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Vascular leakage: Analyzing mechanisms behind a severe side effect with an irAOP as tool

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Objectives:
The EU/IMI-funded project imSAVAR envisions improving pre-clinical safety of immunotherapeutics by establishment and/or refinement of nonclinical test-systems and side effect-specific biomarkers. Immunotherapeutic modalities, such as CAR T-cells or checkpoint inhibitors, are associated with vascular leakage (VL). In severe cases, induction of the secondary systemic capillary leakage syndrome can lead to further toxicities and death (lethality rate 20 – 30%). However, due to its non-specific symptoms, VL remains underdiagnosed in the clinics. Within imSAVAR, we characterize activation patterns of endothelial cells (EC), their interaction with immune cells, and potential correlations between EC-activation and leakage-induction. We seek to identify potential biomarkers and to establish an in vitro pre-clinical assay, with which we can reflect or even predict VL as severe side effect of immunotherapeutics.
Methods:
For efficient knowledge structuring, we use immune-related adverse outcome pathways (irAOPs), as theoretical tool for the arrangement of complex toxicity-related immuno-biological mechanisms. Here, we use interleukin-2 immunotherapy, for which VL is a common severe side effect, as a use case to organize existing literature around this pathology.
Results:
Using the irAOP-concept, we generated a first model of drug-induced VL. With this, we were able to identify gaps as basis for (1) hypothesis-generation and experimental work, (2) strategies for biomarker development, and (3) approaches for pre-clinical assay development. Integration of novel experiment-based knowledge into the existing irAOP will close a “feedback-loop” by enabling irAOP-refinement and identification of new questions.
Conclusion:
The novel attempt of imSAVAR to use irAOPs enabled a straightforward way of identifying scientific questions and necessary action points throughout the various tasks of the consortium. We provide an overview of VL-development from an immunological perspective. Our EC-characterization study alongside with the development of an immunocompetent VL assay approximates a better understanding and improved safety assessment of VL as severe side effect.