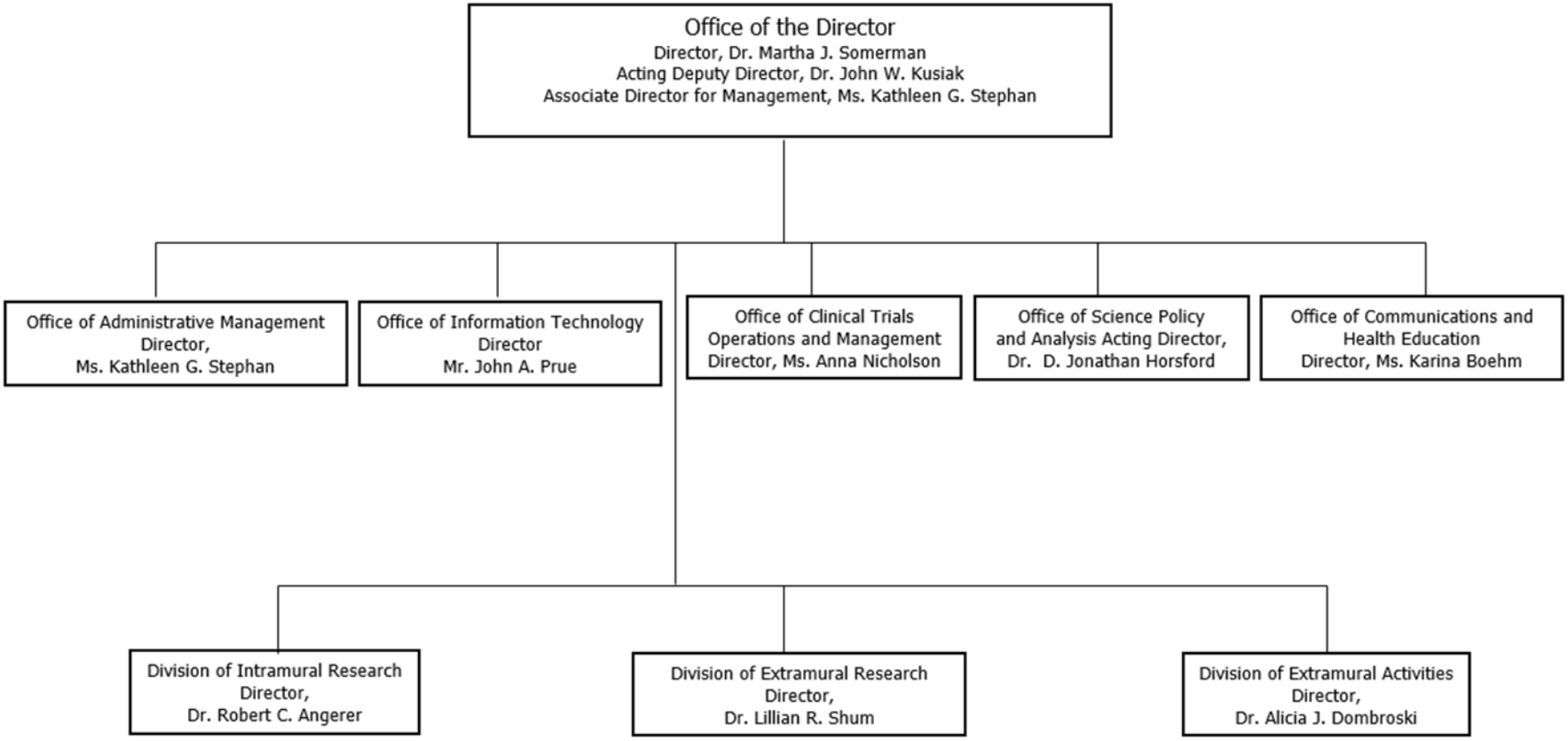
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research (NIDCR)

National Institute of Dental and Craniofacial Research



NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research

For carrying out section 301 and title IV of the PHS Act with respect to dental and craniofacial diseases, $320,749,000.

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

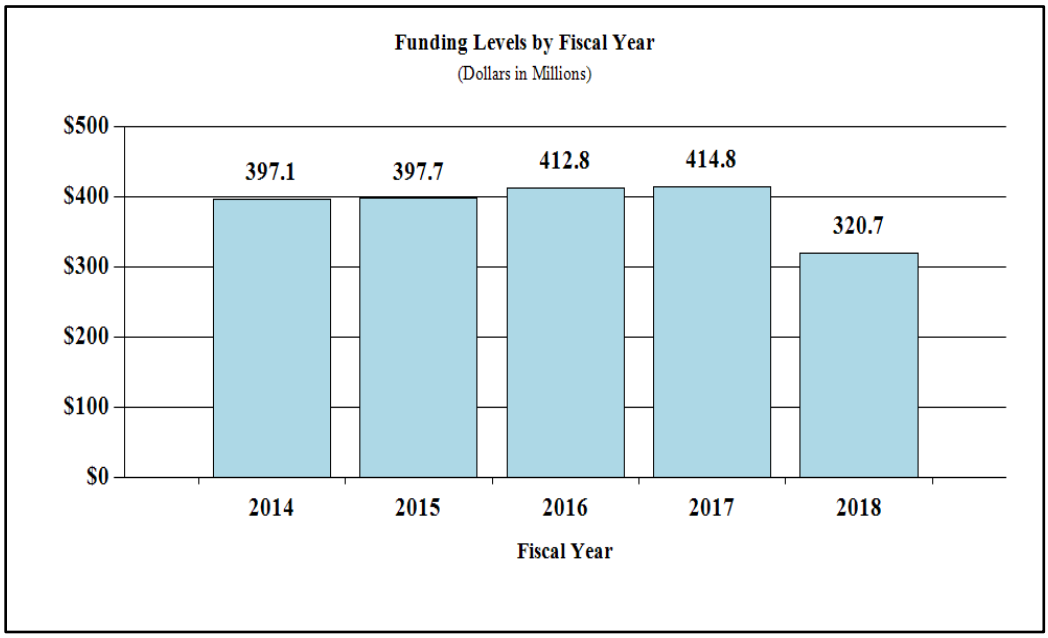
Amounts Available for Obligation[1]
(Dollars in Thousands)

