Mycology newsletter

The ECMM/CEMM Mycology Newsletter is mailed to the members of the national societies affiliated to the European Confederation of Medical Mycology (about 3000 in 23 different countries)

1/2005

ECMM
European Confederation of Medical Mycology
CEMM
Confédération Européenne de Mycologie Médicale

A farewell, and some thoughts for the future

First of all, let me offer you a very warm welcome to Berlin for the second Trends in Medical Mycology meeting. Our colleagues in Berlin have worked hard to put together an exciting scientific programme, and I am sure you will not be disappointed with the result. Thanks to the efforts of the Congress Care organization and the generosity of our industrial sponsors, you will enjoy a really first-class experience exploring Berlin as well as attending the sessions. We hope the TIMM meetings, to be continued every two years into the future, will continue to represent the major European venue for presentation of scientific and clinical research into fungal diseases.

The ECMM now has a website (www.ecmm.org)! It is not an all-singing, all-dancing site with lots of interactive features, but it represents a start that can be developed by future ECMM committees. Please take a look. Please let us know of your ideas for expansion and your criticisms of what we have produced.

Jacques F.G.M. Meis, new ECMM President

This will be the last piece I write for the ECMM Newsletter in the capacity of ECMM Chairman. It has been an interesting experience to represent the Confederation for the last three years. We have had two very successful meetings - the first TIMM in Amsterdam and the last ECMM-only meeting in Wroclaw - and I am sure our current TIMM in Berlin will be equally well received. The ECMM is now finding its place as a valuable asset to the international medical mycology community, and I am sure my successor, Jacques Meis, who was elected by the Committee of your national representatives, will be an energetic and inspiring Chairman to lead the Confederation into the future. I wish Jacques every success with the Confederation. I would also like to thank our Secretary, Emmanuel Roilides, our Treasurer, Martin Schaller, and our Newsletter Editor, Maria Anna Viviani, for the very hard work they have done for this society.

Perhaps you'll allow an outgoing Chairman a few final comments. The position of medical mycology as a discipline feels insecure, to judge from remarks I have heard from many member countries. There seems to be funding available for basic research involving fungi that infect humans, but the support for diagnostic medical mycology is often minimal and chronically threatened with shut-down. To judge, at least, from the situation in the UK, it is difficult to recruit good scientists to the diagnostic field. More and more we produce graduate scientists whose training leaves them excited to explore the mechanisms of gene function and regulation but less interested to run routine laboratory diagnostic tests on a day-to-day basis.

It is one thing to complain about the lack of interest of governments in funding diagnostic mycology, but it is another to do something about it. Many of you have a genuine love for the beauty of fungal colony forms and microscopic structures. I share that love; I fully understand how easy it is to complain that we are losing people with the

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Membership 2005: 270
National meeting: 4th Russian Congress of Medical Mycology, March 2006
Website: www.mycology.ru

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Membership 2005: 142
National meeting: Every two years. A workshop meeting ("Forum Micológico") is scheduled the years between National Meetings
Journal: Revista Iberoamericana de Micología
Website: www.reviberoammicol.com/AEM

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National meeting: twice a year
Website: www.oegmm.at

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National meeting: March 26-28, 2006, Dublin
Newsletter: BSMM Newsletter
Website: www.bsmm.org

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Membership 2003: 41
Website: www.bam-bg.net

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Membership 2005: 15
National meeting: 2006
Newsletter: Bulletin of CSSM

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Membership 2004: 25
National meeting: twice a year
Newsletter: Report from the Danish Society for Mycopathology

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Treasurer: P. Mayser
ECMM delegate: M. Schaller
Membership 2005: 488
National meeting: September 7-9, 2006, Innsbruck
Journal: Mycoses
Newsletter: Mykologie Forum (4 issues/year)
Website: www.dmykg.de/start2.html

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Membership 2005: 160
Newsletter: FIMUA news
National meeting: November 2006, Firenze

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Membership 2005: 82
Newsletter: Sienet ia Terveys (Fungi and Health)

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Membership 2005: 71
National meeting: June 2007
Website: www.hsmm.gr

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Membership 2005: 59

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National meeting: twice a year

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Membership 2003: 19
National meeting: twice a year

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Membership 2004: 155
National meetings: October 2005, Utrecht
Newsletter: NVMy Newsletter

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Treasurer: D.M.L. Saunte
Membership 2005: 85
Scientific Meeting: June 2006, Oslo
Newsletter: at web site
Website: www.nsmm.nu

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Secretary: J.C. Szepietowski *(ECMM delegate)*
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Membership 2005: 98
National meeting: September 2006, Bialowieza
Journal: Mikologia Lekarska (Medical Mycology)

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Treasurer: C. Lacroix
Membership 2005: 400
National meeting: November 25-26, 2005, Paris
Journal: Journal de Mycologie Médicale
Website: www.mycolmed.chez.tiscali.fr

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Membership 2005: 85
National meeting: November 2005

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Secretary: A. Ağaçfidan
Treasury: D. Yaylali
ECMM delegate: E. Tümbay
Membership 2005: 150
Newsletter: Bulletin of the Turkish Microbiological Society.

A farewell, and some thoughts for the future

(continued from page 1)

expertise to recognize and identify fungal species from their morphologies. But it is important for all of us to understand the sheer power that DNA-based techniques bring to our field. It should be possible, within a relatively short time, to use DNA-based methods of identification that will tell physicians which fungus is infecting their patient more rapidly and - believe me! - ultimately more cheaply than having someone spend hours gazing down a microscope. So "pure" mycologists need to embrace the advances in molecular technology, not just because they will make things easier and better in the long run, but also because a positive attitude to them will let young, newly graduating scientists see that diagnosis of fungal disease can be close to the cutting edge of biomedical science.

Within Europe it has always surprised me how differently individual countries view fungal diseases. For some, the diagnosis and management of superficial mycoses seems to be the dominant interest, while for others most people are concerned only with invasive diseases in immunocompromised hosts. Of course, the dominance of superficial vs systemic fungal infections often reflects economic concerns, as well as political ones, so perhaps the differences are to some extent inevitable. However, personally I think it is a shame to overemphasize one area of mycology over another. The fact that many physicians now regard dermatophytosis and genital *Candida* infections as simple clinical issues is something mycologists should regard as a successful outcome of the work they did in the 20th century. But those "simple" mycoses have previously revealed fascinating insights into possibly unusual interactions between fungi and (local) host immune responses: what a pity therefore that so very little basic, molecular research is being done in the field of superficial mycoses.

Let me end by expressing the hope that you will continue to keep the name "medical mycology" in the eye of the public and of governments. Some people who work daily with fungal pathogens regard themselves as molecular biologists, or geneticists, or immunologists, but never think of themselves as "medical mycologists". Despite this, organizations such as the ECMM continue to thrive under the medical mycology flag, and they consistently attract the interest of the diverse other specialities that utilize or research fungal pathogens. So let's be proud to distinguish invasive fungal diseases as a discipline that merits its own status. When someone asks you what you do, say "I'm a medical mycologist" and enjoy the way the conversation proceeds from that start!

Frank Odds
ECMM President

The Pan-African Medical Mycology Society founded

The *Pan-African Medical Mycology Society* (PAMMS) was founded on 25 January 2005 during a small but very successful meeting, entitled, *Medical Mycology*: The African Perspective, that was held in Hartenbos, South Africa.
The meeting was held under the auspices of the International Society for Human and Animal Mycology (ISHAM) and the European Confederation of Medical Mycology (ECMM). The PAMMS aims to stimulate contacts between clinicians and researchers with a particular interest in medical mycology from the African continent and abroad.
Diverse topics in medical mycology were presented during the meeting, ranging from yeast infections caused by *Candida* and *Cryptococcus*, to mycetoma, subcutaneous and systemic infections, and diseases caused by lesser-known fungi. This meeting indicated that Africa has much to offer in medical mycology, both from a clinical and a scientific point of view. Presenters were sponsored ISHAM, ECMM, and by the newly initiated *Africa Fund for Fungal Biodiversity and Mycotic Infections*.

Health problems in Africa are still enormous and in many parts of the continent geographically restricted and unique. In contrast to the industrial world, where prevalent and emerging disease entities are primarily linked with immunosuppression in leukemia patients or transplant recipients, African mycoses occur in healthy individuals or are associated with HIV/AIDS. The impact of cryptococcosis as an AIDS-defining disease in Southern Africa is particularly dramatic and shows high morbidity and mortality rates in spite of antifungal prophylaxis in trial subjects. The incidence of AIDS is as high as 16% of the total population, while less than 1% of AIDS patients receive antiretroviral therapy in this area. Concerted action is therefore needed to establish the incidences of fungal diseases and to decrease morbidity and mortality of major mycoses in Africa. Much progress has been made with molecular diagnostics, animal models and therapy of fungal mycetoma, particularly in areas such as the Sudan where the disease still has a high incidence. An impressive demonstration of the disease 'Noma', occurring among the poor in Sahel Africa, showed an extremely mutilating disorder of which the aetiological agent is still unknown.

