

Addressing the Opioid Crisis: A Microphysiological Model of Synaptic Transmission of Pain

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Microphysiological Systems (MPS): Bridging Human and Animal Research

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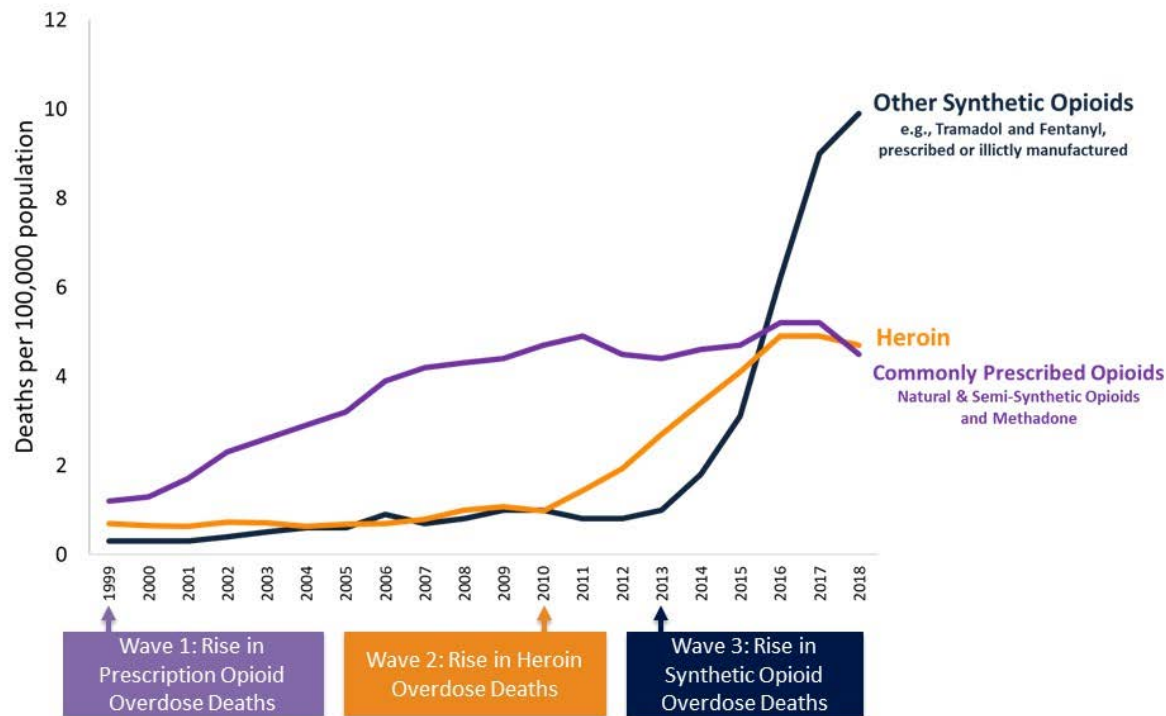




Opioid Overdose Epidemic



3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

cdc.gov/drugoverdose/epidemic

THE OPIOID EPIDEMIC BY THE NUMBERS



130+

People died every day from opioid-related drug overdoses³ (estimated)



10.3 m

People misused prescription opioids in 2018¹



47,600

People died from overdosing on opioids²



2.0 million

People had an opioid use disorder in 2018¹



808,000

People used heroin in 2018¹



81,000

People used heroin for the first time¹



2 million

People misused prescription opioids for the first time¹



15,349

Deaths attributed to overdosing on heroin (in 12-month period ending February 2019)²



32,656

Deaths attributed to overdosing on synthetic opioids other than methadone (in 12-month period ending February 2019)²

SOURCES

1. 2019 National Survey on Drug Use and Health, Mortality in the United States, 2018
2. NCHS Data Brief No. 329, November 2018
3. NCHS, National Vital Statistics System. Estimates for 2018 and 2019 are based on provisional data.

