NEW KIDS ON THE BLOCK: ANTIFUNGAL DRUG PIPELINE

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Consultant: FDA, CDC, NIH, Astellas, Merck, Scynexis, Amplyx, Sfunga

Grant support: NIH, Merck, Amplyx, Scynexis, Cidara, Matinas, sFunga

Co-founder: Symbiotica
Outline

- Fungal infection scope
- Currently approved antifungals
- Antifungal needs
- Drugs in clinical development
  - Existing MOA improvement
  - Novel target
- Drugs in preclinical development
# Worldwide Fungal Infections

>1 billion infections annually, 1.6 million deaths

<table>
<thead>
<tr>
<th>Fungal disease</th>
<th>Estimated cases per year</th>
<th>Estimated mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcosis</td>
<td>&gt;1,000,000</td>
<td>20%–70%</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>&gt;400,000</td>
<td>10%–75%</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>&gt;200,000</td>
<td>30%–95%</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>&gt;11,000</td>
<td>30%–90%</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>~3000</td>
<td>&lt;2%–68%</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>~20,000</td>
<td>&lt;1%–70%</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>~25,000</td>
<td>28%–50%</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td>~4000</td>
<td>5%–27%</td>
</tr>
<tr>
<td>Penicilliosis</td>
<td>&gt;8000</td>
<td>2%–75%</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>&gt;400,000</td>
<td>20%–80%</td>
</tr>
</tbody>
</table>
The Current Armamentarium


Amphotericin B (1966)
Amphotericin B Lipid Complex
Amphotericin B Colloidal Dispersion
Caspofungin
Micafungin
Posaconazole
Voriconazole
Isavuconazole
Anidulafungin

Flucytosine (1971)
Fluconazole
Itraconazole
Liposomal Amphotericin B

Last new drug class discovered in 1970s
Limited Antifungal Targets

Molds

Yeast

Triazoles

Amphotericin B

Ergosterol binding or synthesis (14α-demethylase)

Echinocandins

β 1,3-D glucan synthase inhibitor

Flucytosine

Pyrimidine analogue/thymidylate synthase inhibitor

Cell membrane

Cell wall

DNA translation
Challenging Efficacy vs Toxicity Bar

- Eukaryotic conservation of biology and drug targets
The Achilles Heel of Triazole Antifungals

CYP51A

CYP3A4

Homology of fungal and mammalian targets (e.g., P450 enzymes)
Antifungal Gaps

**Toxicity**
- AmB > Azoles

**Limited Efficacy**
- Mortality > 20%

**Parenteral Only**
- Candins/AmB

**Drug Interactions**
- Azoles

**Limited PK Distribution**
- CNS/Eye
- Urine

**Emerging Resistance and Pathogens**
- MDR C auris
- Candin-R C glabrata
- Azole-R Aspergillus
- Fusarium/Scedosporium/Zygomycetes
Emerging Resistance

- **C. auris**
  - CDC urgent threat pathogen
  - 80% azole R, 30% MDR
  - >60% mortality

- **C. glabrata**
  - Echinocandin resistance 1.6% to 15%

- **A. fumigatus**
  - Triazole resistance 5-50%
  - US 5%

- **Other molds**

CDC.gov
Toda MMWR Surveill Summ 2019
Alexander et al CID 2013
Wiederhold Curr Opin Infect Dis 2020
Drug Interactions and Toxicity

- **Triazole drug interactions**
  - >80% hospitalizations
  - 20-60% contraindicated interactions

- **AmB**
  - Renal insufficiency
    - >60%, reversible but reduces likelihood of survival

- **Triazole**
  - Teratogenicity
  - Hepatitis 1-15%
  - QTc prolongation
  - Voriconazole
    - Visual 30%
    - Skin
    - CNS
    - Bone

