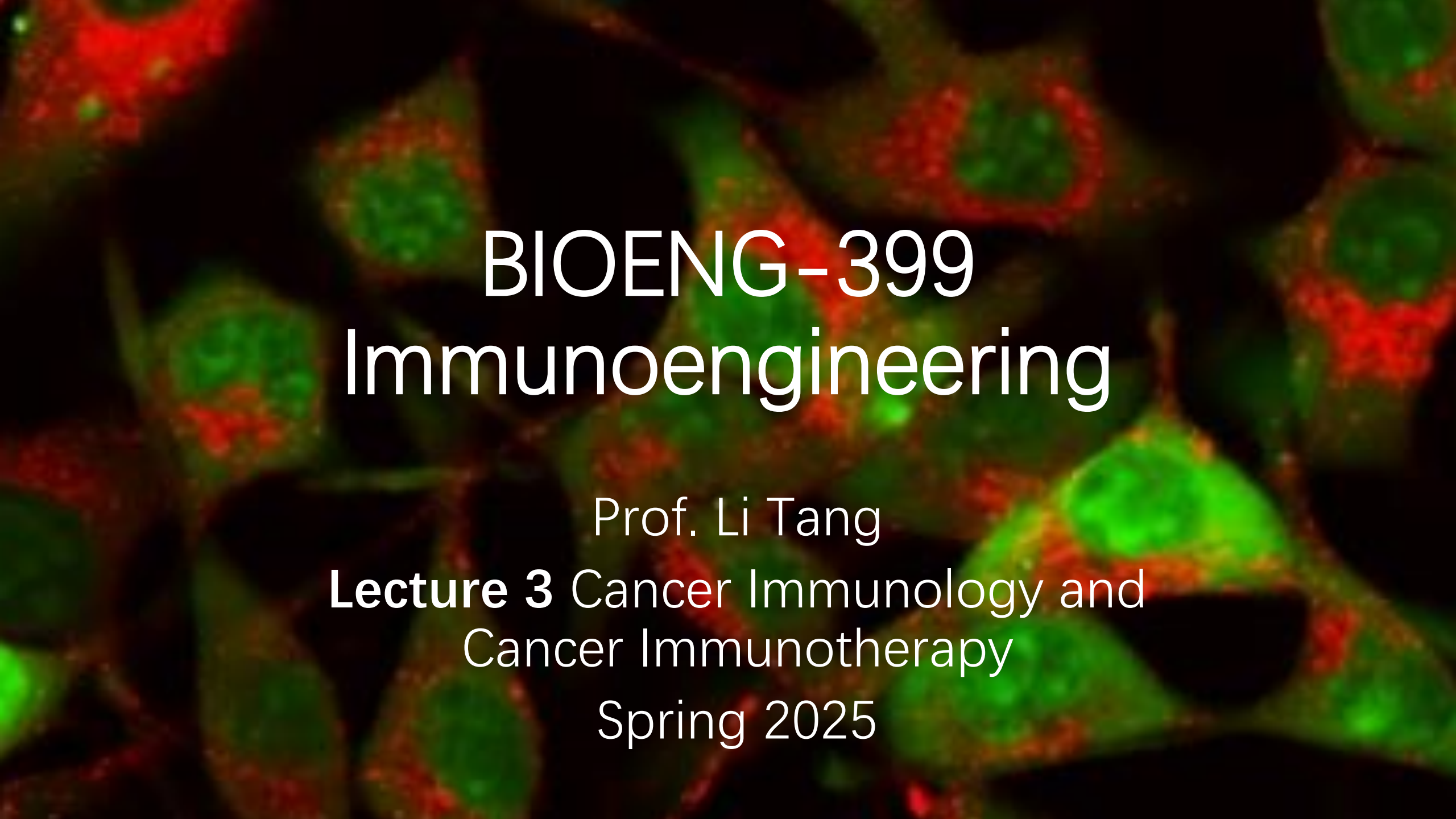


BIOENG-399 Immunoengineering

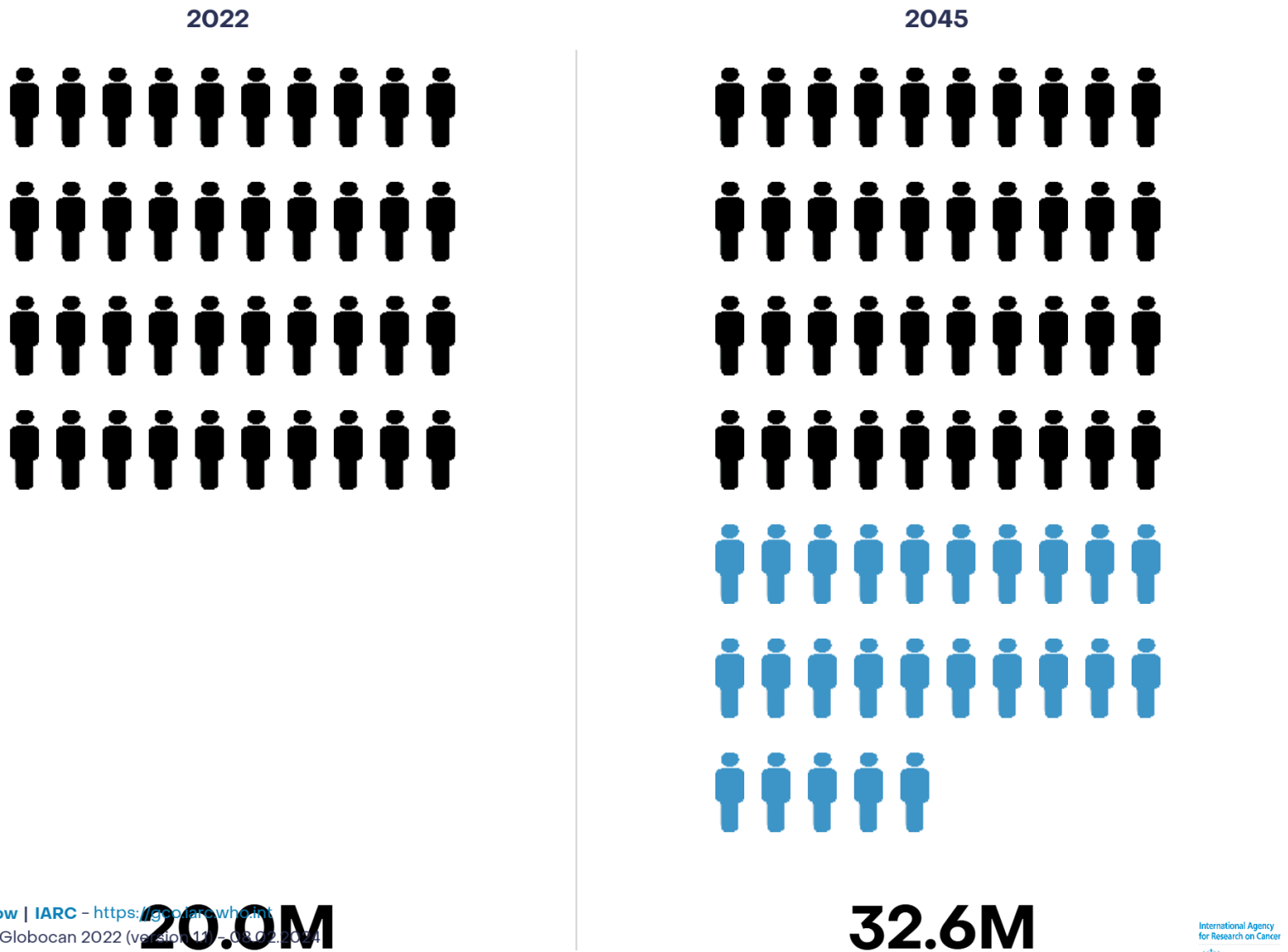
Prof. Li Tang

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



Cancer Tomorrow | **IARC** – https://gco.iarc.who.int
Data version: Globocan 2022 (version 1.1 – 03.02.2024)
© All Rights Reserved 2025

International Agency for Research on Cancer
World Health Organization

https://gco.iarc.fr/

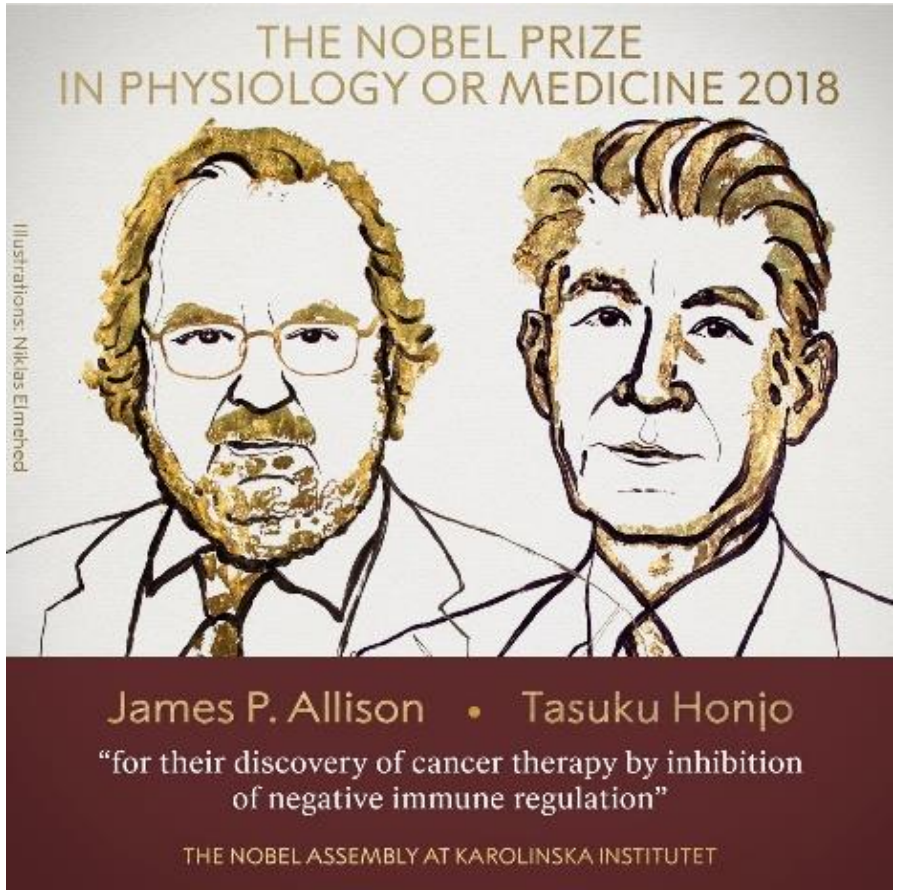
Some facts:

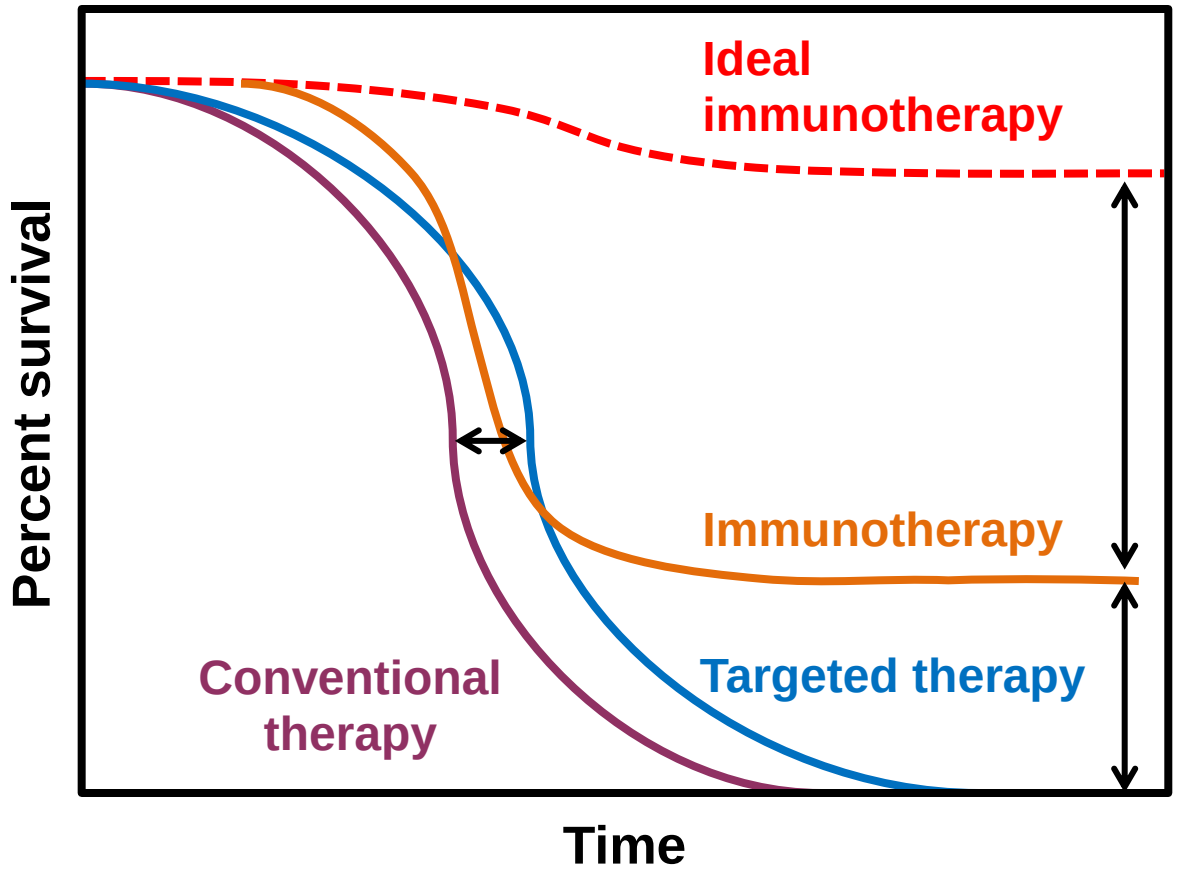
- Globally, one in five people worldwide develop cancer during their lifetime.
- In US, approximately 40.5% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2017–2019 data).
- Generally, cancer rates are highest in countries whose populations have the highest 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/

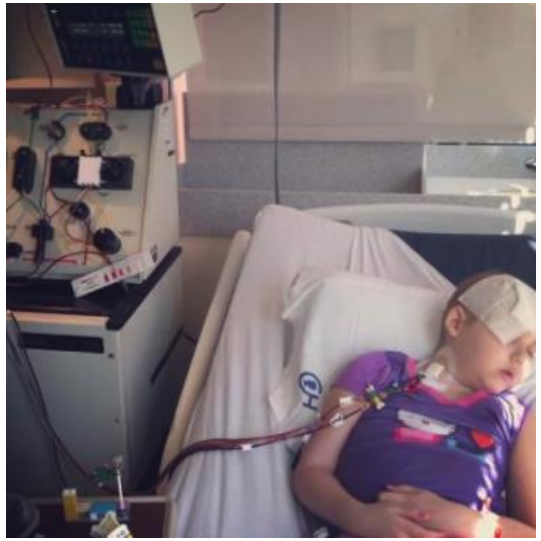
Immunotherapy improves fraction of long term survival





Sharma P et al. *Cell* 2015 (adapted)

Emily's story: a young girl beats cancer with immunotherapy



Cancer Research Institute, 2013
http://emilywhiteheadfoundation.org

What is the role of immune system in cancer?

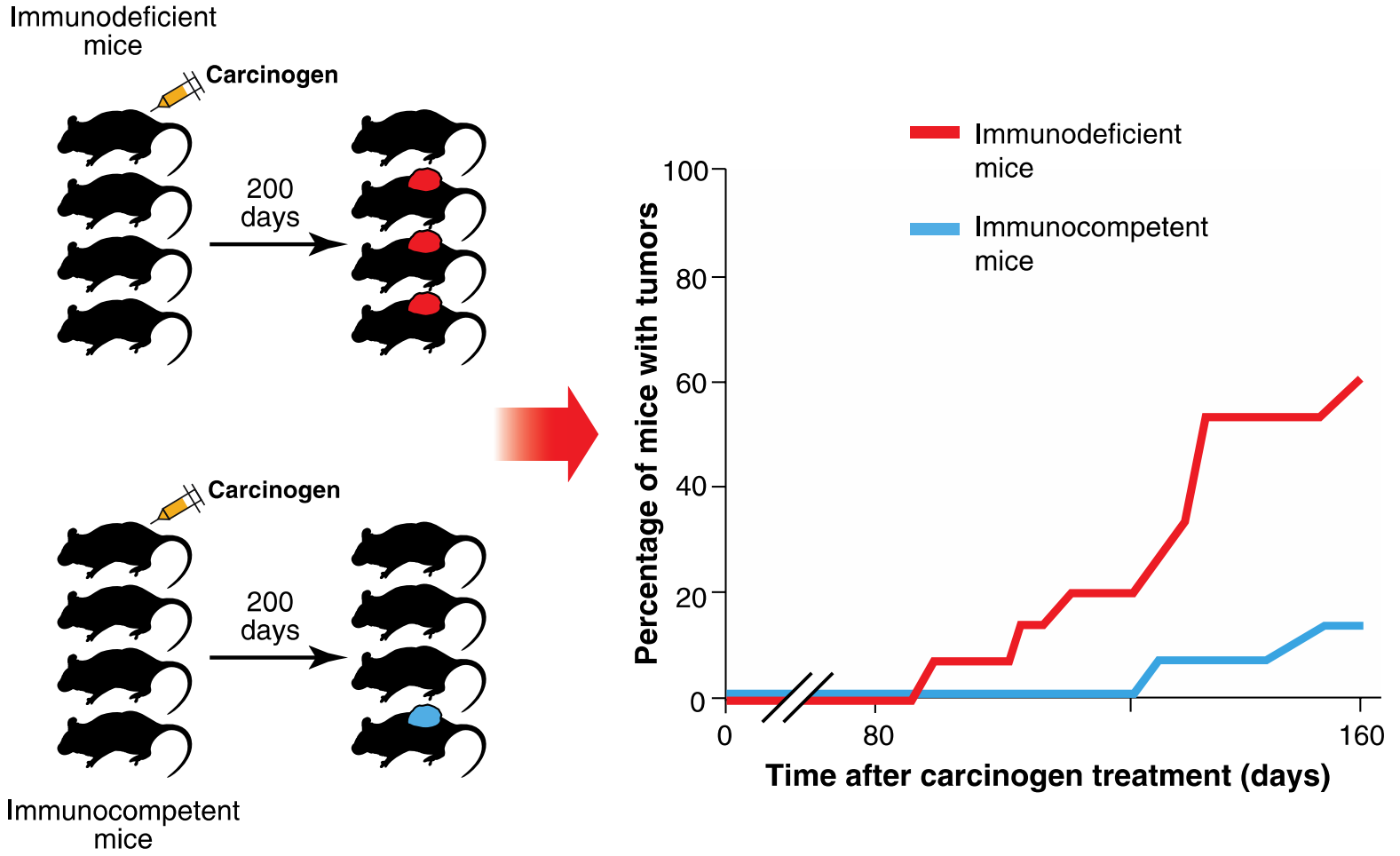
The immunosurveillance hypothesis and the debate

- 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

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

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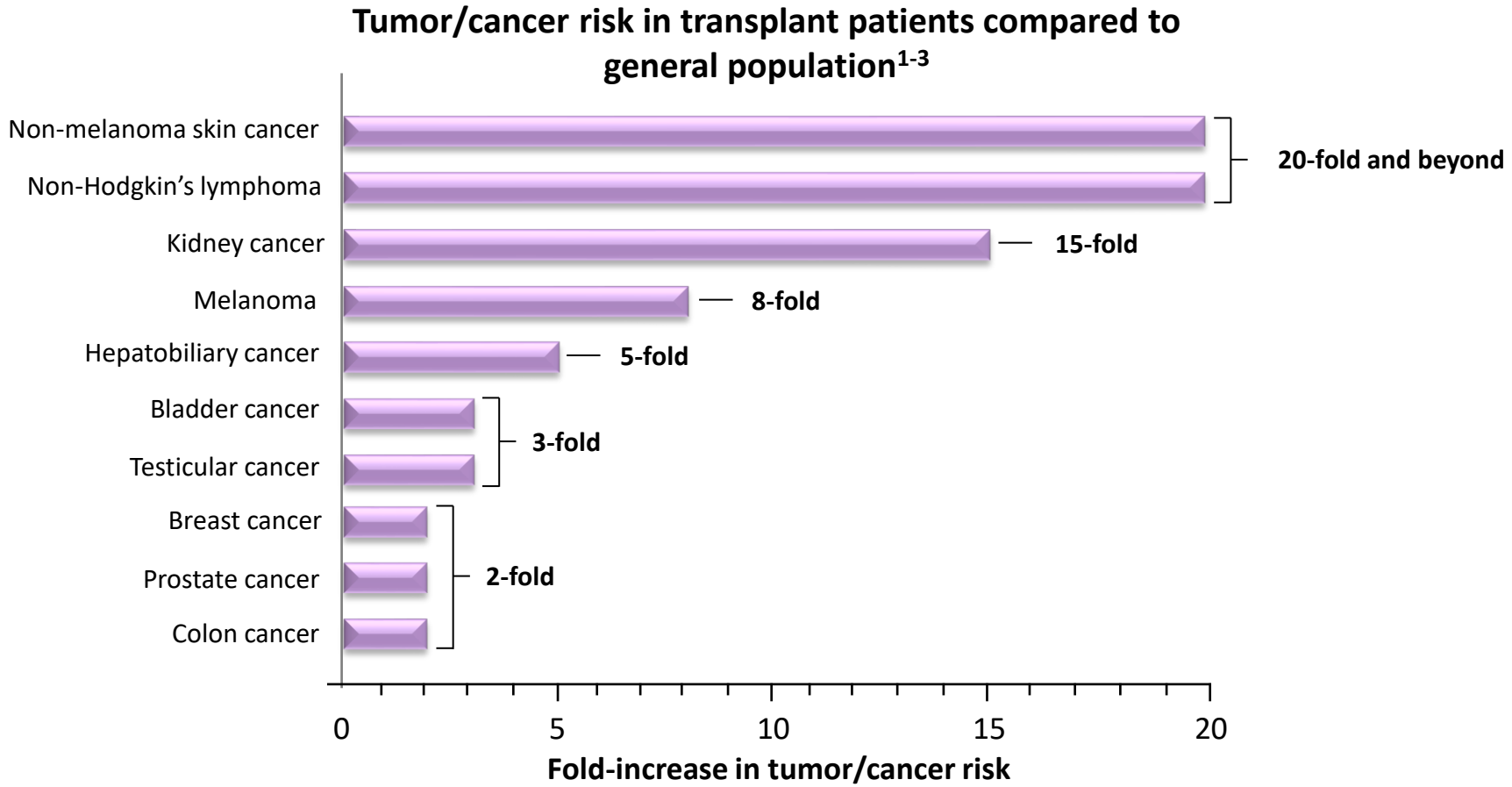
Increased Incidence of Cancer in Immunocompromised Individuals

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

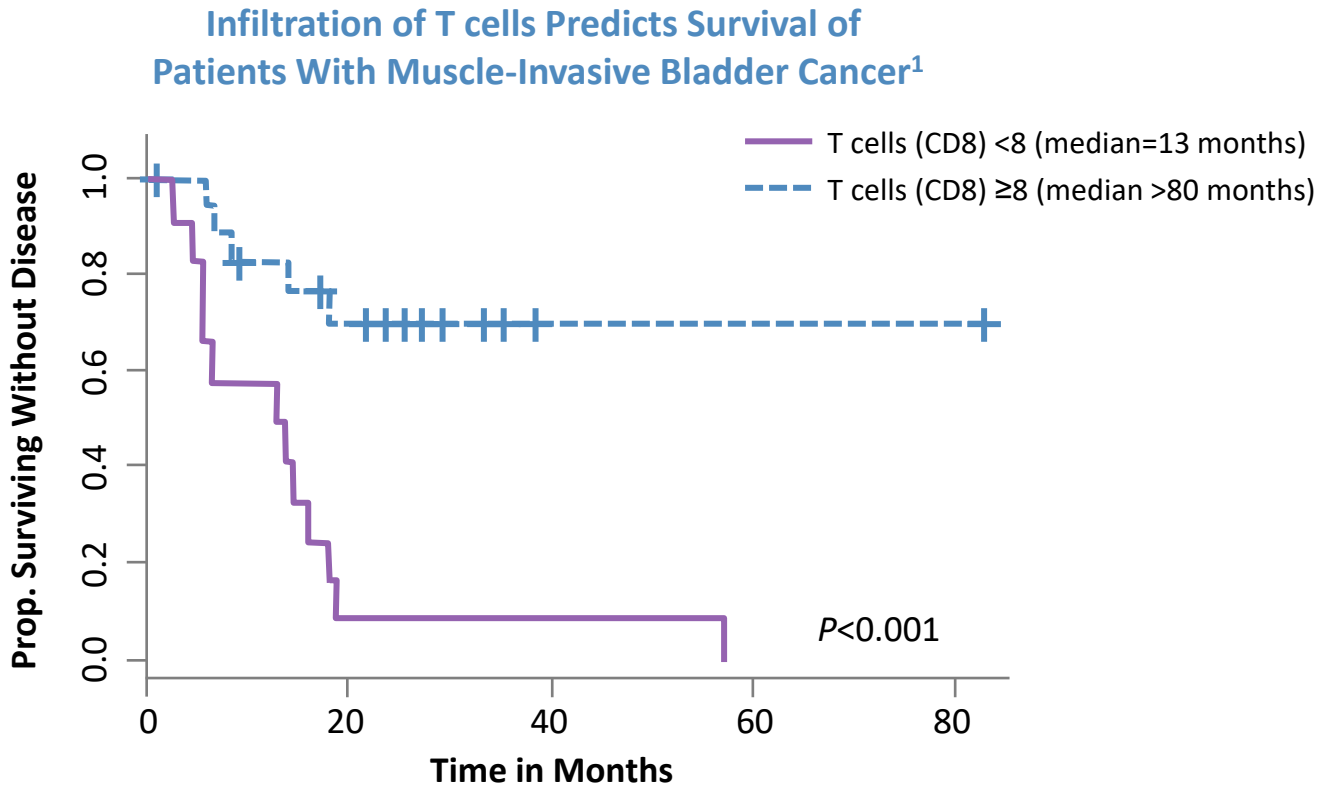


1. Kasiske BL, Wang C, et al. *Am J Transplant.* 2004;4(6):905-913.
2. Le Mire L, Wojnarowska F, et al. *Br J Dermatol*. 2006;154(3):472-477.
3. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

This slide is not required.

Immune Cells Within Tumors Predict Overall Survival

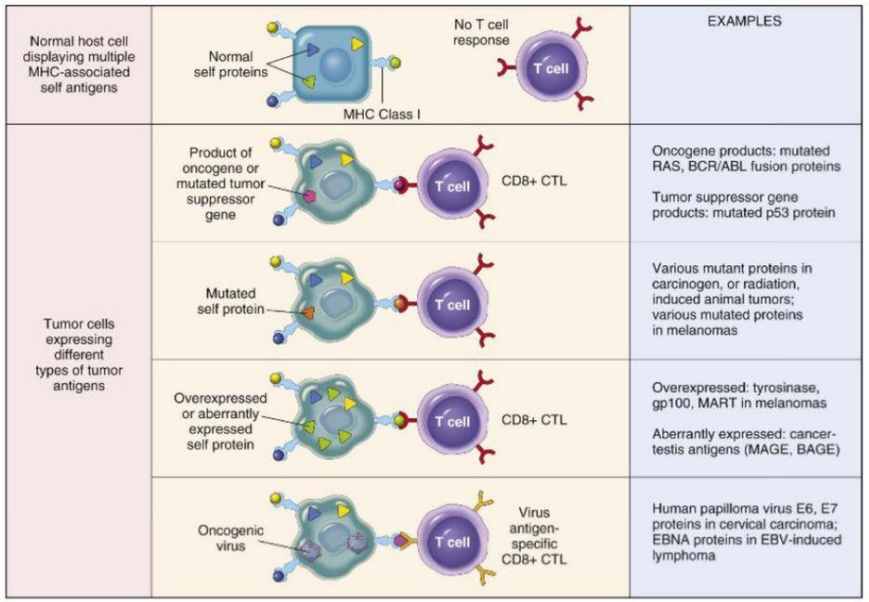
- T-cell infiltration within tumors predicts overall survival (OS) in multiple cancer types including bladder cancer[1-3]



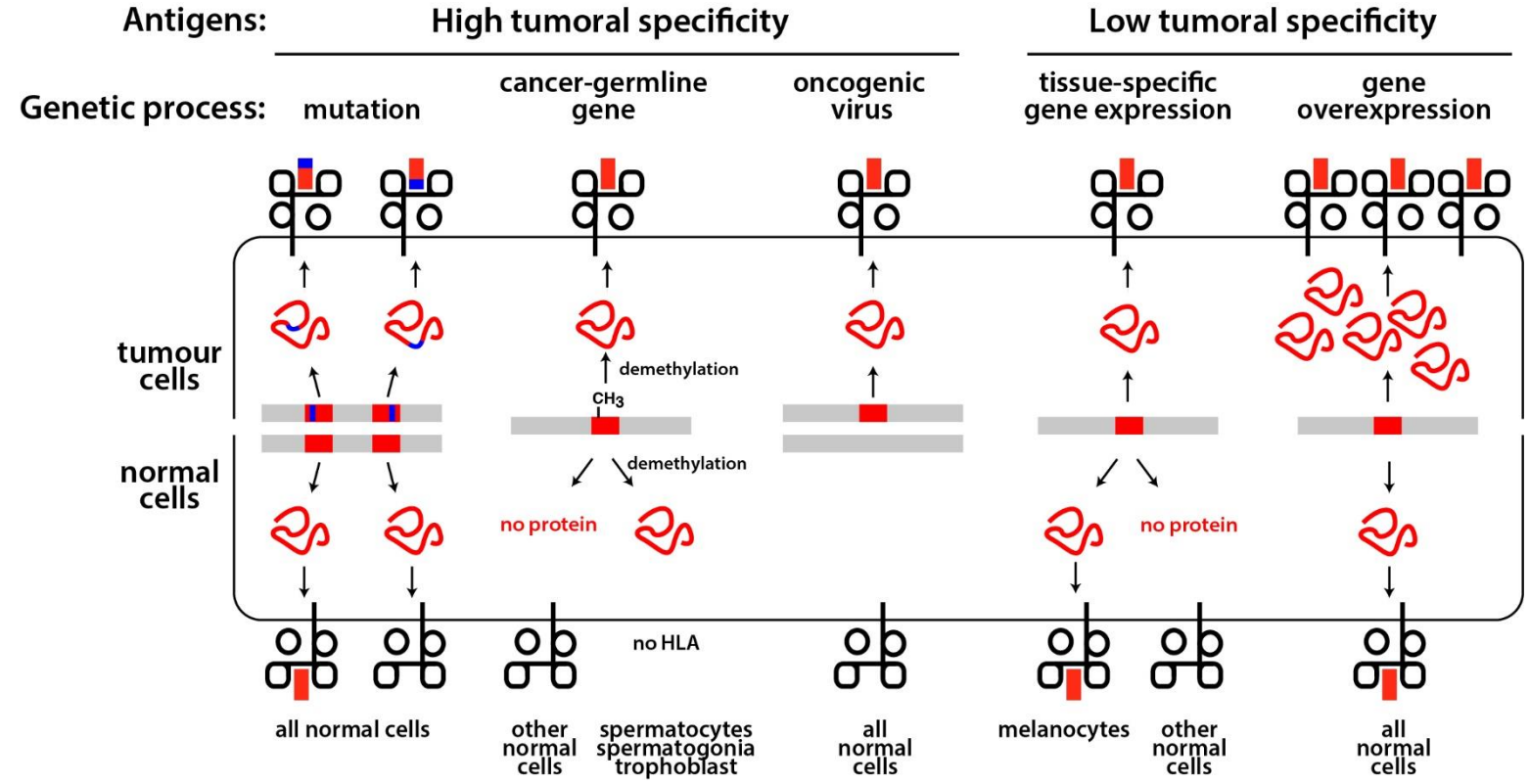
Reprinted from Sharma P, Sato E, et al.[1]

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?



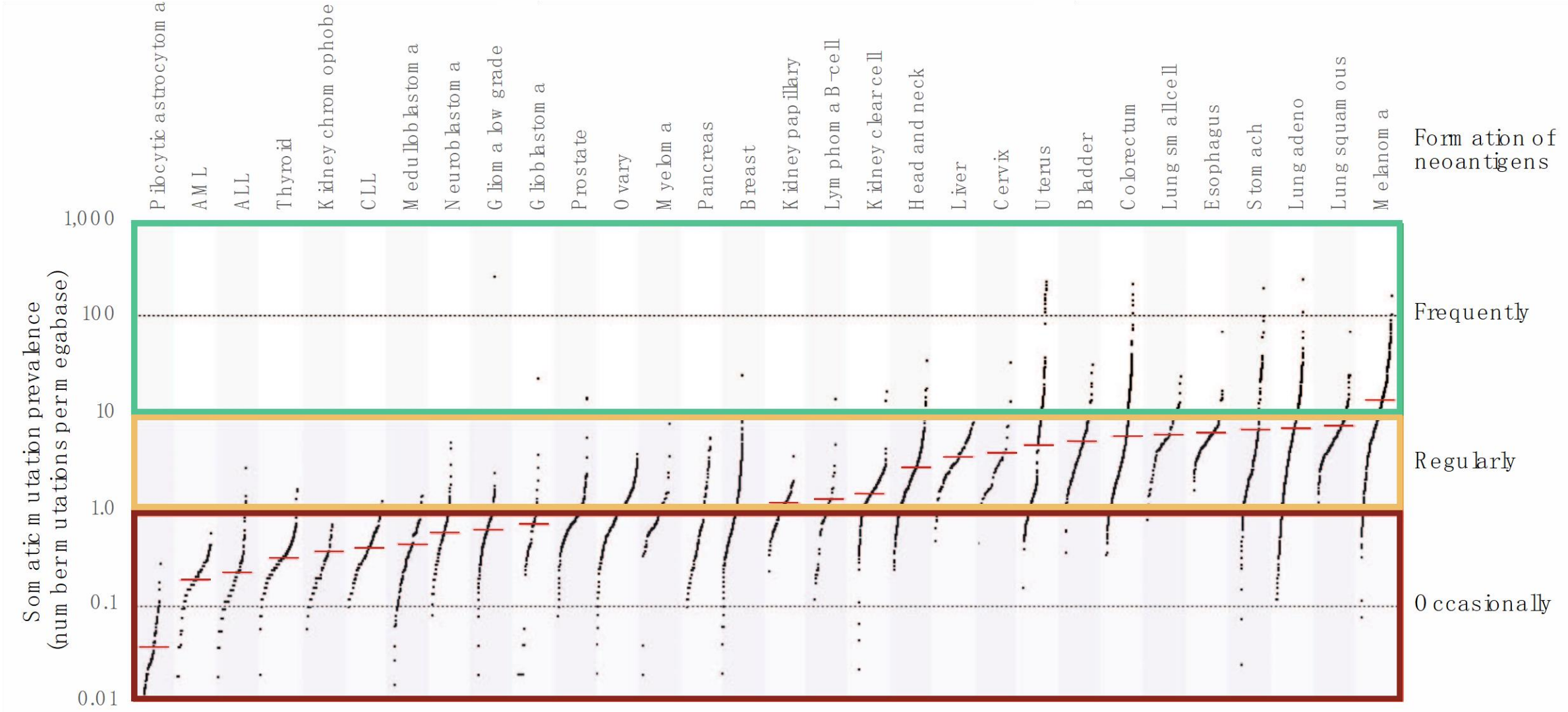
Tumor antigens recognized by CD8+ T cells.



