BIOENG-399 Immunoengineering

Prof. Li Tang

Lecture 3 Cancer Immunology and Cancer Immunotherapy

Spring 2025

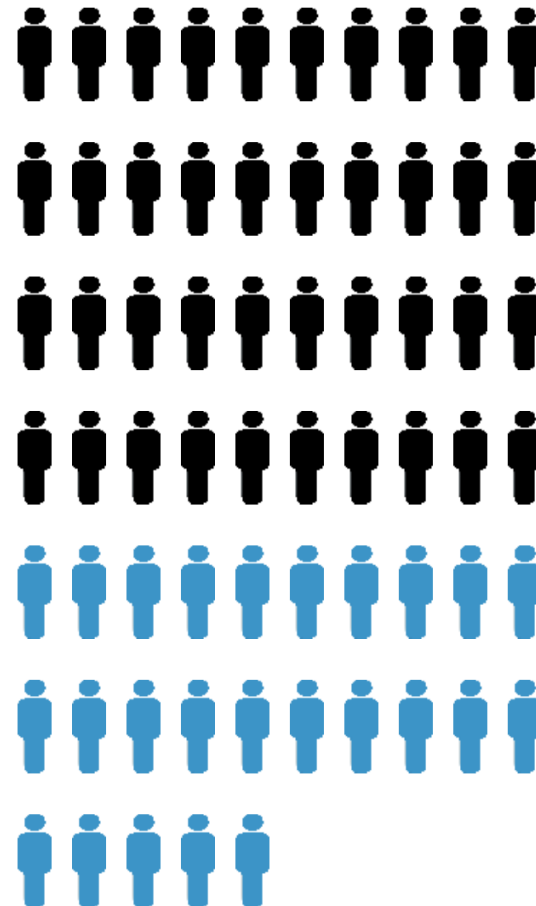Estimated number of new cases from 2022 to 2045, Both sexes, age [0-85+]
All cancers
World
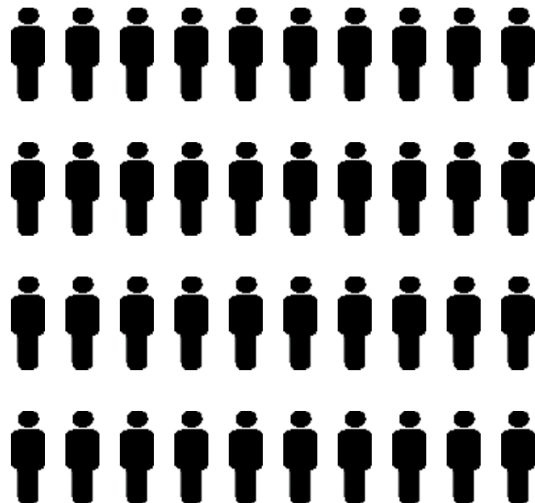
GLOBAL CANCER OBSERVATORY

2022

2045

20.0M

32.6M

International Agency for Research on Cancer

World Health Organization

https://gco.iarc.fr/

Some facts:

- Globally, one in five people worldwide develop cancer during their lifetime.

- In US, approximately 40.5% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2017–2019 data).

- Generally, cancer rates are highest in countries whose populations have the highest life expectancy, education level, and standard of living. But for some cancer types, such as cervical cancer, the reverse is true, and the incidence rate is highest in countries in which the population ranks low on these measures.

https://www.cancer.gov/about-cancer/understanding/statistics

https://gco.iarc.fr/

Immunotherapy improves fraction of long term survival


Sharma P et al. *Cell* 2015 (adapted)
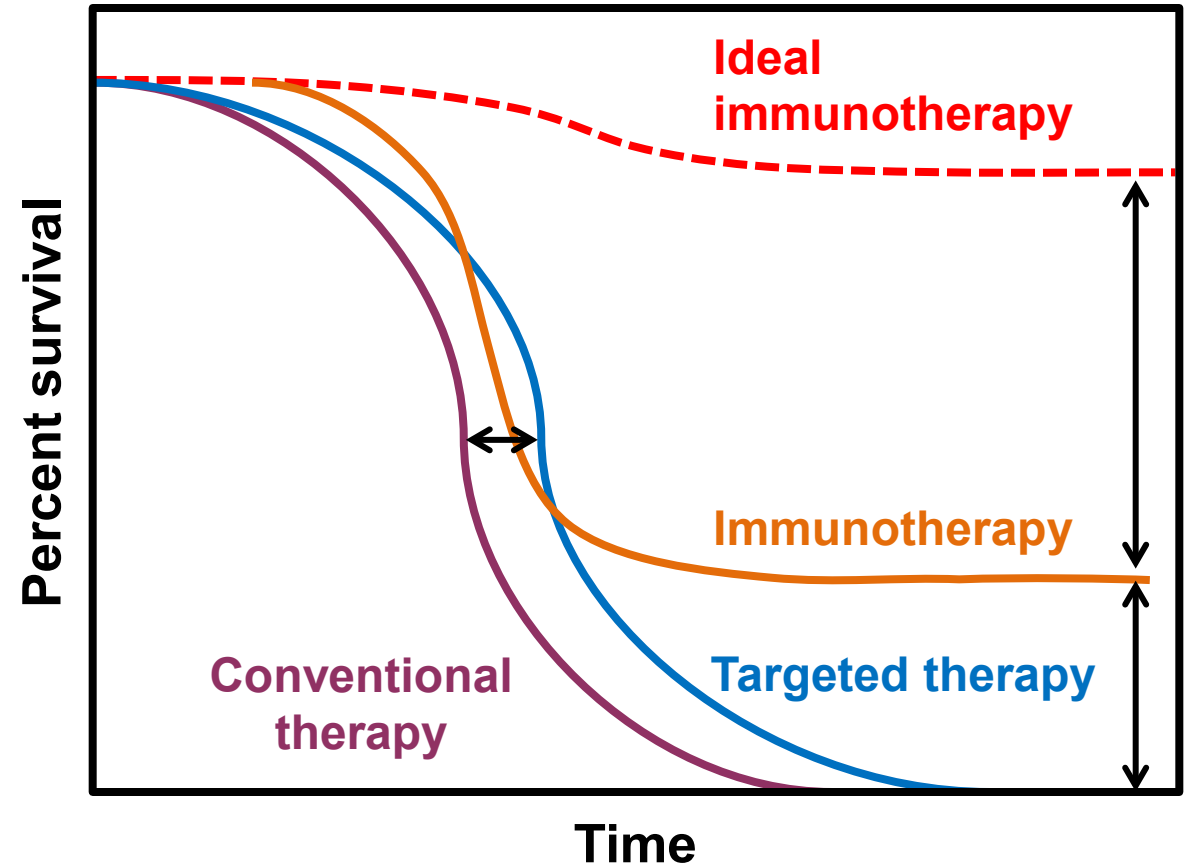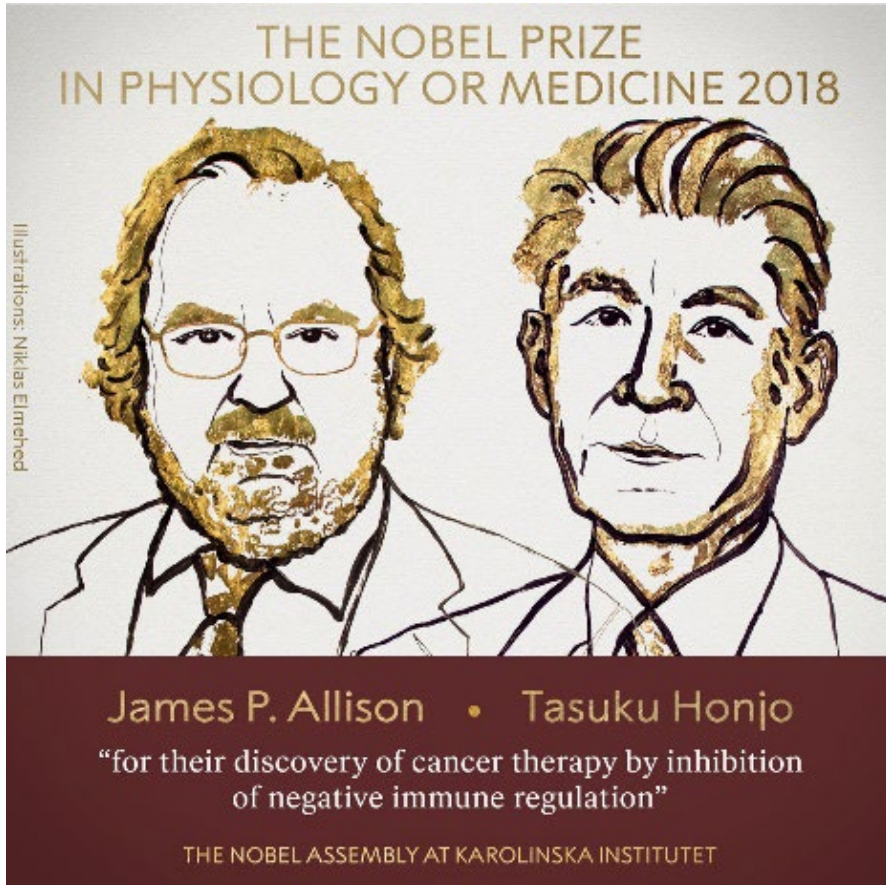
Emily's story: a young girl beats cancer with immunotherapy

What is the role of immune system in cancer?

The immunosurveillance hypothesis and the debate

- 1909: Paul Ehrlich first to conjecture that cancer would be rampant in long-lived organisms if not for immune response (…but no details of immune system understood at this point to even propose a model for how this could work)

- A long debate on immunosurveillance

- In 1990's, cancer immunoediting hypothesis by **Robert D. Schreiber**
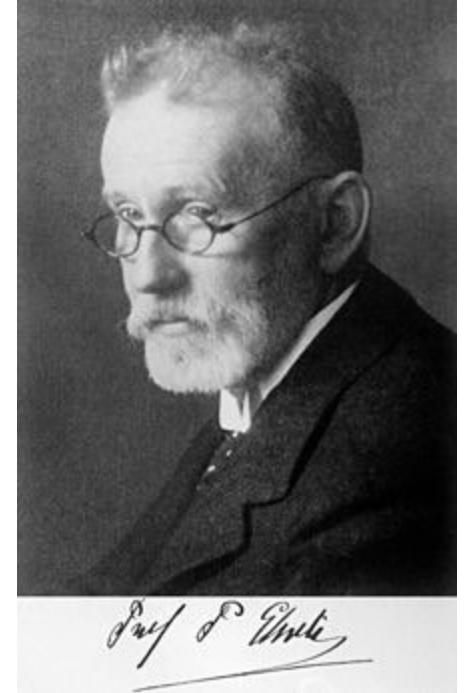
Paul Ehrlich

https://en.wikipedia.org/wiki/Paul_Ehrlich
Dunn, G. P., et al. (2002). "Cancer immunoediting: from immunosurveillance to tumor escape." Nature Immunology **3**(11): 991-998.

Immune system acts spontaneously against tumors

Schreiber, R. D., Old, L. J., & Smyth, M. J. *Science, 331*(6024), 1565–1570 (2011)

D. H. Kaplan et al., PNAS 95, 7556 (1998).

V. Shankaran et al., Nature 410, 1107 (2001).
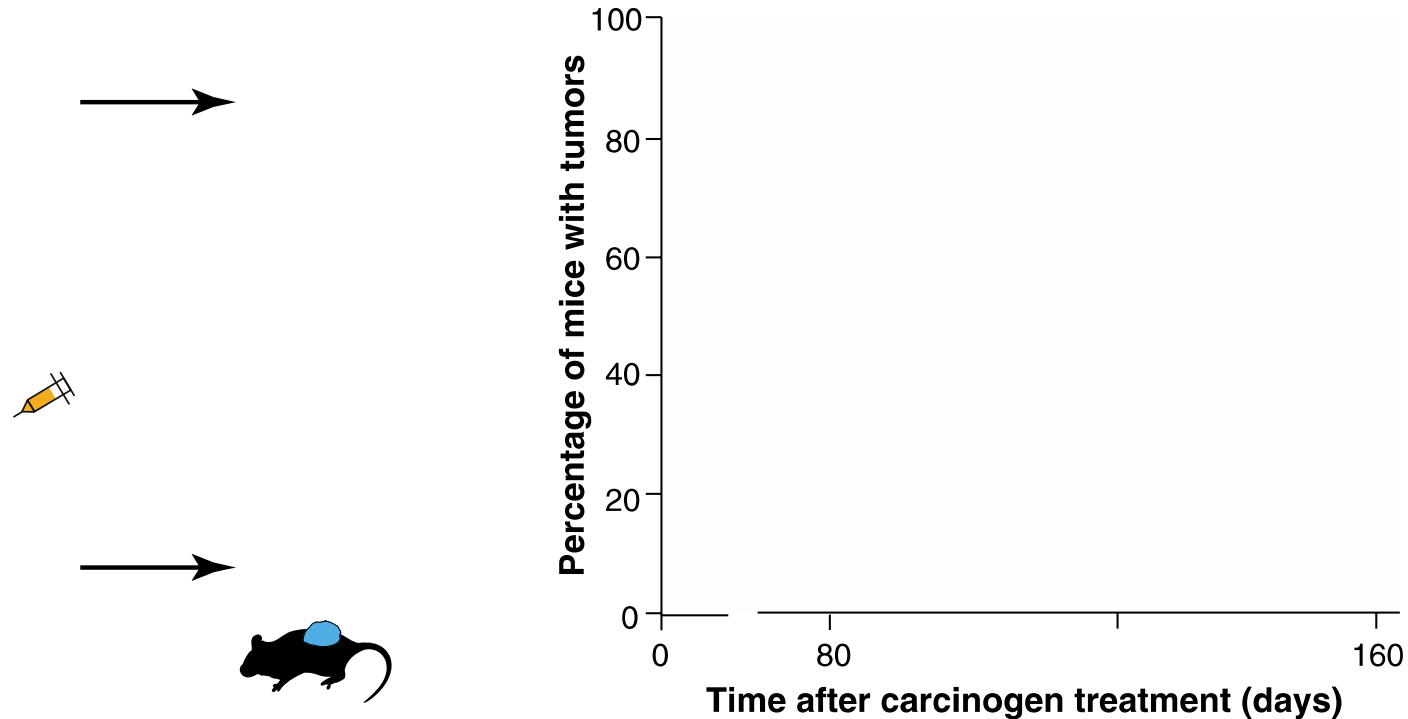
Evidence that the immune system acts spontaneously against tumors

