DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

# FY 2008 Budget for the National Institutes of Health: A New Vision for Medical Research

Witness appearing before the
Senate Subcommittee on Labor-HHS-Education Appropriations

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Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH). The Fiscal Year (FY) 2008 budget request for NIDCR is $389,722,000.

## FACING THE FUTURE:
## INTEGRATIVE APPROACHES TO ADVANCE PUBLIC HEALTH

Innovation has long been the great engine of progress in American life, including the tremendous progress made in improving the Nation's oral health over the last half century. From the tube of fluoridated toothpaste in the medicine cabinet to the high-resolution digital X-ray unit in the dentist's office, scientific innovations have helped more people than ever keep their teeth for a lifetime.

The Nation's oral and craniofacial researchers stand on the threshold of even greater innovations to improve the lives of millions of Americans. No longer must they attempt to understand health and disease one gene and protein at a time. Today, they can click the computer mouse on their desks and call up vast databases of biological information. In essence, thousands of pieces to the biological puzzle are now on the table. If we meet the challenge to integrate the pieces - intentionally blurring in the process the lines that have defined the traditional research disciplines - great progress can be made in understanding the molecular underpinnings of oral and craniofacial health and disease. This year, I would like to offer a few of the many examples of how integrative science will lead to greater innovation. I'd also like to highlight how this innovation ultimately will lead to more personalized dentistry and medicine in which treatment can be tailored to a patient's specific disease and healthcare needs.

## CRANIOFACIAL CONSTRUCTION AND RECONSTRUCTION

The human face has been celebrated in art and literature since time immemorial and rightfully so. It is among the body's most distinctive structures and, is also one of the most developmentally complex structures of nature. Tremendous progress has been made in recent years in unraveling the genetic programs that are activated in the embryo to produce the face and the skull. Similar progress has been made in pinpointing which genes can go awry to produce a cleft lip and/or palate.

But much work remains. We must decipher the developmental programs that give rise to the various craniofacial tissues, hard and soft. By knowing how the craniofacial complex is assembled, it will be possible to better reassemble tissues that are damaged, either at birth or due to injury later in life. Exciting research is under way to explore the viability of regenerating damaged bone, teeth, and soft tissues with stem cells, novel biomaterials, and growth-promoting proteins. NIDCR-supported researchers recently reported success using stem cells to engineer a replacement root/periodontal complex that could support a porcelain crown and provide normal tooth function in studies with mini pigs. Other investigators are well on the way to creating a replacement gum tissue that can be produced in sufficient quantity to repair large oral defects.

The developmental programs will be helpful not only in treating craniofacial abnormalities but in preventing them. This year, for example, a team of NIDCR grantees determined that women who smoke during pregnancy and carry a fetus whose DNA lacks both copies of a gene involved in detoxifying cigarette smoke substantially increase their baby's chances of being born with a cleft lip and/or palate. About a quarter of babies of European ancestry and possibly up to 60 percent of those of Asian ancestry lack both copies of this gene. This finding reinforces in a concrete, personal way the public health message that women, especially those who are pregnant, should not smoke.

## HEAD AND NECK CANCER

The NIDCR also has made a major investment in promoting integrative approaches to head and neck cancer. Our intent is to move beyond the current imprecise clinical definitions of these tumors, which are generally based on their appearance and patterns under a microscope. We need to examine the genetic hard drives of these tumors' cells to understand their abnormal and often deadly behaviors. This work already is taking place. NIDCR scientists have compiled comprehensive profiles of proteins expressed in some head and neck cancers. This information should help in developing true biomarkers with diagnostic and prognostic value.

NIDCR-supported scientists are also developing new and exciting visualization tools and approaches to improve diagnosis of oral cancer. One such tool being tested is called the VELscope®. It is a simple hand-held device that emits a cone of blue light into the mouth, which excites various molecules within the tissue, causing the tissue to absorb the light's energy and re-emit it as visible fluorescence. Because changes in the natural fluorescence of healthy tissue generally are different from those indicative of developing tumor cells, the VELscope® allows dentists to observe telltale differences.

