How the Body Resolves Pain: the Potential Mechanism of ACS Analgesic Efficacy

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SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PAIN

Acute inflammatory response via neutrophil activation protects against the development of chronic pain

Marc Parisien[1]†, Lucas V. Lima[2]†, Concetta Dagostino[3]†, Nehme El-Hachem[1], Gillian L. Drury[1], Audrey V. Grant[1], Jonathan Huising[4], Vivek Verma[1], Carolina B. Meloto[1], Jaqueline R. Silva[5], Gabrielle G. S. Dutra[2], Teodora Markova[2], Hong Dang[6], Philippe A. Tessier[7], Gary D. Slade[8], Andrea G. Nackley[9], Nader Ghasemlou[5], Jeffrey S. Mogil[2]*, Massimo Allegri[10,11]*, Luda Diatchenko[1]*

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The Telegraph

Anti-inflammatory drugs like ibuprofen could worsen back pain, study suggests

The Guardian

Short-term use of ibuprofen may increase chance of chronic pain, study suggests

The New York Times

Common Medications Can Prolong Back Pain, Study Says

CBC

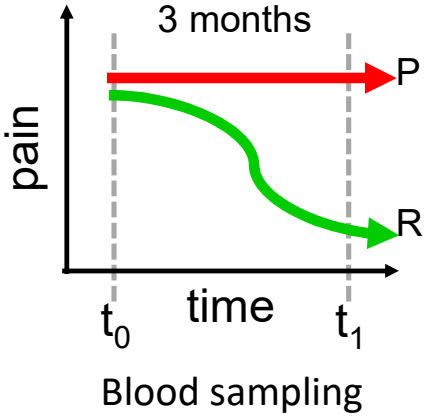
The usual treatment for back pain could actually be making it worse

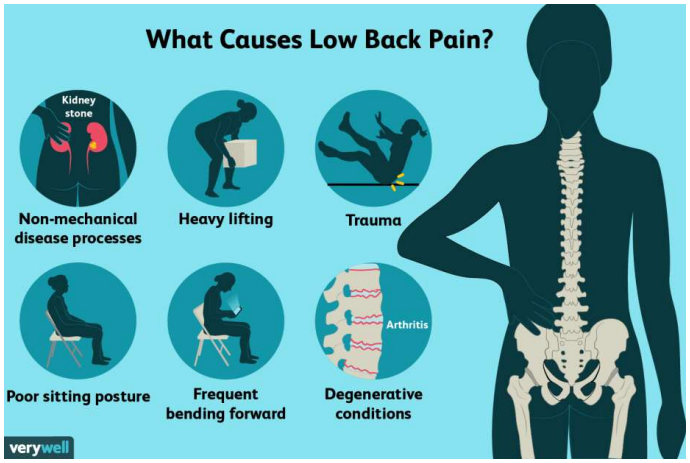
CBC, 20 May 2022

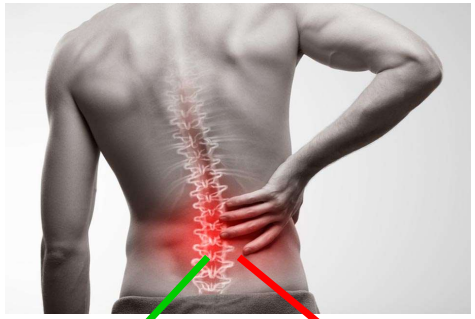
Many take anti-inflammatory drugs for acute pain, but study suggests inflammation is key to healing A study conducted by...

Differential Gene Expression in the Blood of LBP patients: Study Design

- A cohort of 100 Caucasian patients comprised of males (58%) and females (42%) older than 18 years old with acute LBP.
- Whole blood RNA analysis at two time points:
  - t_0 = within 6 weeks of acute episode
  - t_1 = 3 months after enrollment



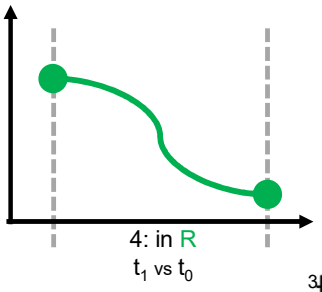


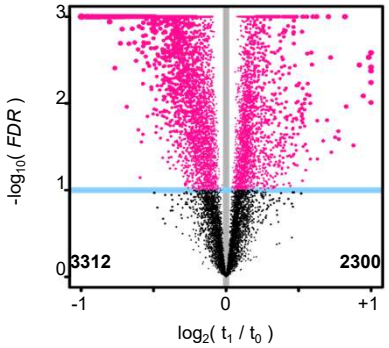


Resolvers (R) **Persistent (P)**

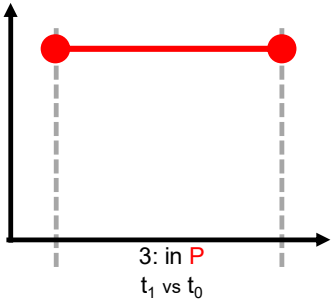
Differential Gene Expression in the Blood of LBP patients

