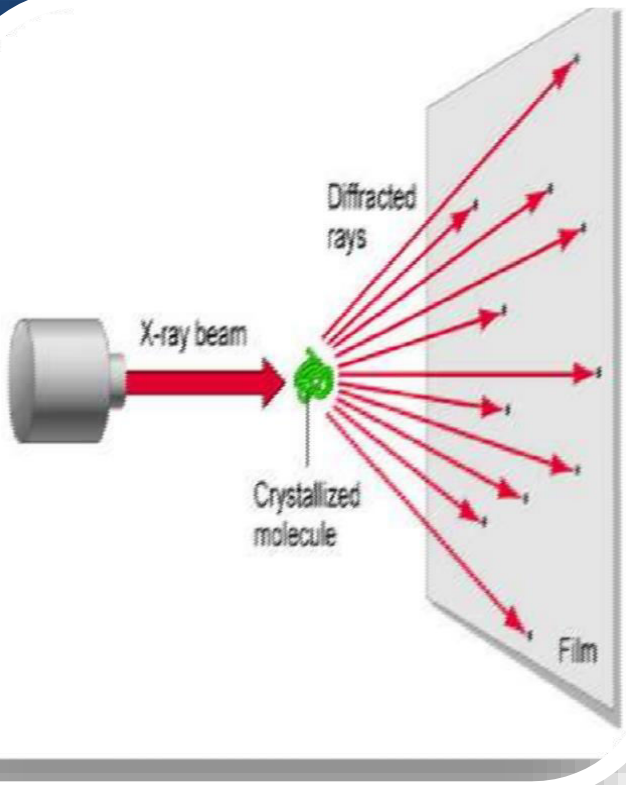
FACULTY OF ENGINEERING AND TECHNOLOGY

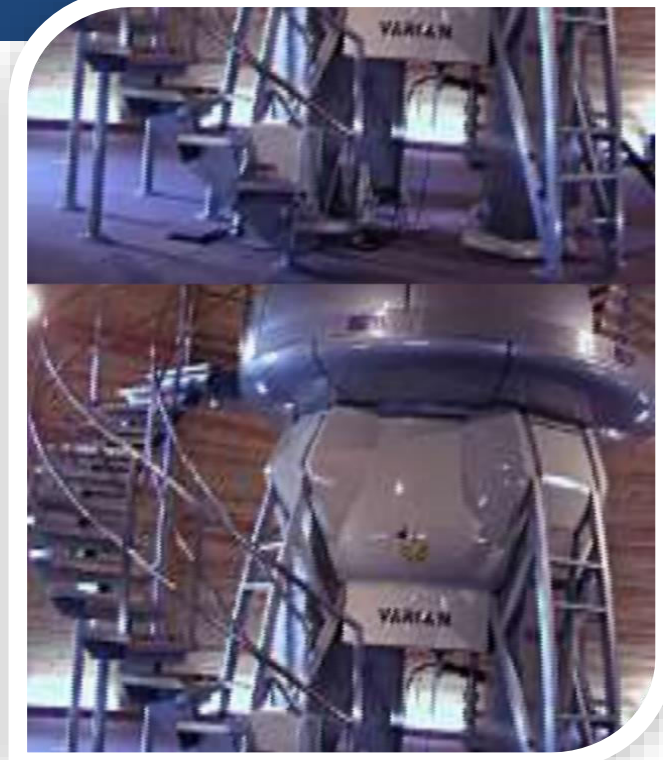
Department of Biotechnology

Target Based Approaches

- Structure-based drug design (or **direct drug design) relies** on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.
- If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein.
- Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist.



X-ray Crystallography



NMR Spectroscopy

Homology Modelling

- Structure-based design is one of the first techniques to be used in drug design.
- Structure based drug design that has helped in the discovery process of new drugs.
- In parallel, information about the structural dynamics and electronic properties about ligands are obtained from calculations.
- This has encouraged the rapid development of the structure based drug design.
- structure-based drug design can be divided roughly into two categories.

