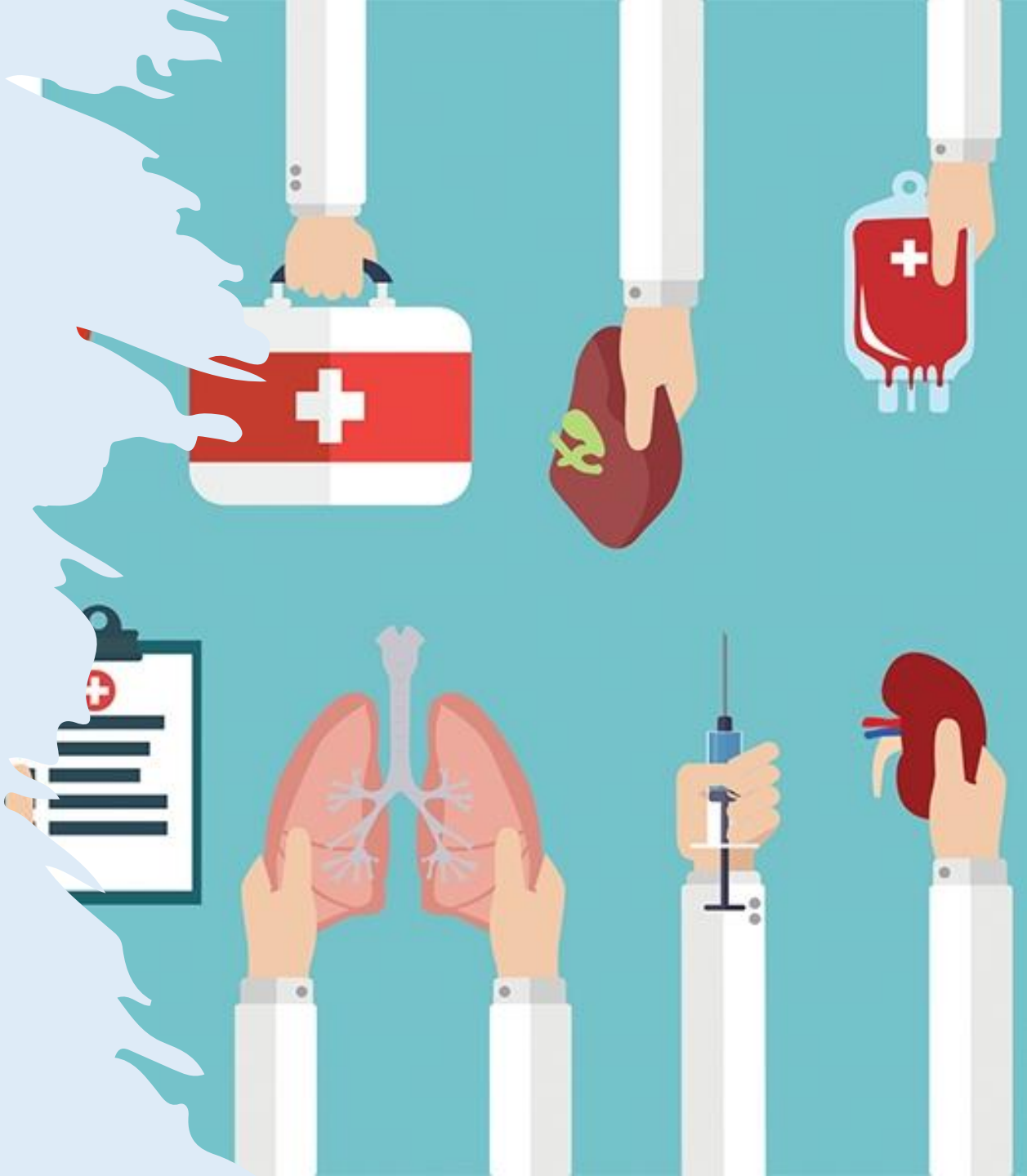
Immune Hypersensitivity Reactions and Transplantation

