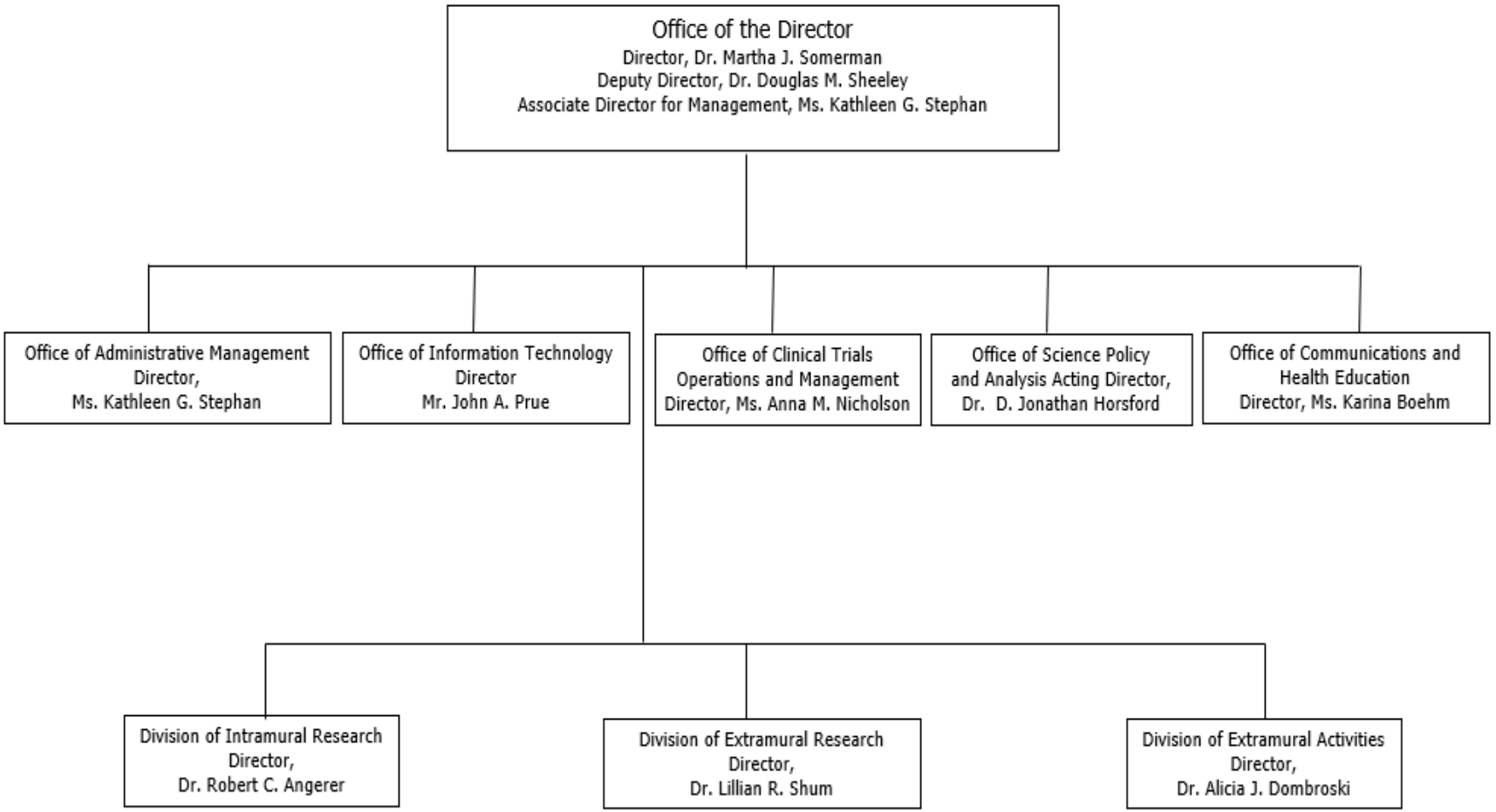
DEPARTMENT OF HEALTH AND HUMAN SERVICES

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, $413,196,000.

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

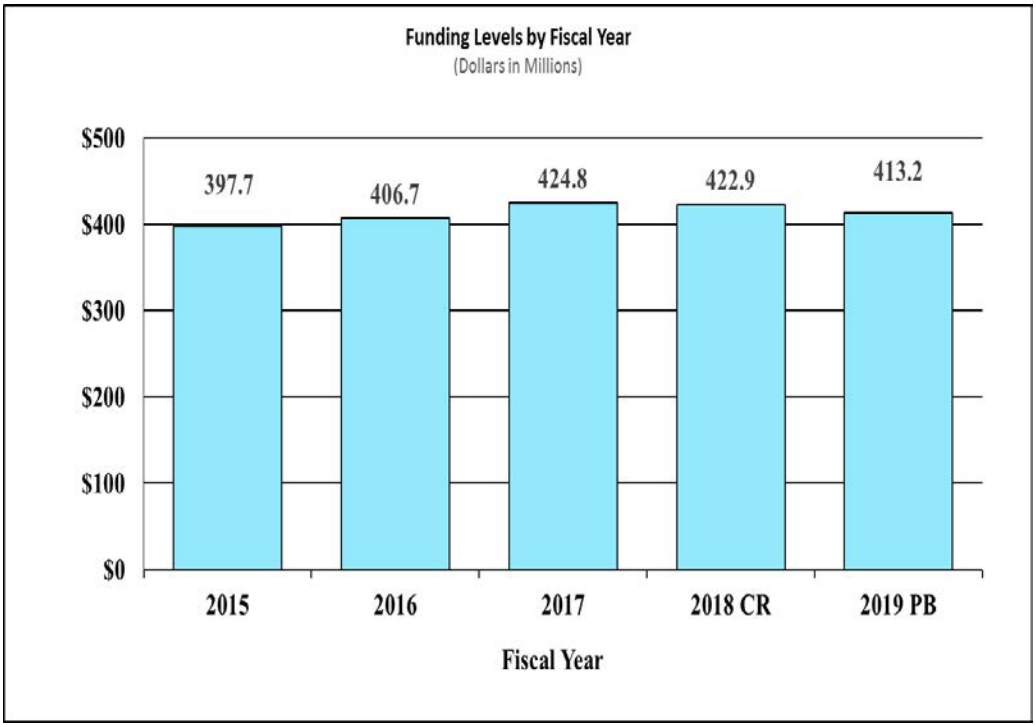
Amounts Available for Obligation[1]
(Dollars in Thousands)

