Looking Deeper into the Science of Immuno-Oncology

Utilizing the body's own immune system to fight cancer

Instructions

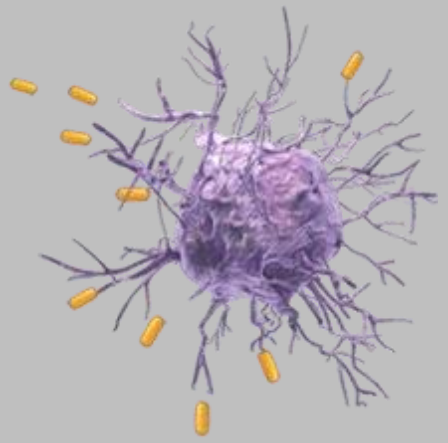
Topic 1

Topic 2

Topic 3

Topic 4

Slides have been color-coded based on educational topic to help gain an understanding of Immuno-Oncology (I-O).



At the back of this document, there are resources and images about I-O.

Topics covered (by subject)

INTRODUCTION TO I-O THERAPY

- What's I-O
- History of immunotherapy
- Hallmarks of cancer
- The immune system and cancer: immunoediting
- I-O therapy regimens
- Potential applicability of I-O for different tumors

THE IMMUNE SYSTEM

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- Components of the immune system
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  - Antigen-presenting cells (APCs)
  - T cells
  - B cells
  - Antibodies
  - NK cells
- T-cell activation

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  - CD40
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  - LAG-3
  - CTLA-4
  - B7-H3
  - PD-1

I-O THERAPY CLASSES AND AEs

- Passive immunotherapies
  - Tumor-directed monoclonal antibodies
  - Cell therapies
- Active immunotherapies
  - Vaccines
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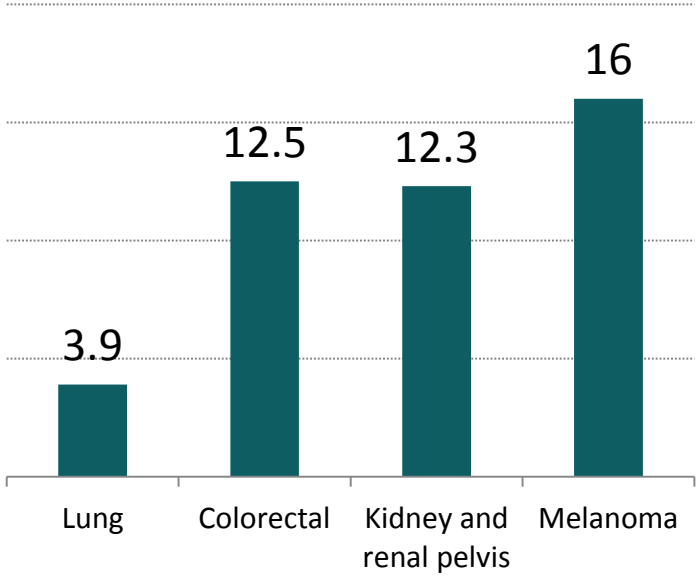
  - Mediators of T-cell activation
- Adverse effects (AEs)
- Clinical implications of immune-associated AEs

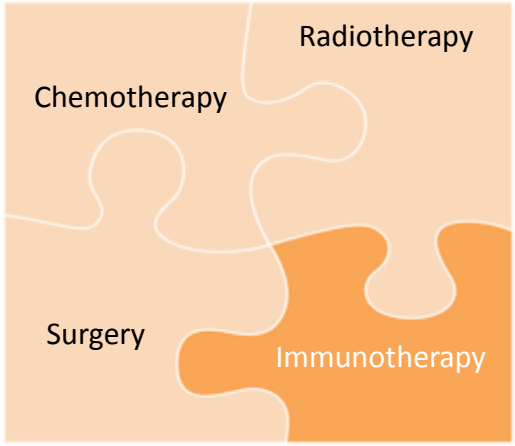
What's immuno-oncology (I-O)

Improved survival remains a challenge in some advanced cancers. 5-year survival remains poor for many patients with metastatic solid tumors.[1] There is an ongoing need for new treatments and therapeutic modalities for patients with advanced cancers.[2]

5-year survival (%)[1]



Pillars of Cancer Therapies



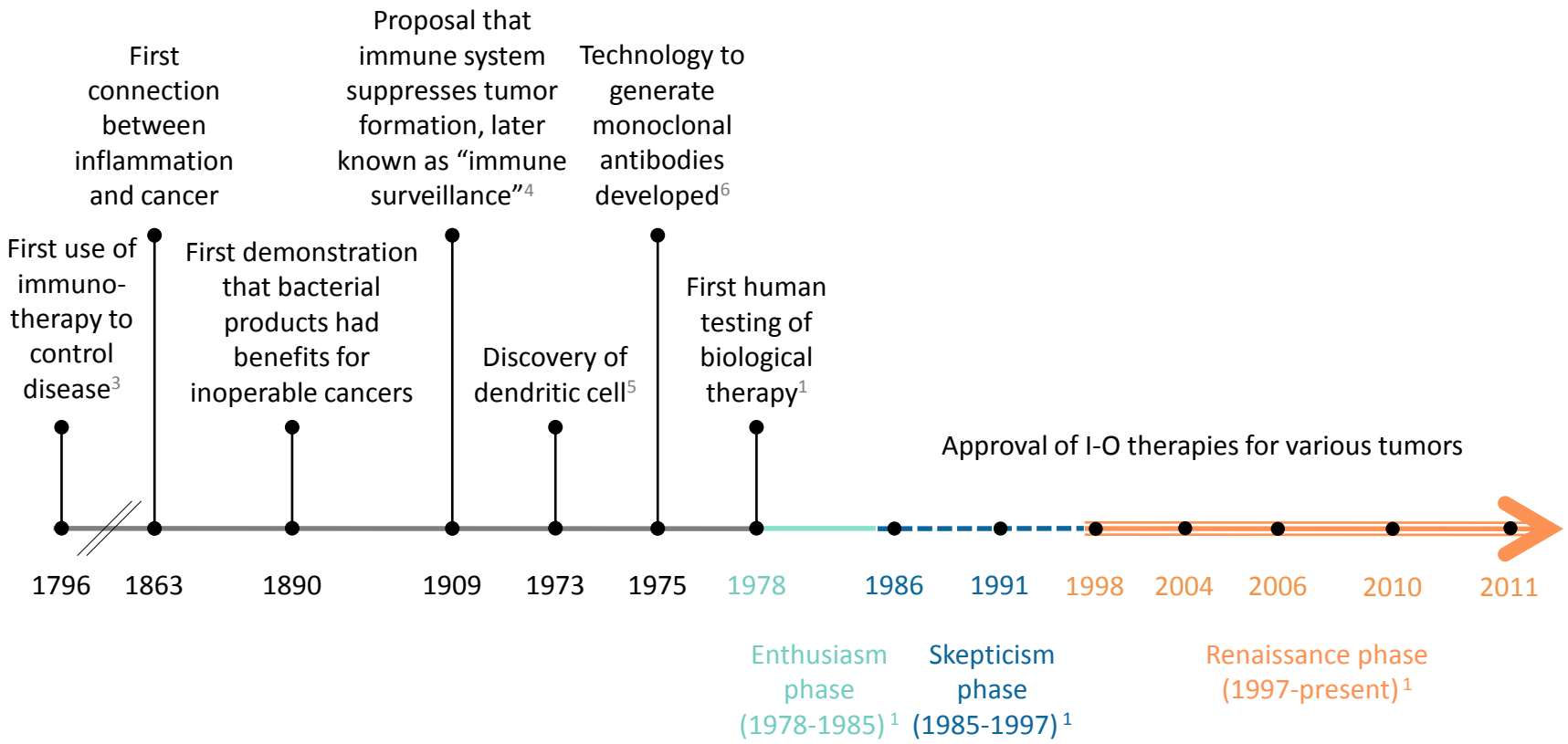
I-O therapies are being investigated in an attempt to utilize the body's own immune system to fight diseases.[3-5]

There are over 900 oncology clinical trials of immunotherapy in various phases of development.[6]

