TargetTri: A toxicity-based triaging system for novel drug targets

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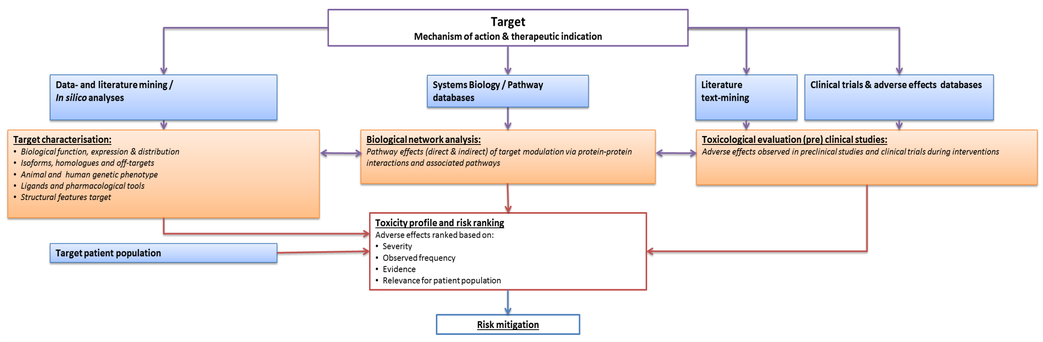
SUMMARY

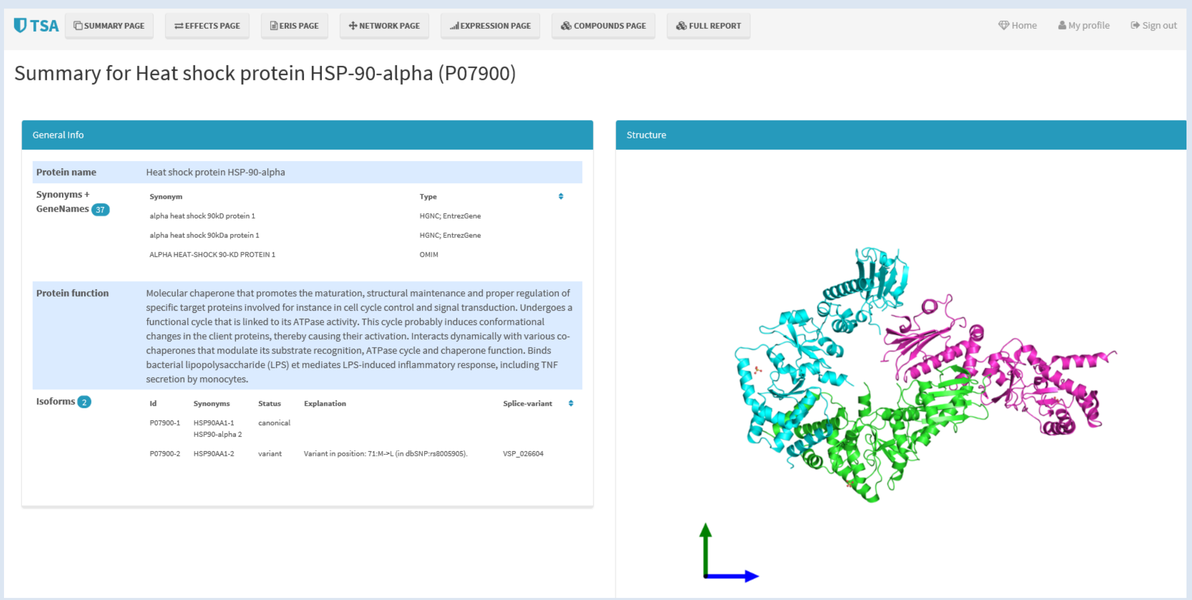
High drug attrition rates in recent decades have motivated pharmaceutical companies to tackle the underlying causes as early as possible in their pipelines. In regards to safety, this involves assessing liabilities of drug targets and developing de-risking strategies in the nomination stage. With an expansive variety of information now available via data-mining, text-mining, and systems biology, this effort weighs on resources and can hamper efficient prioritization of multiple targets.

