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Systematic Discovery of Novel Combination Drugs for Huntington Disease

June 7, 2008, Pittsburgh

Strategies to discover multi-target therapeutics

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Traditional Approach

Intuitive/obvious combinations

***Very few* combinations can be tested**

Unlikely to discover novel multi-target mechanisms

vs.

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

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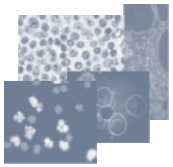


Phenotypic Cell-Based Assays

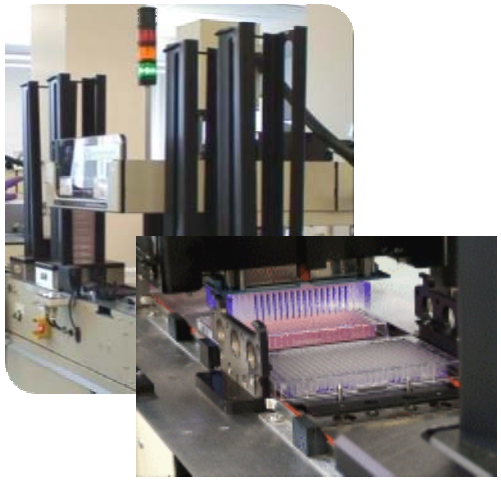
CRXX Library
Global Rx Pharmacopeia and probes

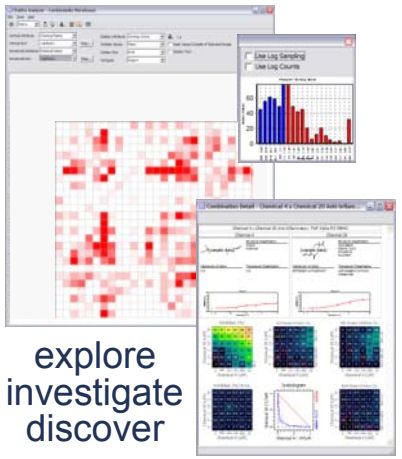
cHTS
Screening millions of pair-wise combinations

