REPOTRIAL

An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777111.

Deliverable D1.8
"Drugome 1.0 network"

Work Package
WP1 Data integration and in-silico trial prediction

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Document information

Grant Agreement Number: 777111				**Acronym: REPO-TRIAL**
Full title	An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes			
Topic	In-silico trials for developing and assessing biomedical products			
Funding scheme	RIA - Research and Innovation action			
Start Date	1 February 2018	**Duration**	60 months	
Project URL	https://repo-trial.eu/			
EU Project Officer	Bangin Brim, Programme Officer, European Commission			
Project Coordinator	Prof. Dr. Harald H.H.W. Schmidt, Universiteit Maastricht (UM)			
Deliverable	D1.8. Drugome 1.0 network			
Work Package	WP1 Data integration and in-silico trial prediction			
Date of Delivery	**Contractual**	31/01/2022	**Actual**	31/01/2022
Nature	Other	**Dissemination Level**	Public	
Lead Beneficiary	03 UNEW			
Responsible Author(s)	David James Skelton			
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Keywords	Drugome, Drug Repurposing			

History of changes

Version	Date	Contributions	Contributors (name and institution)
V0.1	12/01/2022	First draft	David James Skelton, Anil Wipat (UNEW)
V0.2	24/01/2022	Comments	Ana I Casas (UM)
V0.3	25/01/2022	Draft	David James Skelton, Anil Wipat (UNEW)
V1	26/01/2022	Final version	David James Skelton, Anil Wipat (UNEW)
V1	26/01/2022	Final approval	Harald Schmidt (UM)
V1	31/01/2022	Submission	Miriam Simon (concentris)

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Table of Content

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1 Objectives of the deliverable based on the Description of Action (DoA)

The objectives of this deliverable were determined as follows:

1. Decide on the purpose of Drugome v1.0
2. Based on (1), determine method for constructing Drugome v1.0
3. Create Drugome v1.0 using the method established in (2)
4. Evaluate Drugome v1.0 and determine plans for future versions

2 Executive Summary

A drugome is a network consisting of nodes, representing drugs, and edges, representing the relationships between drugs. In the context of the REPO-TRIAL project, constructing a drugome in which the edges represent mechanistic similarities between drugs could provide further evidence to support repurposing predictions. Therefore, in this report, “mechanistic similarity” refers to drugs that exert similar effects via similar interactions with specific biological molecules.

Using drug-target data information stored in NeDRexDB, an integrated database also constructed within the REPO-TRIAL project, the drugome was created in which edges between two drugs represent one or more shared drug targets, based on which a possible shared mechanism is inferred. The resultant drugome contained 4,765 drugs and 119,387 edges, including approximately one-third of all drugs in NeDRexDB and two-thirds of all drugs marked as approved in NeDRexDB. However, the remaining drugs did not have any targets that were shared with at least one other drug. While so-called “target-based drug-drug similarity networks” are not novel – for example, Udrescu *et al.* recently published such a network (Udrescu et al, 2020) – version 1.0 of the REPO-TRIAL drugome builds on Udrescu and colleagues’ work by sourcing drug-target data from multiple databases. By contrast, the network published by Udrescu and colleagues is based only on DrugBank.

In the process of constructing version 1.0 of the drugome, several opportunities were identified for improving the drugome. These opportunities are detailed in section six, and will form the basis for a refined, novel drugome in D1.10.

3 Introduction (Challenge)

The ultimate goal of this deliverable was to create the first version of a drugome. A drugome is a network in which the nodes represent *drugs* and the edges represent *a relationship* between drugs. The precise nature of this “relationship” is not explicitly defined by the term “drugome” – meaning that, by modifying the definition of “relationship”, different drugomes can be created, each with different potential applications. For instance, Udrescu and colleagues recently published a drugome based on drug-target relationships stored in DrugBank (Udrescu *et al.*, 2020). Additionally, another type of drugome used for drug repurposing was developed by Brown and Patel, in which edges represent a measure of similarity based on MeSH terms associated with the drugs (mined from literature) (Brown, 2016). Similarly, although with a different purpose, a drug-drug interaction network was generated in which an edge represents that one drug may alter the action of the other drug (Liu *et al.*, 2016).

