# Bioengineered Probiotics – A Solution to Broaden Probiotics Efficacy!

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## Editorial

Probiotics are defined by the Food and Agriculture Organization as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host". Broadly, probiotics promote good health and prevent diseases. More specifically, in infants, consumption of probiotics may promote perinatal health; prevent obesity, irritable bowel syndrome, eczema or atopic dermatitis and asthma; however, the supporting research data are inadequate [1,2]. In adults, probiotics may be used as prophylactic or therapeutic agents against enteric pathogens, antibiotic associated diarrhea, lactose intolerance, ulcerative colitis, irritable bowel syndrome, colorectal cancer, cholesterol reduction, and control of obesity and metabolic disorders [1,3]. Some probiotics may also have therapeutic attributes towards non-alcoholic fatty liver disease [4]. These beneficial attributes are largely derived from the immune-modulatory activity and microbial homeostasis provided by supplemented probiotic bacteria in the gut. Therefore, probiotic preparations consisting of multiple species or strains are highly desirable and functionally superior to preparations containing monocultures. Multi-culture probiotics may have synergistic effects whereas monocultures lack such positive attributes. Concerns of antibiotic resistance and the need for protection against harmful infective agents have led to a renewed interest in prophylactic and therapeutic application of probiotics. Of late, probiotics are gradually becoming an integral part of the modern day healthy life-style. Even though, the perceived beneficial attributes are accepted with great caution, general appeal towards probiotics is on the rise. Research has generated valuable information and scientific data but more in-depth studies are required to fully understand the health potential of probiotics. Despite all the scientific advancement, many questions still remain unanswered. Do probiotics work on all individuals with equal efficiency against different types of ailments? How long does one need to consume probiotics? Can the probiotic effect be modulated by diet, resident gut microbiota, age, gender, or other traits? If a probiotic fails to provide protection, can this be modified to control a specific disease? Safety of probiotics use, effective dosage, and duration of intake also need to be carefully monitored, especially in severely immune compromised host, where lactic acid bacteria mediated bacteremia and endocarditis or other health related complications have been reported.

Although probiotics have been used to fight infections, their mode of action is generic and not targeted against specific pathogen. Is it possible to use a probiotic in the prevention of a specific disease? A designer probiotic approach may be the answer. The concept started in the last decade when scientists from Stanford University attempted to express HIV-1 surface protein receptor (Gp120) that interacts with CD4 molecule on the host cells, into *Lactobacillus jensenii* isolated from a female vaginal tract [5]. This approach was based on the premises that colonized bioengineered probiotics expressing recombinant Gp120 would compete with incoming HIV-1 and protect the host against acquired immunodeficiency syndrome (AIDS). The concept was novel. Similar approach has been used to control several enteric bacterial infections. One such system uses toxin receptor mimicry system to combat enteric infections [6]. Host cell oligosaccharide receptors

that interact with toxins of enteric pathogens such as *Escherichia coli, Vibrio cholera, Clostridium difficile,* and *Clostridium perfringens*, were expressed on probiotic bacteria. The toxins produced by these microbes exhibit strong avidity towards the receptor expressed on the surface of innocuous resident bacteria thus preventing toxins from acting upon the host cells. Similar strategy was also used to control *Helicobacter pylori* infection by expressing urease, a colonization factor in host gastric cells, in probiotic bacteria, creating a competitive environment to exclude *H. pylori* colonization. Similarly, expression of *Listeria* adhesion protein on probiotics was able to reduce *Listeria monocytogenes* infection *in vitro* [7]. *Salmonella* infection was also controlled by expressing flagellar proteins which resulted in a protective immune response against salmonellosis.

Another interesting development in recent years is the use of engineered probiotics to deliver therapeutic or prophylactic molecules to the mucosal membrane [8]. Antigens and interleukins are expressed or co-expressed on probiotics to induce mucosal immunity to protect host from various infective agents such as *Streptococcus, Erysiplothrix, Plasmodium falciparum*, tetanus, and viruses. Such approach has also been tested to control chronic inflammatory bowel diseases. These strategies are promising and support the idea that individual pathogen infection can be controlled by the designer probiotic approach.

In spite of all the advantages, use of designer probiotics raises many questions and concerns. Importantly, what are the consequences of prolonged consumption of genetically modified probiotics? How will these engineered probiotics be accepted by consumers? From the regulatory perspective, what properties need to be scrutinized? To gain health promoting benefits, probiotic containing products often need to be consumed daily since a certain bacterial population must be maintained in the gut. Can such daily dietary intakes of large doses be recommended for designer probiotics or should they be used – only when needed? What are the consequences of prolonged consumption of designer probiotics that are carrying adhesion or invasion genes of pathogens? Can an enhanced immunity be expected since the colonized or internalized probiotics have greater access to the mucosal immune cells? Does the probiotic safety become an important issue for people with suppressed immunity? Even though probiotics are expected to enhance immunity; the consequential long-term effects must be thoroughly examined so that recombinant designer probiotics are safe. In conclusion, the most important consideration to the use of probiotics should be – "do benefits outweigh the ill-effects?

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