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505b2 Drug Repurposing: From AI Targets Prediction to Clinical Drug Formulation

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Abstract*—Advancements both in AI and database curation have dramatically improved drug discovery, facilitating more efficient identification of 505b2 drug's new indication which save time in drug discovery. The success of a 505b2 drug's application relies not only on early-stage drug repurposing prediction, but also the PK/PD simulation prior to clinical study, underscoring the importance of accurate predictive models. Several essential databases, like Protein Data Bank (PDB), OpenTarget, PubChem, SEA and ChemBL etc., have made 505b2 drug research easier with the use of fast AI drug-target interactions computation, streamlining the drug repurposing process. In drug dosage design, the oral formulation is still the most commonly needed due to its convenience in administration. Recently oral dosage simulation have shown that PBPK modeling may lead to better prediction of ADME. In addition, an alternative method using FDA-approved PK database and PAMPA dissolution also contributed to the improvement of repurposing oral formulation, providing complementary approaches for formulation optimization. Hence, a better prediction of repurposing drug from AI to clinical drug formulation could be conducted to enhance the success rate of oral formulation development.*

***Keywords*—** *Protein data bank, In vitro to in vivo correlation, Maximum plasma concentration, Parallel Artificial Membrane Permeability Assay, Administration Distribution Metabolism and Excretion, Reference Listed Drugs*.

I. INTRODUCTION

The drug-target interactions has become the crucial database that has enabled successful application of machine learning (ML) tools to accurately predict new target structures[1,2]. Public availability of scientific data makes drug research and development easier. The artificial intelligence (AI) will continue to benefit from open access to structural, biological, chemical, and biochemical data as new algorithms are applied to predicting small-molecule, ligand binding and protein-protein interactions[3]. In addition, there are many databases, such as OpenTarget, Uniprot, PubChem, ChEMBL, DrugBank, SEA and SwissTarget etc., that are available to integrate diverse information of molecular pathways, crystal structures, binding affinities, drug targets, disease relevance, chemical properties and biological activities. Example of SEA predicting of related proteins by means of Similarity Ensemble Approach[4] relates proteins based on the set-wise chemical similarity among their ligands. These databases can be used to rapidly search manifold compounds data and to build cross-target similarity maps much faster.

Artificial intelligence and machine deep learning[5,6] are a faster and more accurate method in defining disease cure. All of these efforts in 505b2 drug's new indications development would eventually lead to the dosage forms design, including injection and or oral formulation. Furthermore, the oral formulation is preferred due to its convenience in both carrying and administration. However, the complexity in oral drugs ADME (absorption, distribution, metabolism, and excretion) processes makes drugs formulation difficult to design. Currently, there are various ADME simulation methods available to help oral drugs formulation design[7,8]. The dissolution experiments were used to examine the performance of oral drug formulations. However, a number of issues existed, for example, the buffer solutions used in dissolution tests as required per the U.S Food and Drug Administration (FDA) guidance, which often falls short in mimicking conditions in the gastrointestinal (GI) tract, resulting in poor in vitro and in vivo correlation (IVIVC) data.

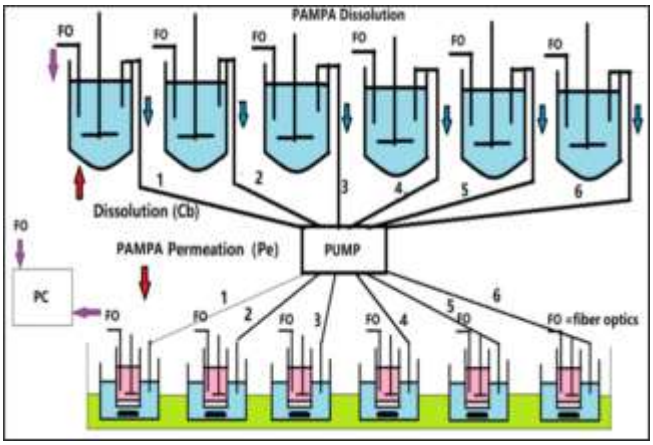

Fig. 1. PAMPA Dissolution apparatus

To improve IVIVC for oral drugs prediction[9,10], a Parallel Artificial Membrane Permeability Assay (PAMPA)[11] is therefore invented, which uses a chemically-based membrane instead of live cells but has been proven to be able to accurately mimic the human small intestine using biorelevant media[12,13,14]. A PAMPA Dissolution system shown in Figure 1 is an instrument that combines dissolution and permeation in a way that closely simulates in vivo conditions. It measures the two necessary parameters—dissolution and permeation—for

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finding oral drug's dissolution and permeation. These graphs enable the calculation of fraction dose absorbed via previously validated equation F (drug absorbed) = Cb*Pe*Area[15,16], which aid in predicting oral formulation.

