A novel method to predict fatty liver drugs in context of metabolic network

Priyanka Banerjee[1,2], Nikolaus Berndt, Robert Preissner, Hermann-Georg Holzhütter[1,2]

[1] *Computational Systems Biochemistry, Institute of Biochemistry, Charité – Universitätsmedizin Berlin, Germany;*
[2] *Computational Systems Biology, Humboldt-Universität zu Berlin, Berlin, Germany*

Hepatocytes exhibits a wide range of functions extending from removal of toxic substances, homeostatic regulations and synthesis of most plasma membrane constituents as well as production of bile and hormones. Hepatocytes have higher metabolic activity in human and play an important role in human metabolism. Deficiency or alterations in the metabolism of hepatocytes can lead to complicated liver diseases like hepatitis, non alcoholic fatty liver disease (NAFLD), cirrhosis and liver cancer, and can be serious threats to public health. NAFLD is considered as the hepatic manifestation of obesity and metabolic syndrome as a result of series of pathological changes, which ranges from reversible fatty liver (steatosis) to a non-alcoholic steatohepatitis (NASH).

In recent years, the most common cause of chronic liver disease in USA is contributed by NAFLD. A recent study shows the need and cost associated with medication related to liver diseases as well as organ transplantation. Increase rates of obesity diabetes and high cholesterol have results in growing concern for liver diseases. NAFLD and Steatohepatitis are well linked but rare forms of drugs induced liver injury. In addition, fatty liver is often chronic than acute even when drug induced. Even though it is well known that the lipid accumulation in the liver is a hallmark of the NAFLD; the underlying mechanism leading to steotosis and further transition to NASH is still remains elusive. It is therefore difficult to track the onset and progression or to diagnose and design effective therapeutic techniques. The adverse outcome of this pathology may be possibly prevented once the molecular mechanisms involved in the metabolism of Hepatocytes are unraveled. On the other hand, this requires understanding of the coordinated behavior of a very large number of interconnected networks of drugs, molecular target as well as off-target, pathways, metabolic network and metabolites. Recent developments in the field of computational systems biology made it possible to predict the functional effects of systems perturbations using large scale network models. Subsequently, advances in the field of structural bioinformatics and chem-informatics have led to the prediction of protein-drug off-target effects based on their ligand structures and binding site information. Integration of these expertises provides a platform for evaluating metabolic drug response *in silico*. The combination of these approaches was applied to investigate the drugs that can cause fatty liver disease in human. Currently, there is no efficient treatment or explanation involved in the mechanism of NAFLD.

This study represents a novel integration of the trio ’computational systems biology, structural bioinformatics and cheminformatics’ approaches to predict drugs involved in metabolic syndrome and the possible underlying mechanism.