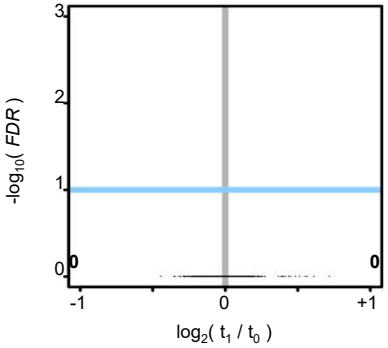
RESOLVERS





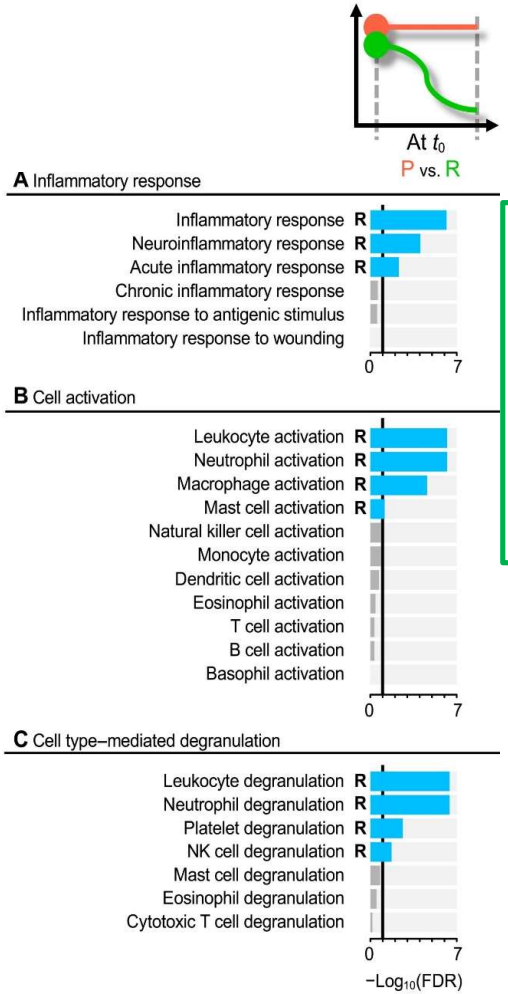
PERSISTANT



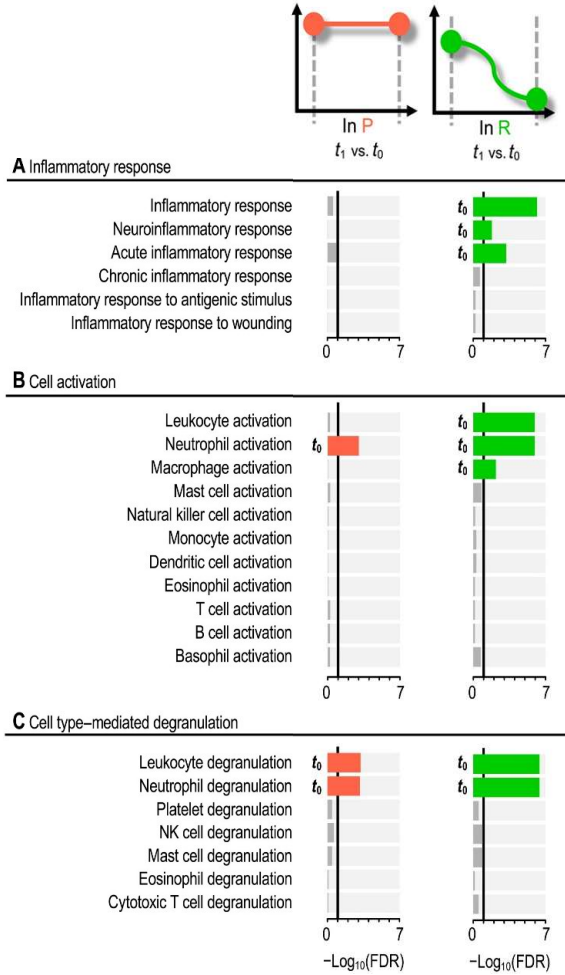


Parisien et al *Sci Transl Med*, 2022

Functional differences between the resolved and persistent pain groups



- **Elevated** cell activation and immune responses in the R group at t0 (compared to P)
- Driven by neutrophil activation and degranulation



- Inflammatory response is down regulated over time (t1 compared to t0) in resolvers

