



Systematic Drug Repurposing: Some Successes, Caveats, and Directions



Christopher P. Austin, M.D.
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National Institutes of Health



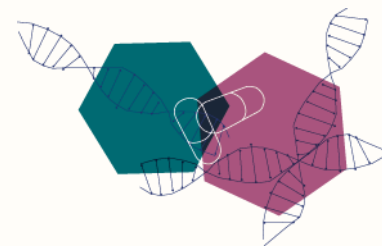
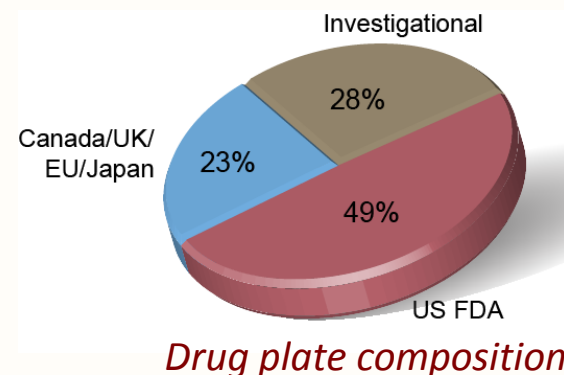
*IOM Roundtable on Translating Genomic-Based Research for Health
March 20, 2012*



NCATS: Tools and Reagents

NCATS Pharmaceutical Collection (NPC)

- A comprehensive resource of 3,800 approved and investigational medicines
- Facilitates repurposing of medicines by the scientific community
- Exists as:
 - Database (<http://tripod.nih.gov/npc>)
 - A sample repository for DPI screens



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

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

Small-molecule compounds approved for use as drugs may be “repurposed” for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

The NCGC Pharmaceutical Collection - Windows Internet Explorer

http://tripod.nih.gov/npc/

File Edit View Favorites Tools Help

★ Favorites

The NCGC Pharmaceutical Collection

The NCGC Pharmaceutical Collection current version 1.1.0

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What is the NCGC Pharmaceutical Collection (NPC)?

The NCGC Pharmaceutical Collection (NPC) is a comprehensive, publically-accessible collection of approved and investigational drugs for high-throughput screening that provides a valuable resource for both validating new models of disease and better understanding the molecular basis of disease pathology and intervention. The NPC has already generated several useful probes for studying a diverse cross section of biology, including novel targets and pathways. NCGC provides access to its set of approved drugs and bioactives through the [Therapeutics for Rare and Neglected Diseases](#) (TRND) program and as part of the compound collection for the [Tox21 initiative](#), a collaborative effort for toxicity screening among several government agencies including the US Environmental Protection Agency (EPA), the National Toxicology Program (NTP), the US Food and Drugs Administration (FDA), and the NCGC. Of the nearly 2750 small molecular entities (MEs) that have been approved for clinical use by US (FDA), EU (EMA), Japanese (NHI), and Canadian (HC) authorities and that are amenable to HTS screening, we currently possess 2400 as part of our screening collection.

How do I get access to the NPC?

The NPC resource currently consists of (i) the physical collection suitable for high throughput screening (HTS) and (ii) the informatics browser and database. Putting together the physical collection has been surprisingly challenging in terms of the time and effort required in the informatics, compound management and synthetic chemistry related activities required for this endeavor. We provide access to the NPC screening library through collaboration. Please contact our Scientific Director Dr. [Chris Austin](#) for additional information.

The other half of the NPC resource is the NPC browser. This is a self-contained software that is actively developed and maintained by the informatics group to provide electronic access to the NPC content. The latest version of the NPC browser for various platforms can be downloaded [below](#). Please let us know if your platform is not listed. Note that a fairly modern hardware (preferably with at least 2Gb of memory) is required to run the browser effectively.

How do I download the NPC browser?

