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A Project on Computer Aided Drug Designing For Targeted Drug Delivery System

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DECLARATION
We declare that project entitled "**Computer aided drug designing for targeted drugdelivery System**" is Benefited work carried out by us, under the guidance of ASST.PROF.ROKADE V.G.We further declare that this project report has not previously formed the basis of any degree associate ship or other similar degree's.

MISS. RATHOD KAVITA ANNASAHEB

ABSTRACT
Discovery and development of a new drug is generally known as a very complex process which takes a lot of time and resources. So now a day's computer aided drug design approaches are used very widely to increase the efficiency of the drug discovery and development course. Various approaches of CADD are evaluated as promising techniques according to their need, in between all these structure-based drug design and ligand-based drug design approaches are known as very efficient and powerful techniques in drug discovery and development. These both methods can be applied with molecular docking to virtual screening for lead identification and optimization. In the recent times computational tools are widely used in pharmaceutical industries and research areas to improve effectiveness and efficacy of drug discovery and development pipeline. In this article we give an overview of computational approaches, which is inventive process of finding novel leads and aid in the process of drug discovery and development research.

Keywords:
Computer aided drug discovery, structure-based drug design, ligand-based drug design, virtual screening and molecular docking.

I. INTRODUCTION

People in every civilization have used drugs of plant or animal origin to prevent and treat disease. The quest for substances to combat sickness and to alter mood and consciousness is nearly as basic as the search for food and shelter. Many drugs obtained from natural sources are highly valued, but most drugs used in modern medicine are the products of advances in synthetic organic chemistry and biotechnology. Thus a drug can be defined as a substance of either natural or synthetic origin that is used in the diagnosis, cure, relief, treatment, or prevention of disease or intended to affect the structure or function of the body. Thus a drug is a chemical that affects the body and its processes.

A Little History of Computer-Aided Drug Design:
1960s Review the target-drug interaction
1980s Automation: High-throughput target/drug selection
1980s Databases (information technology): Combinatorial libraries
1980s Fast computers: Docking

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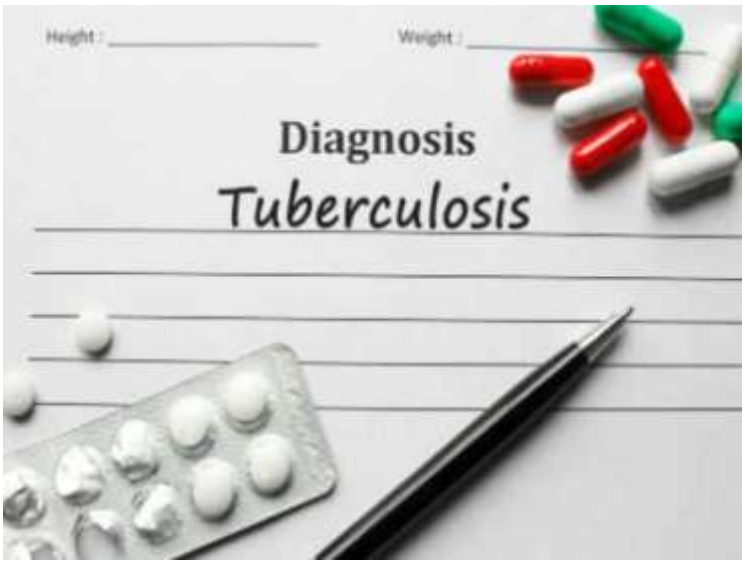
1990s Fast computers: Genome assembly, genomic-based target selection
2000s Vast information handling: Pharmacogenomics

Drug: A chemical substance that affects the processes of the mind or body which is used in-
1)DIAGNOSIS:Medications for **Diagnosis** and Investigation refers to something that is used to determine the cause of an illness or disorder



2) MEDICATION:your medical questions on **prescription drugs**, vitamins and Over the Counter medications. Find medical information, terminology and advice including

3) TREATMENT:Drug treatment can include behavioral **therapy** (such as cognitive-behavioral **therapy** or contingency management), **medications**, or their combination. The specific type of **treatment** or combination of **treatments** will vary depending on the patient's individual needs and, often, on the types of **drugs** they use

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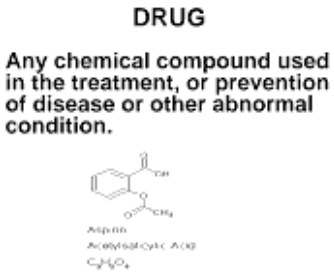
4) PREVANTION OF DISEASE OR OTHER ABNORMAL CONDITION:

"**Cancer**" is the term given to a large group of diseases that vary in type and location but have one thing in common: abnormal cells growing out of control.



Drug design: Drug design, is the inventive process of finding new medications based on the knowledge of a biological target. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the molecular target with which they interact and bind. The drug is most commonly an organic small molecules that activates or inhibits the function of a biomolecules such as a protienswhich in turn results in a therapeutic benefit to the patients.

Designed molecule should be:

- **Organic small molecule:** A small molecule (or metabolite) is a low molecular weight organic compound, typically involved in a biological process as a substrate or product.
- **Complementary in shape to the target:** In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bio-molecular target with which they interact and therefore will bind to it. A more accurate term is ligand design (i.e., design of a molecule that will bind tightly to its target).

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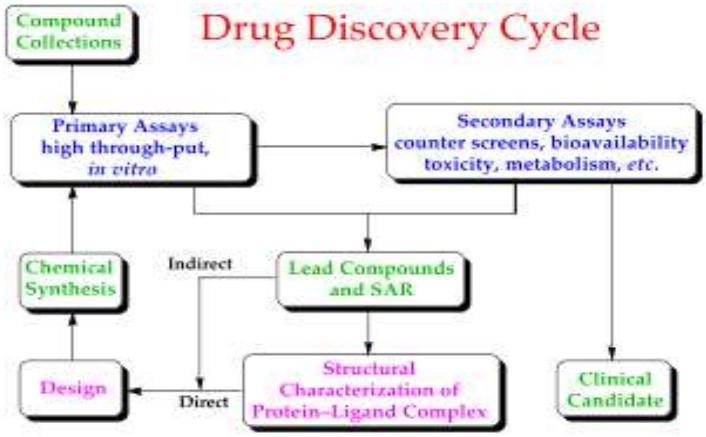

• **Oppositely charge to the bimolecular target**:Drug design is an splendid inventive process of new medication on the basis of biological target. It is also known as rational drug design or rational design. That is the invention in medical history in order to yield significant therapeutic response. The drug is an organic molecule, when it is bind to target site it can either inhibit or activate the function of a biomolecule which results in therapeutic benefit. The drug design involves the design of such molecules that are similar to the bio molecular target site in shape and charge in order to bind to it. Drug design relies on the knowledge of the three dimensional structure of bimolecular targets.

Types of drug design:

1) **Ligand Based Drug Design:**In LBDD, 3D structure of the target protein is not known but the knowledge of ligands which binds to the desired target site is known. These ligands can be used to develop a pharmacophore model or molecule which possesses all necessary structural features for bind to a target active site.

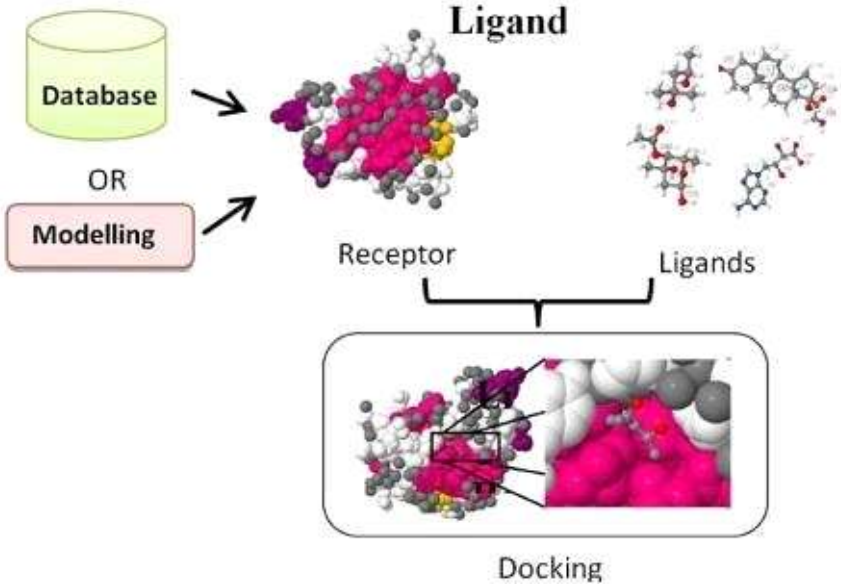

Fig: Outline of process involved in LBDD

Generally ligand-based techniques are pharmacophore based approach and quantitative-structure activity relationships (QSARs). In LBDD it is assumed that compounds which having similarity in their structure also having the same biological action and interaction with the target protein.

