Recent developments in the prediction of drug-induced phospholipidosis

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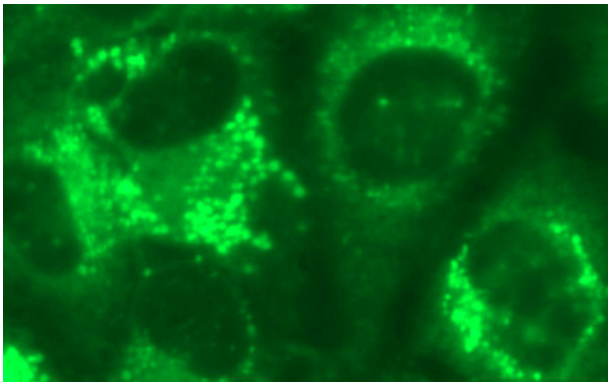
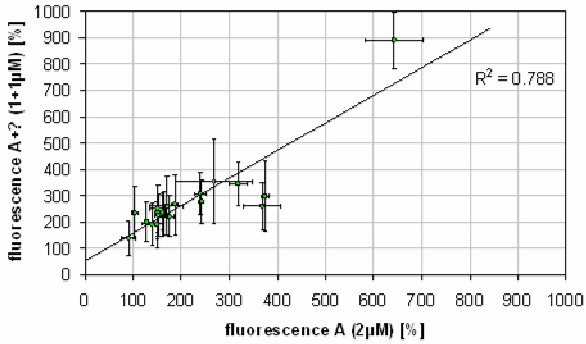
Drug induced phospholipidosis (PLD) is characterized by an excessive accumulation of phospholipids within cells, mainly lysosomes. Although it is not clearly known which enzymatic pathway is responsible to reduce the phospholipids degradation, several well-known drugs induce PLD. This effect can be monitored *in vitro* using a fluorescence-labeled phospholipid assay [1], where a green fluorescent phospholipids mix accumulates for PLD inducing drugs. We tested approximately 300 drugs for their effect on the cellular phospholipids level and identified 55 drugs that resulted in a significant increase of the phospholipid fluorescence at a concentration of 10µM [2].

Based on these experimental results we established an *in silico* prediction system. One of the major objectives for the prediction systems was to keep the number of descriptors low and subsequently the models interpretable and intuitive. A random forest algorithm (N=5) resulted in a validated accuracy of 84.7% using 3 descriptors and 86.3% using 4 descriptors.





In an additional study we examined PLD induced by combinations of two drugs. The main goal of this study was to find out if the total drug concentration is decisive for PLD beyond individual drug effects, which would implicate that drug-induced PLD can be considered as an additive effect. To test this hypothesis we used binary combinations of 21 drugs. For an additive mechanism the PLD induced by combinations should be available via linear combinations of the individual results.

$$fluorescence(A) + fluorescence(B) - 100\% = fluorescence(A+B)$$

Remarkably, this equation is able to generate reasonable estimates for drug-induced PLD of binary combinations. Altogether, an additive mechanism can be assumed for drug-induced PLD. PLD caused by combinations can be estimated using PLD induced by the individual drugs.

[1] N. Mesens, et al., *Toxicology In Vitro*, **2009**, *23(2)*, 217-226.
[2] M. Muehlbacher, et al. *ChemMedChem*, **2012**, *7(11)*, 1925-1934.