



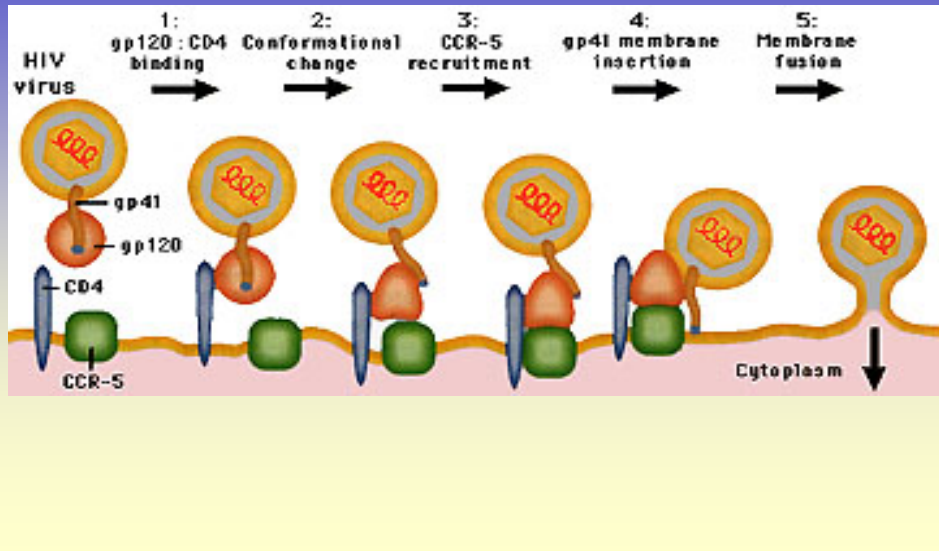
CHEMOKINE RECEPTORS IN HIV: STRUCTURAL SIMILARITY BETWEEN BOVINE RHODOPSIN RECEPTOR, CCR5 AND CXCR4

Isabelle, Miha and Connie

Introduction to HIV

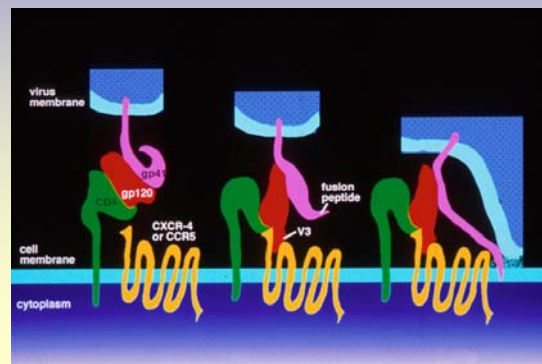
- HIV (Human Immunodeficiency Virus) is a retrovirus that invades the CD4⁺ T cells in the immune system
- CD4⁺ T cells play an important role in the body natural defence system thus decline of these cells causes the body to lose its ability to defend against microscopic invaders
- Five million new cases of HIV were diagnosed last year and it is estimated that about half the people with HIV will develop AIDS (Acquired Immunodeficiency) within 10 years after becoming infected
- There is currently no cure for AIDS and medical treatments aim to slow down the rate at which HIV weakens the immune system

