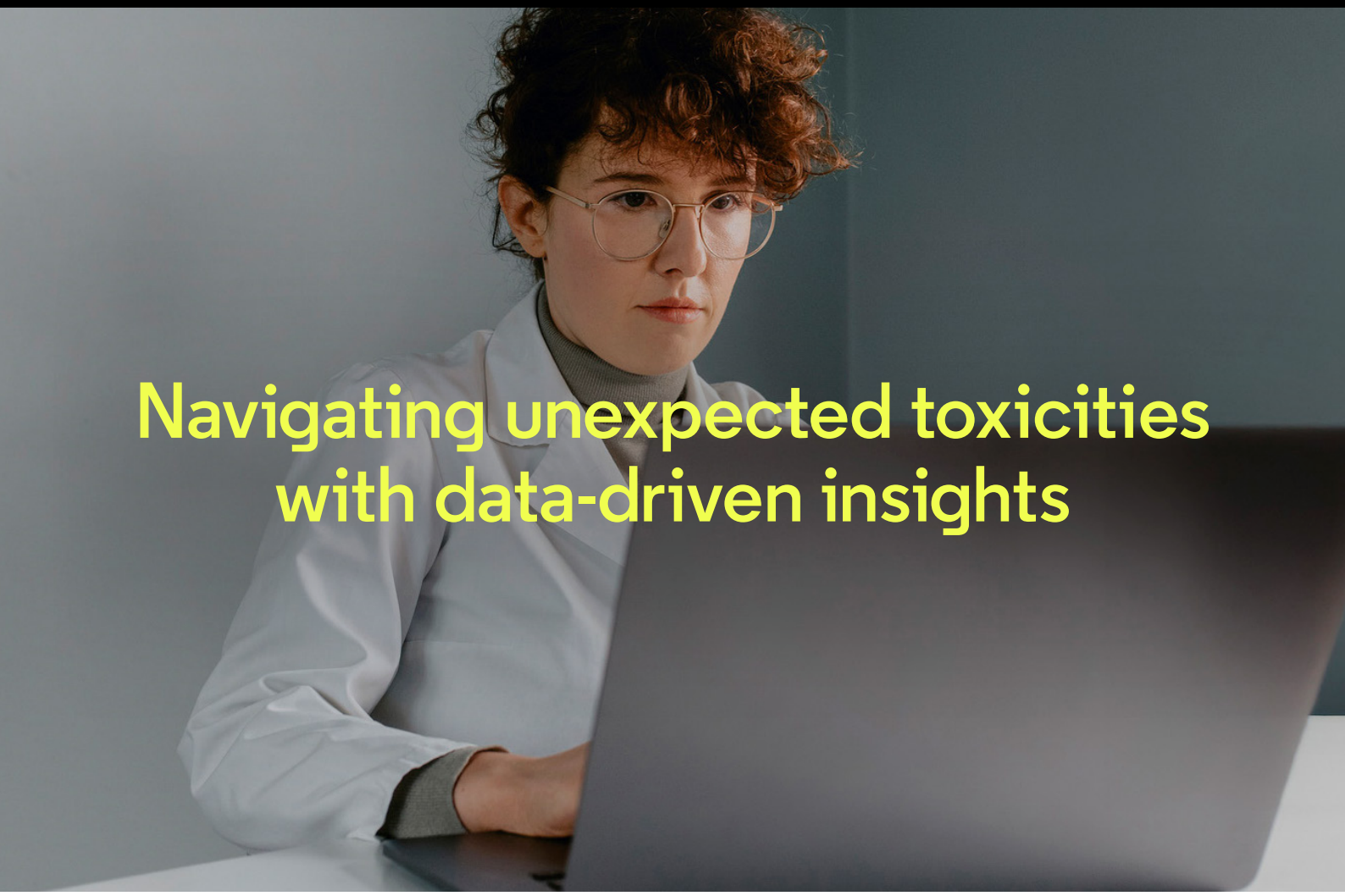


Navigating unexpected toxicities with data-driven insights

Understanding the causes behind unanticipated toxicity findings to guide experimental studies and support de-risking strategies.