2) **Structure-based drug design:** In SBDD, structure of the target protein is known and interaction or bio-affinity for all tested compounds calculate after the process of docking; to design a

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new drug molecule, which shows better interaction with target protein.

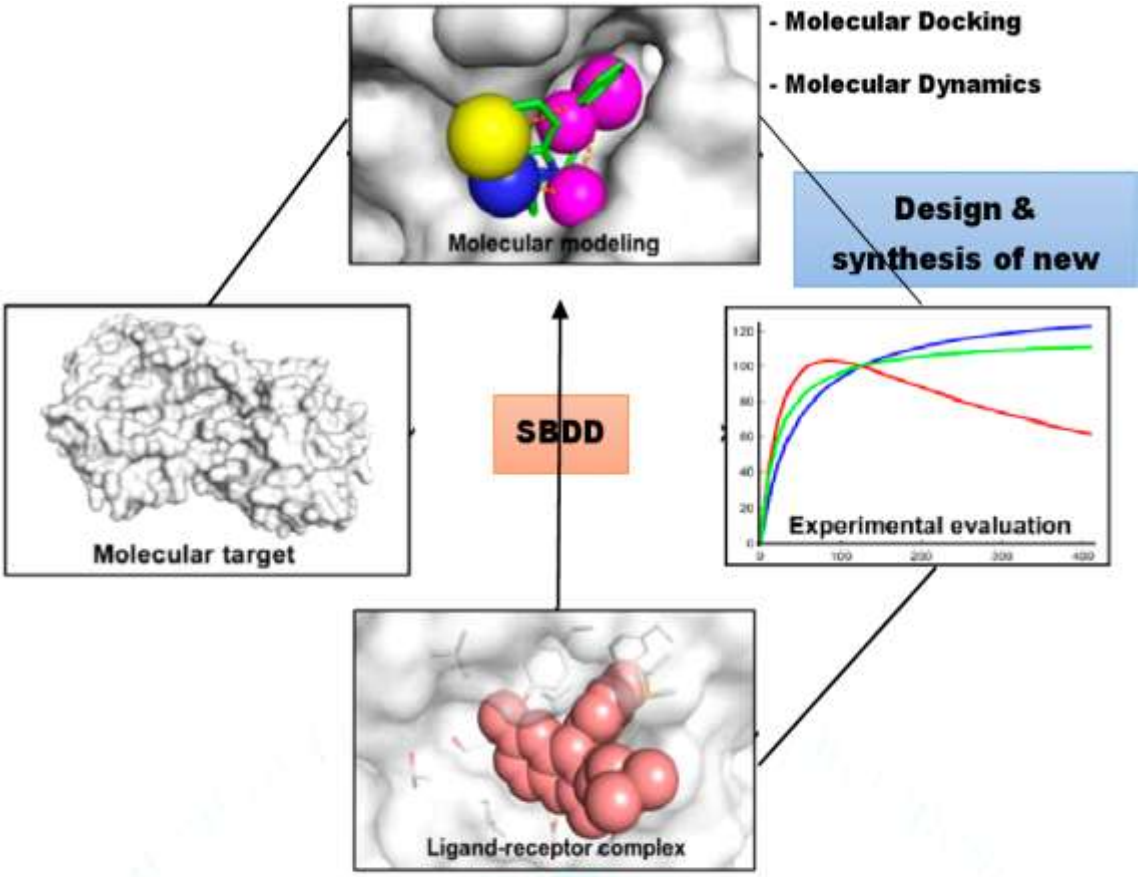

Figure 4: Layout of SBDD [5].

Overview of the process involved in SBDD:SBDD runs through multiple cycles before the optimized lead reached into clinical trials. The first cycle comprises isolation, purification and structure determination of the target protein by one of three key methods: like X-ray crystallography, homology modeling or NMR. Using compounds comes through virtual screening of different databases are placed into a selected region (active site) of the protein. These compounds are scored and ranked on the bases of steric, hydrophobic, electrostatic interaction of these molecules with the active site of target protein. Top ranked compounds are tested with biochemical assays. Second cycle comprises structure determination of the protein in complex with the most optimistic lead of the first cycle, the one with minimum micro-molar inhibition in-vitro, and shows sites of the compound which can be optimized for further increment in the potency. After several additional cycles like synthesis of lead, further optimization of lead through complex structure of protein with lead compound, the optimized compounds generally show marked increment in the target specificity and binding affinity

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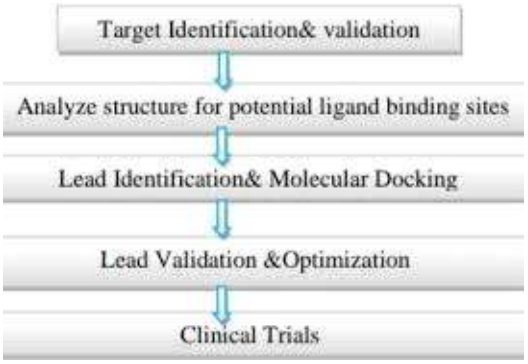

Fig:Steps involved in SBDD

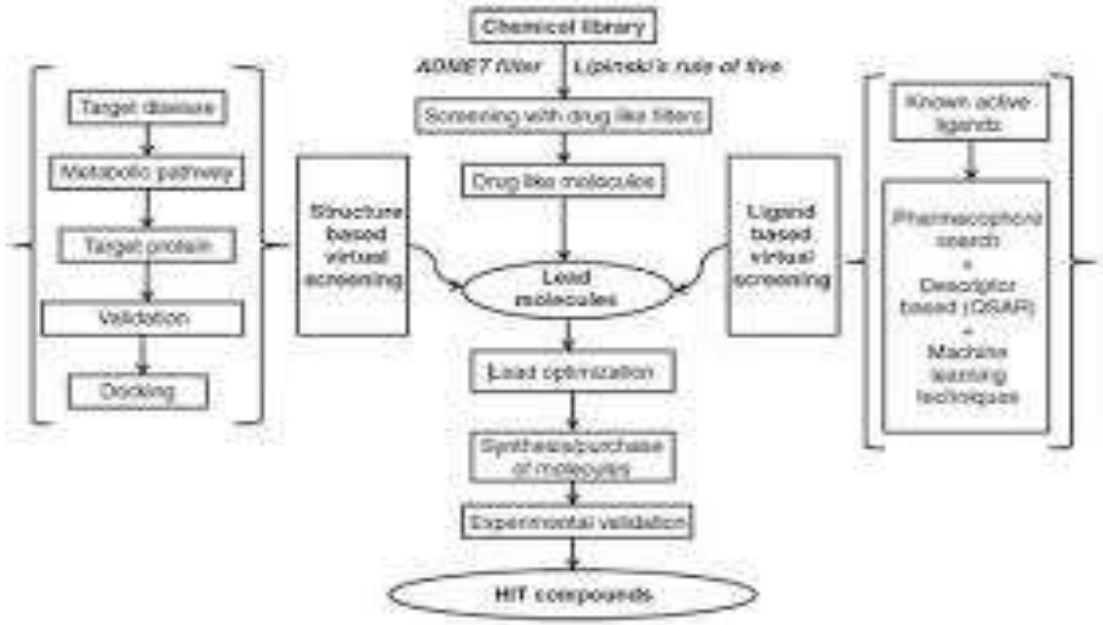

Fig:Schematic diagram of VS process for SBDD & LBDD

Modern drug design:

High Throughput Screening:

-Fast and automatic, Very expensive, High Success Rate.

