Pharmacology & Pharmacy, **2011, 2, 354-360**
doi:10.4236/pp.2011.24046 Published Online October 2011 (http://www.SciRP.org/journal/pp)

Basic Research—Significance of Detection and Clinical Impact of *Candida albicans* in Non-Immunosuppressed Patients

Petra Heizmann[1], Frank Klefisch[2], Wolfgang R. Heizmann[3]

[1]St. Wolfgang Clinic, Internal Medicine, Bad Griesbach, Germany; [2]Paulinenhaus Krankenanstalt e.V., Berlin, Germany; [3]Centre for Medical Microbiology and Infectiology, Berlin, Germany.
Email: wrheizmann@aol.com

Received May 15th, 2011; revised September 14th, 2011; accepted September 30th, 2011.

ABSTRACT

***Background*:** *The clinical significance of the detection of Candida albicans on mucous membranes of the respiratory or intestinal tract from patients in intensive care units is still not finally clarified. Many patients reveal colonization, although, despite increased risk, there are only a few invasive infections detectable. Therefore, antimycotic therapy in this setting is strongly discouraged. In reality, however, many patients receive antimycotics as a pre-emptive therapy. To elucidate this point, a literature research was performed.* ***Results*:** *In the light of new results on the pathogenicity of C. albicans, the recommendation not to treat should be discussed anew. Without becoming invasive, C. albicans influences the immune system negatively in an anti-inflammatory sense (Th2) by means of at least two distinct mechanisms [action on toll like receptors (TLR), production of farnesol], which will be discussed.* ***Conclusion*:** *It is believed that patients in the phase of CARS or MARS can be further endangered by concomitant colonization of mucous membranes by C. albicans, i.e., in the sense of an anti-inflammatory immune response. Treatment with azole preparations, like fluconazole, which interacts with ergosterol synthesis in this phase of the disease, may trigger an additional effect on the patient, through increase of farnesol concentration by way of a negative feedback. Results of animal experiments on the immune system and concomitant therapeutic consequences indicate the need for verification through clinical trials.*

***Keywords*:** *Candida Albicans, Farnesol, Azole, Echinocandin, TLR, Immune Answer, Th Cell*

1. Introduction

"The diagnosis of pulmonary moniliasis (*C. albicans*-Infection) is fraught with difficulties … Actually there are no indisputable criteria for establishing the diagnosis…" [1]. Even after 50 years the clinical significance of a detection of *Candida* in the respiratory or intestinal tract is greatly disputed. Based on the results of studies performed on non-neutropenic patients, the detection of *Candida* species in specimen of the deep respiratory tract, even in high concentrations, is regarded as colonization of mucous membranes rather than invasive infection [2], Therefore, in many cases, administration of anti-fungal drugs is regarded as unwarranted and expensive [3].

On the other hand, colonization of mucous membranes represents a significant risk factor for invasive *Candida*-infections [4-6]. For example, in a previous study, growth of *Candida* in at least one specimen was positive in 215 of 357 patients (60.2%) [7]. *Candida* was mostly detected in secretions of the respiratory tract (49.8%), in rectal smears (48.3%) and in wounds (20.1%). The relative part of *Candida albicans* was 72%, *Candida glabrata* 16%, *Candida tropicalis* 5%, *Candida parapsilosis* 3% and *Candida krusei* 2%. A colonization—particularly in several localizations—together with other risk factors such as loss of skin and mucous membrane barrier function, major surgical procedures (in particular abdominal), burns, total parenteral nutrition, acute renal failure and haemodialysis, high APACHE II scores, antacids and artificial respiration can contribute to an increased risk of invasive *Candida* infections. However, the number of proven invasive infections (detection in blood cultures, Candida endophthalmitis, growth from usually sterile specimen such as pleural or peritoneal fluid) based on the number of patients with colonization, is rather rare. Of a total of 1669 patients, 719 patients had no colonization or

infection; in 883 patients colonization was detected, but only 97 patients (5.8%) had an infection [8].

Consequently the conclusion seems obvious: detection of *Candida* from the deep respiratory or intestinal tract has no further significance for affected patients, unless they have additional risk factors for an invasive infection e.g. colonization in multiple body sites. Nevertheless, based on personal experience, a large number of ICU patients are treated with antifungals without detection of an invasive infection. The question arises as to whether a pathogenic correlation does exist that justifies the "empirical therapy" (better: prophylaxis or "pre-emptive therapy").