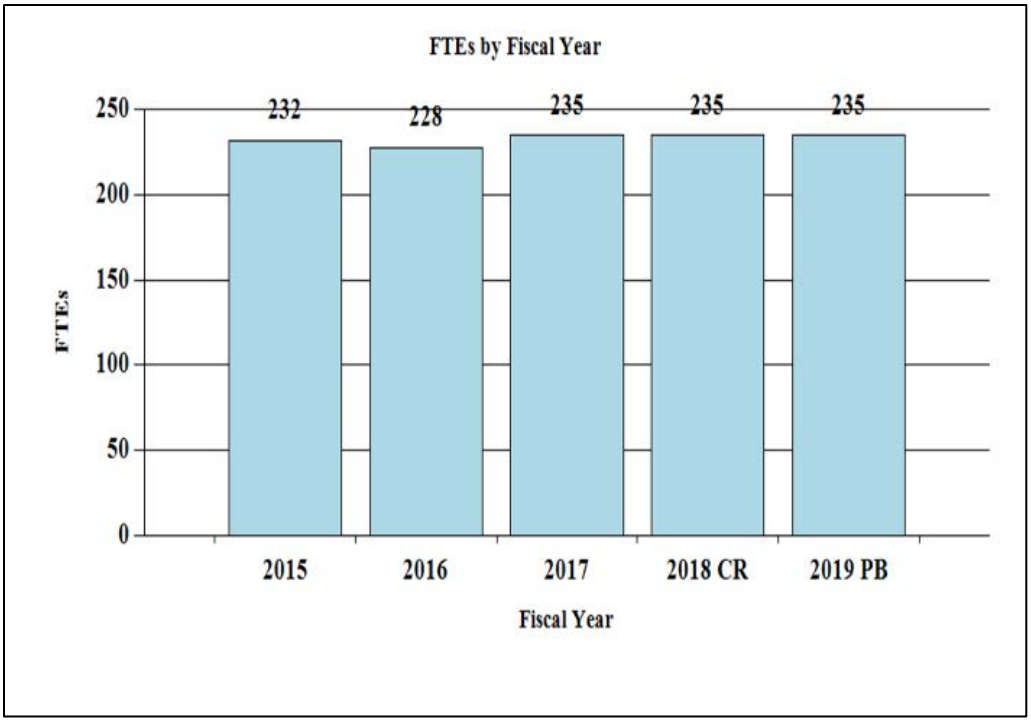
Source of Funding	FY 2017 Final	FY 2018 Annualized CR	FY 2019 President's Budget
Appropriation	$425,751	$425,751	$413,196
Mandatory Appropriation: (non-add)			
Type 1 Diabetes	*(0)*	*(0)*	*(0)*
Other Mandatory financing	*(0)*	*(0)*	*(0)*
Rescission	0	-2,891	0
Sequestration	0	0	0
Secretary's Transfer	-954		
Subtotal, adjusted appropriation	$424,797	$422,860	$413,196
OAR HIV/AIDS Transfers	0	0	0
Subtotal, adjusted budget authority	$424,797	$422,860	$413,196
Unobligated balance, start of year	0	0	0
Unobligated balance, end of year	0	0	0
Subtotal, adjusted budget authority	$424,797	$422,860	$413,196
Unobligated balance lapsing	-15	0	0
Total obligations	$424,782	$422,860	$413,196

[1] Excludes the following amounts (in thousand) for reimbursable activities carried out by this account:
FY 2017 - $1,569 FY 2018 - $1,031 FY 2019 - $758

Fiscal Year 2019 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	2018 Amount Authorized	FY 2018 Annualized CR	2019 Amount Authorized	FY 2019 President's Budget
Research and Investigation	Section 301	42§241	Indefinite	$422,859,725	Indefinite	$413,196,000
National Institute of Dental and Craniofacial Research	Section 401(a)	42§281	Indefinite		Indefinite	
Total, Budget Authority				$422,859,725		$413,196,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	$425,751,000
Rescission				$0
2018	$320,749,000	$432,363,000	$439,738,000	$425,751,000
Rescission				$2,891,276
2019	$413,196,000			

[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 2017 Final	FY 2018 Annualized CR	FY 2019 President's Budget	FY 2019 +/- FY 2018
BA	$424,797,000	$422,859,725	$413,196,000	-$9,663,725
FTE	235	235	235	0

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

Director's Overview

The National Institute of Dental and Craniofacial Research (NIDCR) improves the nation's dental, oral, and craniofacial (DOC) health by supporting research discoveries that advance prevention and treatment options for all Americans. These investments are leading to a deeper understanding of the complex underlying biological, behavioral, and social factors that support DOC health or cause disease, and of the relationship between oral and overall health. The Institute continues its commitment to training the next generation of researchers, increasing diversity in the workforce, and fostering partnerships to accelerate scientific breakthroughs.