To aid in the triaging of novel drug targets, TNO is developing the web-based system TargetTri that builds upon a previously designed Target Safety Assessment (TSA) workflow. TargetTri can extract and visualize data on-the-fly for any of the 20k reviewed human proteins deposited in UniProt. Via multiple views — here illustrated for HSP90 —highly efficient toxicological assessments and triaging of drug targets can be performed.



HSP90 ANALYSIS

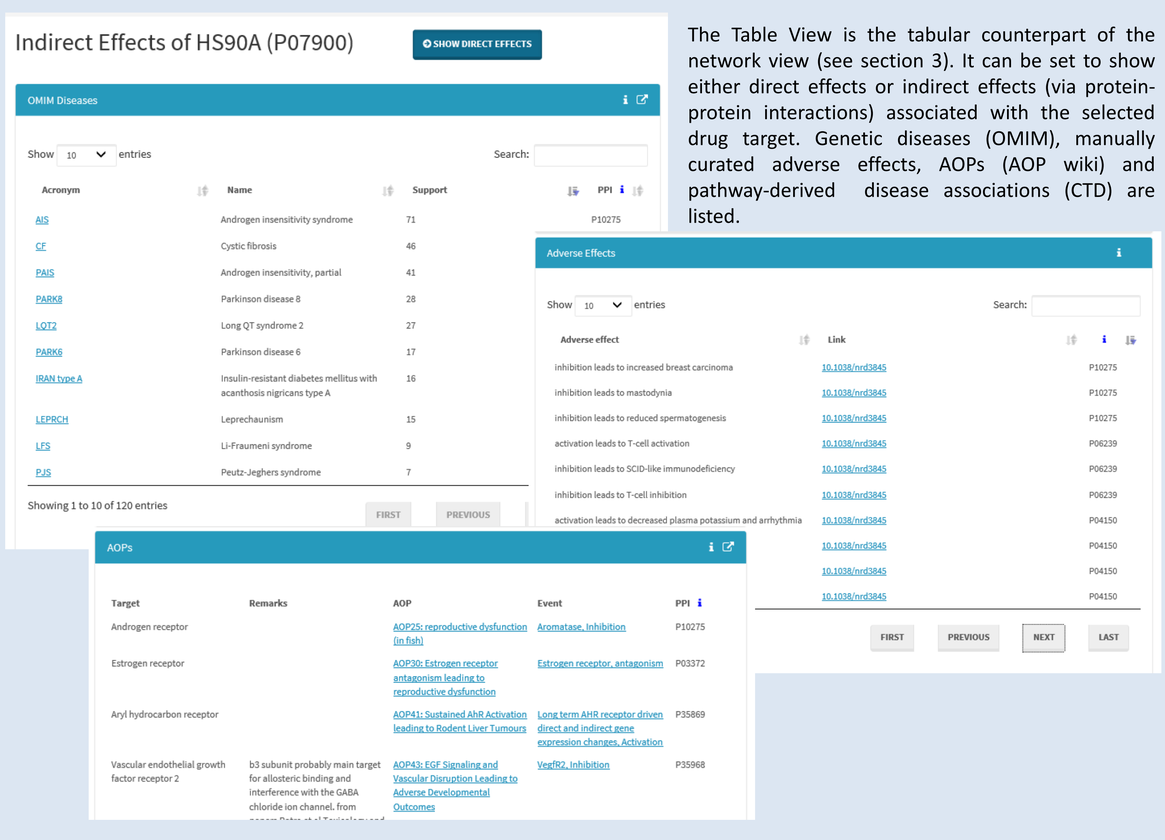
1. Summary View



The Summary View is visualized once the name of the drug target being scrutinized — heat shock protein 90 alpha — has been entered and selected. General information is reported such as the target's biological function, name and synonyms, and isoforms (UniProt). Structural information (PDB) is also displayed when available.

