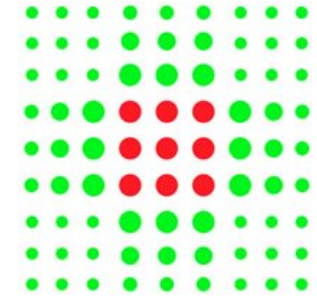




# PROGETTO EMATOLOGIA ROMAGNA

Rimini, 8 aprile 2017

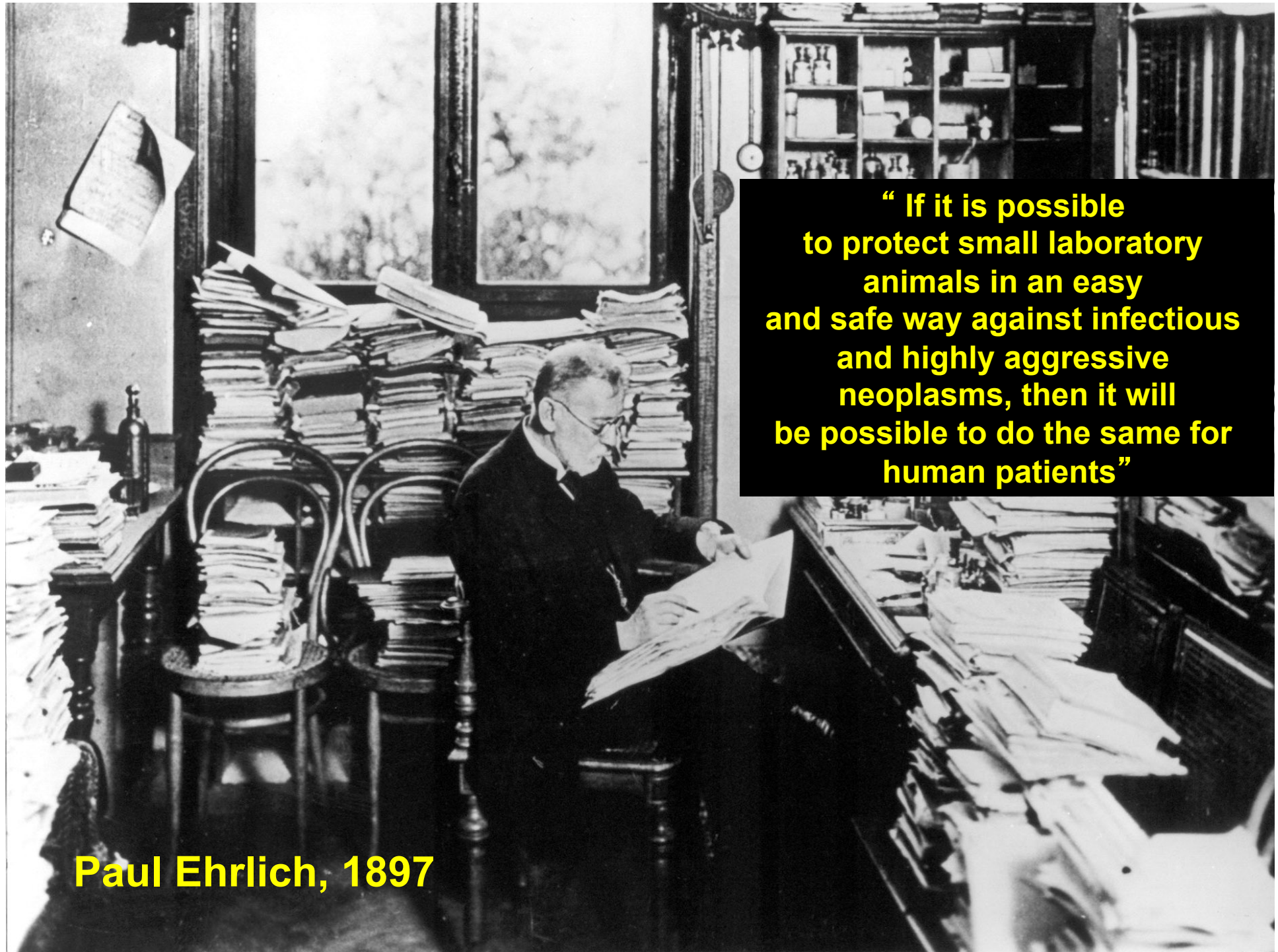


## Immunologia e tumori introduzione

**Antonio Curti**

Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale  
Istituto di Ematologia "L. e A. Seràgnoli", Università degli Studi di Bologna

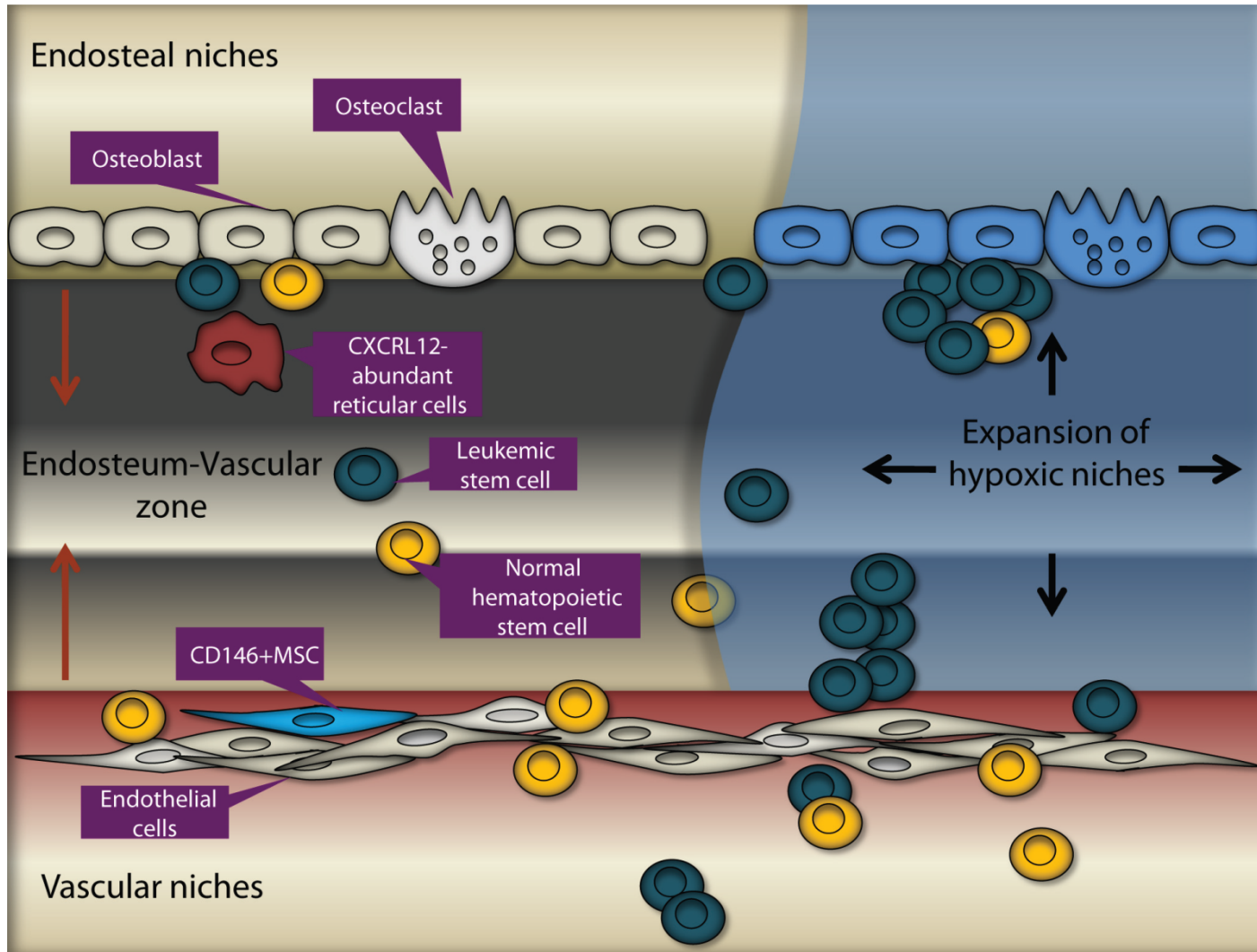




**“ If it is possible to protect small laboratory animals in an easy and safe way against infectious and highly aggressive neoplasms, then it will be possible to do the same for human patients”**