Table 1

Immunodeficient mouse strains that develop spontaneous tumors

Strain	Description	Phenotype	Reference
SCID	Lack T and B cells	Mice develop T cell lymphomas (15% of mice)	118
$Rag2^{-/-}$	Lack T and B cells	Mice develop intestinal adenomas (~50%), or adenocarcinoma of the intestine (~35%) or lung (~15%); tumors detected at 15–16 months of age	3
$Rag2^{-/-}Stat1^{-/-}$	Lack T and B cells, deficient for type I and II IFN signaling	Mice develop intestinal adenomas like $Rag2^{-/-}$ mice (~20%), but also develop adenocarcinoma of the breast (~40%), colon (~10%), or breast and colon (~20%); tumors detected at 12–18 months of age	3
$Perforin^{-/-}$	Lack perforin	Mice develop B cell lymphomas at 14–21 months of age	4
$Ifng^{-/-}$	Lack IFN-γ	Mice develop lymphomas (predominantly T cell) at 13–19 months of age; effect is strain dependent (C57BL/6 are susceptible, BALB/c are resistant)	5
$Perforin^{-/-}Ifng^{-/-}$	Lack both perforin and IFN-γ	Mice develop B cell lymphomas similar to those observed in perforin-deficient mice, but with earlier onset and increased frequency	5
$Perforin^{-/-}B2m^{-/-}$	Lack both perforin and MHC class I expression	Mice develop B cell lymphomas similar to those observed in perforin-deficient mice, but with earlier onset and increased frequency	6
$Lmp2^{-/-}$	Defective MHC class I antigen presentation	Mice develop uterine neoplasms (36%) by 12 months of age	119
$Trail^{-/-}$	Lack TRAIL	About 25% of mice develop lymphomas late in life (>400 days)	8
$Gmcsf^{-/-}Ifng^{-/-}$	Lack GM-CSF and IFN-γ	Mice develop a range of malignancies, including lymphomas and solid tumors (predominantly ovarian choriocarcinoma, luteomas, or teratomas)	11
$Il12rb2^{-/-}$	Lack IL-12Rβ2	Mice develop plasmacytomas, lung carcinomas, or both (50%)	10

This slide is not required.

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Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems[1-3]

Tumor/cancer risk in transplant patients compared to general population[1-3]

Cancer type	Fold-increase in tumor/cancer risk
Non-melanoma skin cancer	20-fold and beyond
Non-Hodgkin's lymphoma	20-fold and beyond
Kidney cancer	15-fold
Melanoma	8-fold
Hepatobiliary cancer	5-fold
Bladder cancer	3-fold
Testicular cancer	3-fold
Breast cancer	2-fold
Prostate cancer	2-fold
Colon cancer	2-fold

Fold-increase in tumor/cancer risk (0, 5, 10, 15, 20)

1. Kasiske BL, Wang C, et al. *Am J Transplant.* 2004;4(6):905-913.
2. Le Mire L, Wojnarowska F, et al. *Br J Dermatol.* 2006;154(3):472-477.
3. Abbas AK, Lichtman AH. *Basic Immunology.* 3rd ed. 2011.

This slide is not required.

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10

Immune Cells Within Tumors Predict Overall Survival
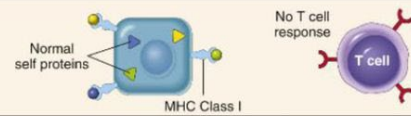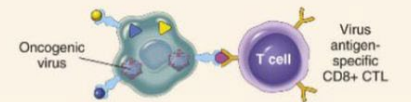
- T-cell infiltration within tumors predicts overall survival (OS) in multiple cancer types including bladder cancer[1-3]

Infiltration of T cells Predicts Survival of Patients With Muscle-Invasive Bladder Cancer[1]
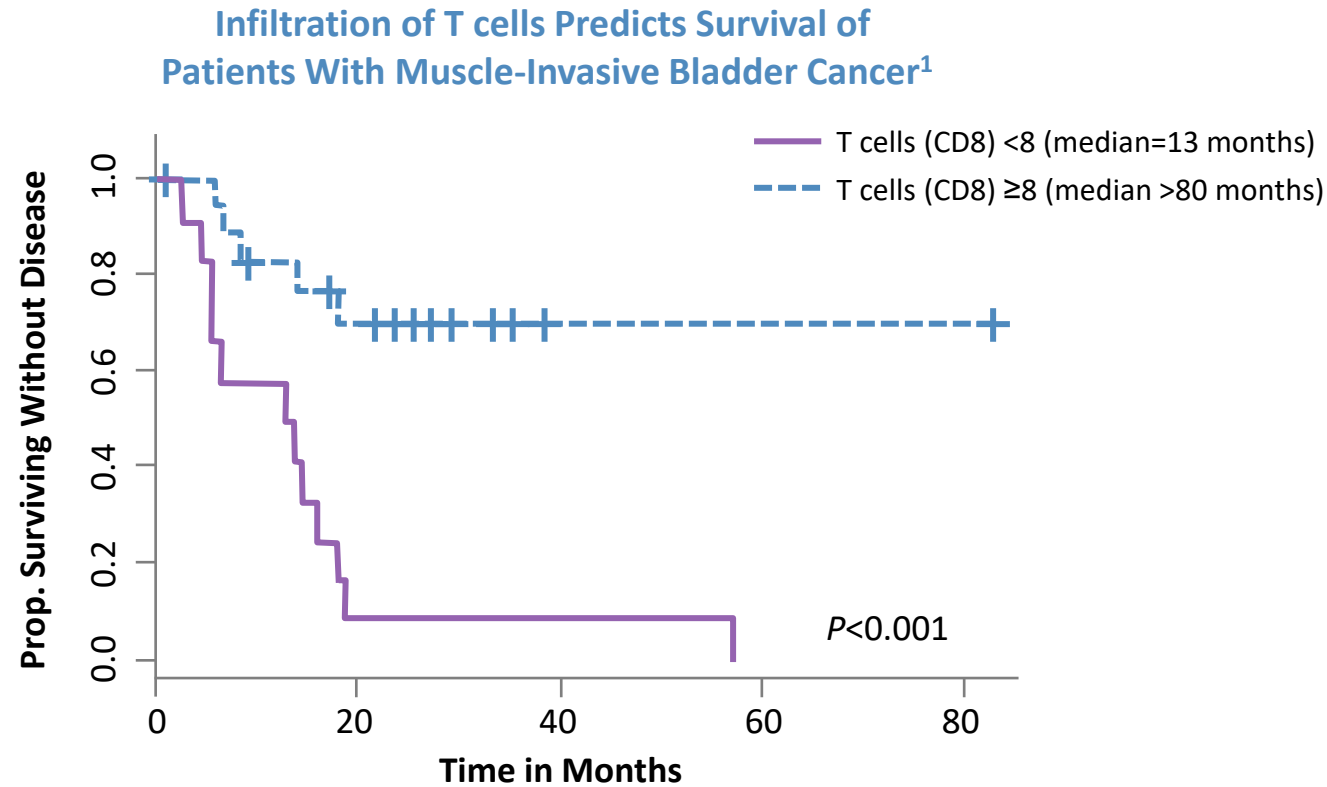
Reprinted from Sharma P, Sato E, et al.[1]

1. Sharma P, Sato E, et al. *Proc Natl Acad Sci U S A*. 2007;104(10): 3967-3972.
2. Zhang L, Coukos G, et al. *N Engl J Med*. 2003;348(3):203-213.
3. Galon J, Pagès F, et al. *Science*. 2006;313(5795):1960-1964.

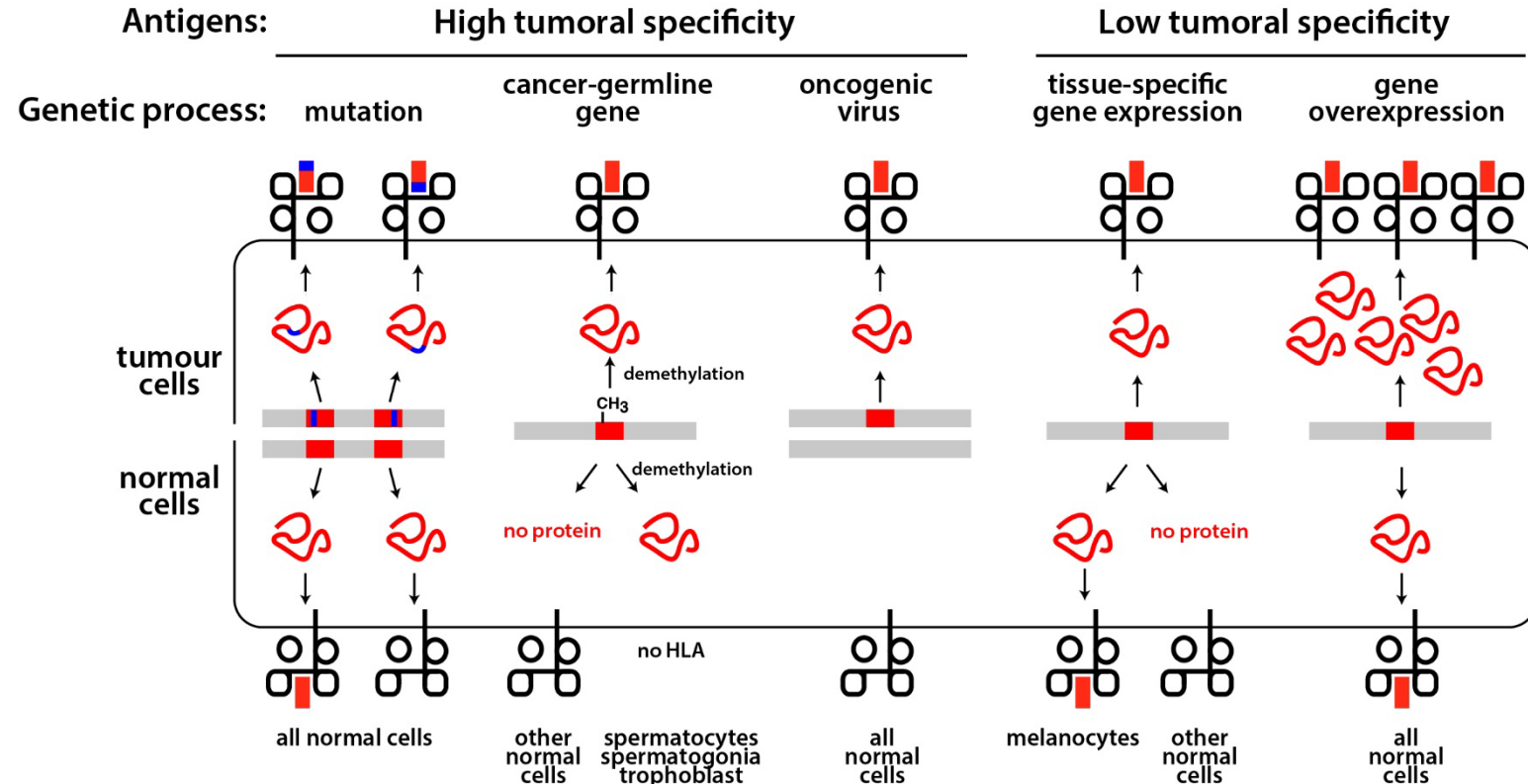# What antigens are T-cells responding to?

Tumor antigens recognized by CD8+ T cells.

- Neo-antigens
- Cancer-testis antigens (CT Ags, or oncofetal Ags, such as MAGE, NY-ESO-1; expressed only in germ cells but not somatic (tissue) cells
- Viral antigens

http://slideplayer.com/slide/11983008/   https://www.slideshare.net/csbrprasad/neoplasia-robbins-path-13540987

Patient-specific neoantigens: prime target of immune response to cancer?

Schumacher, T. N., & Schreiber, R. D. (2015). Neoantigens in cancer immunotherapy. *348*(6230), 69–74.

This slide is not required.