2. Material and Methods

A literature review was performed using PubMed and the following key words: *Candida albicans*, immune system, therapy, fluconazole, echinocandin, farnesol, TLR.

3. Results from Basic Research

3.1. An Alternative Way for Pathogenesis

To be clinically relevant, *C. albicans* would have to possess virulence factors that can negatively influence the homeostasis in a patient, independently from an invasion.

A connection between *C. albicans* and the development of an allergic reaction of the respiratory system has already been postulated over 50 years ago [1]. First publications of systematic studies on this topic appeared almost 20 years ago. In 10 out of 13 children with allergic asthma and *C. albicans* specific IgE antibodies a reaction with *Candida* antigen of 46 kDa was detected [9]. In an additional study, sera from 105 patients with *C. albicans*-specific IgE antibodies reacted with 42 different candida antigens in the immunoblot—42% with the 46 kDa antigen and 28% with a 27 kDa antigen [10]. According to Ito K. *et al*. [11], the 46 kDa antigen is an enolase; antibodies directed against enolase were detected in 37% of patients, all positive for *C. albicans* IgE antibodies.

The detection of *C. albicans*-specific IgE antibodies indicates that the immune system reacts to a *C. albicans* antigen stimulus with a Th2 ("anti-inflammatory") response. In animal experiments, the administration of IL-4 and IL-10 (Th2) was the reason for a fatal progression which was linked to the inhibition of IL-12 and a Th2-dominance [12]. In 1999, Talluri G *et al*. [13] could demonstrate, in patients with candiduria and candidemia, that the production of interleukins of the Th2 cell lineage (IL-4, IL-10; "anti-inflammatory") was increased and that the IL-2 concentration (Th0, Th1, "inflammatory") was decreased. The immune system of patients with symptoms of chronic mucocutaneous candidiasis also shows a shift of the T-cells towards the Th2-population [14]. This anti-inflammatory response of the immune system with a prevalence of the Th2-cell lineage results in insufficient or no elimination of pathogens, and thereby in a relative immune weakness.

3.2. Growth Form of *C. albicans* and Immune Response

There are two different types of *C. albicans* growth forms: yeast cells (blastoconidia) and hyphae, which can alternate depending on the external conditions (see below). Therefore, a differentiation between these two forms is significant as this controls the interaction between micro- organisms and the immune system.

The production of various interleukins as a reaction to *C. albicans* antigen is controlled by toll-like receptors (TLR) of antigen presenting cells. In animal testing, mice with and without TLR2 were infected with *C. albicans*. In this case, mice *without* TLR2 ($TLR2^-$) survived longer than those *with* TLR2 ($TLR2^+$), the colony counts in the kidneys of $TLR2^-$-mice was lower by a factor of 100 ($p < 0.01$). At the same time, the IL-10 production in $TLR2^-$-mice was reduced, the IFN-γ concentration increased and the destruction of *Candida* by macrophages improved [15]. IL-10 appears to be a key to the immune defence of *C. albicans* infections. In the event of a systematic infection, knockout mice without IL-10 production were able to eliminate significantly more *C. albicans* cells in the kidneys than controls with IL-10 production ($p > 0.05$). This phenomenon could be caused by a direct influence of IL-10 on the function of neutrophilic granulocytes [16].

The stimulation of dendritic cells with zymosan (derivative of yeast cell walls) leads to an induction of IL-10- and of TGF-β (transforming growth factor beta), with simultaneous suppression of IL-12, IL-6 and TNF-α (pro-inflammatory), whereby both TLR-2 (as heterodimers together with TLR-6) and Dectin-1 control the signal transduction [17,18].

According to the model of Van der Graaf [19], the growth form of *C. albicans* significantly influences the immune response. If the cell grows as blastoconidium (yeast cell), it interacts with TLR4 of antigen-presenting cells. This trigger leads to a pro-inflammatory (Th1) response with a significant increase of IFN-γ and TNF-α. However, if *C. albicans* switches to the hyphal form, the anti-inflammatory (Th2) response overbalances with an increase of IL-10 production controlled by TLR2.

