

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

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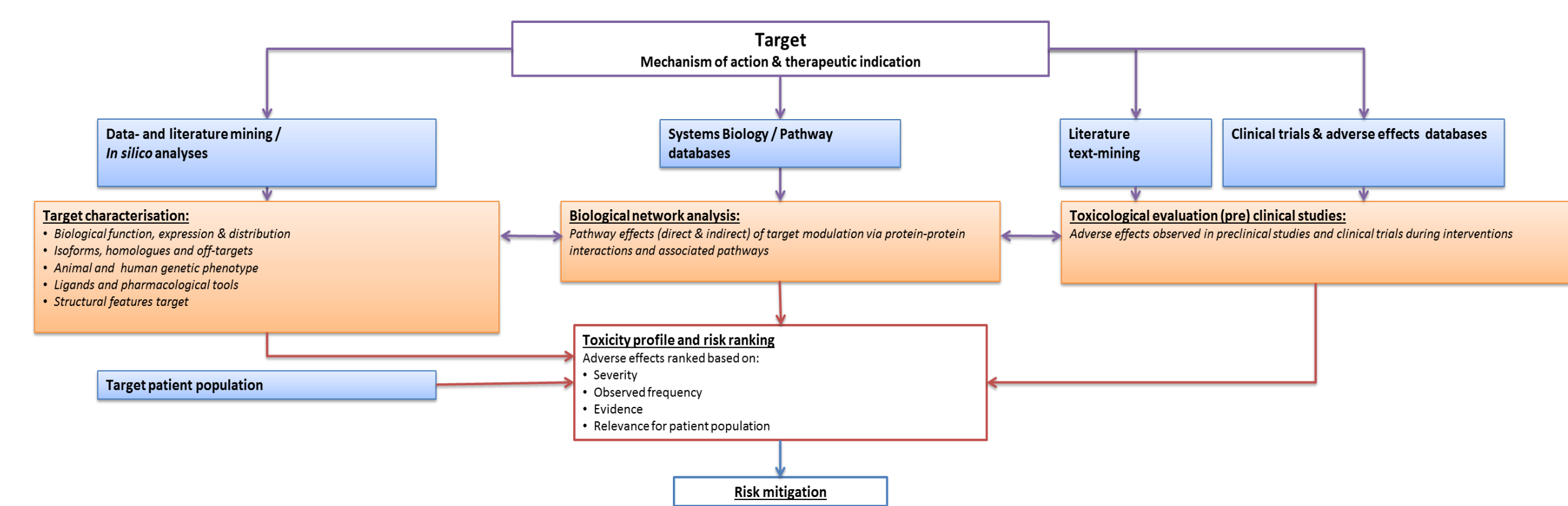
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## SUMMARY

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

Id	Synonyms	Status	Explanation	Splice variant
P07900.1	HSP90A1.1	canonical		
P07900.2	HSP90A2.1	variant	Variant in position: 71;M;A; (in dbSNP rs805905)	VSP_23604

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

Acronym	Name	Support	PP1
AS	Androgen insensitivity syndrome	71	P10275
CF	Cystic fibrosis	46	
AS	Androgen insensitivity, partial	41	
PK	Parkinson disease 8	28	
LO	Long QT syndrome 2	27	
PK	Parkinson disease 6	17	
IR	Insulin-resistant diabetes mellitus with acanthosis nigricans type A	16	
LE	Leproschaum	15	
LI	Li-Fraumeni syndrome	9	
JS	Peutz-Jeghers syndrome	7	

Target	Remarks	AOP	Event	PP1
Androgen receptor		AOP23: reproductive dysfunction (in SAS)	Aromatase_inhibition	P10275
Estrogen receptor		AOP30: Estrogen receptor antagonism leading to reproductive dysfunction	Estrogen_receptor_antagonism	P03372
Aryl hydrocarbon receptor		AOP41: Sustained AHR Activation leading to Rodent Liver Tumours	Long-term AHR receptor driven direct and indirect gene expression changes, Activation	P35869
Vascular endothelial growth factor receptor 2	b3 subunit probably main target for allosteric binding and interference with the GASA chloride ion channel, from	AOP43: EGF Signaling and Vascular Disruption Leading to Adverse Developmental Outcomes	VEGFR_inhibition	P35968

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.

