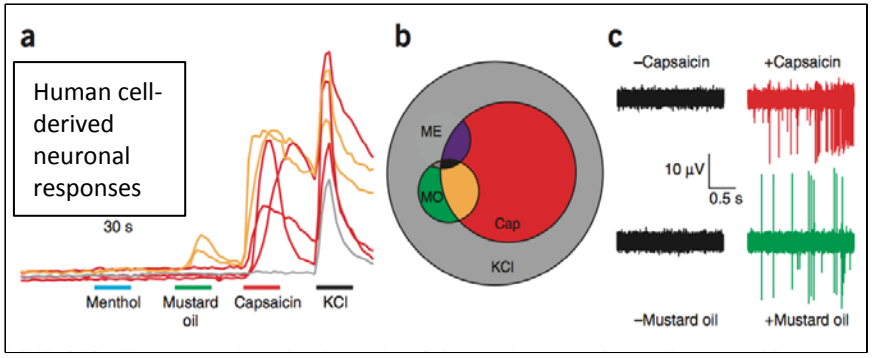
Human skin derived-fibroblasts converted into peripheral sensory neurons – a new pain model

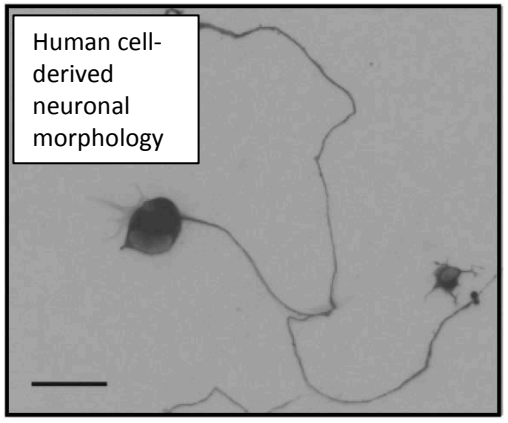
- Concern about translational value of rodent physiology to human conditions
- Human nervous system tissue is difficult to obtain
- Easy-to-obtain human skin-derived fibroblasts were reprogrammed into functional classes of neurons, including nociceptors, using a cocktail of lineage-determining transcription factors
- The cells exhibit appropriate morphological and biophysical characteristics and reflect human disease states (*i.e.* familial dysautonomia)
- This constitutes a major advance in modeling human pain conditions

nature neuroscience

Modeling pain *in vitro* using nociceptor neurons reprogrammed from fibroblasts

Wainger et al. *Nature Neuroscience* 18, 17–24 (2015)





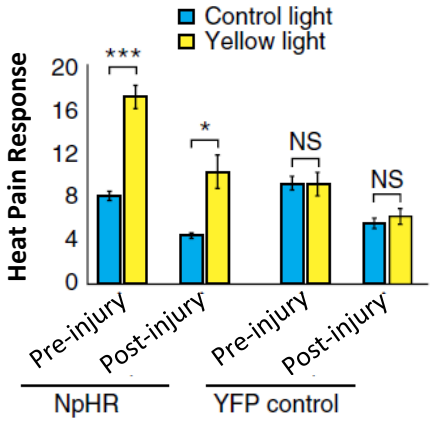
nature neuroscience

Selective conversion of fibroblasts into peripheral sensory neurons

Blanchard et al. *Nature Neuroscience* 18, 25–35 (2015)

Using optics to turn pain on and off

Video snapshot of transdermal optogenetic activation of nociceptors (Iyer and Montgomery)



Neuropathic pain mouse model
Modified

LETTERS

nature biotechnology

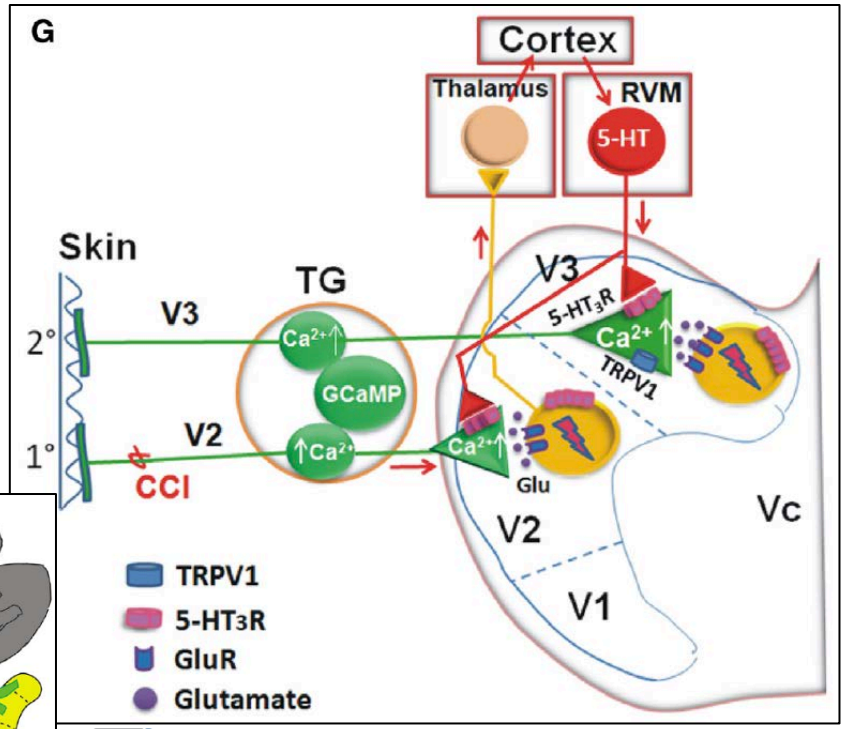
Virally mediated optogenetic excitation and inhibition of pain in freely moving nontransgenic mice

Iyer et al., *Nature Biotechnology* 32, 274-278 (2014

- Optogenetics allows fast, specific neuronal modulation
  - Recently used to probe transmission of pain signals
  - Avoids expensive, time-consuming development of transgenic mice
- Virally-mediated optogenetic regulation
  - **ChR2** (blue light-sensitive, excitatory) or **NpHR** (yellow light-sensitive, inhibitory)
- **ON** in WT mice: activation of ChR2 elicited pain behaviors (*i.e.*, paw licking and flinching)
- **OFF** in neuropathic pain model: activation of NpHR increased withdrawal latency to painful heat
- Valuable tool for *in vivo* study of pain mechanisms

Targeting non-opioid pathways for analgesia: TRPV1 and 5HT3$_A$ receptors

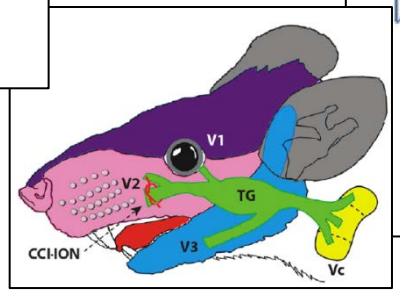
- TRPV1 function is well described on peripheral terminals of sensory afferents (heat, capsaicin "chili pepper" receptor)
- However, the role of TRPV1 on central terminals is unclear
- Collaborative group from USA and China describe pain-enhancing role of central TRPV1 and 5HT-3$_A$ receptors in a mouse model of nerve injury-induced hypersensitivity
- Descending serotonergic input from the brain onto central terminals increases TRPV1 activity and pain sensitivity
- These represent novel targets for analgesic drug development



Neuron
Article

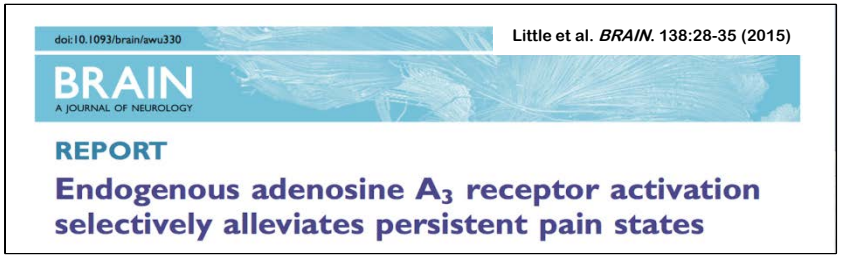
Central Terminal Sensitization of TRPV1 by Descending Serotonergic Facilitation Modulates Chronic Pain