Monitoring and understanding the preclinical and clinical safety of drug candidates within the same class as your drug of interest can unveil critical safety insights to inform your risk management plans.

In this case study we explore the insights OFF-X offers to support hypotheses for an unexpected phase 2 trial discontinuation due to serious adverse events.

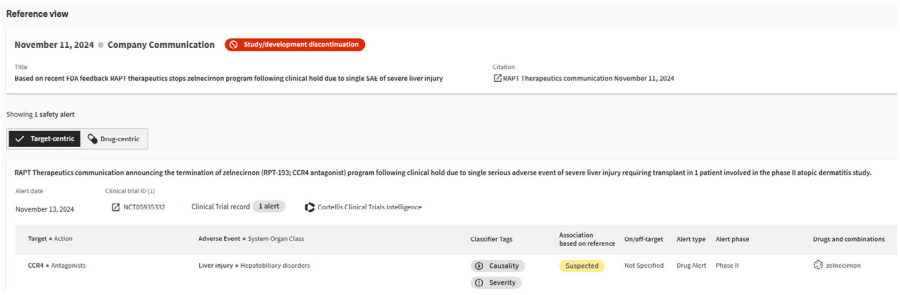
Confidently inform your risk management plans

Clarivate

1. Starting point: keeping track of unexpected toxicity events

OFF-X empowers you to easily keep up with critical safety information impacting drugs and targets of interest with daily updates from multiple data sources delivered straight to your inbox. In this case, OFF-X alerts us about a recent drug development discontinuation due to a serious adverse event of liver injury reported in a phase 2 atopic dermatitis study. Let's explore what information is available on OFF-X to help explain this unexpected event.

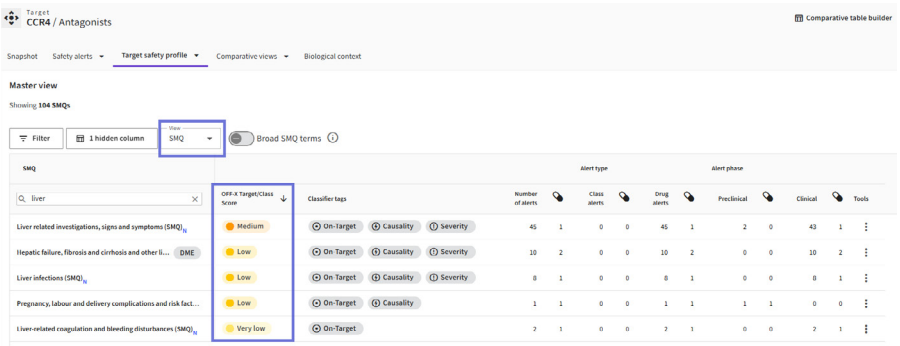
Figure 1: Notification of a study discontinuation due to a serious adverse event



2. Evaluating the safety profile of the target

First, we assess the safety profile of the target the drug asset binds to, the receptor CCR4. For this analysis, we want to look at Standardised MedDRA Queries (SMQs), which are validated groupings of terms representing a condition of interest. We narrow down the results of the table by searching for 'liver', and we can observe that for this target, there is medium evidence for liver symptoms and low evidence for liver damage[1].

Figure 2: Assessing the safety profile of CCR4 antagonists



[1] Based on the OFF-X advanced rule-based algorithms that measure the evidence of associations, ranking level of association between a drug and an adverse event, or a target class and an adverse event.