In cases where the relationship chosen is something that may indicate a functional similarity, for example shared drug-targets, then drugs that share edges could indicate repurposing opportunities

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based on possible mechanistic similarities. Additionally, when the edges are *scored,* for instance, based on how similar the target profiles of the two drugs involved in the edge are, then the scores could be used to indicate the degree of mechanistic similarity and, thus, how likely one drug is to be a repurposing opportunity for another. A further advantage of a scored drugome is that clustering could result in collections of drugs that could suggest multiple repurposing opportunities for a drug. This scenario is beneficial, for example, where contraindications prevent the use of the highest-scoring drug, and could also be used to propose new (as-yet-unknown) mechanisms for existing drugs.

4 Methodology

For version 1.0 of the drugome, drug-target interactions were chosen as the basis on which to construct the first version of the drugome. Drug-target interaction data were selected for three main reasons. Firstly, this data is readily available in the NeDRex database (NeDRexDB), integrated from DrugBank and Drug Central (Sadegh et al., 2021). Secondly, comparing drugs based on the similarity of biological targets that they have can be used as a proxy for mechanistic similarity and, thus, identifying possible drug repurposing opportunities (Davis, 2020). Finally, the source databases from which drug-target interaction data is sourced are heavily curated, meaning that the data is more likely to be accurate.

Construction of the drugome starts with a bipartite network of drug-target relationships. A bipartite network is a network in which the nodes can be separated into two distinct groups (in this case, “drugs” and “targets”) and edges only connect nodes in one partite to a node in the other. An example of a drug-target network is shown in Figure 1. Drug-target interactions used to construct the drug-target network included all drug-target relationships from DrugBank and drug-target relationships from Drug Central where the mechanism of action is tagged as “known”.

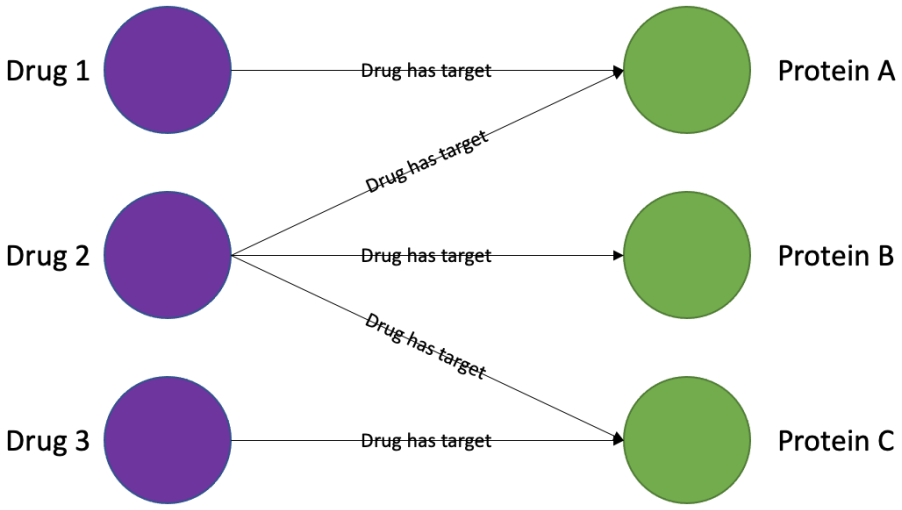

***Figure 1**: **A simple drug-target network.** The network consists of two groups, drugs and proteins, with edges connecting drugs to protein targets. “Drug 1” shares a target with “Drug 2”, and “Drug 2” also shares a target with “Drug 3”. However, “Drug 1” and “Drug 3” share no targets.*

The drugome is then created by creating a network consisting only of drug nodes, with an edge existing between two drug nodes if they share a protein target. The set of all targets of a particular drug is referred to as its “protein target profile”. Each edge in the network is weighted based on the similarity of the protein target profiles using the Jaccard index. The Jaccard score for two drugs is

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calculated as the number of unique, shared drug targets of the two drugs divided by the number of unique drug targets of either of the two drugs.

$$J(A,B) = \frac{|A \cap B|}{|A \cup B|}$$

For example, in Figure 1, Drugs 1 and 2 would have a score of 0.33 (1/3) whereas Drugs 1 and 3 would have a score of 0.0 (0/2).

