Society for Immunotherapy of Cancer (SITC)

Immunology and Immunotherapy 101 for the Non-Immunologist

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Moffitt Cancer Center

Advances in Cancer Immunotherapy™
December 10, 2016

Society for Immunotherapy of Cancer

Presenter Disclosure Information

Jose R Conejo-Garcia

The following relationships exist related to this presentation:

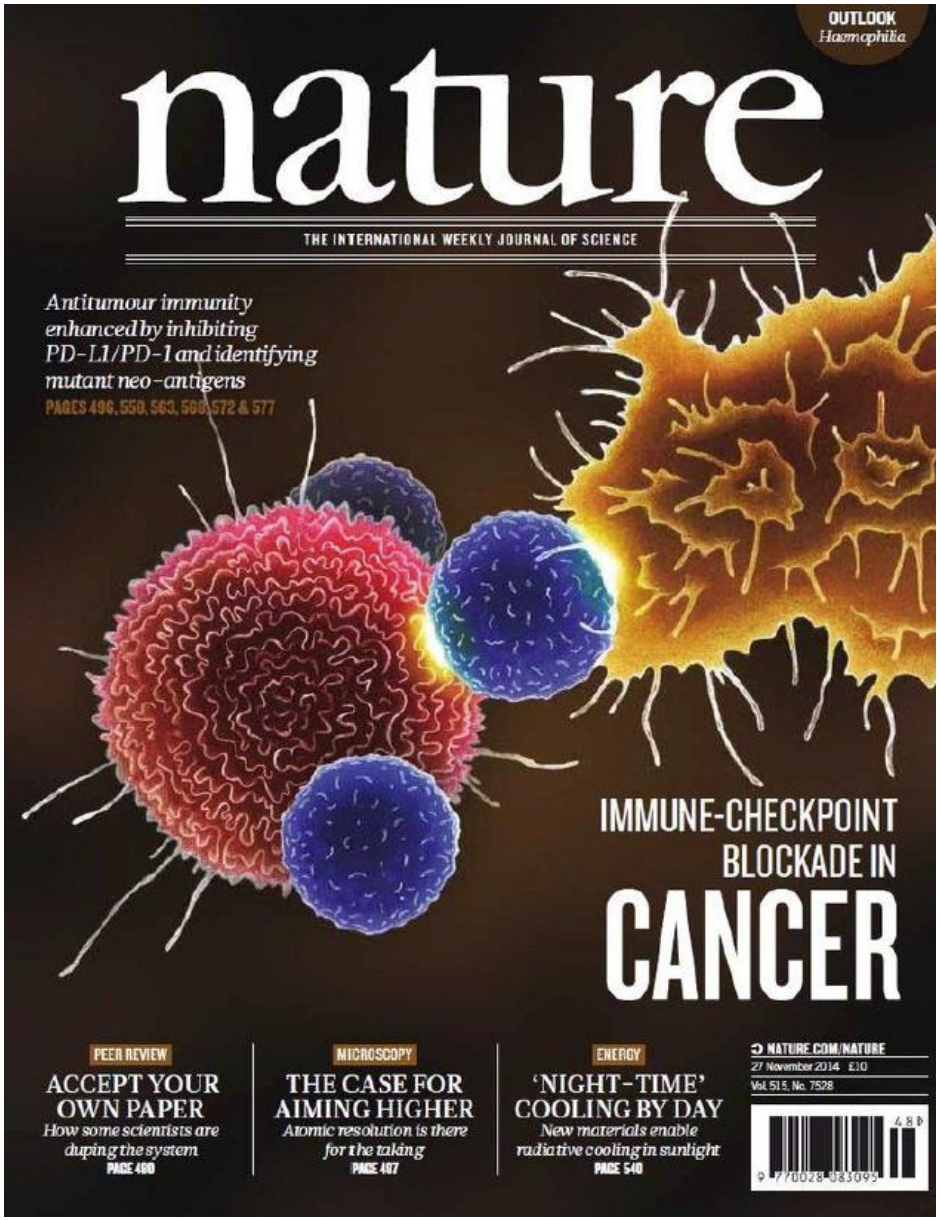
QUENTIS THERAPEUTICS, Scientific Advisory Board

ONCOSEQ, Scientific Advisory Board

COMPASS THERAPEUTICS, grant support

I will not be discussing non-FDA approved treatments/indications during my presentation


