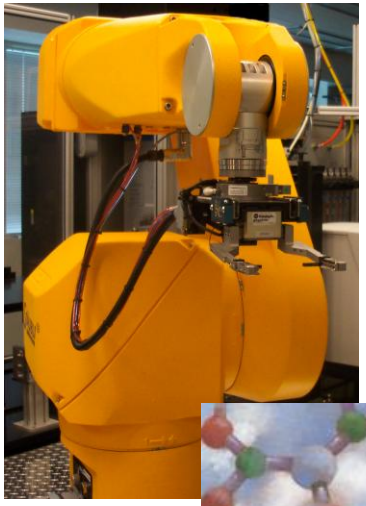
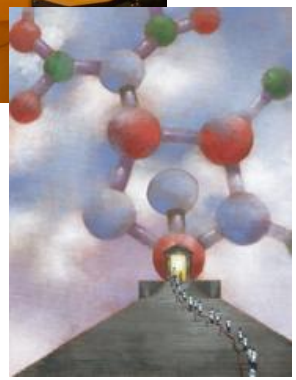
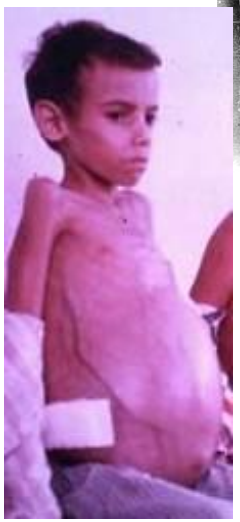




Systematic Drug Repurposing: Some Successes, Caveats, and Directions



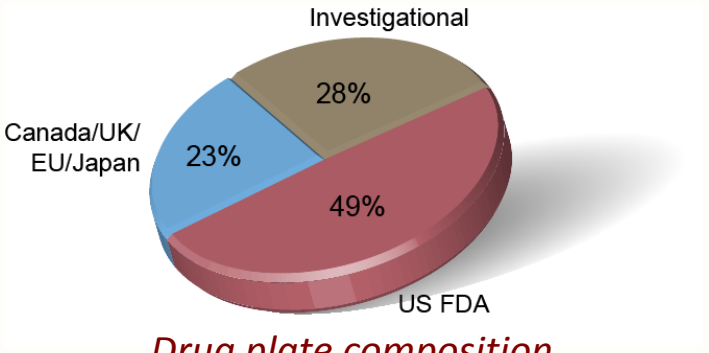
Christopher P. Austin, M.D.
Director, Division of Preclinical Innovation
National Center for Advancing Translational Sciences
National Institutes of Health

