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The development of probiotics for women's health

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Abstract

The idea you could use lactic acid bacteria to treat and prevent recurrence of vaginal infections was ridiculed in the early 1980s. Bacteria were the bad guys to be eradicated by current and emerging antibiotic classes. Thirty years later, probiotic administration of microbes is widespread worldwide, including for vaginal and bladder health in women, and the scientific basis and clinical efficacy data for this and multiple other applications prove the viability of this concept. The development of this approach, the creation of a definition for probiotics and the expansion to other areas of women's health form the basis of this review.

Key Words: probiotics, vaginal, urinary tract, Lactobacillus, fermented food

The clinical insight

The foundation of our work on probiotics originated from a clinical observation by Dr. Andrew Bruce in 1973. He noted that women who never had a urinary tract infection (UTI) were colonized in the vagina by lactobacilli, whereas women with recurrent UTI were colonized by the coliforms that ascended and infected the bladder (Bruce et al. 1973). This led to Bruce hypothesizing that lactobacilli could be a protective factor in healthy women. While a number of researchers in the field decided to work on the *E. coli* pathogenesis in UTI, mostly the adhesion of *E. coli* to the uroepithelium (Reid and Sobel, 1987), with a view to developing a vaccine, we chose to investigate the health-associated bacteria. The *E. coli* research route essentially failed to deliver either insight or new therapies that would improve the management of this disease or the quality of life of women. On the contrary, using beneficial microbes to promote host health has become a major area of research and probiotic products, many shown to be clinically effective, have become a \$50 billion industry.

Lactobacilli properties and early evidence of benefits in humans

By 1999, contrary to the opinion of the President of the American Society for Microbiology that “Probiotics may be today’s snake oil...fraudulently peddled by hawkers from the backs of covered wagons” (Atlas 1999), we had published 58 papers on lactobacilli and developed the foundation for probiotic applications in women. We showed that strains could interfere with the adhesion of bacterial and fungal pathogens and their growth not only to uroepithelial cells but also to polymeric substrates that form

urinary devices known to increase the risk of UTI (Reid et al. 1987; 1988; 1995; Millsap et al. 1994; Reid & Tieszer, 1993; Velraeds et al. 1998). Some studies used electron microscopy to visualize bacterial adhesion and their outer surfaces (Cook et al. 1988), areas of science pioneered by outstanding Canadian microbiologists, Dr. Bill Costerton and Dr. Terry Beveridge (Cook et al. 1988; Reid et al. 1995). A picture can indeed be worth a thousand words, and in our case it helped us understand how these organisms behaved in different media, and interacted with the host and other bacteria in the urogenital environment. Twenty-eight years later, studies identified lactobacilli surface glycoproteins and showed they not only convey health benefits such as gut barrier function (Tytgat & De Vos 2016), but pili in probiotic *Lactobacillus rhamnosus* GG help outcompete attachment of the potential pathogen *Enterococcus* (Tytgat et al. 2016) at the epithelium. In addition, we showed that urogenital probiotic *L. rhamnosus* GR-1 lectin-like protein mediates tissue-specific adhesion to the vaginal epithelium and mediates inhibition of urogenital pathogen attachment (Petrova et al. 2016a).

It was clear to us, even by the late 1990s, that such surface-mediated interactions represent natural means for lactobacilli to compete with pathogens, and we developed this concept as an alternative to the broad spectrum antibiotic approach which was aimed at eradicating pathogens but which also killed beneficial microbes. Indeed, in one study with Scandinavian colleagues, we showed that a simple 7-day course of amoxicillin or bacampicillin to treat UTI disrupted the vaginal microbiota for at least six weeks (Reid et al. 1999). This helped explain why recurrences of UTI were so common and reiterated that antibiotics were not designed to restore bacterial

homeostasis. We felt lactobacilli contributed to restoring and maintaining homeostasis and health and these benefits became our continued research focus.

