Application of Caries Vaccine to Humans

Noel K. Childers, DDS, MS, PhD
University of Alabama at Birmingham
Department of Pediatric Dentistry
School of Dentistry
Birmingham, Alabama
Mechanisms involved in *S. mutans* colonization and pathogenesis

- Sucrose-independent attachment (Ag I/II)
- Sucrose-dependent reaction (glucosyltransferase)
- Bacterial metabolic activities with lactic acid production
Preclinical (Animal) Studies

Numerous studies in rodents at UAB have shown *S. mutans* whole bacterium, lysates, purified AgI/II, purified GTF/AgI/II, recombinant SBR, and recombinant GLU to confer significant protection following oral or nasal immunization.

Additionally, similar investigations by the Forsyth group using GTF, GTF peptides and glucan binding protein from *S. sobrinus* have shown protection following local, oral, and nasal immunization.
Mucosal Immunization

- Antigen alone
  low adsorption, degradation, poor immunogenicity
- Antigen conjugation
  Cholera toxin B subunit
- Antigen packaging
  Microencapsulation (starch, polyacrylamide, co-polymers lactate-glycolate)
  Liposomes
- Adjuvants
  Monophosphoryl lipid A, cholera, muramyl dipeptide
- Antigen expression in colonizing bacteria (*E. coli, Salmonella*) or viruses (polio)
Mechanisms of Liposome Adjuvanticity

• Antigen protection from acidic and enzymatic degradation in intestines (oral vaccines).

• Particulate antigen is taken up more effectively than soluble antigen by M cells.

• Antigen depots (maintain antigen at local sites - minimizes systemic absorption)
Human Studies
Phases of Clinical Studies

- **Phase 1: 20-80 Subjects (Safety)**
  - Pharmacology, metabolism, side effects
  - Early evidence of effectiveness
- **Phase 2: 100-300 Subjects (+Scientific quality)**
  - Controlled clinical studies
  - Effectiveness, short term side effects
- **Phase 3: 300-30000 Subjects (+Marketing potential)**
  - Randomized Clinical Trial (Field Trial)
  - Effectiveness and Safety
FDA Phase 1 Studies at UAB (BB IND #2439)

• Seven Phase 1 studies
  – 3 Oral Immunization Studies
  – 4 Nasal (with one topical tonsillar) Immunization Studies

• Total Participation 89 Subjects (for 79 Immunizations)

• No Adverse Effects
Potential Caries Vaccine Strategies

- topically applied vaccines
  - intranasal
  - palatine tonsil
  - salivary glands
- adjuvants
  - cholera toxin subunits
  - monophosphoryl lipid A
- recombinant vaccines
  - cloned antigens
  - recombinant vector
HUMAN PROTOCOL HGTF-4

• Twenty Volunteers
  randomize 2 groups (double blind)
  immunized intranasally with 250 µg liposomal (A) or free (B) antigen (65 µl each side)
  twice (7 day interval)
• Collect blood, nasal wash and parotid saliva
  • 2 weeks before immunization began
  • the day of immunization (Day 0)
  • weekly for 7 weeks following nasal immunization
Nasal IgA1 Response following Nasal Immunization

Graph showing the percentage of IgA in nasal samples over time for two groups, A and B, with the y-axis representing the anti-GTF-Agl/II/total IgA and the x-axis representing days from -14 to 56.
Salivary IgA Response Following Nasal Immunization (Combined Data)
Summary of Clinical Phase 1 Immunization Studies with *S. mutans* antigens

- Oral, nasal, tonsillar (topical) antigen administration were safe.
- Nasal spray vaccine induced antigen specific mucosal IgA responses. Response appeared to be dose specific (three separate studies).
- Re-immunization (18 months after first immunization) resulted in higher responses compared to newly immunized group.
- IgA response appears to be associated with delayed recolonization of oral cavity with *S. mutans*. 
Clinical Approach to Develop a Caries Vaccine

- Adult Phase 1 studies
- Pre-adolescent Phase 1 and 2 studies
- Pre School Children Phase 1 and 2 studies
- Infant Phase 1, 2, 3 studies
The main target population for a caries vaccine would be young children/infants.

Safety issues are more stringent in children.

Most adults have already experienced dental caries therefore, may not see “good” responses.

Senescence of some of the mucosal immune tissues in adults (e.g., tonsils) which may be active in children.
Unique Aspects of Infancy

• Teeth are erupting
• Oral cavity is being colonized
• Breast feeding is discontinued
• Immune system is developing
Opportunities

“A vaccine for tooth decay”

- Window of infectivity (multiple?)
  - prior to tooth eruption
- Development of mucosal immune system
- Surrogate for endpoint in early studies
  - secretory immune responses
  - infection
Important Considerations:
“A vaccine for dental caries”

• FDA approvals
  – Safety concerns

• Funding
  – NIH resources
  – Patent-ability issues for private funding

• Efficacy studies
  – Chronic disease
  – Long-lasting immune responses
Acknowledgements

- Suzanne Michalek, Ph.D.
- Fuming Li D.D.S., Ph.D.
- Katharine Kirk, Ph.D.
- Ananda Dasanayake, B.D.S., Ph.D.
- Jannet Katz, D.D.S., Ph.D.
- Christina Jespersgaard, Ph.D.
- Ping Zhang, D.D.S., Ph.D.
- Michael W. Russell, Ph.D.
- Helen Kalapoda, D.D.S., MS
- Kelley Black, Ph.D.

- Supported by grants from the NIH
  - AI069569
  - DE09846
  - DE08182
  - DE09081
Questions?