Cancer–immunity cycle

Chen, D. S. and I. Mellman (2013). Immunity **39**(1): 1-10.
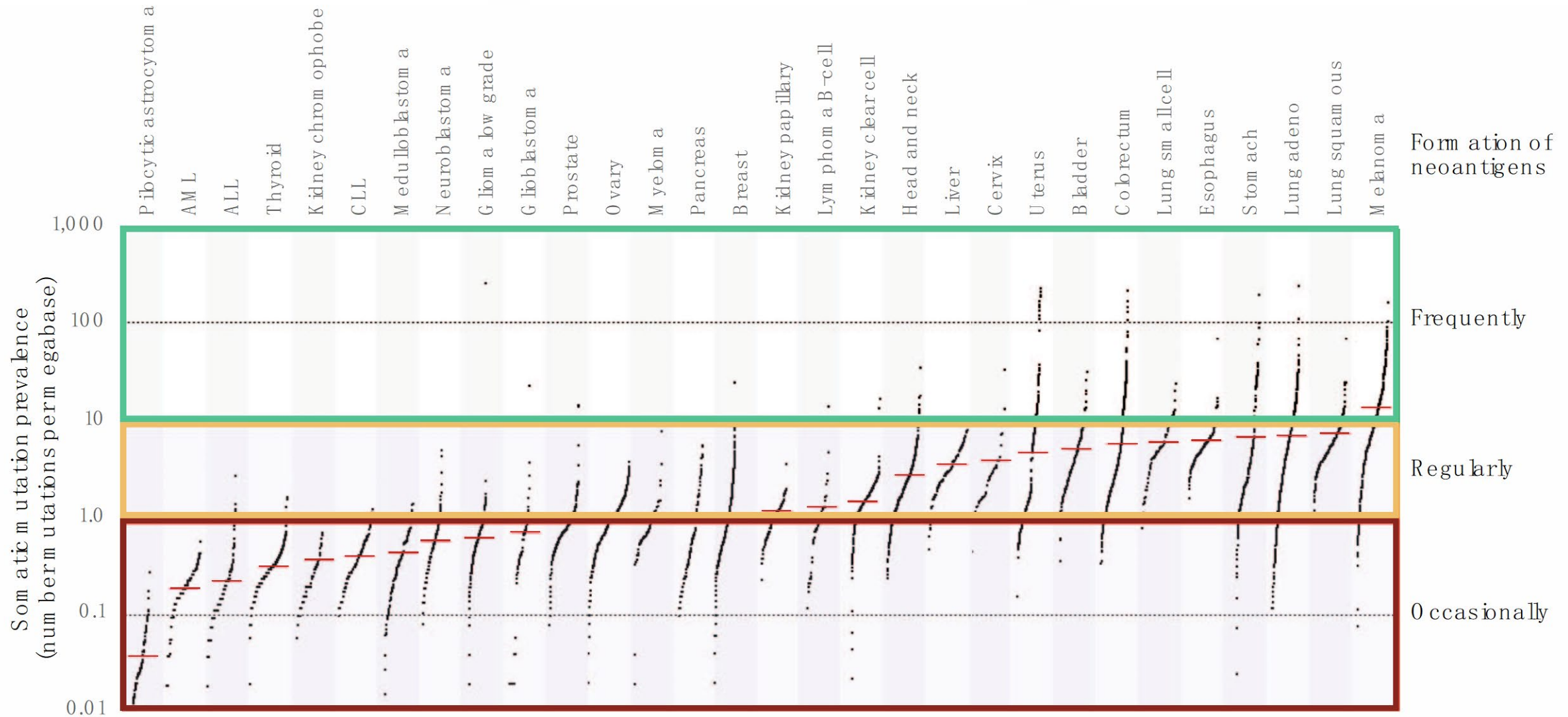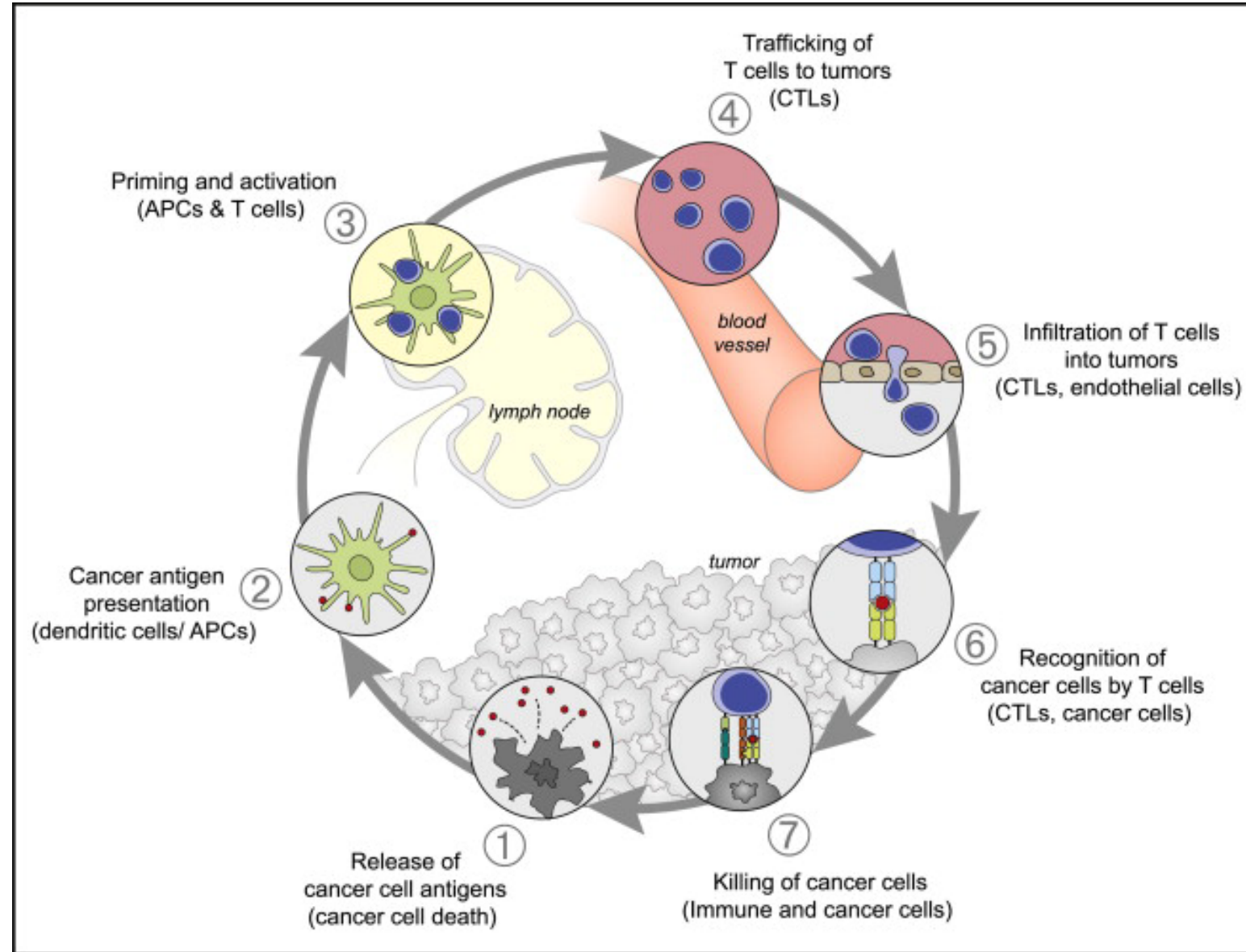
If the immune system is acting against tumors, why aren't all tumors rejected?

Experimental evidence for immunoediting of tumors
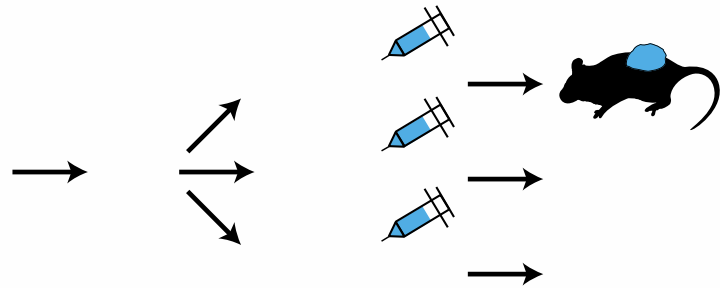
- 100% of tumors grown in immunocompetent mice and transplanted to immunocompetent mice are progressors (edited progressors)
- ~50% of tumor cell lines derived from carcinogen-induced tumors in immunodeficient mice are rejected when transplanted into WT mice (unedited regressors)

- The immune system can spontaneously recognize and respond to tumors, leading to elimination, equilibrium, or escape
- Immune editing allows elimination/equilibrium, but may also contribute eventually to escape

Schreiber, R. D., Old, L. J., & Smyth, M. J. *Science*, *331*(6024), 1565–1570 (2011)

What are the interactions between tumor and immune system? ♭

A puzzle: inflammatory/immune cells are nearly ubiquitous components of the tumor microenvironment, yet tumors commonly progress...

Coussens and Werb *Nature* **420** 860 (2002)

This slide is not required.

Immune cells can be protagonists or antagonists of growing tumors

TILs in Cancer

Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al. (2015). *Annals of Oncology*. Oxford University Press.

Immune cells can be protagonists or antagonists of growing tumors

Gentles, A. J., Newman, A. M., Liu, C. L., Bratman, S. V., Feng, W., Kim, D., et al. (2015). *Nature Medicine*, 1–12.

This slide is not required.

Roles of the immune system in promoting tumor initiation and progression

INITIATION BY INFLAMMATION

Epithelial cells (green=initiated or transformed cell)

PROMOTION BY STROMA

PROMOTION BY INITIATED CELLS

PROINFLAMMATORY CYTOKINES AND CHEMOKINES | GROWTH FACTORS | MATRIX METALLO-PROTEASES | ROS FREE RADICALS | COX ENZYMES | ANGIOGENIC FACTORS

Stromal cells

Bone marrow stem cells repopulate the epithelium and become initiated
OR
Tissue stem cells are mutated by free radicals Generated by chronic inflammation

e.g stomach cancer

Initiated tissue stem cells are subject to tumour promotion by chronic inflammatory mediators

e.g. colon cancer
liver cancer

Initiated stem cells produce inflammatory mediators that attract tumour promoting inflammatory cells and set up cytokine networks

e.g skin cancer
liver cancer
ovarian cancer

"Smoldering and polarized inflammation" in cancer initiation:

Chronic inflammation promotes immune cell recruitment and slow changes that promote tumor initiation and development

Key players in tumor-promoting inflammation
- TAM: tumor associated macrophage
- MDSC: myelod-derived suppressor cells
- Treg: regulatory T cells

Balkwill, F., et al. (2005). "Smoldering and polarized inflammation in the initiation and promotion of malignant disease." Cancer Cell **7**(3): 211-217.

Roles of the immune system in promoting tumor initiation and progression

Elimination: Immune System Eradicates Cancer Cells
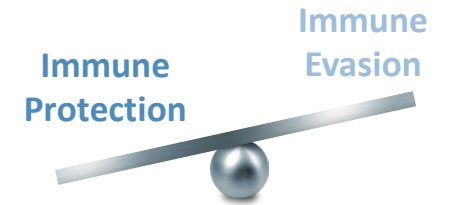
- A natural process involved with early disease[2]
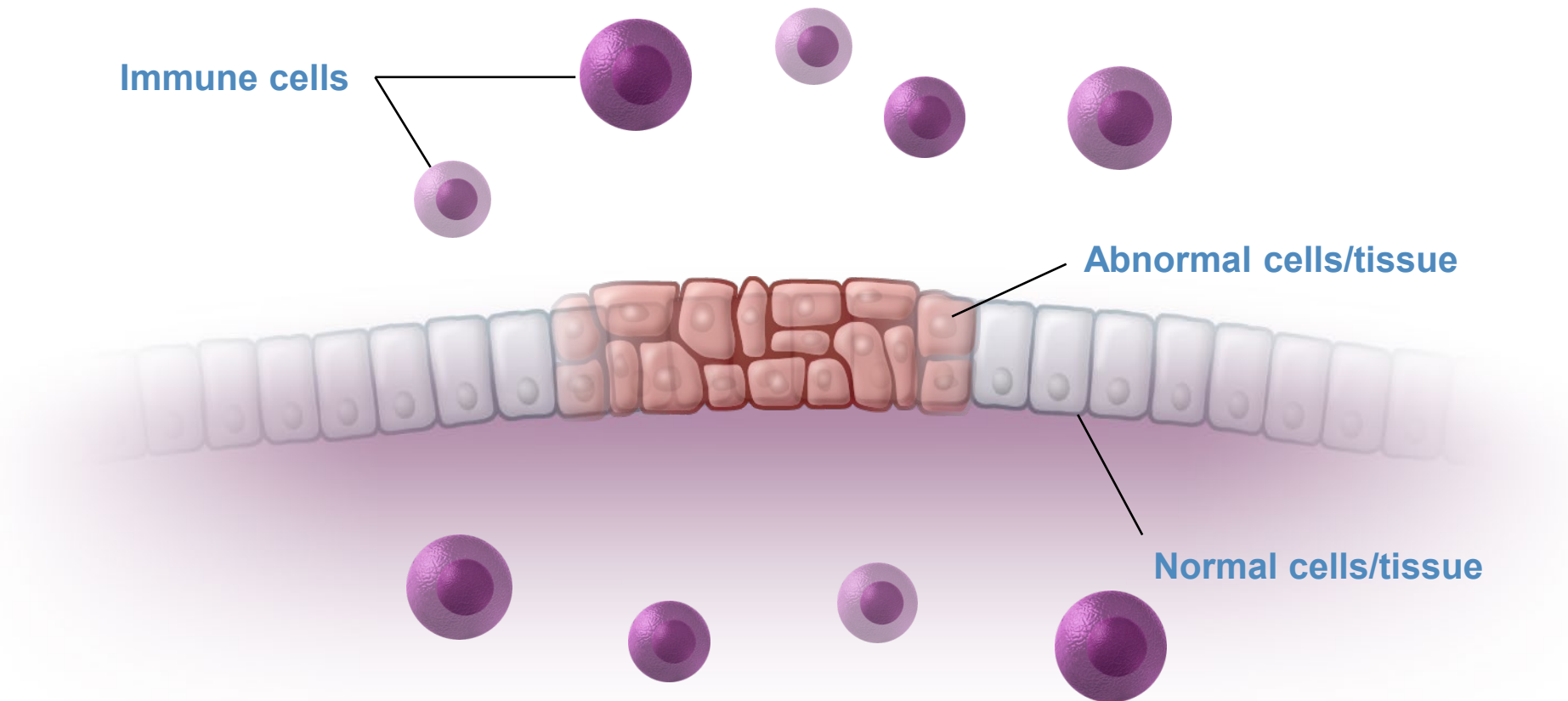
Immune cells

Abnormal cells/tissue

Normal cells/tissue

Adapted from Dunn GP, Schreiber RD, et al.

1. Dunn GP, Schreiber RD, et al. *Nat Rev Immunol.* 2006;6(11):836-848.
2. Trinchieri G. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.