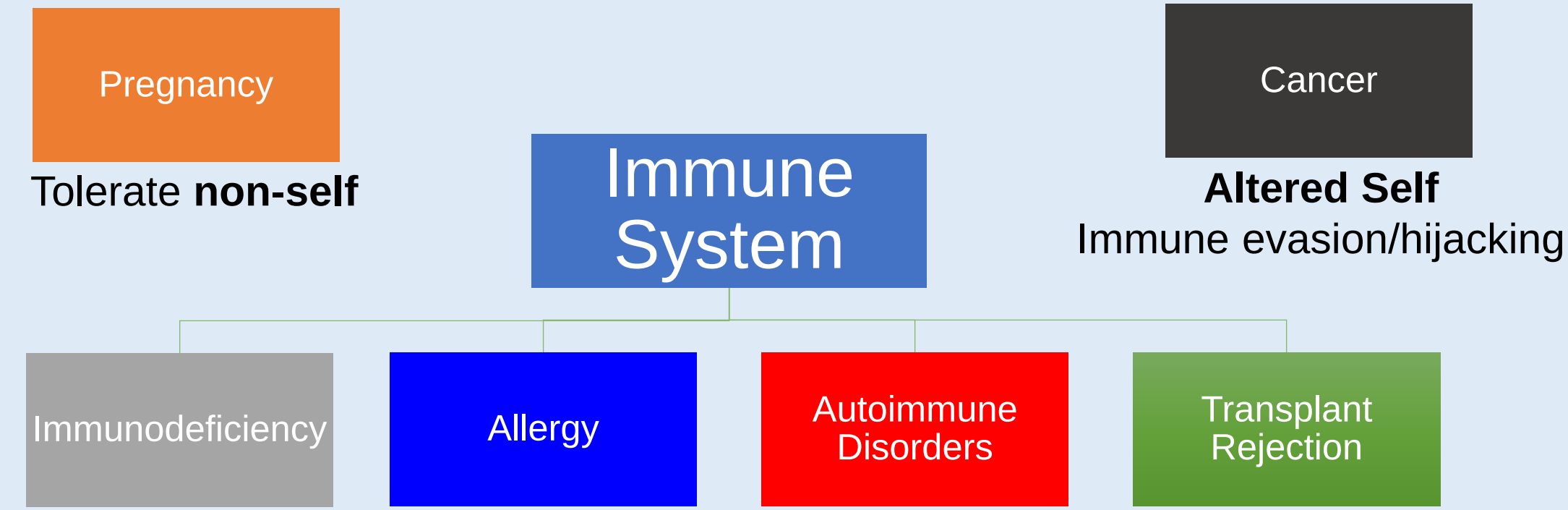
Dr Geraldine O’Connor

go-connor1@lancashire.ac.uk



Lesson Overview

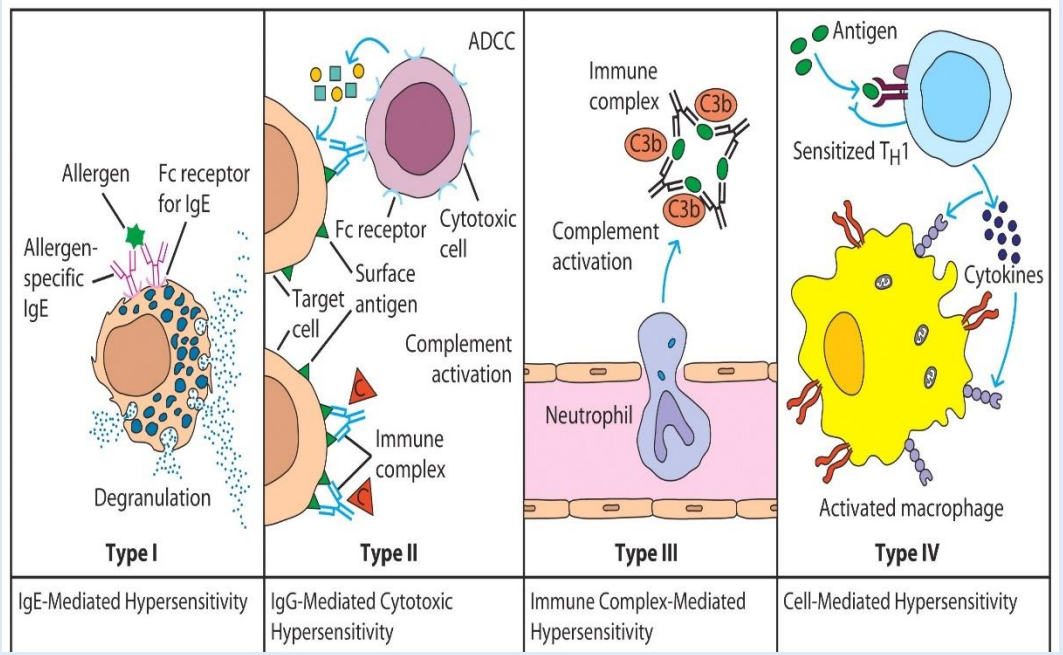
- Overview of Year 2 Immunology
- Recap of hypersensitivity reactions
- The immunological challenges of transplantation
- The role of HLA
- Immunological basis of transplant rejection including hyper-acute, acute, and chronic rejection.


Pregnancy
Tolerate **non-self**
Immune System
Cancer
Altered Self
Immune evasion/hijacking
Immunodeficiency
Allergy
Autoimmune Disorders
Transplant Rejection
Immunodeficiency
Inappropriate response to **foreign**
Inappropriate response to **self**
Appropriate (but **unwanted**) response to foreign

Recap: Hypersensitivity Reactions

Inappropriate or excessive immune responses can lead to tissue damage. These hypersensitivity reactions can be classified into 4 types based on the underlying mechanism.

- Types I-III involve antibodies, while Type IV is cell mediated immune responses
- It is common for more than one type of hypersensitivity reaction to be involved in mediating tissue damage



Type IV Hypersensitivity Reactions

Type IV: Stimulation of immune **cells** leads to production of chemokines and cytokines that recruit cellular effectors that mediate damage

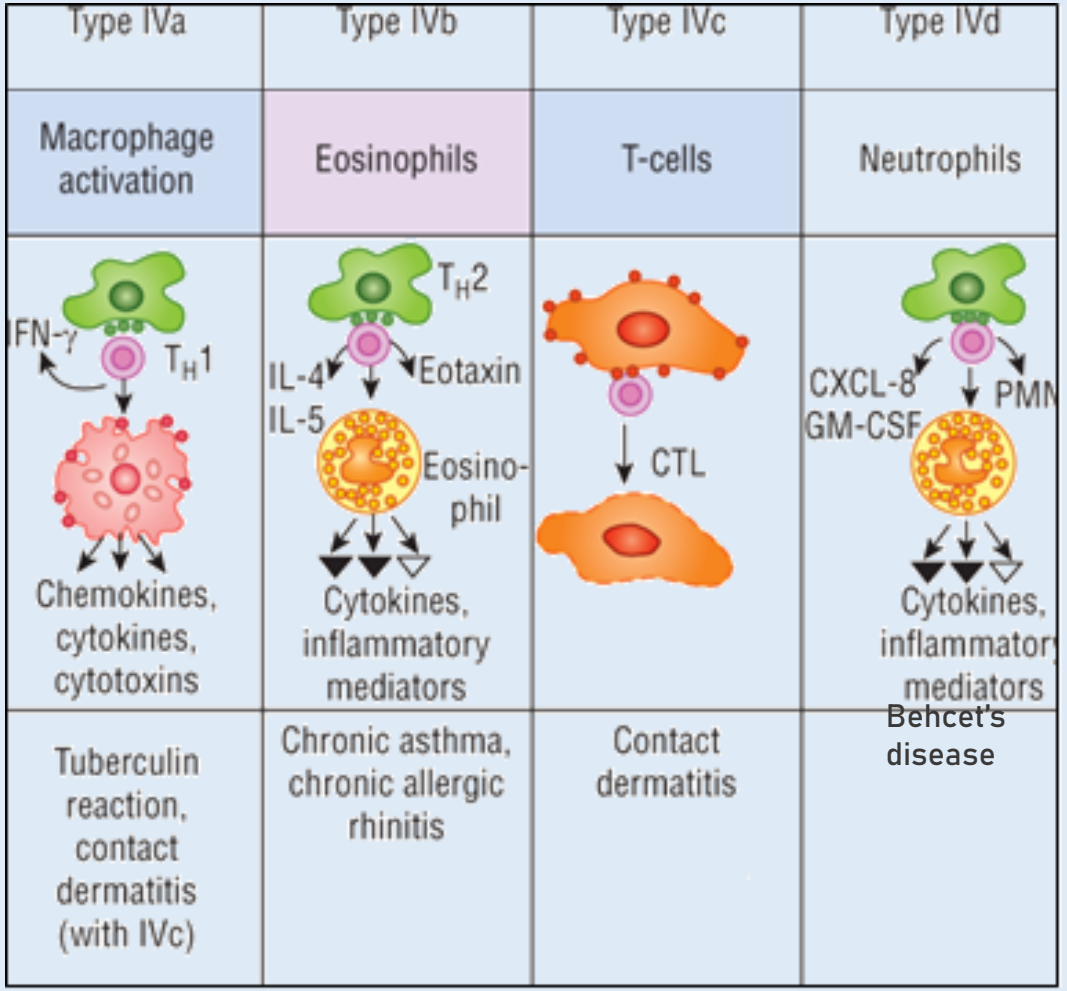
<u>Effectors</u>

IVa macrophages (via IFN-γ)