Chalice
Automated Selection and Prioritization

Validation in secondary assays and animal models

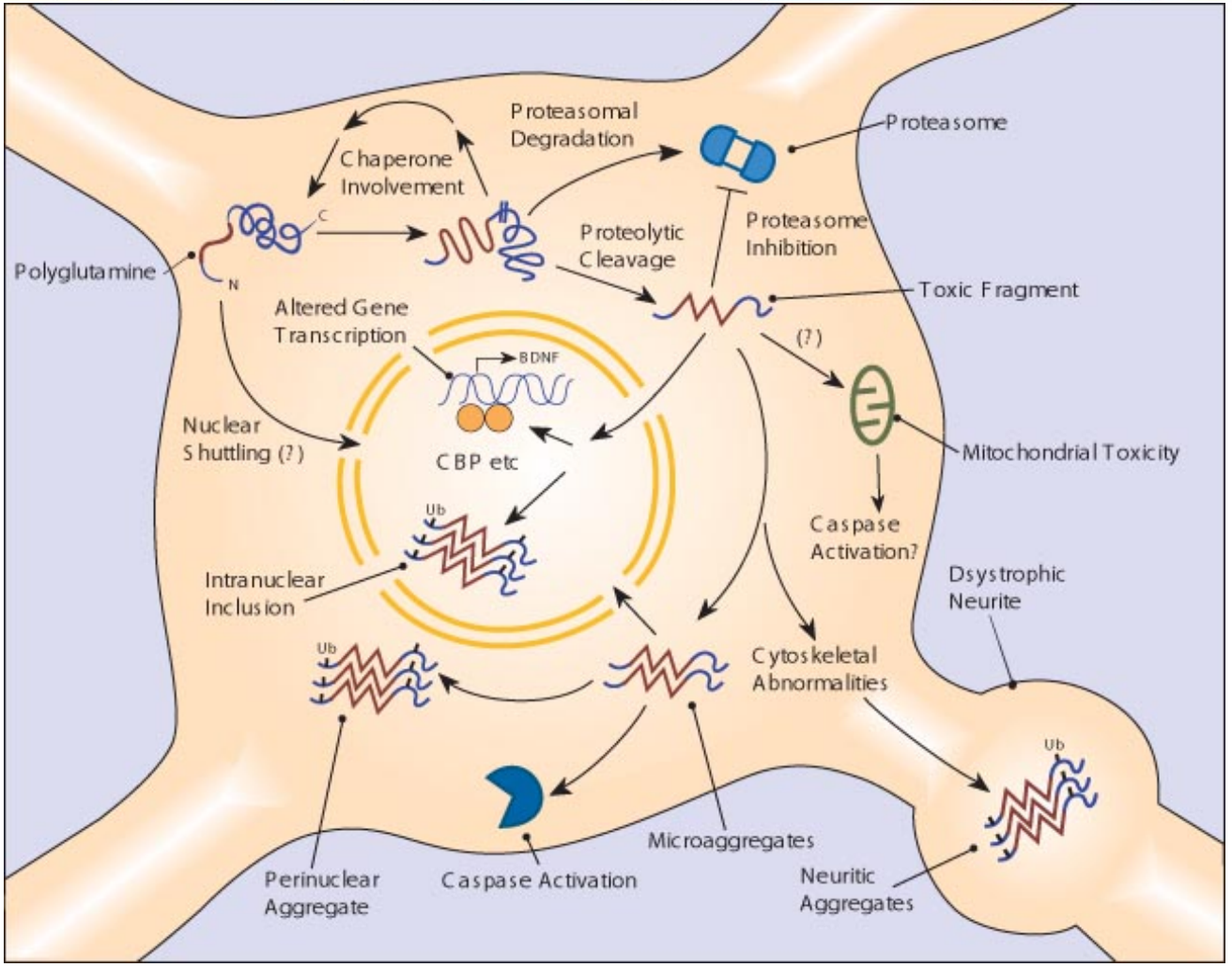
Advance leads to clinical trials





explore
investigate
discover

HD systems biology: diverse therapeutic targets



Complex disease biology ⟷ combination therapeutics

"In Vivo BBB permeability, Safety & Tox"

