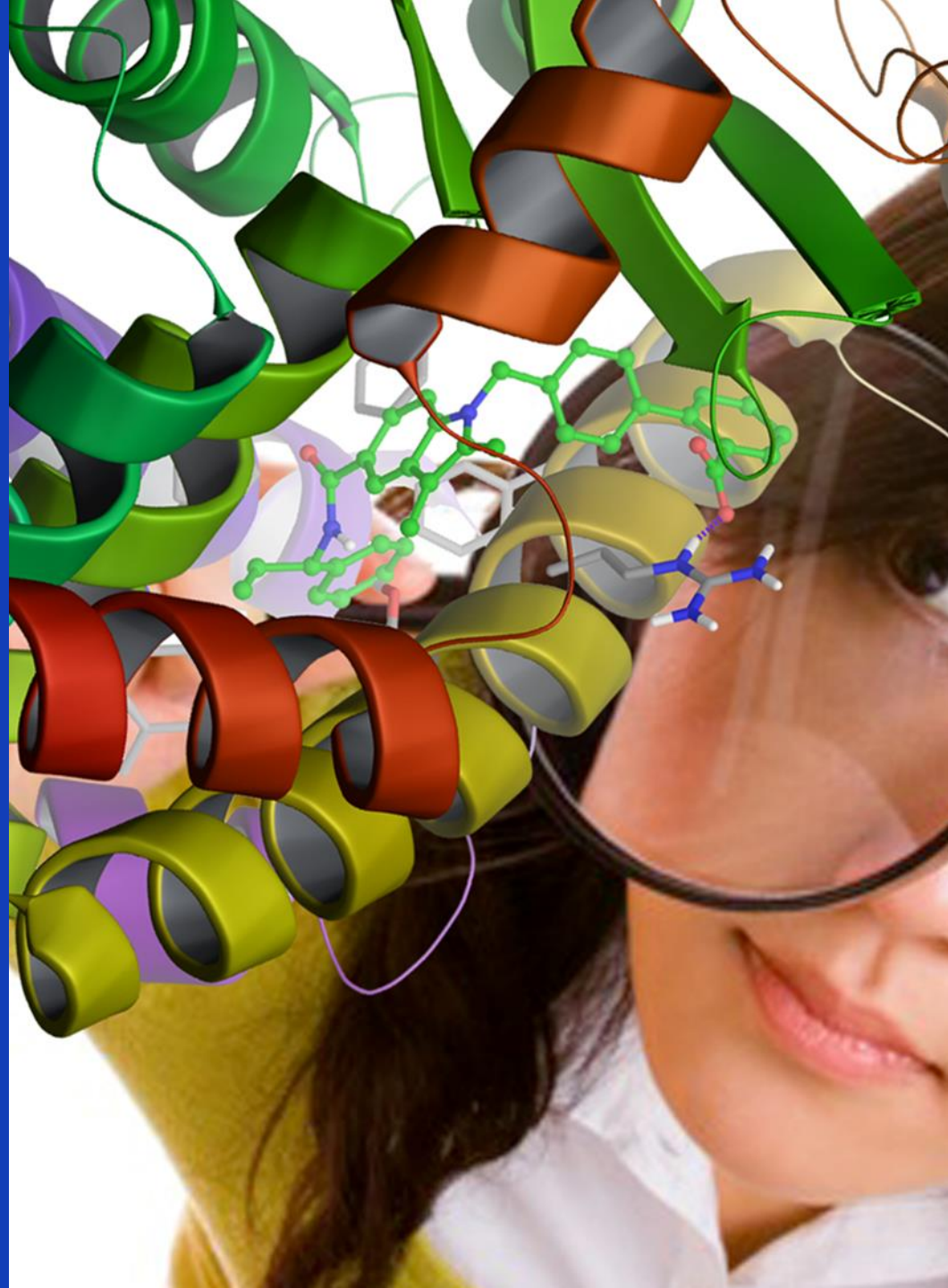
TargetTri: Drug Target Assessment

Classification of drug target modulation and associated effects

Leiden | The Netherlands

Jennifer McCormack - Venhorst

