

ISHAM WORKING GROUP

APPLICATION FORM

1	Name(s) of coordinator(s), including title, proposing the working group Flavia De Bernardis PhD. Director of Mycoses Unit, Istituto Superiore di Sanità, Rome, Italy
2	Coordinator(s) full contact information, including voice/fax numbers Flavia De Bernardis Mycoses Unit – Department of Infectious, Parasitic and Immunemediated Diseases, Istituto Superiore di Sanità. Viale Regina Elena 299 00161 Rome Italy e-mail: flavia.debernardis@iss.it tel. :++390649902809 fax: 390649902809
3	Names and contact information of working group members Stavroula Antonopoulou, Research Fellow, Mycology Laboratory, Microbiology Dept. Medical School, University of Athens, Greece . Tel.: +30 2107462146 Fax: +30 2107462147, antonopoulou@mail.com Jose Pontón and Guillermo Quindos – Department of Immunology, Microbiology and Parasitology, Faculty of Medicine and Dentistry, University of the Basque Country, Bilbao, Spain jose.ponton@ehu.es (waiting for his answer) Daniel Poulain, Physiopathologie des Candidoses, Faculté de Medecine, Pole Recherche1 Place de Verdun, 59045 Lille; France , dpoulain@univ-lille2.fr (waiting for his answer) Jack Sobel, Division of Infectious Diseases, Wayne State University School of Medicine, 3990 John R str., Detroit, MI 48201, U.S.A. , jsobel@med.wayne.edu
4	Please provide a brief description (500-1000 words) of the working group, including its objectives and expected outcomes, with a timeline as to when the outcomes will be met

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The working group activities will be coordinated by Mycoses Unit of the Department of Infectious, Parasitic and Immunomediated Diseases, Istituto Superiore di Sanità, Rome, Italy.

The group will focus on the mucosal candidiasis (oropharyngeal and vaginal candidiasis), and, through ISHAM, wishes to include colleagues from all parts of the world with similar interests. *Candida albicans* is an opportunistic fungal pathogen that causes severe infections especially in immunodeficient individuals. Although a certain number of antifungal agents are available, the need for new drugs against *C. albicans* is escalating due to both the widespread occurrence of mucosal infections caused by *Candida*, and the development of resistance against available drugs. In fact, oropharyngeal and vaginal candidiasis caused by *Candida* spp., particularly *C. albicans*, continue to be present in the HIV patients, sustained by the virulence potential of this yeast. Moreover, vaginal candidiasis, mostly caused by *C. albicans*, is a common mucosal infection affecting a large proportion of women of reproductive age, some of them affected by recurrent often intractable forms. However, in contrast to systemic candidiasis, relatively little is known about the role of mucosal immunity in protection against *Candida*. Therefore, understanding the components of the host-fungus interaction at the mucosal level can lead to a better understanding of the pathogenesis of mucosal candidiasis and result in the optimization of preventive and therapeutic antifungal strategies. Among the numerous factors associated with virulence in *C. albicans*, hyphal morphogenesis and secretion of aspartyl proteinase (Sap) are likely the most important. Hyphal development from yeast cells is critical for adherence, an essential first step in microbial colonization and the pathogenic process. Adherence may involve both glycosylated and non-glycosylated cell wall proteins acting as adhesins. That the ability to secrete Sap, a nine gene family, is a relevant aspect of mucosal candidiasis is also suggested by the repeated observations that strains of *C. albicans*, with particularly high Sap production, were more frequently isolated from the oral as well as the vaginal cavities of HIV⁺ than HIV⁻ subjects (De Bernardis F. et al. 2001. Med. Mycol. 39, 303). In this context, we have demonstrated that inhibitors of HIV enzyme exert a direct anticandidal effect which is entirely due to the PI capacity to inhibit one or more *C. albicans* Sap, which belong to the same family as HIV-proteinase

The aim of this project is to extend previous clinical and microbiological investigations and, through international collaboration, to understand host-parasite interactions in candidiasis and try to generate novel efficient therapeutic and/or immunological tools. Particularly, we will try to understand the fungal and host components involved in the pathogenesis of mucosal candidiasis.

