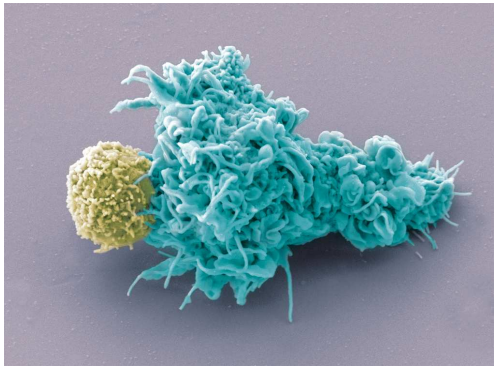
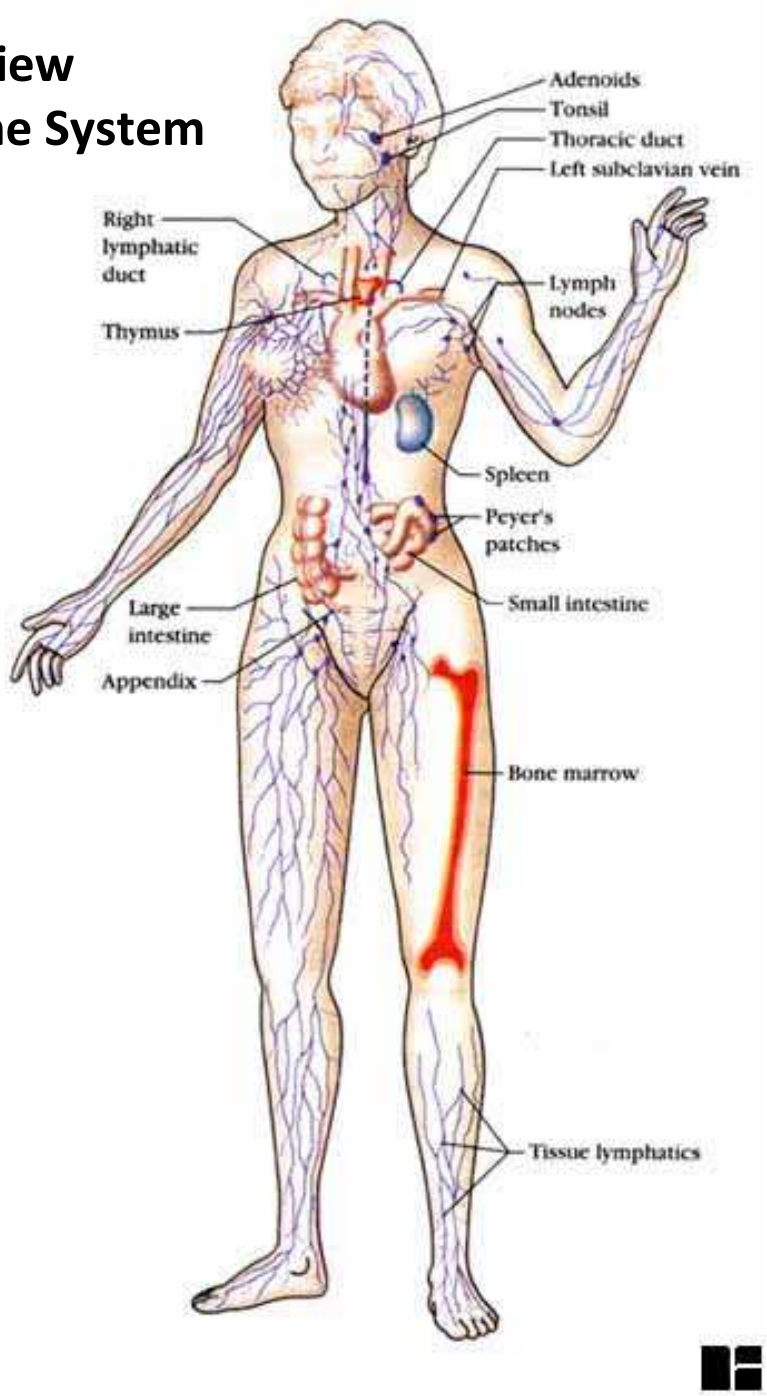
SITC-ACI Seattle
"Tumor" Immunology 101

