GSK core course: Neuron – cancer interactions

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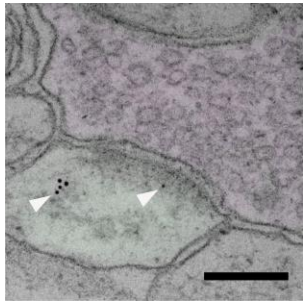
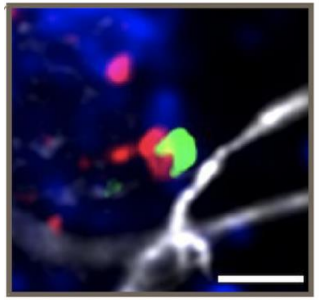
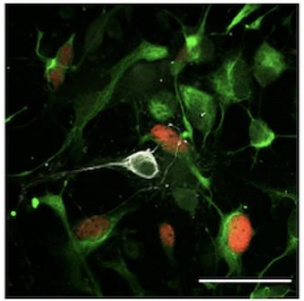






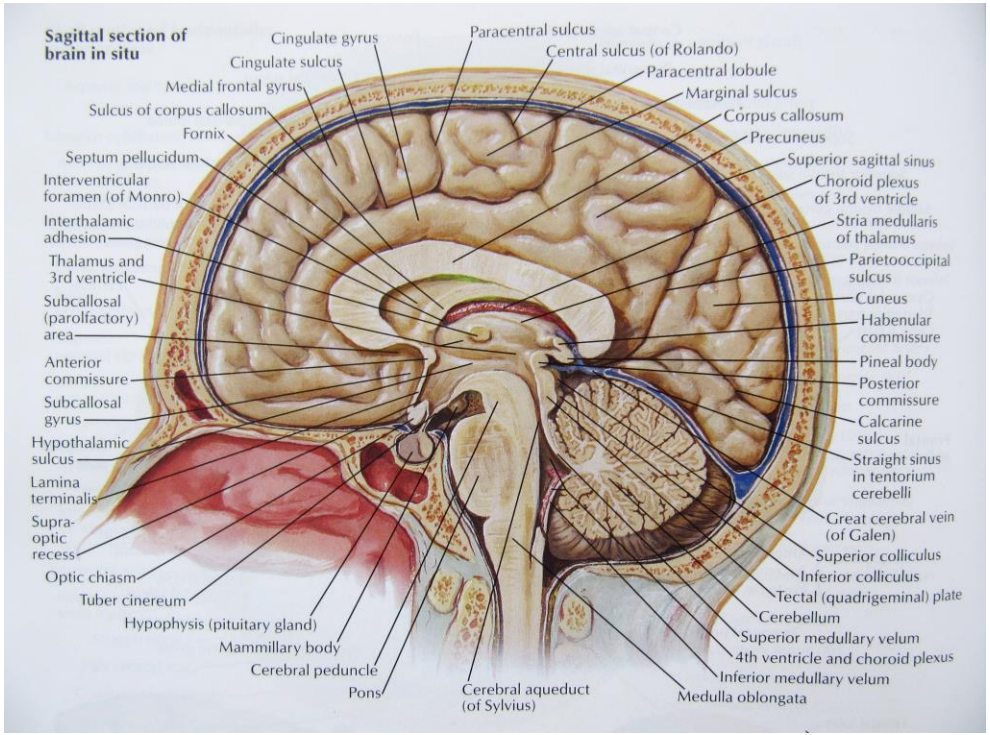
Outline

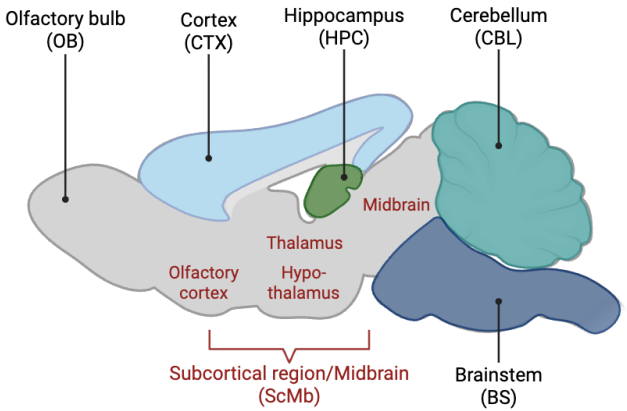
- Neuroscience basics
- Techniques in cancer neuroscience
- Neuron-cancer interactions
  - CNS cancers: High grade glioma
  - Brain metastases
  - PNS cancers:
    - Perineural invasion
    - tumor microenvironment
- Project ideas

Neuroscience basics

Central Nervous System (CNS)
Peripheral Nervous System (PNS)
Electrical excitability

Neuroscience basics - anatomy





Netter, 2006 (Plate 106)