-Diversity of chemical compounds: Combinatorial Chemistry.

PubChem Bioassay:

-231 M bio-actives (leads) and in-actives/1.22M AID depositions/>10636 drug targets and 4771 human drug targets 22M CID's and 35M SID's

Chem EMBL Bioassay: 14.67 Lakh bio-actives/Leads/1.3M AID -11538 drug targets, 67000 publications.

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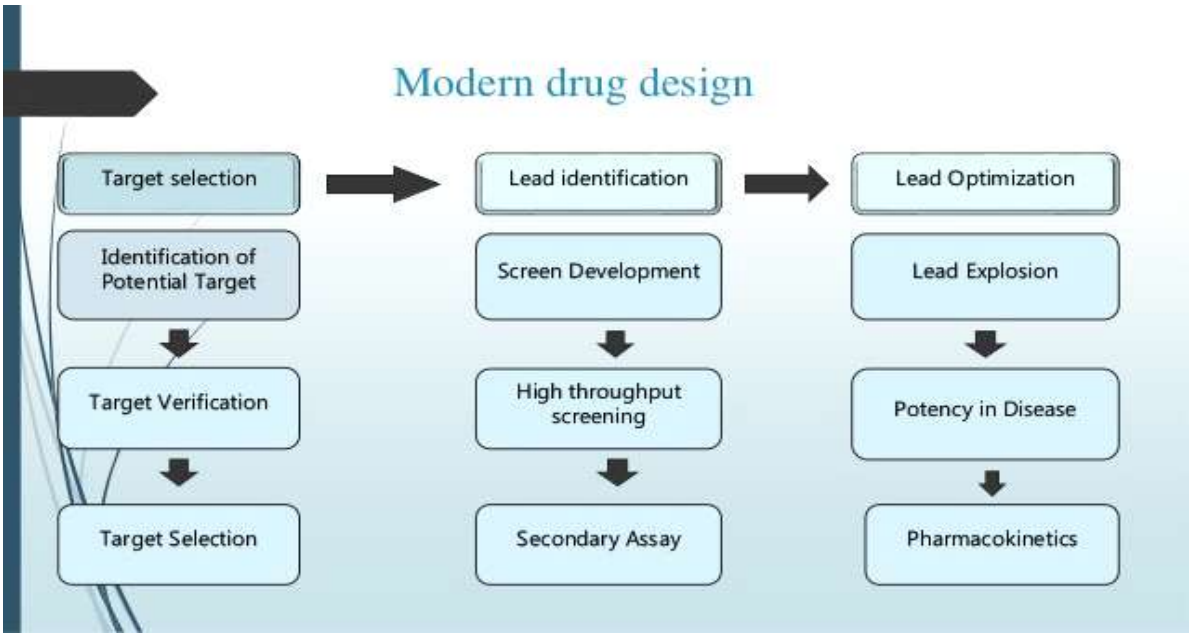

Fig: Modern drug design

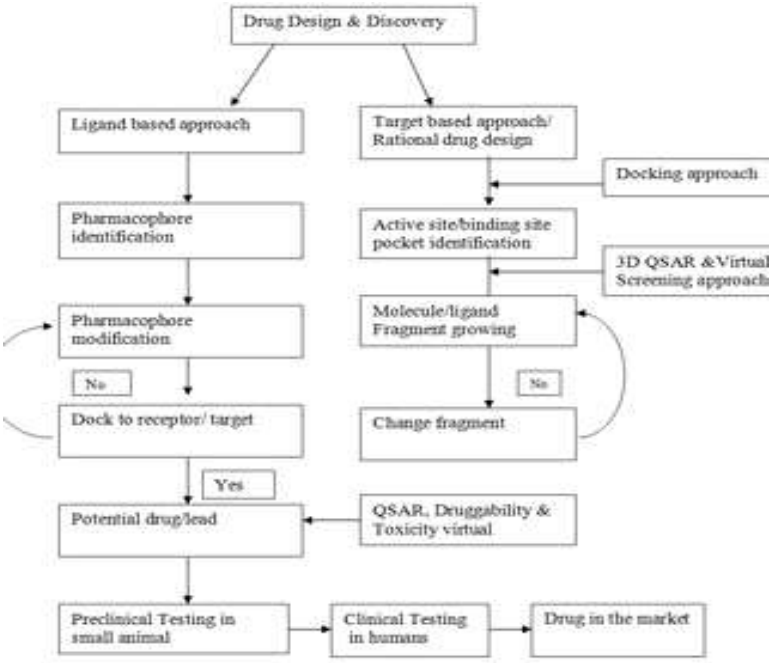

Fig: Modern drug design cycle

Introduction to CADD

Computational approaches in drug design, discovery and development process gaining very rapid exploration, implementation and admiration. Introducing a new drug in a market is a very complex, risky and costly process in terms of time, money and manpower. Generally it is found that drug discovery and development process takes around 10-14 years and more than 1 billion dollars capital in total.

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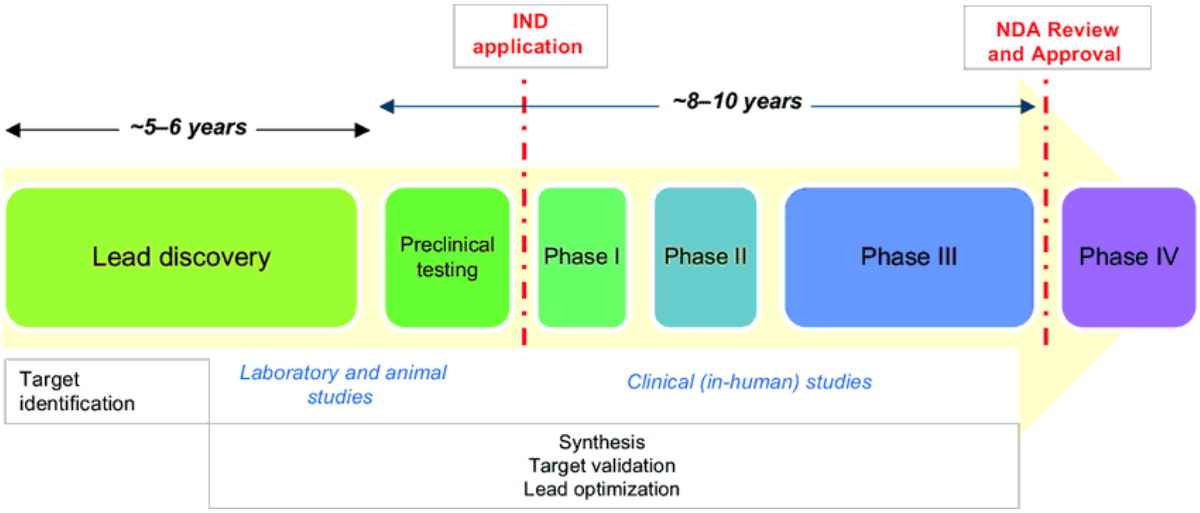

Fig: Traditional process of drug discovery and development.

So for reducing time, cost and risk borne factors computer aided drug design (CADD) method is widely used as a new drug design approach. It has been seen that by the use of CADD approaches we can reduced the cost of drug discovery and development up to 50%. CADD consist use of any software program based process for establishing a standard to relate activity to structure.

Drug design with the help of computers using:

- **Molecular docking:** Molecular docking is in-silico method which predicts the placement of small molecules or ligands within the active site of their target protein (receptor). It is mainly used to accurate estimation of most favorable binding modes and bio-affinities of ligands with their receptor, presently it has been broadly applied to virtual screening for the optimization of the lead compounds.

