Curing Idiopathic Pulmonary Fibrosis with Thyroid Hormone Mimetics

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The Team

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- 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
Idiopathic Pulmonary Fibrosis

- A lethal progressive scarring chronic lung disease of unknown origin
- 190,000 patients in the US; 6M worldwide
- Median survival 3 years (30,000 deaths a year)
- The 2 FDA approved drugs have significant side effects and do not have an obvious impact on survival or quality of life
- Sales in 2015 Esbriet (>300M, Roche), Ofev ($300M, Boehringer Ingelheim)
- The need is – a safe drug with a positive effect on survival and quality of life
Key Finding: Thyroid Hormone Agonism Reverses Pulmonary Fibrosis

Yu et al. Nature Medicine December 2017; https://www.nature.com/articles/nm.4447
Our Approach

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

<table>
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<tr>
<th>Year</th>
<th>Events</th>
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<tr>
<td>1998</td>
<td>Sobetirome - A highly potent thyroid hormone agonist, lacking any thyrotoxic side effects and orally available&lt;br&gt;Off formulation patent</td>
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<td>2005-08</td>
<td>Licensed to QuatRx for treatment of hypercholesterolemia&lt;br&gt;FDA approved clinical development (Phase 1)&lt;br&gt;Clinical proof of concept demonstrated</td>
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<td>2010</td>
<td>Neurovia acquired IND for Sobetirome&lt;br&gt;Development of treatment of X-linked Adrenoleukodystrophy (X-ALD)</td>
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<td>2017</td>
<td>Completed Phase 1a, now in X-ALD patients (Phase 1, 2)&lt;br&gt;Orphan neurologic disease designation&lt;br&gt;Secured investors: Novartis Venture Funds, Sanofi-Genzyme, BioMed Ventures, ENSO ($14M, Series A)</td>
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Sobetirome Resolves Established Lung Fibrosis in vivo

Sobetirome (GC-1) Restores Mitochondrial Homeostasis and Bioenergetics After Bleomycin Injury

Yale PCT filed 6.29.2017, NK lead inventor

Yu et al. Nature Medicine December 2017; https://www.nature.com/articles/nm.4447
# Development

<table>
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<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
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<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
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## RAT GLP (oral and local)
- **Q1**:
  - PK/PD
  - Dose optimization
  - Detailed toxicology

## Real world dog efficacy
- **Year 1**:
  - Protocol Approval
  - Recruitment
  - Performance of study

## Regulatory
- **Year 1**:
  - Engage Regulatory Consultants
  - Negotiation with Neurovia
- **Year 2**:
  - Orphan Drug Designation
  - IND Application

*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 but no fibroblastic foci
- 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)
Potential for Further Development of TH Mimetics to Treat Fibrosis

Market in Billions!