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Fourth Scientific Meeting of The TMJ Association

A Systems Approach to the Understanding of TMJ as a Complex Disease

In This Issue…

The TMJ Association is a national, non-profit organization whose mission is to improve the diagnosis, care and treatment of everyone affected by temporomandibular joint and muscle disorders through fostering research, education and other activities with the ultimate goal of preventing TMJ problems.

Preface

The TMJ Association's (TMJA) fourth scientific meeting, ***A Systems Approach to the Understanding of TMJ as a Complex Disease***, was held in September 2006 in Bethesda, Maryland. As with the Association's previous three meetings, the organizers invited TMJD patients, research investigators knowledgeable about temporomandibular joint and muscle disorders (TMJDs), and experts from other fields of science and medicine. These individuals brought new perspectives and fresh ideas to a health problem lacking a coherent body of knowledge of etiology and pathogenesis. Each of the earlier meetings added to our understanding of TMJDs, providing insights concerning the blood supply and microvasculature of joint tissues, the mechanics of joint and muscle function, characteristics of chronic inflammation and immune system responses, and important neural, endocrine and immune system interactions. In addition, the pathophysiology and management of chronic pain associated with TMJDs were issues addressed at all the meetings, as were the concerns of patients in need of safe and effective treatments. Each meeting resulted in a summary accompanied by a body of research recommendations circulated to the scientific community to advance TMJD research.

The fourth meeting was unique in that it represented a major paradigm shift in the way policy makers and the scientific community view TMJDs. Building upon the post-genomic emergence of integrative systems approaches to the understanding of complex diseases, TMJDs emerged at this meeting as more than a problem of dysfunction and pain of the jaw joint. The TMJD patient should be seen as a whole individual, one who expresses one or more phenotypes that reflect the range of co-morbidities many TMJD patients experience. These include generalized muscle pain, fatigue, sleep disorders, cardiovascular disorders, and many symptoms resembling those described for fibromyalgia, irritable bowl syndrome, dysautonomias, depression, and a variety of chronic pain syndromes. Based on the presentations from experts and patients, it was clear that TMJDs should be characterized as a complex disease, just as are arthritis, atherosclerosis, hypertension, heart failure, and many other common diseases.

Following the formal presentations, basic scientists and clinical investigators at the meeting proposed recommendations on how interdisciplinary and integrated systems approaches, (e.g., a systems biology approach) now applied to the study of other complex diseases, could help reshape the research agenda for understanding the etiology, diagnostics, and treatment of TMJDs. Toward that end, recommendations were made on how teams could be created within Academic Health Centers and the National Institutes of Health to facilitate the research effort. Recommendations also were made on how current education curricula and research training could be improved to encourage young clinical investigators from appropriate clinical specialties to become engaged in TMJD-related research.

The active participation of patients in these discussions was invaluable. It was also gratifying to see an increasing number of student investigators involved in addressing the challenges of TMJDs and, it is hoped, ready to assume a future leadership role. As always, I want to express my thanks to the TMJA Scientific Meeting Program Committee for their numerous contributions to the planning and organization of this outstanding fourth meeting.

Allen W. Cowley, Jr., Ph.D.
Chairman, Scientific Meeting Program Committee

A Word from the NIDCR Director

The TMJ Association has once again distinguished itself by sponsoring a scientific meeting. This meeting, titled ***A Systems Approach to the Understanding of TMJ as a Complex Disease***, is the fourth in a series of biennial scientific events sponsored by the Association. Collectively, these meetings are aimed at addressing important emerging issues facing both patients and researchers. The most recent meeting continued this tradition by addressing the fact that temporomandibular joint and muscle disorders (TMJDs) do not exist alone. They are part of a collection of disorders that are both influenced by, as well as influence, other medical conditions such as chronic fatigue syndrome, cardiovascular disorders, hearing problems such as tinnitus, digestive and gastrointestinal disorders, and sleep disorders, to name a few. In short, TMJDs are part of a very complex system. This meeting focused on the reality of pain and dysfunction faced by many TMJD patients on a daily basis. The ultimate goal of the meeting was to shape research that will help alleviate the pain and suffering experienced by TMJ patients. As in past meetings there was active involvement of and input from patients suffering from TMJDs and co-morbid conditions. This is key in helping to ensure that research remains focused on those who benefit from outcomes.

A very exciting and important aspect of this meeting was the involvement of 19 student investigators, the future of research on TMJDs. Some of them were invited to make short presentations about their research in addition to being available to discuss their research during organized poster sessions. The quality of the presentations, along with the specific research topics addressed in the posters, augers well for the future of TMJD research. Once again The TMJ Association is to be congratulated for its innovation and creativity in including these students in the program.

Lawrence A. Tabak, D.D.S., Ph.D.
Director, National Institute of Dental and
Craniofacial Research

Scientific Meeting Program Committee

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Fourth Scientific Meeting of The TMJ Association

A Systems Approach to the Understanding of TMJ as a Complex Disease

The Fourth Scientific Meeting of The TMJ Association, ***A Systems Approach to the Understanding of TMJ as a Complex Disease***, was driven by concerns, long held by temporomandibular joint and muscle disorder (TMJD) patients, that there is more to this complex condition than dysfunction and pain of the jaw joint and muscles. The diverse set of co-morbid conditions found in the population of TMJD patients indicates that this is a multifaceted disorder and that diagnostic and therapeutic procedures must involve interdisciplinary approaches.

The overall goal of this meeting was to move research and treatment of TMJDs forward in the next decade by developing recommendations to meet the scientific and clinical challenges in creating an integrated systems approach appropriate to TMJD as a complex disease. To this end, scientists from diverse fields were invited to:

1. Characterize the multiple symptoms and co-morbid conditions found in TMJD patients.

2. Develop recommendations for strategies and initiatives that could facilitate the development of cross-disciplinary and interdisciplinary research programs within our Academic Health Centers and across the Institutes and Centers of the National Institutes of Health.

3. Identify and recommend ways and means by which young clinical investigators from a variety of clinical specialties can become engaged in TMJD-related research.