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



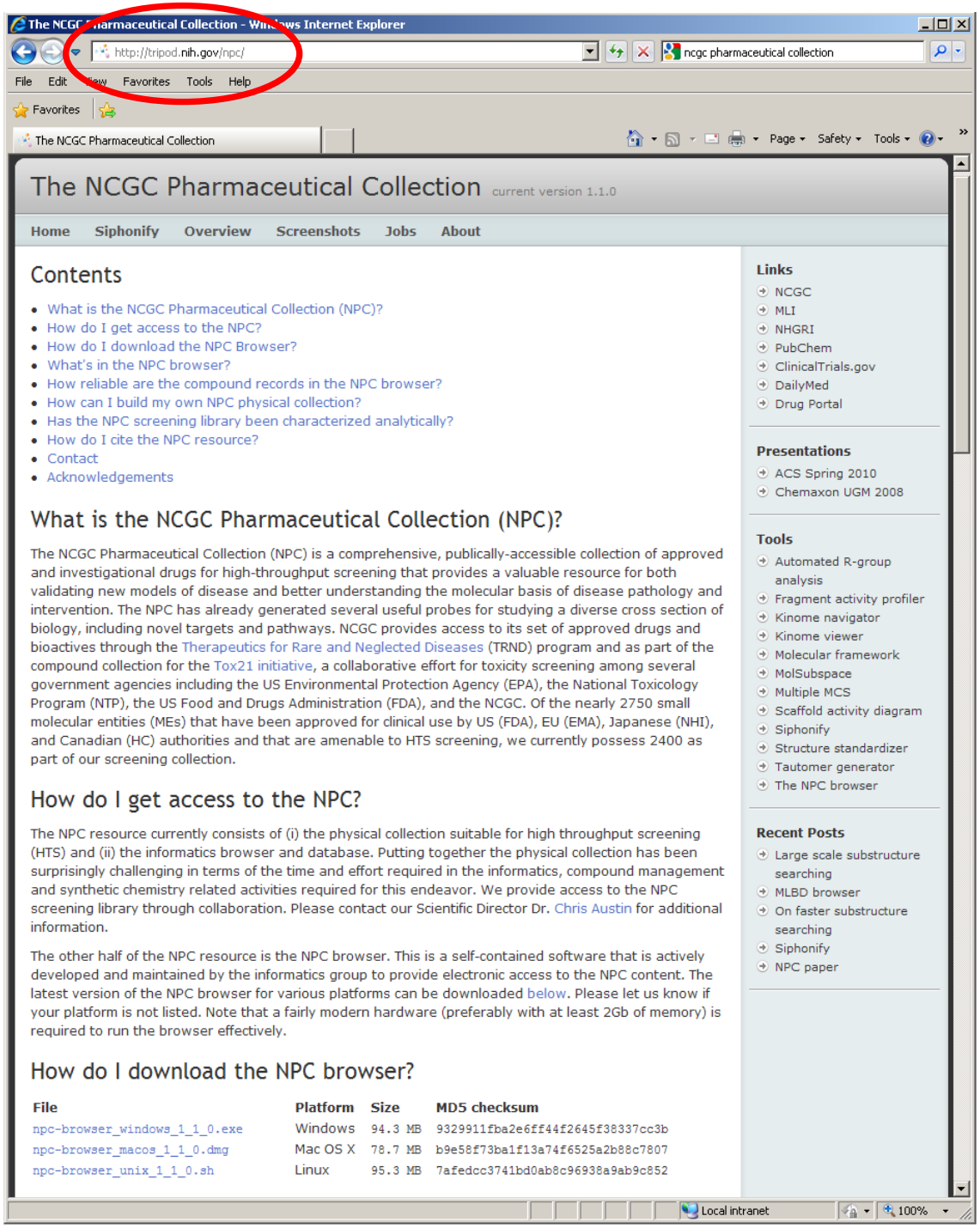
Drug plate composition

PHARMACOLOGY

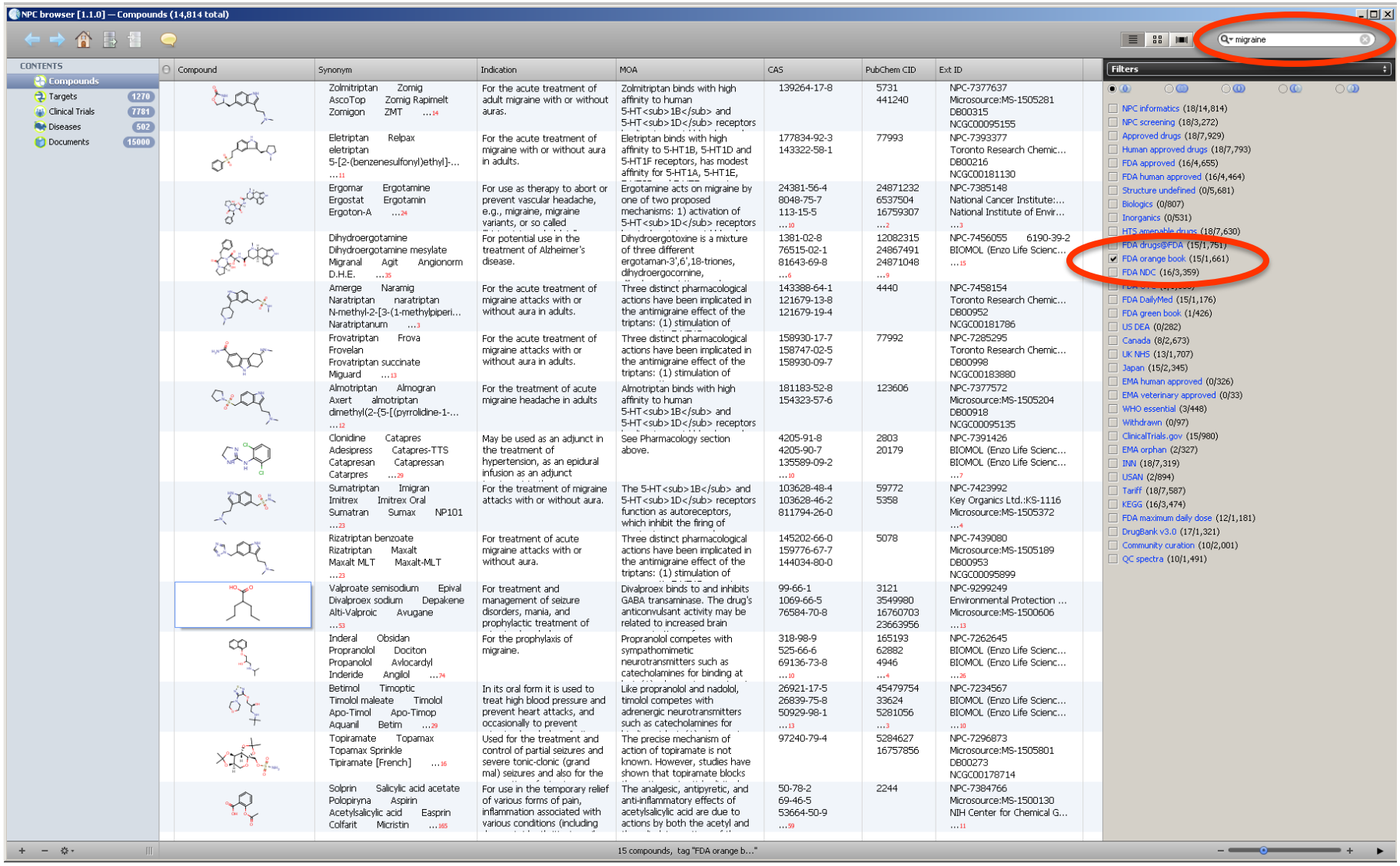
The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