Scientifically, the continent provides very interesting disease models and materials for epidemiology and population genetics. An African clade that stands out as a separate entity is known within *Candida albicans*, with clinical predilection differing from that of other clades, is being explored. Systemic infections by melanized fungi occur throughout the continent. Much progress has been made with sporotrichosis and *Sporothrix schenckii*, and presentations given at the Congress of the Southern African Society for Plant Pathology (SASPP), which was held concurrently in Hartenbos, presented much new information. Other presentations were concerned with dermatophytes, hyaline fungi, and *Histoplasma*.

The Abstracts of oral presentations and posters of the Hartenbos symposium can be viewed at www.cbs.knaw.nl, and some hard copies of the proceedings still can be obtained for free at info@cbs.knaw.nl.

The inaugural meeting of the PAMMS, the *Pan-African Medical Mycology Society*, of which mycologists of the African continent will automatically be assumed to be a member, followed the scientific symposium. A steering committee, consisting of Hester Vismer (Tygerberg, South Africa), Ifeoma Enweani (Ekpoma, Nigeria) and El Sheikh Mahgoub (Khartoum, Sudan), will look after PAMMS during its first few years. Membership of the PAMMS is free, as the *Africa Fund for Fungal Biodiversity and Mycotic Infections*, initiated by Sybren de Hoog and Jacques Meis, will cover the initial costs of the Society. Please apply for membership with Hester Vismer (hester.vismer@mrc.ac.za). The *Africa Fund for Fungal Biodiversity and Mycotic Infections* has limited resources for training of African students in Europe; applications may be sent to de.hoog@cbs.knaw.nl. A second meeting of PAMMS is scheduled for the year 2007 in South Africa.

Sybren de Hoog
Hester Vismer

Above: The famous mycetoma-group from Northeast Africa. Standing from left to right: A.H. Fahal (Khartoum, Sudan), H.M. Al-Abdely (Riyadh, Saudi Arabia), A. Moharram (Assiut, Egypt), E.S. Mahgoub (Khartoum, Sudan); sitting A.O.A. Ahmed (Khartoum, Sudan).

Below: P.A. van Damme (Nijmegen, The Netherlands) presenting on "Noma", an African disease with a very high morbidity and for which the cause is as yet unkown; maybe it is of fungal origin.

Special report on...

The 15th annual Focus on Fungal Infections conference

by
John Graybill
William J. Steinbach
Maria Anna Viviani

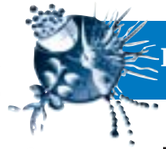
The 15th annual Focus on Fungal Infections conference was held at at the Sheraton Bal Harbor resort on Florida's Gold Coast, March 16th through 18th, 2005. Elias J. Anaissie from the University of Arkansas and Michael G. Rinaldi from the University of Texas at San Antonio co-chaired the meeting and assembled leading investigators, practising infectious diseases specialists, and laboratory microbiologists to review the state-of-the-art in disease diagnosis and management.

In his presentation and celebration of the Focus 15-year anniversary, Dr. Rinaldi remembered the discussion he had with Dr. Anaissie, after the 1st Focus meeting, concerning their project of the meeting series, the opportunity of an annual or biannual organisation, the fear of a scanty participation. Ever since, Focus meetings met with positive and ever growing appreciation from young and old mycologists.

This year's meeting hosted more than 450 attendees from 25 different countries.

Some of the current major issues facing clinicians in the management of invasive fungal infections as presented during the meeting are reported here.

Miami, Florida
16-18 March 2005



Focus on Fungal Infections

Observational surveillance programs: new trend?

The clinical evaluation of new antifungal drugs for the treatment of invasive fungal infections in high risk patients represents one of most challenging areas. Comparative clinical trials are difficult or not feasible in many areas within this field. The pressing need for new sources of clinical information relevant to the management of patients with invasive fungal infection has aroused great interest in prospective clinical surveys. (This topic was also analytically commented on by John Perfect from Duke University in his lecture given at the 6th ICCC in Boston - see box on this page). Over the last few years a variety of observational surveillance programs have been implemented and final or interim results were presented during the meeting.

Luis Ostrosky-Zeichner (University of Texas, Houston) and Alison Freifeld (Nebraska Medical Center) spoke about the Collaborative Exchange of Antifungal Research (CLEAR) registry which was sponsored by Enzon Pharmaceuticals and designed to enrol only patients treated with ABLC as primary or salvage therapy between 1996 and 2000. ABLC efficacy and safety data from 3514 patients treated in >160 hospitals in the Unites States and Canada were discussed. Analyses concerning the treatment of different fungal infections are now in press and will shortly be available.

Peter Pappas (University of Alabama at Birmingham) commented on the Transplant Associated Infection Surveillance Network (TRANSNET). The program, cosponsored by the CDC and various pharmaceutical companies, was started in March 2001 and is currently ongoing with the participation of 25 US transplant centres. As of March 2005 nearly 1000 solid organ and hematopoietic stem cell transplanted patients with invasive fungal infections have been enrolled.

More recently Fujisawa Healthcare (now Astellas Pharma US, Inc.) working with an independent scientific advisory board has developed the Prospective Antifungal Therapy Alliance (PATH Alliance™), a large network of centres in the US and Canada collecting data from all patients with invasive fungal infections regardless of antifungal treatment strategy and underlying disease. The prospective survey was introduced with a poster by Michael Pfaller (University of Iowa) and other members of the Advisory Board. Patient data are captured prospectively over a 12-week follow-up period using a Web-based electronic case report form and include assessment at diagnosis of the invasive fungal infection, systemic antifungal therapy and outcome at 12 weeks. Participants have access via the Internet to view site-specific or aggregate data through a wide variety of reports designed to provide clinically relevant information and have the flexibility to customise reports to focus on specific types of patients.

These prospective registries will provide a unique complement to randomised, controlled trials as they have the ability to capture routine clinical practice data on all patients with invasive fungal infections, offering an increased understanding of changing patterns in the fungal landscape across a broad geographic area. These capabilities are particularly relevant for rare pathogens and combination therapy, topics difficult to study in a clinical trial setting.

Maria Anna Viviani

How will prospective databases help us manage our patients with mycoses?

"… There is also an enlarging therapeutic arsenal of antifungal drugs and diagnostics. These occurrences would support more evidence-based comparative studies in these diseases. However, despite the increasing importance of these mycoses and some prospective randomized studies, many of the clinician's questions are not and will not be answered by direct comparative studies. There are a variety of reasons for lack of comparative studies in mycoses including: 1) costs; 2) subject participation; 3) length of study; 4) multicenter nature; 5) complicated patient needs; 6) rarity of infection; 7) biases of the underlying disease; 8) informed consent issues; 9) physician biases. Since widespread evidence-based studies will be limited, should we be creating retrospective and prospective databases to collect information to help allow us to understand trends in management and make decisions about therapeutic strategies? Despite its uncontrolled nature and risk for biases, I believe the answer to this question is yes!"

(From Dr. Perfect's lecture at the 6th ICCC in Boston)

Focus on Fungal Infections

Miami, Florida
16-18 March 2005

Update on antifungals

Ben de Pauw (Radboud University Nijmegen) first reviewed the status of triazole antifungals, concentrating on the emerging role of voriconazole. Voriconazole is as effective as fluconazole for mucosal and disseminated candidiasis, and about 50% of patients with fluconazole resistant candidiasis respond. However, because of the cross resistance of the CDR class of MDR pumps mediating *Candida* resistance to triazoles, voriconazole has assumed a predominant role in the treatment of mycelial infections. Voriconazole is clearly superior to amphotericin B as primary treatment for aspergillosis, including pulmonary disseminated, and central nervous system disease. The 45% response in CNS aspergillosis for voriconazole versus 9% for other licensed drugs is perhaps the most striking demonstration of efficacy. Voriconazole also prevented more breakthrough mycoses in febrile neutropenic patients than amphotericin B, though a complex evaluation showed both drugs to be similar. When used as secondary prophylaxis for patients who have survived invasive aspergillosis, voriconazole prevented breakthrough relapse in all of 11 patients. For a variety of other invasive mould infections, voriconazole had responses in the range of 30-45%, except for *Penicillium marneffei*, where 90% of patients responded. One hole for voriconazole is zygomycosis, which occurs with disturbing frequency in patients receiving voriconazole. It is unclear whether there is something specific favoring breakthrough zygomycosis or whether voriconazole prevents infections with higher virulence *Aspergillus* and other moulds, thus allowing longer survival and a lower state of immune defense which is more permissive to zygomycosis. An alternative triazole, posaconazole, in open studies of aspergillosis seems generally similar to voriconazole in salvage therapy of 40-50% of patients with invasive aspergillosis, and also had 56% responses in zygomycosis. For other moulds posaconazole appeared similar to voriconazole. While voriconazole is very well absorbed, tolerance and drug interactions with agents metabolized by cytochrome enzymes are significant limitations. Posaconazole appears to be better tolerated and with fewer drug interactions, but is available only orally and is incompletely absorbed. How posaconazole will stand in relation to voriconazole has yet top be defined. Both of these new triazoles are likely to see their major use as drugs of choice in treatment or prevention of mycelial mycoses rather than *Candida*.