- 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

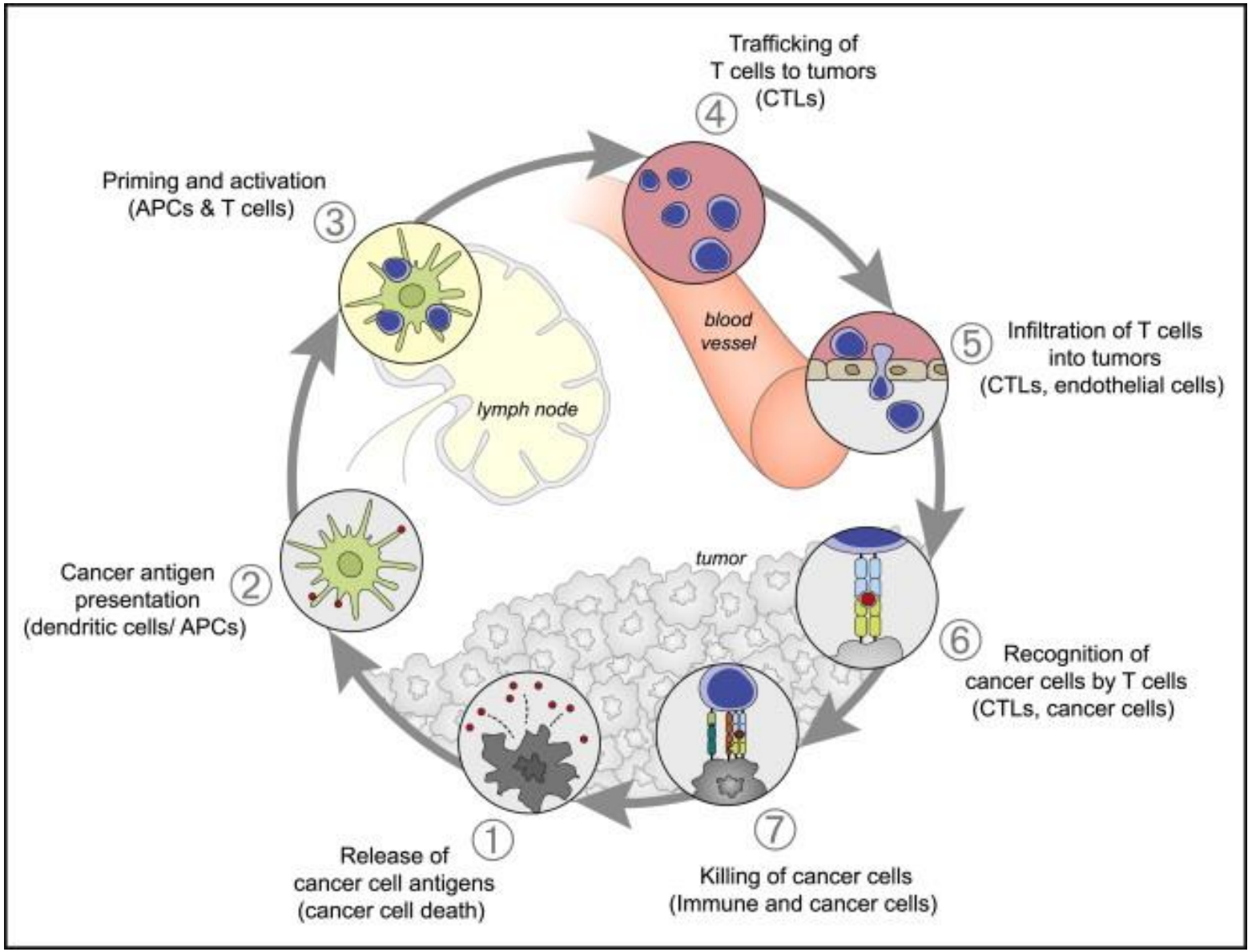
Patient-specific neoantigens: prime target of immune response to cancer?



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

This slide is not required.

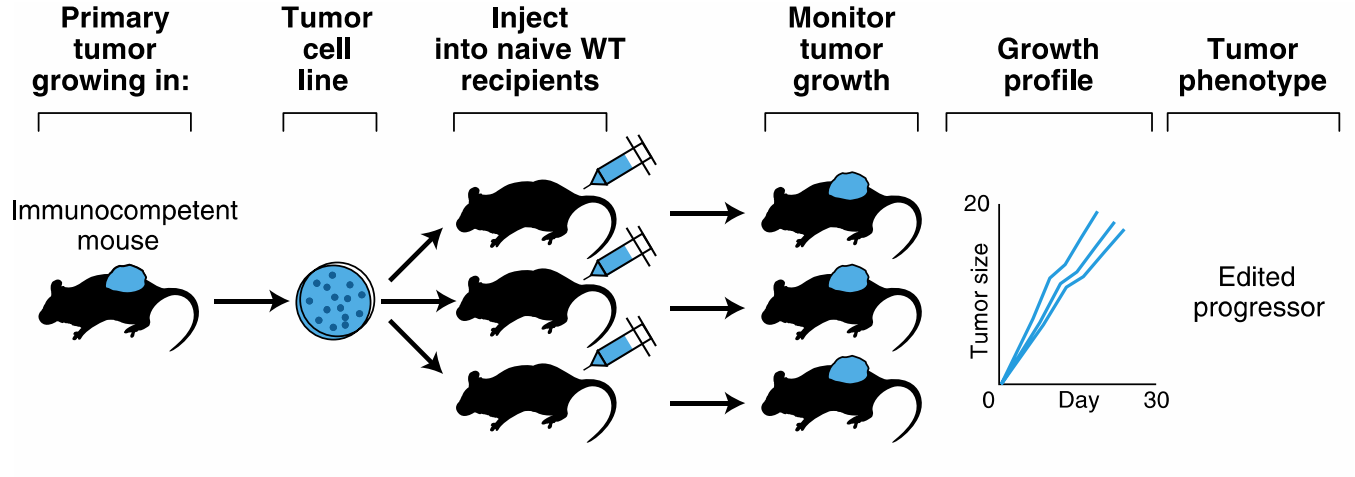
Cancer-immunity cycle



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

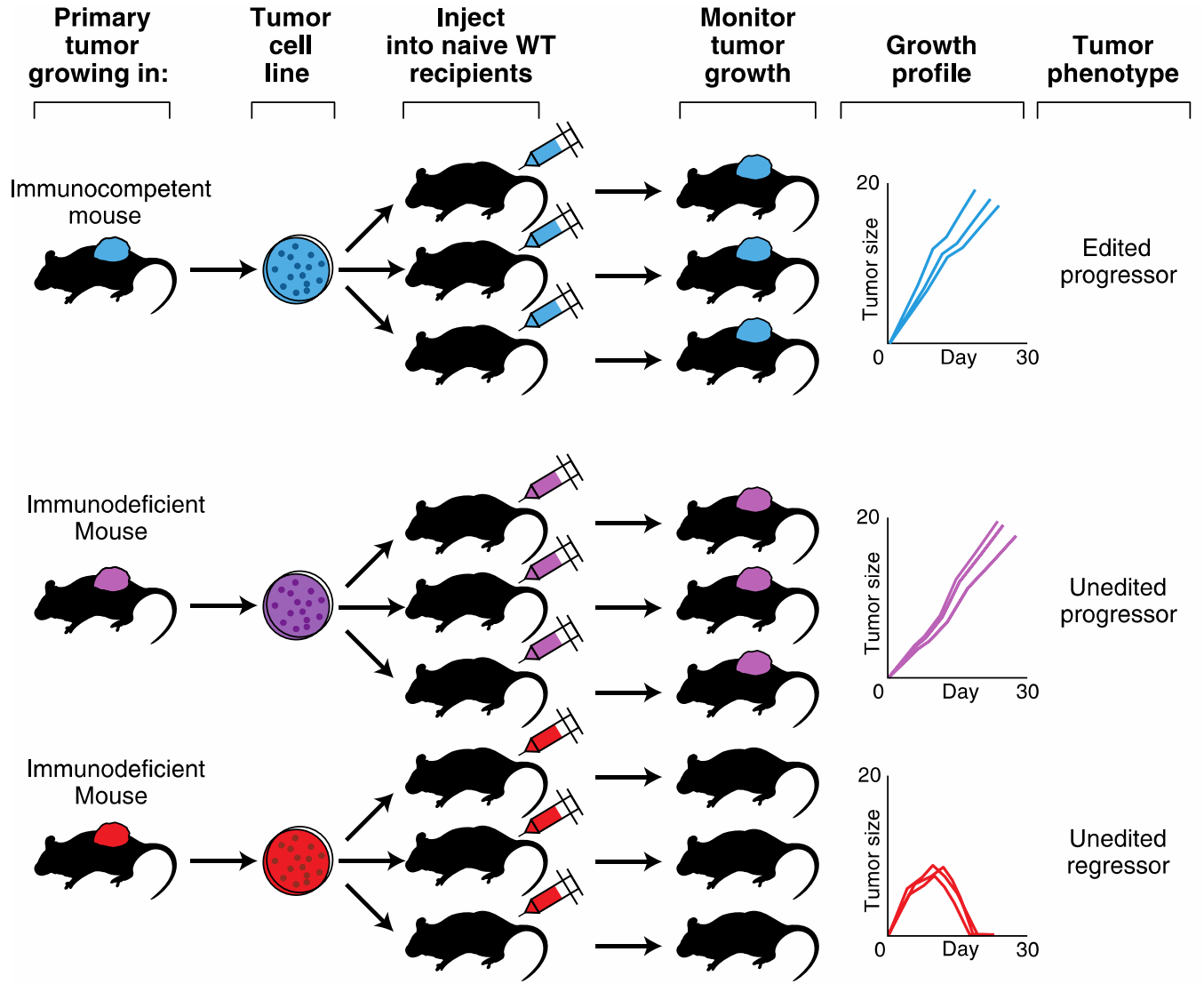


- 100% of tumors grown in immunocompetent mice and transplanted to immunocompetent mice are progressors (edited progressors)
- ~50% of tumor cell lines derived from carcinogen-induced tumors in immunodeficient mice are rejected when transplanted into WT mice (unedited regressors)

- 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)

Experimental evidence for immunoediting of tumors



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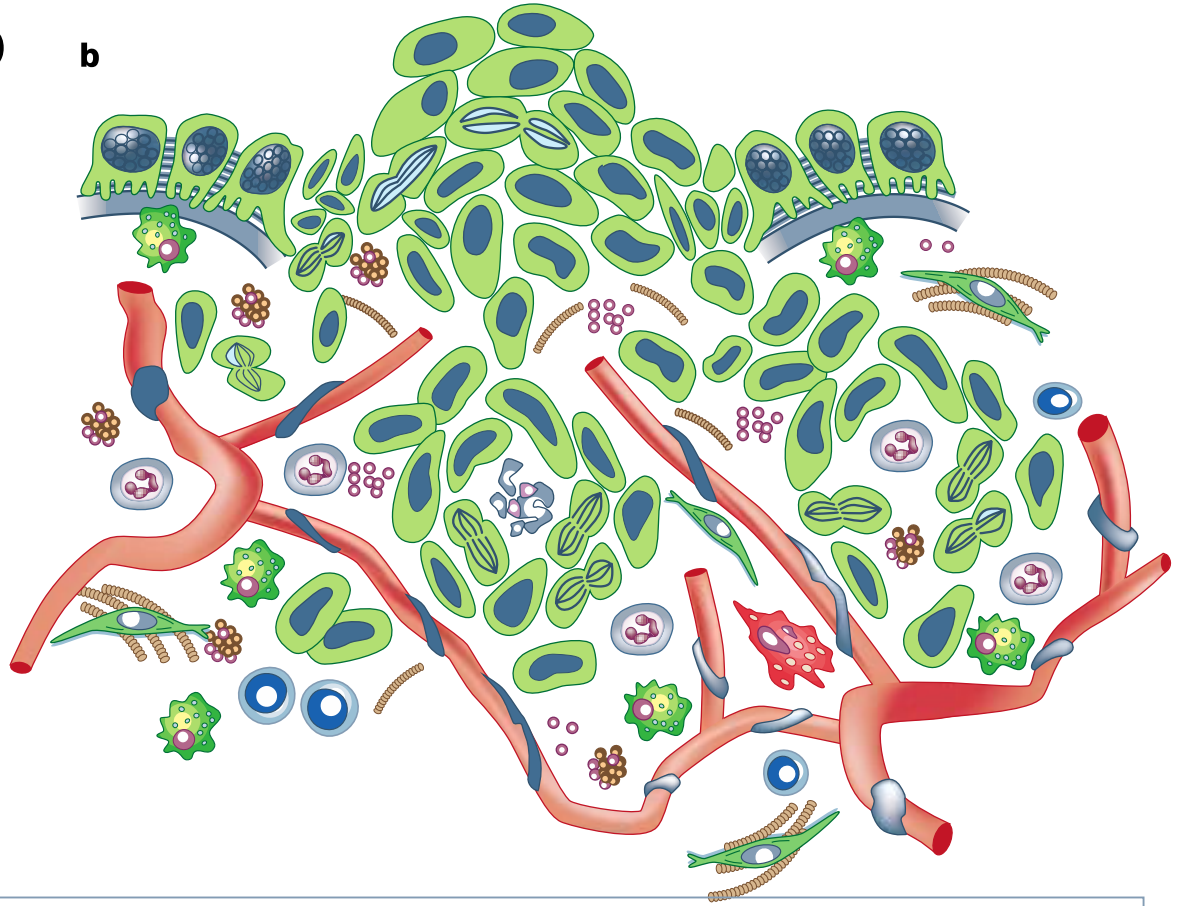
Schreiber, R. D., Old, L. J., & Smyth, M. J. *Science*, *331*(6024), 1565–1570 (2011)

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)

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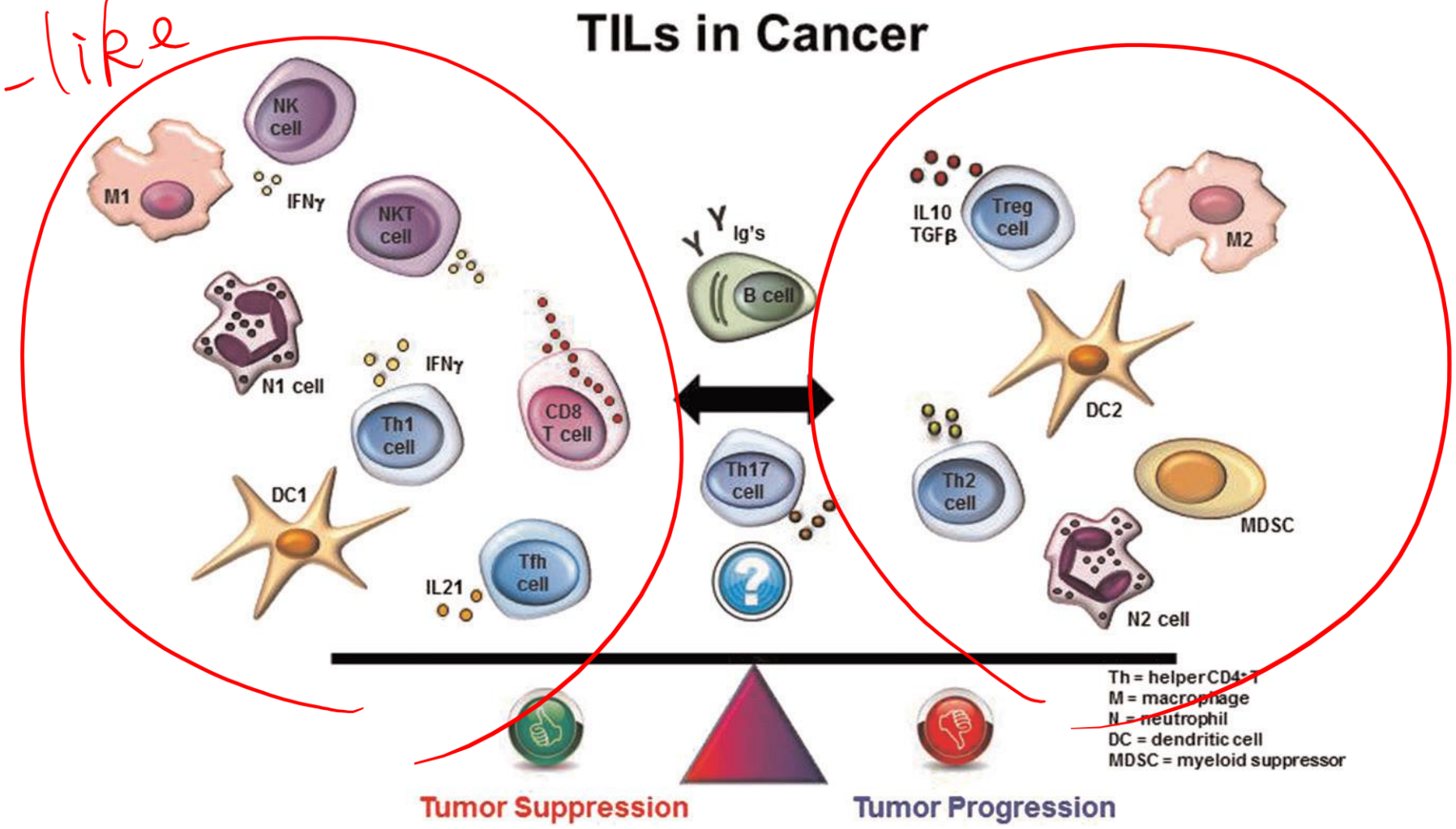
Immune cells can be protagonists or antagonists of growing tumors



