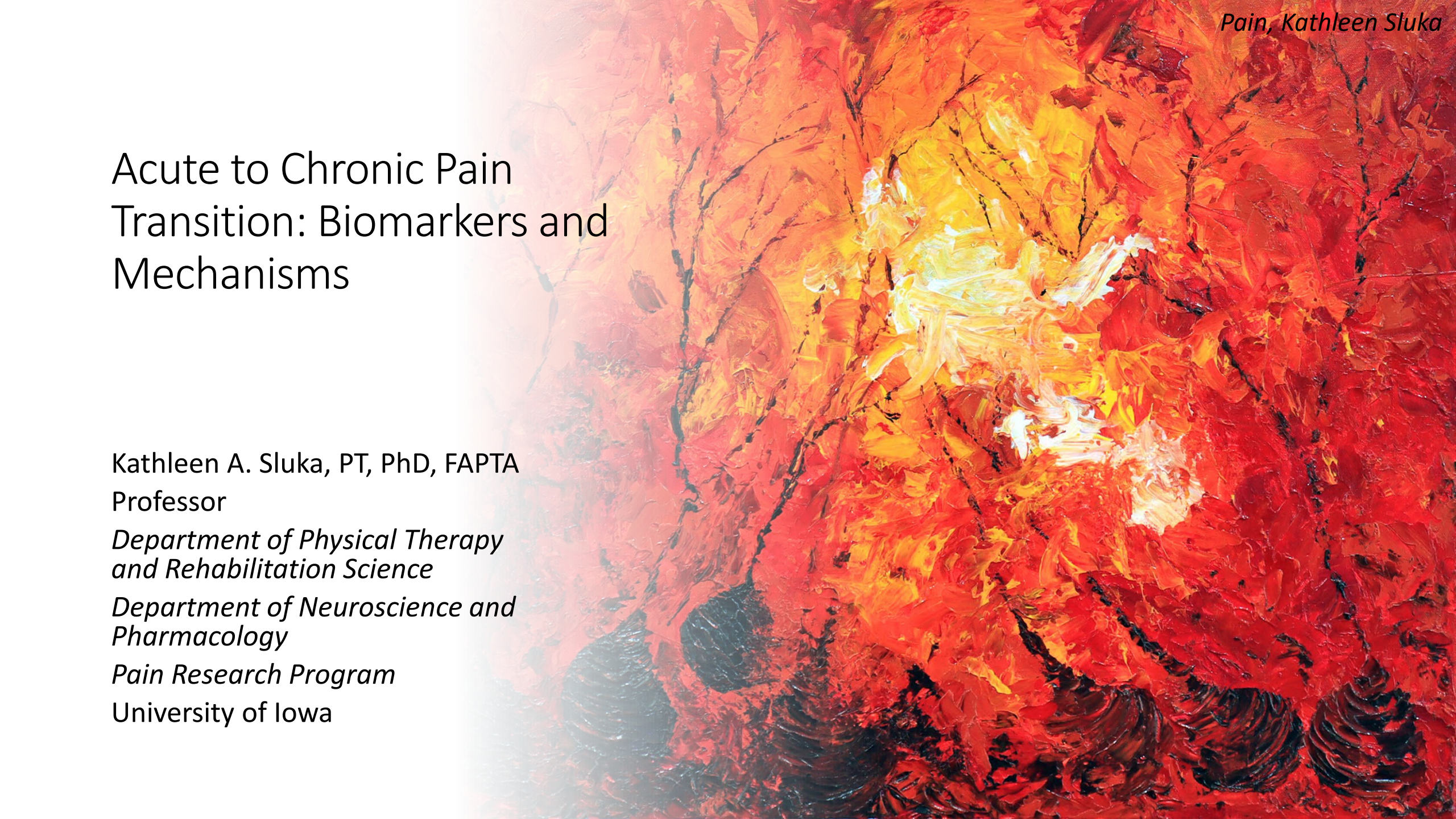

Acute to Chronic Pain Transition: Biomarkers and Mechanisms

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Pain Research Program

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Emine Bayman, PhD
Barb Van Gorp, PT, OCS
Giovanni Berardi, PT, PhD
Laura Frey Law, PT, PhD
Gregory Bernhard
Angela Smith
Ashley Plumb
A2CPS consortium

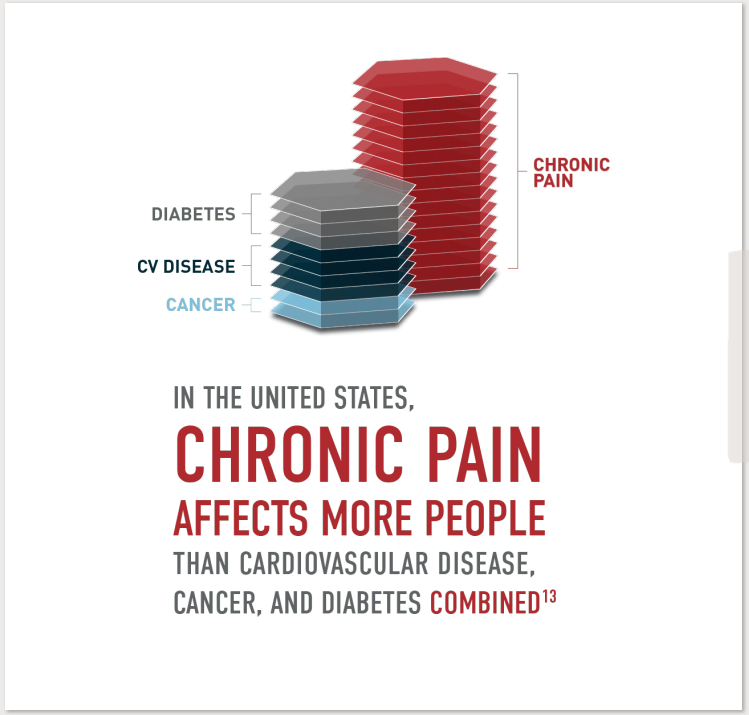
National Institutes of Health to KAS: R01AR053509, R01AR052316, R01AR061371, R01AR06338, R01AR073187;

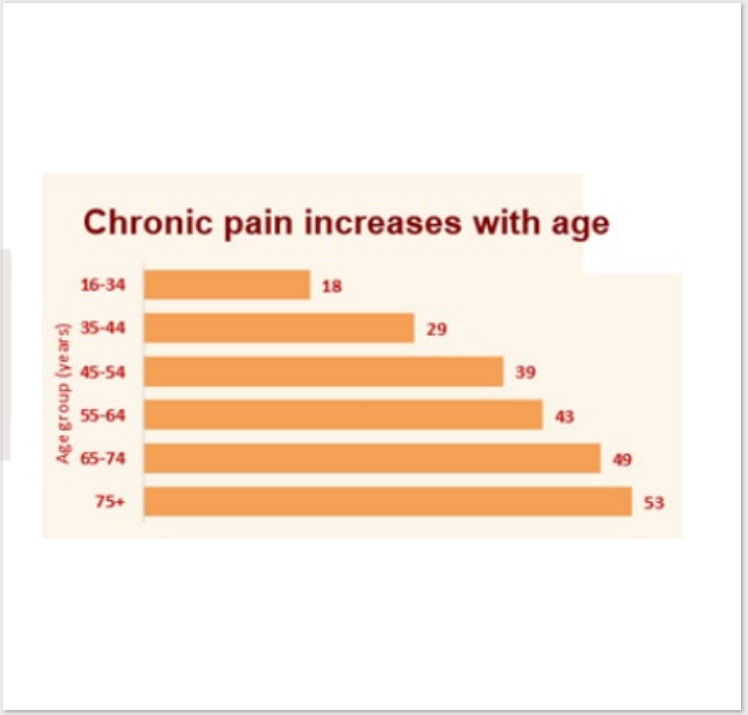
A2CPS funded through the Common Fund of the National Institutes of Health: NS112873, NS118922, DA049110, NS112874, DA049115, DA049116, DA049113


Analgesia, Kathleen Sluka

Objectives

- Biomarkers and Predictors of Acute to Chronic Pain Transition
- Mechanisms of Transition to Chronic Pain
  - Central Nervous System
  - Peripheral Nervous System
  - Immune System
- Acute to Chronic Pain Signatures Program





Chronic Pain is a Major Health Problem

Transition from Acute to Chronic Pain

20-50% Report Chronic Pain After Acute Injury

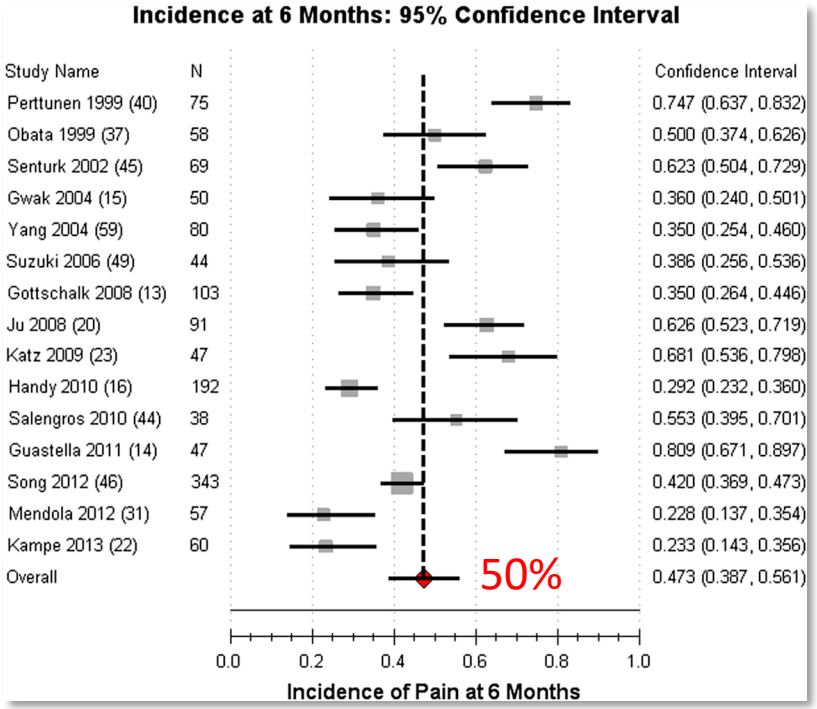
Injury state	Healthy	Acute	Subacute	Chronic
Pain state	Predisposition	Transition		Maintenance
Biomarker type	Susceptibility/risk	Predictive/prognostic		Predictive
Biological	Sex, genetic variants, epigenetics, mRNA, proteins, metabolites, immune system, endocrine system, peripheral nervous system, central nervous system			
Self report	Pain, fatigue, physical activity, sleep, socioeconomic status, anxiety, depression, pain catastrophizing, fear of movement, distress, self-efficacy			

Rates of Chronic Pain Development Depend on Outcome, Definition, and Surgery

Total Knee Replacement

	Rest		Movement	
	US N=104	BR N=100	US N=104	BR N=100
None	84%	86%	68%	50%
Mild	12%	5%	22%	30%
Mod-sev	4%	9%	10%	20%

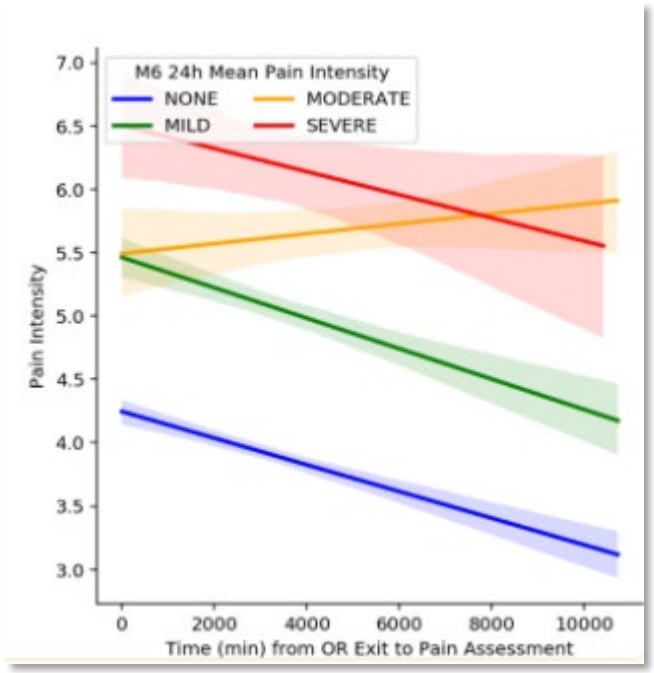
Thoracotomy



DeSantana et al., unpublished; Bayman and Brennan 2014; Sluka et al., 2023

Current pain predicts the transition to chronic pain

- Pain
  - Intensity
    - Preoperative
    - Postoperative/Post-injury
    - Trajectory after injury/surgery
  - Movement-evoked
  - Widespread pain



TKA	Moderate/Severe Pain with ROM (vs. Mild/No pain)		
Variable	**Odds Ratio**	**95% CI**	**p-value**
Preoperative Pain with ROM test (Severe)	**10.15**	[2.50-41.28]	0.001
Anxiety	1.40*	[1.09-1.79]	0.009

Noiseaux et al., 2014; Mehta et al., 2015; Fregoso et al., 2019; Bayman et al., 2017, McLean and Clauw, 2004, Giordano et al., 2022, Sluka et al., 2023, Smith et al., 2021, and many, many more

Psychological Factors Predict Development of Chronic Pain

- *Anxiety*
- *Depression*
- *Pain Catastrophizing*
- *Fear of Movement*

TKA	Moderate/Severe Pain with ROM (vs. Mild/No pain)		
Variable	**Odds Ratio**	**95% CI**	**p-value**
Preoperative Pain with ROM test (Severe)	**10.15**	[2.50-41.28]	0.001
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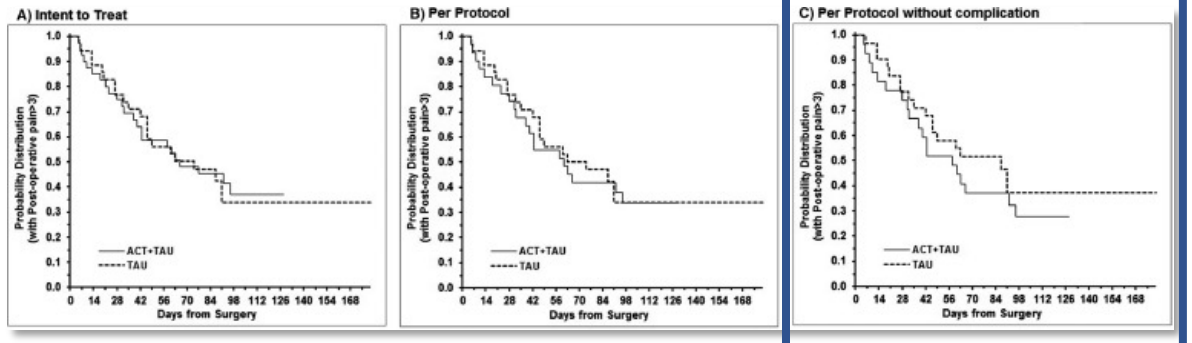
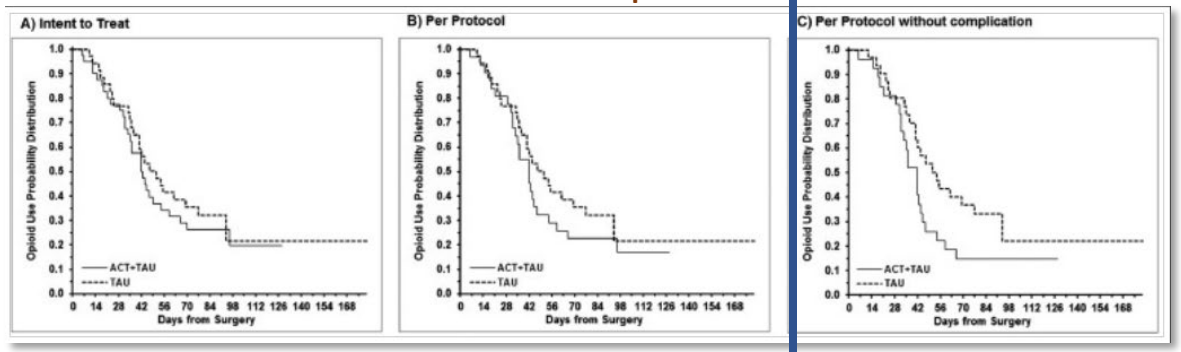
Noiseaux et al., 2014; Mehta et al., 2015; Fregoso et al., 2019; Bayman et al., 2017, McLean and Clauw, 2004, Giordano et al., 2022, Sluka et al., 2023, Smith et al., 2021, and many, many more