3.3. *C. albicans* and Farnesol Formation—Impact on the Immune System

C. albicans produces a lipophilic substance called farnesol. Farnesol is produced from farnesyl diphosphate, a

molecule that interestingly represents a precursor of cholesterol in humans, ergosterol (cell membrane) in yeasts and staphyloxanthin (yellow pigment, virulence factor) in S*taphylococcus aureus*. For *C. albicans*, the E,E-Isomer has the function of a "quorum sensing molecule" (QSM), *i.e*., it is significant for the communication of yeast cells amongst each other and, for example, controls the transition of the blastoconidia to the hyphal form [20], depending on time of exposure. In addition, the lipophilic farnesol interacts with host cell membranes, *i.e*., it can possibly make way for an invasive infection. It also interferes with the immune response and protects *C. albicans* from the impact of oxygen radicals [21,22]. In physiological concentrations, farnesol reduces the effect of H_2O_2 on the *Candida* cell, strains with farnesol production are ~20 times more resistant than strains without [23,24].

In an animal model, mice infected with farnesol pretreated or farnesol-producing *C. albicans* strains die more quickly [25,26]. In the control group with *C. albicans* knockout strains without farnesol production, the survival rate was significantly higher ($p < 0.0014$). Farnesol actually suppresses the production of IL-12 and IFN-γ, both necessary for an adequate defence against *C. albicans* infections (Th1) and it also increases the IL-5 level (Th2) [22].

In addition, farnesol modulates the expression of genes (*TUP*1, *CRK*1, *PDE*2) which regulate the hyphal formation in terms of an increased formation of hyphae [27].

These experimental data show that *C. albicans* has a negative impact on the immune system (growth in hyphal form and interaction with TLR2; farnesol production) with a shift of the T-cell response towards Th2 (anti-inflammatory), independent from invasiveness.

3.4. Factors That Can Impact the Production of Farnesol through *C. albicans*

As mentioned previously, farnesol is generated from two molecules of farnesyl diphosphate. Farnesyl diphosphate is an early precursor in the synthesis of ergosterol, a significant part of the cytoplasmic membrane of yeast cells. If *C. albicans* cells are exposed to azoles, the farnesol production increases significantly. This effect is also used in the various previously described infection models [23,25,28]. As azoles, e.g., fluconazole are inhibiting the ergosterol synthesis through inhibition of the lanosterole 14-α-demethylase, a negative feedback must be presumed. Clinical isolates of *C. albicans* strains produce 2 to 4 μM farnesol with a cell density of 10^8 cells/ml. Under the influence of subinhibitory concentrations of substances which, like azoles, inhibit the sterol biosynthesis, the production increases by the factor of 10 - 45 [27]. Abe *et al*. (2009) were able to demonstrate that farnesol concentrations of ~56 μM and higher suppress the inhibitory activity of macrophages on hyphae formation of *C. albicans* and also leads to an apoptosis of the macrophages [29]. Evidently, farnesol also increases the apoptosis of cells of an oral squamous epithelial carcinoma cell line [30].

3.5. Mucous Membranes Intersection—*C. albicans* and the Local Immune System

Anaerobic conditions, as they exist in biofilms on mucous membranes, lead to a growth of *C. albicans* in hyphal form, the growth form that controls the anti-inflammatory shift of T-cells via TLR2. In experimentally produced biofilms, antifungal drugs such as amphotericin B, clotrimazole, fluconazole, miconazole and ketoconazole do not inhibit the growth of *C. albicans* [31]. The only effect of the azole would therefore be the increase of farnesol concentration with subsequent suppression of IL12 and IFN-γ. In fact, in the model of a mucocutaneous Candida infection, the suppression of inflammatory leukocytes could be observed [32]. This is also true in recurrent vulvovaginal candidosis [33].

Candida cells incorporated in biofilms of mucous membranes e.g. of the gut are in close contact to the mucous membrane-associated immune system (MALT). The M-cells of the MALT are situated at the boundary surface both exogenously (gut lumen) and endogenously in close contact with the micro-organisms existing in the gut lumen, like hyphae of *C. albicans*. Without having to become invasive, *C. albicans* can control the differentiation of Th0-cells towards Th2-cells via the TLR2 of M-cells [34] in this situation [19]. Animal testing actually demonstrates that the immune system of the intestine is able to influence cytokine levels in lymph nodes and in the blood [35].

In the model of the gastrointestinal *Candida* infection, the administration of IL-10 and IL-4 lead to an induction of CD4+ cells in the Peyer's patches with production of high levels of IL-10 and IL-4 [12]. At the same time, this negative effect on the immune system is increased through farnesol (**Figure 1**).

