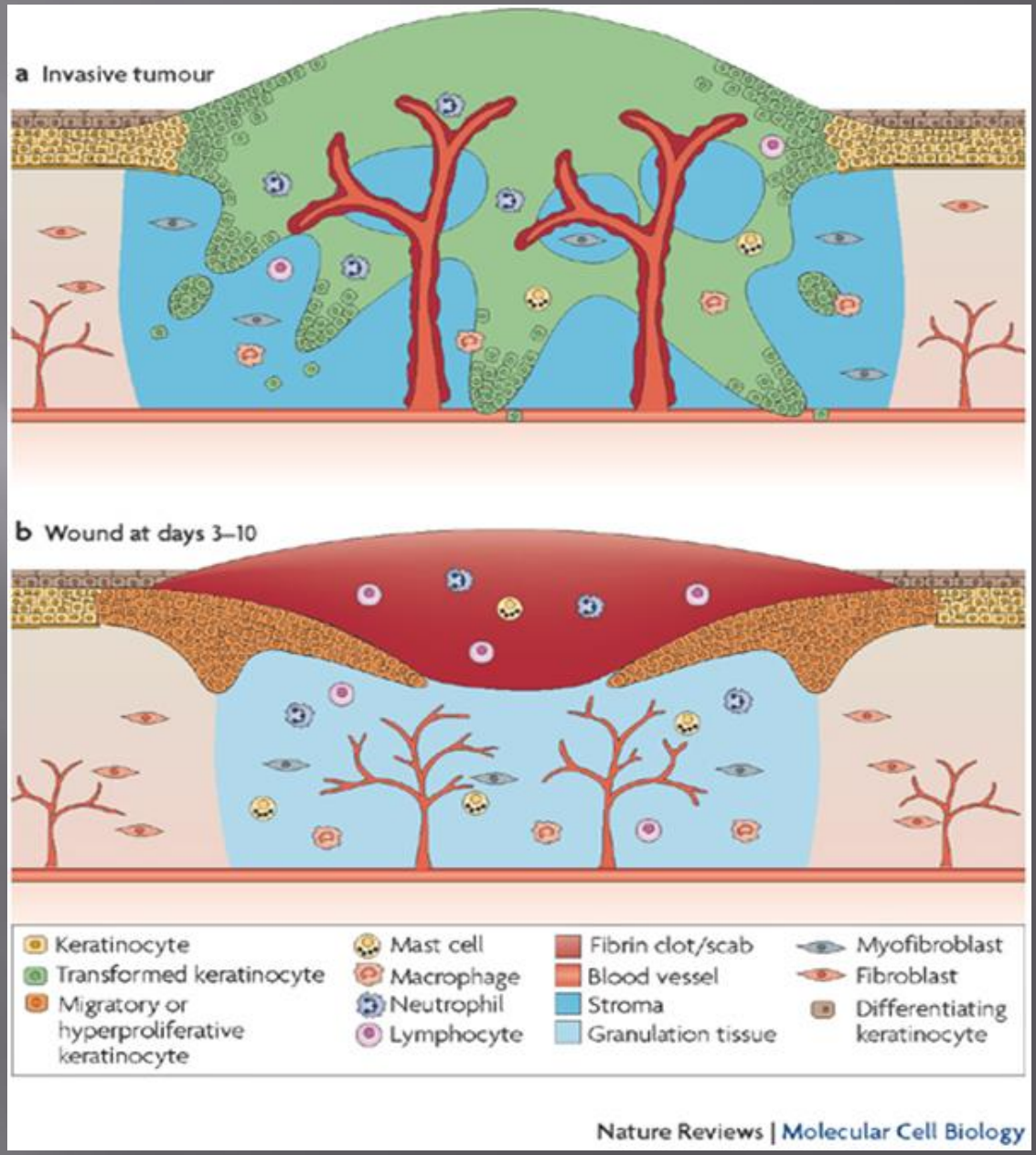


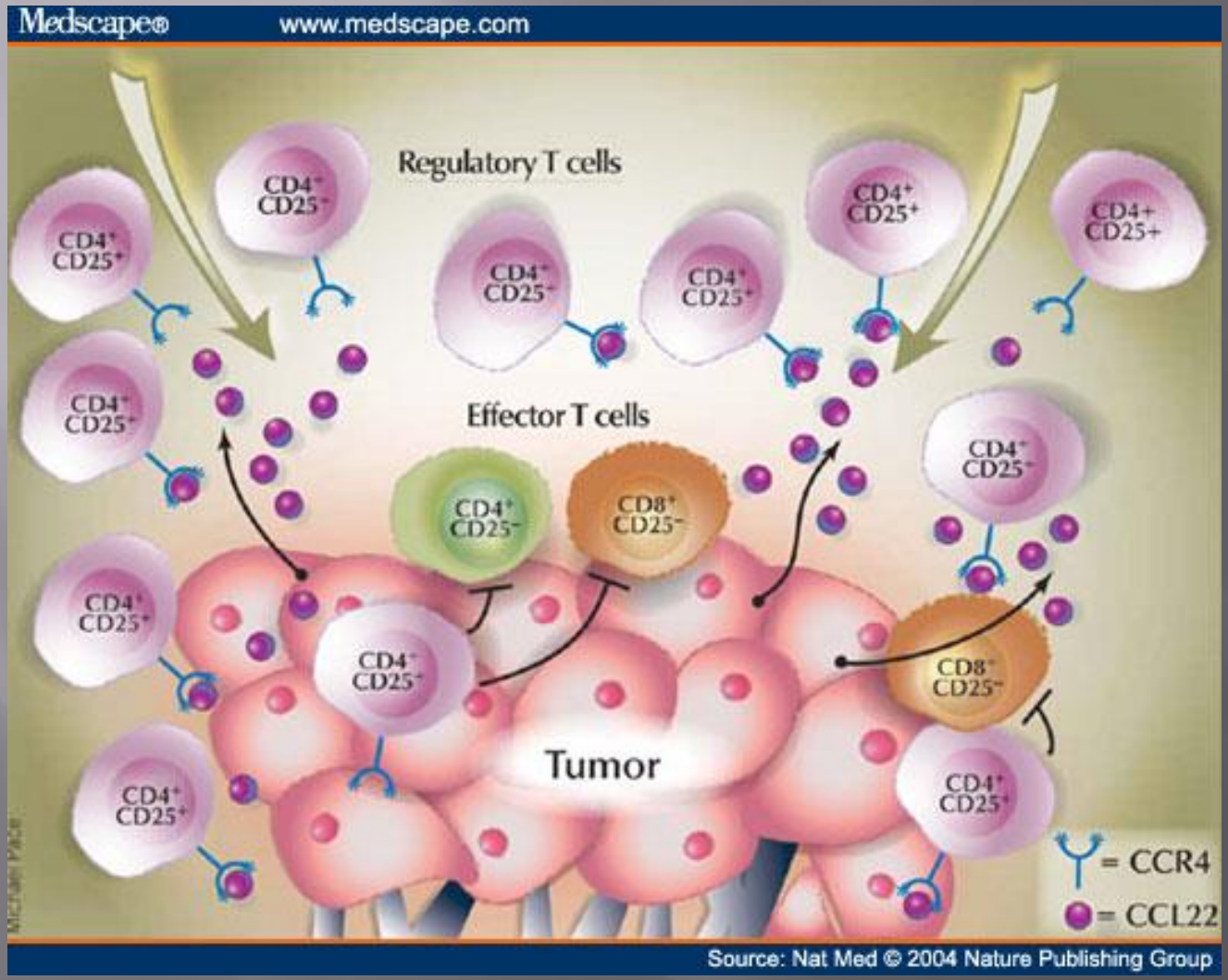
Figure 17.13 The Immune System, 4th ed. (© Garland Science 2015)

Immuno-evasion: Tumor micro-environment resembles a healing wound

Many of the anti-inflammatory and immunosuppressive aspects of a healing would are found in the tumor microenvironment