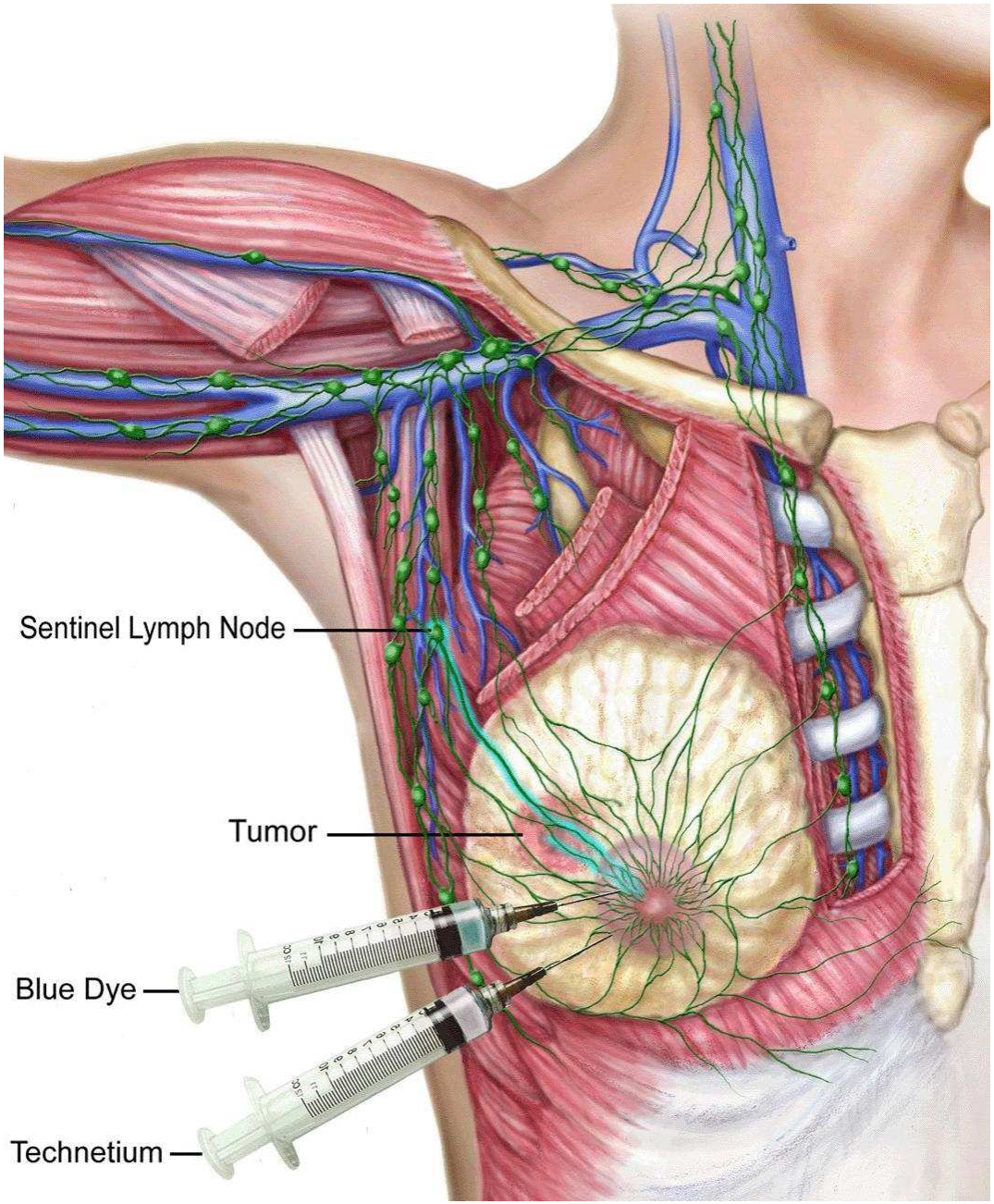


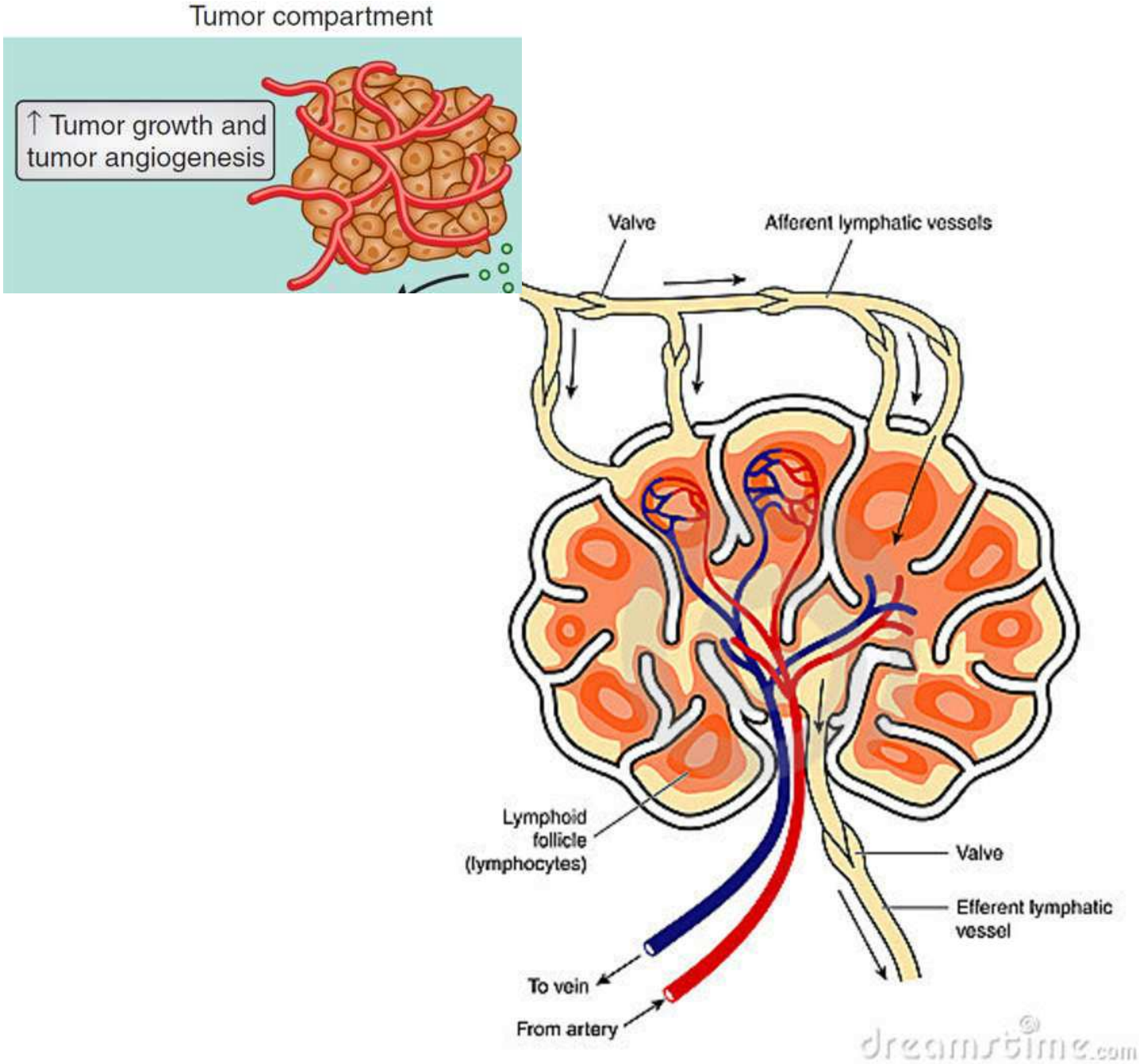
Andrew Weinberg, PhD
EACRI, Providence Cancer Center

- **Physiology of the Immune Response to Cancer**
- **Innate and Adaptive Immunity**
- **How does the Immune Response Handle Diversity?**
- **Antigen presentation to T cells**
- **Discriminating "Self" from "non-Self"**
- **Clonal T cell Expansion**
- **Negative and Positive Signals Delivered to T cells**
- **Applying Immunologic Principals to the Clinic**

Physiologic View of the Immune System

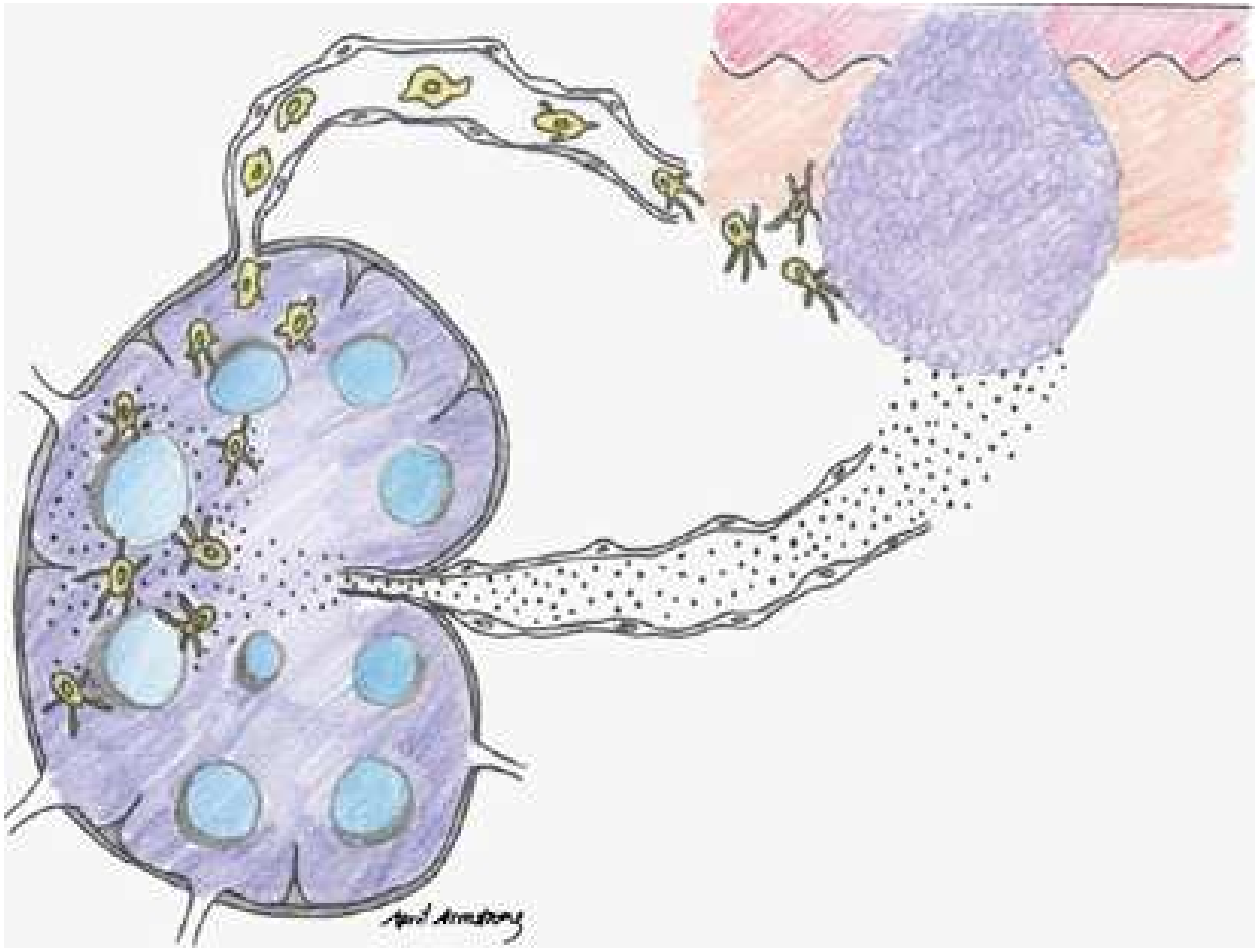



Sentinel Lymph Node
Tumor
Blue Dye
Technetium


Tumor compartment
↑ Tumor growth and tumor angiogenesis
Valve
Afferent lymphatic vessels
Lymphoid follicle (lymphocytes)
Valve
Efferent lymphatic vessel
To vein
From artery
dreamstime.com

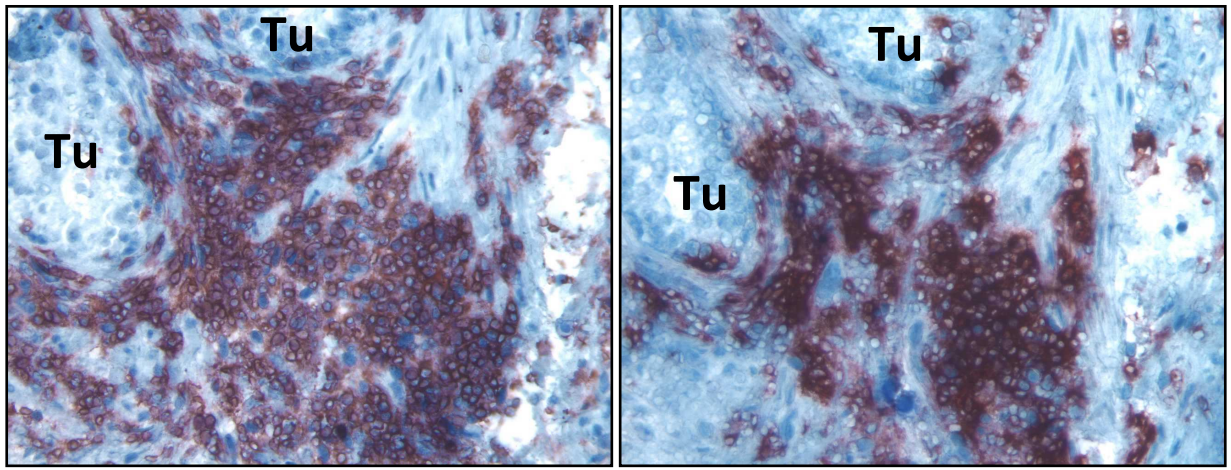

A
xenograft
C
tumor
artery
B
n
vein

Artist Drawing of Tumor Ag Specific Immune Priming



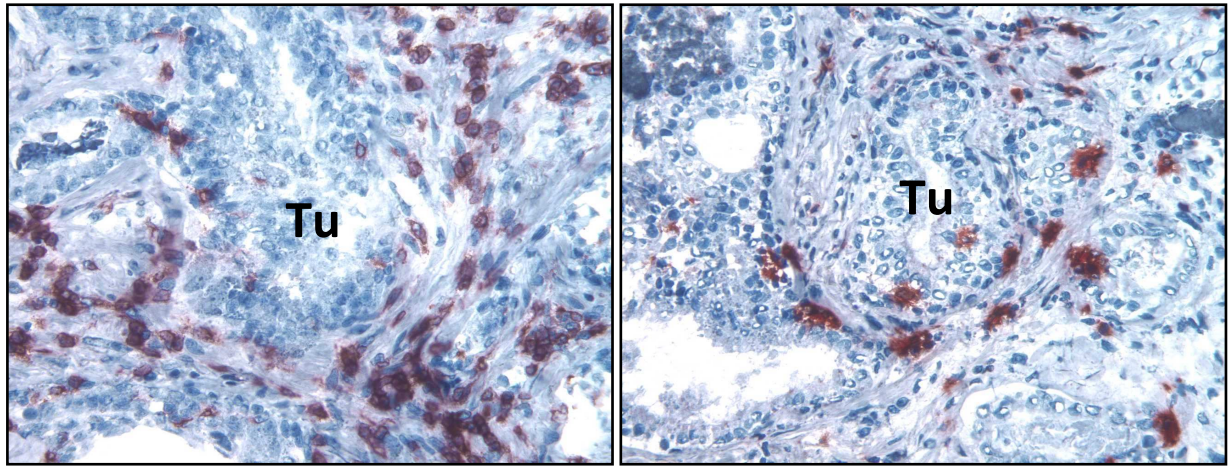
T Cell Activation in Prostate Cancer
(Androgen Ablation prior to Surgery)

