

Tumor immunology and immunotherapy

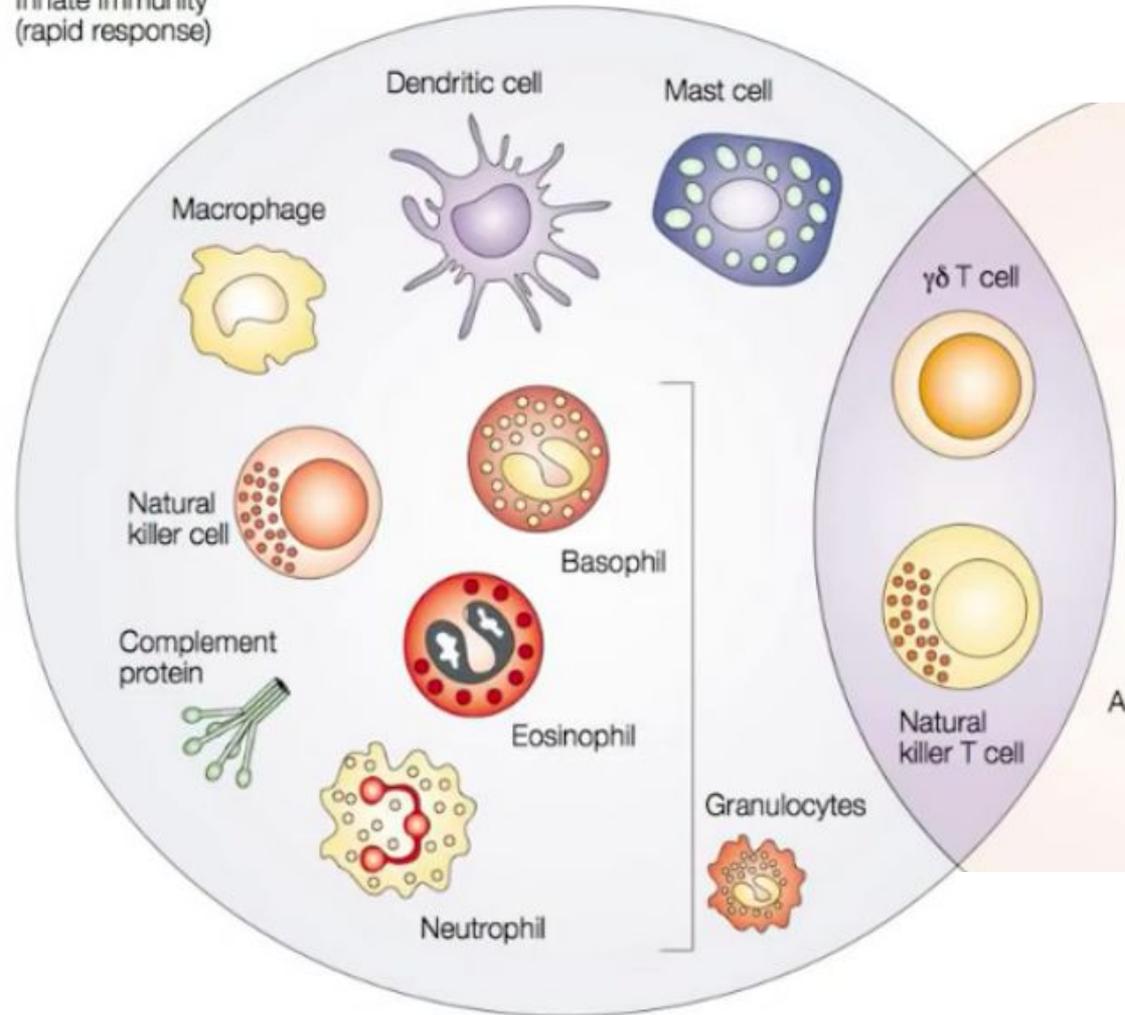
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What are the different parts of the immune system?

Innate immune system:

- The **first** line of defense,
- It is **pre-existing** and ready to respond to infection, inflammation or cancer.
- Examples: Macrophages and neutrophils.
- **Not educated and not selective**, (kill first, ask later)

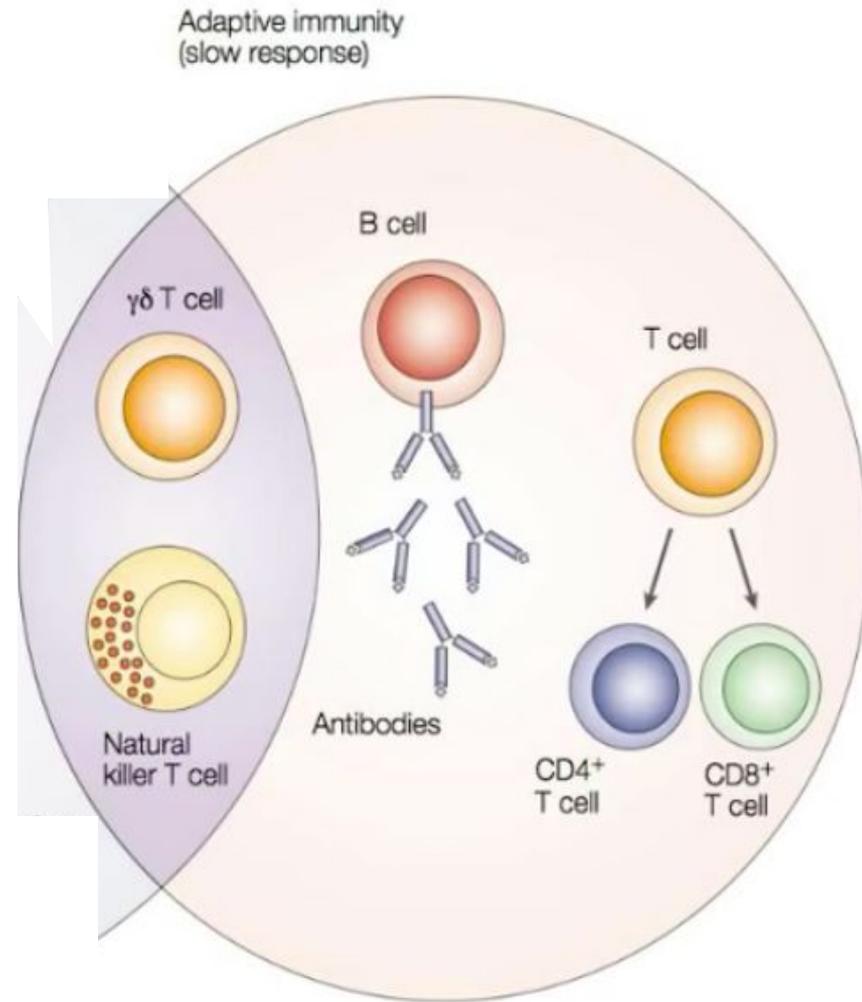
Innate immunity
(rapid response)



What are the different parts of the immune system?

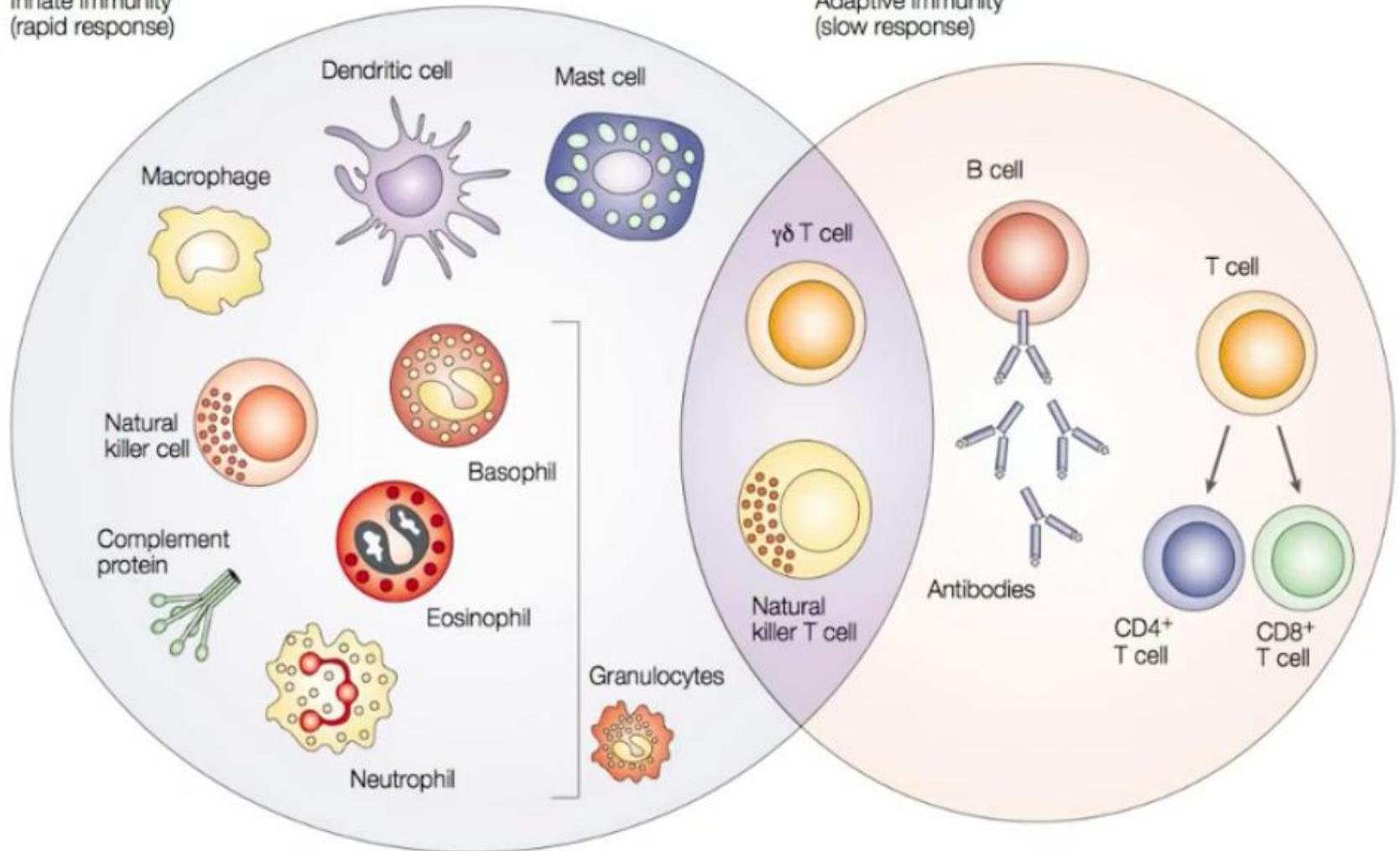
Adaptive immunity:

