# T
# ONC 9 – Pharmacology of Cancer Immunotherapy

## Define Cancer Immunotherapies

**Immunotherapy** is a specific approach to treatment that uses the immune system to fight disease either by;

- Stimulating immune system to work *smarter/harder* to fight cancer cells
- Aiding immune system by providing a *targeting system* through the use of antibodies

There are different types of cancer immunotherapies with strategies including;

| *Strategy/Approach* | *Description* |
|---|---|
| **Antibodies** | Antibodies that are made specifically to target (and attach) to abnormal proteins and other substances that are expressed in cancerous cells to **mark them** for destruction by the innate immune system;<br>• Can be directly Cytotoxic → Direct *Apoptosis*<br>• Can mediate antibody associated destruction → Other immune cells |
| **Checkpoint Inhibitors** | **Disinhibition** of certain proteins that normally *inhibit* the immune system that are overexpressed and taken advantage of by cancerous cells<br>• Trying to reverse "*immune evasion*" of cancerous cells |
| **Vaccines** | Train the immune system to respond better to cancer? |
| **T-Cell Transfers** | T-Cells **synthesized in vivo** and then placed *in vitro* into our bodies that are tailor made to target specific substances in tumors |

## Describe the rational use of monoclonal antibodies in anti-cancer treatments

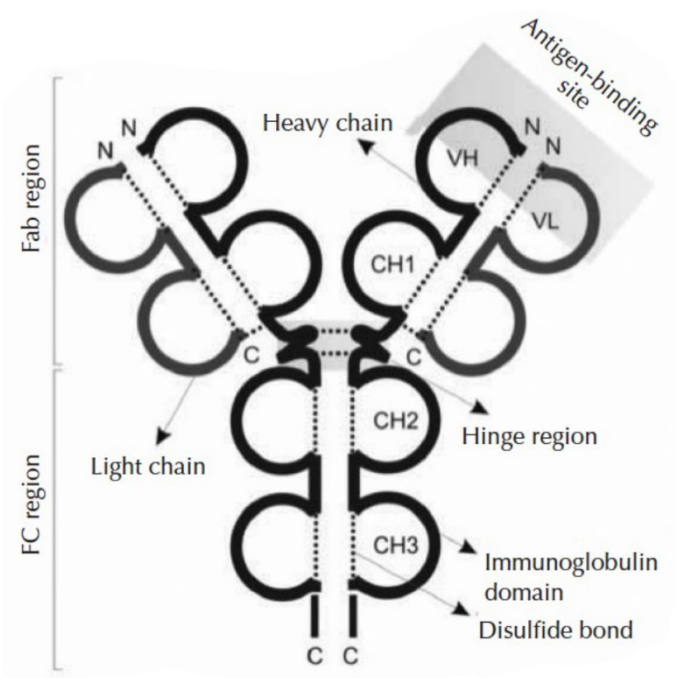
**Immunoglobulins** are a family of globular proteins (Ig*x*), otherwise known as **antibodies**, bind with various *specificity* and *affinity* to **antigens**.

**$F_{ab}$ Region:**

Contains the antigen binding site that imparts specificity. Will be unique for each type of antigen.

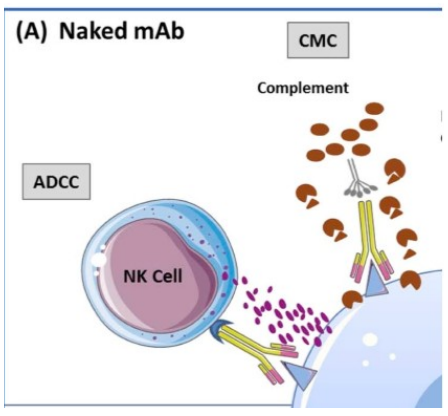
**$F_c$ Region:**

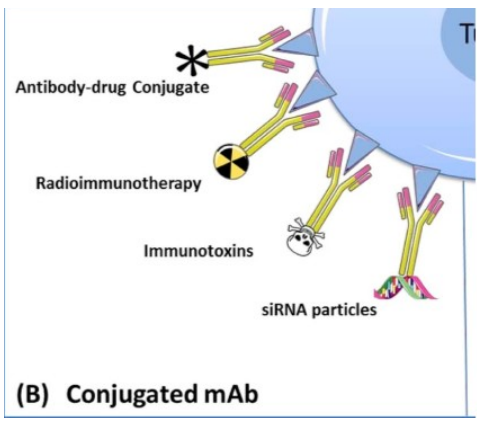
The "constant" region that will dictate the **class** of antibody and interact with **other immune cells** once it has found it's "target"/antigen.