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Equilibrium: Immune System Controls Cancer Cells[1]
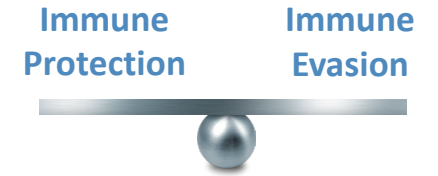
- Occurs with later stage tumors[2]
- Represents a balanced "dynamic" between the immune system and cancer[1,2]

Immune cells

Abnormal cells / tissue outgrowth controlled

Adapted from Dunn GP, Schreiber RD, et al.[1]
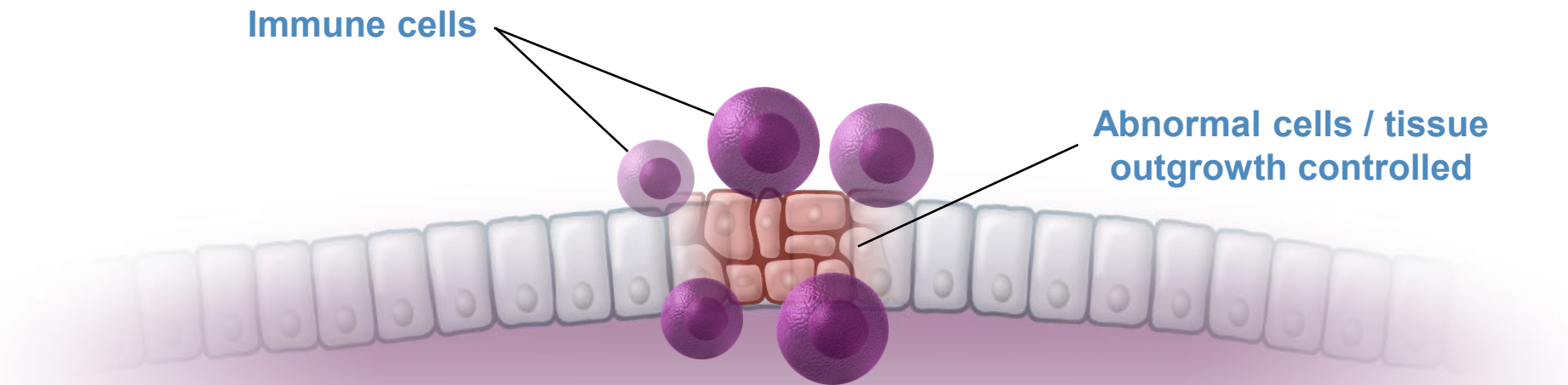
1. Dunn GP, Schreiber RD, et al. *Nat Rev Immunol.* 2006;6(11):836-848.
2. Trinchieri G. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.

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Escape: Cancer Cells Evade Immune System
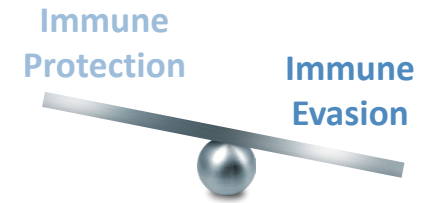
- Tumor cell variants grow, resulting in progressive disease

Immune cells

Abnormal cells / tissue

Abnormal cells / tissue continue to replicate

Adapted from Dunn GP, Schreiber RD, et al.

Dunn GP, Schreiber RD, et al. *Nat Rev Immunol.* 2006;6(11):836-848.
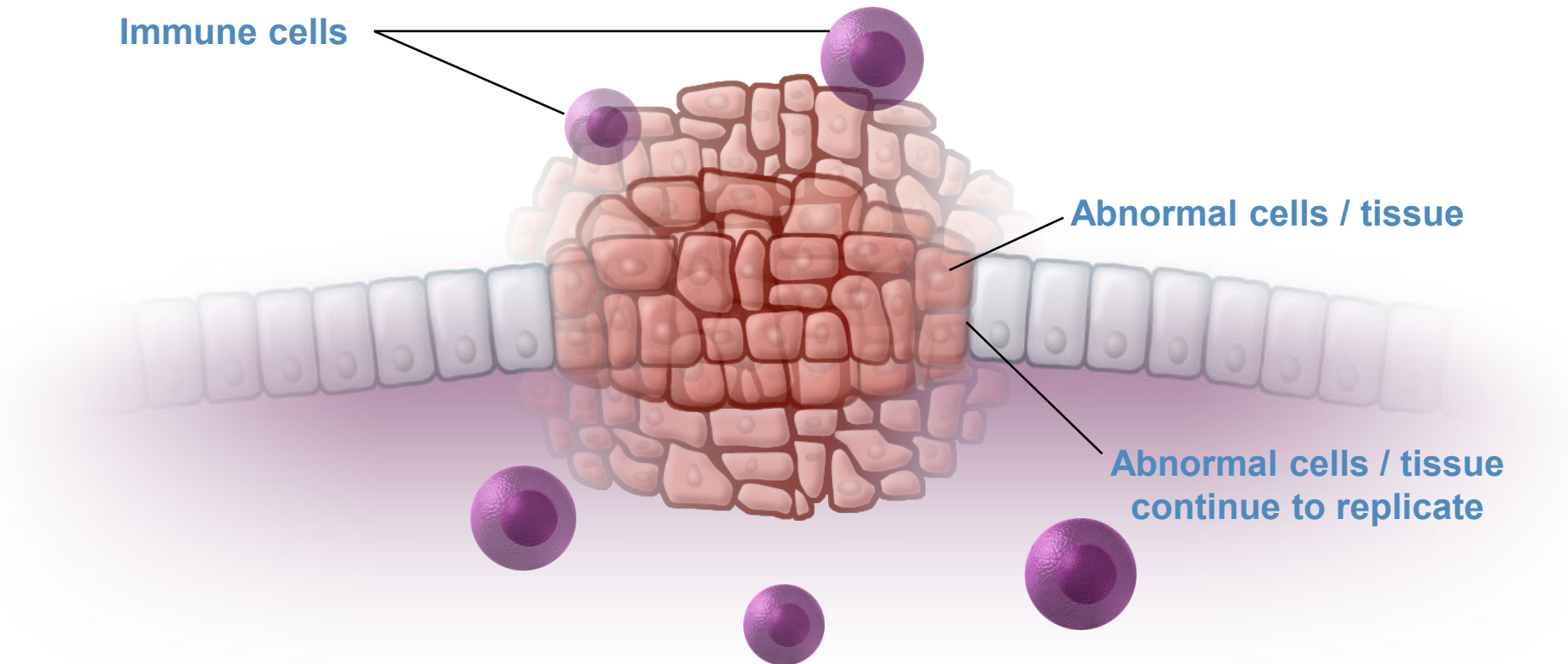
The immunoediting hypothesis

Cancer immunoediting encompasses three process.

(a) Elimination corresponds to immunosurveillance.

(b) Equilibrium represents the process by which the immune system iteratively selects and/or promotes the generation of tumor cell variants with increasing capacities to survive immune attack.

(c) Escape is the process wherein the immunologically sculpted tumor expands in an uncontrolled manner in the immunocompetent host.

Schreiber, R. D., Old, L. J., & Smyth, M. J. *Science*, *331*(6024), 1565–1570 (2011)
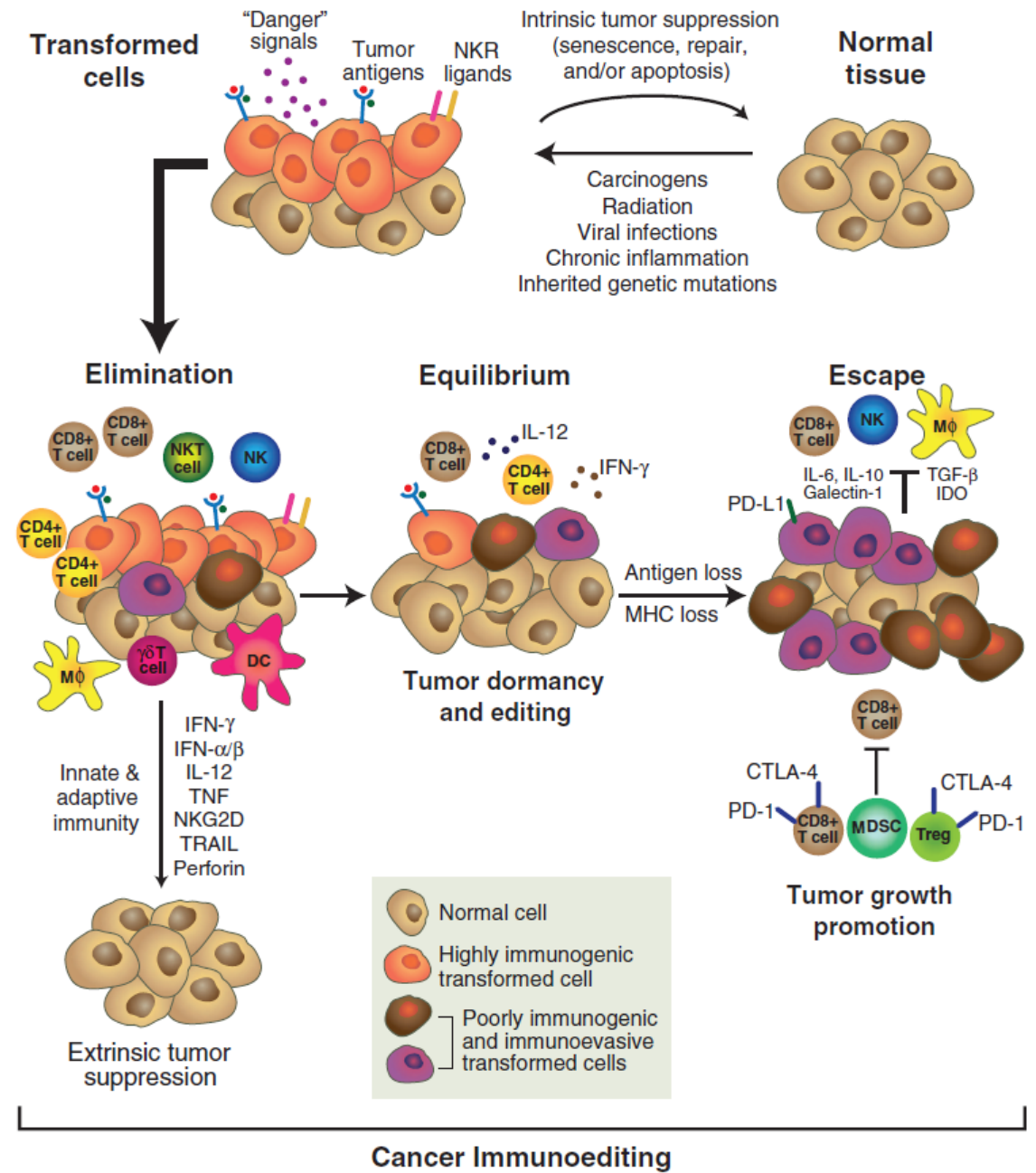
How does tumor escape from immune pressure?

Blocking CD8 T-cell Infiltration in tumor

"Cold" ----→ "Hot"

Immune desert | T-cell exclusion | Inflamed tumor
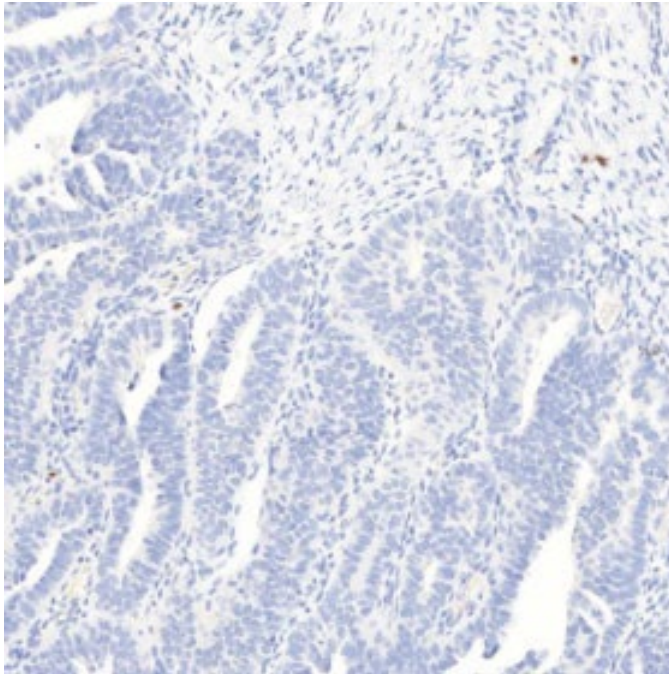
Low CD8 T-cells infiltration

Bad prognosis

Brown dots: "killer cells" CD8 T-cells
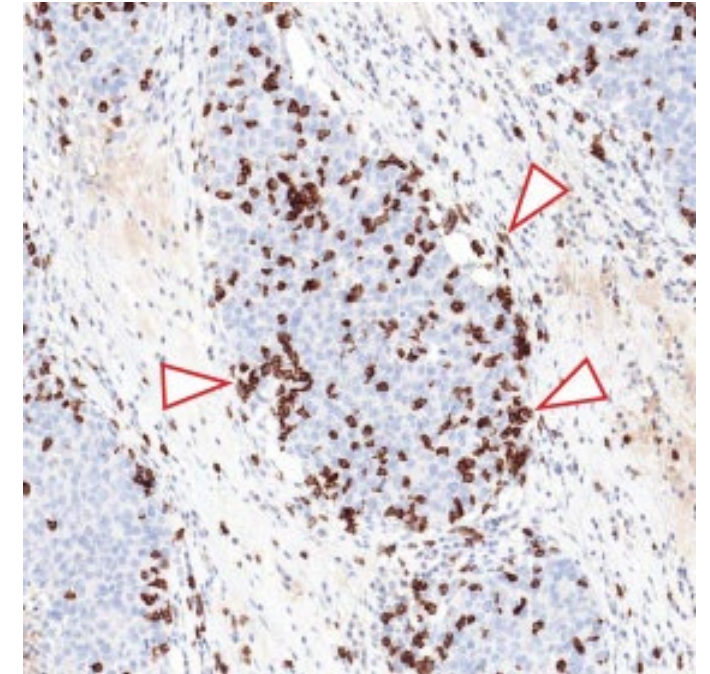
High CD8 T-cells infiltration

