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Preface

Preface - Animal models in liver disease

Almost 300.000 clinical trials, which test novel therapeutic concepts in human beings, are currently listed at clinicalTrials.gov. However, apart from these highly regulated clinical trials, researchers usually do not get started with experiments in human. Due to the anatomical, physiological and genomic similarities between human and mammals, scientists study disease mechanisms and drug therapies in animal models prior transferring new concepts to and testing discoveries in humans. The use of animal models to understand human anatomy and (patho)physiology has a long-lasting very successful tradition and dates back to ancient Greece, Aristoteles and Galen [1]. Among the animal models, a majority of studies have been performed in mice, because of their availability, high reproductive rates, relatively low cost of maintenance and ease of handling and the possibility of genomic manipulation. However, not all results from animal models can be directly translated into humans and there is a continuous research for better “humanized” animal models across all disease entities. Despite all the advances in the “creation” of ever-more sophisticated animal models for scientific purposes, the achievements should always build on the rules of animal protection and welfare, which have become evident as the ‘the three Rs rules’, for replacement, reduction and refinement and have first been proposed by Russel and Burch in 1959 [2].

This special issue in *BBA – Molecular Mechanisms of Disease* focuses on animal models in liver disease and comprises a series of reviews covering anatomical considerations, physiological principles and disease-specific aspects of various liver diseases. Attention is paid to include comprehensive overviews on the primary readout markers as well as advantages and disadvantages of the single models but also on feasibility issues when attempting to establish such models in one's own laboratory.

Wouter Lamers and colleagues provide a conceptual overview on the microarchitecture of the liver among different animal species, the nature of having or having not a gallbladder and the increasing role and consequences the hepatic arterial perfusion in larger animals has [3].

Günter Hämmerle and Achim Lass highlight the physiological role of lipases and their regulators which govern the mobilization of neutral lipid esters and how this connects to diseases such as non-alcoholic fatty liver disease or cholesterol-ester storage diseases. They provide a summary of targeted mouse models on hepatic neutral lipid ester hydrolases [4].

Jianing Li and Paul Dawson summarize mouse models to elucidate the core pathways controlling bile acid homeostasis. They point out the important differences in bile acid metabolism between species, which represents a significant obstacle for translatability rodent findings to humans and the resulting consequence for establishing mouse models with “humanized” bile acid compositions [5].

Annika Wahlström reviews our current knowledge on the impact of the gut microbiome on liver diseases. She highlights how dysbiotic changes may particularly affect non-alcoholic and cholestatic liver diseases and future strategies to treat liver diseases by targeting the gut microbiome and gut barrier function ref.

Mario Strazzabosco and colleagues review recent technical advances and potential applications in the iPSC stem cell field and liver organoids as the next-generation tool to model liver diseases in-vitro ref.

Helmut Denk and his co-authors provide an overview on the aspects of NAFLD from the pathologist's viewpoint. He introduces dietary, toxin-induced and genetic animal models of NASH and discusses that despite metabolic similarities most animal models fail to develop the typical morphological features of NASH such as hepatocyte ballooning and well-defined Mallory-Denk-Body formation [6].

Andreas Geier and colleagues discuss NAFLD models from the hepatologist's point of view. The authors put emphasize on the dietary compositions to induce NAFLD and discuss the metabolic features, which a NAFLD model should ideally have, such as obesity, insulin resistance, hyperlipidemia but also progression of disease with increasing liver fibrosis [7].

Luca Fabris and his team summarize current models of cholangiopathies, mainly primary sclerosing cholangitis and primary biliary cholangitis. In the past bile duct ligation was the commonly used cholestatic model. To better understand the complex network of dysregulationed pro-inflammatory and pro-fibrotic signals for cholangiopathies newer models using chemical induction, xeno- or self-immunization and of course genetic manipulation are utilized and their pros and cons discussed ref.

Carlo Spirli and coworkers compared the current available animal models for cystic fibrosis and their applicability for the study of the liver type. They also introduce non-rodent models of CF, such as the pig and ferret, which, in contrast to mice, have a spontaneous liver phenotype and a pronounced intestinal disease involvement [8].

Urs Christen reports on animal models of autoimmune hepatitis. He introduces the requirements for breaking liver tolerance in an animal model and how an ideal experimental AIH model would like. In addition, he discusses the models in the context of feasibility of induction, similarity of the clinical outcome to human AIH and their potential usefulness for future therapies [9].

