

National Institute of Dental and Craniofacial Research

National Advisory Dental and
Craniofacial Research Council

Minutes of Meeting
May 25, 2018

Building 31
Conference Room 10
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 25, 2018

The 218th meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on May 25, 2018, at 8:00 a.m., in Building 31, Conference Room 10, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public from 8:00 a.m. until 12:23 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 1:55 p.m. Dr. Martha Somerman presided as Chair.

OPEN SESSION

Members Present

Dr. Shenda M. Baker
Dr. Yang Chai
Dr. Richard Peters Darveau
Dr. Nisha J. D'Silva
Ms. Tracy Hart
Dr. Daniel Malamud
Dr. Daniel W. McNeil
Dr. Phillip B. Messersmith
Dr. Sanjay Shete

Ad Hoc Members

Dr. Kathryn Marie Albers
Dr. David J. Couper
Dr. Clark M. Stanford
Dr. Joel L. Strom

Members of the Public

Dr. Marcelo W. B. Araujo, Vice President, Science Institute, American Dental Association (ADA), Washington, D.C.
Dr. Robert Burns, Manager, Legislative and Regulatory Policy, ADA, Washington, D.C.
Mr. Omar Contreras, Director of Policy Research, Office of Policy, Research, and Diversity, American Dental Education Association (ADEA), Washington, D.C.
Dr. Brian Cook, Senior Vice President for Educational Research and Analysis, Office of Policy, Research, and Diversity, ADEA, Washington, D.C.
Ms. Kacie Crowell, Intern, ADEA/Sunstar Americas, Inc./Harry W. Bruce, Jr. Legislative Internship, ADEA, Washington, D.C.

Dr. Christopher Fox, Executive Director, International Association of Dental Research (IADR)/
American Association of Dental Research (AADR), Alexandria, VA
Dr. Raul Garcia, Immediate Past President, IADR/AADR, Alexandria, VA
Mr. B. Timothy Leeth, Chief Advocacy Officer, Advocacy and Government Relations, ADEA,
Washington, D.C.
Mr. Matthew Makara, Director of Research, Sjögren's Syndrome Foundation, Reston, VA
Dr. Bruce L. Pilstrom, Associate Editor for Research, *Journal of the American Dental
Association*, Bethesda, MD
Dr. Denice Stewart, Chief Policy Officer, Office of Policy, Research, and Diversity, ADEA,
Washington, D.C.
Dr. Jeffrey Stewart, Senior Vice President for Educational Leadership and Innovation, Learning,
ADEA, Washington, D.C.
Ms. Christina McWilson Thomas, Director for Government Affairs, Advocacy and Government
Relations, ADEA, Washington, D.C.

National Institute of Dental and Craniofacial Research

Dr. Martha J. Somerman, Director
Dr. Alicia Dombroski, Executive Secretary, and Director, Division of Extramural Activities
(DEA)
Dr. Douglas M. Sheeley, Deputy Director
Dr. Lillian Shum, Director, Division of Extramural Research (DER)
Dr. Robert Angerer, Scientific Director, Division of Intramural Research (DIR)
Dr. Matthew P. Hoffman, Deputy Scientific Director, DIR
Dr. Nisan Bhattacharya, DEA, Scientific Review Branch (SRB)
Ms. Karina Boehm, Office of the Director (OD), Office of Communications and Health
Education (OCHE)
Dr. Latarsha Carithers, DEA, SRB
Dr. Preethi Chander, DER, Integrative Biology and Infectious Diseases Branch (IBIDB)
Dr. Jay Chiorini, DIR, Adeno-Associated Virus Biology Section
Dr. Lois K. Cohen, Consultant
Ms. Vicki Contie, OD, OCHE, Science Communication and Digital Outreach Branch (SCDOB)
Ms. Michelle Cortes, DER IBIDB
Ms. Mary Cutting, DER, Center for Clinical Research (CCR)
Ms. Mary Daum, OD, OCHE, Health Information and Public Liaison Branch (HIPLB)
Mr. Bret Dean, OD, Office of Administrative Management (OAM), Financial Management
Branch (FMB)
Mr. Jimmy Do, OAM, FMB
Dr. Olga Epifano, DEA
Dr. Catherine Evans, OD, OCHE, SCDOB
Dr. Dena Fischer, DER, CCR
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)
Ms. Jeannine Helm, DER
Mr. Gabriel Hidalgo, DEA, GMB

Dr. Lynn Mertens King, DEA, Research Training and Career Development Branch (RTCDB)
Dr. Wendy Knosp, OD, Office of Science Policy and Analysis (OSPA)
Ms. Iman Lee, DEA, SRB
Dr. Janice S. Lee, DIR, Office of the Clinical Director (OCD)
Ms. Carol Loose, OAM, FMB
Mr. Orlando Lopez, DER, IBIDB
Dr. Nadya Lumelsky, DER, IBIDB
Dr. R. Dwayne Lunsford, DER, IBIDB
Dr. Kevin McBryde, DER
Ms. Susan Medve, DEA, GMB
Mr. Paul Newgen, DEA, GMB
Ms. Anna Nicholson, OD, Office of Clinical Trials Operations and Management (OCTOM)
Dr. Morgan O'Hayre, OD
Ms. Lisa Peng, OD, Office of Information Technology (OIT)
Mrs. Debbie Pettitt, DEA, GMB
Mr. John Prue, OD, OIT
Dr. Melissa Riddle, DER, Behavioral and Social Sciences Research Branch (BSSRB)
Ms. Delores Robinson, DEA
Mrs. Diana Rutberg, DEA, GMB
Dr. Yasaman Shirazi, DEA, SRB
Dr. Kathryn Stein, DER, Translational Genomics Research Branch (TGRB)
Ms. Kathleen Stephan, OD
Mr. Brian Sullivan, OD, OIT
Mr. Joseph Tiano, OD, OSPA
Dr. Yolanda Vallejo-Estrada, DER, IBIDB
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
Ms. Dolores Wells, OD, OSPA, Science Policy and Planning Branch (SPPB)
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. Martin Chiang, Project Leader, Biomaterials for Oral Health, VRC, NIST, DoC,
Gaithersburg, MD
Rear Admiral Bruce A. Doll, Assistant Vice President for Technological Research and
Innovation, Uniformed Services University for the Health Sciences, Bethesda, MD
Dr. Thomas Hart, Senior Director, VRC, NIST, DoC, Gaithersburg, MD
Dr. Roland Owens, Associate Director, Research Workforce Development, Office of Intramural
Research, NIH

Dr. Rochelle Rollins, Senior Policy Advisor, Office of the Surgeon General, Office of the Assistant Secretary for Health, and Member, Oral Health Coordinating Committee, Health Resources and Services Administration, U.S. Department of Health and Human Services, Rockville, MD

I. WELCOME AND INTRODUCTIONS

Dr. Martha Somerman, Director, NIDCR, called the open session of the 218th meeting of the Council to order. She thanked the Council members and staff for their efforts during a very active past few months. She introduced four ad hoc members who attended the meeting and will join the Council when their appointments are official. These are Dr. Kathryn Marie Albers of the University of Pittsburgh, Dr. David J. Couper of the University of North Carolina at Chapel Hill, 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.

