World-Café
Wrap-up

HFP2019: Molecular Mechanisms of Host-Pathogen Interactions and Virulence in Human Fungal Pathogens

18-24 May 2019 | La Colle sur Loup, France

19 May 2019

What is it about

- Large group dialogue
- One table-one topic
- Each table has:
  - One expert
  - One moderator
  - Up to 5 participants

- 3 rounds of discussion with rotations in between
  1. What are the recent discoveries that influenced the field?
  2. What are the main challenges in the field?
  3. What should we aim for?

- Aim: to collect and exchange ideas on a topic of mutual interest

Participants

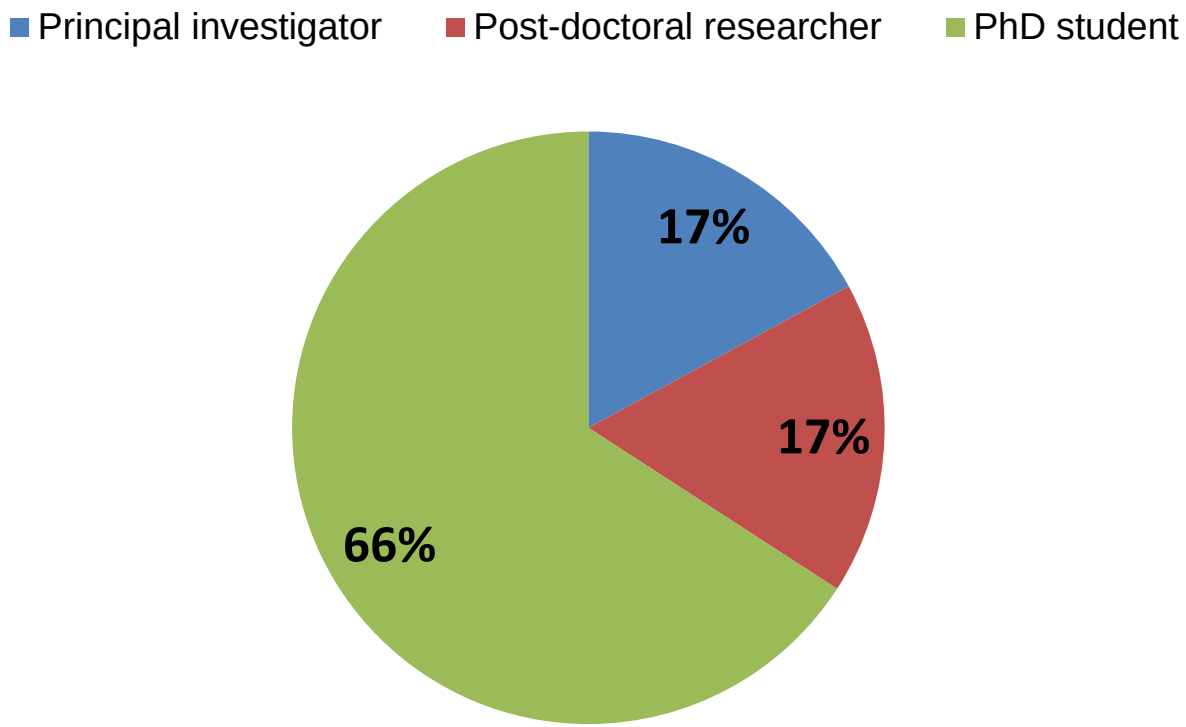

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Table / topics

1. How far we are in understanding **fungal pathogenicity** mechanisms?

Expert: Janet Quinn,
Moderator: João Oliveira Pacheco

2. Which **antifungal weapons** do we have to fight against fungal infections?

Expert: Jose Lopez-Ribot,
Moderator: Mansoureh Vatanshenassan

3. **Underestimation** of fungal infections

Expert: Oliver Kurzai,
Moderator: Antonio Pérez Hansen

4. Small talks within the **microbiome** members

Expert: Christian Pérez,
Moderator: Elise Iracane

5. **NGS** and the future of diagnostics of fungal pathogens

Expert: Christina Cuomo,
Moderator: Verónica Mixão

6. Attempts to solve the **host response**

Expert: Ilse Jacobsen,
Moderator: Marina Pekmezovic

7. Development of **diagnostic tools**, modern technologies in the global regulatory landscape

Expert: Markus Kostrzewa,
Moderator: Frank Sauer

8. **Virulence (and avirulence) factors** of fungal pathogens

Expert: Bernhard Hube,
Moderator: Sofia Siscar-Lewin

Table 1

How far we are in understanding fungal pathogenicity mechanisms?

