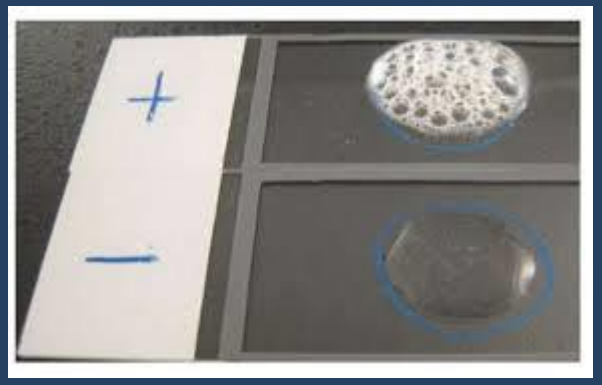
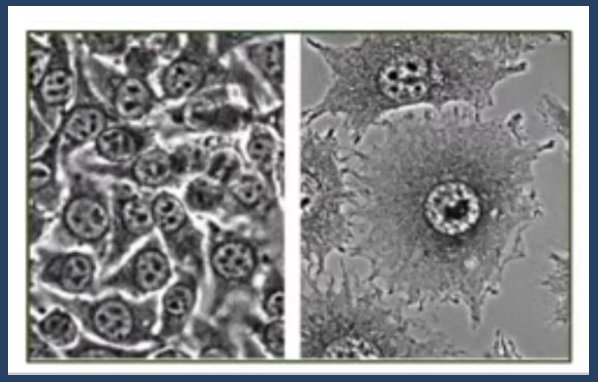
MOLECULAR DOCKING

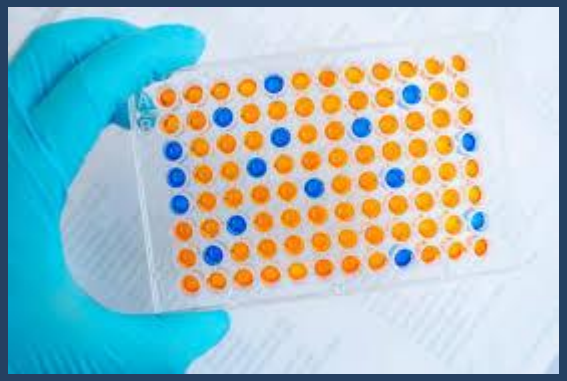
Presented By

Dr. Rawaa Saladdin Jumaa

Biochemical Reactions







Catalase test
Catalase enzyme convert H_2O_2 into $H_2O + O_2$

Target
Cells change morphology on addition of an inhibitor

Ligand binding assay
Color of the reaction mixture change on ligand binding

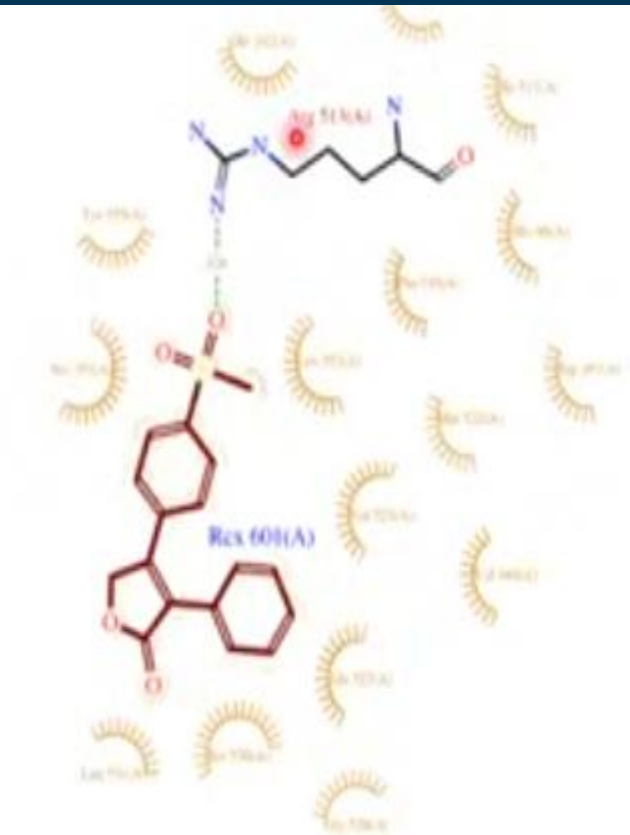
Molecular Recognition

- Every cellular process happens due to interactions between molecules
- These interactions are governed by various intermolecular forces of attraction
- Goal of docking = given structure of 2 biomolecules, determine if
  - They interact favorably
  - If Yes, then what is the orientation which maximizes interaction & minimizes energy

