FROM MOLECULE TO PATIENT

Using Human Genetic Variation to Repurpose Existing Medications for New Diseases

ASCPT Symposium on Drug Repurposing
March 16, 2019

Jill Pulley, MBA
Executive Director
Vanderbilt Institute for Clinical and Translational Research
Vanderbilt University Medical Center

FROM MOLECULE TO PATIENT

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

Practical steps to *move forward, **beyond ideas***

FROM MOLECULE TO PATIENT

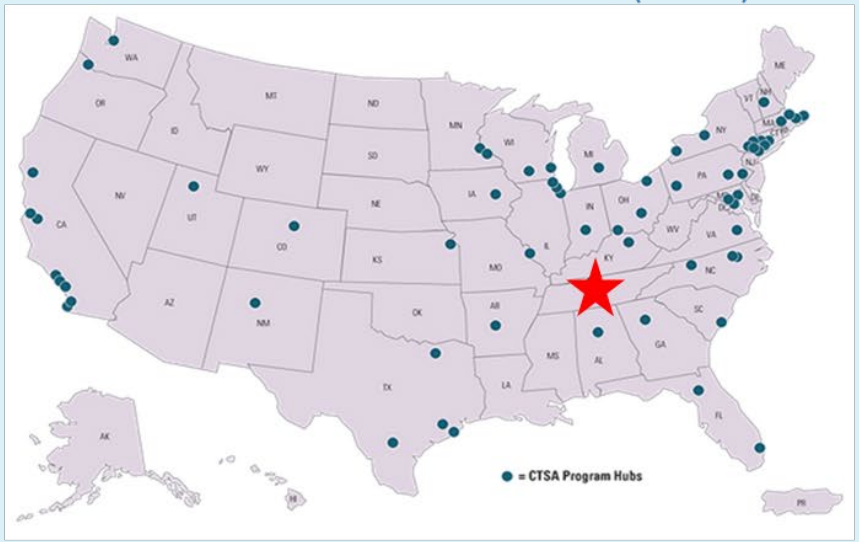
- Secure seed/infrastructure funding
- Create novel methodologies
- Set up structure
- Run the data algorithms
- Perform prospective validation experiments confirming utility *(not an informatics exercise)*
- Conduct human proof of concept clinical trials
- Consider ways to share, disseminate, commercialize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

