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Computational Analysis of Discontinued Neurological Drugs without Defined Primary Target Pharmacology

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Computational Toxicology Top 3 Abstracts of 2023
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Agenda

- Background of Drug Repurposing
- Drug Discovery Approaches – Target and Phenotypic Assay Based
- Dataset of Phenotypically Derived Discontinued Drugs
- Computational Framework for Drug Repurposing
- Results of Predicted Interactions of Discontinued Drugs with Undefined Pharmacology
- Summary and Next Steps

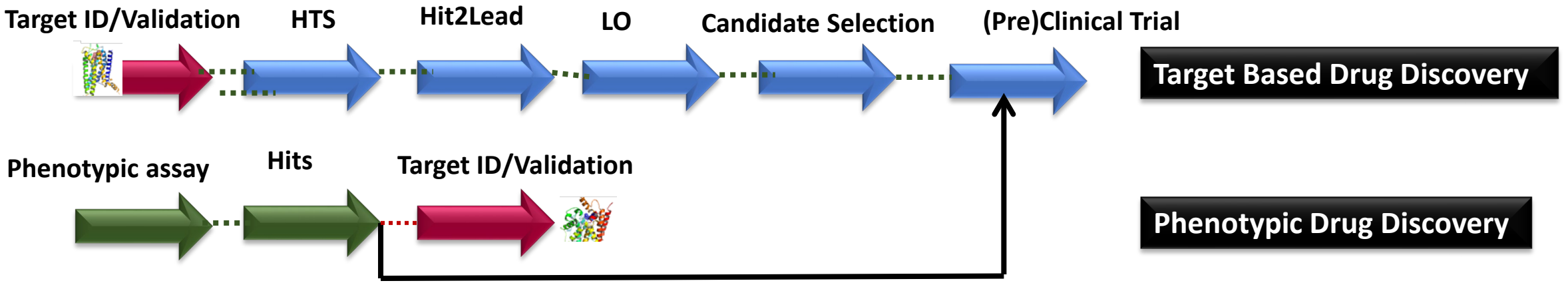
Why Consider Drug Repurposing?

- Nonclinical & Clinical Challenges: The pharmaceutical industry faces high attrition rates in nonclinical/clinical stages due to efficacy and safety concerns (Phase I to Marketing < 10%)

Drug Repurposing:

- To mitigate attrition in drug discovery, the industry increasingly turns to drug repurposing
- Involves identifying unintended target(s) interactions in specific tissues or using intended target(s) in different tissues to discover new applications for FDA-approved or internally/externally discontinued drugs
- Cost-Effective and Faster - Drug repurposing is a quicker and more cost-effective alternative to traditional drug research and development processes
- Example in CNS Drugs – For example, a discontinued/approved CNS drug may be repurposed for a different indication, such as endocrinology or oncology, if it demonstrates efficacy for an unrelated disease

Target Based Vs Phenotypic Assay Based Drug Discovery



Target-Based:

- Begins with identified molecular target(s)
- Offers a clear mechanistic understanding during throughout development process
- Suited for diseases with established pathways
- Faces challenges in optimizing compounds for cell permeability, cellular activities, or crossing the blood-brain barrier (BBB) before preclinical testing

Phenotypic Assay-Based:

- Begins by screening compounds based on observed effects (e.g., reduction of seizures)
- Prioritizes hits that are both cell permeable and disease-relevant (no need for optimization regarding cell permeability or BBB permeation)
- Takes into account complex disease contexts
- Suitable for diseases with unclear or undefined underlying mechanisms
- Effective hits can proceed directly to preclinical studies; identification/validation of target(s) **is optional**, but aids in understanding the mechanism of efficacy

Dataset

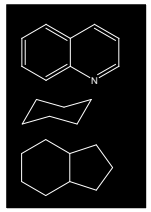
Citeline[1] and Cortellis[2] Databases were used to extract compounds meeting the following criteria:

- Discontinued or no development
- CNS-active small molecule
- Undefined target pharmacology
- This process resulted in a total of 528 drugs meeting the criteria