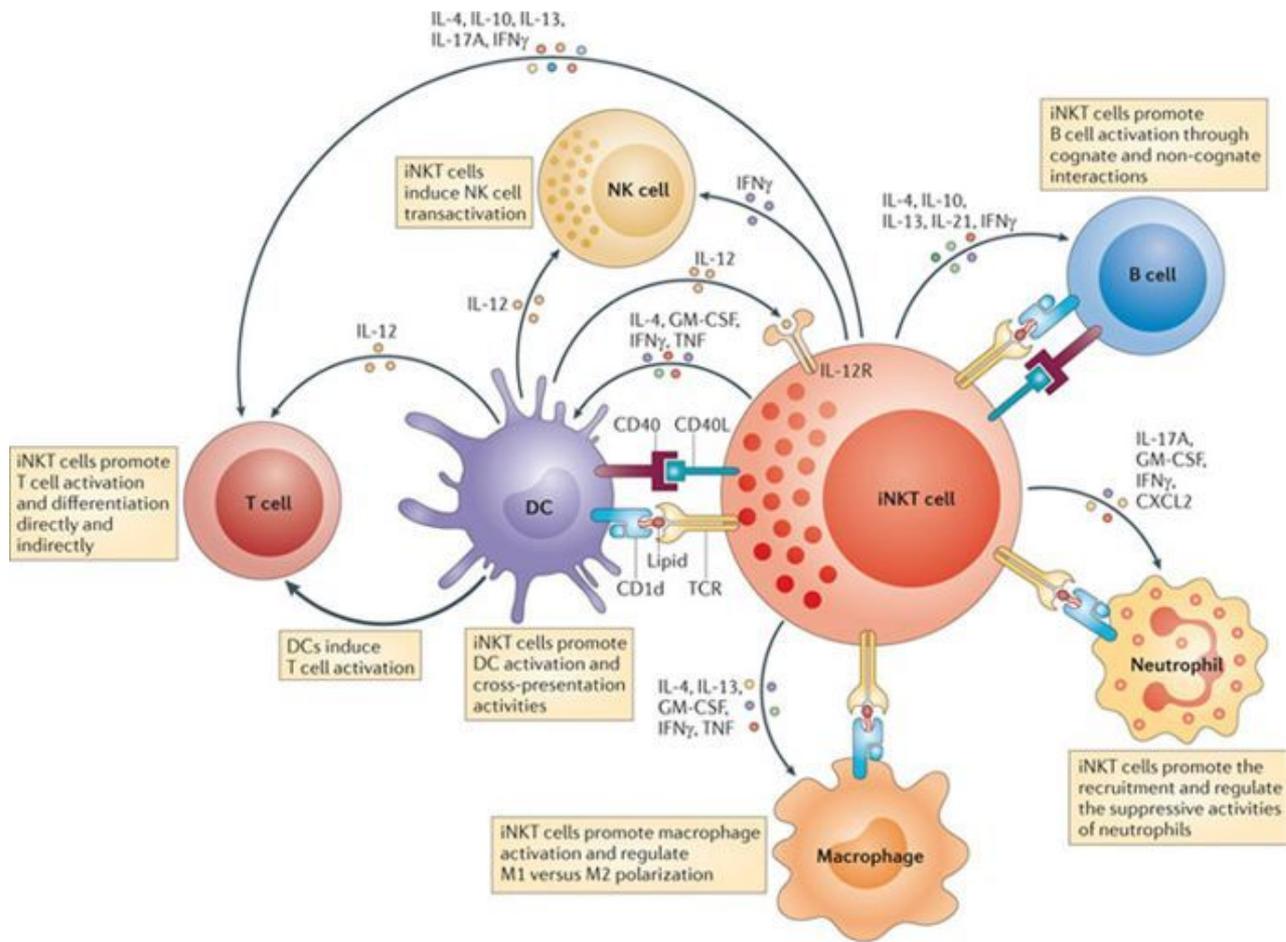
- B and T cells, they are
- Selective
- They are “educated” in that they can “learn”
- Have memory and recall prior exposure to bacteria or other stimuli.
- It is specific and have selective not general action.



Innate immunity
(rapid response)

Adaptive immunity
(slow response)





Innate vs. Adaptive immunity

	Innate immunity	Adaptive immunity
Encoding of receptors	Germline	somatic
Distribution of receptors	Non Clonal (not specific)	Clonal (very specific)
Repertoire of receptors	Limited	Very large
Speed	Fast	Slow
Long-lasting memory	No	Yes

Tumor

Many **genetics** and **environmental** factors can cause tumors to form for instance UV radiation from the Sun can damage DNA and other structures of **melanocytes**; the pigment producing cells in the skin.

Chronic damage to melanocytes by UV radiation leads to most cases of melanoma, which is a type of skin cancer.

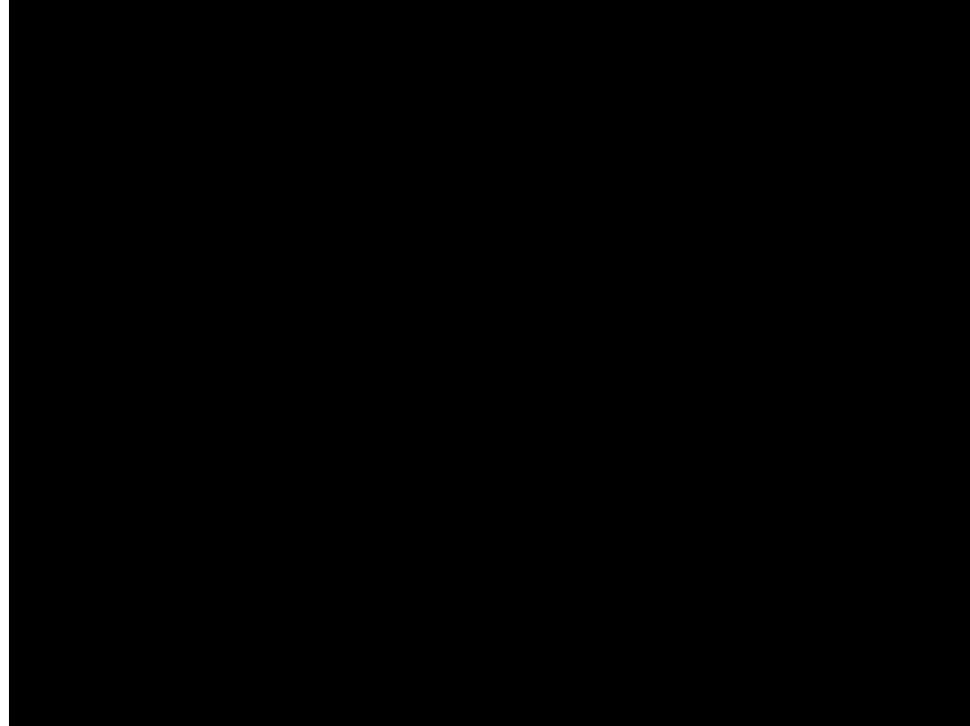


As melanoma grow they can eventually spread to other sites in the body such as the lunge and the liver.

The cells of the immune system are continuously monitoring our tissues

1- Natural killer cells cells, recognize **Stress-associated molecules** on damaged and cancerous cells

2- Dendritic cells activate cytotoxic T cells which can sense **Tumor-associated antigens**, using their T cell receptor and their Co receptors.



Once activated NK cells and cytotoxic T cells release perforin and granzymes, these molecules punch holes in the surface of the tumor cells causing them to die by apoptosis.



3- Helper T cells support these responses, they help DCs to activate cytotoxic T cells

and

they produce cytokines such as IFN-gamma that recruit and activate more NK cells.



As the tumor evolves genetic changes occur that can give some tumor cells a **survival advantage**.

This means that tumors are often **heterogeneous**, for instance tumor cells may **no longer express** the molecules that are sensed by killer immune cells as the immune system continues to kill the tumor cells it can recognize.

The cells it cannot sense are more prevalent, this is **immuno-editing**, it leads to emergence of a tumor that **cannot be detected by the immune system**.

Tumor cell protect itself

- Some tumor cells actively **suppress T cells** by expressing inhibitory molecule such as PD L1.
- **PDL1** binds the **PD1** receptor on T-cells and deactivates them this is an immune checkpoint.