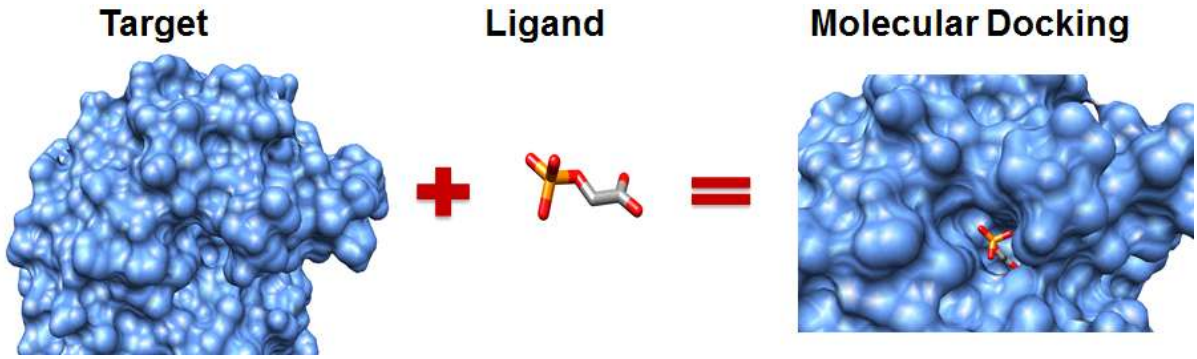

Fig:Process of Docking

Molecular docking methodology comprises mainly three goals which are interconnected to each other like: prediction of binding pose, bio affinity and virtual screening. In the molecular docking method the basis tools are search algorithm and scoring functions for creating and analyzing conformations of the ligand.

b) Virtual screening: Virtual screening has been worked as a most convenient tool now a day to find out the most favorable bioactive compounds with the help of information about the protein target or known active ligands. In the recent time virtual screening is known as a mind blowing alternative of high-throughput screening mainly in terms of cost effectiveness and probability of finding most appropriate novel hit through filter the large of libraries of compounds.

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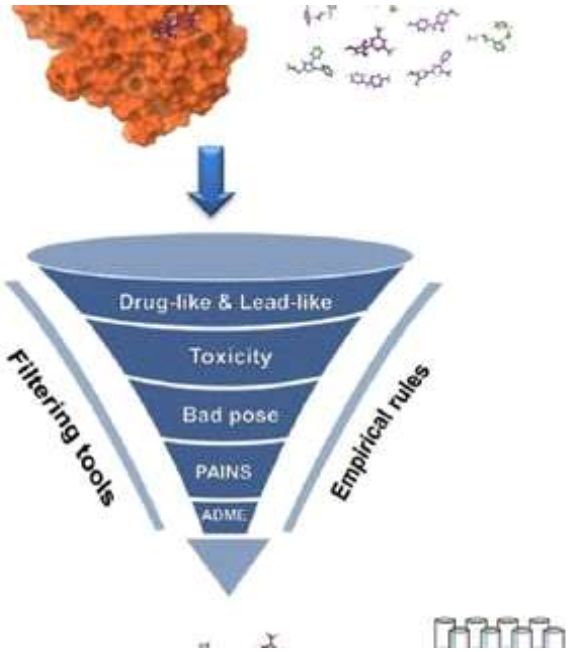

Fig:Overview of Virtual screening process

There are generally two types of virtual screening approaches like structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS), SBVS method rely on the structure of target protein active site and LBVS method is based on estimation of calculated similarity between the known active and compound come from databases.

c) QSAR: (Quantitative structure–activity relationship) - Models (**QSAR** models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable(Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable.

In QSAR modeling, the predictors consist of physic-chemical properties or theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. Second, QSAR models predict the activities of new chemicals

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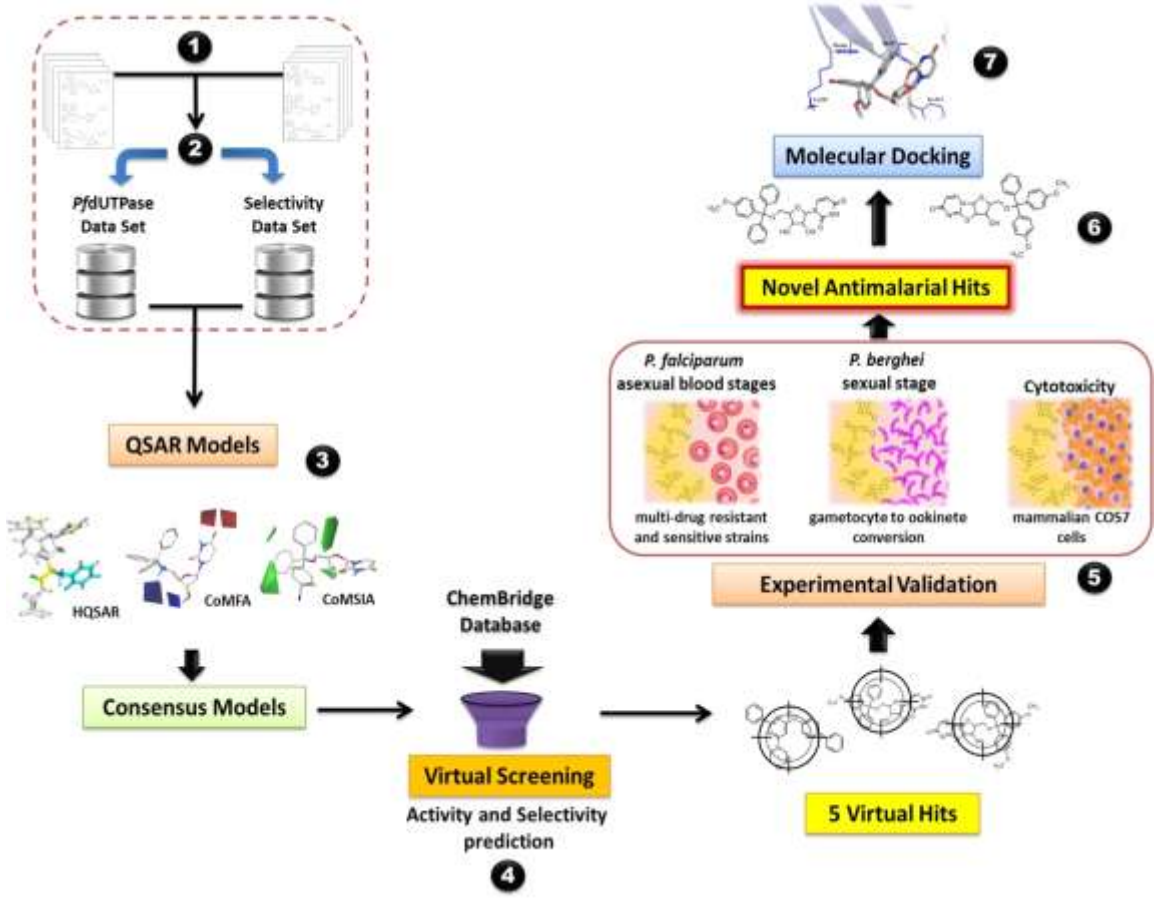

Fig: QSAR driven design

Objective of CADD:
To change from:
- Random screening against disease assays
- Natural products, synthetic chemicals

To:
- Rational drug design and testing
- Speed-up screening process
- Efficient screening
- De novo design
- Integration of testing into design process
- Fail drugs fast.

Steps involved in drug designing:

a)Target Identification:
- A target is a molecule (protein) which is present within an organism.
- The approaches of identifying targets include protein expression, protein biochemistry, structure function studies, study of biochemical pathways.

b) Target Validation:
- As there are a plethora of new potential therapeutics drug targets that are being discovered , selection and validation of novel molecular targets has become important.
- It needs to be confirmed that the targets identified will affect an appropriate biological response - Targeted gene disruption is a term that refers to several different methods of target validation.

c) Lead identification:
- A lead is a compound that demonstrates a desired biological activity on a validated molecular target.
- To be termed as a lead, the compound must exceed a specific potency threshold against the target.

d) Lead optimization:
- Once a lead compound is established in the identification process we need to optimize the desirable targets of the lead.
- To be considered for further development lead should be amenable for chemistry optimization.
- The compounds used as potential leads can be from many sources. The most important sources of leads is libraries of molecules.

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Important Techniques of Drug Design:

a)X-ray crystallography:

X-ray crystallography (XRC) is the experimental science determining the atomic and molecular structure of a crystal, in which the crystalline structure causes a beam of incident X-rays to diffract into many specific directios.

-X-ray crystallography is often the starting point for gathering information from mechanistic drug design.