While we had performed studies in mice and rats which showed positive effects against UTI pathogens (Reid et al. 1985; 1989), we never felt they came close to reflecting the human situation, thus we tried whenever possible to test ideas in humans. The first study in 1988 informed us that while *L. rhamnosus* GR-1 appeared to reduce colonization of the vagina by Gram negative pathogens (Bruce and Reid, 1988), it did little to interfere with enterococci, a common UTI agent. The addition of *L. fermentum* B-54 was made because of its *in vitro* ability to inhibit Gram positive cocci (Reid et al. 1987), but was replaced by *L. reuteri* RC-14 because it produced biosurfactants which reduce surface tension and adhesion by pathogenic bacteria and *Candida albicans* (Velraeds et al. 1998). Unlike patent protected commercial strains of *L. reuteri* (Talarico et al. 1988), the RC-14 strain did not produce reuterin (Cadiuex et al. 2008), and thus its mode of action was not through bacteriocin-like compounds. The ability to reduce yeast colonization is particularly important given the high incidence of vulvovaginal candidiasis (VVC) (Goncalves et al. 2016). Although VVC is not due to a depletion of lactobacilli, our studies suggest that application of probiotic GR-1, might be therapeutic by up-regulating IL-8 and IP-10 secretion by vaginal cells (Martinez et al. 2009a) and affecting *C. albicans* metabolic activity via increased expression of stress-related genes, and improve efficacy of anti-fungals by lowering expression of genes involved in fluconazole resistance (Kohler et al. 2012). The latter might explain the increased cure of the disease when probiotic and anti-fungal therapy were conjointly administered (Martinez et al. 2009b). Confirmatory studies have shown that *L. rhamnosus* can inhibit *Candida*

biofilms through reduced hyphal differentiation (Matsubara et al. 2016) and activation of IL-1 α and IL-1 β expression by an alternate signal transduction pathway (Wagner and Johnson 2012).

There were very few groups in the world working on urogenital lactobacilli in the late 90s, and of those the *Lactobacillus* species selected to function in women, were chosen based upon their prevalence in the vagina. Had we done this, we would have originally chosen *L. acidophilus* in the 1980s and *L. crispatus*, or *L. jensenii* in the 1990s, only to discover in 2002 that fastidious *L. iners* is the most abundant in the healthy vagina (Burton and Reid, 2002; Anukam et al. 2006b; Zhou et al. 2010; Gajer et al. 2012). Rather, our approach was to combine strains RC-14 with GR-1 to perform specific tasks, such as interfere with a range of urogenital pathogens' adherence and growth, and restore homeostasis by allowing the host's own lactobacilli to recover post-therapy. We proved in clinical studies that this did indeed occur (Macklaim et al. 2015), which was all the more intriguing since the probiotics were administered orally, yet their effect occurred in the vagina.

The idea of oral administration came from the knowledge that many urogenital infections are a result of ascension of pathogens from the rectum to the perineal skin and then vagina and bladder. Thus, if the pathogens could do it, why couldn't lactobacilli which are well adapted to vaginal colonization? Evidence that orally administered lactobacilli could reach the vagina came from three human studies (Reid et al. 2001a; 2001b; 2003) and the concept was subsequently confirmed by others (Morelli et al. 2004). Of significance to pregnant women, one recent Taiwanese study has shown that ingestion of capsules containing the GR-1/RC-14 strains reduced vaginal and rectal

colonization by group B streptococci (GBS) (Ho et al. 2016). GBS is a leading cause of primary neonatal sepsis, pneumonia, and meningitis in the first week of life, and a primary reason for intrapartum parenteral antibiotic prophylaxis at 35–37 weeks of gestation. Given the potentially adverse effects of early life exposure to antibiotics (Blaser 2016), the option of using lactobacilli prophylactically in pregnancy is now worthy of serious consideration.

