Analysis of orphan diseases
with a KNIME workflow using Open PHACTS, with the potential of drug repurposing

Jana Gurinova, Daniela Digles, Gerhard F. Ecker
University of Vienna, Department of Pharmaceutical Chemistry, Althanstraße 14, 1090, Vienna

Introduction

Worldwide around 400 million people are affected by orphan diseases [1], orphan meaning affecting less than 1 in 2000 citizens [2]. The low prevalence coupled with the sheer number of orphan diseases (about 5000-8000) is the main reason there are so few marketing approvals, amounting to treatments for roughly 200 conditions in the US and only about 45 in the European Union [1]. Drug repurposing therefore embodies an attractive option of reaching many patients with treatments that have already been deemed safe.

Aim

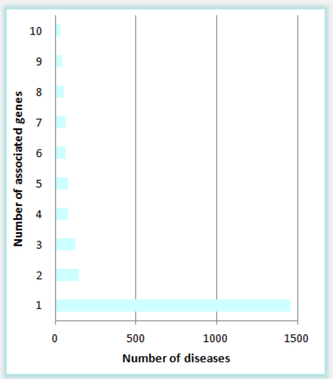
The workflow aims at providing an overview of linked targets and drugs for orphan diseases, with a special focus on involved transporters.

Methods

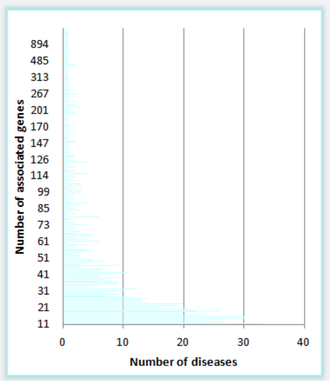
The workflow was created with the KNIME Analytics Platform software.
For data retrieval from the Open PHACTS Discovery Platform nodes developed by Ronald Siebes (VU University Amsterdam), which are available from https://github.com/openphacts/OPS-Knime, were used.

The workflow

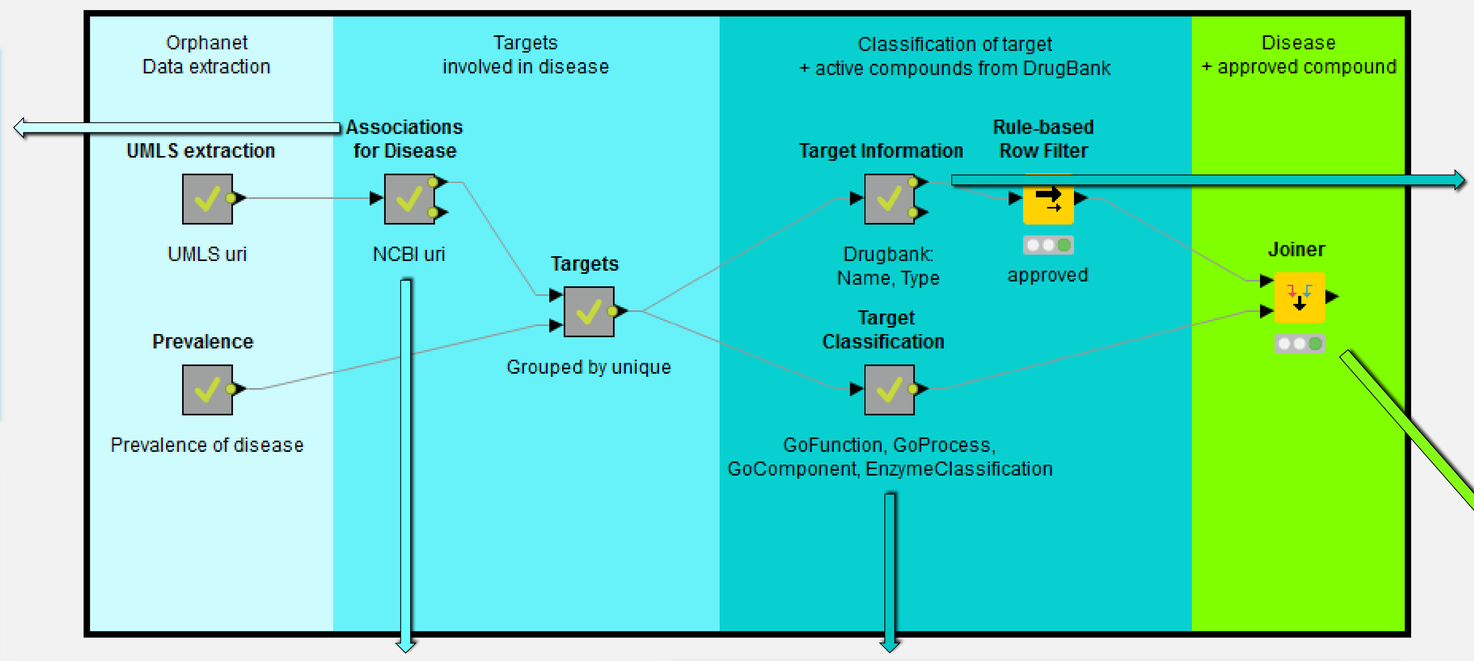
The biggest European platform for orphan diseases is Orphanet [3], and as of now, 2901 of the 9000 listed disorders including their sub-types are equipped with a UMLS identifier which was used in the workflow for retrieval of disease-related data from DisGeNET [4].