*An IgG antibody (most common)*

As described earlier, **monoclonal antibodies** will exert their effect through various mechanisms;




| *Mechanism* | *Description* |
|---|---|
| **Antibody-Dependent Cellular Toxicity** | Specific **cancerous antigens** (proteins and other substances not usually produced) are marked by antibodies → **natural killer cells** and **neutrophils** to come in to destroy. |
| **Complement-Mediated Cellular Toxicity** | Specific **cancerous antigens** (proteins and other substances not usually produced) are marked by antibodies → **activation** of the **complement system/cascade** that will eventually form the **MAC** (*membrane attack complex*) to drill a hole → death |
| **Direct Apoptosis** (not displayed in graphic) | Antibody binding will cause a signal cascade eventually resulting in **apoptosis** of the cell. |
| **Conjugation** | Antibody may be **conjugated** to a particular substance such as;<br>• Cytotoxic Drug<br>• Immunotoxins<br>• Radioimmunotherapy Agents<br><br>Simply being used as an accurate *targeting* system without damaging healthy cells |

Another unique example of a mAB are **Bispecific Monoclonal Antibodies** in which;

- 1 arm attaches to **antigen** on cancerous cell
- 1 arm attaches to **T Cells** in circulation
- This brings both cells into close proximity allowing for appropriate **T-Cell mediated response** to tumor

**Chimeric**

Majority of mAB is from human DNA but parts are from other animal sequence (*eg. Mouse*)

**Humanized**

Same as Chimeric but ↓ Non-Human sequence

**Human**

↓ Concern about immunogenecitiy

| Common Antibody Origin | INN substem | Representative Examples |
|---|---|---|
| Chimeric | -xi- | Rituximab, Cetuximab |
| Humanized | -zu- | Trastuzumab Bevacizumab |
| Human | -u- | Panitumumab Ipilimumab |

# List clinical uses and the properties of trastuzumab, bevacizumab, cetuximab and panitumumab

## Trastuzumab

**Trastuzumab** is a humanized, monoclonal antibody that blocks **HER-2/*neu* receptors**.

**Human Epidermal Growth Factor 2 Receptors** are involved in *epidermal tissue growth* and is *overexpressed* in some Breast Cancers.

- Involved in a tyrosine kinase pathway that mediates cell growth, differentiation and survival
- Upon binding to receptors, Trastuzumab blocks signal propagation but **also activates immune response** against the target cell (for destruction)

| *Parameter* | *Notes* |
|---|---|
| **Efficacy** | Antibody that binds to **HER2/*neu* receptors** inhibiting uncontrolled cell proliferation and marking for immune response |
| **Safety** | **Infusion Reactions** are common with Trastuzumab use which may need premedication.<br><br>**Cardiomyopathy** (similar to Anthracycline Antibiotics) |
| **Resistance** | ↑ EGFR/HER2 Receptor activity → dominates antagonism (overcomes our antagonist)<br>**HER1** use bypassing HER2 pathway |

## Bevacizumab

**Bevacizumab** is a humanized, monoclonal antibody that binds to **VEGF.**

**Vascular Endothelial Growth Factor** is a protein involved in *angiogenesis* which supports the metabolic demand of a tumor.

- Binding of Bevacizumab to VEGF → ↓ Angiogenesis → ↓ Nutrients → **Starvation of Tumor**

| *Parameter* | *Notes* |
|---|---|
| **Efficacy** | Antibody that binds to **free VEGF** inhibiting Angiogenesis surrounding tumor cells. |
| **Safety** | **GI system** is in a dynamic state (high cell turnover, very dependent on VEGF) therefore inhibition of VEGF → GI Effects (*eg*. **GI Perforations**)<br><br>Cardiomyopathy (similar to Anthracycline Antibiotics) but **less than Trastuzumab** |
| **Resistance** | Use of other growth factors (**non-VEGF**) to mediate Angiogenesis |

