

Predictors for CIPN

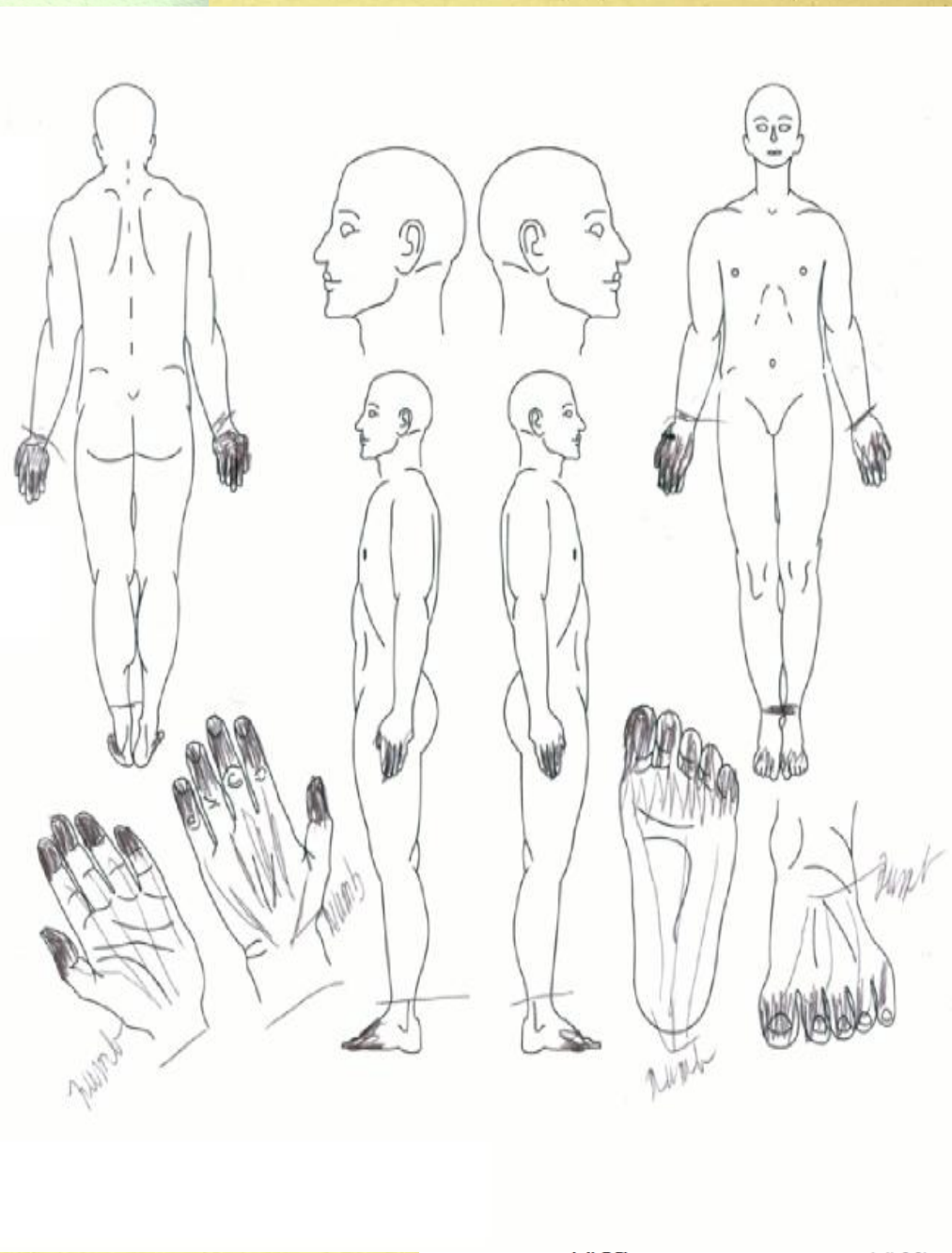
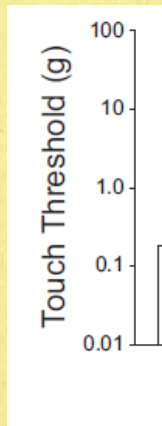
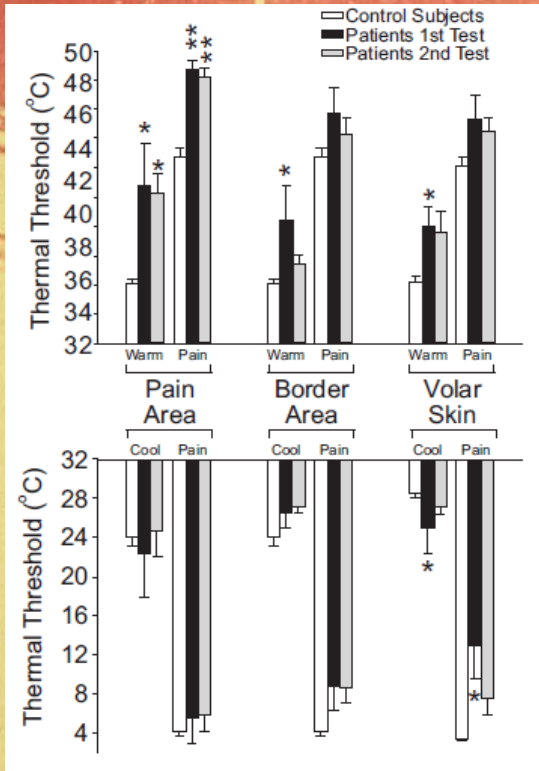
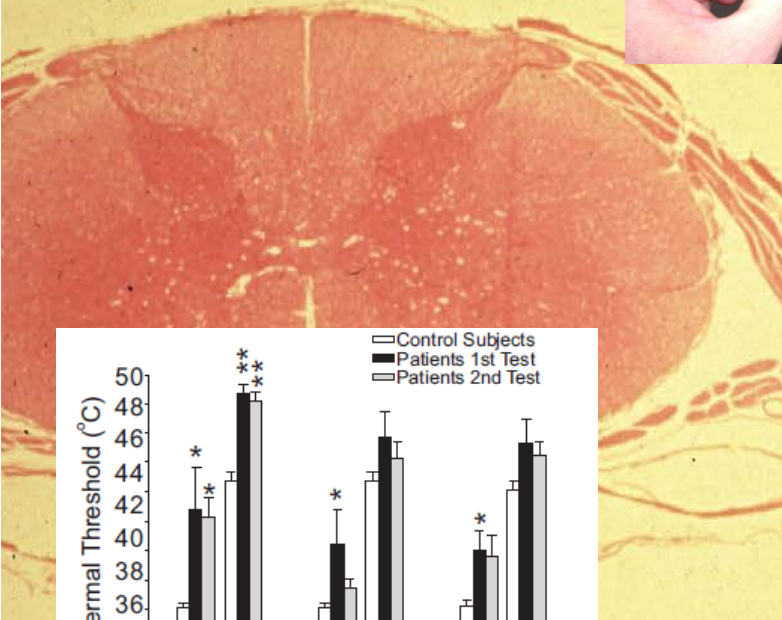
Patrick M. Dougherty, Ph.D., Professor
The Department of Anesthesiology & Pain Research
The University of Texas M.D. Anderson Cancer Center