File	Platform	Size	MD5 checksum
npc-browser_windows_1_1_0.exe	Windows	94.3 MB	9329911fba2e6ff44f2645f38337cc3b
npc-browser_macos_1_1_0.dmg	Mac OS X	78.7 MB	b9e58f73ba1f13a74f6525a2b88c7807
npc-browser_unix_1_1_0.sh	Linux	95.3 MB	7afedcc3741bd0ab8c96938a9ab9c852

Links

- NCGC
- MLI
- NHGRI
- PubChem
- ClinicalTrials.gov
- DailyMed
- Drug Portal

Presentations

- ACS Spring 2010
- Chemaxon UGM 2008

Tools

- Automated R-group analysis
- Fragment activity profiler
- Kinome navigator
- Kinome viewer
- Molecular framework
- MolSubspace
- Multiple MCS
- Scaffold activity diagram
- Siphonify
- Structure standardizer
- Tautomer generator
- The NPC browser

Recent Posts

- Large scale substructure searching
- MLBD browser
- On faster substructure searching
- Siphonify
- NPC paper

Local intranet 100%

NPC browser [1.1.0] — Compounds (14,814 total)

Search: **migraine**

CONTENTS	Compound	Synonym	Indication	MOA	CAS	PubChem CID	Ext ID	Filters
Compounds 1270		Zolmitriptan Zomig Zomig Rapimelt Zomigon ZMT ...14	For the acute treatment of adult migraine with or without aura.	Zolmitriptan binds with high affinity to human 5-HT_{1B} and 5-HT_{1D} receptors	139264-17-8	5731 441240	NPC-7377637 Microsource:MS-1505281 D800315 NCGC00095155	☐ NPC informatics (18/14,814) ☐ NPC screening (18/3,272) ☐ Approved drugs (18/7,929) ☐ Human approved drugs (18/7,793) ☐ FDA approved (16/4,655) ☐ FDA human approved (16/4,464) ☐ Structure undefined (0/5,681) ☐ Biologics (0/807) ☐ Inorganics (0/531) ☐ HTS amenable drugs (18/7,630) ☐ FDA drugs@FDA (15/1,751) ☒ FDA orange book (15/1,661) ☐ FDA NDC (16/3,359)
Targets 7781		Eletriptan Relpax S-[2-(benzenesulfonyl)ethyl]-... ...11	For the acute treatment of migraine with or without aura in adults.	Eletriptan binds with high affinity to 5-HT _{1B} , 5-HT _{1D} and 5-HT _{1F} receptors, has modest affinity for 5-HT _{1A} , 5-HT _{1E} .	177834-92-3 143322-58-1	77993	NPC-7393377 Toronto Research Chemic... D800216 NCGC00181130	☐ FDA DailyMed (15/1,176) ☐ FDA green book (1/426) ☐ US DEA (0/282) ☐ Canada (8/2,673) ☐ UK NHS (13/1,707) ☐ Japan (15/2,345) ☐ EMA human approved (0/326) ☐ EMA veterinary approved (0/33) ☐ WHO essential (3/448) ☐ Withdrawn (0/97) ☐ ClinicalTrials.gov (15/980) ☐ EMA orphan (2/327) ☐ INN (18/7,319) ☐ USAN (2/894) ☐ Tariff (18/7,587) ☐ KEGG (16/3,474) ☐ FDA maximum daily dose (12/1,181) ☐ DrugBank v3.0 (17/1,321) ☐ Community curation (10/2,001) ☐ QC spectra (10/1,491)
Diseases 582		Ergotamine Ergostat Ergotam-A ...24	For use as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so called ...	Ergotamine acts on migraine by one of two proposed mechanisms: 1) activation of 5-HT_{1D} receptors	24381-56-4 8048-75-7 113-15-5 ...10	24871232 6537504 16759307 ...2	NPC-7385148 National Cancer Institute: ... National Institute of Envir... ...3	
Documents 15000		Dihydroergotamine Dihydroergotamine mesylate Migranal Agit Angionorm D.H.E. ...35	For potential use in the treatment of Alzheimer's disease.	Dihydroergotamine is a mixture of three different ergotamine-3',6',18-triones, dihydroergocornine, ...	1381-02-8 76515-02-1 81643-69-8 ...6	12082315 24867491 24871048 ...8	NPC-7456055 6190-39-2 BIOMOL (Enzo Life Scienc... ...15	
		Naramig Naratriptan N-methyl-2-[3-(1-methylpiperi... Naratriptanum ...3	For the acute treatment of migraine attacks with or without aura in adults.	Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans: (1) stimulation of	143388-64-1 121679-13-8 121679-19-4 ...10	4440	NPC-7458154 Toronto Research Chemic... D800952 NCGC00181786	
