Tumor immunology and immunotherapy

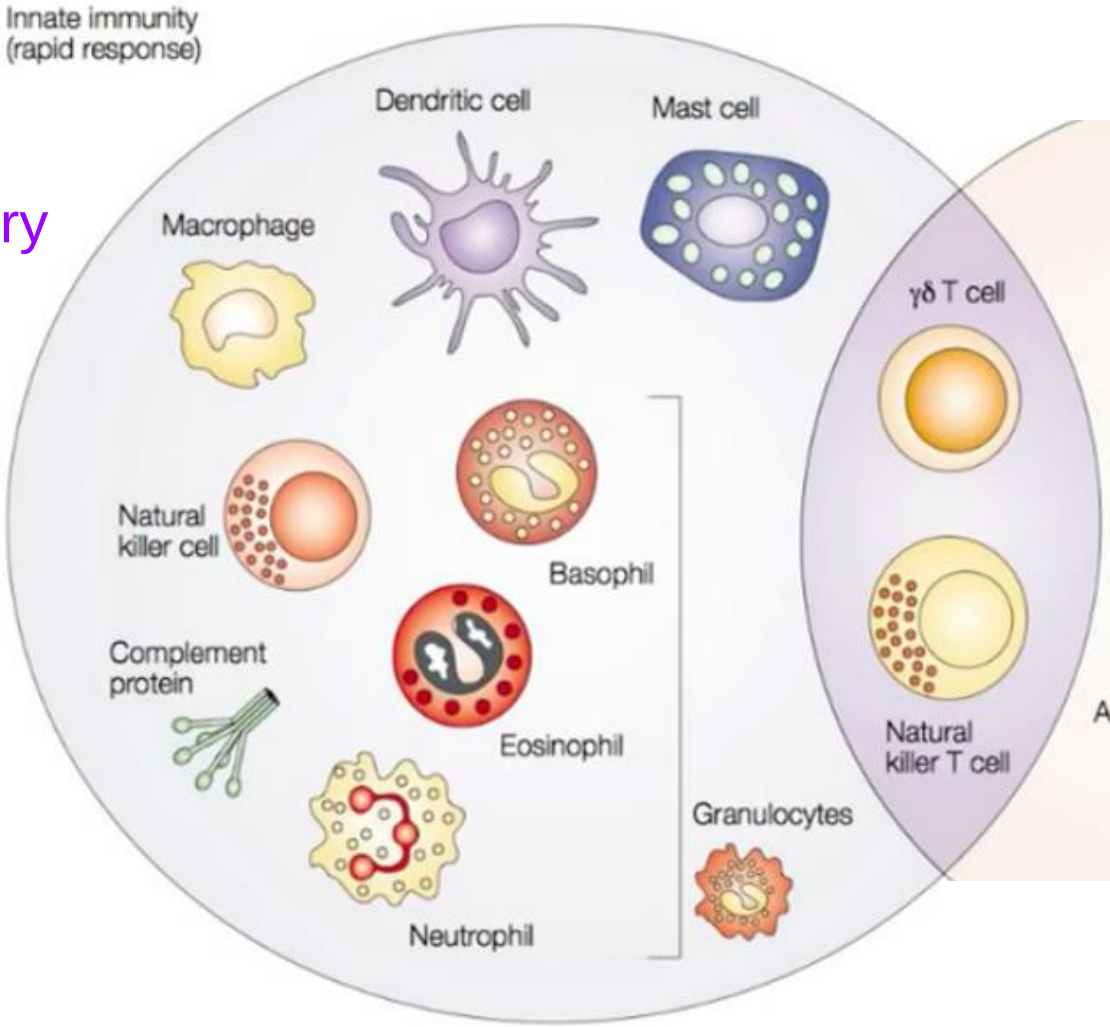
Dr.Belal Azab

What are the different parts of the immune system?

No memory

Innate immune system:

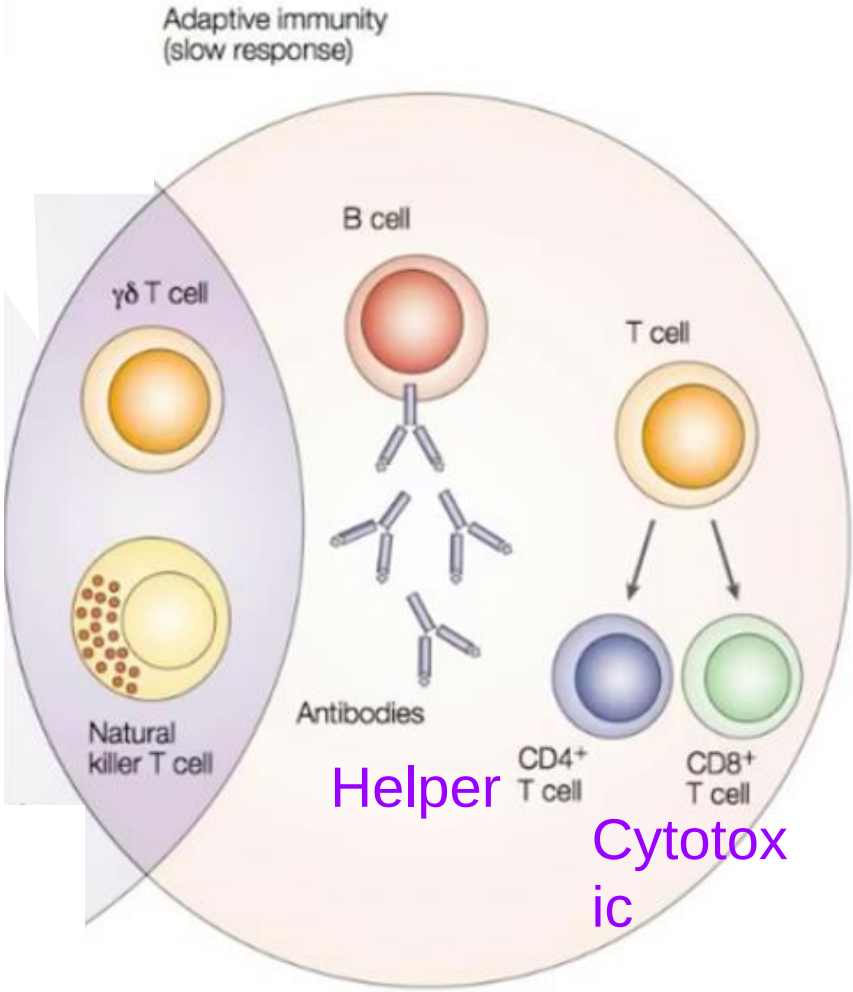
- The first line of defense,
- It is pre-existing and ready to respond to infection, inflammation or cancer.
- Examples: Macrophages and neutrophils.
- Not educated and not selective, (kill first, ask later)