$A\beta$: Touch

$A\delta$: pin prick

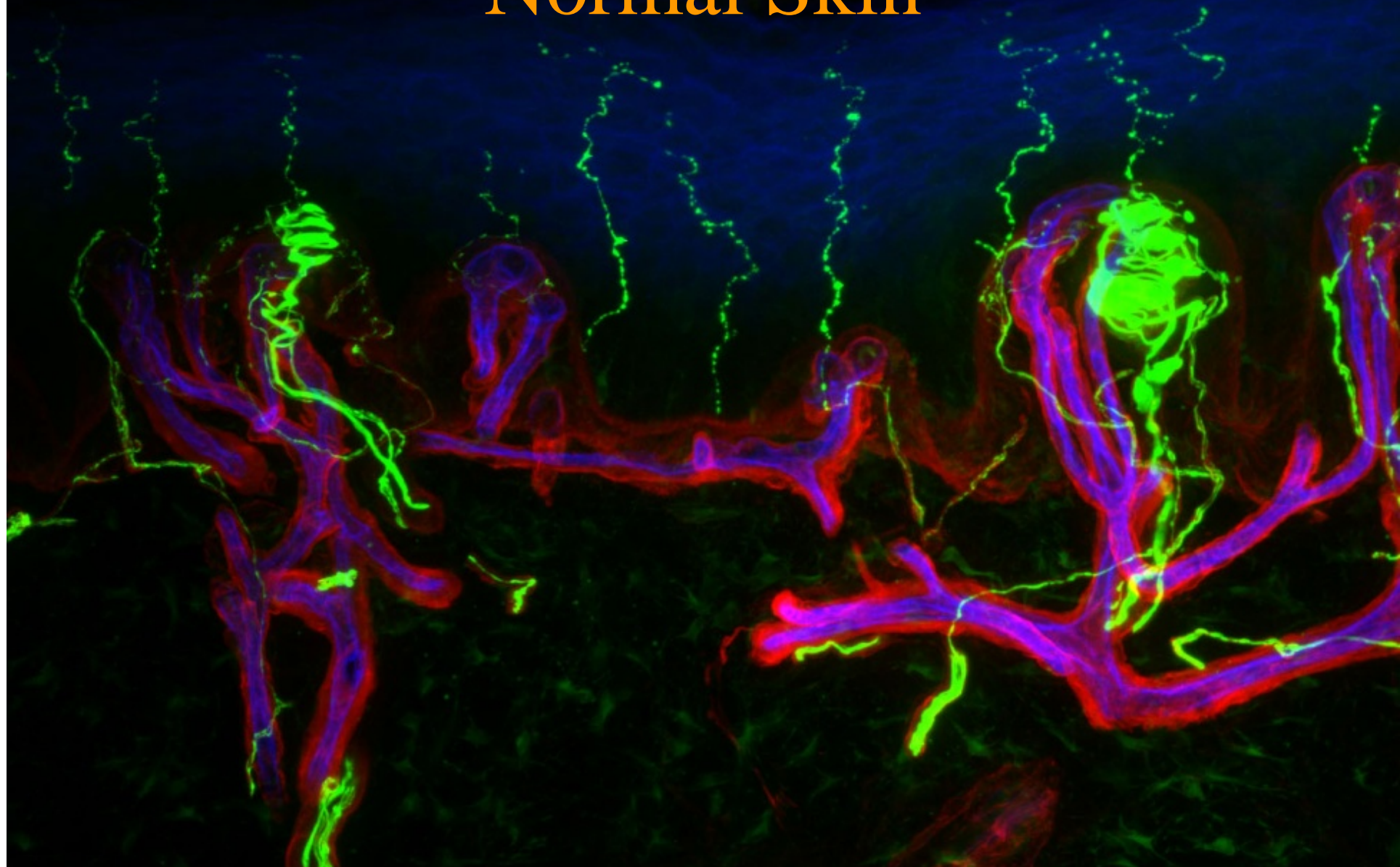
C: Pain, hot



100 μm

Site A

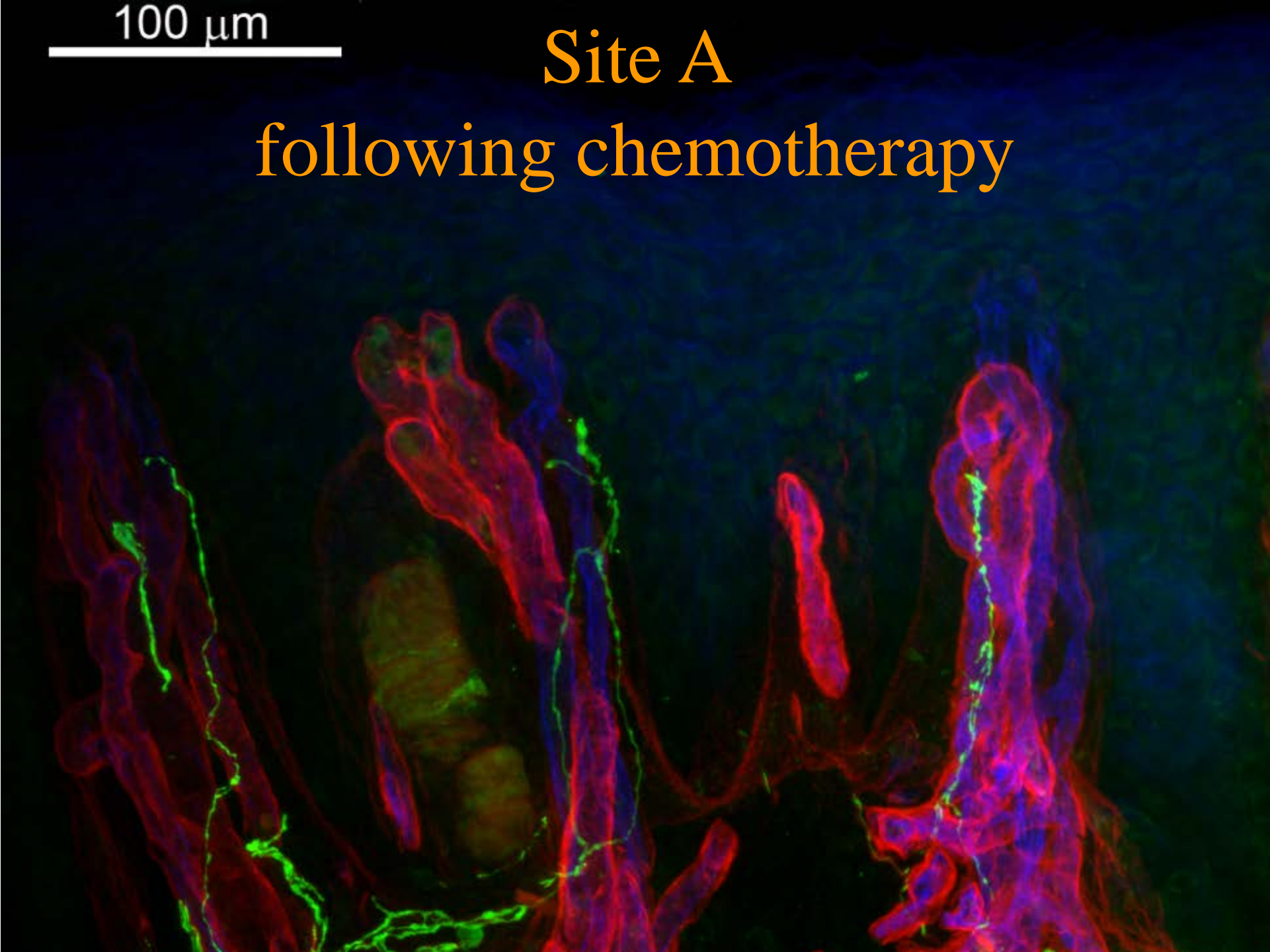
Normal Skin

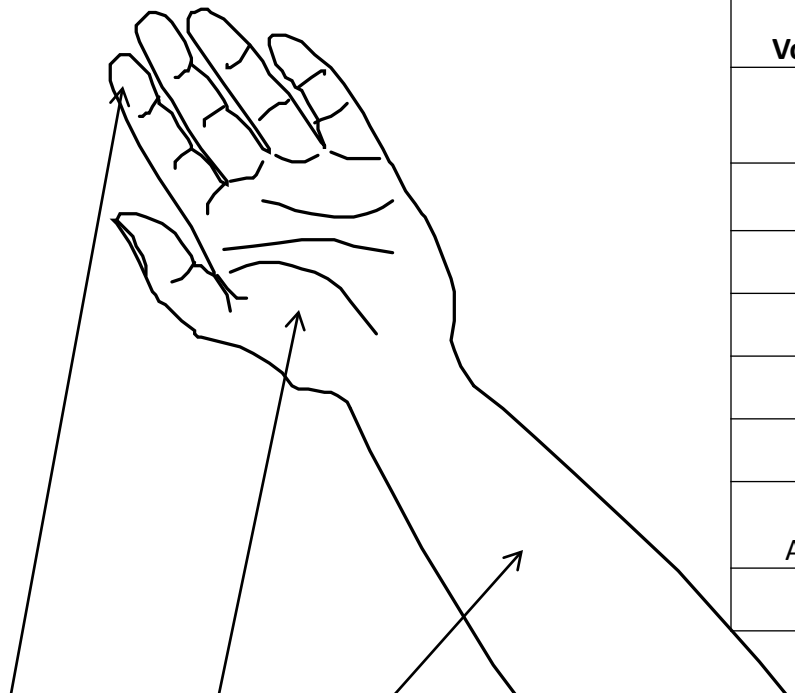


100 μm

Site A

following chemotherapy

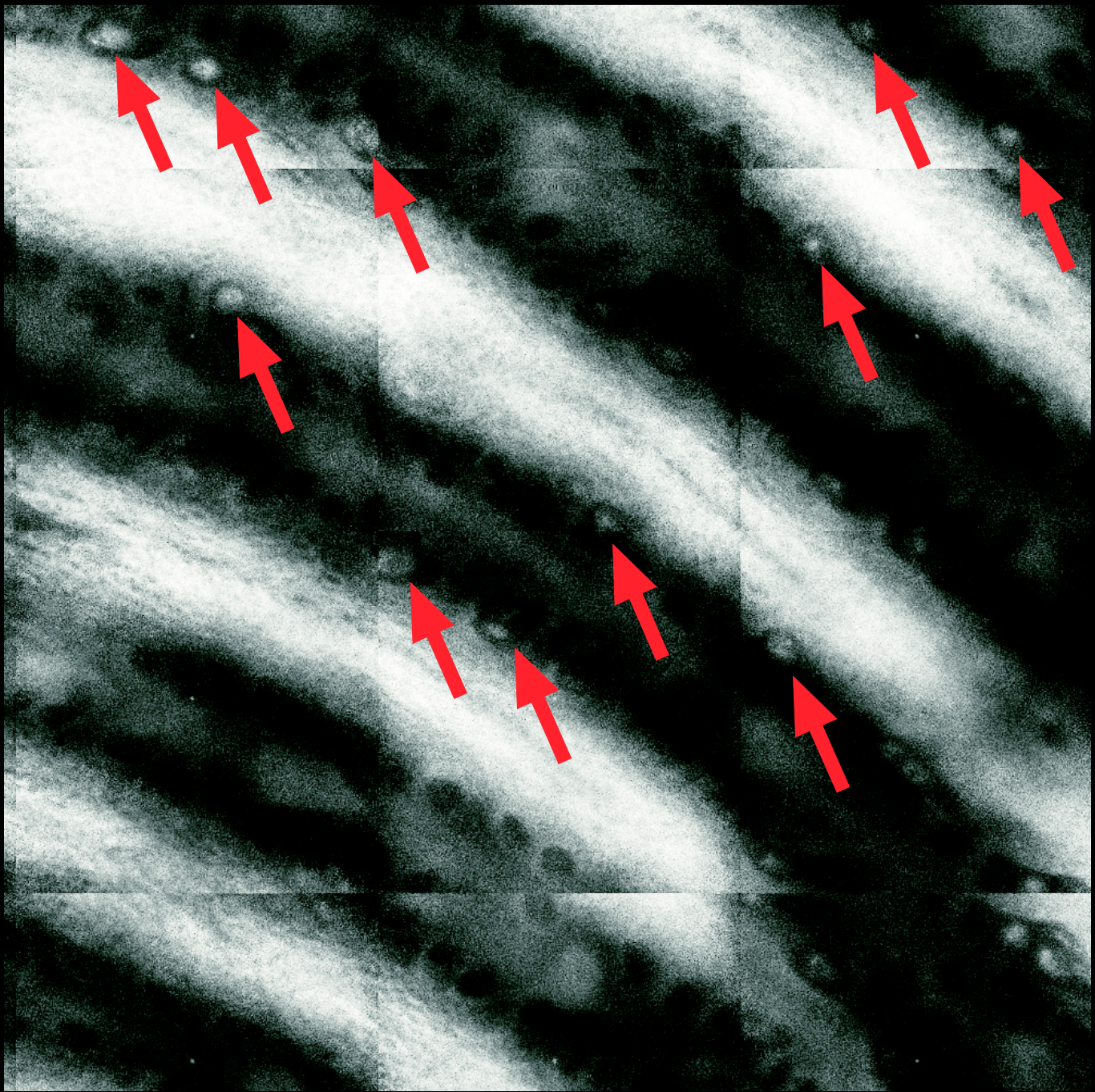


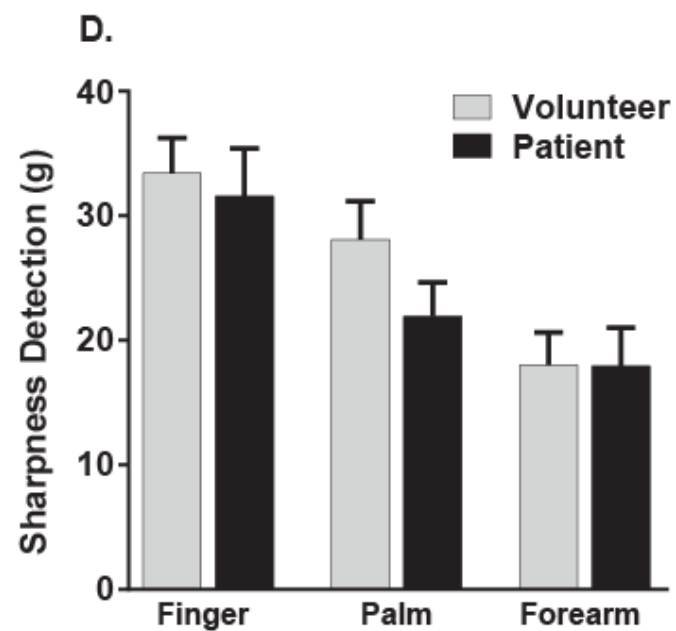
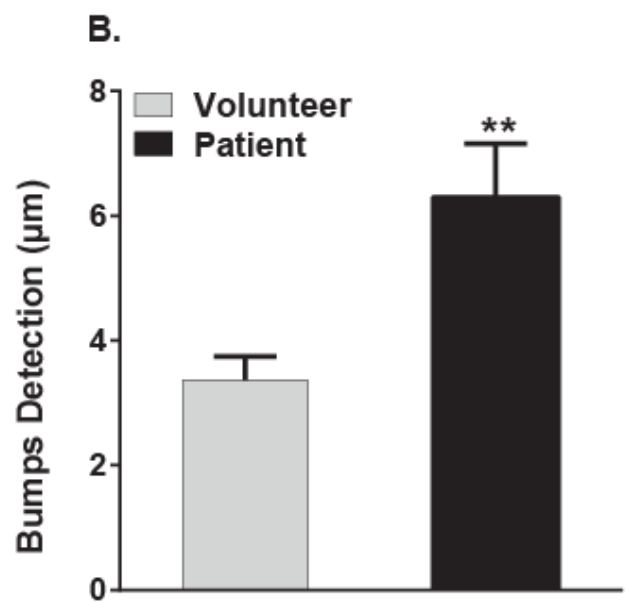
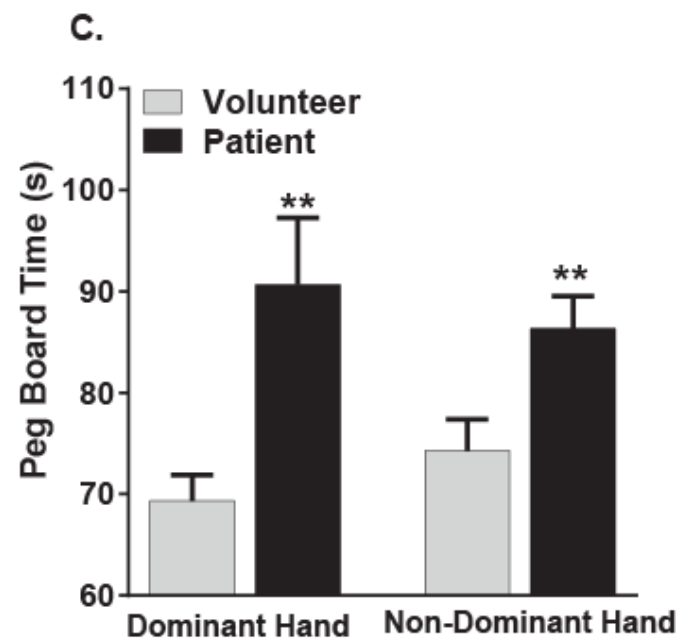
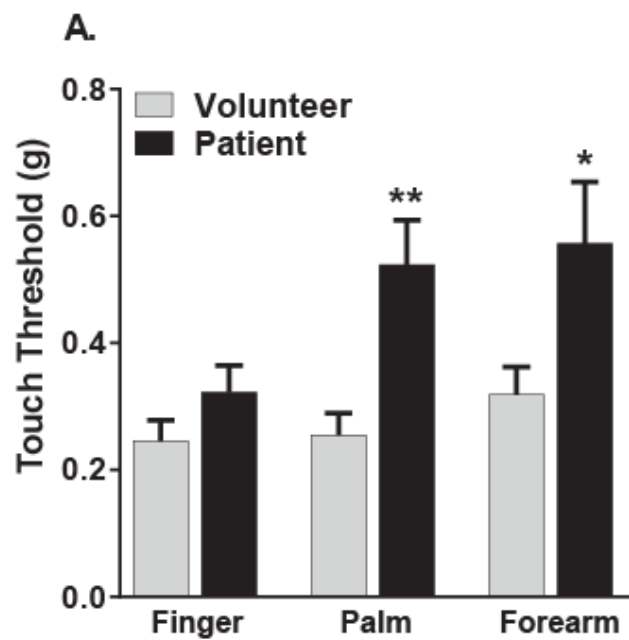


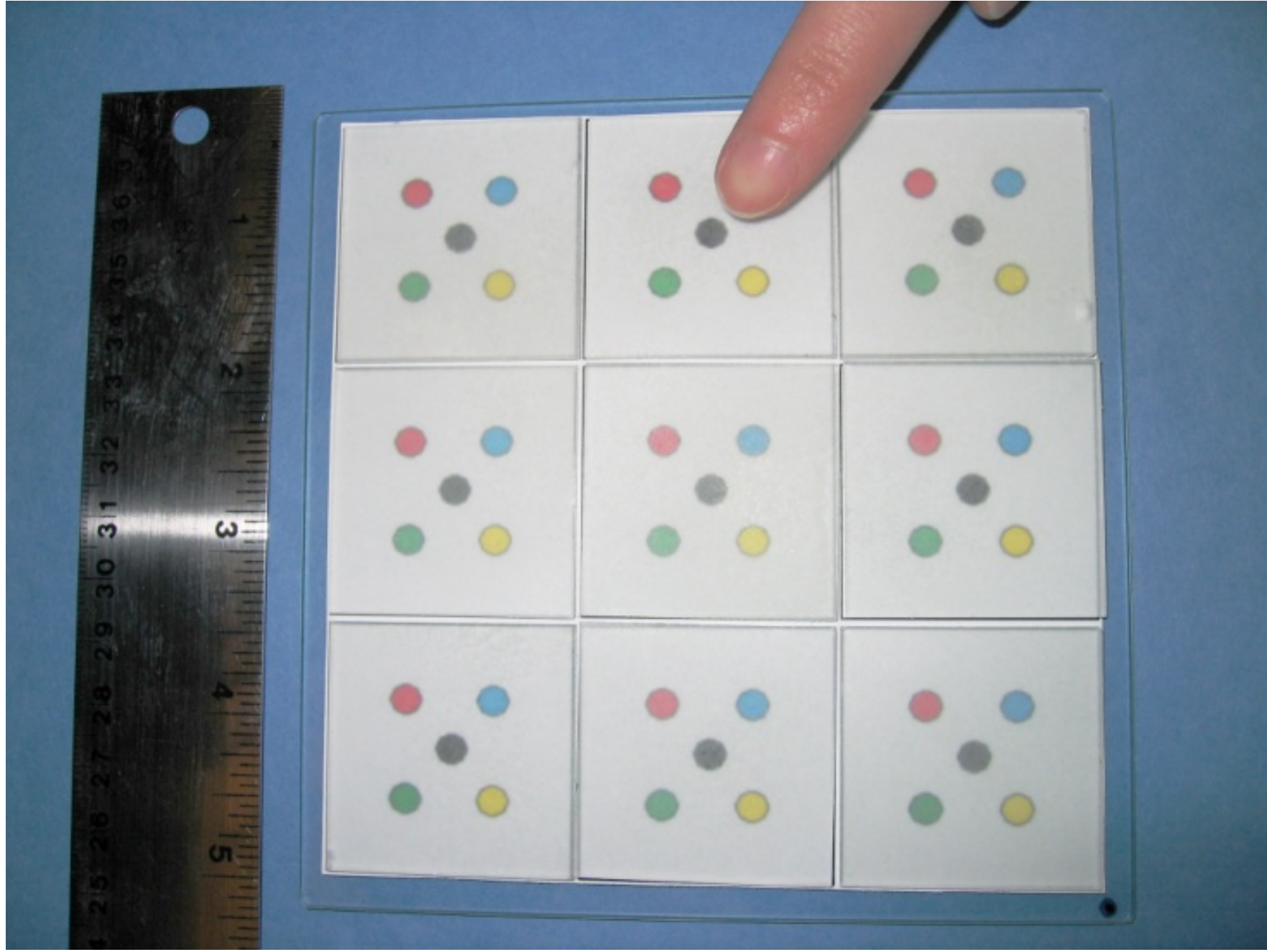
Volunteer	Sample A	Sample B	Sample C
1	12.39	15.67	29.20
2	7.23	14.37	21.56
3	4.16	17.01	35.73
4	10.19	9.83	15.44
5	3.23	13.81	27.72
6	1.06	23.47	39.05
Average	5.92	12.04	31.16
SD	4.15	6.41	9.32

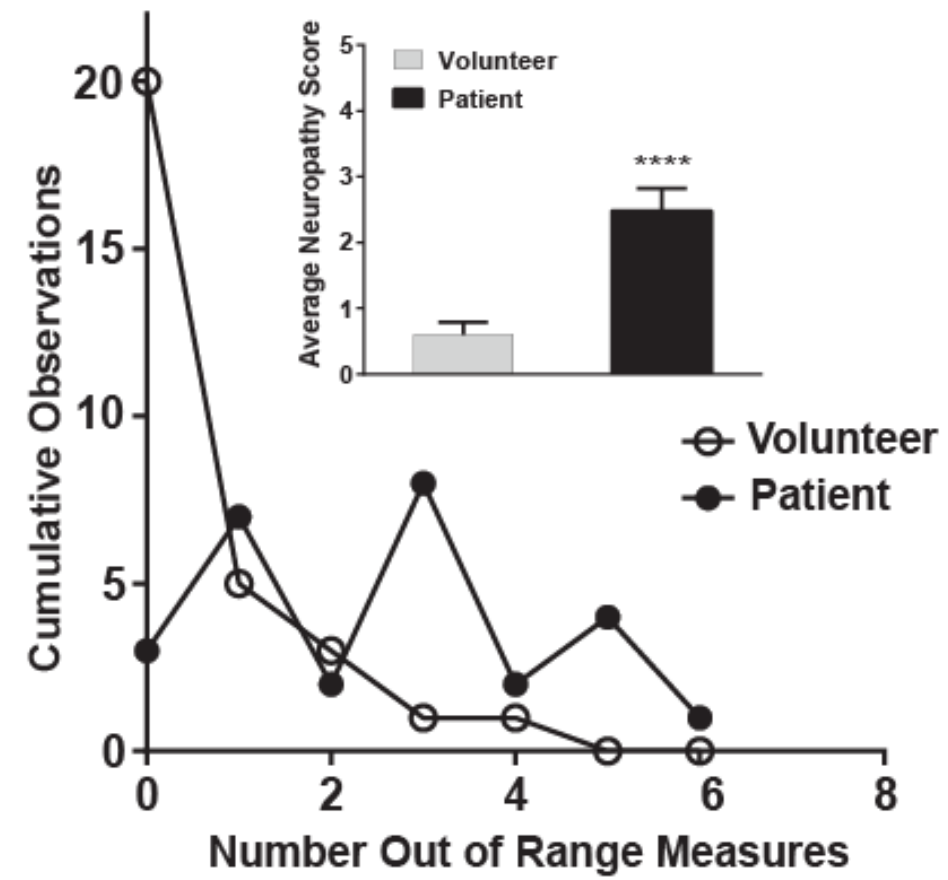
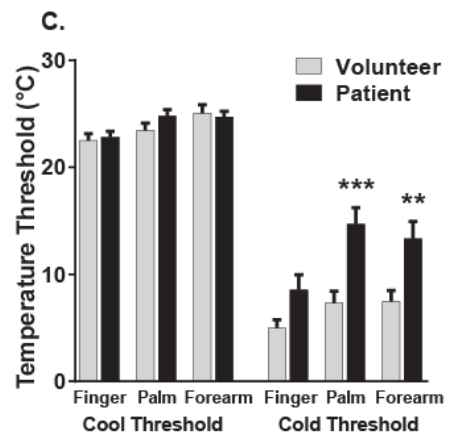
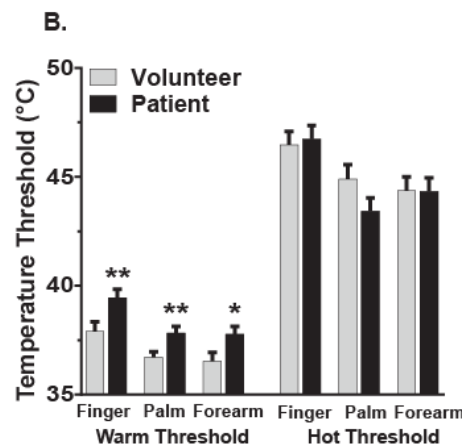
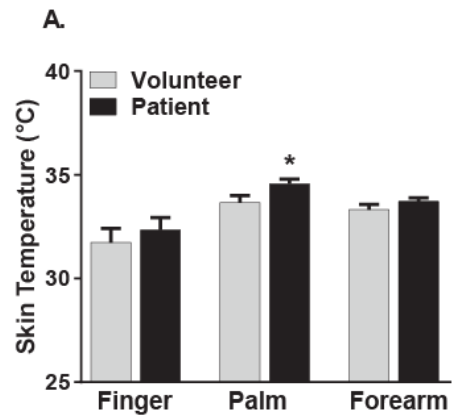
Patient	Sample A	Sample B	Sample C
1*	10.53988	10.62645	28.02009
2*	5.495411	19.43038	16.64313
3	1.238135	1.898854	14.59428
4	1.600286	3.553299	25.20261
5	0	13.24233	18.58923
6	0	2.5	6.54
Average	2.96	8.541888	18.26489
SD	3.85529	7.078407	7.706849