FROM MOLECULE TO PATIENT

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*

Practical steps to *move forward,* ***beyond ideas***

FROM MOLECULE TO PATIENT

- Secure 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

Leveraging Vanderbilt precision medicine resources for drug repurposing

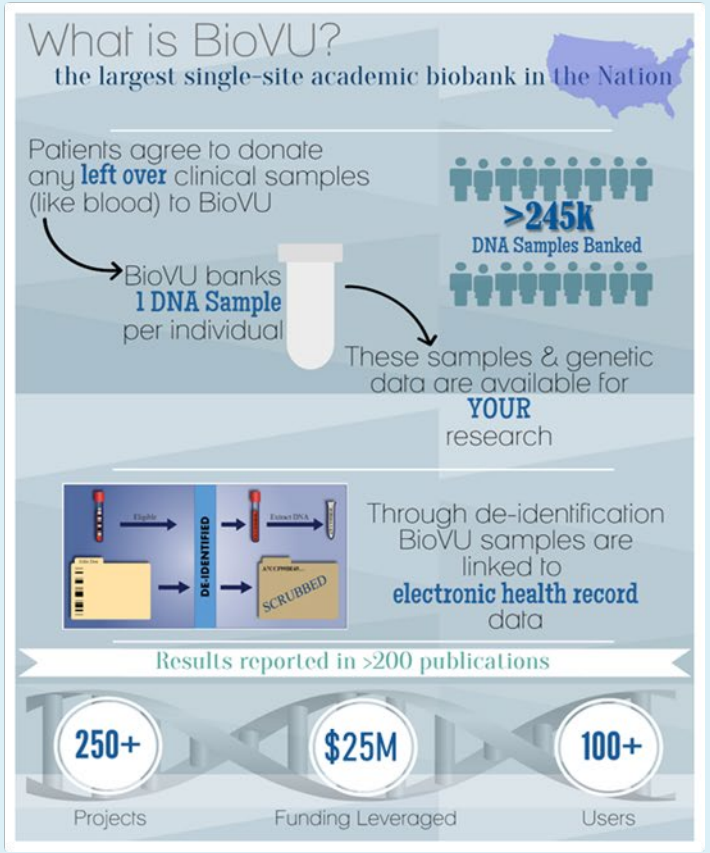
FROM MOLECULE TO PATIENT

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

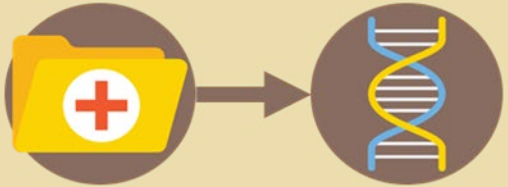
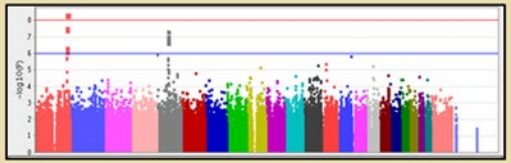
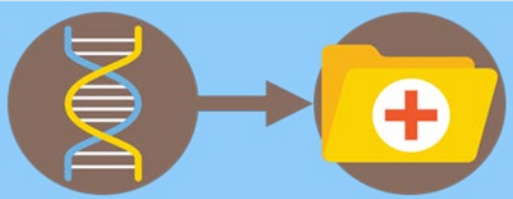
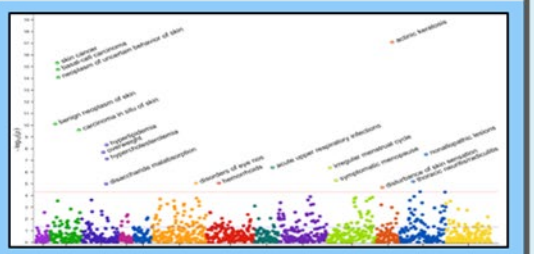
Synthetic Derivative