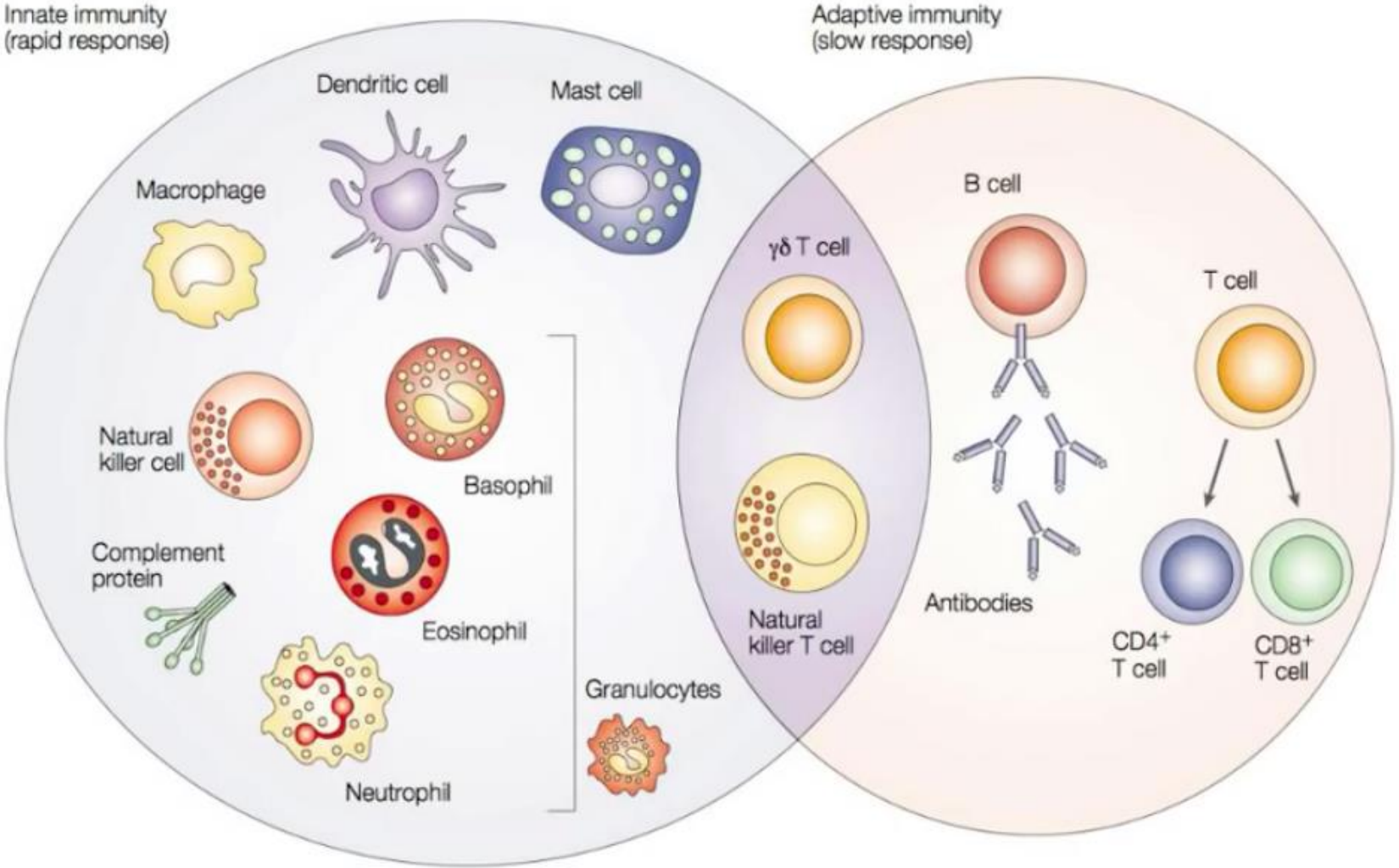


What are the different parts of the immune system?

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)
Dendritic cell
Mast cell
Macrophage
γδ T cell
B cell
T cell
Natural
killer cell
Basophil
Complement
protein
Eosinophil
Natural
killer T cell
Antibodies
CD4+
T cell
CD8+
T cell
Granulocytes
Neutrophil

Somatic: not found since the zygote (are not found in other cells)

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

Thanks to its somatic nature

Germline: a gene found since the zygote, all cells have them

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.

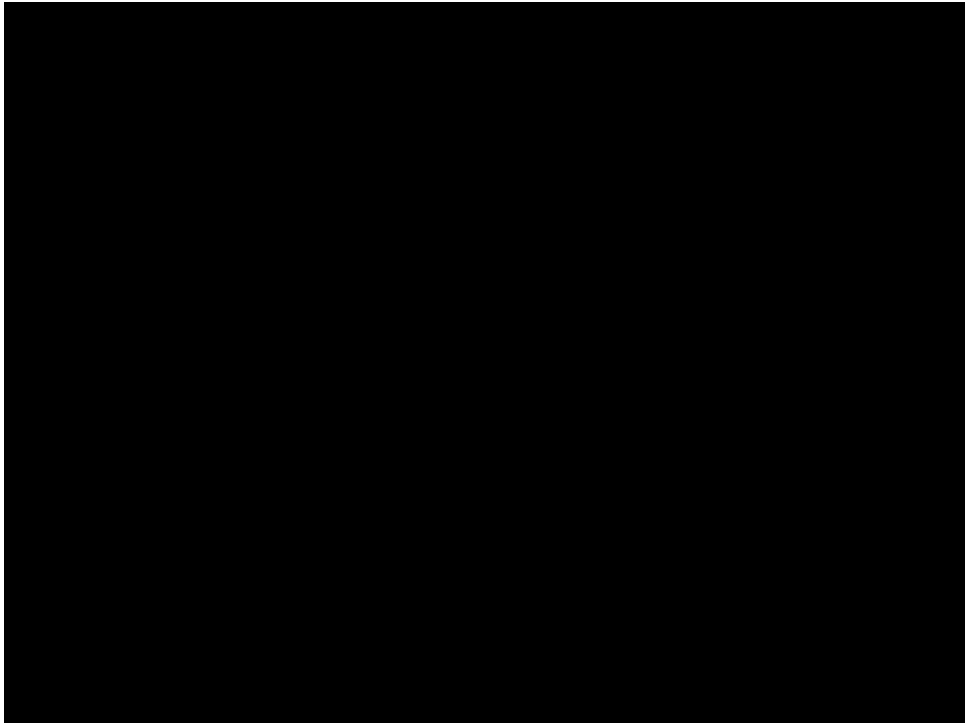
As melanoma grow they can eventually spread to other sites in the body such as the lunge and the liver. Metastasis

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.

Microenvironment: is the region where a tumor is located, contains immune cells



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

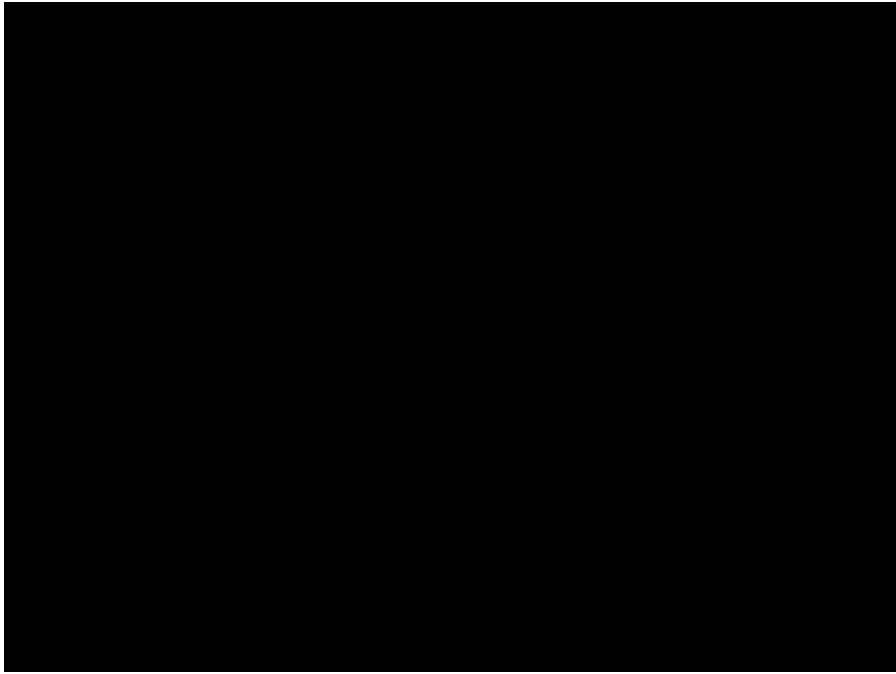
and Helper T cells

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.

