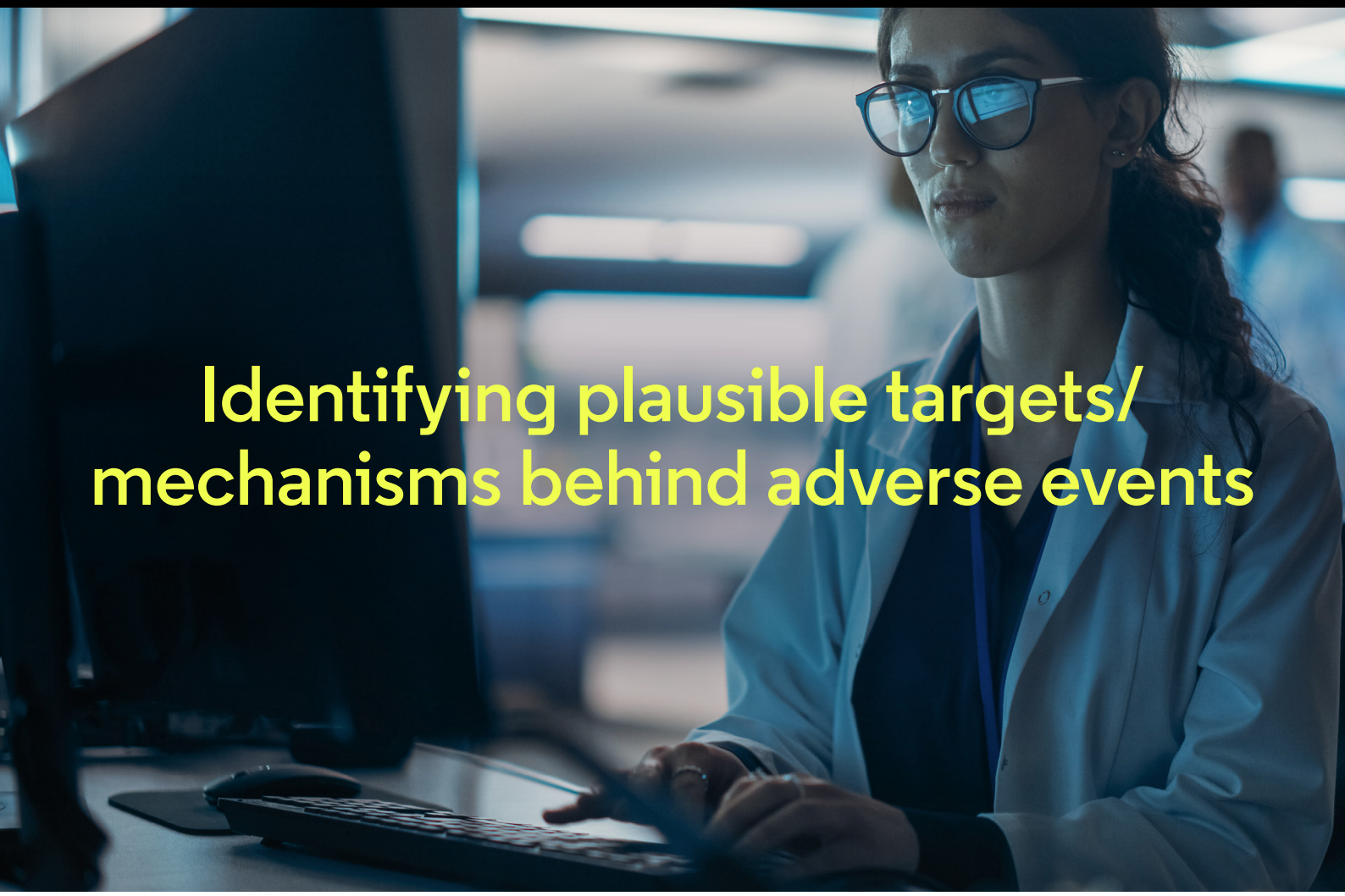


Identifying plausible targets/ mechanisms behind adverse events

Possible mechanisms associated with the anaphylactoid reaction observed in rats.

This case study how OFF-X's Translational Safety Intelligence can be used to identify mechanisms potentially associated with unexpected toxicities observed in rats.

During preclinical safety studies, unpredictable toxicities can occur when assessing investigative new molecular entities. Understanding the cause and mechanism behind these toxicities can help in risk assessment and influence medicinal chemistry design strategies for risk reduction.