IVb eosinophils

IVc cytotoxic T cells

IVd neutrophils



University of Lancashire

Transplantation

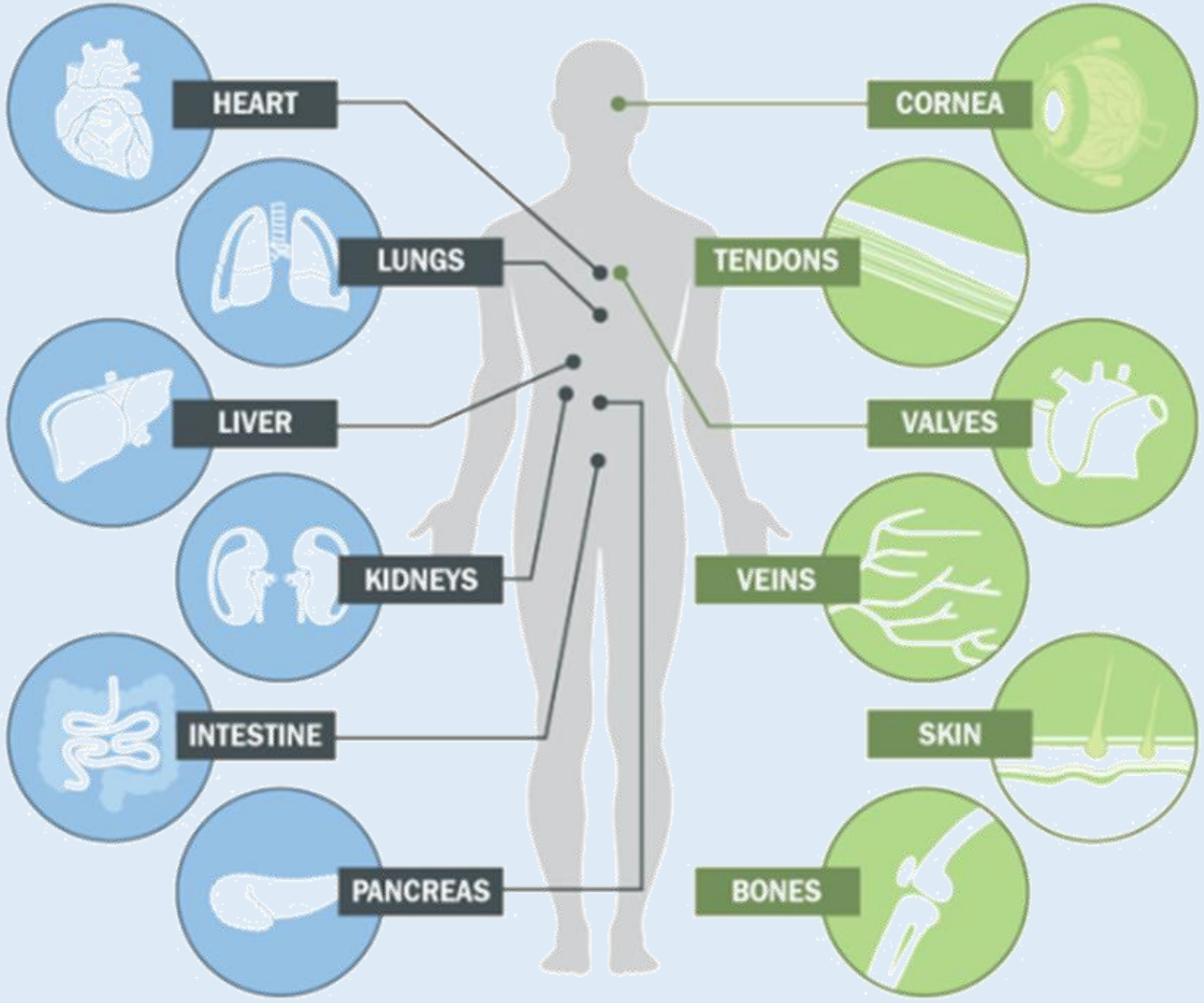
Transplantation

- NHS Blood and Transplant report 8,089 people in the UK are on a transplant waiting list and 1750 people received a transplantation from a deceased donor April-September 2025.

Transplantation

A wide variety of solid organs can now be transplanted. Kidney is one of the most common in the UK. Also liver, lung and heart transplantations.

Bone marrow (haematopoietic stem cell) transplantation is considered in malignancy, haematological conditions and immunodeficiency. Immunologically complex – will be considered separately.

