Cancer Immunology

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Disclosure slide

Karen Willard-Gallo, Ph.D.

I have no financial relationships to disclose

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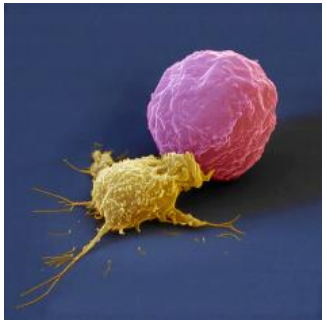
Cancer Immunology: Three key elements

I. The immune response (IR) can provide effective anti-tumor immunosurveillance.

II. The immune response can promote tumor formation and progression.

III. The immune response can be harnessed to treat cancer.



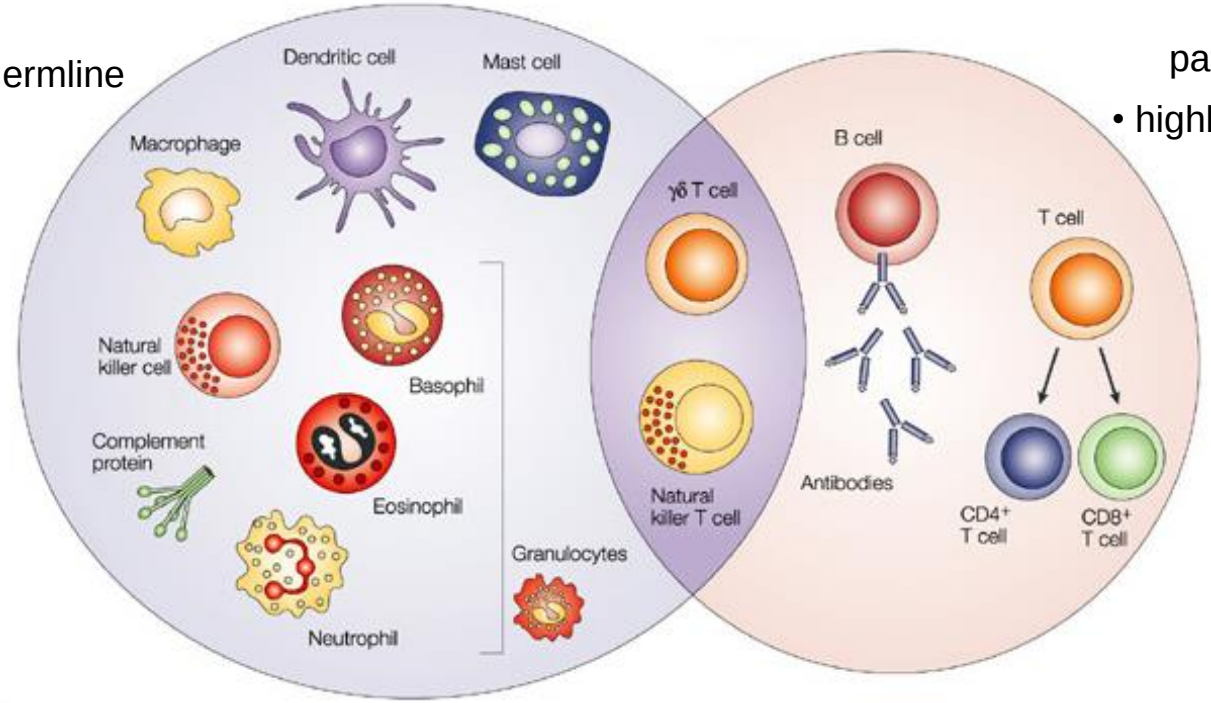
Key players in the immune response

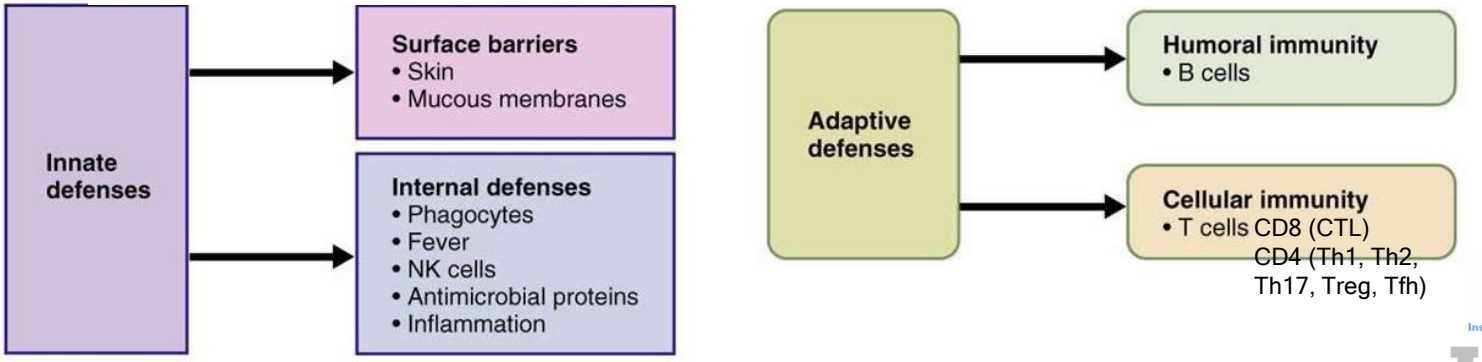
Innate Immunity:

- immediate response, initiated within seconds
- targets groups of pathogens/antigens
- diversity: limited # germline encoded receptors
- NO memory!

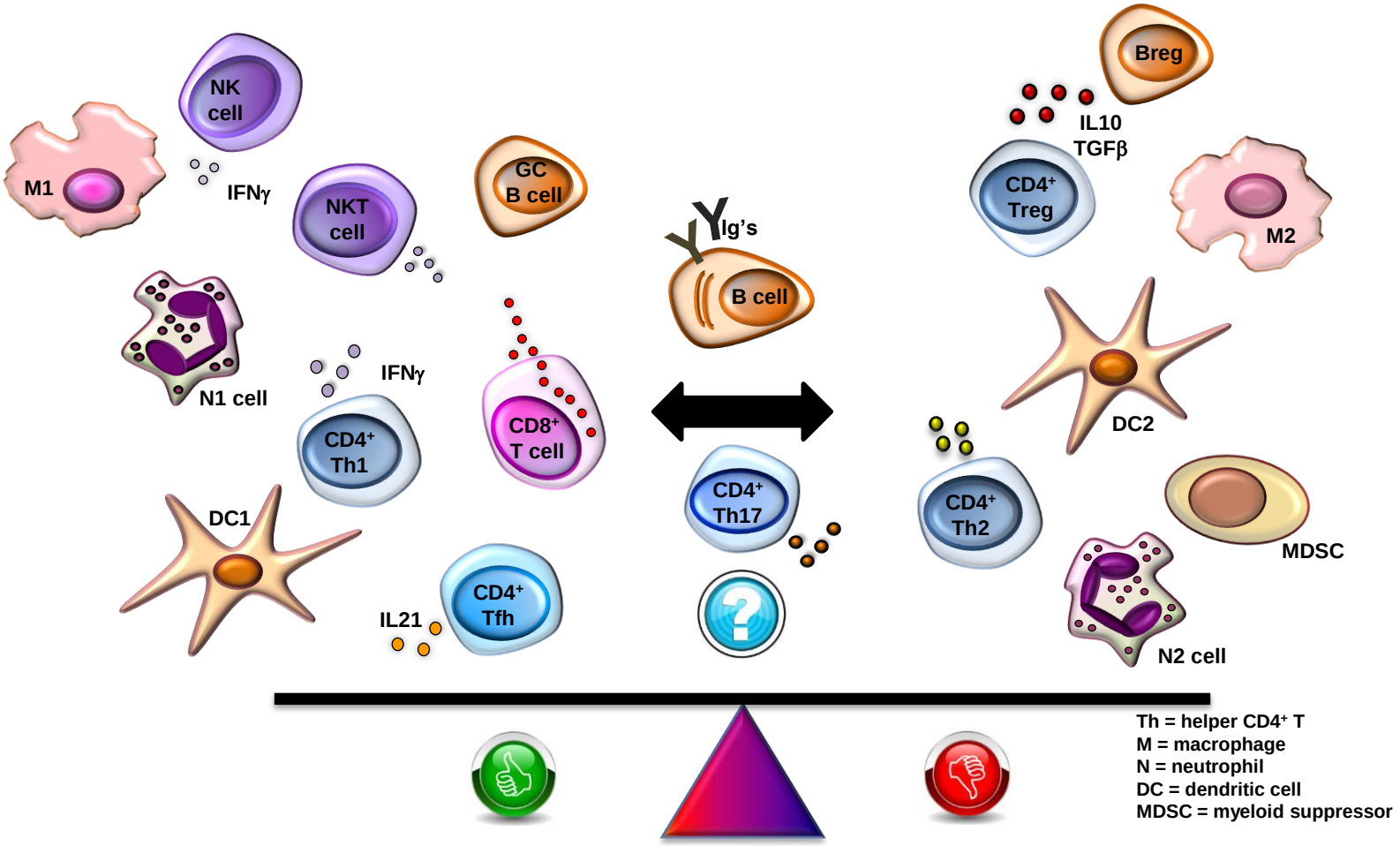
Adaptive Immunity:

- gradual response, generated over hours to days
- targets specific pathogens/antigens
- highly diverse: TCR & BCR repertoire
- MEMORY!