- Longitudinal, de-identified EHR linked to BioVU samples



PheWAS reverses GWAS approach to identify novel phenotype associations

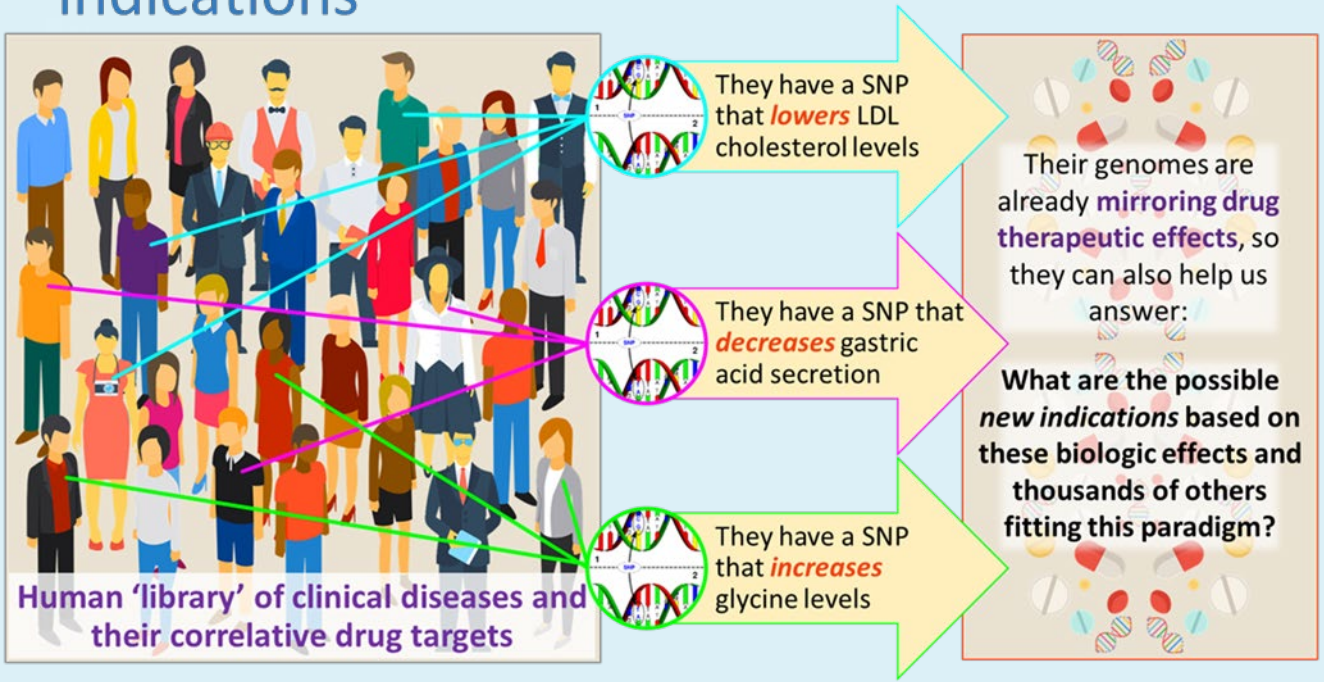
FROM MOLECULE TO PATIENT

Approach	P-value correlation	Output
GWAS Genome-Wide Association Study	 Target phenotypes *to* Genetic markers (SNPs)	 Chromosomal Location
PheWAS *Phenome-Wide* Association Study	 Target genetic markers (SNPs) *to* Phenotypes	 Diagnosis Code

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

FROM MOLECULE TO PATIENT



We have clinical data available **before:**

- The first dose of an investigational new drug is ever given
- A new preclinical program is launched

Practical steps to *move forward,* ***beyond ideas***

FROM MOLECULE TO PATIENT

- Secure infrastructure funding
- Create novel methodologies
- **Set up structure**
  - Operations team
  - Faculty experts
  - Processes
  - Integration of databases
  - FDA regulatory pathways
  - Commercialization and exclusivity
- 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

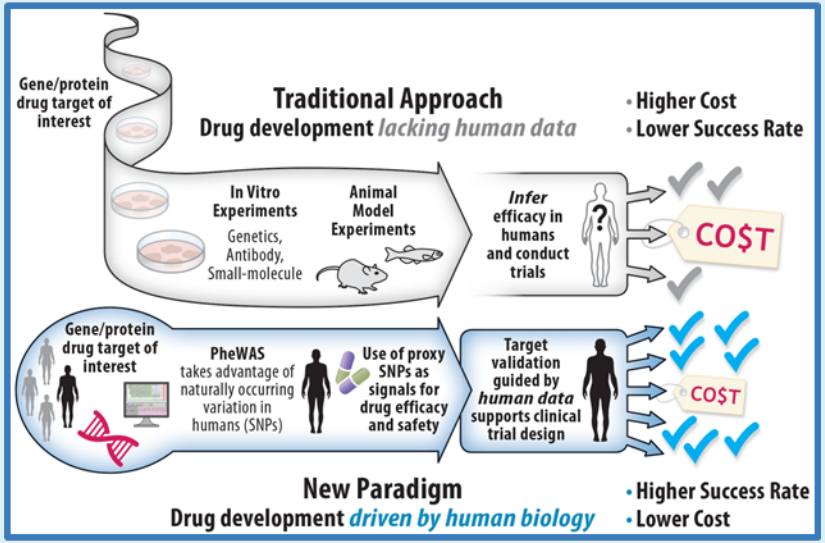
Vanderbilt's Accelerating Drug Discovery & Repurposing Incubator (ADDRI)

