THE NORTHERN HOSPITAL

PEMBROLIZUMAB

"Tears in the rain"; Rutger Hauer in "Blade Runner", 1982

.....I've seen things you people wouldn't believe.

Attack ships on fire off the shoulder of Orion.

I watched C-beams glitter in the dark near the Tannhäuser Gate.

All those moments will be lost in time… like …tears in the rain.

....Time to die.

Rutger Hauer in "Blade Runner", 1982

We are going to die, and that makes us the lucky ones. Most people are never going to die because they are never going to be born. The potential people who could have been here in my place but who will in fact never see the light of day outnumber the sand grains of Arabia. Certainly those unborn ghosts include greater poets than Keats, scientists greater than Newton. We know this because the set of possible people allowed by our DNA so massively exceeds the set of actual people. In the teeth of these stupefying odds it is you and I, in our ordinariness, that are here….

The lottery starts before we are conceived. Your parents had to meet, and the conception of each was as improbable as your own. And so on back, through your four grandparents

and eight great grandparents, back to where it doesn't bear thinking about…Not just Napoleon, but the humblest medieval peasant had only to sneeze in order to affect something which changed something else, after a long chain reaction, led to the consequence that one of your would be ancestors failed to be your ancestor and became someone else's instead. I'm not talking about "chaos theory" or the equally trendy "complexity theory", but just about the ordinary statistics of causation. The thread of historical events by which our existence hangs is wincingly tenuous….

There is another respect in which we are lucky. The Universe is older than a hundred million centuries. Within a comparable time the Sun will swell to a red giant and engulf the Earth. Every century of hundreds of millions has been in its time, or will be when its time comes, the "present century". Interestingly some physicists don't like the idea of a moving present, regarding it as a subjective phenomenon for which they find no house room in their equations. But it is a subjective argument I am making. How it feels to me, and I guess to you as well, is that the present moves from the past to the future, like a tiny spotlight, inching its way along a gigantic ruler of time. Everything behind the spotlight is in darkness, the darkness of the dead past. Everything ahead of the spotlight is in the darkness of the unknown future. The odds of your century being the one in the spotlight are the same as the odds that a penny, tossed down at random, will land on a particular ant crawling somewhere along the road from New York to San Francisco. In other words, it is overwhelmingly probable that you are dead.

Richard Dawkins,
The Anaesthetic of Familiarity
in Unweaving the Rainbow, 1998.

In the far distant future humanity has finally managed to escape a failing Earth. Overpopulated and polluted, with every possible natural resource exhausted, most species apart from humans, long ago extinct, the earth is dying. A small number however of the very best and fittest of humanity is privileged to leave the Earth and migrate to other worlds that can now be reached albeit with great difficult. These lucky few blaze a pioneering trail terraforming planets into new gardens of Eden. But left behind are untold billions of the weak and the poor who must make meagre impoverished livings as best they can. But unknown to those on Earth, there is a very dark side to the glamorous frontiers. There are dark hints of clashes with alien civilisations. In order to blaze the difficult trail genetically engineered super-humans are being produced to do the initial colonizing of hostile worlds, and even to fight wars against their civilizations, that "normal" humans are unwilling or unable to fight. In effect these super-humans are slaves to the pioneers, exploited and then programmed to die. The pioneers fear them, with quite some justification. Unless they had this inbuilt genetic programming that terminated their lives in just four years, in short time they would be the masters, and the pioneers redundant.

The super-humans, who are termed "replicants" have come to realise the horrific situation they are in. They are every bit as human as "real" humans, with feelings, emotions, ambitions, loves, anxieties and hates - they experience the full passions of life - but a hundred fold more intensely as they know they will have so little of it. A revolt breaks out among them, they are no longer willing to serve as slaves. The most brilliant

among them now leads the others, but with death programmed into them there is never any time left to them to achieve anything before they die and are simply replaced. A most advanced "Nexus 6" being, Roy Batty decides he must lead small group back to Earth and seek out Eldon Tyrell, the brilliant genius behind the Earth based humanoid genetic engineering program. He will seek him out and demand justice for the replicants - they must be allowed to live full and normal lives just like any "normal" human. But the Tyrell corporation has no sympathy for its "children". It is a brutal organization who sees their creations only as commodities by which they grow unimaginably rich. As more and more rebel replicants make their way back to Earth to demand justice, the Tyrell corporation grows ever more desperate, now employing specialist assassins called "Blade Runners" - experts in detecting replicants. Once detected they are then immediately killed.

