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Probiotics/direct fed microbials for *Salmonella* control in poultry

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ABSTRACT

Bacterial antimicrobial resistance in both the medical and agricultural fields has become a serious problem worldwide. During the last 15 years, our laboratories have worked toward the identification of probiotic candidates for poultry which can actually displace *Salmonella* and other enteric pathogens which have colonized the gastrointestinal tract of chickens and turkeys, indicating that selection of therapeutically efficacious probiotic cultures with marked performance benefits in poultry is possible, and that defined cultures can sometimes provide an attractive alternative to conventional antimicrobial therapy. Our studies have been focused on specific pathogen reduction, performance under commercial conditions, and effects on both idiopathic and defined enteritis. We have also confirmed that selected heat-resistant spore-forming *Bacillus* species can markedly reduce *Salmonella* and *Clostridium* when administered in very high numbers, and we have developed a novel and simple technique for obtaining cultured *Bacillus* spore counts, providing a cost-effective feed-stable inclusion in commercial poultry diets. In order to select even more effective isolates, we are still currently focused on the mechanistic action of the *Lactobacillus* probiotic previously developed as well as new *Bacillus* candidates. Current indications are that mechanism of action involves rapid activation of innate host immune responses, providing an exciting possibility for identification of vastly superior and more potent probiotics. In this review, we summarize the safety and efficacy of individual monocultures for prophylactic and/or therapeutic efficacy against *Salmonella* infections under both laboratory and field conditions as well as the development of a novel, cost-effective, feed-stable direct-fed microbials (DFM) with potential for widespread utilization and improved production, delivery and clinical efficacy for animal use.

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1. Introduction

Salmonella enterica serovars continue to be among the most important food borne pathogens worldwide due to the considerable human rates of illness reported, the wide host species that are colonized by members of this remarkable pathogen genus, which serve as vectors and reservoirs for spreading these agents to animal and human populations. Furthermore, the public concern for the appearance of resistant strains to many antibiotics, particularly among zoonotic pathogens such as common *Salmonella* isolates, is also challenging the poultry industry to find alternative means of control (Boyle, Bishop, Grassl, & Finlay, 2007). For example, in January 2006 Europe implemented a complete ban of growth-promoting antibiotics in animal feed (Anadon, Martinez-Larranaga, & Aranzazu Martinez, 2006). Thus, while attempting to deal with these human food-borne pathogens, poultry producers are simultaneously challenged to improve production in the face of increasing feed costs while using fewer antibiotics due to increased restriction of

antimicrobial usage. These internal regulations, as in Europe, were implemented because of export market restrictions and consumer or customer preferences in local markets. For these reasons, continued research on sustainable alternatives to antibiotic growth-promoters for animal production such as: a) probiotics or direct fed microbials (DFM) consisting of live or dead organisms and spores (Patterson & Burkholder, 2003); b) non-traditional chemicals (Ko, Mendoncam, Ismail, & Ahn, 2009); c) bacteriophages (Andreotti Filho et al., 2007; Bielke, Higgins, Donoghue, Donoghue, & Hargis, 2007; Higgins, et al., 2005; J.P. Higgins et al., 2008); and d) organic acids and other plant extracts and essential oils (Aengwanich & Suttajit, 2010; Allen-Hall, Arnason, Cano, & Lafrenie, 2010; Bagchi et al., 2000; Kubena, Byrd, Young, & Corrier, 2001; Over, Hettiarachchy, Johnson, & Davis, 2009; Van Immerseel et al., 2006) is increasingly more important. These potential solutions have emerged in the last decades as some of the tools that could be potentially useful in the near future for pathogen control and poultry performance improvement.