		Frova Frovatan Frovatan succinate Miguard ...13	For the acute treatment of migraine attacks with or without aura in adults.	Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans: (1) stimulation of	158930-17-7 158747-02-5 158930-09-7 ...10	77992	NPC-7285295 Toronto Research Chemic... D800998 NCGC00183890	
		Almotriptan Almogran Avert almotriptan dimethyl(2-(5-(pyrrolidine-1-... ...12	For the treatment of acute migraine headache in adults	Almotriptan binds with high affinity to human 5-HT_{1B} and 5-HT_{1D} receptors	181183-52-8 154323-57-6 ...10	123606	NPC-7377572 Microsource:MS-1505204 D800918 NCGC00095135	
		Catapres Adesipress Catapresan Catapresan Catapres ...29	May be used as an adjunct in the treatment of hypertension, as an epidural infusion as an adjunct	See Pharmacology section above.	4205-91-8 4205-90-7 135589-09-2 ...10	2803 20179	NPC-7391426 BIOMOL (Enzo Life Scienc... BIOMOL (Enzo Life Scienc... ...7	
		Imigran Imitrex Imitrex Oral Sumatran Sumax NP101 ...23	For the treatment of migraine attacks with or without aura.	The 5-HT_{1B} and 5-HT_{1D} receptors function as autoreceptors, which inhibit the firing of	103628-48-4 103628-46-2 811794-26-0 ...10	59772 5358	NPC-7423992 Key Organics Ltd.:KS-1116 Microsource:MS-1505372 ...4	
		Rizatriptan benzoate Rizatriptan Maxalt Maxalt-MLT ...23	For treatment of acute migraine attacks with or without aura.	Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans: (1) stimulation of	145202-66-0 159776-67-7 144034-80-0 ...10	5078	NPC-7439080 Microsource:MS-1505189 D800953 NCGC00095899	
		Valproate semisodium Epival Divalproex sodium Depakene Alt-Valproic Avugane ...53	For treatment and management of seizure disorders, mania, and prophylactic treatment of	Divalproex binds to and inhibits GABA transaminase. The drug's anticonvulsant activity may be related to increased brain	99-66-1 1069-66-5 76584-70-8 ...10	3121 3549980 16760703 23663956 ...13	NPC-9299249 Environmental Protection ... Microsource:MS-1500606 ...13	
		Inderal Obsidan Propranolol Dacotin Propanolol Avlocardyl Inderide Angiolol ...74	For the prophylaxis of migraine.	Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at	318-98-9 525-66-6 69136-73-8 ...10	165193 62882 4946 ...4	NPC-7262645 BIOMOL (Enzo Life Scienc... BIOMOL (Enzo Life Scienc... ...26	
		Betimol Timoprol Timolol maleate Timolol Apo-Timol Apo-Timop Aquaniil Betim ...29	In its oral form it is used to treat high blood pressure and prevent heart attacks, and occasionally to prevent	Like propranolol and nadolol, timolol competes with adrenergic neurotransmitters such as catecholamines for	26921-17-5 26839-75-8 50929-98-1 ...13	45479754 33624 5281056 ...3	NPC-7234567 BIOMOL (Enzo Life Scienc... BIOMOL (Enzo Life Scienc... ...10	
		Topiramate Topamax Topamax Sprinkle Topiramate [French] ...16	Used for the treatment and control of partial seizures and severe tonic-clonic (grand mal) seizures and also for the	The precise mechanism of action of topiramate is not known. However, studies have shown that topiramate blocks	97240-79-4 ...10	5284627 16757856 ...11	NPC-7296873 Microsource:MS-1505801 D800273 NCGC00178714	
		Aspirin Salicylic acid acetate Polopiryna Aspirin Acetylsalicylic acid Easprin Coffart Micristin ...85	For use in the temporary relief of various forms of pain, inflammation associated with various conditions (including	The analgesic, antipyretic, and anti-inflammatory effects of acetylsalicylic acid are due to actions by both the acetyl and	50-78-2 69-46-5 53664-50-9 ...99	2244	NPC-7384766 Microsource:MS-1500130 NIH Center for Chemical G... ...11	

15 compounds, tag "FDA orange b..."

