Finding Promiscuous Old Drugs for New Uses

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Why old drugs ?

- More cost effective R&D?
- Repurposing/ repositioning -Quicker to bring to market?
- Recent focus on neglected & rare diseases
- Over 7000 diseases affecting less than 200,000
- 1000's of diseases with no treatments
- >300 orphan drugs approved since 1983

Just some of the many rare disease groups

Abigail Alliance for Better Access to Developmental Drugs
Addi & Cassi Fund
American Behcet's Disease Association
Amschwand Sarcoma Cancer Foundation
BDSRA (Batten Disease Support and Research Association)
Beyond Batten Disease Foundation
Blake's Purpose Foundation
Breakthrough Cancer Coalition
Canadian PKU & Allied Disorders
Center for Orphan Disease Research and Therapy, University of Pennsylvania
Children's Cardiomyopathy Foundation
Cooley's Anemia Foundation
Dani's Foundation
Drew's Hope Research Foundation
EveryLife Foundation for Rare Diseases
GIST Cancer Awareness Foundation
Hannah's Hope Fund
Hope4Bridget Foundation
Hypertrophic Cardiomyopathy Association - HCMA
I Have IIH
ISRMD (International Society for Mannosidosis and Related Diseases)
Jacob's Cure
Jain Foundation
Jonah's Just Begun-Foundation to Cure Sanfilippo Inc.
Kids V Cancer
Kurt+Peter Foundation
LGMD2I Research Fund
Lymphangiomatosis & Gorham's Disease Alliance
MAGIC Foundation
Manton Center for Orphan Disease Research
MarbleRoad
Mary Payton's Miracle Foundation
Midwest Asian Health Association (MAHA)

MPD Support
National Gaucher Foundation
National MPS Society
National Organization Against Rare Cancers
National PKU Alliance
National Tay-Sachs & Allied Diseases Association
New Hope Research Foundation
NextGEN Policy
Noah's Hope - Batten disease research fund
Our Promise to Nicholas Foundation
Oxalosis and Hyperoxaluria Foundation
Partnership for Cures
Periodic Paralysis Association
RARE Project
Ryan Foundation for MPS Children
Sanfilippo Foundation for Children
Sarcoma Foundation of America
Solving Kids' Cancer
Taylor's Tale: Fighting Batten Disease
Team Sanfilippo Foundation
The Alliance Against Alveolar Soft Part Sarcoma
The Life Raft Group
The NOMID Alliance
The Transverse Myelitis Association
The XLH Network, Inc.
United Pompe Foundation

Many of these groups are
doing R&D on a shoestring
how can we help?

One example of why Pharmaceutical R&D needs disrupting

Jonah has Sanfilippo Syndrome – Mucopolysaccharidosis type III – cannot degrade heparan sulfate - Neurodegeneration

Jonah's mum, Jill Wood started a foundation, raises money, awareness, funds ground breaking research happening globally. Willing to sell her house to fund research to save Jonah.

She is in a race against time – what can we do to translate ideas from bench to patient faster?

How do we get more ideas tested, can we focus on approved drugs?

How can we help parents and families ?

Availability of libraries of FDA drugs

PRODUCT DATA SHEET

BML-2841

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MicroSource
Your first step in discovery

US Drug Collection

An important collection of 1040 drugs that have reached clinical trial stages in the US has been assigned USAN or USP status and is included in the USP Dictionary (U.S. 2005), the authorized list of established names for drugs in the USA.

Order

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Advanced search

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FDA Approved Drug Library (96-well)

Order no.: L1300-D-0001 (Size: 100µL/well (10mM solution))

Description & Advantages

- A unique collection of 381 FDA approved drugs for high throughput screening (HTS) and high content screening (HCS)

Prestwick Chemical Library®

The Prestwick Chemical Library® contains 1200 small molecules, 100% FDA approved drugs, thus it presents the greatest possible degree of « drug-likeness ». The active compounds were selected for their high chemical and pharmacological diversity as well as for their known bioavailability and safety in humans. The Prestwick Chemical Library® was designed to reduce the risk of "low quality" hits, reduce the cost of the initial screening, and accelerate lead discovery.