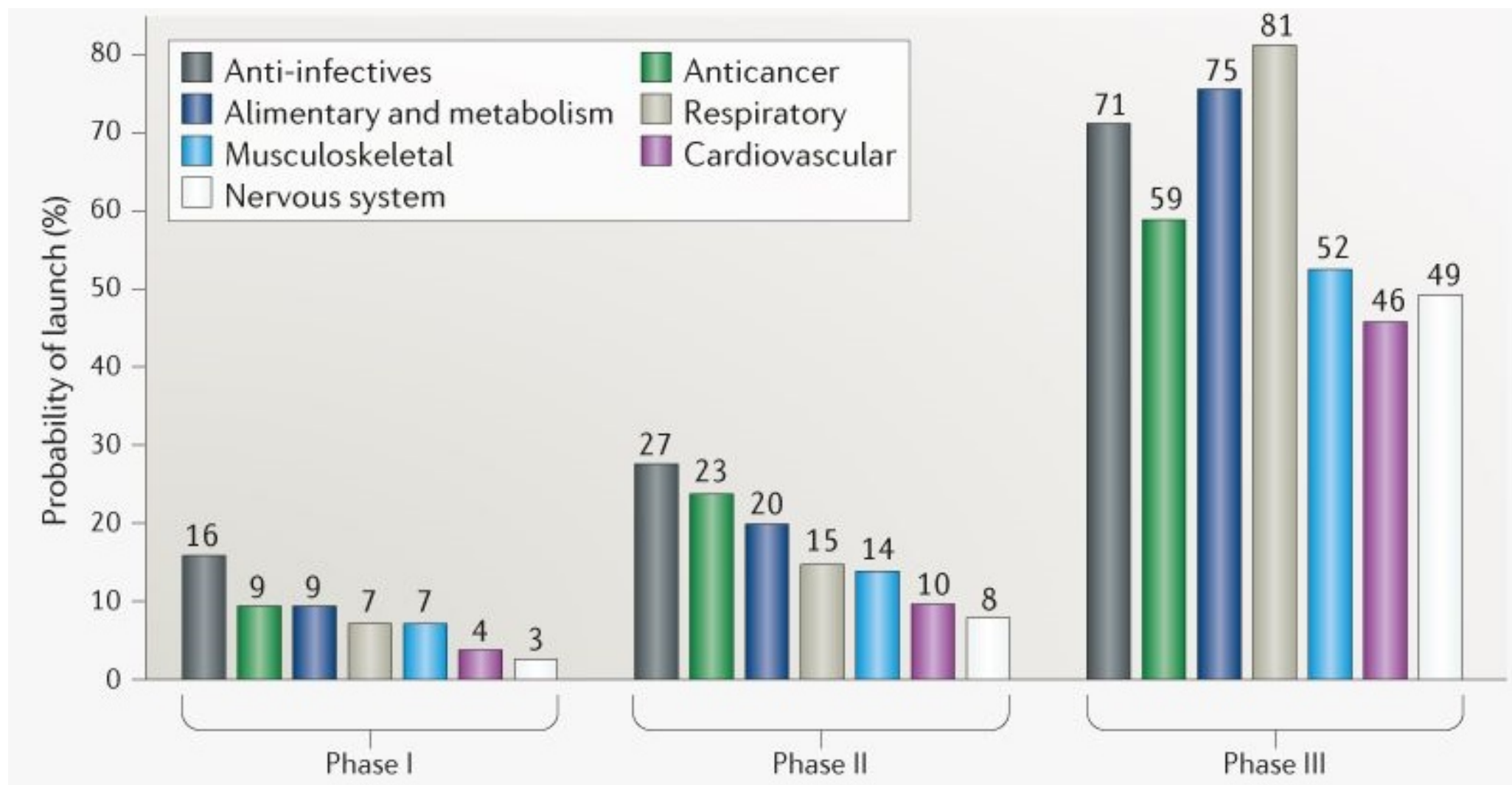
hhs.gov/opioids

hhs.gov/opioids



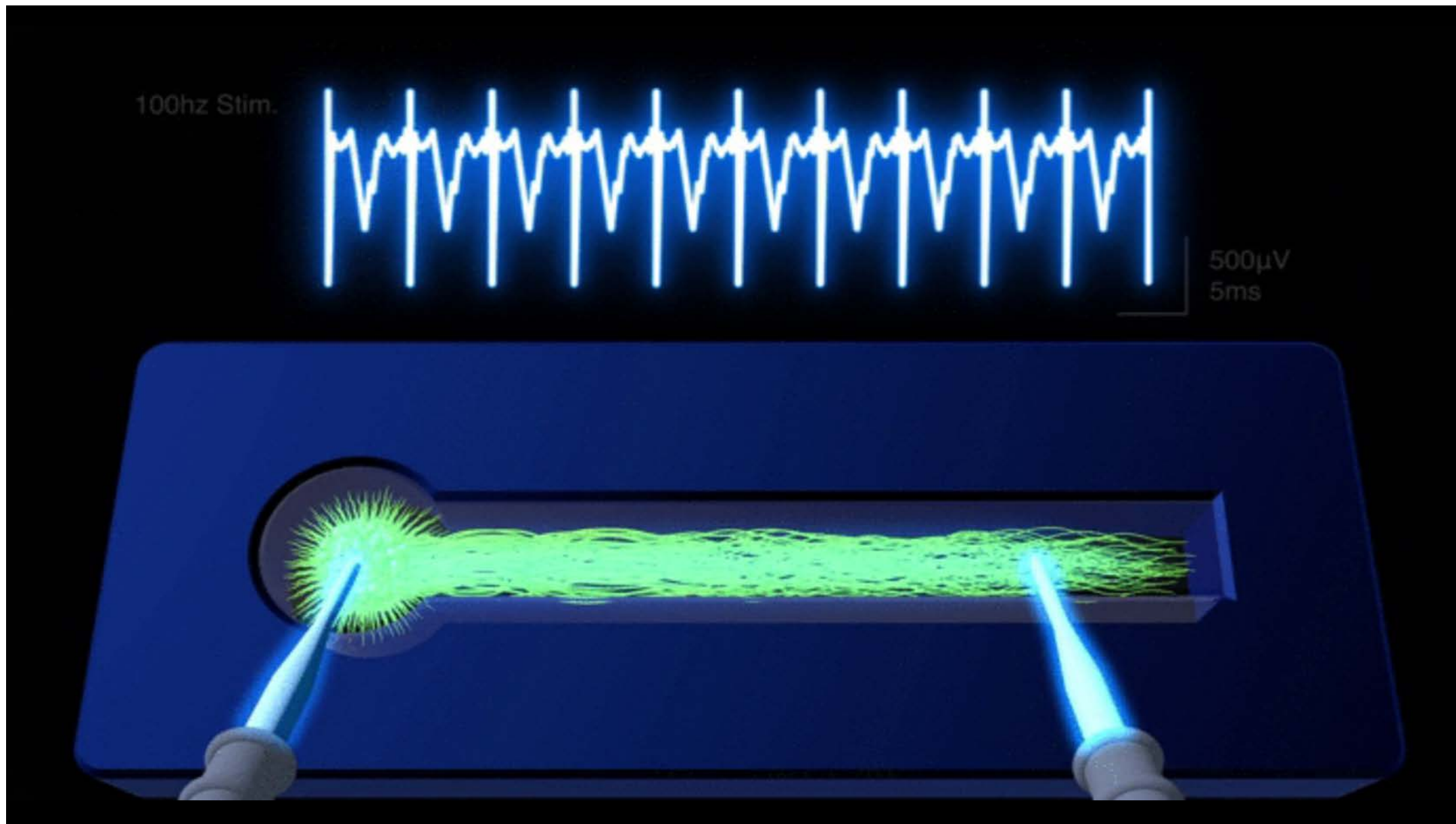


Drug Development Especially Poor in Nervous System



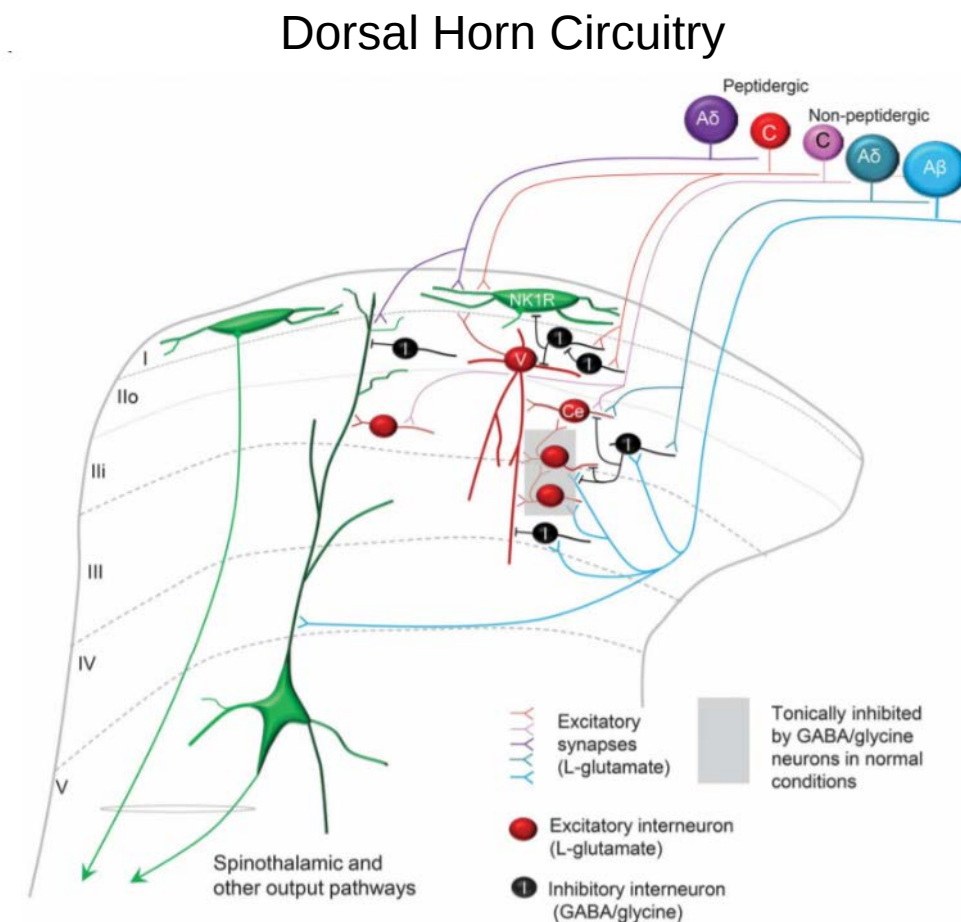
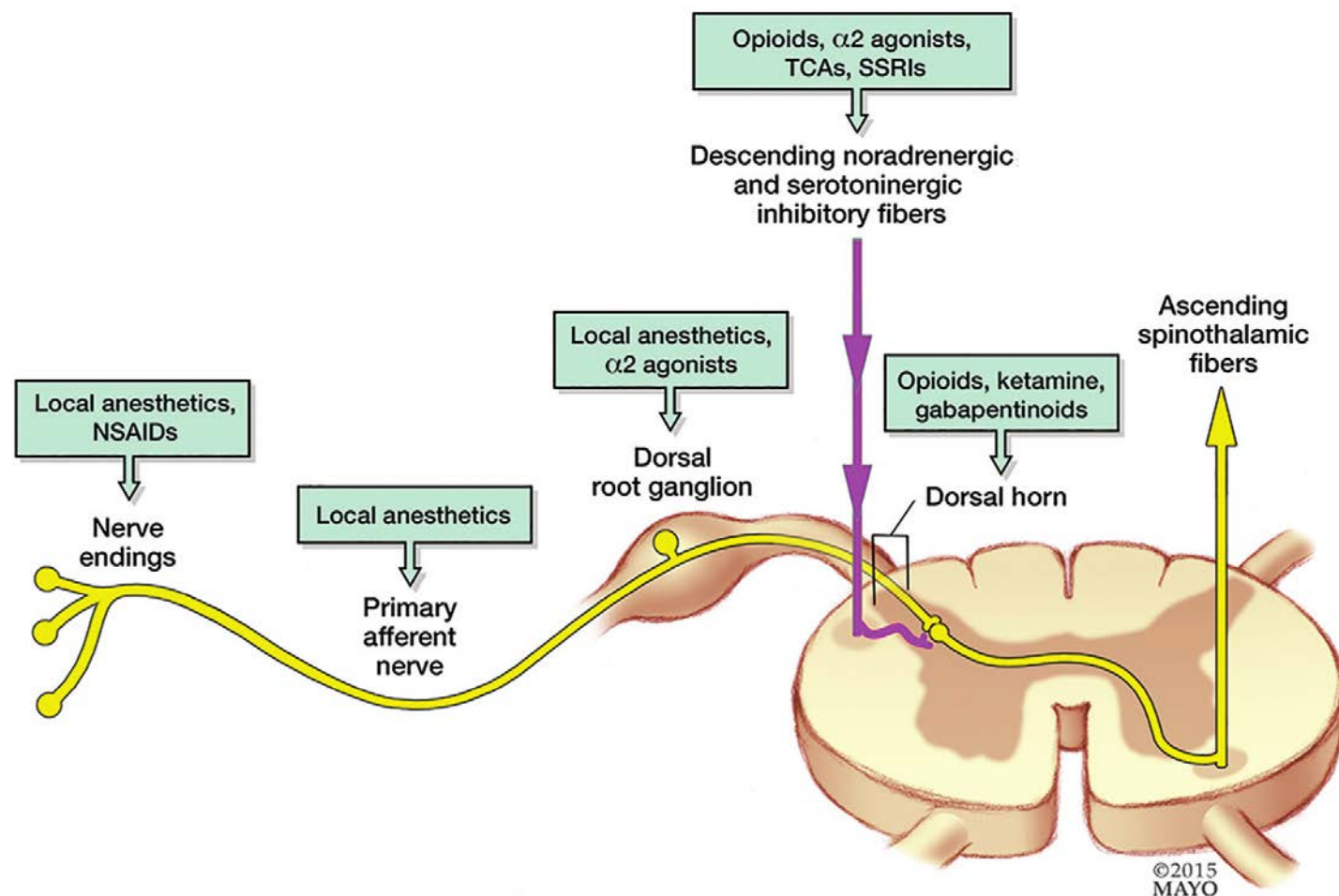


