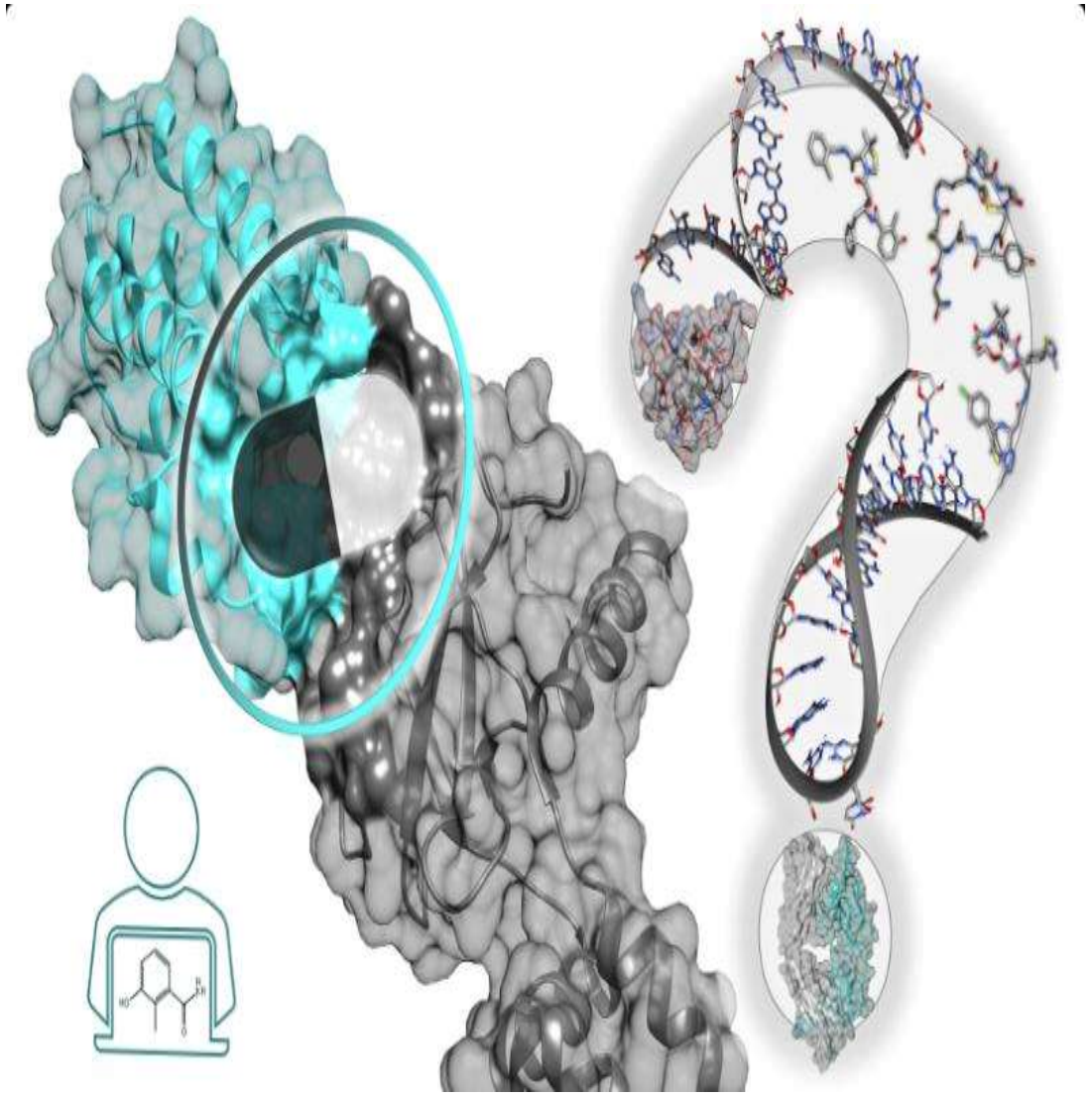
DRUG DESIGN strategy

- DISCOVERY & DRUG DESIGN
  Purpose of Drug Design: To improve selectivity of action To improve ADME (Absorption, Distribution, Metabolism & Excretion) Profile. To obtain drug having more desirable properties than the lead compound in terms of potency, toxicity & specificity. To obtain marketable alternative drug that can compete with an existing one. To reduce cost of bulk production Exploitation of side effects of existing drug Invention of drugs De Novo DRUG DISCOVERY & DRUG DESIGN Improvement of Drug Selectivity Drug selectivity is a primary objective in the discovery and optimization of a compound on the path toward developing a drug.

