Learning Intention:

- To describe the development of immunotherapy strategies
- To explain the use of monoclonal antibodies for the treatment of autoimmune diseases and cancer.

Success Criteria:

- I can describe the development of immunotherapy strategies.
- I can explain the use of monoclonal antibodies for the treatment of autoimmune diseases and cancer.

Study design dot point

- the development of immunotherapy strategies, including the use of monoclonal antibodies for the treatment of autoimmune diseases and cancer.

Warm up

Watch the video and have a discussion on the key idea.

https://www.youtube.com/watch?v=F3ZTSSVLi6I

Immunotherapy

Immunotherapy is a form of medical treatment that modulates the functioning of the immune system in order to treat disease. There are two broad categories of immunotherapy:

- **Activation immunotherapies-** which aim to induce or amplify an immune response
- **Suppression immunotherapies-** which aim to prevent or reduce an immune response

Table 1 Examples of immunotherapy

Treatment	Description
Dendritic cell therapy	Involves the priming of dendritic cells with tumour-associated antigens (TAAs) to facilitate the activation of lymphocytes, priming them to kill any cells expressing the tumour antigen. This priming can be achieved via a vaccination with TAAs, or by removing dendritic cells from the body and priming them with TAAs externally before infusing them back into the patient (Figure 1).
CAR-T therapy	Involves the modification of T cells to recognise and destroy cancer cells. T cells are extracted from the patient, and scientists add a gene coding for an antigen receptor into its DNA. This protein then gets made by the cell and inserted into its membrane, allowing it to recognise cancer cell antigens. These cells with **chimeric** antigen receptors (CAR) are then reintroduced into the patient and seek out and destroy cancer cells (Figure 2).
Antibody therapy	Involves the creation and use of antibodies to stimulate and enhance the functioning of the immune system, and is often used in the treatment of cancer. Antibodies used in antibody therapy are typically **monoclonal antibodies**.
Cytokine therapy	Involves the use of immune signalling molecules such as interferons and interleukins to modulate the effect of the immune system.

