Targeting HIV:
Case studies in drug design

Chem 210

4/21/00

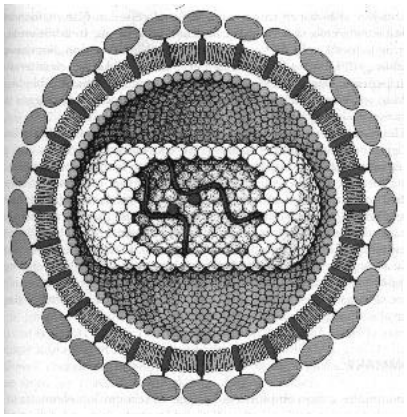
"Magic bullets" are the holy grail of drug design

- The term "magic bullet" coined in 1910s by Paul Erlich
  - A compound which could destroy a pathogen but not harm the host
- Difficult to target drugs using the screening approach
- Molecular biology opens the opportunity to target drugs to inhibit or alter specific biological processes.
  - Obtain a description of biological system
  - Identify proteins involved
  - Determine the structure and mechanism of the protein(s)
  - Design molecule to bind to/interfere with the proteins mechanism
  - Synthesize and test molecule

AIDS: Acquired Immune Deficiency Syndrome

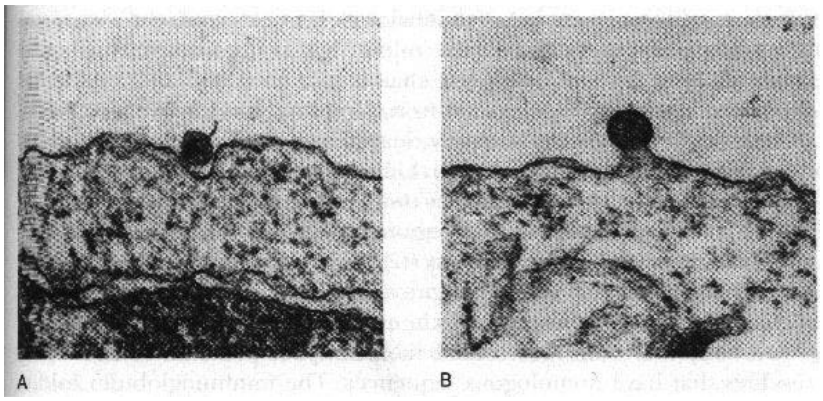
- Through 1999 cummulative AIDS-related deaths numbers approximately 16.3 million.
- Worldwide 33.6 million people living with AIDS/HIV infection (1999).
- 5.6 million new HIV infections occurred in 1999 (15,000 per day).

HIV is the infectious agent behind AIDS

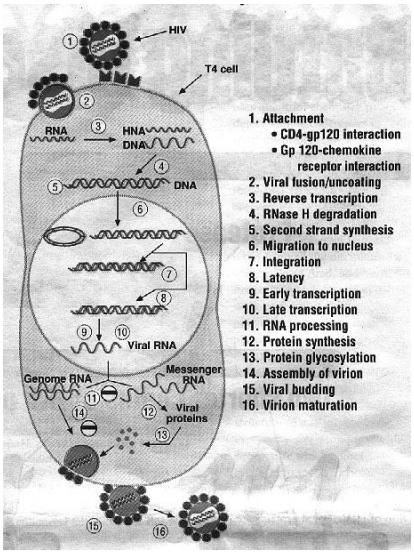


- HIV = Human Immunodeficiency Virus
- Virus: parasitic particle which contains genetic material, but can replicate only using the machinery of a host cell
- HIV is a *retrovirus*: genetic material is a single strand of RNA
- Reverse transcriptase:catalyzes synthesis of a DNA chain using RNA template

HIV infects cells of the immune system

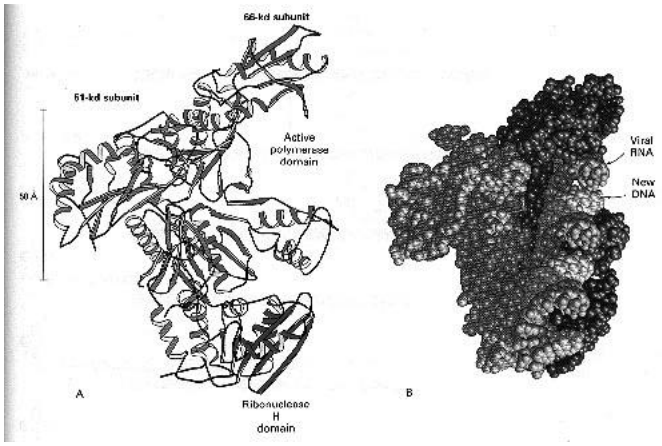


Potential targets for drug design can be found in the life cycle of HIV

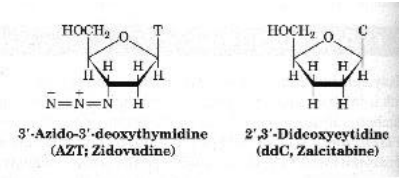


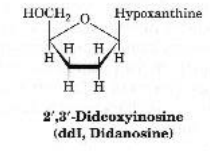
- Inhibit attachment of virus to cell
  - (CD4-gp120 interaction)
- Inhibit RNA --> DNA
  - (reverse transcriptase)
- Inhibit protein processing
  - (HIV protease)

Reverse transcriptase contains two polypeptide chains



The first available anti-HIV drugs were reverse transcriptase inhibitors

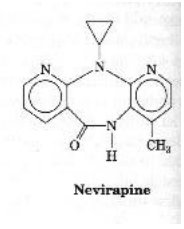




- Nucleoside analogs: molecules which look like nucleosides, but which can't be added into DNA chains.
- Bind in active site of the enzyme and inhibit its function
- These analogs also effect other enzymes which utilize nucleosides

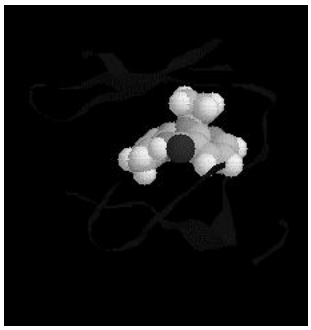
These analogs block active site

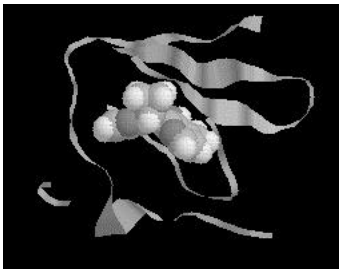
Non-nucleoside analogs bind to other sites on the protein



Nevirapine

Nevirapine binds in a hydrophobic cleft of reverse transcriptase

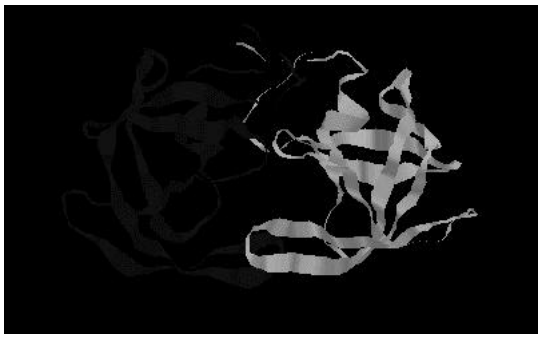




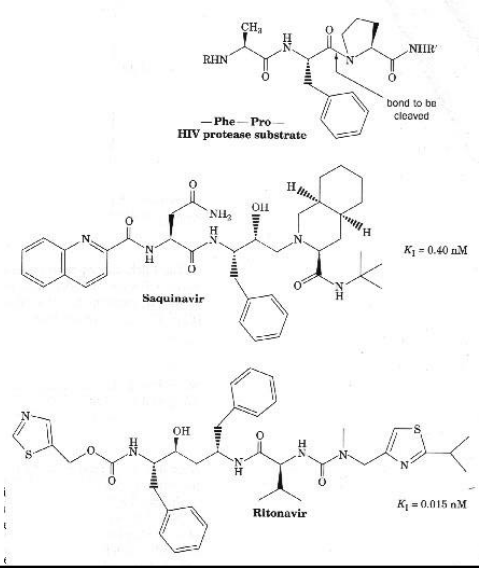
HIV protease is an enzyme essential for processing of viral proteins