1. Surveillance, Epidemiology and End Results (SEER) Program. Retrieved May 6, 2014, from http://seer.cancer.gov 2. Rosenberg SA. *Sci Transl Med*. 2012;4(127ps8):1-5
3. DeVita BT, Rosenberg SA. *N Engl J Med*. 2012;366:2207-2214 4. Kirkwood JM, et al. CA *Cancer J Clin*. 2012;62:309-335 5. Murphy JF. *Oncology*. 2010;4:67-80 6. Clinicaltrials.gov. Accessed September 16, 2013

History of immunotherapy

I-O has progressed considerably since 1986 with approvals for the use of various I-O therapies, including vaccines, cytokines, tumor-directed monoclonal antibodies, and immune checkpoint inhibitors.[1,2]



1. Kirkwood JM, et al. CA *Cancer J Clin*. 2012;62:309-335 2. CenterWatch. FDA Approved Drugs for Oncology. http://www.centerwatch.com/drug-information/fda-approvals/drug-areas.aspx?AreaID=12. Accessed May 8, 2014 3. Murphy JF. *Oncology*. 2010;4:67-80 4. National Cancer Institute. 250 Years of Advances Against Cancer - 1900s. www.cancer.gov/aboutnci/overview/250-years-advances/1900s. Accessed May 8, 2014 5. Steinman RM, Cohn ZA. *J Exp Med*. 1973;137:1142-1162 6. National Cancer Institute. 250 Years of Advances Against Cancer - 1970s. www.cancer.gov/aboutnci/overview/250-years-advances/1970s. Accessed May 8, 2014

Hallmarks of cancer

As normal cells ***progressively evolve to a neoplastic state***, they can acquire a succession of **hallmark capabilities**[1]:

*Emerging hallmarks

For **Immuno-Oncology therapies (I-O therapies)** to work, they generally incorporate an understanding of the *mechanisms of tumor escape*.[2,3]

I-O therapies seek to modulate the immune system to *promote antitumor activity*, and counteract this hallmark.[4]

1. Hanahan D, Weinberg RA. *Cell*. 2011; 144(5) 646-674. 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 3. Kirkwood JM, et al. CA *Cancer J Clin*. 2012; 62:309-335
4. Mellman I, et al. *Nature*. 2011;480:480-489

The immune system and cancer: immunoediting

The process by which the immune system recognizes, destroys, and sculpts tumors is known as **immunoediting**.[1] There are 3 phases in immunoediting[1,2]:

- **ELIMINATION** (cancer immunosurveillance) - Cancer cells are detected by the immune system and/or eliminated.[1,2] Tumor cells not destroyed may enter the equilibrium phase.[1,2]
- **EQUILIBRIUM** (cancer dormancy) – Some cancer cells persist, but the immune system prevents tumor outgrowth.[1,2]
- **ESCAPE** (cancer progression) – Resistant variant cancer cells acquire the ability to evade immune detection or elimination.[1,2] This results in clinically apparent disease.[2]

The goal of I-O therapy is to restore the ability of the immune system to eliminate cancer cells by either **activating the immune system** directly or by **inhibiting mechanisms of suppression by tumors.**

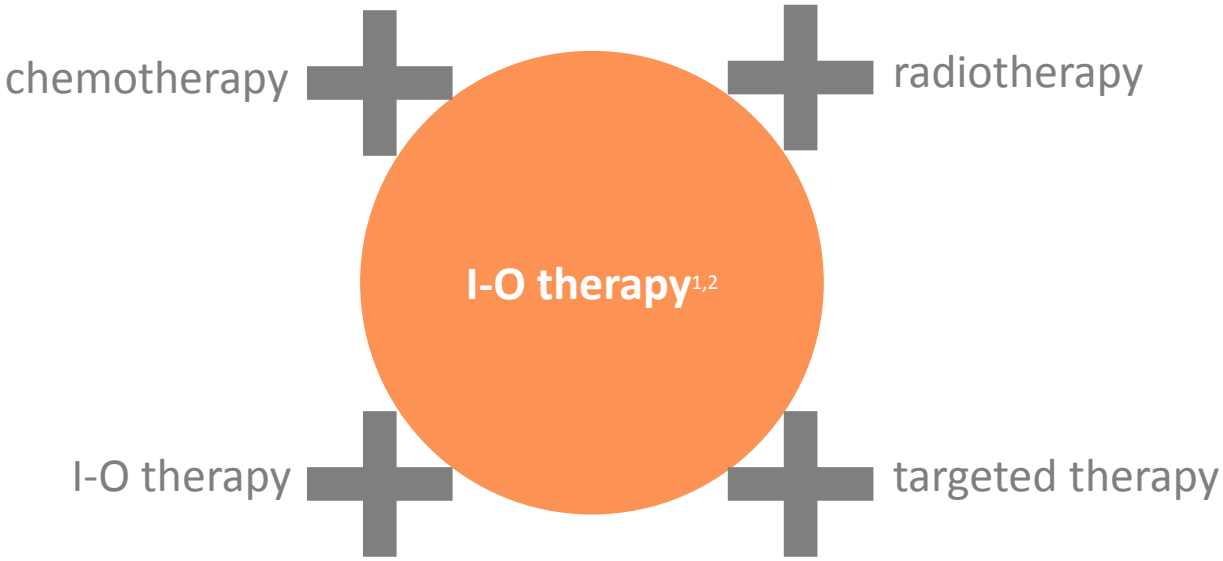
Some tumors may **escape** the immune system by interfering with various mechanisms of immune system activation and suppression.

1. Vesely MD, et al. *Ann Rev Immunol*. 2011;29:235-271 2. Schreiber RD, et al. *Science*. 2011;331:1565-1570

I-O therapy regimens

I-O therapies have the potential to be used as *monotherapy* or *part of combination regimens*.[1]

- I-O therapies are designed for various specific targets in the antitumor immune response; because of this, it is thought that combinations of complimentary I-O therapies may have the potential to enhance antitumor effects.[1,2] There is also a potential for enhanced antitumor activity in combining I-O therapies with other cancer treatment modalities.[1,2]



1. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46 2. Ribas A, et al. *Curr Opin Immunol*. 2013:25:291–296

Potential applicability of I-O for different tumors

Tumor type	Infiltrating immune cells reported	Evidence of tumor-associated immunosuppression reported	Tumor-immune interactions known to correlate with clinical prognosis
Bladder	3	16,19	3,16
Breast	11,12	1,6	11,18
Colorectal	3,4,5,11	17	1,3,4,5,11
Esophageal	3,11	6	3,11
Gastric	17	6,17	17
Head and neck	7	7,20	7
Hepatocellular	8	2,8	8
Leukemia	—	22	—
Lung	9,15	1,6,17,21	1,2,9,15
Lymphoma	—	1	—
Melanoma	1,2,10,11	1,2,23	1,2,10,11
Ovarian	3,11	1,2,6,24	3,11,24
Pancreatic	12,13	17	—
Prostate	11	—	2,11
Renal cell carcinoma	3,11,14	2,14	3,11,14

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 2. Mellman I, et al. *Nature*. 2011;480:480-489 3. Sharma P, et al. Proc *Natl Acad Sci* USA. 2007;104:3967-3972 4. Pages F, et al. *N*
2. *Engl J Med*. 2005;353:2654-2666 5. Salama P, et al. *J Clin Oncol*. 2009;27:186-192 6. Ichihara F, et al. *Clin Cancer Res*. 2003;9:4404-4408 7. Badoual C, et al. *Clin Cancer Res*. 2006;12:465-472 8. Gao Q, et al. *Clin Cancer Res*. 2009;15:971-979 9. Dieu-Nosjean MC, et al. *J Clin Oncol*. 2008;26:4410-4417 10. Taylor RC, et al. *J Clin Oncol*. 2007;25:869-875 11. Zhang L, et al. *N Engl J Med*. 2003;348:203-213 12. Liyanage UK, et al. *J Immunol*. 2002;169:2756-2761 13. Kärjä V, et al. *Anticancer Res*. 2005;25:4435-4438 14. Thompson RH, et al. *Clin Cancer Res*. 2007;13:1757-1761 15. Hiraoka K, et al. *Br J Cancer*. 2006;94:275-280 16. Winerdal ME, et al. *BJU Int*. 2011;108:1672-1678 17. Kono K, et al. *Cancer Immunol Immunother*. 2006;55:1064-1071 18. Rody A, et al. *Breast Cancer Res*. 2009;11:1-13 19. Inman BA, et al. *Cancer*. 2007;109:1499-1505 20. Schaefer C, et al. *Br J Cancer*. 2005;92:913-920 21. Woo EY, et al. *J Immunol*. 2002;168;4272-4276 22. Karube K, et al. *Br J Haematol*. 2004;126:81-84 23. Chapon M, et al. *J Invest Dermatol*. 2011;131:1300-1307 24. Hamanishi J, et al. *PNAS*. 2007;104:3360-3365