What's the ideal use of the library ?

The strategy we recommend is the "SOSA Approach" (C.G. Wermuth, J. Med. Chem. 2004, 47, 1303-1314). It consists of submitting to the target only a limited number of highly diverse drug molecules for which bioavailability and toxicity studies have already been performed and which have proven usefulness in humans. This initial screening will provide hits that will then be used as starting points for a drug optimization program which will rely on medicinal chemistry expertise. It can be

noticed that, if the initial hit has sufficient affinity for the target, it could be immediately tested in patients.

Johns Hopkins Clinical Compound library- made compounds available at cost

Finding Promiscuous Old Drugs for New Uses

- In late 2010...searched the literature
- Many groups in vitro HTS
- Libraries of FDA approved drugs against various whole cell or target assays
- Research published in the prior six years - 34 studies -.
- 1 or more compounds with a suggested new bioactivity
- 13 drugs were active against more than one additional disease in vitro
- Perhaps screen these first?

Finding Promiscuous Old Drugs for New Uses

Amlodarone

Amitriptyline

Clomipramine

Chlorprothixene

Daunorubicin

Digoxin

Hydroxyprogesterone

Mitoxantrone

Ouabain

Prochlorperazine

Pyrvinium

Thioridazine

Trifluoperazine

Multiple tricyclics

Finding Promiscuous Old Drugs for New Uses

- Amitriptyline and clomipramine = suppress glial fibrillary acidic protein
- Cho et al., Human Mol Genet (2010) 19: 3169-78
- Amitriptyline and clomipramine = mitochondrial permeability transition
- Stavrovskaya et al., J Exp Med (2004) 200: 211-22

- Pyrvinium Pamoate (anthelmintic) = anti Tuberculosis
- Loughheed et al., Tuberculosis (2009) 89: 364-70
- Pyrvinium Pamoate (anthelmintic) = anti Antiprotozoal C. parvum
- Downey et al., Antimicrob Agents Chemother (2008) 52: 3106-12
- Pyrvinium Pamoate (anthelmintic) = anti Antiprotozoal T. Brucei
- Mackey et al., Chem Biol Drug Des (2006) 355-63

Analysis of datasets

Dataset	ALogP	Molecular Weight	Number of Rotatable Bonds	Number of Rings	Number of Aromatic Rings	Number of Hydrogen bond Acceptors	Number of Hydrogen bond Donors	Molecular Polar Surface Area
Compounds identified <i>in vitro</i> with new activities (N = 109) *	3.1 ± 2.6	428.4 ± 202.8	5.4 ± 3.8	3.8 ± 1.9	2.0 ± 1.4	5.6 ± 4.2	2.0 ± 1.9	89.6 ± 69.3
Compounds identified <i>in vitro</i> with multiple new activities (N = 13)	3.6 ± 2.7	442.8 ± 150.0	5.1 ± 3.1	4.2 ± 1.5	1.8 ± 1.2	5.5 ± 4.6	2.2 ± 3.3	79.5 ± 78.8

- Promiscuous repurposed compounds are more hydrophobic,
- orphan repurposed hits are less hydrophobic

Finding Promiscuous Old Drugs for New Uses

- 109 molecules were identified by screening in vitro
- Promiscuous compounds do not appear different to whole dataset
- Molecules are close to natural product lead like (MW<460, LogP <4.2)
- Rosen et al., J Med Chem (2009) 52: 1953-62
- 1193 Oral drugs mean MW 343.7 CLOGP 2.3
- Vieth et al., J Med Chem (2004) 47: 224-32
-
- Others have shown GPCR promiscuous cpds vs selective have higher MW and clogP
- Azzaoui et al., ChemMedComm (2007) 2: 874-80
- Our promiscuous cpds had carbon skeletons identified as promiscuous

FDA Rare Disease Research Database

- The FDA resource, the rare disease research database (RDRD),

(<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm>)

- Lists Orphan-designated products with at least one marketing approval for a common disease indication, for a rare disease indication, or for both common and rare disease indications.
- In the last category there are less than 50 molecules (including large biopharmaceutical drugs).
- These tables do not capture the high throughput screening (HTS) data generated to date
- FDA databases for rare disease research are XL files!!

