Introduction
Drug efficacy and toxicity are controlled by interplay of pharmacokinetic, pharmacodynamic, and genetic factors. Most pharmaceutical compounds are active against more than a single target. Off-target profiling is a recently established tool to identify critical liabilities, which can lead to drug toxicity. Combined in silico/in vitro profiling strategies are found to be most effective when conducting compound safety assessments.

In-silico off-target profiling
We have developed a tiered strategy to optimally support drug safety profiling. Computational models for numerous off-target interactions allow for systematic prediction of drug-target interactions. Target engagement in adverse pathways can be analyzed with pathway databases, supporting the toxicity risk assessment and mode-of-toxicity evaluation of drugs.

Tier I: Off-Target Prediction
Concept: Chemo-centric mining of protein-ligand interactions
• Sanofi and public bioassay data (CHEMBL, lupus, PDSP, BindingDB)
• Chemotargets CTLink as a platform to build and apply predictive off-target models
  • Activity prediction using kNN models with distance weighting interpolation

Tier II: Off-Target Profiling by QSAR
Concept: Global QSAR models for critical off-Targets
• Sanofi and CEREPI bioassay data
• Cubist regression trees based on MOE descriptors
  • Evaluation of applicability domain by similarity to training set

Tier III: ADR Prognosis based on Biological Networks and Mining in Pathway Databases
Concept: Pathway mining to identify relationships between predicted off-targets and modes of toxicity for novel drug candidates
• Particularly for cardiac and reproductive toxicity, causal relationships between off-target interaction and mode of toxicity can often be assumed

Cardiotoxicity
- Antifungal Lead Compound
- Causal Network
- Predicted target inhibition

Hepatotoxicity
- Bradykinin B1 antagonist
- Predicted target inhibition

Reproductive Toxicity
- Neurokinine antagonist
- Predicted target inhibition

Summary
In-silico off-target profiling at Sanofi includes a growing portfolio of models, currently including > 6000 similarity-driven CTLink models and 414 QSAR models. These models are regularly curated and the model applicability domain is controlled to ensure a maximum of correct predictions. Evidence for toxicity of drugs is generated by data mining in pathway databases. In-silico toxicity analyses inform about potential safety concerns of new molecules. Off-target profiling and PredictFX are regularly applied. These methods serve as cost-effective tools to select compounds prior to screening.

In discovery, in silico predictions help to initiate focused experimental follow-up studies and to enhance hit and lead selection. These methods are also applied in development to support risk assessments for regulatory purpose, e.g. to create hypotheses and to better understand mechanisms of toxicity. Further method development will foster a better characterization of clinically relevant adverse effects based on published knowledge and relevant target-side effect networks and, as a next evaluation step, considering inter-individual genetic differences.