Creating novel antifungals that target the Achilles' heel of fungal pathogens:

Self-Splicing RNAs

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Founders

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- Yale, Sterling Professor, NAS
- Howard Hughes Medical Institute
- RIGImmune

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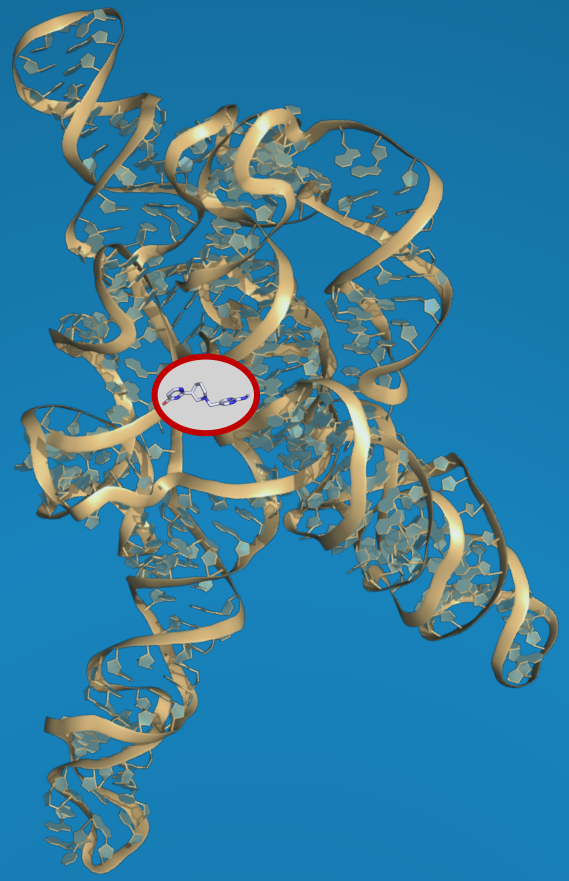


Intron$_X$ Company Overview

Intron$_X$

01 **Small molecule targeting of RNA molecules** unique to pathogens

02 **Active small molecules** targeting fungal RNA splicing identified, patented

03 Patented **high-throughput assay** for specific RNA targeting

04 Not found in mammals, fungal RNA splicing is an **ideal target,** enabling treatments for **Systemic Invasive Fungal Infections (IFI)**

05 **Broad expertise** in RNA targeting and infectious disease

06 Validation of platform allows expansion to **human-specific RNA splicing disorders**

The need for antifungal solutions

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

- Chronic lung infections
- Neonatal mortality
- Implant malfunction (stents, joints)
- Transplant failure (bone marrow)
- Disrupted cancer chemotherapy
- Immunocompromised patient infections

Fungal infections are hard to kill without making people sicker

Fungi are eukaryotes, like humans

We share a similar proteome and cellular organization

As a result, available antifungal drugs can be highly toxic to humans and animals

Intron$_X$

To meet this need,

we developed Intronistats, which target RNA enzymes that are unique to fungi and yeast

Existing drugs do not meet the needs of patients

Invasive Fungal Infections (IFI)

listed as top Urgent Threats, CDC and WHO

- High mortality (20-40%)
- Growing multi-drug resistance
- Emerging untreatable pathogens, e.g., Candida auris

Our strategy creates new classes of **small-molecule** antifungals that **maximize efficacy** and **minimize toxicity**

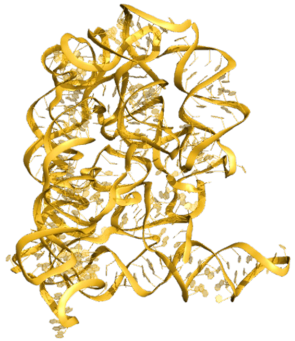
Antifungal Classes	Polyenes	Azoles	Echinocandins
Year of Introduction	1960-	1980-	2000-
Number of Compounds	1 (Amphotericin B)	5	3
Type of Compounds	Large Molecule	Small Molecule	Large Molecule
Antifungal Activity	Broad	Broad	Narrow
Safety	Highly Toxic	Moderately Toxic	Well Tolerated
Resistance	Growing	Major concern	Growing
Flexibility	Only IV	IV/Oral	Only IV