[1]https://citeline.informa.com/

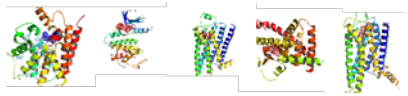
[2]https://www.cortellis.com/intelligence/home.do

Framework of Off-Target Prediction and Drug Repurposing For 528 Drugs



528 drugs

1

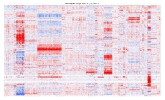


Predict Off-Targets

Target Prediction Methods

- SAS
- SIM
- SAR
- SEA
- MLM
- XPI
- 3Decision*

2



Off-targets Expression in various tissues

3

Open Targets DisGeNET

OFF-X

Off-target – Disease Association analysis

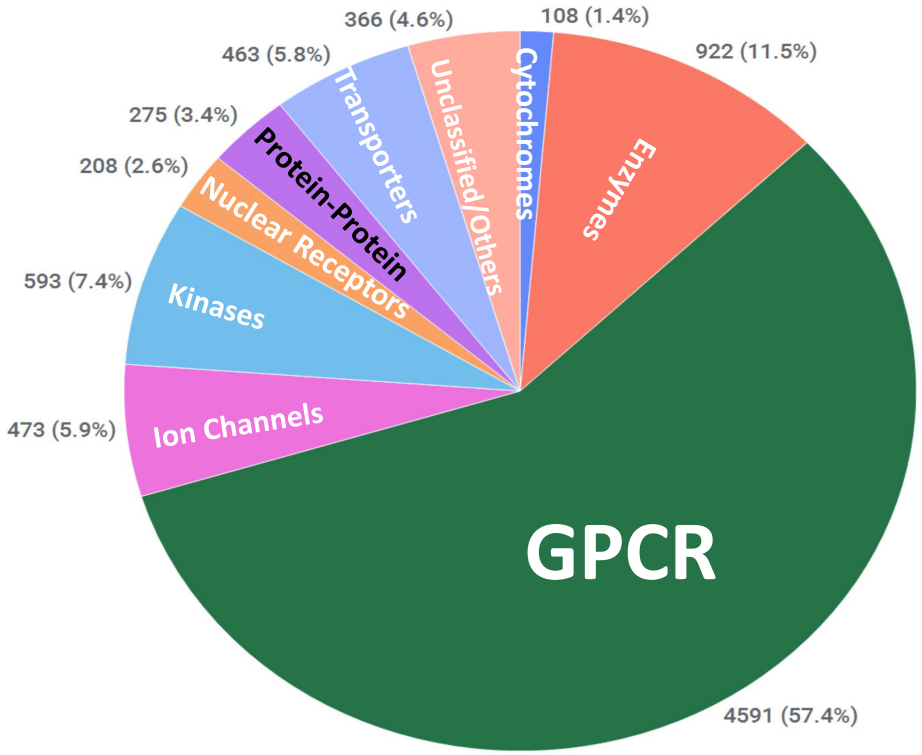
4

Select Key Drugs for Repurposing

- **Data Collection: Collect chemical structure information on Cortellis & Citeline**
- **Prediction of Off-Targets (Step 1): Use machine learning and chemical informatics algorithms to predict potential off-targets for each drug based on its chemical structure information**
- **Normal Baseline Expression (Step 2): Gather normal baseline expression data for the predicted off-targets in various tissues using GTEx (also in preclinical species)**
- **Gene-Disease Association Analysis (Step 3): Use available disease association databases, such as DisGeNET, OpenTargets and Off-X to identify diseases associated with the tissue-specific off-targets**
- **Validation and Prioritization (Step 4): Validate the identified drug repurposing candidates using published in vitro and prioritize the most promising candidates for potential development**

Predicted Interactions for 528 Drugs with Undefined Pharmacology

Predicted Target Classes for 528 Drugs



- Computationally Predicted Off-Target Interactions for 528 Unique Discontinued CNS Drugs
  - A total of 8000 interactions were predicted, involving 1085 distinct protein off-targets
  - Of these, only 635 secondary interactions (e.g., CEREP) were confirmed in vitro
  - On average, each drug was predicted to have 15 interactions
  - A substantial portion (57.4%) of the predicted interactions were associated with GPCRs