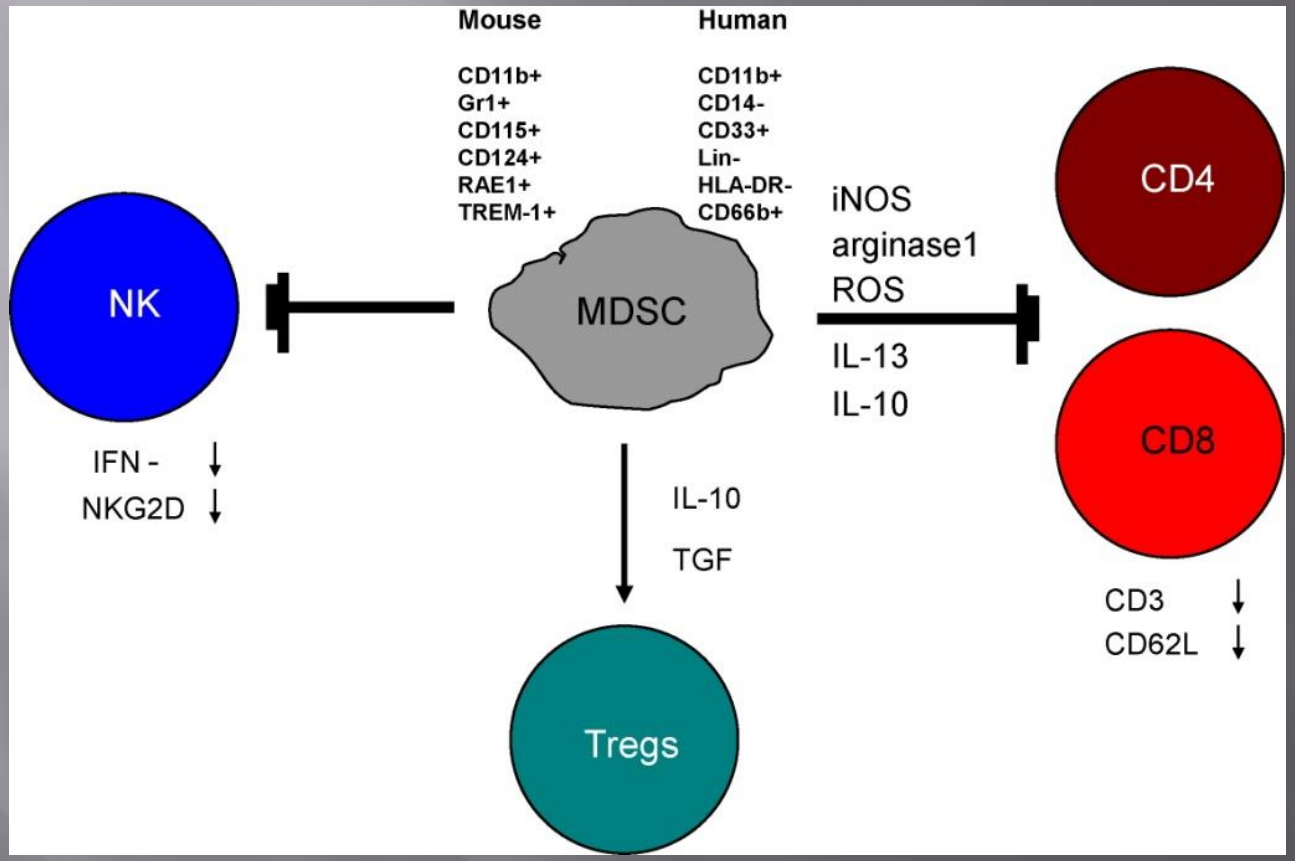
Regulatory T cells suppress tumor immunity



Tumors express chemo-attractants such as the CCL22 chemokine, which decorates blood vessels, and is followed by CCR4-expressing regulatory T cells to the tumor.

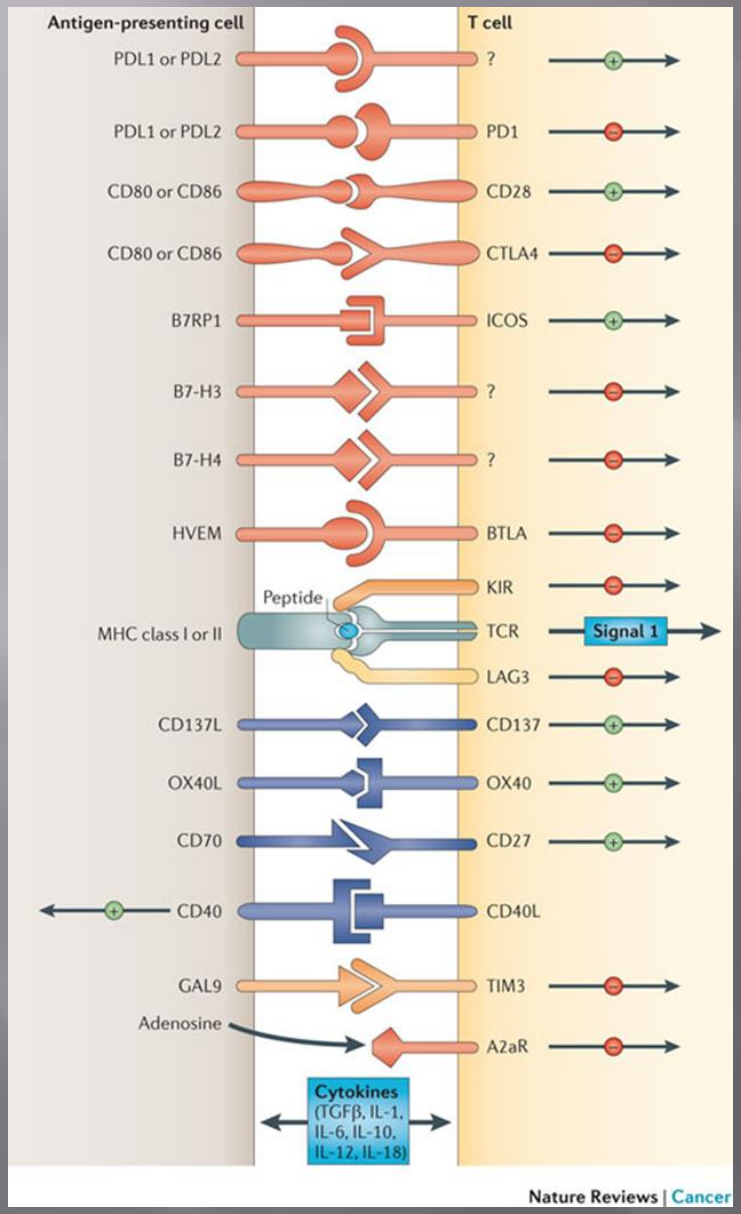
Once in the tumor environment, regulatory T cells can prevent the activation and attenuate the function of effector T cells

Immature myeloid cells are mobilized by tumors



Immature myeloid cells are commonly mobilized in cancer patients . They secrete cytokines and enzymes that can suppress effector T cell and NK cell function and promote the development and activity of regulatory T cells.