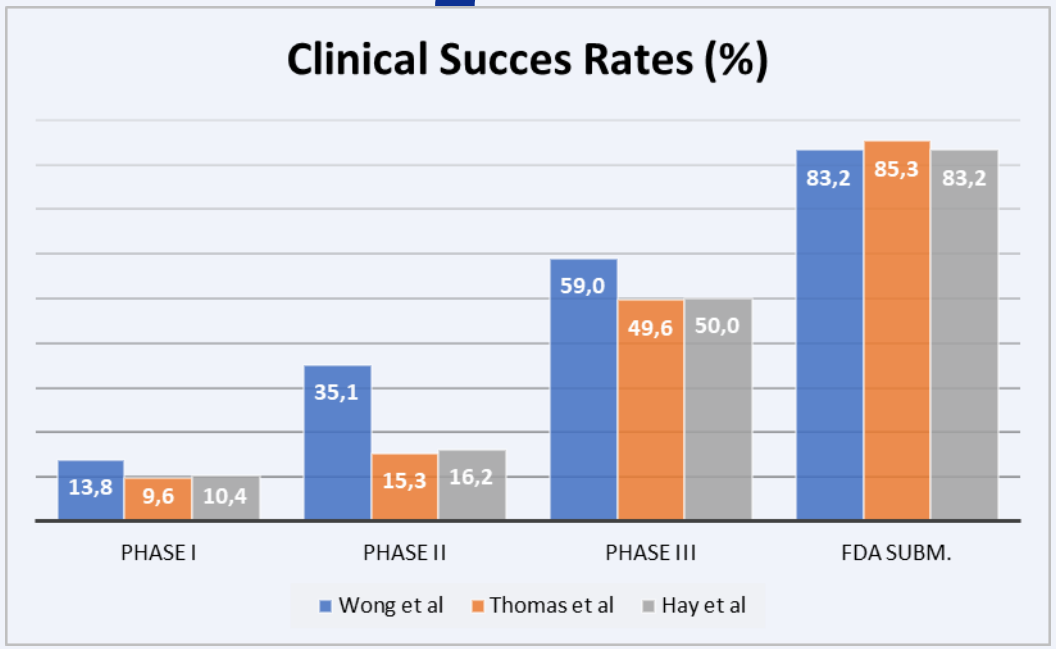
TNO innovation for life



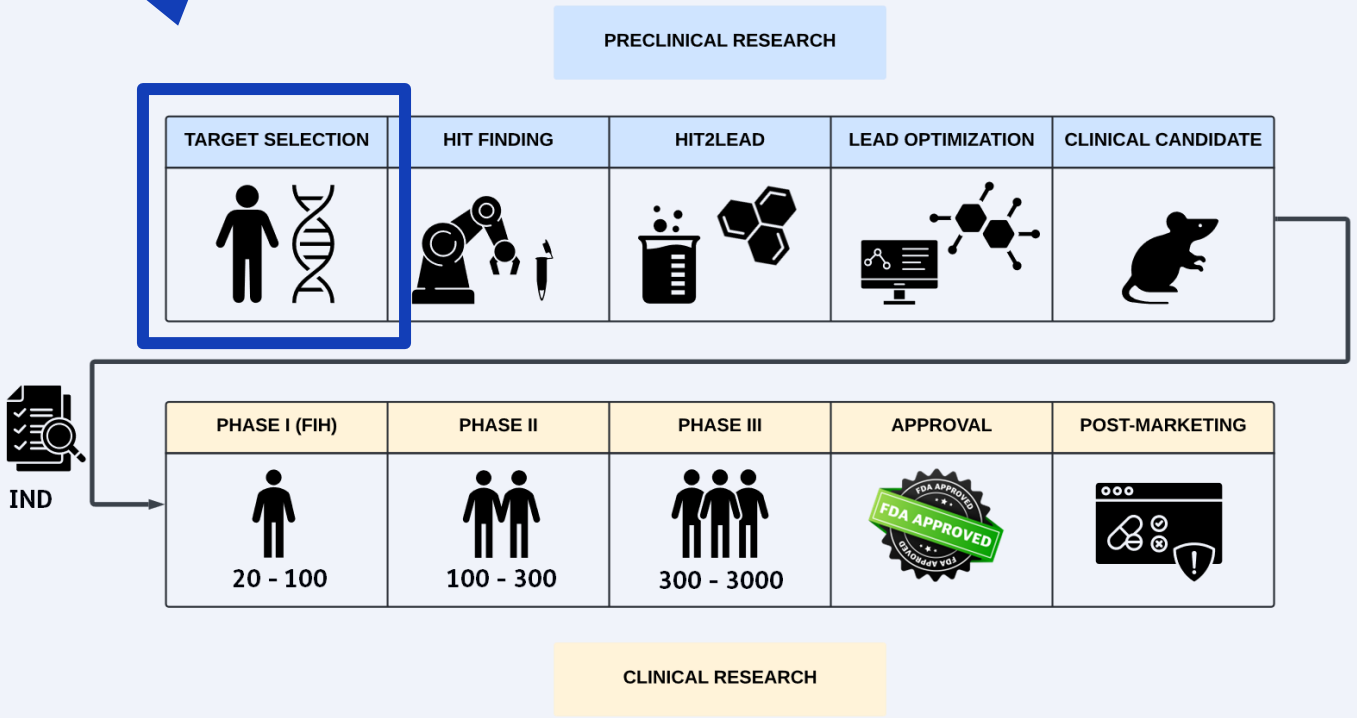
Outline

1. Overview
2. BERT models
3. Use cases
4. Conclusions

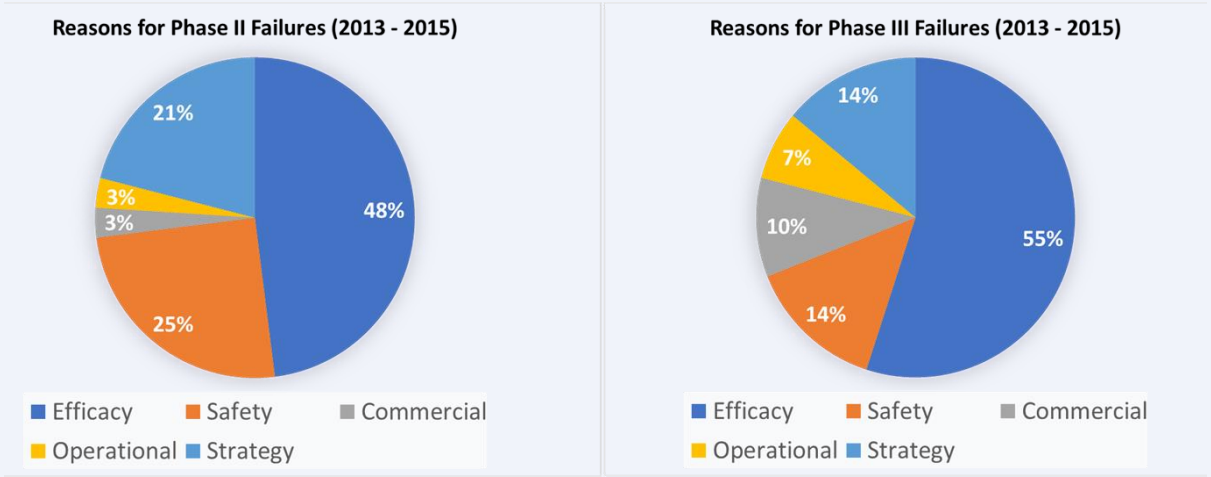