Treatment of Psychological Factors Before Surgery Reduces Pain and Opioid Use

Reduction in Pain <3

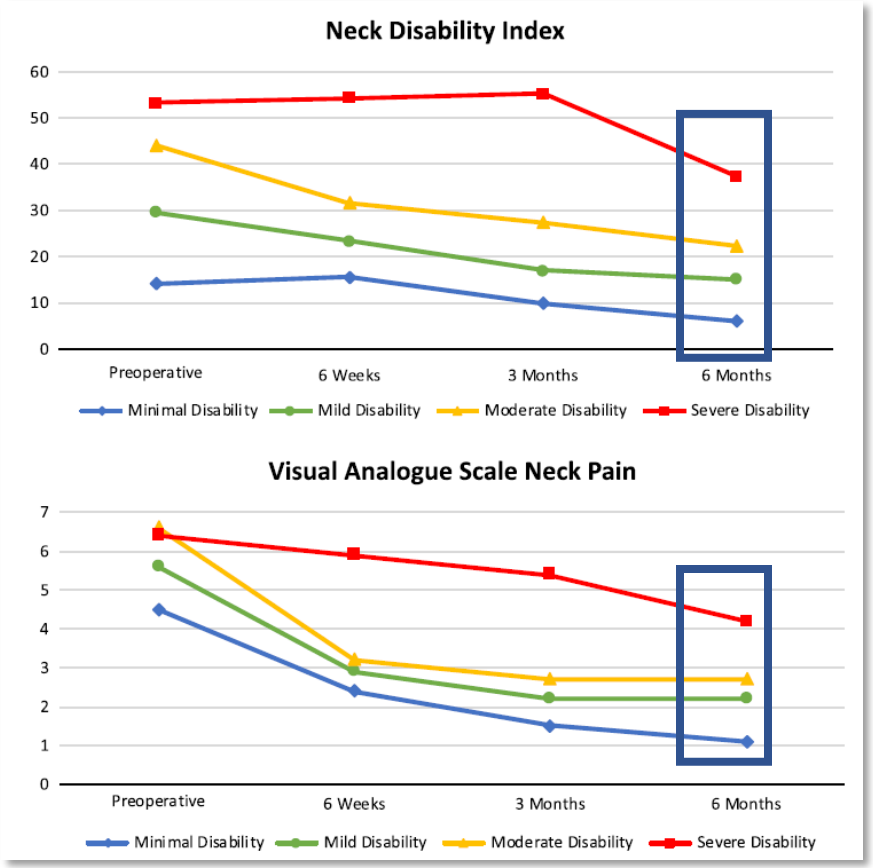


Cessation of Opioid Use



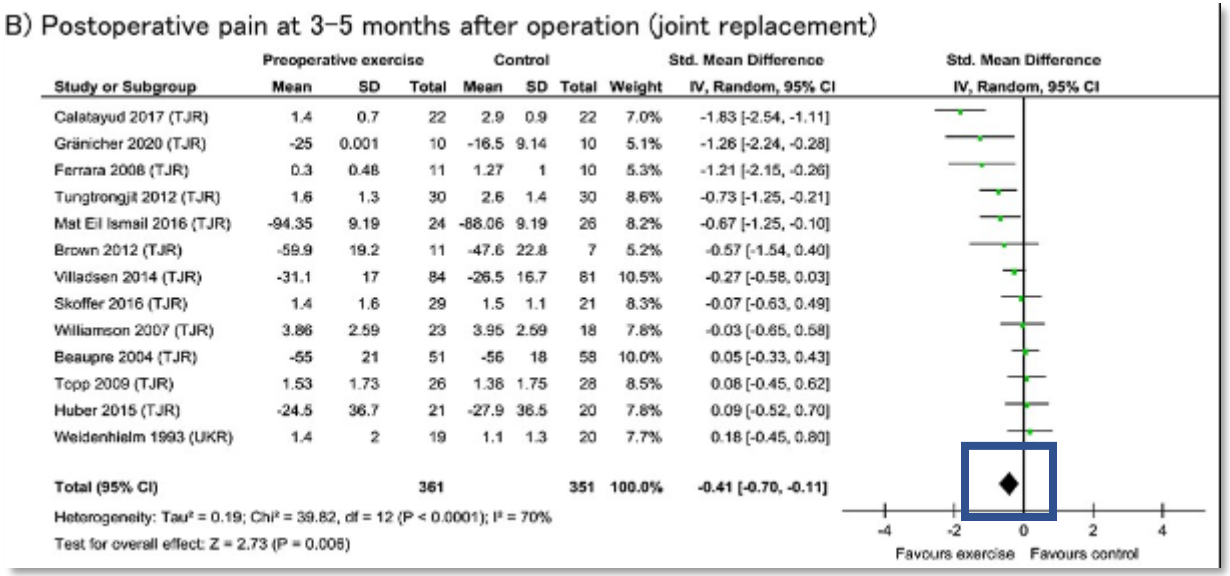
Dindo et al., 2018; Azam et al., 2017

Function and Disability Predict Outcome After Surgery



Perrish et al et al., 2023

Preoperative Exercise Reduces Pain, and Improves Function after TKA Surgery



Hayashi et al., 2023

PAIN® 152 (2011) 2241–2247

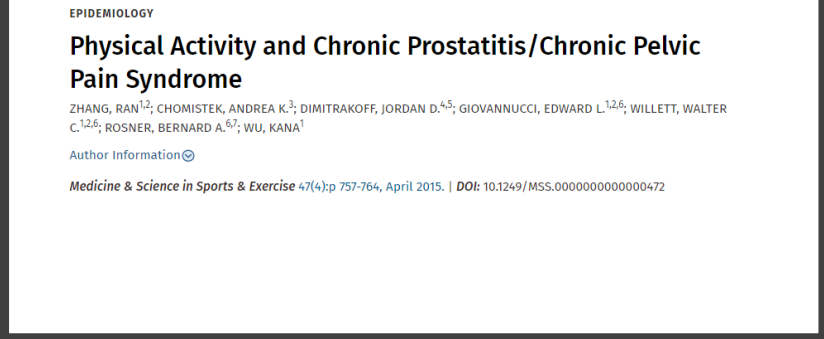
PAIN®

www.elsevier.com/locate/pain

Associations between recreational exercise and chronic pain in the general population: Evidence from the HUNT 3 study

Tormod Landmark [a,b,*], Pål Romundstad [c], Petter C. Borchgrevink [b,d], Stein Kaasa [a,e], Ola Dale [d,f]

[a] Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[b] National Competence Centre for Complex Symptom Disorders, St Olavs University Hospital, Trondheim, Norway
[c] Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[d] Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[e] Department of Oncology, St Olavs University Hospital, Trondheim, Norway
[f] Department of Anaesthesia and Emergency Medicine, St Olavs University Hospital, Trondheim, Norway



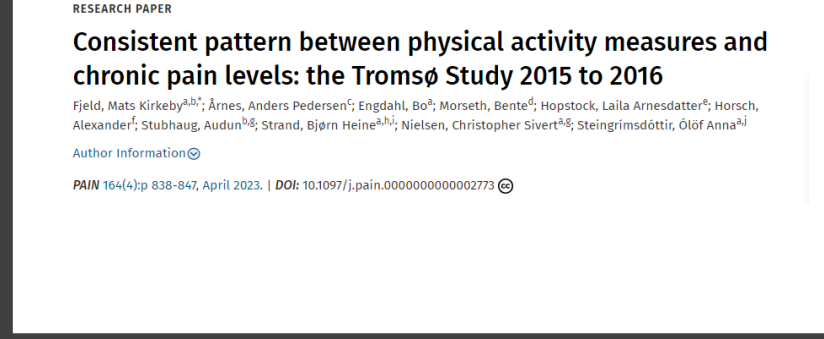
EPIDEMIOLOGY

Physical Activity and Chronic Prostatitis/Chronic Pelvic Pain Syndrome

ZHANG, RAN[1,2]; CHOMISTEK, ANDREA K.[3]; DIMITRAKOFF, JORDAN D.[4,5]; GIOVANNUCCI, EDWARD L.[1,2,6]; WILLETT, WALTER C.[1,2,6]; ROSNER, BERNARD A.[6,7]; WU, KANA[1]

Author Information

Medicine & Science in Sports & Exercise 47(4):p 757-764, April 2015. | **DOI:** 10.1249/MSS.0000000000000472



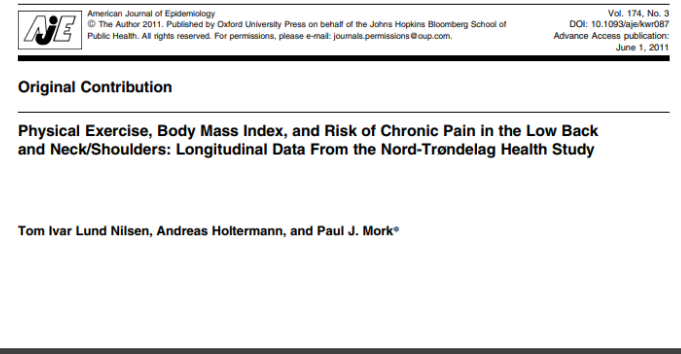
RESEARCH PAPER

Consistent pattern between physical activity measures and chronic pain levels: the Tromsø Study 2015 to 2016

Fjeld, Mats Kirkeby[a,b,*]; Årnes, Anders Pedersen[c]; Engdahl, Bo[a]; Morseth, Bente[d]; Hopstock, Laila Arnesdatter[e]; Horsch, Alexander[f]; Stubhaug, Audun[b,g]; Strand, Bjørn Heine[a,h,i]; Nielsen, Christopher Sivert[a,g]; Steingrímsdóttir, Ólöf Anna[a,j]

Author Information

PAIN 164(4):p 838-847, April 2023. | **DOI:** 10.1097/j.pain.0000000000002773



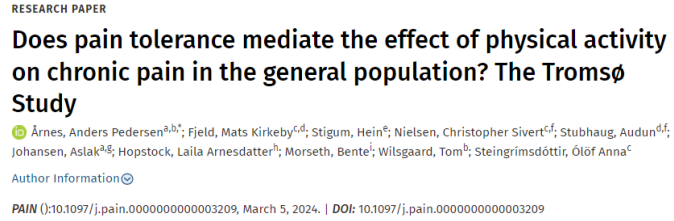
American Journal of Epidemiology

Vol. 174, No. 3
DOI: 10.1093/aje/kwr087
Advance Access publication: June 1, 2011

Original Contribution

Physical Exercise, Body Mass Index, and Risk of Chronic Pain in the Low Back and Neck/Shoulders: Longitudinal Data From the Nord-Trøndelag Health Study

Tom Ivar Lund Nilsen, Andreas Holtermann, and Paul J. Mork*



RESEARCH PAPER

Does pain tolerance mediate the effect of physical activity on chronic pain in the general population? The Tromsø Study

Årnes, Anders Pedersen[a,b,*]; Fjeld, Mats Kirkeby[c,d]; Stigum, Hein[e]; Nielsen, Christopher Sivert[c,f]; Stubhaug, Audun[d,f]; Johansen, Aslak[a,g]; Hopstock, Laila Arnesdatter[h]; Morseth, Bente[i]; Wilsgaard, Tom[b]; Steingrímsdóttir, Ólöf Anna[c]

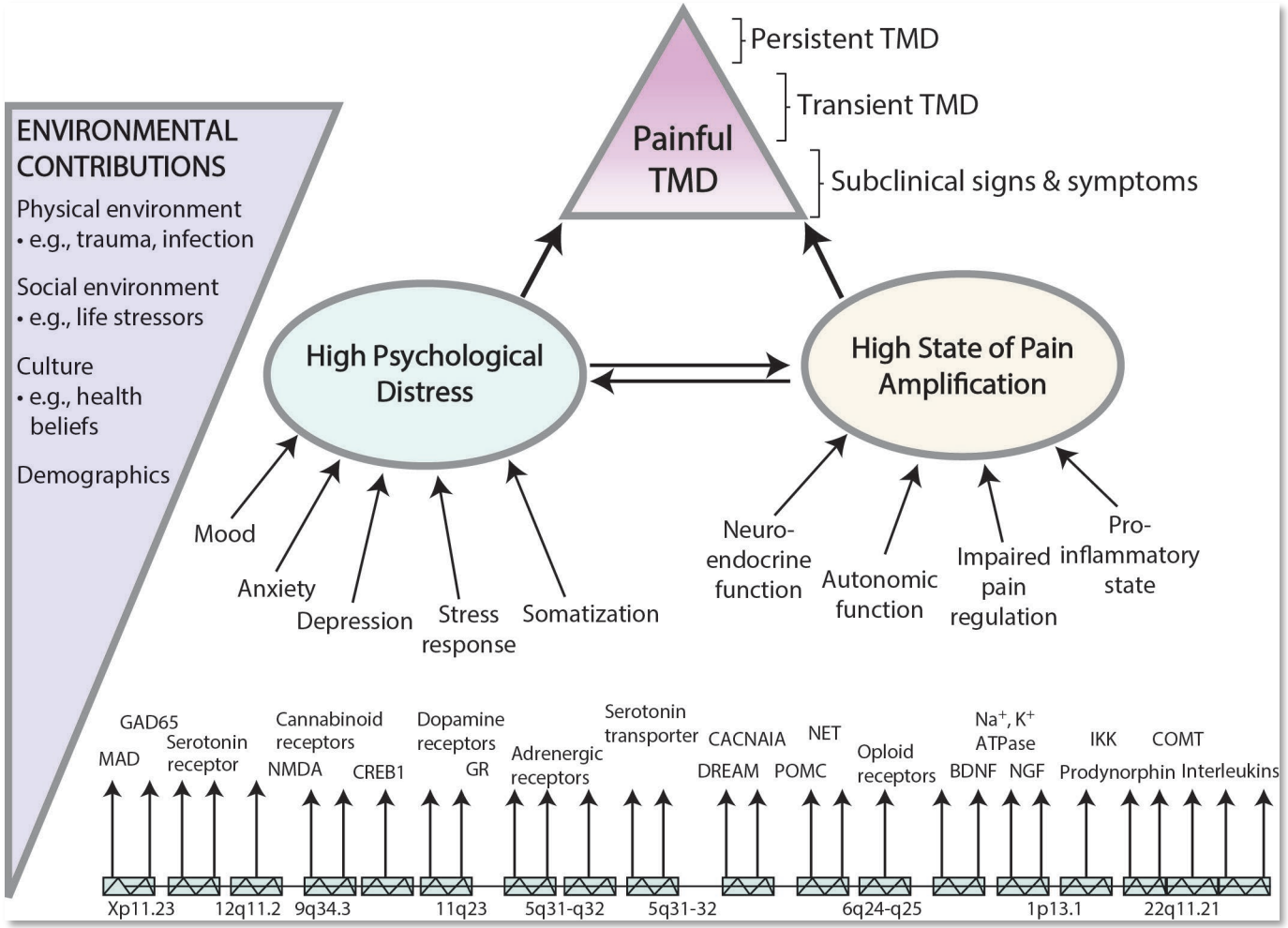
Author Information

PAIN ():10.1097/j.pain.0000000000003209, March 5, 2024. | **DOI:** 10.1097/j.pain.0000000000003209