Science
20 December 2013
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS


OUTLOOK
Haemophilia
nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
Antitumour immunity enhanced by inhibiting PD-L1/PD-1 and identifying mutant neo-antigens
PAGES 496, 559, 563, 568, 572 & 577
IMMUNE-CHECKPOINT BLOCKADE IN CANCER
PEER REVIEW
ACCEPT YOUR OWN PAPER
How some scientists are duping the system
PAGE 480
MICROSCOPY
THE CASE FOR AIMING HIGHER
Atomic resolution is there for the taking
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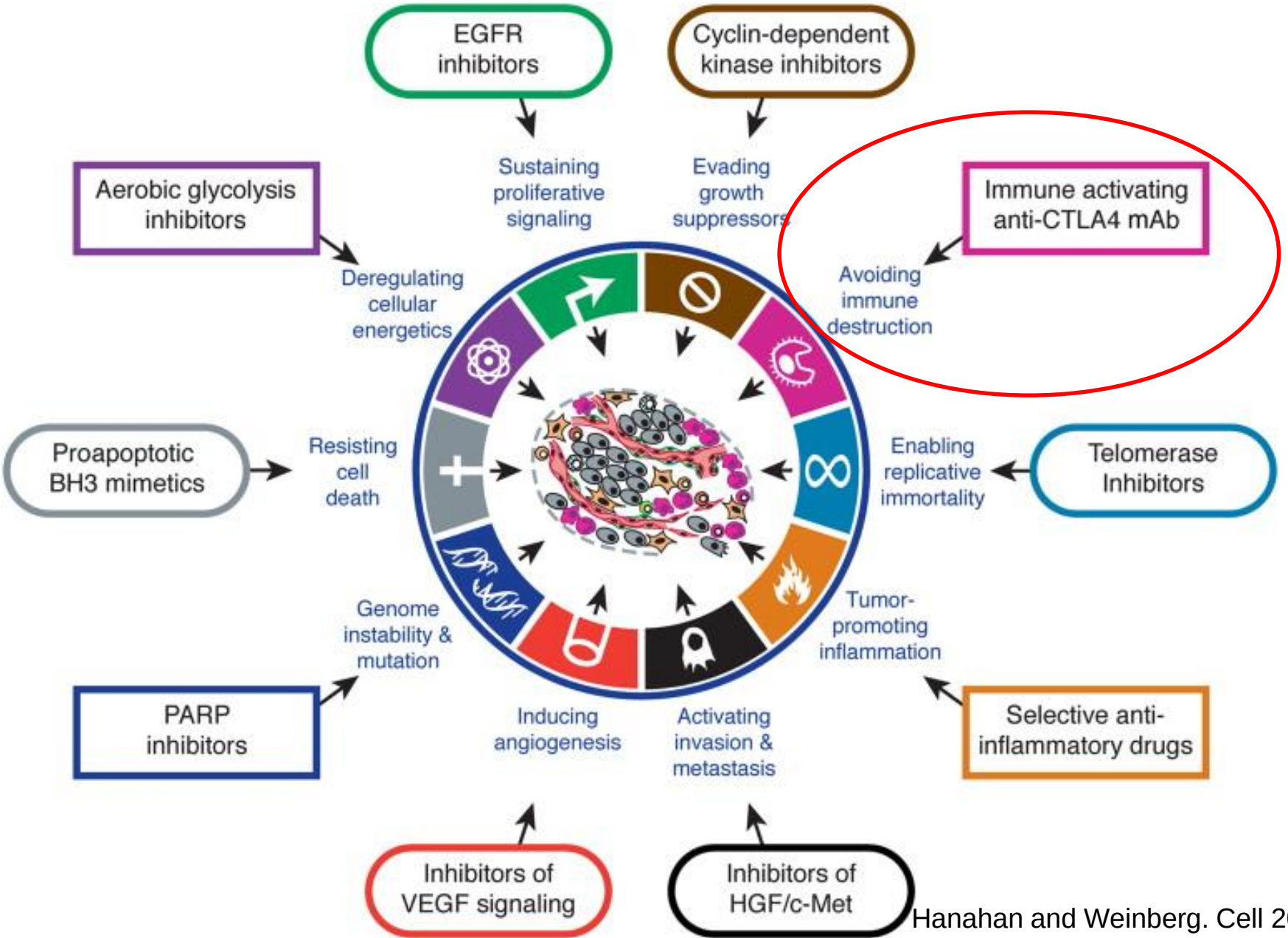
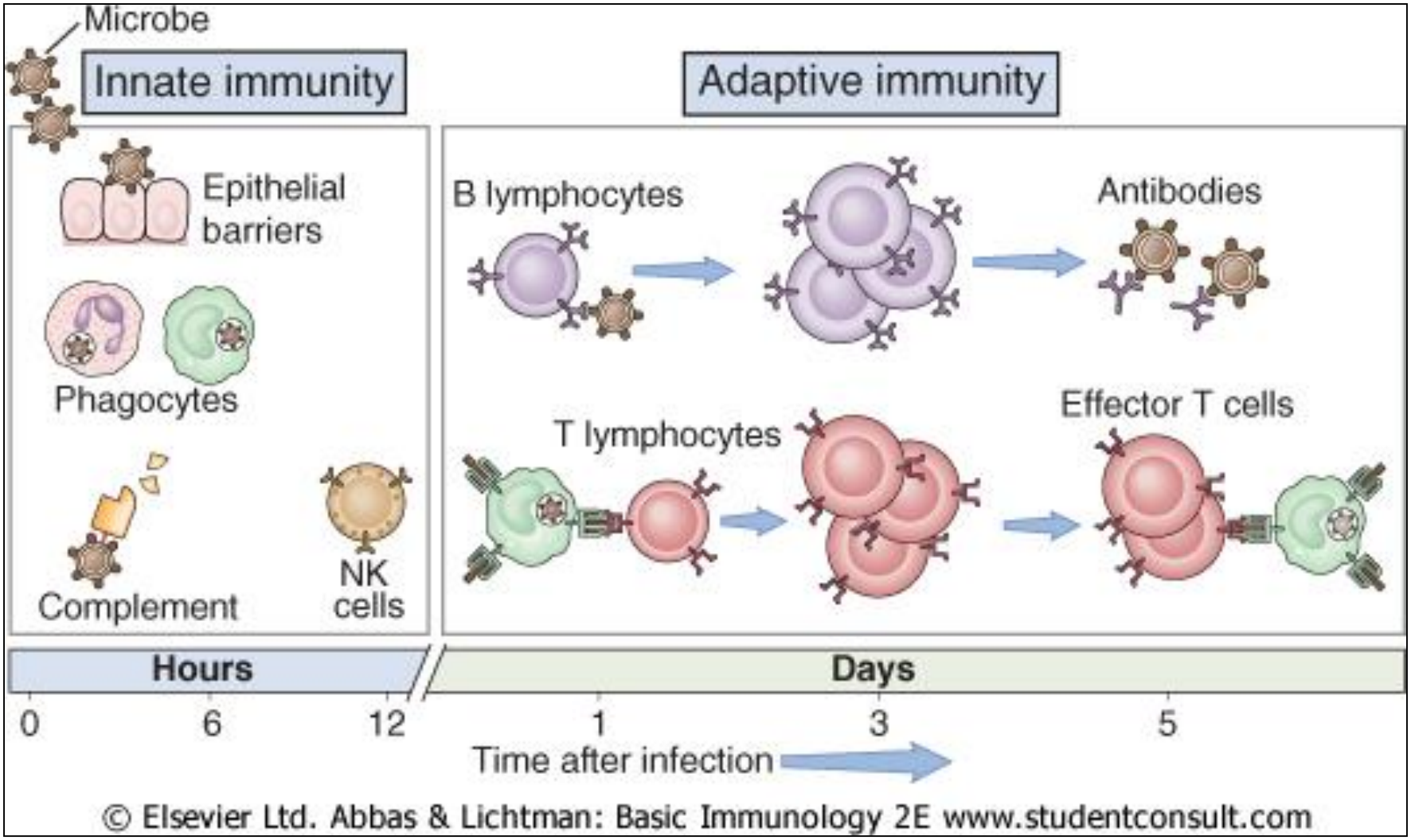
ENERGY
'NIGHT-TIME' COOLING BY DAY
New materials enable radiative cooling in sunlight
PAGE 540
NATURE.COM/NATURE
27 November 2014 £10
Vol. 515, No. 7528

Hallmarks of cancer: The next generation



Hanahan and Weinberg. Cell 2011



So, what immune mediators recognize tumor cells?

Effector mechanisms in established tumors

-**CD8+ T cells** are the only cell type consistently associated with protection against malignant progression in human cancer

- **CD4+ T cells** produce high levels of IFNg and express CD40L, but include tumor-promoting subsets.

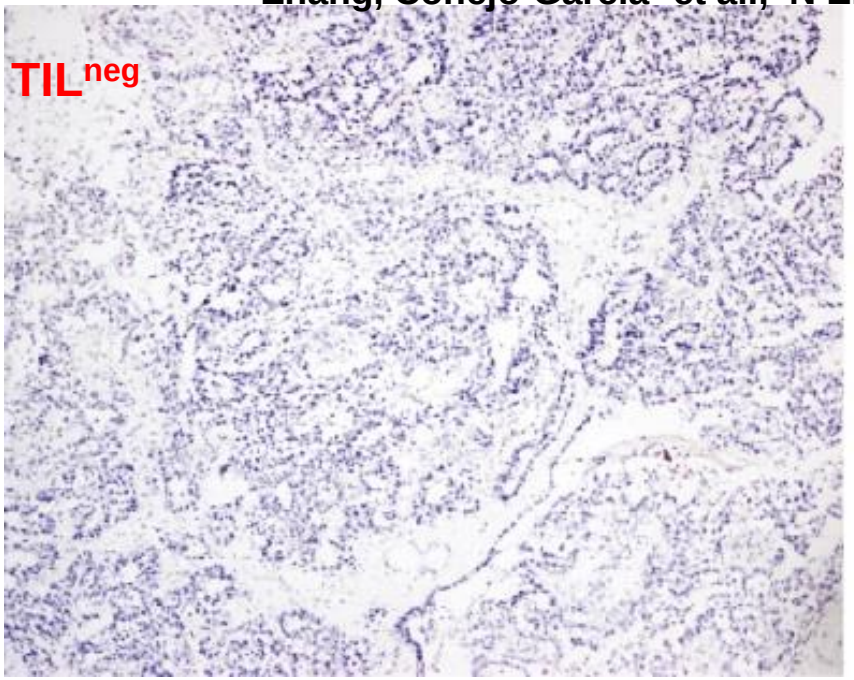
-**NK cells** are important to prevent tumor initiation, but they are not associated with clinically relevant immune pressure in advanced human tumors.

