



Dear readers,

Please note that the second Microphysiological Systems World Summit will take place in Berlin, Germany on June 26-30, 2023 (<https://mpsworldsummit.com/>), and the 12th World Congress on Alternatives and Animal Use in the Life Sciences will take place in Niagara Falls, Canada on August 27-31, 2023 (<https://www.wc12canada.org/>). *ALTEX Proceedings* will be publishing both Abstract books shortly before the conferences (<https://proceedings.altex.org/>).

ChatGPT-4 and artificial intelligence are all over the international news and sparking discussions about ethics and the potential and limitations of the technology. But what if such technologies became more human-like – either by approaching human learning and reasoning better by improved design based on neurodevelopmental discoveries or by harnessing human brain models for computational technology applications? These are just some of the questions posed by Lena Smirnova and colleagues in their Food for Thought ... on organoid intelligence.

Izuru Mizoguchi and colleagues present a test model to distinguish between respiratory sensitizers and skin sensitizers. The model is based on the exposure of human airway epithelial cells and monocyte-derived cells to the chemicals followed by addition of naïve CD4⁺ T cells to the system and measurement of the upregulation of interleukin-4 mRNA in response to respiratory but not skin sensitizers.

Aiming to develop methods to assess developmental toxicity of chemicals on the retinoid pathway, Nancy Baker and colleagues assemble a set of reference chemicals from the literature that have been shown to target ten protein families in the retinoid system. A case study on the compound citral investigates whether the literature supports its key role in an adverse outcome pathway of developmental toxicity.

Physiologically based kinetic (PBK) model simulations can estimate internal exposure to chemicals after oral dosing based on *in vitro* experimental data. Ans Punt and colleagues explore how experimental variation in the values for relevant parameters impact the model predictions. They argue that experimental conditions and the applicability domain of different models must be clearly described in guidance documents to ensure the generation of robust data that can be used for regulatory purposes.

Keith Houck and colleagues report on an extensive screen of 147 perfluoroalkyl substances (PFAS) for immunosuppressive activity in a panel of 12 human primary cell systems by measuring 148 biomarkers. Comparison to four pharmacological immunosuppressants reveals only few correlations of individual substances; however, correlation with a data-

base of environmental chemical responses and pharmacological probes identifies potential mechanisms of bioactivity for some PFAS that may help to categorize the substances for safety assessment.

A transcriptomics-based biomarker is a selection of genes known to be modulated by toxins with a common mode of action. Anouck Thienpont et al. report on an optimization of the GENOMARK biomarker for genotoxicity in human liver cells, based on data from additional reference chemicals and new prediction models, and make their results available for use by other groups as an online application.

Quantitative adverse outcome pathway networks allow the prediction of adverse outcomes by mathematical models by capturing the relationships between key events in adverse outcome pathways and the biological complexities in the causal network on a quantitative basis. Yang Cao and colleagues compare two modeling approaches for construction of such a network based on ecotoxicological data and discuss their advantages and limitations.

Giovanni Offeddu et al. present a microphysiological model of the human hypodermal vasculature to determine subcutaneous bioavailability of injected protein therapeutics and how this is influenced by the microenvironment. The model is composed of human dermal endothelial cells, fibroblasts, and adipocytes in three-dimensional, perfusable microvessels that express extracellular matrix and allows the measurement of biophysical parameters that impact protein kinetics and distribution.

In a review article of our Special Issue *Microphysiological Systems in Drug Discovery and Safety* (doi:10.14573/altex.22S1), Xiaoting Wang et al. discuss the potential contexts-of-use for immunocompetent and immune organ microphysiological systems in drug development such as for the evaluation of immunotherapies and the challenges of predicting immunotoxicity.

A Letter by Alexandra Schaffert and colleagues contributes to the discussion on the need to determine the cardiotoxic potential of chemicals, and two Meeting Reports as well as the Corners update you on recent developments. Please check our website for 3Rs-related news and upcoming events.

Hoping you enjoy this issue of ALTEX,

Sonja von Aulock
Editor-in-chief