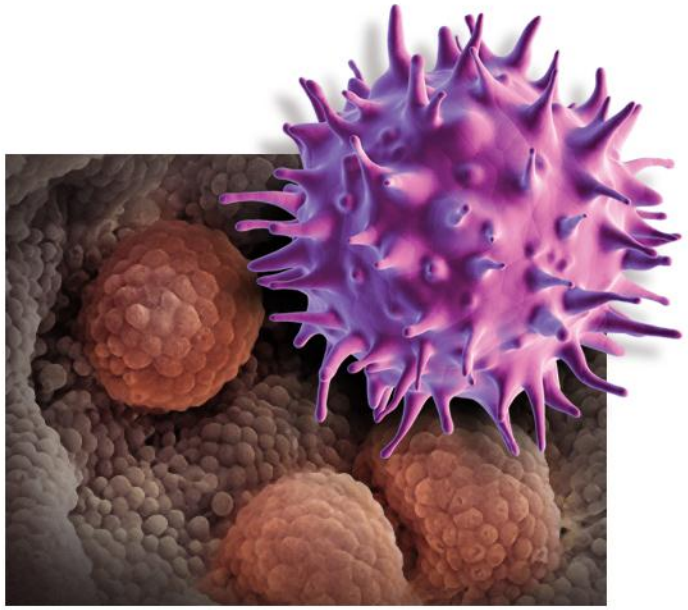
Cancer Immunotherapy: Fundamental Concepts and Emerging Role

Oncology Perspective



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Speaker Disclosures

- Click here to note your disclosure information

Learning Objectives

- Review the evidence supporting the immune system's role in cancer and the characteristics of an immune response
- Describe several mechanisms of immunotherapy
- Discuss treatment considerations for cancer immunotherapy

Program Agenda

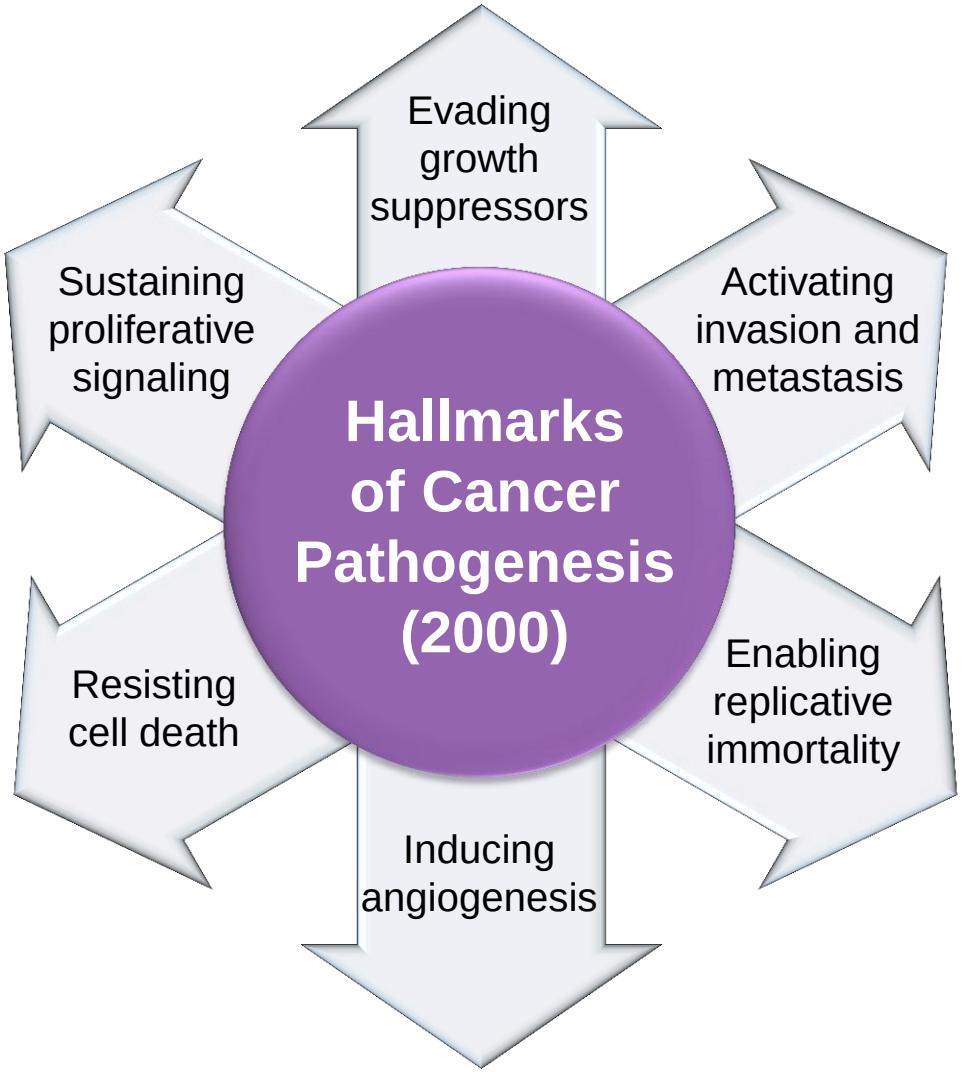
Immune System's Role in Cancer

Immunotherapy Landscape

Clinical Considerations of Immunotherapy

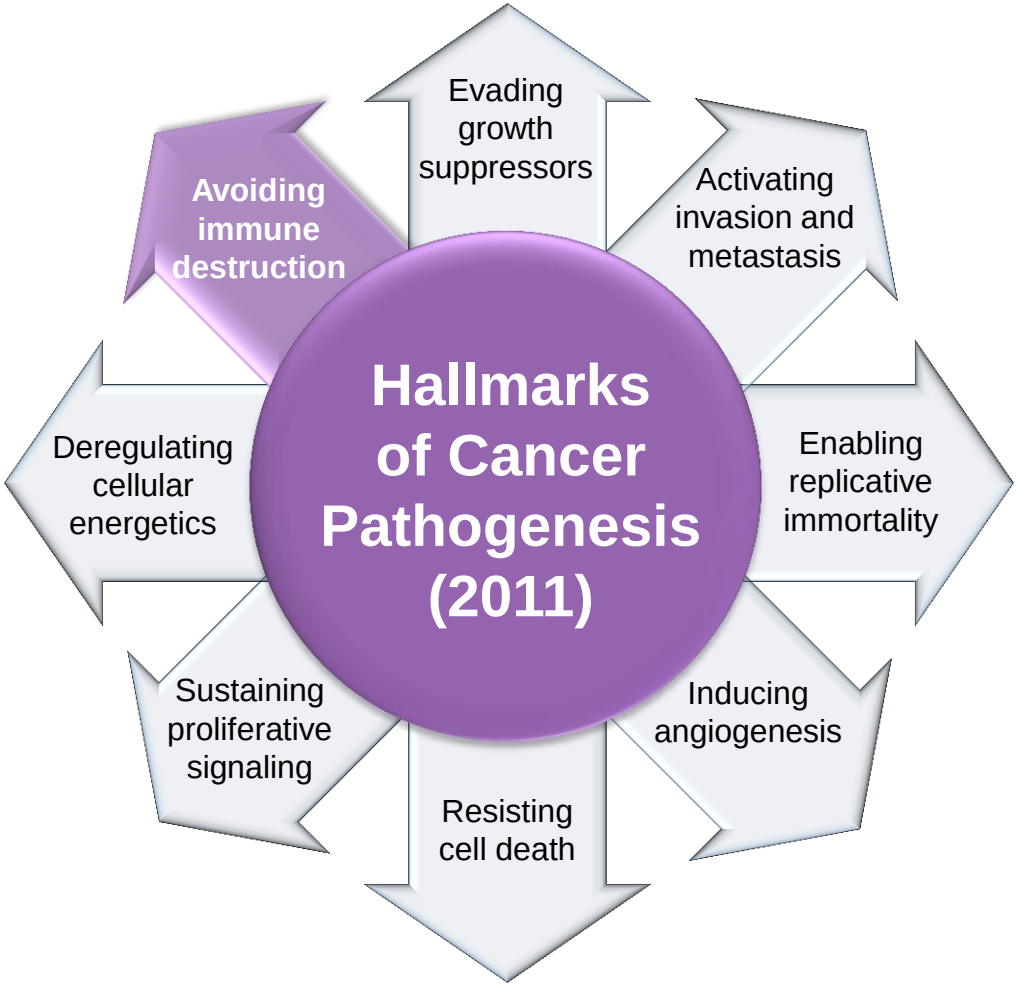
State of Immunotherapy

Cancer Pathogenesis: Formerly Characterized by 6 Hallmarks



Hanahan D, Weinberg RA. *Cell*. 2000;100(1):57-70.