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

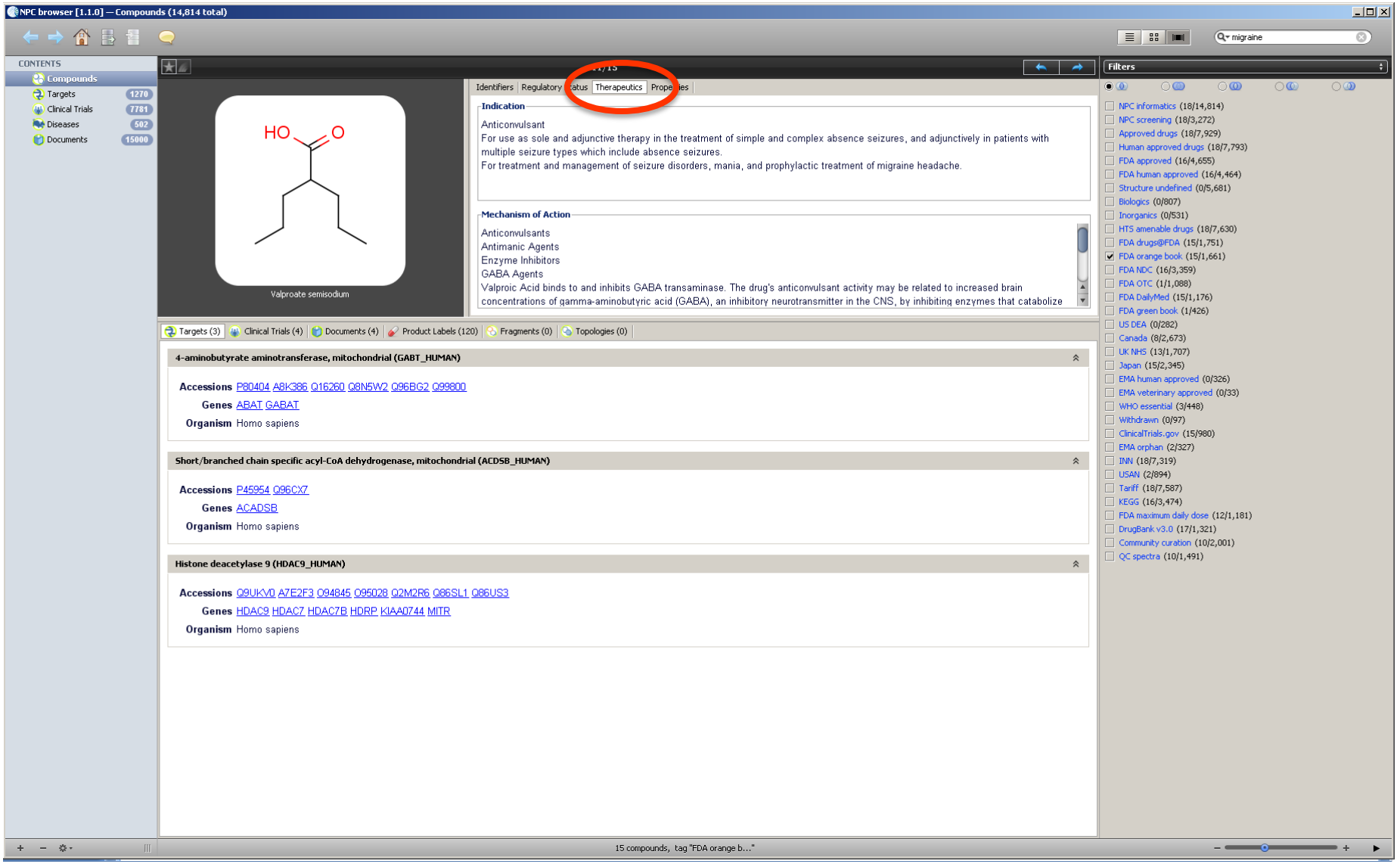
Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across 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.



