

# Can the Immune system fight cancer

Course	 <a href="#">Immunology</a>
Date	@April 13, 2024
Status	Completed
Reading	<input checked="" type="checkbox"/>

## Cancer and immune surveillance

- The lifetime risk of developing cancer is one in two

Increase in life expectancy leads to increase in cancer incidence.

- An older population is a population which will be heavily affected by cancer posing challenges for our health systems.

## The biology of cancer

- Cells are mutating all the time
  - Most of the time there is no negative clinical outcome because immune system
- Cancer starts from one cell gaining **proliferative advantage** among the  $10^{13}$  individual cells in the human body
  - As the cell accumulate it may start to spread (metastasis)
  - Malignant cancer growth

**Cancer is a genetic disease** and the immune system has the ability to specifically detect mutated proteins present in cancer cells.

- Humans have approx. 40,000 genes, and **all** genes are present in all cells.
- However, less than 10,000 genes are active in each cell
  - Define cell function
  - Define cell division.
- Mutations and abnormal gene activity results in enhanced division

- Could be gene deletion, overexpression, fusion (change in sequence which are not specifically mutation)



The most common cause of cancer in humans is mutational changes in the genome

### **Concept of immunological surveillance**

- A monitoring process of the immune system to constantly detect and destroy virally infected and neoplastically transformed cells in the body

Because cancer cells carry mutations, they are different from self.

An intact immune system can attack and eliminate cancer cells (**immune surveillance**, elimination phase).

- The immune status of mice is a critical determinant of the susceptibility to tumors induced by chemical carcinogens
  - Immunodeficient mice: Mice with KO RAG2, which is required in VDJ recombination
    - Unable to initiate VDJ rearrangement thus fail to generate mature T and B cells
  - Higher percentage of developing tumour than immunocompetent mice
  - Same results obtained in other kinds of immune depletion such as CD4, IFNgamma
    - Always more likely to develop cancer
- Tumour infiltration of cytotoxic T cells is associated with favorable prognosis
  - Higher proportion of survival when the tumour infiltration level are high, i.e., more T cells into the tumor microenvironment
- There appears to be a link between activating immune responses and tumour regression
- But how can we prove that immune cells directly recognise and destroy malignant cells?

### **How might the immune system prevent cancer?**

1. It protects the host against viral infection - important for virus-induced tumours.
2. It prevents the establishment of an inflammatory environment which is pro-tumourogenesis (chronic inflammation) by clearing pathogens and mediating rapid resolution of infection (limit inflammation)
3. It eliminates developing tumors which express new cancer antigens

## How are malignant cells recognised?

- Tumour immunosurveillance depends on the existence of cancer rejection antigens

Cancer cell	Shared	Normal cell
Tumour specific antigen (TSA), i.e. new antigens	<p>Tumour-associated antigen (TAA)</p> <ul style="list-style-type: none"> <li>• Non-mutated: deletion or gene fusion</li> <li>• Mutated (neoantigens): point mutation</li> <li>• Viral antigens (viral induced tumour)</li> </ul> <p>Cancer/testis antigens (NY-ESO, MAGE)</p>	Self antigen

Note that not all patients have TSA, lots only have TAA.

- Thus it is better to target in therapy TAA because there is more presentation in population
  - Also note that TSA apart from the viral antigens are completely person specific
- Problem: tumour antigens are usually similar to the self antigen thus not good response to them

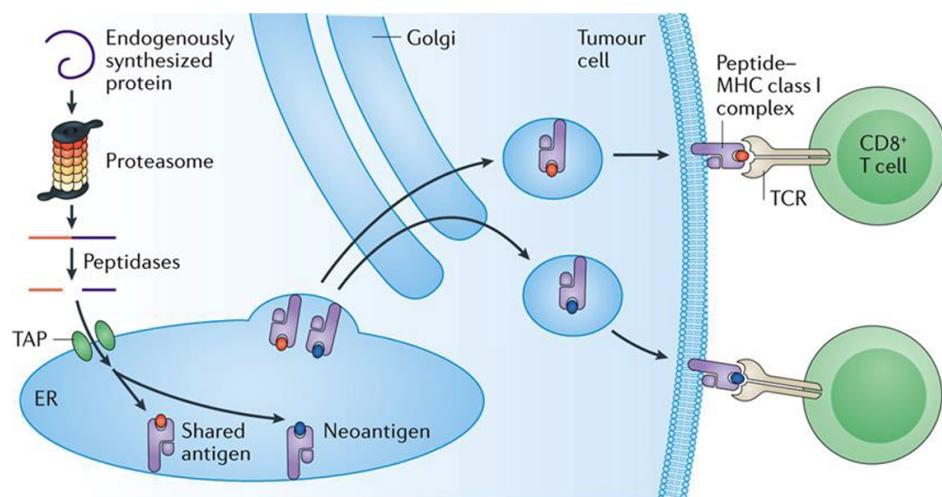
T cells can recognise mutated proteins in cancer cells.