Qualitative evaluation of the drugome was carried out by clustering the drugome using the Louvain algorithm Python implementation (`python-louvain` (Aynaud, 2020)). The purpose of this evaluation was to determine whether drugs in the drugome tend to have stronger (e.g., higher-scoring) connections to other drugs with similar indications/physical properties than they do to other drugs in the network. Louvain was selected because it aims to optimise modularity (with a tunable resolution parameter), allowing different granularities of clusters to be generated. Further, many key properties of the clusters (e.g., the number of clusters and the size of the clusters) are not specified as parameters to the algorithm; rather, these emerge as a consequence of the modularity of the clustering. Clusters were generated by incrementing the `resolution` parameter of `python-louvain`'s `best_partition` function from 0.0 to 1.0 in 0.01 increments to generate clusters at a range of resolutions. For a selection of use-cases the first five most granular clusters containing more than one drug were manually curated to establish whether the clusters generated are reasonable (e.g., contain drugs of similar classes or indications).

5 Results

5.1 Construction of a drug-target interaction network

The drug-target interaction network, constructed using drug-target relationships sourced from DrugBank and DrugCentral, contained:

- 4,890 drugs
  - This means that 34.16% of all drugs in NeDRexDB (total number: 14,315) had at least one known target.
  - These 4,890 drugs included 1,411 (68.60%) of the approved drugs in NeDRexDB (total number: 2,057).
- 2,513 proteins
  - This means that 1.24% of all proteins in NeDRexDB (total number: 202,160) had at least one known drug that targets them.
- 14,320 edges
  - Based on 4,890 drugs and 2,513 proteins, this results in a network density of 1.165×10^{-3} , meaning that the drug-target network is comparatively sparse, containing only 0.1165% of the maximum possible number of edges.

The degree distribution of drugs (i.e., number of proteins reported to be targeted by a drug) in the network is shown in Figure 2. The vast majority of drugs have comparatively few targets, with the majority having only one. However, at the most extreme, one drug – Fostamatinib, a tyrosine kinase inhibitor – is reported to have 303 drug targets.

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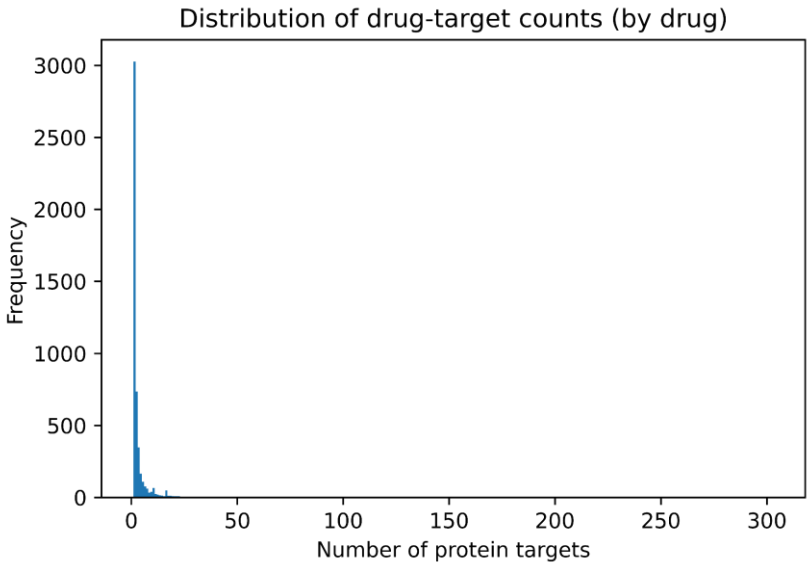

Figure 2: *Distribution of the number of drug-target edges that drug nodes are involved in.*

Similarly, Figure 3 shows the degree distribution of protein nodes in the drug-target interaction network. Again, while the majority of protein targets have few known drugs targeting them; however, there are some proteins that have a large number of drugs targeting them with one target – P24941, Cyclin-dependent kinase 2, a serine/threonine-protein kinase involved in the control of the cell cycle – having 119 associated drugs.

