# Caries Vaccine : A Review

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**Abstract**

Dental caries is one of the most common diseases in humans. In modern times, it has reached epidemic proportions. Dental caries is an infectious microbiologic disease of the teeth that results in localized dissolution and destruction of the calcified tissue. Dental caries is a mulitifactorial disease, which is caused by host, agent and environmental factors. The time factor is important for the development and progression of dental caries. A wide group of microorganisms are identified from carious lesions of which S. mutans, Lactobacillus acidophilus and Actinomycesviscosus are the main pathogenic species involved in the initiation and development of dental caries to prevent dental caries. Various experimental trials have been conducted utilizing rat and primate models with protein antigens derived from S. Mutans or S. Sobrinus to prevent oral colonization by S. Mutans and subsequent dental caries. Numerous strategies have been developed to induce high levels of salivary antibodies that can persist for prolonged periods and to establish immune memory by through different routes of administration. Therefore elimination of caries is the main objective of the health professionals. Still more clinical trials are needed to evaluate the safety of these vaccines so that potential risks are eliminated.

## Introduction

Dental caries is one of the most common diseases occurring in humans which is prevalent in developed, developing and underdeveloped countries and is distributed unevenly among the populations. In the modern world, it has reached epidemic proportions. This global increase in dental caries prevalence affects children as well as adults, primary as well as permanent teeth, and coronal as well as root surfaces.[1] Dental caries remains one of the most widespread diseases of mankind. Advances in prophylactic measures to deal with this disease have significantly reduced the overall caries rate in the United States.

In developing countries, dental caries is often at epidemic proportions, especially among the poor. For example; at least 25% of three-year-old children from various areas of Brazil have detectable caries lesions, many developing lesions within the first 18 months of life. This high caries rate continues among the less economically advantaged in the face of efforts to introduce fluoride at an early age. Similarly, an oral health survey in China revealed that three-quarters of five-year-old children studied had evidence of significant dental decay.[2,3]

A strong association exists between level of colonization with Mutans Streptococci and dental caries, although other organisms, such as Lactobacilli, have also been implicated in this disease. Studies of the natural history of Mutans Streptococcal colonization of infants have revealed several interesting features .Under normal circumstances of diet and challenge, children become permanently colonized with Mutans Streptococci between the middle of the second year and the end of the third year of life, during a so-called "Window of Infectivity".[4]

Currently various caries preventive strategies are in use like oral health education, chemical and mechanical control of plaque, use of fluorides, application of pit and fissure sealants etc. Many of these approaches can be broadly effective. The latest approach for combating dental caries is through the development of an effective vaccine that is well suited for public health applications especially in environments that do not lend themselves to regular health care.

## Molecular Pathogenesis of the Disease

The molecular pathogenesis of Mutans Streptococci appears to involve several phases each of which may offer targets for immunological intervention. Acidogenic Streptococci require the hard surfaces furnished by teeth for sustained colonization and accumulation. Initial attachment to the tooth is achieved via the interaction of bacterial proteins with lectins in the dental pellicle covering the tooth surface. This trait is characteristic of a family of Streptococcal adhesins, referred to as antigen I/II or PAc in Streptococcus Mutans, which have been demonstrated to bind to salivary components in experimental tooth pellicles. Lamont and co-workers have evidence to suggest that the S. Mutans antigen I/II adherence to saliva-coated Streptococcus Sanguis and Actinomycesviscosus is mediated through an acidic, mucin-like glycoprotein (agglutinin) found in parotid and sub-mandibular saliva 4. Other binding properties have also been attributed to antigen I/I. At least 2 binding regions of antigen I/II may be involved in salivary-component-mediated adhesive activities. The ultimate pathogenicity of mutans streptococci occurs through erosion of the hydroxy-apatite-like mineral in dental enamel by lactic acid, a bacterial metabolic end-product. However, significantly destructive concentrations of this acid require the substantial accumulation of these acidogenic streptococci in dental plaque. This accumulation process is initiated by the activity of extracellular glucosyltransferases (GTF), several of which are constitutively secreted by mutans streptococci. In the presence of sucrose, GTFs synthesize several forms of high-molecular- weight branched extracellular glucans. GTFs that synthesize insoluble forms of glucan (S. Mutans GTF-B and GTF-C) have been most closely associated with pathogenicity. These glucose polymers provide scaffolding for the aggregation of Mutans and other oral streptococci through interaction with bacterial cell-associated glucan-binding proteins. Several glucan- binding proteins have been described in S. Mutans and S. sobrinus. Although each of these GBPs has the ability to bind to certain forms of glucan, and some have been shown to be cell associated, their unique contributions to in vivo plaque development are as yet unclear4. GTFs also contain glucan-binding domains which permit binding to glucans. The interactions of glucans with cell-associated glucan-binding domains of GTFs and GBPs combine to cause extensive accumulation of Mutans Streptococci in the dental biofilm. Since GTFs and GBPs are also secreted into the extracellular environment, their specific or non-specific incorporation into the salivary pellicle would also provide binding sites for Mutans Streptococci. Theoretically, the next phase of pathogenesis results from the metabolic activities of these masses of accumulated Mutans Streptococci (and possibly of other accumulation-associated micro-organisms). Mutans Streptococci are the most prolific producers of lactic acid in these accumulations although other "low pH bacteria" may also contribute. Dental caries then ensues, because the resulting increase in lactic acid synthesis cannot be sufficiently buffered to prevent enamel dissolution.[5,6,7]

