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INTRODUCTION

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An overview of immune safety avatar: mimicking the effects of immunomodulatory therapies on the immune system

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ABSTRACT

Innovative therapeutics like biologicals that modulate the immune system are on the rise. However, their immune-modulating characteristics can also lead sometimes to the induction of adverse effects, by triggering unintended immune reactions. Due to the complexity and target-specificity of such therapeutics, these drug-induced adverse events could remain undetected during non-clinical development, if the test systems are, for example, animal-based, and only emerge in clinical development when tested in humans and subsequently lead to discontinuance of otherwise promising drug candidates. To identify adverse effects on the human immune system at an early stage, new approaches, assays, and technologies are needed. The Innovative Medicine Initiative (IMI) cooperation Immune Safety Avatar (imSAVAR) project aims to develop a tool for integrated non-clinical safety assessment for immune-modulatory new therapeutic drugs and clinical trial applications. To achieve this goal, imSAVAR has relied on the Adverse Outcome Pathway (AOP) framework to gather knowledge in a structured approach and to design, select or develop, when needed, appropriate test systems for prediction of the immune-related adverse outcomes. So far, the imSAVAR consortium has identified the "mode of action" for certain classes of drugs that needed improved risk assessment, including chimeric antigen receptor T cells (CAR T cells), immune checkpoint inhibitors (ICIs), and recombinant proteins (e.g. interleukin [IL]-2), has linked those to their immune-related adverse outcomes and has formulated literature-based immune-related AOPs (irAOPs). Models to measure those immune-specific perturbations were selected, adjusted, or newly developed. The imSAVAR work described in this special issue of *The Journal of Immunotoxicology* supports our understanding of immune-mediated adverse effects and their early discovery during development to improve the safety of innovative biomedicals.

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Main text

Challenges in the evaluation of the immunotoxicity of biotherapeutics

Innovative therapeutics such as immunomodulatory biologicals and advanced therapeutic medicinal products represent a new group of medications that selectively target and modulate components and functions of the immune system. They include recombinant proteins, monoclonal antibodies, cytokines, growth factors, gene therapy products, vaccines, cell-based products such as CAR-T-cells and many others (Carter und Lazar 2018; Johnson 2018). These drugs specifically either reduce inflammation as for autoimmune diseases and transplant rejections or activate immune cells to target cancer, and infections (Hansel et al. 2010). However, the non-clinical pharmacology and toxicology of these biotherapeutics differs from that of chemical entities (Johnson 2018; Leach et al. 2024). Most immunomodulatory effects elicited by biotherapeutics are intended and necessary for achieving clinical efficacy. Nonetheless, the range of immunomodulatory effects extends beyond therapeutic intentions, encompassing the activation or suppression of non-target immune cells and mediators, irreversible alterations to immune target cells/pathways, and adverse effects inherently linked to the intended pharmacological activity. These include, but are not limited to, severe infusion reactions, cytokine release syndrome (CRS), cellular and tissue damage, inflammation due to, for example, hypersensitivity reactions, increased susceptibility to infections, and oncogenesis (Da Sim et al. 2016). These adverse effects represent a concern in both the development and clinical application of biotherapeutics (Leach et al. 2024), underlining the need for predictive approaches in immunotoxicology. Such approaches must extend beyond mere risk assessment, aiming to provide translational relevance to predict clinical outcomes more accurately.

The selection of assays for assessing the immunotoxicity of biotherapeutics is tailored to each specific drug, varying significantly from one case to another (FDA/CDER 2023). In general, non-clinical animal studies are required for safety assessment of novel drugs but the predictive value of existing *in vivo* test systems used for immunotoxic evaluation of biotherapeutics, such as transgenic mouse models, is compromised by interspecies variances, notably in aspects like target expression, biological pathways, and genetic background (Marshall et al. 2023). Therefore, new human-based *in silico*, *in vitro*, and *ex vivo* assays and technologies are constantly emerging and evolving. However, it can be difficult for researchers to determine which tests best identify potential hazards associated with their molecule and which dosing and monitoring are best for the first-in-

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human clinical trial. Consequently, these test systems must then not only include a description of appropriate controls and deliver clear, quantifiable results but also demonstrate that they are suitable for their purpose. Understanding the specific molecular initiating event or mode of action is therefore important when determining which assay is most appropriate for evaluating potential hazards. It may also be beneficial to adopt frameworks such as the adverse outcome pathway concept from chemical toxicology to guide the process for assay selection used for the evaluation of biotherapeutics. This approach could also contribute to ongoing efforts to reduce or replace animal testing, reflecting the shift in legal and regulatory perspectives as scientific understanding evolves (Leach et al. 2024).