FROM MOLECULE TO PATIENT

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

~10 publications to date



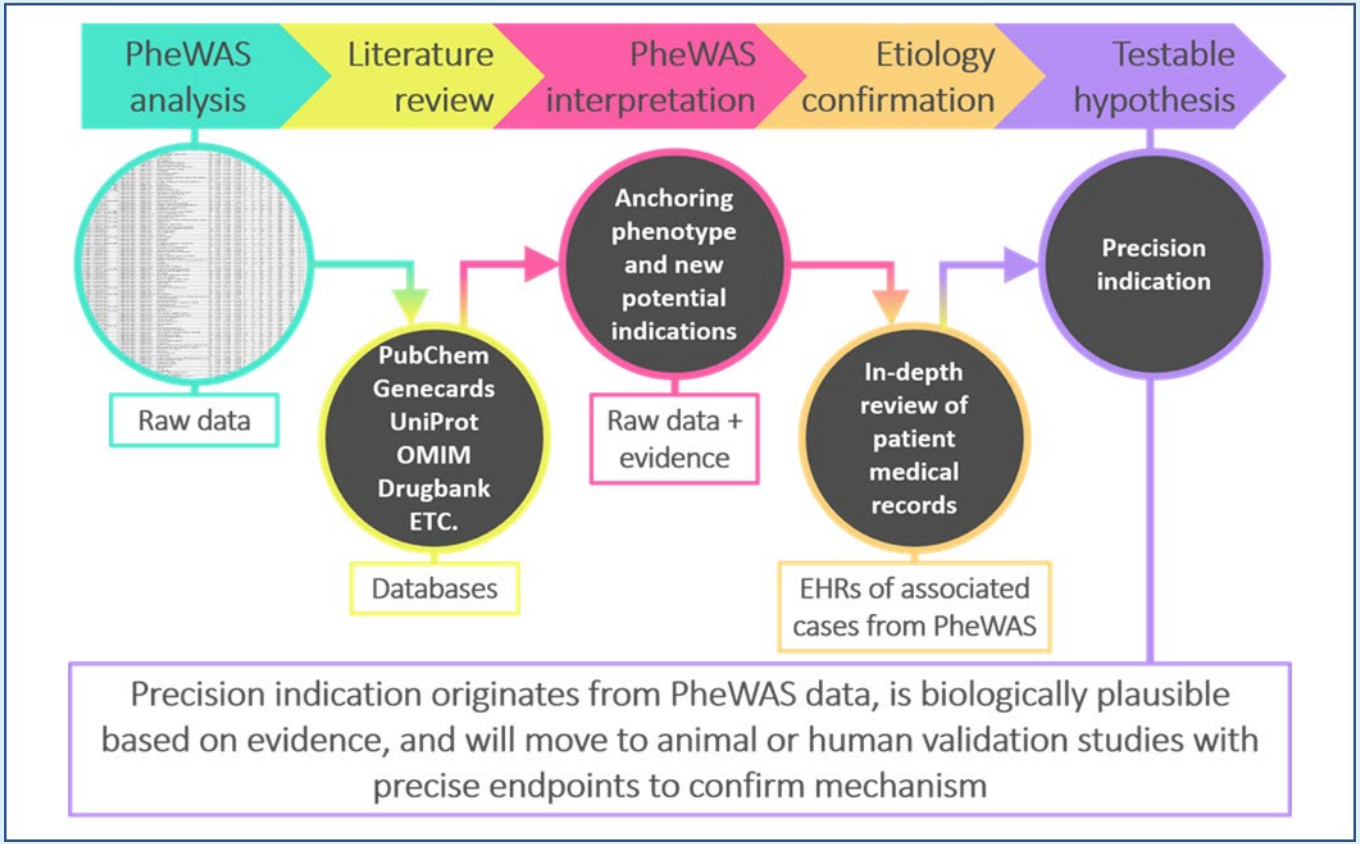
FROM MOLECULE TO PATIENT

Practical steps to *move forward,* ***beyond ideas***

- Secure infrastructure funding
- Create novel methodologies
- Set up structure
  - Operations team
  - Faculty experts
  - Processes
  - Integration of databases
  - FDA regulatory pathways
  - Commercialization and exclusivity
- 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

