Bioinformatics approach in reducing cancer drug attrition

Katica Jankovic[1]*, Tamara Krsmanovic[1], Toni Franjkic[1], Benedetta Leoni[1], Gordana Apic[1], Robert B. Russell[2]

[1] Metisox, Cambridge, UK; [2] University of Heidelberg, Cell Networks, Heidelberg, Germany, *katica.stojanov@metisox.com

OBJECTIVES

Development of oncology drugs has been reported to have a persistent attrition rate of greater than 95% (1,2), highlighting the disparity between positively assessed preclinical drug activity and subsequent inactivity in patients. Improved target validation is required for better decision-making before launching clinical trials.

The aim of this study was to help in target validation by assessing the potential toxicities associated with target manipulation before they enter clinical trials using the preexisting data. For this purpose, we generated a comprehensive database and software, with computable internally curated and various publicly available data on proteins, biologically active chemicals, their interactions, pathways and pathologies.

We validated the system by exploring PARP1 protein as a potential drug candidate for metastatic castration-resistant prostate cancer (mCRPC) treatment. Typical treatment for patients with mCRPC includes androgen-blocking therapy or chemotherapy, but most patients survive less than three years with these treatments. The PARP1 protein plays a role in regulating androgen receptor (AR) target genes by promoting AR recruitment to the promoters of its target genes and is involved in DNA repair.

METHODS

In our knowledge base (Figure 1), we catalogued 4 million references supporting each database entry, with protein-protein and protein-chemical interactions hyperlinked to appropriate PubMed articles as support, while proteins and chemicals were hyperlinked to EntrezProtein and PubChem respectively. We developed toxicology ontology with over 2,500 toxicity endpoints. The software used to query this database allows for enrichment of experimental data set with known protein and chemical interactions and effective data interpretation.

We addressed 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 databases containing information on compounds, proteins, functional data, clinical studies etc.

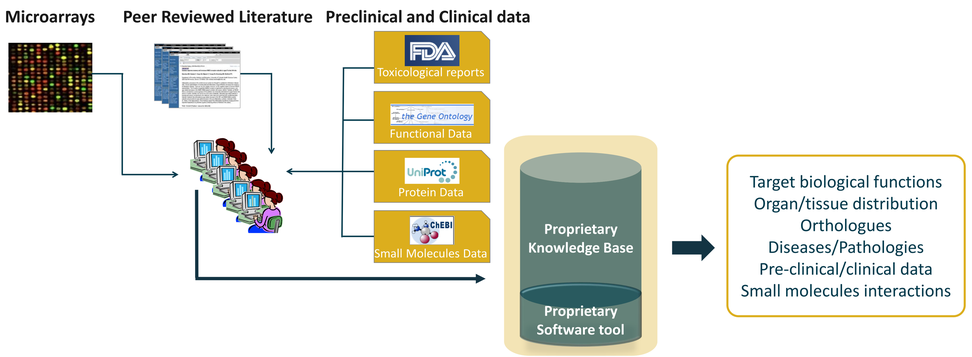

Figure 1. Manually curated database. Data was extracted from many diverse sources. Database contains complete human interactome, 2,500 organ and tissue pathologies, 500,000 synonyms/ontologies, 4 million linked articles (PubMed, FDA, clinical, patents), >10 million relationships, 50,000 biologically active chemicals.

RESULTS

Mapping PARP1 onto Gene Ontology (GO) module within the system identified PARP1 biological functions (Table 1). Mapping PARP1 together with its protein interaction network onto Diseases module within our system, associated PARP1 with several cancers, and also to other diseases (Table 2). Mapping PARP1 together with its interacting proteins onto Organ and tissue pathologies module demonstrated association with cancers of a various tissues and related toxicities, as well as cardiovascular system, immune and hematopoietic system pathologies (Table 3). Further analysis of corresponding clusters reveals the potential indication of PARP1 inhibitors or identifies their potential toxicity. Detailed analysis of the Prostate carcinoma cluster revealed that PARP1 is activated in metastatic prostate cancer cells. Therefore PARP1 has the potential for a therapeutic intervention in mCRPC patients. Literature evidence suggests hypertension and anemia as potential adverse effects of PARP inhibitors (3, 4).

Table 1. A sample of PARP1 biological functions (GO knowledge base function)

GO function
Protein amino acid ADP-ribosylation
Transcription from RNA polymerase II
Single and double strand break repair
Base-excision repair
T cell and B cell lineage commitment

Table 2. A sample of diseases associated with PARP1 analyzed together with its target molecules

Diseases
Squamous cell carcinoma, retinoblastoma, non-small cell lung cancer, chronic lymphocytic leukemia, T-cell lymphoma, cervical cancer
Ataxia telangiectasia
Systemic lupus erythematosus; arthritis; psoriasis
Parkinson's disease; Amyotrophic lateral sclerosis
Liver cirrhosis

Table 3. A sample of organ and tissue pathologies associated with PARP1 analyzed together with its target molecules.