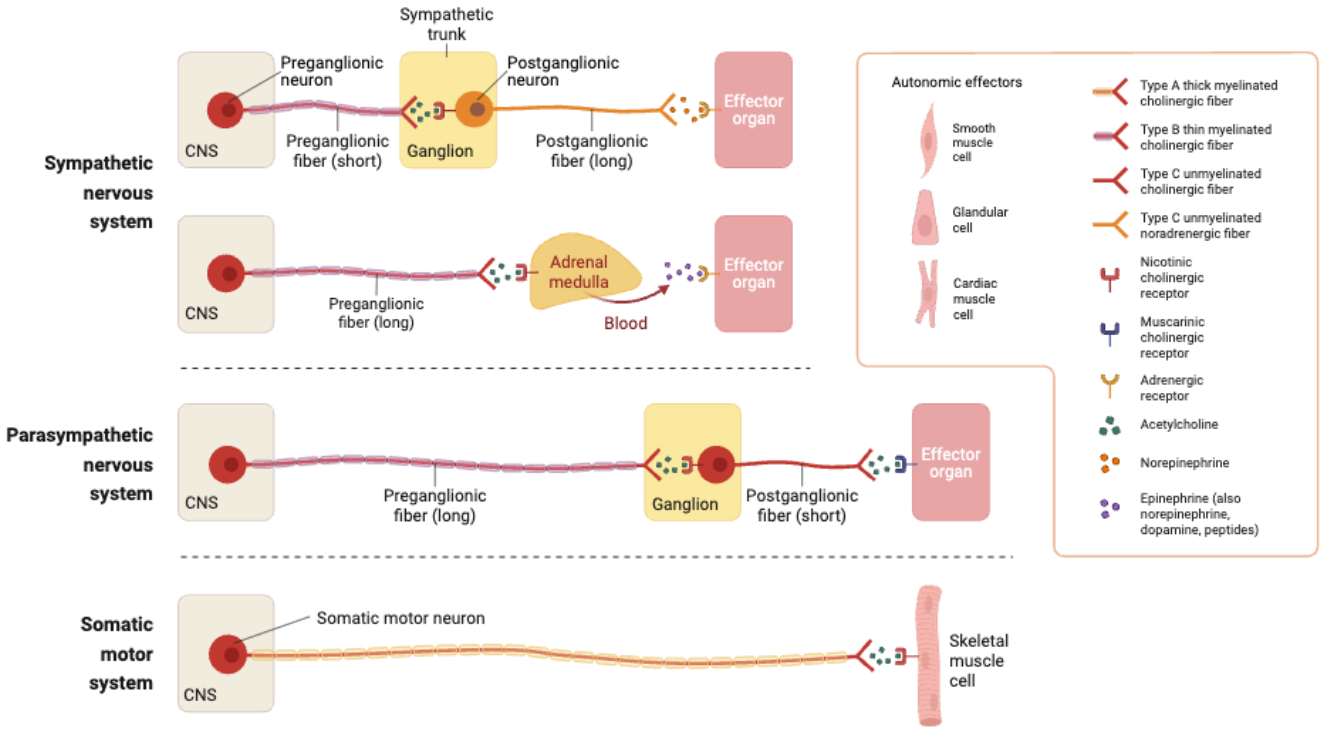
Neuroscience basics - anatomy

Central nervous system (CNS)

- Brain, spinal cord, & retina
- Group of cell bodies = “Nucleus”
- Myelinating cells = oligodendrocytes

Peripheral nervous system (PNS)

- Autonomic nervous system (ANS)
  - SNS/PNS
- Enteric nervous system
- Motor nerves
- Somatosensory nerves
- Vagal sensory nerves
- Group of cell bodies = “Ganglia”
- Myelinating cells = Schwann cells



Neuroscience basics - anatomy

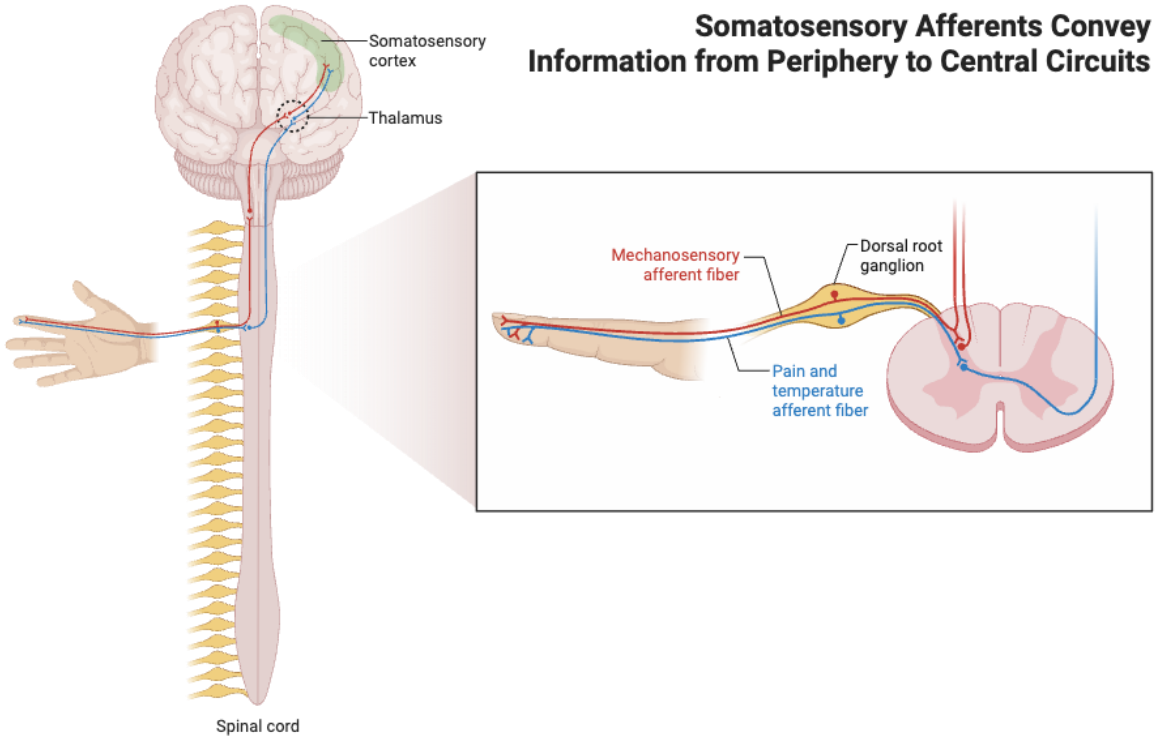
Four modes of sensory inputs:

Dorsal root ganglion (DRG)
- Internal organs
- Appendages

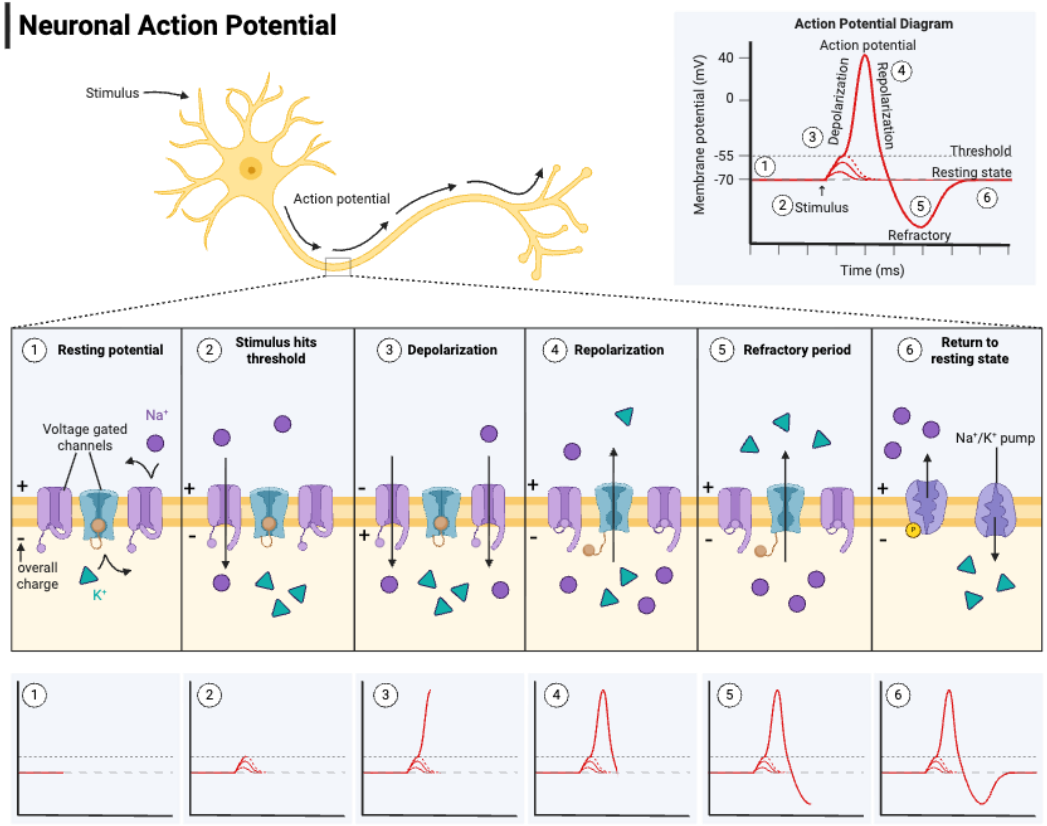
Vagal sensory neurons (Nodose/jugular)
- Internal organs