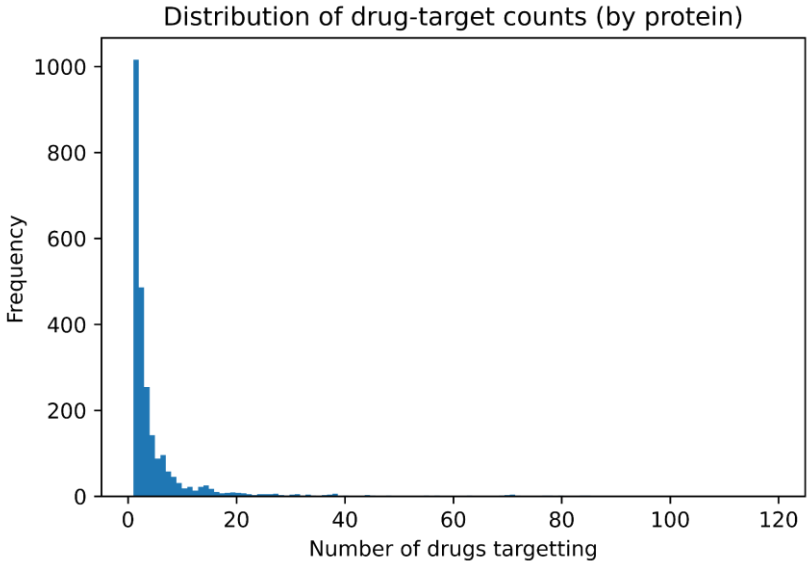

Figure 3*: Distribution of the number of drug-target edges that protein nodes are involved in.*

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5.2 Construction of the drugome

The drugome contained:

- 4,765 drugs
  - This is slightly fewer than the number of drugs with at least one known target edge in the drug-target interaction network. This difference occurs because, for a drug to be in the drugome, it needs to share at least one target with another drug (which is not the case for some drugs).
  - Of all approved drugs, 1,394 (67.77%) are in the drugome.

- 119,387 edges
  - This results in a network density of 1.165×10^{-3}, indicating a spare network.

Figure 4 shows the degree distribution (number of neighbours) of drugs in the drugome. While it can be seen that most drugs tend to have a small number of neighbours, the distribution appears to be multi-model, indicating that there are groups of drugs that have similar numbers of neighbours (e.g., as a result of many, well-studied drugs in the same class with similar mechanisms of action). Additionally, while some drugs may have a large number of neighbours, these edges will have a low Jaccard index if the neighbouring drug only shares a small number of those edges. Consequently, the large number of neighbours does not necessarily present a problem for clustering.

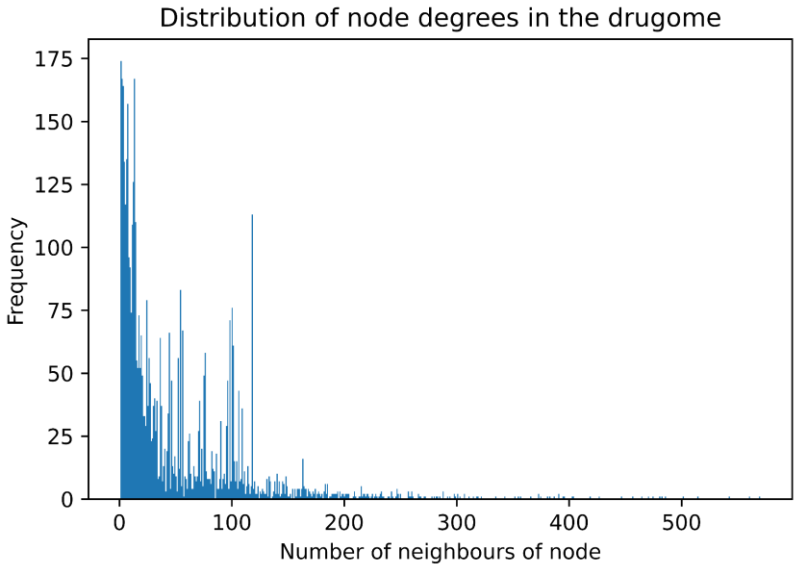

Figure 4: *Distribution of the number of neighbours of drugs in the drugome.*

Figure 5 shows the distribution of Jaccard index scores annotated on edges in the network. The most common (modal) score on edges is 1.0, which indicates edges between drugs that share all of the same targets. However, other common values include 0.5 (half of drugs in the union are shared), and 0.33 (one third of drugs in the union are shared). The median Jaccard score was 0.33, meaning that at least half of the edges had a Jaccard score of 0.33 or lower (Q1 0.125, Q3 1.0).