The Fourth Scientific Meeting of The TMJ Association:
A Systems Approach to the Understanding of TMJ as a Complex Disease
Federation of American Societies for Experimental Biology
Bethesda, MD
September 11-12, 2006

Monday, September 11, 2006

8:00 – 8:10 a.m. **Welcome**
Martin Frank, Ph.D., Executive Director, American Physiological Society, Bethesda, MD

Opening Remarks
Allen W. Cowley, Jr., Ph.D., Program Committee Chairman, Medical College of Wisconsin, Milwaukee, WI

NIH Welcome and Directives
Lawrence A. Tabak, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research, Bethesda, MD

Session 1: ***TMJDs as a Model of a Complex Disease Influenced by Environmental and Iatrogenic Risk Factors***

Session Chairman: Christian S. Stohler, D.M.D., Dr. Med. Dent., University of Maryland Dental School, Baltimore, MD

8:10 – 8:20 a.m. **Introduction to the Patient Survey**
Terrie Cowley, The TMJ Association, Milwaukee, WI

8:20 – 8:50 a.m. **Factors Characterizing TMJ Diseases and Disorders: A Survey of Affected Individuals**
Jane M. Kotchen, M.D., M.P.H., Medical College of Wisconsin, Milwaukee, WI

8:50 – 9:00 a.m. **A Patient's Perspective**
Linda Hoover, Toledo, OH

9:00 – 9:30 a.m. **Interdisciplinary Approaches for the Study of TMJ Patients: Co-morbid Conditions that can Arise from Chronic Pain**
Christian S. Stohler, D.M.D., Dr. Med. Dent., University of Maryland Dental School, Baltimore, MD

9:30 – 10:00 a.m. **The C1-C2 Spinal Cord: Nociceptive Processing of Input from the Vagus and the Neck and Jaw**
Robert D. Foreman, Ph.D., University of Oklahoma Health Sciences Center, Oklahoma City, OK

10:00 – 10:15 a.m. **Break**

10:15 – 10:45 a.m. **Uncovering the Local Biochemical Milieu of Myofascial Trigger Points: Implications in TMJ-Related Pain**
Jay P. Shah, M.D., Clinical Center, National Institutes of Health, Bethesda, MD

10:45 – 11:15 a.m. **Brief Poster Summaries**

Regulation of CGRP Expression in an in Vivo Model of TMJ Inflammation
Vinit Patil, M.S.
V. Patil and P. Durham, Missouri State University, Department of Biology, Springfield, MO

Activation of Trigeminal Nociceptors by Mechanical Stimulation via Integrins
Samantha A. Moore, Ph.D.
S. A. Moore, Y. Cui, R. Gomex, J. Wirthlin, C. Pokorney, G. Zardeneta, and S. B. Milam, Department of Oral and Maxillofacial Surgery, University of Texas Health Science Center-San Antonio, San Antonio, TX

Effect of Interleukin-1Beta on NRI-Serine 896 Phosphorylation in the Rat Spinal Trigeminal Nucleus
Wei Guo, M.D., Ph.D.
W. Guo, M. Watanabe, S-P. Zou, R. Dubner, and K. Ren, Department of Biomedical Sciences, Dental School and Program in Neuroscience, University of Maryland, Baltimore, MD

The Effect of Interleukin-10 and Fluorocitrate on Masseter Inflammatory Hyperalgesia
Kohei Shimizu, D.D.S.
K. Shimizu, R. Dubner, and K. Ren, Department of Biomedical Sciences, Dental School and Program in Neuroscience, University of Maryland Dental School, Baltimore, MD

Sex Differences in the Nociceptive Processing of Temporomandibular Disorders (TMD) Patients
Eleni Sarlani, D.D.S., Ph.D.
E. Sarlani, E. Grace, D. Rodriguez, D. Pennington, and J. Greenspan, University of Maryland Dental School, Research Center for Neuroendocrine Influences on Pain, Baltimore, MD

Sensory Feedback from Mechanical Nociceptors in the Masseter Muscle can be Presynaptically Modulated
Dean A. Dessem, Ph.D.
D. Dessem and R. Ambalavanar, Department of Biomedical Sciences and Program in Neuroscience, University of Maryland Dental School, Baltimore, MD

11:15 – 12:15 p.m. **Break-out Group Discussions to Discuss Strategies on How to Develop Optimal Cross-Disciplinary Platforms for TMJ Research**

Discussion Leaders:
Group A: Christian S. Stohler, D.M.D., Dr. Med. Dent., University of Maryland Dental School, Baltimore, MD
Group B: Stephen B. Milam, D.D.S., Ph.D., University of Texas Health Science Center - San Antonio, San Antonio, TX
Group C: James P. Lund, B.D.S., Ph.D., McGill University, Montreal, Quebec, Canada

12:15 – 1:45 p.m. **Lunch/Poster Session**

Session 2: ***Chronic Pain as a Model of Clinical Complexity***
Session Chairman: Ronald Dubner, D.D.S., Ph.D., University of Maryland Dental School, Baltimore, MD

1:45 – 2:15 p.m. **Translating New Insights in Our Understanding of Chronic Pain from the Bench to the Bedside**
Ronald Dubner, D.D.S., Ph.D., University of Maryland Dental School, Baltimore, MD

2:15 – 2:45 p.m. **Pain and the Complex Entity of Reflex Sympathetic Dystrophy**
Wilfrid Jänig, M.D., Christian-Albrechts-Universität, Kiel, Germany

2:45 – 3:00 p.m. **Break**

3:00 – 3:30 p.m. **Evidence of Nociceptive-Neuroendocrine Control of Pain**
Jon D. Levine, M.D., Ph.D., University of California, San Francisco, CA

3:30 – 4:30 p.m. **Break-out Group Discussions to Determine How Lessons Learned from Pain Research can Guide Efforts to Develop Similar Strategies for TMJ Research**

Discussion Leaders:
Group A: Ronald Dubner, D.D.S., Ph.D., University of Maryland Dental School, Baltimore, MD
Group B: Stephen L. Gordon, Ph.D., Healthonics, Inc., Bethesda, MD

Group C: Jon D. Levine, M.D., Ph.D., University of California at San Francisco, San Francisco, CA

Group D: William Maixner, D.D.S., Ph.D., University of North Carolina at Chapel Hill, Chapel Hill, NC

Tuesday, September 12, 2006

Session 3: ***Diverse Approaches Used to Study Other Complex Diseases***

Session Chairman: Allen W. Cowley, Jr., Ph.D., Medical College of Wisconsin, Milwaukee, WI

8:00 – 8:30 a.m. **Integration and Multiscale Analysis of Biological Pathways Responsible for Complex Diseases Such as TMJ**
Allen W. Cowley, Jr., Ph.D., Medical College of Wisconsin, Milwaukee, WI

8:30 – 9:00 a.m. **Is Menopausal Hormone Therapy a Protective Factor or a Risk Factor? Challenges of Managing a Complex Hormonal State**
Judith L. Turgeon, Ph.D., University of California-Davis School of Medicine, Davis, CA

9:00 – 9:30 a.m. **Genetics as the Glue for Translational Research**
Howard J. Jacob, Ph.D., Medical College of Wisconsin, Milwaukee, WI

Session 4: ***How to Create a Workforce Within our Academic Healthcare Centers to Match the Science Required***

Session Chairman: Theodore A. Kotchen, M.D., Medical College of Wisconsin, Milwaukee, WI and National Center for Scientific Review, National Institutes of Health, Bethesda, MD

9:30 – 10:00 a.m. **Training Multidisciplinary Translational Clinical Scientists**
Sharon M. Gordon, D.D.S., M.P.H., Ph.D., University of Maryland, Baltimore, MD