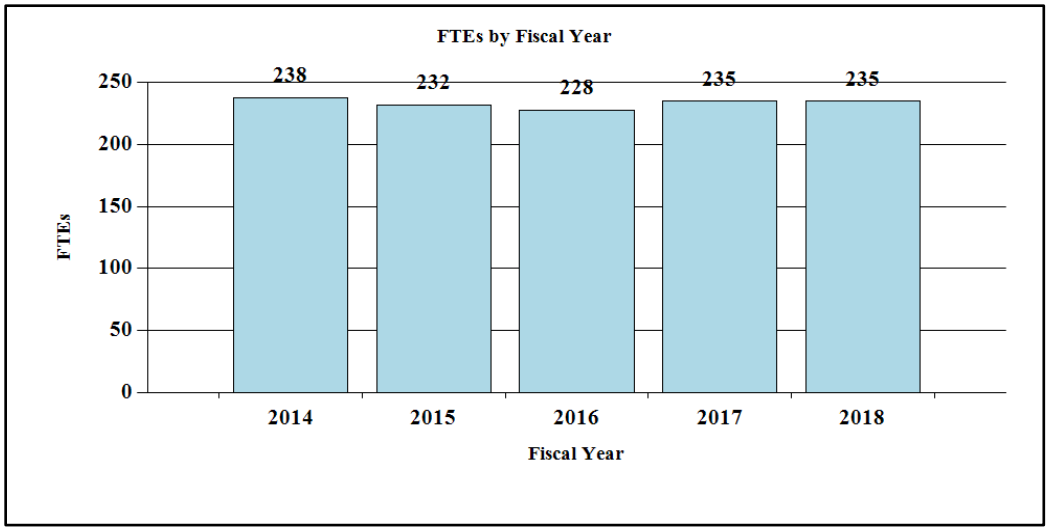
Source of Funding	FY 2016 Final	FY 2017 Annualized CR	FY 2018 President's Budget
Appropriation	$415,582	$415,582	$320,749
Mandatory Appropriation: (non-add)			
Type 1 Diabetes	*(0)*	*(0)*	*(0)*
Other Mandatory financing	*(0)*	*(0)*	*(0)*
Rescission	0	-790	0
Sequestration	0	0	0
Zika Intra-NIH Transfer	-575	0	0
Subtotal, adjusted appropriation	$415,007	$414,792	$320,749
OAR HIV/AIDS Transfers	-2,186	0	0
Subtotal, adjusted budget authority	$412,821	$414,792	$320,749
Unobligated balance, start of year	0	0	0
Unobligated balance, end of year	0	0	0
Subtotal, adjusted budget authority	$412,821	$414,792	$320,749
Unobligated balance lapsing	-33	0	0
Total obligations	$412,788	$414,792	$320,749

[1] Excludes the following amounts for reimbursable activities carried out by this account:
FY 2016 - $998 FY 2017 - $1,042 FY 2018 - $885

Fiscal Year 2018 Budget Graphs

History of Budget Authority and FTEs:





NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2017 Amount Authorized	FY 2017 Annualized CR	2018 Amount Authorized	FY 2018 President's Budget
Research and Investigation	Section 301	42§241	Indefinite	$414,791,979	Indefinite	$320,749,000
National Institute of Dental and Craniofacial Research	Section 401(a)	42§281	Indefinite		Indefinite	
Total, Budget Authority				$414,791,979		$320,749,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
2008	$389,722,000	$395,753,000	$398,602,000	$396,632,000
Rescission				$6,929,000
Supplemental				$2,075,000
2009	$390,535,000	$403,958,000	$401,405,000	$402,652,000
Rescission				$0
2010	$408,037,000	$417,032,000	$409,241,000	$413,236,000
Rescission				$0
2011	$423,511,000		$422,845,000	$413,236,000
Rescission				$3,628,459
2012	$420,369,000	$420,369,000	$404,997,000	$411,488,000
Rescission				$777,712
2013	$408,212,000		$409,449,000	$410,710,288
Rescission				$821,421
Sequestration				($20,614,832)
2014	$411,515,000		$409,947,000	$398,650,000
Rescission				$0
2015	$397,131,000			$399,886,000
Rescission				$0
2016	$406,746,000	$404,847,000	$415,169,000	$415,582,000
Rescission				$0
2017[1]	$413,396,000	$425,578,000	$430,544,000	$415,582,000
Rescission				$790,000
2018	$320,749,000			

[1] Budget Estimate to Congress includes mandatory financing.

Justification of Budget Request

National Institute of Dental and Craniofacial Research

Authorizing Legislation: Section 301 and title IV of the Public Health Service Act, as amended.

Budget Authority (BA):

	FY 2016 Actual	FY 2017 Annualized CR	FY 2018 President's Budget	FY 2018 +/- FY 2017
BA	$412,820,815	$414,791,979	$320,749,000	-$94,042,979
FTE	228	235	235	0

Program funds are allocated as follows: Competitive Grants/Cooperative Agreements; Contracts; Direct Federal/Intramural and Other.

Director's Overview

The oral health of Americans has improved dramatically in the past half-century. These gains are due in large part to research investments by the National Institute of Dental and Craniofacial Research (NIDCR). NIDCR plays a unique role in the world of biomedical research funding as it seeks to bridge the long-held dental/medical divide between oral health and the overall health of the body. Almost seventy years after our founding we remain at the forefront of visionary science, formulating novel research and training opportunities directed toward discovering biomedical and behavioral mechanisms underlying health and dental, oral, and craniofacial disorders, translating discoveries to clinical applications, and conveying those discoveries to researchers, the health care community, and the American public.