Population Studies Show Physical Activity Reduces Risk for Development of Chronic Pain

OPPERA study suggests multiple factors contribute to development of chronic pain

Biosignature combining multiple factors

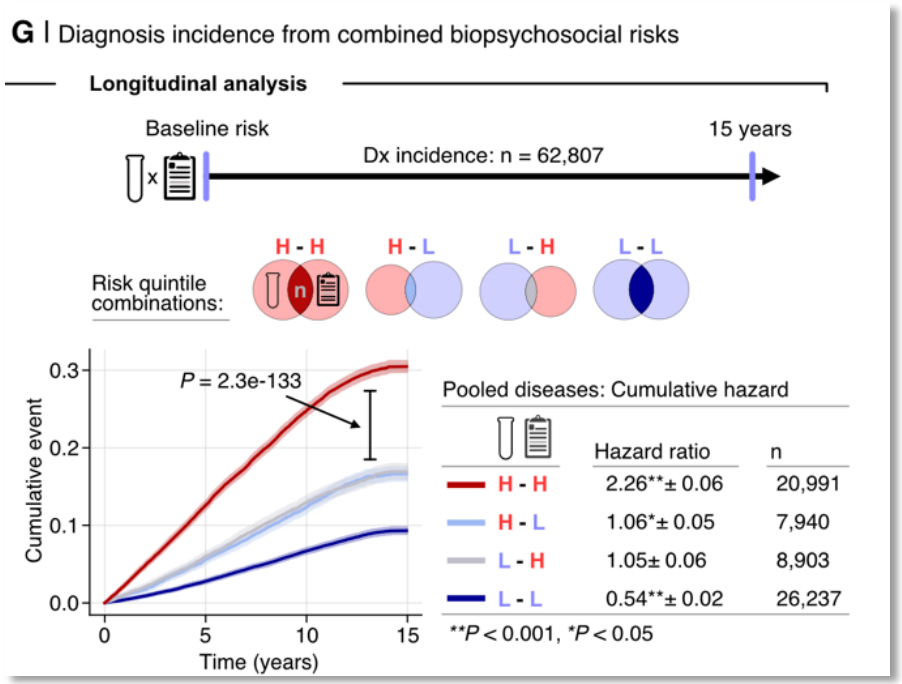


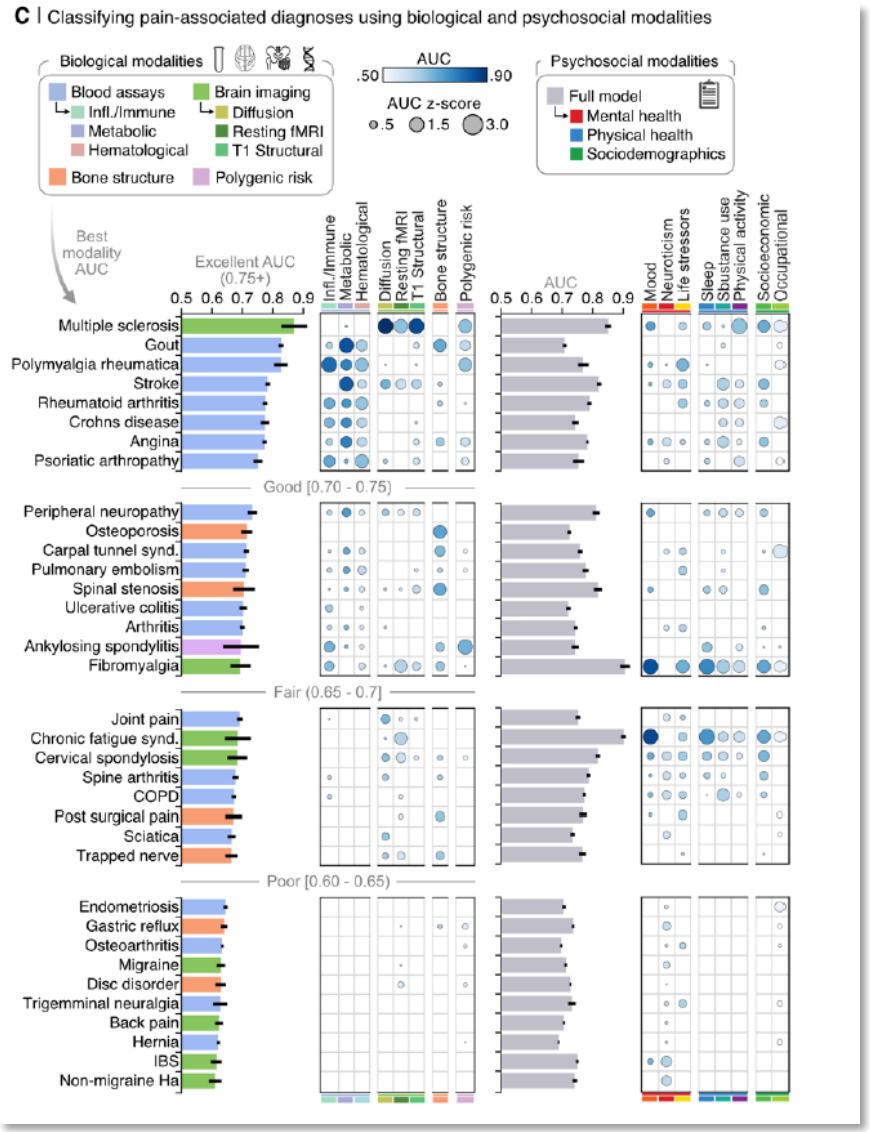
Maixner and colleagues

Combining Biological and Psychological Factors Enhances Prediction of Chronic Pain

UK Biobank to train and validate biomarkers for pain-related medical conditions and self-reported pain (n=493,211)
Generalizability tested in All of Us Research Program (n=27,151)

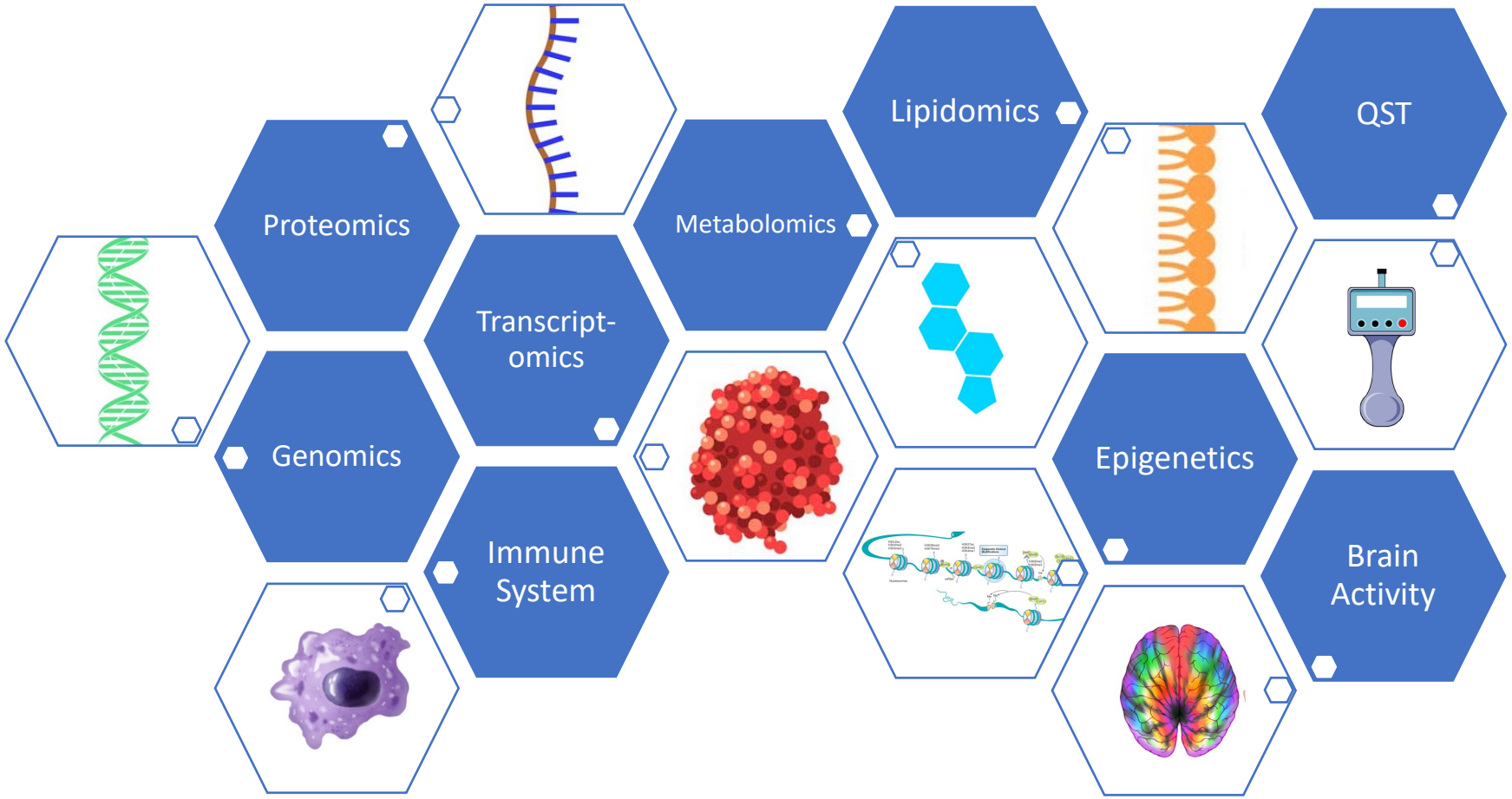
Blood assays, bone structure, brain imaging, polygenic risk score, psychosocial factors





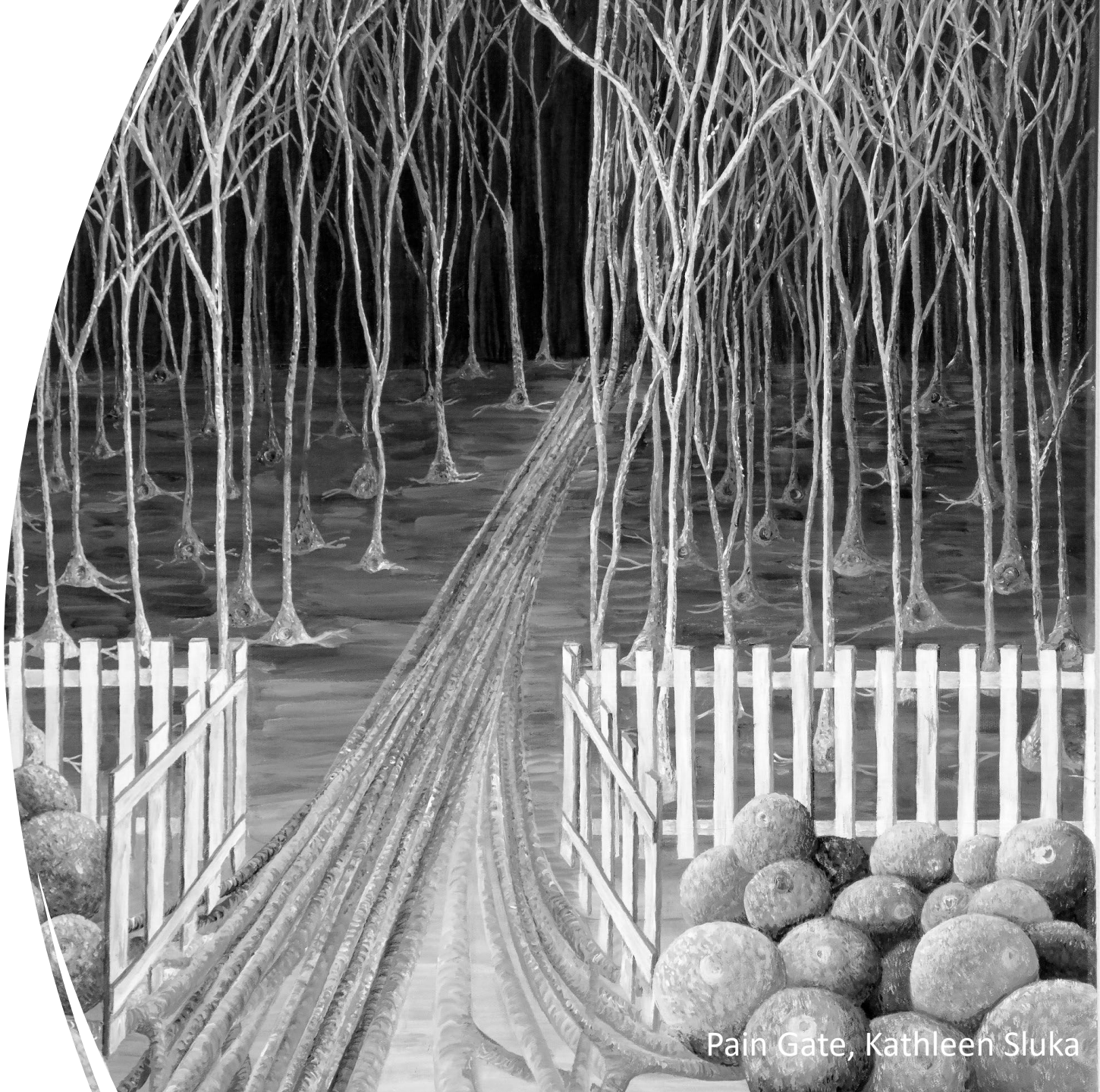
Fillingim et al., 2024

Biological Markers



Sluka et al., 2023; Vargas-Alarcon, Fragoso et al. 2007, Cargnin, Magnani et al. 2013, Martinez-Jauand, Sitges et al. 2013, Rut, Machoy-Mokrzynska et al. 2014, Omair, Mannion et al. 2015; Kolesnikov, Gabovits et al. 2013, Linnstaedt, Hu et al. 2015; Storm, Stoen et al. 2013, Bartosova, Polanecky et al. 2015; Di Lorenzo, Di Lorenzo et al. 2009, Vossen, Kenis et al. 2010, Vasant, Payton et al. 2013, Tian, Liu et al. 2018; Lindstedt et al., 2011; Tour et al., 2017; Stannus et al., 2012; Merriwether et al., 2019; Attur et al., 2013; Lotz et al., 2014; Mabey and Honsawek, 2014; Nguyen et al., 2017; Daghestani and Kraus, 2015; Parisien et al., 2022; Arendt-Nielsen et al., 2010; Kosek and Orderberg, 2000; Yarnitsky et al., 2008, 2012; Luna et al., 2017; Georgopoulos et al., 2020, Apkarian et al., Curr Opin Neurol. 201; Turnball et al., 2024