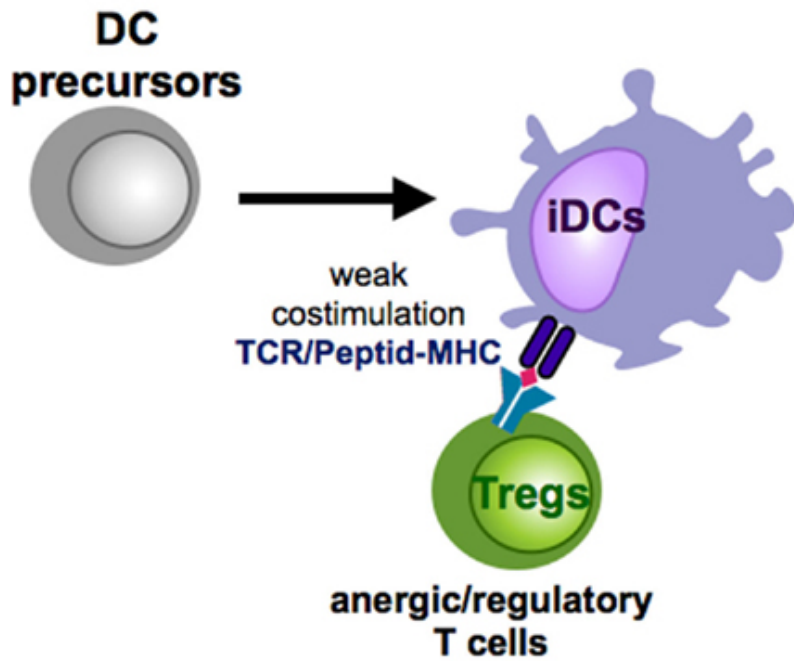
**Paul Ehrlich, 1897**

# Leukemia Stem Cells and Microenvironment: Biology and Therapeutic Targeting

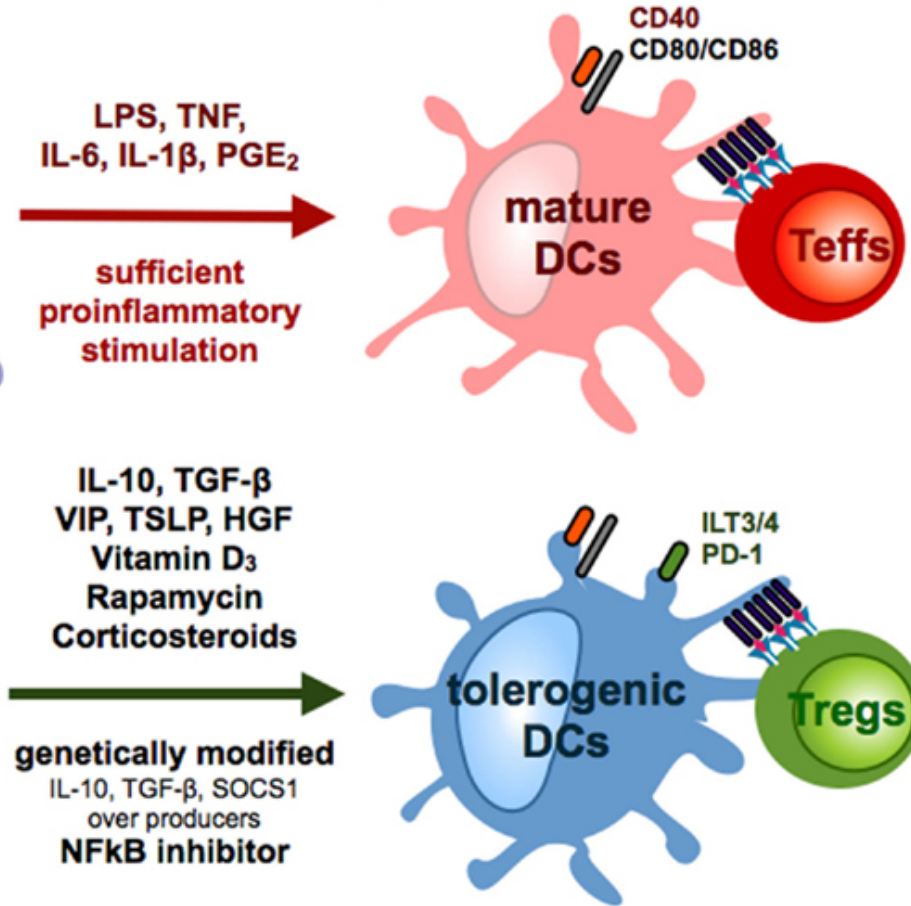


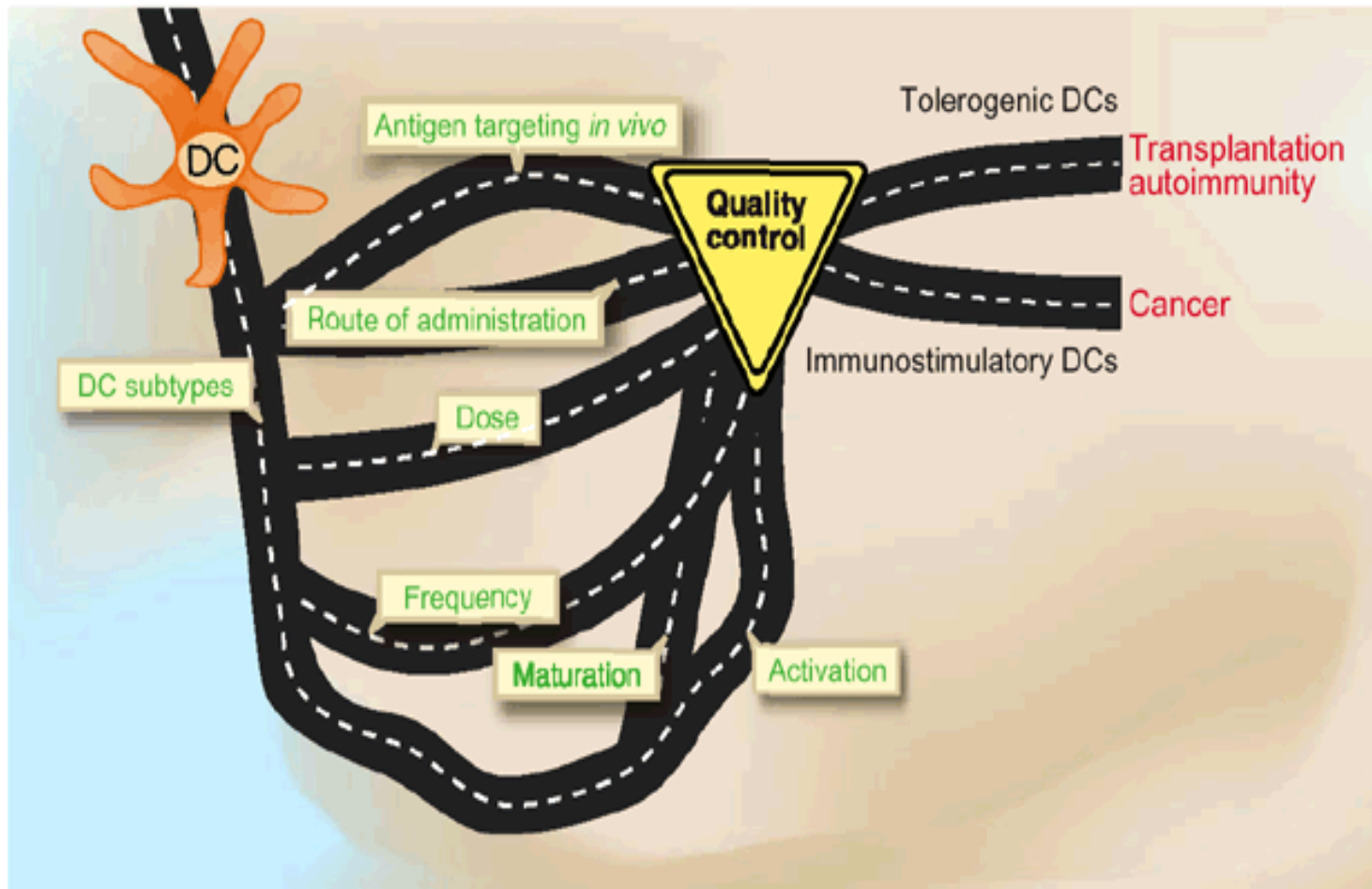
*J Clin Oncol 29:591-599. 2011*

differentiation



type of maturation





## Dendritic cell immunotherapy: mapping the way (Melief C. et al., Nat Med., 2004)

Early clinical trials clearly show the potency of DC therapy, but there are still important questions to be solved before its introduction as a standard cancer treatment.

# Beyond Self vs Non-Self: the Danger Model

*Annu. Rev. Immunol.* 1994. 12:991–1045

## TOLERANCE, DANGER, AND THE EXTENDED FAMILY\*

*Polly Matzinger*

Laboratory of Cellular and Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 10, Room 111, Bethesda, Maryland 20892

KEY WORDS: antigen presentation, immunity, T cells, dendritic cells, viruses

### Abstract

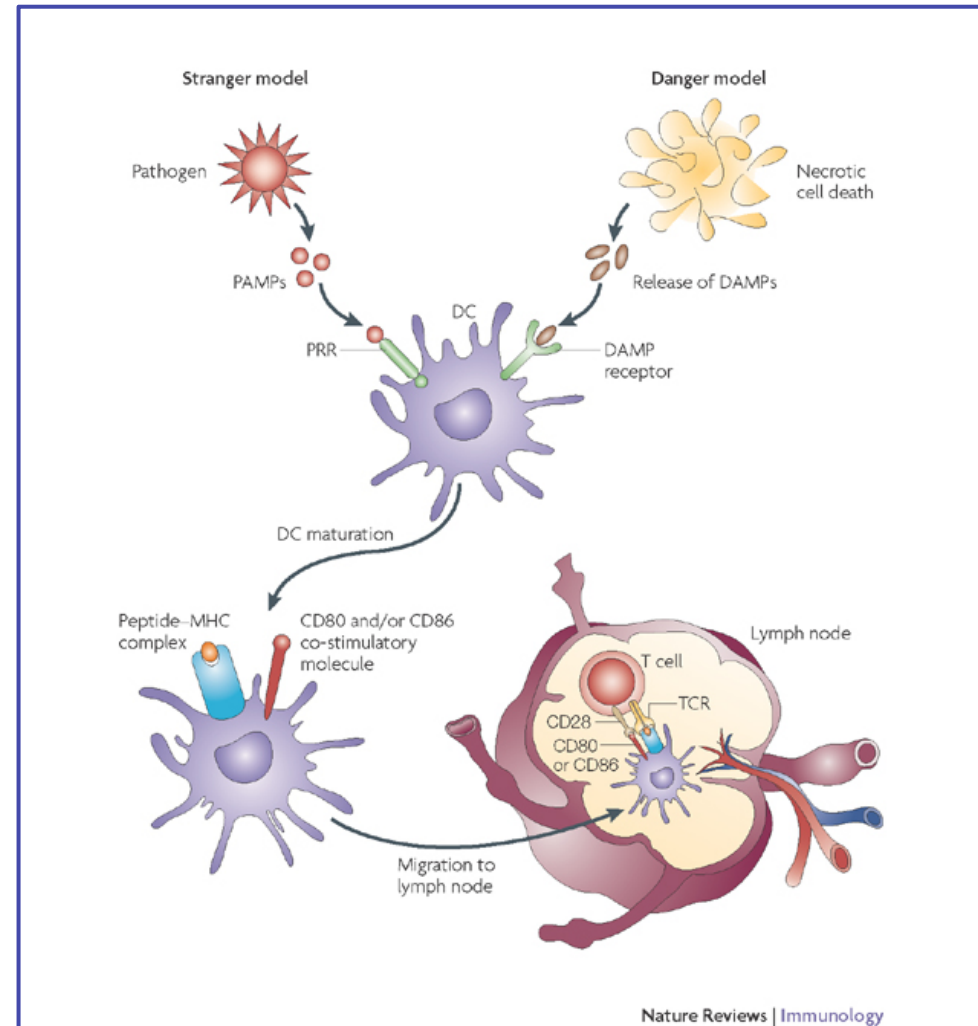
For many years immunologists have been well served by the viewpoint that the immune system's primary goal is to discriminate between self and non-self. I believe that it is time to change viewpoints and, in this essay, I discuss the possibility that the immune system does not care about self and non-self, that its primary driving force is the need to detect and protect against danger, and that it does not do the job alone, but receives positive and negative communications from an extended network of other bodily tissues.