	neoplasms	cell death	cell abnormals processes (besides cell death)	other pathological processes	metabolism	unspecified effect	inflammation/infection	unspecified toxicity	hyperalasia/hyperaesthesia	injury
liver	0	0	0	0	0	1	0	1	0	0
liver: portal	1	1	1	0	0	0	0	0	0	0
digestive system	1	1	1	2	0	1	2	0	0	1
endocrine system	0	0	0	0	1	0	0	0	0	0
cardiovascular system	0	0	0	1	0	0	0	0	0	0
heart	0	0	0	0	0	0	0	1	0	0
intestine system	1	0	0	0	0	0	0	0	0	0
kidney	0	1	0	0	1	0	0	0	0	0
lung	2	2	2	1	0	0	1	0	0	0
muscles	0	1	0	0	0	0	0	0	0	0
sense organs	0	0	0	1	0	0	0	0	0	0
vascular: blood	0	0	1	0	0	0	0	0	0	0
vascular: system	0	2	0	1	0	0	0	0	0	0

Title	Snippet	Effect	Author(s)	Journal Title	Year	PMID
Reactive oxygen species mediate hepatotoxicity induced by the Hsp90 inhibitor geldanamycin and its analogs.	Reactive oxygen species mediate hepatotoxicity induced by the Hsp90 inhibitor geldanamycin and its analogs.	hepatotoxicity		Free radical biology "AND" medicine	2010	20211249
17-DMCHAG, a new geldanamycin derivative, inhibits prostate cancer cells through Hsp90 inhibition and survivin downregulation.	Geldanamycin is a well-known inhibitor of Hsp90, but its associated liver toxicity limited its clinical development. Here, we report a highly effective and low-hepatotoxic geldanamycin derivative that exhibits antitumor activity against human prostate cancer cells.	liver toxicity		Cancer letters	2015	25813406
17-DMCHAG, a new geldanamycin derivative, inhibits prostate cancer cells through Hsp90 inhibition and survivin downregulation.	Geldanamycin is a well-known inhibitor of Hsp90, but its associated liver toxicity limited its clinical development.	liver toxicity		Cancer letters	2015	25813406
Accelerated neurodegeneration through chaperone-mediated oligomerization of tau.	Our data support a model in which age-associated increases in PRK31 levels and its interaction with Hsp90 promote neurotoxic tau accumulation.	neurotoxic		The Journal of clinical investigation	2013	23999428
A triazine compound 506 inhibits proinvasive crosstalk between carcinoma cells and stromal fibroblasts via binding to heat shock protein 90.	Importantly, 506 did not induce hepatic toxicity, a side effect associated with well-known Hsp90 inhibitors.	side effect		Chemistry "AND" biology	2011	22185560
Efficacy of an EGFR-specific peptide against EGFR-dependent cancer cell lines and tumor xenografts.	Disruptin markedly inhibits the growth of EGFR-driven tumors without producing the major toxicities caused by the Hsp90 inhibitor geldanamycin or by cisplatin.	toxicities		Neoplasia (New York, N.Y.)	2014	24708418
Inhibition of gastric tumor growth by a novel Hsp90 inhibitor.	Whereas Hsp90 inhibitors such as 17-AAG exert promising antitumor effects in clinical trials, current efforts focus on developing agents targeting Hsp90 with improved efficacy and lower toxicity.	toxicity		Biochemical pharmacology	2013	23415900
Retinal toxicity induced by small-molecule Hsp90 inhibitors in beagle dogs.	Considering that two structurally distinct Hsp90 inhibitors induced a retinal toxicity in dogs after repeated administration, and that visual disorders were also reported in some clinical trials of Hsp90 inhibitors, it would seem highly likely that Hsp90 inhibition induces retinal toxicity.	toxicity		The Journal of toxicological sciences	2014	24418710
Retinal toxicity induced by small-molecule Hsp90 inhibitors in beagle dogs.	Retinal toxicity induced by small-molecule Hsp90 inhibitors in beagle dogs.	toxicity		The Journal of toxicological sciences	2014	24418710
Hsp90 inhibitor as a sensitizer of cancer cells to different therapies (review).	On the contrary, some Hsp90 inhibitors increased toxicity and resistance of cancer cells induced by heat shock response, and through the interaction of survival signals, that occurred as side effects of treatments, could be very effectively limited via combination of therapies.	toxicity		International journal of oncology	2015	25501619

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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