

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).

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:

Adverse event

Anaphylactoid reaction

TargetsDrugs and biologics

Translational safety

Showing 10 target-actions

Filter

Columns

Target-action (10)Clear all filters

TargetAction	OFF-X Target/Class Score	Biological Role & Preclinical Pharmacological Evidence					Clinical Pharmacological Evidence							Tools
		Target Expression	Human Genetic variants	Off-Target Animal data	In vitro Data / Patient samples	Preclinical	Phase I	Phase II	Phase III	Clinical Regulatory	Pharmaco-marketing	Phase not specified		
MRGPRX2Agonists	High				77	127					66	23		
ENT1Inhibitors	Medium					1						11		
GlucosylceramidaseAnalogues	Medium						11	1	11	52	22			
Nicotinic receptorAntagonists	Medium				22	22				44	98			
Adipo1 receptorAntagonists	Low					11								
D2 receptorAntagonists	Low				22	11				54	21	11		
FKBP prolyl isomerase 1AInhibitors	Low				11	21				11				
5-HT2A receptorAntagonists	Very low				22	11				11	21	11		

Adverse event

Pruritus

Targets

Drugs and biologics

Translational safety

Showing 10 target-actions

Filter

Columns

Target - action (10)

Clear all filters

Target + Action	OFF-X Target/Class Score	Biological Role & Preclinical Pharmacological Evidence						Clinical Pharmacological Evidence							Tools
		Target Expression	Human Genetic variants	Off-Target Animal data	In vitro Data / Patient samples	Preclinical	Phase I	Phase II	Phase III	Clinical Regulatory	Postmarketing	Phase not specified			
MRGPRX2 + Agonists	High	DE			Species 1 1	Species 1 4 4	1 1				1 1				
GPBA receptor + Agonists	High	DE				Species 1 3 2		1 1		1 1	1 1	4 3			
HER + Inhibitors	Very high	DE				Species 1 2 3	117 64	117 36	44 16	54 18	68 20	44 21			
EGFR + Inhibitors	Very high	DE				Species 1 2 3	98 50	108 31	42 14	47 14	58 16	46 21			
PKC + Activators	Low					Species 1 2 1						2 1			
Tubulin + Polymerization inhibitors	Low					Species 1 1 1	47 28	41 18	16 6	19 8	15 7	10 5			
KIT + Inhibitors	Medium	DE				Species 1 1 1	9 5	6 5	23 6	6 5	7 2	6 3			
FKBP prolyl isomerase 1A + Inhibitors	Medium	DE				Species 1 1 1		1 1		4 2	6 1	4 2			

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.

MRGPRX2 • Agonists

Alerts

Read across

Showing 12 preclinical alerts for Anaphylactoid reaction and MRGPRX2 Agonists

4

June 26, 2020 • Congress Alert

Suspected

On-Target

Causality

Study in mice suggesting that tacrolimus induces pseudo-allergic reactions (including skin inflammatory reactions) by activating MRGPRX2.

Adverse Event

Anaphylactoid reaction

DME

Alert Phase

Preclinical

Species

mouse

Drugs (1)

tacrolimus

Show structures

Type

On/off-target

Drug Alert

On-Target

Source information

See all alerts

Reference date

May 13, 2020

Title

Tacrolimus induced pseudo-allergic reaction via Mas-related G protein coupled receptor-X2

Citation

Society for Investigative Dermatology (SID) Annual Meeting Virtual Conference 2020, Abstract 346

5

December 11, 2019 • Journal

Suspected

On-Target

Causality

Preclinical studies investigating the role of MRGPRX2 in pseudo-allergic and anaphylactoid reactions. The MRGPRX2-agonistic peptide GSK3212448 induced anaphylactoid symptoms in rats, which were considered on-target effects. Vancomycin can cause red man syndrome by activating MRGPRX2.

Adverse Event

Anaphylactoid reaction

DME

Alert Phase

Preclinical

Species

rat

Drugs (1)

GSK 3212448

Show structures

Potential target list for further investigation

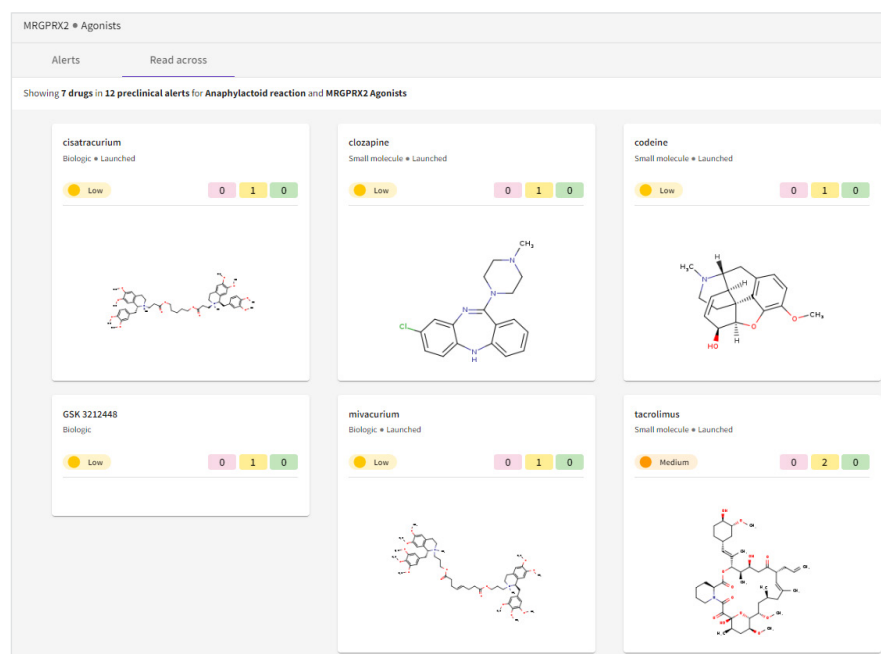
Several targets were ruled out when secondary pharmacology screening data confirmed the compound under study lacked activity. MRGPRX2 was a common target across all adverse events. Follow-up investigation focused on MRGPRX2.

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 1a, 1b, 1la, 1lb (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)

3

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.



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 Che¹, Jue Wang¹, Yuanyuan Ding¹, Rui Liu¹, Jiao Cao¹, Yongjing Zhang¹, Yajing Hou¹, Hongli An², Zijun Gao³, Tao Zhang⁴

346

Tacrolimus induced pseudo-allergic reaction via Mas-related G protein coupled receptor-X2

X. Du¹, Y. Zheng¹, B. Peng¹, D. Che¹, Y. Hao¹, S. Geng¹

¹Department of Dermatology, Northwest Hospital, The Second Hospital Affiliated to Xi'an Jiaotong University, Xi'an, Shaanxi, China, ²School of Pharmacy, Xi'an Jiaotong University, Xi'an, China

Tacrolimus is widely used in atopic dermatitis (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 MrgrprB2^{-/-} mice were used to observed local inflammation by Haematoxin & 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 MrgrprB2^{-/-} 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/MrgrprB2 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

© 2024 Clarivate. Clarivate and its logo, as well as all other trademarks used herein are trademarks of their respective owners and used under license.