Mapping the Oral Biofilm to Disrupt Dental Decay

Many diseases are caused by biofilms, complex communities of microorganisms that live within a self-supporting structural and biochemical matrix. Dental decay (caries) is the result of harmful oral biofilms that create a highly acidic microenvironment that dissolves tooth enamel. The most successful approach to eradicate caries is to prevent the formation of harmful biofilms. NIDCR-supported researchers developed a method to map the 3D architecture of the biofilm of the most common caries-causing oral pathogen – a bacterium called *Streptococcus mutans* – and can now pinpoint at the molecular level where damaging acids accumulate and how the bacteria and the matrix encourage biofilm growth.[1] Future studies may focus on finding ways to alter the microenvironment in hopes of developing therapeutic approaches for a variety of biofilm-associated diseases.

Developing Novel Strategies to Treat Chronic Dry Mouth

Radiation treatment of head and neck cancer destroys salivary gland cells. Consequently, patients can develop chronic dry mouth, which creates difficulties swallowing and speaking, and increases the risk for oral infections and tooth loss. Current remedies for chronic dry mouth offer only temporary relief. One of the major hurdles in the development of new drugs to spare

[1] Hwang G, Liu Y, Sun V, Aviles-Reyes A, et al. Simultaneous spatiotemporal mapping of in situ pH and bacterial activity within an intact 3D microcolony structure. Sci Rep. 2016; 6:32841.

salivary glands is the inability to efficiently test potential drugs in human salivary gland tissue in the laboratory. NIDCR-funded researchers are overcoming this challenge by creating salivary gland tissue chips, small devices that contain live human salivary gland cells that model the functions of intact salivary glands in the body. These chips can then be used to rapidly test drugs to identify the ones that protect salivary gland cells from radiation damage. Other NIDCR-supported scientists are exploring a treatment strategy that takes advantage of the body's innate ability to repair and regenerate damaged tissues. In a collaboration among investigators on the NIH campus and around the country, investigators isolated a type of adult stem cell from human salivary gland tissue and then manipulated the cells to secrete several components of saliva in a first step towards forming new salivary gland tissue in the laboratory.[2] Further research could refine methods needed to extract cells from the patient's salivary tissue prior to radiation treatment, use these cells to grow tissues in the laboratory, and successfully implant new, functional salivary gland tissue to provide permanent relief from chronic dry mouth without risk of immune rejection.

Targeting Cancer Stem Cells Offers New Hope for Treating Head and Neck Cancer

A growing body of research has demonstrated that a subset of cells, known as cancer stem cells (CSCs), are critical for initiating malignant tumor growth and promoting metastasis. Chemotherapy and radiation therapy are used to kill tumor cells, but CSCs can survive and go on to form recurring cancers in the same spot or in other parts of the body. NIDCR-supported investigators are studying molecular characteristics and cellular behavior of CSCs within head and neck squamous cell carcinomas (HNSCC) to better understand how they evade anti-cancer therapies. The researchers showed that these CSCs produce a protein called Bmi1, which promotes continuous cell division – a hallmark of cancer. The investigators demonstrated that CSCs producing Bmi1 not only drove tumor formation, growth, and metastasis, but also were good at avoiding death from cisplatin, a common chemotherapeutic drug. In a mouse model of HNSCC, the scientists used a compound called PTC-209, which specifically inhibits Bmi1 production, to selectively destroy CSCs and reduce tumor size. Further, they demonstrated that adding PTC-209 to cisplatin treatment for HNSCC was more successful than treatment with cisplatin alone. These findings suggest that a combination therapy regimen of PTC-209 and cisplatin, which targets both CSCs and HNSCC tumor cells, may be a much more effective treatment option.[3] Moving forward, clinical trials using combination therapy could lead to better outcomes and increased survival rates.

Supporting Early and Mid-Career Investigators

NIDCR is committed to supporting training and career development to ensure a robust, diverse, and well-trained research workforce. In the last two years, the Institute has added new strategies to support investigators through challenging career stages – such as when they first seek funding, or when they move into a mid-career stage and want to expand their research programs. Many biomedical scientists in early to middle years of their careers are justly concerned about their long-term stability in an increasingly competitive funding environment. Consequently, NIDCR provides support at many critical stages throughout an investigator's research career. In

[2] Srinivasan PP, Patel VN, Liu S, Harrington DA, et al. Primary Salivary Human Stem/Progenitor Cells Undergo Microenvironment-Driven Acinar-Like Differentiation in Hyaluronate Hydrogel Culture. Stem Cells Transl Med. 2017; 6(1):110-120.

