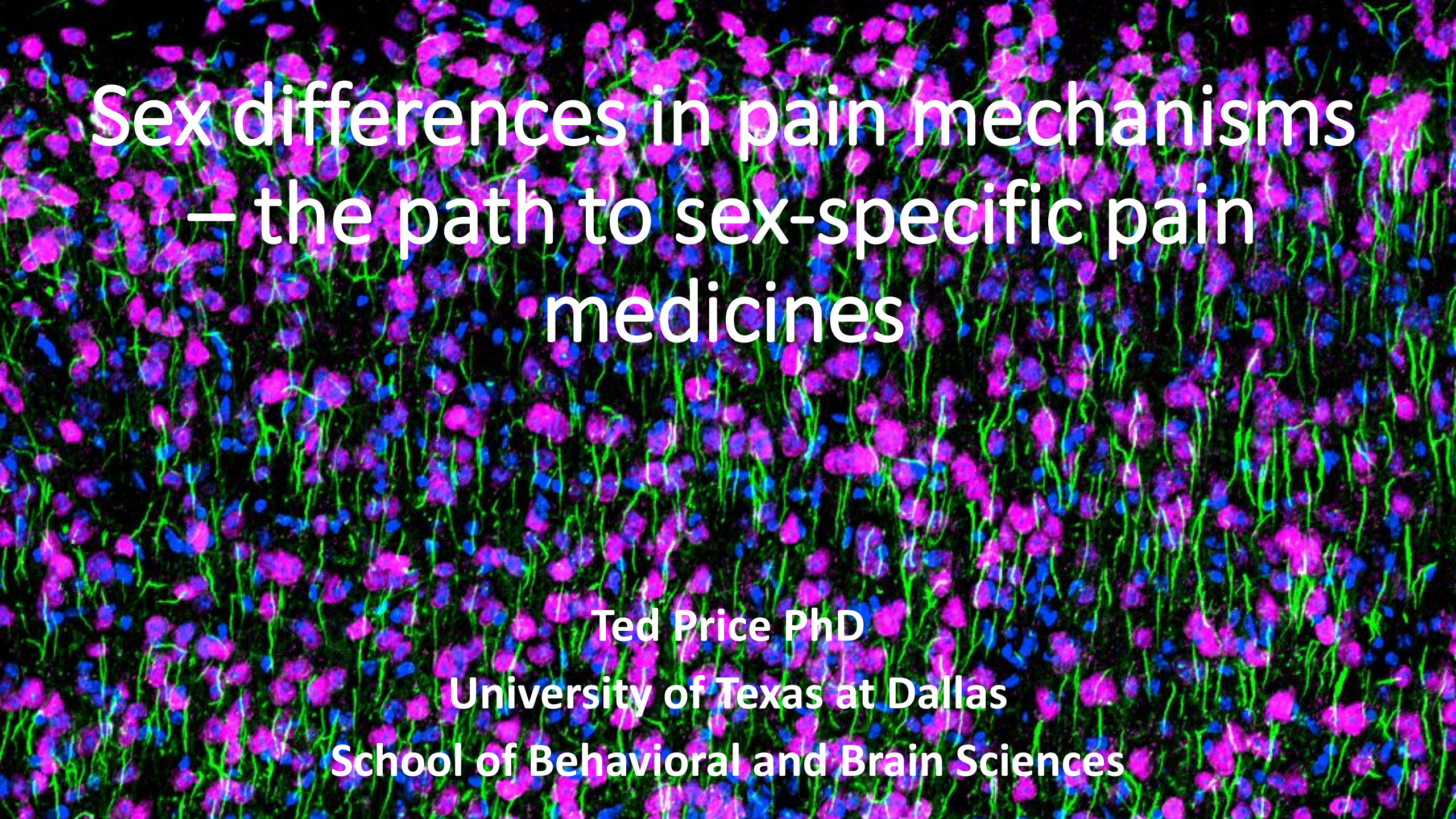


Sex differences in pain mechanisms – the path to sex-specific pain medicines

Ted Price PhD
University of Texas at Dallas
School of Behavioral and Brain Sciences

