Basic Principles of Tumor Immunotherapy

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- **Unlabeled/Unapproved Uses Disclosure**: This presentation includes discussion of cell therapies that have not received a clinical indication and should be considered as unlabeled and unapproved clinical use.

Learning Objectives

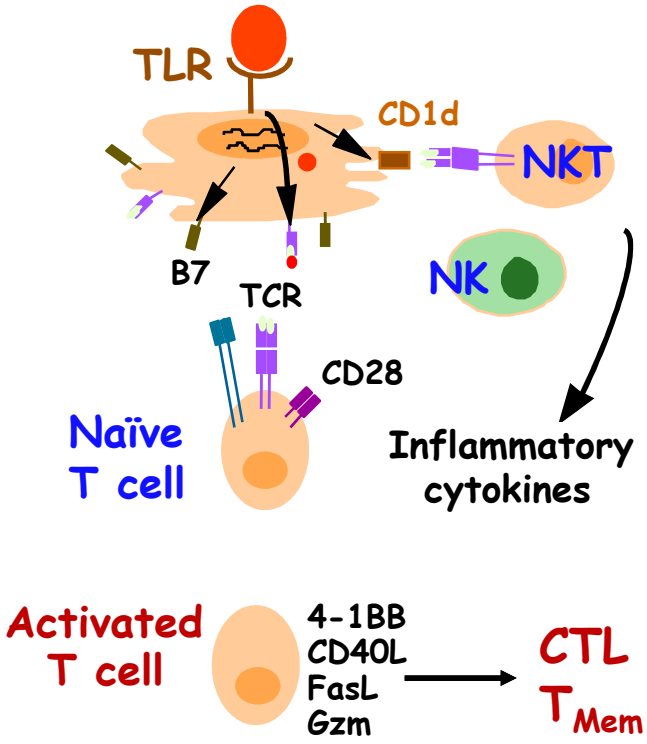
1. To understand the evolution of the concept of tumor immunosurveillance and immunotherapy

2. To be aware of challenges associated with effectively using immunotherapy for cancer care

3. To review the various approaches by which the immune system can be modulated for the treatment of cancer

Evolutionary Preparation of the Immune System

Pathogen



Innate

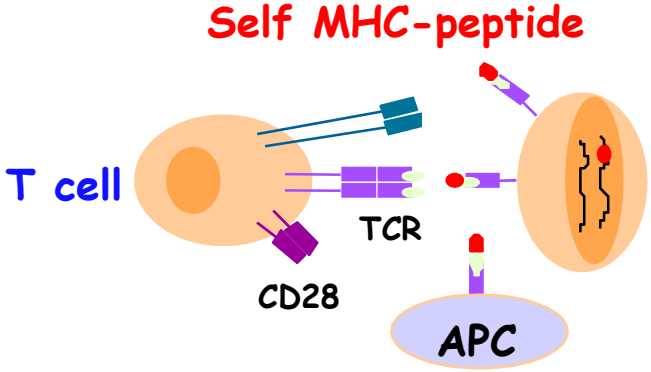
Stress-induced
Rae-1/HL60/MULT

NKG2D

Adaptive

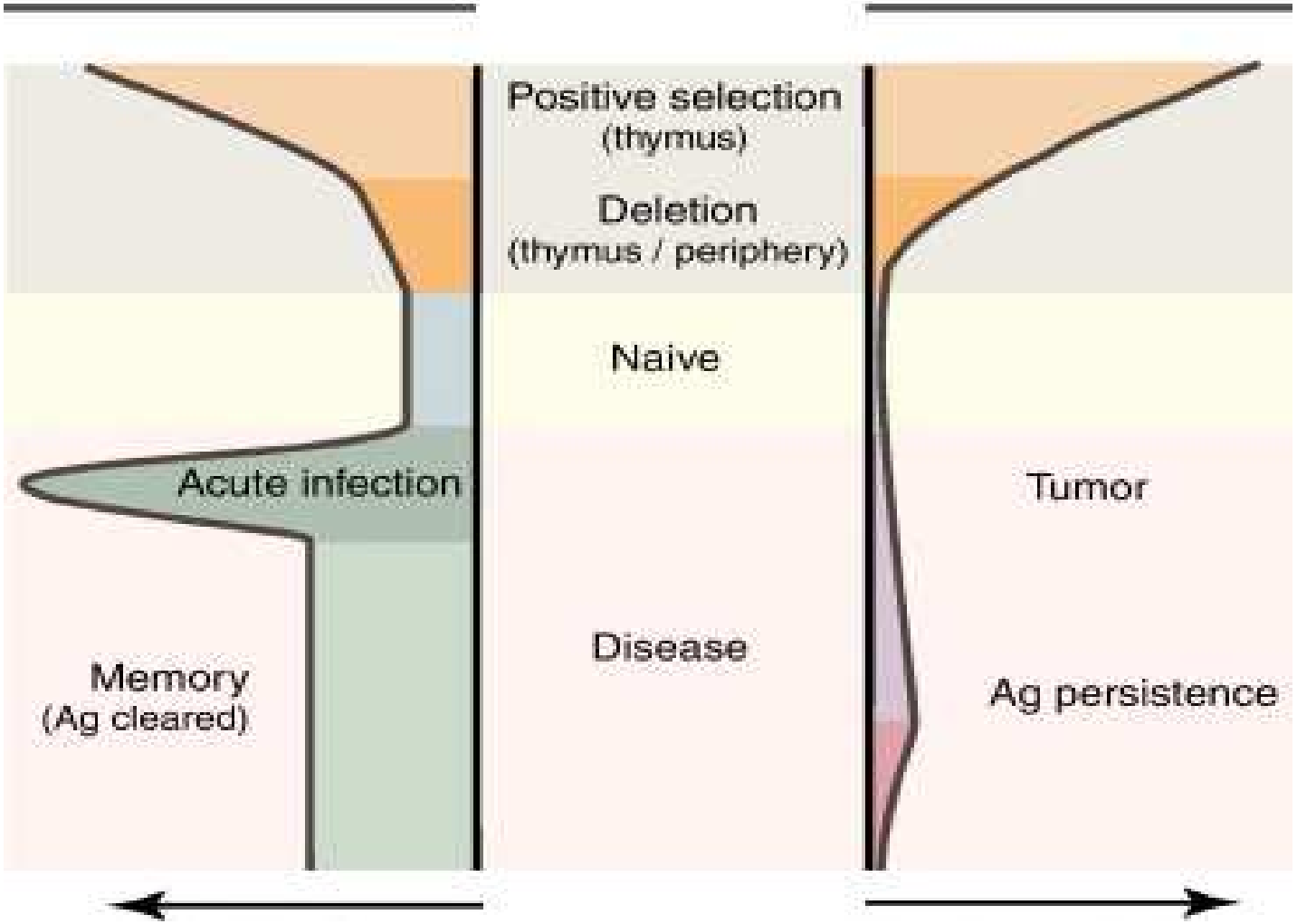
Tumor

Transformed normal cells



T cell activation ?

NK cell activation ?



Adapted: Baitsch et al, *Trends Immunol* 2012

Does our immune system react to tumors?

Early evidence for the association of immunity with cancer

Virchow R. Berlin, Germany
Handbuch der speciellen Pathologie und Therapie,
ed. Bd. 1, Erlangen, 1854

- Noted enlarged supra-clavicular nodes due to 'leucoreticular infiltrates' as one of the earliest sign of gastrointestinal malignancy (Virchow's node).

- Suggested a relationship between immune inflammation and tumorigenesis.

