National Institute of Dental and Craniofacial Research

National Advisory Dental and Craniofacial Research Council

Minutes of Meeting
January 27, 2021

Via Videoconference

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

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NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

MINUTES OF THE
NATIONAL ADVISORY DENTAL AND CRANIOFACIAL RESEARCH COUNCIL

January 27, 2021

The 226th meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on January 27, 2021, at 10:00 a.m., via video teleconference. The meeting was open to the public from 10:00 a.m. until 1:15 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 2:26 p.m. Dr. Rena D'Souza presided as Chair.

OPEN SESSION

Members Present

Dr. Kathryn Marie Albers
Dr. Patricia Arola, *ex officio*
Dr. Joel Collier
Dr. David J. Couper
Dr. Nisha J. D'Silva
Dr. Frank Ebetino
Dr. Raul I. Garcia
Dr. Daniel W. McNeil
Dr. Lee A. Niswander
Dr. Wenyuan Shi
Dr. Clark M. Stanford
Dr. Joel Strom
Dr. Axel Visel

National Institute of Dental and Craniofacial Research

Dr. Rena D'Souza, Director
Dr. Jonathan Horsford, Acting Deputy Director
Dr. Alicia Dombroski, Executive Secretary, and Director, Division of Extramural Activities (DEA)
Dr. Matthew P. Hoffman, Scientific Director, Division of Intramural Research (DIR)
Dr. Janice S. Lee, Clinical Director, DIR
Dr. Lillian Shum, Director, Division of Extramural Research (DER)
Ms. Tamara Addison, Office of the Director (OD), Administrative Management Branch (AMB)
Ms. Carol Beasley, OD, AMB
Dr. Nisan Bhattacharya, DEA, Scientific Review Branch (SRB)
Dr. Alison Boyce, DIR

Mr. Brian Brito, OD, Office of Information Technology (OIT)
Dr. Latarsha Carithers, DEA, SRB
Dr. Preethi Changer, DER, Integrative Biology and Infectious Diseases Branch (IBIDB)
Ms. Tiffany Chen, OD, Office of Communication and Health Education (OCHE) Science Communication and Digital Outreach Branch (SCDOB)
Dr. Zhong Chen, DER, IBIDB
Mr. Starsky Cheng, OD, OIT
Ms. Jennifer Chi, OD, Office of Clinical Trials Operations and Management (OCTOM)
Ms. Alicia Chou, DER, Translational Genomics Research Branch (TGRB)
Dr. Lois Cohen, OD
Ms. Vickie Contie, OD, OCHE, SCDOB
Ms. Michelle Cortes, DER, IBIDB
Ms. Mary Daum, OCHE, Health Information and Public Liaison Branch (HIPL)
Mr. Bret Dean, OD, Financial Management Branch (FMB)
Mr. Jimmy Do, OD, FMB
Mr. Shravan Donthi, OD, OIT
Dr. Bruce Dye, Office of Science Policy and Analysis (OSPA), Program Analysis and Reporting Branch (PARB)
Dr. Olga Epifano, DEA, OD
Dr. Catherine Evans, OD, OCHE, SCDOB
Dr. Dena Fischer, DER, Center for Clinical Research (CCR)
Dr. Leslie Frieden, DEA, Research Training and Career Development Branch (RTCDB)
Dr. Nicole Garcia Quijanona, OCHE, HIPL
Ms. Angelica Gomez, OD, AMB
Dr. Margaret Grisius, DER, CCR
Mr. Joel Guzman, DER
Dr. Sue Hamann, OSP
Ms. April Harrison, DEA, Grants Management Branch (GMB)
Ms. Stacey Hawkins, OD, OCHE, SCDOB
Ms. Jeannine Helm, DER
Mr. Gabriel Hidalgo, DEA, GMB
Mr. Tem Ibidapo, OD, OIT
Dr. Hiroko Iida, DER, Director, HIV/AIDS & Oral Health Research Program
Ms. Jennifer Jackson, DEA, SRB
Dr. Leila Khaki, DER, Behavioral and Social Sciences Research Branch (BSSRB)
Dr. Emir Khatipov, DER, TGRB
Dr. Jimok Kim, DEA, SRB
Ms. Andriece King, OD AMB
Dr. Lynn King, DEA, RTCDB
Ms. Robin Latham, OCHE
Dr. Advait Limaye, DIR
Dr. Yuanyuan (Kevin) Liu, DIR
Ms. Amber Lowery, OD, OMB
Dr. Nadya Lumelsky, DER, IBIDB
Ms. Jayne Lura-Brown, DER
Ms. Susan Macharia, DEA