## Cetuximab

**Cetuximab** is a chimeric, monoclonal antibody that **blocks HER-1/*neu* receptors.**

| *Parameter* | *Notes* |
|---|---|
| **Efficacy** | Antibody that binds to **HER1/*neu* receptors** inhibiting uncontrolled cell proliferation and marking for immune response |
| **Safety** | **Infusion Reactions** can be quite severe (similar to Trastuzumab)<br><br>**Cardiopulmonary Arrest** in rare cases<br><br>Other delayed onset toxicities include;<br>• Skin Rash<br>• Hypomagnesemia<br>• **Interstitial Lung Disease** |
| **Resistance** | **Uncoupling** of **KRAS** and **BRAF** to HER2 receptor (and thereby EGFR substrate).<br>• **KRAS** and **BRAF** are downstream **oncogenes** that need to be *wildtype* (normal fx) as they are what mediates activity following EGFR binding<br>• If these are **uncoupled** to HER2 receptors, than even if we block the receptor there will still be cell growth |

## Panitumumab

**Panitumumab** is a human, monoclonal antibody that **blocks HER-2/*neu* receptors.**

| *Parameter* | *Notes* |
|---|---|
| **Efficacy** | Antibody that binds to **HER2/*neu* receptors** inhibiting uncontrolled cell proliferation but **does not activate innate, immune response**. |
| **Safety** | ↓ **Infusion Reactions**<br><br>Delayed toxicities include;<br>• Skin Rash/**Dermatological Toxicities**<br>• Hypomagnesemia<br>• Interstitial Lung Disease<br>(similar to Cetuximab) |
| **Resistance** | Same as Cetuximab |

# Explain T-cell inhibitory signals and the mechanism of immune checkpoint therapy

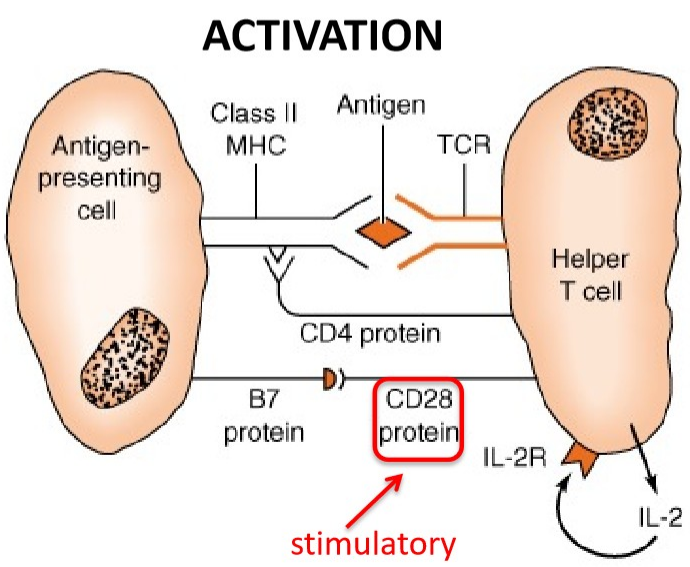
**T-Cell Inhibition** is an innate system in our bodies as we do not want *chronic activation* of cytotoxic and immune activity.

## T-Cell Activation

Activation of T-Cell (and thereby T-Cell mediated events) requires 2 signals.

1. **Recognition** – An *antigen presenting cell* must come in and present **MHC II** (with an antigen attached to its tip) that matches a **T-Cell Receptor** on a *helper T-cell*. **CD4** from the helper T-cell also binds to **MHC II**

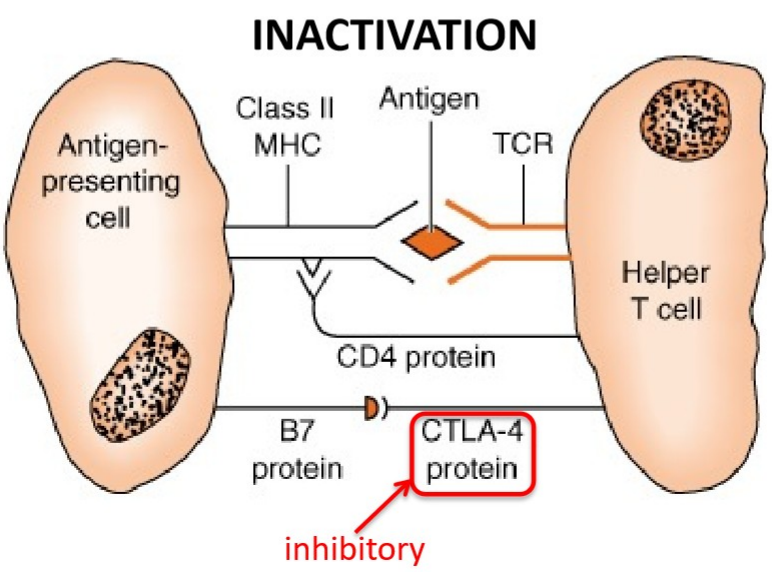
2. **Verification** – A protein called **CD28** binds to **B7-H1** or **B7-H2** which is *stimulatory*