## Effective Molecular Targets for Dental Caries Vaccines

Several stages in the molecular pathogenesis of dental caries are susceptible to immune intervention. Micro-organisms can be cleared from the oral cavity by antibody-mediated aggregation while still in the salivary phase, prior to colonization. Antibody could also block the receptors necessary for colonization (e.g. Adhesins) or accumulation (e.g. Glucan-binding domains of GBPs and GTF) or inactivate GTF enzymes responsible for glucan formation. This review will concentrate on adhesins, GTFs and GBPs as vaccine targets, since most of the recent experimental effort has been directed toward these components.

### (a) Adhesins

Adhesins from the two principal human pathogens, Streptococcus Mutans (variously identified as antigen I/II, PAc, or P1) and Streptococcus Sobrinus (SpaA or PAg), have been purified.

Russell and Lehner initially described the S. mutans component in 1978. Antigen I/II (AgI/II) was found both in the culture supernatant as well as on the S. Mutans cell surface. This 185-kDa protein is composed of a single polypeptide chain of approximately

1600 residues[7]. Significant sequence homology (66%) exists between S. Mutans AgI/II and S. Sobrinus SpaA as well as with at least one adhesin from Streptococcus gordonii, a noncariogenic oral Streptococcus.[8]

However, despite the homology between the two Mutans Streptococcal Adhesins, each appears to bind to separate components in the pellicle. S. Mutans Ag I/II contains an alanine-rich tandem repeating region in the N-terminal third and a proline-rich repeat region in the center of the molecule. These regions have been associated with the Adhesin activity of Ag I/II. Crowley and colleagues and Nakai and co-workers have each described a region within or near the alanine-rich region that can bind salivary components in experimental tooth pellicles. Lehner, Kelly and co-workers suggested that the proline-rich central portion contains an adhesion epitope, basing their conclusions on adhesion inhibition assays involving recombinant fragments of Ag I/II. Immunological approaches support the adhesin-related function of the AgI/II family of proteins and their repeating regions. For example, abundant in vitro and in vivo evidence indicates that antibody with specificity for S. Mutans AgI/II or S. sobrinus SpaA can interfere with bacterial adherence and subsequent dental caries.[2,9] Antibody directed to the intact antigen I/II molecule or to its salivary-binding domain blocked adherence of S. Mutans to saliva-coated hydroxyapatite. Furthermore, numerous immunization approaches have shown that active immunization with intact antigen I/II or passive immunization with monoclonal or transgenic antibody to putative salivary-binding domain epitopes within this component can protect rodents, primates, or humans from dental caries caused by S. Mutans. Immunization of mice with synthetic peptides (residues 301-319) from the alanine-rich region of antigen I/II suppressed tooth colonization with S. mutans. Immunization with S. Sobrinus SpaA constructs protected rats from caries caused by S. Sobrinus infection. Protection in these experiments could conceivably occur by antibody blockade of initial colonization events or antibody-mediated agglutination and clearing of adhesinbearing bacteria from the saliva.[9,10]