The delivery of GR-1 and RC-14 to the vagina and intestinal tract, and even in one case directly to the bladder (Hagberg et al. 1989), made us consider how the strains interacted with other species and the host immune response. One study showed inhibition of intestinal pathogens and stimulation of host defences and reduced gut translocation and infectivity of *Salmonella* in mice (Reid et al. 2002), and another showed an ability to inhibit or kill viruses, including HIV (Reid 2006). Perhaps the ultimate assessment of immune modulation is in patients with inflammatory bowel disease. Ingestion of yogurt containing the GR-1 and RC-14 strains showed serum IL-12 concentrations and proportions of IL-2(+) and CD69(+) T cells from stimulated cells decreased in these patients, and more importantly there was an increase in CD4(+) CD25(high) T cells and decrease in the percentage of TNF-alpha- or IL-12-producing monocytes and dendritic cells (Baroja et al. 2007). These anti-inflammatory effects paralleled the expansion of a peripheral pool of putative T(reg) cells in the patients, with few effects in healthy controls. Such benefits on T(reg) cells and gut barrier function have since been shown to have importance in local and distant site effects, such as atopic dermatitis (Iemoli et al. 2012).

In terms of potentially reducing the risk of preterm labour caused by inflammation, a series of studies, summarized in a recent review (Yang et al. 2015) have shown that *L. rhamnosus* GR-1 can enhance anti-inflammatory IL-10 and colony-stimulating factor 3 (CSF3) production in macrophages, and primary human placental trophoblast cells via JAK/STAT and MAPK pathways, as well as down-regulate inflammatory LPS-induced TNF α output through c-Jun-N-terminal kinases (JNKs) inhibition. This makes it possible to consider using GR-1 and RC-14 to prevent preterm deliveries, but studies to date have had too small a sample size to confirm efficacy (Krauss-Silva et al. 2011; Bocking et al. submitted).

Defining the term probiotic

Such was the growing interest in probiotics in the late 1990's, the Argentinian government asked the United Nations Food and Agriculture Organization to organize an Expert Panel to come up with a definition for probiotics, at least for food. The World Health Organization partnered and I was fortunate to be invited to Chair the Panel. The Panel members extensively reviewed the literature and past iterations of probiotic terminology. The resultant definition, "Live microorganisms which when administered in adequate amounts confer a health benefit on the host", was chosen to cover present and future products including recombinant strains (FAO/WHO, 2001). It did not stipulate how many live organisms were needed, or their origin or target: that is up to the researcher to provide the evidence. The 'health benefit' was also not set in stone, as 'health' is poorly defined by the WHO, and physiological benefits can come in many forms. Despite criticism and repeated efforts to adapt it, the definition has stood the test

of time and been accepted world wide, with only one grammatical change from 'which' to 'that' (Hill et al. 2014). While probiotics were not part of the clinical arsenal for prevention and treatment of disease or maintenance of health 10-15 years ago (Reid et al. 2003), as we predicted and hoped, they most certainly are now for certain conditions in many countries.

Extending the translation to women's health

A key to acquiring evidence that a scientific concept based upon a clinical discourse, is actually relevant is to prove it in the target host, and in this case humans. We obtained sufficient evidence of safety, proof-of-concept and preliminary efficacy for use of the probiotic strains to persist in the vagina for some time, improve treatment of infection, and prevent recurrence of UTI and bacterial vaginosis (Reid et al. 1994; Cadieux et al. 2002; Burton et al. 2003; Anukam et al. 2006a; Hummelen et al. 2010). Confirmation by others using these strains solidified the evidence (Falagas et al. 2006; Beerepoot et al. 2012; Vujic et al. 2013). Having been the first to sequence *L. iners* (Macklaim et al. 2011), we could then show, using transcriptomics, that it has an incredible ability to adapt to the changed environment of BV, altering its metabolism to take advantage of carbohydrate availability (Macklaim et al 2013). This does not mean it should be considered as a probiotic, as it appears there are clones of the species associated with an increased risk of BV, and the role it plays is unclear (Petrova et al. 2016b). By further developing methods to interrogate the metabolic read-out of bacteria in the vagina, we subsequently discovered not only that succinate was not a marker for BV, as some had proposed (Srinivasan et al. 2015), but gamma beta hydroxybutyrate

