In silico approach for drug target safety assessment

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Objectives

Typically, out of 10 drug candidates entering clinical development, only one will successfully be launched (1). Attrition can result from a failure to identify hazards at all stages of drug discovery and development, suboptimal risk assessment in predicting human safety or inability to optimally manage the risk and mitigate safety signals (2).

The aim of this study was to develop a comprehensive database and software that can be used as a tool for target safety assessment – to give quick insight into the target involvement in biological/pathological processes, signaling pathways and chemical interactions.

We validated the system by exploring vascular endothelial growth factor receptor 2 (VEGFR2), a high data density target with known safety liabilities.

Methods

In our knowledge base we catalogued 4.000.000 references supporting each database entry, with hyperlinked interactions to appropriate PubMed articles as support, while proteins and chemicals are hyperlinked to EntrezProtein and PubChem respectively. We developed toxicology ontology with over 2500 toxicity endpoints.

We address to the three broad data sources (Figure 1).

- Data sets from high-throughput analysis relevant to target
- Peer-reviewed published literature from both *in vivo* and *in vitro* studies including humans, rat and mouse models
- Publicly available knowledge bases containing notification on compounds, proteins, functional information, clinical studies etc.

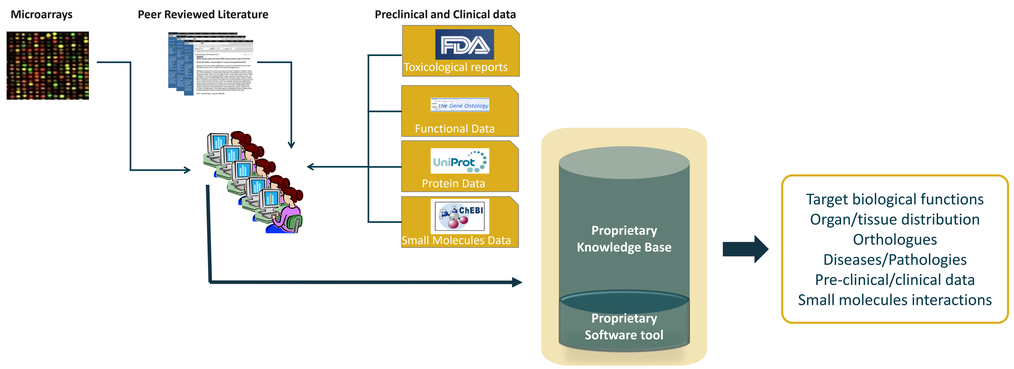

Figure 1. Manually curated database. Data were extracted from many diverse sources. Database contains 50,000 compounds, nearly 700 biological pathways (metabolic and signaling) and more than 4 million articles related to targets and their characteristics, such as biological function, orthologues, and pre-clinical and clinical drug studies data. Additionally, we have identified and curated all small molecules associated with a target allowing possible investigation of mechanistic hypothesis.

As a result of this approach we developed a powerful knowledge database for target safety assessment, by collecting and processing available knowledge about target characteristics - including internally curated and various publicly available data on proteins, biologically-active chemicals, their interactions, pathways and pathologies.

We tested the system by exploring potential VEGFR2 safety concerns.

Results

In order to test our system, we focused on the VEGFR2 and its characterization. Using our software tool (Gene function (GO) module), we quickly identified VEGFR2 biological functions, such as alveolus development, branching morphogenesis of an epithelial tube, vasculogenesis, ovarian follicle development and hematopoiesis. VEGFR2 is involved in those processes either directly or via down- and up-stream molecules (Table 1).

