

National Institute of Dental and Craniofacial Research

National Advisory Dental and
Craniofacial Research Council

Minutes of Meeting
May 23, 2019

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

May 23, 2019

The 221st meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on May 23, 2019, at 9:05 a.m., in Building 35A, Conference Rooms 620/630, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public from 9:05 a.m. until 12:30 p.m.; it was followed by the closed session for Council business and consideration of grant applications from 2:00 p.m. until adjournment at 2:57 p.m. Dr. Martha Somerman presided as Chair.

OPEN SESSION

Members Present

Dr. Kathryn M. Albers
Dr. Shenda M. Baker
Dr. David J. Couper
Dr. Nisha J. D'Silva
Dr. Daniel Malamud
Dr. Daniel W. McNeil
Dr. Phillip Messersmith
Dr. Sanjay Shete
Dr. Clark M. Stanford

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. Christopher Fox, Executive Director, International Association of Dental Research (IADR)/ American Association of Dental Research (AADR), Alexandria, VA
Dr. Anthony Palatta, Chief Learning Officer, American Dental Education Association (ADEA), Washington, DC
Ms. Susan Apollonio, Senior Director of Educational Leadership and Faculty Development Programming, ADEA, Washington, DC

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. Jonathan Horsford, Office of the Director (OD), Acting Director, Office of Science Policy & Analysis (OPSA)

Dr. Janice S. Lee, Clinical Director, DIR

Dr. Dwayne Lunsford, Director, Microbiology Program and Coordinator for Dental Small Business (SBIR/STTR), DER

Dr. Marion Young, Deputy Scientific Director, DIR

Dr. Lynn Mertens King, Chief, Research Training & Career Development Branch, DEA

Dr. Lu Wang, Chief, Translational Genomics Research Branch (TGRB), DER

Dr. Laura Kerosuo, Stadtman Tenure-Track Investigator, Neural Crest Development and Disease Unit, DIR

Dr. Nisan Bhattacharya, DEA, Scientific Review Branch (SRB)

Dr. Preethi Chander, DER, Integrative Biology and Infectious Diseases Branch (IBIDB)

Ms. Jennifer Chi, Health Specialist, Office of Clinical Trials Operations and Management (OCTOM)

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 Daum, OD, OCHE, Health Information and Public Liaison Branch

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. Catherine Evans, OD, OCHE

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)

Ms. April Harrison, DEA, Grants Management Branch (GMB)

Mr. Gabriel Hidalgo, DEA, GMB

Dr. Jamie Kugler, Scientific Program Specialist, DIR

Dr. Orlando Lopez, DER, IBIDB

Dr. Nadya Lumelsky, DER, IBIDB

Ms. Jayne Lura-Brown, DER

Ms. Susan Medve, DEA, GMB

Dr. Yun Mei, DEA, SRB

Ms. Yasamin Moghadam, DER, CCR
Mr. Rickey Moore, DEA, SRB
Ms. Anna Nicholson, OD, OCTOM
Dr. Morgan O'Hayre, OD
Ms. Debbie Pettitt, DEA, GMB
Dr. Deborah Philp, DIR, Office of Intramural Training
Mr. Ben Rassuli, OD, OIT
Dr. Melissa Riddle, DER, Behavioral and Social Science Research Branch (BSSRB)
Ms. Delores Robinson, DEA
Ms. Diana Rutberg, DEA, GMB
Dr. Yasaman Shirazi, DEA, SRB
Mr. Larry Sutton, OD, OAM
Mr. Joseph Tiano, OD, OSPA
Dr. Jessica Walrath, OD, OSPA
Dr. Jason Wan, DER, IBIDB
Dr. S. Chiayeng Wang, DER, IBIDB
Dr. Darien Weatherspoon, DER, CCR
Dr. Marian Young, DIR
Dr. Gary Zhang, DEA, SRB

Other Federal Employees

Dr. Michael Lauer, Deputy Director for Extramural Research, National Institutes of Health, Bethesda, MD

I. WELCOME AND INTRODUCTIONS

Dr. Martha Somerman, Director, NIDCR, called the open session of the 221st Advisory Council meeting to order. She welcomed those in attendance and asked Council members, participants, and guests to introduce themselves.

II. APPROVAL OF MINUTES FROM PREVIOUS MEETING

Dr. Dombroski invited the Council to consider and approve the minutes of the January 23rd, 2019, Council meeting. The Council unanimously approved the minutes.

III. REPORT OF THE DIRECTOR, NIDCR

Dr. Somerman's written May 2019 Director's Report to the Council was provided to the Council members and is available on the NIDCR website (<http://www.nidcr.nih.gov>). Her remarks cover NIDCR's budget, a trans-NIH update, NIDCR update, and selected research highlights. First, Dr. Somerman introduced two new NIDCR employees: Dr. Alicia Chou, who will be joining the Translational Genomics Research Branch, and Mr. Ricky Lee Moore, NIH Pathways Intern. She also announced that Dr. Debara L. Tucci will be joining NIH as the new

Director of the National Institute on Deafness and Other Communication Disorders (NIDCD) starting in September.

