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AI Prediction of Pharmacotherapy in NAFLD and its Drug Formulation

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Abstract**—***Non alcoholic fatty liver disease (NAFLD) is a prevalent disease globally. The disease causing is a multi-factorial process, and can lead to cirrhosis and hepatocellular carcinoma. There are currently only one thyroid hormone receptor-β agonist MGL-3196 (Resmetirom) approved by US Food and Drug Administration (FDA) for treatments of NAFLD in 2024; however, this is a field of active research. In this study, we have chosen three targets, namely, PPAR-gamma, THR-beta, and CCR2/5 as the targets for new and or re-purpose molecules predicted by AI algorithm. These selected targets are believed to have potential in ameliorate the progression of NAFLD. Finally, an alternative method of NDA drug formulation using FDA drug database and PAMPA dissolution was proposed for first in human (FIH) clinical study. The use of FDA drug ADME P\parameters are compared with the new molecules' in vitro ADME parameters for the design of FIH oral drug formulation is addressed.*

Keywords**—** *Protein data bank (PDB), In vitro to in vivo correlation (IVIVC), Maximum plasma concentration, Parallel Artificial Membrane Permeability Assay (PAMPA), Administration Distribution Metabolism and Excretion (ADME), Non alcoholic fatty liver disease (NAFLD).*

I. INTRODUCTION

The drug-target interactions has become the crucial parameters that has enabled successful application of machine learning (ML) tools to accurately predict new molecules structures[1,2]. 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 and online prediction tools, 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[4,5,6]. For oral drug formulation, currently, there are various ADME simulation software available to help oral drugs formulation design[7,8]. To further 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].

Various treatments have been investigated for the NAFLD. Fig. 1 shows the pathogenic pathways of NAFLD[15] into Gut-liver, metabolic, inflammation, and fibrosis.

Current pharmacological agents used in the treatment of NAFLD[16] is shown in Table 1. There are three main targeting therapies, namely, insulin and de novo lipogenesis, apoptosis, and fibrosis.

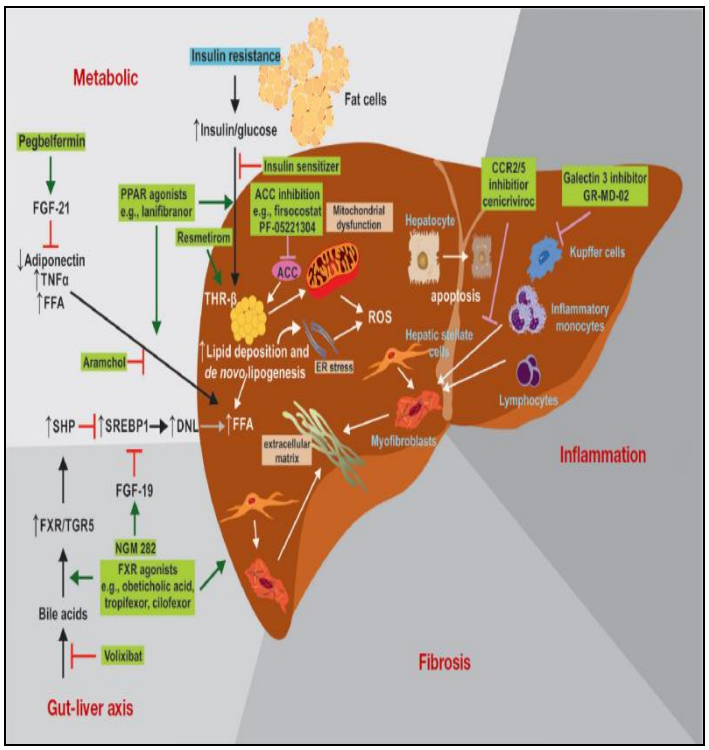

Figure 1. Therapeutic targets in liver fibrosis

II. MATERIALS AND METHODS

In order to perform AI prediction of new molecules for NAFLD, software and database are required, for example, PDB, PubChem, Uniprot, Open Targets, SwissTarget, SwissADME, ChemBL and ChimeraX etc. For the AI prediction purpose, the disease targets of NAFLD can be referred from a number of review articles[17,18,19]. Due to its characteristics of multi-factorial disease in NAFLD, e.g., potential targets include correction of insulin resistance,