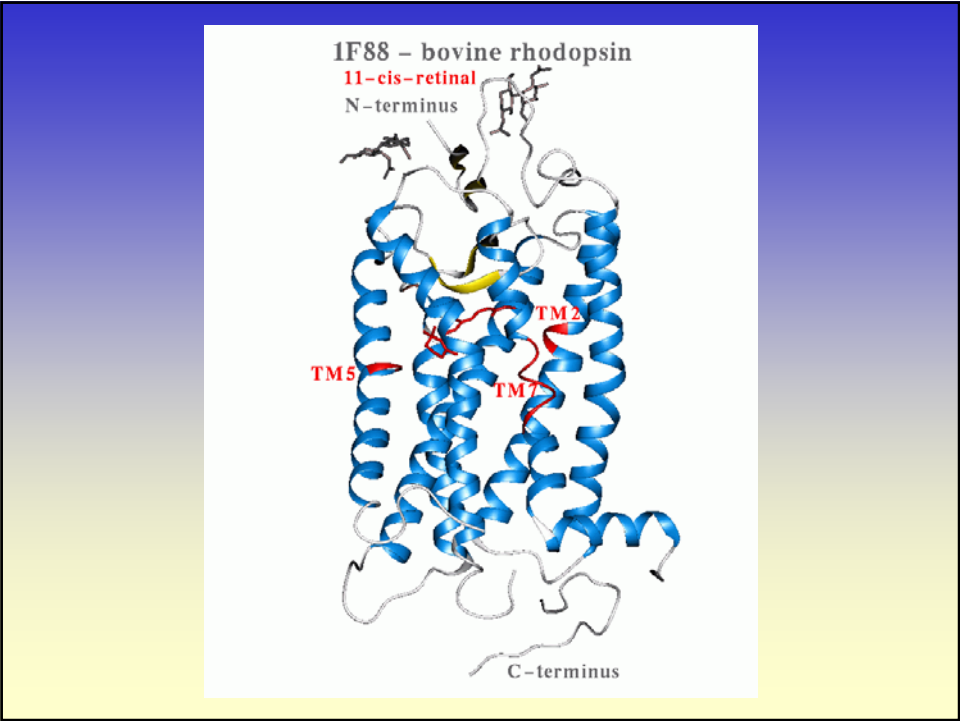
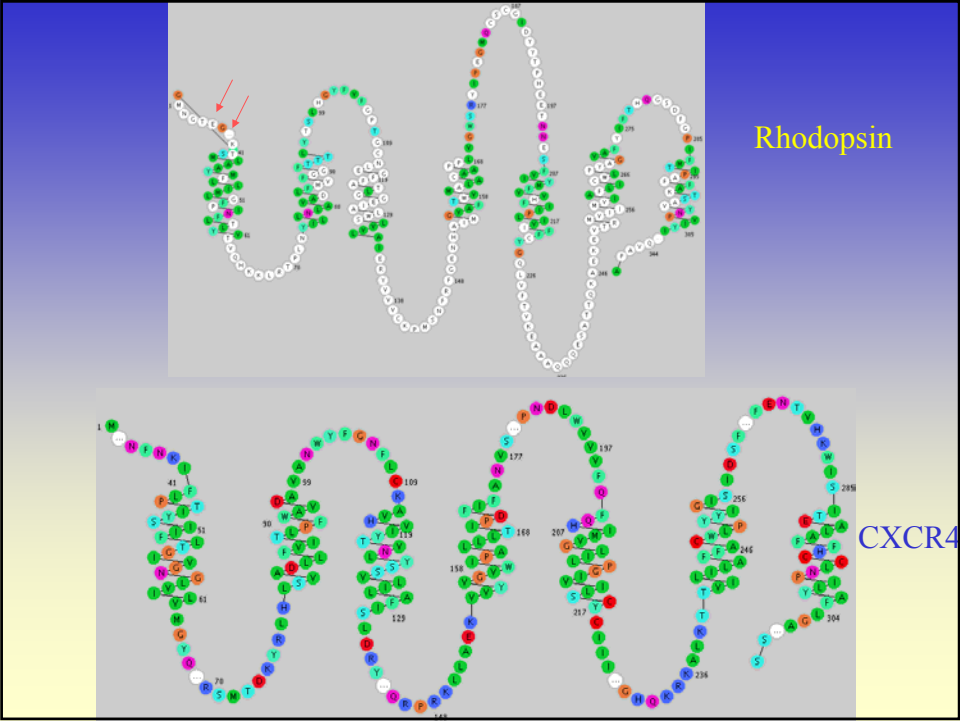
Mechanism of HIV Infection

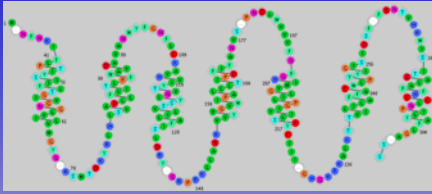


Aims of this project

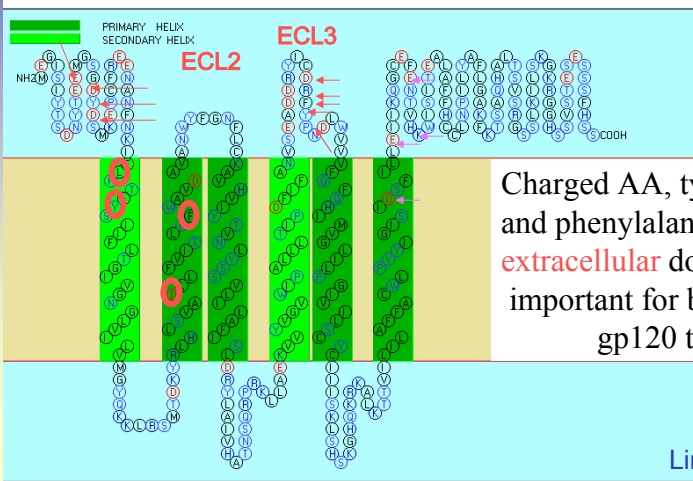
- To determine if the virus binds at the chemokine receptor agonist and antagonist binding site.
- To compare the structure of the chemokine receptor with the classical structure of bovine rhodopsin.