John R. Graybill

John Perfect (Duke University, Durham) reviewed recent advances in echinocandin therapy. In contrast to the mycelial fungal pathogens, the major role of this class is likely to be against *Candida*. There is activity in aspergillosis and several other moulds, but not *Cryptococcus*. Caspofungin has clearly changed the paradigm for treatment of invasive candidiasis. By MITT caspofungin is as effective but much less toxic than amphotericin B, but in evaluable patients it is more effective. Caspofungin is also broadly effective against isolates known to be resistant to fluconazole. Anidulafungin appears to be superior to fluconazole for treatment of invasive candidiasis. Micafungin appears effective as well, but with much less data available. Resistance thus far is minimal. All of these drugs are very well tolerated, though all can be given only parenterally. It appears clear that, except for price, this class of drugs would be the first choice for severe *Candida* infections. Because of efficacy in open studies for salvage of patients with aspergillosis, echinocandins have been used in empiric therapy of febrile neutropenia or as primary prophylaxis. Caspofungin is more efficacious than liposomal amphotericin B in suppressing baseline occult mycelial infections (a mix of *Candida* and *Aspergillus*) and in survival.

Kieren Marr (University of Washington, Seattle) commented on the use of polyenes in recent years. One development has been the use of inhaled amphotericin B and more recently ABLC for lung transplantation. Twelve and 14% of patients failed, but ABLC was better tolerated than amphotericin B desoxycholate. On the other hand, nystatin in liposomes was poorly tolerated and will not be further developed. Finally, there has been increasing emergence of pathogens with relative or absolute resistance to amphotericin B. These include *Candida tropicalis*, *Aspergillus flavus*, *A. terreus*, and most recently, *A. lentulus*, species nova. Competition for caspofungin has finally emerged in micafungin, which was just licensed for antifungal prophylaxis and mucosal candidiasis.

Each of these speakers commented on the use of their class of drugs in combination therapy. This was discussed in further detail by John Graybill (University of Texas, San Antonio). At present we routinely use amphotericin B and flucytosine for the first weeks of therapy for meningeal cryptococcosis. A large study comparing fluconazole with combined amphotericin B and fluconazole suggested a very modest advantage of the combination, which is countered by toxicity of amphotericin B and the need to "cherry pick" patients using the APACHE II score … thus the combination may not be generalizable for all forms of invasive candidiasis. However, the major focus at present is on invasive aspergillosis, wherein both *in vitro* and animal studies show either synergy or indifference, but no antagonism, of echinocandins with azoles or amphotericin B. The clinical experience with invasive aspergillosis consists of collections of anecdotes, generally inadequate to be conclusive, and one more solid historically controlled study of salvage patients published by Marr et al in "Clinical Infectious Diseases". In that study both clinical responses and survival were higher with the combination of voriconazole and caspofungin than with caspofungin alone. Evaluation was based on survival, with clear definitions of death attributable and not attributable to invasive aspergillosis. However, the groups were small, not concurrent, and it is impossible to avoid selection bias in this study. The results, while not enough to support changing medical practice, are sufficient to prompt a comparative trial of single versus combination therapy. Voriconazole and an echinocandin for primary aspergillosis would seem to be the best comparator against voriconazole alone. The Mycoses Study Group would seem ideally situated to perform such a study, but unfortunately, it is uncertain whether support will be sufficient to conduct this critical study.

John Graybill

Miami, Florida
16-18 March 2005

Focus on Fungal Infections

Kid's corner: managing pediatric fungal infections

In the pediatric mycology session there were several talks on the nuances of invasive fungal infections in children, including unique diagnostic tools and management strategies. Thomas Walsh (National Cancer Institute, Bethesda) began with an excellent overview of pediatric antifungal pharmacokinetics. Due to the generally larger volume of distribution of agents in children, there are important dosing adjustments. For instance, voriconazole pharmacokinetics are linear in children, as opposed to the non-linear kinetics in adults. This therefore requires much higher dosing to achieve comparable serum levels. In caspofungin, the dosing is done on a mg/m^2 basis, and not using a weight-based formula.

Next William Steinbach (Duke University, Durham) covered a patient population that is often neglected, patients with primary immunodeficiencies. He outlined the difficulty in diagnosing invasive aspergillosis in a patient with chronic granulomatous disease, where patients may have few or no symptoms of disease. The pathophysiology of aspergillosis also differs in chronic granulomatous disease patients, where often there is a lack of angioinvasion and a trend toward more *Aspergillus nidulans* infections.

William J. Steinbach

Finally, Daniel Benjamin, Jr. (Duke University, Durham) covered the difficulties in prophylaxis and treatment of invasive candidiasis in neonatal patients. He outlined the importance of risk stratification, where there is far more disease in the smallest and youngest infants, and the concerns about antifungal prophylaxis or treatment absent extensive antifungal testing in this youngest age cohort.

William J. Steinbach

Focus on Fungal Infections

Miami, Florida
16-18 March 2005

Fungal genomics and pharmacogenomics: a primer for clinicians

Brahm Segal (Roswell Park Cancer Institute, Buffalo) explained that fungal genomics is the study of the full complement of genes that make up a particular fungal organism. Gene expression can be studied by microarray analyses that provide a snapshot of all the genes active in a cell at a particular time. Microarray analyses in *Candida*, *Cryptococcus* and *Aspergillus* species was the topic of the special lecture of Dr. Segal. He emphasized that the goal of fungal microarray analyses is to study the effect of various antifungal regimens on fungal gene expression, allowing scientists to identify pathways that the fungus uses to remain viable under the stress of a particular antifungal agent. For example, caspofungin causes the upregulation of genes involved in cell wall integrity in *Candida albicans*. This knowledge may facilitate the future development of novel antifungal agents that inhibit these pathways.

Scott Penzak (Clinical Pharmacokinetics Research Laboratory in Bethesda) commented on the advances of pharmacogenetics and pharmacogenomics. Pharmacogenomics aims to utilize pharmacogenetic information for the discovery of new therapeutic targets and pharmacologic entities. Recently, genetic differences among individuals have been recognized for their contribution to inter-patient variability in drug response; this includes both treatment efficacy and host toxicity. Dr. Penzak pointed out that pharmacogenetic research focuses largely on genetic polymorphisms in drug-metabolizing enzymes and how they translate into inherited differences in drug effects. Azoles are the only class of systemic antifungal agents extensively metabolized by the cytochrome P450 enzymes. Fluconazole, itraconazole, ketoconazole, and posaconazole are all metabolized by CYP3A4, an enzyme that exhibits wide inter-patient variability in its catalytic activity. Fortunately, however, the safety index of these azoles is quite high, meaning that elevated exposure to these agents is unlikely to result in life-threatening toxicities. On the contrary, voriconazole demands greater attention from clinicians as this agent undergoes biotransformation through CYP2C9 and 2C19 in addition to CYP3A4. Both CYP2C9 and 2C19 exhibit relevant genetic polymorphisms with certain alleles being associated with reduced catalytic activity that may cause higher than normal systemic exposure to voriconazole. This may result in advantageous or in deleterious effects as it may lead to improved antifungal activity or to increased drug toxicity. According to Dr. Penzak, in the future pharmacogenomics testing may allow clinicians to predict antifungal drug exposure in their patients, assisting in optimal drug selection and dosing.

Maria Anna Viviani

In his overview on drug-drug interactions of antifungal agents Paul Gubbins (University of Arkansas, Little Rock) remarked that azoles can interact with a vast array of compounds, and the interaction can occur at different organs, by one or more mechanisms. Clinicians must optimize the use of the systemic azoles discerning interactions of clinical significance from those of theoretical significance. Dr. Gubbins also stated that the echinocandins appear to be associated with little significant toxicity because these drugs are not metabolized by cytochrome P450, and may ultimately prove to be the safest class of antifungal agents.

Maria Anna Viviani

Special report on...

6th International Conference on *Cryptococcus* and Cryptococcosis

by
Maurizio Del Poeta
Stuart M. Levitz
Juneann W. Murphy
Kirsten Nielsen
Peter G. Pappas
Peter R. Williamson

The 6th International Conference on Cryptococcus and Cryptococcosis was held in Boston, USA from June 24-28, 2005. Attendance exceeded 250 people, which is truly phenomenal for a meeting devoted to a single fungal pathogen. Due to the generous support of private and government sponsors, 94 graduate students and postdoctoral scientists received scholarships covering their registration costs.