Dendritic cell therapy

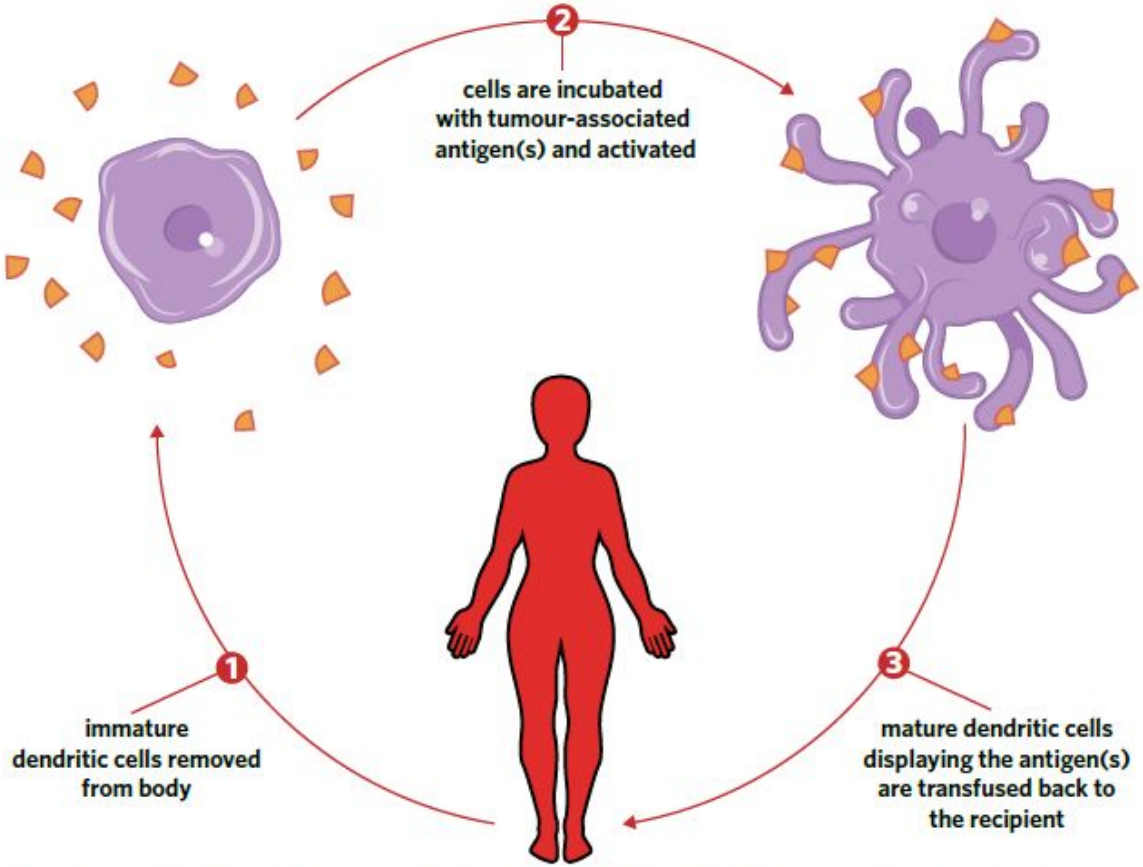


Figure 1 How dendritic cell therapy works. Note that the dendritic cells are first removed from the patient and combined with tumour-associated