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

Michael J. Moore, PhD

Professor of Biomedical Engineering, Tulane University

Co-Founder and Chief Science Officer, AxoSim

Microphysiological Systems (MPS): Bridging Human and Animal Research

January 19 -20, 2021

The National Academies Institute for Laboratory Animal Research

Tulane University

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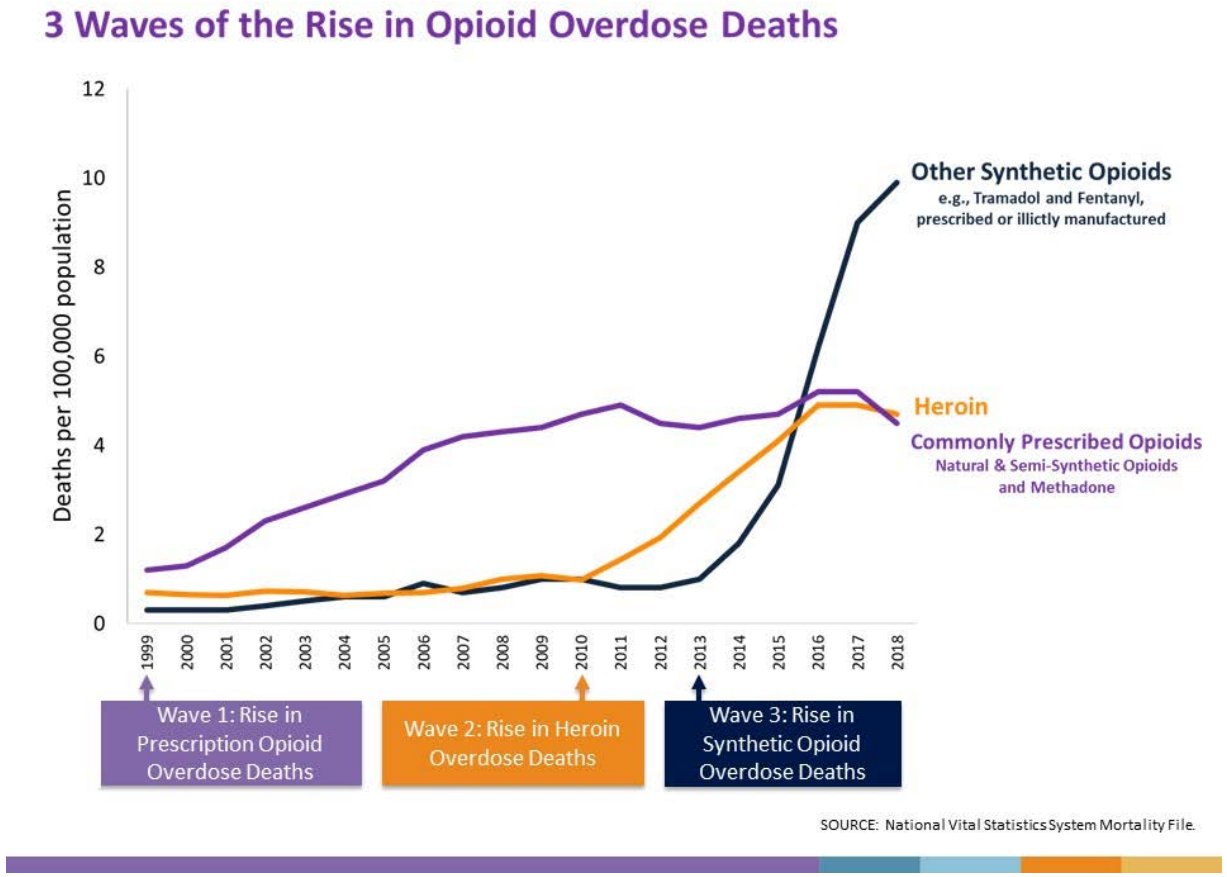
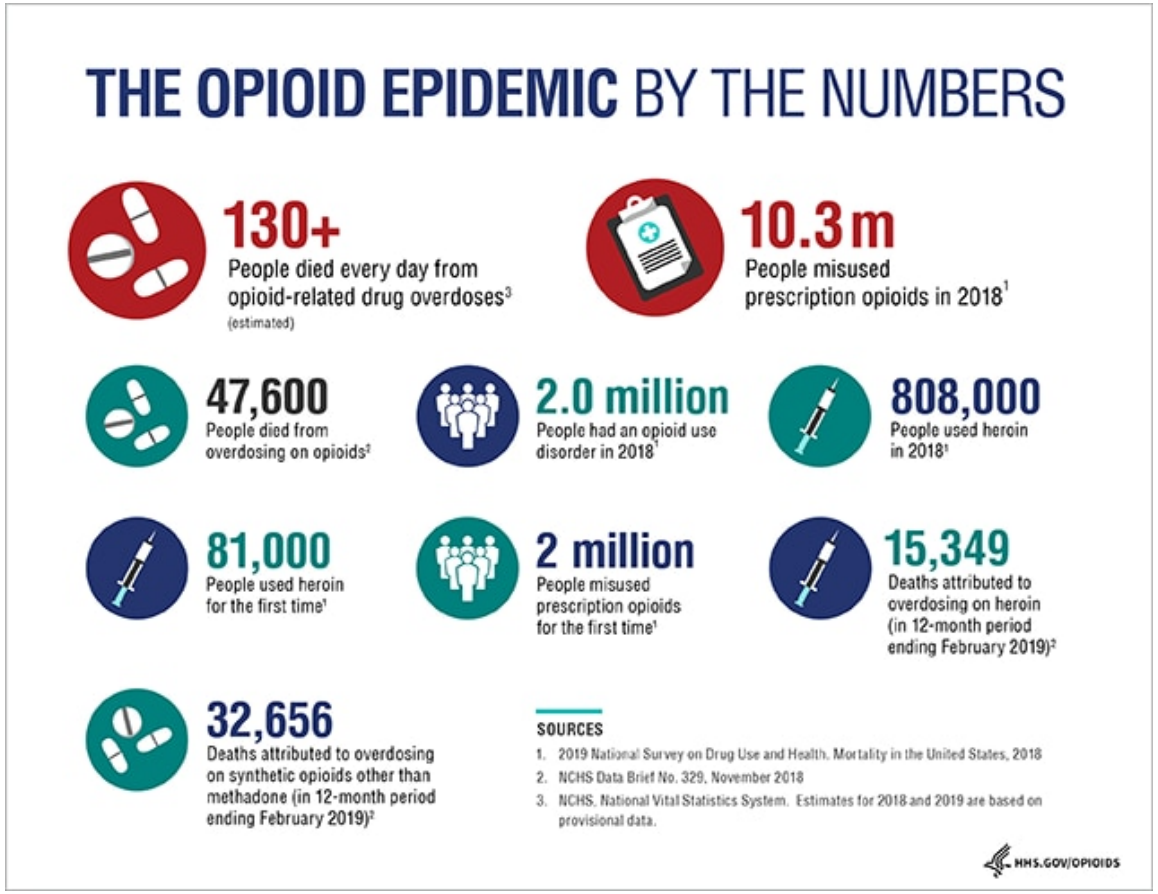
Opioid Overdose Epidemic

