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Rising to the challenge of multiple *Cryptococcus* species and the diseases they cause

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ABSTRACT

Cryptococcus neoformans and *Cryptococcus gattii* are well-studied basidiomyceteous yeasts that are capable of causing disease in healthy and immunocompromised people. The Conference on *Cryptococcus* and Cryptococcosis (ICCC) is held every three years: the accompanying Special Issue stems from the 9th ICCC and covers a subset of the topics related to these fungi in detail. This conference started with a revised and reduced estimate of disease burden globally, in part due to improved treatment for HIV$^+$ people. However, mortality from cryptococcosis remains consistently high for those unfortunate to have limited access to therapies or without underlying immunodefiencies. As such, there are yet still great distances to be covered to address antifungal drug availability, the need for new antifungal agents and the timing and doses of these agents in conjunction with antiviral therapy, underscoring the importance of continued research. A notable point from the 9th ICCC was the research addressing the variation in the pathogen and host populations. Analysis of cryptococcal strain variability, particularly at the molecular level, has resolved distinct lineages with the consequence of a taxonomic revision that divides *C. neoformans* and *C. gattii* into seven *Cryptococcus* species. Similarly, analysis of host factors in so called "immune-competent" individuals revealed previously unrecognized risk factors. Research on these species has established them as important model organisms to understand gene evolution and function in other fungi and eukaryotes. The stage is set for the refinement of research directions, leading ultimately to better treatment of this pathogenic monophyletic clade in the genus *Cryptococcus*.

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1. Introduction

Cryptococcus neoformans was first described over a century ago as a yeast growing from an environmental source and from a human patient (Perfect and Casadevall, 2011; Srikanta et al., 2014). Since that time and particularly as a consequence of AIDS, the fairly rare fungus in clinical settings emerged to become one of the world's most problematic killers (Park et al., 2009). The medical mycology community stepped up to face this challenge at the start of the AIDS pandemic, brought in a number of new investigators and explored different angles of the fungus and disease it causes. One consequence was the organization of the International Conference on *Cryptococcus* and Cryptococcosis (hereafter ICCC), held roughly every three years since 1989 (Kwon-Chung et al., 2012). First held in Jerusalem and then subsequently Milan, Paris, London, Adelaide, Boston, Nagasaki, and Charleston, the 9th conference was held in Amsterdam, 15–19 May 2014, bringing together the largest group thus far of 303 investigators to discuss the latest discoveries on the fungus and disease.

In addition to the trends of change and adoption of new technologies that are often presented at scientific meetings, a notable feature of the 9th ICCC was the research indicating that this is neither a single pathogen nor a single patient population. The variability between pathogens and hosts has been appreciated for many years. From the fungal side this has resulted in the separation of strains into different serotypes, varieties, groups based on molecular markers, and establishing two species *C. neoformans* and *Cryptococcus gattii* (Kwon-Chung, 1976; Kwon-Chung et al., 2002). Hosts include diverse animal species (Malik et al., 2011), and for the human host a separation into immune status such as HIV$^+$, otherwise immunosuppressed, and other unknown susceptibilities. However, there is now greater realization of the different fungal subtypes and their biology and the underlying immune

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status of the patient population, and consequences in clinical outcome.

This issue has 10 articles that provide the current state-of-the-art in specific areas related to the biology of the *Cryptococcus* species and host factors that shape the outcome of the infection. These are selected to highlight some key areas in the field, and by no means would this collection be considered comprehensive. Two books on the topic are valuable references (Casadevall and Perfect, 1998; Heitman et al., 2011). The abstracts from the talks and posters from the 9th ICCC are also available in a special issue of *Mycoses* (2014 volume 57). We can anticipate a series of exciting publications based on the data presented at the conference. With the rest of this editorial we aim to unite the papers in this issue in a wider context of the latest developments in research on *Cryptococcus* and beyond, and draw attention to the overlaps between particular topics.

2. Cryptococcosis as a major global health problem

How serious a problem is cryptococcosis? A much cited article on the global incidence and impact of cryptococcosis estimated 624,700 deaths each year, within wide confidence intervals of 125,000 to 1,124,900 (Park et al., 2009). Most articles use the 625,000 figure, and the cryptococcosis calculations are the basis of global estimates of mortality due to all fungal diseases (e.g. Armstrong-James et al., 2014; Brown et al., 2012). At the 9th ICCC David Boulware presented revised estimates of cryptococcosis mortality that drop that of Park et al. by about half. While this is still within the original range proposed by Park et al., this decreased mortality is also in part due to improved treatment that occurred in the last five years and reflects genuine medical advances in some countries. Other talks addressed the changing demographics of the patient population with cryptococcosis. For example, the trend presented by John Perfect at the ICCC was for decreased mortality in the HIV positive population in developed countries, but not amongst the "otherwise healthy" group. This is borne out by recent estimates of mortality rates in the United States, with 80% of people succumbing to the disease in the last 11 years not being HIV positive, in contrast to the early days of the AIDS pandemic (Barragan et al., 2014).