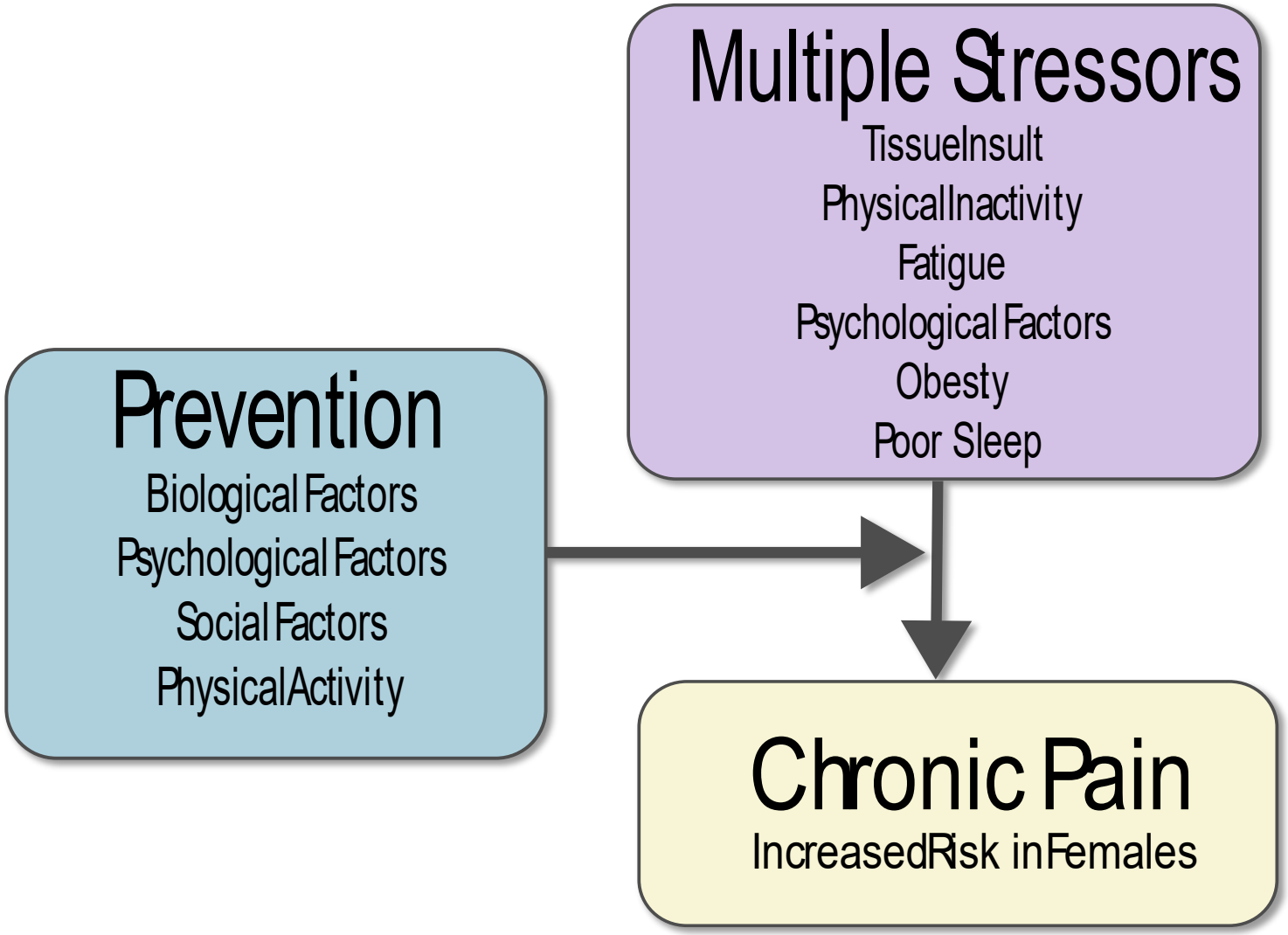
Mechanisms for Transition to Chronic Pain



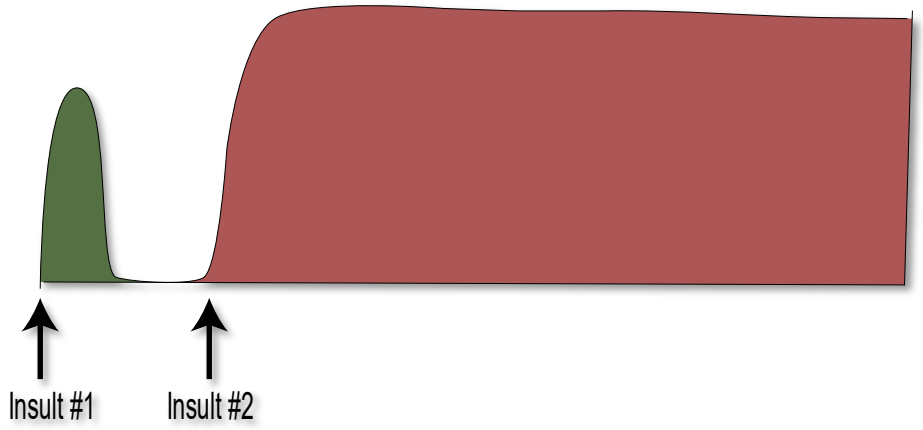
Pain Gate, Kathleen Sluka

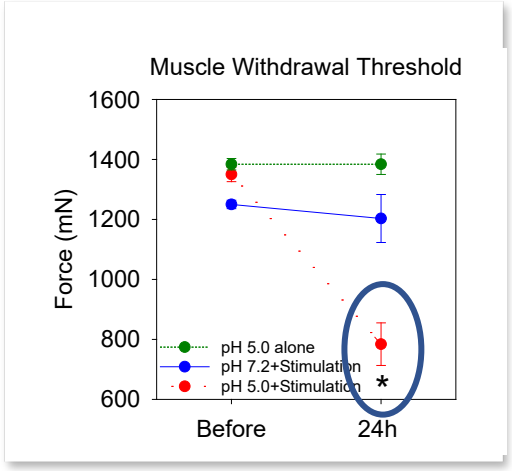
There are multiple ways to induce chronic pain

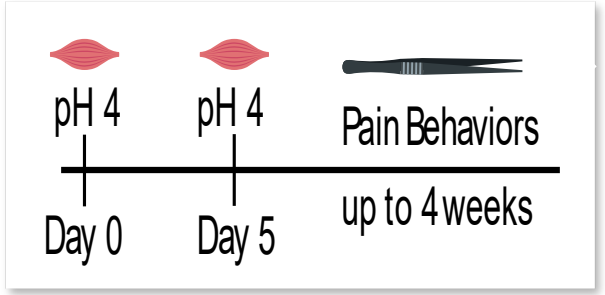
There are multiple ways to protect from chronic pain

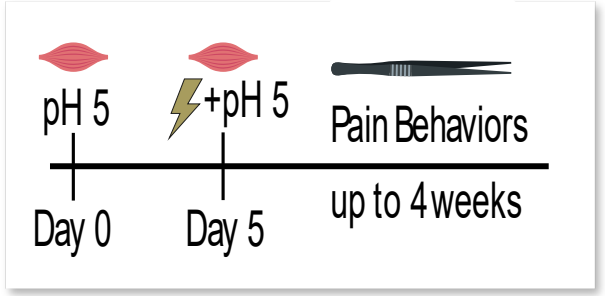


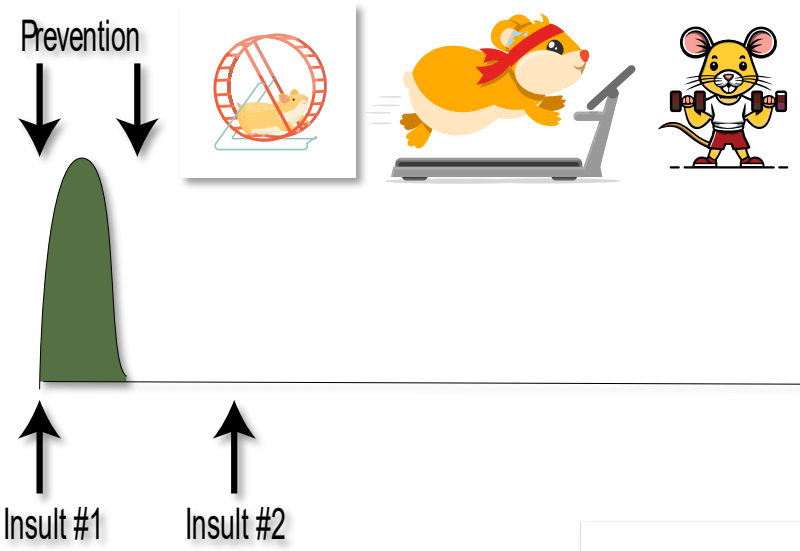
Animal Models for Transition to Chronic Pain

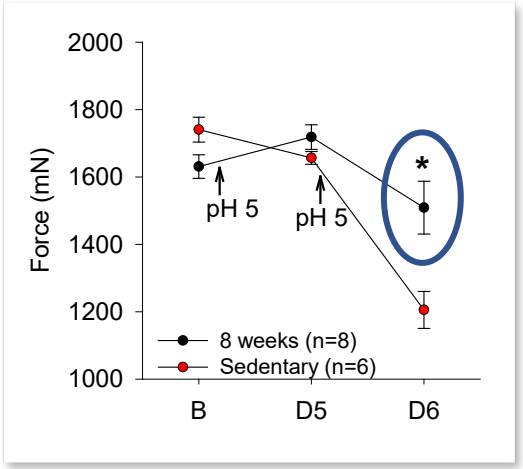


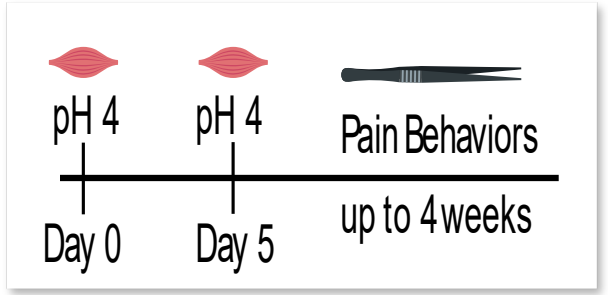


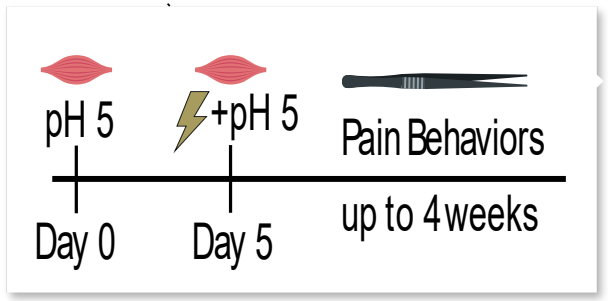








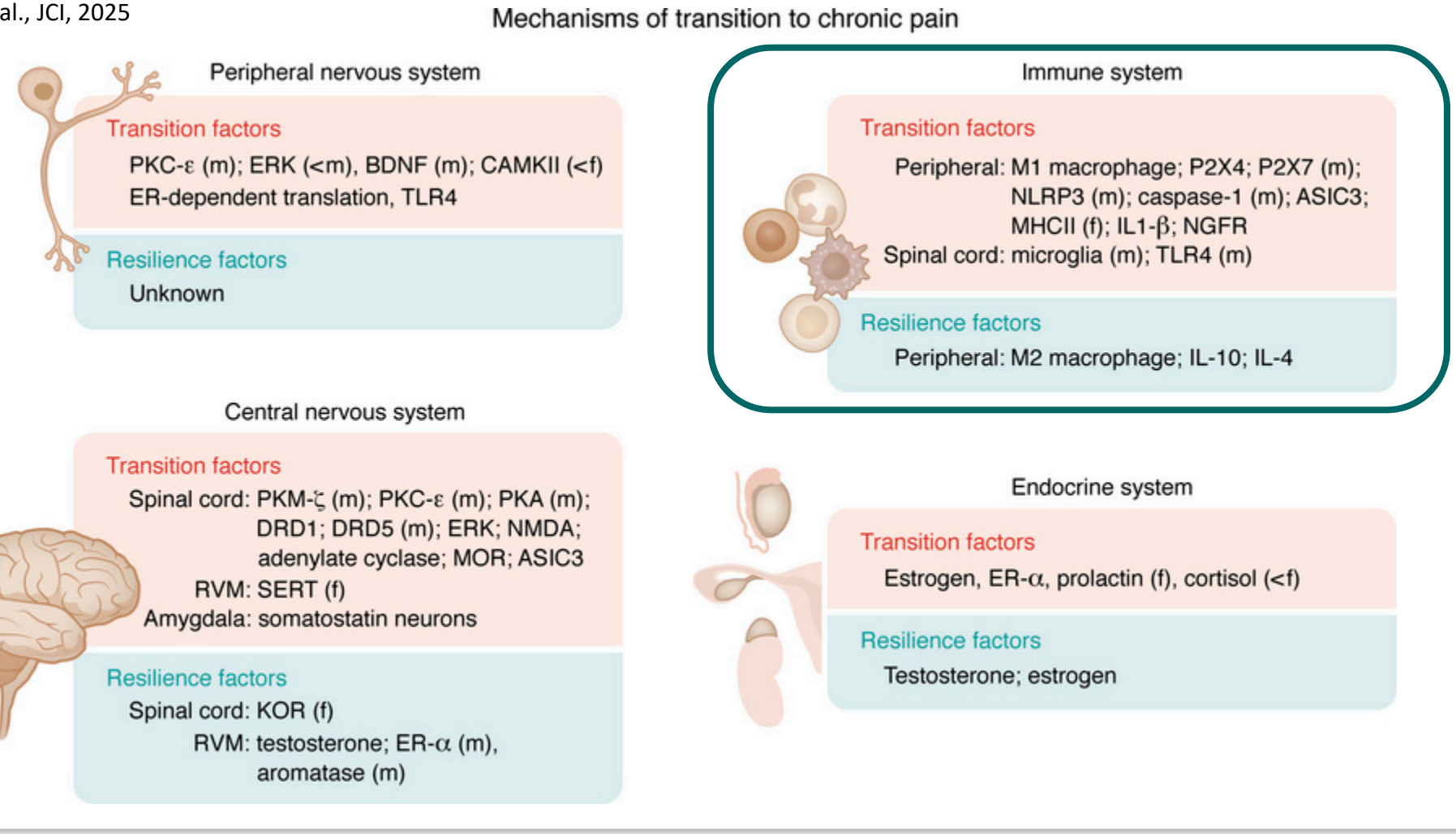




Sluka et al., 2001; Yokohama et al., 2007; Sluka et al., 2009; Sluka and Rasmussen, 2010; Gregory et al., 2013