Cancer Pathogenesis: Immune Evasion Now Recognized as a Hallmark

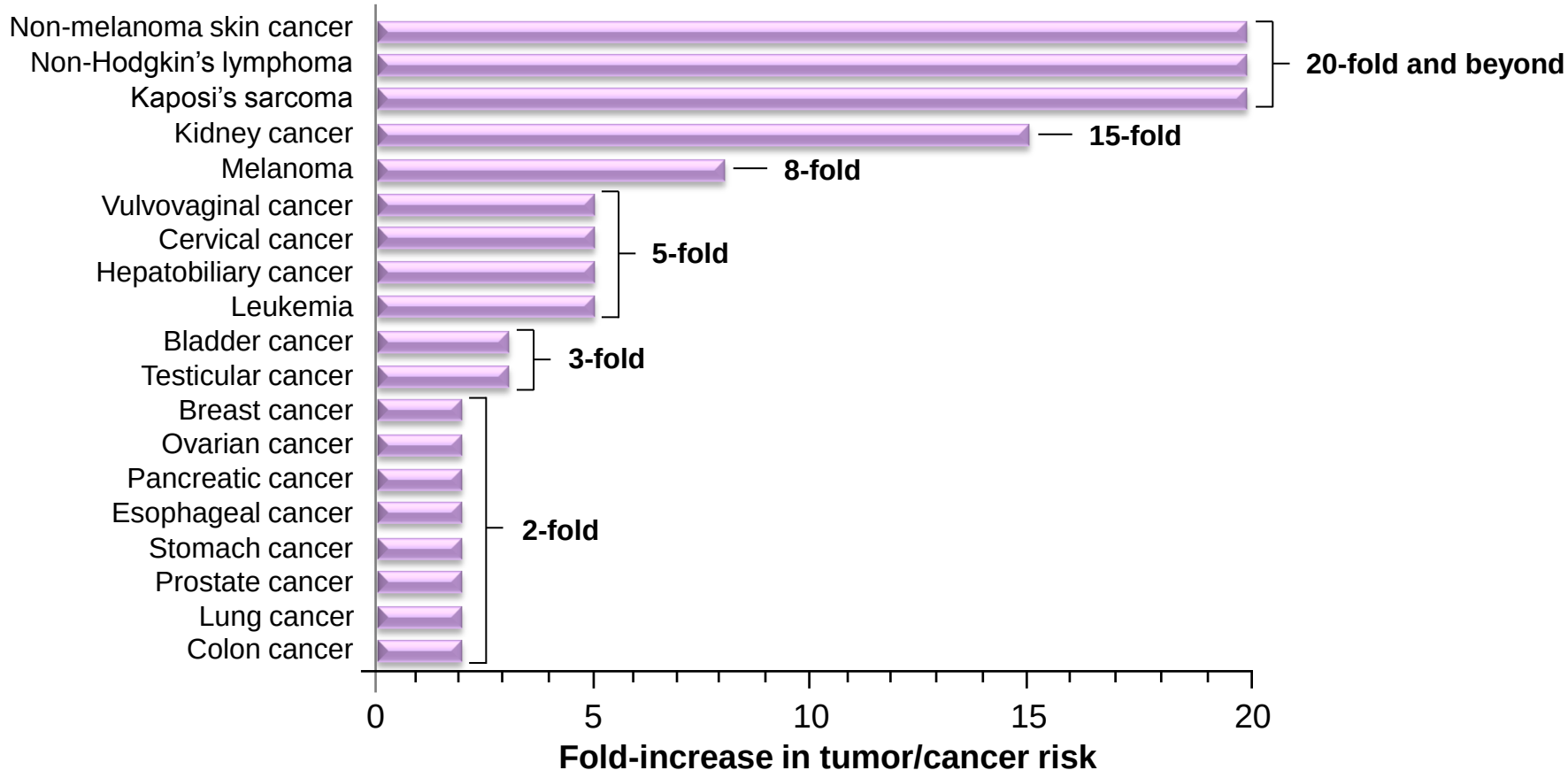


Hanahan D, Weinberg RA. *Cell*. 2011;144(5):646-674.

Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems[1-4]

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

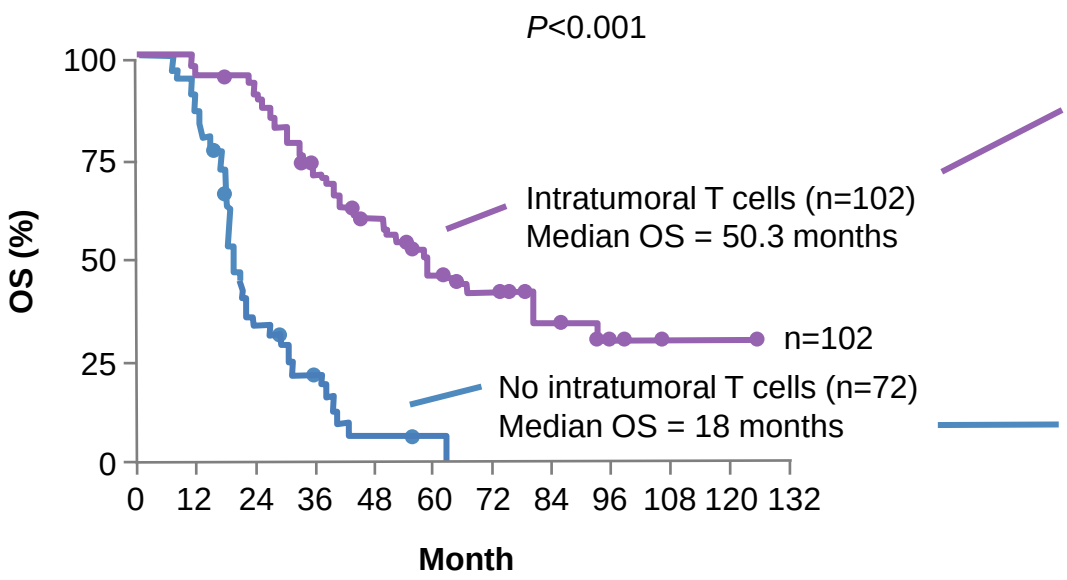


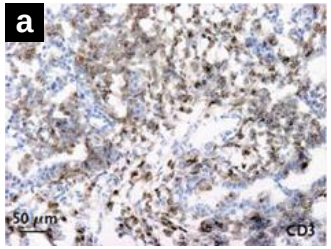
1. Kasiske BL, Wang C, et al. *Am J Transplant.* 2004;4(6):905-913.
2. Le Mire L, Wojnarowska F, et al. *Br J Dermatol*. 2006;154(3):472-477.
3. Herrero JI. *Liver Transpl.* 2009;15(suppl 2):S90-S94.
4. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

Immune Cells Within Tumors Predicts Overall Survival

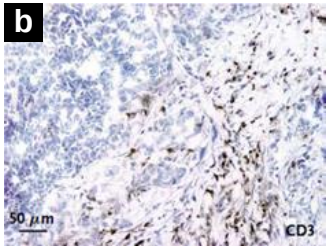
- T-cell infiltration within tumors is associated with overall survival (OS) in patients with different cancers[1,2]

Kaplan-Meier Curve for OS in Advanced Ovarian Cancer[1]





a) T cells infiltrating tumor cells



b) No intratumoral T cells detected: T cells restricted to tissue surrounding tumor

Adapted with permission from Zhang L, Coukos G, et al.

1. Zhang L, Coukos G, et al. *N Engl J Med*. 2003;348(3):203-213.
2. Galon J, Pagès F, et al. *Science*. 2006;313(5795):1960-1964.

Immunotherapy Proven Effective in Cancer

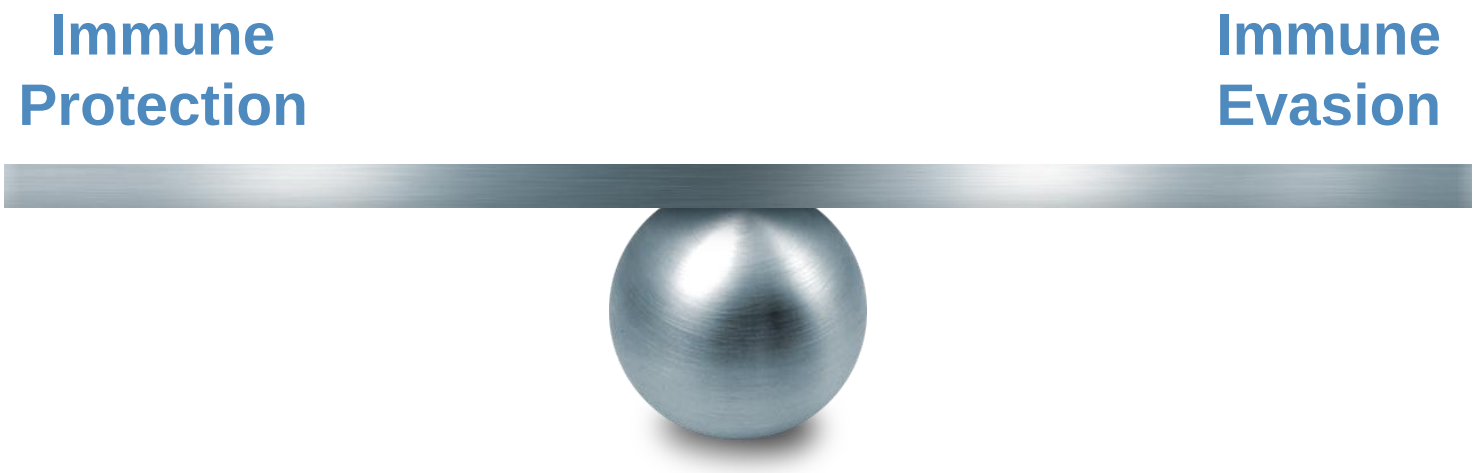
- Therapies that engage the immune system have been shown to improve patient survival in randomized, phase 3 cancer trials[1-3]

- Immunotherapies (cytokines, checkpoint inhibitors, therapeutic vaccines, monoclonal antibodies) have been approved by the FDA to treat certain cancers[4]

1. Robert C, Wolchok JD, et al. *N Engl J Med*. 2011;364(26):2517-2526.
2. Hodi FS, Urba WJ, et al. *N Engl J Med.* 2010;363(8):711-723.
3. Kantoff PW, Schellhammer PF, et al. *N Engl J Med*. 2010;363(5):411-422.
4. Mellman I, Dranoff G, et al. *Nature.* 2011;480 (7378): 480-489.