Cancer regressed following an acute bacterial infection

Fehleisen F.
Die Etiologie des Erysipels. Berlin, Germany 1883.

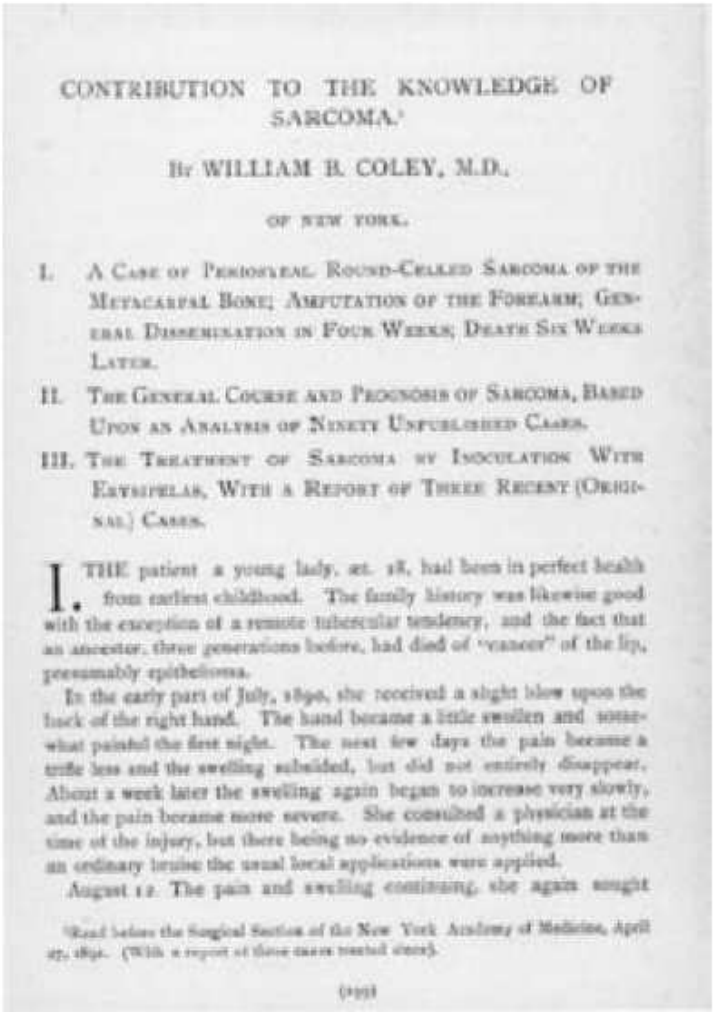
Robert Koch, Louis Pasteur and Emil von Behring

Observed that *Streptococci* bacterial infection during erysipelas coincided with cancer regression.

Coley's Toxin: Heat-killed *Streptococci* & *Serratia marcescens*
The First Immunotherapy

William B. Coley
(1862 – 1936)

Chief, Bone Sarcoma Unit
Memorial Hospital
New York



CONTRIBUTION TO THE KNOWLEDGE OF SARCOMA.[1]

By WILLIAM B. COLEY, M.D.,

OF NEW YORK.

I. A Case of Periosteal Round-Celled Sarcoma of the Metacarpal Bone; Amputation of the Forearm; General Dissemination in Four Weeks; Death Six Weeks Later.

II. The General Course and Prognosis of Sarcoma, Based Upon an Analysis of Ninety Unpublished Cases.

III. The Treatment of Sarcoma by Inoculation With Erysipelas, With a Report of Three Recent (Original) Cases.

I. THE patient a young lady, æt. 18, had been in perfect health from earliest childhood. The family history was likewise good with the exception of a remote tubercular tendency, and the fact that an ancestor, three generations before, had died of "cancer" of the lip, presumably epithelioma.

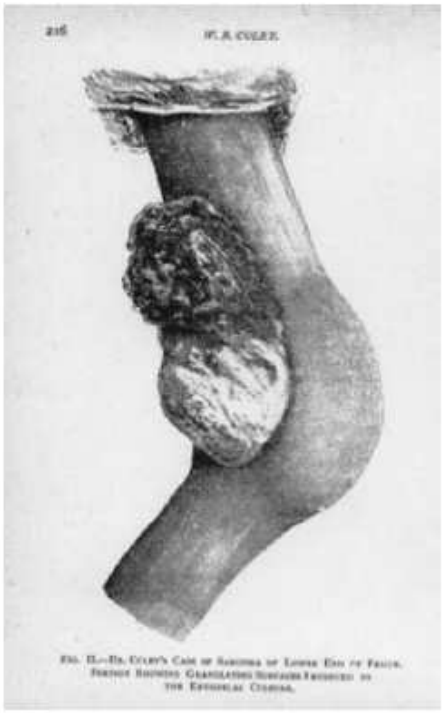
In the early part of July, 1890, she received a slight blow upon the back of the right hand. The hand became a little swollen and somewhat painful the first night. The next few days the pain became a trifle less and the swelling subsided, but did not entirely disappear. About a week later the swelling again began to increase very slowly, and the pain became more severe. She consulted a physician at the time of the injury, but there being no evidence of anything more than an ordinary bruise the usual local applications were applied.

August 12. The pain and swelling continuing, she again sought

[1]Read before the Surgical Section of the New York Academy of Medicine, April 27, 1891. (With a report of three cases treated since).

(199)

