



An Update from the NIH and NIDCR on Temporomandibular Joint Disorders & Pain Research

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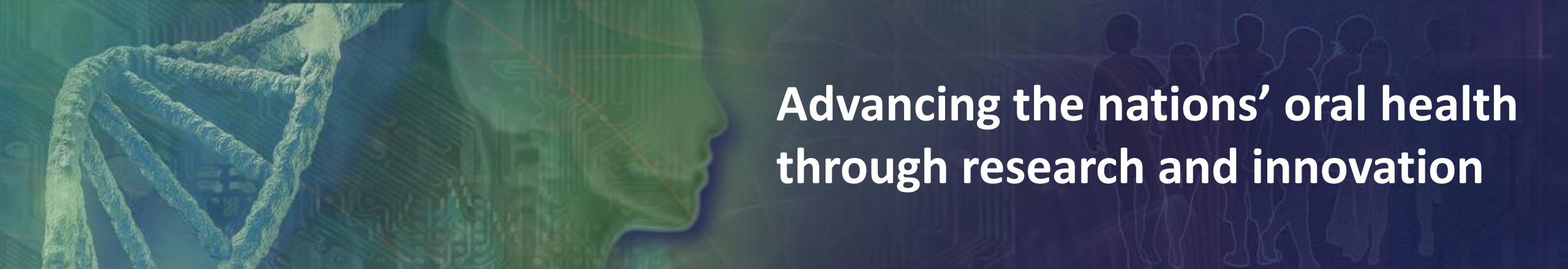
Director, Neuroscience of Orofacial Pain & Temporomandibular Disorders Program

March 28, 2019



National Institute of Dental
and Craniofacial Research

NIDCR at a Glance



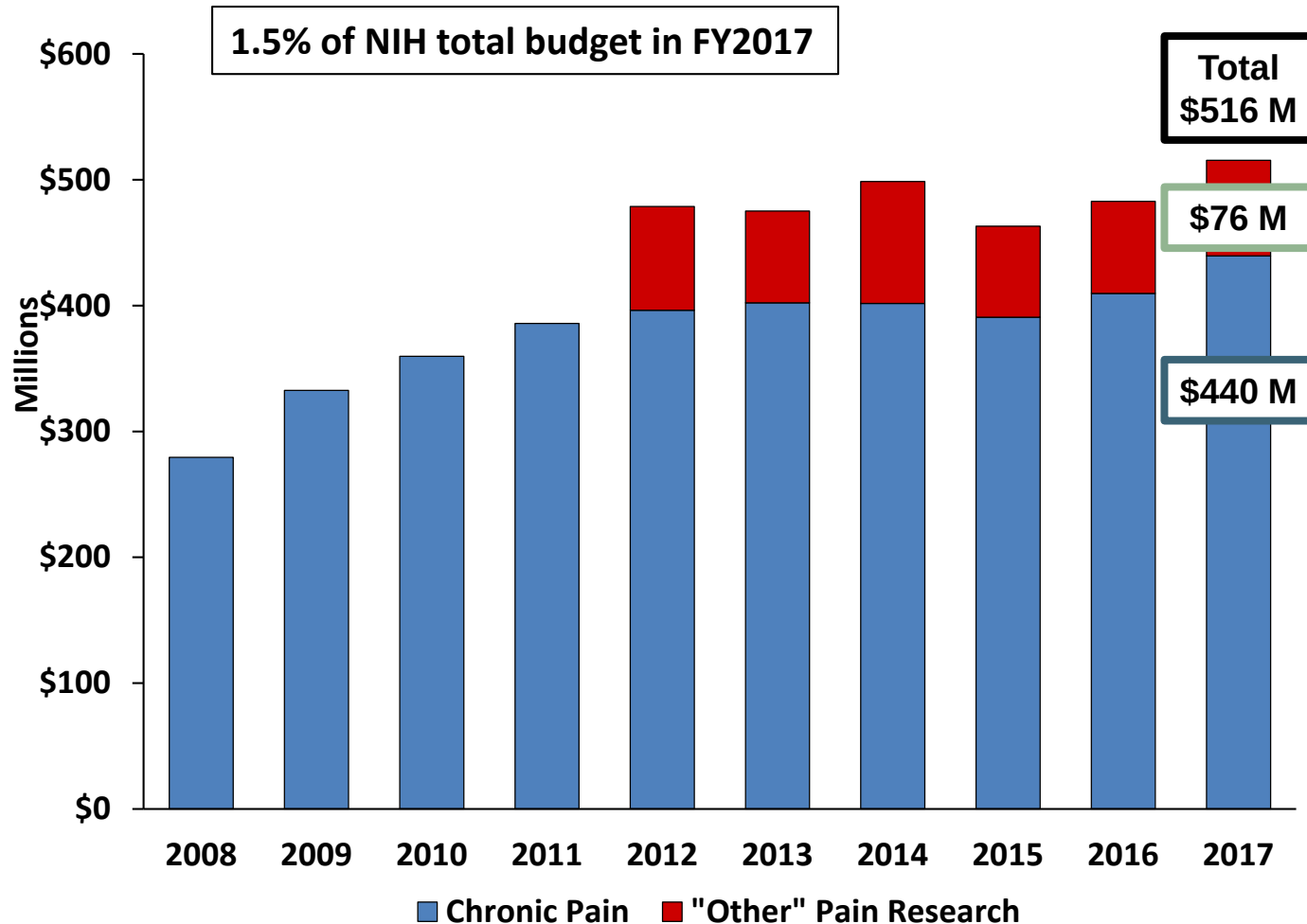
**Advancing the nations' oral health
through research and innovation**