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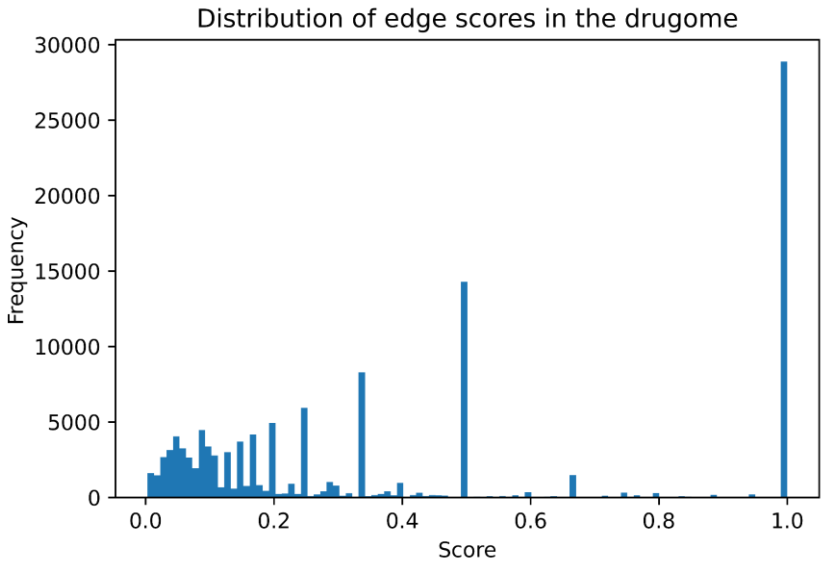

Figure 5: *Distribution of edge scores in the drugome. It can be seen that a score of 1.0, indicating that all drug targets are shared between two drugs, is the most common score.*

5.3 Clustering

The drug investigated as a clustering use-case was Riociguat, a drug indicated "for persistent or recurrent chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension" (DrugBank, 2021). This drug was selected as it has been of interest to the REPO-TRIAL project and, thus, the relevance of the high-ranking drugs can be evaluated in consultation with colleagues on the REPO-TRIAL project.

Drug	Run 1 resolution	Run 2 resolution	Run 3 resolution
Isosorbide dinitrate	0.01	0.01	0.01
Isosorbide mononitrate	0.01	0.01	0.01
Linaclotide	0.01	0.01	0.01
Molsidomine	0.01	0.01	0.01
Nitric oxide	0.01	0.01	0.01
Nitroglycerin	0.01	0.01	0.01
Plecanatide	0.01	0.01	0.01
Arginine	0.38	0.34	0.37
L-Lysine	0.38	0.34	0.37
Levamlodipine	0.38	0.34	0.37
Tolrestat	0.56	0.54	0.54

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Table 1: *Drugs clustering with Riociguat when iteratively clustering the drugome using the Louvain algorithm.*

The results are shown in Table 1. Note, due to stochasticity, iterated Louvain clustering was repeated three times to account for run-to-run variation. All of the drugs identified at a Louvain resolution of 0.01, with the exception of plecanatide and linaclotide, are all vasodilators, similar to riociguat, indicated for conditions such as angina pectoris. Plecanatide and linaclotide, by contrast, are both drugs indicated for the treatment of IBD. Interestingly, despite linaclotide and plecanatide being guanylate cyclase C agonists, neither of these drugs have a drug-target interaction with a guanylate cyclase C in NeDRex. However, according to DrugBank, riociguat is a stimulator of soluble guanylate cyclase (DrugBank, 2021). Thus, perhaps, this result suggests that there are instances where drugs with similar (but not identical) mechanisms could be used to suggest additional mechanisms. However, this use-case also demonstrates that drugs with similar mechanisms and indications can cluster together.

