November 2, 2018

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Re: Immune System Balance and Flexibility in Maintaining Good Oral Health

Dear Dr. Somerman:

On behalf of the 3,400 individual and 103 institutional members of the American Association for Dental Research (AADR), thank you for the opportunity to provide input on the NIDCR 2030 proposed research initiative, “Immune System Balance and Flexibility in Maintaining Good Oral Health”. The goals, research opportunities and specific areas of interest described in the concept clearance are congruent with the priorities of AADR members conducting research in microbiology and immunology, oral medicine and pathology, salivary biology and geriatric oral health. These members have identified the research gaps and potential therapeutic applications described below.

**Early programming of the immune system.** The immune system is constructed to enable a very broad, almost infinite ability to respond to antigenic challenges, including those derived from the oral microbiome related to periodontitis and caries. This concept has been described as the immunobiography of each individual and is a composite of challenges and responses early in life that may program the immune system for the characteristics of responses later in life. Much of the data in periodontitis has focused on the immunobiography that is expressed later in life, while we have little insight into early programming that enhances and detracts from immune system flexibility at the individual level. This immunobiography also represents features of immune memory (adaptive immune responses) and trained immunity (innate immune responses), albeit there exist rather limited data for the immunobiology of the oral cavity.

**Changes to the antigenic ecospace in disease.** The antigenic ecospace can be defined as “the universe of antigens that [have] driven [immune system] evolution.” How this ecospace changes on the individual level during the initiation and progression of disease, such as periodontitis, and how the individual host immune capacity reacts to these changes remains ill-defined.

**The effect of biological aging on immune responses in the oral cavity.** While work on immune responses in the oral cavity and studies of periodontitis have demonstrated changes with aging, it is not clear which of these features are truly driven by aging processes. Moreover, virtually all of these studies have focused on chronological aging. However,
recent innovative approaches in other disciplines have begun to explore the concept of "biological aging" as a better descriptor for risk of age-associated diseases. Inflamm-aging has been defined as aging combined with “chronic, sterile, low-grade inflammation” while immunosenescence is the “progressive modification of the immune system that leads to greater susceptibility to infections, neoplasia and autoimmunity”. Studies of inflamm-aging and immunosenescence as measures of immune system flexibility related to periodontitis are still not robustly documented.² ³

**Commensal flora-immune system interactions.** The commensal flora-immune system interactions that help to maintain oral health is an understudied area. The flexibility of the immune system related to the immunobiography and aging effects on this response repertoire clearly has a critical component of interactions with the commensal or autochthonous microbiome of an individual. We still know little regarding how commensal bacteria help program symbiotic immune responses, nor how changes in the commensals or emergence of pathogens can undermine the profile of symbiotic response interactions leading to an immune system that contributes to pathophysiological processes and clinical features of periodontitis. Specific research questions include:

1) Are there members of the commensal flora that produce anti-inflammatory agents or other beneficial immunomodulatory functions?
2) Does the commensal flora play a role in educating the oral immune response?
3) Can the commensal flora reverse a pathogenic immune response during disease?
4) What is/are the keystone species promoting oral immune homeostasis?

**Efficacy of modern therapeutics against oral diseases.** As data has been gathered documenting roles of various host responses in the deleterious consequences of the persistent inflammation in periodontitis, as well as the unique feature of resolution response biomolecules, modern tools for host response modulation (i.e., array of monoclonal antibody drugs for chronic inflammatory diseases) have generally not been evaluated related to periodontitis. If we are to increase the breadth and depth of the treatment toolbox for periodontitis in the 21st Century, studies of these therapeutics and their impacts on the gingival immune repertoire and immune system flexibility need to be implemented.

**Immune hyperactivity in Sjögren's Syndrome.** The specific areas of interest enumerated in the concept clearance would help advance research on Sjögren’s Syndrome. The underlying reasons for immune hyperactivity in this disease are poorly understood. It is critical to understand what factors drive this pathologic activation in order to maintain immune homeostasis in these individuals.

Once again, AADR appreciates the opportunity to provide input on this important proposed research initiative. AADR stands ready to work with NIDCR to advance research on understanding immune system balance and flexibility in maintaining good oral health. If you have any further questions, please contact Dr. Seun Ajiboye, Director of Science Policy and Government Affairs, at sajiboye@iadr.org.
Sincerely,

Christopher H. Fox, DMD, DMSc
Chief Executive Officer

Maria Emanuel Ryan, DDS, PhD
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References