Cancer cells often have large numbers of mutations, but only a few give rise to neo-antigens (only present in cancer cells and not in normal tissues).

- **Neoantigens** are tumour specific antigens which are produced by mutated genes.
  - These cancer neo-proteins are the ideal target for T cell therapy (also sometimes referred to as **tumour specific antigens, TSA**).
  - However, there are substantial difficulties in targeting mutated antigens.
    - Melanoma and lung cancer have approx. 30,000 mutations
    - The protein coding exome is 1% of the genome
    - Only non-synonymous mutations create novel protein sequences
    - Proteasome cleavage needs to create the mutant peptide
    - The mutant peptide needs to bind to the HLA of the patient
    - Each patient has a unique set of mutations

Hence, despite a large number of mutations, only few MHC-presented neo-antigens will be available for T cell recognition.

### TAA VS. neoantigens



#### Tumour associated antigen

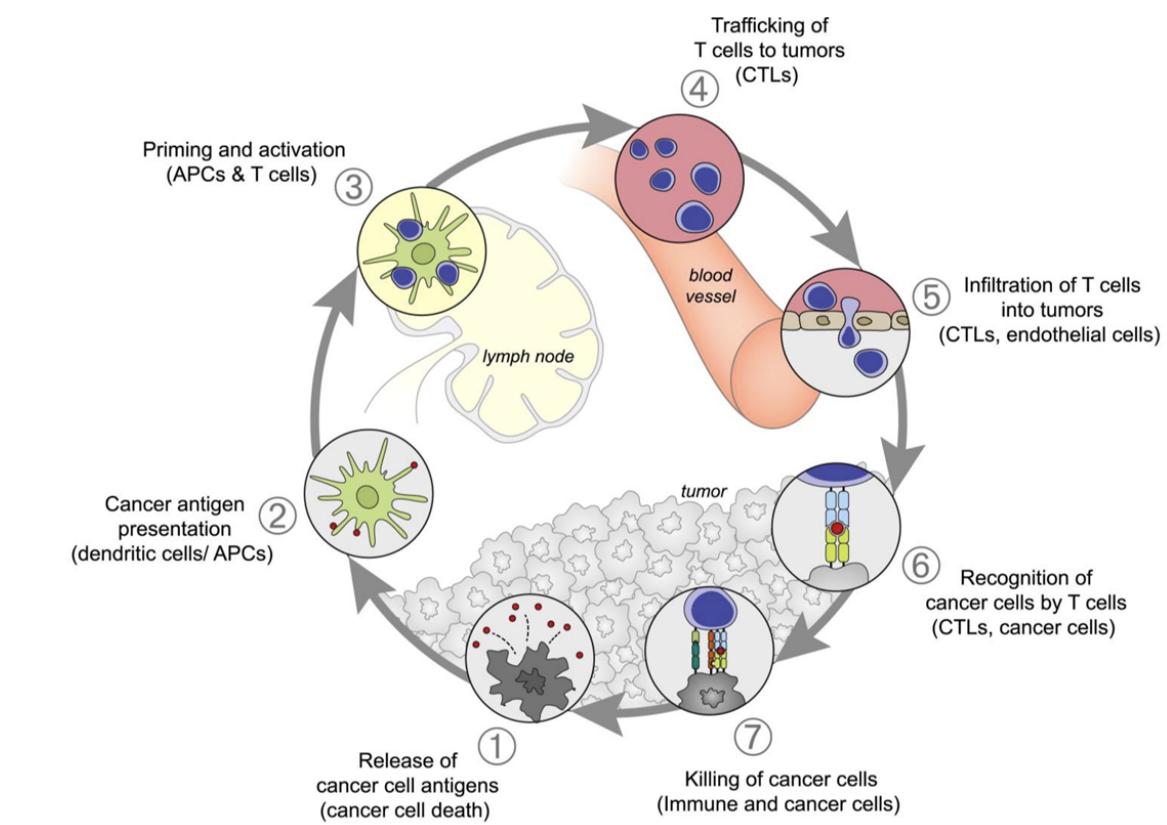
- Expressed in multiple tumours
- Higher risk of self tolerance
- Higher risk of autoimmunity