NIDCR: Partnering Across NIH and Other Federal Agencies

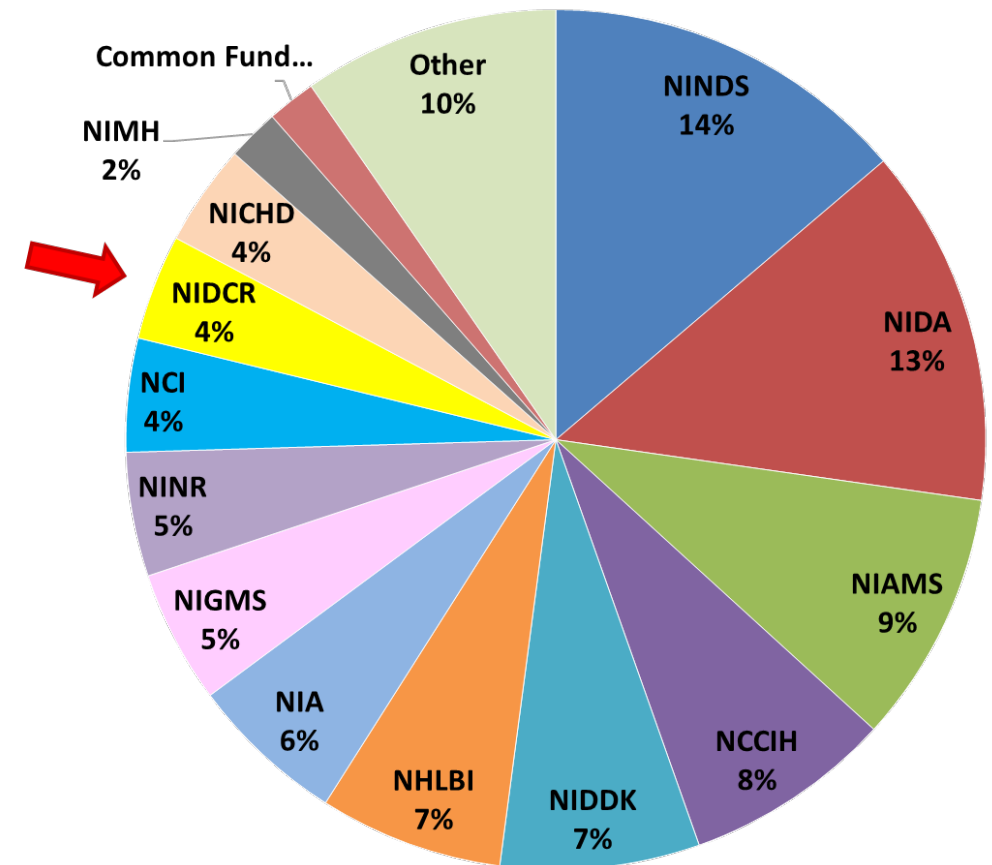
- NIH Pain Consortium
<https://painconsortium.nih.gov/>
- NIH Interagency Pain Research Coordinating Committee
<https://iprcc.nih.gov/>
- FDA Medical Device Epidemiology Network TMJ Patient-Led RoundTable
<http://www.mdepinet.org/tmj-patient-led-roundtable-crn/>
- NIH Blueprint for Neuroscience Research
<https://neuroscienceblueprint.nih.gov/>
- NIH Helping to End Addiction Long-term (HEAL) Initiative
<https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative>