Coley WB. Annals of Surgery 1891;14:199–200



Coley's First Bone Sarcoma Case

49% success rate

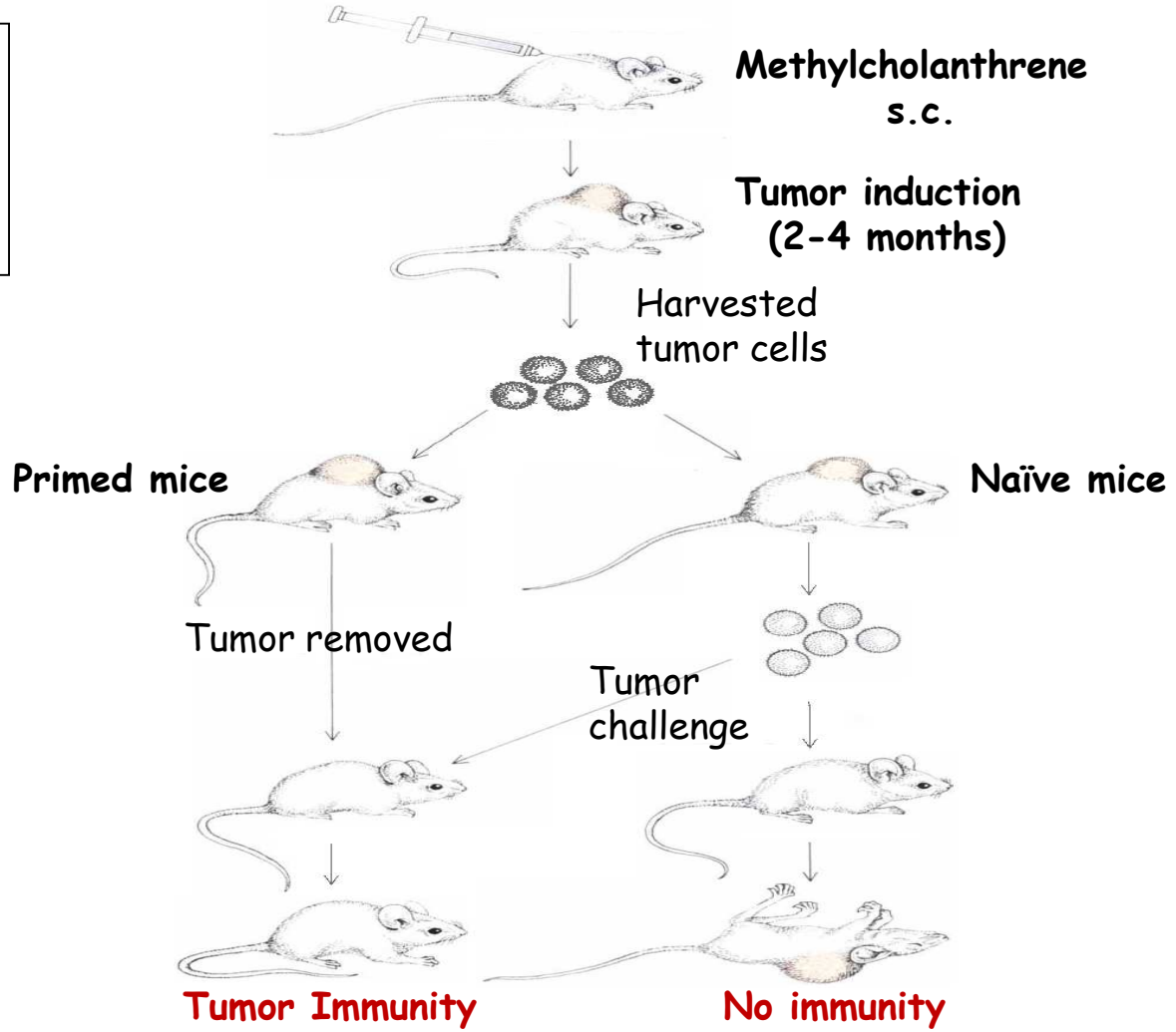
McCarthy EF. *IOWA Orthop J*, 2006

Beginnings of cancer immunosurveillance hypothesis

Ehrlich P. Germany
Über den jetztigen Stand der Karzinomforschung.
Ned Tijdschr Geneeskd 1909; 5: 273-290

Cancer would occur at incredible frequency if immune defense did not work. Hypothesized that the immune system could control cancer development.

Demonstration of tumor immunity in inbred mice



Immunity to methylcholanthrene-induced sarcomas.
Prehn RT, Main JM. *J Natl Cancer Inst.* 1957 Jun;18(6):769-78

Demonstration of resistance against methylcholanthrene-induced sarcomas in the primary autochthonous host.
Klein G, Sjogren HO, Klein E, Hellstrom KE. *Cancer Res.* 1960 Dec;20:1561-72.

Cancer—a biological approach. 1. The process of control.
Burnet FM. 1957 Br Med J. 1:779–782. (Australia)

In: Cellular and humoral aspects of the hypersensitive States.
Thomas L. 1959. Lawrence HS, ed., Hoeber-Harper (New York)

Formulated the concept of tumor immunosurveillance

Treatment of primary fibrosarcoma in the rat with immune lymphocytes.
Delorme EJ, Alexander P. (London)
Lancet. 1964;2:117–120.

Therapy of cancer using the adoptive transfer of activated killer cells and interleukin-2.
Topalian SL, Rosenberg SA. (NIH)
Acta Haematol. 1987; 78:75-6.

IL-2 approved as anti-cancer therapy


NOVEMBER 25, 1985
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GORBACHEV VS. THE SOVIET ECONOMY
CANCER BREAKTHROUGH
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sterile Water for
NANT INTERLEUKIN-2,
des-alanyl, serine-125
Lyophilized Preparation
2-8°C — For single use
with sterile Water for
Cetus Corp.'s tumor-zapping Interleukin-2

Identification of Cancer Antigens

Presence on a human melanoma of multiple antigens recognized by autologous CTL.
Van den Eynde B, Hainaut P, Hérin M, Knuth A, Lemoine C, Weynants P, van der Bruggen P, Fauchet R, **Boon T**.
Int J Cancer. 1989; 44:634-40

A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma
Van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, **Boon T**.
Science. 1991; 254:1643-7

Cancer-germline self antigens

Humans: MAGE, BAGE, GAGE, RAGE, NY-ESO, MUCINS
Mouse: P1A

Antigenic Cancer Cells Grow Progressively in Immune Hosts without Evidence for T Cell Exhaustion or Systemic Anergy.

Wick M, P Dubey, H Koeppen, CT Siegel, PE Fields, L Chen, JA Bluestone, H Schreiber

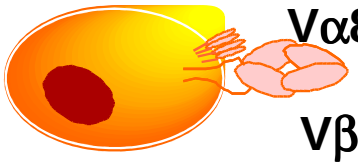
J Exp Med. 1997;186:229–238.

Established tumors failed to attract and activate tumor-specific T cells at the tumor site.

Do functional T cells develop against self tumor antigens?

TCRP1A transgenic mice

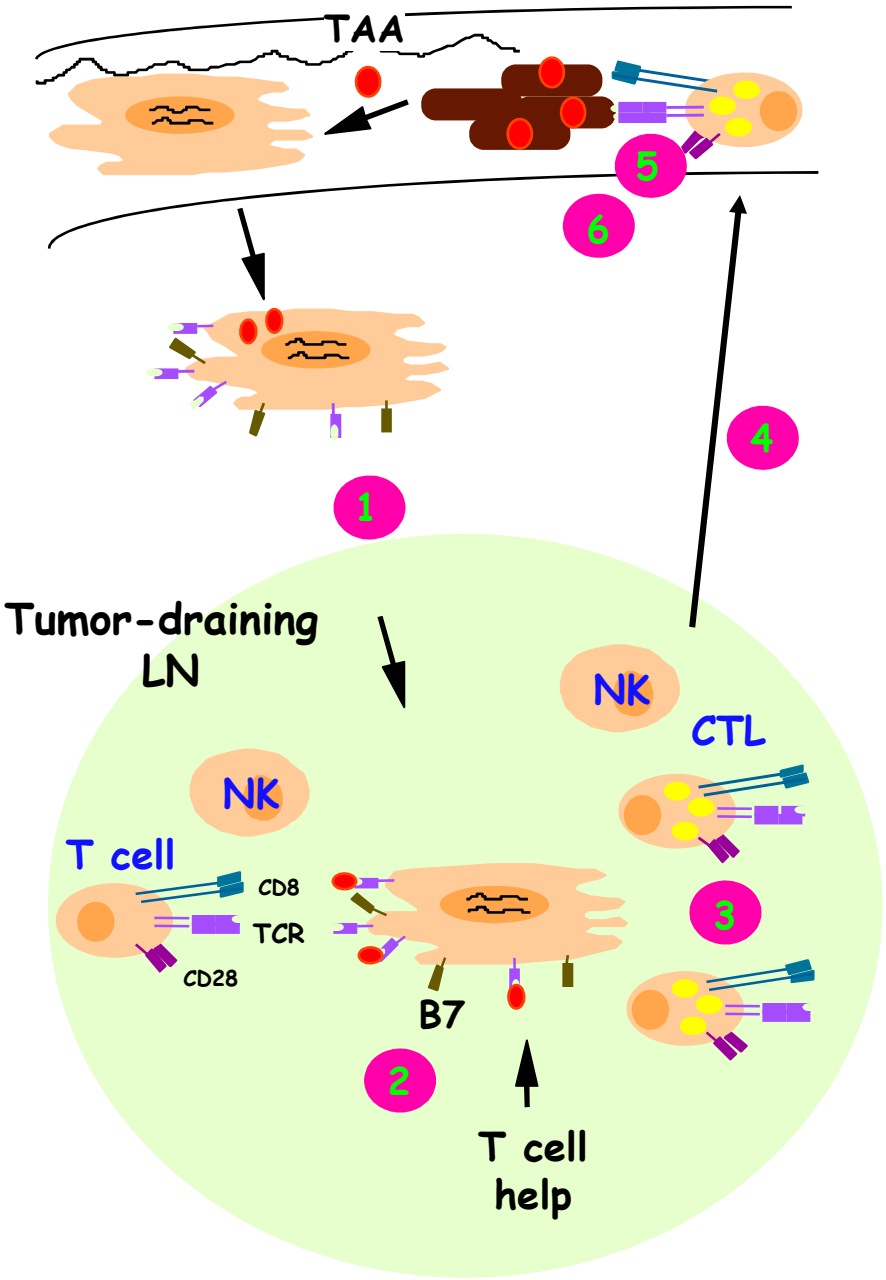
DBA/2, B10.D2



TCR anti-L^d:P1A (LPYLGWLVF)