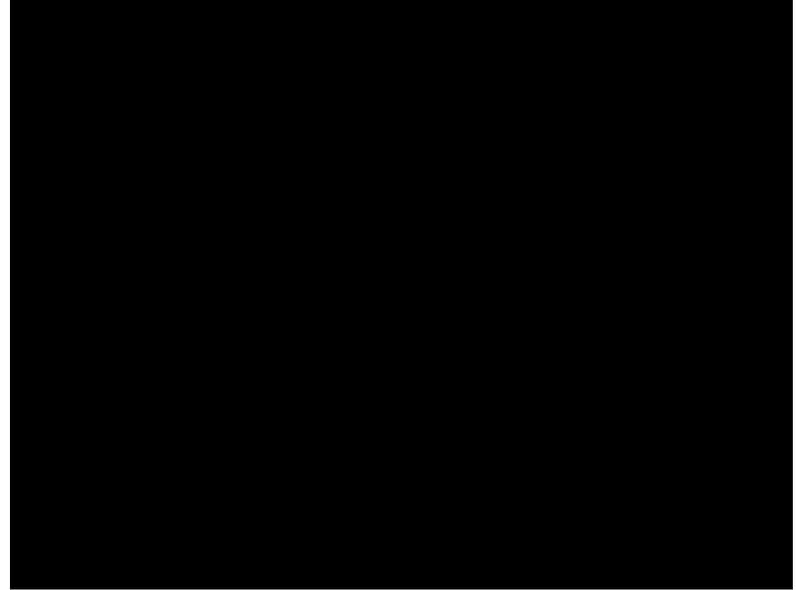
Tumor cell protect itself

In addition, tumor cells can **attract immune cells that suppress** the activity of other immune cells thereby supporting tumor growth.

These immunosuppressive cells, **include regulatory T cells** and certain types of **myeloid cells**.

Therefore the tumor **microenvironment** is like the scene of battle between two opposing immune responses.

One side of the immune system is attacking the tumor while the other side is helping it. to grow scientists are developing immunotherapies to help strengthen the immune attack.



There are more than 200 different types of cancers.

Chemotherapy: drugs that induce cancer cells to die

Immunotherapy: using the body's own immune system to fight cancer.

Involves activating immune cells and getting them to recognize cancer tissue as different from body cells

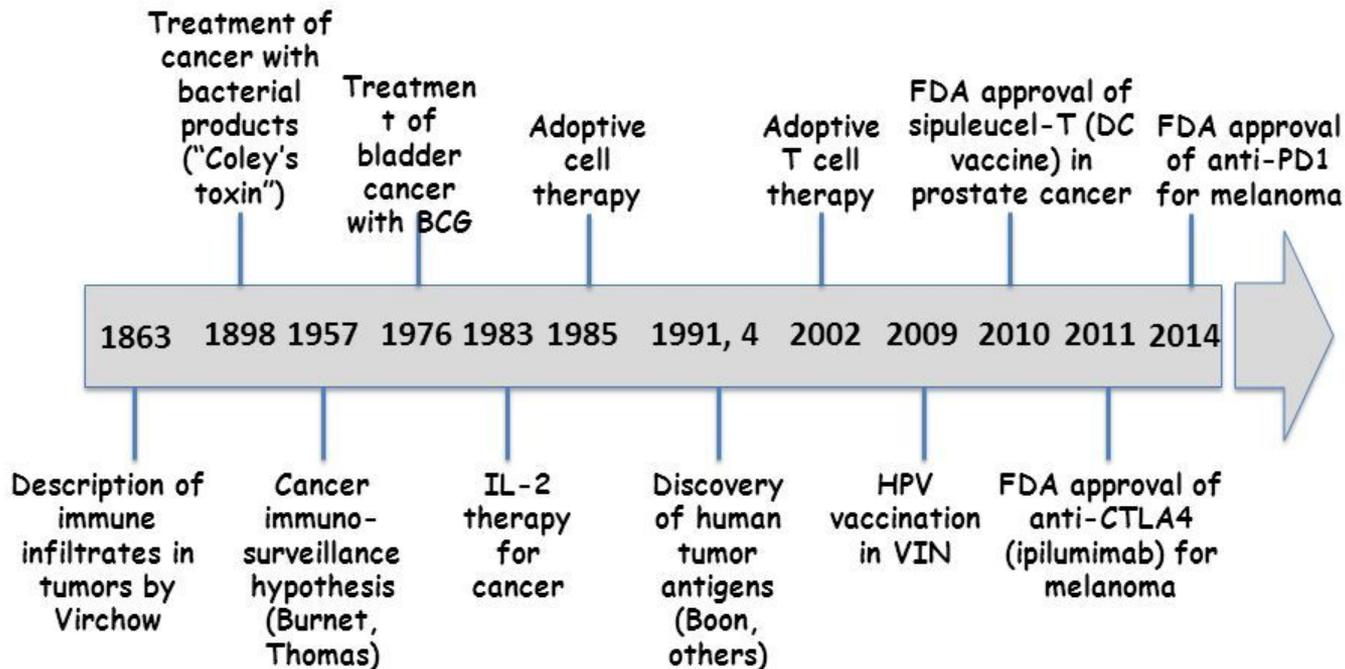


The history of cancer immunotherapy: from empirical approaches to rational, science-based therapies

The idea goes back to the 17th century!

to

William Coley



Coley toxin

- Heat-inactivated bacteria to induce inflammation (acute)



Figure 1 | Treatment with Coley's toxins. A patient with a large abscess of the jaw and a deformed mandible was treated by Coley in 1894. a | Photograph after 23 injections with Coley's toxins; tumor had diminished to about half its original size. b | Photograph after further treatment with Coley's toxins. In his 1910 lecture at the Royal Society of Medicine Coley reported that the patient was still alive and well, though emaciated. (with permission, from [1], 17-18) (1910) Royal Society of Medicine.



Cancer Immunotherapy



“In 1891, William B. Coley injected streptococcal organisms into a patient with inoperable cancer. He thought that the infection he produced would have the side effect of shrinking the malignant tumor. He was successful, and this was one of the first examples of immunotherapy. Over the next forty years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. These products became known as Coley's Toxins. He and other doctors who used them reported excellent results, especially in bone and soft-tissue sarcomas.”

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1888599/>

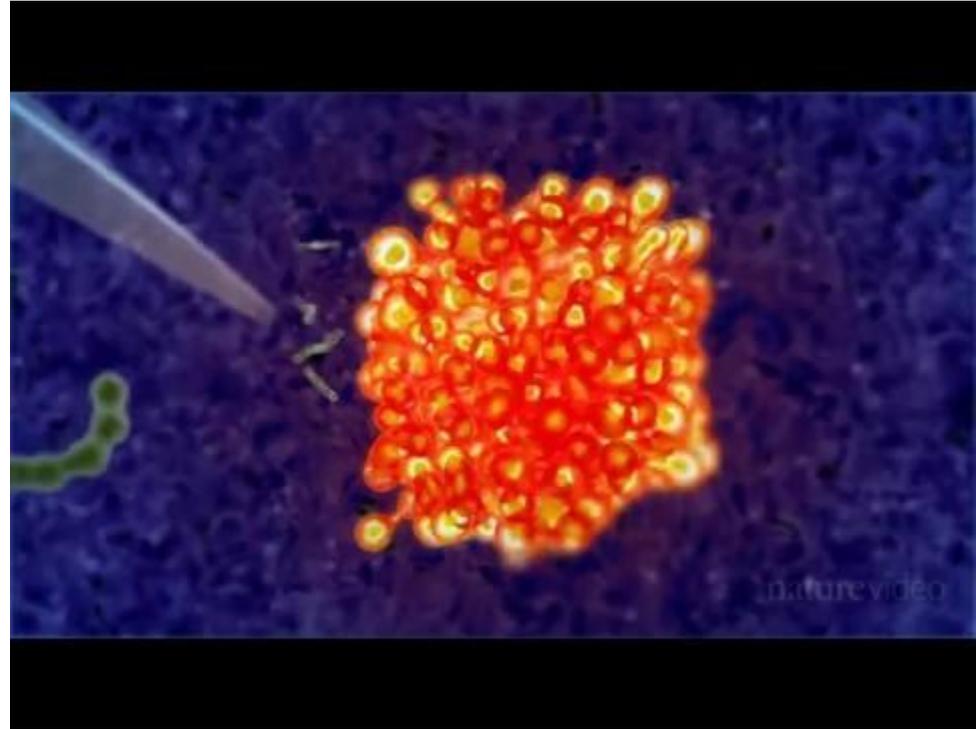
Coley's toxins

Coley injected bacteria into tumors and watched them shrink!