Infiltrating Leukocytes (TIL): Their balance is critical

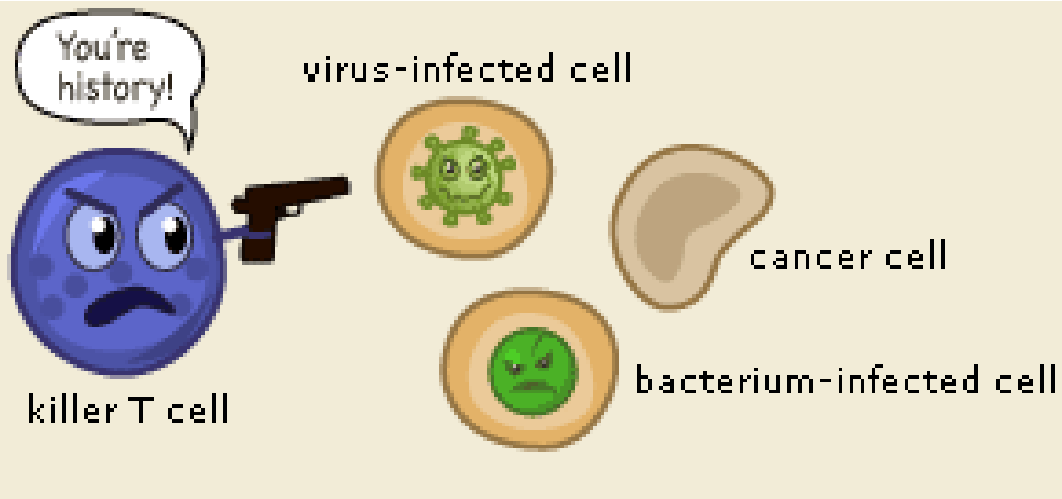


Gu-Trantien *et al.* (2013) J Clin Invest
Salgado *et al.* (2015) Ann Oncol
Garaud *et al.* 2015

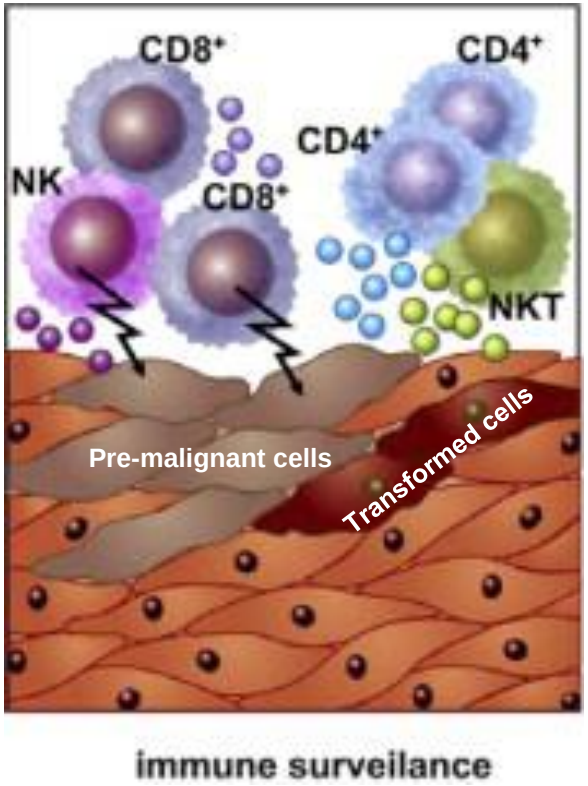
Cancer Immunology: 1st key element

I. The immune response can provide effective anti-tumor immunosurveillance.

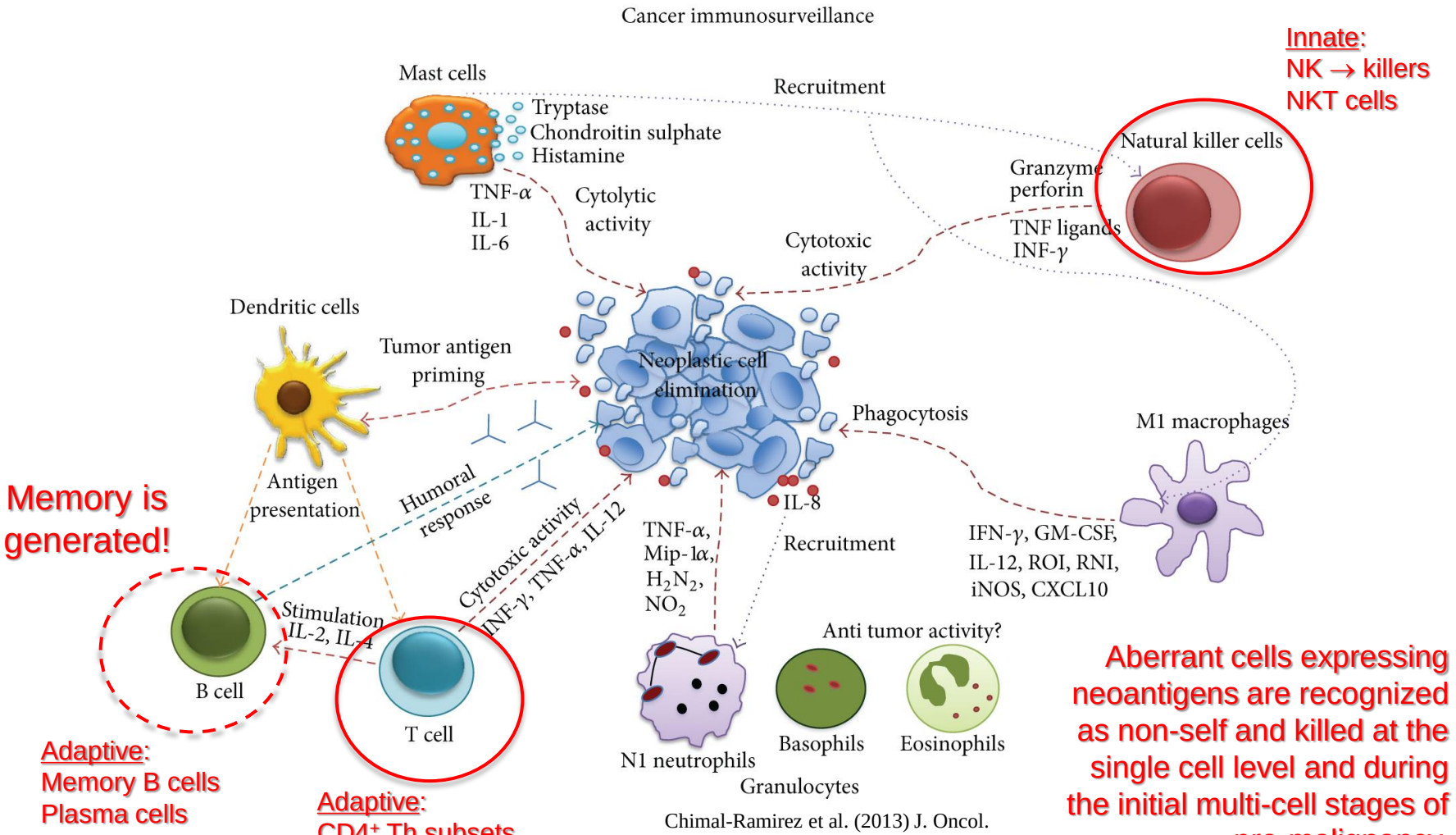
Is there evidence that the immune response controls early tumor progression in humans?



Killer cells, including CD8+ T cells and NK cells, routinely directly kill cells infected with a virus or bacterium, and are capable of killing tumor cells they recognize as non-self

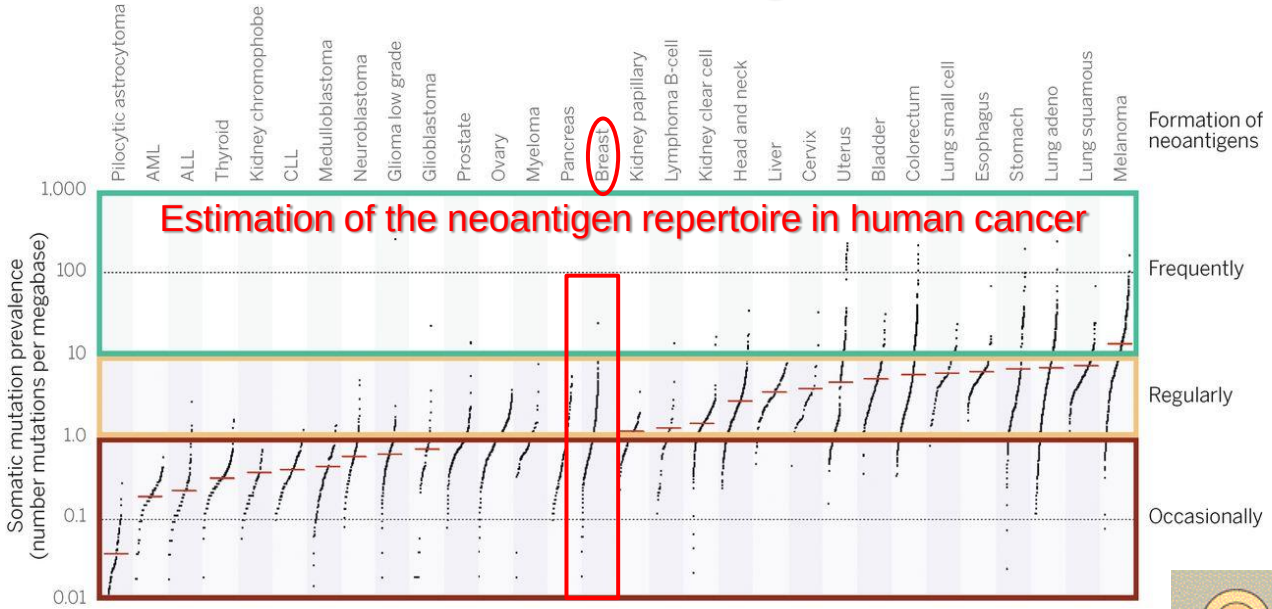


Elimination: an orchestrated immune response

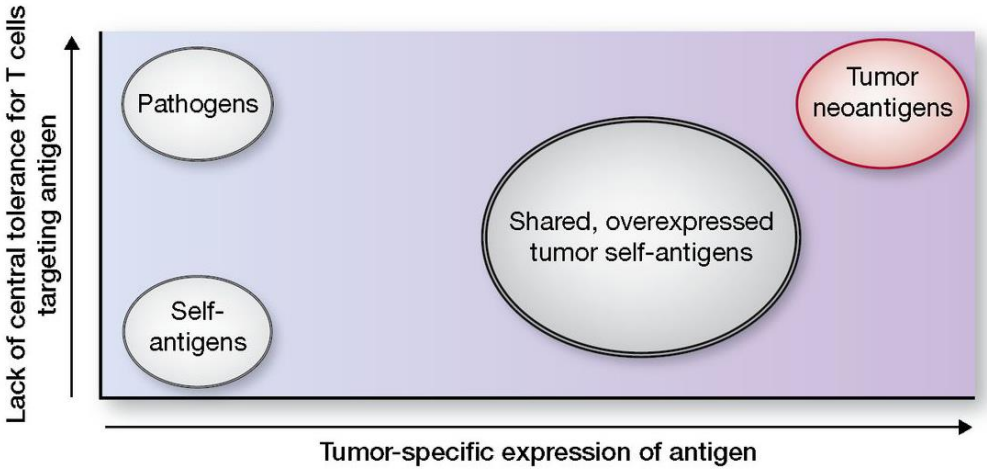


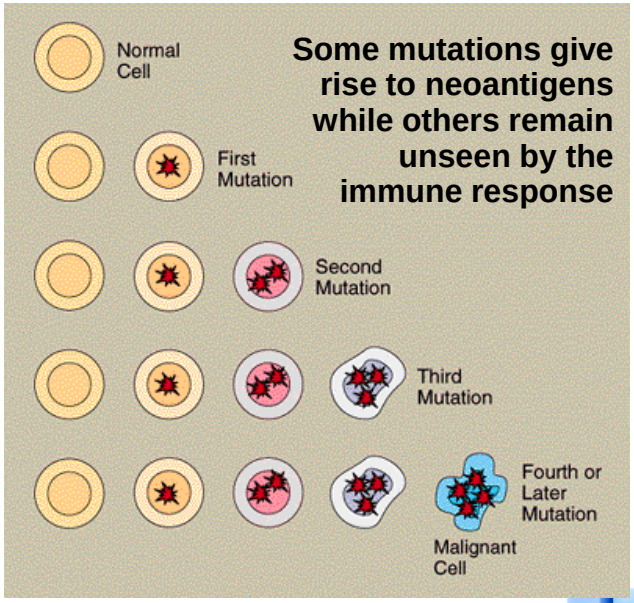
Aberrant cells expressing neoantigens are recognized as non-self and killed at the single cell level and during the initial multi-cell stages of pre-malignancy.

