

Foundation Funded Drug Discovery in a Virtual Model : Lessons Learned

*Celia Dominguez, Ph.D.
Vice President, Chemistry*

***IOM: Forum on Neuroscience and Nervous System Disorders
Venture Philanthropy Strategies Used by Patient Organizations to Support
Translational Research - A Workshop***



Outline

- u What is CHDI?
- u Key Points for Translational Research
- u Two Case Studies: Compare and Contrast
 - Company X vs Company Y
 - What worked and what did not?
- u Summary of Key Points

CHDI Foundation: A New Model

- u In 2008, CHDI, Inc. and High Q Foundation (NYC) were combined into one organization: the CHDI Foundation, Inc.
- u Non-for profit, 501 (c) (3) status
 - Motivated by time not money
- u Private
 - All monies are derived from private (anonymous) donors
 - 2007 spend was >\$60MM
- u Virtual
 - No wet lab space
- u Exclusively focused on 1 aim: Therapeutics for Huntington's Disease
- u Outsourcing
 - >400 FTEs worldwide, chemistry, biology, pharmacology, PK, and formulation
- u Internal organization – 41 FTEs
 - Discovery Biology – Princeton
 - Drug Discovery – Los Angeles
 - Clinical Development – Princeton
 - Administrative/Business/Legal – New York
- u Internal expertise – 25 PhDs/MDs
 - Medicinal and computational chemistry, cheminformatics, IT
 - Biology: pharmacology, structural, neurobiology, developmental, PK, toxicology, molecular and cellular biology, bioinformatics

“Rapidly discover and develop drugs that delay or slow Huntington’s disease”



Mission Enabling Strategies

U CHDI-driven fully integrated programs

- Target is believed of importance in the pathophysiology of HD but is not being prosecuted within the pharma or biotech sectors
- We have primary responsibility for oversight and progression from HTS through registration
- We generate the validating ligands
- We generate and own the intellectual property

U Leverage integrated biotech's

- Facilitate entry into HD by funding an HD program
- Collaborative effort across both organizations
- We share the intellectual property

U Enable HD Translational Efforts

- Centralized biological and chemical repositories
- Oversight of quality & validation
- No IP constraints, minimal costs
- HD efficacy models

U Outreach

- Access advanced validating ligands that have not been disclosed - the good stuff!
- Access undisclosed earlier stage compounds
- We have in vivo capacity in our efficacy models to test your compounds

Key Points for Translational Research

U It's the patients...stupid

- Nothing is more precious to a drug hunter than an observation in humans
- Most neurodegenerative diseases (even monogenic ones like HD) have not been described to a sufficient level of detail to enable drug discovery

U We need to know which targets are well validated and how to modulate them

- Even in orphan diseases having a molecular target & and well understood mechanism of action is key to success.

U Robust preclinical filtering gives compounds a real “at bat”

- Formulation, profiling, PK
- Guarantee exposure to give target coverage

U Pharmacodynamics and pseudoefficacy can give you confidence that it is worth waiting for the longer (clinically meaningful) outcome

- Ensure target engagement
- Definitive outcome: Move forward with a drug candidate or eliminate a target/mechanism

U Consider novel approaches

- Alternate modalities
- Central delivery
- Combine the molecular specificity of drugs with the spatial-temporal precision of devices

Key Points for Translational Research

U Intellectual Property (IP)

- Reagents, tools and animals models **must be free of IP to enable researchers** in academic, foundation and industry to do research.
- IP for composition of matter and freedom to operate must be obtained for the therapeutic (i.e. the compound) to enable downstream development by the Biotech/Pharma industry