NPC browser [1.1.0] — Compounds (14,814 total)

Contents: Compounds (1270), Targets (7781), Clinical Trials (582), Diseases (15000), Documents

Search:

Filters: ☐ NPC informatics (18/14,814), ☐ NPC screening (18/3,272), ☐ Approved drugs (18/7,929), ☐ Human approved drugs (18/7,793), ☐ FDA approved (16/4,655), ☐ FDA human approved (16/4,464), ☐ Structure undefined (0/5,681), ☐ Biologics (0/807), ☐ Inorganics (0/531), ☐ HTS amenable drugs (18/7,630), ☐ FDA drugs@FDA (15/1,751), ☒ FDA orange book (15/1,661), ☐ FDA NDC (16/3,359), ☐ FDA OTC (1/1,088), ☐ FDA DailyMed (15/1,176), ☐ FDA green book (1/426), ☐ US DEA (0/282), ☐ Canada (8/2,673), ☐ UK NHS (13/1,707), ☐ Japan (15/2,345), ☐ EMA human approved (0/326), ☐ EMA veterinary approved (0/33), ☐ WHO essential (3/448), ☐ Withdrawn (0/97), ☐ ClinicalTrials.gov (15/980), ☐ EMA orphan (2/327), ☐ INN (18/7,319), ☐ USAN (2/894), ☐ Tariff (18/7,587), ☐ KEGG (16/3,474), ☐ FDA maximum daily dose (12/1,181), ☐ DrugBank v3.0 (17/1,321), ☐ Community curation (10/2,001), ☐ QC spectra (10/1,491)

Identifiers | Regulatory | **status** | Therapeutics | Properties

Indication
Anticonvulsant
For use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures.
For treatment and management of seizure disorders, mania, and prophylactic treatment of migraine headache.

Mechanism of Action
Anticonvulsants
Antimanic Agents
Enzyme Inhibitors
GABA Agents
Valproic Acid binds to and inhibits GABA transaminase. The drug's anticonvulsant activity may be related to increased brain concentrations of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the CNS, by inhibiting enzymes that catabolize

Valproate semisodium

Targets (3) | Clinical Trials (4) | Documents (4) | Product Labels (120) | Fragments (0) | Topologies (0)

4-aminobutyrate aminotransferase, mitochondrial (GABT_HUMAN)

Accessions [P80404](#) [A8K386](#) [Q16260](#) [Q8N5W2](#) [Q96RG2](#) [Q99800](#)
Genes [ABAT](#) [GABAT](#)
Organism Homo sapiens

Short/branched chain specific acyl-CoA dehydrogenase, mitochondrial (ACDSB_HUMAN)

Accessions [P45954](#) [Q86CX7](#)
Genes [ACADSB](#)
Organism Homo sapiens

Histone deacetylase 9 (HDAC9_HUMAN)

Accessions [Q9UIK0](#) [A7E2F3](#) [Q94845](#) [Q95028](#) [Q2M2B6](#) [Q86SL1](#) [Q86US3](#)
Genes [HDAC9](#) [HDAC7](#) [HDAC7B](#) [HDRP](#) [KIAA0744](#) [MITR](#)
Organism Homo sapiens

15 compounds, tag "FDA orange b..."

NPC browser [1.1.0] — Compounds (14,814 total)

Contents: Compounds (1270), Targets (7781), Clinical Trials (502), Diseases (15000), Documents

Valproate semisodium

Regulatory Status

U.S. Approved
[FDA drugs@FDA](#)
[Approved Drug Products \(Orange Book\)](#)
[FDA National Drug Code Directory \(NDC\)](#)

World Approved
[Dictionary of Medicines and Devices \(UK\)](#)
[Therapeutic Products Directorate \(Health Canada\)](#)
[The Japanese Pharmacopeia, Fourteenth Edition](#)

Other
[WHO International Nonproprietary Names \(INN\)](#)
[Harmonized Tariff Schedule of the United States](#)
[FDA Maximum \(Recommended\) Daily Dose](#)
[KEGG Drug](#)