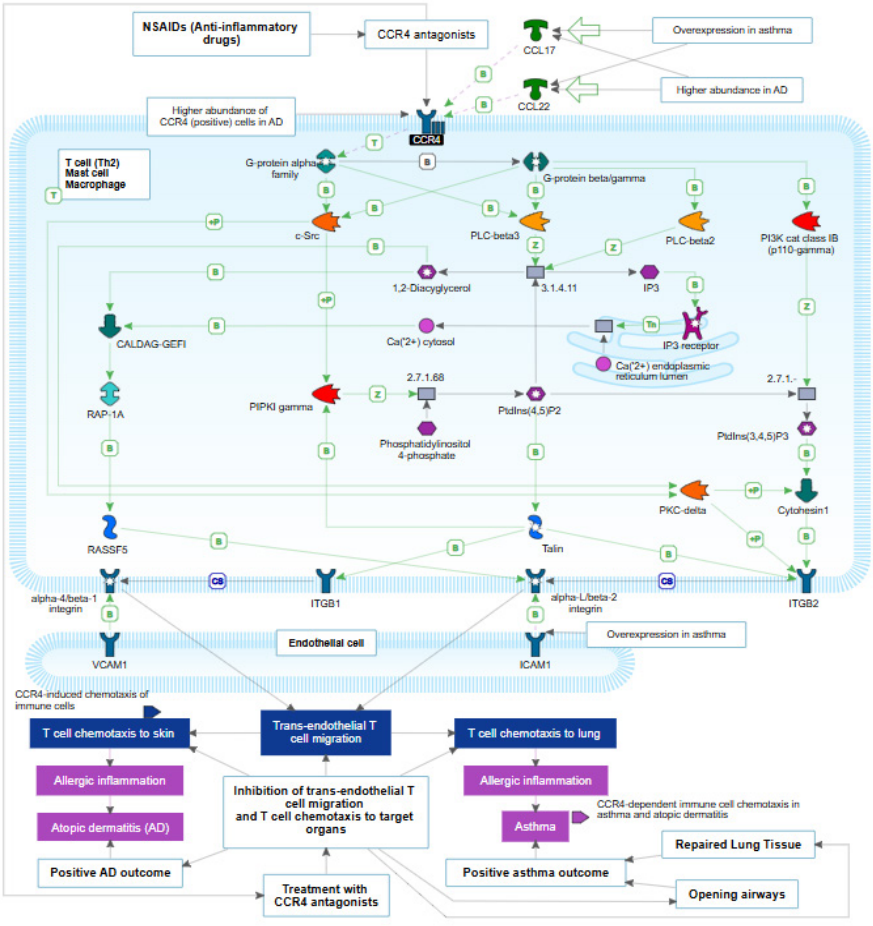
3. Assessing the safety liabilities for targets either upstream or downstream in the signaling pathway to the target of interest

As CCR4 antagonists are not highly associated with liver damage, we want to explore other insights that could help assess this potential association, for example, information coming from other proteins belonging to the same signaling cascade as the target of interest.

The pathway maps in OFF-X visually represent a series of interactions among biological molecules that lead to changes in the cell. Based on published medical literature, they are critical for understanding the biological rationale behind a disease or mechanism of action and for drug target discovery and validation. With OFF-X safety data overlaid on them, you can use pathway maps to quickly assess the safety liabilities for targets either upstream or downstream in the signaling cascade to your target of interest.

Among the numerous pathway maps associated with the target of interest, CCR4, we select the 'Mechanism of action of CCR4 antagonists in asthma and atopic dermatitis' map as the adverse event was reported in an atopic dermatitis study.

