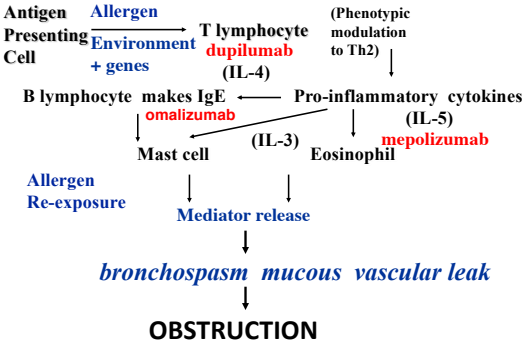
L18: IMMUNOPHARMACOLOGY

Allergic Disease

- atopy: genetic tendency to produce more IgE
- cross link IgE & antigen → activate mast cell → release bioactive lipids (PGs, LTs) & preformed histamine → allergy pathophysiology (allergic asthma) → SM constriction, leaky blood vessel → airway wall swelling (oedema), mucous hypersecretion → block lumen, WBC infiltration
- treatment
  - prevent original sensitisation & avoid allergens: difficult, constituting factor
  - ↓ release of mast cell mediator: disodium cromoglycate
  - ↓ action of mast cell product: antihistamine (good in treating hayfever only), LT/ACh more impact
  - prevent IgE binding to mast cell (omalizumab)
- mast cell activation
  - host exposed to antigen → produce antigen-specific IgE
  - allergen crosslink IgE → activate FcεR1 → PLC (transducer) → degranulation of mast cell → PG/LT
  - host re-exposed to antigen → activate Ca^{2+} & kinase
- **omalizumab**
  - humanised murine monoclonal antibody
  - administered sc, non-immunogenic (✗ killed by our antibody)
  - binds Fc portion of IgE → steric hindrance/competitive inhibition → prevent IgE binding to FcεR1 α chain → disarm mast cell → ↓ serum IgE, ↓ asthma symptom, fever, allergic rhinitis & hayfever symptom
  - few & mild adverse effect
  - more effective in children, less effective in airway
- diff patient got diff response to the pathway → cost effectiveness



- rolling leukocytes
  - mast cell mediators activate endothelium (barrier for WBC recruitment to tissues)
  - selectins on cell surface: rolling
  - cellular adhesion mol (CAMs): stationary binding
- target integrins/cell adhesion mol → fixed to endo cells
  - Natalizumab: humanised Mab against α4β1 co-ligand for VCAM & fibronectin
  - Multiple Sclerosis: progressive disorder, demyelination of neurons
    - antibody neutralise integrins → WBC ✗ bind → ↓ WBC entry to CNS/other sites
  - system blocked → leukencephalopathy (progressive multi-focal, fatal, viral/opportunistic)

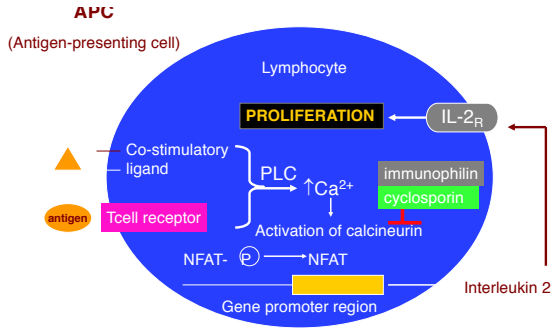
Autoimmune Disease: Rheumatoid Arthritis (RA)

- IgG against citrullinated proteins
- pathology: infiltration of T cell, neutrophils, macrophage into joint → remodel tissue
- ↑ connective tissue (fibroblast, blood vessels), ↓ bone mass
- symptoms/signs: swelling, reddening, pain (PG)
- PG & joint inflam
  - contribution
    - PGE2: vasodilate, ↑ blood flow, red
    - sensitise pain fibres to stimuli (hyperalgesic)
    - ↑ bone cells → bone resorption → bone lost
    - ↑ blood vessel formation (angiogenesis)
  - now overproduction → bad
  - drugs (NSAIDs, aspirin, indomethacin)
  - prevention
    - ↓ WBC activation & migration across endo
    - ↓ endo cell activation
    - ↓ cytokine release

- **NSAIDs** (non-steroidal anti-inflammatory drugs)
  - palliative: relieve pain & swelling but ✗ cure disease
  - may cause stomach ulcer
  - inflam → COX-2 → PG
  - now inhibit COX-2 → ↓PG in inflam w/o compromising COX-1 to produce PGE2 (protect stomach from ulcer)
  - celecoxib (↑ MI risk)

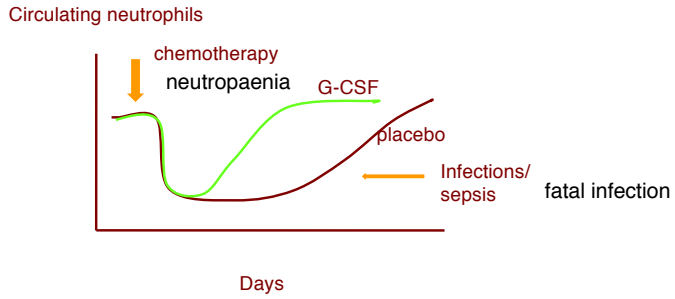
Graft Rejection

- heart, lung, kidney, liver, foreign tissue
- host/recipient immune cells recog foreign cells → ↑ T/B lymphocytes → antibody & T cells attack graft → graft rejected → life threatening consequence (failure of vital organs)
- persistent process
- immunosuppression treatment for life → adverse effects
  - stop T & B cells attack graft → vascular supply fails → ischaemic → cancer/infection risk
- **cyclosporin**
  - revolutionised transplantation medicine, 1st specific immunosuppressant, antimicrobial agent
  - cyclic peptide from soil fungus: unusual structure, side chain ✓ metabolised by cytochrome P450
  - oral bioavailability
  - variable PK
  - adverse effect: renal failure
  - TCR recog specific antigen + co-stimulatory ligand (↓prob to happen, to prevent autoimmune disease) → PLC → ↑Ca^{2+} → activate calcineurin (phosphatase) → NFAT-P (nuclear factor of activated T cell, TF) → NFAT translocate to nucleus → binds promoter on IL2 → ↑IL2 → IL-2_R (protein, proliferative agent for lymphocyte) → more T cells → attack more graft
  - cyclosporin binds immunophilin → inhibit calcineurin → prevent IL2 generation → ↓ graft specific T-lymphocyte



Cancer Chemotherapy

- inhibit dividing cells (hair loss, nausea, vomiting, lose appetite)
- non-selective cytotoxic drug (azathioprine) → suppress cell division in bone marrow
- **neutropenia** (anti-proliferative drug): ↓ neutrophils → ✗ phagocytose microbes → ↑ infection
- if use ↓ dose of chemotherapy, ✗ prolong patient's life
- **G-CSF** (granulocyte colony-stimulating factor) in bone marrow
  - **recombinant G-CSF** (adjunct to chemotherapy)
  - ↑ neutrophil precursor, ↑ neutrophils → ↓ infection



- drugs modulate immune response, immunosuppression:
  - beneficial: transplantation, autoimmune disease, allergic disease
  - detrimental (adverse consequence of 1° drug treatment): cancer, autoimmune/transplantation