TargetTri: Safety Assessment and De-risking of Novel Drug Targets

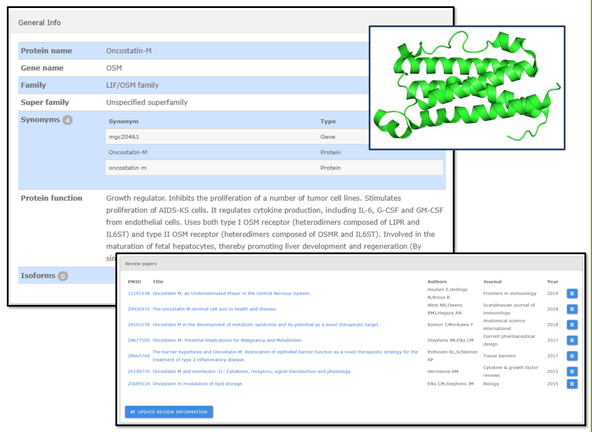
Jennifer Venhorst, Gino J. Kalkman, Tanja Rouhani Rankouhi, Eugene P. van Someren and Simon Folkertsma, *TNO, Zeist, The Netherlands*

TNO innovation for life

Case Study: Oncostatin M (OSM)

The TargetTri platform has been applied to analyze and de-risk Oncostatin M (OSM), identified as a potential therapeutic target for cardiovascular disease / atherosclerosis by the CarTarDis consortium. To this end, all information regarding OSM relevant for a safety assessment in the context of the mechanism of action (inhibition) was first extracted from TargetTri by navigating through separate views, which are organized by information type and source. The extracted data was subsequently subjected to expert analysis.

Target Characteristics

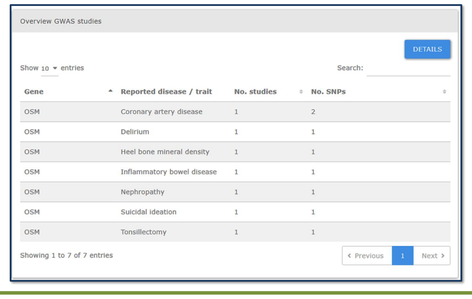


High level target characteristics were retrieved with TargetTri's target summary and review papers view, showing that OSM signalling has been implicated in a wide range of physiological (e.g. bone remodelling, hepatic cell differentiation and haematopoiesis) and pathological (e.g. endothelial dysfunction) processes. Its effects are exerted via two receptor complexes:

1) OSMRβ/gp130 (OSM type II receptor complex)
2) LIFR/gp130 (OSM type I receptor complex)

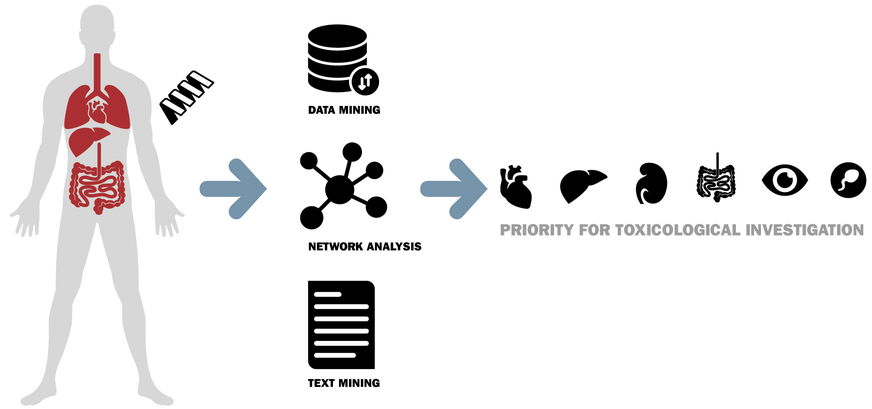
Human phenotypes (DM)

The Genome-wide association (GWAS) studies view shows that variants in the OSM gene have been associated with cardiovascular disease, supporting the envisaged therapeutic indication. Other associations include among others effects on bone, kidney and the gastrointestinal tract. Additional insight on genetic diseases is offered by the target-related effects view (DM; next panel).



TargetTri

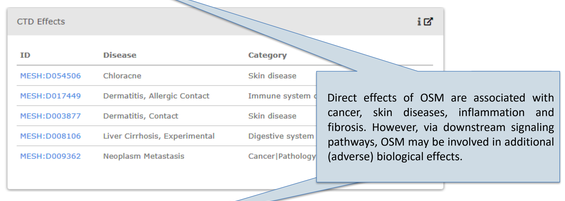
To aid in the toxicological triaging of novel drug targets, TNO has developed the web-based system TargetTri that builds upon our manual, customizable Target Safety Assessment (TSA) service. Via multiple views, derived from data-mining, network analysis and text-mining, highly efficient toxicological assessments and triaging of drug targets can be performed.