Inhibition of the molecular chaperone HSP90alpha has been studied as an anti-cancer therapy, originating from HSP90's overexpression in various cancer cells. In addition, many of the HSP90 client proteins play crucial roles in establishing cancer cell hallmarks. More recently, interest has extended to the treatment of neurodegenerative diseases that involve aberrantly folded proteins.

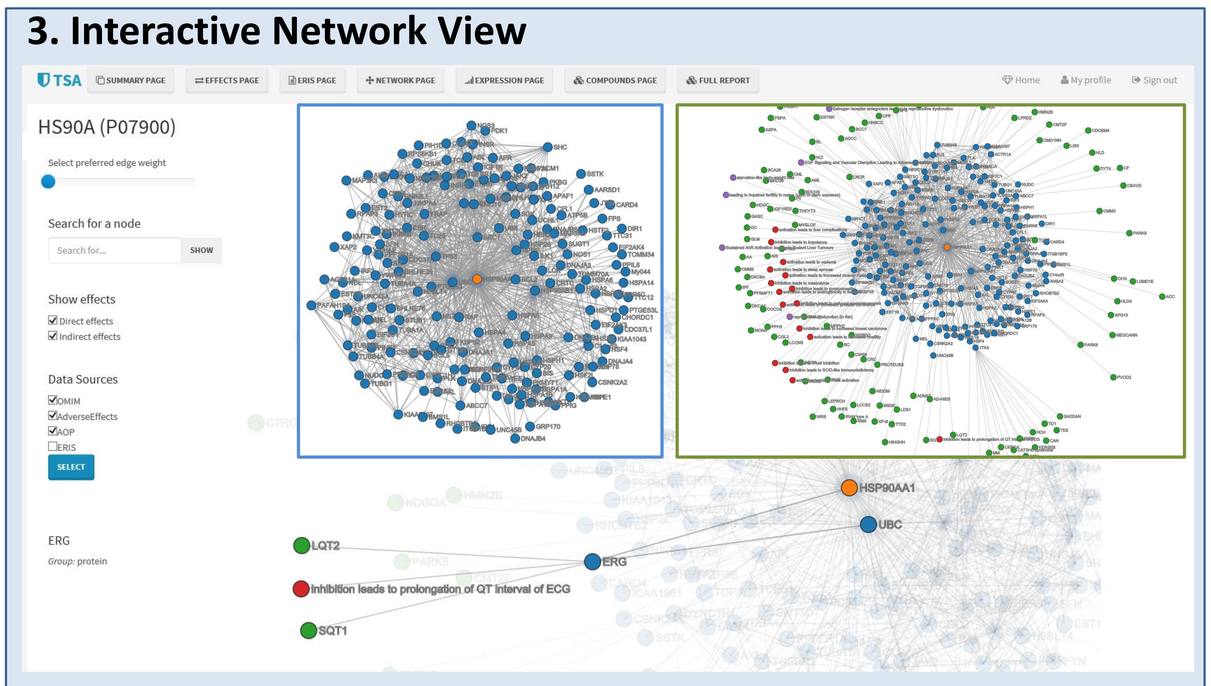
2. Table View



The Table View is the tabular counterpart of the network view (see section 3). It can be set to show either direct effects or indirect effects (via protein-protein interactions) associated with the selected drug target. Genetic diseases (OMIM), manually curated adverse effects, AOPs (AOP wiki) and pathway-derived disease associations (CTD) are listed.

In line with the therapeutic indications of HSP90alpha, this protein is mainly associated with cancer pathways according to the CTD *(direct effects view, data not shown).* Analysis of the indirect effects infers, for example, a potential association with Parkinson's Disease (PD) and androgen receptor-mediated effects. The association with PD corresponds with the interest in this target for neurodegenerative diseases. Male infertility, i.e. reduced spermatogenesis due to inhibition of the androgen receptor, has been observed in HSP90alpha (conditional) knock-out mouse models.

