

National Institute of Dental and Craniofacial Research

National Advisory Dental and  
Craniofacial Research Council

Minutes of Meeting  
September 13, 2018

Building 35A  
Conference Rooms 620/630  
National Institutes of Health  
Bethesda, Maryland

U.S. DEPARTMENT OF HEALTH  
AND HUMAN SERVICES  
NATIONAL INSTITUTES OF HEALTH



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
NATIONAL INSTITUTES OF HEALTH  
NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

MINUTES OF THE  
NATIONAL ADVISORY DENTAL AND CRANIOFACIAL RESEARCH COUNCIL

September 13, 2018

The 219<sup>th</sup> meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on September 13, 2018, at 8:32 a.m., in Building 35A, Conference Rooms 620/630, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public from 8:32 a.m. until 12:22 p.m.; it was followed by the closed session for Council business and consideration of grant applications from 1:30 p.m. until adjournment at 1:53 p.m. Dr. Martha Somerman presided as Chair.

**OPEN SESSION**

**Members Present**

Dr. Kathryn Marie Albers  
Dr. Patricia E. Arola (*ex officio*)  
Dr. Shenda M. Baker  
Dr. Yang Chai  
Dr. David J. Couper (via telephone)  
Dr. Richard Peters Darveau (via telephone)  
Dr. Nisha J. D'Silva  
Ms. Tracy Hart  
Dr. Daniel Malamud (via telephone)  
Dr. Daniel W. McNeil  
Dr. Sanjay Shete  
Dr. Clark M. Stanford  
Dr. Joel L. Strom

**Ad Hoc Members**

Dr. Raul I. Garcia  
Dr. Shi Wenyan

**Members of the Public**

Dr. Judith Albino, Co-lead on U.S. Surgeon General's Report on Oral Health, and President Emerita, University of Colorado; Professor, Department of Community and Behavioral Health, Colorado School of Public Health; and faculty, Colorado University School of Dental Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO  
Dr. Marcelo W. B. Araujo, Vice President, Science Institute, American Dental Association (ADA), Washington, D.C.

- Dr. J. Chad Brenner, Assistant Professor, Department of Otolaryngology-Head and Neck Surgery; Director, Michigan Otolaryngology and Translational Oncology Laboratory; and Co-director, Head and Neck Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI
- Dr. Robert Burns, Manager, Legislative and Regulatory Policy, ADA, Washington, D.C.
- Dr. Thomas E. Carey, Professor, Department of Otolaryngology-Head and Neck Surgery; Professor, Department of Pharmacology; and Co-director, Head and Neck Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI
- Dr. Christopher Fox, Executive Director, International Association of Dental Research (IADR)/ American Association of Dental Research (AADR), Alexandria, VA
- Dr. Faye M. Johnson, Associate Professor, Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
- Mr. B. Timothy Leeth, Chief Advocacy Officer, Advocacy and Government Relations, ADEA, Washington, D.C.
- Dr. Ruth Lipman, Director, Scientific Information, ADA, Chicago, IL
- Dr. Jeffrey N. Myers, Alando J. Ballantyne Distinguished Chair of Head and Neck Surgery, Department of Head and Neck Surgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX
- Dr. Anthony Palatta, Chief Learning Officer, Learning, ADEA, Washington, D.C.
- Dr. Curtis R. Pickering, Assistant Professor, Department of Head and Neck Surgery – Research, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX
- Dr. Jeffrey Stewart, Senior Vice President for Interprofessional and Global Collaboration, Office of the President and CEO, ADEA, Washington, D.C.
- Dr. John B. Sunwoo, Professor, Department of Otolaryngology – Head and Neck Surgery Divisions; Director, Head and Neck Cancer Research; and Leader, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA

***National Institute of Dental and Craniofacial Research***

- Dr. Martha J. Somerman, Director
- Dr. Douglas M. Sheeley, Deputy Director
- Dr. Alicia Dombroski, Executive Secretary, and Director, Division of Extramural Activities (DEA)
- Dr. Lillian Shum, Director, Division of Extramural Research (DER)
- Dr. Matthew P. Hoffman, Scientific Director, Division of Intramural Research (DIR)
- Dr. Nisan Bhattacharya, DEA, Scientific Review Branch (SRB)
- Dr. Munder Ben Omran, Office of the Director (OD), Office of Science Policy and Analysis (OSPA), Program Analysis and Reporting Branch (PARB), NIDCR Informatics–Dental Public Health Fellowship Program
- Dr. Preethi Chander, DER, Integrative Biology and Infectious Diseases Branch (IBIDB)
- Dr. Lois K. Cohen, Consultant
- Ms. Vicki Contie, OD, Office of Communications and Health Education (OCHE), Science Communication and Digital Outreach Branch (SCDOB)
- Ms. Michelle Cortes, DER, IBIDB
- Ms. Mary Cutting, DER, Center for Clinical Research (CCR)

