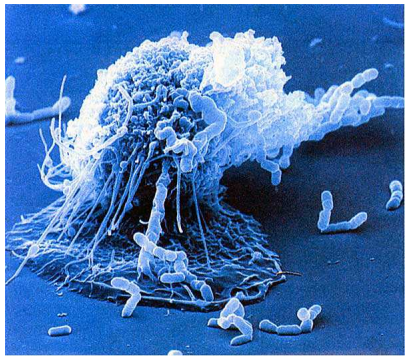
The basics of the immune system: our friends and foes

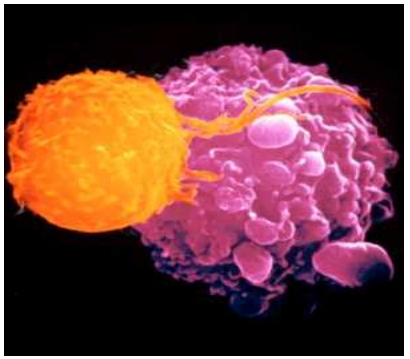
I. The immune system

II. Cancer and the immune system

III. The basics of cancer immune therapy

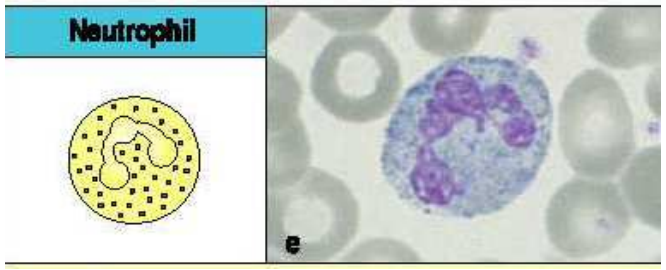
The immune system



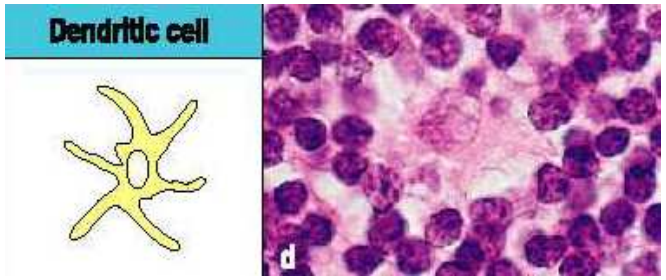


CHARACTERISTICS	INNATE	ADAPTIVE
Specificity	Non-specific	Specific
Antigens	Not needed	Required
Memory	None	Generated
Time course	Immediate	Slowly developing
Duration	Transient	Lifelong
Cell types	MØ, DC, NK, neutrophil	T cells, B cells
	First line of defense *Immune sensors*	*Effectors*

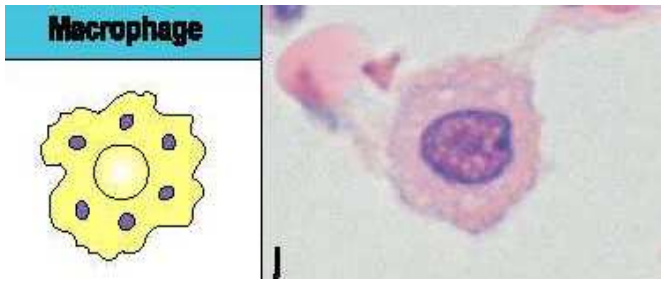
Cells of the innate immune system



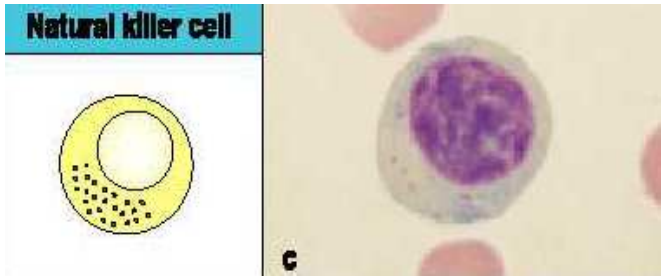
Phagocytosis and debris clean up
Secrete chemokines that call in other innate immune cells



Potent antigen presenting cells
Uptake and process antigen
Both “class I” and “class II” pathways
Will stimulate both CTL and T helper cells

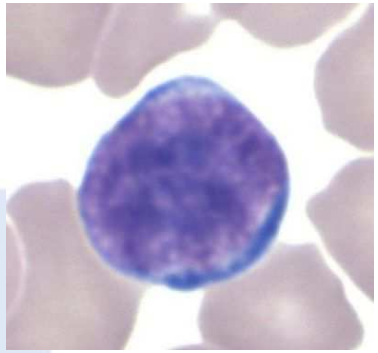


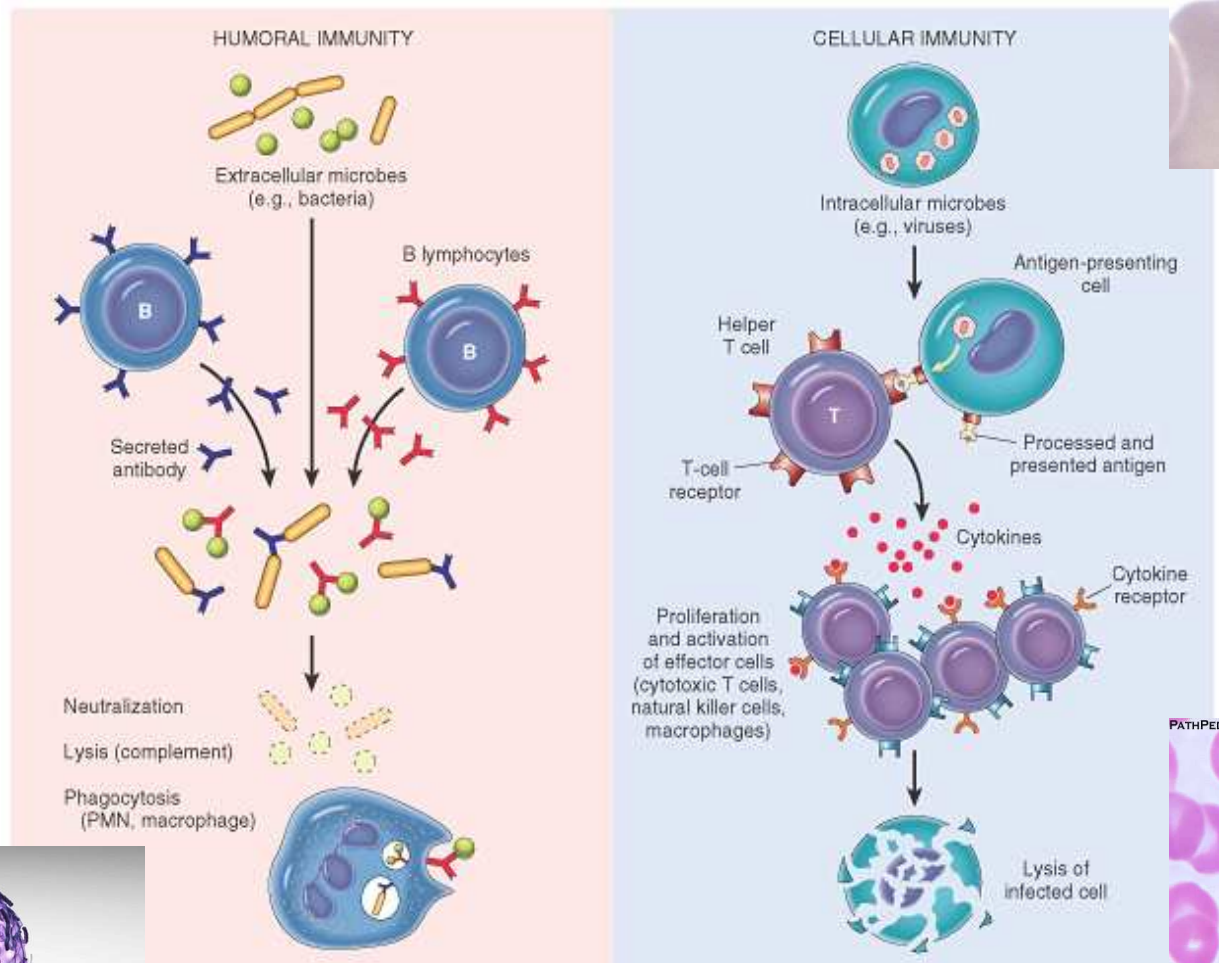
Phagocytosis and cleaning up debris, secrete cytokines
Type 1 can turn on adaptive immunity
Type 2 will limit adaptive immunity