Multiple mechanisms underlie the transition to chronic pain

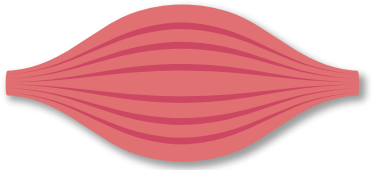
Review: Smith et al., JCI, 2025

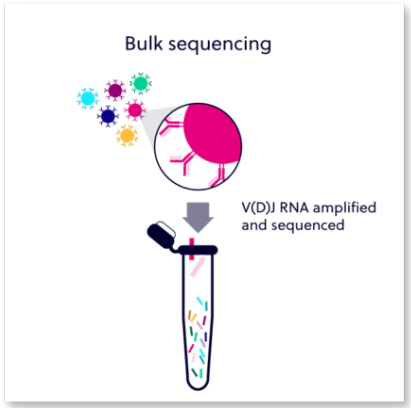


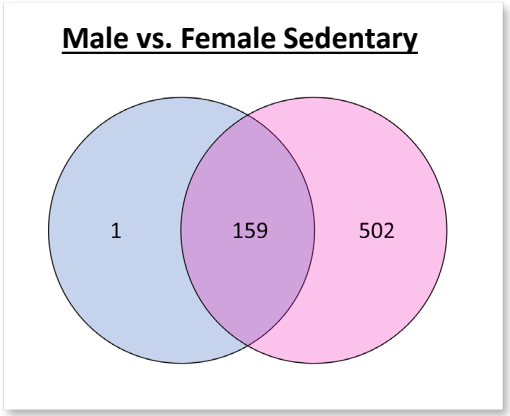
Reichling and Levine, 2009; Kandasamy and Price, 2015; Parada et al., 2005; Sun and Chen, 2016; Tillu et al., 2009; DaSilva et al., 2010; Radhakrishnan and Sluka 2010; Brito et al., 2017; Cheng et al., 2011; Bobinski, 2017; Leung et al., 2016; Megat et al., 2018

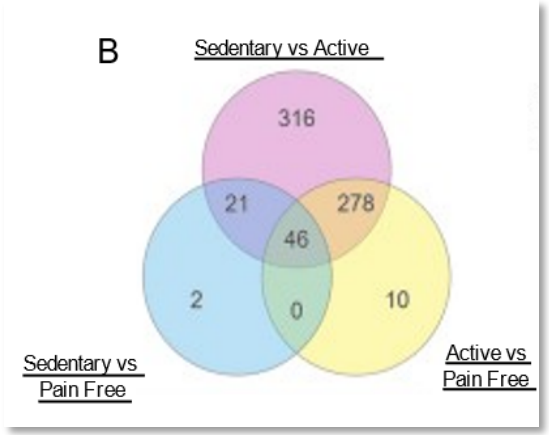
Immune System Mechanisms

Immune System Altered by Muscle Insult and Exercise









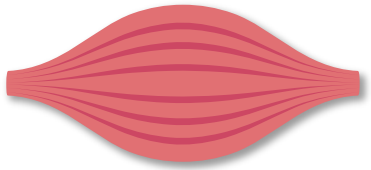
D

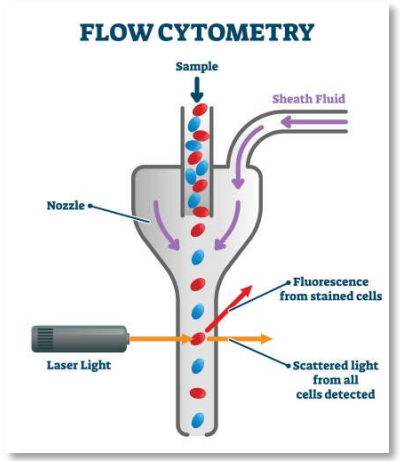
Female Physically Active Pathway Analysis

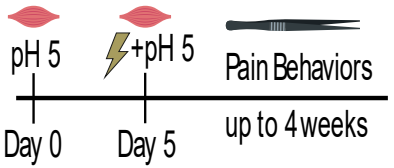
Name	Sedentary vs Pain Free		Sedentary vs Exercise	
	% DEG of Total	adj-p	% DEG of Total	adj-p
Chemokine signaling pathway	23%	3.1E-06	13%	2.3E-06
Antigen processing and presentation	***34%***	***1.1E-05***	***20%***	***7.4E-05***
Viral protein interaction with cytokine and cytokine receptor	47%	1.5E-05	30%	9.1E-05
Cytokine-cytokine receptor interaction	32%	3.4E-05	18%	9.0E-05
Neutrophil extracellular trap formation	24%	4.1E-05	18%	9.9E-05
Natural killer cell mediated cytotoxicity	30%	4.5E-05	22%	9.0E-05
Osteoclast differentiation	27%	4.6E-05	19%	2.3E-06
Toll-like receptor signaling pathway	25%	6.1E-05	19%	1.0E-04
Complement and coagulation cascades	29%	8.7E-05	18%	5.6E-04
NOD-like receptor signaling pathway	23%	8.7E-05	14%	7.0E-05

Lesnak et al., 2023

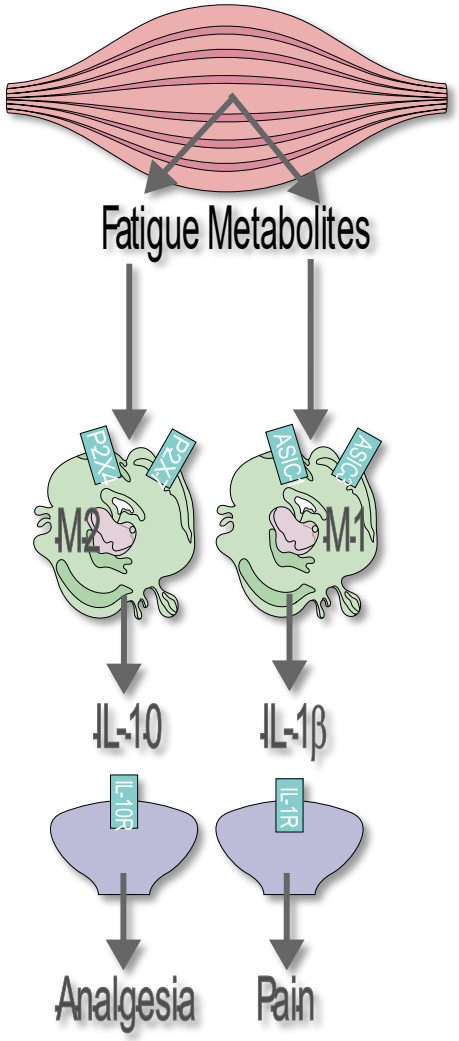
Macrophages play a key role in transition and resilience to chronic pain

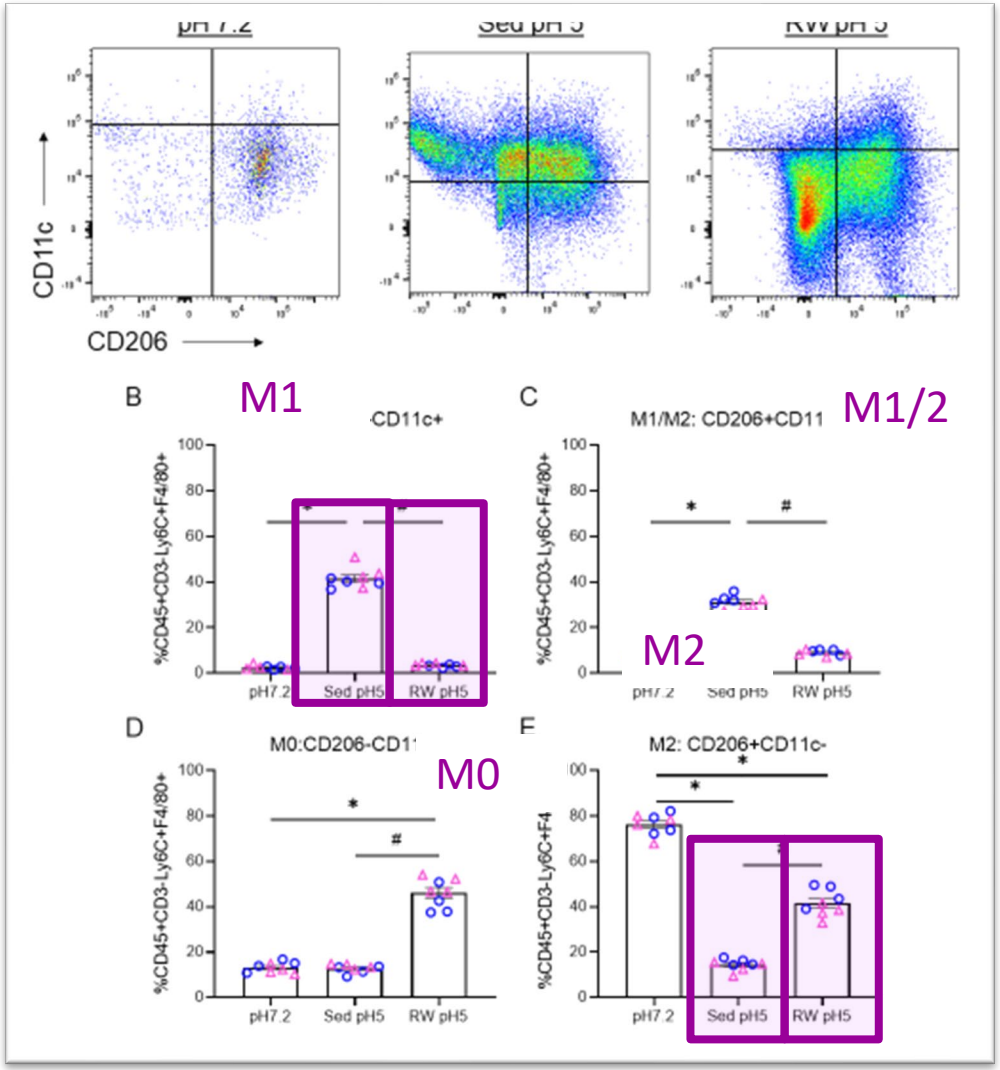






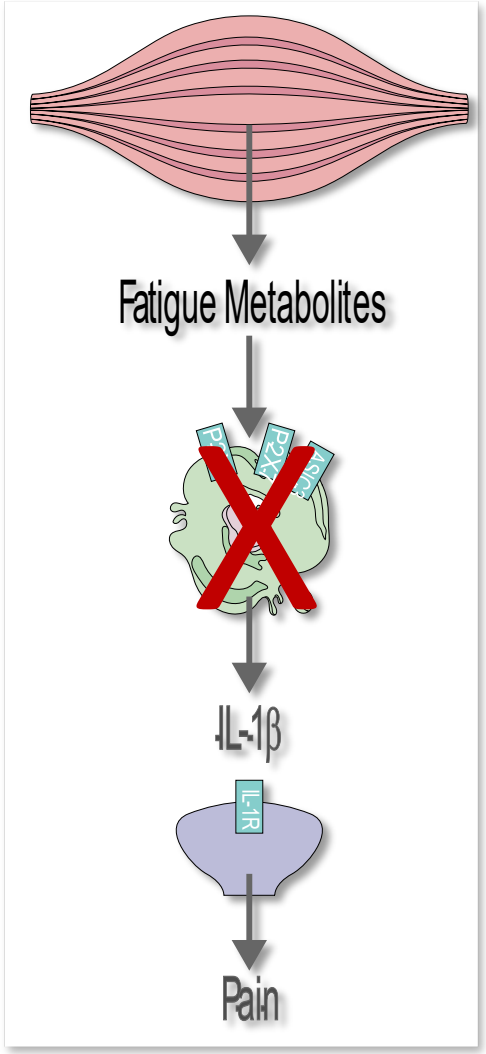
Lesnak et al., 2023

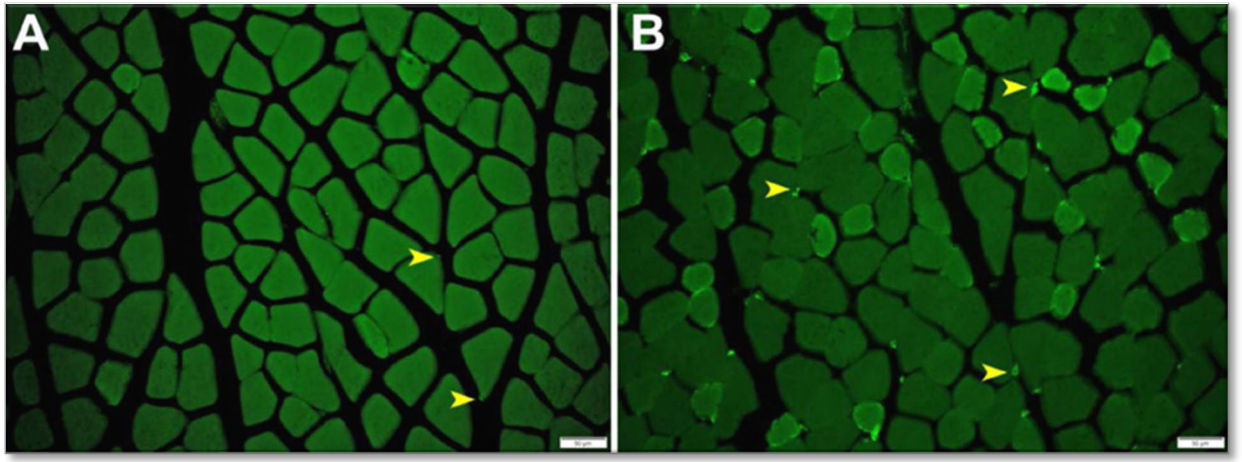


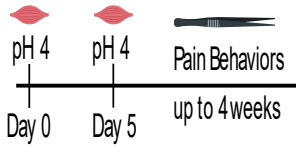


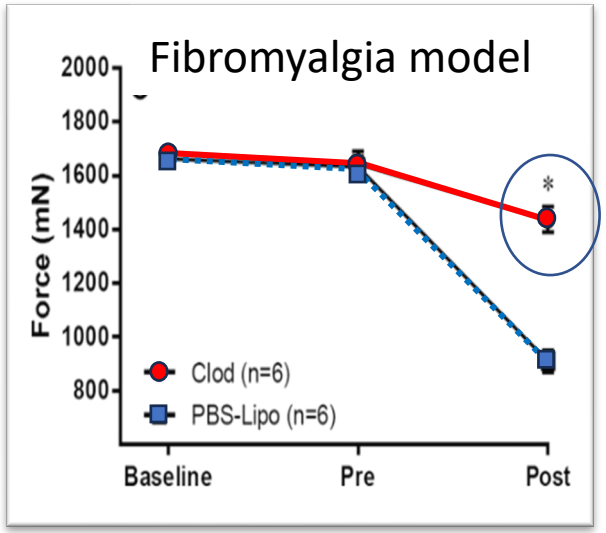
Immune System Mechanisms

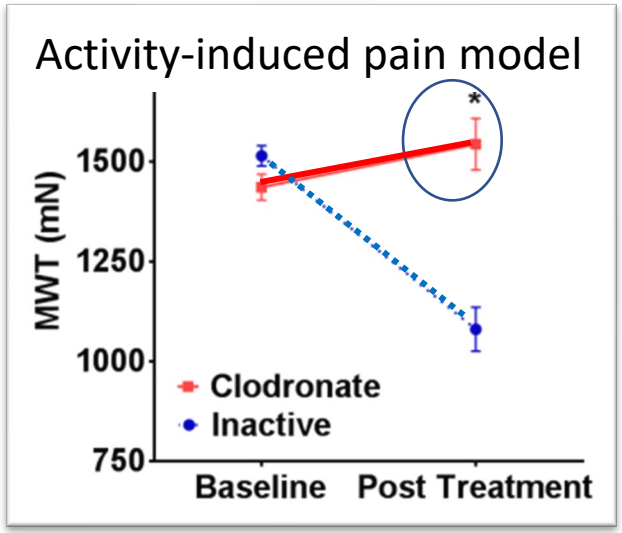
Macrophages in muscle are necessary for development of muscle pain