(GHB) produced by *Gardnerella vaginalis* was a marker (McMillan et al. 2015). This has been further confirmed in a large data set of vaginal samples analyzed by meta-transcriptomics and metabolomics (Macklaim et al. unpublished). In practical terms, if a woman or physician detected GHB and odour, therapy could target *G. vaginalis*, perhaps including the use of probiotic lactobacilli to disrupt their biofilms and eradicate some of them (McMillan et al. 2011).

The ability of the strains introduced directly into the vagina to effectively treat BV was a significant breakthrough and a rare instance of such probiotic efficacy (Anukam et al. 2006c). With no new therapy for this highly prevalent condition in 40 or more years, the potential to offer a new option to women needs to be explored urgently. Unfortunately, regulatory systems are not set up for replenishing beneficial microbes in the host, making the translation impossible without huge financial support. The National Institutes of Health in the US has supported the development and testing of *L. crispatus* CTV05 for intravaginal administration, but strangely the protocol first requires antibiotic therapy followed by lactobacilli instillation (Stapleton et al. 2011). For acute UTI antibiotics are needed, but for BV as we showed, probiotics could be a treatment per se, thus hopefully if CTV05 is eventually approved as a drug, it can be used on its own and not just following antibiotic therapy, especially given the many issues with antibiotics: poor efficacy, poor eradication of biofilms, destruction of commensal lactobacilli, antibiotic resistance induction, and various short and long term side effects (Reid et al. 1990; Schwebke & Desmond, 2007; 2011; Swidsinski et al. 2008; Beerepoot et al. 2012).

Unlike the CTV05 strain whose properties have been barely studied apart from *in vitro* adhesion to epithelial cells, and hydrogen peroxide production which likely plays little or no role in defence against recurrent infection, both the GR-1 and RC-14 strains have been extensively assessed to further our understanding of how they function in humans. In the first studies to use microarrays and transcriptomics for this purpose, we showed that vaginal cells 'sense' the GR-1 strain resulting in up-regulation of pattern recognition receptors, antimicrobial peptide psoriasin, mucin 4, cytokine receptors for IL-1 β , IL-8, IL-18 and especially Caspase-8, a proapoptotic protease which has a key role in lymphocyte activation and protective immunity (Kirjavainen et al. 2008). A study in which GR-1 and RC-14 or placebo capsules were introduced vaginally again showed an ability to modulate protective immunity (Bisanz et al. 2014c).

These studies provided a foundation from which a product emerged to help women in over 30 countries, and the concept initiated other groups to set up their own research on the application of probiotics for feminine health. PubMed searches of "probiotics AND vagina" show 6 publications prior to the year 2000 and 262 thereafter; and 5 studies under "probiotics AND urinary tract infection" prior to 2000 with 174 afterwards. If we played a small part in this transformation, it is satisfying if only to increase awareness of the adversity vaginal and bladder infections bring to the quality of life of females. Any new therapeutic approach that subsequently emerges, will be long overdue.

Another application to improve cardiovascular health through GR-1 lowering cholesterol (unpublished data) or improving cardiac remodeling by increasing the adiponectin to leptin ratio (Gan et al. 2014), evolved because the strains were being