Roy Batty and his group have proved especially difficult and are loose in Los Angeles, where it will be only a matter of time before one of them catches up with Tyrell. Rick Deckard is the best in the business when it comes to Blade Runners - and so Eldon Tyrell employs him to hunt down and "terminate" Batty and his accomplices. But first he tests Deckard's ability to detect a replicant on a beautiful woman called Rachel, who in fact is a replicant but who has been given false memories of a childhood and so she believes she is a normal human. Rachel is a new super advanced prototype. After an unprecedentedly difficult and protracted testing Deckard finally discovers that she is a replicant. Tyrell is satisfied he has his man. But then things become complicated. Deckard falls hopelessly in love with Rachel. He tells her the truth about what she is, and she, distressed beyond endurance, runs away. Tyrell orders Decker to kill her along with the other replicants.

Decker hunts down the replicant Zhora in a strip bar and kills her, but then is discovered by Leon a second replicant who is immensely strong and disarms him. Just as Leon is about to kill Deckard, Rachel appears and shoots Leon dead. Deckard lets Rachel go. Later he catches up with the "pleasure model" replicant Pris, and kills her too. Now only Roy Batty is left. But now Deckard becomes the hunted, and Roy finally corners him on the top of bleak abandoned building during a relentless icy climate change induced storm. Deckard is no match for Roy, who cripples his hand then simply plays with him, as if unable to bring himself to kill, even though he has just killed Tyrell when he revealed the fact that there was no way to reverse the genetic programming of his premature death. "The light that burns twice as bright, burns half as long", Tyrell had told him, "and you have burned so very very brightly Roy". Deckard suddenly slips from the top of the building, but Roy reaches out like lightning and catches him up in one arm saving his life. Deckard watches helplessly injured, still expecting the final coup de grace to be delivered once Roy has had his "fun". He closes his eyes and waits for the end. But nothing happens. He opens his eyes again and Roy is looking at him intently. It is clear his body is now failing him, but still he cannot bring himself to kill Deckard. He catches a white dove in mid-air with a lightning reflex, and holds it close to himself.

After some moments of silence, he whispers, "I've seen things you people wouldn't believe!" Deckard is confused but dares not move or say a word, he only listens.

"...Attack ships on fire off the shoulder of Orion. I watched C-beams glitter in the dark near the Tannhäuser Gate".

He slumps towards the ground, now lost in his own sad distant thoughts.

"All those moments will be lost in time… like …tears in the rain…..Time to die"

Roy's head hangs motionless, the icy rain now coming down on his lifeless body even heavier than before. His hand opens and the dove flits up into the bleak sky above. Deckard now grapples with a profound sadness, he cannot quite understand. Suddenly a vaguely familiar voice calls out behind him.

"Too bad she won't live…..but then none of us will".

Deckard gets up slowly, he must go and be with Rachel.

In the 21st century the vision of Ridley Scott's future is closer to hand than we may appreciate. In one of the greatest scientific endeavors since Watson and Crick discovered the structure of DNA in 1953, the human genome was sequenced in its entirety by 2001. We stand on the threshold of a new revolution in medical history. Twenty first century medicines will increasingly involve the manipulation of the very genetic material of life. We understand more about the processes of "programmed cell death", and now for the first time we may develop drugs such as the miraculous pembrolizumab that can directly and specifically alter some of the these primal programs that determine the life and death of cells.

With this god-like knowledge will also come great responsibility in the future. Already drug companies are attempting to patent genes. So far, mercifully, courts of laws in the US have disallowed this disgusting concept. We must however remain vigilant against those who would play god in order to enrich themselves, lest the nightmare of a Tyrell corporation become a reality.