4. Possible Effects for Patients

The colonization of patients with high *C. albicans* cell counts is in most cases an event of a prolonged hospital stay, often also the result of a previous or existing antibiotic treatment [36,37]. However, this means that the affected persons could be in a CARS or MARS condition [38]. In this phase, multiple organ dysfunctions or organ failure could occur, the condition of the patient deteriorates and the fatalities could increase [39].

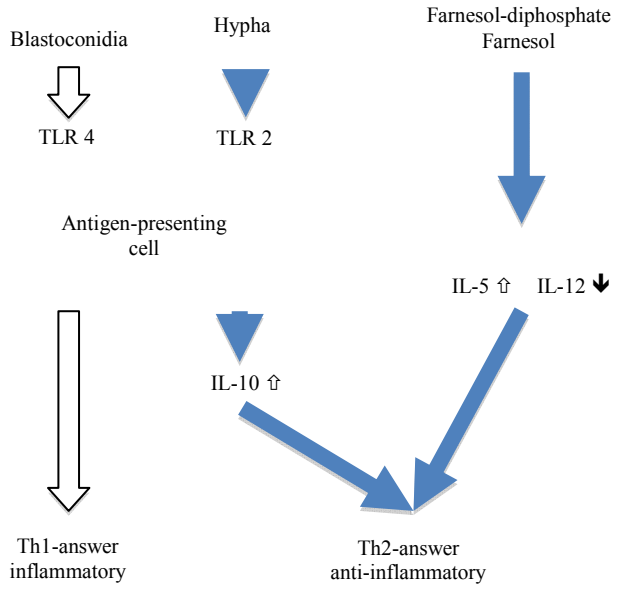

Figure 1. Impact of *C. albicans* on the immune system. Blastoconidia cause the stimulation of the inflammatory Th1 response by TLR4 mediated activation of antigen-presenting cells. Hyphae stimulate TLR2 signalling and production of IL-10 which promotes an anti-inflammatory Th2 response. Farnesol leads to up-regulation of IL-5 and down-regulation of IL-12 and IFNγ promoting the Th2 response.

In patients with a colonization of the mucous membranes through *C. albicans,* the immune system could be weakened via the above-mentioned mechanisms during this critical period of illness. If it is now decided—often also because previous antibiotic treatments have not resulted in an improved clinical condition—to eliminate the yeasts by administering antifungal drugs, fluconazole is often selected nowadays.

However, this decision in particular could be associated with serious disadvantages for the patient, in light of the illustrated pathogenic processes. In the case of a sepsis through a Gram-negative pathogen like *Escherichia coli*, the production of IL-12 usually increases via the release of liopolysaccharides of the cell wall. A Th1-response develops that leads to an inflammatory response and therefore to elimination of the pathogen. However, Navarathna *et al*. [26] demonstrated in their experiment that, under the influence of farnesol, this IL-12 stimulation remains absent: therefore, a significant function of the immune system fails (**Table 1**).

5. Conclusion and Therapeutic Consequences

Basic research of previous years has demonstrated how actively *C. albicans* can impact the host immune system via TLR and farnesol production in terms of an anti-inflammatory (Th2) immune response. Thus, the detection of *C. albicans* on mucous membranes obtains—at least in some patients—a completely new, clinically relevant significance. Precisely in those patients who are in the phase of CARS or MARS with reduced cellular defence, an increase of this process in phases with bacterial translocation could lead to a worsening in the course of the disease.

Table 1. Changes of the IL-12 production under the influence of LPS, IFN-γ and farnesol [26].

Pre-treatment	Average IL-12 production (pg/ml)	
	p40	p70
None	1.5	4.25
Farnesol (100 µM)	0.33	2
IFN-γ + LPS	3215	40.8
Farnesol + IFN-γ + LPS	1.7	7.1

Due to the results of basic research, a rational basis exists nowadays to treat these patients with antifungal drugs in order to interrupt the pathogenic process of the immune modulation. Azole should subsequently not be prescribed for critically ill patients as this would result in an increase of farnesol formation by a negative feedback through inhibition of the ergosterol synthesis.

Contrary to azoles, echinocandins like caspofungin or anidulafungin do not inhibit the ergosterol metabolism of *C. albicans* and are effective in biofilms [40]: *C. albicans* is eliminated without directly resulting in an increase of the farnesol concentration through negative feedback.

