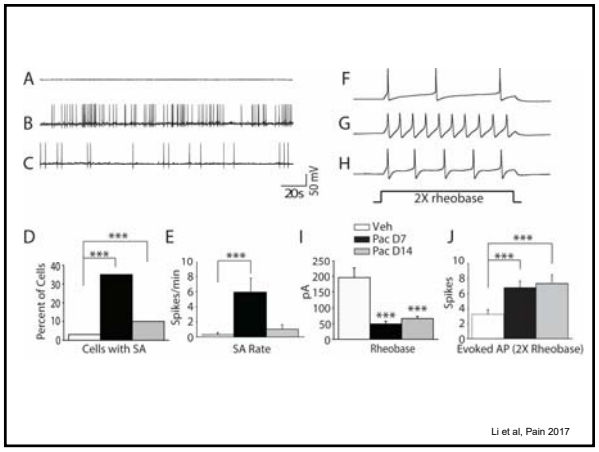
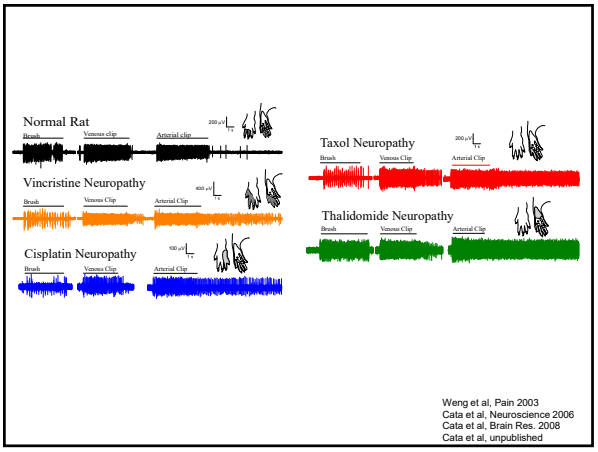
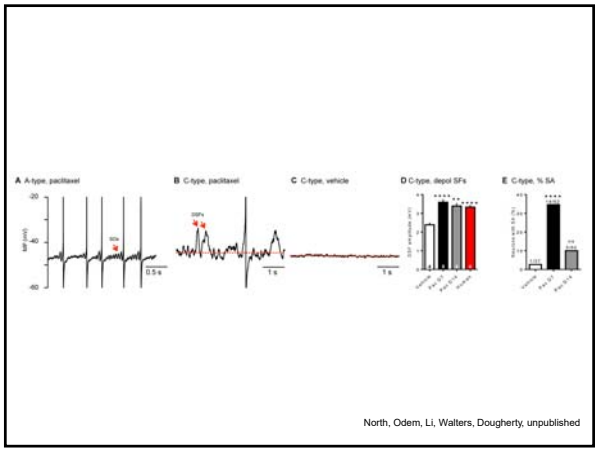


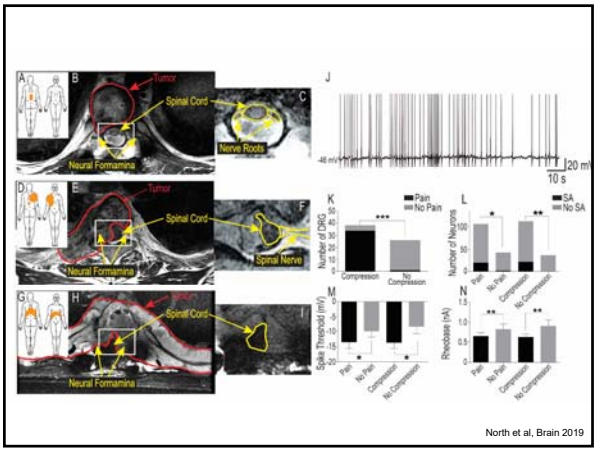
Li et al, Pain 2017



Weng et al, Pain 2003
Cata et al, Neuroscience 2006
Cata et al, Brain Res. 2008
Cata et al, unpublished