Legislative and Budget Updates

Dr. Somerman began her budget overview by presenting a summary of FY2019 and FY2020 budget events. For the current year, NIH has received its appropriations from Congress. The President has presented his proposed 2020 budget to Congress, which will have until October to pass a budget or, in the event an agreement cannot be reached, a continuing resolution. She presented the final FY2018 actuals mechanism table to the Council, noting that her staff closely monitor the Research Project Grants (RPGs), Small Business Innovation Research (SBIR) Grants, and the Small Business Technology Transfer (STTR) Grants. NIDCR is looking for ways to develop a more robust small business portfolio and Dr. Somerman encouraged any Council members with suggestions in this regard to reach out to staff. NIDCR is currently under its FY2019 operating budget, which totals \$461.8M. Dr. Somerman noted that this total is an approximately 3.4% increase from NIDCR's FY2018 operating budget.

Dr. Somerman thanked the American Association for Dental Research (AADR) and the American Dental Education Association (ADEA) for their efforts reaching out to Congress in support of NIDCR and related activities. Dr. Somerman also noted the recent visit by members of the Friends of NIDCR Advisory Council, an umbrella group to AADR, comprising non-profit organizations that work together to advance dental, oral, and craniofacial health research. The group toured NIDCR labs and visited the NIDCR Center for Clinical Research.

NIH Updates

Trans-NIH Activities. Dr. Somerman discussed NIDCR's participation in the NIH Helping to End Addiction Long-term (HEAL) Initiative, which is a trans-agency effort to speed scientific solutions to address the national opioid public health crisis. The budget for the HEAL Initiative totals approximately \$850M for this fiscal year, which by mandate, has to be spent by the end of the fiscal year. Dr. Yolanda Vallejo, who was unable to attend today's meeting, has been spearheading NIDCR's participation in the initiative and Dr. Somerman applauded her for her efforts. NIDCR's HEAL Initiative grants have been focused on temporomandibular disorders (TMD) and de-implementation of opioid use disorder. Requests for Applications (RFAs) continue to be released and Dr. Somerman encouraged Council members to spread the word among their respective research communities. NIDCR is participating in the following multi-Institute RFAs: Tissue Chips to Model Nociception, Addiction, and Overdose; Discovery and Validation of Biomarkers, Endpoints and Signatures for Pain Conditions; and Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM).

Dr. Somerman next briefed the Council on NIDCR's participation in an NIH Workshop on Health Screening in Childhood, which took place in early May. The workshop identified methodological challenges in evaluating child health outcomes, discussed novel and rigorous approaches to evaluating child health, and considered steps forward to improve the child health screening process.

NIDCR is closely following NIH programs and initiatives related to artificial intelligence and machine learning, in particular the Artificial Intelligence Working Group of the Advisory Committee to the NIH Director (ACD). Dr. Somerman believes these fields hold great promise for improving diagnoses, among many other potential benefits. She highlighted facial recognition technology as one aspect that could be of great import to NIDCR's field of research.

On May 6th, in conjunction with its one-year anniversary, the NIH All of Us Research Program held a symposium entitled "From Data to Discoveries: Creating a Research Program for All of Us." Speakers included Dr. Francis Collins, NIH Director; Mr. Eric Dishman, Director of the All of Us Research Program; Dr. Gary Gibbons, Director of the National Heart, Lung and Blood Institute (NHLBI), and Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA), among others. The goal of the program is to enroll one million participants; currently, there are approximately 143,000 active participants and 87,000 registered. NIDCR is working to get an oral health component into the program as soon as possible.

Dr. Somerman also updated the Council on NIDCR's efforts to raise awareness and educate the community about sexual harassment. Several workshops have been held on the topic and Dr. Somerman has been encouraged by the level of participation among staff. Several NIDCR staff members have been involved in this topic at the NIH-wide level, two of whom, Dr. Kelly Ten Hagen and Dr. Deborah Philp, will be receiving NIH Director's Awards for their work in drafting new policies for the NIH.

NIDCR Activities

NIDCR 2030 Vision and Timeline. Dr. Somerman said NIDCR 2030 remains a priority area for NIDCR. Along these efforts, one of the issues that the strategic plan 2020-2025 hopes to address is the fact that dental, oral, and craniofacial health and disease continue to be left out or siloed in the context of whole-body health and related research.

Craniofacial Research Symposium. On May 6th, as part of its 70th anniversary celebration, NIDCR hosted a craniofacial research symposium entitled "Looking Back and Facing the Future: From NIDR to NIDCR." The event showcased research accomplishments in craniofacial biology, from basic science to clinical applications, and commemorated the addition of "Craniofacial" to the Institute name in 1998. Speakers included two former Directors of the Institute, Dr. Lawrence Tabak and Dr. Harold Slavkin.

National Academies Study on Temporomandibular Disorders. Dr. Somerman updated the Council on the status of the committee that has been convened to draft this consensus study. NIDCR representatives have attended several of the committee's public sessions. Dr. Somerman noted that these committees generally take a year to 18 months to complete their work.