		ENFs/mm			MCs/mm	
		Painful fingertip	Border palm	Non-Painful forearm	Painful fingertip	Border palm
CHEMO	1*	10.54	10.63	28.02	0.1	0.00
	2*	5.49	19.43	16.64	0.3	0.30
	3	1.23	1.90	14.59	0.5	0.30
	4	1.60	3.55	25.20	0.5	0.30
	5	0	13.24	18.59	0.1	0.00
	6	0	2.50	6.54	0	0.00
	Average	3.14	8.54	18.26	0.25	0.15
SD	4.15	7.08	7.71	0.22	0.16	
NORMAL	1	12.39	15.67	39.02	1.2	1
	2	7.23	14.37	21.56	2.1	0.4
	3	4.16	17.01	35.73	1.8	0.2
	4	10.19	9.83	15.44	1.7	
	5	3.06	23.47	39.05	2.1	0.8
	6	3.21	8.01	41.57	1.3	0.5
	Average	7.41	16.07	30.16	1.70	0.60
SD	3.94	4.94	10.95	0.38	0.32	

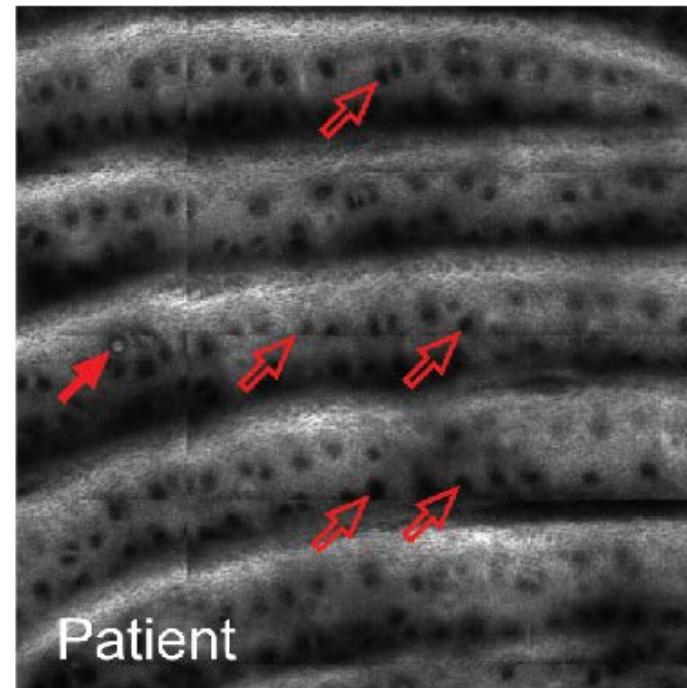
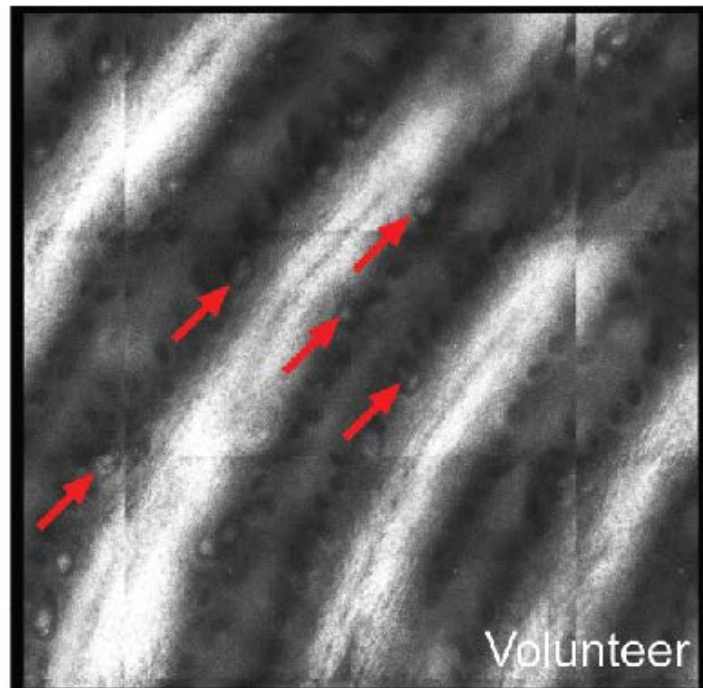




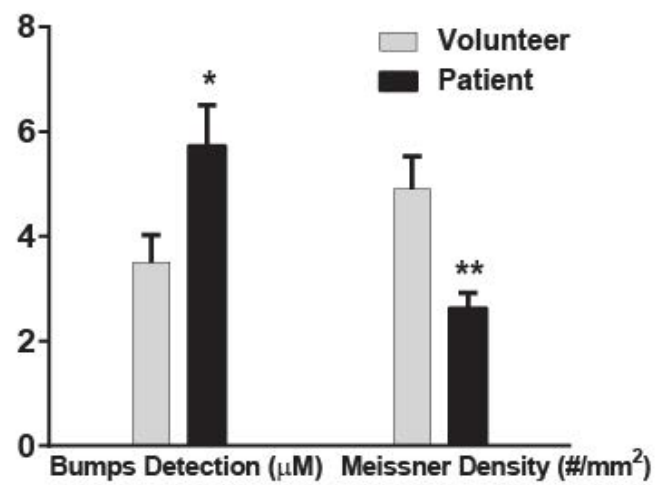




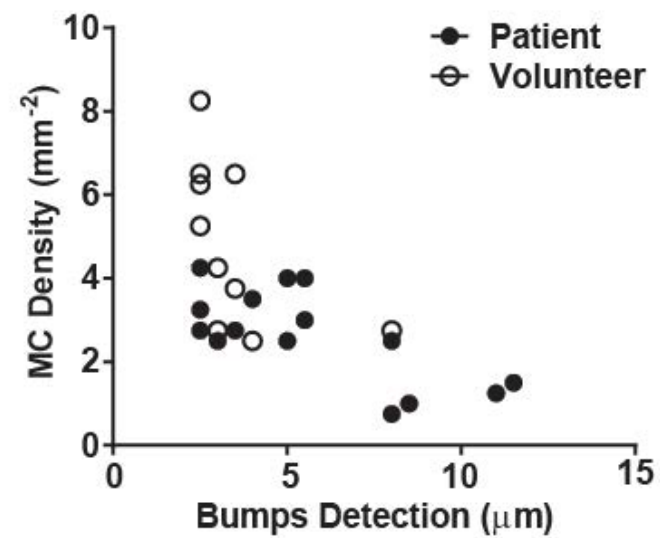
A.

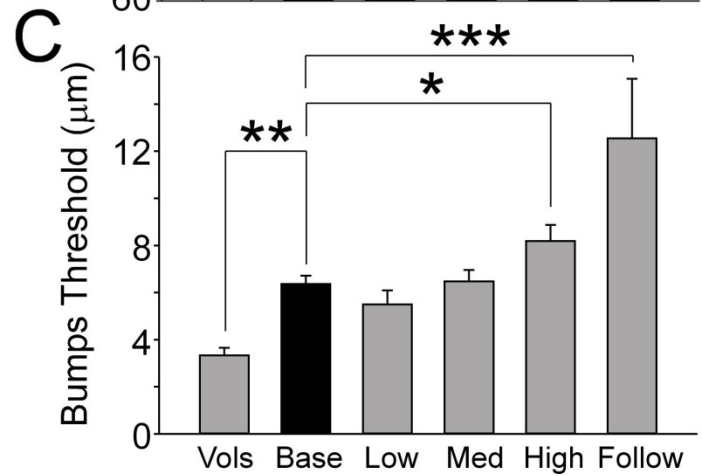
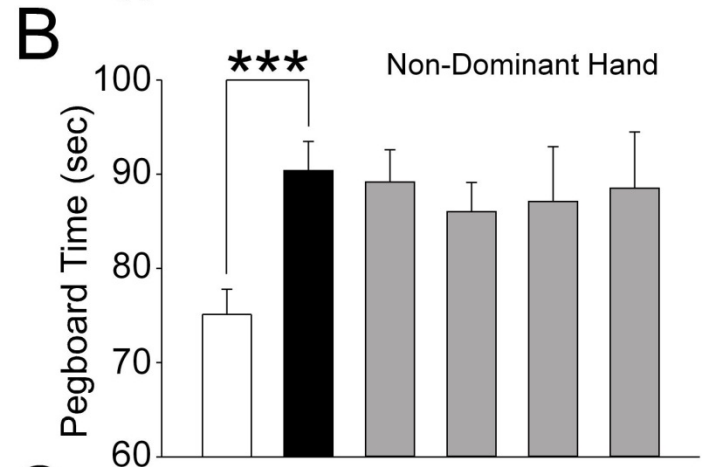
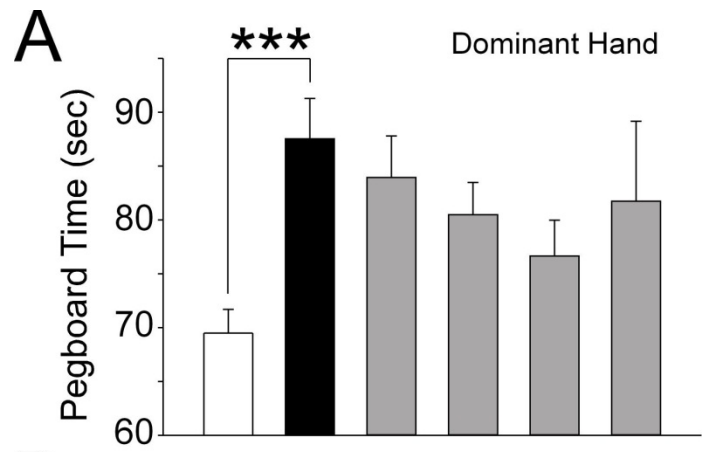


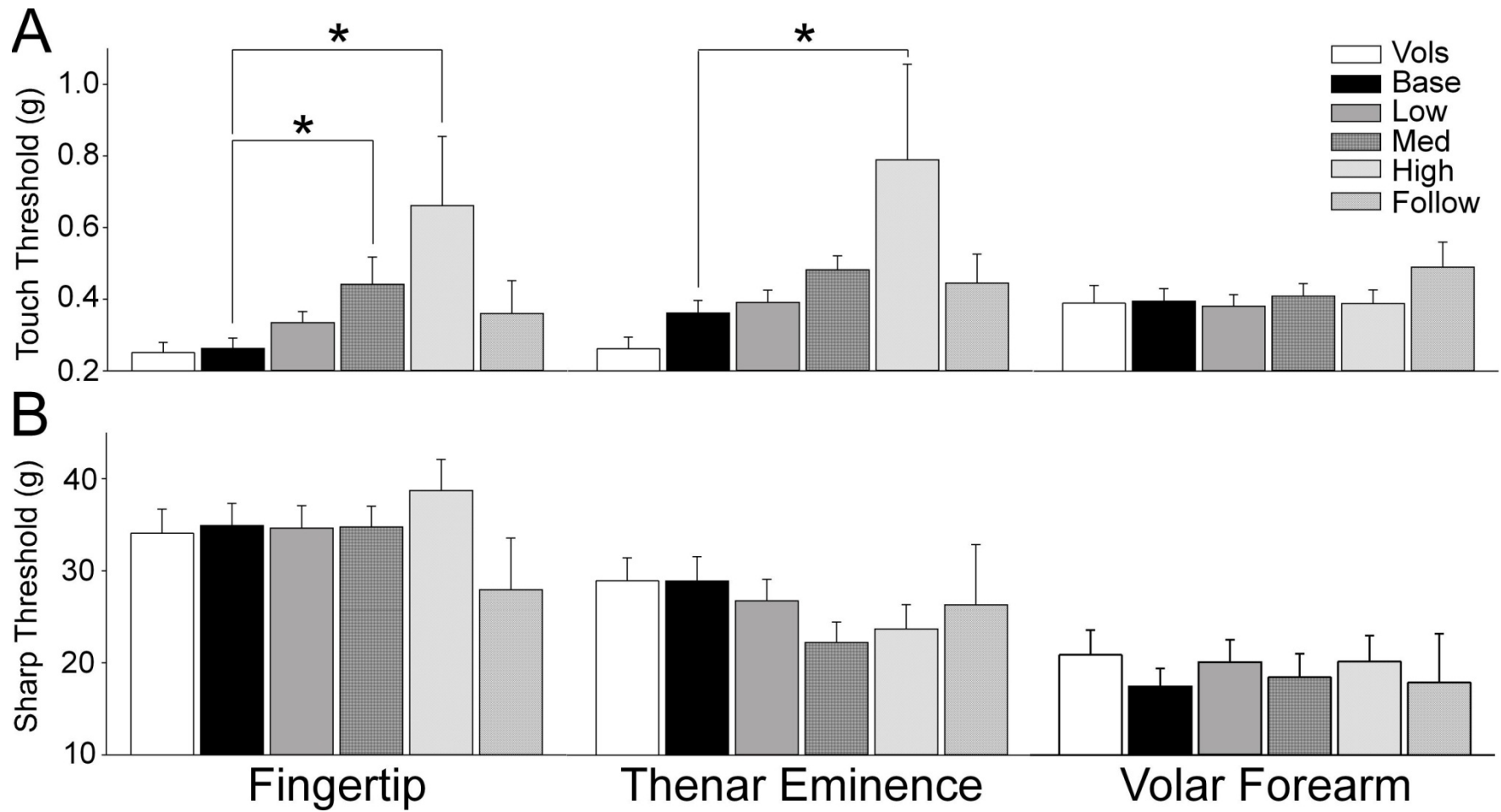
B.