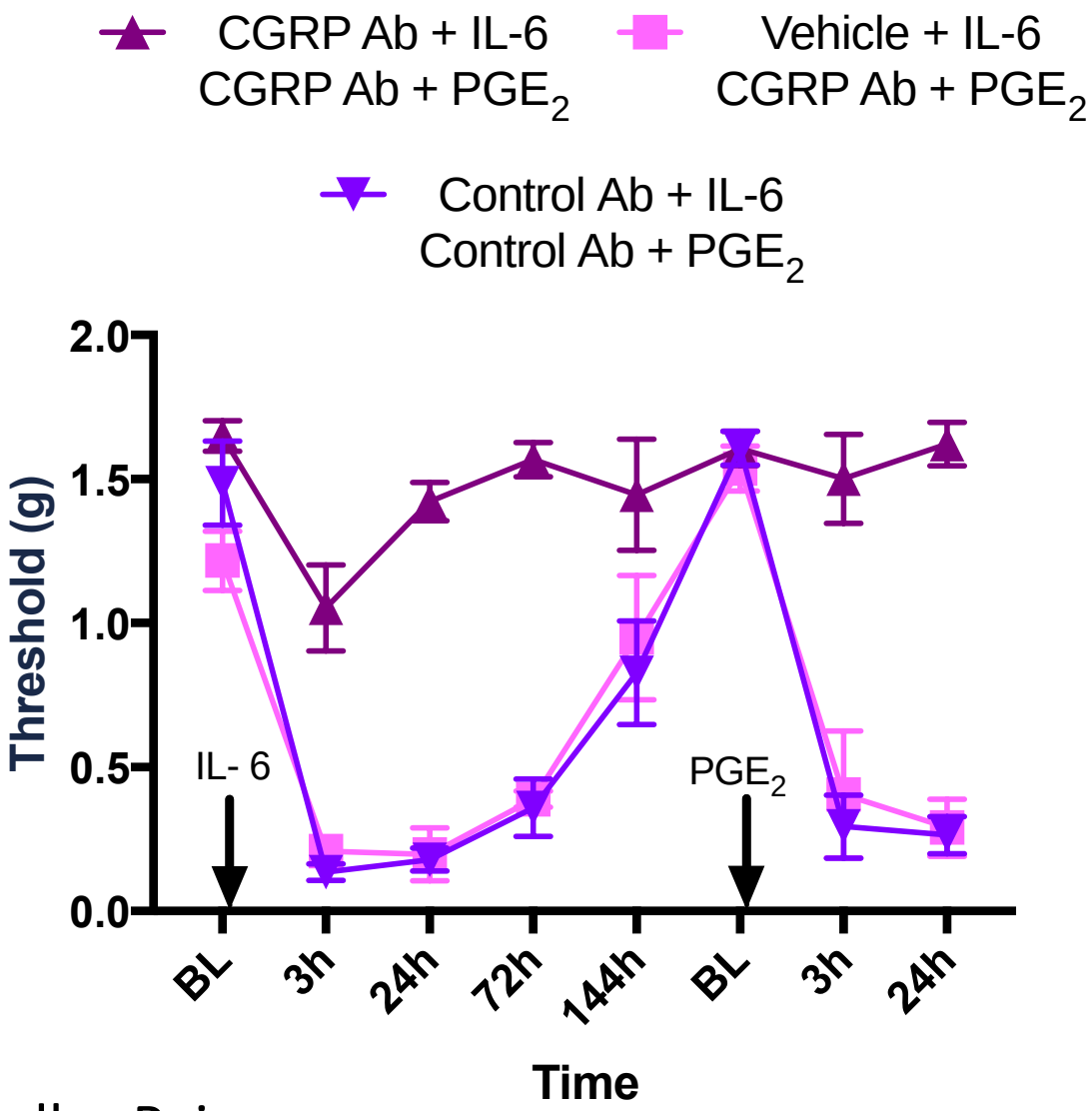

Center for Advanced Pain Studies
UTD
RITA ALLEN FOUNDATION
NIH National Institutes of Health
Turning Discovery Into Health

Women and men perceive pain similarly, but mechanisms of chronic pain are likely different

Prominent example is microglial P2X4-BDNF signaling as a male-specific driver of neuropathic pain

What causes chronic pain in women?

CGRP sequestering antibody blocks pain sensitization only in female mice



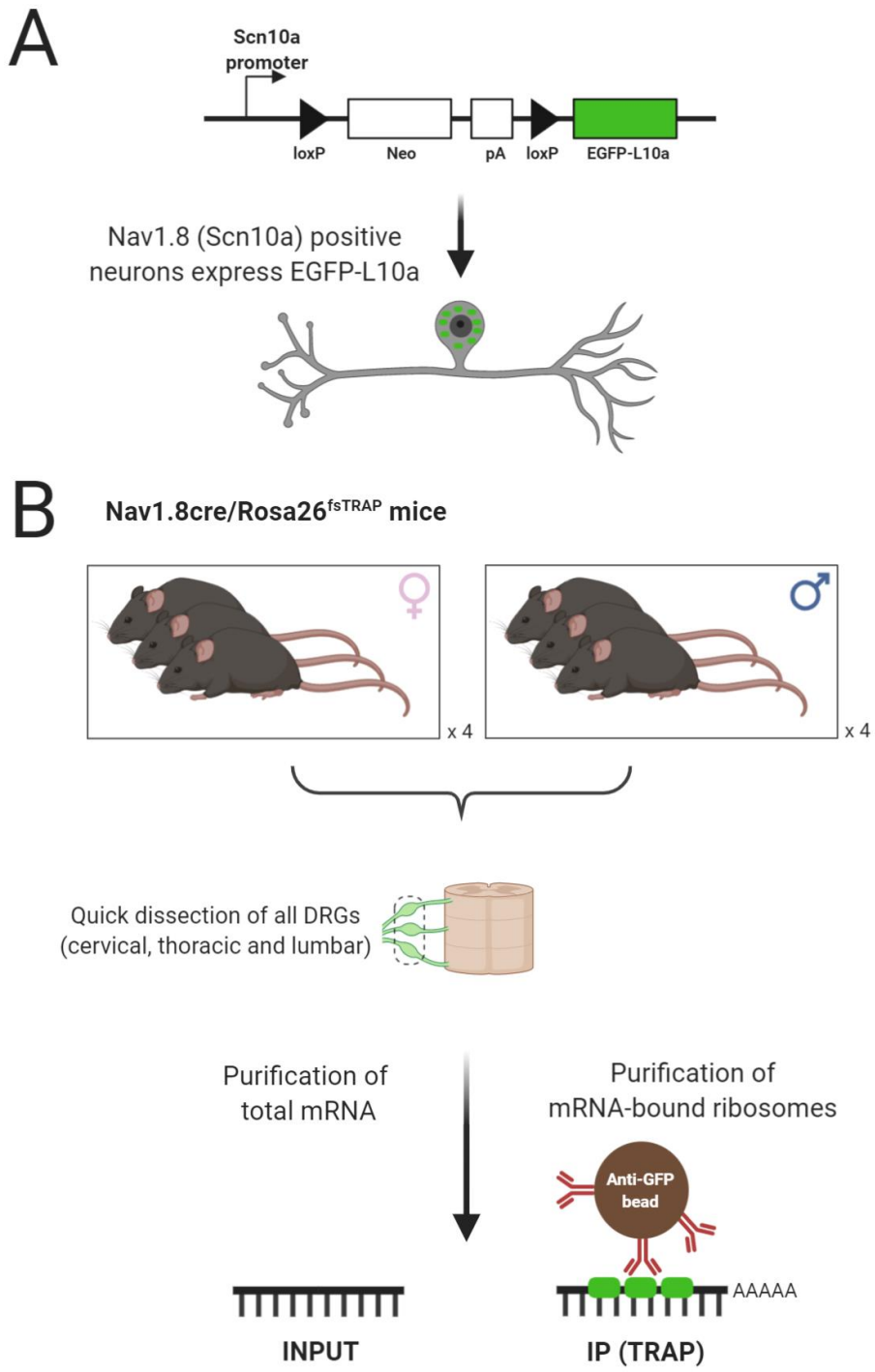
Candler Paige

CGRP therapeutics approved for migraine in 2018

Studies to date on sex differences in dorsal root ganglion and/or nociceptor transcriptomes have been underwhelming

Maybe we need to assess the “translatome”