Greg Gores and colleagues introduce animal models of cholangiocarcinoma. Models include carcinogen-based models, genetically engineered models, syngeneic orthotopic models as well as xenograft tumors derived from xenotransplantation of CCA cells, organoids or patient-derived tissue. The existing models are compared to an ideal CCA model, where the tumor should arise from the biliary tract in an immunocompetent host with a species-matched microenvironment, should be time-efficient and mimic human CCA [10].

Mark Gorrell and colleagues discuss various animal models of

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hepatocellular carcinoma including chemical-induced models, genetically engineered mouse models as well as graft models with or without additional metabolic insults to accelerate experimental HCC development. The review summarizes criteria for the ideal HCC animal model and advantages/disadvantages of the currently used models. It also contains the histopathological features of mouse liver tumors ref.

Elizabeth Ottinger and coauthors give an overview on translational *invivo* and *invitro* models for rare liver diseases. They discuss animal models for Alagille syndrome, alpha-1-anti-trypsin deficiency, hereditary hemochromatosis, Wilson's disease, glycogen storage disease, hereditary tyrosinemia, Crigler-Najjar syndrome, and lysosomal-acid lipase deficiencies. In addition, they discuss modern ex vivo models including 3D liver models and their potential for liver research [11].

Thomas Reiberger and team present common animal models of liver disease with PHT – including pre-hepatic, intra-hepatic and post-hepatic PHT in rodents. They discuss methodology for induction, considerations for disease etiology, advantages and limitations and practical issues of these animal models [12].

Hartmut Jaeschke and coworkers provide a review of the most popular animal models of DILI, and discuss the future of DILI research. They introduce models of intrinsic DILI but also approaches to model idiosyncratic DILI, which presents greater challenges, but promising new models have recently been developed [13].

We strongly feel that this special issue of BBA provides a unique comprehensive up-to-date overview of pivotal aspects on the most important current models for liver diseases which should give a robust orientation for researches interested in this rapidly evolving research area. We would like to give our sincere thanks to all the contributing authors for their outstanding contributions!

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Peter Fickert is a clinical gastroenterologist and hepatologist and currently the head of the department of gastroenterology and hepatology at the University Hospital of Graz. He started his professional career at the Medical University of Graz and completed subspecialty training in internal medicine (1999), pathology (1999), gastroenterology and hepatology (2002) and intensive care medicine (2005). Since 2011 he leads the laboratory for experimental and molecular hepatology, and since 2014 he is head and chair of the department of gastroenterology and hepatology at the medical University of Graz. Dr. Fickert was trained in internal medicine, gastroenterology, and hepatology by Günter J. Krejs and Was a Fellow in the Laboratory of Helmut Denk. Dr. Fickert is an acknowledged expert in the diagnosis and management of cholangiopathies especially primary sclerosing cholangitis (PSC). Consequently his research focus was for decades the development and characterisation of animal models for PSC with the aim to design overall treatment strategies and drugs for the treatment of PSC patients in the best sense of translational research. Testing of *norUDCA* in MDR2 (Abcb4) knockout mice as a now well accepted model system for sclerosing cholangitis led to the so far successful clinical development of *norUDCA* as a novel treatment for PSC patients which ist currently tested in a phase III clinical trial. His laboratory focuses on the pathophysiology of extraintestinal complications of cholestatic liver diseases more specifically on cholemic nephropathy and the hepatoadrenal syndrome. New concepts on the regulation of hepatic nuclear receptors is a leading topic in his laboratory. Peter Fickerts bibliography contains 301 publications with a h-index of 37.

Martin Wagner is a clinical gastroenterologist and hepatologist and Associated Professor at the Department of Gastroenterology and Hepatology at the Medical University Graz, Austria. Dr. Wagner got his degree in Medicine in 2001 from the Karl-Franzens University in Graz, Austria and his board exam for internal medicine in 2014 at the Medical University Graz. From 2002 to 2005 he received postdoctoral training in hepatobiliary transport in the laboratory of Prof. Michael Trauner at the Medical University Graz. He continued his postdoctoral training in the laboratory of Prof. David Moore at the Baylor College of Medicine, Houston, USA from 2010 to 2013 on nuclear receptor regulation. Currently, he is head of the research unit on “Translational nuclear receptor research in liver metabolism” and part of the “Omics Center Graz” at the Medical University Graz. Martin Wagners' research activity is focused from the beginning on nuclear receptor mediated signaling in metabolic liver diseases, with particular interest in genomic nuclear receptor regulation in non-alcoholic fatty and cholestatic liver diseases as well as the process of autophagy.

Peter Fickert*, Martin Wagner
Department of Gastroenterology and Hepatology, Medical University Graz, Austria
E-mail address: peter.fickert@medunigraz.at (P. Fickert).

* Corresponding author.