Dr. Jacqueline Mays, DIR
Dr. Kevin McBryde, DER
Dr. Tamara McNealy, DER, IBIDB
Ms. Susan Medve, DEA, GMB
Dr. Yun Mei, DEA, SRB
Dr. Alissa Meister, OD
Dr. Amanda Melillo, DER, IBIDB
Ms. Amy Mhatre-Owens, OD, OCTOM
Ms. Yasamin Moghadam, DER, CCR
Mr. Ricky Moore, DEA, SRB
Ms. Mable Nee, OD, OAM, FMB
Mr. Paul Newgen, DEA, GMB
Ms. Anna Nicholson, OD, OCTOM
Ms. Lisa Peng, OD, OIT
Ms. Liz Perruccio, DEA, SRB
Ms. Debbie Pettitt, DEA, GMB
Mr. John Prue, OD, OIT
Mr. Ben Rassuli, OD, OIT
Dr. Elise Rice, DER, BSSRB
Dr. Melissa Riddle, DER, BSSRB
Ms. Diana Rutberg, DEA, GMB
Dr. Yasaman Shirazi, DEA, SRB
Mr. Jason Shockey, DEA, GMB
Dr. Ashley Smith, OD, OIT
Dr. Denise Stefrick, OSPA
Dr. Katie Stein, DER, TGRB
Ms. Kathleen Stephan, OD
Ms. Allisen Stewart, OCHE, SCDOB
Dr. Shoba Thirumangalathu, DEA, RTCDB
Dr. Yolanda Vallejo, DER, IBID
Mr. J.D. Ventura, OCHE
Ms. Patrice Waggoner-Davis, DER
Dr. Jessica Walrath, OD, OSPA
Dr. Jason Wan, DER, IBIDB
Dr. Lu Wang, DER, Chief, TGRB
Dr. Darien Weatherspoon, DER, CCR
Dr. Marian Young, DIR

National Institutes of Health

Ms. Tanjier Belton, NIH Training Center
Dr. Thomas Boddie, Office of the Director, Science Policy Coordination, Collaboration and Reporting Division
Ms. Laura Cramp, NIH Training Center
Mr. Daniel Marmorstein, Office of Research Services, Events Management

Guests

Dr. Christopher Fox, American Association for Dental Research
Mr. Matthew Miller, Neal R. Gross & Co.

I. WELCOME AND INTRODUCTIONS

Dr. Rena D'Souza, Director, NIDCR, called the open session of the 226th Advisory Council meeting to order at 10:00 a.m. She welcomed Council members and staff to the virtual meeting. Dr. Alicia Dombroski, Executive Secretary to the Advisory Council, reviewed the logistics for the virtual meeting and noted that the Council would be accepting questions and comments from the public via email (NIDCRcouncilmail@nidcr.nih.gov) until February 12.

II. APPROVAL OF MINUTES FROM PREVIOUS MEETING AND ANNUAL REVIEW OF COUNCIL OPERATING PROCEDURES

Dr. Dombroski asked the Council if there were corrections or comments on the minutes of the September 20, 2020, Council meeting. There were no comments and Council voted to unanimously approve the minutes. Dr. Dombroski next asked the Council to review and approve the Council's operating procedures. This process is conducted annually by the Institute and Council. This year, NIDCR is not recommending any changes to the operating procedures. The Council voted unanimously to approve the Council operating procedures.

III. REPORT OF THE DIRECTOR, NIDCR

Dr. D'Souza's written January 2021 Director's Report to the Council was provided to the Council members and is available on the NIDCR website (http://www.nidcr.nih.gov). In order to help introduce herself to the Council and staff, Dr. D'Souza began her first Director's Report by briefly describing her scientific and career journey that led her to NIDCR. Dr. D'Souza maintains an active dental license and one of her interests as a clinician-scientist is to use clinical questions to drive scientific inquiry and the translation of discovery into practice. She looks forward to engaging the Advisory Council throughout her tenure as Director. Dr. D'Souza noted that NIH has also recently announced new directors for four other Institutes: Dr. Michael Chiang at the National Eye Institute, Dr. Lindsey Criswell at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Dr. Rick Woychik at the National Institute of Environmental Health Sciences, and Dr. Shannon Zenk at the National Institute of Nursing Research. Dr. D'Souza noted that Dr. Criswell has had a long relationship with NIDCR and the Institute looks forward to strengthening its partnership with NIAMS during her tenure.

