Industrializing Rare and Neglected Disease Therapy
Discovery and Development

Sean Ekins, Ph.D., D.Sc.
CEO

Collaborations Pharmaceuticals, Inc.
Rare Diseases in Art

Christina’s world - Andrew Wyeth

Charcot-Marie-Tooth

MOMA

Pitt-Hopkins
William Kent - Peter the Wild Boy

Kensington Palace
Introduction

In silico repositioning of approved drugs for rare and neglected diseases

Sean Ekins\textsuperscript{1,2,3,4}, Antony J. Williams\textsuperscript{5}, Matthew D. Krasowski\textsuperscript{6} and Joel S. Freundlich\textsuperscript{7}

1. Collaborations in Chemistry, 601 Rennymede Avenue, Jenkintown, PA 19046, USA
2. Collaborative Drug Discovery, 1633 Bayshore Highway, Suite 342, Burlingame, CA 94010, USA
3. Department of Pharmaceutical Sciences, University of Maryland, College Park, MD 20742, USA
4. Collaborations Pharmaceuticals, Inc.

CEO

Phoenix Nest INC
Finding treatments for families.

CEO

Collaborations Pharmaceuticals, Inc.

CSO

HEREDITARY NEUROPATHY FOUNDATION

SAB

PITTS HOPKINS RESEARCH FOUNDATION
Sanfilippo Syndrome (MPS IIIC) - MPS IIIC caused by genetic deficiency of heparan sulfate acetyl CoA: α-glucosaminide N-acetyltransferase, (HGSNAT).

- Heparan Sulfate accumulation
- No treatment for this fatal disorder

- Founded JJB in 2010

http://jonahsjustbegun.org/
- **Multiple Sulfatase Deficiency** - Mutations in the SUMF1 gene encode formylglycine-generating enzyme, post translational modification of every sulfatase
- Missing 6 lysosomal enzymes
- Gene Therapy at The Telethon Institute of Genetics and Medicine has stopped MSD in lab tests
- Foundation started 2015 - raised >Euro 600K

Multiple Deficient Enzymes (6 in the Lysosome)

- Arylsulfatase A
- Metachromatic leukodystrophy (MLD)
- Arylsulfatase B
- Manoteaux-Lanoy syndrome (MPS VI)
- Galactosamine 6 sulfatase
- Marquio A syndrome (MPS IVA)
- Glucosamine 6 sulfatase
- Sanfilippo D syndrome (MPS IID)
- Heparan N sulfatase
- Sanfilippo A syndrome (MPS IIIA)
- Iduronate 2 sulfatase
- Hunter syndrome (MPS II)

http://www.savingdylan.com/
Pitt Hopkins Syndrome (PTHS) is a rare genetic disorder affecting a specific gene in chromosome 18, called TCF4.

Developmental delay, breathing problems, recurrent seizures/epilepsy, gastrointestinal issues, lack of speech.

Foundation started in 2013.

2014-2015: grants = $430,000.

Funds basic and applied science.

Helped identify drug targets.

https://pitthopkins.org/research/
Rare Disease Parent Odyssey

Most rely on Google
How to get to the clinic?

Gene therapy for Giant Axonal Neuropathy (GAN) developed over 7 years for ~$6M

Gene therapy for a form of Batten Disease (CLN6) developed in less than a year for ~$3M

Could the cost and time for development decrease further?
Bridging academia – industry gap

- Academic may get only so far then be unable to get NIH funding to continue
Gaps and Solutions

- Find Contract Research Organizations that can validate and expand the academic work
  - Jackson Labs - mouse models and studies
  - Icagen - ion channels
  - Perlara - Worm and fly models

- Identify FDA approved drugs to test in vitro vs target or animal model
- File orphan drug designation
- Find clinician that can do investigator initiated clinical studies
Phoenix Nest Inc.

Founded 2012
Obtained 3 NIH STTRs (~$2M raised non dilutive)
1 pending STTR ($225K)
1 pending RO1 ($2M)
Licenses technologies
Collaborates globally

Jill Wood, CFO
MPSIIIC parent
Founded JJB
Rare disease advocate
Founded ConnectMPS
Phoenix Nest Inc. Strategy

**Benefits**
- Apply for STTR/SBIR grants
- License treatments
- More control
- Create and own IP
- Ensure a treatment comes to market

**Hurdles**
- Grant process slow/complex
- Hard to fund non-US science
- Company registration
- Need grant writer/PI with PhD
- Need lawyers for contracts
- Limited funds

Ensure academic files provisional patent application
STTR max 60% of total funds can go to academic
SBIR max 40% of total funds can go to academic
LABioMed team Dr. Patricia Dickson (MD, PhD) has previously developed Laronidase enzyme replacement therapy (BioMarin / Genzyme)

Recognized world expert on MPS III

Currently supported by 2 STTRs (MPS IIID Enzyme replacement therapy and MPS IIIB stem cell / gene therapy)

PN funds 3 research associates
# Phoenix Nest Pipeline

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Mechanism</th>
<th>Disease</th>
<th>Stage</th>
<th>Funding</th>
<th>IP</th>
<th>Funds needed to get to next stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PN-1</td>
<td>ERT</td>
<td>MPS IIID</td>
<td>Mouse model</td>
<td>~$1.75M 2 NIH grants</td>
<td>Co-Inventor with LABioMed licensed</td>
<td>&gt;$2.5M</td>
</tr>
<tr>
<td>PN-2</td>
<td>Stem cell /gene therapy</td>
<td>MPS IIIB</td>
<td>Cell model</td>
<td>$225K NIH grant</td>
<td>Co-Inventor with LABioMed</td>
<td>~$1.5M</td>
</tr>
<tr>
<td>PN-3</td>
<td>Gene therapy</td>
<td>MPS IIIC</td>
<td>Sheep biodistribution</td>
<td>$850,000 JJB/HANDS</td>
<td>Licensed</td>
<td>&gt;$1M</td>
</tr>
<tr>
<td>PN-4</td>
<td>Chaperone</td>
<td>MPS IIIC and MPS IIID</td>
<td>Hit optimization, cell models</td>
<td>$100,000 JJB/HANDS $225K grant pending</td>
<td>Licensed</td>
<td>~$1.5M</td>
</tr>
<tr>
<td>PN-5</td>
<td>Gene therapy</td>
<td>MPS IIIB</td>
<td>Vector optimization</td>
<td>$225K grant submitted</td>
<td></td>
<td>$1.5M</td>
</tr>
</tbody>
</table>
Crowdfunding rare disease science

Funding gene therapy research/development for Sanfilippo Type A

Funding gene therapy research/development / Chaperone research for Sanfilippo Type C

Sanfilippo Syndrome - funds raised in ~ 2 years
“Most companies working on rare diseases address a small number of them. Such rare disease efforts are focused on creating a treatment for a single disease rather than finding a way that all diseases can benefit. **What is proposed here is a fundamentally different approach.** To build the scale that could handle orders of magnitude more diseases ... Centralizing efforts on rare diseases would also need to bring with it the relevant expertise necessary to go from the preclinical to clinical stages.
Industrializing rare disease R&D

Need to centralize - address multiple diseases - need for economies of scale

Therapeutic approach

Collaborative researchers
+ Clinicians + Patients / advocates
Create a production line for treatments
Clinical trials

Nature Biotechnology, 35: 117-118, 2017
Enabling Anyone to Translate Clinically Relevant Ideas to Therapies

Sean Ekins, Natalie Díaz, Julia Chung, Paul Mathews, Aaron McMurray

Person with idea to test
- Researcher
- Clinician
- Citizen Scientist/Rare disease

Lab status
- Has lab
- No lab

Funding status
- Has funding
- No funding

How to fund
- Government Funding
- Foundation Funding
- Crowd Funding
- Self Funding

Where to do experiments
- Own Lab
- Collaborator Lab
- CRO Lab
- Open Lab

Collaborations Pharma
The Collaborations Vision

*Why does every new disease foundation have to find expert support from scratch every time?*

- Create a One Stop Shop for rare and neglected disease families / foundations to get to the clinic: lean Biotech for small molecule, protein, gene production
- Build core internal expertise in preclinical, clinical, regulatory, etc. to liaise between the foundations and the clinic
- Gather and Qualify key external partners for outsourcing GLP Tox and GMP production, cell banks, GMP analytical, and clinical supply
- Small scale in house labs and Quality infrastructure for preclinical and GMP compound management, characterization, and partner/supply management
Collaborations Pharmaceuticals Inc.