-This technology has the potential to determine total structural information about a molecule.

- Furthermore it provides the critically important coordinates needed for the handling of data by computer modeling system.

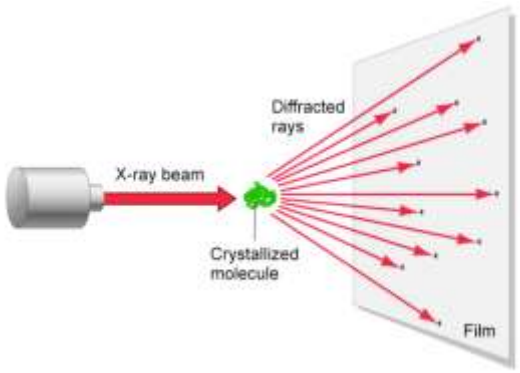

Fig. x-ray crystallography

b)NMR Spectroscopy:

NMR spectroscopy is a Spectroscopy technique used by chemists and biochemists to investigate the properties of organic molecules, although it is applicable to any kind of sample that contains nuclei possessing spin. For example, the NMR can quantitatively analyze mixtures containing known compounds.

-NMR uses much softer radiation which can examine molecules in the more mobile liquid phase, so the three dimensional information obtained may be more representative of the molecule in its biological environment.

-Another advantage of NMR is its ability to examine small molecule macromolecule complexes, such as an enzyme inhibitor in the active site of the enzyme.

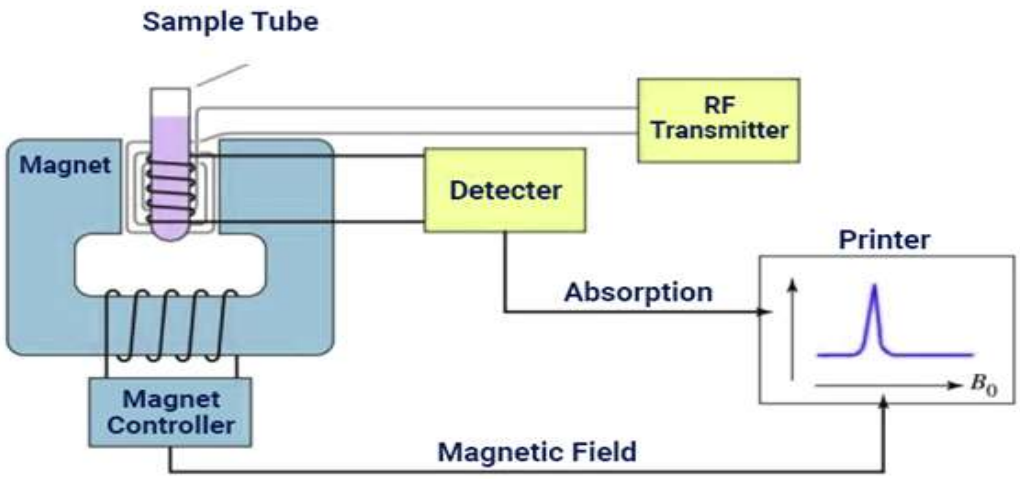

Fig:NMR spectroscopy

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Software for drug designing:

Categories of software:

- Databases & Draw Tools

Example: Zinc database, Chem draw

- Molecular Modeling & Homology

Example: CHARMM, Modeller

- Binding site prediction & Docking

Example: MED-Sumo, Auto-dock

- Ligand design Screening–QSAR

Example: c QSAR

- Binding free energy estimation

Example: Hyde, X-score

- ADME Toxicity

Example: Vol Surf, Gastro Plus

Advantages of CADD:

1. Time
2. Cost
3. Accuracy
4. Information about the disease
5. Screening is reduced
6. Database screening
7. Less manpower is required.

Success stories of CADD:

1 .Target structure analysis (possible binding site detection), candidate molecule generation, docking of generated molecules with target, give them rank according to bio affinities and optimization of molecules for further improvement.

2. CADD applied in the field of Research and development, target identification validation and preclinical study (Pharmacokinetic; ADMET prediction). By using technologies like the automation in which high throughput screening offers leads to drug discovery more fast in it millions of compound could be synthesized as soon as possible.

3. It takes approximately 7 - 12 years and $ 1.2 billion for new drug to the market and also approx. Five out of 40,000 reach to a stage of preclinical testing, finally 1 out of 5 reach to clinical trials.Success rates of molecules have been shown in **Fig.**

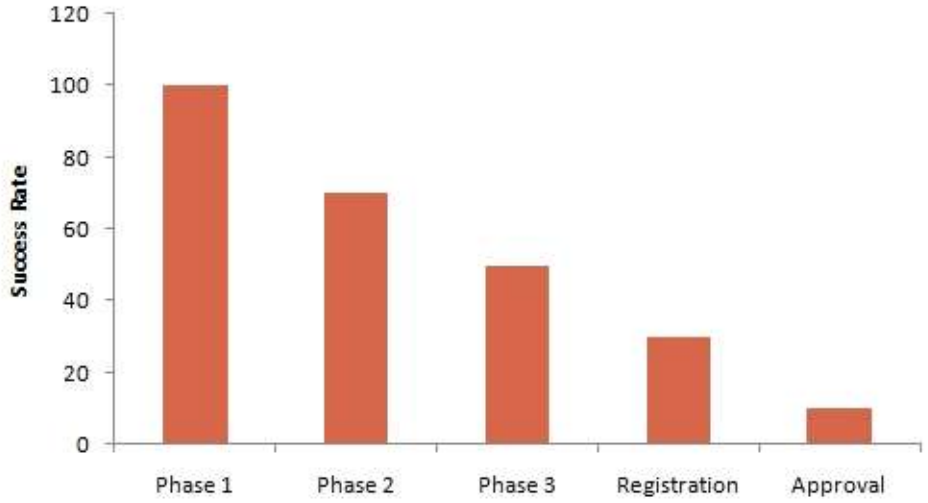

Fig .SUCCESS RATES OF CANDIDATE MOLECULES IN CLINICAL TRIALS

a. K+ ion channel blocker

Structural based discovery

Example: Sotalol is indicated for the treatment of atrial or ventricular tachyarrhythmia.

b. Ca2+ antagonist / T-channel blocker

Chemical descriptor based discovery

Example: Amlodipine is used to treat high blood pressure and coronary artery disease.

C .Thrombin inhibitor

Docking, de-novo design

Example: Hirudin has a blood anticoagulant property.

Targeted drug delivery System:

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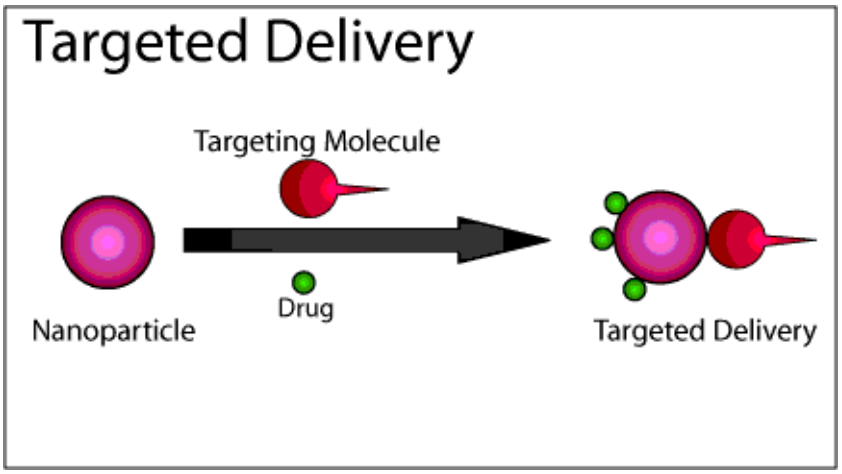

A) What do we understand by Drug Target?

a) Targeted drug delivery system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body; therefore avoiding any damage to the healthy tissue via the drug.

b) Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at preselected targets in therapeutic concentration, while restricting its access to non-target normal cellular linings, thus minimizing toxic effects and maximizing therapeutic index.