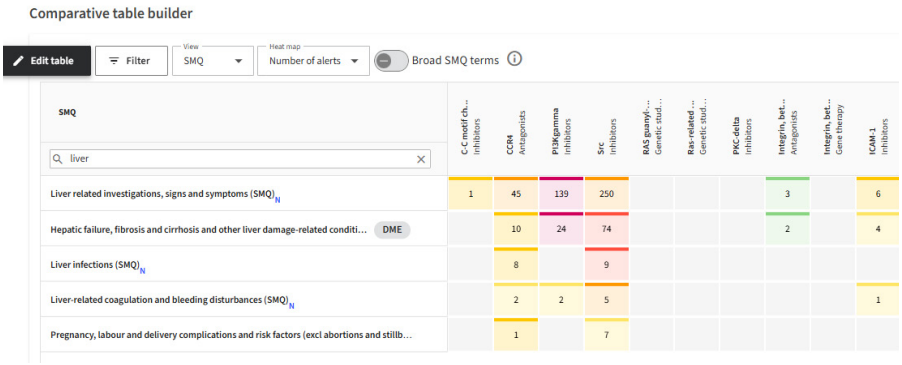
Figure 3: MoA of CCR4 antagonists in asthma and atopic dermatitis



OFF-X allows us to easily build a comparative table that includes the manually curated safety information for all targets found on the pathway map. We can easily search the comparative table for liver SMQs.

Interestingly, two targets downstream to CCR4 have high and very high evidence[1] for liver symptoms and liver damage: PI3Kgamma Inhibitors and Src Inhibitors.

Figure 4: Comparing safety information for all targets on the pathway map



By harnessing the granularity of OFF-X's data, we can uncover valuable insights that would otherwise require significant time and effort to identify. Filtering the comparative table by 'On-target' and 'Causal' alerts, based on the insights manually extracted from the original sources, reveals relevant evidence of the association between these targets and liver damage.

Figure 5: Drilling down to reveal more granular insights

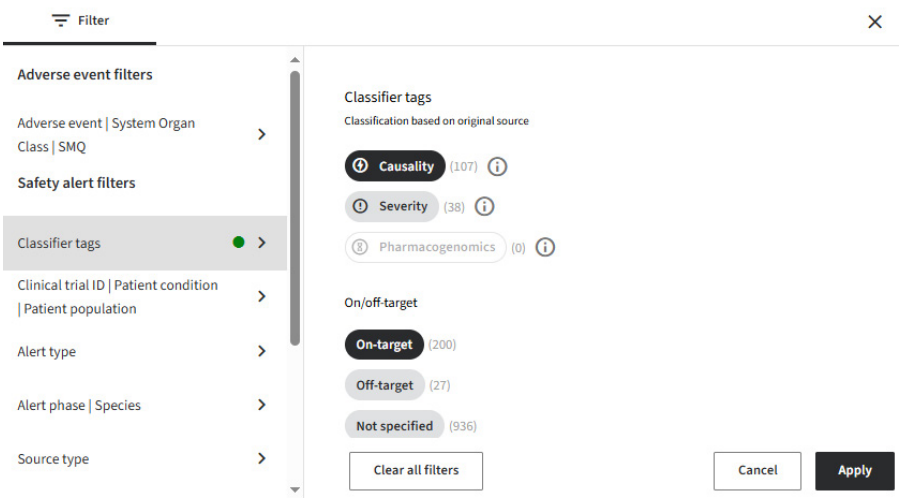
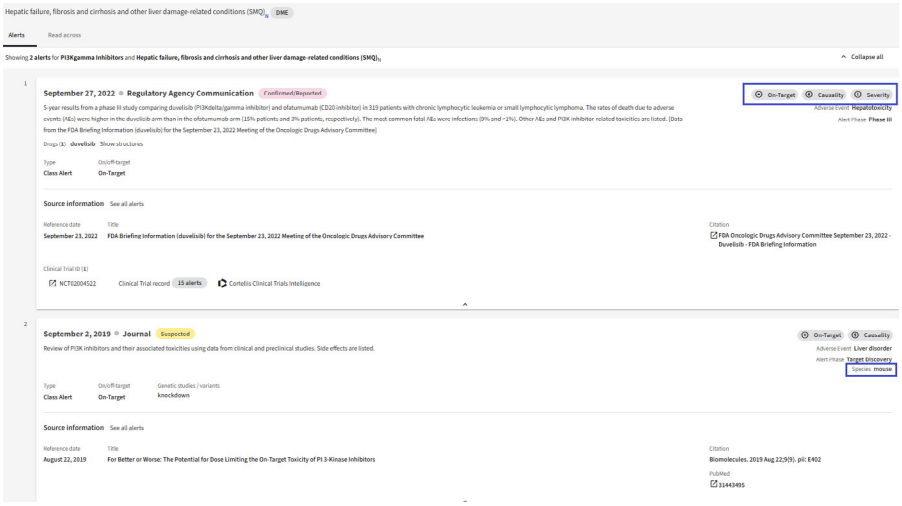