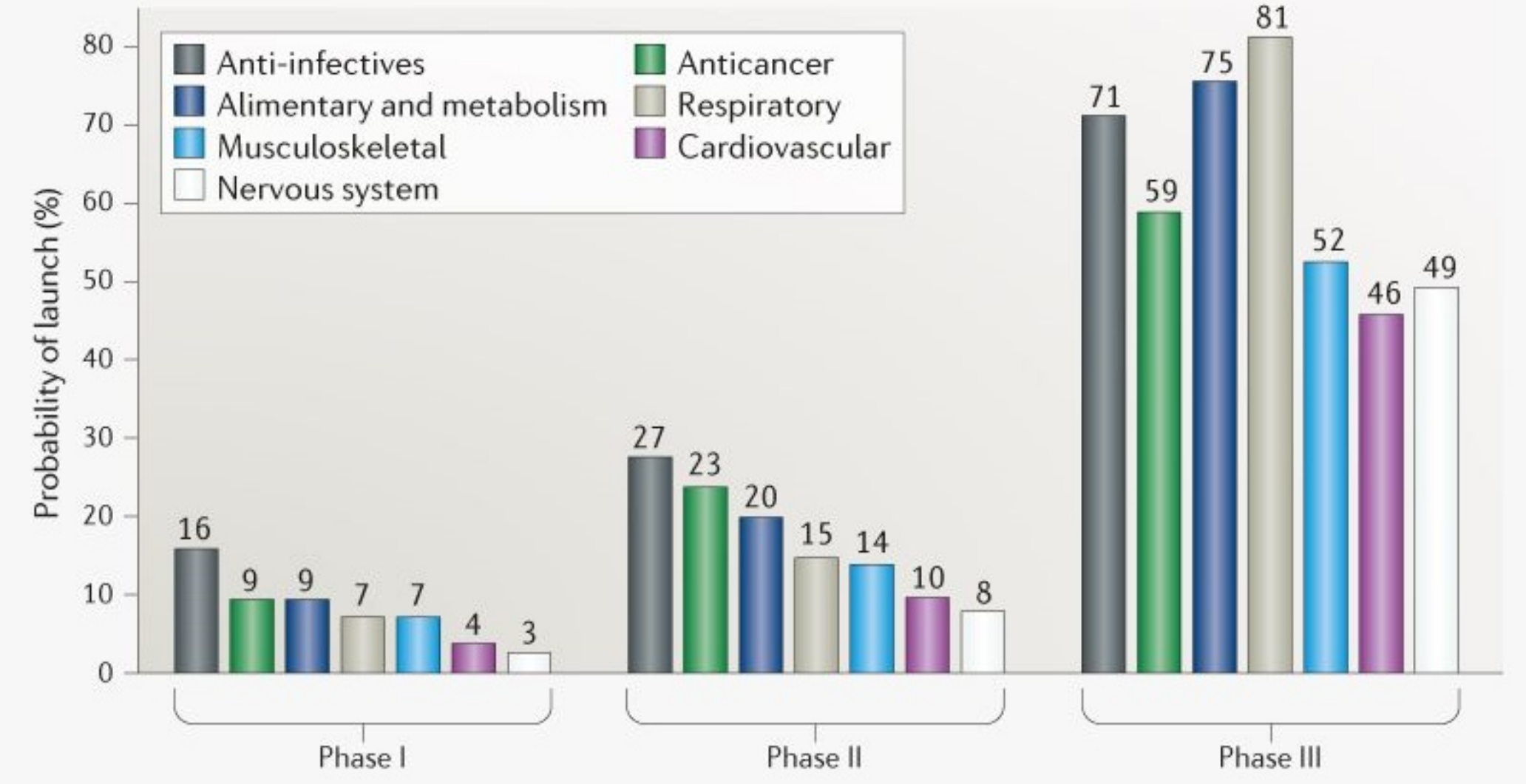


cdc.gov/drugoverdose/epidemic



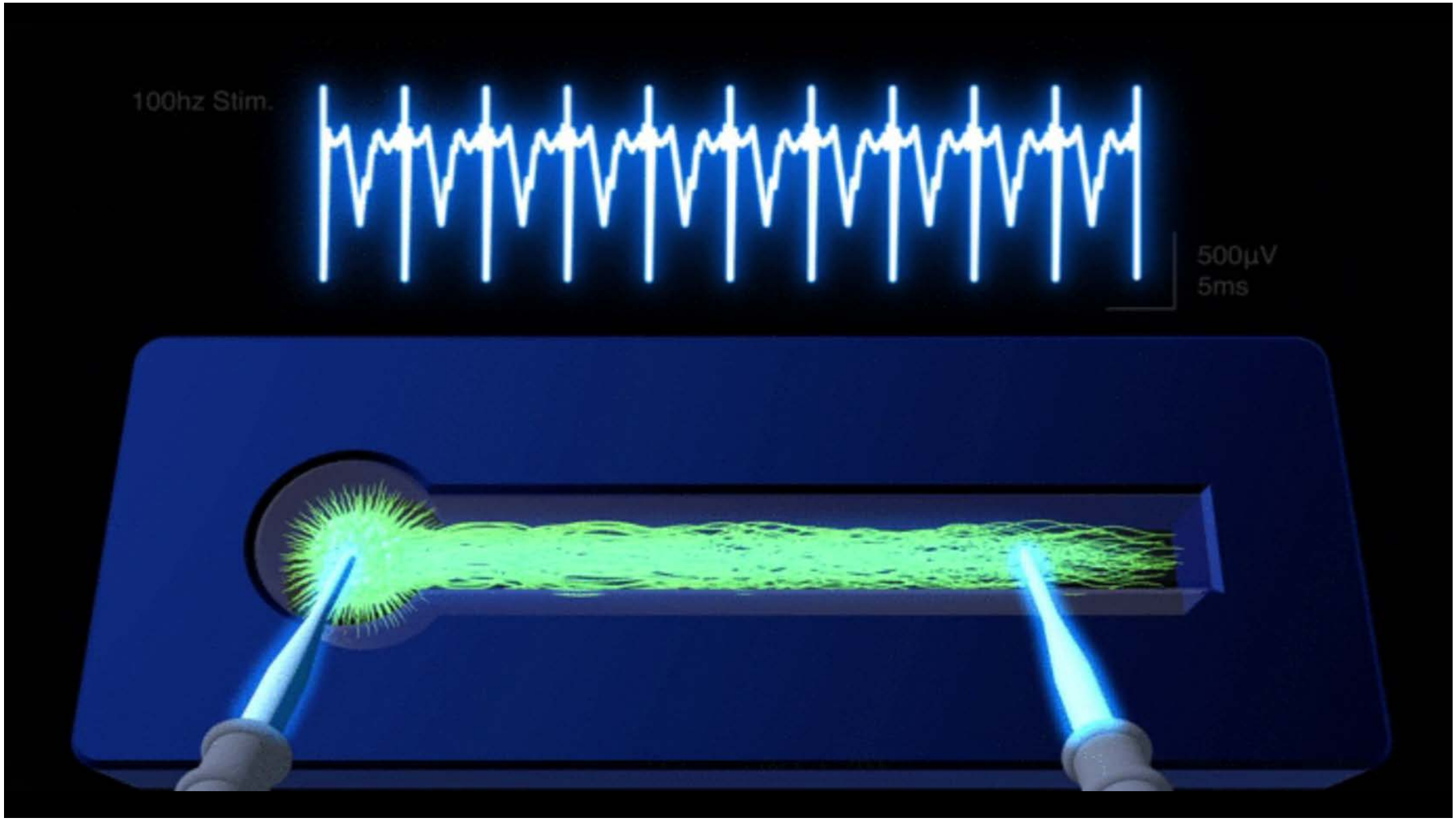
hhs.gov/opioids

Drug Development Especially Poor in Nervous System

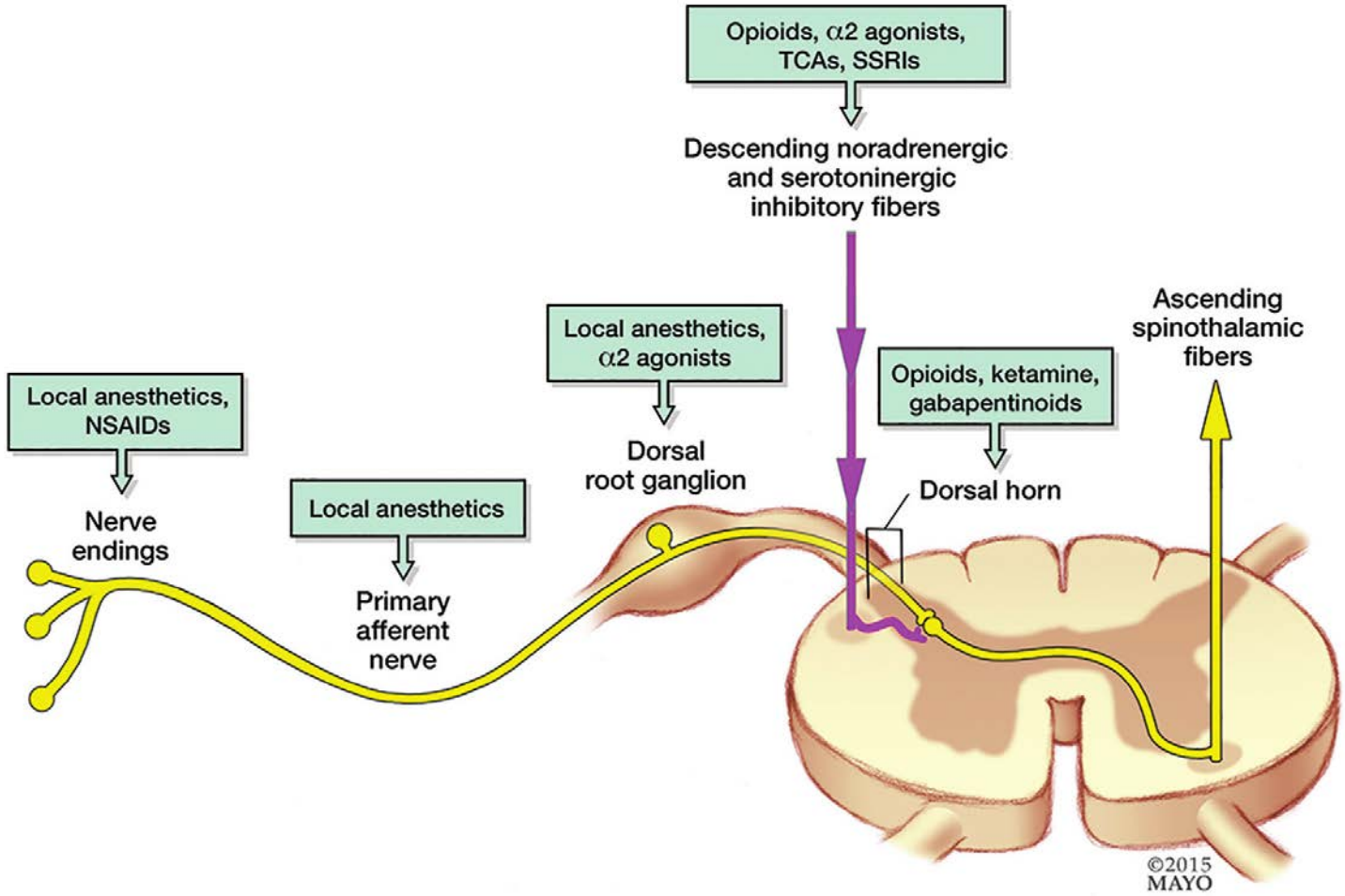


Dowden & Munro, *Nat Rev Drug Disc* 2019, 18:495