Genomic Studies Reveal Pathways to Non-Communicable Diseases

Inside the mouth is a network of microorganisms known as the oral microbiome. A burgeoning research field is studying the composition and function of the oral microbiome to understand non-communicable bacterial diseases, such as periodontal disease. Periodontal disease is a progressive oral disease that affects half of all U.S. adults, and close to 20 percent of people over the age of 65 have a severe, chronic form of the condition.[1] Periodontal disease is caused by an amplified inflammatory response to dental plaque, which is the sticky film of bacteria that infects the bone and connective tissue that support your teeth. If left untreated, periodontal disease can lead to oral pain, difficulty chewing, and tooth loss. Previous research suggests that periodontal disease is associated with a shift in the normal composition of oral bacteria from healthy to disease-causing communities. An NIDCR-funded genome-wide association study analyzed DNA from about 1,000 people with different levels of severity of periodontal disease and identified six different complex periodontal traits associated with unique disease profiles and

[1] Eke, P.I., Dye, B.A., Wei, L., Slade, G.D., Thornton-Evans, G.O., Borgnakke,W.S., Taylor, G.W., Page, R.C., Beck, J.D. and Genco, R.J. (2015) Update on prevalence of periodontitis in adults in the United States: NHANES 2009–2012. J. Periodontol., 86, 1–18.

specific types of bacterial communities. These fundamental studies suggest that periodontal disease may not be a single disorder, but a group of harmful conditions, each with a distinct genetic, bacterial, and inflammatory signature. Moving forward, these findings will advance our understanding of periodontal disease and lead to new tools for targeted prevention, diagnosis, and treatment strategies.

Prioritizing Zika Virus Research

As the numbers of non-travel related Zika virus (ZIKV) infections continues to grow in southern Florida and spread throughout the Americas and the Caribbean, NIDCR is strategically targeting its ZIKV-related funding in two important areas – basic science investigations to determine why ZIKV infection causes birth defects and the development of rapid, point-of-care salivary diagnostic tools for ZIKV. In 2016, NIDCR also participated in a trans-NIH initiative that provided expedited funding for research on ZIKV and its complications. One study supported in part by NIDCR is focused on determining how the molecular pathways of two (NS4A and NS4B) of the 10 proteins found in ZIKV work together to stunt brain development. Another team is investigating how ZIKV infects cranial neural crest cells, which are the cells that give rise to most of the tissues of the craniofacial region, and how this infection causes the disruption of normal fetal development of cranial and facial structures. Knowledge from these studies has significant potential to lead to treatments that will target these molecular pathways and prevent ZIKV-associated craniofacial abnormalities. NIDCR is also playing a pivotal role in ZIKV research by bringing together teams of scientists to develop rapid and effective tools for diagnosing ZIKV. Two groups of researchers, including one supported by a small business grant, are working on diagnostic devices that use easily obtained saliva samples to test for ZIKV infection to offer health care professionals a quick and accurate diagnostic tool.

Probiotics to the Rescue

Tooth decay – dental caries – is one of the most prevalent chronic diseases worldwide. Dental caries is caused by pathogenic bacteria in dental plaque, which feed on sugars and other carbohydrates to produce acids that eat away at tooth enamel. NIDCR-supported investigators are studying the oral microbiome to understand how different communities of bacteria function within the mouth. By analyzing their distinct interactions, scientists are hoping to find an approach to prevent dental caries in the form of a probiotic therapy that would supercharge beneficial bacteria already in the mouth and boost their protective power. One group of researchers has recently conducted a study looking at the differences in the oral microbiome between people with many decayed teeth and those with none. They used whole-genome sequencing techniques to analyze plaque samples and were able to identify a specific strain of bacteria, A12, which hinders the activities of Streptococcus mutans, a bacteria known to be a significant contributor to dental caries. The researchers are investigating the therapeutic application of a probiotic supplement that contains the A12 bacteria, which could be taken by mouth to keep bad bacteria in check and prevent dental caries.

NIDCR 2030 – Charting the Direction of Emerging Science

NIDCR has created a bold plan to focus on the most promising science and align with the most urgent public health concerns to make sure its investments result in discoveries that improve dental, oral, and craniofacial health, inform prevention strategies, and help overcome health disparities. This long-term strategic initiative – called NIDCR 2030 – sets out five major themes

to prioritize emerging areas of scientific inquiry that are ripe for significant advances over the next 15 years. These themes include: encouraging research approaches that study diseases within the context of the whole body, rather than in isolated systems; optimizing precision health care and prevention across all communities; advancing the development and use of "autotherapies" (such as immunotherapies) to treat disease; creating tools and technologies to monitor health and treat disease in real time using devices in and around the mouth, and; building a diverse community of researchers who can work across scientific disciplines. As we move forward, NIDCR will reach out to the scientific community, biomedicine stakeholders, and the public to help guide our scientific priorities and refine future directions.

Overall Budget Policy: The FY 2018 President's Budget request for NIDCR is $320.749 million, which is a decrease of $94.043 million compared with the FY 2017 Annualized CR level. These reductions are distributed across all programmatic areas and basic, epidemiology or clinical research.

Program Descriptions and Accomplishments

Oral and Craniofacial Biology: The Oral and Craniofacial Biology program supports robust basic, translational, and clinical research in salivary biology and immunology, oral and salivary gland cancer, neuroscience of orofacial pain and temporomandibular disorders, microbiology, tissue engineering and regenerative medicine, dental biomaterials, and mineralized tissue physiology. The goal of these programs is to provide the scientific foundation for advancing the prevention, diagnosis, and treatment of dental, oral, and craniofacial (DOC) diseases.

Program Portrait: DOCTR-C – Strategic Investment in Regenerative Medicine

Regenerative medicine research – research that aims to develop strategies to replace or regenerate tissues – has become a high priority for NIDCR. This is driven not just by the rapid pace of advances in basic research and the creation of new tools and technologies in the field, but also because of the opportunity to improve substantially the lives of those with DOC diseases. A notable gap in regenerative medicine's past has been the lag in translating basic research into products that can be safely and effectively used in people. Product advances are often hindered because many of them incorporate cells, molecules, and biomaterials in novel ways that result in complex combinations that fall outside traditional pharmaceutical models and regulatory processes. Encouraging collaboration between scientists and clinicians is also important to ensure that regenerative medicine products that reach the marketplace are addressing a well-defined clinical problem with a clearly beneficial impact.