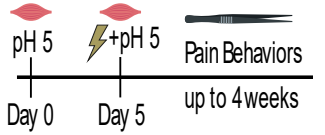






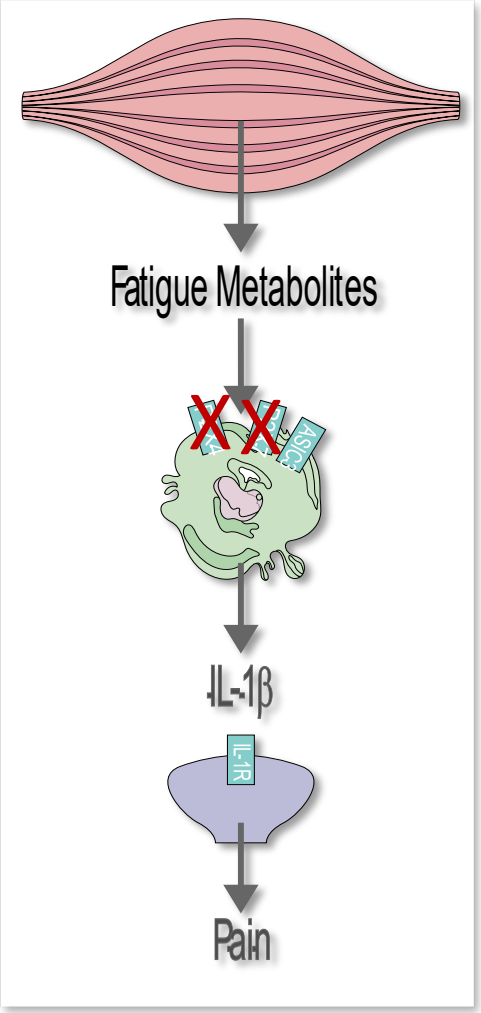


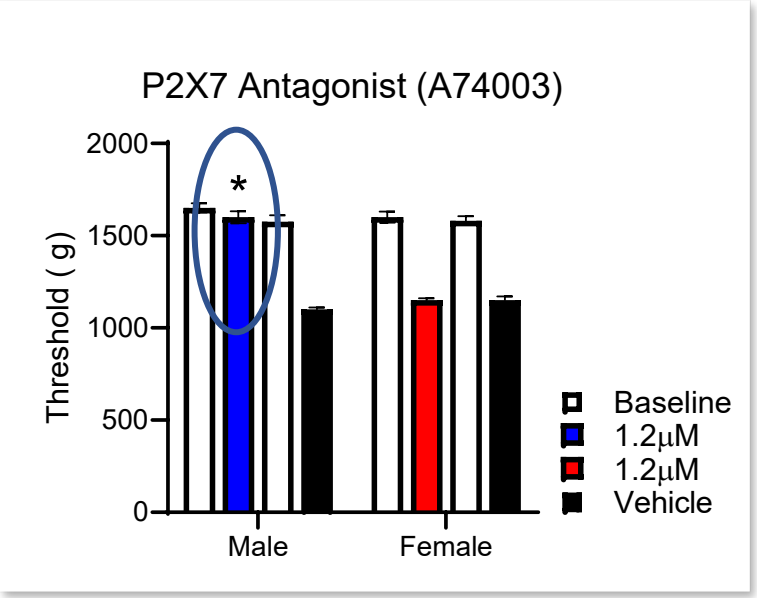


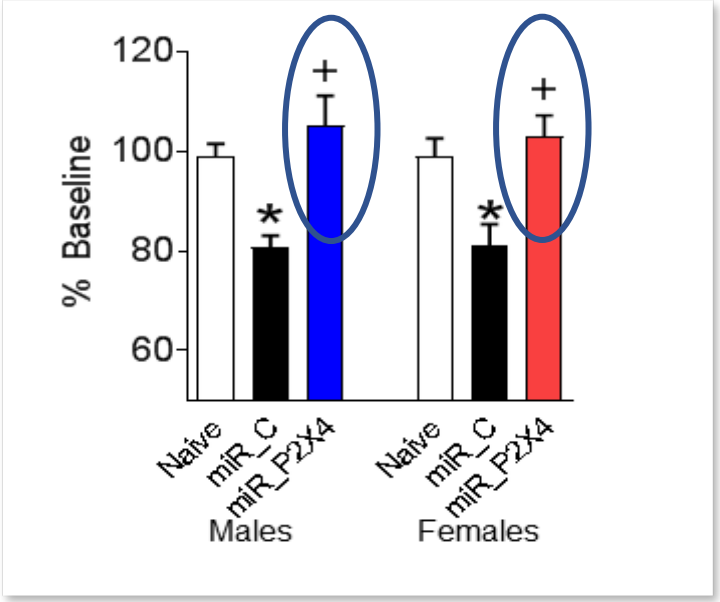


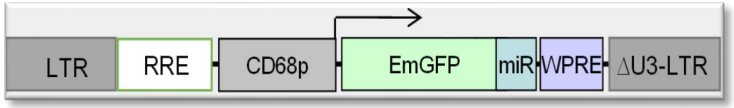
Gregory et al., 2015, 2018; Gong et al., 2016; Fusaro et al., 2020

P2X4 and P2X7 on muscle macrophages promotes development of chronic pain





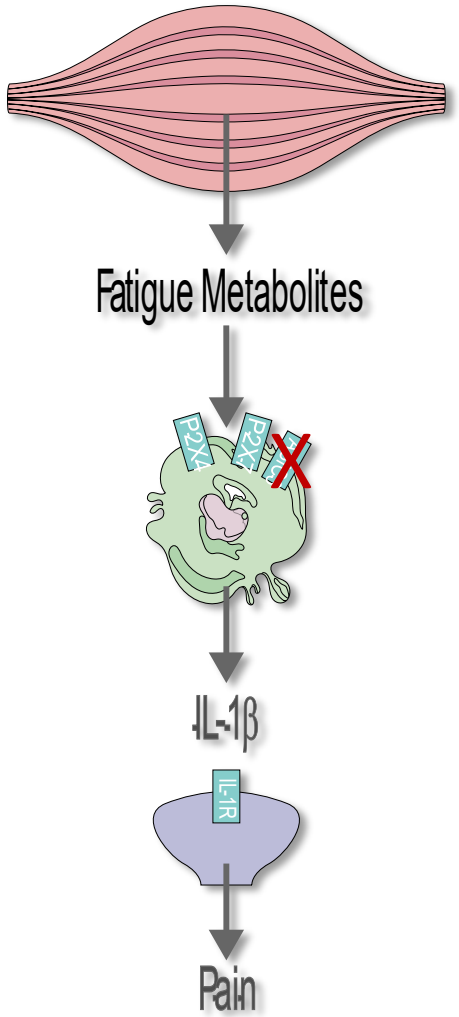


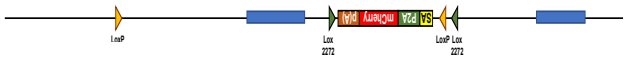


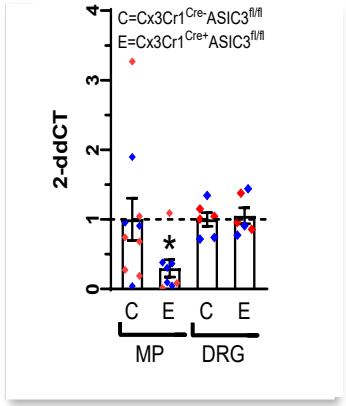
Fusaro et al., 2020; Hayashi et al., 2023

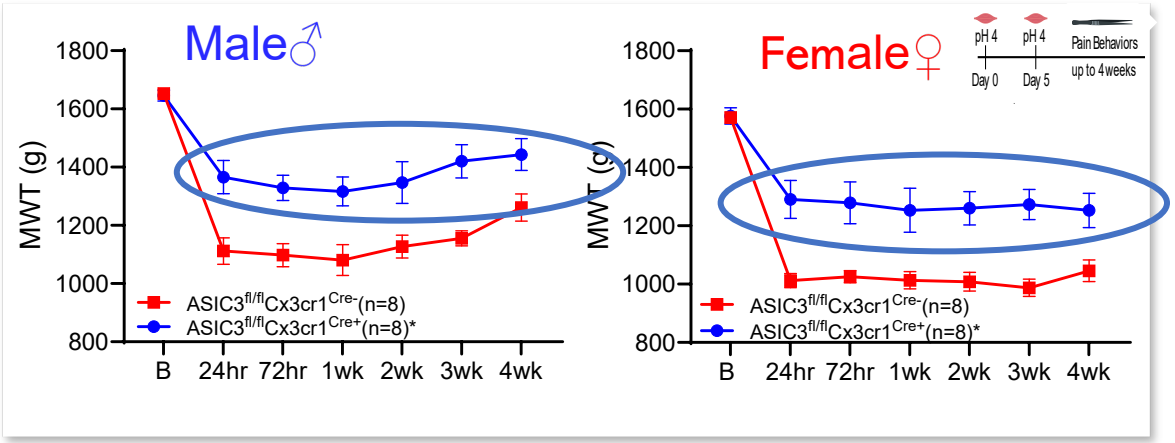
Immune System Mechanisms

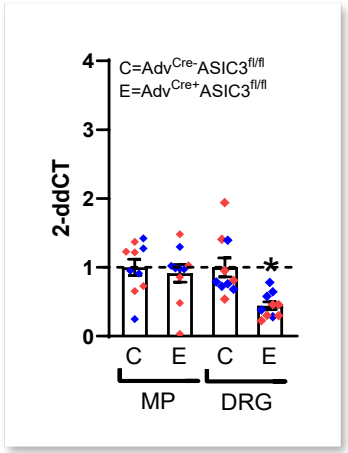
ASIC3 on muscle macrophages necessary for development of chronic pain