Conference summary

Immediately prior to the start of the meeting, a genome workshop organized by Jennifer Lodge (St. Louis University) took place. Several cryptococcal genomes have been fully or partially sequenced, and the workshop featured comparative analyses of the sequences along with cutting edge discussions of methods to mine the databases. Then, the meeting began with an opening address by Arturo Casadevall (Albert Einstein College of Medicine, Bronx, NY) entitled, "The Uniqueness of *Cryptococcus neoformans*". Dr. Casadevall presented some of the latest data from his research group, including work on the use of radiolabeled antibodies for the treatment of not only cryptococcal infections but also human melanomas. The upbeat presentation highlighted many of the ways in which *C. neoformans* serves not only as a model pathogen but also exhibits distinctive biology.

The next four days featured sessions devoted to a wide range of topics including new insights into clinical cryptococcosis, epidemiology, molecular biology, pathogenesis, and immunology. Special sessions were devoted to signal transduction, mating, the capsule, and how the fungus crosses the blood brain barrier. Two sessions were devoted to discussions and viewing of the 129 poster presentations.

A highlight of the meeting was a lively debate moderated by Ira Salkin entitled: "How many species and varietal states are there?". Participants included Wieland Meyer (University of Sydney), June Kwon-Chung (National Institutes of Health, Bethesda) and Teun Boekhout (Centraalbureau voor Schimmelcultures, Utrecht). With the recent decision to raise *C. neoformans* var. *gattii* to species level, the etiologic agent of cryptococcosis is presently classified into two species, *C. neoformans* (serotype A, D) and *C. gattii* (serotype B, C). However, the debaters disagreed over whether more species should be named. Dr. Kwon-Chung argued for keeping the number of species at two and summarized her reasoning as follows. "Intra-specific genetic diversity has also been revealed as more strain typing methods have been applied for each serotype. As a result, the number of scientifically valid species within *C. neoformans* is a controversial issue because of differing opinions among taxonomists on the definition of species. There are three major species concept that govern classification of organisms: phenetic (morphological, phenotypic), biologic (interbreeding) and cladistic (evolutionary, phylogenetic) species concepts. No one concept is ideal to be applied for the classification of all the biological species since each concept has strengths as well as weaknesses. It is, therefore, proper to ask which species concept is most reasonable to be applied for a particular group of organisms. Classification of *C. neoformans* into two species was based on phenetic as well as biological species concept which is also supported by cladistic species concept.

In contrast, Drs. Meyer and Boekhout felt that a greater number of species likely exist. Dr. Boekhout summarized his arguments. "Based on genetic and molecular evidence using sequence data of a number of mitochondrial, nuclear and ribosomal genes (and spacers) the *C. neoformans* species complex consists of 6 different entities if the various hybrids genotypes are excluded. Within *C. neoformans* the serotypes A and D seem to be genetically and molecularly separated and they seem to represent individual species, which is also supported by comparison of the entire genome data. The *C. gattii* complex comprises four distinct groups which may represent individual species as well. Hybridization is possible between some of these putative species and this may complicate our phylogenetic analysis." Finally, based upon molecular characterization, Dr. Meyer divided the *C. neoformans* species complex into eight major types. "The genotypic variation found between the eight major molecular types lies within the range comparable to that obtained from established fungal species, suggesting that evolution and speciation is an ongoing process".

Stuart M. Levitz, Chair of the 6th International Conference on Cryptococcus and Cryptococcosis

Social events included an opening reception, a Boston harbor cruise (which got cryptococcologists on their feet and dancing!) and a closing dinner in the New England Aquarium.

In conjunction with the meeting, FEMS Yeast Research will be publishing a thematic issue on *Cryptococcus* and cryptococcosis for which I will be the Guest Editor.

Further details about the meeting, including the agenda and all the conference abstracts, can be found at the conference web site www.bu.edu/cme/iccc.html. In addition, work has begun on preparing a DVD from the presentations that were digitally captured at the meeting. There is limited availability but if you would like a DVD of the conference, please contact me (slevitz@bu.edu) and I will try to get you one.

Finally, start making plans to attend the 7th International Conference on Cryptococcus and Cryptococcosis in Nagasaki, Japan in 2008! Nagasaki is a beautiful city with a rich culture and fascinating history. Dr. Shigeru Kohno will be hosting the conference and I am sure he will do a fantastic job.

Stuart M. Levitz
Conference Chair

Participants to the debate entitled: "How many species and varietal states are there?", from left to right: Ira Salkin, convener, June Kwon-Chung, Teun Boekhout, Wieland Meyer

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Insights from clinical studies

New insights from clinical studies were presented by four experts from around the globe at the recent International Conference on Cryptococcus and Cryptococcosis. In the first presentation, Olivier Lortholary (Institut Pasteur, Paris) presented data from the French Cryptococcosis Database focusing on the immune reconstitution inflammatory syndrome (IRIS) during AIDS-associated cryptococcosis during 1996-2000. These investigators have reported 120 HIV-infected adult patients with first episode, culture confirmed cryptococcosis who were treated with HAART. Among these patients, 10 developed IRIS a median of 8 months following the diagnosis of cryptococcosis. The investigators collected detailed radiologic, histopathologic, and immunologic data from these patients. Three patients with IRIS died. Compared to patients without IRIS, these investigators noted that independent predictors of development of IRIS included previously unknown HIV infection, CD4 count <7, fungemia, and initiation of HAART within 2 months of diagnosis of cryptococcosis. The investigators concluded that early initiation of antiretroviral therapy following the diagnosis of cryptococcosis is associated with IRIS, and that it may be prudent to delay HAART to allow for better control of the infection using antifungal therapy.

In the second lecture, Thomas Harrison (St. George's University, London) described the use of quantitative CSF cultures for the assessment of fungicidal activity of various antifungal regimens for patients with HIV-associated cryptococcal meningitis. The data is based on recently published results of 64 Thai patients with HIV-associated cryptococcal meningitis, and supports the use of quantitative cultures at baseline, 3, 7, and 14 days following initiation of therapy to determine the relative cidality of each regimen. In the study described, Dr. Harrison and his colleagues were able to demonstrate that the combination of amphotericin plus 5FC led to CSF culture-negativity significantly more rapidly compared to amphotericin B alone, amphotericin B combined with fluconazole, or triple therapy with amphotericin B, fluconazole and 5FC. Notably, the numbers of patients in each arm of this trial are insufficient to determine the clinical importance of these observations, but these observations provide a potentially powerful *in vivo* tool on assessing the activity of antifungal regimens in this population.

Peter G. Pappas

In the third presentation, Peter Pappas (University of Alabama, Birmingham) discussed his experience with cryptococcosis in transplant recipients, describing the clinical results from patients from 6 US transplant centers from 1990 to 2000. Over 100 patients were described in this review, with all but 2 of these patients being solid organ transplant recipients. The most notable observations in this study include the late onset of patients with transplant associated cryptococcosis (median 400 days post-transplant), the strong association with solid organ transplantation, and outcomes that are very similar to patients without significant underlying disease. This latter observation suggests that either (1) transplant recipients who develop cryptococcosis are followed very closely and that disease is diagnosed very early, or (2) that the natural history of cryptococcosis in these patients is somehow altered by the chronic immunosuppressive agents to allow for a generally favorable outcome.

In the last discussion, Anastasia Litvintseva (Duke University, Durham) discussed a multi-locus sequence typing method to investigate the population structure and mode of reproduction for *Cryptococcus neoformans* var. *grubii* from isolates around the world. Dr. Litvintseva reported having genotyped more than 1,000 strains of serotype A, and reported a genetically distinct subpopulation having been found only in Botswana. She suggests that these findings may have clinical implications and offer insights about the evolution of *C.neoformans* var. *grubii*.

Finally, it should be noted that there are few ongoing clinical trials in the epidemiology and treatment of cryptococcosis. Several of the presenters noted the relative lack of clinical studies in cryptococcosis and urged the development of newer trials, possibly to include voriconazole and the immunomodulator IFN-gamma in the primary therapy of this disorder. An ongoing BAMSG trial of combination therapy with amphotericin B and varying doses of fluconazole (400 mg and 800 mg) for AIDS-associated cryptococcosis in the US and Thailand was briefly discussed. Also mentioned was a potential international ACTG trial comparing varying doses of fluconazole (800 mg to 2000 mg daily) as primary therapy for AIDS-associated cryptococcosis.