Andes et al AAC 2016
Key Pharmacokinetic Characteristics

Urine Penetration
- Fluconazole > 90%
- Flucytosine > 90%
- Everything else < 1%

CNS/Eye Accumulation
- Fluconazole 80%
- Flucytosine 75%
- Voriconazole 60%
- Ambisome > other polyenes
- Everything else < 1%
Antifungal Discovery-Development Groups

Similar MOA

Improved Features
- Rezafungin
- Tolsura
- VT-1161
- VT-1129
- VT-1598
- MAT2203

Novel Target/MOA
- Ibrexafungerp
- Fosmanogepix
- Olorofim
- Nikkomycin
- T-2307
- AR-12
- MGCD290
- VL-2397
- Aureobasidin
- BHBM
- Tamoxifen
- Sertraline
- Turbinmicin

Pianalto and Alspaugh, J of Fungi 2016
Similar MOA – Improved Features

- **Rezafungin (CD-101)**
  - Cidara Therapeutics
  - 1,3-β-glucan synthase inhibitor – similar spectrum including many C auris strains
  - Echinocandin: structural analog of anidulafungin
  - Improved pharmacokinetics:
    - Intravenous (long-acting >100h)
    - Improved solubility/stability
    - Topical/vaginal
Rezafungin – P2
Candidemia and IC (NCT02734862)

PI Assessment of Clinical Response D14

Overall Response D14

1° endpoint component Ph3 – EMA

All-Cause Mortality D30

1° endpoint Ph3 – FDA

Rezafungin: Exposure Shape Matters
PK/PD determinant of antifungal efficacy

Antimicrobials with:
Concentration-dependent killing
Long half-life
Safety

Allows
Front-Loaded Dosing*

High drug exposure following once-weekly dosing vs divided doses (same weekly exposure)

Greater Fungal Killing

*High drug exposure early in therapy

Dose fractionation of rezafungin 2 mg/kg in neutropenic mice (n=5/grp)

Rezafungin – P2
Candidemia and IC (NCT02734862)

- RZF 19.5 h vs CAS 22.8 h (median, time to negative blood culture; ad hoc p=0.02)
- Maximum difference in probability of negative blood culture ~24 hours after first dose

Sandison T. RICAI, 2019; Thompson GR et al. *Clin Infect Dis*. 2020
Rezafungin P3
Candidemia & Invasive Candidiasis (NCT03667690)

- Open and enrolling
- Target N=184 (mITT)
  from >130 sites
  in 18 countries

Rezafungin

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose</th>
<th>Optional dose</th>
<th>Global Response (1st ENDPOINT – EMA)</th>
<th>Global Response &amp; All cause mortality (1st ENDPOINT – FDA)</th>
<th>Global Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>200/(200)mg</td>
<td>0</td>
<td>30(-2)</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>15</td>
<td>8</td>
<td>35</td>
<td>59</td>
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<td>5</td>
<td>2</td>
<td>49</td>
<td>56</td>
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</table>

Caspofungin

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<thead>
<tr>
<th>Week</th>
<th>Dose</th>
<th>Global Response</th>
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<tbody>
<tr>
<td>1</td>
<td>70mg</td>
<td>50mg Dose</td>
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<tr>
<td>2</td>
<td>3</td>
<td>50mg Dose</td>
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<tr>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

Rezafungin P3 (ReSpect)
Antifungal prophylaxis in allogeneic blood and marrow transplant setting
Bone Marrow Transplantation (NCT04368559)

Current Antifungal Prophylaxis Regimens

- Fluconazole
- Fluconazole, Posaconazole or Voriconazole
- Bactrim, dapsone or atovaquone

SOC for Candida and Aspergillus
SOC for Pneumocystis

Rezafungin

- Candida, Aspergillus and Pneumocystis

- Open and enrolling, Fungal free survival at day 90
- Hematology centers in the EU
- Target N=~450
P3 Trial of Rezafungin Prophylaxis
Bone Marrow Transplantation (NCT04368559)

Rezafungin Arm (n=300)

