OPDDR Research Collaboration Phase 2 Final Report

Introduction

This report is submitted in accordance with the Lilly Resarch Collaboration Agreement between Eli Lilly & Co (Lilly) and Data2Discovery, executed on June 11, 2015. The work is part of an ongoing collaboration involving Lilly, NIH-NCATS, and Data2Discovery. The role of Data2Discovery is informatics: transforming and integrating data to enhance semantic value, development of a Knowledge Network (KN), a publicly shared Open Phenotypic Drug Discovery Resource (OPDDR, aka PD2) which can be used to identify relationships between National Pharmaceutical Collection (NPC) compounds, phenotypic assays, ontological classes of assays, and associated public data on related molecular targets.

Accomplishments

- As per the agreement, the OPDDR has been developed and deployed, hosted by NCATS[1].
- Related publication: Novel Phenotypic Outcomes Identified for a Public Collection of Approved Drugs from a Publicly Accessible Panel of Assays , Lee JA, Shinn P, Jaken S, Oliver S, Willard FS, Heidler S, Peery RB, Oler J, Chu S, Southall N, Dexheimer TS, Smallwood J, Huang R, Guha R, Jadhav A, Cox K, Austin C AP, Simeonov, Sittampalam GS, Husain S, Franklin N, Wild DJ, Yang JJ, Sutherland JJ, Thomas CJ, (2015) PLoS ONE 10(7): e0130796. doi: 10.1371/journal.pone.0130796.
- The recently and significantly revised (June 2015) PubChem RDF data model was integrated, informed via engagement with PubChem team (Bolton et al.) initiated by Data2Discovery.
- BioAssay Ontology (BAO) integration informed by discussions with BAO team (S. Schurer), and with AstraZeneca (O. Enqvist) regarding their assay annotation template.
- OpenPHACTS (OP) integration informed by discussions with OP, which entailed major revisions in the KN, and also revisions in the OP data model and API, to handle phenotypic assays.

Knowledge Network Description

The initial version of the KN is intended to provide a clear and easily comprehensible first step of describing the OPDDR compounds and assays in accordance with standardized community ontologies and namespaces, and relating these to protein targets from ChEMBL. Biological networks can be extremely complex, and many further entity classes can be integrated in future (e.g. pathways), and will be facilitated by this initial KN.

Ontologies Used

The KN uses the following ontologies:

[1] https://ncats.nih.gov/expertise/preclinical/pd2

PubChem RDF[2]	Primary reference for this project. Mainly because assays and substances have been deposited into PubChem. <http://rdf.ncbi.nlm.nih.gov/pubchem/>
BAO[3]	Bioassay classification. Initially using a minimal set based on annotation template provided by AstraZeneca. Only bao_vocabulary_assay.owl is required currently. <http://www.bioassayontology.org/bao#>
ChEMBL RDF[4]	ChEMBL, Reactome, Uniprot endpoint & downloads available. CCO = ChEMBL Core Ontology <http://rdf.ebi.ac.uk/terms/chembl#>
OBO[5]	Open Biological and Biomedical Ontologies BFO = Basic Formal Ontology <http://purl.obolibrary.org/obo/>
SIO[6]	Semanticscience Integrated Ontology <http://semanticscience.org/resource/>

Entities:

entity [abbr] namespace	**example**
substance <http://rdf.ncbi.nlm.nih.gov/pubchem/substance/>	SID124893119
compound <http://rdf.ncbi.nlm.nih.gov/pubchem/compound/>	CID1131
assay (bioassay) <http://rdf.ncbi.nlm.nih.gov/pubchem/bioassay/>	AID1117354
measuregroup (measureg) <http://rdf.ncbi.nlm.nih.gov/pubchem/measuregroup/>	AID1117354
endpoint <http://rdf.ncbi.nlm.nih.gov/pubchem/endpoint/>	SID124893119_AID1117354
protein <http://rdf.ncbi.nlm.nih.gov/pubchem/protein/>	GI124375976
target	CHEMBL3038470

[2] https://pubchem.ncbi.nlm.nih.gov/rdf/
[3] http://bioassayontology.org/
[4] https://www.ebi.ac.uk/rdf/
[5] http://www.obofoundry.org/
[6] http://semanticscience.org/

