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November 15, 2019

Martha J. Somerman, DDS, PhD
Director, National Institute of Dental and Craniofacial Research
National Institutes of Health Building 31, Room 2C39
31 Center Dr.
Bethesda, MD 20814

Re: Proposed Research Initiative for Fiscal Year 2021

Dear Dr. Somerman:

On behalf of the 3,350 individual and 107 institutional members of the American Association for Dental Research (AADR), thank you for the opportunity to comment on NIDCR's proposed research initiatives for fiscal year (FY) 2021. AADR engaged its Board of Directors, Committee on Diversity and Inclusion and the International Association for Dental Research (IADR) scientific groups and networks to gather the following input on these initiatives.

NIDCR Predoctoral to Postdoctoral Transition Award for a Diverse Dental, Oral, and Craniofacial Research Workforce

AADR strongly supports this initiative and praises NIDCR for its targeted emphasis on and critical resource allocation for promotion of diversity, equity and inclusion and for its commitment to improving structures for the recruitment and retention of a more diverse workforce. Specifically, this initiative will help facilitate use of the K99/R00 mechanism by F31 recipients. This transition award should encourage interaction with the upcoming NIDCR Mentoring Network to Support a Diverse Dental, Oral and Craniofacial Research Workforce and/or the NIH National Research Mentoring Network.

Engaging Dental Health Professionals to "End the HIV Epidemic"

This is an important research initiative for the reasons stated in the proposal. Additionally, it should be noted that 27 million people each year have a dental visit but no medical visit (Vujicic et al. JADA 145 (2):118-121), so the dental clinic presents an important opportunity to test people for HIV and move them quickly into treatment. This research initiative is congruent with Oral Health objective 14, OH-14, of Healthy People 2020 to increase the proportion of adults who receive preventive interventions in dental offices (https://www.healthypeople.gov/2020/topics-objectives/topic/oral-health/objectives). For example, in the state of New York, the Ending the Epidemic Blueprint recommends the expansion of HIV testing to other medical settings such as pharmacies, dental care and mental health settings

+1.703.548.0066
+1.703.548.1883
1619 Duke Street
Alexandria, VA 22314-3406, USA
www.aadr.org

(https://www.health.ny.gov/diseases/aids/ending_the_epidemic/docs/blueprint.pdf; pg. 17). However, many state dental practice regulations view these types of activities as the practice of medicine and therefore are not allowed in dental clinics, so the research from this initiative could have important policy implications.

NIDCR should consider adding dental patients' willingness and attitudes toward chairside screenings for HIV to the initiative's Scientific Areas of Interest. There are few current studies in this area (listed below):

Davide SH, Santella AJ, Furnari W, Leuwaisee P, Cortell M, Krishnamachari B. 2017. Patients' willingness to participate in rapid HIV testing: a pilot study in three New York City dental hygiene clinics. Journal of Dental Hygiene. 91(6): 41-48.

Brondani M, Chang S, Donnelly L. 2016. Assessing patients' attitudes to opt-out HIV rapid screening in community dental clinics: a cross-sectional Canadian experience. BMC Research Notes. 9(1): 264.

These scientific questions are also globally relevant. Below are some citations from studies in Australia, England, China, and India.

Santella AJ, Schlub TE, Schifter M, Tolani M, Hillman RJ. 2016. Australian dentists' perspectives on rapid HIV testing. Australian Dental Journal. 61(3): 270-276.

Santella AJ, Conway DI, Watt RG. 2016. The potential role of dentists in HIV screening. British Dental Journal. 220(5): 229.

Wang L, Santella AJ, Huang R, Kou L, You L, Zhang X, Wang S, Wang J, Gao L, Yin J, Zhuang G. 2015. Knowledge of HIV and willingness to conduct oral rapid HIV testing among dentists in Xi'an China. PLoS One. 10(3): e0119274.