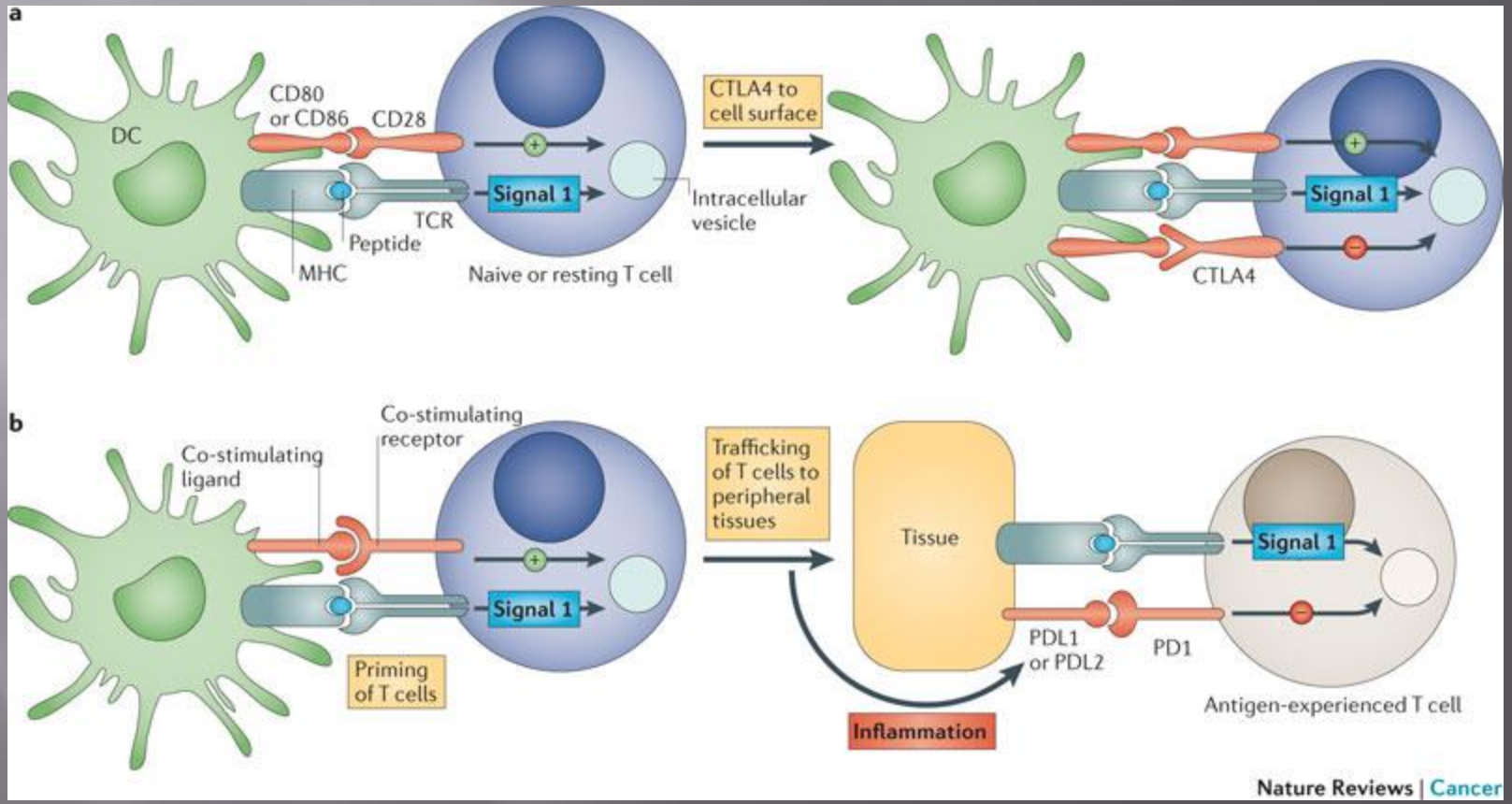
Checkpoint molecules



- A large array of molecules are expressed on the surface of activated T and NK cells in response to chronic stimulation
- These molecules serve to prevent immunopathology; genetic knockouts often develop autoimmunity or over-exuberant immune responses.
- Antibodies blocking checkpoint molecules have shown promising efficacy in melanoma, NSCLC and Hodgkins lymphoma and others.