Initial steps to establish a precision indication

FROM MOLECULE TO PATIENT



Practical steps to *move forward,* ***beyond ideas***

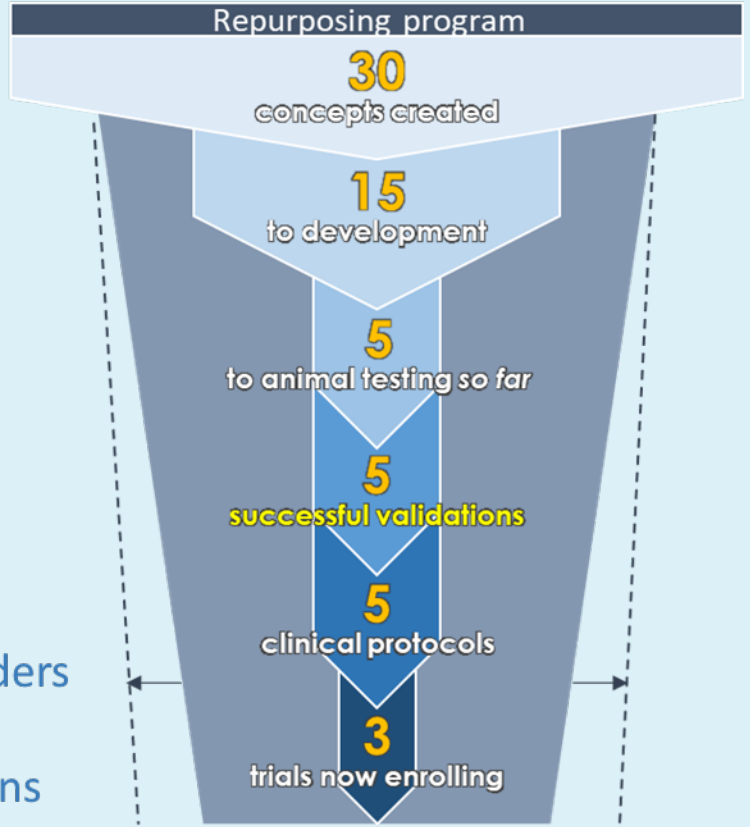
FROM MOLECULE TO PATIENT

- Secure infrastructure funding
- Create novel methodologies
- Set up structure
  - Operations team
  - Faculty experts
  - Processes
  - Integration of databases
  - FDA regulatory pathways
  - Commercialization and exclusivity
- 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

Pipeline is efficient, diverse, and does not “squeeze shut”

FROM MOLECULE TO PATIENT

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

FROM MOLECULE TO PATIENT

- 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

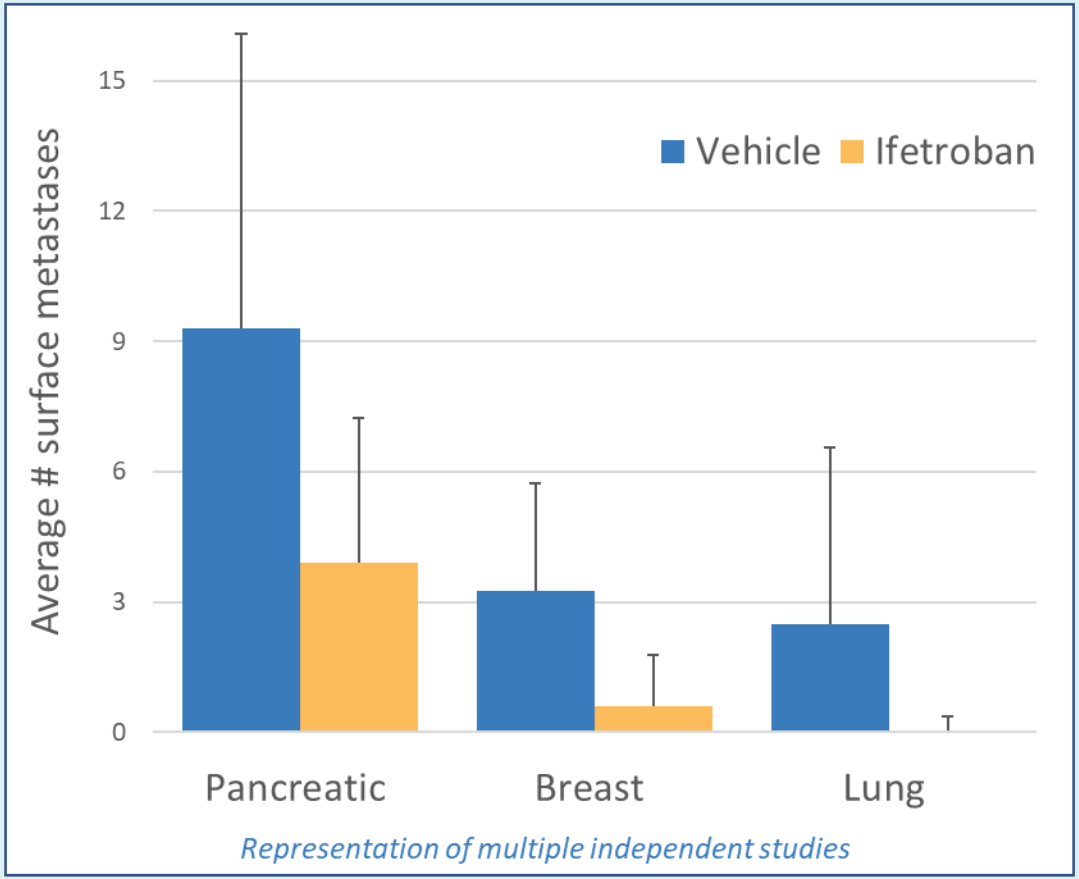
Ifetroban decreases hematogenous metastasis of breast, pancreatic and lung cancer cells