#### Neoantigens

- Unique to an individual tumour
- Lower risk of self tolerance

- Related to therapy to promote T-cell response reacting to Ag in normal cells
- Antigen loss variants less common
  - Some tumours escape by stop expressing MHC I thus no killing by CD8 T cells (Ag loss variant)
- Lower risk of autoimmunity

How the immune response recognises and responds to tumour?



## Summary - 1

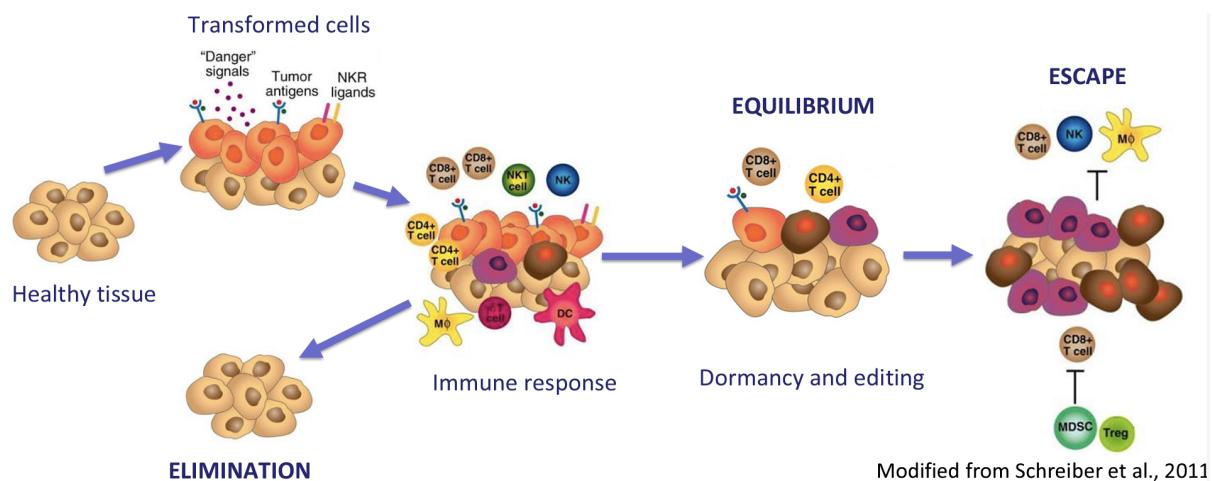
- Experimental evidence has proven a relationship between the immune system and malignant cells
- Detection of tumours by the immune system depends on the production of foreign or altered-self antigens by mutated cells
- Dying tumours release danger signals to activate DC

## Cancer immunoediting

Cancer cells evolve and develop mechanisms to escape immune attack (**immune evasion**).

- Escaped cancer cells can grow as malignancy in an uncontrolled fashion.
- **Escape** from immune surveillance is essential for cancer development.