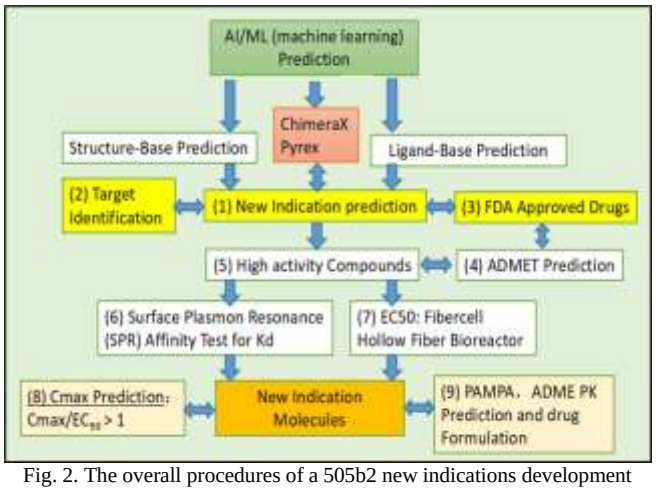

Fig. 2. The overall procedures of a 505b2 new indications development

A schematic diagram shown in Figure 2 has depicted the crucial steps of a 505b2 drug's new indication formulation development with AI molecular prediction. Details of each step is illustrated in the next section.

II. Materials and Methods

In order to perform AI prediction of 505b2 new indications, software and database are required, for example, PDB, PubChem, Uniprodt, Open Targets, SwissTarget, SwissADME, ChemBL, SEA, Pyex, and ChimeraX etc.

III. Results and Discussion

A. AI and 505b2 Drugs Prediction

（i）Target discovery and molecular docking

PDB is used to explore the spatial arrangements of amino acids, nucleotides, and other molecular components within proteins. By using visualization and analysis of these 3D structures, scientists understand the molecular mechanisms that drive these processes, including enzyme catalysis, protein folding, and molecular recognition. These knowledge help in developing new pharmaceuticals and the prediction of interactions between ligands and target proteins[17,18,19].

OpenTarget, PubChem, Uniprot, PDB, ChemBL, SEA, SwissTarget, SwissADME, Pyrx, and ChimeraX are tools used in computational biology and drug discovery, each contributing distinct functions to various aspects of the drug development process such as shown in Table 1 where sitagliptin phosphate new indications are predicted. Particularly, HMG-CoA reductase has been clinically studied (in blue) for hypercholesterolemia which proves model prediction of 505b2 drug's new indications in Table 1 is accurate.

OpenTarget is a platform that integrates genetic and genomic data with molecular pathways that enables researchers to correctly identify potential drug targets implicated in various diseases. Through OpenTarget's approach, researchers gain access to multiple data sets, which analyze disease mechanisms and target identification for drug intervention. Data obtained from ChEMBL, SEA, SwissTarget can also be seamlessly integrated into OpenTarget, enriching the platform with insights into compound bioactivity and structure-activity relationships. By combining diverse data-sets, OpenTarget enhances understanding of complex diseases and helps researchers develop targeted strategies that address medical needs. Smile codes from PubChem can be used in SwissTarget, SEA and ChemBL to facilitate the collaborative nature of biomedical research and drug discovery.

TABLE 1. Sitagliptin phosphate new indication prediction

Sitagliptin Phosphate H2O	AI predicted：New Target Name	70% Confidence	80% Confidence	90% Confidence	AI predicted：New Indication	Affiliation Score (0-1)
Indication：Type 2 diabetes	Coagulation factor X	empty	empty	active	1. Congenital factor X deficiency 2. factor X deficiency	0.83 0.70
Original Target：DPP-4	Lysosome-specific docosahexaenoic acid transporter	empty	empty	active	1. Syndromic X-linked intellectual disability Claes-Jensen type 2. clear cell renal carcinoma	0.8 0.62
Affiliation Score=0.64	Dihydrofolate reductase	empty	empty	active	1. Constitutional megaloblastic anemia with severe neurologic disease 2. acute lymphoblastic leukemia	0.78 0.62
	Carbonic anhydrase II	active	active	active	1. Osteoporosis with renal tubular acidosis 2. autosomal recessive osteopetrosis	0.75 0.72
	Sodium channel protein type III alpha subunit	empty	active	active	1. Partial epilepsy 2. epilepsy	0.72 0.65
	Ubiquitin carboxyl-terminal hydrolase 7	empty	empty	active	1. Hao-Fountain syndrome 2. neurodegenerative disease	0.72 0.53
	Adenosine A1 receptor	empty	empty	active	1. Asthma 2. migraine disorder	0.78 0.61
	HMG-CoA reductase	empty	active	active	1. Hypercholesterolemia 2. cardiovascular disease	0.68 0.66 Phase 4 drug
	Muscarinic acetylcholine receptor M3	empty	active	active	1. Parkinson disease 2. chronic obstructive pulmonary	0.67 0.60
	Carbonic anhydrase XII	active	active	active	1. Isolated hyperchlorhidrosis 2. glaucoma	0.65 0.61
	Acetyl-CoA carboxylase 1	active	active	active	1. Neurodegenerative disease 2. Alzheimer disease	0.65 0.46
	Tyrosine-protein kinase SRC	active	active	active	1. Cancer 2. neoplasm	0.63 0.59
	Poly [ADP-ribose] polymerase 2	empty	active	active	1. Ovarian cancer 2. neoplasm	0.63 0.57
	Synaptic vesicular amine transporter	active	active	active	1. attention deficit hyperactivity disorder 2. Huntington	0.63 0.59