Intramural Research Highlight. Dr. Somerman presented to the Council two NIDCR-supported research highlights. On the intramural side, Dr. Mark Hoon, Senior Investigator in NIDCR's Molecular Genetics Unit, and colleagues recently published an article in *Cell* called "Nppb Neurons Are Sensors of Mast Cell-Induced Itch." The natriuretic polypeptide b (Nppb)-expressing class of sensory neurons, when activated, elicits scratching responses in mice, but it is

unclear which itch-inducing agents stimulate these cells and the receptors involved. Dr. Hoon and his team identified receptors expressed by Nppb neurons and demonstrate the functional importance of these receptors as sensors of endogenous pruritogens released by mast cells. In addition, their search for receptors in Nppb neurons reveals that they express leukotriene, serotonin, and sphingosine-1-phosphate receptors. Targeted cell ablation, calcium imaging of primary sensory neurons, and conditional receptor knockout studies demonstrate that these receptors induce itch by direct stimulation of Nppb neurons and neurotransmission through the canonical gastrin-releasing peptide (GRP)-dependent spinal cord itch pathway. Together, the results define a molecular and cellular pathway for mast cell-induced itch.

Extramural Research Highlight. Dr. Somerman next presented a NIDCR-funded research highlight from the extramural community. Dr. Hyun Koo from the University of Pennsylvania School of Medicine and colleagues published an article titled “Catalytic antimicrobial robots for biofilm eradication” in *Science Robotics*. Biofilms are intractable, firmly attached structures associated with drug-resistant infections and surface destruction. Dr. Koo et al. designed catalytic antimicrobial robots (CARs) that precisely, efficiently, and controllably killed, degraded, and removed biofilms. CARs exploiting iron oxide nanoparticles (NPs) with dual catalytic-magnetic functionality (i) generated bactericidal free radicals, (ii) broke down the biofilm exopolysaccharide (EPS) matrix, and (iii) removed the fragmented biofilm debris via magnetic field-driven robotic assemblies. Dr. Koo and his team developed 2D and 3D versions of CARs and demonstrated applications of CARs to target highly confined anatomical surfaces in the interior of human teeth. These “kill-degrade-and-remove” CARs systems might help fight persistent biofilm infections and mitigate biofouling of medical devices and diverse surfaces.

IV. CONCEPT CLEARANCES

Dr. Dombroski, Director, DEA, stated that 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. The NIDCR staff presented two concepts, and designated Council members led the discussion of each, as summarized below.

Reissue: NIDCR Small Research Grants for Data Analysis and Statistical Methodology Applied to Genome-wide Data

Dr. Lu Wang, Director, Translational Genetics & Genomics Program and Chief, Translational Genomics Research Branch, DER, presented the reissue concept. The goal of the program is to support projects investigating questions about dental, oral, or craniofacial conditions by reanalyzing existing genome-wide omics data. Data resources include FaceBase, Human Oral Microbiome Database, Human Microbiome Project Data Portal, the Encyclopedia of DNA Elements (ENCODE), The Cancer Genome Atlas (TCGA), the database of Genotypes and Phenotypes (dbGaP), and the Knockout Mouse Project (KOMP) Repository, among others. Program-supported research utilizes a myriad of data types, such as genotypes; DNA, RNA, or methylation sequences; microbiome sequences; single cell DNA/RNA sequences; associated clinical, phenotypic, and environmental data; and associated metadata. The statistical and

computational approaches used in funded projects were both previously existing and developed through the funded projects.

The program has been reissued twice since its first issuance in 2009. Over its lifespan, the program has received applications for 77 unique projects, the number of which has increased with each funding cycle, and has funded 20 applications, so far. Dr. Wang noted that the cycle has not yet concluded. Research funded through the program has led to approximately 90 publications, which Dr. Wang divided into three broad categories: biological insights obtained on DOC-related gene regulatory networks, genetic risk factors, or gene-environment interactions, disease risk prediction models, and novel analytical tools. Dr. Wang emphasized that the novel analytical tools are applicable to analysis of multi-omics data relevant to dental, oral, or craniofacial conditions and beyond. Recent applications have included proposals for development of deep machine learning algorithms and their uses in functional genomics studies. Dr. Wang believes reissuance is justified based on past success, the need for more data sources that can be used for validation of discoveries made or for obtaining deeper and more global biological insight, increased data volume and types, improved data quality, as well as improved analysis, statistical, computational, and ontological tools. In addition, reissuance will hopefully lead to more mechanistic insight about DOC and the human body as a whole, more robust analytical tools, as well as the contributions to the knowledge of factors that impact oral health, including social economic factors

The Council's lead discussants, Dr. David J. Couper and Dr. Sanjay Shete, expressed strong support for the reissuance of this funding mechanism. Dr. Couper reiterated the importance of integrating more and more data in 'omics studies. Larger data pools are needed to provide large enough sample sizes to give studies sufficient statistical power and support reproducibility. There are very few mechanisms that provide funding to integrate data across multiple studies, which makes this program very valuable. Dr. Shete concurred with Dr. Couper and added that the program will remain highly relevant as the number of types of data included in omics data continues to increase. Dr. Shete suggested expanding the scope of the program to include three-year R01s in addition to R03s in order to open the mechanism to more senior investigators. PIs in R03s are typically junior investigators and the complexity of the data in some cases may require more long-term commitment and experience. Dr. Wang said staff will consider Dr. Shete's recommendation. She added that the last two Funding Opportunity Announcements (FOAs) allowed for applications including experimental validation.

The Council unanimously approved the concept.

