27O-ISMS26 **Construction of a Novel System for the Prediction of Major Clearance Pathways of Drugs only from Their 2D Chemical Descriptors**

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Information on clearance pathway of drugs is important to predict the change in pharmacokinetics of drugs when the function of a certain metabolic enzyme/transporter is changed by several factors such as drug interactions and genetic polymorphisms. However, estimation of clearance pathway of drugs from in vitro experiments is labor-intensive with the use of multiple cell types. Thus, we have previously established an in silico system named "CPathPred" to predict a major clearance pathway among five pathways (metabolism mediated by CYP3A4, CYP2C9, CYP2D6, renal excretion and OATP-mediated hepatic uptake) only by four "basic descriptors" (net charge at pH7.0, plasma protein unbound fraction, molecular weight and logD(pH7.0)). Then, to further improve the predictability, we introduced support vector machines (SVMs) and some chemical descriptors in addition to basic descriptors ("CPathPred ver. 2"). In the current study, to increase the practicality of this system in the drug development, we expanded the number of predictable clearance pathways (5 → 8) and added the ability to predict multiple major clearance pathways (>25% of total clearance). SVM-based predictors with the two-step focusing approach with subset clustering resulted in the highest prediction performance. The feature-selection of additional descriptors based on a greedy algorithm was also employed. Finally, the prediction accuracy for each pathway was increased to more than 0.73 with the exception of the CYP2D6 pathway (0.63). In conclusion, we successfully constructed an SVM-based predictor for the multiple major clearance pathways of a higher coverage of predictable drugs in humans based on 2D chemical structures.