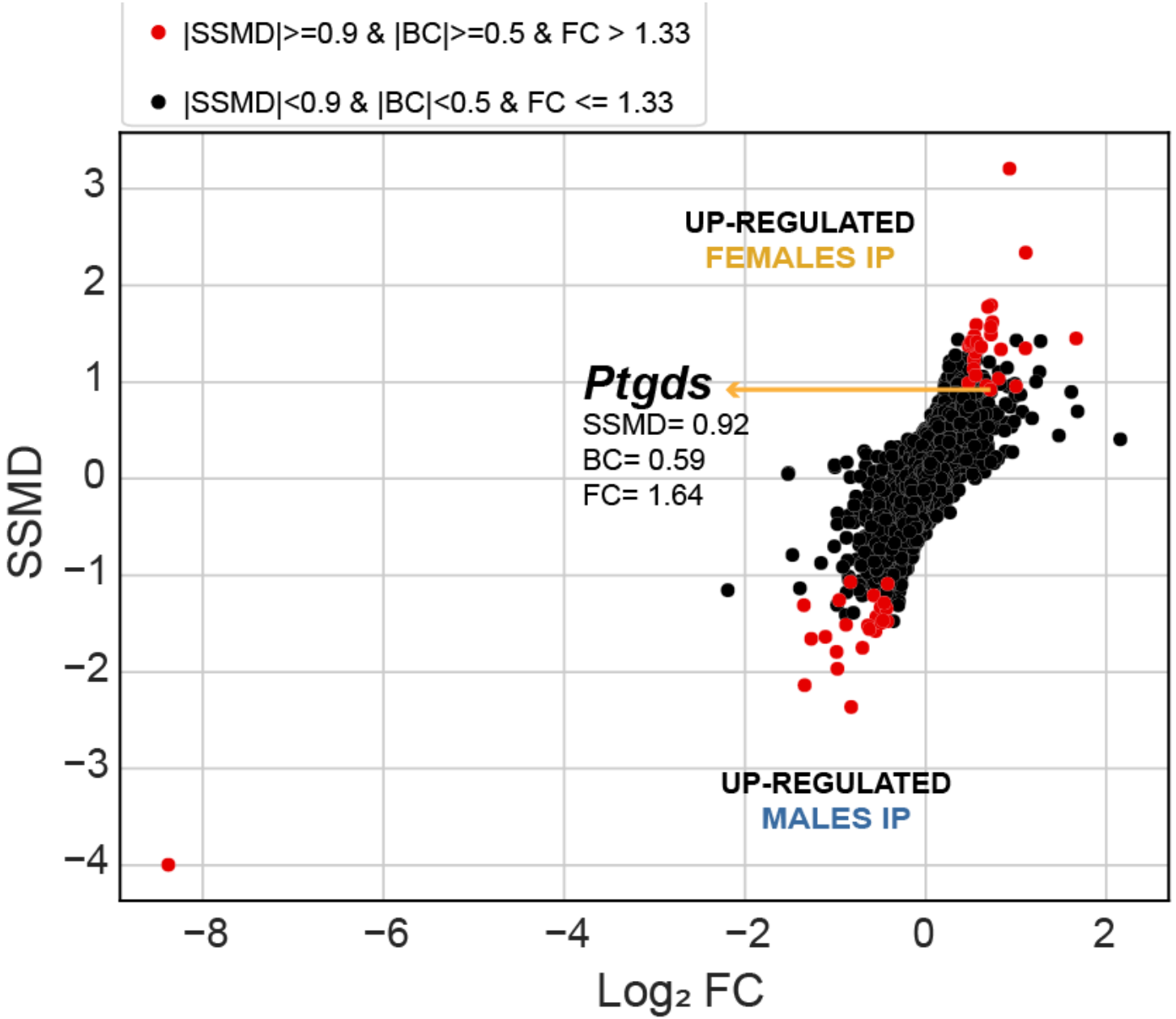
Sex differences in nociceptor translatome using TRAP technology



Discovery of ~80 differentially translated genes in murine nociceptors

Focus on *Ptgds* for validation because was significantly enriched in female translatome

Enzyme synthesizes prostaglandin D_2

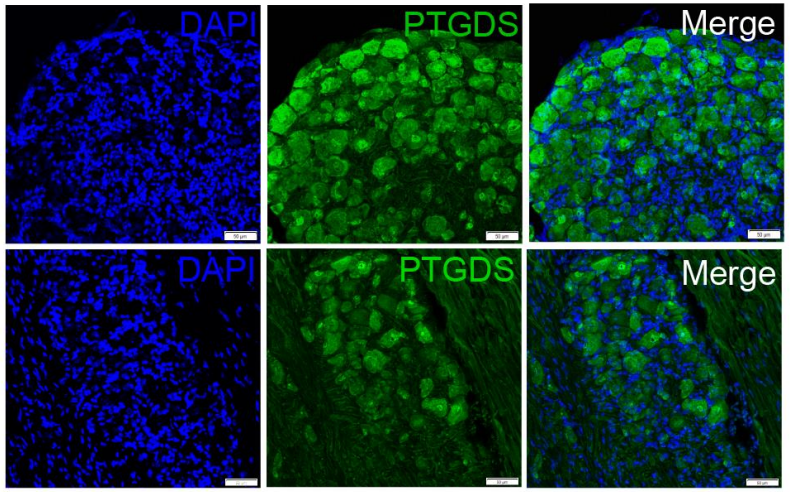


Validated that Ptgds protein expression is higher in female DRG (D and E) and brain (not shown)

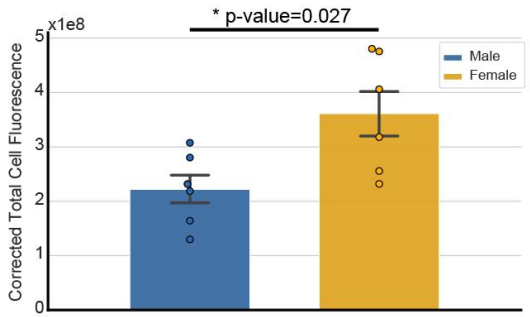
and

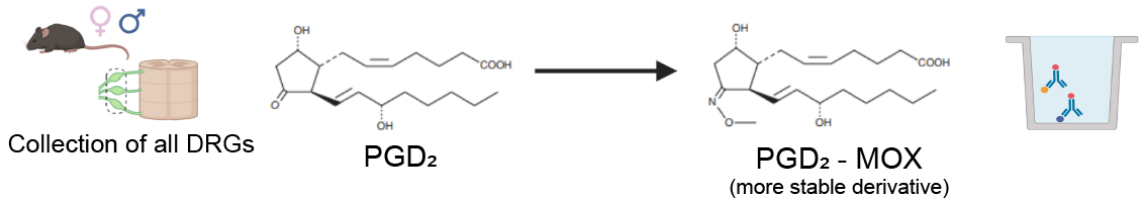
that PGD_2 levels are increased in female