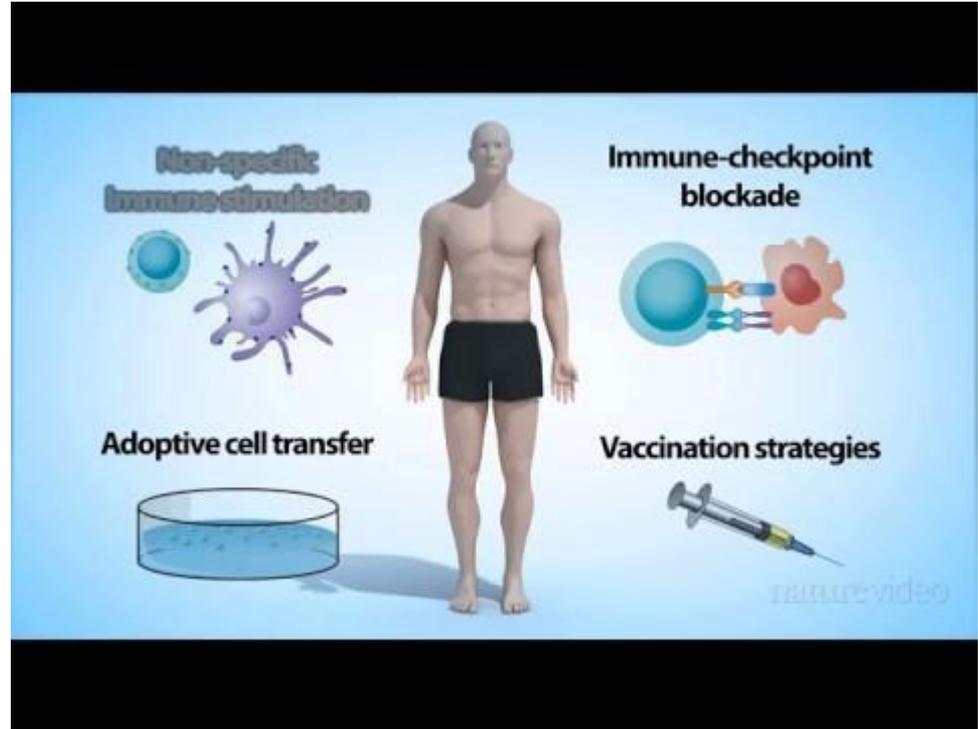
The bacteria seemed to provoke immune response

The immune system is highly complex and during the 20th century scientists struggled to turn Coley's observation into effective cancer treatments

In the 21 st century variety of immunotherapies are finally making their way into the clinic



Immunotherapy four general strategies



Non-specific immune stimulation strategy: **injecting molecules**

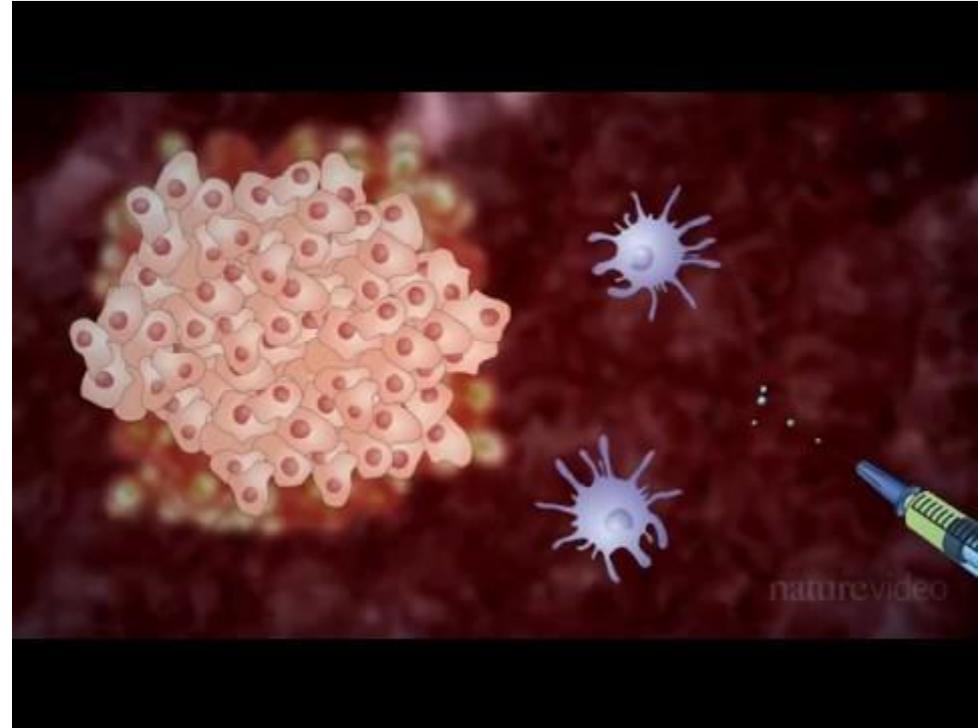
Used to give a **general boosts** to the immune system *in vivo*

Some of the immune cells, such as APCs need to be activated

By injecting molecules that bind to receptors and activate them

This alert other immune cells to be activated such as these T cells

When activated T cells attack and kill malignant cells



Non-specific immune stimulation strategy: IL-2 and IFN α

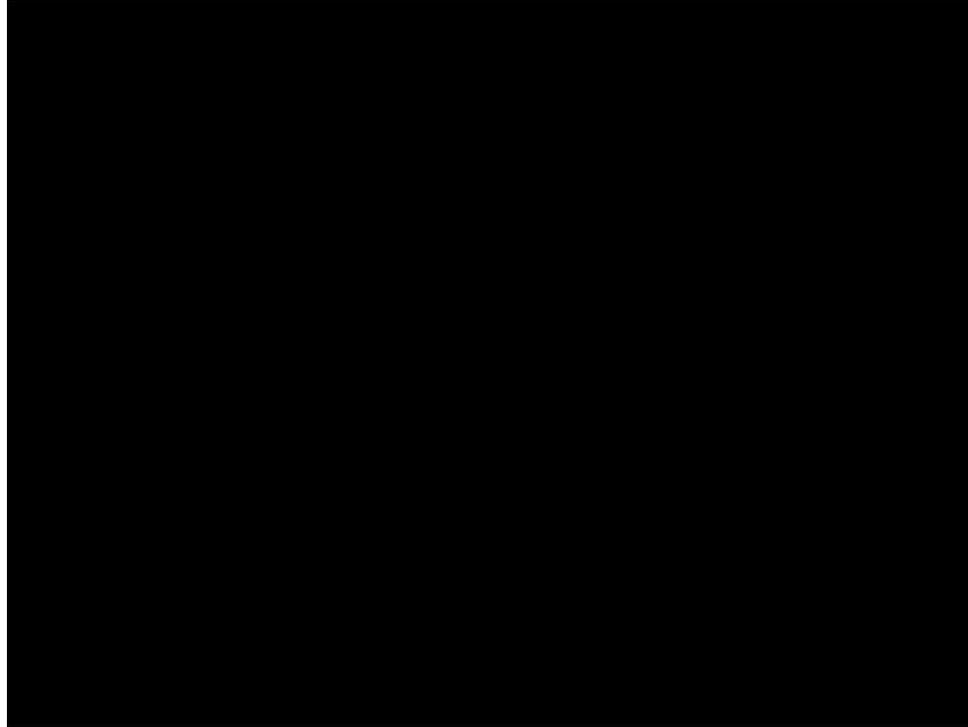
For full activation the cytokines (small signaling molecules) are needed

IFN α and IL-2 have been developed as drugs.

They have been approved for treatment of some forms of cancer including melanoma

Non-specific immune stimulation strategy: IL-2 and IFN α

- Treating patients with cytokines such as IL-2 and IFN α can also boost the activity of anti-tumor immune cells.

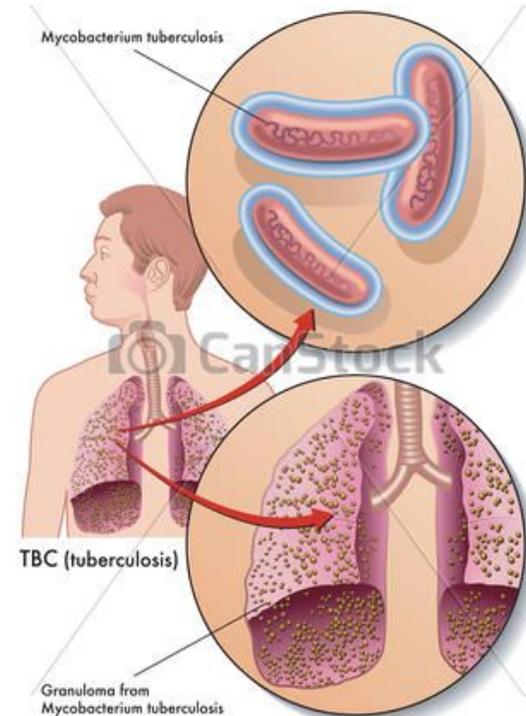


Bacillus Calmette-Guerin (BCG) Vaccine

BCG vaccine is a weakened but live *Mycobacterium bovis* vaccine primarily used against tuberculosis (TB)

Tuberculosis (TB) is an infectious disease usually caused by *Mycobacterium tuberculosis* (MTB) bacteria.