10:00 – 10:15 a.m. **Break**

10:15 – 10:45 a.m. **Understanding and Treating TMJ Disorders: A Modest Proposal**
Theodore A. Kotchen, M.D., Medical College of Wisconsin, Milwaukee, WI and National Center for Scientific Review, National Institutes of Health, Bethesda, MD

10:45 – 11:15 a.m. **Brief Poster Summaries**

TMJ Chondrocytes Isolated from Biglycan/Fibromodulin Double-Deficient Mice have Altered Proliferation and Differentiation in Vitro

Mildred C. Embree, B.S.
M. Embree, B.S.[1,2], Y. Bi, Ph.D.[1], C. Inkson, Ph.D.[1], T. Kilts[1], and M. Young, Ph.D.[1]
[1]Molecular Biology of Bones and Teeth Unit, Craniofacial and Skeletal Diseases Branch, NIDCR, NIH, Bethesda, MD
[2]Medical University of South Carolina, College of Dental Medicine, Charleston, SC

Nociceptive Modulation of Jaw Muscle Spindle Activity Requires Fusimotor Drive
Radi Masri, B.D.S, Ph.D.
R. Masri, J. Y. Ro, and N. Capra, Department of Biomedical Sciences, Baltimore College of Dental Surgery, University of Maryland Dental School, Baltimore, MD

Analgesia Produced by Epoxyeicosatrienoic Acid in the Ventral Periaqueductal Gray of the Rat
Maia Terashvili, Ph.D.
M. Terashvili[1], P. F. Pratt[2], and D. Harder[1]
[1]Department of Physiology
[2]Department of Anesthesiology, Pharmacology and Toxicology
Cardiovascular Research Center, Medical College of Wisconsin, Milwaukee, WI

Mechanical Signals Generated by Appropriate Physical Therapies can Prevent Fibrocartilage Degradation and Induce Repair in TMJ Disorders (TMJDs)
Danen Sjostrom, B.S.
D. Sjostrom, T. J. Knobloch, and S. Agarwal, Ohio State University, College of Dentistry, Section on Oral Biology, Columbus, OH

Gap Junction Proteins in Reactive Astrocytes Contribute to Inflammatory Hyperalgesia
Hu Wang, M.D., Ph.D.
H. Wang, S-P. Zou, R. Dubner, and K. Ren, Department of Biomedical Sciences, Dental School and Program in Neuroscience, University of Maryland, Baltimore, MD

Identification of Proteoglycan 4 in the Temporomandibular Joints of Baboons
Jennifer L. Schulze, M.S.
J. L. Schulze, S. B. Milam[1], and R. G. LeBaron
Department of Biology, University of Texas at San Antonio
[1]Department of Oral and Maxillofacial Surgery, University of Texas Health Science Center - San Antonio, San Antonio, TX

11:15 – 12:15 p.m. **Break-out Group Discussions to Determine how Diverse Approaches can be Formulated into Cross-Disciplinary Research Programs and How to Create a Workforce Required for These Efforts Within our Medical and Dental Institutions**

Discussion Leaders:

Group A: Howard J. Jacob, Ph.D., Medical College of Wisconsin, Milwaukee, WI

Group B: Allen W. Cowley, Jr., Ph.D., Medical College of Wisconsin, Milwaukee, WI

Group C: Theodore A. Kotchen, M.D., Medical College of Wisconsin, Milwaukee, WI and National Center for Scientific Review, National Institutes of Health, Bethesda, MD

12:15 – 1:45 p.m. **Lunch/Poster Session**

1:45 – 2:45 p.m. **Panel of Discussion Leaders to Summarize and Consolidate a Set of Overall Recommendations**

2:45 – 3:00 p.m. **Closing Remarks**
Lawrence A. Tabak, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research, Bethesda, MD

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National Institute on Drug Abuse
National Institute of Neurological Disorders and Stroke
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Mr. John D. Benjamin
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Ms. Anne Breslin
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Ms. Jaqueline N. McVay
Ms. Paula Miller
Ms. Audrey Norman
Mr. Larry Reingold
Mrs. Kaye H. Shive
Mrs. Joanne Walsh

The TMJ Association would like to thank Dr. Martin Frank, Ms. Linda Allen, and Ms. Aira Sumpter for their assistance to the Association in coordinating this meeting at the FASEB Conference Center, and the TMJ patients who made presentations as well as the many for whom the conference offers hope through research.

A Systems Approach to the Understanding of TMJ as a Complex Disease

By Judy Randal

The temporomandibular joints—they are paired—are located at the upper ends of the lower jaw at the points, just in front of each ear, where the lower jaw meets the skull. Besides being essential to biting and chewing food, their actions enable people to talk, sing, smile, whistle, kiss, and even breathe. Truly multipurpose, they are exceptionally hardworking and susceptible to temporomandibular joint and muscle disorders, a set of conditions called TMJDs. The hallmark features of these conditions are pain in the jaw and surrounding tissues and limitations in jaw movements.

Over ten million American adults have these conditions at any given time. By far, more women than men experience symptoms, with the majority—about 90 percent—being women of childbearing age. While often mild and transient, TMJDs can be severe and persistent. Some sufferers, for example, are indefinitely on liquid diets, because their mouths will not open wide enough to accommodate solid foods. Some have such intractable pain that they are housebound, require constant care, some even needing pain pumps to administer medication. According to The TMJ Association, a national patient advocacy group based in Milwaukee, Wisconsin, some of the most seriously affected become so despondent that they commit suicide.

Very little is known about the condition's predilection for women or, for that matter, why some women get it and others don't. The same goes for the rest of its proclivities, which include having symptoms that vary in extent and severity from one patient to another and even in the same patient over time. An intricate mix of genetic susceptibility, environmental exposures and other factors—among them stress and trauma—is thought to underlie these disorders. But as things now stand, virtually everything about their causation and behavior is unexplained.

The clinical picture is similarly confusing. Billions of dollars a year are spent on treating TMJDs, yet virtually none of the therapies used for the purpose have been rigorously studied to determine how well—or poorly—they work. "We know little about what we are calling TMJDs," said Terrie Cowley, President and co-founder of The TMJ Association at its fourth scientific meeting. "And we don't know what to recommend for treating patients either." (The meeting was held September 11-12, 2006 on the Bethesda, Maryland campus of the Federation of American Societies for Experimental Biology.)

Christian S. Stohler, D.M.D., Dr. Med. Dent., University of Maryland Dental School, echoed Cowley's remarks in an opening address decrying the fact that current diagnostic systems fail to capture the often multiple systemic problems TMJD patients experience, affecting sensory, motor, and autonomic nervous systems. Systematic research and an appreciation of individual differences in response patterns are essential, he said. Meanwhile, the lack of validation of

current therapies continues to bedevil TMJD care, with potential harm to patients.

Unfortunately, many TMJD sufferers are unaware of this situation and risk making treatment decisions they may later regret. Linda Hoover, an invited speaker at the September 2006 meeting, served as a textbook case of what can ensue.