- There are two important aspects in drug
- design and drug strategies to improve :
- 1. Pharmacodynamics properties: to optimize
- the interaction of the drug with its target.
- 2. Pharmacokinetics properties: to improve the
- drug's ability to reach its target & to have
- acceptable lifetime.
- □ Pharmacodynamics and pharmacokinetics
- should have equal priority in influencing
- which strategies are used and which
- analogues are synthesized.



- **Drug Discovery:** It is an effort to produce new drug molecules from a lead compound by applying variety of approaches of design. Drug design approach is the prerequisite for drug discovery.

- **Drug Development:** Drug development is the process of establishing and marketing a biologically active compound obtained by drug design, as a suitable drug by observing pharmacokinetic (ADME), toxicological and clinical parameters.

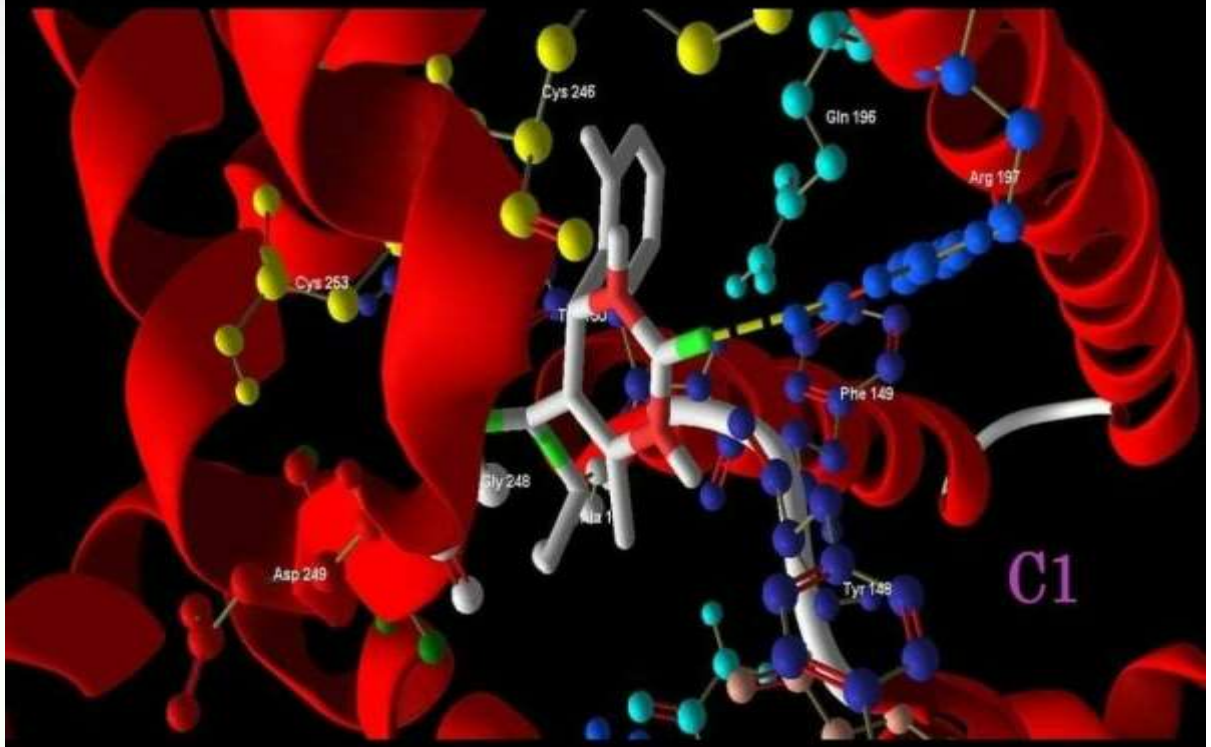
DRUG DESIGN

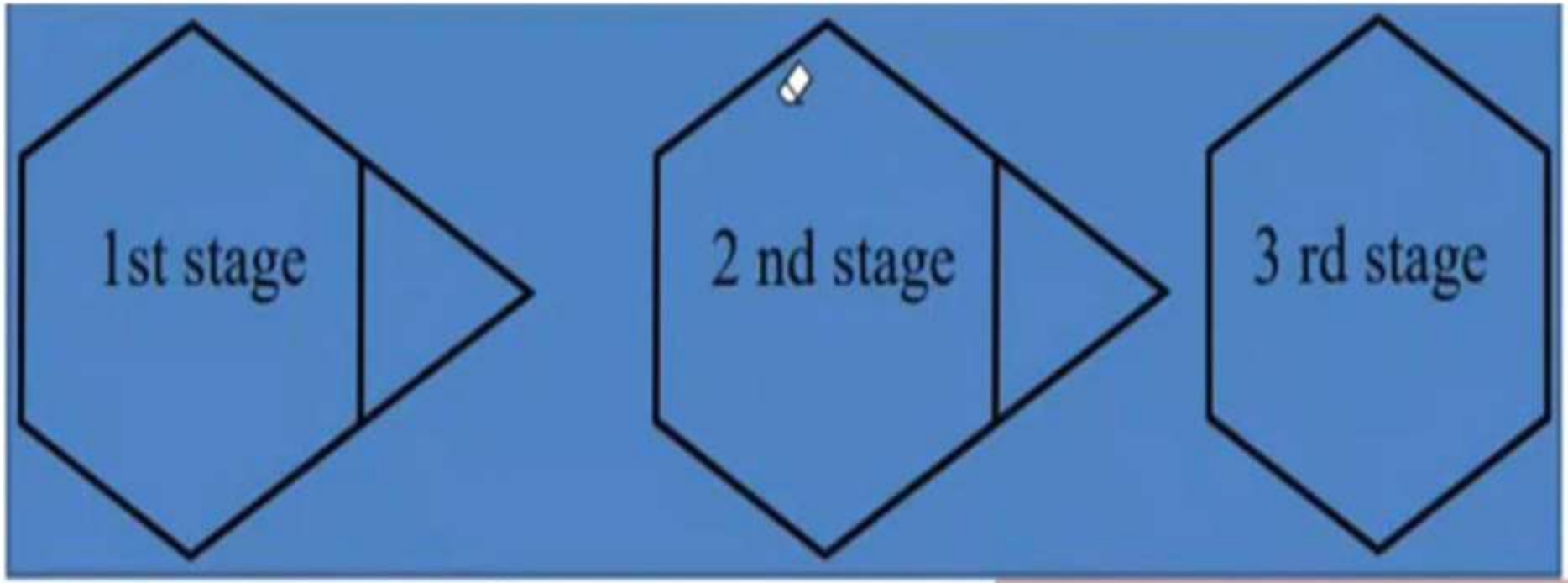
2 ways:

A) Development of ligands with desired properties for targets having known structure and functions.

B) Development of ligands with predefined properties for targets whose structural information may be or may not be known.

This, unknown target information can be found by global gene expression data.