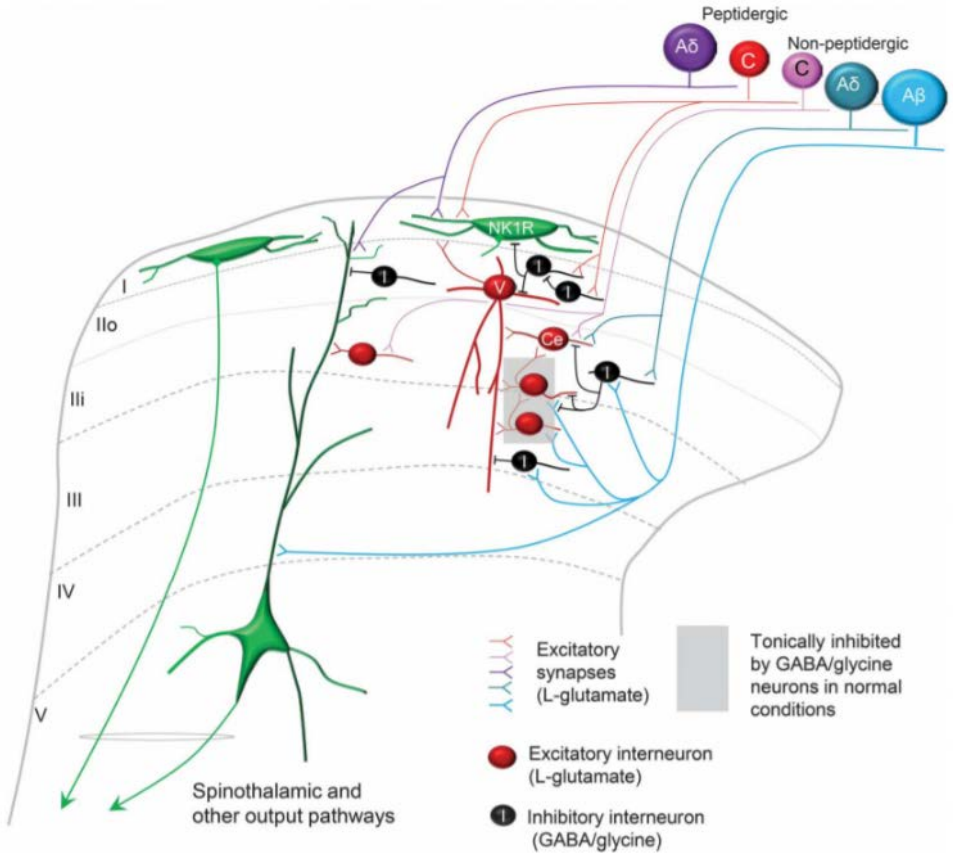
Peripheral “Nerve-on-a-Chip” Platform



Afferent Nociceptive Signaling – Physiological Pain

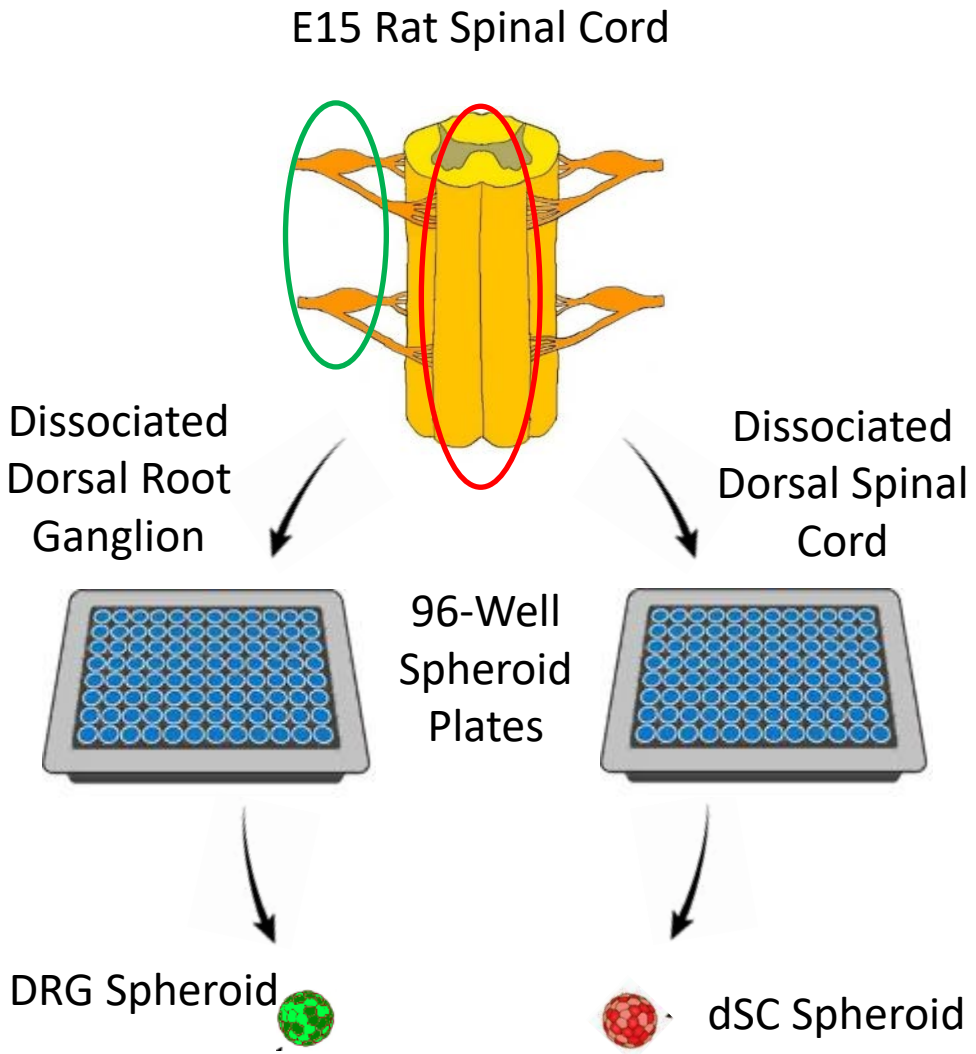


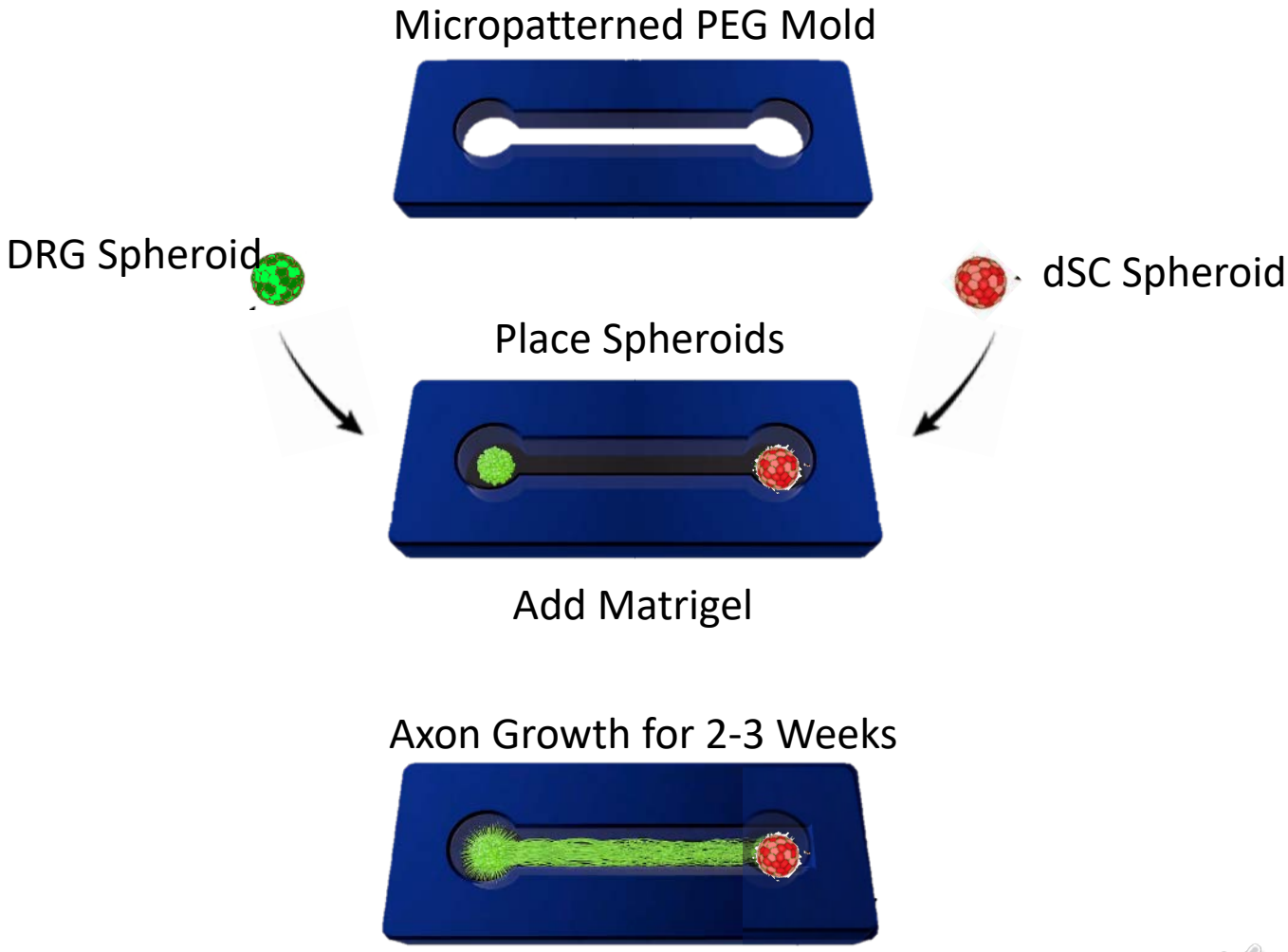
Dorsal Horn Circuitry



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