Central sensory (cranial) nerves
- Face/head

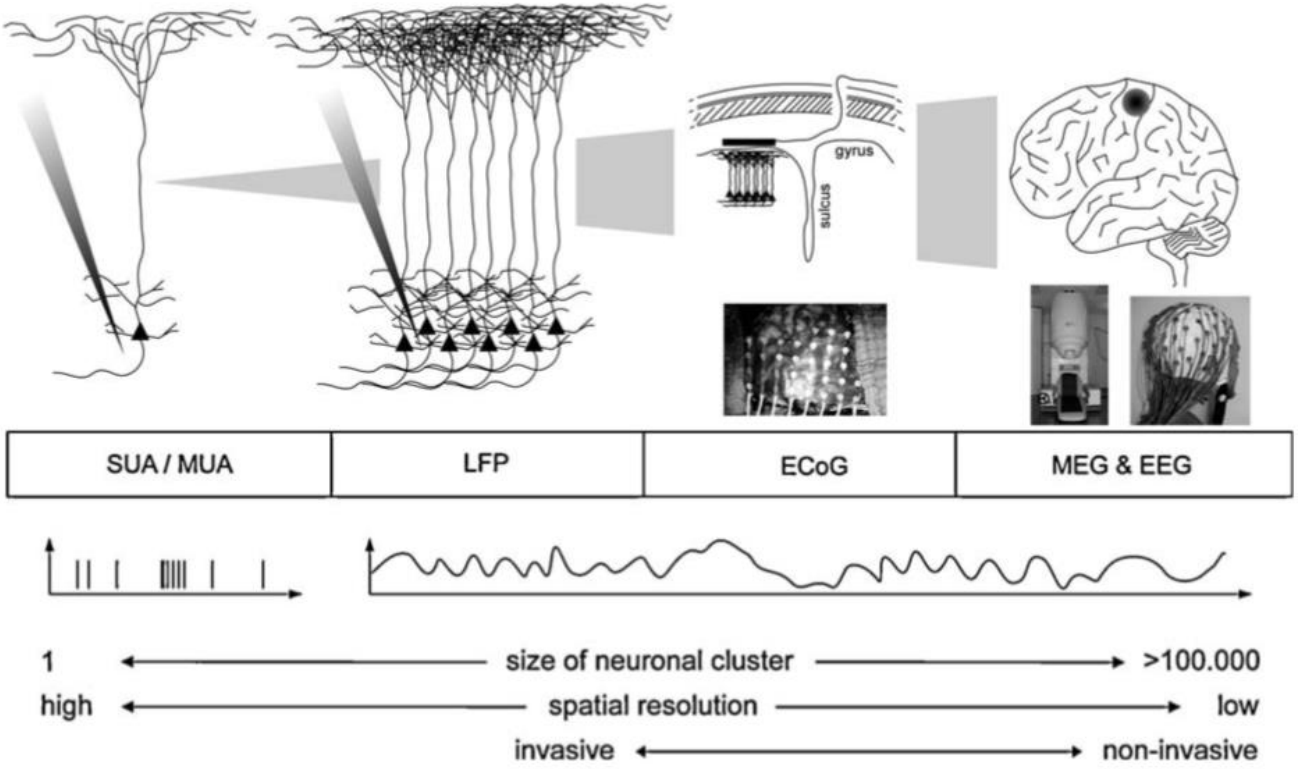
Neuroendocrine signaling
- Humoral state of body
  - (e.g., leptin signaling)