## How tumour escape immune recognition or elimination: the “3 Es”



- Regularly there are healthy cells transformed and they are detected by the immune system
  - By danger signals from the dying cells
  - By tumor antigens
  - By NKR ligands (NK cells receptors)
- Immune response: This activates the immune system
  - Both innate and adaptive immunity are involved
- Most of the time, the transformed cells are cleared - **Elimination**
- Dormancy and editing: If the transformed cells are not eliminated, T cells are in **equilibrium** with the tumour cells
  - Not detectable clinically
  - Tumour is not growing but cannot be eliminated: T cells actively killing proliferating tumour cells
    - Dormant from a tumour perspective but active process

- During dormancy, tumour cells are under evolutionary pressure and continuously mutate
  - This can influence the surrounding area and tumour microenvironment (TME)
  - Lose tumour-specific antigen (TSA) - T cell unable to recognise
  - MHC I down-regulated (Ag loss variant) - CD8 T cells unrecognisable
    - Backup: Downregulation of MHC I is susceptible to NK cell killing
  - Release or recruit other inhibitory molecules or cells to tumour
    - Recruit Tregs so that no effective immune response
    - Depending on the balance, immune response might be dampened down to a level for tumour to **escape**
    - From this point onward, it is clinically called a tumour



T cells are most essential for the control of tumour growth



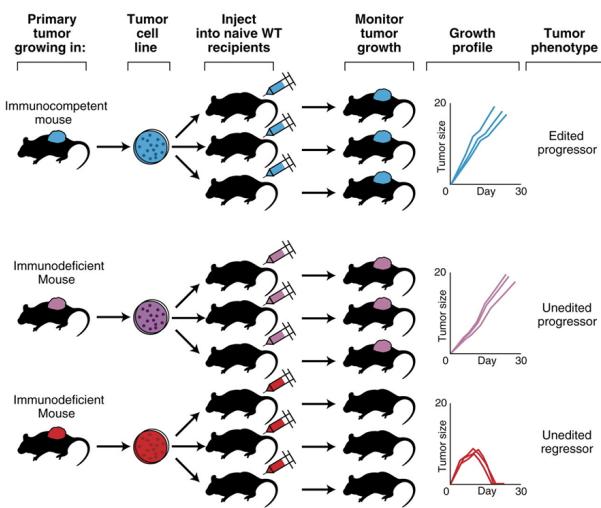
Carcinogenesis has 3 steps: initiation, promotion, and progression; describes the process from a normal cell to a cancer cell

## Experimental evidence of Immunoediting

- Immune system recognises protein antigens in cancer cells
- Killer cells eliminate cancer cells
- Cancer cells lose proteins recognised by killer cells
- Cancer cell can grow despite the presence of killer cells
- Cancer developing in the absence of an immune system can be rejected by killer cells

**Tumours in immunocompetent mice are qualitatively different from tumours in immunodeficient mice**

- Experimental evidence supporting that tumour changes under pressure exerted by immune system



Tumour from immunodeficient mouse is unable to growth in WT

- Primary tumour growing in:
  - Immunocompetent mouse (WT)
  - Immunodeficient mouse
- Inoculate the tumour cell into naive WT recipients
  - Grow in WT results in tumour growth
  - Tumour grown without pressure, no editing, normal immune system is able to eliminate

### Mechanisms of escape

1. Increased resistance to killing by CTL
  - a. upregulation of anti-apoptotic molecules
  - b. E.g. upregulation of BCL-2
2. Reduced expression of tumour-rejection antigens (tumour-intrinsic)
  - a. Evolution of tumour cells that do not express dominant T cell antigens
  - b. Loss of MHC I molecules
  - c. Loss of antigen-presenting function so peptides are not displayed on MHC I
3. Generation of an immunosuppressive environment in the tumour (tumour-extrinsic)
  - a. Secreting inhibitory or anti-inflammatory molecules or recruit inhibitory cells or changes in metabolic pathway
  - b. TGFbeta (IL-10), VEGF (vascular endothelial growth factor), IDO, Treg

### Summary - 2

1. The interaction between the immune system and neoplastic cells can be defined as the 3 E's: elimination, equilibrium, escape
2. The adaptive immune system may maintain tumours in a state of dormancy or equilibrium
3. Tumours evolve mutations to escape immune surveillance
  - a. This always happen if living long enough

## Immunotherapy of cancer

Because the immune system is capable to recognise cancer, we can use strategies to exploit its abilities to clear tumours.

- This is called immunotherapy.
- We distinguish immunotherapies in active and passive.

### Active immunotherapy

- Dependent on the patient's immune system to generate an appropriate immune response
  - E.g. vaccination

Vaccination can be **prophylactic** or **therapeutic**.