NIH Pain Research Funding FY 2008 -2017

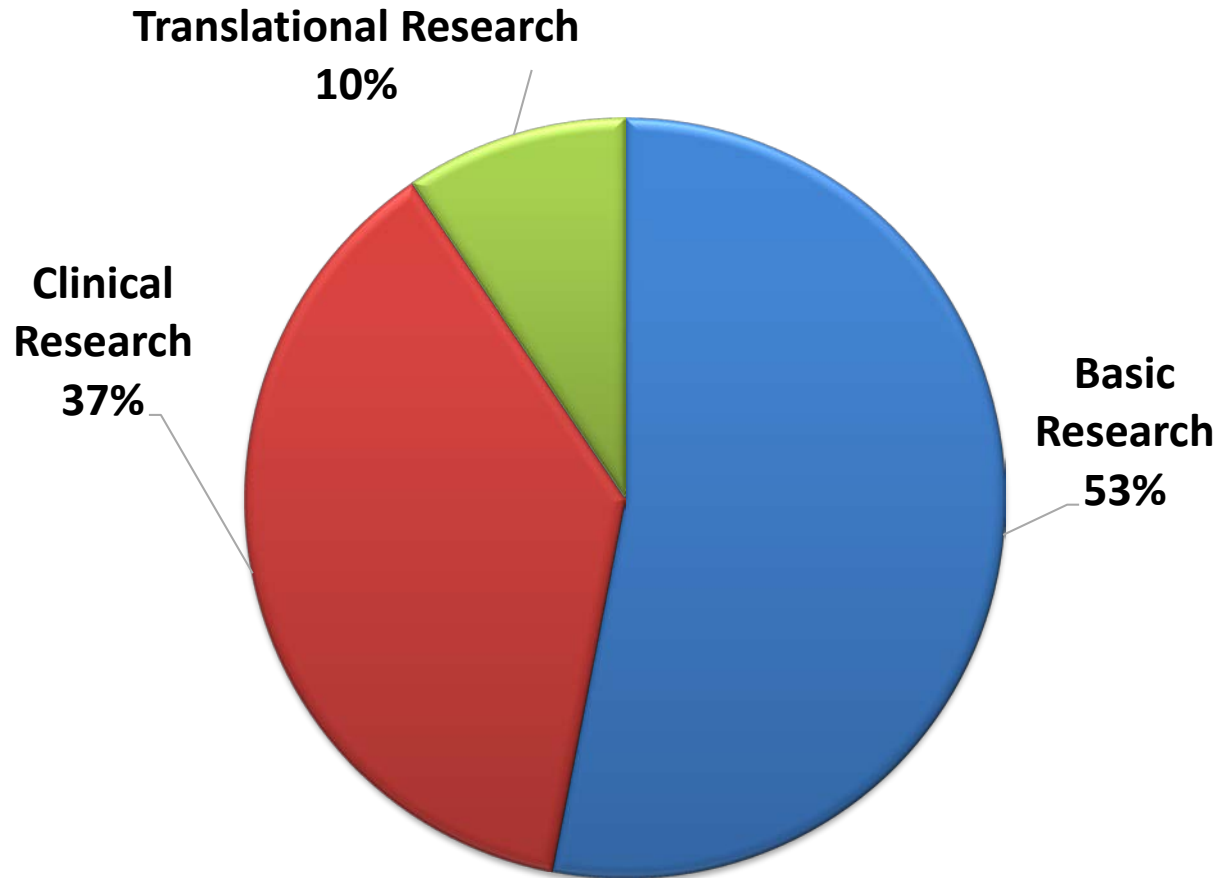


FY 2017 Distribution Across NIH

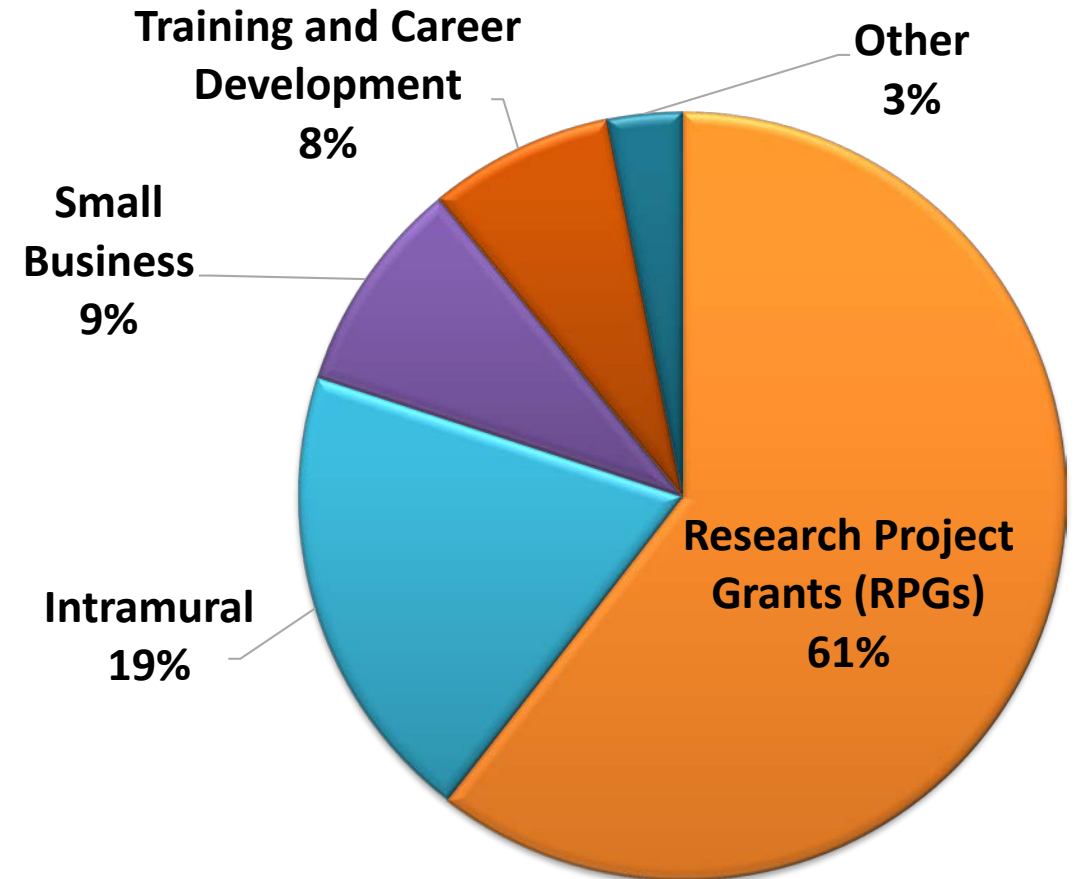


FY2017 NIDCR Pain Research

Funding by Research Type



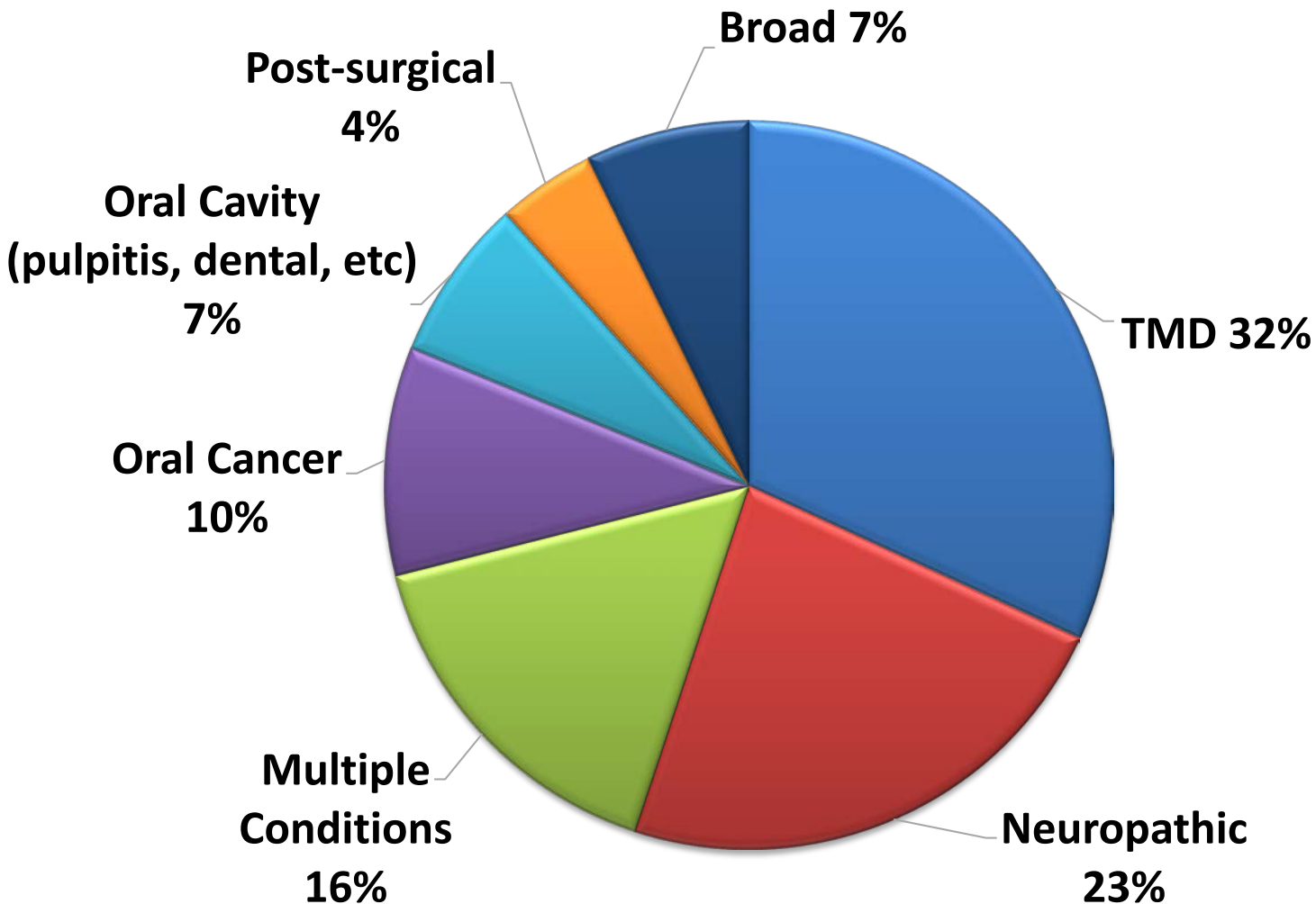
Funding by Mechanism Type



~5% of total NIDCR budget in FY2017

NIDCR's Pain Research by Condition

FY2016

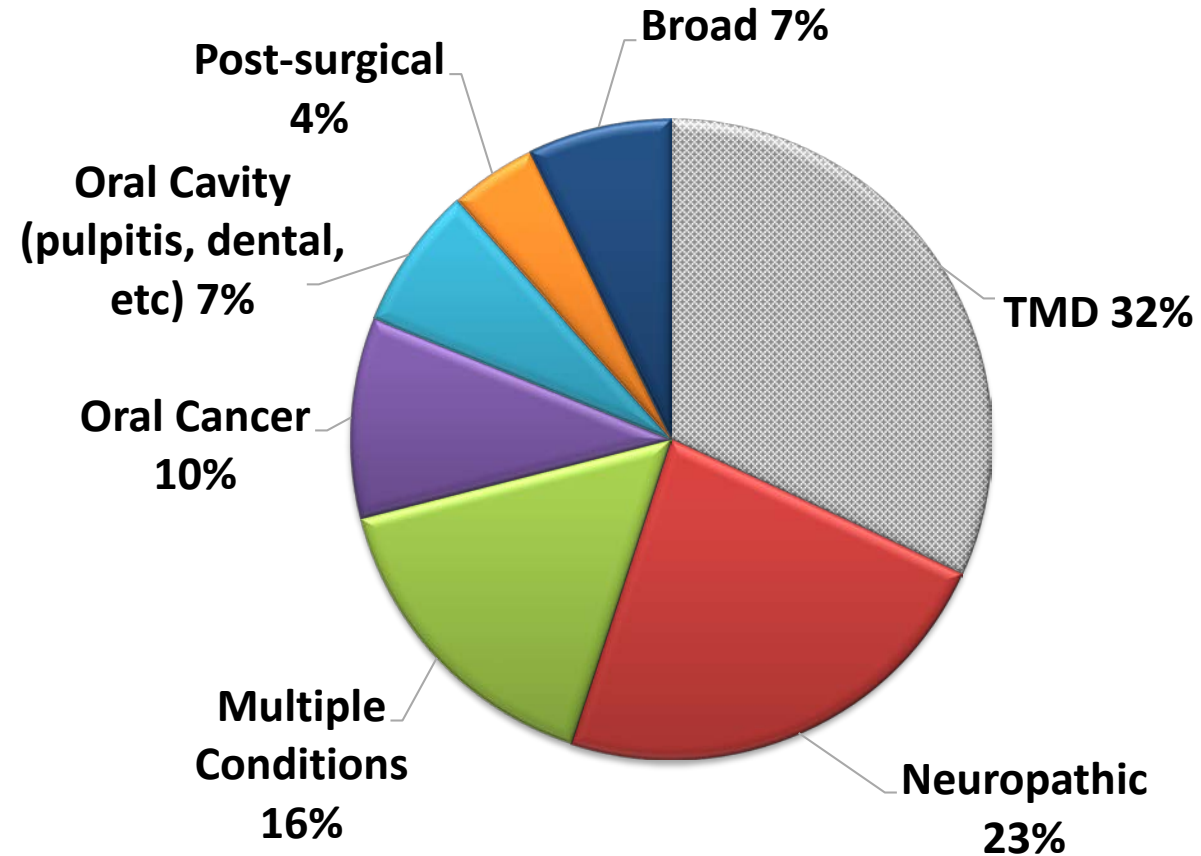


