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Systems Biology in drug development - cardiotoxicity prediction

Cardiac liability testing of the drugs candidates during development process has gained increased regulatory and public attention due to a growing awareness of the cardiac risks across a variety of marketed products. Nowadays, cardiac safety assessment in pre-approval clinical trials is obligatory and possible failure at this late stage of the R&D pipeline has tremendous impact on pay-off of the whole process. Thus it is desirable to screen compounds as early as possible, before large amounts of time and money have been spent. Traditional pre-clinical in vivo and ex vivo animal studies employed in risk assessment are criticised due to the ethical and meritorious reasons and in vitro cell lines based studies are currently effectively utilized. Results extrapolation from the in vitro tests to in vivo human risk became an issue and systems biology approach is proposed to derive appropriate conclusions from in vitro lab observations. Developed system is hybrid in nature and combines mathematical model of the human left ventricle cardiomyocyte with in vitro assessed drug induced ionic channels inhibition. The third main element is a virtual population generator. Based on the data derived from available scientific literature dynamic database of the population was developed. Randomly chosen virtual individuals are described by physiological and genetic parameters, namely cardiomyocyte volume, sarcoplasmic reticulum volume, cell electric capacitance, potassium channels genetic polymorphism, which are used as simulation parameters. Therefore the system allows for the inter-individual variability assessment which is a fundamental advantage comparing with animal in vivo and other available muli-scale models. Combination of above-described approach with physiology based pharmacokinetic models (PBPK) used for plasma and tissues drug concentration changes prediction can be used for concentration dependent in vitro - in vivo extrapolation of the cardiotoxic effect for new chemical entities.