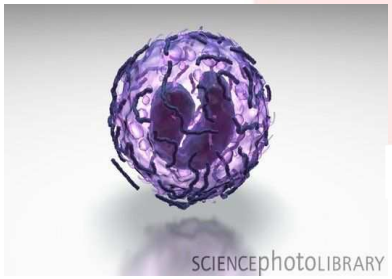


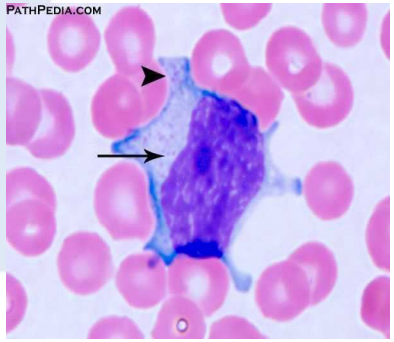
Can directly kill tumor without docking to MHC
Secrete high levels of IFN-gamma (critical cytokine)
Antibodies can activate them via FC receptor (ADCC)

Cells of the adaptive immune system

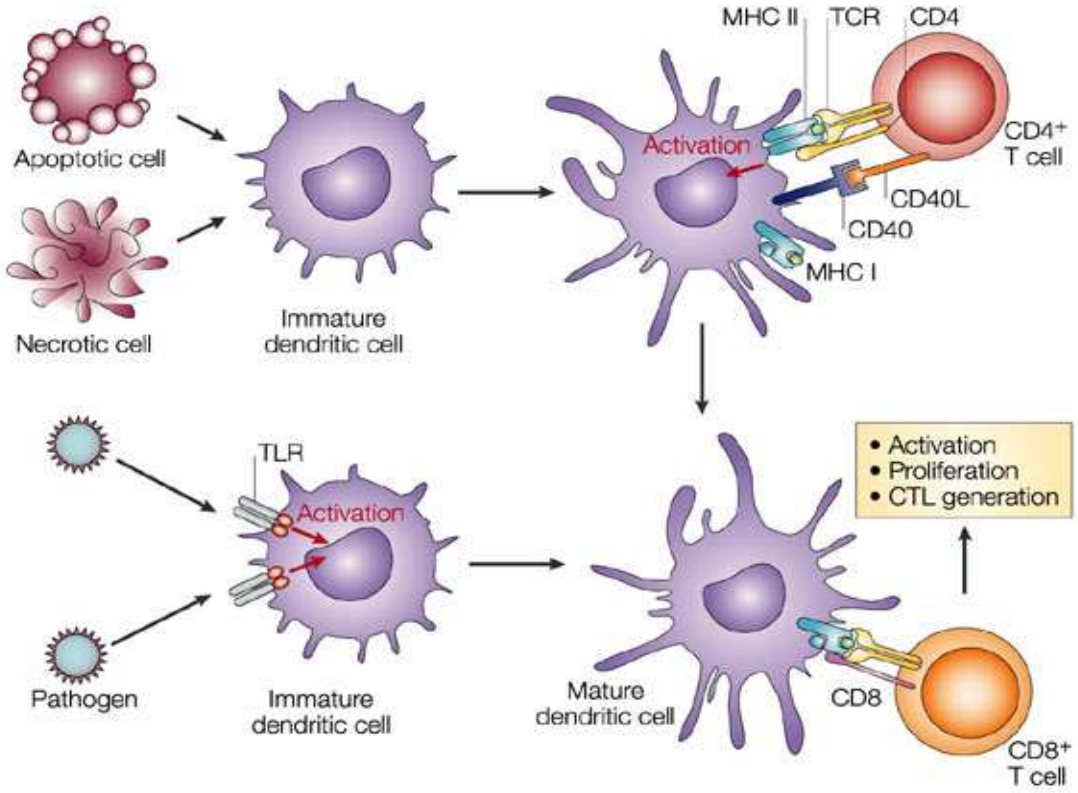






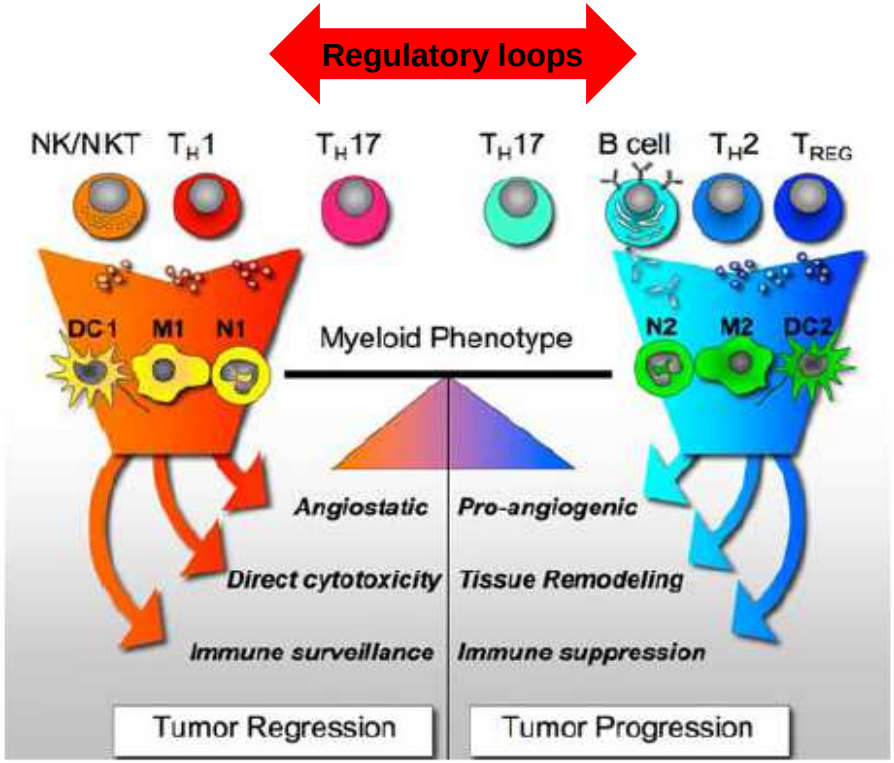


Critical link between innate and adaptive immunity



Bevan, Nat Rev Immunol, 2004

The immune system is all about "checks and balances"