COVID-19 Update

Dr. D'Souza presented the most recent case data on the pandemic. According the John Hopkins University Coronavirus Resource Center, as of January 26th, 2021, a total of

100,032,461 confirmed cases had been reported globally, of which 25,362,794 were in the United States. A total of 2,149,818 deaths have now been reported globally. The toll of the pandemic has been devastating but the scientific response has been remarkable, notably with the development of new technologies in previously unheard of timeframes. The pandemic has deeply impacted the biomedical workforce, and Dr. D'Souza praised NIDCR's efforts to ensure the safety and wellbeing of its staff throughout the pandemic.

NIH Response. Dr. D'Souza reviewed the initiatives that have been launched at NIH in response to the pandemic. NIH quickly developed a trans-NIH strategic plan for COVID-19 research. The plan provided a framework for accelerating the development of therapeutic interventions, vaccines, and diagnostics. The NIH-led Accelerating COVID-19 Therapeutic Interventions and Vaccine (ACTIV) partnership helped accelerate the mRNA-based vaccine developed by Moderna and NIAID, which is one of the vaccines that received an Emergency Use Authorization (EUA) from the FDA and is now being distributed to the public. Pfizer, the manufacturer of the second vaccine to receive an EUA, was also a partner in ACTIV. Dr. D'Souza also updated the Council on the COVID-19 Prevention Network (CoVPN), which helps support large-scale Phase III clinical trials of investigational vaccines and therapeutics, including monoclonal antibodies. Dr. D'Souza was particularly encouraged by NIH's efforts to increase trust and participation among African American and Native American communities. The third major NIH initiative is the Rapid Acceleration of Diagnostics (RADx) program, which aims to accelerate innovation, development, commercialization, and implementation of COVID-19 testing technologies. One RADx grantee, Ellume, recently received an EUA for its rapid home test, the first such test to be approved by the FDA for COVID-19. Dr. D'Souza expressed the hope that some of the diagnostic technologies that have been developed for COVID-19 will have applications related to craniofacial conditions in the future.

NIDCR COVID-19 Initiatives. Dr. D'Souza next discussed NIDCR's COVID-19-related activities. To date, NIDCR has dedicated approximately $3.9M to extramural research on protecting and ensuring the safety of personnel and patients in dental practices during the pandemic. Study topics include the efficacy of personal protective equipment (PPE) use in dental settings, aerosol and droplet transmission in dental settings, the acceptance and usability of teledentistry, oral healthcare and access for low-income urban families, and sensors to detect SARS-CoV-2 in saliva. Dr. D'Souza noted that a second round of COVID-19 funding is expected in the coming months. One particular research topic NIDCR will be interested in supporting is the long-term effects of COVID-19 on dental and oral tissues. On the intramural side, NIDCR investigators have ongoing studies on quantitative antibody testing of COVID-19 infection, the transmissibility and viral load of SARS-CoV-2 via oral secretions, and the structure of the SARS-CoV-2 spike protein in saliva.

Dr. D'Souza informed the Council about the HHS Combat COVID webpage (https://combatcovid.hhs.gov/) which provides information on how to participate in vaccine and treatment clinical trials as well as other relevant information for patients and healthcare providers. Dr. D'Souza encouraged Council members to view the website and share it with interested parties.

Budget Update

Dr. Souza next updated the Council on NIH and NIDCR's budget for the coming fiscal year. NIH received a $1.25B increase, or 3 percent, to its congressional appropriations. NIDCR received a 1.6 percent increase, or $7.5M, over last year's budget. Dr. D'Souza noted that there are currently five dental professionals serving as members of Congress. NIDCR plans to engage with these members directly in the coming months as part of its general outreach efforts to Congress. Overall, the newly arrived Biden administration has put science at the front of its agenda, as indicated by the decision to elevate the Office of Science and Technology Policy (OSTP) to the cabinet level. Dr. Eric Lander has been nominated to lead the OSTP.

Dr. D'Souza presented a slide indicating NIDCR's funding levels over the past four years. The appropriations have increased steadily over the years, although in numbers adjusted for inflation the total has been relatively flat. Dr. D'Souza discussed the distribution of NIDCR's budget. Nearly 80% of NIDCR's budget goes towards extramural research, while 15% goes towards the intramural program and 7% for administrative costs. Of the extramural funds, the vast majority go towards Research Project Grants (RPGs). NIDCR's RPG success rate remains comparable to the NIH average.