In addition, echinocandins possess a further significant property. They interfere with the cell wall of *C. albicans*, which mainly consists of β-glucans and that have an impact on the immune system in terms of a pro-inflammatory response. However, this characteristic does not usually occur as the β-glucans are not accessible to the immune system through an external mannan layer. Only when *C. albicans* cells are exposed to sub-inhibitory concentrations of caspofungin the level of TNFα (Th1-response) increases three to four times under experimental conditions, in comparison to untreated *Candida* cells [41].

The model presented here—immune modulating effects of *C. albicans*—could also explain the debated superior clinical outcome of anidulafungin in comparison to fluconazole in *C. albicans* infections [42].

Of specific interest are future clinical studies in which the design is applied such that it can demonstrate which patients with *C. albicans* colonization ideally benefit from an echinocandin therapy.

REFERENCES

[1] E. L. Keeney, "Pulmonary Mycotic Infections; Allergic and Immunologic Factors," *California Medicine*, Vol. 81, No. 6, 1954, pp. 367-378.

[2] J. Rello, M. E. Esandi, E. Diaz, D. Mariscal, M. Gallego and J. Valles, "The Role of Candida sp Isolated from Bronchoscopic Samples in Nonneutropenic Patients," *Chest*, Vol. 114, No. 1, 1998, pp. 146-149. doi:10.1378/chest.114.1.146

[3] J. Barenfanger, P. Arakere, R. D. Cruz, A. Imran, C. Drake, J. Lawhorn, S. J. Verhulst and N. Khardori, "Improved Outcomes Associated with Limiting Identification of *Candida* spp. in Respiratory Secretions," *Journal of Clinical Microbiology*, Vol. 41, No. 12, 2003, pp. 5645-5649. doi:10.1128/JCM.41.12.5645-5649.2003

[4] D. Pittet, M. Monod, P. M. Suter, E. Frenk and R. Auckenthaler, "Candida Colonization and Subsequent Infections in Critically Ill Surgical Patients," *Annals of Surgery*, Vol. 220, No. 6, 1994, pp. 751-758. doi:10.1097/00000658-199412000-00008

[5] D. R. Reagan, M. A. Pfaller, R. J. Hollis and R. P. Wenzel, "Characterization of the Sequence of Colonization and Nosocomial Candidemia Using DNA Fingerprinting and a DNA Probe," *Journal of Clinical Microbiology*, Vol. 28, No. 12, 1990, pp. 2733-2738.

[6] A. Voss, R. J. Hollis, M. A. Pfaller, R. P. Wenzel and B. N. Doebbeling, "Investigation of the Sequence of Colonization and Candidemia in Nonneutropenic Patients," *Journal of Clinical Microbiology*, Vol. 32, No. 4, 1994, pp. 975-980.

[7] M. Laverdiere, A. C. Labbe, C. Restieri, C. Rotstein, D. Heyland, S. Madger and T. Stewart, "Susceptibility Patterns of *Candida* Species Recovered from Canadian Intensive Care Units," *Journal of Critical Care*, Vol. 22, No. 3, 2007, pp. 245- 250. doi:10.1016/j.jcrc.2006.10.038

[8] C. Leon, S. Ruiz-Santana, P. Saavedra, B. Almirante, J. Nolla-Salas, F. Alvarez-Lerma, J. Garnacho-Montero and M. A. Leon, "A Bedside Scoring System ("*Candida score*") for Early Antifungal Treatment in Nonneutropenic Critically Ill Patients with *Candida* Colonization," *Critical Care Medicine*, Vol. 34, No. 3, 2006, pp. 730-737. doi:10.1097/01.CCM.0000202208.37364.7D

[9] J. Savolainen, M. Viander and A. Koivikko, "IgE-, IgA- and IgG-Antibody Responses to Carbohydrate and Protein Antigens of *Candida albicans* in Asthmatic Children," *Allergy*, Vol. 45, No. 1, 1990, pp. 54-63. doi:10.1111/j.1398-9995.1990.tb01084.x

[10] J. Savolainen, "A Standardized Densitometric Immunoblotting Analysis of *Candida albicans* Protein Allergens," *Clinical & Experimental Allergy*, Vol. 25, No. 4, 1995, pp. 357-363. doi:10.1111/j.1365-2222.1995.tb01054.x