They are heterogenous because each cell goes crazy with random, different mutations

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 continue to kill the tumor cells it can recognized.



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

Regulatory T cells are found normally to prevent auto-immunity

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. They recruit them by producing certain cytokines

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.

Chemotherapy kills all dividing cells, whether cancer or not. However, immunotherapy is selective (there could be side effects but they are minimal)

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.

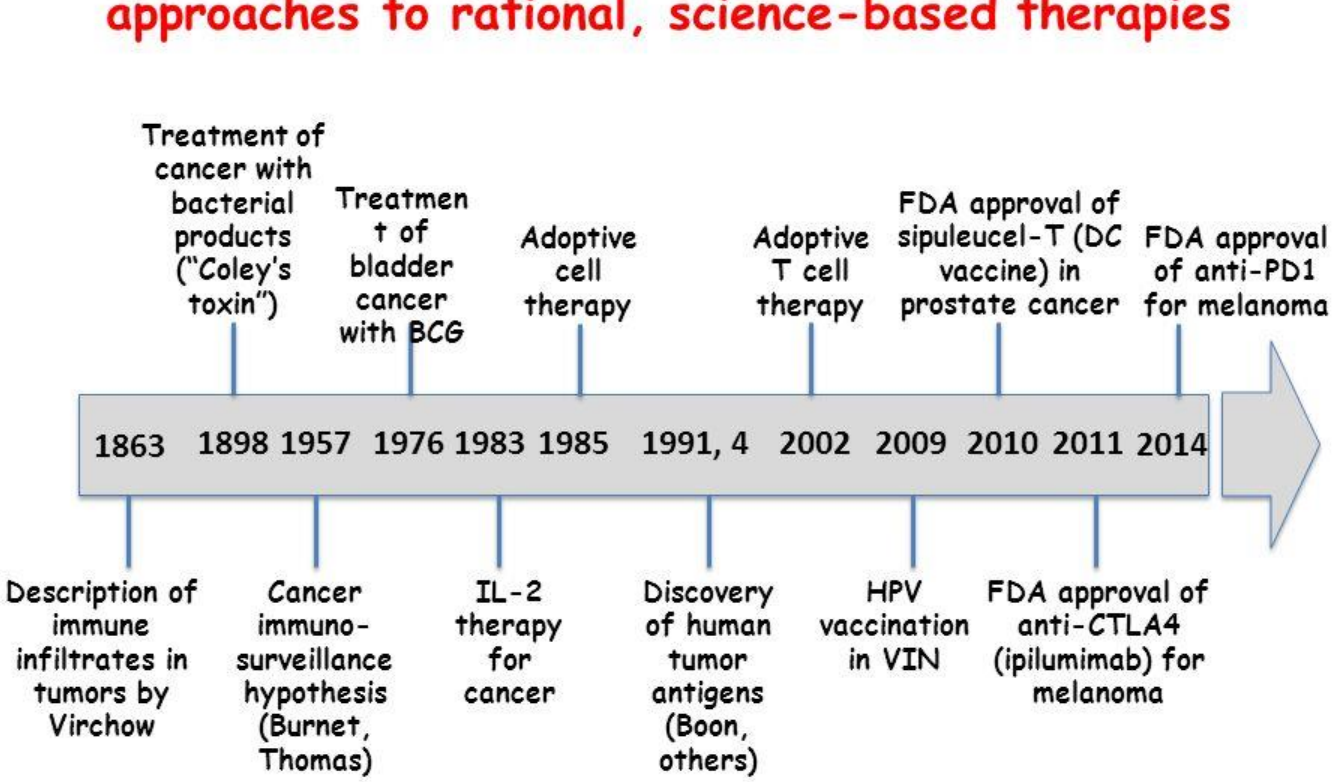
Involves activating immune cells and getting them to recognize cancer tissue as different from body cells

Skip

The idea goes back to the 17th century!

to

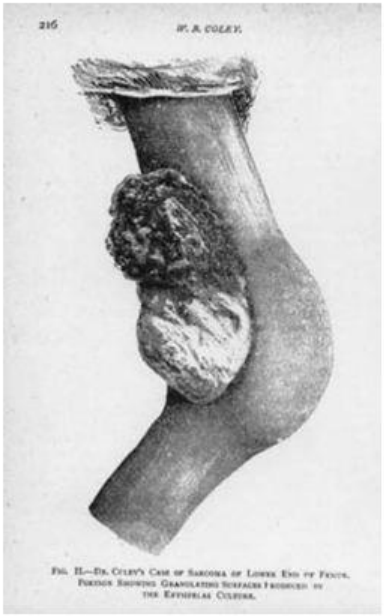
William Coley



Skip

Coley toxin

- Heat-inactivated bacteria to induce inflammation (acute)



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/PMC1899599/

Heat inactivated bacteria, of course

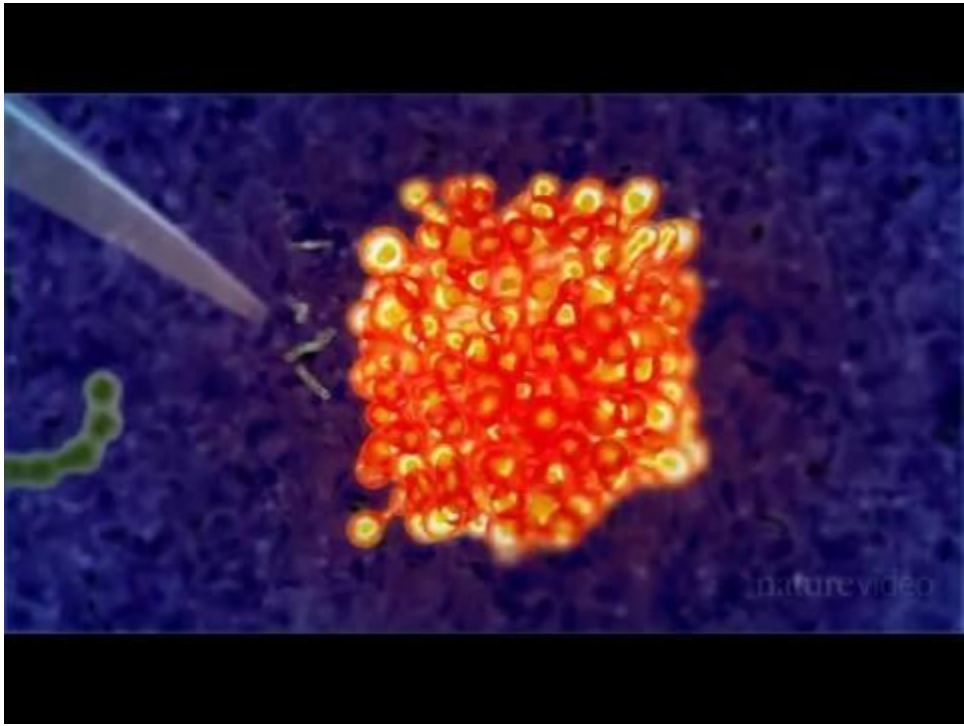
Coley’s toxins

Coley injected bacteria into tumors and watched them shrink!