IL-12, IL-2, IFN-g, TNF-a IL-4, IL-5, IL-10, TGF-b

DeNardo et al, Ca Met Rev, 2010

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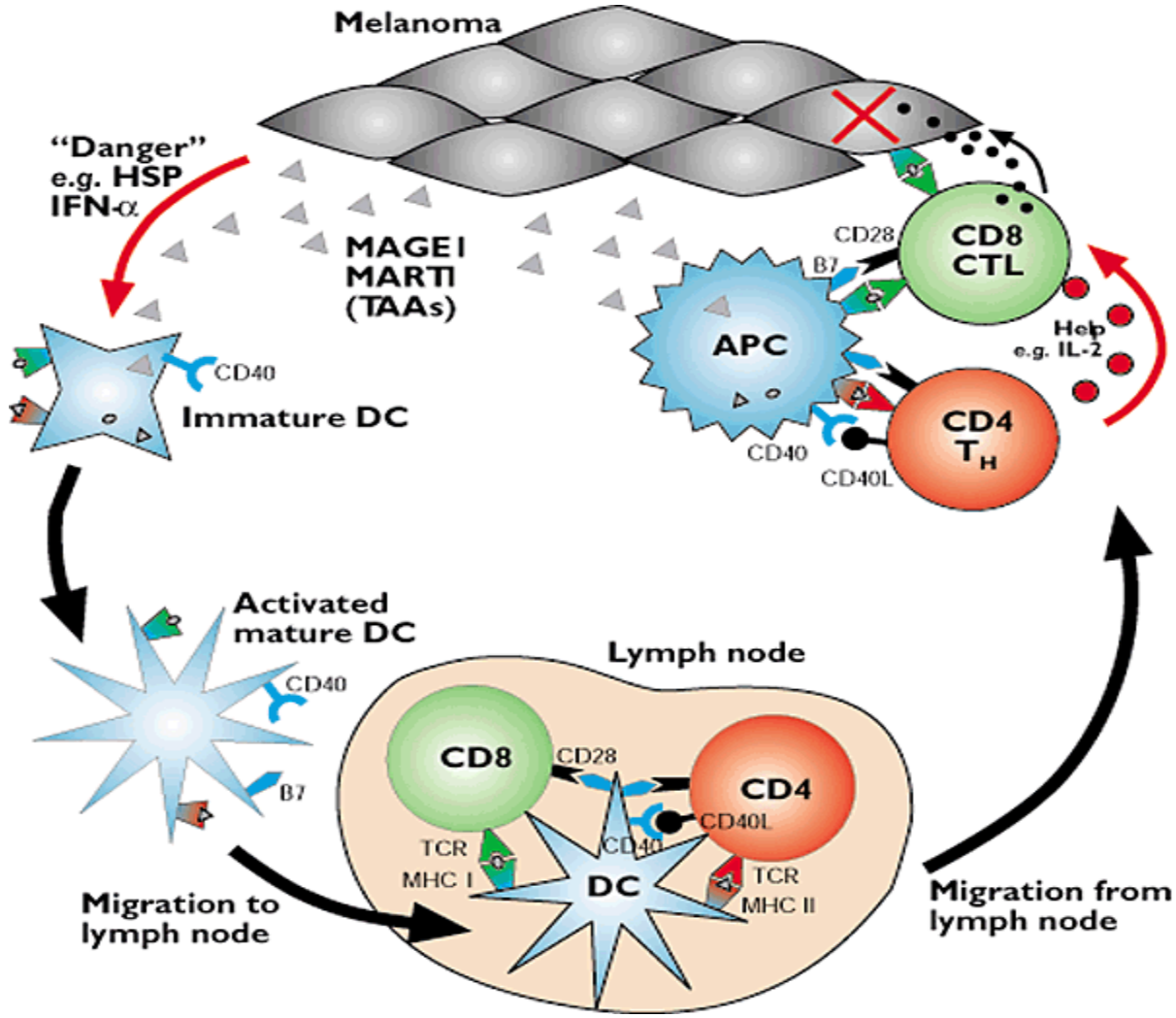
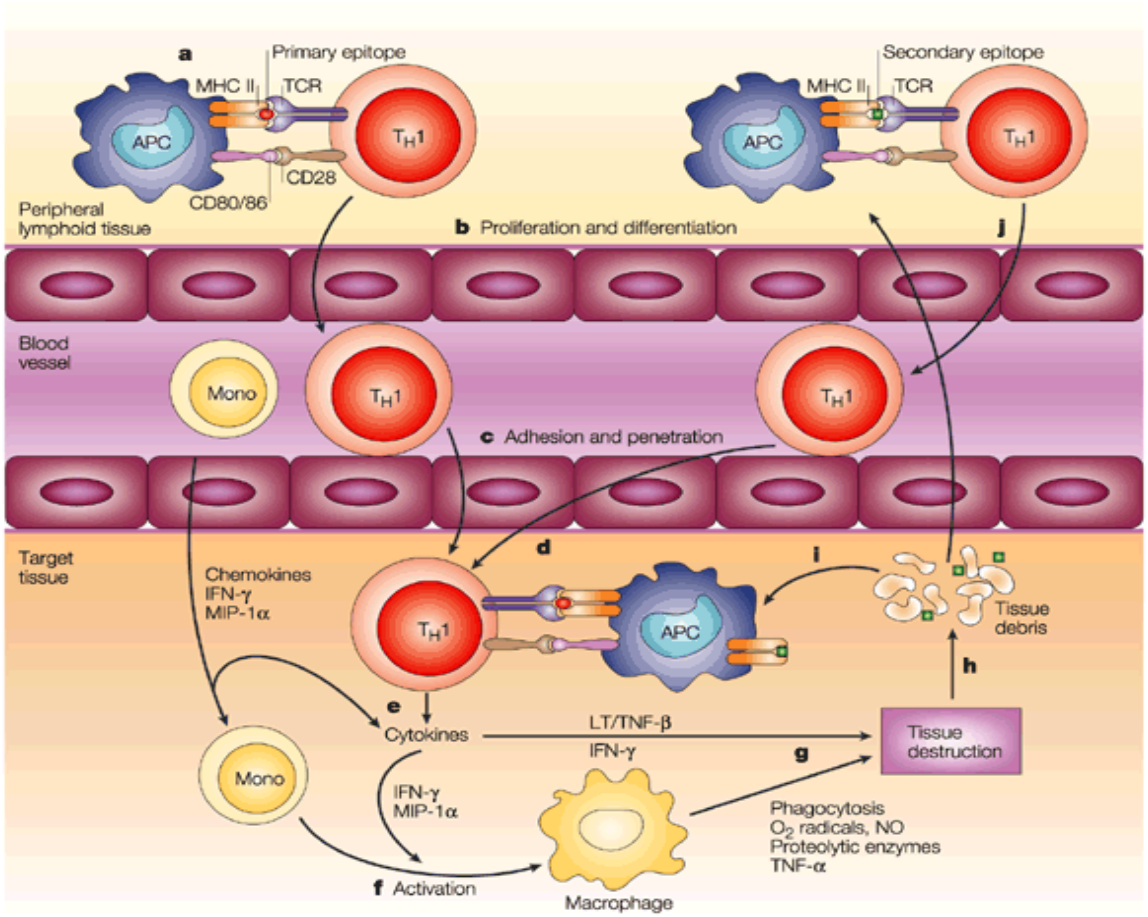
The steps in stimulating cancer specific immunity