Peter Pappas

Virulence

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On the first full day of the conference, John Perfect (Duke University, Durham) led off with a talk, "*Cryptococcus neoformans*, the yeast that likes it hot!!". Dr. Perfect presented some hot data on molecular studies of temperature tolerance in the fungus. He emphasized that while over 1.5 million fungal species exist in the biosphere, only 270 species have been reported to cause disease by mechanisms that include tolerance to mammalian host temperatures. In *C. neoformans*, over 40 genes have been linked to high temperature tolerance including a number of signaling, stress-response and metabolic pathways. Notable for the latter is the apparent disconnect between the repression of a number of amino acid and pyrimidine synthetic rates at elevated temperatures and their importance to virulence at these same temperatures, expanding the expression/importance conundrum first encountered by Eric Jacobson in regards to the virulence factor, laccase.

Jennifer Lodge (St. Louis University) next described studies on resistance to oxidative and nitrosative stress, including her studies on the thioredoxin system, which she has shown to be important for vegetative growth, oxidative and nitrosative resistance and virulence.

Following this, Bettina Fries (Albert Einstein College of Medicine, Bronx, NY) provided an update on phenotypic switching of *C. neoformans* which has now been described in three serotypes of *C. neoformans*. Phenotypic switching was found to occur *in vivo* in a chronic infection model and was accompanied by differential gene expression resulting in changes in capsule and virulence, resulting in alterations in phagocytosis, intracellular killing and qualitative changes in the inflammatory response of the host. In turn, switching was found to be influenced by chemotherapeutic and immunological antifungal interventions suggesting that switching may be an important mechanism of virulence and immune evasion of the fungus.

Following this, two selected oral presentations described methods for patch clamp techniques to study a plasma membrane calcium channel important to calcium-dependent pathways including signaling (Angie Gelli, University of California-Davis), and mass spectrometric analysis of cryptococcal capsule used to characterize micro-heterogeneity in the polysaccharide polymer elements (Diane McFadden, Albert Einstein College of Medicine, Bronx, NY).

Peter Williamson

Peter R. Williamson

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Capsule

The importance of the polysaccharide capsule in cryptococcal pathogenesis led to several symposia on the cell biology and immunology of this virulence factor. Leading off was a summary of a program of systematic disruption of genes involved in capsule biosynthesis in a serotype A strain by Guilhem Janbon (Institut Pasteur, Paris). These studies highlighted the complexity of the polysaccharide biosynthetic machinery and identified many possible regulatory targets important to the overall virulence composite of the pathogen.

The following talk by Tamara Doering (Washington University, St. Louis) highlighted proximal steps involved in capsule synthesis, integrating methods of cell biology, molecular biology and carbohydrate chemistry to understand the kinetics of capsule synthesis. Several unique biosynthetic processes were highlighted including the transport of GDP-mannose, the substrate for building the polysaccharide mannose backbone and several xylose transferases.

Next, Thomas Kozel (University of Nevada, Reno) discussed interesting studies of complement and antibody interactions with *C. neoformans*. These studies probed the macromolecular architecture of the capsule and characterized the capsule in terms of a porous matrix whose variable density has profound effects on the kinetics of complement and antibody deposition. For example, incubation of tissue-derived cryptococci in mouse serum produce a denser matrix and allows more efficient deposition of complement near the capsule edge. These studies suggest the importance of additional mechanisms of cryptococcal pathogenesis and provide insights into the uniqueness of *C. neoformans* as a fungal pathogen.

Peter Williamson

Boston, MA
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Host responses to *Cryptococcus* and its products

The mechanisms by which *Cryptococcus neoformans* and its products modulate the host innate and adaptive immune responses are important features of the host/organism interactions that dictate prognosis in this disease. A number of presentations given during the 6th International Conference on Cryptococcus and Cryptococcosis provided insights into the mechanisms that either control *C. neoformans* during infection or undermine the host resistance strategies. Anna Vecchiarelli (University of Perugia) presented data showing that glucuronoxylomannan (GXM), the high molecular weight polysaccharide produced abundantly *in vivo* by many isolates of *C. neoformans*, interacts with Toll-like receptor 4 to induce a long-lasting and potent up-regulation of Fas ligand (FasL) on GXM-ladened macrophages. Macrophages with increased surface FasL have the potential to interact with activated T cells and cause apoptosis in the T cells. Considering that activated T cells are essential to protection against *C. neoformans*, the great loss of activated T cells by this mechanism would be quite detrimental to the host.

Insights into the life of *C. neoformans*, a neurotropic yeast, during its residence in the lungs and on its travels and entry into the brain were presented in a session entitled "The Road from the Lung to the Brain". In the first presentation of this session, Juneann Murphy (University of Oklahoma, Oklahoma City) pointed out that isolates of *C. neoformans* vary with respect to the time they spend in the lungs after being inhaled. Some isolates, such as the highly virulent isolate, NU2, remain in the lungs continuously after infection and disseminate to the brain relatively slowly. Although such isolates that linger in the lungs initially induce in the host a protective anticryptococcal cell-mediated immune (CMI) response, the cryptococci and their products eventually trigger host cells to produce IL-10 which has a negative effect on the protective anticryptococcal CMI response. Macrophages in the lungs of mice with increased levels of IL-10

Juneann W. Murphy

were shown to be alternatively activated macrophages. Such macrophages make large amounts of arginase I that converts arginine into L-ornithine and urea. Urea can be used by *C. neoformans* as a nitrogen source, so the excess urea might enhance growth of the organisms in the lungs. Furthermore, alternatively activated macrophages retain the ability to phagocytize organisms but have lost their ability to effectively kill organisms. Consequently, *C. neoformans* continues to multiply uncontrolled in the lungs as well as travels to the brain and other tissues.

Until recently the mechanism(s) by which *C. neoformans* crosses the blood brain barrier (BBB) has not been known. There were two very eloquent talks given with magnificent photomicrographs showing *C. neoformans* crossing the BBB. Using both *in vitro* and *in vivo* models and a serotype D isolate of *C. neoformans*, Yun Chang (National Institutes of Health, Bethesda) demonstrated that the organism enters the brain from the blood stream by transcellular crossing of the endothelium of the BBB. Dr. Chang did not observe damage to the endothelium where *C. neoformans* had crossed the BBB. He also noted the organism entered into the neurophil by 3 h after an iv injection into mice and later was found in the brain parenchyma but was never observed associated with the choroid plexus. A mutational approach is being taken by Dr. Chang to identify genes of *C. neoformans* needed for invasion and growth in the brain. He has identified many clones that fail to associate with the BBB or grow under hypoxia, and those clones are being evaluated for function.

After injecting H99, a serotype A isolate of *C. neoformans*, iv into mice, Françoise Dromer (Institut Pasteur, Paris) observed that the organism entered the brain within 6 h, and entry was via the cortical capillaries. She also reported that the choroids plexus was not involved. Unlike findings by Dr. Chang, Dr. Dromer reported that the crossing of *C. neoformans* through the capillaries was associated with severe damage to the structure of the microvessels. In addition, Dr. Dromer indicated that the cryptococci could enter the brain not only by transcellular crossing but by being taken into the brain inside of mononuclear cells. There seemed to be some disagreement between Drs. Chang's and Dromer's reports concerning whether *C. neoformans* enters the brain solely by transcellular crossing or by a combination of mechanisms

including transcellular crossing. It is possible that the serotype D isolate used by Dr. Chang only enters the brain by transcellular crossing without damage to the endothelium; whereas, the serotype A isolate used by Dr. Dromer enters the brain in multiple ways and causes vessel damage.

Studies by Tania Sorrell (University of Sydney) established that phospholipase B produced by *C. neoformans* facilitates invasion of mouse lung tissue and is required for dissemination from the lung into the blood and lymph. Once *C. neoformans* cells enter the brain from the blood, they establish cerebral cryptococcomas and their metabolites can be found in tissues and cerebral spinal fluid (CSF). Dr. Sorrell showed that nuclear magnetic resonance (NMR) spectroscopy was a potentially useful tool for defining *C. neoformans* metabolite profiles in spinal fluid. She suggested that NMR profiling of cryptococcal metabolites in CSF could become a valuable tool for diagnosis of cryptococcosis and for monitoring therapeutic responses of a patient with cryptococcal meningitis.

In a session on innate and acquired host immune responses, Gary Huffnagle (University of Michigan, Ann Arbor) discussed the importance of TNFalpha in the initial induction of T helper 1 cells and the protective anticryptococcal cell-mediated immune response. He found that products of the arachidonic acid pathway down-regulate TNFalpha production. In chronic infections with *C. neoformans* a T helper 1 response can shift to a T helper 2 response, and Dr. Huffnagle said results of his recent studies suggest that CD4 T cell polarization is largely controlled locally rather than in the draining lymph nodes. When T cell polarization shifts toward a T helper 2 response, Huffnagle and coworkers noted the development of alternatively activated macrophages which contribute to disease pathology. The host's innate and immune mechanisms tend to control a cryptococcal infection but never completely eliminate the organism from the body, thus the immunocompetent host maintains a strong anticryptococcal CMI response that is protective against subsequent incounters with *C. neoformans*.