Dr. D'Souza next showed a slide detailing NIH and NIDCR funding for dental schools, a topic she had been concerned about prior to coming on as Director. Currently, approximately 47% of NIDCR's extramural funding goes to dental schools. Out of NIH's total funding for dental schools, 67% comes from NIDCR. Both NIH and NIDCR's funding for dental school has increased steadily since 2013; in 2020, NIH spent over $250M on funding for dental schools. Dr. D'Souza said the NIDCR will be exploring ways to improve and develop the research capacity and infrastructure for clinical trials at dental schools, particularly for those institutions that have not received NIH funding.

Dr. D'Souza reviewed the Requests for Applications (RFAs) funded by NIDCR in 2020 and those proposed for 2021. She particularly applauded the concepts that seek to address the weak points in the dentist-scientist career pathway.

Other NIDCR Updates. Dr. D'Souza gave a brief update on the Institute's 2021-2026 Strategic Plan. NIDCR is currently in the process of updating the previous draft of the strategic plan to further define NIDCR's vision, mission, core values, and strategic research priorities for the coming years. The Institute will rely on previous stakeholder feedback, while continuing to allow further opportunities for input as the process moves forward. NIDCR will also incorporate the findings of the Surgeon General's Report on Oral Health once it is released. A draft framework for the strategic plans is projected for later in the spring, with a final product to be presented over the summer. Dr. D'Souza looks forward to vibrant engagement with the Council and other stakeholders during the strategic plan development. NIDCR is also focusing on continuing its work on diversity and inclusion at the Institute, and is developing programs and initiatives in this vein. Dr. D'Souza plans to engage the dental associations and academia in this process, as well. Additional priorities for the Institute include career training and improving clinical research infrastructure and capacity.

Accelerating Medicines Partnership (AMP). Dr. D'Souza next discussed NIH's Accelerating Medicines Partnership (AMP), which is an exciting initiative to foster collaboration

to address complex and compound diseases. AMP is a precompetitive public-private partnership designed to unite the resources of NIH, industry, and nonprofits to advance the understanding of disease pathways and to facilitate better selection of targets for treatment. To date, AMP has invested over $400M across a number of projects in research areas such as Alzheimer's disease, Type 2 diabetes, Parkinson's disease, schizophrenia, and autoimmune diseases. The AMP Autoimmune and Immune-Mediated Diseases (AMP AIM) program is the successor to the AIM Rheumatoid Arthritis and Lupus program. AMP AIM is of particular interest to NIDCR because it includes Sjogren's syndrome as one of the conditions it will study. The goal of the program is to extend disease deconstruction in order to index and map target cells and pathways and to expand the repertoire of high-dimensional single-cell analyses via omics research. The result will hopefully enable the discovery of how innate and adaptive immune system cells and tissue resident cells interact to cause inflammation and disease, as well as accelerate the discovery of mechanisms of disease and targets for intervention. AMP AIM will leverage the combined resources of three NIH ICs (NIDCR, NIAMS, and NIAID) as well as its industry partners.

Other Updates. Dr. D'Souza reviewed the many NIH meetings and stakeholder outreach activities she has participated in since coming on board as Director. She also updated the Council on the status of the Temporomandibular Joint Disorders (TMJD) Multi-Council Working Group, co-chaired by Dr. Clark Stanford. The Working Group is tasked with responding to the findings of the National Academies consensus study, "Temporomandibular Disorders: Priorities for Research and Care," released in March 2020. The Working Group will report its roadmap on prioritized research strategies to the NIDCR Advisory Council in the coming months.

Dr. D'Souza briefly updated the Advisory Council on the status of the Surgeon General's Report on Oral Health. The report is near competition and President Biden's nominee for Surgeon General, Dr. Vivek Murthy, is still awaiting Senate confirmation. Dr. D'Souza also updated the Council on the National Toxicology Program's Fluoride Monograph, which is currently undergoing a second round of peer review at the National Academies. The report from the peer review is expected to be released in the coming weeks. NIDCR plans to work with its stakeholders to respond to the findings of the peer review.