What is drug targeting:

The therapeutic response of a drug depends upon the interaction of drug molecules with cell on cell membrane related biological events at receptor sites in concentration dependent manner. Selective and effective localization of the pharmacologically-active moiety at preidentified target(s) in therapeutic concentration, while restricting its access to non-target(s) normal cellular linings, thus minimizing toxic effects and maximizing the therapeutic index. Target cell Normal Cell Normal Cell

Reasons for Drug Targeting Drug instability Low absorption Short half-life Large volume of distribution Low specificity Low therapeutic index

Common Approaches of Targeted Drug Delivery Controlling the distribution of drug by incorporating it in a carrier system Altering the structure of the drug at molecular level Controlling the input of the drug into bioenvironment to ensure a programmed and desirable bio-distribution

Properties of Ideal Targeted Drug Deliver Nontoxic, biocompatible and physicochemical stable in vivo and invitro.Restrict drug distribution to target cells or tissue or organ or should have uniform capillary distribution. Controllable and predictable rate of drug release.Minimal drug leakage during transit. Carrier used must be biodegradable or readily eliminated from the body without any problem. Its preparation should be easy or reasonably simple, reproductive and cost effective.

Important Properties Influencing Drug Targeting Drug Concentration, Particulate location and Distribution Molecular Weight, Physiochemical properties Drug Carrier Interaction Carrier Type, Amount of Excipients, Surface Characteristics, size, Density In Vivo Environment PH, Polarity, Ionic Strength, Surface Tension, Viscosity, Temperature, Enzyme, Electric Field

Drug Targeting strategies Passive Targeting Inverse Targeting Active Targeting Ligand- mediated TargetingPhysical Targeting Dual Targeting Double Targeting Combination Targeting

Passive Targeting:

It utilizes the natural course of biodistribution of the carrier.

The colloids which are taken up by the reticulo-endothelial system (RES) can be ideal vectors for passive targeting of drugs to RES predominant compartments.

Passive capture of colloidal carriers by macrophages offers therapeutic opportunities for the delivery of anti-infective agents.

Inverse Targeting:

It is a result of the avoidance of passive uptake of colloidal carriers by the RES. It can be

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achieved by suppressing the function of RES by pre- junction of a large amount of blank colloidal carriers or macromolecules like dextran sulphate.
Other strategies include modification and defined manipulation of the size, surface charge, composition, surface rigidity & hydrophilicity characteristics of carriers for desirable biofate.

Active Targeting:

It involves the modification or functionalization of the drug carriers so that the contents are delivered exclusively to the site corresponding to which the carrier is architected. Active targeting can be affected at different levels –

1.First order targeting (organ compartmentalization)
2. Second order targeting (cellular targeting)
3. Third order targeting (intercellular organelles targeting)

Active Targeting First Order Targeting Second Order Targeting Third Order Targeting Restricted distribution of the drug carrier system to the capillary bed of a pre-determined target site, organ or tissue. The selective drug delivery to a specific cell type such as tumor cells (& not to the normal cells) Drug delivery specifically to the intracellular organelles of the target cells

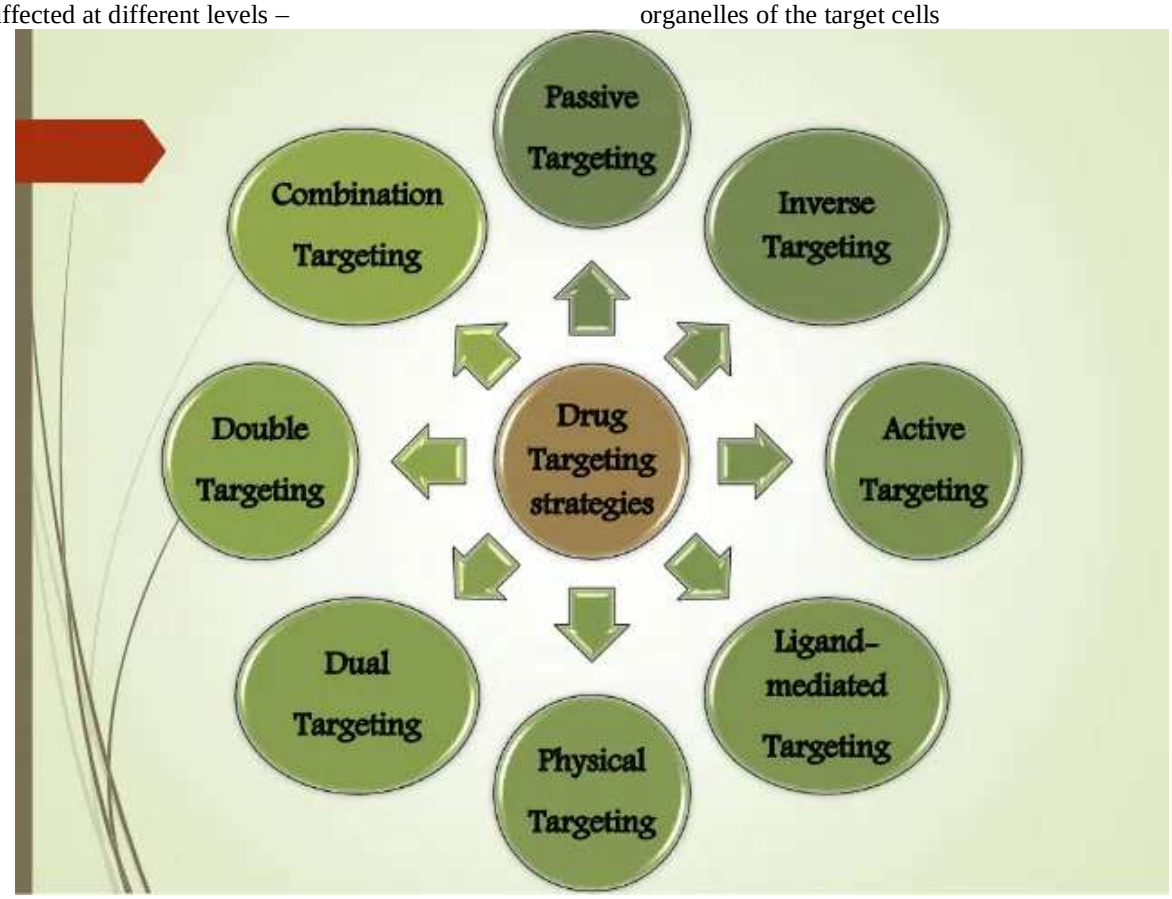

FIG.Drugtarget strategies

Strategies for Drug Targeting:

Ligand-mediated Targeting: Ligands are carrier surface group(s), which can selectively direct the carrier to the pre-specified site(s) housing the appropriate receptor units to serve as 'homimg device' to the carrier/drug. Most of the carrier systems are colloidal in nature & can be specifically functionalized using various biologically-relevant molecular ligands including antibodies, polypeptides, oligosaccharides, viral proteins &fusogenicresidues.The ligands confer recognition & specificity upon drug carrier & endow them with an ability to approach the respective target selectivity & deliver the drug

Examples of Ligands Ligands Target: Tumor target Folate Folate receptor Overexpression of folate receptor Transferrin Transferrin receptor Overexpression of transferrin receptor GalactosamineGalactosamine receptors on hepatocytes Hepatoma

Physical Targeting Characteristics of environment changes like pH, temperature, light intensity,

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electric field, and ionic strength. This approach was found exceptional for tumor targeting as well as cytosolic delivery of entrapped drug or genetic material.

Physical Targeting Physical Targeting Formulation System Mechanism for Drug Delivery Heat Liposome Change in Permeability Magnetic Modulation Magnetically Responsive Microspheres Containing Iron oxide Magnetic Field can retard fluid Flow of particles. Ultrasound Polymers Change in Permeability Electrical Pulse Gels Change in Permeability Light Photo responsive Hydro gels Containing Azo- Derivatives Change in Diffusion Channels, Activated by Specific Wavelength

Dual Targeting: In this targeting approach, carrier molecule, itself have their own therapeutic activity and thus increase the therapeutic effect of drug.A carrier molecule having its own antiviral activity can be loaded with antiviral drug and for the synergistic effect of drug conjugate.