CRXX-CHDI Collaboration: Strategy

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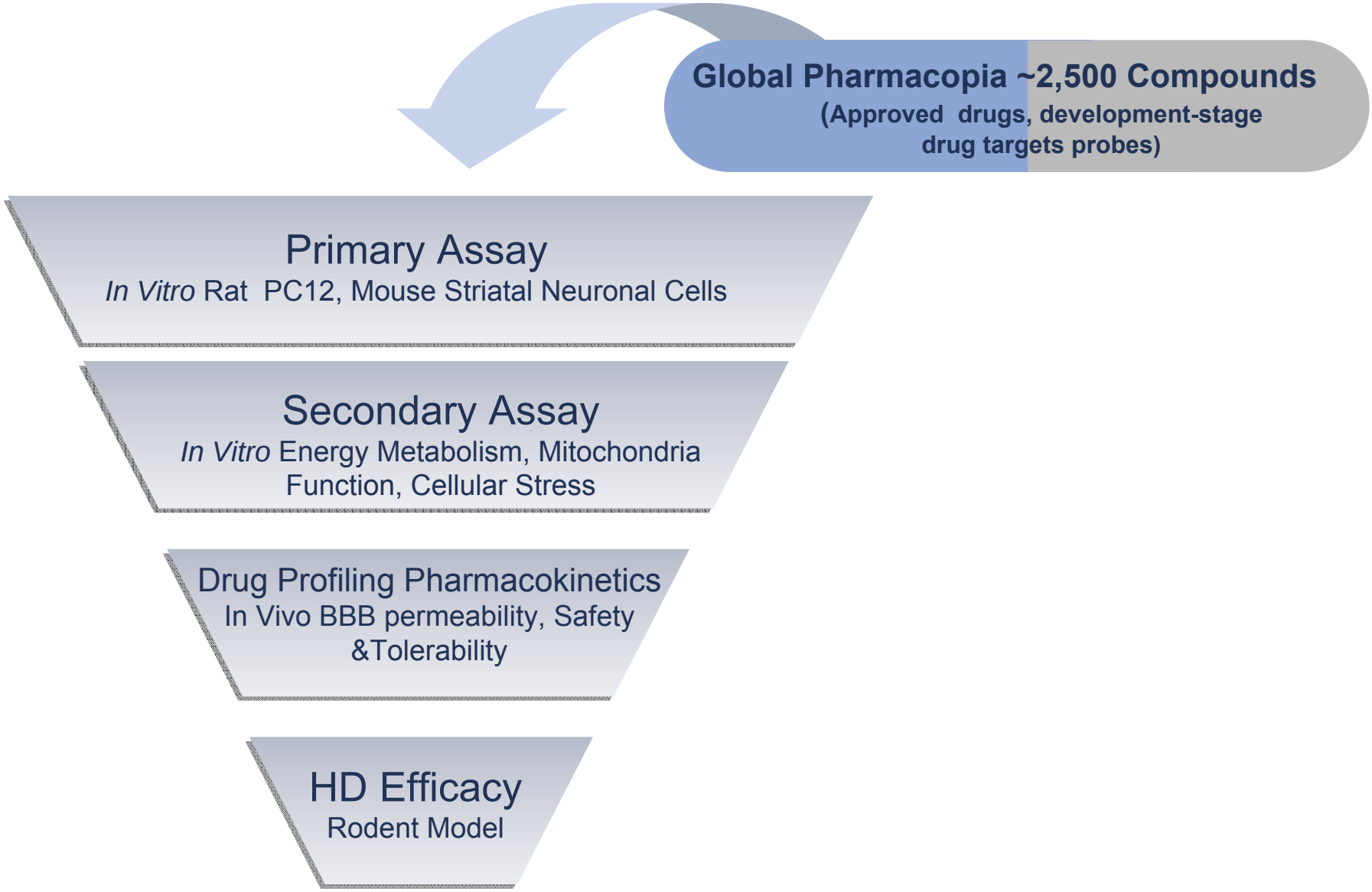
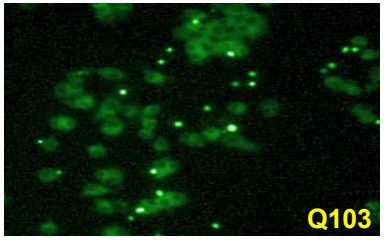


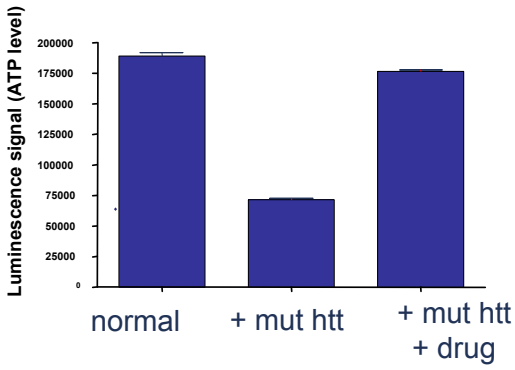
HD drug discovery: diverse screening campaigns

- **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

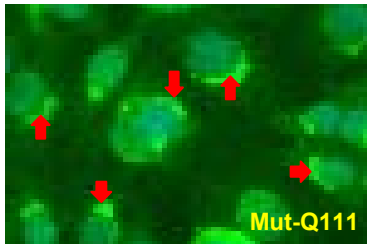
Rat pheochromocytoma PC12 cell line (HttN90Q103 cytotoxicity)