The bacteria seemed to provoke immune response

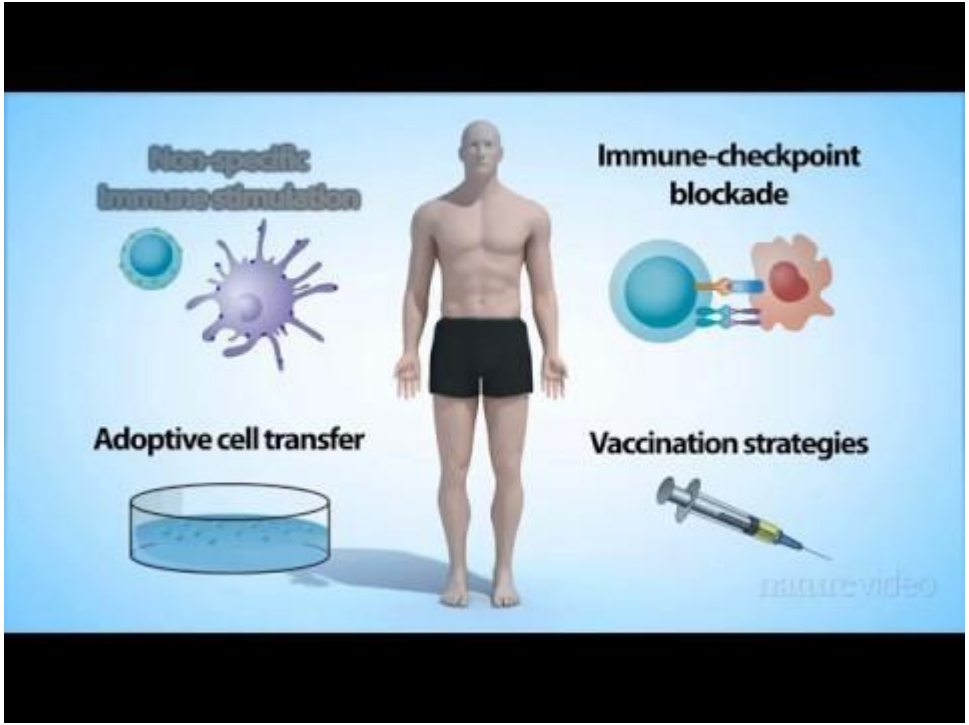
The immune system is highly complex and during the 20th century scientists struggled to turn Coley’s observation into effective cancer treatments

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



Immunotherapy four general strategies

1. Non-specific immune stimulation
2. Immune checkpoint blockade
3. Adoptive cell transfer
4. Vaccination



Non-specific immune stimulation strategy: injecting molecules

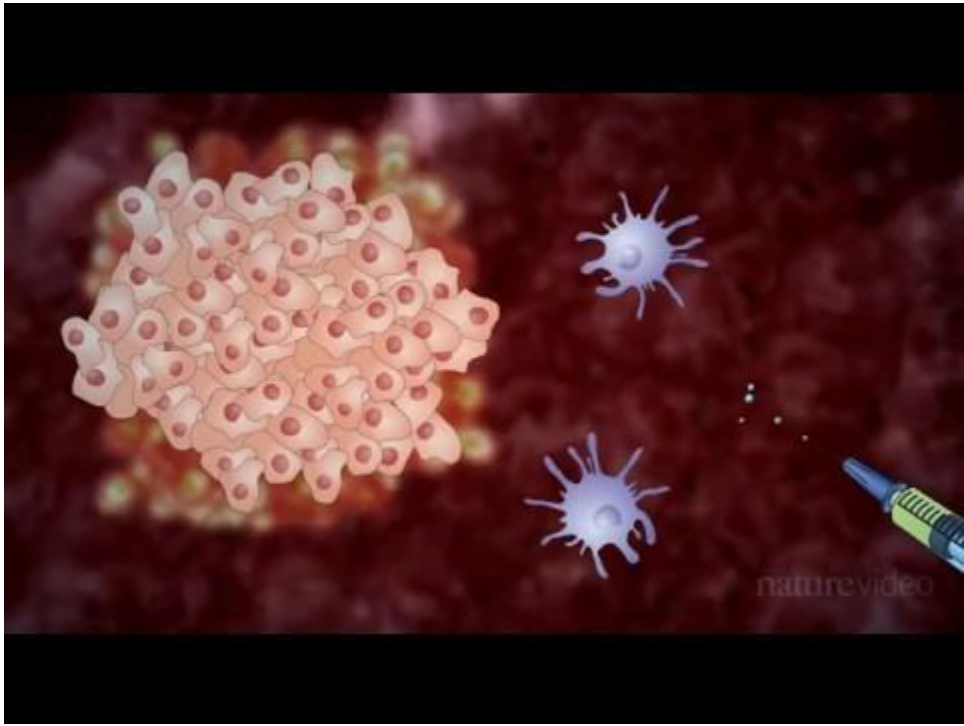
Used to give a general boosts to the immune system *in vivo*

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 IFNα

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

IFNα and IL-2 have been developed as drugs.