Neoantigens in Cancer



Schumacher and Schreiber Science 2015;348:69-74





Neoantigens seen by the immune response elicit memory

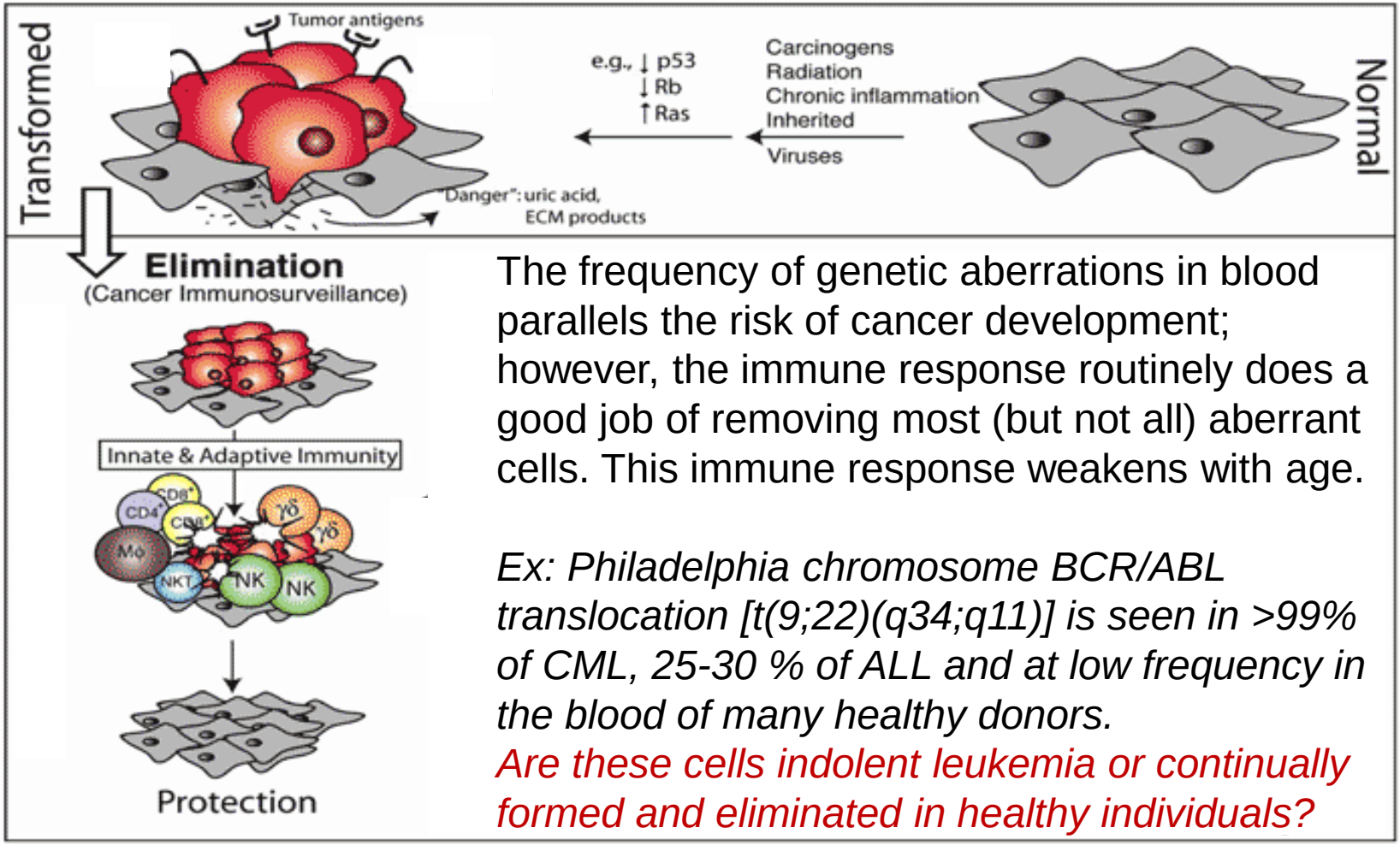
Chronic infections induce about ~ 20% of cancers

but, at a low incidence in healthy immunocompetent individuals – in immunodeficient individuals (transplant patients, AIDS…) the frequency dramatically increases!

Evidence exists for an increased risk of cancer due to chronic infection with	
Hepatitis B virus (HBV)	Sufficient: hepatocellular carcinoma
Hepatitis C virus (HCV)	Sufficient: hepatocellular carcinoma Probable: non-Hodgkin lymphoma
Helicobacter pylori bacterium (H. Pylori)	Sufficient: stomach carcinoma, non-Hodgkin lymphoma (MALT)
Human papillomavirus (HPV)	Sufficient: cervix, vulva, other external genitalia
HIV - Kaposi's sarcoma associated herpesvirus (KSHV)	Sufficient: Kaposi's sarcoma
HIV - Epstein Barr virus (EBV)	Sufficient: non-Hodgkin lymphoma in AIDS
Epstein Barr virus (EBV)	Sufficient: nasopharyngeal cancer, undifferentiated, Burkitt and other non-Hodgkin lymphoma and Hodgkin's disea
HTLV-I (Human T cell leukemia virus	Sufficient: Adult T cell leukemia

chronic infection → viral antigens (neoantigens) and chronic inflammation

Genetic aberrations can also be detected by the immune reponse



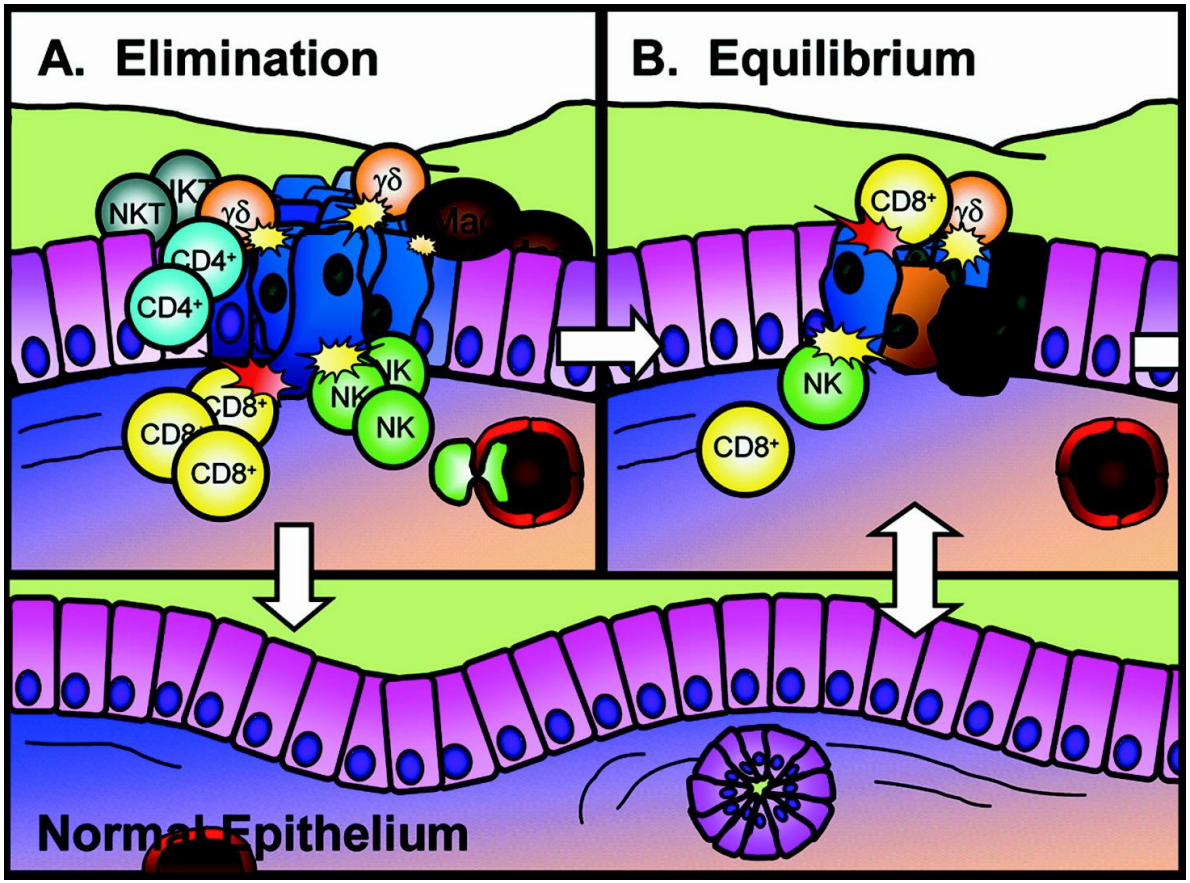
The frequency of genetic aberrations in blood parallels the risk of cancer development; however, the immune response routinely does a good job of removing most (but not all) aberrant cells. This immune response weakens with age.

Ex: Philadelphia chromosome BCR/ABL translocation [t(9;22)(q34;q11)] is seen in >99% of CML, 25-30 % of ALL and at low frequency in the blood of many healthy donors.

Are these cells indolent leukemia or continually formed and eliminated in healthy individuals?

Schreiber, *et al*. Immunoediting, various review papers

Equilibrium: a balance of opposing forces



Schreiber, *et al*. Immunoediting, various review papers

Accumulating advantageous growth and survival mutations in indolent aberrant cells slowly change the balance: an equilibrium phase with balanced growth and killing of aberrant cells ensues.