### INTRODUCTION

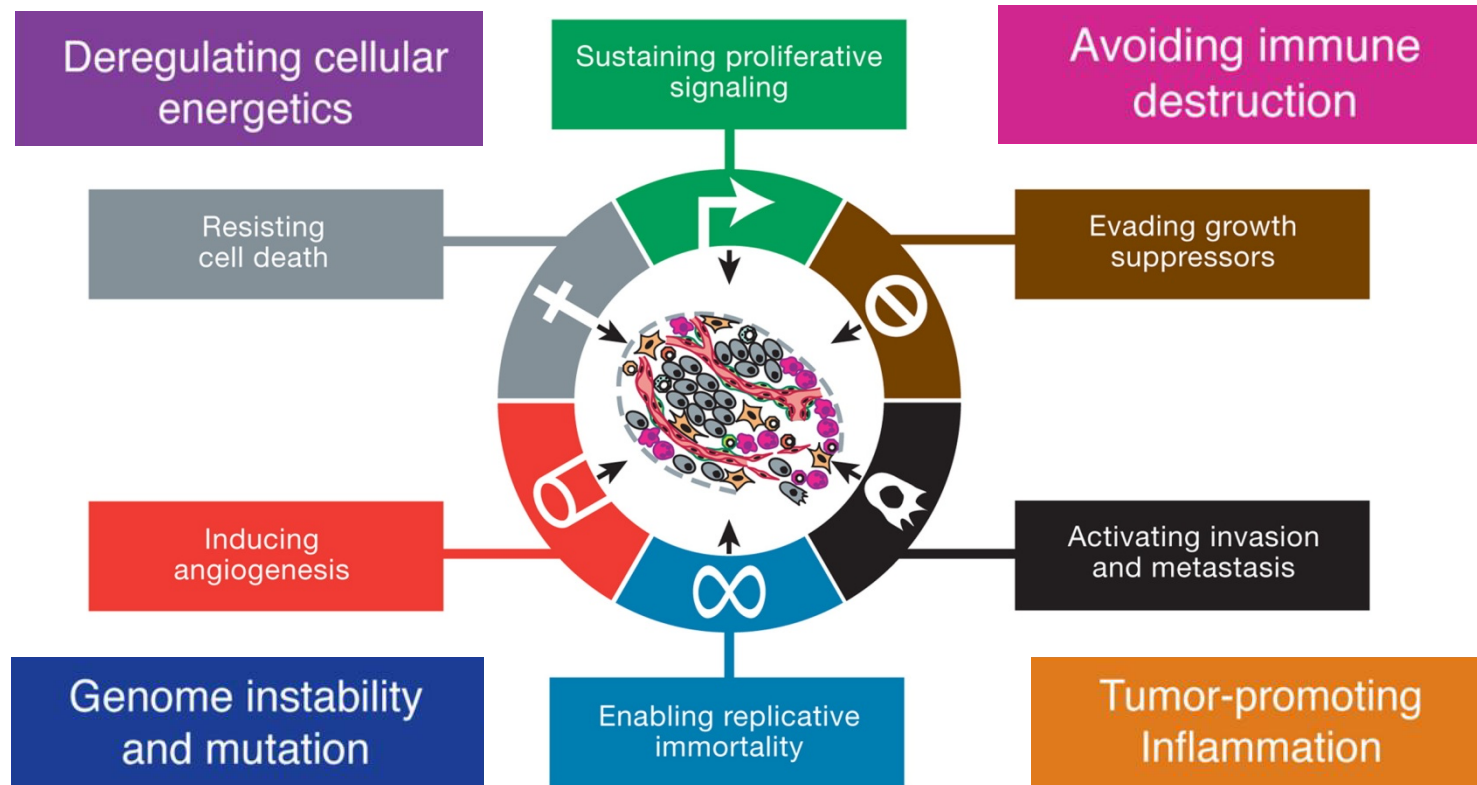
Among the fundamental questions in immunology, there are three that lie at the heart of the regulation of immunity. They are: 1) How is self-tolerance induced and maintained? 2) How is memory induced and maintained? and 3) How is the class of response determined? This essay is about the first one, tolerance (actually T cell tolerance), but it is also about something deeper, something that affects the way we think about every aspect of immunity. It is about the belief that the immune system's primary driving force is the need to discriminate between self and non-self. I have abandoned this belief.

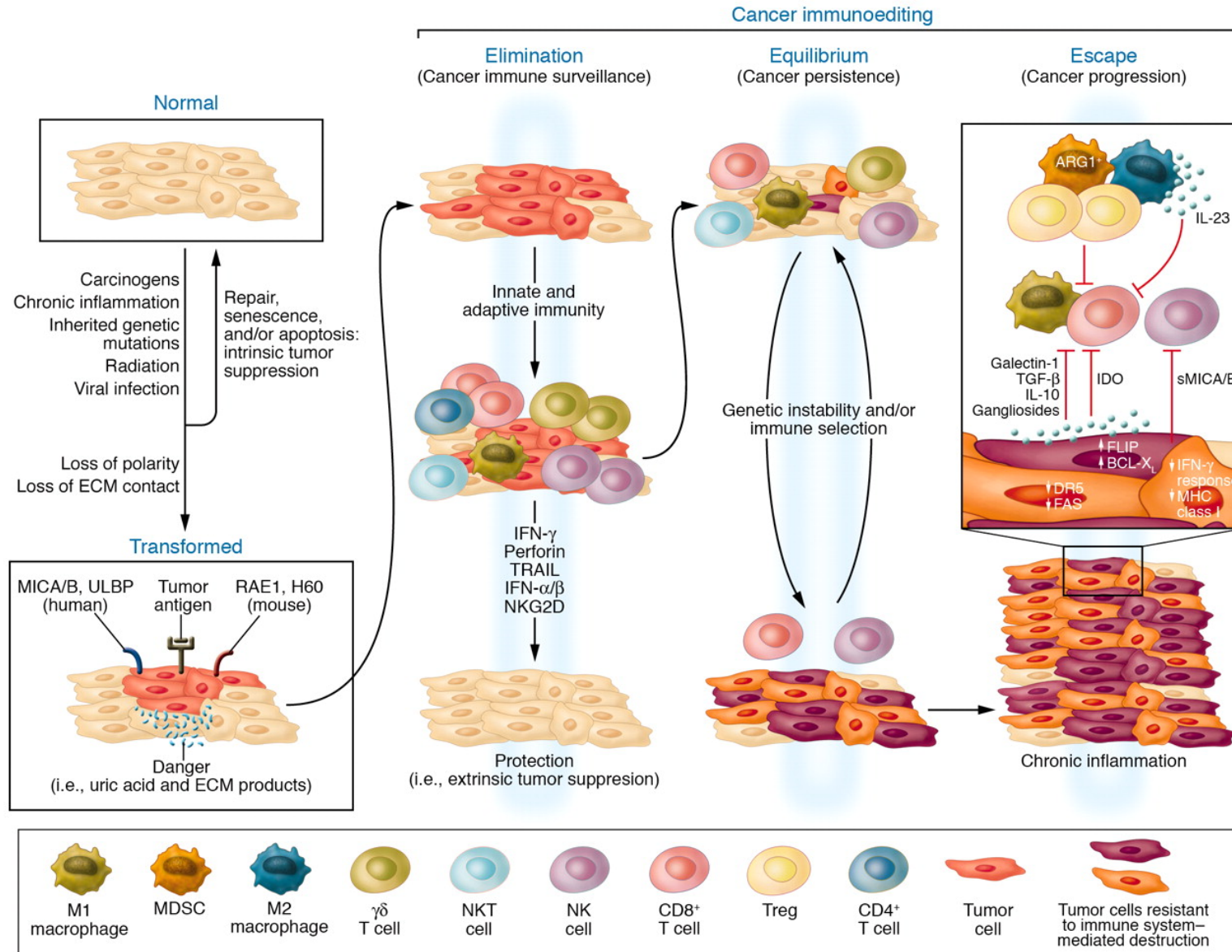
Over the years that I have been trying to understand immunological tolerance, I have been intrigued, mystified, and dissatisfied by a range of

\*The US government has the right to retain a nonexclusive, royalty-free license in and to any copyright covering this paper.