Thymocyte-intrinsic genetic factors influence CD8 T cell lineage commitment and affect selection of a tumor-reactive TCR
Shanker A, Auphan-Anezin N, Chomez P, Giraudo L, Van den Eynde B, Schmitt-Verhulst AM.
J Immunol. 2004, 172: 5069-5077

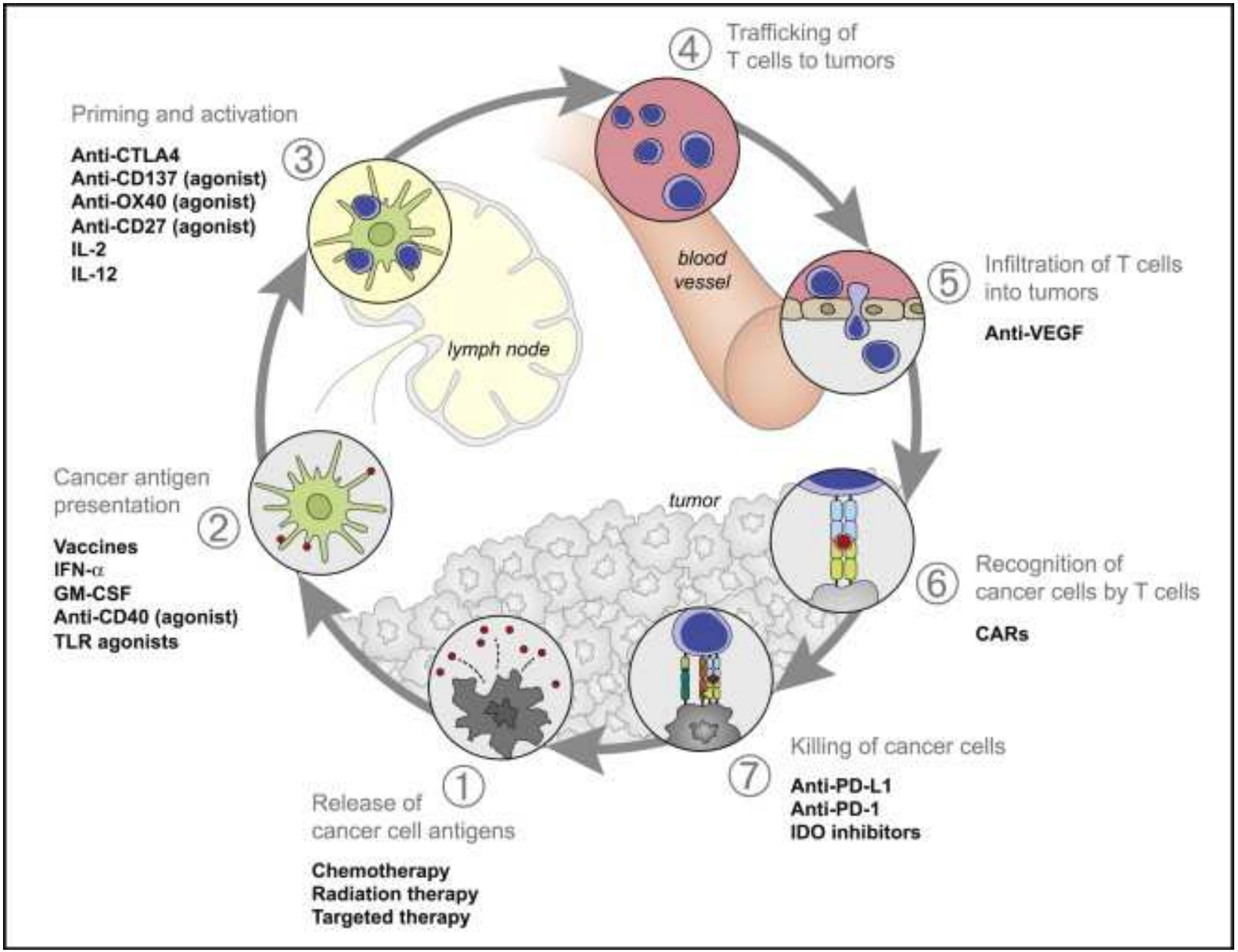
CD8 T cell help for innate antitumor immunity
Shanker A, Verdeil G, Buferne M, Inderberg-Suso EM, Puthier D, Joly F, Nguyen C, Leserman L, Auphan-Anezin N, Schmitt-Verhulst AM.
J Immunol. 2007, 179: 6651-6662



Where can an antitumor T cell response go wrong?

1. Tumor Ag presentation
2. Costimulation /T cell help
3. Quality of activation /differentiation
4. Migration /chemotactic recruitment
5. Local cytokine milieu
6. Frequency of effectors