Reissue: NIDCR Small Grant Program for New Investigators (R03)

Dr. Dwayne Lunsford, Director, NIDCR Microbiology Program and Coordinator for Dental Small Business (SBIR/STTR), DER, presented the reissue request to the Council. The purpose of this grant program is to support scientists in the early stages of establishing an independent research career in oral, dental, and craniofacial research. In addition, the program aims to support pilot or feasibility studies and developmental research projects with the intention of obtaining sufficient preliminary data for a subsequent investigator-initiated R01 or equivalent application. The program began in 2007 with several subsequent iterations. Unlike the parent NIH R03 mechanism, which provides \$50K direct costs per year for two years, this program

allows for direct costs of up to \$100K per year for two years. The program is only open to new investigators and excludes R21 awardees from any IC. In addition, for multi-PI applications, all the PIs involved must be new investigators. New investigators are defined as researchers who have never received significant NIH funding (i.e., their first R01). Applications must include a conceptual framework for a subsequent R01 or equivalent.

Dr. Lunsford reported that the program remains popular, especially with new investigators who have no prior experience with the peer review process. An extensive portfolio analysis was conducted at the end of the previous cycle, which found that investigators who were awarded this R03 were two times more likely to apply for their first R01, and three times more likely to be awarded their first R01. For this cycle, 165 applications have been received thus far, with 18.1% awarded a grant, a slightly higher percentage than the past two cycles.

The Council's lead discussants, Dr. Nisha J. D'Silva and Dr. Kathryn M. Albers were very supportive of the concept reissuance, particularly lauding the higher funding level. Dr. Albers also felt requiring applications to describe a framework for future studies was a valuable feature of the program. Dr. Daniel W. McNeil asked why R21 awardees are excluded. Dr. Lillian Shum, Director, Division of Extramural Research, said that, in general, NIDCR encourages investigators to apply for R01s because it is a larger award, more stable, and is renewable. This R03 is designed for early stage investigators who do not have preliminary data to support a research platform for an R01 application. R21 awardees generally do have some preliminary data, and ideally, they would therefore move to the R01 as their next step. The R03 in question was designed to limit the pool to investigators who truly need it, but if the Council feels it is overly restrictive Dr. Shum said staff would be willing to reconsider that requirement. Dr. Clark Stanford asked whether this R03 could help fill the transitional gap for postdocs looking to start their career on their own. Dr. Shum said the grant is designed for researchers who are already demonstrably independent. Dr. Stanford said some research universities are beginning to rethink their promotion and tenure approach away from the traditional lone independent researcher model and more towards team-based science. Dr. McNeil suggested that NIDCR consider removing the requirement that all PIs in a multi-PI study must be new investigators as a way of addressing Dr. Stanford's point.

The Council unanimously approved the concept.

V. NIDCR Strategic Plan

Dr. Jonathan Horsford, Acting Director, Office of Science Policy & Analysis (OSPA), presented an update on NIDCR's Strategic Plan for 2020-2025. OSPA develops and coordinates NIDCR's activities in the areas of science policy, scientific strategic planning, evaluation, science coding, reporting, and legislative affairs. The Office also includes the Institute's dental, oral, and craniofacial epidemiology research group and Dental Public Health Residency program.

The previous strategic plan concludes this year. The strategic plan was viewed positively by stakeholders and was seen as a successful means of communicating the Institute's priorities in research and training. Since the last NIDCR strategic plan was published, the NIH released a

strategic plan of its own at the behest of Congress. Dr. Horsford briefly discussed the NIH Strategic Plan's general framework and noted that it contains segments addressing NIH's role in setting priorities and enhancing stewardship in the scientific and medical communities. Because these were areas Congress specifically wanted NIH to address in its strategic plan, they will also be areas that NIDCR will also include in its next strategic plan. Other drivers for the next strategic plan are NIDCR 2030, released a few years ago as NIDCR's vision of the future, and the 21st Century Cures Act, which includes specific language that requires IC strategic planning to address women, minorities, and health disparities and to include related metrics.

Dr. Horsford next presented an outline of the proposed 2020-2025 NIDCR Strategic Plan. The plan will emphasize NIDCR's role in researching dental, oral, and craniofacial diseases in an integrated manner. One of the themes of the strategic plan will be biomedical research synergy. NIDCR improves the national dental, oral, and craniofacial health by conducting and supporting the entire spectrum of biomedical research, from basic research to implementation in public health interventions. The strategic plan identifies five priority focus areas: oral health and overall health, precision oral health, regenerative medicine, health disparities, and diverse workforce. Internally, NIDCR is working to identify objectives in these priority areas and metrics for evaluating success. The strategic plan will address stewardship by calling for the development and implementation of evidence-based, data-driven strategies to assure that NIDCR investments are directed in ways that maximize scientific output. Dr. Horsford presented the next steps for the drafting of the strategic plan. After today's meeting, NIDCR will release a public request for information. The drafting and finalizing of the strategic plan will take place this fall and winter, leading up to the release of the strategic plan at the International Association for Dental Research General Session in Washington, D.C., in March 2020.

VI. 2020 Surgeon General's Report on Oral Health

Dr. Judith Albino, President Emerita, University of Colorado, and Professor, Colorado School of Public Health and School of Medicine, University of Colorado Anschutz Medical Campus, updated the Council on 2020 Surgeon General's Report on Oral Health.