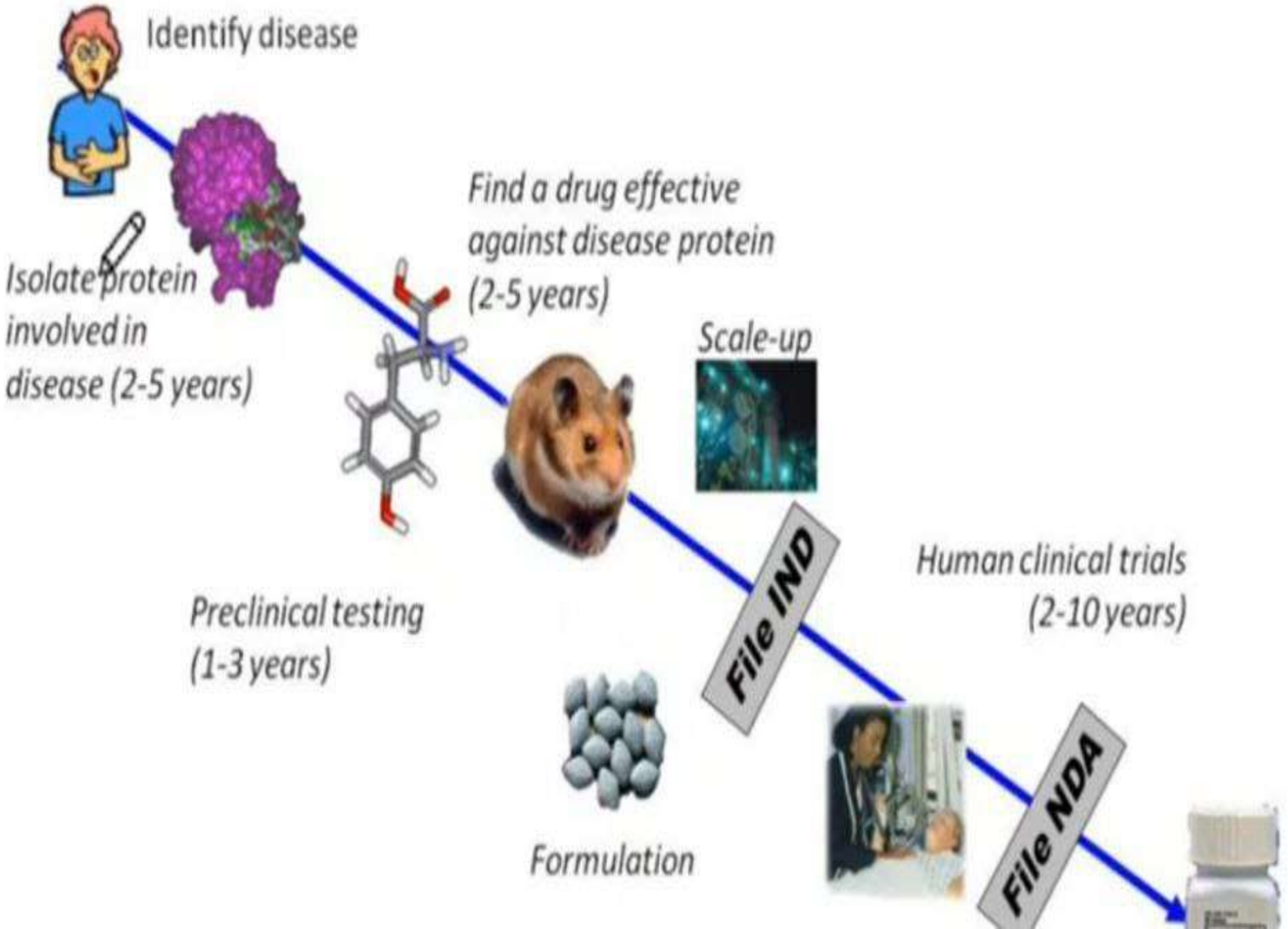




Identification of lead compound and prepared from natural sources, organic chemical reactions or

optimization of lead structure to improve potency, selectivity and to reduce toxicity.

development stage, which involves optimization of synthetic route for bulk production and modification of pharmacokinetic and


Identify disease
Isolate protein involved in disease (2-5 years)
Find a drug effective against disease protein (2-5 years)
Scale-up
Preclinical testing (1-3 years)
File IND
Human clinical trials (2-10 years)
Formulation
File NDA

