“Where’s the Fun in Fungus?”
An Introduction to the Antifungal Space

Literature Talk
February 13th, 2024

Iona Mathis McWhinnie
MacMillan Group
Princeton University
Another Public Health Crisis?

BARDA makes support available for development of novel antifungals to boost national preparedness

WEB ANNOUNCEMENT

Another Public Health Crisis?

BARDA is seeking private sector partners who are developing late-stage, broad-spectrum, next-generation antifungal drugs to treat high-priority fungal infections. Patients affected by any mass casualty emergency, such as a chemical, biological, radiological, or nuclear (CBRN) incident, pandemic influenza, and other emerging infectious diseases, are at an increased risk of developing a secondary fungal infection, which can contribute to increased morbidity and mortality and prolong patient recovery.

Congress Reintroduces the Pasteur Act

May 1, 2023
John Parkinson

Members of both branches brought it back to gain support and passage of a bill aimed at greater development of antibiotics.

“The PASTEUR Act brings together the public and private sectors to address these drug development market failures, increase public health preparedness, and help usher in a new era of antibiotic development,” said Ferguson in a statement. “This essential legislation will also improve appropriate antibiotic use across the healthcare system while enhancing and safeguarding new antibiotic development. Simply put, we must act now to keep research and development from falling behind.”

Increasing Threat of Spread of Antimicrobial-resistant Fungus in Healthcare Facilities

Press Release

For Immediate Release: Monday, March 20, 2023
Contact: Media Relations
(404) 639-3286

Candida auris (C. auris), an emerging fungus considered an urgent antimicrobial resistance (AMR) threat, spread at an alarming rate in U.S. healthcare facilities in 2020-2021, according to data from the Centers for Disease Control and Prevention (CDC) published in the Annals of Internal Medicine. Equally concerning was a tripling in 2021 of the number of cases that were resistant to echinocandins, the antifungal medicine most recommended for treatment of C. auris infections. In general, C. auris is not a threat to healthy people. People who are very sick, have invasive medical devices, or have long or frequent stays in healthcare facilities are at increased risk for acquiring C. auris. CDC has deemed C. auris as an urgent AMR threat because it is often resistant to multiple antifungal drugs, spreads easily in healthcare facilities, and can cause severe infections with high death rates.

WHO releases first-ever list of health-threatening fungi

25 October 2022 | Departmental news | Reading time: 3 min (715 words)

WHO today published a report highlighting the first-ever list of fungal “priority pathogens” – a catalogue of the 19 fungi that represent the greatest threat to public health. The WHO fungal priority pathogens list (FPPL) is the first global effort to systematically prioritize fungal pathogens, considering the unmet research and development (R&D) needs and the perceived public health importance. The WHO FPPL aims to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance.
Invasive Fungal Infections

Immunosuppression
3% US Population
90% invasive fungal infections
Invasive Fungal Infections

**Immunosuppression**
- 3% US Population
- 90% invasive fungal infections

**Candidiasis**
- >400k worldwide
- 46-75% mortality

**Aspergillosis**
- >200k worldwide
- 30-95% mortality

**Rare Molds**
- 20-30k worldwide
- 30-90% mortality

$3.8 billion market and high unmet need
Antifungal Development and Resistance

Development

- Polyenes (1960)
- Azoles (1980)
- Echinocandins (2000)
- Fungers (2020)

Adapted from Scynexis Corporate Presentation, January 2024.
Antifungal Development and Resistance

- **Development**
  - 1960: Amphotericin B
  - 1970: Fluconazol Tablets USP 200 mg
  - 1980: Micafungin for Injection 50 mg per vial
  - 2000: Ibexafungerp tablets 150 mg per tablet
  
- **Resistance**
  - 1960: Polyenes
  - 1970: Azoles
  - 1980: Echinocandins
  - 1990: Drug resistant fungi (Aspergillus, Morales)

Adapted from Scynexis Corporate Presentation, January 2024.
Antifungal Development and Resistance

Development:
- **1960**: Polyenes - Amphotericin B
- **1970**: Azoles - FLUCONAZOLE Tablets USP 200 mg
- **1980**: Echinocandins - Micafungin for Injection 50 mg per vial
- **1990**: Fungersps - EEXAFEMI

Resistance:
- **1970**: Azole resistance
- **1980**: Echinocandin resistance
- **2000**: Increase in vulnerable population
- **2010**: Drug resistant fungi (Aspergillus, Morales)

Adapted from Scynexis Corporate Presentation, January 2024.
Challenges in Antifungal Treatment

- Metabolically similar to human cells
- Significant time to confirmed diagnosis
- Rare strain identification
- Lack of broad spectrum drugs
- Poor safety profiles

Antifungal Targets

- Inhibition of nucleic acid synthesis: fluoytosine
- Inhibition of protein synthesis: sodarins, azasordarins
- Disruption of microtubules and inhibition of mitosis: griseofulvin
- Disruption of cell wall: echinocandins, nikkomycin
- Disruption of cell membrane: azoles, allylamines