1° Endpoint: Fungal Free Survival at Day 90

Follow up

Comparator Arm (n=150)

Size and timing pending additional regulatory input. Cidara Therapeutics Inc
Similar MOA – But Novel Class

- **Ibrexafungerp (SCY-078)**
  - Scynexis
  - 1,3-β-glucan synthase inhibitor
  - Triterpene: First in class (distinct from echinocandins)
  - Mostly similar spectrum to candins
  - IV and oral formulations
  - 20h half-life
  - Limited urine/CNS penetration

Apgar et al. 2015 Bioorg Med Chem Lett
Ibrexafungerp (SCY-078)

Spectrum of Activity

36 Candida isolates
FKS1/FKS2 mutations

% with non-WT MIC

Echinocandin

C. albicans

SCY-078

C. glabrata

FKS2: F659
L6662
S663

C. albicans

FKS1: F641

Pfaller et al. 2017 AAC
# Ibrexafungerp: Development Status

<table>
<thead>
<tr>
<th>Indications</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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</thead>
<tbody>
<tr>
<td><strong>Vulvovaginal Candidiasis</strong></td>
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<tr>
<td><strong>Invasive Aspergillosis Combo</strong></td>
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<tr>
<td><strong>Refractory Invasive Fungal Diseases</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive Candidiasis</strong></td>
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</tbody>
</table>

**Additional indications under consideration:** Chronic Fungal Infections, Prophylaxis
Key Inclusions:

- Moderate to severe VVC (signs and symptoms of ≥7)
- KOH +
- pH ≤4.5

~30 patients per arm

Primary population for analysis mITT = Culture-confirmed VVC
DOVE Ibrexafungerp P2b VVC

Day 10 (Test-of-Cure)

- Clinical Cure (0 S&S) *: 52% for Ibrexafungerp 600mg Dose (n=27), 70% for FLU (n=24)
- 0 or 1 S&S *: 58% for Ibrexafungerp 600mg Dose (n=27), 71% for FLU (n=24)
- Mycological Eradication: 63% for both Ibrexafungerp 600mg Dose (n=27) and FLU (n=24)

Day 25 (Follow-up)

- 0 S&S *: 70% for Ibrexafungerp 600mg Dose (n=27), 50% for FLU (n=24)
- 0 or 1 S&S *: 81% for Ibrexafungerp 600mg Dose (n=27), 58% for FLU (n=24)
- Mycological Eradication: 48% for Ibrexafungerp 600mg Dose (n=27), 38% for FLU (n=24)
Two Phase 2 studies: Completed

- Ibrexafungerp showed efficacy at all dose regimens tested
  - One day dose was selected for Phase 3

VANISH (1 and 2):
- TWO, randomized double blind, Phase 3 studies in patients with ACUTE VVC
- Oral ibrexafungerp: One day treatment
- Ongoing in US and EU

CANDLE:
- ONE randomized, double blind, Phase 3 study in patients with RECURENT VVC
- Oral ibrexafungerp: One day treatment every month for 6 months
- Ongoing in the US and EU.
Ibrexafungerp P2 Invasive Candidiasis
(NCT02244606)

27 patients

Micafungin IV (3-10 days)

SCY-078
1250 mg x 1
750 mg PO daily

SCY-078
1000 mg x 1
500 mg PO daily

Standard:
Micafungin/
Fluconazole

Favorable global response (6 wk)

6 of 7
(86%)

5 of 7
(71%)

6 of 8
(75%)
CARES Ibrexafungerp P3 C. auris
(NCT03363841)

- Phase 3, open-Label, orally administered Ibrexafungerp (ongoing)
- Subjects with documented Candida auris infections
- Treatment naïve or refractory or intolerant to standard of care antifungal agents
- Preliminary N=10, 80% complete response
FURI Ibexafungerp P3 Refractory/Intolerant Candidiasis (NCT03059992)

N=74 patients included in the first analysis (86%) patients had complete, partial or stable responses