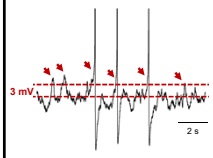


North, Odem, Li, Walters, Dougherty, unpublished

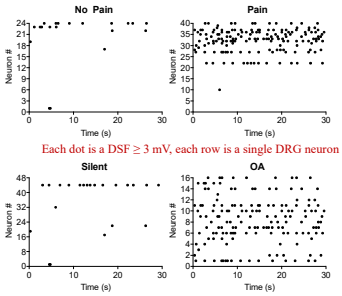


North et al, Brain 2019

Pain and OA are associated with a significant increase in the incidence of large DSFs in human DRG neurons

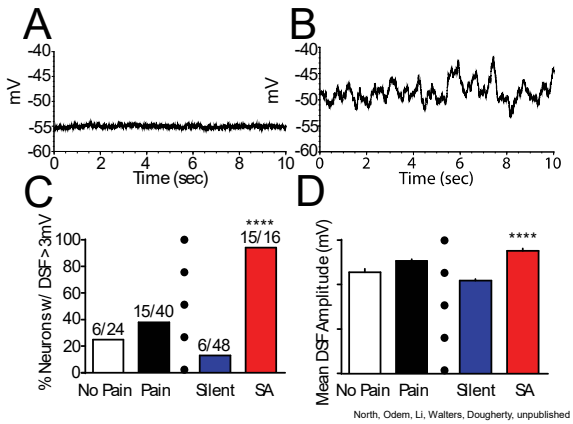


Also depolarized RMP and reduced AP threshold



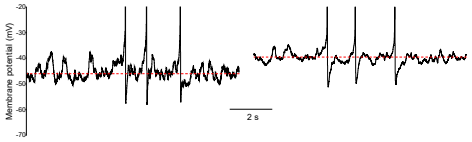
Each dot is a DSF ≥ 3 mV, each row is a single DRG neuron

North, Odem, Li, Walters, Dougherty, unpublished



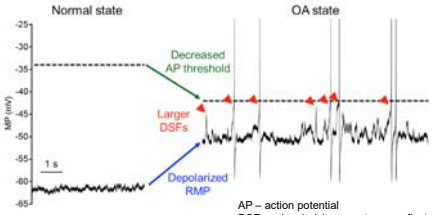
North, Odem, Li, Walters, Dougherty, unpublished

Which is human and which is rat?



North, Odem, Li, Walters, Dougherty, unpublished

In the absence of brief extrinsic depolarizing inputs, only three basic electrophysiological alterations can (in principle) produce OA

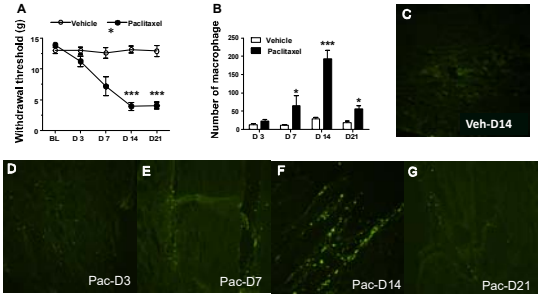


AP – action potential
DSFs – depolarizing spontaneous fluctuations
RMP – resting membrane potential