Neuroscience basics – electrically excitable cells

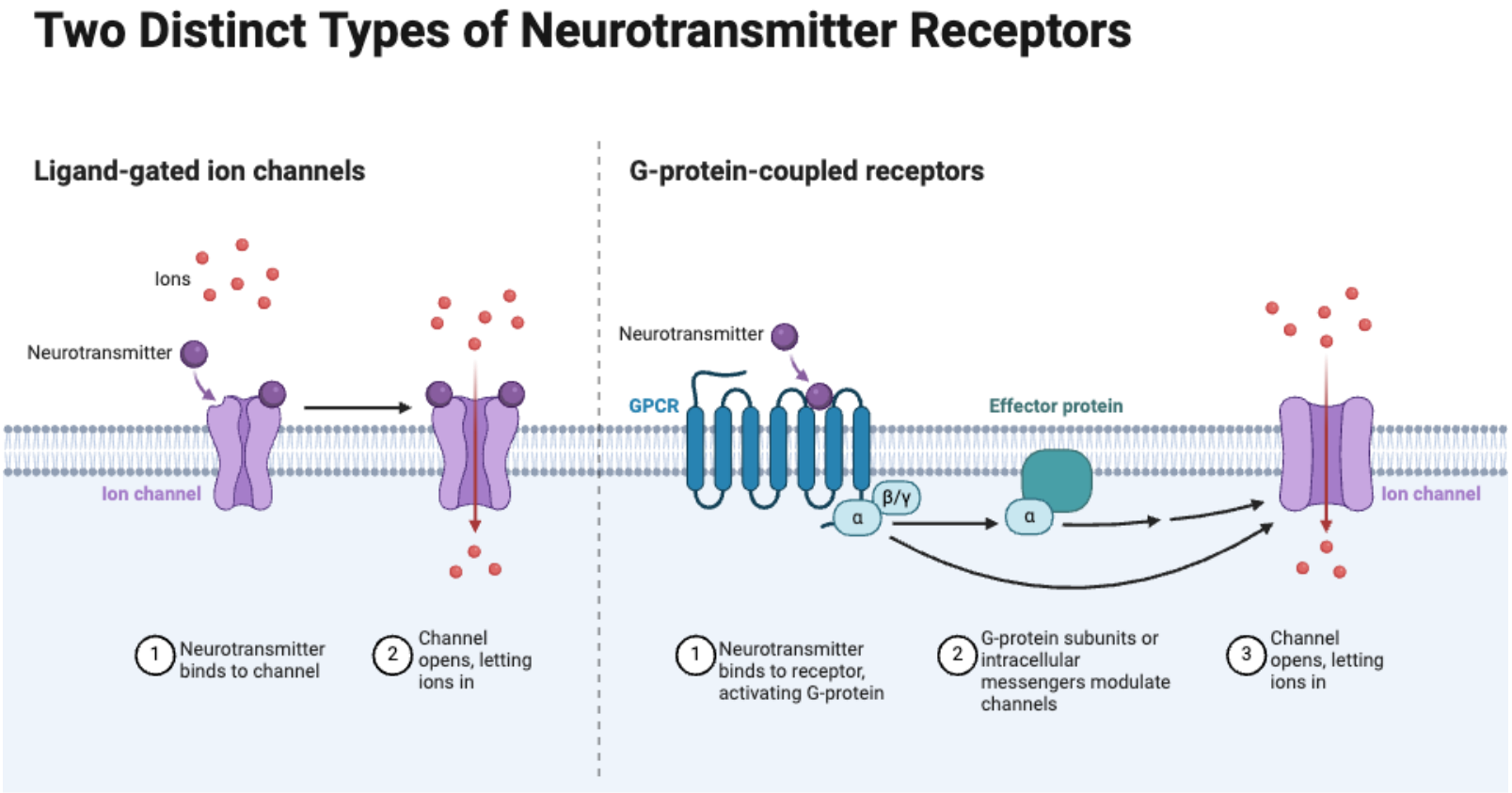


Neuroscience basics - electrophysiology



Jerbi et al., 2013 *IRBM*

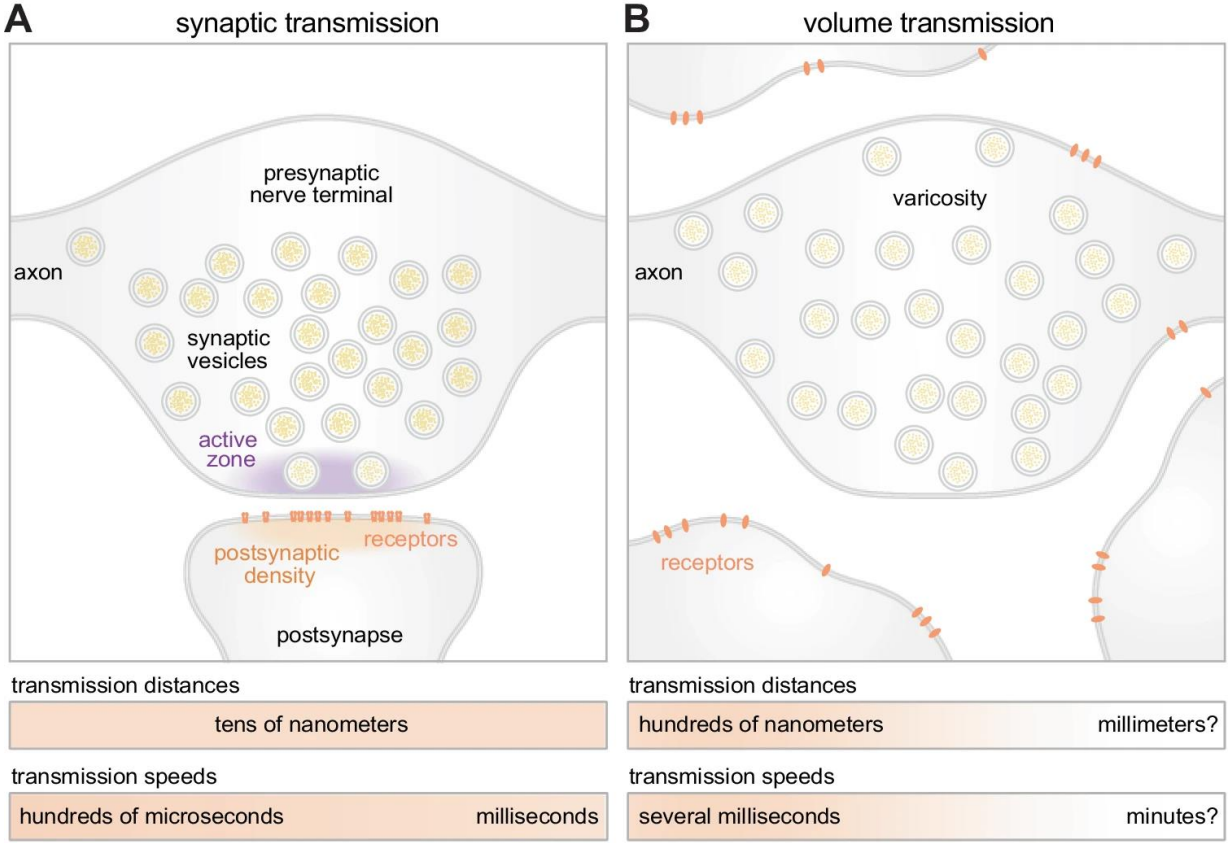
Neuroscience basics – signaling at the membrane