### (B) Glucosyltransferases (GTFS)

S. Mutans and S. Sobrinus each synthesize several glucosyltransferases. The deduced sequences of these enzymes vary from 1400 to nearly 1600 amino acid residues and contain considerable sequence homology, despite differences in the water-solubility and linkages among the glucans synthesized. Genes responsible for glucan synthesis in S. Mutans are gtfB, which synthesizes an a-1, 3-linked insoluble glucan, gtfC, which synthesizes glucan with both a- 1, 3 and a-1, 6 linkages, and gtfD, which synthesizes a soluble a-1, 6-linked glucan. Similarly, the products of gtfI and gtf genes of S. Sobrinus synthesize insoluble and soluble glucan products, respectively. Mutational inactivation techniques have shown that each of these gene products is important to the cariogenicity of the respective Mutans streptococcal strain.

The activity of GTF is mediated through both catalytic and glucan-binding functions. The catalytic activity of GTF appears to be associated with several, sequentially separate, residues in the N-terminal third of the molecule. These residues have been identified by a variety of methods, including the labeling of catalytic intermediates and site-directed mutagenes. Insight into catalytically important residue identification has been obtained by sequence alignment techniques, which have revealed significant homology between GTFs and alpha amylase with respect to several invariant residues important to the catalytic activity of the alpha amylase family, suggesting that the amylase (b, a) 8 barrel element may also be a feature of the GTF catalytic domain. Collectively, these studies have identified several residues within this putative (b, a) 8 barrel element which may be involved in the catalytic activity of GTF.

### (C) Glucan-Binding Proteins

The ability of mutans streptococci to bind to glucans is presumed to be mediated, at least in part by cell-wall-associated glucan-binding proteins (Gbp). Many proteins with glucanbinding properties have been identified in Streptococcus Mutans and Streptococcus sobrinus. Each glucan-binding protein has the ability to bind a 1-6 glucan, although other glucan linkages potentially may impart higher binding constants. S. Mutans secretes at least three distinct proteins with glucan-binding activity: GbpA, GbpB, and GbpC . GbpA has a deduced sequence of 563 amino acids. The molecular weight for the processed protein is 59.0 kDa. The carboxy-terminal two-thirds of the GbpA sequence has significant homology with the putative glucanbinding regions of Mutans streptococcal GTFs. This C-terminal region contains 16 repeating units which, together, have been shown to represent the full glucan-binding domain of this protein.[11] GbpA has a greater affinity for water-soluble than for water-insoluble glucan. The expressed GbpB protein is 431 residues long and has a calculated molecular weight of 41.3 kDa (Mattos-Graner et al. 2001). Its sequence is unrelated to those reported for other S. Mutans GTFs or Gbp's, paralleling the lack of reaction of anti-GbpB antibody with these proteins. The N-terminal third contains several immunodominant regions, which may explain the significant apparent immunogenicity of this protein in humans and animals. Although the function of this protein in the native environment is as yet unresolved, biofilm formation on plastic surfaces by strains of S. Mutans is directly correlated with expression of GbpB, suggesting a role for GbpB in this process.[12]

## Vaccines

### 1. Subunit Vaccines

Subunit vaccines, which contain structural elements of the Ag I/II adhesin family, GTFs or GbpB have been designed for a variety of reasons. It had been observed that immune responses in animals protected by immunization with intact proteins were associated, at least in part with in vitro measures of functional inhibition. Thus, more recent studies have attempted to optimize immune responses to functional epitopes associated with salivary binding, catalytic processes or glucan-binding activities by designing subunit vaccines whose constructs contain single or multiple copies of epitopes from these domains. In addition, potentially enhanced protection could be achieved by including, in the subunit vaccine construct, regions of the virulence component containing strong immunological binding properties for induction of the desired arm of the immune response. Furthermore, multivalent subunit vaccines could be constructed of multiple epitopes which target different functions on the same component (e.g. GTF catalytic and glucanbinding activities) or functions on different components (e.g. AgI/II salivary binding and GTF catalytic activity).