CXCR4

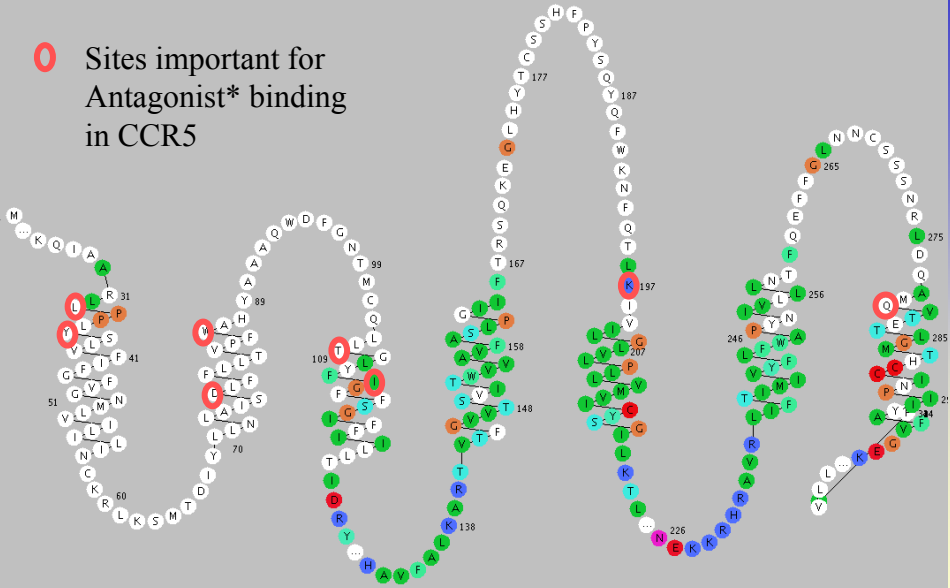


Charged AA, tyrosines and phenylalanines in **extracellular** domains are important for binding of gp120 to CXCR4

Lin *et al.* 2003

Non-Competitive binding of antagonist

○ Sites important for Antagonist* binding in CCR5



* SCH-351125 and SCH-350581

CRR5-gp120 binding

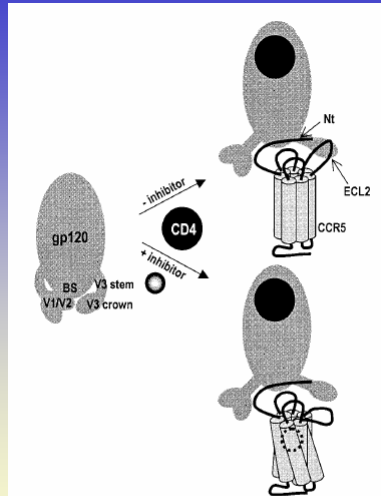
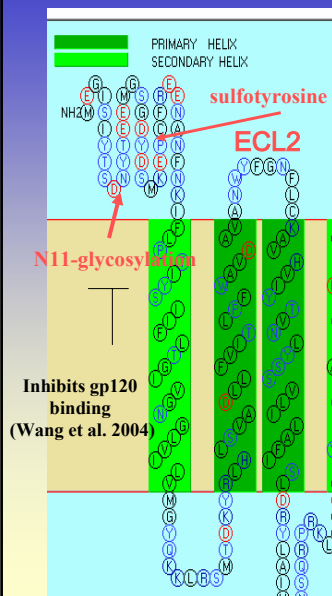


FIG. 4. Model of the mechanism of action of small-molecule inhibitors of CCR5 coreceptor function. gp120 is initially in a closed state, wherein the V1/V2 and V3 loops conceal the coreceptor binding site. Upon CD4 binding to gp120, conformational changes create and/or expose the coreceptor binding site. In the absence of inhibitor, the CCR5 Nt interacts with residues in the bridging sheet (BS) and the V3 stem, whereas ECL2 interacts with the V3 crown. In the presence of inhibitor, the conformation of ECL2 is modified such that it can no longer interact with the V3 crown, thus inhibiting viral entry.