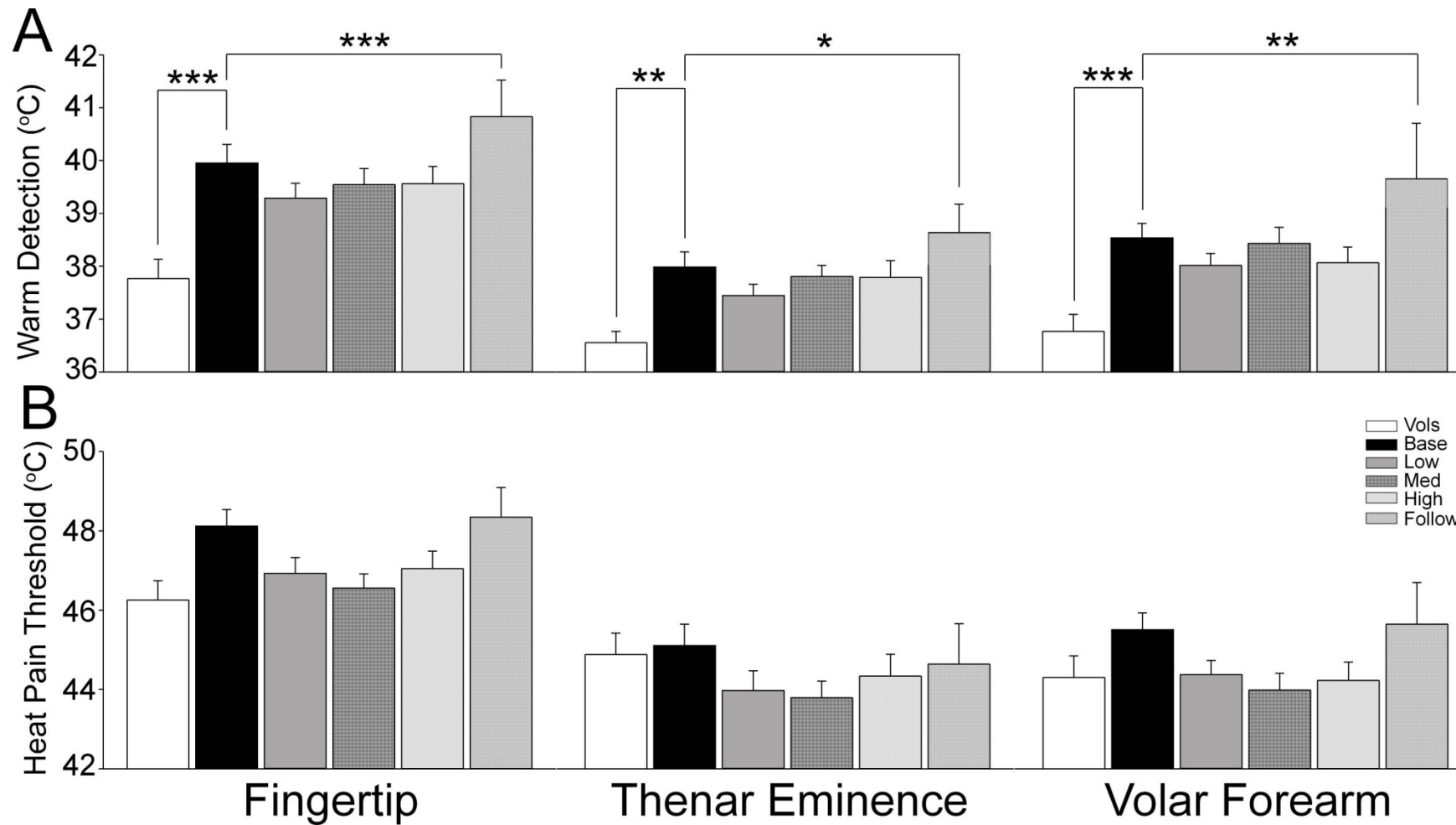


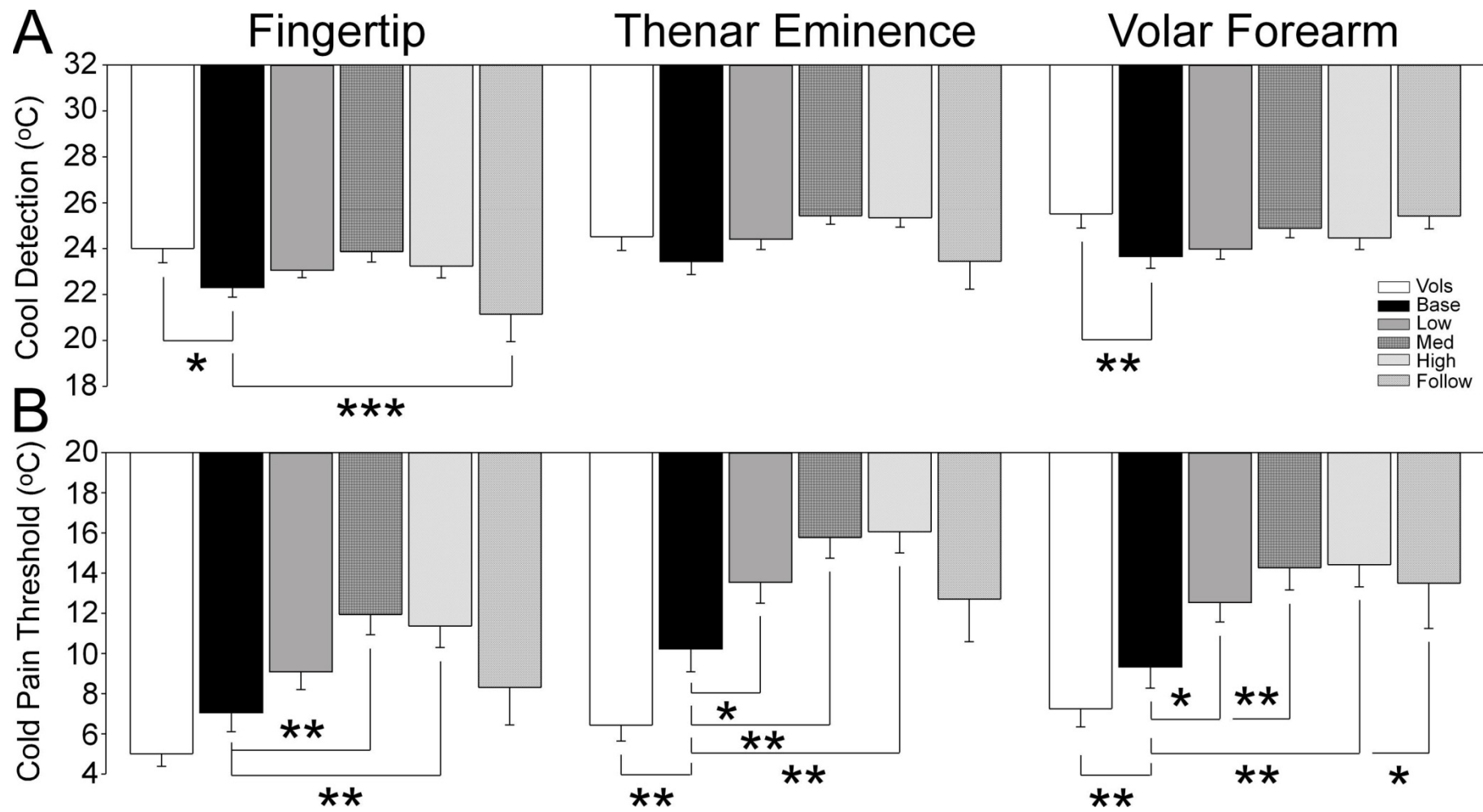
C.

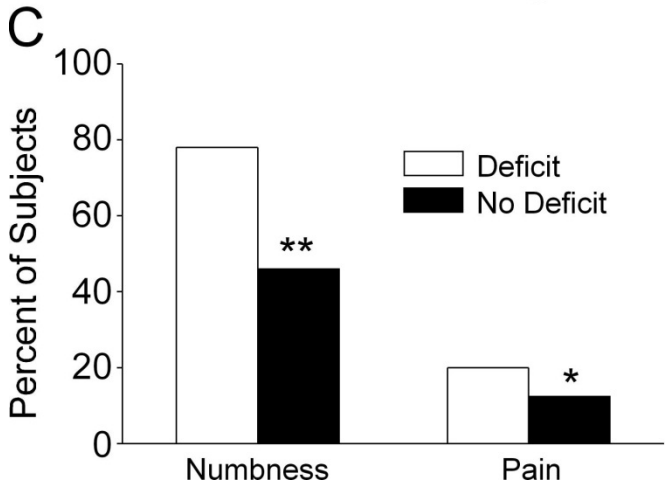
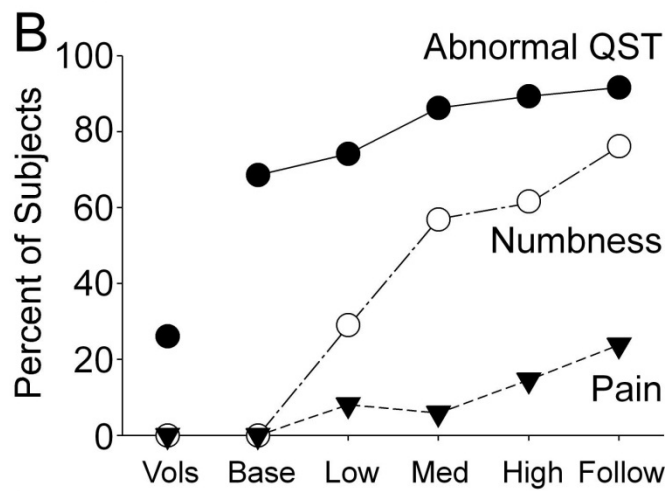
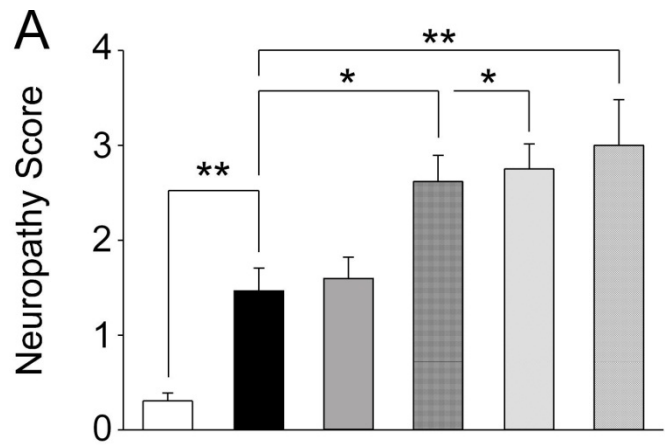






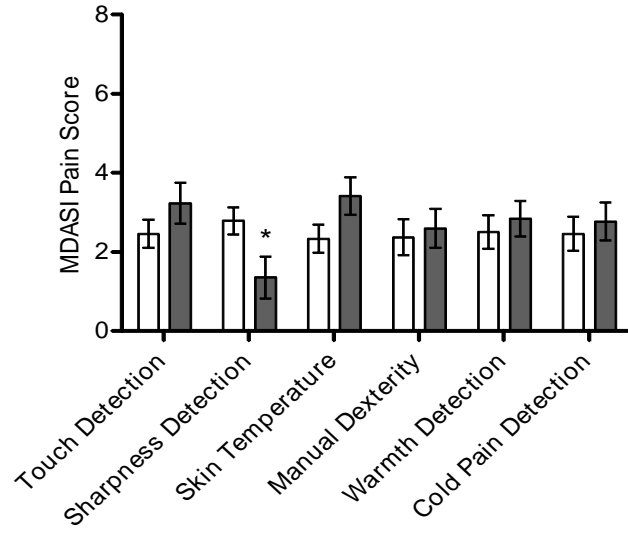




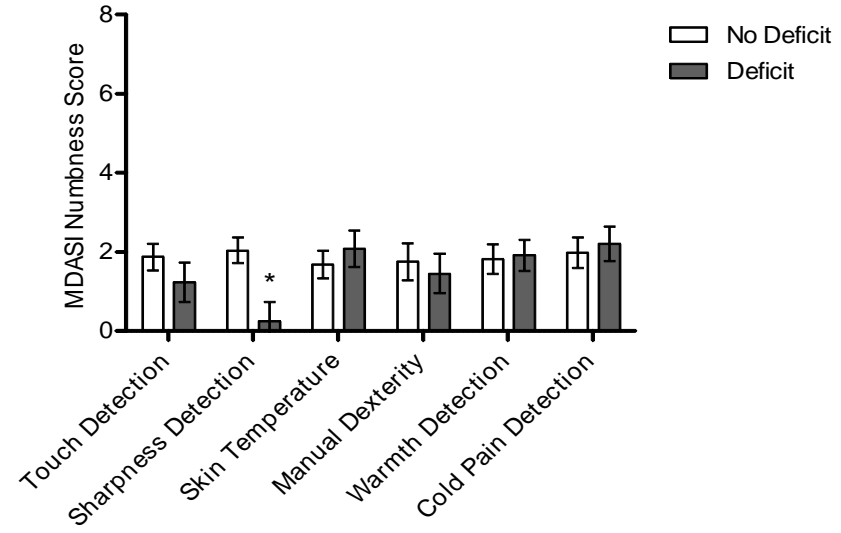


Induction Phase

A

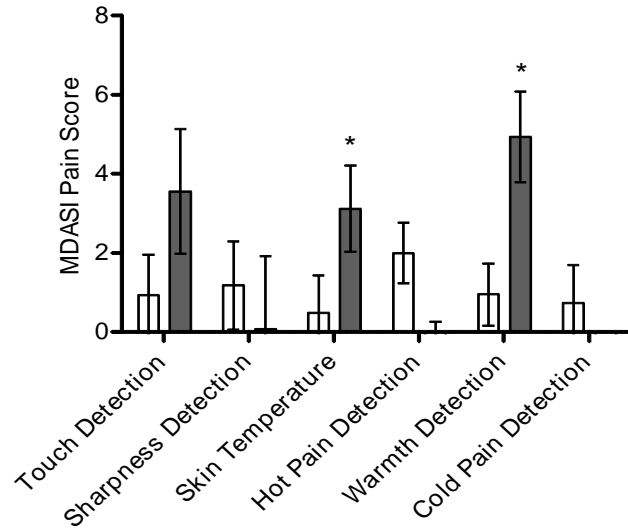


B



Maintenance Phase

C



D

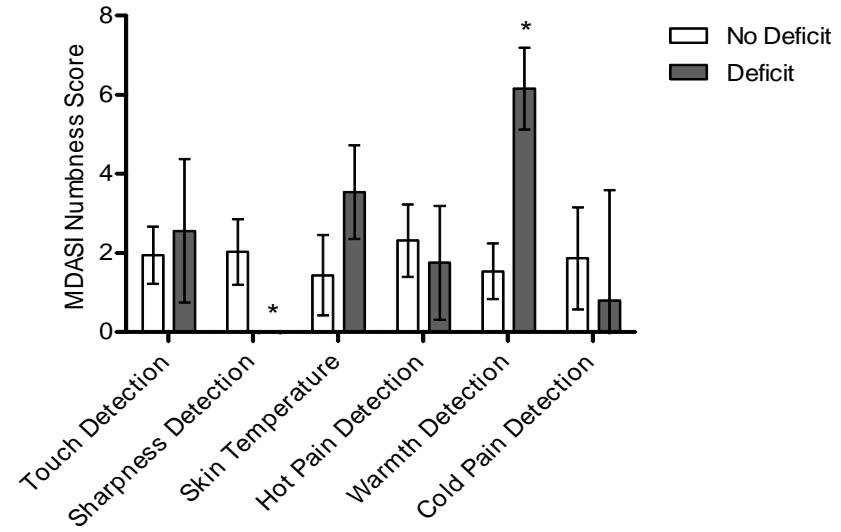
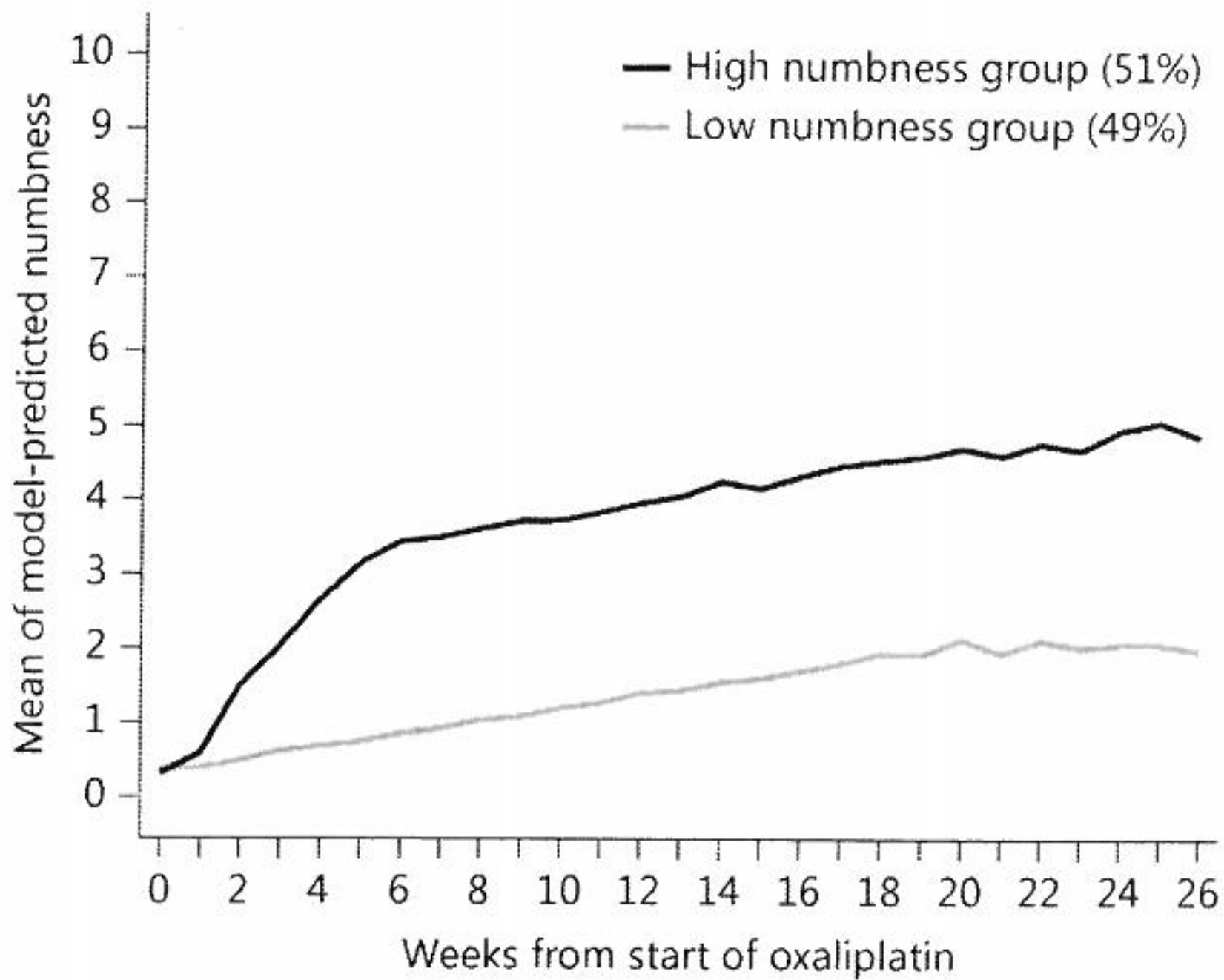


Table 2. Predictive value of baseline QST on development of CIPN symptoms: multivariate analysis (n = 60, 704 observations)

Effect	Estimate	Standard error	p > t
<i>Touch detection</i>			
Bumps Detection test	0.109	0.035	0.002
von Frey filament			
Painful area	0.218	0.333	0.513
Border area	-0.250	0.476	0.600
Volar area	0.221	0.462	0.633
<i>Sensorimotor function</i>			
Grooved Pegboard test			
Dominant hand	-0.012	0.008	0.136
Nondominant hand	0.024	0.008	0.002
<i>Other variables</i>			
Female vs. male	0.956	0.241	<0.0001
ECOG PS (1-2 vs. 0)	0.607	0.208	0.004
BMI	0.038	0.016	0.020
Opioid use (yes vs. no)	0.567	0.184	0.002

ECOG PS = Eastern Cooperative Oncology Group performance status. Multivariate mixed model, with all other factors controlled.