The Cancer-T Cell Immunity Cycle



Chen & Mellman, *Immunity* 2013

December 20, 2013

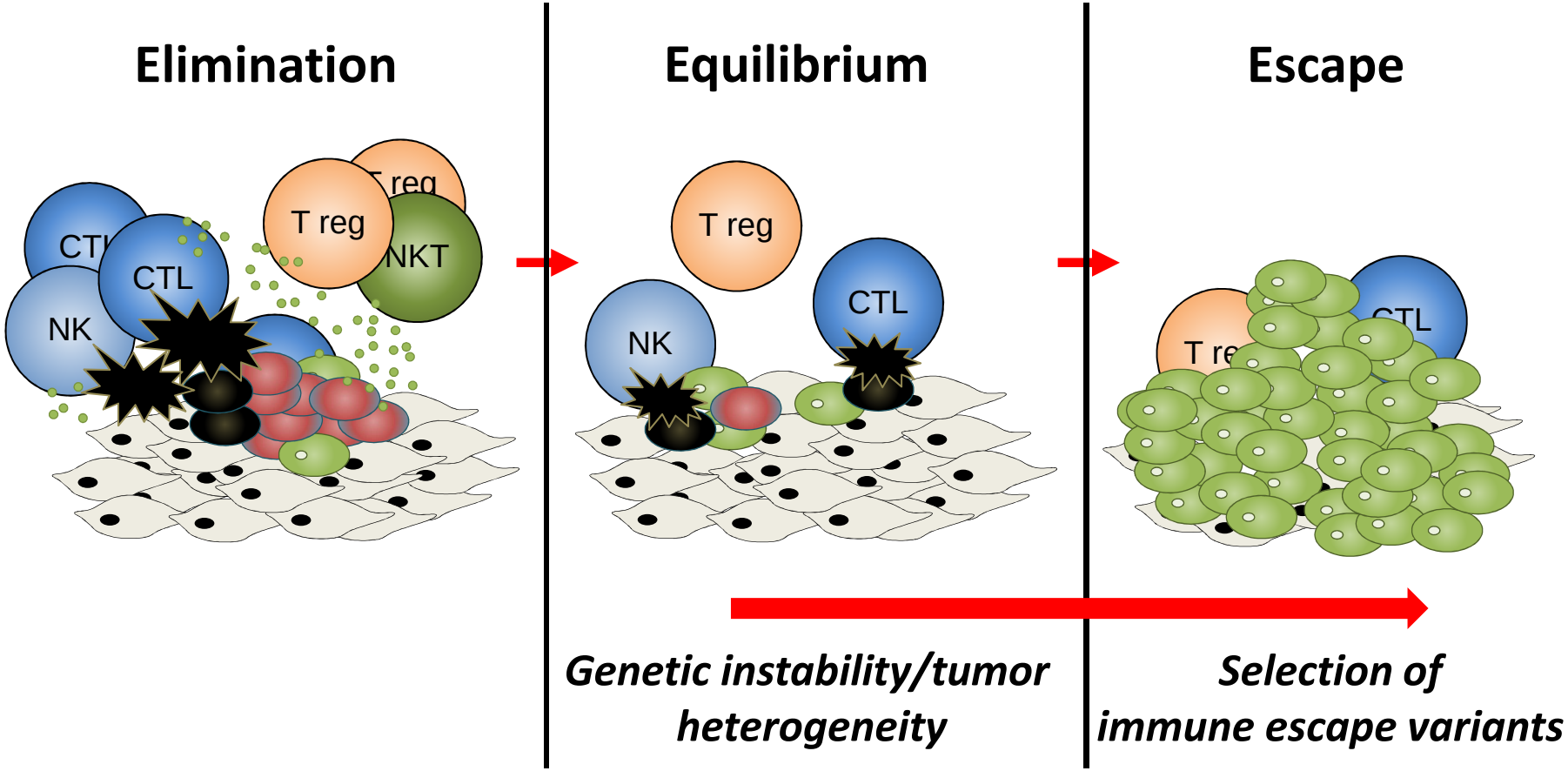
Challenges in T cell immunotherapy

- Tumor immunosuppression and evasion
- Immumnoediting of tumor cells
- Checkpoint control of T cells

Tumor Immunoediting

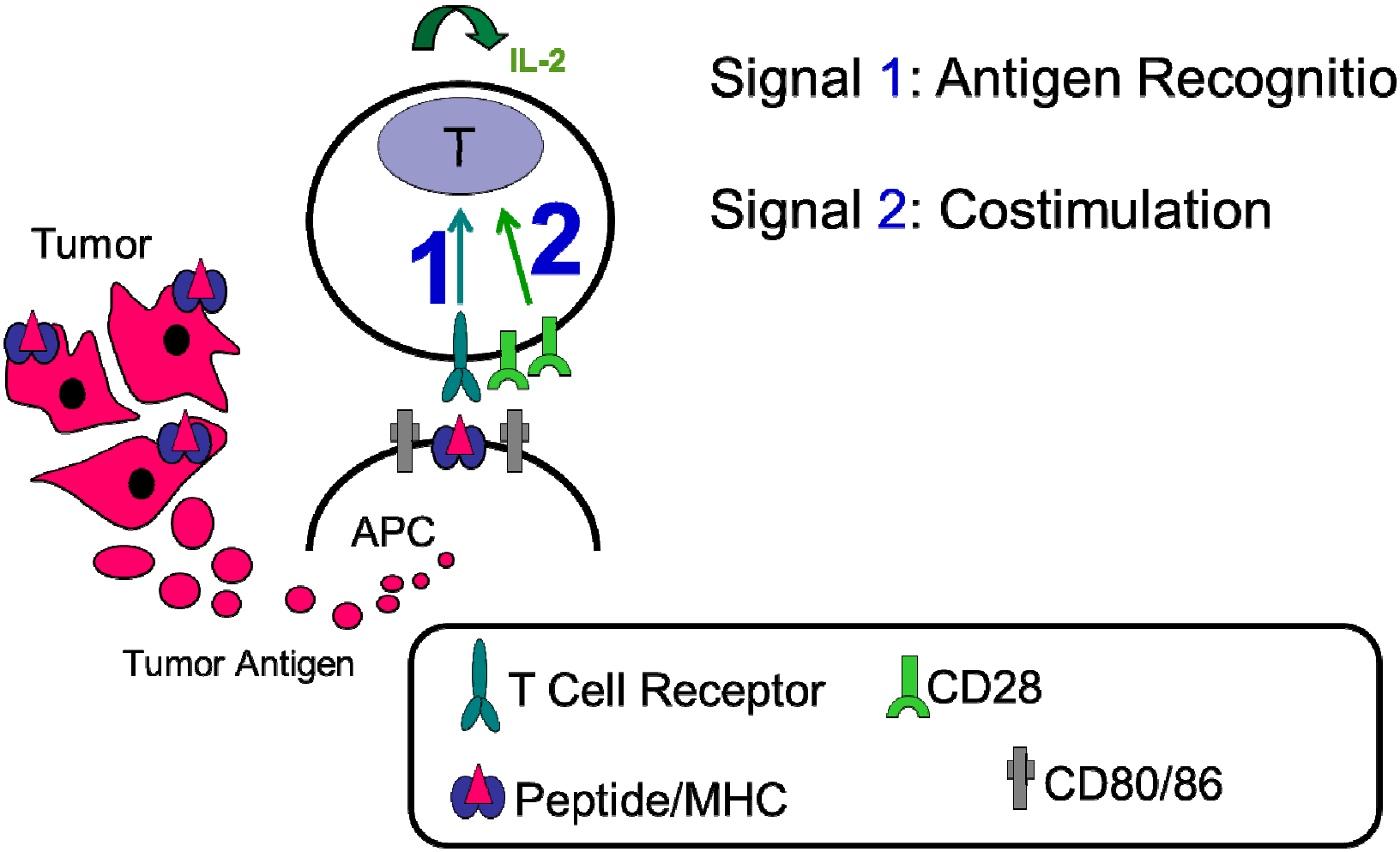
Schreiber RD and Smyth MJ

The immune system controls tumor quantity as well as edits tumor quality



Dunn GP et al. *Nat Immunol*. 2002;3:991-998. Schreiber R et al. *Science*. 2011;331:1565-1570.
Mittal D et al. *Curr Opin Immunol*. 2014;27:16-25.