NIDCR pain research is diverse & includes investigation into aspects of :

- Biopsychosocial & genetic determinants of pain
- Neuroimmune interactions
- Sex Differences
- Model development
- Chronic overlapping pain conditions
- Behavioral science approaches
- Transition from acute to chronic pain

Thinking Broadly about NIDCR's Pain Research Portfolio

FY2016

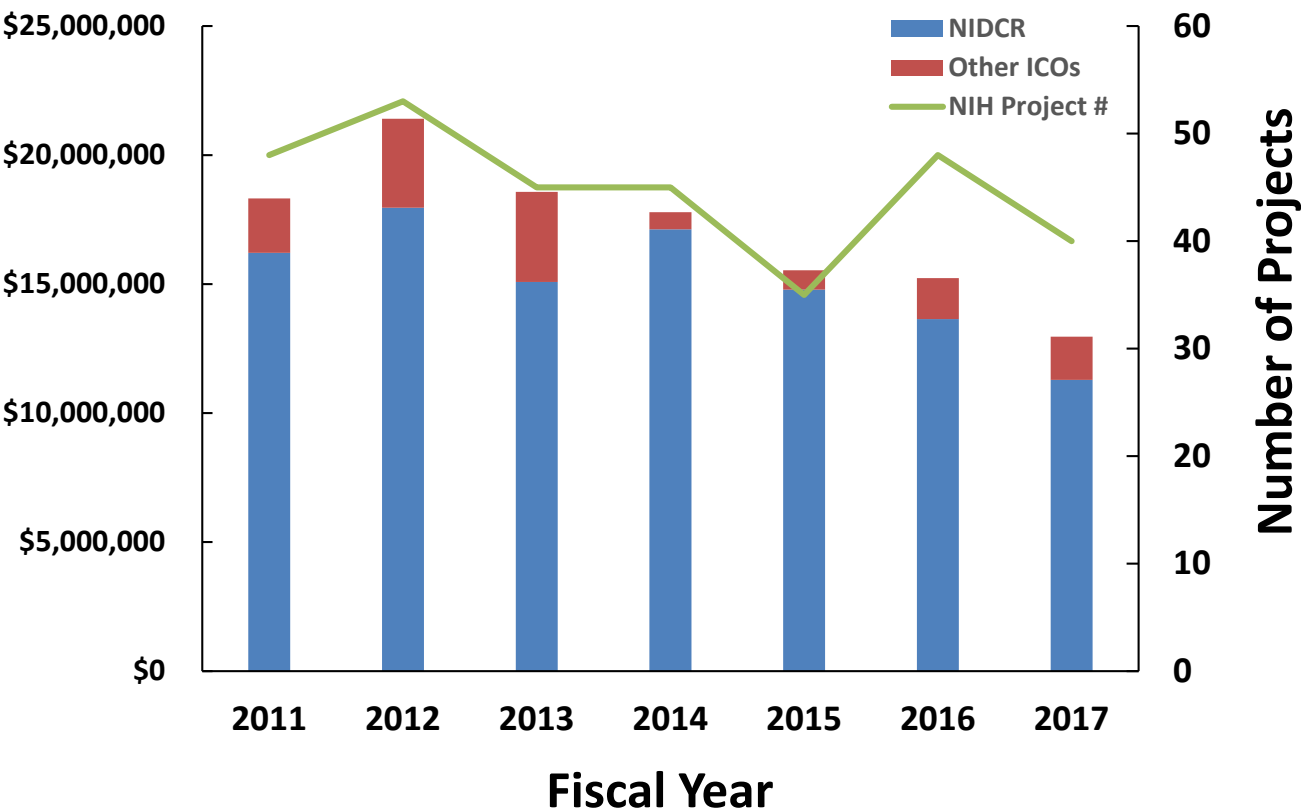


