Journal of Bacteriology and Parasitology

Carmo et al., J Bacteriol Parasitol 2017, 8:1
DOI: 10.4172/2155-9597.1000e125

Editorial Open Access

Therapeutic DNA Vaccines: The Final Step for Success

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Received date: March 27, 2017; **Accepted date:** March 30, 2017; **Published date:** April 03, 2017

Editorial

Therapeutic DNA vaccines are mostly plasmidic constructs 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 [1–5]. Currently, at least 114 open clinical studies are recruiting patients for distinct clinical phases using a DNA vaccine approach.

Different routes like intramuscular, intradermal, intravenous, intranasal and oral can be used for the delivery of such vaccines. Oral administration is the most commonly used route to deliver live bacteria considered safe or "GRAS" (Generally Recognized as Safe), a state designated in the United States by the Food and Drug Administration agency [6]. The use of Lactic Acid Bacteria harboring therapeutic DNA plasmids as protective delivery vehicles targeting plasmids to the cells offers a key advantage, because they protect the plasmid against degradation and denaturation by nucleases, besides acting as adjuvants.

The intestinal mucosa is an attractive target for the delivery of biologically active molecules, as it regulates the delicate balance between 1) protection against infections and 2) prevention of inflammatory or autoimmune diseases [7]. Mucosal route vaccination strategies are associated with reduced side effects, offer easier administration, and can reduce the costs of production and implementation [8]. Furthermore, this route offers to significant advantages over the parenteral administration, as molecules are administered locally and have the ability to stimulate immune responses of the Gut-Associated Lymphoid Tissue, the largest immunological structure of the body [9]. However, the use of bacteria in humans is hampered by the susceptibility to the lyophilization process and bacterial death within the gastrointestinal tract (GIT). In this context, more efficient means of delivery at the mucosal level for therapeutic lactic bacteria are being developed [10–12].

Despite the time and effort to improve DNA vaccines efficiency, only some candidates are being tested for prophylactic and therapeutic applications in different disease models and showed positive results *in vivo* [13–16].

Probiotic bacteria have also been bioengineered to modulate the immune response. Very encouraging studies using the anti-inflammatory cytokine interleukin-10 (IL-10), an important regulator in the context of chronic intestinal inflammation, have not succeeded in reducing inflammation in humans. Moreover, they require high levels of IL-10, increasing the cost of production and side effects in the patients [17–21]. In a different approach, the most likely study using a genetically modified lactic acid bacteria, *Lactococcus lactis* producing human IL-10, aims to increase the mucosal bioavailability of IL-10 for preventing and treating Crohn's disease patients in a phase-II clinical trial. However, this study showed that clinical results were unsatisfactory and no statistically significant therapeutic effect was found [22].

Although the majority of genetically engineered bacteria are, for now, only being used in "proof-of-concept" studies, the development of a protective matrix is needed for efficiently delivering these bacteria to their specific site.

The key step to achieve this aim consists in improving technologies for enhancing protection of bacteria against adverse conditions of the GIT. Selecting Lactic Acid Bacteria probiotic strains exhibiting the highest tolerance towards GIT environmental stress might increase *in vivo* efficacy. Indeed, the tolerance of bacteria towards digestive conditions is highly dependent on the strain used [12]. Among the considerations regarding the choice of bacterial strains, adherence to epithelial cells and mucus, as well as immunomodulatory properties are crucial to improve delivery efficiency of biologically active molecules or antigens [23].

The relevant literature proposes the use of encapsulation techniques to stabilize bacteria, thereby enhancing their viability during production, storage, and handling [24]. This can be performed using different strategies like emulsion, extrusion and recently spray-drying techniques [25–27]. Moreover, microorganisms have been immobilized within semipermeable and biocompatible matrices including food-grade biopolymers like alginate, pectin and cellulose acetate phthalate or milk proteins. By wrapping bacteria in a protective matrix, this improves both stability and addressing of active compounds to specifics sites [28]. There is a variety of protective food-grade matrices that are commonly used for probiotics within tablets [29], chewing gum [30-32], sachets [33] and capsules [34]. Innovative probiotic delivery strategies should also take lessons from traditional fermented foods. Indeed, fermented milk and cheese [23,35,36] are highly versatile food products and may confer to dairy bacteria a level of stress tolerance that's hard to exceed. Indeed, they constitute a protective matrix rich in proteins and lipids allowing protection towards digestive enzymes. Moreover, they trigger sublethal doses of stress in these bacteria, leading to overexpression of key adaptation proteins [37], to the accumulation of compatible solutes and thus to enhanced tolerance acquisition. Designer fermented food products can thus be developed [35,36] and could constitute versatile delivery vehicles to target engineered bacteria used for DNA vaccine delivery.

Such innovations open new perspectives for the delivery of biotherapeutic molecules by Lactic Acid Bacteria with enhanced efficacy when facing the adverse conditions of the human GIT. They might have an impact on the consolidation of controlled release of biotherapeutic molecules, on the delivery site and on the quality of therapeutic effects.

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