Center for Pain Research

The Ernest J. Del Monte Institute for Neuroscience

Eli Eliav, DMD, PhD
In 2012, health care providers wrote 259 million prescriptions for opioid pain medication, enough for every adult in the United States to have a bottle of pills…

Drug overdose is the leading cause of accidental death in the US, with 47,055 lethal drug overdoses in 2014. Opioid addiction is driving this epidemic, with 18,893 overdose deaths related to prescription pain relievers, and 10,574 overdose deaths related to heroin in 2014.

Research and treatment should aim to improve pain and/or pain management, and also to improve patient physical, psychological, and work and social role functioning.

**Multidisciplinary Pain Center**

**Multidisciplinary Diagnosis and Treatment**

**Clinicians work in the same space:**
- Physician (Neurologists, Anesthesiologists, Oncologists, pediatricians)
- Nurses
- Mental health professionals
- Physical therapists
- Dentists (orofacial pain, OMFS)

**Methods:**
- Sensory Testing
- Nerve Blocks
- Pharmacological treatment
- Surgical Interventions
- Physical Therapy/Exercise
- Non-surgical intervention
- Brain imaging

**Examples for Chronic Pain Conditions:**
- Back Pain, Headaches, CRPS, Neropathic Pain,
- Cancer pain, Chronic Abdominal and Pelvic pain,
- Orofacial Pain (TMD), Post traumatic neuropathies

**Research**
- Animal studies
- Brain imaging
- Clinical research
- Clinical trials
- Precision medicine

**Education**
- Patients
- Health care professionals
Pain Research and Clinics at URMC

**EIOH**

**Research**
- XiuXin Liu DDS PhD
- Yanfang Ren DMD PhD
- Jund Khan BDS MPH PhD
- Eli Eliav DMD PhD
- Takano Takahiro PhD

Clinical research assistants
Laboratory assistants

**Orofacial Pain and Sensory Testing Clinic**
- Ross Tallents DDS
- Jund Khan BDS MPH PhD
- Eli Eliav DMD PhD

**Neurosurgery**

**Neuromedicine Pain Management Program**
- Drs. Markman and Villareal

**Translational Pain Research**
- Dr. John Markman

**Anesthesiology**

**Pain treatment Center**
- Drs. Kent, Thakur, Koh, Philip and Smith

**Center for Translational Neuromedicine**
- Dr. Nedegaard lab

**Physical Medicine Rehabilitation**

**Orthopedics**

**Neurology**
- Dr. Villanueva
Nociceptive transduction mechanism for Dentine Hypersensitivity

Environmental stimulation triggers ATP release from odontoblasts via pannexin channels to activate P2X3 receptors on adjacent nerve fibers and induce pain.

Pannexin Channel Blocker Reduces External Dentin Stimulation-induced ATP release
The role of ecto-nucleotidases in the pathogenesis of orofacial neuropathic pain.

Purinergic signaling are determined by ecto-nucleotidases that control ATP degradation and adenosine generation.

Disruption of ecto-nucleotidase (NTPDase3 and CD73) trigeminal neuronal expression and presynaptic terminal localization caused by chronic inflammation, local constriction and trigeminal nerves injury may contribute to the pathogenesis of orofacial neuropathic pain.
Takano lab
Adenosine-mediated acupuncture analgesia

• We discovered that repetitive acupuncture treatments induce an increase of extracellular adenosine at acupuncture point, which lead to a long-term pain suppression.

• We hope to develop a novel therapeutic strategy to treat both acute and chronic pain conditions.
Orofacial Pain Genetics

Analysis

Burning Mouth Syndrome:
- Tumor Necrosis Alpha receptor (TNFRSF1B) and Lacto Erin (LTF)

Atypical Odontalgia:
- Tumor Necrosis Alpha receptor (TNFRSF1B)

HIV Related Myalgia:
- GTP cyclohydrolase 1 (GCH1), nuclear factor kappa- B, subunit 1 (NFKB1) and oxytocin receptor (OXTR)