Organ and tissue pathologies	
Cancer and related toxicities	Prostate carcinoma, pancreas carcinoma, mammary cancer and endometrium carcinoma, prostate hyperplasia, intestine metaplasia and cervical neoplasia
Cardiovascular system pathologies	Hypertension, atherosclerosis
Immune system and hematopoietic system pathologies	Stomach or gut inflammation, hematopoietic toxicity, neutrophil or lymphocyte apoptosis

Mapping PARP1 onto chemical classification module demonstrated the association between PARP1 and existing drugs suggesting the potential for combined therapy (Figure 2). Indeed, literature evidence showed that Temozolomide (an alkylating agent - WHO ATC L01AX03) and PARP1 inhibitors were more effective in treatment of mCRPC patients pre-treated with docetaxel, than Temozolomide alone (5).

Rank	Molecular Mechanism	P-val	Endpoint Category	Molecules Inside	Molecules Next To
1	Caries prophylactic agents drug cluster (ATC: A01AA)	0.0001	WHO ATC classifications		PARP1
2	Other alkylating agents drug cluster (ATC: L01AX)	0.0005	WHO ATC classifications		PARP1
3	Antiinflammatory agents, non-steroids drug cluster (ATC:	0.0005	WHO ATC classifications		PARP1
4	Acetic acid derivatives and related substances drug	0.001	WHO ATC classifications		PARP1
5	Other sex hormones and modulators of the genital	0.001	WHO ATC classifications		PARP1
6	Cytotoxic antibiotics and related substances drug cluster	0.001	WHO ATC classifications		PARP1
7	Antineoplastic agents drug cluster (ATC: L01)	0.001	WHO ATC classifications		PARP1
8	Other anti-acne preparations for topical use drug cluster	0.001	WHO ATC classifications		PARP1
9	Stomatological preparations drug cluster (ATC: A01A)	0.001	WHO ATC classifications		PARP1
10	Anthracyclines and related substances drug cluster	0.001	WHO ATC classifications		PARP1
11	Anti-acne preparations for topical use drug cluster (ATC:	0.005	WHO ATC classifications		PARP1
12	Mineral supplements drug cluster (ATC: A12)	0.005	WHO ATC classifications		PARP1
13	Hepatic and reticulo endothelial system drug cluster	0.005	WHO ATC classifications		PARP1
14	Other agents for local oral treatment drug cluster (ATC:	0.005	WHO ATC classifications		PARP1
15	Antimetabolites drug cluster (ATC: L01B)	0.005	WHO ATC classifications		PARP1
16	Antibiotics drug cluster (ATC: A07AA)	0.005	WHO ATC classifications		PARP1
17	Plant alkaloids and other natural products drug cluster	0.005	WHO ATC classifications		PARP1
18	Antivirals drug cluster (ATC: D06BB)	0.005	WHO ATC classifications		PARP1
19	Salicylic acid and derivatives drug cluster (ATC: N02BA)	0.005	WHO ATC classifications		PARP1
20	Antidiarrheals, intestinal antiinflammatory/antiinfective	0.005	WHO ATC classifications		PARP1
21	Alkylating agents drug cluster (ATC: L01A)	0.005	WHO ATC classifications		PARP1
22	Anilides drug cluster (ATC: N02BE)	0.005	WHO ATC classifications		PARP1

Figure 2. Chemical classification module within our proprietary database. A sample of existing drugs (WHO ATC classification-endpoint category) that present a potential for combined therapy with PARP1 inhibitors. Molecules inside are directly connected to the molecular mechanism, and molecules next to are "guilty by association".

CONCLUSION

- On the example of PARP1 inhibition for the treatment of metastatic castration-resistant prostate cancer we showed that our tool can contribute to a better understanding of target role in a disease, therapeutic potential of a target inhibition and quick target toxicological assessment.

REFERENCES

1. Jentzsch *et al.*, JAMA Netw Open. **2023** Jul 3;6(7):e2324977. **2. Dowden *et al.*,** Nat Rev Drug Discov. **2019** Jul;18(7):495-496. **3. Chen *et al.*,** BMC Cancer. **2023** Jan 1;23(1):107 **4. Friedlander *et al.*,** Am Soc Clin Oncol Educ Book. **2023** Jun:43:e390876. **5. Hussain *et al.*,** Invest New Drugs. **2014** Oct;32(5):904-12.