Tuberculosis generally affects the lungs, but can also affect other parts of the body



Non-specific immune stimulation strategy: BCG Vaccine

Another way to stimulate immune cells in vivo is to inject bacteria, like William Coley did

Direct injection of the weakened bacteria in BCG can help patients with bladder cancer

The bacteria causes **inflammation** which increases the number of immune cells around the cancer

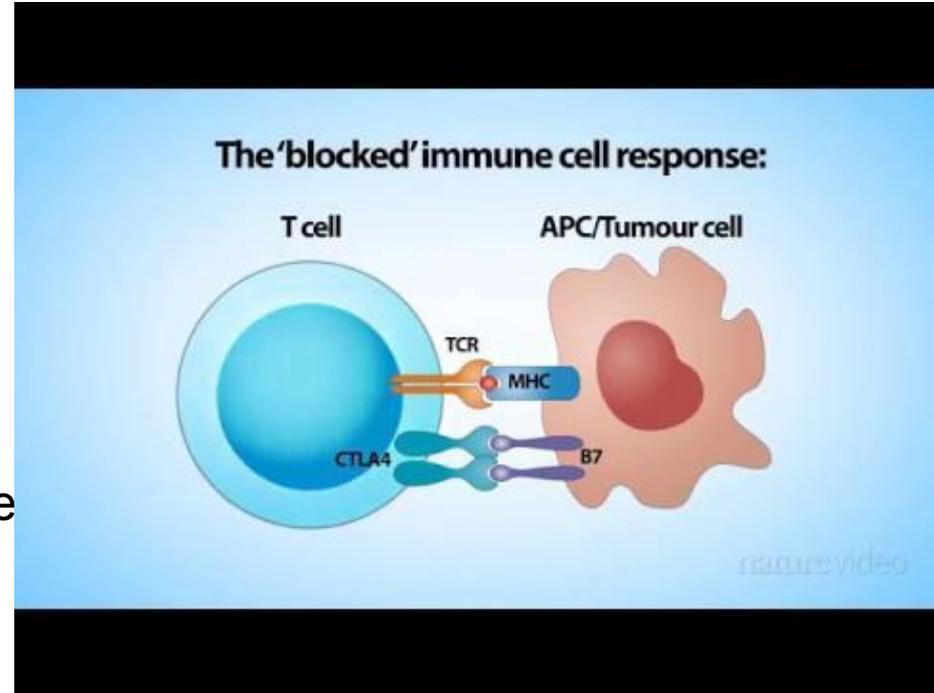


Removing Immune-checkpoint blockade strategy: CTLA-4

Non-specific immunity can also be achieved by removing immune checkpoint blockades

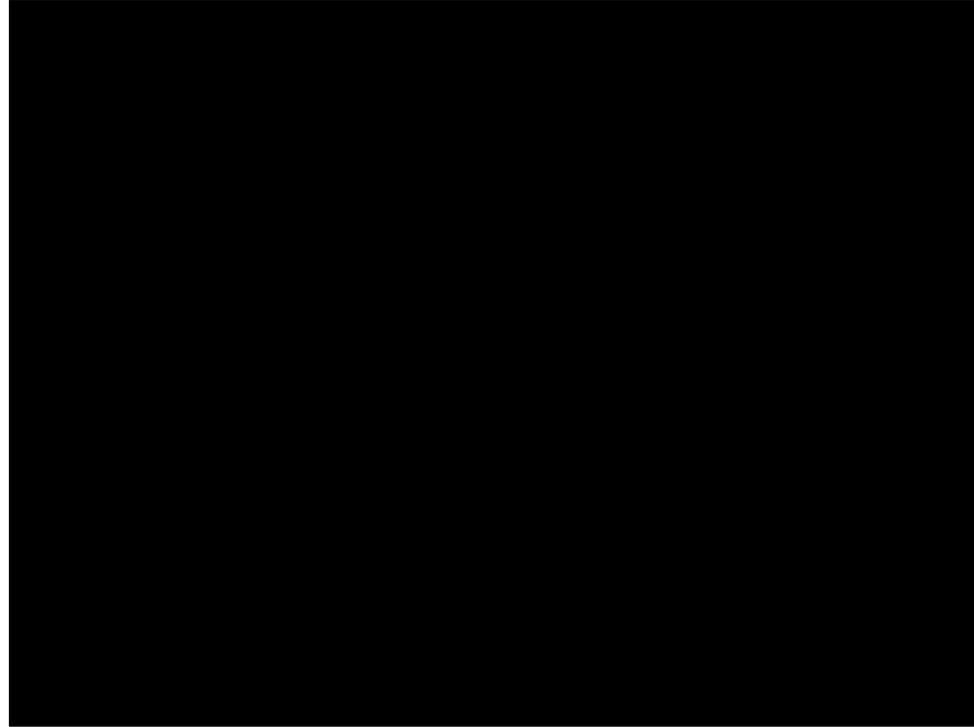
These blockades dampen down the immune response to prevent collateral damage to healthy tissue

To fight cancer those blockades need to be removed to make the immune system stronger



Removing Immune-checkpoint blockade: CTLA-4

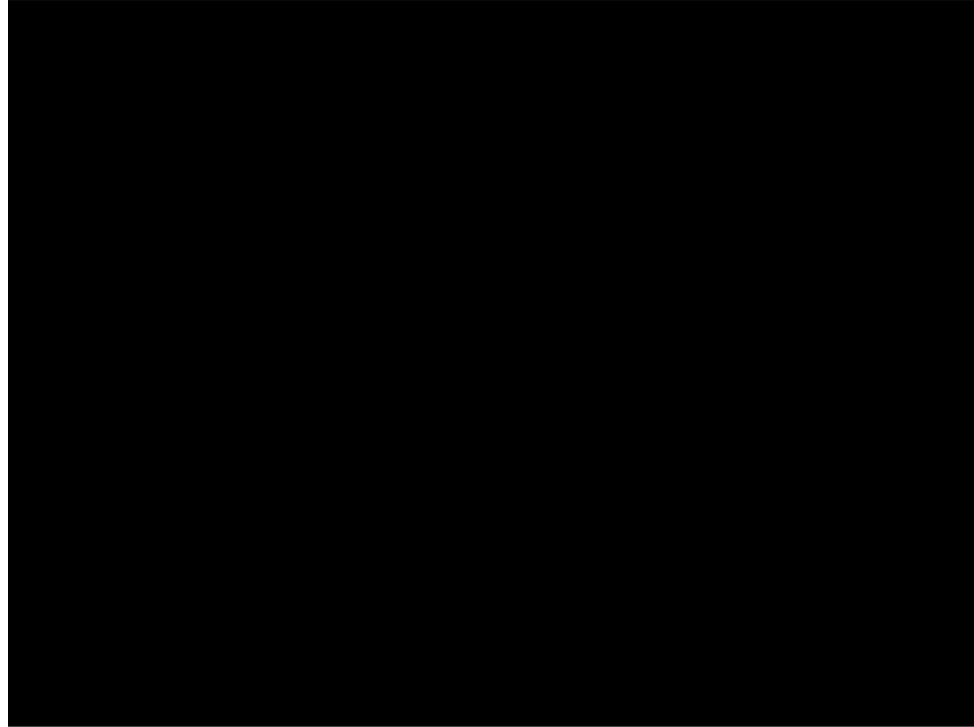
- blocking CTLA-4 this molecule helps DCs to drive anti-tumor T cell responses.
- The Ab Ipilimumab targets CTLA4.
- Approved for advanced stage melanoma in 2011 and being tested for other types of cancer

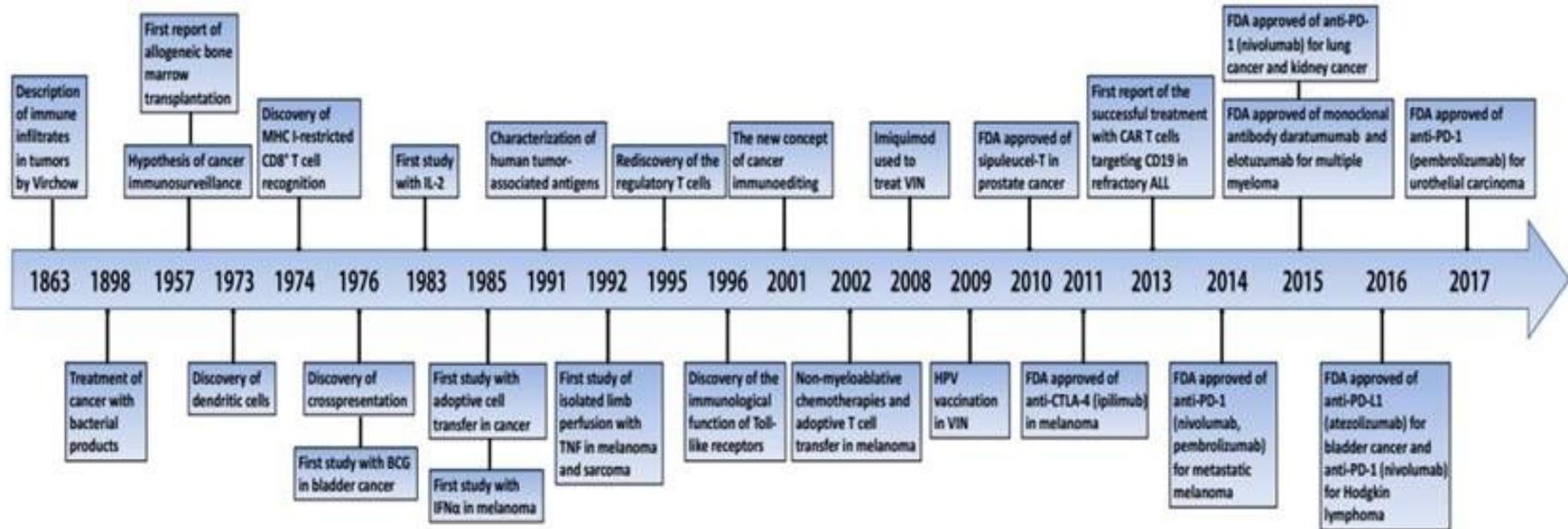


Removing Immune-checkpoint blockade strategy: PD1

targeting the immune checkpoints:

antibodies that binds to PD1 stop this molecule form switching off cytotoxic T cells.