Giuseppe Teti (University of Messina) defined and discussed the potential of some cryptococcal proteins with the capability of protecting the organism from the host immune mechanisms.

Augmentation of the protective anticryptococcal CMI response (T helper 1 response) can be achieved by immunization of mice with cytosine-phosphate-guanosine-containing oligodeoxynucleotides (CpG ODN) as shown by Kazuyoshi Kawakami (Tohoku University, Sendai). Dr. Kawakami indicated that the CpG-ODN signals through TLR9 to activate dendritic cells (DC) to produce IL-12 and express co-stimulatory molecules such as CD40 that are necessary for induction of a strong T helper 1 cell response. Activated DC were shown to promote CD8 T cells to produce IFNgamma early in the T helper 1 induction process. The IFNgamma polarizes T cells toward a protective T helper 1 response. These results suggest that CpG ODN has therapeutic potential in cryptococcosis. Dr. Kawakami also showed that CpG ODN in conjunction with cryptococcal mannoprotein (MP) can induce a protective anticryptococcal immune response in mice.

Exciting findings by Stuart Levitz (Boston University) have begun to define the mechanisms responsible for the potent immunostimulatory activity of MP. Dr. Levitz reported that MP binds to the mannose receptor, DC-SIGN, on DC and co-localizes intracellularly with CD206 and CD209 in the DC. He found that this was a necessary step in the induction of the protective T helper 1 response. B cells and peritoneal macrophages would not substitute for DC when MP was used to stimulate T cells. Dr. Levitz concluded that DC provide a crucial link between innate and adaptive immune responses to *C. neoformans* via a process whereby MP is efficiently taken up by mannose receptors.

In summary from the results presented at this meeting, it is clear that MP is an important component of *C. neoformans* for induction of a protective cell-mediated immune response and induction of the CMI response is dependent on the DC-SIGN on dendritic cells. The protective CMI response can be up-modulated by treatment with CpG ODN and down-modulated in at least two ways either by FasL on macrophages causing apoptosis of activated CD4 T cells or by the induction of alternatively activated macrophages that are induced by a the production of IL-10 or by a shift to T helper 2 response. *C. neoformans* can cross the BBB by transversing the endothelial cells and the organisms presence in the brain can be monitored by NMR profiling of its metabolites. These findings bring us one step closer to developing diagnostic and prognostic procedures and to devising immunomodulatory therapies.

Juneann Murphy

Boston, MA
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6th ICCC

Pathogenesis

The Session 5 of the 6th International Conference of Cryptococcus and Cryptococcosis was entitled "Pathogenesis" and it was supported by the Ellison Medical Foundation.

The first speaker was Frank Coenjaerts (University Medical Centre Utrecht) who presented very interesting studies on the analysis of gene expression profiles of *Cryptococcus neoformans* B3501 strain upon interaction with human umbilical vein endothelial cells (HUVEC). He identified a stress response regulator gene, *C. neoformans* SKN7, which is up-regulated upon fungal-host interaction. Dr. Coenjaerts showed that the *C. neoformans* delta-skn7 mutant is hyper-susceptible to oxidative stress and its virulence is decreased compared to *C. neoformans* wild-type strain in a mouse model. These studies suggest a role of *SKN7* gene in the regulation of survival of *C. neoformans* in the host environment.

The second speaker was Peter Williamson (University of Illinois, Chicago), who proposed the intriguing hypothesis that a virulence-associated DEAD-box protein of *C. neoformans*, *VAD1*, is a master regulator of multiple virulence pathways. In particular, *VAD1* regulates the expression of *NOT1*, a component of the Ccr4-Not complex that senses glucose depletion and other environmental stresses. In addition, *VAD1* also regulates PCK1, which encodes phosphoenolpyruvate carboxykinase, *TUF1*, which encodes an elongation factor for mitochondrial protein translation, and *MPF3*, which may encode a mannoprotein. These proteins have roles in gluconeogenesis, mitochondrial function, and cell wall integrity, respectively. Finally, *VAD1* also regulates laccase activity, the enzyme responsible for melanin production of *C. neoformans*. Since melanin is a virulence factors these studies suggest that *VAD1* not only regulates normal metabolic pathways upon infection but also promotes the expression of factor(s) directly involved in the virulence of *C. neoformans*.

The third speaker was Maurizio Del Poeta (University of South Carolina, Charleston), who presented a study on the role of glucosylceramide synthase 1 gene (*GCS1*) in the pathogenicity of *C. neoformans*. The *GCS1* gene was isolated and biochemically characterized in *Saccharomyces cerevisiae*, a yeast that does not produce glucosylceramide. The *C. neoformans* Gcs1 protein showed different substrate specificity than the human homolog and it is not susceptible to inhibitors targeting the human enzyme. The *C. neoformans* delta-gcs1 mutant is viable but it does not survive in conditions mimicking the lung environment. Considering that biochemical differences between *C. neoformans* and human Gcs1 exist and that *C. neoformans GCS1* plays a key role in the regulation of pathogenicity, these findings may have important implications for the development of new cryptococcal therapeutic strategies.

Maurizio Del Poeta

The fourth speaker was Julianne Djordjevic (University of Sydney), who presented results showing that secretion of cryptococcal phopsholipase B1 (Plb1) may be regulated by a glycophosphatidylinositol (GPI) anchor protein. *C. neoformans* wild type and mutated Plb1 proteins were expressed in *Saccharomyces cerevisiae* and the growing medium and cell pellet were assayed for the presence of Plb1 protein and activity. The results showed that the GPI motif localized at the 3' of Plb1 protein is required for cell wall anchoring. Dr. Djordjevic highlighted that the location of Plb1 in the cell wall via GPI anchoring may permit immediate release of the enzyme in response to changing environmental conditions and may represent part of a novel mechanism for regulation of secretion of a fungal virulence factor.

The last speaker was Jatin Vyas (Harvard Medical School, Boston), who presented a talk entitled "CD63 is selectively recruited to phagosomes containing *Cryptococcus neoformans* in primary mouse bone marrow dendritic cells". CD63 is a tetraspanins expressed in antigen presenting cells, including macrophages and dendritic cells. Using a live fluorescent microscopy, Dr. Vyas illustrated that, within 15 minutes of phagocytosis, CD63 was recruited to cryptococcal phagosomes. This recruitment was still present when a *C. neoformans* acapsular strain or when heat-killed *C. neoformans* cells were used. Interaction of fungal cells with the myd88 Toll-like receptor was also not required, because CD63 recruitment was observed in dendritic cells from myd88-/- mutant mice. Interestingly, phagocytosis of polystyrene beads did not stimulated CD63 recruitment. These studies suggest that the content of the phagosome dictates CD63 recruitment and not the phagocitic process *per se*.

Maurizio Del Poeta

Kirsten Nielsen

Boston, MA
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Sex, signaling, and the mating type locus

This session concentrated on two important aspects of *Cryptococcus* biology - mating and signaling - and how each of these relates to virulence. Three talks focused on mating processes in *Cryptococcus*. June Kwon-Chung (National Institutes of Health, Bethesda) gave an intriguing talk discussing whether *Cryptococcus* species are dioecious organisms in which MATα cells function as male while MAT**a** cells function as female. As evidence for dioecism, Dr. Kwon-Chung cited the difference between **a** and α cell pheromone production in response to environmental signals, the observation that the cell content from α cells moves into **a** cells during mating, formation of dikaryotic hyphae by MAT**a** cells, uniparental inheritance of MAT**a** mitochondria, and that tup1Δ mutations in the two mating types confer different phenotypes. If *Cryptococcus neoformans* is truly sexually dimorphic it will be distinct among unicellular fungi in which the two mating type cells are normally isogamous.

Joseph Heitman (Duke University, Durham) presented an elegant talk on the evolution of the mating type locus and the role mating plays in virulence. A comparative analysis of the MAT locus from var. *neoformans* (serotype D), var. *grubii* (serotype A) and the sibling species *C. gattii* (serotype B) revealed sequential evolutionary events that fused two unlinked loci to form the large, highly unusual extant structure. Further evidence showed that α strains preferentially disseminate to the central nervous system during coinfection with **a** strains.

Xiaorong Lin from the Dr. Heitman laboratory presented evidence that monokaryotic fruiting, which was previously thought to be asexual, is a modified form of the sexual cycle that occurs between partners of only one mating type to produce recombinant haploid progeny. The evolutionary utility of this process was highlighted by the observation that the most common genotype identified in the recent outbreak of cryptococcal meningoencephalitis on Vancouver Island, Canada appears to have descended from two α parents. Thus, this cryptic same-sex reproduction may have enabled the expansion of *C. gattii* into a new geographical niche that has profound implications for human health.