Interconnectedness of orofacial pain conditions

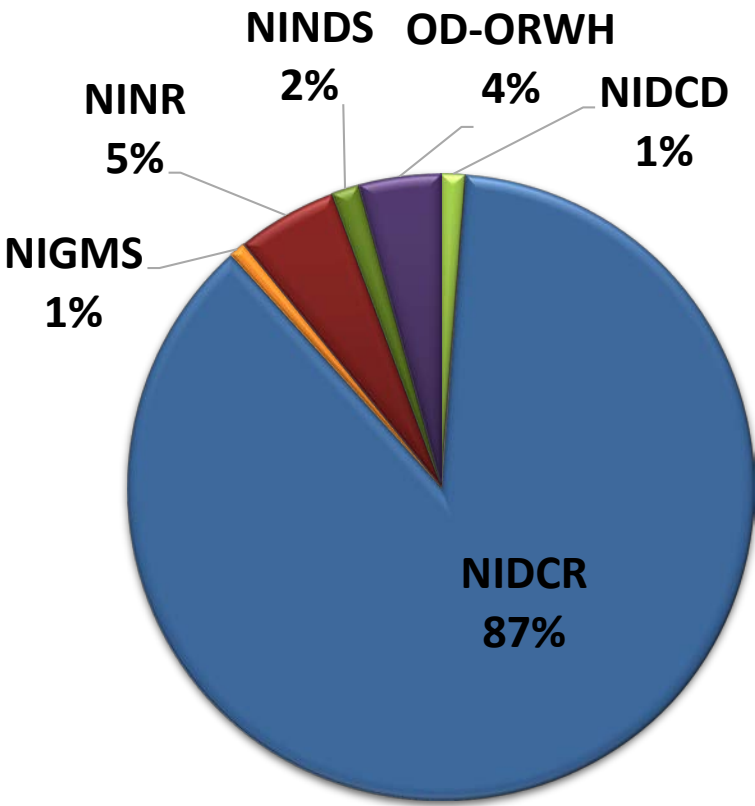
- Epigenetic basis for pain vulnerability
- Neuronal and glial interactions of neuropathic pain
- A new animal model for stress-induced transition from acute to chronic pain
- Defining the generators of spontaneous trigeminal pain
- Sex differences in serotonergic modulation of trigeminal pain
- Primary afferent plasticity in chronic pain