The need for drug targets assessments



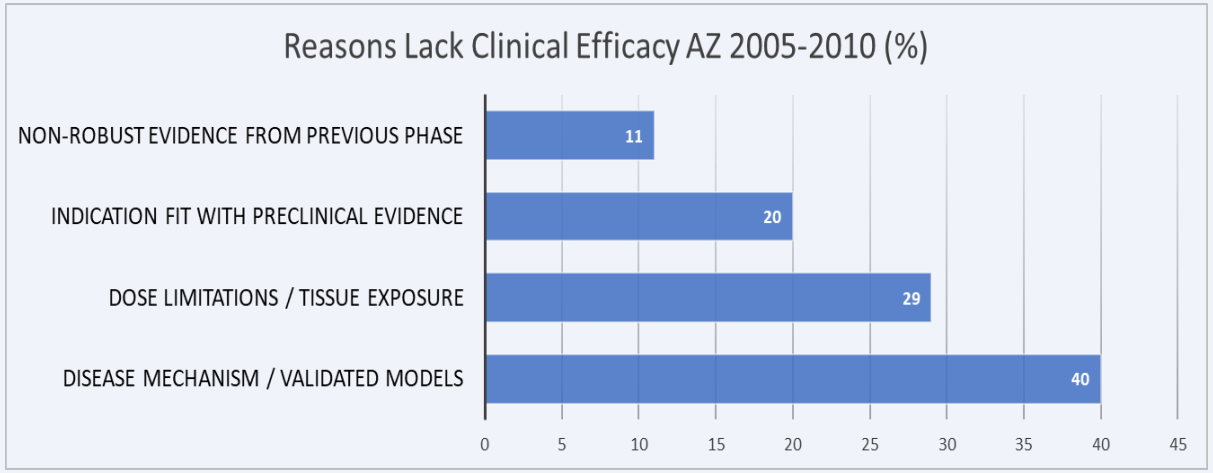
Wouters, 2020; PMID: 32125404



Target safety and efficacy: mechanism-based insights



(Harrison, 2018; PMID: 27811931)