Different checkpoints for different functions?

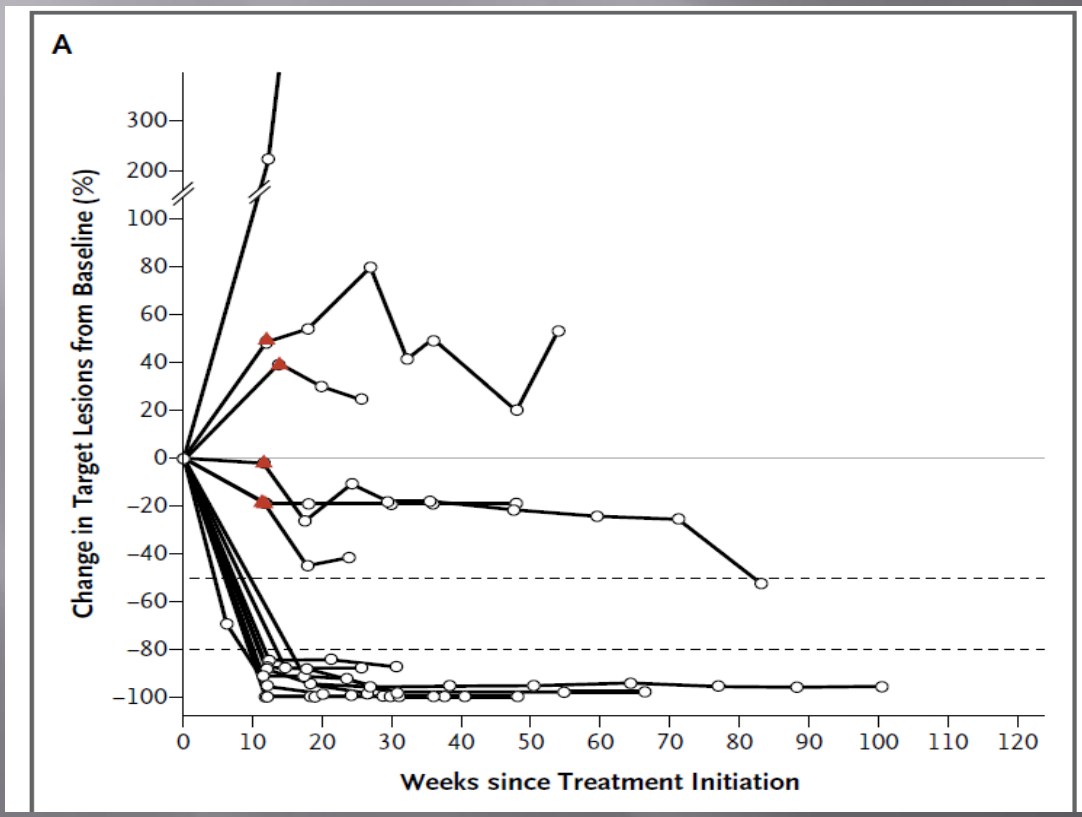
CTLA-4 is induced acutely on T cells by initial TCR engagement and prevents activation of naïve T cells

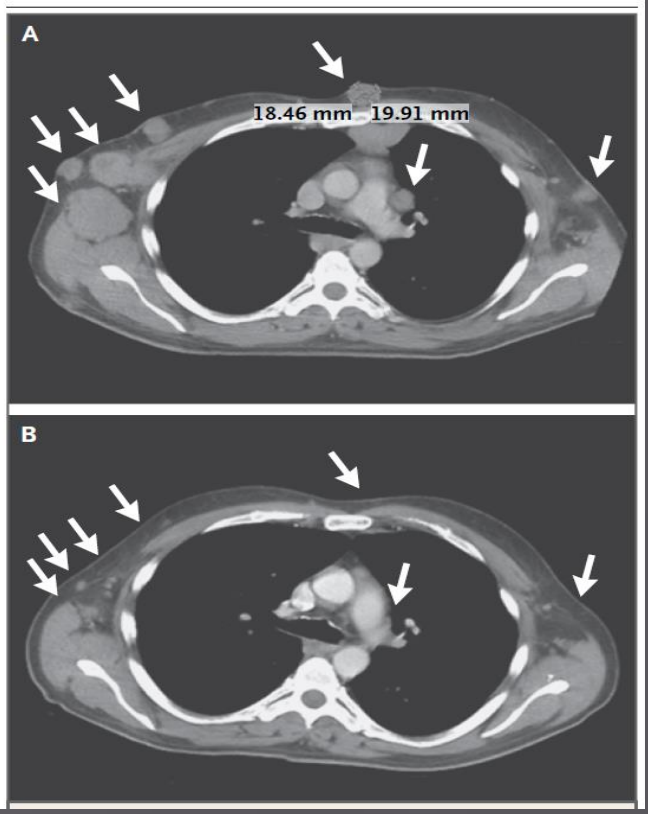


PD-1 is upregulated over a period of 2-3 days and constrains effector T cell activity against PD-L1 expressing cells in the periphery

