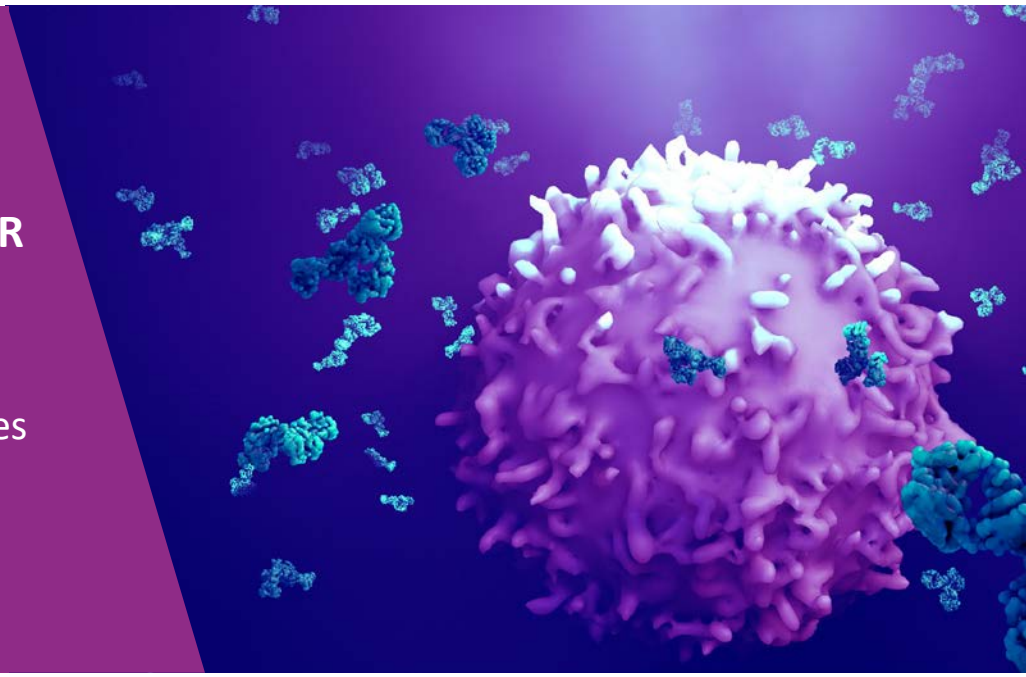
imSAVAR

IMMUNE SAFETY AVATAR

Nonclinical mimicking of the immune system effects of immunomodulatory therapies



Deliverable 4.5

First iteration to characterize molecular mechanism leading to immune-related adverse events

DELIVERABLE REPORT

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 853988.
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Abstract

Work package 4 (WP4) focuses on the development of biomarkers for predicting the risk of observing harmful adverse outcomes in first-in-human (FIH) studies of immunomodulatory therapeutics. Current preclinical models to assess safety of immunotherapies are often species-dependent and incomplete, since they reflect only limited areas of the human immune system, which often leads to wrong predictions of human immune-related adverse events (irAEs). Hence, WP4 aims at establishing biological characteristics (biomarkers) that are measurable and evaluable and can be integrated into safety models in order to (i) assess if the model mimics the underlying human biological processes leading to an immune-related adverse outcome as closely as possible, to (ii) assess if the biomarker is reliably predicting the risk of harmful adverse outcomes in FIH studies, and to (iii) support safe starting dose selection for FIH studies.

In imSAVAR four firstly defined mode of actions (MoAs) of immunomodulatory therapeutics will be addressed and require development and confirmation of biomarkers: (i) CAR (chimeric antigen receptor) T-cells, (ii) BiTEs (bispecific T-cell engagers), (iii) CPI (checkpoint inhibitors) and (iv) IL-2 as first chosen MoA for inflammatory disease therapeutics. We align biomarker development with immune-related AOPs (irAOPs) to foster a common understanding of the processes triggered through a molecular initiating event and eventually leading to adverse outcomes.

With Deliverable D4.5, we describe a first version of a machine-readable, interactive and expandable model for molecular mechanisms leading to rhIL-2 (recombinant human interleukin-2) mediated skin rash. The model is a public demonstrator, is continuously being developed and serves as a proof-of-concept study for other irAOPs addressed in imSAVAR.