Mr. Bret Dean, OD, Office of Administrative Management (OAM), Financial Management Branch (FMB)  
Mr. Jimmy Do, OD, OAM, FMB  
Dr. Bruce Dye, OD, OSPA, PARB, NIDCR Informatics–Dental Public Health Fellowship Program  
Dr. Olga Epifano, DEA  
Dr. Dena Fischer, DER, CCR  
Dr. Leslie Frieden, DEA, Research Training and Career Development Branch (RTCDB)  
Dr. Crina Frincu, DEA, SRB  
Dr. Gallya Gannot, DER, CCR  
Mr. Joel Guzman, DER, Translational Genomics Research Branch (TGRB)  
Mr. Gabriel Hidalgo, DEA, Grants Management Branch (GMB)  
Dr. Wendy Knosp, OD, OSPA  
Dr. R. Dwayne Lunsford, DER, IBIDB  
Ms. Yasamin Moghadam, DER, CCR  
Dr. Kevin McBryde, DER  
Dr. Yun Mei, DEA, SRB  
Dr. Dawn Morales, DER, Behavioral and Social Sciences Research Branch (BSSRB)  
Ms. Anna Nicholson, OD, Office of Clinical Trials Operations and Management (OCTOM)  
Ms. Lisa Peng, OD, Office of Information Technology (OIT)  
Mr. John Prue, OD, OIT  
Ms. Delores Robinson, DEA  
Dr. Yasaman Shirazi, DEA, SRB  
Dr. Kathryn Stein, DER, TGRB  
Ms. Kathleen Stephan, OD  
Mr. Brian Sullivan, OD, OIT  
Mr. Joseph Tiano, OD, OSPA  
Dr. Jessica Walrath, OD, OSPA  
Dr. Jason Wan, DER, IBIDB  
Dr. Lu Wang, DER, TGRB  
Dr. S. Chiayeng Wang, DER, IBIDB  
Dr. Darien Weatherspoon, DER, CCR  
Dr. Achim Werner, DIR, Stem Cell Biochemistry Unit  
Dr. Gary Zhang, DEA, SRB

***Other Federal Employees***

Dr. Styliani (Stella) Alimperti, Principal Investigator, Research: Oral Microfluidics, ADA Foundation Volpe Research Center (VRC), National Institute of Standards and Technology (NIST), Department of Commerce (DoC), Gaithersburg, MD  
Dr. Leah Hubbard, Program Director, Translational Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD  
Dr. Jeffrey Kim, Principal Investigator, VRC, NIST, DoC, Gaithersburg, MD  
Dr. Kimberlee Potter, Office of Research and Development, U.S. Department of Veterans Affairs, Washington, D.C.

## **I. WELCOME AND INTRODUCTIONS**

Dr. Martha Somerman, Director, NIDCR, called the open session of the 219<sup>th</sup> meeting of the Council to order. She welcomed everyone and asked Council members, participants, and guests to introduce themselves.

Dr. Alicia Dombroski, Executive Secretary, NADCRC, and Director, Division of Extramural Activities (DEA), invited NIDCR staff to introduce new staff members. Mr. Jimmy Do, NIDCR budget officer and chief of the Financial Management Branch (FMB), Office of Administrative Management (OAM), introduced Mr. Bret Dean, NIDCR's new Deputy Budget Officer. Dr. Somerman reported that Dr. Matthew P. Hoffman was named NIDCR Scientific Director, effective July 18, after a national search. He will lead the NIDCR Division of Intramural Research (DIR) and has been an investigator in the DIR for nearly 25 years, serving most recently as deputy scientific director since August 2016. Dr. Hoffman noted two new appointments in the DIR: Dr. Marian Young, as deputy scientific director, and Dr. Laura Kerosuo as a Stadtman Tenure-Track Investigator. Neither could attend the present meeting and will be formally introduced to the Council at its next meeting, in January 2019.

Dr. Yasamin Shirazi, chief of the Scientific Review Branch (SRB), DEA, introduced Dr. Yun Mei, scientific reviewer. Dr. Lu Wang, chief of the Translational Genomics Research Branch (TGRB), Division of Extramural Research (DER), reported that Dr. Kathryn Stein was promoted to director of the Developmental Biology and Genetics Program.

Dr. Somerman noted that the terms of the following three Council members are expiring: Dr. Yang Chai, Dr. Richard Peters Darveau, and Ms. Tracy Hart. She thanked them for their service and presented a certificate of appreciation and an NIDCR cup to Dr. Chai and Ms. Hart. As Dr. Darveau was attending via telephone, his certificate and gift will be mailed to him.

Dr. Somerman welcomed and introduced four new members to the Council: Dr. Kathryn Marie Albers of the University of Pittsburgh, Dr. David J. Couper of the University of North Carolina at Chapel Hill (who was attending via telephone), Dr. Clark M. Stanford of the University of Illinois at Chicago, and Dr. Joel L. Strom of Strom & Klein Dental Associates in Beverly Hills, California. She also welcomed and introduced two Council member nominees attending as ad hoc members: Dr. Raul I. Garcia, from Boston University School of Dental Medicine, and Dr. Shi Wenyuan, from The Forsyth Institute. A third nominee, Dr. Lee Niswander, from the University of Colorado, Boulder, was unable to attend the meeting.

Dr. Dombroski welcomed everyone, including those participating via the NIH videocast (<http://videocast.nih.gov>).

## **II. FUTURE MEETING DATES**

January 23, 2019  
May 23, 2019

September 09, 2019  
January 29, 2020  
May 19, 2020  
September 10, 2020

### **III. APPROVAL OF MINUTES FROM PREVIOUS MEETING**

Dr. Dombroski invited the Council to consider and approve the minutes of the May 25, 2018, Council meeting. The Council unanimously approved the minutes.

### **IV. REPORT OF THE DIRECTOR, NIDCR**

Dr. Somerman opened her report by extending congratulations on NIDCR's 70<sup>th</sup> birthday. She noted that the former National Institute of Dental Research was created by the National Dental Research Act signed by President Harry Truman on June 24, 1948; is one of the first institutes at the NIH; and was funded to confront an issue of rampant dental caries that disqualified men from military service. She remarked that in the past 70 years, the NIDCR has made incredible progress and advances in prevention, assessment of risk, and treatment of dental, oral, and craniofacial diseases and in attention to patients' health outcomes.