<http://rdf.ebi.ac.uk/resource/chembl/target/>	
targetcomponent (target_cmpt) <http://rdf.ebi.ac.uk/resource/chembl/targetcomponent/>	CHEMBL_TC_1927
UniprotRef (uniprot) <http://rdf.ebi.ac.uk/terms/chembl#UniprotRef>	P53350
assay <http://rdf.ebi.ac.uk/resource/chembl/assay/>	CHEMBL987214
activity <http://rdf.ebi.ac.uk/resource/chembl/activity/>	CHEMBL_ACT_2470294
molecule <http://rdf.ebi.ac.uk/resource/chembl/molecule/>	CHEMBL44884

Note that PubChem *compounds* are required in addition to *substances*. Compounds refer to canonically defined and identifiable chemical entities which can be linked across databases; Substances refer to specific samples of compounds as provided by a supplier. We thus include both, to be as comprehensive and specific as possible. Note also that PubChem measuregroups are defined for each assay, for example, the measuregroup URI for AID12345 is http://rdf.ncbi.nlm.nih.gov/pubchem/measuregroup/AID12345. PubChem endpoints represent activity outcomes. ChEMBL RDF represents bioactivities somewhat differently than PubChem, but we can rigorously link these data via chemical structure and CIDs.

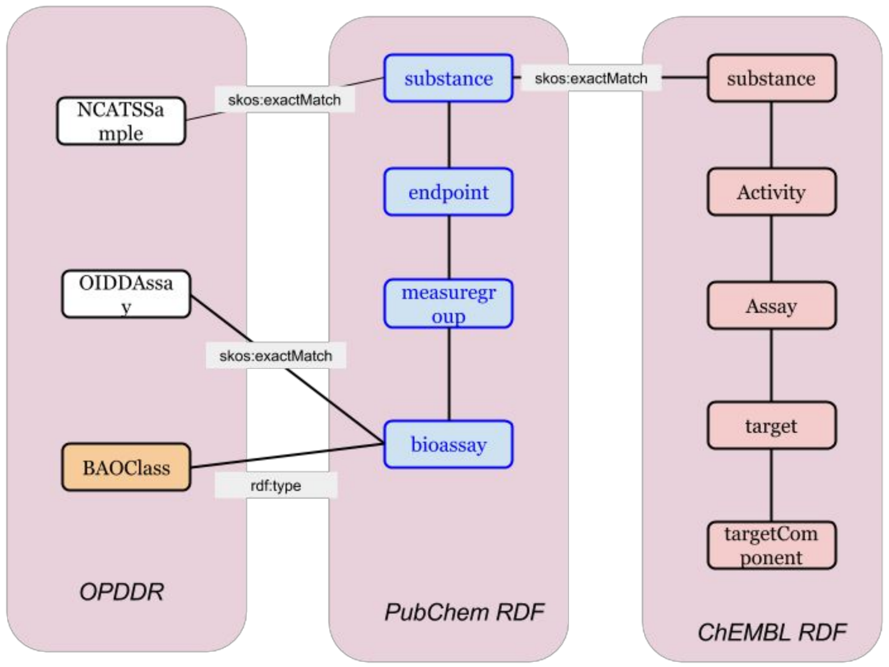
KN Statistics

type	count	notes
substance	2511	PubChem SIDs
compound	2511	PubChem CIDs
assay	35	PubChem AIDs. Summary AID is 36th.
measuregroup	35	PubChem AIDs. Default for assay.
endpoint	2511*35	PubChem SID-AID pairs.
targets	4977	ChEMBL IDs. All single-component.
protein	4977	A.k.a. target component. With UniprotRefs.
protein activity	584,157	From ChEMBL, but includes PubChem data.
PD2 activity	5320	All “ACTIVE” outcomes from results.

assay classifications	155	Manually curated PD2 to BAO associations. Exported from worksheet.