Adoptive cell transfer strategy

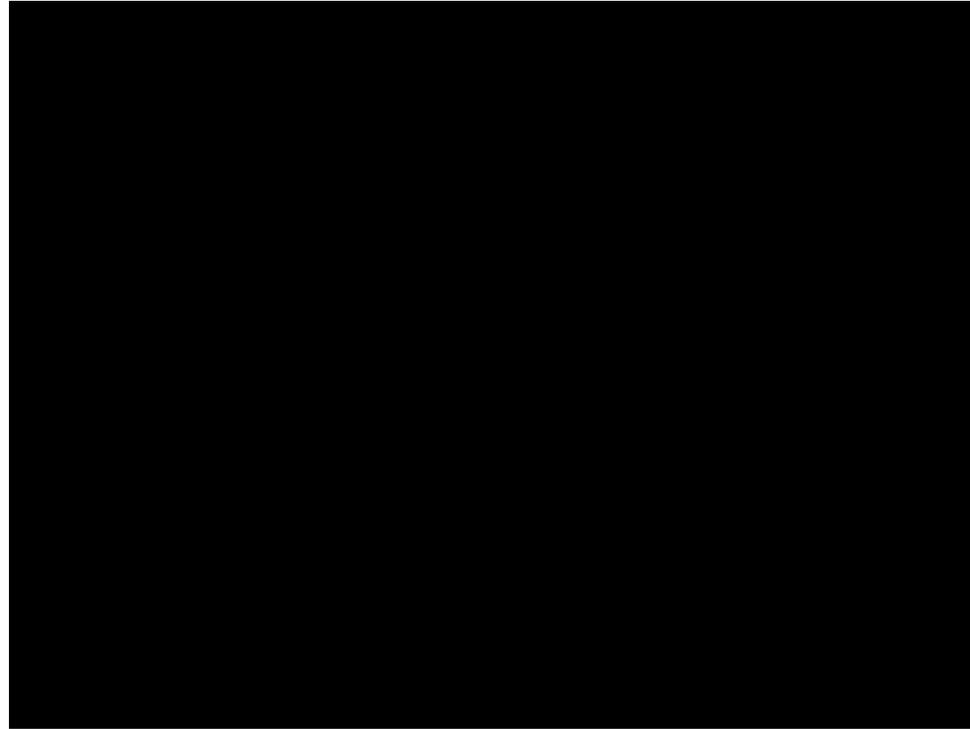
Activating the immune cells inside the body can be difficult

Adoptive cell transfer strategy is based on extracting the immune cells outside the patient

And

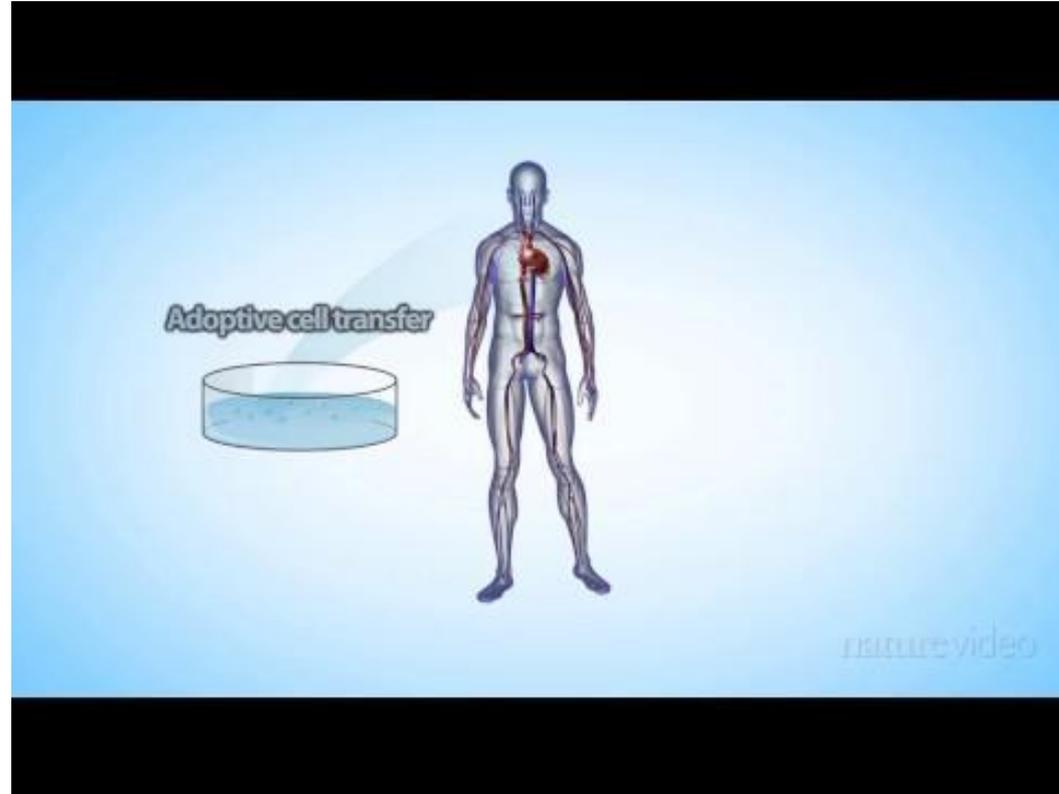
Activating them outside the body

It enables specific targeting the cancer tissue



Adaptive immune transfer Strategy: Tumor

It is difficult to extract enough immune cells from the tumor but the advantage is that the cells have already learned to recognize the tumor

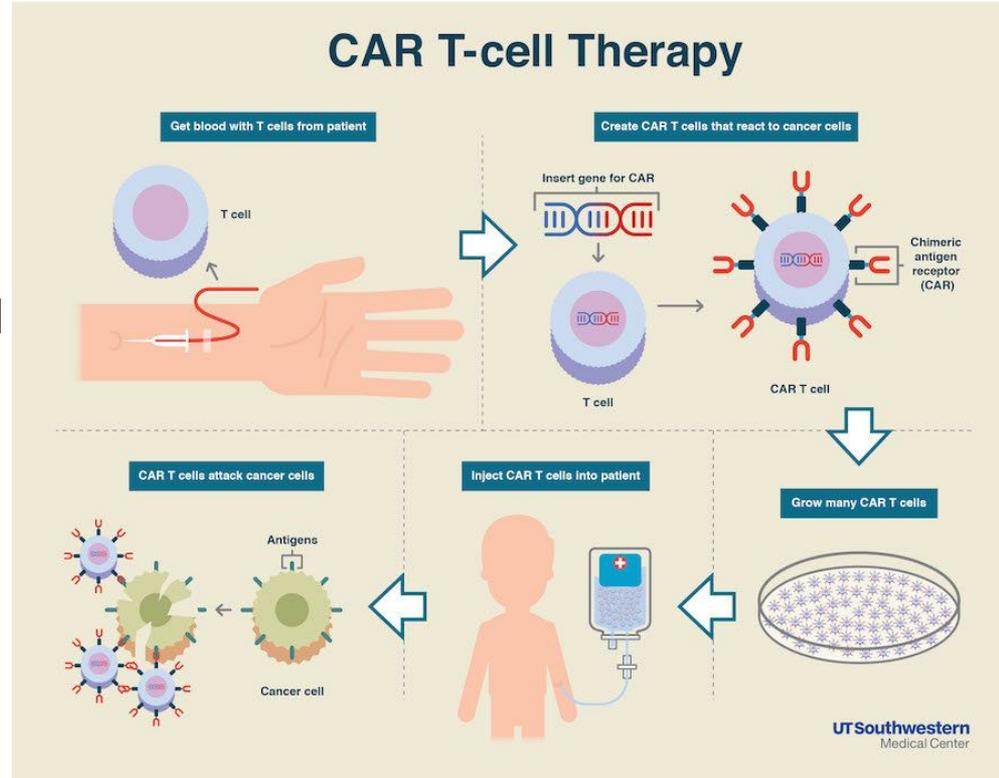


Adaptive immune transfer: Blood

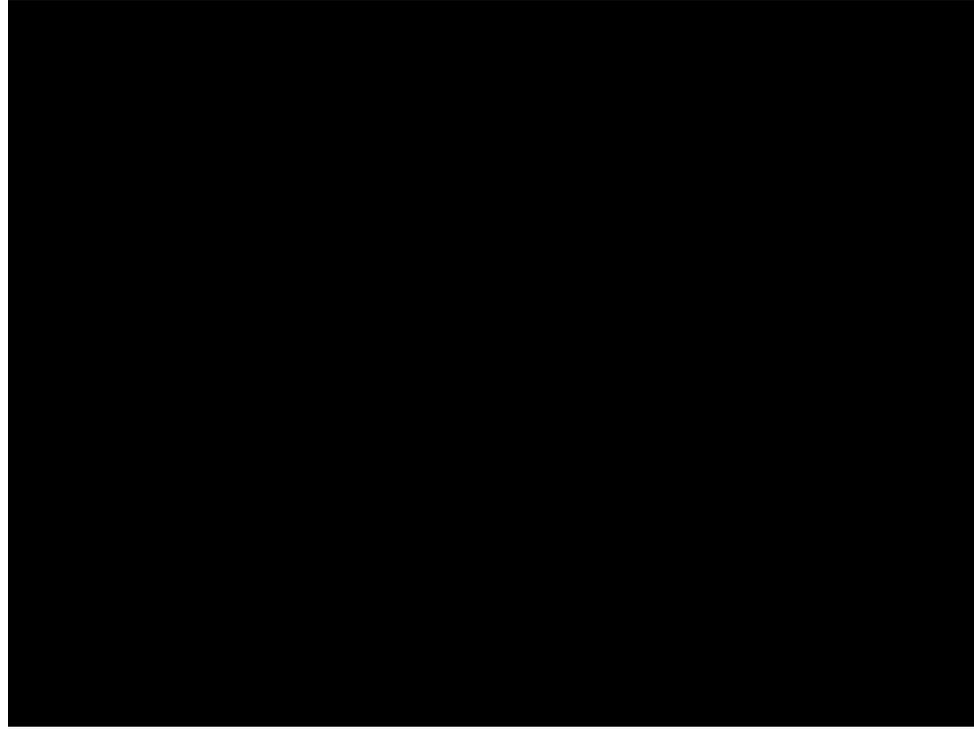
Taking cells from the blood is much easier