Conjugation of functionally associated peptides to carbohydrate components for example glucan or to other vaccine proteins (e.g. tetanus toxoid) also would increase the immunogenicity of the peptide and broaden the reach of the vaccine. Designing vaccines in this way also permits one to eliminate regions which may induce unwanted antibody specificities.[13]

### (a) Synthetic Peptide Vaccines

As indicated above, at least two regions of the AgI/II-protein family appear to be associated with salivary-binding functions. Monoclonal antibody, raised by immunization with intact Ag I/II, that reacted with the fragment containing the proline-rich region also inhibited the formation of experimental dental caries . Similarly, workers in France demonstrated that a 14-mer peptide derived from a proline-rich region of the SR antigen, a member of the S. Mutans serotype f Ag I/II family of proteins, was reactive with antibody to the native protein. Synthetic peptide approaches have also shown the alanine rich repeat region of Ag I/II to be immunogenic and to induce protective immunity. For example, subcutaneous immunization with a synthetic peptide derived from the alanine-rich region of Ag I/II from S. Mutans (residues 301-319: PAcA) induced higher levels of serum IgG antibody reactive with recombinant Ag I/II than a synthetic peptide derived from the proline-rich region (residues 601-629). Intranasal immunization with PAcA, coupled to cholera toxin B subunit, Suppressed colonization of mouse teeth by S. Mutans. Fusion proteins containing PAcA also inhibited sucrose-independent adhesion

of S. Mutans to saliva-coated hydroxyapatide bead. Thus, this S. Mutansadhesin contains multiple functionally based epitopes that are sufficiently immunogenic to be considered for dental caries vaccines. B- and T-cell epitopes have been found in a cell-associated 3.8-kDa protein component antigen. Lehner and his colleagues applied free synthetic peptides containing immune dominant sequences of the 3.8- kDa antigen of S. Mutans to the gingival mucosa of macaques, resulting in the formation of both salivary IgA and gingival IgG antibody. Anti-peptide antibody elicited by this topical application method prevented colonization of the teeth by S. Mutans. The identification of functionally relevant residues/ domains in glucosyltransferases has led to the design of several synthetic peptide vaccines. Monoclonal or polyclonal antibody preparations which were directed to one of several N-terminal GTF peptides, each of which contained different catalytically implicated residues, have been shown to inhibit GTF activity.[14] Several of these synthetic peptides which contained strong Bcell epitopes were synthesized on lysine backbones to contain four or eight copies of the respective sequence. These constructs induced protective immunity against experimental dental caries. Synthetic peptide constructs have also been based on sequence derived from the repeating sequences in the C-terminal third of GTF, which has been shown to be associated with primer-dependent glucanbinding. A synthetic peptide associated with a putative glucan-binding site was shown to contain both B- and T-cell epitopes to induce antibody which could inhibit the enzymatic activity of GTF, and to induce protective immune responses in the rat caries model . Furthermore, di-epitopic constructs of this peptide and a peptide from the catalytic domain could be shown to enhance the protective effect, presumably because antibody was raised to two functional targets and because the glucan-binding domain peptide provided additional T-cell help for the B-cell epitopes on both peptides. All of the GTF synthetic peptide sequences which showed protective effects in the above experiments are highly conserved among S. Mutans and often, among S. Sobrinus GTFs as well. Antibody directed to these epitopes could therefore be expected to reduce the activity of many of the GTF isozymes expressed by these mutans streptococci, thus extending the protective effect across species lines. In this regard, protection from dental caries caused by either S. Mutans or S. Sobrinus infection in the rat model has been demonstrated after immunization with synthetic peptides from either the catalytic or glucan-binding domains of one GTF isozyme. These studies suggested that protection could be achieved by immunization with discrete epitopes associated with several virulence characteristics.[14] Combining epitopes from adhesins and GTFs into one construct and enhancing the immune response with additional sequences (e.g. cholera toxin subunits) could theoretically increase and possibly extend the protective effect of these subunit vaccines. Some recombinant protein approaches, described below have used this design.

**(B) Recombinant Vaccines/Attenuated Expression Vectors**

Recombinant approaches afford the expression of larger portions of functional domains than can be accommodated by synthetic peptides. Also, gene fusions of a functionally relevant sequence linked to a mucosal adjuvant sequence can result in chimeric proteins inherently able to enhance immune responses to the functional epitopes. Furthermore, attenuated mutant vectors such as Salmonella, which contain plasmids expressing recombinant peptides can target the vaccine to appropriate inductive lymphoid tissue for mucosal responses. Several of these approaches have successfully induced protective immune responses for experimental dental caries in rats or mice by means of chimeric proteins or vectors expressing either adhesin or GTF epitopes.