antigens in a lab before being transfused back into the patient in an effort to combat the tumour.

CAR-T therapy

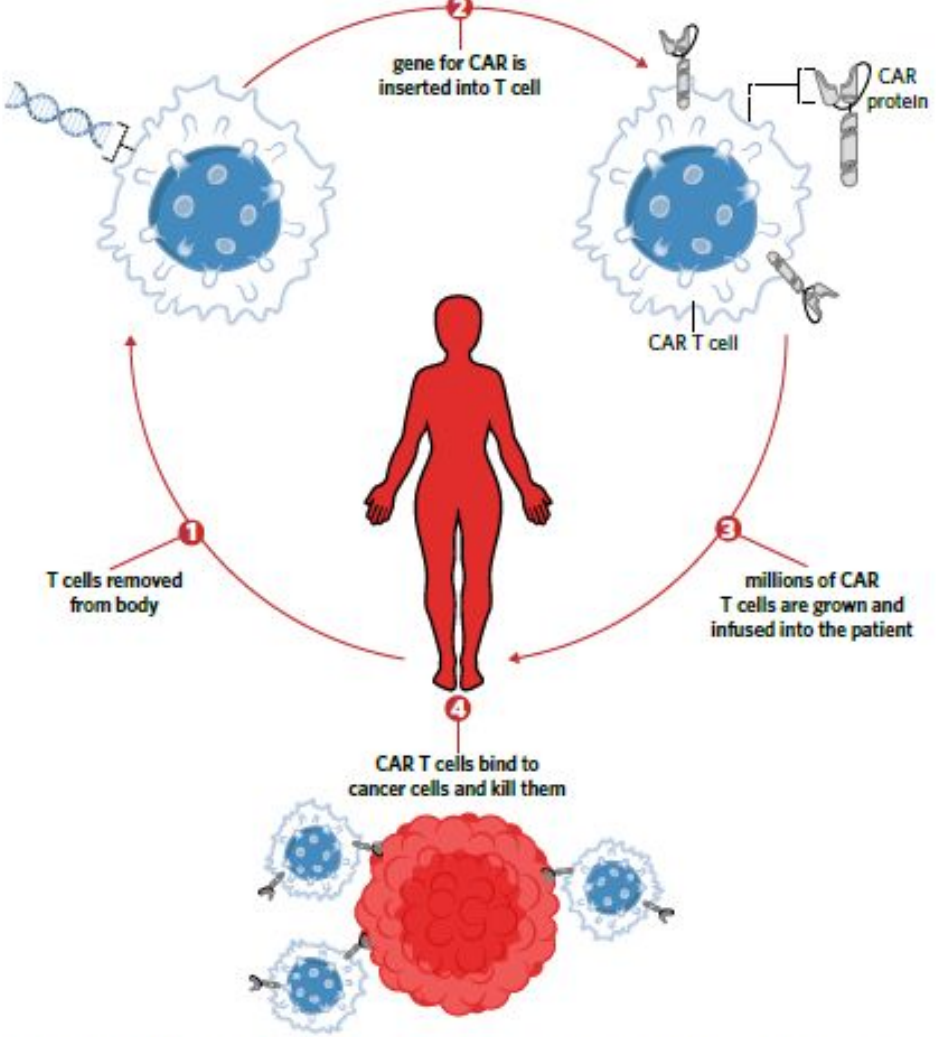
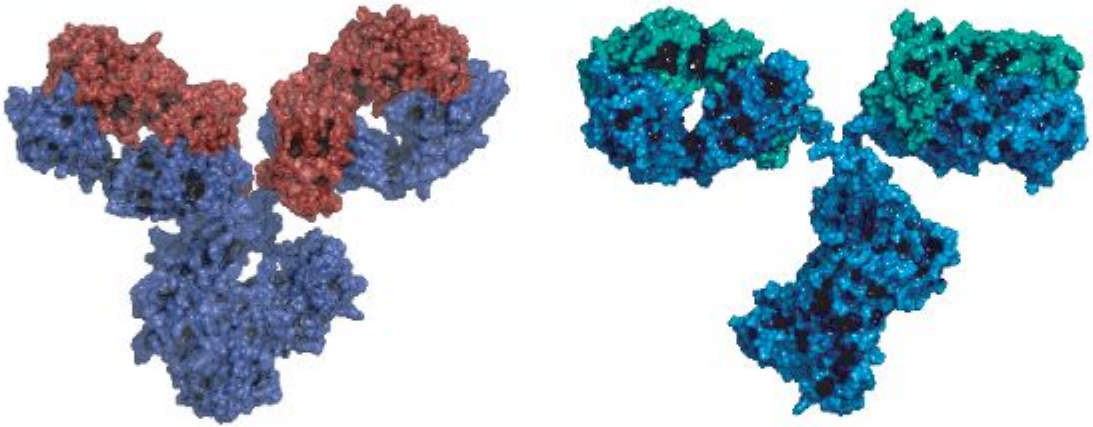