[3] Chen D, Wu M, Li Y, Chang I, et al. Targeting BMI1+ Cancer Stem Cells Overcomes Chemoresistance and Inhibits Metastases in Squamous Cell Carcinoma. Cell Stem Cell. 2017; 20(5):621-634.

partnership with the National Library of Medicine (NLM), the Institute is supporting trainees pursuing research careers in biomedical informatics and data science. Another program, designed to provide clinician scientists with research training, is the Dental Specialty and PhD Program, an integrated program of clinical training and supervised research leading to a PhD in biomedical or behavioral sciences. In 2015, NIDCR created the Sustaining Outstanding Achievement in Research (SOAR) awards to provide up to eight years of grant support to mid-career investigators. This provides time and money to pursue ambitious, high-risk, and longer-term projects that have the potential to generate breakthrough discoveries. NIDCR's SOAR awards were at the leading edge of what is now a trans-NIH effort to implement strategies to retain talented scientists during challenging career stages. The 2017 SOAR awards went to four scientists investigating research topics that include skeletal tissue regeneration, craniofacial malformations, head and neck cancer, and the links between viral infections and oral inflammation.

Program Descriptions and Accomplishments

Oral and Craniofacial Biology

The Oral and Craniofacial Biology program supports a diverse and comprehensive basic, clinical, and translational research portfolio. The goal of this program is to provide the scientific foundation for advancing the prevention, diagnosis, and treatment of dental, oral, and craniofacial (DOC) diseases. Major research areas include DOC tissue development, regeneration, and repair; dental materials; salivary gland biology; infections and immunity; oral complications from systemic diseases; head and neck and salivary gland cancers; chronic orofacial pain; and overlapping pain conditions.

Advancing DOC regenerative medicine

To accelerate the translation of basic research into products that can be used in regenerative medicine treatments, NIDCR established the Dental, Oral, and Craniofacial Tissue Regeneration Consortium (DOCTR-C) to engage multidisciplinary teams that include scientists, engineers, clinicians, dentists, private industry members, and regulatory affairs specialists. In FY 2017, NIDCR funded two DOCTR-C resource centers to more efficiently shepherd new therapies through pre-clinical studies and into human clinical trials. Specific tissue regeneration approaches will soon be advancing through the translational pipeline to preclinical testing and validation in preparation for clinical trials.

Fostering partnerships to accelerate DOC research

Basic research on proteins that build bone has led to an interagency collaboration between NIH and NASA to send mice to the International Space Station (ISS) to test an experimental osteoporosis treatment. Outer space is an excellent environment for studying bone loss because without gravity astronauts can lose around 1.5 percent of their bone mass each month. A decade ago, NIDCR supported basic research on the NELL-1 protein and its role in craniosynostosis, the premature fusion of the fibrous joints of an infant's skull. The scientists found that NELL-1 inhibits bone-absorbing cells and stimulates bone-forming cells, and with additional NIH funding and training support from NIDCR, developed an experimental drug that stimulates bone growth. Based on these promising results, NASA funded a preclinical study that sent mice to the ISS to test the experimental drug's ability to prevent bone loss. Supporting early-stage basic research and interagency collaborations is advancing science and encouraging new discoveries.

NIDCR co-leads the National Academy of Medicine Forum on regenerative medicine, which brings together experts from diverse backgrounds and organizations to overcome challenges and accelerate development of new cures. This partnership with other Government agencies (e.g., the FDA and the U.S. Department of Veterans Affairs), non-profit foundations, patient advocates, universities, and private industry groups has supported multiple workshops to develop and share research strategies for the regenerative medicine community. These strategies include determining which cell types work best for developing therapies, and optimizing the manufacturing assembly line to generate safe and high-quality cells. By providing best-practices and encouraging collaboration, the Forum is speeding up the translation of regenerative medicine therapies into the clinical pipeline and onto the market.

Improving dental materials for clinical use
The Institute continues to support research to increase the longevity and durability of dental materials. Placing dental restoratives or capping the tooth following a routine root canal are the standard treatments for caries. However, after being exposed to the stresses of the mouth, such as chewing, many restorative materials crack, weaken, or fall out and need to be replaced within 8-10 years. One NIDCR-supported group has found inspiration in nature, and are exploring the use of a compound called proanthocyanidin, found in many plants such as apples and grapes. This compound stimulates the linking together of proteins that increase tooth strength, helping dental materials bind to the tooth surface more securely.

Developing non-opioid pain management therapies
Opioid overdoses have quadrupled since 1999 and nearly half of opioid overdose deaths involve a prescription opioid.[4] Doctors often have limited options for acute pain relief other than opioids, which are initially effective but require higher doses over time, and come with a risk for post-treatment drug abuse and addiction. NIDCR-supported investigators are developing a pain management therapy for cancer pain —by taking advantage of endorphins, the body's natural pain relief molecules that opioid drugs mimic. Both endorphins and opioids suppress pain by interacting with a receptor molecule called OPRM1. Scientists introduced OPRM1 into cancer cells in mice and found it stimulated production of natural endorphins that remained in the local cancer environment and reduced cancer pain. The investigators are testing this cancer pain relief strategy for safety and efficacy, and for future use in human clinical studies.

In related research, NIDCR-supported scientists are studying a condition called allodynia, where non-painful stimuli provoke a sensation of severe pain. Allodynia often leads to chronic pain, which is linked to long-term opioid use. To better understand the underlying biology of allodynia, researchers are developing a state-of-the-art imaging technique to simultaneously monitor activity of thousands of sensory neurons in live mice. Using this approach, the investigators demonstrated that, in allodynia, when non-pain-sensing neurons send signals to the brain they inadvertently turn on nearby pain-sensing neurons, which results in a heightened sensation of pain. This advance could help lead to development of novel, non-addicting therapies for allodynia and other chronic pain conditions such as temporomandibular joint disorders.