Checkpoint blockade is effective

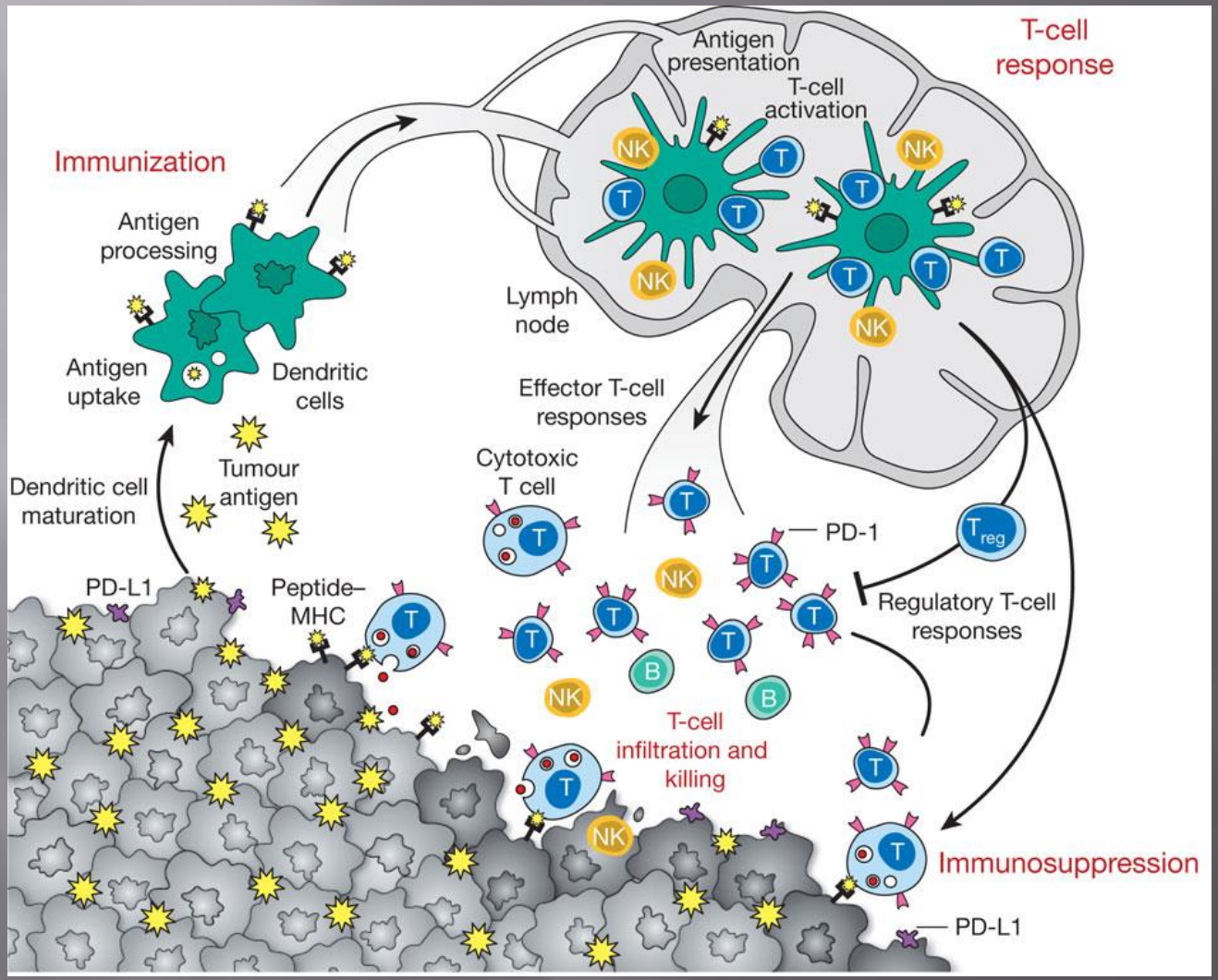
Clinical activity of antibodies that block checkpoint molecules





Wolchock et al http://www.nejm.org/doi/full/10.1056/NEJMoa1302369

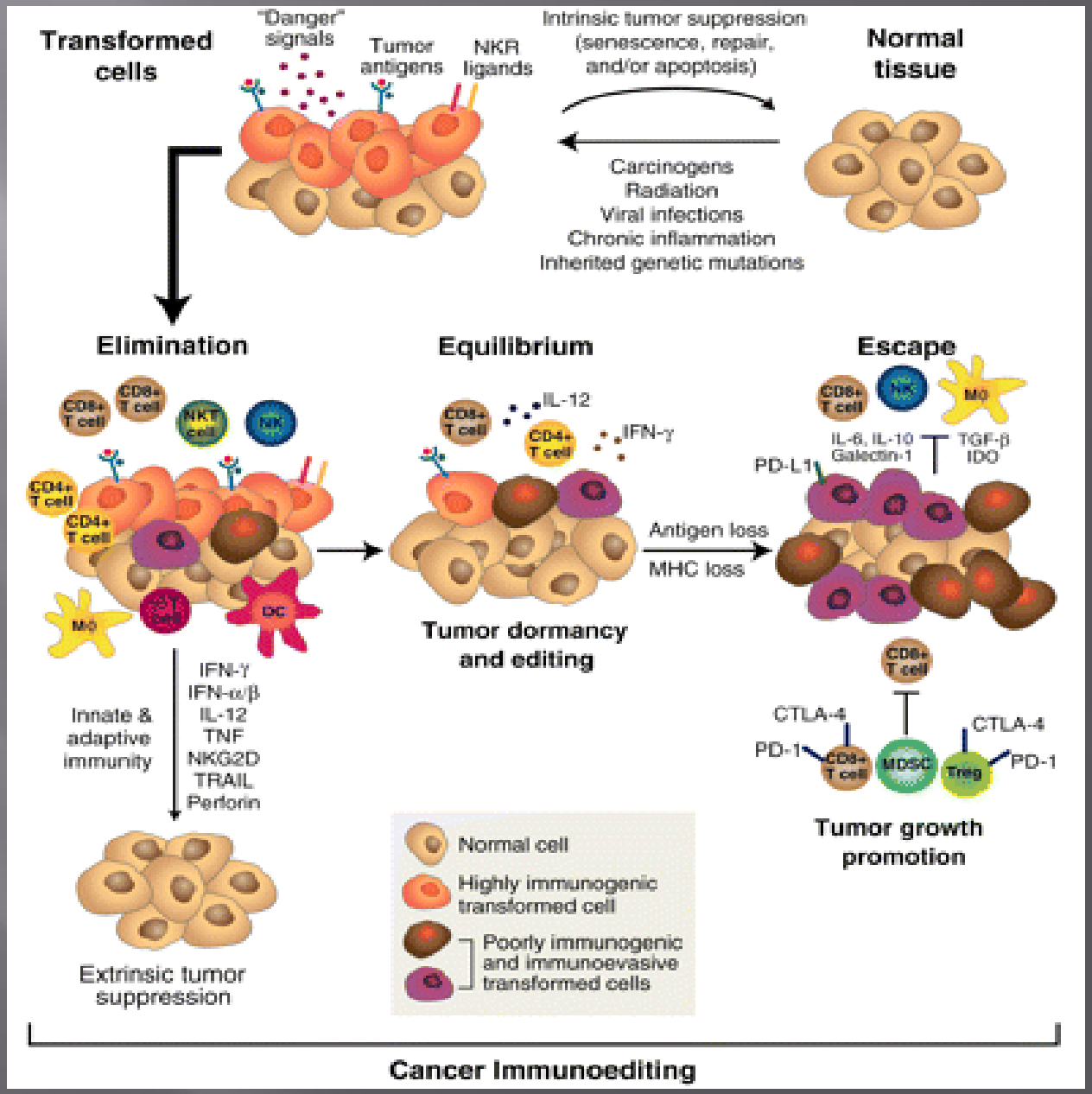
Summary of adaptive immunity to tumors and immune evasion



http://www.nature.com/nature/journal/v480/n7378/images/nature10673-f1.2.jpg

Immunosurveillance sculpts the tumor

- Elimination
- Equilibrium
- Escape



IMMUNE THERAPY: NEXT-GEN IMPROVEMENTS

Approach	Example
Genetic modification of lymphocytes to introduce new recognition specificities	Tumor-Ag-specific TCR
Genetic modification of lymphocytes to alter function functions of T cells	Costimulatory molecules (CD8, 41BB) Cytokines (IL-2, IL-12, IL-15) Homing molecules (CD62L, CCR7) Prevention of apoptosis (Bcl-2)
Modify host lymphodepletion	Selective depletion of CD4+ cells or T regulatory cells
Block inhibitory signals on reactive lymphocytes	Antibodies to CTLA-4 or PD-1
Administer vaccines to stimulate transferred cells	Recombinant virus, peptides, dendritic cells
Administer alternative cytokines to support cell growth	IL-15, IL-21, IL-12
Stimulate antigen presenting cells	Toll-like receptor agonists
Overcome antigen escape variants	NK cells