Figure 2 How CAR-T therapy works. Note the presence of CAR proteins on the surface of CAR T cells – these

Monoclonal antibodies (Mabs)

Monoclonal antibodies (MAbs) are:
- artificially produced antibodies that bind to one specific type of antigen
- produced in the laboratory by stimulating the production of B lymphocytes in mice injected with a specific type of antigen.

FIGURE 6.35 Different monoclonal antibodies (IgG1 and IgG2a respectively)



Monoclonal antibodies

Laboratory-made proteins that can be used to treat a number of different diseases.
Production of Monoclonal antibodies:
Step 1 Identification of antigen: Scientists identify and isolate an antigen that is present on a desired target cell.
Step 2: Scientists vaccinate an animal. This results in the selection and proliferation of a B lymphocyte that matches the antigen.
Step 3: Extraction of B cells
Step 4: The extracted B lymphocytes are fused with rapidly-dividing cancerous human plasma cells known as **myeloma cells**. The products of this fusion are called **hybridomas.**
Step 5: Hybridomas are screened so that only the cells with the appropriate antibody are selected. The hybridomas that produce the specific antibody are cloned, which results in the mass production of these antibodies.
Step 6: Antibodies are then collected and purified before being administered to a patient.

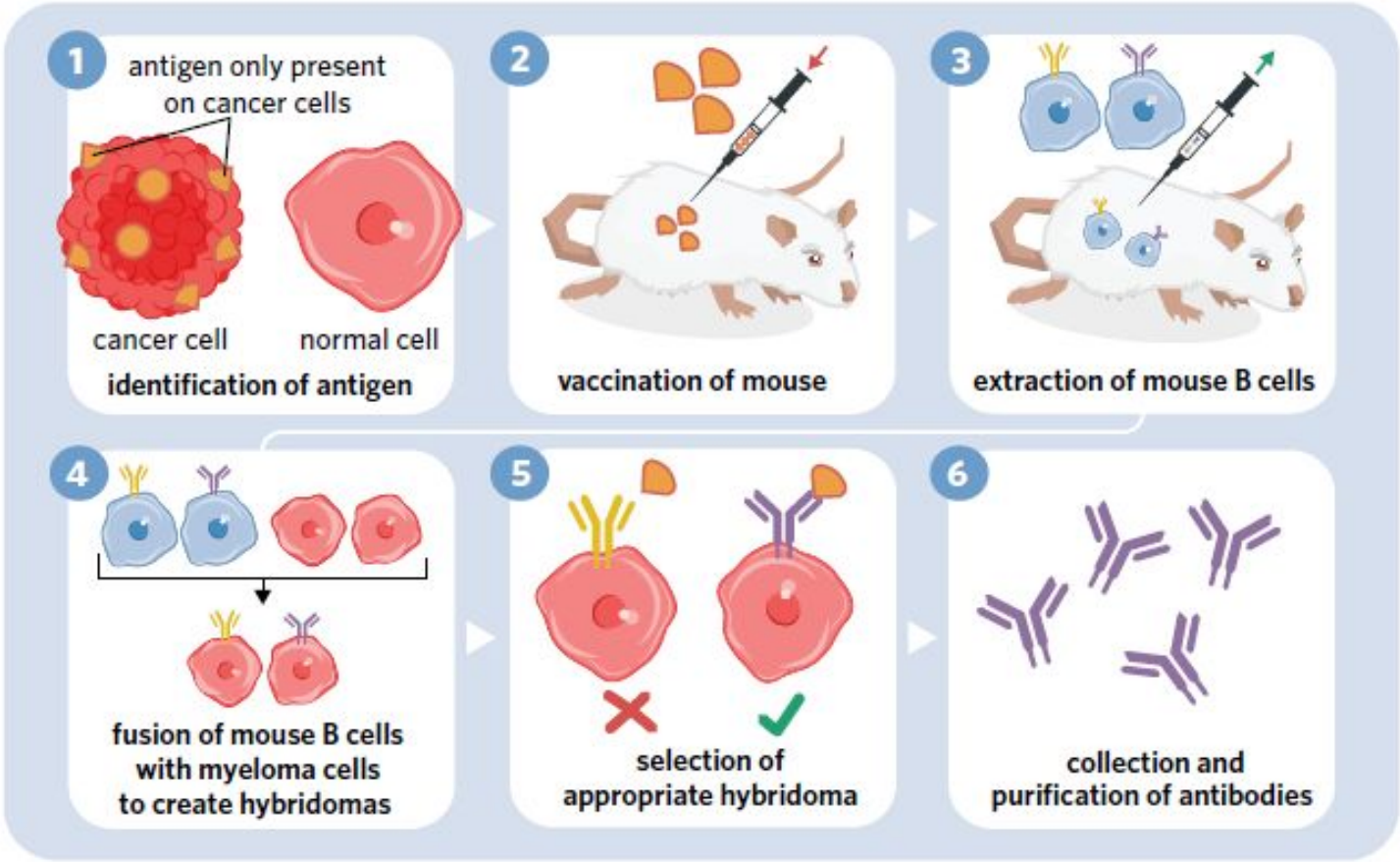


Figure 3 The process of producing monoclonal antibodies

Monoclonal antibodies for treating cancer

Cancer is caused by the uncontrolled and unregulated replication of cells that then invade other sites of the body. Cancerous cells, are sometimes able to evade the immune system or develop mutations that allow them to suppress the immune response against them.

The four main modes of action of MAbs are to:

- stop the growth of new blood vessels
- signal immune cells to attack
- block growth factors
- deliver anticancer or radioisotopes to cancer cells.

The development of cancer due to the failure of the immune system to do its job of destroying abnormal cells. So immunotherapy is used to treat cancers. Different ways monoclonal antibodies are used are:

- Activation immunotherapy
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Complement activation
- Checkpoint inhibition

Activation immunotherapy

Monoclonal antibodies used in cancer treatments can be divided into:

- Naked MAbs - monoclonal antibodies that do not have any other molecules attached to them
- Conjugated MAbs – monoclonal antibodies with other molecules (e.g. chemotherapy drugs or radioisotopes) attached to them

Antibody-dependent cell-mediated cytotoxicity (ADCC)

Monoclonal antibodies bind to cancer cells and interact with cells natural killer cells (NK cells), causing them to recognise the antibody-coated cancer cell as foreign and kill it