Both Retrospective & Prospective CIPN Studies indicate differential effects of chemotherapy on primary afferent fibers:

- Loss of Function in $A\beta$ fibers: Meissner's & Merkel Disks signaling impaired; sensorimotor impairment
- Partial Loss of Function in $A\delta$ fibers: Cool and warm detection impaired while sharpness detection mostly preserved.
- Partial Loss of Function in C fibers: Warmth and cool detection impaired while heat detection preserved

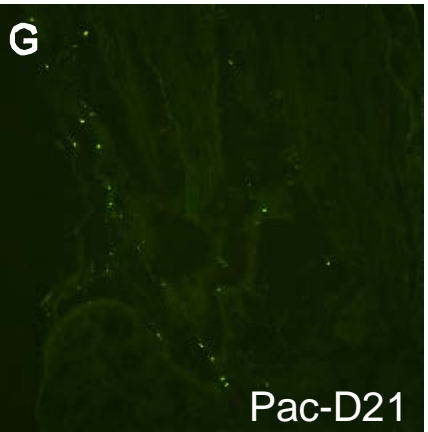
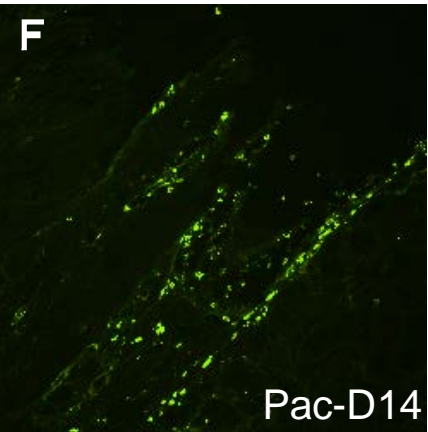
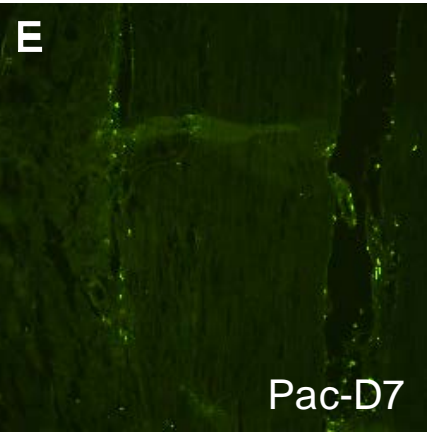
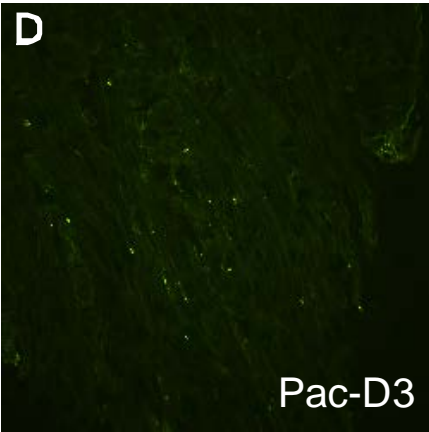
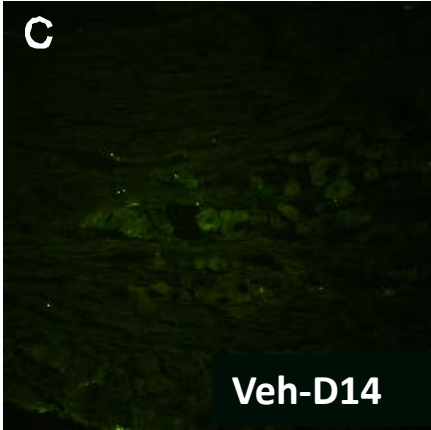
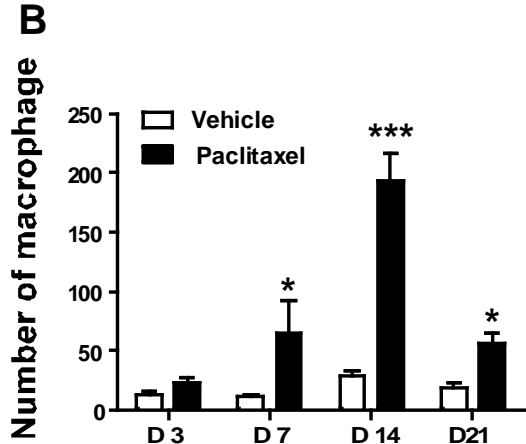
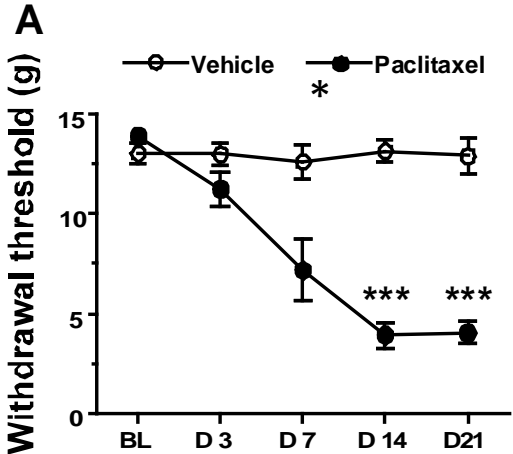
Chronic CIPN Patients:

- Loss of ENF's in areas of Pain
- Numbness, Tingling (Pins and Needles)
- Burning



Taxol induced the expression of CD68 in DRG

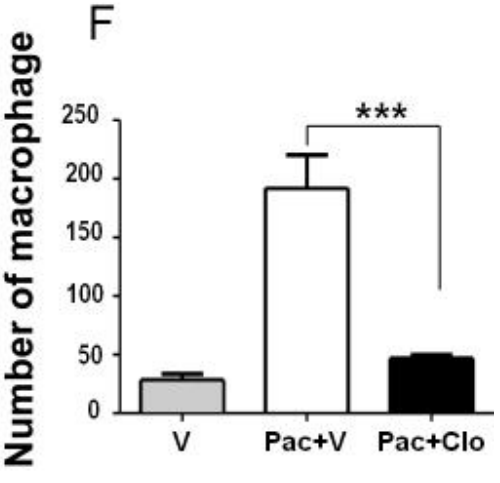
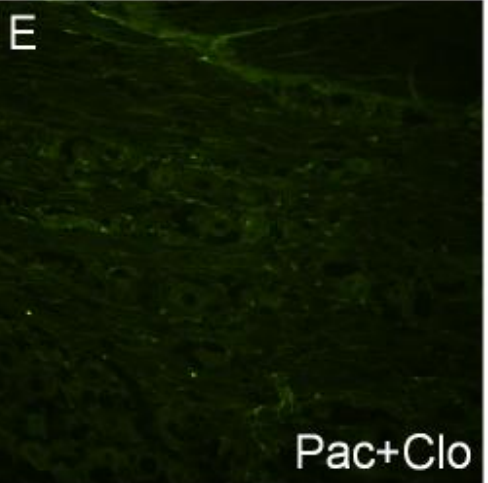
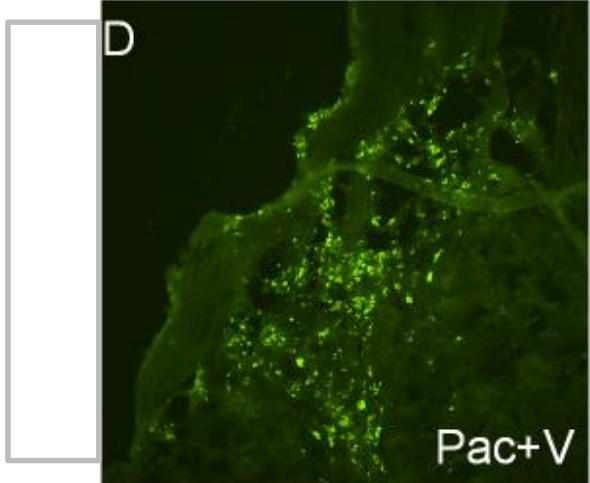
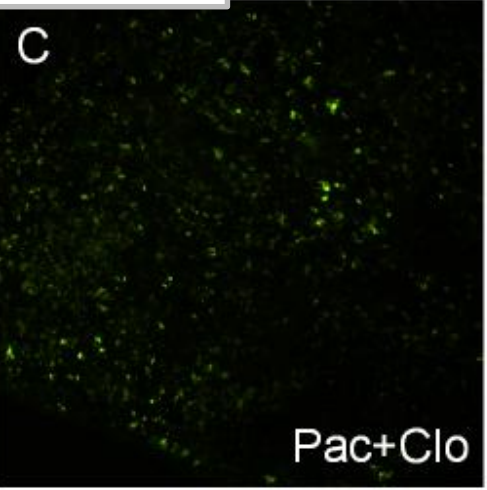
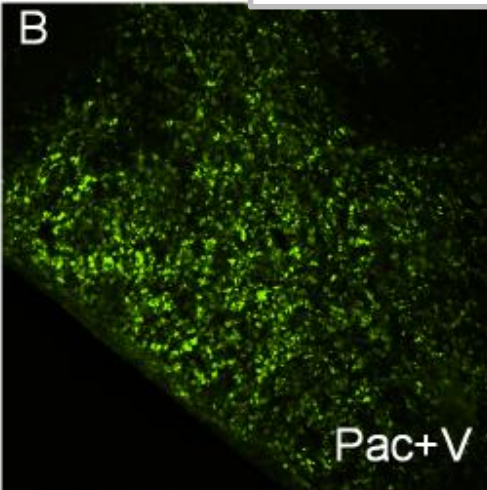
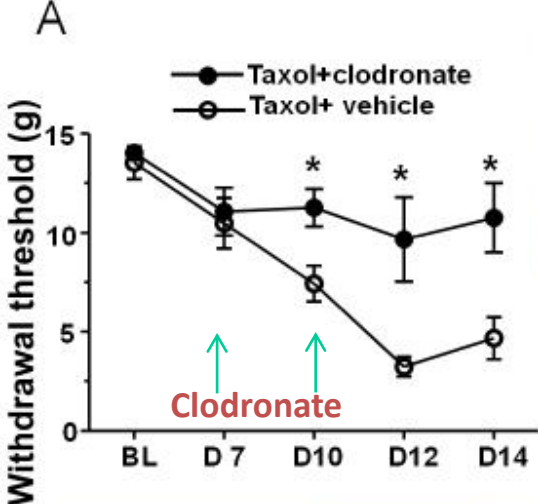
Macrophage (CD68 staining) immunoactivity was detected in the L4-5 DRG



Pac-Paclitaxel Veh-Vehicle

Clodronate reduced CD68 expression in treated rat DRG and partially reverse the neuropathic pain induced by taxol

Clodronate is a macrophage killer



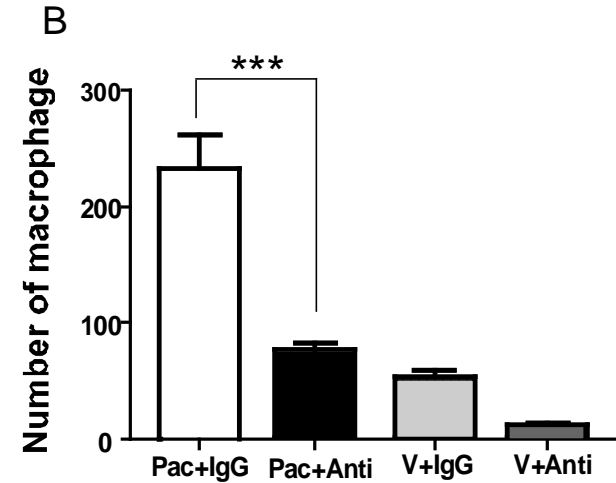
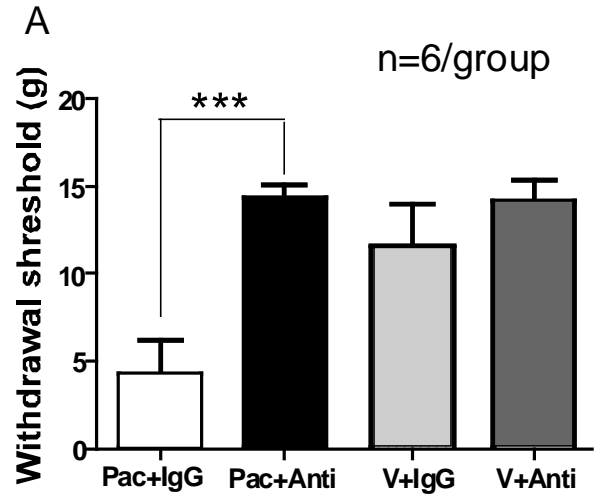
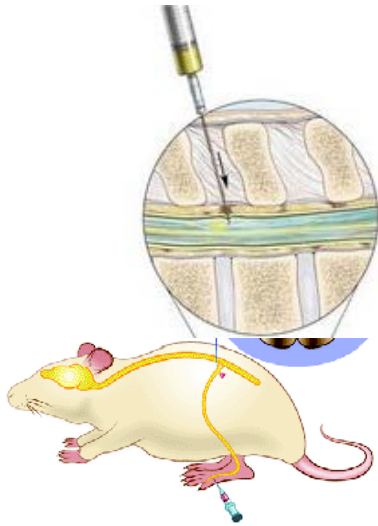
Pac-Paclitaxel

Clo-Clodronate

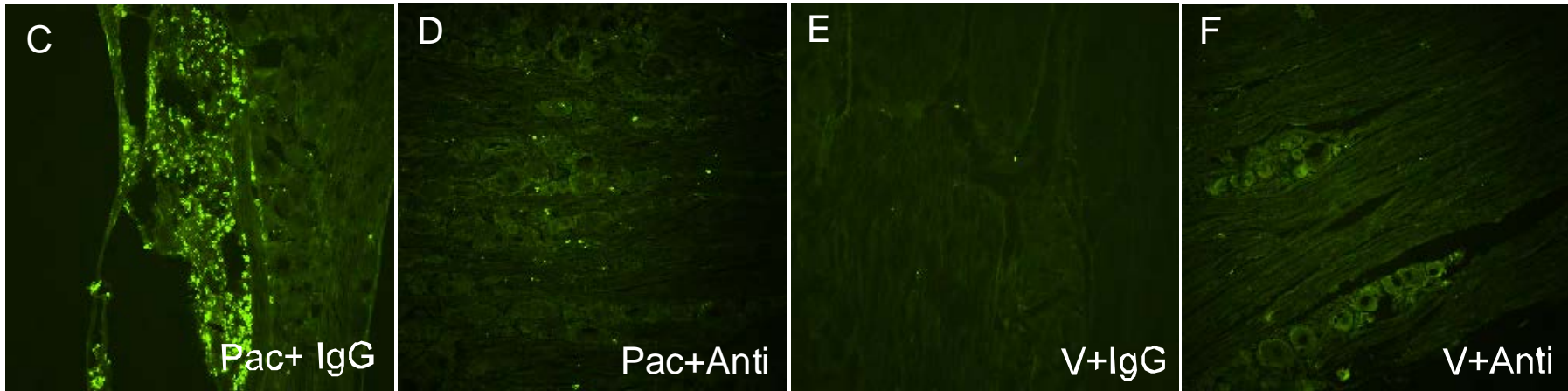
V-Vehicle

Intrathecal anti-MCP-1 totally blocked taxol induced neuropathic pain on D14 and prevent the infiltration of macrophage in DRG

