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Therapeutic DNA Vaccines: "Future strategies"

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Abstract: *Therapeutic DNA vaccines are simple rings of DNA containing a strong promoter that allows in situ transcription and translation of one or many encoded antigens to induce all types of desired immunity. Lactic acid probiotic bacteria harboring therapeutic DNA plasmids used as protective delivery vehicles targeting plasmids to the target cells protect the plasmid against degradation and denaturation by nucleases. Lyophilization process and gastrointestinal tract (GIT) hamper these plasmid harboring bacteria. Probiotic Encapsulation Technology (PET) can be used to protect the bacteria during production, storage and handling but still there are some challenges to overcome. Fermented milk and cheese allow protection towards digestive enzymes by forming a matrix, so these can be used to develop a technique for safe delivery of bacteria used for DNA vaccine delivery. These innovations might have control on the release of therapeutic molecules on the delivery site and on therapeutic efficacy.*

Keywords: *Probiotics; Probiotic Encapsulation Technology; recombinant DNA vaccine*

1. INTRODUCTION

Edward Jenner in 1798 demonstrated that pus from cowpox lesion, on inoculation, was providing protection against smallpox infection [1]. His experiment lead to various works in the field of immunology. The invention and development of vaccines became one of the most astonishing and important application in the field of medicine. The various types of vaccines are bacterial toxoids (diphtheria and tetanus); killed entire organisms (e.g. typhoid, cholera, pertussis and the Salk polio vaccine); or live attenuated organisms (reduced pathogenicity) (e.g. *Bacillus Calmette Guerin*, yellow fever, the Sabin polio vaccine, measles, mumps and rubella) [2].

Many diseases still require vaccines to be developed against them as millions of people die every year from infections like HIV/AIDS and malaria. Vaccines against these infections as well as cancer and others diseases is the need of the hour. The fear of bioterroism has created an urgency to develop new vaccines with higher safety profile and easily administrable to large populations [3].

Vaccines in current use are predominantly composed of killed pathogens, pathogen subunits, or live attenuated viruses. Killed vaccines generally do not provide life-long immunity while live-attenuated vaccines can induce more-prolonged immunity. The degree of attenuation can significantly decrease the immunogenicity of live vaccines and the development of live vaccine strategies becomes challenging when the target is multiple viral subtypes or pathogens. Theoretically, there is few safety concerns associated with the use of both killed and attenuated approaches. Such limitations continue to drive the need to develop new vaccine platforms that offer broader immunogenicity.

In 1990s, the DNA vaccines first sparked into the scientific community when it was reported that the use of DNA vectors to drive both humoral and cellular immune responses against viral and non viral agents *invivo* [4-7]. There are more than 114 open clinical studies currently recruiting patients for distinct clinical phases using a DNA vaccine approach.

Therapeutic DNA vaccines are simple rings of DNA containing a strong promoter that allows *in situ* transcription and translation of one or many encoded proteins/antigens to induce protective cellular and humoral immune responses against different pathogenic organisms [3]. These properties make DNA vaccines as third generation vaccines. Different routes of administrations can be used but oral route is considered as safe or "GRAS" (Generally Recognized as Safe) [8]. The Lactic Acid Bacteria harboring therapeutic DNA plasmids used as protective delivery vehicles targeting plasmids to the cells offers a key advantage, as they also protect the plasmid against degradation and denaturation by nucleases. However, the use of bacteria is

hampered by the susceptibility to the lyophilization process and bacterial death within the gastrointestinal tract (GIT). So, more efficient means of delivery for therapeutic lactic bacteria are under development [9-11].

Very few DNA vaccines are being tested for prophylactic and therapeutic applications with *in vivo* positive results seen against few infectious agents like Human Immunodeficiency virus, Influenza virus, Sub Acute Respiratory Syndrome virus and Hepatitis B virus [12-15].

Probiotics have also been bioengineered to modulate the immune response. Bermúdez-Humarán LG, *et al* used a genetically modified *Lactococcus lactis*, a lactic acid bacteria producing human IL-10, aiming to increase the mucosal bioavailability of IL-10 for preventing and treating Crohn's disease patients in a phase-IIA clinical trial. The clinical results of this study showed no statistically significant difference in mucosal healing versus placebo[16].

Most of these experimental probiotic bacteria are being used to explore and demonstrate the feasibility of recombinant DNA vaccine concept. A protective matrix development is required, which can protect against adverse environment of GIT, for efficient delivery of these bacteria to their specific site. Tolerance against GIT conditions is strain dependent, so choosing a tolerant strain can increase the *in vivo* efficacy [11]. The adherence to epithelial cells and mucus, as well as immune modulatory properties of the strain is also important to enhance the delivery efficiency of biologically active molecules or antigens [17]. Gbassi GK *et al* demonstrated that Probiotic Encapsulation Technology (PET) can be used to protect the bacteria during production, storage and handling but still there are some challenges to overcome before PET can deliver the bacteria safely into gut [18]. Strategies like emulsion, extrusion and recently spray-drying techniques can be used for performing PET [19–20]. The probiotic bacterial stability and binding to the specific sites can be improved by immobilizing them within semipermeable and biocompatible matrices including food-grade biopolymers like alginate, pectin and cellulose acetate phthalate or milk proteins [21]. Traditional fermented foods like fermented milk and cheese constitute a protective matrix rich in proteins and lipids allowing protection towards digestive enzymes [17,22]. They also trigger sublethal doses of stress in these bacteria which leads to over expression of key adaptation proteins [23], to the accumulation of compatible solutes and thus to enhanced tolerance acquisition. Newer fermented food products can thus be designed [24] to deliver the target engineered bacteria used for DNA vaccine delivery.

2. CONCLUSION

DNA vaccines are third generation vaccines which can elicit either humoral or cellular immune responses or both without the need for live vectors or complex biochemical production techniques. They are rapidly advancing in clinical trials and need few challenges to overcome specially the adverse action of GIT environment. Novel strategies like PET and designer traditionally fermented food products can guide newer outlook for safe delivery of DNA vaccines by Probiotic bacteria with more appreciable efficacy against the detrimental environment of the GIT. These innovations might have control on the release of therapeutic DNA vaccines on the delivery site. A better therapeutic efficacy can be seen in future with these innovations.

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