Intranasal administration of this chimeric protein with CT resulted in significant reductions in dental caries caused by infection of Fischer rats with S. Mutans UA130. The SBR-CTA2/B, expressed in an attenuated S. Typhimurium BRD509 vaccine strain containing an nirB promoter, which was administered intranasally or intragastrically to antibiotic-pre-treated BALB/c mice, resulted in salivary antibody to the SBR and a significant reduction in the number of S. mutans PC3379 recovered from dental plaque after challenge intranasally immunized BALB/c mice with an E. coliexpressed recombinant GTF peptide based on a 290-residue glucan-binding domain sequence or with a chimeric protein combining this sequence with thioredoxin. Immunization with either peptide resulted in protective effects on experimental S. Mutans infection and on resulting dental caries.

**2. Conjugate Vaccines**

Another vaccine approach which may intercept more than one aspect of mutans streptococcal molecular pathogenesis is the chemical conjugation of functionally associated protein/peptide components with bacterial polysaccharides. Added to the value of including multiple targets within the vaccine is that the conjugation of protein with polysaccharide enhances the immunogenicity of the T-cell-independent polysaccharide entity. This principle was first demonstrated by Landsteine and Avery and Goebel and has been applied with great success in the Hemophilusinfluenzae type b (Hib) conjugate vaccines to induce protective immunity to the capsular polysaccharide of H. Influenzae in infants and young children. Two groups have applied this approach to dentally relevant components. Lett and co-workers covalently coupled an adhesin-associated 14- mer synthetic peptide to the serogroup f polysaccharide of S. Mutans strain OMZ 175 by reductive amination. Subcutaneous injection with the conjugate induced systemic IgM and IgG antibody responses to both peptide and polysaccharide which could be boosted upon subsequent injection. The presence of both B and T-epitopes in the peptide was required for effective responses. Intragastric intubation of the conjugates associated with liposomes induced primary and secondary salivary IgA antibody to both components .

**Routes to Protective Responses**

Mucosal applications of dental caries vaccines are generally preferred for the induction of secretory IgA antibody in the salivary compartment, since this immunoglobulin constitutes the major immune component of major and minor salivary gland secretions. Many investigators have shown that exposure of antigen to mucosally associated lymphoid tissue in the gut, nasal, bronchial, or rectal site can give rise to immune responses not only in the region of induction, but also in remote locations. This has given rise to the notion of a "common mucosal immune system". Consequently, several mucosal routes have been used to induce protective immune responses to dental caries vaccine antigens.

**(A) Oral**

Many of the earlier studies relied on oral induction of immunity in the gut-associated lymphoid tissues (GALT) to elicit protective salivary IgA antibody responses. In these studies, antigen was applied by oral feeding, gastric intubation or in vaccine-containing capsules or liposomes. Although the oral route was not ideal for reasons including the detrimental effects of stomach acidity on antigen, or because inductive sites were relatively distant, experiments with this route established that induction of mucosal immunity alone was sufficient to change the course of mutans streptococcal infection and disease in animal models.

**(B) Intranasal**

More recently, attempts have been made to induce protective immunity in mucosal inductive sites that are in closer anatomical relationship to the oral cavity. Intranasal installation of antigen, which targets the nasal-associated lymphoid tissue (NALT), has been used to induce immunity to many bacterial antigens, including those associated with mutans streptococcal colonization and accumulation. Protective immunity after infection with cariogenic mutans streptococci could be induced in rats by the IN route with many S. Mutans antigens or functional domains associated with these components. Protection could be demonstrated with S. Mutans AgI/II, the SBR of AgI/II, a 19-mer sequence within the SBR, the glucan-binding domain of S. Mutans GTF-B, S. Mutans GbpB and fimbrial preparations from S. Mutans with antigen alone or combined with mucosal adjuvants.

### (C) Tonsillar

The ability of tonsillar application of antigen to induce immune responses in the oral cavity is of great interest. Tonsillar tissue contains the required elements of immune induction of secretory IgA responses, although IgG, rather than IgA, response characteristics are dominant in this tissue. Nonetheless, the palatine tonsils and especially the nasopharyngeal tonsils have been suggested to contribute percursor cells to mucosal effector sites such as the salivary glands.