But then genetic engineering is needed to arm them with tumor specific receptors

Either way, the cells are activated by cytokines and multiplied in petri dishes before being reintroduced into the patient



Vaccination strategy

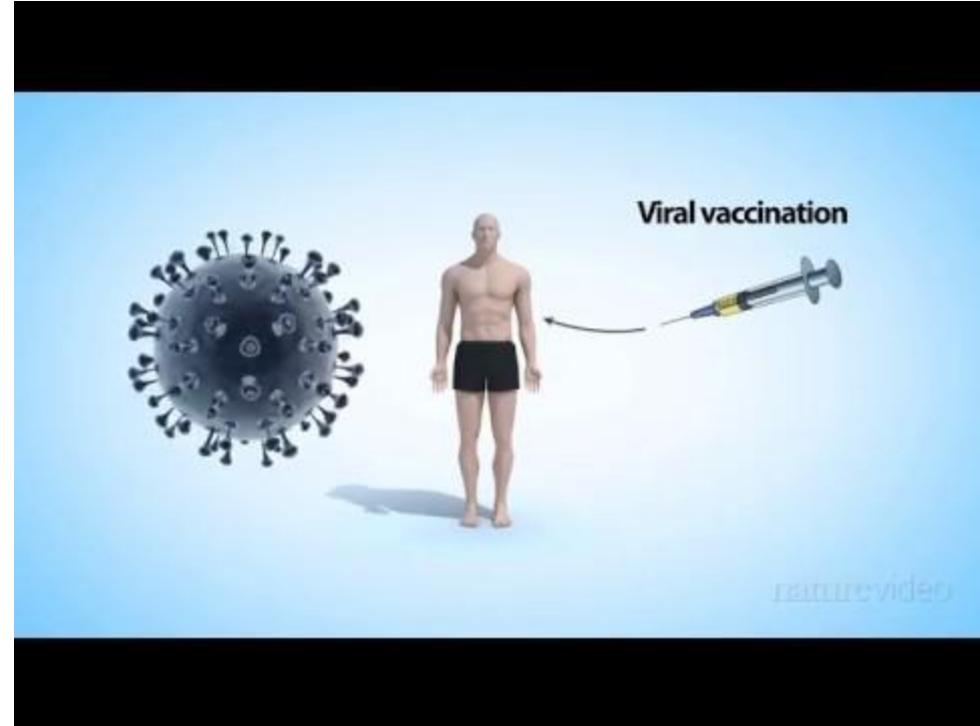


Vaccination strategy: viruses

Unlike the BCG vaccine which targets the immune system in a general way

these vaccines are used to direct the immune cells **specifically** to the cancer tissue

Viral vaccines: e.g. **weakened** version of HSV modified to produce an immune stimulating factor is being developed against melanoma and head and neck cancer



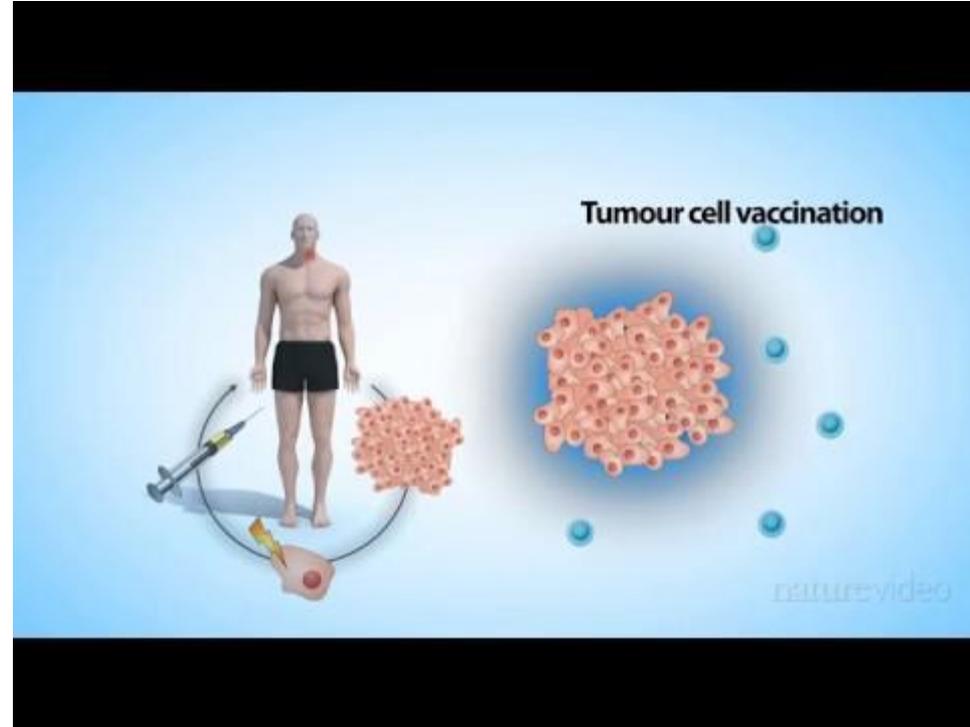
Adoptive cell transfer strategy: Tumor cell

Patient own tumor cells are extracted

Irradiated to prevent them from spreading

Engineered to secrete activating growth factors

When the cells are injected into the patient, the growth factors alert the immune system to the cancer



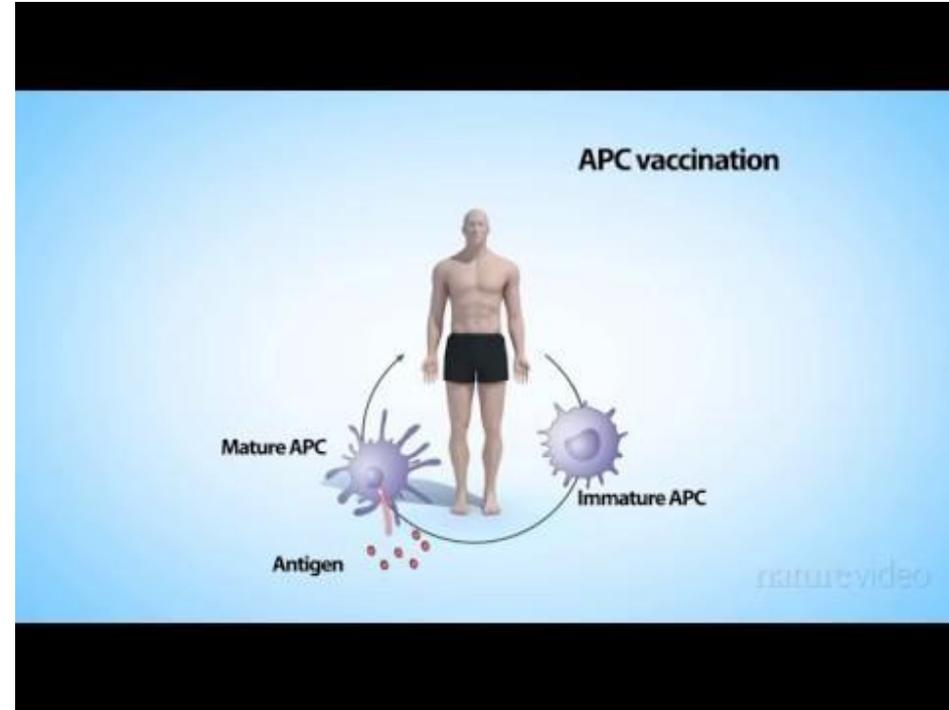
Vaccination strategy: APC vaccination

It is possible to vaccinate with the person's immune cells

For instance APC are taken from the patient

Mature outside the body and loaded with tumor antigen

When the cells are reintroduced into the patient, the Ag stimulate the immune cells and helps them recognize the tumor



Provenge/ Sipuleucel-T first APC vaccination FDA approved in 2010 against prostate cancer

Immunotherapy

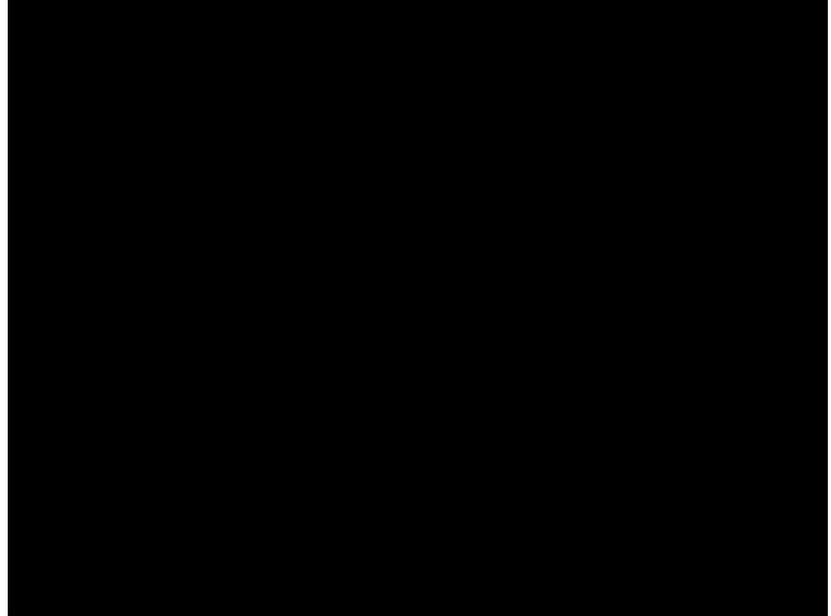
- Not all patients will respond to these immunotherapies and some responses will be delayed.
- Combining immunotherapy with chemotherapy or radiotherapy can lead to a better responses in some patients.
- Immunotherapies can themselves be combined.
- For example PD1 and CTLA-4 blockade can improve response when administered in combination.