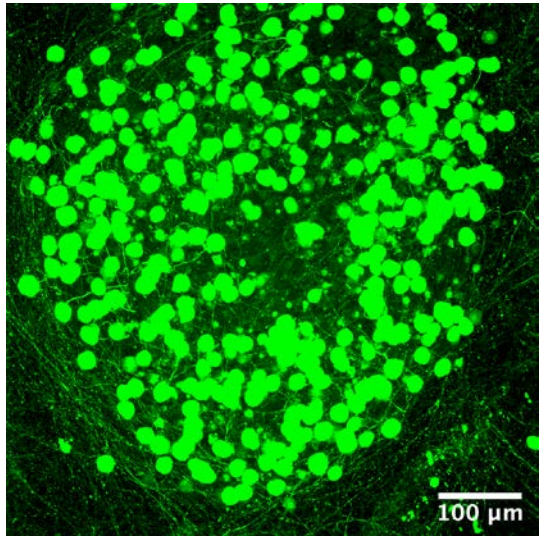
Model of Afferent Nociception – Physiologic “Pain”

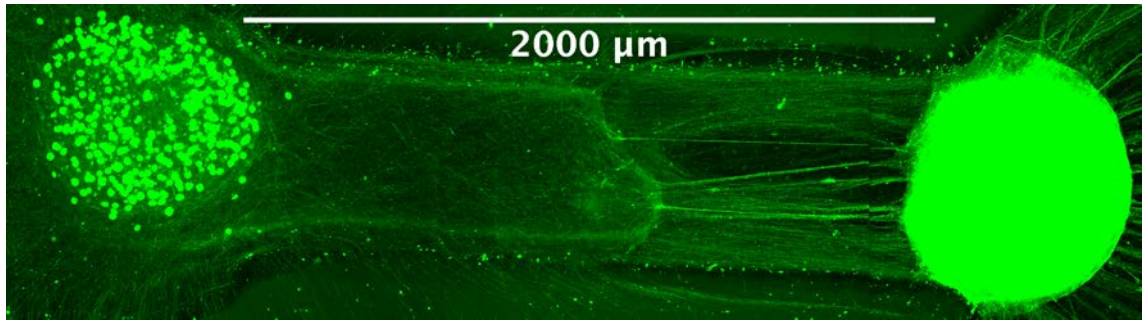


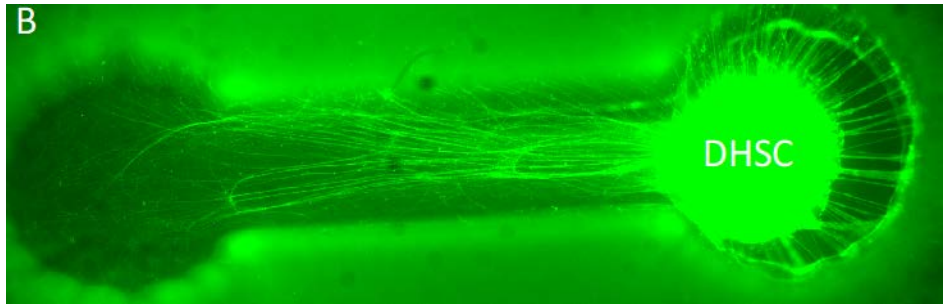


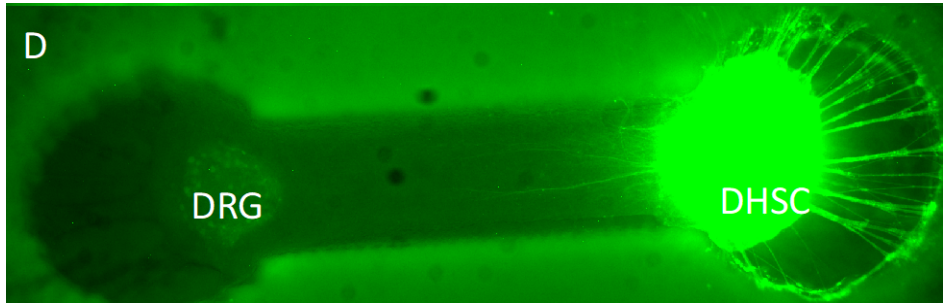
Morphology Revealed by Virally-Encoded GFP