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

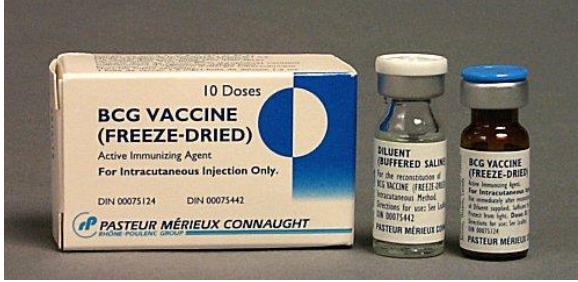
IL-2: T-cell growth factor

Non-specific immune stimulation strategy: IL-2 and IFNα

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

Helper T cells, and NK cell are activated

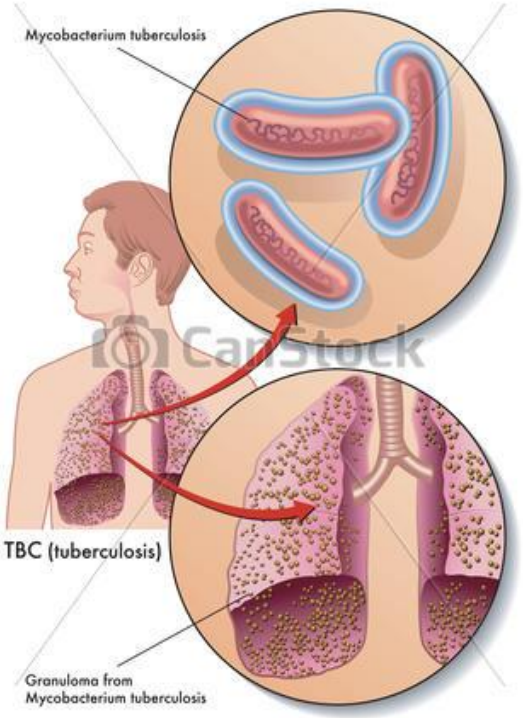
Bacillus Calmette-Guerin (BCG) Vaccine



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

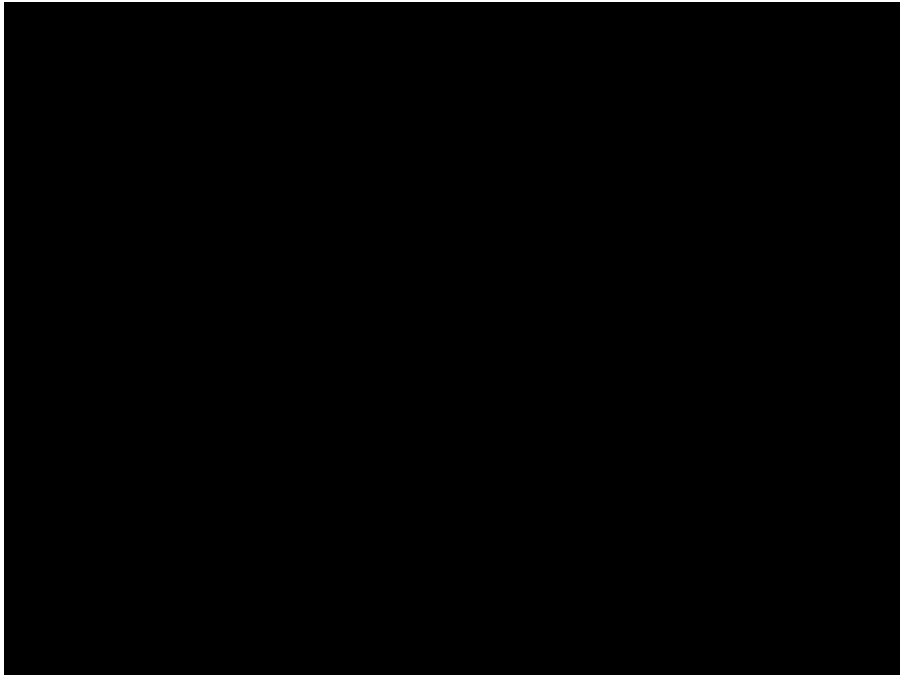


Non-specific immune stimulation strategy: BCG Vaccine

Another way to stimulate immune cells in vivo is to inject bacteria, like Wiliam 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



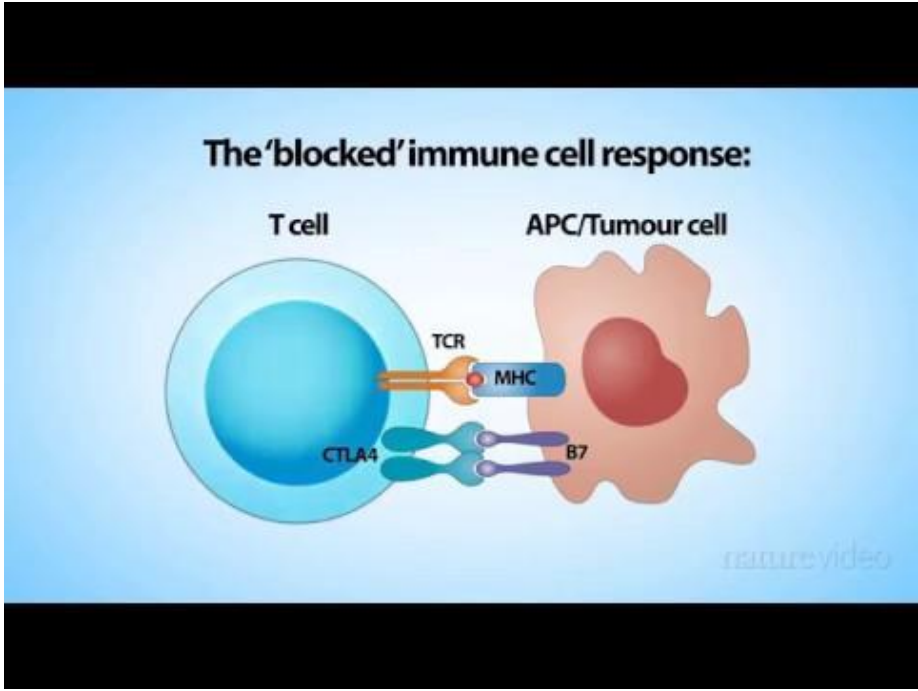
Removing Immune-checkpoint blockade strategy: CTLA-4

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

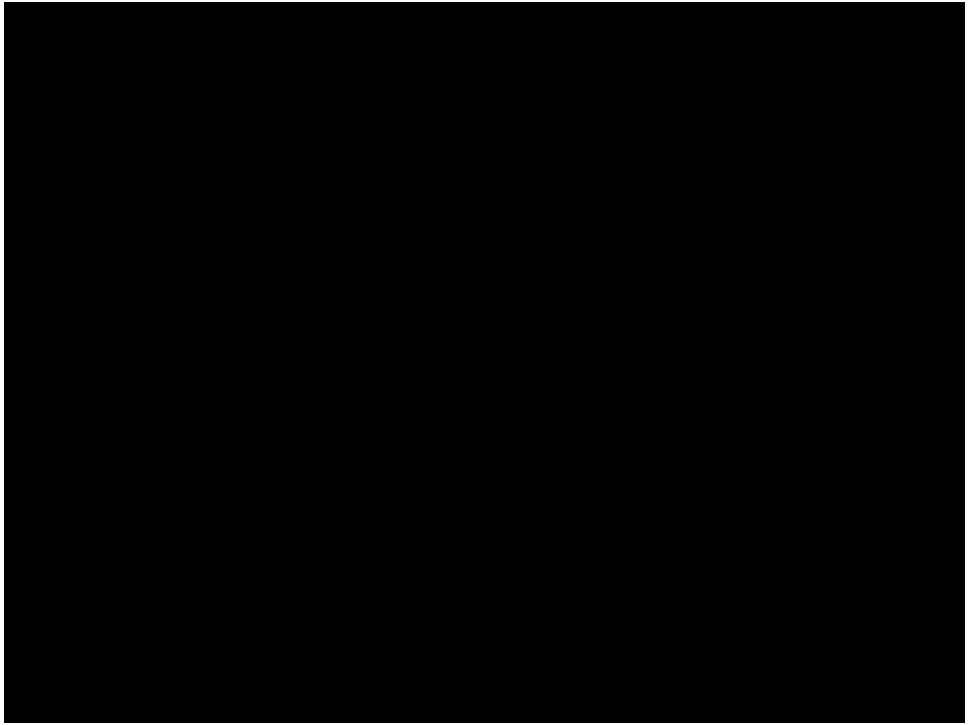
So we use a neutralizing antibody, such as Ipilimumab, which will mask the CTLA-4. Therefore, no inhibition takes place and T cell بتاخد راحتها with tumor cells



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.

Same mechanism as the previous one

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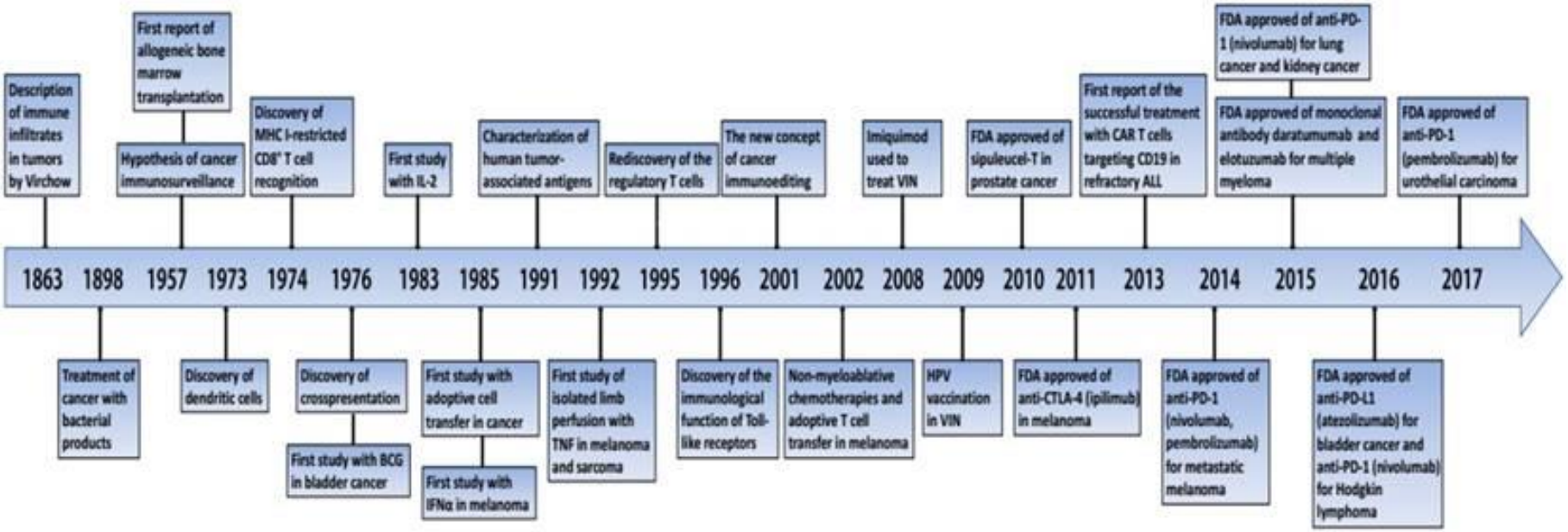