T cell Activation: 2 signals

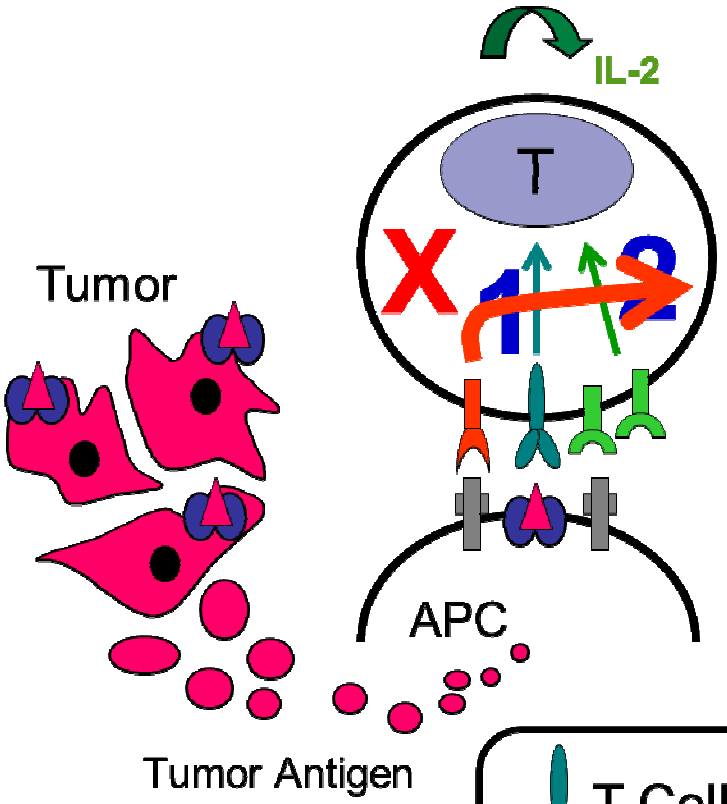


Signal 1: Antigen Recognition

Signal 2: Costimulation

adapted from JP Allison

T cell Activation: 2 signals



Signal 1: Antigen Recognition

Signal 2: Costimulation

Signal X: Checkpoint

T Cell Receptor

CD28

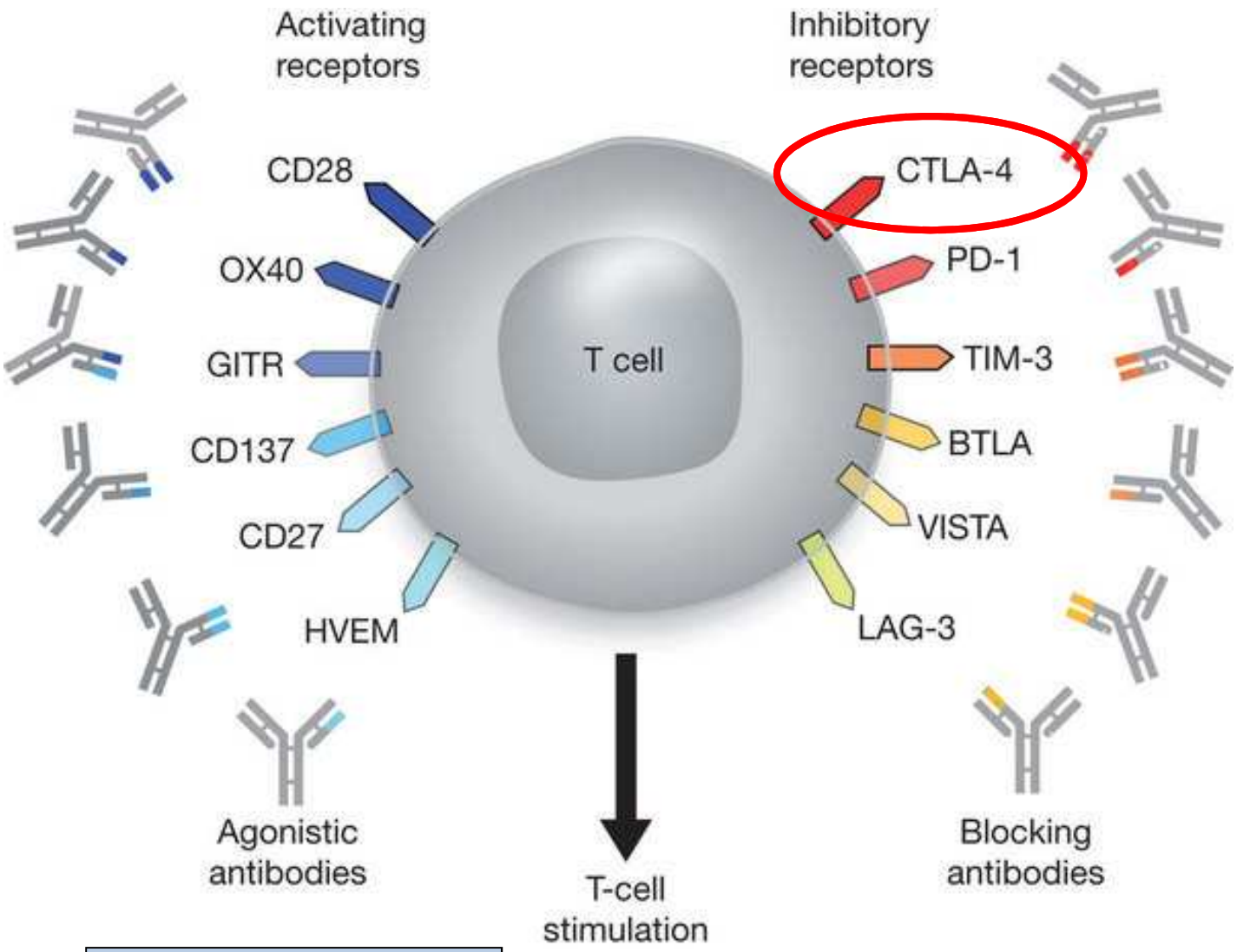
CTLA-4

