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Symposium Highlights the Clinical Use of Probiotics, Prebiotics, and Enzymes

Reno, NV, November 15, 2008 · On November 14th and 15th, the University of Nevada School of Medicine hosted the Second Annual Symposium on Probiotics, Prebiotics, and Enzymes: Clinical Applications in Human Health. The Symposium was organized and sponsored by Klaire Labs, a division of ProThera[®], Inc. An international faculty provided attendees with recent research and hypotheses on the mechanisms of action and use of probiotics, prebiotics, and digestive enzymes to maintain and improve both physical and mental health.

Dr. Gary Elmer, Professor Emeritus of Medicinal Chemistry at the University of Washington and authority on the use of probiotics to prevent and manage antibiotic-associated diarrhea and *Clostridium difficile* disease, provided an introduction to probiotics and sought to dispel the common myths that probiotics are not well-studied and are only effective for diarrheal illnesses. He emphasized that adequate probiotic doses are essential to ensure good clinical outcomes and noted that recovery of organisms from stool cultures does not always correlate with benefit. Dr. Elmer called for enhanced funding of basic research on probiotics and optimization of existing therapies with proven probiotics.

Dr. Charalabos Pothoulakis, Professor of Medicine at the David Geffen School of Medicine at UCLA and Director of the UCLA Inflammatory Bowel Disease Center presented two lectures. On day one, he focused on probiotic mechanisms of action reviewing research performed in his laboratory showing that *Saccharomyces boulardii*'s beneficial effect in *C. difficile*-associated disease is due in part to prevention of inhibitory κB degradation. This effect prevents *C. difficile*'s toxin A from activating nuclear factor- κB (NF- κB), which is how toxin A causes colonocyte death. Dr. Pothoulakis also reported that supernatant from *S. boulardii* culture inhibits inflammatory interleukin-8 production and blocks NF- κB -mediated gene transcription. He reviewed evidence that supernatant from a multispecies probiotic formulation inhibits tumor necrosis factor- α (TNF- α) stimulation of NF- κB and presented evidence that *Lactobacillus*

rhamnosus GG produces two proteins that rescue colonocytes from TNF- α induced damage and apoptosis. On day two, Dr. Pothoulakis reviewed the evidence for the role of probiotics in inflammatory bowel disease and concluded that a multispecies preparation has clear benefit in pouchitis complicating ulcerative colitis and that *S. boulardii* has benefit by reducing production of proinflammatory cytokines.

Dr. Maria Oliva-Hemker, Chief of the Division of Pediatric Gastroenterology and Nutrition at Johns Hopkins University School of Medicine, discussed the neonatal acquisition of a normal gastrointestinal microflora. She outlined factors that may disrupt an infant's microbiota and the health consequences of such disruptions, which include gastrointestinal disturbances and immune dysfunction. Dr. Maria Oliva-Hemker reviewed the research supporting the use of probiotics to reduce the incidence of necrotizing enterocolitis (NEC) in preterm, low-birth weight infants and concluded that *L. rhamnosus* GG, *Bifidobacterium infantis*, *B. bifidum*, and *S. boulardii* have all shown benefit and, most importantly, proven to be safe in this highly vulnerable patient group.

Drs. Katzman and Lord concluded the first day of the Symposium with their thought-provoking lectures. Dr. Martin Katzman, Assistant Professor of Psychiatry at the University of Toronto and Director of the Stress, Trauma, Anxiety, Rehabilitation and Treatment Clinic presented the intriguing hypothesis that probiotics may have a role in the treatment of patients with depression and anxiety. Dr. Richard Lord, Chief Science Officer of the Metametrix Institute, reviewed the clinical laboratory use of DNA amplification of microbial genetic material isolated from stool samples to assess the composition of the gastrointestinal microbiota and to detect pathogenic organisms and parasites. The technique avoids the well-known limitations of traditional stool cultures although the precise role of the testing in guiding probiotic selection is not yet clear.