FROM MOLECULE TO PATIENT

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



Representation of multiple independent studies

FROM MOLECULE TO PATIENT

Practical steps to *move forward,* ***beyond ideas***

- Secure infrastructure funding
- Create novel methodologies
- Set up structure
  - Operations team
  - Faculty experts
  - Processes
  - Integration of databases
  - FDA regulatory pathways
  - Commercialization and exclusivity
- 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

Conducting proof of concept clinical trials

Approval to conduct trials is itself validating

FROM MOLECULE TO PATIENT

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. Ifetroban, 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

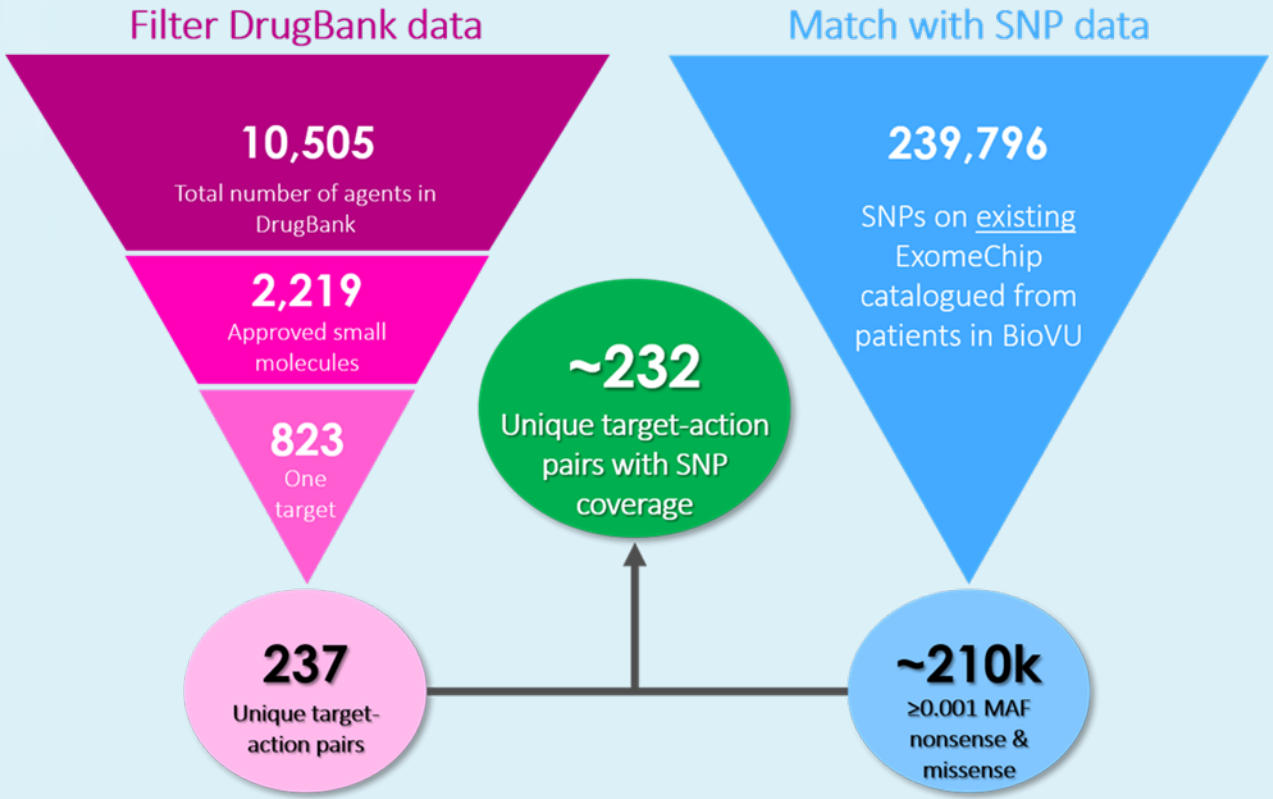
Practical steps to *move forward,* ***beyond ideas***