Cook, 2014; PMID: 24833294

TargetTri

- ✓ Efficiency
- ✓ Centralized data sources
- ✓ No user-bias

TargetTri: Overview

Platform for target-centric analyses with an emphasis on text-mining

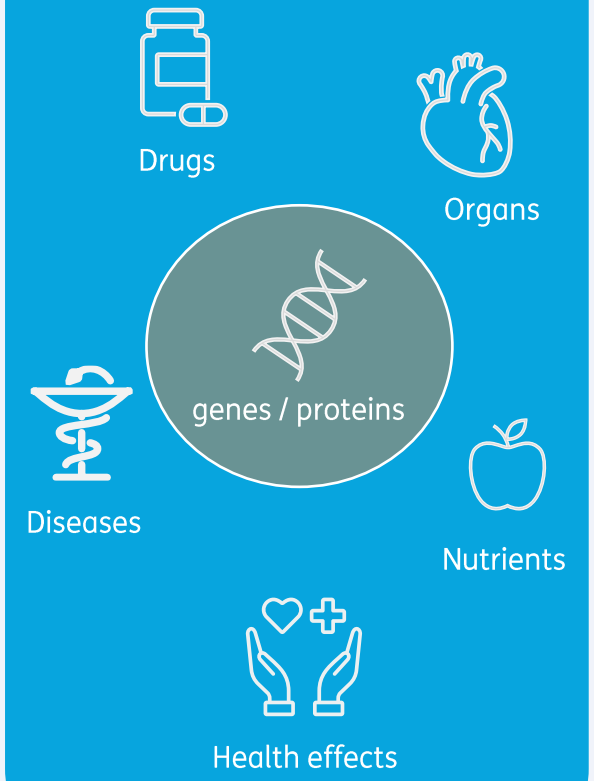
- Inception during collaborative project with pharma
- Covers the complete health space
- Drug targets (proteins / genes), health-related effects (disease, physiology), organs and compounds
- Integration of various data sources (databases and literature)
- Scheduled updating schemes in place

Access:

- Web-based interface for target-centric queries
- Off-line use for customized research questions and big data analyses
  - Includes target discovery

TargetTri: 3 main integratively-used tools

ONTOLOGIES



TEXT-MINING / RELATION CLASSIFICATION

PubMed

TargetTri

DATA-MINING

UP
HPA
GWAS Catalog
ClinVar
Clinically relevant variation
STRING
ChEMBL
NIH
ClinicalTrials.gov
FOODB

TargetTri: TNOs text-mining USPs

Sentence level text-mining of PubMed

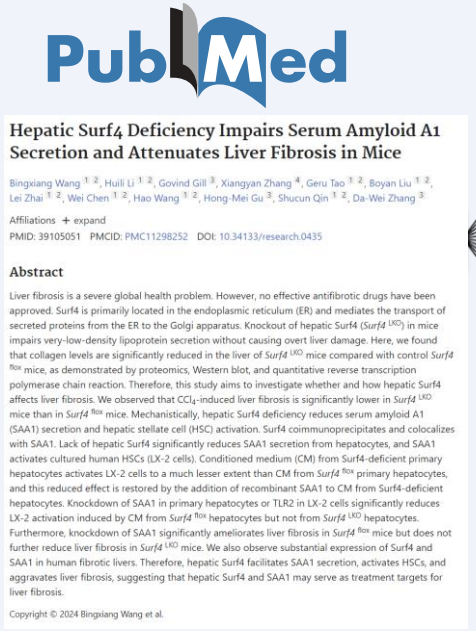
- Custom, hierarchical ontologies for entities: proteins, health effects, organs, compounds
  - beyond standard ontologies such as MESH; expert-curated terms
  - linked via source identifiers
- Abbreviation handling with confidence scores
- Filtering options (e.g. development phase, study condition)
- Natural language processing pipeline

Text-mining interface

- Interactive, fully dynamic heatmap showing ‘hot spots’
  - zoom in on desired entity
- Visualization underlying PubMed sentences and publications

Natural Language Processing

Daily workflow



Hepatic Surf4 Deficiency Impairs Serum Amyloid A1 Secretion and Attenuates Liver Fibrosis in Mice

