




**Cancer Immunology:**  
The Best Offense is a Good Defense





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**Take Home Message**

Scientific discoveries are helping us to better understand how the immune system can be used to fight cancer.





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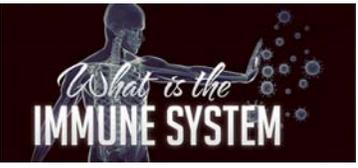
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**The Immune System has 3 Main Roles:**

1. Protect us from infections.
2. Provide a barrier from foreign substances.
3. **Defense against cancer.**





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**If the immune system protects us from cancer, why does it still occur?**

- o Compromised immune system can contribute.
- o Healthy people get cancer. Why?
- o Cancer poses several challenges to the immune system. While cancers can express unique proteins (antigens) that can be recognized by the immune system, cancer is not a "foreign" tissue - so it can hide from immune detection.




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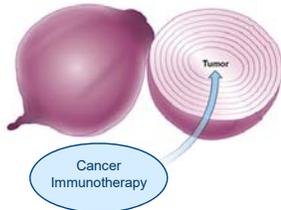
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**Our Immune System is Designed to Ignore 'Self' Tissues**

-Cancer takes advantage of the fact that it is a 'self' tissue.




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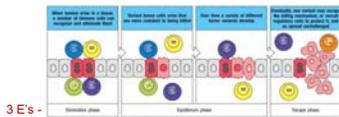
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**History of Cancer Immunology: Periods of Enthusiasm and Skepticism**

-The Immune Surveillance Hypothesis (late 1950s)



-Immune Surveillance Hypothesis Modified to Immunoediting Model (2002 - Schreiber & colleagues)




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## Results of Early Cancer Immunotherapies Contributed to Skepticism

From the 1970s through the 1990s, the field focused on:

1. Only strategies that directly activated the immune system
2. Use of single-arm therapies

*\*\* It has become clear that cancer immunotherapies will be most successful when used in combinations with other immunotherapies or other types of treatments.*




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## Cancer Immunotherapy Formally Recognized

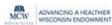
Science Magazine's Breakthrough of the Year - 2013



*-Recognized cancer immunotherapy & the science behind it*

Spurred by advances in 2 main areas:

1. Immune checkpoint blockade
2. CAR T cell therapies




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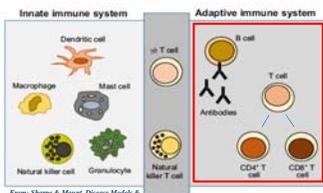
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## Cancer Immunotherapy: Which Cells?

Innate Immunity:  
(immediate responders)  
NK cells  
Dendritic cells  
Macrophages  
Granulocytes  
 $\gamma\delta$  T cells  
NKT cells

Adaptive Immunity:  
(delayed responders)  
B cells  
T cells



From: Sharpe & Munn, Disease Models & Mechanisms, 8:357, 2015.




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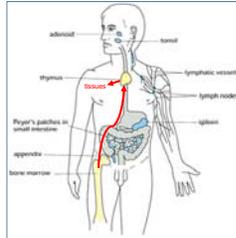
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## Cancer Immunology: Focus on T Cells

- T cell precursors migrate from bone marrow to the thymus
- T cells mature & become "educated" in the thymus to recognize foreign substances
- T cells are very important to cancer immunity



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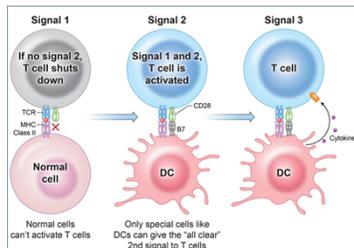
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## How does a T cell become activated?



- Signals 1 & 2 are required for a T cell to become fully activated
- Once a T cell is fully activated it no longer requires Signal 2; it only needs to see its antigen (Signal 1)
- The fully-activated T cells can kill cancer if they see the antigen on surface



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## Types of Cancer Immunotherapy

1. Vaccines
2. Antibodies, including those that block immune checkpoint proteins
3. Cell therapies



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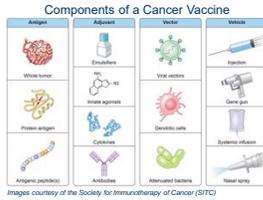
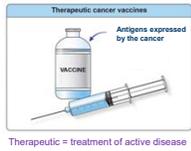
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## Vaccines



-A better way to use cancer vaccines could be as prevention (e.g., HPV vaccine), or in combination with other immunotherapies.



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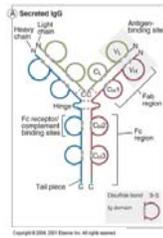
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## Monoclonal Antibodies

- These proteins are made by B cells. Only one type of antibody is made by a single B cell.
- Technology developed in 1975 by Kohler, Millstein & Jerne (Nobel Prize awarded in 1984).
- Monoclonal antibodies have been used throughout medicine, and have become important agents in treating cancer.
- They have been used to block "immune checkpoint proteins", and the antigen-binding portions have been used to make chimeric antigen receptors (CARs).