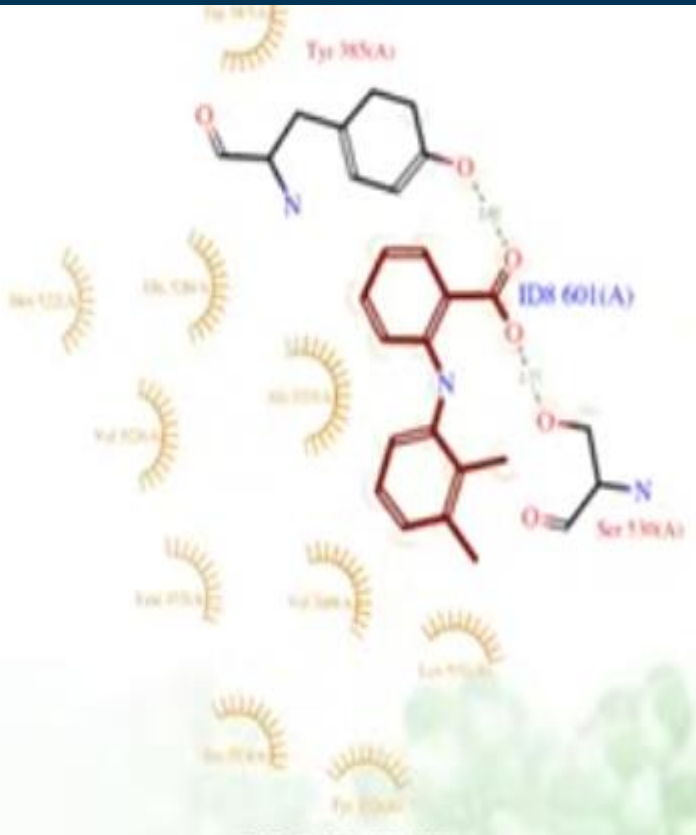
Molecular Interaction
Interatomic Interaction

- Enzyme substrate complex is formed with geometric as well as electrostatic complementarity
- A large number of interaction contribute towards molecular recognition, include
  - Van der Waals
  - Dipole-Dipole
  - Ion-Dipole
  - Ion- Ion
  - Hydrogen bond (receptor ligand interaction)
  - Covalent interactions

H bond Contribution

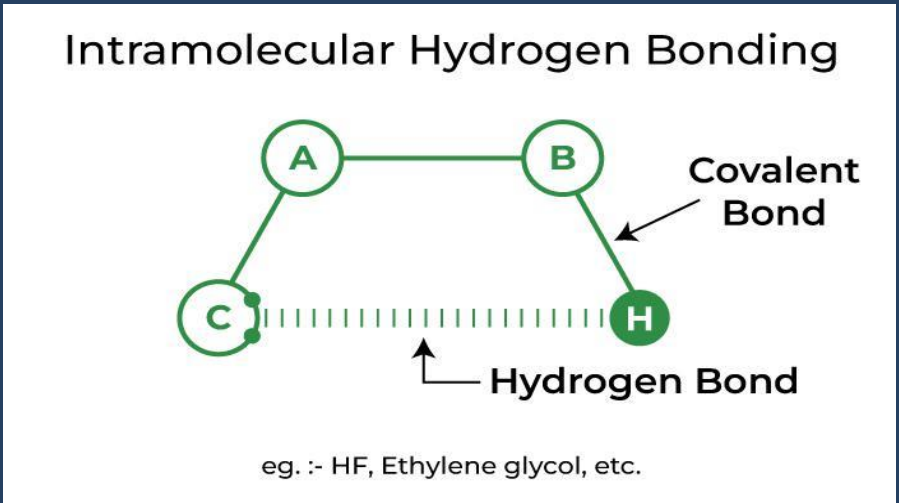


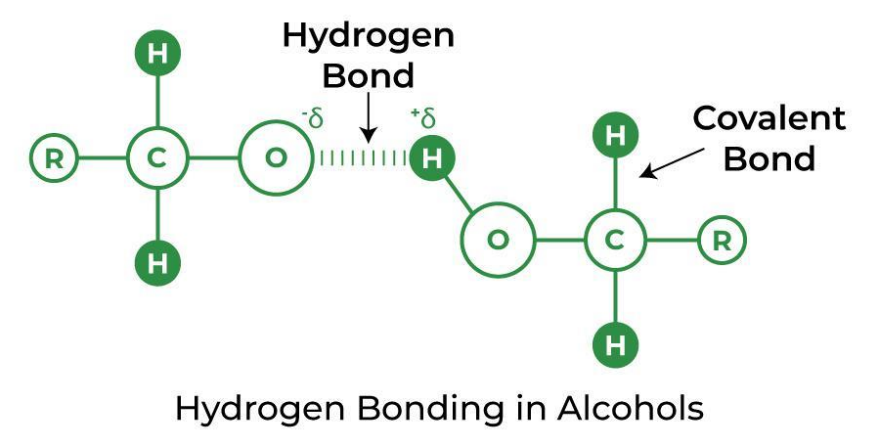
PDB ID: 5KIR
Vioxx (Rofecoxib) Bound to Cox-2
IC50: 3400nM



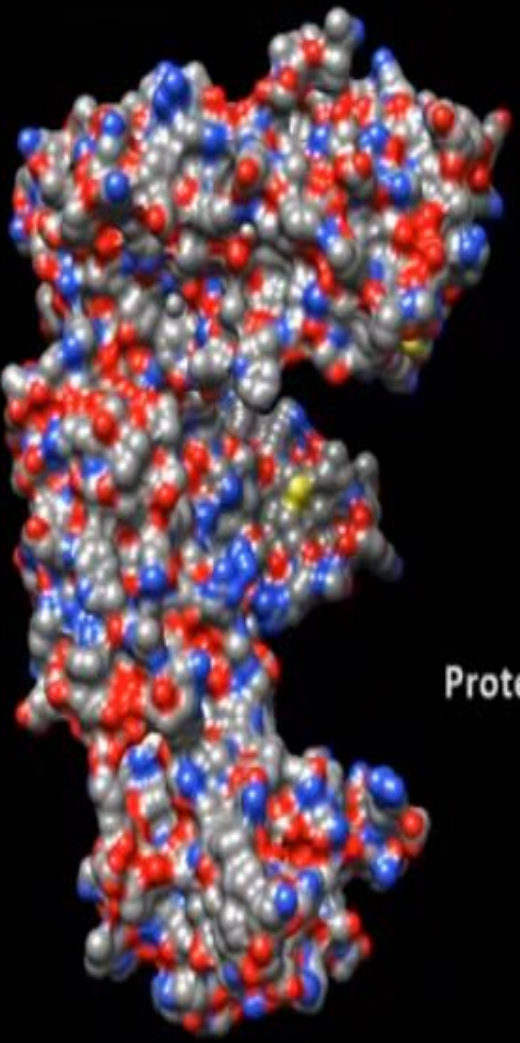
PDB ID: 5IKR
Mefenamic Acid Bound to Cox-2
IC50: 2900nM

H bond Contribution



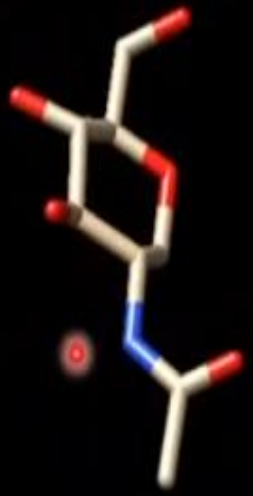


Bio-molecular Structure



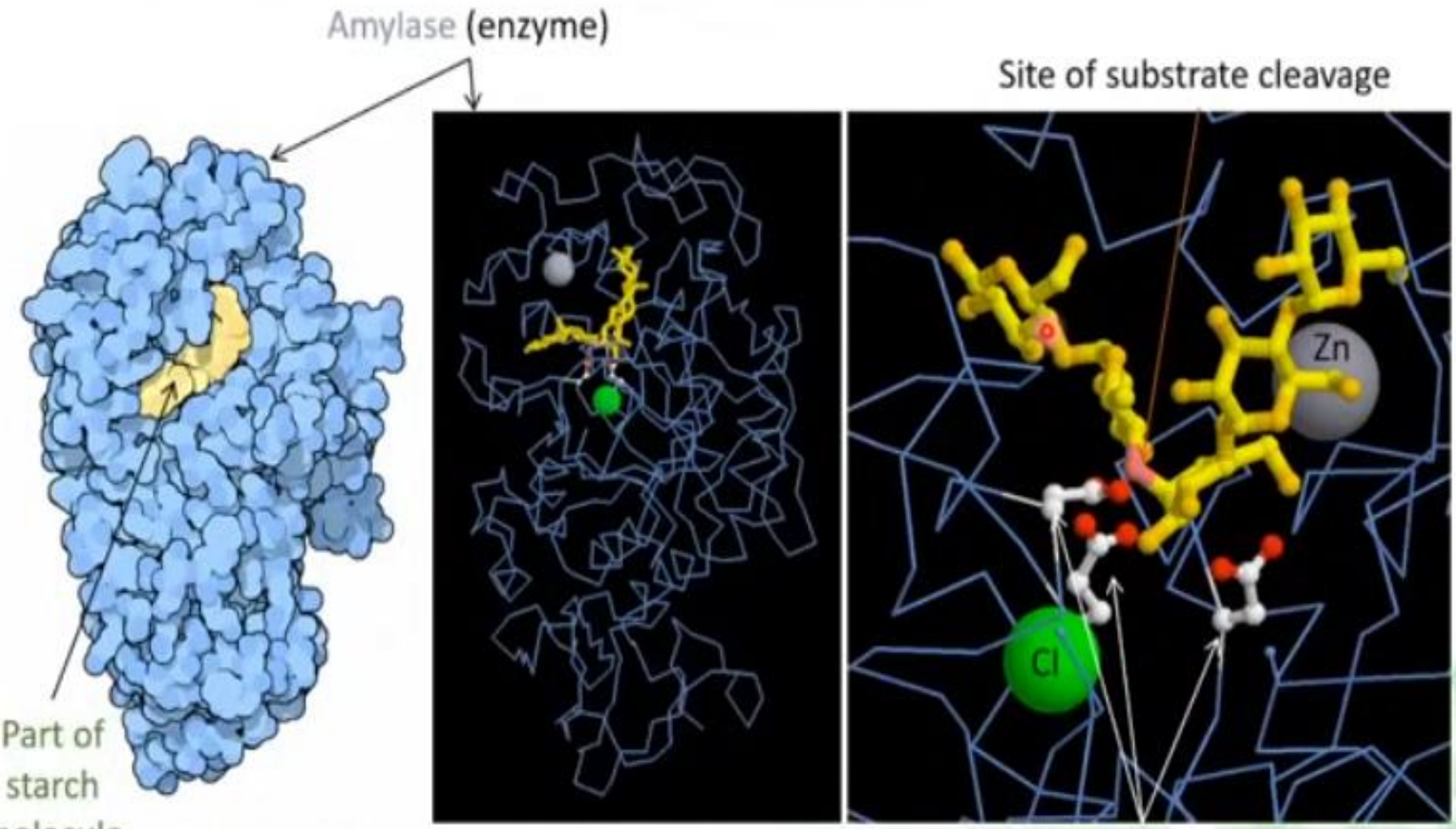
Proteins

Nucleic Acids



Other like lipids, carbohydrates, sugars and many other molecules

Sites


Amylase (enzyme)
Site of substrate cleavage
Part of starch molecule (substrate)
Zn
Cl
http://pdb101.rcsb.org/motm/74
Active site residues
Glu 233, Asp 197, Asp 300