FROM MOLECULE TO PATIENT

- Secure infrastructure funding
- Create novel methodologies
- Set up structure
  - Operations team
  - Faculty experts
  - Processes
  - Integration of databases
  - FDA regulatory pathways
  - Commercialization and exclusivity
- 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

Lots of runway in the identification of repurposing targets

FROM MOLECULE TO PATIENT



Practical steps to *move forward,* ***beyond ideas***

FROM MOLECULE TO PATIENT


Secure seed/infrastructure funding


Create novel methodologies


Set up structure


Run the data algorithms


Perform prospective validation experiments confirming utility
(not an informatics exercise)

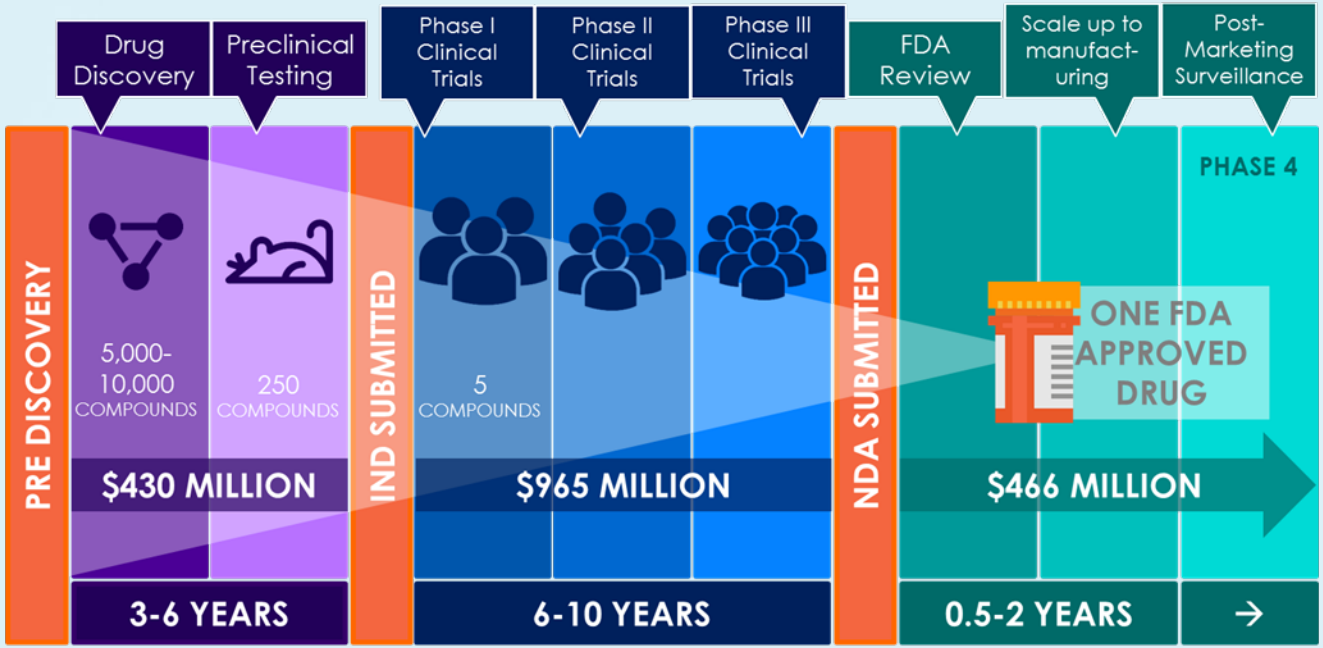

Conduct human proof of concept clinical trials


Consider ways to share, disseminate, commercialize and grow


Evaluate effect on speed of translation and human health

Drug Repurposing Efficiency Will be Measured

FROM MOLECULE TO PATIENT



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.

FROM MOLECULE TO PATIENT

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