In a recent follow-up study, the scientists reported that the VELscope® performed extremely well in accurately and rapidly delineating the real borders between tumor and healthy oral tissue during biopsies in the clinic. Intriguingly, 19 of the 20 examined tumors in the study had fluorescence changes that extended in at least one direction beyond the clinically visible tumor. These extensions, which are undetectable to the unaided eye and thus would likely not be excised, extended up to an inch beyond the visible lesion. Leaving these abnormal cells in the mouth increases the chance of other tumors arising over time. The instrument was developed as one component of an integrative approach to oral cancer detection and treatment that combines cytology, molecular biology, and staining to improve early detection. This finding and others will allow practitioners to gain a better molecular characterization of developing tumors, providing the intellectual basis for more personalized treatment and a future in which fewer people will undergo disfiguring surgery to fight the disease and/or die from these cancers.

## SALIVARY DIAGNOSTICS

Other diagnostic tools are under development as well. The NIDCR is a national leader in development of the use of saliva as a diagnostic fluid. Several Institute grantees are working to develop tiny automated machines, which can rapidly and precisely perform many diagnostic functions that previously required painful needle sticks. One group recently fabricated the first disposable, low-cost, miniaturized diagnostic platform that can process small amounts of saliva, amplify its DNA and detect the levels of genetic sequences of interest. Work is proceeding to ultimately create a fully functional hand-held instrument for everyday use to detect conditions ranging from oral cancer to cardiovascular disease to AIDS.

## TEMPOROMANDIBULAR MUSCLE AND JOINT DISORDERS

Integrative approaches are proving productive in our ongoing efforts to understand temporomandibular muscle and joint disorders, or TMJDs. Previously, NIDCR-supported scientists found that different sets of common sequence variations in the COMT gene correlate with low, moderate, and high susceptibility to chronic pain. This finding makes good biological sense. The COMT gene encodes an enzyme that helps to inactivate nerve signaling compounds and stop the transmission of an unpleasant sensation. The scientists recently showed that each of these sets of sequence variations changes the resulting structure of the corresponding messenger RNA. When a gene is expressed, it is copied into messenger RNA which, like an order form, contains the information to produce a specific protein. The scientists determined that the genetic variations that correlate with high sensitivity to pain produce messenger RNA with long, rigid loops in their structure, which reduces the rate of COMT protein synthesis and thus slows the nerve's ability to turn off an unpleasant sensory signal. The likely result: those with the "sensitive" variations will personally experience the sensation of pain longer and possibly more intensely.

Such findings are particularly exciting because these studies could not have been conducted just a generation ago. Not enough was known about the basic mechanisms of pain. But as more of the biochemical pieces to the puzzle are found in the years ahead, great progress in controlling pain will be possible, and the NIDCR will help in leading the way for all those battling chronic pain conditions, including TMJDs, to find relief through a more accurate diagnosis and more personalized care.

## DENTAL DISPARITIES: RIGOROUS SCIENCE, PRACTICAL RESULTS

It now has been seven years since the U. S. Surgeon General issued the report *Oral Health in America.* As many will recall, that report pulled together for the first time the stark statistics of the Nation's "silent epidemic" of tooth decay and other oral diseases among its minority and underserved populations. The reasons for these disparities are complex, but two facts were indisputable in the report: Many oral diseases are either preventable or easily controlled, and new strategies are needed to ensure that all Americans are aware of and ultimately benefit from the latest research advances.

To meet this need, the Institute established five Centers for Research to Reduce Oral Health Disparities in 2001. This approach allows scientists to assemble multi-disciplinary research teams that lend a greater wealth of expertise to understand and address the complex elements underlying oral health disparities at the community level. Building on the knowledge and evidence amassed by the initial health disparities centers, the Institute has begun preparations to re-compete its center grants with a specific public health aim. That aim is to assemble a more seamless investigative team structure that can take a well-defined clinical issue and with the participation of a community-based population, test the effectiveness of promising interventions on a wider scale. This approach holds considerable promise to yield rigorous science, participatory research with those in underserved communities, and a significant reduction in oral health disparities.

## PRACTICE-BASED RESEARCH NETWORKS

The Institute awarded grants in early 2005 that established three regional practice-based research networks, or PBRNs. Their mission is to create networks of practicing dentists and dental hygienists with their patient populations to participate in clinical studies on a variety of pressing everyday issues in oral healthcare. In 2006, the PBRNs were enlisted to investigate an important emerging health issue. Millions of Americans currently take a type of drug called bisphosphonates, typically to ease cancer-related pain or to prevent osteoporosis. But recent reports indicate that newly formulated bisphosphonates can cause in some people a debilitating thinning of the jawbone called osteonecrosis. What remains unclear is the prevalence of this unwanted side effect and, more importantly, who precisely is at risk. A few years ago, NIDCR would have lacked the clinical infrastructure in place to investigate these and other related questions. The PBRNs have changed the equation. The NIDCR has rapidly organized the needed studies to investigate the problem and will provide in the near future more meaningful data for the millions of Americans at risk.