Dr. Somerman addressed four topics in her report: legislative and budget updates, NIH updates, NIDCR activities, and the NIDCR cancer portfolio. Her written Director's Report to the Council: September 2018 was provided to the Council members and is available on the NIDCR website (<http://www.nidcr.nih.gov>).

#### Legislative and Budget Updates

Dr. Somerman reported that the NIDCR appropriation for Fiscal Year (FY) 2018 is \$447.7 million—a 5 percent increase above that in FY 2017. She thanked the NIH leadership and NIDCR's supporters for helping to sustain budget increases over the past several years. The overall NIH appropriation for FY 2018 is \$37.1 billion—an 8.8 percent increase. The fiscal year ends on September 30, 2018.

Dr. Somerman noted that U.S. Senator Tom Udall of New Mexico visited the NIH on July 30 and, in discussions with her and other institute and center (IC) directors, expressed interest in microbiome research and communication of research gains to the public.

#### NIH Updates

*Trans-NIH Activities.* Dr. Somerman said there is synergy across ICs and IC directors and the NIDCR is involved in more than 150 trans-NIH projects. She highlighted several, including collaboration with the Office of Research on Women's Health, Office of AIDS Research, and Office of Scientific Workforce Diversity; NIH Common Fund activities such as the Glycoscience Program, for which the NIDCR and National Institute of General Medical Sciences (NIGMS) are

co-leads; and the Regenerative Medicine Innovation Program (RMIP), which is funded through the 21<sup>st</sup> Century Cures initiative. She encouraged Council members to discuss Common Fund opportunities at their institutions, such as the Human Microbiome Project and Glycoscience Program, and to “stay tuned” to the many activities and new initiatives in NIH pain research. She also encouraged Council members to listen to the NIH videocast of the Pathway to Prevention (P2P) Workshop: Drug Therapies and Osteoporotic Fracture Prevention, on October 30–31, 2018. She noted as well that the NIDCR is participating in the Rare Diseases Clinical Research Consortia (RDCRC) Funding Opportunity Announcement (FOA).

Dr. Somerman said that glycoscience activities are a strong research area for the NIDCR and that the Common Fund Glycoscience Program has made significant progress over the past 3 years in development of robust, accessible approaches for glycan synthesis, analytical tools, and glycoinformatics infrastructure. She noted that Dr. Douglas M. Sheeley, Deputy Director, is the NIDCR co-lead of the program and that, in July, two NIDCR trainees were poster award winners at the Glycoscience Research Day hosted by the NIH and Food and Drug Administration (FDA).

Elaborating on the RMIP, Dr. Somerman stated that research on regenerative medicine is highly visible at the NIDCR and that the NIH has allocated \$30 million to the RMIP for the next 5 years. In FY 2018, \$10 million will support an NIH–FDA Regenerative Medicine Innovation Workshop and FOAs seeking investigator-initiated proposals to forge partnerships and collaborations that move the science from basic research to clinical studies, with a focus on adult stem cells. Dr. Somerman noted that the NIDCR will co-chair the National Academy of Medicine’s Regenerative Medicine Forum, and she strongly encouraged Council members to stay apprised of the Dental, Oral, and Craniofacial Tissue Regeneration Consortium (DOCTRC) activities in Phase 2 and as it moves into Phase 3. The NIDCR currently supports four RMIP cooperative grants; two of these, a research project and a clinical trial, are investigator-initiated, and two are small business projects.

*NIH Opioids Update.* Dr. Somerman reported that the NIH has doubled funding for research on opioid misuse/addiction and pain, through the Helping to End Addiction Long-term (HEAL) Initiative, from approximately \$600 million in FY 2016 to \$1.1 billion in FY 2018. The foci are to prevent addiction through enhanced pain management and improved treatments, moving basic research findings into translational and clinical studies. Dr. Yolanda Vallejo is the NIDCR contact for this initiative.

Dr. Somerman said the American Dental Association (ADA) visit to the NIH to discuss ADA’s new policy on opioids and potential opportunities for collaboration was a highlight for the NIDCR. She noted that the meeting was very positive and that Dr. Nora Volkow, Director, National Institute on Drug Abuse (NIDA), congratulated the ADA on dentistry’s new approaches to prescription practices. Dr. Somerman referred the Council to a commentary which was coauthored by her and Dr. Volkow, entitled “The Role of the Oral Health Community in Addressing the Opioid Overuse Epidemic,” and published in the *Journal of the American Dental Association*.

*Down Syndrome Research.* Dr. Somerman reported that the NIH has launched the INCLUDE (Investigation of Co-occurring Conditions across the Lifespan to Understand Down Syndrome) project in response to a Congressional directive in the FY 2018 Omnibus

Appropriations. The NIH estimates funding of approximately \$58 million in FY 2018 for research plans to conduct targeted, high-risk, high-reward basic science studies on chromosome 21 and to assemble a large population of individuals with Down syndrome, including individuals in clinical trials. INCLUDE will support 48 awards and include one NIDCR award for the design of dental clinics appropriate for Down syndrome patients.

### NIDCR Activities

*NIDCR 2030 Vision and Timeline.* Dr. Somerman said the NIDCR is actively pursuing NIDCR 2030: Envisioning the Future, Together, which is focused initially on five areas: oral health + overall health, precision health, autotherapies, oral biodevices, and workforce diversity. Launched in 2017, this effort continues to utilize the IdeaScale to obtain input from and communicate input to NIDCR stakeholders (see <https://nidcr2030.ideascale.com/>).