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

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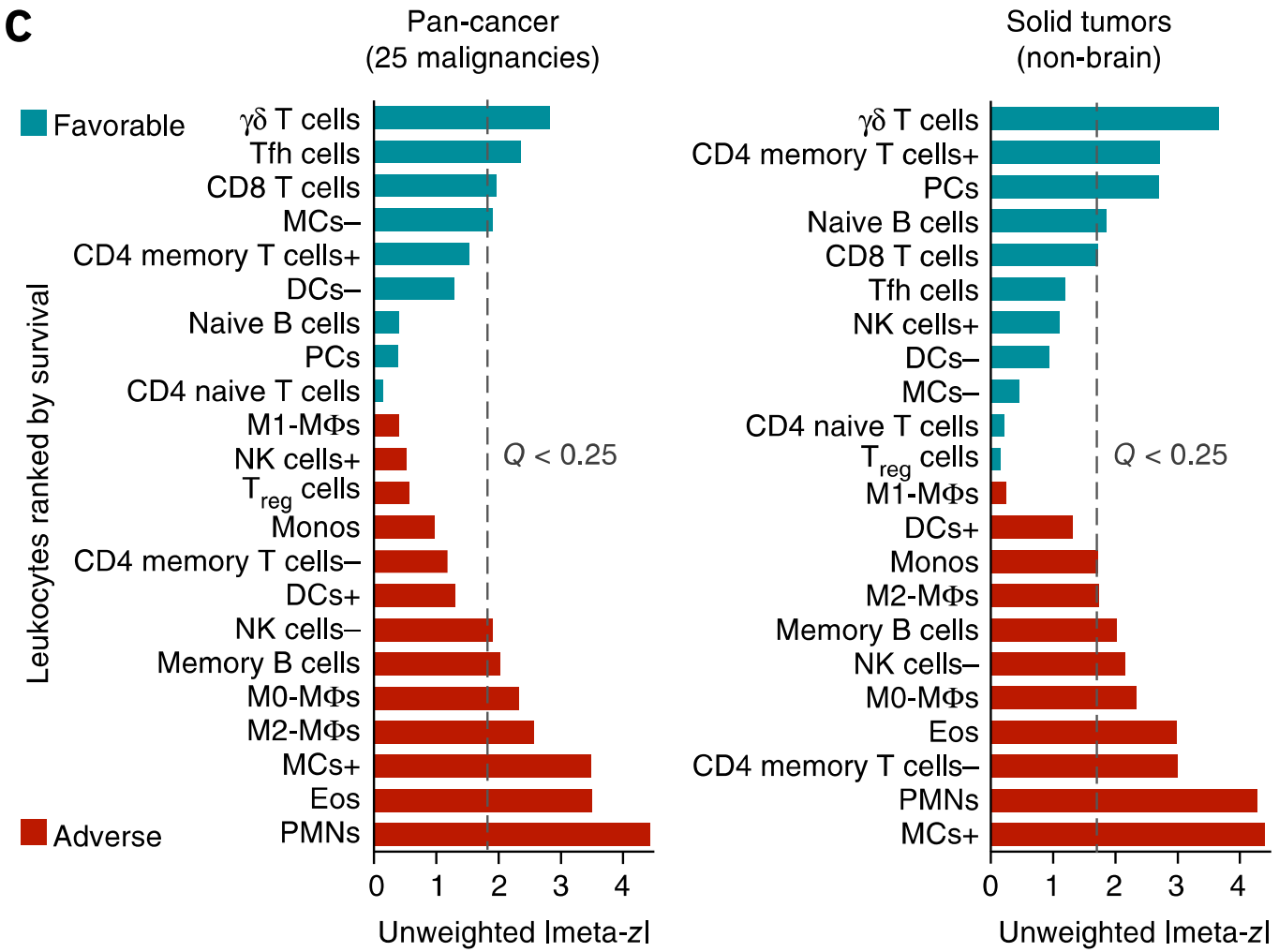
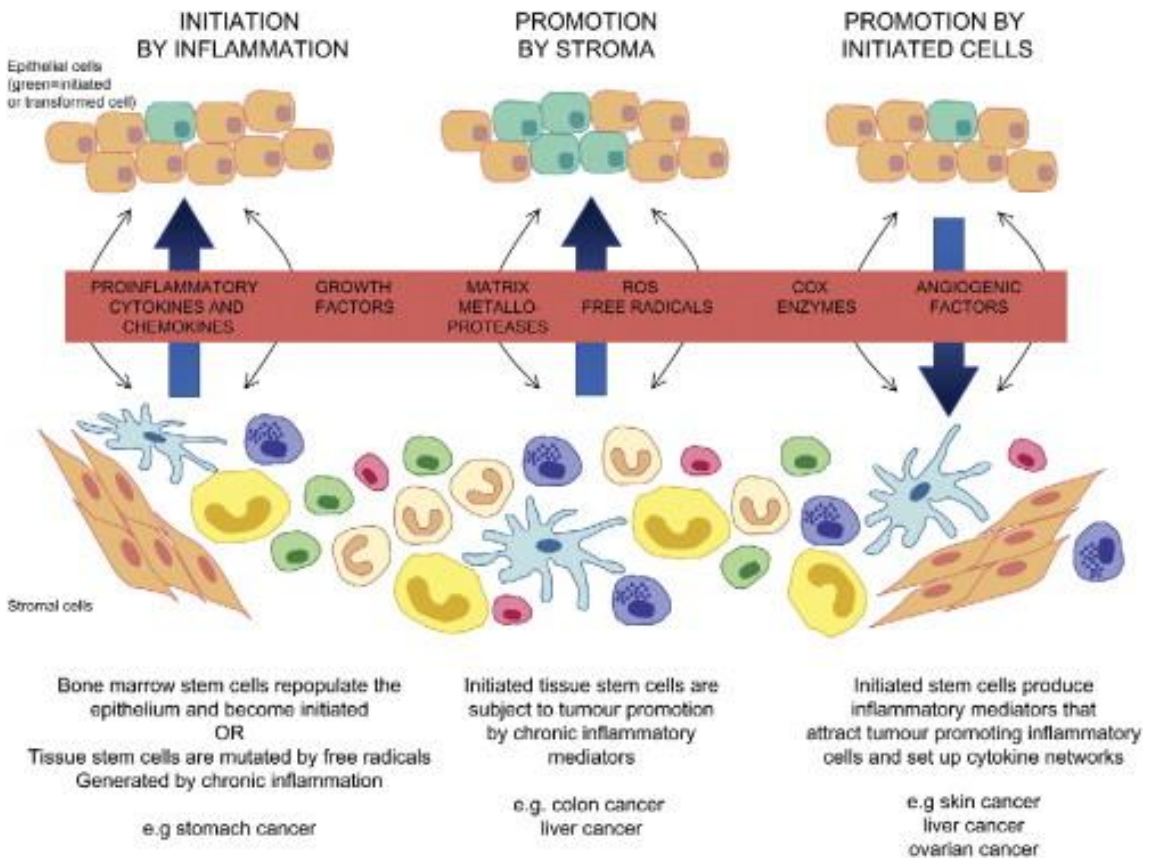


Gentles, A. J., Newman, A. M., Liu, C. L., Bratman, S. V., Feng, W., Kim, D., et al. (2015). *Nature Medicine*, 1–12.

This slide is not required.

Roles of the immune system in promoting tumor initiation and progression



"Smoldering and polarized inflammation" in cancer initiation:

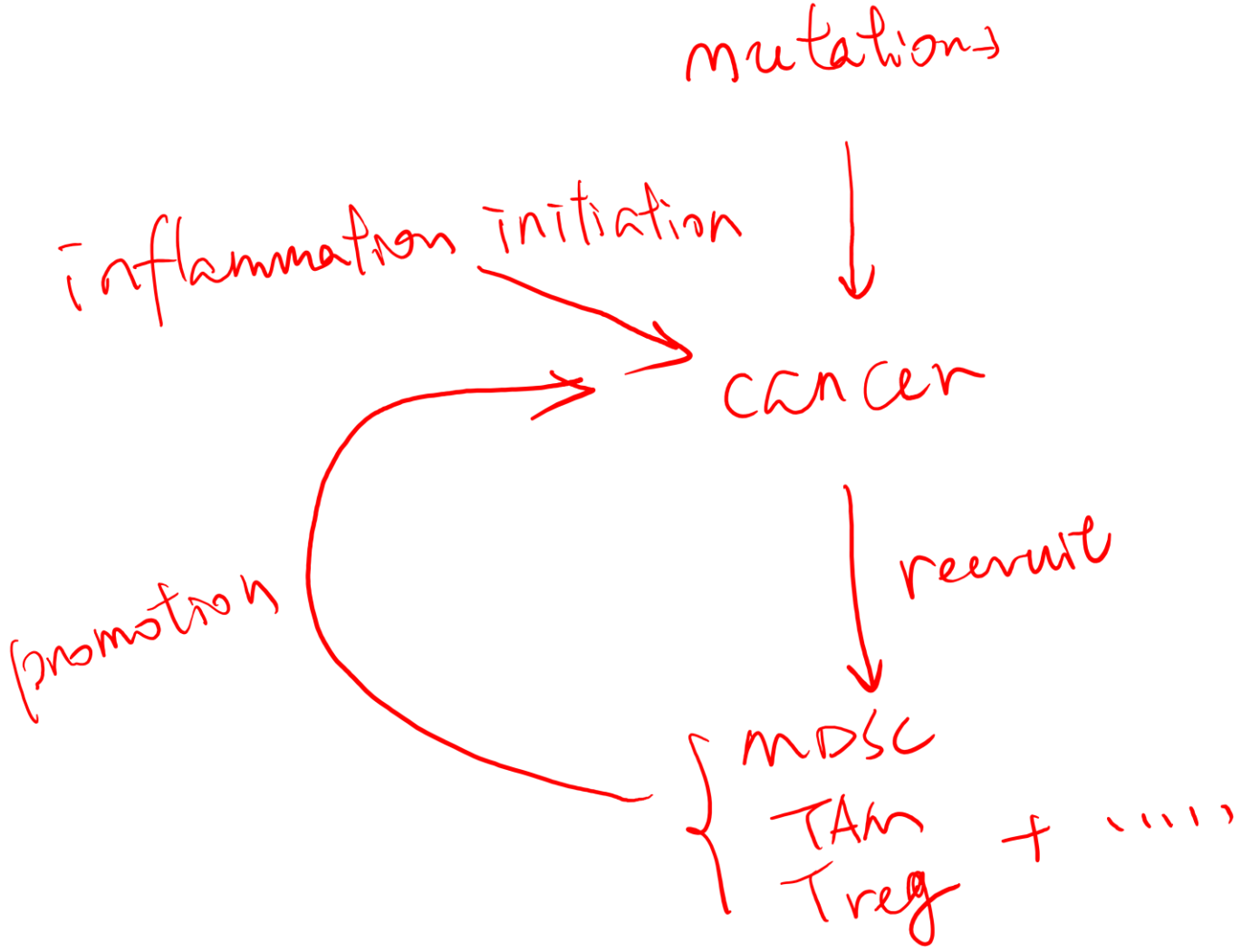
Chronic inflammation promotes immune cell recruitment and slow changes that promote tumor initiation and development

Key players in tumor-promoting inflammation

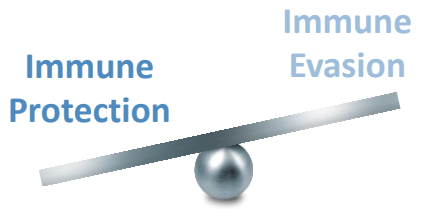
- TAM: tumor associated macrophage
- MDSC: myelod-derived suppressor cells
- Treg: regulatory T cells

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

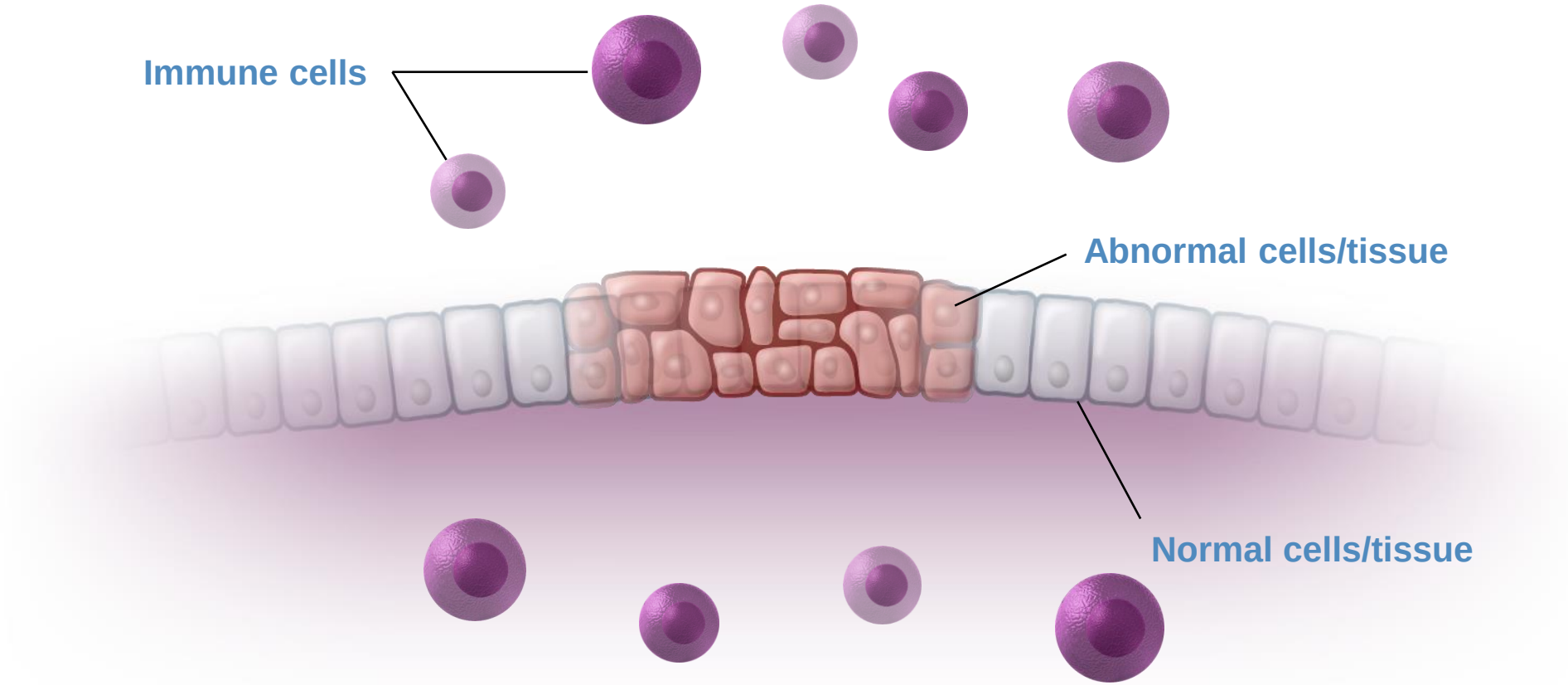
Roles of the immune system in promoting tumor initiation and progression



Elimination: Immune System Eradicates Cancer Cells



- A natural process involved with early disease[2]

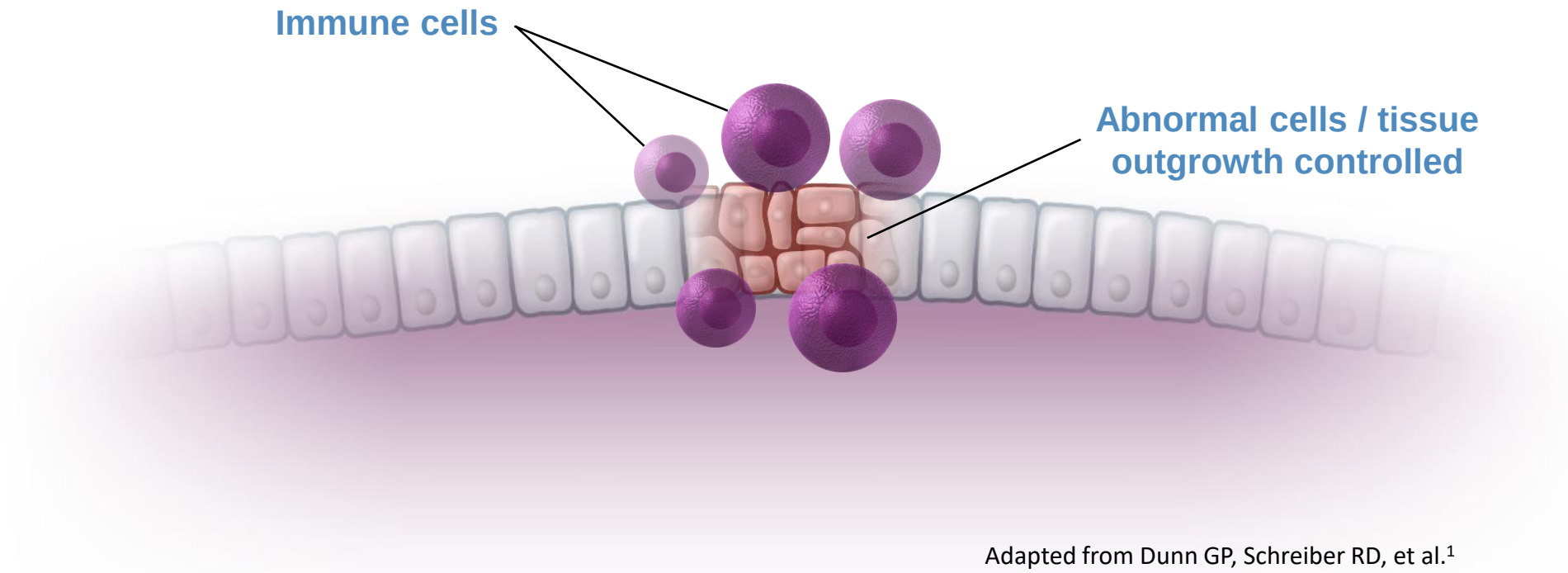


Adapted from Dunn GP, Schreiber RD, et al.