Ngaihte PC, Santella AJ, Ngaihte E, Watt RG, Raj SS, Vatsyayan V. 2016. Knowledge of human immunodeficiency virus, attitudes, and willingness to conduct human immunodeficiency virus testing among Indian dentists. Indian Journal of Dental Research. 27(1): 4.

Finally, the proposal should include among the Scientific Areas of Interest research on training dental care providers to address patient psychological responses pre- and post-testing. Dental care providers must be trained to address immediate emotional needs for patients with positive results and to provide guidance to patients with negative results about risky behaviors that could eventually lead to infection.

Reissuance of Administrative Supplement for Collaborative Science (ASCS)

This program has had positive outcomes for both publications and grant renewals and is a very good mechanism for supporting new collaborative efforts. It should continue to be considered as one of the proposed research initiatives for FY 2021. In analyzing the effectiveness of this mechanism, NIDCR should study whether or not outcomes are substantially better for investigators who receive funding from this collaborative supplement than for investigators who do not.

Defining Mechanisms of Disease Recurrence in Dental, Oral and Craniofacial Tissues

This is an important initiative that has broad implications for improving dental, oral, craniofacial (DOC) and systemic health. The specific area of interest for transcriptional programming and epigenetic rewiring has great potential importance in numerous areas including taste preference development and its relationship to dental disease and diet. Furthermore, an expanded portfolio for immune-related mechanisms underpinning DOC tissue homeostasis is crucial to guide next-generation therapies or consumer products in collaboration with industry

partners that would promote healthy teeth and gums. This topic is timely and also understudied in the background of oral diseases. Thus, AADR is excited about this research proposal.

To maximize this initiative's success, this initiative should explicitly identify periodontitis and oral cancers as diseases with relevant recurrence mechanisms, including roles for CD8+ T resident memory cells.

In addition to the entities listed in this initiative, such as oral lichen planus, dentists also treat oral leukoplakia or oral erythroplakia on a daily basis. These two potentially pre-malignant diseases are the focus of neither the National Cancer Institute (NCI), which focuses on established tumors nor National Institute of General Medical Sciences, which tends to fund non-disease-oriented basic studies. Therefore, there is a crucial role for NIDCR in this space. The management strategy of pre-malignant lesions beyond surgical removal remains very limited. Investigators at the University of Michigan were recently awarded a Cancer Moonshot Immunoprevention Program U01 co-funded by NCI and NIDCR to develop new immunoprevention approaches for early lesions. However, there is still a significant knowledge gap regarding when and how oral leukoplakias/erythroplakias thwart immune sensing and progress to cancer.

This initiative should include R01 mechanisms to support the immune plasticity/fitness in oral leukoplakia/erythroplakia that are different from NCI and NIGMS research foci and represent a major practice-changing opportunity to prevent oral cancer.

In addition to R01 mechanisms, this portfolio would benefit from companion clinical research programs. There is a plethora of life-changing clinical protocols taking place at the NIH campus for patients with solid tumors. Many of these therapies have the potential to be moved up to earlier pre-malignant lesions. A partnership between extramural investigators and intramural clinical programs, such as through U01s or U19s, would bring synergistic transformative progress into routine dental care.

Finally, immune markers have been written into many clinical protocols for cancer patients, e.g., PD-L1 CPS scores for neoadjuvant trials. Tissue regeneration has been a significant portion of the NIDCR extramural program. However, it remains understudied whether the immune system represents an untapped source for predicting regenerative outcomes in oral diseases such as peri-implantitis, the outcomes of which are currently unpredictable. The current patient recall schedule is largely based on third-party payers' recommendations instead of on a scientific basis. Novel immune-based biomarker strategy, such as machine learning-assisted algorithms, can revolutionize the way we manage these patients.

Institutional Research Training for a Dental, Oral and Craniofacial Research Workforce

This is a vitally important program for the future of DOC research, and AADR supports this initiative.