PEMBROLIZUMAB

Introduction

Pembrolizumab (trade name, "**Keytruda**") is a humanized anti‑PD‑1 monoclonal antibody that *inhibits* the **programmed death 1 (PD‑1) receptor** from binding to its ligands (**PD‑L1 and PD‑L2**) on **tumour cells**. This results in a reactivation of cytotoxic T lymphocytes and hence **anti-tumour activity**.

It is one of a novel class of anti-cancer agents known as an **immune checkpoint inhibitors** (or "**ICIs**").

The FDA initially approved pembrolizumab to treat metastatic melanoma.

In 2017 it approved it for *any* unresectable or metastatic solid tumor with **certain genetic anomalies** (mismatch repair deficiency or microsatellite instability).

It was the first time the FDA had approved a cancer drug **based on tumor genetics** rather than *tissue type* or *tumor site*.

Immune checkpoint inhibitors (ICIs) have *revolutionised* the treatment of **advanced** cancers over the past 5 years, with 15 - 20 % of these patients now achieving **long term disease control** *beyond* 5 years.

Unprecedented improvements in survival have, in particular, been seen in patients with **metastatic melanoma** and **lung cancer**.

Emergency Physicians need to be aware of the potential toxicities of these agents.

See also separate document on Immune Related Adverse Events (irAE), in Oncology folder.

History

Ipilimumab was the first ICI antibody introduced into clinical practice in 2011 for treatment of melanoma

Pembrolizumab was approved by the FDA to treat metastatic melanoma in 2014.

In 2017 however the FDA approved it for *any* **unresectable** or **metastatic solid tumor** with **certain genetic anomalies** such as mismatch repair deficiency or microsatellite instability

This was the first time in history the FDA had approved a cancer drug based on **tumor genetics** *rather* than **tissue type** or **tumor site**.

Chemistry

Humanized antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans.

The process of "humanization" is usually applied to monoclonal antibodies developed for administration to humans (for example, antibodies developed as anti-cancer drugs).

Physiology - Immunology

Immune checkpoints:

Immune checkpoints are *regulator molecules* (proteins) of immune cell activation.

They play a key role in maintaining immune homeostasis and preventing autoimmunity.

They are crucial pathways for self-tolerance, which prevents the immune system from attacking cells indiscriminately.

In cancer, immune checkpoint mechanisms are unfortunately often activated to suppress the early anti-tumor immune response.

This has led to the development of several checkpoint inhibitor antibody drugs that are currently being tested in ongoing clinical trials or have already been approved for a number of cancers.

Currently approved checkpoint inhibitors block **CTLA4** and **PD-1** and **PD-L1 (a ligand of PD-1)**

Programmed cell death protein 1:

Programmed cell death protein 1, (**PD-1**) is a **cell surface receptor** that plays an important role in **down-regulating** the immune system.

PD-1 binds two ligands, **PD-L1** and **PD-L2**. (A ligand is a substance that forms a complex with a biomolecule to initiate a biological function. In protein-ligand binding, the ligand is usually a molecule which produces a signal by binding to a site on a target protein).

PD-1 promotes self tolerance by suppressing T cell inflammatory activity.

PD-1 is known as an "**immune checkpoint**" that guards against autoimmunity through a dual mechanism of:

- **Promoting apoptosis** (programmed cell death) in antigen-specific T-cells in lymph nodes

And

- **Reducing apoptosis** in regulatory T cells (anti-inflammatory, suppressive T cells).

Through these mechanisms, PD-1 inhibits the immune system.

It **prevents autoimmune diseases**, *however* it can also **prevent the immune system from killing cancer cells**.

See also Appendix 1 below

Classification

Immune checkpoint inhibitors currently used in Australia include:

1. Anti-PD-1 antibodies:
    - Nivolumab
    - **Pembrolizumab**
    - Pidilizumab
2. Anti-PD-L1 antibodies:
    - Avelumab
    - Atezolizumab
    - Durvalumab
3. Anti-CTLA-4 antibodies:
    - Ipilimumab
    - Tremelimumab

Preparations

Pembrolizumab as:

Ampoules:

- 50 mg (as powder for reconstitution).
- 100 mg - as 25 mg/mL in 4 mL

Mechanism of Action

Immune checkpoint inhibitors or **ICIs** are **monoclonal humanized antibodies** which **block cell surface molecules** involved in the **regulation of T cell activation**, including cytotoxic T lymphocyte antigen 4 (**CTLA-4**), programmed cell death protein 1 (**PD-1**) and its **ligand** (**PD-L1**).