To address these challenges, NIDCR launched the Dental, Oral, and Craniofacial Tissue Regeneration Consortium (DOCTR-C) to maximize opportunities for turning innovative ideas into preclinical products that are capable of becoming successful treatments. At the core of DOCTR-C is the early engagement of practicing dentists and physicians to make sure that meeting critical clinical needs is at the forefront of the research. By requiring the participation of multidisciplinary teams that include researchers, engineers, clinicians, industry members, and regulatory affairs specialists, this program is also helping investigators surmount the hurdles that keep products from reaching the marketplace.

The first phase of DOCTR-C in 2015 awarded planning grants to 10 teams to allow them to design innovative strategies and assemble a multi-disciplinary team. Phase Two awards funded in FY 2017 will fund a select group of these teams to build resources, capacity, and infrastructure. Phase Three awards, expected to launch in mid-2020, will support specific tissue regeneration approaches as they advance through the translational pipeline to preclinical testing, validation, and preparation for clinical trials.

NIDCR supports a diverse portfolio of grants to understand the underlying biology of DOC regenerative medicine. In a seminal study, investigators focused on characterizing the skeletal stem cells in mouse bone marrow that go on to form a number of tissues, including bone, cartilage and connective tissue. They found that these cells could be sorted into groups, each with a different ability to form a specific kind of tissue. By analyzing each of these groups, researchers can pinpoint specific proteins that regulate the type of tissue into which a cell will develop. The identification of similar stem cells and regulatory proteins in humans may lead to new therapeutic approaches for the regeneration of skeletal tissues.

Other regulators of stem cell function and differentiation are special types of small RNAs called miRNAs that work by turning off specific genes within a cell. Because miRNAs can't easily enter cells on their own, NIDCR-supported scientists have developed a two-stage delivery method that encloses the miRNAs within a capsule that carries them into stem cells and then gradually releases them. In a proof-of-principle experiment in mice, researchers used this capsule technology to deliver miRNAs into stem cells to regenerate and repair a craniofacial bone defect. Further advances in this technology could result in strategies that repair bone in a number of diseases, and could also provide a way to deliver other types of therapeutic molecules.

NIDCR recognizes that research to advance imaging technologies is a priority for improving the detection, diagnosis, monitoring, and treatment of a variety of DOC diseases. Scientists have developed synthetic fluorescent molecules that illuminate bone cells and allow the visualization of bone breakdown and formation. Researchers plan to use these new molecules to test and improve bone disease therapies, since they allow them to visualize real-time changes in living bone. The Institute also supports research to develop more accurate and reproducible imaging to identify dental caries to help dental practitioners choose the most appropriate treatment option for their patients. NIDCR-funded investigators are developing a novel imaging method that uses polarized light and thermal technology to advance the clinical detection and monitoring of dental caries.

The standard treatment for tooth decay is to remove the damaged tissue and fill the cavity with a dental restoration, or filling, made from tooth-colored resin composites. Although resins are a strong and durable material, they usually have to be replaced within 8-10 years. Restorations often fail because of degradation by oral bacteria, poor bonding to the tooth, and cracking. NIDCR is funding the development of innovative and longer lasting next-generation composite materials. Scientists are creating self-healing dental materials using microcapsules that break open to release a liquid that fills and seals the crack automatically. A small business is also tackling the problem of poor bonding by creating an adhesive that bonds the restoration with the tooth surface and has long-lasting antimicrobial activity to protect the restoration from bacterial degradation.

NIDCR has a history of investing in research to improve the use of dental implants, which are the metal posts that are inserted into the jaw bone to hold replacement teeth. Although implants have been a successful way to replace lost teeth, they sometimes fail. NIDCR-supported scientists have demonstrated that smoking shifts the normal balance of the bacterial communities surrounding the implant towards the types of bacteria that are associated with oral diseases and infections. This research may lead to personalized approaches to prevent and treat bacterial

infections, which would increase the service life of implants. Other investigators are developing a novel technique that uses antimicrobial peptides to combat bacterial growth and create infection-free surfaces on implants. This innovation could be applied to infection prevention for a wide range of implant devices, including both oral and orthopedic implants.

NIDCR funds a comprehensive research portfolio focused on the development, structure, function, regeneration, and replacement of the temporomandibular joint (TMJ). Studies also include chronic orofacial pain, which is associated with temporomandibular disorders (TMDs). NIDCR supports a large clinical study called Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) aimed at identifying the factors that predict the transition from acute to chronic TMDs. OPPERA scientists have uncovered links between TMDs, chronic pain, and an anti-inflammatory molecule called omentin-1. Individuals with chronic painful TMDs have lower than normal levels of omentin-1 in their blood, suggesting that TMD pain may be affected by inflammation signaling molecules throughout the body. Low levels of omentin-1 have been associated with other chronic inflammatory conditions such as osteoarthritis, irritable bowel disease, and obesity, which indicates a common mechanism may underlie these overlapping conditions.

Women are at greater risk for common forms of chronic pain, including orofacial pain, but little is known regarding the role that sex and gender play in pain processes. NIDCR-supported investigators studied the interactions between immune cells and neurons in a mouse model of persistent neuropathic pain, which is pain usually caused by damage or injury of the nerves. The scientists found that male and female mice use different cell types to relay pain signals from immune cells to the nervous system. Female mice used a type of immune cell called T cells found in the blood and bone marrow, while male mice used microglia, the immune cells of the brain and spinal cord. Interestingly, the use of T cells or microglia to transmit pain signals is dependent upon testosterone. When female mice with neuropathic pain were given testosterone, they switched from using T cells to microglia to transmit the pain signals. This intriguing result suggests that pain therapies targeting these two cell types may need to be different between men and women.