1863
Description of immune infiltrates in tumors by Virchow
1898
Treatment of cancer with bacterial products
1957
First report of allogeneic bone marrow transplantation
Hypothesis of cancer immunosurveillance
1973
Discovery of dendritic cells
1974
Discovery of MHC I-restricted CD8+ T cell recognition
1976
Discovery of crosspresentation
First study with BCG in bladder cancer
1983
First study with IL-2
1985
First study with adoptive cell transfer in cancer
First study with IFNα in melanoma
1991
Characterization of human tumor-associated antigens
1992
First study of isolated limb perfusion with TNF in melanoma and sarcoma
1995
Rediscovery of the regulatory T cells
1996
Discovery of the immunological function of Toll-like receptors
2001
The new concept of cancer immunoediting
2002
Non-myeloablative chemotherapies and adoptive T cell transfer in melanoma
2008
Imiquimod used to treat VIN
2009
HPV vaccination in VIN
2010
FDA approved of sipuleucel-T in prostate cancer
2011
FDA approved of anti-CTLA-4 (ipilimub) in melanoma
2013
First report of the successful treatment with CAR T cells targeting CD19 in refractory ALL
2014
FDA approved of anti-PD-1 (nivolumab, pembrolizumab) for metastatic melanoma
2015
FDA approved of anti-PD-1 (nivolumab) for lung cancer and kidney cancer
FDA approved of monoclonal antibody daratumumab and elotuzumab for multiple myeloma
2016
FDA approved of anti-PD-L1 (atezolizumab) for bladder cancer and anti-PD-1 (nivolumab) for Hodgkin lymphoma
2017
FDA approved of anti-PD-1 (pembrolizumab) for urothelial carcinoma

Adoptive cell transfer strategy

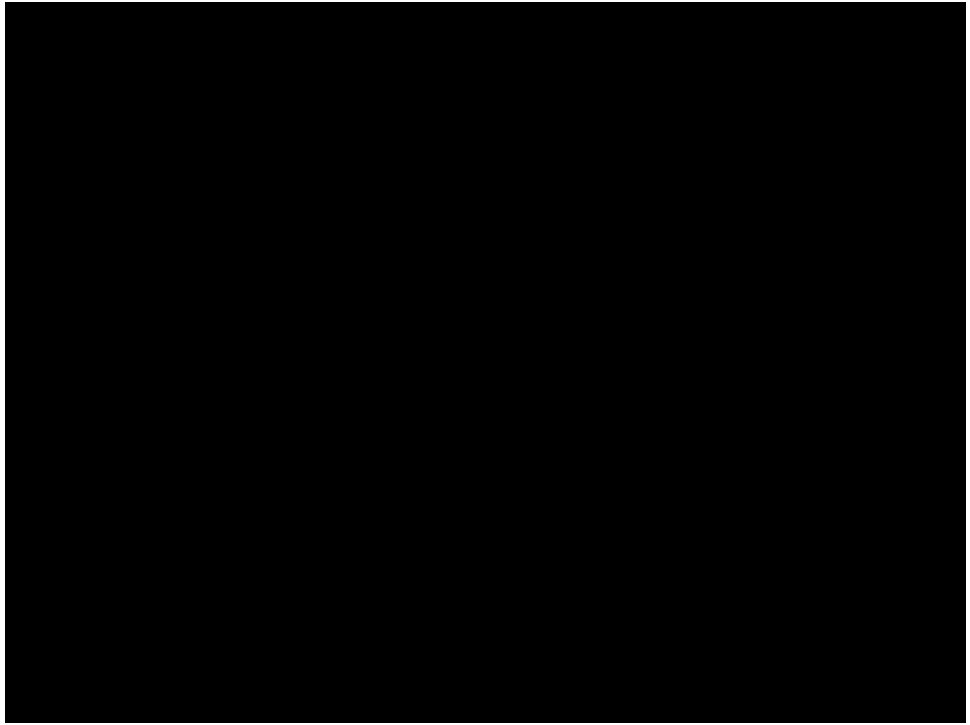
Activating the immune cells inside the body can be difficult

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

And

Activating them outside the body

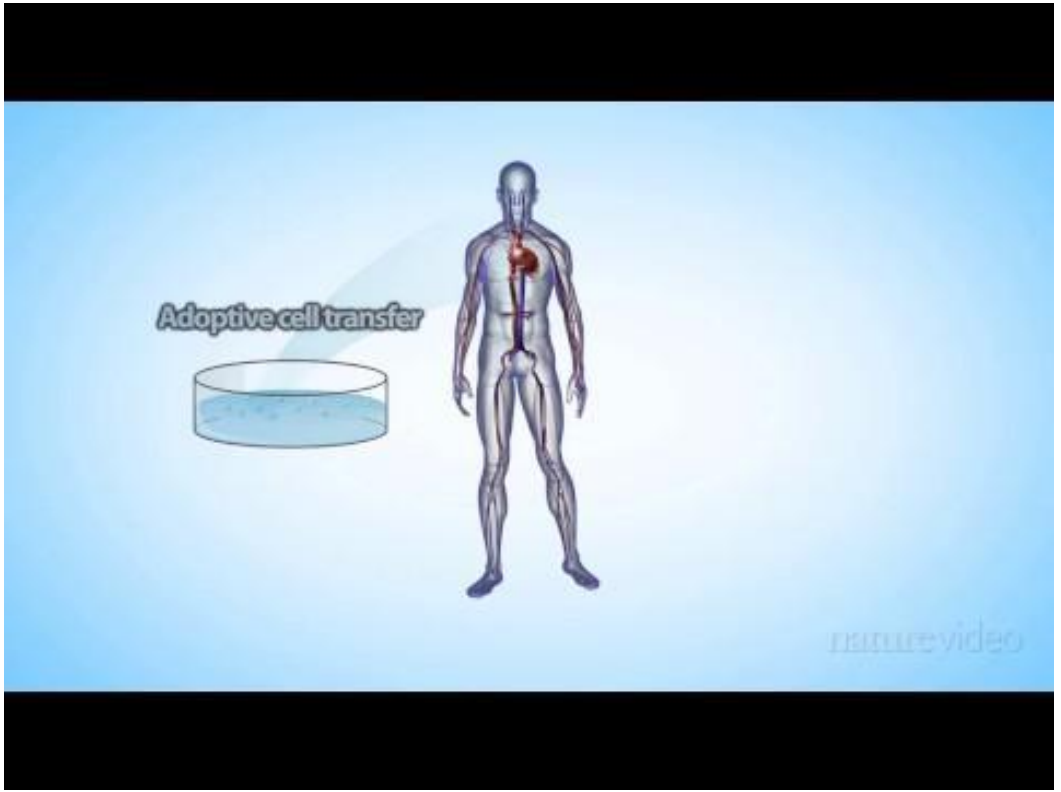
It enables specific targeting the cancer tissue



