Periodontal Vaccines: A Vision or Mission

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ABSTRACT
Vaccine is the name applied generally to a substance of the nature of dead or attenuated living infectious material, introduced into the body with the object of increasing its power to resist or get rid of a disease. Vaccines are generally prophylactic, i.e. they ameliorate the effects of future infection. One such vaccine considered here is the ‘periodontal vaccine’. Till date, no preventive modality exists for periodontal disease and treatment rendered is palliative. Thus, availability of periodontal vaccine would not only prevent and modulate periodontal disease, but also enhance the quality of life of people for whom periodontal treatment cannot be easily obtained. The aim of the research should be development of a multispecies vaccine targeting the four prime periodontal pathogens, viz Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola and Aggregatibacter actinomycetemcomitans. Success is still elusive in case of periodontal vaccine due to the complex etiopathogenesis of the disease.

Keywords: Immunization, Multispecies, Periodontal disease, Vaccine.

HISTORY OF PERIODONTAL VACCINE
Louis Pasteur coined the term ‘vaccine’. These are preparations of live or killed microorganisms or their products used for immunization. Vaccines increase host immune response by artificially producing a degree of resistance, sufficient to prevent a clinical attack of natural infection, without causing ill effects to the recipient.

Vaccines may be live, attenuated, component, recombinant, synthetic oligopeptide and deoxyribonucleic acid (DNA). A new type called subunit vaccine, prepared by purifying important antigens of microorganisms, has also been developed.

Periodontal vaccines were new additions to the vaccine family and were invented in early 20th century.

BACKGROUND FOR DEVELOPMENT OF PERIODONTAL VACCINES
Periodontal disease comprises a group of infections involving supporting tissues of teeth. These range in severity from mild and reversible inflammation of gingiva to chronic destruction of periodontal tissues with eventual loss of teeth.

Classification of various manifestations of periodontal disease is continuously changing and the diseases also range in severity, rate of progression, number of teeth affected and at different age groups. Nature of pathogenic agents varies among different diseases, and even between different sites within a patient because of site specificity. Though there is great amount of information about human diseases, little has been accomplished by way of preventing or treating the disease. There remains a need for safe and effective vaccine for treating and preventing periodontal disease.

Some microorganisms were considered as key pathogens in periodontal disease as they were strongly associated with disease status, disease progression and unsuccessful therapy. These were Porphyromonas gingivalis, Tannerella forsythia and Aggregatibacter actinomycetemcomitans. These were considered as key organisms as they satisfied the Socransky’s modification of Koch’s postulate.
Periodontal vaccines under trial are hence being developed mainly against these few microorganisms.

PATHOGENESIS OF PERIODONTITIS
Pathogenic bacteria produce an array of antigens which stimulate proinflammatory cells and leads to production of wide variety of cytokines. These antigens may stimulate T-helper cells 1 or 2 (Th1 or Th2 respectively) cells. Antigens are taken up by dendritic cells and presented to CD4 or CD8 cells along with major histocompatible complex (MHC) antigens.4

Host produces antibacterial substances, like defensins and cathelicidins which protect host tissues from bacterial products and form first line of defense. However, sometimes these are inactivated by bacterial virulence factors.

Once bacteria break this barrier, cytokines are produced, which can be both proinflammatory and anti-inflammatory. Production of inappropriate cytokines results in periodontitis.

BASIS FOR DEVELOPMENT OF PERIODONTAL VACCINE
The bacteria most frequently associated with periodontitis include P. gingivalis, P. intermedia, T. forsythia (forsythensis), Treponema denticola, Aggregatibacter actinomycetemcomitans, and Fusobacterium spp.5 Such bacteria and their by-products can elicit strong immune responses.6

As it was found that few key pathogenic micro-organisms were almost always responsible for development of periodontal diseases, an attempt was made to immunize against these common pathogenic microorganisms by vaccines; which, in turn, helps in preventing the occurrence of periodontal disease.