Competitive binding of antagonist



➤ **Sulfated tyrosines** on the N-terminal of CCR5 contribute to the binding to its ligands (MIP-1 α , MIP-1 β , and HIV-1 gp120/CD4 complexes) and to the ability of HIV-1 to enter cells expressing CCR5 and CD4

➤ Sulfopeptides corresponding to these N-terminal sequence inhibit gp120-CD4 binding to CCR5

Agonist (SDF1) binding to CXCR4

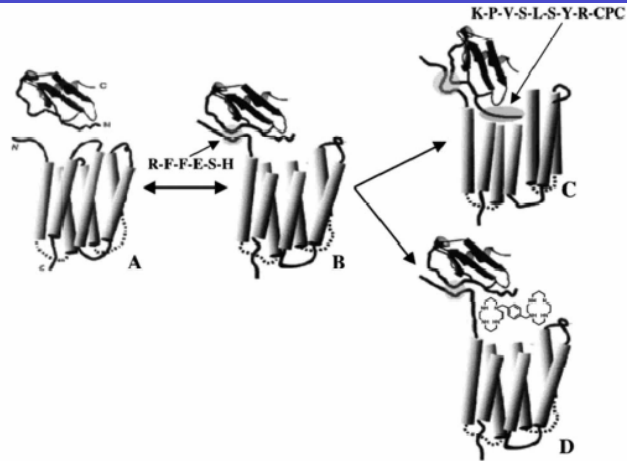
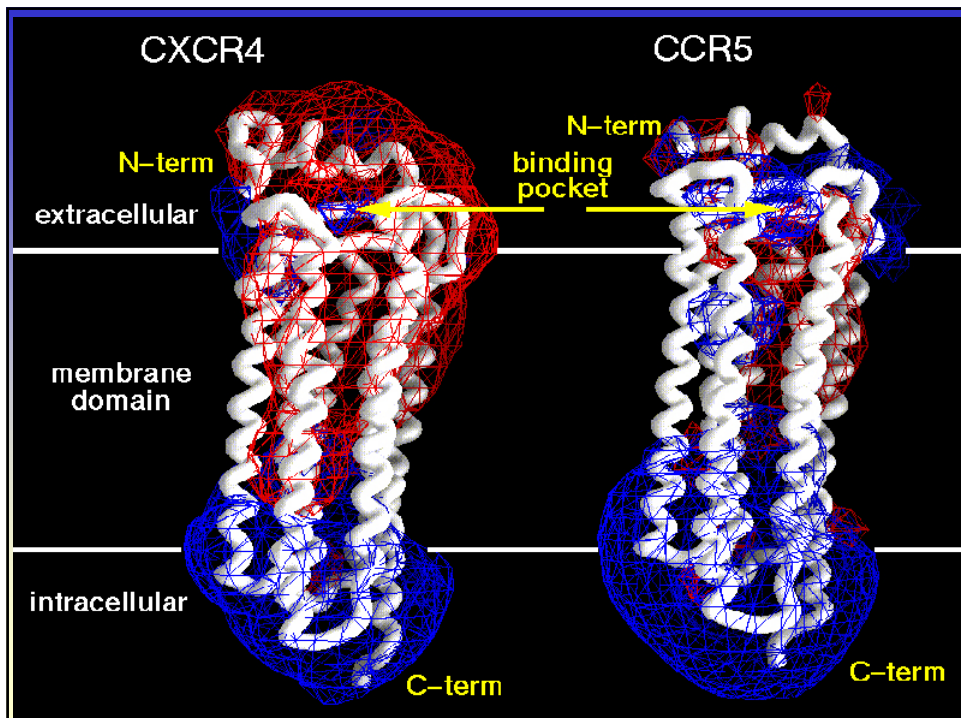
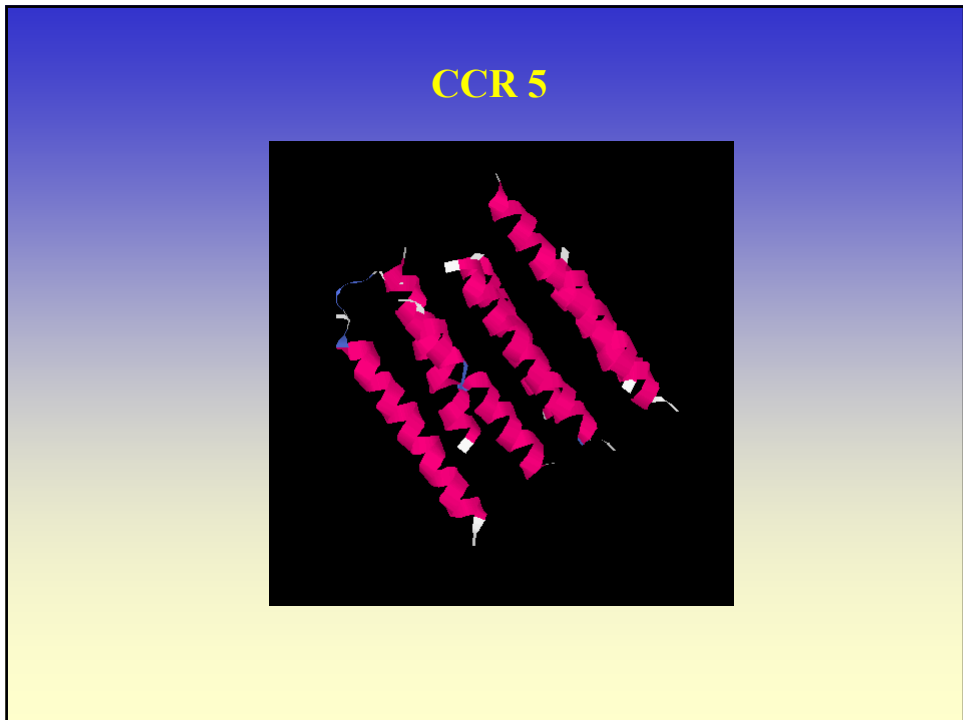
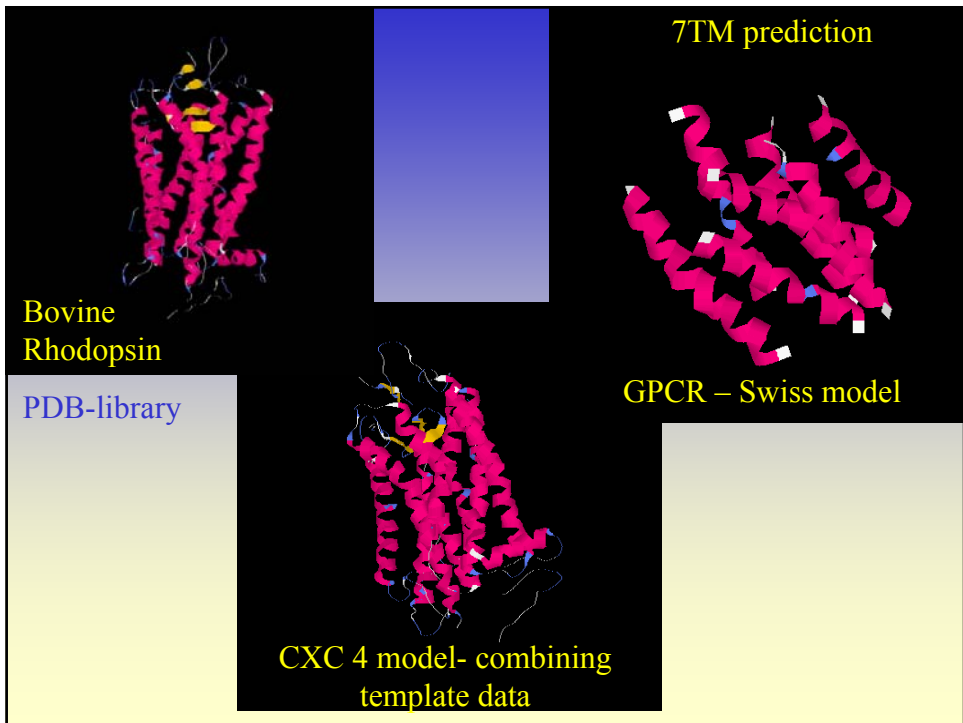


Fig. 3. Pharmacological evidence for the schematic model from Crump et al. [18], depicting interaction of SDF-1 α with CXCR4. (A) and (B) The initial docking step occurs between the N-terminal residues of CXCR4 and the R-F-F-E-S-H motif of SDF-1 α . (C) Conformational changes lead to interaction of the extracellular loops of CXCR4 with aa 1–11 of SDF-1 α . (D) Interaction of a small molecule antagonist like AMD3100 inhibits functional signal transduction without displacement of radiolabeled SDF-1 α .

Gupta *et al.* 2001





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