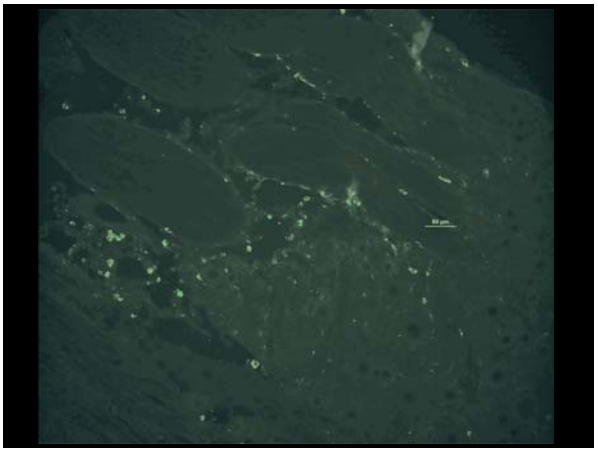
Odem et al, Pain 2018

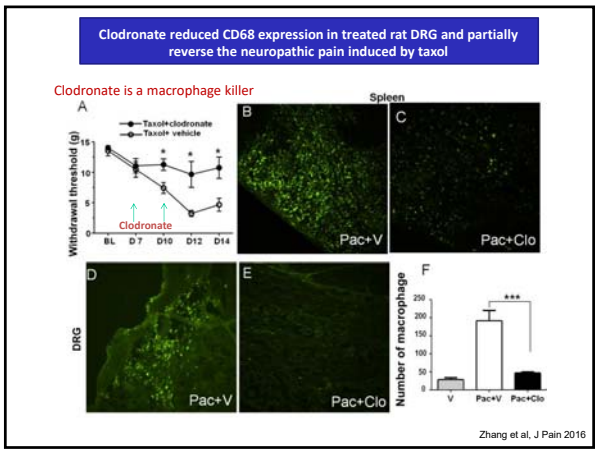
Taxol induced the expression of CD68 in DRG

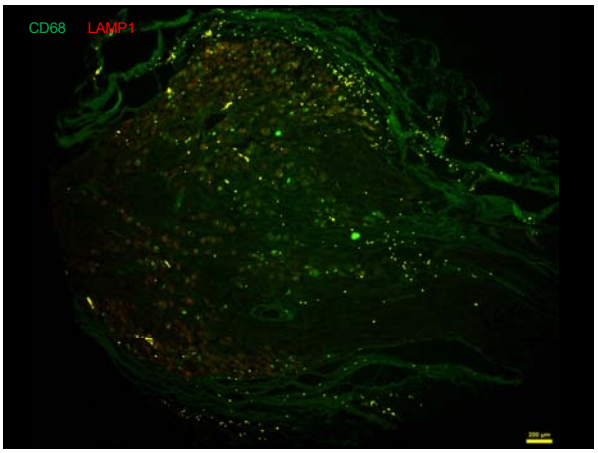
Macrophage (CD68 staining) immunoactivity was detected in the L4-5 DRG