Dr. Somerman reported that, in 2018, the NIDCR held an Autotherapies Symposium and Workshop, which led in part to an opinion piece, entitled “Autotherapies: Enhancing Endogenous Healing and Regeneration,” that was published in *Trends in Molecular Medicine*. In addition, the NIDCR proposed initiatives in oral biodevices, digital dentistry, and pain research; established the intramural Director’s Diversity Postdoctoral Fellowship; and enhanced its partnerships with the International Association of Dental Research/American Association of Dental Research (IADR/AADR), American Dental Education Association (ADEA), and ADA. Two upcoming joint efforts are a September 14 conference, with the AADR, on Oral Health Effects of Tobacco Products: Science and Regulatory Policy, and a proposed November workshop, with the ADA, on precision medicine.

Plans for the future include potentially advancing other research areas (mechanisms of pain, oral microbiome and immunity, oral cancer treatment targets, health disparities research, and integrated care and research); focusing on two workforce diversity areas (a mentoring network and, in partnership with the ADEA, a research workforce analysis with a focus on gender); and pursuing the next phase of the NIDCR Strategic Plan, which will be released in 2020.

*Integrating Oral and Overall Health.* Dr. Somerman highlighted an article, entitled “The Importance of Oral Health in Comprehensive Health Care,” that was co-authored by Dr. Janice S. Lee, NIDCR Clinical Director, and herself and published in JAMA’s *Viewpoint*, along with a 7-minute oral exam video. She noted also that dental, oral, and craniofacial research is mentioned more often now in research articles published in the *New England Journal of Medicine*.

*Surgeon General’s Report on Oral Health.* Dr. Somerman reported that the U.S. Surgeon General, Dr. Jerome Adams, has requested a 2020 report on the oral health of the nation, which would be the 20th anniversary of the last report, which was published in 2000. She noted that the NIDCR is very busy with this effort. The two project leads are Captain Bruce Dye, who is director of the NIDCR Informatics–Dental Public Health Fellowship Program, which is sponsored in partnership with the National Library of Medicine, and Dr. Judith Albino, who is President Emerita of the University of Colorado, a professor in the Department of Community and Behavioral Health, Colorado School of Public Health, and a faculty member in the Colorado University School of Dental Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO.

*National Academies Study on Temporomandibular Disorders.* Dr. Somerman noted that the NIDCR participates in the TMJ Patient Round Table hosted by the FDA and that this group has identified the need for a comprehensive study, entitled Temporomandibular Disorders (TMD): From Research Discoveries to Clinical Treatment. The National Academies will lead the stakeholder activities, which will include a public workshop, and the NIDCR and NIH Office of the Director are providing support. The effort is expected to last 18 months, and the National Academies will report to the Congress on its conclusion.

*The Disconnect: Where to Begin.* Dr. Somerman reported on the NIDCR–ADA Collaboration on Bridging Research with Clinical Practice. This effort, to facilitate communication of research and research progress between researchers and practitioners, is supported under an NIDCR–ADA Collaboration Agreement and involves three tasks. Dr. Somerman noted that task 1 (to review existing data in published literature and NIDCR and ADA internally) and task 2 (to conduct focus groups with practicing dentists, which were held in Bethesda and Chicago) have been completed and that task 3 (to review findings and identify next steps) is under way.

#### NIDCR Cancer Portfolio

Dr. Somerman said the NIDCR has an exciting portfolio of cancer research. In FY 2017, the NIDCR allocated approximately \$55.5 million of its total budget to cancer research. This amount represents about 12 percent of the total budget, a percentage that has stayed consistent over the past 5 years. In FY 2017, the NIDCR supported 168 projects, more than 75 percent of which were investigator-initiated extramural research project grants. Other mechanisms of support included intramural research (6 percent), small business awards (10 percent), research centers (5 percent), and research training and career development (2 percent). The distribution by research type was 44 percent for basic research, 41 percent for clinical research, and 15 percent for translational research.

In closing, Dr. Somerman encouraged everyone to stay connected with the NIDCR via [www.nidcr.nih.gov](http://www.nidcr.nih.gov) as well as Twitter, LinkedIn, and YouTube for NIDCR updates, science news, and information on grants and funding.

## **V. CONCEPT CLEARANCES**

Dr. Dombroski, Director, DEA, stated that the NIDCR is required to present the purpose, scope, and objectives of proposed concepts for research initiatives to the Council in a public forum for the Council’s review, discussion, and approval and for public comment. Concepts approved by the Council are published on the NIDCR website, and proposed concepts are posted to <https://nidcr2030ideascale.com> for public comment. The NIDCR staff presented three concepts, and designated Council members led the discussion of each, as summarized below.

#### Rethinking Immune System Plasticity: Towards Robustness of Dental, Oral, and Craniofacial Health

Dr. Preethi Chander, Director, Salivary Biology and Immunology Program, Integrative Biology and Infectious Diseases Branch (IBIDB), DER, presented a proposed concept to encourage state-of-the-art, systematic research approaches that elucidate the role of immune system plasticity in health and in the pathogenesis of dental, oral, and craniofacial (DOC) diseases. She noted that immune system plasticity is a research area of long interest to the NIDCR and that the 2018 NIDCR Autotherapies Symposium and Workshop highlighted many immune concepts in DOC diseases and conditions that are incorporated into the proposed concept. The NIDCR anticipates that the proposed research will generate new knowledge to facilitate development of novel, personalized immunomodulatory-based therapies for DOC diseases.