Patient #1



T Cell Marker OX40

Patient #2



T Cell Marker OX40

IMMUNOLOGICAL PARADIGM

- The major function of the immune system is to recognize and eliminate harmful entities within the body without destroying “self” tissue

Immunity
is divided into two entities termed
"*INNATE*" and "*ADAPTIVE*"

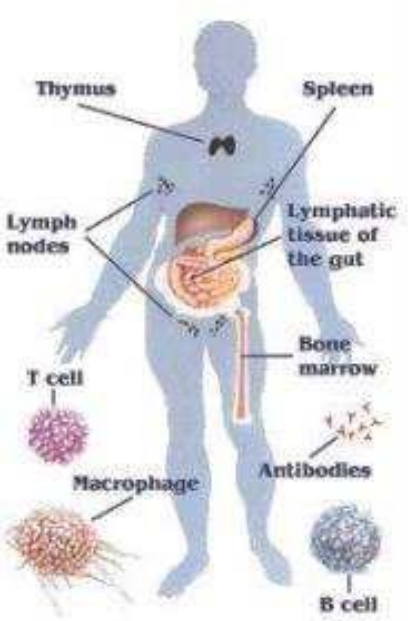
- **INNATE IMMUNITY**
  - State of immunity with which one is born. It exists prior to exposure to foreign substance or pathogen (antigen) and is not improved by repeated exposure to the same antigen.

- **ADAPTIVE IMMUNITY**
  - State of immunity that is developed as a result of exposure to a foreign substance or pathogen (antigen). It is specific for the particular protein/antigen and is enhanced following repeated exposure to the same antigen ("immunologic memory").

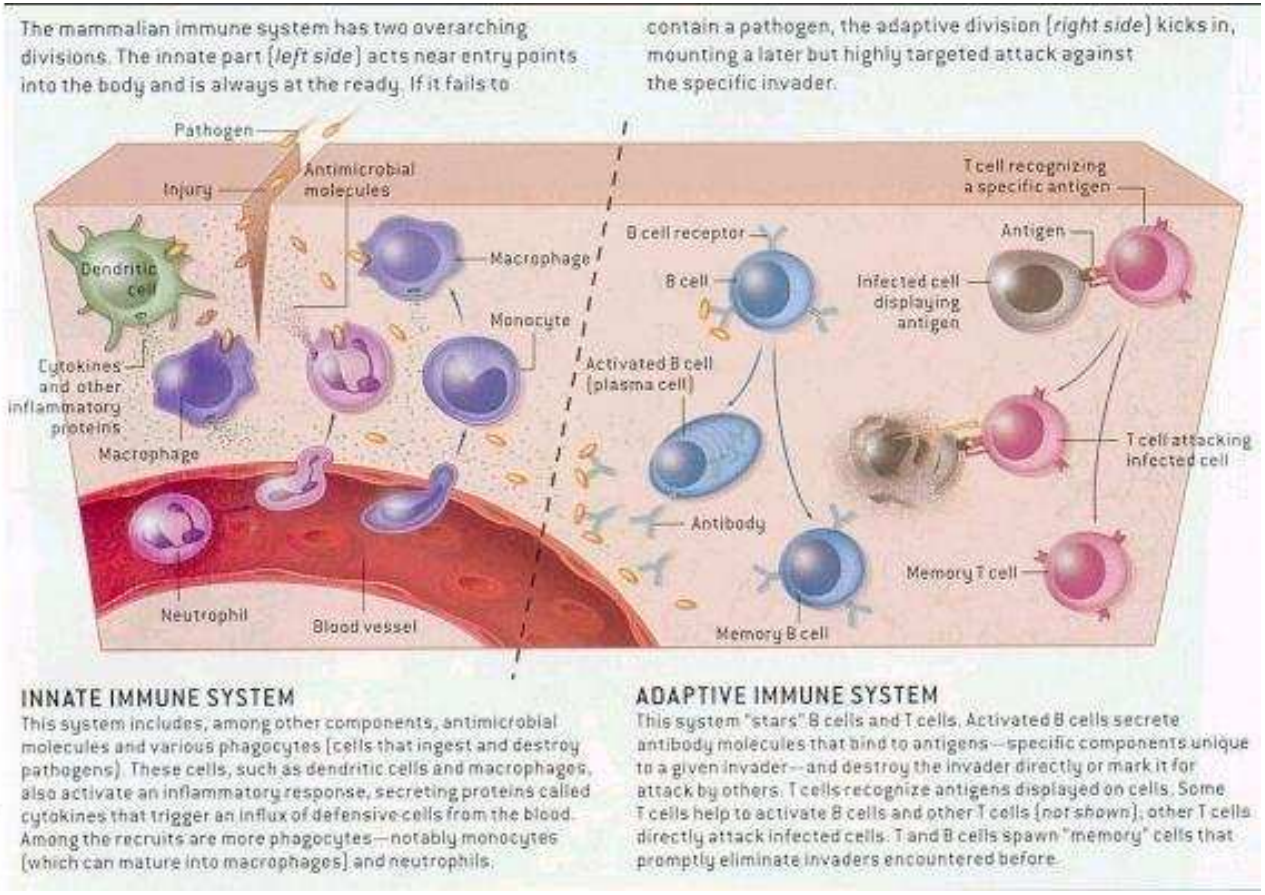
The Innate and Adaptive Arms of Immunity

Innate
Macrophage, DC

Adaptive
T and B Cells



Among the most dangerous enemies we humans face are our own distant relatives, the microbes. No human being can long withstand their onslaught unprotected. We survive because the human body has a variety of effective defenses against this constant attack.