Discussion

Dr. Lee Niswander welcomed Dr. D'Souza to NIDCR and applauded the Institute's focus on diversity and inclusion in the biomedical and public health workforce. She raised the concern that the NIH cohort grant program places too much of a financial burden on the host institutions in the current financially-constrained climate caused by the pandemic, and thus would prohibit smaller or less well-funded institutions from participating. Dr. D'Souza expects that NIH will help to address the problem by releasing more targeted grant programs in the near future. Dr. Daniel McNeil noted that many of the changes wrought by the COVID-19 pandemic in the field of dentistry and dental research are likely to be permanent. With that in mind, he asked Dr. D'Souza to comment on what life at NIDCR will look like a year or two from now. Dr. D'Souza said she agreed with Dr. McNeil's assessment. NIDCR must feel obligated to learn lessons from any crisis. As an example, Dr. D'Souza described how the lack of in-person Council meetings has caused NIDCR to reach out more directly and continuously with Council members throughout the year. It seems likely that virtual working will outlast the pandemic itself for a

large portion of the workforce. More practically, the Institute and the field of dentistry have to be better poised for the next crisis and ready to play more of a frontline role.

IV. CONCEPT CLEARANCE

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, and proposed concepts are posted to https://nidcr2030ideascale.com for public comment. NIDCR staff presented one concept, and designated Council members led the discussion, as summarized below.

Reissuance of NIDCR Clinical Trial Planning and Implementation Grant Program

Dr. Dena Fischer, Director, Center for Clinical Research, DER, presented the concept. Since 2018, NIDCR has supported most of its clinical trials using a milestone-driven and phased cooperative agreement mechanism. The mechanism starts with a planning phase, which is followed, if successful, by a transition to a clinical trial implementation phase. The existing set of Funding Opportunity Announcements (FOAs) through which NIDCR solicits clinical trials research is expiring in May 2021. The objective of this concept is to continue NIDCR's investigator-initiated clinical trials program using a similar cooperative agreement mechanism. The FOA that has been issued as a Program Announcements with special receipt, referral and/or review considerations (PAR). Dr. Fischer described the key features of the program and an overview of the planning and implementation phases. Dr. Fischer also discussed the two existing FOAs under the program, NIDCR Clinical Trial Planning and Implementation Cooperative Agreement (PAR-18-547) and NIDCR Behavioral and Social Intervention Clinical Trial Planning and Implementation Cooperative Agreement (PAR-18-656).

The Council's lead discussants for the concept were Dr. Raul Garcia and Dr. Daniel McNeil. Dr. McNeil noted that the number of trials initiated under the two FOAs, 24 for PAR-18-547 and 31 for PAR-18-656, indicates that the program is being utilized in a productive manner. He felt it was appropriate to separate social and behavioral trials into a separate FOA and believed the two FOAs are appropriately demanding of the investigators. As such, Dr. McNeil was very supportive of the concept and felt it was an appropriate use of NIDCR resources. Dr. Garcia concurred with Dr. McNeil's comments. He particularly praised the cooperative nature of the program, but noted that it is still too early to fully assess what percentage of the trials transition to full implementation. Dr. Fischer said that, thus far, NIDCR has seen a 100% transition success rate, although the number that have advanced to that point is small. Dr. Garcia also noted that NIDCR used to separate the two phases into separate programs, as other ICs still do. While he believes the current approach is better, he wondered whether some investigators who did not need as much support in the planning phase feel hampered by the dual approach. Dr. Stanford urged NIDCR to encourage investigators to take advantage of the clinical trial support networks that exist at many institutions, such as Clinical and Translational Science Award (CTSA) programs. Dr. D'Souza suggested that language to that effect be added to the concept. Dr. Fischer acknowledged the benefits of taking advantage of existing infrastructure, but

noted that not all institutions have these kinds of clinical trial support programs. Dr. Dombroski said NIDCR can encourage investigators to take advantage of existing resources but should avoid making specific requirements in that regard because it might disadvantage some candidates.

The Council unanimously approved the concept.

V. NIDCR INTRAMURAL RESEARCH PRESENTATIONS

Dr. Dombroski invited Dr. Matthew Hoffman, NIDCR Scientific Director, to introduce the speakers for this session. Dr. Hoffman said that the presentations are from newer investigators at NIDCR, noting that all three presenters became tenure-track in the past year. Two of the speakers, Dr. Jacqueline Mays and Dr. Alison Boyce, are Lasker Clinical Research Scholars. The third, Dr. Yuanyuan (Kevin) Liu, was jointly recruited by NIDCR and the National Center for Complementary and Integrative Health (NCCIH) as a Stadtman Investigator. Dr. Hoffman provided brief background sketches for the three presenters, including their current roles and research fields.