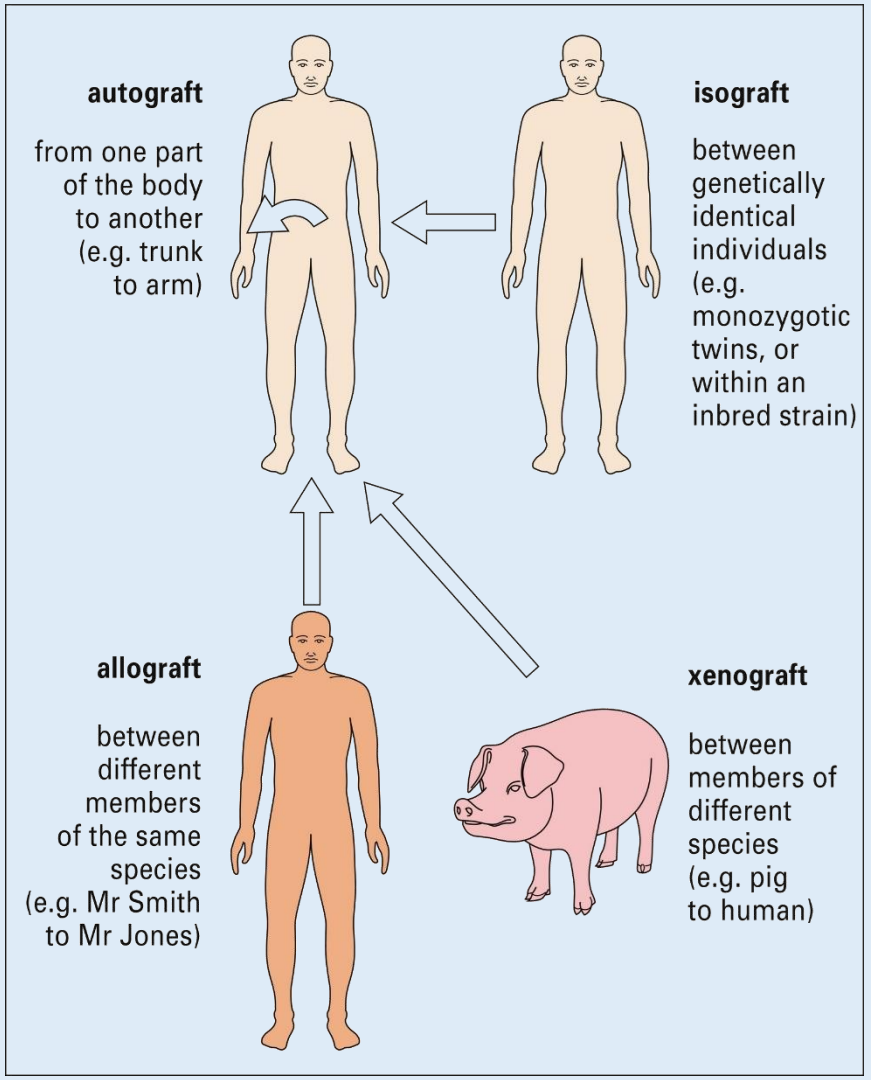


Types of Transplantation

Grafts from the donor may be

- autographs
- isographs
- allografts
- xenografts

The main barrier to transplantation is the **genetic disparity** between donor and recipient. If the recipient's immune system recognises the graft as non-self it will destroys the graft and local vascular tissue i.e. cause **rejection**.



Immunological Barriers

Rejection may be

- Hyper-acute
- Acute
- Chronic

	When	Immune component	Antigen Recognised
Hyperacute	Minutes	Pre-existing antibodies	Often ABO blood group antigens HLA antigens
Acute	Weeks to months	T cell responses Newly formed antibodies	Donor HLA molecules
Chronic	Months to years	CD4+ T cells	Non-HLA molecules

Rejection = Host versus graft

Hyper-Acute Rejection

Hyper-acute Rejection

Happens within minutes – during transplantation surgery

Due to the presence in the recipient of **pre-formed antibody** against donor antigens.

These donor antigens may be

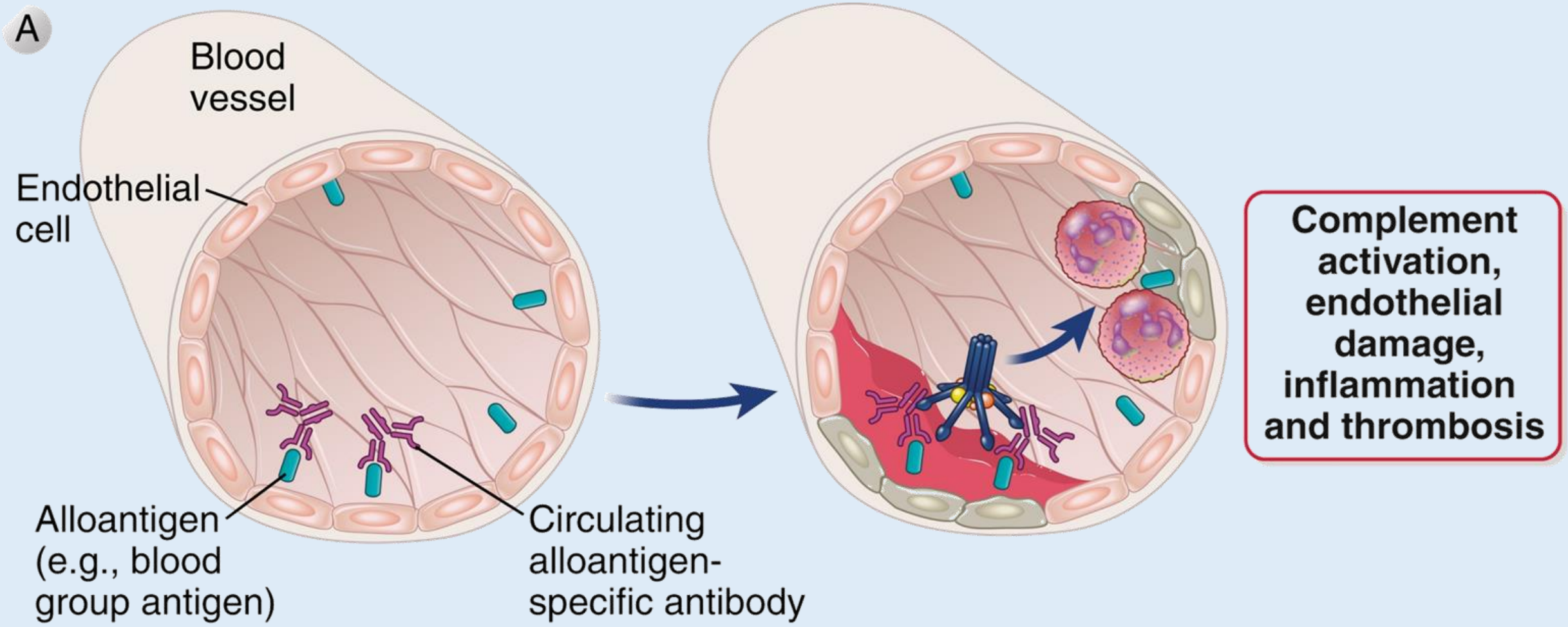
- ABO blood group antigens (“natural” antibodies in recipient, do not require prior exposure)
- HLA antigens (recipients may generate anti-HLA antibodies if exposure to antigens during pregnancy, blood transfusion and previous transplantation)

Rare. Failure of screening; Graft must be removed.