Smythe et al, Nat Med, 2001

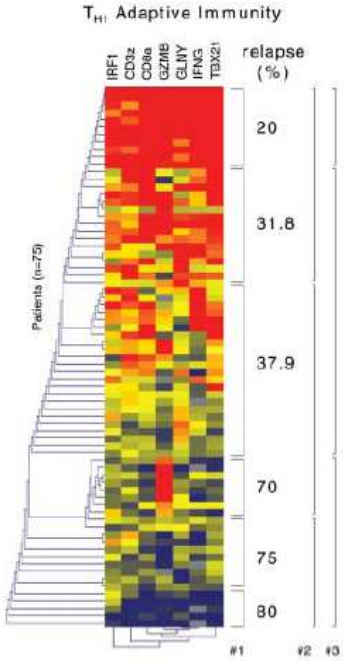
Epitope spreading is the endpoint of an effective immune response in cancer



Vanderlught et al, Nat Rev Immunol, 2002

What is needed for clinically effective anti-tumor immunity?

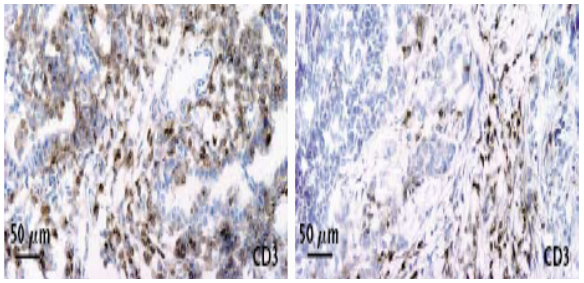
Type I inflammation

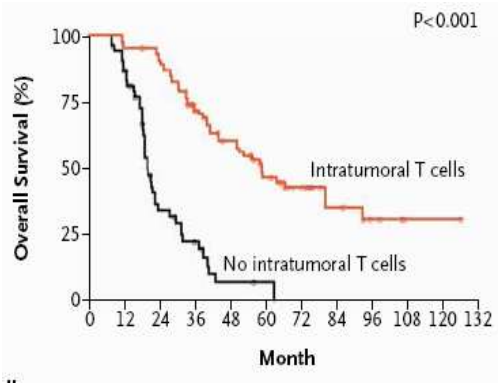


- 75 colorectal cancers
- 7 gene classifier
- Inverse correlation of gene expression and relapse

Galon et al, Science, 2006

High density of T-cells penetrating tumor

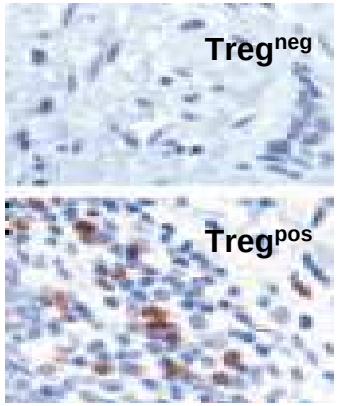


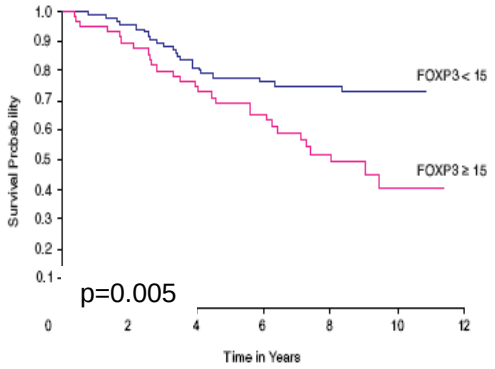


- 186 advanced ovarian cancers
- MVA: Intratumoral T cells independent predictor survival

Zhang et al NEJM, 2003

Modulation of self-regulation

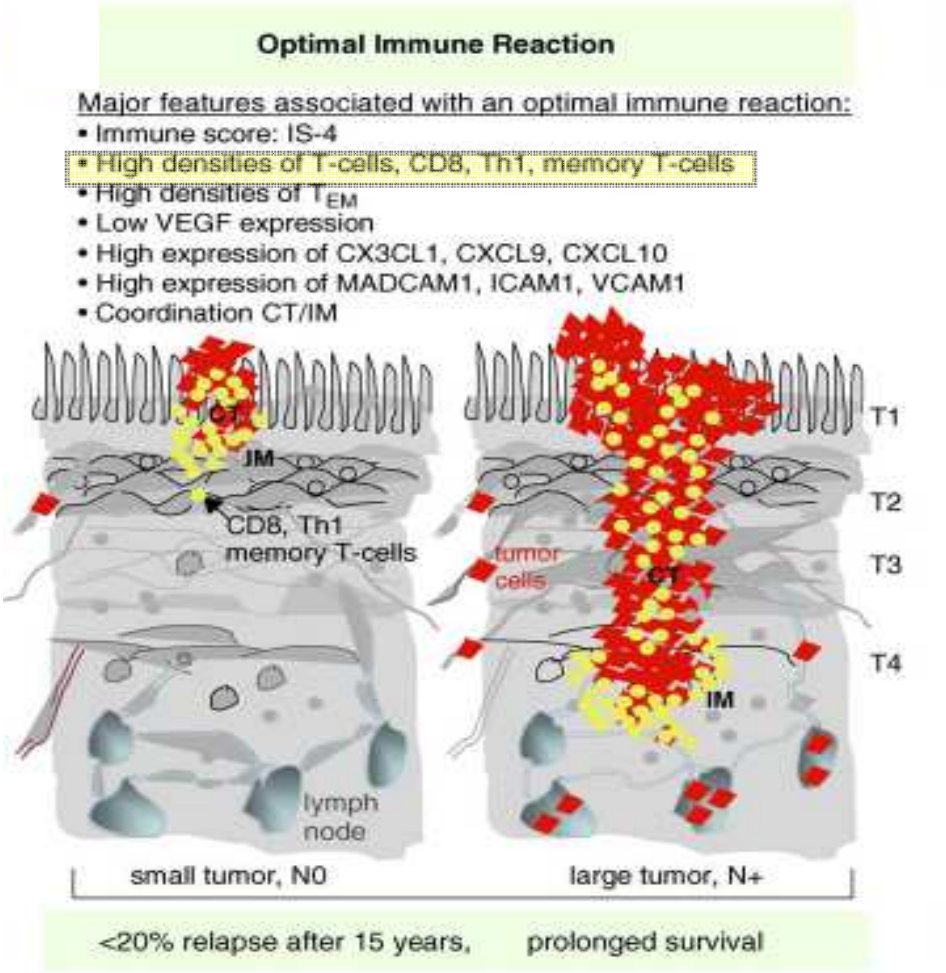




- 237 breast cancers
- MVA: Density of $Treg^{+}$ in ER^{+} tumors predictor of survival