Dr. Chander noted that the immune system is increasingly being recognized as the guardian of homeostasis, but this role is not well understood. Key functional components include the training of immune responsiveness (at the oral mucosal barrier site) through exposure to various internal and external assaults, inflammation-driven phenotypic plasticity (e.g., chronic inflammation and resolution, or wound healing, oral cancer, and autoimmunity), and immune memory of molecular and cellular events and processes. All of these need to be explored further and understood. Dr. Chander noted that there are unprecedented opportunities now to align this research with NIDCR's ongoing areas of interest. Specific examples of studies that could be supported under the concept include identifying molecular and cellular processes that contribute to immune robustness in DOC tissues, deriving approaches and models to modulate functional plasticity of the immune system, and investigating mechanisms of crosstalk of the immune system with other physiological systems. Additional examples of research include developing clinically applicable immune strategies to maintain DOC health and to treat or prevent DOC disease, validating and optimizing immune strategies to treat DOC diseases, and developing tools and technologies for modulation of immune system function.

The Council's lead discussants, Dr. Richard Peters Darveau and Dr. Nisha J. D'Silva, expressed enthusiasm for the concept, saying it was very important and exciting. Dr. Darveau said the concept fits with a holistic understanding of whole-body interaction and the recognition that restoration of homeostasis is key to health. He noted that the combination of innate and adaptive response processes is a step forward in research and that emphasis on the restoration of homeostasis and the immune system as a guardian of homeostasis changes one's thinking in doing and proposing research. Dr. D'Silva suggested it is important to include oral inflammation and its systemic effects, as well as the oral cavity's manifestation of systemic and autoimmune diseases, and to focus on individuals in studying restoration of homeostasis.

In discussion, the Council commented that recovery and restoration of the immune system are not functionally independent, but involve crosstalk. Dr. Chander clarified that other physiological systems include, for example, neuronal, vascular, adipose, stem cells, and the microbiome.

The Council unanimously approved the concept.

Oral and Dental Health in People Living with HIV and Additional Non-Communicable Diseases

Dr. Gallya Gannot, Director, Clinical Research and Clinical Technologies Program and HIV/AIDS and Oral Health Research Program, Center for Clinical Research (CCR), DER, presented a proposed concept to understand the combined effects of HIV, antiretroviral therapy, and non-communicable diseases (NCDs) on oral health. She noted that people living with HIV (PLWH) have increased rates of age-related co-morbidities such as NCDs, compared with HIV-negative individuals in the same age range. The NIDCR anticipates that the proposed research could help to generate evidence for dental treatment guidelines tailored to the needs of dental patients with HIV.

Dr. Gannot said that although oral diseases are more prevalent and severe in PLWH than in HIV-negative individuals, greater knowledge is needed about oral and dental diseases in PLWH who also have additional NCDs. This specifically includes more research on the prevalence and severity of oral and dental diseases in this population, as well as approaches to and outcomes of treatment for them. Dr. Gannot noted that the long-term success of different treatment and restorative approaches for oral diseases in PLWH, and especially in PLWH with NCDs, is not known. The proposed concept would support research to examine and compare the oral and dental health status and oral health care in PLWH with and without NCDs and HIV-negative individuals with NCDs with similar sociodemographic backgrounds. Specific areas of interest include the extent and progression of caries and periodontal disease and of pre-malignant and malignant oral lesions, success or failure of dental implants, extent and natural history of osteonecrosis and osteoradionecrosis of the jaw, approaches to oral disease prevention, effectiveness of standard-of-care treatment, and long-term successes of different treatment and restorative approaches.

The Council's lead discussants, Dr. Daniel W. McNeil, Dr. Clark M. Stanford, and Dr. Daniel Malamud were very supportive of the proposed concept. Dr. McNeil noted that approximately 40,000 individuals were newly diagnosed with HIV in the United States in 2016 and that HIV/AIDS remains a significant public health problem. While life expectancy for PLWH has increased and may be comparable to that of HIV-negative individuals when PLWH receive immediate treatment near the time of diagnosis, NCDs in this population have become more important. Dr. McNeil strongly encouraged a focus on the oral health and quality of life of individuals newly diagnosed with HIV/AIDS and across the lifespan for PLWH. Dr. Stanford noted that the proposed concept is complementary to and overlaps the previous concept addressing immune system restoration. He remarked that PLWH often are affected by various complicating diseases and conditions and that data on the negative effects of antiretroviral therapy are unclear as to whether they link to HIV status or, perhaps, for example, NCDs. Dr. Malamud highlighted (via telephone) the need for updated clinical guidelines and easy-to-use tests to assess NCDs and other complicating factors in PLWH (both children and adults) and in relation to prevention and treatment of DOC diseases. The Council commented on the financial burden and stress that PLWH endure, which may impede them from seeking dental or other treatments. Dr. Gannot noted that socioeconomic comparisons are included in the concept.

The Council unanimously approved the concept.

Interdisciplinary Approaches to Promote Adolescents' Oral Health and Reduce Health

## Disparities

Dr. Darien Weatherspoon, Director, Health Disparities Research Program, CCR, DER, presented a proposed concept to encourage interdisciplinary research to improve the oral health of adolescents and reduce observed disparities by addressing knowledge gaps and exploring approaches that integrate oral health promotion into overall health promotion. He noted that national data indicate that dental caries prevalence and disparities, especially of untreated dental caries, among adolescents have not improved much over the past decade. Adolescents are a unique population for research. They possess common risk factors for both oral health and overall health conditions, are more independent from adult caregivers, and are at increased risk for poor diets and of cigarette and other substance use compared to younger children.