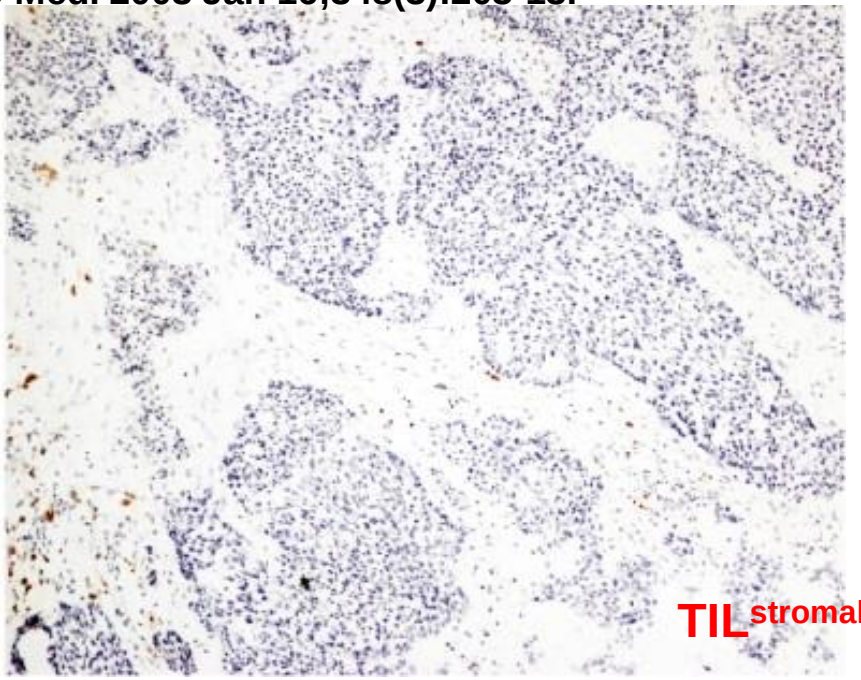
-**Abs** against multiple tumor antigens are universally generated by virtually all tumors, but most of them are completely irrelevant for tumor progression.

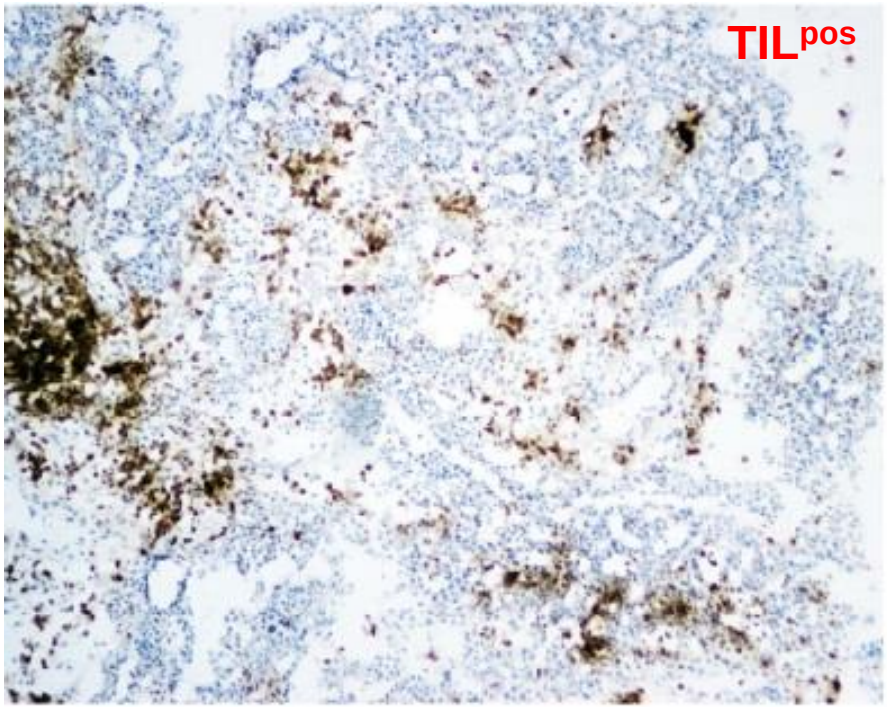
-Other innate lymphocytes? $\gamma\delta$ T cells; NKT cells; MAITs (Vit.B metabolites); ILC1/2/3; Lti)

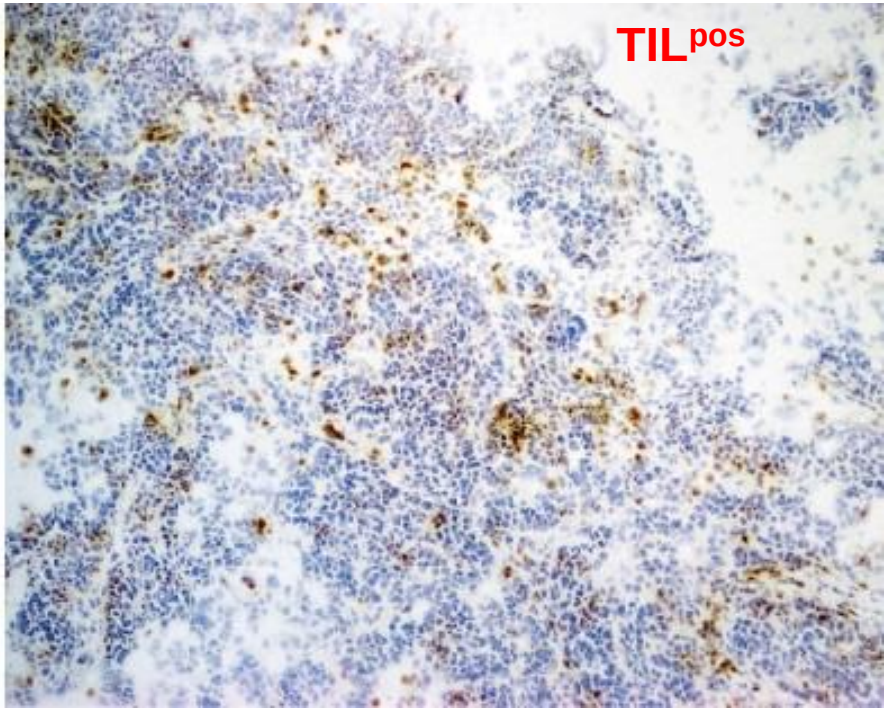
What is the role of protective T cells?

Zhang, Conejo-Garcia* et al., N Engl J Med. 2003 Jan 16;348(3):203-13.

