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EDITORIAL

In vitro systems: current limitations and future perspectives

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At the end of each year, the Archives of Toxicology analyzes the most intensively studied fields of research published in our journal. This includes particularly research topics where important progress beyond the state of the art has been achieved. Moreover, the editors analyze the topics to which most manuscripts have been submitted and where most citations have been counted, try to identify the present state of the art and give recommendations how further progress beyond the state of the art can be achieved. Of course, these analyses represent individual opinions and have no influence which manuscripts will be published in future; in this regard, only scientific quality is of relevance. Clearly, in vitro systems represent one of the most popular topics in our journal (Godoy et al. 2013; Azqueta and Collins 2013; Hessel et al. 2013; Jiang et al. 2013; Liu et al. 2013; Fraczek et al. 2013; Leist and Hartung 2013). This seems to represent a general trend in toxicological sciences (Weng et al. 2014; Waldmann et al. 2014; Karlsson et al. 2013; Onrubia et al. 2013; Lake et al. 2013; Houston et al. 2012; Hardelauf et al. 2011; Ilowski et al. 2011; Gabriel et al. 2012; Hammad et al. 2013) but also in other disciplines of biomedical research (Zellmer et al. 2010; Godoy et al. 2009, 2010a, b; Ilowski et al. 2010; Meyer et al. 2011). In the Archives of Toxicology, in vitro systems are used to study mechanisms of action of toxic compounds, a traditional strategy since decades (Chen et al. 2013; Qu et al. 2013; Qing et al. 2013; Doricakova et al. 2013; Ren et al. 2013). In recent years, a strong increase in the number of publications has been observed aiming to establish and improve in vitro systems (Ireno et al. 2014; Seeliger et al. 2013; Godoy 2011). The most cited example in Archives of Toxicology in 2013 was the successful development of embryonic stem cell-based test systems that recapitulate specific phases of human development during which the in vitro system can be exposed to the test compounds (Krug et al. 2013a). Several further studies based on in vitro systems with neurons or neuronal precursor cells have been published (van Thriel 2011; Krug et al. 2013b; Hoelting et al. 2013; Da Silva et al. 2013; Bolt 2013). A particularly high number of in vitro studies focus on hepatotoxicity (e.g., Hadi et al. 2013; Schaap et al. 2012; Burkhardt et al. 2012). Goals of these studies are to improve differentiated functions by 3D cultivation conditions (Messner et al. 2013; Schyschka et al. 2013) to study metabolites (Sierra-Santoyo et al. 2012; Watzek et al. 2013; Abdelhamid et al. 2013; Tolosa et al. 2013) and drug transporters hepatocytes (Wassermann et al. 2013). Moreover, zebrafish-based test systems have been studied as an alternative method to identify hepatotoxic compounds (Driessen et al. 2013; Scholz 2013). Compared to the high number of studies based on in vitro systems the fraction of in vivo studies published in the Archives of Toxicology has become relatively small (Rossato et al. 2013; Yu et al. 2013; Early et al. 2013; Cordova et al. 2013; Saito et al. 2013; Hammad et al. 2014). Moreover, studies systematically comparing the functions of in vitro systems to the in vivo situation are rare (Schug et al. 2013; Heise et al. 2012). This leads to a situation where huge sets of data including omics analyses are available but a limitation is that the in vivo relevance particularly the relationships to adverse effects remain unclear. Bridging this gap will be a major challenge for toxicological research in future.

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One possibility would be to identify compounds for which in vivo blood concentrations (nonprotein bound) in humans are known and the risk of adverse effects in humans is clearly established. An important question is whether the many recently established in vitro systems for liver, kidney, neuro- and cardiotoxicity differentiate between concentrations known to be associated with an increased risk of in vivo toxicity and concentrations that can be considered as harmless. This question seems to be simple and straightforward but has not yet been systematically addressed by currently published in vitro studies. However, a clear differentiation is a precondition for acceptance by regulators. Progress in this direction would clearly advance in vitro research beyond the current state of the art.

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