Emulating Human Immunity *in vitro*: The Human Artificial Lymph Node Model (HuALN) for Biopharmaceutical Testing and Disease Modelling

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Abstract:
As modern biopharmaceuticals show a very high degree of species-specificity, conventional animal models are inadequate for drug development and to assess efficacy and safety. The Mode of Action (MoA) is complex, so simplified cell culture models using human cells often fail. Customized animal models, e.g. immune deficient, transgenic, and humanized animals as well as xenograft models are big in business but they show limitations in reproducibility and relevance to a certain extent. In particular for the human immune system, drawbacks in the pharmaceutical arena during the last years have raised significant doubts about their value and predictability for assessing immune modulation and immunogenicity. New "humanoid" models are required for new promising pharmaceutical treatments, e.g. by immune modulators, checkpoint inhibitors, and cell- and gene therapeutics.
The dramatically increased animal consumption triggered by customized animal model technologies pushes the ethical concerns on animal testing for pharmaceutical R&D, efficacy and toxicity testing, and risk assessment.
The Human Artificial Lymph Node Model (HuALN) is a micro physiological system (MPS) mimicking immunity in a continuously perfused 3D culture system and suitable for long-term treatment (e.g. 28 d) and repeated dosing. The MPS serves as a human micro-organoid lymph node model for induction or modulation of cellular and humoral immune responses. The implementation of stromal cells improves organoid formation. The HuALN model is designed for testing immunomodulation (e.g. MoA of checkpoint modulators), to assess unwanted immunogenicity reactions (e.g. ADA formation, sensitization) or efficacy of vaccines, adjuvants and formulation. T cell responses and shifts in the TH1/TH2 pathway are continuously monitored by cytokine secretion profiles. The induction of primary humoral responses is demonstrated by B cell activation, plasma cell formation and antibody secretion profiles for IgM and IgG. Cells can be harvested from 3D matrix at the end of the MPS culture time and used for flowcytometric analysis and functional tests, e.g. ELISPOT assays.
By integration of tumour cells or tumour spheroids the HuALN platform is extended towards disease models.
The HuALN model will be introduced, selected results of biopharmaceutical testing will be presented and the opportunities using the HuALN for modelling tumour treatment will be discussed.