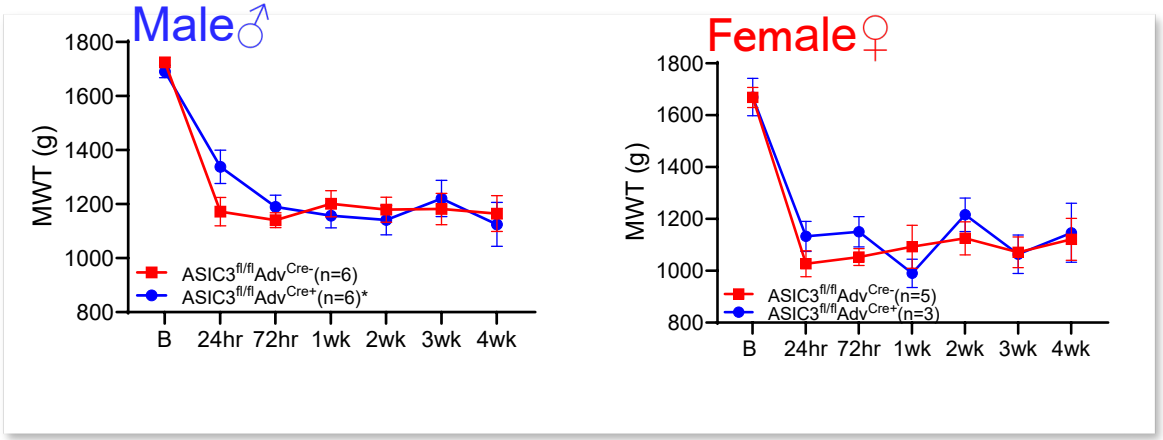








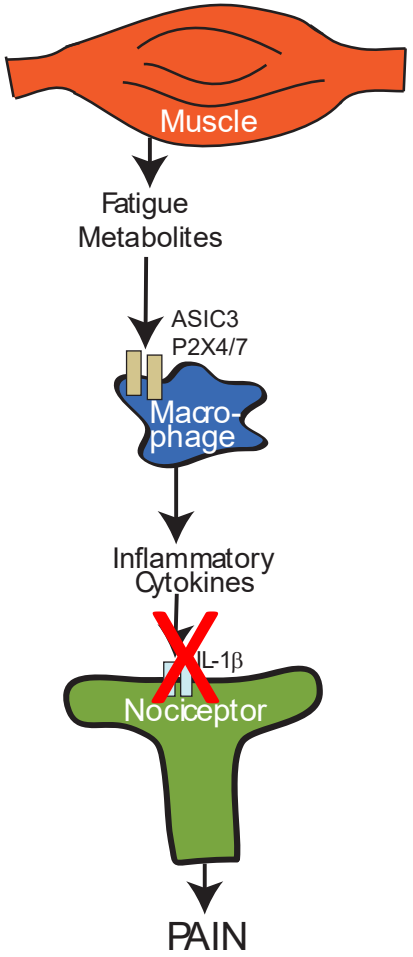


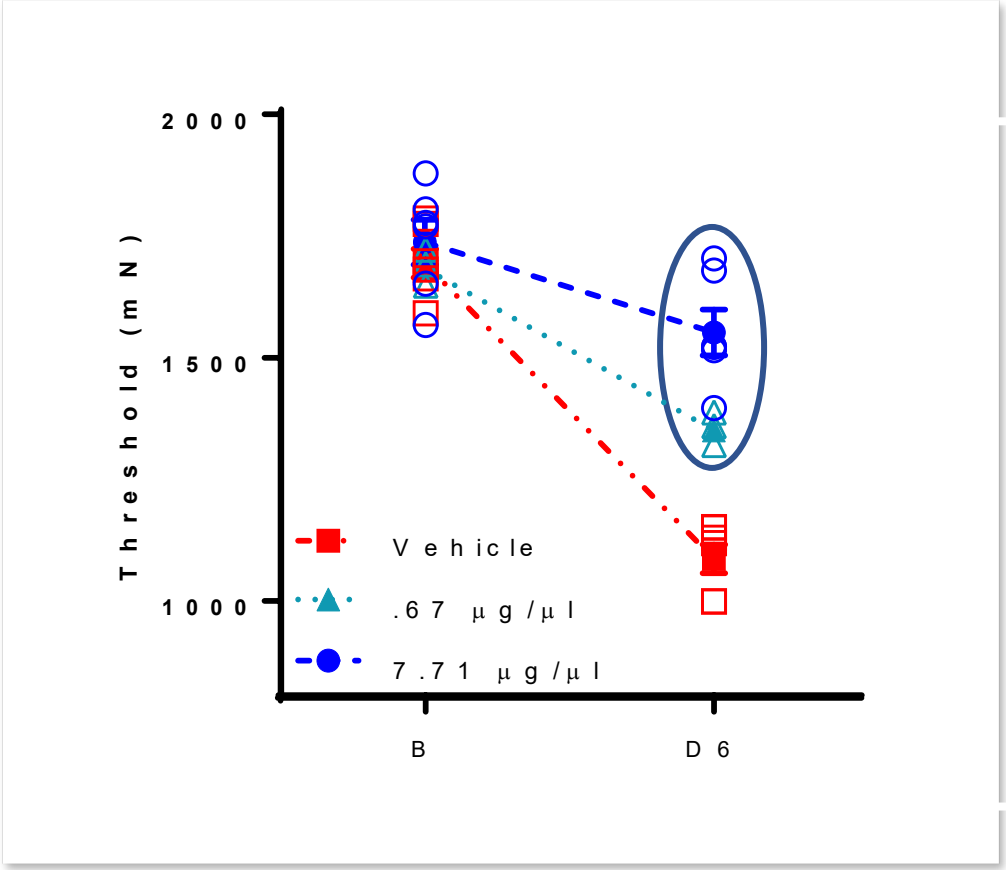


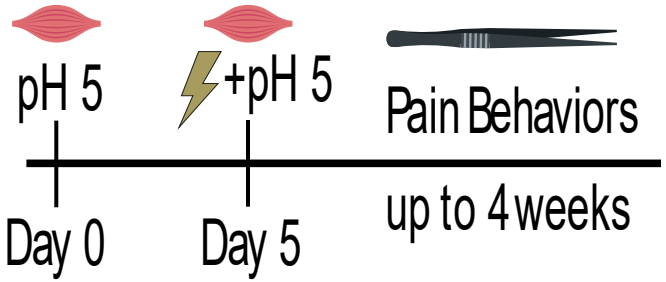
Hayashi et al., 2025

Immune System Mechanisms

IL1-β promotes development chronic pain



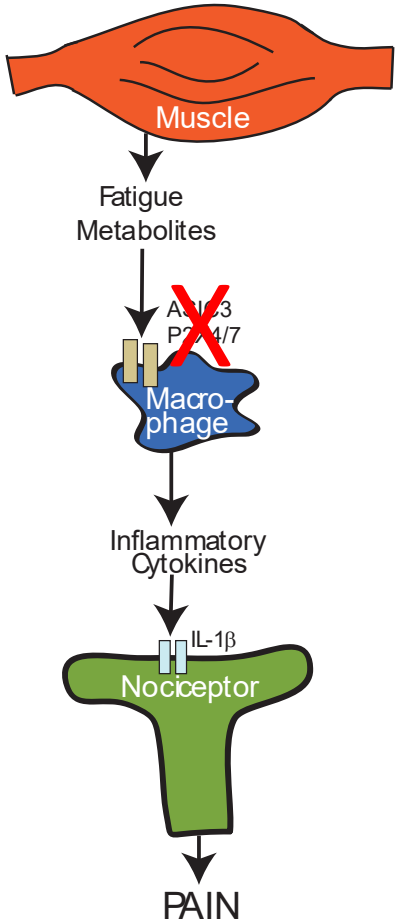


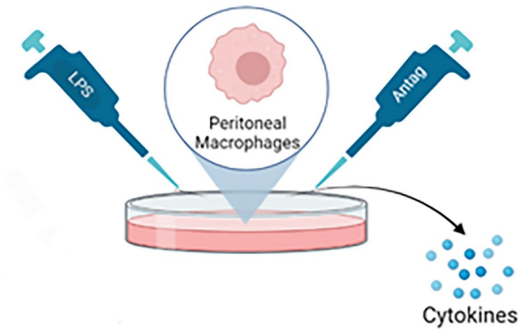


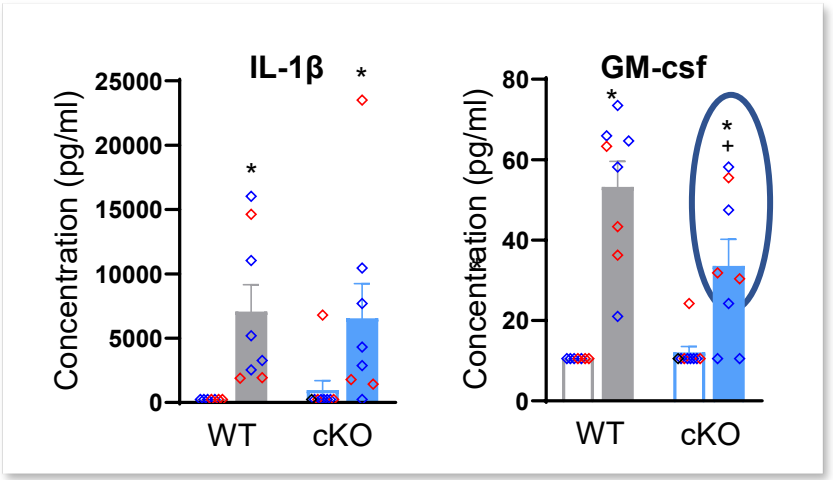
Fusaro et al., 2020; Hayashi et al., 2023

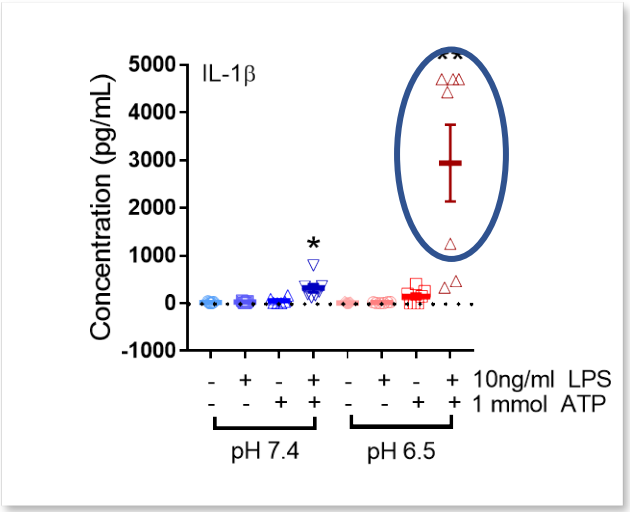
Immune System Mechanisms

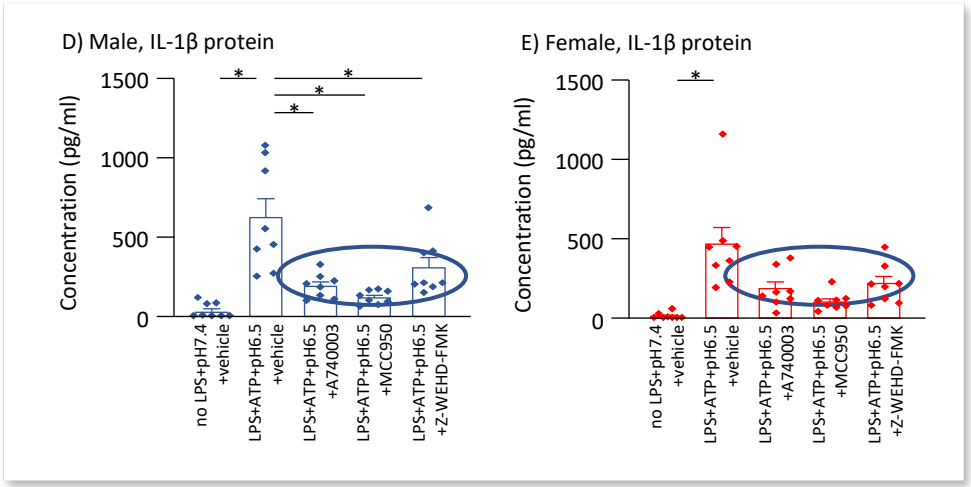
Macrophage release of IL-1β is prevented by blockade of P2X7





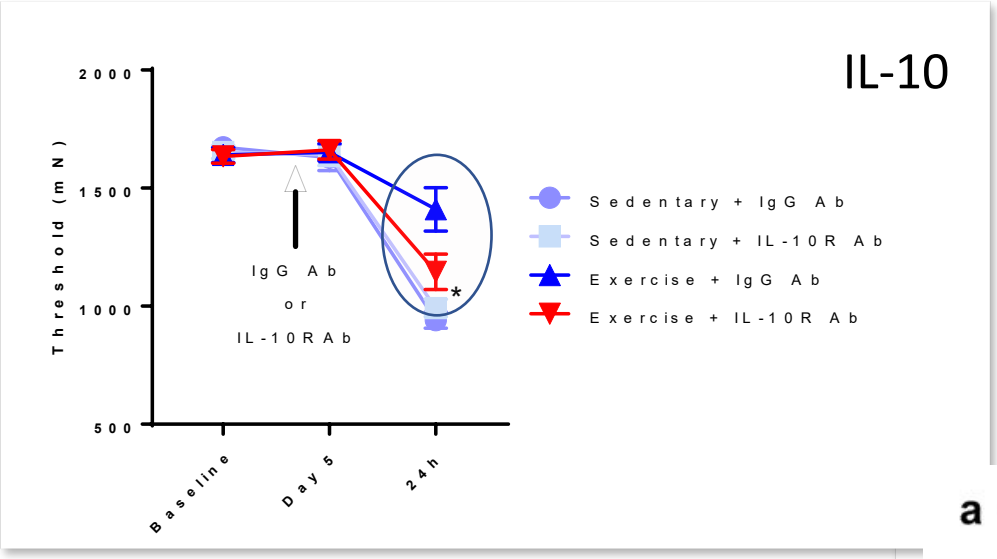


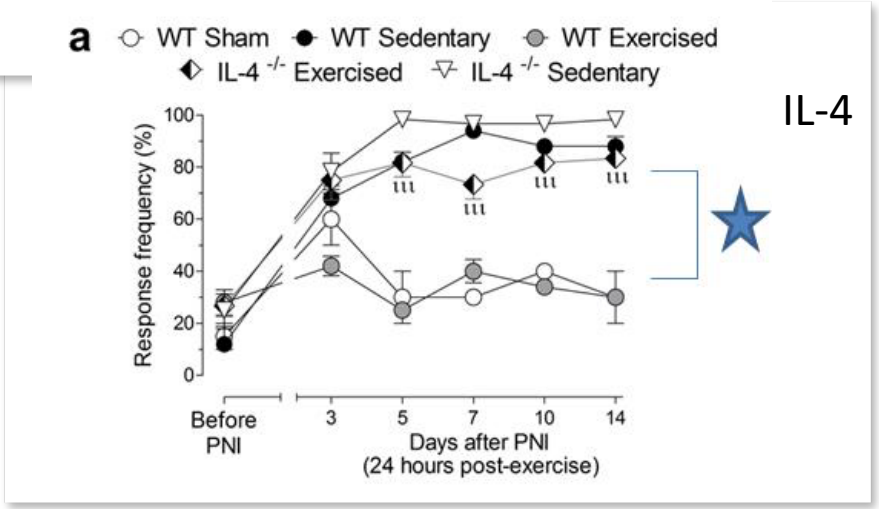


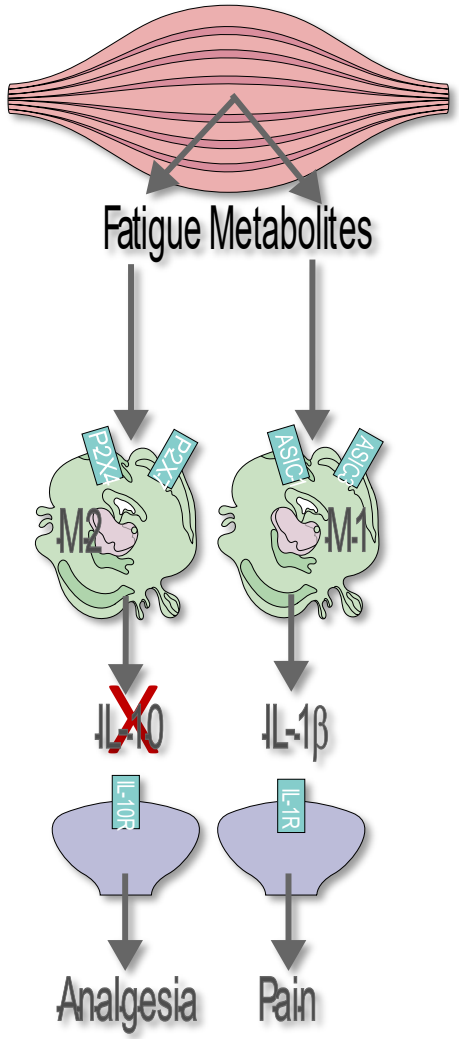


Fusaro et al., 2020; Hayashi et al., 2023; Hayashi et al. 2025

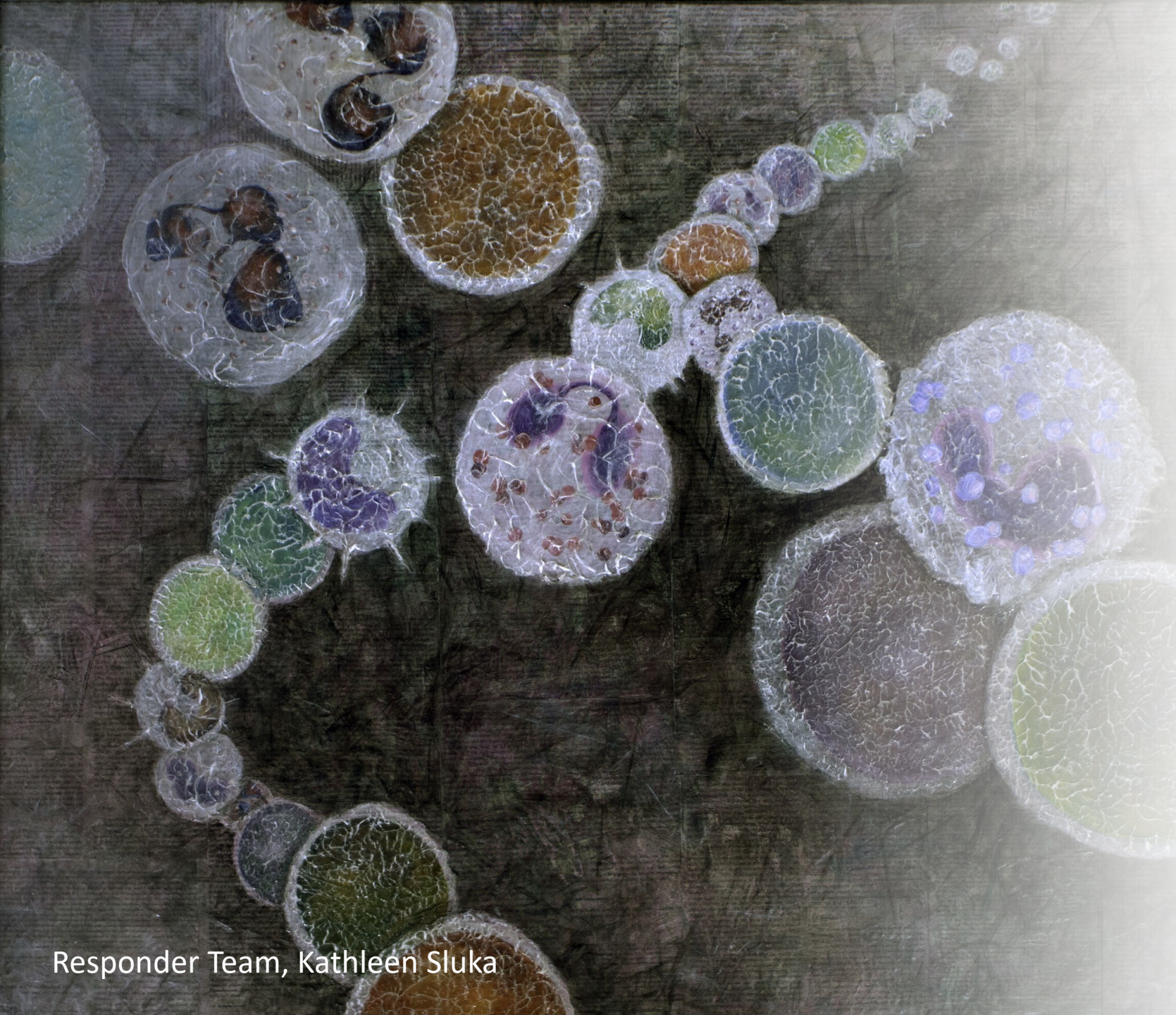
Immune System Mechanisms
IL-10 protects from development of chronic pain