During a toxicology study in rats, an investigative compound caused a set of allergy-type symptoms akin to anaphylactic/anaphylactoid reaction. These symptoms were characterized by rapid-onset itching, red skin, red and watery eyes and labored breathing:

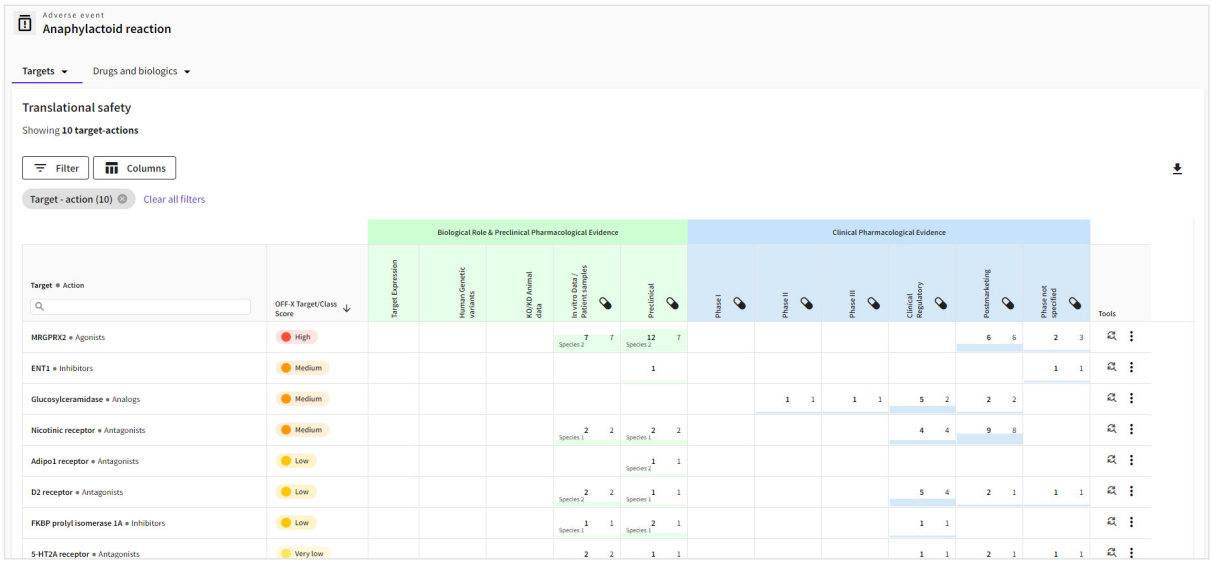
- No link to primary target
- No activity detected in secondary pharmacology screening studies to identify potential off-target mechanism(s).