Rising rates of oral human papillomavirus (HPV) infection are causing an increase in the incidence of cancers, including HPV-associated head and neck squamous cell carcinomas (HPV-HNSCC). To improve our understanding of HPV-HNSCC, NIDCR supports research to identify potential biomarkers for the initiation and progression of HPV-HNSCC, and also to develop new approaches to target tumors that are resistant to standard treatment. Investigators have discovered that increased levels of human epidermal growth factor (HER) proteins are linked to HPV-HNSCC. Using a drug called Afatinib, which inhibits HER action, the scientists significantly reduced cancer cell growth. These findings suggest that targeting HER proteins may be an effective strategy to treat HPV-HNSCCs that are resistant to standard therapies. Another promising treatment is immunotherapy, which uses a person's own immune cells to specifically detect and eliminate cancer cells. NIDCR is encouraging basic and preclinical studies to identify and test head and neck cancer-associated immunotherapy targets that can then be used as effective therapeutic agents in the treatment of these cancers.

Immunotherapies may also hold promise for treating the autoimmune disease Sjögren's syndrome (SS), which causes salivary gland dysfunction and impaired oral health. One characteristic of SS is the presence of autoantibodies, which are antibodies against an individual's own proteins. Autoantibodies to a protein called Ro52 are commonly found in SS and are currently used to help diagnose the disease. Until recently it was not clear what function Ro52 plays in autoimmunity and SS. NIDCR investigators demonstrated in a mouse model that Ro52 autoantibodies induce salivary gland dysfunction by activating the immune system to attack the salivary glands, a key step in the development of SS. This finding sheds light on the role of Ro52 autoantibodies in SS and supports the use of immunotherapy treatments to treat SS and other autoimmune diseases.

NIDCR's support of oral mucosal immunology research includes studies related to oral HIV infection and oral complications that affect people with HIV/AIDS. The Institute is leveraging investments in salivary diagnostics to construct a microfluidics system to detect both anti-HIV antibodies and viral RNA in the same specimen of either blood or saliva. This new tool can identify HIV infections early by detecting viral RNA present in the beginning stages of infection, before anti-HIV antibodies have developed, and could lead to significant reduction in the transmission of HIV.

Improving oral health for all Americans depends not just on the research advances that drive new and more effective treatments, it also requires a talented, well-prepared, and diverse workforce. NIDCR makes targeted and strategic investments in training and career development programs. A new training opportunity called the combined Dental Specialty/PhD Program will support early career stage dentist-scientists to prepare them for research careers as highly skilled investigators and leaders in the full scope of DOC health research. This training program is intended to encourage a unique dentist-scientist research career pathway, ensure a supportive environment for both specialty and PhD training, and facilitate the transition to an independent research career.

Clinical Research: This program encourages investigations to translate findings from NIDCR's basic research portfolio into clinical applications through the support of a range of investigative approaches, including complex clinical trials, interventions delivered by dental practitioners, and community-based studies that aim to reduce and eliminate oral health disparities. The program addresses a wide array of diseases and conditions of the DOC region, such as dental caries; periodontal diseases; birth defects such as cleft lip and palate; chronic orofacial pain conditions; oral and pharyngeal cancers; and oral manifestations of systemic diseases, such as Sjögren's syndrome (SS), diabetes, and HIV infection.

NIDCR's investment in small business programs helps to generate drugs, tools, and technologies to improve DOC health outcomes and stimulate economic activity. NIDCR-funded researchers are creating innovative surgical instrument systems and software to optimize surgery for periodontal disease and craniofacial disorders. The Institute also provided support to test a new drug to treat oral mucositis. Oral mucositis occurs when cancer therapies damage the cells lining the inside of the mouth, resulting in painful sores and problems with eating, talking, and swallowing. It is a common debilitating complication of head and neck cancer therapy. The drug Dusquetide regulates the immune system to limit inflammation, a key factor in the

development of oral mucositis. A small pilot clinical trial suggests that Dusquetide reduces oral mucositis and could therefore be an important tool to help reduce these painful side effects of cancer therapies.

The main goal of dental practice-based research is to conduct studies on topics of importance to practitioners and patients, to provide evidence that will be useful in daily patient care, and to facilitate the translation of research findings into clinical practice. NIDCR's National Dental Practice-Based Research Network (NDPBRN) is a nationally coordinated program with over 6,000 practitioners in all 50 states, which was designed to yield study results that better reflect the diverse needs of the U.S. population. A large number of studies of interest to practitioners has been deployed in the NDPBRN. For example, figuring out the best way to treat patients with cracked and painful teeth is a challenge. An NDPBRN study is following a large group of patients for four years to determine the characteristics associated with significant tooth problems from cracks to develop an evidence-base for the decision making process and improve treatments. Another study is assessing the feasibility of performing HPV screening in dental offices as a new way to identify those at risk for HPV-associated oropharyngeal cancer (OPC). Given the increasing number of individuals who are diagnosed with HPV-associated OPC, screenings in a dental setting could detect cancers earlier, leading to faster treatment and a higher likelihood of survival.

Another NIDCR-supported study worked to promote early detection and prevention of head and neck cancer among low-income rural, racial, and ethnic minority individuals. The research focused on black men, because they have a high risk of dying from OPC. In a close partnership with the community, scientists launched a multi-media campaign to communicate the importance of regular OPC screening. This method of increased message exposure was associated with a higher likelihood of OPC screening and demonstrates that engaging communities and improving the quality and relevance of health messaging can be an effective way to improve oral health, particularly for those most in need.

In close collaboration with other NIH ICOs, NIDCR supports the NHLBI-led Hispanic Community Health Study/Study of Latinos, which encompasses a variety of different U.S. Hispanic/Latino groups, including Cubans, Dominicans, Mexicans, and Puerto Ricans. The study is looking at multiple aspects of health such as cardiovascular disease, stroke, asthma, lung disease, sleep disorders, hearing impairment, diabetes, kidney and liver disease, cognitive impairment, dental caries, and periodontal disease. Researchers are gaining substantial new knowledge about the oral health of these communities, including the finding that oral health status differs depending on Hispanic or Latino background, even after adjusting for age, sex, and other characteristics. Armed with this knowledge, scientists can develop oral health prevention and treatment strategies tailored to the unique needs of these populations.