Drug design strategies

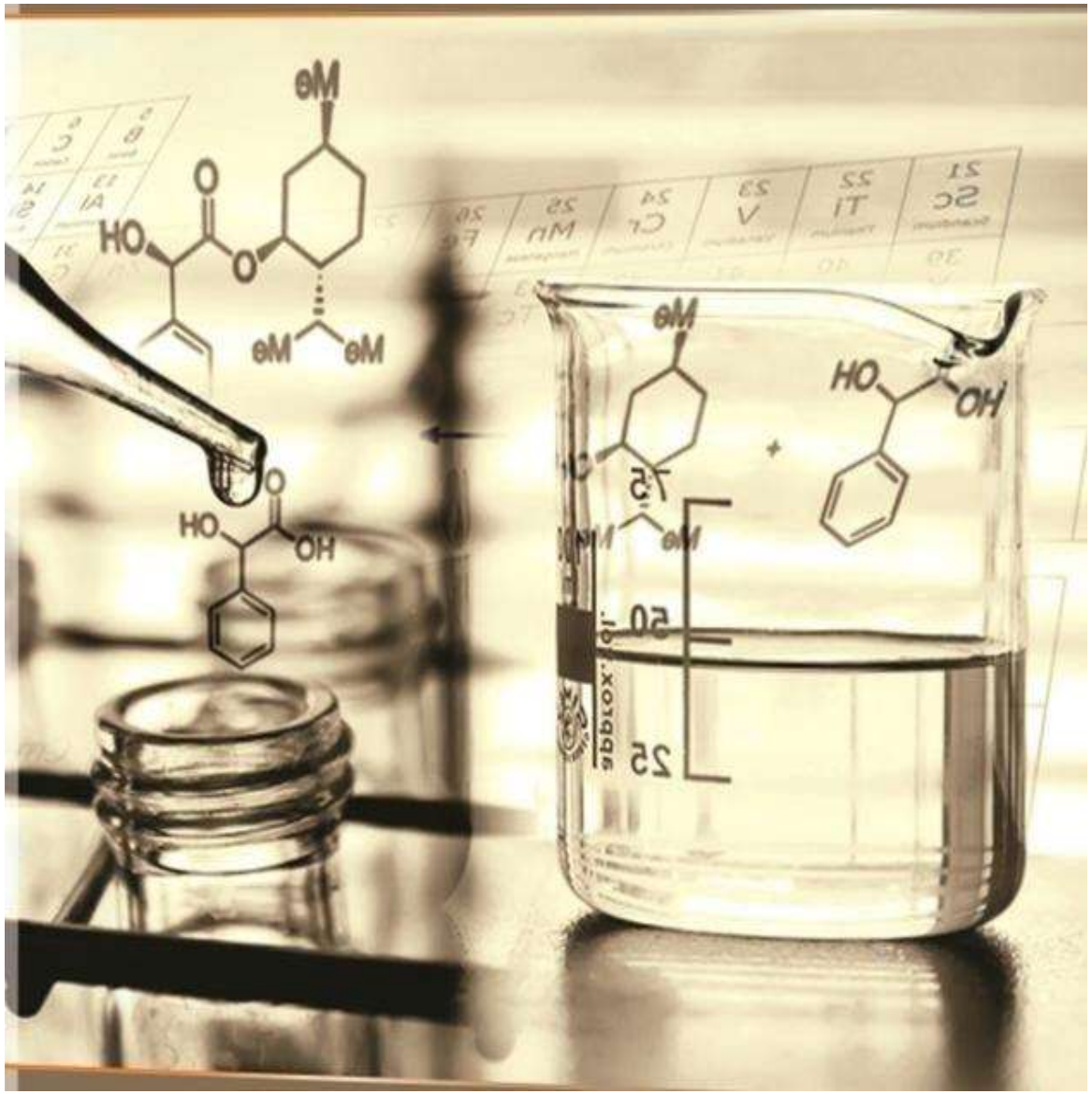
- Structure Activity Relationships
- (SAR)
- Once the structure of lead compound is known, the
- medicinal chemist moves on to study its SAR.
- The aim is to discover which parts of the molecule are
- important to biological activity and which are not.
- X-ray crystallography and NMR can be used to study and
- identify important binding interactions between drug and
- active site.
- SAR is synthesizing compounds, where one particular
- functional group of the molecule is removed or altered.
- in this way it is possible to find out which groups are
- essential and which are not for biological effect

Drug design strategies

- Structure Activity Relationships
- (SAR)
- This involves testing all analogues for biological activity
- and comparing them with the original compound.
- If an analogue shows a significant lower activity, then the
- group that has been modified must be important.
- If the activity remain similar, then the group is not
- essential.
- it may be possible to modify some lead compounds
- directly to the required analogues and other analogues
- may be prepared by total synthes

DRUG DESIGN strategy

- optimizing target interactions
- Once the lead compound has been discovered it can be
- used as the starting point for drug design.
- There are various aims in drug design:
- 1. The drug should have a good selectivity for its target
- 2. The drug should have a good level of activity for its
- target
- 3. The drug should have minimum side effects
- 4. The drug should be easily synthesized
- 5. The drug should be chemically stable
- 6. The drug should have acceptable pharmacokinetics
- properties
- 7. The drug should be non-toxic