Peripheral “Nerve-on-a-Chip” Platform





Afferent Nociceptive Signaling – Physiological Pain

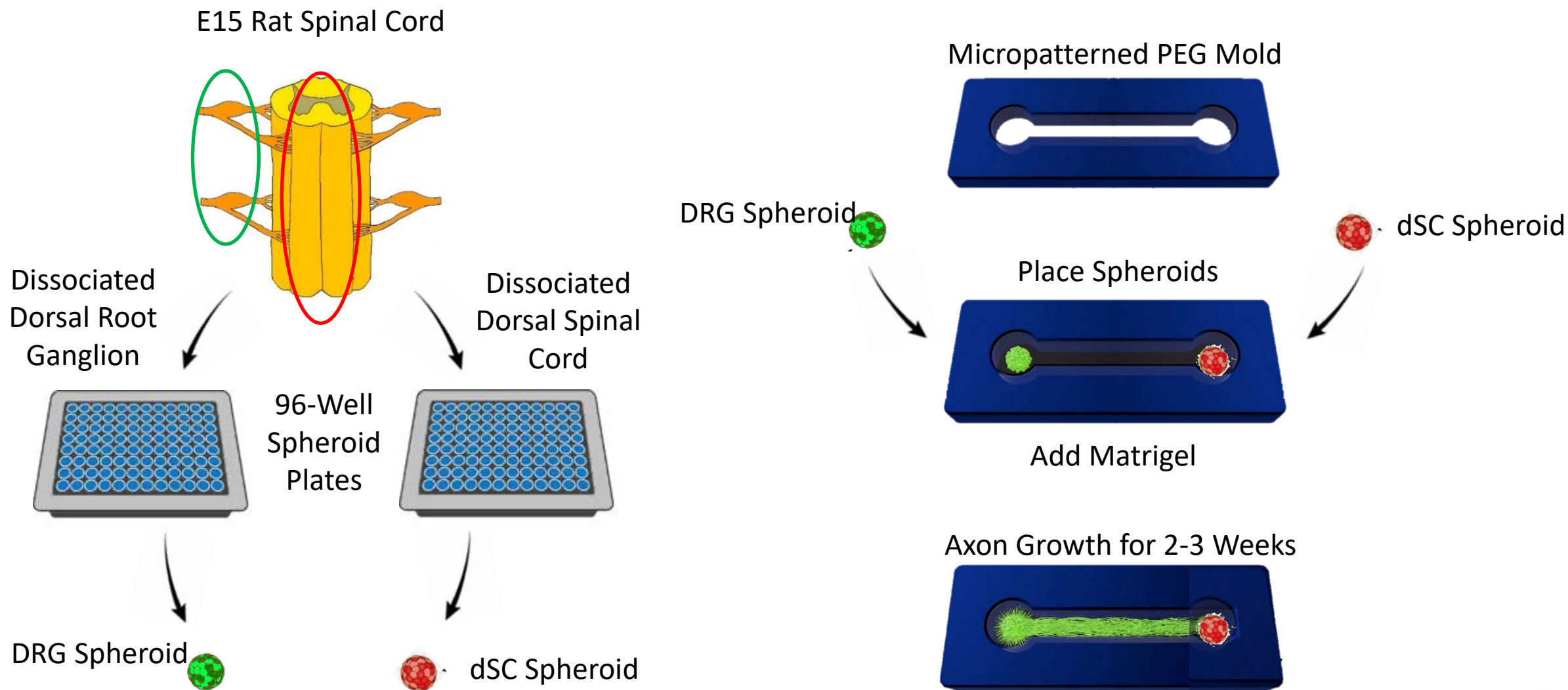


Gorlin et al., *J. Anaesthesiology Clin. Pharm.* 2016





Model of Afferent Nociception – Physiologic “Pain”

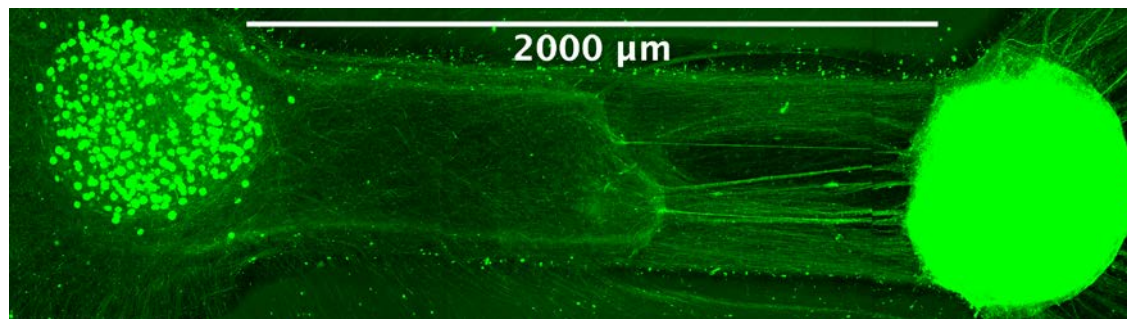
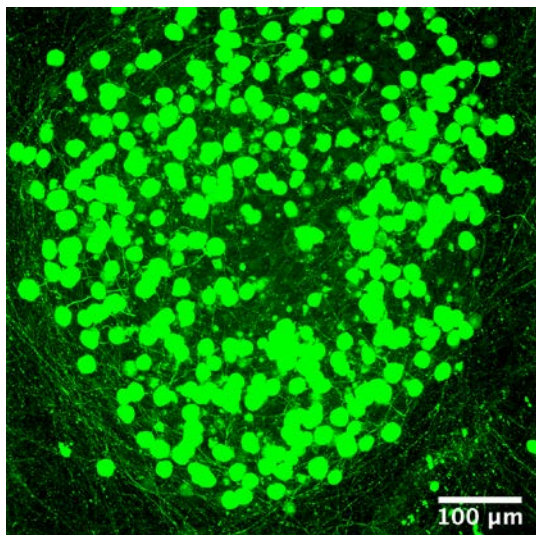