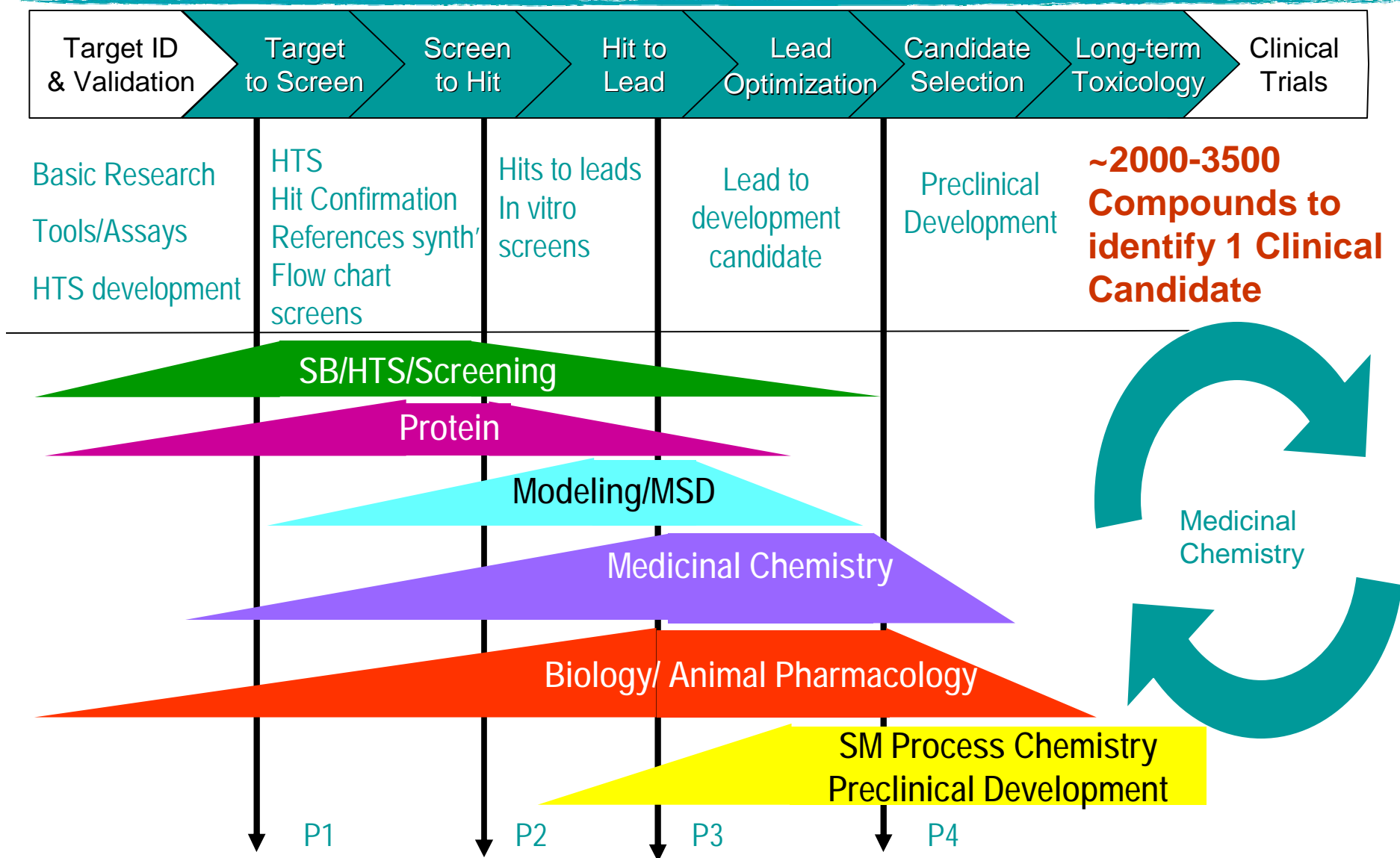
U Leverage people/institution's strengths

- Academic vs CRO vs Biotech/Pharma

U Understand people/institution's motivations

- Academic vs Biotech/Pharma
- Foundation vs Biotech/Pharma

It Takes a Village with Different Skill Sets



Biotech Case Study # 1

CHDI interested in a particular enzymatic platform with lead like molecules that were amendable to be BBB permeability

