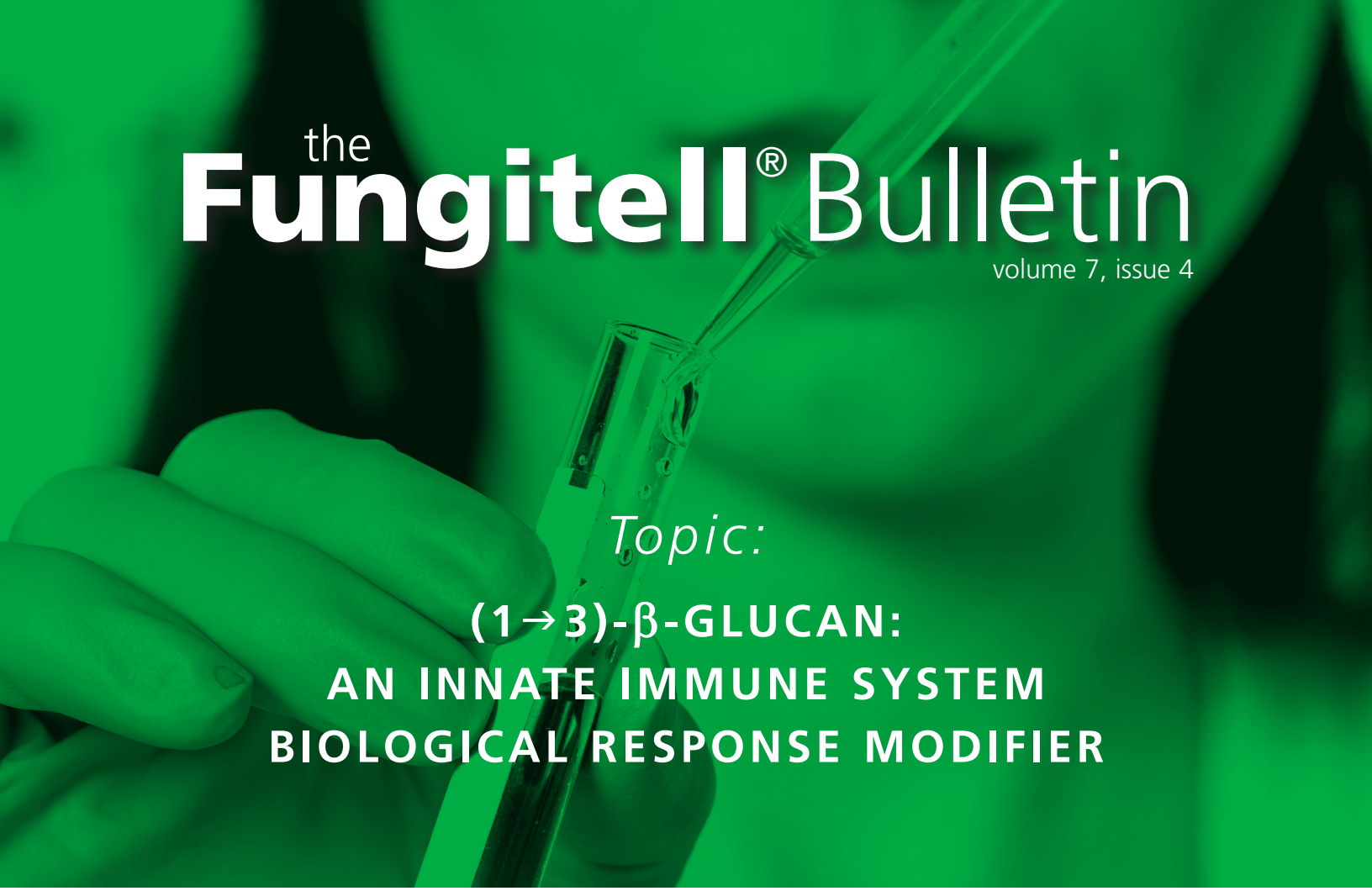

the Fungitell® Bulletin
volume 7, issue 4

Topic:

(1→3)-β-GLUCAN: AN INNATE IMMUNE SYSTEM BIOLOGICAL RESPONSE MODIFIER

Discussion:

The introduction of Fungitell®, for serum (1→3)-β-glucan (BG) measurement, greatly expanded the diagnostic armamentarium for invasive fungal disease (IFD) diagnosis through the ability to detect and quantitate minute levels of blood-borne BG[1]. While validated as a biomarker of IFD[2] BG has also been shown to have a significant role in innate immunity, suggesting a concomitant role in immunopathology associated with IFD and other forms of BG exposure[3,21]. Over the past four decades, (1→3)-β-glucan has been shown to be a potent activator of the innate immune system and to play a role as a biological response modifier in many immune function circuits[4,5]. These various activities have been elucidated in greater detail through studies of BG-influenced cellular responses, BG receptor knock-outs, and, more recently, the direct measurement of minute levels of BG in biological fluids of animal models and patients and their correlation with immunopathology and outcome[6]. The experimental designs that have enabled this work have included, in pre-clinical models, the administration of BG by intravenous routes[7] by cecal ligation and puncture[8,9] by gavage or ingestion[10] and inflammatory injury to the intestinal epithelium[11]. Measured effects have included changes in cytokine and chemokine elicitation, immune pathway cell differentiation, eicosanoid metabolism, epigenetic modification of chromatin, and others[12,22].