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.

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]

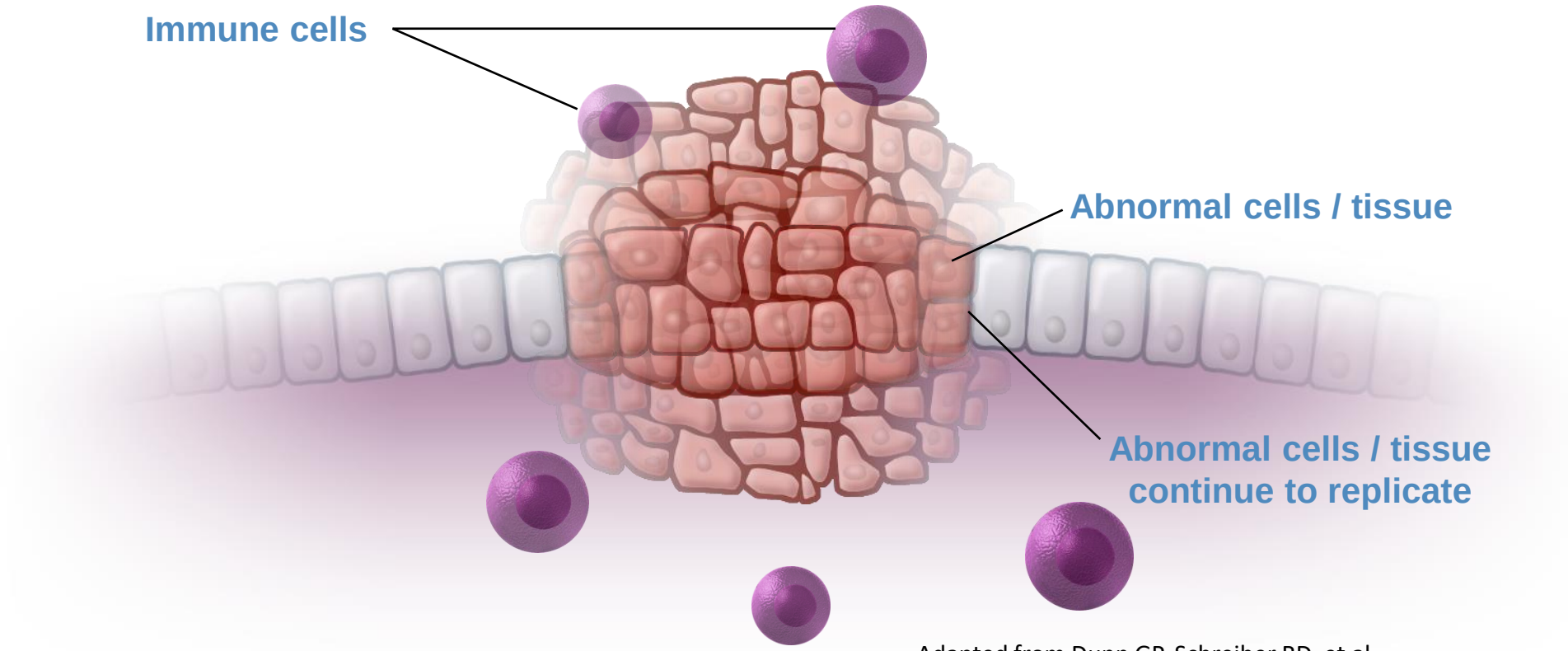


Adapted from Dunn GP, Schreiber RD, et al.[1]

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.

Escape: Cancer Cells Evade Immune System

- Tumor cell variants grow, resulting in progressive disease

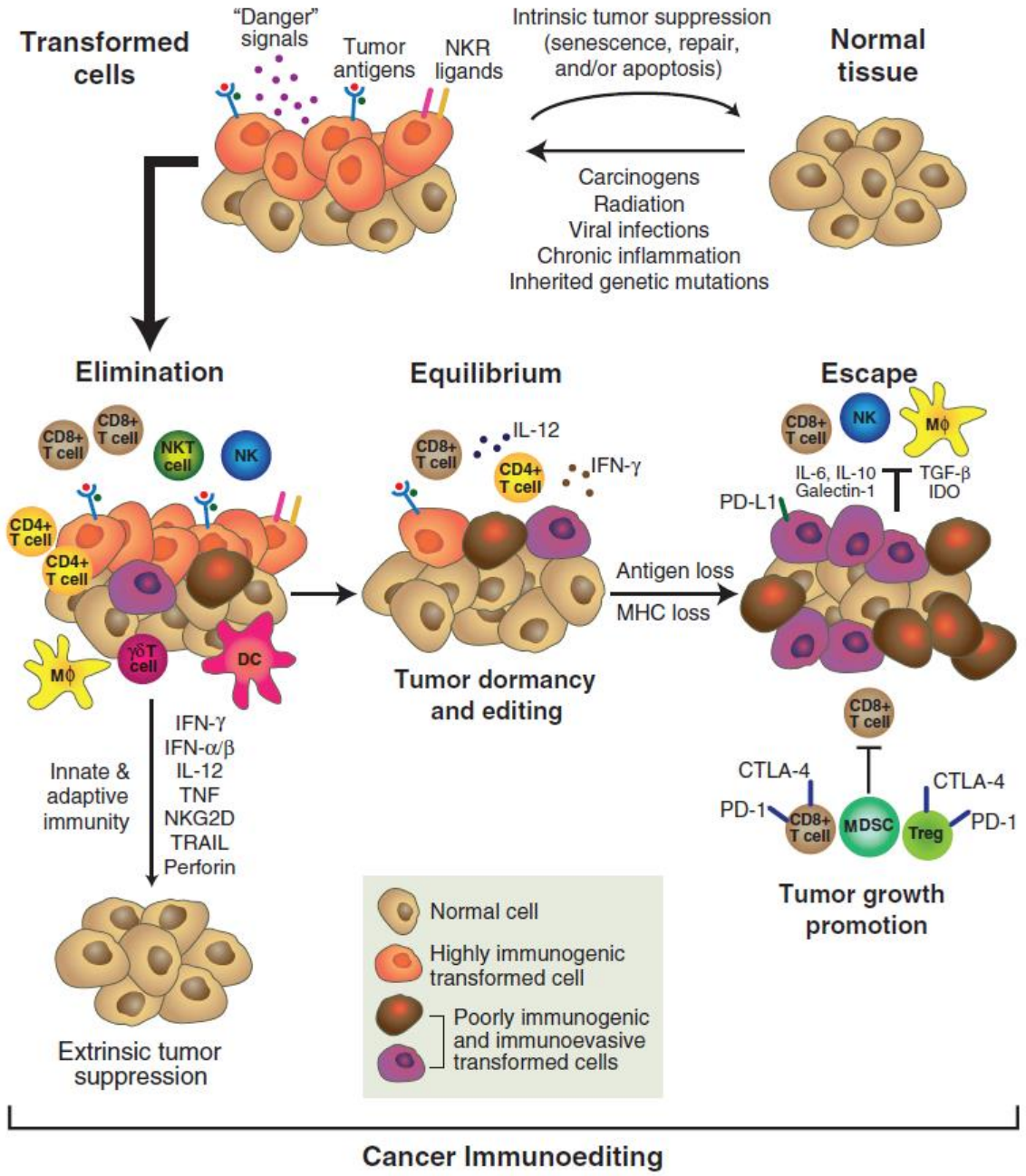


Adapted from Dunn GP, Schreiber RD, et al.

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.



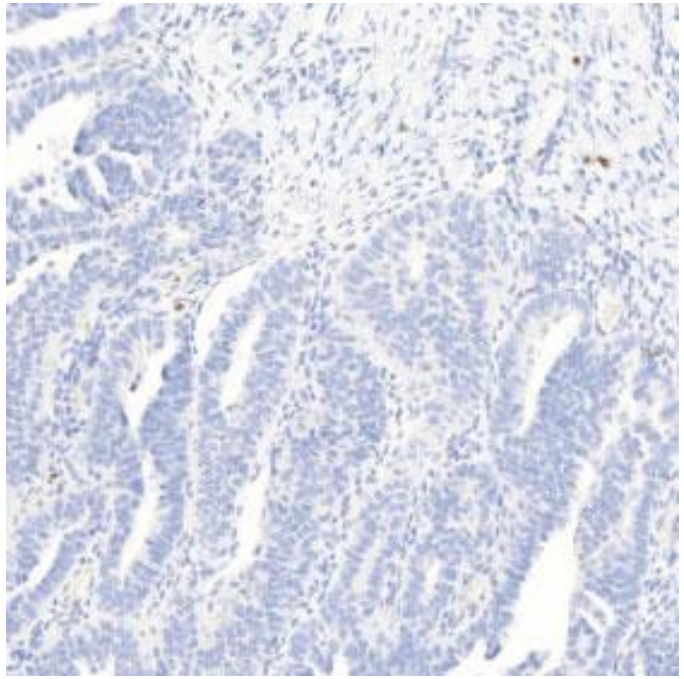
Schreiber, R. D., Old, L. J., & Smyth, M. J. *Science*, *331*(6024), 1565–1570 (2011)

How does tumor escape from immune pressure?