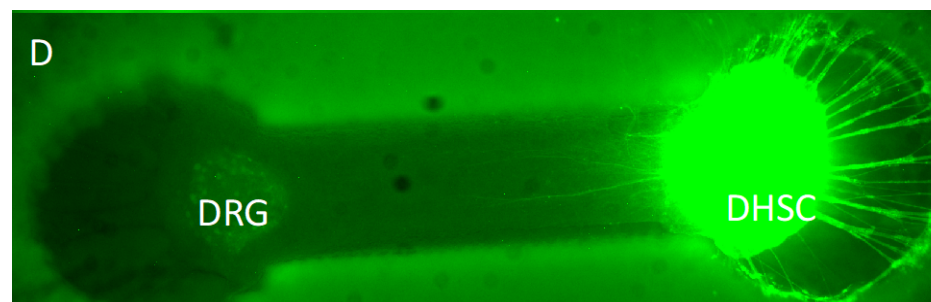
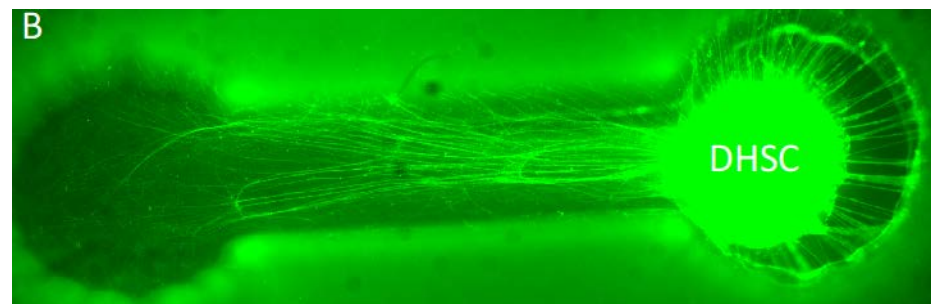
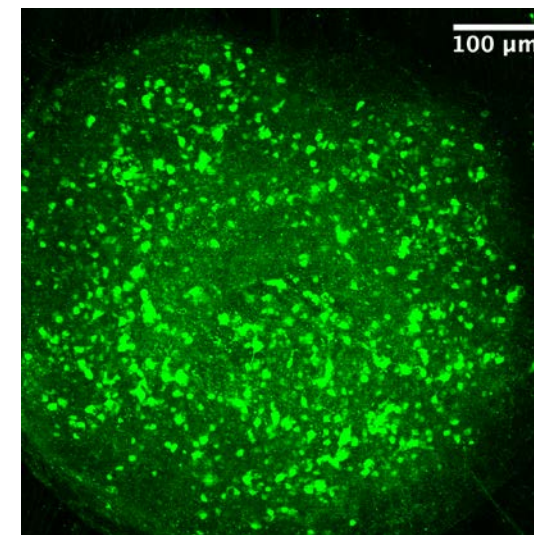
Morphology Revealed by Virally-Encoded GFP



DRG Spheroid



DHSC Spheroid



Spontaneous Unidirectional Neurite Outgrowth

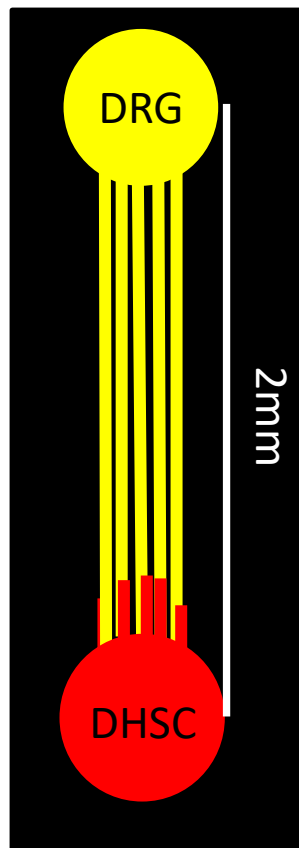




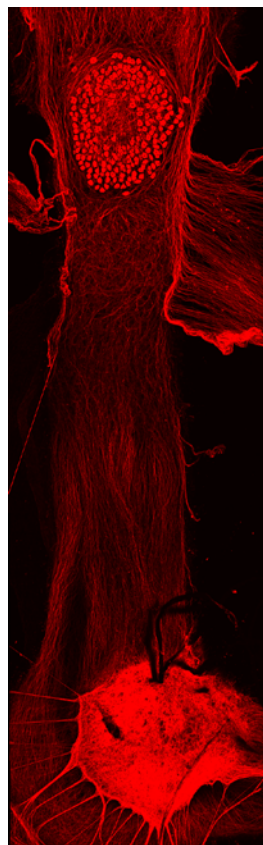
IHC Mapping of Relevant Tissue Markers



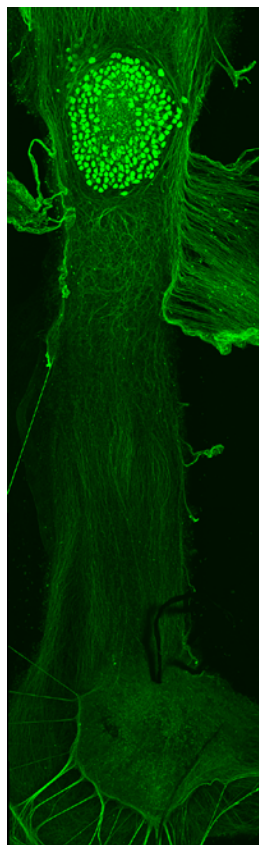
Tissue Map
Schematic



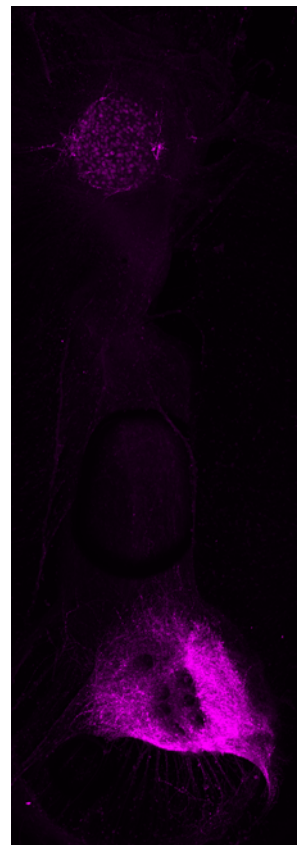
B3-Tubulin
(All Neurites)



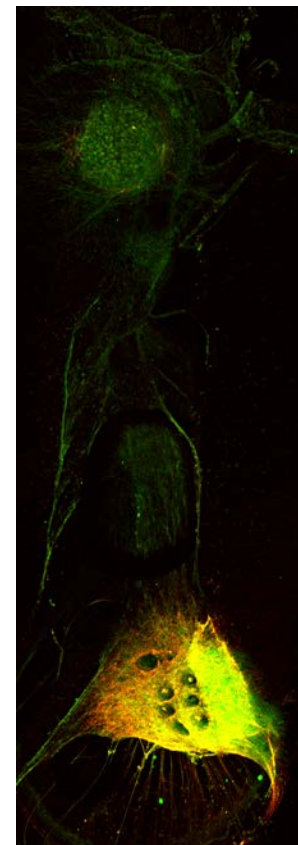
Peripherin
(PNS Tissue)



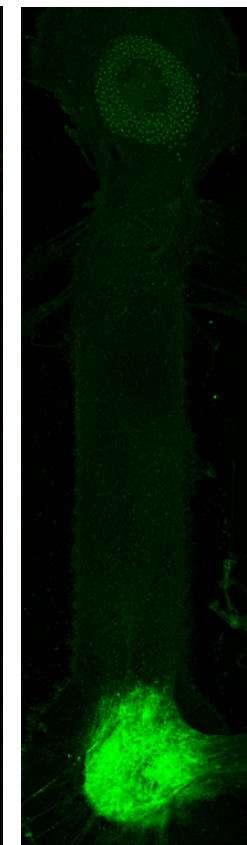
MAP2
(Dendrites)