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interference with free fatty acid generation, triglyceride uptake, lipolysis and prevention of autophagy, endoplasmic reticulum stress, and mitochondrial functions. Particularly, the accumulation of excess lipids in the liver, causing lipotoxicity that might progress to metabolic-associated steatohepatitis (NASH), liver fibrosis. Therefore, we have chosen three most possible disease causing targets namely, PPAR-gamma, THR-beta, and CCR2/5 as the targets for AI prediction of the new molecules.

TABLE 1. Current pharmacological agents in clinical study

Drug	Mechanism/target	Clinical improvements					Current phase
		IR	Steatosis	NASH	Apoptosis	Fibrosis	
Therapies targeting insulin resistance and *de novo* lipogenesis							
Obeticholic acid	FXR agonist		•	•		•	III
Cilofexor (GS-9674)	FXR agonist		•				II
Tropifexor	Non-steroidal FXR agonist		•	•			II
Firsocostat (GS-0976)	ACC inhibitor		•	•		•	II
Cilofexor + firsocostat	FXR agonist + ACC inhibitor	•	•	•		•	II
TVB-2640	FASn inhibitor		•				II
Aramchol	SCD1 inhibitor		•	•			III
Pradigastat	DGAT1 inhibitor		•				II
Elafibranor	PPARα/β agonist			•			III[1]
Seladelpar (MBX-8025)	PPARδ agonist	•					II[2]
Saroglitazar	PPARα/γ agonist			•			II
25-hydroxycholesterol3-sulfate	LXR inhibitor		•	•		•	I
Pegbelfermin (BMS-986036)	FGF21 analogue		•				II
NGM-282	FGF19 analogue		•	•		•	II
Ursodeoxycholic acid (UDCA)	Bile acid		•	•			II
Therapies targeting apoptosis							
Emricasan	Caspase inhibitor			•	•	•	II[3]
Selonsertib	ASK1 inhibitor		•	•		•	III[4]
Simtuzumab	Antibody against LOXL2		•	•		•	II
Selonsertib + simtuzumab			•	•		•	II
Therapies targeting fibrosis							
Cenicriviroc	CCR2/5 antagonist	•				•	III[5]
Belapectin (GR-MD-02)	Galactin-3 inhibitor			•		•	II

ACC, acetyl-coA carboxylase; ASK1, apoptosis signal-regulating kinase 1; CCR2/5, C-C chemokine receptor type 2/5; DGAT1, diacylglycerol acyltransferase 1; FASn, fatty acid synthase; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; IR, insulin resistance; LOXL2, lysyl oxidase-like 2; LXR, liver X receptor; PPAR, peroxisome proliferative activated receptor; SCD1, steroyl-coA desaturase 1.

[1] Phase III has been stopped because elafibranor failed to reach the primary endpoint

[2] Phase IIb trial had to be halted after the appearance of liver cell damage and signs of inflammation in some participants.

[3] Phase II trials of emricasan failed to reach their primary endpoints.

[4] Phase III trial of selonsertib failed to reach its primary endpoint.

[5] Phase III trial of cenicriviroc was terminated early due to a lack of efficacy.