The imSAVAR project

In the wake of this rationale, the Immune Safety Avatar (imSAVAR) project, funded by the Innovative Medicines Initiative (IMI), formed in order to develop a standard for integrated non-clinical safety assessment for immune-modulatory new therapeutic drugs and clinical trial applications (imSAVAR 2022).

The concept of imSAVAR included a range of new improved tools to adequately assess the safety and efficacy profile of immuno-modulatory drugs and therapies with the integration of immune-specific biomarkers for models that adequately reflect diseases complexity and are able to predict reliably the immune related adverse events (imSAVAR 2021). In a tiered approach these new tools were developed and the platform was build up with: (a) the "mode of actions (MoAs)" for certain groups of drugs that need improved risk assessment, such as CAR T cells, CD3-bi-specific constructs, immune checkpoint inhibitors (ICIs), and recombinant proteins (e.g., IL-2), have been identified and immune-related pathologies leading to adverse effects have been described by applying the AOP concept, (b) existing and newly developed models such as cell and tissue models, OoC and *in vivo* models that reflect the immune-specific interaction have been selected, (c) the establishment of a platform, and (d) the outreach beyond the funding period for a long-term success of the whole concept and the continually improvement of safer therapies for patients. For more information, please visit the imSAVAR website (https://imsavar.eu/).

On the one side the efforts focused on the refinement and exploration of new models for different immuno-oncology MoAs (CAR T cells, CD3-bi-specific constructs, and ICIs). Moreover, the focus was and is on therapeutics for immuno-inflammatory diseases. The selection of relevant models for immuno-inflammatory safety assessments, either existing ones which can be refined or new ones using new technologies (e.g., disease modeling with human immune-competent organotypic and microphysiological systems) were the first steps. In the process, these models were looked at closer regarding their ability to reflect certain outcomes described in the clinics. Most models that rely on animals or are based on cells collected from healthy human donors were too simple and did not express the same pathway biology as seen in diversity of patients with disease. All this made a comparative assessment mandatory to consider differences in interaction, susceptibility, and adverse effects between healthy and patients derived cells or tissue.

The adverse outcome pathway (AOP) concept

Pathway-based approaches enhance safety assessment by providing deeper insights into the mechanisms leading to adverse outcomes. The question arose whether it would be possible to use comprehensive mechanistic understanding to inform about drug safety. The concept of Adverse Outcome Pathway (AOP) originates from regulatory toxicology and serves as a valuable tools to facilitate the extrapolation of data obtained at low biological level of organization, such as molecular and cellular-based methods, to outcomes observed in organs, individuals, or populations (Ankley et al. 2009). An AOP describes a logical sequence of causally-linked key events (KEs) at different levels of biological organization (molecular, cellular, tissue, organ) which follows exposure to a stressor and leads to an adverse outcome. AOPs are intended to capture existing knowledge concerning the biologically plausible and empirically-supported foundations for predicting apical toxicity from mechanistic data. Hence, AOPs can provide a scientific framework for integration of new testing paradigms by linking the understanding of mechanisms at the different biological levels with appropriate targeted test systems. By definition, KEs of the pathway have to be essential to trigger the outcome and be measurable in a clinical or laboratory setting. As KEs are measurements of biological state or change in state with regard to a control or reference, the confidence in a KE is dictated by the accuracy and precision with which that biological state can be measured (Villeneuve et al. 2014). Hence, KEs can serve as anchors to implement new non-animal methodologies such as complex and physiologically relevant, for example, patient-derived cell cultures, organ-on-a-chip and tissue models. By doing so, AOPs were envisioned as an important component of a new immunotoxicity paradigm shift that was expected to increasingly rely on mechanistic data.