Good prognosis

Research Cancer_Immunotherapy_Roche

Antigen loss

Tumors can mutate or lose expression of MHC or antigen processing machinery:

28
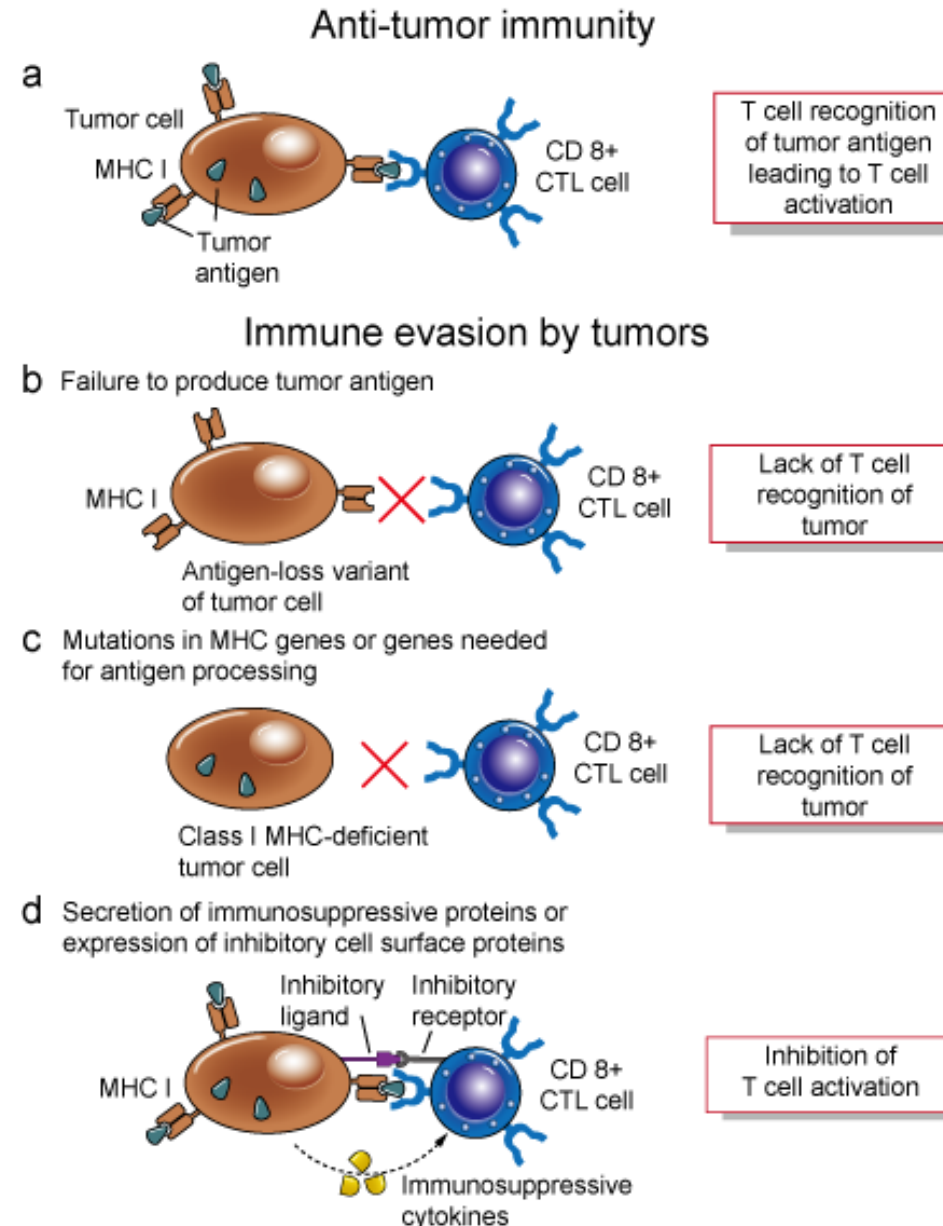
Tumor-derived immunosuppressive factors

Tumor Microenvironment

Elimination

Escape
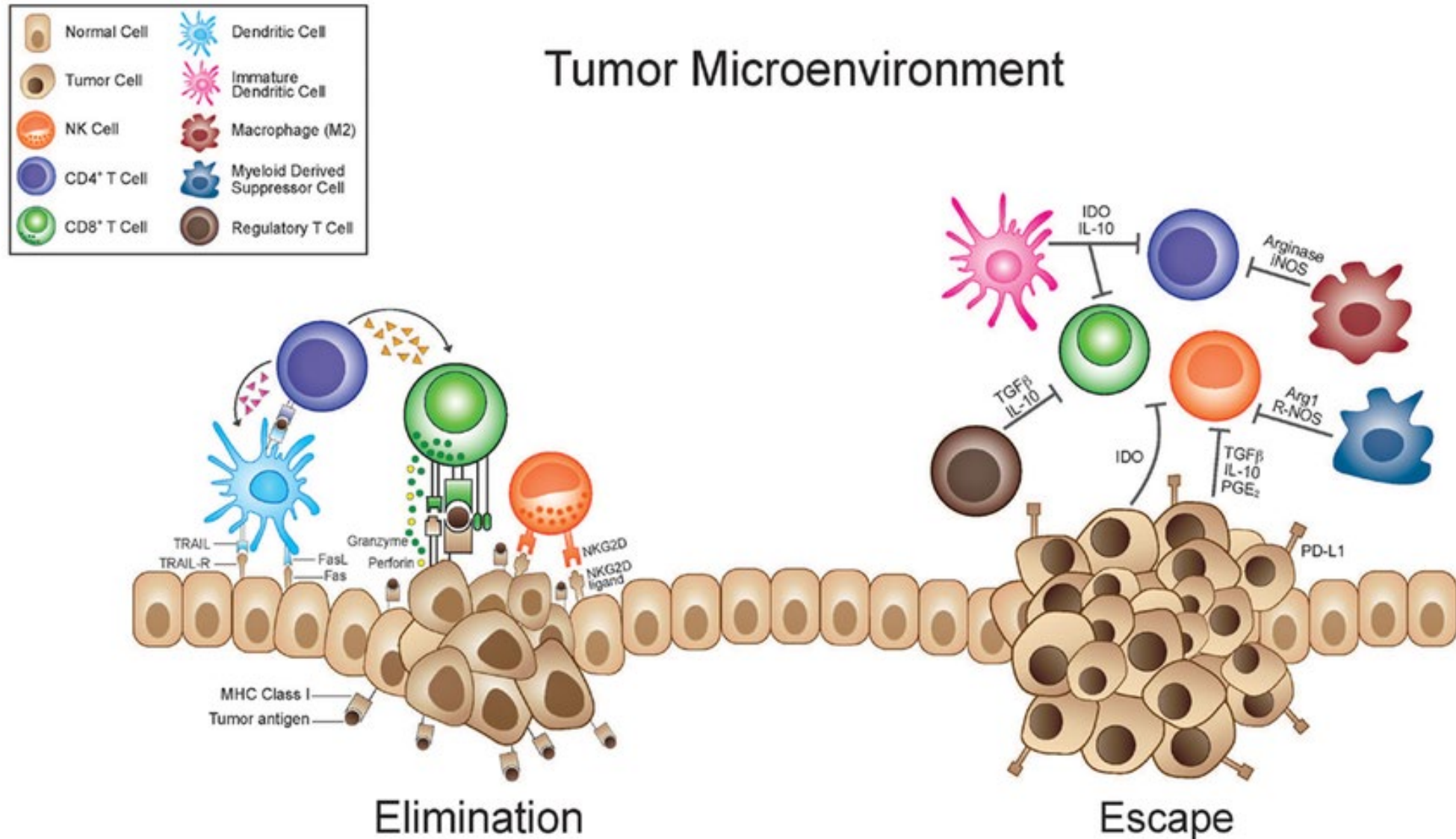
Tumor microenvironment factors: hypoxia

Hypoxia in tumors:
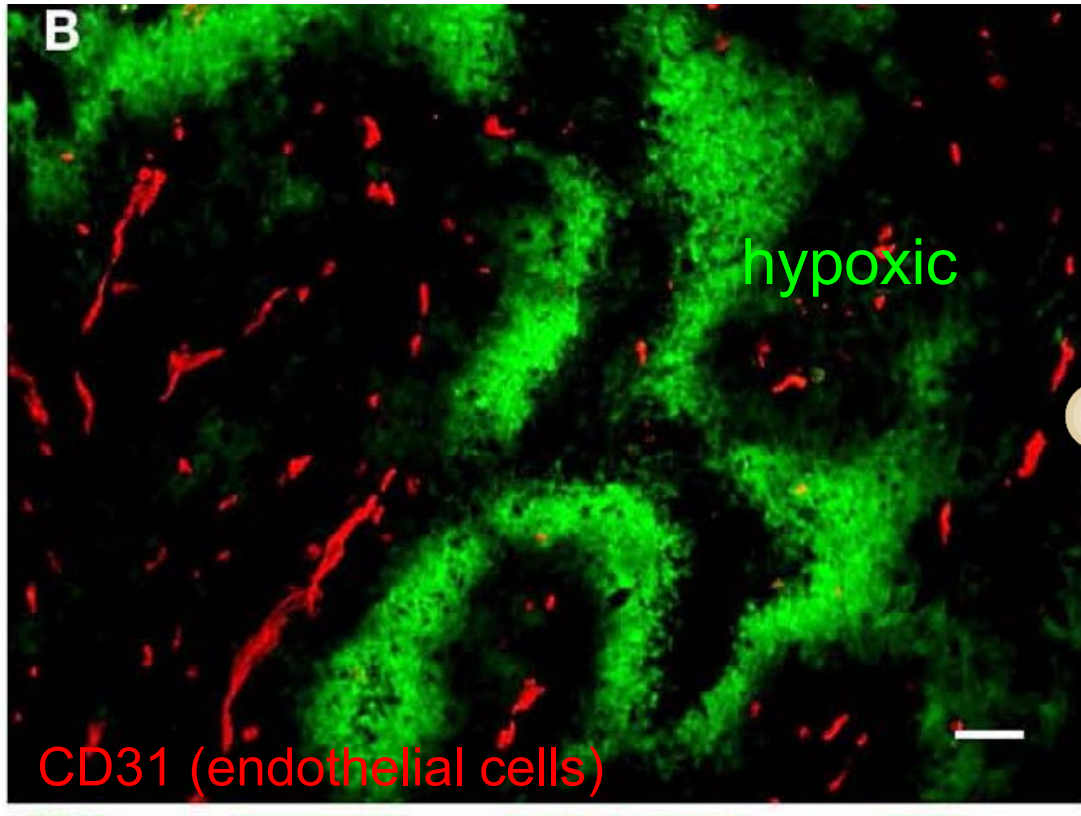
The mechanism is not required.

hypoxic

CD31 (endothelial cells)

Chiang, C.-S., Fu, S. Y., Wang, S.-C., Yu, C.-F., Chen, F.-H., Lin, C.-M., & Hong, J.-H. (2012). *Frontiers in Oncology*, 2, 89.

Sitkovsky *Nat. Rev Immunol.* **5** 712 (2005)

Mechanisms of cancer immunosuppression

- Dysfunctional antigen presentation
- Blocking immune infiltration
- Tumor microenvironment factors
- Co-opted host immune cells
- Stromal cells in tumors
- Adaptive resistance

- What is cancer immunotherapy?

- How does it work?

- What is the history and current status?

Introduction to cancer immunotherapy

Cancer immunotherapy is a treatment that uses the

power of your own immune system to fight cancer.