Dr. Albino began by recalling that the last Surgeon General's Report on Oral Health was released 19 years ago, in 2000. That report emphasized the importance of oral health in the overall health and well-being of Americans. It also stressed that safe and effective measures exist to improve oral health and prevent disease, and that health risk factors, such as tobacco use and poor dietary practices, affect oral and craniofacial health.

However, much has changed in the United States in the past 20 years. The overall population is aging, which has placed strain on the nation's health infrastructure. The U.S. population now consists of almost 54 million people aged 65 or older. Between 1950 and 2010, life expectancy for Americans increased from 66 to 76 for men and from 71 to 81 for women. These trends are predicted to continue into the future. Oral health disparities in underserved populations continue to persist and even increase in some segments. According to the Health Resources and Services Administration (HRSA), each of the 50 states has at least 10 or more Dental Health Professional Shortage Areas (HPSAs), affecting almost 60 million people. HRSA

estimates that 10,593 dental health practitioners would be needed today to fill those gaps. This shortage has led to the development of alternative service delivery models, settings, and technologies. The opioid crisis has also affected the oral health field in the last decade. Opioids, methamphetamine, and other drugs of abuse affect the oral environment in ways that create susceptibility to disease. For example, methamphetamine users have twice the number of decayed, missing, and filled teeth as non-users. Moreover, users of these substances are less likely to be able to access the dental care that they need. Dr. Albino also pointed to individuals suffering from mental health as another large and growing segment of the population that often lacks access to appropriate dental care.

The increase in health care costs in recent decades is another major obstacle to care that has arisen since the last report. Even adjusting for inflation, the cost of dental care in the U.S. has more than doubled in the last 20 years. Dental care continues to present a higher cost barrier than other types of health care. This is particularly an issue among working age adults aged 19 to 64, the majority of the population.

Dr. Albino also highlighted several public health threats that have emerged in the past two decades. Incidence in HPV-associated oropharyngeal cancer has increased significantly, particularly among men. Another public health threat that directly impacts dental, oral, and craniofacial health is the rise in popularity of e-cigarettes. Although initially designed as smoking cessation tools, only 19.3% of e-cigarette users are former cigarette smokers and nearly 50% are current smokers. E-cigarettes have surpassed cigarettes as the most common tobacco product used among high schoolers, which prompted a 2018 Surgeon General Advisory on e-cigarette use among youth.

Acknowledging these changes, oral health was one of the six priority areas identified by the Surgeon General, Vice Admiral Jerome M. Adams, M.D. Last year, he authorized the 2020 Surgeon General's Report on Oral Health, and asked NIDCR to take responsibility for the development of the report. Dr. Albino and Dr. Bruce Dye, NIDCR Director of the Health Informatics and Dental Public Health Fellowship, were named Project Co-Directors and Scientific Editors. The charge from the Surgeon General was to "describe and evaluate oral health and the interaction between oral health and general health throughout the lifespan, considering advances in science, health care integration, and social influences to articulate promising new directions for improving oral health and oral health equity across communities." The report will address the current state of the science, progress made since the 2000 report, the challenges that have emerged or persist since the last report, and promising new directions for research.

Dr. Albino described the process by which stakeholder input was solicited, such as listening sessions, webinars, and outreach to the Association of State and Territorial Dental Directors, with an emphasis on inclusivity. More than 400 individuals will have been involved in drafting the report. The 2020 report will consist of six sections:

- Effect of Oral Health on the Community, Overall Wellbeing, and the Economy
- Oral Health in Children and Adolescents
- Oral Health in Working-Age and Older Adults
- Oral Health Integration, Workforce, and Practice

- Substance Use Disorders, the Opioid Epidemic, High Risk Behaviors, and Mental Health
- Emerging Technologies and Promising Science to Transform Oral Health

The 2020 Surgeon General's report will be available by the fall. Dr. Albino expects the report to deliver findings that will impact population health, the economy, national security, health profession education, and public policy. The report will identify promising directions and strategies for research in oral health. It will also indicate productive approaches to achieving oral health equity for the diverse communities in America and others with special needs. Ultimately, the report will strive to provide a road map to optimal oral health for all.

Dr. Albino thanked NIDCR for their considerable support throughout this process.

VII. NIDCR Research Training Updates

Dr. Lynn Mertens King, Chief, Research Training & Career Development Branch, NIDCR, updated the Advisory Council on NIDCR's research training programs. NIDCR's objectives are to ensure a diverse and highly-trained pool of investigators and to support institutional and individual research training and career development awards across career stages. Dr. King emphasized the importance of diversity to NIDCR, and while it will not be the subject of the day's presentation, it will be the focus of ongoing evaluation and presentation to the Council in future meetings.

Dr. King presented a slide describing the career stages over which NIDCR provides training opportunities. NIDCR supported 352 trainees in FY2018, from grants for graduate and dental students to mid-career Independent Scientist Awards. The majority of the grants are focused on individual fellowships and institutional training grant awards for predoctoral students and postdocs. Individual fellowships are awarded to students and postdocs who apply for independent research training to support their graduate or postdoctoral research experience. Institutional awards are given to predoctoral and postdoctoral individuals selected by program directors with an institutional training grant. Both programs are grouped together as Ruth L. Kirschstein National Research Service Awards (NRSA). The individual training grants are classified under the T32 and T90 granting mechanisms, while the individual fellowships fall under the various F grant mechanisms. Dr. King briefly described the eligibility requirements, one of which, notably, is U.S. citizenship, and funding and length of support provided by the awards.