<table>
<thead>
<tr>
<th>Complete/ Partial Response</th>
<th>Stable Disease</th>
<th>Progression of Disease</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>46 (62%)</td>
<td>18 (24%)</td>
<td>6 (8%)</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>
SCYNERGIA Combination therapy in Invasive Aspergillosis (NCT3672292)

Phase 2, double-blind, randomized (ongoing)

Population:
- Pulmonary invasive Aspergillosis
- Hematological malignancy
- Positive Galactomannan test in blood

Endpoints include:
- Survival
- Global response
- GMI profile

Approximately 60 subjects from ~30 sites in US and EU
Similar MOA – Improved Features

- **VT-1161 (Oteseconazole)**
  - Mycovia (Viamet)
  - Tetrazole (next generation azole)
  - Designed for improved fungal CYP51 specificity
  - Spectrum Candida, dermatophytes, endemics
  - Improved pharmacokinetics
    - Half-life >48h
    - CNS penetration
    - Oral bioavailable (73%)
  - Fewer off-target effects
    - Minimal drug interactions
    - Predictable drug levels

Warrilow et al. 2014 AAC
VT-1161
Mechanism of Action

CYP51 $K_d$ Candida/human

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotrimazole</td>
<td>2.1</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>543</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>4.8</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>229</td>
</tr>
<tr>
<td>VT-1161</td>
<td>&gt;2000</td>
</tr>
</tbody>
</table>

VT-1161 P2a VVC (NCT01891331)

55 patients randomized
VT-1161
- 300 mg daily x 3
- 600 mg daily x 3
- 600 mg BID x 3
Fluconazole 150 mg x 1
Similar cure rates (D28)
Similar adverse events
Recurrence higher for fluconazole (47% v. 0%)
VT-1161 Phase 2b: Recurrent Vulvovaginal Candidiasis (REVIVE)

- Week 12
  - 150 mg once-weekly
  - Placebo
  - 300 mg once-weekly
  - Placebo
  - 150 mg once-weekly
  - Placebo
  - 300 mg once-weekly
  - Placebo

- Week 24
  - Interim analysis

- Week 48
  - Primary analysis

7 day, once-daily loading phase at same dose as weekly phase

VT-1161 Phase 2b: Recurrent Vulvovaginal Candidiasis (REVIVE)

- 215 patients randomized
- Adverse events similar to placebo
- Recurrence:
  - 52% Placebo
  - 0-5% VT-1161
VT-1161 and Siblings

VT-1161
- Recurrent VVC P3 (NCT03561701/NCT03840616)
- Tinea P2 (NCT02267382)
- Onychomycosis P2 (NCT02267356)

VT-1598 – Cryptococcus, Coccidioides, Aspergillus, Zygomycetes

VT-1129 - Cryptococcus

Garvey et al. 2015 AAC, Gebremariam et al. 2017 AAC, Shubitz et al. 2015 AAC, Long et al ECCMID 2015, Pollack et al. 2015 APMA Annual Scientific Meeting
Similar MOA – Improved Features

- **Tolsura**
  - Suba-Itraconazole
  - Mayne Pharma
  - pH-sensitive microparticle
  - Oral, improved/predictable bioavailability
  - Same spectrum
  - P1 safe
  - P2 endemic fungal infections (MSG15)

![Bar chart showing % of patients with C_{trough} Geometric Mean of 1034 ng/ml or Higher]
Similar MOA – Improved Features

- **MAT-2203**
  - Matinas BioPharma
  - Encholeated AmB – release in infected tissue
  - Oral
  - Same spectrum
  - P1 safe
  - P2a mucocutaneous candidiasis (NCT02629419)
  - EnACT P1/2 cryptococcal meningitis (NCT04031833)