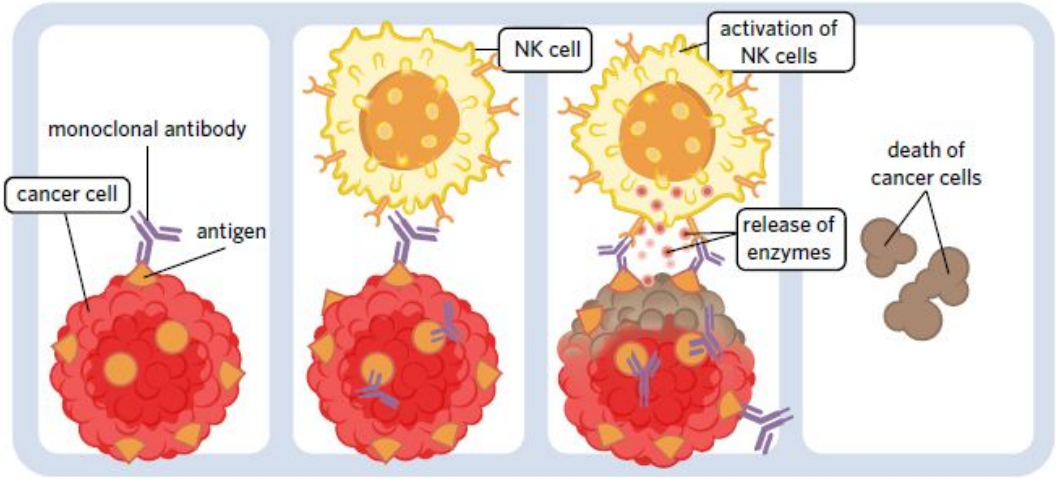


Figure 4 Monoclonal antibodies attaching to a cancer cell, causing a NK cell to recognise it as foreign and kill it.

Complement activation

Monoclonal antibodies bind to cancer cells and interact with complement proteins which can destroy the cancerous cell either by forming a membrane attack complex (MAC) or by enhancing the function of other immune cells.

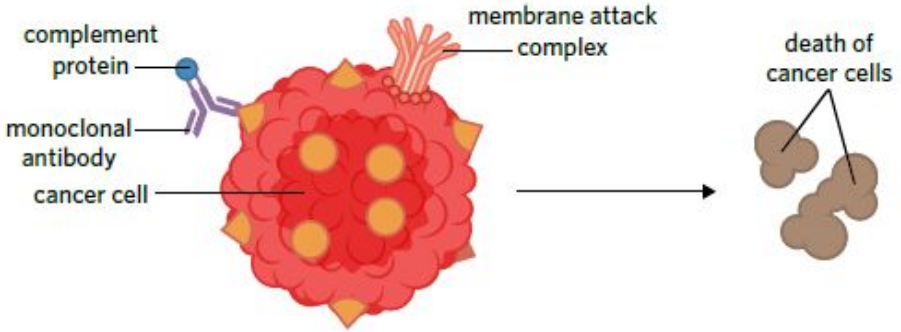


Figure 5 A monoclonal antibody interacting with a complement protein, initiating the formation of a MAC.

Checkpoint inhibition

Immune checkpoints are regulators in the immune system that, when activated, suppress the immune system. Monoclonal antibodies can be used to block immune checkpoints, so the immune system is able to function at a greater capacity and destroy cancer cells more easily.

Other non-immunotherapy ways monoclonal antibodies can be used to treat cancer include:

- blocking cell growth by blocking the connection between a cancer cell and proteins that promote cell growth
- triggering cell membrane destruction or apoptosis.

Monoclonal antibodies and autoimmune diseases

Sometimes, lymphocytes fail to recognise the MHC self-markers and end up inducing an immune response against self-cells causing autoimmune disease e.g. rheumatoid arthritis, type 1 diabetes, and coeliac disease. The symptoms of autoimmune diseases are brought on by both B and T cells responding to self-tissues as if they were foreign. B cells release **autoantibodies** and T cells become **autoreactive**.

Note: Treatments for autoimmune diseases have normally involved suppressing a patient's whole immune system via immunosuppressant medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids making patients **immunodeficient** and more susceptible to developing infections and cancer.

Suppression immunotherapy

Monoclonal antibodies are a can be used to reduce the immune response in a few different ways:

- Cytokine inhibition – Monoclonal antibodies that bind to and inhibit cytokines can be used to reduce the immune response
- B cell and T cell depletion and inhibition – Monoclonal antibodies that bind to autoreactive B and T cells can be used to either inhibit these cells or stimulate other immune cells to destroy them.