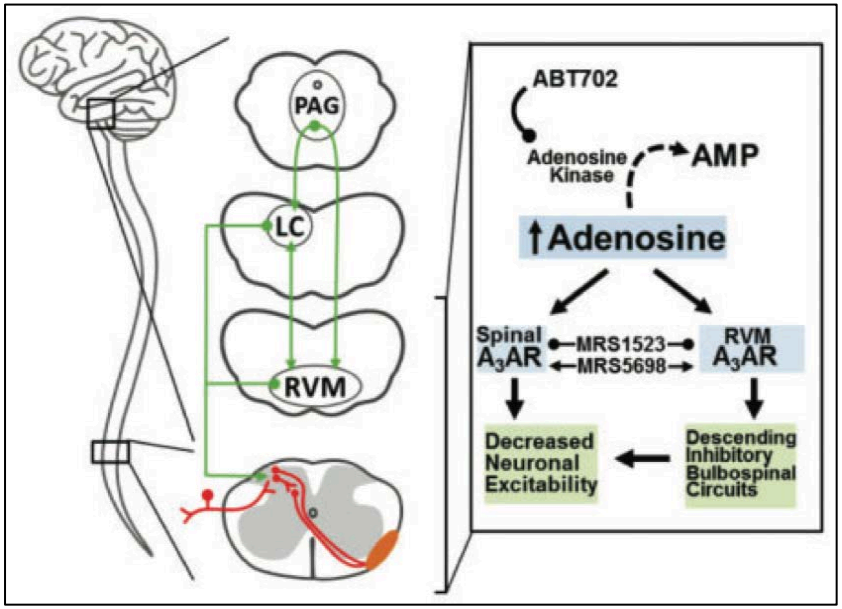
Kim et al. *Neuron*. 81(4):873-87. (2014)



Targeting non-opioid pathways for analgesia: Central A_3 receptors

- Opioid analgesics exhibit undesirable side effects (*e.g.* tolerance, addiction, abnormal sensation)
- Report from collaborative group from USA and UK, including NIH intramural researchers, describes analgesic efficacy of adenosine subunit A_3 agonists
- Adenosine A_3 activation alleviated pathological pain, with no effect on normal sensation
- Adenosine A_3 activation did not engage endogenous opioid system, and alleviated pain without producing inherent reward
- Existing A_3 agonists exhibit good safety profiles in clinical trials as anti-inflammatory/anti-cancer agents
- Represents promising new approach for pain relief





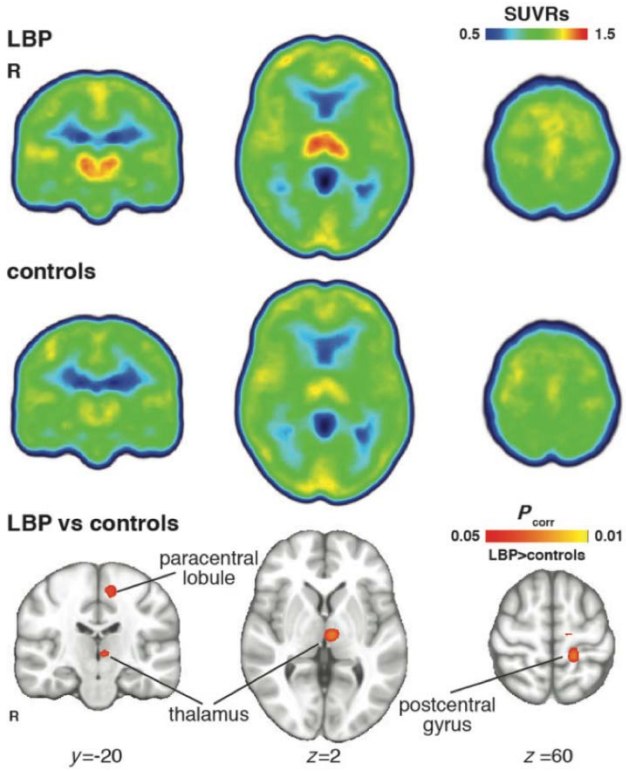
First evidence of neuroinflammation in brains of chronic pain patients

doi:10.1093/brain/awu377 BRAIN 2015: 138; 604–615 | 604

BRAIN
A JOURNAL OF NEUROLOGY

Evidence for brain glial activation in chronic pain patients

Marco L. Loggia,[1,2,*] Daniel B. Chonde,[1] Oluwaseun Akeju,[3] Grae Arabasz,[1] Ciprian Catana,[1] Robert R. Edwards,[2,4] Elena Hill,[5] Shirley Hsu,[1] David Izquierdo-Garcia,[1] Ru-Rong Ji,[2,6] Misha Riley,[1] Ajay D. Wasan,[2,4,7] Nicole R. Zürcher,[1] Daniel S. Albrecht,[1] Mark G. Vangel,[1] Bruce R. Rosen,[1,8] Vitaly Napadow[1,2,9] and Jacob M. Hooker[1]



- Glial activation contributes to establishment and maintenance of chronic pain, as shown in animal models
- PET imaging was used to observe brain levels of TSPO, a marker of glial activation
- Patients with chronic low back pain had elevated levels of radioligand binding to TSPO in thalamus, pre- and postcentral gyri, and paracentral lobule
- Thalamic levels of TSPO were negatively correlated with clinical pain and circulating levels of IL-6
- These results are an important step towards developing biomarkers for pain