4-aminobutyrate aminotransferase, mitochondrial (GABT_HUMAN)
Accessions [P80404](#) [A8K386](#) [Q16260](#) [Q8N5W2](#) [Q96BG2](#) [Q99800](#)
Genes [ABAT](#) [GABAT](#)
Organism Homo sapiens

Short/branched chain specific acyl-CoA dehydrogenase, mitochondrial (ACADSB_HUMAN)
Accessions [P45954](#) [Q96C7](#)
Genes [ACADSB](#)
Organism Homo sapiens

Histone deacetylase 9 (HDAC9_HUMAN)
Accessions [Q9UUKV0](#) [A7E2F3](#) [Q94845](#) [Q95028](#) [Q2M2R6](#) [Q86SL1](#) [Q86US3](#)
Genes [HDAC9](#) [HDAC7](#) [HDAC7B](#) [HDRP](#) [K1AA0744](#) [MITR](#)
Organism Homo sapiens

Filters: NPC Informatics (18/14,814), NPC screening (18/3,272), Approved drugs (18/7,929), Human approved drugs (18/7,793), FDA approved (16/4,655), FDA human approved (16/4,464), Structure undefined (0/5,681), Biologics (0/807), Inorganics (0/531), HTS amenable drugs (18/7,630), FDA drugs@FDA (15/1,751), ☒ FDA orange book (15/1,661), FDA NDC (16/3,359), FDA OTC (1/1,088), FDA DailyMed (15/1,176), FDA green book (1/426), US DEA (0/282), Canada (8/2,673), UK NHS (13/1,707), Japan (15/2,345), EMA human approved (0/326), EMA veterinary approved (0/33), WHO essential (3/448), Withdrawn (0/97), ClinicalTrials.gov (15/980), EMA orphan (2/327), JMW (18/7,319), USAN (2/894), Tariff (18/7,587), KEGG (16/3,474), FDA maximum daily dose (12/1,181), DrugBank v3.0 (17/1,321), Community curation (10/2,001), QC spectra (10/1,491)

15 compounds, tag "FDA orange b..."

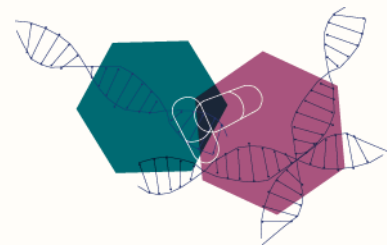
NCATS: Innovative Approaches Finding New Uses for Approved Medicines

The Problem: Chronic Lymphocytic Leukemia (CLL)

