TARGET SAFETY ASSESSMENT

TNO innovation for life

Safety-related drug attrition represents a major hurdle in the development of innovative therapeutics. A comprehensive assessment of the potential safety liabilities induced by target modulation is therefore an essential part of successful drug discovery. TNO offers a modular or full integrative target safety assessment service, based on an in-house developed approach that incorporates all aspects of target safety. Subsequent risk mitigation strategies are designed upon request.

One of the causes for high drug attrition is that safety liabilities of a drug and its associated target are not placed in a broad enough context. At TNO we have therefore developed, in collaboration with pharmaceutical companies, a holistic target safety assessment workflow that incorporates all aspects of target safety. As illustrated in Figure 1 this includes on-target, off-target and pathway effects. General characteristics of the target under scrutiny, such as expression profile and binding site conservation are also taken into account.

WORKFLOW

Target Description

In the first step of the Target Safety Assessment general features of the target of interest are evaluated. This includes among others its biological function, expression profile, organ distribution and species variation. Using computational chemistry and bioinformatics approaches, binding site(s) and ligand selectivity are explored in detail. This also encompasses the identification of homologues / isoforms, biological tools, endogenous ligands etc. The data mined in this part of the workflow serves as input for the next steps of the assessment.

On-target Toxicity

On-target toxicity constitutes the adverse effects that may arise by direct modulation of the target. The immediate downstream effects are analysed using text mining, data mining and systems biology analyses. Potential feedback mechanisms and redundancy are investigated as well. Reported toxicity is categorized per organ on the level of evidence (clinical, *in vivo* preclinical and *in vitro* preclinical) in a comprehensive overview. When data

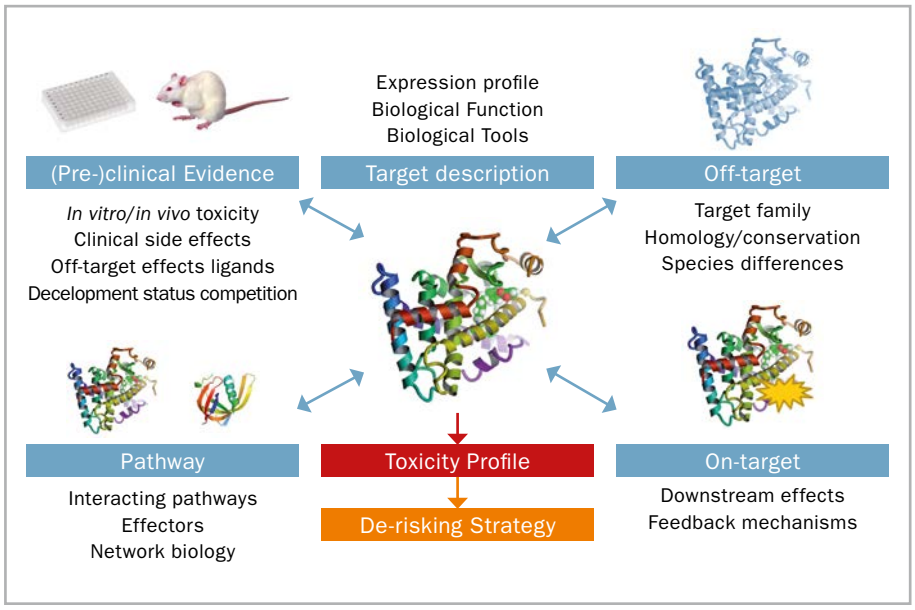

Figure 1. The target safety workflow

allows, toxicity is classified as mechanism- or structure-based using clustering analysis.

Off-target toxicity

Off-target effects are due to the lack of selectivity of a potential new drug. As many small molecule drugs give rise to off-target toxicity, this is an essential part of the full target safety assessment workflow. To evaluate the risks associated with homologous targets, the procedure described under Target Characteristics and On-target Toxicity is repeated for the identified homologues / isoforms.

Pathway effects

Another aspect of target safety that cannot be ignored is the role and function the target plays in biological pathways. Through protein-protein interactions multiple pathways may be activated or inhibited, ultimately leading to adverse effects. Large prior-knowledge databases are mined to identify and rank potential adverse outcomes of target modulation on a pathway level. When possible, these outcomes are compared and benchmarked against toxicity data resulting from text mining and data mining approaches in order to get an insight in the underlying mechanism of the observed toxicity.

INTERPRETATION AND REPORTING

The data and insights resulting from the workflow are combined in a comprehensive Target Safety Assessment report (Figure 2). In this report, the identified safety liabilities are ranked based on their severity, reported frequency, level of evidence and relevance for the patient population for which the target has therapeutic potential. Together with the company providing target information, a joint risk mitigation strategy can be designed, catering to specific needs or interests.

Box 1	Box 2	Box 3	Box 4
Target characterization › Primary target › Subtypes › Homologues › Distribution target/ subtypes/ homologues › Endogenous ligands › Organ distribution › Species distribution Matching distribution pattern with effects; no match -> secondary pharmacology	**Biological relevance associated with target** › CNS/autonomic nervous system › Cardiovascular › Respiratory tract › Renal/urinary system › GI tract & liver, pancreas › Reproductive organs › Reproductive development › Immune system › Endocrine system › Clinical chemistry/ hematology › Microbiome › Other	**Pharmaceuticals associated with target** › Clinical trials › Post marketing information › Therapeutic area › Mode of action/ primary target › Secondary pharmacodynamics › Safety pharmacology › Target organs of toxicity › Side effects › Other sources	**Secondary Pharmacology** › Biological relevance associated with subtypes/ homologues (see box 2) › Compensatory mechanisms
Pathway and network related analyses			

Figure 2. Types of data used in the end report.

TARGET SAFETY ASSESSMENT TEAM

The collection and analysis of the full spectrum of safety aspects of a drug target requires a multi-disciplinary approach. At TNO we have formed a dedicated team that performs Target Safety Assessment studies. This team consists of experts in the fields of toxicology, text mining, systems biology and computational chemistry. Together, they ensure not only that all relevant data is mined and analysed, but that this data is interpreted in an integrative way allowing strategic decisions on how to further progress the target in light of its therapeutic effect.

TOOLS

The tools used in a Target Safety Assessment study range from commercial software and databases, to public resources and proprietary tools.

TNO.NL

TNO HEALTHY LIVING

TNO initiates technological and societal innovation for healthy living and a dynamic society.

TNO
Utrechtseweg 48
3704 HE Zeist
The Netherlands

Dr. Simon Folkertsma
P +31 88 866 47 45
E simon.folkertsma@tno.nl