SwissADME is a web tool and application designed to predict pharmacokinetic properties of small molecules. Using SwissADME, researchers can estimate key parameters such as bioavailability, which is critical for determining a compound's properties and potential for further development. By integrating models based on molecular descriptors and algorithms, SwissADME aids researchers in prioritizing lead compounds with optimal pharmacokinetic profiles, accelerating drug discovery while minimizing the risk in later stages of development.

Pyrx is a software used for virtual screening and molecular docking studies. PyRx provides an interface for performing docking simulations[20,21], where researchers can predict the binding affinities and orientations of small molecule ligands with target proteins. By incorporating PyRx's computational capabilities, researchers can explore potential targets with high binding affinity to the approved drug, expediting the process of new indications discovery.

ChimeraX is a powerful molecular visualization and analysis tool, particularly renowned for its structural biology and macromolecular modeling applications[22]. Chimerax enables researchers to visualize and manipulate 3D structures of proteins, nucleic acids, and small molecules. Beyond visualization, ChimeraX helps in molecular docking simulations, electrostatic surface calculations, and structural analysis, providing insights into the mechanisms of molecular recognition and interactions. By integrating ChimeraX into drug discovery, researchers can study structure-activity relationships, optimize lead compounds, and design therapeutics with enhanced information.

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(ii) SPR and cell lines confirmation

Using Surface Plasma Resonance (SPR) to confirm the affinity of drug to the target protein[23]. Further confirmation of drug to various cell lines are needed to confirm the EC50 and EC90 concentration for the drug efficacy design.

B. Clinical PAD Estimation

According to the USFDA guidance[24], a pharmaceutical active dose (PAD) is recommended following MRSD (maximum recommended starting dose). Usually, the ADME simulation with PBPK model is employed to predict PAD for clinical study. An alternative PAD estimation in Figure 3 may also be performed using FDA approved drugs PK database and PAMPA dissolution from J. Chou.

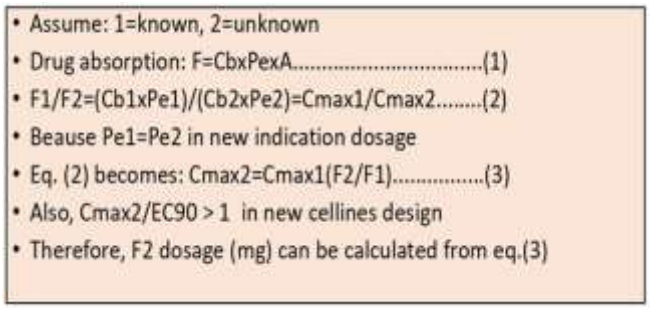

Fig. 3. Calculation of the new indication dosage

IV. CONCLUSION

Integrating AI prediction with target and chemical databases marks a significant shift in traditional drug development, moving away from animal preclinical studies[25] (Figure 4). Normally it takes 10-17 years to develop a well performed drug, however, using AI prediction significantly reduce the time to 3-12 years. Concurrently, AI and biotech advancements have illuminated the intricate relationship between diseases and their pathways, enhancing our understanding of pathophysiology. Leveraging tools such as AI docking, Databases, PAMPA Dissolution, and the FDA-approved drugs PK database holds promise in optimizing the design of oral drug formulation. These innovative approaches represent a shift in drug development, offering more efficient strategies for addressing drug challenges.

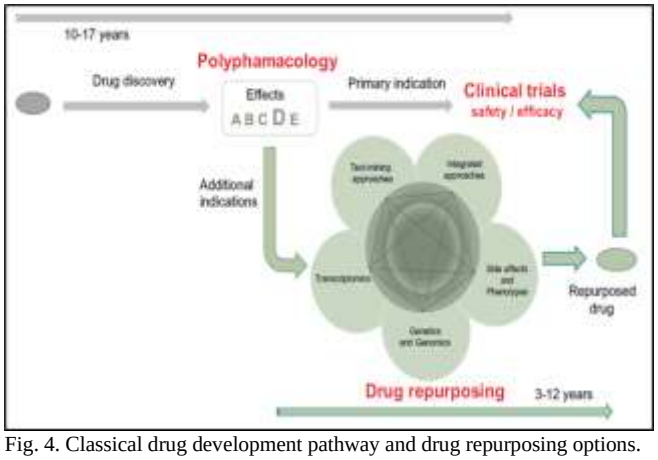

Fig. 4. Classical drug development pathway and drug repurposing options.

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