PHAR2811: Drug Discovery and Design A

Proteins

- amino acids' unique structures due to R-group/side chain
- secondary structures = alpha helices + beta sheets (made of beta strands) + loops/coils (non-alpha or -beta)
- genes → proteins (in steps)
- introns + exons = eukaryotic genes
  - introns spliced out
- α-amino acids are chiral and tetrahedral except glycine
- CORN rule: if corn spelled out in clockwise direction, L-stereoisomer
- non-polar, aliphatic R-group: hydrophobic
- aromatic R-group absorb UV 270-280nm
- polar, uncharged R-group can form H-bonds
- positive charged R-groups = basic
- negative charged R-groups = acidic

Proteins II

- globular in aqueous environment; globular protein function = biological catalysis
- coagulation cascade involves serine proteinases, calcium, phospholipids
  - HIV-1 therapies target a proteinase
- ion concentration inside and outside cells regulated by gated ion channels
  - sequence of amino acids important in function of proteins, i.e. ion channels
- inside of cell ≈ -70mV
- $2K^+$ in, $3Na^+$ out
- protein + ligand have induced fit complementarity
- myoglobin: storage of oxygen
- amino acids not very good at binding oxygen by themselves
- haem group = strong chromophore; absorbs UV and visible range
- CO similar shape and size to O_2 but CO 20 000 x better at binding to haem
  - carbon in CO has filled lone electron pair that can be donated to vacant d-orbitals on the iron ion
- changing affinity of myoglobin to oxygen does not improve its ability as an oxygen transporter
- affinity to oxygen changed with multiple binding sites; interaction between binding sites known as cooperativity and must occur for change in affinity to oxygen
  - positive cooperativity = first binding event increases affinity at remaining or other sites
  - negative cooperativity = first binding event reduces affinity at remaining or other sites
  - haemoglobin has 4 binding sites
- at neutral pH, carboxyl group is deprotonated but amino group is protonated; as net charge is zero, this is known as a zwitterion

- amino acids with ionisable side chains can be titrated as well
- peptides are smaller than proteins, they are small condensation products of amino acids
- helices either shown as spring or cylinder
- strands more like arrows, the arrowhead is an indication of which end it is running in (i.e. bottom is N-terminus, top is C-terminus)

Proteins: fundamentals & structure II

- X-ray crystallography: X-rays shot through protein crystal to view electron density
  - X-rays diffracted by electrons so when electrons are diffracted, relatively pale where fewer electrons
  - more electrons an atom has = brighter the spots; number of electrons gives us a clue to which atom it is (e.g. O will scatter more than a H)
- X-ray crystallography done in 4 dimensions to get the best possible picture of the protein structure
- d = distance between two atoms = bond length
- F = structure factor → related to intensity
- we use F to work backwards to find the electron density
- we don't know the phase of the diffracted X-rays that come out – we have to guess this
- phase determination by these methods:
  - heavy atom method (MIR): soak the protein in a solution with heavy metals
  - anomalous scattering (MAD): heavier atoms display larger "ripples" or diffraction
  - molecular replacement (MR): use already known structure of a similar protein to work out the phases of the unknown structure
  - brute force/shake and bake: very computationally expensive, just guessing for phases
- temperature factor = how much atoms are moving → less the atoms are moving, less blurring of electron density
- the more data = the higher the resolution of the Fourier transformation (final image) = the lower Å
- lower the R-factor = more accurate
- NMR spectroscopy used to study a wide variety of nuclei (H, C, N, F, P)
  - all nuclei have odd mass numbers, which gives them nuclear spin to generate a magnetic field
  - number of signals = number of different kinds of protons
  - location of signals = how shielded/deshielded the proton is
  - intensity of signals = numbers of protons of that type
  - signal splitting = number of protons on adjacent atoms