The immune-related AOPs within the imSAVAR project

Exploiting AOPs in biomedical research is new. Recently, an international project, called CIAO (Modeling the Pathogenesis of **C**OV**I**D-19 using the **A**dverse **O**utcome Pathway framework), has explored the applicability of the framework to support systematic organization of the fast-evolving knowledge on COVID-19 pathogenesis (Nymark et al. 2021; Clerbaux et al. 2022a) (3/altex.2112161). A dozen AOPs depicting the perturbations triggered by SARS-CoV-2 and leading to diverse adverse outcomes were proposed and evidence supporting their occurrence highlighted knowledge gaps (Hogberg et al. 2022; Shahbaz et al., 2022; Clerbaux et al. 2022b). Interestingly, excessive inflammatory response is one of the main causes of severe and fatal COVID-19 and series of KEs capturing these events were tentatively developed within CIAO relying on the previously-proposed hub KEs, describing hallmarks of inflammation that can be independently measured (Villeneuve et al., 2018). The three hub KEs out of common similarities of inflammatory process across various tissues are (Figure 1): (1) Tissue resident cell activation, (2) Increased pro-inflammatory mediators, and (3) Leukocyte recruitment/activation. Based on this harmonization of inflammation-related KEs and their correlation in a modular structured AOP, the link between a series of AOPs could be drawn. Ever since, the number of linked AOPs that have inflammation integrated is increasing.

KEs leading to (excessive) inflammation might be the same whether triggered by chemicals, pathogens or drugs. Within the imSAVAR project, the concept of immune-related AOPs (irAOPs) was introduced as a framework to (i) define pathways' hypothesis into a structured approach that need to be proven with evidence, (ii) help to design and develop appropriate test systems, and (iii) identify relevant biomarkers for prediction of the immune-related adverse outcomes. Yet, the application of AOPs have never been used for immunotherapies before, and it was not guaranteed that it will be a useful and appropriate tool for biologicals and their immune-mediated adverse effects.

The initial step within imSAVAR was to formulate appropriate hypothesis on the potential biologicals-induced irAOPs based on

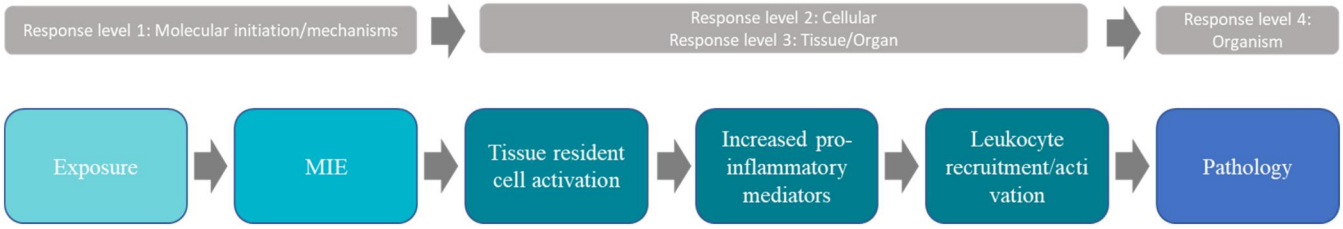

Figure 1. Tissue independent master pathway for inflammation representing sequential steps involved as defined by Villeneuve et al.

biological plausibility and to collect existing data to support evidence and to identify knowledge gaps and inconsistencies. A major limitation encountered was that hardly sufficient information about the underlying mechanisms was available. Even for diseases that have been the focus of extensive research in recent years, the mechanisms often remained unclear or were supported by only weak evidence. Based on these irAOPs, the project then moved forward to design, select, or develop (when needed) appropriate test systems. The selected models included advanced immune-competent multicellular test systems (*in vitro*, *ex vivo*, microphysiological systems such as organ-on-a-chip, and induced pluripotent stem cells) as well as elaborated animal disease models. This approach ensured a broad and innovative toolbox for exploring and understanding the immunotoxicity of biological therapeutics. In the next step, we looked at our approaches used for CRS in the regulatory context. The recent FDA guidance only requires the hazard to be identified with a relevant assay system, such as cytokine release assays (FDA/CDER 2023). Therefore, under these regulatory guidelines, there is no mandate for further refinement of current assays solely for the purpose of hazard identification. However, beyond the scope of regulatory compliance, there exists the potential to refine these assays to deepen the understanding of the mechanisms underlying drug-induced CRS. Such advancements could lead to better clinical translatability, the identification of more relevant biomarkers for patient stratification, and more precise predictions of dosing for the first-in-human (FiH) trials.