[4] https://www.cdc.gov/drugoverdose/data/overdose.html

Program Portrait: Repairing Damaged Tissues with a Bio-Adhesive Inspired by Slug Slime

Medical glues, adhesives that are like Super Glue™, have been used for decades to close surface wounds on the skin, but are not suitable for oral injuries or craniofacial surgeries. Any adhesive used to repair or reconstruct soft tissues and bone must meet three critical requirements: it must attach securely in wet conditions, stretch and bend in the dynamic environment of the body, and be non-toxic to surrounding tissues and organs. An adhesive that meets these criteria had eluded scientists, but now a group of NIDCR-supported researchers have created an adhesive that surmounts these challenges by taking a clue from a frequent garden dweller, *Arion subfuscus*, commonly known as the Dusky slug.

The Dusky slug has a unique defense mechanism. When threatened, it exudes a sticky yellow-orange slime that makes it difficult for predators to snatch it up, even in wet grass or leaves. This ability to adhere in wet environments attracted the interest of researchers who develop biomaterials known as hydrogels — water-based gels that feature molecules strung together into 3D chains called polymers. Slug slime appeared to be a natural version of a perfect hydrogel adhesive, one that could form strong bonds with wet surfaces while remaining highly flexible.

Taking a clue from the chemical composition of the Dusky slug's slime, the scientists synthesized a similar material in the laboratory by combining two components — a super-sticky adhesive layer topped by a polymer-chain layer that disperses movement throughout the material so that it flexes easily. The result is a hydrogel patch that can be cut to any size, and bonds using an applied liquid. The researchers tested their bio-glue on several animal tissues, including skin, cartilage, artery, and liver. They used it to patch a hole in an artificially beating pig heart that was then able to withstand thousands of inflations and deflations. This new adhesive could be used in various dental, oral, and craniofacial procedures, including the repair of traumatic injuries or cleft lip and/or palate — improving wound closure and healing while decreasing the risk of infection and scarring. And it has the exciting potential to be used to attach devices within the oral cavity that can monitor health status in real-time or permit the slow-release of local or systemic therapies. The flexibility and biocompatibility of this new material also makes it an attractive candidate for use in tissue regeneration, where it could anchor stem cells at specific sites to promote and speed-up tissue repair. With a patent pending, the scientists are looking forward to clinical trials, and are working on developing biodegradable versions that can dissolve once they have served their purpose.

Researching Zika virus: from molecular mechanisms to salivary diagnostics

Zika virus infections are known to cause devastating birth defects. NIDCR-supported investigators are developing rapid, non-invasive, point-of-care salivary diagnostics to improve detection of Zika virus infections in pregnant women and other vulnerable individuals. These efforts include a U.S.A.-Panama collaboration and a small business grant to adapt and apply rapid HIV detection technologies to more quickly assess the presence of the Zika virus. These studies are expanding our understanding of Zika virus detection so that, in the future, researchers can devise strategies to prevent birth defects.

Improving targeted treatments for oral cancers

Head and neck squamous cell carcinomas (HNSCC) are a common form of cancer around the world. A further understanding of the cancer's initiation, progression, and metastasis could lead to new tools for risk assessment, diagnosis, and treatment. NIDCR-funded scientists have shown that aggressive cases of HNSCC with poor survival rates are linked to a specific group of proteins that are part of the Hippo-YAP pathway. These proteins work together to drive cancer cell growth and metastasis. In the future, targeting this pathway may provide an alternative approach for treating HNSCC in patients who do not respond to standard therapies. Another team of investigators, studying drug resistance in oral cancer cells, identified a role for a protein called COX-2. A COX-2 inhibitor in combination with the standard cancer treatment, called paclitaxel, effectively reduced tumor growth in mice while paclitaxel alone did not. This COX-2 inhibitor may be a potential new combination therapy for drug-resistant oral cancer.

Cancer stem cells (CSC) can initiate and spread certain types of tumors; however, CSCs are traditionally challenging to study in the laboratory and there are few strategies to target them in cancer patients. NIDCR-supported scientists identified a unique CSC chemical signature, or biomarker, called a MYB gene fusion, in a particularly aggressive and hard-to-treat form of malignant salivary gland cancer called adenoid cystic carcinoma (ACC). This biomarker can be used to specifically identify ACC CSCs, which will make it easier to find and study these cells, and enable more rapid discovery of specific drug targets.

Program Portrait: Uncovering a Link Between Periodontal Disease and Rheumatoid Arthritis

More than 45 percent of adult Americans (64.7 million people[5]) have periodontal disease, a condition that causes inflamed gums and tooth loss, if left untreated. Periodontal disease is associated with many chronic conditions such as rheumatoid arthritis (RA), which is an autoimmune inflammatory disease that causes painful swelling in the joints. NIDCR-supported researchers are investigating the biological underpinnings of these two diseases to develop novel diagnostic, prevention, and treatment strategies for both conditions.

The researchers focused their studies on a key feature of RA — abnormal buildup in cells of modified proteins with a specific alteration called citrullination. Citrullinated proteins trigger release of destructive antibodies that attack and induce painful inflammation in the joint. NIDCR-supported researchers discovered these same protein modifications in gum tissue of individuals with periodontal disease, suggesting the process of citrullination may be a common connection between the two diseases.