Hyper-acute Rejection

University of Lancashire

Type II Hypersensitivity Response



MHC - Recap

University of Lancashire

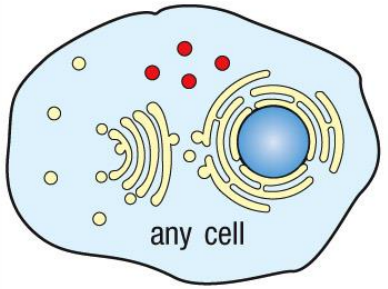
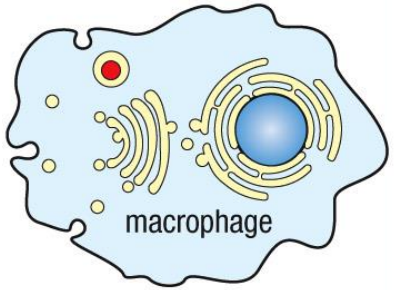
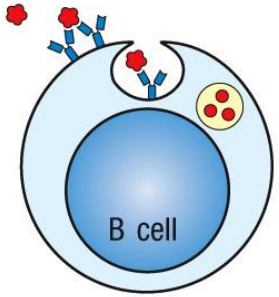
	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
			
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	Effector CD8 T cells	Effector CD4 T cells	Effector CD4 T cells
Effect on presenting cell	Cell death	Activation to kill intravesicular bacteria and parasites	Activation of B cells to secrete Ig to eliminate extracellular bacteria/toxins

Figure 6.2 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Acute Rejection

Acute Rejection

Type IV Hypersensitivity Response

Acute rejection is due to **T cell mediated response** to the foreign graft based on genetic difference between donor and host

Histocompatibility Genes

- Major Histocompatibility Complex (MHC)

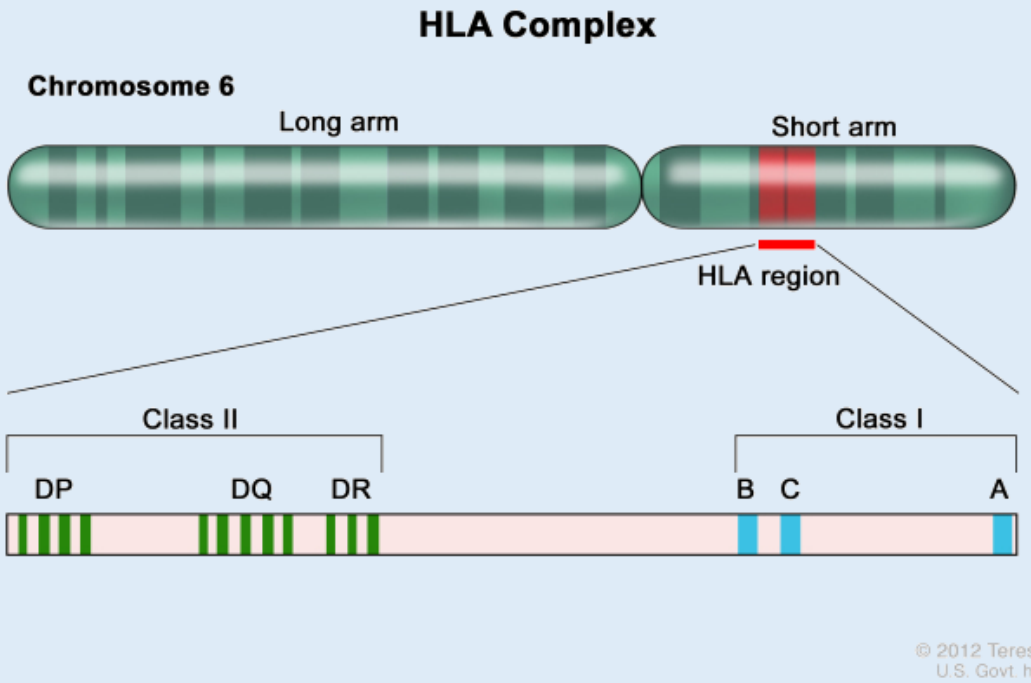
    Class I: HLA-A, -B, -C

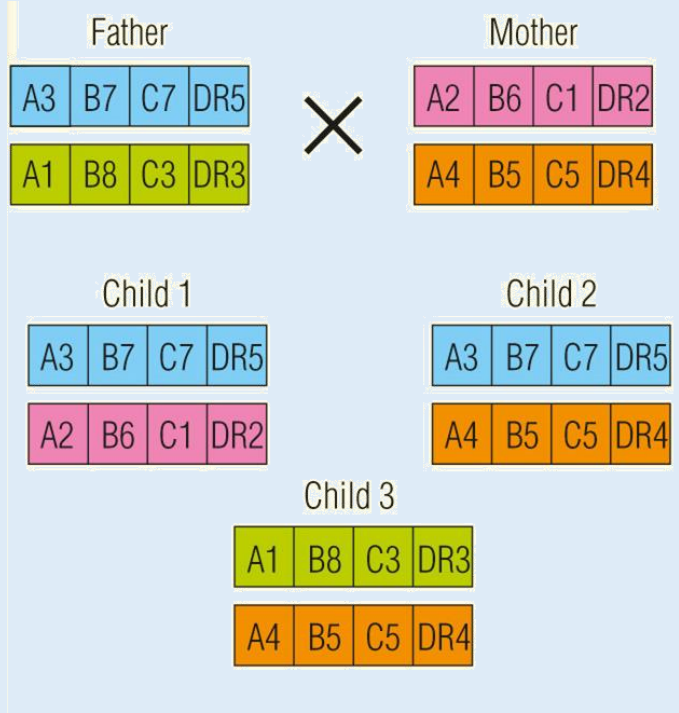
    Class II: HLA-DP, -DQ, -DR

These genes are present on a cluster on chromosome 6, inherited as a unit and expressed co-dominantly.