Brief introduction of the manuscripts of this special issue

The current issue collects eight manuscripts covering different aspects of efficacy and safety testing for immunomodulatory drugs and cells.

In the manuscript "*Using interactive platforms to encode, manage, and explore immune-related adverse outcome pathways*" by Alexander Mazein et al., the authors address the need for modeling and predicting adverse effects in immunotoxicology to improve non-clinical safety and efficacy assessments of immunomodulatory therapies (Mazein et al. 2024). For their integrated approach, they include the irAOP concept and an online available medicine disease map approach. This way they expanded the linear AOP into a conceptual molecular interaction model. This shows how knowledge related to immunotoxic events can be integrated, encoded, managed, and explored to benefit the field. This mapping and expansion of the AOP information in a computer-readable disease map format contributes to connection of data following the FAIR (findable, accessible, interoperable, and reusable) principles (Mortensen et al. 2022).

The manuscript "*Novel strategies to assess cytokine release mediated by CAR T cells based on the irAOP concept*" by Alb and colleagues shed some light on non-clinical safety assessment for immuno-oncology related novel CAR T cell immunotherapy (Alb et al. 2024). In immuno-oncology the non-clinical development of new and innovative immunotherapies struggles with inadequate *in vitro* and *in vivo* models unable to mimic the complexity of a human immune system in general and the altered immune system of a cancer patient in particular. With the focus to develop new models to assess cytokine release syndrome to overcome these hurdles, the authors developed the irAOP and brought it into the context of current challenges and pitfalls of non-clinical *in vitro* and *in vivo* models.

An actual application of a selected CRS-related assay utilizing a cytokine release assay (CRA) module of a preclinical human in vitro 3D co-culture platform called the Modular Immune *In Vitro* Construct (MIMIC®) is described by Dinhle et al. in "*Identifying CD19-targeted CAR-T cells induced immune profile through the MIMIC®-based cytokine release assay*" (Dinhle et al. 2024). Here potential effects induced by human CD4 and CD8 CD19-targeted CAR-T cells are evaluated in regard to changes in cytokine secretion and cell phenotype.

To make the transition in this special issue from immuno-oncology related therapies to models for immunomodulatory therapy safety assessment the first example for a biological is described in an interleukin-2 (IL-2) introduction part entitled "*Revival of IL-2 therapy – approaches from the past until today*" by Roser and colleagues. In this review, the Authors collected information about the first anti-cancer immunotherapeutic that received marketing authorization regarding its historical use and associated side effects, as well as the still ongoing search for new IL-2 variants with less adverse effects (Roser et al. 2024).

The manuscript "*Type 2 responses determine skin rash during recombinant interleukin-2 therapy*" by Sommer and associates describes the development of a literature-based irAOP to identify key players and mediators in recombinant IL-2 (recIL-2)-mediated skin rash. Subsequently, based on the irAOP the Authors hypothesized that initial recIL-2-dependent activation of group 2 innate lymphoid cells and possibly Type 2 T-helper cells seem to drive Type 2 driven immune responses responsible for the side effects in skin. Moreover, the Authors used the irAOP to identify knowledge gaps in regard to recIL-2 induced dermatitis which might be used to design experimental set ups to close these knowledge gaps in order to more adequately predict skin rashes in recIL-2-related therapies (Sommer et al. 2024).

The manuscript "*IL-2-mediated hepatotoxicity: Knowledge gap identification based on the irAOP concept*" by Roser and collagues focuses on recIL-2 induced hepatotoxicity utilizing the irAOP as a tool to provide an overview. They described in the manuscript their identified MoA as well as the main key players as potential read-outs or sources for biomarkers for the development of adequate pre-clinical models for safety assessment (Roser et al. 2024).

The manuscript "*Analyzing IL-2-induced vascular leakage with an irAOP as tool*" by Patricia Gogesch describes the development of an irAOP for recIL-2-mediated vascular leakage as one of the most important adverse outcomes. The Author provides a comprehensive overview of vascular leakage from an immunological point of view. Additionally, the Authors identified with the irAOP knowledge gaps and putative biomarkers for the improvement of safety assessment of recIL-2 derived immunotherapies (Gogesch et al. 2024).