Adaptive immune transfer Strategy: Tumor

You take part of the tumor from the patient, and extract immune cells from it

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



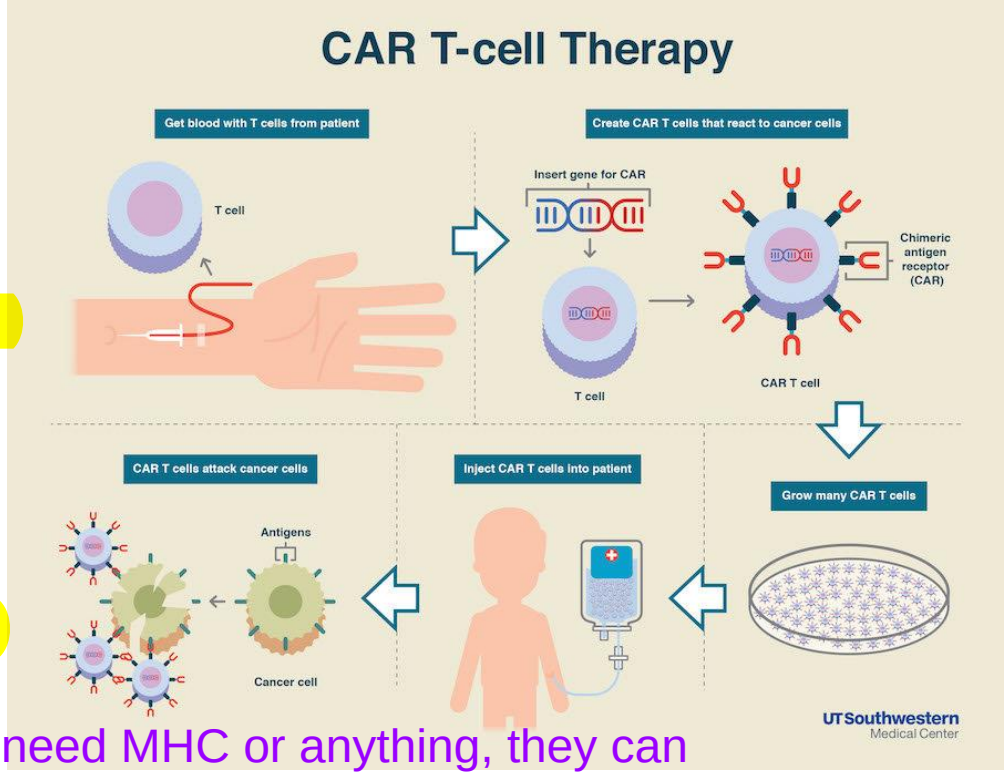
Adaptive immune transfer: Blood

Taking cells from the blood is much easier

But then genetic engineering is needed to arm them with tumor specific receptors Such as "CAR'

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

These cells (Car T cells) don't need MHC or anything, they can recognize the tumor right away



Vaccination strategy

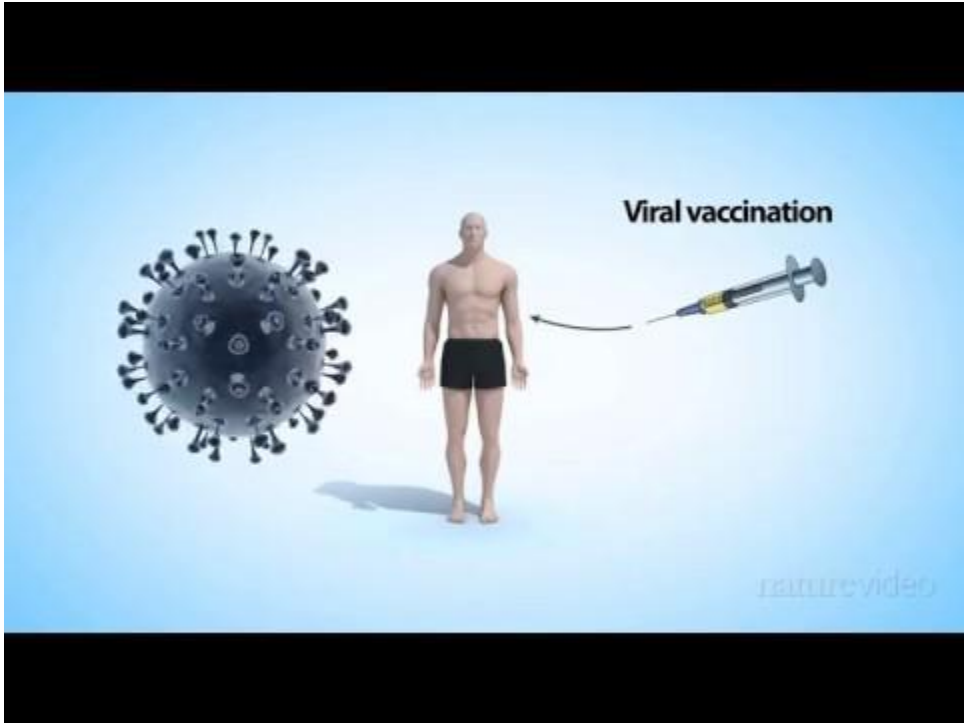
BCG vaccine was used to induce a general inflammation, but the story here is different. We engineer the virus (add a tumor antigen to it) so the immune system carries out a response and attack that tumor (we trick our immune system)