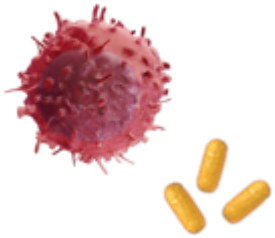
Introduction to the immune system

In order to protect an individual, the immune system:

1. detects the presence of an infection or malignant cells,[1]
2. carries out effector functions to contain or to eliminate the affected cells,[1]
3. performs self-regulation to minimize collateral damage to healthy cells in the body,[1] and
4. generates immunological memory so that subsequent exposures to the same antigen are dealt with efficiently.[1]

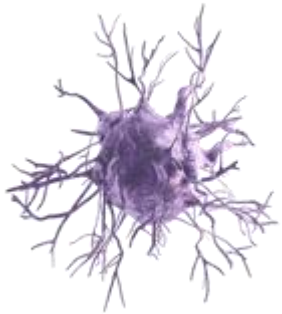
1. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

Components of the immune system



Tumor-associated antigens

- are abnormal cell substances/proteins (tumor antigens) which can be recognized and responded to by the immune system[1]



Antigen-presenting cells

- take up antigens from infected or malignant cells and processes them into shorter peptide segments[2]
- present antigen to T cells to mobilize an immune response[2]

T cells[1]

- have T-cell receptors, which can recognize tumor-associated antigens
- play a major role in killing infected or malignant cells when activated
- help perpetuate ongoing immune responses

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 2. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

Components of the immune system

B cells[1]

- display B-cell receptors, which can bind free floating antigens in the blood or lymph
- once activated, B cells differentiate to become plasma cells which can secrete large quantities of antibodies against a specific antigen[1]

Antibodies

- are secreted by activated B cells, called plasma cells[1]
- tag antigen-containing cells for attack by other parts of the immune system, or neutralize their targets directly by blocking important mechanisms[1]

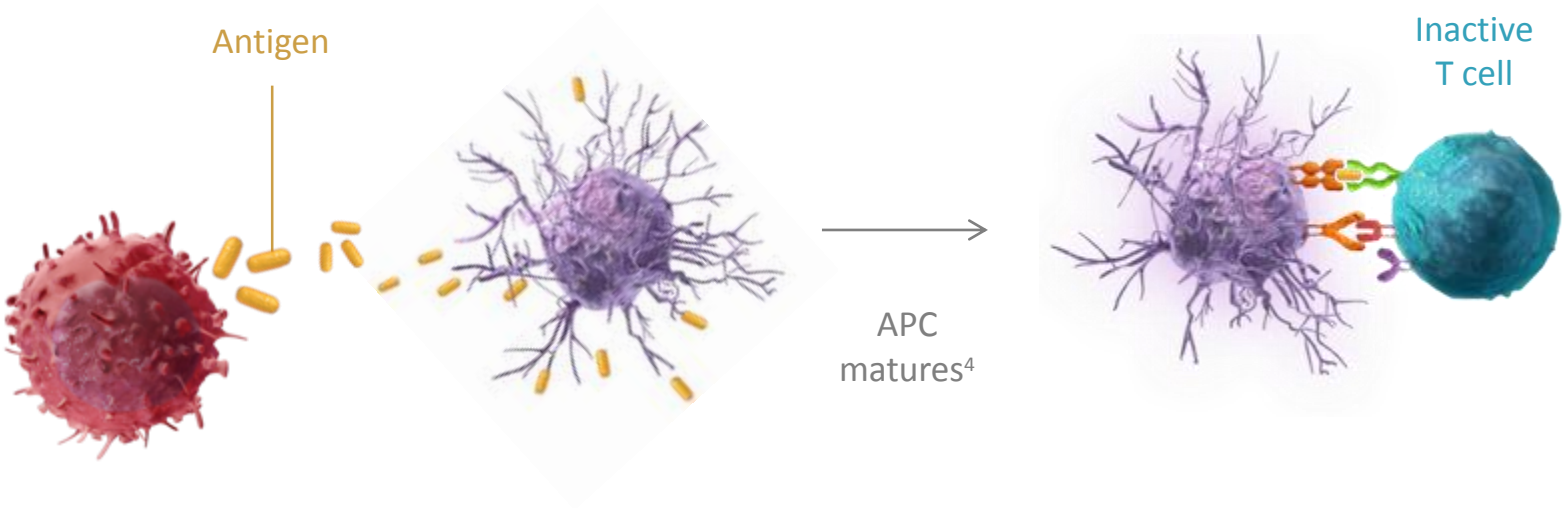
NK cells[1]

- can recognize infected or malignant cells innately without contact with an antigen-presenting cell or antibody (this allows NK cells to launch rapid responses against stressed cells)
- can also attack based on recognition of antibodies on a cell surface

1. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

T-cell activation: tumor-associated antigens

Tumor-associated antigens can trigger a tumor-specific immune cell response:



1
Tumors express a multitude of proteins, known as **tumor-associated antigens**[1,2,3,4]

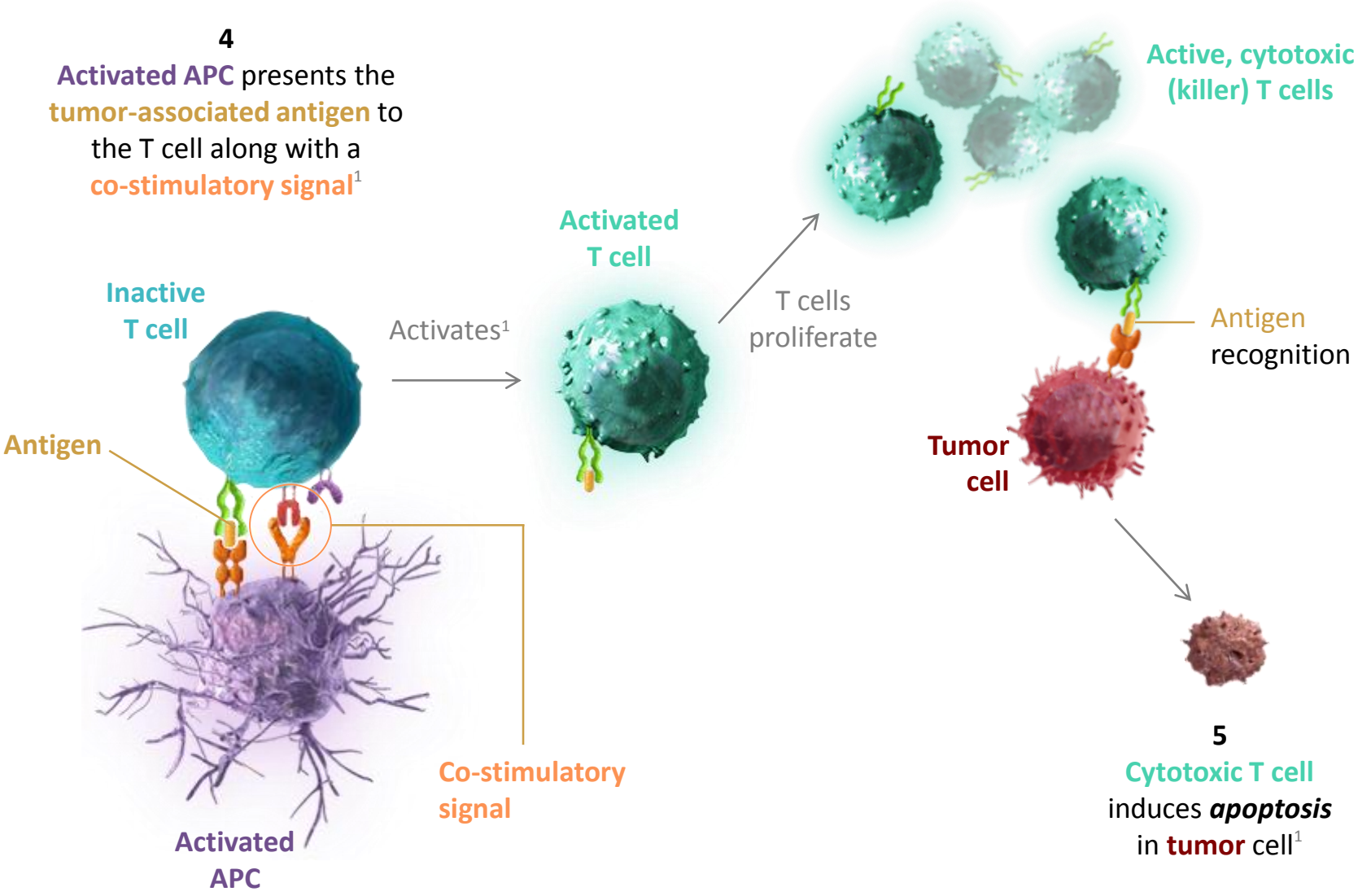
2
Antigen presenting cell (APC) captures **tumor-associated antigens**[2]