In normal homoeostasis, these **inhibitory molecules** are involved in **preventing excessive inflammation** and **autoimmunity**.

However, in the **tumour microenvironment**, these molecules are **over expressed** and so **promote immune tolerance** *rather* than tumour destruction.

Blockade of these **ICIs** can restore the appropriate anti-tumour response and improve patient survival.

Other inhibitory and activating molecules are also involved in balancing T cell regulation, some of which are currently undergoing further research as therapeutic targets.

Pharmacodynamics

Immunotherapy agents induce a tumour-directed immune response through T-cell activation (see Appendix 1 below).

Immune checkpoint inhibitors (ICIs) have *revolutionised* the treatment of **advanced** cancers over the past 5 years, with 15 - 20 % of these patients now achieving **long term disease control** *beyond* 5 years.

Unprecedented improvements in survival have, in particular, been seen in patients with **metastatic melanoma** and **lung cancer**.

Pharmacokinetics

Absorption:

- Pembrolizumab is administered intravenously.

Distribution

- Distribution is consistent with extravascular volume, at a steady state it is around 7.5 Liters.
- The degree of protein binding is unknown, however as an antibody, pembrolizumab is not expected to bind to plasma proteins in a specific manner.
- It is unknown if pembrolizumab can cross the human placenta.

- It is unknown if pembrolizumab is excreted into human breast milk.

Metabolism and excretion:

- Pembrolizumab is catabolised through non-specific pathways
- Half-life is around **22 days**.

Indications

In *general* terms ICIs - including **pembrolizumab** have, to date, been *most* utilised in the management of:

1. Advanced melanomas
2. Non-small cell lung cancers
3. Metastatic renal cell carcinomas.

However, they have also shown benefit in a range of other malignancies including:

4. Hodgkin's lymphoma
5. Gastric cancer
6. Prostate cancer.

Therefore, the indications and so the number of patients receiving ICIs is very likely to increase over the coming years.

It should also be noted, that is not only tumor type, but also the exact genetic characterises of any given case, that must be known before it can be determined if ICI treatment is appropriate.

Contra-indications/precautions

The following are largely precautions only, which must be balanced against the prospect of poor prognosis without treatment.

1. Pre-existing autoimmune diseases is a relative contraindication
2. Further research is required into the use of ICIs in patients with existing autoimmune disorders, as such patients have traditionally been excluded from clinical trials.
3. Evidence from case reports and case series suggests that while some patients do tolerate ICIs, others experience flares of their underlying disease.

4. Previous severe irAE to another ICI (monitor closely).

5. Diabetes mellitus may be worsened.

6. Patients taking corticosteroids or immunosuppressants should be stopped before starting pembrolizumab as these may reduce its effectiveness.

7. Pregnancy and breastfeeding - contraindicated (see below).

    - Women of child-bearing age should use contraception when taking pembrolizumab.

Pregnancy

Pembrolizumab is a category D class drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Reports describing the use of pembrolizumab in human pregnancy have not been located.

Animal studies have reported an increased risk of fetal loss when pembrolizumab is used during pregnancy due to a disruption in the tolerance to the fetus.

The manufacturer recommends women of child-bearing potential use adequate contraception during therapy, and for at least 4 months after the last treatment.

Breast feeding

Reports describing the use of pembrolizumab during breastfeeding have not been located.

Due to the potential risk of severe immune-mediated adverse reactions in the breastfed infant, consider an alternative treatment or avoid breastfeeding during pembrolizumab therapy.

Adverse Effects

Immune related adverse events (i.e **irAEs**) of **ICIs as a group** are as follows:

Most commonly:

1. Dermatological toxicity:

    Skin irAEs generally develop within a few weeks of commencing treatment, although delayed onset of rash has also been reported.