Probiosis, although not a new concept, has only recently begun to receive an increasing level of scientific interest. In agriculture, probiotics/DFM used in animal feed are becoming accepted as potential alternatives to antibiotics for use as growth-promoters, and in select cases, for control of specific enteric pathogens (Anadón, Rosa Martínez-Larrañaga, & Aranzazu Martínez, 2006; Boyle et al.,

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2007; Cartman, La Ragione, & Woodward, 2008; Vila et al., 2009; Williams, Burdock, Jimenez, & Castillo, 2009). For these reasons the development of new and more effective probiotic products that can be licensed for animal use continues to receive considerable interest (Hong et al., 2008a; Hong, Duc le, & Cutting, 2005; Jadamus, Vahjen, & Simon, 2001; Osipova, Makhailova, Sorokulova, Vasil'eva, & Gaiderov, 2003; Williams, 2007b; Wolken, Tramper, & van der Werf, 2003).

Currently, there is no universal class of probiotic bacterium although the most common types that have been indisputably effective involve lactic acid bacteria. These bacteria are found normally in the gastrointestinal tract (GIT) of vertebrates and invertebrates, and the use of some lactic acid bacterial cultures is able to restore the natural microflora within the gut (Shahani & Ayebo, 1980). Lactic acid bacteria (LAB) include the genera *Lactobacillus*, *Pediococcus*, and others that have long been associated with health benefits and which have been used for fermentation of certain foods. While speciation of members of these genera is difficult and inconsistent, these organisms are uniformly safe and not associated with disease in healthy animals or humans (Tellez, Higgins, Donoghue, & Hargis, 2006).

A second classification of probiotic cultures are those microorganisms that are not normally found in the GIT (allochthonous flora). For example, *Saccharomyces boulardii* has been shown to be effective in preventing the recurrence of *Clostridium difficile* infections (Czerucka, Piche, & Rampal, 2007) and some colibacillosis in humans (Czerucka & Rampal, 2002). Other allochthonous probiotic microbes are the spore-forming bacteria, normally members of the genus *Bacillus*. Recent progress in this area from our laboratory will be described below.

2. A lactic acid bacteria-based probiotic for *Salmonella* control and performance in poultry

Several years ago, our laboratory evaluated a simple method to select for individual enteric bacteria capable of inhibiting *Salmonella* growth *in vitro* and the ability of selected oxygen tolerant bacteria, in combination, to protect neonatal poult from *Salmonella* infection following challenge. Concurrently, we also worked toward the isolation, selection, further evaluation and combination of LAB to control additional food borne pathogens (Tellez et al., 2006). Extensive laboratory and field research conducted with this defined LAB culture has demonstrated accelerated development of normal microflora in chickens and turkeys, providing increased resistance to *Salmonella* sp. infections (Farnell et al., 2006; J. P. Higgins et al., 2008; Higgins et al., 2010; S. E. Higgins et al., 2008; Vicente et al., 2008; Wolfenden, Pixley, Higgins, Higgins, et al., 2007; Wolfenden, Pixley, Vicente, Aviña, et al., 2007; Wolfenden, Vicente, Bielke, Pixley, et al., 2007; Wolfenden, Vicente, Higgins, Andreatti, et al., 2007). Published experimental and commercial studies have shown that these selected probiotic organisms are able to reduce idiopathic diarrhea in commercial turkey brooding houses (Higgins et al., 2005). Large scale commercial trials have indicated that appropriate administration of this probiotic mixture to turkeys and chickens increased performance and reduced costs of production (Torres-Rodriguez et al., 2007; Torres-Rodriguez et al., 2007; Vicente et al., 2007; Vicente, Aviña, Torres-Rodriguez, Hargis, & Tellez, 2007; Vicente et al., 2007).

These data have clearly demonstrated that selection of therapeutically efficacious probiotic cultures with marked performance benefits in poultry is possible, and that defined cultures can sometimes provide an attractive alternative to conventional antimicrobial therapy. This lactic acid bacteria based probiotic (FloraMax-B11[®]) consists of 11 bacteria related to the genus *Lactobacillus* which was licensed to a commercial company (Pacific Vet Group USA Inc., Fayetteville AR 72703) and has become one of the more successful ante *Salmonella* strategies used in the drinking water by the poultry industry to date. The bacterial composition is listed in the next section.