The scientists found that the citrullination found in RA can be caused by one of the bacterial species associated with periodontal disease — *Aggregatibacter actinomycetemcomitans* (*Aa*). *Aa* secretes a toxin called leukotoxin A that attacks human immune cells and makes them overproduce citrullinated proteins associated with inflammation. Interestingly, study participants with RA were much more likely to have an *Aa* infection, establishing another connection between *Aa* and RA. These findings identify the periodontal pathogen *Aa* as a possible environmental trigger of autoimmunity in RA and suggest that protein citrullination is a long-sought link between the two diseases. Future studies on the *Aa* bacteria and citrullination could potentially lead to new preventive measures and treatments to benefit people with periodontal disease, and RA or other autoimmune diseases.

Supporting research to reduce HIV Infection and Transmission

Over the last three decades, survival for those with HIV infections has greatly improved but a cure has remained elusive. This is due, in part, to the virus's ability to go dormant following infection, often residing in oral tissues until reactivation produces more virus, which can lead to development of AIDS. NIDCR-funded scientists demonstrated that a group of proteins called the mTOR complex could regulate HIV reactivation, and then showed that treatment with mTOR inhibitors prevented HIV reactivation in patient cells grown in the lab. This finding could pave the way for new therapeutic approaches to keep HIV permanently dormant.

Clinical Research

NIDCR's Clinical Research program encourages investigations that translate findings from the basic research portfolio into evidence-based clinical applications. The program supports a range of research, including complex clinical trials, clinical studies conducted in dental practices, and community-based trials 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 (tooth decay); periodontal diseases; birth defects such as cleft lip and/or palate; chronic orofacial pain

[5] Eke PI, Dye BA, Wei L, Thornton-Evans GO, et al. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. J Periodontal. 2015; 5:611-22.

conditions; oral and pharyngeal cancers; and oral manifestations of systemic diseases, such as Sjögren's syndrome, diabetes, and HIV infection.

Engaging practicing dentists in research
Since 2005, over 7,000 dental practitioners and 60,000 patients in all 50 states have participated in NIDCR-supported National Dental Practice-Based Research Network (National Dental PBRN) studies. National Dental PBRN studies aim to answer questions of everyday relevance to dental practitioners and their patients. The findings from over 50 studies in progress or completed are creating the evidence base required for improving patient care. For example, one study is linking specific characteristics of cracked teeth to successful treatment strategies — generating evidence that can be used to individualize treatments for patients. Other ongoing areas of research include opioid prescribing practices, management of dentin hypersensitivity (a type of painful toothache), and treatment recommendations for crown placement. This research dovetails with other NIDCR investments in implementation science, which seeks to identify, understand, and overcome the barriers that delay the use of evidence-based clinical practices.

Improving oral health can boost overall health
Periodontal disease, the result of chronic infection and inflammation of tissues that surround and support the teeth, is associated with a number of other serious health conditions such as heart disease and type 2 diabetes. Pro-inflammatory molecules are increased in individuals with periodontal disease. These molecules may inhibit insulin function and contribute to elevated blood sugar levels in type 2 diabetes. NIDCR-supported researchers analyzed data from a large clinical study of older American veterans with periodontal disease and type 2 diabetes, and found that regular treatments for periodontal disease were associated with long-term improvements in blood sugar levels. This study demonstrates that oral health care can benefit overall health.

Targeting oral infections in children, families, and communities
The mouth is home to a diverse community of microbial species, including *Streptococcus mutans* (*S. mutans*), the primary bacterium that causes dental caries. There are distinct *S. mutans* sub-types, distinguished from each other by small molecular differences in their genetic makeup. NIDCR-supported investigators analyzed these genetic differences and found that children have anywhere between one and nine of these sub-types in their mouths, and that children infected with multiple *S. mutans* sub-types were more than twice as likely to have dental caries. Uncovering the impact of the genetic diversity of bacteria on oral health could lead to improved risk assessment and prevention strategies for dental caries.

Advancing research to improve the oral health of vulnerable children
NIDCR is committed to reducing and eliminating oral health disparities in vulnerable populations. Early childhood caries (ECC) is a very severe form of dental caries that develops in the primary (baby) teeth of children before age six. Children from low-income households or from minority populations, such as American Indians and Native Alaskans, Latinos, and African Americans, are disproportionately affected by ECC. NIDCR has supported studies on community-based interventions for ECC in high-risk populations, including several studies using fluoride varnish as part of multiple levels of preventive interventions. Fluoride varnish is a coating material applied by health professionals onto teeth to prevent caries. Using data from three NIDCR-supported studies that used fluoride varnish to prevent caries in 2,500 children,

scientists found no evidence of varnish-related side effects. This research provides additional data supporting the use of fluoride as a safe and effective way to prevent tooth decay in children.

Behavioral and Social Sciences Research
The Behavioral and Social Sciences Research Program supports basic and applied research to understand how behavioral and social factors influence oral health and how they can be used to develop approaches for effective interventions to prevent and treat oral diseases, support recovery from oral diseases, and promote life-long habits to improve oral health.

Investing in de-implementation science to reduce opioid use
It is well known that there is a significant delay in the uptake of evidence-based interventions in patient care. De-implementation research helps develop approaches to stop practices that are not evidence-based and that do not appear to provide optimal care. NIDCR-supported researchers are testing strategies to de-implement the use of opioid analgesics for the management of pain following dental extractions using a clinical decision support tool embedded within the electronic dental record. This strategy will instead implement the use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, decreasing unnecessary opioid prescriptions and addressing an important public health issue.