# Emerging Hallmarks of Cancer

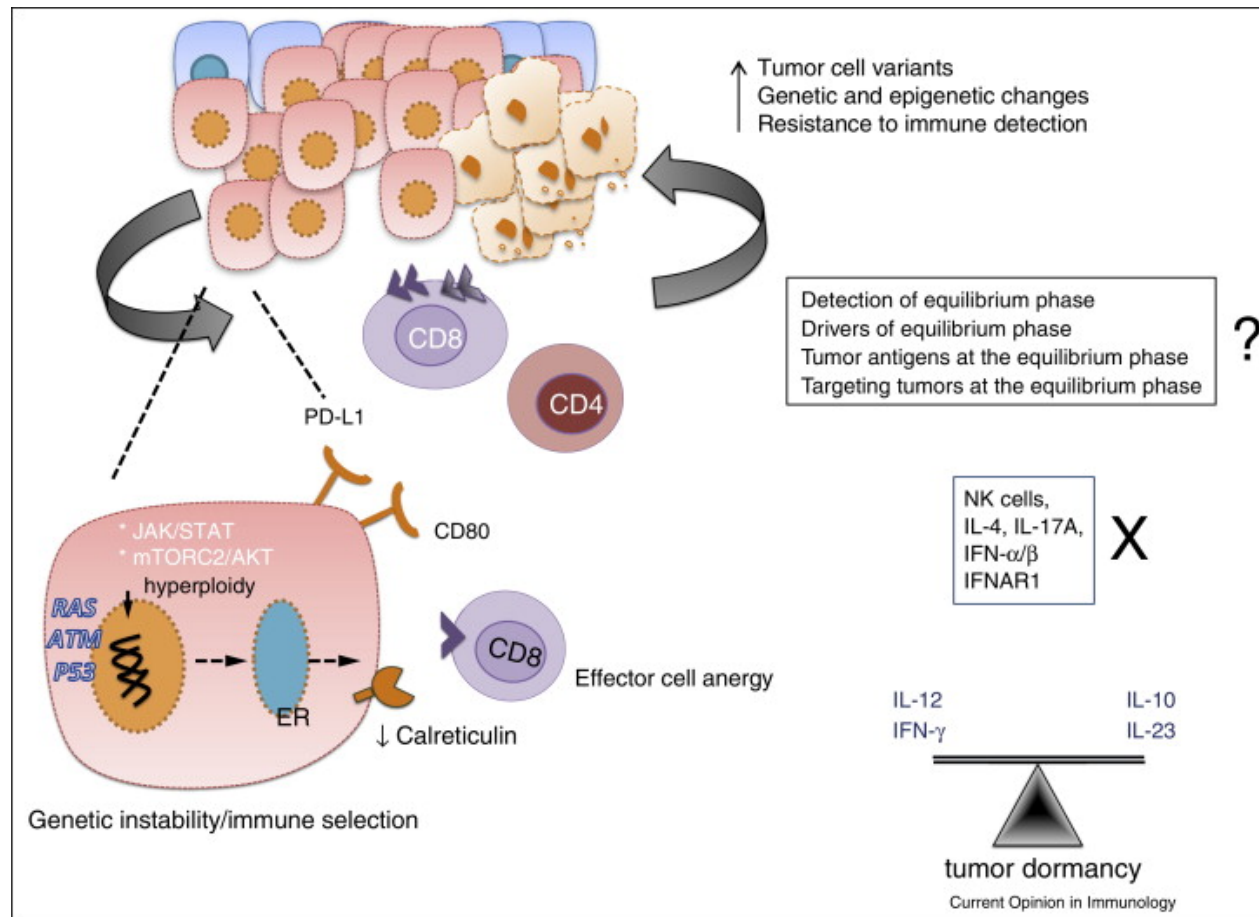




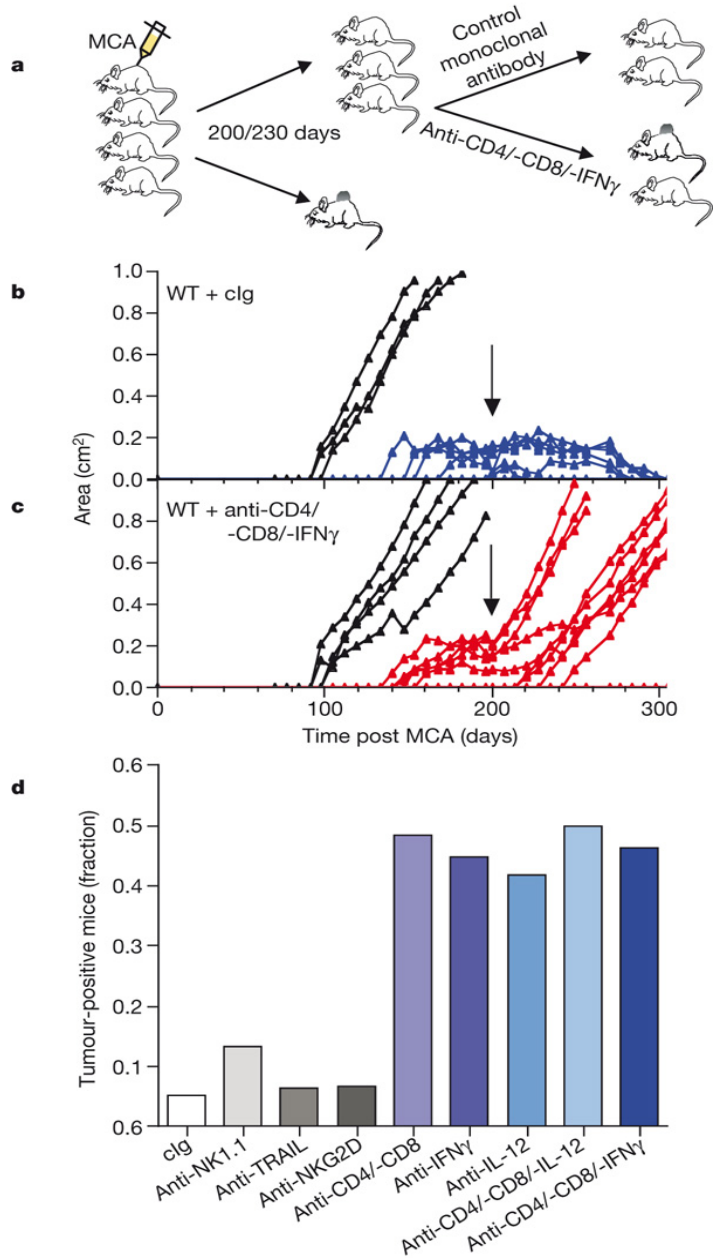
Swann and Smyth *J. Clin. Invest.* **117**:1137-1146 (2007)



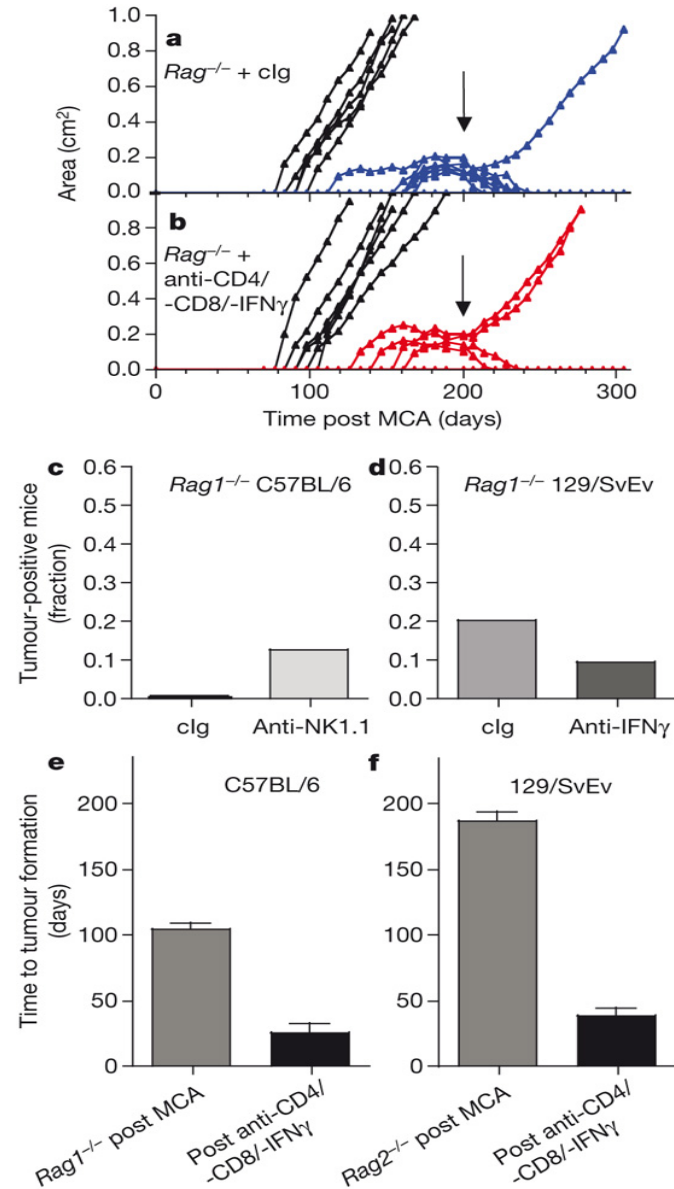
# Cancer immunoediting: Equilibrium



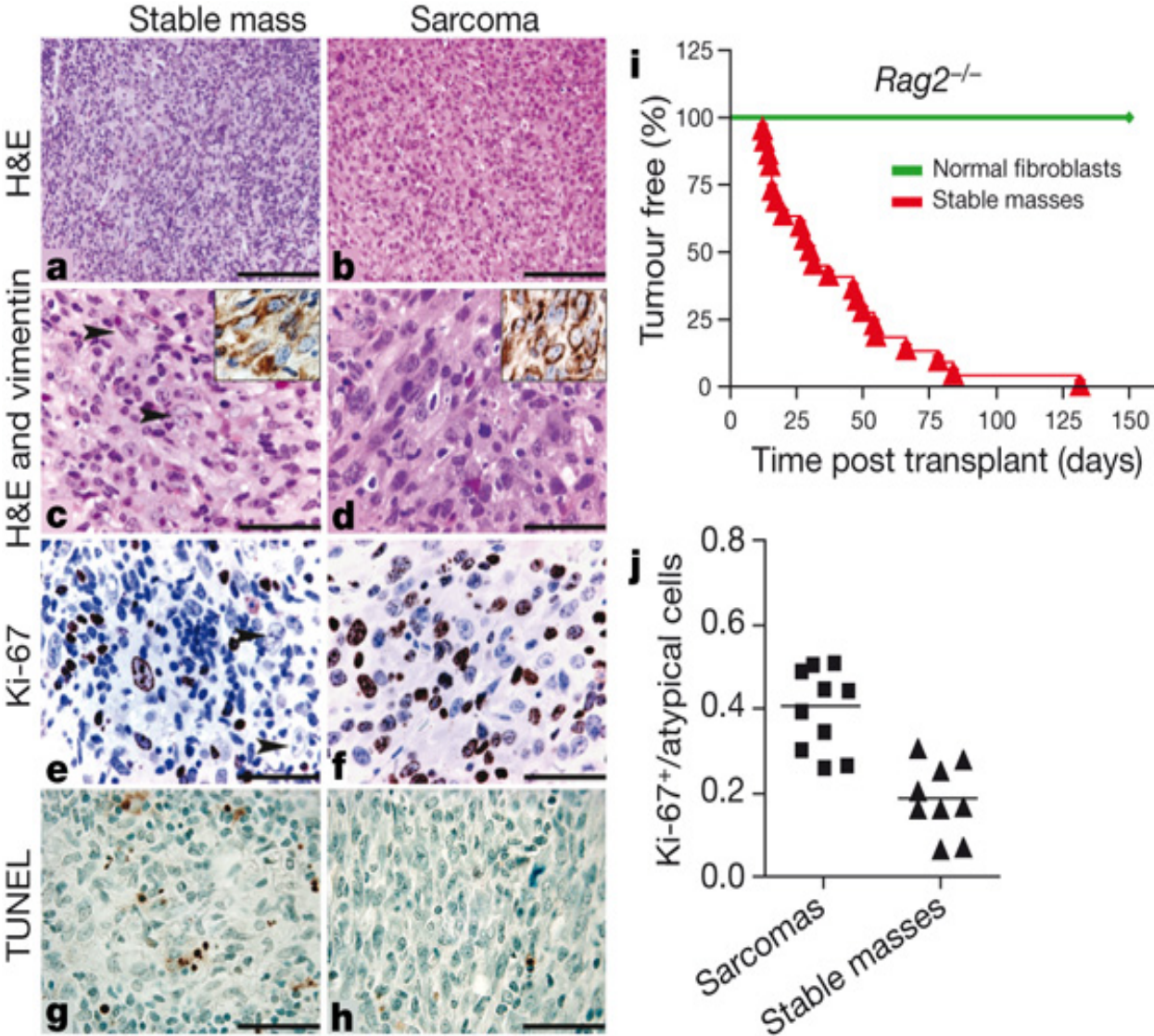
# The adaptive immune system promotes an equilibrium state in primary MCA-induced sarcomas.



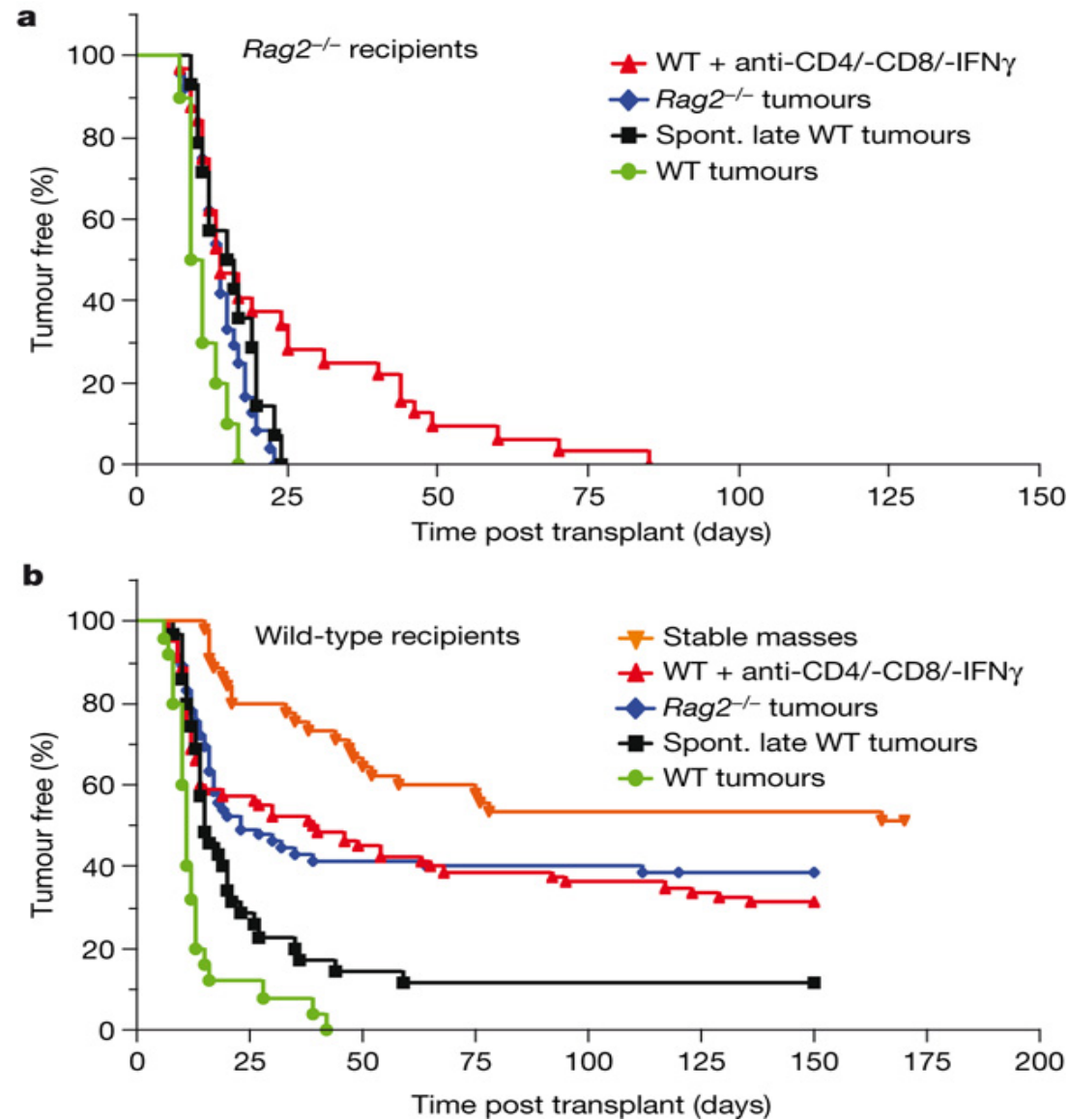
# Antibody-induced equilibrium disruption does not occur as a result of prolonged *de novo* transformation