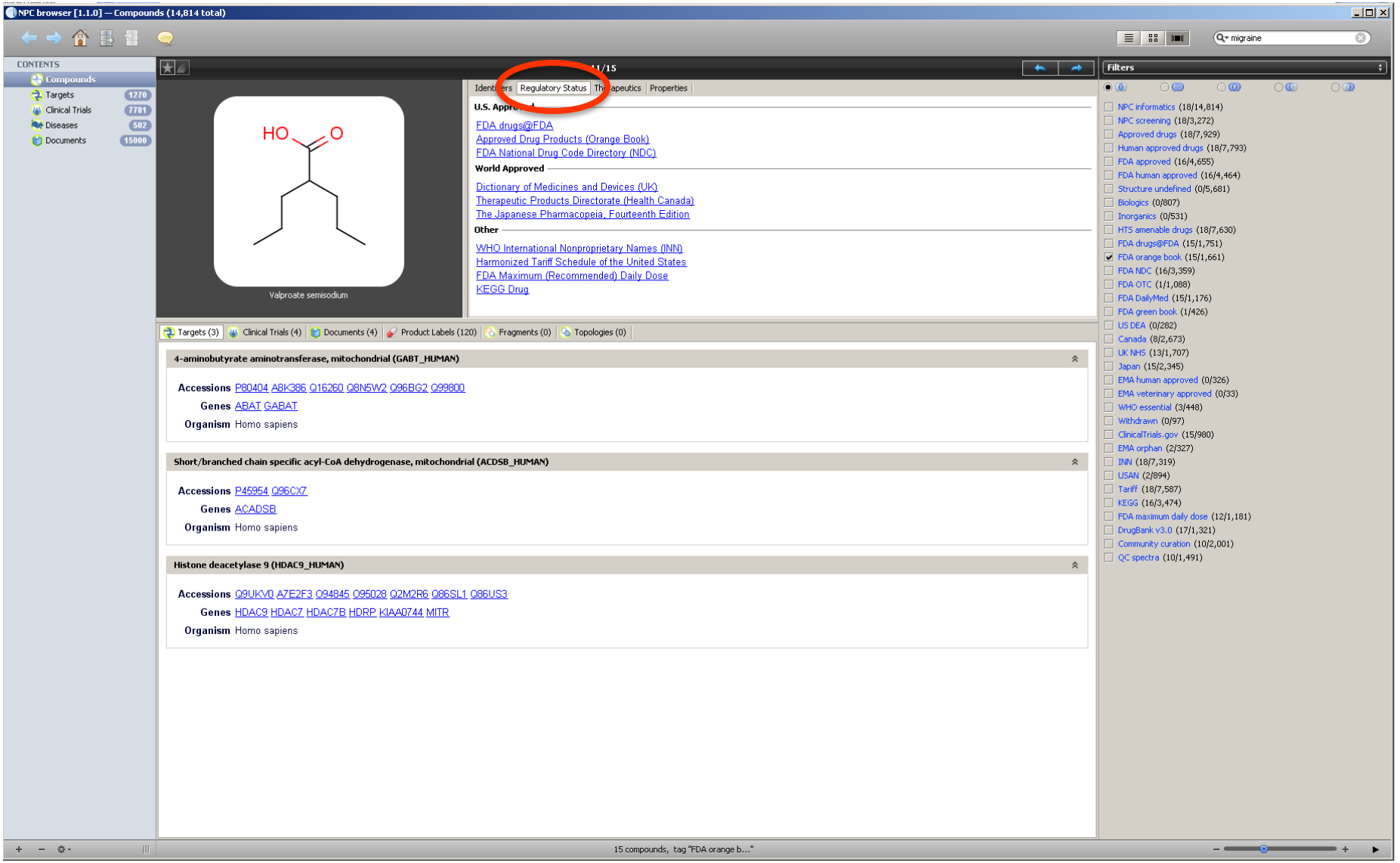
NIH Chemical Genomics Center



NIH Chemical Genomics Center



NIH Chemical Genomics Center



NIH Chemical Genomics Center

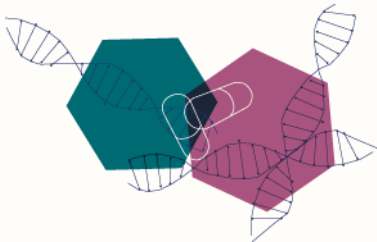
NCATS: Innovative Approaches Finding New Uses for Approved Medicines