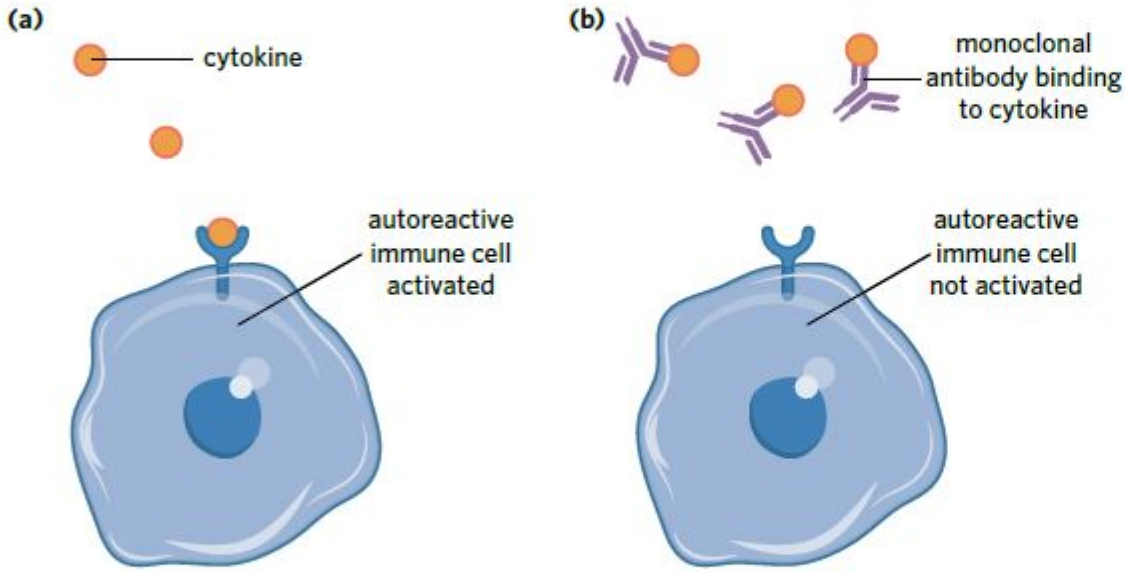


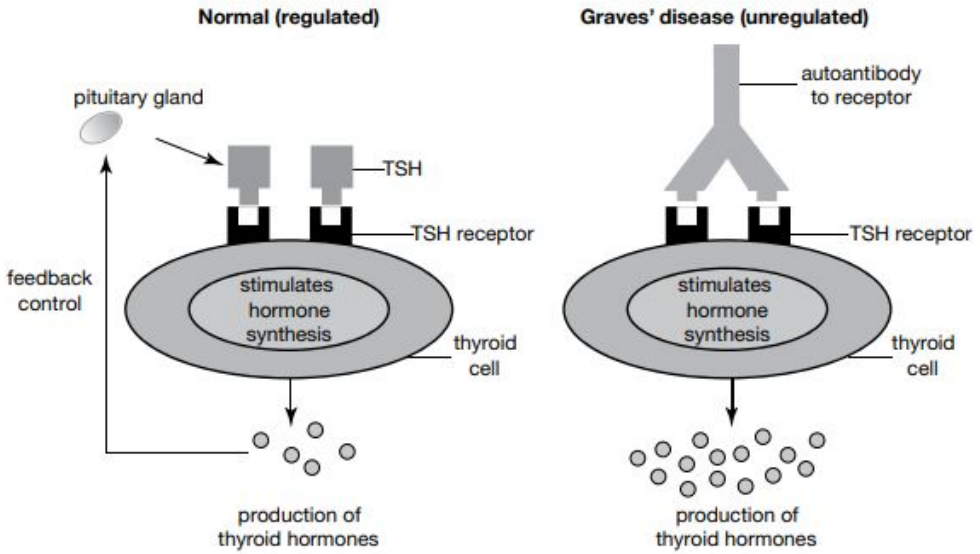
Figure 7 **(a)** Cytokines activating an immune cell; **(b)** monoclonal antibodies binding with cytokines before they reach the immune cell, preventing its activation

Worked example

C. the presence of autoantibodies overstimulates the thyroid

Question 10 (1 mark)

Graves' disease is an autoimmune disease in which the production of thyroid hormones by thyroid cells is unregulated. The following diagrams outline what occurs in regulated and unregulated thyroid cells. TSH stands for thyroid stimulating hormone.



From the information given in the diagrams it is reasonable to claim that

A. TSH inhibits the production of thyroid hormones.
B. positive feedback control occurs with regulated cells.
C. the presence of autoantibodies overstimulates the thyroid.
D. individuals with Graves' disease lack appropriate receptors on thyroid cells.

Summary

- Monoclonal antibodies (MAbs) are produced by a single clone of a cell and consist of identical antibody molecules that bind to the same antigen.
- Monoclonal antibodies are being used in the treatment of various cancers.
- Various monoclonal antibodies block the division of cancer cells through different modes of action.
- Some monoclonal antibodies are attached to other chemotherapy drugs and radioisotopes which are also used for targeted delivery to cancer cells.
- Monoclonal antibodies may also be used in the treatment of autoimmune diseases and target immune cells to decrease the immune response against self cells.

Reflection

Edrolo 8D Q1-4, 10-13