Understanding social networks to reduce oral health disparities among Mexican Americans
NIDCR-supported scientists are studying cultural blending to develop strategies to decrease the oral health disparities between Mexican Americans and other Americans. Mexican Americans are at higher risk for oral diseases such as caries, gingivitis, and chronic periodontitis. By analyzing oral healthcare use patterns of hundreds of Mexican Americans, researchers identified specific characteristics of their social networks that impact their knowledge and access to oral health services. They found that Mexican Americans who have social networks that include individuals with comparatively higher levels of schooling sought oral care, including preventive services, more frequently. Interestingly, this held true regardless of the person's own level of education. The next step is to use these findings to tailor optimally-effective and culturally-sensitive strategies to improve oral health in Mexican American populations.

Translational Genetics and Genomics
The Translational Genetics and Genomics program supports the transfer of discoveries in genetics, genomics, and developmental biology into improved prevention and treatment of DOC disorders. In addition, the program supports research in emerging data science fields that require the development of tools and technologies to collect, integrate, and disseminate large sets of data. This portfolio includes studies that range from uncovering molecular mechanisms in model organisms and humans to population-level studies, with the aim of translating basic science into clinical practice.

Tackling complex diseases and conditions using the power of genome-wide analyses
NIDCR-funded scientists performed the first international, multi-ethnic genome-wide association study (GWAS) of Sjögren's syndrome. Diverse populations were included to increase genetic variability, which allowed easier detection of unique genetic differences. Researchers identified several new genomic regions that may affect the onset and severity of Sjögren's syndrome, one of which might help protect certain individuals from developing the disease. This discovery could also lead to new individualized strategies to diagnose and treat Sjögren's syndrome. In a

separate GWAS, investigators identified genetic variants that increase susceptibility to oral cancer and oropharyngeal cancer (OPC). One genomic region is particularly interesting, because it includes genes involved in our immune system's ability to fight cancer cells. The linkage with this genomic region was even stronger in human papillomavirus (HPV)-positive OPCs, suggesting that genetically some people are better primed to fight (HPV)-positive OPC. In the future, this could result in new strategies that take advantage of our immune system to target cancers.

Decoding the genetics of facial development using FaceBase
Facial development is a complex process involving precisely timed coordination among many cells, genes, proteins, and signaling molecules. To promote collaboration and accelerate the pace of discovery, the NIDCR-supported FaceBase Consortium generates, integrates, and distributes data on craniofacial development and associated disorders. Researchers used GWAS to identify areas of the genome that are associated with facial shape in individuals of European ancestry, including several already known to play roles in craniofacial development or syndromes. Another study in African Bantu children identified two genes associated with face size. These findings are providing insights into facial development and may improve the ability of forensic scientists to use DNA to generate images of individual faces.

Intramural Research
Scientists in the NIDCR Intramural Research Program (IRP) conduct pioneering DOC research at the NIH Campus, including the NIDCR Clinical Research Center, part of the NIH Clinical Center. Intramural investigators study topics of importance to oral health: the biology of pain, itch, and taste; oral and craniofacial genetics and development; immunology and oral inflammation; salivary gland development, function, and pathology; and stem cell biology and tissue regeneration. A cornerstone of the IRP is a strong focus on training the next generation of researchers. The program draws highly talented trainees from diverse backgrounds to participate in a variety of research training programs.

Uncovering a mobile genetic messaging system in salivary glands
To tackle the problem of chronic dry mouth, NIDCR scientists are uncovering key molecular signals and cell types that are essential for salivary gland development and regeneration. Researchers have discovered mobile genetic messages within the salivary gland that are transported in tiny particles called exosomes which shuttle information between cells. The scientists discovered one specific genetic message, called miR-133b-3p, that regulates salivary gland stem cells. In the future, scientists may be able to use these mobile genetic messages to instruct stem cells to regenerate or repair salivary glands and other damaged organs in the body.

Preventing autoimmune diseases with naturally occurring sugars
NIDCR intramural researchers discovered that a naturally occurring sugar called D-mannose could prevent the progression of autoimmune disease in mice. Autoimmune diseases occur when the immune system attacks and destroys healthy cells within the body. T regulatory cells (Tregs) are a type of immune cell that acts as a check-point security guard, preventing the immune system from attacking the body. Scientists found that D-mannose helped to protect mice from developing type 1 diabetes by boosting the activity of Tregs. Basic research like this could lead to new prevention strategies for a wide variety of autoimmune diseases such as Sjögren's syndrome.

Program Portrait: Integrating Clinical Practice and Basic Research to Develop Novel Therapies

When clinicians and basic scientists work together, they make a powerful team. NIDCR's Clinical Research Center—a part of the NIH Clinical Center—brings together dentists, physicians, and scientists to offer a new chance at life for individuals with rare, undiagnosed, or difficult-to-treat diseases. Integrated by design, the patient-care facilities are nearby the basic science laboratories, and the collaborative spirit among intramural staff enables translation of scientific observations and discoveries into new approaches for diagnosing, treating, and preventing dental, oral, and craniofacial disease. The unique environment at the Clinical Research Center fosters groundbreaking research advances, which often come as a result of serendipity—being in the right place at the right time, with the right tools and resources at hand.

NIDCR basic scientists have investigated bone development over several decades with a specific focus on molecules called proteoglycans. Proteoglycans function outside of cells as part of connective tissue, which provides strength and stability to structures like blood vessels, cartilage, teeth, and bone. Mice that lack a proteoglycan called biglycan have defects in the skeleton and aorta. Researchers discovered that these abnormalities arise from impaired TGF-beta signaling, an important molecular pathway that controls how cells function and behave. In 2016, five people were identified with mutations in the biglycan gene (*BGN)* and with clinical signs similar to those in biglycan-deficient mice. The patients are also clinically similar to people with a rare condition called Loeys-Dietz syndrome, caused by mutations in TGF-beta pathway genes. Individuals with Loeys-Dietz syndrome have weakened connective tissues, resulting in striking similarities to biglycan-deficient mice, including aortic aneurisms, poorly mineralized teeth, and craniofacial abnormalities.