- Many additional minor histocompatibility genes

HLA Compatibility





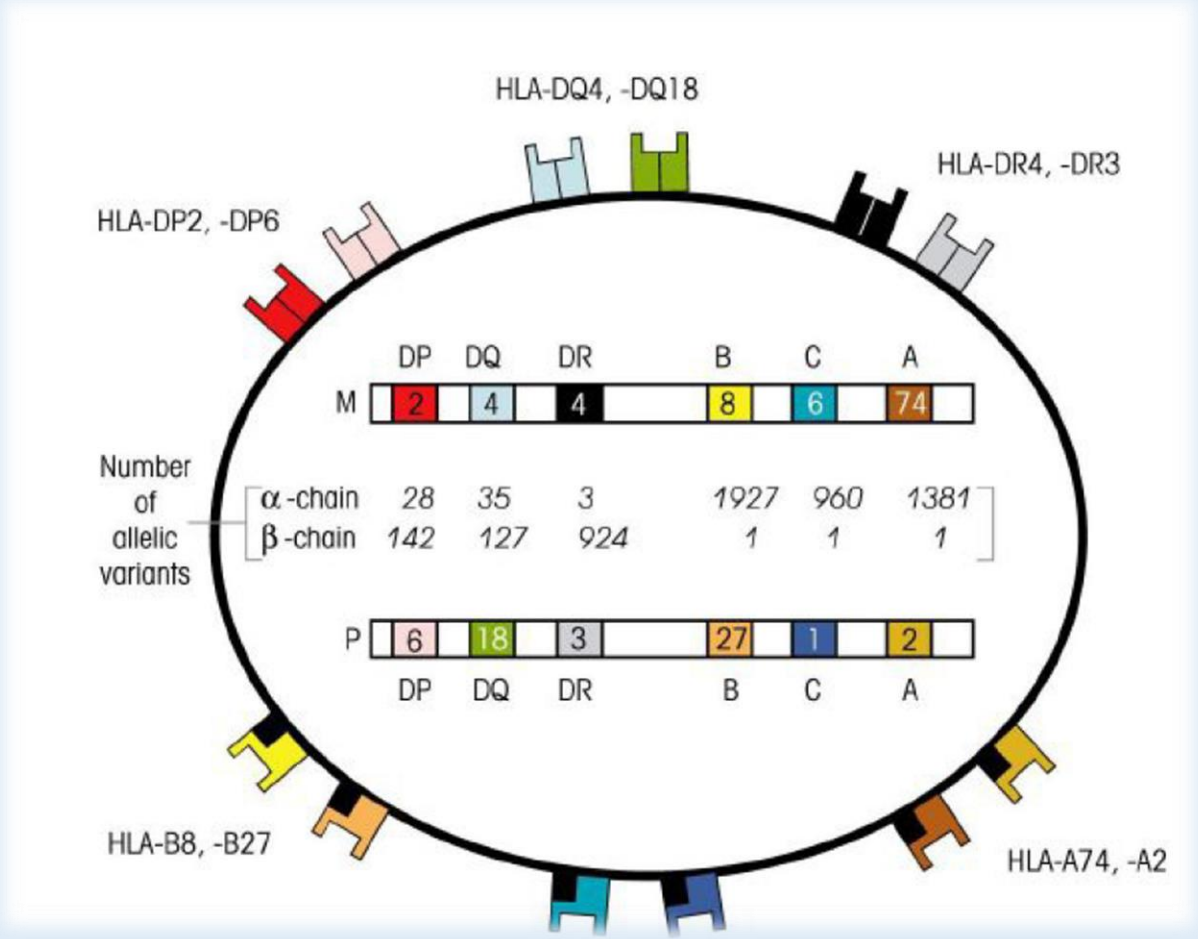
Due to their close physical proximity HLA genes are inherited as a unit (haplotype) from each parent

HLA Compatibility

- HLA genes are co-dominantly expressed – i.e. you will express both the paternally and maternally inherited copy of each gene

- HLA genes are VERY polymorphic

HLA	A	B	C
Alleles	7,562	9,000	7,513
Proteins	4,399	5,414	4,157

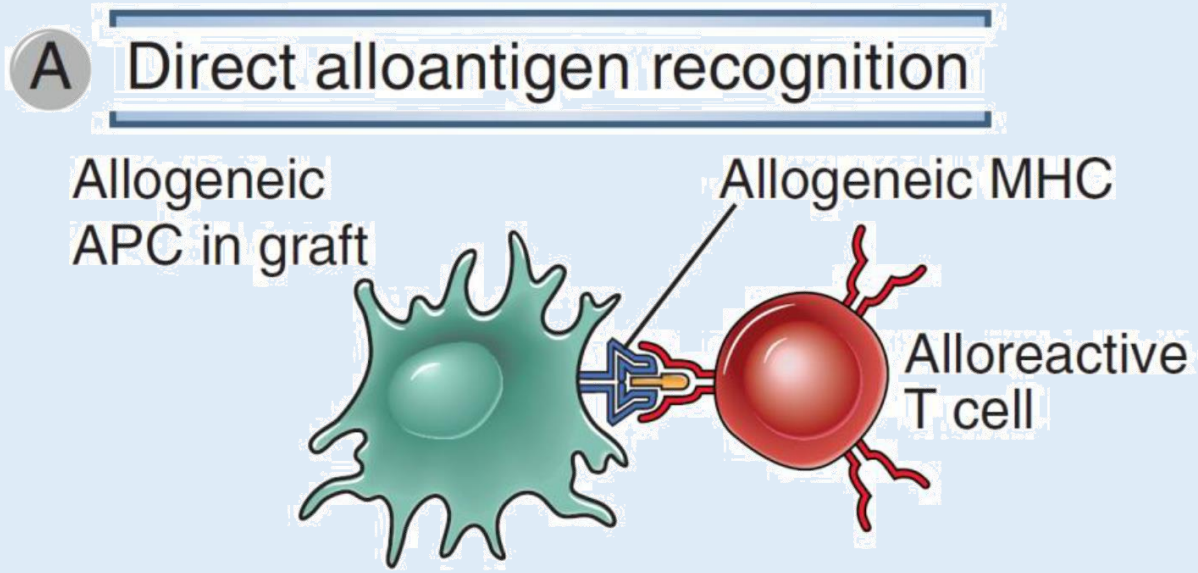


Data taken trom https://www.ebi.ac.uk/ipd/imgt/hla/about/statistics/ . Accessed on 11.09.2022

Acute Rejection

T cells may recognise non-self antigens on the graft directly or indirectly.