Dynamics Between Cancer and the Immune System

- In a **dynamic** process, the immune system can either
  - Block tumor growth, development, and survival
  - Allow tumor outgrowth



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

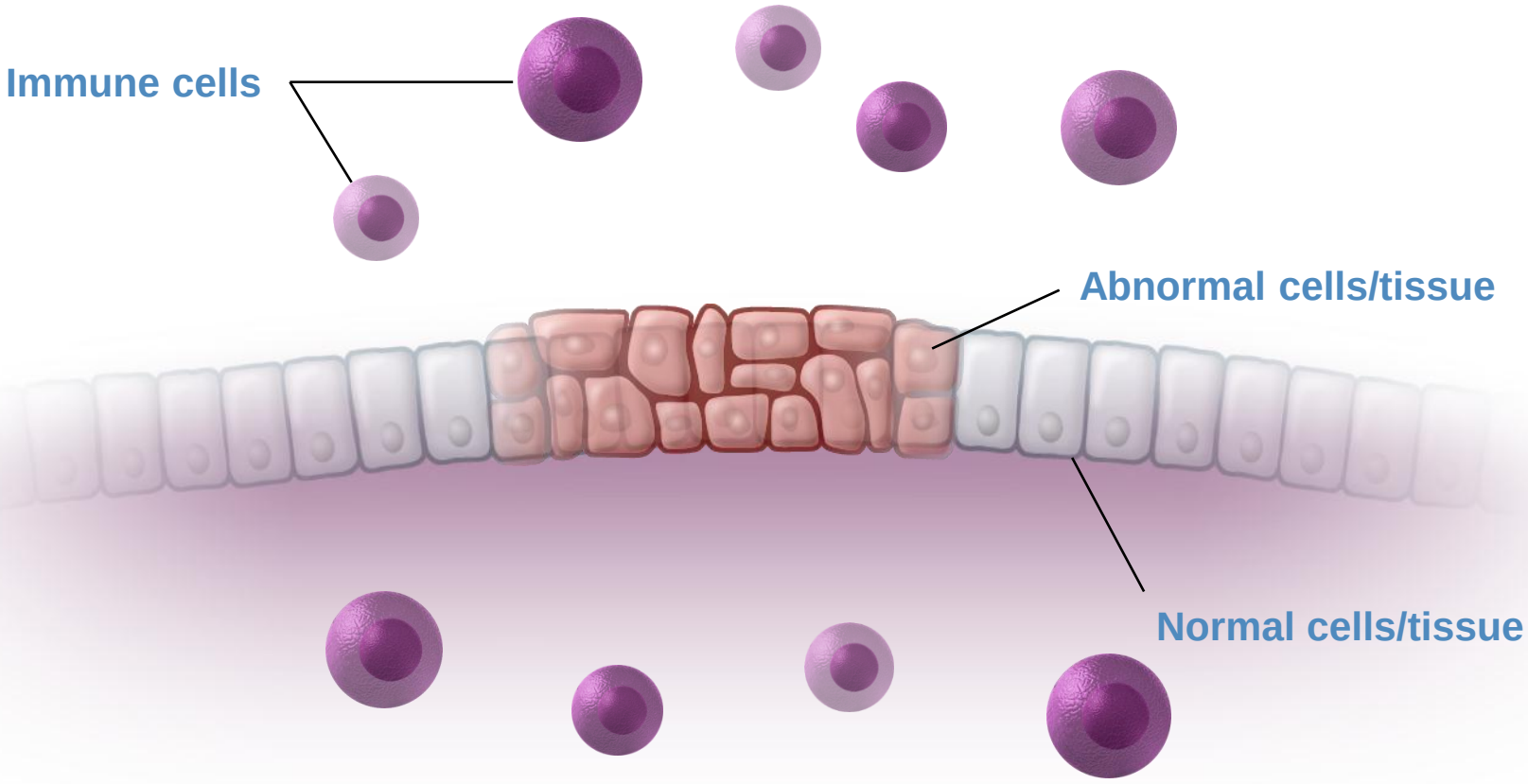
Dynamic Process Described by 3 Phases

- The 3 E’s
  - Elimination
  - Equilibrium
  - Escape

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

Elimination: Immune System Eradicates Cancer Cells[1]

- A natural process involved with early disease[2]

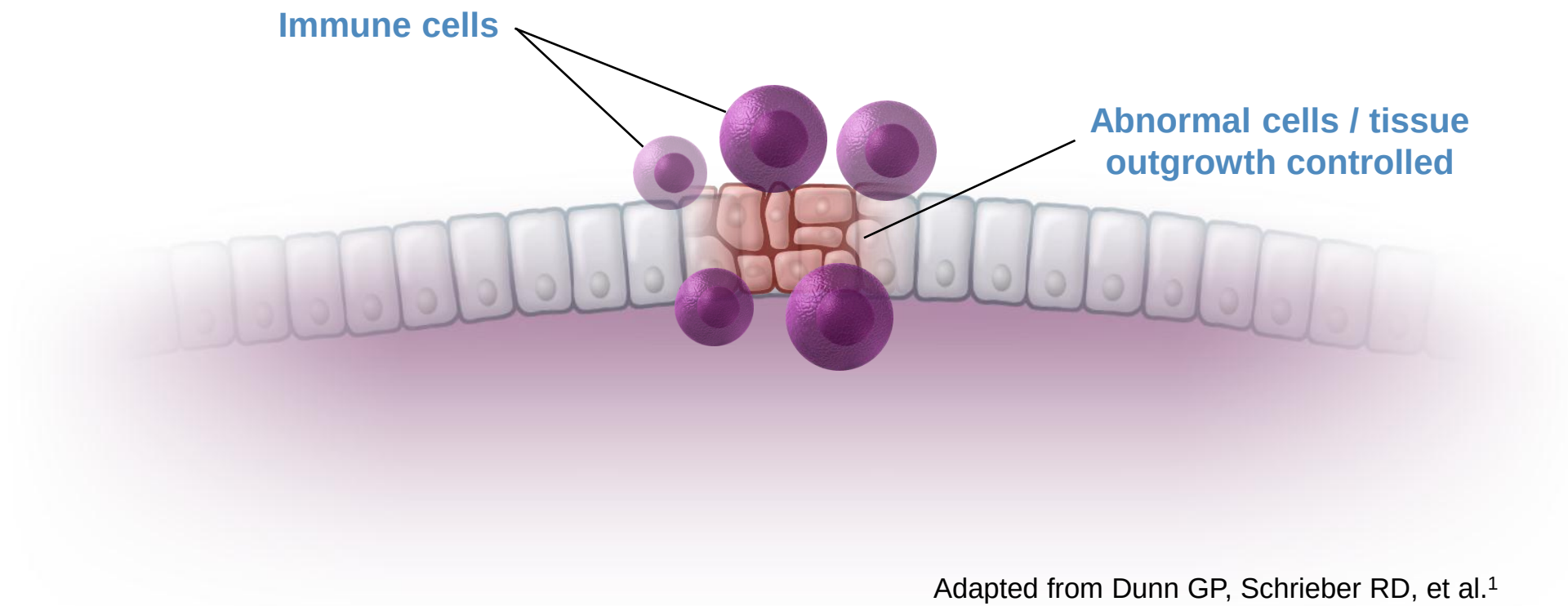


Adapted from Dunn GP, Schreiber RD, et al.[1]

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.