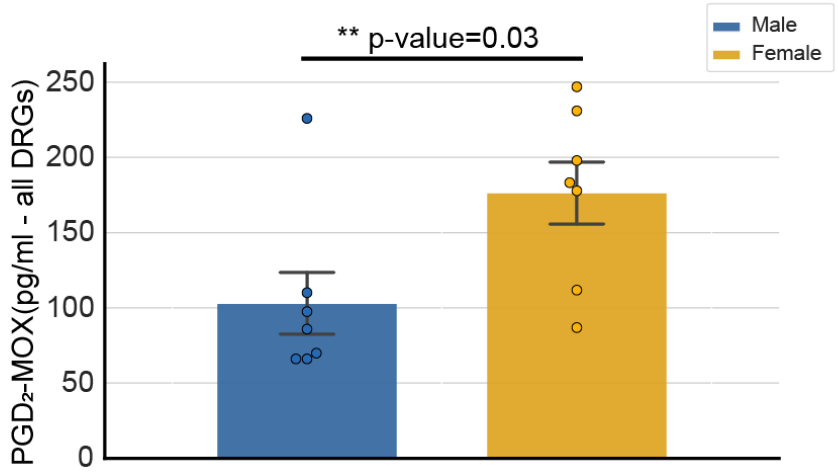
D



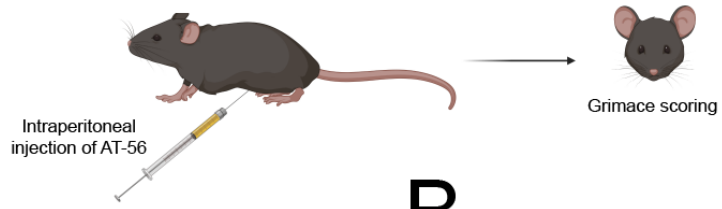
E



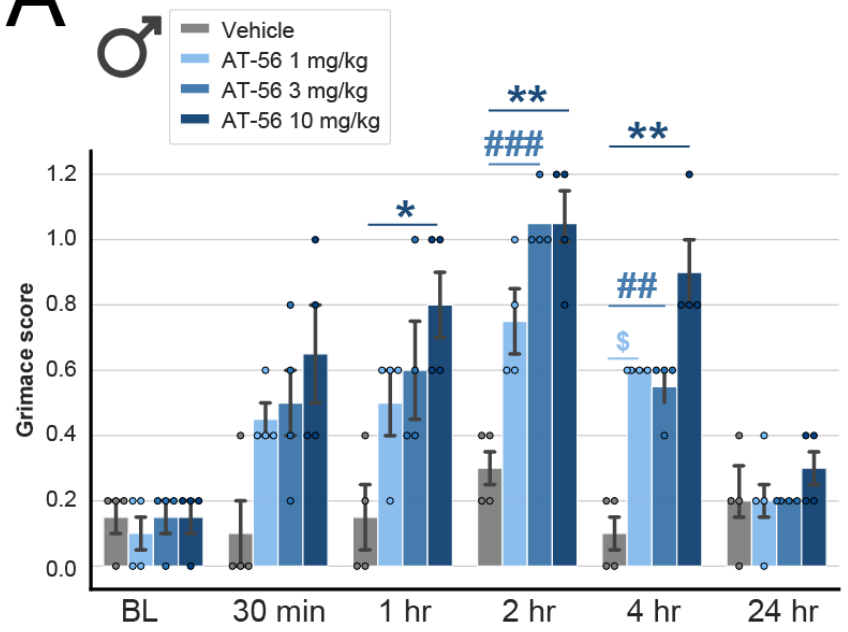




Inhibition of Ptgds causes robust pain behaviors in males suggesting that higher levels of PGD_2 in females are pain protective



A



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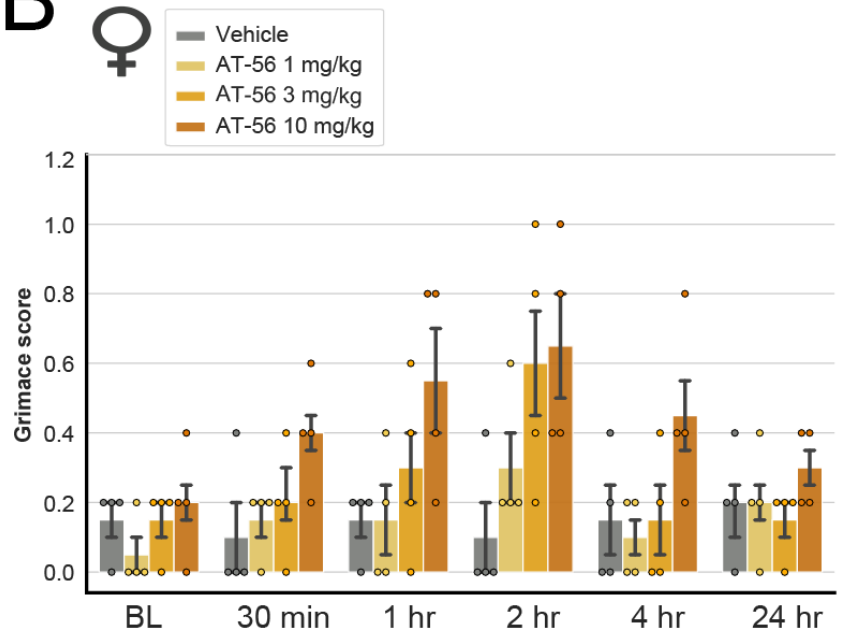
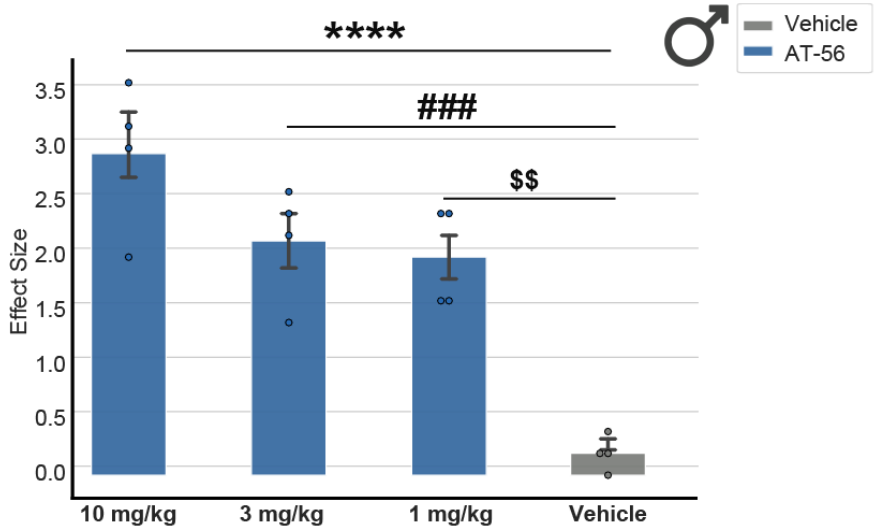
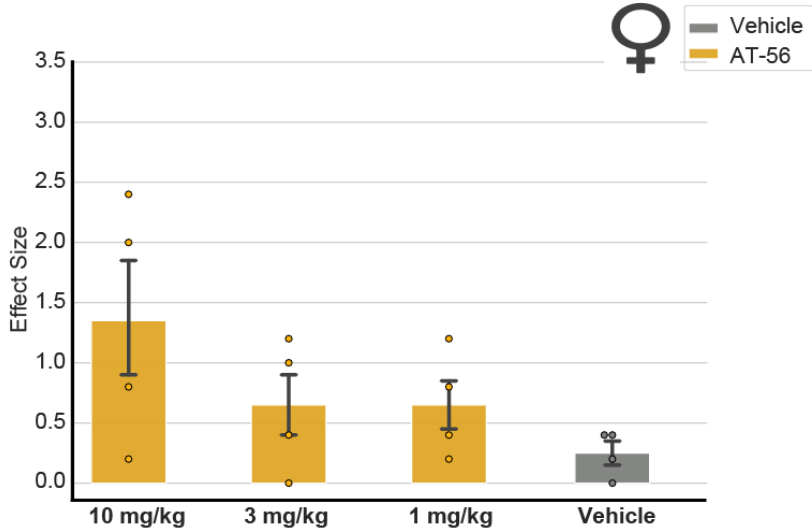