The main opportunities (and gaps) for research include developing interdisciplinary collaborations to promote adolescent oral health and reduce disparities; understanding the unique causal factors and multi-level determinants of adolescent oral health (e.g., individual, interpersonal, family, and policy factors); understanding the efficacy and effectiveness of interventions that integrate oral health promotion into overall health promotion across settings serving adolescents; and understanding the mechanisms of action in interventions to change adolescents' oral health behaviors. This research could include, but is not limited to, interventions on common risk factors and in adolescent settings; role of families, peers, and social networks on oral health behaviors; multi-level interventions to reduce oral health disparities and enhance oral health; mechanisms of action for novel interventions to change oral health behaviors (e.g., use of mobile platforms, apps); and feasibility, acceptance, and provision of general health promotion (e.g., diet/nutrition screening, smoking cessation, obesity counseling) for adolescents in dental offices.

The Council's lead discussants, Dr. Clark M. Stanford and Dr. Raul I. Garcia, remarked that the proposed concept is important, timely, and addresses a knowledge gap. Dr. Stanford commented that while adolescence is a research gap in understanding oral and overall health, it is a time when adult health behaviors are established. He noted that the dental office is a place of health promotion, particularly for adolescents, and that practitioners can have a mentoring role in preventing or intervening in risky health behaviors (e.g., use of vaping, prevention of HIV and HPV infection). Dr. Garcia noted the need to understand behavior change in a theory-grounded way, as a means to implement effective interventions, and to understand the barriers to health equality, in order to reduce or eliminate health disparities. He also mentioned that the social determinants of health, health literacy, and oral cancer risk factors can impact oral health in this age group. The Council noted that the proposed concept is incredibly important. Members emphasized the need to incorporate technology, including Internet approaches, in interventions aimed at changing adolescents' behavior and the need for education and follow-up among underserved, vulnerable populations in major cities.

The Council unanimously approved the concept.

## **VI. CONCEPT UPDATE**

## Interdisciplinary Collaborations to Promote Clinical Research in Oral Health and Aging

Dr. Darien Weatherspoon presented an update on a concept approved by the Council at its meeting on January 24, 2017. The goal of this concept is to address, through interdisciplinary research, knowledge gaps in the etiology and management of DOC diseases associated with aging. Following the Council's approval, the NIDCR issued a Request for Applications (RFA) to stimulate collaborative, investigator-initiated research on the biology of aging in DOC tissues as it relates to other tissues and organs [RFA-DE-18-009/010 (R01/R21): Biology of Aging Dental, Oral, and Craniofacial Tissues].

Dr. Weatherspoon reported that the NIDCR is planning to issue a second, related FOA to solicit applications focusing on clinical research in older adults. This research could include, for example, development of evidence on effective approaches to support oral health and quality of life in older adults and on the importance of oral health in vulnerable populations (e.g., in nursing homes).

In discussion, the Council suggested that the FOA also include research on older adults' cultural sensitivities to health care (e.g., among Holocaust survivors) and a clear definition of the link between DOC health and disease and the oral microbiome, so as to attract researchers studying the microbiome. In response to questions, Dr. Weatherspoon said the FOA would encompass investigation of biomechanical aspects of being elderly (e.g., frailty) and the impact of polypharmacy among older adults, a topic that could be addressed in collaboration with pharmacy schools and public health researchers.

## **VII. SPECIAL SESSION ON TARGETING CO-DEPENDENT MOLECULAR PATHWAYS IN ORAL CANCER**

Dr. Chiayeng Wang, Director, Oral and Salivary Cancer Biology Program, IBIDB, DER, introduced the session topic. Following her remarks, she introduced three NIDCR-supported, extramural principal investigators, who separately described their research on co-dependent molecular pathways in oral cancer. The presentations are summarized below.

### Introduction

Dr. Wang noted that, for decades, the triad of treatments for cancer has consisted of chemotherapy, radiation, and surgery and researchers are now looking for new and better ways to treat cancer with reduced side effects. In recent years, the focus has been on targeted approaches, drawing on the discovery of genomic maps of various tumors and the identification of potential candidate targets such as small molecules. Dr. Wang noted, however, that the clinical benefit of targeted treatments, used singly, varies widely in patients and that this approach has had limited effects particularly in patients with head and neck cancer, a complex disease requiring the use of multiple, targeted drugs.

In 2014, the NIDCR sought to stimulate research on treatment of head and neck cancer using targeted approaches by issuing RFA-DE-15-004 (U01): Targeting Co-dependent Molecular

Pathways in Oral Cancer. The purpose was to support multidisciplinary projects aimed at the development of new targeted and effective therapies through systematic use and leveraging of recently identified genomic abnormalities and attendant changes in gene and/or protein expression profiles in human oral/head and neck cancer samples. The long- and short-term goals were to identify co-dependent survival and proliferation pathways in oral/head and neck cancer cells and to elucidate potential signaling pathways that can be targeted with combination therapy approaches. The emphasis of the RFA was on the conceptual phase of target identification and exploration and included proof of concept.

Following the review of applications received, the NIDCR funded three Cooperative Agreement (U01) awards to principal investigators at the University of Michigan, University of Texas MD Anderson Cancer Center, and Stanford University, respectively. These investigators described their research, as follows, at the Council meeting.

Functional Genomics Profiling Defines Mechanisms of Compensatory Resistance to PI3K and EGFR Targeted Therapies in HNSCC

Dr. J. Chad Brenner, Assistant Professor, Department of Otolaryngology-Head and Neck Surgery; Director, Michigan Otolaryngology and Translational Oncology Laboratory; and Co-director, Head and Neck Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, noted his interest in precision medicine and use of genetics to improve the effectiveness of medical treatment. In his presentation, he suggested a paradigm for how to modify precision medicine approaches to improve survival and outcomes of patients treated for head and neck squamous cell cancer (HNSCC). He thanked the NIDCR for enabling him to pursue this research.