L5-L6 intervertebral space



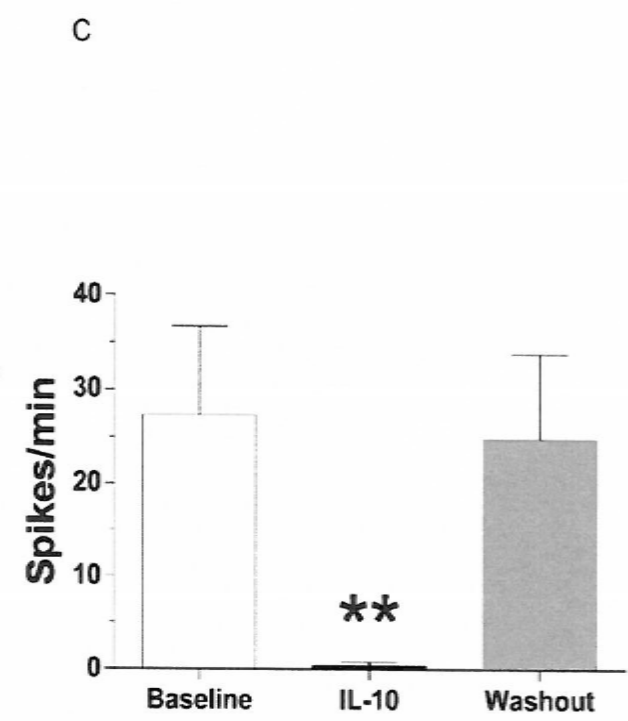
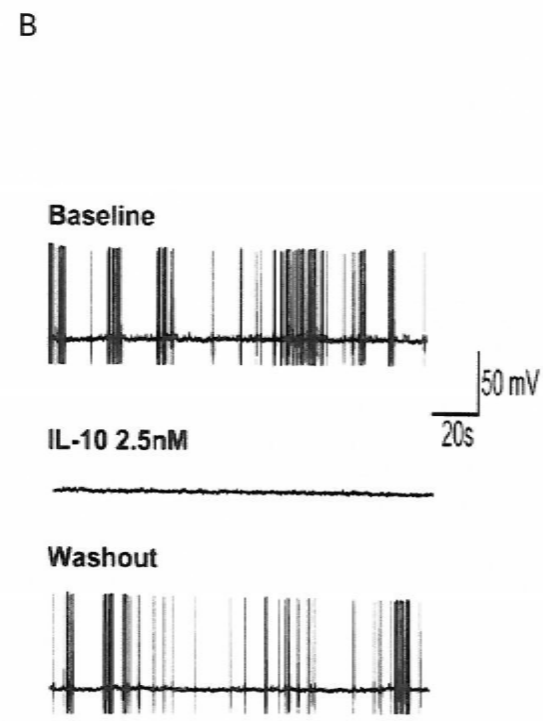
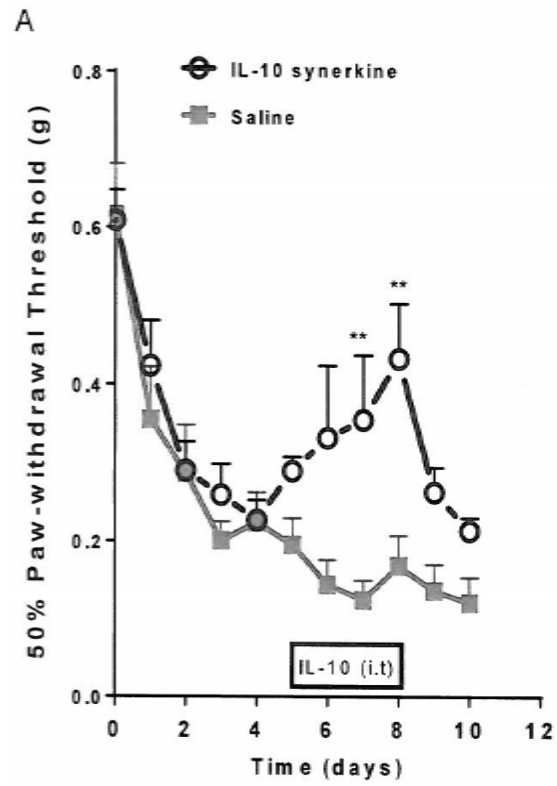
Immunoactivity of macrophage in DRG



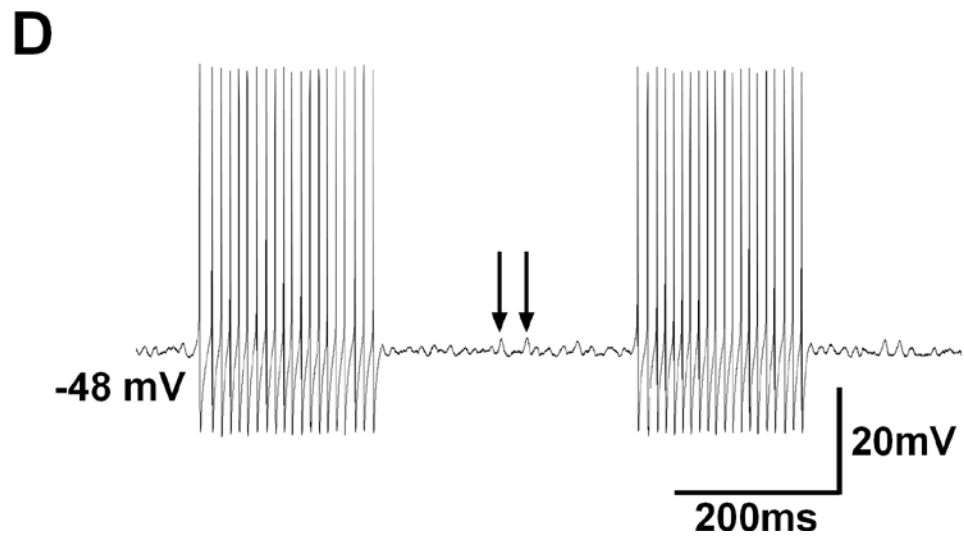
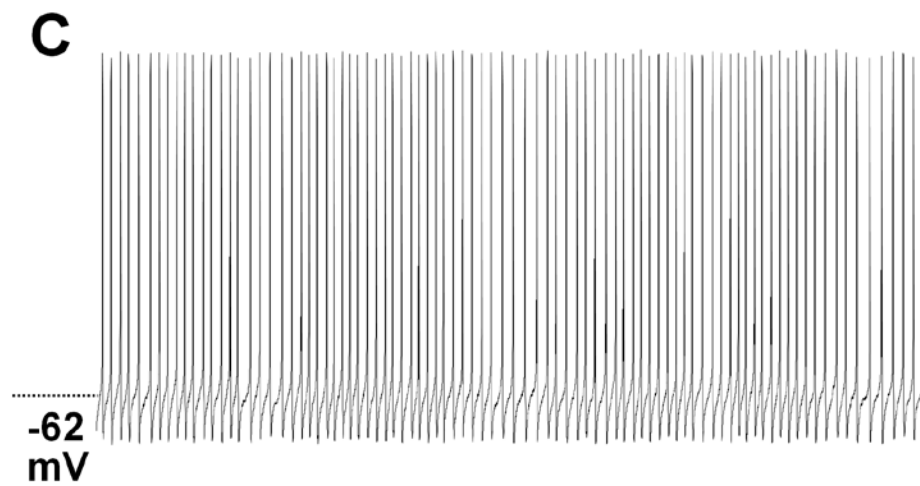
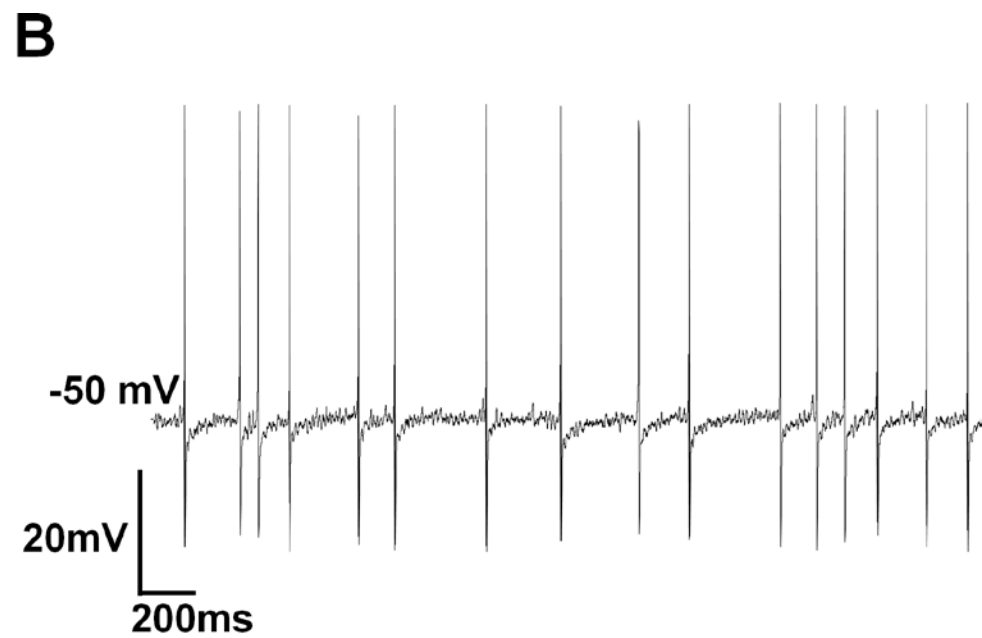
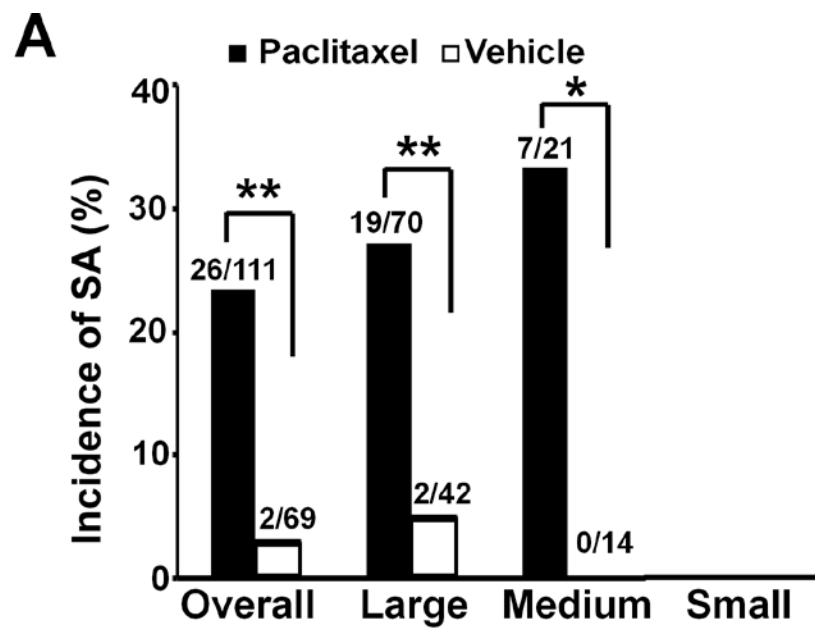
Pac-Paclitaxel

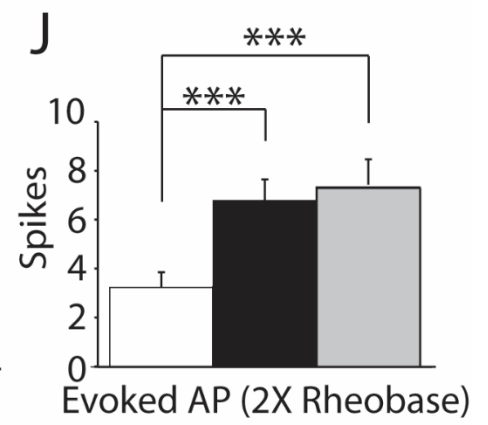
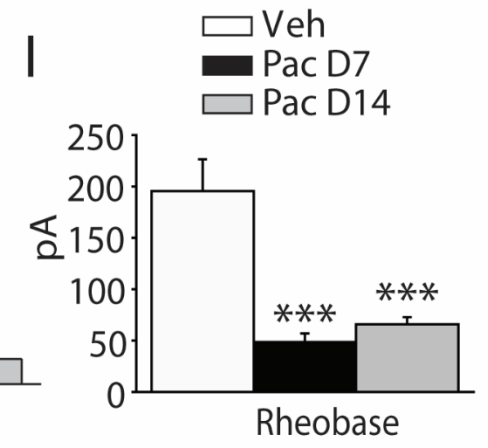
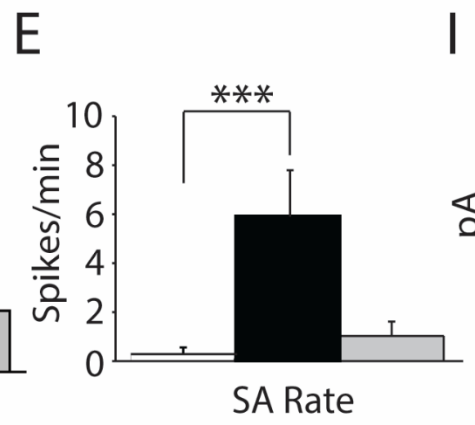
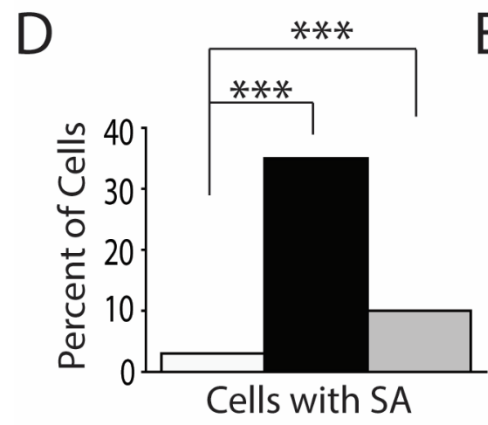
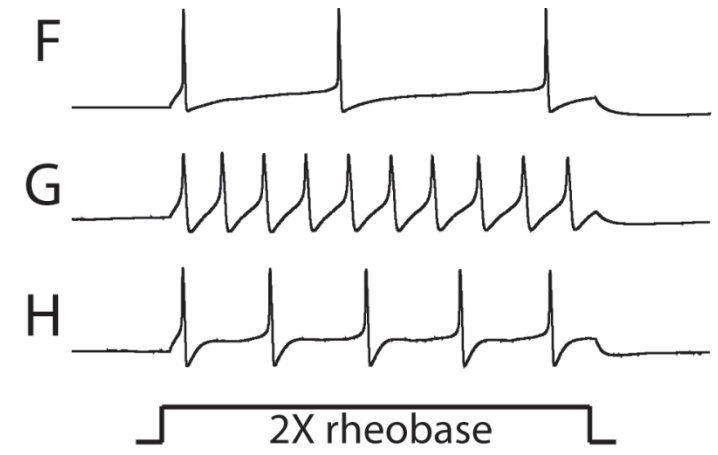
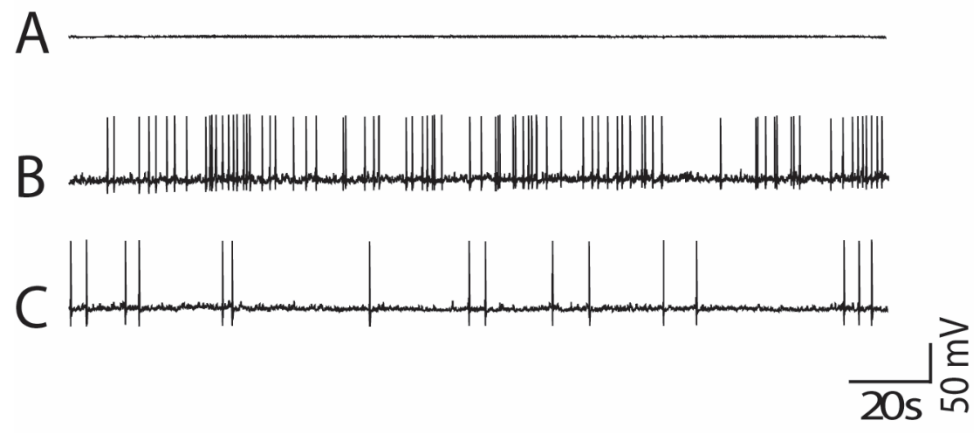
V-Vehicle