Early childhood caries (ECC) is a very severe form of dental caries that develops in the primary teeth of children. ECC is more common in children from disadvantaged backgrounds or minority populations, such as American Indians (AI). Research has shown that a number of factors, including microbial and biological influences, are associated with ECC. NIDCR-supported investigators have demonstrated that AI children acquire Streptococcus mutans, a caries-associated bacteria, earlier in childhood. They found additional bacterial pathogens linked

with ECC and demonstrated that successful treatment of ECC changes the microbiota composition. Additional research on oral bacteria in children with ECC could lead to innovative strategies to prevent and treat this disease.

Behavioral and Social Sciences Research: The Behavioral and Social Sciences Research program funds a diverse portfolio of basic and applied research to understand how to improve DOC health by targeting behavioral and social factors. This program is focused on developing effective ways to prevent and treat oral disease and promote life-long habits to improve oral health. NIDCR encourages multidisciplinary teams to conduct investigations on health behaviors, stress and health, health communications, and approaches to managing serious and chronic illness. The program encourages studies to address the needs of specific U.S. populations, including racial and ethnic groups, and to create models, methods, and measures to solve today's oral health problems. The Institute also supports training and career development to equip scientists to conduct behavioral and social science-related oral health research.

Craniofacial disorders, including cleft lip and/or palate (CL/P) are among the most common birth anomalies. Children with these conditions have a range of physical, behavioral, and social challenges. Many undergo difficult surgeries and have problems with speech and language, hearing, and facial expressions. NIDCR-funded researchers are taking a multi-pronged approach to identify strategies to improve the quality of life for these children. A group of scientists are teaming up to follow children with craniofacial microsomia, a condition in which the lower part of the face is smaller than normal, and which can cause dental problems and difficulties eating, speaking, and hearing. This study will focus on understanding how these facial abnormalities change emotion-related facial movements and how this affects changes in hearing, speech, socialization, and behavior. Results from this research will ultimately lead to new strategies to help these children function better in their day-to-day lives.

Other researchers are identifying ways to improve the quality of life of the people who care for children with CL/P. The treatment for CL/P is long and arduous, starting in infancy and often lasting into young adulthood. A new technique called nasoalveolar molding (NAM) uses plastic plates on the nose to change the shape of the face, thereby reducing the need for additional surgery. Since NAM is fairly new, it is unclear how stressful this therapy is for caregivers, as opposed to an additional surgery. NIDCR-funded researchers have found that people caring for NAM-treated babies experienced more rapid declines in anxiety and depression and better coping skills over time than caregivers whose infants had traditional care. Improvements in the emotional and behavioral state of a caregiver will likely also benefit the children in their care. This study demonstrates the importance of considering caregiver quality of life and the value of holistic approaches to CL/P treatment decision-making.

NIDCR has a long history of investing in prevention strategies to advance oral health, and this remains a high priority. Since regular tooth brushing using fluoridated toothpaste is a well-established foundation for oral health, behavioral and technological approaches to improve tooth brushing behavior will positively impact oral health. One group of NIDCR-supported researchers is using a new behavioral measure called the Tooth Brushing Observation System, to explore the importance of parent and caregiver supervision to improve daily oral health behaviors in children. Further studies are expected to identify additional interventions to

improve tooth brushing behavior. A third group of scientists is cataloging oral disease in a large group of methamphetamine users with high rates of dental and periodontal disease, especially among women and cigarette smokers. Understanding the impact of methamphetamine use on oral health could offer an opportunity to use dental office visits to engage with this hard-to-reach population.

NIDCR is committed to supporting research that addresses emerging public health challenges, such as the current nationwide opioid epidemic. Because dentists prescribe opioid medication for dental pain, it is critical to understand how they and other clinicians make pain management decisions. Disparities in pain management for patients of different sexes, genders, races, and ages are well known. Researchers are using a novel computer-based virtual human technology to characterize the dynamics between clinicians and patients in managing pain treatments. Moving forward, these studies will characterize the factors involved in clinical decision making so that dentists and physicians have an evidence-based strategy to improve pain management treatments.

Translational Genetics and Genomics: A detailed knowledge of the individual genetic variations that contribute to both health and disease is one of the foundations of precision medicine. The Translational Genetics and Genomics program aims to improve understanding of the genetic and molecular mechanisms underlying DOC development and disease in children and adults. The program supports research using a range of genetic and genomic approaches including genome-wide association studies (GWAS), exome and whole genome sequencing, comparative genomic hybridization, and studies in model organisms. The ultimate goal of the program is to translate findings from basic research and population-based data analyses into clinical studies that will improve preventive measures, diagnostic testing, and treatments to minimize the impacts of DOC disorders.

Program Portrait: FaceBase – How We Face the World

Craniofacial abnormalities – caused by changes in the normal development of the face or head – are among the most common of all birth defects. Human facial development is intricate and involves multiple genes that are turned on or off in specific places for particular periods of time, with some having a greater effect than others. Recent advances in biomedical research, technologies, and informatics, along with a substantial decrease in the cost of gene sequencing, have led to an explosion of genetic and genomic data available to researchers who study craniofacial development. However, the datasets are scattered across labs and use different approaches and techniques to gather and sort the information. This has made it difficult for researchers to access and explore the data and make the kinds of interdisciplinary connections that are needed to advance our understanding of normal and dysfunctional craniofacial development.