Binding Sites

PROTEIN STRUCTURE

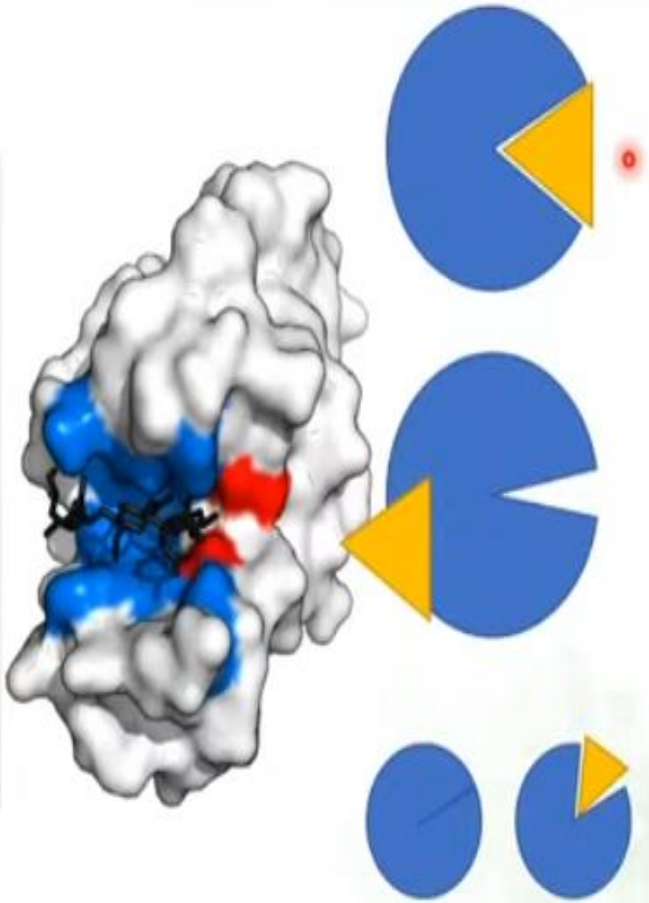
Scaffold to support and position active site

ACTIVE SITE

BINDING SITES
Bind and orient substrate(s)

CATALYTIC SITE
Reduce chemical activation energy

Thomas Shafee



Binding Site
Ligand molecules bind and exert action

Allosteric Binding Site
Ligand molecules bind at one place and action takes place at another site through relay of conformational changes

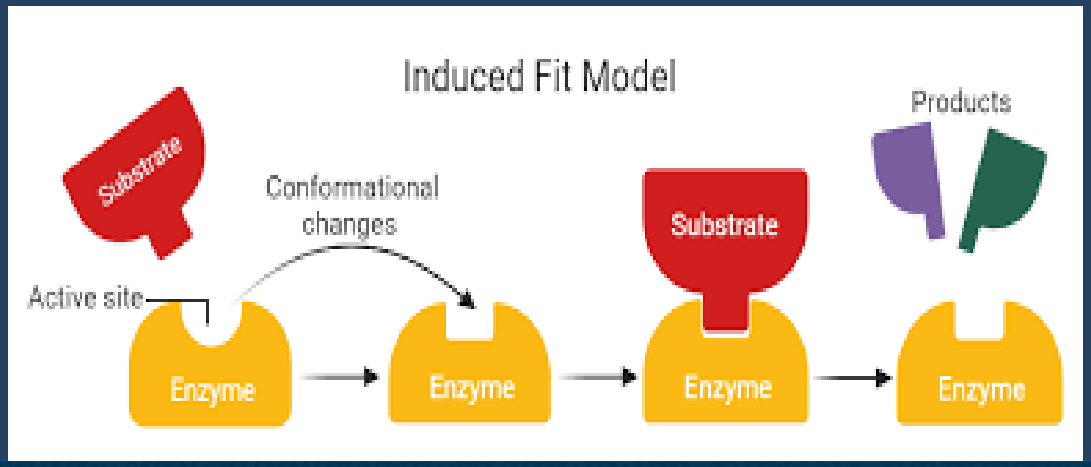
Cryptic Binding Site
Ligand molecules bind at one place and action takes place at another site through relay of conformational changes