Dr. Somerman invited guests to introduce themselves. She then asked staff to introduce new personnel. Ms. Kathleen Stephan, Associate Director for Management, introduced Mr. Jimmy Do, NIDCR's new budget officer and chief of the Financial Management Branch (FMB), Office of Administrative Management (OAM). Dr. Yasaman Shirazi, Chief, Scientific Review Branch (SRB), Division of Extramural Activities (DEA), introduced Ms. Iman Lee, a student intern in the NIH Pathways Program, who is assisting the SRB.

Dr. Alicia Dombroski, Executive Secretary, NADCRC, and Director, DEA, welcomed the Council and guests, including those participating via the NIH videocast (<http://videocast.nih.gov>).

II. FUTURE MEETING DATES

September 13, 2018
January 23, 2019
May 23, 2019
September 13, 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 January 31, 2018, Council meeting. The Council unanimously approved the minutes.

IV. REPORT OF THE DIRECTOR, NIDCR

Dr. Somerman reported on the NIDCR budget, programs, and activities and presented an update on NIH activities. Dr. Somerman's written Director's Report to the Council: May 2018 was provided to the Council members and is available at (<http://www.nidcr.nih.gov>).

NIDCR Budget

In FY 2018, the overall NIH budget increased 8.8 percent (to \$37.1 billion), and most institute and center (IC) budgets, including the NIDCR budget, increased about 5 percent. The total NIDCR appropriation for FY 2018 is \$447.7 million. Dr. Somerman thanked NIDCR Council members and research advisors for their efforts to sustain a positive funding trend over the past 3 years. She noted that the NIDCR continues to allocate most of its funding to extramural programs in support of research project grants (RPGs) and collaborative science. In FY 2017, the NIDCR budget was distributed as follows: 63 percent for RPGs, 1 percent for research centers, 16 percent for intramural research (basic operations and taps), and the remaining to research training and career development, research contracts, and other research, along with 6 percent for research management support.

NIDCR Extramural and Intramural Programs

Dr. Somerman reported that approximately 80 percent of the NIDCR budget supports extramural research and training at some 230 universities, hospitals, and research institutions, including dental schools, in 40 states. The NIDCR provides funding for approximately 6,500 oral health researchers and, each year, receives about 1,300 competing applications and funds more than 250 new awards.

Dr. Somerman said the 16 percent of the NIDCR budget allocated to intramural research supports more than 350 staff, trainees, and volunteers conducting research and training across the research spectrum. The program is highly collaborative and focused on five areas: craniofacial developmental, cell, and matrix biology; epithelial and salivary gland biology and dysfunction; immunology and inflammation; sensory biology; and skeletal biology. It includes more than 20 active trials at the NIH Clinical Center, collaboration with other ICs, and approximately 3,600 outpatient visits at the NIH Dental Clinic each year.

Dr. Somerman highlighted NIDCR's broad support for research training on the NIH campus. This intramural effort, which is led by Dr. Deborah Philp, director of intramural training, Office of Education, Scientific Director's Office, includes programs for high school, college, and predoctoral students and postdoctoral fellows. Opportunities are available through the NIH Summer Internship Program, two programs for dental or dual-degree students (the Summer Dental Student Award, and the 1-year Medical Research Scholars Program), and four training programs for dentist scientists (Individual Fellowships, Dental Clinical Research Fellowship, a new D.P.H. Bioinformatics Residency program, and Career Transition Awards). To enhance diversity in dental, oral, and craniofacial research, the NIDCR initiated the NIDCR Director's Postdoctoral Fellowship, which supports fully funded fellowships for up to 5 years in the intramural program for up to three fellows per year.

Dr. Somerman reported a change in the long-standing NIDCR Dental Public Health Residency Program. This program has supported 1-year training to prepare dentists to be board certified in dental public health and, in 2016, was expanded to include a 2nd year option to train dentists in oral informatics in partnership with the National Library of Medicine. In 2017, the NIDCR conducted an external review of the alignment of the residency program with the NIDCR mission and, based on the findings, is closing the 1-year dental public health component and will focus the 2-year program on advancing oral informatics.

NIDCR Activities

NIDCR 2030 Timeline. Dr. Somerman noted that approximately 1 year ago, the NIDCR launched NIDCR 2030: Envisioning the Future, Together. After much input and review, this vision for the future embraces five areas: oral health + overall health, precision health, autotherapies, oral biodevices, and workforce diversity. Dr. Somerman said the NIDCR will continue, via the NIDCR IdeaScale (<https://nidcr2030.ideascale.com/>), to seek input on new programs in development. She noted that in January 2018, the NIDCR hosted a well-received autotherapies symposium and workshop and sought Council's review of a proposed research initiative on oral biodevices, on which public feedback was gathered during January and February. The NIDCR plans to focus in the near future on other research areas to advance (integrated care and research, mechanisms of pain, oral microbiome and immunity, health disparities, oral cancer treatment targets, and rare diseases) and two aspects of workforce diversity (a mentoring network and an intramural program of workforce diversity). Dr. Somerman noted that separate development of the next phase of the NIDCR Strategic Plan, to be released in 2020, is contributing helpful insights for NIDCR 2030.

Patient Advocacy Organizations. On February 26, 2018, nine representatives from the Friends of NIDCR Patient Advocacy Council met with NIDCR staff and representatives from the American Dental Education Association (ADEA) and the American Dental Association (ADA) to foster an ongoing conversation on patient needs and research advances, gaps, and opportunities. Additional meetings and discussions are expected to take place.

American Association of Dental Research (AADR) Annual Meeting. NIDCR staff participated in the 2018 AADR meeting. NIDCR-hosted activities included the National Dental Practice-Based Research Symposium and Workshop, which had more than 200 attendees, including dental school deans; a mentoring lunch; and a Regenerative Medicine (DOCTR-C) Symposium. Staff met with investigators and trainees at the NIDCR Booth, presented posters and led symposia, and participated in the Institutional Section and Research Deans' Meeting. Dr. Somerman urged Council members to encourage junior faculty to attend this annual event and other meetings to connect with NIDCR staff and help advance research.

USA Science and Engineering Festival. On April 6–8, 2018, in Washington, D.C., NIDCR staff participated once again in this annual festival to inform young people about oral health in a fun, interactive, and informative setting. The NIDCR focus this year was Bacteria, Brushing, and Biosensors; the participants learned about biosensors to measure bacteria and how brushing helps remove bacteria.