DRG Spheroid

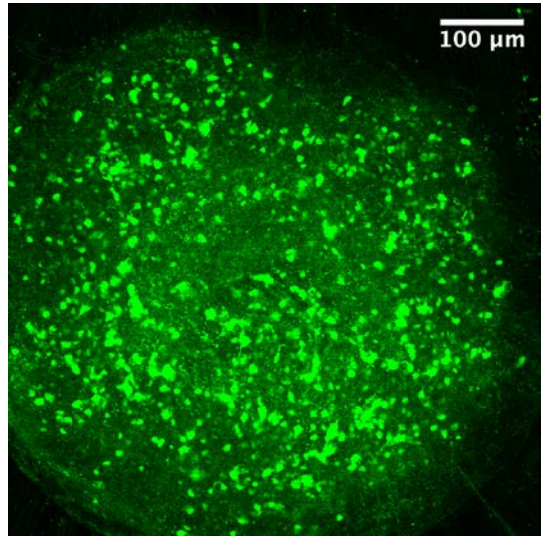








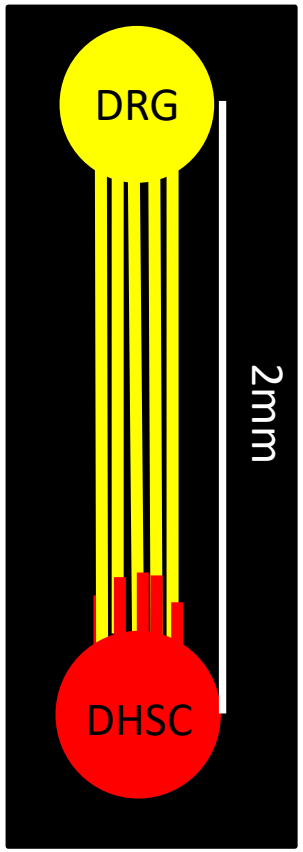
DHSC Spheroid



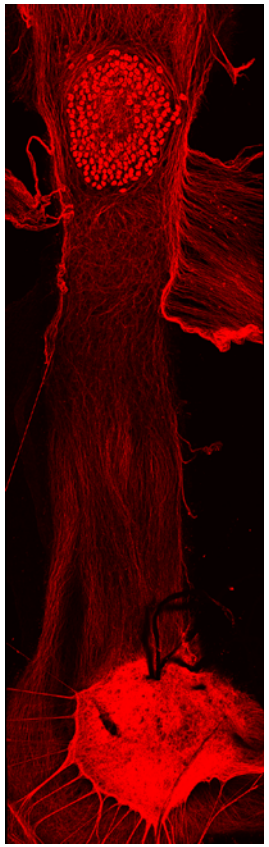
Spontaneous Unidirectional Neurite Outgrowth

IHC Mapping of Relevant Tissue Markers

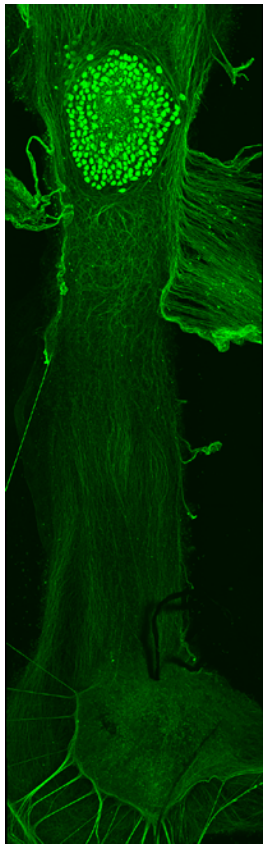
Tissue Map Schematic



B3-Tubulin (All Neurites)

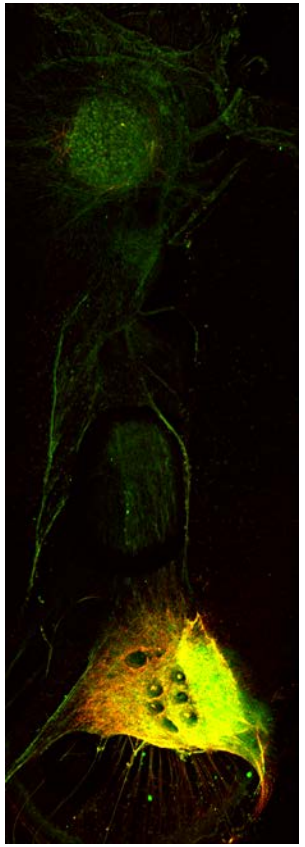


Peripherin (PNS Tissue)

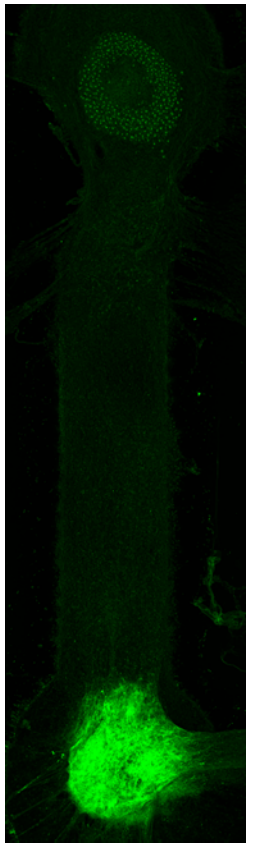


MAP2 (Dendrites)

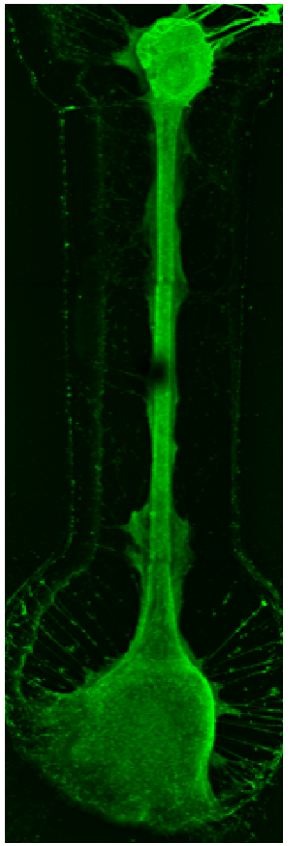
Synapsin-I/PSD95 (Pre/Post Synaptic)



vGAT (GABA Receptor)

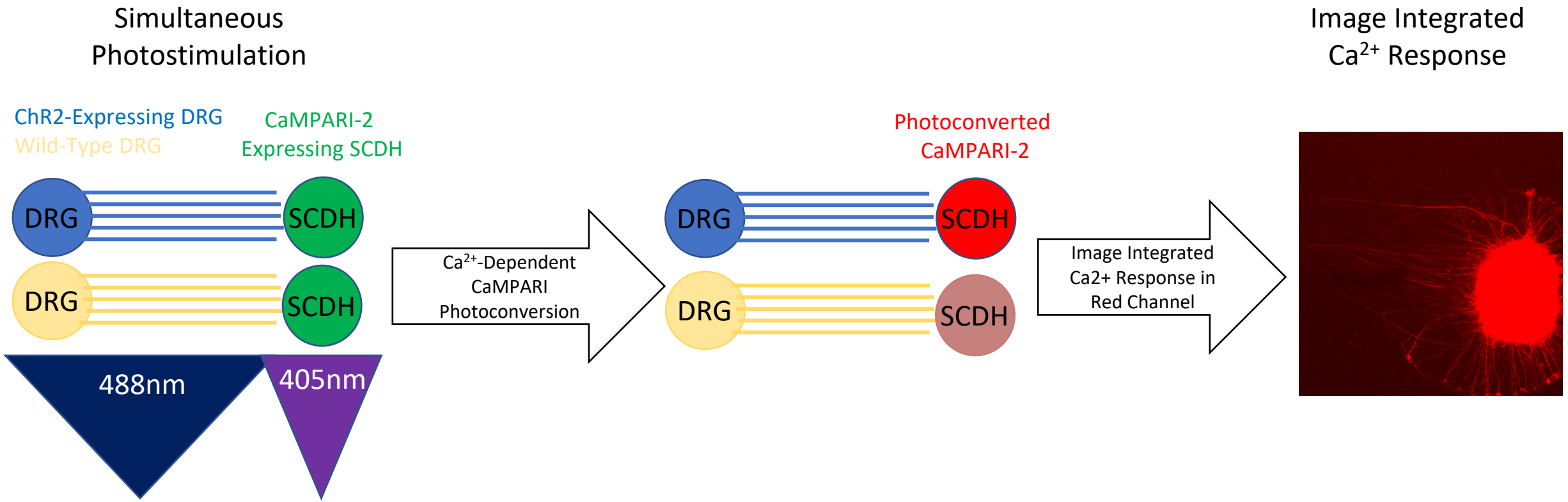


μ-Opioid Receptor



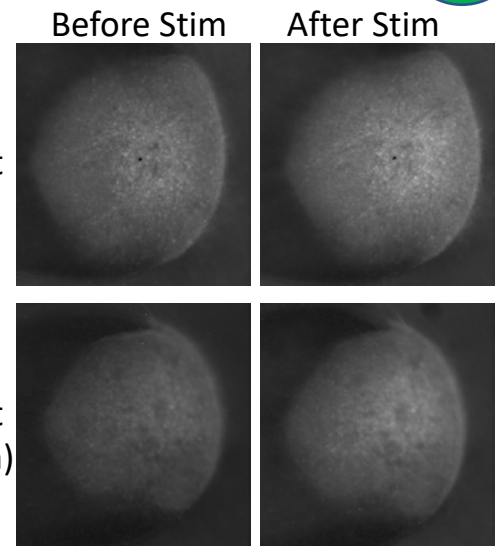
Functional Connectivity Shown by Optogenetics & Ca^{2+}