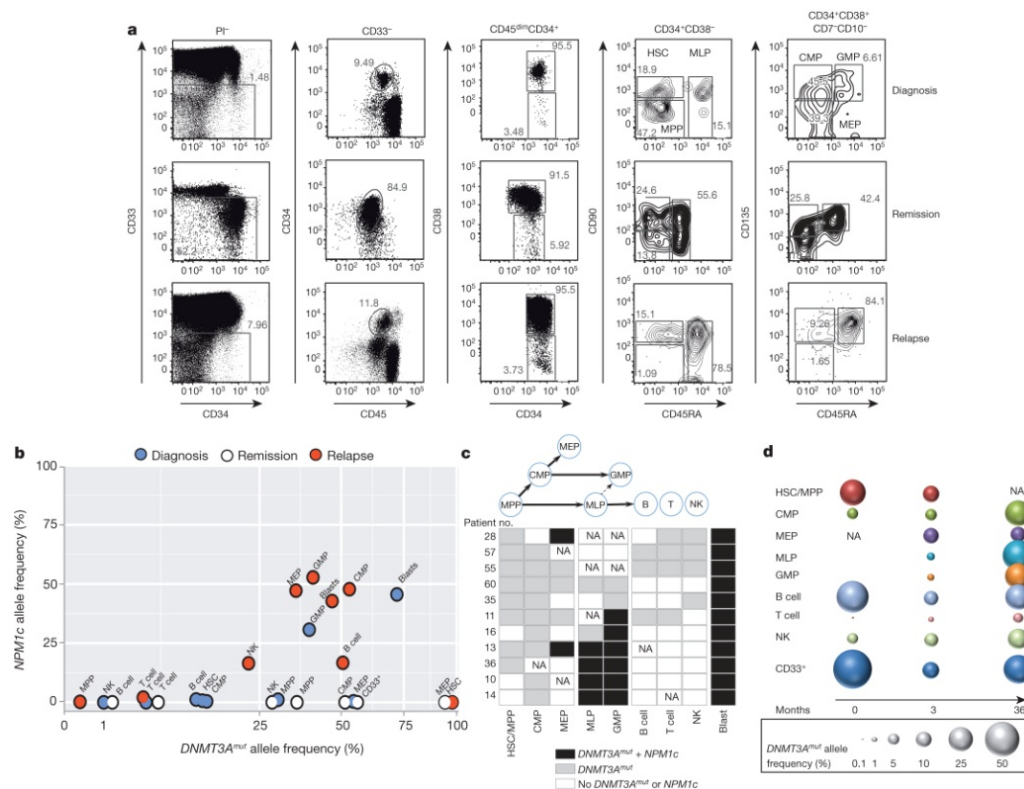
# Demonstration of occult cancer in immunocompetent mice in the equilibrium phase of cancer immunoediting



# Sarcoma cells in equilibrium show high immunogenicity, whereas those spontaneously exiting equilibrium have attenuated immunogenicity



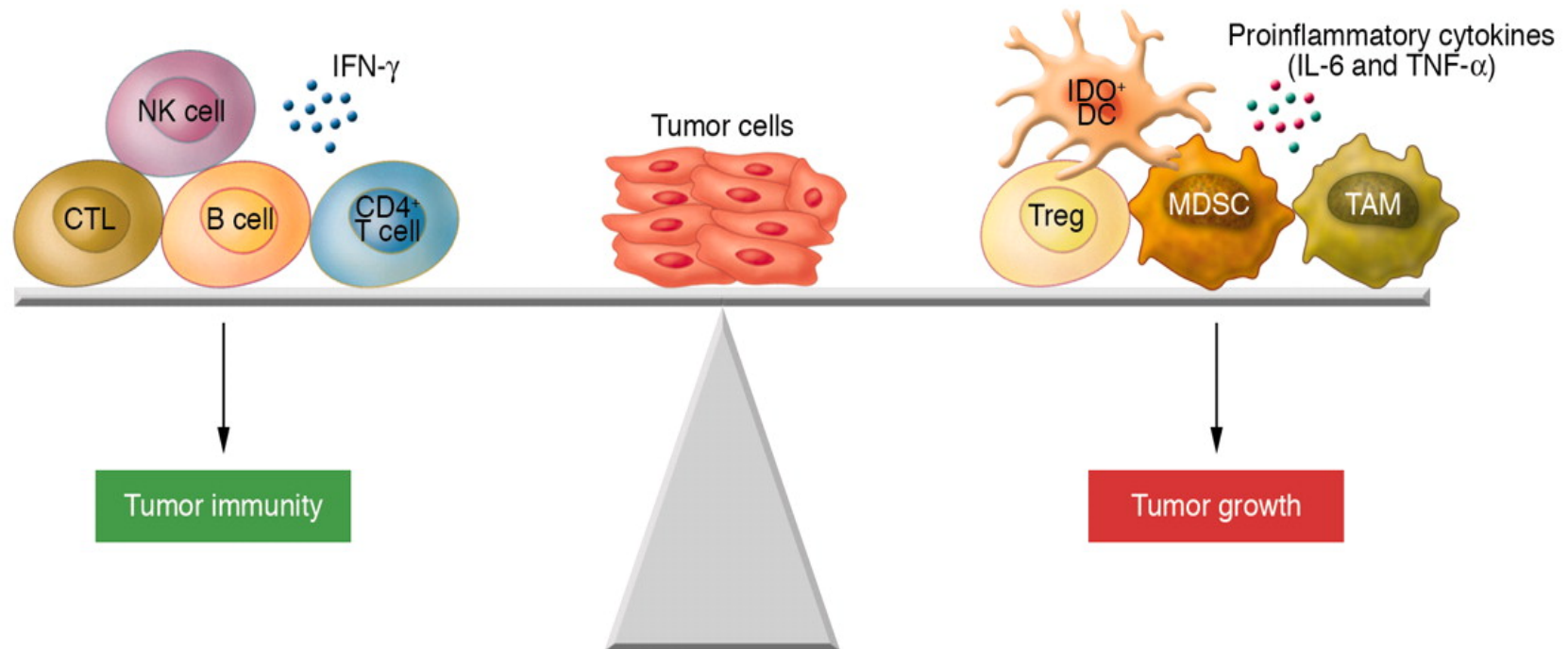
*DNMT3A* mutation precedes *NPM1* mutation in human AML and is present in stem/progenitor cells at diagnosis and remission.



LI Shlush *et al. Nature* **000**, 1-6 (2014) doi:10.1038/nature13038

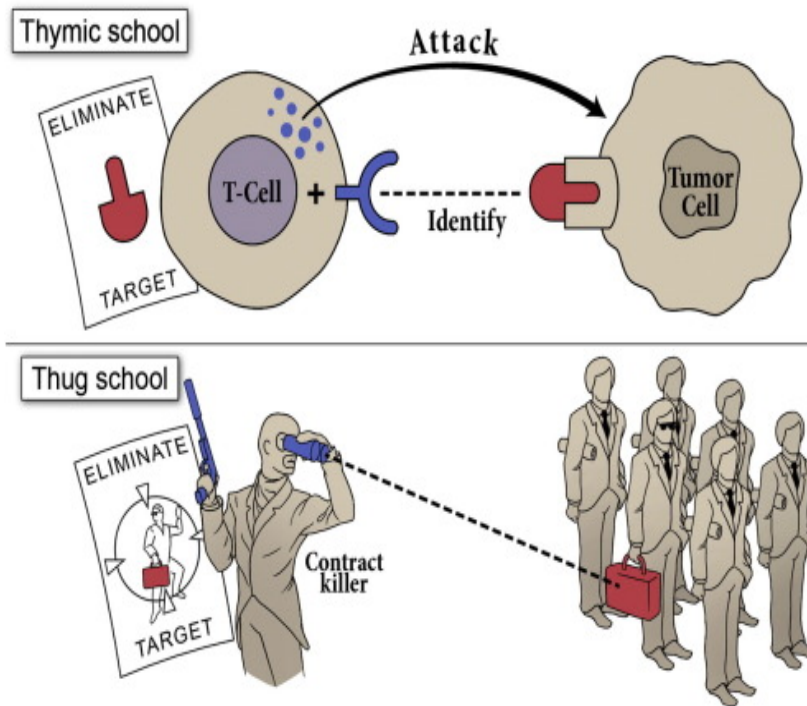
nature

# How to harness the immune system against cancer



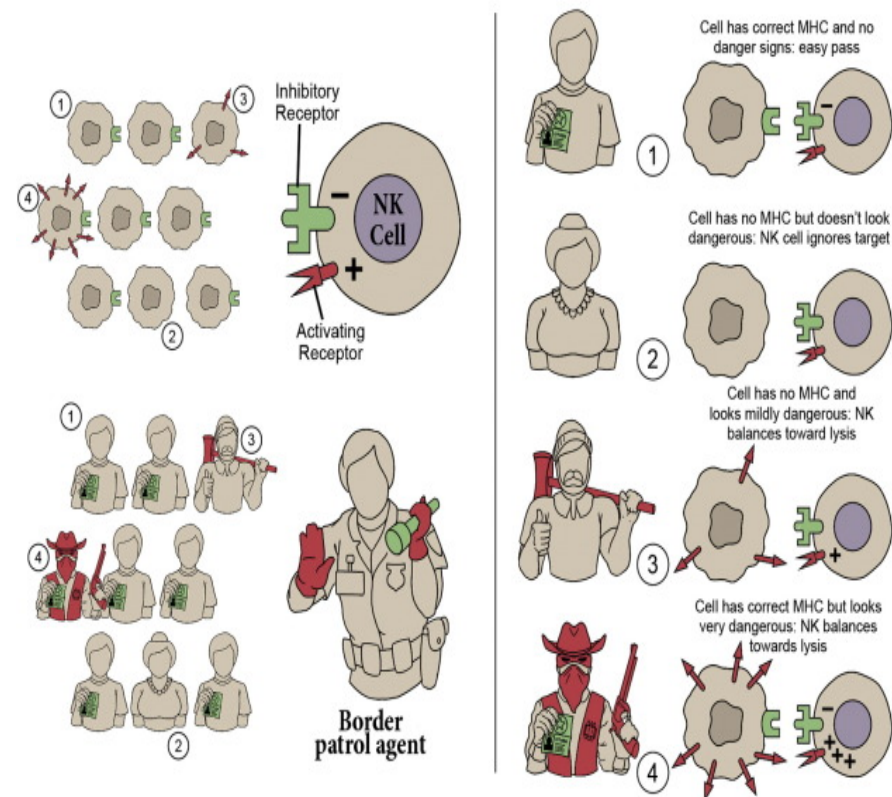
# T cells versus NK cells : differences and similarities

