

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The predominant polymicrobial infection of mankind is expressed clinically as periodontal disease, which afflicts nearly 1/2 of the population by 50 years of age, and is related to development of a microbial biofilm colonizing the subgingival sulcus. The suggested mechanisms of pathogenesis are varied, in most part due to the complex microbial community consisting of numerous bacterial taxa, viruses, and fungi. Nevertheless, certain of these subgingival microbial consortia are consistently correlated with a progressive destruction of soft and hard tissue that have been well documented to occur in clinical settings (*i.e.* periodontitis). Various *in vivo* and *in vitro* investigations have suggested that the dominance of selected species in the subgingival ecology results from both microbial synergistic and antagonistic relationships. These have been linked to the nature of available surfaces for colonization, available nutrients, and physiologic "food webs" that exists within the community. Molecular microbiologic studies have described nearly 500 species of bacteria that can inhabit this ecological niche, although several specific microbial complexes have been described at sites of progressing tissue destruction. A predominant consortia identified in a majority of adult periodontitis patients consists of *Porphyromonas gingivalis*, *Tannerella Forsythensis* [*Bacteroides forsythus*], and *Treponema denticola*. The correlation of this consortia with disease has been proposed to result from synergistic physiological, host evasion, and/or tissue destructive capabilities among the component species. The objectives of this R01 application are to test an hypothesis that this polymicrobial consortia comprises a "virulence web" that synergistically increases tissue destructive host responses, and that host immune responses are modified by the consortia to be less effective. Three specific aims are proposed using an animal model system to test this hypothesis: (1) To determine molecular interbacterial synergistic virulence effects of *P. gingivalis*, *T. forsythensis*, and *T. denticola* in an *in vivo* calvarial bone resorption model, (2) To determine the characteristics of acquired humoral immune responses to a polymicrobial infection and the ability of this response to modulate *in vivo* calvarial bone resorption, and (3) To determine the characteristics of active humoral immune responses to polymicrobial immunization and ability of this response to modulate bone resorption. The long-range goals from this study will be to document microbial interactions, virulence synergisms, characterize both acquired & active immune responses, and relate these to alterations in tissue destruction and bone resorption. The significance of this grant is that clinical observations have shown the ability of oral microorganisms to translocate into the circulation and manifest systemically as endocarditis, brain/kidney/lung, and intra-abdominal infections as well as contributing to risks of diabetes, coronary artery disease, osteoporosis, obesity, and preterm birth. Consequently, the host response to these chronic infections must be considered as critical to general health.

PERFORMANCE SITE(S) (*organization, city, state*)

University of Kentucky, Center for Oral Health Research, College of Dentistry (COD), UK Microarray Core Facility, College of Medicine (COM), and College of Arts and Sciences (CAS), Lexington, Kentucky.

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	Organization	Role on Project
Lakshmyya Kesavalu	UK COD	Principal Investigator
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Jeffrey Ebersole	UK COD	Co-Investigator
James Drummond	UK COD	Co-Investigator
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Disclosure Permission Statement. Applicable to SBIR/STTR Only. See instructions. Yes No