3
Activated APC can interact with T cells[4]

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;11:252-264 2. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011;480:480-489 3. Heemskerk B, Kvistborg P, Schumacher TNM. The cancer antigenome. *EMBO J*. 2013;32(2):194-203 4. Boudreau JE, Bonehill A, Thielemans K, Wan Y. Engineering dendritic cells to enhance cancer immunotherapy. *Mol Ther*. 2011;19(5):841-853

T-cell activation: cytotoxic T cells

4
Activated APC presents the **tumor-associated antigen** to the T cell along with a **co-stimulatory signal**[1]



1. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

Immune system pathways

- Under normal conditions, there are a number of immune activation and inhibition pathways that **modulate the immune response** and protect healthy tissues from collateral damage during an immune response.[1,7]
- Tumor evasion of the immune system may be associated with an imbalance in immune activation and inhibition.[1-5]

Tumors may *down-regulate co-stimulatory pathways.* [2-3]
Co-stimulatory receptors include:

- CD28
- CD40
- OX40
- CD137

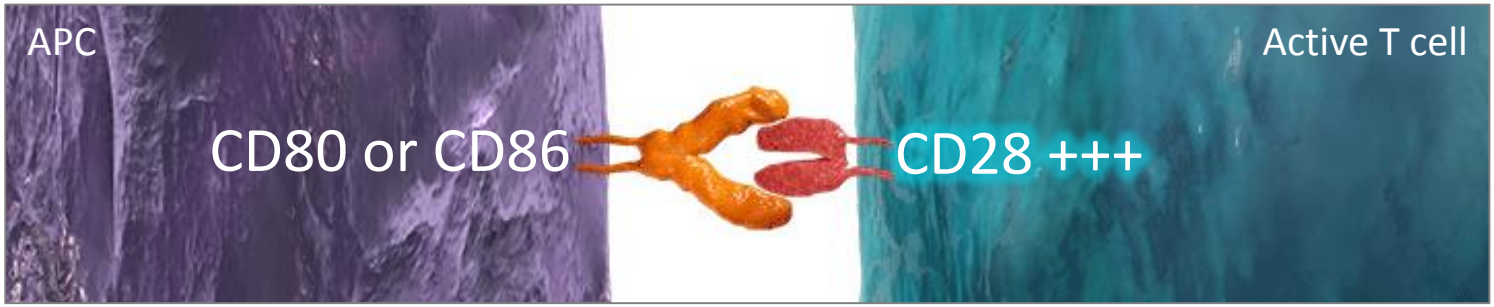
Tumors may *up-regulate immune checkpoints* (inhibitory signaling pathways). [2,3,5,6] Checkpoint pathway molecules include:

- LAG-3
- CTLA-4
- B7-H3
- PD-1

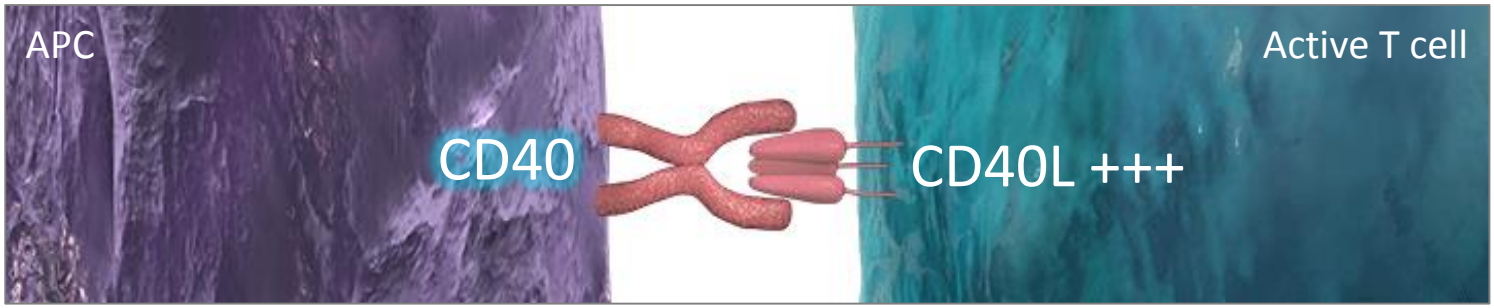
1. Baruah P, et al. *Immunobiology*. 2012;217(7):669-675 2. Hemon P, et al. *J Immunol*. 2011,186:5173-5183 3. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 4. Kirkwood JM, et al. CA *Cancer J Clin*. 2012;62:309-335 5. Zang X, et al. *PNAS*. 2007;104(49):19458-19463 6. Leitner J. *Eur J Immunol*. 2009;39:1754-1764. 7. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

Known molecules involved in activation

CD28 binding to its ligand CD80 or CD86 **enhances T-cell activation** via co-stimulation.[1,3]



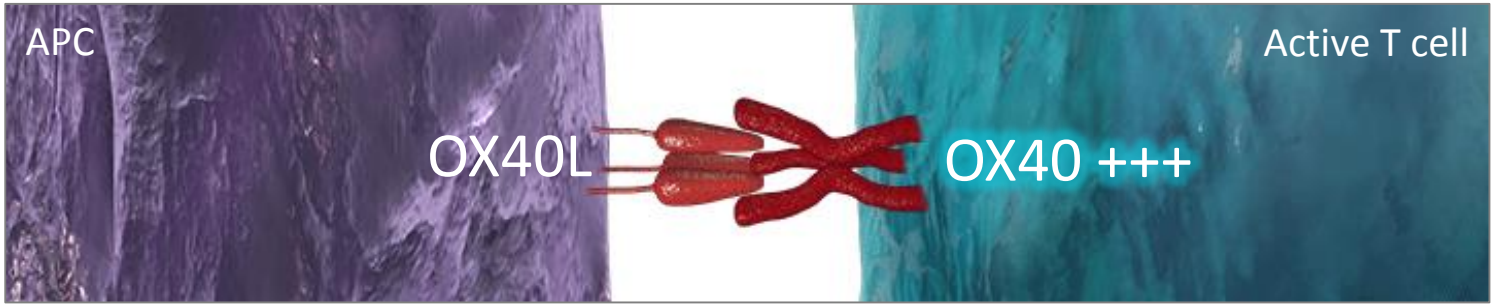
CD40 signaling **promotes APC activation** and enhances the antitumor immune response.[1,2]