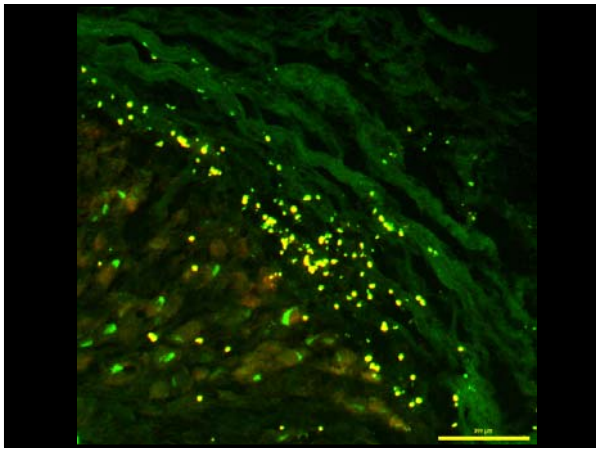


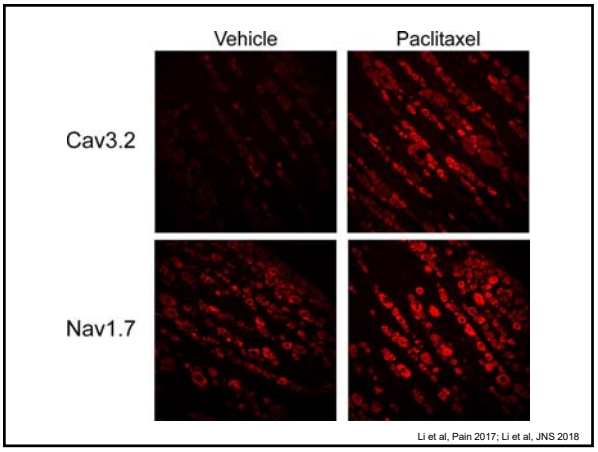
Zhang et al, J Pain 2016

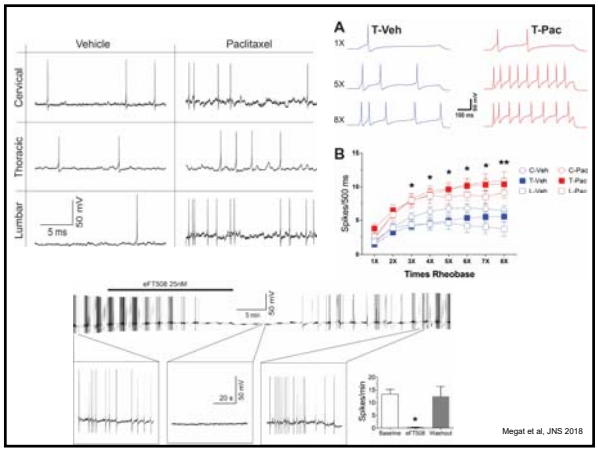


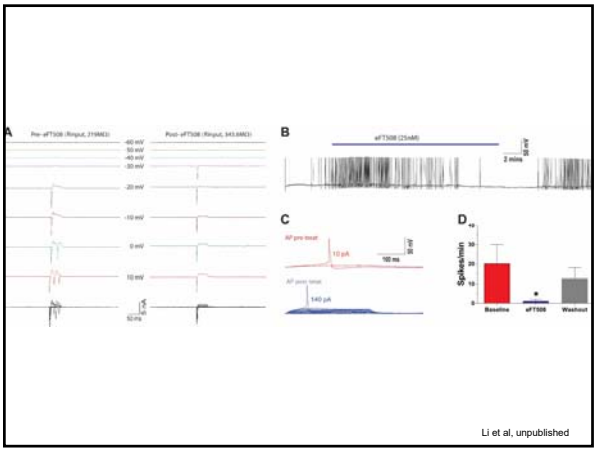

Clodronate reduced CD68 expression in treated rat DRG and partially reverse the neuropathic pain induced by taxol
Clodronate is a macrophage killer
Spleen
Taxol+clodronate
Taxol+ vehicle
Withdrawal threshold (g)
Clodronate