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

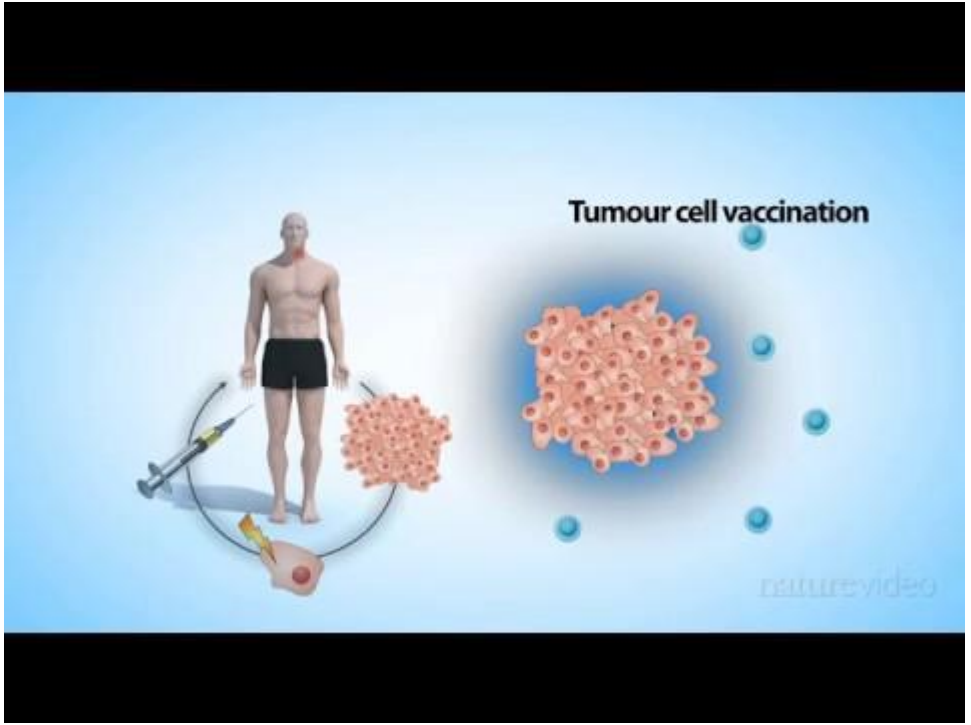
Patient own tumor cells are extracted

Irradiated to prevent them from spreading Weakening them

Engineered to secret activating growth factors

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

It is like a tumor vaccine



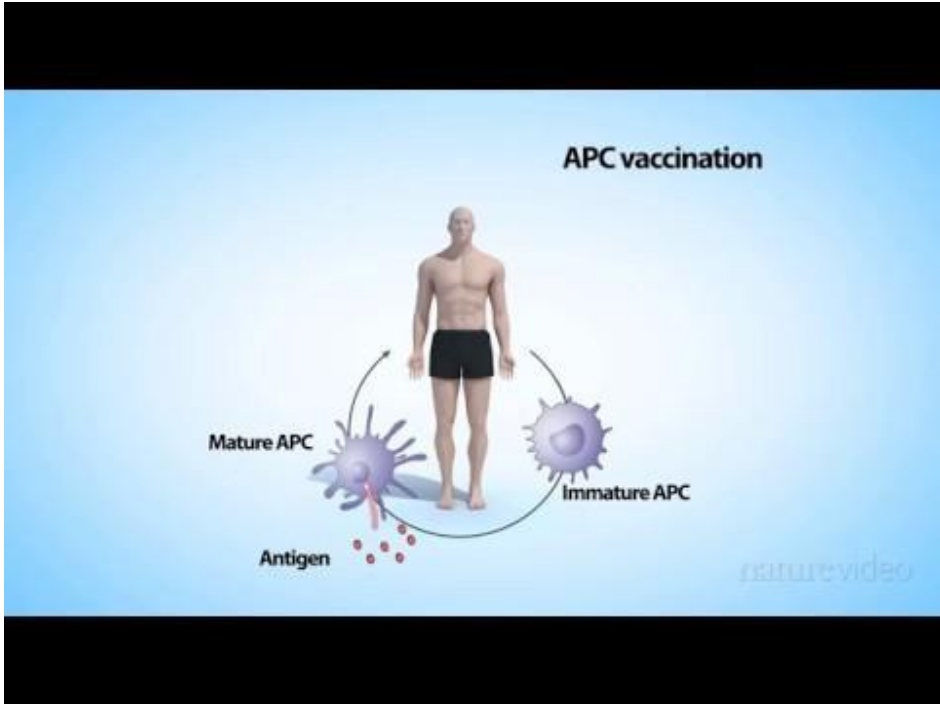
Vaccination strategy: APC vaccination

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. Cuz we have different immunities
- 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.

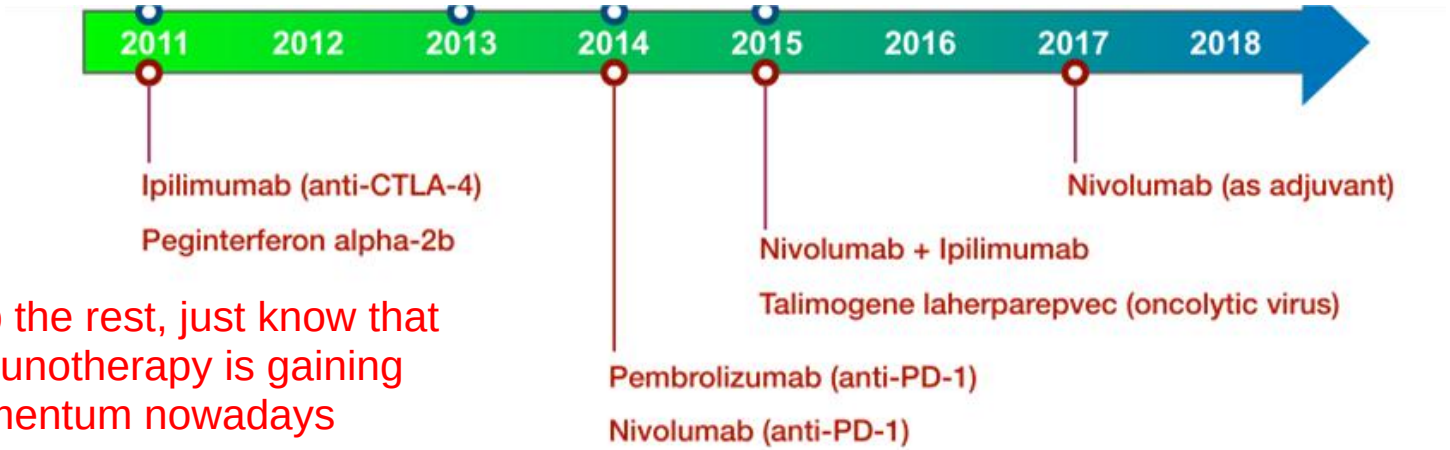
Immunotherapy risks

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

Nevertheless there have been encouraging results from clinical trials.

Immunotherapies can be used to treat many different types of cancer

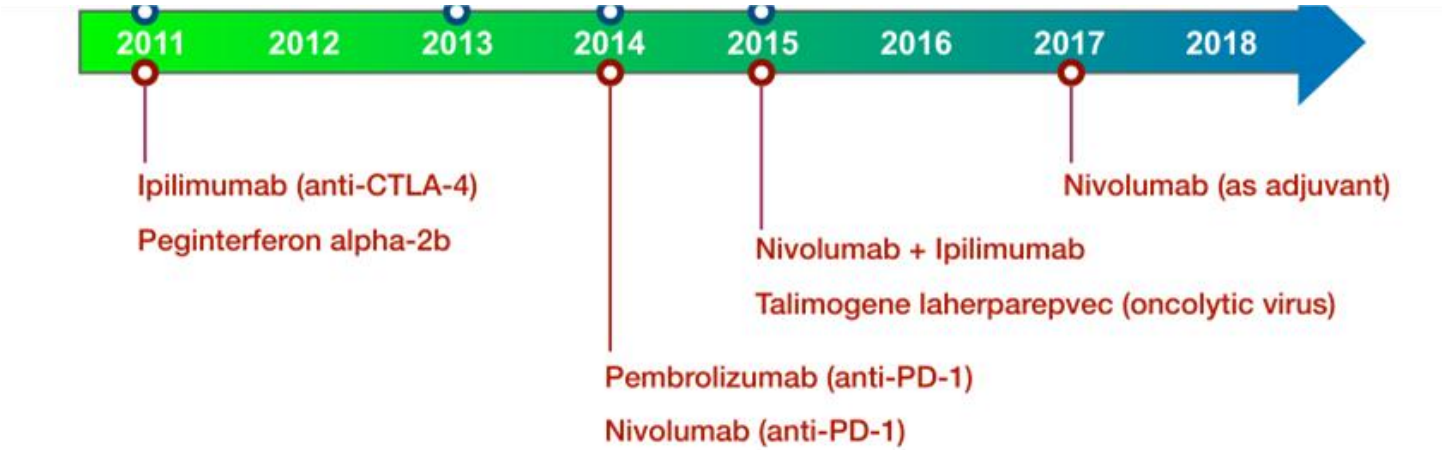
Timeline of FDA-approved immunotherapies for advanced melanoma



Skip the rest, just know that immunotherapy is gaining momentum nowadays

- 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



- 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.

Types of immunotherapy

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