Origin of innate and adaptive immune cells

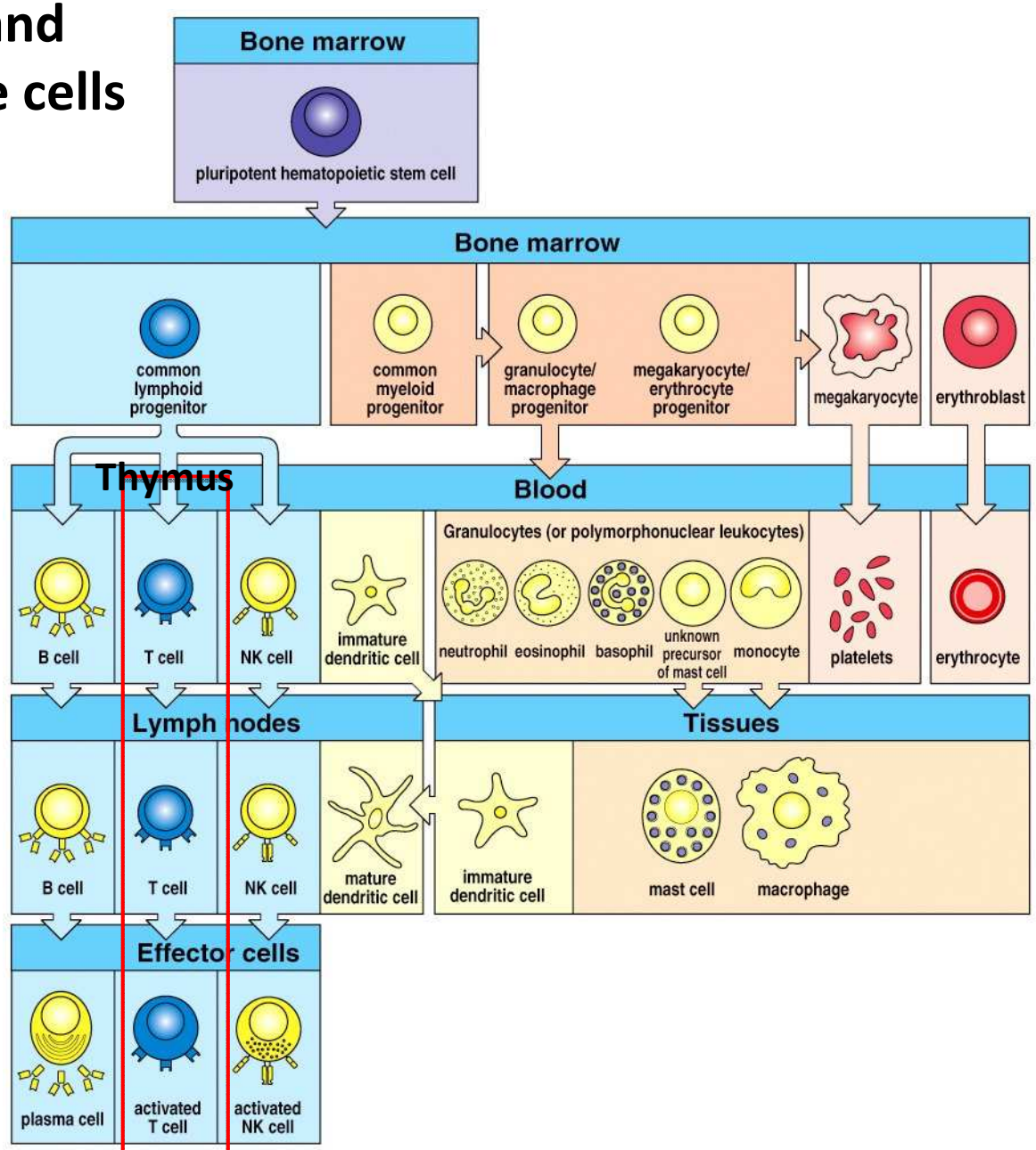


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

T and B cell Diversity is Essential for the Immune System to be Successful

Achieved through the **T** and **B Cell Receptors**

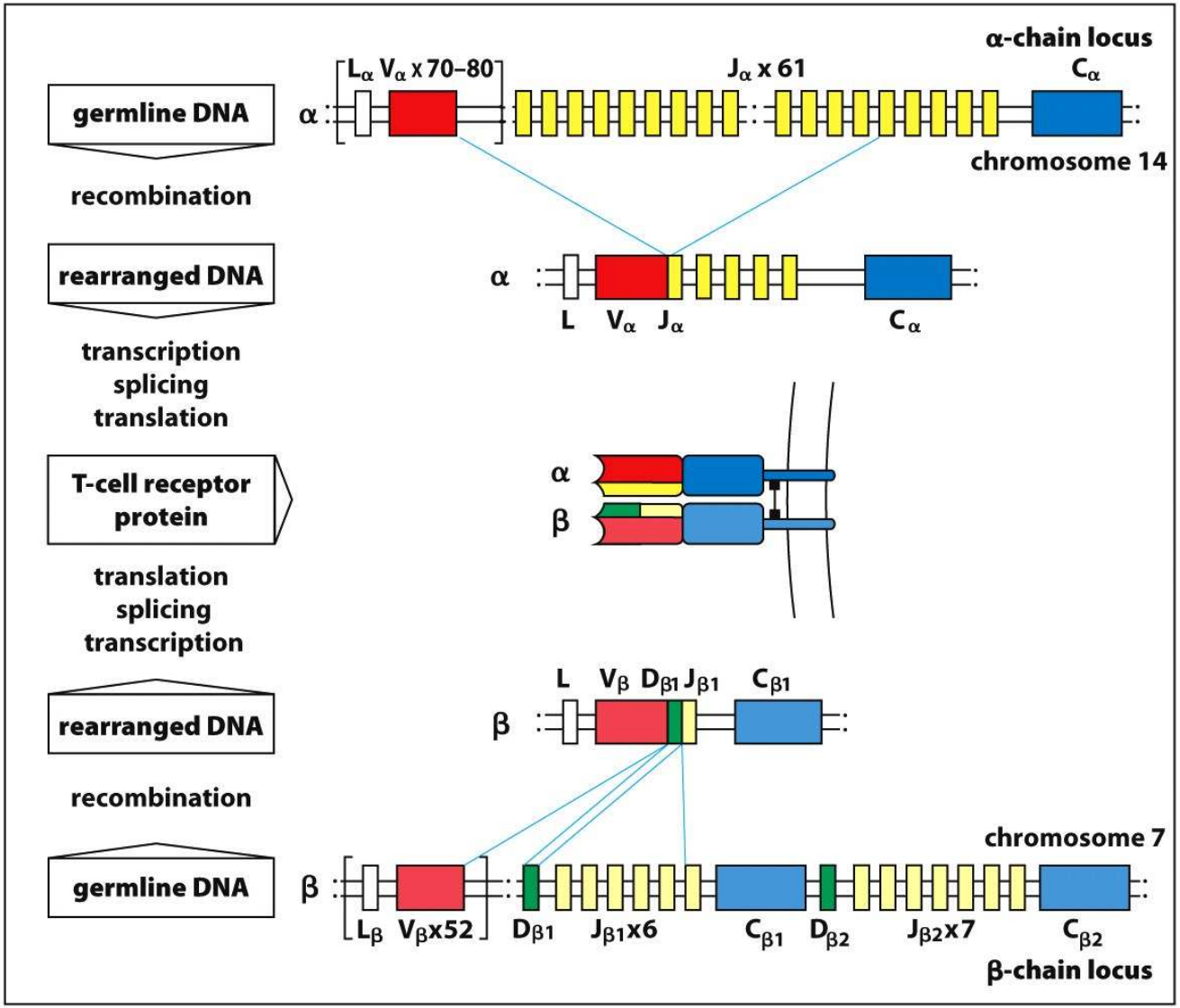
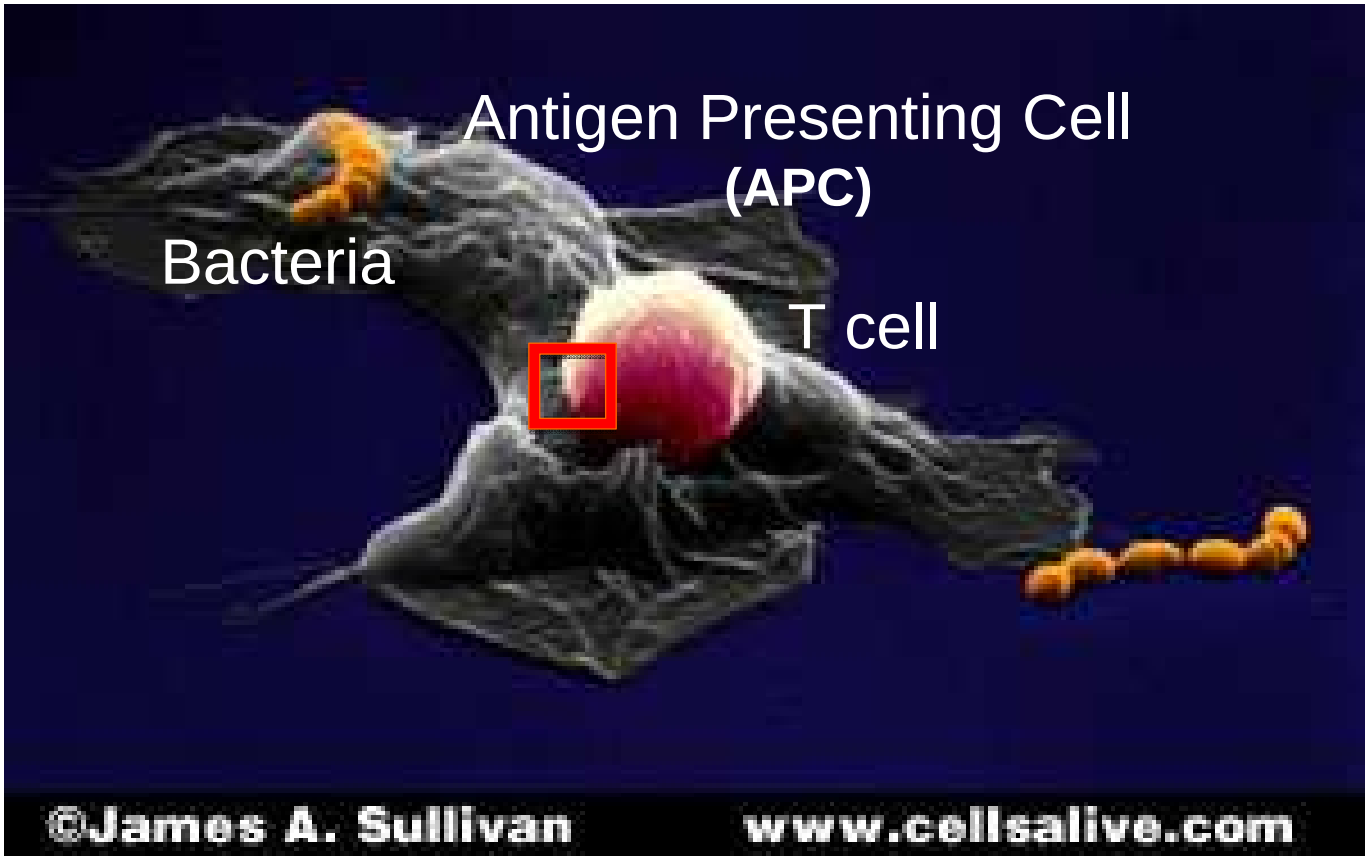


Figure 5.3 The Immune System, 3ed. (© Garland Science 2009)