Collaborations between NIDCR basic researchers and clinical scientists are revealing the molecular underpinnings of Loeys-Dietz syndrome. In the last two years, NIDCR clinician scientists have seen more than 30 patients with Loeys-Dietz syndrome and their families. Quality of life for people with this condition is severely affected by craniofacial defects and oral pain that results from tooth demineralization. NIDCR's clinical research team is now investigating how TGF-beta mutations lead to craniofacial, skeletal, and dental abnormalities seen in Loeys-Dietz syndrome patients. The ultimate goal is to develop effective treatments for this disorder. Such translational partnerships and further studies on mouse disease models will accelerate the pace of discovery for new therapies for Loeys-Dietz syndrome and associated conditions.

Gaining new insights into the oral immune response

The mucosal tissue that lines the inside of our mouth, digestive tract, nose, and other organs keeps us healthy by forming both a physical and an immune system barrier against invading microbes. How the immune system of the oral mucosa develops and functions is not fully understood. NIDCR intramural researchers discovered that the mechanical stimulation caused by chewing activates specialized immune cells called T helper cells (Th17). These cells are triggered by a protein called IL-6, which is released from the oral mucosal tissue. The oral Th17 response ramps up the body's protective immunity, but, it may also increase inflammation in the gums and contribute to periodontal disease. Future studies of Th17 could further compare these two different outcomes and try to reduce or prevent the contribution of Th17 cells to periodontal soft tissue and bone loss, while retaining its protective effects on oral immunity.

Research Management and Support (RMS)

The RMS mechanism supports the scientific and administrative management processes needed to efficiently lead and direct the world's largest oral health research enterprise. NIDCR's extramural staff scientists and grant specialists serve as liaisons with nearly 800 grantees and provide stewardship for NIDCR's strategic investment in research and training. The Institute's Office of Science Policy and Analysis develops and analyzes science policy, coordinates program planning and evaluation, leads stakeholder outreach, and oversees NIDCR's Residency Program in Dental Public Health. These analyses and evaluations of the Institute's intramural and extramural research and training programs inform research prioritization and help improve

efficiencies. 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 and its implications for health to researchers, health professionals, patients, the general public, and the media. Looking to the future, NIDCR is conducting a strategic visioning initiative – NIDCR 2030 – that uses an interactive web-based platform to seek input from stakeholders and the public to help guide and focus research priorities and plan the tactics for efficiently implementing them for the next 15 years.

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Detail of Full-Time Equivalent Employment (FTE)

OFFICE/DIVISION	FY 2017 Final			FY 2018 Annualized CR			FY 2019 President's Budget		
	Civilian	Military	Total	Civilian	Military	Total	Civilian	Military	Total
Division of Extramural Activities									
Direct:	18	-	18	17	-	17	18	-	18
Reimbursable:	1	-	1	1	-	1	1	-	1
Total:	19	-	19	18	-	18	19	-	19
Division of Extramural Research									
Direct:	28	-	28	26	-	26	27	-	27
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	28	-	28	26	-	26	27	-	27
Division of Intramural Research									
Direct:	140	-	140	140	-	140	140	-	140
Reimbursable:	5	-	5	5	-	5	5	-	5
Total:	145	-	145	145	-	145	145	-	145
Office of Administrative Management									
Direct:	14	-	14	15	-	15	14	-	14
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	14	-	14	15	-	15	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:	7	-	7	7	-	7	7	-	7
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	7	-	7	7	-	7	7	-	7
Office of Information Technology									
Direct:	8	-	8	8	-	8	8	-	8
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	8	-	8	8	-	8	8	-	8
Office of Science Policy and Analysis									
Direct:	7	-	7	8	-	8	7	-	7
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	7	-	7	8	-	8	7	-	7
Office of the Director									
Direct:	5	-	5	6	-	6	6	-	6
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	5	-	5	6	-	6	6	-	6
Total	235	-	235	235	-	235	235	-	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
2015	0.0
2016	0.0
2017	11.8
2018	11.7
2019	11.7

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Detail of Positions[1]

GRADE	FY 2017 Final	FY 2018 Annualized CR	FY 2019 President's Budget
Total, ES Positions	1	1	1
Total, ES Salary	180,114	182,681	183,549
GM/GS-15	15	14	14
GM/GS-14	29	28	28
GM/GS-13	40	41	41
GS-12	32	32	32
GS-11	17	17	17
GS-10	0	0	0
GS-9	9	9	9
GS-8	8	8	8
GS-7	11	11	11
GS-6	4	5	5
GS-5	0	0	0
GS-4	0	0	0
GS-3	1	1	1
GS-2	1	1	1
GS-1	0	0	0
Subtotal	167	167	167
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	0	0	0
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	2	2	2
Ungraded	85	85	85
Total permanent positions	167	167	167
Total positions, end of year	256	256	256
Total full-time equivalent (FTE) employment, end of year	235	235	235
Average ES salary	180,114	182,681	183,549
Average GM/GS grade	11.8	11.7	11.7
Average GM/GS salary	101,142	102,583	103,070

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