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Accurate prediction of human organ-specific toxicities

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Evaluating the toxicity of chemicals, drug candidates, natural compounds and nanomaterials requires predictive methods. Animal models are of limited predictivity and are too slow and costly for screening of the large and increasing numbers of compounds that need to be tested. Also, changes in legislation (e.g. animal bans for cosmetics testing) and other developments steeply increase the demand for alternative methods. However, many alternative methods are of unknown predictivity, and accepted alternative methods for predicting toxicity for human internal organs are not available. This problem is addressed by our work, which was initially focused on the kidney. Recently, we have developed the first animal-free platforms for the accurate prediction of nephrotoxicity in humans. These platforms include the only available predictive methods based on human induced pluripotent stem cell-derived renal cells and a predictive high-throughput platform. The high-throughput platform is currently applied in collaboration with the US Environmental Protection Agency to predict the human nephrotoxicity of ToxCast compounds. The test balanced accuracies of our predictive methods range between ~ 80%-90%, and these methods also reveal injury mechanisms and compound-induced cellular pathways. Based on a similar methodology we are now developing high-throughput platforms for predicting toxicity for other human organ systems, including liver and vasculature, and we are also establishing predictive organ-on-chip technologies for efficient repeated dose testing.

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