Biological processes	Direct involvement	Involvement via other molecules
Alveolus development	FGF10, KDR	GATA4, GRB2, FGF8, PECAM1, TGFB1, VEGFA, HAND1, HAND2, HEY2 …
Branching morphogenesis of an epithelial tube	FOXA2, FGF10, KDR, NOTCH1	PTCH1, FGF8, FGF2, FGFR2, PECAM1, CASP3, HAND2, MAPK3, MAPK1 …
Vasculogenesis	HEHEY1, RASA1, NKX2-5, T, KDR, WT1, SHH	VEGFA, PDGFRA, PDGFRB, PECAM1, GATA4, CASP3, EGFR, NOCH1 …
Ovarian follicle development	ANG, KDR	VEGFA, SPH, PECAM1, HIF1A, VEGFA, TGFB1, FGF2, CASP3, EGFR …
Hematopoiesis	TAL1, DLL1, NOTCH4, NKX2-5, JAG1, KDR, KIT, CTNNB1	PDGFRA, NOTCH1, VEGFA, PECAM1, GATA1, CASP3, FGFR2, FLT1, GATA4 …

Table 1. A sample of biological processes (GO module) in which VEGFR2 is having direct or indirect role

Furthermore, our tool associated VEGFR2 with several pathologies and toxicities related to dysplasia, anemia and various cancers. The system associated VEGFR2 with other pathologies on cellular, organ and organ-system level related to male and female reproductive system (ovary carcinoma and prostate hypertrophy), cardiovascular system (hypertension, atherosclerosis and heart fibrosis), lymphatic system (lymph node neoplasia and toxicity), and GI system (pancreas toxicity) (Table 2).

Organ and tissue pathologies		Diseases
Ovary carcinoma	Lymph node neoplasia	Anemia
Prostate hypertrophy	Kidney carcinoma	Multiple sclerosis
Atherosclerosis	Pancreas toxicity	Diabetic nephropathy
Hypertension	Leukemia	Renal cell carcinoma
Heart fibrosis	Cervical carcinoma	Squamous cell carcinoma

Table 2. A sample of VEGFR2 associated pathologies and diseases.

We also identified proteins that interact with VEGFR2. Among them, there are also proteins known for their involvement in ovary carcinoma (Figure 2).

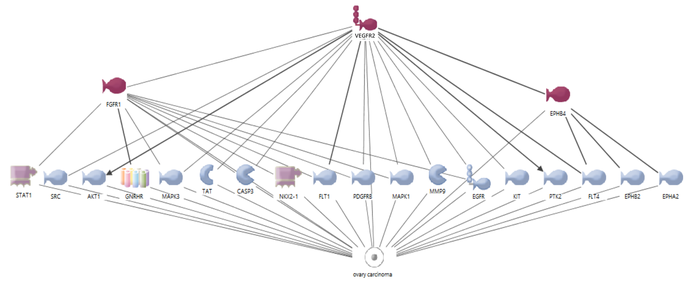

Figure 2. A segment from the VEGFR2 protein interaction network. Violet coloured are proteins involved in ovary carcinoma.

Vast amount of processed data in our system presents the potential for generation of valuable mechanistic hypothesis. Analyzing VEGFR2 together with its chemical interaction partners (agonists and antagonists) identified a role for VEGFR2 in renal cell carcinoma (Figure 3) that corresponds to VEGFR2 antagonist therapeutic application (3).

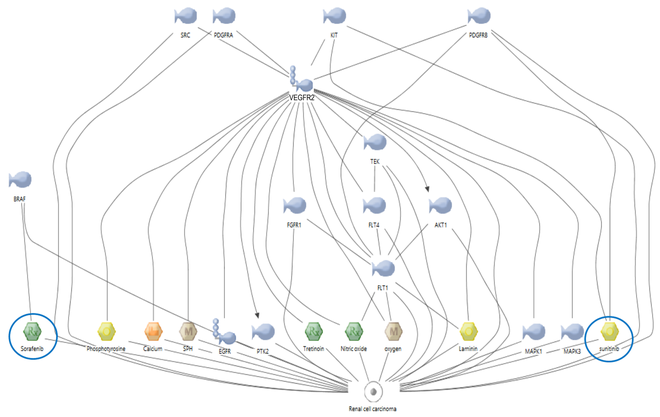

Figure 3. A segment from Renal cell carcinoma analysis. Molecules encircled in blue are drugs interacting with VEGFR2.

Conclusion

- In this study we presented manually curated database that can be used for target safety assessment studies.
- On example of VEGFR2, we showed that our tool can contribute to quick target toxicological assessment and a better understanding of therapeutic potential of a target manipulation.
- We plan to continually maintain, update and review the database with new target safety annotations and discoveries.

References

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