Targeted Therapy for Fibrous Dysplasia/McCune-Albright Syndrome: Lessons Learned and New Approaches

Dr. Boyce began her talk by briefly describing the two related syndromes her research is focused on, fibrous dysplasia and McCune-Albright syndrome. Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a complex mosaic disorder of G_s alpha subunit activation. The disease can involve any part of the skeleton and many parts and combinations of the endocrine system. This complexity makes FD/MAS a prime condition to study the effects of G_s alpha activation and its interplay in different systems. FD/MAS arises from ligand-independent activation of G_s alpha signaling G-protein-coupled receptors (GPCRs) due to GNAS mutations. Dr. Boyce described the genetic repercussions of this mutation that lead to the presentation of FD/MAS. The condition is also noteworthy as an example of somatic mosaicism. The bone lesions caused by fibrous dysplasia occur in a mosaic distribution and can range from affecting only one or a few sites to severe cases that can affect the entire skeleton. Dr. Boyce noted that FD/MAS is not an inherited disease and there are no known cases of vertical transmission. Dr. Boyce discussed the disease pathogenesis and how the mutations in G_s alpha impair differentiation of skeletal progenitor cells, instead producing abnormal osteoblasts. The disruption of this differentiation process is what leads to bone lesions.

Dr. Boyce moved on to discuss recent studies in FD/MAS, most of which make use of NIDCR's Protocol 98-D-0145, Natural History Study in FD/MAS, which has been ongoing since 1998. The protocol allowed for the creation of a standardized data set and collection of clinical specimens for future research. Prospective and retrospective analyses have looked at defining disease spectrum and natural history, establishing a standard of care, and identifying therapeutic targets, among others. The protocol has 300 subjects representing the entire lifespan and allows for follow-up up to 25 years. Dr. Boyce presented findings of studies that used data collected in the natural history protocol. The studies looked at age-related phenotype in FD, region-specific phenotype, and the clinical sequelae of FD in the different skeletal regions. The natural history

protocol has also enabled studies looking for risk factors that can predict severe disabilities in patients. MAS endocrinopathies, such as hypophosphatemia and hyperthyroidism, have been identified as key risk factors and they have been shown to increase skeletal morbidity in fibrous dysplasia patients.

Dr. Boyce next presented studies looking to identify therapeutic targets for fibrous dysplasia. FD lesions are in a state of high bone remodeling as the lesions expand and invade areas of normal bone. This observation has led researchers to ask whether antiresorptive medications could be an effective treatment for FD. Dr. Boyce described studies looking at a class of antiresorptive medications called bisphosphonates, which are used to treat low bone mass or high bone turnover disorders. One study using alendronate, an oral bisphosphonate, found no changes in fracture rate, physical performance of the participants, or the radiographic appearance of FD lesions. In general, bisphosphonates studies have found no evidence of beneficial effects on bone quality or other skeletal outcomes, in both adults and children. Other studies have looked at osteoclasts and the receptor activator of nuclear factor kappa-B ligand (RANKL) protein. There is growing evidence that RANKL plays a key role in the pathogenesis of FD. Studies have shown that serum RANKL levels correlate with skeletal disease burden in FD patients. On the therapeutics side, one study of an anti-RANKL antibody in mice models found evidence of new bone formation within FD lesions, increased mineral content, and improved mechanical properties. After discontinuation of the treatment, lesions recurred and new lesions formed. The drug denosumab is a commercially available human RANKL monoclonal antibody that has been approved by the FDA to treat osteoporosis, large bone tumors, and skeletal metastases. Dr. Boyce described a compassionate use study using denosumab to treat fibrous dysplasia in a single patient with a severe case of FD. The study found immediate pain relief benefits, enabling the patient to cease taking narcotics. The tumor expansion rate also slowed considerably. However, there were some concerning side effects on discontinuation. There is an ongoing NIH pilot study (18-D-0041) to further examine the safety and efficacy of denosumab in adults with FD, including post-discontinuation. Preliminary findings based on the first four patients have shown decreased formation and resorption markers. Dr. Boyce also discussed efforts that use the natural history protocol to identify surrogate markers for FD activity to better enable the research community to assess the efficacy of treatment. Looking prospectively, research areas of interest include determining the role of RANKL pathway signaling in FD skeletal progenitor cell proliferation and the use of denosumab as a preventative treatment in children.