Combination Drug Therapy

- Pregabalin
- Diclofenac
- Duloxetine
- Ibuprofen
- Ketoprofen

Use of Topical Medications for Neuropathic Pain

- Pregabalin
- Diclofenac
- Duloxetine
- Ibuprofen
- Amitriptyline

Quantitative Sensory Testing (QST) for the Diagnosis and Evaluation of Chronic Pain Conditions

Peripheral Nervous System
- Thermal Detection and Pain Threshold
- Electrical Detection Threshold
- Mechanical Stimulus Test
- Cold Test

Central Nervous System
- Temporal Summation
- DNIC: Diffuse Noxious Inhibitory Control
- CPM: Conditioned pain Modulation

The role of inflammation in neuropathic pain

Pro/Anti inflammatory Cytokines: (IL-6, IL-1, IL-12, IL-17, IL-18, IL-10, IL-2, IL-4, IL-27)

Mechanisms
- Opioid System (Kappa receptor)
- Anti Inflammatory System

Cytokines as treatment for Pain?
- Local and Systemic Injections

Exercise Induced Hypoalgesia

Basic Science
- Endo Cannabinoid System
- Opioid System
- Inflammation

Clinical
- Orofacial Pain conditions

Orofacial Pain Genetics Analysis

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Khan / Eliav Lab

Pain Modulation System
- HIV Subjects
- Muscle Pain
- TMJ Disorders
- Headaches
- Acute Dental Procedures

Drug A

Drug B

Use of Topical Medications for Neuropathic Pain

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In order to execute the research, what new human capital might be needed to engage in the work

- Interaction with all the pain clinics / Labs
- Brain Imaging
- Geneticist
- Psychologist
- Physical Therapy

What it would take to get a group of scientists working in the area to a point where they might be able to submit a program project grant. Are there key facility or major equipment needs?

- Establish a team and collaborative work
- Define a common theme (precision, tailored treatment for chronic pain patients)

Briefly provide as concrete a plan as possible for how to grow the idea, program or center over the coming 36-48 months.

- Recruitments
- Establish URMC pain group, common research projects
- Publications
Pain Modulation
Inhibition of Pain

- PAG/RVM
  Periaqueductal gray/Rostral ventromedial medulla
  - Down regulating pain inhibitory system
- Endogenous opioid system
- Serotonin
- Noradrenaline
Inhibitory Pain Modulation is known to be activated by:

**Exercise**
- Aerobic
- Isometric contraction

**Painful stimulus**
- Cold
- Hot
- Mechanical
- Electrical
David Yarnitsky,
Role of Endogenous modulation in Chronic Pain mechanisms and treatment.
PAIN 156 (2015)
Posttraumatic Trigeminal Neuropathy

Patients with Chronic Neuropathic Orofacial Pain Have Less Efficient Pain Modulation System
Patients with Chronic Masticatory Muscles myalgia

Baseline Pain Level

1 Min Following Exercise

5 Min Following Exercise

15 Min Following Exercise

5 minutes, 50% max

30 stimuli 26g

Patients with Chronic Muscle Pain Have Less
Efficient Pain Modulation System
Conditioned Pain Modulation (CPM) in the dominant forearm decreases with age ($P=0.0005$) and is associated with subjects' number of COMT Low Pain Sensitivity (LPS) haplotypes ($P=0.006$ for additive model). Specific genotypes are associated with pain modulation and chronic pain.
Not all patients are on even playing field
Exercise Induced Hypoalgesia, Rat Model

BL % responses

3 min exercise on Rotarod

% responses 1, 5, 10 min following exercise
EIH by High, Low

Mean ± SEM % response to 30 stimuli of 60g von Frey filament

Time since cessation of Roto-Rod exercise (minutes)

High

Low

* Significant difference
Low Pain Modulation rats develop significantly more pain following exercise.

Only Low Pain Modulation rats develop mirror-image pain

Low Pain Modulation Rats Respond Better to Duloxetine

Cannabinoid antagonists reverse exercise effect on Pain

Pain Assessment, 7 Days following surgery
Summary

• Central modulation of pain can be activated by external stimuli and exercise

• Pain modulation profile assessment
  May predict development of chronic pain
  May support more targeted treatment selection

• Pre-emptive pharmacological treatment prior surgery in patients at risk should be further studied

• Activation of the inhibitory pain modulation system may alleviate pain