Blocking CD8 T-cell Infiltration in tumor

“Cold” → **“Hot”**

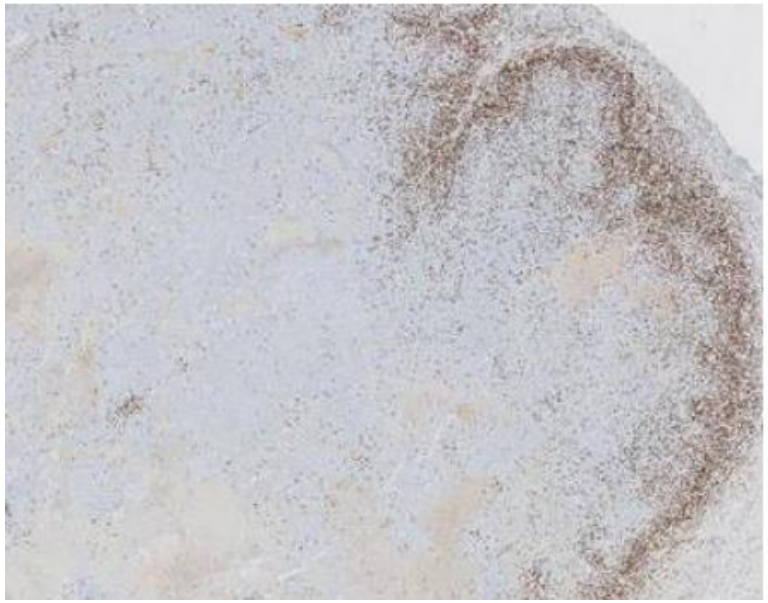
Immune desert



Low CD8 T-cells infiltration

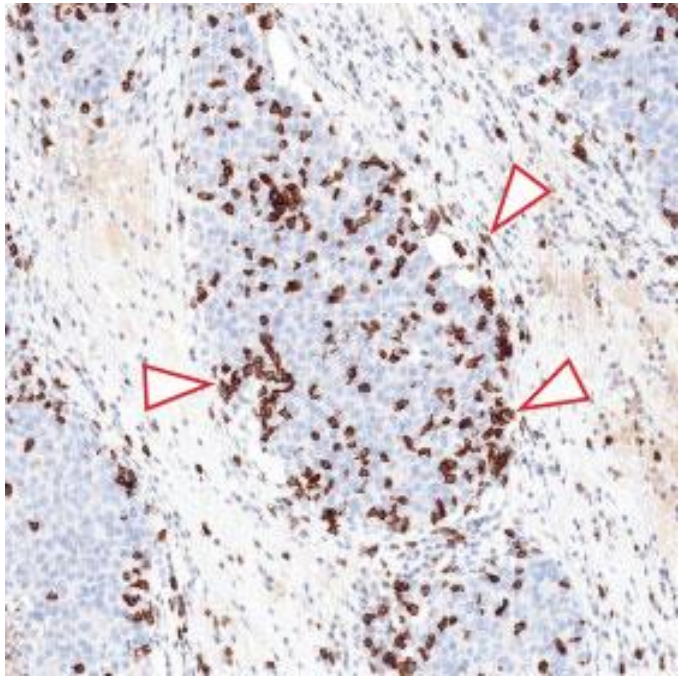
Bad prognosis

T-cell exclusion



Brown dots: “killer cells” CD8 T-cells

Inflamed tumor

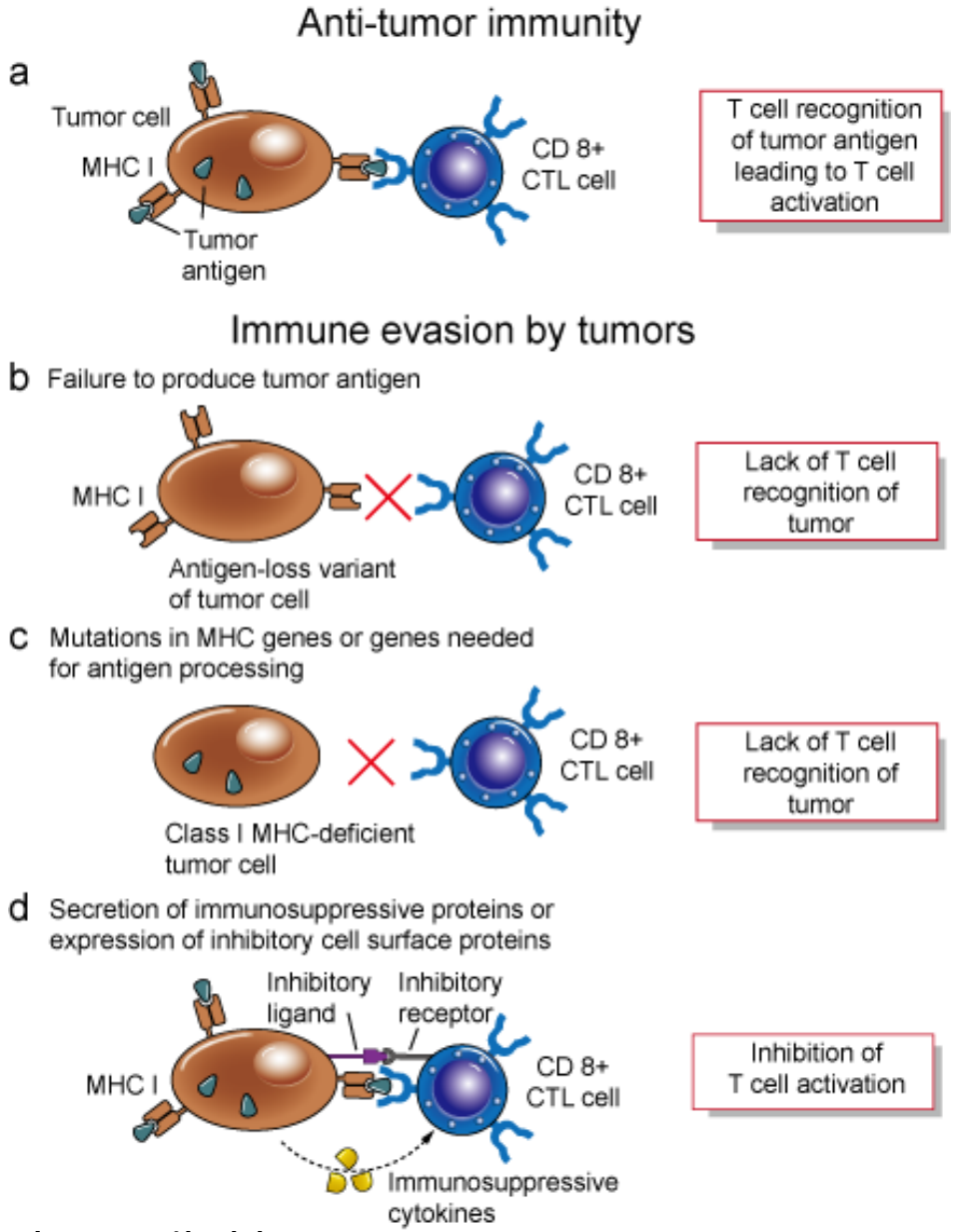


High CD8 T-cells infiltration

Good prognosis

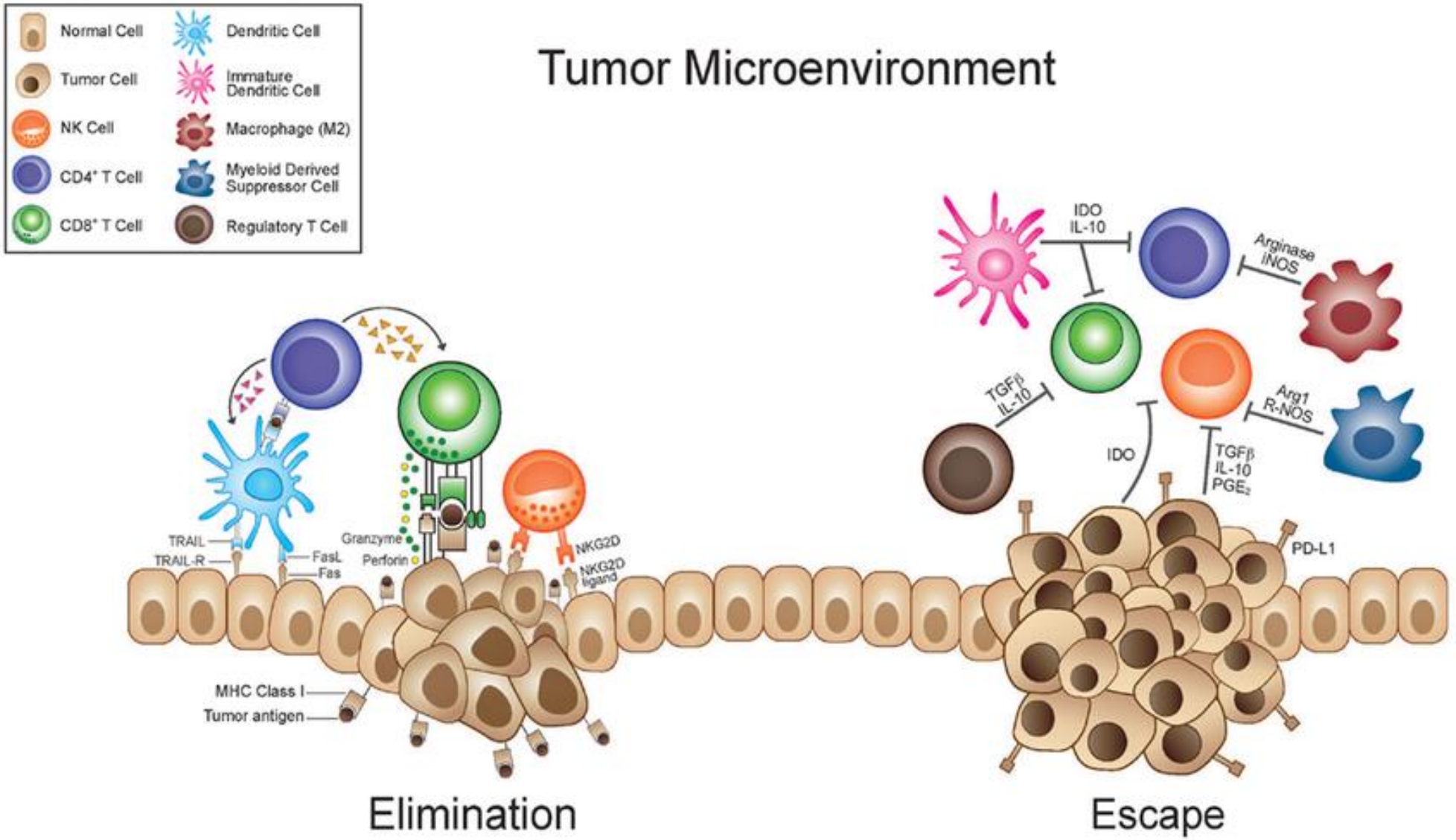
Antigen loss

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



https://www.creative-diagnostics.com/Tumor-Immunity.htm

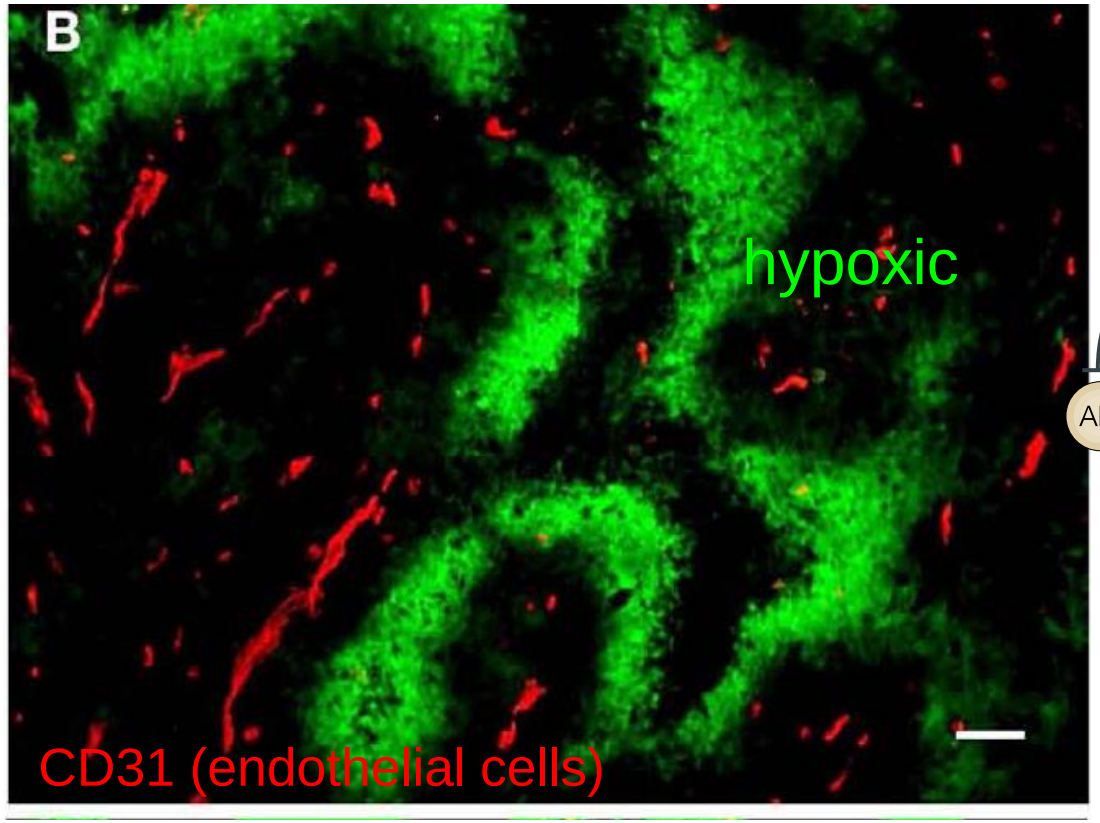
Tumor-derived immunosuppressive factors



Frontiers in Oncology 3:197

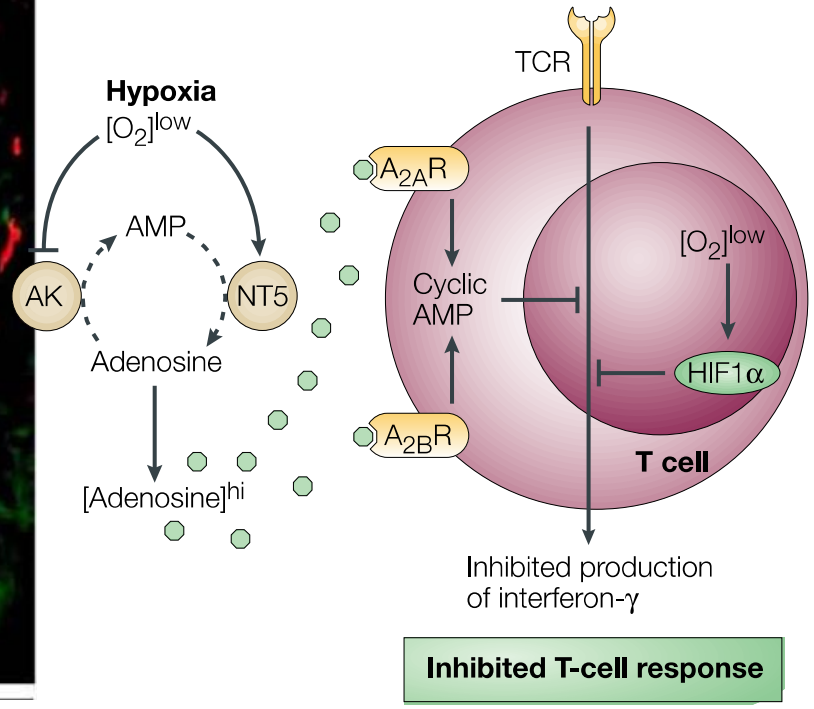
Tumor microenvironment factors: hypoxia

Hypoxia in tumors:



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.

The mechanism is not required.



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

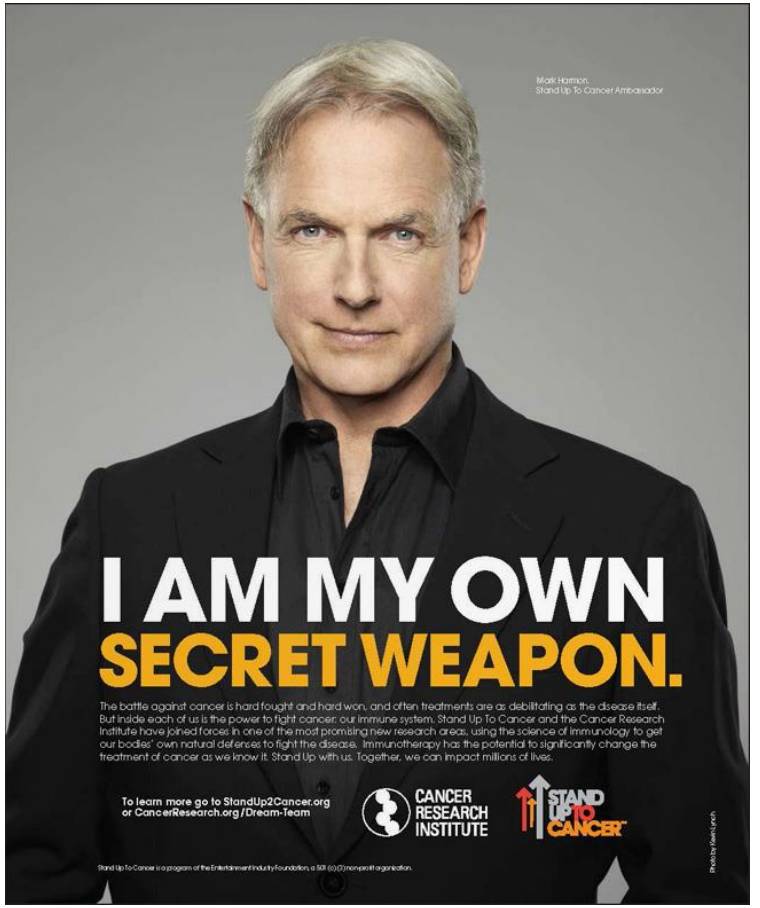
Mechanisms of cancer immunosuppression

- 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.

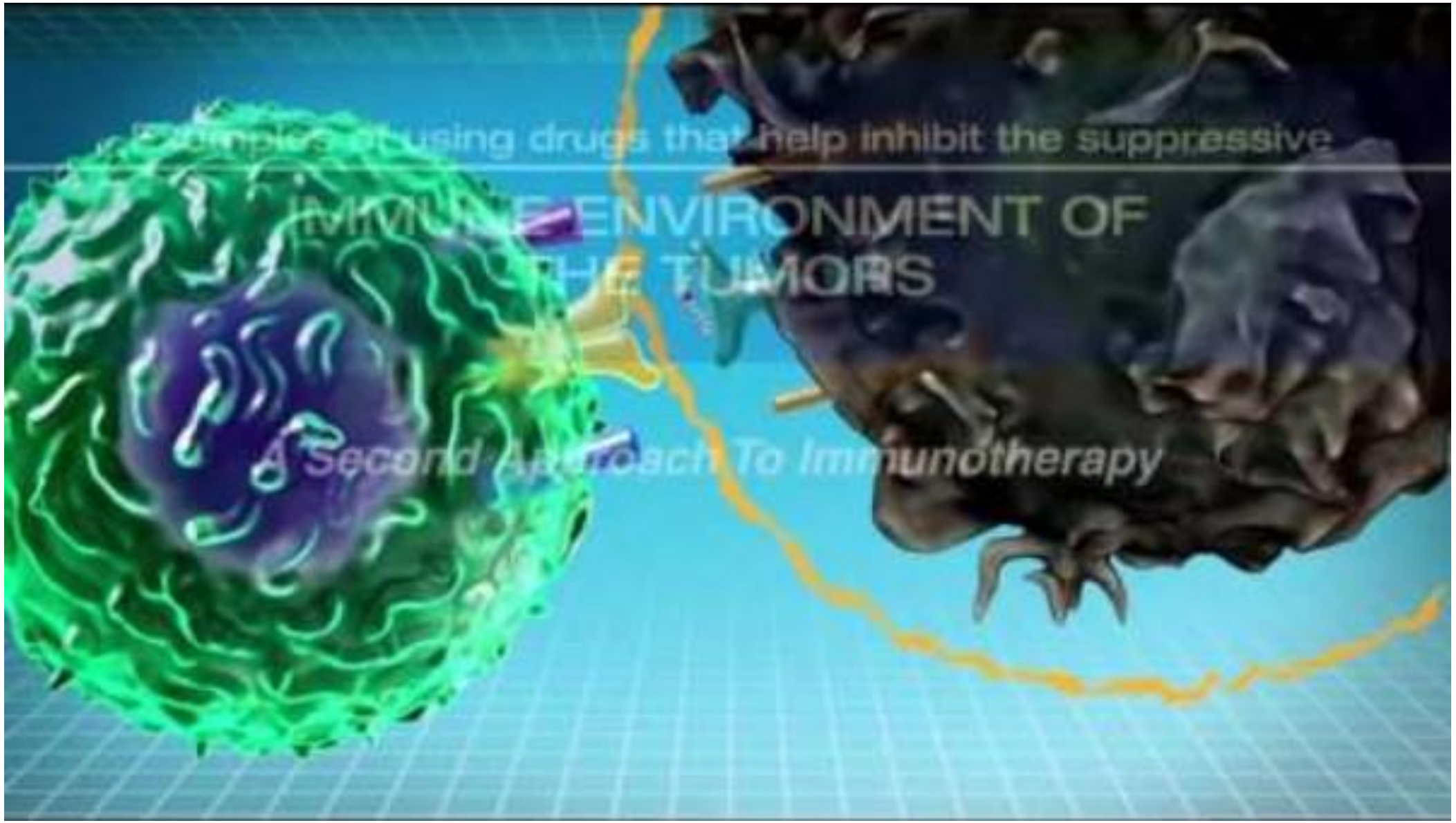


It works in two important ways:

- **Boosts your immune system** to help eliminate cancer cells
- Enhances the immune response by providing your body with **additional support**

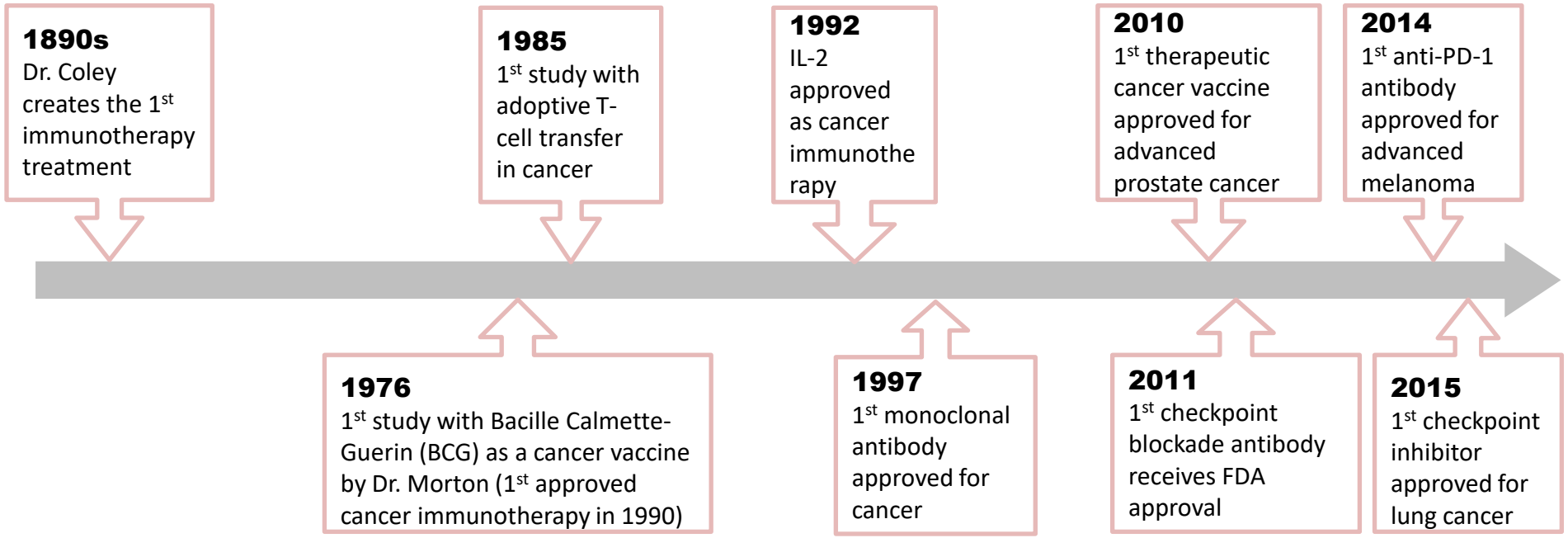
CRI, http://www.theanswertocancer.org/
Sharma P, Allison JP, et al. Nat Rev Cancer. 2011;11(11):805-812.

