Systematic Discovery of Novel Combination Drugs for Huntington Disease

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Strategies to discover multi-target therapeutics

Traditional Approach

Intuitive/obvious combinations

Very few combinations can be tested

Unlikely to discover novel multi-target mechanisms

Systematic Approach

A priori agnostic of mechanism

Millions of combinations can be tested

Can uncover truly novel combination biology

Requires an in vitro discovery platform
Wet Science meets High Tech Automation

CRXX Library
Global Rx Pharmacopeia and probes

cHTS
Screening millions of pair-wise combinations

Chalice
Automated Selection and Prioritization

Validation in secondary assays and animal models
Advance leads to clinical trials

explore
investigate
discover
HD systems biology: diverse therapeutic targets

Complex disease biology ↔ combination therapeutics
CRXX-CHDI Collaboration: Strategy

Global Pharmacopia ~2,500 Compounds
(Approved drugs, development-stage drug targets probes)

Primary Assay
*In Vitro* Rat PC12, Mouse Striatal Neuronal Cells

Secondary Assay
*In Vitro* Energy Metabolism, Mitochondria Function, Cellular Stress

Drug Profiling Pharmacokinetics
*In Vivo* BBB permeability, Safety & Tolerability

HD Efficacy
Rodent Model
Maximize opportunity to identify meaningful new combinations through suite of disease-relevant cHTS assays
- Mutant htt-specific phenotype
- Quantitative endpoints amenable to cHTS

**Mutant htt-induced Cytotoxicity**

**Striatal Knock-in cell line**

*Rat pheochromocytoma PC12 cell line (HttN90Q103 cytotoxicity)*

**HCS-htt Protein Disposition**

*Striatal Knock-in cell line (high content)*

**HD-relevant secondary assays for hit prioritization**
- Energy metabolism, mitochondria function, cell survival under stress
### Interesting MOA
- Drug A may act on protein aggregation
- Drug B may act as a neuroprotectant by enhancing trophic factor release

### Desirable *in vivo* profile
- Excellent brain exposure: both compounds reach concentrations required for *in vitro* activity
- Safe and well-tolerated in HD mice based on a 2-wk tolerability study

### Next steps
- Combination tolerability study in HD mice
- Efficacy testing in HD animal models
- Additional MOA study
Top combination from htt-protein disposition assay

Primary assay: anti-htt Ab (1F8) perinuclear staining

Secondary assay: mitochondria membrane potential

### Interesting MOA
- Drug C: a CNS drug with neurotrophic effect by promoting neurogenesis
- Drug D: may act as a neuroprotectant and autophagy enhancer

### Desirable *in vivo* profile
- Excellent brain exposure
- Both drugs have been used chronically in human

### Next steps
- Tolerability study in HD mice
- Efficacy testing in HD animal models
- Additional MOA study
Summary

- Complex disease suited to combination therapeutics
- cHTS discovery in multiple HD-relevant assays
- Top combination identified from each cellular campaign
- HD relevant secondary assays to evaluate and prioritize combination hits
- Preclinical *in vivo* PK/ADMET study on-going followed immediately by efficacy testing in HD animal models
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