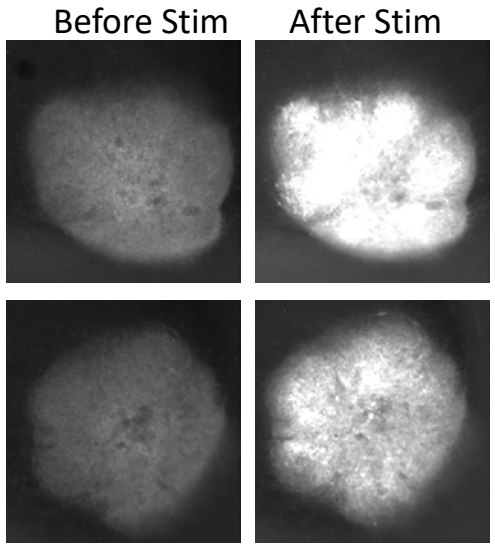
CaMPARI (Calcium Modulated Photoactivatable Ratiometric Integrator)



Stimulate DRG tissue with ChR-2 and 488 nm light | Record Integrated Ca2+ Response in SCDH tissue

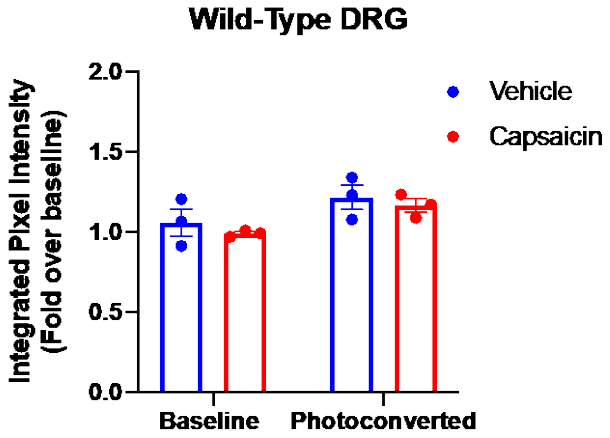
Functional Connectivity Shown by Optogenetics & Ca^{2+}

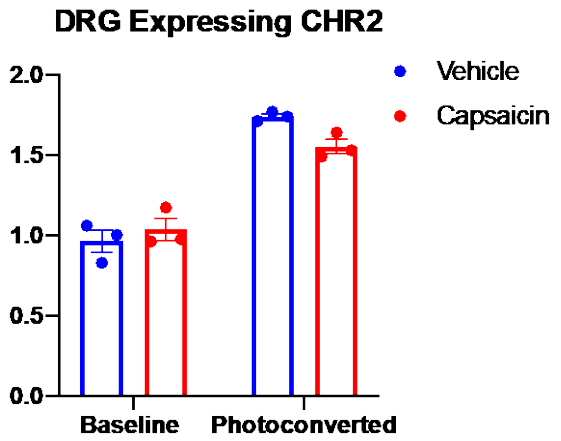




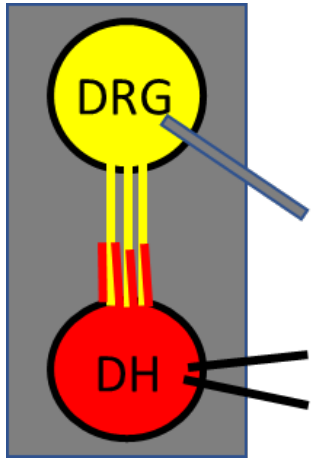
ChR2 activation of DRG increases Ca^{2+} influx in SC