Neuroscience basics – Synaptic and volume transmission

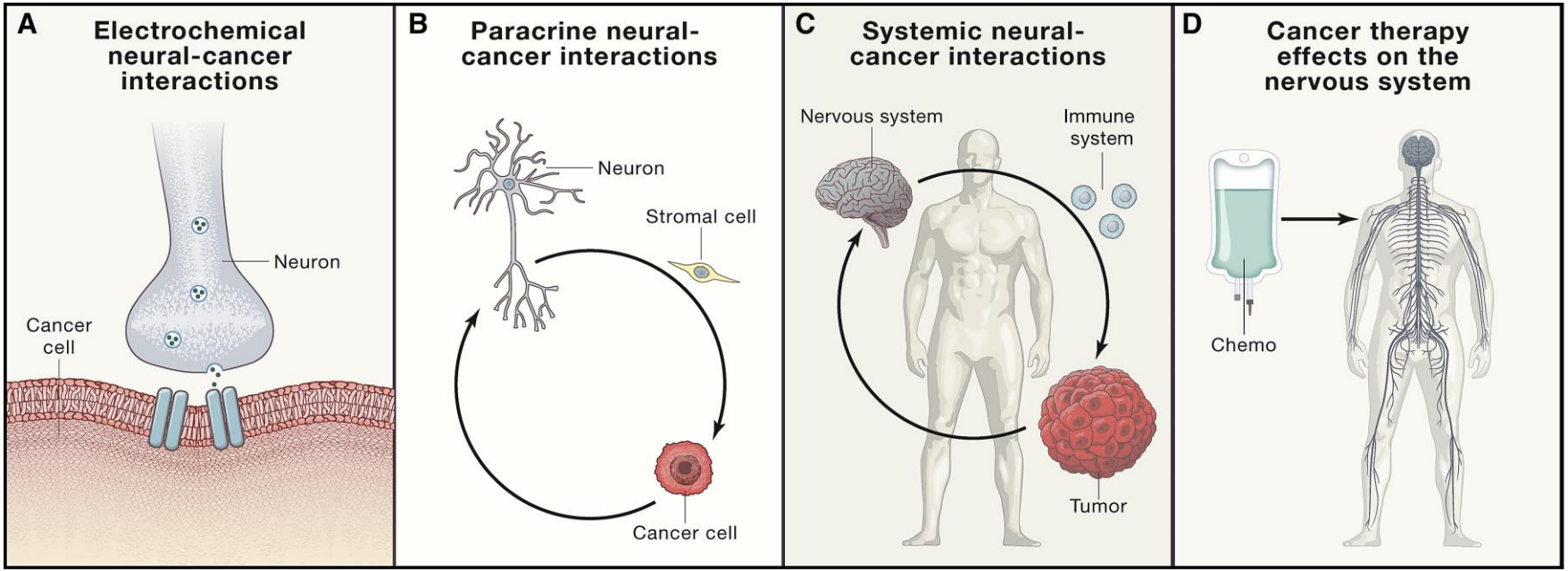
Neurotransmitters:
- Glutamate (Excitatory)
- Aspartate (Excitatory)
- Glycine (Inhibitory)
- GABA (Inhibitory)

Neuromodulators:
(monoamines/neuropeptides)
- Norepinephrine
- Dopamine
- Histamine
- Oxytocin
- Serotonin
- Acetylcholine
- Orexin/hypocretin



Özçete et al, 2024 *Mol Psychiatry*

Cancer Neuroscience



Monje et al., *Cell*, 2020.

Historical context of neuron-cancer interactions

THE AMERICAN JOURNAL OF CANCER

A Continuation of The Journal of Cancer Research

VOLUME XXXIV NOVEMBER, 1938 NUMBER 3

STRUCTURAL DEVELOPMENT IN GLIOMAS

H. J. SCHERER, M.D.

(From the Department of Pathology, Bunge Institute, Antwerp, Belgium)

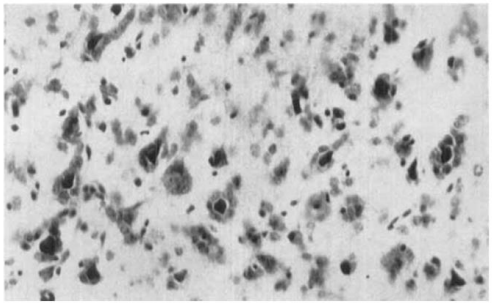


FIG. 1. PRECOCIOUS PERINEURAL STRUCTURES FORMING CAPSULES ABOUT NERVE CELLS. CASE 6/36 NISSL

VOLUME II JANUARY, 1897 No. 1

THE JOURNAL OF EXPERIMENTAL MEDICINE

ON THE PRESENCE OF NERVES IN TUMORS AND OF OTHER STRUCTURES IN THEM AS REVEALED BY A MODIFICATION OF EHRLICH'S METHOD OF "VITAL STAINING" WITH METHYLENE BLUE.

BY HUGH H. YOUNG, M. D.

(From the Anatomical Laboratory of the Johns Hopkins University.)