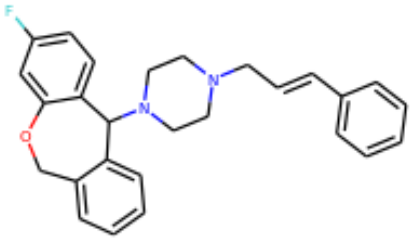
Baseline Human Tissue Expression of 1085 unique protein off-targets

- **1085 Off-targets express in Brain, Heart, Colon, Cervix, Kidney and Skin**

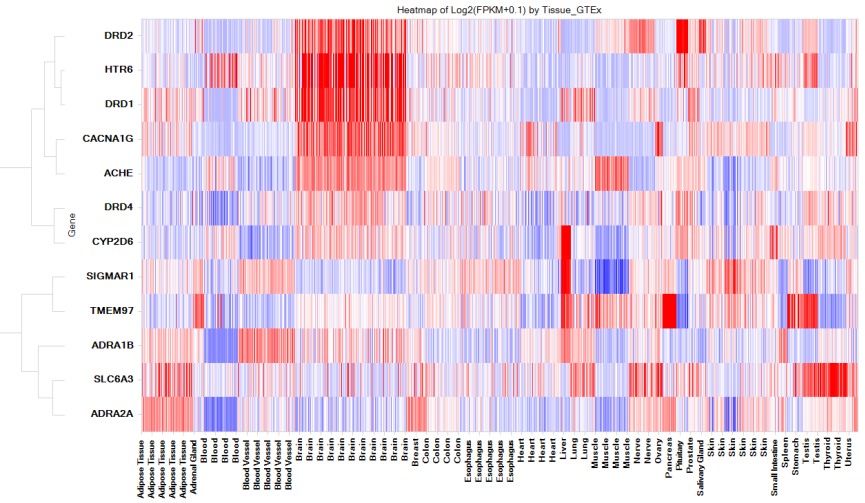
Red to blue is high to low expression

Case Study: Target Deconvolution for Discontinued Neuro Drug for Cerebral Vasospasm Protection

AJ-3941



Tissue Expression of Predicted Targets



Red to blue is high to low expression

- Drug Status: Discontinued
- Disease: Neuro (unspecified)
- Highest Development Stage: Preclinical
- In Rat & Dog Studies: Demonstrated protection against cerebral vasospasm
- Mechanism: Inhibits calcium-dependent and independent glutamate release
- High Scoring Predicted Targets & Toxicity:
- Targets: SIGMAR1, DRD2, DRD4, TMEM97, ADRA1B, SLC6A3, CACNA1G, HTR6, ADRA2A, ACHE, CYP2D6, DRD1, NPYR
- ACHE, DRD1/2, CACNA1G HTR6, DRD2 are implicated in cerebral vasospasm
- All expressed high in CNS tissues
- Toxicities: Thrombosis, Depressed level of consciousness, Phospholipidosis, Mitochondrial toxicity, Pneumotox withdrawal

Summary & Next Steps

- Developed Computational Framework for Repurposing Discontinued Drugs
- Application of Computational Framework to 528 Discontinued Drugs
  - Prediction of 8000 Off-Target Interactions Involving 1085 Unique Targets
- Primary Expression Tissues of the Predicted 1085 Unique Targets
  - Heart, Kidney, Skin, Brain, Colon, Liver, Lung, Testis, and Blood
- Potential for Tissue-Specific Drug Repurposing
  - Compounds initially developed for specific tissues to target the same proteins expressed in different tissues, based on cross-species tissue expression
  - Different targets expressed in intended tissues where in vivo phenotypes were observed to contextualize findings with targets

Next Steps

- Strengthening the AI/ML Prediction Framework

  Enhancement of the reliability of our AI/ML prediction framework through validation of selected predicted interactions using follow-up in vitro and in vivo methods

Thank You!