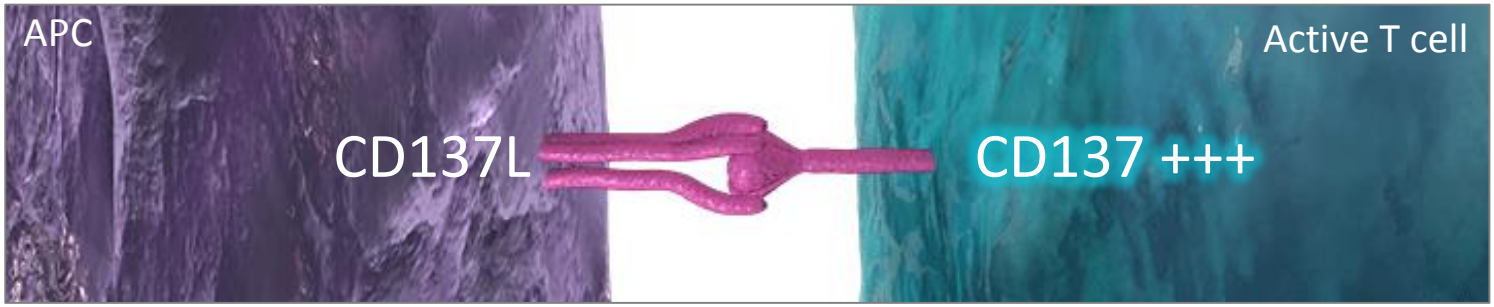
1. Pardoll DM. *Nat Rev Cancer*. 2012;11:252-264 2. Howland KC, et al. *J Immunol*. 2000;164(9):4465-4470 3. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004

Known molecules involved in activation

OX40 (aka CD134) promotes antitumor immune responses by **promoting T-cell proliferation and survival**.[1,2]



CD137 (aka 4-1BB) promotes the **activation and proliferation of T cells**.[1,3]

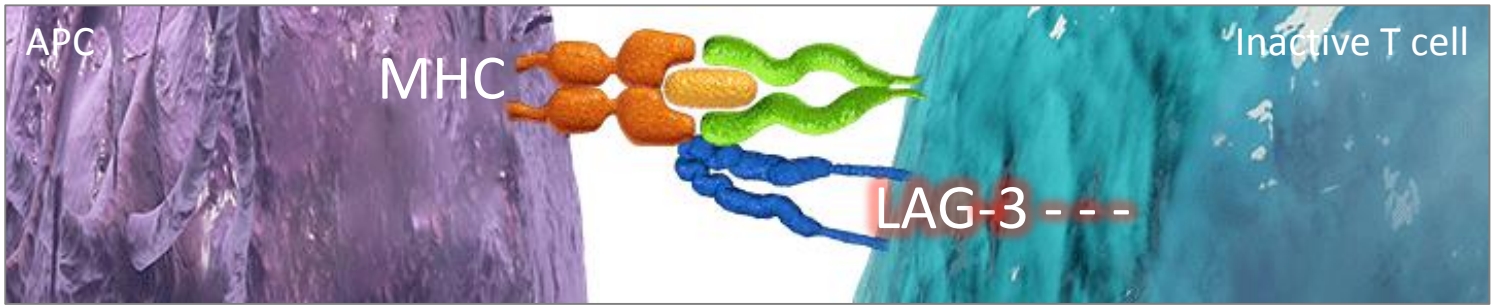


1. Pardoll DM. *Nat Rev Cancer*. 2012;11:252-264 2. Redmond WL, et al. *Crit Rev Immunol*. 2009;29(3):187-201 3. Palazon A, et al. *Cancer Res*. 2011;71:801-811

Known molecules involved in inhibition

LAG-3 (aka CD223) is an immune "checkpoint" molecule.[1]

- It can **inhibit T-cell activity** and serve as a modulator of T-cell activation.[1,2]



CTLA-4 is an immune "checkpoint" receptor that plays a key role in modulating T-cell function.[1,3]

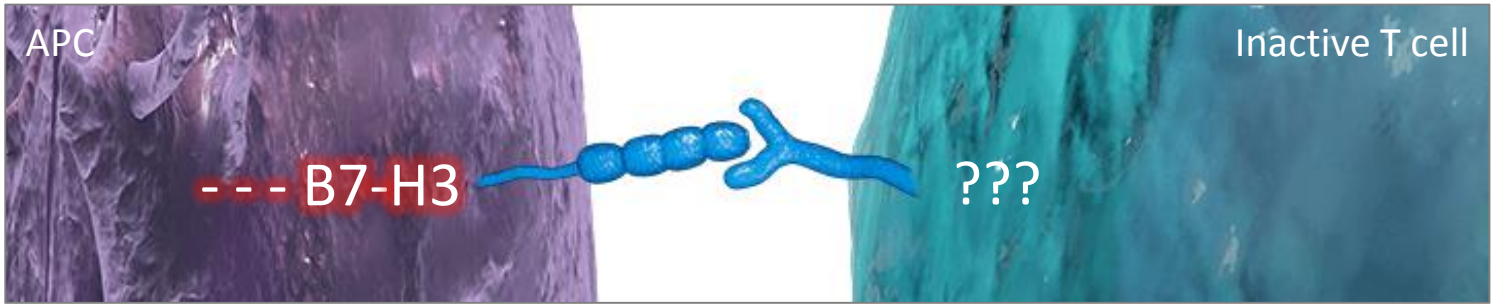
- Interaction of CTLA-4 on T cells with its ligand CD80 (aka B7-1) and CD86 on APCs leads **to T-cell inhibition**.[1,3]

1. Pardoll DM. *Nat Rev Cancer*. 2012;11:252-264 2. Workman CJ and Vignali DAA. *Eur. J Immunol.* 2003;33:970-979 3. Hastings, WD et al. *Eur J Immunol*. 2009 September: 39(9): 2492-2501

Known molecules involved in inhibition

B7-H3 (a member of the B7 family) is thought to be an immune "checkpoint" pathway.[1]

- It may **inhibit the T-cell response** beyond CD80/CD86 T-cell response.[2]
- Precise mechanism is under investigation.



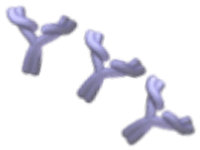
PD-1 is an immune "checkpoint" receptor that **inhibits the T-cell response** and plays a key role in modulating T-cell function.[1]

1. Pardoll DM. *Nat Rev Cancer*. 2012;11:252-264 2. Leitner J, et al. *Eur J Immunol*. 2009;39(7):1754-1764

Passive immunotherapies

Passive immunotherapies act on the tumor, in some cases using immune-based mechanisms to fight cancer, but they **do not require** the patient's own immune system to initiate a response.[1-4]

They include:



Tumor-directed monoclonal antibodies[5-6]

- Unconjugated
- Conjugated
- Single-armed

Cell therapies[7-9]

- Lymphokine-activated killer-cell therapy
- Tumor-infiltrating lymphocyte with IL-2
- Gene-modified lymphocytes

1. Brody J, et al. *J Clin Oncol*. 2011;29:1864-1875 2. Smits ELJM, et al. *Oncologist*. 2009;14:240-252 3. Rescigno M, et al. *Biochimica Biophys Acta*. 2007;1776:108-123 4. Mellman I, et al. *Nature*. 2011;480:480-489 5. Weiner LM, et al. *Nat Rev Immunol*. 2010;10:317-327 6. Merchant M, et al. *PNAS*. 2013;E2987-E2996 7. West EJ, et al. *Br J Cancer*. 2011;105:787-795 8. Chacon JA, et al. *PloS One*. 2013;8:e60031 9. Rosenberg SA. *Sci Transl Med*. 2012;4(127ps8):1-5

