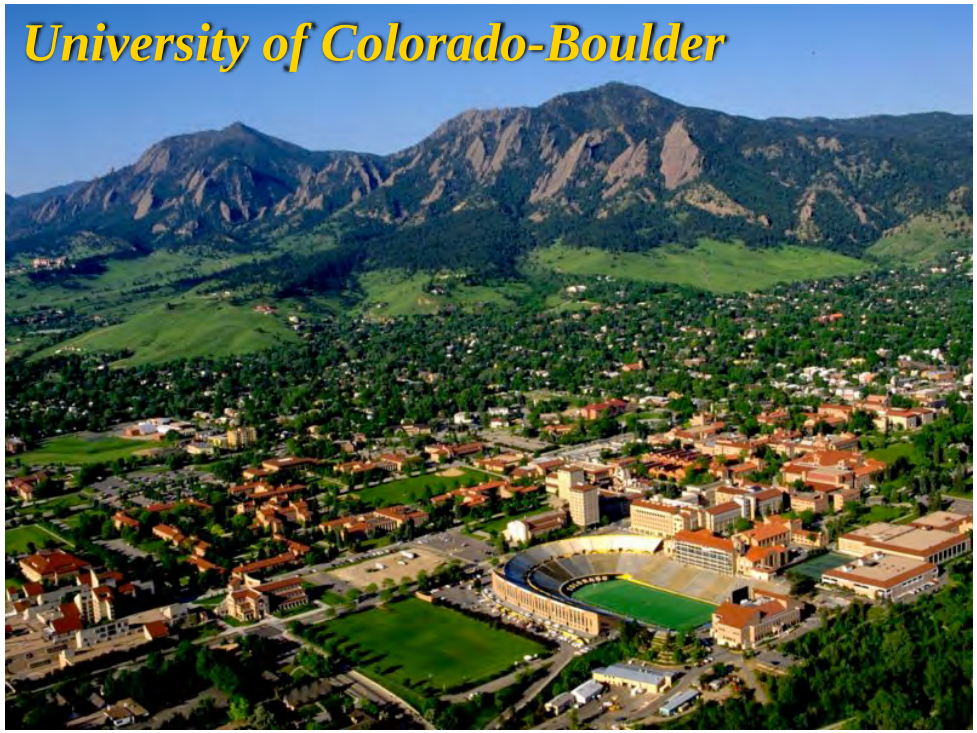


Financial Disclosures

- **Research funding from:**
  - > NIH (NIDCR, NIDA, NINDS)
  - > Department of Defense
  - > Amyotrophic Lateral Sclerosis Alliance
  - > Prize4Life
  - > National Multiple Sclerosis Society
  - > McManus Charitable Trust
  - > Adenosine Therapeutics
  - > Targacept
  - > Craig Hospital
  - > Paralyzed Veterans of America
  - > American Kennel Club
- **Xalud Therapeutics:**
  - > Co-Founder
  - > Co-Chair Scientific Advisory Board

  Early stage startup;

  entirely Preclinical

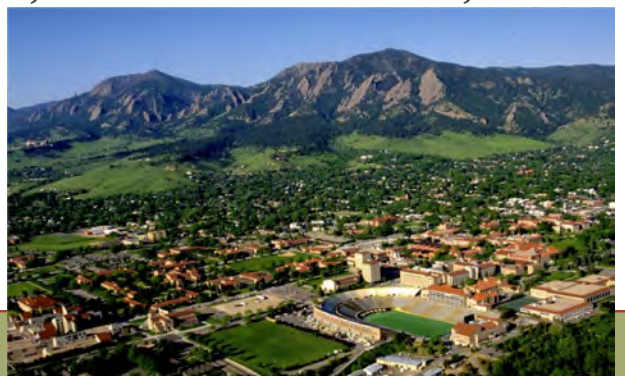
"Listening" & "Talking" to Neurons: Clinical Implications of Glial Dysregulation of Pain, Opioid Actions & Drugs of Abuse

Moving from Concept to Clinical Trials!

Linda R. Watkins

Psychology & Neuroscience, Univ. Colorado-Boulder

co-Founder, co-Chair Sci. Advis. Board, Xalud Therapeutics



"Listening" & "Talking" to Neurons: Clinical Implications of Glial Dysregulation of Pain, Opioid Actions & Drugs of Abuse

Moving from Concept to Clinical Trials!

Linda R. Watkins

Psychology & Neuroscience, Univ. Colorado-Boulder

co-Founder, co-Chair Sci. Advis. Board, Xalud Therapeutics

Global Concepts

- Views of pathological pain are changing
- Recognition of Non-Neuronal players in pain: Glia (*microglia & astrocytes)* in spinal cord & trigeminal nuc.
- Recognition of Non-Neuronal players in *opioid actions:* Glia disrupt the clinical efficacy of opioids, including morphine, oxycodone, remifentanyl, codeine, etc.
- Clinical implications of glial dysregulation of pain & opioid actions ... *glia targeting therapeutics are approaching clinical trials!*

Global Concepts

- Views of pathological pain are changing
- Recognition of Non-Neuronal players in pain: Glia (*microglia & astrocytes)* in spinal cord & trigeminal nuc.
- Recognition of Non-Neuronal players in *opioid actions:* Glia disrupt the clinical efficacy of opioids, including morphine, oxycodone, remifentanyl, codeine, etc.
- Clinical implications of glial dysregulation of pain & opioid actions ... *glia targeting therapeutics are approaching clinical trials!*

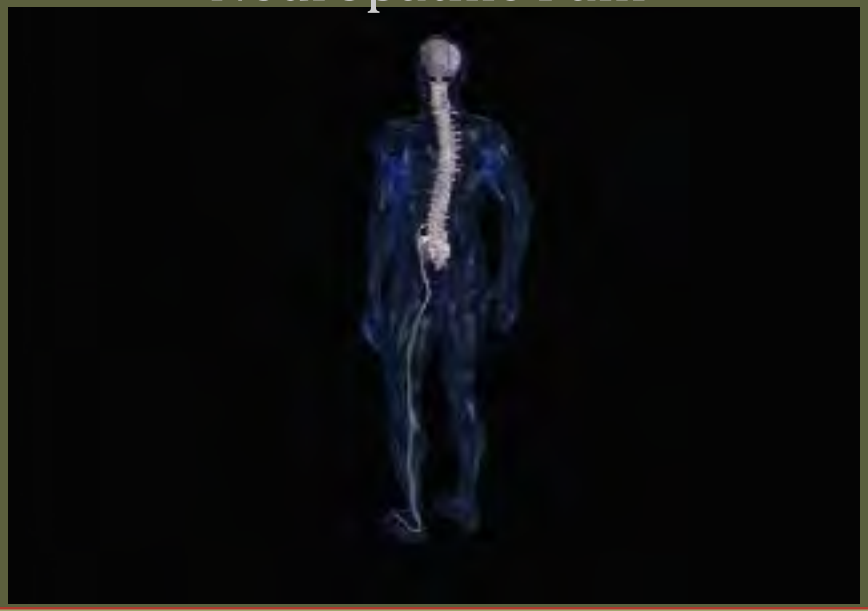
Global Concepts

- Views of pathological pain are changing
- Recognition of Non-Neuronal players in pain: Glia (*microglia & astrocytes)* in spinal cord & trigeminal nuc.
- Recognition of Non-Neuronal players in *opioid actions:* Glia disrupt the clinical efficacy of opioids, including morphine, oxycodone, remifentanyl, codeine, etc.
- Clinical implications of glial dysregulation of pain & opioid actions ... *glia targeting therapeutics are approaching clinical trials!*

Global Concepts

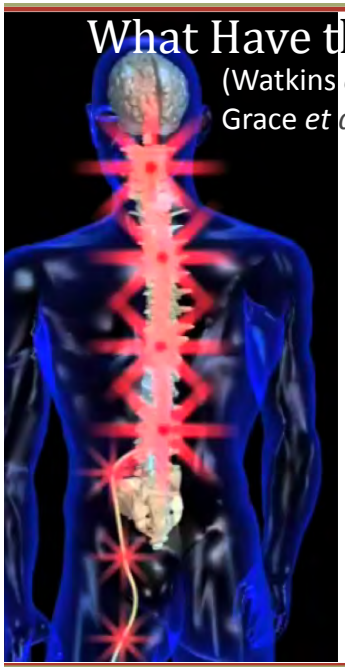
- Views of pathological pain are changing
- Recognition of Non-Neuronal players in pain: Glia (*microglia & astrocytes)* in spinal cord & trigeminal nuc.
- Recognition of Non-Neuronal players in *opioid actions:* Glia disrupt the clinical efficacy of opioids, including morphine, oxycodone, remifentanyl, codeine, etc.
- Clinical implications of glial dysregulation of pain & opioid actions ... *glia targeting therapeutics are approaching clinical trials!*

Neuropathic Pain



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 nerve 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…

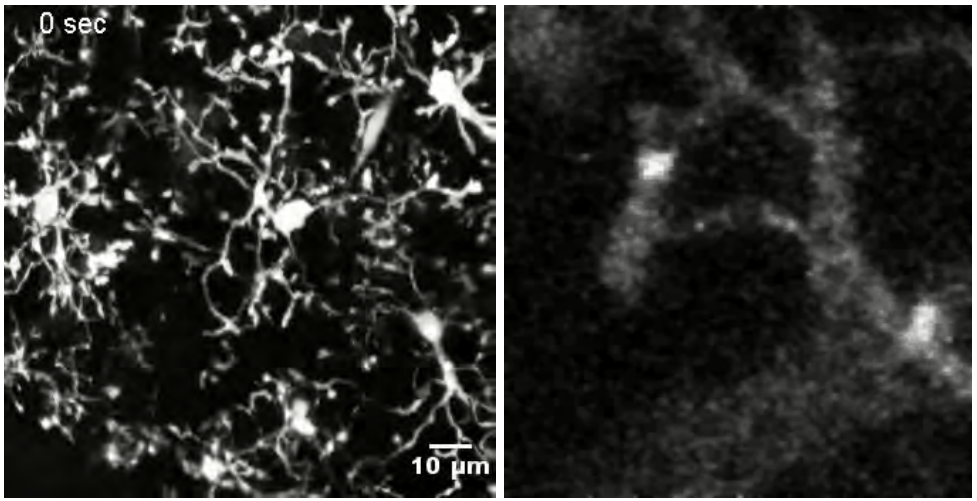
Suppressing spinal & trigeminal glial activation &/or glial proinflammatory cytokines:

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

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

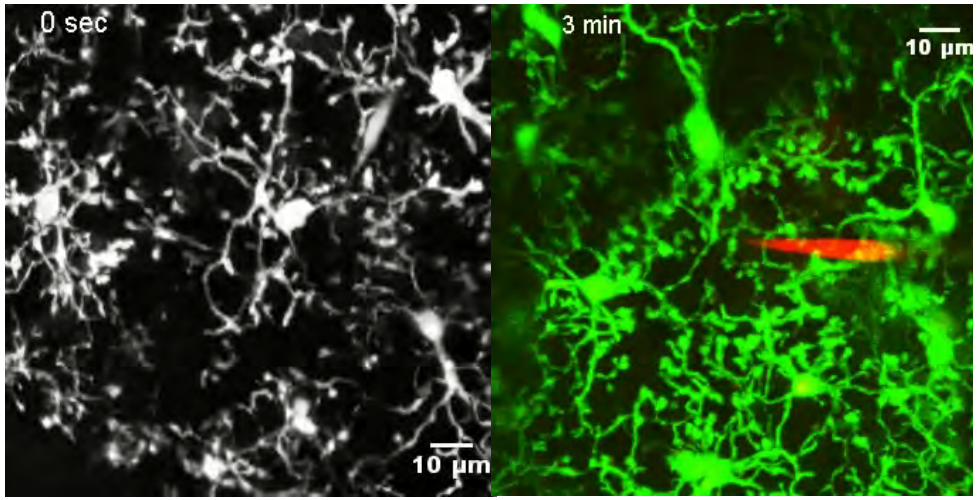
- Improve opioid analgesia
- Suppress opioid tolerance
- Suppress opioid dependence
- Suppress opioid reward linked to drug craving/drug abuse
- Suppress both opioid-induced respiratory depression & constipation

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

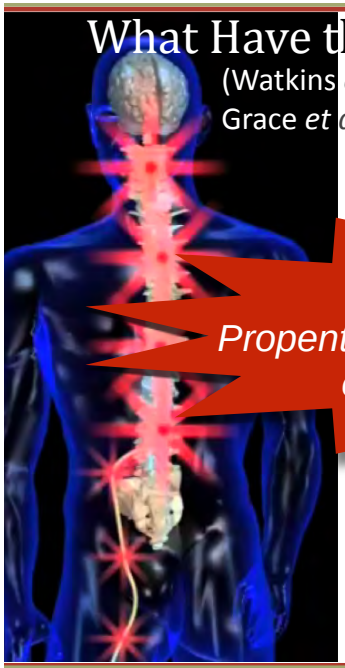
Microglia Actively Survey the CNS & Rapidly Respond to Challenge



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

What Have the Past 25 Years Revealed?

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



Glia (microglia, astrocytes) are *activated in every clinically-relevant model of enhanced*

But … Wait!

Propentofylline, minocycline, ibudilast, etc also affect neurons!

Suppressing glial activation &/or glial proinflammatory cytokines:

- *suppresses pain in every clinically-relevant model*
- returns pain to *normal*

CHEMO-GENETICS

provides proof of microglial dysregulation of pain

DREADDs: **D**esigner **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

CHEMO-GENETICS

definitive proof of microglial dysregulation of pain

DREADDs: **D**esigner **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

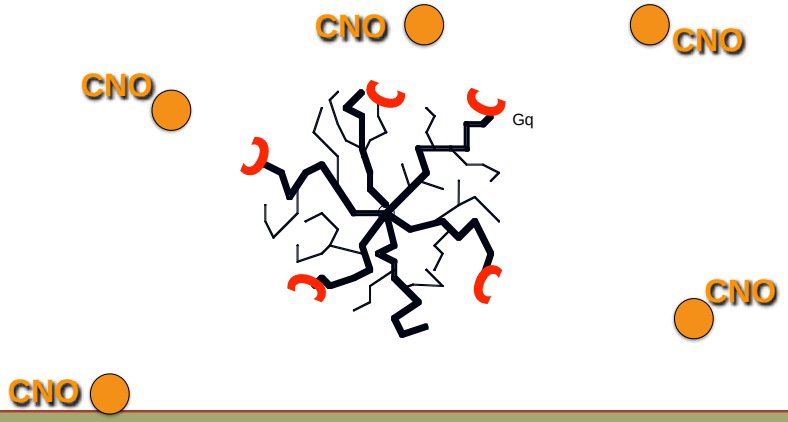
Gene Therapy is used to express, in a **cell type specific manner *in vivo***, either **excitatory** or **inhibitory** designer receptors that can *only* be activated by **CNO** (Clozapine-N-oxide, the designer drug)

Now, for the first time, we can very specifically turn "on" and turn "off" microglia at will!!

Urban and Roth, *Ann. Rev. Pharmacol. Toxicol.*, 2014

DREADDs: **D**esigner **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

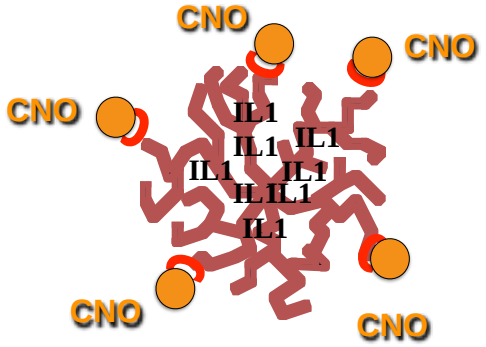
Excitatory DREADDs: CNO binds to expressed receptors *in vivo*, ***activating only*** microglia (CD68 promoter)



Grace et al. *Proc Soc Neurosci* '14; Grace et al. MS in review, '15

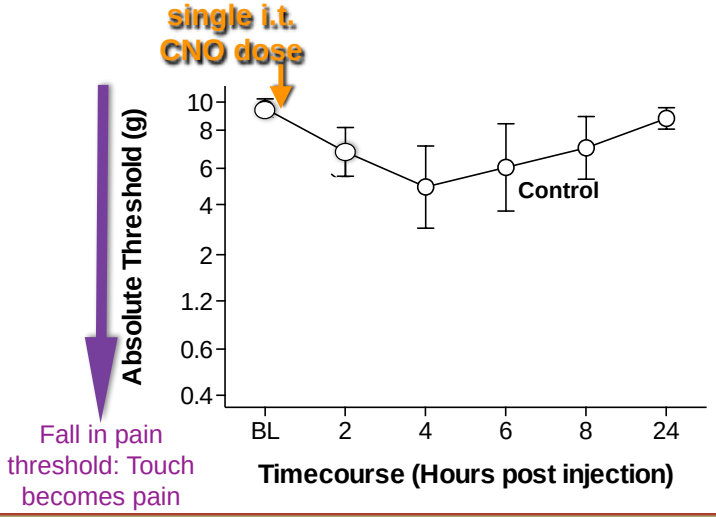
DREADDs: **D**esigner **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

Excitatory DREADDs: CNO binds to expressed receptors *in vivo*, ***activating only*** microglia (CD68 promoter)



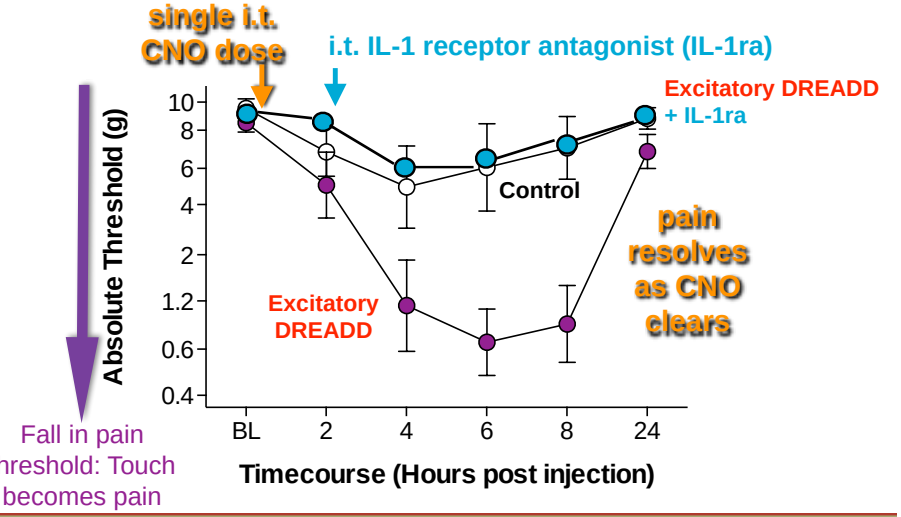
Grace et al. *Proc Soc Neurosci* '14; Grace et al. MS in review, '15

Excitatory DREADD: Selective microglia activation in spinal cord creates Interleukin-1 mediated pain



Grace et al. *Proc Soc Neuroscience* 2014; Grace et al. MS in review 2015

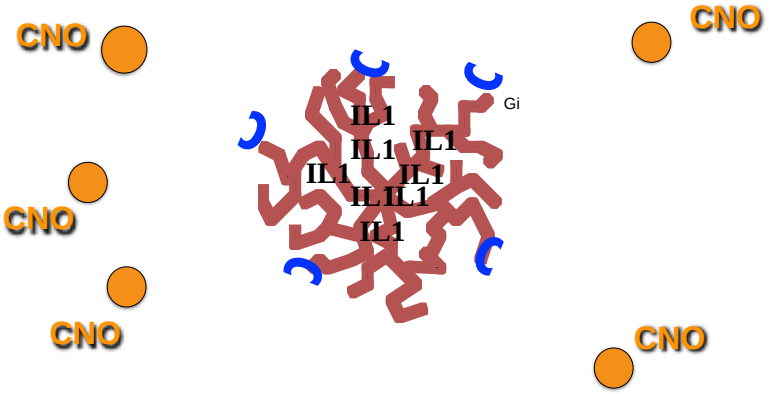
Excitatory DREADD: Selective microglia activation in spinal cord creates Interleukin-1 mediated pain



Grace et al. *Proc Soc Neuroscience* 2014; Grace et al. MS in review 2015

DREADDs: **D**esigner **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

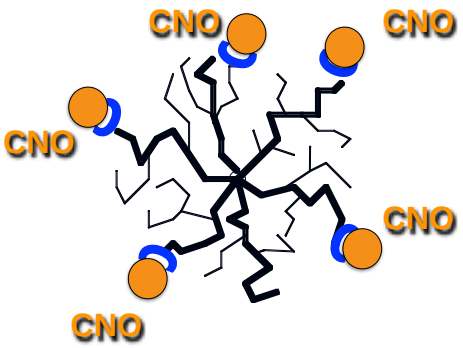
Inhibitory DREADDs: CNO binds to expressed receptors *in vivo*, **inhibiting *only*** microglia (CD68 promoter)



Grace et al. *Proc Soc Neurosci* '14; Grace et al. MS in review, '15

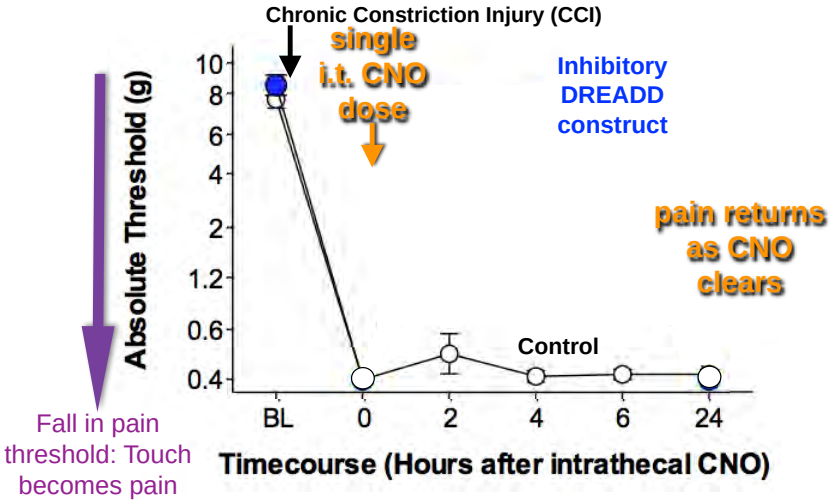
DREADDs: **D**esigner **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

Inhibitory DREADDs: CNO binds to expressed receptors *in vivo*, **inhibiting *only*** microglia (CD68 promoter)



Grace et al. *Proc Soc Neurosci* '14; Grace et al. MS in review, '15

Inhibitory DREADD: First definitive proof that microglial inhibition suppresses neuropathic pain

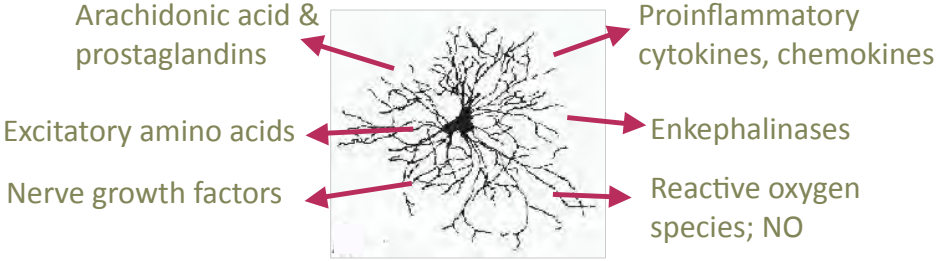


Grace et al. *Proc Soc Neuroscience* 2014; Grace et al. MS in review 2015

Glia Release Neuroexcitatory, Pain Enhancing Substances

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

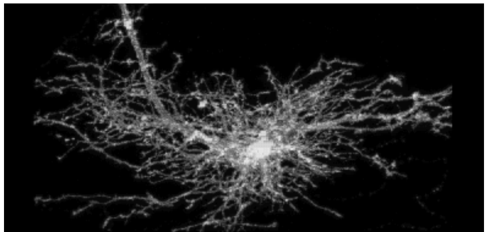
Activated glia release:



- ***Amplify pain signaling to spinal cord***
- ***Amplify pain transmission to 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 Response to Opioids



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

Proinflammatory Cytokines:

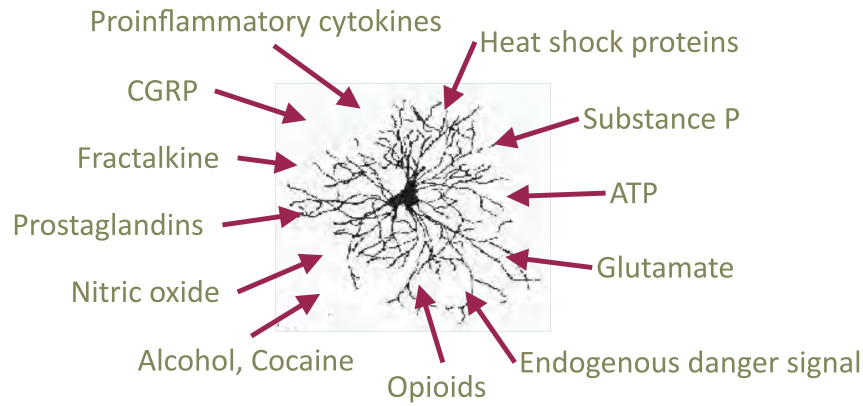
Tumor Necrosis Factor
Interleukin-1
Interleukin-6

↓

Neuroexcitation!

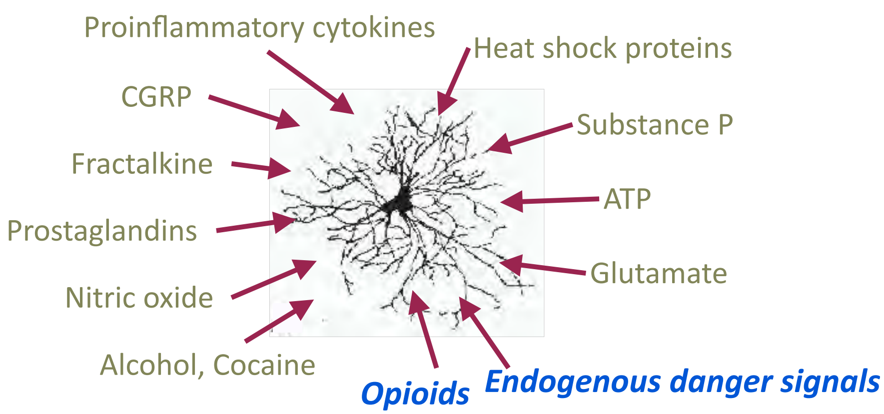
By *Enhancing* pain,
Opposes opioid analgesia

What Activates Glia?



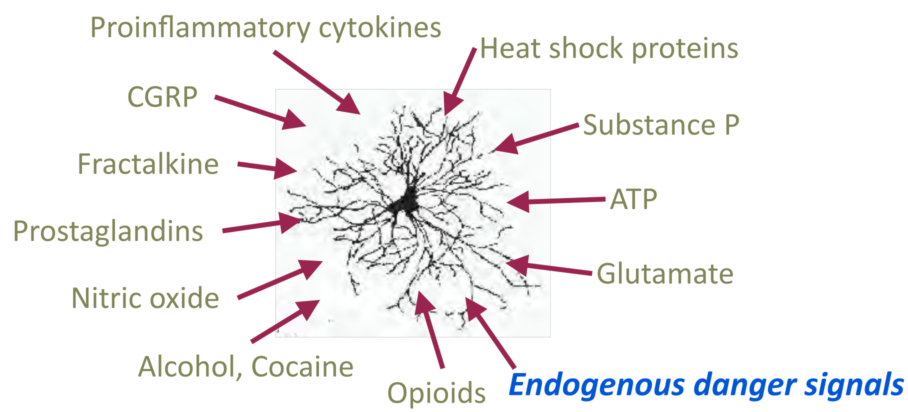
Watkins & Maier, *Nature Rev Drug Disc* 2003
Hutchinson *et al.*, *Pharmacol Reviews* 2011

What Activates Glia?



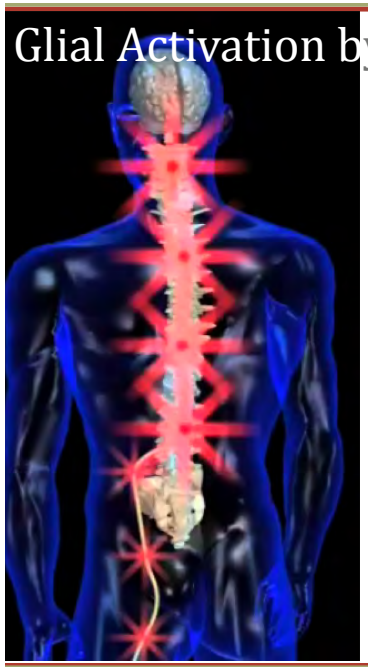
Watkins & Maier, *Nature Rev Drug Disc* 2003
Hutchinson *et al.*, *Pharmacol Reviews* 2011

What Activates Glia?



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

Glial Activation by Endogenous Danger Signals

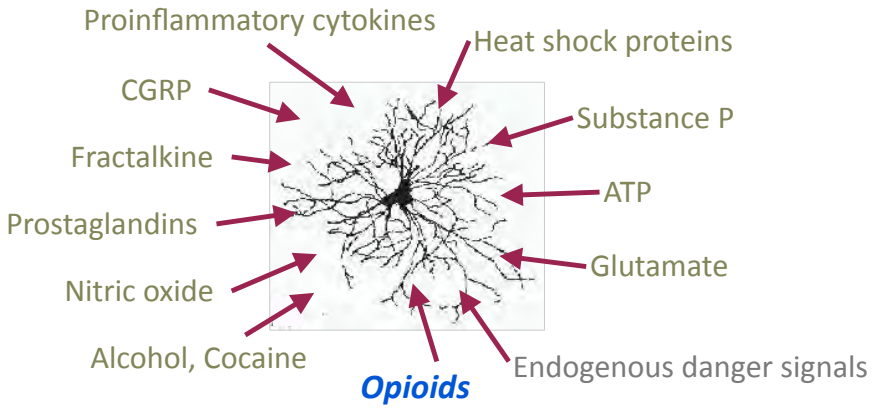


Endogenous danger signal activation of glia (microglia, astrocytes) implicated in pain in multiple rodent models, such as:

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

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

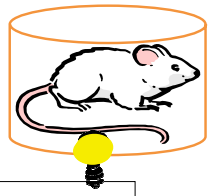
What Activates Glia?

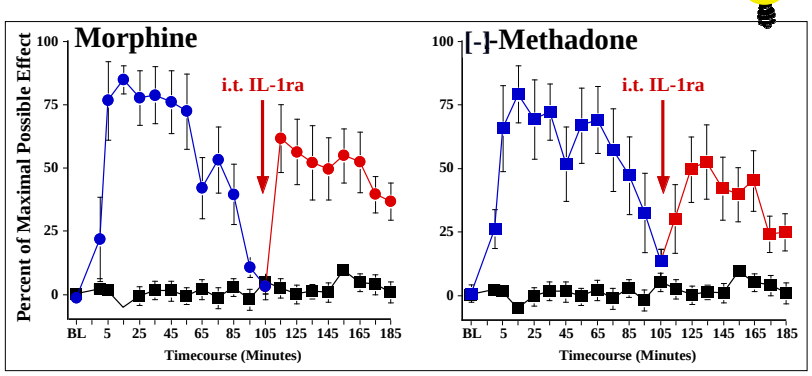


Watkins & Maier, *Nature Rev Drug Disc* 2003
Hutchinson *et al.*, *Pharmacol Reviews* 2011

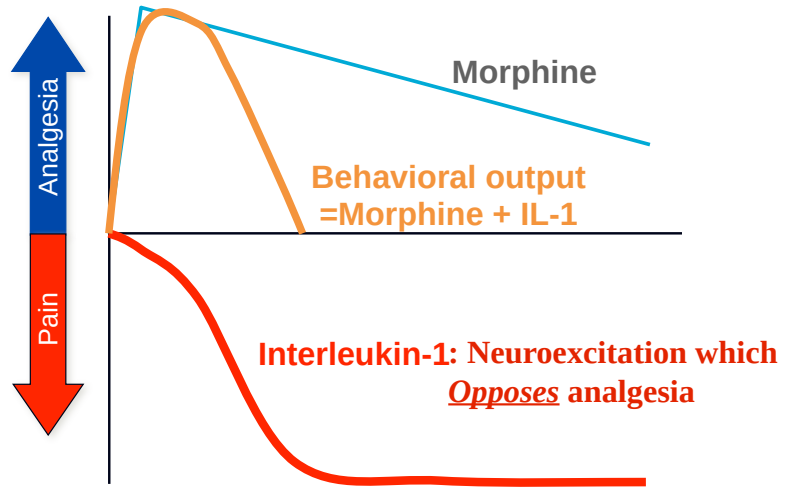
Spinal Glial Activation Opposes Both Intrathecal Morphine & Intrathecal Methadone Analgesia

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



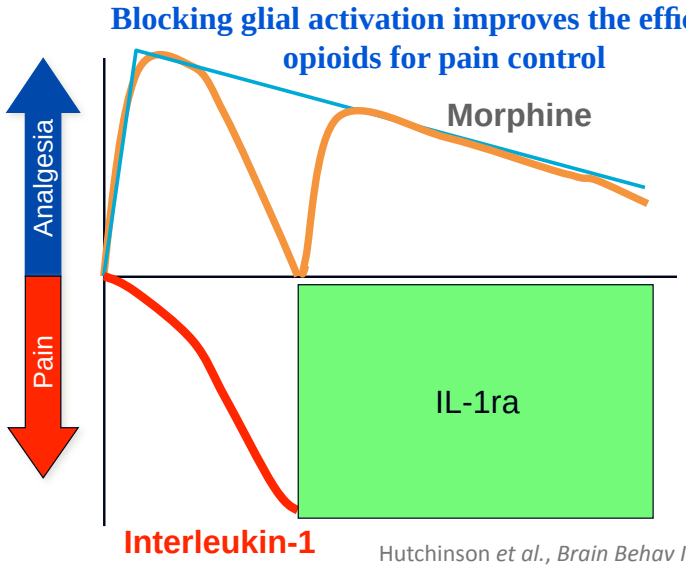


Blocking Spinal Interleukin-1 Unmasks Morphine Analgesia



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

Blocking Spinal Interleukin-1 Unmasks Morphine Analgesia



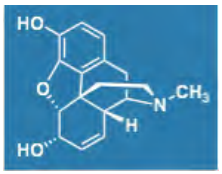
Hutchinson *et al.*, *Brain Behav Immunity* 2008

Opioid effects are different for neurons & glia

Opioids exist as mirror-image stereo-isomers

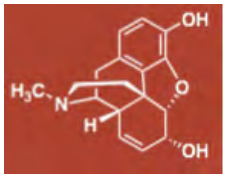
(-)-Morphine

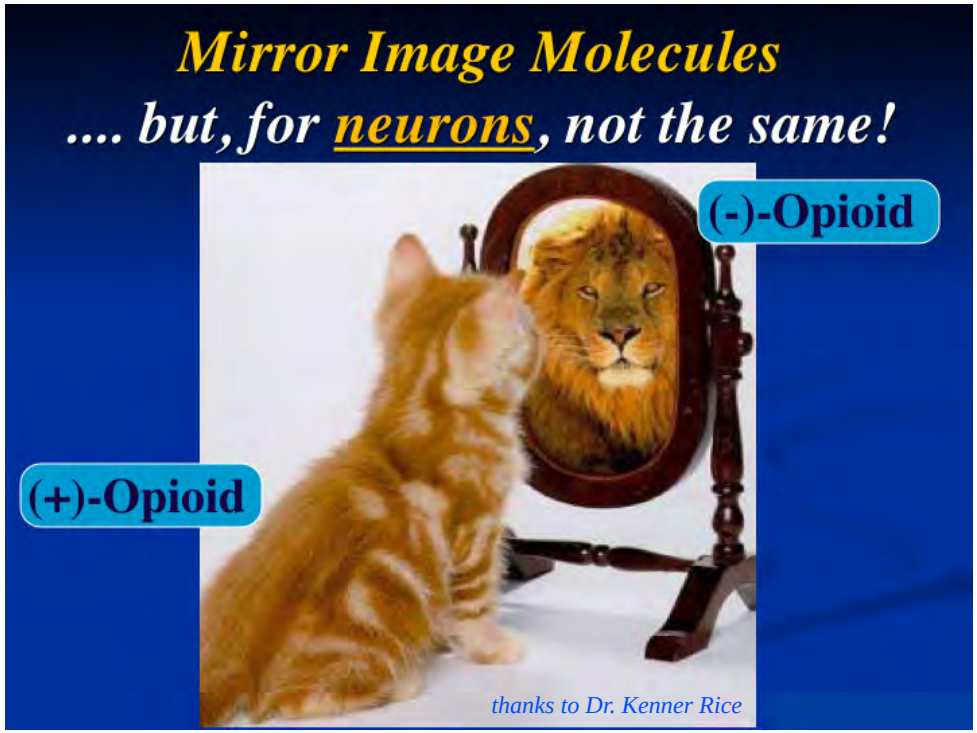
- Binds to μ-opioid receptors
- Powerful analgesic



(+)-Morphine

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

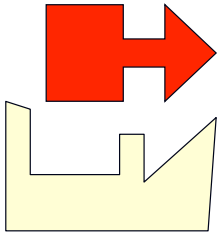




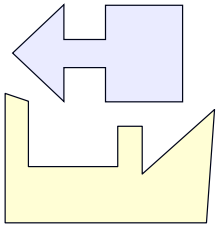
Opioid Effects are Different for Neurons vs. Glia

Neuronal Receptors are Stereoselective

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



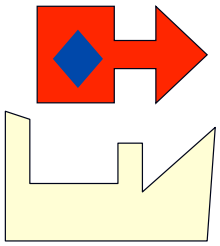
[+]Morphine:
INActive Agonist
at Classical Opioid Receptors
on Neurons



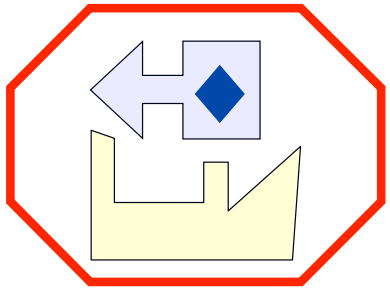
Opioid Effects are Different for Neurons vs. Glia

Neuronal Receptors are Stereoselective

[-]-Naloxone & [-]-Naltrexone:
Active Antagonists
at Classical Opioid Receptors
on Neurons



[+]-Naloxone & [+]-Naltrexone:
INactive Antagonists
at Classical Opioid Receptors on
Neurons



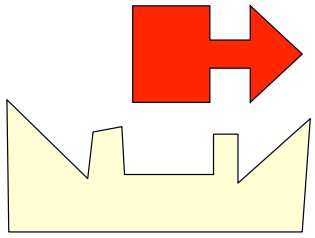
This Point is KEY

Opioid Effects are Different for Neurons vs. Glia

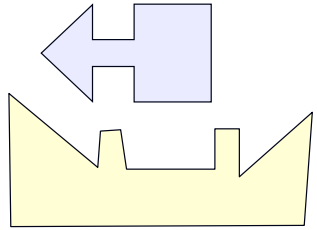
GLIAL Receptors are <u>Not</u> Stereoselective

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

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



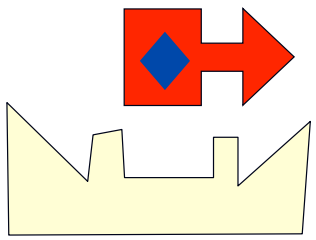
[+]-Morphine:
Active Agonist
at Glial Opioid Receptor



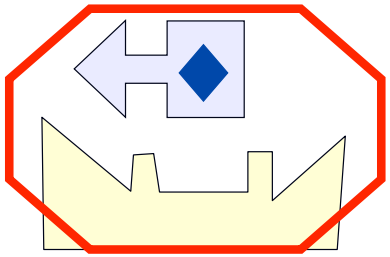
Glial opioid receptor -- Fits BOTH [-] & [+]-enantiomers

Glial Non-Stereoselectivity Extends to Opioid Antagonists!

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

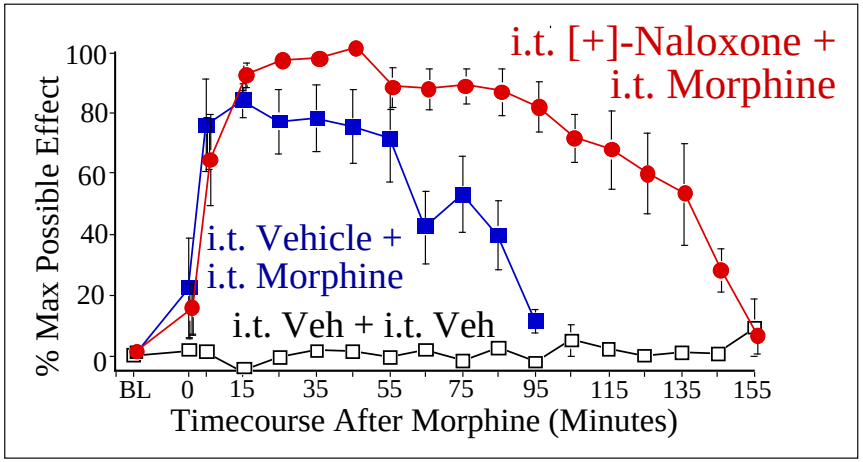


[+]-Naloxone &
[+]-Naltrexone:
Active Antagonists
at Glial Opioid receptor



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

Neuronally INACTIVE (+)-Naloxone 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 prevent glial activation, *or*
* create a long-lasting version of (+)-naloxone that only blocks glia

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

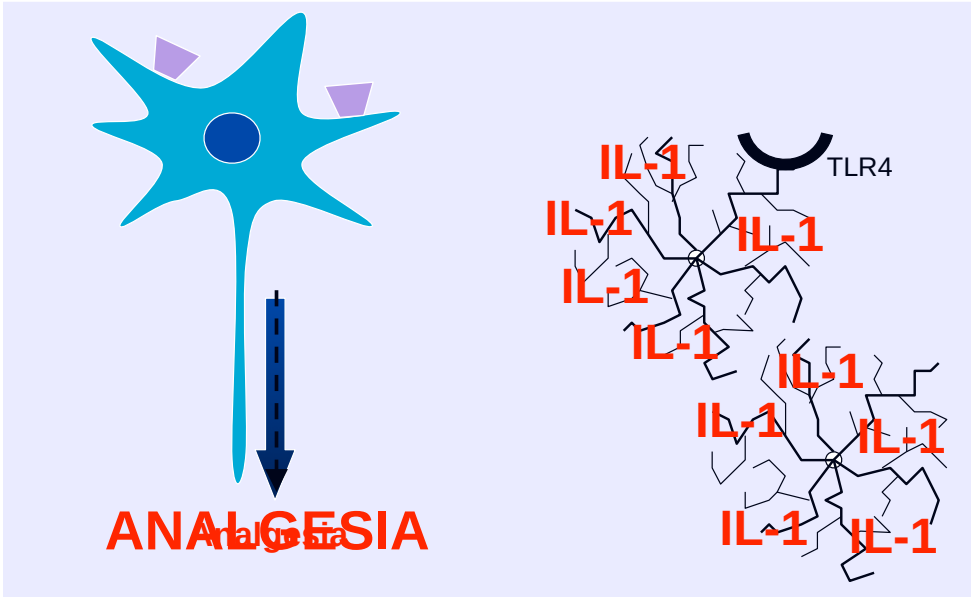
TLR4 detects:

* Bacteria (lipopolysaccharide; LPS)
* endogenous danger signals (stress/damage/death)

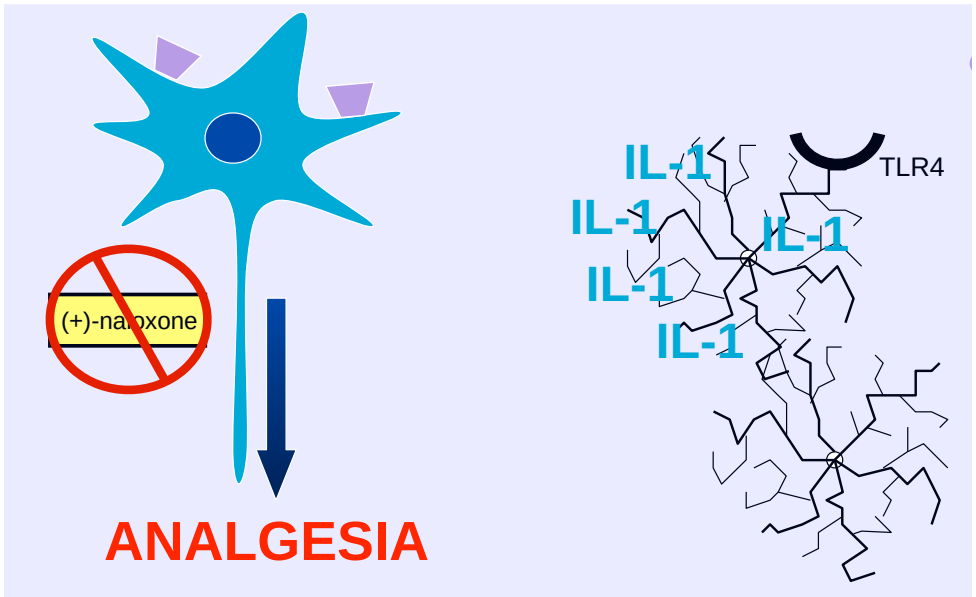
* ***All classes of opioids used clinically***

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

Opioid Activation of Glia Suppresses Analgesia



Opioid Activation of Glia Suppresses Analgesia: Blocked by (+)-Naloxone



Glial TLR4

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

is also activated by Endogenous Danger Signals that drive Neuropathic Pain

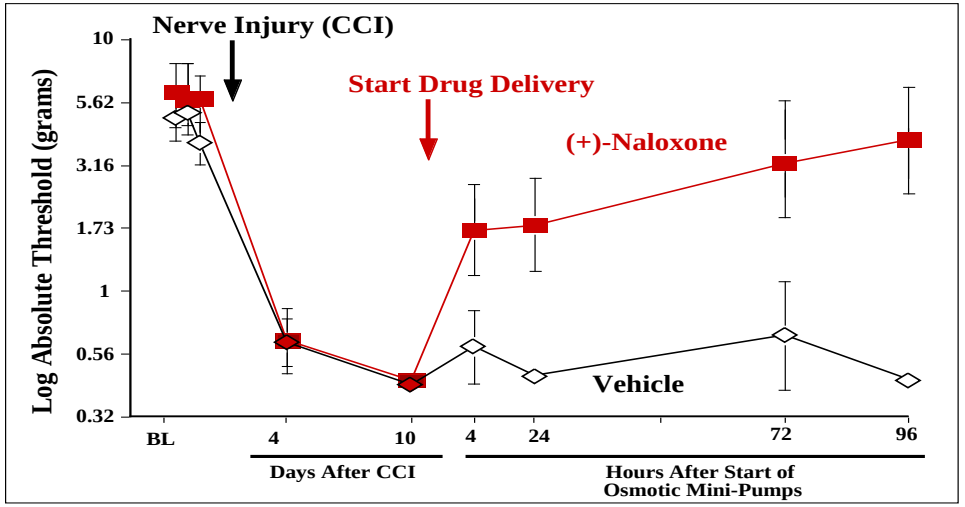
If that is True, then....

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

* Might (+)-Naloxone also be a stand-alone treatment for neuropathic pain?

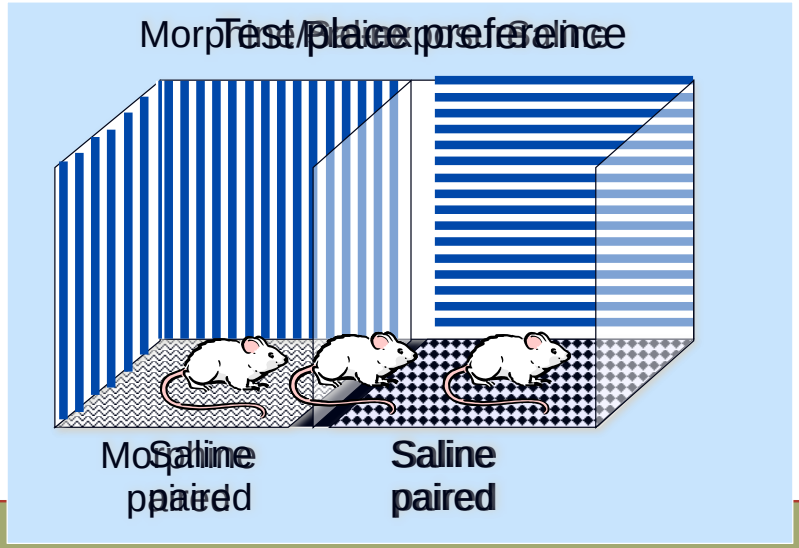
Toll Like Receptor-4 (TLR4):

(+)-Naloxone, a *non*-opioid TLR4 antagonist, reverses neuropathic pain and inhibits glial activation

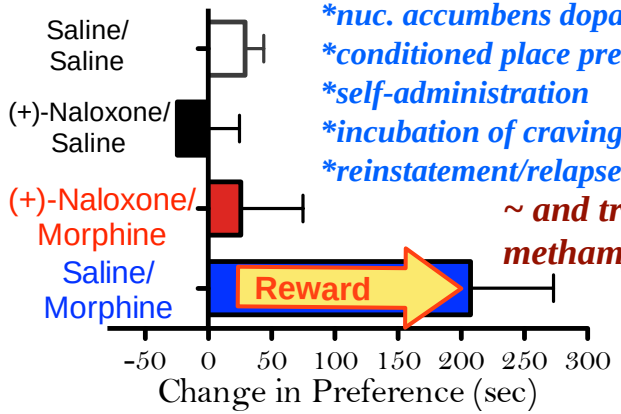


Hutchinson et al., *Brain Behav. Immun.* 2008

Glia & Opioid Reward: Conditioned Place Preference



(+)-Naloxone Blocks Morphine Reward: Blockade of Morphine-Induced Conditioned Place Preference



Suppresses opioid:

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

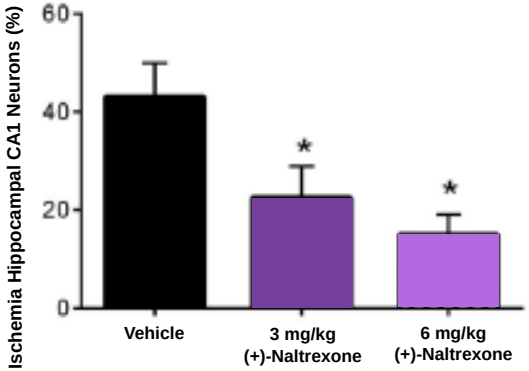
~ and true for cocaine, and methamphetamine as well

Opioids: Hutchinson et al., *Journal of Neuroscience*, 2012; Theberge et al., *Biol. Psychiatry*, 2013;
Cocaine: Northcutt et al., *Molecular Psychiatry* 2015

Beyond Pain! (+)-Naltrexone Inhibits:

Brain Neuronal Death after Heart Attack/CPR

(CA1 region of Hippocampus)



Dosing: 2x daily for 2 days starting 30 minutes AFTER heart attack & cardiopulmonary resuscitation

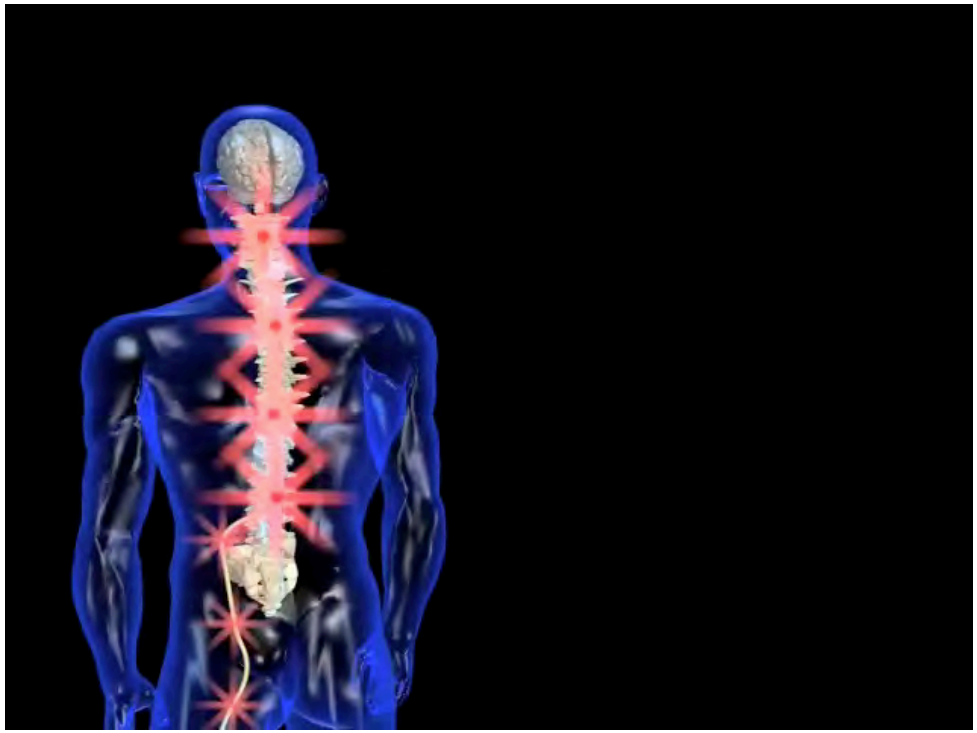
HA/CPR: Grace et al., *BBI*, 2015 in press

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 it won't just be for opioids (e.g. effects of alcohol, cocaine, methamphetamine are all amplified by glia!!)

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



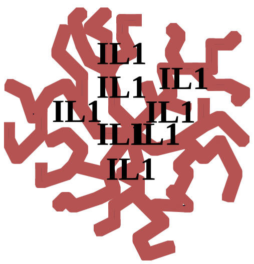
States of Glial Activation: Not Just "Off" or "On" Anymore!

Basal State: Boring but Vigilant

Hains et al. *Journal of Pain* 2010; Hains et al. *Journal of Neuroimmunology* 2011; Loram et al. *Brain Behavior Immunity* 2012; Grace et al., MS in prep. 2014

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

Activated State: Proinflammatory

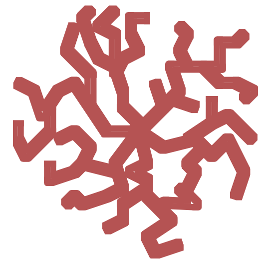


Hains et al. *Journal of Pain* 2010; Hains et al. *Journal of Neuroimmunology* 2011; Loram et al. *Brain Behavior Immunity* 2012; Grace et al., MS in prep. 2014

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. *Journal of Pain* 2010; Hains et al. *Journal of Neuroimmunology* 2011; Loram et al. *Brain Behavior Immunity* 2012; Grace et al., MS in prep. 2014

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??

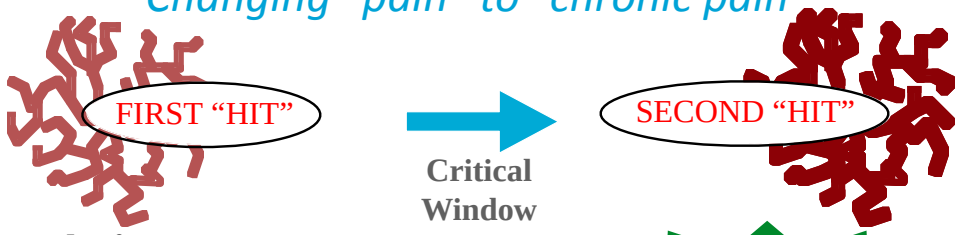
2-Hit Hypothesis: A 2nd "Hit" Can Create a Faster, Strong, Longer Glial Response

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

Critical Window of Time

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; *J. Neuroimm.* '11; Loram et al. *BBI* '11; Grace et al., in review '15

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

Changing "no pain" to "pain"

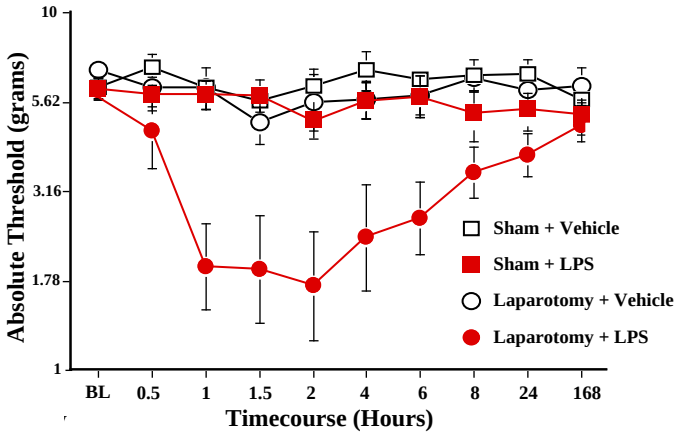
Exploratory Abdominal Surgery (Laparotomy) OR Sham

Mild Systemic Inflammation (Lipopolysaccharide) OR Vehicle

Hains et al. *J. Pain* '10; Hains et al. *J. Neuroimm.* '11; Loram et al. *BBI* '11

Prior Surgery (Laparotomy): Changes "no pain" to "pain"

Prior Surgery: "Primes" for Pain



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

Changing "acute pain" to "chronic pain"

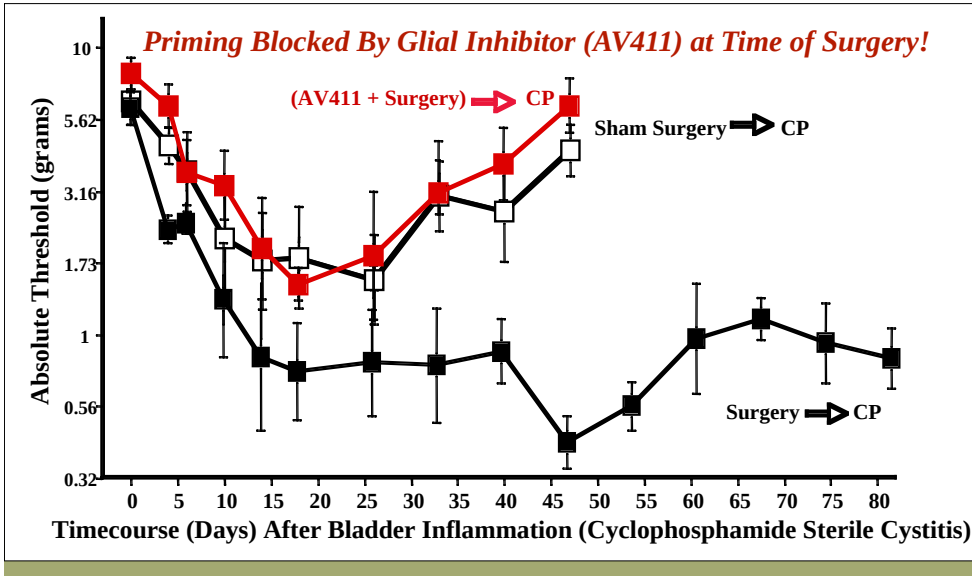
Exploratory Abdominal Surgery (Laparotomy) OR Sham

(+/- Glial Inhibitor)

Sterile Bladder Inflammation

Hains et al. *J. Pain* '10; Hains et al. *J. Neuroimm.* '11; Loram et al. *BBI* '11

Prior Surgery: Changes "pain" to "chronic pain" ~ prevented by glial activation inhibitor



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

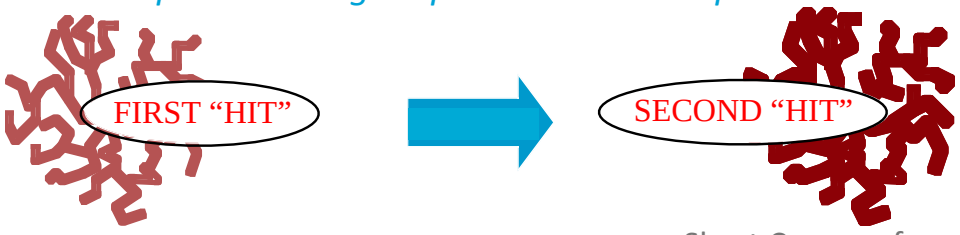
Then …..

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!

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"



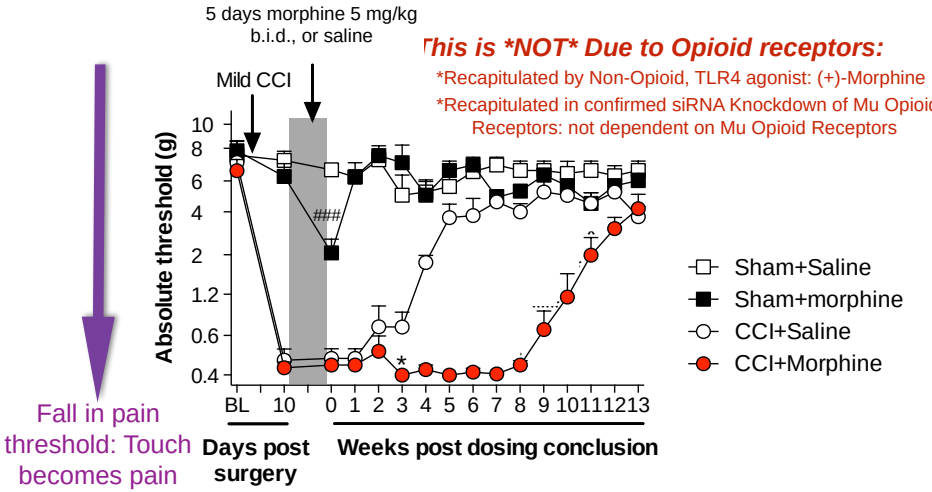
Trauma versus Sham

Short Course of Morphine Early Post-Trauma

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

Grace et al. *Proc Soc Neuroscience* 2014; Grace et al. MS in prep; Ellis et al. MS in prep

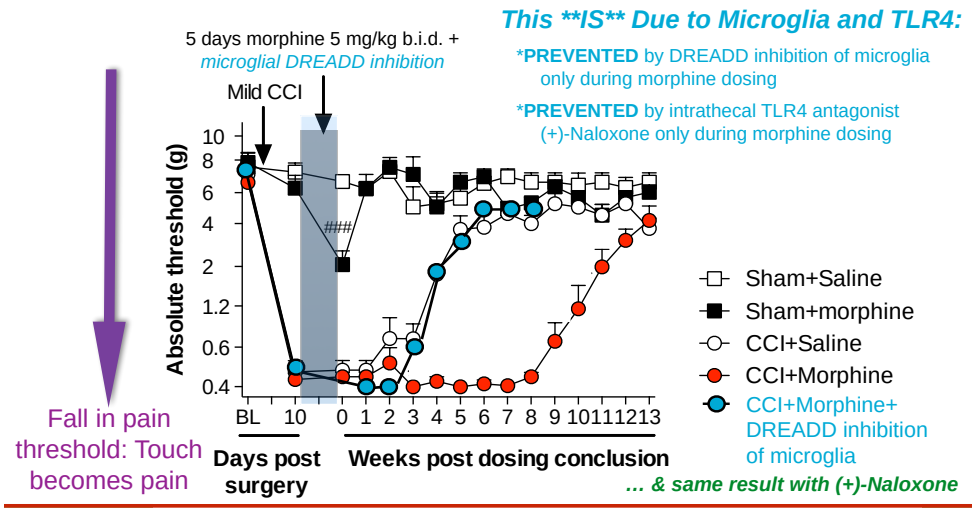
Peri-Trauma Morphine: Changes "pain" to "chronic pain" after peripheral nerve injury



Fall in pain threshold: Touch becomes pain

Grace et al., *Soc. for Neuroscience* 2014; Grace et al. *MS in review 2015*

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



This **IS** Due to Microglia and TLR4:

*__PREVENTED__ by DREADD inhibition of microglia only during morphine dosing

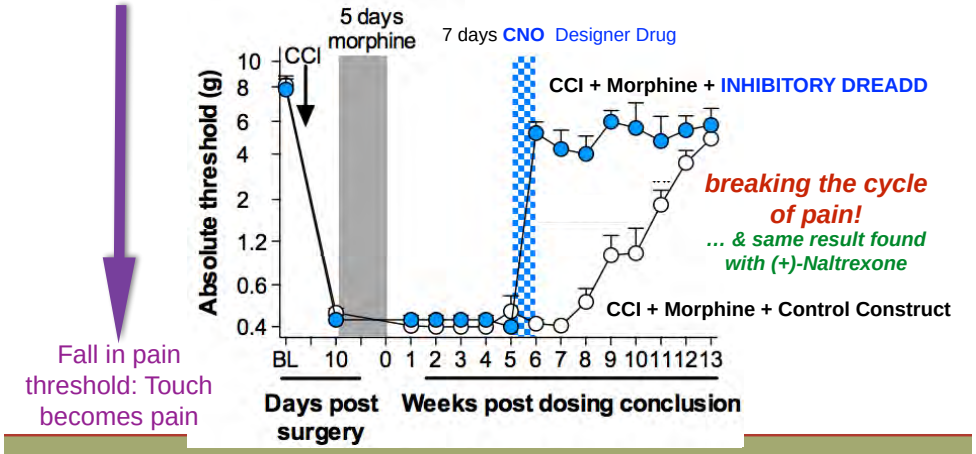
*__PREVENTED__ by intrathecal TLR4 antagonist (+)-Naloxone only during morphine dosing

... & same result with (+)-Naloxone

Grace et al., *Soc. for Neuroscience* 2014; Grace et al. *MS in review 2015*

Peri-Trauma Morphine: Conversion of "pain" to "chronic pain" driven by **Microglia** & **TLR4**

Long Duration Maintenance of Morphine-Amplified Pain **IS** Due to Microglia and TLR4: PERMANENTLY REVERSED by treatment >1 month later



Grace et al., *Soc. for Neuroscience* 2014; Grace et al. *MS in review 2015*

Based on the Strength of the 25 year Glial Story for Pain, Across Labs & Across Diverse Animal Models: *Translation to Clinical trials for Osteoarthritis & Neuropathic Pain*

Xalud Therapeutics (entirely pre-clinical/pre-IND to date)

XT202: (+)-Naltrexone; *blood brain barrier permeable TLR4 antagonist*;
Awarded a Depart. of Defense grant to expedite moving to Investigational New Drug status in 2016 for neuropathic pain and drug abuse; DoD grant for spinal cord injury pain

XT101, XT150: *non-viral interleukin-10 (IL-10) gene therapies*;
Awarded an NIH U44 grant to move to Investigational New Drug status in 2015; applying for osteoarthritis (OA; intra-articular) & neuropathic pain (intrathecal); positioning for Clinical Trials in humans and veterinary populations; NIH SBIR grant for multiple sclerosis; American Kenner Club grant for translation to dogs

A Focus on Interleukin-10 (IL-10)

a potent endogenous Anti-inflammatory cytokine

The importance of central *pro*-inflammatory cytokines across many neuropathic pain models, across so many independent labs, suggested that an *anti*-inflammatory cytokine approach to suppress glial activation might prove successful for neuropathic pain control

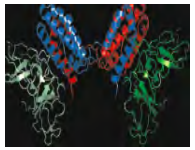
Plus ~ proinflammatory cytokines are important in diseases like ARTHRITIS: might local, intra-articular IL-10 help arthritis as well?

***1992:** Our University of Colorado-Boulder research lab began studying spinal glial dysregulation of pain by pro-inflammatory cytokines; pure basic science*

*** 2000:** We began studying Interleukin-10 for its potential in pain control, spearheaded by Dr. Erin Milligan (now Associate Professor, Univ. New Mexico)*

*** 2009:** Therapeutic potential for Neuropathic Pain of peripheral and central origin led to the formation of Xalud Therapeutics to move IL-10 gene therapy to clinical trials*

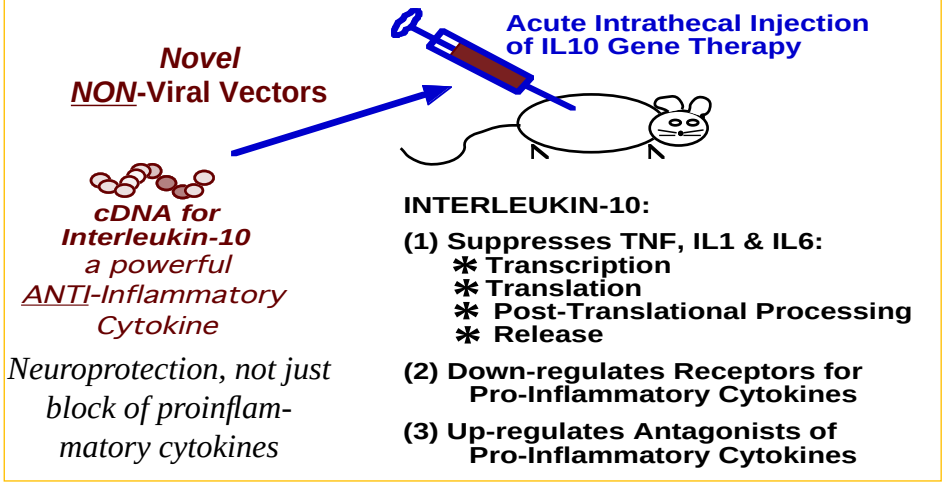
*** 2015:** After 10 generations of improvements since 2000, and testing in mice, rats, and pet dogs, now preparing Investigational New Drug application to the FDA*



IL-10 Protein

Xalud Therapeutics

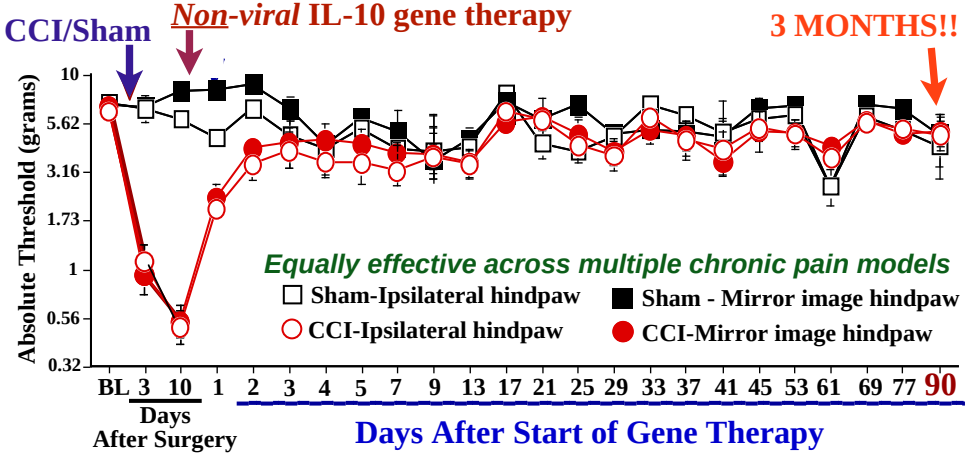
pronounced "Salud!" ~ "To your health!";
"X" for IL-10
Non-Viral Gene Therapy to Induce Interlelukin-10,
your Body's Own *ANTI*-inflammatory Cytokine



Neuroprotection, not just block of proinflam-matory cytokines

Intrathecal *Non*-Viral Interleukin-10 Gene Therapy (XT-101) Reverses CCI-Induced Neuropathic Pain for 3+ Months

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



Extending XT-101 to Pet Dogs in chronic pain

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!

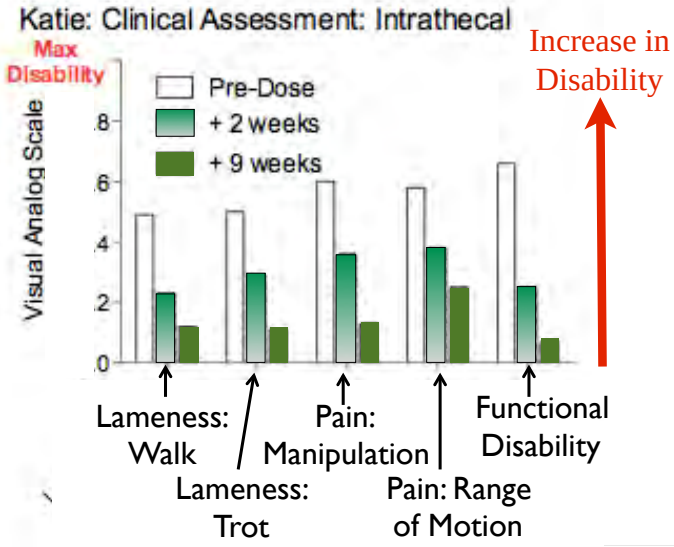
Subjects in the initial Blinded Osteoarthritis Study to date

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

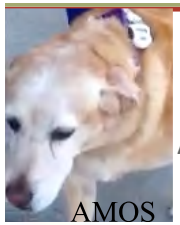
pet dogs otherwise euthanized as nothing else works

Canine Neuropathic Pain

single XT-101 dose



NEUROPATHIC PAIN - INTRATHECAL

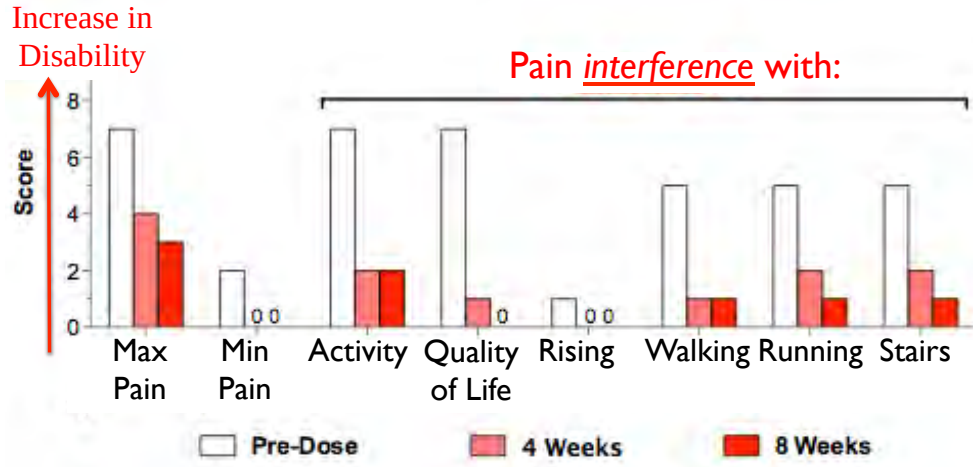


Canine Osteoarthritis

single XT-101 dose

Amos: Owner Assessment: Intra-articular (elbow)

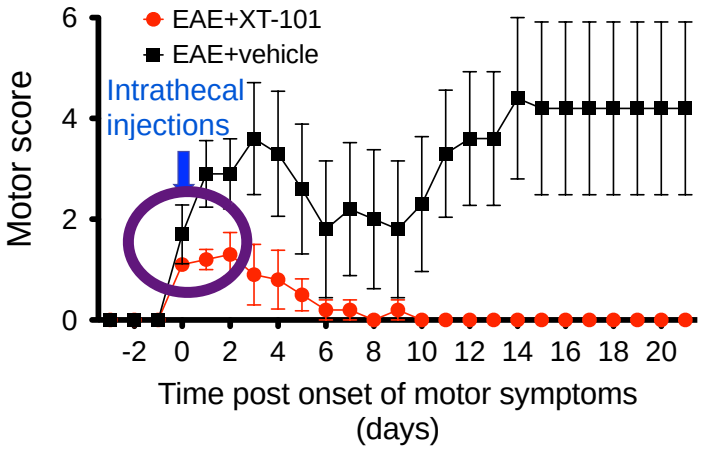
50% Reduction in Concomitant Medications



OSTEOARTHRITIS / INTRA-ARTICULAR

Blockade of Rat Multiple Sclerosis (EAE) Paralysis by i.t. Non-Viral IL-10 Gene Therapy (XT101)

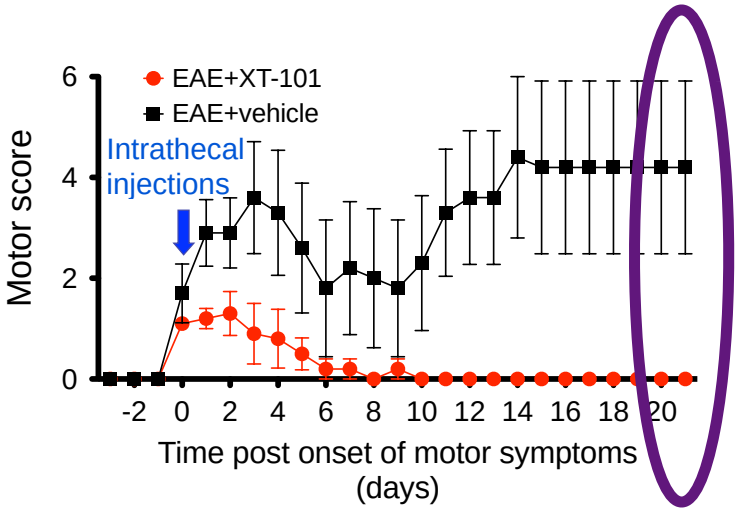
Grace et al., 2014 MS in prep



0=normal; 1 = tail tip paralysis; 2 = full tail paralysis;
3 = hindleg weak; 4 = partial hindleg paralysis;
5 = full hindleg paralysis; 6 = partial foreleg paralysis

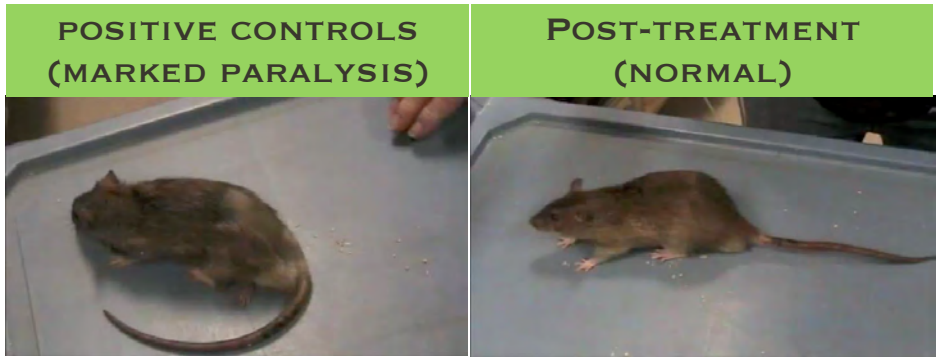
Blockade of Rat Multiple Sclerosis (EAE) Paralysis by i.t. Non-Viral IL-10 Gene Therapy (XT101)

Blockade of Rat Multiple Sclerosis (EAE) Paralysis by i.t. Non-Viral IL-10 Gene Therapy (XT101)

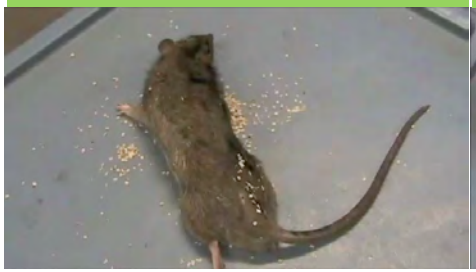
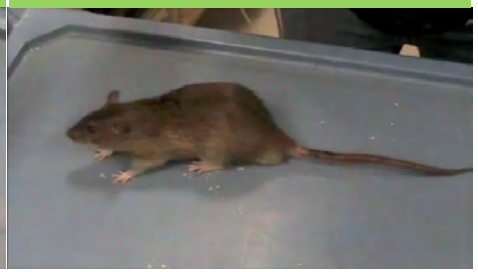


0=normal; 1 = tail tip paralysis; 2 = full tail paralysis;
3 = hindleg weak; 4 = partial hindleg paralysis;
5 = full hindleg paralysis; 6 = partial foreleg paralysis

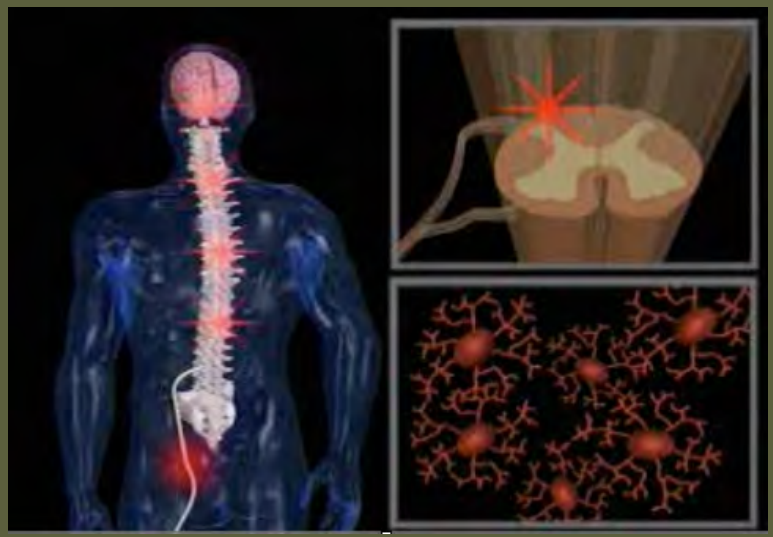
Blockade of Rat Multiple Sclerosis (EAE) Paralysis by i.t. Non-Viral IL-10 Gene Therapy (XT101)



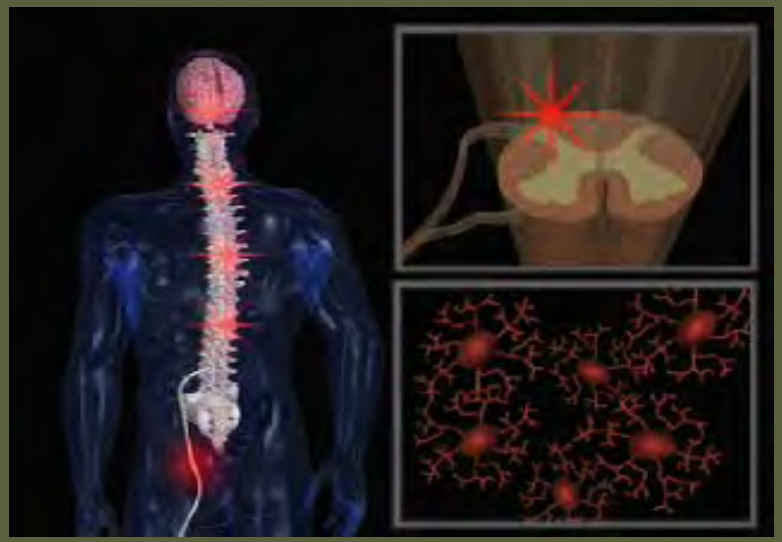
Blockade of Rat Multiple Sclerosis (EAE) Paralysis by i.t. Non-Viral IL-10 Gene Therapy (XT101)

POSITIVE CONTROLS (MARKED PARALYSIS)	POST-TREATMENT (NORMAL)
	

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



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



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

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

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

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

Conclusions

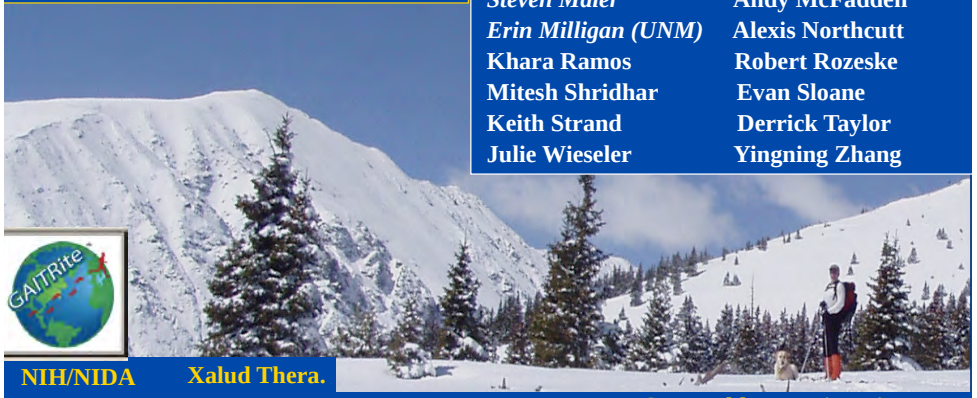
- Immunology is important; glial cells: volume controls
- Glial cells do not care about normal pain
- Glial responses can create and maintain enhanced pain:
  - *Physiologically* as part of the ancient Sickness Response
  - *Pathologically* when triggered by neuropathy, cancer, etc
  - *Pharmacologically* 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

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

With Thanks to all my Collaborators, NIH Review Panels, NIDA, NINDS, NIDCR, DoD, American Kennel Club!

CU-Boulder - Watkins/Maier lab:
Jose Amat — **Amanda Ellis**
Peter Grace — ***Mark Hutchinson (UA)***
Susannah Lewis — **Lisa Loram**
Steven Maier — **Andy McFadden**
Erin Milligan (UNM) — **Alexis Northcutt**
Khara Ramos — **Robert Rozeske**
Mitesh Shridhar — **Evan Sloane**
Keith Strand — **Derrick Taylor**
Julie Wieseler — **Yingning Zhang**



NIH/NIDA
Kenner Rice
Jon Katz
Yavin Shaham

Xalud Thera.
Ray Chavez
John Forsayeth

CU-Boulder: Biochem/Chem
Xiaohui Wang
Hubert (Hang) Yin

Mountain Ridge Vet
Rob Landry, D.V.M.

CU-Boulder: MCDB
Leslie Leinwand

Univ. NC
Dan Urban. ***Bryan Roth***

CU-Boulder: Engineering
Ryan Soderquist, ***Melissa Mahoney***

CU-Boulder: Neurosci
Casey O'Neil, Ryan Bachtell

CU-Denver: Medicine
Paco Herson