- Prophylactic: prevent cancer development
  - Liver cancer: HBV vaccine
  - Cervical cancer: HPV vaccine (Gardasil and Cervarix)
- Therapeutic: clear existing cancer
  - Dendreon Provenge: a prostate cancer vaccine produced with patients' own cells
    - DC vaccine: knowing peptide (Ag) paired to DC in vitro - giving to patient for an immune response
    - Expensive and slow due to personalisation
- More success has been had with prophylactic than therapeutic immunotherapy.

Some human cancers are caused by viruses and other pathogens.

- **Vaccines** against these viruses can protect against cancer development (prophylactic vaccines).

**Table 1.** Examples of cancers caused by viruses.

Infectious Agents	Type of Organism	Associated Cancer(s)
hepatitis B virus (HBV)	virus	hepatocellular carcinoma
hepatitis C virus (HCV)	virus	hepatocellular carcinoma
human papillomavirus (HPV) types 16 and 18,	virus	cervical cancer; vaginal cancer; vulvar cancer;
<u>Epstein-Barr virus</u>	virus	Burkitt lymphoma; non-Hodgkin lymphoma; Hodgkin lymphoma; nasopharyngeal cancer
human T-cell lymphotropic virus 1 (HTLV1)	virus	acute T-cell leukemia
<u>Helicobacter pylori</u>	bacterium	stomach cancer
schistosomes ( <i>Schistosoma hematobium</i> )	parasite	bladder cancer
liver flukes ( <i>Opisthorchis viverrini</i> )	parasite	cholangiocarcinoma

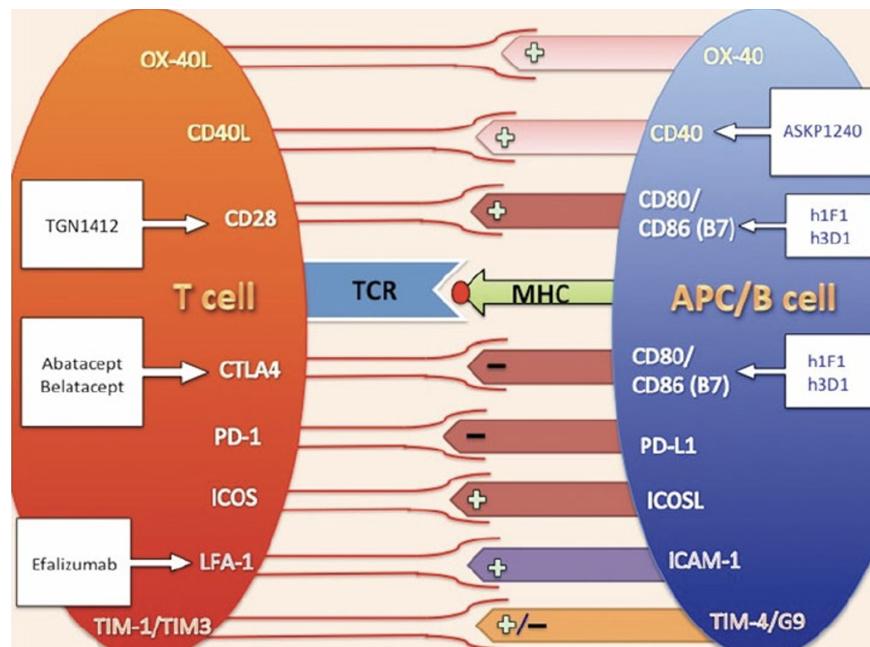
## Passive immunotherapy

- Can be used in patients with a defective immune system.
- Cells of the immune system or antibodies are administered to establish immunity.
- Includes:
  - Antibody therapy (e.g. checkpoint inhibition)
  - Cell therapy (eg. CAR-T cells)
  - Gene therapy