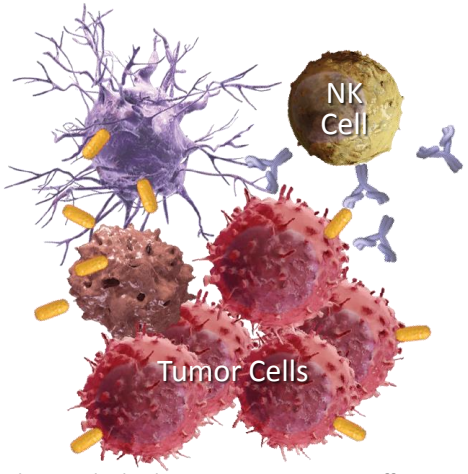
Tumor-directed monoclonal antibodies

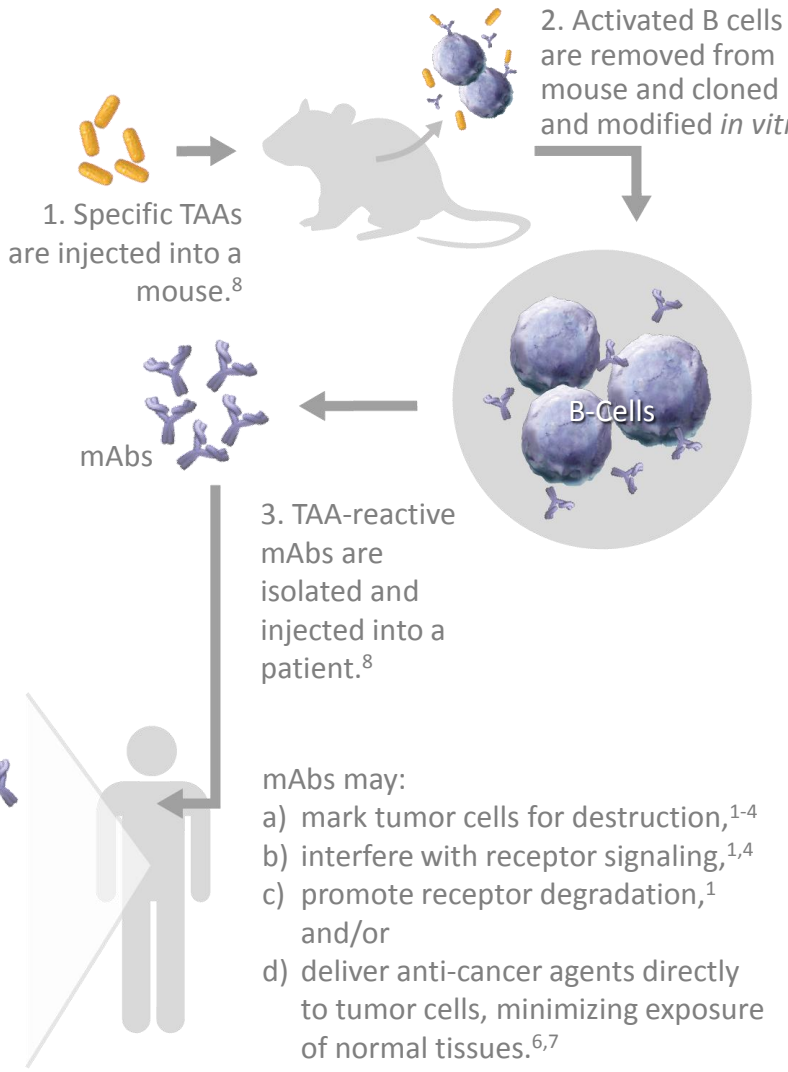
About

Monoclonal antibodies (mAbs) can be produced with an affinity to a specific tumor-associated antigen (TAA).[1] They are widely used in oncology therapy today.[5]

Potential adverse effects

Toxic autoimmune responses may arise against non-malignant cells with the same antigens, or even against cells containing *other* self-antigens.[9]





1. Hudis CA. *N Engl J Med*. 2007;357:39-51 2. Lundin J, et al. *Blood*. 2002;100:768-773 3. Coiffier B, et al. *Blood*. 2008;111:1094-1100 4. Smith MB, et al. *Drugs Today*. 2012;48:713-722 5. CenterWatch. http://www.centerwatch.com/drug-information/fda-approvals/drug-areas.aspx?AreaID=12. Accessed May 8, 2014 6. Verma S, et al. *N Engl J Med*. 2012; 367:1783-1791 7. Bodet-Milin C, et al. *Front Oncol*. 2013;3:1-13 8. Ossipow V & Fischer N. Monoclonal Antibodies: Methods and Protocols. 2nd ed. New York, NY; 2014 9. Amos SM, et al. *Blood*. 2011;118:499-509

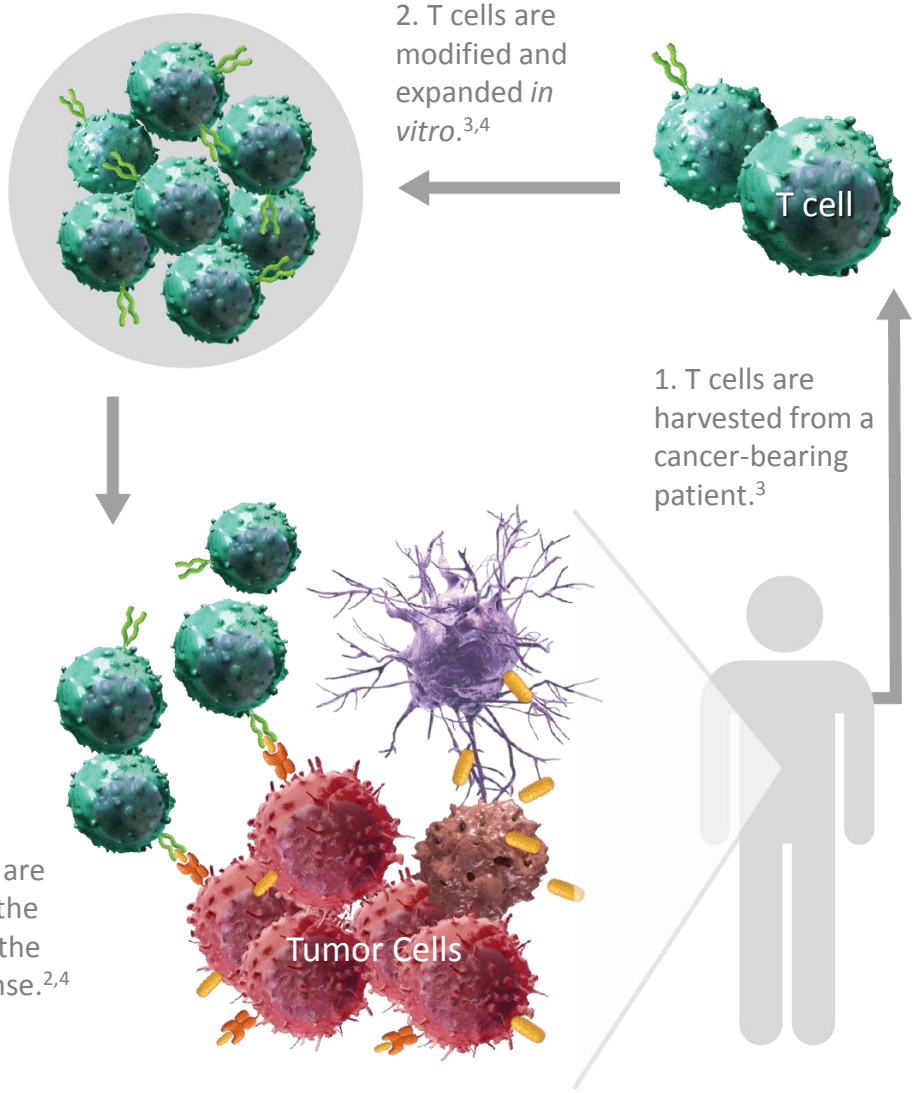
Cell therapies

About

Autologous immune cells are removed from the cancer-bearing patient, then activated and expanded in culture away from the immunosuppressive tumor environment.[1-4]

Potential adverse effects

Re-injected immune cells can target normal cells as well as tumor cells if they share the same target antigens.[1]



1. Amos SM, et al. *Blood*. 2011;118:499-509 2. West EJ, et al. *Br J Cancer*. 2011;105:787-795 3. Chacon JA, et al. *PloS One*. 2013;8:e60031 4. Rosenberg SA. *Sci Transl Med*. 2012;4(127ps8):1-5

Active immunotherapies

Active immunotherapies act directly on the body's **own immune system** to elicit an immune response to fight cancer.[1-4]

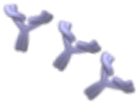
They include:

Therapeutic cancer vaccines[5]

- Dendritic-cell vaccines
- Tumor-cell vaccines
- Peptide/protein-based vaccines
- Recombinant vector vaccines

Cytokines[6]

- Interleukins
- Interferons
- Tumor necrosis factor-α
- Granulocyte-macrophage colony-stimulating factor
- Immunocytokines



Mediators of T-Cell activation[7]

- Immune checkpoints: CTLA-4, PD-1, PD-L1, LAG-3, B7-H3, B7-H4
- Co-stimulatory pathways: OX40, CD28, CD40, CD137