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]

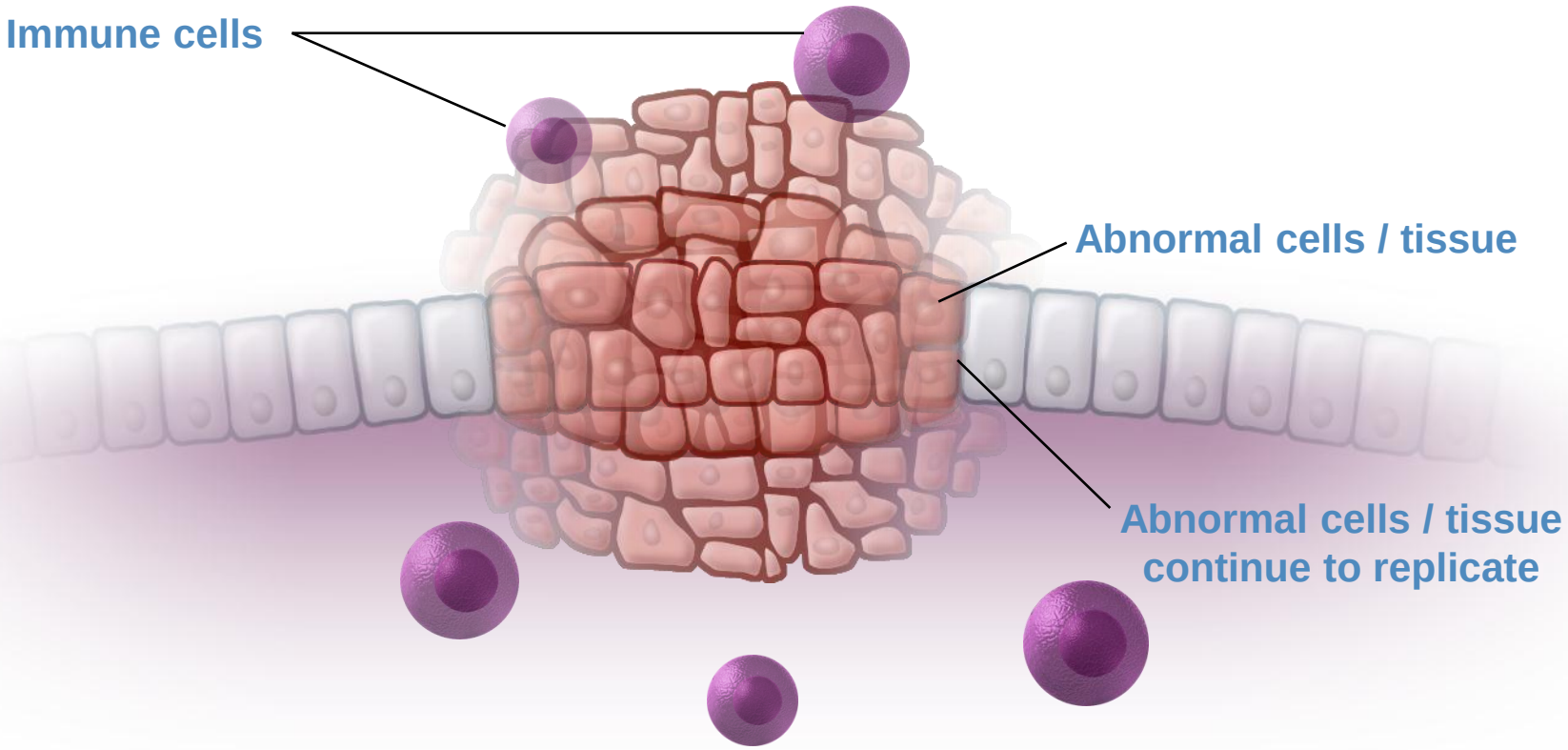


Adapted from Dunn GP, Schrieber RD, et al.[1]

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.

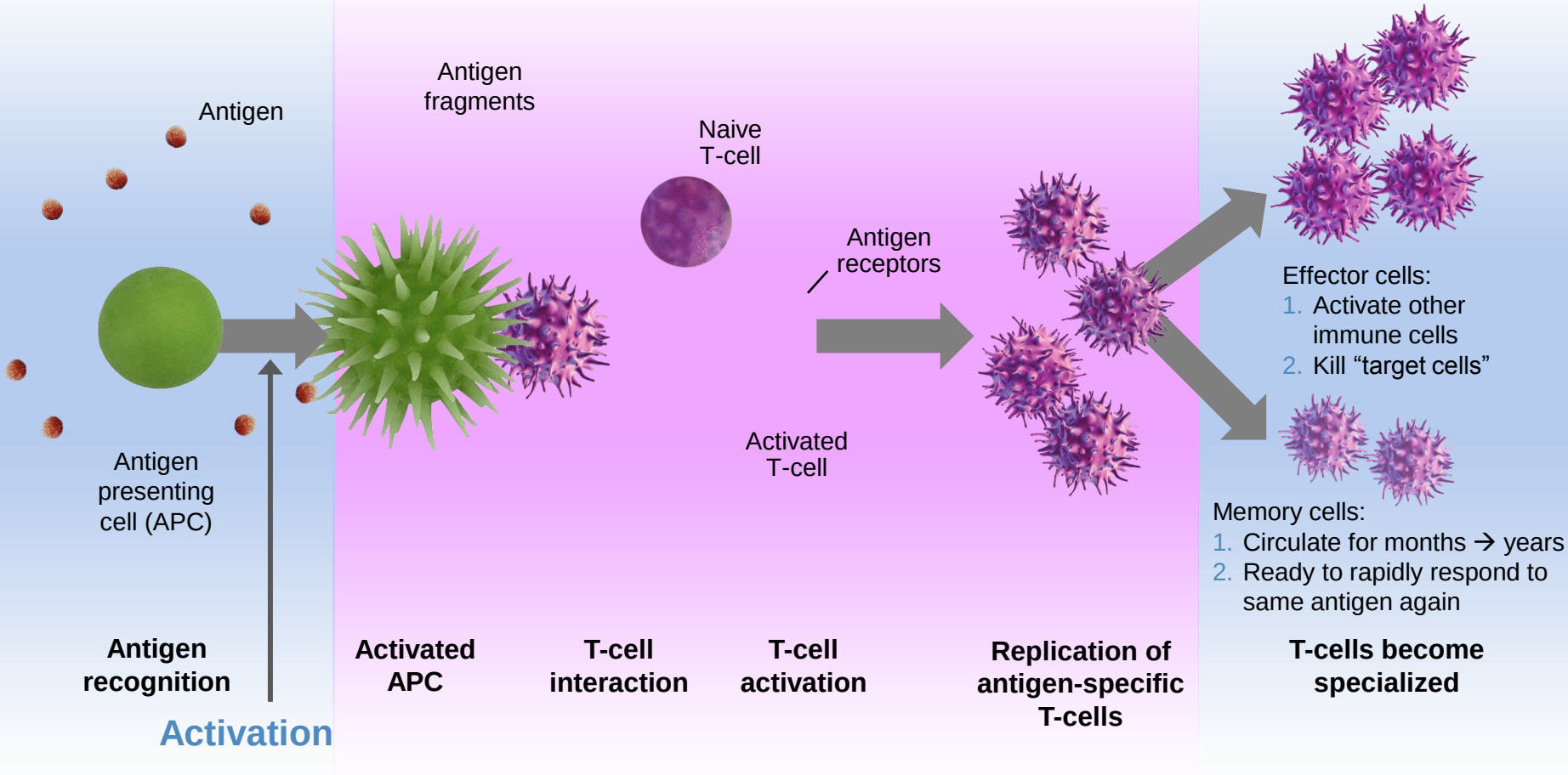
Dunn GP, Schreiber RD, et al. *Nat Rev Immunol.* 2006;6(11):836-848.

Key Components Involved in the Immune Response

- **Antigens**
  - Molecules produced by microbes or foreign agents that bind to T cells and antibodies
- **Antigen presenting cells (APCs)**
  - Identify and uptake foreign antigens
  - Present them to T cells
- **T cells**
  - Activated by APCs
  - Recognize and destroy cells containing foreign antigen
- **B cells**
  - Produce antibodies specific to foreign antigens

Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

Initiation of Immune Response: Key Components



Adapted from Abbas AK, Lichtman AH.

Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

Features of an Effective Immune Response[1,2]

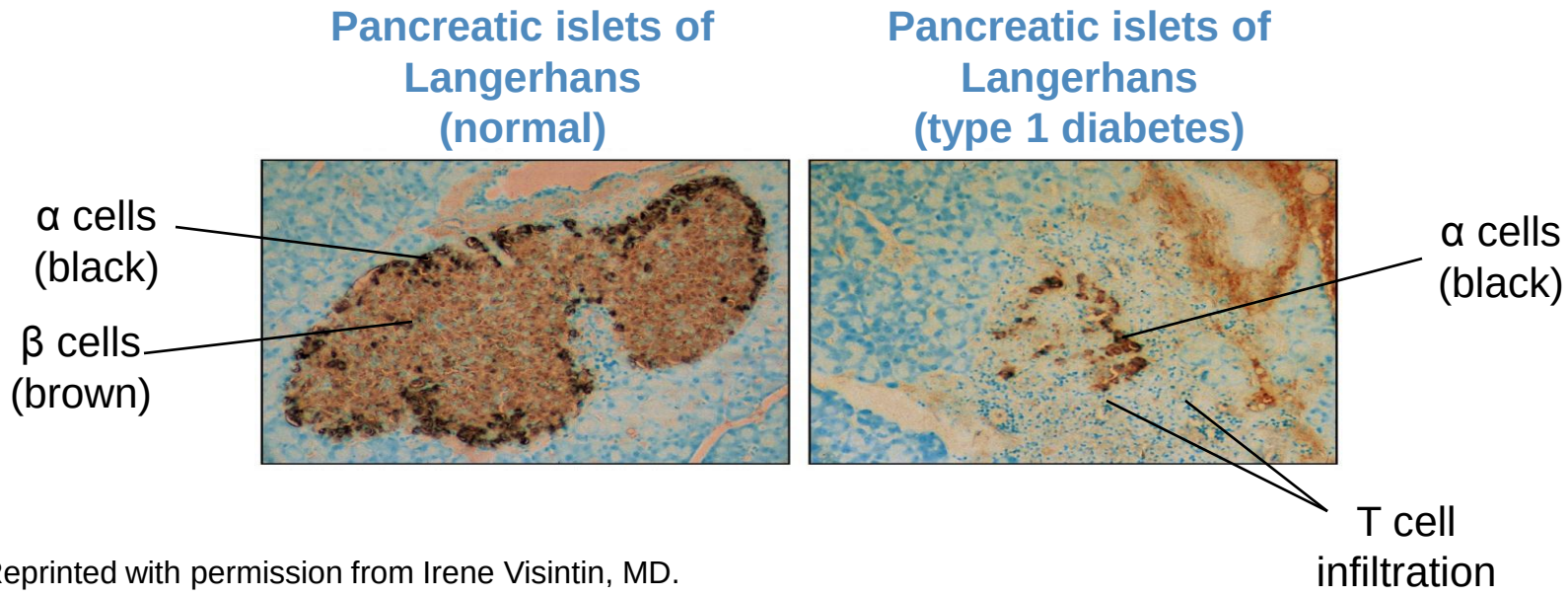
- Specificity
- Trafficking
- Adaptability
- Target elimination
- Durability (immune memory)

1. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.
2. Drake CG. *Nat Rev Immunol*. 2010;10(8);580-593.

Immune Response: Specificity

- Ability of immune cells to identify and target a specific antigen[1]

In type 1 diabetes, T cells recognize and destroy only β cells[2]

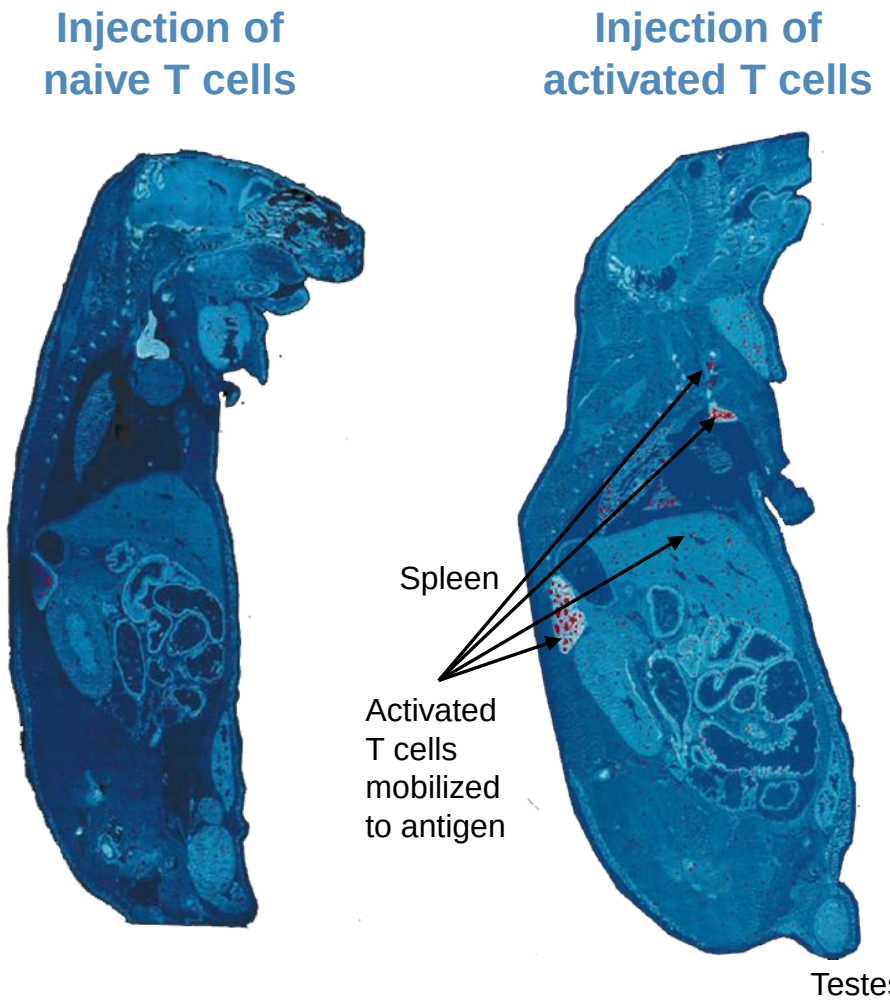


Reprinted with permission from Irene Visintin, MD.

1. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.
2. Murphy K. *Janeway's Immunobiology*. 8th ed. 2012.

Immune Response: Trafficking

- Ability of activated immune system cells to migrate to particular antigens throughout the body[1-3]
- In this example, activated T cells were mobilized to areas containing antigen[1]

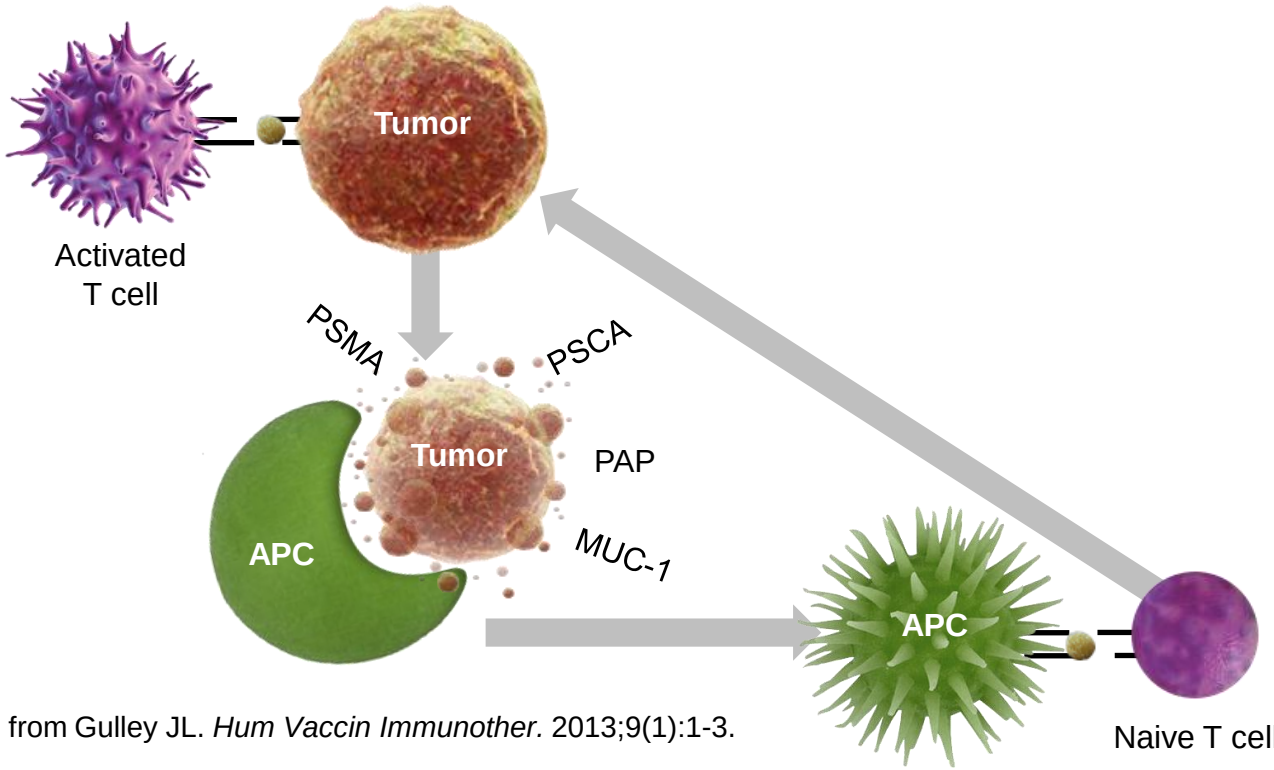


Reprinted with permission from Reinhardt RL, Jenkins MK, et al.[1]

1. Reinhardt RL, Jenkins MK, et al. *Nature.* 2001;410(6824):101-105.
2. Drake CG. *Nat Rev Immunol.* 2010;10(8):580-593.
3. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

Immune Response: Adaptability

- Allows for a broader immune response[1] (eg, immune response to additional antigens[2])



Adapted from Gulley JL. *Hum Vaccin Immunother.* 2013;9(1):1-3.