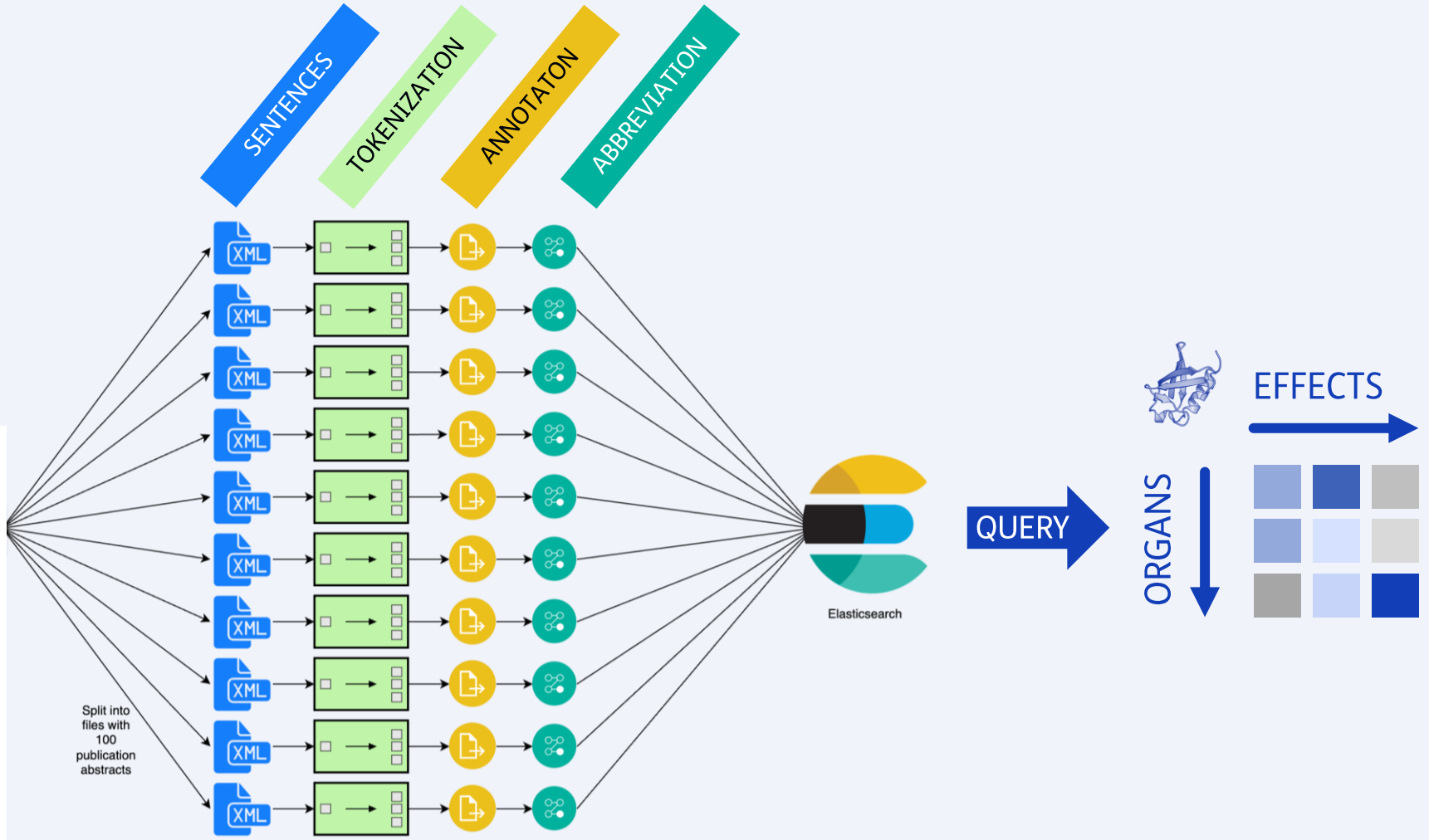
Bingxiang Wang [1, 2], Huili Li [1, 2], Govind Gill [3], Xiangyan Zhang [4], Geru Tao [1, 2], Boyan Liu [1, 2], Lei Zhai [1, 2], Wei Chen [1, 2], Hao Wang [1, 2], Hong-Mei Gu [3], Shucun Qin [1, 2], Da-Wei Zhang [3]