## The T-Cell is like a contract killer

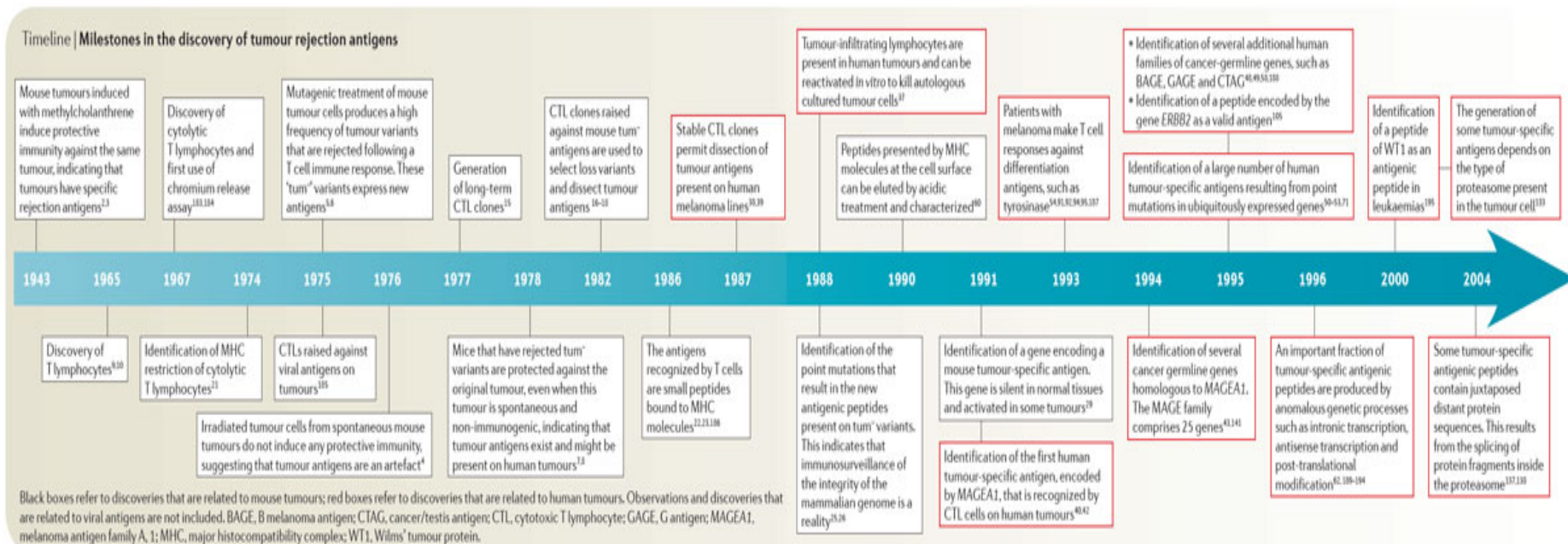


Unlike T cells that rearrange gene segments to generate antigen-specific receptors, NK cells recognize their target ligands using an array of germ-line encoded receptors.

## The NK Cell is like a border patrol agent

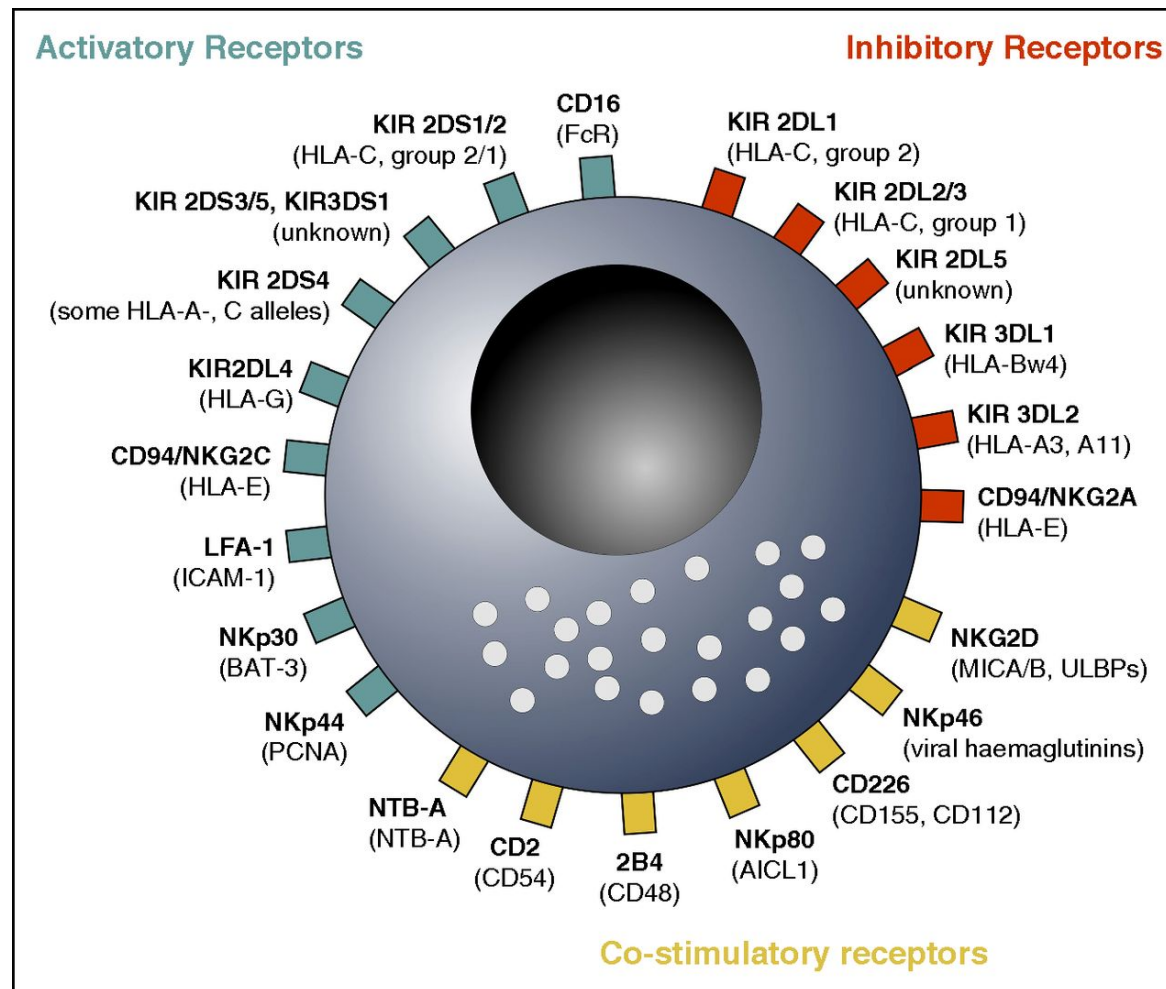


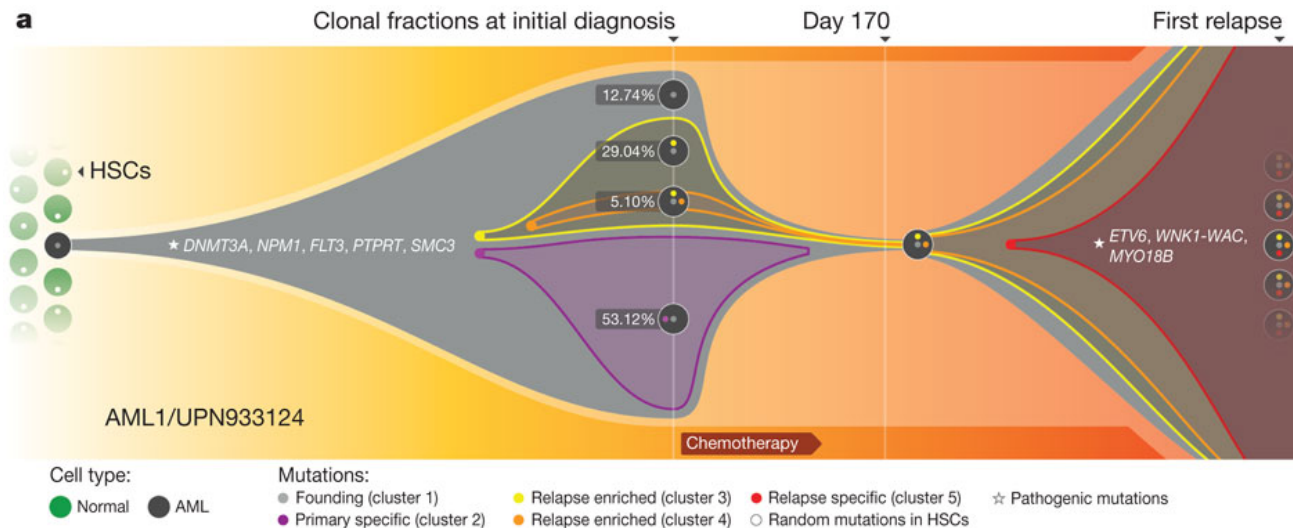
# Tumour antigens and T lymphocytes: “*croce e delizia*” for immunologists



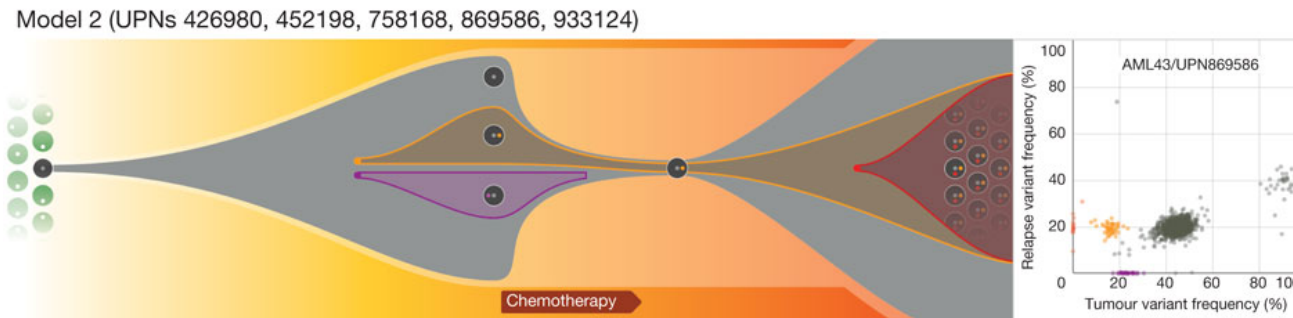
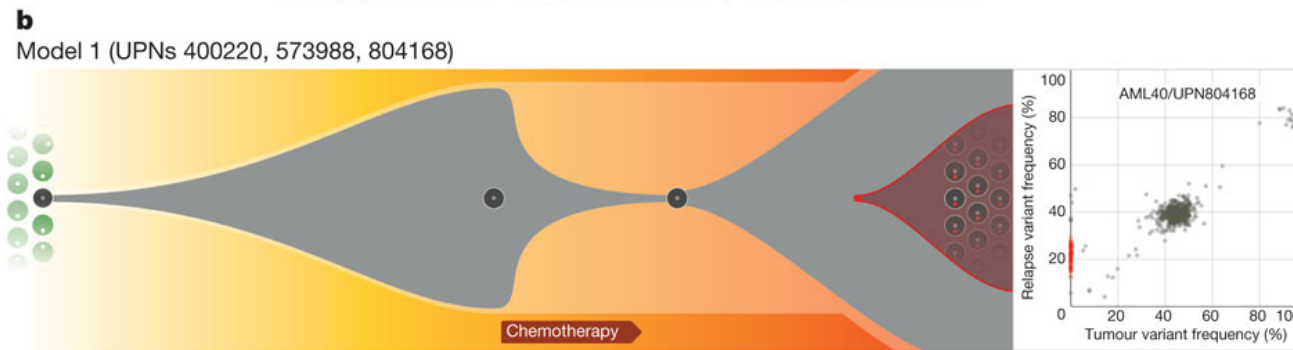