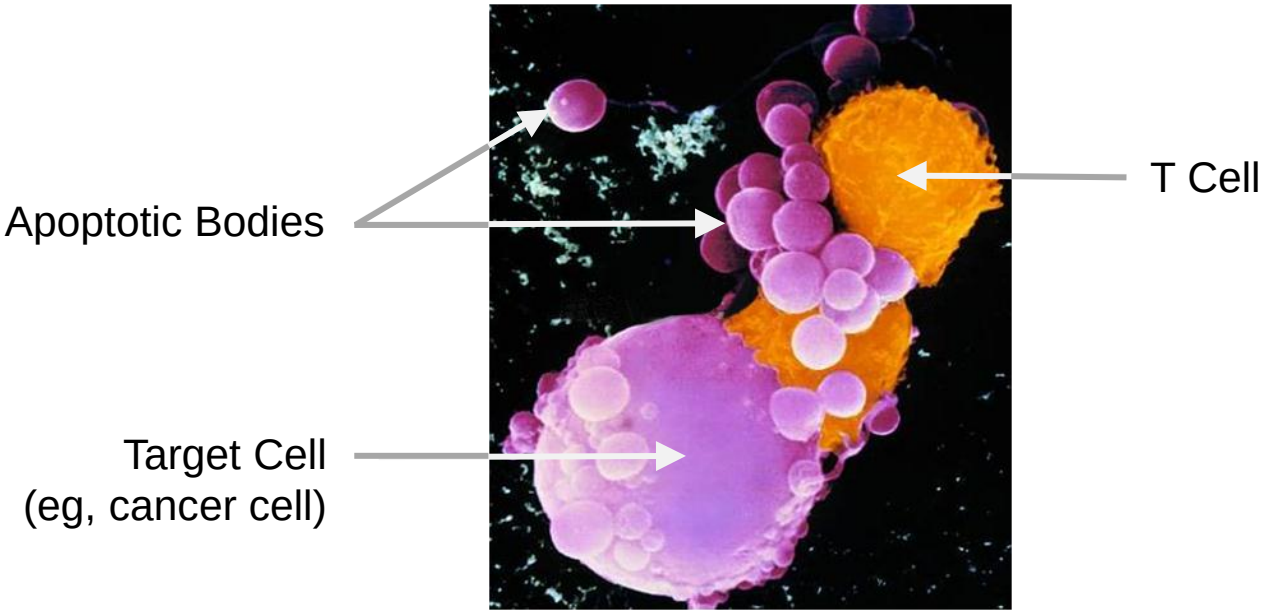
PSMA, prostate-specific membrane antigen; PSCA, prostate stem cell antigen; PAP, prostatic acid phosphatase; MUC-1, mucin-1.

1. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.
2. Nesslinger NJ, Gulley JL, et al. *Clin Cancer Res*. 2010;16(15):4046-4056.

Immune Response: Target Elimination

- Ability of immune cells to destroy their target (eg, cancer cells)[1,2]
  - Usually via induction of apoptosis[3]

Target cell death[3]:
Scanning Electron Micrograph showing T cells inducing a target cell to undergo apoptosis



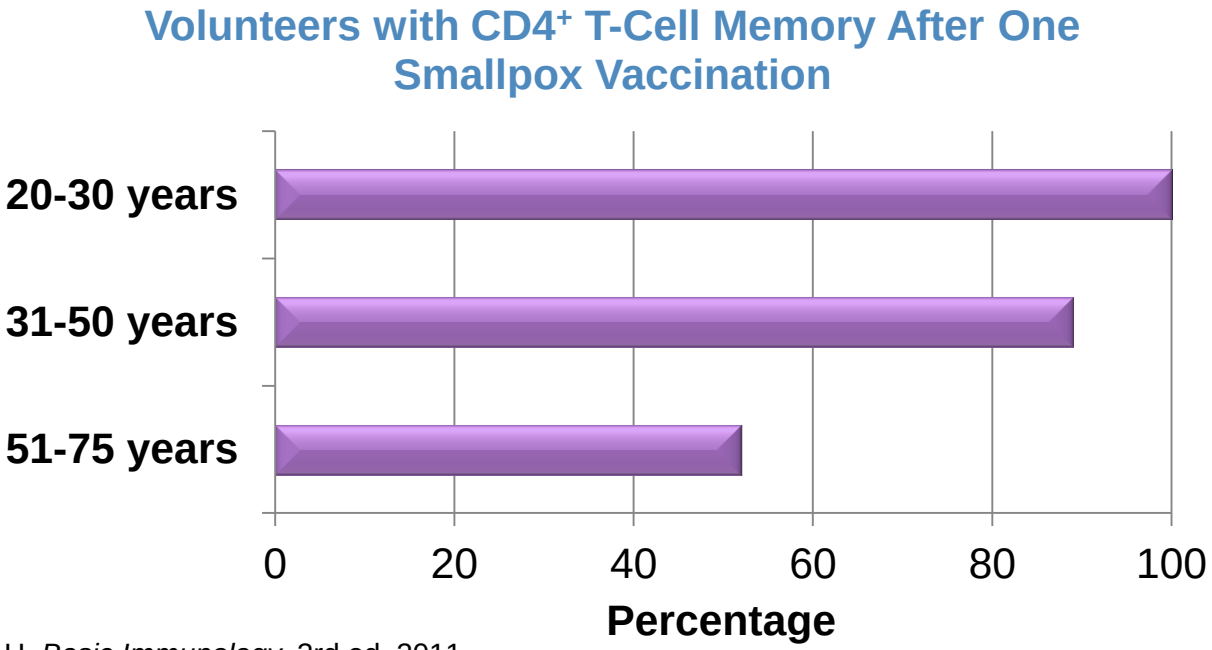
Courtesy of sciencesource.com

1. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.
2. Boissonnas A, Amigorena S, et al. *J Exp Med.* 2007;204(2):345-356.
3. Trapani JA, Smyth MJ. *Nat Rev Immunol*. 2002;2(10):735-747.

Immune Response: Durability (Immune Memory)

- Ability of immune system to recognize an antigen to which it has previously been exposed and provide long-lasting protection against it[1]

Shown is the durable virus-specific T-cell response after smallpox vaccination[2]



1. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.
2. Hammarlund E, Slifka MK, et al. *Nat Med*. 2003;9(9):1131-1137.

Program Agenda

- Immune System's Role in Cancer
- **Immunotherapy Landscape**
- Clinical Considerations of Immunotherapy
- State of Immunotherapy

Immunotherapy

Definition[1]

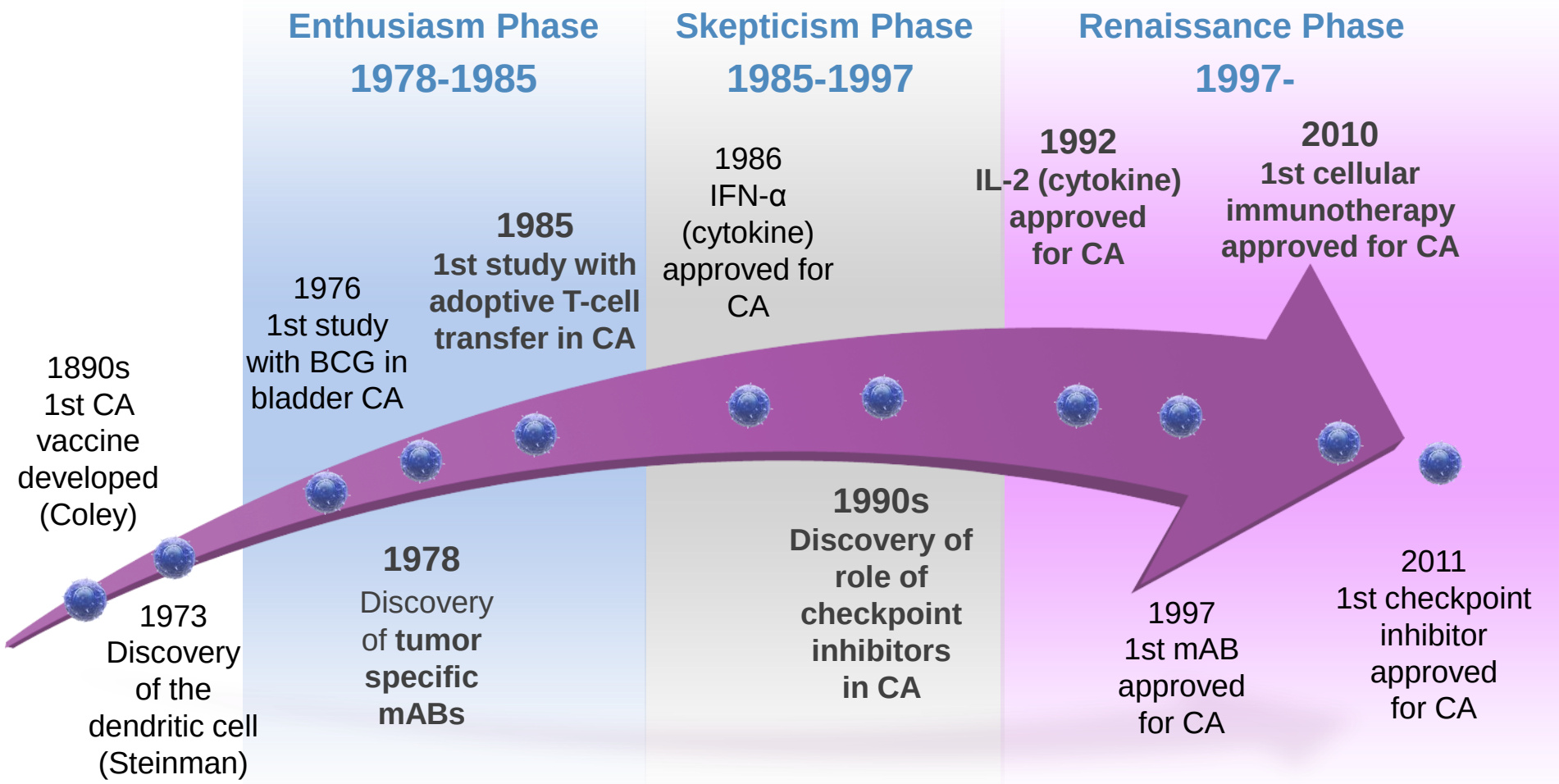
- Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases

Examples in cancer[2]

- Monoclonal antibodies
- Cytokines
- Checkpoint inhibitors
- Therapeutic vaccines

1. National Cancer Institute. Cancer terms. http://www.cancer.gov/dictionary/?print=1&cdrid=45729. Accessed October 5, 2012.
2. Mellman I, Dranoff G, et al. *Nature*. 2011;480(7378):480-489.