[11] K. Ito, A. Ishiguro, T. Kanbe, K. Tanaka and S. Torii, "Detection of IgE Antibody against *Candida albicans* enolase and Its Crossreactivity to *Saccharomyces cerevisiae* Enolase," *Clinical & Experimental Allergy*, Vol. 25, No. 6, 1995, pp. 522-528. doi:10.1111/j.1365-2222.1995.tb01089.x

[12] L. Tonnetti, R. Spaccapelo, E. Cenci, A. Mencacci, P. Puccetti, R. L. Coffman, F. Bistoni and L. Romani, "Interleukin-4 and -10 Exacerbate Candidiasis in Mice," *European Journal of Immunology*, Vol. 25, No. 6, 1995, pp. 1559-1565. doi:10.1002/eji.1830250614

[13] G. Talluri, V. K. Marella, D. Shirazian and G. J. Wise, "Immune Response in Patients with Persistent Candiduria and Occult Candidemia," *Journal of Urology*, Vol. 162, No. 4, 1999, pp. 1361-1364. doi:10.1016/S0022-5347(05)68288-2

[14] D. Lilic, I. Gravenor, N. Robson, D. A. Lammas, P. Drysdale, J. E. Calvert, A. J. Cant and M. Abinun, "Deregulated Production of Protective Cytokines in Response to *Candida albicans* Infection in Patients with Chronic Mucocutaneous Candidiasis," *Infection and Immunity*, Vol. 71, No. 10, 2003, pp. 5690-5699. doi:10.1128/IAI.71.10.5690-5699.2003

[15] M. G. Netea, R. Sutmuller, C. Hermann, C. A. van der Graaf, J. W. van der Meer, J. H. van Krieken, T. Hartung, G. Adema and B. J. Kullberg, "Toll-Like Receptor 2 Suppresses Immunity against *Candida albicans* through Induction of IL-10 and Regulatory T Cells," *Journal of Immunology*, Vol. 172, No. 6, 2004, pp. 3712-3718.

[16] A. Vazquez-Torres, J. Jones-Carson, R. D. Wagner, T. Warner and E. Balish, "Early Resistance of interleukin-10 Knockout Mice to Acute Systemic Candidiasis," *Infection and Immunity*, Vol. 67, No. 2, 1999, pp. 670-674.

[17] S. Dillon, S. Agrawal, K. Banerjee, J. Letterio, T. L. Denning, K. Oswald-Richter, D. J. Kasprowicz, K. Kellar, J. Pare, T. van Dyke, S. Ziegler, D. Unutmaz and B. Pulendran, "Yeast Zymosan, a Stimulus for TLR2 and Dectin-1, Induces Regulatory Antigen-Presenting Cells and Immunological Tolerance," *Journal of Clinical Investigation*, Vol. 116, No. 4, 2006, pp. 916-928. doi:10.1172/JCI27203

[18] M. G. Netea, F. van de Veerdonk, I. Verschueren, J. W. van der Meer and B. J. Kullberg, "Role of TLR1 and TLR6 in the Host Defense against Disseminated Candidiasis," *FEMS Immunology & Medical Microbiology*, Vol. 52, No. 1, 2008, pp. 118-123. doi:10.1111/j.1574-695X.2007.00353.x

[19] C. A. van der Graaf, M. G. Netea, I. Verschueren, J. W. van der Meer and B. J. Kullberg, "Differential Cytokine Production and Toll-Like Receptor Signaling Pathways by *Candida albicans* Blastoconidia and Hyphae," *Infection and Immunity*, Vol. 73, No. 11, 2005, pp. 7458-7464. doi:10.1128/IAI.73.11.7458-7464.2005

[20] D. D. Mosel, R. Dumitru, J. M. Hornby, A. L. Atkin and K. W. Nickerson, "Farnesol Concentrations Required to Block Germ Tube Formation in *Candida albicans* in the Presence and Absence of Serum," *Applied and Environmental Microbiology*, Vol. 71, No. 8, 2005, pp. 4938-4940. doi:10.1128/AEM.71.8.4938-4940.2005

[21] J. M. Hornby, E. C. Jensen, A. D. Lisec, J. J. Tasto, B. Jahnke, R. Shoemaker, P. Dussault and K. W. Nickerson, "Quorum Sensing in the Dimorphic Fungus *Candida albi-*

cans Is Mediated by Farnesol," *Applied and Environmental Microbiology*, Vol. 67, No. 7, 2001, pp. 2982-2992. doi:10.1128/AEM.67.7.2982-2992.2001