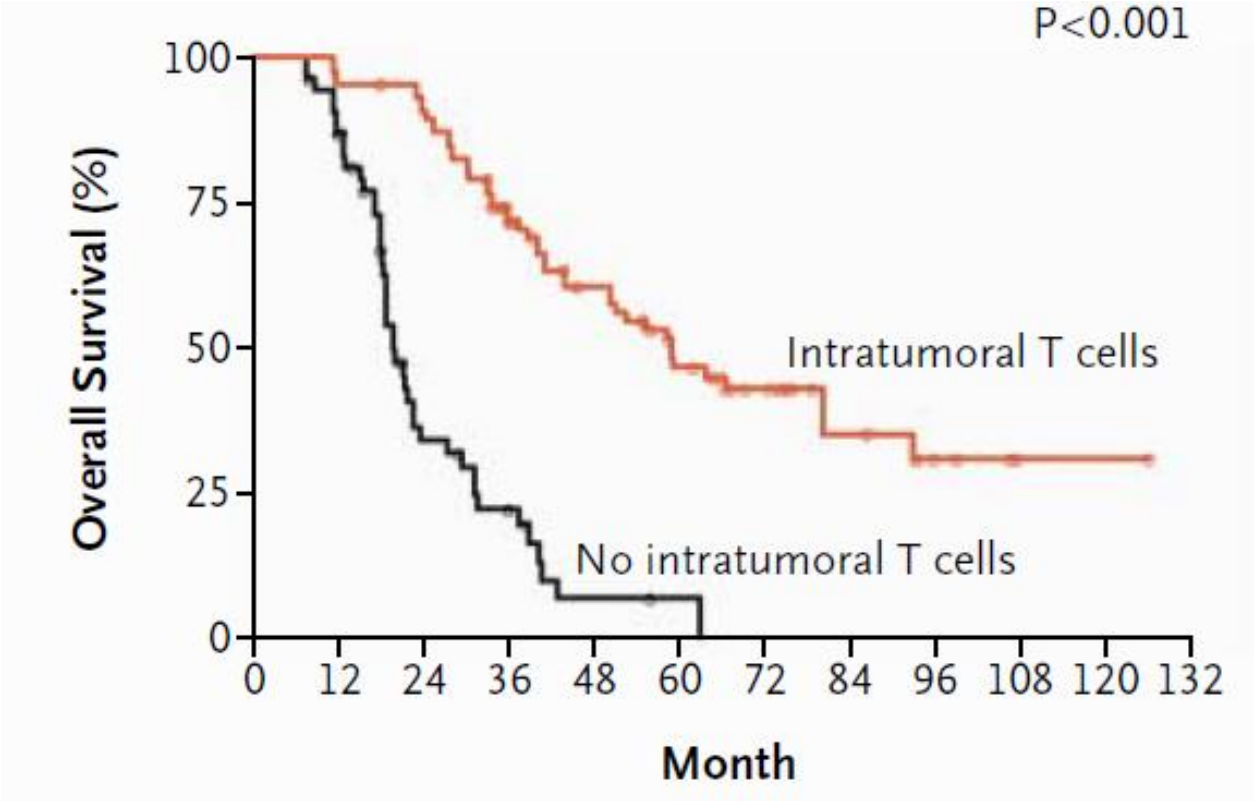






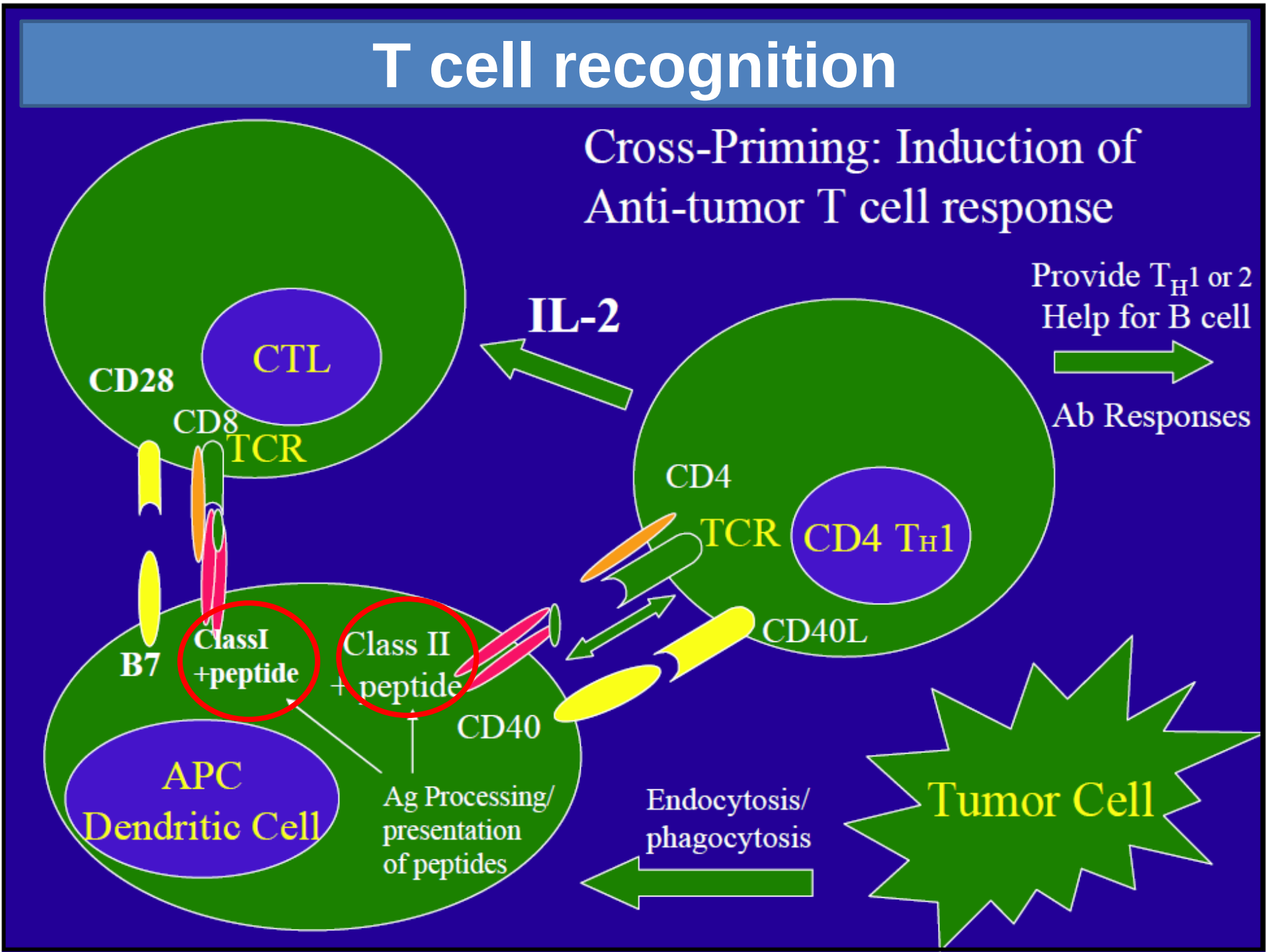


The pattern of T cell infiltration determines the survival of ovarian cancer patients