In 2008, NIDCR conducted an evaluation of the Institute's investment in NRSA training programs from 1995 to 2003. Dr. King highlighted two outcomes of note identified from that evaluation. The first is subsequent NIH grants received by NRSA awardees, specifically receiving an R01 award, which is seen as the hallmark of an independent investigator. The 2008 evaluation found that 5% of NRSA recipients over that timespan went on to receive an R01 or equivalent; 3.7% of T award trainees and 12.5% of F award fellows. The second outcome Dr. King highlighted was professional outcomes. Fifty-five percent of the dentist-scientist trainees over the period went on to full-time research or academic positions. As a result of the finding showing a gap between the trainees and fellows regarding future R01 achievement, NIDCR

instituted efforts to encourage the T awardees to transition into F award fellowships. NIDCR began participation in the F31 predoctoral fellowship award and created a T90/R90 award that supports non-citizen dentist postdoctoral training. NIDCR also began requiring dual degree T awardees to apply for a subsequent individual fellowship award during their tenure as a trainee.

These policy and program changes, and others, led to a nearly fourfold increase in the number of trainees applying for F individual fellowships from FY2008 to 2016. From FY2000 to 2007, there were 57 such applications; from FY2008 to 2016 that number rose to 217. The number of awardees rose apace, from 36 to 138. The award rate at NIDCR was 70%. In general, NIDCR has intentionally shifted investments away from T grants to F awards over the past eight years. Recent data has shown that F-supported individuals complete their postdoctoral degrees at a higher rate than T-supported individuals. Dr. King also presented data indicating that F awardees in recent years have higher success rates for subsequent Research Project Grants (RPGs) and R01s.

Dr. King discussed data from the T90/R90 program for non-citizen dentists. Since 2011, there have been 41 participants over 11 supported programs, 9 of which are active. In terms of outcomes, 33 participants have completed the training program; 15% of those achieved subsequent funding, 85% have remained in research or related activities, and 24% have returned to their country of origin. The outcomes are similar between the T90 and R90 cohorts.

In conclusion, the NIDRC Research Training and Career Development Branch will continue to assess and monitor outcomes of NIDCR research training programs to ensure they accomplish the Institute's research mission. NIDCR will also assess and promote diversity in the research training pipeline, including gender, race, ethnicity, and disability. The Institute will continue to strive to be inclusive at all career levels to foster a diverse research workforce.

VIII. Update on NIH Next Generation Researchers Initiative (NGRI)

Dr. Michael Lauer, NIH Deputy Director for Intramural Research, began his update with a quote from *Nature's* 2016 special issue on the difficulties young researchers experience in the medical research field. Young scientists felt like they are under enormous pressure to publish and secure funding, are working exceedingly long hours, and yet lack the freedom and wherewithal to pursue creative science. One of the root causes identified by this series of articles was the considerable increase in the number of applicants over the years competing for a pool of grants that had not seen a corresponding increase in number. In the United States, funding success rates for all age brackets at the time of the *Nature* issue were less than half what they were in the 1980s. As a result, early career researchers have had to spend more and more time seeking funding, leading to more conservative research.

Dr. Lauer presented NIH grant data to illustrate the hyper-competitive status of the medical research field. The number of applicants for NIH RPGs steadily increased from 2003 onward while the number of awardees stayed essentially flat. However, Dr. Lauer noted that the number of applicants seems to have plateaued since 2014 and the number of awards has increased since then as well. This increase can be attributed to improved budget circumstances and NIH's deliberate focus

on funding more Early-Stage Investigators (ESI). Other data have shown that the dropout rate for those investigators who do receive funding for the period of 2006 to 2010 increased in comparison to past cohorts. About 50% of first-time R01-funded investigators in the 2006-2010 period dropped out after approximately 6 years. These data highlight the “hard to break in, hard to stay in” nature of contemporary medical research.

To help address these issues, the 21st Century Cures Act, passed by Congress in 2016, calls on the Director of the NIH to “develop, modify, or prioritize policies, as needed ... to promote opportunities for new researchers and earlier research independence, such as policies to increase opportunities for new researchers to receive funding ... and enhance workforce diversity.” In response, NIH Director Francis Collins convened a Next Generation Researchers Initiative Working Group, under the Advisory Committee to the Director, to advise Dr. Collins on how best to address the situation. Over a year and half, the group met for 14 teleconference meetings and three in-person meetings. The group held collaborative briefings with its sister working group at the National Academy of Sciences and representatives from the Rescuing Biomedical Research organization.