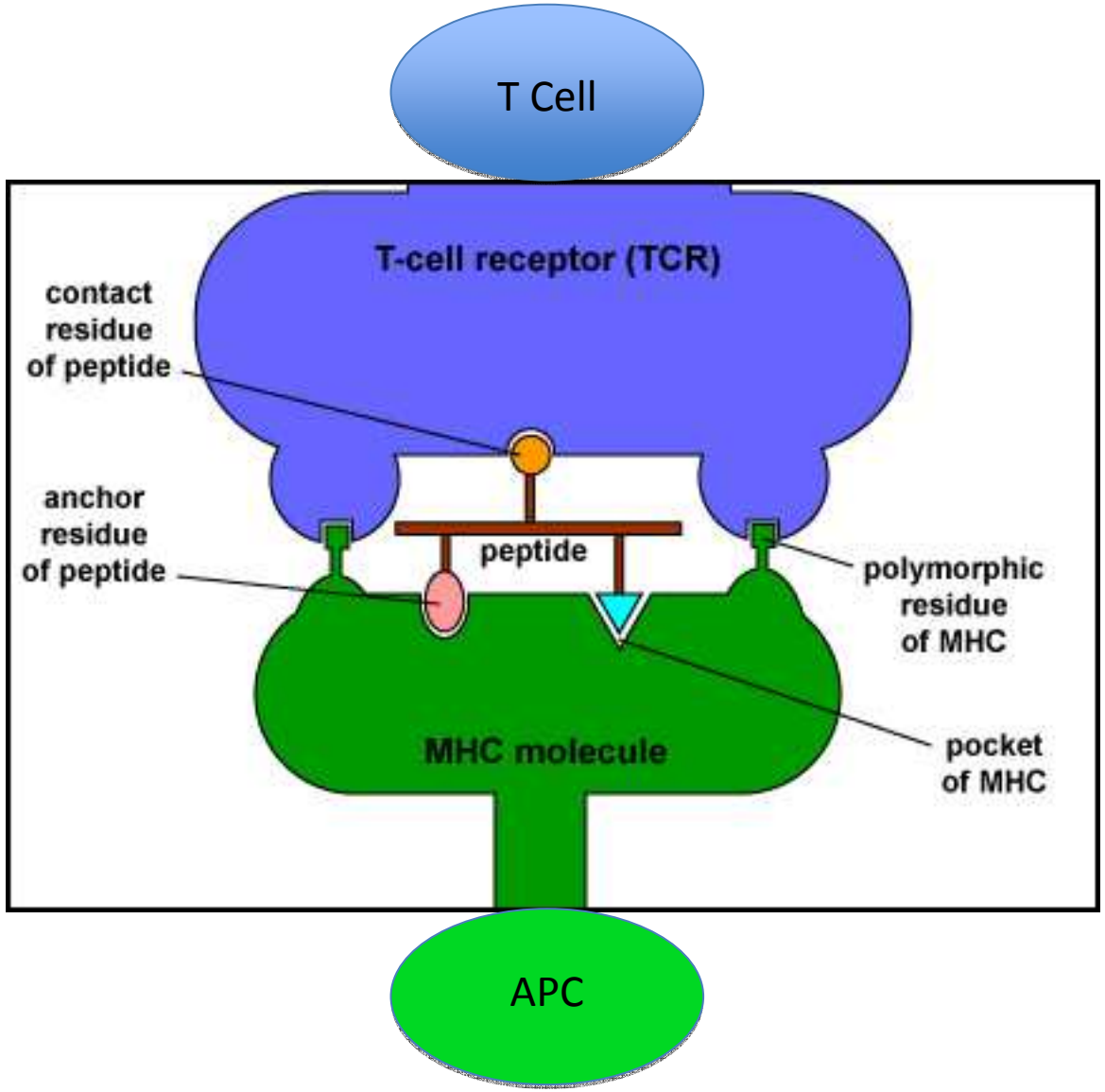
Extent of Adaptive Diversity

	B cells		T cells	
Element	Immunoglobulin		αβ receptors	
	H	κ+λ	β	α
Variable segments (V)	51	69	52	~70
Diversity segments (D)	~30	0	2	0
D segments read in 3 frames	rarely	–	often	–
Joining segments (J)	5	5	13	61
Joints with N and P nucleotides	2	(1)	2	1
Number of V gene pairs	3519		3640	
Junctional diversity	$\sim 10^{13}$		$\sim 10^{13}$	
Total diversity	$\sim 10^{16}$		$\sim 10^{16}$	

The Innate Immune System Educates the Adaptive arm through Antigen Presentation Through Cell-Cell Contact



T Cell Receptor Recognition of Antigenic Peptide in the context of Self MHC Molecules



THYMUS
Discriminating “self” from “non-self”

- Pre-T cells migrate to the thymus from the fetal liver or bone marrow under the influence of thymic hormones

- Pre-T cells arriving at the thymus are “double negative” (CD4-, CD8-) and don’t express a TCR

- Pre-T cells then acquire TCR, CD4 and CD8 markers (“double positive” ,CD4+ CD8+) in the cortex

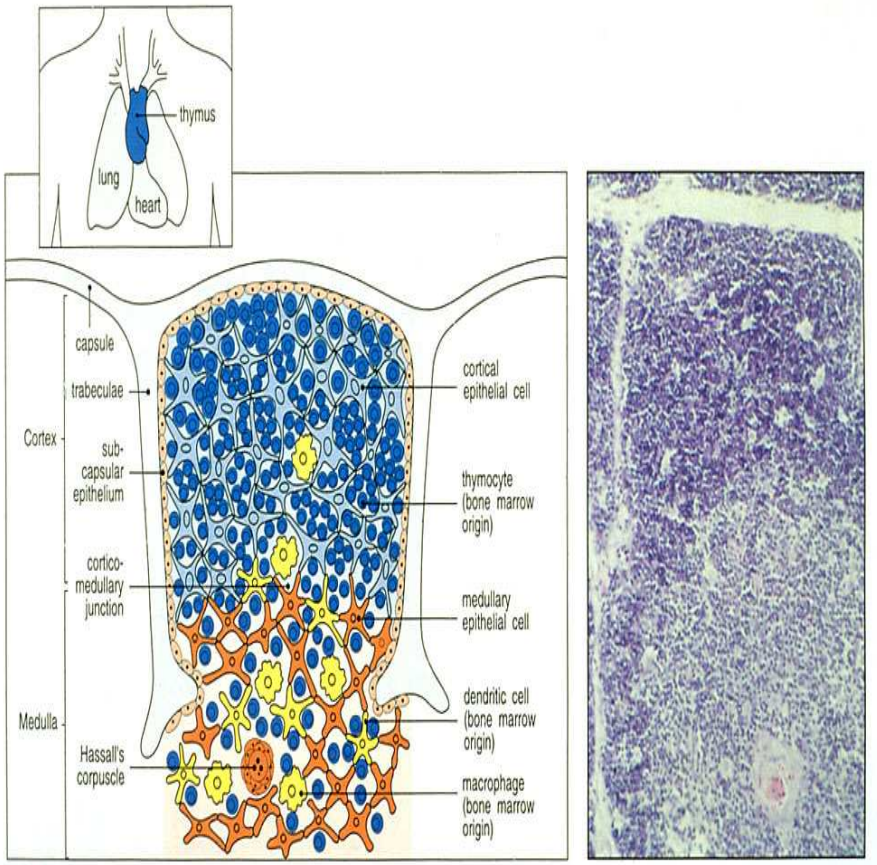
- As cells transverse cortex to medulla they undergo “**positive and negative**” selection and become single positive either as CD4+ TCR+ (T_{helper}), CD4+ TCR+($T_{regulatory}$) or CD8+ TCR+($T_{cytotoxic}$)

Positive Selection – If the TCR recognizes self MHC molecules the cells are selected to survive.

Negative Selection – TCR recognizes a “self” peptide Ag with too high an affinity and the cell dies and is eliminated from the body

- Cortical T cells migrate to the medulla during development from where they enter the peripheral circulation

- They eventually seed the secondary lymphoid organs where they encounter and respond to antigenic stimulation