NIH Temporomandibular Muscle/Joint Disorders Funding

FY2011-2017

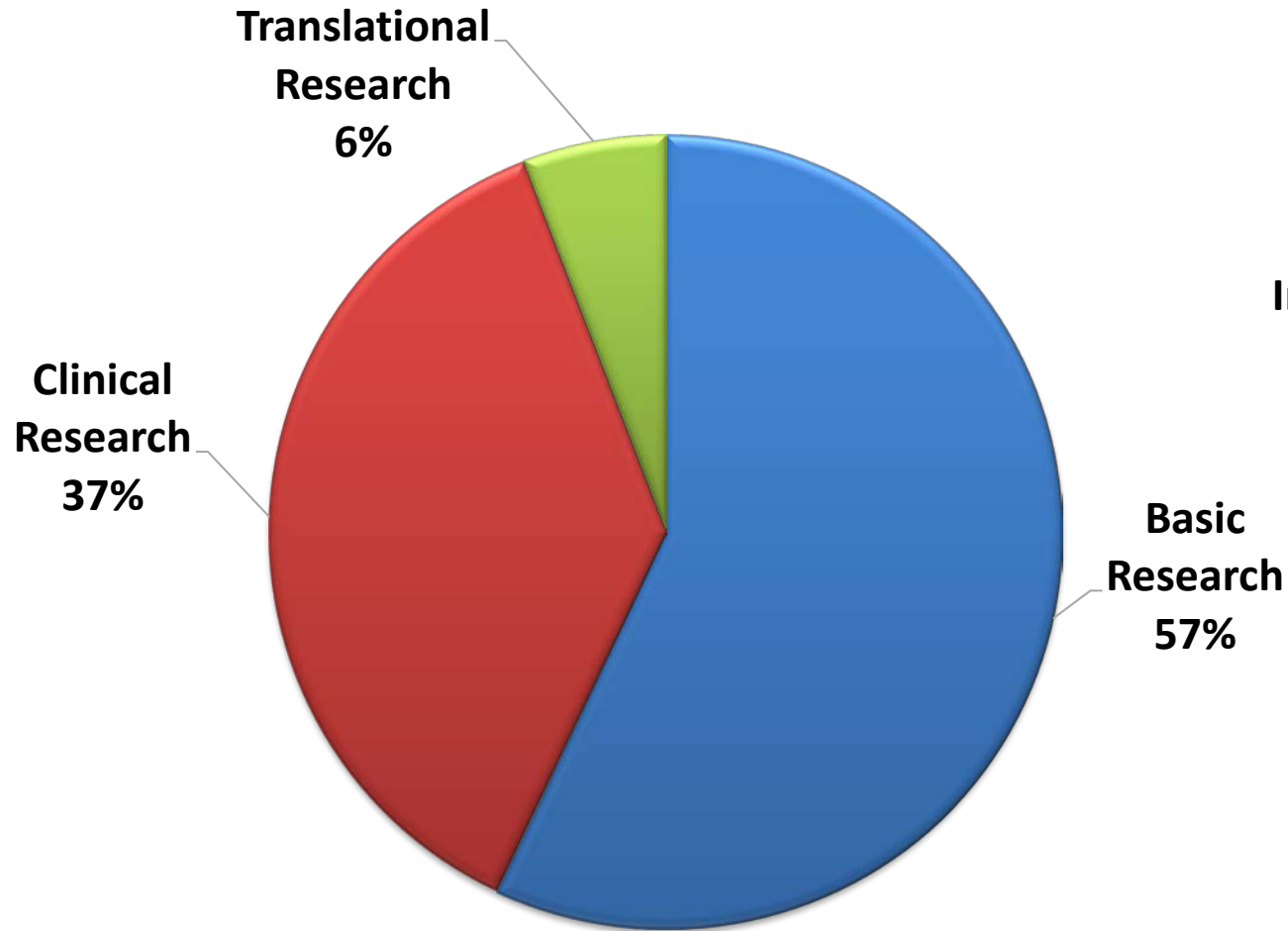


2017 NIH Distribution

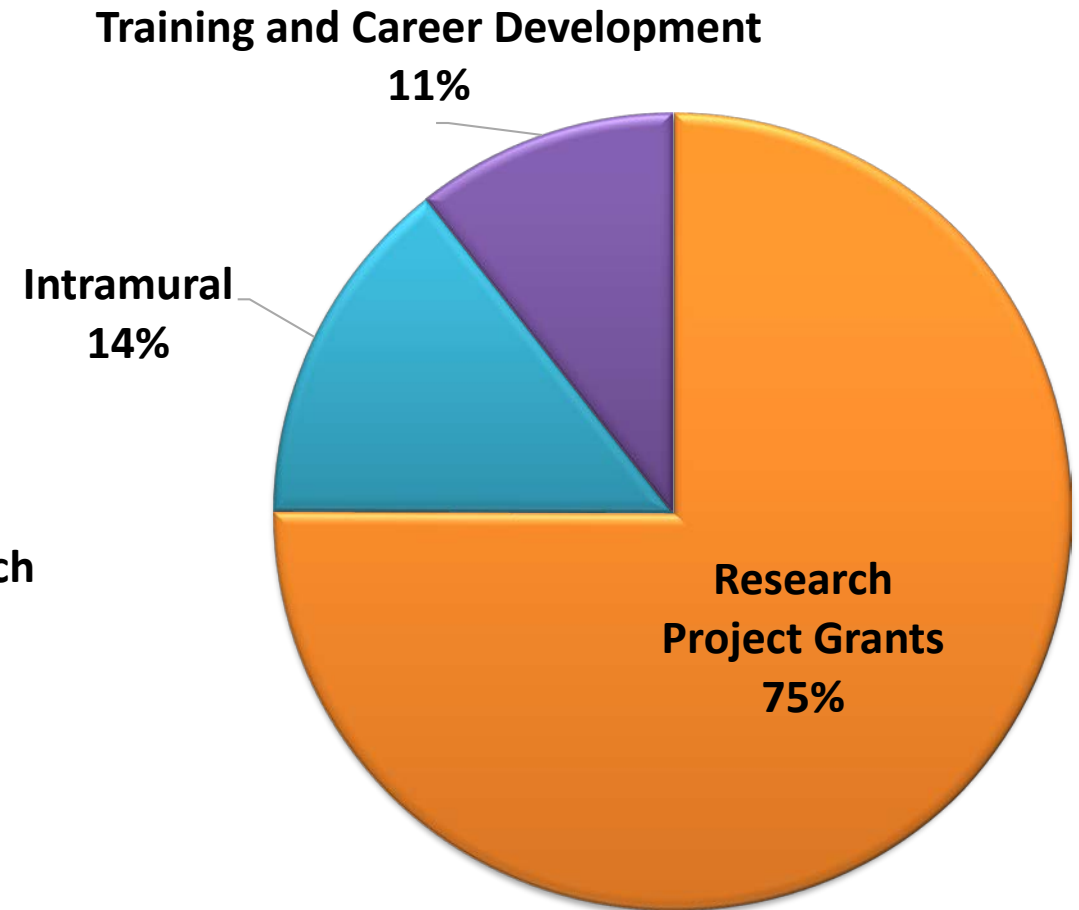


FY2017 NIDCR Temporomandibular Muscle/Joint Disorder (TMJD) Research

Funding by Research Type



Funding by Mechanism Type



NIDCR & TMD

NIDCR invests in a wide breadth of areas, with the goal of improving the health of those who suffer from TMDs including:

- Genomics and proteomics to compare the characteristics of normal & diseased TMJ tissue
- Systems biology to define the role of nervous, immune & circulatory systems in regulating jaw function in health and disease
- Tools & technologies to model masticatory muscles of the TMJ
- Joint mechanobiology using imaging and jaw tracking to examine TMJ pathology in relationship to loading, tissue nutrition & cell function
- Regenerative medicine
- Behavioral research to improve management of TMDs
- Dissemination and Implementation Research

The Impact of NIDCR's Diverse Basic Research Portfolio

nature
neuroscience

A craniofacial-specific monosynaptic circuit enables heightened affective pain

Erica Rodriguez¹, Katsuyasu Sakurai¹, Jennie Xu¹, Yong Chen², Koji Toda³, Shengli Zhao¹, Bao-Xia Han¹, David Ryu¹, Henry Yin³, Wolfgang Liedtke² and Fan Wang^{1*}

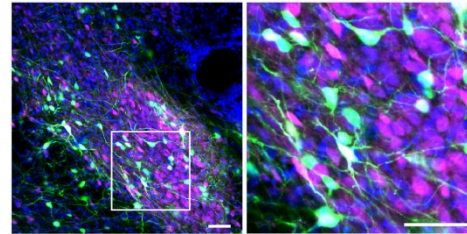
nature
neuroscience

Different immune cells mediate mechanical pain hypersensitivity in male and female mice

Robert E Sorge^{1,2,10}, Josiane C S Mapplebeck^{1,3-5,10}, Sarah Rosen¹, Simon Beggs³⁻⁵, Sarah Taves⁶, Jessica K Alexander³⁻⁵, Loren J Martin¹, Jean-Sebastien Austin¹, Susana G Sotocinal¹, Di Chen¹, Mu Yang⁷, Xiang Qun Shi⁷, Hao Huang⁷, Nicolas J Pilon⁸, Philip J Bilan⁸, YuShan Tu³, Amira Klip⁸, Ru-Rong Ji⁶, Ji Zhang^{7,9}, Michael W Salter³⁻⁵ & Jeffrey S Mogil^{1,9}



Brings VE and Zylka MJ. (2015) *Nature Neuroscience*.



www.nature.com/scientificreports

SCIENTIFIC REPORTS

Estrogen Promotes Mandibular Condylar Fibrocartilage Chondrogenesis and Inhibits Degeneration via Estrogen Receptor Alpha in Female Mice

Jennifer L. Robinson^{1,3}, Paola Soria², Manshan Xu², Mark Vrana¹, Jeffrey Luchetti¹, Helen H. Lu³, Jing Chen² & Sunil Wadhwa²

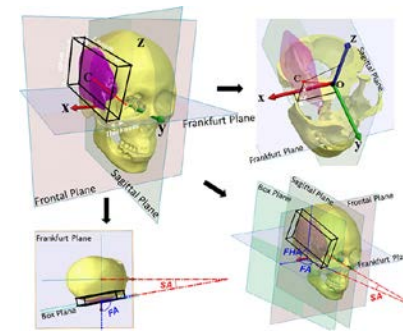
Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech

www.JBiomech.com

Three-dimensional temporomandibular joint muscle attachment morphometry and its impacts on musculoskeletal modeling

Xin She^a, Feng Wei^a, Brooke J. Damon^{a,b}, Matthew C. Coombs^{a,b}, Daniel G. Lee^c, Michael K. Lecholop^c, Thierry H. Bacro^d, Martin B. Steed^c, Naiquan Zheng^e, Xiaojing Chen^f, Hai Yao^{a,b,g}