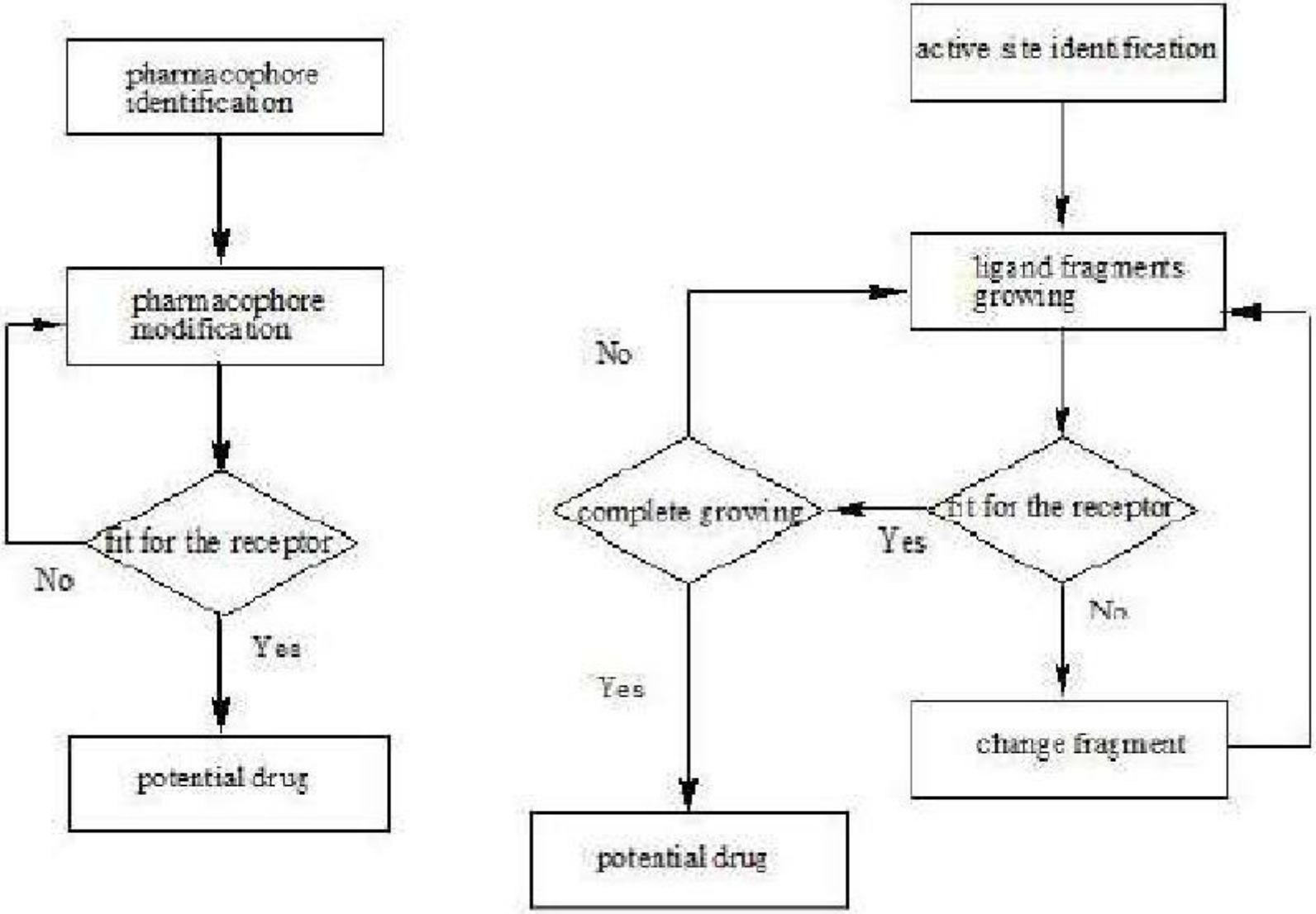
1. Ligand based Drug Design Or Database Searching
2. Receptor based Drug Design

LIGAND BASED DRUG DESIGN

- The first category is about “finding” ligands for a given receptor, which is usually referred as database searching.
- In this case, a large number of potential ligand molecules are screened to find those fitting the binding pocket of the receptor.
- This method is usually referred as ligand-based drug design.
- The key advantage of database searching is that it saves synthetic effort to obtain new lead compounds.