Affiliations + expand

PMID: 39105051 PMCID: PMC11298252 DOI: 10.34133/research.0435

Abstract

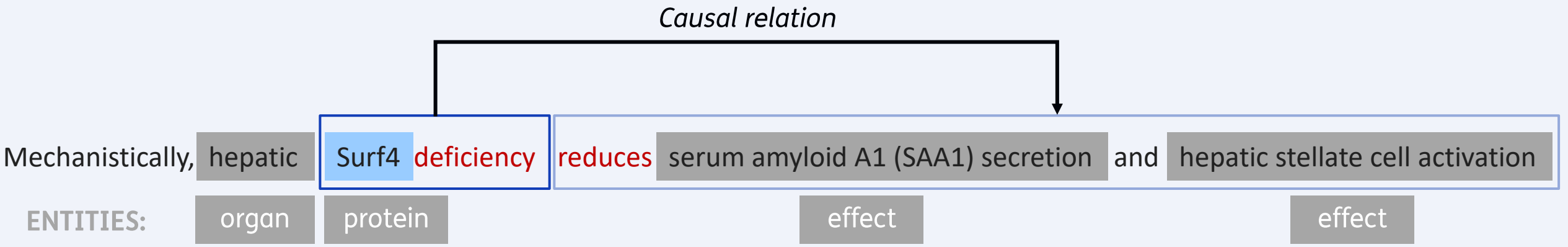
Liver fibrosis is a severe global health problem. However, no effective antifibrotic drugs have been approved. Surf4 is primarily located in the endoplasmic reticulum (ER) and mediates the transport of secreted proteins from the ER to the Golgi apparatus. Knockout of hepatic Surf4 (*Surf4* ^{LKO}) in mice impairs very-low-density lipoprotein secretion without causing overt liver damage. Here, we found that collagen levels are significantly reduced in the liver of *Surf4* ^{LKO} mice compared with control *Surf4* ^{flox} mice, as demonstrated by proteomics, Western blot, and quantitative reverse transcription polymerase chain reaction. Therefore, this study aims to investigate whether and how hepatic Surf4 affects liver fibrosis. We observed that CCl_4-induced liver fibrosis is significantly lower in *Surf4* ^{LKO} mice than in *Surf4* ^{flox} mice. Mechanistically, hepatic Surf4 deficiency reduces serum amyloid A1 (SAA1) secretion and hepatic stellate cell (HSC) activation. Surf4 coimmunoprecipitates and colocalizes with SAA1. Lack of hepatic Surf4 significantly reduces SAA1 secretion from hepatocytes, and SAA1 activates cultured human HSCs (LX-2 cells). Conditioned medium (CM) from Surf4-deficient primary hepatocytes activates LX-2 cells to a much lesser extent than CM from *Surf4* ^{flox} primary hepatocytes, and this reduced effect is restored by the addition of recombinant SAA1 to CM from Surf4-deficient hepatocytes. Knockdown of SAA1 in primary hepatocytes or TLR2 in LX-2 cells significantly reduces LX-2 activation induced by CM from *Surf4* ^{flox} hepatocytes but not from *Surf4* ^{LKO} hepatocytes. Furthermore, knockdown of SAA1 significantly ameliorates liver fibrosis in *Surf4* ^{flox} mice but does not further reduce liver fibrosis in *Surf4* ^{LKO} mice. We also observe substantial expression of Surf4 and SAA1 in human fibrotic livers. Therefore, hepatic Surf4 facilitates SAA1 secretion, activates HSCs, and aggravates liver fibrosis, suggesting that hepatic Surf4 and SAA1 may serve as treatment targets for liver fibrosis.

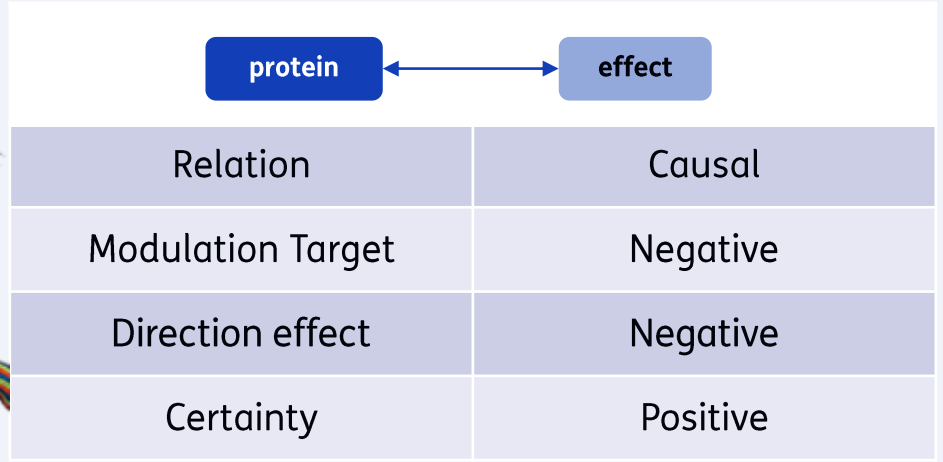


Mechanistically, hepatic Surf4 deficiency reduces serum amyloid A1 (SAA1) secretion and hepatic stellate cell activation

ENTITIES: organ protein effect organ effect

Relation classification: fine-tuning PubMed BERT





Relation	Causal
Modulation Target	Negative
Direction effect	Negative
Certainty	Positive

Use case: target discovery for liver fibrosis

TargetTri

Protein + liver fibrosis terms

ONTOLOGY CLUSTERS FIBROSIS

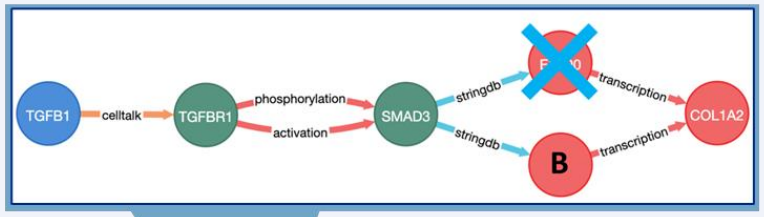
- Liver fibrosis
- HSC activation
- Collagen deposition

