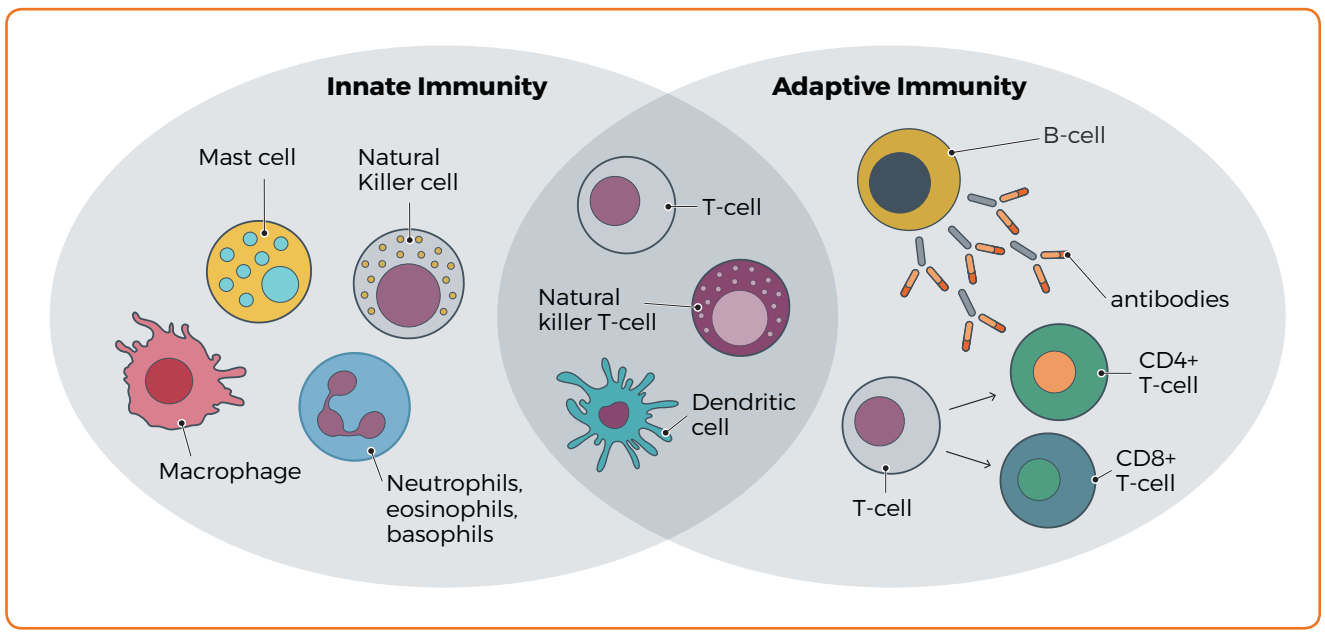
At a glance: The immune system

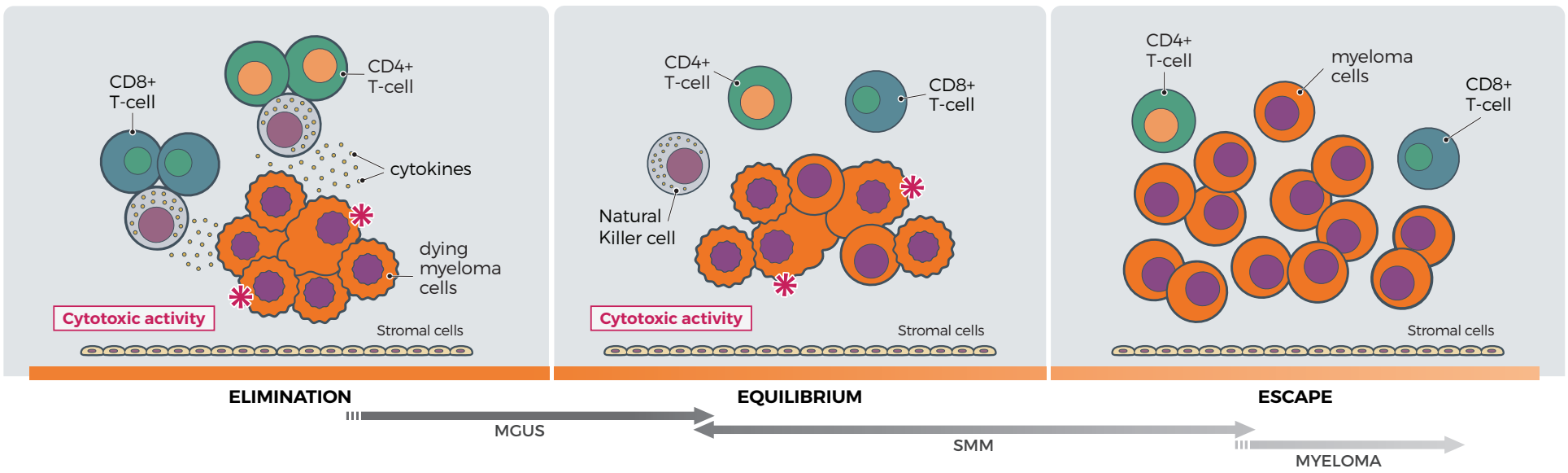
The immune system

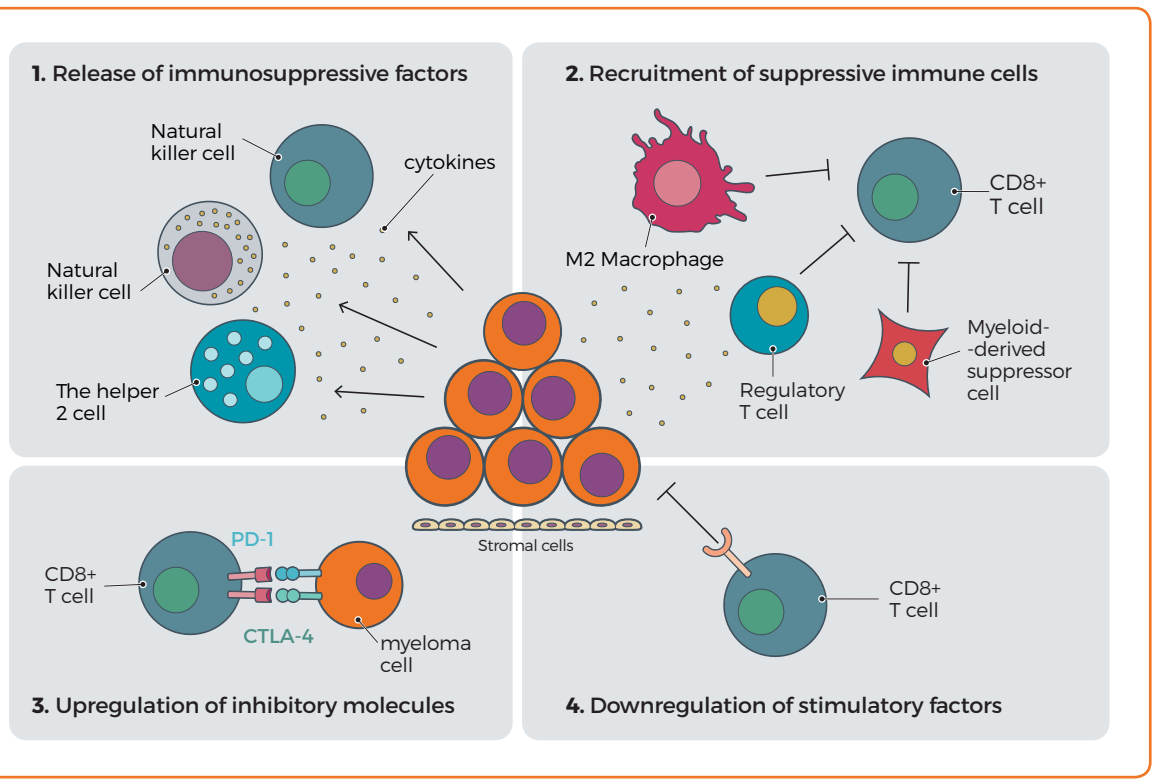
The immune system is a complex network of cells, tissues and molecules that protect the body primarily from foreign substances. Immune responses can be divided into reactions of innate and adaptive immunity (see Module 1). Innate immunity involves rapid non-antigen specific that are carried out by phagocytic cells e.g. neutrophils, macrophages, natural killer cells. Adaptive immunity is a slower, more refined antigen-specific response involving T cells which are activated via antigen-presenting cells (e.g. dendritic cells), and B cells which are activated to secrete antibodies. Together, the innate and adaptive arms of the immune system constantly survey the body, identifying and destroying any threats that may cause harm.