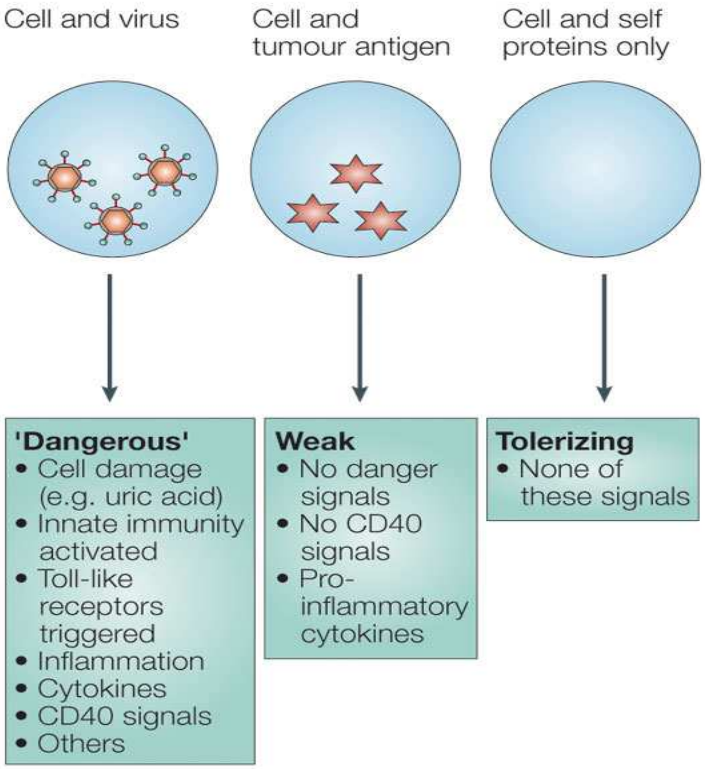
Bates et al, JCO, 2006

In many cancers patients have demonstrated an “optimal immune reaction”



Bindea et al, Curr Opin Immunol, 2010

What does the immune system see in cancer?



Lake et al, Nat Rev Cancer, 2005

Antigens Associated with Clinical Response

Foreign Antigens	Self Antigens	
LMP2	HER2	GD2
HPV	WT1	CEA
HepB	MUC1	MART-1
	MAGE A2	gp100
	NY-ESO-1	PR1
	PSMA	Tyrosinase
	PSA	PAP
	PSCA	NA17

Cheever et al, Clin Ca Res, 2009

Why do most tumor evade immune recognition?

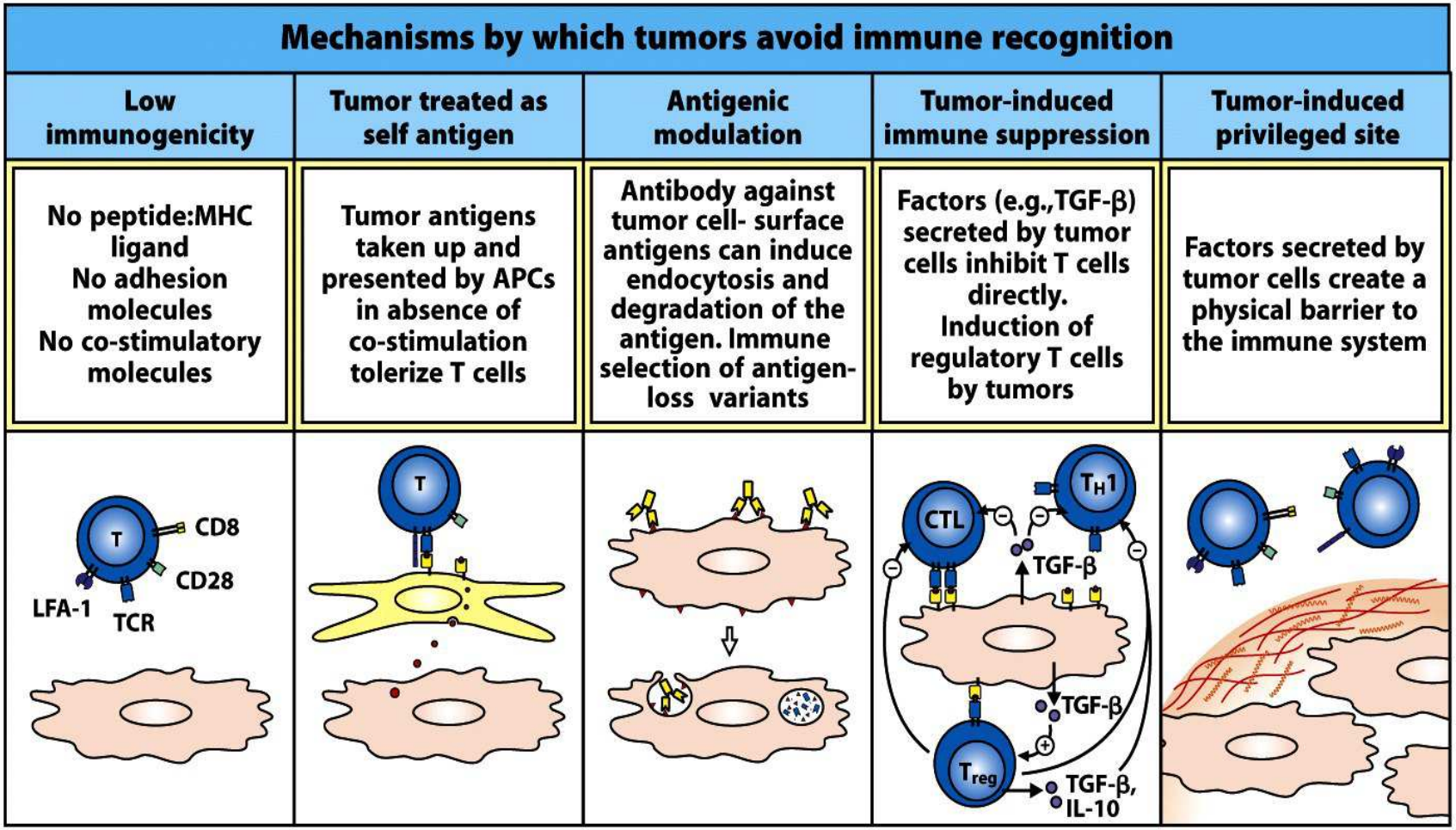
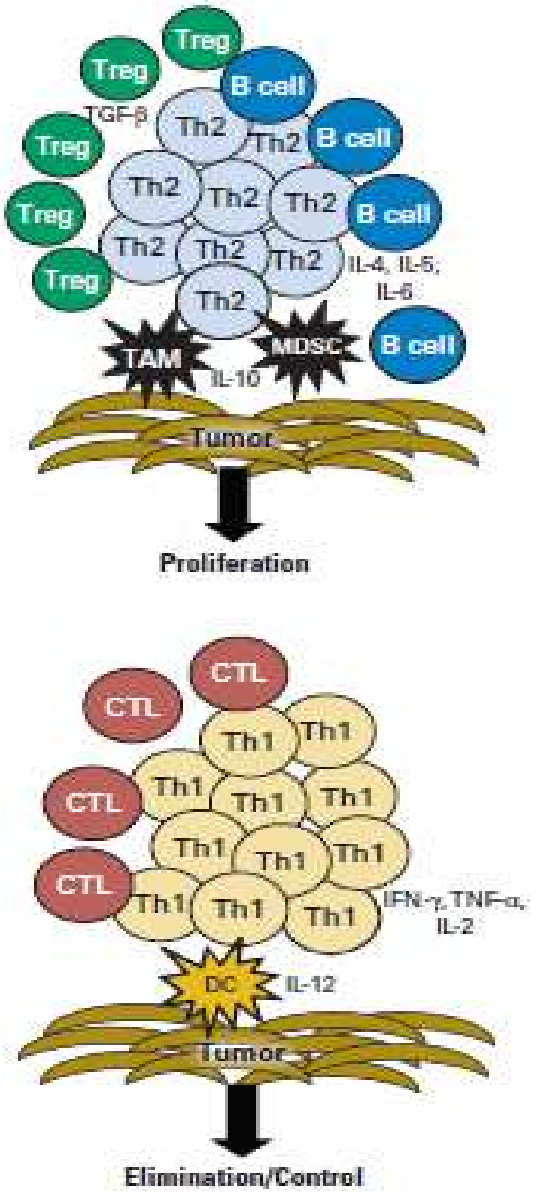


