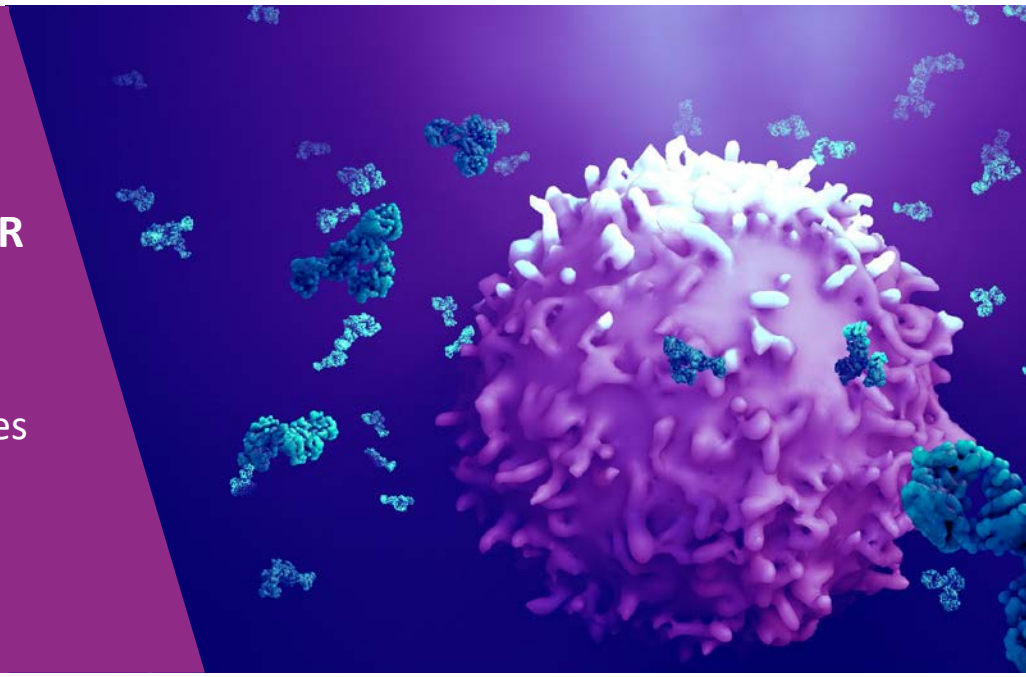
imSAVAR

IMMUNE SAFETY AVATAR

Nonclinical mimicking of the immune system effects of immunomodulatory therapies



Deliverable 2.1
Preliminary irAOP - CAR-T & BiTE MoAs

DELIVERABLE REPORT

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 853988.
The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and JDRF INTERNATIONAL.

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Abstract

Within imSAVAR, we follow the strategy to define immune-related adverse outcome pathways (irAOPs) to guide the development of novel test systems. Adverse Outcome Pathways (AOPs) are a conceptional framework to support research teams of diverse expertise to describe the current knowledge of biological effects triggered by an initiating event leading to adverse health effects (Users' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways; available online at https://www.oecd-ilibrary.org/content/paper/5jlv1m9d1g32-en). In detail, AOPs describe the link between a molecular initiating event (MIE) and a series of key events (KEs), i.e. measurable and critical biological events, at different response levels (e.g. molecular, cellular, organ, organism) leading to adverse health effects [1]. In the context of immunomodulatory therapeutics, we interpret irAOPs as the link between a certain Mode of Action (MoA) interacting with the immune system and a series of key events (KEs) at different organisational levels of the immune system leading to an adverse immune response. Terminology of irAOPs comprises Mode of Action (MoA), key event (KE), key event relationship (KER), and adverse outcome (AO).

Document Information

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1. Methods

Based on the OECD Guidance Document for developing and assessing AOPs, we developed a preliminary irAOP for the MoA CAR-T (T cells genetically engineered to express a chimeric antigen receptor [CAR]) and the adverse outcome Cytokine Release Syndrome (CRS).

2. Results

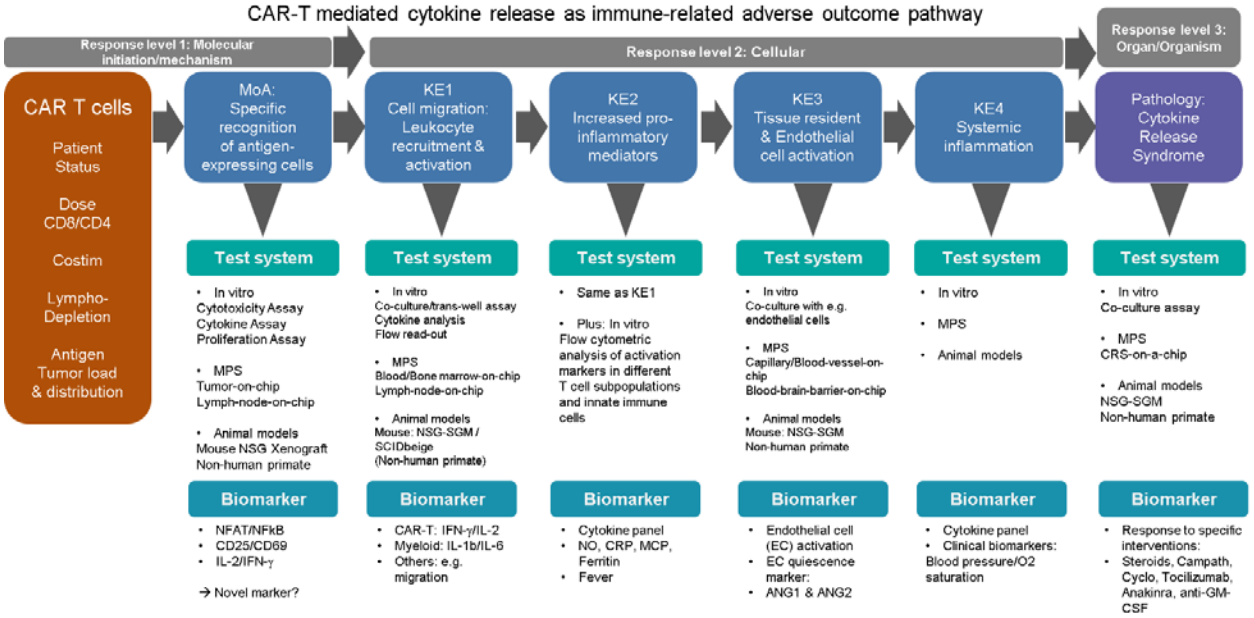

Figure 1: Preliminary irAOP for MoA CART-T and adverse outcome CRS

3. Discussion

To further develop and refine the preliminary irAOP for CAR-T, we conducted a survey among the EFPIA partners involved in WP 2. The results of this survey will provide additional information for the currently available test systems (in vitro and in vivo) and will help to refine the irAOP for CAR-T and to develop the irAOP for BiTE (bispecific T-cell engagers).

4. Conclusion

The irAOP for MoA CAR-T and adverse outcome CRS will guide the development of novel test systems to assess the (proposed) KEs that finally lead to CRS. Likewise, such irAOPs for additional MoAs (BiTE, CPI) will guide the development of novel test systems for these MoAs and AOPs, respectively. Furthermore, the continuous improvement of the irAOPs will also provide a better insight on the existing gaps in these AOPs.

References

1. Ankley, G.T., et al., *Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment.* Environ Toxicol Chem, 2010. **29**(3): p. 730-41.

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