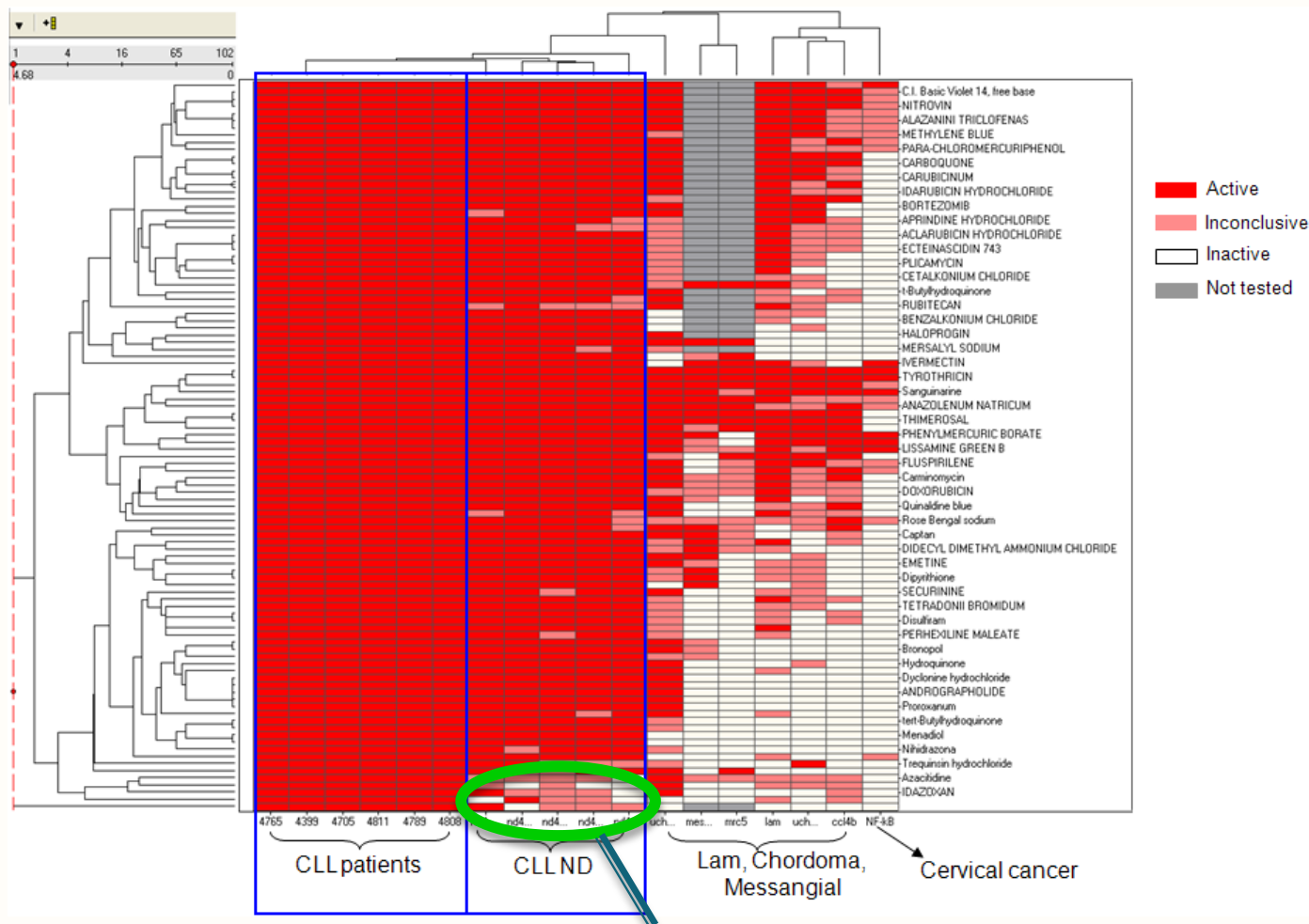
- About 30% of adult leukemia
- 15,000 new U.S. diagnoses per year, 80% age 60+
- Many refractory to current treatments

The NCATS Approach

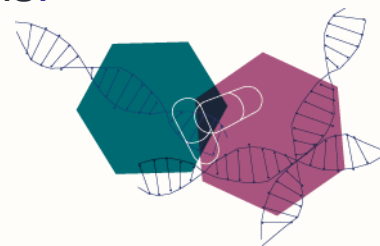
- DPI – screens the NCATS Pharmaceutical Collection
- DCI – rapid clinical trial
- Collaboration with non-profit sector



102 CLL Pan-Actives vs. Normal B Cells



Kills CLL but not normal donor cells!



Capitalizing on Strengths

Discovering and developing drugs for the treatment of rare hematological malignancies



National Institutes of Health
NATIONAL CENTER FOR ADVANCING
TRANSLATIONAL SCIENCES



- Bench to bedside translation in drug repurposing
- National leadership in medicinal and pharmaceutical chemistry
- Pharma experience

- Focus on rare and neglected diseases
- Industrial scale HTS, medicinal chemistry, and bioinformatics capabilities
- Pharma experience



LEUKEMIA &
LYMPHOMA
SOCIETY
fighting blood cancers

- ~ 400 active research projects
- World-wide network of blood cancer experts
- Track record of commercial partnerships
- Pharma experience

KUMC News

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November 01, 2011

By KUMC News

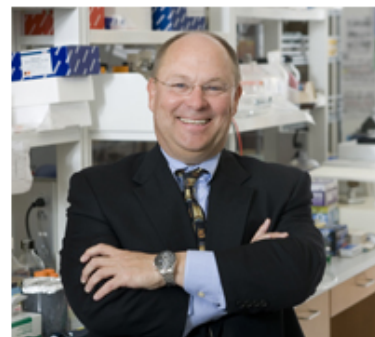
As part of an aggressive effort to speed delivery of treatments to patients by finding new uses for approved drugs, researchers at the University of Kansas Medical Center have begun a clinical trial targeting the most common form of adult leukemia with a drug first approved to treat arthritis more than 25 years ago.