Target-related effects (DM)

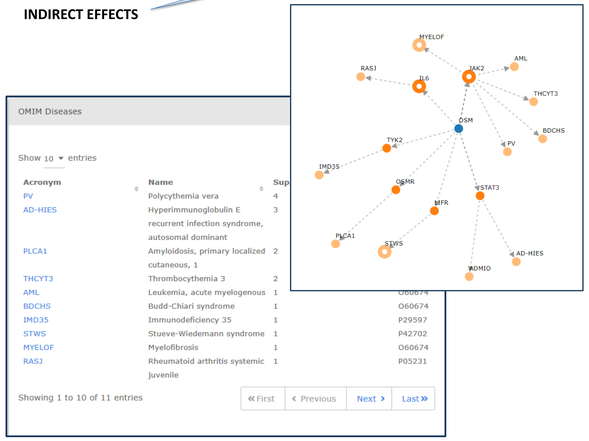
Datamining (DM) of both direct and indirect effects (via protein-protein interactions) is performed in TargetTri using several databases.

DIRECT EFFECTS



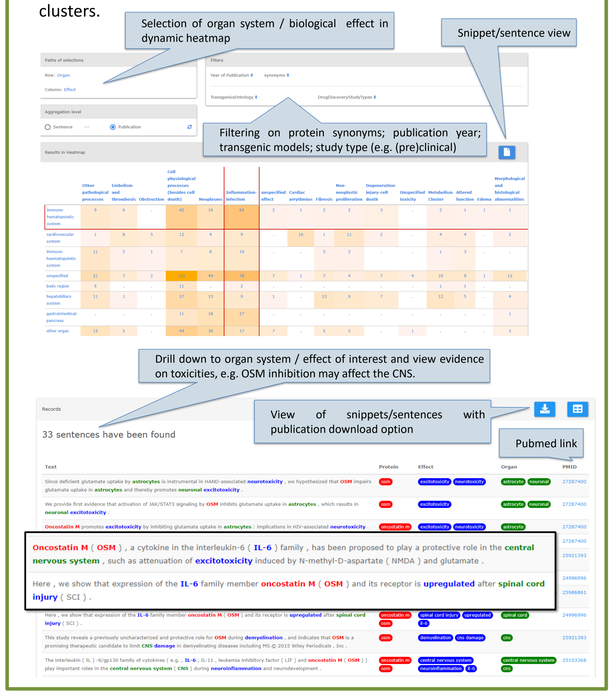
Direct effects of OSM are associated with cancer, skin diseases, inflammation and fibrosis. However, via downstream signaling pathways, OSM may be involved in additional (adverse) biological effects.

INDIRECT EFFECTS



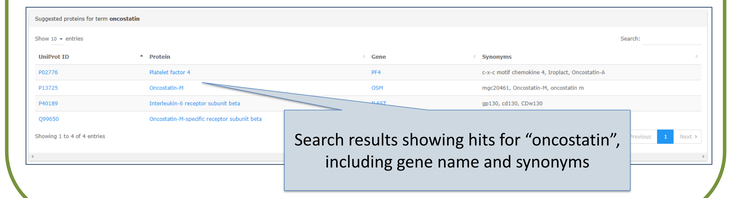
Target-related effects (TM)

TargetTri uses a proprietary ontology and text-mining system to mine protein – effect/disease relationships from literature. Results are presented in an interactive heatmap based on organ system and effect clusters.



Input Query

TargetTri can extract and visualize data on-the-fly for any of the 20k reviewed human proteins present in UniProt. To start an assessment, simply enter the name of the target of interest, its gene name or any of its synonyms.



Collaboration Opportunities

TargetTri is currently in a research phase and expanding towards new application areas, such as target discovery and efficacy/toxicity biomarker predictions. If you are interested in joining any of the ongoing TargetTri activities, please get in touch.

ACKNOWLEDGEMENTS *This research was supported by the Dutch Ministry of Economic Affairs*

Expert evaluation

The data and literature retrieved by TargetTri, including clinical data pertaining to the anti-OSM compounds GSK2330811 and GSK315234 (rheumatoid arthritis; data not shown), was subjected to an expert safety assessment. Potential safety liabilities of OSM inhibition deemed to be of high priority for further investigation are shown in the table below. Specific patient populations at risk are listed (A+: atherosclerosis patients; G: general population; or otherwise indicated specific diseases). TargetTri's assay module may be used to identify suitable assays to de-risk the identified safety liabilities (not shown).

CONCLUSIONS			
Affected organ system / process	**Adverse effect**	**Priority for investigation**	**Patient population at risk**
Cardiovascular system	Reduced myocardial remodelling in acute myocardial infarction	High	A+/Acute heart injuries
Immune system	Increased susceptibility to infections /number of immune cells↓	High	G
Haematopoiesis	Platelets↓ / erythrocytes↓ → anaemia	High	G
CNS/PNS	Impaired CNS repair/ neuroprotection	High	Pre-existing CNS disease (MS, nerve injury)
Cancer and cell proliferation	Cancer cell growth/progression (e.g., breast cancer chondrosarcoma, osteosacroma)	High	G/Pre-existing cancer

Risk ranking/prioritization was performed based on the severity of the effect, observed frequency in studies and evidence level. The latter included in vitro, in vivo, in vivo transgenic, human genetic and clinical trial data.