Two presentations discussed the role of G-protein signaling in virulence of *C. neoformans*. Ping Wang (Louisiana State University, New Orleans) characterized the pheromone response signaling cascade and showed a link between signaling and virulence by analyzing Crg1, a regulator of G-protein signaling. Dr. Wang observed that crg1Δ strains are hypervirulent in var. *grubii* but not var. *neoformans*, suggesting that the signaling pathways leading to virulence may differ between the two varieties. Crg1 physically interacts with the Gα protein Gpa2, implicating Crg1 as the GAP protein that functions in the mating pathway. Andrew Alspaugh (Duke University, Durham) discussed the role of G-protein signaling via Gpa1 in production of the important virulence factors melanin and capsule. A microarray analysis of the *gpa1*Δ mutant implicated the transcription factor Nrg1 as a candidate PKA effector regulating capsule but not melanin. The Nrg1-dependent transcriptome was characterized to identify downstream genes specific to capsule production in *Cryptococcus*. These studies underscore the diverse biology of *Cryptococcus* that makes it an excellent model organism and highlight aspects specific to virulence.

Kirsten Nielsen

Dr. Shigeru Kohno will be hosting the 7th International Conference on Cryptococcus and Cryptococcosis in Nagasaki, Japan in 2008.

ECMM Working Group on *Pseudallescheria/ Scedosporium* Infections

Dear Friends,

this is to remind you of the forthcoming meeting of our Pseudallescheria / Scedosporium Network in Berlin, Sunday, October 23. The session starts at 08.00; for information, see www.timm2005.org. We hope you will all be there.

I would like to announce our next meeting already: this will take place in Angers, France, 23 and 24 June 2006, prior to the ISHAM Congress at Paris. This meeting will be organized by the Host-Parasite Interaction Study Group (Raymond Robert - Jean-Philippe Bouchara) from Angers University. The meeting will start on Friday afternoon and continues on Saturday 24th, ending with plenary discussion to plan future activities. A dinner will then be organized, and participants can travel together to Paris on Sunday 25th in the morning, to register for the ISHAM congress. There is a high speed train Angers-Paris every hour, and it takes about 1 h 45.

For the Angers meeting we would like to have as many speakers and posters as possible. Our aim is to overview all our activities of the Network since the first meeting in Utrecht, April 2004. Please volunteer for a presentation with a mail to de.hoog@cbs.knaw.nl. We intend to send abstracts to all of you prior to the meeting; deadline for submission is 1 June 2006. Presentations will be centered around themes of the subgroups; I would like to ask the steering committees in particular to stimulate group-members to actively participate. A preliminary program will be mailed by the end of 2005.
Hope to see you all at any of our meetings,

G. Sybren de Hoog

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Programm ECMM/TIMM Satellite Workshop Pseudallescheria / Scedosporium Infections

Sunday, October 23,
Berlin Congress Center 08.00 - 11.00 AM.
Presentations are 25 minutes including time for discussion.
Chair: Sybren de Hoog

08.00 - 08.25
J. Cano, F. Gilgado, J. Gené & J. Guarro *(Unitat de Microbiologia, Reus, Spain)*
Molecular biology of the *Pseudallescheria boydii* complex, with the description of two new species.

08.25 - 08.50
B.L. Rottier[1], S. van der Heide[2], H. Hovenga[2] & H.F. Kauffman[2] *([1]Beatrix Children's Hospital, [2]Laboratory for Allergology and Pulmonology, [3]University Medical Centre Groningen, The Netherlands)*
A case of a child with cystic fibrosis and infection with *Aspergillus fumigatus* and a Pseudallescheria boydii: clinical parameters and serology.

08.50 - 09.15
J.-P. Bouchara, B. Cimon, O. Lima & G. Larcher *(GEIHP Groupe d'Etude des Interactions Hôte-Parasite, Angers, France)*
Recent advances in epidemiology and physiopathology of Scedosporium apiospermum infections in patients with cystic fibrosis.

09.15 - 9.40
A. Velegraki[1], E. Alexopoulos[1] & G.S. de Hoog[2] *([1]Mycology Reference Laboratory, Medical School, National University of Athens, Greece; [2]Centraalburerau voor Schimmelcultures, Utrecht, The Netherlands)*
Different methods for susceptibility testing of *Scedosporium* against licensed antifungal agents and posaconazole.

09.40 - 10.05
J. Rainer, A. Zacke, E. Lackner & J. Kaltseis *(Institute of Microbiology, Leopold Franzens University Innsbruck, Austria)*
Dynamics in *Pseudallescheria boydii*: patterns and interrelationships of phenomena affecting growth and change within populations.

10.05 - 10.45
F. Symoens[1], D. Garcia Hermoso[2], V. Robert[3], E. Dannaoui[2], G. S. de Hoog[3] & R. Horré[4] *([1]BCCM/IHEM Culture Collection, Scientific Institute of Public Health, Brussels, Belgium; [2]Molecular Mycology Pasteur Institute, Paris, France; [3]Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands; [4]Federal Institute for Drugs and Medical Devices, Bonn, Germany)*
The *Pseudallescheria* data base and Culture Collection, preceded by an additional note on the emergent character of *Scedosporium* infections.

10.45 - 11.00
Discussion and any other business.

A fungal course at the 2nd Trends in Medical Mycology: "Burning Questions in Diagnostics"

At the occasion of this TIMM, a short course in fungal diagnostics will be offered. A number of topics have been selected which are clinically relevant, highly controversial and where significant developments were witnessed during the last few years. The topics will be introduced and explained by experts in these fields. The afternoon session will be devoted to hands-on microscopy of the main organisms concerned.

Course chairpersons: Kathrin Tintelnot and Sybren de Hoog.
Times: Saturday 22 Oct. 2005, 09.30 - 13.00, 14.00 - 17.00.
Venue: The course will be held at the Charité Berlin, Campus RVK, Augustenburger Platz 1, D-13353 Berlin.
Course fee: € 80,– to be paid at the registration desk.
Registration: only a limited number of 25 participants can be admitted. Please register as soon as possible with Kathrin Tintelnot, Robert Koch-Institute, Nordufer 20, D-13353 Berlin, e-mail: tintelnotk@rki.de, fax: +49-30-4547 2614.

LECTURES & TOPICS COVERED

1. Zygomycete infections: Eric Dannaoui.
Severe Zygomycete infections are gradually increasing. The number of diabetic and immunocompromised patients is increasing in the Western world, having a higher risk of acquiring zygomycosis. Also cases resulting from post-traumatic inoculation were reported after the Asian tsunami. Zygomycete species are phylogenetically remote from each other and respond differently to antifungals. Quick and correct identification of the etiologic agent is essential to save the patient's life.

2. Coccidioides diagnostics: Matthew Fisher.
There are good reasons to assume that another species exists next to *Coccidioides immitis*: *C. posadasii*. The species have different patterns of association with human movements. But how do we distinguish them in the clinical lab?

3. Molecular diagnostics of dermatophytes: Yvonne Gräser.
Dermatophyte taxonomy has gone through a process of reshuffling on the basis of molecular data, and this not always matches with classical criteria. Are our protocols for dermatophyte still valid?

4. Pseudallescheria and Scedosporium: Josep Guarro.
This group of emerging, highly therapy-refractory fungi are among the most frequently misidentified organisms. In addition, the group has recently become even more complex by the discovery of a number of new species.

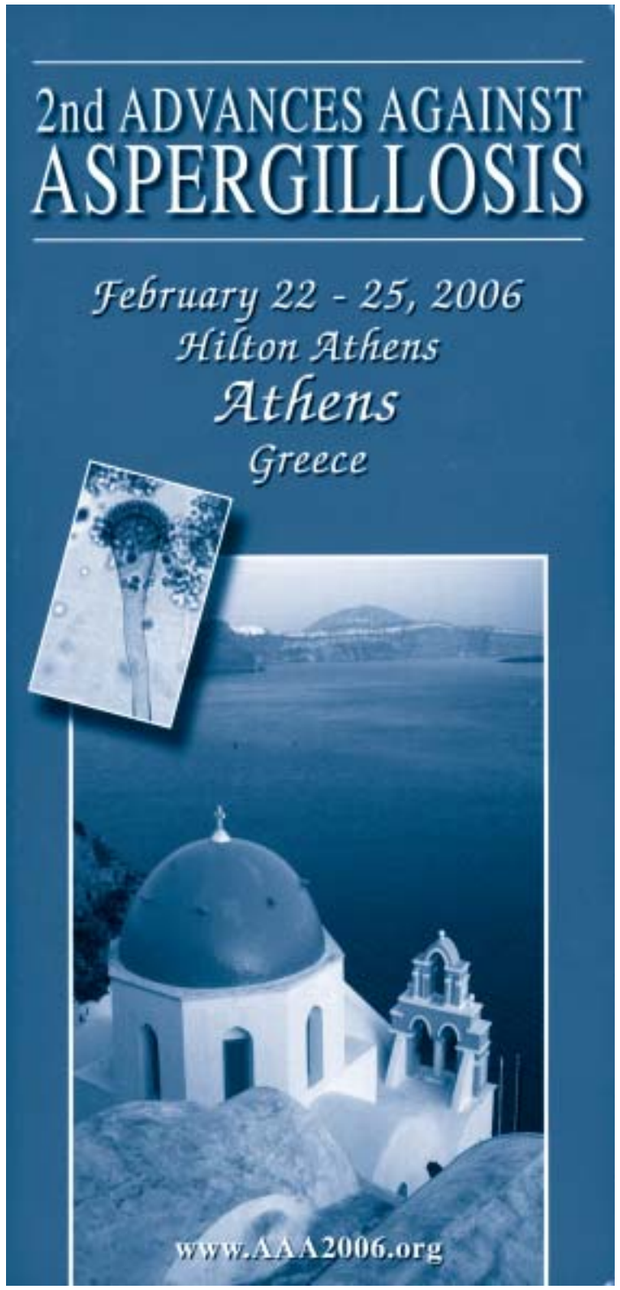
5. Black yeasts as agents of human mycoses: Sybren de Hoog.
Black yeasts of the genus *Exophiala* have always been known as the classical diagnostic nightmare. On the basis of molecular data, a number of new species has recently been described. But there is light at the end of the tunnel: it seems that the spectrum of species occurring on humans is no longer expanding.