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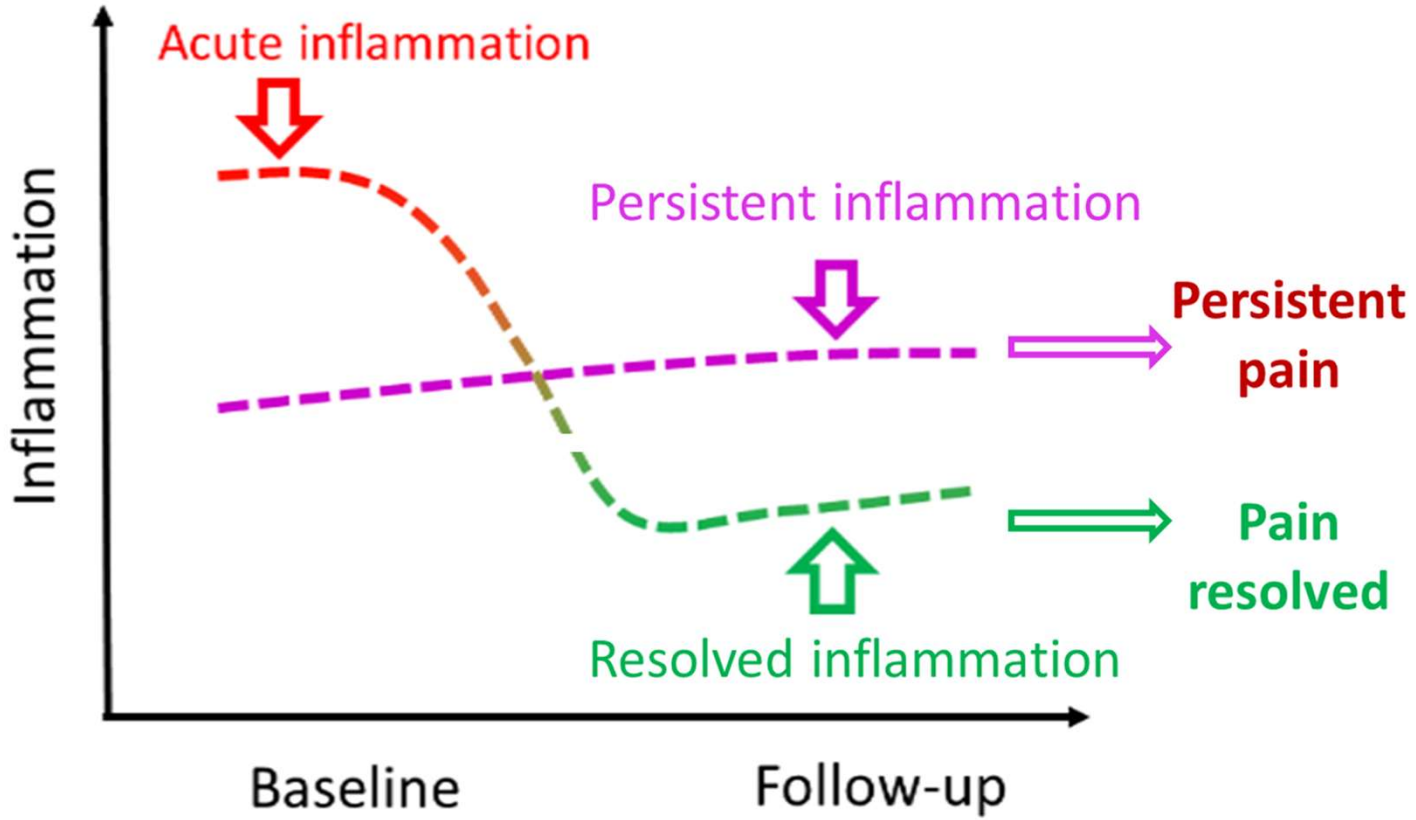
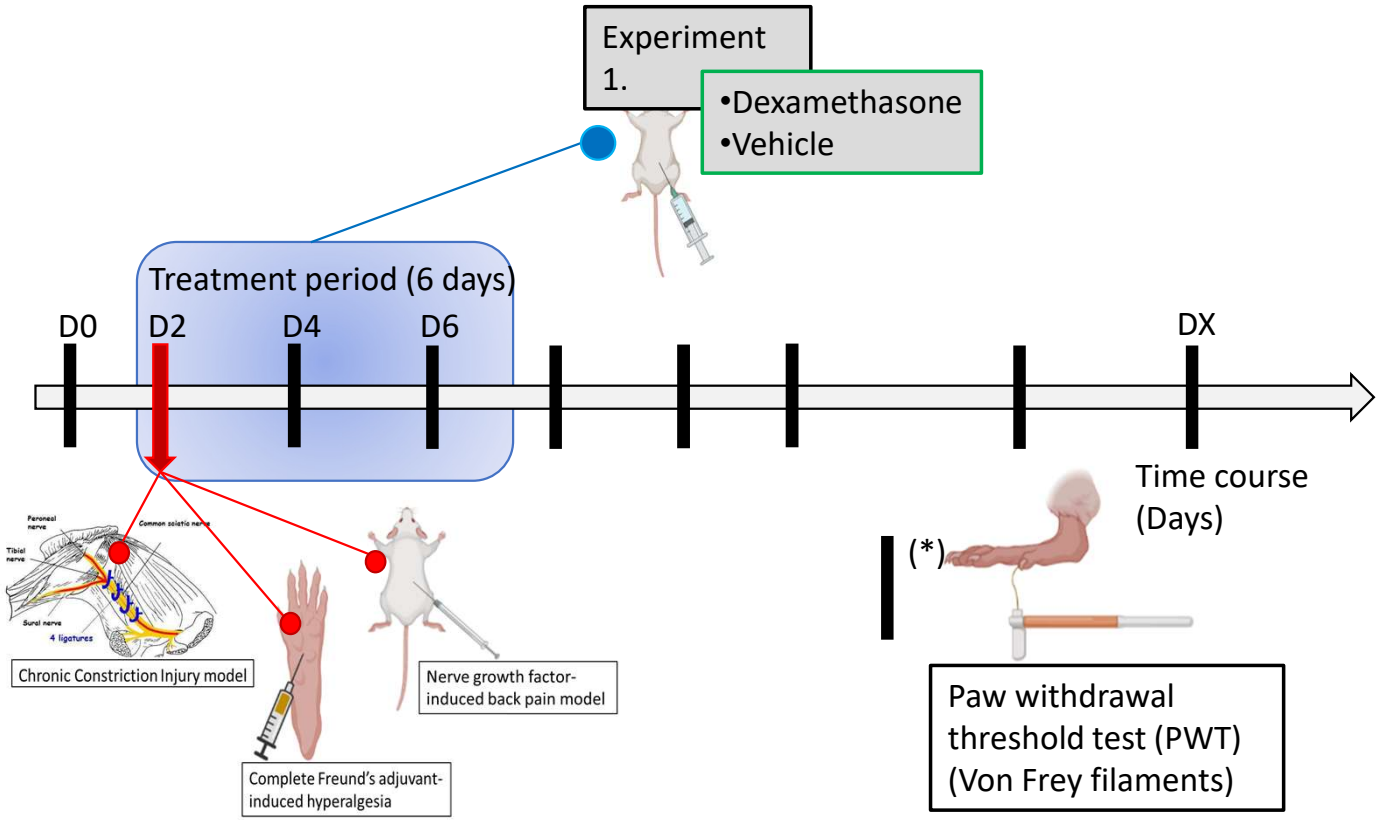
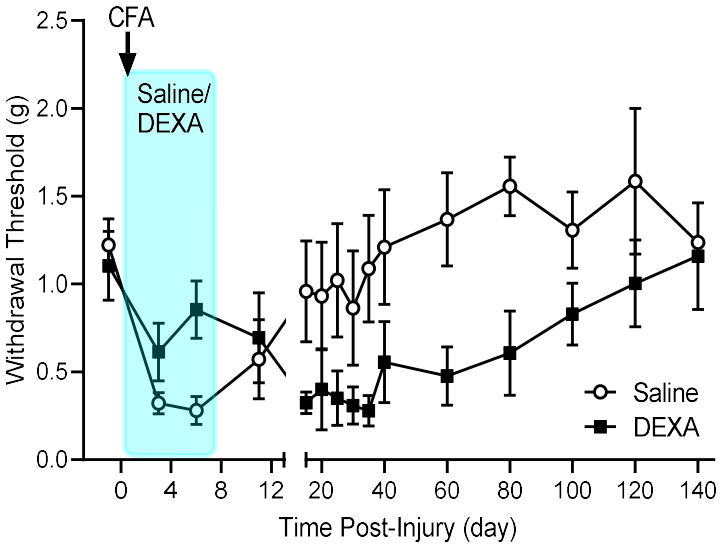
Acute to Chronic Pain Transition: Adaptive Response Model

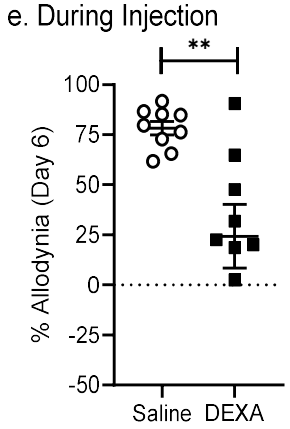


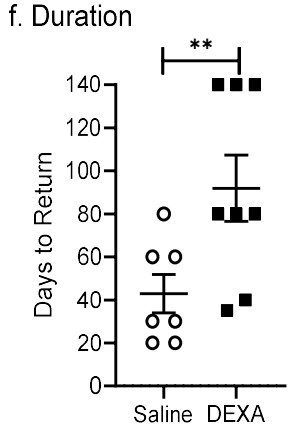
Hindering the inflammatory response in injured mice delays their recovery?



Inhibition of Immune Response in Mouse Inflammatory Model Produce Pain Chronification