BL D7 D10 D12 D14
Pac+V
Pac+Clo
DRG
Number of macrophage
V Pac+V Pac+Clo
Zhang et al, J Pain 2016

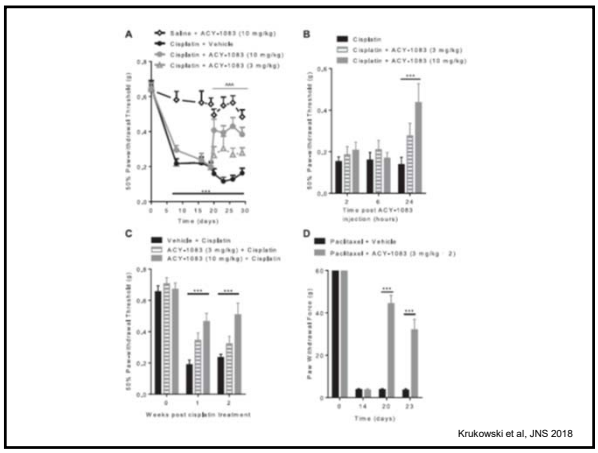

CD68
LAMP1



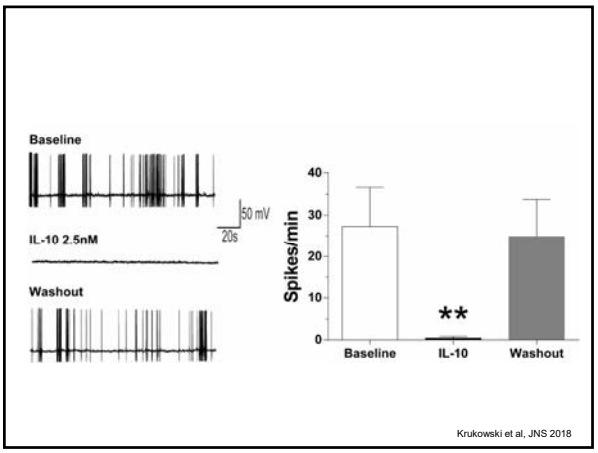

Vehicle
Paclitaxel
Cav3.2
Nav1.7
Li et al, Pain 2017; Li et al, JNS 2018


Vehicle
Paclitaxel
Cervical
Thoracic
Lumbar
5 ms
50 mV
T-Veh
T-Pac
Times Rheobase
Spikes/500 ms
Spikes/min
Baseline
Washout
Megat et al, JNS 2018