Figure 15-14 Immunobiology, 7ed. (© Garland Science 2008)

Multiple factors impact the tumor immune microenvironment

	Pro-tumorigenic inflamation	Anticancer immunosurveillance
Cell types	M2 macrophages Myeloid-derived suppressor cells Neutrophils Foxp3$^+$ T reg, Th17 cells	Dendritic cells M1 macrophages Cytotoxic CD8$^+$ T cells with a memory effector phenotype
Cytokine profiles	Th2 Th17	Th1 CX3CL1 CXCL9, CXCL10
Distribution	Peritumoral	Intratumoral, close to cancer cells, as well as in the invasive front
Associated features	Stat3 phosphorylation	High endothelial venules
Functional impact	Negative prognostic impact	Positive prognostic and predictive impact

Cancer Research Reviews AACR



Fridman et al, Ca Res, 2001

Disis, JCO, 2010

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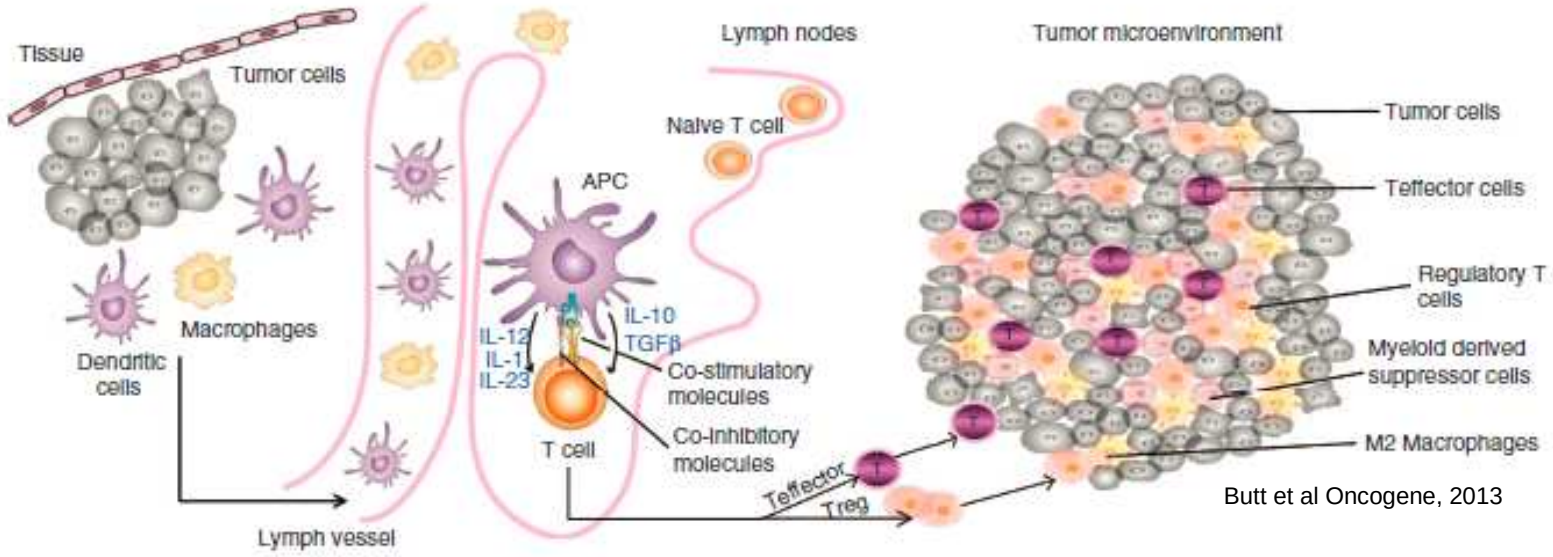
Types of immune therapy

PASSIVE	ACTIVE
Transferred	Generated
Ready made	Must be developed
Immediate protection	Takes time
No memory	Long lived
Immune system may function poorly	Requires functional immune system
Ig infusions, Some MoAB therapy, T cell transfer	*Vaccines, anti-CTLA-4*

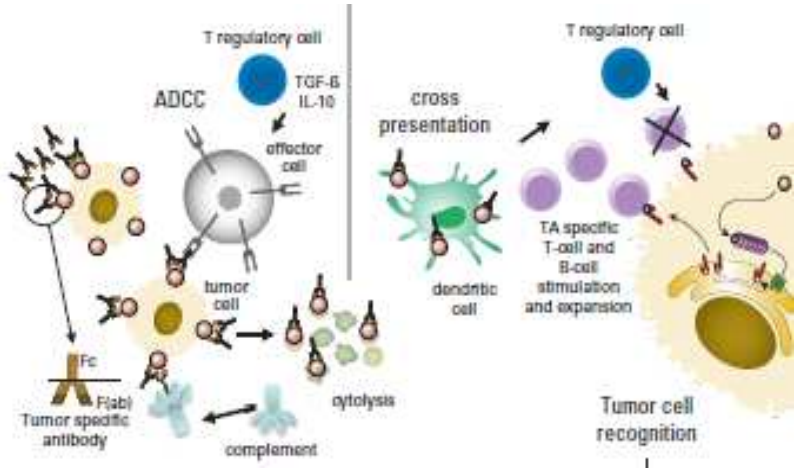
How to generate the optimal immune reaction?