The cellular organization of the thymus

Peripheral T cell Lineages and Their Function

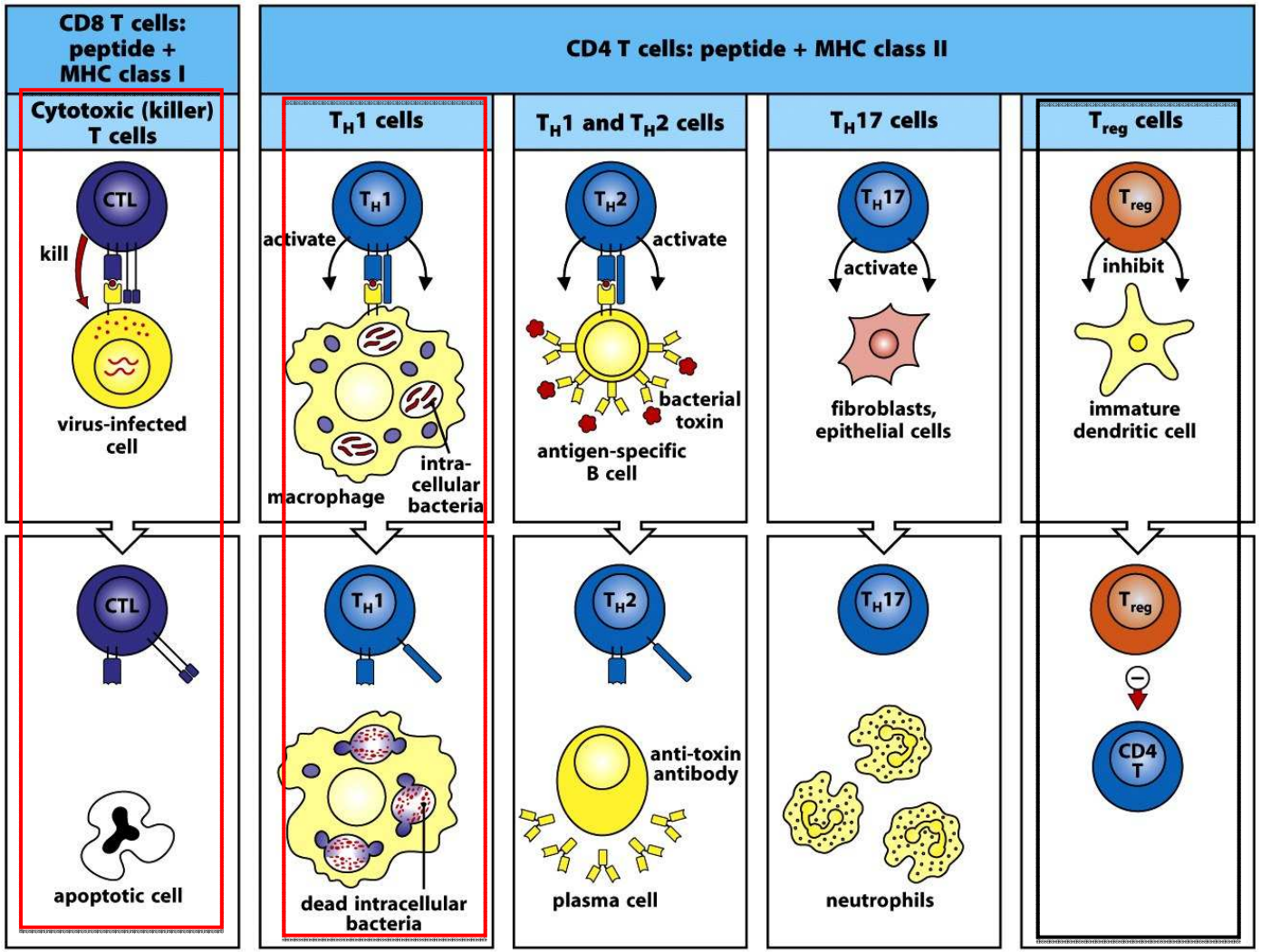
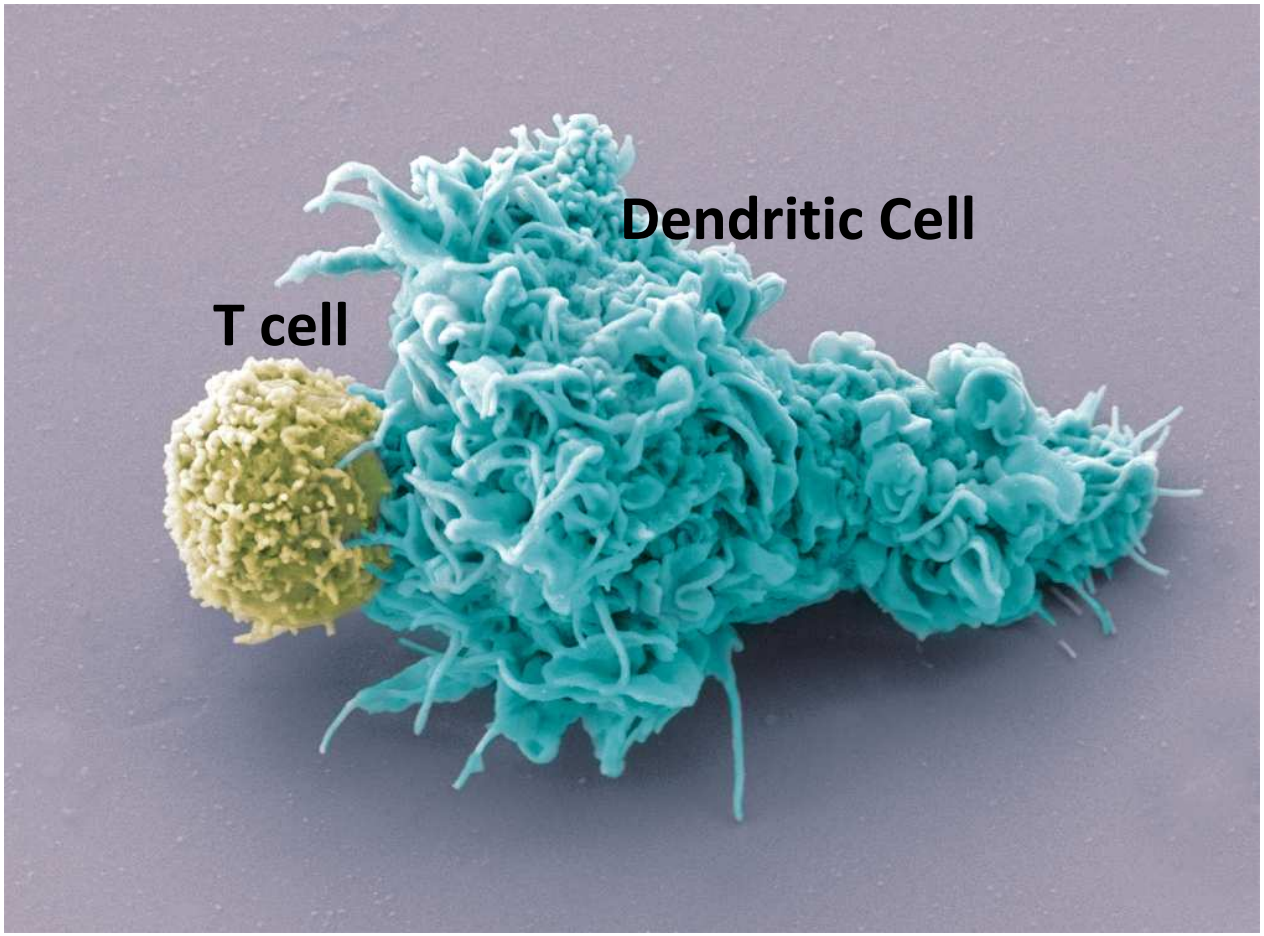


Figure 8-27 Immunobiology, 7ed. (© Garland Science 2008)

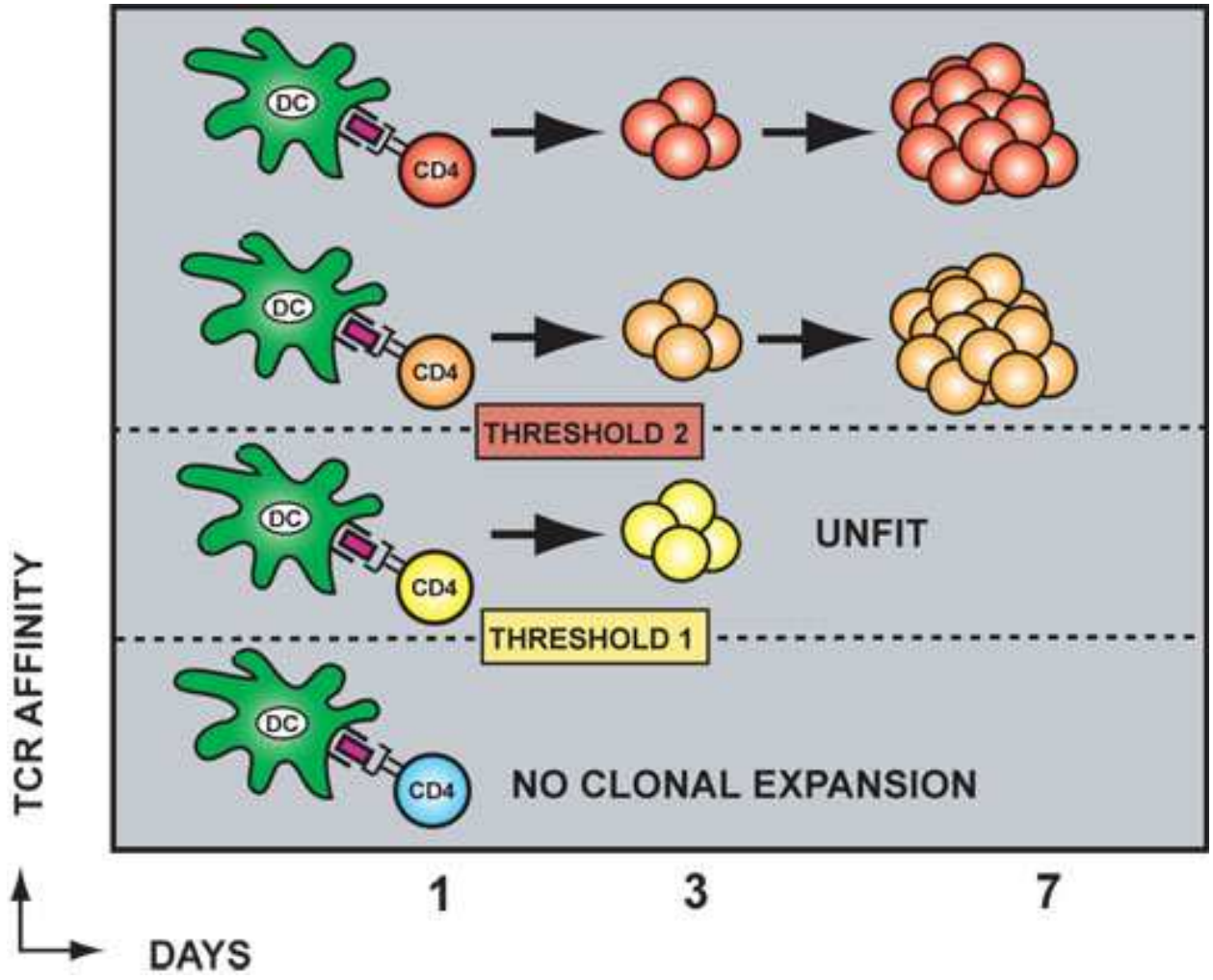
T cell Encounters Ag in a Lymph Node and T cell Activation Occurs