Deciphering Corticospinal Circuits in Controlling Touch and Tactile Neuropathic Pain Sensitivity

Dr. Liu began his talk by describing the current model of corticospinal sensorimotor control. In this model, the primary somatosensory cortex receives and processes the ascending somatosensory information while the primary motor cortex interprets signals from multiple cortical regions and serves as direct output to control goal-directed movements. There are multiple descending pathways connecting the cortex with the spinal cord, both direct and indirect. Dr. Liu's research focuses on the direct pathway via the corticospinal tract (CST). The literature on this direct pathway raises a number of observations that have yet to be fully explained. Dr. Liu briefly discussed a series of studies that show CST axons terminate in the deep dorsal horn of the spinal cord, where a number of mechanosensory afferents innervate. Notably,

this pattern exists in all mammals. This is a surprising finding because the ventral horn, not the deep dorsal horn, is more commonly associated with motor function.

Dr. Liu next presented some of his research on this topic, with the greater goal of exploring the extent to which the mind can control the experience of pain. One study in mice involved the ablation of CST axons in the brain stem via a procedure called pyramidotomy. Although the spinal projections are ablated, this technique allows for the soma and subcortical projections of corticospinal neurons (CSNs) to remain intact, enabling the researchers to isolate the role of spinal projections. The study found that CST ablation selectively impairs light-touch response; however, the mice had normal sensitivity to higher mechanical forces, including noxious stimuli. Dr. Liu next discussed his subsequent research to dive deeper into the function of CST axons and the termination in the deep dorsal horn. One study looked at possible correlation of CST termination with nociceptive and tactile afferent termination. Dr. Liu has also worked to optimize an intersectional virus-based tool to target corticospinal neurons in order to enable researchers to functionally dissect CSNs located in different regions. He described studies that utilized this technique to explore which population of CSNs is responsible for sensory modulation and the extent to which somatosensory CSNs contribute to tactile sensitivity.

Dr. Liu also applied the CST ablation research technique to study the role of the corticospinal tract in the modulation of mechanical allodynia, a prominent feature of peripheral neuropathic pain. The study found that corticospinal inputs are necessary for the induction of allodynia. Conversely, similar studies of other types of pain hypersensitivity, such as cold allodynia and hyperalgesia, found that corticospinal inputs are not affecting other types of pain phenotypes, supporting the theory that the reduction of mechanical allodynia is not due to compromised motor response. Dr. Liu then discussed a study using CSN ablation to see if somatosensory CSN ablation can cause the loss of mechanical allodynia. This study found that ablation of dorsal horn projections was sufficient to reduce both punctate and dynamic allodynia. His research showed that somatosensory CSNs contribute to both the establishment and maintenance of mechanical allodynia. Overall, Dr. Liu's research indicates that the descending outputs from the somatosensory cortex contribute to both tactile and neuropathic pain sensitivity. To complement this view, Dr. Liu conducted further research on the ascending pathway and whether somatosensory CSNs respond to peripheral sensory stimulation. His studies found that somatosensory CSNs are in fact activated by tactile stimulation. Further research attempted to identify which neurons in the spinal dorsal horn mediate the CST-dependent facilitation of tactile processing, focusing primarily on cholecystokinin (CCK) interneurons which receive input from the CST in the dorsal horn. Dr. Liu found that CST inputs onto CCK-positive interneurons can sensitize the processing of tactile input. Overall, Dr. Liu's research describes a spinal-cortical-spinal feed-forward sensitization loop that is crucial for both the physiological and pathological nature of tactile and mechanical allodynia. Dr. Liu's future research will attempt to identify the inputs to somatosensory CSNs and explore how ascending tactile information activates somatosensory CSNs.