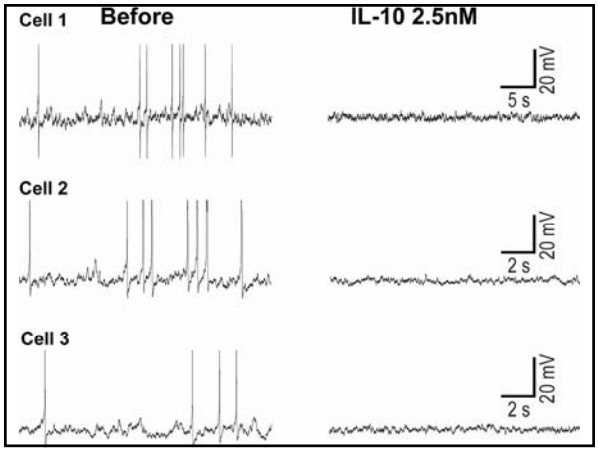

Spikes/min
Baseline
Washout
Li et al, unpublished

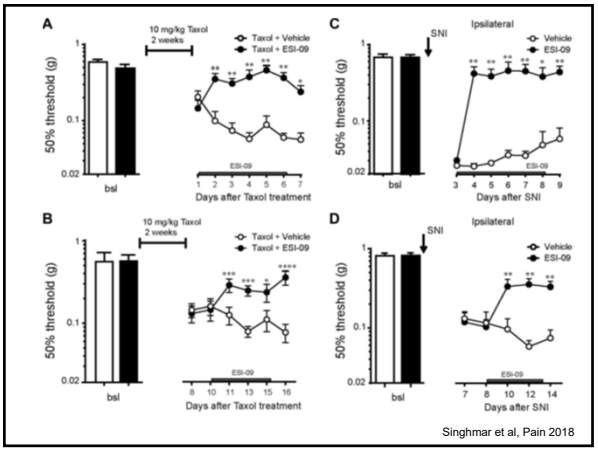


Krukowski et al, JNS 2018

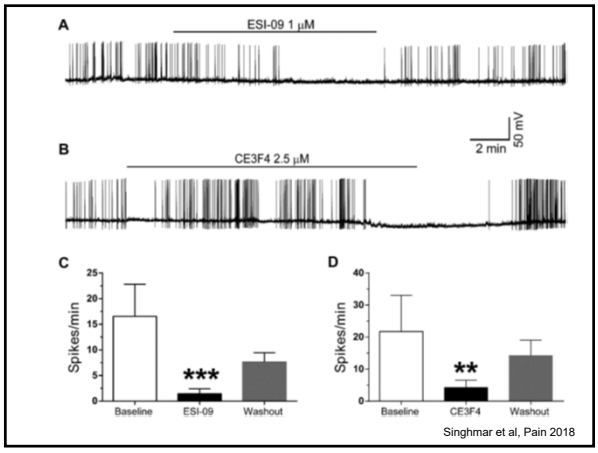


Krukowski et al, JNS 2018



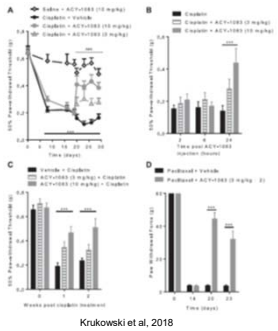


Singhmar et al, Pain 2018

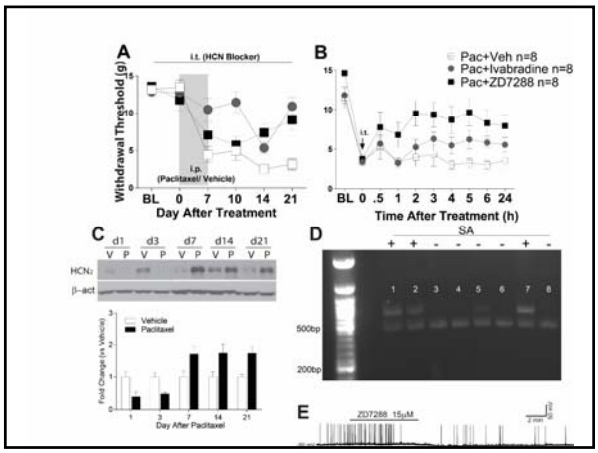


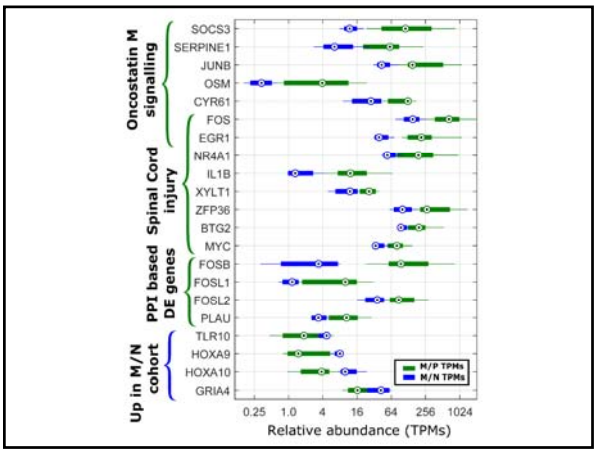
Singhmar et al, Pain 2018

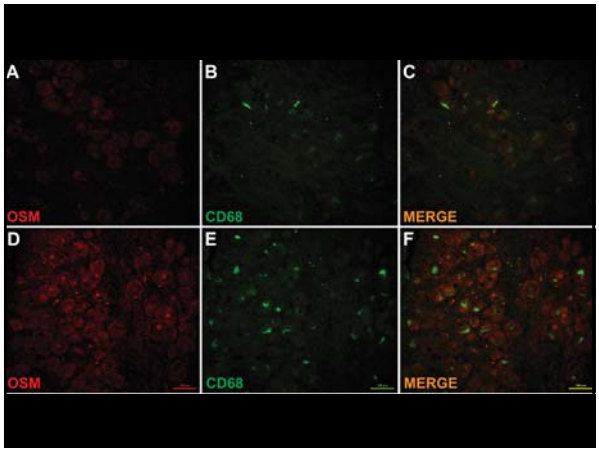
HDAC 6

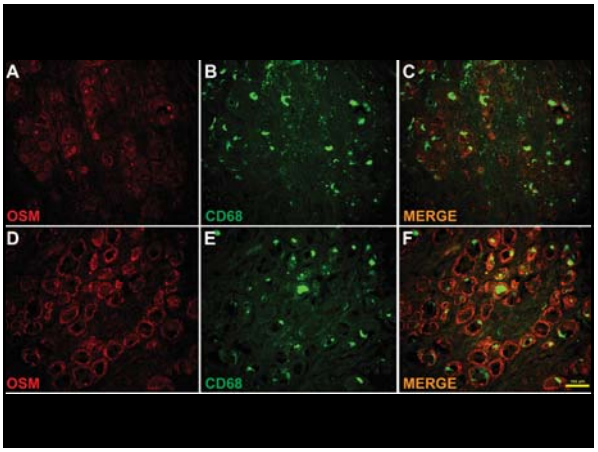


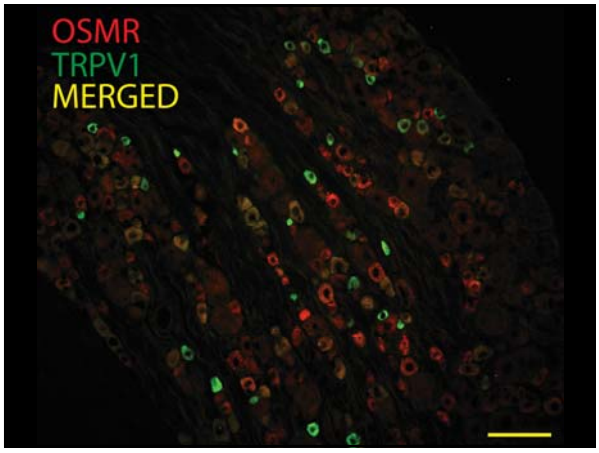
Krukowski et al, 2018

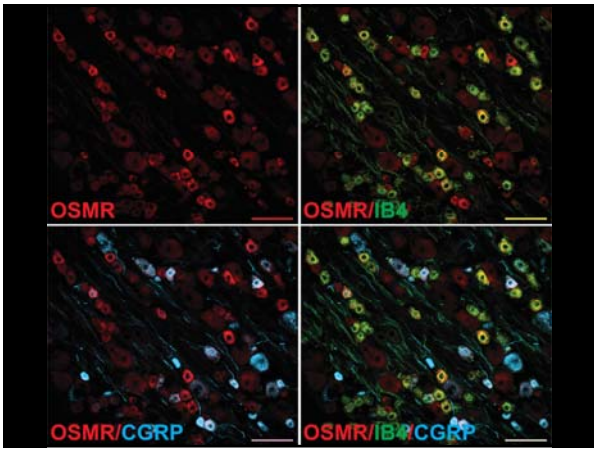

A
i.t. (HCN Blocker)
