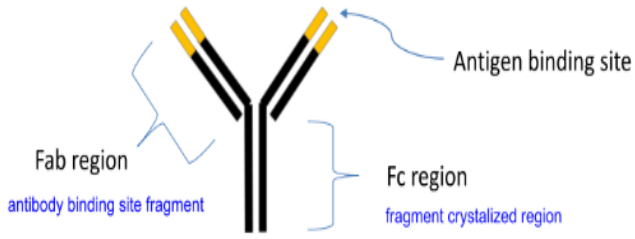
Biologics in RA: treatment alternative for rheumatoid arthritis when traditional DMARDs are inadequate

Antibodies

What are antibodies/immunoglobulins?

- Y-shaped proteins
- Produced mainly by B-cells/plasma cells of immune system
- Identify & neutralize pathogens (bacteria & viruses)
  - Bind to foreign matter (antigens) that elicits an immune response



Ig classes: IgA, IgD, IgE, IgG, IgM

- IgG antibodies most abundant, found in all body fluids, and protect against infections
  - 4 subclasses (IgG1, IgG2, IgG3, and IgG4)
  - Engineered therapeutic monoclonal antibodies mostly IgG1
  - IgG1 MW 150 kDa

Therapeutic monoclonal antibodies (mAbs): antibodies that are engineered and are specific to one antigen

- PK characteristics similar to IgG1
- First mABs produced by mouse cells
- Humanized antibodies have more human components than chimeric antibodies

Route of delivery

Small molecule: primarily delivered by oral administration
→ other routes used at times

mAbs: primarily delivered by IV administration
→ some SC
→ less common IM

Absorption

Small molecule: GI tract (mostly small intestine)

- Oral absorption of small molecule very complex & involves multiple processes
  - Dissolution of oral dosage form (pill, capsule)
  - Permeation across intestinal membrane

mAbs:

- Not required after IV administration
- Limited or no oral absorption after oral administration
  - Difficulty crossing intestinal membranes due to size
  - Cannot survive harsh conditions in GIT
- Mechanisms of SC absorption not well known, but involve convection & subsequent uptake via lymphatic system

Distribution

Small molecule: quickly distributes to tissues (secs – minutes) depending on rate of perfusion by blood (blood flow = limiting rate)

- Partition into tissues dependent on lipid & water solubility, binding to macromolecules (plasma proteins)
- Some cases, saturable drug transport processes into & out of tissue may play role in tissue distribution

mAbs: slowly distributes to tissues (mins-hours)

- Vd not much larger than plasma volume
- Lymphatic system important role in movement of mAbs throughout body
- Clearance mechanisms (catabolism & target mediated drug disposition = TMDD) are present in tissues

Elimination

Small molecule: typically involves metabolism of drug to increase its polarity, followed by excretion by kidneys

Metabolism: LIVER

- Hepatic metabolism in liver by cytochrome P450 enzymes common
- Other metabolic routes include glucorindation, sulfation
- Metabolism by enzymes typically saturable in high enough concentrations
  - Non-linear clearance but typically not observed at therapeutic observations

Excretion

- Drug metabolites or intact drug can be cleared by kidney into urine
- Some excretion in bile but far less common compared to kidney

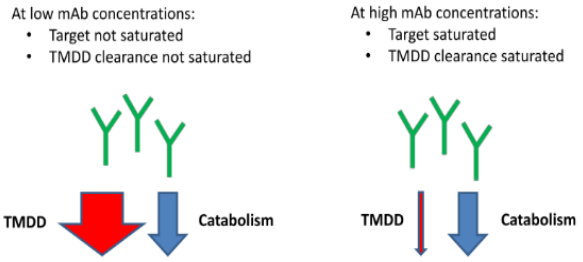
mAbs: elimination occurs at much slower rate than small molecules = $t_{1/2}$ in order of **days** (rather than minutes/hours)

Catabolism: in endosomal space of cells

- Major elimination route
- Antibodies protected from catabolism by binding to neonatal Fc receptor (FcRn)
- Catabolism is a high capacity elimination process (not saturated)

Target mediated drug disposition: TMDD

- TMDD occurs following interaction of the mAb with its biological target
  - mAb-target complex is eliminated
- TMDD can serve as a significant clearance pathway for mAbs
  - Low capacity elimination (can be satured)
- TMDD observed for some mAbs and is dependent on both target and mAb dose



Typical dose: saturating concentratins where catabolism prevails