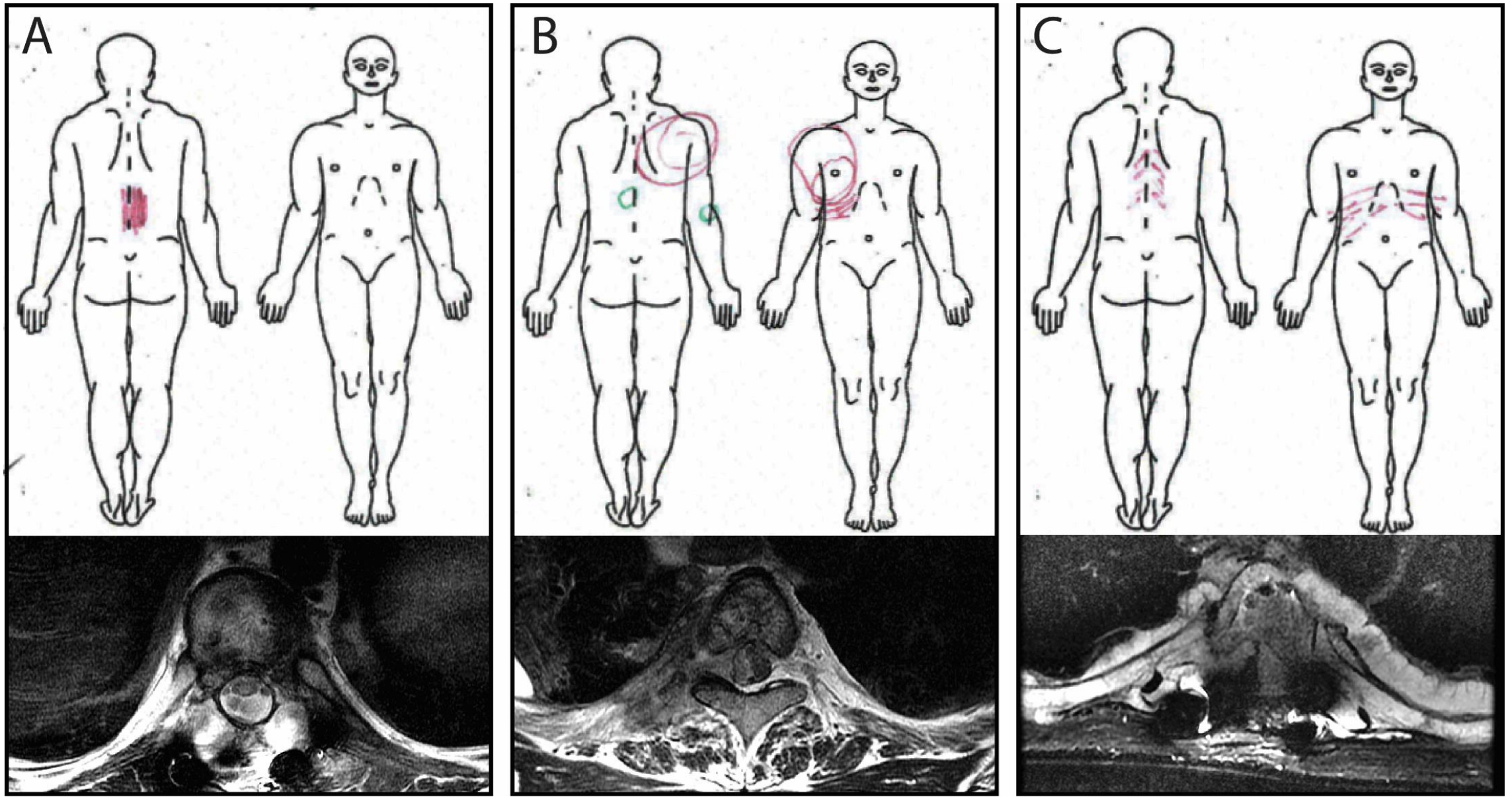
Sex-dependent translation may reveal female-specific pain mechanisms

Prominent sex difference in prostaglandin signaling in male versus female DRG driven by *Ptgds* translation.

See also Paige et al. *Journal of Neuroscience* 2020 on prolactin receptor translation at central terminals

Human DRG samples from MD Anderson:

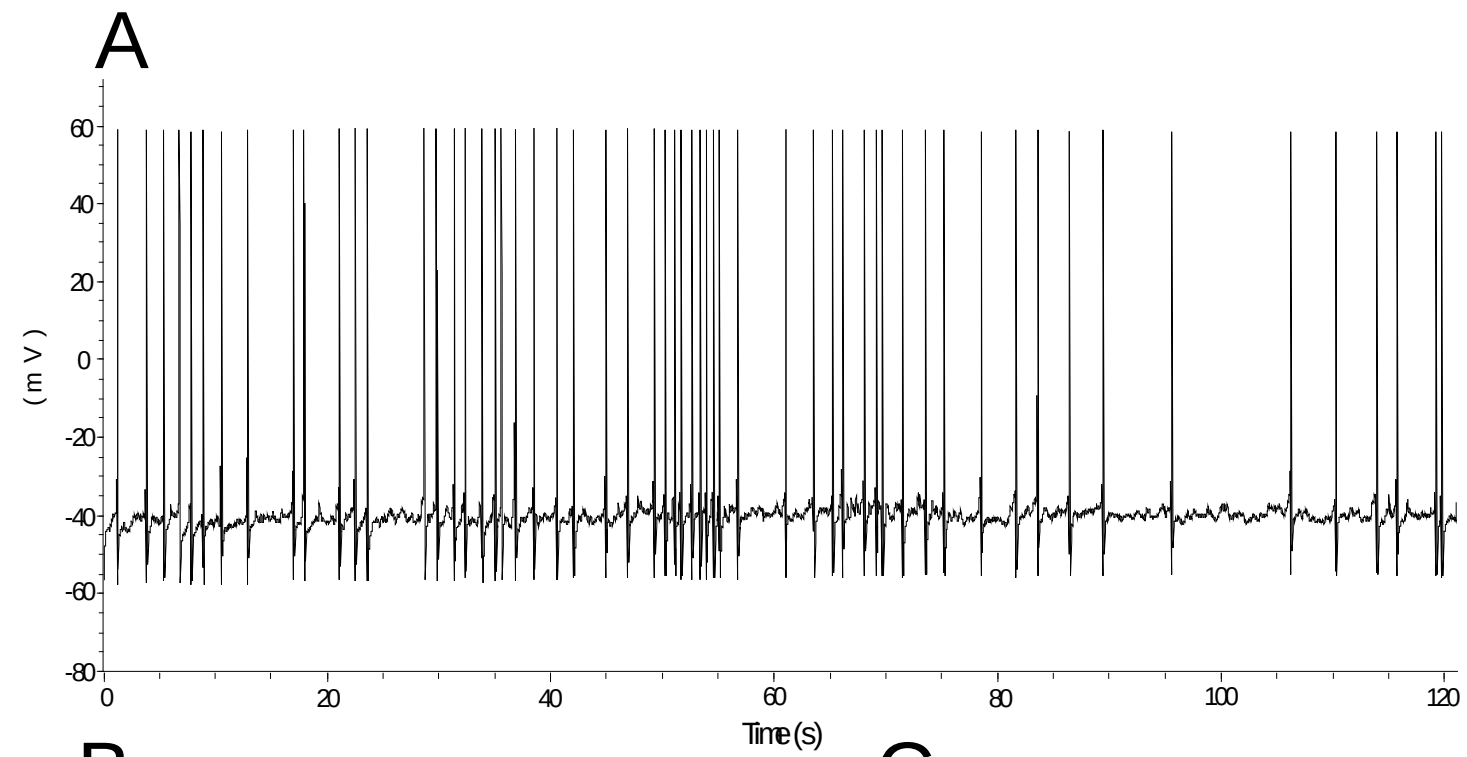
What drives chronic pain in clinical neuropathies?

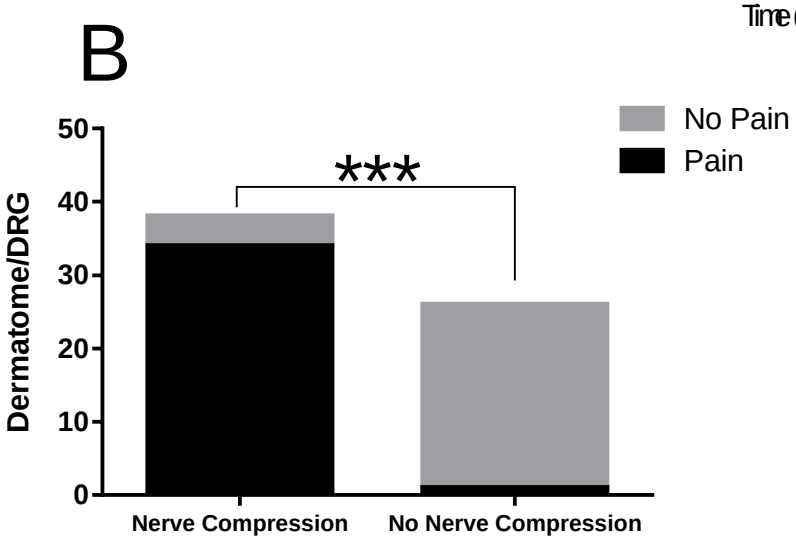


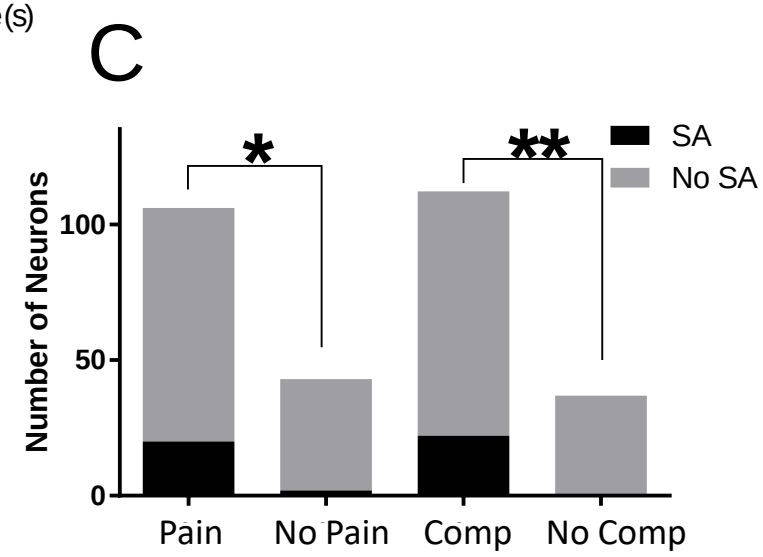
Human DRG samples from MD Anderson:

What drives chronic pain in human neuropathies?

