Structural Genomics Consortium and CHDI: Open access partnership for Huntington's Disease research

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Ryan Schoenfeld, Director, Medicinal Chemistry, CHDI
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@thesgconline
We will cure Huntington’s Disease!

But by when? 
By 2020? By 2025? By 2100?

How do we accelerate the search?
What’s the biggest problem in drug discovery?

We do not understand human biology
In part because we search under the light
And we spend money redundantly
So... is more funding necessarily the answer?

[Graph showing publications for Alzheimer's genes PSEN1, PSEN2, APOE, APP, TAU from 2003 to 2013.]
It does not matter where bus drives
Another problem:

Industry relies on academia to identify new targets
Academics shine light, industry searches for the keys
A lesson from history (Willson, GSK)

Academic research is driven by access to research tools

How to make global science focus more resources on the “right hand side” of the curve?

Chemical probe available

No chemical probes available

[CITATIONS]

NUCLEAR HORMONE RECEPTOR
Open access partnership concept

Public/Private Partnership

Research tools

SGC
Screening
Structure
Cell activity

Pharma
Chemistry

Public Domain

Academics use them

No IP
No restrictions
Publication

Industry

Industry takes ideas and develops drugs

(re)Screening
Chemistry
Lead optimization
Pharmacology
DMPK
Toxicology
Chemical development
Clinical development

Creative Commons

Proprietary
Has JQ1 induced system change?

Research on bromodomain family

Release of SGC/GSK probes
Pioneer work on epigenetics regulator bromodomains unveiled a completely new therapeutic target family

Open Access stimulates Innovation, rapidly!

(http://www.nature.com/nrd/journal/v11/n5/fig_tab/nrd3735_T1.html)
# Progressing towards patients! Bromodomain inhibitors in clinical trials

<table>
<thead>
<tr>
<th>Company</th>
<th>Inhibitor</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>GSK525762</td>
<td>NUT midline carcinoma, Mult. Myeloma, small cell lung cancer, colorectal cancer, neuroblastoma and MYCN-amplified solid tumours</td>
</tr>
<tr>
<td>Oncoethix</td>
<td>OTX015</td>
<td>Haematological malignancies: Acute Myeloid Leukaemia (AML), Acute Lymphoblastic Leukaemia (ALL), DLBCL and Mult. Myeloma</td>
</tr>
<tr>
<td>Resverlogix</td>
<td>RVX-208/RVX000222</td>
<td>Dyslipidemia; Atherosclerosis; Acute Coronary Syndrome; Cardiovascular Disease</td>
</tr>
<tr>
<td>Constellation</td>
<td>CPI-0610</td>
<td>Progressive Lymphoma</td>
</tr>
<tr>
<td>Tensha</td>
<td>TEN-010</td>
<td>NUT midline carcinoma</td>
</tr>
</tbody>
</table>
High-quality chemical probe set

SGC

ULTRA-DD

Academia

Pharma

CHDI

Montreal Neurological Institute

Rouleau

Hospital for Sick Children

Dirks

Karolinska Institute

Klareskog

Kennedy Institute (U Oxford)

Feldmann

ALS CSF and iPS cells

Glioblastoma stem cells

SLE, myositis, RA

Fibrosis, RA, Ank. Spond.
CHDI Foundation: How we work...
What is CHDI?

A privately funded, nonprofit, biomedical research organization

Our mission: to rapidly and collaboratively develop therapies that slow the progression (delay onset) of Huntington’s disease

We operate through a novel virtual model that encourages scientific partnership - **collaborative enabler**

**Aim** – to develop and “de-risk” therapeutic programs so that pharma will take the drugs to market
What is CHDI... exactly?