The Problem: Chronic Lymphocytic Leukemia (CLL)

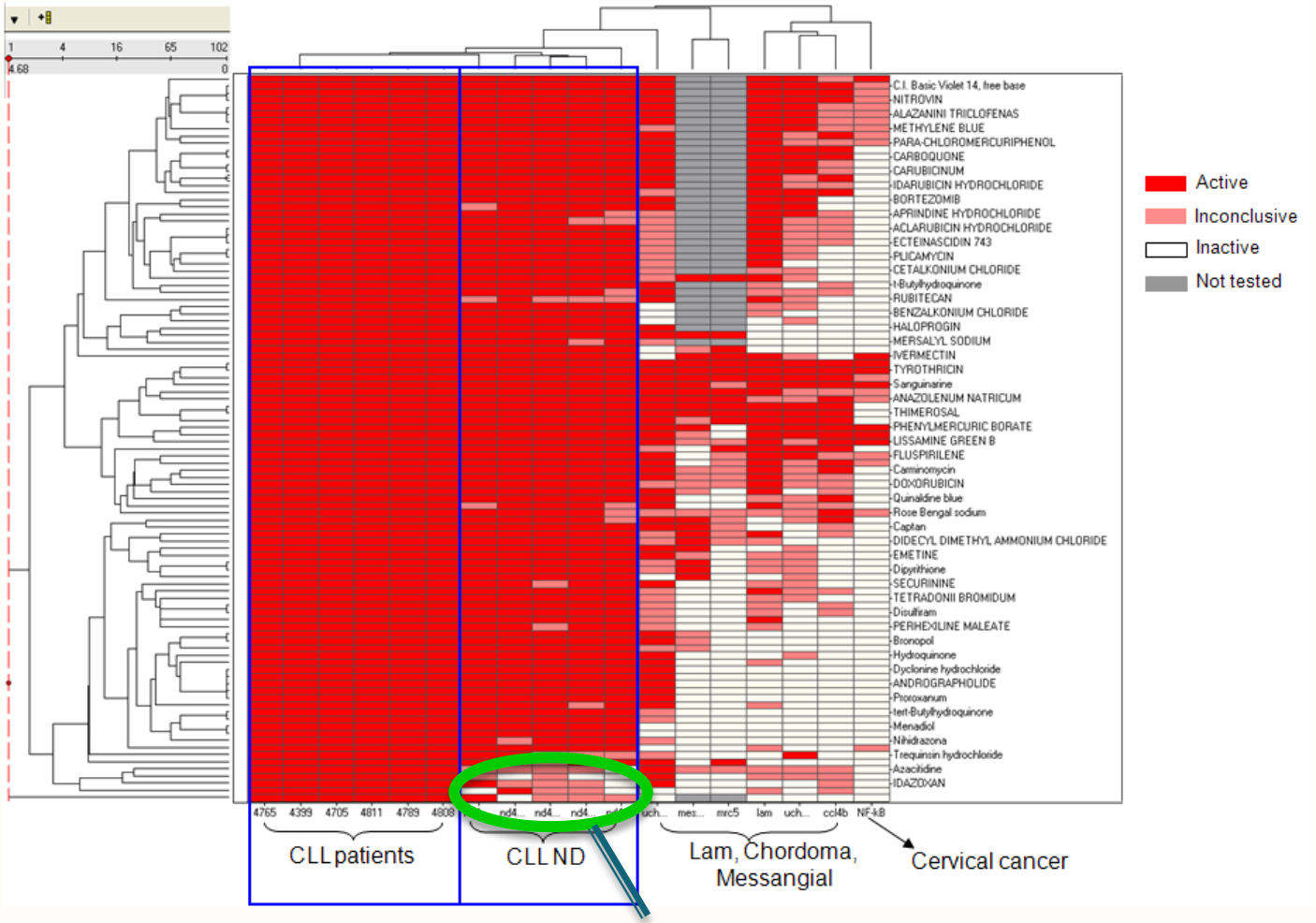
- About 30% of adult leukemia
- 15,000 new U.S. diagnoses per year, 80% age 60+
- Many refractory to current treatments