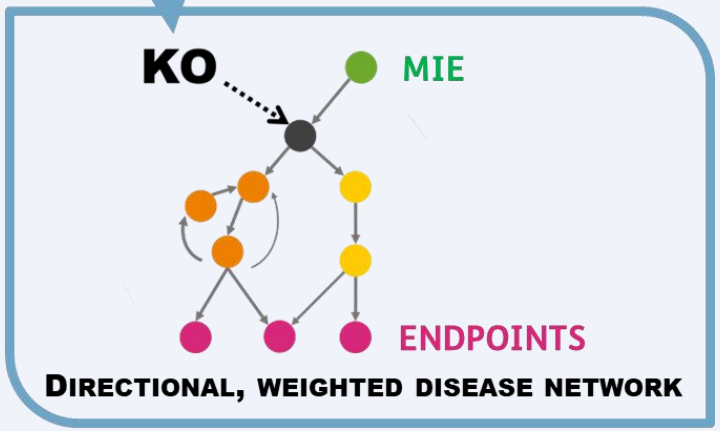
SELECTED DISEASE NODES

IPA

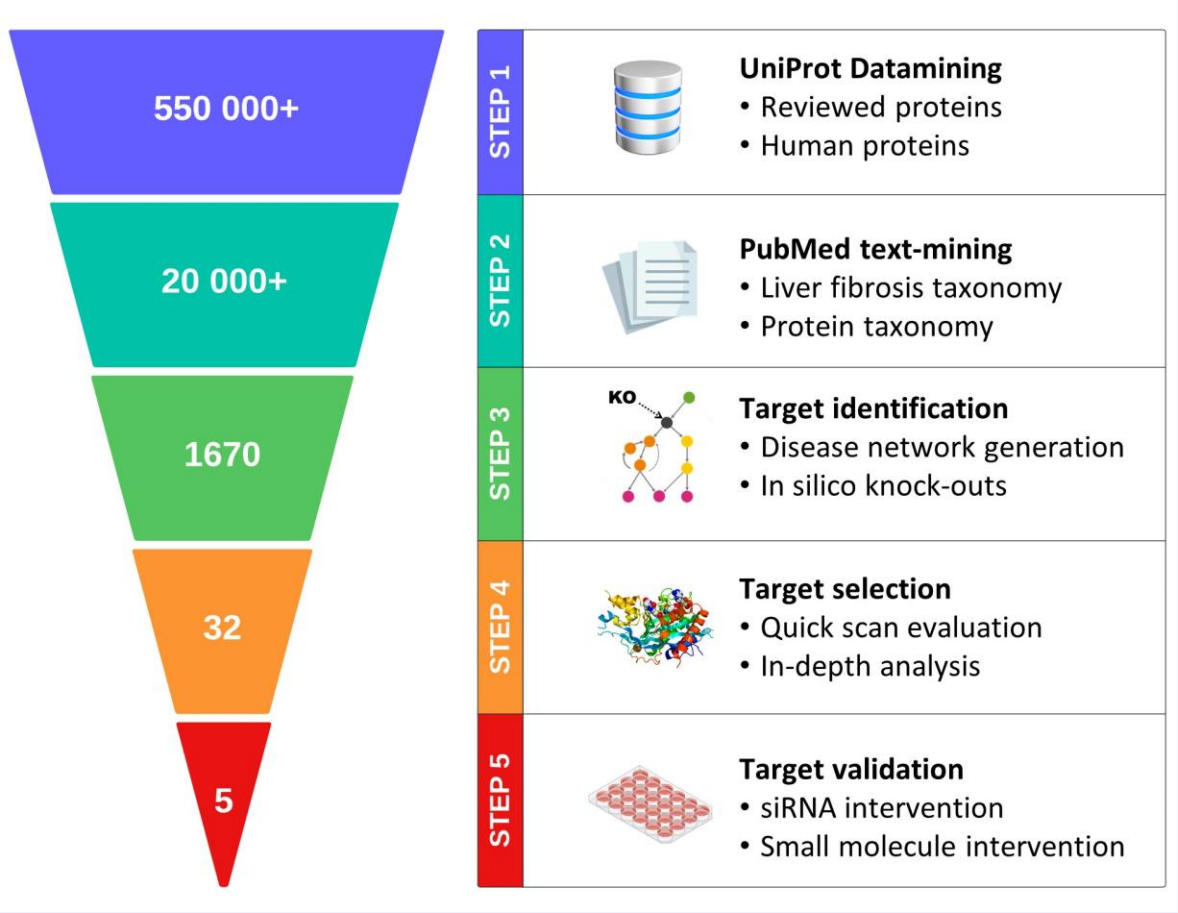
DIRECTIONAL PPI

WEIGHTED EDGES FROM PATIENTS





Use case: target discovery for liver fibrosis



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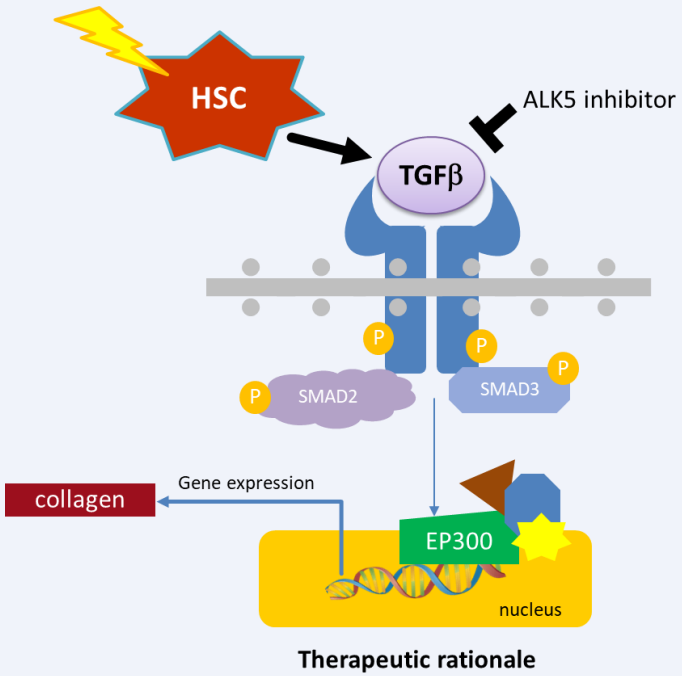
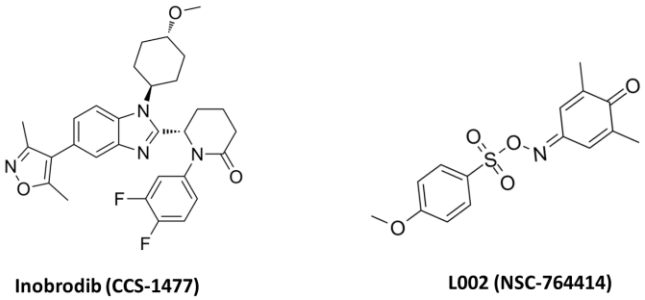
Use case: target discovery for liver fibrosis

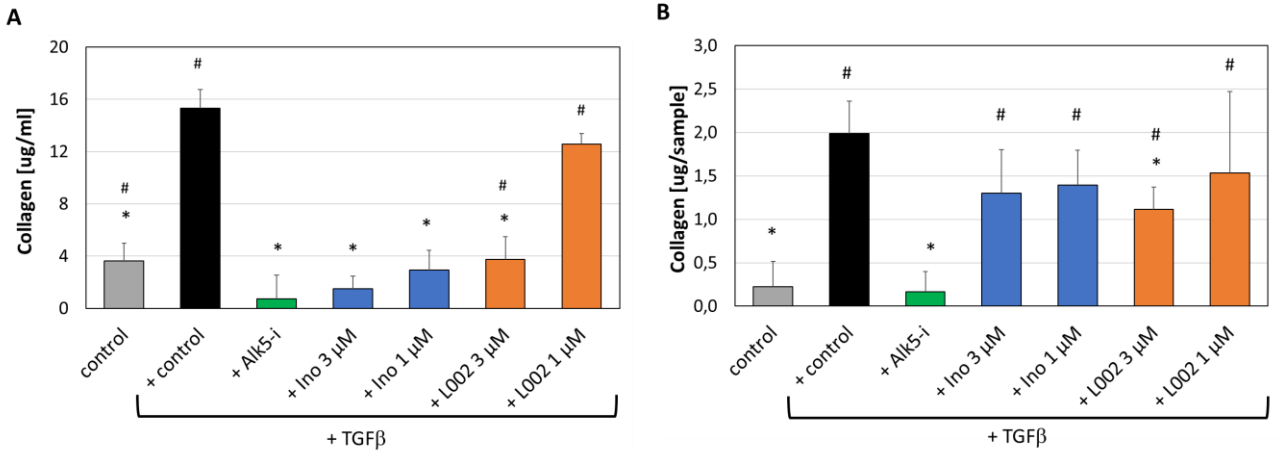


Therapeutic rationale



Inobrodib (CCS-1477)

L002 (NSC-764414)



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Conclusions

TargetTri can efficiently be used to investigate (exploratory) targets

- Heatmap
- Relation classification
- Filtering options

Future developments:

- Drug-centric exploration
- Data-driven entity recognition for text-mining results
- Automated data interpretation

TargetTri is accessible: www.targettri.com

- Free for academic use

Thank you for your attention

TargetTri team

Gino Kalkman

Erik Lemcke

Jochem de Vries

Bart van Venrooij

Marlies Otto

Tanja Rouhani Rankouhi

Simon Folkertsma

Jennifer McCormack-Venhorst

Network biology team

Remon Dulos

Martien Caspers

Joline Attema

Christa de Ruiter

Roeland Hanemaaijer

Lars Verschuren

jennifer.mccormack@tno.nl

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