Ms. Hoover, a Toledo, Ohio teacher, has been living with TMJD problems for almost a quarter century—ever since loosening teeth and an overbite that grew worse came on in her early 20s. This led, when she was 28, to her first jaw operation. Nine more such surgeries followed. Among them were three that fitted her with jaw implants, the three it took to remove them—they had shattered into fragments and were causing her tremendous pain—and one in which the culprit implants were replaced with grafts from two of her ribs.

Along the way, she has had to contend with ear pressure and hearing problems, with nerve damage that has affected her vision, with migraine-type headaches and with mitral valve prolapse (damage to a part of heart), not to mention staggering dental bills due to ongoing and seemingly unavoidable problems with her teeth. None of this makes Ms. Hoover unique or even unusual. Co-morbid conditions of many kinds, including allergies, chronic fatigue syndrome, fibromyalgia, interstitial cystitis, irritable bowel syndrome, sleep disorders, cardiac arrhythmias, vertigo, tinnitus, ear pain, as well as the headaches and other complaints that have troubled her—are common in people who have TMJDs.

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The theme of The TMJ Association's fourth scientific meeting was ***A Systems Approach to the Understanding of TMJ as a Complex Disease***. All of the Association's previous scientific meetings dealt with avenues of research that hold promise for TMJD patients and this one did, too. For example, Jay P. Shah, M.D., of the Clinical Center of the National Institutes of Health (NIH), is interested in the effect of trigger points on certain muscles that serve the head, neck or jaws and spoke of work he and his colleagues have done which sheds light on the biochemical behavior of these sites and its possible relationship to the pain of TMJDs. The meeting's major focus, however, was on a young and innovative field called "systems biology" and the further opportunities it could open to make headway against these conditions.

Reductionism—The Bottom-up Approach

In brief, the traditional bottom-up approach says that living things can best be understood by learning more and more about ever smaller parts of them—down, in fact, to the molecular level of genes and proteins. This approach, called reductionism, has long been the driving force behind biomedical research. But as good as it is at getting detailed information about individual parts of the body and the molecules that comprise them, reductionism has a weakness: it is not good at determining how that information plays out in the complex and dynamic universe that is the body as a whole. "Systems biology," by contrast, aims to explain how the information plays out in the whole body.

Allen W. Cowley, Jr., Ph.D., who chairs the Scientific Meeting's Program Committee, is, in addition to being Terrie Cowley's husband, a professor and Chairman of the Department of Physiology at the Medical College of Wisconsin in Milwaukee. There he heads a team that has enlisted the systems biology approach in an effort to understand what accounts for the many manifestations of "essential hypertension," meaning high blood pressure of unknown cause. As TMJDs similarly come in what Cowley calls "many flavors," also of unknown causes, he and some of his colleagues spoke at the meeting about aspects of their research that might serve as a template for the study of TMJDs.

Starting with the basics, Cowley noted that the issues and diseases that systems biology deals with are too complex for any one research specialty to tackle by itself, though this is the norm in the bottom-up approach world. By constrast, the systems approach engages researchers from a broad range of scientific disciplines who collaborate—on more or less equal footing—so that advantage can be taken of their differing perspectives and skills. As it has been accepted practice when a biomedical study is undertaken to have one scientist serve as the "principal investigator" who outranks all the others, the systems approach is a departure from the traditional way of doing things.

Two of the tools that are invaluable to systems biology studies were featured in Cowley's presentation. One of those was the use of animal models that have been developed for some human diseases—i.e., animals having a trait or traits often observed in people having that illness. For example, because a high salt intake often elevates human blood pressure, the animals the hypertension project is using for its experiments are salt-sensitive laboratory rats. The other was bioinformatics, a collection of computer-driven mathematical and statistical techniques that can make sense of reams of numerical data that would otherwise defy analysis.

These tools are especially adept at cutting through complexity when used in conjunction with each other. Many genes, for example, are polymorphic, meaning that there are several versions of them, any of which can occupy a particular spot on a particular chromosome. The genes that determine blue or brown eye color are a familiar example. Thanks to genetic engineering methods, these variants can be individually studied in the animal model (assuming there is one) for a given disease. And thanks to that and the power of bioinformatics, it has begun to be possible to get a handle on which variants have what biological effects.

From Research Results to Clinical Practice—and Back Again

It is, of course, one thing to make fundamental discoveries about complex diseases in animal models and quite another to do the so-called "translational research" which builds on those discoveries to ready them for clinical trials. Cowley's colleague, Howard J. Jacob, Ph.D., spoke on this topic at the meeting, stressing that genetic studies will be needed at every step along the way, if those clinical trials are to materialize.

More specifically, Jacob reported that a technique called gene resequencing can be expected to help researchers identify genes and sets of genes that predispose people to one or another complex illness with a degree of certainty not now possible. Also

on the horizon, though more distantly, he said, are other innovations, including techniques that in a single day and for about $1,000 will detect and map the entirety of an individual's genome, thus putting on record what there is about him or her that is genetically unique.

The goal here is to provide physicians with sharper tools for the diagnosis of complex diseases and patients who have these illnesses—or are at risk for them. Once individualized genomes become available, for example, doctors should be able to use them not only to determine what is wrong with someone (or will be), but also to customize his or her overall healthcare and therapy for optimal results. Though the day of such highly personalized medicine is not yet here, Jacob predicted it will come.

Another of the meeting's speakers, Ronald Dubner, D.D.S., Ph.D., of the University of Maryland Dental School, also has high hopes for translational research. Besides shortening the time it takes to ready basic research findings for clinical trials, he said, the process can be expected to work in reverse. In other words, the translational approach, when working properly, will encourage clinical researchers to make a habit of paying close attention to how diseases behave and of passing their observations back to basic researchers for exploration in the laboratory.

The Quest for Pain Control

Dubner further noted that treatment for pain "still relies mainly on drugs that have been available in one form or another since the early 20th century." Though doubting that the translational research model will produce "a silver bullet for persistent pain," he is nonetheless confident that its interdisciplinary approach can be counted on to change the situation for the better.

Sharon Gordon, D.D.S., M.P.H., Ph.D., a colleague of Dubner's at the University of Maryland Dental School, and before that at the National Institute of Dental and Craniofacial Research (NIDCR), did not disagree. Moreover, she applauded the efforts the National Institutes of Health, including the NIDCR, are making to get the biomedical research community to change its ways.

However, she warned the meeting of several institutional barriers that will need to be overcome if the effort is to succeed. For example, universities have traditionally separated training for clinical researchers from basic researchers, they have excluded some health and allied health professionals from research training, and to this day medical school curricula include little teaching about pain, the control of pain, and literally nothing about TMJDs.

But Theodore Kotchen, M.D., still another speaker at the meeting, had a somewhat different view. Besides being a professor and department head at the Medical College of Wisconsin, Kotchen is a Scientific Advisor to the National Institutes of Health and so had a hand in developing a recently launched NIH program which he thinks could benefit the TMJD community.