The Renaissance of Immunotherapy[1-5]



Adapted with permission from Lesterhuis WJ, et al[2] and Kirkwood JM, et al. *J Clin Oncol*. 2008;26(20):3445-3455.

BCG, Bacille Calmette-Guerin; mABs, monoclonal antibodies; CA, cancer; IFN-α, interferon alpha; IL-2, interleukin-2

1. Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin*. 2012;62(5):309-335.
2. Lesterhuis WJ, Punt CJ, et al. *Nat Rev Drug Discov*. 2011;10(8):591-600.
3. Krummel MF, Allison JP. *J Exp Med.* 1995;182(2):459-465.
4. Lotze M. In: *Cancer: Principles & Practice of Oncology*. 9th ed. 2011.
5. Leget GA, Czuczman MS. *Curr Opin Oncol.* 1998;10(6):548-551.

Types of Immunotherapy

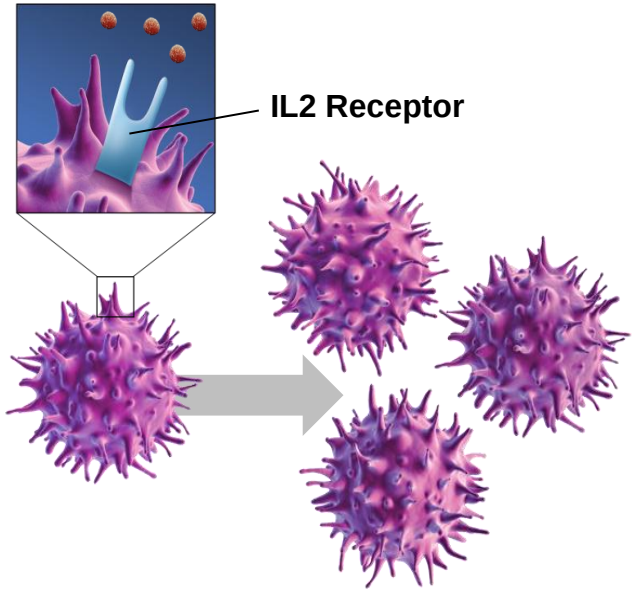
- Cytokines
- Monoclonal antibodies
- Checkpoint inhibitors
- Therapeutic cancer vaccines

Mellman I, Dranoff G, et al. *Nature*. 2011;480(7378):480-489.

Cytokines

- **Proteins that are naturally secreted by immune system cells**[1]
- **Mechanism of action**[2]
  - Interleukin-2 (IL-2) stimulates T-cell proliferation
- **Examples**[2]
  - Interleukins, interferons
- **Efficacy**[3]
  - High dose IL-2 administration resulted in long term disease-free survival in patients with melanoma and renal cell carcinoma

IL-2 Stimulation of T-cell Proliferation[2]

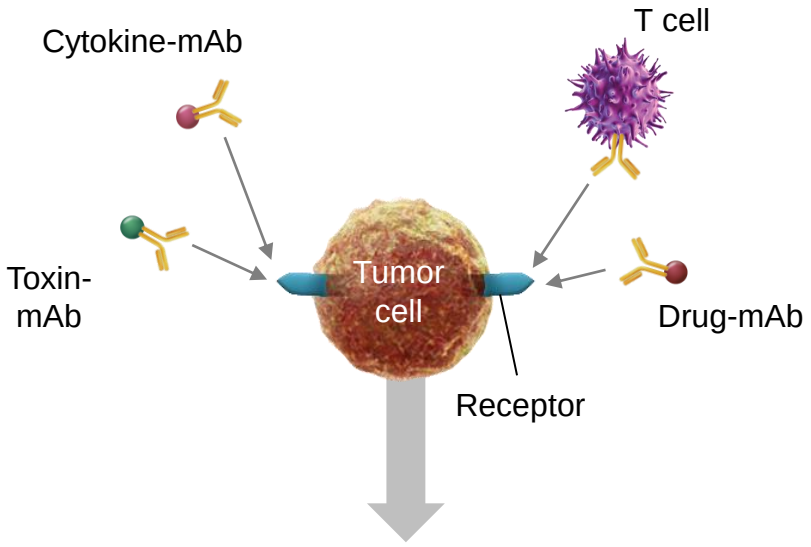


1. Abbas AK, Lichtman AH. *Basic Immunology.* 3rd ed. 2011.
2. Bachmann MF, Oxenius A. *EMBO Rep*. 2007;8(12):1142-1148.
3. Lotze M. In: *Cancer: Principles & Practice of Oncology*. 9th ed. 2011.

Monoclonal Antibodies (mABs)

- **Mechanism of action**[1,2]
  - Differs between agents
  - Bind to their specific target antigen ultimately causing cell death
- **Efficacy**[3-7]
  - Improved overall and progression-free survival (PFS) in randomized, phase 3 clinical trials in breast cancer, colorectal cancer, leukemia, and head and neck cancer

Potential mechanisms of mABs in cancer

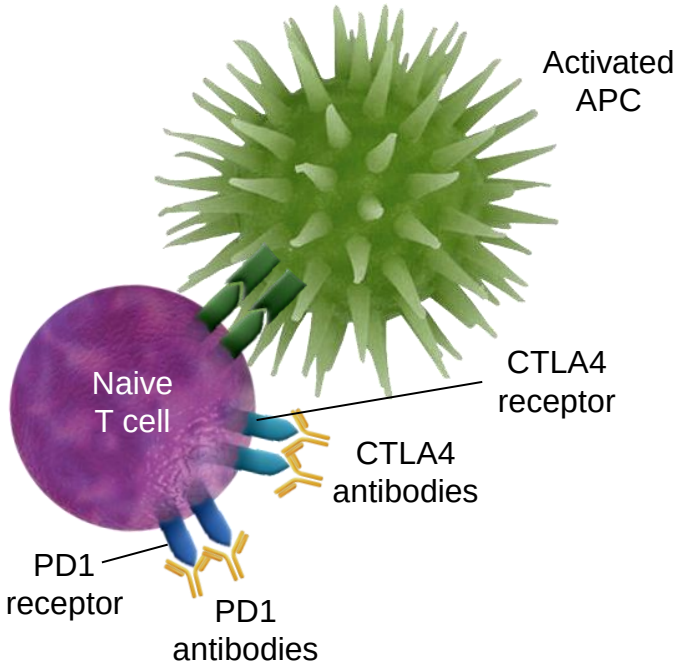


Adapted from Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin*. 2012;62(5):309-335.

1. Cheson BD, Leonard JP. *N Engl J Med*. 2008;359(6):613-626.
2. Weiner LM, Wang S. *Nat Rev Immunol*. 2010;10(5):317-327.
3. Slamon DJ, Norton L, et al. *N Engl J Med*. 2001;344(11):783-792.
4. Curran D, Bonner JA, et al. *J Clin Oncol*. 2007;25(16):2191-2197.
5. Vermorken JB, Hitt R, et al. *N Engl J Med*. 2008;359(11):1116-1127.
6. Jonker DJ, Moore MJ, et al. *N Engl J Med*. 2007;357(20):2040-2048.
7. Robak T, Moiseev SI, et al. *J Clin Oncol*. 2010;28(10):1756-1765.