A new strategy:

Target RNAs unique to fungal pathogens

Leverage the unique features of fungal metabolism to build a new generation of nontoxic drugs

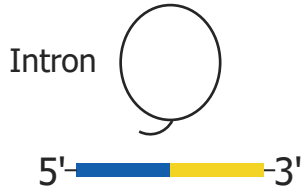
- Candida albicans
- Candida auris
- Candida parapsilosis
- Aspergillus
- Cryptococcus
- ...and more



The genes of these pathogenic fungi contain something that animals don't have:

Specialized RNA enzymes called "self-splicing introns"

Unspliced



Spliced

Same RNA Target is shared by these pathogens

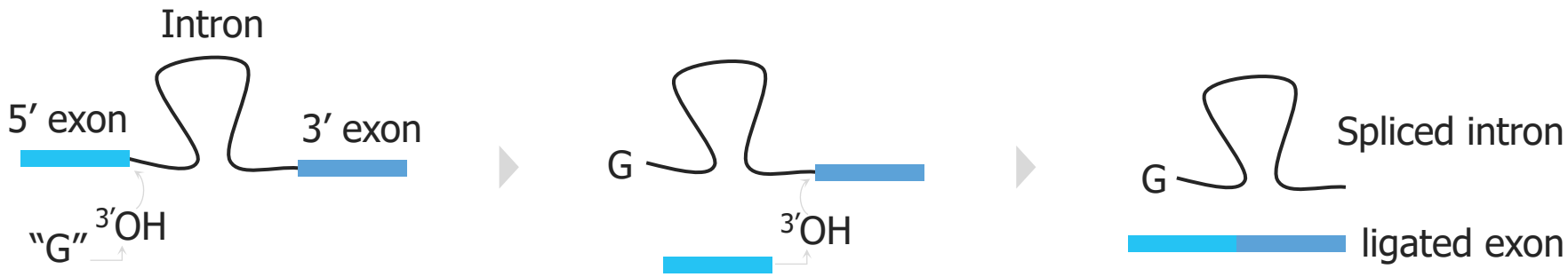
We patented a fast, sensitive assay to find pan-fungal drugs

Molecular Beacon Assay

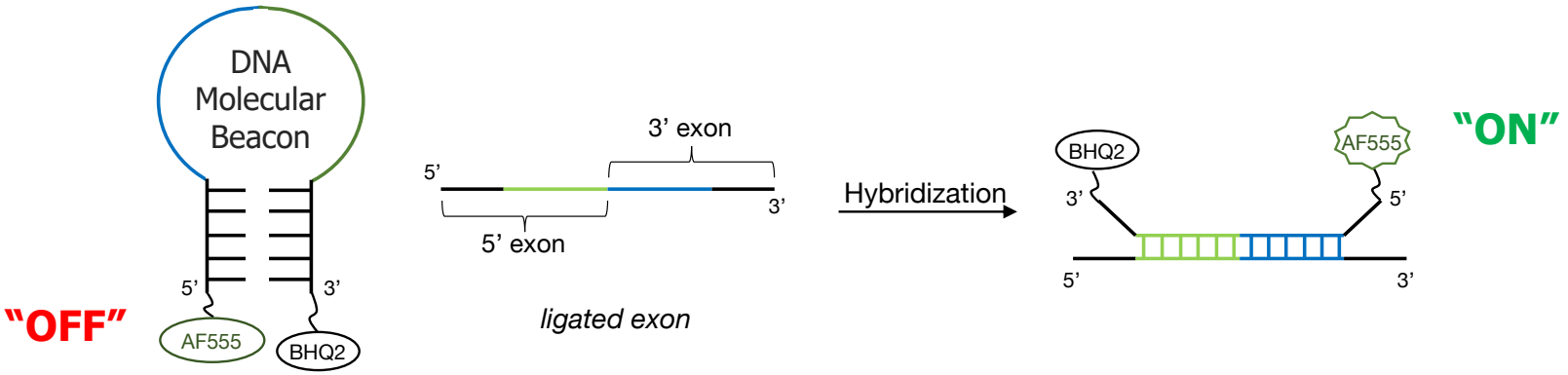
To sensitively monitor intron self-splicing and the effect of drugs, we needed a new type of assay: **A bright Molecular Beacon.**

This is a scalable tool that enables sensitive high-throughput screening for drugs targeting the splicing of any gene, in any organism.