In brief, the program is meant to encourage the development of Academic Health Centers (AHCs), which are more familiarly known as medical schools and their teaching hospitals. The AHCs will be encouraged to get into the translational research swing of things by providing them with funding to train laboratory scientists, clinical investigators and others

to collaborate, as appropriate. As Kotchen sees it, a plan built around TMJDs that an AHC could use to apply for one of the new program's so-called Clinical and Translational Science Awards should have a reasonable chance of being funded.

Learning from Other Models

Also discussed at the meeting was what might be learned about TMJDs by studying diseases that have some features in common with it. One of those diseases is Reflex Sympathetic Dystrophy Syndrome (RSDS), an older descriptive term that is being replaced by "Complex Regional Pain Syndrome" (CRPS), which comes in two types: one involving nerve injury, the other not. Both typically cause swelling in one or more of a patient's limbs along with a change in color and temperature of the skin over the affected body parts. What makes both types somewhat like TMJDs is that they overwhelmingly occur in women and that the pain can be extraordinarily difficult to relieve.

Wilfrid Jänig, M.D., of Christian Albrechts University in Kiel, Germany, has proposed that CRPS entails pathophysiological interactions between the central and peripheral nervous systems. He stated that brain research based on this hypothesis could help to sort out what sets this "puzzling syndrome" in motion and keeps it going to the point where CRPS pain, instead of getting better or stabilizing over time, actually worsens. Since Jänig believes that abnormalities of neural regulation play a role in TMJDs and other complex disorders that predominantly target women, including fibromyalgia, irritable bowel syndrome, and rheumatoid disease, he suggested that brain research could be important in improving understanding of all of these conditions.

Also discussing pain syndromes at the meeting was Jon D. Levine, M.D., Ph.D., of the University of California, San Francisco. His topic was generalized pain syndromes, a technical term for chronic painful conditions that some consider to be strictly psychological because there are no definitive laboratory tests to diagnose them. TMJDs are included among them, as well as many others that predominantly strike women (again, fibromyalgia and irritable bowel syndrome, to mention just two).

Generalized pain syndromes tend to share some symptoms and many patients who have one of these disorders have one or more of the others, too. Levine's educated guess is that this overlap is due to interactions between the nervous system and endocrine (hormonal) factors. He and his colleagues are using laboratory rats whose vagus nerves in the abdomen have been surgically severed, a condition which results in a chronic generalized state of increased sensitivity to pain (hyperalgesia), more so in female rats. The vagus nerves—one arises on each side of the brain stem—supply nerve fibers to the throat, larynx, trachea (windpipe), lungs, heart, esophagus, chest, abdomen, and part of the colon. Of particular interest, Levine reported, is that when the test animals are chronically exposed to intermittent stress—much as many people are—the measurable pain responses of the females are greater than those of the males, presumably due to activation of the sympathetic nervous system and the neuro-endocrine pathways that lead to the release of the so-called stress hormones from the adrenal glands.

Robert D. Foreman, Ph.D., of the University of Oklahoma, is another scientist with an interest in the behavior of the vagus nerves and whose work

may have relevance to TMJD research. In brief, some patients with angina pectoris, an often painful heart disorder, experience pain in the chest and upper arm while others primarily experience it in the jaw and neck. Animal studies done by Foreman and his colleagues have demonstrated that certain fibers of the vagus nerves are the pathway through which anginal pain radiates from the heart to the neck and jaw.

Foreman suggested that experiments based on the angina findings could be used to improve understanding of the jaw pain of TMJDs. He further noted that angina pectoris and gastroesophageal reflux disease (familiar to many as GERD or heartburn) can be difficult to tell apart because of the chest pain they have in common. Again, he said, a better understanding of the nervous system pathways that contribute to the confusion between the two disorders might also be helpful in studying TMJDs.

The issue of hormonal involvement in TMJDs was also discussed by Judith L. Turgeon, Ph.D., University of California-Davis School of Medicine, but in the context of controversial results of clinical studies and trials using female sex hormone replacement therapy in post-menopausal women. Her point was that much remains unknown about the effects, whether harmful, neutral, or beneficial, of varying levels of estrogens and progestins on organs and systems outside the ovaries. More research is needed to unravel the effects of sex hormones on target tissues, as well as how the estrogens, in particular, affect inflammatory processes.

What Patients Say

Much of what is known about many diseases was discovered with the help of epidemiological studies and this could certainly be true for TMJDs. Jane M. Kotchen M.D., M.P.H., an epidemiologist at the Medical College of Wisconsin, and her colleagues made a start in that direction when they developed a questionnaire and e-mailed it to 10,000 of the 100,000 people in The TMJ Association's patient database.

Kotchen called the web-based survey "a work in progress," noting that it lacked a sizeable control group and had other limitations. For example, only 1,540 of the people who were sent the questionnaire responded. This response level can be explained by some of the following factors: computer technical issues, such as programming errors, the user's computer speed, web browser incompatibility, security, obsolete e-mail addresses, full in-box and spam box settings. Some indicated the questionnaire was too long, others didn't want to involve a friend as a control, some no longer had a TMJD problem, for some there were legal reasons, some felt uncomfortable providing information via the internet, others stated the survey evoked too many bad memories and feelings of hopelessness, and some were simply too busy to participate. Nonetheless, as a vehicle for obtaining preliminary information on the past experience of TMJD patients, it was a success.

That preliminary information could well spark future studies that could be of immediate practical benefit. The responses to a survey question that asked patients to rate the effectiveness of 22 therapies—none of which were drugs or surgery—was a case in point.

The top five responses, in order, about effective pain relief remedies were: hot and cold compresses, Jacuzzi or hot baths, craniosacral therapy, chiropractic therapy, and acupressure. Bringing up the rear were other measures such as aromatherapy, bridgework and dentures, magnetic therapy, equilibration (teeth ground down) and Facial Flex (an exercise system that uses elastic bands). More formal validation of these findings could potentially steer patients to treatments more likely to help them and not do them lasting harm.

Some of the survey's other findings were:

- 89.9% of the survey respondents were women.

- The average age of the respondents was 40.8 years. Their average age at the onset of symptoms was 25.4 years, though the average age at diagnosis was almost 5 years later: 30 (29.5 years).

- Only 6% of the respondents reported having been free of TMJ-related pain "in the past four weeks" and most said the pain had interfered with their activities, to at least some degree. The pain was most often described as being "off and on"—in other words occurring unpredictably, rather than at any particular time of day.

- When it came to prescription drugs for pain relief that survey respondents had used, anti-inflammatories and antidepressants (in that order) were the winners. However, over-the-counter pain remedies were not far behind. This may have been due in part to another of the survey's findings: 37.8% of the respondents reported difficulty in obtaining pain medications (presumably those only available on prescription) and 12.1% reported it as having been "impossible."