### Antibody therapy: checkpoint inhibitors

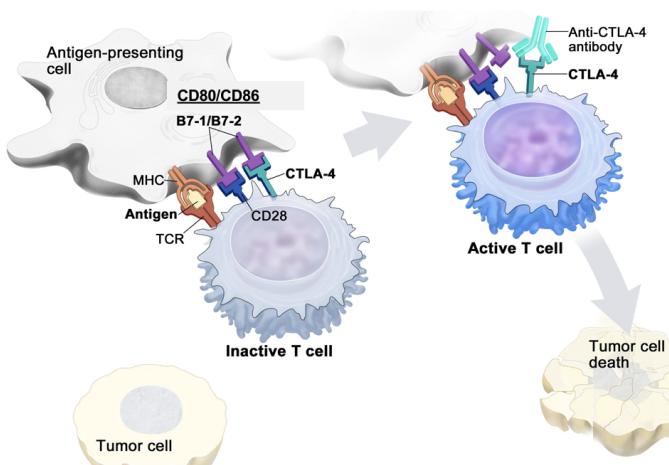
- **Monoclonal antibodies** have been used successfully in the treatment of cancer.
  - Some of the most successful monoclonal antibodies can activate cancer-specific immune cells *in vivo*.
  - This occurs by antibody **binding to negative regulators**, such as **PD1** and **CTLA4**, that are expressed by cancer-specific immune cells.
  - The blocking of negative regulation enables the immune cells to get activated and attack cancer cells.
- Cancer cells are normal cells with abnormal gene activity, thus T cells do not normally attack normal cells due to tolerance

- The key is to break the tolerance and allow T cells to kill
- T cell activation requires multiple signals
  - Signal 1: TCR - peptide presented by MHC
  - Signal 2: Co-stimulation by CD80/86 binds to CD28
  - Signal 3: Cytokines released by APC
- T cell activation is dependent on a balance between positive and negative signals



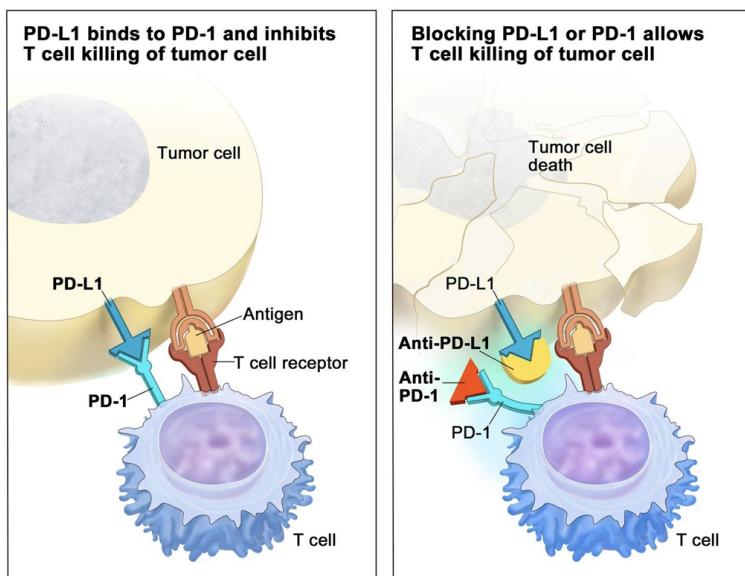
- CTLA4 and PD-1 are on T cells that prevent T cells activation

### Nobel prize for Dr Alison: CTLA-4 regulation



- CTLA4-B7 binding inhibits T cell activation and prevent co-stimulation of CD28-B7
- Blocking CTLA4-B7 binding allows T cell activation and killing of tumour cells
  - Leaves CD80/86 free to bind to CD28
- However, because this is non-specific, can lead to autoimmune disease

### Nobel prize for Dr Honjo: PD-1 regulation



- PD-L1 binds to PD-1 and inhibits T cell killing of tumour cells
- Blocking PD-L1 or PD-1 allows T cell killing
- Less side effect because
  - Presentation of PDL1 is an escape mechanism of tumour cells - thus gives some specificity to tumour cells
  - PD1 is more often or increased on continuously activated T cells (rather than naive T cells)
    - E.g. in chronic viral infection or tumours
- Clinical uses of PD1 blockade
  - Lung and renal cancer and melanoma
  - Clinical responses in approximately 30% of patients
  - Responses are durable without continued treatment

Note that checkpoint inhibitors are only functioning if there is functional T cells present

- The treatment DOES NOT specifically inhibits regulatory T cells.
- The treatment is NOT highly specific for cancer-reactive T cells.
- The treatment activates cancer-reactive T cells. The treatment involves blockade of pathways that negatively regulate T cells.
- The treatment is particularly effective when cancer cells have large numbers of mutations.