Defining Lineage Plasticity and Endogenous Regeneration Capacity of Dental, Oral and Craniofacial Tissues

This initiative has good long-term potential for addressing pathologies affecting salivary glands, periodontal apparatus, bone, dental pulp and other critically important DOC tissues. Generally, the initiative clearly points out the Gaps and Opportunities, but the phrase "develop practical approaches for generation of abundant supply of high-quality cell sources for regeneration of DOC tissues from the endogenous tissue-resident cells" under Scientific Areas of Interest may be erroneously interpreted to mean the establishment of cell banks in vitro for transplantation and might be better deleted or replaced. Finally, lineage reprogramming might be better defined by the broader term "de-differentiation" rather than "trans-differentiation".

Accelerating Discovery and Characterization of Genetic Variants Underlying Dental, Oral, and Craniofacial Diseases and Conditions

This initiative is important and will provide new information that can translate to improved health outcomes. AADR researchers have been discussing such an initiative for a few years now and most recently at the 9th AADR Fall Focused Symposium: Advances in Precision Oral Health Research (Divaris K. Adv Dent Res. 30(2): 40-44), so this is very welcome and well-aligned with the genomics research that is being done in the oral health domain. The ability to generate a lot of data from genome-wide association studies (GWAS) is increasing, so there is an intentional effort here to pair these large-scale projects with more targeted mechanistic, experimental or bioinformatic pipelines that can help either validate or at least prioritize the influx of new findings and/or provide answers as to "how". This proposal even mentions the sub-clinical phenotypes that several groups have been working on.

However, the patient voice is a key missing piece from this initiative. Having input from patients and patient advocacy groups that deal with DOC hereditary conditions should be included as a critical part of the work to improve their health to understand which aspects of the conditions are of most concern to the affected individuals and families and whether targeted therapies can help manage or ameliorate those clinical manifestations. This would be downstream of identifying genes (many of which are now known for the more common Mendelian traits) and molecular mechanisms driving phenotype development, but these are essential elements to the research being done to identify the molecular basis of disease, the clinical phenotype and the way this impacts the lives of those affected and their families.

As an example, there are over 5,600 hereditary conditions listed in the OMIM database that have a known molecular basis, yet only a handful of these have therapies that can really address the morbidities that most afflict affected people. The initiative should be more directed at moving these conditions and new discoveries of molecular based-pathology towards translation of improved treatments that specifically address those issues deemed critical by affected individuals.

Similarly, to increase the impact of this research initiative, AADR recommends adding careful and sophisticated clinical phenotypic characterization of genetic study populations, particularly those that may have a wide spectrum of associated clinical phenotypes to the initiative's Specific Areas of Interest. This is a major obstacle to translation of the data from these large genome-wide association studies.

Finally, while animal model studies and human genetic studies have independently identified many genes and gene variants as likely pathogenic for craniofacial diseases and conditions, the integration of human and animal model studies addressing susceptibility and mechanism are still lacking. Animal models do not always recapitulate a human phenotype, similarly human genetic studies may not be sufficient to prove a given genes' relevance in a disease or condition. Major advances would come from those studies combining human and animal model data to avoid the parallels of those studies performed independently. In that regard, the initiative could be stronger if a collaborative approach between investigators in animal and human studies was emphasized.

Other input

NIDCR may want to consider finding alternatives to animal models for research as a future initiative. Legislation in many regions around the world have or are adapting regulations that prohibit testing ingredients on animals. In recent years, tissue model development has made significant strides and are used to test ingredients. Research to develop models for use for oral care research would be welcome.

Thank you, once again, for the opportunity to provide input and for your thoughtful consideration of these comments. AADR stands ready to assist NIDCR in any way it can. Please do not hesitate to reach out to Dr. Seun

Ajiboye, Director of Science Policy and Government Affairs, at sajiboye@aadr.org if you need any additional information.

Sincerely,

Christopher H. Fox, DMD, DMSc
Chief Executive Officer

J. Timothy Wright, MS, DDS
President