Drug	Run 1 resolution	Run 2 resolution	Run 3 resolution
Camphor	0.01	0.02	0.01
Capsaicin	0.01	0.02	0.01
Dronabinol	0.02	0.01	0.02
Rimonabant	0.02	0.01	0.02
Cannabidiol	0.03	0.03	0.03
Antipyrine	-	0.03	0.03
Metamizole	-	0.03	0.03

Table 2: *Drugs clustering with acetaminophen when iteratively clustering the drugome using the Louvain algorithm.*

The second clustering use-case investigated was acetaminophen (paracetamol), and was chosen because paracetamol is a widely-used and well-researched drug, with its mechanisms of action broadly characterised. These results are shown in Table 2. Unlike the riociguat example, run-to-run variation in the order that drugs clustered with acetaminophen was seen, demonstrating that stochasticity in louvain clustering can affect the results.

Manual inspection of the results demonstrates that the drugs clustering with acetaminophen have a variety of different mechanisms, although most are used for pain relief. For example, cannabidiol and acetaminophen share only the cannabinoid receptor 1 protein (P21554) as a target, whereas camphor and acetaminophen share only the transient receptor potential cation channel subfamily V member 1 protein (Q8NER1) as a target. Furthermore, cannabidiol and camphor do not share any targets. As a result, it is clear that two drugs in the same cluster may not necessarily share a common mechanism, and thus do not represent repurposing opportunities for one another, but may cluster due to common mechanisms with other drugs.

The third use-case selected was fostamatinib, a spleen tyrosine kinase. This drug was selected as it was identified as part of the inflammatory bowel disease use-case in the NeDRex Nature Communications publication. Additionally, having 303 edges, looking at the clustering of fostamatinib

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may give insights into the effect, if any, of sharing targets with such a large number of drugs. The results are shown in Table 3 (in section 11). Despite having at least one mechanism shared with 303 other drugs, the high-resolution clusters contain many drugs that are at least functionally similar – for example, many of the drugs ending in -nib are also tyrosine kinase inhibitors, suggesting that the Jaccard index and clustering results in some prioritisation of drugs. Thus, this suggests that clustering may be used to get groups of drugs that are more mechanistically similar to one another than they are to other drugs in the drugome.

6 Open issues

In the process of developing the drugome, four open issues were identified, forming the basis for future development of the drugome.

Firstly, the drugome, at present, only takes into account whether a relationship between a drug and a target exists. However, the nature of the relationship is also important, and not currently represented in the drugome. For example, two drugs may have the same target, but one may be an agonist and the other an antagonist. Incorporating this data into the drugome would help to refine drug repurposing predictions, and the best way to do so is an open question. An additional complication to this challenge is that the nature of a relationship between a drug and its target is not always known.

Secondly, the drugome is currently built only from drug-target interactions, but there are other data which may help suggest shared mechanisms (to different extents). For example, a drugome could be constructed based on shared-indication data; while this may also indicate a shared mechanism, it is also possible that two drugs indicated for the same disorder may treat different aspects of the disorder, or treat the same aspect via different mechanisms. Consequently, combining a drug-target-based drugome with an indication-based drugome would require a method that takes into account the nuances of each drugome. How to approach this situation is currently an open issue. At present, as far as the authors are aware, existing drugomes are either based only on one type of data, or have not been updated based on recent data (for example, the drugomes discussed in the Introduction, and Yıldırım and colleagues' drug-target-based network, published in 2007). Version 1.0 of the drugome extends previous research by using REPO-TRIAL´s state-of-the-art NeDRexDB so that it is based on the latest, most up-to-date data.

A third open issue is deciding how best to use the drugome to inform drug repurposing efforts. For example, the acetaminophen use case demonstrates that when clustering is used, two drugs chosen at random from a cluster may not share a mechanism and, thus, not be repurposing opportunities. This may be partly remedied by the open issue discussed in the previous paragraph.