3. The mechanism of action of probiotics against *Salmonella*

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Among the many benefits associated with the consumption of probiotics, modulation of the immune system has received the most attention (Borchers, Keen, & Gershwin, 2002; Borchers, Selmi, Meyers, Keen, & Gershwin, 2009).

Previously, it was thought that administration of bacteria such as probiotics to neonates directly reduced infection by pathogens due to 'competitive exclusion' between the bacteria. Competitive exclusion was first described in 1973 by Nurmi and Rantalla (1973), citing that bacteria compete with each other for space and nutrients. Their data indicated that early administration of 'good' bacteria prevented infection by pathogens. Since Nurmi and Rantala proposed that competitive exclusion could be used as a method to prevent *Salmonella* infection, numerous researchers have reported the ability of live bacterial cultures (Callaway et al., 2008; Corrier et al., 1998; Hollister, Corrier, Nisbet, & DeLoach, 1999; Hume, Corrier, Nisbet, & DeLoach, 1998; Nisbet et al., 1998; Wagner, Paine, & Cerniglia, 2003) and probiotic organisms (Higgins et al., 2007; Higgins et al., 2010; S. E. Higgins et al., 2008; Patterson & Burkholder, 2003; Vicente et al., 2008) to also reduce colonization of opportunistic pathogens in the gastrointestinal tract. Yet our understanding of how probiotics mediate these health benefits, specifically reduction of *Salmonella* infection, is very limited.

Balanced colonic microflora and immunostimulation are major functional effects attributed to the consumption of probiotics (Amit-Romach, Uni, & Reifen, 2010; Boirivant, Amendola, & Butera, 2008; Boirivant & Strober, 2007; Flint, O'Toole, & Walker, 2010; Flore, Francois, & Felicite, 2010; Ibrahim et al., 2010; Klein, Sanders, Duong, & Young, 2010; Nayak, 2010). Many probiotic effects are mediated through immune regulation, particularly through balance control of proinflammatory and anti-inflammatory cytokines (Di Giacinto, Marinaro, Sanchez, Strober, & Boirivant, 1950; Folineg et al., 2010; Haciní-Rachinel et al., 1950; Jobin, 2010; Li, Xia, & Li, 2009). However, several animal and human studies have provided unequivocal evidence that specific strains of probiotics are able to stimulate several aspects of innate immunity (Amit-Romach et al., 2010; Boirivant et al., 2008; Boirivant & Strober, 2007; Farnell et al., 2006; Romanin et al., 2010; Weiss et al., 2010) as well as to increase humoral immunity (Fang, Elina, Heikki, & Seppo, 2000; Galdeano, de Leblanc Ade, Carmuega, Weill, & Perdigon, 2009; Leblanc, Fliiss, & Matar, 2004; Nermes, Kantele, Atosuo, Salminen, & Isolauri, 2011).

Using the *Salmonella* challenge model, we have observed an increase in *Salmonella enteritidis* (SE) incidence in cecal tonsils over the initial 12 h post-treatment (Higgins et al., 2007; Higgins et al., 2010), which indicates that the SE is continuing to cause infection despite theoretically coming into contact with the probiotic organisms within approximately 2 h (neonatal chick gastrointestinal transit time). In a recent study conducted in our laboratory, microarray analysis revealed gene expression differences in birds treated with a *Lactobacillus* based probiotic when compared to saline treated birds. At 12 h post probiotic treatment, 170 genes were significantly different ($P < 0.05$), but by 24 h post treatment, the number of differentially regulated genes was 201. Pathway analysis revealed that at both time points, genes associated with the NF- κ B complex were significantly regulated, as well as genes involved in apoptosis. Probiotic-induced differential regulation of the genes *GAS2* and *CYR61* may result in increased apoptosis in the caecae of chicks. Because *Salmonella* is an intracellular pathogen, we suggest that increased apoptosis may be a mechanism by which FloraMax-B11[®] reduces *Salmonella* infection (Higgins et al., 2011).