Ca^{2+} influx reduced when transmitter release impaired



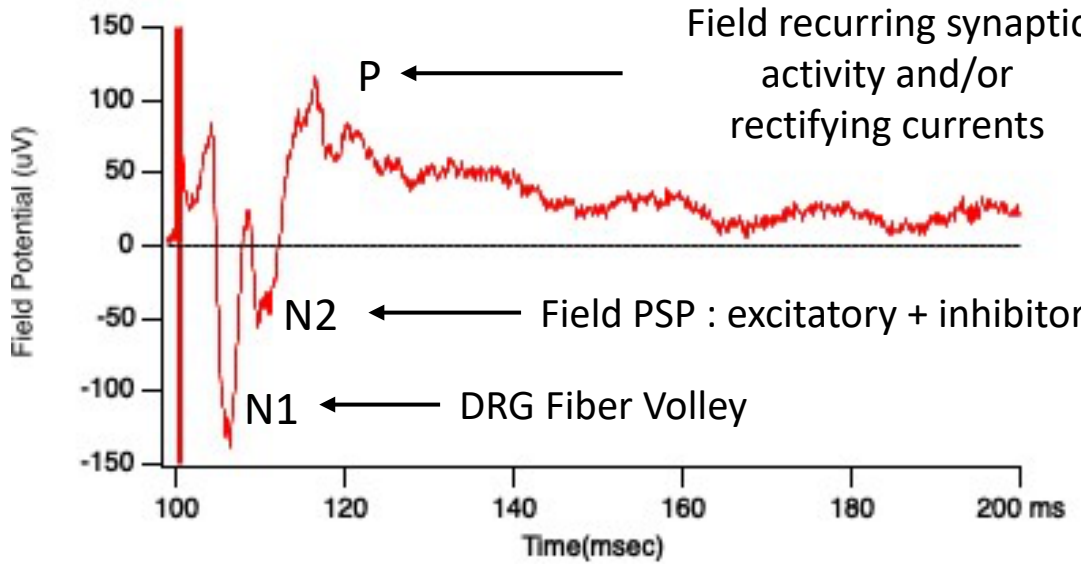


Extracellular Field Recording Resolves Physiology



Electrical Stimulation

Extracellular Field Recording

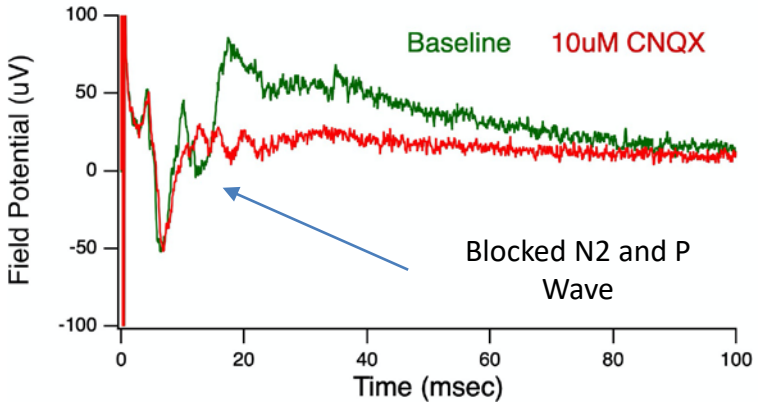


Field recurring synaptic activity and/or rectifying currents

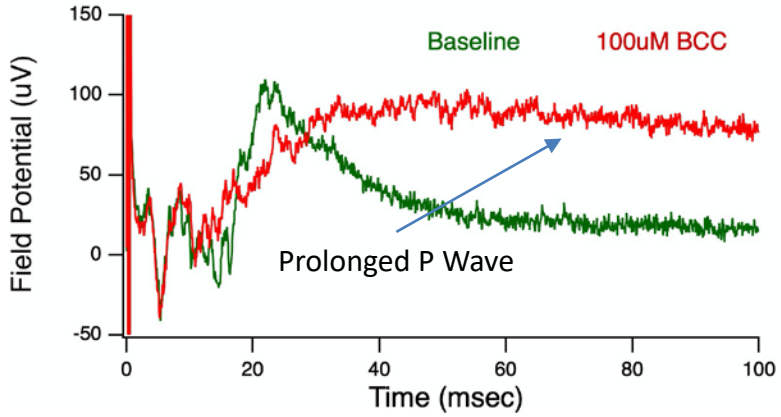
Field PSP : excitatory + inhibitory

DRG Fiber Volley

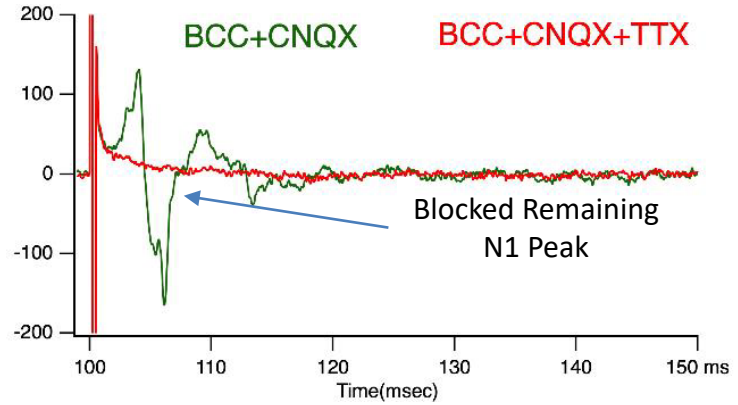
Chelate Ca^{2+} or Block AMPA Receptors



Block GABA Receptors

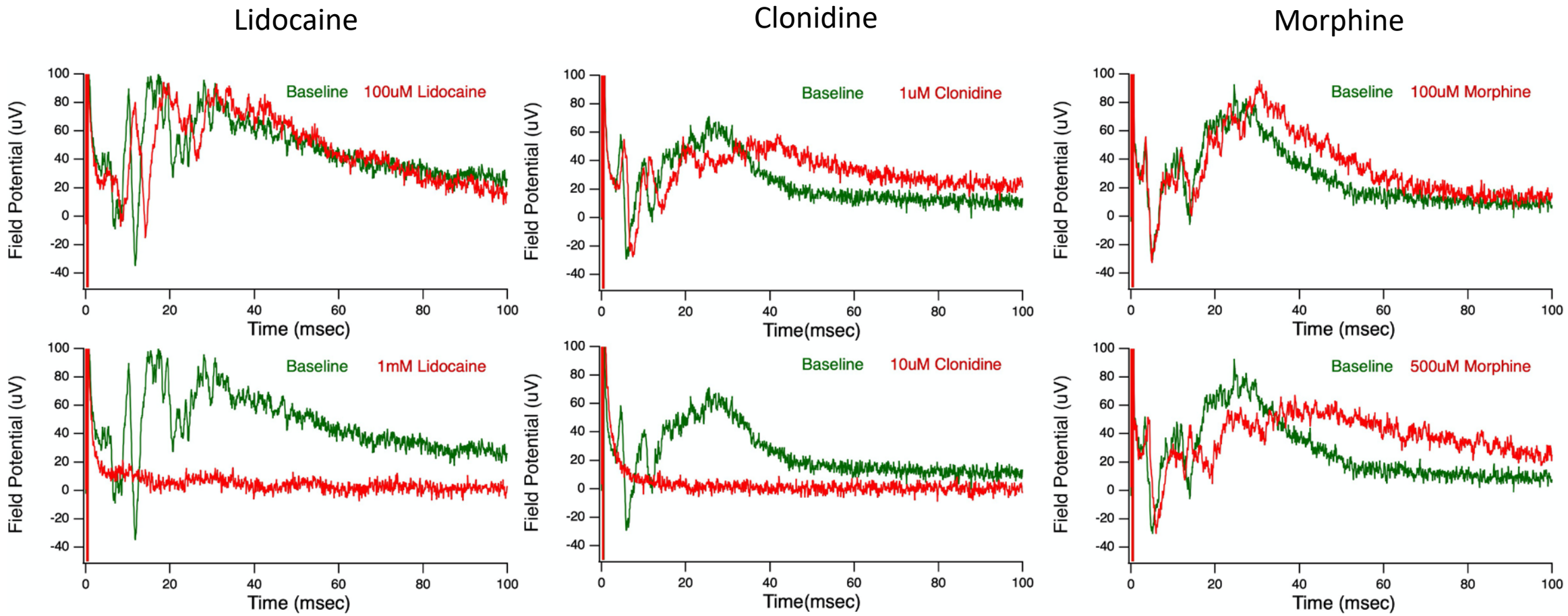


Block GABA + AMPA + Na^{+} Channels



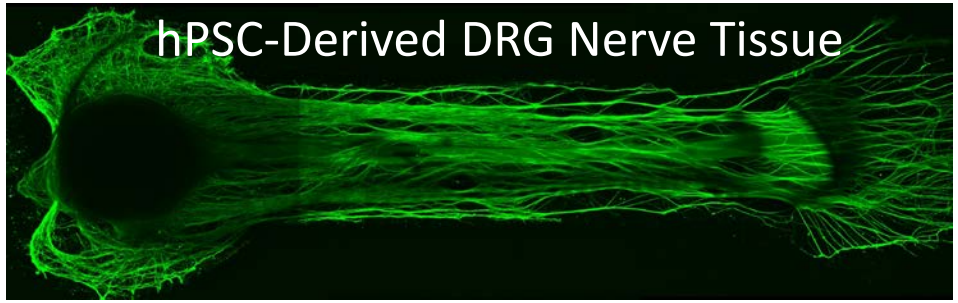
Tissue Model Recapitulates Key Aspects of Afferent Sensory Physiology

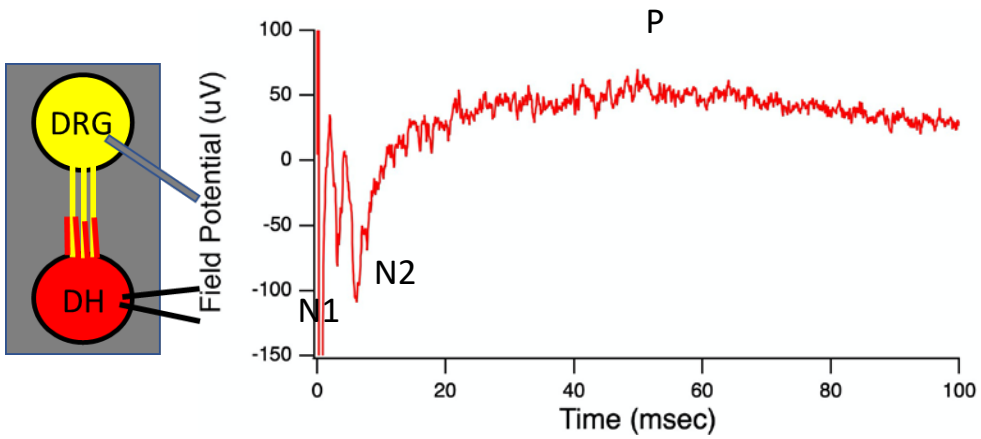
Electrophysiological Responses to Analgesics



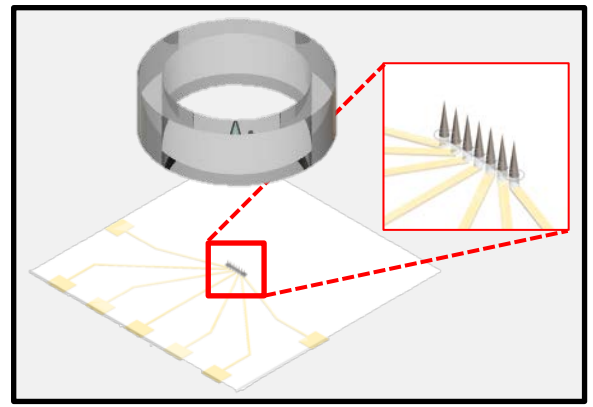
Model Responds to Each Analgesic in Unique Way – Provides a Drug “Signature”

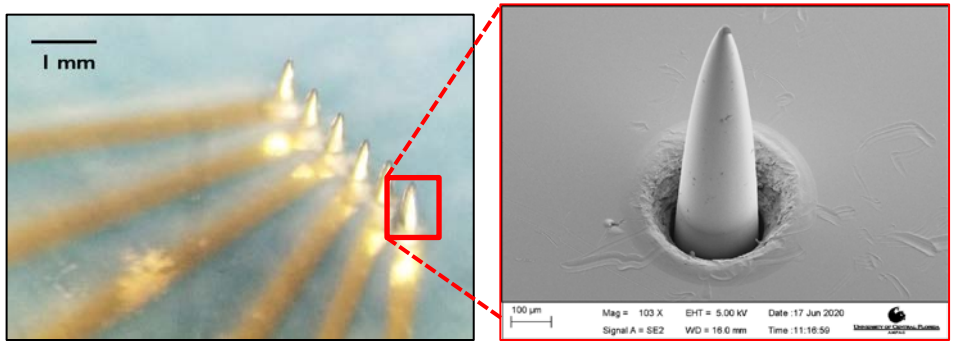
Human PSC-Derived Afferent Synapse “On-a-Chip”