We have curated the data and uploaded in CDD with the help of Antony Williams at the Royal Society of Chemistry

Public Data

- ☐ CDD - Sean Ekins
- ☐ IDRI cpds
- ☐ Joel Malaria
- ☒ FDA Drugs Repurposed using HTS methods
- ☐ FDA/Orphan Drugs
- ☐ IUPUI - Distributed Drug
- ☐ JHU JHCCL Plasmodium
- ☐ LIPID MAPS Structure D
- ☐ Malaria/Trypanosome: S
- ☐ Malaria: Drexel Public D
- ☐ Malaria: Johns Hopkins
- ☐ Malaria: Natural Product

by structures

- ☐ Novartis GNF-Pf Database
- ☒ Orphan-designated products with at least one marketing approval for a common disease indication
- ☐ Orphan-designated products with at least one marketing approval for a rare disease indication

by molecule keywords

any field

by chemical properties

Molecular weight

log P

H-bond donors

H-bond acceptors

Lipinski violations

pKa

Exact mass

Heavy atom count

Polar surface area

Rotatable bonds

Example: mol1 OR synonym2 AND NOT userfield3

Save this search...

Analysis of datasets

Dataset	ALogP	Molecular Weight	Number of Rotatable Bonds	Number of Rings	Number of Aromatic Rings	Number of Hydrogen bond Acceptors	Number of Hydrogen bond Donors	Molecular Polar Surface Area
Orphan designated products with at least one marketing approval for a common disease indication (N = 79) [#]	1.4 ± 3.0 ^b	353.2 ± 218.8 ^a	5.3 ± 6.4	2.8 ± 1.7 ^a	1.2 ± 1.3 ^b	5.3 ± 6.0	2.5 ± 3.0	99.2 ± 110.7
Orphan designated products with at least one marketing approval for a rare disease indication (N = 52) [#]	0.9 ± 3.3 ^b	344.4 ± 233.5 ^a	5.3 ± 5.3	2.4 ± 1.9 ^b	1.3 ± 1.4 ^a	6.2 ± 4.2	2.7 ± 2.8	114.2 ± 85.3

orphan repurposed hits are less hydrophobic smaller MW than in vitro screening cpds

Molecules close to lead-like and closer to oral drugs

Dataset Intersection

Do these represent frequent actives or promiscuous compounds?

Finding Promiscuous Old Drugs for New Uses

- In vitro screening compounds repurposed –
- Statistically more hydrophobic (log P) and higher MWT than orphan-designated products with at least one marketing approval for a common disease indication or one marketing approval for a rare disease from the FDA's rare disease research database.
- Created multiple structure searchable databases in CDD
- Data for repurposing in publications is increasing but who is tracking it?
- Limited follow up of compounds from in vitro to in vivo..
- Will any of these compounds from in vitro be approved?
- Then the NPC browser was released early 2011

Government Databases Should Come With a Health Warning Openness Can Bring Serious Quality Issues

Database released and within days 100's of errors found in structures

PERSPECTIVE

Science Translational Medicine 2011

NPC Browser <http://tripod.nih.gov/npc/>

PHARMACOLOGY

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruilu Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn,
Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Drug Discovery Today

FIGURE 2

Stereochemistry issues with the content of the NPC browser database: left hand side 'NCGC Structures' and right hand side 'Correct Structures'.

Antony J. Williams

Sean Ekins

medicine and now drug repositioning or repurposing efforts. Their utility depends on the quality of the underlying molecular structures used. Unfortunately, the quality of much of the chemical structure-based data introduced to the public domain is poor. As an example we describe some of the errors found in the recently released NIH Chemical Genomics Center 'NPC browser' database as an example. There is an urgent need for government funded data curation to improve the quality of internet chemistry and to improve the proliferation of errors and wasted efforts.

