IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Drug Repurposing Guidebook

Building Block I437

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Network databases
References	KEGG database: https://www.genome.jp/kegg/pathway.html doi: 10.1093/nar/gkp896 MSIG database: http://www.gsea-msigdb.org/gsea/msigdb/index.jsp doi: 10.1016/j.cels.2015.12.004 WikiPathways: https://www.wikipathways.org/index.php/WikiPathways doi: 10.1093/nar/gkv1024 Reactome: https://reactome.org/ doi: 10.1093/nar/gkab1028 GeneOntology: http://geneontology.org/ doi: 10.1038/75556 NDEX: https://www.ndexbio.org/#/ doi: 10.1016/j.cels.2015.10.001 LINCS database: https://lincs.hms.harvard.edu/db/ doi: 10.1039/c4mb00677a
Description	General biological pathway and network databases such as KEGG, MSigDB, WikiPathways, Reactome, GeneOntology and NDEX, contain information on molecular pathways, some of which are druggable. Unfortunately, these resources contain few pathway descriptions that reflect the molecular action of drugs. The molecular mRNA expression signatures changing after exposure to drugs have been recorded in the LINCS databases.

ITEM	DESCRIPTION
Category	Compound and network databases and tools to use them
Type of BB	Development resource
Geographical scope	International
Availability	Webversions are open. Downloads are also allowed without restrictions with the exception of KEGG
Scope of use	Drug repurposing candidate discovery or prioritization. General biological pathway and network databases such as KEGG, MSigDB, WikiPathways, Reactome, GeneOntology and NDEX, may be used to identify druggable molecular pathways with aberrant activity from molecular (omics) profiling experiments. The molecular mRNA expression signatures changing after exposure to drugs have been recorded in the LINCS databases. A way to identify drug repurposing candidates is to determine which mRNA expression disease signatures are changing in an opposite direction after drug exposure. Alternatively, molecular disease signatures are intersected with known protein targets from existing drugs, such as recorded in ChEBI (see building block 'Chemical compound databases')
Stakeholders involved	Intended audience are preclinical researchers from academia and industry
Enablers/ Requirements	All tools are equipped with a web interface but advanced use may required bioinformatics skills
Output	Druggable pathways and drug repurposing candidates
Best time to apply and time window	Drug repurposing candidate discovery

ITEM	DESCRIPTION
Expert tips	The pathway databases are generic. Not all pathways may be active in all cells or tissues. The LINCS database is limited in the cell lines included. For some rare disorders, no or limited data on relevant cell types may be present. The LINCS database is quite noisy, i.e. replicate experiments may not always correlate well. Additional manual review of drug repurposing candidates may be required.