# NK cells “naturally” kill cell targets without prior sensitization

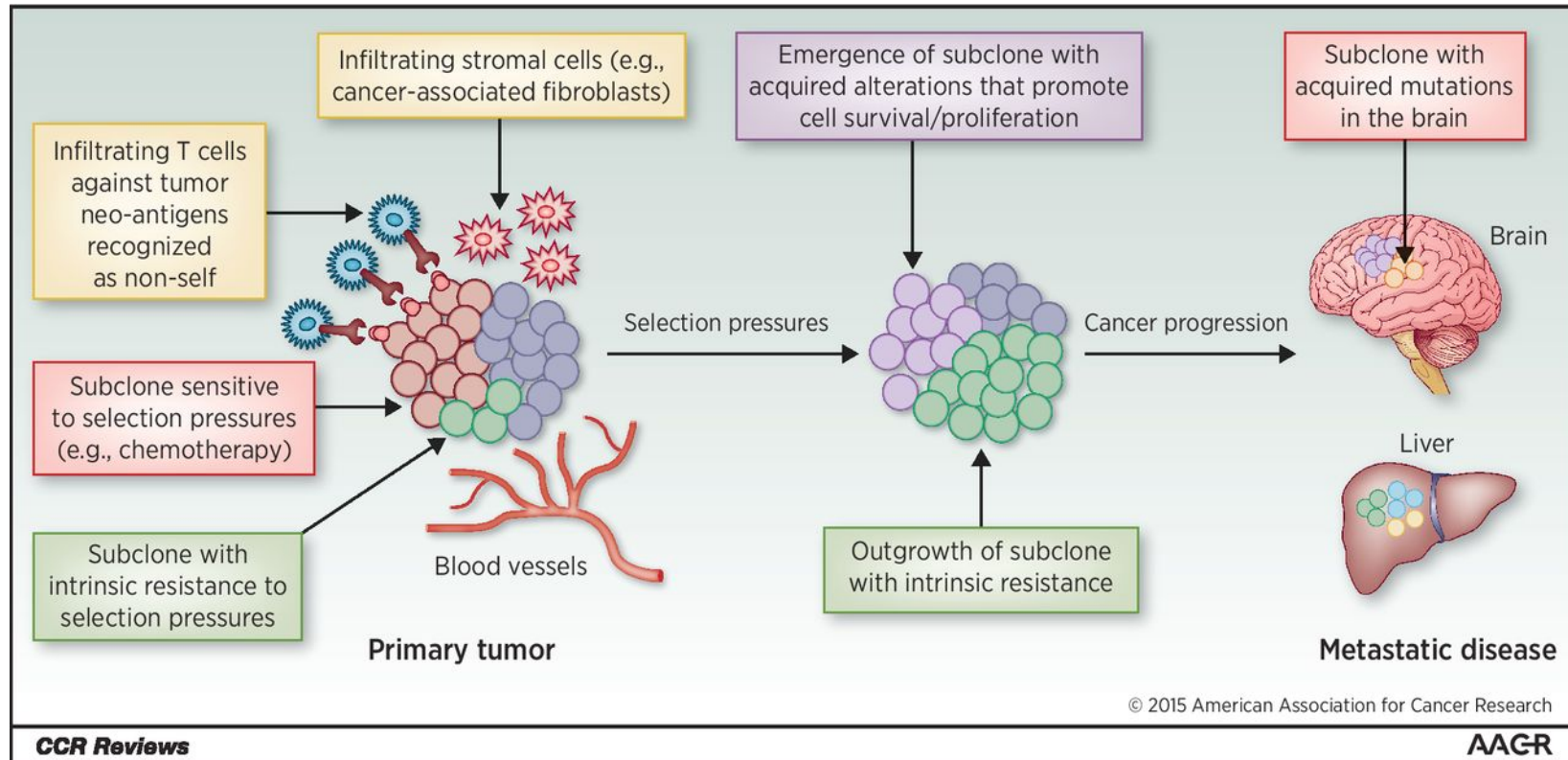


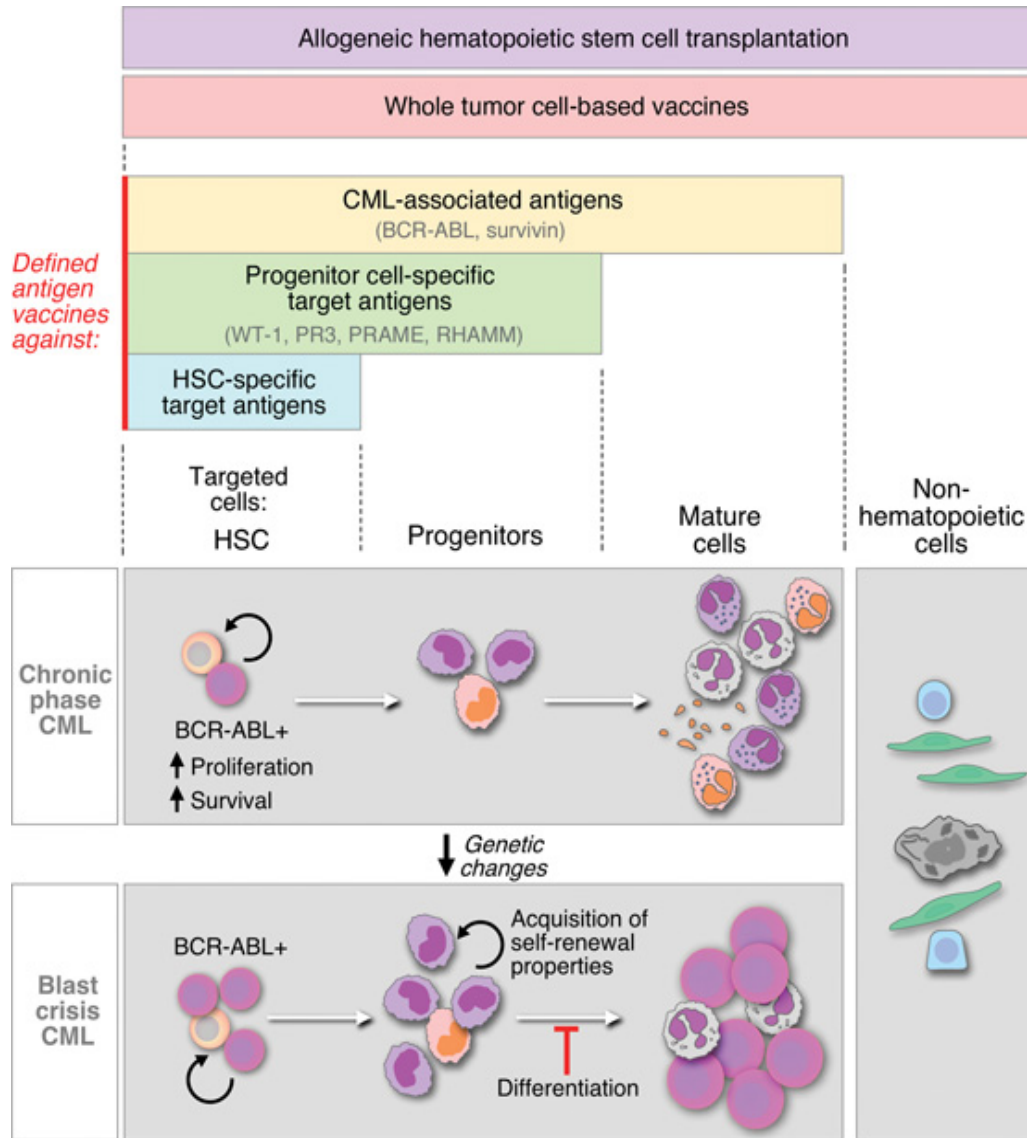


Graphical representation of clonal evolution from the primary tumour to relapse in UPN 933124, and patterns of tumour evolution observed in eight primary tumour and relapse pairs.