A. Agonists for proliferator-activated receptors (PPAR)

PPAR are nuclear hormone receptors with the potential to ameliorate NAFLD owing to their effects on lipid metabolism, insulin sensitivity, and inflammation. Both PPAR alpha and delta receptors promote fat metabolism (for instance, fatty acid oxidation), while PPAR delta also exhibits anti-inflammatory properties. PPAR gamma is involved in the regulation of glucose metabolism alongside fat cell differentiation and fatty acid storage. In a study20 conducted by Renata Belfort et al., a low-calorie diet (500-kcal/d deficit from weight-maintaining caloric intake) paired with 45 mg/d pioglitazone for 6 months showed improvement in metabolism and liver histology for NASH patients. Comparable results21 were also provided by Kenneth Cusi et al. A treatment protocol with the identical intervention conditions outlined above for 18 months was deemed safe and effective in patients with prediabetes or T2DM and NASH, along with enhancements in their liver histology without aggravating fibrosis. In light of this information, the EASL-EASO-EASD, AASLD, and NICE practice guidelines for managing NAFLD endorse pioglitazone usage in patients with NASH. Nonetheless, pioglitazone may not be appropriate for every patient. It might aggravate lower extremity edema; therefore, caution should be taken in patients with severe obesity, diastolic dysfunction, congestive heart failure, etc. Another dual-PPAR agonist, saroglitazar[22], has been shown to improve lipid and glucose parameters by predominant PPAR-alpha and moderate PPAR-gamma agonist activity. At week 16, a significant proportion of patients showed >30% reduction in the liver fat content with 4 mg saroglitazar as compared to placebo (40.7% vs 8%, P = 0.006).

B. Thyroid hormone receptor (THR-Beta) agonist

THR-beta is involved in various metabolic pathways, such as glycolipid and cholesterol metabolisms in the liver. Resmetirom (MGL-3196), a novel THR-beta agonist, targets the liver. A 36-week randomized, double-blind, placebo-controlled, multicenter phase II clinical trial[23] conducted by Harrisons team showed significant reductions in the liver fat contents in NASH patients after 12 and 36 weeks of oral treatment with 80 mg/day of MGL-3196. In 2024, Resmetirom was the first drug approved by USFDA for NAFLD treatment.

C. C-C motif chemokine receptor-2/5 (CCR2/5)

Several agents that combat fibrosis have been assessed for treating NASH accompanied by moderate to severe fibrosis. Cenicriviroc acts as an antagonist of CCR2/5 (C-C motif chemokine receptor-2/5) and displays anti-fibrotic properties by inhibiting the migration and activation of collagen-producing HSCs while enhancing insulin sensitivity. A phase IIb trial (CENTAUR study) indicated an enhancement of fibrosis without exacerbation of NASH after one year of treatment with cenicriviroc in 20% of patients as opposed to 10% for the placebo.

D. AI prediction of new molecules for PPAR-gamma, THR-beta, and CCR2/5

Due to the promising clinical data for the above three disease targets. With the help of AI and databases, we are able to predict and analyze the new and or repurposed molecules for these promising targets. Data shown in Table 2 indicate the AI predicted results.

TABLE 2. Targets prediction of small molecules inhibits CCR2/5, PPAR-gamma, and THR-beta

CCR5/2--Patent	Mol. Wt.	Type	Value	GI absorption	BBB permeant	Pgp substrate	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4 inhibitor
EP-1656345-B1-2003	491.6	IC50	=10 nM	High	No	No	No	No	Yes	Yes	
AU-2005317928-B2-2004	428.36	IC50	=22 nM	High	No	Yes	No	No	No	Yes	No
US-6476054-B1-2002	522.69	IC50	=25 nM	High	No	Yes	No	Yes	Yes	Yes	Yes
PPAR-gamma--Patent	Mol. Wt.	Type	Value	GI absorption	BBB permeant	Pgp substrate	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4 inhibitor
EP-1539746-B1-2002	460.57	Ratio	=0.1	High	No	Yes	No	Yes	Yes	Yes	Yes
EP-1539746-B1-2002	464.52	Ratio	=0.1	High	No	Yes	No	Yes	Yes	Yes	Yes
EP-1539746-B1-2002	473.36	Ratio	=0.2	High	No	Yes	No	Yes	Yes	Yes	Yes
THR-beta--Patent	Mol. Wt.	Type	Value	GI absorption	BBB permeant	Pgp substrate	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4 inhibitor
US-8263659-B2-2003	510.13	IC50	=46 nM	High	No	No	No	Yes	Yes	Yes	No
NA	408.41	EC50	=48 nM	High	No	No	Yes	Yes	Yes	Yes	Yes
US-7557143-B2-2003	405.23	IC50	=50 nM	High	No	No	No	Yes	Yes	No	No