Reactions can range from mild to severe and potentially life-threatening.

Mild reactions may be maculopapular

Severe reactions have included:

- Stevens - Johnson syndrome
- Toxic epidermal necrolysis
- DRESS
- Pyoderma gangrenosum-like ulceration

Vitiligo has been reported in patients treated for melanoma but not in other cancers. Interestingly, however, vitiligo is considered to be potentially predictive of durable response to ICIs.

2. Gastrointestinal toxicity:

GIT complications include:

- **Colitis** with:
  - ♥ Diarrhoea - this occurs *frequently* with ICIs.
  - ♥ GIT perforation
  - ♥ Obstruction
- Ischaemic gastritis
- Pancreatitis

3. Endocrinopathies:

Endocrinopathies related to ICIs include:

- Thyroid dysfunction
  - ♥ Transient, asymptomatic elevation of thyroid-stimulating hormone occurs in some patients and may progress to hypothyroidism.
  - ♥ Hyperthyroidism is less common and may be due to transient thyroiditis which then progresses to hypothyroidism.
- Hypophysitis, (i.e inflammation of the pituitary gland).

- ♥ Hypophysitis can result in hypopituitarism leading to:
  - ♥♥ Hypoadrenalism
  - ♥♥ Hypothyroidism
  - ♥♥ Hypogonadism

- Primary adrenal insufficiency (rare)
  - ♥ Primary (or secondary) adrenal insufficiency can present as an adrenal crisis.

- Type 1 diabetes mellitus (rare)

Less commonly, the following may be seen:

4. Hepatotoxicity:

Immune-mediated hepatitis causing abnormal liver function tests occurs quite frequently with ICIs, particularly with combination therapies.

Fulminant hepatitis causing liver failure however is fortunately rare.

Other causes of liver dysfunction should be also considered, particularly **viral hepatitis**, **other hepatotoxic drugs**, **alcohol** or **liver metastases**.

Liver biopsy may ultimately be necessary to exclude alternative diagnoses.

5. Pulmonary toxicity:

Pneumonitis may occur uncommonly.

Interestingly, the incidence is higher with anti-PD-1 therapy for lung cancer than for melanoma.

Symptoms include **dry cough, dyspnoea** and **hypoxia.**

6. Rheumatological toxicity:

The following may be seen:

- **Arthralgia** and **myalgia** are relatively frequent with all ICIs. These are predominantly mild or moderately severe.

Less commonly:

Polyarticular inflammatory arthritis

- Myositis
- Vasculitis

7. Neurological toxicity:

Neurological toxicity is uncommon, but the following have been reported:

- Peripheral neuropathies which may be sensory, motor or mixed.
- Myasthenia gravis
- Chronic inflammatory demyelinating polyneuropathy
- Transverse myelitis
- Guillain-Barré syndrome.
- Aseptic meningitis
- Cranial nerve palsy
- Posterior reversible encephalopathy syndrome (PRES)

8. Nephrotoxicity:

The following have been reported:

- Interstitial nephritis
- Granulomatous nephritis
- Lupus-like glomerulonephritis

9. Ocular:

- Uveitis

Reactions related to giving the infusion itself:

Infusion-related reactions include:

1. Fever
2. Rash

3. Hypotension

4. Rigors / chills

5. Wheezing

6. Pruritis / flushing

Dosing

Treatment protocols are individualized by Medical Oncologists according to:

- The cancer stage
- The type of cancer, including its exact genetic profile.
- Patient response
- Patient tolerance

In *general* terms, usual dosing of pembrolizumab for adults is:

- IV infusion 2 mg/kg every 3 weeks.