Dr. Brenner described research he and his team have undertaken to clarify the varying effectiveness of cancer therapies. Pursuing the hypothesis that some cell lines are autonomous, for which single, targeted therapies can be effective, while others are non-autonomous, allowing for functional compensation to therapy via compensatory cell signaling, they focused on small molecule cell signaling in 10 HNSCC cell line models. In initial studies, the researchers found that different models and unique clusters of models are sensitized in vitro to epidermal growth factor receptor (EGFR) inhibition by different drugs and that multiple drugs independently reverse EGFR inhibitor resistance in different models. They also found that different models are sensitized to EGFR inhibitors by different gene knockouts and that multiple genes independently drive EGFR inhibitor resistance in different models. Subsequently, they observed that, like EGFR inhibition, tumors have multiple compensatory pathways driving resistance to tumor inhibitors, such as phosphatidylinositol 3-kinase (PIK3), and that multiple inhibitor combinations, such as PIK3 and anaplastic lymphoma kinase (ALK), are highly synergistic in PIK3CA mutant models.

Dr. Brenner emphasized the overall message from this research: Tumors adapt to therapy, and adaptive clinical trials are needed. He highlighted three conclusions: Different tumors utilize multiple different compensatory pathways to survive precision guided therapy (e.g., EGFR or PI3K inhibitors); di-therapy combinations will kill tumors if the right compensatory pathway is targeted; and di-therapy combinations will *not* kill tumors if the wrong

compensatory pathway is targeted. Dr. Brenner proposed that this research be extended and validated through analysis of mid-treatment, interim biopsies obtained from clinical trials after a single dose of cetuximab—to better understand how tumors respond to inhibitors in real time. He noted that preliminary data indicate that tumors elevate different response pathways and clusters of response following a single dose of cetuximab.

Dr. Brenner noted three directions for future research: Continue to build on current understanding of the diversity of compensation pathways for common HNSCC therapies; advance techniques for real-time monitoring compensation and disease progression; and use this information to design next-generation precision medicine trials that adapt to tumor-specific compensation. He depicted a schema for an adaptive clinical trial in which a biomarker-driven intervention begins in real time and proceeds with evaluation of the pathways of response by determining variables in real time (compensatory mechanisms and markers of tumor response) and with adaptation of the intervention accordingly, using machine-learning algorithms to predict the optimal time for modifying the intervention.

In closing, Dr. Brenner acknowledged and thanked all members of the University of Michigan team, whose research is supported by the NIDCR and the National Cancer Institute (NCI).

#### In Vivo Functional Genomics Identifies Tumor Dependencies and Candidate Targets

Dr. Curtis R. Pickering, Assistant Professor, Department of Head and Neck Surgery – Research, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, focused on functional genomics screening to identify tumor dependencies and candidate targets. He noted that his research team includes investigators from various groups at MD Anderson, as well as Baylor College of Medicine, and that funding is provided by NIDCR, NCI, and other sources.

Dr. Pickering said that he and his team have been studying the genomics of HNSCC since 2011 and, in 2015, adopted a big-scale approach to address the integrated genomics of HNSCC. This research has shown that human papilloma virus (HPV)-driven SCC is a unique disease; most SCC are genomically similar, though tissue site matters; SCC are heterogeneous; and SCC are primarily driven by loss of tumor suppressor genes. Dr. Pickering outlined key pathways and genes involved in HNSCC and noted two overriding research questions: (i) Are there genomic subtypes of HNSCC (i.e., what are the key driver genes and pathways, and which drivers are clinically relevant and at what stage of disease), and (ii) how do we target HNSCC (i.e., are key tumor suppressor genes and pathways targetable, and which genes are targetable).

Dr. Pickering said that his team's approach to these questions is to look at HNSCC tumors globally and computationally in three stages: computation (i.e., big data and network analysis), discovery (i.e., in vivo shRNA screening), and mechanism (mapping of pathways in vivo). In the first stage, which is not yet complete, the team is integrating evolutionary action with cohort integrals to identify key driver (mutated) genes as potential candidate targets for drug development. In the second stage, the team is screening shRNA libraries in vivo (in mice) for 6 HNSCC cell lines having diverse genomic status. They are analyzing the data comparatively in

vitro and in vivo under three treatment conditions (control, chemotherapy, radiation) to identify and validate commonalities across cell lines, identify top screening hits [e.g., PI3K, 5' adenosine monophosphate-activated protein kinase (AMPK)], and identify mutant cell lines that are sensitive to inhibition via radiation and/or chemotherapy (e.g., CREBBP/EP300), leading to apoptosis.

Dr. Pickering noted the following key findings from this research approach: Candidate driver genes can be identified through evolutionary-based mutation analysis; low-frequency drivers can be identified through network integration; in vivo-specific sensitivities can be identified through in vivo shRNA screening; CREBBP/EP300 may be a new therapeutic target for radiosensitization; and CREBBP/EP300 mutations may be a biomarker for therapeutic targeting. He also highlighted some lessons learned, as follows: It is difficult to derive strong conclusions from a medium-scale (6 cell lines) functional genomics study (30–40 cell lines are needed), and very large scale or individual gene projects may be more fruitful; most identified candidates from screens may not be translatable, and previous studies may bias interpretation; and the research field will have to resolve how to deal with single-gene versus pathway studies, as pathway and network analysis lacks a clearly defined validation approach and it may be necessary to revert to single-gene validation. Dr. Pickering commented that there is a lack of funding for validation and translation of large-scale projects and most successful grants are gene-centric. He noted that given the 1–2 years needed to generate enough preliminary data on each hit for a competitive R21 or R01 grant, the number of gene studies that can be followed up is limited and, generally, very few hits from a large screen are ever studied.