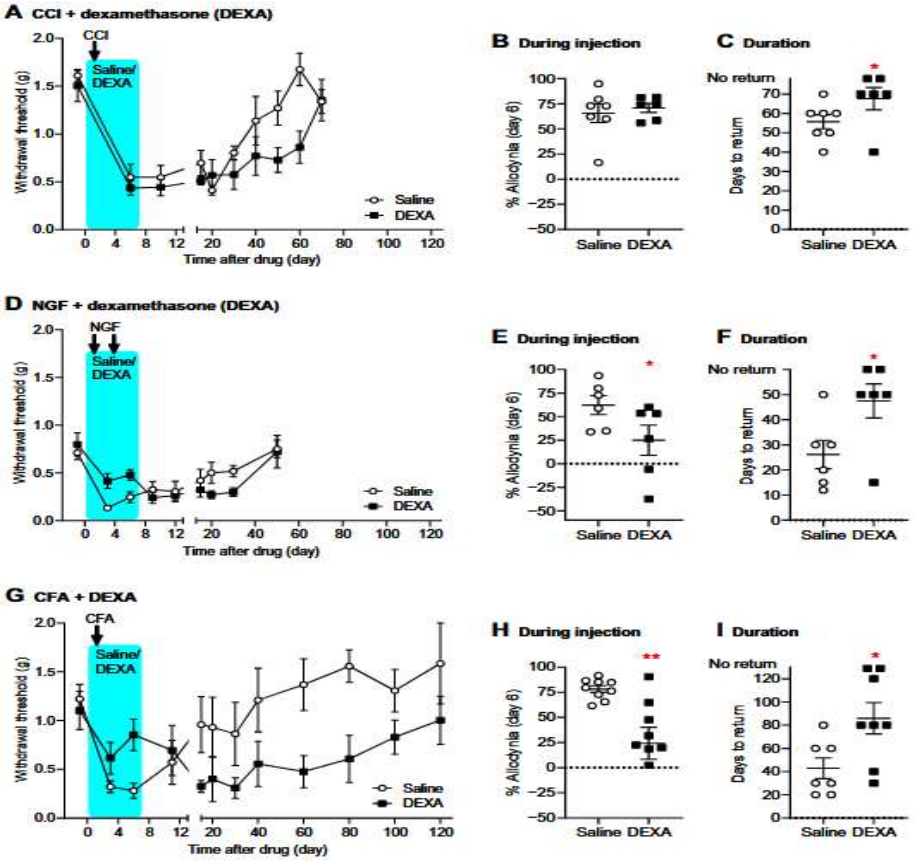






Parisien et al *Sci Transl Med*, 2022

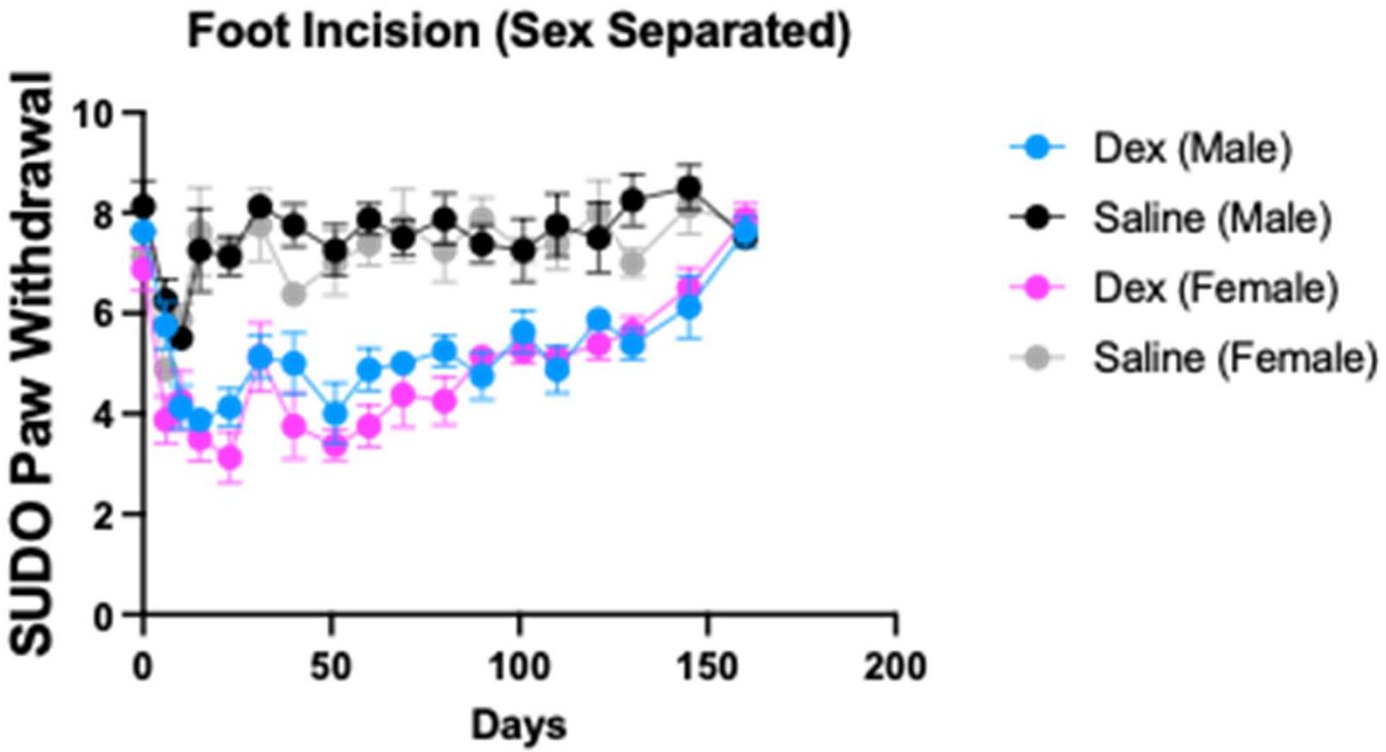
Dexamethasone delays the recovery from CCI, NGF and CFA-induced hyperalgesia



Dexamethasone produced an acute anti-allodynic effect in the CFA but not CCI and NGF injured mice, but significantly delayed PWT recovery to baseline in all groups

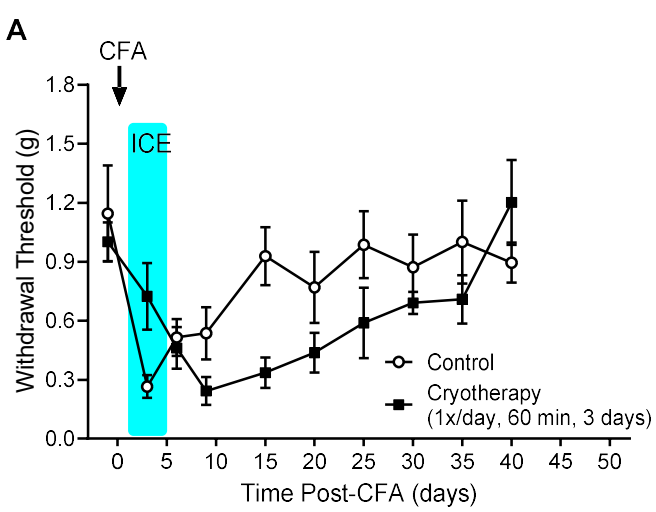
Parisien et al *Sci Transl Med*, 2022

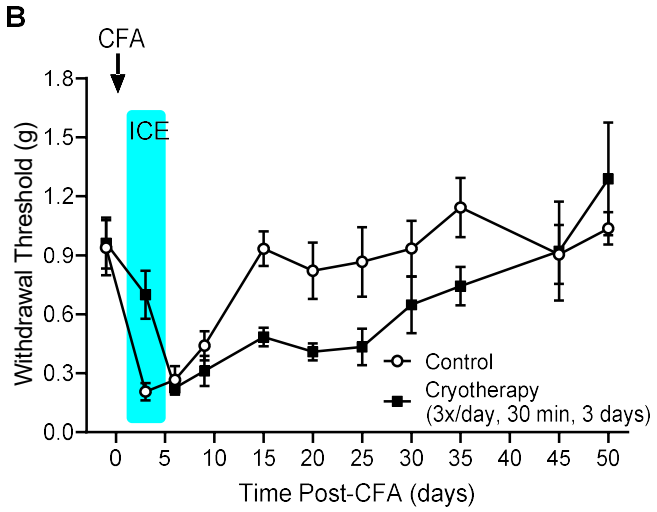
Also True for Mouse Model of Postoperative Pain