ingested and studies using other probiotic lactobacilli had shown effects on heart health (Lam et al. 2012). While cardiovascular disease is the number one killer in women, breast cancer is the leading cancer in North American women. Continuing with our interest in women's health and knowing that breast feeding reduced the risk of cancer, we hypothesized that beneficial microbes may play a role in this protection. Studies of human milk showed the presence of lactic acid bacteria (Urbaniak et al. 2016a) and the rapid change to dysbiosis caused by chemotherapy (Urbaniak et al. 2014). With bacteria having access through the nipple to the mammary gland, it made sense that even in those women who never become pregnant or lactate, bacteria could still be within the mammary gland. Hypothesizing that species more accustomed to causing disease and carcinogenic reactions might be present and associated with breast cancer, we conducted two studies. We were the first to describe a breast microbiome and demonstrate the differences in the breast microbiome between women with cancer and those who are healthy, suggesting a breast microbiome may indeed have some protective properties (Urbaniak et al. 2014; 2016b). While not proving cause and effect, the discoveries could open a new line of investigation into 'environmental' factors inducing cancer, and a new method to modify this microbiome to one associated with health. In fact, Spanish researchers have shown that consumption of lactobacilli can not only cure mastitis, but it can deliver the organisms to the breast milk (Arroyo et al. 2010). This has important implications for women's breast health, as well as for transferring bacterial species that can aid in infant development.

Reaching impoverished communities

Some of the most documented attributes of probiotics have been to prevent and treat intestinal infections that cause high morbidity and mortality in developing countries (Guarino et al. 2012; Pattani et al. 2013; Banupriva et al. 2015; Guarino et al. 2015). Yet, ironically, these products, including ones actually tested in poor communities to prove efficacy, are not distributed in these developing countries because the markets do not provide sufficient returns on investment. Even in developed countries, the price of probiotic foods and dietary supplements is beyond the finances of many families. It would be disparaging to brand all people living in impoverished communities as poor, but I made it my personal mission to draw the world's attention to the need for probiotics to benefit all people, not just those with higher financial means. It was in 2004, through a program called Western Heads East initially to provide relief for HIV/AIDS patients that this mission began in a tangible way.

In Mwanza, Tanzania, we provided the GR-1 strain for local women's groups to produce probiotic yogurt for their communities. The GR-1 strain was stored and propagated at the National Institute for Medical Research. Despite many challenges (Dols et al. 2011; Reid et al. 2013), the incredible work ethic of the women and the overwhelming receptivity of the community to the yogurt led to expansion to 10 kitchens in the city. It would have been more but for the limitations in providing starter culture and our inability to raise additional funding for expansion. A transformational step took place following the visit of a Dutch colleague, Dr. Remco Kort, to our Mwanza site. A microbiologist by training, he and his friend, Dr. Wilbert Sybesma, were passionate about community outreach efforts. Stimulated by our project, they established Yoba-for-life, a non-profit organization. Recognizing the need to resolve the issue of availability of

the probiotic, they made two innovations. For the first, they recognized that patents for *L. rhamnosus* GG had expired and thus the strain could be used by others. They isolated and renamed it *L. rhamnosus* Yoba, referring to it as a generic version of probiotic. Although not a popular decision amongst companies producing and selling GG, the step was perfectly legal and meant they could use the industry's most documented probiotic. Secondly, they spent two years identifying a *Streptococcus thermophilus* strain that would produce a flavourful yogurt in combination with Yoba. Normally, *L. delbrueckii* subsp. *bulgaricus* is required to ferment the milk, and indeed the definition of yogurt requires co-cultivation of this species with *S. thermophilus*. However, Kort and Sybemsma felt that the *L. delbrueckii* might interfere with the probiotic activity of *L. rhamnosus* Yoba, so they showed that the *L. delbrueckii* was not necessary. They then prepared a 1g sachet containing the Yoba and *S. thermophilus* in a seal that retained viability for two years (Kort et al. 2015). Armed with this sachet, they set up community kitchens (which they refer to as production plants) in Uganda in which groups of people produced probiotic Yoba yogurt. Realising the enormity of this breakthrough, we joined forces with Yoba-for-life and under a grant from the International Development Research Council of Canada, we now help provide over 100,000 people in poor communities with access to affordable probiotic yogurt, with the goal of reaching one million in two years. Yoba-for-life are also embarking on similar outreach in Nepal, the Sahara and other developing countries.