While countries like the U.S.A. and in Europe may have made major inroads in treating cryptococcosis and mortality overall has decreased, other parts of the world are not so fortunate. Dr. Boulware described experiences in testing the timing of the initiation of antiviral treatment in cryptococcosis patients in Uganda (Boulware et al., 2014a), and commented that a medical innovation was a set of hooks placed in the walls from which to hang drips. His comments about the severity of cryptococcosis in Uganda were also supported by Thomas Harrison in the opening address, noting that mortality rates are consistently at about 75% in South Africa. This is borne out by other experiences in Africa. For example, recent studies looking at two doses of fluconazole treatment in Malawi reported 10-week mortality rates at 55% and 57% (Gaskell et al., 2014; Rothe et al., 2013).

One article in this issue covers the raising concerns of cryptococcosis in China (Fang et al., 2015). The impact on cryptococcosis on the world's most populous country remained little known for many years (Yuchong et al., 2012), and the current article provides a snap shot of the progression of this disease and the causative agents. Many of the patients are described as immune-competent, indicating that there may be some genetic or other risk factors associated with this ethnic group. One risk correlates with alleles of the Fcγ receptor that bind opsonized pathogens (Hu et al., 2012). Other articles and talks at the 9th ICCC addressed the distribution of the disease and strains in other parts of the world. In light of the estimates of global disease burden, accurate assessments are vital to provide a rationale to agencies to invest in efforts to combat this disease.

Research on *Cryptococcus* species and the diseases should remain a priority in terms of finding new or refining current strategies for treatment and to elucidate the underlying basic biology needed to bring these to fruition. However, clinical findings provide evidence that treating cryptococcosis is complex, the outcome is heavily influenced by socioeconomic conditions, and that combating the disease requires more than just administration of antifungals to a patient.

3. The *Cryptococcus* species and their detection

A mycology trend has been the revision of the names of species, usually based on insight gained from molecular approaches of cryptic species, but also driven by abolishing sections of the Code of Botanical Nomenclature under which fungi were named (de Hoog et al., 2013). Characterization of *Cryptococcus* strains from around the world has resolved distinct groups, and hence *C. neoformans* and *C. gattii* are further divided into serotypes, varieties, VN or VG subgroups, or molecular marker profile numbers. It is striking to note that the first talk of the inaugural ICCC in 1989 was titled "Genetic basis for the current taxonomic system of *Cryptococcus neoformans*" as given by June Kwon-Chung, and discussions on revisions to naming – possibly with groups being species – have been spirited at subsequent meetings (Kwon-Chung et al., 2012). Hagen and colleagues provide a new and long-awaited nomenclature for the organisms in what is sometimes termed the "*Cryptococcus neoformans* species complex" (Hagen et al., in press). There have been challenges to produce a new naming system; for instance, many isolates in different lineages are capable of fusion with others during the sexual cycle. Indeed the type strain for *C. neoformans* is a hybrid of two species (Hagen et al., in press; Kwon-Chung and Varma, 2006). Under the new nomenclature, *C. neoformans* refers to those strains considered serotype A or var. *grubii*, and *C. deneoformans* for serotype D or var. *neoformans*. Strains of *C. gattii* will be divided into five species: *C. gattii*, *C. bacillisporus*, *C. deuterogattii*, *C. tetragattii* and *C. decagattii*. This nomenclature provides a way to refer to these organisms rather than the current mix of non-standard terms.

An essential step in the treatment of cryptococcosis is first being able to make an accurate diagnosis and to do so as quickly as possible (Perfect and Bicanic, 2015). The methods to do this have changed over time, with the latest being a lateral flow assay (LFA) that relies on antibody detection of the fungal glucuronoxylmannan in the capsule. This assay offers a number of benefits over previous methods, including accuracy (Boulware et al., 2014b; Tang et al., 2015). One disadvantage of LFA is the inability to resolve the strain subtypes (or species) with the pathogenic *Cryptococcus* species clade, as was possible using the serotyping system from Iatron Laboratories (Tokyo, Japan) that is no longer available. It is worth reflecting that the need for rapid and accurate strain classification in different groups was instrumental in the development of molecular-based methods that then revealed underlying unique subgroups within the species (e.g. Meyer et al., 1993, 1999). At the same time, finding standard, easy to use and cheap clinical tools to define to species level continues to remain a goal.

4. Pathogenicity and disease

The seven species within the *C. neoformans* species complex are a rarity amongst those species in the genus *Cryptococcus* by being pathogenic to humans. MycoBank recognizes 322 legitimate species names in the genus (accessed 29 November, 2014). This monophyletic group within the genus therefore has specific capabilities

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