Surgeon General's Report on Oral Health. Dr. Somerman reported that Surgeon General Dr. Jerome Adams visited the NIH to meet with IC directors and is considering development of a 2020 report on the oral health of the nation. The last report, *Oral Health in America: A Report of the Surgeon General*, was issued in 2000. Staff from the NIDCR and Surgeon General's office are meeting to speed this effort forward.

NIH Updates

Trans-NIH Activities. Dr. Somerman noted that many trans-NIH activities are under way. Within the NIH Common Fund, the NIDCR continues to be a leader in the Human Microbiome Project and is the co-lead (with the National Institute of General Medical Sciences) on the Glycoscience Program. She encouraged the dental research community to participate more in Common Fund programs. Among other trans-NIH activities in which the NIDCR is participating are several pain-related research groups (the NIH Blueprint for Neuroscience Research, NIH Pain Consortium, Interagency Pain Research Coordinating Committee); collaborations with the Office of Research on Women's Health, Office of AIDS Research, and Office of Scientific Workforce Diversity; and committees such that guiding the Regenerative Medicine Innovation Project, which is supported by 21st Century Cures funding.

NIH Opioids Update. The NIDCR is participating in the NIH Helping to End Addiction Long-term (HEAL) Initiative, which aims to bolster research across NIH to prevent addiction through enhanced pain management and to improve treatments for opioid misuse disorder and addiction. Dr. Somerman noted that the NIH is nearly doubling its research funding on opioid misuse/addiction and pain, from approximately \$600 million in FY 2016 to \$1.1 billion in FY 2018. She encouraged the dental community to be proactive in staying attuned and responding to NIH Funding Opportunity Announcements (FOAs), and she encouraged Council members to inform their institutions and communities as new opportunities arise. She noted that the 2018 NIH Pain Consortium Symposium, to be held May 31–June 1, will be live-streamed via the NIH videocast.

Dr. Somerman noted that staff of the NIH, NIDCR, and ADA met recently to discuss ADA's new policy on opioids and potential opportunities for collaboration. The meeting was organized by Dr. Nora Volkow, Director, National Institute on Drug Abuse, and was attended by Dr. Larry Tabak, Principal Deputy Director, NIH; Dr. Somerman; Dr. Joseph Crowley, ADA President, and Dr. Kathleen O'Loughlin, ADA Executive Director. Dr. Volkow praised dentistry and the ADA for their leadership in the NIH opioid initiative.

All of Us. Dr. Somerman reported that the NIH *All of Us* Research Program was launched on May 6, 2018. The long-term vision is to enroll a national cohort of more than 1 million volunteer partners as participants in an effort to accelerate research and improve health through precision medicine, by mapping and analyzing their genomics, environment, nutrition, lifestyle, behaviors, etc.

Dr. Somerman noted that one of her main goals is to enhance communication between research, clinical practice, and education by facilitating communication among practitioners, communities, and researchers. She emphasized that if communication is lacking and data are not

being shared, “it’s not working.” She encouraged everyone to stay connected with the NIDCR through www.nidcr.nih.gov.

In closing, Dr. Somerman thanked two NIDCR leaders who left or are leaving the NIDCR. Ms. Carol Loose, former Chief, Financial Management Branch, left the NIDCR after almost 40 years of Federal service and approximately 17 years at the NIDCR. Dr. Robert Angerer, Scientific Director, NIDCR, is leaving the NIDCR for new ventures after almost 14 years at the NIDCR.

V. 2018 ADVISORY COUNCIL REPORT CERTIFYING COMPLIANCE WITH NIH INCLUSION GUIDELINES

Dr. Dombroski noted that the Council is required to report on NIDCR’s implementation of the NIH policy on inclusion of women and minorities in clinical research and to vote on acceptance of the report by all Council members. Dr. Dena Fischer, Acting Director, Center for Clinical Research (CCR), DER, summarized the report prepared by staff, which is entitled “2018 Advisory Council Report Certifying Compliance with the NIH Policy on Inclusion Guidelines” and was provided to all Council members.

Dr. Fischer stated that each NIH IC is required by the NIH Revitalization Act of 1993 and, subsequently, the 21st Century Cures Act (passed in December 2016), to prepare a report for its advisory council describing the IC’s activities in complying with the requirement for inclusion of women and minorities in NIH-funded clinical research. She noted that the 21st Century Cures Act amended the reporting requirements to include the results of valid analyses of Phase III clinical trials and data on the age of participants. In addition, it amended the reporting requirement, which was initially biennial, to triennial reports, which will begin in 2019 and will include data from FY 2016, FY 2017, and FY 2018. Dr. Fischer noted that the last biennial report prepared for the Council (January 2015) certified inclusion data for FY 2013 and FY 2014.

The present report (May 2018) certifies data for FY 2015 and FY 2016. The NIDCR utilized the NIH Inclusion Management System (IMS) to obtain inclusion data entered by principal investigators (PIs) and submitted to NIH by grantee institutions. Dr. Fischer stated that on June 9, 2018, the IMS system will be replaced by a new Human Subjects System (HSS) which will integrate data entered on grant applications and Research Progress Performance Reports (RPPRs). Investigators’ progress reports that are completed before June 9 will be migrated into the new system, and those that are not completed before June 9 can be completed and submitted after that date.

Dr. Fischer summarized the data in the May 2018 report as follows. In FY 2015, 88 extramural applications involving human subjects were awarded and 87 of them met the inclusion requirements at the time of review; in FY 2016, 64 extramural awards involving human subjects were made, and 63 met the inclusion requirements at the time of review. The number of enrolled subjects in extramural and intramural NIH-defined clinical research was 41,183 (in 91 studies) in FY 2015 and 65,215 (in 119 studies) in FY 2016. Dr. Fischer noted that the data on sex/gender, ethnicity, and race of subjects are self-reported and are similar for FY 2015 and FY

2016. For the respective years, female enrollment was 51.9 percent and 54.2 percent, male enrollment was 45.7 percent and 43.7 percent, and unknown sex/gender was 2.4 percent and 2.1 percent. Hispanic or Latino ethnicity was 13.1 percent and 12.1 percent, not Hispanic or Latino was 82.9 percent and 84.3 percent, and unknown or not-reported ethnicity was 3.9 percent and 3.7 percent. Whites comprised 63.1 percent and 65.0 percent of enrollees, black/African Americans 14.7 percent and 15.6 percent, Asians 10.2 and 9.1 percent, American Indian/Alaska Natives 0.5 percent and 0.5 percent, and Hawaiian/Pacific Islanders 0.1 percent and 0.1 percent. Those reporting more than one race were 6.3 percent and 4.3 percent, and those of unknown race were 5.1 percent and 5.5 percent.