Spontaneous activity that is preserved *in vitro*





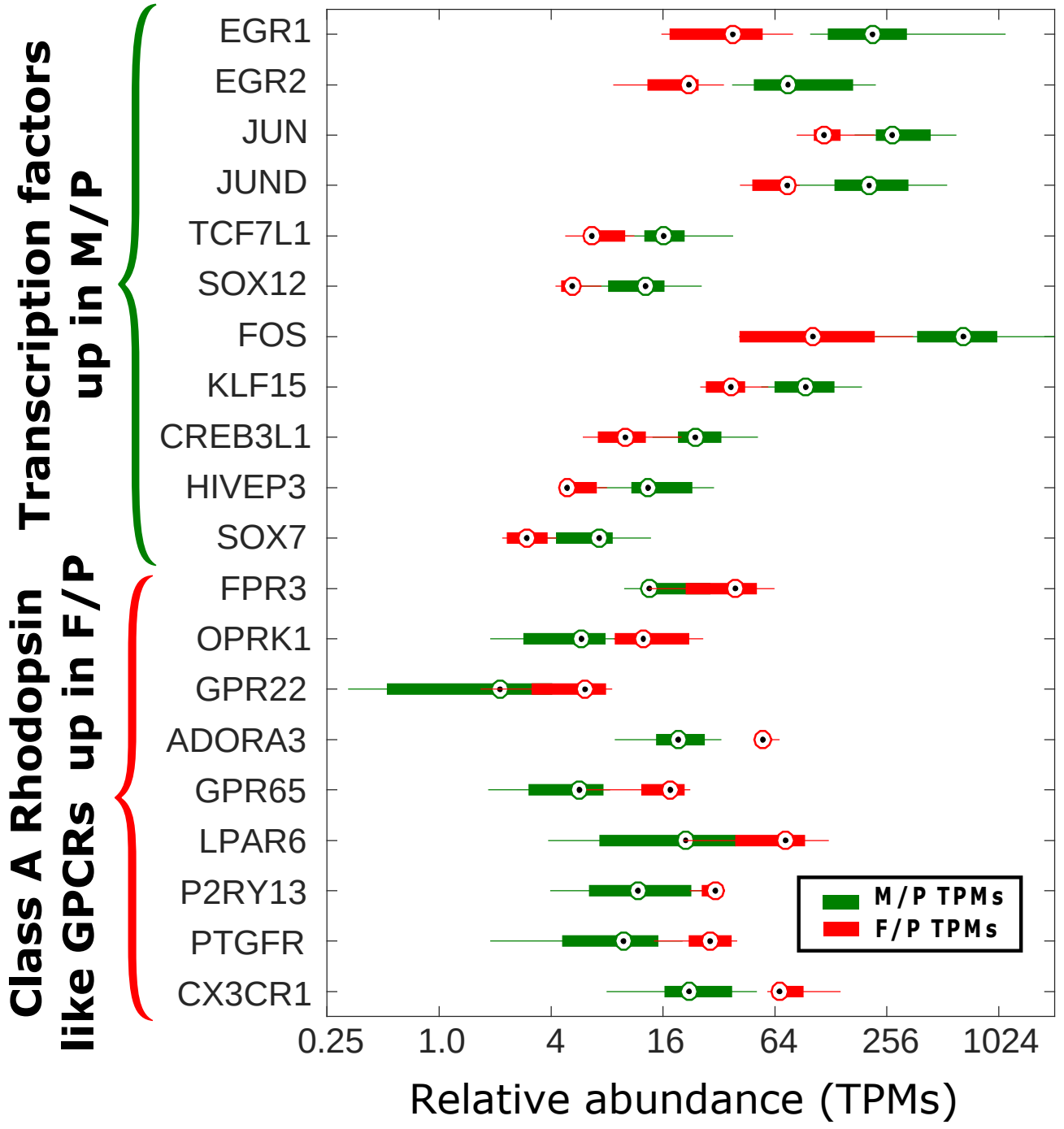


North, Li and Ray et al., Brain *2019*

Sexual Dimorphic

Transcriptome changes in humans with chronic pain: RNA sequencing from DRG samples