Expert: **Janet Quinn**

Institute for Cell and Molecular Biosciences
Newcastle University
United Kingdom

Moderator: **João Oliveira Pacheco**

Conway Institute
University College Dublin
Ireland

Table 1

How far we are in understanding fungal pathogenicity mechanisms?

1. Looking for only one or few traits of virulence - instead of looking to the pathogen as multifactorial platform
2. Good data is out there, but we are still missing accessible tools to mine that data
3. Define better pathogenicity

1.Moving away from the classical virulence traits like the morphology and look more at the metabolic side of it
2. "Listen" more what the host has to "say"
3. Is YPD the best medium to perform our experiments? Can we do it better?

1.Genotype-phenotype correlation from a more complex context such as microbiome correlation with infection
2. Single cell biology
3. Build new infection models, less artificial
4. Immuno-therapy

Table 2

Which antifungal weapons do we have to fight against fungal infections?

Expert: **Jose Lopez-Ribot**

Department of Biology
The University of Texas at San Antonio
USA

Moderator: **Mansoureh Vatanshenassan**

Bruker Daltonic
Bremen
Germany

Table 2

Which antifungal weapons do we have to fight against fungal infections?

- **Limited number and efficacy of current antifungals – we need new and better drugs!**
- **New antifungals under development**

❖ **"New" molecule, but "old" target**

1- Company: Viamet	Target: Ergosterol synthesis
2- Company: Cidara Therapeutics	Target: β-glucan synthesis (Extended life echinocandins)
3- Company: Scynexis Inc.	Target: β-glucan synthesis

❖ **New molecule (component), and new target**

1- Company: Amplyx Pharmaceuticals	Target: GPI anchor of cell wall proteins
2.- Company: F2G	Target: Fungal pyrimidine biosynthesis

Table 2

Which antifungal weapons do we have to fight against fungal infections?

Challenges to develop a new antifungal drug

- Limited number of “selective” targets
- Consideration of Toxicity/Resistance
- Poor *In vivo*/*In vitro* correlation
- Time and Money (15 years and 2 billion dollars)

A better future by:

- Increase awareness of fungal infections
- Better diagnostics and develop a new rapid susceptibility method
- New antifungals (better possibilities for combination = better treatment)
- Advances in formulations
- Role for Anti-virulence approaches?
- OVERALL: Towards individualized treatment of fungal infections

Table 3

Underestimation of fungal infections

Expert: **Oliver Kurzai**

University of Würzburg
Germany

Moderator: **Antonio Pérez Hansen**

Medical University of Innsbruck
Austria

Table 3

Underestimation of fungal infections

-Concept of underestimation:

Political-underestimation

Scientist-overestimation

-Resistance and clinical impact

-Raising awareness

Proper scientific communication

Collaboration across fields

Table 4

Small talks within the microbiome members

Expert: **Christian Pérez**

University of Würzburg
Germany

Moderator: **Elise Iracane**

University College Dublin
Ireland

Table 4

Small talks within the microbiome members

Mycobiome

Underestimation of the fungi compared to bacteria in the microbiome

➔ Need a strong fungal database and DNA extraction technics toward fungal DNA extraction

Area post metagenomics: How to go from genes to isolated strains?

➔ Need to go back to basic microbiology culture technics

Micro-organisms interactions and how to study them

➔ Need to start by study them 1 to 1 and then add more complexity

Future of the field needs new technics like:

➔ Single cell imaging to follow species localization or gene expression
➔ Creation of a synthetic community for personalized medicine, including the host genetic background

Table 5

NGS and the future of diagnostics of fungal pathogens

Expert: **Christina Cuomo**

Broad Institute
USA

Moderator: **Verónica Mixão**

Centre for Genomic Regulation
Spain

Table 5

NGS and the future of diagnostics of fungal pathogens

1. Are we using NGS in clinical labs? Why?

- The first thing we need to define is: **"What do we want?"** -> question raised in all rounds
- Is it worth to use use NGS for **identification** when we have MALDI? -> Clinical labs want immediate result
- What about **resistance**? PCR is still a good option, and phenotype is more important than knowing all SNPs in the genome
- There are other solutions (eg. microscopic changes to give an MIC output in hours (BioFire))

NGS is still far from being present as a routine in clinical mycology labs

2. So how could NGS be applied?

- There is a shift in the **epidemiology** -> study of outbreaks (*Candida auris*, are there more?)
- Can **transcriptomics** be used to **monitor host response** and use it to chose the treatment? -> We need signatures of host response
- Need for better extraction, adapt to the low volume samples, …
- Personalized medicine