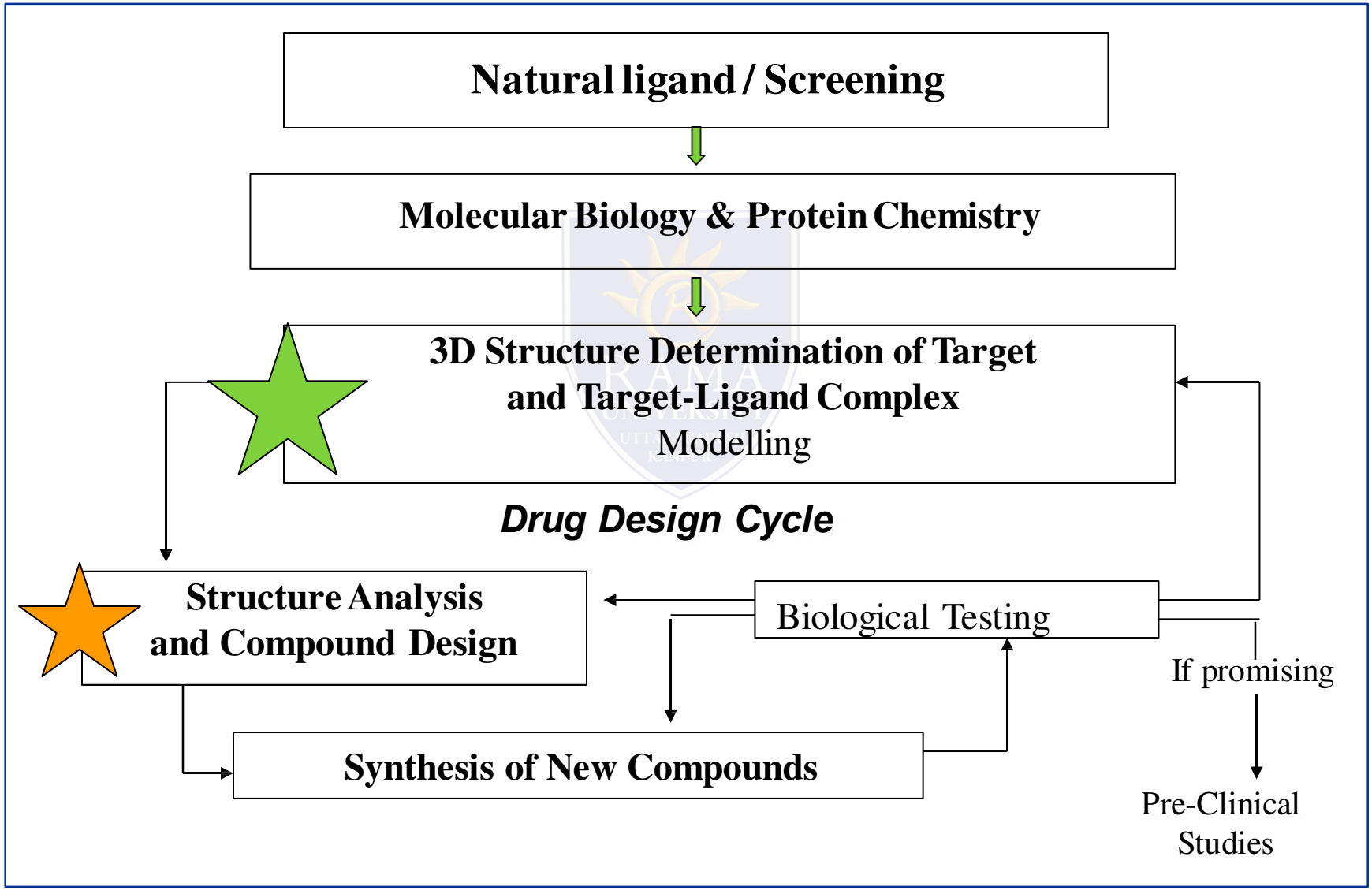
RECEPTOR BASED DRUG DESIGN

- Another category of structure-based drug design methods is about “building” ligands, which is usually referred as receptor-based drug design.
- In this case, ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner.
- These pieces can be either individual atoms or molecular fragments.
- The key advantage of such a method is that novel structures, not contained in any database, can be suggested.



Flow charts of two strategies of structure-based drug design

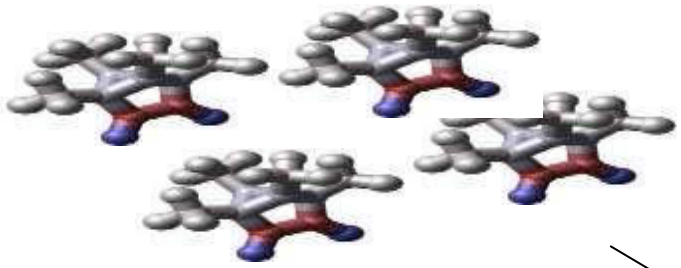
Structure-based Drug Design (SBDD)



Structure-based Drug Design (SBDD)

xyz

abc



Ligand database

Target Protein

Molecular docking

Ligand docked into protein's active site

Pharmacokinetic and Pharmacodynamic optimization

DOCKING

- Docking refers to the ability to position a ligand in the active or a designated site of a protein and calculate the specific binding affinities.
- Docking algorithms can be used to find ligands and binding conformations at a receptor site close to experimentally determined structures.
- Docking algorithms are also used to identify multiple proteins to which a small molecule can bind.
- Some of the docking programs are GOLD (Genetic Optimization for Ligand Docking), AUTODOCK, LUDI, HEX etc.