- Almost as many of the 284 respondents who reported having had a single bilateral TMJ surgery, had had 2 or 3 surgeries; some patients had undergone 6 to 9 surgeries, with some having had even more.

- Of those answering the question about alcohol for pain relief, 20% said they had used it for this purpose. Less than 10% of the respondents had (in addition or instead) sought to ease their pain with smoking or recreational drugs.

- A key finding was that 29% of the respondents—a significantly greater percentage than in the U.S. adult population as a whole—has never married. While the survey did not specifically ask the respondents whether they felt that having to cope with TMJD problems had affected their marital status (or marriages), that seems a reasonable possibility. In any case, the questionnaire left little doubt that TMJDs can have a considerable negative impact on the patient's quality of life. As Terrie Cowley commented, "There is, besides the physical discomfort involved, the stigma of having a condition that is poorly understood."

The meeting participants were very interested in the findings of the survey. Howard Jacob was particularly emphatic on this point, saying that the Association's patient database could be invaluable in a range of studies, from exploring the role of genetic factors to facilitating clinical trials of candidate therapies. "Finding patients that meet rigorous study criteria and who are willing to be studied is arguably the single largest bottleneck for translational research, and that bottleneck typically eats up 50-75% of the dollars a clinical study costs," Jacob told the meeting. Thus his view that "The TMJ Association and its active members offer a chance to build a resource" that is now in short supply. Patient groups are becoming important partners to researchers and physicians searching for cures.

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Lawrence A. Tabak, D.D.S., Ph.D., heads the National Institute of Dental and Craniofacial Research, which co-sponsored The TMJ Association's fourth scientific meeting. Dr. Tabak is also deeply involved in the so-called Roadmap Initiative of the National Institutes of Health which, among other things, is promoting systems biology and translational research as a way to speed up the application of new knowledge to patient care.

At the meeting's opening session, Dr. Tabak encouraged the young scientists present to do TMJD research, organized along the multidisciplinary lines the NIH Roadmap Initiative advocates, saying that this would bring them "into this field on the ground floor" and thus give them "opportunities to make trailblazing discoveries that likely would improve patients' lives."

But as the meeting drew to a close, Dr. Tabak—though again placing his faith in the rising generation of scientists—made the disturbing observation that, despite the enthusiasm of the meeting's more seasoned scientists for tackling TMJDs with interdisciplinary research, little had been done to get such a program going.

"The truth," Dr. Tabak said, "is that there have been abundant opportunities in the last few years through grants offered in connection with the Roadmap Initiative to work towards the very things you suggest." Yet, he reported, "not a single grant application dealing with TMJ" that would provide the kind of interdisciplinary training that would be necessary for this purpose has been submitted to the NIH. He issued the challenge to bridge the divide between what is possible and current practice.

Research Recommendations from

The Fourth Scientific Meeting of The TMJ Association, September 2006

A Systems Approach to the Understanding of TMJ as a Complex Disease

Goal I. Characterize the signs, symptoms and conditions experienced by TMJD patients beyond pain and dysfunction affecting the jaw and associated tissues.

Reports by TMJD researchers, clinicians, and patients at the meeting, as well as a body of information gathered by The TMJ Association over the years, affirm that a substantial number of patients diagnosed with TMJDs experience other body symptoms or co-morbid conditions.

These observations are consistent with a 2001 Agency for Healthcare Research and Quality report which found TMJD patients use significantly more healthcare services and generate more costs than non-TMJD patients and that most of the care used by the patients is not directly related to TMJD conditions. This indicates that a significant portion of patients with TMJDs have other health problems, and that in many patients, TMJD itself may be a symptom or manifestation of one or more health problems. It is evident that TMJDs are a complex family of conditions influenced by genetics, gender and environmental and behavioral triggers mediating the vulnerability of patients to TMJDs and manifesting as more than dysfunction and pain of the jaw joint and muscles.

See *Exhibit 1* on pg. 23 for a list of symptoms and co-morbid conditions which was developed at the meeting. These are not rank-ordered by prevalence or severity, although it is evident that the vast majority of patients present multiple symptoms and co-morbid conditions to their healthcare providers.

Initiative: There is a need for updated epidemiological and demographic data on the prevalence of TMJDs in the community at large, as well as those subsets of individuals who seek care, and, of that group, those who proceed to chronic TMJD pain and jaw dysfunction. Especially needed is information on the number of TMJD patients who report other body symptoms or co-morbid conditions and their nature and severity. For all of these studies it will be important to have appropriate control groups for comparison of the prevalence of co-morbidities in patients with TMJD.

Goal II. Develop strategies and initiatives to facilitate cross-disciplinary and interdisciplinary research programs of basic, translational, and clinical research on TMJDs within Academic Health Centers and across the Institutes and Centers of the National Institutes of Health.

The mechanism of choice to meet this goal is through the establishment of Regional Centers of Excellence (CoE). Such CoEs could be positioned within one or among several Academic Health Centers or institutions, working in collaboration with community caregivers. The Centers should be venues for the conduct of basic and clinical research, as well as the establishment of integrated multidisciplinary educational programs. Furthermore, CoEs would provide the resources and infrastructure necessary to manage large, complex projects in translational and clinical research.

A Regional TMJD CoE to advance research in this field should be established and supported by the NIDCR. This should be a multidisciplinary program incorporating the various scientific and clinical disciplines required to study this complex disease. The CoE should develop and disseminate information to the broader community of investigators who are involved in TMJD research. This program would aim to provide tools, data, reagents, and training to enable researchers to confidently approach research related to TMJDs. As the resources and knowledge become available, links to information about their availability and distribution would be provided by this site.

CoEs could be affiliated with Clinical and Translational Science Award (CTSA) programs developed by the National Center for Research Resources. The role of the CTSA would be to support an infrastructure for multidisciplinary clinical research and clinical research training. A CTSA program would provide the opportunity to develop a model TMJD proposal for the type of multidisciplinary program that the NIH is encouraging and supporting through NIH Roadmap Initiative resources. Such an approach could provide both the flexibility and stimulus for institutions to pool their resources and expertise with the goal of increasing the efficiency and speed of clinical and translational research. If investigators funded for TMJD research are a part of a CTSA program, trainees from a variety of disciplines could be attracted to these potential mentors.

At present, translational research remains inefficient, slow, and in need of major infrastructure changes to meet the needs of advancing the understanding, diagnosis and treatment of complex diseases/syndromes such as TMJDs. A database of TMJD patients (as maintained by The TMJ Association) can provide a valuable resource which TMJD Centers can draw upon for patient volunteers in translational (bench to bedside and bedside to community) and clinical research studies.

Programs that are developed within the CoEs should partner with other institutions with strong research programs in basic research (benchside), excellent clinical practice (bedside), and strong healthcare programs (community). They should integrate the many facets of TMJDs using interdisciplinary approaches in research, prevention, diagnosis, and treatment.

