***Malassezia*: from skin to model species**

From July 4-6, the Westerdijk Fungal Biodiversity Institute, Utrecht, the Netherlands hosted a post-ISHAM2018 workshop focusing on *Malassezia* research. Organizers Teun Boekhout (Westerdijk Fungal Biodiversity Institute, the Netherlands) and Thomas Dawson Jr. (Skin Research Institute of Singapore, A\*STAR, Singapore) brought together 65 scientists, clinicians and industry representatives from 25 countries to share expertise and strengthen future *Malassezia* research. Additionally, this opportunity was used to explore the feasibility of combining forces between the ISHAM *Malassezia* working group and the *Malassezia* Research Consortium. Divided over 4 main themes, 30 experts in the field shared their latest research and perspectives on *Malassezia* related topics.

**Ecology, diversity and microbiome**

After the genus *Malassezia* was created by Baillon in 1889, it consisted of only *M*. *furfur* and *M*. *pachydermatis* for over a century. Multiple new species have since been described from human skin and various animal hosts and the genus currently stands at 18 species with significantly more complexity at the strain and phenotype level. In recent years, sequence based approaches such as metagenomics have found *Malassezia* in wider ecological niches such as insects, nematodes, corals, sponges, deep-sea environments, and soils. Historically, *Malassezia* were considered to grow only at higher temperatures (of around 30°-40oC) and be lipid dependent, so these recent environmental sightings indicate that more research is needed to elucidate the role of environmental *Malassezia*.

Clearly, in the vast majority of microbiome studies most attention went to bacteria via 16S sequencing. Only recently have metagenomics and ITS technology based approaches enabled inclusion of fungi (specifically *Malassezia*, being the most abundant fungal component in the skin mycobiome) and thus they been receiving more attention for their role in microbial communities in and on the human body. However, there is still a lack of insight on the complex interplay between *Malassezia*, other microbes and the human host. From multiple presentations, it also became clear that the exact role of *Malassezia* on and in humans and animals needs further exploration: is it a commensal, a pathogen or beneficial microbe, or can it switch between these states?

Association and causation for involvement in various skin disorders has been generally accepted but *Malassezia* is also present as a skin commensal and a recent publication by Li et al (J. Invest. Dermatol. 2018) reported on the potentially beneficial role of *Malassezia* for skin health by secretion of a protease which reduces biofilm formation by *Staphylococcus aureus*.

**Host Microbe and Biochemistry**

In cases where *Malassezia* seem to be involved in pathogenesis, other than the fatty acid mediated induction of scalp flaking, the mechanisms remain largely unclear. Various groups have developed model systems to study the interactions between *Malassezia* and its host. The Leibundgut lab in Zürich, Switzerland has a working mouse model but due to EU regulations for materials to be included in cosmetic products industry seems reluctant to be involved in animal work. Also, translation of results from animal models to humans is a point of contention. A number of human *in vitro* models such as 2D and 3D skin models and organoids are available or under development for studying host-*Malassezia* interactions. Various presenters zoomed in on facets of these interactions, such as specific host immune response triggering, exosome-like nanovesicles carrying allergens, and virulence factors adhesion, cell surface hydrophobicity (CSH) and biofilm formation. Lipid dependence in *Malassezia* is now being more deeply explored to understand how this yeast uptakes fatty acids from the host and how these are incorporated into lipid metabolic pathways and/or used for *Malassezia*/host signaling. Additionally, lipidomic analyses have revealed branched fatty acid esters of hydroxy fatty acids (FAHFAs) - a new class of lipids - potentially being involved in host anti-inflammatory effects.

**Clinical, Therapy and Diagnostics**

As most clinical testing uses standard (low lipid) culture media and therefore may cause significant under diagnosis of *Malassezia* mediated disease, the use of lipid supplementation needs to be promoted for clinical use. Recent research findings may lead to improved culture conditions that more accurately resemble *in vivo* environments. For multiple *Malassezia* species, intraspecies variability exists for features traditionally used for identification, such as morphology and physiology. These methods are often difficult to reproduce. How do we define species boundaries and are multiple species or genotypes involved in pathogenesis, including sepsis? There are some developments for improved diagnosis of *Malassezia*-related disorders/diseases applying molecular approaches such as Q-PCR. Both the veterinary and human clinical fields would benefit from such assays after being validated for clinical use. From multiple presentations and the general discussion it became clear that there is a need for standardization concerning antifungal species/strain typing and susceptibility testing as well as treatment guidelines. Some occasions of *Malassezia* antifungal resistance have already been reported, which stresses the need for alternative drugs in future treatment strategies. Some potential drugs and drug targets were discussed in the workshop presentations. A point of concern is that (alternative) treatments may also affect commensal microbiota impacting the potentially protective role of *Malassezia* on skin.

**Molecular Biology, Genetics and Genomics**

In recent years, many advances were made in genomics and genetics, paving the way for studying functional aspects of *Malassezia* and its host interactions. Several presentations elaborated on the presence of mating loci suggesting *Malassezia* may sexually reproduce. Some preliminary data were shown on a possible mating within *M. furfur.* The presence of hybrids in *Malassezia furfur*, a heterogenous species complex, was discussed and another speaker reported on multiple horizontally transferred genes, which allowed *Malassezia* to acquire features from bacteria. Comparative genomics of *Malassezia pachydermatis* was used to pinpoint the genomic origin of ketoconazole resistance illustrating the potential of such approaches for understanding resistance mechanisms for diagnostics and treatment. Finally, successful recent development of transformation and gene deletion approaches in *Malassezia* made gene function studies possible and will significantly contribute to the further unravelling of the role of *Malassezia*.

**Concluding remarks**

The workshop ended with a general discussion to reflect on topics presented and to explore future needs. A clear need emerged for standardization in various fields of *Malassezia* research, ranging from better-defined taxonomic boundaries, diagnostics guidelines, susceptibility testing, treatment, and model systems for studying *Malassezia*/host interactions.

To advance the *Malassezia* field and enhance cross talk between clinically oriented and basic scientists, a merger of the ISHAM *Malassezia* working group and the *Malassezia* Research Consortium was strongly promoted. To realize this merger a new board (2018-2021) with Teun Boekhout (chair), George Gaitanis (secretary), and Annika Scheynius and Carol Munro (members) was established. Several subgroups will deal with clinical aspects, e.g. standardization of diagnostics and susceptibility testing, how to assess diversity, including metagenomics, and basic sciences aiming to better understand functional relationships on and in humans and animals. Longitudinal cohort studies are needed not only focusing on single *Malassezia* strains but also on entire microbial communities including *Malassezia*, skin inhabiting mites, and host parameters. In order to achieve all this, there is a strong need for funding and a white paper stressing the need for *Malassezia* research funding opportunities.

We look back at a very successful meeting that opened many opportunities for further and new collaborations. A follow up workshop is planned for 2020 in Singapore.

July 23, 2018, Bart Theelen and Adriana Celis