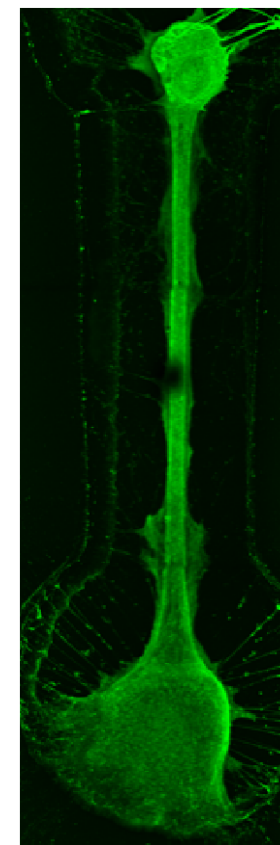
Synapsin-I/PSD95
(Pre/Post Synaptic)



vGAT
(GABA Receptor)



μ -Opioid
Receptor





Functional Connectivity Shown by Optogenetics & Ca^{2+}

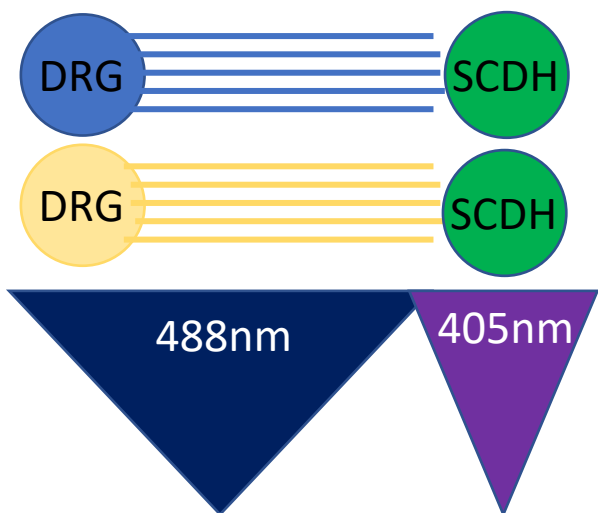


CaMPARI (Calcium Modulated Photoactivatable Ratiometric Integrator)

Simultaneous
Photostimulation

ChR2-Expressing DRG
Wild-Type DRG

CaMPARI-2
Expressing SCDH



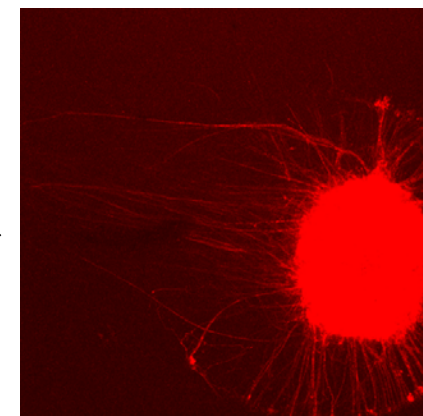
Ca^{2+} -Dependent
CaMPARI
Photoconversion

Photoconverted
CaMPARI-2



Image Integrated
 Ca^{2+} Response in
Red Channel

Image Integrated
 Ca^{2+} Response

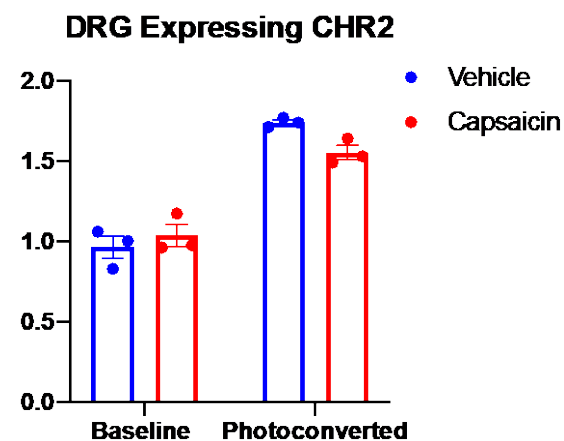
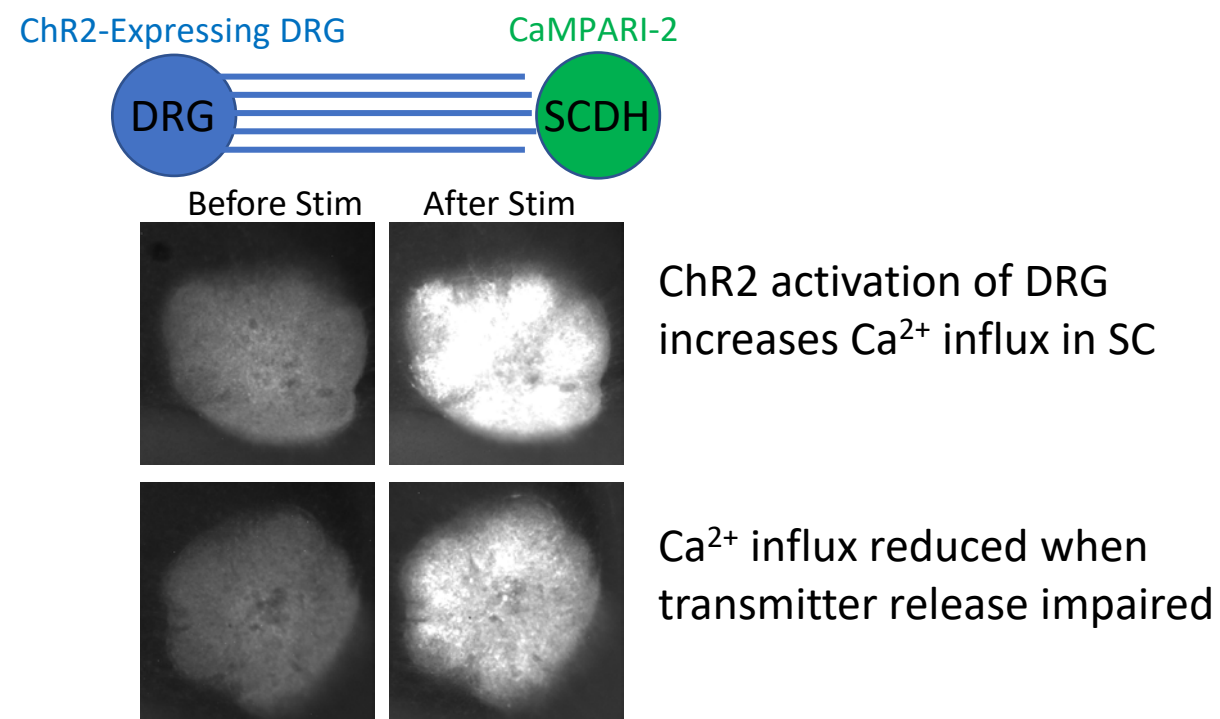
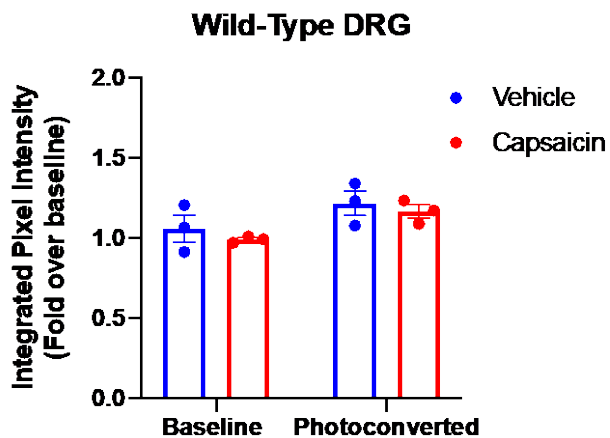
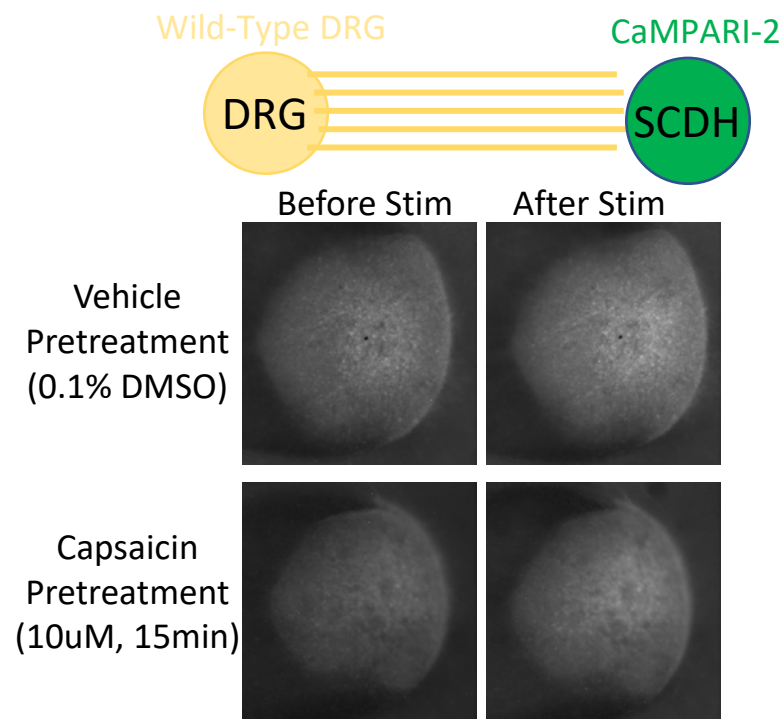