- HIV proteins are synthesized in a single, long polypeptide chain.
- HIV protease is the enzyme which cleaves this polypeptide into smaller, individual pieces.
- These protein pieces are then assembled into a new virus.
- Idea: if HIV protease function can be blocked, then new viruses cannot be assembled; HIV replication blocked.

HIV protease is a dimer of identical polypeptide chains



Inhibitors of HIV protease mimic the shape of the substrate



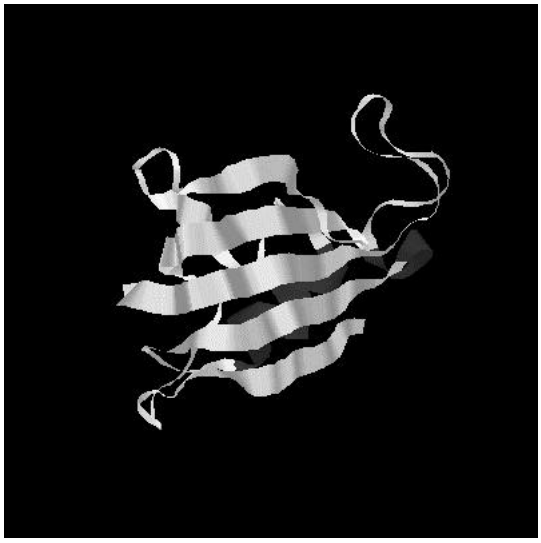
FK506 is a powerful immunosuppressant drug

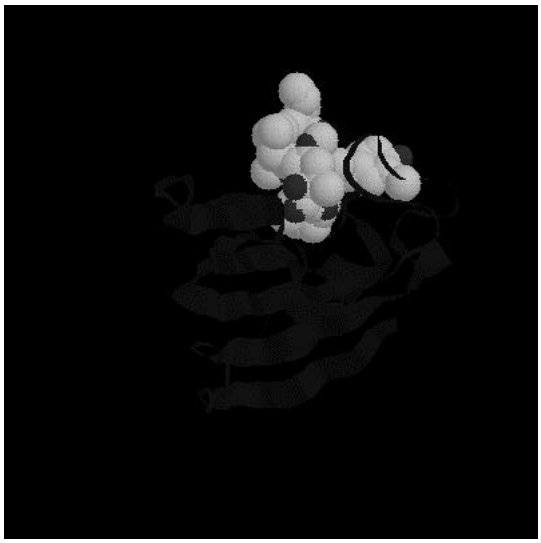
- Can be used to reduce immune response in transplant cases--minimize rejection of transplanted tissues/organs.
- Also may be a treatment for auto-immune disorders (MS, lupus, arthritis, etc.).
- Problem: FK506 is really toxic--not useful as a general, all purpose drug.
- Goal of Vertex Pharmaceuticals: identify the protein target of FK506, and "redesign" the molecule to be a "magic bullet" (have unique affinity for this one protein).

This process is long and involves complex collaboration

- FK506 protein needs to be isolated: protein biochemists isolate protein from tissue.
- Structure of protein needs to be determined by either x-ray crystallography or NMR
  - Difficult to grow protein crystals
  - Need a lot of protein for both x-ray and nmr studies
- Once structure is known, new molecules can be designed by computer modeling.
- These molecules need to be synthesized and tested.

FK506 binding protein





FK506 has been redesigned for tighter binding