Leung et al., 2016; Bobinski et al., 2011, 2017; Lesnak et al., 2023



Responder Team, Kathleen Sluka

Summary

The local immune system – macrophages - promotes the development of chronic pain through multiple mechanisms

Balance between excitatory and inhibitory cytokines determines phenotype of macrophages and response to injury

Acute to Chronic Pain Signatures Program

A2CPS
Acute to Chronic Pain Signatures

Goal: Examine whether *putative* biomarkers alone or in combination predict susceptibility or resilience to development of chronic pain *6 months after surgery*

frontiers | Frontiers in Medicine

STUDY PROTOCOL
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Multi-Site Observational Study to Assess Biomarkers for Susceptibility or Resilience to Chronic Pain: The Acute to Chronic Pain Signatures (A2CPS) Study Protocol

OPEN ACCESS

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Comprehensive Review

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Predicting chronic postsurgical pain: current evidence and a novel program to develop predictive biomarker signatures

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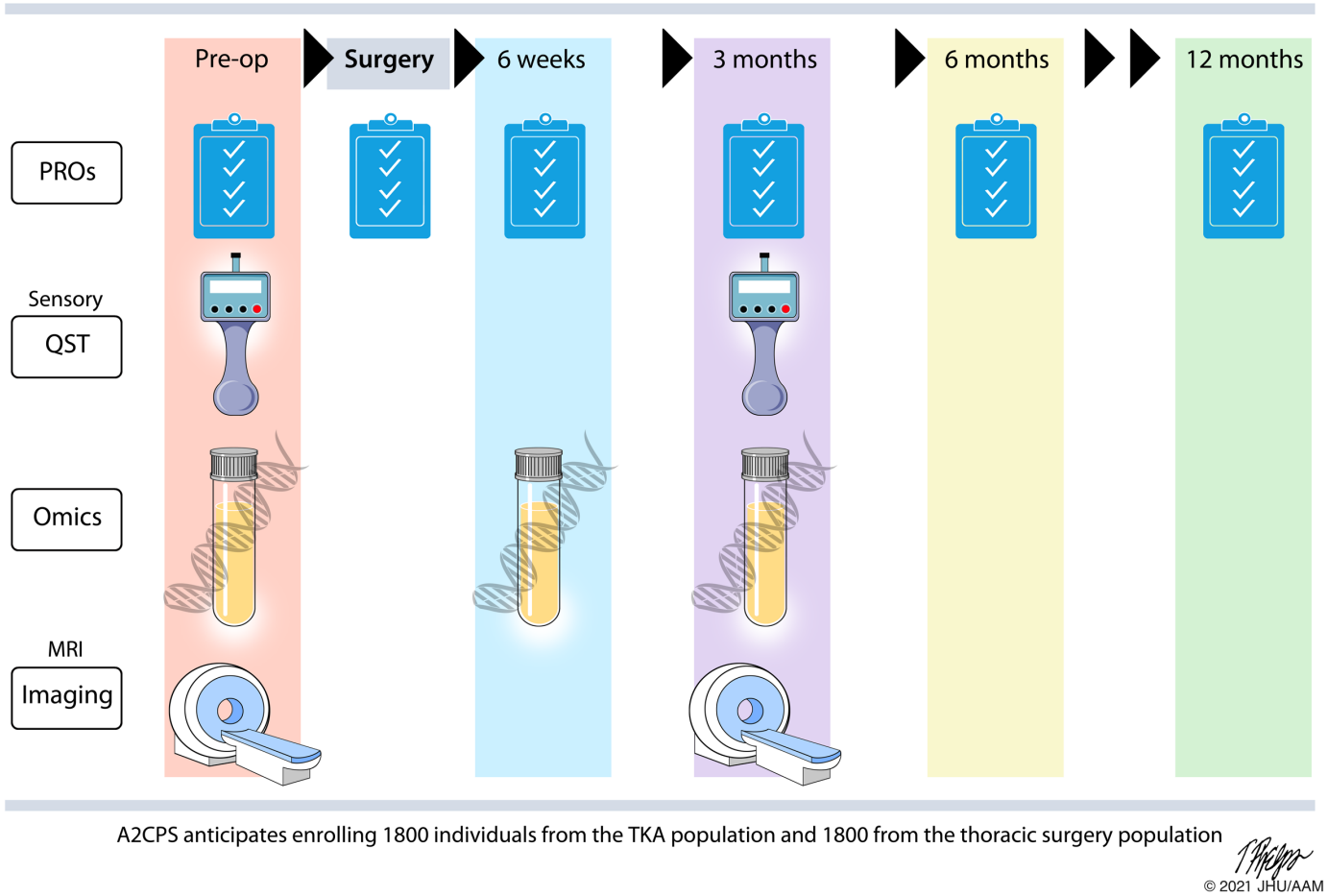
Protocol

Knee replacement
Thoracic Surgery
Target enrollment: n=2800
Current enrollment: n>2300



Sluka et al., 2023; Berardi et al., 2022

A2CPS includes biomarkers across multiple domains

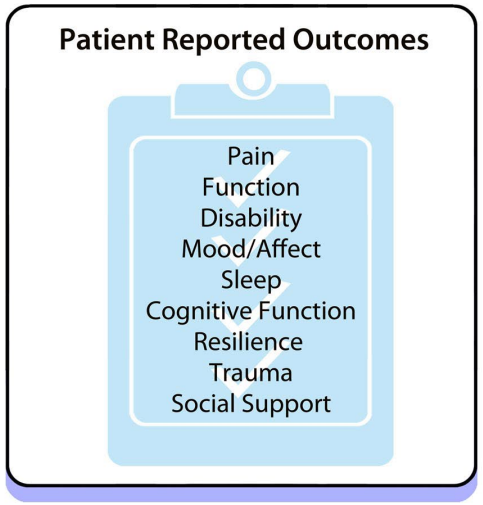
39 Primary Biomarkers

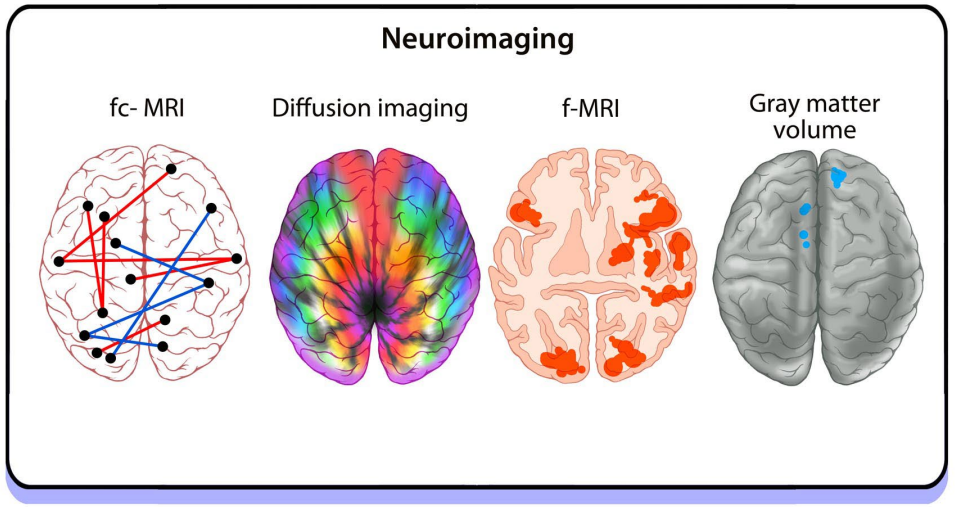
High power with sufficient evidence in human subjects

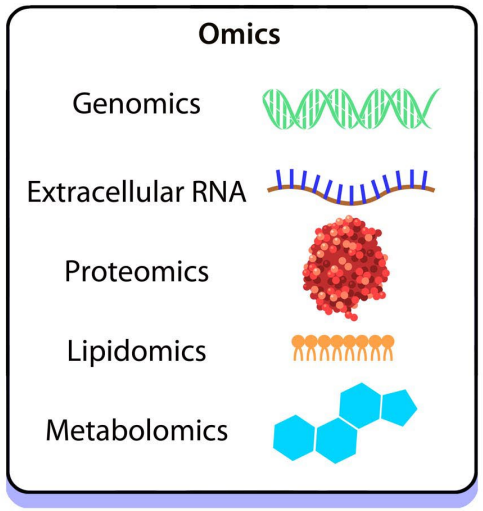
>70 Secondary Biomarkers

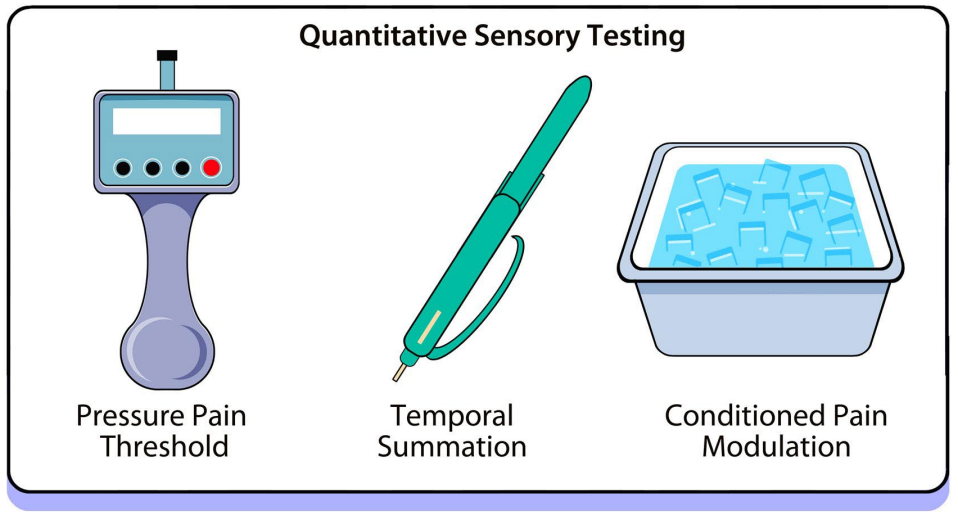
Weaker evidence

100s of Exploratory Biomarkers









A2CPS
Acute to Chronic Pain Signatures

Sluka et al., 2023; Berardi et al., 2022

Baseline Characteristics

	Thoracic (N=204)	TKA (N=604)	Overall (N=808)
Sex			
Females	112 (54.9%)	365 (60.4%)	477 (59.0%)
Males	91 (44.6%)	231 (38.2%)	322 (39.9%)
Age			
Mean (SD)	58.7 (13.7)	65.0 (8.47)	63.4 (10.4)
Median [Min, Max]	61.0 [22.0, 83.0]	66.0 [34.0, 83.0]	65.0 [22.0, 83.0]
BMI			
Mean (SD)	29.5 (6.33)	31.4 (6.03)	31.0 (6.14)
Median [Min, Max]	28.8 [17.5, 54.8]	31.0 [1.98, 64.1]	30.7 [1.98, 64.1]
Race			
American Indian or Alaska Native	6 (2.9%)	7 (1.2%)	13 (1.6%)
Asian	3 (1.5%)	13 (2.2%)	16 (2.0%)
Black or African-American	21 (10.3%)	154 (25.5%)	175 (21.7%)
Not Reported	4 (2.0%)	8 (1.3%)	12 (1.5%)
Other	1 (0.5%)	9 (1.5%)	10 (1.2%)
Unknown	1 (0.5%)	3 (0.5%)	4 (0.5%)
White	168 (82.4%)	410 (67.9%)	578 (71.5%)
Pain Duration(yrs)			
Mean (SD)	1.61 (1.94)	3.16 (2.72)	2.94 (2.67)
Median [Min, Max]	1.00 [0.0833, 10.0]	2.17 [0.0833, 11.0]	2.00 [0.0833, 11.0]

Baseline Outcome Data

	Knee	Thoracic
BPI-Worst Pain	4.2 ± 2.0 (0-10)	2.2 + 2.8 (0-10)
BPI-Interference	4.2 + 2.6 (0-10)	1.1 + 2.0 (0-9.4)
Anxiety – GAD	3.9 + 4.7 (0-21)	4.8 + 5.3 (0-21)
Depression - PHQ	4.4 + 4.7 (0-24)	5.4 + 5.4 (0-24)
Pain Catastrophizing (6-item)	6.5 + 5.8 (0-24)	6.3 + 5.6 (0-24)
Fear of Movement	14.9 + 6.3 (0-24)	8.9 + 6.5 (0-24)
Symptom Severity Index	4.4 + 4.6 (0-24)	5.4 + 5.5 (0-21)
Pain Resilience Score	38.5 + 10.8 (0-56)	35.8 + 11.0 (0-56)

Number of Pain Areas by Cohort

number_of_pain_areas	Thoracic	TKA
0	41.6% (82)	17.2% (100)
1	8.1% (16)	23.2% (135)
2	16.2% (32)	23.8% (138)
3	9.1% (18)	15.5% (90)
4	10.7% (21)	9.8% (57)
5	5.1% (10)	5.3% (31)
6	3.0% (6)	3.3% (19)
7	3.6% (7)	1.0% (6)
8	1.5% (3)	0.5% (3)
9	1.0% (2)	0.3% (2)
Total	100.0% (197)	100.0% (581)

Future

Expected enrollment complete in 2025

Data and resources will be placed in a public repository

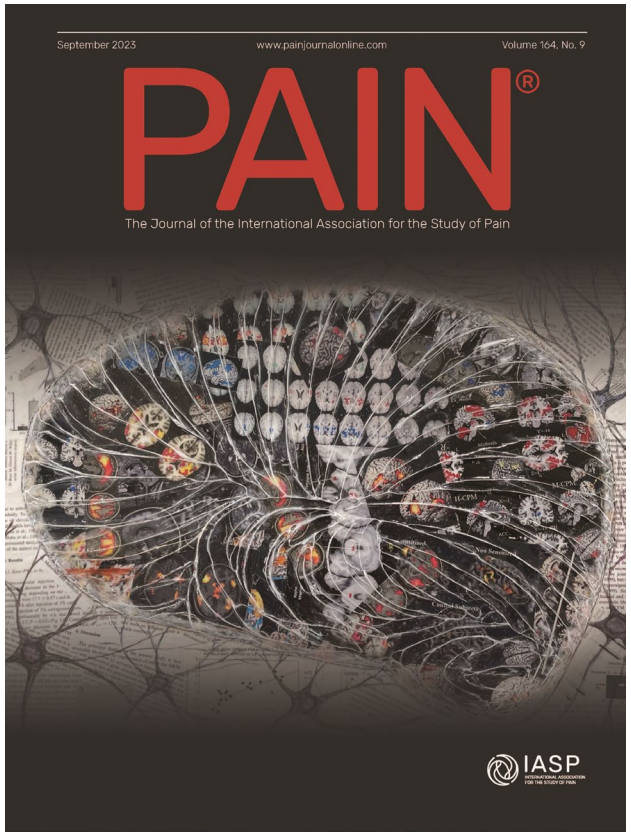
Available to the scientific community for future questions

Significance of Biomarker Research

Inform	Future mechanistic hypothesis of pain pathophysiology
Identify	Potential therapeutic targets
Improve	Methods for monitoring treatment success
Implement	Individualized treatments based on patient response

Conclusion

- Multiple factors work together contribute to the transition to chronic pain
- These factors likely include multiple clinical pain mechanisms, psychosocial and biological factors that are unique to the disease and the individual



Sluka et al., PAIN; 2020; Smith et al., JCI, 2025