It works in two important ways:

➢ **Boosts your immune system** to help eliminate

  cancer cells

➢ Enhances the immune response by providing

  your body with additional support

CRI, http://www.theanswertocancer.org/
Sharma P, Allison JP, et al. Nat Rev Cancer. 2011;11(11):805-812.
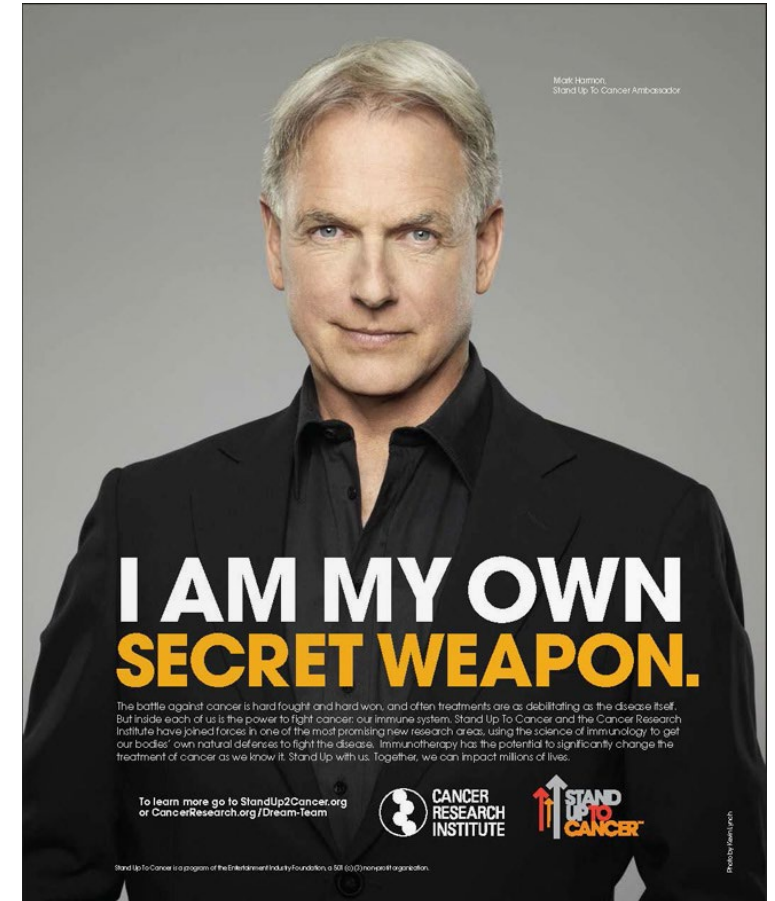
IMMUNOTHERAPY: The Path to a Cancer Cure
by Society for Immunotherapy of Cancer (SITC)

https://youtu.be/UbFjiWOBErA

The History of Immunotherapy

1890s
Dr. Coley creates the 1st immunotherapy treatment

1985
1st study with adoptive T-cell transfer in cancer

1992
IL-2 approved as cancer immunotherapy

2010
1st therapeutic cancer vaccine approved for advanced prostate cancer

2014
1st anti-PD-1 antibody approved for advanced melanoma

1976
1st study with Bacille Calmette-Guerin (BCG) as a cancer vaccine by Dr. Morton (1st approved cancer immunotherapy in 1990)

1997
1st monoclonal antibody approved for cancer

2011
1st checkpoint blockade antibody receives FDA approval

2015
1st checkpoint inhibitor approved for lung cancer

The History of Immunotherapy: The beginning…

1890s
Dr. Coley creates the 1st immunotherapy treatment

1985

1992

2010

2014

1976
1st study
Guerin (B
by Dr. Mc
cancer im

Coley's toxin

Sometimes referred as MBV for mixed bacterial vaccine, Coley's toxin was the first attempt to use immunotherapy and hyperthermia against cancer. William B. Coley MD, a bone surgeon at MSK from 1893 to 1936 developed interest when his first patient, a young girl died from metastatic sarcoma.

Dr. William B Coley

The History of Immunotherapy: continue…

1890s
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Microscopic image of the Bacille Calmette-Guerin (BCG)

Dr. Donald Morton

The History of Immunotherapy: continue…

1890s
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1st study with adoptive T-cell transfer in cancer

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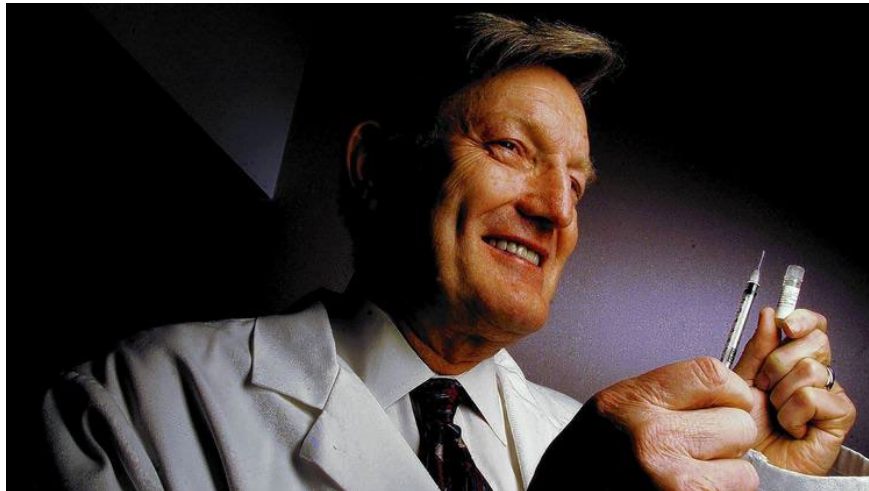**2010**
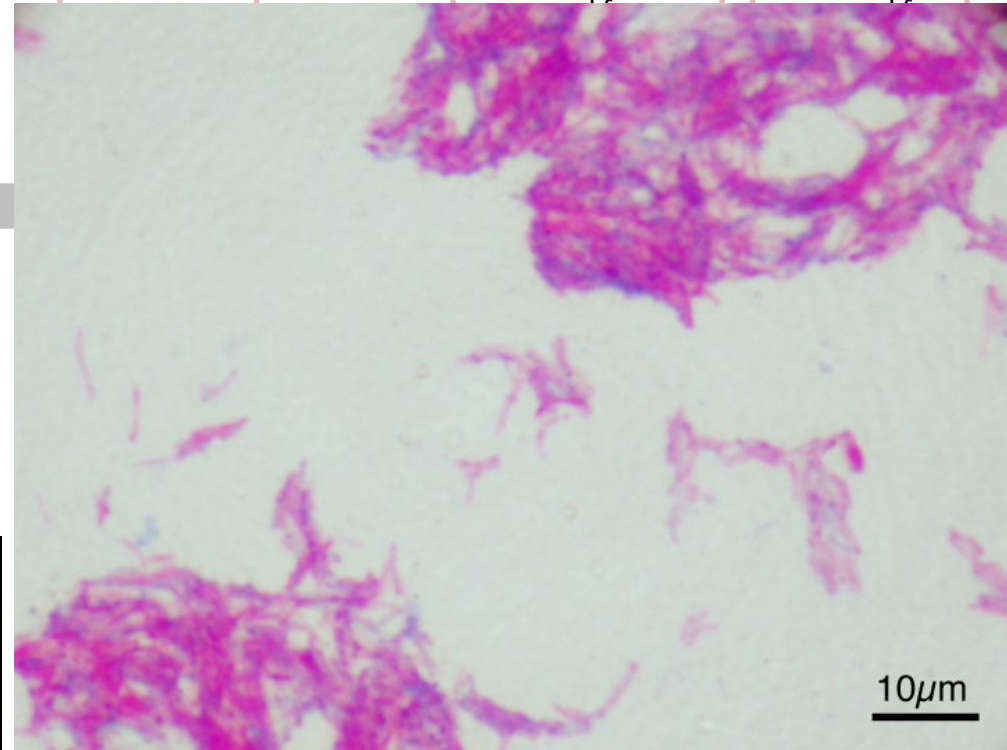1st therapeutic cancer vaccine approved for advanced prostate cancer

2014
1st anti-PD-1 antibody approved for advanced melanoma

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12-7-87

A. Rosenberg et al., N. Engl. J. Med. 319, 1676–1680 (1988)
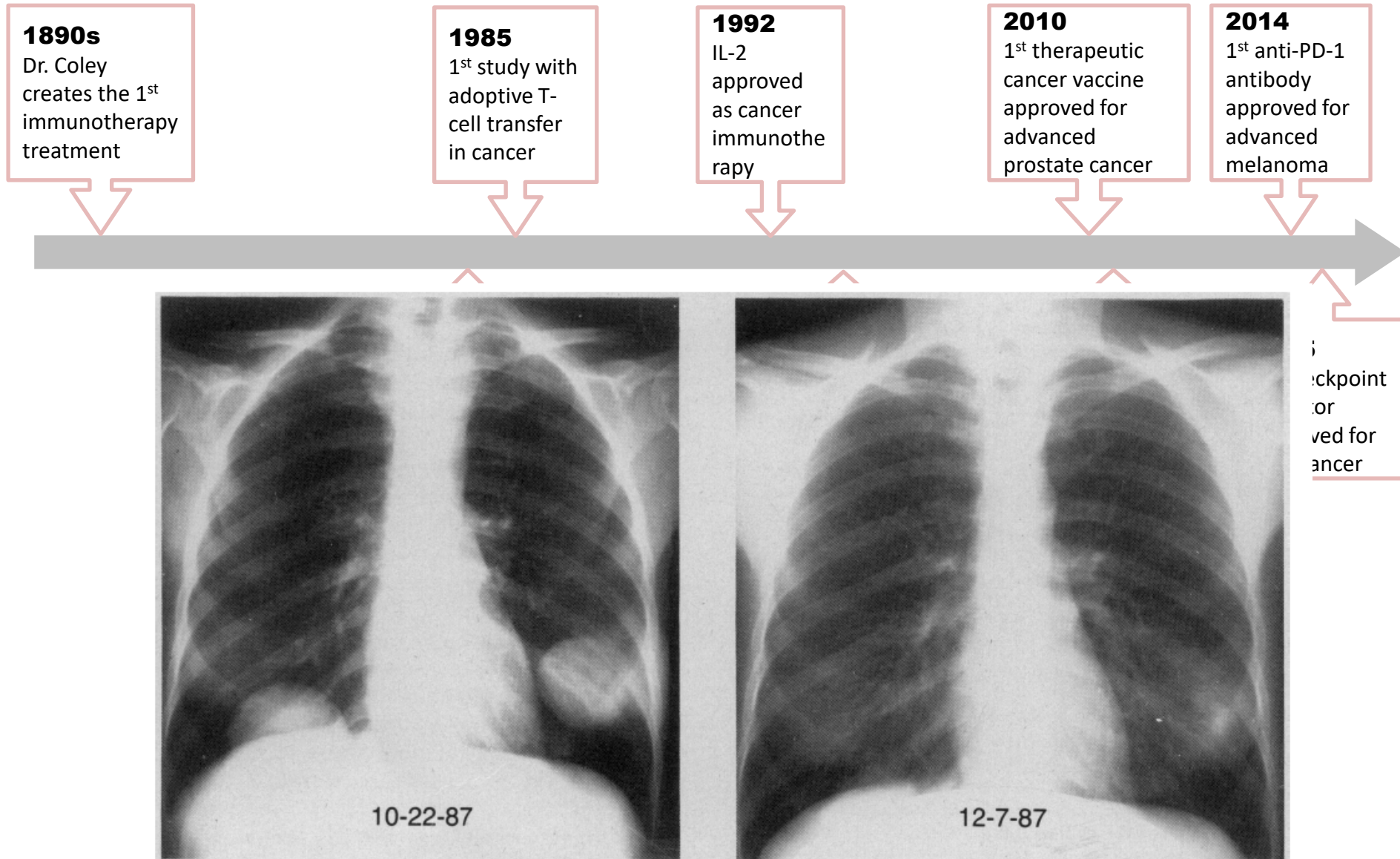
The History of Immunotherapy: the renaissance

1890s
Dr. Coley creates the immunot treatmen

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2011
1st checkpoint blockade antibody receives FDA approval

2015
1st checkpoint inhibitor approved for lung cancer

J. Couzin-Frankel, **Science** 2013, 342, 1432-1433
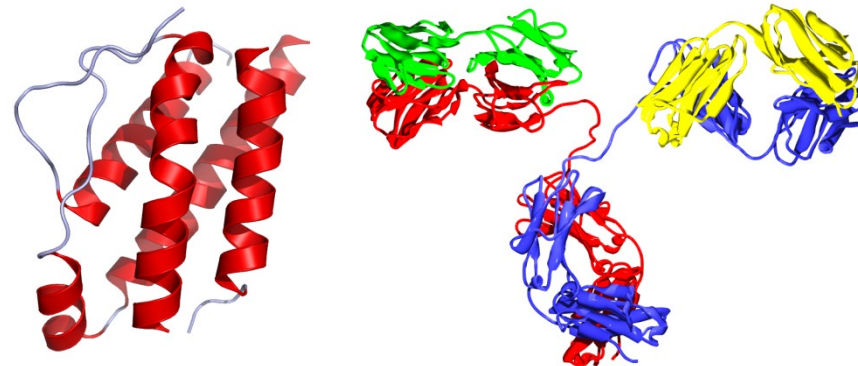
Recent immunotherapy drug approvals

Recent immunotherapy drug approvals

2015 FDA Approved Immunotherapies

March	April	September	October	November
Unituxin for neuroblastoma	Cyramza for colorectal cancer	Yervoy and Opdivo combination for melanoma	Keytruda for NSCLC	Darzalex for multiple myeloma
			Opdivo for NSCLC	Opdivo for renal cell carcinoma
			Imlygic for melanoma	Portrazza for NSCLC
				Empliciti for multiple myeloma
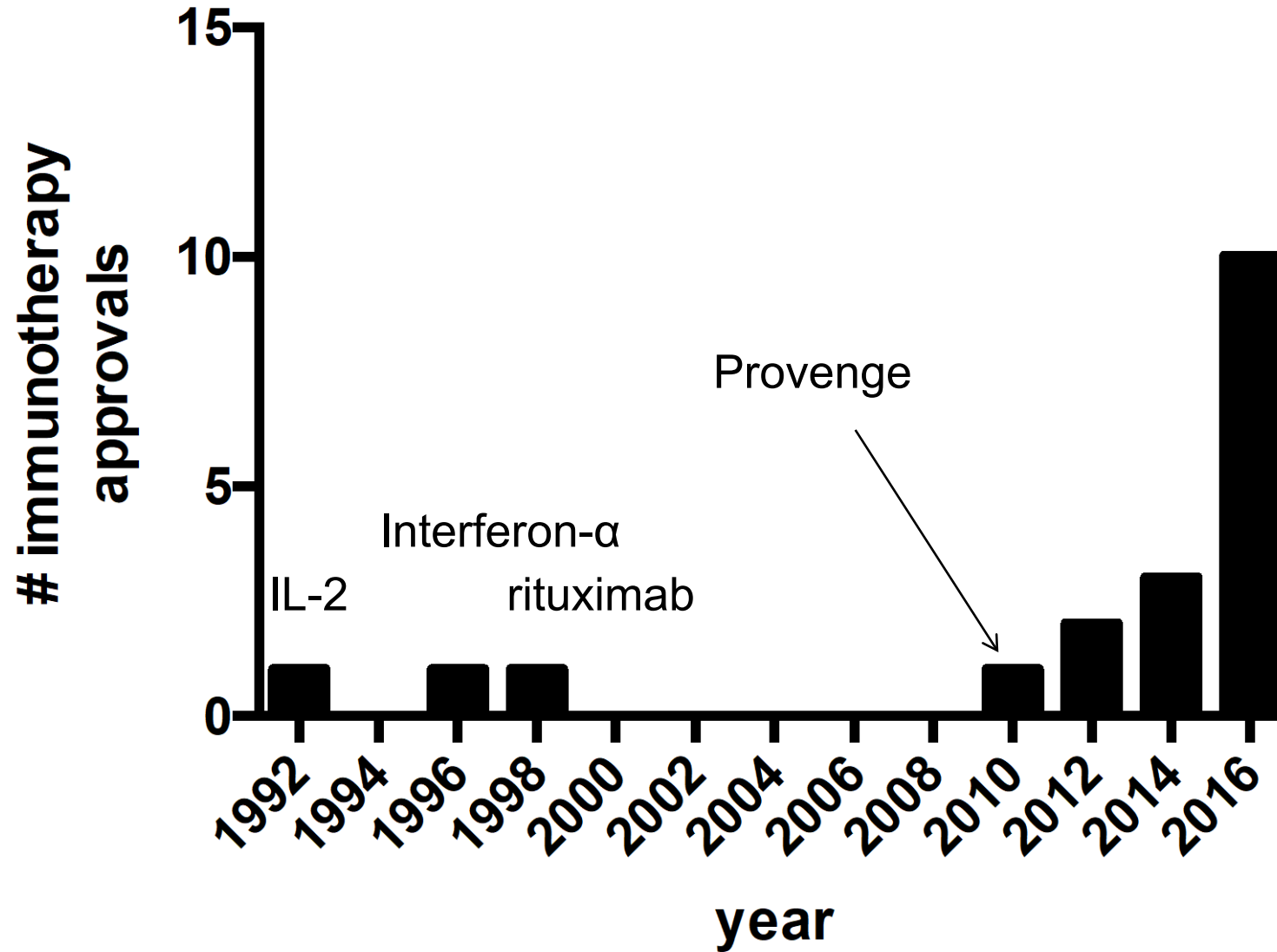
Generation and regulation of antitumor immunity

