What are the common predicted toxicities from target safety assessments?

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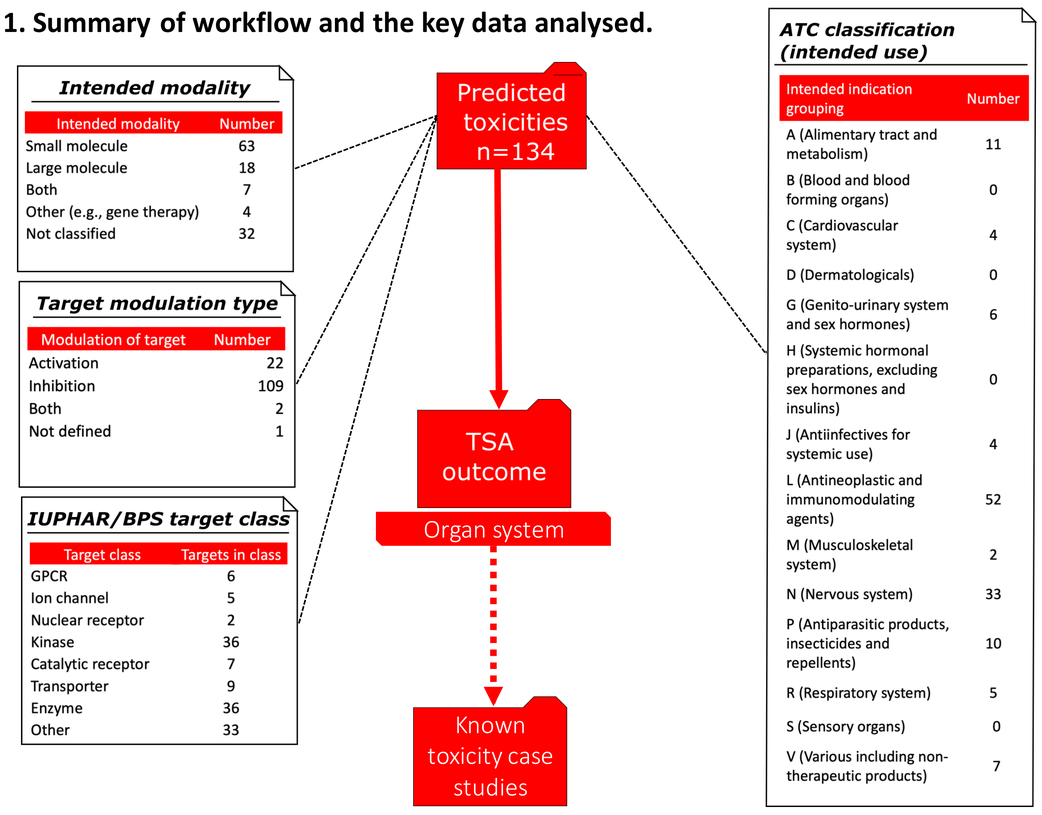
Introduction

- Target safety assessments (TSAs) use target biology, gene and protein expression data, genetic information from humans and animals, and competitor compound intelligence to understand the potential safety risks associated with modulating a drug target.
- TSAs are used within drug projects to identify and mitigate risks, helping with informed decision making and resource management.
- The aim of this work was to determine whether predicted toxicities from TSAs are consistent with known drug safety insights (i.e. modality associations, mechanisms) and qualitatively similar to toxicities observed during drug development. This was achieved by:
  - Analysing the pattern of predicted toxicities from our TSA database based on drug modality, mechanism of action (MoA), drug development status, drug target class, and therapeutic class.
  - Evaluating whether predicted toxicities from our TSA database have a similar distribution and characteristics to known toxicities described in published case studies.

Methods

- Using our TSA database, we performed a qualitative analysis of predicted toxicities by organ system. Only predicted toxicities with a high or moderate risk of occurrence were included.
- The data were further stratified based on drug modality, MoA, Open Targets small molecule drug development status, Anatomical Therapeutic Chemical (ATC) classification and IUPHAR/BPS Guide to Pharmacology drug target class.
- We compared our TSA database to a literature survey of 52 case studies of known drug-induced target-related toxicities.

Table 1. Summary of workflow and the key data analysed.



Results

Modality and MoA

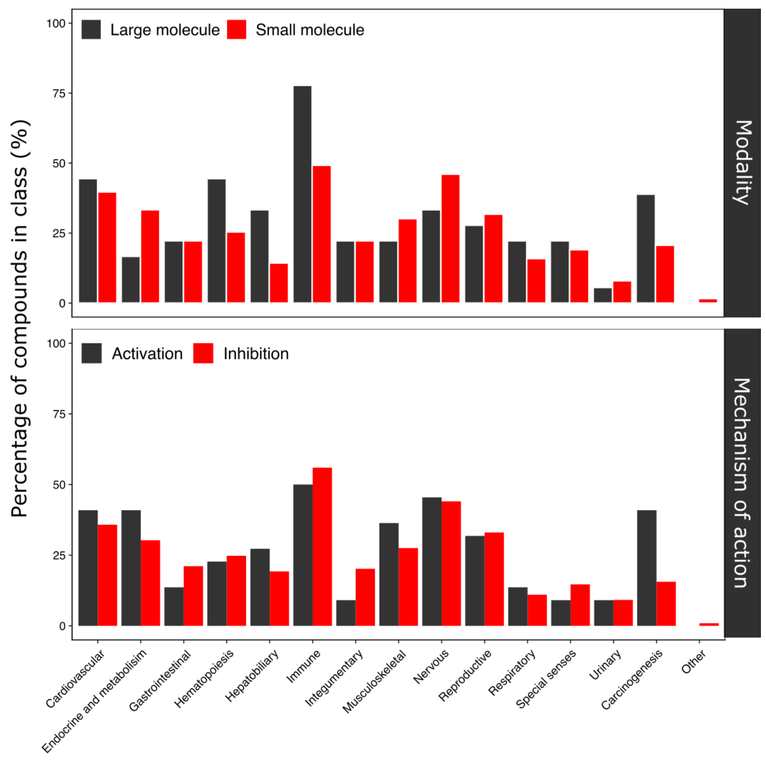


Figure 1. Predicted toxicities by intended modality and MoA.

The percentage of targets for small and large molecule compounds with predicted toxicities in each organ system is shown.

Target development status

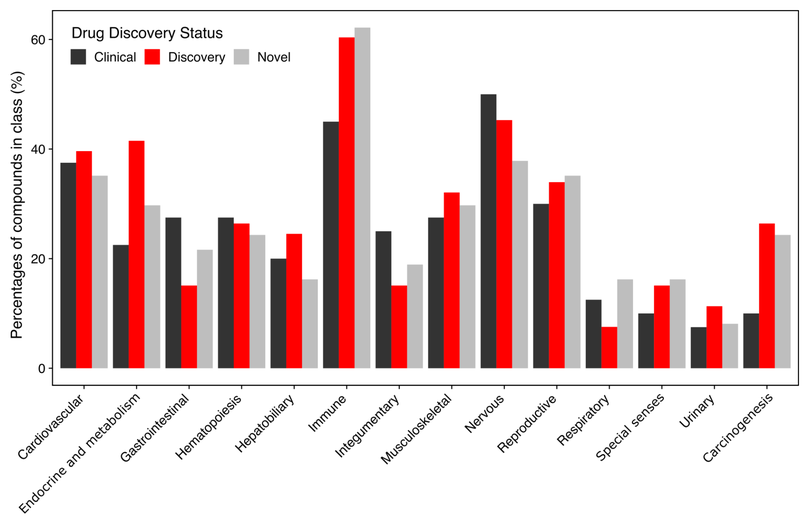


Figure 2. Predicted toxicities by Open Targets development status of each target.

The percentage of targets for intended inhibition and development status with predicted toxicities in each organ system is shown.

Drug target class

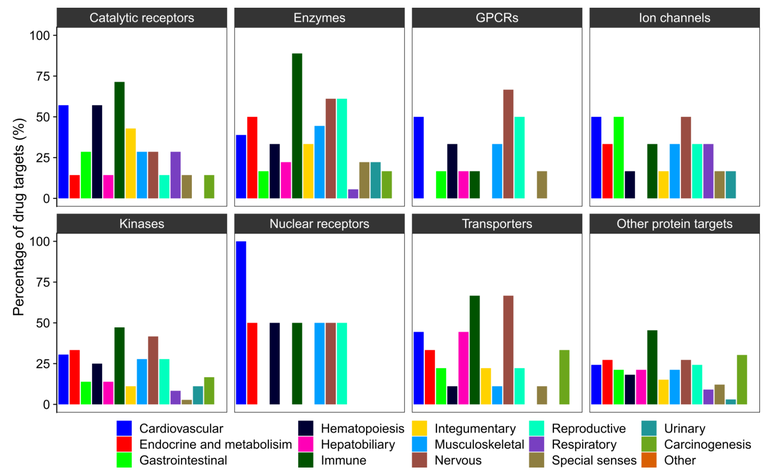


Figure 3. Predicted toxicities of targets by IUPHAR/BPS class. The percentage of targets with predicted toxicities in each organ system is shown for each IUPHAR/BPS class.

Therapeutic class

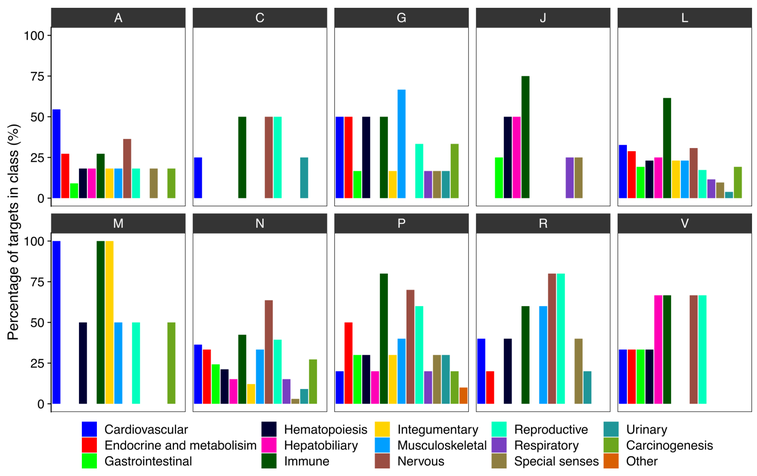


Figure 4. Predicted toxicities of targets by ATC classification. The percentage of compounds with predicted toxicities in each organ system is shown for the ATC classification of the intended indication (Table 1). There were no data for B, D, H, and S, ATC classifications.

Cardiovascular toxicity

Figure 5. Cardiovascular predicted toxicity distribution.

Predicted toxicities for cardiovascular toxicity were grouped according to major adverse event class and mechanistic sub-class. Data are presented as a proportion of the frequency of each predicted toxicity class.

Predicted and known target organ toxicities

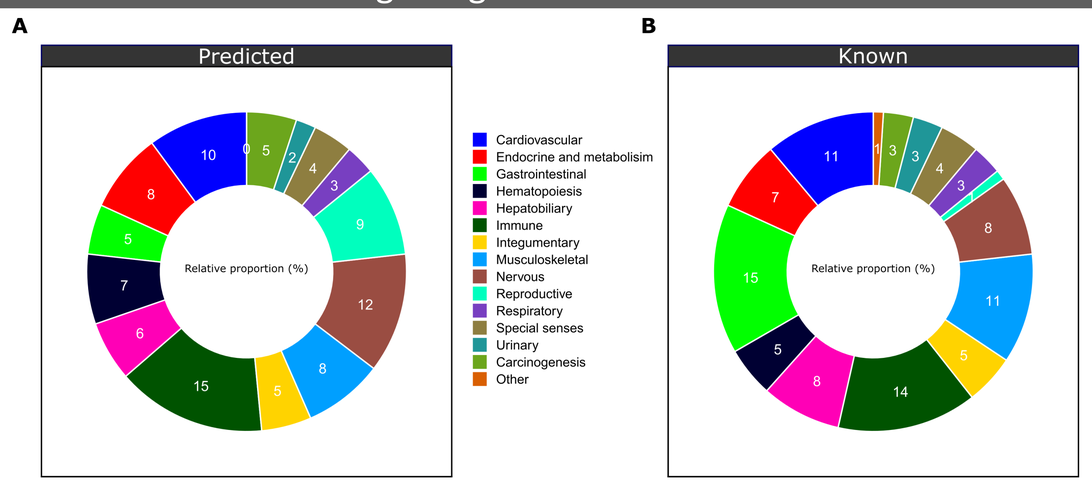


Figure 6. Distribution of predicted toxicities in each organ system from (A) TSAs compared to (B) known toxicities from published case studies.

Conclusions

- There were no consistent organ system trends in the predicted toxicities for modality, MoA, target development status, drug target class or therapeutic class.
- Specific trends were found that were consistent with known drug safety insights:
  - Large molecules were more likely to be associated with immune system toxicities compared to small molecules.
  - Activators were more likely to be associated carcinogenesis compared to inhibitors.
  - There was a trend for some predicted toxicities to be higher or lower for discovery and novel targets compared to clinical targets. TSAs for early targets are more likely to based on genetic evidence which might over or underestimate the actual drug toxicities seen clinical targets.
  - Apart from arrythmia, predicted cardiovascular toxicities adverse event classes and mechanistic sub-classes were similar to typical cardiovascular toxicities observed in nonclinical safety testing and clinical development.
- The data also demonstrated that toxicities predicted from TSAs have a similar distribution among organ systems as the known toxicities described in case studies.
- This preliminary data collectively suggests that TSAs are a valid approach for predicting target mediated toxicities.