This illustrates that social business and grass root mechanisms are feasible and necessary if we are to improve access to probiotics. The concept, is sustainable as it empowers people, allows them to gain financial reward for hard work, and provides

health benefits to adults and children in their neighborhoods (Reid et al. 2013). The current challenge is to prove that the model works on a larger scale and that the sachet usage is sustainable and effective. To further support the initiative, we have shown that the GR-1 probiotic yogurt can be safely consumed by HIV/AIDS patients in Canada (Hemsworth et al. 2012) and in Africa (Anukam et al. 2008; Irvine et al. 2010).

Recognizing the highly polluted nature of Lake Victoria from which locals in Mwanza extracted fish as part of their daily diet, we investigated whether the GR-1 strain could sequester heavy metals and pesticides. Discovering that this indeed occurred and that small silver fish were most contaminated by mercury, we performed a study of school children and pregnant women, two groups particularly affected by heavy metal poisoning, and showed that daily intake of the probiotic yogurt significantly reduced uptake of mercury and arsenic (Bisanz et al. 2014a). Carrying this concept to Kenya where aflatoxins produced by *Aspergillus* on maize cause death and morbidity following consumption, we showed in a pilot study of school children that daily intake of the probiotic yogurt can reduce toxin uptake (Nduti et al. 2016). Given the use of pesticides, the high amounts of heavy metals in lakes and the problem of aflatoxins in food in eastern Africa (Ochieng et al. 2007; Kilonzo et al. 2014; Kang et al. 2015; Okonya & Kroschel, 2015; Arinaitwe et al. 2016), any method of lowering risk of toxicity must be considered and pursued.

The future

A personal goal of making well documented probiotics available worldwide to all people, despite financial means, continues to present challenges. In hospital settings,

recognition of the value of beneficial microbes is happening, with use of probiotics to reduce mortality and morbidity of low-birth weight premature babies (Sawh et al. 2016) (including in London, ON after 10 years of advocating), and to prevent antibiotic associated diarrhea including *Clostridium difficile* infections (Hickson et al. 2007; Maziade et al. 2015), albeit not all studies have shown efficacy (Allen et al. 2013). The success of fecal microbiota transplant in curing *C. difficile* infections further emphasizes the impact of beneficial microbes (van Hood et al. 2013). However, this use is far from universal, in part because some clinicians are not convinced, products may not be available or administrators are concerned with law suits. Improving the quality checks of products will allay some of these fears (Sanders et al. 2016).

Having contributed to Health Canada's stoic efforts to properly regulate probiotics and health claims, I find it incredibly frustrating that the politics of regulatory systems in Europe and the US have stymied progress and even banned the word 'probiotic' on labels in Europe. In one application for a claim to use GR-1/RC-14 for vaginal health, the European Food Safety Authority stated that "The vagina is considered irrelevant to human nutrition. This means the vagina is not affected by the intestine or by the nutrients we consume." Clearly, the panel members do not understand human physiology nor the link between the gut and reproductive tract. Thus, as much as the scientific and clinical documentation demonstrates the effects of probiotics in vaginal health, if regulators block translation, the manufacturers have to fight these decisions, find ways around them, or try to generate more data to satisfy the authority, assuming that will ever be possible.

In my view, while most microbiome research has focused on the gut, the health of the reproductive tract of women is a critical area of study. The failure of drug and diagnostic companies to adequately manage aberrant conditions in this area means that other innovations must be sought. Probiotics and prebiotics are not magic bullets, but they can contribute to the health of the female and fetus. Since early life nutrition and microbiotas are critical for a life long health trajectory (Barker 1990; Reid 2016), continued research on the composition, function and dynamics of the urogenital microbiome in females and in male sexual partners, will make an enormous impact on life over the next 20 years and beyond.

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