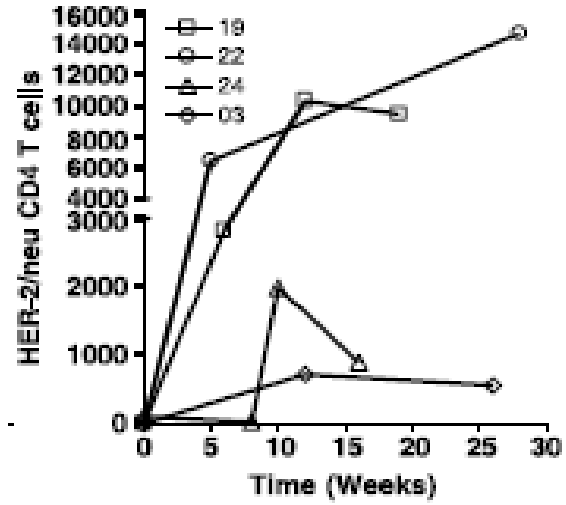
Butt et al Oncogene, 2013

Increase effector T-cells	Enhance existing immunity	
Vaccines Adoptive T-cell Therapy	Checkpoint inhibitors Cytokine Therapy (IL-15, IL-7) Depletion Tregs MoAB (X-IL-10, TGFb)	Modulate the tumor microenvironment

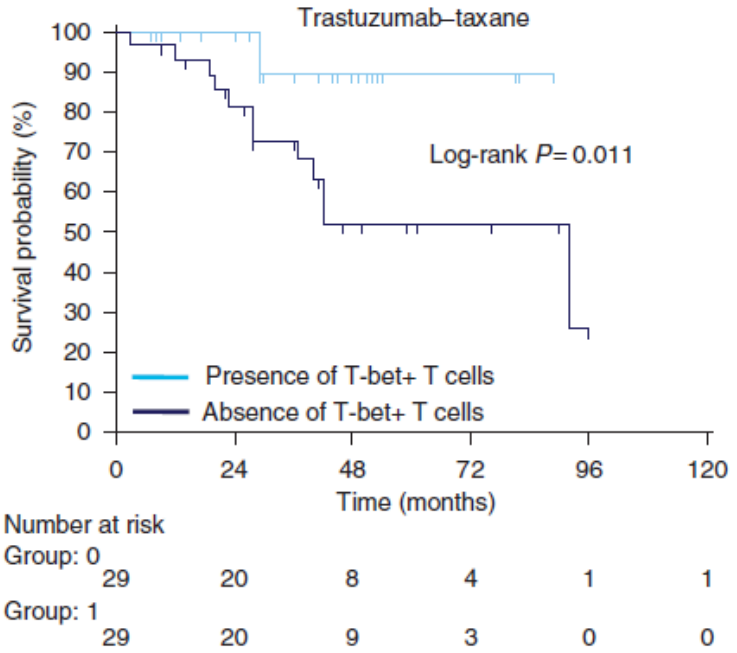
Monoclonal antibody therapy- trastuzumab