As illustrated by the template represented in *Figure 1* on pg. 24, TMJDs could be the prototype of a complex disease as part of a broader translational academic research center. Such a research center would recognize the value of research teams and the contributions of multiple co-principal investigators. The overall goal is to develop programs that range from pre-clinical models to clinical research and translation into the community. The Center would be broad in scope, campus-wide, and encompass multiple institutions and campuses as required.

Central Core infrastructure. The program would be built around a core of shared resources to advance interdisciplinary and translational training and research. This core infrastructure would logically include the resources of a CTSA program and we would recommend that this be the case. Core resources would:

- Establish cost-efficient methods to recruit participants into a system-wide research database. The TMJ Association is a valuable partner for recruiting TMJD patients.
- Develop a TMJD-wide ontology (standardized nomenclature) linked to the database and existing ontologies to facilitate linking investigators within multidisciplinary research programs.
- Provide access to emerging technologies in the areas of high-throughput genomic sequencing, high-throughput genome-wide association studies, proteomics, imaging (fMRI, etc.), and computational biology.
- Provide a bioinformatics infrastructure and biostatistics core to support these diverse multidisciplinary activities. The core could be used to develop research questions from various studies and track outcomes based on the use of new diagnostics and clinical therapies.
- Support pilot collaborative projects and align new programmatic efforts with the clinical needs of hospital partners.
- Facilitate partnerships with community, state and regional patient support groups, hospitals, disease control centers, public heath programs, emergency care consortiums, to enable translation from bedside into the community.
- Establish training programs in interdisciplinary and translational research.
- Organize workshops and conferences focused on translational research and education.
- Develop educational programs for patients and healthcare providers (e.g., to define the disease and recommend treatments to conform to the standards of best practice based on outcomes; teach healthcare providers how to utilize new diagnostic tools and approaches).

Satellite TMJD Research Team with portal of entry to Central Core. Surrounding the Central Core of the Regional Center would be multidisciplinary teams of investigators focused on specific diseases. The TMJD research team would utilize the patient database of the Central Core and other core resources, as would all of the surrounding satellites associated with the Regional Center. The TMJD research team would include multidisciplinary pre-clinical and clinical scientists, physicians, dentists, nurses, and physical therapists. The satellite research teams must be mutually complementary to encourage and make available interdisciplinary collaborative studies of complex diseases. These activities

would be expected to be closely linked to a CTSA program. The TMJD research team may best be served by other satellite research teams with research focused on related areas such as pain, neurological diseases, allergy and immune disorders, arthritis and other musculoskeletal disorders, sleep disorders, endocrine, and cardiovascular disorders.

Strategies for conducting TMJD research within the research satellite.

- Use an integrated and cross-disciplinary platform (e.g., systems biology) approach to re-examine the etiology, diagnosis, and treatment of patients with TMJDs.
- Emphasize co-morbidity aspects of TMJDs and utilize multivariate analysis approaches to determine what clusters with TMJDs.
- Conduct outcome studies using standardized measures to determine therapeutic responses as part of the multivariate analysis of this complex disease.
- Develop animal models that mimic various aspects of complex TMJDs.
- Organize workshops involving business and academic leaders to support patient care, research and educational programs.
- Create a clearinghouse to disseminate quality information to patients, researchers and clinicians. This should be supported with web-based resources to facilitate interdisciplinary collaborations.
- Define functional goals of a systems-based study of TMJDs.
- Identify and recommend avenues whereby young clinical investigators from diverse clinical specialties can become engaged in TMJD-related research. For example:

    - Increase awareness by supporting seminars or workshops at national meetings attended by young clinical investigators.
    - Conduct workshops at national education meetings that will stimulate interest in developing relevant curricula in medical, dental and allied health schools.
    - Persuade accreditation agencies to increase medical and dental education requirements to include the state of scientific knowledge regarding TMJDs.
    - Expand career development programs at the NIH. Investigate the potential of additional federal (e.g., Department of Defense) and private funding opportunities (e.g., insurance companies).
    - Utilize NIH-related loan repayment programs and develop other financial incentives as needed.

Special TMJD Thought Leaders Conference. The Director of the NIDCR should convene a broadly constituted think tank of thought leaders to brainstorm strategies to achieve the goals of integrative and translational research, as well as the establishment of integrated, multidisciplinary education programs. Special emphasis should be placed on the development of viable business models that would support the establishment of functional multidisciplinary clinics (i.e., involving clinicians from medical specialties and other allied health areas) to serve as a core element of the proposed CoEs. Such a think tank should include outstanding:

- Basic and clinical scientists experienced with integrated programmatic research activities.
- Medical and dental school administrators.
- Hospital administrators.

- Expert business executives in fields related to healthcare systems.
- NIH administrators and scientists from multiple institutes/agencies engaged in advancing NIH Roadmap Initiatives.
- Representatives of the TMJD Interagency Working Group of the NIH and of the trans-NIH Neurosciences and Pain Consortium groups.

Reconstitution of NIDCR Program Project Grant Mechanism for TMJDs. To provide an immediate "jump start" for collaborative, interdisciplinary research and training in the TMJD field, the NIDCR should provide set-aside funding for program project grants focused on TMJDs as exemplifying a complex disease.

Goal III. Identify ways and means to attract and prepare young investigators from diverse clinical specialties for careers in TMJD-Related Research.

It was made abundantly clear at the Fourth Scientific Meeting of The TMJ Association that TMJD is a complex disease and to make meaningful progress in research, diagnosis and treatment, it will be necessary to bring together interdisciplinary groups of young investigators who can work with those who are trained to translate existing and new knowledge into treatment and practice. As currently defined by the NIH Roadmap Initiative, "multidisciplinary research" represents that which is applied to phenomena with multiple, diverse and varied causes that cannot be understood, managed or controlled through scientific activity organized on traditional disciplinary lines. "Translational research" is defined as that research linking bench laboratory results and patients' needs by facilitating the application of basic science findings to clinical care through multidisciplinary research.

Following are recommendations for creating a workforce required for these efforts related to TMJDs:

- Develop within the proposed Regional Centers of Excellence training programs that incorporate the paradigm shift required to carry out multidisciplinary and translational research. These graduate and post-doctoral training programs require programmatic support that would move the education and training of these scientists away from the institutional and educational cultures that have fostered scientific and clinical silos. These programs can be supported by existing NIH Roadmap Initiatives with a focus on complex diseases that foster:

  - Large multidisciplinary and translational program announcements.
  - Novel training programs that incorporate emerging areas of science, high risk/high impact research.
  - The concept of multiple Principal Investigators (PIs).
  - Clinical and Translational Science Awards.
  - Ph.D. training programs in translational methods as exemplified by the focus of new NIH intramural training programs.