The data on extramural and intramural Phase III trials show that 553 subjects were enrolled in three trials in FY 2015 and 1,634 subjects were enrolled in five trials in FY 2016. The majority of subjects were female: 60.2 percent in FY 2015 and 67.3 percent in FY 2016. For the respective years, data on race and ethnicity indicate that whites comprised 88.1 percent and 65.1 percent of enrollees, black/African Americans 1.8 percent and 22.5 percent, and those of unknown race 2.0 percent and 5.5 percent; Hispanic or Latino ethnicity was 0.0 percent and 12.7 percent, and unknown or not-reported ethnicity was 90.6 percent and 33.4 percent. Dr. Fischer emphasized that the FY 2015 data were skewed by one Phase III trial in which most (500) of the subjects, who were recruited from the United Kingdom, Scandinavia, and Brazil, self-identified as white or of unknown ethnicity.

Following a brief discussion, the Council unanimously approved and accepted the 2018 Advisory Council Report Certifying Compliance with the NIH Policy on Inclusion Guidelines.

VI. 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 five concepts, summarized below, and designated Council members led the discussion of each concept.

Clinical Research Operations Management and Support (CROMS)

Ms. Anna Nicholson, Director, Office of Clinical Trials Operations and Management (OCTOM), Office of the Director (OD), presented a proposed concept to continue to fund a comprehensive operations and management support contract for NIDCR-funded intramural and extramural clinical research studies. She noted that the CROMS contractor provides both adjunct expertise and resources not available at the NIDCR and a centralized and standardized approach to clinical management and oversight for these projects. Major activities supported by the current contract include preparation and review of clinical study documents, data and safety monitoring, clinical site monitoring, development and support of information systems, tracking of

safety and problem events, and training. Additional activities may include systems enhancement and development, more robust regulatory support, and tailored, study-specific training.

The Council's lead discussants, Dr. Daniel Malamud, Dr. David Couper, and Ms. Tracy Hart, strongly supported the concept. Dr. Malamud suggested that new and less experienced clinical research investigators would benefit from this support contract. Dr. Couper commented on the importance of standardization in clinical research and suggested that investigators would find it useful to be able to communicate with NIDCR or CROMS concerning the research support they need. Ms. Hart said that having well-designed clinical studies with standardization and oversight is important for patients and patient advocacy groups.

The Council unanimously approved the concept.

The Role of Dentistry in the Prevention of Opioid Drug Misuse and Abuse

Dr. Dena Fischer, Acting Director, CCR, DER, presented a proposed concept to establish effective interventions or programs to manage, reduce, or prevent opioid drug misuse or abuse and to align the opioid-prescribing practices of dental providers with scientific evidence. She noted that the opioid crisis is of high importance to the NIH. In 2016, drug overdose was the leading cause of accidental death in the United States and accounted more than 63,000 deaths, of which two-thirds involved an opioid. Recent findings indicate that short-term opioid exposure in opioid-naïve patients is associated with long-term opioid use. In 2009, dentists prescribed 8.0 percent of the opioid analgesics dispensed by outpatient U.S. retail pharmacies and were the highest prescriber group for patients ages 10–19 years old.

Dr. Fischer said the aim of NIH's HEAL initiative, mentioned earlier by Dr. Somerman, is to speed scientific solutions to stem the national public health opioid crisis. She noted that the Centers for Disease Control and Prevention (CDC) and the ADA and ADEA have offered guidance relative to their missions. The *CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016* provides recommendations for acute pain management; the ADA issued in March an *Interim Board Policy on Opioid Prescribing*; and the ADEA issued a *Policy Brief on the Role of Dental Education in the Prevention of Opioid Misuse*. The latter two documents support prescribing opioids consistent with evidence-based recommendations, dentists registering with and utilizing prescription drug monitoring programs, educating dental providers to screen and refer patients for substance misuse/abuse, and managing substance use disorders as a chronic disease.

Dr. Fischer emphasized that the NIDCR and dental research community have an opportunity to be at the forefront of and play a specific role in stemming the crisis. Examples of potential research topics that could be supported under the proposed concept include determining the efficacy, adverse events, and optimal medication course of different classes of analgesics to manage acute pain; implementing clinical decision support systems to modify dental providers' opioid prescribing toward evidence-based recommendations for pain management; and designing and implementing screening for opioid use disorder in dental care settings. Additional examples include optimizing risk-mitigation clinical tools prior to prescribing opioids for pain management

and exploring expectations of dental providers and patients to better manage the acute post-procedure pain experience.

The Council's lead discussants, Dr. Nisha D'Silva, Dr. Daniel McNeil, and Dr. Joel Strom, strongly supported the concept. They remarked that the concept is well-articulated, has unique aspects, and is very important, promising, and timely. Dr. D'Silva reported additional data on mortality and economic burden associated with opioid misuse/abuse and noted that the statistics are alarming. She expanded on the role of dentistry and states' mandatory prescription drug monitoring programs, and she emphasized the availability of alternative, non-opioid pain treatments and the need to align prescription of opioids with evidence on safe, effective, and optimal treatments and on screening for potential opioid use disorder (OUD). Dr. McNeil noted that his home state (West Virginia) has the highest incidence of OUD in the country and that efforts are also needed to prevent OUD and to help practitioners relate effectively to and manage their patients in pain. He suggested having young researchers and professionals in the field to facilitate these efforts. Dr. McNeil noted that NIDCR leadership and interaction with others in this arena are essential and imperative. Dr. Strom raised a concern about the lack of time in clinicians' practices to answer surveys and questions about patients' behaviors. He noted that public-private partners and software developers could be engaged to support the research and acquisition of evidence-based information.

In discussion, Council members noted the overuse of antibiotics as another drug epidemic that needs to be "tagged" for dental practitioners and the need for more research and tailoring of appropriate, evidence-based treatment for chronic pain conditions.

The Council unanimously approved the concept.

Advancing Practice-Based Digital Dentistry

Dr. Orlando Lopez, Director, Dental Materials and Biomaterials Program, Integrative Biology and Infectious Diseases Branch (IBIDB), DER, presented a proposed concept, entitled "Advancing Imaging, Device Production, and Clinical Capabilities in Digital Dentistry," to foster use of digital tools to enable and enhance delivery of dental health care for diagnosis and treatment of patients. The goals are (i) to advance essential core technologies and patient-centered solutions in digital dentistry to enable more efficient and safe oral health care delivery, and (ii) to improve clinical decision-making and treatment outcomes by advancing digital imaging, incorporating expert software systems, and enhancing current and developing new capabilities for production, design, and manufacturing of high-performance materials.

Dr. Lopez noted that the concept targets key research gaps and opportunities. It would address the need to meet the growing demand on practice-based productivity without compromising quality care and to develop and clinically implement advanced imaging technologies for diagnosis of oral diseases and conditions. Integration of advanced imaging, surgical expert systems, and computer-aided manufacturing could improve treatment outcomes, and 3D printing and high-performance materials could be optimized into the digital dentistry workflow to complement existing capabilities.