Ferris et al, JCO, 2010

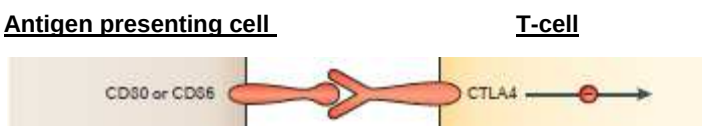


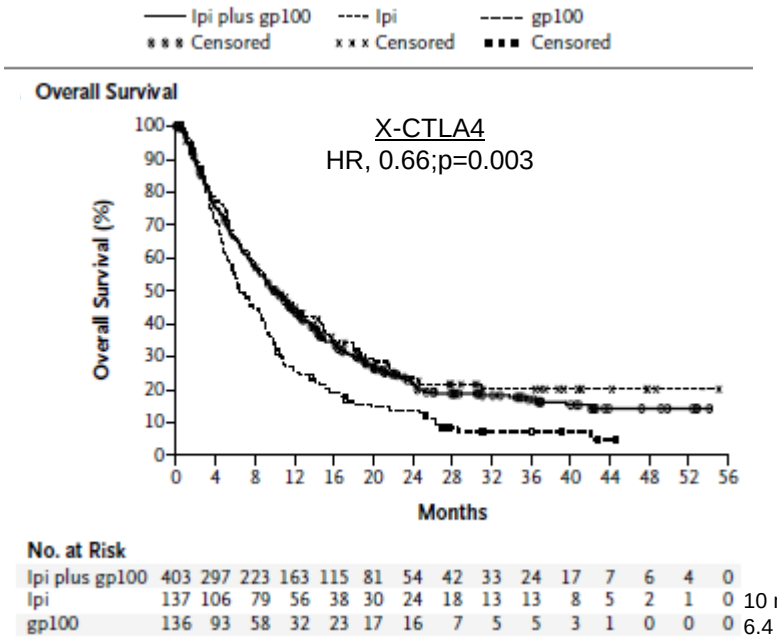
Taylor et al, Clin Ca Res, 2007



Ladoire et al, BJC, 2011

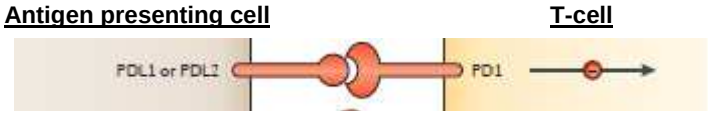
Checkpoint blockade

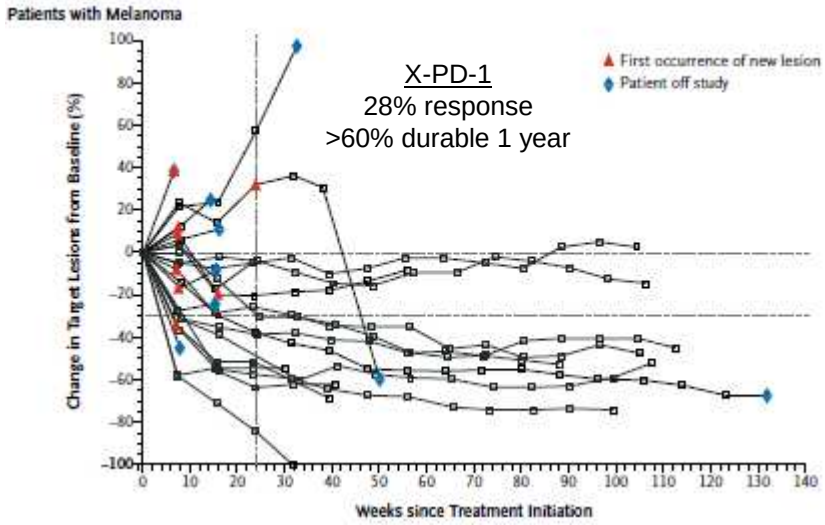




Previously treated MM

Hodi S et al, NEJM, 2010
Pardoll, Nat Rev Ca, 2012

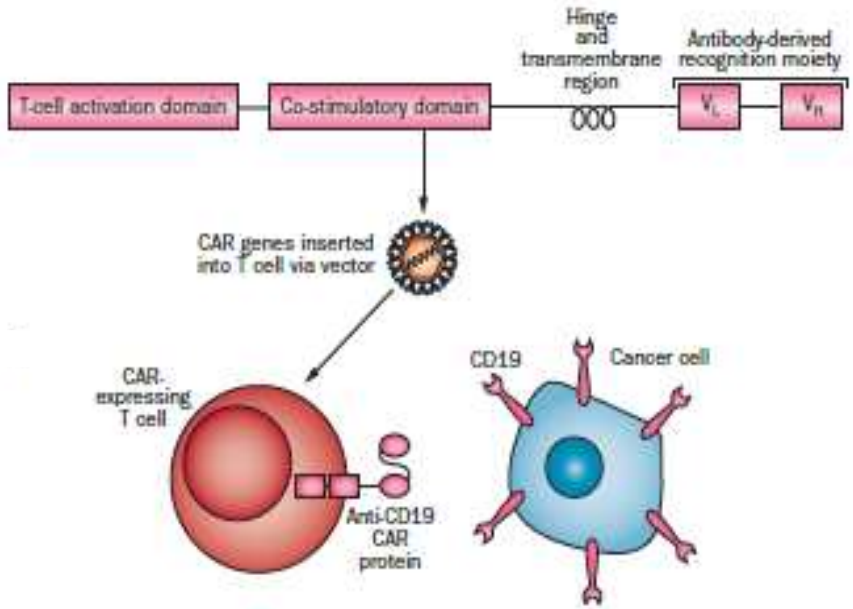




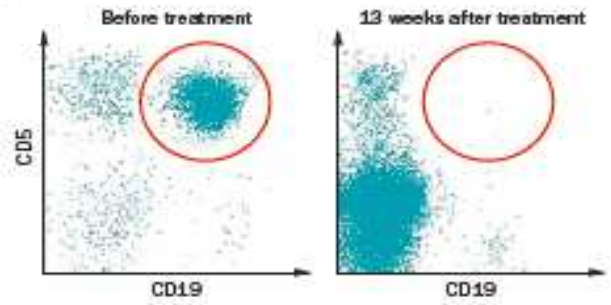
Previously treated MM

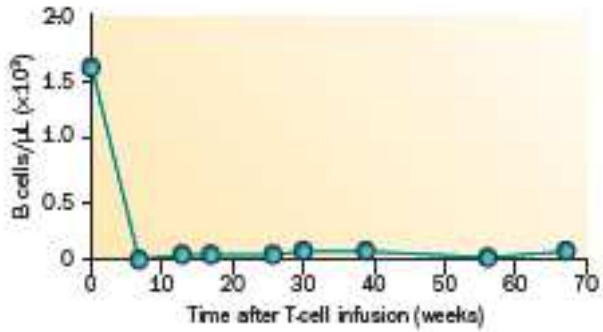
Topalian S et al, NEJM, 2012
Pardoll, Nat Rev Ca, 2012

Infusion of engineered T-cells



Kochenderder et al Nat Rev Clin Oncol, 2013





Points to remember:

- Innate immunity, our first responders that don't require antigen recognition, can support and enhance the efficacy of adaptive immunity-cells that are specific to an invader.

- Therapeutic immunity can be either passive (supplying an antibody response) or active (vaccinating to create your won antibody response)- which requires your immune system to do the work.

- There is strong evidence that most cancers stimulate the immune system.

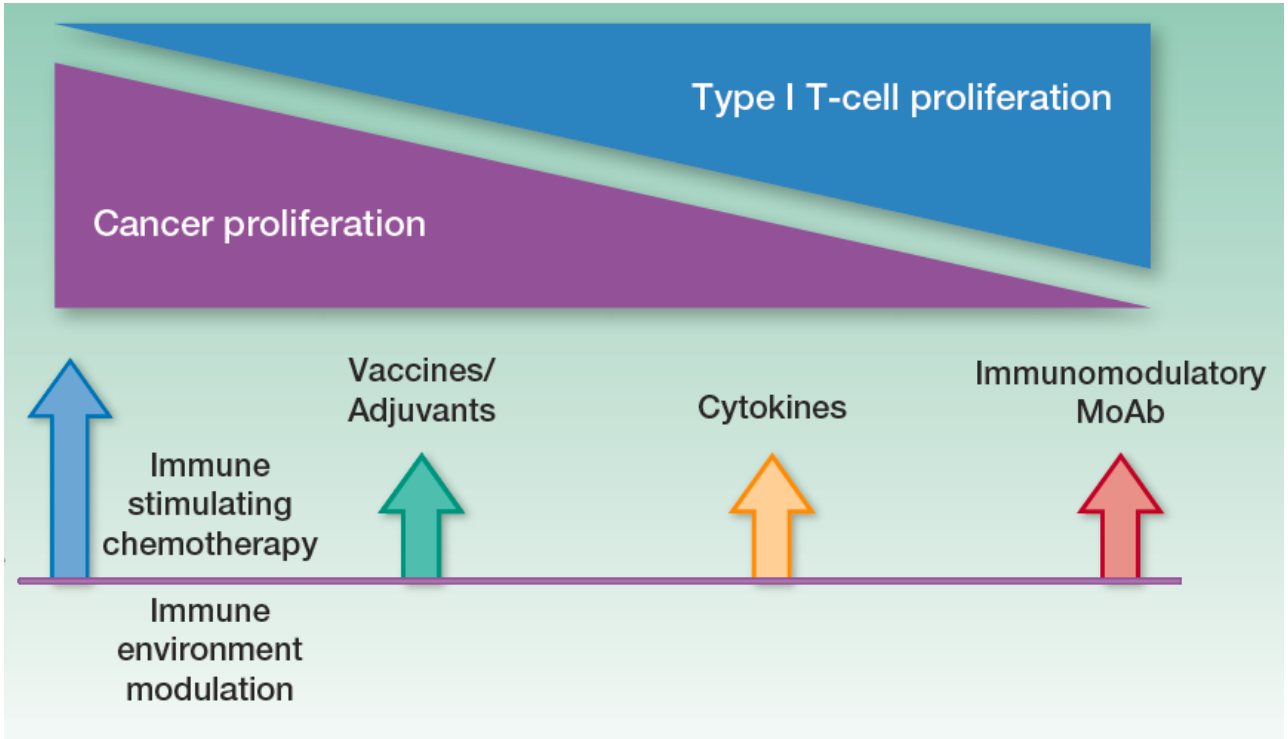
- Efficacy of cancer induced immunity is limited by both factors secreted by the tumor and stroma, but also normal defense mechanisms activated to prevent autoimmunity.

- Our improved understanding of tumor-immune system interactions has led to design of therapeutic approaches that both stimulate immunity and address mechanisms of immune escape.

- There are now several promising immunologic agents that have demonstrated significant anti-tumor efficacy in advanced stage clinical trials or have been approved for standard of care use.

A new paradigm for cancer therapy

Evidence of immunity?
Immune score?
Blood-based marker?



Disis et al, CCR Focus, 2013