U Company X Strength:

- Purified Enzyme Platform available
- Selectivity profiling
- Cellular assays: engagement of molecular target in a cellular context
- Pharmacodynamic markers
 - On mechanism assays
- Pharmacokinetic
- Experienced medicinal chemists (proven track record)
- Experienced molecular pharmacologist

U Company X Weakness:

- Smaller Biotech
 - Limited resource & CNS expertise
 - Limited financial resources
 - Company stability

U Company Motivations/Drivers:

- Science based
- Interested in Neuro-degeneration
- Desire to help the foundation
- Pressure to meet VC demands

Biotech Case Study # 2

CHDI interested hits or lead compounds with activity in primary neuronal assays

U Company Y Strengths:

- Expertise in primary neuronal assay

U Company Y Weakness

- Target unknown
- Mechanism unknown
- No medicinal chemistry expertise
- No Pharmacodynamic markers
- Small Biotech
 - Limited resources & lack medicinal chemistry expertise
 - Limited financial resources
 - Company Stability

U Company Motivation/Driver:

- Science based
- Pressure to meet VC demands
 - Clinical candidate

What worked and What did not?

U Collaboration X:

- Excellent communications
 - Good understanding of the challenges in R & D
- Good biochemical Platform
- Good cellular Platform
 - Confirm activity cell
 - Mechanism of action
- PK/PD readout
 - Confirm in vivo engage of target and or pathway

U Outcome:

- Potent compounds with SAR
- BBB permeable
- Confirmed engagement of target via PD marker ex vivo
- Proof of concept molecule in HD Tg studies ongoing
- Generated novel IP

U Collaboration Y:

- Communication not optimal
- No molecular target unknown
- Cellular assay was not robust
 - Highly variable
 - Phenotypic assay
- Flat SAR
 - Chemistry no path forward

U Outcome:

- No molecule pursued
 - Only one hit wonder
- No IP
- Termination of collaboration
- Utilization of primary neuronal assay as general tertiary screen

Key Points for Translational Research

U Intellectual Property (IP)

- Reagents, tools and animals models **must be free of IP to enable researchers** in academic, foundation and industry to do research.
- **IP for composition of matter and freedom to operate** must be obtained for the therapeutic (i.e. the compound) enable downstream development by the Biotech/Pharma industry

U Even in orphan diseases having a molecular target & and well understood mechanism of action is key to success.

- Biochemical
- Cellular assays-expression molecular target

U PK/PD-coverage of target

- Compound engages target in vivo

U Leverage people/institution's strengths

- Academic vs CRO vs Biotech/Pharma

U Understand people/institution's motivations

- Academic vs Biotech/Pharma
- Foundation vs Biotech/Pharma

Thank You!

CHDI LA, NY & Princeton

Collaborators and HD Researchers

Drug Discovery: A Medicinal Chemist's Perspective

- u Chemically tractable- does not have to be easy
- u Molecular target key player in pathway
- u Biochemical Assay- Molecular Target (Human + other species)
 - Robust and sensitive assay to allow SAR
 - Species difference or not
- u Cellular Assay: Molecular target expressed in cells
 - Relevant to animal model
 - Mechanism of action: engagement of target in cellular context
 - Possible readout adapted as a PD marker
- u Cellular Assay as primary screening
 - Needs to be robust and sensitive to drive SAR (max 10 fold difference)
 - Pathway screening can lead to a hit, but need to find molecular target
- u Phenotypic screens difficult to drive SAR
 - Good secondary or tertiary screens
 - Identify hit we need to fine the molecular target
- u Pharmacodynamic readouts: Linked to target engagement and ideally disease progression
 - Enables understanding of PK/PD relationships
 - Understanding of dose and target engagement (IC_{25} , IC_{50} or IC_{90})
- u Disease Animal Model
 - Target expressed
 - Target important in disease
 - PD readout to be the same as in the clinic or vice versa
- u Safety margins

Biological and Chemical Tractability