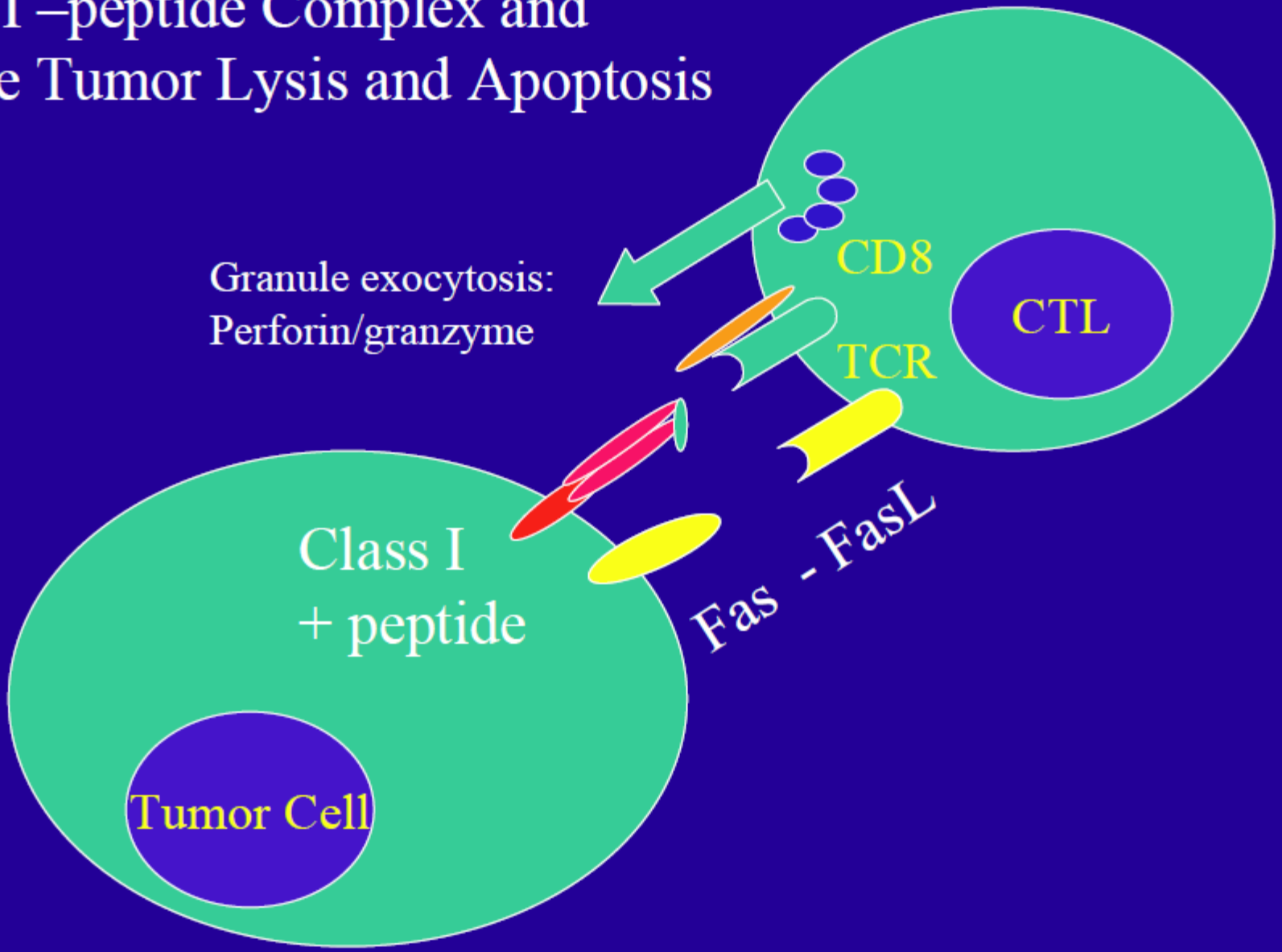
Zhang, Conejo-Garcia* et al., N Engl J Med. 2003 Jan 16;348(3):203-13.

T cell recognition



Cytotoxic (CD8) T cell effector mechanisms

CD8 CTL Can Recognize
Class I –peptide Complex and
Induce Tumor Lysis and Apoptosis



What tumor antigens are recognized by T cells?

Why aren’t tumor cells ignored as “self” by T lymphocytes?

Tumor T cell antigens (There are some tumor unique Ags).

-Tumor Antigens Produced by Oncogenic Viruses (e.g., HPV)

-Products of Mutated Genes: e.g., **mutations** in oncogenes or suppressor genes (e.g., p53). Probably the most effective:

+Mutations in driving *vs.* passenger genes matter.

+Affinity of neo-antigen matters.

+2 kinds of tumors: High rate of missense mutations (e.g., colorectal) vs. high rate of chromosomal deletions, amplifications and re-arrangements (e.g., ovarian)

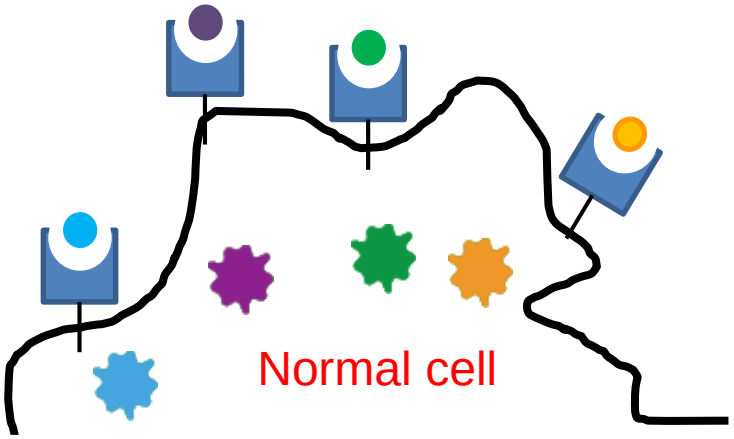
-Altered Cell Surface Glycolipids and Glycoproteins (e.g., MUC1) induce humoral responses (aberrant glycosylation patterns in tumor cells).

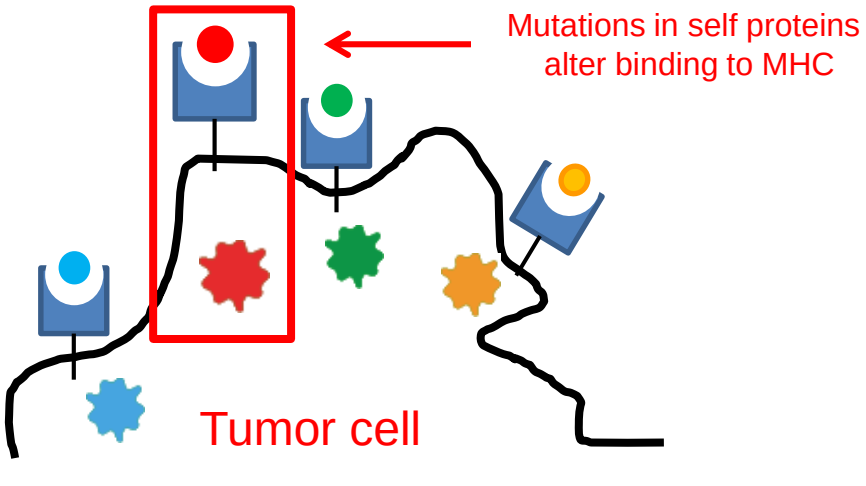
-Endogenous retroviral sequences re-expressed in cancer cells (e.g., OvCar)

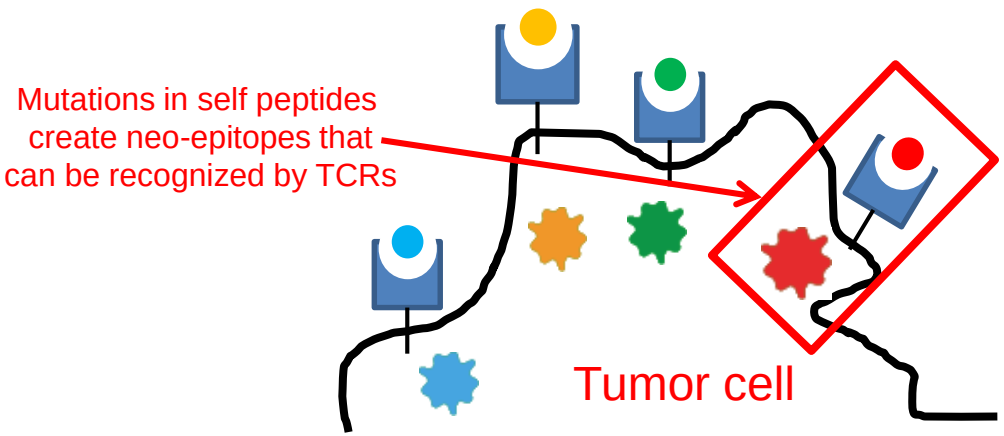
-Oncofetal Antigens (e.g., NY-ESO-1).