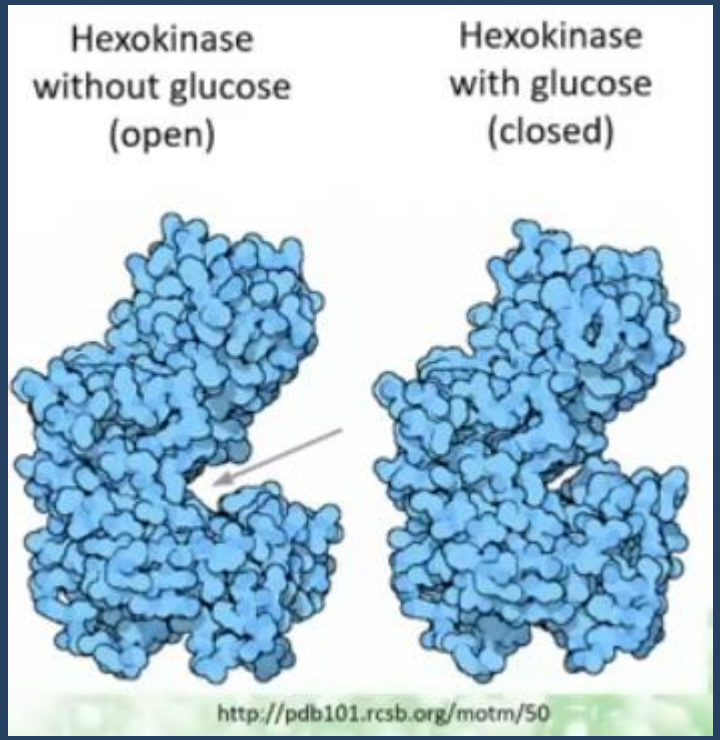
Binding sites

- Are very important when studying the MD
- Properties
  - Usually are pockets or deep cavities on protein surface
  - Lined by a set of a.a. with different properties (charged, polar, hydrophobic)
  - Complementary to their substrate
  - Is flexible & can accommodate variety of related structures

Enzyme Action Models

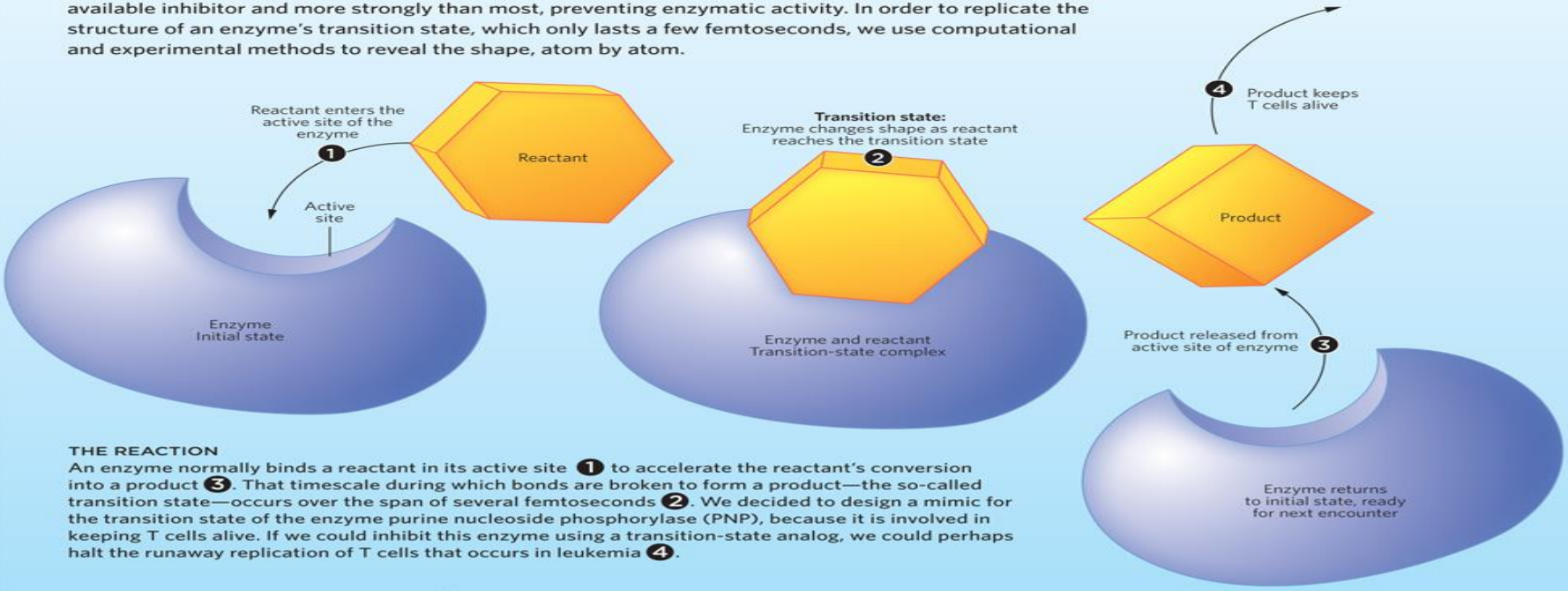
- Lock and key (Rigid shape complementarity)
- Induced fit model (Receptor flexibility)
- Transition State Model
  (Substrate shape is changed in intermediated shape)





