Unit 2
Introduction on active transporters

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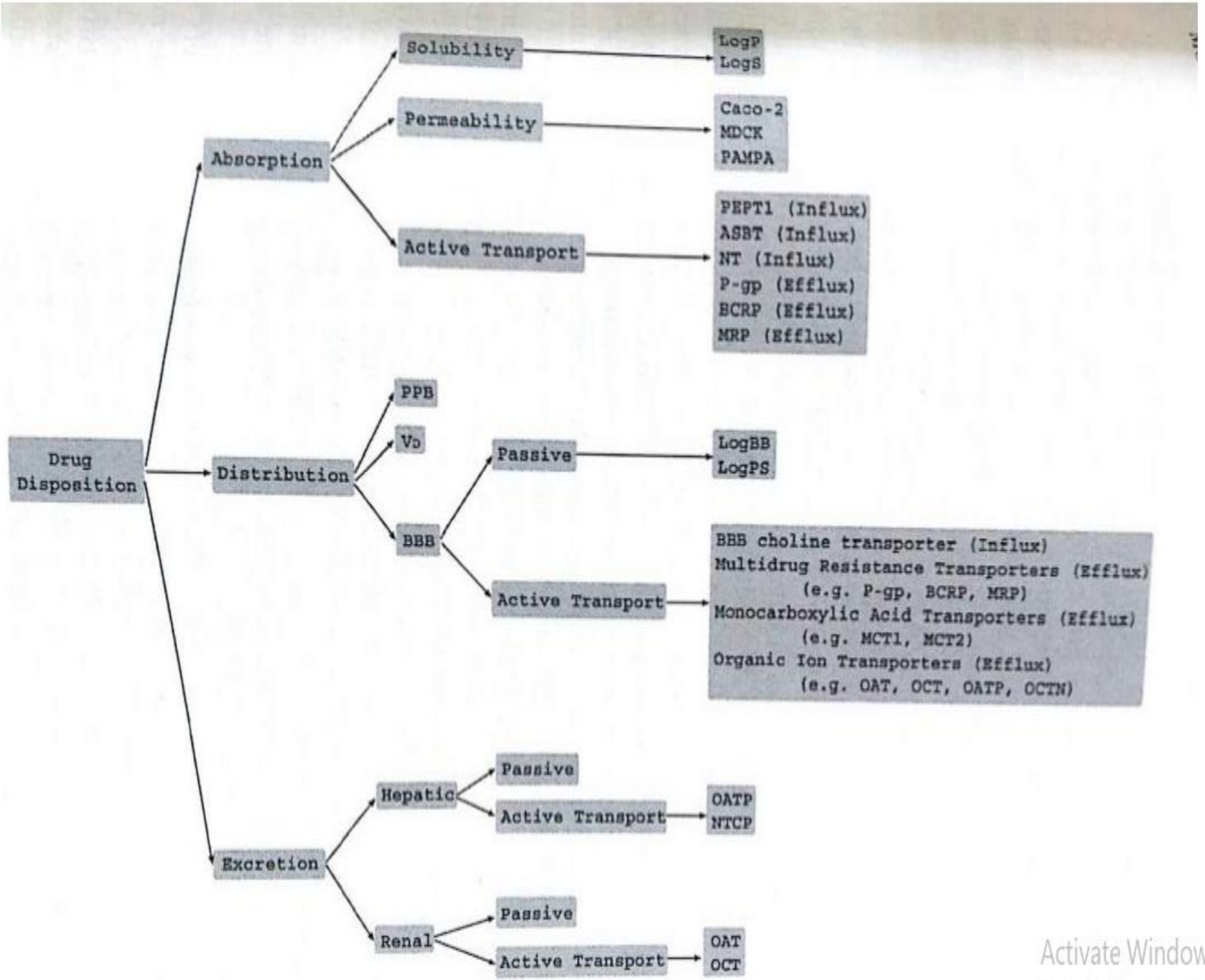
Introduction

- Historically, drug discovery has focused almost exclusively on **efficacy and selectivity against the biological target.**
- As a result, nearly half of **drug candidates fail at phase II and phase III clinical trials** because of the undesirable drug pharmacokinetics properties, including absorption, distribution, metabolism, excretion and toxicity (ADMET).
- The pressure to control the escalating cost of new drug development has changed the paradigm since the mod-1990s.
- **To reduce the attrition rate** at more expensive later stages, in vitro evaluation of ADMET properties in the early phase of drug discovery has widely adopted.

- Many high-throughput *in vitro* ADMET property screening assays have been developed and applied successfully.
- Fueled by the ever-increasing computational power and significant **advances of *in silico* modeling algorithms, numerous computational programs** that aim at modeling ADMET properties have emerged.
- A comprehensive list of available commercial ADMET modeling software has been provided till date.