Withdrawal Threshold (g)
i.p.
(Paclitaxel/ Vehicle)
BL 0 7 10 14 21
Day After Treatment
B
Pac+Veh n=8
Pac+Ivabradine n=8
Pac+ZD7288 n=8
i.t.
BL 0 .5 1 2 3 4 5 6 24
Time After Treatment (h)
C
d1 d3 d7 d14 d21
V P V P V P V P V P
HCN2
β-act
Vehicle
Paclitaxel
Fold Change (vs Vehicle)
Day After Paclitaxel
D
SA
500bp
200bp
E
ZD7288 15μM

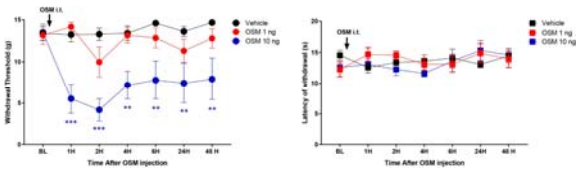

Oncostatin M signalling
SOCS3
SERPINE1
JUNB
OSM
CYR61
Spinal Cord injury
FOS
EGR1
NR4A1
IL1B
XYLT1
ZFP36
BTG2
MYC
PPI based DE genes
FOSB
FOSL1
FOSL2
PLAU
Up in M/N cohort
TLR10
HOXA9
HOXA10
GRIA4
M/P TPMs
M/N TPMs
0.25 1.0 4 16 64 256 1024
Relative abundance (TPMs)