## T-Cell Inhibition

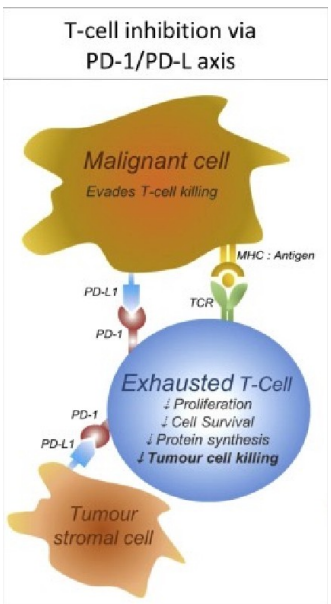
Inhibition of T-Cell (and thereby T-Cell mediated events) involves the *upregulation* of **CD152 (CTLA-4)** which begins to present on *activated T-Cells* through exocytosis.

- **CTLA-4** has a *higher affinity* to **B7-H1** and **B7-H2** receptors and will *displace* CD28 → **Inhibition/Inactivation**




## Programmed Cell Death Protein-1 (PD-1)

Similar to CTLA-4, activated T-Cells begin expressing **PD-1** upon their surface which when recognized leads to **Apoptosis of T-Cells**.




Some cancers *take advantage* of this pathway by **expressing PD-L1/L2** on their cell surfaces which will lead to **Apoptosis of T-Cells** that are supposed to be killing the tumor!

Since these pathways are distinct, using them both in **combination therapy** could have a *Synergistic* effect

# Explain the MoA of the two T-cell-specific monoclonal antibodies ipilimumab and nivolumab

**Ipilimumab** is a human, monoclonal antibody that binds to **CTLA-4** thereby disinhibiting the immune system (to fight cancer cells).

| *Parameter* | *Notes* |
|---|---|
| **Efficacy** | Antibody that binds to **CTLA-4** thereby ↓ *Inactivation of T-Cells* → ↑ Immune response to Tumor Cells |
| **Safety** | Immune-mediated **Enterocolitis** can be life threatening |

**Nivolumab** is a human, monoclonal antibody that binds to **PD-1** (present on T-Cells) which ↓ the *PD-1 and PD-L1/L2* interaction → ↓ Apoptosis

| *Parameter* | *Notes* |
|---|---|
| **Efficacy** | Antibody that binds to **PD-1** thereby preventing the Apoptosis of T-Cells and ↑ Immune response to Tumor Cells |
| **Safety** | GI Toxicities (Diarrhea, Colitis)<br>**↓ risk of immune complications** than Ipilimumab because it is a *later* pathway |

# Discuss the major toxicities with immune checkpoint therapies

Some of the mechanisms of toxicities associated with immune checkpoint therapies are;

| *Mechanism* | *Description* |
|---|---|
| **Unwanted Activation** | Healthy tissue may begin to be targeted by the antibodies → Destruction of healthy cells |
| **Auto-Antibodies** | Overstimulation of the Immune System may lead to Antibodies being produced that are auto-immune in nature |
| **Pro-Inflammatory Cytokines** | Overstimulation of the Immune System will result in excess Cytokine and other inflammatory mediators release → ↑ Inflammation |
| **Unwanted CTLA4 Binding** | CTLA4 may bind to healthy tissue → Chronic Activation of T-Cells! |

Our treatment options are dependent on **how severe** these side effects are. Some options include;

- D/C Therapy (if severe ADRs)
- Immunosuppressive Therapy (*eg*. *Glucocorticoids*) but this is directly the opposite of what are drugs are doing!