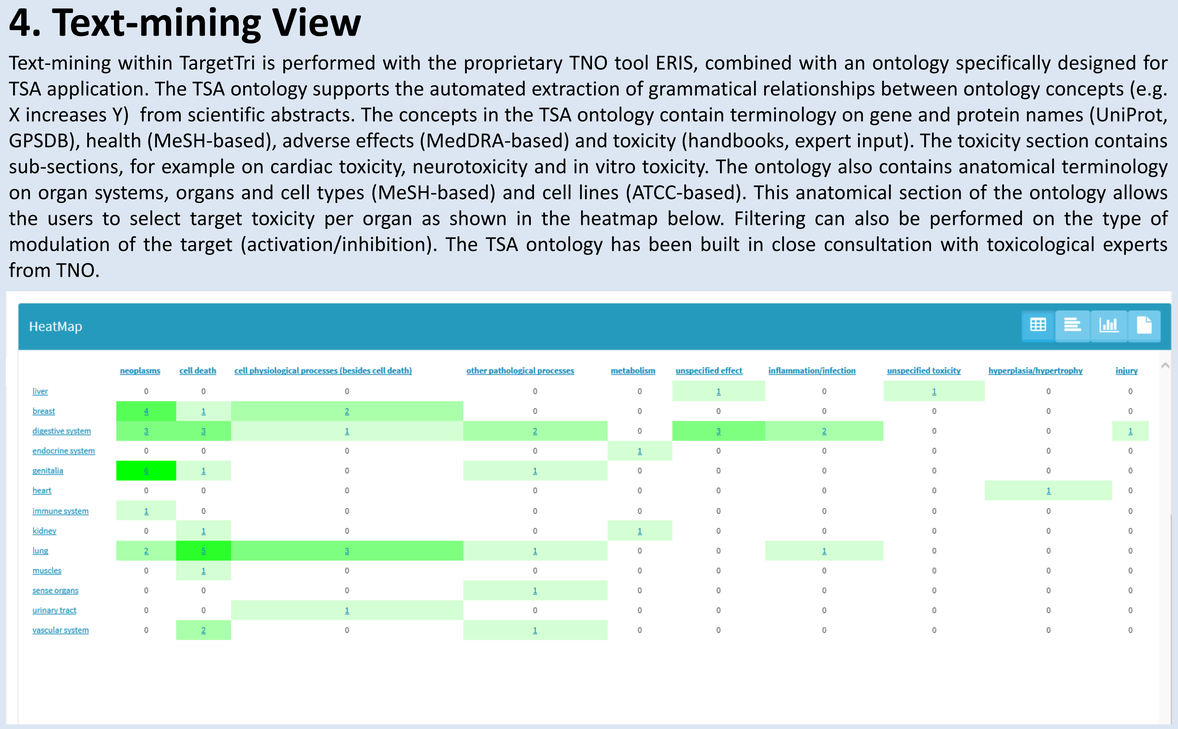
3. Interactive Network View

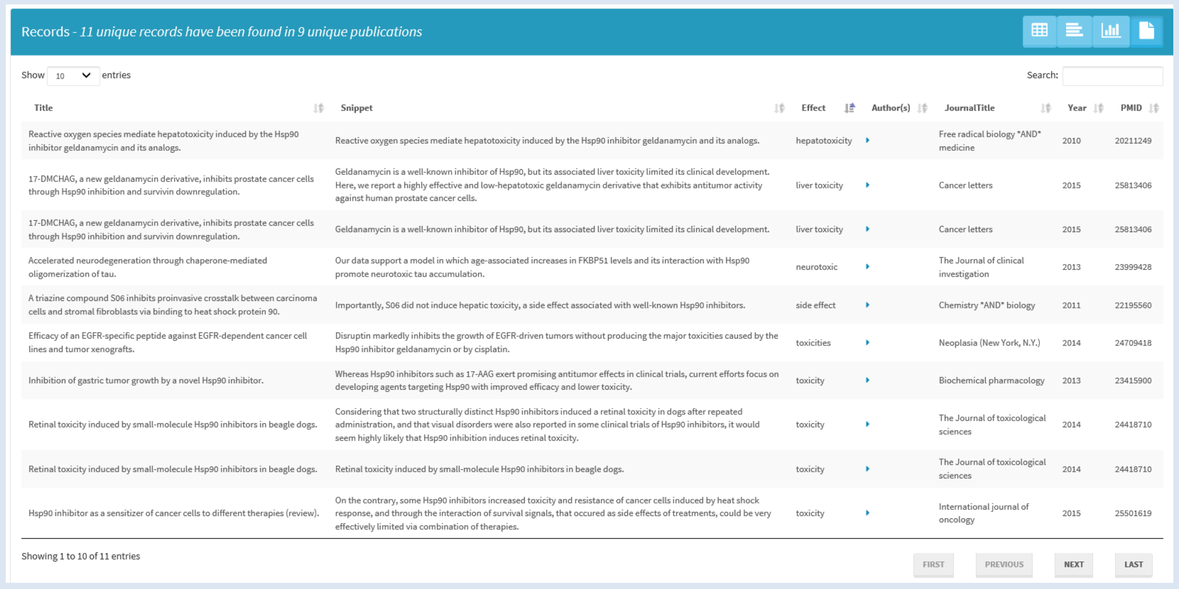


The Network View displays proteins (blue) that interact directly with HSP90alpha (orange). The high number of interacting proteins is due to HSP90's function as a molecular chaperone (see section 1). As shown by the blue framed inset, HSP90alpha is not directly associated with genetic diseases or adverse outcome pathways (AOPs). However, when examining indirect biological effects — mediated via interacting proteins — a multitude of potential adverse effects are high-lighted (green framed inset). Each interacting node (blue) and associated effects (red, green and purple) can be individually examined, showing — for example — that HSP90alpha interacts with the hERG potassium channel. This protein is essential for normal electrical activity in the heart. As such, inhibition of hERG via HSP90alpha may result in prolongation of the QT interval.

4. Text-mining View

Text-mining within TargetTri is performed with the proprietary TNO tool ERIS, combined with an ontology specifically designed for TSA application. The TSA ontology supports the automated extraction of grammatical relationships between ontology concepts (e.g. X increases Y) from scientific abstracts. The concepts in the TSA ontology contain terminology on gene and protein names (UniProt, GPSDB), health (MeSH-based), adverse effects (MedDRA-based) and toxicity (handbooks, expert input). The toxicity section contains sub-sections, for example on cardiac toxicity, neurotoxicity and in vitro toxicity. The ontology also contains anatomical terminology on organ systems, organs and cell types (MeSH-based) and cell lines (ATCC-based). This anatomical section of the ontology allows the users to select target toxicity per organ as shown in the heatmap below. Filtering can also be performed on the type of modulation of the target (activation/inhibition). The TSA ontology has been built in close consultation with toxicological experts from TNO.





With the text-mining results, toxicological effects due to intervention studies with HSP90alpha inhibitors were identified. These included, for example, retinal toxicity observed in beagle dogs and liver toxicity observed with the small molecule 17-DMCHAG. More in-depth analysis of the literature provides insight in mechanistic causes of toxicity. For specific compound clusters, hepatotoxicity was mediated by reactive oxygen species formed during metabolism. Retinal toxicity was attributed to pharmacokinetics, as various compounds were found to accumulate in the retina.

5. Additional Views

In addition to the already described Views, TargetTri also provides information on compounds that are known to bind to the target of interest by extracting structural and biological data from the ChEMBL database. The resulting compound names and synonyms are subsequently queried in the clinical trials database (clinicaltrials.gov), resulting in a clinical trials result view displaying general trial information and a NTC number hyperlink accessing the original webpage with additional information. Expression data can also be retrieved with TargetTri.

6. Further Development

TargetTri is an ongoing research development program for efficient drug target triaging, which will be further optimized and expanded in terms of functionality and application area. TNO has collaboration options available for pharmaceutical partners that are interested in further developing this platform. Parties interested in providing us with feedback or in a potential collaboration are kindly invited to contact us:

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