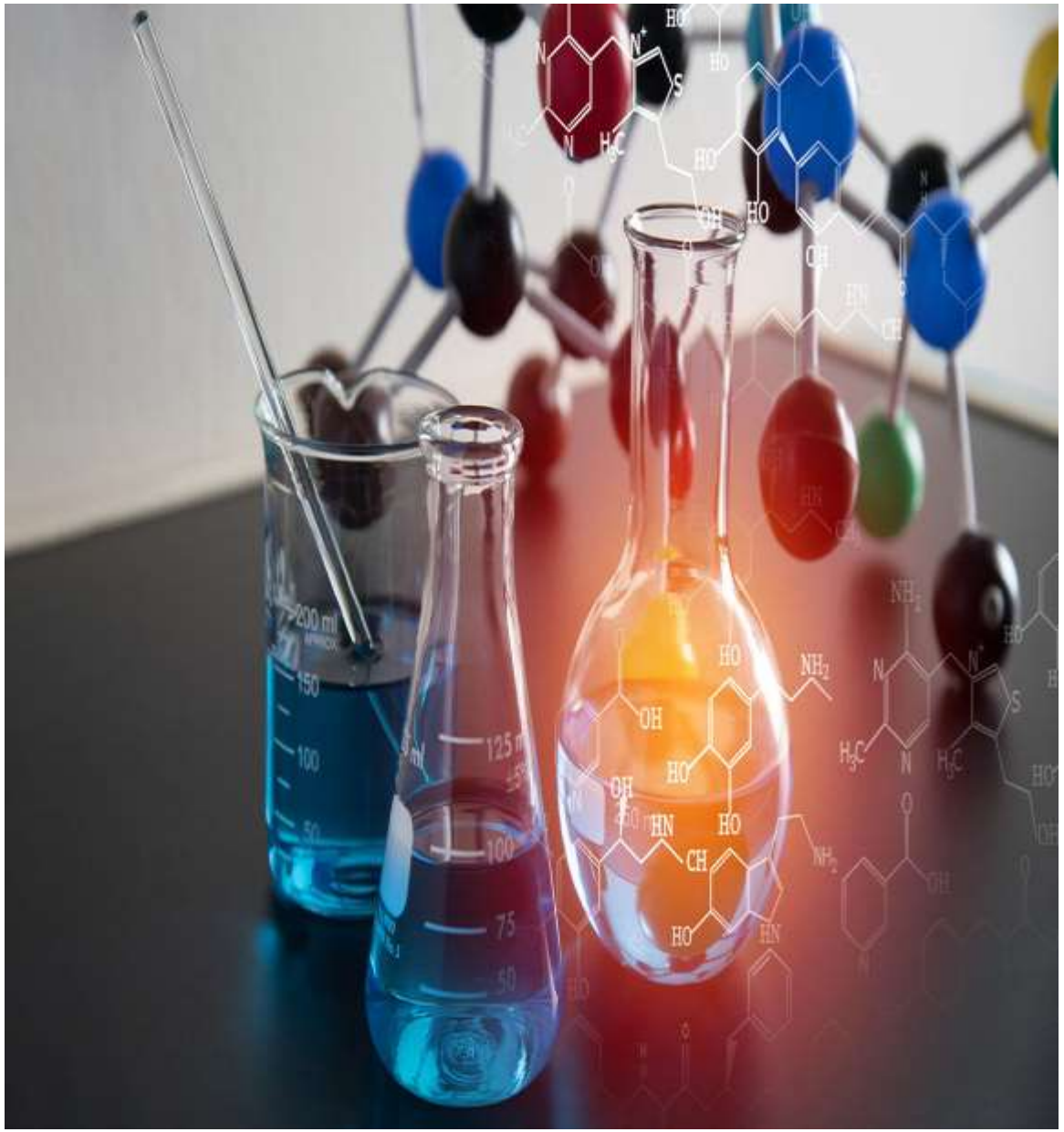
- Drug Optimization:
- Strategies in drug design
- I-optimizing drug target inetractions
- Drug optimization aims to maximize the interactions of a drug with
- its target binding site in order to improve activity, selectivity and
- to minimize side effects.
- designing a drug that can be synthesized efficiently and cheaply is another priority.
- The aim of drug optimization can be achieved by

different strategies or approaches on the lead

- compound SAR, such as;
- 1-variation of substituents (alkyl and aromatic substitution)
- 2- extension of structure (chain extension/contraction, ring
- expansion/contraction),

- 3-ring variation,
- 4-ring fusion,
- 5-isosteres and bioisosteres,
- 6-simplification of the structure,
- 7- rigidification of the structure.
- 8-Conformational blockers

- Drug Design:
- II-optimizing access to the target
- the compound with the best binding interaction is not
- necessarily the best drug to use in medicine.
- The drug needs to pass through many barriers to reach
- its target in the body.
- There are many ways to make the drug to reach its target
- such as linking the drug to polymers or antibodies or
- encapsulating it within a polymeric carrier.
- Thus, the aim is to design drugs that will be absorbed
- into the blood supply (absorption) and will reach their
- target efficiently (distribution) and be stable enough to
- survive the journey (metabolism) and will be eliminated
- in a reasonable period of time (elimination).
- in other words, designing a drug with optimum
- pharmacokinetics can be achieved by different



Example

Cimetidine

Ranitidine

Famotidine

Conclusion .

- Patients receive optimal pharmaceutical therapy
- Enables consistent and predictable treatment from all levels of providers and at all locations
- Allows for improved availability of medicines because of consistent and known usage patterns
- Helps provide good outcomes because patients are receiving the best treatment regimen available
- Lowers cost

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