DESIGNING TRANSITION-STATE INHIBITORS

A transition-state mimic has the power to bind an enzyme at its tipping point as strongly as any available inhibitor and more strongly than most, preventing enzymatic activity. In order to replicate the structure of an enzyme's transition state, which only lasts a few femtoseconds, we use computational and experimental methods to reveal the shape, atom by atom.

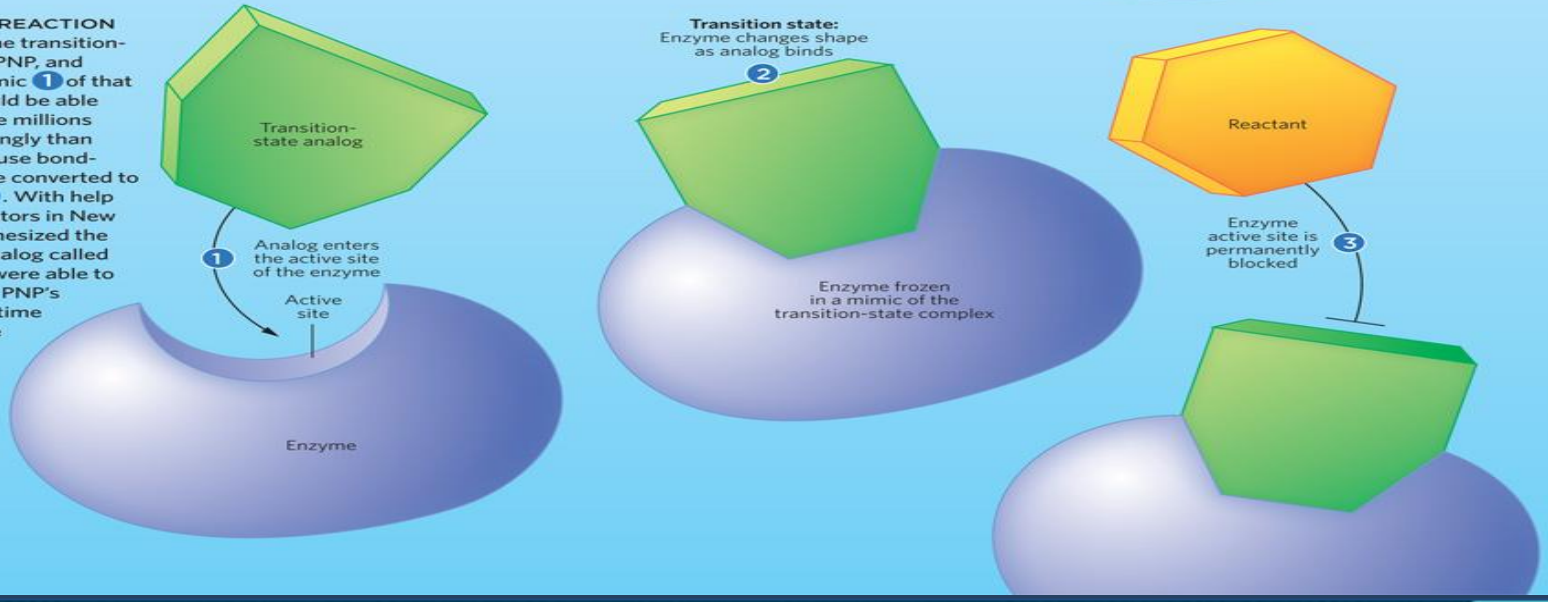


THE REACTION

An enzyme normally binds a reactant in its active site 1 to accelerate the reactant's conversion into a product 3. That timescale during which bonds are broken to form a product—the so-called transition state—occurs over the span of several femtoseconds 2. We decided to design a mimic for the transition state of the enzyme purine nucleoside phosphorylase (PNP), because it is involved in keeping T cells alive. If we could inhibit this enzyme using a transition-state analog, we could perhaps halt the runaway replication of T cells that occurs in leukemia 4.

INHIBITING THE REACTION