Immunotherapy risks

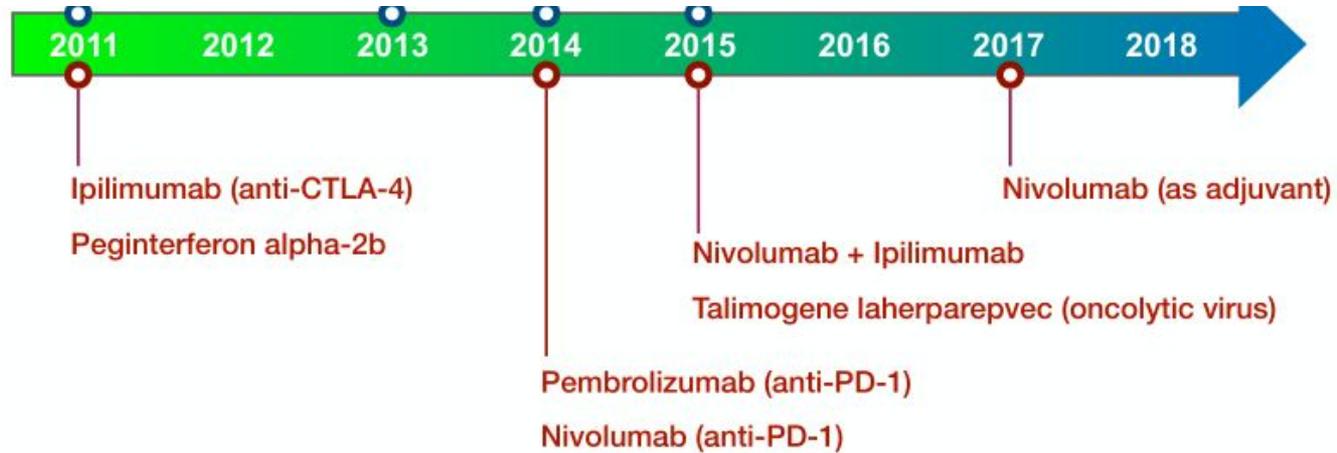
Activating the immune system has risks, some patients develop harmful side effects when their immune system attacks healthy cells.

Nevertheless there have been encouraging results from clinical trials.

Immunotherapies can be used to treat many different types of cancer

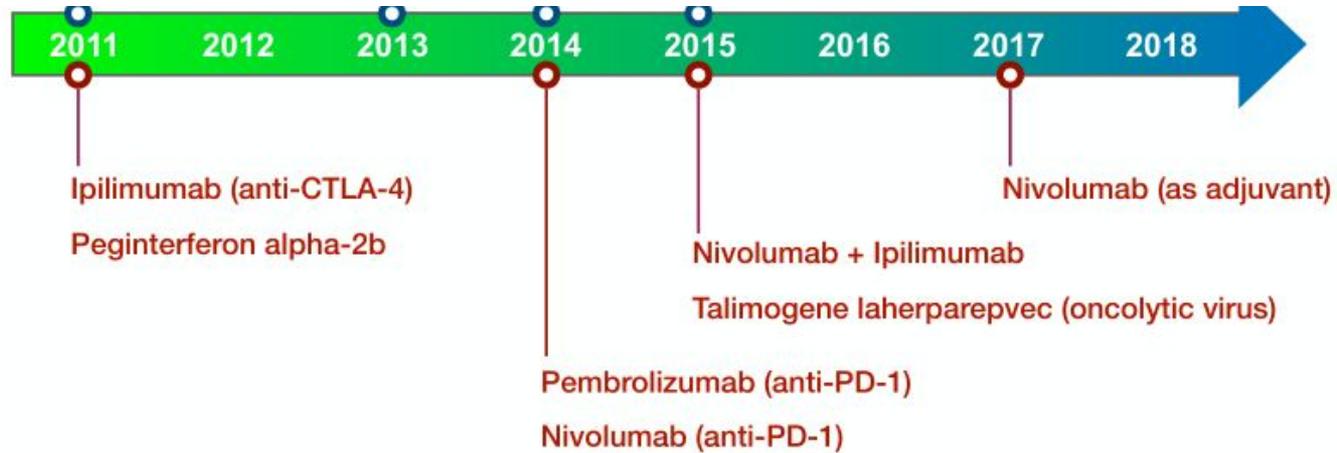


Timeline of FDA-approved immunotherapies for advanced melanoma



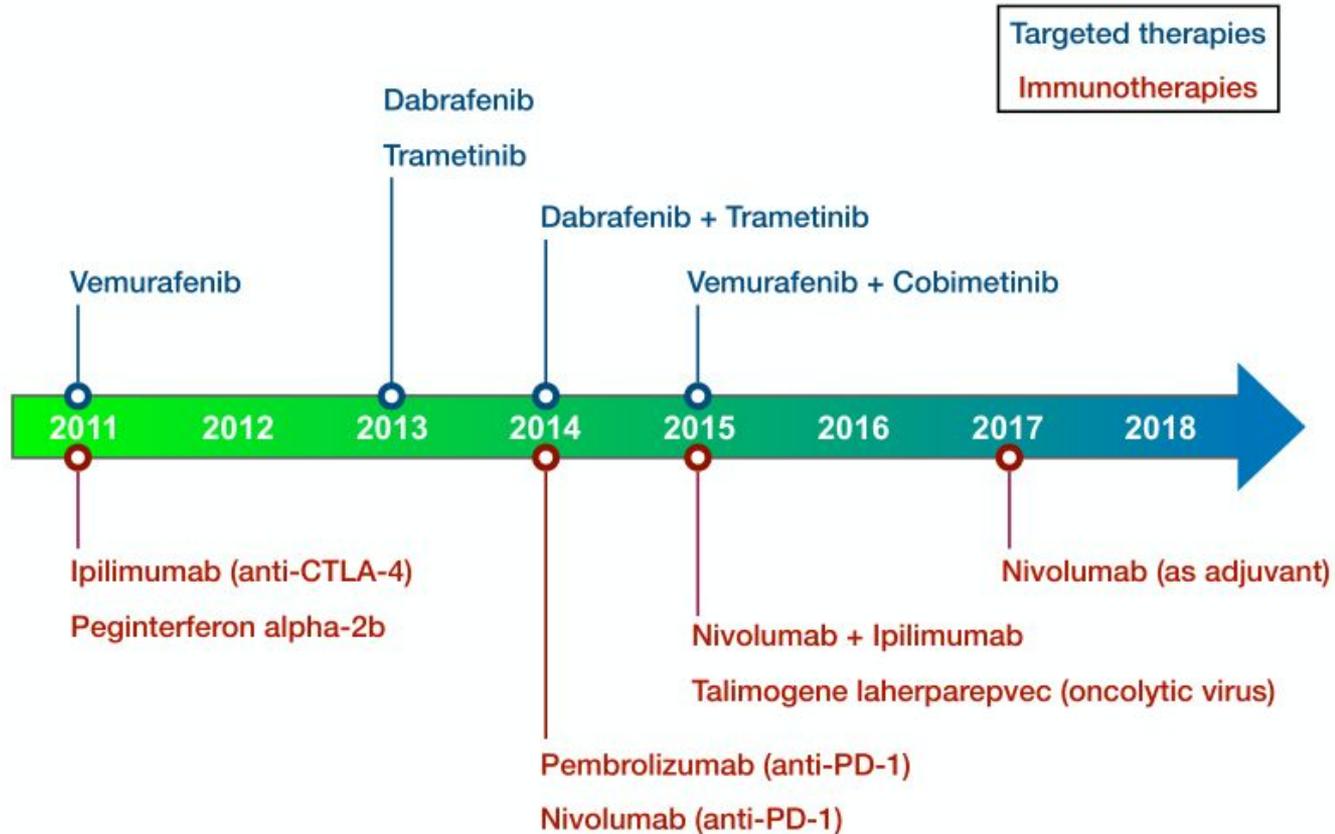
- Since the introduction of ipilimumab (anti-CTLA-4) in 2011, the number of drugs approved for treatment of metastatic melanoma has expanded dramatically.
- Several drugs originally approved as monotherapies are now available as combinations which elicit greater clinical benefits.

Timeline of FDA-approved immunotherapies for advanced melanoma



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- Several drugs originally approved as monotherapies are now available as combinations which elicit greater clinical benefits.

Timeline of FDA-approved drugs for advanced melanoma



Types of immunotherapy

- **Passive immunotherapy:**
 - Administration of monoclonal antibodies which target either tumour-specific or over-expressed antigens.
- **Active immunotherapies:**
 - Cytokines- IL-2 / IFNs / TNF α
 - Cancer vaccines
 - Cell-based therapies
 - tumour-specific CTL
 - tumour-derived APC
 - DC priming