NIDCR launched the FaceBase Consortium in 2009, and expanded it in 2014, to create a central coordination center (the Hub) to gather and manage data relevant to craniofacial research, and to fund projects to generate new data and develop innovative technologies. Nearly 600 datasets are now stored in the Hub and are available to the scientific community, along with tools to help researchers query, organize, manage, and use the information. The power of the FaceBase Consortium is its ability to encourage and accelerate scientific collaborations as well as new ways of examining and combining datasets to create novel insights into craniofacial development. For example, a research team from three different universities received funding to identify genes that regulate the development of the middle region of the face. The group used gene association studies combined with precise 3D imaging technology to detect gene variants that are associated with specific anatomical differences in the midface. Moving forward, they will be using that data to build a comprehensive 3D facial scan library, which could one day be used as a diagnostic aid in clinical settings to more accurately identify specific craniofacial syndromes and improve the management and treatment of craniofacial disorders.

NIDCR supports a diverse portfolio of research that uses cutting-edge techniques to understand the genetic underpinnings of craniofacial development. One approach is to take advantage of the similarities in biological pathways among mice and humans. In collaboration with the National Eye Institute, NIDCR is investing in a genetic approach to use mouse models to identify genes involved in craniofacial development. This strategy has identified 33 different types of mice with genetic variants that play a role in craniofacial development. Further studies with these mice will increase our knowledge about craniofacial development and pinpoint genes that are involved in human craniofacial disorders.

Researchers are also tackling another piece of the puzzle: deducing the environmental factors that contribute to CL/P. Previous studies have demonstrated that mothers who smoke have an increased risk of bearing a child with CL/P, but the effects of second-hand smoking are not well understood. NIDCR-funded scientists have demonstrated that mothers exposed to second-hand smoke are also more likely to have a child with CL/P, and that the increased risk was consistent for different populations and types of CL/P. This research emphasizes the importance of identifying maternal environmental risk factors for CL/P to enable the improvement of prenatal prevention strategies.

Dental caries are also the result of a complex interplay of genetic and environmental factors. Researchers are delving into the question of how individual genetics affect the development of dental caries by taking advantage of the U.S. Hispanic Community Health Study/Study of Latinos. Using GWAS, these scientists identified two genes associated with dental caries in Hispanic adults: NAMPT, which is involved in many biological processes including periodontal healing; and BMP7, a gene involved in tooth and bone development. Additional studies will

verify these associations and explore the possibilities of personalizing caries prevention and treatment.

NIDCR supports research to improve the quality of life of people with head and neck squamous cell carcinoma (HNSCC) and to design tailored treatment strategies. Orofacial pain is one of the first signs of HNSCC and is a factor in the development of chronic pain and overall cancer survival. Scientists used GWAS analyses to identify three genetic variants linked to orofacial pain prior to HNSCC treatment. Surprisingly, these results connect orofacial pain to genes involved in our sense of smell, which may have dual or non-smell related functions. Further research to understand the genetic factors involved in cancer pain could lead to novel individualized treatments.

Intramural Research: The NIDCR Intramural Research Program conducts innovative research on many aspects of DOC health. Taking advantage of the renowned NIH Clinical Center and outstanding collaborations with extramural researchers, NIDCR intramural investigators study topics at the foundation of oral health: salivary gland development and function; oral and craniofacial genetics and development; immunology of the mucosal system; extracellular matrix biology; mineralized tissue; and the biology of itch, touch, and pain. Cornerstones of the intramural research program include promoting the translation of basic science discoveries into clinical practice and training the next generation of clinical scientists who will pursue research careers in oral health.

Program Portrait: Cell Surface Proteases – Master Regulators of Cell Signaling and Behavior

Proteolytic enzymes, or proteases, are proteins that break down other proteins into their component amino acids. Decades ago, proteases were thought to be exclusively involved in food digestion, but further studies revealed that proteases performed other vital functions in the human body, such as the regulation of blood pressure, salt and water balance, blood coagulation, blood clot dissolution, and the elimination of bacteria and parasites. The completion of the sequencing of the human genome opened the doors to an even wider-ranging exploration of the functions of proteases and led to the discovery of genes that encode and control hundreds of previously unknown proteases. Investigators in the Intramural Research Program of NIDCR, in collaboration with other NIH scientists and researchers in laboratories around the world, have spent the past decade identifying and characterizing the functions of new types of proteases, which are called membrane-anchored serine proteases. These proteases are different from other types of proteases because they act upon and are attached to the surface of cells.

This NIDCR-led group of researchers has established that these cell surface proteases are essential both for normal development of the embryo as well as for normal organ function after birth. The most intriguing discovery made by the researchers is that cell surface proteases exert their multiple functions in health and disease by acting as on/off switches that control some of the well-studied intracellular signaling pathways that regulate cell growth, cell migration, and cell communication. For example, several cell surface proteases acting in concert are responsible for directing the cells that form the outer lining of the oral cavity, skin, and intestine to create a protective barrier by sealing gaps between cells. Moreover, they found that when these cell surface proteases fail to regulate properly, they cause a number of specific birth defects and congenital diseases in humans. Improper regulation of cell surface proteases is also associated with the transformation of normal cells into tumor cells in animal models. Because of their location outside the cell, cell surface proteases are easily accessible and may offer important new targets for the development of novel therapeutic agents to treat diseases of the oral cavity, including oral cancers.

NIDCR invests in salivary gland research to identify strategies to regenerate and treat damaged or diseased salivary tissues. Intramural scientists are using real-time imaging, coupled with genetics, to identify factors required for salivary gland secretion. This approach sheds light on

the genes and proteins required for salivary gland function and provides a better understanding of the molecular basis of salivary gland dysfunction in diseases and conditions such as SS. Determining the molecular mechanisms of saliva production and secretion will help inform the design of therapies to improve salivary gland function in people with salivary disorders. Other intramural researchers are studying the underlying causes of SS, including genetic links and environmental factors such as viral infections. One particular virus, called hepatitis delta virus (HDV), was found at low levels in the salivary glands of half of the people tested. To examine whether HDV was a key feature of SS, the researchers engineered mice to abnormally express HDV proteins in their salivary glands and found that these mice produced autoantibodies, a hallmark of autoimmune diseases such as SS. Further, the accumulation of immune cells within the salivary glands and loss of gland function in these mice indicated that HDV could be a critical factor in the development of SS. Scientists are now examining how humans become exposed to this virus and how the virus affects salivary glands, with the goal of blocking the activity of the virus and restoring salivary gland function.