4. Comparisons between genotypic 16S rRNA, MIDI, and Biolog identifications of FloraMax-B11[®] lactic acid bacteria

It is well recognized that the speciation of LAB poses a unique problem for microbial identification. The identification techniques of

choice for many facultative anaerobes are biochemical analyses, but the standard identification system for lactic acid bacteria is cellular fatty acid profiling. Nevertheless, these phenotypic methods can yield variable results. Genotypic methods that rely on comparisons of 16S rRNA sequences from unknown bacteria are proving to be valuable for use in a wide range of genera and are not sensitive to variable culture conditions. Genotypic 16S rRNA identification of organisms from probiotic cultures may be more consistent than the current standard microbial techniques applied separately to different microbial groups. However, this approach comes with its own limitations and issues. As identification is based on specific sequence homology as compared with a known database of microflora previously identified through conventional methodologies, the speciation is dependent upon the closest match with what was previously identified, correctly or incorrectly, in the database. As databases constantly expand and change, the same sequence submission over time may match other names with greater homology. Thus, at this moment it is nearly impossible to really know the speciation of LAB except under specific examples with very highly characterized isolates. In fact, 16S rRNA sequencing of isolates from internationally-known name brands of commercially-produced yogurt with live cultures has consistently resulted in database matches with LAB species that are labeled as other species on the yogurt labels (unpublished from our laboratory). Thus, while 16S RNA sequencing can positively identify one LAB isolate as unique among several, true accuracy of homology comparisons is a somewhat subjective exercise.

Even though there are many new experimental molecular identification techniques, such as microarray hybridization, sequence analysis of 16S rRNA is the predominant molecular technology presently available for microbial identification of these commensal microorganisms (Wagner et al., 2003), even with the known problem of database accuracy and consistency over time. The detailed information needed to identify each species represented in a commercial probiotic product can only be fully obtained from the 16S rRNA at the level of the nucleotide sequence. As an example, our laboratory has devised an identification scheme using the MIDI System ID from two different private laboratories (Micro Test Lab Inc., Agawam, MA 01001, USA; and Microbial ID Inc., Newark, DE 19713, USA) the Biolog ID System (Biolog, Inc., Hayward, CA 94545, USA) and compared those results with the 16S rRNA Sequence Analyses (Microbial ID Inc., Newark, DE 19713, USA) for identification of the individual component bacteria present in the commercial probiotic FloraMax-B11[®] (Table 1). The results of that study showed that the complex populations of bacteria present in FloraMax-B11[®] are not easy to accurately identify, especially with phenotypic techniques. Conventional technologies can detect human pathogens, because they are well-established in comparative databases, but emerging and opportunistic pathogens are not. Despite the fact that uncertainty

exists between different methods of identification of non-pathogenic probiotic bacteria, identification of known pathogens is much more consistent. Therefore, the use of fully defined cultures for competitive exclusion or probiotic use are still inherently safer than undefined cultures or those where organisms are identified after the culture has been produced.