Warrilow et al. 2014 AAC
**Fosmanogepix (APX-001)**

- Amplyx Pharmaceuticals
- GPI inhibitor (Gwt1 = inositol acyltransferase)
- Disrupts cell wall integrity
- Broad spectrum (Candida, Aspergillus, Fusarium, Scedosporium, Zygomycetes, Endemics)
- Oral and IV
- CNS/eye penetration

Fosmanogepix Inhibits Gwt1
Blocks mannoprotein transport
Leads to fungal cell death
Fosmanogepix Trials

- **Candidemia**: Phase 2: Complete
- **Candida auris**: Phase 2: Enrolling
  - Resistant *C. auris*
- **Aspergillus**: Phase 2: Enrolling
  - Invasive Mold Infections
  - COVID-19 Cohort
    - now open
- **Fusarium**: Expanded Access
  - 8 *fusarium* patients
- **Cryptococcus**: Clinical Planning Underway
  - *Cryptococcus* meningitis

- **Positive Phase 2 Data**
Fosmanogepix: Phase 2 Trial in Patients with Candidemia

Study Population
- Non-neutropenic with candidemia
- May have isolates resistant to SOC antifungals
- Positive baseline blood culture required within 96 hours of first dose
- May not have more than 48 hours of prior antifungal therapy for current infection

Study Endpoints
- Primary: End of Study Treatment Success
  - Clearance of infection
  - No additional antifungal therapy required
  - Survival
- Secondary: 30 Day Survival
- Others: Time to first negative blood culture, mycological outcomes, safety, PK/PD

FMGX Dosing Schedule
- Day 1: 1000mg BID IV loading dose
- Days 2-14: 600mg QD IV, or switch to 700mg QD oral (patient may switch to oral after Day 3)

20 sites in Belgium, Germany, Israel, Spain and US

Clinicaltrials.gov Identifier: NCT03604705
# Fosmanogepix P2 Candidemia

- 1000 mg load, the 600 mg/d IV or 700 mg po
- Efficacy: Response at End of Study Treatment and Survival at Day 30

Candidemia patients experienced meaningful clinical benefit from Fosmanogepix therapy

<table>
<thead>
<tr>
<th>Primary Efficacy Endpoint:</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Success¹</td>
<td>16/20 (80%)</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>4/20</td>
</tr>
</tbody>
</table>

Reasons for treatment failure:
- Persistent *Candida* in blood cultures²
- Death (gram-negative *acinetobacter* sepsis)³

<table>
<thead>
<tr>
<th>Secondary Efficacy Endpoint:</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Survival at Day 30</td>
<td>17/20 (85%)</td>
</tr>
<tr>
<td>All-Cause Mortality (none drug related)</td>
<td>3/20</td>
</tr>
</tbody>
</table>

Reasons for mortality³:
- Gram-negative *acinetobacter* sepsis
- Progression of underlying cancers
- Worsening of interstitial pneumonia

**Response at EOST** and **Survival at Day 30** will be primary endpoints for the planned Phase 3 trial

1. Treatment Success at EOST = eradication of *Candida* spp. from blood + no use of other systemic antifungal through EOST + alive at EOST
2. Candida spp.: *C. glabrata* (n=1), *C. albicans* + *C. glabrata* (n=1), *C. parapsilosis* (n=1)
3. Patient deaths not drug-related
Novel Target

- **Olorofim (F901318)**
  - F2G Pharmaceuticals
  - Orotamide class
  - DHODH (Dihydroorotate dehydrogenase) inhibitor - pyrimidine biosynthesis (DNA/RNA)
  - Aspergillus, Scedosporium, Endemics, +/- Fusarium (Not *Candida/Zygomycetes/Cryptococcus*)
  - Oral and IV
  - CNS penetration

Oliver et al. PNAS 113:12809-14, 2016.
Beckmann et al. ICAAC 2015; Fothergill et al. ICAAC 2015; Buil et al. JAC 2017; Rivero-Menéndez et al. ECCMID 2017; Oliver et al. PNAS 2016; Jorgensen et al. TIMM 2017
MDR moulds or refractory of other agents