Double Targeting Spatial Control Temporal Control Double Targeting Targeting drugs to specific organs, tissues, cells or even sub cellular compartment Controlling the rate of drug delivery to target site

Combination Targeting: These targeting systems are equipped with carriers, polymers and homing devices of molecular specificity that could provide a direct approach to target site.

Components for Drug Targeting Target • Specific organ or a cell or group of cells, which in chronic or acute condition need treatment. Carrier • Special molecules or system essentially required for effective transportation of loaded drug up to the pre selected sites

Reasons for drug targeting:

Targeted drug delivery to solid tumors is a very active research area, focusing mainly on improved drug formulation and associated best delivery methods/devices. Drug-targeting has the potential to greatly improve drug-delivery efficacy, reduce side effects, and lower the treatment costs.

a) In the treatment or prevention or diseases.

Pharmaceutical Reason:

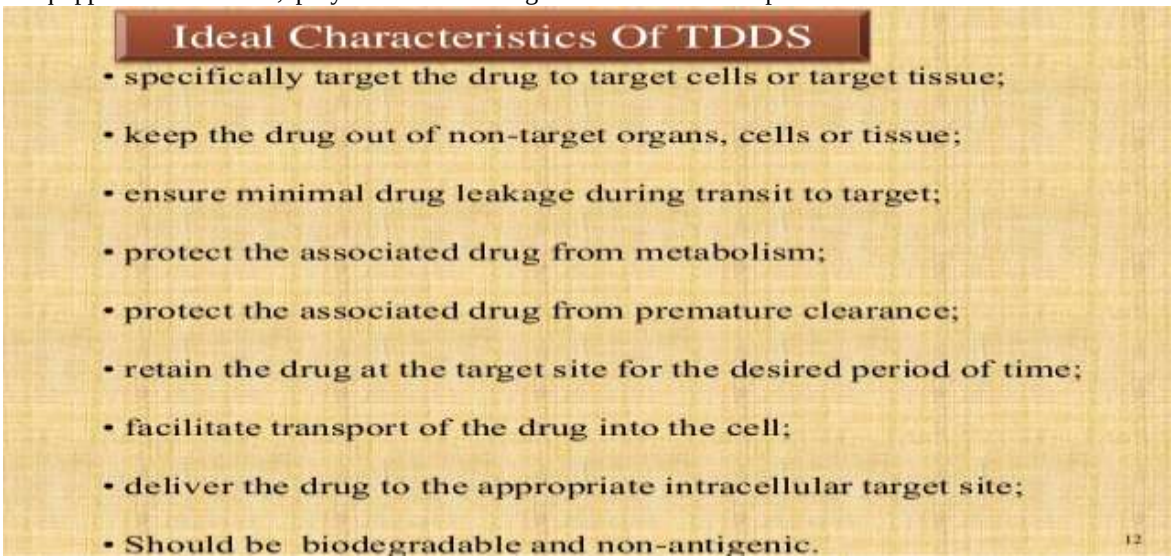
- Drug instability
- Low solubility

Pharmacokinetic Reason:

- Poor absorption.
- Short half life
- Large volume of distribution.

Pharmacodynamics Reason:

- Low specificity.
- Low therapeutic index.



Advantages:

- Drug administration protocols may be simplified.
-Toxicity is reduced by delivering a drug to its target site.
-Reduction of drug side effects
-Reduced frequency of drug intake
-Reduced dose of drug
-Uniform blood level of drug
-Maximize the therapeutic index
-Avoidance of hepatic first pass metabolism.
-No peak and valley plasma concentration.

Disadvantages:

-Rapid clearance of targeted systems.
-Immune reactions against intravenous administered carrier systems.

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-Insufficient localization of targeted systems into tumour cells.
-Diffusion and redistribution of released drugs.
-Requires highly sophisticated technology for the formulation.
-Requires skill for manufacturing storage, administration.
- Drug deposition at the target site may produce toxicity symptoms.
-Difficult to maintain stability of dosage form. E.g.: Resealed erythrocytes have to be stored at 40 C.
-Drug loading is usually law. E.g. As in micelles. Therefore it is difficult to predict /fix the dosage regimen.

Passive Targeting:

It utilizes the natural course of bio distribution of the carrier**.** The colloids which are taken up by the reticulo-endothelial system (RES) can be ideal vectors for passive targeting of drugs to RES predominant compartments.

Passive capture of colloidal carriers by macrophages offers therapeutic opportunities for the

delivery of anti-infective agents.The literature divides targeted nanoparticle delivery strategies into two major categories: (1) passive and (2) active targeting.The goal of these targeting strategies is to deliver nanoparticles and their therapeutic/diagnostic pay loads preferentially to diseased tissues while minimizing nanoparticle accumulation in healthy organs and cells.

Although we focus on passive targeting in this chapter, thefundamental mechanisms of nanoparticle accumulation within malignant tissues are similar for both strategies. In cancer nanomedicine, both targeting strategies exploit atumor's pathophysiological characteristics for nanoparticle accumulation. In addition, researchers use empirically derived nanoparticle design rules with the intention to improve tumor delivery. In contrast to passive targeting nanoparticles, active targeting nanoparticles are engineered with specific nano particle surface ligands. These surface ligands are referred to as targeting ligands. Typical examples of targeting ligands are biomolecules, including nucleic acids, antibodies, and peptides. Such biomolecules can recognize and bind to specific cell surface receptors on cancerous cells with high affinity.Hence, active targeting approaches in nanomedicine are rationally designed strategies to exploit specific biomolecular interactions that may occur between nanoparticle surface ligands and cell surface re ceptors. In comparison with passive targeting, the under lying rationale for the use of active targeting istwo fold:

1) Improved retention of passively accumulated nanoparticles at diseased sites as a result of specific interaction between surface ligands and cell surface receptors, and (2) increased specific interaction of nanoparticles with targeted diseased cells while minimizing nontargetednanoparticleecell interactions.

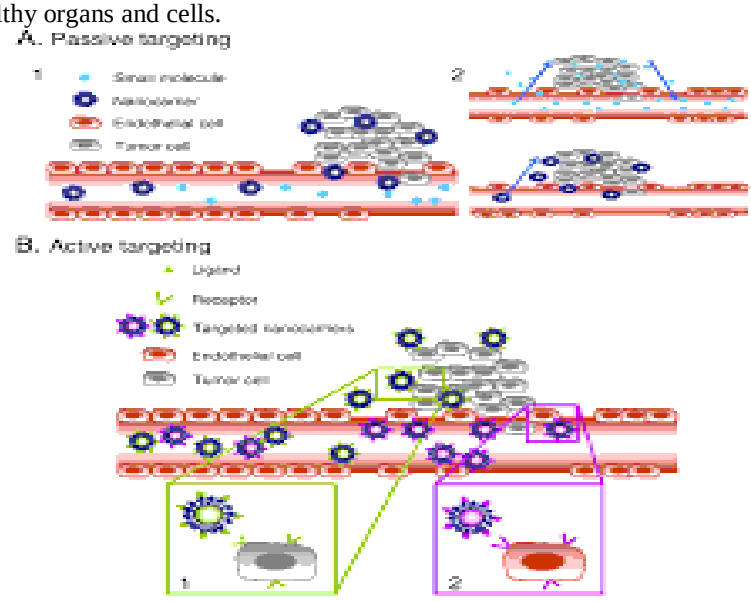

Fig.Passive targeting

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Few examples of passive targeting:

1. The colloids which are taken up by the reticulo-endothelial system (RES) can be ideal vector for passive targeting of drugs to RES predominant compartments.
2. In case of cancer treatment the drug carrier complex can be targeted to the tumor site by employing the Enhanced permeability retention (EPS) effect.
3. Passive targeting may also be directed to lymphoid organs, as these organs are finely structured and nanoparticles may easily penetrate into lymphatic vessels.

Active Targeting:

The concept of active drug targeting was suggested by Ringsdorf in the mid-1970s.