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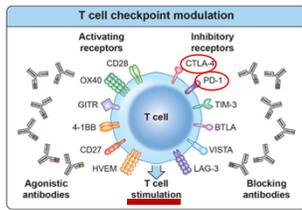
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## Monoclonal Antibodies: Immune Checkpoint Blockade

Antibodies can directly activate T cells by binding to certain receptors



Antibodies can block proteins that "turn the T cells off" (inhibitory)



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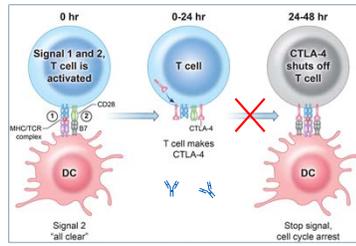
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## The CTLA-4 Immune Checkpoint

- Cytotoxic T-Lymphocyte Associated Protein 4
- Negative regulator of T cell activation
- FDA licensed antibodies are available for treatment of some cancers – “reinvigorates” the T cell immune response
- Does have some negative side effects



Courtesy of the Society for Immunotherapy of Cancer (SITC)



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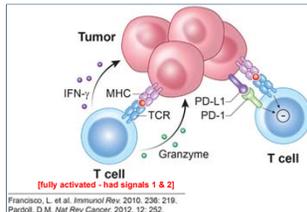
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## The PD-1/PD-L Immune Checkpoint

- PD-1 (programmed death receptor-1) binding “turns the T cells off”
- T cell PD-1 interacts with PD-Ls (1 or 2)
- Cancer cells can express PD-Ls (bind to PD-1) to shut down the T cells
- FDA licensed antibodies available to block PD-1/PD-L binding for some cancers  
---- anti-cancer responses better than CTLA-4 with fewer side effects



Francisco, L. et al. *Immunity Rev* 2010; 236: 219.   
Parodi, D.M. *Nat Rev Clin Oncol* 2012; 12: 252.   
Courtesy of the Society for Immunotherapy of Cancer (SITC)



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## 2018 Nobel Prize in Physiology or Medicine



CTLA-4

PD-1/PD-L

Jim Allison

Tasuku Honjo



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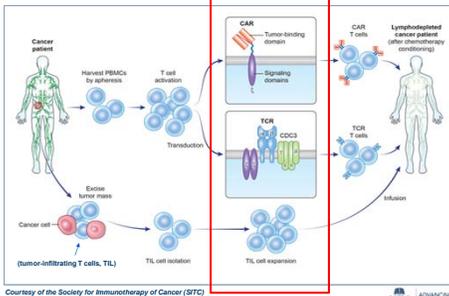
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## T Cell Transfer Therapies: 3 Types

The goal of T cell transfer is to overwhelm the cancer with a large number of T cells that can recognize and kill the cancer.

- Isolate T cells from tumors and expand
- Genetically engineer the T cells and expand



Courtesy of the Society for Immunotherapy of Cancer (SITC)

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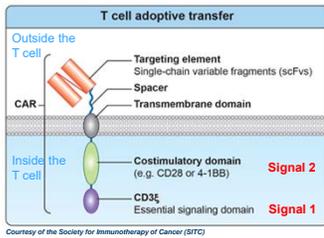
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## CAR (Chimeric Antigen Receptor)



Courtesy of the Society for Immunotherapy of Cancer (SITC)

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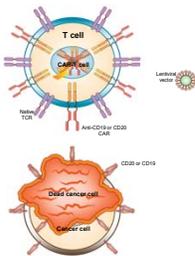
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## How Do the CARs get Expressed?



This "CAR" therapy has had impressive success for patients with B cell leukemias or lymphomas that have failed all other treatments!

Image courtesy of Dr. David Porter and the University of Pennsylvania

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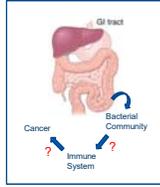
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### Could the bacteria in our gut (microbiome) dictate whether or not cancer immunotherapy works?

Two scientific papers were published in 2015 in the journal 'Science', where certain bacteria had to be present in the guts of mice in order for CTLA-4 or PD-1 blockade to work.



**MORE TO COME!!**



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### SUMMARY

- o It is now clear that the immune system can be mobilized to fight cancer
- o Recent advances in cancer immunotherapy would not have occurred without the persistence of scientists in the field
- o Many more exciting discoveries are on the horizon
- o The best "offense" against cancer will likely require combination immunotherapies



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### Additional Resources



<https://www.sitcancer.org/>

Scientific Article: Dr. Olivera Finn, "A Believer's Overview of Cancer Immunosurveillance and Immunotherapy", The Journal of Immunology, volume 200, pages 385-391.



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