The Working Group drafted five focus areas: modifying the original Next Generation Research Initiative policy, providing support for Early-Stage and At-Risk Investigators, creating training opportunities for diversity and inclusion, monitoring outcomes (including workforce stability), and engaging with scientists across career stages. Dr. Lauer pointed to several related topics of discussion that arose repeatedly during Working Group meetings: the definition of Early-Stage Investigator, whether to discontinue the “Early-Established Investigator” classification, how to support “at-risk” investigators, the possibility of increasing levels of postdoctoral support, the importance of mentoring and individual development plans within research grants, and how to manage access to confidential NIH administrative data. Dr. Lauer specifically noted the discussion regarding the possibility of ESI awards that do not require preliminary data, which would grant ESIs more flexibility in shifting their area of focus early in their career. As a result, NIH will be creating a new R01 grant in which no preliminary research data are allowed. This grant will be named in honor of the late Dr. Steven I. Katz, former Director of the National Institute on Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Dr. Lauer also briefly touched on efforts to increase diversity in NIH training programs. Institutional training programs are required to demonstrate successful efforts to recruit an outstanding and diverse trainee population, including students from underrepresented racial and ethnic groups and students with disabilities. The National Institute of General Medical Sciences (NIGMS) has released a Funding Opportunity Announcement to develop a recruitment plan to enhance diversity among underrepresented populations.

Dr. Lauer presented data on the number of Early-Stage Investigator awardees (R01 equivalents) since 1995. The data show a significant drop around 2013 but significant improvement since then, with the most recent numbers surpassing the previous high from 1995. NIH had specifically targeted funding 1,100 ESIs in 2018, which it ended up exceeding by a considerable amount. Dr. Lauer also presented a graph that showed a similar increase in funding rates over the past few years. The target for 2019 will again be to fund at least 1,100 ESIs. Other

focus areas will be on providing investigators flexibility for family planning or personal medical reasons or other interruptions, as well as ways to support meritorious at-risk investigators.

In discussion with the Advisory Council, Dr. Lauer touched on multi-PI grants, which have increased in recent years. About 30% of R01 applications are now multi-PI. The Council and Dr. Lauer also discussed the consequences of at-risk investigators dropping out, such as the repercussions on their trainees should the research not continue. Dr. Somerman asked whether NIH is seeing more ESI applications and whether there's a correlation between mentorship and increased applications. Dr. Lauer said the number of ESI applications has increased slightly. There are no data yet on the correlation between mentorship and application. The proportion of R01 awardees who had a mentored K award beforehand has increased, however. Dr. Somerman also asked how outcomes are being measured. Dr. Lauer said data are still sparse, but he discussed new ways of tracking researchers when they leave academia for other fields that are still research-related and should be measured. One example is the Institute for Research on Innovation and Science. Dr. Sheeley raised the topic of ESIs losing time by searching for funding and how that might be addressed. Dr. Lauer said the National Cancer Institute is experimenting with an R37 award for ESIs that funds individuals for 5 years but allows for two-year extension if the investigator shows sufficient progress. Dr. Messersmith asked for clarification on how at-risk investigators are determined to be meritorious. Dr. Lauer said that it is based on peer review score, which must be in the top 25th percentile, and a subsequent productivity review of the individual's work by program staff.

IX. Dissecting Neural Crest Stemness in Development and Disease

Dr. Matthew Hoffman, NIDCR Scientific Director, introduced Dr. Laura Kerosuo, Stadtman Tenure-Track Investigator, Neural Crest Development and Disease Unit, DIR, to present her recent research on neural crest development and disease. Dr. Kerosuo joined NIDCR in 2018 from the California Institute of Technology where she conducted postdoctoral work under Dr. Marianne Bronner. Dr. Kerosuo received her Ph.D. from the University of Helsinki.

Dr. Kerosuo began by discussing her background as a developmental biologist exploring the fundamental process of how a single fertilized egg can give rise to a complex organism such as a plant, insect, or animal. Her particular interest is in the development of the neural crest, which is an early stage in an organism's development process. In human development, neural crest development begins very early on, in the second and third week of gestation, before any organs have begun to develop and at the same time as the central nervous system. The neural crest forms from the embryo's ectodermal germ layer. Dr. Kerosuo presented a slide depicting the flat, sheet-like shape of the ectoderm, showing the neural plate, which will wrap around into the neural tube and ultimately become the central nervous system. The lateral parts of the image show the non-neuroectoderm, destined to become the skin system. In between is the neural plate border, from which the neural crest is formed. By the time the neural tube closes, the neural crest will be fully specified into pre-migratory neural crest cells. At this point, the neural crest cells are highly multipotent and go through epithelial-mesenchymal transition (EMT) in which they detach from the neuroectoderm and become mesenchymal cells and migrate to different parts of the body and transition into different cell types. The neural crest stem cells that arise at this juncture lose their stemness when they reach their target. However, where, how, and when this process

occurs remains poorly understood, primarily due to the brief period and rapidity in which it takes place.

Dr. Kerosuo noted that neural crest is very important for development of the head, giving rise to the craniofacial skeleton, parts of the eye, ear, and thymus, and teeth and salivary glands, among other organs. The neural crest also gives rise to the entire peripheral nervous system, as well as skin pigmentation, parts of the heart, and several endocrine tissues, among other portions of the human body. As such, while it is known that neural crest cells are stem cells, little is known about how their stemness is initiated, maintained and regulated, and how fate determination occurs.