(DC/Ag presentation)

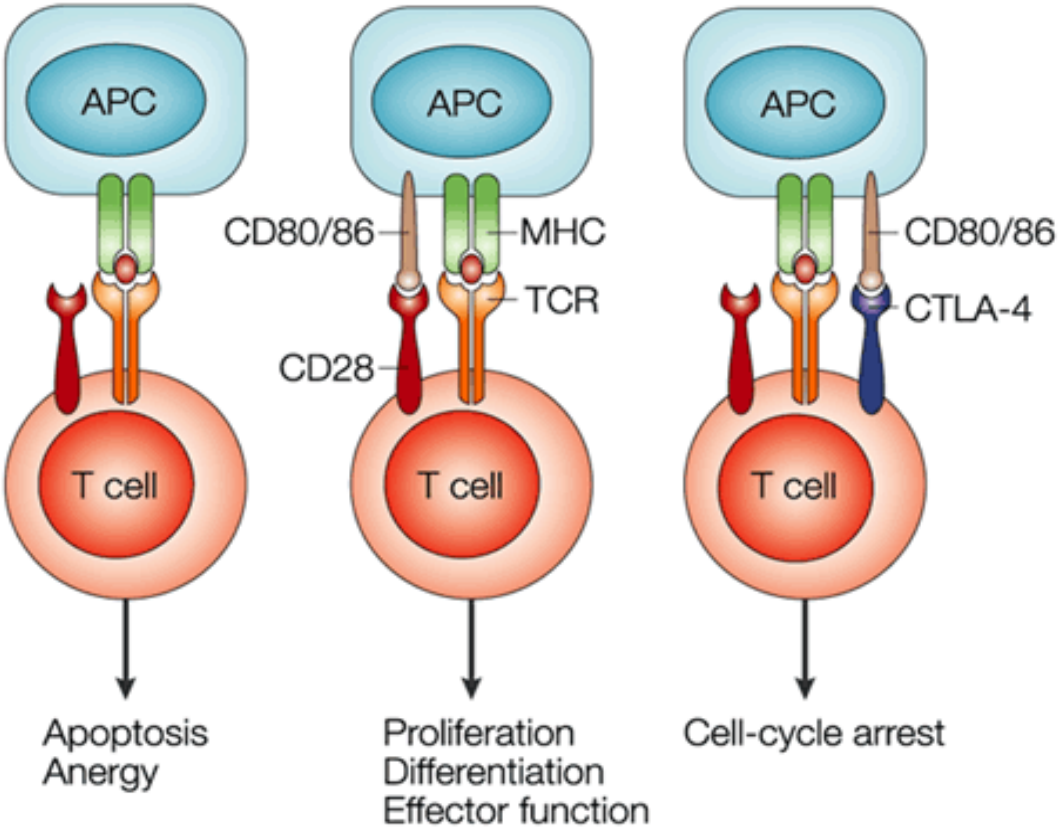


What Happens Next……Clonal Expansion of Peripheral T cells?

T cell Receptor Affinity Affects Clonal Expansion of T cells



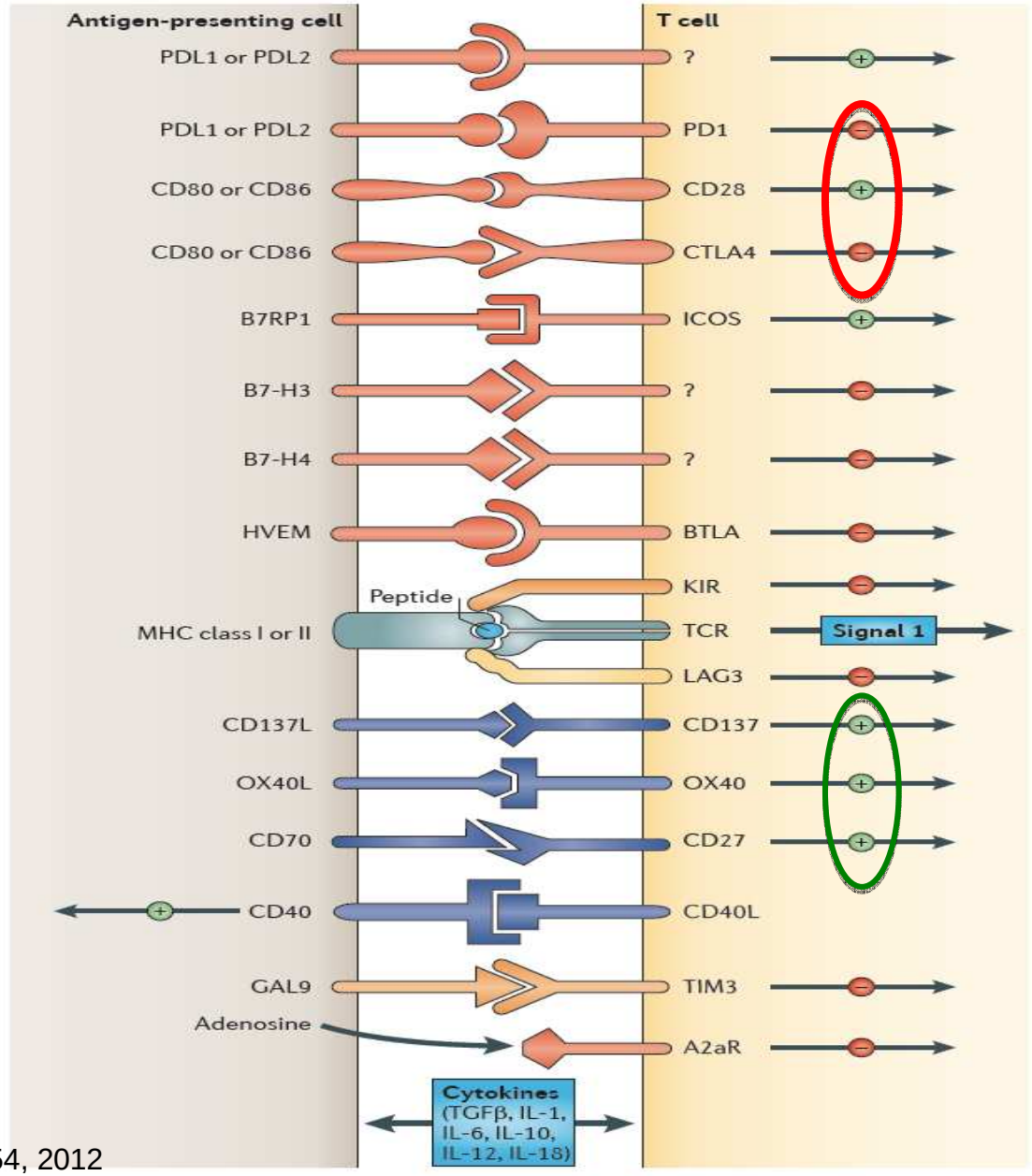
The Two Signal Hypothesis for Productive T cell Activation



One signal Two signals

*Alegre, M-L, Frauwirth, KA, Thompson, CB. T-cell regulation by CD28 and CTLA-4, Nat Rev Immunol *1*: 220-228.

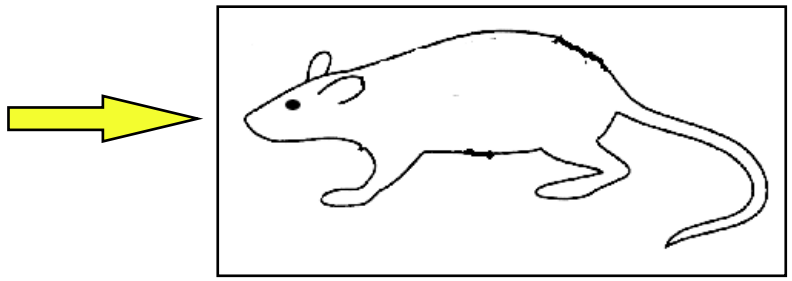
Multiple co-stimulatory and inhibitory interactions regulate T cell responses