Document Information

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1. Background

Immune-related AOP for rhIL-2 mediated skin rash: The development of biomarkers is guided by irAOPs (immune-related adverse outcome pathways). IrAOPs are conceptional frameworks describing the current knowledge of biological effects triggered by an initiating event leading to adverse health effects. WP3 conducted a comprehensive literature search to reveal detailed descriptions of key events and key event relationships for rhIL-2-mediated reactions. Based on this knowledge base WP3 developed irAOPs for rhIL-2-mediated skin rash, vascular leakage and hepatoxicitiy as described in deliverable D3.1.

Representations for immune-related AOPs: Most AOPs are represented using static formats as e.g. graphics outlining the sequence of key events leading to an adverse event. Details of the content and relations between key events are described using a textual format. However, a static and pure textual representation of irAOPs hinders sharing of knowledge and cooperative development. Hence, during the 3rd imSAVAR stakeholder workshop and imSAVAR science days (hold in 04/2021 and 05/2021) we discussed best ways and novel concepts of irAOP representations among imSAVAR partners as well as external stakeholders. We identified a broad agreement in the need for machine readable representations for irAOPs such that interactive modelling of key events and key event relationships will be possible. Digital representations of irAOPs facilitate shared development, evaluation and refinement of mechanisms leading to immune-related adverse events. As a proof-of-concept study and a first iteration to characterize molecular mechanisms leading to immune-related adverse events we selected the irAOP describing rhIL-2 mediated skin rash. For details of the static representation of the irAOP see Figure 2 in D3.1.

Biomarkers for rhIL-2 mediated skin rash: Biological markers (biomarkers) as measurable and evaluable indicators for biological processes support the development and interpretation of novel tools and models for early non-clinical safety assessment. Based on the irAOP for rhIL2-mediated skin rash (see Figure 2 in D3.1) and the knowledgebase resulting from the literature search of WP3 we transferred and extended the static irAOP description (as outlined in D3.1) to a machine-readable representation. In detail, we used the MINERVA (Molecular Interaction NEtwoRk VisuAlization) tool for a machine-readable, interactive and expandable representation of molecular mechanisms triggering rhIL-2 mediated skin rash.

2. Methods – The MINERVA platform

MINERVA (Molecular Interaction NEtwoRk VisuAlization) Platform1-3 is a standalone webserver for visual exploration, analysis and management of molecular networks encoded in systems biology formats, including CellDesigner, SBML and SBGN. MINERVA is a webservice using the Java Server Faces 2 technology. The server side, including data parsing, integration, annotation and verification, is implemented in Java 8. The platform uses the Postgres SQL database for data storage and the Hibernate framework as a middle layer between web server and database. The user web-interface is generated in JavaScript and content is visualized by OpenLayers/Google Maps API. Visualization of uploaded networks generated by the platform is accessible via a web browser to all viewers with the weblink to the resource.

3. Results

In 03/2021 WP4 organized an interactive workshop to define a first version of a molecular interaction network describing key events of rhIL-2 mediated skin rash. The workshop was hold by UNILU and

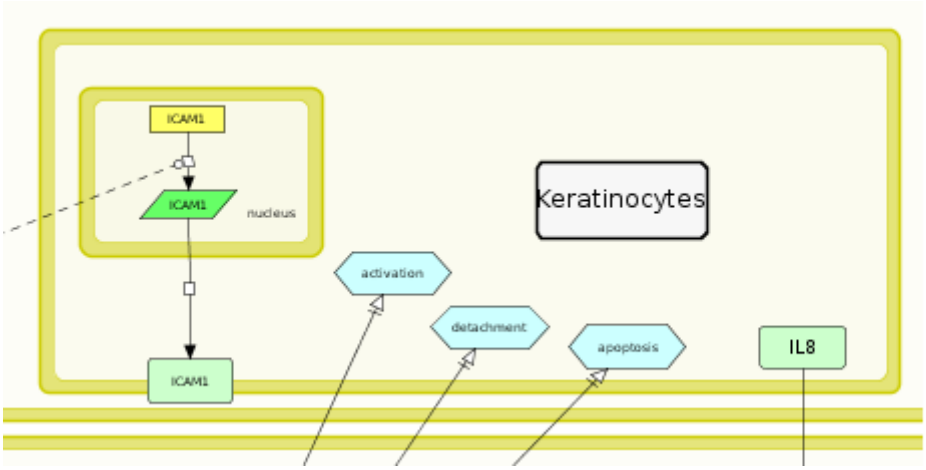
included participants from WP3, WP2 and WP4. The representation of the network as it was defined at the workshop and as it is continuously developed further is available as a public demonstrator at:

URL of a public demonstrator depicting key events and their relationships promoting rhIL-2 mediated skin rash:

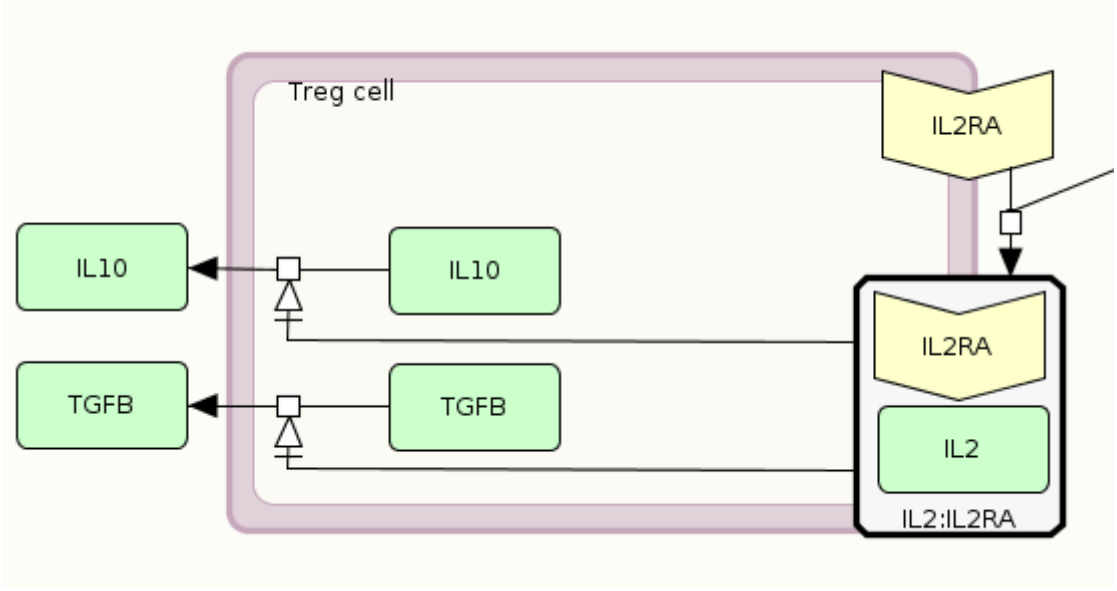
https://pathwaylab.elixir-luxembourg.org/minerva/index.xhtml?id=il2_skin

Epidermis, dermis and blood vessel form the major compartments of the skin involved in rhIL-2 mediated skin rash. For each of the compartments we added a network of interacting molecules as well as associations to signalling pathways and phenotypes, as exemplarily shown for two extracts of the network:

Extract 1 of the MINERVA network for rhIL-2 mediated skin rash depicting key events in keratinocytes:



Extract 2 of the MINERVA network for rhIL-2 mediated skin rash depicting key events in Treg cells:



Based on the results of this proof-of-concept model we established the **irAOP working group (lead: UNILU)** to continuously develop and improve the network described above and to transfer the concept to other selected irAOPs as defined in WPs 2&3.

In summary, we used the MINERVA platform as the modelling method of choice to establish machine readable and sharable representations of irAOPs. With that a first iteration to characterize molecular mechanisms leading to rhIL2-mediated skin rash was implemented. We used the knowledgebase as compiled in the literature search of WP3 as a basis to define interactions between molecules, signalling pathways and adverse pathology. The MINERVA network for rhIL-2-mediated skin rash (see URL in table above) will continuously be developed within the irAOP working group and will also serve as a guide to characterize and evaluate the (molecular) mechanism for other irAOPs addressed in imSAVAR.

4. References

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