- Founded 2015

**Research Partnerships**
- Early Discovery
  - Na+ Channel (cancer)
  - Selective betablockers
  - Na+ Channel (Pitt-Hopkins)
  - Various with RTI

**Technical Development**
- Assay Central
  - HIV RT
  - TB x3 (inhaled, KasA, 2-Drug Combo)
  - Deep Learning

**Foundation Solutions**
- Ebola
- TB (triazine)
- HNPP (PAK1)
- Chagas
- Alpha7 PAM (Alzheimers)
- CLN1 (Batten)

**Production**
- Clinical

**Expert Consulting**
- Funded
- Submitted
- Prospect
For therapies approved by the FDA, there is a highly valuable pediatric priority review voucher that can be sold, most recently for $150m - the top price was $350M.
Neuronal ceroid-lipofuscinoses (NCLs) - infantile onset form CLN1 (A form of Batten disease)

- Mutations (and absence of enzyme activity) in palmitoyl-protein thioesterase-1 (PPT1)
- Enzyme replacement therapy developed by Dr. Sandra Hofmann (UT Southwestern)
- Preclinical studies show increased survival in mouse model
- Submitted NIH BrIDGs proposal to fund tox and manufacture of protein for clinical trial
- Submitted orphan drug designation Dec 2016

Hereditary neuropathy with liability to pressure palsies (HNPP) is caused by a heterozygous deletion of \textit{PMP22} gene. Currently no treatment for it.

Used a \textbf{PAK-1 inhibitor (PF-3758309)} with \textit{Pmp22+/−} mice improved F-actin dysregulation, junction disruption, and abnormal myelin permeability in \textit{Pmp22+/−} nerves.

\textbf{MTA with a big pharma to test their compounds:}
- submitted STTR to fund in vivo testing in mouse
- submitting orphan drug designation
- submitting investigator initiated clinical trial

\textbf{Jun Li - Vanderbilt University}
Antivirals for Ebola

_Ekins et al., F1000Research, 4:1091, 2015_

3 Molecules selected from MicroSource Spectrum virtual screen and tested _in vitro_
All of them nM activity

---

**Graph: % Ebola Infection vs. Log Conc. (M)**

**Table: EC50 (mM) [95% CI] and Cytotoxicity CC50 (µM)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC50 (mM) [95% CI]</th>
<th>Cytotoxicity CC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>4.0 [1.0 - 15]</td>
<td>250</td>
</tr>
<tr>
<td>Pyronaridine</td>
<td>0.42 [0.31 - 0.56]</td>
<td>3.1</td>
</tr>
<tr>
<td>Quinacrine</td>
<td>0.35 [0.28 - 0.44]</td>
<td>6.2</td>
</tr>
<tr>
<td>Tilorone</td>
<td>0.23 [0.09 - 0.62]</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Data from Robert Davey, Manu Anantpadma, Peter Madrid and Joel Freundlich

R21 funding to test pyronaridine in the _in vivo_ mouse

Collaborations Pharmaceuticals Inc. Non-Proprietary Slides.
How do we address 7000 diseases using software:

- Can we identify proteins involved in rare diseases and search for chaperones?
- Use crystal structures and build homology models of other proteins
- Perform docking using distributed computing e.g. IBM WCG
- Create a database of potential chaperones that researchers could test against rare diseases
Opportunities - Creating a manufacturing capability on a shoestring

- Manufacturing bottlenecks globally slow down treatment development for clinical trials.
- Need for GMP manufacturing
  - Enzyme replacement therapies
  - Gene therapy manufacturing / AAV
- Needed for small scale preclinical/ clinical studies
- Investment Needed $5-10M
- Need manufacturing expertise.
- To be continued....
Contact

- Sean Ekins, Ph.D., D.Sc.
- Email collaborationspharma@gmail.com
- Phone 215-687-1320

Acknowledgments:
- Jill Wood
- Lori Sames
- Allison Moore
- Audrey Davidow
- Sharon King
- Amber Olsen
- Alan Finglas
-
- Steven Gray

Collaborations

- Pharmaceuticals projects

  - Mary Lingerfelt
  - Kimberley Zorn
  - Maggie Hupcey
  - Alex Clark
  - Joel Freundlich
  - Peter Madrid
  - Robert Davey
  - Jun Li
  - Sandra Hofmann
  - Alfredo Garzino Demo
  - Vadim Makarov
  - Andrea Barry
  - Valery Tkachenko
  - Aaron McMurray
  - Julia Chung
  - Natalie Diaz
  - Paul Mathews

- Phoenix Nest projects

  - Patricia Dickson
  - Alexey Pshezhetsky
  - Brian Bigger
  - Xiaoyi Zhang
  - Tsui-Fen Chou
  - Steven Le
  - Shih-hsin Kan
  - Matthew Ellinwood
  - Michelina Iacovino
  - Derek Moen
  - Joel Freundlich
  - Shaogang Li

- NIH NINDS
  - 1R41NS089061-01
  - 1R41NS092221-01A1

- NIH NIAID
  - 1R41AI122434-01
  - 1RO1NS102164-01

- NIH NCATS
  - 1R21TR001718-01

- NIH NIGMS
  - 1R43GM122196-01