Asserted triplets, patterns and examples

description	examples
assay to BAO class	bioassay:AID1117354 rdf:type bao:BAO_0000015
assay title	bioassay:AID1117354 dcterms:title "human JAK2 kinase inhibition-screen"@en
assay to measuregroup	bioassay:AID1117354 bao:BAO_0000209 measuregroup:AID1117354
substance to NCGC ID	substance:SID144206486 skos:exactMatch ncats_sample:NCGC00182710-02 .
substance to measure group	substance:SID124882766 obo:BFO_0000056 measureg:AID1117326
endpoint outcome (activity)	endpoint:SID170466632_AID743241 vocabulary:PubChemAssayOutcome vocabulary:inactive
endpoint class	endpoint:SID103164874_AID443491 rdf:type bao:BAO_0000190
substance to compound association	substance:SID124893119 sio:CHEMINF_000477 compound:CID1131
assay to OIDD ID	bioassay:AID1117350 skos:exactMatch oidd_assay:17
ChEMBL target to UniProt	chembl_target:CHEMBL5464 cco:targetXref uniprot:Q13546
ChEMBL target to assay	chembl_target:CHEMBL5464 cco:hasAssay assay:CHEMBL3110727
ChEMBL target to target component	chembl_target:CHEMBL1867 cco:hasTargetComponent chembl_targetcmpt:CHEMBL_TC_180
ChEMBL target component to Uniprot	chembl_targetcmpt:CHEMBL_TC_180 cco:targetCmptXref uniprot:P08913
ChEMBL assay to activity	assay:CHEMBL3110727 cco:hasActivity activity:CHEMBL_ACT_13890030
ChEMBL molecule to activity	chembl_molecule:CHEMBL313842 cco:hasActivity activity:CHEMBL_ACT_14447741
PubChem substance to ChEMBL molecule	substance:SID225144242 skos:exactMatch molecule:CHEMBL1474122



OPDDR RDF schema, simplified, showing source relationships.

Files:

The following files comprise this release. Files are grouped below by source, each file from one source only.

file	source	description
npcpd2_assay.ttl	OPDDR	Assay links to OIDD namespace. `bioassay:AID1117326 skos:exactMatch oidd_assay:4`
npcpd2_bao.ttl	OPDDR	Manually curated BAO classifications. `bioassay:AID1117352 rdf:type bao:BAO_0000219`

npcpd2_substance.ttl	OPDDR	Substance links to NCATS namespace.
		`substance:SID170465644 skos:exactMatch`
		`ncats_sample:NCGC00160518-03`

bao_vocabulary_assay.owl	BAO	BAO module with bioassay class hierarchy.
pubchem_vocabulary.owl	PubChem	PubChem module with bioactivity terms etc.

pubchem_pd2_assay.ttl	PubChem	PubChem RDF, includes titles, measuregroups.
		`bioassay:AID1117356 bao:BAO_0000209`
		`measuregroup:AID1117356`
		
		`bioassay:AID1117351 dcterms:title "Increased HeLa`

		cells with 4N DNA content-IC50"@en
pubchem_pd2_substance.ttl	PubChem	PubChem RDF, includes CIDs, measuregroups. substance:SID124882766 obo:BFO_0000056 measuregroup:AID1117326 . endpoint:SID124882766_AID1117342 obo:IAO_0000136 substance:SID124882766 .
pubchem_pd2_endpoint.ttl	PubChem	PubChem RDF, includes endpoints, activity results. endpoint:SID170464708_AID1117354 obo:IAO_0000136 substance:SID170464708 ; vocabulary:PubChemAssayOutcome vocabulary:inactive . measuregroup:AID1117354 obo:OBI_0000299 endpoint:SID170464708_AID1117354 .
chembl_cco.ttl	ChEMBL	ChEMBL Core Ontology
chembl_target.ttl	ChEMBL	ChEMBL protein targets. chembl_target:CHEMBL2366239 a cco:SingleProtein ; dcterms:title "KLE"
chembl_rdf_activity.ttl	ChEMBL	PubChem substance links to ChEMBL molecules, activities, assays, targets, target components, Uniprots. substance:SID170466134 skos:exactMatch chembl_molecule:CHEMBL1230222 chembl_molecule:CHEMBL44884 cco:hasActivity chembl_activity:CHEMBL_ACT_7667167 . chembl_target:CHEMBL218 cco:hasAssay chembl_assay:CHEMBL1909122 . chembl_target:CHEMBL218 cco:hasTargetComponent chembl_targetcmpt:CHEMBL_TC_172 . chembl_targetcmpt:CHEMBL_TC_172 cco:targetCmptXref uniprot:P21554 . uniprot:P21554 a cco:UniprotRef .

Project Status, Future

This initial KN Beta Version provides sufficient associations for semantic exploration across PD2 phenotypic and public biochemical assays for the NPC substances. The integration with PubChem, ChEMBL, and OpenPHACTS adds value in multiple ways, linking to a large, diverse and expanding ecosystem of public biomedical knowledge. Additional assay annotations can add further value, whereby the knowledge model developed can represent and derive high value from the unique knowledge of domain specialists and facilitate the links which power and advance data intensive research.