Early on, Cook *et. al.,* demonstrated that intravenous (iv) administration of BG to rats, followed, at an interval of three days, by the iv administration of sub-lethal levels of endotoxin resulted in complete lethality[7]. This "BG-priming" effect was shown to potently exacerbate a reticuloendothelial system (RES) response culminating in shock-like symptoms and major physiological perturbation. Panpetch *et. al.,* described similar results, in mice, using gut origin BG and intestinal translocation elicited by dextran sulfate solution (DSS) administration causing

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Corporate Headquarters
Associates of Cape Cod, Inc.
124 Bernard E. Saint Jean Drive
East Falmouth, MA 02536 USA
Tel: (508) 540–3444
www.acciusa.com

United Kingdom
Associates of Cape Cod Int'l., Inc.
Deacon Park, Moorgate Road
Knowsley, Liverpool L33 7RX
United Kingdom
Tel: (44) 151–547–7444
www.acciuk.co.uk

European Office
Associates of Cape Cod Europe GmbH
Opelstrasse 14
D-64546 Mörfelden-Walldorf, Germany
Tel: (49) 61 05–96 10 0
www.acciusa.de

intestinal inflammation[13]. Additional translocated BG effects were observed by Leelahavanichkul *et. al.,* who utilized a murine sepsis model to demonstrate large increases in mortality with the oral administration of dead *Candida albicans* cells[14].

The role of BG and Toll-Like Receptor (TLR) ligand cytokine/chemokine elicitation synergy was demonstrated in a human whole blood model by Kikkert *et. al.*[15], who observed multifold increases in interleukins-6 and -8. Similar findings were made by Dennehy *et. al.,* using macrophage culture and Tumor Necrosis Factor-α as a marker[16]. Liu *et. al.,* observed pleiotropic effects in therarubicin-treated hemopoeitic- and myelopoeitic-lineage cells which received lentinan, a fungal BG, as an experimental therapy. These included blood myeloperoxidase activity increase, increase in the numbers of leukocytes and neutrophils, increases in G-CSF and M-CSF, and an improvement in bone marrow injury[12]. Similar BG effects observations were made by Cramer *et. al.*[17,18].

The role of BG stimulation of cellular cytotoxicity against iC3b-opsonized targets and its potential as an adjunctive antitumor therapy was investigated by Gordon Ross and colleagues, who demonstrated that the ligation of BG to the complement receptor 3 lectin site was a trigger for priming neutrophil cytotoxicity, and the killing of iC3b-opsonized target cells[19]. These and other observations of BG-enhanced cellular cytotoxicity form the basis of the use of BG as an adjunctive therapy in cancer treatment[20].

A role for BG in chronic inflammation-based hepatic disease was recently elucidated by Yang *et. al.,* who showed that gut-originating BG triggered inflammatory responses in the liver[21]. Dectin-1 knockout mice did not demonstrate inflammation. In another aspect of innate immune response impact, BG was shown to have a potentiating effect upon endotoxin-elicited inflammation in that exposure to BG was observed to reverse the epigenetic changes associated with endotoxin tolerance, through epigenetic reprogramming[22].

These studies, and many others, demonstrate that, just as has been done with endotoxin burden assessments, comprehensive analysis of both innate and adaptive immune responses can benefit from assessing BG burdens in both experimental models and, potentially, in patients.

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Corporate Headquarters
Associates of Cape Cod, Inc.
124 Bernard E. Saint Jean Drive
East Falmouth, MA 02536 USA
Tel: (508) 540–3444
www.acciusa.com

United Kingdom
Associates of Cape Cod Int'l., Inc.
Deacon Park, Moorgate Road
Knowsley, Liverpool L33 7RX
United Kingdom
Tel: (44) 151–547–7444
www.acciuk.co.uk

European Office
Associates of Cape Cod Europe GmbH
Opelstrasse 14
D-64546 Mörfelden-Walldorf, Germany
Tel: (49) 61 05–96 10 0
www.acciusa.de

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Corporate Headquarters
Associates of Cape Cod, Inc.
124 Bernard E. Saint Jean Drive
East Falmouth, MA 02536 USA
Tel: (508) 540–3444
www.acciusa.com

United Kingdom
Associates of Cape Cod Int'l., Inc.
Deacon Park, Moorgate Road
Knowsley, Liverpool L33 7RX
United Kingdom
Tel: (44) 151–547–7444
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Associates of Cape Cod Europe GmbH
Opelstrasse 14
D-64546 Mörfelden-Walldorf, Germany
Tel: (49) 61 05–96 10 0
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