1. Brody J, et al. *J Clin Oncol*. 2011;29:1864-1875 2. Smits ELJM, et al. *Oncologist*. 2009;14:240-252 3. Rescigno M, et al. *Biochimica Biophys Acta*. 2007;1776:108-123 4. Mellman I, et al. *Nature*. 2011;480:480-489 5. Schlom J. *J Natl Cancer Inst*. 2012;104:599-613 6. List T, Neri D. *Clin Pharmacol*. 2013;5(suppl 1):29-45 7. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264

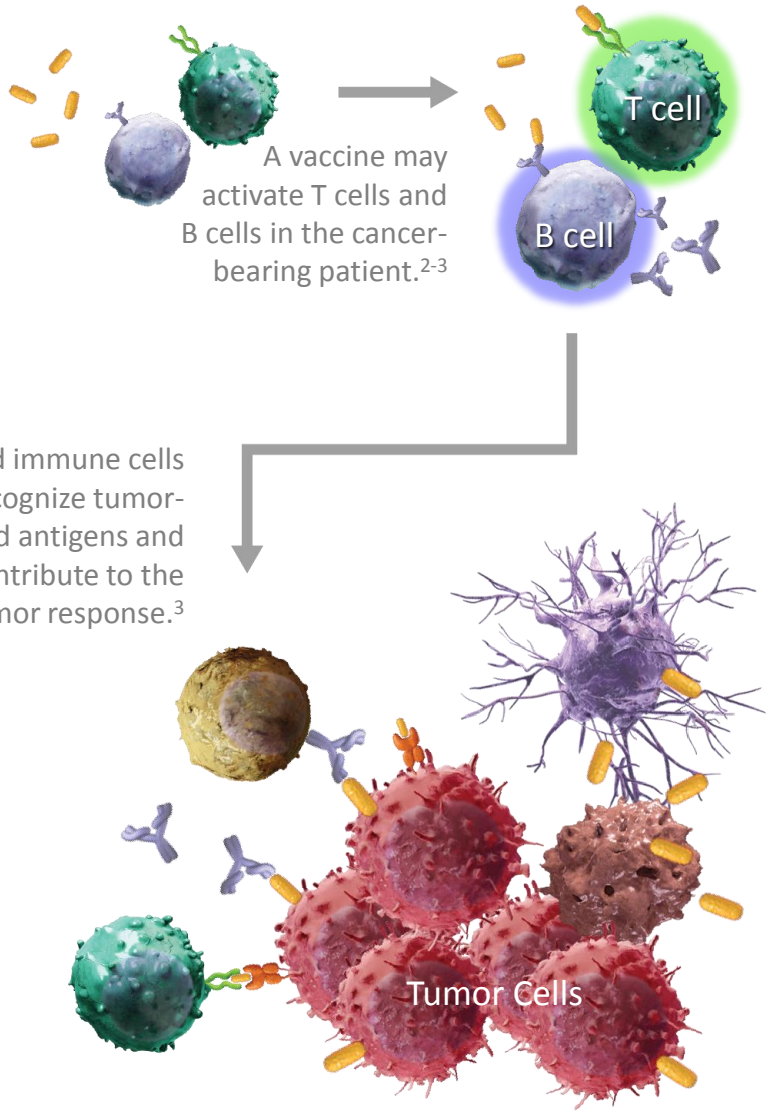
Therapeutic cancer vaccines

About

Therapeutic cancer vaccines may prime the immune system to attack existing cancer cells in the body by introducing immune cells to one or more tumor-associated antigens.[1]

Potential adverse effects

Cancer vaccines may lead to the generation of T cells that attack self-antigens in normal healthy tissue.[4]



1. American Cancer Society. http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/immunotherapy-cancer-vaccines. Accessed May 12, 2014
2. Bedikian AY, Del Vecchio MD. *Expert Opin Biol Ther*. 2008;8:839-844 3. Schlom J. *J Natl Cancer Inst*. 2012;104:599-613 4. Amos SM, et al. *Blood*. 2011;118:499-509

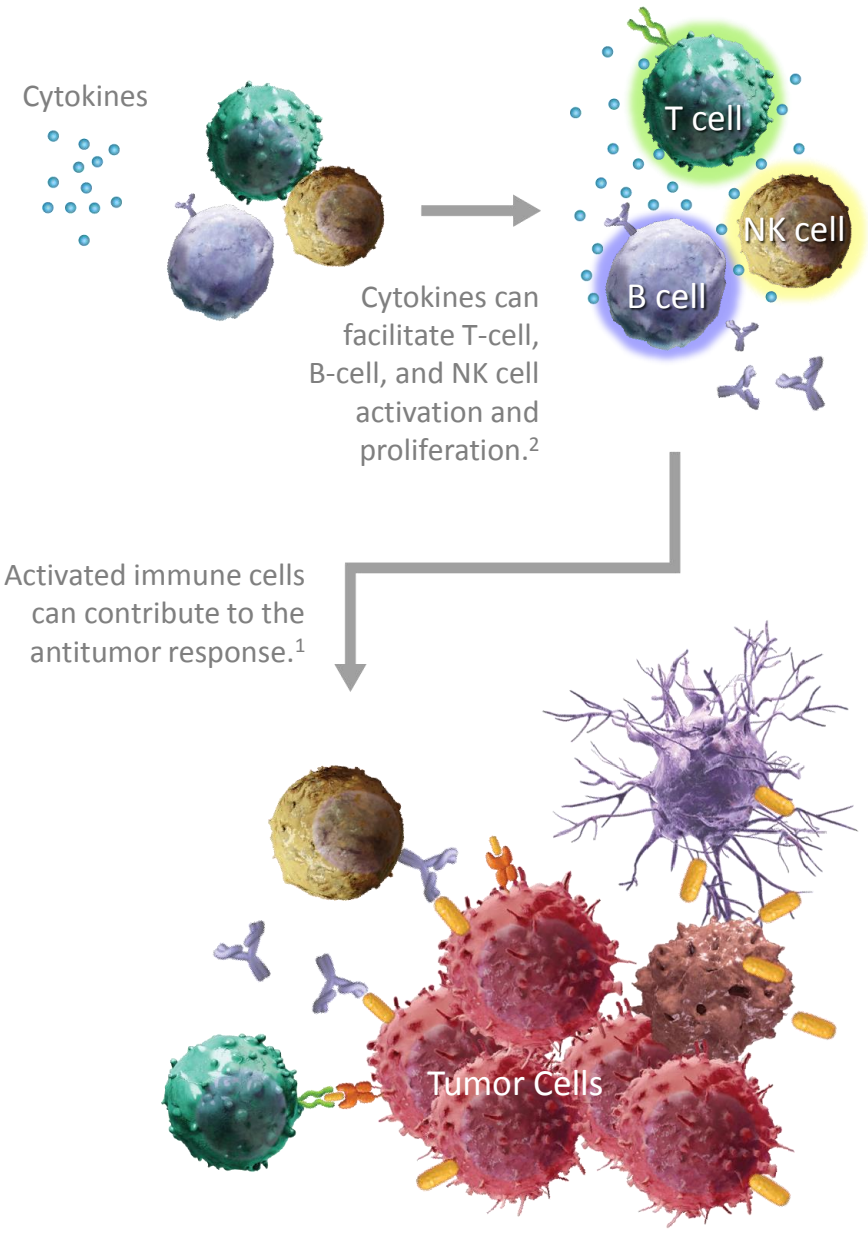
Cytokines

About

Cytokines are small proteins that modulate the proliferation, activation, and survival of lymphocytes[1]. They are thought to boost the effector functions of these cells, thereby strengthening the antitumor response.[2]

Potential adverse effects

Increased lymphocyte activity may be directed against normal tissues, leading to T-cell-, B-cell-, or NK cell-mediated autoimmunities.[1]