A not-for-profit drug discovery organization

- Motivated by **TIME**, not **MONEY**
- No **COMPETITORS**, only **COLLABORATORS**
- Fully integrated research: discovery - translational - clinical

Foundation funded

- All funds from private donors
- Driven by drug candidates, **not** by hype, press releases, or trial initiations

Exclusively dedicated to Huntington’s disease

- FOCUS – HD therapeutics **only**
- Unambiguous, continuity, passion

Use a “virtual” or outsourced model

- 73 internal staff (38 PhDs/MDs)
- All experimentation done externally via collaborative partners and contract research organizations (CROs)
- Manage >600 external staff across our collaborative partners and CROs
Some guiding principles at CHDI…

• Share to the maximum possible – everything!
• Distinguish *use* (e.g., pre-competitive research) from *status* (academic vs. industrial)
• Encourage collaborators to share results - disease foundations are in a unique position to broker, both on a bilateral basis and across a research community
• Think *program* rather than individual grant or project – how does it all fit together and synergize?
• Time is critical - plan ahead
• Drug discovery is complex, interdependent, and highly *iterative*
• Choose the best partner for specialized functions, but place a premium on integration
• Collect and store the *primary* data, not just the conclusions - allows for better integration across programs and post-hoc reanalysis
Four ways that CHDI works

**Collaborative Enablement**
- Provide research funding - *contracts*
- Centralized biosample/data repositories
- Reagents – tools – HD know-how

**Pharma Outreach**
- Lower the barrier for entry into HD
- Repurpose existing drugs

**Biotech Partnering**
- Leverage existing technology/innovation
- True collaborative partnership

**CHDI Internal Projects**
- Orchestrated across a network of fee-for-service CROs
- We design and oversee the research
CHDI’s current translational portfolio

<table>
<thead>
<tr>
<th>Therapeutic Programs</th>
<th>Partner</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE 9 inhibition</td>
<td>Pfizer</td>
<td>Clinical</td>
</tr>
<tr>
<td>PDE 10 inhibition</td>
<td>Pfizer</td>
<td>Clinical</td>
</tr>
<tr>
<td>PDE 4D inhibition</td>
<td>Biotech</td>
<td>Clinical</td>
</tr>
<tr>
<td>HTT RNAi (AAV delivery)</td>
<td>Genzyme / Sanofi</td>
<td>Late pre-clinical</td>
</tr>
<tr>
<td>HTT antisense oligonucleotides</td>
<td>Isis / Roche</td>
<td>Late pre-clinical</td>
</tr>
<tr>
<td>HTT Zn-finger transcription</td>
<td>Sangamo / Shire</td>
<td>Late pre-clinical</td>
</tr>
<tr>
<td>KMO inhibitor</td>
<td>Internal CHDI</td>
<td>In vivo POC</td>
</tr>
<tr>
<td>HDAC Class 2a inhibitor</td>
<td>Internal CHDI</td>
<td>In vivo POC</td>
</tr>
<tr>
<td>HTT PET &amp; direct SM binders</td>
<td>Internal CHDI</td>
<td>Lead optimization</td>
</tr>
<tr>
<td>BDNF/TrkB agonism</td>
<td>Internal CHDI</td>
<td>Lead optimization</td>
</tr>
<tr>
<td>HTT lowering – small molecule</td>
<td>Internal CHDI</td>
<td>Lead discovery</td>
</tr>
<tr>
<td>New Targets (e.g., ATM)</td>
<td>Internal CHDI</td>
<td>Lead discovery</td>
</tr>
</tbody>
</table>

Individual targets | In vitro signal | Pharmacodynamic signal | In vivo efficacy | Clinical efficacy |

In vitro signal Pharamcodynamic signal In vivo efficacy Clinical efficacy

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#P4C2014
Chemical Probes

- High value in screening well-annotated compound collections in phenotypic assays; hits give insight into mechanisms of action
- First example: huntingtin (HTT) quantification in patient-derived cell lines, screening for agents that lower levels of disease-causative protein

Adapted from Weiss et al., J Clin Invest. 2012;122(10):3731-3736. doi:10.1172/JCI64565.
CHDI-Structural Genomics Consortium collaboration

- **Structural Biology**
  - Elucidation of protein structure provides insight into function, enables design of chemical probes useful for target validation
  - HD-relevant examples for future studies: ATM kinase, HDAC4, HTT

from Khalil et al., Biodiscovery 2012; 5: 1.; DOI: 10.7750/BioDiscovery.2012.5.1