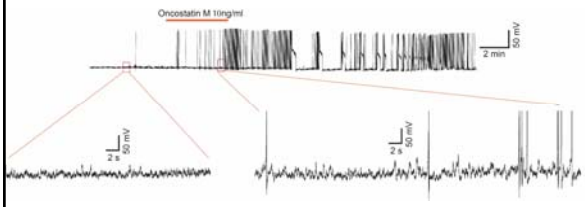

A
B
C
OSM
CD68
MERGE
D
E
F
OSM
CD68
MERGE

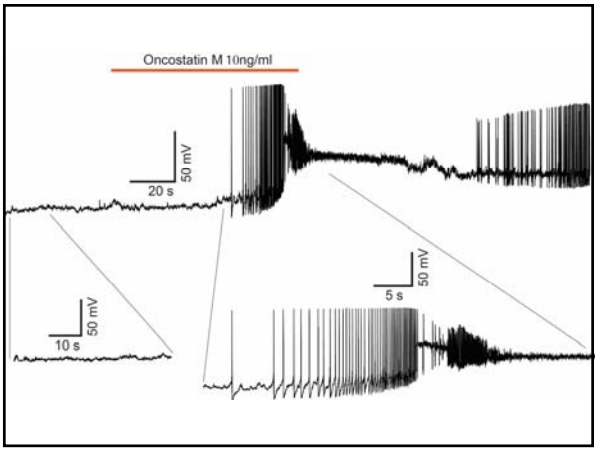

A
B
C
OSM
CD68
MERGE
D
E
F
OSM
CD68
MERGE

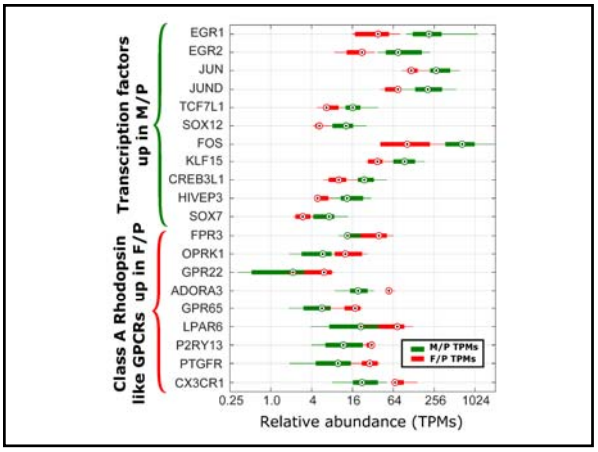

OSMR
TRPV1
MERGED

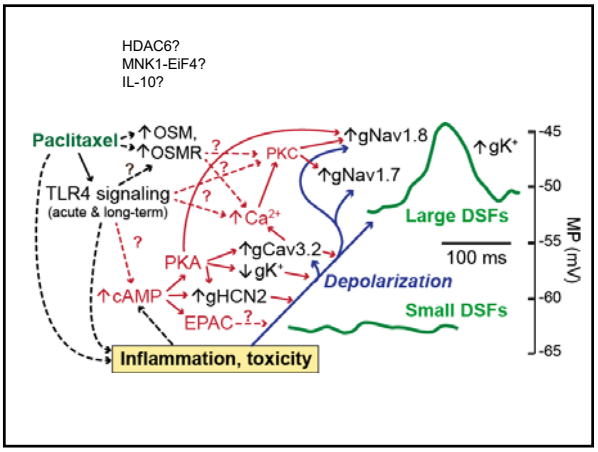

OSMR
OSMR/IB4
OSMR/CGRP
OSMR/IB4/CGRP

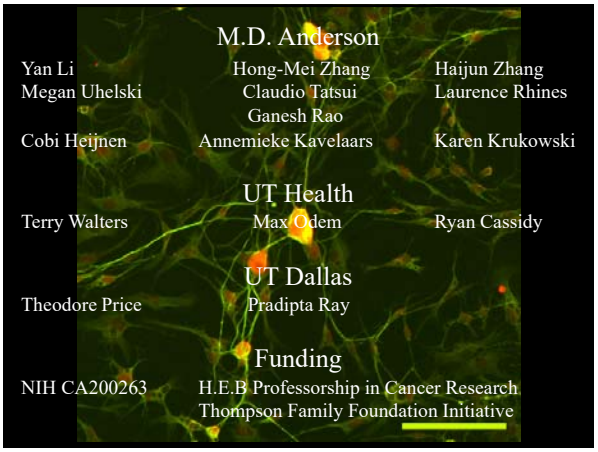

OSM i.t.
Vehicle
OSM 1 ng
OSM 10 ng
Withdrawal Threshold (g)
Time After OSM injection
Latency of withdrawal (s)


Oncostatin M 10ng/ml
2 min
50 mV
2 s


Oncostatin M 10ng/ml
50 mV
20 s
10 s
5 s


Transcription factors up in M/P
Class A Rhodopsin like GPCRs up in F/P
EGR1
EGR2
JUN
JUND
TCF7L1
SOX12
FOS
KLF15
CREB3L1
HIVEP3
SOX7
FPR3
OPRK1
GPR22
ADORA3
GPR65
LPAR6
P2RY13
PTGFR
CX3CR1
M/P TPMs
F/P TPMs
0.25
1.0
4
16
64
256
1024
Relative abundance (TPMs)


HDAC6?
MNK1-EiF4?
IL-10?
Paclitaxel
↑OSM,
↑OSMR
TLR4 signaling
(acute & long-term)
PKC
↑gNav1.8
↑gNav1.7
↑gK+
↑Ca2+
Large DSFs
100 ms
PKA
↑gCav3.2
↓gK+
Depolarization
↑cAMP
↑gHCN2
EPAC
Small DSFs
Inflammation, toxicity
-45
-50
-55
-60
-65
MP (mV)


M.D. Anderson
Yan Li
Hong-Mei Zhang
Haijun Zhang
Megan Uhelski
Claudio Tatsui
Laurence Rhines
Ganesh Rao
Cobi Heijnen
Annemieke Kavelaars
Karen Krukowski
UT Health
Terry Walters
Max Odem
Ryan Cassidy
UT Dallas
Theodore Price
Pradipta Ray
Funding
NIH CA200263
H.E.B Professorship in Cancer Research
Thompson Family Foundation Initiative