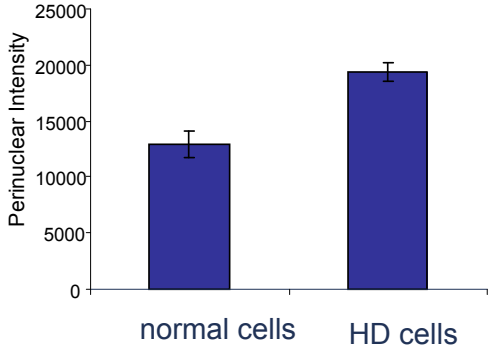




HCS-htt Protein Disposition

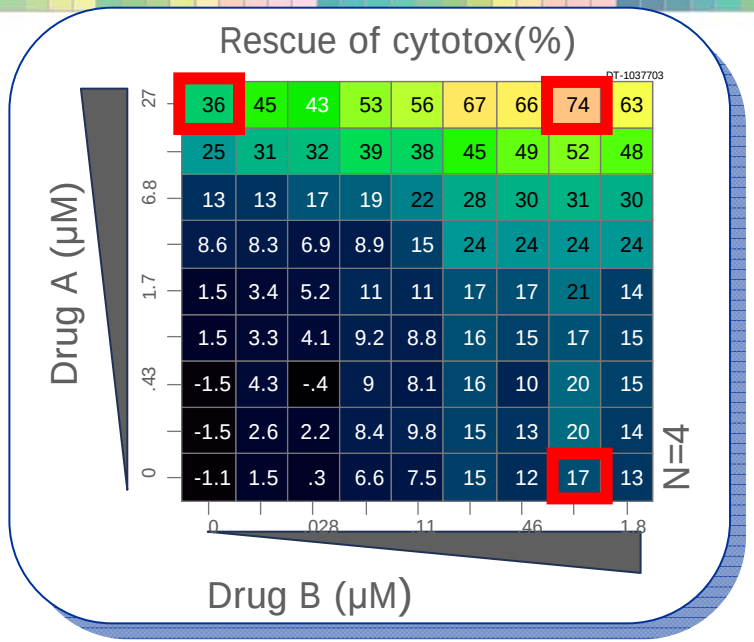
Striatal Knock-in cell line (high content)





- **HD-relevant secondary assays for hit prioritization**
  - Energy metabolism, mitochodria function, cell survival under stress

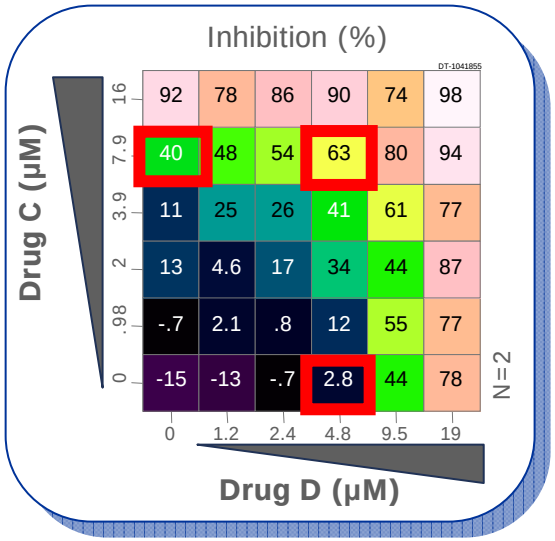
Top combo from PC12 htt-toxicity assay



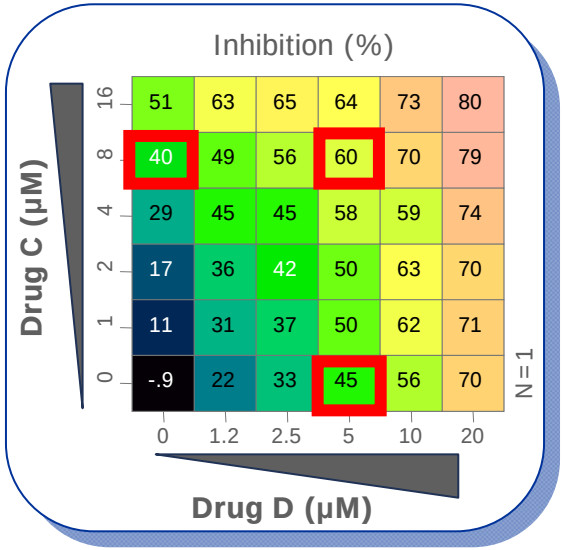
- **Interesting MOA**
  - Drug A may act on protein aggregation
  - Drug B may act as a neuroprotectant by enhancing trophic factor release
- **Desirable *in vivo* profile**
  - Excellent brain exposure: both compounds reach concentrations required for *in vitro* activity
  - Safe and well-tolerated 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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