Checkpoint Inhibitors

- **Mechanism of action**[1,2]
  - Block immune checkpoints that regulate T cell activation/function
- **Examples**[1,2]
  - CTLA-4 and PD1
- **Efficacy**[3-6]
  - Extends overall survival in certain metastatic diseases
  - A significant effect on PFS not consistently observed



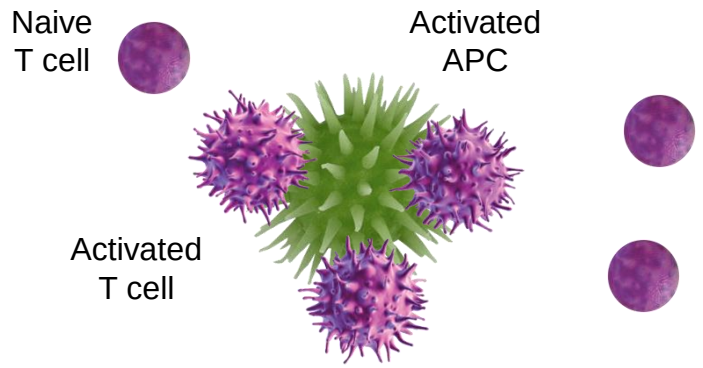
Adapted with permission from Sharma P, Allison JP, et al.[2]

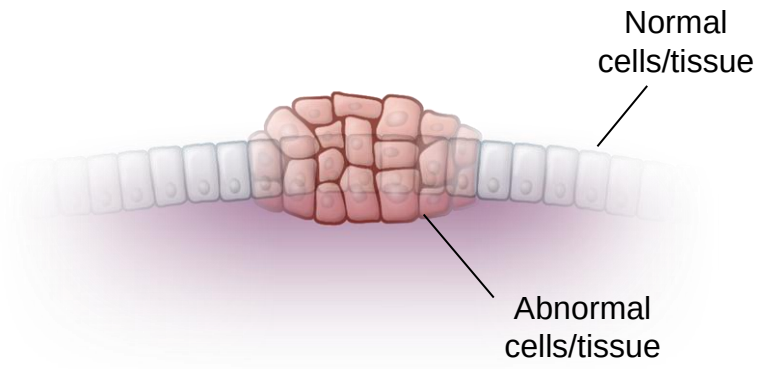
CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD1, programmed cell death protein 1

1. Pardoll D. *Nat Rev Cancer.* 2012;12(4):252-264.
2. Sharma P, Allison JP, et al. *Nat Rev Cancer*. 2011;11(11):805-812.
3. Hodi FS, Urba WJ, et al. *N Engl J Med*. 2010;363(8):711-723.
4. Robert C, Wolchok JD, et al. *N Engl J Med*. 2011;364(26):2517-2526.
5. Brahmer JR, Wigginton JM, et al. *N Engl J Med*. 2012;366(26): 2455-2465.
6. Topalian SL, Sznol M, et al. *N Engl J Med*. 2012;366(26): 2443-2454.

Therapeutic Cancer Vaccines

- **Mechanism of action**[1]
  - Activation of T cells to seek out and destroy target cancer cells
- **Efficacy**[2,3]
  - Extended overall survival in certain metastatic diseases without an effect on PFS





1. Drake CG. *Nat Rev Immunol*. 2010;10(8):580-593.
2. Kantoff PW, Schellhammer PF, et al. *N Engl J Med*. 2010;363(5):411-422.
3. Kantoff PW, Godfrey WR, et al. *J Clin Oncol.* 2010;28(7):1099-1105.

Preventive vs Therapeutic Vaccines

"Cancer treatment vaccines are designed to treat cancers that have already developed. They are intended to delay or stop cancer cell growth; to cause tumor shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment."

- NCI (2011)

National Cancer Institute. Cancer vaccines. http://www.cancer.gov/cancertopics/factsheet/Therapy/. Accessed December 15, 2012.

Characteristics of Immunotherapy

ACTIVE	PASSIVE
Engages immune system	Enhances pre-existing immune response
Durable	Short-lived
Some examples: therapeutic cancer vaccines	Some examples: mABs, cytokines

Rescigno M, Curigliano G, et al. *Biochim Biophys Acta*. 2007;1776(1):108-123.

Characteristics of Therapeutic Vaccines[1,2]

Therapeutic Vaccines	
Target	Immune system
Response Kinetics	Delayed
Potential for Memory Response	Yes
Tumor Evolution Potential	New immunologic targets
Patient Considerations	Requires uncompromised immune system (both systemically and at tumor site)

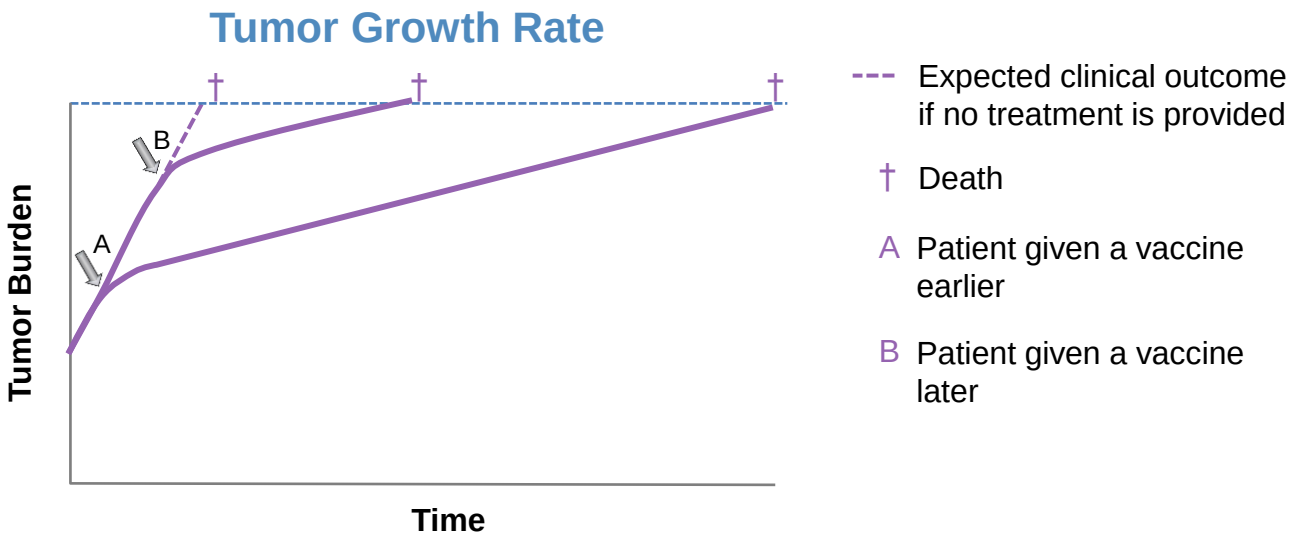
1. Gulley JL. *Hum Vaccin Immunother*. 2013;9(1):1-3.
2. Slovin S. *Clin Adv Hematol Oncol.* 2012;10(2):90-100.

Program Agenda

- Immune System's Role in Cancer
- Immunotherapy Landscape
- **Clinical Considerations of Immunotherapy**
- State of Immunotherapy

Immunotherapy: Treatment Considerations

- Relative efficacy of immunotherapy may be greater with lower tumor burden[1,2]
- Patient given immunotherapy earlier in disease course might have a better outcome[3]



Adapted with permission from Gulley JL, Drake CG.[3]

1. Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin.* 2012;62(5):309-335.
2. Drake CG. *Nat Rev Immunol.* 2010;10(8):580-593.
3. Gulley JL, Drake CG. *Clin Cancer Res.* 2011;17(12):3884-3891.

Immunotherapy: Treatment Considerations

- Standard practice in oncology is the use of combination agents with different mechanisms of action[1-3]
  - Chemotherapy and mABs
  - Radiation and chemotherapy
  - Multiple chemotherapy regimens
- Immunotherapy offers potential for synergy with other therapies[1-6]

1. Vermorken JB, Hitt R, et al. *N Engl J Med*. 2008;359(11):1116-1127.
2. Slamon DJ, Norton L, et al. *N Engl J Med.* 2001;344(11):783-792.
3. Gulley JL, Drake CG. *Clin Cancer Res.* 2011;17(12):3884-3891.
4. Drake CG, Adler AJ, et al. *Cancer Cell*. 2005;7(3):239-249.
5. Mercader M, Kwon ED, et al. *Proc Natl Acad Sci USA*. 2001;98(25):14565-14570.
6. Aragon-Ching JB, Gulley JL, et al. *Front Biosci*. 2007;12:4957-4971.

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Immunotherapy: An Established Treatment Strategy

- More than a dozen different immunotherapy agents have been approved[a], with the majority over the last decade[1-5]
- Immunotherapy agents currently approved target >10 different cancer types[1-5]

FDA-Approved Immunotherapies[a]	
Class	**Approvals**
Checkpoint inhibitor	2011
Therapeutic vaccine	2010
Monoclonal antibodies	1997, 1998, 2000, 2001, 2002, 2003, 2004, 2006, 2009
Cytokines	1986, 1992, 1995, 1998

[a]Not inclusive of all immunotherapy classes.

1. Mellman I, Dranoff G, et al. *Nature*. 2011;480(7378):480-489.
2. Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin*. 2012;62(5):309-335.
3. Lotze M. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.
4. Sondak VK, Hauschild A, et al. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.
5. Robinson MK, Weiner LM, et al. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.

Immunotherapy: Future Promise

- Rapid increase in immunotherapy clinical research
  - Doubling of abstracts at major conferences from 2009 to 2012
  - Approximately 800 clinical trials in various phases ongoing
    - eg, breast, colon, head and neck, kidney
- Trials utilize agents alone and in combination with conventional therapies[2]

Courtesy of sciencephoto.com

SeekingAlpha.com. http://seekingalpha.com/article/667581-immunotherapy-comes-of-age-at-asco-2012. Accessed January 4, 2013.
ClinicalTrials.gov. http://clinicaltrials.gov/. Accessed January 4, 2013.

Summary

- The immune system plays a critical role in controlling cancer[1]
- Key features of an effective immune response include[2]
  - Specificity
  - Adaptability
  - Durability (immune memory)
- Future clinical considerations
  - May elicit better immune system response if used earlier in disease[3,4]
  - Potential for durable clinical effects and synergy with subsequent therapies[5-8]

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Questions?