Stimulate DRG tissue with ChR-2 and 488 nm light | Record Integrated Ca^{2+} Response in SCDH tissue



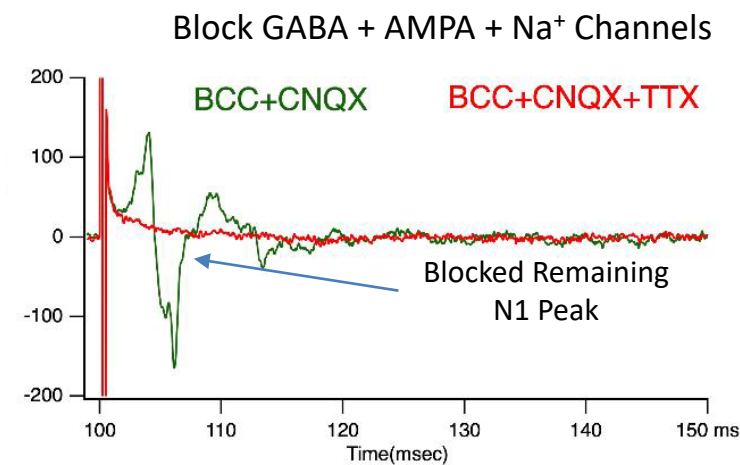
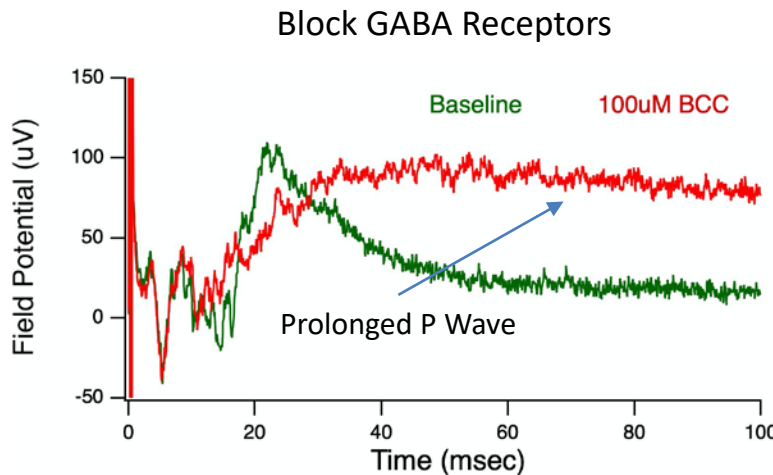
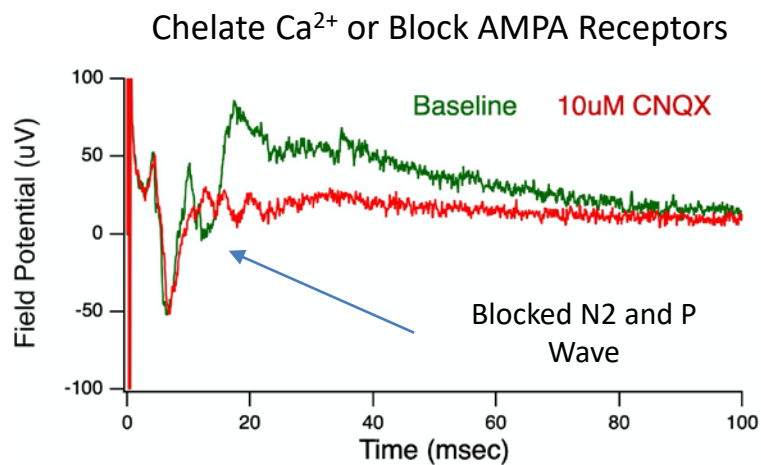
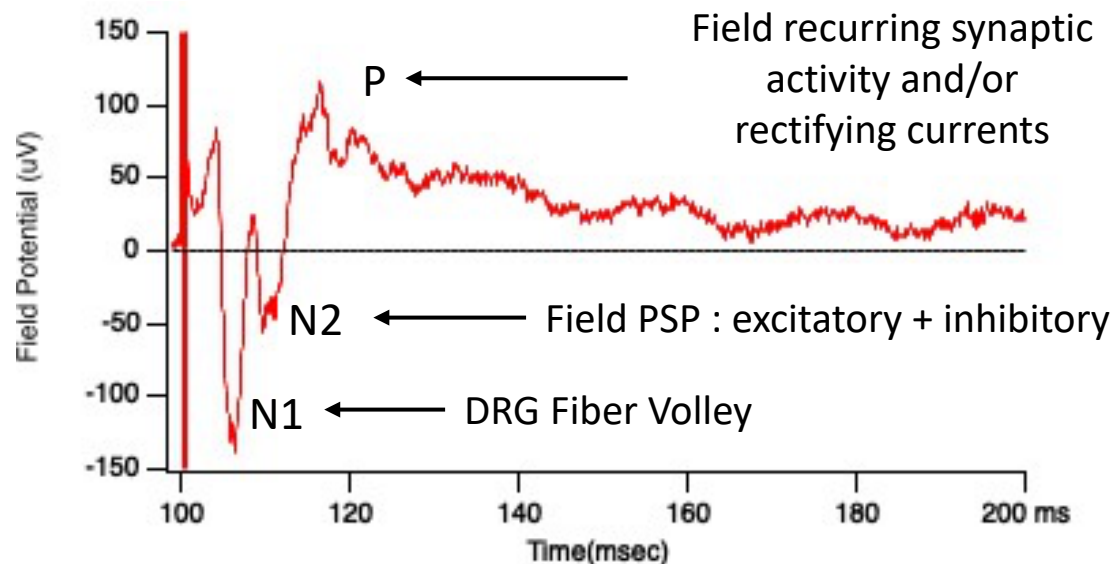
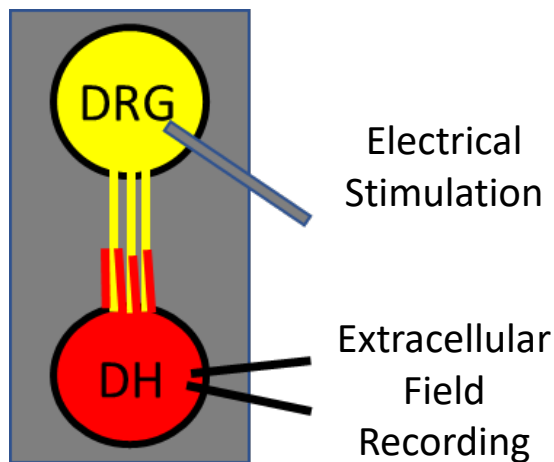


Functional Connectivity Shown by Optogenetics & Ca^{2+}





Extracellular Field Recording Resolves Physiology



Tissue Model Recapitulates Key Aspects of Afferent Sensory Physiology





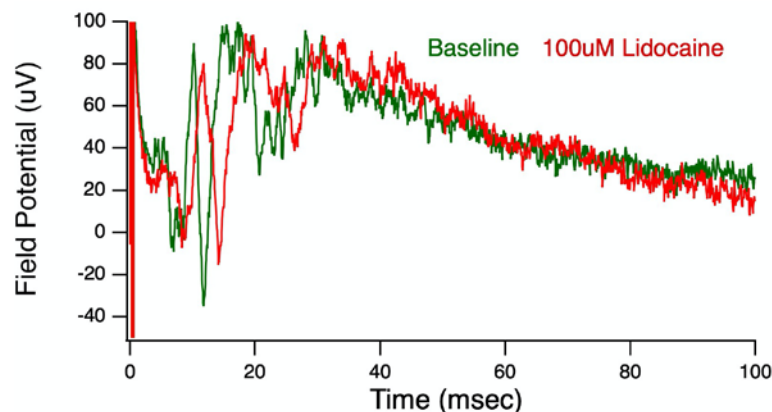
Electrophysiological Responses to Analgesics