- Consolidate, clearly define, and advertise new and existing NIH support mechanisms for new investigators in any request for program grants supporting Regional Centers of Excellence. These currently include:

  - "Pathway to Independence" program (T90)
  - Issuance of more new faculty awards
  - Increase in use of R21 mechanism
  - Clinical research training opportunities such as K30 and K12 Awards.

  Web-sites listing such awards include:

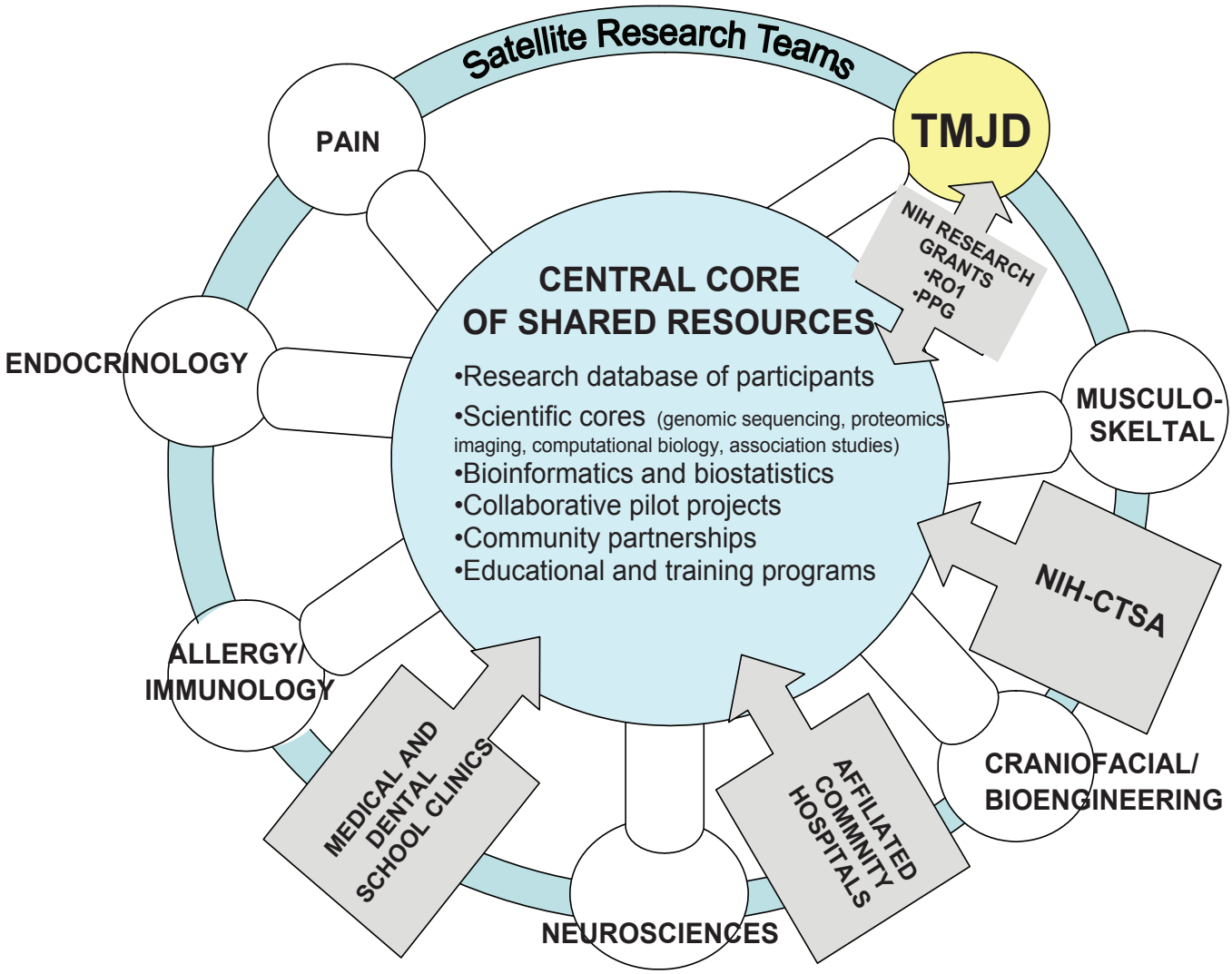
  http://www.ninds.nih.gov/funding/research/translational
  http://www.nimh.nih.gov/datr/datr.cfm
  http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-06-008.html
  http://www.cancer.gov/newscenter/benchmarks-vol6-issue1/page2
  http://grants2.nih.gov/grants/guide/pa-files/PAR-06-357.html
  http://grants2.nih.gov/grants/guide/pa-files/PAR-02-138.html
  http://grants2.nih.gov/grants/guide/pa-files/PAR-06-358.html
  http://grants2.nih.gov/grants/guide/pa-files/PAR-05-023.html
  http://grants2.nih.gov/grants/guide/pa-files/PA-06-322.html

- Develop a white paper to attract young investigators into TMJD research. NIDCR should lead an effort to convene a team of scientific experts to develop a white paper that will emphasize the complexity of TMJDs, the current state of knowledge, and the exciting challenges and opportunities related to basic, clinical and translational research in this field.

Exhibit 1: Multiple Symptoms and Co-Morbid Conditions Found in TMJD Patients:

- Allergies
- Anxiety/Panic Attacks
- Appetite Suppression
- Auditory Dysfunction
- Autoimmune Disorders
- Autonomic Dysfunctions
- Bruxism/Clenching
- Cardiac Arrythmias
- Chronic Fatigue Syndrome
- Communication Problems
- Complex Regional Pain Syndrome
- Depression
- Dizziness/Vertigo/Spaciness
- Environmental/Intolerances/ Chemical Sensitivities
- Facial Disfigurement/ Negative Self Image Impact
- Fatigue
- Fibromyalgia
- Gastrointestinal Disorders
- Generalized Muscle Pain
- Headaches
    - o Migraine
    - o Tension
- Heterotopic Bone Growth
- Hypermobile Joint Syndrome
- Hypertension
- Hypotension
- Inflammation
- Interstitial Cystitis
- Irritable Bowel Syndrome
- Malnutrition
- Mastication Deficiency
- Mitral Valve Prolapse
- Movement Dystonias
- Muscle Pain
- Myofascial Pain
- Neuropathic Pain
- Numbness
- Parethesias/ Dysethesias
- Rheumatoid Arthritis
- Sinusitis
- Sleep Disorders
- Speech Abnormalities
- Swallowing Derangements
- Systemic Arthritides
- Taste and Smell Abnormalities
- Tinnitus
- Tooth Loss and Breakage
- Trigeminal Neuralgia
- Visual Disorders
- Vulvadynia

Figure 1: The concept of a Central Core with satellite research teams representing the specific disease-based focus groups with portal of entry to the Center Core.



The TMJ Association

The TMJ Association is a national, non-profit organization whose mission is to improve the diagnosis, care and treatment of everyone affected by temporomandibular joint and muscle disorders through fostering research, education and other activities with the ultimate goal of preventing TMJ problems.

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