Peptide/MHC

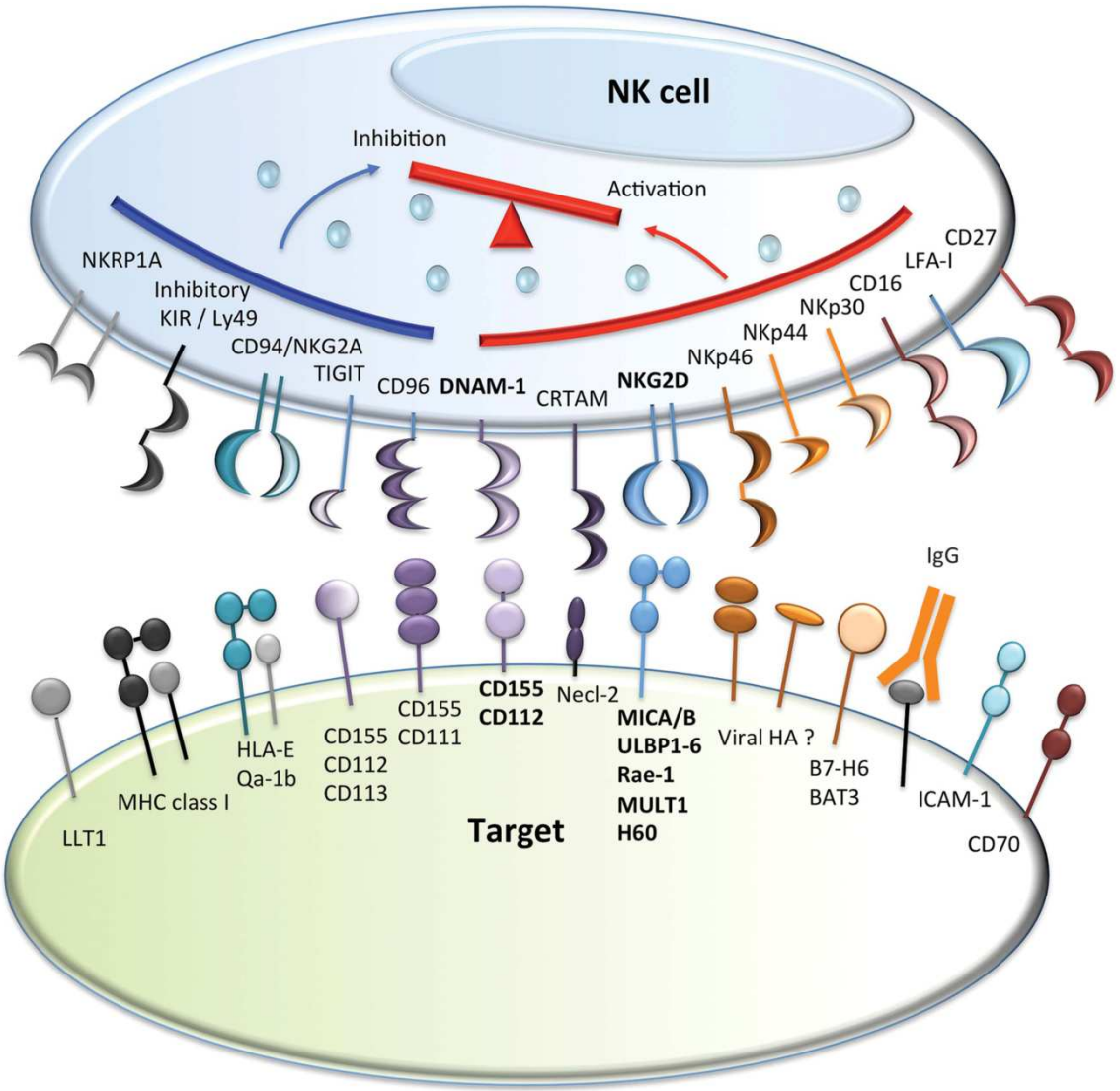
CD80/86

adapted from JP Allison

T cell Checkpoint Receptors

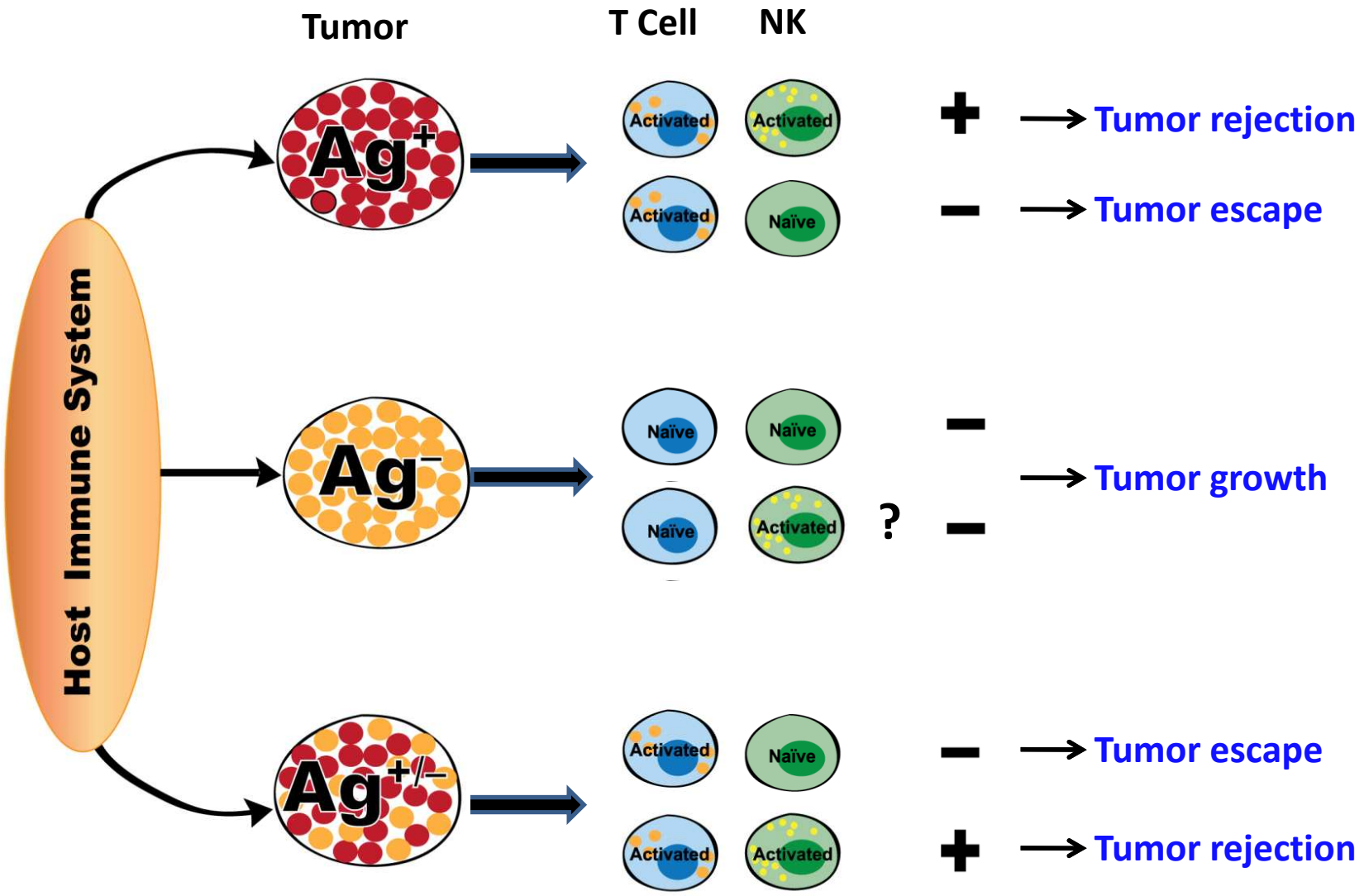


NK cell Checkpoint Receptors



Chan CJ et al, *Cell Death Diff* 2014, 21:5-14

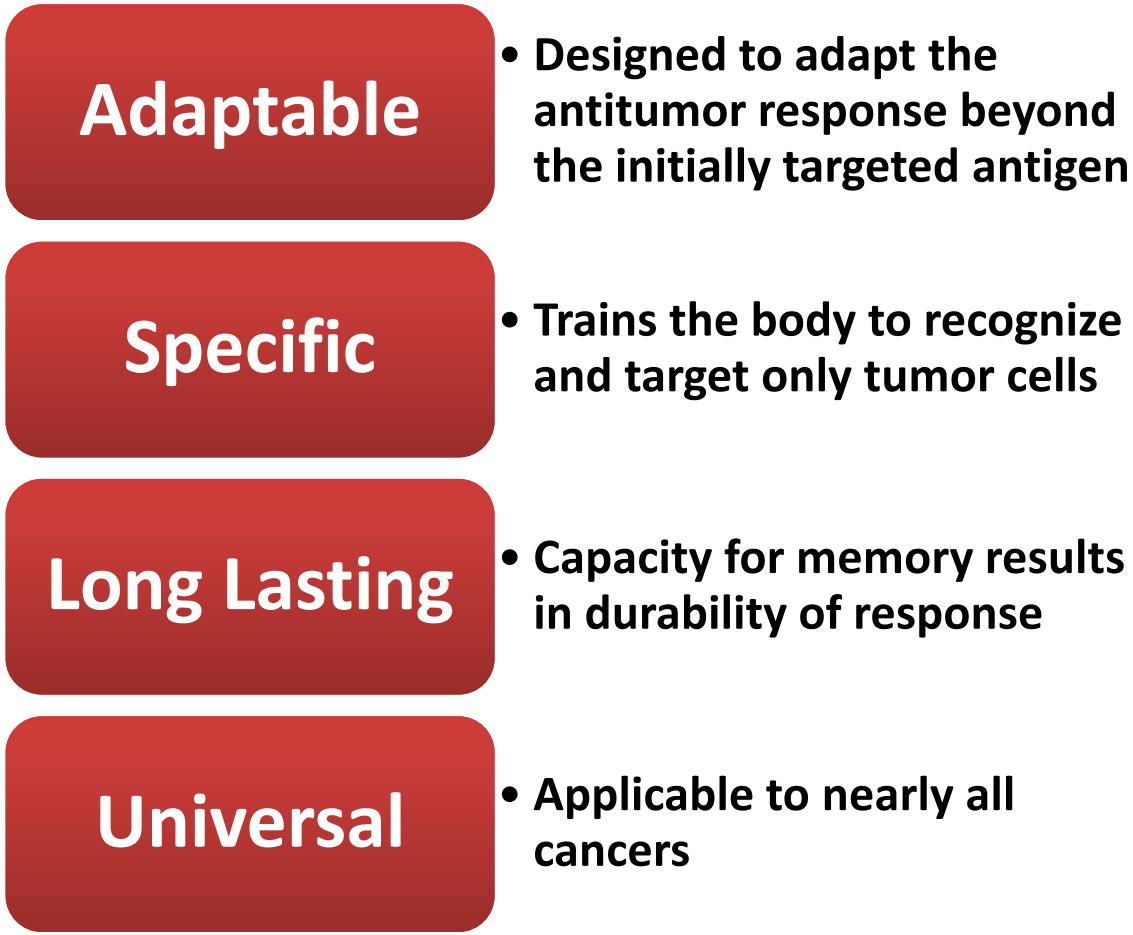
T cell-NK cell cooperativity restricts tumor escape