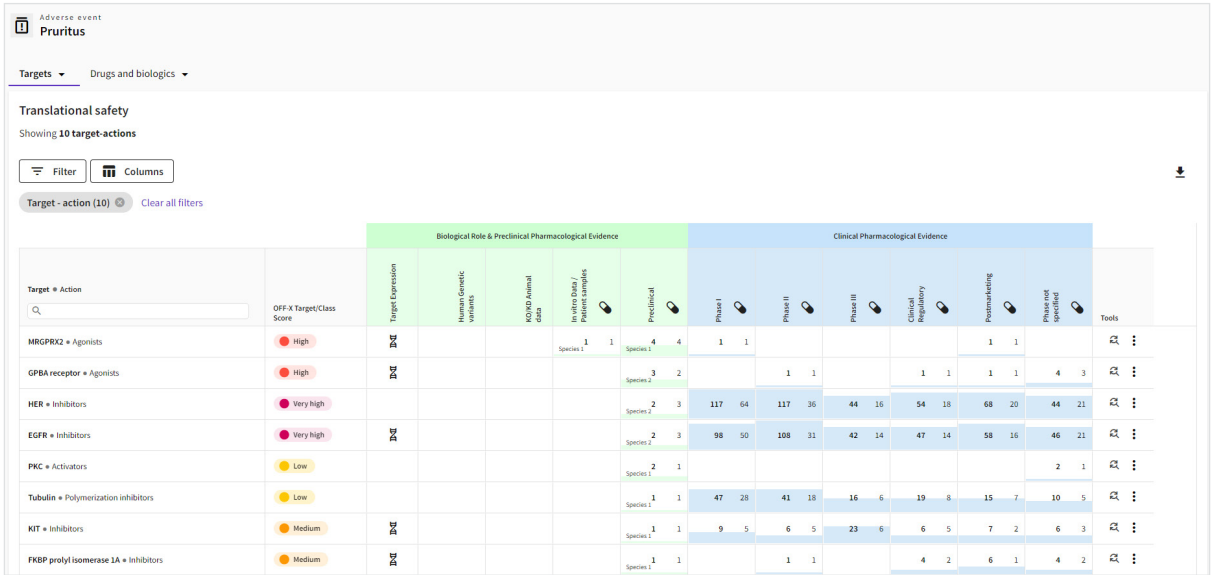
Clarivate™

Starting point: Adverse event

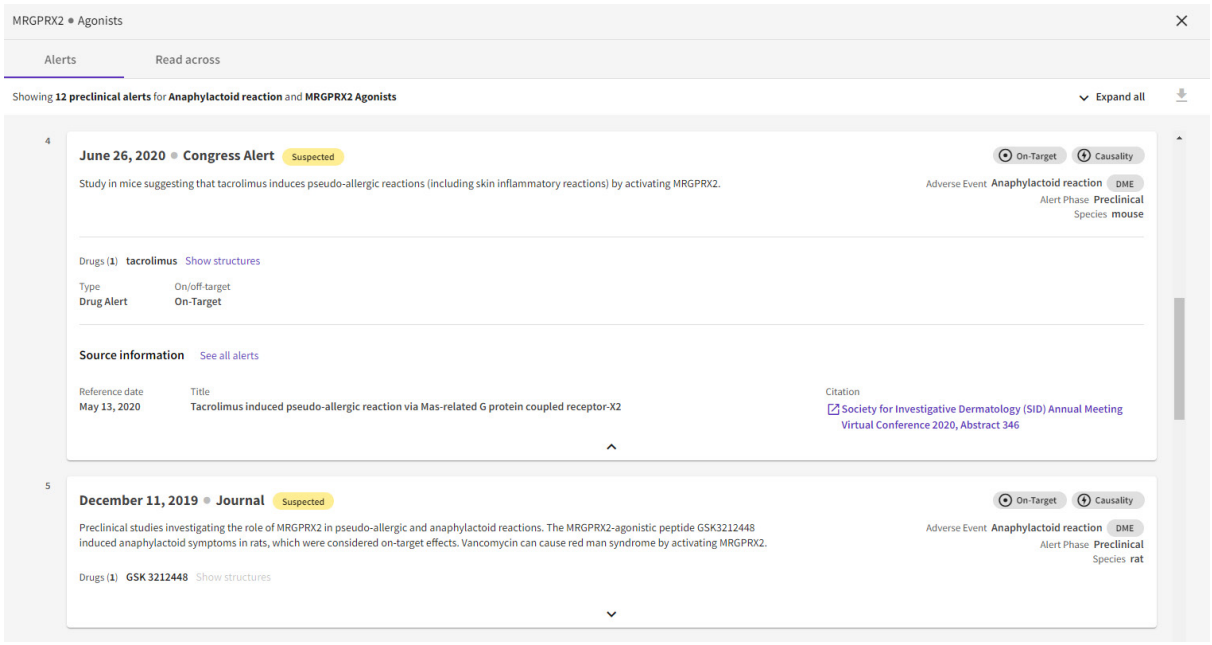
Each adverse event (e.g. anaphylactoid reaction, pruritus) was assessed using the OFF-X Translational Safety view.

Targets associated with preclinical and/or clinical evidence of causing the adverse events under review are shown:





Numbers on the tables are clickable and provide quick access to a manually curated summary of each publication backing these associations and links to the original data source.



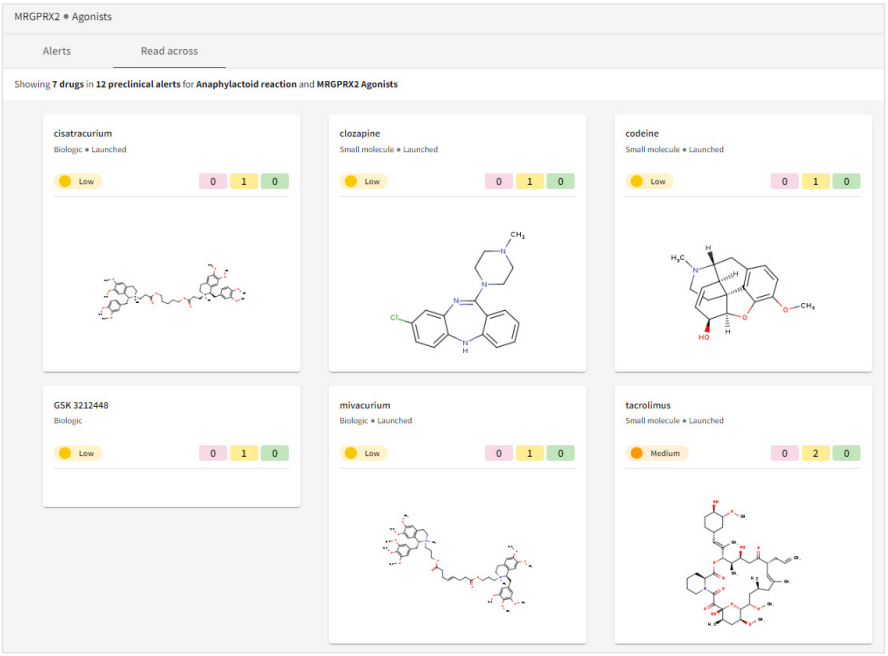
Potential target list for further investigation

Several targets were ruled out when secondary pharmacology screening data confirmed the compound under study lacked activity. MRGPRX2 was a common target across all adverse events. Follow-up investigation focused on MRGPRX2.