Immune surveillance in myeloma

The immune system surveys the body not only for foreign substances but also for changes in cells it no longer recognises as "self" e.g. as a result of autoimmune disease or malignant transformation. In each case, it responds to antigens not found on normal cells and utilises both the innate and adaptive arms to **eliminate** the infected, modified or altered cells. However, malignant cells develop ways to evade or escape the immune system (see Module 1). If they survive, an **equilibrium** is established whereby the malignant clone is relatively well controlled by the immune system but is not completely eradicated. Over time, the malignant cells acquire additional abnormalities that enable them to **escape** from immune control and progress. In myeloma, the equilibrium state likely represents MGUS whereby the disease is neither progressing nor being eradicated. As the clone evolves, it evades immune attack and equilibrium is lost. The disease progresses to smouldering myeloma and then to myeloma once it has fully escaped the immune system.





Mechanisms of immune escape in myeloma

Within the bone marrow, myeloma cells create an environment that fosters their escape from the immune system and promotes disease progression (see Module 2).

These include:

1. Secretion of immunosuppressive factors e.g. IL-6, IL-10, IDO and TGF-ß affecting NK cell, CD8+ T cell and T cell helper activity, and dendritic cell function

2. Recruitment of suppressive immune cells e.g. regulatory T cells, myeloid-derived suppressor cells and M2 macrophages

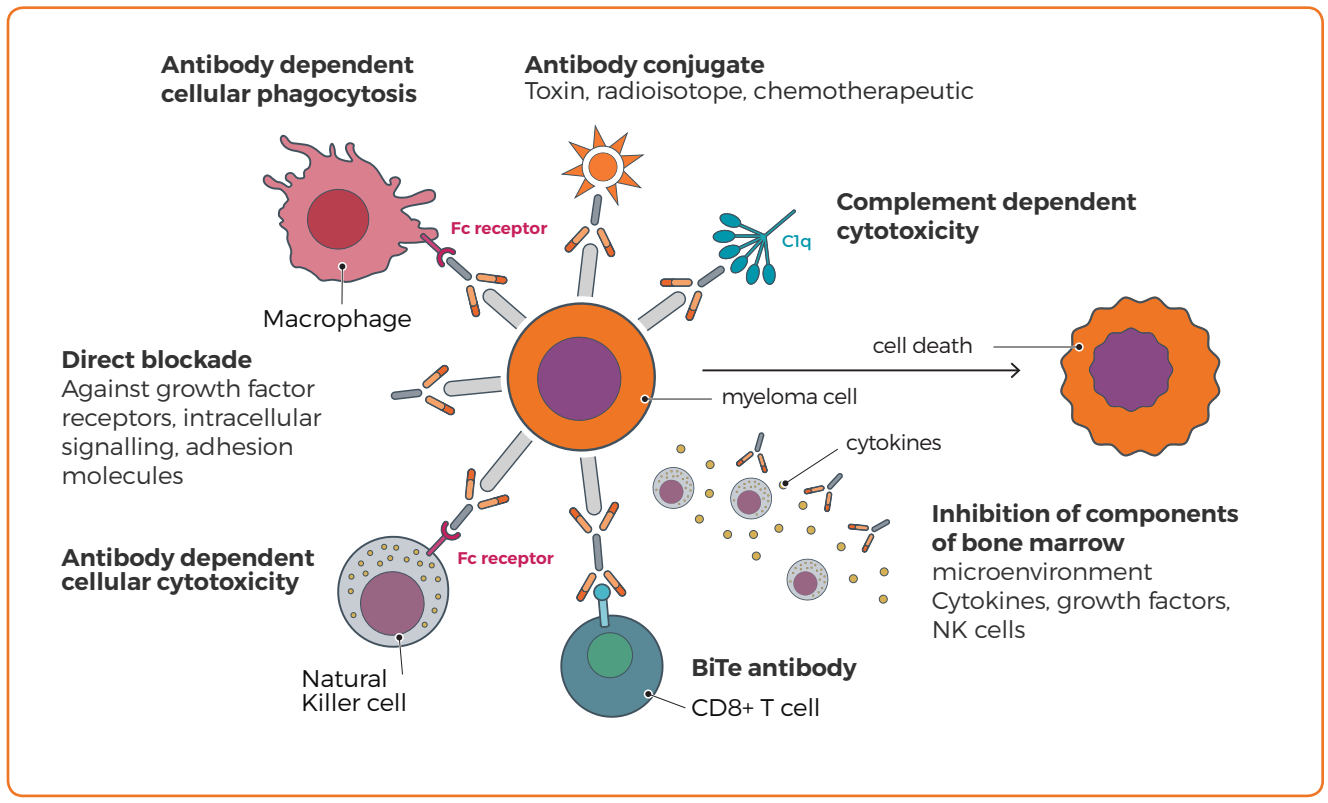
3. Upregulation of inhibitory molecules involved in key immune checkpoint pathways, e.g. PD-1, CTLA-4, preventing tumour-reactive T cell responses

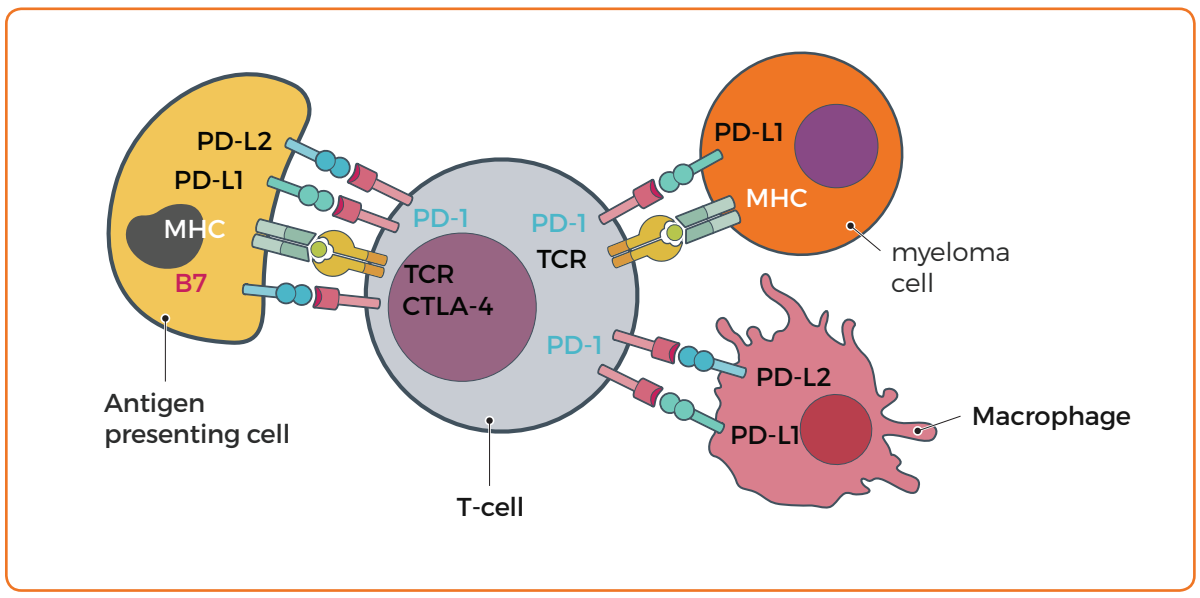
4. Downregulation of stimulatory factors including reduced antigen presentation and processing, and loss of HLA expression, effectively 'hiding' the myeloma cell from tumour-reactive T-cell recognition

Immunotherapy in myeloma

Monoclonal antibodies: mechanisms of action

Myeloma cells express surface antigens that are targets for monoclonal antibodies (see Modules 2 and 3). Once bound, the monoclonal antibodies can mediate their anti-myeloma effects by: interfering with an activation signal (e.g. growth factors, G-protein coupled receptors) and inducing apoptosis, through conjugation with radioisotopes or toxins causing direct cytoxicity, by enhancing the immune system by engaging with Fc receptors expressed on NK cells and macrophages leading to antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), or through activation of the complement cascade, resulting in complement-dependent cytotoxicity (CDC). Another type of antibody, called a bi-specific T cell engager (BiTe), facilitates the interaction between T cells and myeloma cells.



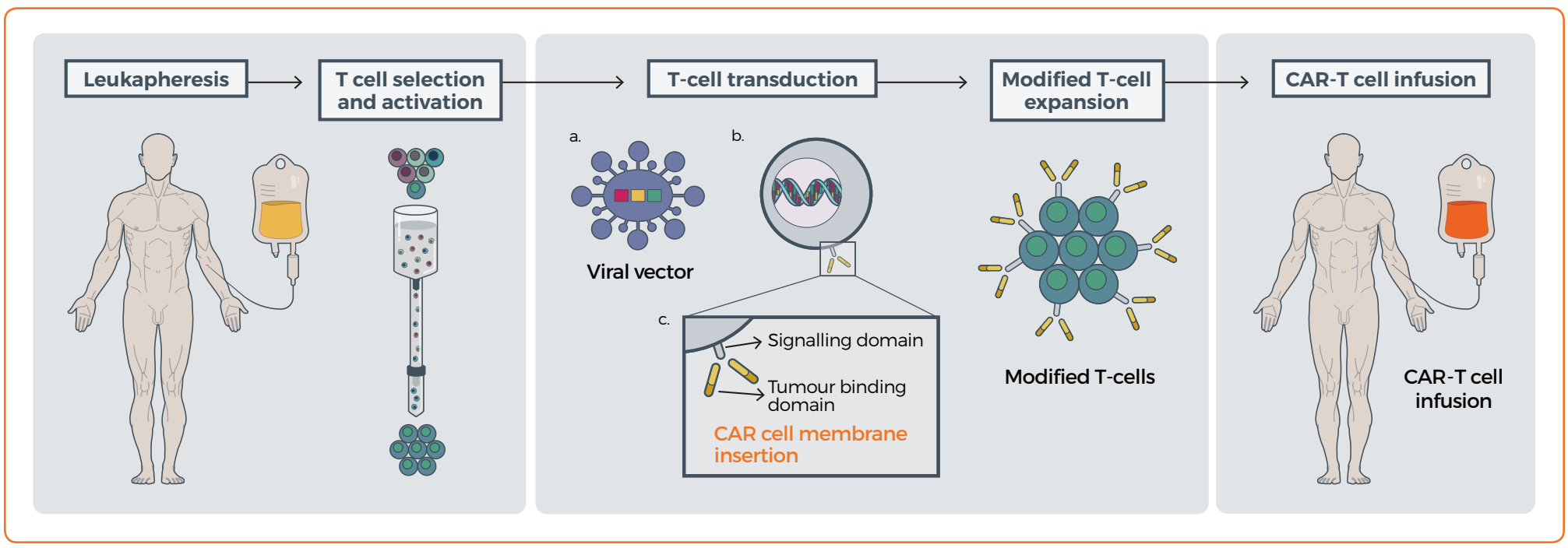


Immune checkpoint inhibition

Immune checkpoints are inhibitory pathways designed to maintain immune system equilibrium and prevent autoimmunity (see Modules 2 and 5). This is primarily achieved by downregulating T cell function through complex interactions between co-stimulatory and co-inhibitory molecules. Myeloma cells can evade the immune system by taking advantage of such immune checkpoints. For example, by expressing checkpoint proteins such as PD-L1 and B7 (CD80), they can bind to PD-1 and CTLA-4 on T cells respectively, and inactivate them. Blocking the binding with immune checkpoint inhibitors maintains T cell activity, allowing them to attack the myeloma cells.

Car T-cell Therapy

Chimeric antigen receptor (CAR) T cell therapy is a type of adoptive T cell therapy which involves the use of autologous T cells genetically engineered to express CARs. (see Module 4). Such molecules combine the extracellular binding domain of an antibody with the signalling domain of a T cell receptor allowing the modified T cell to recognise unprocessed antigens independently of their expression of major histocompatibility antigens. CAR T cells therefore have the ability to circumvent some of the immune escape mechanisms myeloma cells adopt e.g. down regulation of HLA expression and antigen processing. The first step of the process involves the collection of T cells from the patient. These then undergo viral gene transfer to introduce the CAR construct into the T cell and expanded before they are re-infused into the patient. The resulting treatment has the specificity of an antibody with the killing capacity of a T cell. Conventional conditioning Conventional conditioning chemotherapy is often given to myeloma patients alongside CAR-T cell therapy.



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