Baby steps - study WGS alongside other diagnostics… it may take time for clinicians to adopt

Table 5

NGS and the future of diagnostics of fungal pathogens

3. In a potential use of NGS in the clinics, which challenges does this data pose?

- Cost
- Challenges of dealing with “big data” -> needo od pipelines for data analysis -> automation
- Data storage challenges:
  - ✓ Amount of data - use database that contains all information but focus on a specific locus or if using for diagnostics then may not need to save data (if used in research- need to keep data)
  - ✓ New species and need to continually adapt -> misidentifications?
  - ✓ Data storage and security -> possibility for misuse

It is still not clear how to surpass all these problems

Use of NGS in clinical labs might take some years -> join research and diagnostics at the lab

Table 6

Attempts to solve the host response

Expert: **Ilse Jacobsen**

Hans-Knöll Institute,
Germany

Moderator: **Marina Pekmezovic**

Hans-Knöll Institute,
Germany

Table 6

Attempts to solve the host response

Fungal immunology: required cross-sectional approach

Discoveries that shape the research we have today

Lack of knowledge and application of relevant host conditions in our experiments

Ubiquitous presence of fungi/commensalism

Models in the research: limitation, reproducibility

Need for better data integration and relation to each other

Pathogen/host variability

Genetic susceptibility of the host:

Many data, but still lacking of clinical application

Problem of personalized approach: economical aspect and decision making

Translating basic research into the diagnostic

Studies limitations

Panel of parameters?

Future of big data

Table 7

Development of diagnostic tools, modern technologies in the global regulatory landscape

Expert: **Markus Kostrzewa**

Bruker Daltonic
Bremen
Germany

Moderator: **Frank Sauer**

QVQ
The Netherlands

Table 7

Development of diagnostic tools, modern technologies in the global regulatory landscape

- Diagnostics and treatment coexist in the clinical world, both determine the outcome of patients
- Bad quality or erroneous diagnostics/ treatments endanger lives
- In a capitalistic system money sharks will try any way to generate income, therefore regulation control of diagnostics is necessary
- In the USA (FDA) and China (CFDA) state authorities are responsible for regulations and are considered as very strict
- In the EU no state authority is directly involved in regulation, the IVD directive, defines a legal framework manufacturers of diagnostic tools have to comply with
- EU: for low risk diagnostics, self certification by the manufacturers is possible that requires extensive documentation
- EU: For approval of high risk diagnostics about 6 companies within the EU are responsible, the process is very costly

Table 7

Development of diagnostic tools, modern technologies in the global regulatory landscape

- Public funding for diagnostics development is rare
- Validation data acquired in Europe is accepted in many countries around the world, though risk classifications may differ between the countries and impede direct approval
- A supplier of diagnostics has to monitor their performance and is responsible for failures in spite of correct application, this is a heavy financial burden for small companies
- Complexity of diagnostic systems is constantly increasing and pressure towards automation is high
- Diagnostic labs do not necessarily buy the best test system, cost-effectiveness and usability have priority

Table 7

Development of diagnostic tools, modern technologies in the global regulatory landscape

- Due to increasing complexity of the diagnostics systems new IVD regulations will become effective in the EU in 2020, which will make future evaluations simply more complicated and expensive

- Owed to these new regulations it is expected that small diagnostic companies will cease to exist unless they become part of big companies.

Table 8

Virulence (and avirulence) factors of fungal pathogens

Expert: **Bernhard Hube**

Hans-Knöll Institute,
Germany

Moderator: **Sofia Siscar-Lewin**

Hans-Knöll Institute,
Germany

Table 8

Virulence (and avirulence) factors of fungal pathogens

Pathogenicity: ability to cause damage and disease
Virulence: degree of damage that pthogen can cause

How to measure virulence:

- Host side: death, fitness, disease symptoms (fever, body weight..)
- Pathogen side: survival to immune cells (phagocytosis), LDH release..

Virulence factors: microbial effectors that cause damage

- Offensive
- Unspecific

The host context is determinant for the disease outcome of a host-microbe interaction

Avirulence factors: those factors that can be recognized by the host and trigger protective host rsponse, which stops the infection and render pathogen avirulent

Casadevall and Pirofski Nat Rev Microbiol. 1:17-24. The damage-response framework of microbial pathogenesis (2003)

Thank you for your attention!

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