INVENTION OF PERIODONTAL VACCINES
The invention relates to novel bacterial isolates which are identified by their 16S rRNA, DNA that causes periodontal disease in companion animal. Polynucleotide sequences are contained in them. The polypeptides encoded by such polypeptide sequences and vaccines comprising such bacterial isolates have been inactivated or attenuated.7 They also provides the methods for treating and preventing periodontal disease and kits for detecting, treating, and preventing periodontal disease. In addition, methods for assessing efficacy of a vaccine against periodontal diseases in an animal are provided.

Vaccine Candidate Antigens of P. gingivalis
Porphyromonas gingivalis is a potential vaccine candidate because this pathogen carries several high-potent antigens, a lipopolysaccharide capsule, lipids and outer membrane proteins. Whole-cell formalin-killed P. gingivalis has been used as the target antigen.8

Studies have shown that immunization with RgpA–Pgp induces an immunoglobulin G2a response, with a restricted colonization by P. gingivalis and periodontal bone loss in the rat.8

Studies have also demonstrated that transcutaneous immunization of mice with a 40 kDa outer membrane protein of P. gingivalis induces specific antibodies that inhibit coaggregation by P. gingivalis to Streptococcus gordonii.9

VACCINE TRIALS
Vaccine trials in animal models are required for safety and efficacy testing of vaccines. The ideal animal research model for vaccine trials against periodontitis with naturally occurring periodontitis based on the same etiology, pathogenesis, and prevalence in animals as well as in humans does not exist.

Page and Schroeder10 concluded that because of continuous eruption patterns of teeth and alveolar bone changes, mice, rats, and hamsters might not be suitable for clinical periodontitis vaccine efficacy studies.

Dogs have not been considered for periodontal vaccine studies. It is of interest that sheep (bovine) appear to develop naturally occurring periodontitis. At least for P. gingivalis in sheep, there is homology to human strains. There is also a similarity in humoral immune responses and periodontitis responses in sheep and humans.11

Nonhuman primates, including Macaca fascicularis, Macaca nemestrina, marmosets, baboons and chimpanzees, have been considered for periodontal vaccine trials. Naturally occurring periodontitis in M. fascicularis (wild caught or domestically bred) is less than 5%.12

Studies have demonstrated that key pathogens associated with periodontitis can be identified in samples taken from adult M. fascicularis and M. nemestrina and identified by DNA probes, aimed for studies of strains found in humans.13 Thus, the patterns of bacterial presence in older vs young M. nemestrina are consistent with what is known from bacterial patterns in humans.

STUDIES CONDUCTED TO PROVE EFFECTIVENESS OF PERIODONTAL VACCINES
In particular, various studies and trials are under progress for vaccine against P. gingivalis and also few studies against A. actinomycetemcomitans and T. forsythia in animals like rats, dogs, sheeps, etc. Here, few studies are mentioned which were conducted on animals against these organisms.

In a study conducted by Choi J et al on mice, regarding using capsular polysaccharide-fimbrial protein conjugate
vaccine, it was found that it helped in reconstructing human peripheral blood lymphocytes. Study concluded that capsular polysaccharide-fimbrial protein conjugate from *P. gingivalis* could potentially be developed as vaccines against periodontal infection by it.

In a study conducted by Torbjorn and Graham on Wistar rats, it was found that treatment with SRII72 (heat killed *Mycobacterium vaccae*) inhibited progression of established experimental periodontal disease. The SRII72, a preparation of heat killed *M. vaccae* had shown to down regulate Th2 responses and increase Th1 responses to bacteria, and hence have therapeutic effect in periodontal disease.