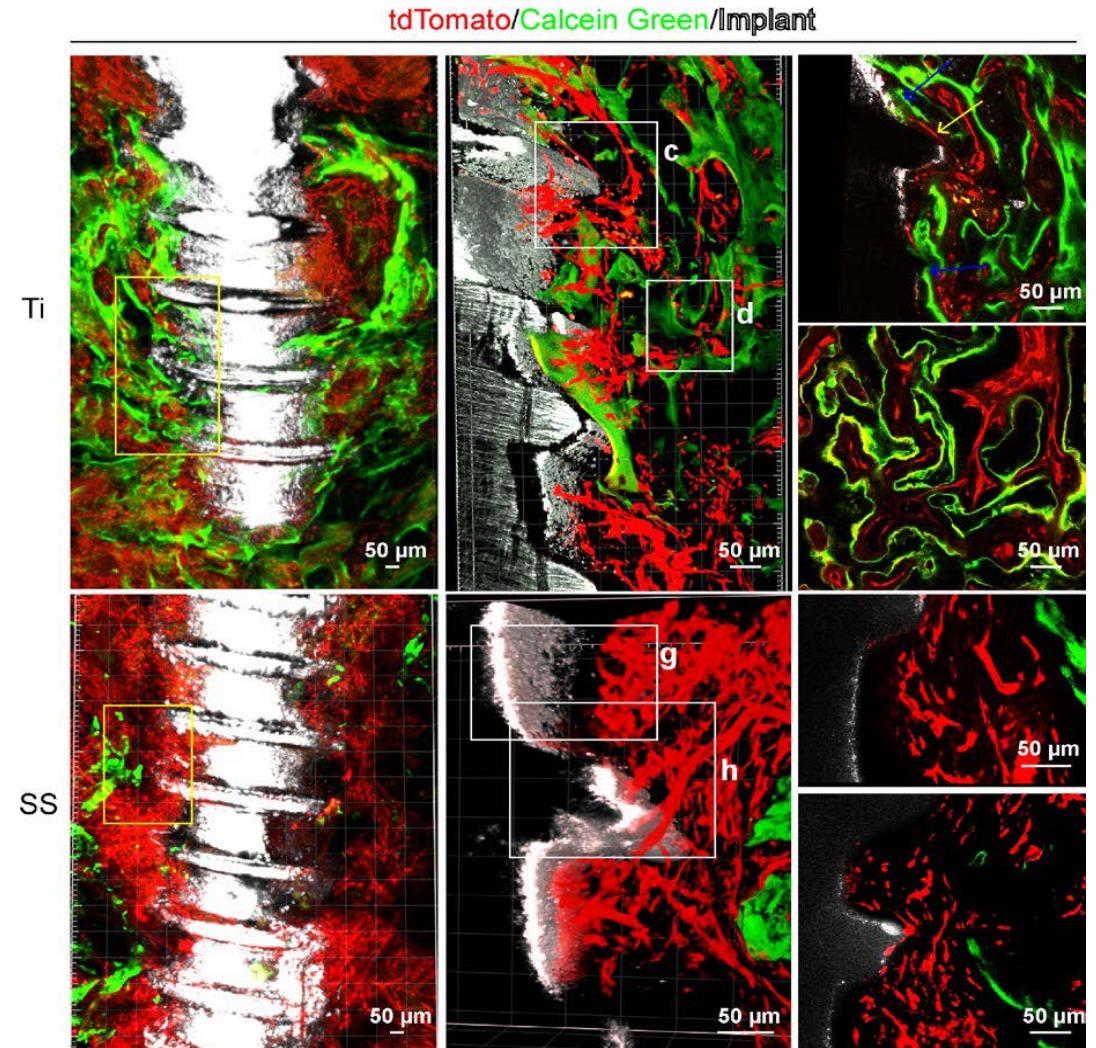
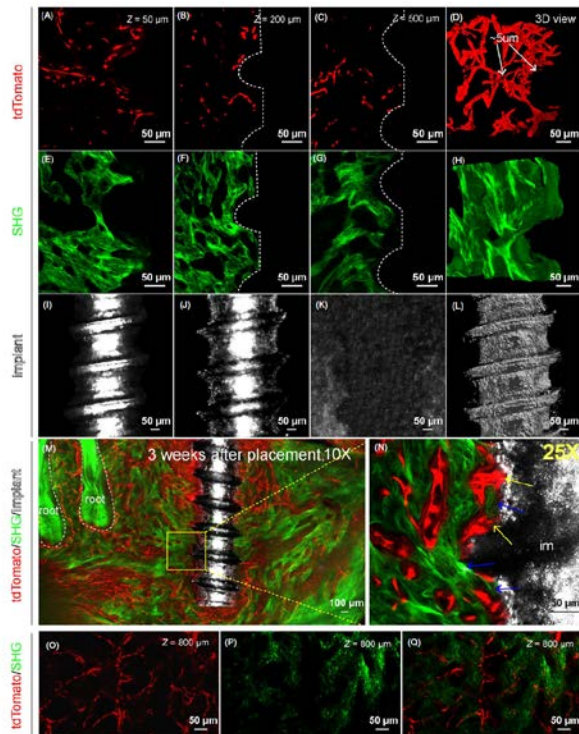
A Novel Approach: Craniofacial Tissue -Material Interactions

ORIGINAL ARTICLE

WILEY Cell Proliferation

3-dimensional visualization of implant-tissue interface with the polyethylene glycol associated solvent system tissue clearing method

Yating Yi^{1,2} | Yi Men² | Dian Jing^{1,2} | Wenjing Luo² | Shiwen Zhang^{1,2} | Jian Q. Feng³ | Jin Liu⁴ | Woo-Ping Ge⁵ | Jun Wang¹ | Hu Zhao² 

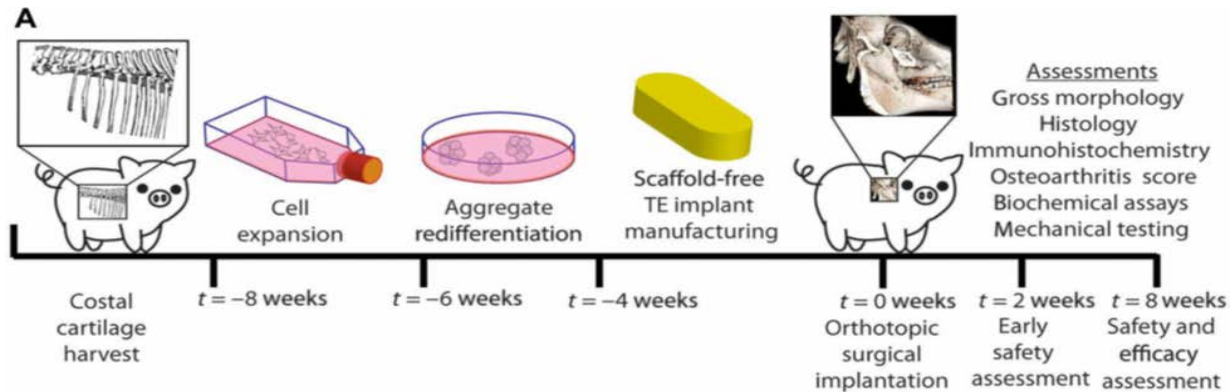


NIDCR Advancing Regenerative Medicine

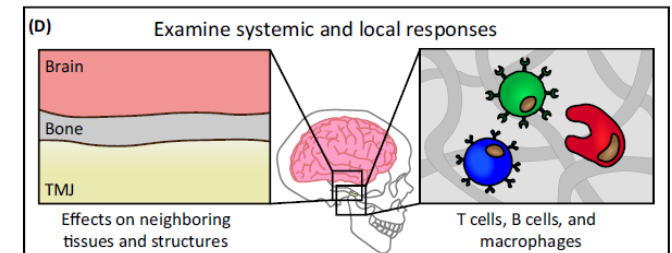
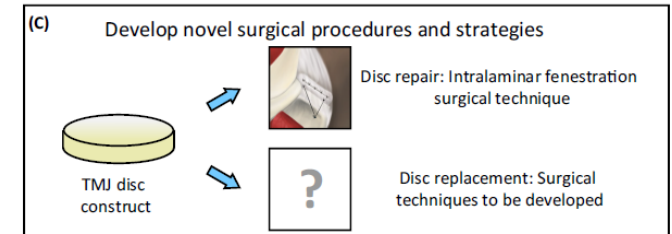
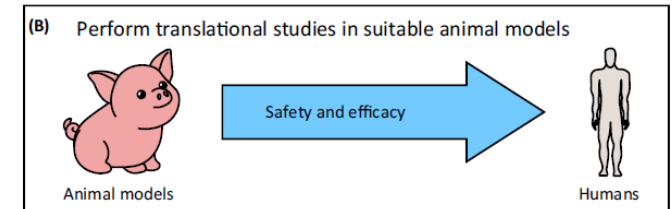
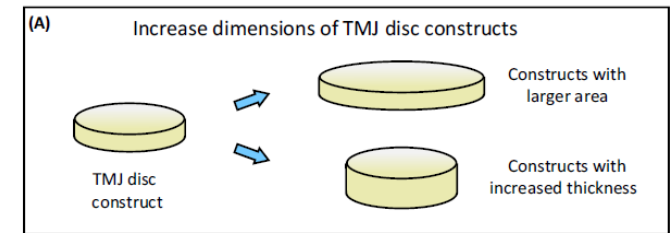
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE
TISSUE ENGINEERING