We first defined the transition-state structure of PNP, and then created a mimic 1 of that structure that would be able to bind the enzyme millions of times more strongly than the reactant because bond-breaking forces are converted to binding energy 2. With help from our collaborators in New Zealand who synthesized the transition-state analog called immucillin-H, we were able to successfully block PNP's activity for the lifetime of the cell 3. The transition-state mimic is now in clinical trials for the treatment of several forms of leukemia.



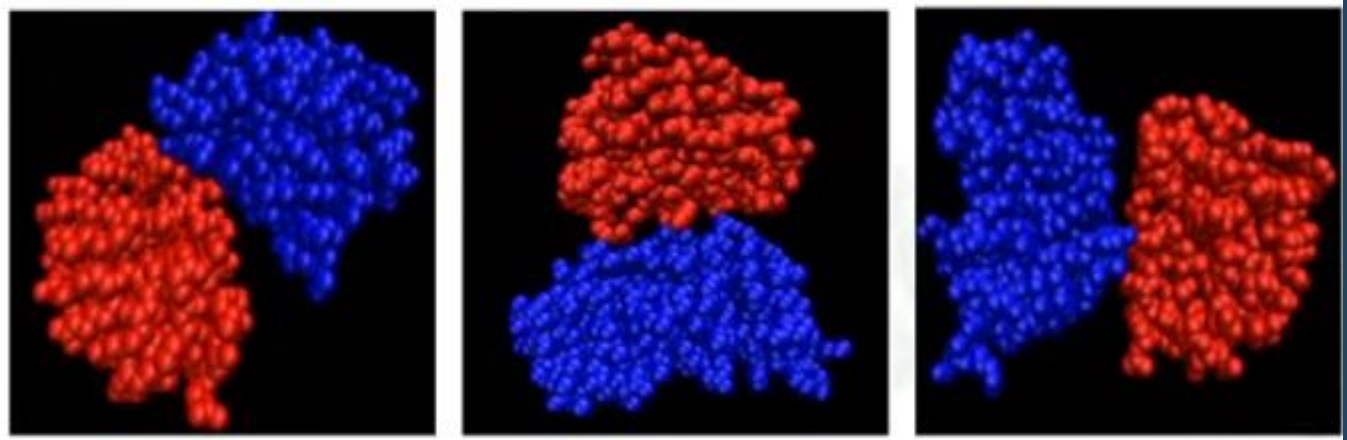
LUCY READING-IKKANDA FOR THE SCIENTIST (MAY 2012)

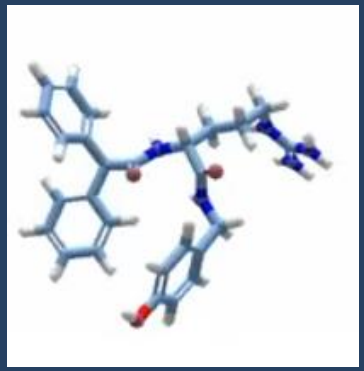
Molecular Docking

- A computer based technique to investigate molecular interaction
- Attempts to find the most probable binding conformation of 2 molecules which minimize the energy through maximized interaction
- An extension of molecular modeling approaches
- Goal is to find stable complex of receptor and ligand with possible energy

Molecular flexibility

- Molecule are flexible in nature and many alter each other's structure when interaction
- Thus interacting molecules possess large DOFs (Degree of Freedom)
- Possible conformations are enormous in number






Thank you
for listening