Another study conducted by Lee et al, it was found that *P. gingivalis* heat shock protein-vaccine reduces the alveolar bone loss induced by multiple periodontopathogenic bacteria. In a study conducted by Decarlo et al on rat periodontitis model, it was found that pre-inoculation with the *P. gingivalis* HA2 binding domain for hemoglobin provided protection from disease. Protection was associated with induced anti-HA2 immunoglobulin G (IgG) humoral antibodies. The IgG subclass ratios suggested that relatively lower Th2/Th1-driven responses were directly associated with protection when rHA2 was administered in saline. Koizumi et al found that nasal immunization with *P. gingivalis* outer membrane protein decreases *P. gingivalis* induced atherosclerosis and inflammation in spontaneously hyperlipidemic mice.

Persson et al demonstrated that immune responses to whole bacterial cell and purified protein preparations as vaccine candidates was found in nonhuman primate models. Data suggested that immunization reduces the rate and severity of bone loss and it is also possible to alter the composition of subgingival microflora. Natural active immunization by therapeutic interventions results in antibody titer enhancement and potentially improves treatment outcome. Passive immunization of humans using *P. gingivalis* monoclonal antibodies temporarily prevents its colonization.

**FUTURE TRENDS**

Advanced human periodontal disease is a common problem in many developing countries, where it often results in multiple tooth loss by early middle age. Giving the vaccine in early adolescence before periodontitis has developed may enhance the quality of life for people for whom periodontal treatment cannot be obtained easily. Therefore, availability of a vaccine for preventing or modulating periodontal disease in humans, dogs and other mammals would be of great benefit in both developed and developing countries.

**WHY PERIODONTAL VACCINE REMAINS A DREAM TILL DATE?**

Though lots of researches have been made and many are still in progress, the concept of vaccination against periodontal disease in humans still remains complex and unresolved. The most probable reason for this failure is that all the studies were conducted on experimental animals and no sufficient data is available to imply the same in humans. Evidence-based literature is necessary to accept the effectiveness of these vaccines in humans.

Moreover, most of the studies conducted were against a particular microorganism. Though the aimed organism was a key pathogenic microorganism, its effectiveness in preventing disease like periodontal disease, which has multifactorial etiology, was questionable.

Proper etiology for periodontal disease is not completely clear as it is multifactorial; it is not only caused by few of these microorganisms but also due to many other local and systemic factors, like smoking, diabetes, emotional stress, and few genetic factors also play role in occurrence of disease.

Therefore, the attempt to prevent periodontal disease by means of periodontal vaccines remains a failure. As studies have concluded, various periodontal vaccines are found to be effective in animals. But, impact of such immunization in humans and its feasibility should be explored. So, further research and study should be carried out to use periodontal vaccines effectively and safely in humans and make it a reality.

**DREAM OR REALITY?**

Although till now periodontal vaccines are not a reality, they surely can be considered as a dream, which may come true as the future looks very bright and promising as per the various researches going on in the field.

Unlike other treatment modalities available today which can only treat the existing disease, vaccines not only treat but also prevent the occurrence of disease. As the saying ‘Prevention is better than cure’, its ability to prevent disease may overtake all other treatment modalities if it succeeds. However, the invention is still in infancy stage and has a long way to go before it can be used in routine practice. Somebody has correctly said ‘Do not’ be afraid of space between your dream and reality. If you can dream it, you can make it so’.

Thus, development of immunotherapy for periodontitis is though a groundbreaking work, it will prove to be an emerging treatment modality in near future.

**CONCLUSION**

The current evidence collected from a large series of diverse and independent studies have clearly demons-
trated that active immunization using vaccines against microorganisms will induce a significant humoral response across animal study models. If passive immunization studies are included, such evidence can also be gathered from human observational studies.

Immunization against microorganisms results in a reduction of the quantity of the target organism in animal models. Microorganism levels at infected periodontal sites are inversely correlated with antibody titers against the pathogen. Collaborative efforts are needed to ensure successful vaccine development against periodontitis.

Hence, from the various efforts taken to develop a periodontal vaccine—‘A magical bullet’, we can see that these efforts are making a dream turn into reality.

REFERENCES