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

- **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**

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

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

KU's Institute for Advancing Medical Innovation, The Leukemia & Lymphoma Society and NIH begin groundbreaking clinical trial for leukemia patients

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.

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

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."

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 off 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

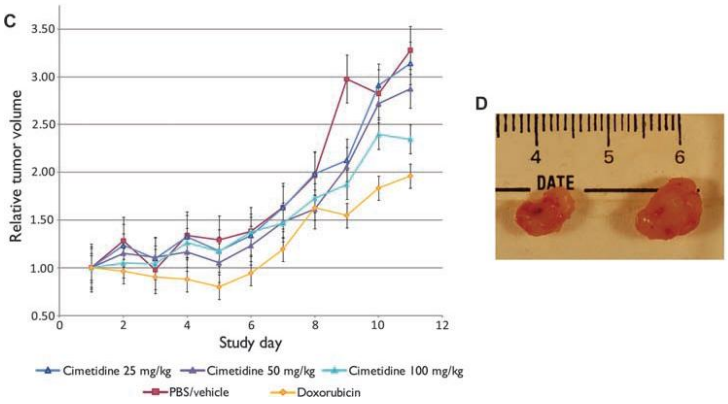
DRUG DISCOVERY

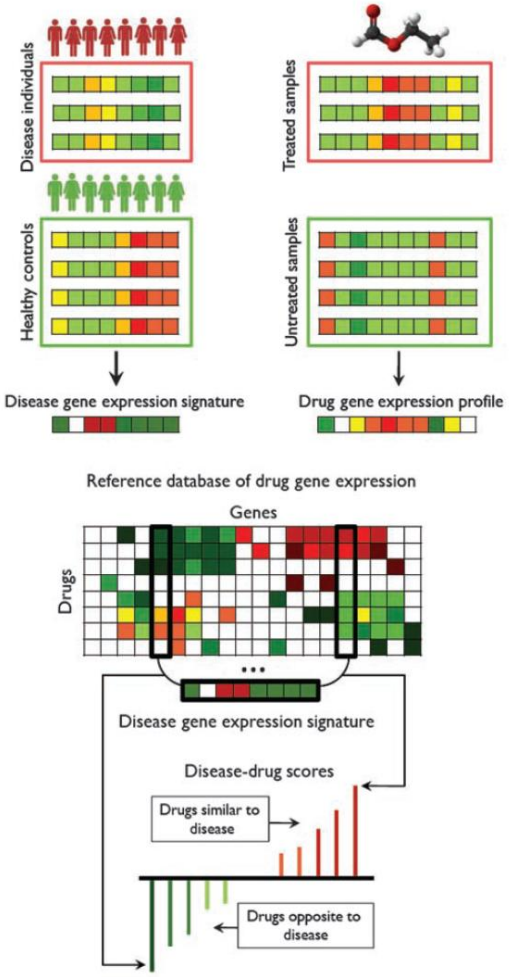
Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data

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