[22] D. H. Navarathna, K. W. Nickerson, G. E. Duhamel, T. R. Jerrels and T. M. Petro, "Exogenous Farnesol Interferes with the Normal Progression of Cytokine Expression during Candidiasis in a Mouse Model," *Infection and Immunity*, 2007, Vol. 75, No. 8, pp. 4006-4011. doi:10.1128/IAI.00397-07

[23] C. Westwater, E. Balish and D. A. Schofield, "*Candida albicans*-Conditioned Medium Protects Yeast Cells from Oxidative Stress: A Possible Link between Quorum Sensing and Oxidative Stress Resistance," *Eukaryotic Cell*, Vol. 4, No. 10, 2005, pp. 1654-1661. doi:10.1128/EC.4.10.1654-1661.2005

[24] A. Deveau, A. E. Piispanen, A. A. Jackson and D. A. Hogan, "Farnesol Induces Hydrogen Peroxide Resistance in *Candida albicans* Yeast by Inhibiting the Ras-Cyclic AMP Signaling Pathway," *Eukaryotic Cell*, Vol. 9, No. 4, 2010, pp. 569-577. doi:10.1128/EC.00321-09

[25] D. H. Navarathna, J. M. Hornby, N. Hoerrmann, A. M. Parkhurst, G. E. Duhamel and K. W. Nickerson, "Enhanced Pathogenicity of *Candida albicans* Pre-Treated with Subinhibitory Concentrations of Fluconazole in a Mouse Model of Disseminated Candidiasis," *Journal of Antimicrobial Chemotherapy*, Vol. 56, No. 6, 2005, pp. 1156-1159. doi:10.1093/jac/dki383

[26] D. H. Navarathna, J. M. Hornby, N. Krishnan, A. Parkhurst, G. E. Duhamel and K. W. Nickerson, "Effect of Farnesol on a Mouse Model of Systemic Candidiasis, Determined by Use of a DPP3 Knockout Mutant of *Candida albicans*," *Infection and Immunity*, Vol. 75, No. 4, 2007, pp. 1609-1618.

[27] Y. Y. Cao, Y. B. Cao, Z. Xu, K. Ying, Y. Li, Y. Xie, Z. Y. Zhu, W. S. Chen and Y. Y. Jiang, "cDNA Microarray Analysis of Differential Gene Expression in *Candida albicans* Biofilm Exposed to Farnesol," *Antimicrobial Agents and Chemotherapy*, Vol. 49, No. 2, 2005, pp. 584-589. doi:10.1128/AAC.49.2.584-589.2005

[28] J. M. Hornby and K. W. Nickerson, "Enhanced Production of Farnesol by *Candida albicans* Treated with Four Azoles," *Antimicrobial Agents and Chemotherapy*, Vol. 48, No. 6, 2004, pp. 2305-2307. doi:10.1128/AAC.48.6.2305-2307.2004

[29] S. Abe, R. Tsunashima, R. Iijima, T. Yamada, N. Maruyama, T. Hisajima, Y. Abe, H. Oshima and M. Yamazaki, "Suppression of Anti-Candida Activity of Macrophages by a Quorum-Sensing Molecule, Farnesol, through Induction of Oxidative Stress," *Microbiology and Immunology*, Vol. 53, No. 6, 2009, pp. 323-330. doi:10.1111/j.1348-0421.2009.00128.x

[30] M. A. Scheper, M. E. Shirtliff, T. F. Meiller, B. M. Peters and M. A. Jabra-Rizk, "Farnesol, a Fungal Quorum-Sensing Molecule Triggers Apoptosis in Human Oral Squamous Carcinoma Cells," *Neoplasia*, Vol. 10, No. 9, 2008, pp. 954-963.

