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► **To cite this version:**

Fillipe Luiz Rosa Do Carmo, Rodrigo Dias Carvalho, Gwénaél Jan, Vasco Azevedo. Therapeutic DNA Vaccines: The Final Step for Success. *Journal of Bacteriology & Parasitology*, 2017, 08 (01), pp.1000e125. 10.4172/2155-9597.1000e125 . hal-01539474

HAL Id: hal-01539474

<https://hal.science/hal-01539474>

Submitted on 14 Jun 2017

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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

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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 specific 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.

References

1. Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, et al. (1990) Direct gene transfer into mouse muscle *in vivo*. *Science* 247: 1465-1468.
2. Chow YH, Chiang BL, Lee YL, Chi WK, Lin WC, et al. (1998) Development of Th1 and Th2 populations and the nature of immune responses to hepatitis B virus DNA vaccines can be modulated by codelivery of various cytokine genes. *J Immunol* 160: 1320-1329.
3. Ulmer JB, Donnelly JJ, Parker SE, Rhodes GH, Felgner PL, et al. (1993) Heterologous protection against influenza by injection of DNA encoding a viral protein. *Science* 259: 1745-1749.
4. Sato Y, Roman M, Tighe H, Lee D, Corr M, et al. (1996) Immunostimulatory DNA sequences necessary for effective intradermal gene immunization. *Science* 273: 352-354.
5. Klinman DM, Klaschik S, Tross D, Shirota H, Steinhagen F (2010) FDA guidance on prophylactic DNA vaccines: analysis and recommendations. *Vaccine* 28: 2801-2805.
6. Schoen C, Stritzker J, Goebel W, Pilgrim S (2004) Bacteria as DNA vaccine carriers for genetic immunization. *Int J Med Microbiol* 294: 319-335.
7. Rottiers P, De Smedt T, Steidler L (2009) Modulation of gut-associated lymphoid tissue functions with genetically modified *Lactococcus lactis*. *Int Rev Immunol* 28: 465-486.
8. Cortes-Perez NG, Lefèvre F, Corthier G, Adel-Patient K, Langella P, et al. (2007) Influence of the route of immunization and the nature of the bacterial vector on immunogenicity of mucosal vaccines based on lactic acid bacteria. *Vaccine* 25: 6581-6588.
9. Bolton DL, Song K, Wilson RL, Kozlowski PA, Tomaras GD, et al. (2012) Comparison of systemic and mucosal vaccination: impact on intravenous and rectal SIV challenge. *Mucosal Immunol* 5: 41-52.
10. Huyghebaert N, Vermeire A, Neiryneck S, Steidler L, Remaut E, et al. (2005) Development of an enteric-coated formulation containing freeze-dried, viable recombinant *Lactococcus lactis* for the ileal mucosal delivery of human interleukin-10. *Eur J Pharm Biopharm* 60: 349-359.
11. Termont S, Vandenbroucke K, Iserentant D, Neiryneck S, Steidler L, et al. (2006) Intracellular accumulation of trehalose protects *Lactococcus lactis* from freeze-drying damage and bile toxicity and increases gastric acid resistance. *Appl Environ Microbiol* 72: 7694-7700.
12. Rokka S, Rantamäki P (2010) Protecting probiotic bacteria by microencapsulation: challenges for industrial applications. *Eur Food Res Technol* 231: 1-12.
13. MacGregor RR, Boyer JD, Ugen KE, Lacy KE, Gluckman SJ, et al. (1998) First human trial of a DNA-based vaccine for treatment of human immunodeficiency virus type 1 infection: safety and host response. *J Infect Dis* 178: 92-100.
14. Drape RJ, Macklin MD, Barr LJ, Jones S, Haynes JR, et al. (2006) Epidermal DNA vaccine for influenza is immunogenic in humans. *Vaccine* 24: 4475-4481.
15. Martin JE, Louder MK, Holman LA, Gordon JJ, Enama ME, et al. (2008) A SARS DNA vaccine induces neutralizing antibody and cellular immune responses in healthy adults in a Phase I clinical trial. *Vaccine* 26: 6338-6343.
16. Tacket CO, Roy MJ, Widera G, Swain WF, Broome S, et al. (1999) Phase I safety and immune response studies of a DNA vaccine encoding hepatitis B surface antigen delivered by a gene delivery device. *Vaccine* 17: 2826-2829.
17. Van Deventer SJ, Elson CO, Fedorak RN (1997) Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's Disease Study Group. *Gastroenterology* 113: 383-389.