Another open issue is deciding how to use (and/or modify) the drugome to repurpose drugs for combination therapies. In brief, NeDRexDB has drugs recorded as single entities (i.e., one drug with one indication). However, in practice, there are instances where several pharmaceutical agents are used in combination towards a single indication. Combination therapy is common in oncology, for example, where multiple drugs are used to prevent the development of treatment-resistant tumours. If this issue were addressed, then novel combination therapies may be devised.

7 Deviations (if applicable)

Not applicable.

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8 Conclusion

The goal of this deliverable was to create version 1.0 of a drugome (with a view to make further refinements to the drugome for deliverable D1.10), which was achieved. This report documents the methods of creating version 1.0 of the drugome, along with a demonstration of one possible way that this first version could be used. In terms of the REPO-TRIAL project, this report describes the strengths and limitations identified with this approach, and thus provides clear next-steps to improving the drugome and researching methods for applications using the drugome for deliverable D1.10. Investigating how to use the range of drug data integrated into NeDRex to make drug repurposing predictions fits directly into the REPO-TRIAL remit ("Setting standards for *in silico* drug repurposing").

9 References

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10 Table of acronyms and definitions

UM	Maastricht University
UNEW	University of Newcastle upon Tyne
WP	Work package

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11 Other supporting documents / figures / tables (if applicable)

Drug	Run 1 resolution	Run 2 resolution	Run 3 resolution
1-(3-HYDROXYPROPYL)-2-[(3-NITROBENZOYL)AMINO]-1H-BENZIMIDAZOL-5-YL PIVALATE	0.01		
N-(5-METHYL-1H-PYRAZOL-3-YL)-2-PHENYLQUINAZOLIN-4-AMINE	0.01		
(E)-[4-(3,5-Difluorophenyl)-3H-pyrrolo[2,3-b]pyridin-3-ylidene](3-methoxyphenyl)methanol	0.02	0.02	0.02
1-Ter-Butyl-3-P-Tolyl-1h-Pyrazolo[3,4-D]Pyrimidin-4-Ylamine	0.02	0.02	0.02
3-(3-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridine	0.02	0.02	0.02
3-[(3-(2-CARBOXYETHYL)-4-METHYLPYRROL-2-YL)METHYLENE]-2-INDOLINONE	0.02	0.02	0.02
3-[4-(1-formylpiperazin-4-yl)-benzylidenyl]-2-indolinone	0.02	0.02	0.02
4-[4-(1-Amino-1-Methylethyl)Phenyl]-5-Chloro-N-[4-(2-Morpholin-4-Ylethyl)Phenyl]Pyrimidin-2-Amine	0.02	0.02	0.02
5-CYANO-FURAN-2-CARBOXYLIC ACID [5-HYDROXYMETHYL-2-(4-METHYL-PIPERIDIN-1-YL)-PHENYL]-AMIDE	0.02	0.02	0.02
Alectinib	0.02	0.02	0.02
Amuvatinib	0.02	0.02	0.02
Avapritinib	0.02	0.02	0.02
Becaplermin	0.02	0.02	0.02

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Cabozantinib	0.02	0.02	0.02
Dasatinib	0.02	0.02	0.02
Erdafitinib	0.02	0.02	0.02
Imatinib	0.02	0.02	0.02
Lenvatinib	0.02	0.02	0.02
Midostaurin	0.02	0.02	0.02
N-(4-chlorophenyl)-2-[(pyridin-4-ylmethyl)amino]benzamide	0.02	0.02	0.02
Nintedanib	0.02	0.02	0.02
OSI-930	0.02	0.02	0.02
Olaratumab	0.02	0.02	0.02
Palifermin	0.02	0.02	0.02
Pazopanib	0.02	0.02	0.02
Pemigatinib	0.02	0.02	002
Pexidartinib	0.02	0.02	0.02
Ponatinib	0.02	0.02	0.02
Quizartinib	0.02	0.02	0.02
Regorafenib	0.02	0.02	0.02
Sorafenib	0.02	0.02	0.02
Sunitinib	0.02	0.02	0.02
Tandutinib	0.02	0.02	0.02
1-{4-[4-Amino-6-(4-methoxyphenyl)furo[2,3-d]pyrimidin-5-yl]phenyl}-3-[2-fluoro-5-(trifluoromethyl)phenyl]urea	0.03	0.03	0.03
3-(2-aminoquinazolin-6-yl)-1-(3,3-dimethylindolin-6-yl)-4-methylpyridin-2(1H)-one	0.03	0.03	0.03
3-(2-aminoquinazolin-6-yl)-4-methyl-1-[3-(trifluoromethyl)phenyl]pyridi	0.03	0.03	0.03

