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EDITORIAL

# Highlight report: New applications of chimeric mice with humanized livers

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Some years ago, chimeric mice with humanized livers have been introduced as a tool to study human drug metabolism (Strom et al. 2010; Kamimura et al. 2010; Scheer and Wilson 2016). These models make use of mice with genetic modifications that cause the deterioration of native hepatocytes (Strom et al. 2010). Most commonly, immunodeficient mice with a knockout of fumarylacetoacetate hydrolase or with overexpression of urokinase-type plasminogen activator are used for this purpose. When human hepatocytes are transplanted into these mice, they repopulate the host liver and may replace up to 95% of the murine hepatocytes. It has been reported that humanized mouse livers show some features of human gene expression patterns and mirror responses of human liver to hepatotoxic drugs (Go 2018). In a recent issue of the Archives of Toxicology, Anja Ekdahl and colleagues used chimeric mice with humanized livers to study the metabolism of fenclozic acid (Ekdahl et al. 2018). Fenclozic acid was developed as an alternative to high-dose therapy with aspirin (Chalmers et al. 1969a, b). Although fenclozic acid showed a good safety profile in experimental animals, it had to be withdrawn from late-stage clinical development because of hepatotoxicity (Ekdahl et al. 2018; Alcock 1970; Hart et al. 1970). The study was performed following oral administration of 10 mg fenclozic acid per kg body weight in bile-cannulated humanized mice (Ekdahl et al. 2018). Interestingly, the authors were able to detect human-specific metabolites, such as fenclozic acid with side-chain extension in plasma and excreta, and could establish differences in metabolic patterns compared to conventional mice.

The use of chimeric humanized mice is attractive because it offers the possibility to study human hepatocytes in the environment of an organ in vivo. Nevertheless, many questions concerning this innovative mouse model remain open. For example, it is well known that isolation and cultivation of hepatocytes cause major changes in cell function and gene expression (Godoy et al. 2009, 2015, 2016a, b, 2018; Zellmer et al. 2010; Grinberg et al. 2014). It remains open to which degree the transplanted human hepatocytes differ when transplanted into mouse livers compared to their state in the human microenvironment. A well-established alternative system to humanized mouse livers is cultivated human hepatocytes (Gu et al. 2018; Deharde et al. 2016; Reif et al. 2015; Ghallab et al. 2016; Kim et al. 2015; Frey et al. 2014), a cell system well established for the purpose of metabolite generation and identification (Hewitt et al. 2007; Godoy et al. 2013).

Unfortunately, little is known about the metabolic capacity of cultivated human hepatocytes compared to their performance in chimeric mouse livers. An obvious advantage of the humanized mice is that both biliary as well as renal excretion can be studied. Bile canaliculi form a complex network that is linked to the interlobular ducts and drains bile to larger ducts and the gall bladder (Vartak et al. 2016). After induction of hepatotoxicity, both canaliculi and bile ducts show major structural changes (Jansen et al. 2017). In chimeric mice, bile canaliculi can be expected to be formed by the apical cell membranes of the human hepatocytes and these structures have to link to the ducts that are formed by mouse cholangiocytes. It would be interesting to learn more about the architecture of these chimeric biliary tracts and whether they recapitulate cholestatic structural changes observed in normal livers. It still has to be established, whether basolateral and apical transport mechanisms known from mice and humans (Reif et al. 2017; Köppert et al. 2018) are maintained in the chimeric animals.

In conclusion, mice with humanized livers represent a fascinating model system but more basic work is required to obtain a better understanding of its possibilities and limitations.

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## Compliance with ethical standards

**Conflict of interest** The author declares that she has no conflict of interest.

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