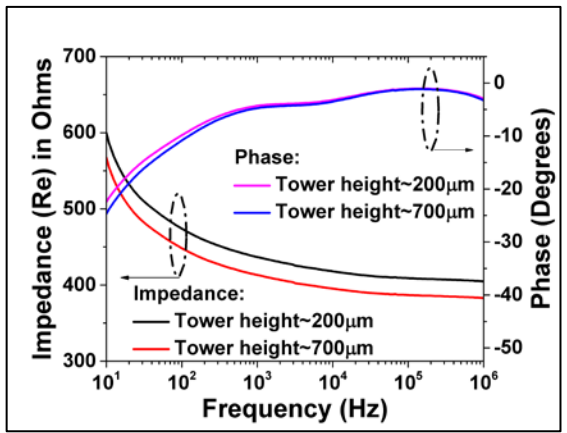




Integrate on-a-chip

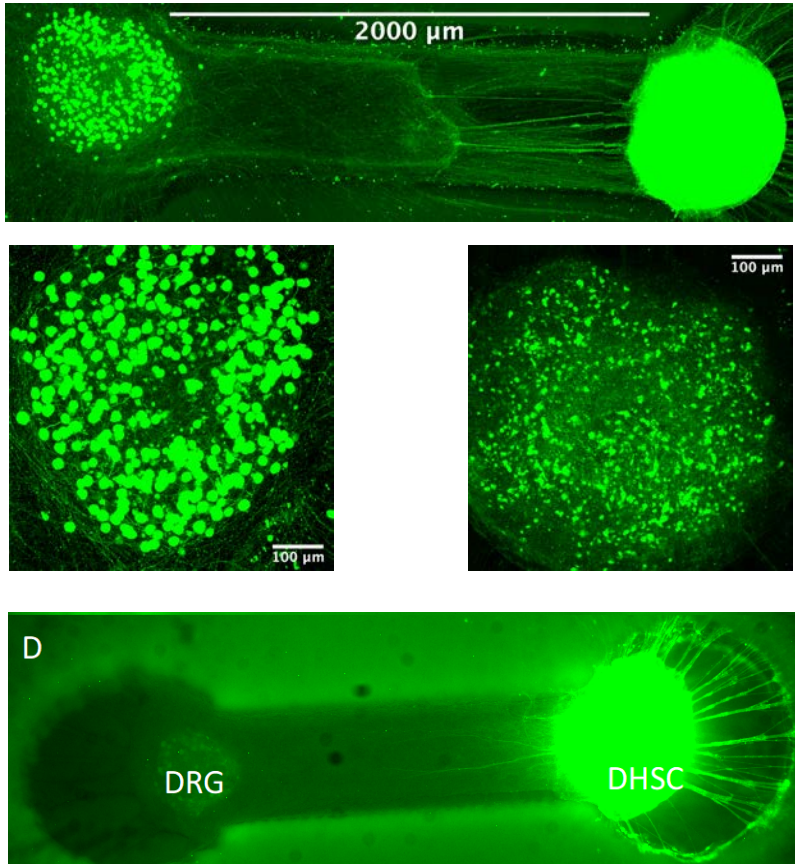




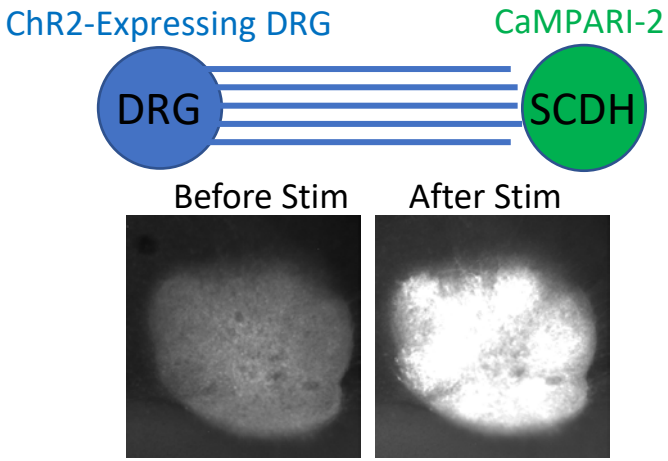


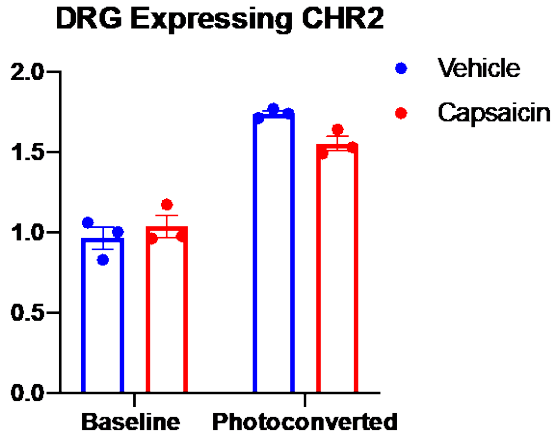
Microphysiolgical Model of Synaptic Pain Signaling

Unidirectional Synaptic Morphology

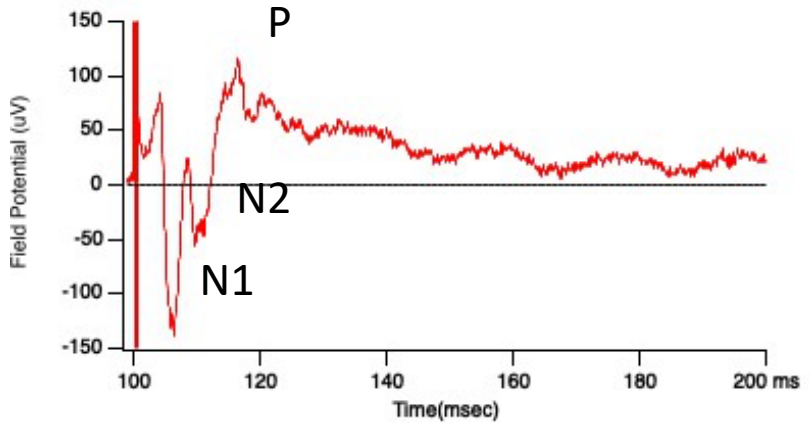


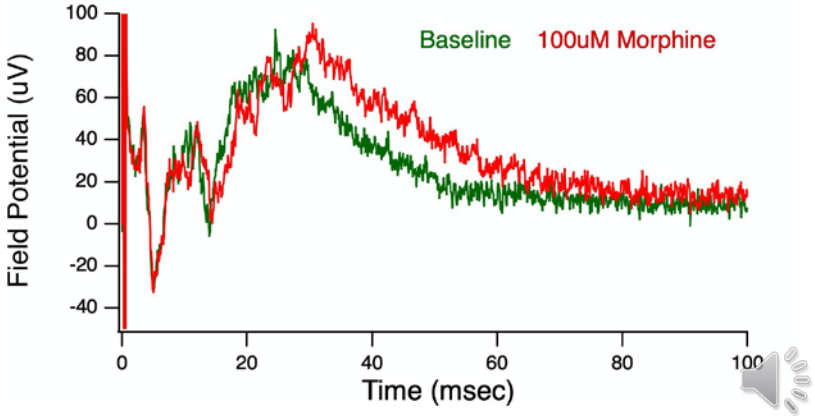
Synaptic Physiology





Measurable Drug Responses





Grateful Acknowledgements

Neural Microengineering Lab,
Tulane University
- Dr. Devon Bowser
- Dr. Kevin Pollard
- Alex Bosak
- Mostafa Meselhe

AxoSim, Inc.
- Dr. J. Lowry Curley
- Dr. Anup D. Sharma
- Dr. Wesley Anderson

Randy Ashton's Lab,
University of Wisconsin
- Dr. Nisha Iyer

Swami Rajaraman's Lab,
University of Central Florida
- Dr. Avra Kundu
- Charles Didier
- Julia Orrico

Funding Sources:
- NIH – NCATS, R42-TR001270
- NIH – NCATS, UG3-TR003150

Contact: mooremj@tulane.edu