Shanker A et al. *J Immunol* 2007; *Immunology* 2009; *Immunol Lett* 2010; *Cancer Immunol Immunoth* 2011

Various tumor immunotherapy approaches

Advantages of Tumor Immunotherapy



Categories of Immunotherapy

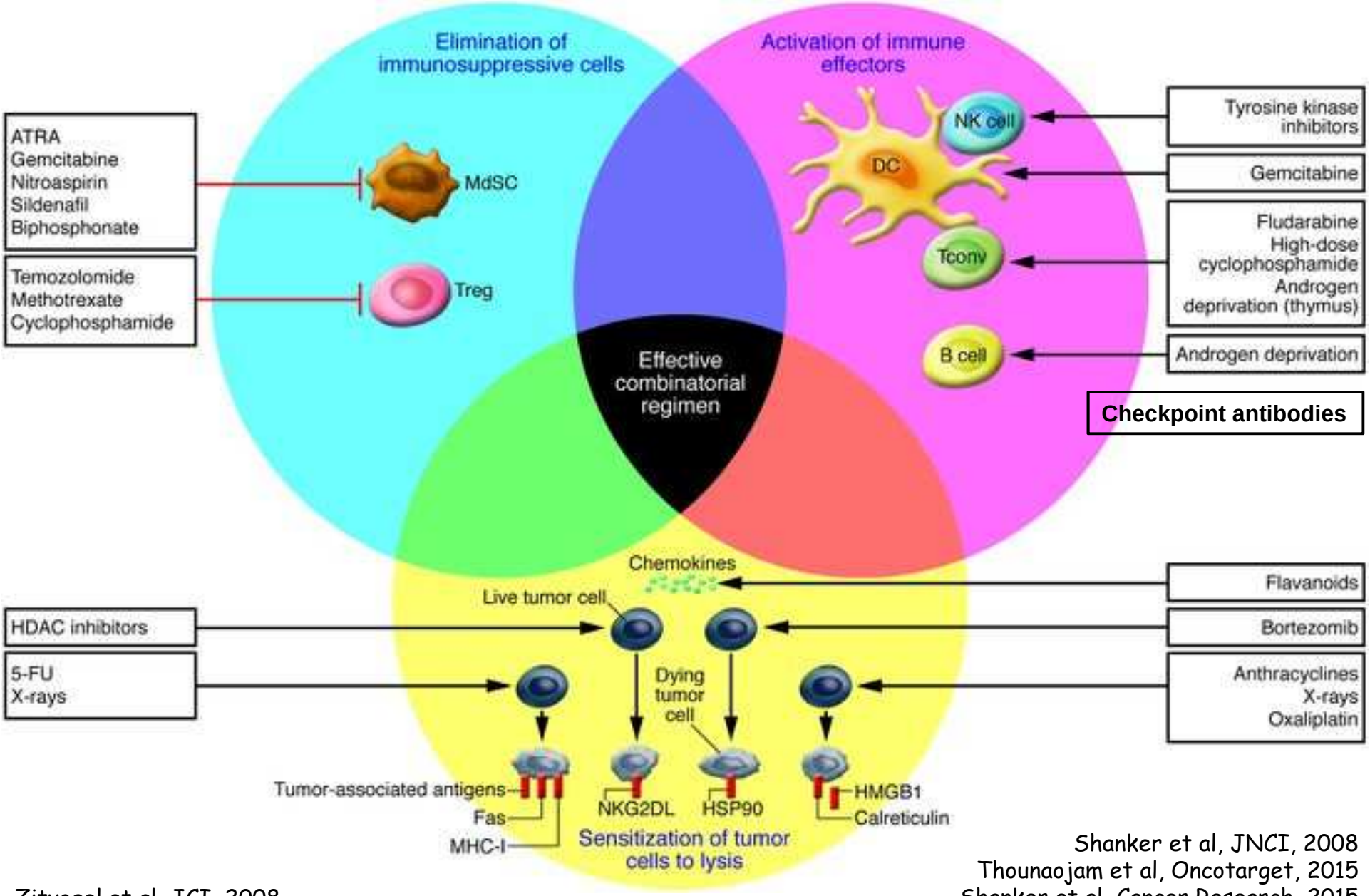
	Active	Passive
Tumor Specific	Vaccines	Monoclonal Antibodies
Tumor Non-Specific	Immunologic Checkpoint Inhibitors	Cytokines

- **Active Immunotherapy**: Dependent upon the patient's own immune system for antitumor effects
- **Passive Immunotherapy:** Administration of antibodies or pretreated immune cells

Major Tumor Immunotherapy Approaches

Approach		Examples
I. Vaccines	**Preventive**	HPV, HBV
	Therapeutic	T-Vec, Sipuleucel-T
II. Antibodies	**Naked**	Alemtuzumab, Trastuzumab
	Conjugated	Ado-trastuzumab emtansine
	Bispecific	Blinatumomab
	Checkpoint Inhibitors	Ipilimumab, Pembrolizumab, Nivolumab
	Co-Stimulatory Activators	GITR, OX40, CD27
III. Cytokines		IL2, Interferon, GM-CSF
IV. Oncolytic Viruses		TVEC
V. Cellular Therapy	Adoptive T Cell Therapy	
	Chimeric Antigen Receptor T Cell Therapy	

Combinatorial regimen for anticancer therapies



Zitvogel et al, JCI, 2008

Shanker et al, JNCI, 2008
Thounaojam et al, Oncotarget, 2015
Shanker et al, Cancer Research, 2015

Lessons and Take Home Messages

- Immunosurveillance has a key role in preventing and fighting cancer.
- Immunotherapy can produce durable antitumor responses in some patients with cancer, provided appropriate immunostimulatory conditions are present.
- Optimization of combinatorial immunotherapy regimens will lead to improved outcomes.

Question # 1

The immune system controls tumor load as well as tumor quality by the process of immunoediting, which includes:

- Tumor elimination
- Tumor equilibrium
- Tumor escape
- None of above
- All of above

Question # 2

What is the overall goal of tumor immunotherapy approaches?

- Restore the capacity of the immune cells to recognize tumor cells
- Overcome immunosuppressive tumor microenvironment
- Improve anti-tumor cytolytic function of immune effector cells
- Enhance lymphocyte trafficking to tumor
- All of above