Modeling technique: 2 Approaches

- The **quantitative approaches** represented by pharmacophore modeling and flexible docking studies investigate the structural requirements for the interaction between drugs and the targets that are involved in ADMET processes.
- These are especially useful when there is an accumulation of knowledge against certain target. For example, a set of drugs known to be transported by a transporter would enable a pharmacophore study to elucidate the minimum required structural features for transport.
- Three widely used automated pharmacophore perception tools are DISCO (DIStance COmparisons), GASP (Genetic Algorithm Similarity Program) and Catalyst/HIPHOP.
- The **qualitative approaches** represented by quantitative structure-activity relationship (QSAR) and quantitative structure-property relationship (QSPR) studies utilize multivariate analysis to correlate molecular descriptors with ADMET-related properties.
- A diverse range of molecular descriptors can be calculated based on the drug structure. Some of these descriptors can be calculated based on drug structure.
- It is essential to select the right mathematical tool for most effective ADMET modeling. Sometimes it is necessary to apply multiple statistical methods and compare the results to identify the best approach.



Drug Absorption

- Because of its convenience and good patient compliance, oral administration is the most preferred drug delivery form.
- As a result, much of the attention of *in silico* approaches is focused on modeling drug oral absorption, which mainly occurs in the human intestine.
- In general, **drug bioavailability and absorption is the result of the interplay between drug solubility and intestinal permeability.**

a) Solubility

- A drug generally must dissolve before it can be absorbed from the intestinal lumen.
- By measuring a drug's **logP value** (log of partition coefficient of compound between water and *n*-octanol) and its melting point, one could indirectly estimate solubility using "general solubility equation".
- To predict the solubility of compound even before synthesizing it, *in silico* modeling can be implemented.
- There are mainly two approaches to model solubility. One is based on the underlying physiological processes, and the other is an empirical approach. The dissolution process involves the breaking up of solute from its crystal lattice and the association of the solute with solvent molecules.
- Empirical approaches, represented by QSPR, utilize multivariate analysis to identify correlations between molecular descriptors and solubility.

b) Intestinal Permeation

- Intestinal permeation describes the ability of drugs to cross the intestinal mucosa separating the gut lumen from the portal circulation.
- It is an essential process for drugs to pass the intestinal membrane before entering the systemic circulation to reach their target site of action.
- The process involves both passive diffusion and active transport.
- It is a complex process that is difficult to predict solely based on molecular mechanism.
- As a result, most current models aim to simulate in vitro membrane permeation of Caco-2, MDCK or PAMPA, which have been a useful indicator of in vivo drug absorption.

Drug Distribution

- Distribution is an important aspect of drug's pharmacokinetic profile.
- The structural and physiochemical properties of a drug determine the extent of distribution, which is mainly reflected by three parameters:

1. **volume of distribution (Vd),**
2. **plasma-protein binding (PPB)** and
3. **blood-brain barrier (BBB) permeability.**

Volume of Distribution (Vd)

- Vd is a measure of **relative partitioning of drug between plasma and tissue**, an important proportional constant that, when combined a drug is a major determinant of how often the drug should be administered.
- However, because of the **scarcity of *in vivo* data** and complexity of the underlying processes, computational models that are capable of prediction Vd based solely on computed descriptors are still under development.

Plasma Protein Binding (PBP)

- Drugs **binding to a variety of plasma proteins** such as serum albumin, as unbound drug primarily contributes to pharmacological efficacy.
- The effect of PPB is an important consideration when evaluating the effective (unbound) drug plasma concentration.
- The models proposed to predict PBB should not rely on the binding data of only one protein when predicting plasma protein binding because it is a **composite parameter reflecting interactions with multiple protein.**

Blood-Brain Barrier (BBB)

- The BBB maintains the restricted extracellular environment in the central nerve system.
- The evaluation of drug penetration through the BBB is an **integral part of drug discovery and development process.**
- Again, because of the few experimental data derived from inconsistent protocols, most BBB permeation prediction models are of limited practical use despite intensive efforts.
- Most approaches model log blood/brain (logBB), which is a measurement of the drug partitioning between blood and brain tissue.
- The measurement is an indirect implication of BBB permeability, which does not discriminate between free and plasma protein-bound solute.

Drug Excretion

- The excretion or clearance of a drug is quantified by **plasma clearance**, which is defined as plasma volume that has been cleared completely free of drug per unit of time.
- Together with **Vd**, it can assist in the calculation of drug half-life, thus determining the dosage regimen.
- **Hepatic and renal clearances** are the two main components of plasma clearance.
- No model has been reported that is capable of predicting plasma clearance solely from computed drug structures.
- Current modeling efforts are mainly focused on estimating **in vivo clearance** from in vitro data.
- Just like other pharmacokinetic aspects, the hepatic and renal clearance process is also complicated by presence of active transporters.

Active Transporters

- Transporters are an integral part of any ADMET modeling program because of their presence on barrier membranes and the substantial overlap between their substrates and many drugs.
- Unfortunately, because of our **limited understanding of transporters**, most prediction programs do not have a mechanism to incorporate the effect of active transport.
- However, interest in these transporters has resulted in a relatively large amount of *in vitro* data, which in turn have enabled the generation of pharmacophore and QSAR models for many of them.
- These models have assisted in the understanding of the complex effects of transporters on drug disposition, including absorption, distribution and excretion.