### (D) Minor Salivary Gland

The minor salivary glands populate the lips, cheeks and soft palate. These glands have been suggested as potential routes for mucosal induction of salivary immune responses, given their short, broad secretory ducts that facilitate retrograde access of bacteria and their products and given the lymphatic tissue aggregates that are often found associated with these ducts. Experiments in which S. Sobrinus GTF was topically administered onto the lower lips of young adults have suggested that this route may have potential for dental caries vaccine delivery. In these experiments, those who received labial application of GTF had significantly lower proportions of indigenous Mutans streptococci/total streptococcal flora in their whole saliva during a six-week period following a dental prophylaxis, compared with a placebo group .

### (E) Rectal

More remote mucosal sites have also been investigated for their inductive potential. For example, rectal immunization with non-oral bacterial antigens such as Helicobacter pylori or Streptococcus pneumoniae, presented in the context of toxin-based adjuvant can result in the appearance of secretory IgA antibody in distant salivary sites. The colo-rectal region as an inductive location for mucosal immune responses in humans is suggested from the fact that this site has the highest concentration of lymphoid follicles in the lower intestinal tract. Preliminary studies have indicated that this route could also be used to induce salivary IgA responses to mutans streptococcal antigens such as GTF. One could, therefore, foresee the use of vaccine suppositories as one alternative for children in whom respiratory ailments preclude intranasal application of vaccine.[2,3]

## Future Prospects and Conclusion

Given that dental caries usually develops slowly and can occur throughout life, it may be anticipated that immune protection would need to be similarly long-lasting. Thus, the duration and anamnestic recall of salivary antibody responses are important factors. While it is now clear that mucosal immune responses can persist and that memory is established if the priming stimulus is sufficient, relatively little is known about the parameters that govern memory in the mucosal immune system. The characteristics of specific mucosal memory cells, their location, and how they can be recalled and directed to particular effector sites such as the salivary glands to produce IgA antibodies for transport into the secretion are important subjects for investigation. Although current understanding holds that oral colonization with mutans streptococci mainly occurs during a 'window of infectivity' at around 2 years of age after primary teeth begin to erupt, it is unclear whether further opportunities for colonization exist, for example when children enter school and mix socially with a much larger group of their peers or when the permanent teeth erupt. Two corollaries arise from such considerations: (i) that it would be necessary to immunize infants or young children in order to provide immune protection prior to initial colonization with mutans streptococci; (ii) that booster immunization to recall responses might be desirable to forestall colonization at later time points. As the transmission of mutans streptococci appears to be primarily from mother to infant [Li and Caufield, 1995], a third possibility is that young mothers might be immunized actively or passively with the objective of reducing their oral load of mutans streptococci (possibly in combination with conventional prophylaxis or other interventions), thereby diminishing the probability and extent of transmission to their infants. If the transferred bacteria are coated with maternal salivary antibodies, this would likely reduce their capacity to colonize the infant's mouth. It has been suggested that immunization of young mothers to induce the generation of antibodies to mutans streptococci in breast-milk could be exploited to provide passive immunity against caries to their infants. However, it seems unlikely that this strategy would have significant impact at least in Western societies, where breast-feeding, if given, usually terminates well before the 'window of infectivity' for mutans streptococci opens. Regardless of the mechanism by which immune protection against dental caries is achieved, further advances to make immunization against caries practicable will depend upon clinical trials aimed at establishing whether the findings from animal experiments can be transferred to humans. Particular goals for such studies include determining whether appropriate immune responses can be safely generated in humans, especially in the susceptible age groups and whether such responses will afford desirable levels of protection. The goals for vaccination against most other, mainly acute, infectious diseases are usually to provide near-complete protection of the individual against infection, and to achieve a sufficiently high prevalence of immunity in a population that the chain of transmission is broken and the pathogen cannot sustain itself in the community. However, the biology of caries is different from that of acute infections, and as with other modalities of intervention, it is conceivable that immunization will not attain complete effectiveness. Nevertheless, efficacy as low as 50% could have significant impact on the burden of disease and the social and economic costs associated with it. Given that the bulk of dental caries occurs among a high-risk sector of the population (at least in the USA), targeting an effective vaccine to such individuals would increase its impact.[2]

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