The following specific objectives will be pursued:

To investigate the relationship between the inhibition of the virulence factors of the fungus and immune reconstitution in HIV⁺ subjects under HAART-PI.

- 1) To characterize gene expression and the specific inhibition of the *C. albicans* aspartyl proteinase (Sap), as correlated to the HAART-PI treatment by monitoring the oral and vaginal fluids taken sequentially from patients.
- 2) To investigate the capacity of more recent PI such as nevirapin, zidovudine, zalcitabine, didanosine, zalcitabine, amprenavir and zalcitabine to inhibit *Candida* Sap to any differential extent as compared to indinavir and zalcitabine and to test new compounds with the property of inhibiting *C. albicans* Sap in vitro and in vivo.
- 3) To characterize gene expression and the specific inhibition of the *C. albicans* aspartyl

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proteinase (Sap), as correlated to the HAART-PI treatment by monitoring the oral and vaginal fluids taken sequentially from patients.

The expected outcomes of this international study on vaginal candidiasis are to provide evidence for the role of virulence factors of *Candida* and to better understand the host immune response at vaginal level.

- 1) To characterize the immune response to *Candida* under treatment with protease inhibitors. To this purpose, in an animal model of mucosal candidiasis, we will study the mechanisms that play a role in the induction of mucosal immunity against *C. albicans* characterizing the interaction between innate and adaptive immunity by analyzing the role of the vaginal dendritic cells (VDCs).
- 2) To assess the protective role of recombinant proteins (Sap2 and mannoprotein) as potential candidate vaccines against mucosal candidiasis.
- 3) The results on the protective anti-*Candida* mechanisms at mucosal level will supply essential data for expanding studies on the development of preventive or therapeutic vaccine against candidiasis.
- 4) The working group is aiming at presenting and disseminating its findings at international events. It also aims to propose and organize a session in the next ISHAM congress in Berlin, 2012. Publication of results is expected at the end of the second year.

5 Expected duration of the working group's operations:

Due to the time-demanding working group activities in order to complete the aforementioned packages of coordinated research work and need for animal studies and the clinical trial period is anticipated that the working group will require a little more than four years (54 months). The following schedule itemizes the outcomes, which can be separately presented and published.

- 1) Isolation and identification of *Candida* spp. from vaginal fluids taken from the two groups of patients, carriers and with recurrent vulvovaginitis respectively, (12 months).
- 2) Expression of *C. albicans* proteinase genes in the vaginal fluids by RT-PCR and Real time PCR (12 months).
- 3) Evaluation of pathogenicity of *Candida* isolates in animal models (12 months).
- 4) Evaluation of protective role of vaginal dendritic cells in mucosal candidiasis (6 months).
- 5) Detection of cytokine expression in women with recurrent vaginitis and carrier by ELISA and by Luminex Multiplex Assays(12 months)

6 If you are applying for ISHAM funds, could you please provide the names and contact information of professional societies, commercial vendors, private foundations, governmental organizations, etc., from which you have also requested funding for your working groups.

Funding will be sought by the working group participants through their Institution and through national and international government organizations and foundations.

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7 **If requesting financial support from ISHAM, please provide a preliminary budget including the initial sum requested and justification for each of the items listed**

As at least one Forum or Workshop is planned, at this point an itemized budget cannot be presented. However, for this event, external funding will be sought. It is anticipated that a maximum sum of \$ 5,000 will only be requested from ISHAM to support this event.

8 **If ISHAM does provide funding, to whom should the support be directed, e.g., coordinators' internal funds management organization – NOTE – Funds will NOT be transferred to any individual.**

9 **Signature of the coordinator(s) – NOTE – electronic signatures are acceptable and only one of the coordinators needs to sign the document:**

Date: