"Listening" and "Talking" to Neurons:
Non-neuronal cells amplify pain and drug reward
~ Pathways from basic science to human and veterinary clinical trials ~

Linda R. Watkins

Psychology & Neuroscience, University of Colorado-Boulder
co-Founder & co-Chair Scientific Advisory Board, Xalud Therapeutics

Disclosures

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  - > Department of Defense
  - > ALS Alliance; Prize4Life (ALS)
  - > National Multiple Sclerosis Society
  - > McManus Charitable Trust
  - > Paralyzed Veterans of America
  - > Craig Spinal Cord Injury Hosp.
  - > Craig Neilson Foundation
  - > Wings for Life
  - > American Kennel Club
  - > MayDay Fdn; Cielo Fdn
  - > Chancellor's Fund, CU
  - > Ohio Vet. Med. Assoc.

- **Xalud Therapeutics:**
  - > Co-Founder
  - > Co-Chair Sci Advisory Board

Early stage startup;

entirely Preclinical (no marketed products), developing non-opioid immunomodulatory pain therapeutics

Human Clinical Trials for Osteoarthritis pain now underway in U.S. (California) & Australia (Adelaide) !!!

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Global Concepts

- Views of pathological pain are changing
- Recognition of Non-Neuronal players in pain: glial cells (*microglia & astrocytes)* in spinal & brain pain pathways; peripheral immune cells in involved tissues
- Recognition of Non-Neuronal players in *opioid actions:* Glia disrupt the clinical efficacy of opioids, including morphine, oxycodone, remifentanyl, methadone, etc.
- Clinical implications of glial dysregulation of pain & opioid actions ... *glia/immune targeting therapeutics are approaching clinical trials!*

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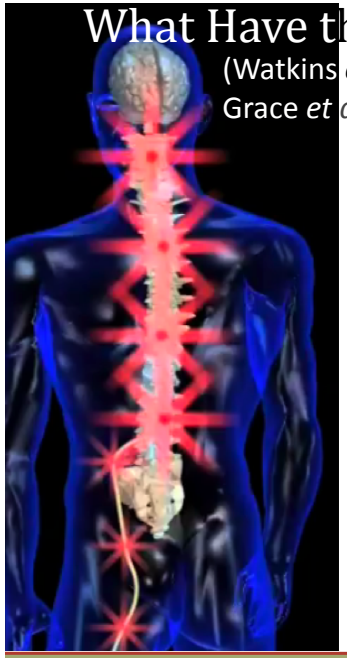
What Have the Past 25+ Years Revealed?



(Watkins *et al.*, *Brain Behav Immunity* 2007;
Grace *et al.*, *Nature Reviews Immunology* 2014)

Spinal & trigminal glia (microglia, astrocytes) are *activated in every clinically-relevant model of enhanced pain*:

- Somatic (sciatic etc.) & trigeminal injury
- TMJD, occlusal interference
- Chronic tooth pulp inflammation
- "Migraine" facial allodynia
- Bone cancer; chemotherapy
- Multiple sclerosis
- Spinal cord injury
- Radiculopathy/herniated discs, and so on…

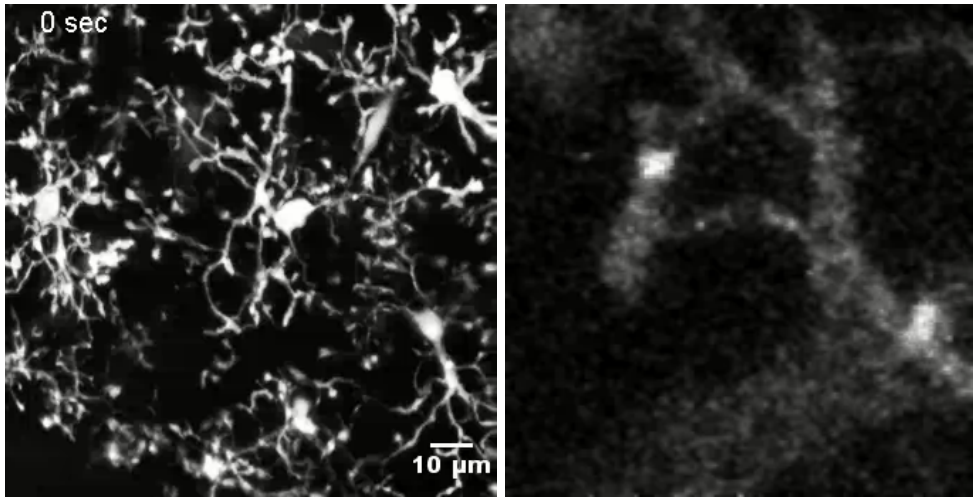
Suppressing spinal & trigeminal glial activation &/or glial proinflammatory cytokines:

- *suppresses pain in every clinically-relevant model,* returning pain to *normal*

~ Beyond Pain ~
For Opioids: The Data Support That Blocking Glial/Immune Activation Will:

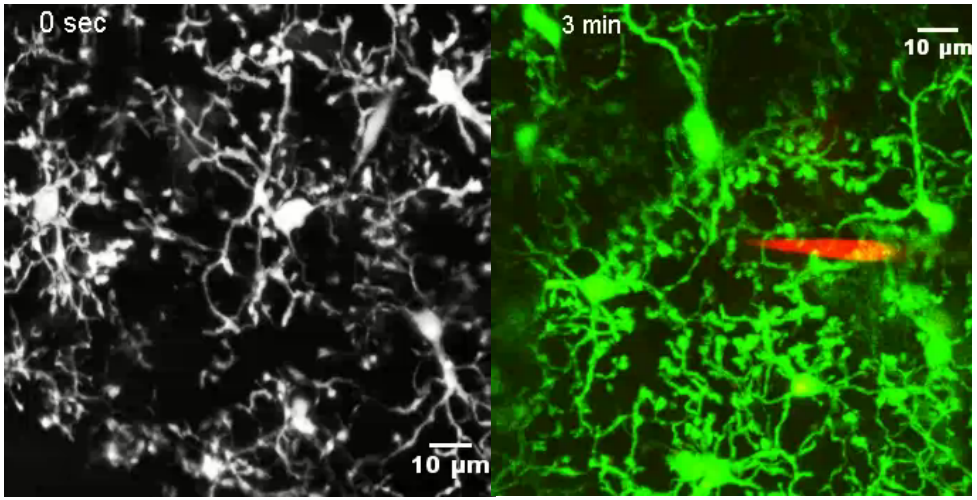
- ❖Improve opioid analgesia
- ❖Suppress opioid tolerance
- ❖Suppress opioid dependence
- ❖Suppress opioid reward linked to drug craving/drug abuse
- ❖Suppress both opioid-induced respiratory depression & constipation

Microglia Actively Survey the CNS & Rapidly Respond to Challenge



Videos from: Davalos et al., *Nature Neuroscience* supplements, 8 (2005) 752-758; & Nimmerjahn et al., *Science* supplements, 308 (2005) 1314-1318

Microglia Actively Survey the CNS & Rapidly Respond to Challenge

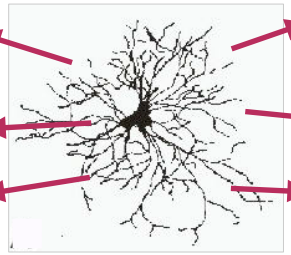


Videos from: Davalos et al., *Nature Neuroscience* supplements, 8 (2005) 752-758

Glia Release Neuroexcitatory, Pain Enhancing Substances

(Watkins *et al.*, *Brain Behav Immunity* 2007)

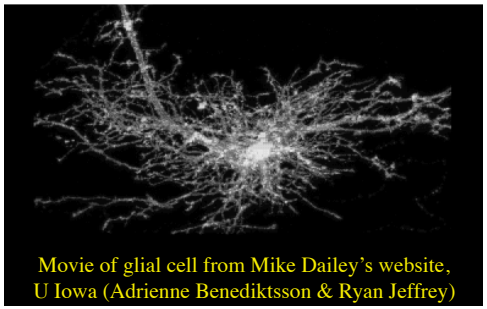
Activated glia release:



- ***Amplify pain signaling from the body to the spinal cord***
- ***Amplify pain transmission from the spinal cord to the brain:***
  - ***upregulate AMPA & NMDA receptor number/function***
  - ***downregulate GABA & outward K+ currents***
  - ***downregulate glial glutamate transporters & GRK2***

Glial Proinflammatory Cytokines: Major Players in Neuroexcitation in Pain

... as well as Opposing opioid analgesia!



Movie of glial cell from Mike Dailey's website, U Iowa (Adrienne Benediktsson & Ryan Jeffrey)

Proinflammatory Cytokines:

Tumor Necrosis Factor
Interleukin-1
Interleukin-6

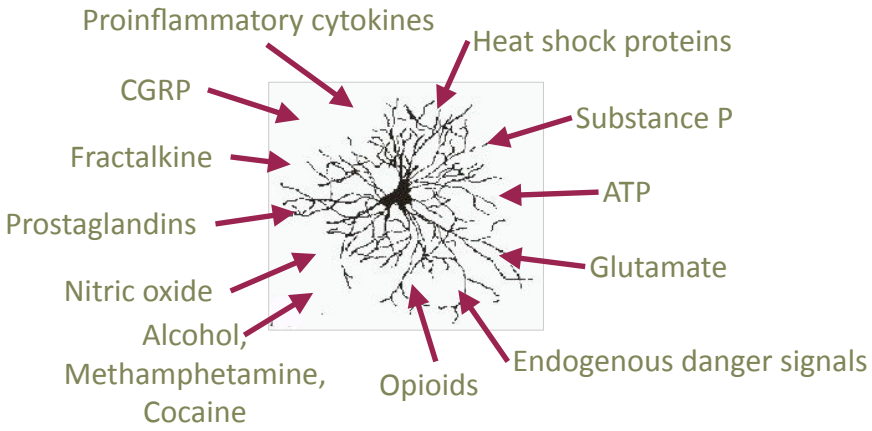
↓

Neuroexcitation!

By *Enhancing* pain,

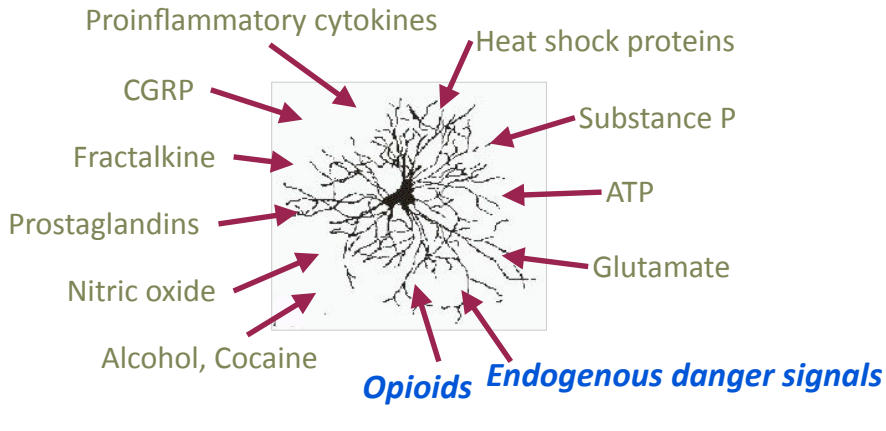
Opposes opioid analgesia

What Activates Glia?



Watkins & Maier, *Nature Rev Drug Disc* 2003
Hutchinson *et al.*, *Pharmacol Reviews* 2011

What Activates Glia?



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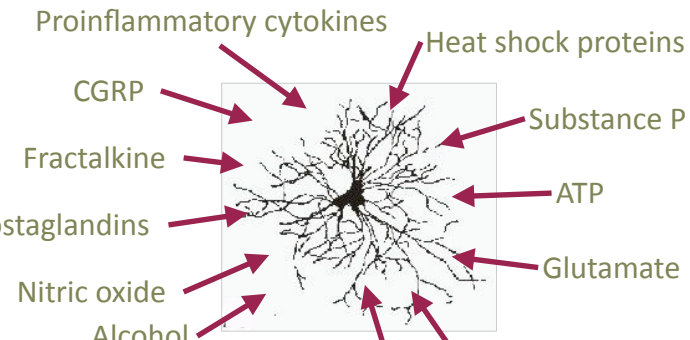

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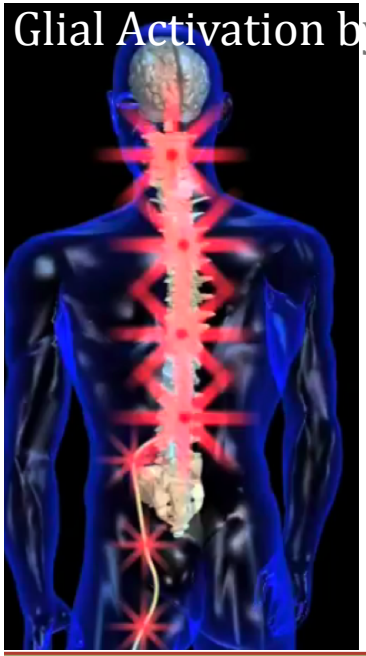
Hutchinson *et al.*, *Pharmacol Reviews* 2011
Bachtell *et al.*, *CNS Neurol Disord Drug Targets* 2015

Glial Activation by Endogenous Danger Signals



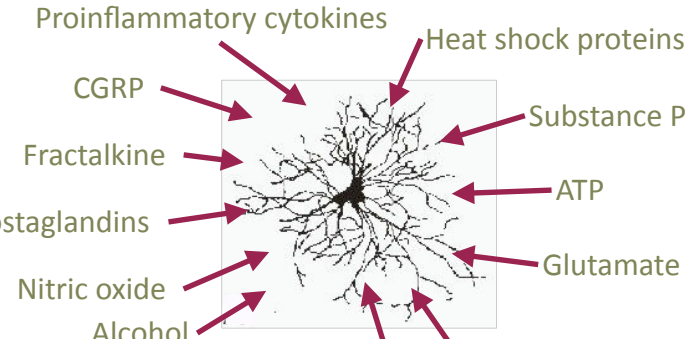
Endogenous danger signal activation of glia (microglia, astrocytes) implicated in pain in multiple rodent models, such as:

- Peripheral nerve injury
- Medication overuse headache, migraine
- Streptozotocin diabetic neuropathy
- Spinal cord injury
- Bone cancer
- Arthritis
- Pancreatitis
- Multiple sclerosis

When bad things happen ... endogenous danger signals are created ... glia are activated... pain is amplified by glial pain-enhancing proinflammatory cytokines

~ Hence perfect target for therapeutics that elevate ANTI-inflammatory cytokines like Interleukin-10

What Activates Glia?



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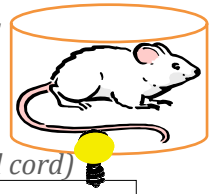
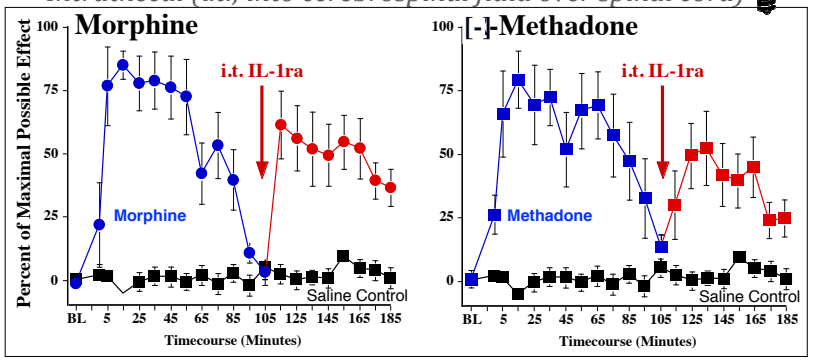
Hutchinson *et al.*, *Pharmacol Reviews* 2011
Bachtell *et al.*, *CNS Neurol Disord Drug Targets 2015*

Spinal Glial Activation Opposes the Ability of Opioids to Suppress Pain

Morphine & Methadone as examples

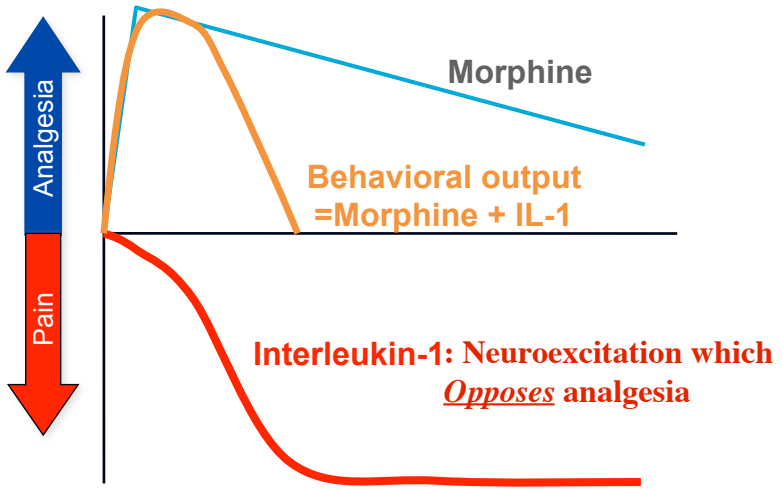


Intrathecal (i.t.; into cerebrospinal fluid over spinal cord)



Hutchinson et al., *Brain Behavior & Immunity*, '08

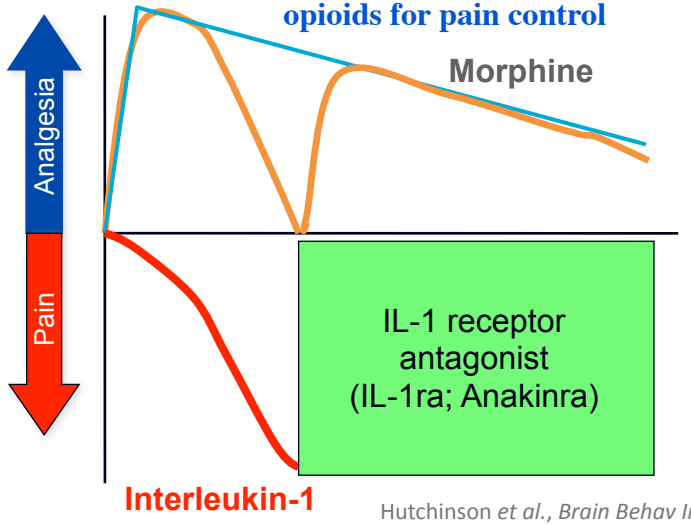
Blocking Spinal Interleukin-1 Unmasks Morphine Analgesia



Hutchinson *et al., Brain Behav Immunity* 2008

Blocking Spinal Interleukin-1 Unmasks Morphine Analgesia

Blocking glial activation improves the efficacy of opioids for pain control



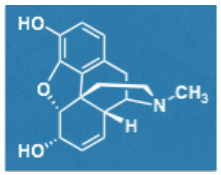
Hutchinson *et al., Brain Behav Immunity* 2008

Opioid effects are *different* for neurons & glia

Opioids exist as mirror-image stereo-isomers

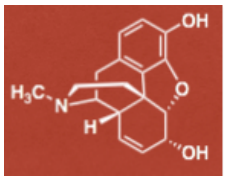
(-)-Morphine

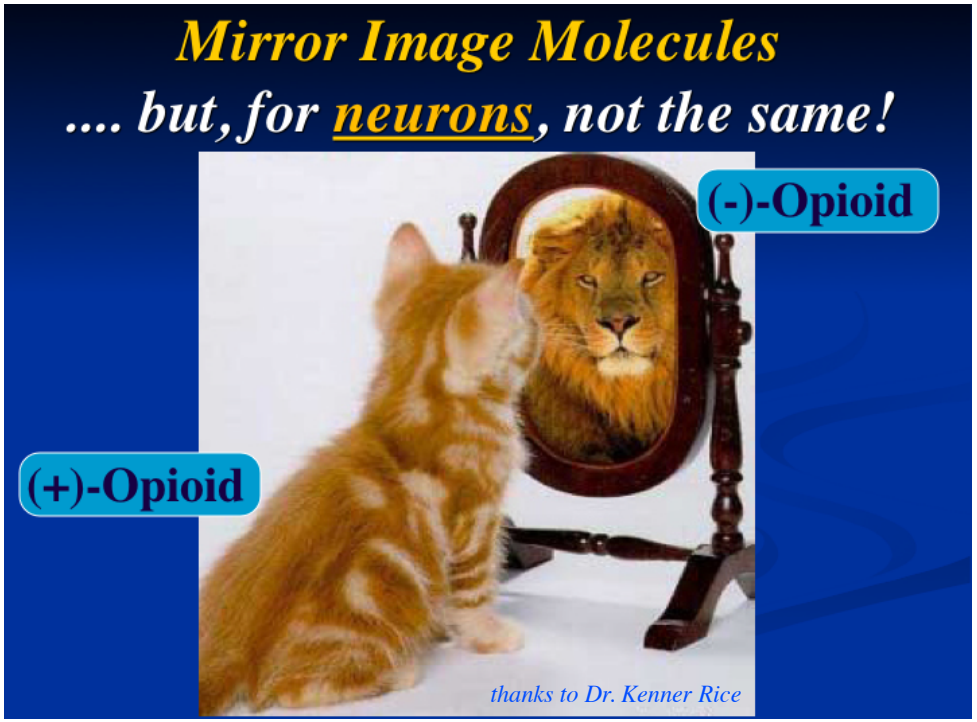
- Binds to μ-opioid receptors
- Powerful analgesic



(+)-Morphine

- **NO** binding to μ-opioid receptors
- **NO** analgesia

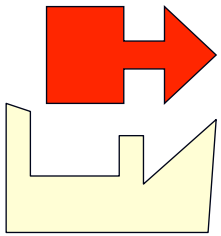




Opioid Effects are Different for Neurons vs. Glia

Neuronal Receptors are Stereoselective

[-]-Morphine:
Active Agonist
at Classical Opioid Receptors
on Neurons



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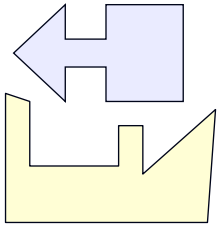

Opioid Effects are Different for Neurons vs. Glia

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[-]-Naloxone & [-]-Naltrexone:
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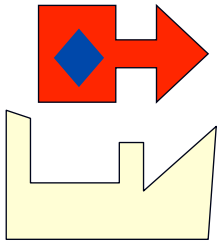
on Neurons



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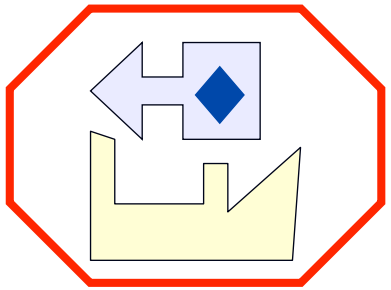


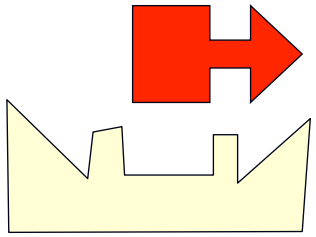
This Point is KEY

Opioid Effects are Different for Neurons vs. Glia

GLIAL Receptors are Not Stereoselective

[-]& [+] Isomers have EQUAL effects on glia

[-]-Morphine:
Active *Agonist*
at Glial Opioid Receptor



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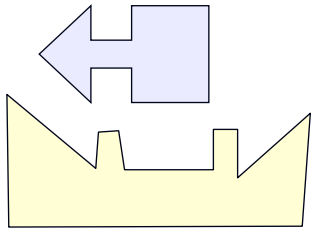
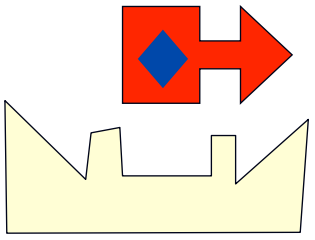


Glial opioid receptor -- Fits BOTH [-] & [+]-enantiomers

Glial Non-Stereoselectivity Extends to Opioid Antagonists!

[-]-Naloxone &
[-]-Naltrexone:
Active *Antagonists*
at Glial Opioid receptor



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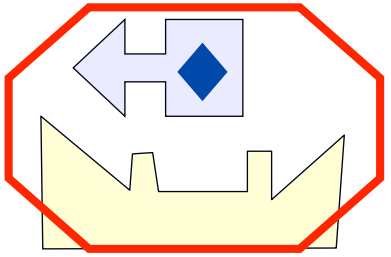
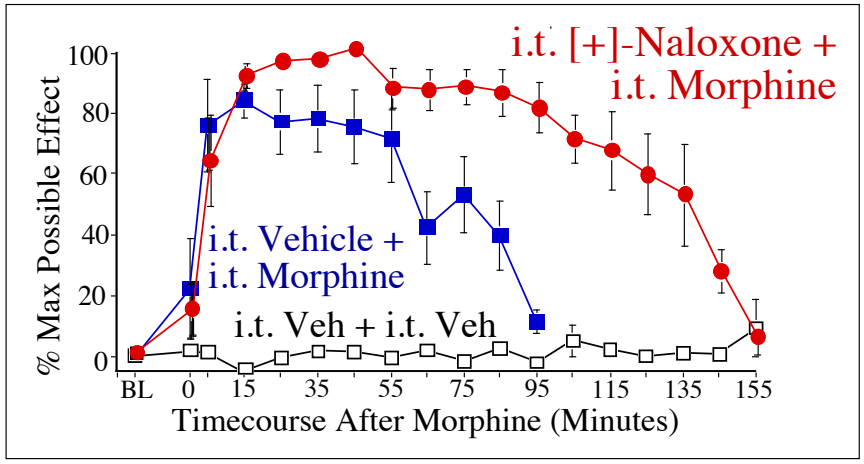


[+]-Naloxone should *POTENTIATE* morphine analgesia by:
(a) *NOT* blocking morphine effects on neurons, yet
(b) Removing glial activation that *OPPOSES* analgesia!

(+)-Naloxone
~which has no effect on neurons ~
Potentiates Morphine Analgesia!



Hutchinson et al., *Brain Behav. Immunity* '09

Why is This Important? This Difference Predicts:

Effects on neurons & glia should be separable

To increase the efficacy of opioids:

*structurally modify opioids to not activate glia, *or*

* create a long-lasting version of (+)-naloxone, or other TLR4 antagonists, that only block glial activation

So .... What is this Mystery Receptor?

To target it, one must know what it is

Toll-Like Receptor 4 (TLR4):

Classically .....

"not me, not right, not OK" receptors

Toll-Like Receptor 4 (TLR4) detects:

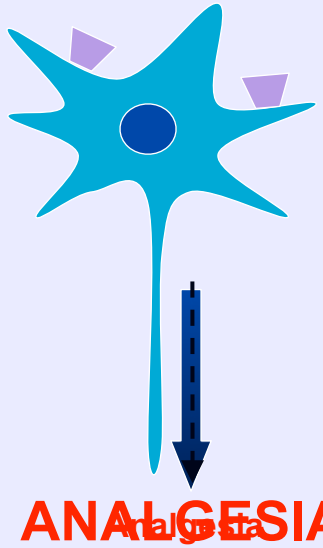
* Bacteria (lipopolysaccharide; LPS)

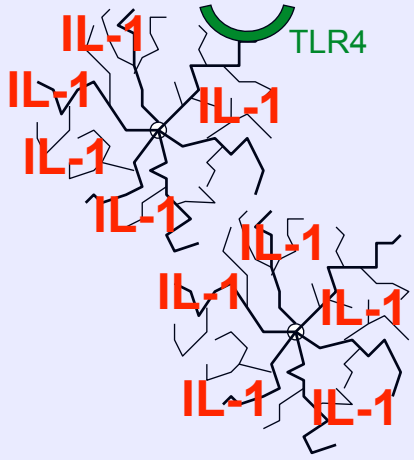
* endogenous danger signals (stress/damage/death)

* ***All classes of opioids used clinically***

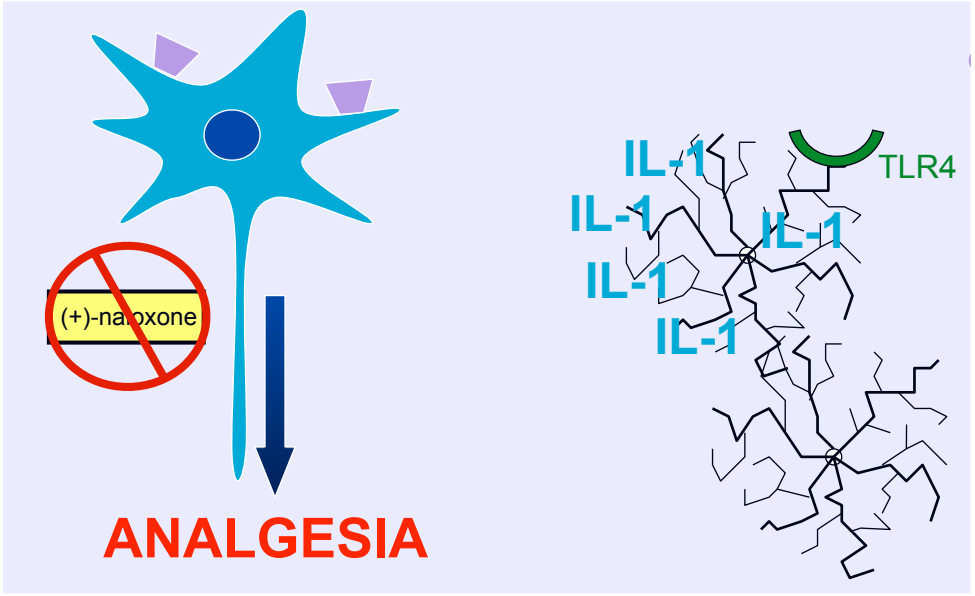
Hutchinson et al., *TSWJ* 2007; *Br Behav Immun* 2008

Opioid Activation of Glia Suppresses Analgesia





Opioid Activation of Glia Suppresses Analgesia: Blocked by TLR4 Antagonists



Glial Toll-like Receptor-4 (TLR4)

~ the *"not me, not right, not okay"* receptor ~

is also activated by Endogenou
that drive Neuropat

And this is TRUE!

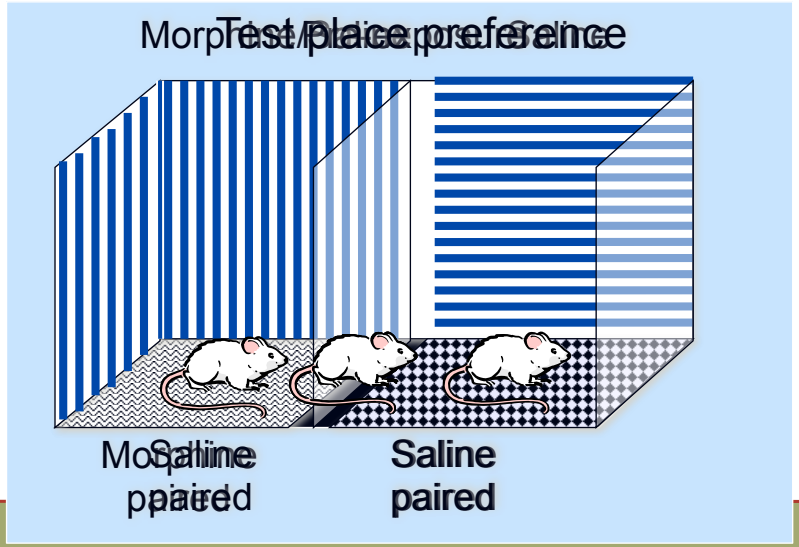
If that is True, then....

* Might that suggest that blocking TLR4 can do more than just potentiate opioid analgesia?

* Might TLR4 antagonists also be stand-alone treatments for neuropathic pain?

Hutchinson et al., *Brain Behav. Immun.* 2008

Glia & Opioid Reward: Conditioned Place Preference

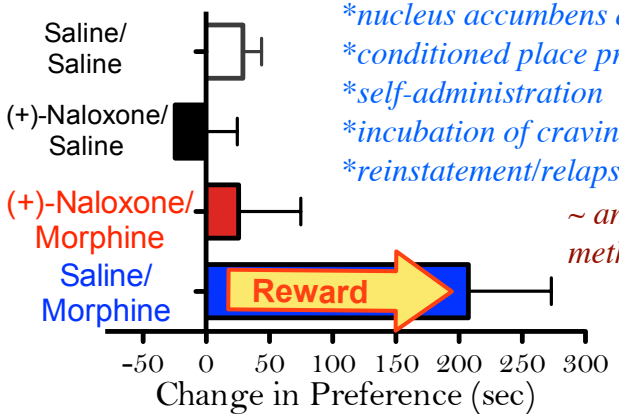


Blocking Toll-like receptor 4 (TLR4) Suppresses Morphine Reward

Blocking Toll-like Receptor 4 suppresses opioid:

**nucleus accumbens dopamine elevation*
**conditioned place preference*
**self-administration*
**incubation of craving*
**reinstatement/relapse*

~ and true for cocaine and methamphetamine as well



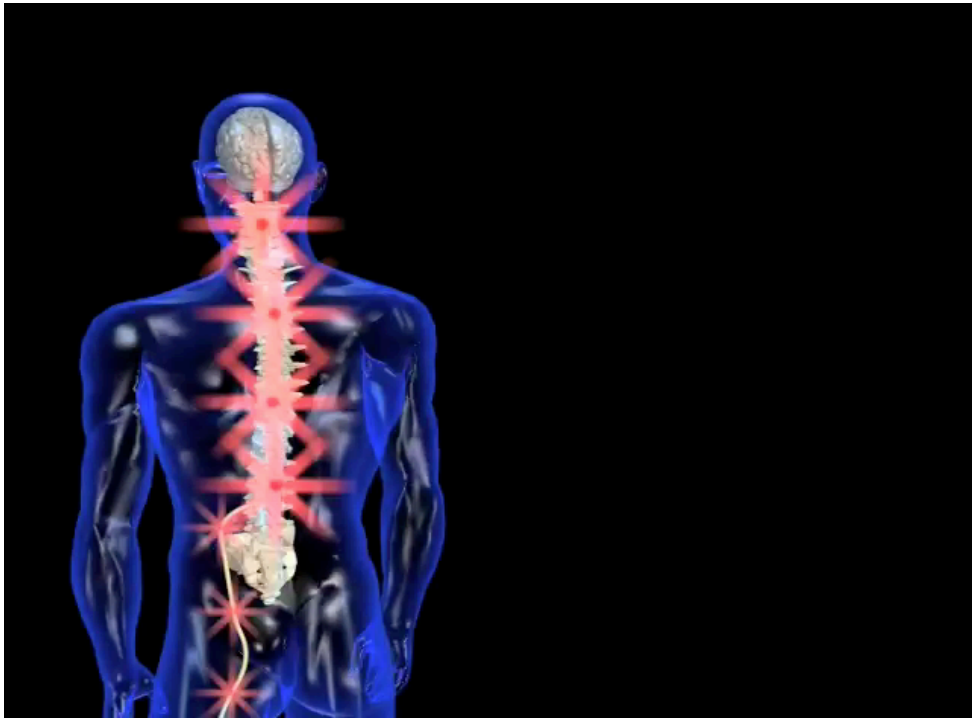
Opioids: Hutchinson et al., *Journal of Neurosci*, 2012; **Cocaine**: Northcutt et al., *Molec Psychiatry* 2015; **Opioids:** Theberge et al., *Biol. Psychiatry*, 2013; **Methamphetamine**: Wang et al., *ACS Chem Neurosci*. 2019

Taken Together, the Data Predict that Blocking Glial / Immune Activation will:

- Suppress pathological pain due to: neuropathy, multiple sclerosis, bone cancer, etc.
- Improve opioid analgesia
- Suppress opioid tolerance
- Suppress opioid dependence
- Suppress opioid reward linked to drug craving/drug seeking
- Suppress respiratory depression, constipation, & (likely) itch

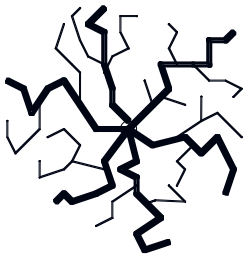
..... and this isn't just for opioids (e.g. effects of cocaine, methamphetamine are also amplified by glia!!)

Watkins et al., *Trends in Pharmacological Sciences* 2009
Hutchinson et al., *Pharmacological Reviews*, 2011



States of Glial Activation: Not Just "Off" or "On" Anymore!

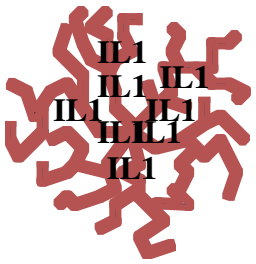
Basal State: Boring but Vigilant



Hains et al. *J Pain* '10; Hains et al. *J Neuroimmunology* '11; Loram et al. *BBI* '12; Ellis et al. *BBI* 2016; Grace et al. *PNAS* 2016; Green-Fulgham et al., *BBI 2019*

States of Glial Activation: Not Just "Off" or "On" Anymore!

Activated State: Proinflammatory



Hains et al. *Journal of Pain* 2010; Hains et al. *Journal of Neuroimmunology* 2011; Loram et al. *BBI* 2012; Ellis et al. *BBI* 2016; Grace et al. *PNAS* 2016

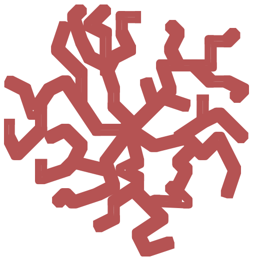
States of Glial Activation: Not Just "Off" or "On" Anymore!

***"Primed"* State:**

* Can occur for a period of time after prior activation

* No longer producing proinflammatory products…

but….Ready for Action!



Hains et al. *J Pain* '10; Hains et al. *J Neuroimmunology* '11; Loram et al. *BBI* '12; Ellis et al. *BBI 2016*; Grace et al. *PNAS* 2016; Green-Fulgham et al., *BBI 2019*

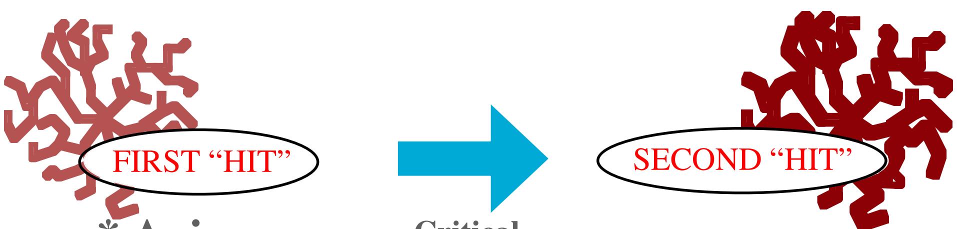
States of Glial Activation: Not Just "Off" or "On" Anymore!

Reactivation from the"Primed" State: *Explodes* into Action in Response to a New Challenge!

Aging
Stress
Trauma
Opioids

Sets the Stage For Chronic Pain??

2-Hit Hypothesis: A 2nd "Hit" Can Create a Faster, Strong, Longer Glial Response

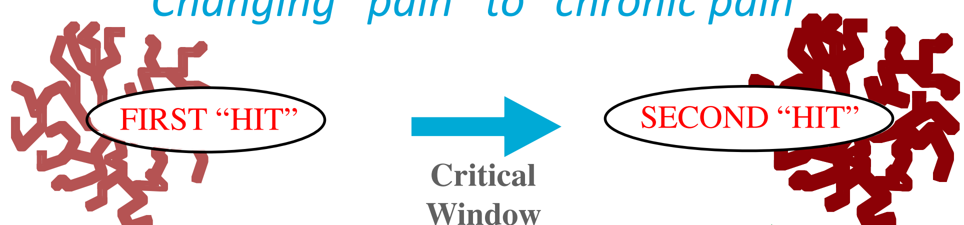


Critical Window of Time

- **Aging**
- **Stress**
- **Trauma/ Inflammation**
- **Opioids**

So…. Does *Prior* glial activation alter the pain response to a *NEW* challenge?

Changing "no pain" to "pain";
Changing "pain" to "chronic pain"



Critical Window of Time

- **Aging**
- **Stress**
- **Trauma/Inflammation**
- **Opioids**

And this is TRUE!

Hains et al. *J Pain* '10; Hains et al. *J Neuroimmunology* '11; Loram et al. *BBI* '12; Ellis et al. *BBI 2016*; Grace et al. *PNAS* 2016; Green-Fulgham et al., *BBI 2019*

But wait a minute… this makes a scary prediction about opioids given post-trauma

Since ~

Trauma (**Hit 1**) leads to Opioids being given to treat the acute pain (**Hit 2**)

And ~

Trauma and Opioids **both** activate glia

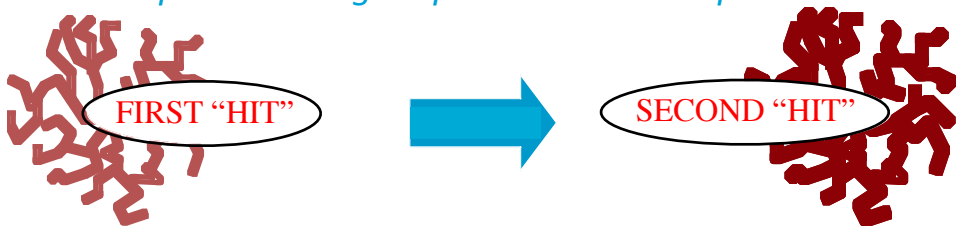
Then …..

If glial priming (**Hit 1 → Hit 2**) amplification of pain is true, then this predicts that opioids (**Hit 2**) given after trauma (**Hit 1**) might have an evil side: a negative long-term consequence of opioids on pain

And this is True! Grace et al., *PNAS* 2016; Green-Fulgham, *BBI* 2019

So…. Does *Prior* glial activation alter the pain response to a *NEW* challenge?

Morphine in the early post-trauma period changes "pain" to "chronic pain"



Trauma versus Sham

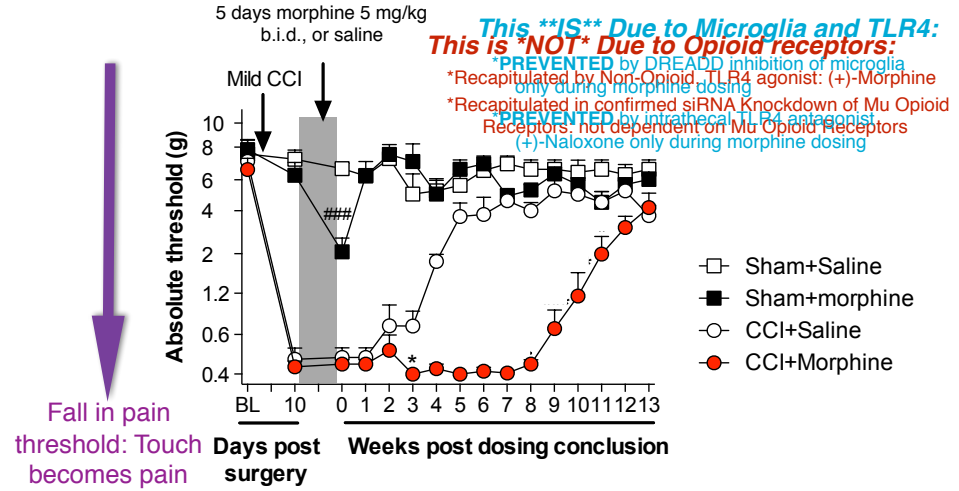
Short Course of Morphine Early Post-Trauma

TRUE for females and males, across rodent strains, and across multiple models (every one studied to date)

Grace et al. *PNAS* 2016; Green-Fulgham et al., *BBI 2019*

Peri-Trauma Morphine: Changes "pain" to "chronic pain" after peripheral nerve injury

TRUE for not just Morphine: TRUE for Oxycodone and Fentanyl as well!



Grace et al. *Proc. National Academy of Sci., '16;* Green-Fulgham et al. *BBI '19*

A Focus on Interleukin-10 (IL-10)

a potent endogenous Anti-inflammatory cytokine

The importance of central ***Pro***-inflammatory cytokines:
**across so many neuropathic pain models*
**across so many independent research labs across the World!*
suggests that an ***Anti***-inflammatory cytokine approach to suppress glial activation might prove successful for neuropathic pain control

Plus ~ proinflammatory cytokines are important in diseases like ARTHRITIS: might local, intra-articular IL-10 help arthritis as well?

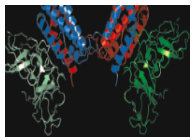
****1991 (28 years ago!):*** *We began studying spinal glial dysregulation of pain by pro-inflammatory cytokines; pure basic science*

****2000-2017: Progression through eight successive generations*** *of approaches to reach a clinically relevant final version:*

8 generations of IL-10 delivery: *protein, pegylated protein, adenovirus, adeno-associated virus, naked plasmid DNA, various DNA encapsulations, PLGA slow-release microparticles, D-mannose formulated naked plasmid DNA*

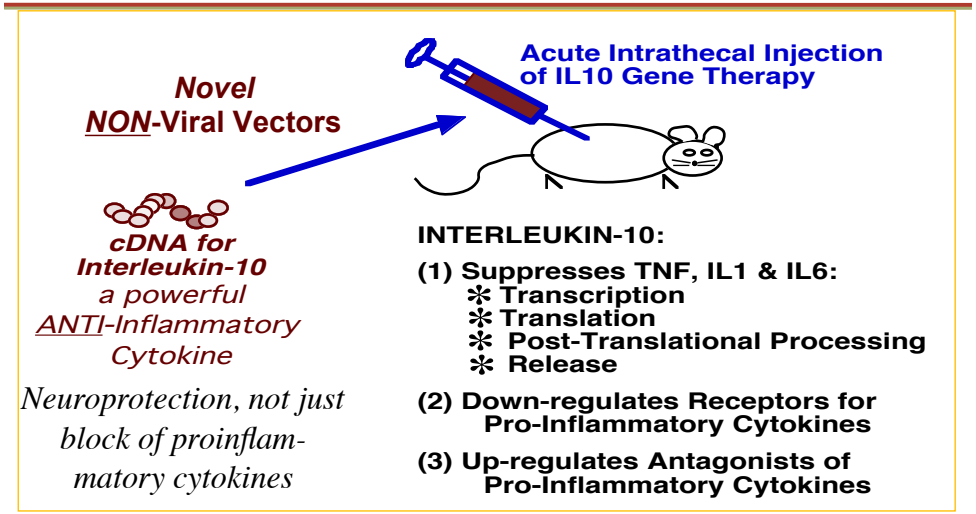
****2009:*** *Xalud Therapeutics was founded*

****2017:*** *Xalud received Investigational New Animal Drug status for dog OA*
****2018-ongoing:*** *U.S. & Australia approval for human OA clinical trials; Underway!*



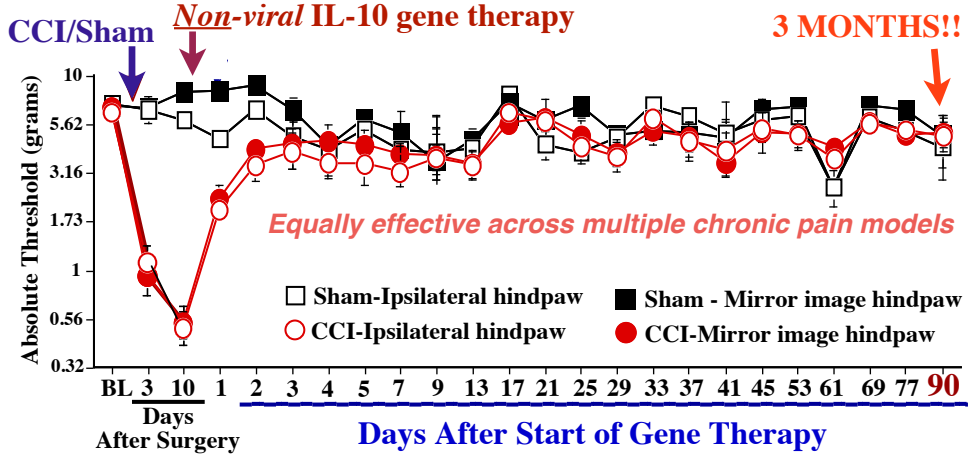
IL-10 Protein

Non-Viral Gene Therapy to Induce Interleukin-10: your Body's Own ***ANTI***-inflammatory Cytokine



Intrathecal *Non*-Viral Interleukin-10 Gene Reverses Chronic Constriction Injury (CCI) Induced Neuropathic Pain for 3+ Months

(Sloane et al., Gene Therapy '09; Soderquist et al. Pharmaceut. Res. '10)



Extending *Non*-Viral Interleukin-10 Gene Therapy to Pet Dogs in chronic pain: *intrathecal, intra-articular*

IL-10 gene therapy treats real disease – disease NOT controlled by any currently available pain drugs -- not just rodent models of pain

pet dogs otherwise euthanized as nothing else works

Dogs, Dogs and more Dogs!

Subjects in the initial Blinded Osteoarthritis Study

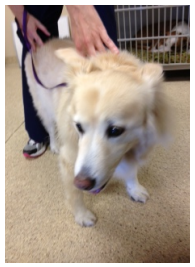
~ new MayDay funding recently awarded to extend this ~

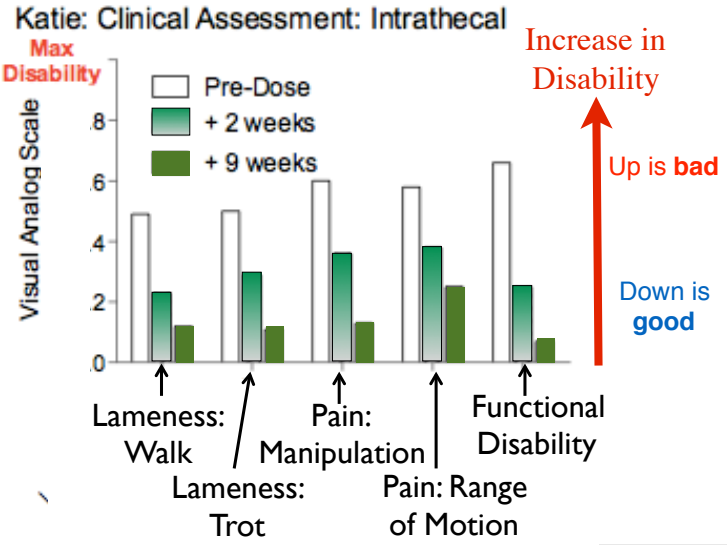
Non-viral IL-10 gene therapy treats real disease – disease NOT controlled by any currently available pain drugs -- not just rodent models of pain

pet dogs otherwise euthanized as nothing else works

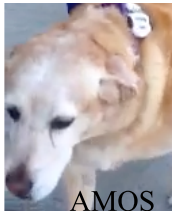
Canine Neuropathic Pain

single dose of non-viral interleukin-10 gene therapy





Chavez et al., MS in prep. 2019



Canine Osteoarthritis

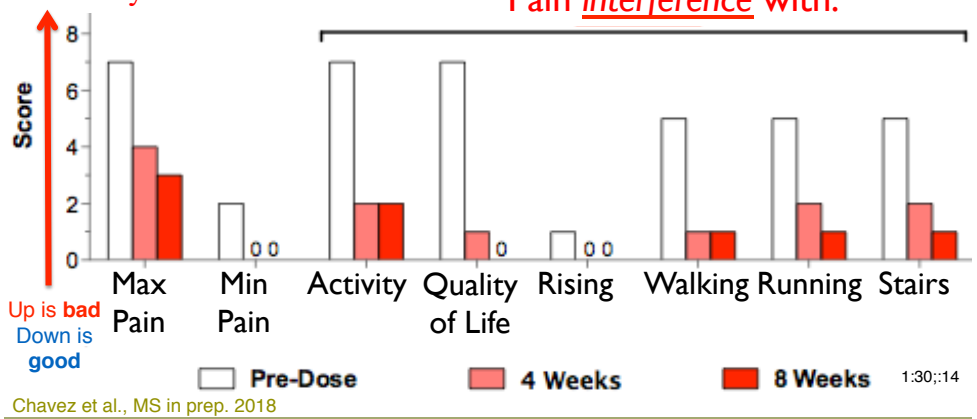
single dose of non-viral IL-10 gene therapy

Amos: Owner Assessment: Intra-articular (elbow)

Long duration efficacy ~ PLUS! :

50% Reduction in Concomitant Medications

Pain *interference* with:



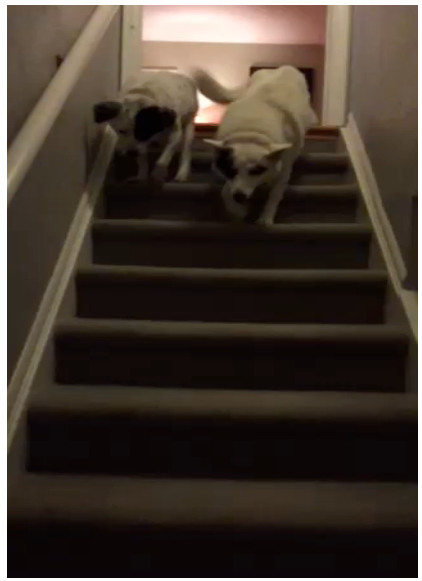
Chavez et al., MS in prep. 2018

Louise

single dose of non-viral interleukin-10 gene therapy

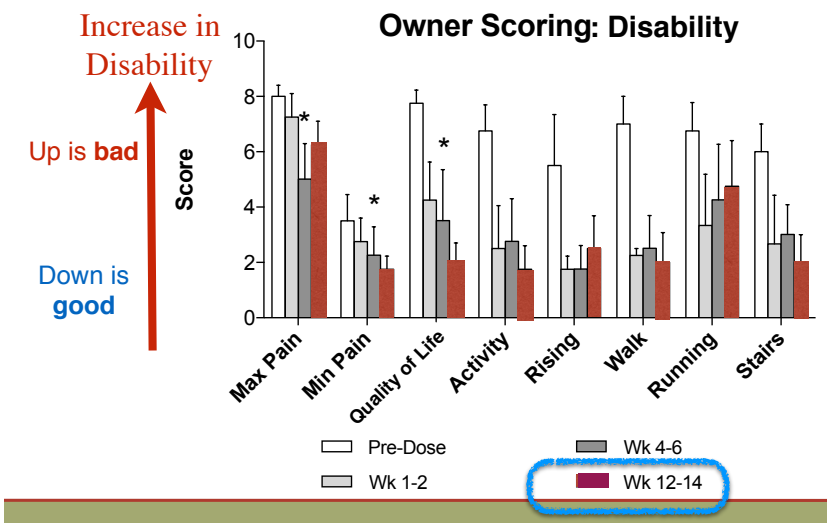
Before Bilateral Elbow Intra-articular Injection