Efforts are underway to develop point-of-care immunoassays that can rapidly and accurately detect antibodies to help diagnose infectious and autoimmune diseases in clinical settings. Currently, only a few such tests are available and the ones that do exist are often imprecise and slow, taking up to several hours to produce results. Intramural investigators at NIDCR and the National Institute of Allergy and Infectious Diseases (NIAID) collaborated to create an economical, robust, and rapid immunoassay technology that can accurately measure antibodies in less than one minute per sample. Researchers have coupled the technology with a handheld, battery-operated instrument for portable detection of different infectious and autoimmune diseases, including HIV, Epstein-Barr Virus, and SS. These types of innovative technologies offer new opportunities for ultra-rapid testing of a variety of diseases in point-of-care settings.

NIDCR intramural scientists are combining clinical treatments with basic research to understand the biological underpinnings of a number of rare DOC diseases. One such rare disorder is called leukocyte adhesion deficiency type 1 (LAD-1). This disease of the immune system impairs the recruitment of immune cells called neutrophils to sites of infection or inflammation. LAD-1 also increases the risk of developing periodontitis, an infection of the tissues that surround and support the teeth. NIDCR and NIAID intramural researchers discovered that the bacterial communities found on the teeth of individuals with LAD-1 are different from those found in either healthy individuals or individuals with other types of severe periodontal disease. LAD-1-associated bacterial communities are characterized by an increase in the overall number of bacteria, but with reduced diversity, primarily due to the loss of bacterial types associated with healthy individuals. Interestingly, specific molecules produced by the bacterial communities in LAD-1 patients were found to move into periodontal tissues, potentially triggering the inflammation associated with periodontitis. This discovery suggests the usefulness of therapies that can correct the imbalance of healthy and disease-causing bacteria and inhibit the molecules responsible for causing periodontal inflammation.

Research Management and Support (RMS): The RMS budget supports the scientific, administrative, information technology, communication, and clinical trial and management activities needed to effectively lead the world's largest oral health research enterprise. These activities provide stewardship for NIDCR's investments, including the review, award, and

monitoring of research grants, training awards, and research and development contracts. The Office of Science Policy and Analysis (OSPA) manages strategic planning, analyses, and evaluation activities along with internal coordination, reporting, and liaison activities with other Federal agencies and Congress. OSPA also oversees the Dental Public Health Residency program, which partners with the National Library of Medicine to train future public health dentists in bioinformatics. The Office of Communications and Health Education develops, implements, and evaluates the Institute's science, health, and digital communication programs. These programs are designed to promote the timely transfer of knowledge gained from research to scientists, health professionals, policy makers, patients, the general public, and the media.

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Detail of Full-Time Equivalent Employment (FTE)

OFFICE/DIVISION	FY 2016 Actual			FY 2017 Annualized CR			FY 2018 President's Budget		
	Civilian	Military	Total	Civilian	Military	Total	Civilian	Military	Total
Division of Extramural Activities									
Direct:	17	-	17	17	-	17	17	-	17
Reimbursable:	1	-	1	1	-	1	1	-	1
Total:	18	-	18	18	-	18	18	-	18
Division of Extramural Research									
Direct:	28	-	28	27	-	27	27	-	27
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	28	-	28	27	-	27	27	-	27
Division of Intramural Research									
Direct:	137	2	139	138	2	140	139	1	140
Reimbursable:	5	-	5	5	-	5	5	-	5
Total:	142	2	144	143	2	145	144	1	145
Office of Administrative Management									
Direct:	12	-	12	14	-	14	14	-	14
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	12	-	12	14	-	14	14	-	14
Office of Clinical Trial Operations and Management									
Direct:	2	-	2	2	-	2	2	-	2
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	2	-	2	2	-	2	2	-	2
Office of Communication and Health Education									
Direct:	6	-	6	7	-	7	7	-	7
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	6	-	6	7	-	7	7	-	7
Office of Information Technology									
Direct:	7	-	7	8	-	8	8	-	8
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	7	-	7	8	-	8	8	-	8
Office of Science Policy and Analysis									
Direct:	7	1	8	8	1	9	8	1	9
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	7	1	8	8	1	9	8	1	9
Office of the Director									
Direct:	3	-	3	5	-	5	5	-	5
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	3	-	3	5	-	5	5	-	5
Total	225	3	228	232	3	235	233	2	235
Includes FTEs whose payroll obligations are supported by the NIH Common Fund.									
FTEs supported by funds from Cooperative Research and Development Agreements.	0	0	0	0	0	0	0	0	0

FISCAL YEAR	Average GS Grade
2014	11.5
2015	11.7
2016	11.7
2017	11.7
2018	11.7

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Detail of Positions[1]

GRADE	FY 2016 Final	FY 2017 Annualized CR	FY 2018 President's Budget
Total, ES Positions	1	1	1
Total, ES Salary	173,187	176,928	179,449
GM/GS-15	16	16	16
GM/GS-14	28	28	28
GM/GS-13	31	39	39
GS-12	35	32	32
GS-11	12	17	17
GS-10	0	0	0
GS-9	13	10	10
GS-8	8	8	8
GS-7	9	10	10
GS-6	5	4	4
GS-5	1	1	1
GS-4	1	0	0
GS-3	0	0	0
GS-2	1	1	1
GS-1	0	0	0
Subtotal	160	166	166
Grades established by Act of July 1, 1944 (42 U.S.C. 207)	0	0	0
Assistant Surgeon General	0	0	0
Director Grade	2	2	2
Senior Grade	1	1	0
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	3	3	2
Ungraded	71	69	70
Total permanent positions	158	162	163
Total positions, end of year	235	249	250
Total full-time equivalent (FTE) employment, end of year	228	235	235
Average ES salary	173,187	176,928	179,449
Average GM/GS grade	11.7	11.7	11.7
Average GM/GS salary	97,310	99,411	100,828

[1] Includes FTEs whose payroll obligations are supported by the NIH Common Fund.