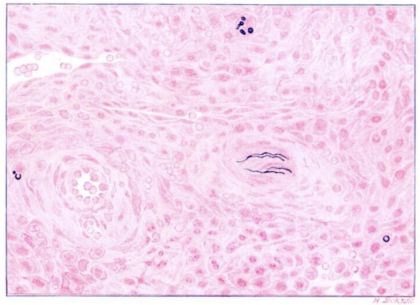
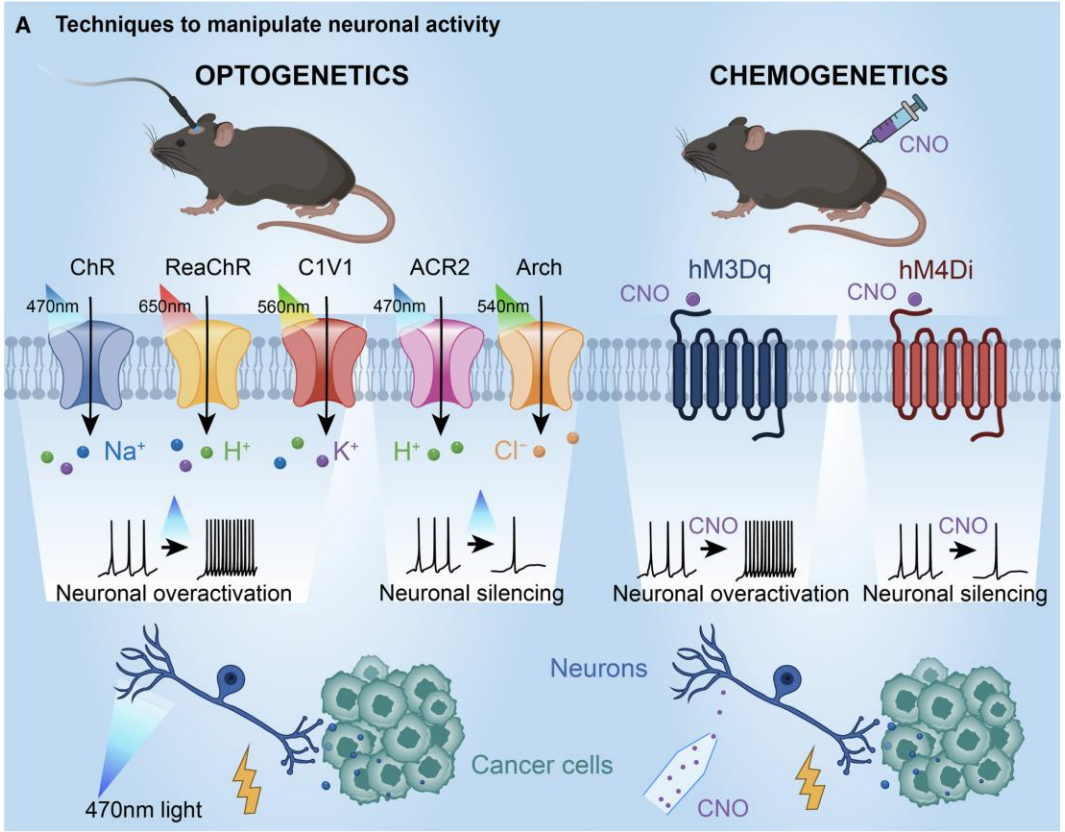


FIG. 1.

Techniques in cancer neuroscience

Optogenetics
Chemogenetics
Electrophysiology
Calcium imaging
Tracing (retrograde, rabies)

Optogenetic toolkit in cancer neuroscience



Theil, Cell Reports, 2025

Optogenetics: genetic and temporal control

nature neuroscience

TECHNICAL REPORT

Millisecond-timescale, genetically targeted optical control of neural activity

Edward S Boyden[1], Feng Zhang[1], Ernst Bamberg[2,3], Georg Nagel[2,5] & Karl Deisseroth[1,4]

Temporally precise, noninvasive control of activity in well-defined neuronal populations is a long-sought goal of systems neuroscience. We adapted for this purpose the naturally occurring algal protein Channelrhodopsin-2, a rapidly gated light-sensitive cation channel, by using lentiviral gene delivery in combination with high-speed optical switching to photostimulate mammalian neurons. We demonstrate reliable, millisecond-timescale control of neuronal spiking, as well as control of excitatory and inhibitory synaptic transmission. This technology allows the use of light to alter neural processing at the level of single spikes and synaptic events, yielding a widely applicable tool for neuroscientists and biomedical engineers.

Neural computation depends on the temporally diverse spiking patterns of different classes of neurons that express unique genetic markers and demonstrate heterogeneous wiring properties within neural networks. Although direct electrical stimulation and recording of neurons in intact brain tissue have provided many insights into the function of circuit subfields (for example, see refs. 1–3), neurons belonging to a specific class are often sparsely embedded within tissue, posing fundamental challenges for resolving the role of particular neuron types in information processing. A high–temporal resolution, noninvasive, genetically based method to control neural activity would enable elucidation of the temporal activity patterns in specific neurons that drive circuit dynamics, plasticity and behavior.

Despite substantial progress made in the analysis of neural network geometry by means of non–cell-type-specific techniques like glutamate uncaging (for example, see refs. 4–7), no tool has yet been invented with the requisite spatiotemporal resolution to probe neural coding at the resolution of single spikes. Furthermore, previous genetically encoded optical methods, although elegant[8–10,11], have allowed control of neuronal activity over timescales of seconds to minutes, perhaps owing to their mechanisms for effecting depolarization. Kinetics roughly a thousand times faster would enable remote control of

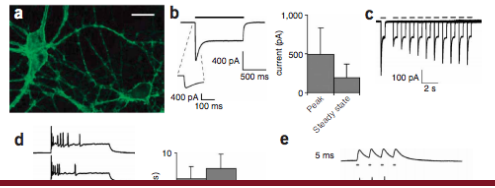
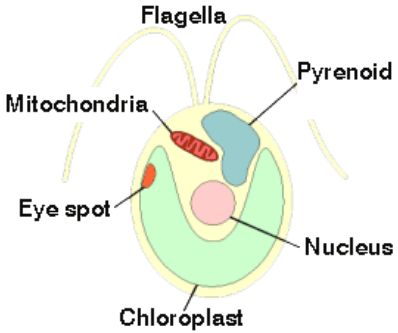


