Drug-induced liver injury (DILI) remains a major obstacle in drug development and a leading cause of late-stage attrition and post-marketing withdrawal. In this context, in vitro liver models are indispensable, reflecting the liver's central role in xenobiotic metabolism and its vulnerability to toxic insult. However, accurately reproducing the liver's complex cellular architecture, dynamic microenvironment, and intricate intercellular communication in vitro continues to be a formidable challenge.

This talk will survey the rapidly evolving landscape of in vitro liver systems, spanning conventional two-dimensional hepatocyte cultures, three-dimensional spheroids, liver organoids, and advanced microphysiological liver-on-a-chip platforms. Their applications in hepatotoxicity assessment will be examined, alongside a critical appraisal of their capacity to recapitulate key aspects of liver function, metabolic competence, and immune-mediated injury.

Particular emphasis will be placed on emerging New Approach Methodologies (NAMs) as both ethically responsible and scientifically robust alternatives for hepatotoxicity testing. Special attention will be given to platforms that integrate multiple hepatic cell types and enable inter-organ crosstalk such as gut–liver and liver–immune co-culture systems, thereby better capturing systemic and chronic toxicity mechanisms.

Finally, the talk will outline future directions to enhance the predictive performance and regulatory acceptance of these models. These include greater standardization, integration with computational modeling, incorporation of human-relevant endpoints, and rigorous validation against clinical data. Collectively, advances in NAM-driven in vitro liver models are poised to transform DILI assessment, enabling more predictive, efficient, and human-relevant drug development.