US funding agencies have been investing in the development of public domain chemistry platforms with the primary attention being given to the informatics platform itself rather than the quality of the data content. This is clearly exemplified by the recently released NPC browser from the NIH Chemical Genomics Center (NCGC) [1]. Public online databases such as PubChem, ChemID-Plus [2] and the EPA's ACToR [3], to name just a few, have rapidly become trusted valuable resources which researchers rely on for downloadable chemical structures and associated data. While online chemistry databases can certainly be of value, we feel the reader should be immediately alerted to consider issues of data quality when using these resources and we call into question both their status and the trust we place in them. To our knowledge the issues we raise, using the example of a recently released database, have not been described elsewhere and the user community, and funding agencies, should not ignore them any longer. The development of cheminformatics platforms without due care given to the data quality they contain, is a poor strategy for long term science.

A quality alert and call for improved curation of public chemistry databases

In the last ten years, public online databases have rapidly become trusted valuable resources upon which researchers rely for their chemical structures and data for use in cheminformatics, bioinformatics, systems biology, translational

In the last decade numerous attempts have been made to expand our understanding of biological mechanisms by producing vast ligand and protein-protein interaction databases and by the application of computational methods to mine the data and, where possible, develop computational models. These approaches have enabled the clustering of biological activity spectra similarity

1556446X/11/\$ - see front matter © 2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.drugdis.2011.07.007

www.drugdiscoverytoday.com

Williams and Ekins,
DDT, 16: 747-750 (2011)

Data Errors in the NPC Browser: Analysis of Steroids

gonane

gon-4-ene

gona-1,4-diene

Substructure	# of Hits	# of Correct Hits	No stereochemistry	Incomplete Stereochemistry	Complete but incorrect stereochemistry
Gonane	34	5	8	21	0
Gon-4-ene	55	12	3	33	7
Gon-1,4-diene	60	17	10	23	10

Review

Toward a gold standard: regarding quality in public domain chemistry databases and approaches to improving the situation

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Available online 8 March 2012.

<http://dx.doi.org/10.1016/j.drudis.2012.02.013>, How to Cite or Link Using DOI

Why drug structure quality is important?

- More groups doing in silico repositioning
- Target-based or ligand-based
- Network and systems biology
- They are all integrating or using sets of FDA drugs..if the structures are incorrect predictions will be too..
- What is needed is a definitive set of FDA approved drugs with correct structures and tools for in silico screening
- Also linkage between in vitro data & clinical data

Repurpose FDA drugs in silico

Key databases of structures and bioactivity data

2D Similarity search with "hit" from screening

Export database and use for 3D searching with a pharmacophore or other model

Suggest *in silico* hits for *in vitro* screening

Suggest approved drugs for testing
- may also indicate other uses if it is present in more than one database

An example for TB and more

- Bayesian models for TB whole cell data
- 200,000 single point
- Over 2000 dose response
- Used publication that identified compounds with whole cell activity FDA drugs 2108 molecules (21 actives)
- **Lougheed et al., Tuberculosis (2009) 89:364-70**
- Numerous examples of pharmacophores screening drugs and finding transporter inhibitors, PXR agonists, PXR antagonists etc..
Ekins et al., Mol Pharmacol, 74(3):662-72 , (2008)
- Could use large datasets for other diseases, targets to build models search FDA drugs....and repurpose

Need to learn from neglected disease research

<http://www.slideshare.net/ekinssean>

Do we really need to screen massive libraries of compounds as we have for TB and malaria?

And groups are screening compounds already screened by others!

Ekins S and Williams AJ, MedChemComm, 1: 325-330, 2010.

Rare diseases: Searching for Potential Chaperones for Sanfilippo Syndrome

- Pshezhetsky et al showed Glucosamine rescues HGSNAT mutants
- **Feldhammer et al., Hum Mutat. 2009 30:918-25**
- Glucosamine used to create a 3D common features pharmacophore using Discovery Studio.
- The pharmacophore + ligand van der Waals shape was used to search multiple 3D databases
- FDA drugs, natural products, orphan drugs, KEGG, CSF metabolome etc.
- The pharmacophore consists of a positive ionizable (red) and 3 hydrogen bond donor groups (purple).
- Selected hits for experimental testing
- Collaboration ongoing!

e.g. Isofagomine maps pharmacophore

A path forwards for rare diseases using old drugs?