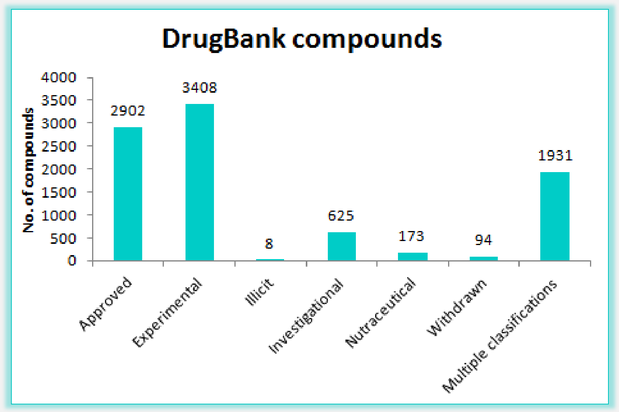


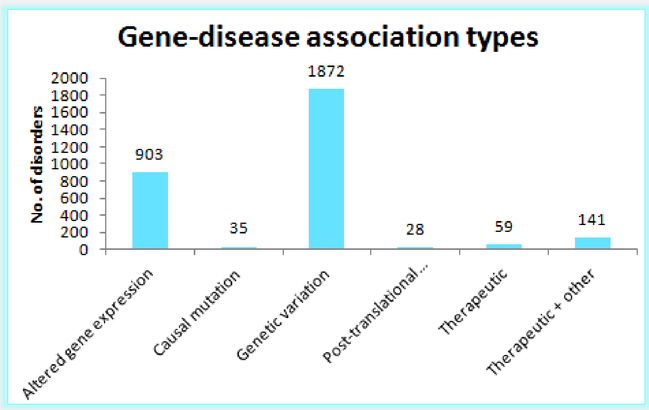
Genes per disease: 1-10

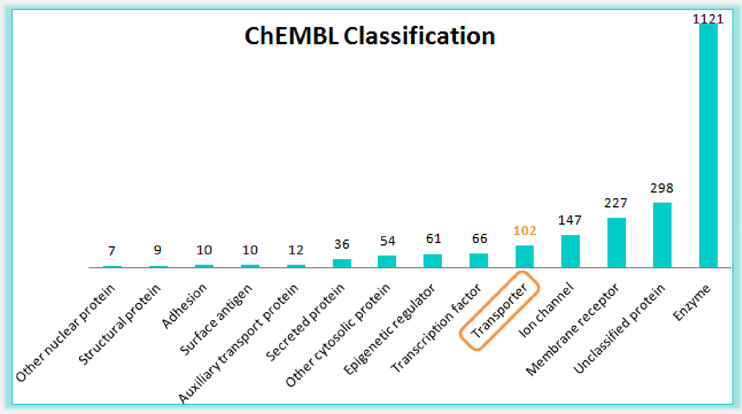


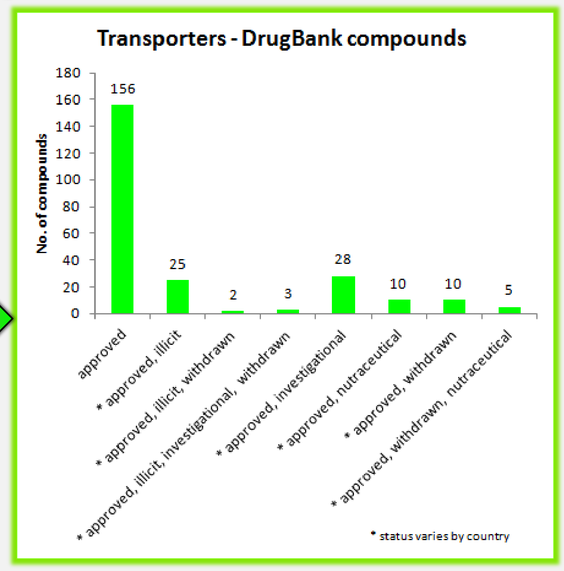
Genes per disease: >11











Results

In ChEMBL 102 of the targets are classified as transporters, whereas the search for transporters in the GO Molecular Function properties yields 311 transport related targets.
Of the latter four are described as having a therapeutic gene-disease association and of these four, synovial sarcoma is the single one that was linked to approved compounds.

Conclusions

The workflow is capable of adapting to the user's needs. Options include filtering by highest cited or multiple genes for a given disease, the gene-disease association (e.g. therapeutic), or the compound type of interest (e.g. approved, investigational). Manual investigation of the resulting compounds and their pharmacological activity (agonist/antagonist) related to the disorder of interest, may result in possible drug repurposing candidates.

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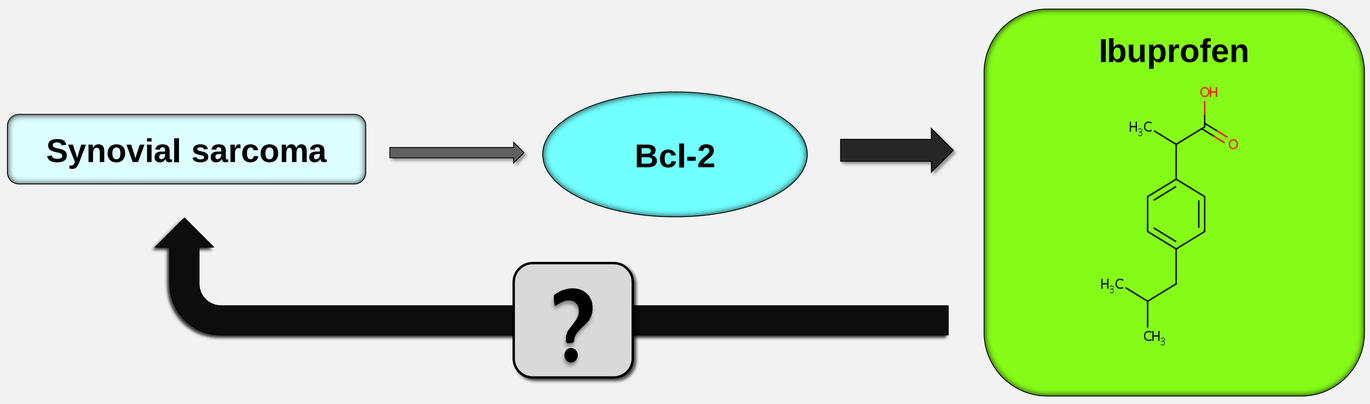
Example: Synovial sarcoma

Given that transporters are of special interest to the research group, the results from the workflow (approved compounds only) were cross-examined with an established list of transport related proteins and yielded among other compounds Ibuprofen. Upon closer examination it became apparent that in synovial sarcoma the antiapoptotic factor Bcl-2 is frequently overexpressed, leading to a lower incidence of apoptosis. Ibuprofen interestingly seems to have the ability to downregulate the mRNA levels of Bcl-2, which would lead to enhanced apoptosis and could therefore have a therapeutic effect.



References:
[1] Kaplan W et al. Priority Medicines for Europe and the World Update 2013, World Health Organization, Geneva, 2013
[2] EURORDIS. Rare Diseases: understanding this Public Health Priority. EURORDIS, Paris, 2005
[3] Orphanet: an online database of rare diseases and orphan drugs. Copyright, INSERM 1997. Available at http://www.orpha.net
[4] Janet Piñero, Núria Queralt-Rosinach, Àlex Bravo, Jordi Deu-Pons, Anna Bauer-Mehren, Martin Baron, Ferran Sanz, Laura I Furlong. DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes. Database (2015) Vol. 2015: article ID bav028; doi:10.1093/database/bav0280