Group I Intron Splicing Pathway



Molecular Beacon Hybridization

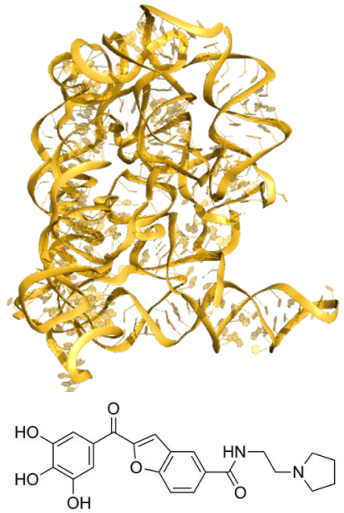


The assay, and selected compounds are within the IP portfolio available to Intron$_X$

Omran, Liu and Fedorova, NAR 2022

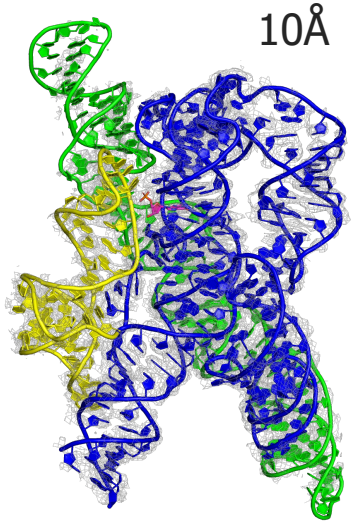
Our discovery engine has already produced novel antifungal compounds

V1 Intronistats (POC)



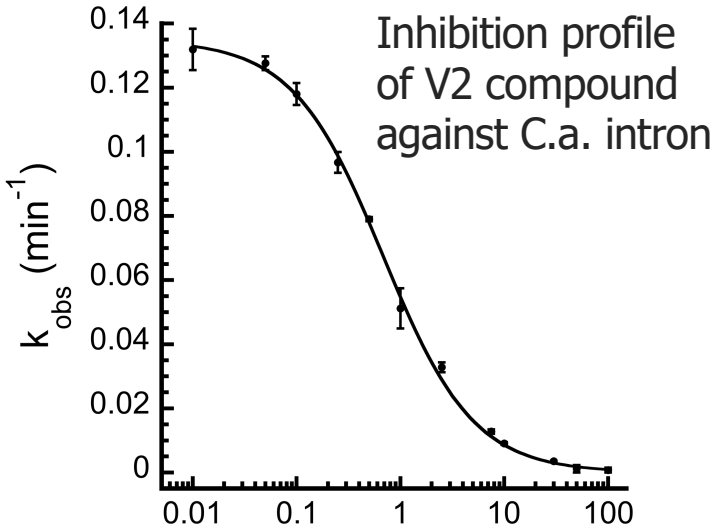
Ki = 0.36 µM
MIC: 3 µg/ml
in-vivo activity

V2 Intronistats:
Pan-fungal, target specific sites on group I introns



Cryo-EM structure

of C.a. intron bound to small molecule cofactor.



K_i = 0.68 ± 0.03 µM

sub-micromolar V2 compound

Fedorova, Pyle et al, Nature Chem Biol 2018
Granted patents on V1 intronistat families

Business Model, Near Term Strategy, Milestones

Business Model

- License existing antifungal assets
- Internal development of new compound classes, partnering for co-development of leads
- Adapt platform for new fungal and mammalian RNA targets

Near Term Strategy

- Raise seed financing
- Pursue non-dilutive federal, state and foundation funding
- Execute Yale licensing agreement
- Hire identified executive team
- Transfer academic laboratory activities to Intron$_x$ lab

Milestone

Series Seed Funds

- Continue high-throughput screening to identify additional antifungal scaffolds
- SAR and optimization of identified compounds, moving to clinical candidate stage
- Achieve scalable screening process against identified in mammalian splicing disorders

Thank You!

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Intron x