The importance of understanding the stemness of neural crest cells is due to their large number of derivatives, which suggests neural crest cells hold great promise for regenerative medicine. With better understanding of the molecular basis of these early processes, one could produce in vitro missing tissue types for patients from their own cells using the induced pluripotent stem cell technique. Another implication relates to the fact that roughly 10 percent of birth defects are neural crest-derived, known as neurocristopathies, characterization and treatments for which might be advanced through neural cell research. In addition, there are significant neural crest-derived diseases, such as melanoma and endocrine tumors, which would also be impacted by advances in neural crest development research.

Dr. Kerosuo next described the techniques and methods her lab uses to study neural crest development. Their main in vivo model is the chicken embryo, which allows for more flexibility in targeted specific time periods in early stage embryo development. It also allows for sophisticated transient transgenics, such the injection of DNA or knockdown reagents on targeted portions of the embryo with a control portion on a different part of the embryo. The lab also utilizes human embryonic stem (ES) cell-derived neural crest cells, which allows the team to study the human molecular mechanisms that might underlie neural crest-derived diseases. The lab's culture conditions induce the ES cells to spontaneously produce neuroepithelial spheres, which mimic the developing neural tube in an embryo and then go through EMT and subsequent migration.

Dr. Kerosuo discussed the discovery of a neural crest stem cell niche from her postdoctoral career. Results from chromogenic in situ hybridization show uniform expression of known neural crest marker genes. The assumption is that all of these markers are expressed in the same cells in the premigratory crest. Dr. Kerosuo's previous work led her to question this assumption and she asked whether there was, in fact, heterogeneity in premigratory neural crest. In partnership with Dr. Long Cai at Caltech, the research team utilized an adaptation of multiplex single molecule fluorescent in situ hybridization (smFISH) to see if they could identify transcriptionally distinct subpopulations in vivo and whether those subpopulations, if identified, could be linked with spatial coordinates. This adapted smFISH technique was named Spatial Genomic Analysis (SGA). In order to identify which transcripts belong to which cell, the team developed a machine learning algorithm-based imaging analysis tool. Dr. Kerosuo searched for neural crest genes, pluripotency factors, lineage markers, and function genes. She presented a slide to the Council showing a heat map displaying the results of the study, which indicated hierarchical clustering that revealed subpopulations. Notably, the stem cell populations expressed

both pluripotency and differentiation markers. The team was then able to conduct a spatial analysis to identify where each of the subpopulations were located in the embryo. This analysis found that the subpopulations do have distinct spatial localization, and that the neural crest stem cell niche is located around the midline. Another notable finding was the presence of differentiation markers at this early stage of development.

Dr. Kerosuo's recent research has been focused on studying how this neural crest niche is formed in the premigratory dorsal neural tube, how it is regulated, and how and when does it disappear. Her team has identified two possibilities, based on previous research, for how the pluripotent niche is formed: either it is preserved from pre-gastrula phases when the embryo has yet to determine any fates, or the pluripotency factors are reprogrammed on the neural crest cells after gastrulation in the neural plate border. To begin studying these questions, Dr. Kerosuo and her team began by looking at a developmental stage four hours earlier than the stage used in their other studies. The SGA heat map this time showed two subpopulations instead of four, committed cells and stem cells. The committed cell populations do not overlap and their spatial organization in the midbrain cross-section largely reflects the traditional understanding of the location of neural crest cells, neural cells, and placodal cells. The heat map of the stem cells contains a large number of cells that express all 35 genes that were tested for and that Dr. Kerosuo classified as highly pluripotent. The rest of the cells were gathered into populations that seemed to be leaning to a certain fate but had not yet made a decision. For example, the 'leaning neural crest' cells had a largest expression of neural crest cells but could still become neural cells because they express a lot of neural markers. However, it is highly unlikely they will become placodes since that expression pattern has already downregulated. The spatial representation of these markers shows much more overlap than was seen in the committed cells spatial analysis.

In conclusion, these SGA studies revealed transcriptionally distinct subpopulations in a spatial context and led to the discovery of a pluripotent premigratory neural crest stem cell niche. The study of an earlier stage showed that developing neural folds consist of a pan-ectodermal stem cell population together with more committed populations. Continued research into other stages at earlier and later points in the developmental process will likely complement this picture.

Finally, Dr. Kerosuo discussed her work on human ES cell-derived neural crest model to confirm her work with the chicken embryos and to confirm whether the pluripotency reaches the protein level. Her lab has been able to show that premigratory neuroepithelial spheres express high amounts of neural crest cells by using the Sox10 marker gene marker, with patches of Nanog/Sox10 double positive cells, suggesting that there might be a human equivalent of the stem cell niche. Her lab has also been working to knockdown the Nanog transcriptional factor in the chicken embryos to look at functional analyses. As expected, loss of Nanog disturbs neural crest specification in vivo. Preliminary observations suggest that the human in vitro neural crest develops similarly to what was seen in the chicken embryo. Dr. Kerosuo believes her lab has the required tools to continue this research avenue and continue to explore the molecular mechanism behind neural crest stem cell formation.

Dr. Kerosuo concluded by acknowledging the work of her colleagues in her lab, Andrew Schiffmacher, Ceren Pajanoja, Jenny Hsin, and Camilo Echeverria, and her other collaborators and mentors.

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

X. ADJOURNMENT

CERTIFICATION

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



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

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

ATTACHMENTS

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