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Quorum Sensing and Other Aspects of the Biology of *Candida albicans*

Kenneth W. Nickerson
University of Nebraska - Lincoln, knickerson1@unl.edu

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Quorum Sensing and Other Aspects of the Biology of *Candida albicans*

Professor Kenneth W. Nickerson
School of Biological Sciences
University of Nebraska
Lincoln, Nebraska USA 68588-0666.

Most dimorphic fungi exhibit cell density dependent effects in that they grow as yeasts when inoculated at $>$ 10^6 cells per ml and as mycelia when inoculated at $<$ 10^6 cells per ml. For *Candida albicans*, we discovered (2001) that this phenomenon (quorum sensing) is due to the production and secretion of the C_{15} isoprenoid trans-trans farnesol. Since then, we found that *C. albicans* cells treated with sublethal levels of zaragozic acid (2003) or fluconazole (2004) produced 10-40X more farnesol and that these fluconazole treated cells were ca. 5X more toxic to mice following tail vein injection. This suggestion that farnesol might act as a virulence factor as well as a QSM was confirmed (2007) when we showed that a mutant of *C. albicans* which produced only 15% as much farnesol was 5X less toxic to mice; both farnesol production and pathogenicity were restored when the mutant was reconstituted. Farnesol production is regulated in that it is increased 18X in *tup1* and *nrg1* mutants (2008) but shut down entirely during anaerobic growth (2004) or in the opaque phase of growth (2007). Farnesol is also a bioactive molecule. For example, we showed (2006) that farnesol triggered apoptosis in both *Aspergillus nidulans* and *Aspergillus fumigatus*.

Four other aspects of *Candida* biology are ongoing in my laboratory and in my collaborations. 1/ The first concerns the mechanisms by which *C. albicans* protects itself from the otherwise toxic effects of excess farnesol. If the *Aspergilli* undergo apoptosis, why not *C. albicans*? We note that the isoprene chain length for ubiquinone is six in *Saccharomyces*, seven in most *Candida* species, and nine in *C. albicans*. Having ubiquinone more firmly embedded in the mitochondria minimizes the farnesol induced production of reactive oxygen species. 2/ The second concerns the mechanisms by which farnesol acts as a virulence factor during pathogenesis. There is no evidence that farnesol blocks mycelial growth or germ tube formation *in vivo*. Instead, a possible mechanism derives from our finding that farnesol acts as a chemoattractant for mouse macrophages. Our current model (the Trojan Horse model) has this engulfment by macrophages contributing to virulence because the *Candida* cells will kill the macrophages and escape 3-5 hours later, after the macrophages have migrated far away from the initial engulfment site. Thus, the macrophage unwittingly acts to spread the infection. 3/ The third concerns the 4-5X decreased virulence in mice of mutants which have lost their ability to use urea as a nitrogen source. An in press paper by Dhammika Navarathna *et al* shows that this enzyme, urea amidolyase, should also be considered as a virulence factor. This idea leads to the correlation that the two organs which are most crucial for patient outcome in candidiasis (kidneys and brain) are also the organs with the highest urea content. 4/ The fourth concerns the role of biotin in *Candida* biology. *C. albicans* is generally considered to be a biotin auxotroph and yet it can still achieve ca. 50% cell yields after repeated transfers in the absence of exogenous biotin. Also, when grown with added biotin, their histones are extensively biotinylated, as detected by both LC/MS/MS and Western blots using an anti-biotin antibody. Similar techniques did not detect biotinylated histones in *Saccharomyces cerevisiae*. Finally, excess biotin can stimulate germ tube formation in *C. albicans*.

CURRICULUM VITAE

Kenneth W. Nickerson, PhD

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School of Biological Sciences
University of Nebraska
Lincoln, Nebraska USA 68588-0666
Email：knickerson1@unl.edu

Kenneth Nickerson is Professor of Biological Sciences at the University of Nebraska in Lincoln, Nebraska. He graduated with degrees in Chemistry from Rutgers University (BS 1963) and the University of Cincinnati (PhD 1969). He did post-doctoral research in Biochemistry & Biophysics and the Microbial Insecticides before coming to the University of Nebraska in 1973 to work in Plant Pathology with James Van Etten on the physiology of fungal spore germination. He joined the faculty in Biological Sciences in 1975. During that time his primary research interests concerned *Bacillus thuringiensis* and the microbial insecticides.

Professor Nickerson's mid career shift to studying yeast-mycelial dimorphism in fungi was influenced by a sabbatical year (1986-87) in New Zealand with Patrick A. Sullivan as well as taking the Molecular Mycology course at the Marine Biology Laboratory in Woods Hole (1999). His current research interests include: cell density dependent effects (quorum sensing) in *Candida albicans*, farnesol as a virulence factor in pathogenesis, urea utilization by fungi, chlamydospores, the anaerobic growth of *C. albicans*, and novel compounds which stimulate germ tube formation and mycelial growth in *C. albicans*. He has published 140 articles in peer reviewed journals.

Professor Nickerson was Editor of Applied & Environmental Microbiology for 10 years (1987-1996) with primary responsibility for the Mycology and Invertebrate Microbiology sections. Since 2007 he has been an Editor for the Journal of Applied Microbiology and Letters in Applied Microbiology. He is a member of the American Academy for Microbiology. He is also a member of the American Society for Microbiology, the Society for General Microbiology (UK), the American Society for Biochemistry and Molecular Biology, and the Medical Mycology Society of America. He is also the middle rung of three generations of yeast/fungal physiologists, being the son of Walter J. Nickerson and the father of Daniel P. Nickerson.

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