Open-Label

Data-Review Committee to adjudicate responses at 6 and 12 weeks

N=26 enrolled thus far

- 16 Aspergillus, 5 Lomentospora, 2 Scedosporium, 3 other moulds
- 8 heme ca, 6 HSCT, 6 lung transplant, 6 other compromised
- 16 lung, 3 sinus, 3 bone/joint, 1 CNS, 1 disseminated, 1 chest wall
# Early Clinical or Preclinical Novel MOA

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Spectrum</th>
<th>Study Phase</th>
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</thead>
<tbody>
<tr>
<td>Nikkomycin</td>
<td>Chitin synthetase inh</td>
<td>Endemics</td>
<td>P2 stalled</td>
</tr>
<tr>
<td>T-2307</td>
<td>Mitochondrial membrane potential</td>
<td>Candida, Cryptococcus, Aspergillus</td>
<td>P1</td>
</tr>
<tr>
<td>MGCD-290</td>
<td>Histone deacetylase inh</td>
<td>Candida, Aspergillus, Moulds</td>
<td>P2 failed</td>
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<tr>
<td>AR12</td>
<td>Acetyl CoA synthetase inh</td>
<td>Candida, Moulds, Endemics</td>
<td>P1</td>
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<tr>
<td>VL-2397</td>
<td>SIT1 uptake (siderophore)</td>
<td>Candida, Aspergillus</td>
<td>P2 stalled</td>
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<td>Aureobasidin</td>
<td>Sphingolipid synthesis</td>
<td>Candida, Aspergillus</td>
<td>Preclinical</td>
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<tr>
<td>Turbinmicin</td>
<td>Vesicle transport</td>
<td>Candida, Aspergillus, Fusarium, Scedosporium</td>
<td>Preclinical</td>
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</tbody>
</table>
Immunotherapeutic Approaches

- Recombinant IFN-γ (adjunctive) for cryptococcosis, candidemia, aspergillosis
- Engineered T-cells: aspergillosis
- Dendritic cell activation?
- Neutrophil/granulocyte infusions
- Gene therapy (gp91 phox X-linked CGD)

## Antifungal pipeline 2021

<table>
<thead>
<tr>
<th>Company</th>
<th>Candidate</th>
<th>Possible indications</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>CIDARA Therapeutics</td>
<td>Rezafungin</td>
<td>Invasive candidiasis; BMT prophylaxis</td>
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<td>Scynexis</td>
<td>Ibrexafungerp</td>
<td>Aspergillus and difficult to treat moulds</td>
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<td>Amplyx</td>
<td>Fosmanogepix</td>
<td>Aspergillosis and C. auris</td>
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<td>F2G</td>
<td>Olorofim</td>
<td>Invasive candidiasis, aspergillois, VVC</td>
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<td>Mycovia Pharmaceuticals</td>
<td>VT-1161; VT-1598</td>
<td>VVC; C. auris, cryptococcus, coccidioid.</td>
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</table>
# Antifungal Gap Checklist

<table>
<thead>
<tr>
<th></th>
<th>MDR Activity</th>
<th>Pharmacokinetics</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Novel MOA</td>
<td>MDR Candida</td>
<td>A. fumigatus</td>
</tr>
<tr>
<td>Rezafungin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ibrexafungerp</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>VT-1161</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tolsura</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fosmanogepix</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olorofim</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Thank you!
Questions?
Symbiosis

Currie et al. 1999 Nature
ANTIFUNGAL DISCOVERY

A marine microbiome antifungal targets urgent-threat drug-resistant fungi

Fan Zhang¹*, Miao Zhao²*, Doug R. Braun¹, Spencer S. Ericksen³, Jeff S. Piotrowski⁴, Justin Nelson⁴, Jian Peng⁵, Gene E. Ananiev³, Shaurya Chanana¹, Kenneth Barns¹, Jen Fossen², Hiram Sanchez², Marc G. Chevrette⁶,⁷,⁸, Ilia A. Guzei⁹, Changgui Zhao¹, Le Guo¹, Weiping Tang¹, Cameron R. Currie⁶,⁷, Scott R. Rajski¹, Anjon Audhya¹⁰, David R. Andes²†, Tim S. Bugni¹†

Zhang et al., 2020
**Ecteinascidia turbinata**  
*Micromonospora* sp.

