Curing Idiopathic Pulmonary Fibrosis with Thyroid Hormone Mimetics

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The Team

- Award winning team
- Over 250 publications in top general and pulmonary journals
- Over 40 million dollars in NIH grants in 10 years
- Track record of discovery and innovation
  - New Molecular targets
  - Biomarkers
  - Industry collaborations and relations
Opportunity – A Fast Path to Patients of a New Therapy for Pulmonary Fibrosis

- Pulmonary Fibrosis, a highly lethal lung disease, with limited efficacy treatments
- Our data indicate that:
  - localized delivery of the thyroid hormone leads to resolution of fibrosis in two animal models of lung fibrosis (Yale US 15/317,276; NK lead inventor, licensed Lifemax)
  - systemic delivery of the well-studied thyroid hormone mimetic, Sobetirome, leads to resolution of fibrosis (Yale PCT filed 6.29.2017, NK lead inventor)
- Novel Mechanism of Action - augment epithelial survival and mitochondrial homeostasis
- Strength - efficacious, well characterized, highly active compound (Sobetirome)
- Team - superb expertise in Pulmonary Fibrosis
- Needs - to fund IND enabling preclinical in vitro and in vivo work

Yu et al. Nature Medicine December 2017; https://www.nature.com/articles/nm.4447
Idiopathic Pulmonary Fibrosis

• A lethal progressive chronic lung disease of unknown origin
• 190,000 patients in the US; 6M worldwide
• Median survival 3 years (30,000 deaths a year)
• 2 FDA approved drugs
  o Slow down disease progression as judged by pulmonary functions
  o No obvious impact on survival
  o No impact on QOL
  o Side effects are significant (high prescription attrition)
    o Sales in 2015 Esbriet (>$300M, Roche), Ofev ($300M, Boehringer Ingelheim)
• While a number of compounds are being developed, most target fibroblasts and extracellular matrix, we target epithelial cells
Thyroid Hormone and Thyroid Hormone Mimetics Reverse Pulmonary Fibrosis

Yu et al. Nature Medicine December 2017; https://www.nature.com/articles/nm.4447
None of Current IPF Clinical Trials Involve Drugs That Target Epithelial Cells

Mora et al., 2017, Nature Reviews, Drug Discovery
Thyroid Hormone Agonism Resolves Lung Fibrosis More Effective Than the 2 FDA Approved Drugs

Data:
A. T3 reverses bleomycin induced mitochondrial injury in alveolar epithelial cells and restores mitochondrial homeostasis

B. Aerosolized T3, started during established fibrosis phase, reduces collagen deposition and tissue fibrosis in two animal models of pulmonary fibrosis

C. Aerosolized T3 is more effective in resolving lung fibrosis than 2 FDA approved drugs

Yu et al. Nature Medicine December 2017; https://www.nature.com/articles/nm.4447
Sobetirome, a Thyroid Hormone Mimetic, Resolves Established Pulmonary Fibrosis

Data:

A) Sobetirome – resolves pulmonary fibrosis in bleomycin animal model when administered IP or orally

B) Sobetirome restores mitochondrial homeostasis and bioenergetics after injury

C) Patients with IPF have abnormal mitochondria in their lungs and high level of mtDNA in their blood – potential biomarker.

D) Same mechanism of T3, but lacks cardiac or muscular toxicity, and thus can be given systemically – orally (!)

Yu et al. Nature Medicine December 2017; Ryu et al. AJRCCM, December 2017;
Our Approach

Repurpose the well characterized thyroid hormone mimetic, Sobetirome, to target pathways directly related to human fibrosis

1998
- Sobetirome - A highly potent thyroid hormone agonist, lacking any thyrotoxic side effects and orally available
- Off formulation patent

2005-08
- Licensed to QuatRx for treatment of hypercholesterolemia
- FDA approved clinical development (Phase 1)
- Clinical proof of concept demonstrated

2010
- Neurovia acquired IND for Sobetirome
- Development of treatment of X-linked Adrenoleukodystrophy (X-ALD)

2017
- Completed Phase 1a, now in X-ALD patients (Phase 1, 2)
- Orphan neurologic disease designation
- Secured investors: Novartis Venture Funds, Sanofi-Genzyme, BioMed Ventures, ENSO ($14M, Series A)
# Development

## Year 1

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Activity</th>
<th>Year 1 Cost</th>
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<tbody>
<tr>
<td>Q1</td>
<td>PK/PD</td>
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<tr>
<td>Q2</td>
<td>Dose optimization</td>
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<tr>
<td>Q3</td>
<td>Detailed toxicology</td>
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<td>Q4</td>
<td>RAT GLP (oral and local)</td>
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## Year 2

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<tr>
<td>Q1</td>
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<tr>
<td>Q2</td>
<td>Recruitment</td>
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<tr>
<td>Q3</td>
<td>Performance of study</td>
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<td>Q4</td>
<td>Analysis of Results</td>
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<td>Real world dog efficacy</td>
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## Year 3

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<tr>
<td>Q1</td>
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<td>Q2</td>
<td>Negotiation with Neurovia</td>
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<td>Orphan Drug Designation</td>
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<td>IND Application</td>
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Phase 1 studies in humans
Real World Sobetirome Efficacy Pilot Trial in West Highland White Terrier Dogs (Yale/Tufts/Westie Foundation collaboration)

- Progressive fibrosis is seen in WHWT
- Shortened survival
- Cough and exercise limitation
- Accentuated subpleural and peribronchiolar fibrosis with occasional “honeycombing” and profound alveolar epithelial changes ci
- CT scans - mosaic ground-glass and mild honeycombing patterns


Dose escalation from 1 to 2.5mcg/Kg – 3 healthy dogs (sobetirome levels, chemistry)

Short term safety – 2 weeks of 2.5 mcg/Kg (sobetirome levels, chemistry, QOL and tox monitoring)

Treatment of IPF dogs (8) for 6 months (CT, 6MWT, QOL, Biomarkers)
Development Plan

• Option I: Developing Sobetirome in partnership with Neurovia – obtain right of reference to data from Neurovia. We will negotiate an option which would allow a start-up to obtain a license (to be paid for out of the Series A, but likely back-end loaded).

• Option II: Developing Sobetirome independently of Neurovia – complete a full toxicology study (rodent and dog or primate), will require 1-3 million more in funding and 2 years of development time.
We have a superb, effective and safe molecule - Why do we need the Blavatnik funding?

To reduce uncertainty and enhance appeal to investors

• To determine the optimal route of administration by performing oral and aerosol efficacy/PK/PD in a second animal model

• To provide “real life” proof of concept of effect in a naturally occurring model of canine pulmonary fibrosis

• To resolve regulatory aspects of commercialization and market differentiation

• Make a plausible case that the road to humans is open
Potential for Further Development of TH Mimetics to Treat Fibrosis

Health for Millions, Market in Billions!