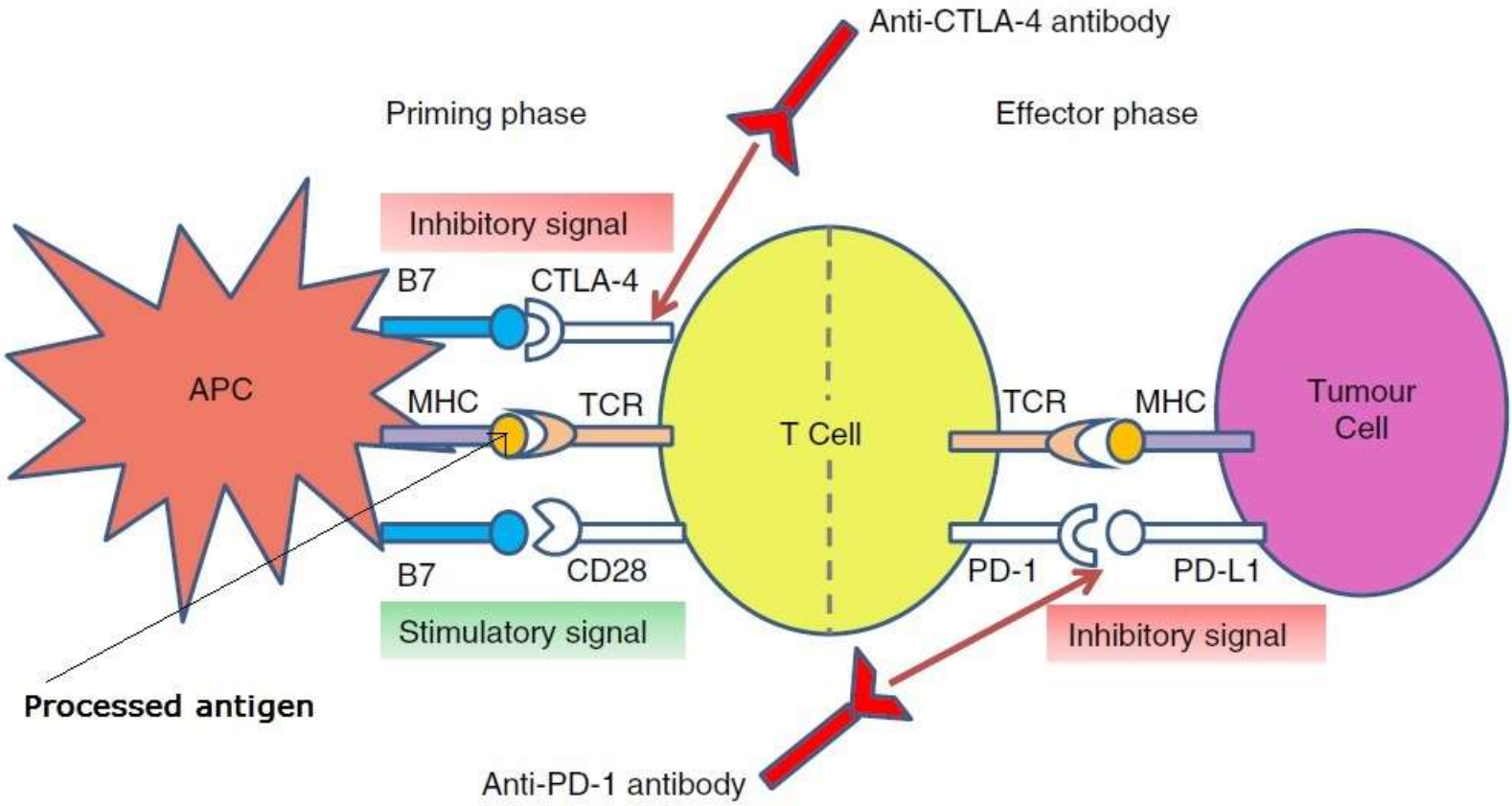
  Infusions are given over 30 minutes via an in-line 0.2 - 0.5 micrometre (micron) filter.

  Emergency treatment for anaphylaxis must be on hand.

  Observe the patient for infusion-related reactions and stop the infusion if they occur.

Appendix 1

T Cell Immunology:



APC:

Antigen-presenting cells (APCs) are a heterogeneous group of immune cells that mediate the cellular immune response. They **process** captured (or phagocytized) antigens and then **present** them for recognition by certain lymphocytes such as T cells. Classical APCs include dendritic cells, macrophages and B cells.