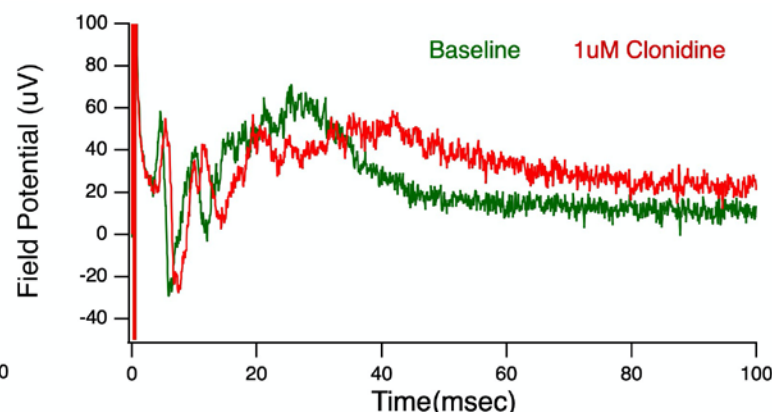
Lowest Effective
Dose

Highest Dose
Tested

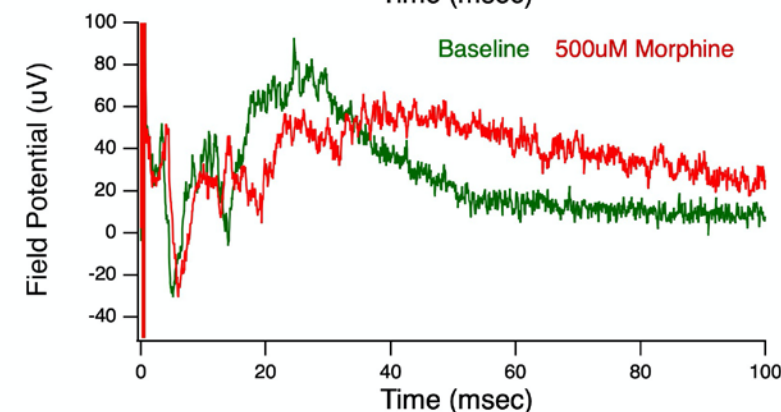
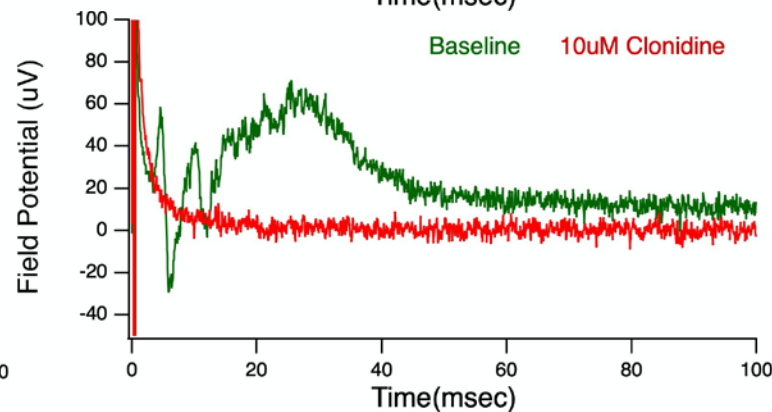
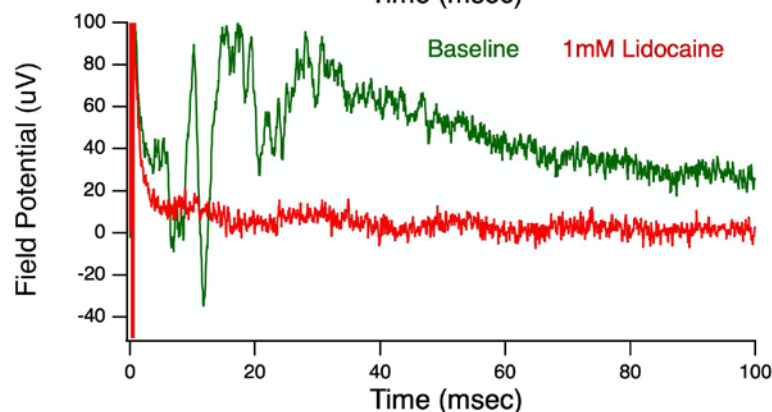
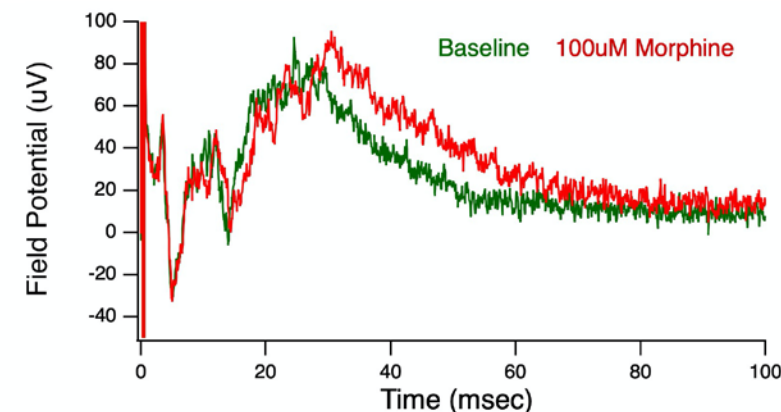
Lidocaine



Clonidine



Morphine

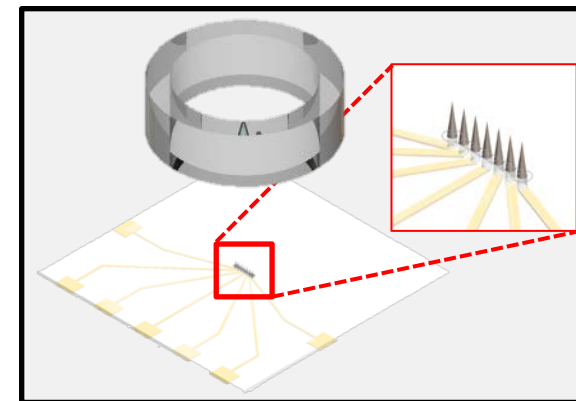


Model Responds to Each Analgesic in Unique Way – Provides a Drug “Signature”