Pardoll: Nature Rev Cancer 12: 254, 2012

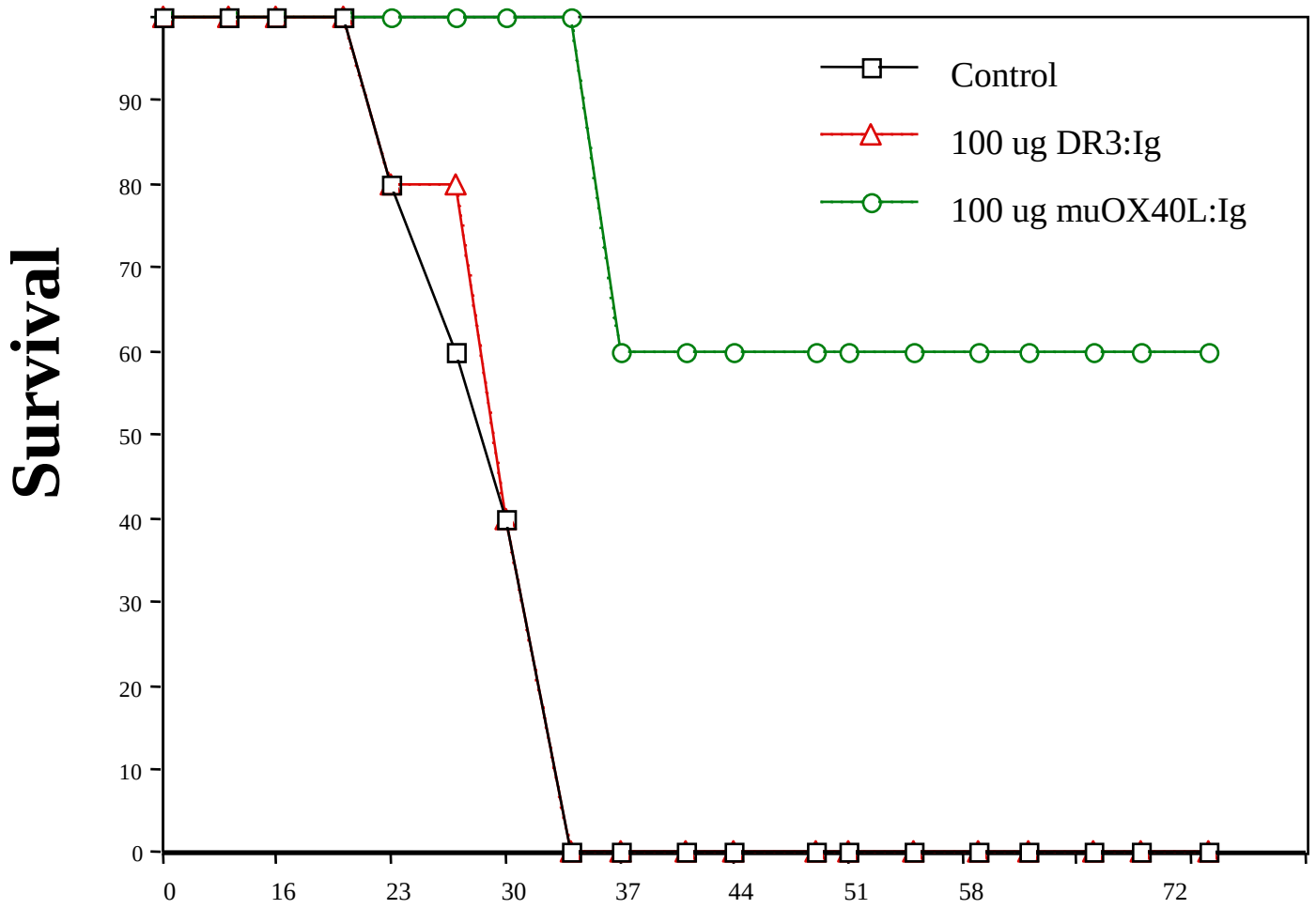
EFFECT of mOX40L:Ig or anti-OX-40 Solid Tumor Growth In Vivo

Solid Tumor
Administered s.c.



- Control
- 150 μg Sol. mu OX40L
- 150 μg anti-OX40
- Control

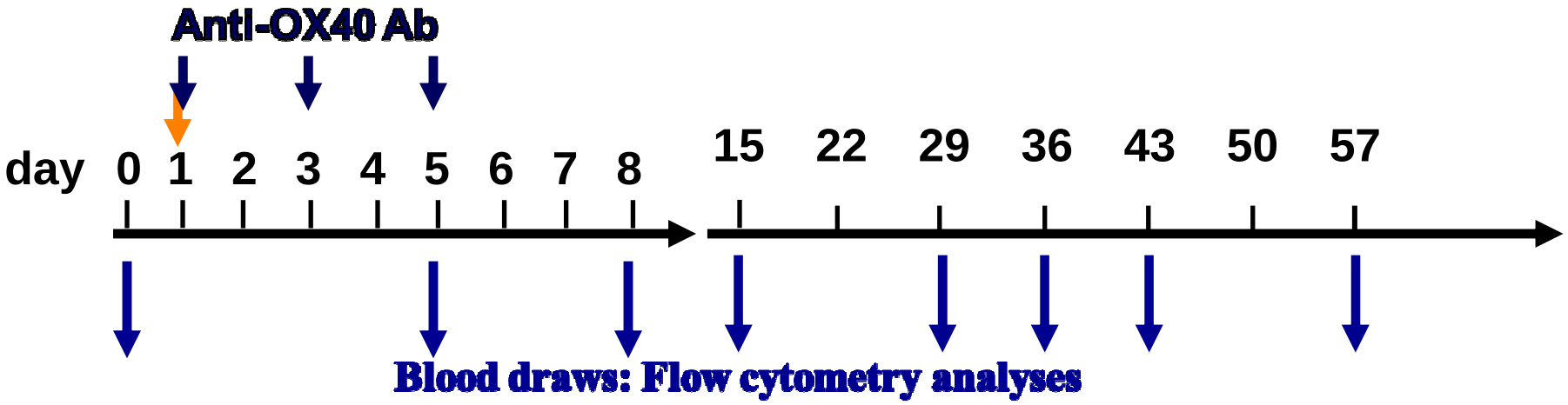
OX40L:Ig Treatment of MCA 303



Anti-OX40 Clinical Protocol

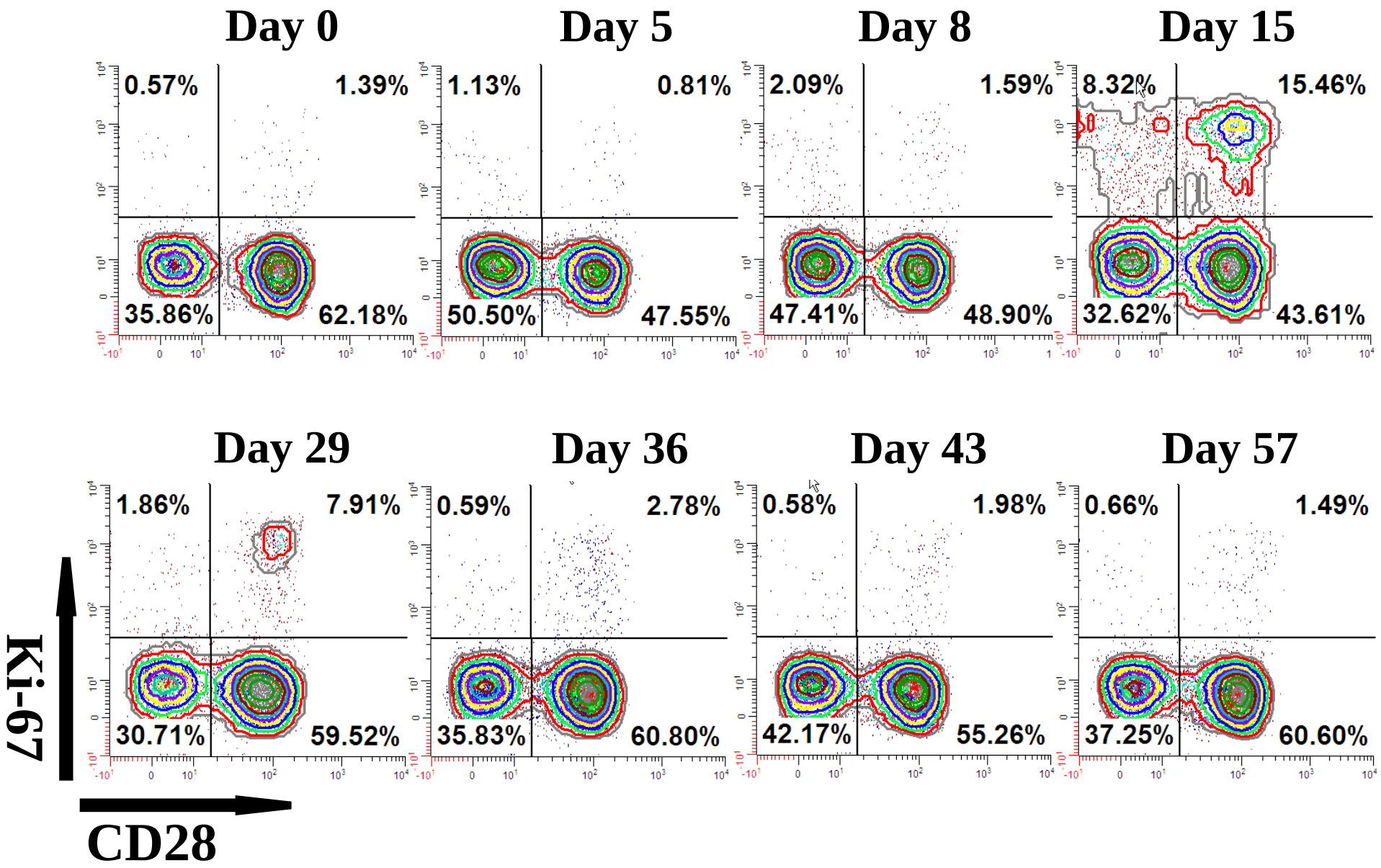
Cohort	# Patients per cohort	Dose of anti-OX40 (mg/kg)
1	10	0.1
2	10	0.4
3	10	2.0

Anti-OX40 Phase I Clinical Trial Time Course



Increased Proliferation of T Cells?

Proliferation of CD8 T cells
Post anti-OX40 treatment



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Healthy volunteers

Coordinators