How Our Approach for Sanfilippo Syndrome Could Be A Prototype For Industrializing Rare Disease Drug Discovery and Development

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Abstract

It has been proposed that patients are key partners in rare disease drug development. We would suggest that patients and more likely their families can do so much more to help understand disease burden, establishing disease end-points and assessing benefit-risk profiles. For example, families are actively partnering with academics to push and fund their ideas for treatments but this has to happen on a much larger scale. In the nearly 5 years since a rare disease parent and scientist formed Phoenix Nest Inc. (PN) (http://www.phoenixnestbiotech.com/) we have defined an approach which could be used to develop and translate treatments for other rare diseases. Initially we formed PN to work on Sanfilippo syndrome (MPS III) Type C, we then expanded to address Type D and Type B as follows: 1. Set up a collaborator network with leading academics and industry, 2. Submitted and won multiple NIH STTR grants to fund research in collaborator labs, 3. Placed PN employees in collaborator labs, 4. Optioned licenses to technologies developed with collaborators (e.g. gene therapy for MPS IIIC and ERT for MPS IIID), 5. Develop Natural history for diseases, clinical outcome measures and biomarkers.

By partnering with academics small rare disease focused companies can help them fund their work and ultimately translate it to the clinic. We continue to identify additional academics and projects to broaden our portfolio to cover all forms of Sanfilippo syndrome. Our strategy can also be used to address additional rare diseases (whether other MPS or beyond) and we continue to pursue funding opportunities. Ultimately if we are to address more of the 7000 rare diseases we need to build the scale that could handle orders of magnitude more diseases this would require the use computational, automation and informatics tools to help identify, create and manufacture treatments and facilitate the collaborations necessary to create a pipeline to bring them to the clinic. We need a production line and PN perhaps represents a small scale prototype.

Introduction

Jonah (8), diagnosed age 2. Has Sanfilippo Syndrome (MPS IIIC) - MPS IIIC caused by genetic deficiency of heparan sulfate acetyl CoA: a-glucosaminide N-acetyltransferase, (HGSNAT).
Jonah's parents founded Jonah's Just Begun (JJB) 501(c)3 Funds raised are invested in the science of MPS IIIC.

Phoenix Nest, Inc (PN) was started to identify treatments for this disease through collaborations. Our efforts have focused on pursuing non-dilutive NIH small business grants. We have not been funded by VCs or Angels to date.

Phoenix Nest Grant Timeline

Early 2012 – Phoenix Nest founded.

2012-2014 - numerous grants were submitted to the NIH on MPS IIIC

Oct 2014 – Phase I STTR (MPS IIID) with LABioMed funded and started.

February 2016 – second phase I STTR (MPS IIIB) funded and started

June 2016 – Phase II STTR (MPS IIID) funded.

Sept 2016 – 2 new phase I NIH STTR submitted (MPSIIIC and IIIB)

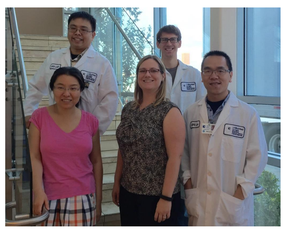
Oct 2016 – R01 Natural history study grant submitted to FDA

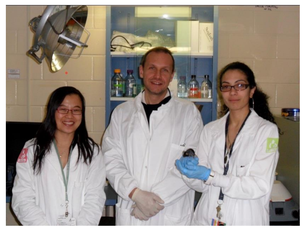
Jan 2017 – resubmitted I NIH STTR IIIB grant

Feb 2017 – MPS IIIC chaperone grant scored 27 pending council review

Our Strategy

1. Set up a collaborator network with leading academics and industry





From L- R Collaborators Include the Brian Bigger lab (university of Manchester), Dr's Patricia Dickson,Tsui-Fen Chou, Michelina iacovino labs and Dr. Alexey Pshezhetsky.

2. Submitted and won multiple NIH STTR grants to fund research in collaborator labs

1R41NS89061-01 Development and in vitro validation of therapy for mucopolysaccharidosis III, STTR Phase I (Ekins, PI and Dickson Co-PI) **$222,296.50**

2R42NS089061-02 Development and in vitro validation of therapy for mucopolysaccharidosis III STTR phase II (Ekins / Dickson) **$1,495,008.00**

1R41NS092221-01A1 Engineering stem cells to make mucopolysaccharidosis IIIB (Ekins / Dickson) STTR phase I **$224,889.39**

3. Placed PN employees in collaborator labs,

To date we have employed 3 scientists in the labs at LABioMed.

4. Optioned licenses to technologies developed with collaborators

To date, gene therapy for MPS IIIC (University of Manchester) and ERT for MPS IIID (LABioMed) are being optioned, in addition we have a pipeline of collaborations and treatments:

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

5. Develop Natural history for diseases, clinical outcome measures and biomarkers.

Designed after Shire's protocol for A and B.
One site with Dr. Paul Levy in collaboration with Minnesota.
5 year longitudinal study, Start date spring 2017, 16 patients.
JJB / HANDS is helping with trial and MRI expenses.

The major incentive we have to obtain outside funding is the ability to pursue a rare pediatric disease priority review voucher. These have increased in value.

Our approach could be used by others as a prototype to streamline rare disease drug discovery and development.

There are however numerous challenges to address.

The Future

Challenges for gene therapies: many competing vectors, patents, and little sharing or open collaboration, year long delays in vector manufacturing, delays caused by a lengthy NIH institutional review board regulatory process.

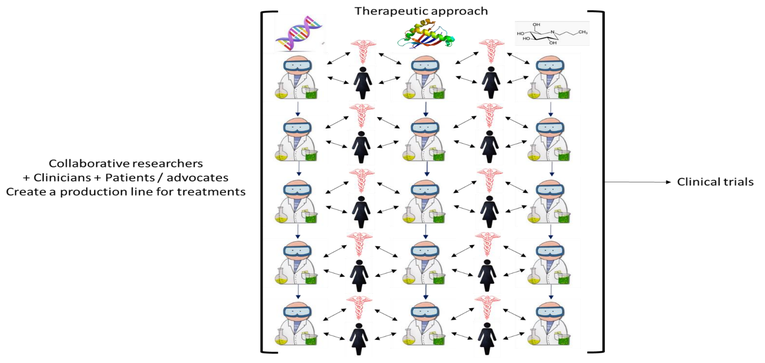
Challenges for the development of protein replacements: purification and expression is as much of an art as a science and know-how is trapped inside companies and academia labs.

To develop economies of scale there needs to be a focus on generalizing the approaches to develop therapeutics across all types of rare diseases. (Figure 1)

Bringing a gene therapy to the clinic can start at $3M-$7M.

Bringing the costs down to $1M per disease would require the identification of the best approaches to: make human proteins, to deliver gene therapies to the brain, find molecules to act as chaperones for many diseases, and scale up the process of expression, purification and analysis of multiple protein replacement therapies.

Figure 1. Schematic of a 'production line' for developing gene therapies, protein replacement and small molecule approaches for rare diseases in which researchers, clinicians, patients and advocates collaborate to bring different treatments for different rare diseases to the point of clinical trials.



Conclusion

Handling orders of magnitude more rare diseases would require the use and integration of many types of different approaches to help identify, create and manufacture treatments.

Collaborations would be necessary to bring them to the clinic. Centralizing efforts would also need the relevant expertise necessary to go from the preclinical to clinical stages.

Learning from the parent-lead successes of treatments brought to the clinic already, provides convincing evidence for the need for investment in creating a rare disease center of excellence.

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