The manuscript "*Fine tuning of the innate and adaptive immune responses by Interleukin-2*" by Christina Sakellariou focuses on the mechanistic immunological events triggered by IL-2 in order to better predict efficacy and safety of recIL-2 and IL-2 variants. The Author comprehensively describes the role of one of the key players of the innate and adaptive immune responses, the dendritic cells (DC). Moreover, the role of immune cells such as DC and T-cells in recIL-2 related pathways in cancer and autoimmune diseases is described (Sakellariou et al. 2024).

By presenting the findings from the imSAVAR consortium on the integrated non-clinical assessments of immunomodulatory therapy safety and efficacy, our aim is to highlight the critical nature of immune-mediated adverse effects and the importance of employing relevant models anchored in a detailed understanding of the underlying pathways. This effort is aimed at advancing the development and delivery of more effective and safer biological treatments for patients who urgently require them. This special issue of the *Journal of Immunotoxicology* serves as an output for disseminating knowledge on this significant challenge, contributing to the broader effort of enhancing therapeutic outcomes and patient safety in the field of immunomodulatory therapy.

Declaration of interest

The authors report there are no competing interests to declare.

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References

Alb M, Reiche K, Rade M, Sewald K, Loskill P, Cipriano M,. Maulana TI, van der Meer A, Weener A, Patel N, et al. 2024. Novel strategies to assess cytokine release mediated by chimeric antigen receptor T cells based on the adverse outcome pathway concept. J Immunotoxicol. 21(S1):S13–S28. doi: 10.1080/1547691X.2024.2345158.

Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, et al. 2009. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environ Toxicol Chem.* 29 (3), S. 730–741. DOI: 10.1002/etc.34.

Carter PJ, Lazar GA. 2018. Next generation antibody drugs: Pursuit of the 'high-hanging fruit'. Nat Rev Drug Discov. 17(3):197–223. doi: 10.1038/nrd.2017.227.

Clerbaux L-A, Amigó N, Amorim MJ, Bal-Price A, Batista Leite S, Beronius A, et al. 2022a. COVID-19 through adverse outcome pathways: Building networks to better understand the disease - 3rd CIAO AOP Design Workshop. ALTEX. 39(2):322–335. doi: 10.14573/altex.2112161.

Clerbaux L-A, Filipovska J, Muñoz A, Petrillo M, Coecke S, Amorim M-J, Grenga L. 2022b. Mechanisms leading to gut dysbiosis in COVID-19: Current evidence and uncertainties based on adverse outcome pathways. JCM. 11(18):5400. doi: 10.3390/jcm11185400.

Da Sim W, Park KH, Park HJ, Son YW, Lee SC, Park J-W, Lee J-H. 2016. Clinical characteristics of adverse events associated with therapeutic monoclonal antibodies in Korea. Pharmacoepidemiol Drug. 25(11):1279–1286. doi: 10.1002/pds.4049.

Dinh-Le T, Escobar J, Poisson L, Adkins K, Culubret MJ, Scheller L, et al. 2024. Identifying CD19-targeted CAR-T cell immune pathways in an in vitro human immune mimetic cytokine release assay. J Immunotoxicol. 21(S1):S29–S37. doi: 10.1080/1547691X.2024.2378729.

FDA/CDER. 2023. Non-clinical evaluation of the immunotoxic potential of pharmaceuticals. Guidance for Industry 2023. Online verfügbar unter https://www.fda.gov/media/169117/download, zuletzt geprüft am 04.04.2024.

Gogesch P, Iannazzo SO, Zimmermann T, Villenave R, Sewald K, Waibler Z. 2024. Analyzing IL-2-induced vascular leakage with an irAOP as tool. J Immunotoxicol. 21(S1):S79–S88. doi: 10.1080/1547691X.2024.2369123.

Hansel TT, Kropshofer H, Singer T, Mitchell JA, George A. J. T. 2010. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov. 9(4):325–338. doi: 10.1038/nrd3003.

Hogberg HT, Lam A, Ohayon E, Shahbaz MA, Clerbaux L-A, Bal-Price A, Coecke S, Concha R, De Bernardi F, Edrosa E, et al. 2022. The adverse outcome pathway framework applied to neurological symptoms of COVID-19. Cells. 11(21):3411. doi: 10.3390/cells11213411.

imSAVAR. 2021. Concept - imSAVAR. Online verfügbar unter https://imsavar.eu/concept/, zuletzt aktualisiert am 08.12.2021, zuletzt geprüft am 16.07.2022.

imSAVAR. 2022. Home - imSAVAR. Online verfügbar unter https://imsavar.eu/, zuletzt aktualisiert am 27.01.2022, zuletzt geprüft am 16.07.2022.