Racial differences in prescription of opioid analgesics

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER
The Journal of Pain, Vol 15, No 4 (April), 2014: pp 447-455
Available online at www.jpain.org and www.sciencedirect.com

Racial Differences in Prescription of Opioid Analgesics for Chronic Noncancer Pain in a National Sample of Veterans

- While awareness of racial disparities in pain care has increased, no trends of improvement have been seen (Meghani et al., 2012 – meta-analysis)
- A large national sample of veterans with chronic pain diagnoses across VA hospitals was assessed
- Blacks were less likely than white counterparts to receive opioid prescriptions for moderate to high levels of pain (<65yrs)
- Racial bias remains an issue for pain care and needs to be addressed

U.S. Department of Veterans Affairs

Source: Burgess et al., *J. Pain* 15, 447-455 (2014)

National Institute of Neurological Disorders and Stroke

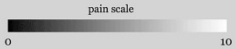
Disparities in Pain Care

Research shows that certain racial/ethnic and socioeconomic groups are more vulnerable to poor pain care and management. This infographic describes some factors that contribute to disparities in pain care.

Bias in Pain Treatment

Across the lifespan and regardless of socioeconomic status, blacks are less likely than whites to receive analgesic medication for pain[1-3]

Primary care providers are more likely to underestimate pain intensity in blacks than in other sociodemographic groups[2,4]

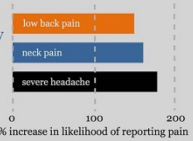


Compared with white patients, black patients were more likely to have:[5]

- more referrals for substance abuse assessment
- fewer referrals to a pain specialist
- increased drug urine tests

Socioeconomic Status

People with incomes below poverty level are more likely to report pain[1,3]



During ER visits, opioids were prescribed more frequently to patients with the highest socioeconomic status[3]

Language Barriers

Less than 20% of health professionals treating Hispanic pain patients reported Spanish proficiency at an advanced level[7]

Non-native English speakers may have:[6]

- limited health literacy
- difficulties navigating the healthcare system
- difficulties understanding healthcare providers

Access to Care

Pharmacies located in minority neighborhoods are less likely to carry sufficient prescription analgesics than those located in white neighborhoods[6]

Impoverished individuals and minorities are more likely to be uninsured or underinsured than non-minorities and people with greater incomes[2]

Reduced access to health care in general, and specialty care in particular, contributes to pain disparities, with racial and ethnic minorities and the poor having decreased access to care[2]

Learn More...

The above information points to a need for a multidisciplinary approach to pain care and treatment including clinicians' awareness of implicit bias. An IOM report on relieving pain in America (see references) called for a comprehensive population health-level strategy for pain, which is currently in progress under the Dept. of Health and Human Services.

Resources for persons with pain:
- Find a doctor
  http://healthfinder.gov/
- Talking with your doctor
  http://www.nih.gov/clearcommunication/talktoyourdoctor.htm
  https://nccih.nih.gov/timetotalk/forpatients.htm
- Learn more about chronic pain
  http://www.ninds.nih.gov/disorders/chronic_pain/detail_chronic_pain.htm

Resources for care providers:
- Cultural & linguistic competency
  http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=34
  http://www.hrsa.gov/publichealth/healthliteracy/
  http://www.nih.gov/clearcommunication/culturalcompetency.htm
- Institute of Medicine report on Relieving Pain in America - http://ow.ly/IBMbC
- Office of Minority Health – Cultural & Linguistic Competency
  http://www.minorityhealth.hhs.gov/omh/browse.aspx?lvl=1&lvlid=6

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3. Joynt, M., et al., The impact of neighborhood socioeconomic status and race on the prescribing of opioids in emergency departments throughout the United States. J Gen Intern Med, 2013. 28(12): p. 1604-10.

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NIH Pain Consortium

Integrative medicine relieves pain and anxiety for cancer inpatients

Effects of Integrative Medicine on Pain and Anxiety Among Oncology Inpatients

J Natl Cancer Inst Monogr (2014)

Jill R. Johnson, Daniel J. Crespin, Kristen H. Griffin, Michael D. Finch, Jeffery A. Dusek

- Pain is common among cancer patients, and treating cancer-related pain is a challenge for healthcare providers
- Johnson *et al*. studied electronic medical records of 1,833 cancer patients who received integrative medicine therapy
- Patients reported their pain and anxiety levels just before and after the therapy
- Integrative medicine therapy reduced pain and anxiety in hospitalized cancer patients by approximately 50%
- Integrative medicine offers an important tool for healthcare providers to treat pain