For the proposed concept, specific areas of research interest include, but are not limited to, the following: development of smart expert systems for treatment planning that account for tissue biomechanics and material properties; development of dynamic surgical guidance for real-time tracking, multimodal image fusion and navigation; and development and clinical implementation of multimodal diagnostic imaging and dedicated image processing tools. The areas also include implementation of advanced image processing and artificial intelligence to support clinical decision-making; validation of optimized 3D printing solutions and high-performance materials for digital dentistry; and development of digital impressions that penetrate gingiva non-invasively without fluid effects.

The Council's lead discussants, Dr. Shenda Baker, Dr. Phillip Messersmith, and Dr. Clark Stanford, said the proposed concept meets a real need and is very exciting. Dr. Baker highlighted the needs for practice- and data-based information for machine learning and for translation and optimization of software to support the developments. Dr. Messersmith commented that while 3D technology and printers are readily available, 3D production of advanced dental materials, such as ceramics, alloys, and composites, is very difficult or impossible and much research on materials is needed. Dr. Stanford cautioned that the United States is falling behind competition from China, as well as other Asian-Pacific countries, where fully machine-based robots are being used for placement of implants. He noted that the machine-based dental industry is moving forward rapidly, and he agreed that research on materials is very important and includes, for example, materials that can age with a patient. He encouraged the NIDCR to be prescriptive and targeted in the research supported and to attract industry participation through its Small Business Innovation Research and Small Business Technology Transfer award programs.

In discussion, Dr. Marcelo W. B. Araujo of the ADA urged the NIDCR to be cognizant of the competition outside the United States and the need for standardization and validation in e-commerce.

The Council unanimously approved the concept.

Pharmacogenomics and Pharmacomicrobiomics of Pain Management across Pain States

Dr. Yolanda F. Vallejo, Director, Neuroscience of Orofacial Pain and Temporomandibular Disorders Program, IBIDB, DER, presented a proposed concept to catalyze the pain research community to explore new pharmacogenomics and pharmacomicrobiomic studies. Emphasis would be given to determining (i) the genetic basis of variability in therapeutic drug responses, adverse events, and vulnerability to OUD in individuals with painful conditions, and (ii) how compositional and functional variations of the microbiome influence delivery, disposition, and co-metabolism of drugs.

Dr. Vallejo noted that there is great variability in how individual patients cope with pain, respond to therapeutic interventions, and are vulnerable to OUD. Studies suggest that in addition to genetic elements, microbiota play an important role and may influence the efficacy and toxicity of a broad range of drugs. Yet, little is known about the diverse and complicated interactions among the microbiome, drugs, and human host that mediate pharmacotherapy

outcomes for individuals. There is need for both precision medicine approaches to pain treatment and OUD and recognition that the genetic basis of variability is complex and multifactorial.

For the proposed concept, specific areas of interest include identification of genetic predictors of therapeutic response and poor outcomes and development of novel pharmacologic and/or pharmamicrobiomic analytical genomic methods. Also included are studies of the pharmacogenomics and/or pharmacomicrobiomics of pain treatment in special populations; genomic variability influencing behaviors, such as somatization, anxiety, self-awareness, and others, that may directly affect therapeutic responses; drug-microbial gene, drug-microbe, and drug-microbiome interactions and their correlation with drug-human interactions; role of microbiota in delivery, disposition, and co-metabolism of drugs; and microbiome, drug, and human host interactions, which would include the influence of sex/gender, race/ethnicity, and diet on these interactions.

The Council's lead discussants, Dr. Sanjay Shete, Dr. Kathryn Albers, and Dr. Richard Darveau, were very enthusiastic and strongly supported the concept. Dr. Shete noted that interaction of the microbiome with therapeutic interventions is a new field of research that holds promise for improving treatments and that little is known about patients' variability in relation to pain and OUD management and outcomes. Dr. Albers noted that study of the interactions among the human genome, microbiome, and nervous and immune systems in relation to diet, environment, sex/gender, etc., and in comparison with animal studies, is needed to understand pain as a systemic disease. Dr. Darveau agreed and noted the need to connect pain-microbiome studies with treatment and to use germ-free mice for animal studies.

The Council unanimously approved the concept.

TMD: Identifying Pathways Involved in Chronic Pain and Endogenous Resolution

Dr. Vallejo also presented a proposed concept focused on temporomandibular disorders (TMD). The goals of this initiative are to (i) catalyze multidisciplinary research addressing central and peripheral plasticity mechanisms that promote chronic TMD and its endogenous resolution, (ii) delineate brain changes in humans and animal models that can be correlated with molecular changes in animal and human craniofacial tissue, and (iii) evaluate TMD animal models to identify those that best recapitulate human pathophysiology for preclinical studies. Dr. Vallejo noted that precision medicine approaches for pain management in TMD will necessitate determination of the mechanisms that sustain or promote resolution of chronic TMD pain and elucidation of strategies to intrinsically and extrinsically modulate these mechanisms. She further noted that technological advances and resources have been developed through several recent NIH initiatives and are available to researchers to help enable significant advances.

Specific areas of interest to be supported under the proposed concept include (i) neuroimaging studies that will elucidate underlying mechanisms that mediate maladaptive and/or adaptive plasticity changes in modulatory circuits that either promote chronic TMD pain or facilitate endogenous resolution; (ii) adapting/utilizing new technologies to assess brain-wide connectivity changes in TMD animal models that can parallel human imaging studies; (iii) developing new lines of research that leverage the availability of human tissue banks with

advancing technology; (iv) elucidating interactions of the skeletal, muscular, cartilage, nervous, immune, and circulatory systems in TMD; (v) developing strategies to address sex-based differences and influences; and (vi) delineating peripheral immune and central neuroimmune functional and/or maladaptive processes at the molecular, cellular, and circuitry levels, and developing approaches to stimulate endogenous resolution mechanisms.

The Council's lead discussants, Dr. Yang Chai and Dr. Daniel McNeil, supported the concept. Dr. Chai remarked on the compromised quality of life of TMD patients, who suffer from both pain and lack of treatment. He noted that new tools and technologies could help overcome challenges in understanding the mechanisms of TMD. He also noted that the possibility of developing animal models which can mimic TMD and mechanisms underlying chronic pain presents an opportunity for drawing correlations between animal and human effects, understanding biopsychological and genetic factors that contribute to TMD onset, and developing innovative treatments. Dr. McNeil commented on NIDCR's important clinical research program on TMD and noted that understanding the pain pathways of TMD as a chronic disorder and developing effective treatment remain elusive. He suggested changing the title of the concept to draw focus to biological neuroimaging, or include variables (e.g., biopsychological) in the title. Dr. Vallejo said the NIDCR would incorporate these suggestions.

The Council unanimously approved the concept.