[31] R. Dumitru, J. M. Hornby and K. W. Nickerson, "Defined Anaerobic Growth Medium for Studying *Candida albicans* Basic Biology and Resistance to Eight Antifungal Drugs," *Antimicrobial Agents and Chemotherapy*, Vol. 48, No. 7, 2004, pp. 2350-2354. doi:10.1128/AAC.48.7.2350-2354.2004

[32] T. Hisajima, N. Maruyama, Y. Tanabe, H. Ishibashi, T. Yamada, K. Makimura, Y. Nishiyama, K. Funakoshi, H. Oshima and S. Abe, "Protective Effects of Farnesol against Oral Candidiasis in Mice," *Microbiology and Immunology*, Vol. 52, No. 7, 2008, pp. 327-333. doi:10.1111/j.1348-0421.2008.00044.x

[33] T. M. Weissenbacher, S. S. Witkin, A. Gingelmaier, C. Scholz, K. Friese and I. Mylonas, "Relationship between Recurrent Vuvovaginal Candidosis and Immune Mediators in Vaginal Fluid," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, Vol. 144, No. 1, 2009, pp. 59-63. doi:10.1016/j.ejogrb.2009.01.010

[34] S. M. Chabot, T. S. Chernin, M. Shawi, J. Wagner, S. Farrant, D. S. Burt, C. Cyr and M. R. Neutra, "TLR2 Activation by Proteosomes Promotes Uptake of Particulate Vaccines at Mucosal Surfaces," *Vaccine*, Vol. 25, No. 29, 2007, pp. 5348-5358. doi:10.1016/j.vaccine.2007.05.029

[35] M. R. Mainous, W. Ertel, I. H. Chaudry and E. A. Deitch, "The Gut: A Cytokine-Generating Organ in Systemic Inflammation?" *Shock*, Vol. 4, No. 3, 1995, pp. 193-199. doi:10.1097/00024382-199509000-00007

[36] E. Mavromanolakis, S. Maraki, A. Cranidis, Y. Tselentis, D. P. Kontoyiannis and G. Samonis, "The Impact of Norfloxacin, Ciprofloxacin and Ofloxacin on Human Gut Colonization by *Candida albicans*," *Scandinavian Journal of Infectious Diseases*, Vol. 33, No. 6, 2001, pp. 477-478. doi:10.1080/00365540152030006

[37] G. Samonis, H. Anastassiadou, M. Dassiou, Y. Tselentis and G. P. Bodey, "Effects of Broad-Spectrum Antibiotics on Colonization of Gastrointestinal Tracts of Mice by *Candida albicans*," *Antimicrobial Agents and Chemotherapy*, Vol. 38, No. 3, 1994, pp. 602-603.

[38] A. Oberholzer, C. Oberholzer and L. L. Moldawer, "Sepsis Syndromes: Understanding the Role of Innate and acquired Immunity," *Shock*, Vol. 16, No. 2, 2001, pp. 83-96. doi:10.1097/00024382-200116020-00001

[39] R. S. Hotchkiss and I. E. Karl, "The Pathophysiology and Treatment of Sepsis," *The New England Journal of Medicine*, Vol. 348, No. 2, 2003, pp. 138-150. doi:10.1056/NEJMra021333

[40] A. Katragkou, A. Chatzimoschou, M. Simitsopoulou, M. Dalakiouridou, E. Diza-Mataftsi, C. Tsantali and E. Roilides, "Differential Activities of Newer Antifungal Agents against *Candida albicans* and *Candida parapsilosis* Biofilms," *Antimicrobial Agents and Chemotherapy*, Vol. 52, No. 1, 2008, pp. 357-360. doi:10.1128/AAC.00856-07

[41] R. T. Wheeler and G. R. Fink, "A Drug-Sensitive Genetic Network Masks Fungi from the Immune System," *PLoS Pathogens*, Vol. 2, No. 4, 2006, p. e35. www.10.1371/journal.ppat.0020035

[42] A. C. Reboli, C. Rotstein, P. G. Pappas, S. W. Chapman,

D. H. Kett, D. Kumar, R. Betts, M. Wible, B. P. Goldstein, J. Schranz, D. S. Krause and T. J. Walsh, "Anidulafungin versus Fluconazole for Invasive Candidiasis," *The New England Journal of Medicine*, Vol. 356, No. 24, 2007, pp. 2472-2482. doi:10.1056/NEJMoa066906

Abbreviations

CARS	Compensatory anti-inflammatory response syndrome
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICU	Intensive care unit
Ig	Immunoglobulin
IL	Interleukin
IFN	Interferon
CFU	Colony forming units
LPS	Lipopolysaccharide
MARS	Mixed anti-inflammatory response syndrome
TGF	Tumour growth factor
Th	T helper cells
TLR	Toll like receptor
TNF	Tumour necrosis factor