A recurrent 6q deletion in patients with lymphocytic variant hypereosinophilic syndrome (clonal CD3⁻CD4⁺T cells)

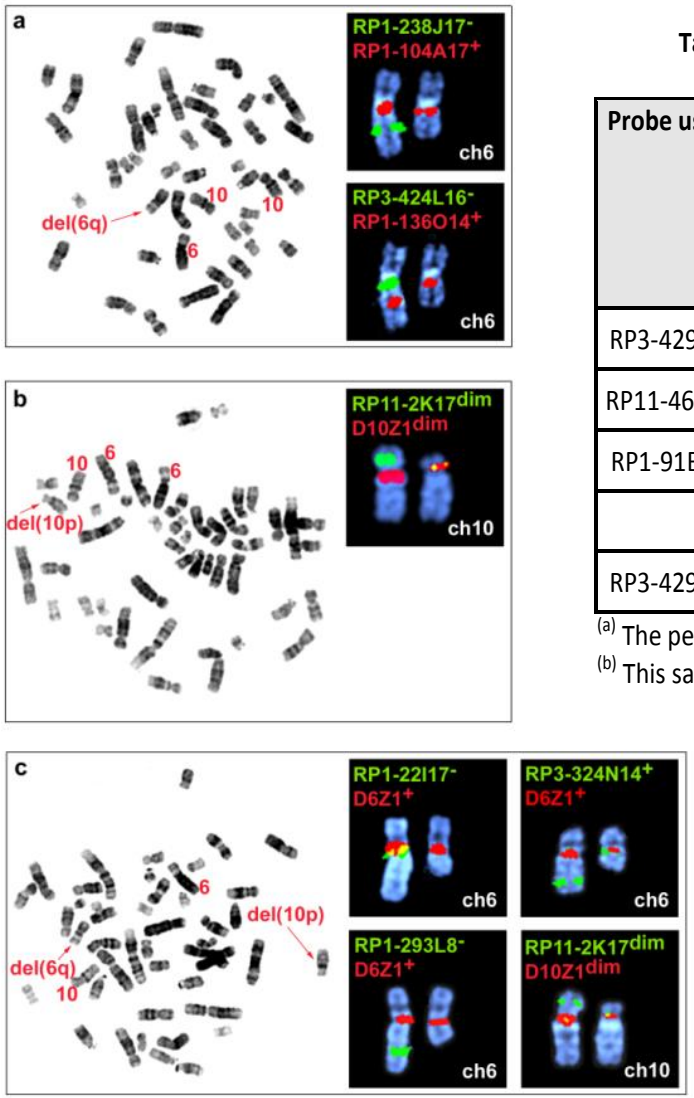


Table II: Evolution of the 6q and 10p deleted clones (percent of total CD3⁻CD4⁺ T cells) in successive purified blood samples from P1 and P2

Probe used	Chromosome location	Subclone(s) represented in the probe-deleted population	% of probe-deleted nuclei in the total CD3⁻CD4⁺ T cell population[a]		
			Chronic phase		T cell lymphoma
			P1-yr.0[b]	P1-yr.4	P1-yr.6
RP3-429G5	6q21	6q⁻ plus 6q⁻10p⁻	77%	80%	91%
RP11-462L8	10p11.22	6q⁻10p⁻ plus 10p⁻	54%	18%	< threshold
RP1-91B17	6q12	6q⁻10p⁻	33%	16%	< threshold
			P2-yr.0	P2-yr.4	
RP3-429G5	6q21	6q⁻	25%	22%	

Equilibrium Escape Elimination Equilibrium

[a] The percentage of probe-deleted cells was normalized to the percentage of CD3⁻CD4⁺ T cells.
[b] This sample was 69% CD3⁻CD4⁺ T cells.

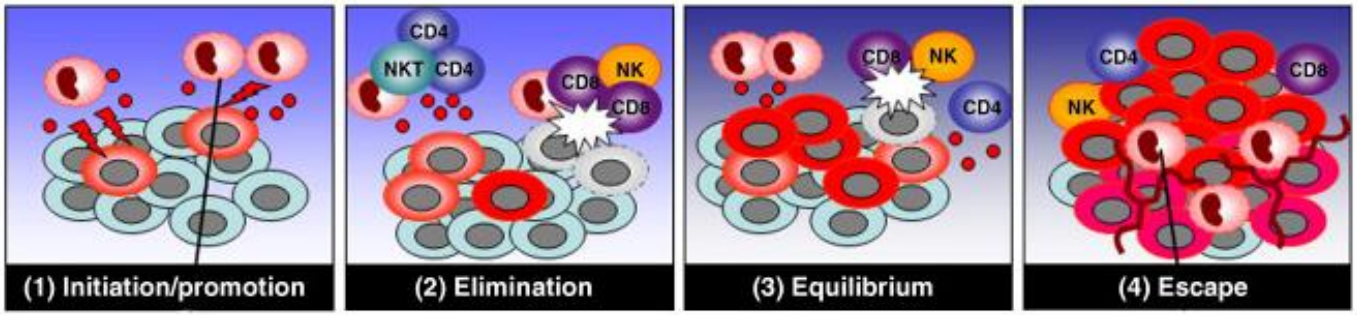
1) loss of TCR/CD3 expression: generation of a 46,XX CD3⁻CD4⁺ T cell clone

- 2a) del(6)(q13q22.1) : generation of the « 6q⁻ » subclone — T lymphoma
- 2b) del(10)(p11.1p13) : generation of the « 10p⁻ » subclone
  - 3) del(6)(q11.1q23.1) : generation of the « 6q⁻10p⁻ » subclone

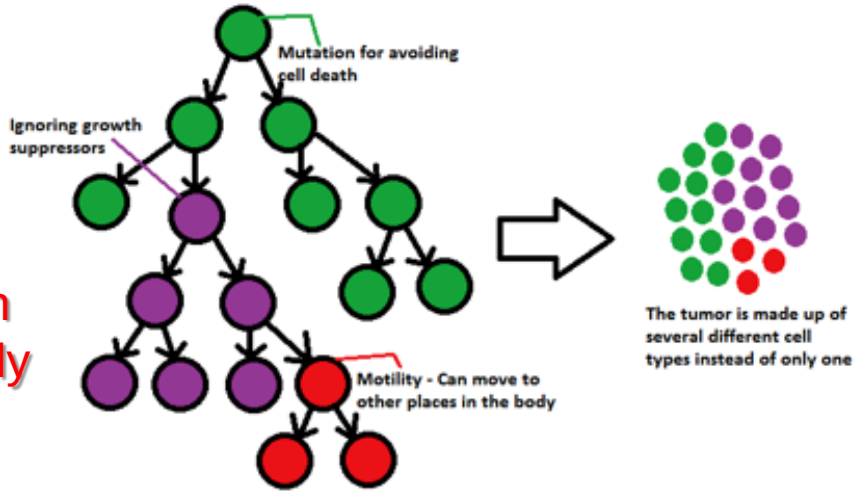
Ravoet et al. 2009 Blood 114:2969

The downside of Equilibrium:

- tumor cells emerge with greater growth/survival capacity;
- slow erosion of effective immune responses as the resulting mutant tumor cells recruit “bad” immune cells;
- tumor-mediated immunosuppression increases.



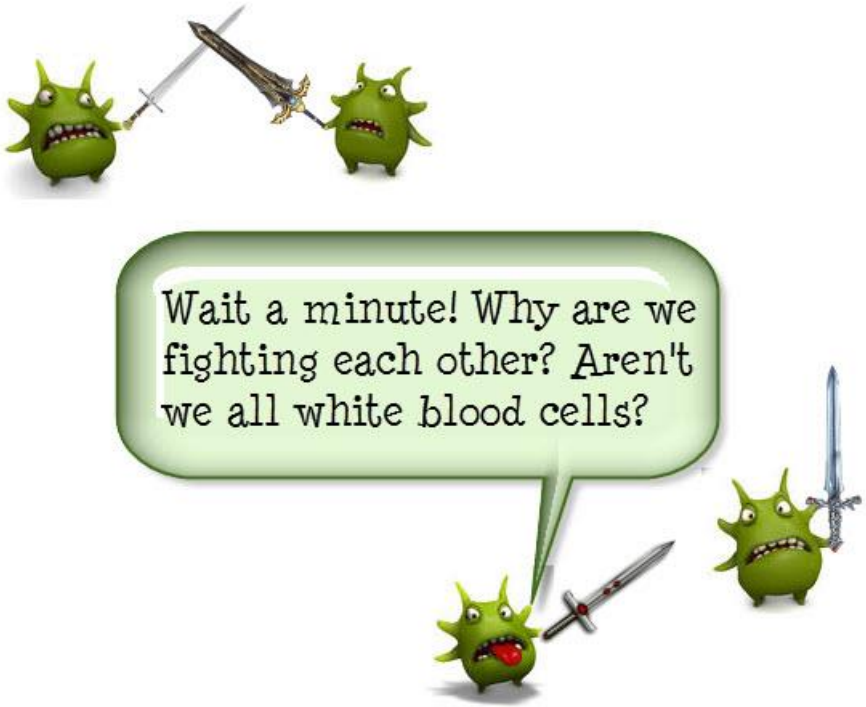
Schreiber, *et al*. Immunoediting, various review papers



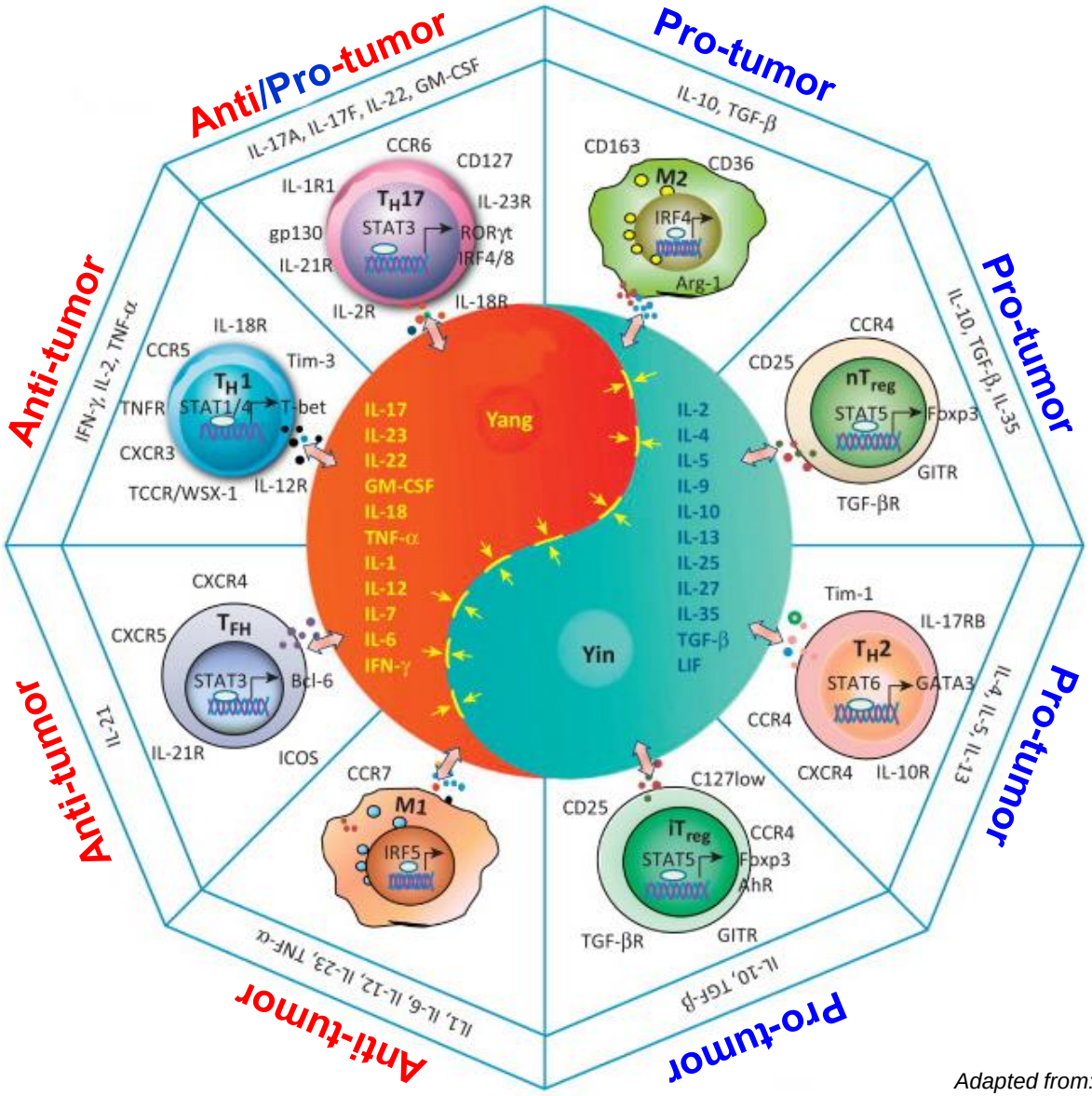
The immune response sees each variant cell differently

Cancer Immunology: Second key element

II. The immune response promotes tumor formation and progression.



The “good” and “bad” guys



A myriad of factors (*lymphokines, cytokines, chemokines*) are known to be produced in the tumor microenvironment (*by immune cells, tumor cells, stromal cells, etc.*), and therefore:

a) their balance is critical

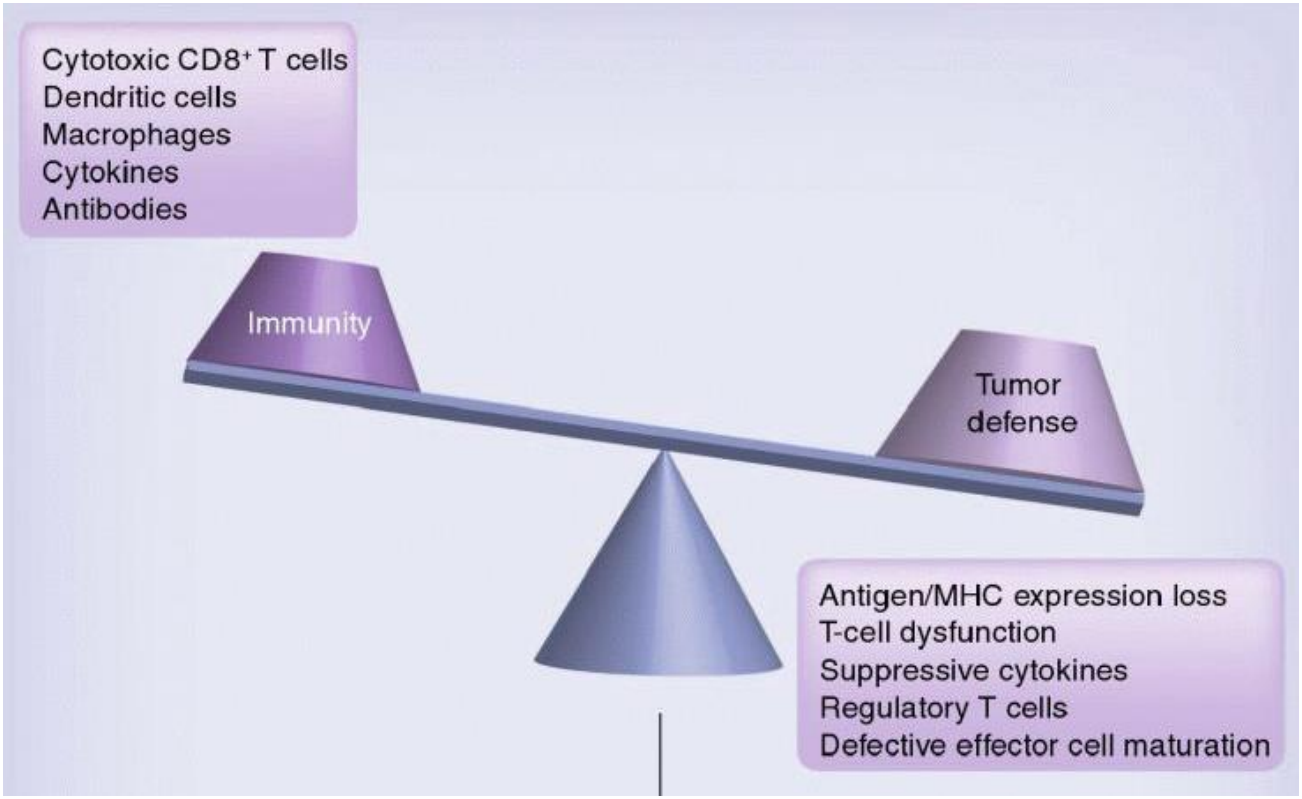
b) their effect is dynamic

c) tumor heterogeneity = cytokine heterogeneity

d) they or their cellular source may antagonize one another

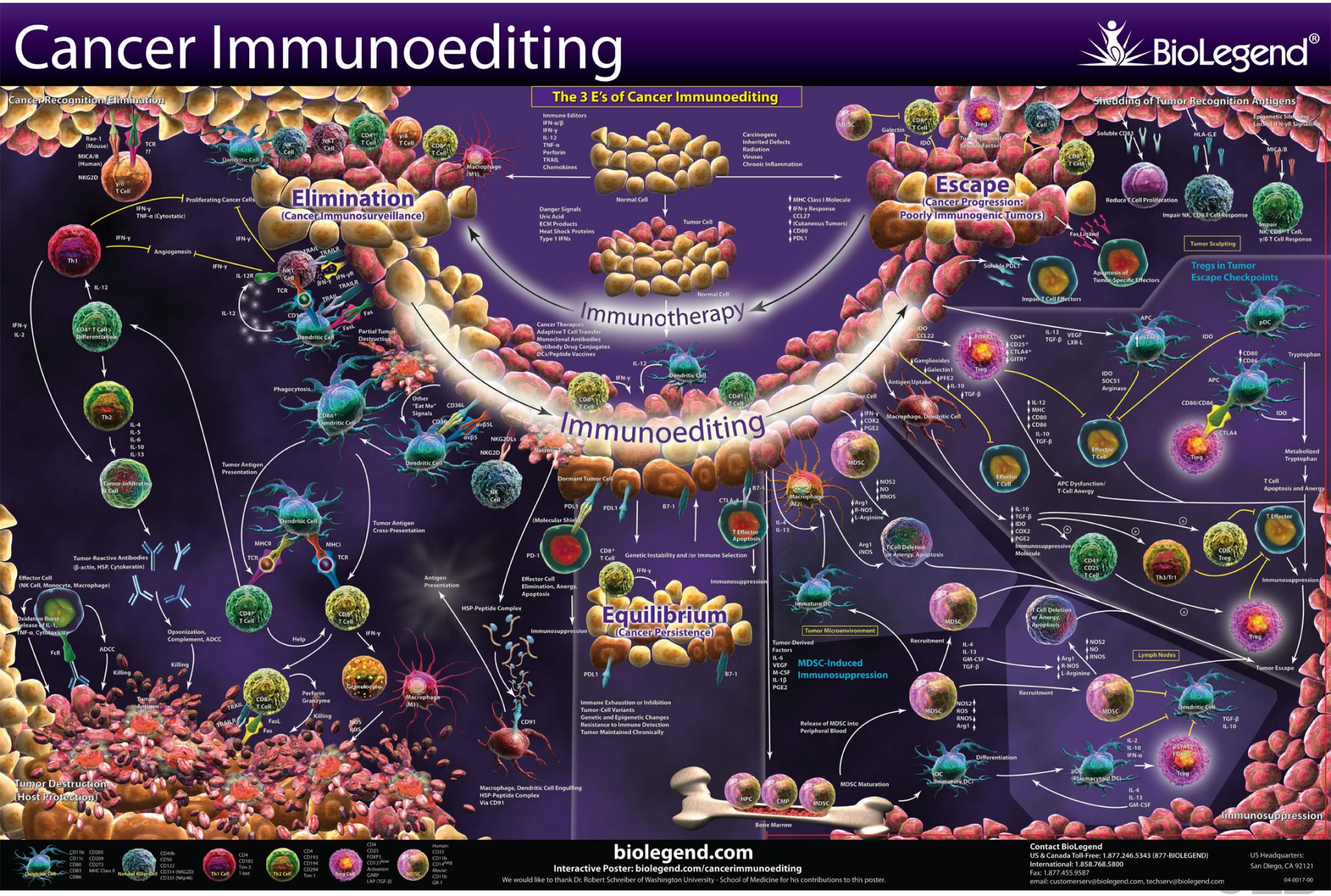
Adapted from:
Liu et al. Trends Immunol. (2013) 34:120-8.

The balance changes constantly in the tumor microenvironment



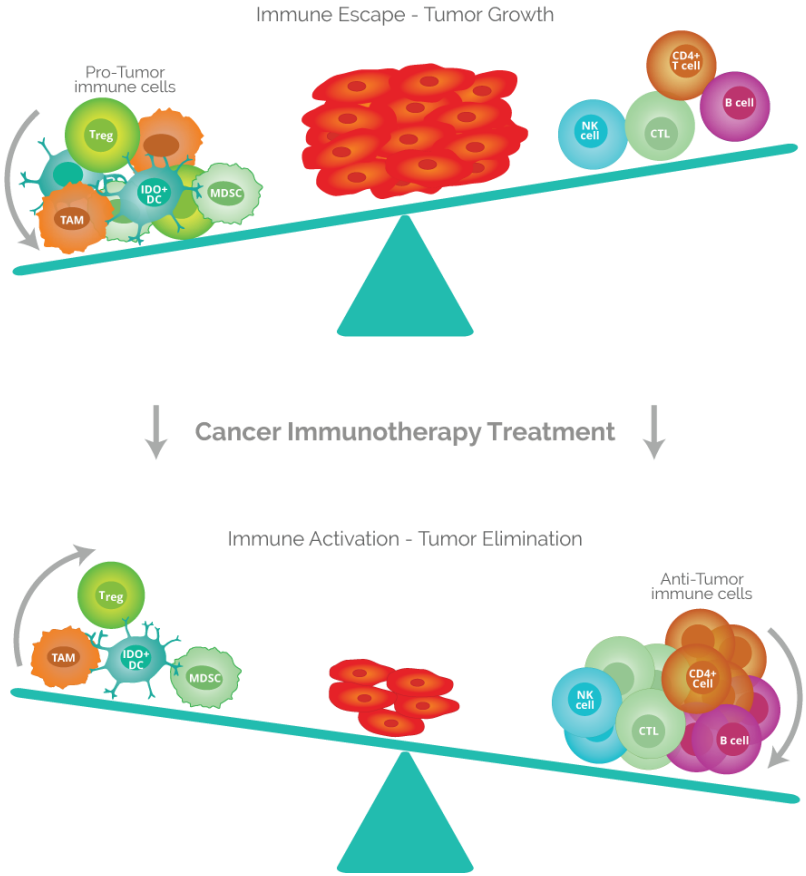
Different immune, stromal, and tumor cell variants continuously change the balance in the tumor microenvironment via the proteins they do/do not produce or express.

All of these activities can be going on simultaneously in different regions of the primary tumor.



Cancer Immunology: Third key element

III. The immune system can be harnessed to treat cancer



From hybridomas to antibody-based therapeutics

1975 — hybridoma technology discovered: **Köhler & Milstein**

1984 — hybridoma technology awarded Nobel Prize: **Köhler & Milstein**

1986 — 1st murine mAb approved (FDA) for transplant patients; **target: CD3**

1994 — 1st chimeric mAb approved (FDA) for cardiac ischemic complications; **target: ITGA2B**

1997 — 1st humanized mAb approved (FDA) for kidney transplant rejection; target: **CD25/IL-2Rα**

1998 — 1st fully human mAbs approved (FDA) for rheumatoid arthritis; **target: TNFα**

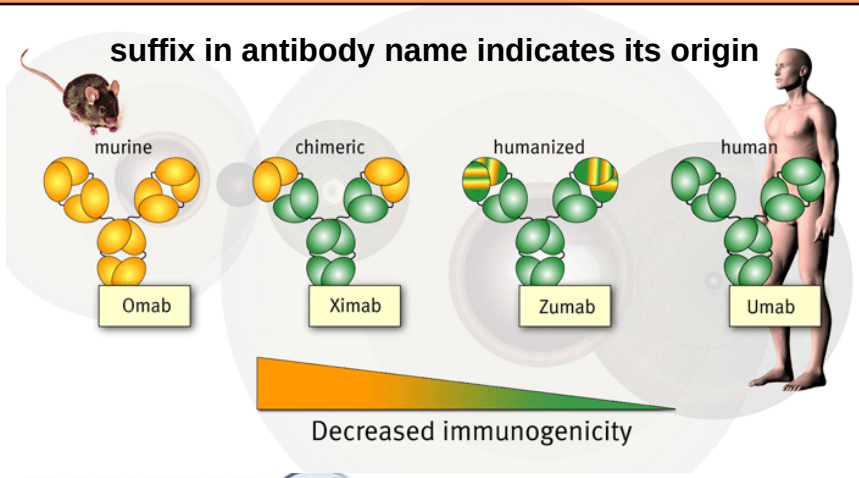
2006 — fully human mAb approved (FDA) for metastatic breast cancer; **target: HER2**

2011 — 1st checkpoint inhibitor mAb approved (FDA) for metastatic melanoma; **target: CTLA4**

2014 — 2nd checkpoint inhibitor mAb approved (FDA) for metastatic melanoma; **target: PD-1**

2015 — Checkpoint inhibitor mAb combinations; **targets: CTLA4 + PD-1/PD-L1 PD-1 + HER2, etc.**

2006 — human mAb approved (FDA) for early breast cancer; **target: HER2**



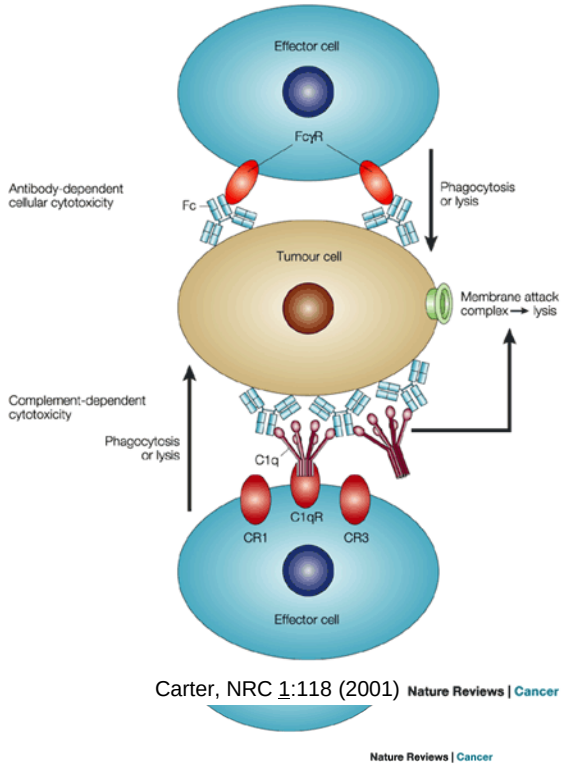
Journal of Clinical Oncology
jco.ascopubs.org

JCO **August 1998** Vol. 16 no. 8 **2659-2671**

Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment.

M D Pegram, A Lipton, D F Hayes, B L Weber, J M Baselga, D Tripathy, D Baly, S A Baughman, T Twaddell, J A Glaspy and D J Slamon

Antibody-mediated killing



Carter, NRC 1:118 (2001)

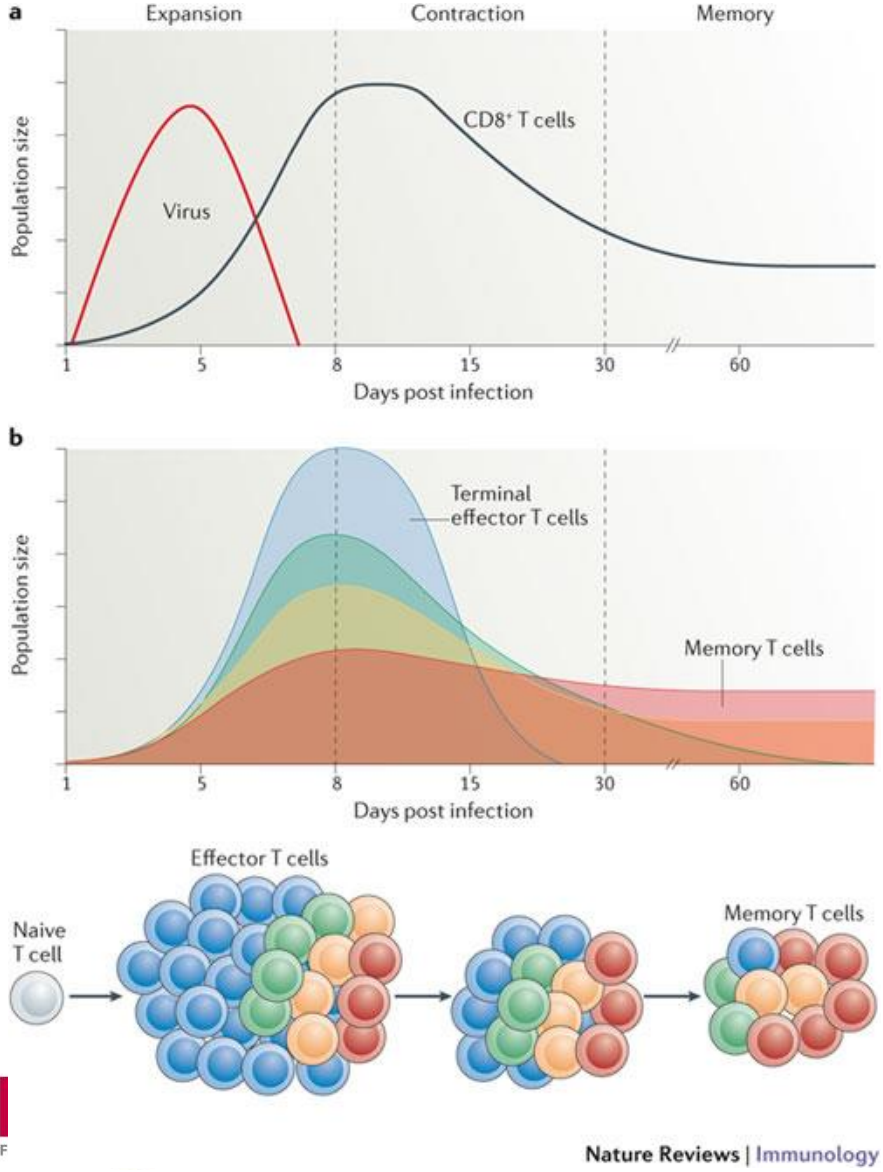
Tumor-associated antigens targeted by monoclonal antibody therapeutics

Antigen category	Examples of antigens	Tumor types expressing antigen
Cluster of differentiation (CD) antigens	CD20	non-Hodgkin lymphoma
	CD30	Hodgkin lymphoma
	CD33	Acute myelogenous leukemia
	CD52	Chronic lymphocytic leukemia
Glycoproteins	EpCAM	Epithelial tumors (breast, colon, lung)
	CEA	Epithelial tumors (breast, colon, lung)
	gpA33	Colorectal carcinoma
	Mucins	Epithelial tumors (breast, colon, lung, ovarian)
	TAG-72	Epithelial tumors (breast, colon, lung)
	Carbonic anhydrase IX	Renal cell carcinoma
	PSMA	Prostate carcinoma
	Folate binding protein	Ovarian tumors
Glycolipids	Gangliosides (e.g., GD2, GD3, GM2)	Neuroectodermal tumors, some epithelial tumors
Carbohydrates	Lewis-Y^2	Epithelial tumors (breast, colon, lung, prostate)
Vascular targets	VEGF	Tumor vasculature
	VEGFR	Epithelium-derived solid tumors
	αVβ3	Tumor vasculature
	α5β1	Tumor vasculature
Growth factors	ErbB1/EGFR	Glioma, lung, breast, colon, head and neck tumors
	ErbB2/HER2	Breast, colon, lung, ovarian, prostate tumors
	ErbB3	Breast, colon, lung, ovarian, prostate tumors
	c-MET	Epithelial tumors (breast, ovary, lung)
	IGF1R	Lung, breast, head and neck, prostate, thyroid, glioma
	EphA3	Lung, kidney, colon, melanoma, glioma, hematological malignancies
	TRAIL-R1, TRAIL-R2	Solid tumors (colon, lung, pancreas) and hematological malignancies
	RANKL	Prostate cancer and bone metastases
Stromal and extracellular matrix antigens	FAP	Epithelial tumors (colon, breast, lung, head and neck, pancreas)
	Tenascin	Glioma, epithelial tumors (breast, prostate)

from Scott, A.M. et al. Cancer Immunity (2012) 12: 14

Effective but still the problem of tumor heterogeneity (ex. HER2+ and HER2– cells) means they are not 100% effective.

Effective immunotherapy generates immunological memory to tumor cell variants

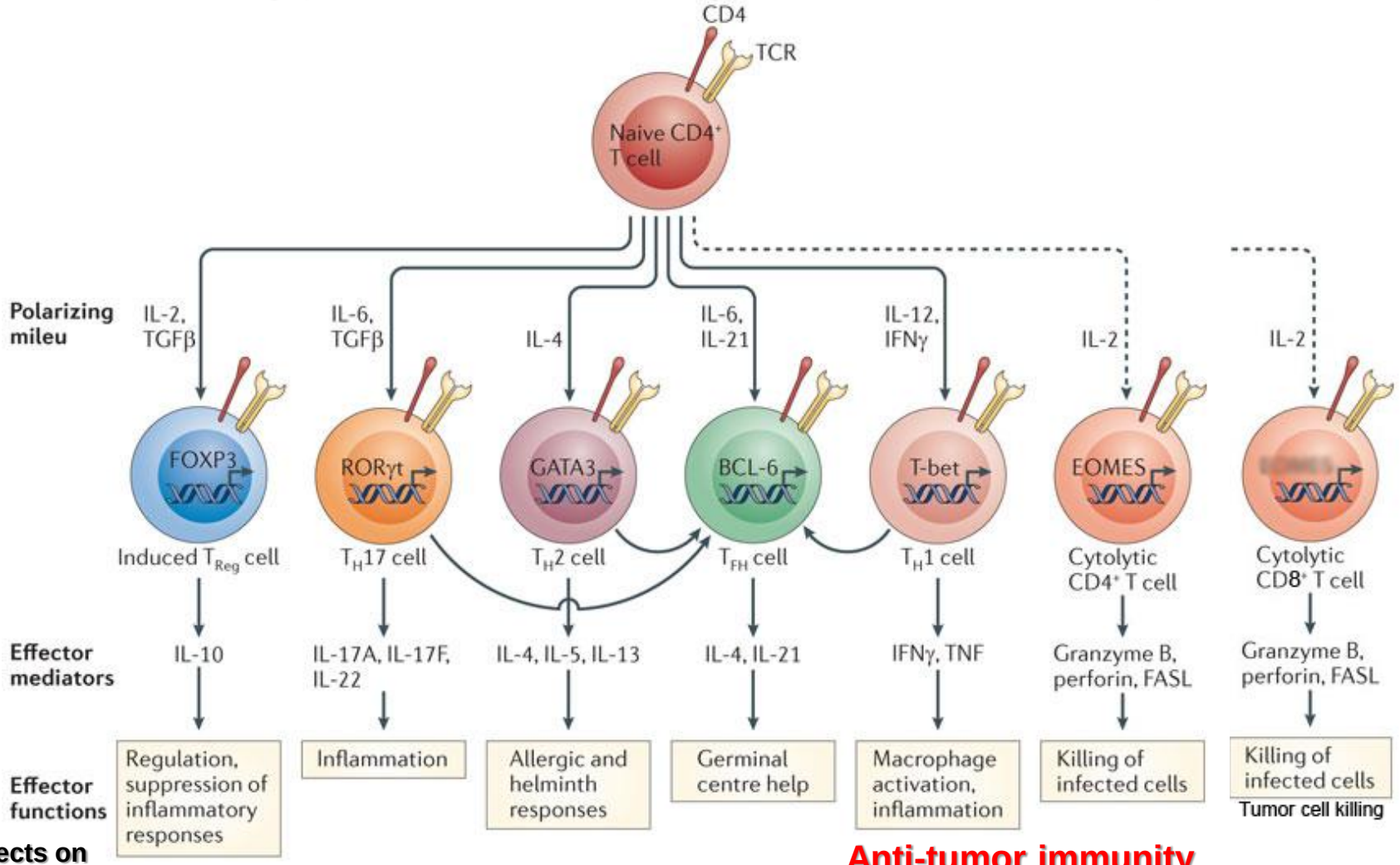


Memory cells can persist from many years to a lifetime!

ex. single shot vaccines, lifetime immunity to childhood diseases, etc.

They may be the only "drug" that can find and kill or suppress the last remaining tumor cell…but has the immune response acquired memory to recent tumor cell mutants/variants?

Which types of memory T cells are important?



Anti-tumor immunity

Effects on progression:

any cancer	↑↓	↑↓	↑↓	↓	↓	?	↓
human BC	↑	↑↓?	↑↓?	↓	↓	?	↓

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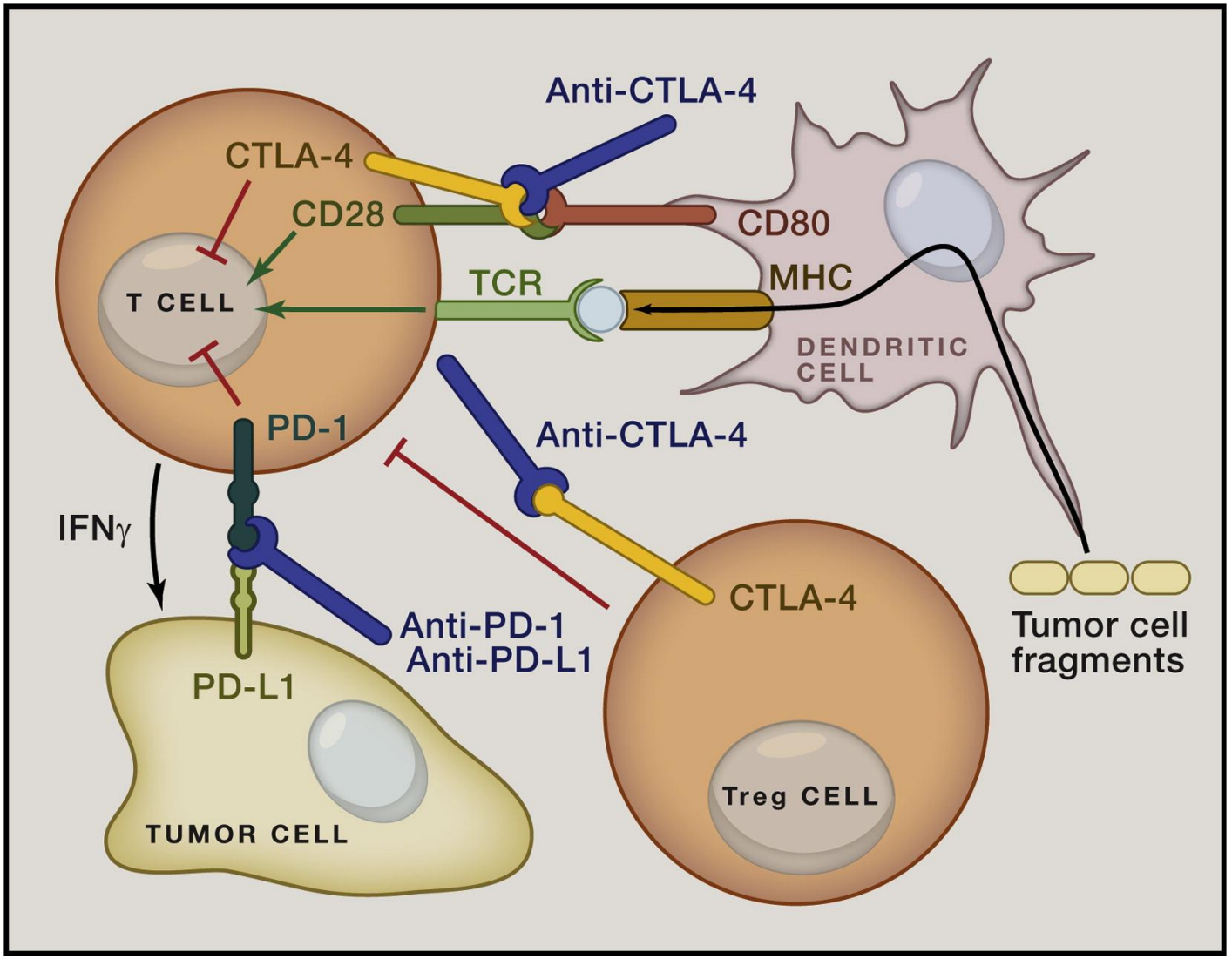
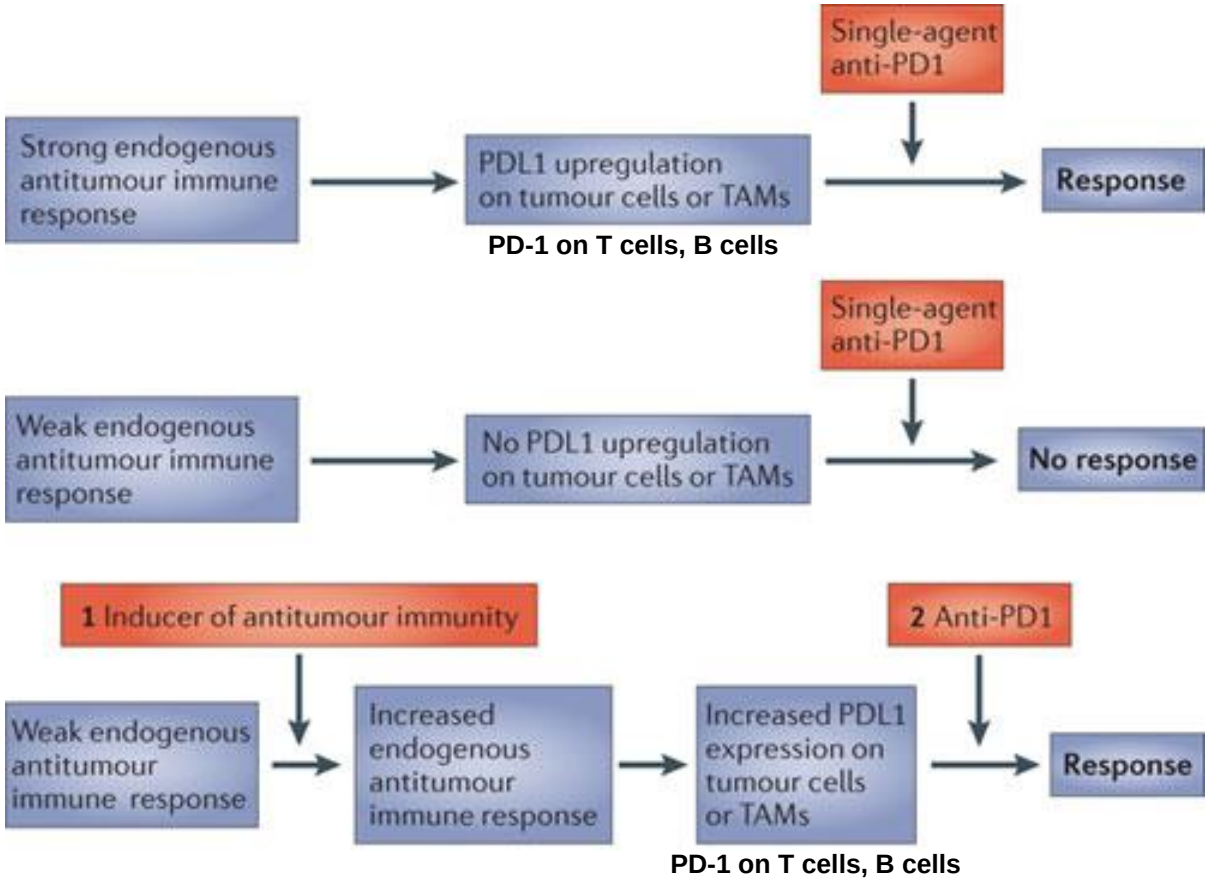
Targeting immune checkpoints