Promote the antigen presentation functions: **therapeutic vaccines**

Promote the production of protective T-cell responses: **cytokines, adoptive T cell transfer**

Activated T cells

Tumor cell

Tumor antigen

Antigen-presenting cell (APC)

Naïve T cell

Activated T cell

Activated T cell

Destroyed tumor cell

Tumor cells release tumor antigens.

APCs gather tumor antigens and prepare to present to naïve T cells.
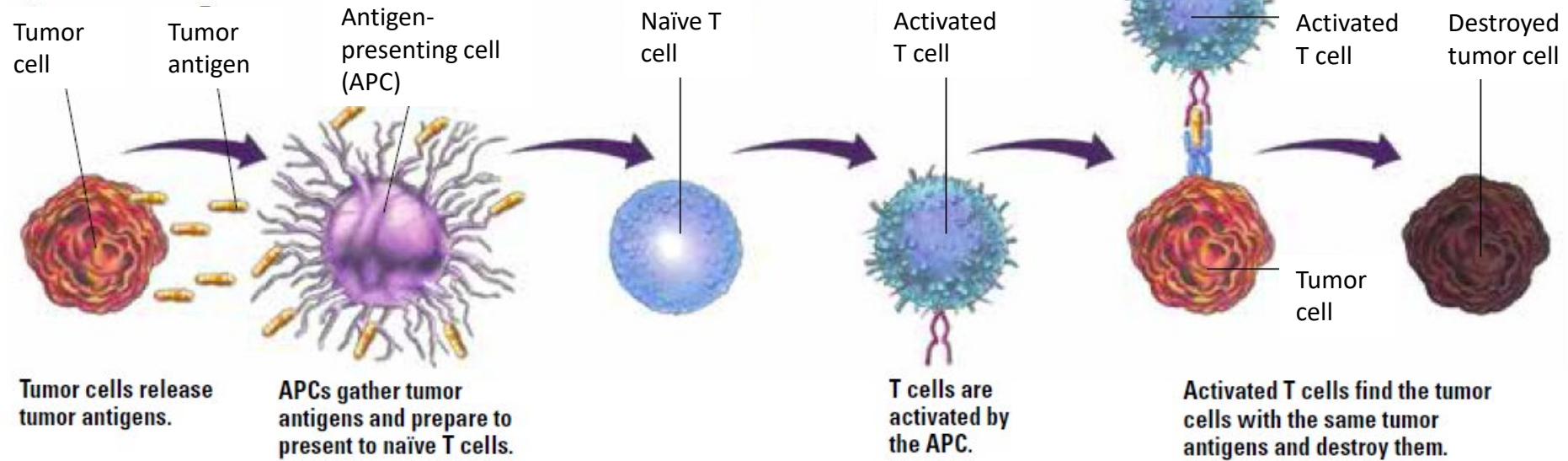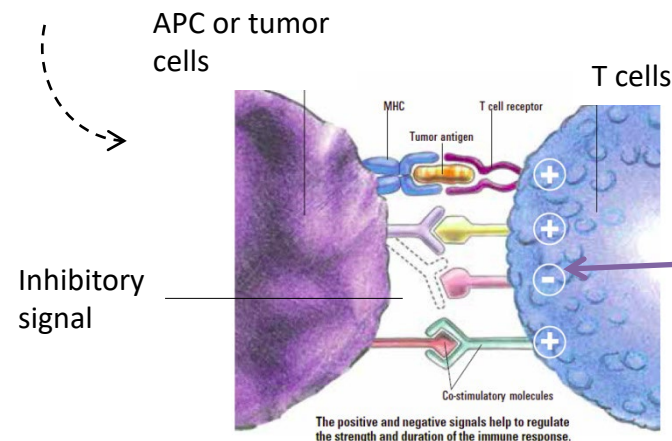
T cells are activated by the APC.

Activated T cells find the tumor cells with the same tumor antigens and destroy them.

Tumor cell

Promote immunity by various mechanisms: **monoclonal antibodies**

APC or tumor cells

T cells

Inhibitory signal

MHC

T cell receptor

Tumor antigen

Co-stimulatory molecules

The positive and negative signals help to regulate the strength and duration of the immune response.

Overcome immunosuppression in tumor: **checkpoint blockade antibody**

Adapted from PatientResource.com

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Different types of cancer immunotherapy

Passive Immunotherapy
- Tumor-specific mAbs
- Cytokines
- Adoptive Cell Transfer

Active Immunotherapy
- Peptide vaccines
- DC vaccines
- Allogeneic whole cell vaccines
- Checkpoint inhibitors
- Oncolytic viruses

Papaioannou NE et al. *Ann Transl Med* 2016
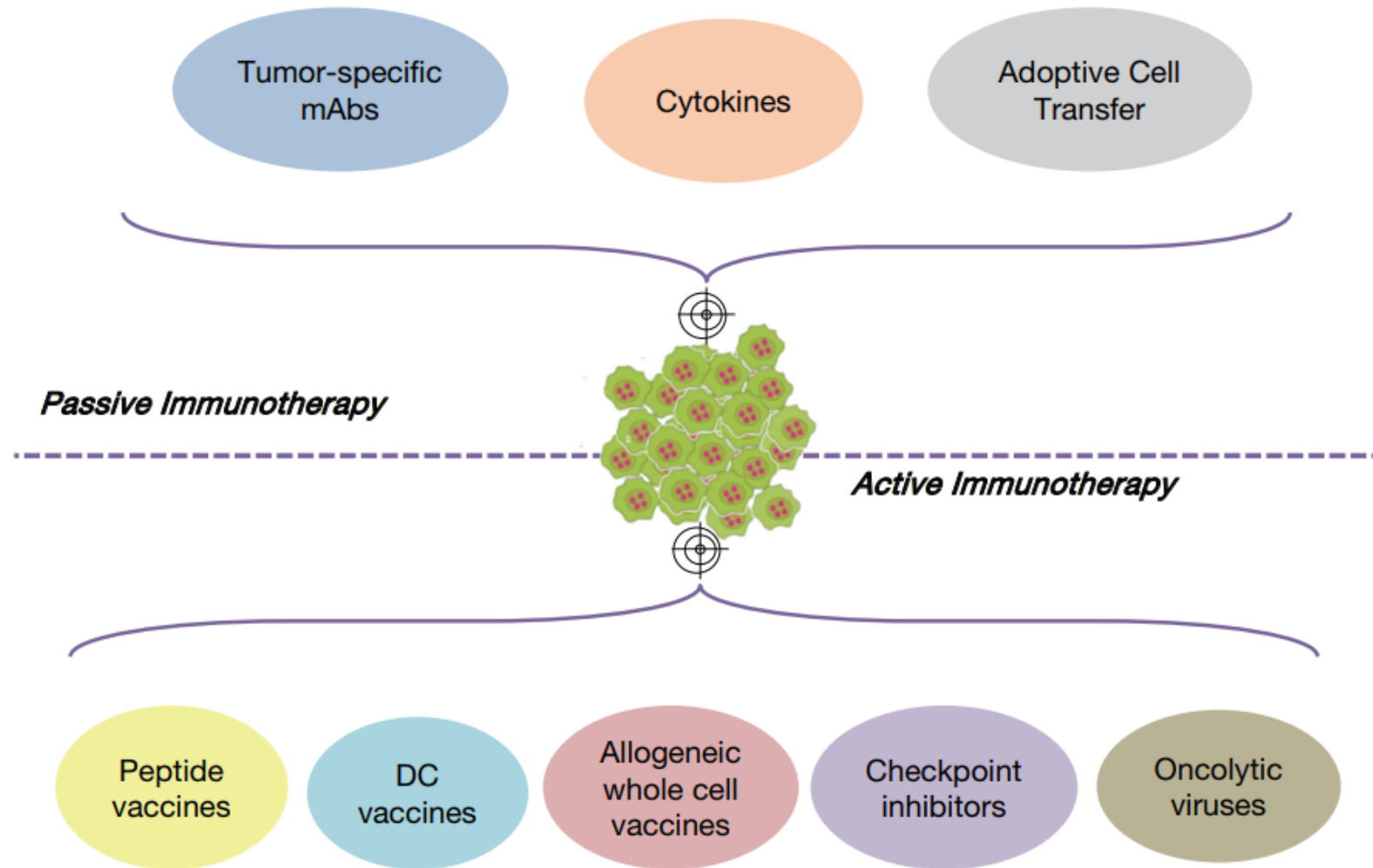
Therapeutic Cancer Vaccines
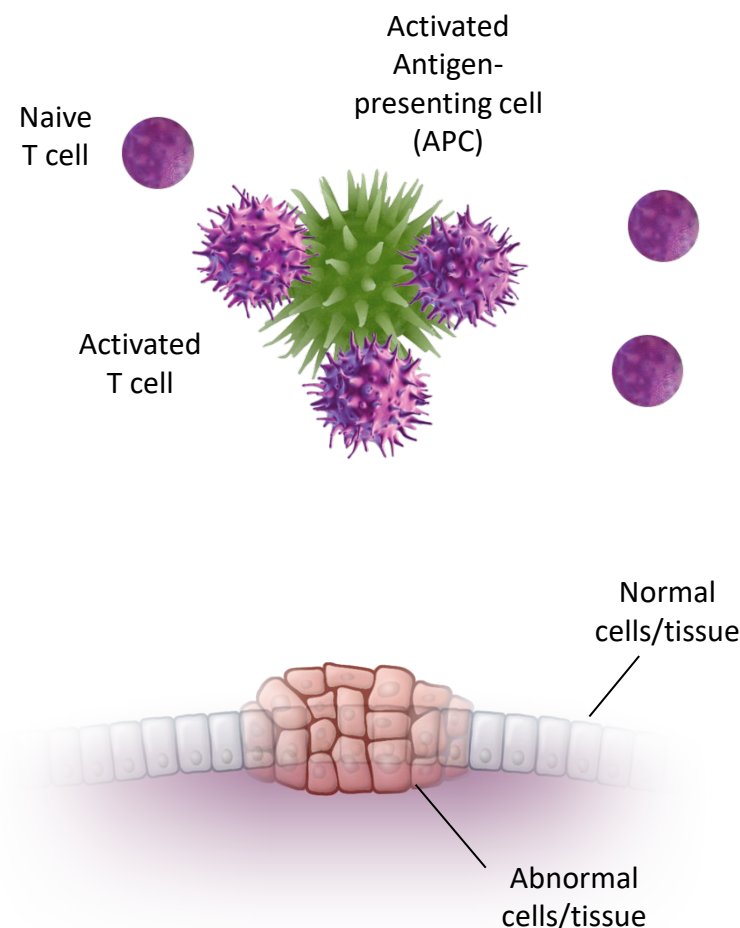
Vaccine: a substance used to stimulate the immune system and provide immunity against diseases without inducing the disease.