Dr. Sandra Macfarlane, Senior Research Scientist for the Division of Pathology and Neuroscience at the University of Dundee, presented cutting edge research on the use of prebiotics used alone or in combination with probiotics (synbiotics) to modify gastrointestinal biofilms. Biofilms are communities of sessile microorganisms residing within a self-produced matrix of exopolymers. Microbes prefer living within biofilms which provide them protection from dislodgement, predation, host immune responses, and antimicrobial agents. Pathogens living within biofilms are highly resistant to efforts to eradicate them and pathogenic biofilms may be a source of recurrent disease. Dr. Macfarlane noted that microbes inhabiting biofilm are more efficient at fermenting long-chain polysaccharides than are free-living luminal bacteria, which appear to chiefly ferment

oligosaccharides. Microorganisms within biofilms in the mucus layer overlying the intestinal mucosa are more likely to interact with the host's immune system and these interactions may be healthful or harmful depending on the organisms involved. She noted data showing that microbial gastrointestinal biofilm communities in patients with ulcerative colitis contain significantly fewer bifidobacteria and higher numbers of anaerobic gram-positive cocci, peptostreptococci, enterococci, and enterobacteria. Dr. Macfarlane reviewed both *in vivo* and *in vitro* evidence that the prebiotic inulin can significantly increase intestinal biofilm bifidobacterial populations while simultaneously decreasing biofilm populations of *Clostridium*, *Bacteroides*, *Fusobacterium*, and *Enterobacteraceae* species, and at the same time inhibit pathogen activity and reduce *C. difficile* toxin concentrations. This evidence led to her hypothesis that treating ulcerative colitis patients with a combination of prebiotics and probiotics could be beneficial. She concluded by presenting data from her recent study on the use of *B. longum* and oligofructose-enriched inulin in patients with ulcerative colitis. The synbiotic caused a marked increase in bifidobacteria populations, a striking reduction mucosal human β -defensin levels, and significant improvements in colonic mucosal inflammation seen on colonoscopy.

Dr. Gary Gray, Professor of Medicine, Emeritus at Stanford University School of Medicine and Director of the Stanford Celiac Sprue Management Clinic, reviewed the pathophysiology of celiac disease and presented his research on the peptidase treatment of dietary gluten. He found that an endopeptidase isolated from barley reduced fat malabsorption in patients with celiac disease in remission. Dr. Andrew Bruce, Emeritus Professor of Urology at the University of Toronto, lectured on the use of a probiotic formulation containing *L. reuteri* RC-14 and *L. rhamnosus* GR-1 to treat vaginal dysbiosis and reduce the incidence of recurrent urinary tract infections in women. He noted that oral probiotic use provides benefit and the organisms do not have to be administered vaginally.

Dr. John Morton, Associate Professor of Surgery and director of the bariatric surgery program at Stanford University, presented fascinating data on the potential role of the gastrointestinal microbiota in the growing worldwide epidemic of obesity. He noted that the rapid spread of obesity in the United States since 1997 has led many investigators to question whether an infectious agent or agents could be involved. It has been established that obesity spreads within networks of friends and families and that treating obese parents with bariatric surgery can result in weight loss in their children. The gut microflora generates 30% of a person's daily caloric intake so the presence of microbes more efficient at extracting energy from the diet has been hypothesized to contribute to overweight and obesity. A relation between alterations in

gastrointestinal microbiota and obesity was first noted by Dr. Jeffrey Gordon's group at Washington University who found that obese mice and people had fewer numbers of bacteria in the Division *Bacteroidetes* and greater numbers in the Division *Firmicutes* than did their lean siblings or controls. Furthermore, this alteration in gut microbiota proved to be transmissible in mice suggesting that disorders in intestinal microbiota could be passed from one person to another resulting in the spread of obesity. Dr. Marko Kalliomäki's group in Finland has published data showing that alterations in gut microbiota during early childhood predict overweight and obesity in later life. These alterations consist of reduced populations of bifidobacteria and increased numbers of *Staphylococcus aureus*. Dr. Morton expounded on the exciting results of a study he recently concluded in which *L. acidophilus* was administered to patients following Roux-en-Y bariatric surgery. The study was undertaken to assess whether a probiotic could reduce the incidence of intestinal bacterial overgrowth in these patients, which it did. However, an unexpected finding was that compared to placebo, patients receiving the probiotic experienced significantly greater weight loss following surgery. This is the first clinical trial to suggest that probiotics may enhance weight loss. Dr. Morton plans a large multicenter trial to follow up on this potentially highly important observation.

A set of CDs and the accompanying Symposium syllabus are available for order at www.ProbioticSymposium.com or by calling 1-888-488-2488. Klaire Labs will organize and fund the third annual Probiotic Symposium delving into the role of probiotics, prebiotics and enzymes in the management of pathogenic gastrointestinal biofilm and modulation of immune function. The third annual Probiotic Symposium is planned for the Fall of 2009.

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