-Cell Type-Specific Differentiation Antigens that break tolerance (e.g., tyrosinase in melanoma).

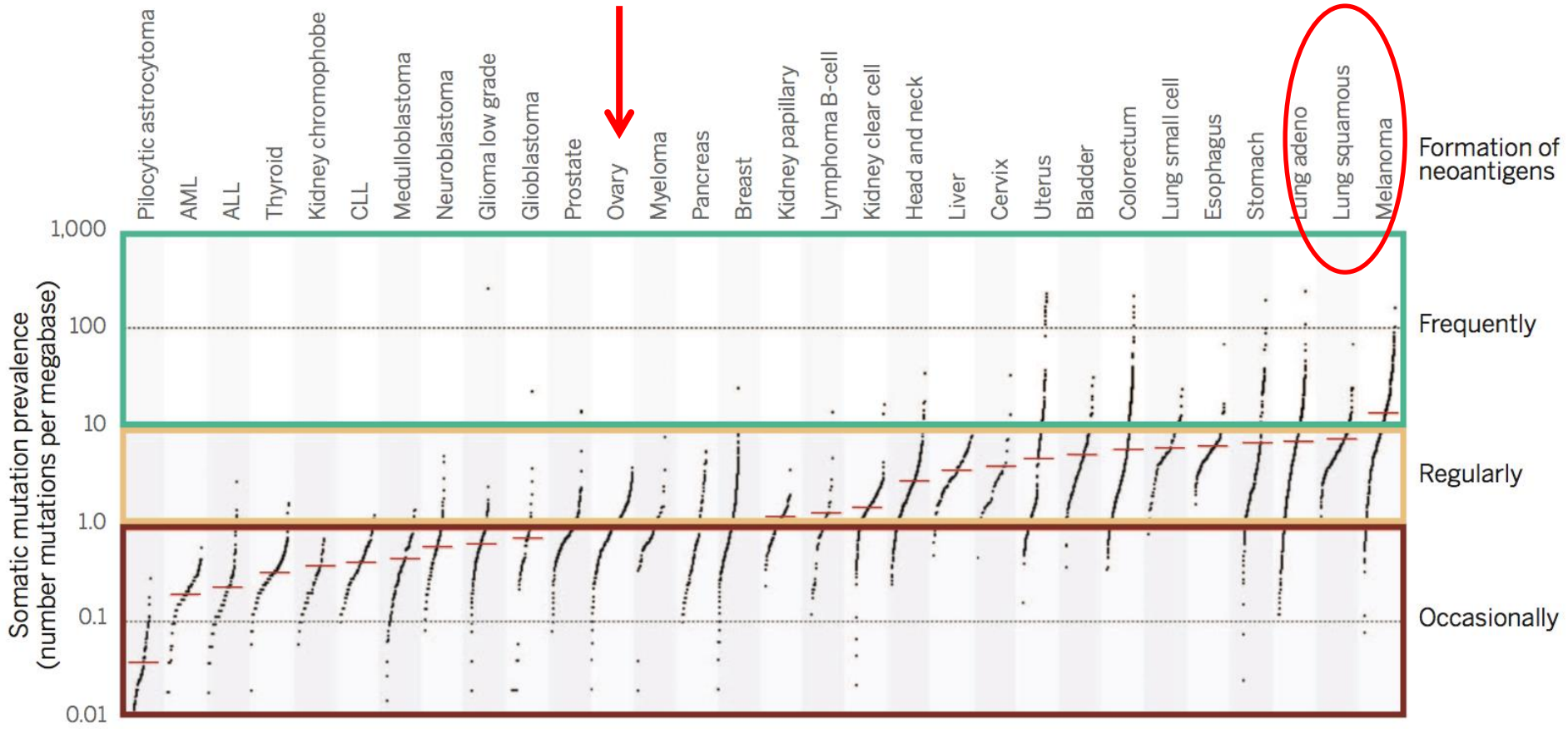
-Proteins overexpressed by tumor cells that break tolerance (e.g., MART-1 in melanoma, mesothelin in ovarian cancer, Her2/neu). Probably the most abundant but: 1) weak; 2) not tumor-specific.


Normal cell


Mutations in self proteins
alter binding to MHC
Tumor cell


Mutations in self peptides
create neo-epitopes that
can be recognized by TCRs
Tumor cell

Mutated tumor neo-antigens take the spotlight (again)



Why some tumors are immunogenic and others are not?

Emerging PD1/CTLA4 inhibitors work, but only in 1/3 of patients.

Not all tumors contain TILs

-Intrinsic antigenicity of different tumors.

OK, then, why TIL-containing tumors progress anyway?

-We only detect failures of the immune system, which become clinically relevant.

-**Tumors get immunoedited**.