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From Table 2, targets assay with molecules except PPAR-gamma show IC50<50 nM, which indicate good inhibition for CCR2/5 and THR-beta. These molecules also have high predicted GI absorption and no BBB permeation. Molecules having pharmacophore may also produce the derived new molecules using QSAR. All new molecules generated shall be further predicted for their docking affinity and toxicity.

E. An alternative method in oral NDA formulation development

Traditionally, scale-up factors are introduced in predicting FIH (First in Human) dosage from pre-clinical study. In order to better predicting clinical oral dosage, the following procedures are proposed in Fig. 2, which is based upon MRSD (Maximum Recommended Starting Dose), PAD (Pharmaceutical Active Dose), PAMPA Dissolution, and FDA approved PK database, proposed by J. Chou et al[25].

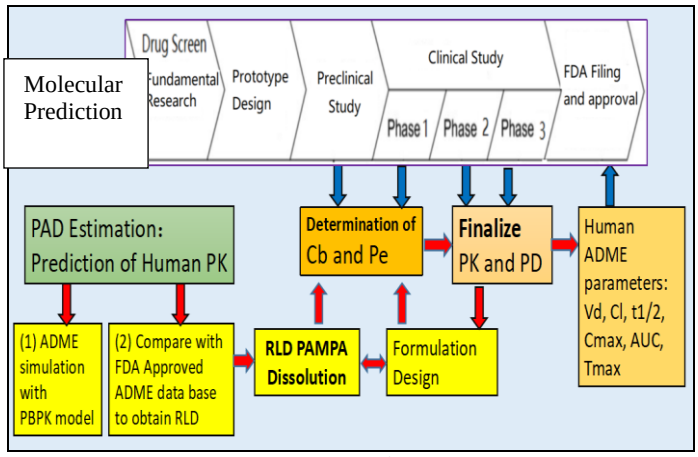

Figure 2. Alternative NDA scheme for oral drug development

As shown in green and yellowish boxes of Fig. 2, the proposed oral NDA formulation[26] steps are:

1. Based on preclinical and in vitro hepatocyte data, NCE drug's permeability (Pe) of Caco2, clearance rate (Cl), and volume of distribution (Vd) can be derived for human PK prediction.
2. Proceed ADME simulation with PBPK modeling (1) and or
3. Compare predicted human ADME data with FDA approved ADME database to obtain comparable RLD (2).
4. Perform PAMPA Dissolution of above RLD to obtain permeation for NDA formulation design.
5. Develop oral NDA formulation with respect to both PAMPA Dissolution and stability study.
6. Proceed with Phase I study.

III. Conclusion

NAFLD is the result of multiple hits to the liver from dietary, impaired hormonal signaling (particularly insulin), defects in cellular metabolism that regulate hepatocellular lipid handling, changes in the intestinal microbiome, and augmented proinflammatory/profibrotic processes. Therefore, steatosis occurs when an imbalance between the mechanisms that regulate lipid handling within the liver. Insulin resistance is also an important driver of lipogenesis. Mechanisms to attenuate hepatic steatosis include increased mitochondrial fatty acid oxidation, decreased hepatic lipogenesis, and enhanced lipid export from the hepatocytes. Furthermore, the accumulation of toxic lipid species can trigger the development of lipotoxicity, oxidative stress, as well as immune cell and stellate cell activation, leading to the development of hepatic inflammation and fibrosis. In this study, three selected targets (PPAR-gamma, THR-beta, and CCR2/5) with the AI calculated molecules aiming in ameliorating NAFLD were conducted. In addition, with the help of alternative oral NDA formulation design, the development of FIH formulation for clinical study can be easily performed.

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