Martin, in preparation

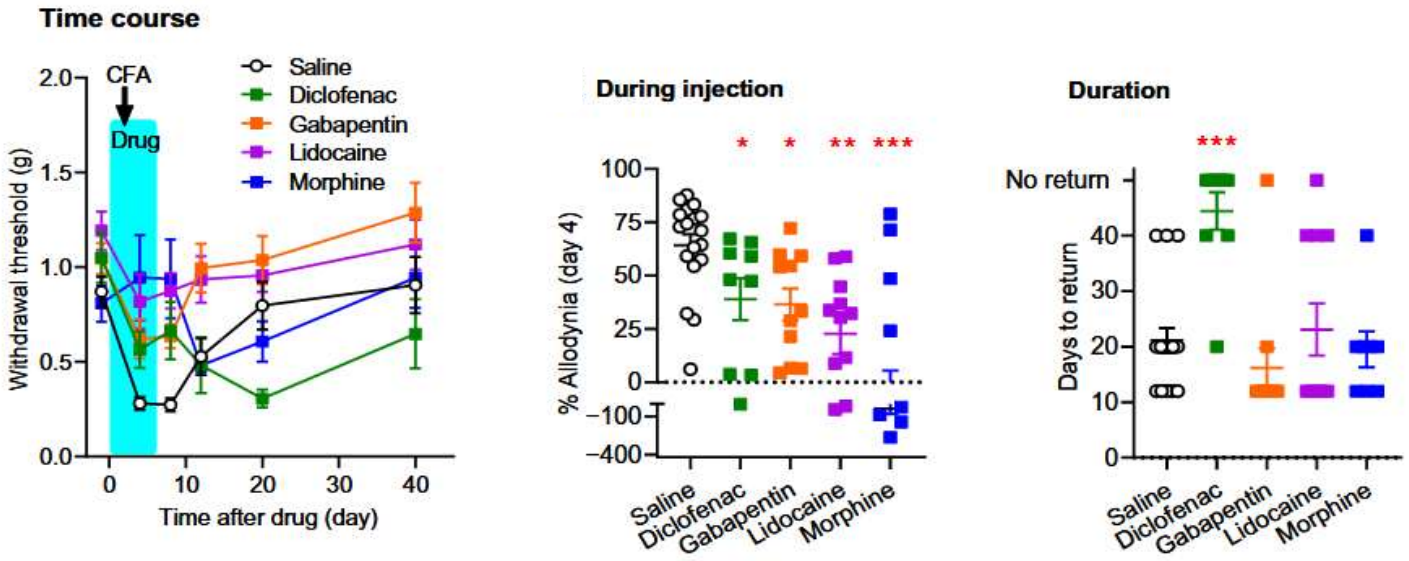
Also True for Ice Application in Mouse Inflammatory Model – Sport Injury Model





Lima, in revision

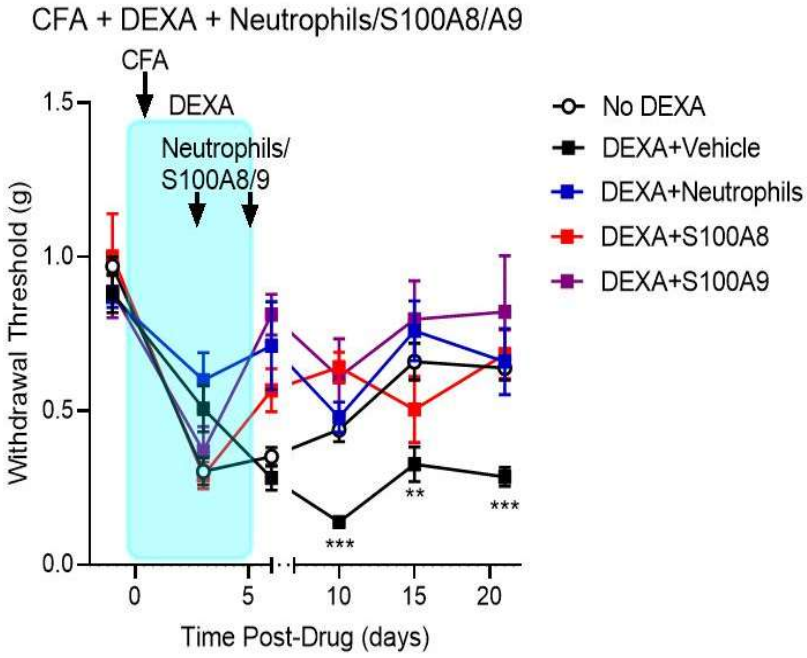
Diclofenac, but not gabapentin and lidocaine, delays the recovery from CFA-induced hyperalgesia

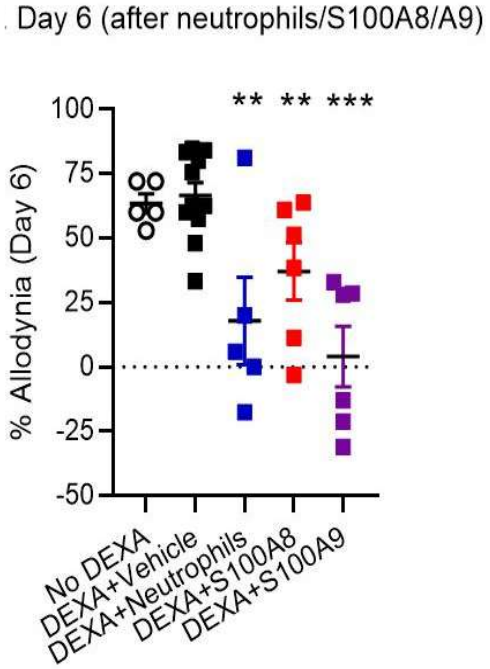


Delay in recovery is due to the reduction of inflammation and independent from analgesic effects

MOGILab

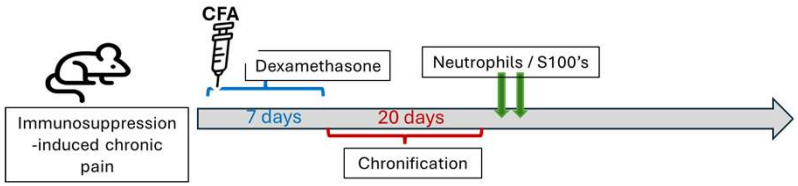
Injection of neutrophils or neutrophil-specific proteins prevents dexamethasone-induced pain

