Using Human Genetic Variation to Repurpose Existing Medications for New Diseases

ASCPT Symposium on Drug Repurposing
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Practical steps to *move forward, beyond ideas*

- Secure seed/infrastructure funding
- Create novel methodologies
- Set up structure
- Run the data algorithms
- Perform prospective validation experiments confirming utility *(not an informatics exercise)*
- Conduct human proof of concept clinical trials
- Consider ways to share, disseminate, commercialize and grow
- Evaluate effect on speed of translation and human health
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NIH, NCATS Clinical and Translational Science Award (CTSA) Network

Vanderbilt’s Institute for Clinical and Translational Research (VICTR)

Jill Pulley, MBA
VICTR Executive Director

Gordon Bernard, MD
VICTR Program Director, Executive Vice President for Research

- **NCATS funded**, 5 year cycles (renewed 2 years ago)
- Speed translation of discoveries from “bench to bedside”
- Broad range of activities; one of them is drug repurposing
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Leveraging Vanderbilt precision medicine resources for drug repurposing

**BioVU**
- De-identified DNA extracted from leftover blood after clinically-indicated testing of Vanderbilt patients who have consented
- >245K DNA samples, ~100K with genome-wide genotyping

**Synthetic Derivative**
- Longitudinal, de-identified EHR linked to BioVU samples
PheWAS reverses GWAS approach to identify novel phenotype associations

<table>
<thead>
<tr>
<th>Approach</th>
<th>P-value correlation</th>
<th>Output</th>
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<tbody>
<tr>
<td><strong>GWAS</strong></td>
<td>Target phenotypes to Genetic markers (SNPs)</td>
<td>Chromosomal Location</td>
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<td>Genome-Wide Association Study</td>
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<td>Diagnosis Code</td>
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<tr>
<td><strong>PheWAS</strong></td>
<td>Target genetic markers (SNPs) to Phenotypes</td>
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PheWAS identifies phenotypes of interest for a given genetic marker linked to specific drugs, often revealing previously unknown linkages.
Experiments of nature: connecting genome and phenome to find new drug indications

- They have a SNP that lowers LDL cholesterol levels
- They have a SNP that decreases gastric acid secretion
- They have a SNP that increases glycine levels

Human ‘library’ of clinical diseases and their correlative drug targets

Their genomes are already mirroring drug therapeutic effects, so they can also help us answer:

What are the possible new indications based on these biologic effects and thousands of others fitting this paradigm?

We have clinical data available before:
- The first dose of an investigational new drug is ever given
- A new preclinical program is launched
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- Operations team
- Faculty experts
- Processes
- Integration of databases
- FDA regulatory pathways
- Commercialization and exclusivity

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Vanderbilt’s Accelerating Drug Discovery & Repurposing Incubator (ADDRI)

ADDRI is a multidisciplinary think tank of experts in various therapeutic areas including:

- Basic scientists and clinical researchers
- As well as IP attorneys and other experts in:
  - Legal, business, regulatory affairs, evidence synthesis and information science
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Initial steps to establish a precision indication

Precision indication originates from PheWAS data, is biologically plausible based on evidence, and will move to animal or human validation studies with precise endpoints to confirm mechanism.
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Pipeline is efficient, diverse, and does not “squeeze shut”

Traditional drug development starts with 5k-10k compounds to get **ONE** Approved Drug.

**Disease areas include:**
- Cancer
- Infectious diseases
- Gastroenterological disorders
- Autoimmune disorders
- Neuropsychiatric conditions
Validation examples are ‘5 for 5’
Meaning, 5 out of 5 studies (animal efficacy) attempted were successful

• Two examples that moved from concept to Phase II clinical trial activation in under 2 years:

  • A SNP in *PTGER2*, associated with the phenotypes representing indication for *misoprostol* (prevention of NSAID-induced gastric ulcers) was used to develop a new indication for prevention of recurrent *C. difficile* colitis

    • **Phase II is trial enrolling**

  • A SNP in *TBXA2R*, associated with phenotypes representing intended indications for ifetroban, was used to develop a new indication for the prevention of metastasis across multiple cancers
Ifetroban decreases hematogenous metastasis of breast, pancreatic and lung cancer cells.

Across THREE cancer types, ifetroban treatment led to 70% FEWER surface metastases.

Data courtesy of
Rebecca Cook, PhD
Associate Professor of Cell and Developmental Biology

Average # surface metastases

Vehicle | Ifetroban
---|---
Pancreatic | 9
Breast | 3
Lung | 1

Representation of multiple independent studies
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Conducting proof of concept clinical trials

*Approval to conduct trials is itself validating*

**Approval involves:***

- A PI willing to devote substantial time
- Institutional IRB approval assessing risk benefit FDA approval for IND
- Agreement from the sponsor/funder that the project is compelling and methodologically sound

**4 human trials now approved and underway:**

1. Misoprostol, explained previously
2. Iftetroban, explained previously
3. Memantine – A rare SNP in *GRIN2A* shows validation in BioVU with aphasia and a new association with very specific presentations of Systemic Lupus Erythematosus
4. Guanfacine – A SNP in *ADRA2B* shows validation with general pain phenotypes and a new association with trigeminal nerve disorders
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Lots of runway in the identification of repurposing targets

Filter DrugBank data

10,505
Total number of agents in DrugBank

2,219
Approved small molecules

823
One target

Match with SNP data

239,796
SNPs on existing ExomeChip catalogued from patients in BioVU

~232
Unique target-action pairs with SNP coverage

237
Unique target-action pairs

~210k
≥0.001 MAF nonsense & missense
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GOAL in NCATS sponsored CTSA program: Assess the program’s pace of achieving downstream regulatory and commercialization milestones compared to traditional methods, using ‘Time To’ analyses.
Issues faced by our program

- Few traditional economic incentives for repurposing safe and low cost generics
- Willingness/ability of pharma to share ‘shelved’ compounds
- Novel funding and partnership models

Our next steps

- Push all 15 new therapeutic uses through human clinical trials
- Seek exclusivity when feasible
- Seek licensing to a manufacturer and/or publication of results