They are prepared from the causative agent of a disease, its products, or a synthetic substitute, treated to act as an antigen

- **Mechanism of action**
  - Stimulation of immune system

- **Examples**
  - Sipuleucel-T (antigen-loaded dendritic cells)

Naive T cell

Activated Antigen-presenting cell (APC)

Activated T cell

Normal cells/tissue

Abnormal cells/tissue

Dendreon
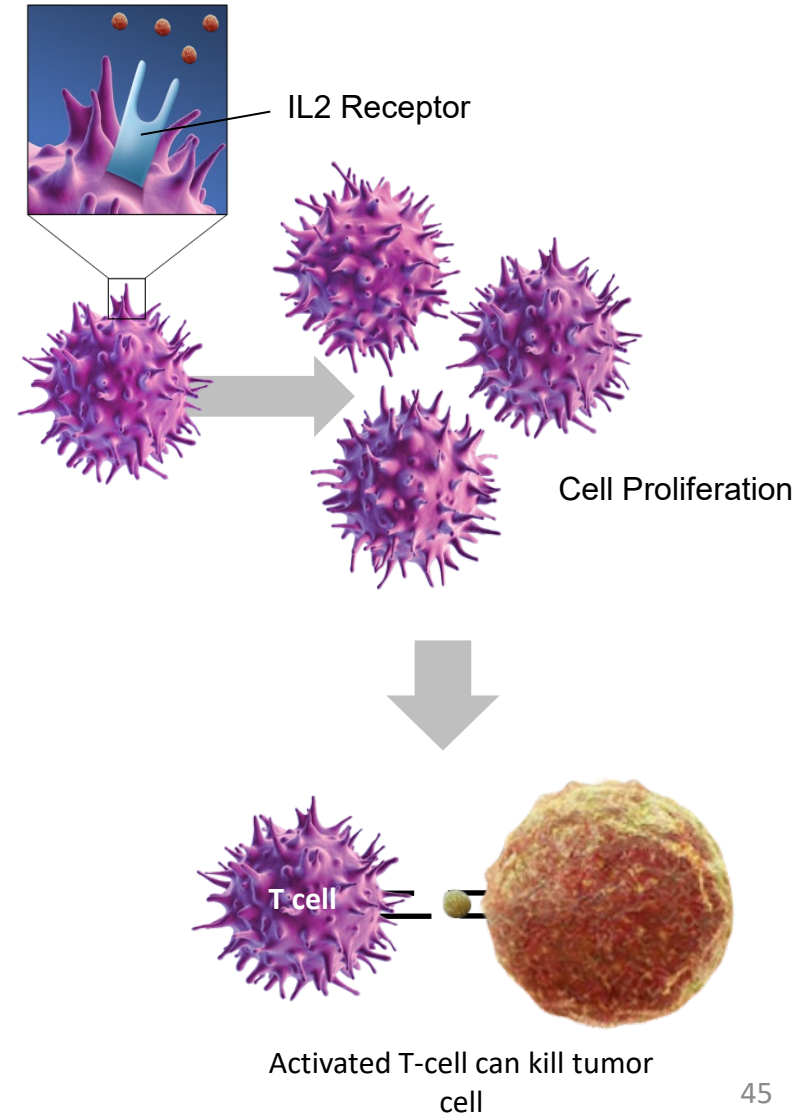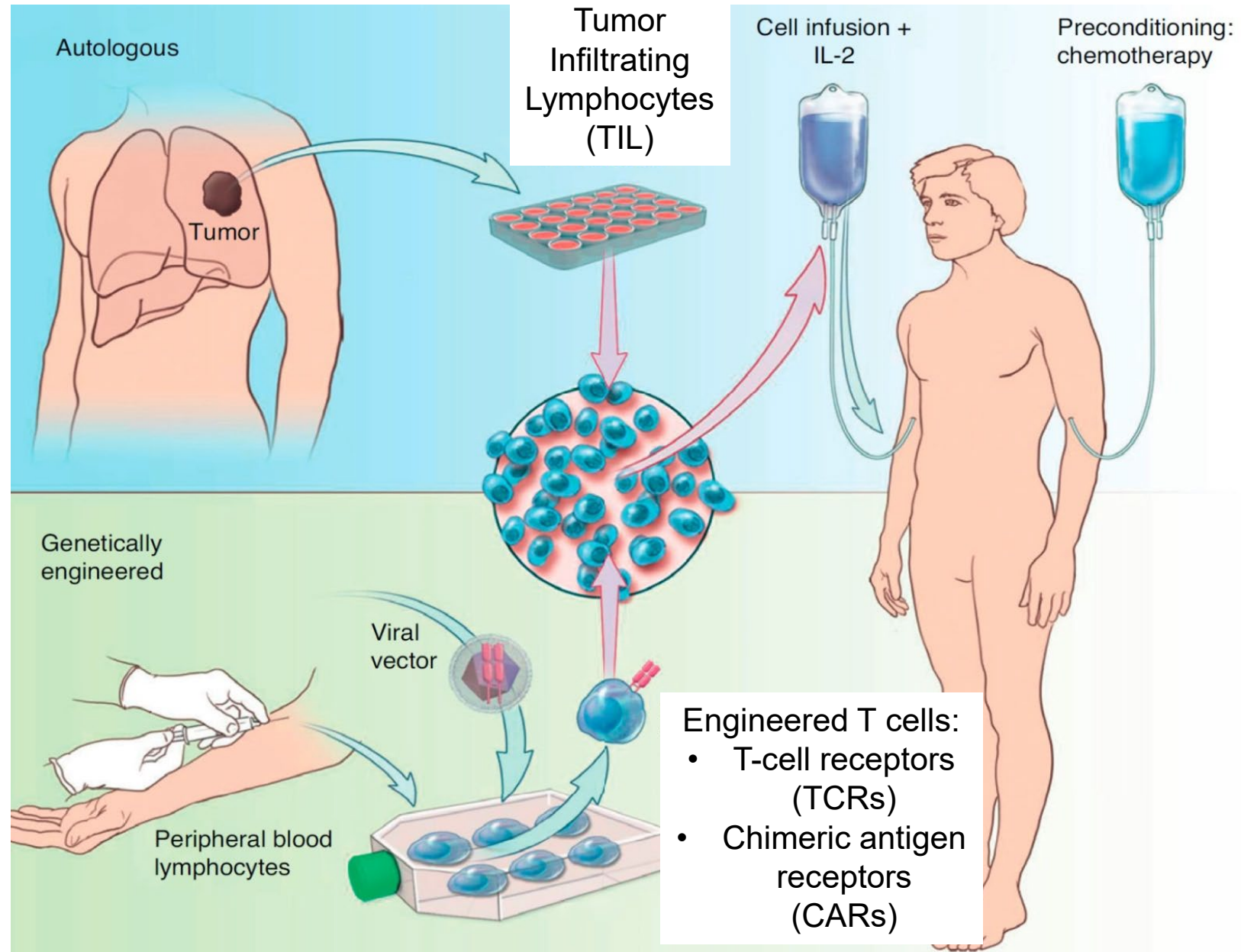*Targeting Cancer, Transforming Lives®*

Cytokines

Cytokines are proteins that are naturally secreted by immune system cells

- **Mechanism of action**
  - Interleukin-2 (IL-2) stimulates T-cell proliferation, as well as innate immunity

- **Examples**
  - Interleukin-2 (IL-2)
  - interferon-α (IFN-α)

IL-2 Stimulation of T-cell Proliferation

IL2 Receptor

Cell Proliferation

T cell

Activated T-cell can kill tumor cell

Adapted from Dendreon, Cancer Immunotherapy: Fundamental Concepts and Emerging, 2013

Adoptive T cell therapy

Autologous

Tumor

Tumor Infiltrating Lymphocytes (TIL)

Cell infusion + IL-2

Preconditioning: chemotherapy

Genetically engineered

Viral vector

Peripheral blood lymphocytes

Engineered T cells:
- T-cell receptors (TCRs)
- Chimeric antigen receptors (CARs)

Checkpoint Inhibitors

Checkpoint Inhibitor inhibits tumor-induced suppression of T-cell activation or function

- **Mechanism of action**
  - Antibodies target immune checkpoints to enhance antitumor response

- **Examples**
  - Anti-CTLA-4
  - Anti-PD1 or anti-PD-L1

CTLA-4, cytotoxic T lymphocyte-associated antigen 4;

PD1, programmed death 1

Sharma P, Allison JP, et al. Nat Rev Cancer. 2011;11(11):805-812.
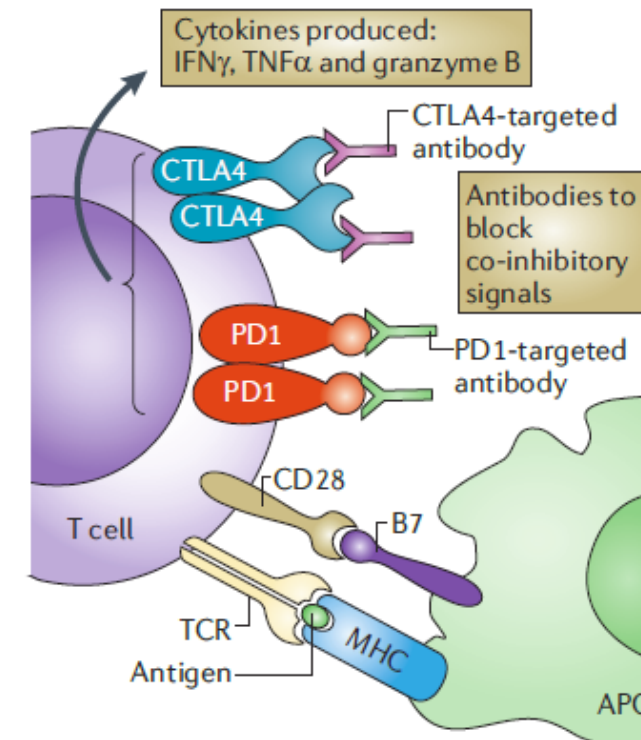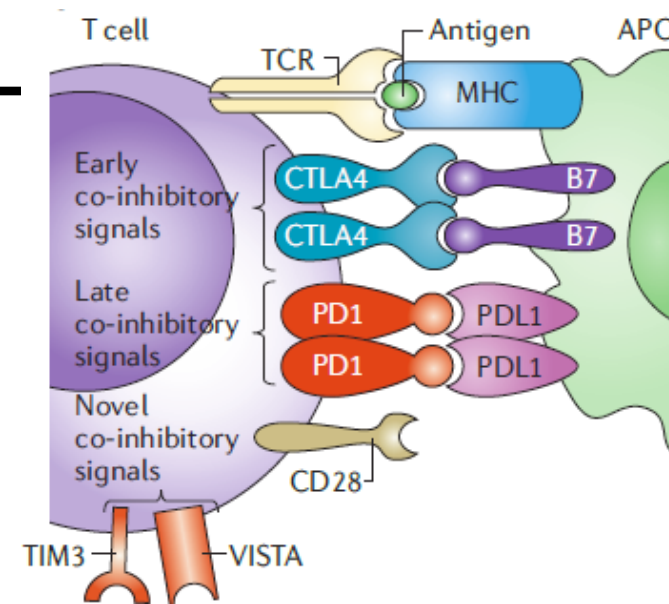
Monoclonal Antibodies (mAbs)

Antibodies are proteins designed to bind to specific substances in the body
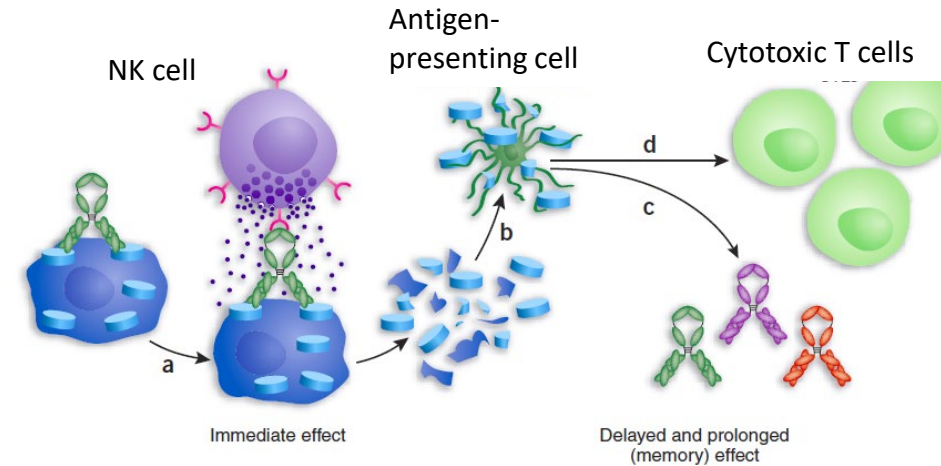
- **Mechanism of action**
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Signal transduction changes
  - Immunomodulation (eg. checkpoint inhibitor, co-stimulatory Ab)
  - Delivery of cytotoxic payloads
  - others

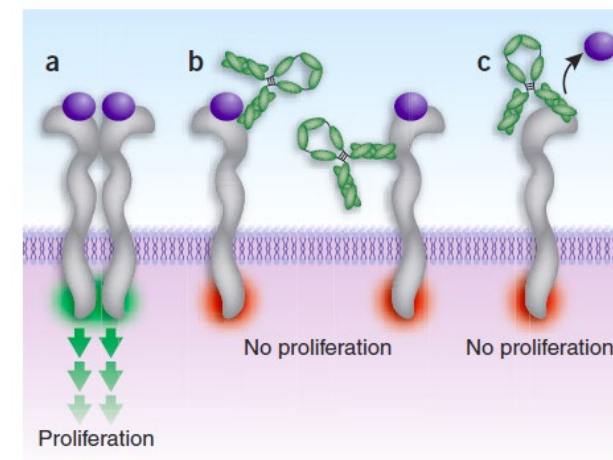- **Examples**
  - Anti-Her2
  - Anti-CD20
  - Anti-VEGF

Antibody-dependent cell-mediated cytotoxicity (ADCC)-mediated adaptive immunity switch

NK cell   Antigen-presenting cell   Cytotoxic T cells

Immediate effect   Delayed and prolonged (memory) effect

Antibody-mediated signaling inhibition

No proliferation   No proliferation

Proliferation

Nat. Biotechnol. **2005**, *23*, 1147-1157

Summary: Features of an effective cancer immunotherapy

- Specificity

- Trafficking

- Adaptability

- Durability (immune memory)

- Versatility

- Reduced side effects

Why Immunotherapy?

POWERFUL
Attacks the cancer systemically, through-out the body

SPECIFIC
Trains the immune system to recognize & target only cancer cells

MEMORY/ PROTECTION
Capacity for memory means durability of protection

INTRINSIC/ UNIVERSAL
A treatment approach that can be applied to nearly all cancers

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