Tissue engineering toward temporomandibular joint disc regeneration

Natalia Vapniarsky^{1*}, Le W. Huwe^{2*}, Boaz Arzi³, Meghan K. Houghton⁴, Mark E. Wong⁵, James W. Wilson⁵, David C. Hatcher⁶, Jerry C. Hu⁷, Kyriacos A. Athanasiou^{7†}

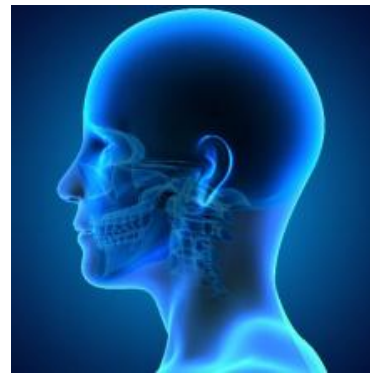


Toward the Path to Translation



Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA)

- Genetic risk factors for TMD based on GWAS studies
- Psychological risk factors for TMD including heightened somatic awareness and stress
- Sleep complaints associated with chronic pain
- Differences in clinical pain perception between different ethnic groups
- Women are more likely to transition from acute to chronic pain



OPPERA: TMD Research & Beyond

PAIN

Research Paper

Genome-wide association reveals contribution of *MRAS* to painful temporomandibular disorder in males

Shad B. Smith^a, Marc Parisien^b, Eric Bair^{c,d}, Inna Belfer^e, Anne-Julie Chabot-Dore^f, Pavel Gris^b, Samar Khoury^b, Shannon Tansley^{b,f}, Yelizaveta Torosyan^g, Dmitri V. Zaykin^h, Olaf Bernhardtⁱ, Priscila de Oliveira Serrano^j, Richard H. Gracely^c, Deepti Jain^k, Marjo-Riitta Ja^l, rvelin^{m,n,o}, Linda M. Kaste^p, Kathleen F. Kerr^k, Thomas Kocher^l, Raija La^{hdesma^q, Nadia Laniado^s, Cathy C. Laurie^k, Cecelia A. Laurie^k, Minna Ma^{nnikko^{m,t}, Carolina B. Meloto^b, Andrea G. Nackley^a, Sarah C. Nelson^k, Paula Pesonen^u, Margarete C. Ribeiro-Dasilva^v, Celia M. Rizzatti-Barbosa^l, Anne E. Sanders^{c,w}, Christian Schwahn^x, Kirsi Sipilä^{y,z,q,r}, Tamar Sofer^{aa,bb}, Alexander Teumer^{cc}, Jeffrey S. Mogil^{b,f}, Roger B. Fillingim^{dd}, Joel D. Greenspan^{ee}, Richard O. Luda Diatchenko^{b,*}}}

Research Paper

PAIN

Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the **OPPERA** study

Eric Bair^{a,b,c,*}, Sheila Gaynor^d, Gary D. Slade^{a,e,f}, Richard Ohrbach^g, Roger B. Fillingim^h, Joel D. Greenspanⁱ, Ronald Dubner^j, Shad B. Smith^{a,c}, Luda Diatchenko^j, William Maixner^{a,c}

Cell Reports

Effect of Human Genetic Variability on Gene Expression in Dorsal Root Ganglia and Association with Pain Phenotypes

Authors

Marc Parisien, Samar Khoury, Anne-Julie Chabot-Dore^f, ..., Jeffrey S. Mogil, Inna Belfer, Luda Diatchenko

The Journal of Clinical Investigation

RESEARCH ARTICLE

Epiregulin and EGFR interactions are involved in pain processing

Loren J. Martin^{1,2}, Shad B. Smith³, Arkady Khoutorsky⁴, Claire A. Magnussen⁵, Alexander Samoshkin⁶, Robert E. Sorge¹, Chulmin Cho², Noosha Yosefpour⁵, Sivaani Sivaselvachandran², Sarasa Tohyama², Tiffany Cole⁷, Thang M. Khuong⁷, Ellen Mir³, Dustin G. Gibson³, Jeffrey S. Wiskopf¹, Susana G. Sotocinal¹, Jean Sebastien Austin¹, Carolina B. Meloto⁶, Joseph H. Gitt³, Christos Gkogkas⁴, Nahum Sonenberg⁴, Joel D. Greenspan⁸, Roger B. Fillingim⁹, Richard Ohrbach¹⁰, Gary D. Slade¹¹, Charles Knott¹², Ronald Dubner⁸, Andrea G. Nackley³, Alfredo Ribeiro-da-Silva⁵, G. Gregory Neely⁷, William Maixner³, Dmitri V. Zaykin¹³, Jeffrey S. Mogil¹ and Luda Diatchenko⁶



PAIN.
Incident injury is strongly associated with subsequent incident temporomandibular disorder: Results from the **OPPERA** study.

Sonia Sharma; Jean Wactawski-Wende; Michael LaMonte; Jiwei Zhao; Gary Slade; Eric Bair; Joel Greenspan; Roger Fillingim; William Maixner; Richard Ohrbach;

NIDCR Supported TMD Clinical Research

Non-Opioid Analgesics



Pharmacologic



- Effect of COMT genetic polymorphisms on responses to propranolol therapy in Temporomandibular Disorder (SOPPRANO study)
- Preliminary Safety Study of Botulinum Toxin for Treatment of Myofascial TMJD Pain
- Genetic effects on expectancy -induced analgesia (placebo) in TMD

Non -Pharmacologic

- High-definition transcranial direct stimulation (HD -tDCS) for endogenous μ -opioid receptor modulation and lasting pain relief in chronic TMD
- Patient-centered, web-based program, to educate and engage TMD patients in a personalized program to improve exercise, diet, sleep, and oral health behaviors aimed at decreasing and preventing pain.

Lessons Learned

- Studies indicate TMDs are multifactorial conditions influenced by genetics, sex and gender, environmental and psychological factors but significant gaps remain in our mechanistic understanding of peripheral and central adaptations and psychosocial influences that promote chronification or resolution of TMDs.
- TMD patients with the most severe symptoms exhibit the greatest burden of comorbid conditions pointing to a multi-system disorder.
- The absence of a firm mechanistic understanding of TMD and clear etiological targets has precluded development and clinical implementation of safe and effective evidence-based treatments.
- TMDs are highly complex necessitating effective patient stratification approaches to facilitate precision medicine approaches.
- TMD models that recapitulate human pathophysiology are critical to development of safe and effective therapeutic interventions.
- Determination of the mechanisms that sustain or promote resolution of chronic TMD pain and strategies to intrinsically and/or extrinsically modulate these mechanisms present therapeutic opportunities.
- A fuller understanding of sex-based differences/influences underlying TMDs will facilitate development of therapeutic interventions.
- Leveraging recent technological advances and resources developed through the NIH BRAIN, Blueprint, and SPARC Initiatives are poised to enable significant advances.

Thank You!