2nd Advances Against Aspergillosis Athens, February 2006

The Second International Meeting on Advances Against Aspergillosis will be held in Athens, Greece in February 22-25, 2006. After the undoubtful success of the First Meeting in San Francisco, the meeting in Athens promises to become an even better event. Well-known basic scientists and clinicians from all around the world are expected to gather in Athens to share their knowledge and research thoughts on the fast advancing field of aspergillosis and its management. The *Aspergillus* field is in a state of rapid advancement, including the publications of the genomes of *Aspergillus fumigatus*, *A. nidulans* and *A. oryzae* providing a huge impetus for basic research. Additionally, the launch of several newer antifungals in the last few years and anticipated clinical trials of several more is an important therapeutic step forward, without precedent in mycology. Despite the increased incidence of invasive aspergillosis and that aspergillosis has become the leading fungal cause of patient mortality, there had been little communication among experts in the area before the conception of these meetings. This is another chance to gather the world's aspergillosis experts in one venue.

The meeting venue, Athens Hilton, is located at the heart of the Greek capital, a few kilometers away from Acropolis and Athens historic town. The organizing committee, led by Dr.'s David A. Stevens, David W. Denning and William J. Steinbach, are preparing a very complete and ambitious program of symposia, plenary sessions, oral and poster sessions that span the whole area of the broad field of *Aspergillus* and aspergillosis.

Information on the program can be found at the website of the meeting www.aaa2006.org. For further information please contact the congress secretariat at Congress Care
info@congresscare.com.
Phone: 31-73-690-1415 or info@aaa2006.org.



16th Congress of the International Society for Human and Animal Mycology (ISHAM)

Bertrand Dupont, President of the 16th Congress of the ISHAM

It is my distinct pleasure to announce the 16th Congress of the International Society for Human and Animal Mycology (ISHAM) to take place 25-29 June 2006 in Paris, France. The venue is the Palais des Congrès, Porte Maillot, in the North-West of Paris. This is a superb and spacious Congress Centre with two large international hotels. It is close to the heart of Paris and to the Champs Elysées. As President of this Congress and on behalf of the French Society of Medical Mycology, I am very pleased to invite you to attend this scientific event.

The French Society of Medical Mycology was created in 1956 by Gabriel Segretain, François Mariat and Edouard Drouhet. It is a very dynamic society which consists of about 400 active members, including 50 foreign French speaking mycologists. They are namely microbiologists, clinicians in infectious diseases, oncohematology and intensive care, dermatologists, pathologists and veterinarians. The Society held two national meetings a year. It has a national review: the "Journal de Mycologie Médicale", its web site is: www.mycolmed.chez.tiscali.fr. Teaching mycology is an important activity of the Society and many of its members attended the Medical mycology course at the Pasteur Institute. This course created in 1953 is still ongoing each year with a full time 2 months teaching as well as a Diploma of Medical Mycology at the University René Descartes Paris 5. This teaching is conferring an excellent level of knowledge of mycology in University Hospitals and all over the country.

The famous trio of mycologists at the Pasteur Institute were among the founders of ISHAM in Rome in 1953 and Professor Edouard Drouhet was President of a former ISHAM Congress in Paris in 1972. I had the privilege, with a few European mycologists, to found the European Confederation of Medical Mycology in 1993 which is now composed of 23 countries.

The program of the 2006 ISHAM Congress is now completed, chair persons are being solicited, invited speakers are contacted and the call for abstracts was mailed to potential participants with a dead line on January 16 2006. The organizer is Imedex who organized the previous Congress in 2003 in San Antonio (Texas) and is familiar with this kind of international Congress. Information is available at www.imedex.com.

I am very grateful to the National Scientific Committee, the International Scientific Committee and ISHAM officers for their help in building this program. The opening ceremony will be held on Sunday June 25 with a keynote lecture and a welcome cocktail reception. The scientific sessions will start the next day with four simultaneous symposiums, three times per day avoiding overlap between the topics, a poster - wine and cheese- session and a keynote lecture. The Chair persons will invite speakers and propose an oral short communications to authors of selected abstracts on the topic. Satellite symposiums will be scheduled the morning before the sessions, luncheon symposiums will also probably be offered. The Gala Dinner will take place at the Carousel du Louvre with a visit of the Louvre Museum on June 28th. The ISHAM General Assembly is on the last day June 29th as indicated on the program at a glance reported below.

All our efforts are concentrated to propose a memorable outstanding scientific and social program. Looking forwards seeing you in Paris, I wish you an enjoyable stay in France and a very fruitful meeting.

Bertrand Dupont
President of the Congress

ISHAM 2006 — Program, 25-29 June, Paris, France

	Sunday, 25 June 2006	Monday, 26 June 2006	Tuesday, 27 June 2006	Wednesday, 28 June 2006	Thursday, 29 June 2006
7:00					
		7:15 -8:15 Satellite Symposium	7:15 -8:15 Satellite Symposium	7:15 -8:15 Satellite Symposium	7:15 -8:15 Satellite Symposium
8:00		8:30 -10:30	8:30 -10:30	8:30 -10:30	8:30 -10:30
		Comparative genomics; Glycobiology and host interplay; Antifungals: Pharmacokinetics and pharmacodynamics; (ECM-MISHAM): Molecular taxonomy	Biofilms; T cell immunity; Epidemiological trends in fungal infections; Combination therapy *in vitro/in vivo*	Cell wall; Immunotherapy; Mycetoma; Fungi indoors and outdoors	Fungal virulence and morphogenesis; New antifungals; Superficial mycoses in animals; Mycotoxins
9:00					
10:00		Break	Break	Break	Break
		11:00 -12:30	11:00 -12:30	11:00 -12:30	General Assembly
11:00		Postgenomic and transcript profiling; Cytokines and host-fungus interaction; New challenges in dermatomycoses; New immunological tools for fungal diagnosis	Sex in fungi; Antifungal antibodies: Do they matter?; Endemic mycoses; Molecular epidemiology	Resistance mechanisms; Genetic susceptibility of the host; Systemic mycoses in animals; Regulation, quality control and education	
12:00		LUNCH	LUNCH	LUNCH	LUNCH
13:00					
14:00		14:00 -15:30	14:00 -15:30	14:00 -15:30	14:30 -16:00
		Population dynamics of fungal pathogens; Antifungal vaccines; New challenges in allogenic and solid organ transplantation; Advances in *in vitro* antifungal susceptibility testing	Signaling, adaptation and virulence; Endothelium and epithelium crossing; Mycoses in pediatrics; New molecular tools for fungal diagnosis	The yeast-intestine interface: Colonization, infection, tolerance and inflammation; Filamentous fungi and chronic respiratory diseases; Applications of proteomics and metabolomics; To be determined	Functional genomics; Clinical cases (interactive session); Non culturable fungal pathogens; To be determined
15:00		Break	Break	Break	
16:00		16:00 -17:30 Poster Session	16:00 -17:30 Poster Session	16:00 -17:30 Poster Session	
17:00		Break	Break	Break	
18:00	Opening Ceremony & Welcome Reception Keynote Lecture: Impact of animal models in antifungal therapy	17:45 Keynote Lecture: Host fungus interactions Dr. Arturo Casadevall	17:45 Keynote Lecture: New strategies in antifungal treatment Dr. John E. Edwards	Gala Dinner	
19:00					

INVASIVE FUNGAL INFECTIONS

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