Traditional research approaches have produced extraordinary benefits to the Nation's public health. But we now face a new scientific frontier, and new possibilities confront our researchers. These opportunities require novel approaches that fall under the rubric of integrative science. From this coordinated approach to science, the biological complexity before us will give way to simplicity and once unimaginable public health advances in which personalized health and medicine become a reality.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Biographical Sketch

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| NAME | Lawrence A. Tabak |
| POSITION | Director, National Institute of Dental and Craniofacial Research |
| BIRTHPLACE | Brooklyn, New York |
| DATE | December 15, 1951 |
| EDUCATION | B.S., Biology and Chemistry, City College of CUNY, 1972<br>D.D.S., Dentistry, Columbia University, 1977<br>Ph.D., Oral Biology, SUNY at Buffalo, 1981<br>Certificate of Proficiency in Endodontics, SUNY at Buffalo, 1985 |
| EXPERIENCE | |
| 2000-present | Director, National Institute of Dental and Craniofacial Research, NIH |
| 2000-present | Adjunct, Senior (2006) Investigator, Section of Biological Chemistry National Institute of Diabetes and Digestive and Kidney Diseases, NIH |
| 2000 | Adjunct Professor of Dentistry and of Biochemistry and Biophysics, University of Rochester |
| 1998-2000 | Senior Associate Dean for Research, School of Medicine and Dentistry, University of Rochester |
| 1998-2000 | Co-Director, Institutional Medical Scientist Training Program (MSTP) |
| 1998-2000 | Professor of Dentistry and of Biochemistry and Biophysics |
| 1998-2000 | Director, Center for Oral Biology, Aab Institute of Biomedical Sciences, University of Rochester |
| 1996-2000 | Director, Institutional Dentist Scientist Program |
| 1996-1997 | Professor, Dental Research and Biochemistry and Biophysics, University of Rochester |
| 1995-1997 | Chair, Department of Dental Research, University of Rochester |
| 1992-1996 | Professor, Dental Research and Biochemistry, University of Rochester |
| 1988-1994 | Director, Graduate Study, Department of Dental Research, University of Rochester |
| 1986-1992 | Associate Professor, Dental Research and Biochemistry, |

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|---|---|
| | University of Rochester |
| 1985-1986 | Associate Professor, Endodontics and Oral Biology, SUNY/ Buffalo |
| 1985-1986 | Director, Graduate Study (Ph.D.), Oral Biology, SUNY/ Buffalo |
| 1982-1983 | Visiting Scientist, NIDR, Bethesda, MD |
| 1981-1985 | Assistant Professor, Endodontics and Oral Biology, SUNY/ Buffalo |
| 1980-1981 | Research Assistant Professor, Oral Biology, SUNY/Buffalo |

HONORS AND AWARDS

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|---|---|
| 2006 | Honorary Doctorate, University of Medicine and Dentistry of NJ |
| 2004 | Named a Columbia University Alumnus "Ahead of the Times" |
| 2002 | Elected Member of the Institute of Medicine |
| 1998 | Elected Fellow of AAAS |
| 1997-2000 | USPHS MERIT Award (R37) |
| 1997 | Alumnus of the Year, School of Dental and Oral Surgery, Columbia University |
| 1996 | IADR Distinguished Scientist Award – Salivary Research |
| 1994 | Manuel D. Goldman Prize for Excellence in First Year Teaching, School of Medicine and Dentistry, University of Rochester |
| 1994-1997 | Dean's Senior Teaching Fellow, School of Medicine and Dentistry, University of Rochester |
| 1993 | Alumni Award for Excellence in Graduate Education, University of Rochester |
| 1991 | Salivary Research Award (Salivary Research Group, IADR) |
| 1987 | IADR Young Investigator Award |
| 1984-1989 | USPHS Career Development Award (K04) |
| 1984 | Student Research Association Award (SUNYAB) |