### Autoimmune side effects

	Ipilimumab	PD-1 inhibitors	Ipilimumab + nivolumab
Any body system	27%	16%	56%
Colitis*	12%	3%	15%
Skin	3%	2%	6%
Endocrinopathy • hypopituitarism • hypothyroidism	3% <1%	<1% 1%	NR 1%
Liver	2%	3%	20%

\*Most common cause of death from IrAEs is colonic perforation  
NR=not reported

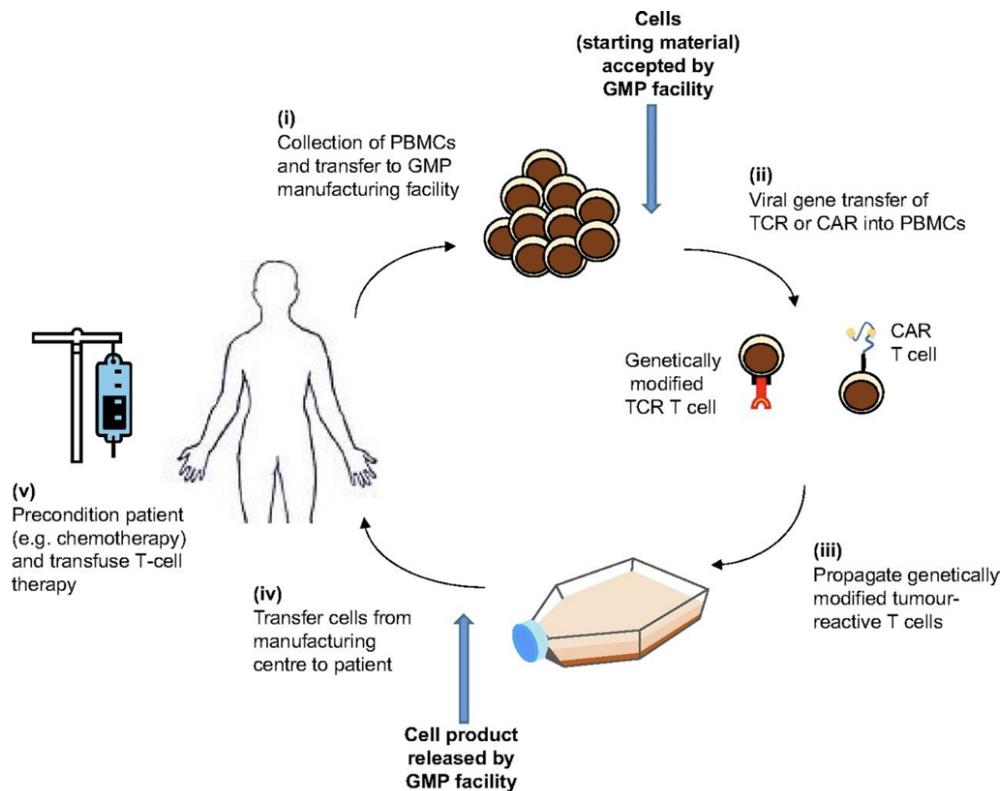
### Live medicines: Adoptive T cell therapy

- First trial:
  - Extract infiltrated T cells from tumour
  - Grow in vitro for large amount
  - Give back to the patients
  - Problem is that specificity not clear
- Genetic engineering to produce cancer-specific T cells
- Adoptive transfer into patients
- T cells persist and form immunological memory
- One dose of T cells has lasting effects