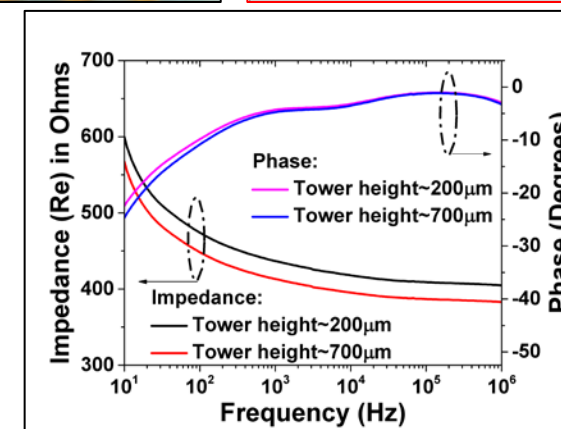
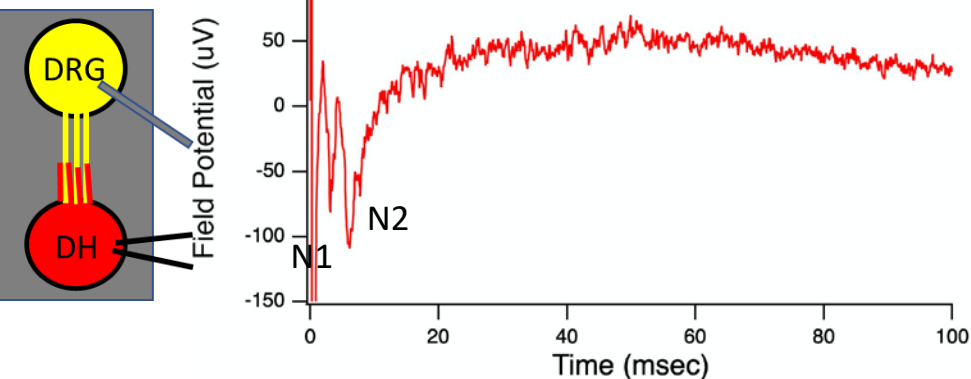
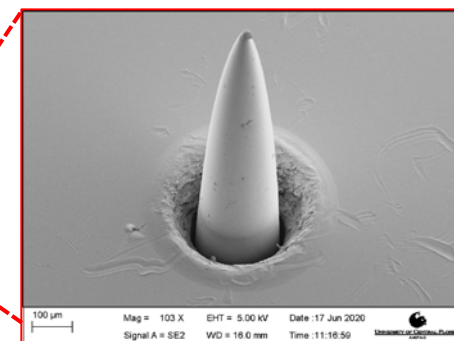
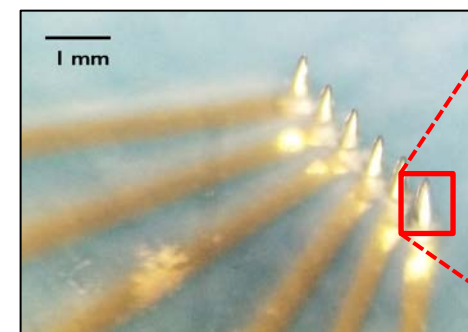
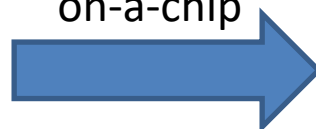




Human PSC-Derived Afferent Synapse “On-a-Chip”



Integrate
on-a-chip

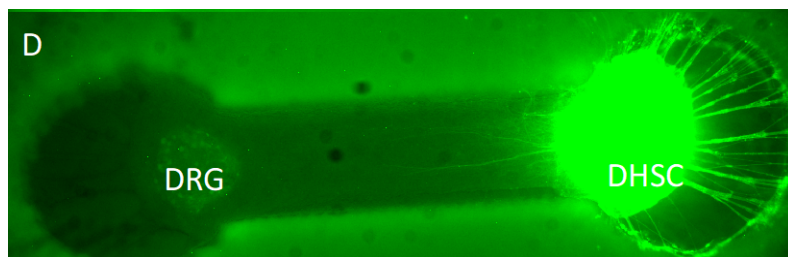
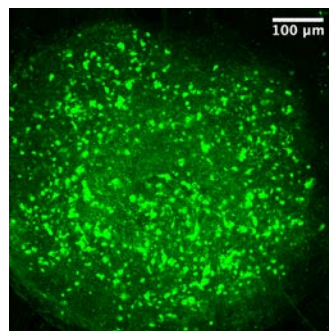
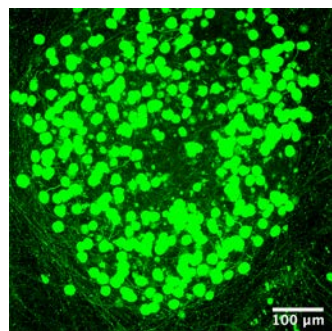
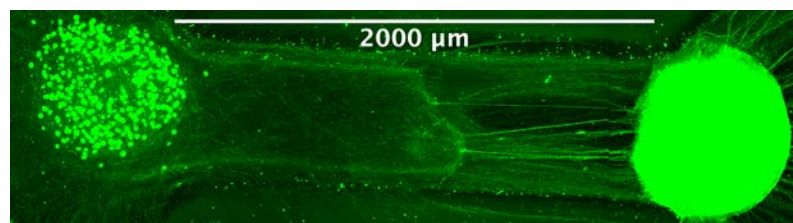




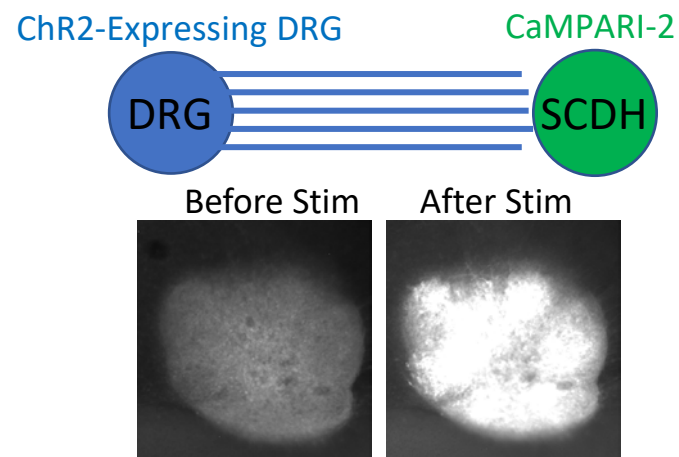
Microphysiological Model of Synaptic Pain Signaling



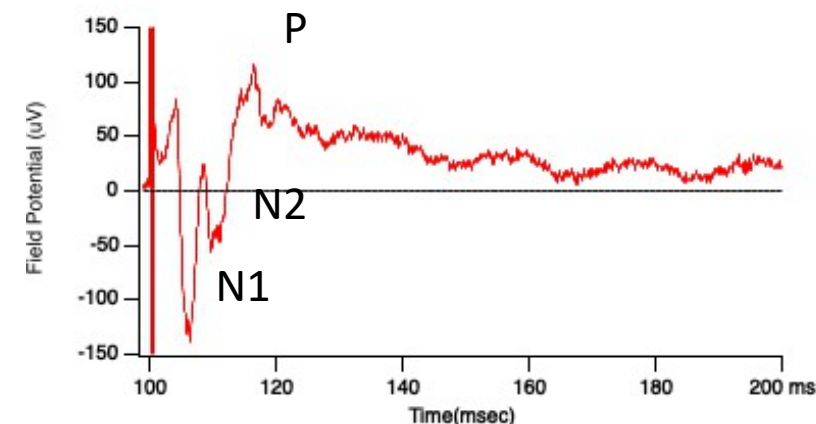
Unidirectional Synaptic Morphology



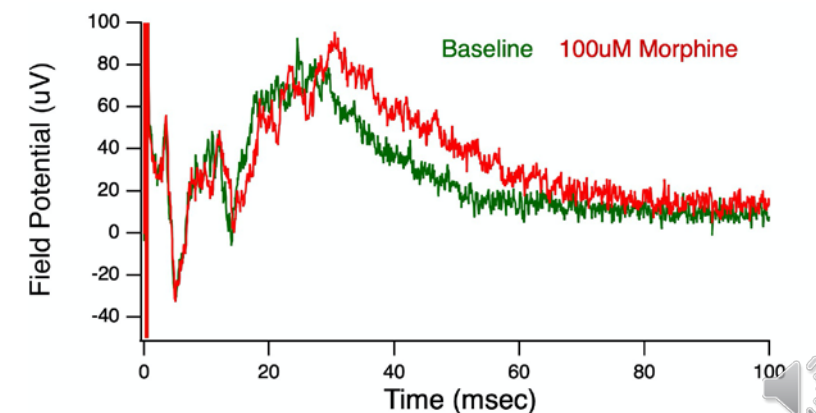
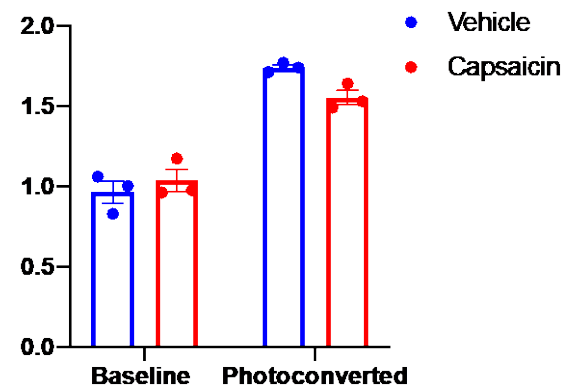
Synaptic Physiology



Measurable Drug Responses



DRG Expressing CHR2



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