We propose generalizable methods utilizing transcriptomic, system-wide chemical biology datasets combined with chemical informatics and, where possible, repurposing of FDA approved drugs for pre-clinical orphan disease therapies.

A generalizable pre-clinical research approach for orphan disease therapy Chandree L. Beaulieu et al., submitted 2012

Crowdsourcing Project “Off the Shelf R&D”

DAMIEN HIRST
B.1965
PHARMACEUTICALS

How can we access more chemistry space?

All pharmas have assets on shelf that reached clinic
“Off the Shelf R&D”

Get the crowd to help in repurposing / repositioning these assets

How can software help?

- Create communities to test
- Provide informatics tools that are accessible to the crowd - enlarge user base
- Data storage on cloud – integration with public data
- Crowd becomes virtual pharma-CROs and the “customer” for enabling services

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Update 2011-2012

[Antivir Chem Chemother.](#) 2012 Feb 28. doi: 10.3851/IMP2080. [Epub ahead of print]

Inhibition of Influenza A Virus Replication by Antagonism of a PI3K-AKT-mTOR Pathway Member Identified by Gene Trap Insertional Mutagenesis.

[Murray JL](#), [McDonald NJ](#), [Sheng J](#), [Shaw MW](#), [Hodge TW](#), [Rubin DH](#), [O'Brien WA](#), [Smees DF](#).

[Invest Dermatol.](#) 2011 Dec;131(12):2467-76. doi: 10.1038/jid.2011.300. Epub 2011 Sep 22.

Rapamycin suppresses self-renewal and vasculogenic potential of stem cells isolated from infantile hemangioma.

[Greenberger S](#), [Yuan S](#), [Walsh LA](#), [Boscolo E](#), [Kang KT](#), [Matthews B](#), [Mulliken JB](#), [Bischoff J](#).

[Neuro Oncol.](#) 2011 Sep;13(9):974-82. Epub 2011 Jul 15.

Antiparasitic mebendazole shows survival benefit in 2 preclinical models of glioblastoma multiforme.

[Bai RY](#), [Staedtke V](#), [Aprhys CM](#), [Gallia GL](#), [Riggins GJ](#).

everolimus

5-fluorouracil

[Cancer Cell.](#) 2011 Sep 13;20(3):384-99. doi: 10.1016/j.ccr.2011.08.013.

An integrated in vitro and in vivo high-throughput screen identifies treatment leads for ependymoma.

[Atkinson JM](#), [Shelat AA](#), [Carcaboso AM](#), [Kranenburg TA](#), [Arnold LA](#), [Boulos N](#), [Wright K](#), [Johnson RA](#), [Poppleton H](#), [Mohankumar KM](#), [Féau C](#), [Phoenix T](#), [Gibson P](#), [Zhu L](#), [Tong Y](#), [Eden C](#), [Ellison DW](#), [Priebe W](#), [Koul D](#), [Yung WK](#), [Gajjar A](#), [Stewart CF](#), [Guy RK](#), [Gilbertson RJ](#).

ceftriaxone

[J Cell Physiol.](#) 2011 Oct;226(10):2484-93. doi: 10.1002/jcp.22609.

Role of excitatory amino acid transporter-2 (EAAT2) and glutamate in neurodegeneration: opportunities for developing novel therapeutics.

[Kim K](#), [Lee SG](#), [Kegelman TP](#), [Su ZZ](#), [Das SK](#), [Dash R](#), [Dasgupta S](#), [Barraclough PM](#), [Hedvat M](#), [Diaz P](#), [Reed JC](#), [Stebbins JL](#), [Pellecchia M](#), [Sarkar D](#), [Fisher PB](#).

Could In silico / in vitro repositioning find leads-drugs quicker?

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Everyone that has shared data in CDD..

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Blog: <http://www.collabchem.com/>

Website: <http://www.collaborations.com/CHEMISTRY.HTM>