Fungal Cell

- **inhibition of nucleic acid synthesis**
  - flucytosine

- **inhibition of protein synthesis**
  - sodarins
  - azasordarins

- **disruption of microtubules and inhibition of mitosis**
  - griseofulvin

- **disruption of cell wall**
  - echinocandins
  - nikkomycin

- **disruption of cell membrane**
  - azoles
  - allylamines
  - polyenes
Three Major Classes

Polyenes

Natamycin

Azoles

Efinaconazole

Echinocandins

Caspofungin

Three Major Classes

Polyenes

Echinocandins

Azoles
Polyenes

Nystatin
1950

Amphotericin B
1956

Natamycin
1954

Polyenes

Amphotericin B
1956

Mycosamine

Lipophilic region

Hydrophilic region

Polyenes – Mechanism of Action

Polyenes – Mechanism of Action

Polyene → sponge complex → Sterols → polyene-sterol complex

Pore formation
Loss of intracellular ions
Membrane deformation
Sterol depletion

Polyenes – Mechanism of Action

Polyenes – Mechanism of Action

Polyenes – Mechanism of Action

Elion Therapeutics – Amphotericin B Derivative

Elion Therapeutics – Amphotericin B Derivative

Amphotericin B
- potent
- renal toxic

C2’EpiAmpB

Elion Therapeutics – Amphotericin B Derivative

Elion Therapeutics – Amphotericin B Derivative

Sterol Sponge Complex

polyene
sterol

Elion Therapeutics – Amphotericin B Derivative

Amphotericin B
potent
renal toxic

C2′EpiAmpB
Less potent
renal sparing

Elion Therapeutics – Amphotericin B Derivative

Amphotericin B
potent
renal toxic

C2’EpiAmpB
Less potent
renal sparing

AM-2-19

AM-243-2
more potent
renal toxic

Elion Therapeutics – Amphotericin B Derivative

Azoles
Azoles

Fluconazole
1990

Efinaconazole
2014

Isavuconazole
2015

Azoles

Fluconazole
1990

Efinaconazole
2014

Isavuconazole
2015

Azole Target – Ergosterol Biosynthesis

Azole Target – Ergosterol Biosynthesis

Squalene → Lanosterol → Ergosterol

Azole Target – Ergosterol Biosynthesis

Azole Target – Ergosterol Biosynthesis

Lanosterol → CYP51 → Ergosterol
Azole Target – Ergosterol Biosynthesis

Lanosterol

CYP51

Azole Target – Ergosterol Biosynthesis

Lanosterol

CYP51

Azole Target – Ergosterol Biosynthesis

Lanosterol

CYP51

Azole Target – Ergosterol Biosynthesis

Lanosterol

CYP51

Azole Target – Ergosterol Biosynthesis

Lanosterol

CYP51

Azole Target – Ergosterol Biosynthesis

Lanosterol

CYP51

Azole Target – Ergosterol Biosynthesis

Lanosterol

CYP51

α-methyl Ergosterol

toxic to fungi, cell membrane deformed

Echinocandins

Caspofungin
2001

Micafungin
2005

Echinocandins

Caspofungin
2001

Micafungin
2005

Cyclic peptide

Lipophilic side chain

Echinocandins – Mechanism of Action

Inhibition of glucan synthase weakens cell wall fungal specific

Drawbacks

- Poor Oral Bioavailability: echinocandins, polyenes
- Non-Specific Binding: azoles, polyenes
- Strain-Variable Activity: all classes
- Drug Resistant Strains: emerging problem

*the development of novel antifungals is essential to combat these issues*

Novel Drugs, Novel Mechanisms, Novel Delivery

Ibrexafungerp
Rezafungin
Fosmanogepix
Opelconazole
Olorofim

Novel Drugs, Novel Mechanisms, Novel Delivery

Ibrexafungerp
Rezafungin
Fosmanogepix
Opelconazole
Olorofim

Rezafungin – Cidera

Second Generation Echinocandin
FDA approved, March 2023

Candidiasis
>400k worldwide
46-75% mortality


phase 3 clinical trials
prophylaxis for allogeneic blood
And marrow transplantations
Anidulafungin derivative

Novel Drugs, Novel Mechanisms, Novel Delivery

Opelconazole – Pulmocide

Significantly increased potency
improvement over standard care

Aspergillosis
usually lung localized

Lung retention
low systemic exposure

designed for inhalation
first triazole of this design

https://pulmocide.com/opelconazole/
Opelconazole – Pulmocide

Aspergillus Fumigatus in lung transplant patients

https://pulmocide.com/opelconazole/

Opelconazole – Pulmocide

Aspergillus Fumigatus in lung transplant patients

Patient 1

pre-treatment

Patient 2

pre-treatment

https://pulmocide.com/opelconazole/
Aspergillus Fumigatus in lung transplant patients

Patient 1

Pre-treatment

2 weeks treatment

Patient 2

Pre-treatment

2 weeks treatment

https://pulmocide.com/opelconazole/
Opelconazole – Pulmocide

Aspergillus Fumigatus in lung transplant patients

Patient 1

pre-treatment 2 weeks treatment off treatment

Patient 2

pre-treatment 2 weeks treatment 4 weeks treatment

https://pulmocide.com/opelconazole/
**Novel Drugs, Novel Mechanisms, Novel Delivery**