1. Amos SM, et al. *Blood*. 2011;118:499-509 | 2. List T, Neri D. *Clin Pharmacol*. 2013;5(suppl 1):29-45.

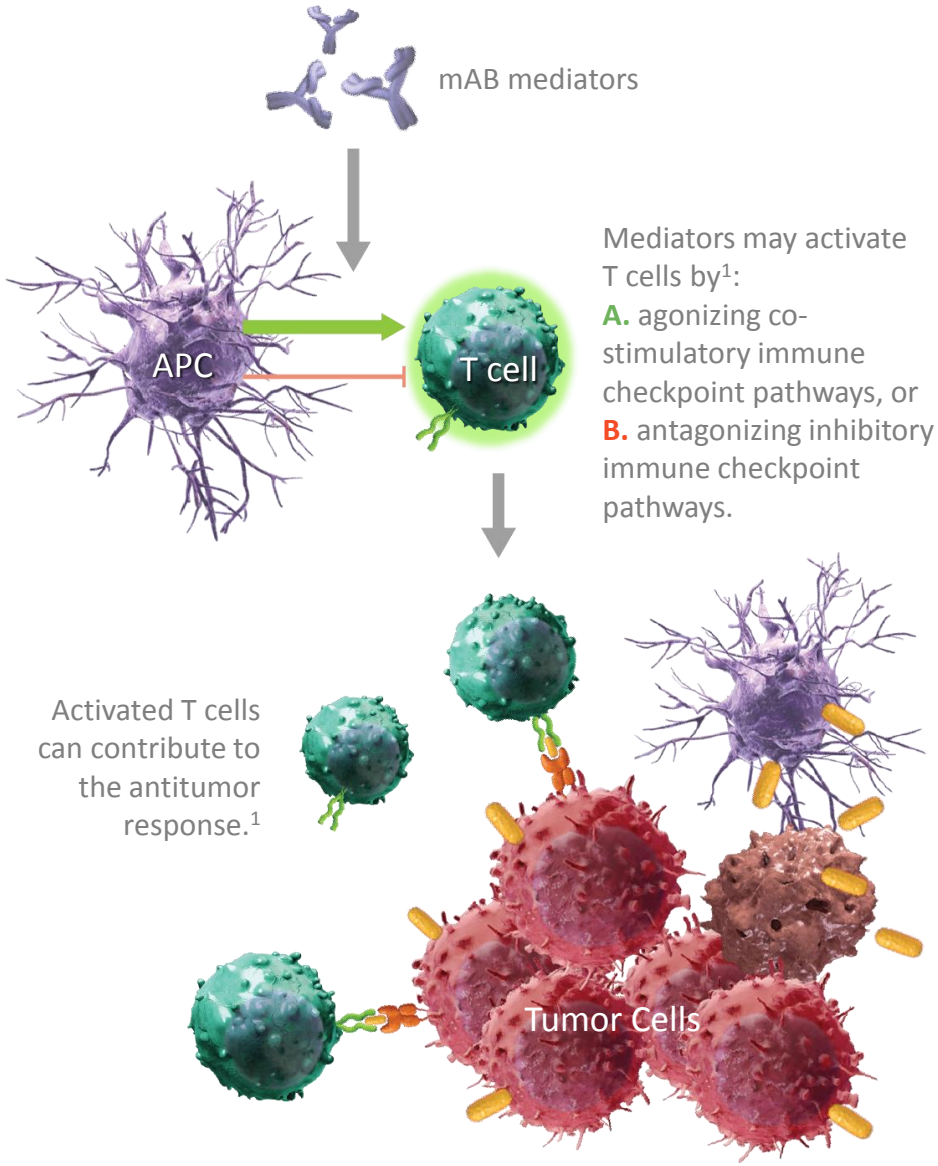
Mediators of T-cell activation

About

Mediators of T-cell activation are monoclonal antibodies that have been engineered to either agonize or antagonize specific immune pathways thought to be manipulated by cancer cells to impede the antitumor response. In doing so, they may be able to strengthen the antitumor response.[1]

Potential adverse effects

Interfering with immune checkpoints can cause a general disruption in immune homeostasis, leading to a greater number of self-reactive T cells that attack healthy tissues.[2]



1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 2. Amos SM, et al. *Blood*. 2011;118:499-509 2. Amos SM, et al. *Blood*. 2011;118:499-509

I-O therapy-associated AEs

I-O therapy-associated adverse events (AEs) target certain organ systems[1]:

- Skin[1-5]
- Endocrine system[2,4-8]
- Liver[2,5,9,10]
- Gastrointestinal tract[2,5,7,11]
- Nervous system[5,8,12,13]
- Eyes[1,4,14-16]
- Respiratory System[1,5,8,13,17]
- Hematopoietic cells[7,10,18,19]

1. Amos SM, et al. *Blood*. 2011;118:499-509 2. Phan GQ, et al. *PNAS*. 2003;100:8372-8377 3. Rosenberg SA, White DE. *Immunother Emphasis Tumor Immunol*. 1996;19:81-84 4. Chianese-Bullock KA, et al. *J Immunother*. 2005;28:412-419 5. Chow LQ. *Am Soc Clin Oncol Educ Book*. 2013:280-285 6. Soni N, et al. *Cancer Immunol Immunother*. 1996;43:59-62 7. Ronnblom LE, et al. *Ann Intern Med*. 1991;115:178-183 8. Fraenkel PG, et al. *J Immunother*. 2002;25:373-378 9. Lamers CH, et al. *J Clin Oncol*. 2006;24:e20-e22 10. Roskrow MA, et al. *Leuk Res*. 1999;23:549-557 11. Parkhurst MR, et al. *Mol Ther*. 2011;19:620-626 12. Pellkofer H, et al. *Brain*. 2004;127:1822-1830 13. Smalley RV, et al. *Blood*. 1991;78:3133-3141; 14. Dudley ME, et al. *J Clin Oncol*. 2008;26:5233-5239 15. Yeh S, et al. *Ophthalmology*. 2009;116:981-989 16. Robinson MR, et al. *J Immunother*. 2004;27:478-479 17. Morgan RA, et al. *Mol Ther*. 2010;18:843-851 18. Kochenderfer JN, et al. *Blood*. 2010;116:4099-4102 19. Lin TS, et al. *J Clin Oncol*. 2010;28:4500-4506

Clinical implications of immune-associated AEs

Because most tumor-associated antigens are also expressed by some amount of normal cells in the body, the potential exists for toxicity against these healthy tissues.[1]

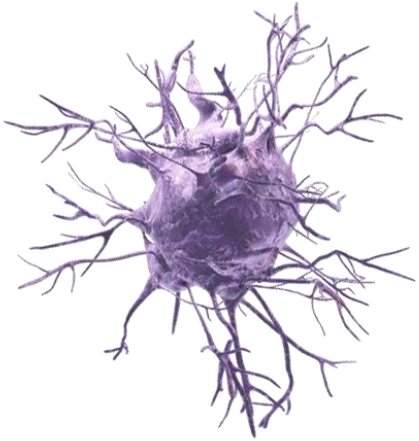
- AEs can be serious and potentially fatal
- Remain vigilant throughout and after treatment
  - Educate and encourage patients to monitor for and report symptoms of immune-associated AEs

Not all AEs can be managed and some patients may have to discontinue treatment. To give patients the best chance of therapeutic success, follow management guidelines for immune-associated AEs.

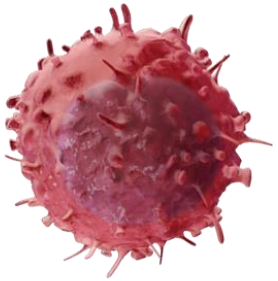
1. Amos SM, et al. *Blood*. 2011;118:499-509

Image legend

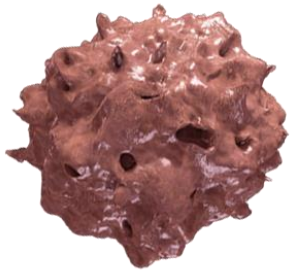
Antigen



APC



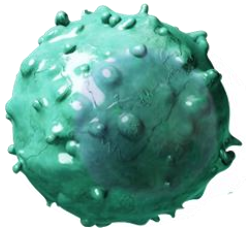
Tumor cell



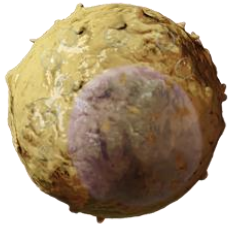
Apoptotic tumor cell

Antibodies

B cell



T cell



NK cell