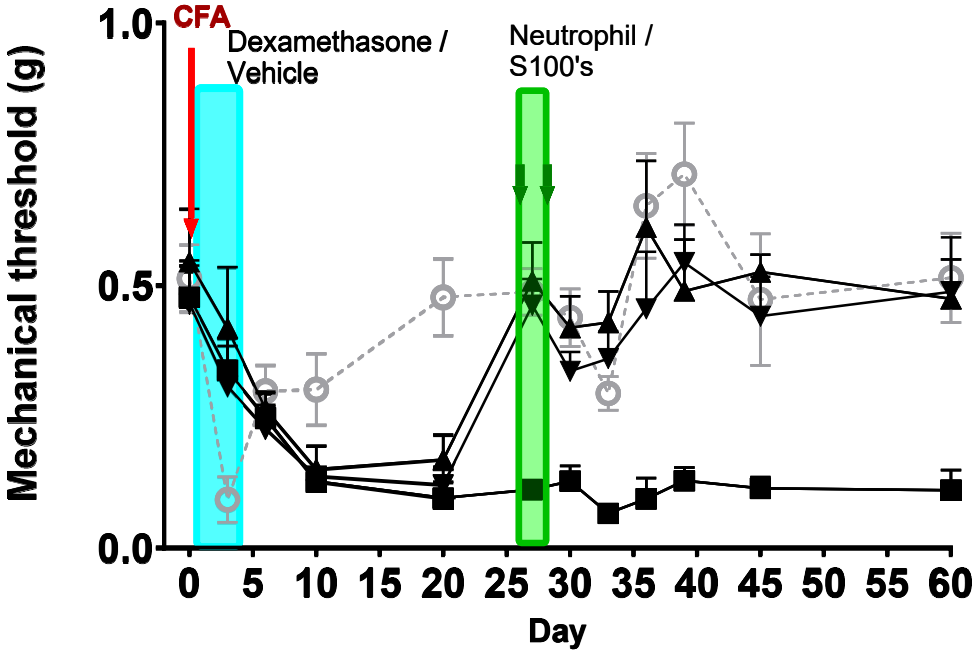


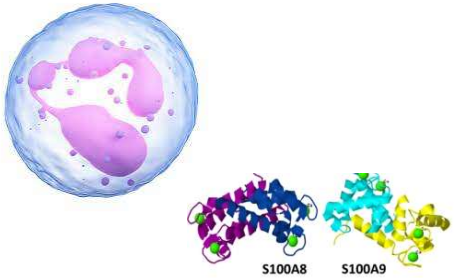


Dexamethasone delays allodynia recovery by directly affecting neutrophils

Reversal of chronic PO pain with neutrophils / s100's



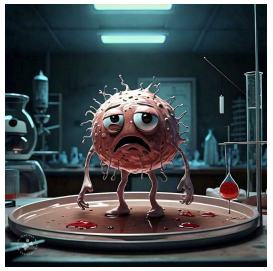


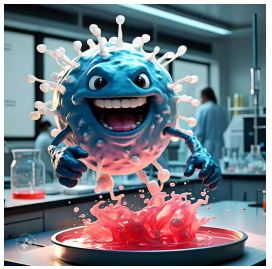


- Dexa + vehicle
- Vehicle + Vehicle
- Dexa + neutrophils
- Dexa + S100A 8/9

(Lima et al., unpublished)

Conclusions





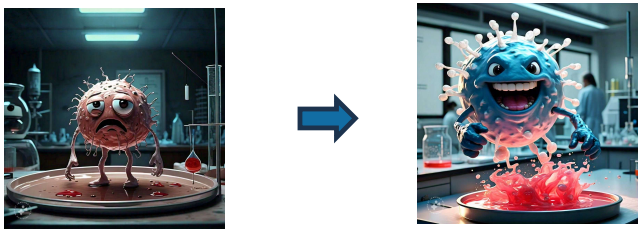
- There is an active adaptive component of immune system in acute to chronic pain transition in chronic pain conditions
- The same active adaptive component of immune system may underlie chronic pain resolution
- Inhibiting this immediate active adaptable immune response in the humans may lead to pain chronification

- In drug development protecting against chronic pain, our animal models should target pain resolution rather than analgesic efficacy
- In drug development protecting against chronic pain we may target activation of immune response instead of inhibition
- Despite high analgesic efficacy at early time points, the inhibition of acute inflammatory response in pain management may be counterproductive for long-term outcomes of LBP sufferers

Conclusions

- There is an active adaptive component of immune system in acute to chronic pain transition in chronic pain conditions
- The same active adaptive component of immune system may underlie chronic pain resolution
- Inhibiting this immediate active adaptable immune response in the humans may lead to pain chronification

- Proper stimulatory response in neutrophil may underly pain resolution in chronic pain patients



- Can ACS represents the treatment that allows this adaptive activation?

ACS Preparation

Aseptic blood draw (15mL)

3-6 h incubation

3 min 1500 g centrifugation

Vial extraction (ACS 4-6 mL)

Orthogen® Device vet

ACS mediators overview

Ingredient	Details/Effects
Cytokines	IL-1Ra, IL-10, IL-4, MCP-1, TNF, Rantes et al.
Growth Factors (PDGF, VEGF, IGF et al.)	Regenerative (cell division, vascularization et al.)
Lipid Mediators (omega3-derived SPM)	resolve inflammation, Macrophage shift M1→M2
Extracellular Vesicles (incl. Exosomes)	Immune-modulation, resolve Inflammation, transfer Mitochondria
Mitochondrial derived peptides	modulate adaptative responses to metabolic stress
Neutrophil mediators	Alarmins
Others (Gelsolin, Thy-1, SDF-1a, SCGFb, NFkB et al.)	Multiple modes of action

The proposed mechanisms of ACS therapeutic activity:

1. Innitiate an anti-inflammatory responce
2. Reduces free radicals, improves mitochondria function
3. Provides cytokines, growth factors, resolvins, exosomes and building blocks for tissue repair

ACS enables the local requirements for healing.

ACS enables tissue to enter the resolution phase.

What does ACS contain?

