Multiscale simulation in the prediction of drug-induced cardiotoxicity: Integrating molecular, cellular and tissular levels

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The preclinical assessment of drug-induced ventricular arrhythmia, a major concern for regulatory authorities, is typically based on experimental or computational models focused on the potassium channel hERG (human ether-a-go-go-related gene, Kv11.1). Even if the role of this ion channel in the ventricular repolarization is of critical importance, the complexity of the events involved make the cardiac safety assessment based only on hERG has a high risk of producing either false positive or negative results. We introduce a multiscale simulation system aiming to produce a better cardiotoxicity assessment. At the molecular scale, the proposed system uses a combination of docking simulations on two potassium channels, hERG and KCNQ1, plus three-dimensional quantitative structure-activity relationship modeling for predicting how the tested compound will block the potassium currents IKr and IKs. The obtained results have been introduced in electrophysiological models of the cardiomyocytes and the ventricular tissue, allowing the direct prediction of the drug effects on electrocardiogram simulations. The usefulness of the whole method is illustrated by predicting the cardiotoxic effect of several compounds, including some examples in which classic hERG-based models produce false positive or negative results, yielding correct predictions for all of them. These results can be considered a proof of concept, suggesting that multiscale prediction systems can be suitable for preliminary screening in lead discovery, before the compound is physically available, or in early preclinical development stages.[1]

The present prediction strategy for the prediction of drug-induced cardiotoxicities is being applied within the eTOX project (http://www.etoxproject.eu/),[2] which is funded in the framework of the European Innovative Medicines Initiative (IMI).[3]

1. Obiol-Pardo C, Gomis-Tena J, Sanz F, Saiz J, Pastor M. A multiscale simulation system for the prediction of drug-induced cardiotoxicity. *J Chem Inf Model* 2011; 51: 483-92.

2. Briggs K, Cases M, Heard D, Pastor M, Pognan F, Sanz F, Schwab C, Steger-Hartmann T, Sutter A, Watson D, Wichard J. Inroads to predict in vivo toxicology – An Introduction to the eTOX Project. *Int J Mol Sci*. In press.

3. Goldman M. The Innovative Medicines Initiative: A European Response to the Innovation Challenge. *Clin Pharmacol Therap* 2012; 91(3): 418-25.

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