Earlier this month, KU researchers treated the first trial participant, a Kansas City-area patient suffering from chronic lymphocytic leukemia or CLL, with the drug auranofin, which has long been used to treat patients with arthritis.

The trial is one key piece of a larger collaboration between KU, The Leukemia & Lymphoma Society (LLS) and the National Institutes of Health (NIH) to accelerate discovery and development of safe, effective and affordable cancer treatments. Over the last two years, the group discovered that auranofin kills CLL cells in test tubes, and received approval to test the drug in CLL patients.

"Today's process of discovering and developing new drugs for patients takes too much time and costs too much money," said Louis J. DeGennaro, Ph.D., executive vice president and chief mission officer, LLS. "The collaboration between KU, LLS and NIH is committed to giving new hope to patients by reducing sharply the time and costs associated with developing new therapies. Auranofin is a great example of what is possible through an effective public-private partnership."

"Spending more than \$1 billion and taking more than a decade to deliver new therapies to patients is simply not sustainable," said Scott Weir, PharmD, PhD, director of KU's Institute for Advancing Medical Innovation. "Our group moved this new discovery into a clinical trial in just two years and for about \$1 million, representing significant time and cost savings from business as usual."



Scott Weir, PharmD, PhD, is director of KU's Institute for Advancing Medical Innovation

Clinical trial sites:
KU (Bhalla)
NIH (Wiestner)
OSU (Byrd)



FasterCures Webinar Collaboration in Action

The Learning Collaborative™

21 March 2012

Presenters

- **Christopher P. Austin, MD**
 - Director of Preclinical Innovation
 - National Center for Advancing Translational Sciences
 - National Institute of Health
- **Louis J. DeGennaro, PhD**
 - Chief Mission Officer
 - Leukemia & Lymphoma Society
- **Scott J. Weir, PharmD, PhD**
 - Director
 - Institute for Advancing Medical Innovation
 - University of Kansas Cancer Center

What was important?

- Auranofin project supported by NIH, LLS, philanthropic and economic development funding sources
- Rapid results lead to philanthropic funding opportunities
- “Marrying” funding sources (and restrictions) to support specific project activities
- Integrate technology transfer into teams
- Defining, capturing and maximizing exclusivity path(s) to interest for-profit partners
- Address regulatory science issues that impact the repurposing of patent and/or abandoned drugs

What was important?

Regulatory Science

- Each project is unique, but in general, projects employ one or two “common” strategies
 - Therapeutic indication
 - ◆ Related indication (e.g., blood cancer indication leads to study in solid tumors)
 - ◆ Unrelated indication (e.g., auranofin, FDA approved arthritis agent, currently in use, for the treatment of CLL)
 - Improved delivery
 - ◆ Elimination of excipients associated with safety issues
 - ◆ Different route of administration
 - ◆ Combination products
 - ◆ Overcome pharmacokinetics issues
- 505(b)2 path
- Accessing data generated by innovator firms

What was important?

Defining Exclusivity Path(s) and Reimbursement Strategies

- Difficulties in establishing exclusivity for approved drugs has deterred industry from drug repurposing
- Requires multiple, innovative approaches integrated into one comprehensive strategy
- Regulatory science plays a critical role in defining
- It's never too early to develop reimbursement strategies
- May require public policy initiatives to encourage drug repurposing for rare and neglected diseases
- ValueMaP™ (“Value Maximization Path”) under development