**Turbinmicin – A Novel Antifungal**

<table>
<thead>
<tr>
<th>Target Pathogen</th>
<th>Turbinmicin MIC (µg/ml)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. auris</em> B11211</td>
<td>0.25</td>
<td>Pan-R (Fluc 256, Mica 4, AmB 2)</td>
</tr>
<tr>
<td><em>C. glabrata</em> 4720</td>
<td>0.5</td>
<td>FKS2 S645P (Mica 4)</td>
</tr>
<tr>
<td><em>A. fumigatus</em> 11628</td>
<td>0.03</td>
<td>Cyp15 G54R (Posa 8)</td>
</tr>
</tbody>
</table>

**Minimum Inhibitory Concentration (µg/ml)**

- 0.125
- 0.250
- 0.500
- 4.000
- 6.000
- 8.000

**Zhang et al., 2020**
Turbinmicin – Safe In vivo

Ecteinascidia turbinata

Micromonospora sp.

Hemolysis

Concentration (μg/mL)

Inhibition (%)

MTD > 256 mg/kg
**Turbinomicin – Safe and Potent In vivo**

- **Ecteinascidia turbinata**
- **Micromonospora sp.**

**Log10 CFU/Kidney**
- Candida auris
- Aspergillus fumigatus

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Turbinomicin Dose</th>
<th>Control</th>
<th>0.25 mg/kg</th>
<th>0.5 mg/kg</th>
<th>1 mg/kg</th>
<th>2 mg/kg</th>
<th>4 mg/kg</th>
<th>Mica</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0</td>
<td></td>
<td></td>
<td>5.5</td>
<td>6.0</td>
<td>6.5</td>
<td>7.0</td>
<td>7.5</td>
<td>7.54</td>
</tr>
</tbody>
</table>

**Log10 CE/mL Lung**

- **Aspergillus fumigatus**
Turbinomicin MOA – Vesicle Trafficking Cell Biology

**Graph:**
- **Y-axis:** GFP-Snc1 in bud (%)
- **X-axis:** DMSO, turbinomicin
- **Data:** DMSO: 0, turbinomicin: ***0***

**Figure:**
- **Legend:**
  - GFP-Snc1
  - Sec7-MARS

**Images:**
- **DMSO:**
  - GFP-Snc1 and Sec7-MARS are shown with a few vesicles indicated by arrows.
- **3 μg/ml turbinomicin:**
  - Similar to DMSO, but with a significant increase in vesicle formation indicated by arrows.

**Scale Bar:** Not specified in the image.
Vesicles are Produced by Biofilm Cells and Incorporate in Matrix
Turbinmicin Inhibits Biofilm EV Release

** P < 0.01
Turbinmicin Inhibits Biofilm Extracellular Matrix Accumulation

Matrix biomass (as a % of control) vs. Turbinmicin concentration

** P < 0.01

Matrix biomass (ug/biofilm sample) vs. Turbinmicin concentration

** P < 0.01
Turbinmicin Exhibits Activity Against *C. albicans* Biofilms
Wisconsin Antimicrobial Drug Discovery Research Center

David Andes - Director
Pharmacology - Fungal Pathogenesis

Cameron Currie
Evolutionary Biology

Rod Welch
Bacterial Pathogenesis

Mike Hoffmann
In vitro Screening

Bruce Klein
Fungal Pathogenesis

Jon Clardy
Natural Product Chemist

Tim Bugni
Natural Product Chemist

U19AI142720-01
U19AI109673-01
R43AI134541-01