18. Fedorak RN, Gangl A, Elson CO, Rutgeerts P, Schreiber S, et al. (2000) Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. *Gastroenterology* 119: 1473-1482.
19. Tilg H, Kaser A, Propst A, Schreiber S, Gregor M, et al. (1998) Recombinant human interleukin-10 (rHuIL-10) therapy in steroid-refractory chronic active Crohn's disease (CACD): Induction of neopterin, a degradation product of the pteridine pathway regulated by interferon-gamma. *Gastroenterology* 114: A1100.
20. Colombel JF, Rutgeerts P, Malchow H, Jacyna M, Nielsen OH, et al. (2001) Interleukin 10 (Tenovil) in the prevention of postoperative recurrence of Crohn's disease. *Gut* 49: 42-46.
21. Braat H, Rottiers P, Hommes DW, Huyghebaert N, Remaut E, et al. (2006) A phase I trial with transgenic bacteria expressing interleukin-10 in Crohn's disease. *Clin Gastroenterol Hepatol* 4: 754-759.
22. Bermúdez-Humarán LG, Kharrat P, Chatel JM, Langella P (2011) Lactococci and lactobacilli as mucosal delivery vectors for therapeutic proteins and DNA vaccines. *Microb Cell Fact* 10 Suppl 1:S4.
23. Uroić K, Novak J, Hynönen U, Pietilä TE, Pavunc AL, et al. (2016) The role of S-layer in adhesive and immunomodulating properties of probiotic starter culture *Lactobacillus brevis* D6 isolated from artisanal smoked fresh cheese. *LWT - Food Sci Technol* 69: 623-632.
24. Gbassi GK, Vandamme T (2012) Probiotic Encapsulation Technology: From Microencapsulation to Release into the Gut. *Pharmaceutics* 4: 149-163.
25. Huang S, Cauty C, Dolivet A, Le Loir Y, Chen XD, et al. (2016) Double use of highly concentrated sweet whey to improve the biomass production and viability of spray-dried probiotic bacteria. *J Funct Foods* 23: 453-463.
26. Huang S, Méjean S, Rabah H, Dolivet A, Le Loir Y, et al. (2017) Double use of concentrated sweet whey for growth and spray drying of probiotics: Towards maximal viability in pilot scale spray dryer. *J Food Eng* 196: 11-17.
27. Huang S, Rabah H, Jardin J, Briard-Bion V, Parayre S, et al. (2016) Hyperconcentrated Sweet Whey, a New Culture Medium That Enhances *Propionibacterium freudenreichii* Stress Tolerance. *Appl Environ Microbiol* 82: 4641-4651.
28. De Prisco A, Mauriello G (2016) Probiotication of foods: A focus on microencapsulation tool. *Trends Food Sci Technol* 48: 27-39.
29. Klayraung S, Viernstein H, Okonogi S (2009) Development of tablets containing probiotics: Effects of formulation and processing parameters on bacterial viability. *Int J Pharm* 370: 54-60.
30. Caglar E, Kavaloglu SC, Kuscü OO, Sandalli N, Holgerson PL, et al. (2007) Effect of chewing gums containing xylitol or probiotic bacteria on salivary mutans streptococci and lactobacilli. *Clin Oral Investig* 11: 425-429.
31. Cruywagen CW, Jordaan I, Venter L (1996) Effect of *Lactobacillus acidophilus* supplementation of milk replacer on preweaning performance of calves. *J Dairy Sci* 79: 483-486.
32. Bruno FA, Shah NP (2003) Viability of Two Freeze-dried Strains of *Bifidobacterium* and of Commercial Preparations at Various Temperatures during Prolonged Storage. *J Food Sci* 68: 2336-2339.
33. Lavermicocca P (2006) Highlights on new food research. *Dig Liver Dis* 38 Suppl 2: S295-299.
34. Cousin FJ, Jouan-Lanhouet S, Dimanche-Boitrel MT, Corcos L, Jan G (2012) Milk fermented by *Propionibacterium freudenreichii* induces apoptosis of HGT-1 human gastric cancer cells. *PLoS One* 7: e31892.
35. Plé C, Richoux R, Jardin J, Nurdin M, Briard-Bion V, et al. (2015) Single-strain starter experimental cheese reveals anti-inflammatory effect of *Propionibacterium freudenreichii* CIRM BIA 129 in TNBS-colitis model. *J Funct Foods* 18: 575-585.
36. Plé C, Breton J, Richoux R, Nurdin M, Deutsch SM, et al. (2016) Combining selected immunomodulatory *Propionibacterium freudenreichii* and *Lactobacillus delbrueckii* strains: Reverse engineering development of an anti-inflammatory cheese. *Mol Nutr Food Res* 60: 935-948.
37. Gagnaire V, Jardin J, Rabah H, Briard-Bion V, Jan G (2015) Emmental Cheese Environment Enhances *Propionibacterium freudenreichii* Stress Tolerance. *PLoS One* 10: e0135780.