Genomics-based computational approaches

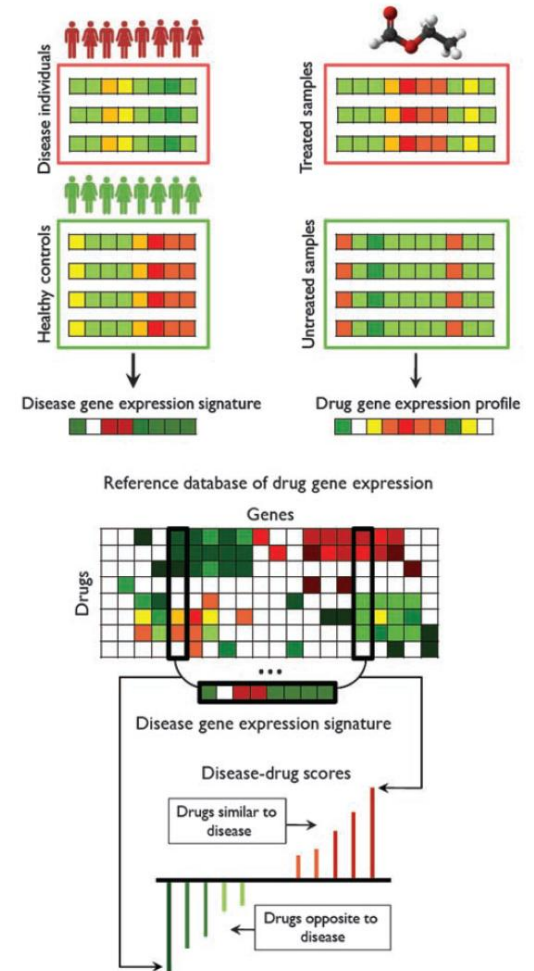
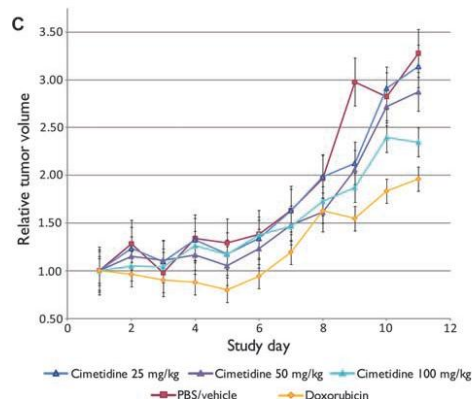
DRUG DISCOVERY

Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data

Marina Sirota,^{1,2,3*} Joel T. Dudley,^{1,2,3*} Jeewon Kim,⁴ Annie P. Chiang,^{1,2,3} Alex A. Morgan,^{1,2,3}
Alejandro Sweet-Cordero,^{1,5} Julien Sage,^{1,5,6} Atul J. Butte^{1,3,5†}

Published 17 August 2011; revised 28 September 2011

The application of established drug compounds to new therapeutic indications, known as drug repositioning, offers several advantages over traditional drug development, including reduced development costs and shorter paths to approval. Recent approaches to drug repositioning use high-throughput experimental approaches to assess a compound's potential therapeutic qualities. Here, we present a systematic computational approach to predict novel therapeutic indications on the basis of comprehensive testing of molecular signatures in drug-disease pairs. We integrated gene expression measurements from 100 diseases and gene expression measurements on 164 drug compounds, yielding predicted therapeutic potentials for these drugs. We recovered many known drug and disease relationships using computationally derived therapeutic potentials and also predict many new indications for these 164 drugs. We experimentally validated a prediction for the antiulcer drug cimetidine as a candidate therapeutic in the treatment of lung adenocarcinoma, and demonstrate its efficacy both in vitro and in vivo using mouse xenograft models. This computational method provides a systematic approach for repositioning established drugs to treat a wide range of human diseases.



What has worked

- Rational repurposing based on knowledge of disease pathogenesis and drug pharmacology
 - Intended target: sildenafil for ED, PAH
 - Adventitious target: losartan for Marfan's
- Computational (pathway or pattern based) approaches in selected cases
 - Comprehensive informatics resource assists
 - Validation in humans generally lacking
- Phenotypic screening of human patient-derived cells across comprehensive small molecule screening resource
 - e.g., auranofin for CLL
- Disease-focused teams with *comprehensive* and complementary expertise

What has not worked so well

- Repurposing based solely on animal model data
 - Often unclear whether is due to non-human applicability of model or poorly performed animal study
- Computational (pathway or pattern based) approaches without experimental testing
 - Lots of algorithm papers, some preclinical validations, very few clinical (human) translations
 - But absence of evidence is not evidence of absence
- Phenotypic screens without prospective plan for translating to human – often best intentions but lack of translational/clinical resources frequently result in project arrest
- Repurposing generic drugs to through registration trials for new indication is difficult – new funding paradigm needed