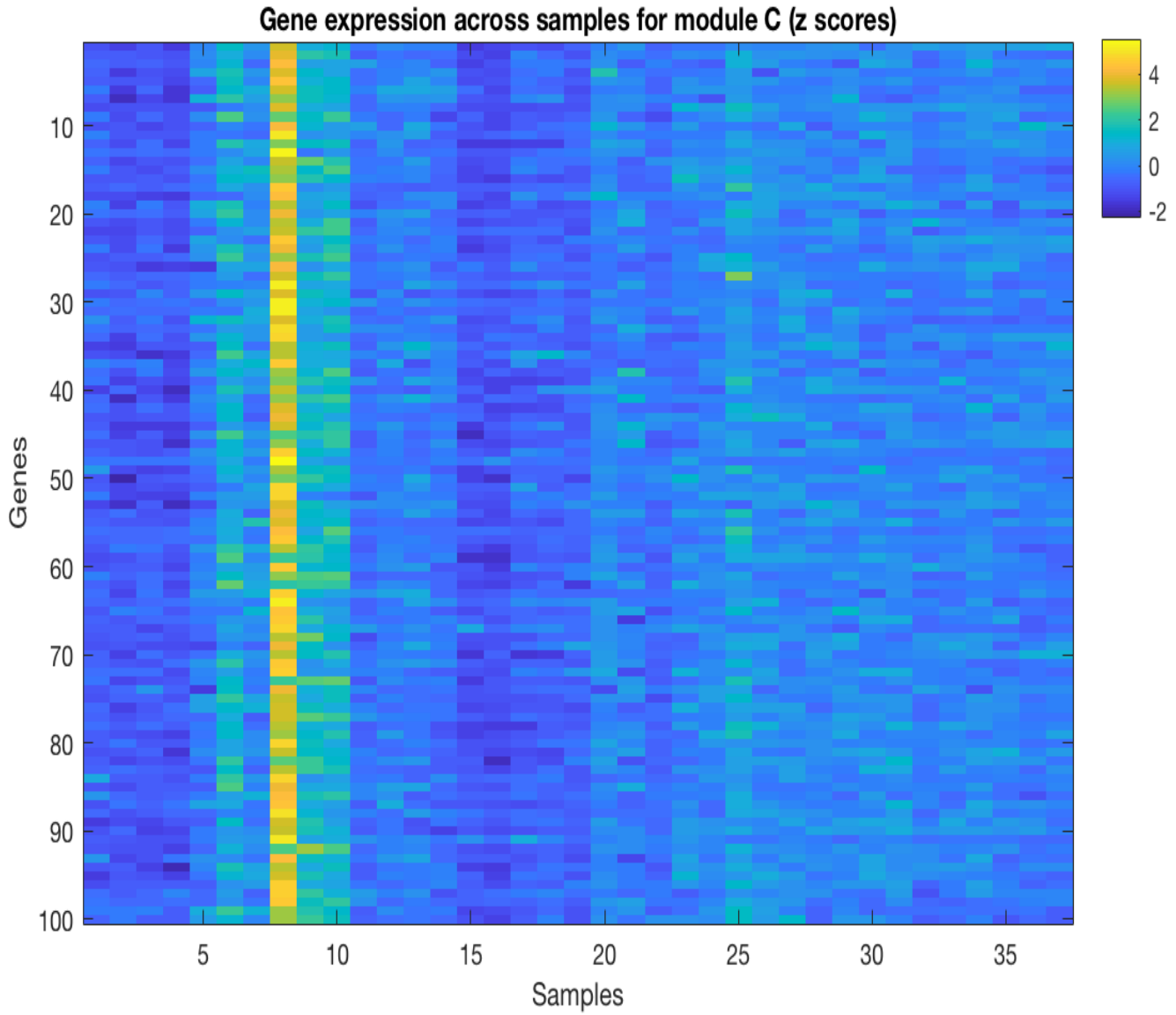
Pain samples, males versus females



North, Li and Ray et al., Brain *2019*

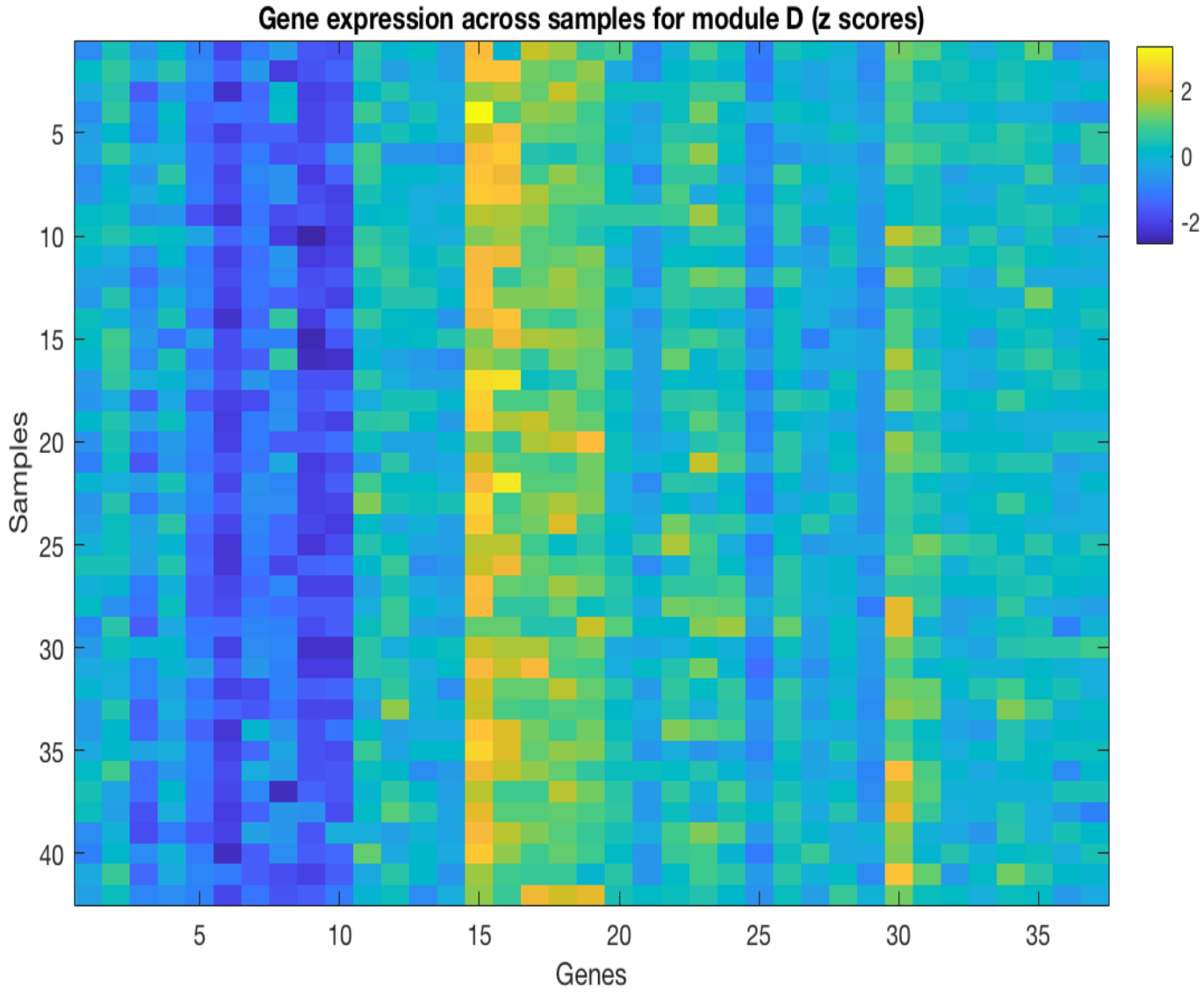
Module C (genes coregulated with FOS and JUN)

- Cohort samples with highest expression (Top 15% / 6 samples) : 4 male pain samples, 2 male non-pain sample (one with similar phenotype to male pain samples)
- Relevant genes : TRPC5, OSM, FOSL1, LAIR1, NKX6-1, IL1B, GFRA4, NEFH



Module D – Mystery mechanism cohort

- Cohort samples with highest expression (3 of top 8 are female pain samples and top 6 are pain samples)
- Moderately enriched for female pain samples (lower proportion of female neuropathy samples in our data : 10 of 37)
- Relevant genes : ADORA1, SCARB1, MMP3, FCER2, RASGRP3



Clear sex differences in gene expression in chronic pain in humans

Changes in gene expression in males fit well with our “model mechanisms”, which have mostly come from male animals.

Differences in females are distinct and far less is known about these genes. Paying the price for our biases, but exciting opportunities ahead.

Price Lab

Postdoc Fellows

Salim Megat PhD

Pradipta Ray PhD

Diana Ferreira PhD

Stephanie Shiers PhD

Saad Yousuf PhD

Amelia Balmain PhD

PhD Students

Andy Wangzhou

Candler Paige

Moeno Kume

DJ Naik

Ish Sankaranarayanan

Rachel Wilhelm

Juliet Mwirigi

Eric David

Carolyn Guzman

Technical Staff

Galo Mejia

Ayesha Ahmad

Clay Smithhart

Collaborators:

Greg Dussor, University of Texas at Dallas

Michael Burton, University of Texas at Dallas

Zachary Campbell, University of Texas at Dallas

Tae Hoon Kim, University of Texas at Dallas

Joseph Pancrazio, University of Texas at Dallas

Robert Gereau IV, Wash U

Cobi Heijnen, MD Anderson

Annemieke Kavelaars, MD Anderson

Pat Dougherty, MD Anderson

Josef Vagner, University of Arizona

Scott Boitano, University of Arizona

National Institute of Neurological Disorders and Stroke