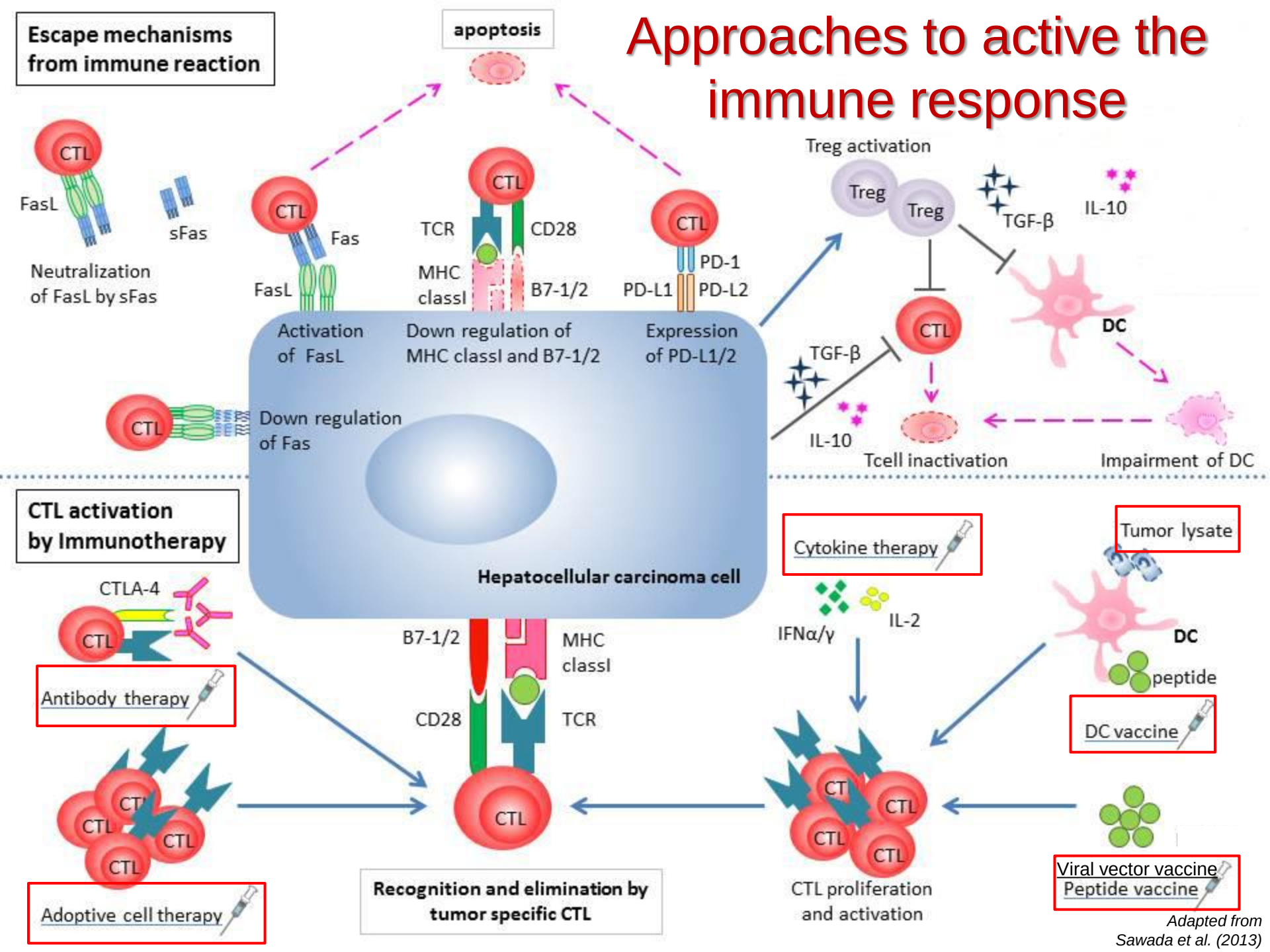


relieving tumor-mediated immunosuppression works where memory T cells have been generated but anergized

Patients who do not respond need to generate a *de novo* response

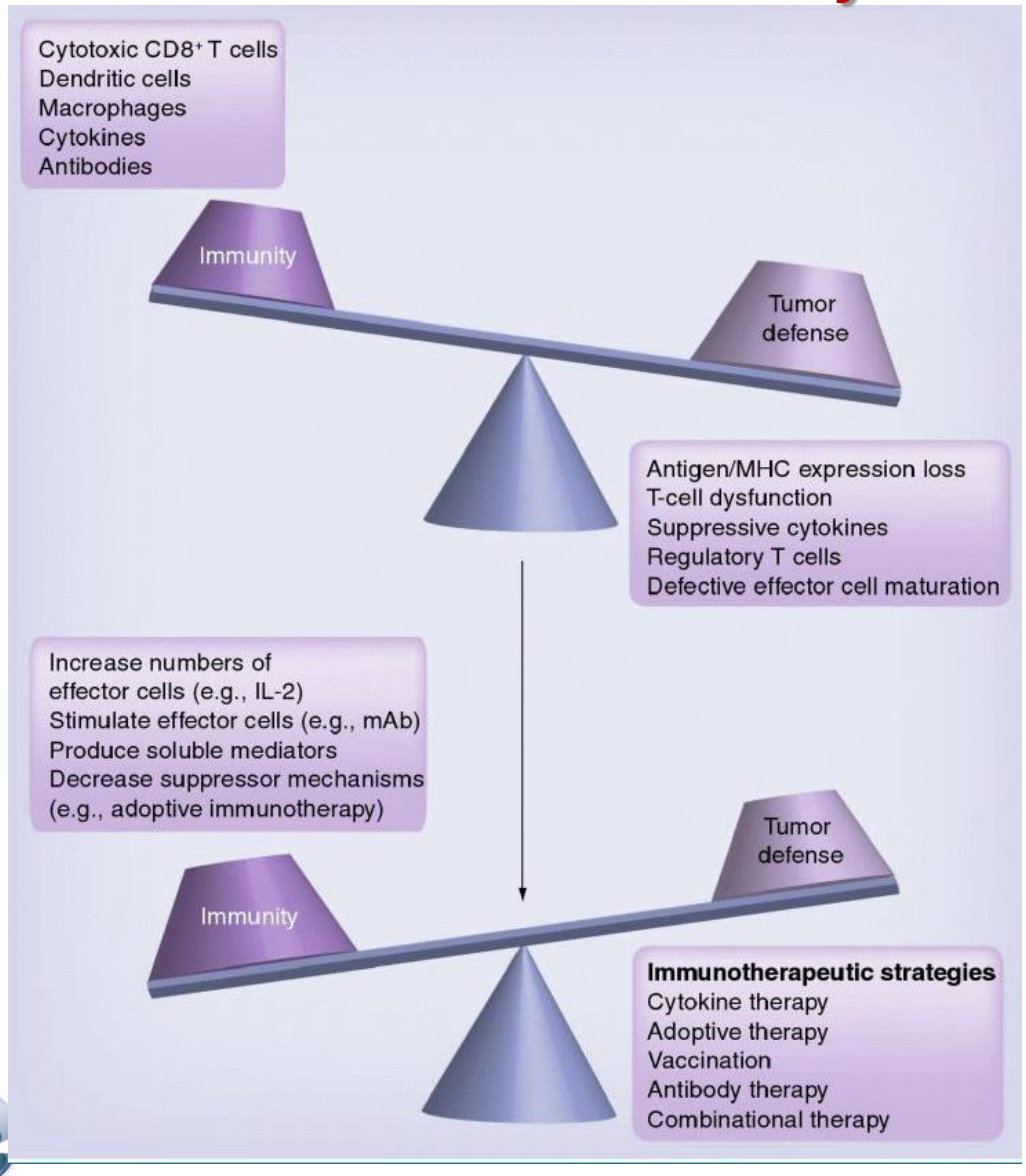


Approaches to active the immune response



Adapted from Sawada et al. (2013)

Regaining the balance in favor of anti-tumor immunity




STAY TUNED
SOMETHING
BIG
IS COMING...