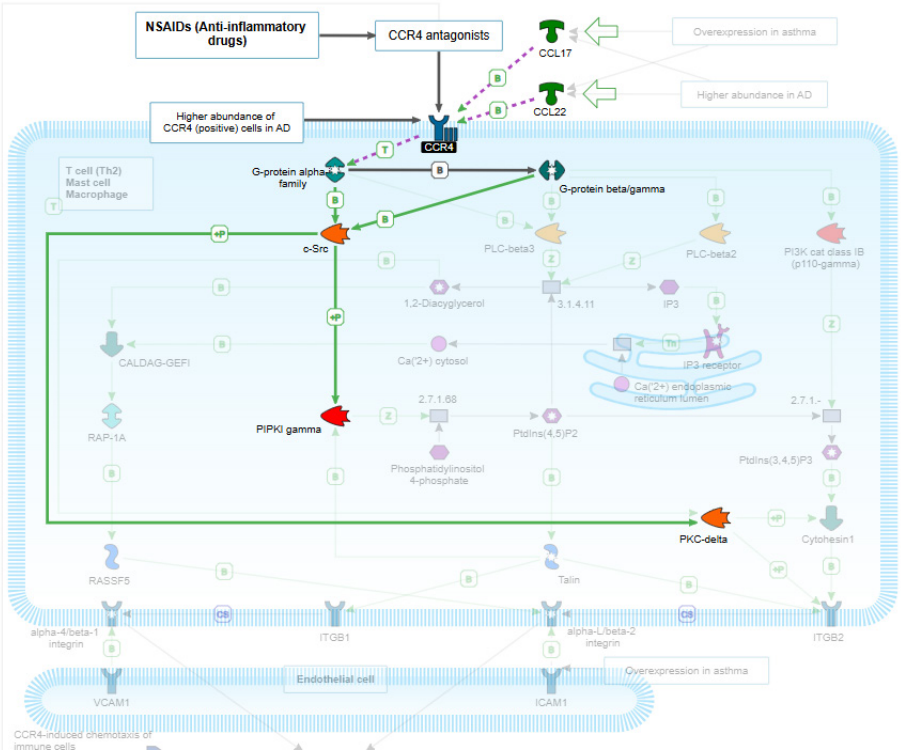
Figure 6: Evidence of the association between the targets and liver damage



Returning to the pathway map we can observe where these two targets appear downstream to the target of interest, CCR4.

In just a few clicks, OFF-X has provided evidence that the down-modulation of this signaling cascade may be associated with liver disorders.

Figure 7: PI3Kgamma and Src appear downstream to CCR4



4. Conclusions: sound evidence to build next steps

Based on findings like these, researchers now have evidence on which to base hypotheses, or plan safety mitigation strategies, such as:

- Prioritizing in vitro and in vivo tests to verify whether their molecule produces the same effect
- Conducting studies to confirm if upstream inhibition indirectly triggers downstream toxicity
- Performing dose-response studies to find a therapeutic window
- Exploring biomarkers to predict and monitor liver toxicity risks

Quickly identifying which upstream / downstream targets in the signaling cascade are associated with safety liabilities and exploring their safety profile can help you understand unexpected toxicities and unveil critical safety insights to inform your risk management plans.

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About Clarivate

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