III. OPPORTUNITIES FOR FOCUSED ULTRASOUND

-monotherapy

Combinatorial therapy

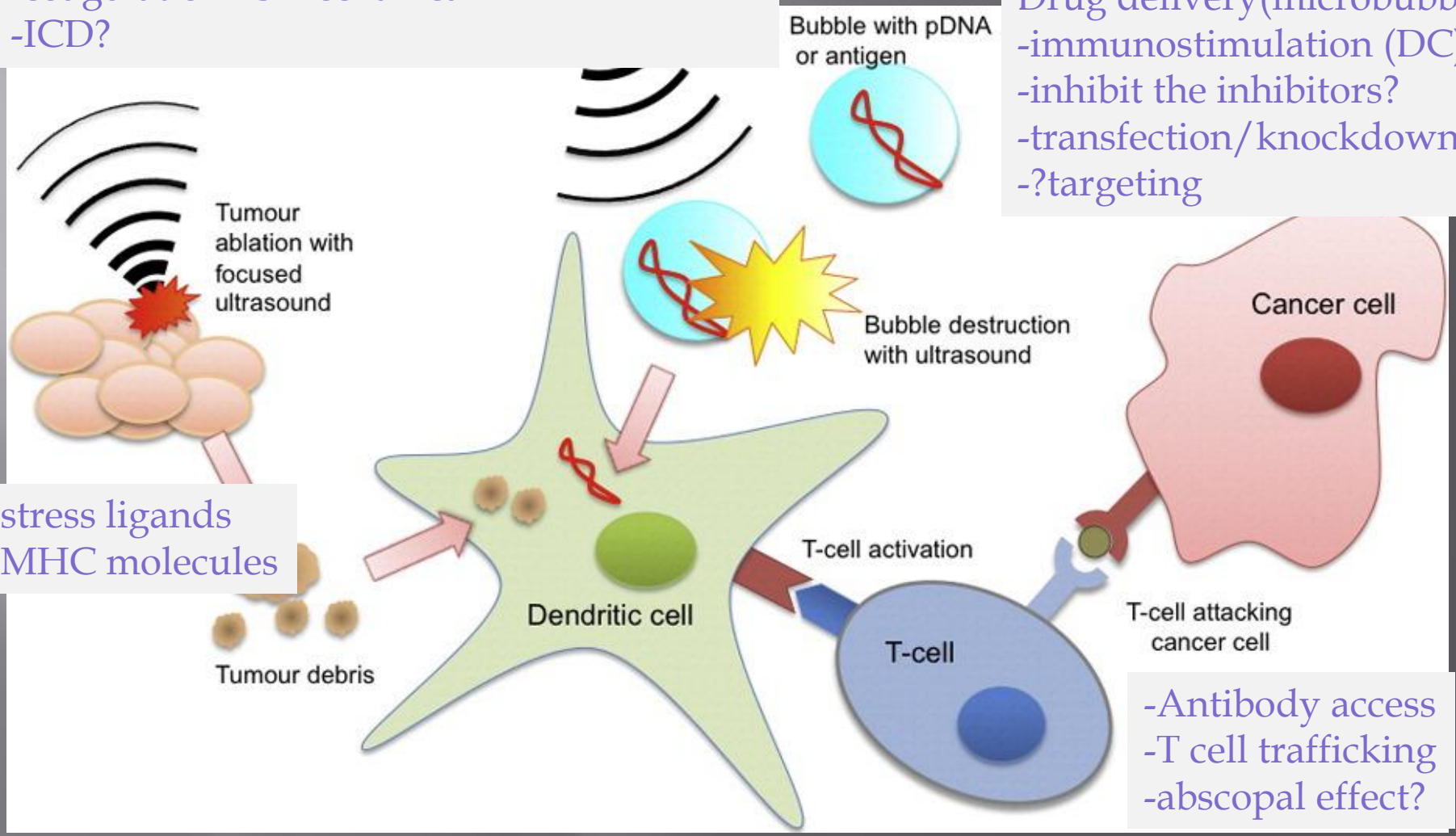
Focused ultrasound and tumor immunity

- HIFU treatment of experimental neuroblastoma induced immunological memory against subsequent tumor challenge.
- HIFU can lead to reduced inhibitory signaling pathways (cytokines?) and increased DC function in TME
- Cellular debris generated from mechanical disruption (compared to coagulation) induces DC activation (ICD;HSPs?).

Increased antigen availability

Direct tumor destruction (auto vaccination)
-HIFU vs LOFU (temp; sonoporation)
-coagulation vs mechanical
-ICD?

Drug delivery(microbubbles)
-immunostimulation (DC)
-inhibit the inhibitors?
-transfection/knockdown
-?targeting



-stress ligands
-MHC molecules

-Antibody access
-T cell trafficking
-abscopal effect?

http://www.sciencedirect.com/science/article/pii/S0169409X14000386

Unknowns (for the immunologist)

- What cellular responses will be elicited by FUS in humans? NK; myeloid?
- What cytokines will be induced? Pro-inflammatory or inhibitory? (IFN; IDO; TGFb)
- What happens to the expression of adhesion molecule ligands on tumor vasculature after FUS?
- Will tumors/stroma express inhibitory molecules after FUS?
- How can tumor penetration by MB be increased?
- Will systemic responses be generated?