VII. SPECIAL SESSION ON THE INTRAMURAL RESEARCH PROGRAM

The session opened with an overview of the NIH Intramural Program, which was followed by two NIDCR presentations—on the NIDCR Intramural Program and the NIDCR Intramural Clinical Research Program. Two senior investigators in the NIDCR Intramural Program then described their respective research.

Overview of NIH Intramural Program

Dr. Roland A. Owens, Associate Director, Research Workforce Development, Office of Intramural Research (OIR), Office of the Director, NIH, described the NIH mission, organization, and resources. He said that more than 80 percent of the NIH budget supports extramural research, while approximately 12 percent supports intramural research. In addition, the NIH Intramural Research Program (IRP) offers selected national resources, which include bioinformatics databases and tools, the National Toxicology Program, videocasts of NIH Clinical Center grand rounds and NIH lectures, and archived webcasts of training events for students and fellows. The NIH comprises the main campus of 75 buildings, including the 240-bed Clinical Center, and facilities in six states. There are approximately 3,600 employee researchers, including more than 800 senior investigators and more than 200 tenure-track investigators; clinicians, scientists, and fellows; and new tenure-track assistant clinical investigators. There are approximately 5,400 research trainees, more than 40 percent of whom are postdoctoral fellows; other trainees include graduate, medical, and dental students, post-baccalaureate trainees, and summer students.

Dr. Owens highlighted key elements and achievements of the IRP. He noted that the IRP is characterized by intellectual freedom to do high-risk, high-impact science in an environment where every PI receives a rigorous, retrospective review by an IC's Board of Scientific Counselors (BSC) every 4 years. Also, the IRP invests in people, rather than projects, to develop a critical mass of talent to stimulate interdisciplinary collaborations and be able to respond rapidly to emerging public health problems. The NIH pool of talent has led to five Nobel Prizes and 17 Nobel Prize winners have been former trainees or employees of the IRP.

Dr. Owens said the Office of Intramural Research "thinks corporatively," working with the ICs' IRPs to promote awareness of the NIH IRP; opportunities for synergy between researchers and ICs through the Shared Resources Subcommittee; core values of equity, civility, mentoring, and inclusion; sharing of best practices; and safety and regulatory compliance. He noted that the IRP-developed list of research areas of interest to multiple institutes includes chronic inflammation, gene and cell-based therapies, microbiome and drug resistance, neuroscience and compulsive behaviors (e.g., opioids/pain), natural products, RNA biology and therapeutics, and vaccines. The NIH's trans-IRP career development and recruitment programs, which are available to all ICs, include the Undergraduate Scholarship Program, Medical Research Scholars Program, Stadtman Tenure-Track Investigator Program, and NIH Lasker Clinical Research Scholars Program. Other trans-IRP activities include mentoring of PIs, implicit-bias awareness training, consolidation of Institutional Review Boards, migration to a single clinical protocol database, and a website to promote optimal use of core facilities. He referred attendees to <http://irp.nih.gov/> for questions and further information.

VIII. NIDCR Intramural Program

Dr. Robert Angerer, Scientific Director, NIDCR, described the work of the NIDCR's BSC and the budget history, workforce, and scientific activities of the NIDCR's Division of Intramural Research (DIR). He specifically elaborated on the DIR "revitalization," a major organizational change under way to improve the management of science. Dr. Angerer, who is retiring from the NIDCR, noted that during his tenure of the past 13 years, DIR investigators have published approximately 2,000 scientific papers.

The NIDCR intramural program, like those of other ICs, supports investigators, not projects, who receive annual prospective allocations (not grants) to conduct high-risk, high-reward research and whose entire program is reviewed retrospectively by the BSC every 4 years. The BSC, an external scientific review body, comprises nine permanent members and two ad hoc subject-matter experts for each PI review. Dr. Angerer noted that in December 2006, the NIDCR convened a BSC Retreat to comprehensively review the board's procedures and consider revisions; the recommendations emanating from this effort led to changes in the support of DIR laboratories and closing of some programs.

Dr. Angerer reported that from FY 2006 to FY 2017, the DIR's purchasing power decreased 15 percent and that although its working budget increased, it is reduced by NIH central "taps" to support, for example, the Clinical Center. During this period, the number of laboratories (PIs) decreased 27 percent, the number of female PIs for all levels increased to 42

percent, and the number of staff scientists increased 85 percent as positions became quasi-permanent. There also was a 75 percent decrease in postdoctoral research fellows, a 150 percent increase in post-baccalaureate trainees, and an increase in contractors to approximately 45 in FY 2017. Dr. Angerer noted that faculty (PI) turnover was relatively steady, averaging 1.3 per year, although there was a net decrease from 32 PIs to 24 PIs. The DIR would like to increase this number to 26–27 PIs and is recruiting for faculty, relying in part on the Stadtman program.

Dr. Angerer said that during his tenure, he sought to increase DIR's instrumentation and establish new support cores. The DIR has a formal Office of Technology Transfer and Innovation Access (OTTIA) which, over the past 10 years, has established over 3,000 agreements, more than 80 percent of which are for material transfers outbound. Dr. Angerer noted that through the OTTIA, the NIDCR obtained the first NIH stem cell license and the first NIH orphan drug transfer; received approximately \$13.5 million in royalties; recovered \$2 million in patent costs through license agreements; and currently manages 304 patents.

On April 1, 2016, the DIR revitalization effort began and continues today. Dr. L. Michelle Bennett led the comprehensive self-evaluation of DIR structure and function. Dr. Angerer noted the aims as follows: to promote scientific interactions and reduce barriers, provide for a flexible administrative structure and evolving scientific groupings and interactions, optimize utilization of resources and reduce redundancies, increase PIs involvement in decision-making, make administrative processes uniform and streamlined, and facilitate interactions between clinical and basic scientists to promote translational efforts. The process has included small-group interviews of DIR faculty and frequent meetings of faculty and of external working groups to address five selected topics (IRP identity, sharing, leadership and organizational structure, career growth, development, and mentoring, and recruitment and retention); consider proposals in the five areas; and continue evaluation and implementation. Dr. Angerer noted that five areas of research focus have been defined for the DIR (craniofacial developmental, cell, and matrix biology; skeletal biology; sensory biology; epithelial and salivary gland biology and dysfunction; and immunology and inflammation) and are complemented by the Dental Clinical Research Core.

The revitalization includes a major revision of the DIR's organizational structure. Dr. Angerer noted that the PIs voted unanimously to convert the previous structure of 27 laboratories located within five branches to a "flat" structure of 27 laboratories (units and sections) reporting directly to the Deputy Scientific Director, Dr. Matt Hoffman, who reports to the Scientific Director. There are four NIDCR cores: gene transfer, veterinary resources, combined technical research, and biomedical research informatics. The cores, the OTTIA, and the Office of the Clinical Director report to the Scientific Director. Dr. Angerer remarked that the revitalization has resulted in a much more enthusiastic atmosphere within DIR, for investigators can belong to any laboratory and move between laboratories, engage in more focus groups for research interaction, and benefit from the availability of high-end equipment and more uniform and streamlined administrative procedures. This revitalization has attracted three new tenure-track Stadtman Investigators, one of whom, Dr. Achim Werner, presented his research to the Council during the meeting (see section X below) and two of whom will join the DIR in July.