5. A *Bacillus* spore-based probiotic for *Salmonella* control and performance enhancement in poultry

In spite of the success shown by the development of the LAB probiotic for use in commercial poultry (above), there is still an urgent need for commercial probiotics that are shelf-stable, cost-effective and feed-stable (tolerance to heat pelletization process) to increase compliance and widespread utilization. Among the large number of probiotic products in use today some are bacterial spore formers, mostly of the genus *Bacillus*. Used primarily in their spore form, some (though not all) have been shown to prevent selected gastrointestinal disorders and the diversity of species used and their applications are astonishing. While not all *Bacillus* spores are highly heat tolerant, some specific isolates are the toughest life form known on earth (Vreeland, Rosenzweig, & Powers, 2000) and can be used under extreme heat conditions. Several studies have shown that either live vegetative cells or endospores of some isolates can prevent colon carcinogenesis (Park, Jeon, Park, & Paik, 2007) or discharge antimicrobial substances against Gram-positive bacteria, such as *Staphylococcus aureus*, *Enterococcus faecium*, and *C. difficile* (O'Mahony et al., 2001). These results provided evidence of colonization and antimicrobial activity of probiotic bacteria, thus, products containing *Bacillus* spores are used commercially as probiotics, and they offer potential advantages over the more common LAB products since they can be used as direct-fed microbials (Anadón et al., 2006; Barbosa, Serra, La Ragione, Woodward, & Henriques, 2005; Duc le, Hong, Barbosa, Henriques, & Cutting, 2004; Hong et al., 2005; Hong et al., 2008a; Hong et al., 2008b; McNulty, Boyle, Nichols, Clappison, & Davey, 2007; Osipova et al., 2003; Williams, 2007a; Wolken et al., 2003). There is scientific evidence suggesting that some but not all isolates of ingested *Bacillus subtilis* spores can, in fact, germinate in the small intestine (Casula & Cutting, 2002; Casula & Cutting, 2002; Duc le & Cutting, 2003; Hoa et al., 2001). Together, these studies not only show that spores are not transient passengers in the gut, but they have an intimate interaction with the host cells or microflora that can enhance their potential probiotic effect. Several commercial spore-forming *Bacillus* cultures have been shown to reduce food borne pathogens (Aureli, Fiore, Scalfaro, Casale, & Franciosa, 2010). However, cost issues associated with achieving necessary concentrations of spores in feed have greatly limited commercial acceptance in the animal industry (Hong et al., 2005).

Table 1

Comparisons between MicroSeq, MIDI, and Biolog identifications of FloraMax-B11[®] lactic acid bacteria. Adapted from Tellez et al., 2006.

LAB ID	16S RNA sequencing (first 500 bp) Microbial ID Inc.	MIDI SYSTEM ID Micro Test Lab Inc.	MIDI SYSTEM ID Microbial ID Inc.	Biolog ID Dept. of Poultry Sc. U. of Arkansas
18	<i>Pediococcus parvulus</i>	<i>Enterococcus cecorum</i>	<i>Lactobacillus gasseri</i>	Unable to identify
24	<i>Weissella confusa</i>	<i>Lactobacillus casei</i>	<i>Lactobacillus casei</i>	<i>Clostridium clostridioforme</i>
27	<i>Weissella confusa</i>	<i>Lactobacillus casei</i>	<i>Lactobacillus casei</i>	<i>Weissella confusa</i>
29	<i>Pediococcus parvulus</i>	<i>Lactobacillus delbreuckii-bulgaricus</i>	<i>Lactobacillus delbreuckii-bulgaricus</i>	<i>Lactobacillus hamsteri</i>
36	<i>Lactobacillus salivarius</i>	<i>Lactobacillus cellobiosus</i>	<i>Lactobacillus casei</i>	<i>Weissella confusa</i>
37B	<i>Weissella confusa</i>	<i>Pediococcus acidilactici</i>	<i>Pediococcus ruminis</i>	Unable to identify
40	<i>Weissella confusa</i>	<i>Lactobacillus casei</i>	<i>Lactobacillus cellobiosus</i>	<i>Weissellaparamesenteroides</i>
44	<i>Weissellaparamesenteroides</i>	<i>Lactobacillus fermentum</i>	<i>Lactobacillus fermentum</i>	Unable to identify
46	<i>Lactobacillus salivarius</i>	<i>Lactobacillus helveticus</i>	<i>Lactobacillus sanfranciscensis</i>	<i>Lactobacillus salivarius</i>
48	<i>Lactobacillus salivarius</i>	<i>Lactobacillus helveticus</i>	<i>Lactobacillus gasseri</i>	<i>Lactobacillus salivarius</i>
52	<i>Pediococcus parvulus</i>	Unable to identify	<i>Lactobacillus cellobiosus</i>	Unable to identify

At the present time, our laboratory's aim is to develop a novel, cost-effective, feed-stable probiotic with widespread utilization and improve probiotic production, delivery and clinical efficacy for human and animal use. We have demonstrated that one *B. subtilis* spore isolate was as effective as our LAB-based probiotic (FloraMax-B11®) for *Salmonella* reduction (Shivaramaiah et al., in press; Wolfenden et al., 2010), was equal to bacitracin for prevention of experimental necrotic enteritis, and was able to markedly reduce necrotic enteritis issues in large scale feed trials (unpublished experiments).