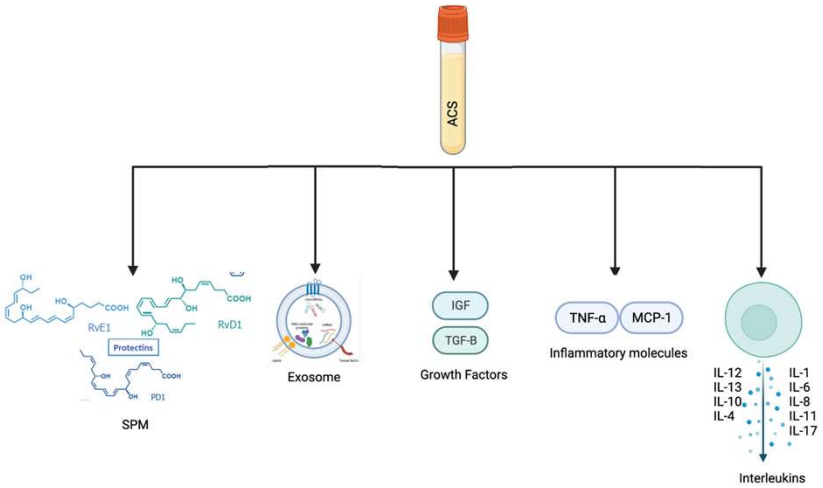


Table 2. Changes in the S100A8/A9 protein levels in conditioned serum over the time of incubation

EDTA baseline		ACS		Paired differences			
Mean	SD	Mean	SD	Mean (95% CI)	SD	FI	P-value
338.6	26.95	5158.38	4156.88	4819.79	415123	**14.2**	0.036

* 6 Patients

Time-dependent changes in the cytokines and growth factors levels in conditioned serum over the time of incubation

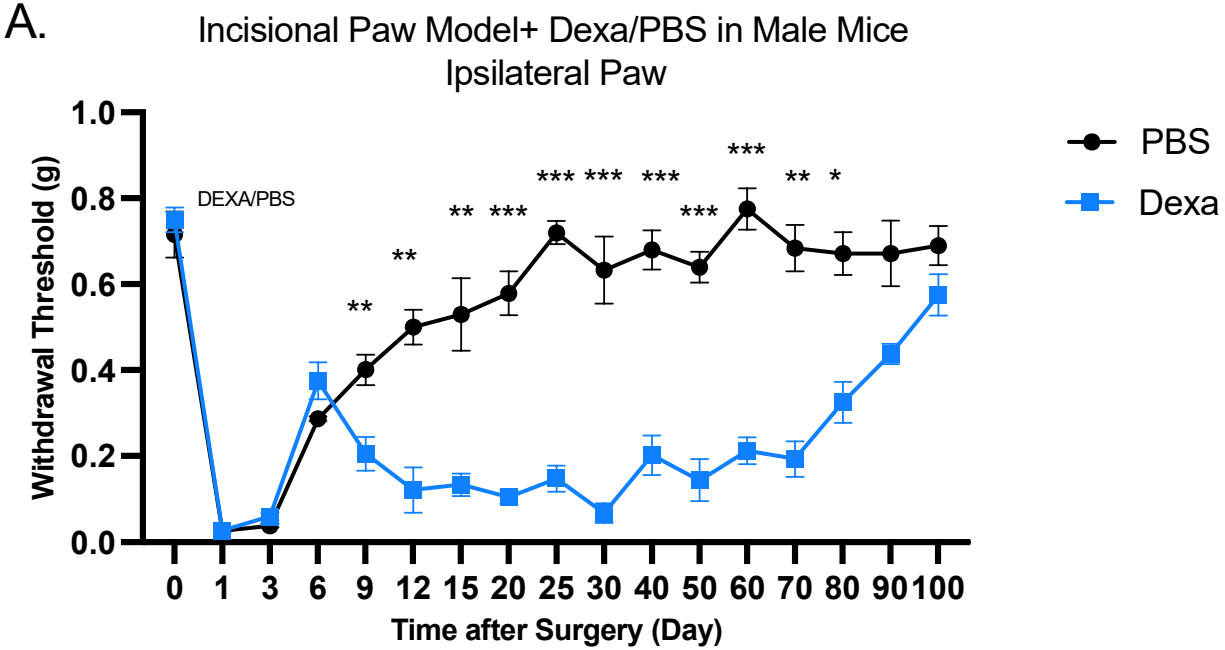
	IL-1b	IL-1ra	IL-2	IL-4	IL-6	IL-8	IL-9	IL-10	IL-13	IL-17	Eotaxin	FGF	G-CSF	GM-CSF	IFN-g	MCP-1	MIP-1a	PDGF-b	MIP-1b	RANTES	TNF-a	VEGF
0h	2	62	6	1	7	12	11	8	13	12	99	38	48	20	10	70	6	7	77	433	21	14
6h	23	291	23	5	69	4592	77	23	12	169	222	135	101	82	80	293	50	5139	1074	48720	165	218
9h	37	351	23	6	614	9195	107	24	12	221	250	139	117	60	81	297	162	5321	2511	56699	313	201
24h	57	481	30	7	3962	26256	158	39	12	278	229	142	319	90	107	533	913	5753	7923	61486	215	248
FI	**29**	**8**	**5**	**7**	**566**	**2188**	**14**	**5**	**1**	**23**	**2**	**4**	**7**	**5**	**11**	**8**	**152**	**822**	**103**	**142**	**10**	**18**

* 2 Patients

Result: Incisional paw + DEXA/PBS

(n=6 per group)

A.



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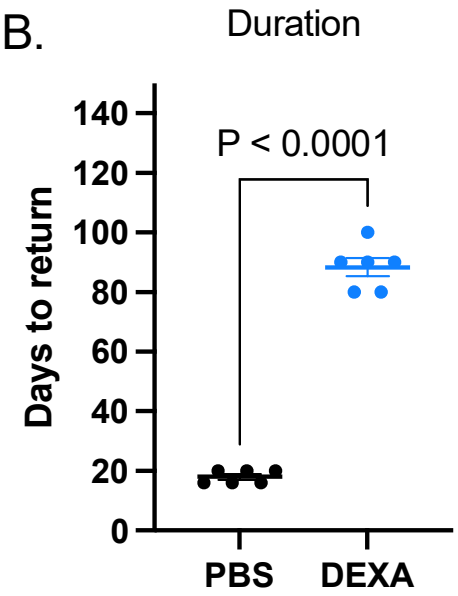
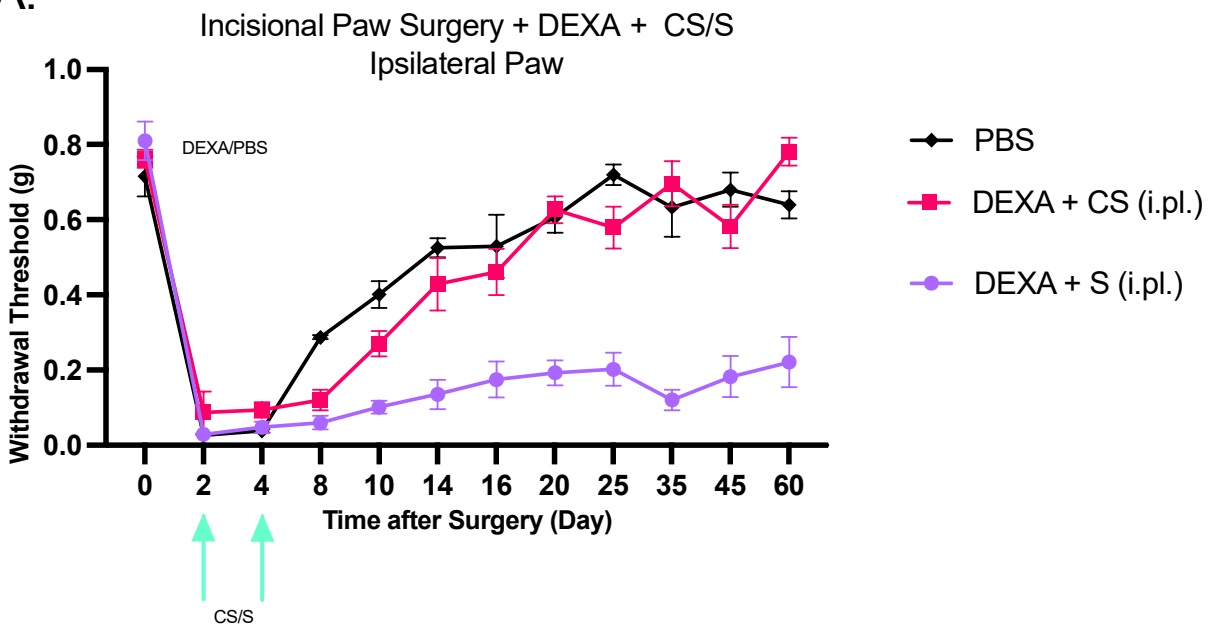