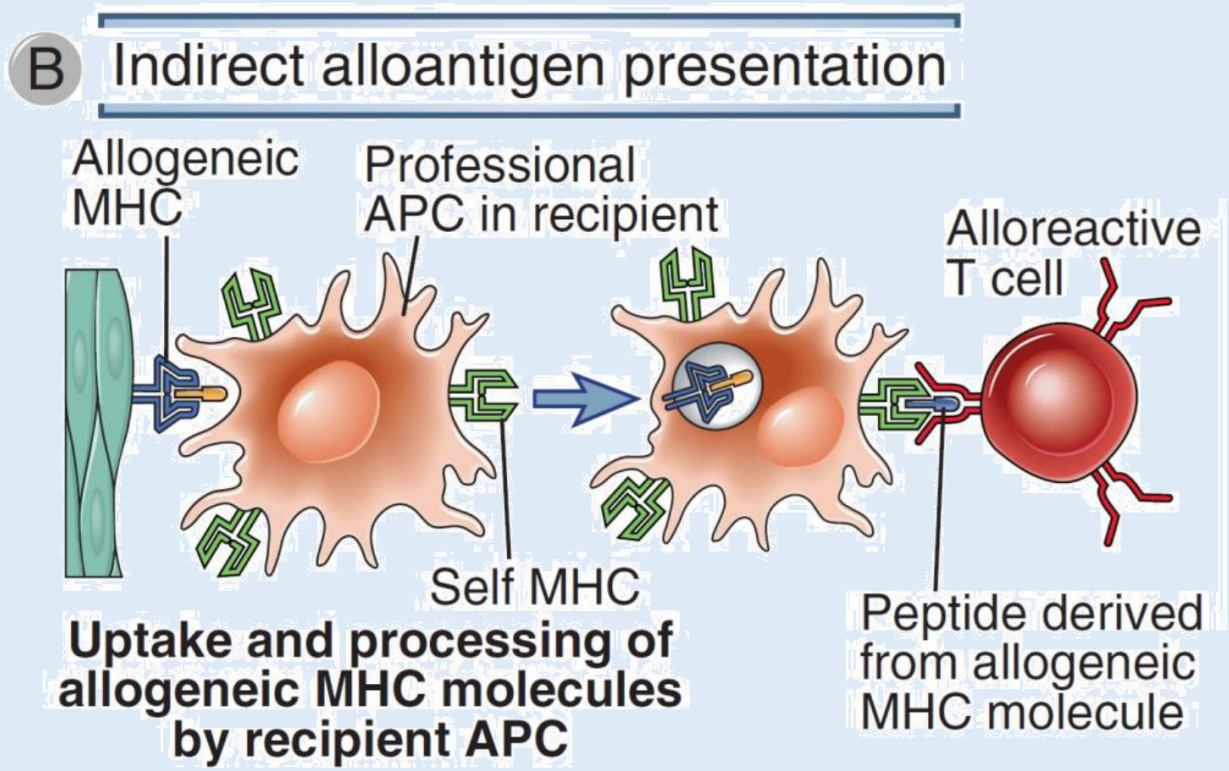
- In **direct** recognition, there is recognition of an **intact** HLA molecule displayed by donor APC in the graft. Involves both CD8+ and CD4+ T cells



Recipient T cell recognises unprocessed foreign HLA molecule on donor APC

Acute Rejection

- In **indirect** recognition, the donor HLA molecule is **processed and presented** by host HLA, in a similar way to other foreign antigens. Involves CD4+ T cells



Presentation of processed peptide of donor HLA molecule bound to recipient HLA molecule

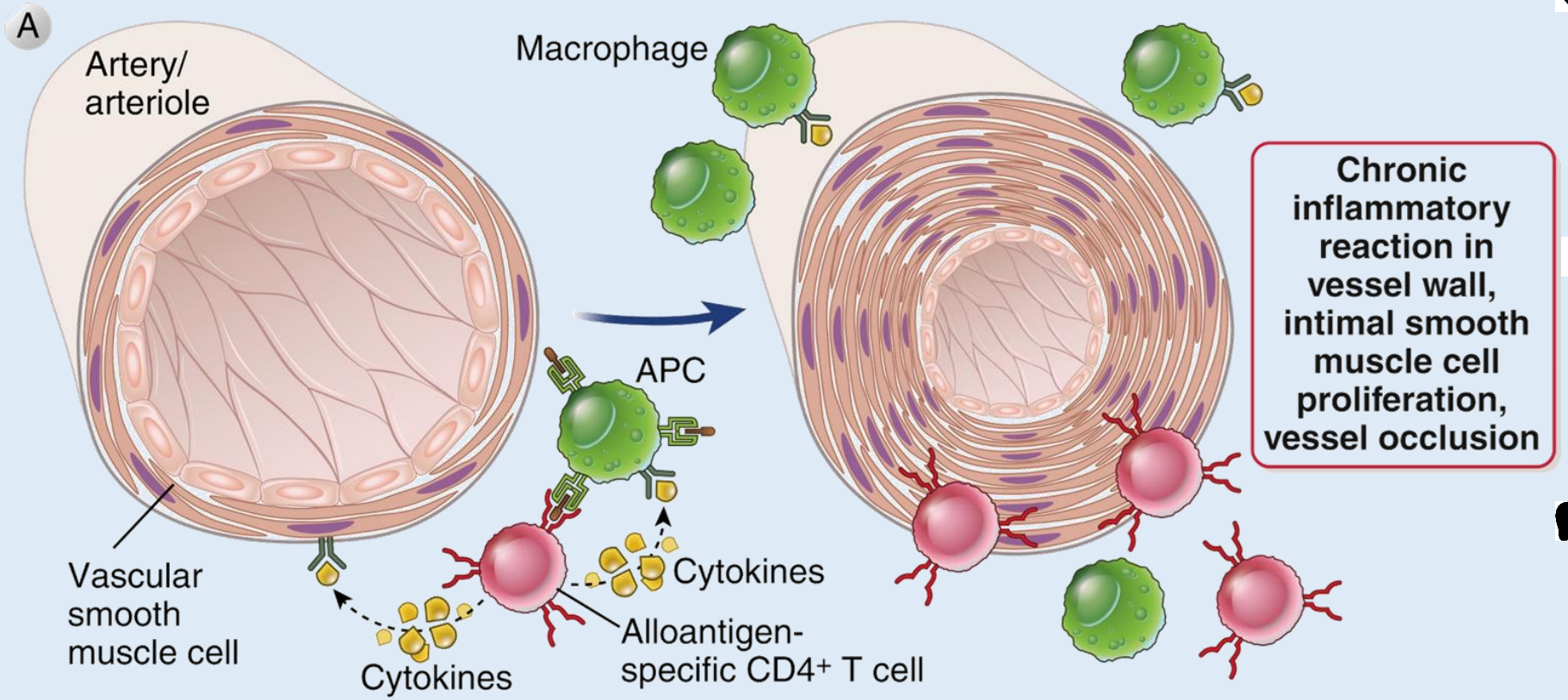
Chronic Rejection

Chronic Rejection

In addition to the major histocompatibility complex differences between individuals, there are many more small differences– these difference are responsible for chronic rejection.