Ibrexafungerp
Rezafungin
Fosmanogepix
Opelconazole
Olorofim

Ibrexafungerp – Scynexis

first non-azole oral treatment for yeast infections

Triterpenoid – First in class 2021


disruption of cell wall
similar mechanism to echinocandins
limited off-target effects

oral and IV administration

novel binding site
activity against echinocandin- and azole-resistant strains

GSK collaboration for IV formulation in clinical trials

Novel Drugs, Novel Mechanisms, Novel Delivery

Fosmanogepix – Ampyx-Pfizer-Basilea
Desired Drug Compound – 2003
Interference with cell wall localization of mannoproteins

1-(4-butylbenzyl)isoquinoline (BIQ)

MIC: 1.56 μg/mL

Fosmanogepix – Amplyx-Pfizer-Basilea

Fosmanogepix – Mechanism of Action
Fosmanogepix – Mechanism of Action
Fosmanogepix – Mechanism of Action
Fosmanogepix – Compound Screening

1-(4-butylbenzyl)isoquinoline (BIQ)

Aspergillosis unaffected by BIQ

metabolically unstable
easily degraded

Fosmanogepix – Compound Screening

Fosmanogepix – Compound Screening

1

\[ \text{Pyridine} \rightarrow \text{Thiazole} \rightarrow \text{Phenyl} \]

3A R1: NH₂; R2: H; R3: m-F

3B R1: H; R2: NH₂; R3: m-F

3C R1/R2: NH₂; R3: H

3D R1/R2: NH₂; R3: p-F

2

\[ \text{Pyrazine} \rightarrow \text{Thiazole} \rightarrow \text{Phenyl} \]

4

\[ \text{Pyrazine} \rightarrow \text{Thiazole} \rightarrow \text{Phenyl} \]

Fosmanogepix – Compound Screening

<table>
<thead>
<tr>
<th>Compound</th>
<th>C. albicans</th>
<th>A. fumigatus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>1.56</td>
</tr>
<tr>
<td>2</td>
<td>0.39</td>
<td>3.13</td>
</tr>
<tr>
<td>3A</td>
<td>1.56</td>
<td>N.T.</td>
</tr>
<tr>
<td>3B</td>
<td>0.05</td>
<td>0.78</td>
</tr>
<tr>
<td>3C</td>
<td>0.78</td>
<td>1.56</td>
</tr>
<tr>
<td>3D</td>
<td>0.39</td>
<td>0.78</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.78</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BIQ</td>
<td>1.56</td>
<td>N.T.</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.39</td>
<td>N.T.</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>1.56</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Lots of variability tolerated

1-2 atom linkers preferred

Isosteres
Pyridinyl, phenyl

Rigidify
Isoxazoles

Optimized

Fosmanogepix – Structure Activity Relationship

- **Optimized**
- **Isosteres**
  - Pyridinyl, phenyl
- **1-2 atom linkers preferred**
- **Rigidify**
  - Isoxazoles
- **Lots of variability tolerated**

**Fosmanogepix – Structure Activity Relationship**

- **Rigidify isoxazoles**
- **1-2 atom linkers preferred**
- **Lots of variability tolerated**

**Optimized**
- **Isosteres**
  - Pyridinyl, phenyl

**Fosmanogepix**
- improved aqueous solubility

*good safety profile, in trials for invasive Candida infections.*

Novel Drugs, Novel Mechanisms, Novel Delivery

Olorofim – F2G

Orotomide – First in class in clinical trials
Olorofim Mechanism of Action – F2G

inner mitochondrial membrane

outer mitochondrial membrane

dihydroorotate dehydrogenase

Olorofim

Oliver, J. D. et al. PNAS. 2016, 113(45), 12809–12814.
Olorofim Mechanism of Action – F2G

Oliver, J. D. et al. PNAS. 2016, 113(45), 12809–12814.
Olorofim Mechanism of Action – F2G

DHODH

Olorofim

Mechanism of Action – F2G

Dihydroorotate  \rightarrow  Olorofim

Orotate

Uridine 5’-monophosphate

Olorofim Mechanism of Action – F2G

- Inhibition of nucleic acid synthesis
- Pyrimidines in RNA/DNA
- Disruption of cell wall
- Glucan and chitin synthesis

Cell cycle arrest

Oliver, J. D. et al. PNAS. 2016, 113(45), 12809–12814.
Olorofim – F2G

**novel mechanism**
activity against multi-resistant strains

**good bioavailability**
oral dosing, good tissue penetration

**CNS activity**
potential *Coccidioidomycosis* treatment

**fungal specificity**
minimal cross reactivity with human DHODH

**unique, complementary spectrum**
activity against molds, thermally dimorphic fungi

At a Glance

**The Past**
- Polyenes
- Azoles

**The Future**
- Echinocandins
- Fungal Cell
- Ibrexafungerp
- Rezafungin
- Fosmanogepix
- Opelconazole
- Olorofim