Future directions for research include development of functional screens with cleaner endpoints (either large- or small-scale), continued testing of new computational tools to understand biology and genomics (working to integrate computational and translational biology), and building of tools and models for studying pathways instead of genes (systems biology). Dr. Pickering suggested that the NIDCR pursue a funding option for validation of screening hits and support the buildup of a large bank of immune-competent in vivo models (50+), which could be chemically induced mouse cell lines, flexible genetically engineered mouse models, or humanized mouse models with matching human cell lines.

### Understanding Genetic Determinants of Head and Neck Cancer Subtypes

Dr. John B. Sunwoo, Professor, Department of Otolaryngology – Head and Neck Surgery Divisions; Director, Head and Neck Cancer Research; and Leader, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, discussed the genetic determinants of head and neck cancer subtypes. He thanked the NIDCR for supporting this research and noted that his presentation includes projects led by Dr. Calvin J. Kuo and Dr. Olivier Gevaert, of Stanford University, who are also principal investigators on the NIDCR research grant. The researchers are working with oral mucosa organoids to model HNSCC development. They are establishing and using organoid molecules as drivers of tumors and sequencing them over time to study their evolution and determine which are important in tumor development.

Dr. Sunwoo described the researchers' efforts to establish and characterize normal and transformed oral mucosa organoids, identify novel oncogenes that are functionally involved in

HNSCC progression, and assess potential drivers of HNSCC methylation subtypes. He said they have been pursuing two different approaches to cancer modeling, a top-down approach using transformed cell lines with oncogenic mutations and a bottom-up approach using normal tissue organoids with no oncogenic mutations. He described the culture methods used to establish normal and transformed organoids and noted that the team has focused on the p53 mutant, which is the more common gene mutant in HNSCC and a target of HPV. Research studies show that p53 deletion in mice enhances proliferation of oral mucosal organoids and induces histologic transformation.

Dr. Sunwoo then described one strategy the researchers are using to identify novel oncogenes functionally involved in HNSCC progression—that is, barcoded cDNA library screening of amplified HNSCC outlier loci in p53-null oral mucosal organoids. This research showed the following: Oral mucosa organoid culture in matrigel and air-liquid interface (ALI) collagen recapitulated a stratified squamous epithelium structure, and p53 null mouse oral mucosa organoids grew significantly faster than wild-type organoids. The researchers were able to generate p53 and candidate co-occurring driver double-knockout oral mucosa organoids and are pursuing histological analysis and in vivo analysis. They screened 107 open reading frame outliers for oral cancer and found that multiple genes were enriched in the terminal time point and that the DYRK2 gene enhanced cell proliferation (was a potential driver) of p53 null oral mucosa organoids in vitro and in vivo. The researchers are testing the effect of kinase activity of DYRK2 on proliferation.

Dr. Sunwoo noted that in their assessment of potential drivers of HNSCC DNA methylation subtypes, the investigators focused on subtype II, which features a higher number of hypomethylated genes than four other methylation subtypes in patients with HNSCC. They found that subtype II is enriched for mutations of nuclear receptor SET domain-containing protein 1 (NSD1), which is associated with malignancy (e.g., in acute myeloid leukemia) and perhaps proliferation (e.g., Sotos syndrome), and that NSD1-associated subtype is associated with lower immune infiltration (TIL) levels. Dr. Sunwoo suggested that these findings may indicate that NSD1 plays a role in HNSCC. He noted that patients' response to immunotherapy correlates with the presence of tumor-infiltrating T cells and the mechanisms that determine immune cell infiltration have not been defined.

Dr. Sunwoo summarized these findings, saying that HNSCC subtypes associated with NSD1 mutations have a higher number of hypomethylated genes and that NSD1 inactivation is a driver of immune cell exclusion in HNSCC. The researchers are investigating whether targeting NSD1 results in an increase in tumor-infiltrating T cells in NSD1-mutant lesions. Dr. Sunwoo said future studies will include identification of chromatin regions associated with NSD1 and assessment of potential drivers of other methylation subtypes in HNSCC.

## **VIII. DISCUSSION**

After each presentation during the special session, the presenter addressed questions from the Council. In the general discussion at the end, Dr. Chiayeng Wang asked all the presenters to comment on how to identify additional cooperative signaling pathways affecting the behavior of

cancer cells, given that intra-tumor heterogeneity is quite high in HNSCC and poses a problem for developing targeted treatments for HNSCC. Drs. Brenner, Pickering, and Sunwoo noted that they are all pursuing different, important approaches to identify drivers of tumors and that all this research will help to identify the most important clones to target for treatment.

Dr. Wang thanked the three speakers for participating in the special session. The Council applauded them for their presentations.

## **CLOSED SESSION**

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

## **IX. REVIEW OF APPLICATIONS**

### Grant Review

The Council considered 409 applications requesting \$149,724,720 in total costs. The Council recommended 244 applications for a total cost of \$106,278,232 (see Attachment II).

## **X. ADJOURNMENT**

The meeting was adjourned at 1:53 p.m. on May 25, 2018.

## **CERTIFICATION**

I hereby certify that the foregoing minutes are accurate and complete.

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Dr. Martha J. Somerman  
Chairperson  
National Advisory Dental and  
Craniofacial Research Council



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Dr. Alicia Dombroski  
Executive Secretary  
National Advisory Dental and  
Craniofacial Research Council

## **ATTACHMENTS**

- I. Roster of Council Members
- II. Table of Council Actions