IX. NIDCR Intramural Clinical Research Program

Dr. Janice S. Lee, Clinical Director, DIR, NIDCR, described the mission, structure, and activities of DIR's Clinical and Translational Research Program (CTRP). She noted that the program is a continuum of research that integrates clinical, cellular, and molecular investigation through human natural history studies, therapeutic trials, animal models, and mechanistic laboratory research. The four missions are patient-centered research, acceleration of discoveries and therapies to impact patient care, excellence in care and the conduct of research, and preparing the future clinician-scientist. The six areas of research are salivary gland function/dysfunction; skeletal disorders/bone metabolism; bone and hard tissue regeneration; craniofacial anomalies, growth, and regeneration; oral surgery/oral pathology/clinical sciences; and oral immunology and microbiology.

Dr. Lee reported that the CTRP has 22 active IRB protocols (led by seven PIs), of which 11 are natural history or characterization studies, 10 are pilot studies/Phase I and IIa trials, and 1 is a tissue procurement and training protocol. The CTRP has agreements for clinical research partnerships with pharmaceutical companies and extramural investigators and may have two more clinical trials within 1–2 years. Dr. Lee noted that the Dental Clinical Research Core is a necessary component of the CTRP, for research support and regulatory and oversight activities. This core works with the OD's OCTOM on the management and oversight of clinical trials. The NIDCR established OCTOM in 2008 to ensure adherence of NIDCR-supported clinical research to patient safety regulations; in 2011, the Clinical Operations Manager was added; and in 2014, the Information Sciences Unit was established to monitor and track the life cycle of all protocols through an open access/open source/customizable Clinical Trials Management System. Dr. Lee noted that this system enables the NIDCR to speed up a clinical trial from concept submission to site visits within 6–8 months potentially, followed by recruitment. Integral to this system is the Research Electronic Data Capture (REDCap) workflow methodology, and the NIDCR is one of the first ICs to use this capability.

Dr. Lee invited the Council members to visit the NIH Dental Clinic on the first floor of the NIH Clinical Center. The clinic's mission is to provide clinical care and consults for patients in NIH protocols and to support NIH clinical research protocols. Dr. Lee said that staff dentists are associate investigators on 15–20 protocols of other NIH institutes and that she chairs the Clinical Center's Patient Safety, Clinical Practice, and Quality Committee. She noted that, since 2010, the number of dental clinic visits has tripled, to approximately 3,500 in 2017, and that there has been a shift in usage by other institutes and the NIDCR. In 2010, patients on other institutes' protocols accounted for 90 percent of visits, whereas in 2017, patients on NIDCR protocols accounted for 28 percent of visits. In addition, the Dental Clinic collaborates with the Clinical Center on intramural and extramural collaborative grants (U01s), with local hospital networks, and on a tri-institute agreement involving the NIH, Walter Reed National Military Medical Center, and Uniformed Services University of the Health Sciences.

Dr. Lee commented that CTRP activities reflect the NIDCR vision that oral health is important to overall health—one of five focus areas in NIDCR 2030. She referred the Council to a recent article, entitled “The Importance of Oral Health in Comprehensive Health Care,” which

is co-authored by herself and Dr. Somerman and appeared in the *Journal of the American Medical Association* on May 3, 2018 (doi:10.1001/jama2017.19777).

Dr. Lee highlighted the NIDCR Clinical Research Fellowship, which the NIDCR established in 2010 to help prepare future clinician-scientists. The goal is to provide mentored research training and a customized career development and research experience for dentists. Applicants must have a D.D.S. or D.M.D. and a demonstrated interest in research. The focus is on research—fellows are required to spend 75 percent of their effort in research and approximately one clinic day per week. They receive 2–4 years of research training and will develop a research proposal with a PI. Dr. Lee noted that there have been 13 fellows since 2010 and 8 have completed the program. The number of applications continues to rise and come from U.S. and foreign dental graduates. One graduate, Dr. Jacqueline Mays, is now an NIH Assistant Clinical Investigator in the DIR.

Dr. Lee said the future directions for CTRP over the next 5 years include continuing to engage potential translational investigators; further streamlining public–private partnerships; applying a methodology for evaluating the scientific value and contribution of protocols to NIDCR mission; enhancing NIDCR’s genetic and genomic data analysis expertise, bioinformatics/medical informatics support, and research information technology support; and assuring mentoring and career development for junior clinical investigators, staff clinicians, and research nurse specialists. She noted that the BSC review of the Office of the Clinical Director will be in 2020.

In discussion, Dr. Lee clarified that natural history studies are longitudinal, observational studies of population cohorts and that clinical research and care at the NIH Clinical Center is focused specifically on rare or undiagnosed diseases. Two examples of this research are the NIDCR-supported legacy studies of McCune-Albright Syndrome and Sjögren’s Syndrome.

X. The Many Faces of Ubiquitin: Molecular Insights into the Neurocristophy Treacher Collins Syndrome

Dr. Achim Werner, Stadtman Investigator, Stem Cell Biochemistry Unit, DIR, described his research, presenting a general overview of the laboratory, ongoing projects and approaches, and future directions. He noted that the goal is to understand how stem cells are modified during development, specifically craniofacial development, and the role of ubiquitin. His two “take-home messages” were that ubiquitylation is a versatile post-translational modification that regulates important aspects of development by diverse mechanisms and is important for craniofacial development. Dr. Werner noted that protein modification with ubiquitin controls cell-fate decisions during development and, by doing so, controls many aspects of stem cell biology. Ubiquitylation controls epigenetic and transcriptional networks, determines the timing of cell-cycle transitions, regulates cell morphology, and controls substrates’ activity, stability, binding partners, or localization. The importance of ubiquitylation in these cell-fate decisions is underscored by the fact that aberrant ubiquitylation has been linked to many diseases, with mutations of ubiquitylation enzymes linked to cancer, developmental diseases, and neurodegeneration.

Dr. Werner described his work to understand the role of KBTBD8, a poorly characterized, vertebrate-specific substrate adaptor which he determined is one of the most dramatically regulated substrate adaptors during differentiation of mouse and human embryonic stem cell (HESC) differentiation. His initial studies suggested that KBTBD8 has a role in neural differentiation; that CUL3–KBTBD8 was required for neural crest cell specification in vitro and in vivo; and that depletion of CUL3–KBTBD8 activity resulted in a switch in cell fate towards central nervous system (CNS) precursor cells. Subsequent studies to elucidate the molecular mechanism led to identification of two KBTBD8 interaction partners (TCOF1 and NOLC1), two paralogous ribosome biogenesis regulators which are essential substrates of KBTBD8 and mono-ubiquitylated by CUL3–KBTBD8. Deletion of KBTBD8 and these partners in differentiated cells resulted in loss of neural crest and gain of CNS precursor cell markers.