Other isolates or combinations of isolates with increased potency and efficacy may be identified with continued research. Some of these environmental *Bacillus* isolates have been evaluated *in vitro* for antimicrobial activity against selected bacterial pathogens, heat stability, and the ability to grow to high numbers. Unpublished experimental evaluations have confirmed improved body weight gain as well as *Salmonella sp.* or *Clostridium perfringens* reduction in commercial turkey and broiler operations when compared with medicated (nitarstone) or control nonmedicated diets respectively. Our preliminary data suggests that these isolates could be an effective alternative to antibiotic growth-promoters for commercial poultry.

Importantly, improved efficiency of amplification and sporulation is absolutely essential to gain widespread industry acceptance of a feed-based probiotic for ante mortem food-borne pathogen intervention; as well as cost effectiveness. Recently, both vegetative growth and sporulation rate have been optimized in our laboratory, which may lead to new efficiencies for commercial amplification and manufacture of a cost-effective product at very high spore counts (Wolfenden et al., 2010). In order to select even more effective isolates, we are currently focused on the mechanistic action of new *Bacillus* candidates. Preliminary studies conducted in our laboratory indicate that a potential mechanistic action of these new *Bacillus* candidates at least partially involves rapid activation of innate host immune mechanisms (system or responses) in chickens and turkeys (unpublished data). This data provides an exciting possibility for identification of vastly superior and more potent probiotics in the near future.

6. Conclusions

The interest in digestive physiology and the role of microorganisms has generated data whereby human and animal well being can be enhanced and the risk of disease reduced. New molecular techniques allow an accurate assessment of the flora composition resulting in improved strategies for elucidating mechanisms. Given the recent international legislation and domestic consumer pressures to withdraw growth-promoting antibiotics and limit antibiotics available for treatment of bacterial infections, probiotics can offer alternative options. New advances in the application of probiotics, are directed to produce significant changes in gut physiology and provide even higher levels of health as well as increase performance parameters in poultry.

Metchnikoff founded the research field of probiotics, aimed at modulating the intestinal microflora (Dobrogosz, Peacock, & Hassan, 2010; Schmalstieg & Goldman, 2010; Weissmann, 2010). However, other parts of the body containing endogenous microflora or problems relating to the immune system may also be candidates for probiotic therapy. Research has shown that probiotics have potential for human health issues such as: vaginal candidiasis (Ehrstrom et al., 2010; Ya, Reifer, & Miller, 2010); dental caries (Chen & Wang, 2010; Stamatova & Meurman, 2009); allergies (Gourbeyre, Denery, & Bodinier, 2011; Schiavi et al., 2010b); autoimmune diseases (Lavasanian et al., 2010; Tlaskalova-Hogenova et al., 2011); urogenital infections (Pascual, Ruiz, Giordano, & Barberis, 2010; Ruiz et al., 2009); atopic diseases (Hoang, Shaw, Pham, & Levine, 2010; Nermes et al., 2011); rheumatoid arthritis (Lee et al., 2010; Mandel, Eichas, & Holmes, 2010); and respiratory infections (Harikrishnan, Balasundaram, &

Heo, 2010; Silvestri et al., 2010). Current research is still heavily biased toward gastrointestinal applications for probiotics, such as: chronic constipation (Bu, Chang, Ni, Chen, & Cheng, 2007; Coccorullo et al., 2010); chronic diarrhea (Preidis et al., 2011; Swidsinski, Loening-Baucke, Verstraelen, Osowska, & Doerffel, 2008); inflammatory bowel disease (Ng, Chan, & Sung, 2011; Vanderpool, Yan, & Polk, 2008); irritable bowel syndrome (Camilleri & Tack, 2010; Enck, Klosterhalfen, & Martens, 1946); and food allergy (Gourbeyre et al., 2011; Schiavi et al., 2010a), but the possibilities for impacting many areas of health are numerous. Much research has been completed in efforts to understand and apply the natural benefits of non-pathogenic bacteria, but there is much still to do.

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