2 Months Later: no further treatment



Compiled Data: Single Dose Open-Label OA Dog Study

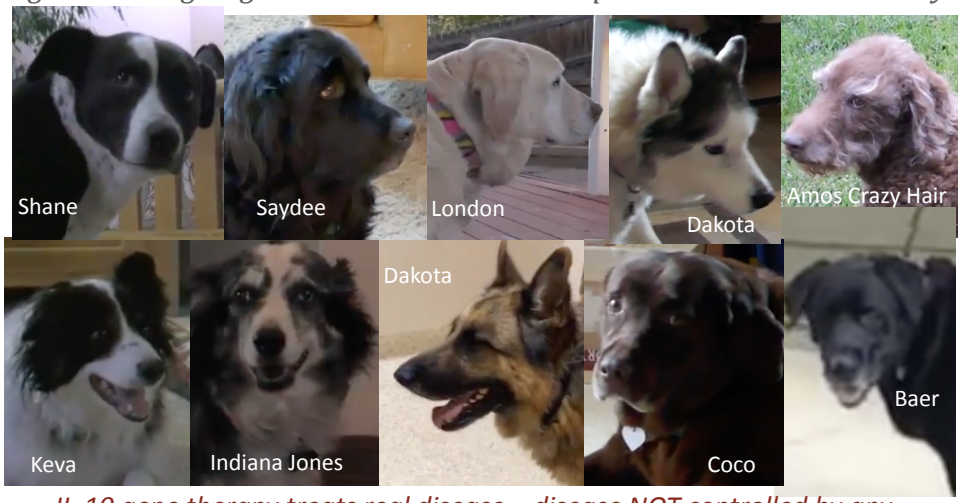
***Single* Intra-articular Dose (Males & Females): effective *3+ Months*!**



Chavez et al., MS in prep. 2018

MayDay Project: Dogs, Dogs and more Dogs!

Dogs in the ongoing Double Blinded Dose Response Osteoarthritis Study



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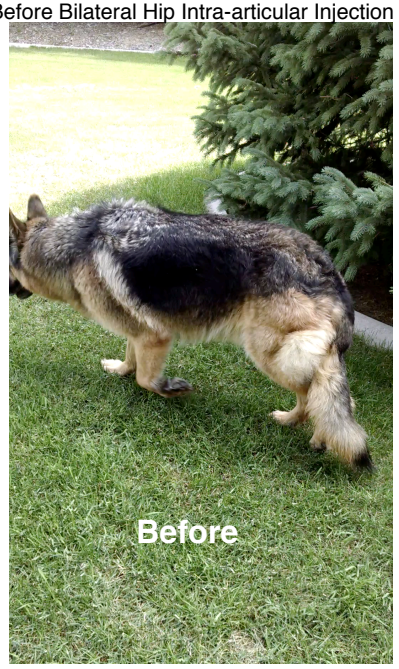
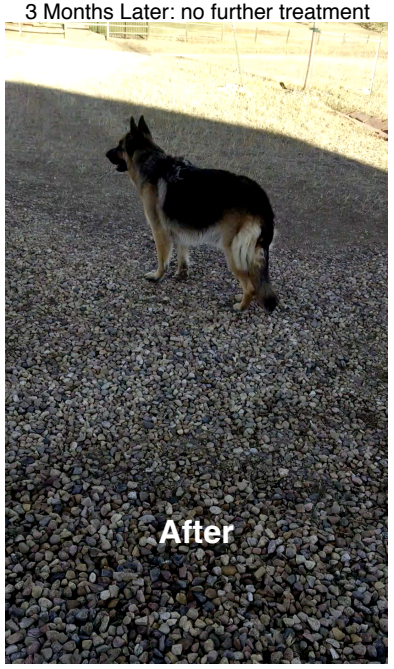
Dakota: in double blinded IL10 osteoarthritis study

Before Bilateral Hip Intra-articular Injection

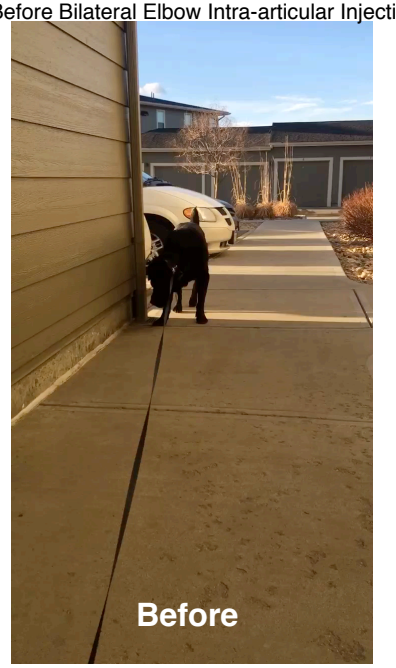


3 Months Later: no further treatment

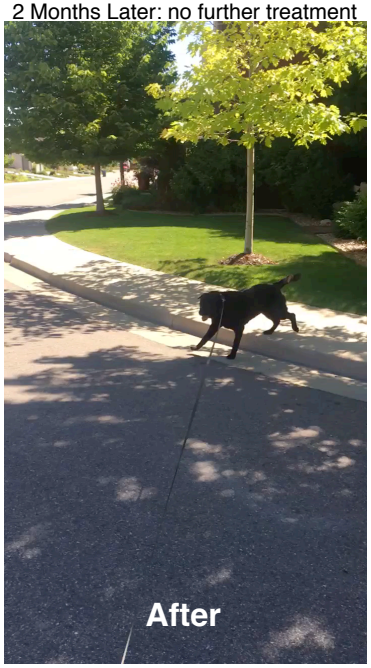


Baer: in double blinded IL10 osteoarthritis study

Before Bilateral Elbow Intra-articular Injection



2 Months Later: no further treatment



61

Ebony: in double blinded IL10 osteoarthritis study

Before Bilateral Elbow Intra-articular Injection

1 Month Later: no further treatment

Owner reports that, before treatment, Ebony had not run in many years

62

Tucker: in double blinded IL10 osteoarthritis study

Bilateral Hip Intra-articular Injection

63

64

How Does i.t. IL-10 Gene Therapy Work?

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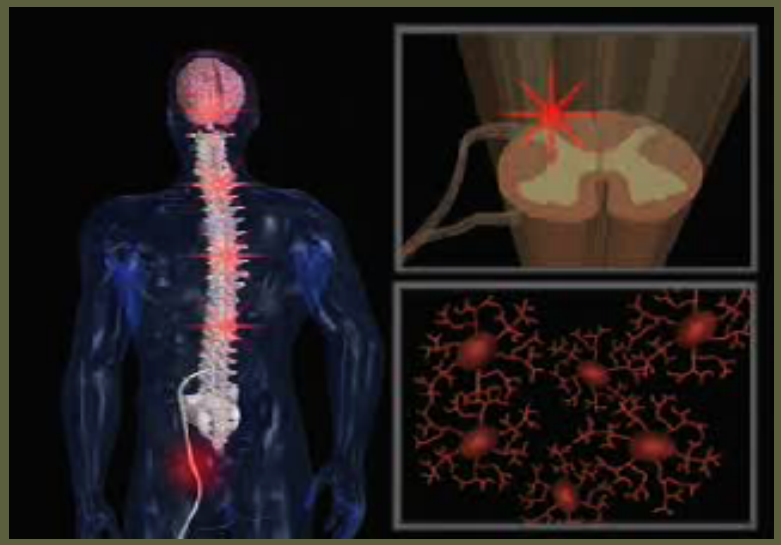

Conclusions

- Immunology is important; glial cells: volume controls
- Glial cells do not care about normal pain
- Glial responses can create and maintain enhanced pain:
  - *Physiologically* as part of the ancient Sickness Response
  - *Pathologically* when triggered by neuropathy, cancer, etc
  - *Pharmacologically* by clinically relevant opioids
- Glial activation now also linked to opioid tolerance, opioid dependence/withdrawal, opioid reward
- Proinflammatory cytokines are key
- Targeting glia & glial products may provide a novel approach to pain control & increases opioid efficacy

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