It involves coupling of targeting ligand to drug-loaded nanocarrier system that binds to specific overexpressed receptors on target cell. The targeting ligands can be polysaccharide, antibodies and their fragments, hormones, proteins, lipoproteins, and low-molecular weight molecule, such as folate and vitamin. These tar geting ligands bind to the cell surface receptors followed by their internalization into the cells. Unlike passive targeting which demonstrate relative tumor selectivity as a consequence of EPR effect, active targeting results in higher intratumoral accumulation of nanocarrier and hence higher cellular concentration of the drug

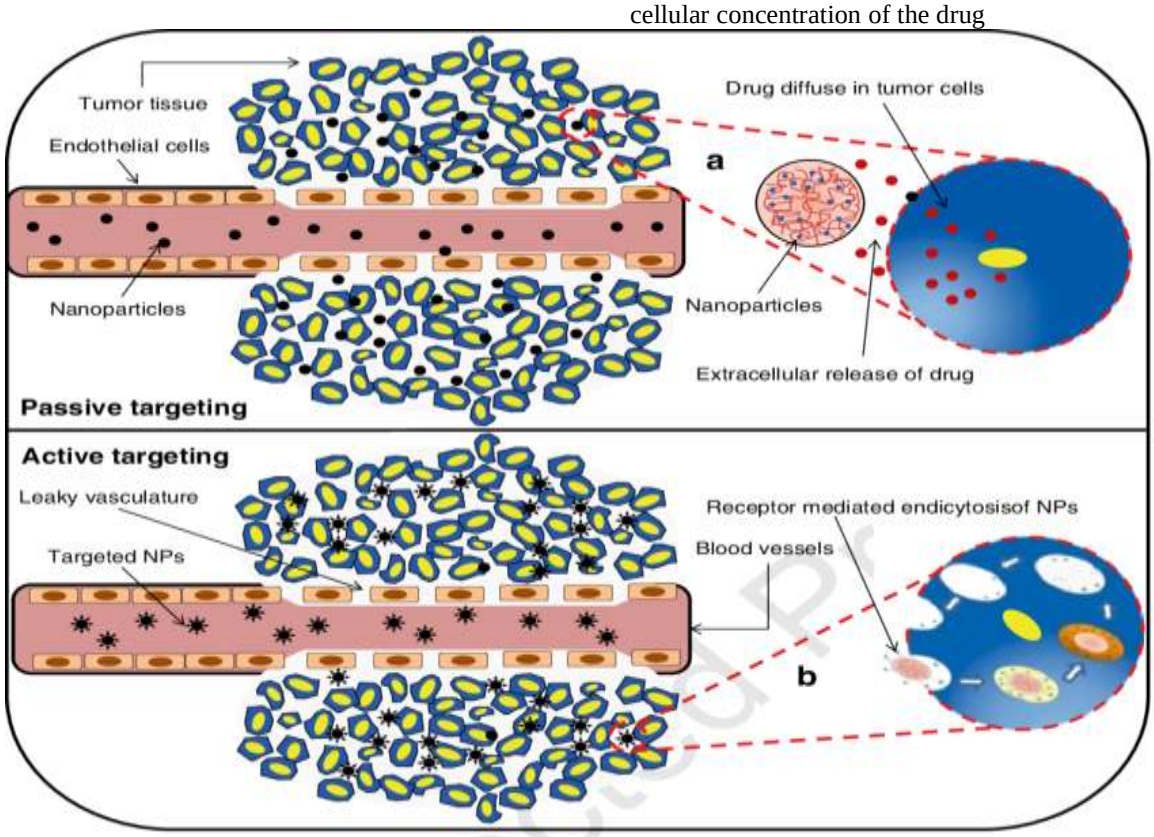

Fig: Active Targeting

It involves the modification or functionalization of the drug carriers so that the contents are delivered exclusively to the site corresponding to which the carrier is architected.

Active targeting can be affected at different levels:

-Third order targeting (intercellular organelles targeting)
-Second order targeting (cellular targeting)
-First order targeting (organ compartmentalization)

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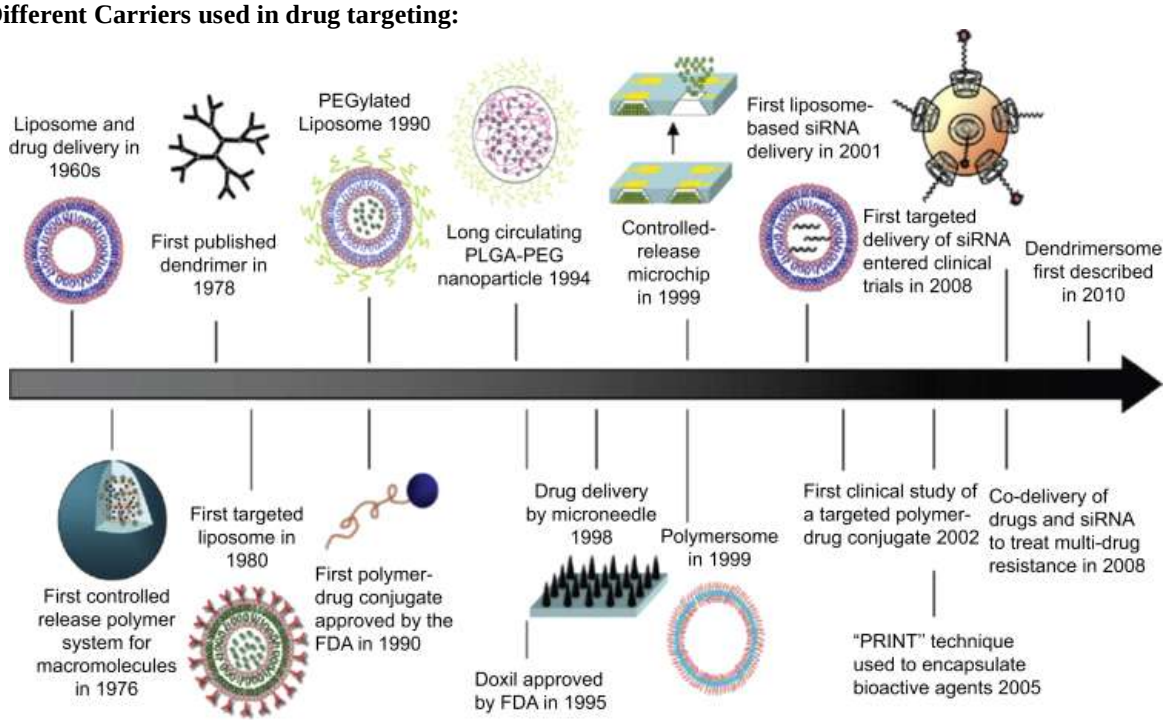
Fig: Active targeting can be affected at different levels

Different Carriers used in drug targeting:



II. CONCLUISION

In the early 1990s, there was a great deal of optimism that CADD would revolutionize the way in which drugs are developed. The enduring exponential increase in computing power progressed to such a point that rudimentary estimations of ligand-receptor complementarities could be performed. Through computer graphics technology,scientists acquired the ability to generate vector models of chemical structures and manipulate them in real time. By using computers, computational chemists believed that they could circumvent much of the time and effort required for drug synthesis and testing simply by generating novel compounds with the help of computers. The con cept of generating virtual lead compounds entirely through the com puter simulation was termed de novo design.The world's largest

pharmaceutical firms spent millions of dol lars on hardware and software to turn de novo design into a reality.Unfortunately, success is rare, and except for few cases, de novo design proved to be an utter failure. De novo design could not prove itself to be an effective method to discover lead compounds. The main rea sons behind are limitations in computing power and a lack of useful software functions. In scientific computing accuracy and processing time are very important. Thus, to make calculations run in a finite period of time, assumptions, algorithms, approximations, and other shortcuts are necessary. This greatly diminished the calculated accu racy of any ligand receptor interactions. Even though chemists postulated numerous chemical structures that potentially could complement the active site based on computer simulations, the calculated binding had no correlation with reality.This remains the most significant challenge in de novo design.Although computers have become exponentially faster, the sheer number of calculations needed to accurately predict the binding of a de novo–generated ligand to its receptor in a useful time frame still requires significant approximations. In de novo design, attempts are being made to generate whole ligands from scratch and dock them within their receptors. However, the problem remains how the pre dicted structure behaves in real life.The second significant problem in computer-aided denovo design is the generation of undesired chemical structures that are of no use.

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