MHC:

The **major histocompatibility complex (MHC**) is a set of **cell surface proteins** essential for the acquired immune system to recognize foreign molecules in vertebrates, (which in turn determines histocompatibility). The main function of MHC molecules is to bind the processed antigens derived from pathogens and display them on the cell surface for **recognition** by the appropriate **T-cells**.

TCR:

The T-cell receptor, (or TCR), is a molecule found on the surface of T cells, or T lymphocytes, that is responsible for recognizing fragments of antigen bound to major histocompatibility complex (MHC) molecules.

PD-1:

Programmed cell death protein 1, (**PD-1**) is an "**immune checkpoint molecule**", i.e a **cell surface receptor** that plays an important role in **down-regulating** the immune system and promoting **self tolerance** by **suppressing** T cell inflammatory activity.

It binds to two "ligand" molecules

B7 protein:

B7 protein is membrane protein found on activated antigen presenting cells (APC) that, when paired with either a **CD28** or **CTLA-4** surface protein on a T cell, can produce a co-stimulatory signal or a co-inhibitory signal to enhance or decrease the activity of a MHC-TCR signal between the APC and the T cell, respectively.

Binding of the **B7** of APC to **CTLA-4** of T-cells causes **inhibition** of the activity of T-cells

CTLA-4:

CTLA-4 (**cytotoxic T-lymphocyte-associated protein 4**) is a protein receptor that, functions as an "immune checkpoint", that down regulates (i.e suppresses) immune responses.

CD28:

CD28 (**Cluster of Differentiation 28**) is one of the proteins expressed on T cells that provide co-**stimulatory** signals required for T cell activation and survival.

T cell stimulation via CD28 in addition to the T-cell receptor (TCR) stimulation can provide a potent signal for the production of various interleukins (IL-6 in particular).

PD-L1:

PD-L1 (Programmed death-ligand 1) is (like CTLA-4) a protein receptor that, functions as an "immune checkpoint", that down regulates (i.e suppresses) immune responses.

Appendix 2 - Monoclonal Antibody Nomenclature

According to the International Nonproprietary Name (INN) Working Group on Nomenclature for Monoclonal Antibodies, the order for combining the key elements of a monoclonal antibody name is as follows:

1. Prefix
2. Infix representing the target or disease
3. Infix indicating the source.
4. Suffix indicating antibody type

Suffix:

Examples include:

1. The suffix "**-mab**" is used for:
    - Monoclonal antibodies
    - Antibody fragments
    - Radiolabeled antibodies.
2. For **polyclonal** mixtures of antibodies, "**-pab**" is used.
    - The -pab suffix applies to polyclonal pools of recombinant monoclonal antibodies, as opposed to polyclonal antibody preparations isolated from blood.

      It differentiates polyclonal antibodies from individual monoclonal antibodies named with -mab.

Target or disease infix:

Target/Disease Class Infixes for Monoclonal Antibodies include:

Infix	**Target/ disease**	**Examples**
tu	Tumors	tuzumab/-tumab/-tomab
li / l	Immunomodulator	Liximab/-lumab/-lixizumab

ba / b	Bacterial	bixumab/-bumab
ci / c	Cardiovascular	cixumab/-cumab
fu / f	Antifungal	fuzumab/-fumab
gro(o)	Skeletal muscle mass related growth factors and receptors as target	grumab
ki / k	Interleukins	kiximab/-kumab
ne / e	Neurons as targets	nezumab/-numab
so / s	Bone	somab/-sumab
vi / v	Viruses, antiviral indications	vizumab/-vumab

Source infix:

A series of infixes which *immediately precede* -mab or -pab indicate the source.

A limited subset of infixes used most often accounts for nearly all the monoclonal antibody names.

The source infixes used most frequently include:

- -zu = humanized
- -o = mouse
- -u = fully human
- -xi = chimeric

Humanized antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans.

Humanized antibodies are distinct from **chimeric antibodies**. The latter also have their protein sequences made more similar to human antibodies, but carry a larger stretch of non-human protein

Harrison Ford, as Rick Deckard, in "Blade Runner", 1982

"Too bad she won't live....but then, none of us will"

"Too bad she won't live…, but then who does?", Mary Sean Young as Rachel in "Blade Runner", 1982.

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