IMMUNOTHERAPY: The Path to a Cancer Cure
by Society for Immunotherapy of Cancer (SITC)



https://youtu.be/UbFjiWOBErA

The History of Immunotherapy



The History of Immunotherapy: The beginning…

1890s
Dr. Coley creates the 1st immunotherapy treatment

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

1985

1992

2010

2014

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
Dr. Coley creates the 1st immunotherapy treatment

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

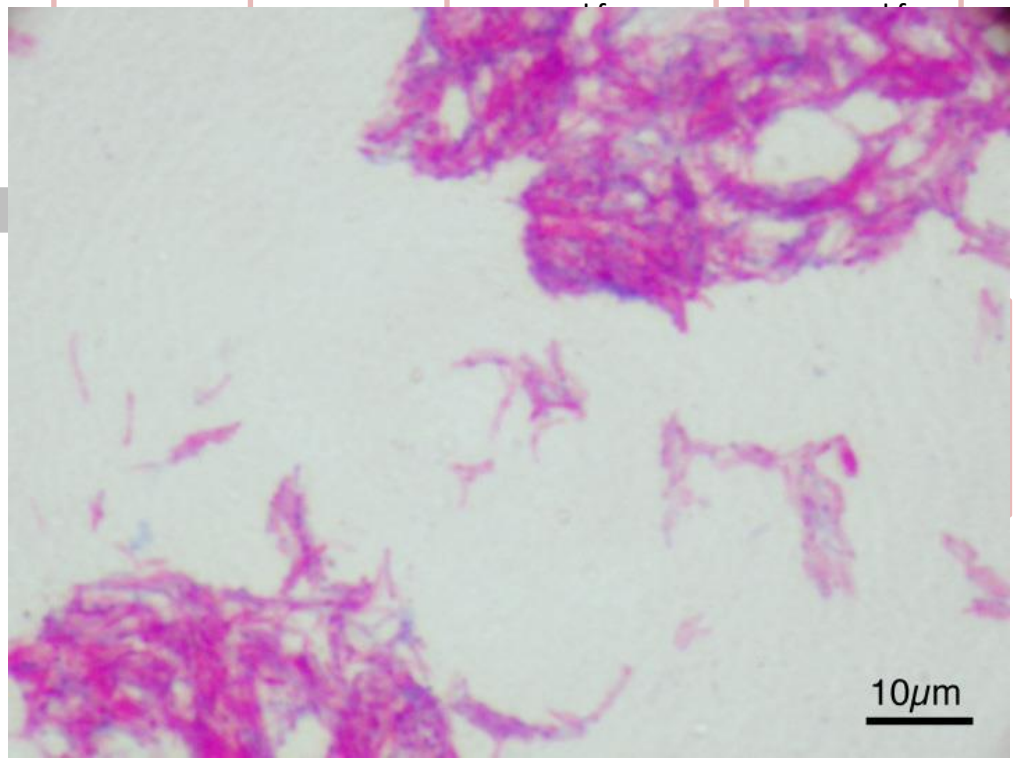
1985
1st study with adoptive T-cell transfer in cancer

1992
IL-2 approved

2010
1st therapeutic cancer vaccine

2014
1st anti-PD-1 antibody

Dr. Donald Morton



Microscopic image of the Bacille Calmette-Guerin (BCG)

The History of Immunotherapy: continue…

1890s
Dr. Coley creates the 1st immunotherapy treatment

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

1992
IL-2 approved as cancer immunothe rapy

2010
1st therapeutic cancer vaccine approved for advanced prostate cancer

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

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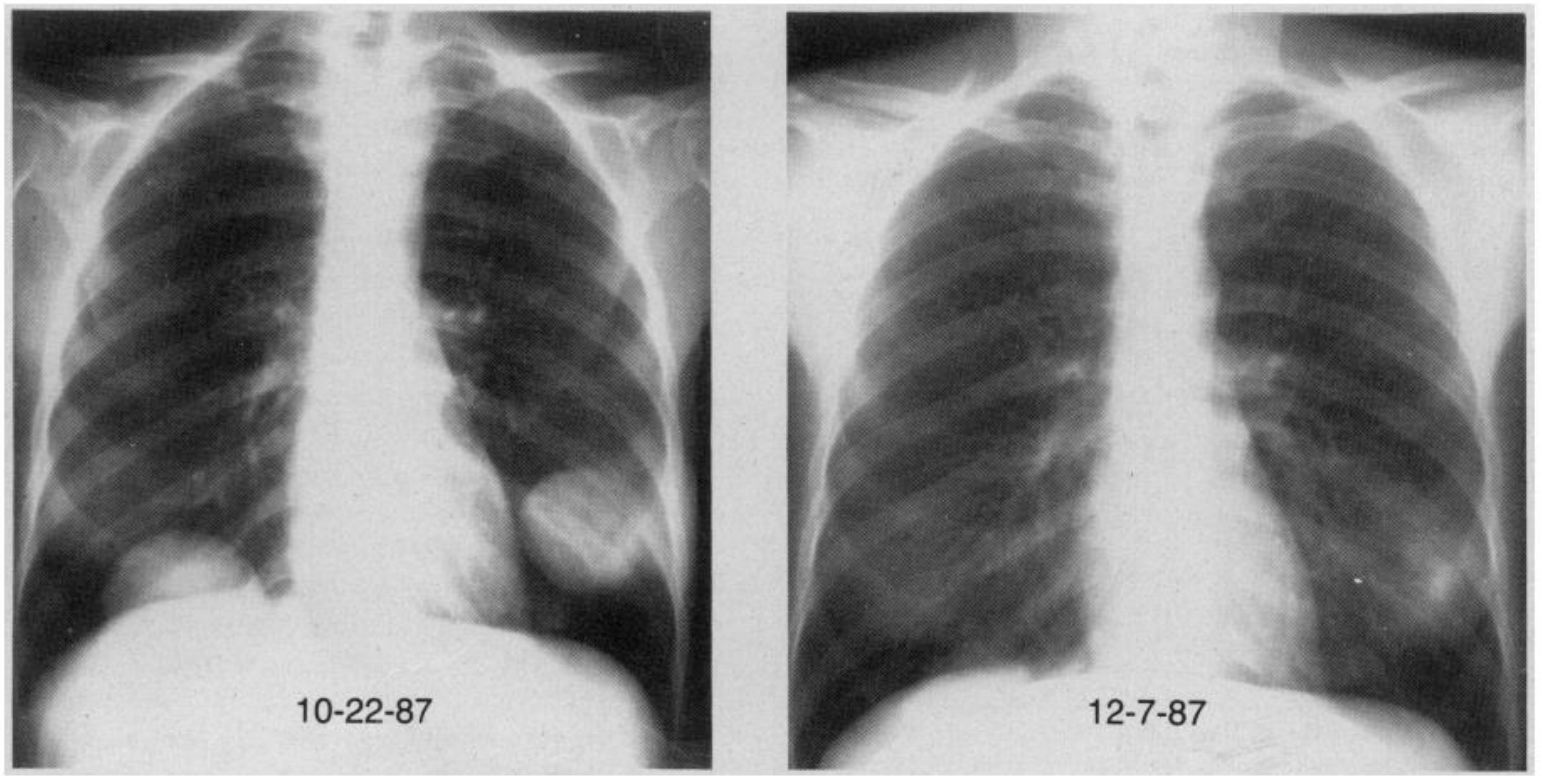

A. Rosenberg et al., N. Engl. J. Med. 319, 1676–1680 (1988)

The History of Immunotherapy: the renaissance

1890s
Dr. Coley
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1992
IL-2 approved as cancer immunothe rapy

1997
1st monoclonal antibody approved for cancer

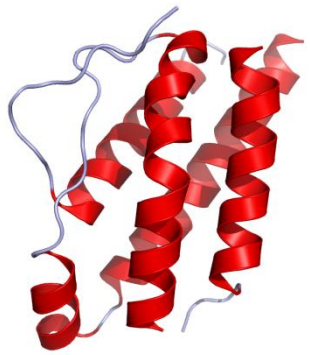
2010
1st therapeutic cancer vaccine approved for advanced prostate cancer

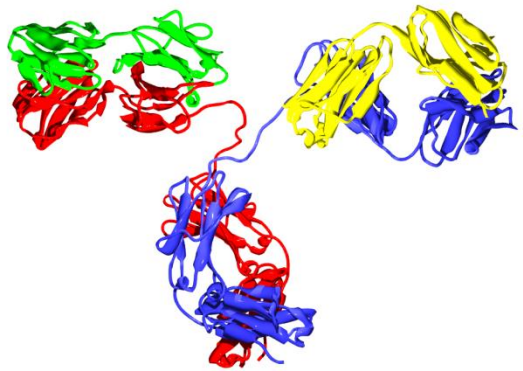
2011
1st checkpoint blockade antibody receives FDA approval

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

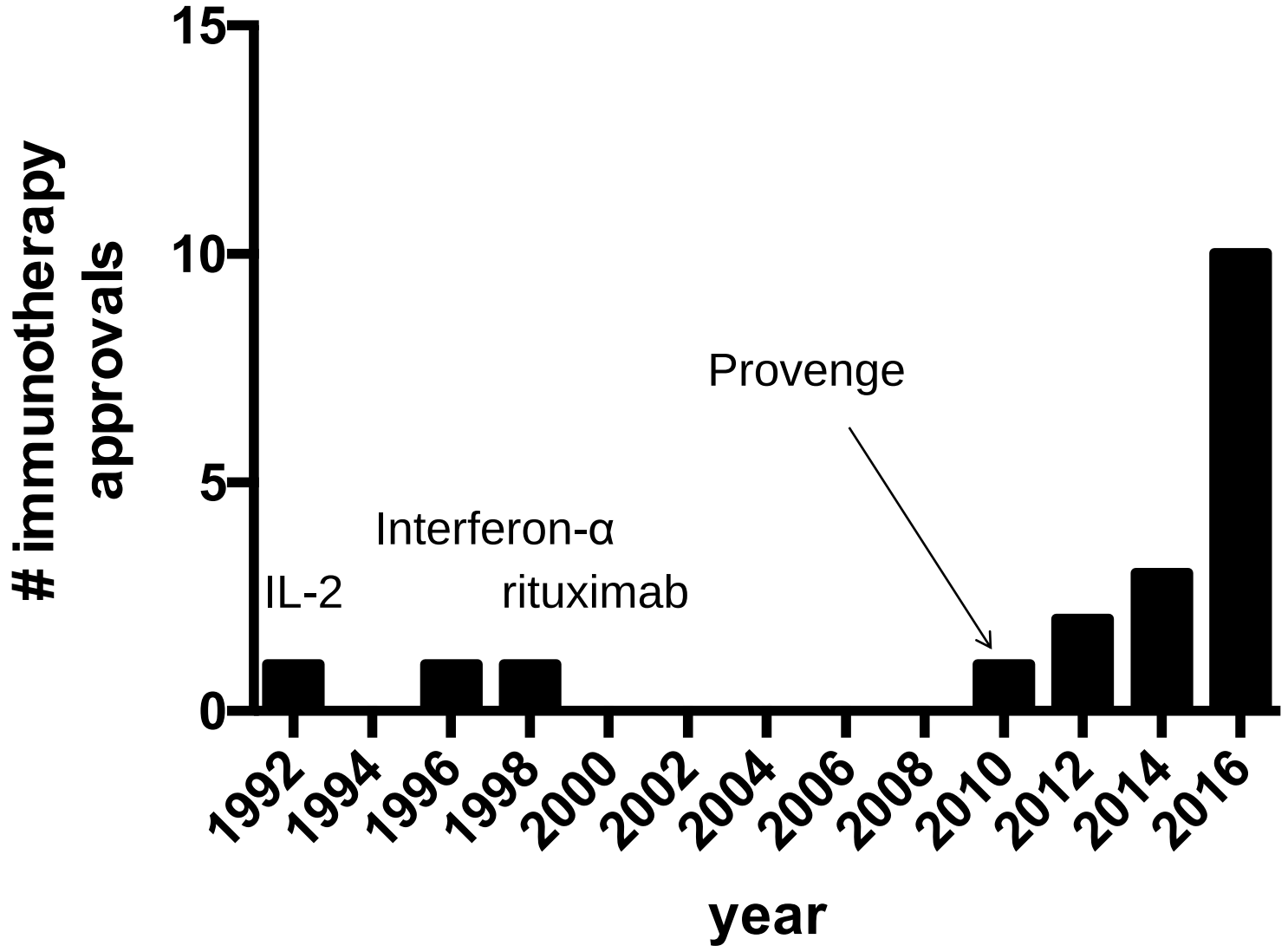
2015
1st checkpoint inhibitor approved for lung cancer

J. Couzin-Frankel, **Science** 2013, 342, 1432-1433





Recent immunotherapy drug approvals



Recent immunotherapy drug approvals

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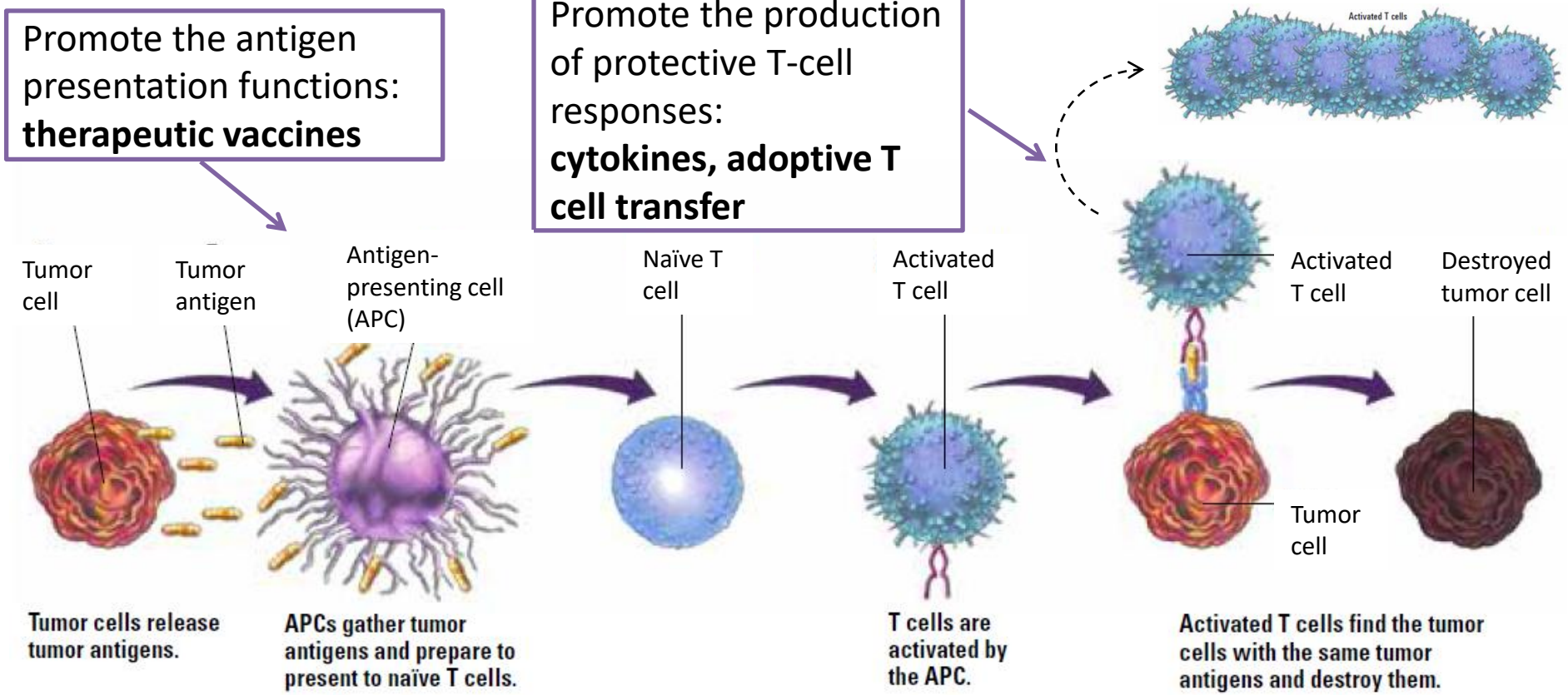
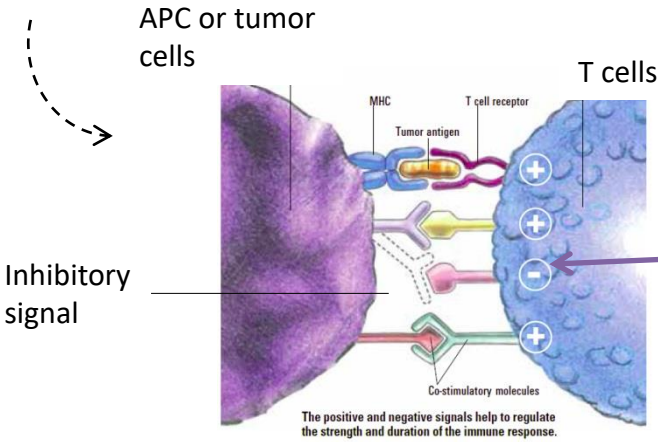
Generation and regulation of antitumor immunity

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

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



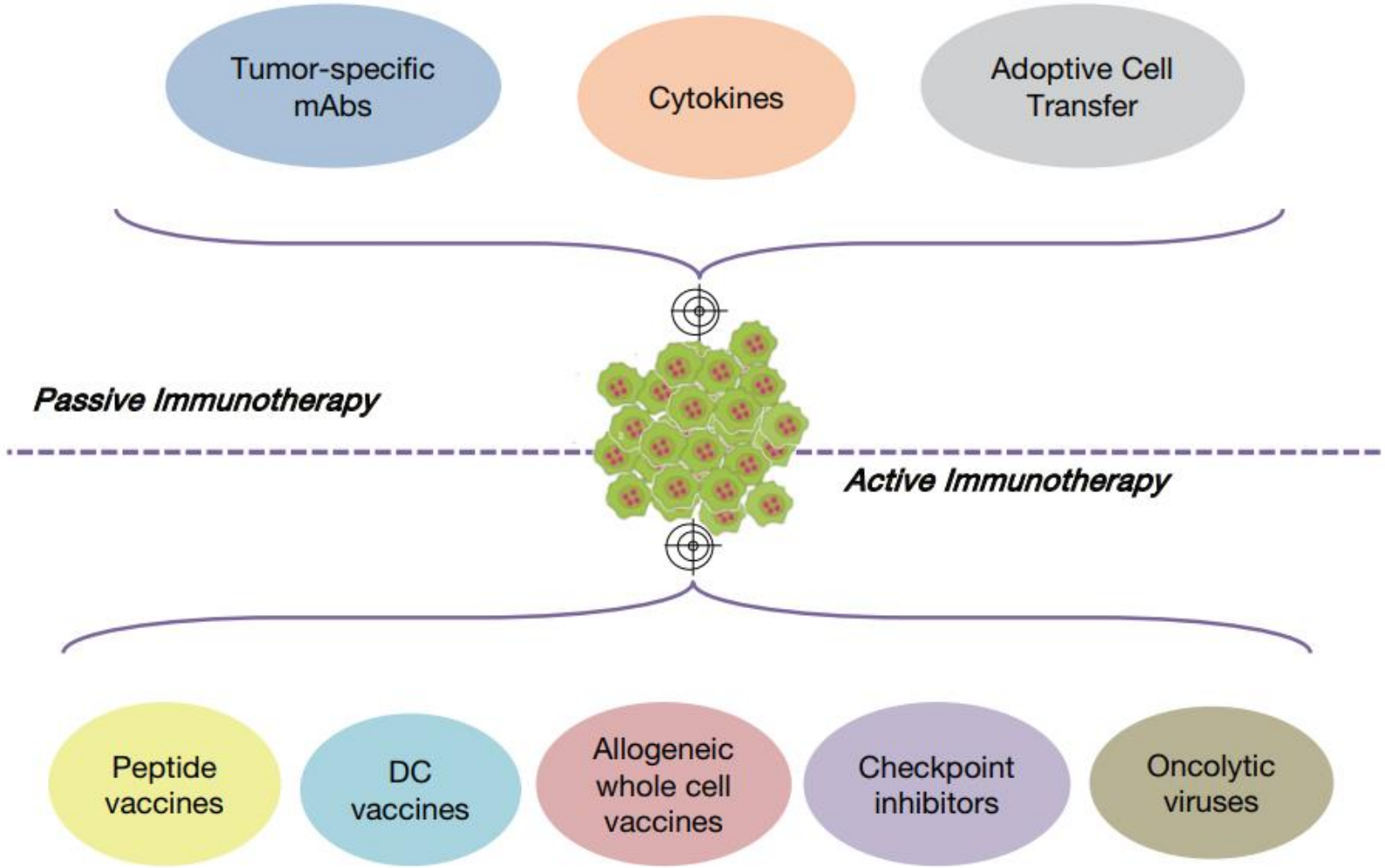
Promote immunity by various mechanisms: **monoclonal antibodies**