Adverse event	Number of targets identified	Potential targets to investigate
Anaphylactoid reaction	5	MRGPRX2 (agonist) FKBP propyl isomerase 1A (inhibitor)
Anaphylactic reaction	14	Ig epsilon chain C region (inhibitor) GITR (agonist) TFPI (inhibitor) Complement C1q (interacting agents) Fc fragment IgG receptor Ia, Ib, IIa, IIb (interacting agents) MRGPRX2 (agonist)
Red man syndrome	2	Lipid II MRGPRX2 (agonist)
Pruritus	31	TRPC4 (activators) EGFR (inhibitors) Her (inhibitors) GPBA receptor (agonists) FKBP propyl isomerase 1A (inhibitor) 50S ribosomal protein KIT (inhibitors) MRGPRX2 (agonist) Tubulin polymerization inhibitors PKC activators MRGPRX1 (agonist)

MRGPRX2: Mechanistic and translational information

The mechanism of agonism of MRGPRX2 appears to drive mast cell degranulation causing a pseudo-allergic reaction. Effects have been demonstrated in mice, rats, and humans. A number of molecules with MRGPRX2 agonist activity have been tested preclinically or clinically.



PRP Pharmacology Research & Perspectives Open Access

ORIGINAL ARTICLE | Open Access

MrgX2 is a promiscuous receptor for basic peptides causing mast cell pseudo-allergic and anaphylactoid reactions

Jak Grimes, Sapna Desai, Neil W. Charter, James Lodge, Rita Moita Santos, Albert Isidro-Llobet, Andrew M. Mason, Zining Wu, Lawrence A. Wolfe III, Lakshmi Anantharaman ... See all authors

Nature. 2015 Mar 12;519(7542):237-41. doi: 10.1038/nature14022. Epub 2014 Dec 17.

Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Benjamin D McNeil [1], Priyanka Pundir [2], Sonya Meeker [3], Liang Han [1], Bradley J Undem [3], Marianna Kulka [4], Xinzhong Dong [5]

› Cell Immunol. 2018 Oct;332:121-128. doi: 10.1016/j.cellimm.2018.08.005. Epub 2018 Aug 10.

Mivacurium induce mast cell activation and pseudo-allergic reactions via MAS-related G protein coupled receptor-X2

Delu Che [1], Jue Wang [1], Yuanyuan Ding [1], Rui Liu [1], Jiao Cao [1], Yongjing Zhang [1], Yajing Hou [1], Hongli An [2], Zijun Gao [3], Tao Zhang [4]

346
Tacrolimus induced pseudo-allergic reaction via Mas-related G protein coupled receptor-X2
X. Du[1], Y. Zheng[1], B. Peng[1], D. Che[2], Y. Hao[1], S. Geng[1]
[1]Department of Dermatology, Northwest Hospital, The Second Hospital Affiliated to Xi'an Jiaotong University, Xi'an, Shaanxi, China, [2]School of Pharmacy, Xi'an Jiaotong University, Xi'an, China
Tacrolimus is widely used in atopic dermatisis (AD), but the side effects of topical application effect the patient's compliance with medication, such as itching and burning, of which the mechanism is not clear. Recent studies have revealed that Mas-related G protein-coupled receptor X2 （MRGPRX2, a receptor on mast cells, mediating pseudo-allergic reaction in many contact dermatitis caused by topical drugs, which is similar to the side effects of tacrolimus. In this study, the mechanism in pseudo-allergic reaction caused by tacrolimus was investigated. Wild-type (WT) and MrgprB2-/- mice were used to observed local inflammation by Haematoxilin & Eosin and immunofluorescence staining. Release of tryptase, histamine and MCP-1 were measured in LAD2 cells with specific knockdown targeting MRGPRX2 by siRNA. We found WT mice exhibited inflammatory reaction in dorsal skin and footpad induced by tacrolimus, while MrgprB2-/- mice showed slighter reaction. The level of tryptase, histamin and other inflammatory cytokines were lower in mutated mice. Downregulation of MRGPRX2 resulted in the reduced degranulation of LAD2 cells. These results reveal tacrolimus could induce pseudo-allergic reaction via MRGPRX2/MrgprB2 in human/mice.

Studies that could support a preclinical investigational plan for the current compound include:

- In vitro binding/cellular activity at MRGPRX2.
- In vitro mast cell degranulation assay.

Contact our experts at:

lifesciences.support@clarivate.com

clarivate.com