Another line of evidence for this regulation came from studies of Treacher Collins Syndrome (TCS). Dr. Werner noted that while the precise molecular origin of TCS is still under debate, he found that it is caused by loss of cranial neural crest cells—the same cell population affected by KBTBD8, TCOF1, and NOLC1 depletion. He described these findings as surprising and exciting. His research showed that mono-ubiquitylation stabilizes a complex of KBTBD8 and its substrates that can recruit enzymatic machineries required for ribosome biogenesis. During differentiation, this ribosome biogenesis platform gives rise to newly synthesized and likely modified ribosomes that inhibit translation of transcripts required for the fate of CNS precursor cells, thereby allowing for differentiation of neural crest cells. The importance of this pathway is underscored by the fact that the essential substrate of this pathway, TCOF1, is mutated in 90 percent of all cases of TSC, a craniofacial development disease caused by loss of cranial neural crest cells.

Dr. Werner noted that at the beginning, the researchers knew that KBTBD8 is expressed in stem cells, but only becomes active during differentiation. Wondering how this activation and its interaction with its substrates are regulated, they hypothesized that regulators would interact with both of its substrates. They will continue their research on important aspects of craniofacial development. This will include further exploring the molecular mechanisms of KLHL4, a poorly characterized CUL3 adaptor that is linked to craniofacial development, is considered a marker for X-linked orofacial clefting, and regulates the morphology of HESC differentiation through actin-dependent cell-fate decisions, with implications for neurocristopathy. Additional work is focused on understanding the functions of OTUD5 in human disease. Studies show that mutations in this deubiquitylase lead to severe developmental defects, including craniofacial defects. The researchers will be studying four patients with OTUD5 mutations who have neurodevelopmental disease partially overlapping the phenotypes of their other cases.

Dr. Werner summarized the many different faces of ubiquitin discovered in his studies: CUL3–KBTBD8 regulates neural crest and craniofacial development by mono-ubiquitylation-dependent control of ribosome biogenesis and translation; CUL3–KLHL4 controls HESC differentiation through actin-dependent cell-fate decisions; and hypomorphic mutations in OTUD5 lead to complex, multiple congenital anomaly disorders. He noted that further study of these mutations promises to reveal fundamental aspects of ubiquitin-dependent control of development.

In discussion, the Council remarked that this research is very exciting and they applauded Dr. Werner on his presentation.

XI. Gene Therapy for Salivary Gland Hypofunction

Dr. John “Jay” Chiorini, Senior Investigator, Adeno-Associated Virus Biology Section, DIR, described his research on applying the tools of gene therapy to re-engineer cells to repair salivary function. Loss of salivary activity is multifactorial and can have a major impact on patients’ quality of life, and there is a significant clinical need for treatment options. Dr. Chiorini described gene therapy as an experimental process that involves altering the genetic composition of cells (by adding a gene to a cell to produce a missing protein or to augment proteins produced by the cell) to treat or prevent disease. He noted that 2017 was a “banner year” for gene therapy, with approval of three new gene therapies, but that gene therapy is still experimental and driven by lack of effective conventional therapy.

Dr. Chiorini noted that finding an effective vector for gene delivery is a main focus of research. He described his research strategy and findings in studies that explored the potential of an adeno-associated virus (AAV) vector system to restore salivary function in patients with radiation-induced xerostomia and Sjögren’s syndrome. Focusing first on xerostomia, he noted that salivary dysfunction-related complications occur in 85 percent of patients annually who undergo radiation for head and neck cancer, that chronic xerostomia affects an estimated 168,000 radiation-treated patients in the United States, and that there are no long-term effective therapies. Dr. Chiorini said he and his colleagues initially used Adh–aquaporin 1 (AQP1) in a minipig animal model to establish proof of concept that the strategy they undertook improved function in irradiated parotid glands. This research was followed by a Phase I clinical trial in patients with radiation-induced xerostomia, which showed that although Adh–AQP1 was helpful, the effects were dose limited. In follow-up animal research, the researchers showed that application of an AAV vector system (AAV2–AQP1), with one-time delivery, recovered salivary gland activity and had long-term efficacy. This finding led to a Phase II trial which began in 2016 in eight patients and is ongoing and expected to end within 2 years.

Turning to Sjögren’s syndrome (SS), Dr. Chiorini noted that SS, as an autoimmune disease, is much more complex than radiation-induced xerostomia and the treatment options are limited and largely not effective. In biopsies from patients’ salivary glands, the researchers identified two genes for study—bone morphogenetic protein (BMP) 6 and AQP5. They were able to create an SS animal model by using transforming growth factor beta (TGF- β) to overexpress BMP6 in mice, observing significant decreases in salivary and lacrimal gland activity, an increase in focus score, and no increases in autoantibodies and serum proinflammatory cytokines. They found, moreover, that BMP6 expression down-regulated AQP5. Dr. Chiorini noted that AQP5 is a key water transport molecule in salivary gland function and patients cannot move water without AQP5. Application of AQP gene therapy in the SS mouse model resulted in systemic and immune system changes, restoring fluid secretion and decreasing inflammation. Dr. Chiorini said the findings raise an interesting question for clinical research: What is the mechanism of systemic action of AQP1 in SS? Perhaps the increased flow

results in increased antimicrobial peptides—or decreased autoantigens—in the saliva and decreased inflammation. The researchers subsequently showed that introduction of AAV2-AQP1 in biopsies of SS patients' minor salivary glands restored some volume change, for an approximately 80 percent recovery. The team is now studying other cohorts of SS patients (e.g., without BMP6) and intend to apply for a Phase I trial within a year.

Dr. Chiorini noted that the results with radiation-induced xerostomia and SS show that AAV is an excellent vector system for restoring function in salivary glands. It is a naturally replication defective parvovirus, nonpathogenic, genetically simple, and easy to manipulate, and it stimulates a minimal host response and enables long-term gene expression. Dr. Chiorini thanked the NIDCR team and investigators at other institutes and institutions who are collaborating on this research.

In discussion, Dr. Chiorini noted that AQP1 works in both acinar and ductal cells, but the mechanism and optimal dose by which AQP1 restores fluid secretion are still to be determined.

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).

XII. REVIEW OF APPLICATIONS

Grant Review

The Council considered 775 applications requesting \$263,997,868 in total costs. The Council recommended 440 applications for a total cost of \$172,182,734 (see Attachment II).

XIII. ADJOURNMENT

The meeting was adjourned at 1:55 p.m. on May 25, 2018.

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 Pombroski
Executive Secretary
National Advisory Dental and
Craniofacial Research Council

ATTACHMENTS

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