The exact causes are unclear but T cells are believed to be involved. The exact pathology depends on the tissue involved but a common feature involved the proliferation of smooth muscles cells lining arterioles leading to occlusion and in turn ischemic damage

Chronic Rejection



- Vascular occlusion and interstitial fibrosis (heart and lungs, kidney)
- Bronchiolitis obliterans – thickening of small airways (lungs)
- Fibrotic and non-functional bile ducts (liver)

Bone marrow transplantation

We have considered solid-organ transplantation, where the immunological consideration are focused on preventing rejection of the transplanted organ by the recipient's immune system (host versus graft).

In **bone marrow transplantation**, donor T cells in the graft may proliferate and attack the recipient’s tissue, graft versus host (GvH). Acute GvH is a type IV reaction, it commonly causes diarrhoea, rash, jaundice and GI haemorrhage, and can be fatal. (more on BMT later in the course).

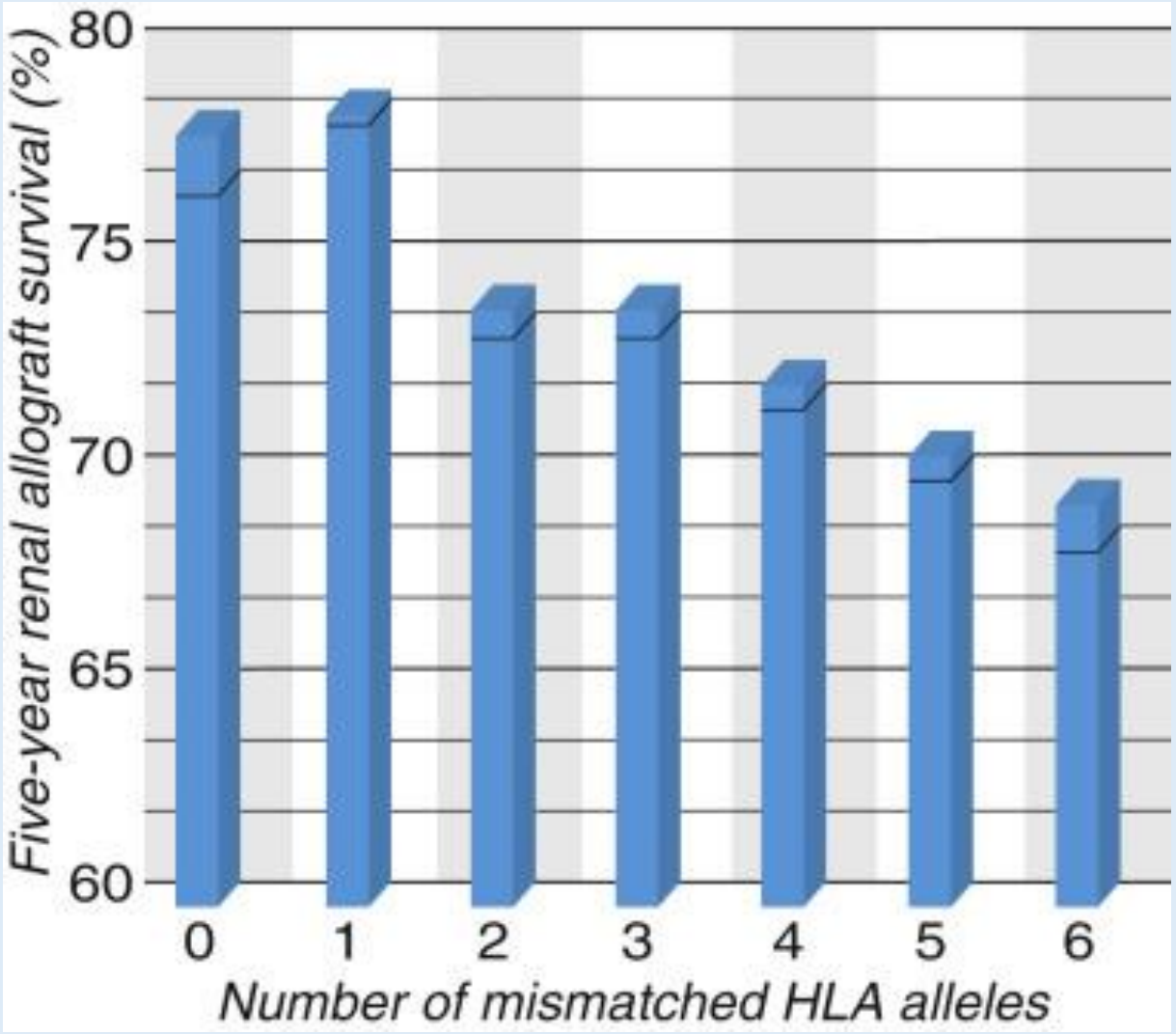
Preventing Rejection

Donor Selection: minimise alloantigenic differences between the donor and recipient

- ABO blood typing: avoid hyper-acute rejection

- HLA alleles. In particular HLA-A, HLA-B, HLA-C and HLA-DR, although may look at HLA-DQ. Zero-antigen mismatches predict the best survival (10/10). Protocols may differ on number of required HLA matches

Preventing Rejection



Preventing Rejection

Immunosuppression: Immunosuppressive drugs are typically required for extended periods, often lifelong

Multiple drugs are used with intensive induction and low dose maintenance

- Cyclosporins act by inhibiting T-cell activation, thus preventing T-cells from attacking the transplanted organ.
- Azathioprines disrupt the synthesis of DNA and RNA and cell division.
- Corticosteroids such as prednisolone suppress the inflammation
- Monoclonal antibodies that: suppress T cell activity; block co-stimulatory signals; deplete mature T-cells from the circulation; block cytokine

Further Reading

- Helbert, M. (2017). Immunology for Medical Students E-Book. Elsevier Health Sciences. Chapter 34 Transplantation Immunology
- Abbas, A. K., Lichtman, A. H., & Pillai, S. (2025). Cellular and molecular immunology E-book. Elsevier Health Sciences. Chapter 17 Transplantation

Both books above are available via Clinical Key Resources. Abbas will contain much more detail on the underlying immunology.

- Explore the NHS-BT transplantation pages

MBBS Learning Objectives

- Describe the principles of hypersensitivity reactions at a molecular level
- Identify the basis of transplantation immunology
- Describe the principles of host versus graft reaction