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New computational approach to predicting adverse drug reactions with higher confidence

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A new integrated computational method helps predicting adverse drug reaction—which are often lethal—more reliably than with traditional computing methods. This improved ability to foresee the possible adverse effects of drugs may entail saving many lives in the future. The study that is being conducted by researchers from IMIM (Hospital del Mar Medical Research Institute), Pompeu Fabra University, and the company Chemotargets, within the framework of the European eTOX project, was chosen for the cover of the journal *Chemical Research in Toxicology*.

Most computer tools employed today to detect possible adverse effects of compounds that are candidates for new medicines are based on detecting labile fragments in the drug's structure. These fragments can potentially transform to form reactive metabolites, which can have toxic properties. This is what is known as idiosyncratic toxicity and is a big headache for the pharmaceutical industry, as it tends to be detected in late development stages of the drug and even when it is already on the market, often causing the drug to be withdrawn.

Jordi Mestres, coordinator of the IMIM and UPF research group on Systems Pharmacology at the Biomedical Informatics Program (GRIB) states 'With this study we have contributed to complementing the detection of these quite unstable fragments, with information on the mechanism of action of the drug, based on three aspects: similarity to

other medicines, prediction of their pharmacological profile, and interference with specific biological pathways. The optimal integration of these four aspects results in a clear improvement of our ability to anticipate adverse effects with higher confidence, which entails an extremely positive impact on society'.

In Europe, nearly 200,000 people die every year from adverse drug reactions, seven times more than in traffic accidents. An estimated 5% of hospitalisations are due to adverse effects and they are the fifth most common cause of hospital death. In addition, elderly people tend to take more than one drug at the same time, which multiplies the chances of suffering from adverse effects due to potential drug-drug interactions. In an increasingly ageing society, this problem is becoming much more serious.

The human and financial costs of adverse effects are very high. That is why the discovery of new medicines is increasingly focused more on predicting possible adverse effects at the initial stages of developing a new drug. This work hopes to contribute to setting the path toward a new generation of more reliable computational tools with regard to predicting the adverse effects of therapeutically-relevant small molecules. Advancing large-scale predictive safety at the pre-clinical phase is now becoming closer than ever, with expectations to lead to safer drugs for the entire population.

More information: Ricard Garcia-Serna et al. Large-Scale Predictive Drug Safety: From Structural Alerts to Biological Mechanisms, *Chemical Research in Toxicology* (2015). DOI: 10.1021/acs.chemrestox.5b00260

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