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n-2(1H)-one			
4-[[2-[[4-chloro-3-(trifluoromethyl)phenyl]amino]-3H-benzimidazol-5-yl]oxy]-N-methyl-pyridine-2-carboxamide	0.03	0.03	0.03
6-chloro-N-pyrimidin-5-yl-3-{[3-(trifluoromethyl)phenyl]amino}-1,2-benzisoxazole-7-carboxamide	0.03	0.03	0.03
Axitinib	0.03	0.03	0.03
Cediranib	0.03	0.03	0.03
Foretinib	0.03	0.03	0.03
N'-(6-aminopyridin-3-yl)-N-(2-cyclopentylethyl)-4-methyl-benzene-1,3-dicarboxamide	0.03	0.03	0.03
N-(4-phenoxyphenyl)-2-[(pyridin-4-ylmethyl)amino]nicotinamide	0.03	0.03	0.03
N-(CYCLOPROPYLMETHYL)-4-(METHYLOXY)-3-({5-[3-(3-PYRIDINYL)PHENYL]-1,3-OXAZOL-2-YL}AMINO)BENZENESULFONAMIDE	0.03	0.03	0.03
N-[5-(ETHYLSULFONYL)-2-METHOXYPHENYL]-5-[3-(2-PYRIDINYL)PHENYL]-1,3-OXAZOL-2-AMINE	0.03	0.03	0.03
N-cyclopropyl-6-[(6,7-dimethoxyquinolin-4-yl)oxy]naphthalene-1-carboxamide	0.03	0.03	0.03
N~4~-(3-methyl-1H-indazol-6-yl)-N~2~-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine	0.03	0.03	0.03
N~4~-methyl-N~4~-(3-methyl-1H-indazol-6-yl)-	0.03	0.03	0.03

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N~2~-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine			
Ramucirumab	0.03	0.03	0.03
Rivoceranib	0.03	0.03	0.03
Semaxanib	0.03	0.03	0.03
TG-100801	0.03	0.03	0.03
Tivozanib	0.03	0.03	0.03
Vandetanib	0.03	0.03	0.03
Vatalanib	0.03	0.03	0.03
2-tert-butyl-9-fluoro-1,6-dihydrobenzo[h]imidazo[4,5-f]isoquinolin-7-one	-	0.01	0.01
4-(3-amino-1H-indazol-5-yl)-N-tert-butylbenzenesulfonamide	-	0.01	0.01
4-{[4-{[(1R,2R)-2-(dimethylamino)cyclopentyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}-N-methylbenzenesulfonamide	-	0.01	0.01
5-phenyl-1H-indazol-3-amine	-	0.01	0.01
ATP	-	0.01	0.01
Baricitinib	-	0.01	0.01
Cenegermin	-	0.01	0.01
Entrectinib	-	0.01	0.01
Fedratinib	-	0.01	0.01
Larotrectinib	-	0.01	0.01
Lorlatinib	-	0.01	0.01
Ruxolitinib	-	0.01	0.01
Tofacitinib	-	0.01	0.01
Upadacitinib	-	0.01	0.01

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2-({5-CHLORO-2-[(2-METHOXY-4-MORPHOLIN-4-YLPHENYL)AMINO]PYRIMIDIN-4-YL}AMINO)-N-METHYLBENZAMIDE	-	-	0.01
7-PYRIDIN-2-YL-N-(3,4,5-TRIMETHOXYPHENYL)-7H-PYRROLO[2,3-D]PYRIMIDIN-2-AMINE	-	-	0.01

Table 3: *Drugs clustering with acetaminophen when iteratively clustering the drugome using the Louvain algorithm.*

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