### Therapy with engineered T cells

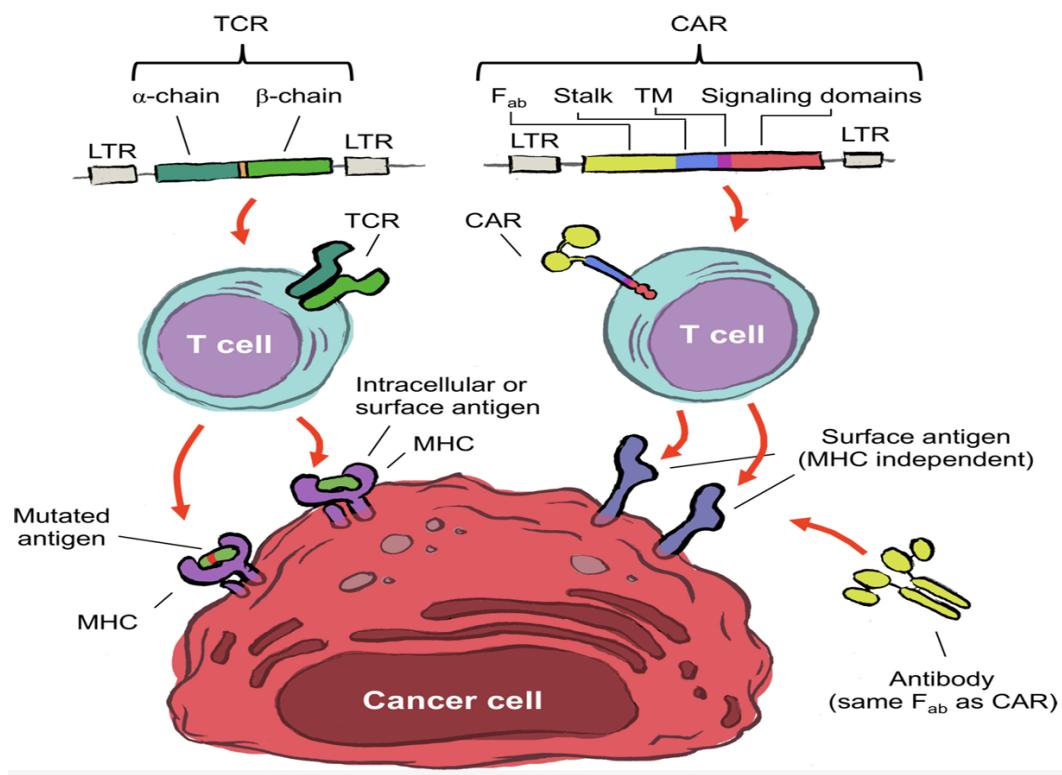
In spite of all the difficulties, **genetic engineering of T cells** has been successfully used to produce cancer-reactive T cells to treat cancer patients.

- Gene constructs encoding **chimeric antigen receptors (CARs)** or **T cell receptors (TCRs)** are used to reprogram the specificity of patient T cells



- Engineered cells mostly autologous (own cells)
- Idea is to generate a off the shelf product (available immediately and does not need to be specially made to suit a particular purpose) that would be cheaper and easier option

## TCR Targeting



## CAR Targeting

### TCR targeting

- Known peptide that is tumour-specific
- Advantage
  - Peptide could be intra or extracellular
- Disadvantage
  - Peptide and TCR must be known (specificity)
  - TSA are very different between people
  - Not functioning if MHC is downregulated or escape by changing TME
- Good to increase the tumour-specific T cells in patients but

### CAR targeting

- Chimeric antigen receptor edited onto T cells
  - Antibody recognition
  - Not recognising peptide but something on the surface
- TCR/CD3 cell signalling domains
- Can add co-stimulatory signals (e.g. cytokines)
  - Thus recognition and stimulation can happen simultaneously
- Advantages

- might not be enough
- TCR-engineered T cells have shown some limited success in **solid** cancers
  - Doesn't require MHC (as no requirement of peptide presentation)
  - Put different signalling domains
- Disadvantages
  - Only recognise surface
- CAR-engineered T cells have been successful to treat patients with **blood** cancers

They are generated by a similar transduction process

TCR-engineered T cells rely on antigen presentation by MHC

CAR-T cells include an antibody domain

They can NOT recognise the same antigens

- TCR recognise peptide
- CAR T antibody domain recognise surface molecules

### **Summary - 3**

- Vaccines are effective in prophylactic setting
- Antibodies are effective in the therapeutic setting
- CTLA-4 and PD1 antibodies can enhance tumour immunity but carry a high risk of autoimmunity
- T cell engineering with CARs and TCR can produce cancer-specific T cells
- CAR T cells have been effective in leukemia patients