# Intratumor heterogeneity and clonal evolution: the immunological pressure

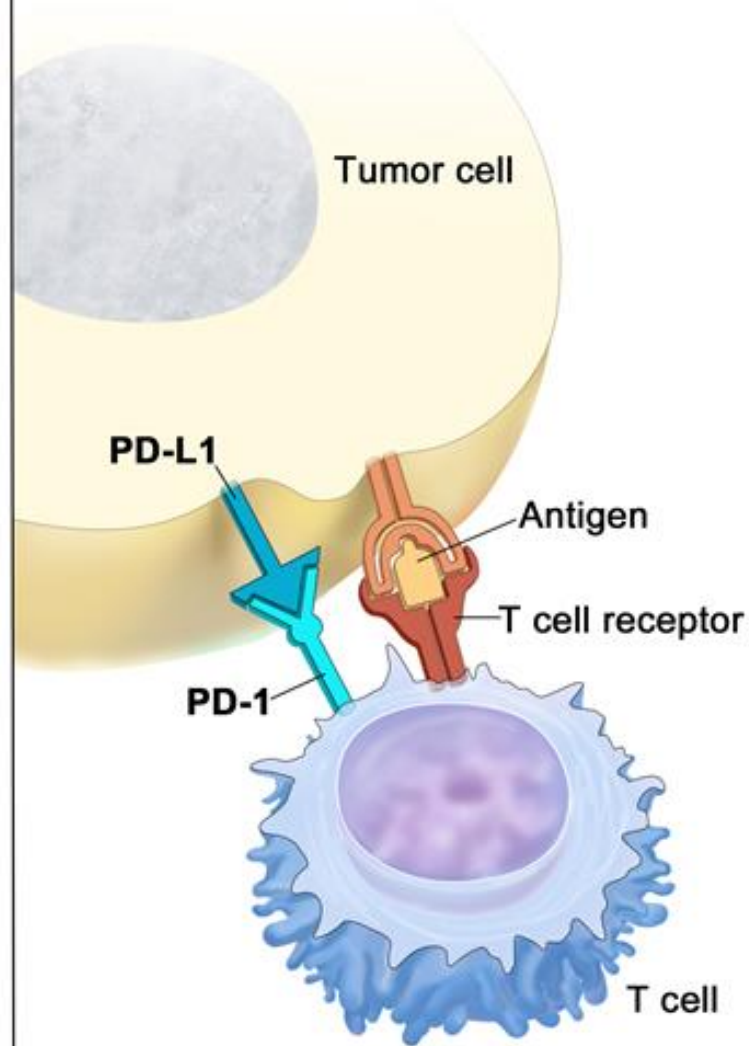




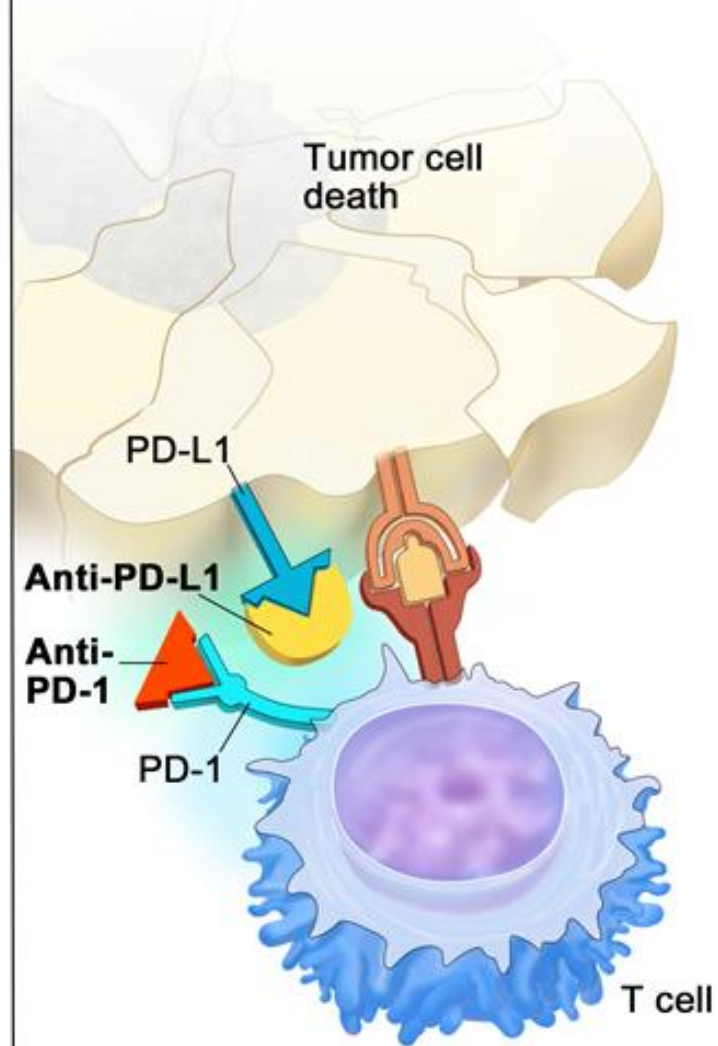
**Specificity of immune responses against the malignant cancer-initiating cell depends on where antigen targets are expressed in the cell differentiation hierarchy**

***The CML model as prototypical of hematopoietic stem-cell disorder where anti-leukemia immunological pressure may be curative, but where antigen-specific approaches have provided dismal results***

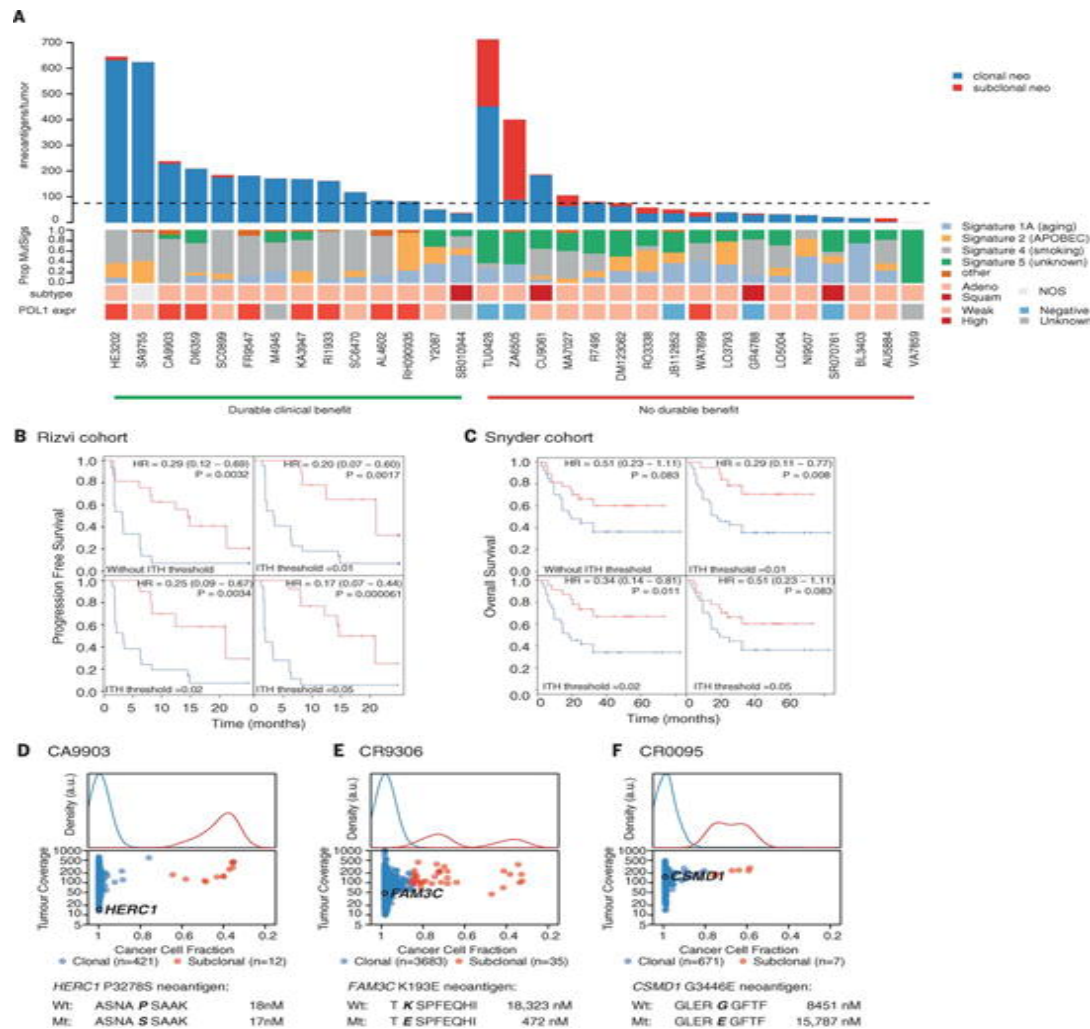
**PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell**



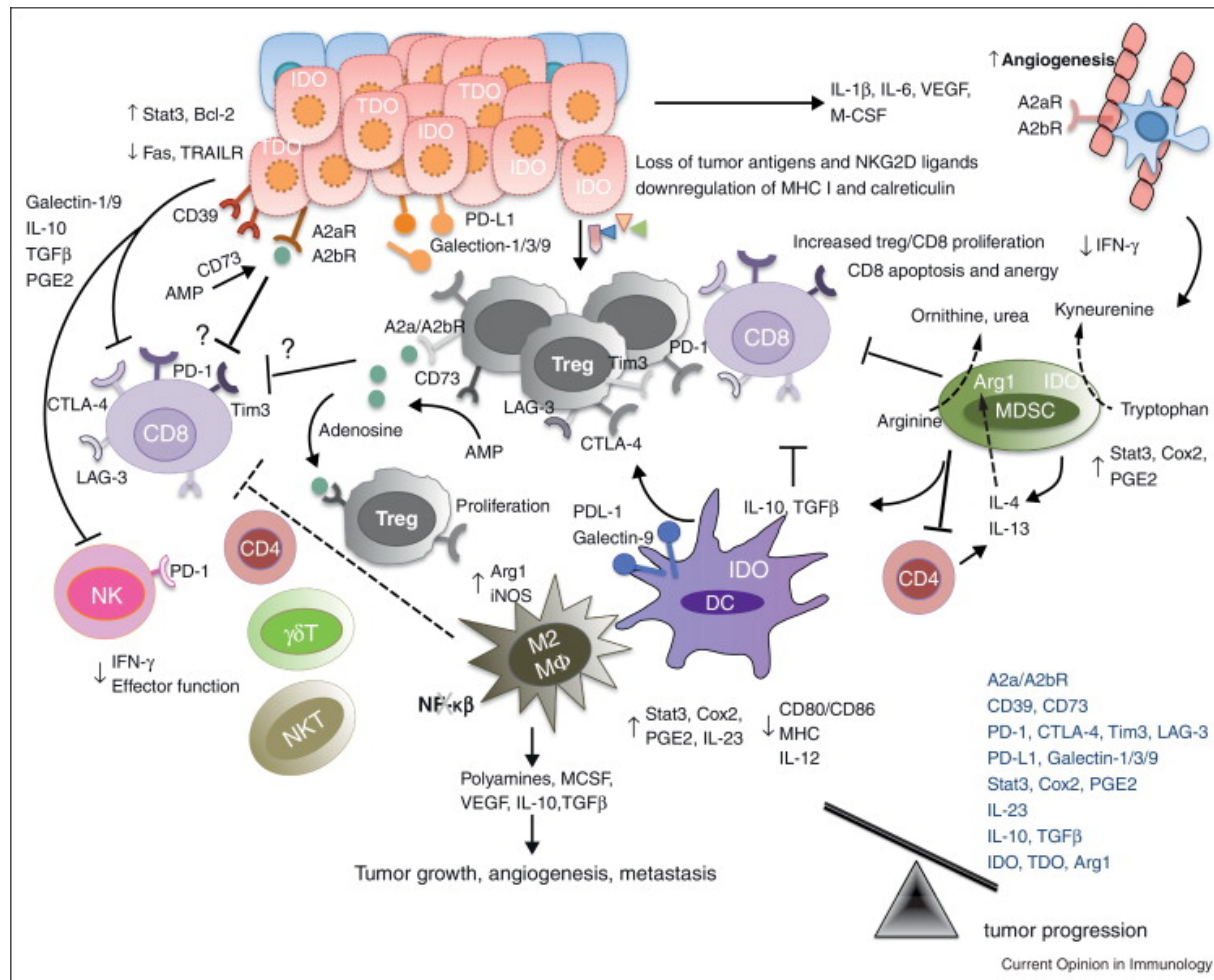
**Blocking PD-L1 or PD-1 allows T cell killing of tumor cell**



# Neoantigen clonal architecture and clinical benefit of immune checkpoint blockade



# Response to novel immunotherapy approaches: the role of tolerogenic pathways





## Science Breakthrough of the year for 2013

*“Science’s editors have chosen cancer immunotherapy as Breakthrough of the Year for 2013, a strategy that harnesses the body’s immune system to combat tumors. It’s an attractive idea, and researchers have struggled for decades to make it work”.*

2015



2011



2009



2012







*Time* magazine in 1998



*Time* magazine April 2016