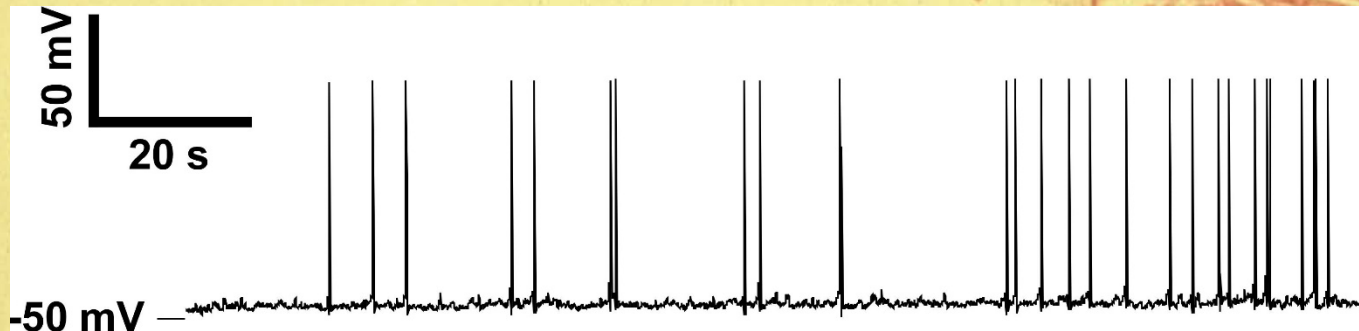
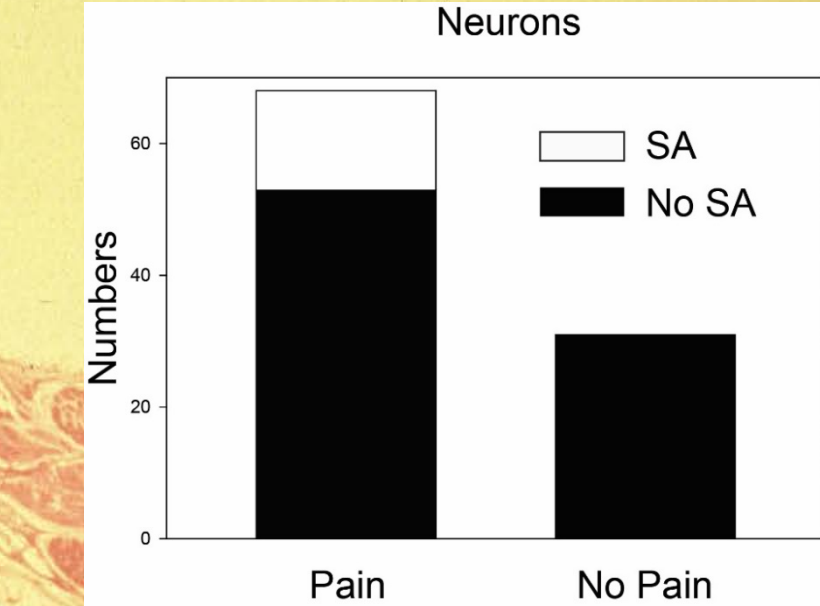
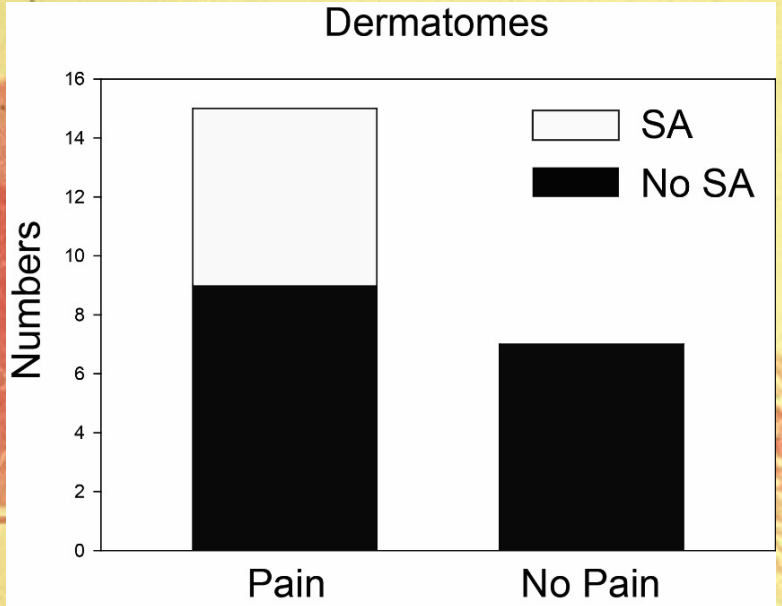
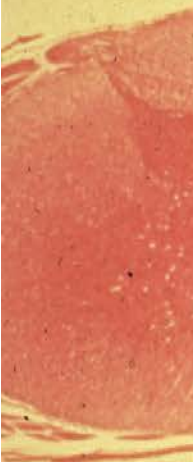
Anti-Anti MCP-1 antibody

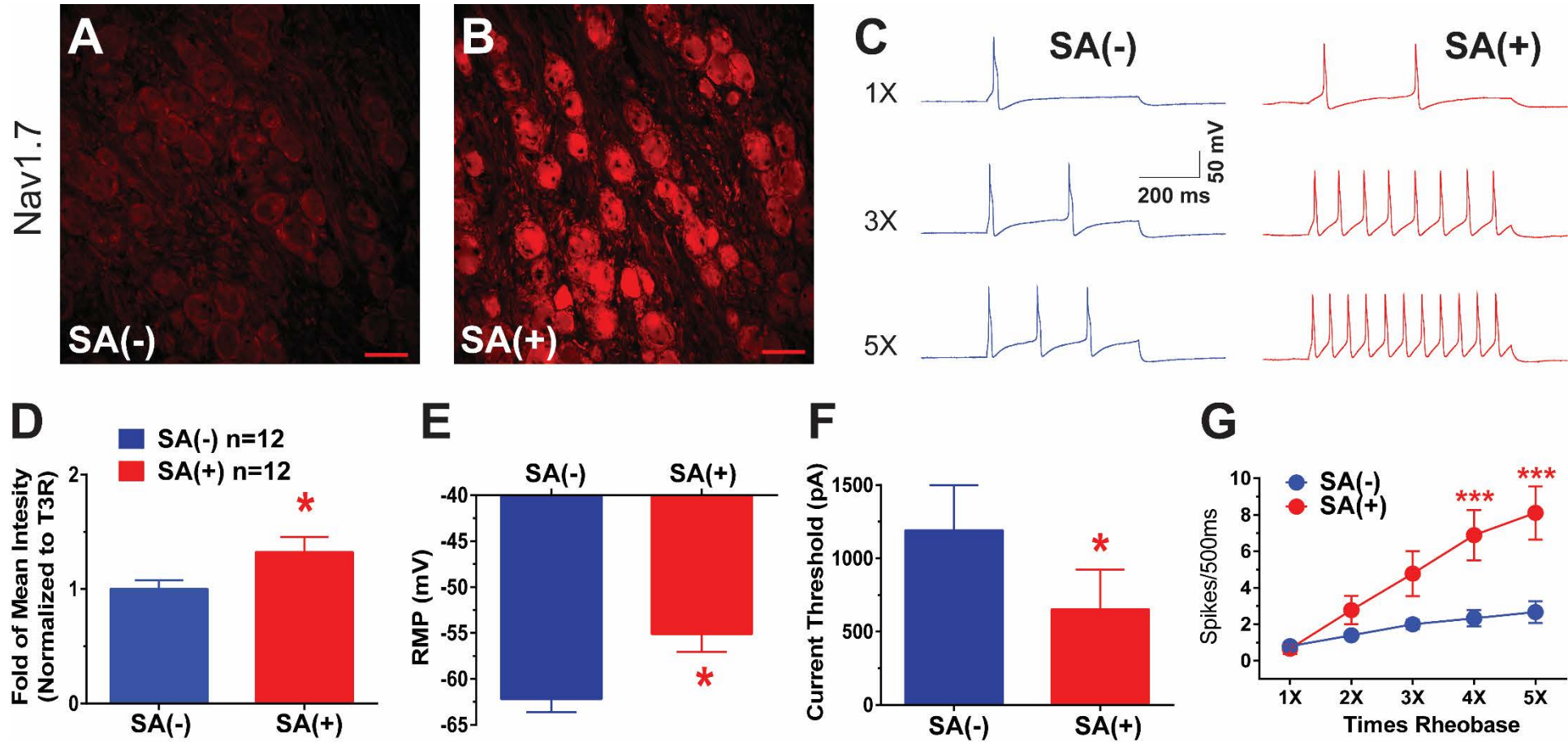


Krukowski et al, 2016

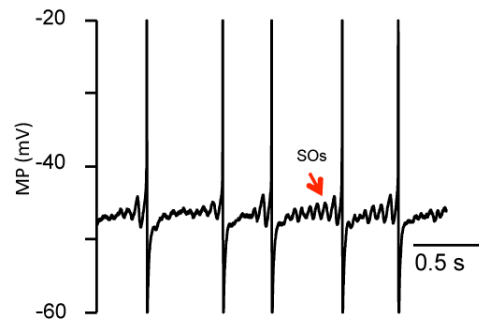




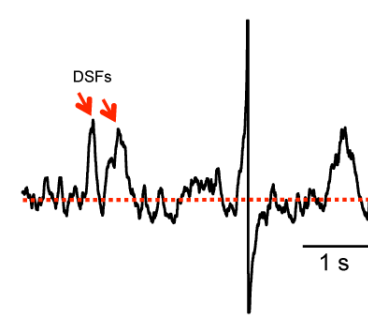




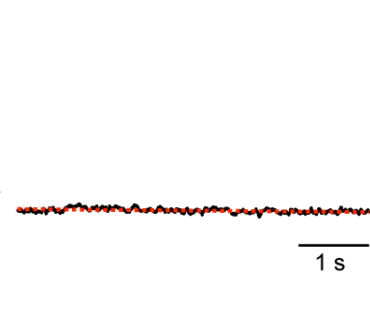
A A-type, paclitaxel



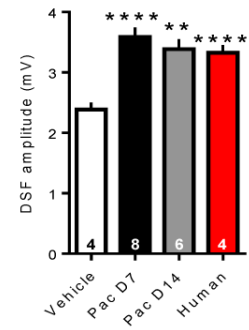
B C-type, paclitaxel



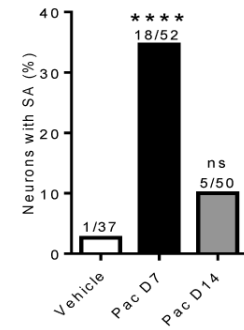
C C-type, vehicle

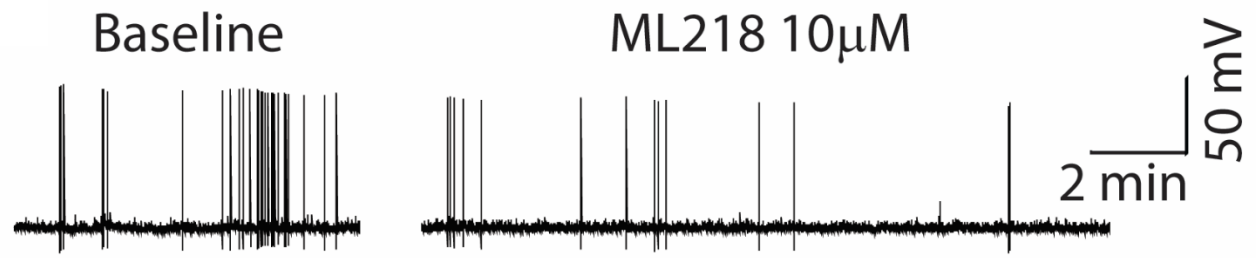
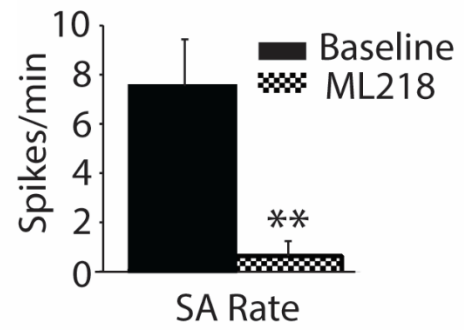


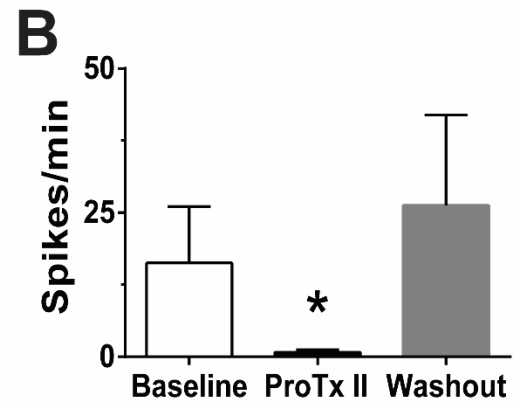
D C-type, depol SFs



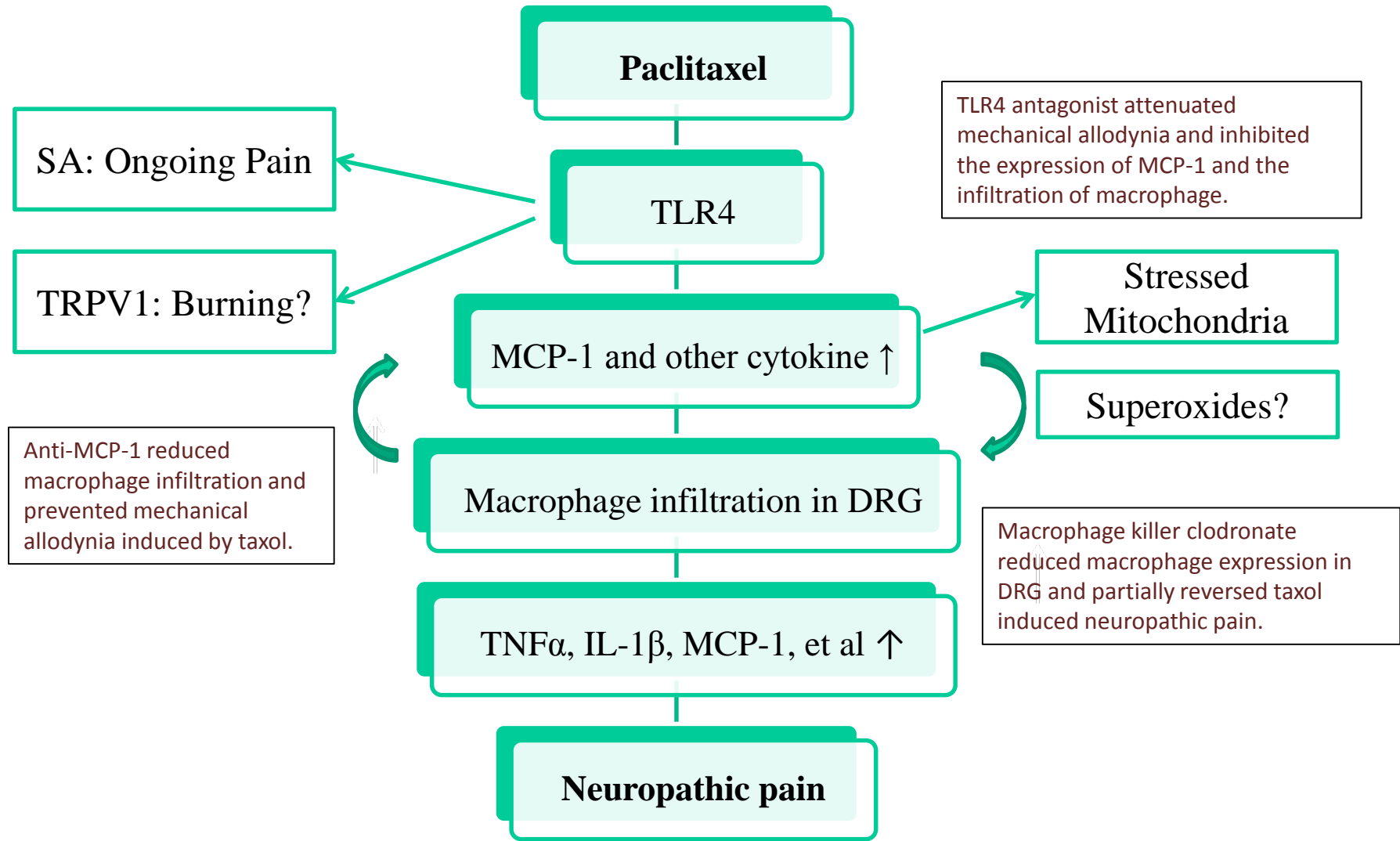
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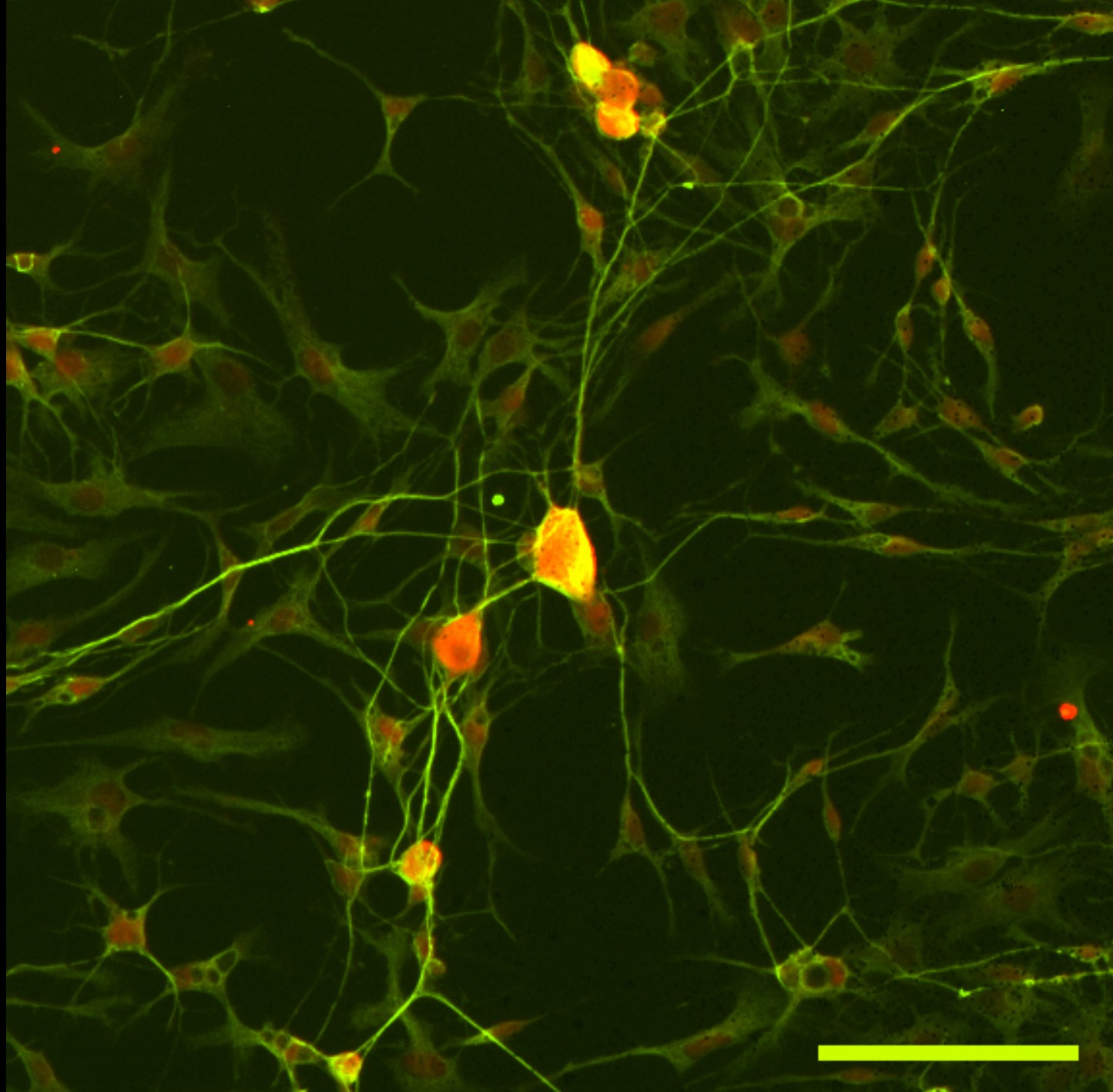