Site Matters: Oral Mucosal Immunity in the Context of Chronic Graft-versus-Host Disease

Dr. Mays began her presentation by providing a brief overview of her program within NIDCR's Oral Immunobiology Unit, which is a translational research laboratory studying the

immunobiology of chronic graft-versus-host disease (cGVHD) in the oral cavity. Dr. Mays described the nature of the condition, which typically arises in response to allogeneic hematopoietic stem cell (HSC) transplants conducted to treat various types of cancers or other nonmalignant diseases. GVHD occurs when the transplanted cells begin to recognize host cells as non-self and begin to attack the host cells. Dr. Mays described the post-transplant pathways that can result in the desired functional tolerance or GVHD. The latter occurs in either acute or chronic form. Acute GVHD is limited in duration and can be very lethal. Chronic GVHD is a heterogeneous, multi-organ disorder of longer duration. In cGVHD, the skin and oral cavity are the first and second most frequently affected organs, respectively. Dr. May discussed some of the manifestations of cGVHD in the oral cavity, which include sclerosis, lichenoid lesions, salivary gland dysfunction, among others. Dr. Mays then presented data on the incidence of oral cGVHD in the U.S. Over 9,000 allogeneic HSC transplants were performed in the U.S. in 2018. Approximately 50% of allogeneic HSC transplant patients will develop cGVHD. Of these, up to 83% could develop oral manifestations.

Dr. Mays next described the focus areas of her lab, which are to identify early immune pathways that initiate oral cGVHD symptoms and advance the diagnosis and treatment of oral cGVHD. The lab utilizes a bedside-to-bench approach based on oral cGVHD natural history and therapeutic clinical trials. Dr. Mays presented two case studies illustrating how cGVHD can manifest itself in patients. One example highlighted how cGVHD targets exocrine glands, leading to alteration of acinar structure and fibrosis. Clinically, this can result in decreased saliva secretion, oral mucosal fragility, and increased susceptibility to oral infections. In this example, Dr. Mays' unit asked whether saliva can be used to identify a diagnostic biomarker profile for oral cGVHD using a salivary proteomics approach. She presented slides detailing the design and workflow of the subsequent proteomic study conducted by the unit. Ultimately, five of the six validation targets failed at validation. The protein that did not fail was zymogen granule protein 16 homolog b (ZG16B), which is a known highly expressed salivary gland gene protein. The study found that ZG16B content decreases with onset of cGVHD. Further research comparing ZG16B in healthy volunteers, post-HSC transplant subjects, and participants with oral cGVHD showed that ZG16B expression is attenuated post-transplant. Further studies looked to identify the locations of ZG16B expression and found acinar cells as the sites where the most expression occurred. Dr. Mays then described ZG16B in more detail and her team's attempts to understand why its expression is affected by the onset of cGVHD. ZG16B is a jacalin-type lectin that complexes with salivary amylase and is also found in the lacrimal gland where it is involved in the production of tear fluid. However, little is known about the protein's function in salivary glands and it remains a topic of ongoing research in Dr. Mays' laboratory.

Dr. Mays next discussed her lab's research on the pathogenesis of oral cGVHD through attempting to identify which cells initiate the alloimmune recognition of transplant cells in the oral tissues and thus drive the graft-versus-host response. This research is based on a working hypothesis that innate lymphoid cell (ILC) dysregulation and T effector or memory cells propel oral alloimmunity, and that this process is activated by tissue stress and/or injury caused by the transplant conditioning or regimen. To conduct these studies, the lab follows a bench-to-bedside sampling strategy that involves the sampling of the oral mucosa and minor salivary gland, along with saliva collection and microbiome swabs, which then undergo analysis via flow cytometry and RNA sequencing. In particular, Dr. Mays discussed findings related to T resident memory

(TRM) cells. These cells are more commonly associated with infection and cancer, but less is known about their connection with autoimmune diseases. Dr. Mays presented some sequencing results looking for the presence of these cells in the minor salivary glands and oral mucosa, which identified certain populations present in patients with cGVHD but not healthy volunteers. Dr. Mays also briefly discussed mice models looking to identify mechanistic targets for intervention, which found similar transcriptional results as the human studies.

Dr. Mays concluded by positing some unanswered questions that her lab has identified for future research. It is still not known why GVHD persists in some tissues but not others, and why systemic therapies are often ineffective for isolated refractory GVHD sites. It is hoped that continued research in this arena will expand science's understanding of the craniofacial immune complex and in the long run lead to the development of targeted pharmacological interventions. During discussion, Council members raised the topics of differences between the sexes, nerve innervation, extrapolation of minor salivary gland findings to the major salivary glands, and the role of total body irradiation as part of the transplant process as areas for future exploration.

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).

VII. REVIEW OF APPLICATIONS

VIII. ADJOURNMENT

CERTIFICATION

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

/Rena D'Souza/
_____
Dr. Rena D'Souza
Chairperson
National Advisory Dental and
Craniofacial Research Council

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

ATTACHMENTS

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