What is Docking?

- Docking attempts to find the "best" matching between two molecules

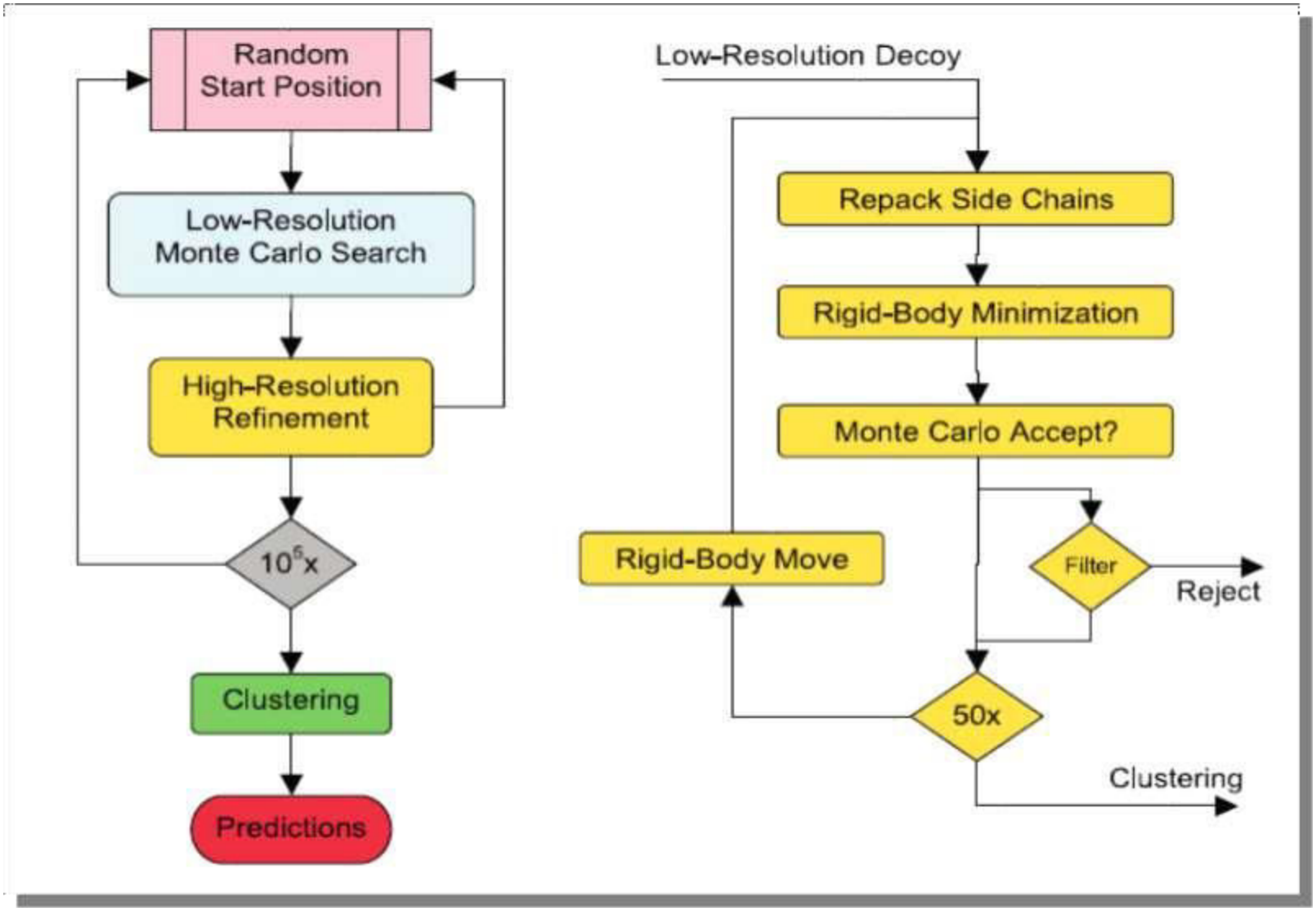
- It includes finding the Right Key for the Lock

- Given two biological molecules determine:

  - Whether the two molecules "interact"
  - If so, what is the orientation that maximizes the "interaction" while min imizing the total "energy" of the complex

✓ **Goal:** To be able to search a database of molecular structures and retrieve all molecules that can interact with the query structure

Docking Protocol



XYZ

abc

XYZ

abc

XYZ

abc

MCQs

1. A
2. A
3. A
4. A
5. A
6. A
7. A
8. A
9. A
10. A