The dexamethasone treatment led to the prolongation of pain in post operative model

Result: Incisional paw + DEXA/PBS + CS/S

A.



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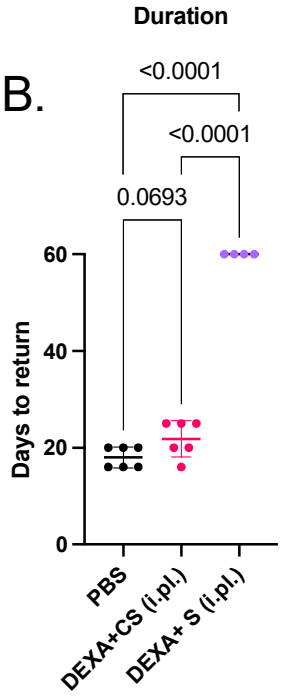
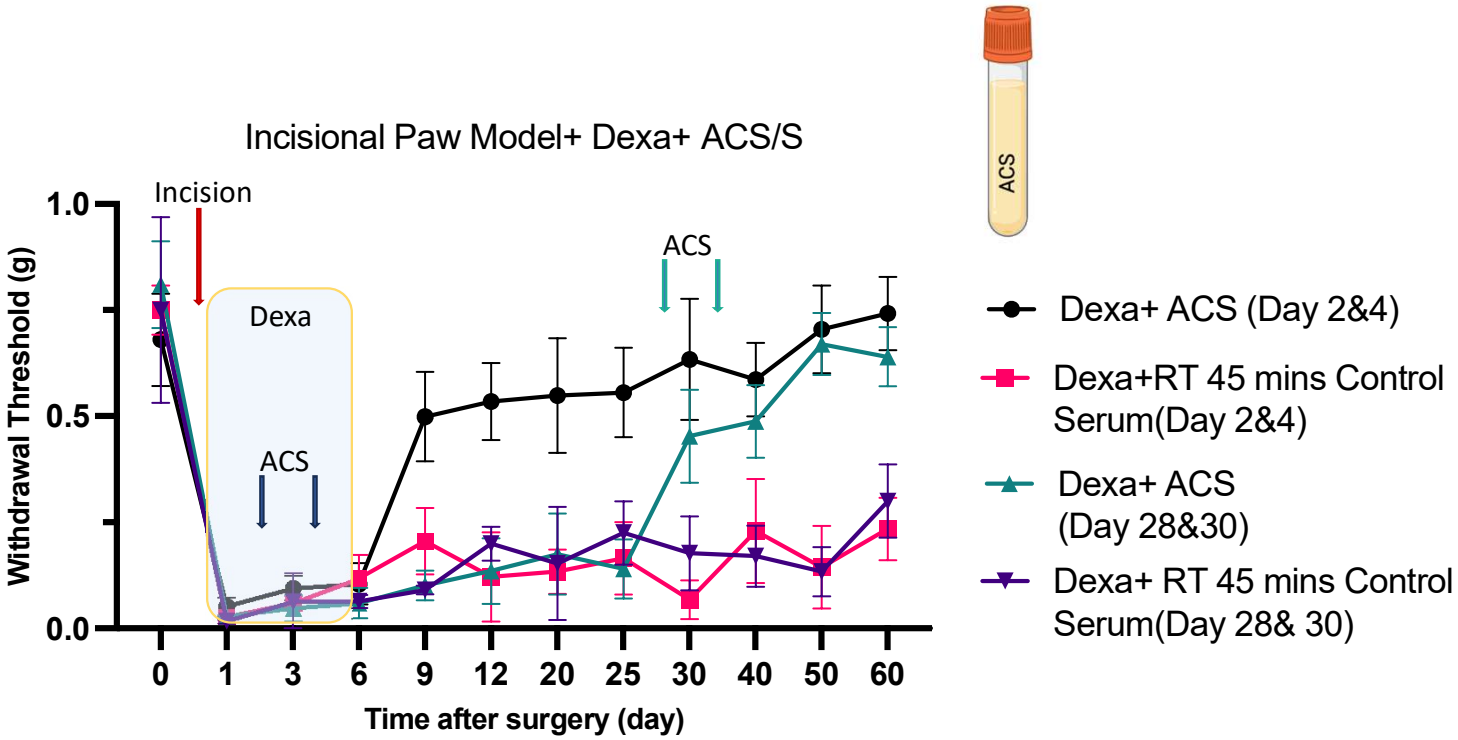


CS injection prevented long-lasting pain induced by Dexa in the post-surgical pain model when injected intraplantar

Pain Resolution Experiment with ACS in Dexamethasone induced Chronic Model



(Oveisi et al., unpublished)

Transciptomics approaches helped us to identify:

Potential negative effects (prolongation of pain)

- **Corticosteroids**
- **NSAIDS**
- **Cryotherapy (icing)**

Potential new therapeutic tools (pro-resolution)

- **Neutrophils / S100A 8/9**
- **PG agonist**
- **Autologous Conditioned Serum**
- **Controlled pro-inflammatory methods**

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Potential new therapeutic tools (pro-resolution)

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- **Controlled pro-inflammatory methods**

Gaps to be addressed

- Understand the molecular mechanisms of autologous serum conditioning
- Understand the difference in ACS between healthy chronic pain patients
- Understand the molecular mechanisms of host responses to ACS
- Identify candidates for response to ACS
- Capture other non-pain phenotypes improved by ACS in animal models.


Welcome to the Human Pain Genetics Program


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PAIN
McGill
Pfizer


Thank You