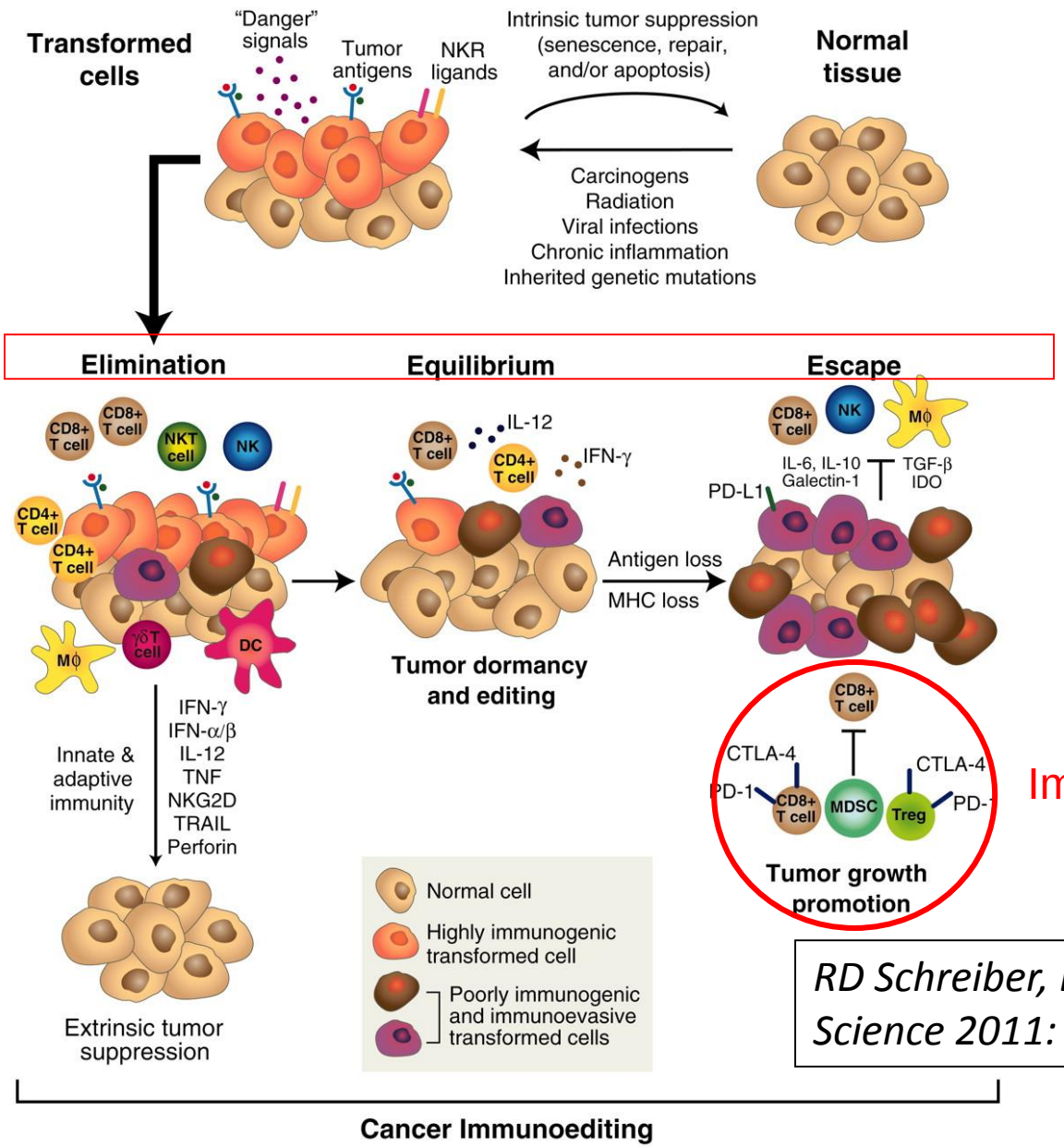
-Antigen presentation could be severely impaired in tumor-bearing hosts.

-Tumors typically occur in old people, who have altered immune responses.

-T cells get exhausted, senescent or simply hyporesponsive after chronic antigen exposure.

-**Multiple mechanisms of immunosuppression operate in the TME**.

The cancer immunoediting framework



Immunosuppression

RD Schreiber, LJ Old & MJ Smyth. Science 2011: Vol. 331, 1565-1570

Intrinsic mechanisms of T cell unresponsiveness in the TME

Anergy:

- Initiated at the time of priming
- Upregulation of Rnf128, Egr2, Egr3, excessive NFAT, decreased Ras activation
- Maintenance is Ag independent
- Reversible with cytokines

Exhaustion:

- Progressive weakening of effector activity; PD1, Tim3, CTLA4; LAG3
- Upregulation of Blimp1 and T-bet or EOMES (mutually exclusibe), excessive NFAT, decreased AP1
- Maintenance depends on suboptimal Ag persistance/TCR signaling
- Reversible by blocking inhibitory pathways in PD-1^{int}(not in $PD1^{high}$) T cells
- Reversible with cytokines

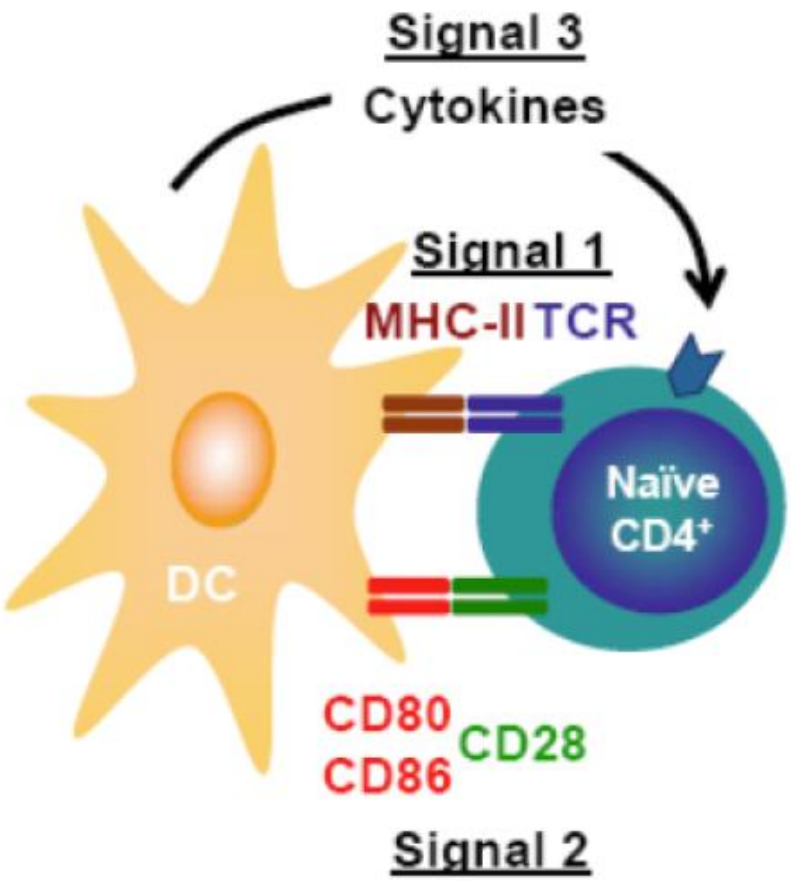
Senescence:

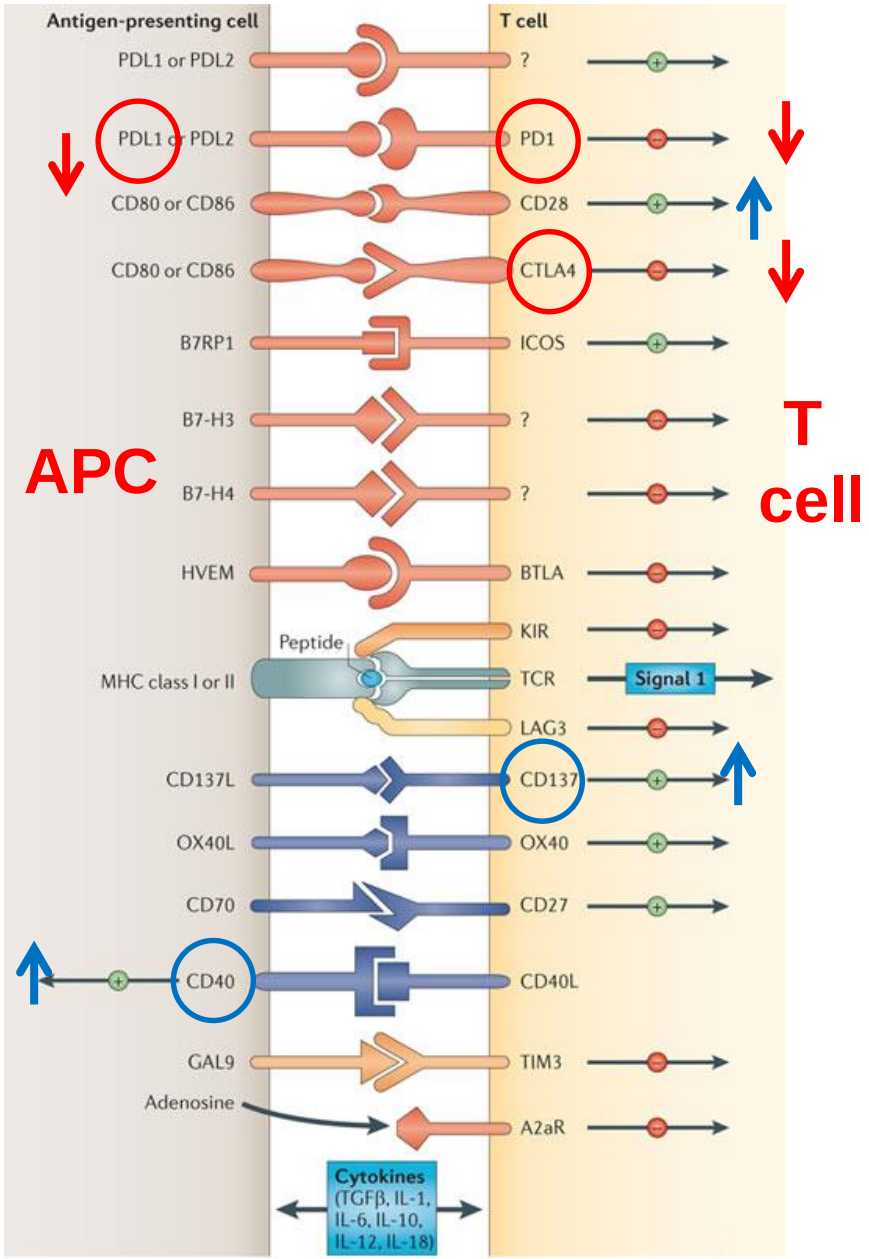
- Typically irreversible, shortened telomers.

Foxp1-dependent quiescence:

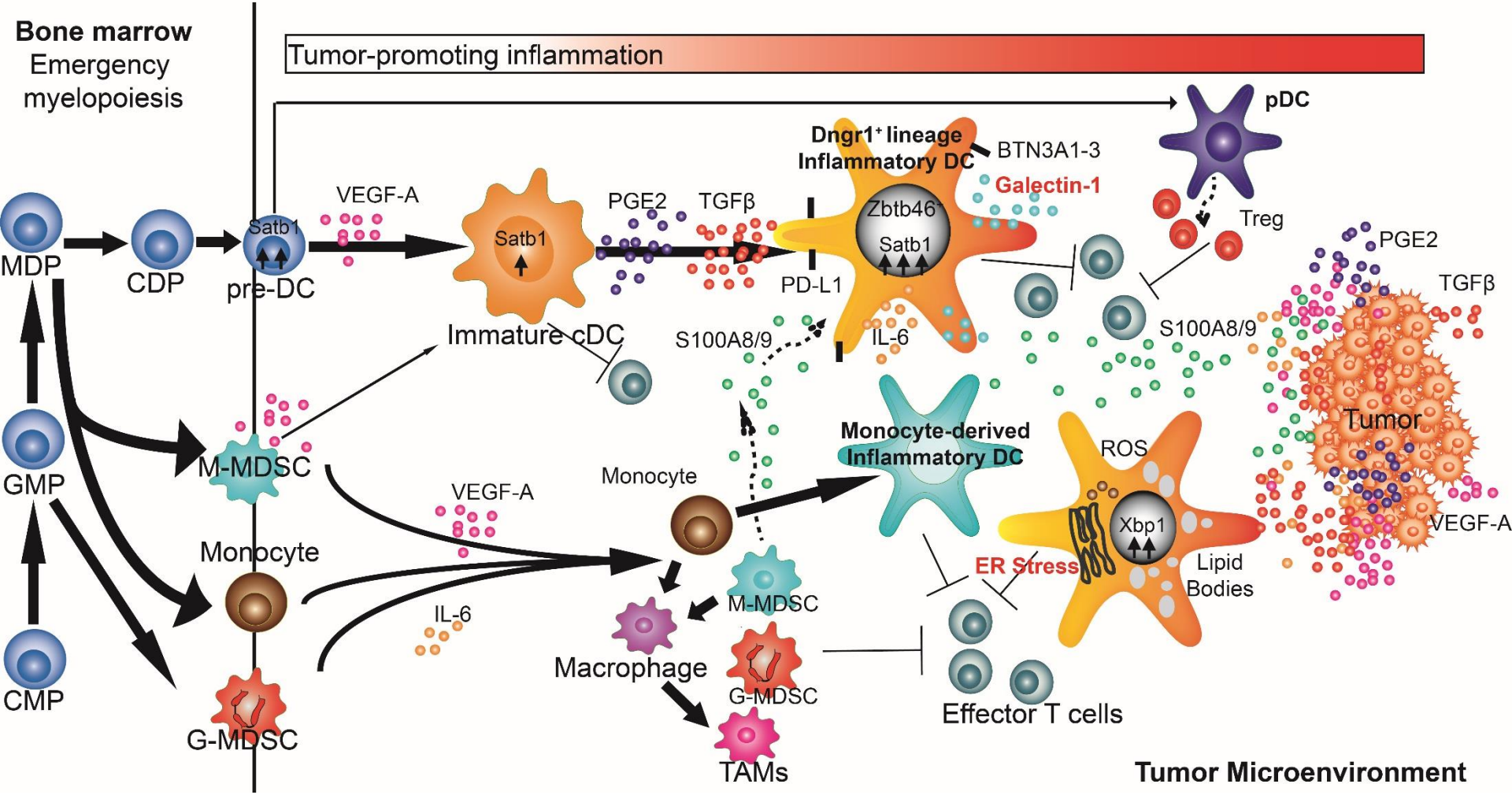
- TGFbeta-mediated suppression is Foxp1-dependent.
- Foxp1 drives additional mechanisms of T cell paralysis specifically in TILs

Immunological checkpoints





De-regulated myelopoiesisresults in the expansion of MDSCs, macrophages and inflammatory DCs that suppress anti-tumor immunity



Conejo-Garcia et al., Pharmacology & Therapeutics 2016 (review)

CONCLUSIONS

-Tumors are recognized by the immune system.

-However, we only detect those tumors that emerge after having overcome immune surveillance.

-**Tumor antigens induce weaker responses** than microbial antigens due to the nature of tumor Ags and because tumors evolve to reduce tumor antigen presentation. However, **mutated neo-antigens** are specific and relatively strong antigens.

-Local and systemic immunoregulatory factors impair or abrogate T cell activity. Understanding immunosuppression is critical.

-The goal of immunotherapy is to boost protective immunity, though passive immunization (antitumor antibodies, adoptive T cell therapy); vaccines; or blocking regulatory negative pathways.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THE AREA AHEAD HAS THE WORST WEATHER IN AMERICA.
MANY HAVE DIED THERE FROM EXPOSURE EVEN IN THE
SUMMER. TURN BACK NOW IF THE WEATHER IS BAD.
WHITE MOUNTAIN NATIONAL FOREST
Welcome to the
ALPINE ZONE
ENJOY the fragile beauty.
BE a caring steward.
STAY on the trail or walk on bare rocks.
CAMP below timberline or
on snowpack at least two feet deep,
except in restricted use areas.
COOK on a stove.
HELP preserve the delicate balance of
the Alpine Zone.
It's a tough place to grow.