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

Adapted from PatientResource.com

Different types of cancer immunotherapy

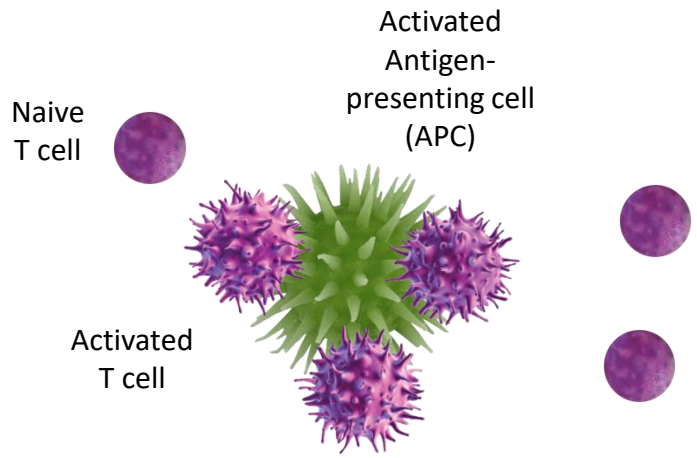


Papaioannou NE et al. *Ann Transl Med* 2016

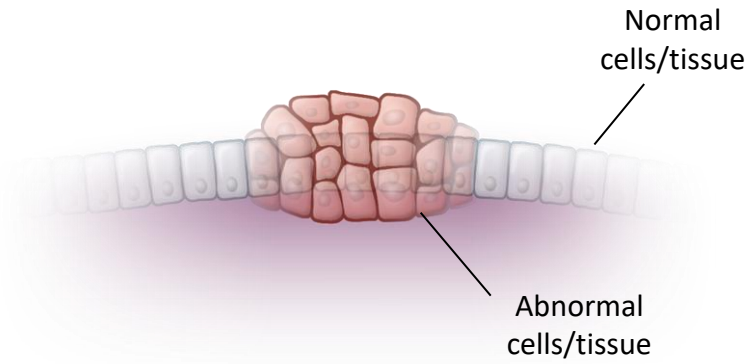
Therapeutic Cancer Vaccines

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)



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

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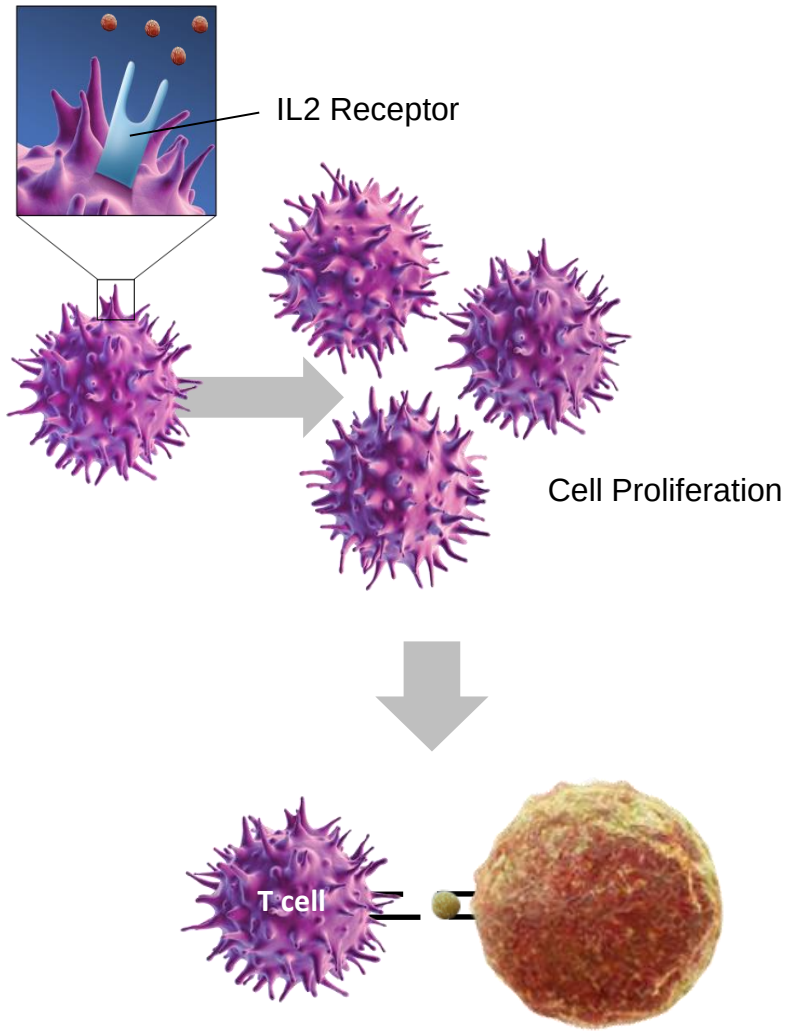
Targeting Cancer, Transforming Lives®

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



Activated T-cell can kill tumor cell

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

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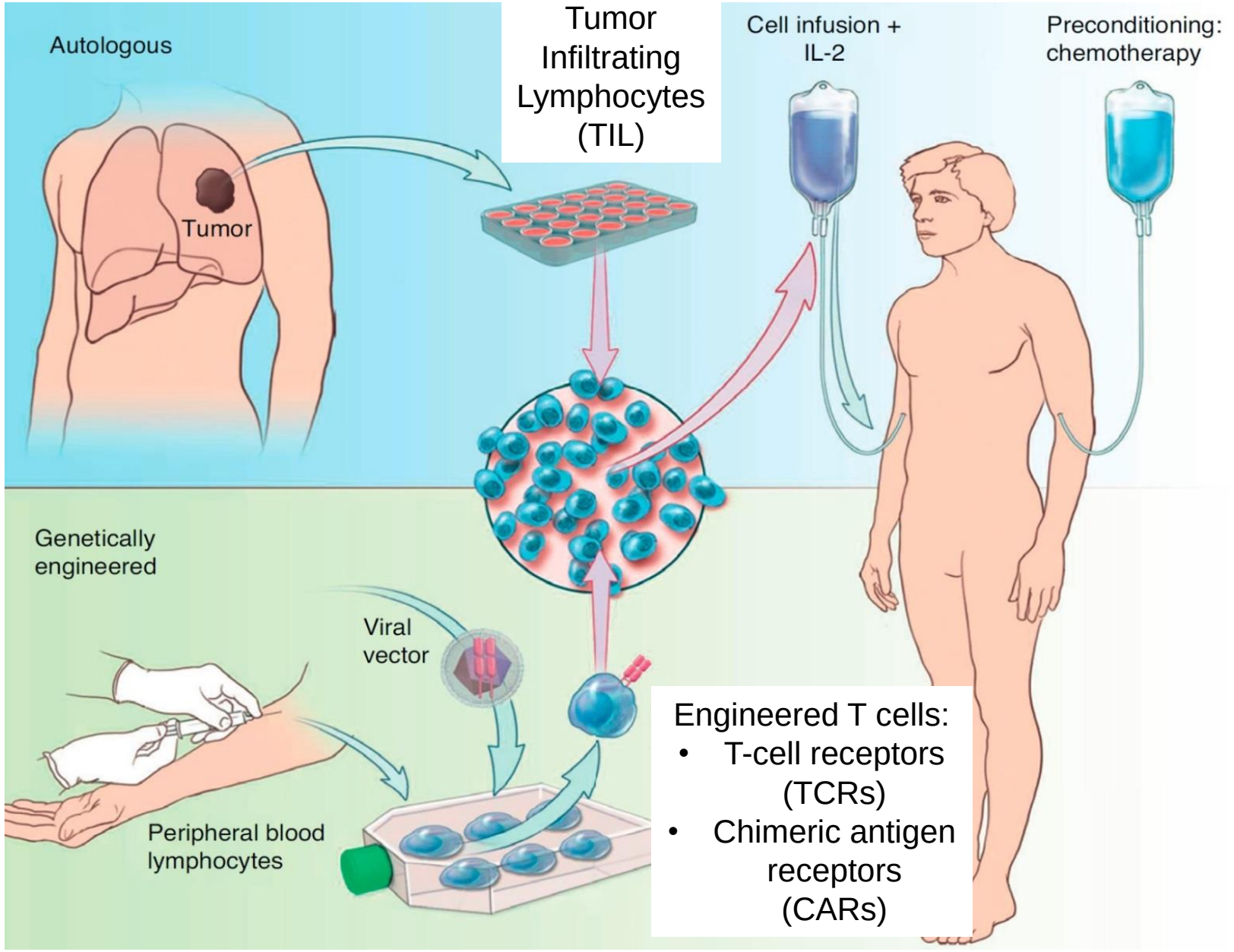
Adoptive T cell therapy

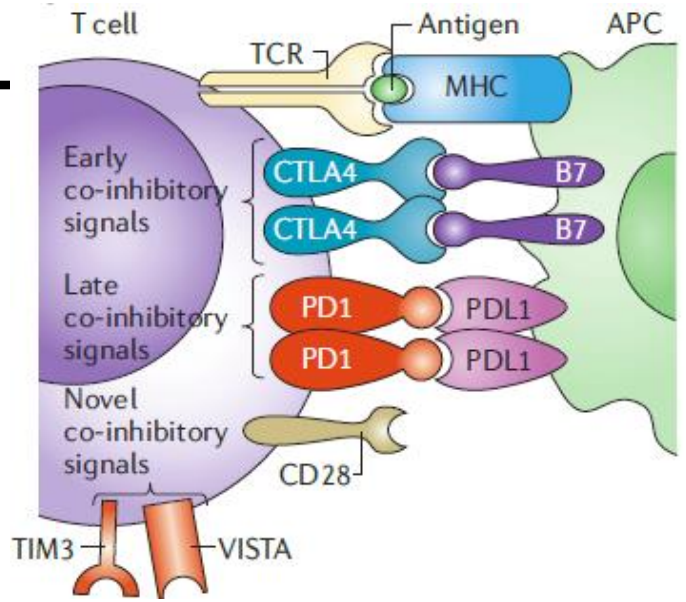


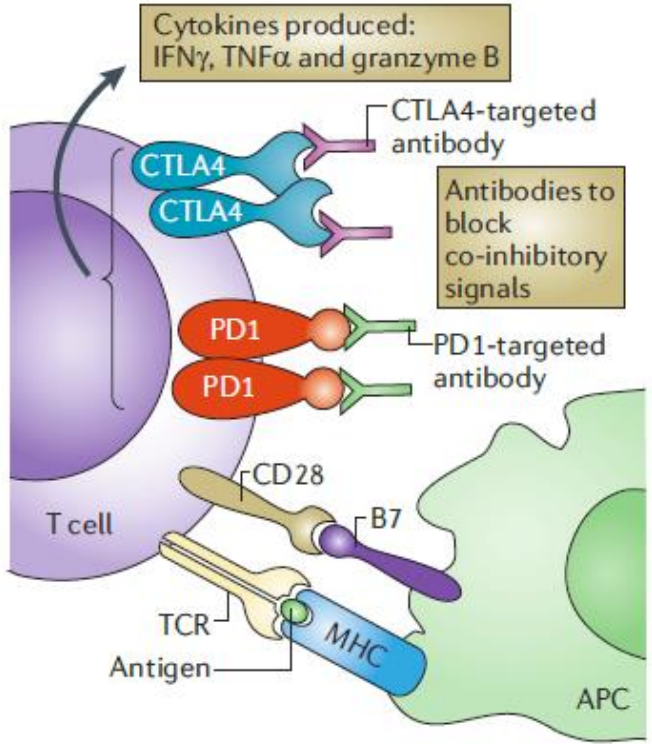
Trends Biotechnol. **2011**, *29*, 550-557

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.

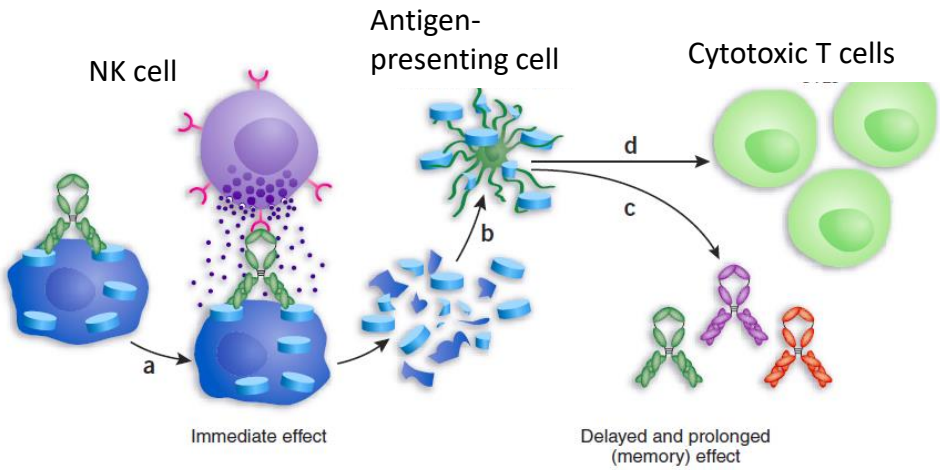
Monoclonal Antibodies (mAbs)

Antibodies are proteins designed to bind to specific substances in the body

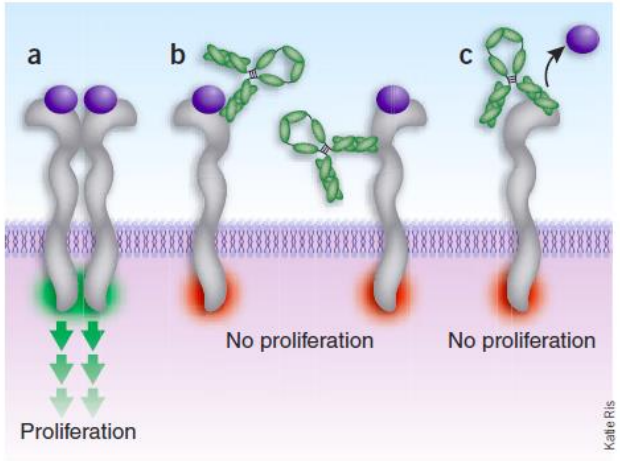
- **Mechanism of action**
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Signal transduction changes
  - Immunomodulation (eg. checkpoint inhibitor, co-stimulatory Ab)
  - Delivery of cytotoxic payloads
  - others

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

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



Antibody-mediated signaling inhibition



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

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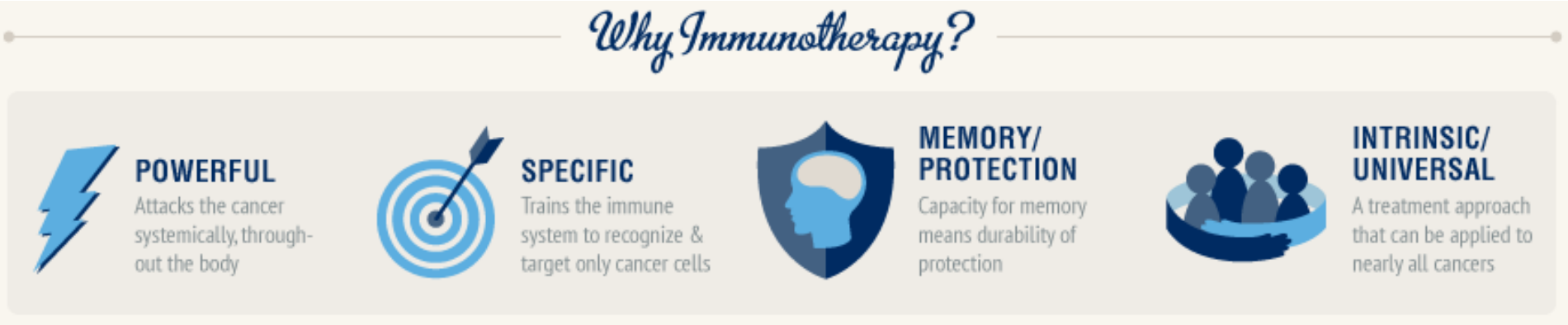
Summary: Features of an effective cancer immunotherapy

- Specificity
- Trafficking
- Adaptability
- Durability (immune memory)
- Versatility
- Reduced side effects



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