Intronistat Therapeutics

Targeting the unique features of fungal metabolism for a new generation of nontoxic drugs

Investigator: Anna Marie Pyle, Ph.D.
William Edward Gilbert Professor of Molecular, Cellular and Developmental Biology and Professor of Chemistry, Yale University

Investigator, Howard Hughes Medical Institute
anna.pyle@yale.edu
**Intronistats**: Potent, specific antifungals

*Pathogenic fungi are a major public health threat, causing...*

- Chronic lung infections
- Neonatal mortality
- Implant malfunction (stents, joints)
- Transplant failure (bone marrow)

*Fungal infections are hard to kill without making people sicker*

- Fungi are “eukaryotes”, like humans
- We share most of the same cellular features
- As a result, available antifungal drugs are highly toxic

*To meet this need, we developed Intronistats, which target An RNA enzyme that is unique to fungi and yeast*
Market for antifungal drugs

8 billion dollars in 2016
(not including topical antifungals)

Grand View Research November 2016
New approach: Target enzymes unique to fungi

Group II introns are “self-splicing” RNA sequences within the respiratory genes of fungi, not in humans. When blocked, fungi cannot “breathe”

The Pyle Laboratory.....
• Solved the first Group II Intron structures
• Determined the chemical mechanism of splicing
• Developed inhibitors for splicing
• Leadership in RNA structure and targeting by small molecules
Pilot Studies

We built a sensitive HTS assay for intron activity, conducted screen of 10,000 compounds and optimized the leads.

Our pilot yielded Intronistat A and B: A potent as the standard of care (AmphotericinB) without its toxicity

Published in *Nature Chemical Biology* 2018
See press reports in *C&E News, G&En News, Nat Revs Drug Discovery*
Next Step: An Expanded Screen

While intronistat A and B are good proof-of-concept molecules, we can identify drugs with even better properties by doing a larger screen.

- 10,000 compounds
  - More stable, drug-like compounds
- 250,000 compounds
  - Improved potency and pharmacokinetics
  - A range of new scaffolds for development
  - An entirely new generation of antifungals
  - Large screen will contain new SAR
Role of Blavatnik Funding

We seek...
- Funds for a large screen, on a fee-for-service basis, to expand and preserve our IP. We will employ a top screening firm with robust libraries (Evotec, CRL, $250K)
- Funds for limited medicinal chemistry ($50K)

**Objective: A $300,000 grant**

The goal...
- IP for creating a new company that builds on our lead compounds
- A Newco that focuses on Intronistat optimization and clinical application
- A new generation of well-tolerated antifungal agents to meet the needs of
  - Transplant patients
  - Implant recipients
  - Neonatal and immunocompromised patients
  - Patients with eye and skin infections
Patents and Strategy:

Intellectual Property:
- *Yale has filed patents on the technology and compounds*

Intronistat Therapeutics Corporate Strategy:

**Attainable short-term goals:**
- Facile approval path for ex-vivo treatment of implants.
- Simplified approval path for treatment of eye infections
- A focus orphan indications

**Compelling long-term vision:**
- Provide well-tolerated, systemic antifungals: A major unmet need
- Meet the needs of an aging population (increase in implants, etc.)
- Provide treatments for emerging fungal infections