

April 2017

OECD ADVERSE OUTCOME PATHWAY

Project Submission Form

If you require further information please contact the OECD Secretariat Delrue
(Nathalie.delrue@oecd.org)

Return completed forms to our generic account (env.tgcontact@oecd.org), and Nathalie

PROJECT TITLE

Inhibition of JAK3 leading to impairment of TDAR

SUBMITTED BY (Country / European Commission / Secretariat)

Japan

DATE OF SUBMISSION TO THE SECRETARIAT

Nov. 30, 2018

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	Japan
Agency/ministry/Other:	AOP Working Group, Testing Methodology Committee, The Japanese Society of Immunotoxicology
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PROJECT CATEGORY

Development of an AOP - applicable to a chemical category

Select the development tool to be used

AOP-Wiki Effectopedia

Guidance document related to AOP development including its evaluation

Knowledge management tool for supporting AOP development including its evaluation

April 2017

Other, please specify below

If other category, please specify:

PROJECT DESCRIPTION

Please provide sufficient information to facilitate the review of the project submission by the OECD secretariat and the Extended Advisory Group with respect to its suitability to be included in the workplan of the AOP programme.

Signal transduction among immune-related cells is dependent on cytokines interacting with cell surface cytokine receptors as well as direct cell-to-cell interaction. Cytokines have a wide range of influences on lymphocyte/leukocyte chemotaxis, proliferation, differentiation and activation.

Some cytokine receptors require activation via Janus kinase (JAK)- Signal Transducers and Activator of Transcription (STAT) system. When a cytokine binds to its specific cytokine receptor, the cytokine receptors form dimers that localize near the JAK molecules. JAK is then activated and phosphorylates the adjacent cytokine receptors. STATs bind to the phosphorylated cytokine receptor sites, and the bound STATs are then phosphorylated by the activated JAK. The phosphorylated STAT dimerizes and translocates to the nucleus where it binds to the promoter regions of cytokine genes triggering the transcription of cytokine genes.

Inhibition of JAK family has the potential to influence on a wide range of immune responses. Here, we will focus on one of the JAK family, JAK3. JAK3 is required for signal transduction by cytokines through the common gamma (γ) chain of interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. These cytokines have broad ranging effects on the T-cell immune response. Therefore, impairment of JAK3 can result in an alteration in immune responses mediated by these cytokines. We propose to develop an AOP for the inhibition of JAK3 (MIE) leading to the impairment of T cell-dependent antibody response (TDAR, AO). TDAR is affected by the immunosuppressive conditions, is one of the major endpoints in preclinical immunotoxicity studies, and has the regulatory relevance. In the proposed AOP, JAK3 selective inhibitors (e.g. Tofacitinib) will be used to trigger the following events; 1. blockade of STAT5 phosphorylation, 2. suppression of binding of STAT5 to the promoter regions of cytokine genes and 3. suppression of IL-2 and IL-4 production. These three events correspond to KE1, KE2 and KE3, respectively as laid out in the flow diagram below.

Note: For AOP Development projects please indicate the extent of the pathway to be described (i.e. the anchor points), the intermediate events that are likely to be addressed, the state of current development, the degree to which this pathway is already understood and described in the literature, and the expectation on the availability of evidence to support the AOP. **Proposers should also indicate if and how the AOP is associated to any regulatory toxicological endpoints (e.g. acute or chronic toxicity, toxicity to reproduction etc.)** Please provide references, links or attachments for supplementary information.

PROJECT PLANNING

In this section, please provide an indication of when the project is likely to commence and the expected duration. Please also make reference to any particular milestones or external factors that will influence project planning, and if the project is linked to programmes of particular organisations or consortia.

The AOP Working Group of the Testing Methodology Committee in the Japanese Society of Immunotoxicology will develop several AOPs for immunotoxicity in the next three years.

The timeline of the development of the present AOP is as follows:

Nov., 2018: to submit the AOP development

Jun., 2019: to complete AOP Wiki input and submit internal review of the AOP

Dec., 2019: EAGMST review

FLOW DIAGRAM

In this section, please provide a flow diagram of the proposed AOP, including the MIE, KEs at the various stages (molecular interaction, cellular response, organ response) and the AO.