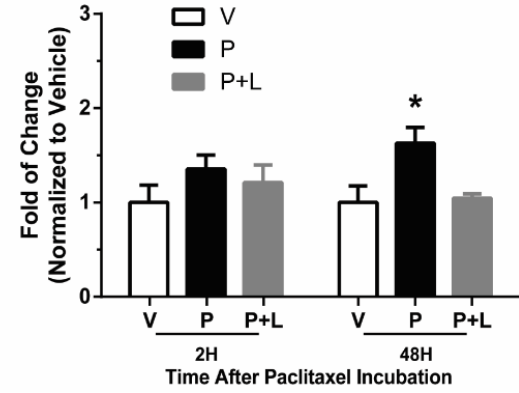
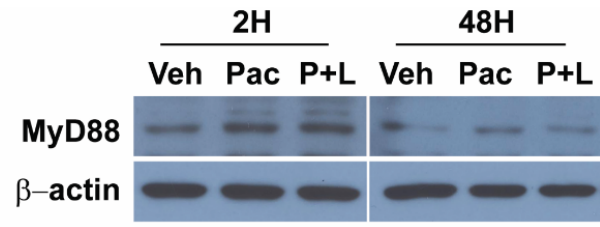
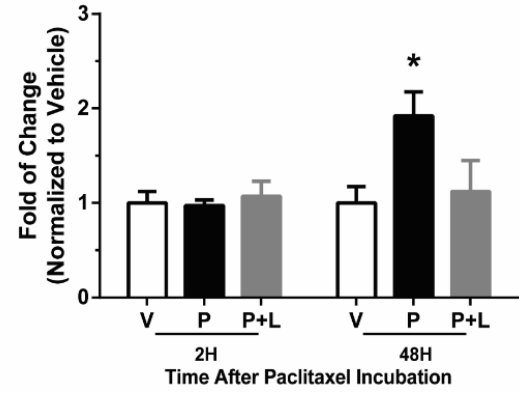
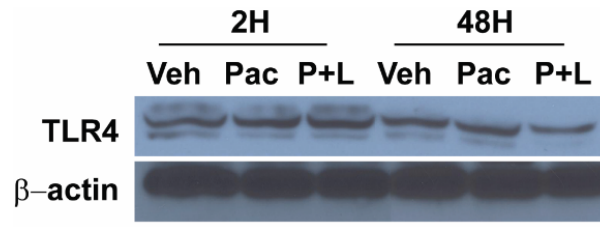


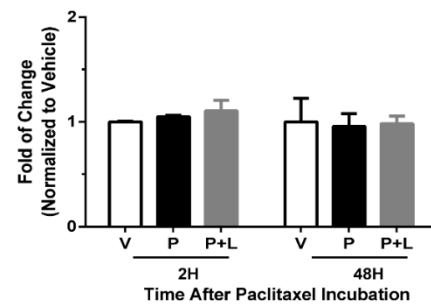
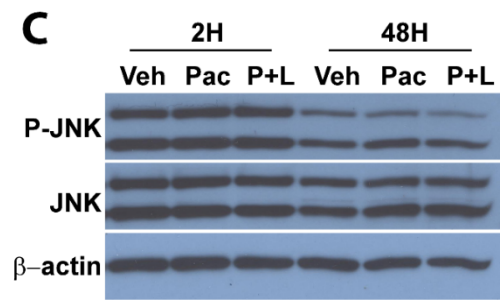
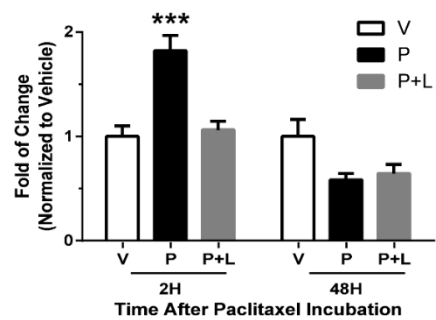
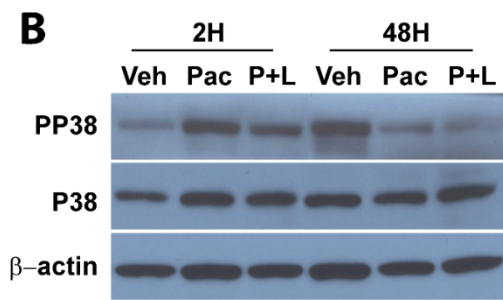
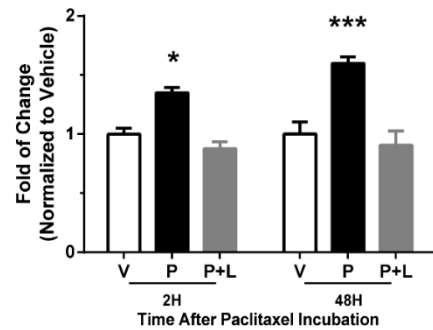
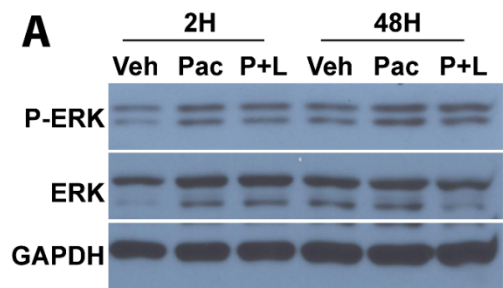


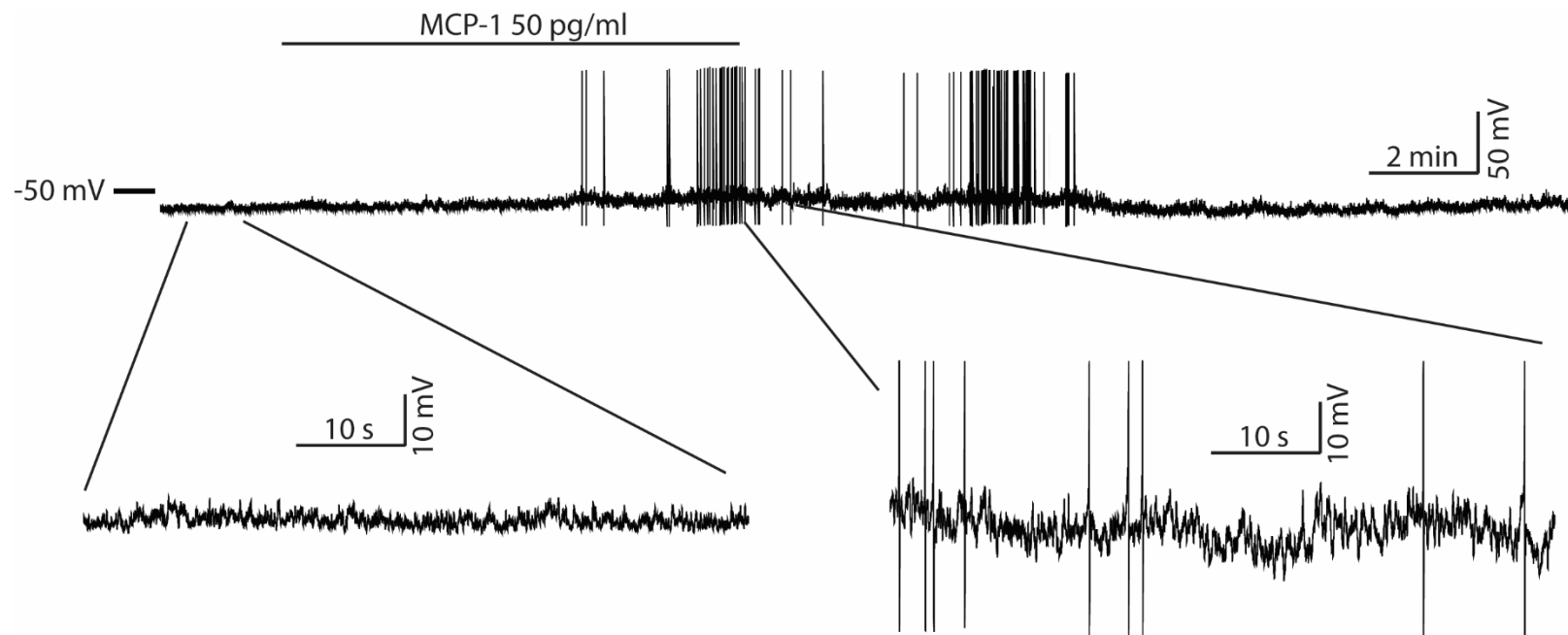
Summary and Conclusion





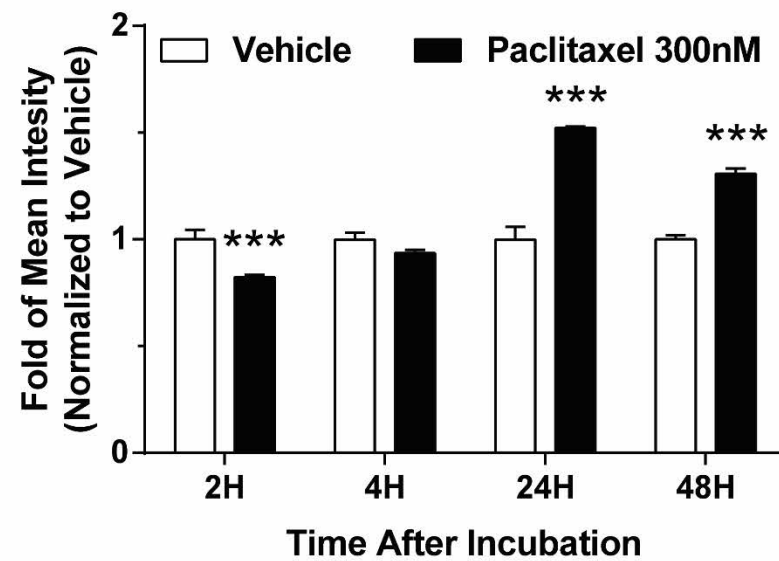
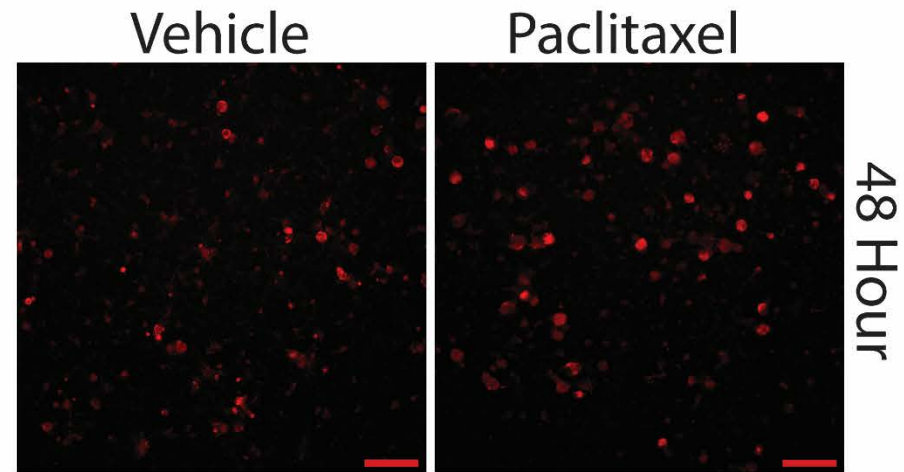
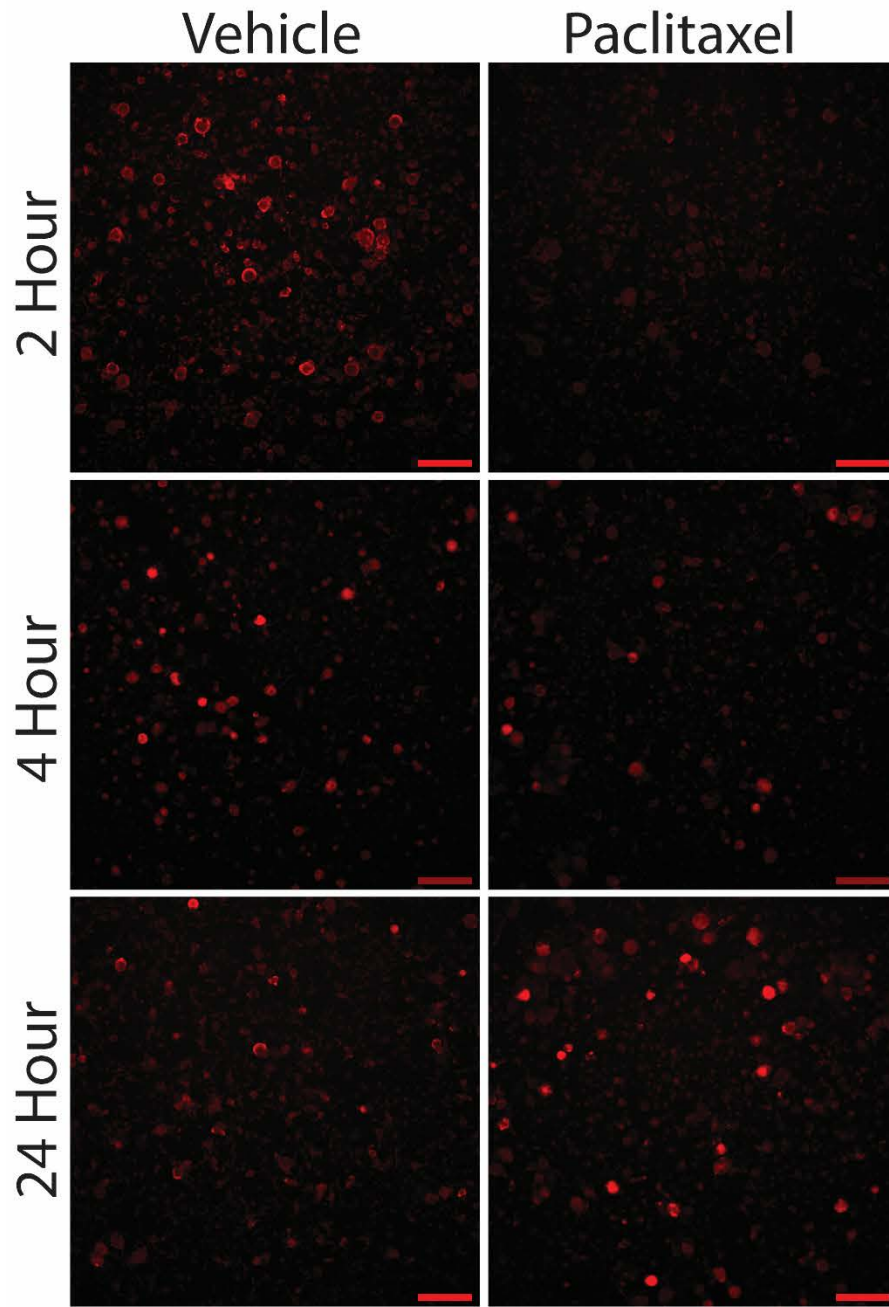






Naïve DRG culture
Small size neuron, no response;
medium size neuron, 8/15 SA or fluctuation.

MitoSOX



Haijun Zhang

Yan Li

Alyssa Kosturakis

Seo-Yeon Yoon

Jessica Boyette-Davis

Allen Burton

Wen-Jun Xin

Hong-Mei Zhang