Johnson DE. 2018. Biotherapeutics: Challenges and opportunities for predictive toxicology of monoclonal antibodies. IJMS. 19(11):3685. doi: 10.3390/ijms19113685.

Leach MW, Rana P, Hu W, Mittapalli RK, Pinkstaff J, Potter D, Qiu XM, Ramaiah L, Rohde C, Xia F, et al. 2024. Translation of non-clinical to clinical safety findings for 27 biotherapeutics. Toxicol Appl Pharmacol. 484:116854. doi: 10.1016/j.taap.2024.116854.

Marshall LJ, Bailey J, Cassotta M, Herrmann K, Pistollato F. 2023. Poor translatability of biomedical research using animals - A narrative review. Altern Lab Anim. 51(2):102–135. doi: 10.1177/02611929231157756.

Mazein A, Shoaib M, Alb M, Sakellariou C, Sommer C, Sewald K, Reiche K, Gogesch P, Roser LA, Iannazzo SO, et al. 2024. Using interactive platforms to encode, manage and explore immune-related adverse outcome pathways. J Immunotoxicol. 21(S1):S5–S12. doi: 10.1080/1547691X.2024.2345154.

Mortensen HM, Martens M, Senn J, Levey T, Evelo CT, Willighagen EL, Exner T. 2022. The AOP-DB RDF: Applying FAIR principles to the semantic integration of AOP data using the research description framework. Front Toxicol. 4:803983. doi: 10.3389/ftox.2022.803983.

Nymark P, Sachana M, Leite SB, Sund J, Krebs CE, Sullivan K, Edwards S, Viviani L, Willett C, Landesmann B, et al. 2021. Systematic organization of COVID-19 data supported by the adverse outcome pathway framework. Front Public Health. 9:638605. doi: 10.3389/fpubh.2021.638605.

Roser LA, Sakellariou C, Lindstedt M, Neuhaus V, Dehmel S, Sommer C, Raasch M, Flandre T, Roesener S, Hewitt P, et al. 2024. IL-2-mediated hepatotoxicity: knowledge gap identification based on the irAOP concept. J Immunotoxicol. 21(S1):S60–S78. doi: 10.1080/1547691X.2024.2332177.

Roser LA, Sommer C, Iannazzo SO, Sakellariou C, Waibler Z, Gogesch P. 2024. Revival of recombinant IL-2 therapy _ approaches from the past until today. J Immunotoxicol. 21(S1):S38–S47. doi: 10.1080/1547691X.2024.2335219.

Sakellariou C, Roser LA, Schiffmann S, Lindstedt M. 2024. Fine tuning of the innate and adaptive immune responses by Interleukin-2. J Immunotoxicol. 21(S1):S89–S95. doi: 10.1080/1547691X.2024.2332175.

Shahbaz MA, De Bernardi F, Alatalo A, Sachana M, Clerbaux L-A, Muñoz A, Parvatam S, Landesmann B, Kanninen KM, Coecke S. 2022. Mechanistic understanding of the olfactory neuroepithelium involvement leading to short-term anosmia in COVID-19 using the Adverse Outcome Pathway framework. Cells. 11(19):3027.doi: 10.3390/cells11193027.

Sommer C, Neuhaus V, Gogesch P, Flandre T, Dehmel S. 2024. Type 2 responses determine skin rash during recombinant interleukin-2 therapy. J. Immunotoxicol. 21(S1):S48–S59. doi: 10.1080/1547691X.2024.2343359.

Villeneuve DL, Landesmann B, Allavena P, Ashley N, Bal-Price A, Corsini E, Halappanavar S, Hussell T, Laskin D, Lawrence T, et al. 2018. Representing the process of inflammation as key events in Adverse Outcome Pathways. Toxicol Sci. 163(2):346–352. doi: 10.1093/toxsci/kfy047.

Villeneuve DL, Crump D, Garcia-Reyero N, Hecker M, Hutchinson TH, LaLone CA, Landesmann B, Lettieri T, Munn S, Nepelska M, et al. 2014. Adverse outcome pathway (AOP) development I: Strategies and principles. Toxicol Sci. 142(2):312–320. doi: 10.1093/toxsci/kfu199.