Figure 1 ChR2 enables light-driven neuron spiking. (**a**) Hippocampal neurons expressing ChR2-YFP (scale bar 30 μm). (**b**) Left, inward current in voltage-clamped neuron evoked by 1 s of GFP-wavelength light (indicated by black bar); right, population data (right; mean ± s.d. plotted throughout; $n = 18$). Inset, expanded initial phase of the current transient. (**c**) Ten overlaid current traces recorded from a hippocampal neuron illuminated with pairs of 0.5-s light pulses (indicated by gray bars), separated by intervals varying from 1 to 10 s. (**d**) Voltage traces showing membrane depolarization and spikes in a current-

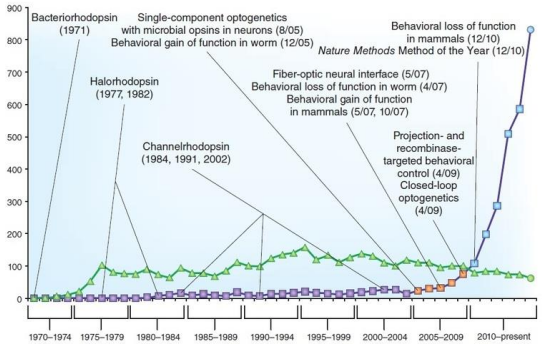
Early optogenetics: Channelrhodopsin-2

Channelrhodopsin-2
- rapidly gated light-sensitive cation channel

Chlamydomonas reinhardtii

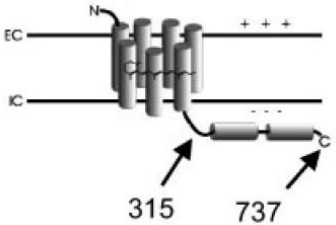


Opsin & Optogenetics Papers

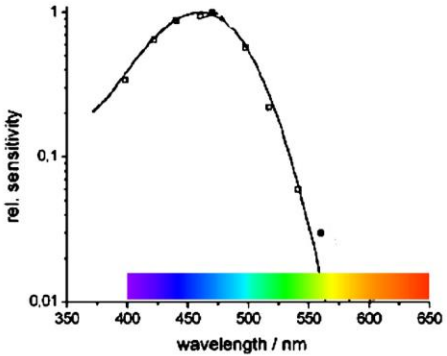


Boyden 2005 *Millisecond-timescale, genetically targeted optical control of neural activity*

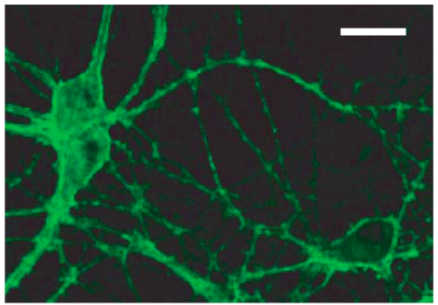
Early optogenetics: Channelrhodopsin-2

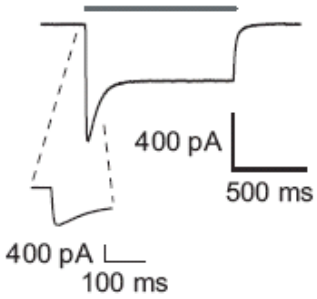


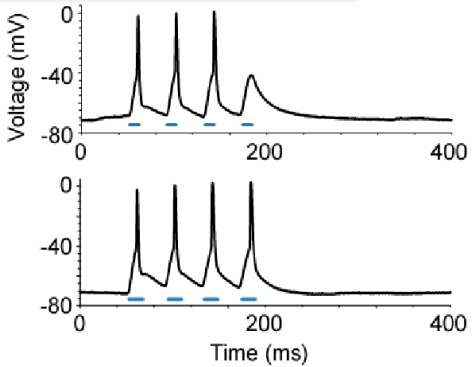
Driven by **blue light** **(10 mW/mm^2)**



Strong homology to the 7-transmembrane protein increases
Conductance of **cations** (**Na^+**, **K^+**, etc.) when gated by light







Boyden 2005 *Millisecond-timescale, genetically targeted optical control of neural activity*

Opsin diversity

I. Faster opsins (ChETA)

II. Spectrally-shifted opsins (VChR1, bReaChES, ChRmine)

III. Bistable opsins (SFO, SSFO)

IV. Inhibitory opsins (NpHR, iC1C2)

V. Opsins for biochemical modulation (OptoXR, RASSL)

Viral options

Wu Tsai Neurosciences Institute | Gene Vector and Virus Core
Stanford University

GVVC ID	Virus name (Click for details)
GVVC-AAV-024	AAV-DJ-CaMKIIa hChR2 (E123A)-eYFP-WPRE
GVVC-AAV-025	AAV-DJ-EF1a-DIO hChR2 (E123A)-eYFP-WPRE
GVVC-AAV-026	AAV-DJ-hSyn1 hChR2 (E123A)eYFP-WPRE
GVVC-AAV-027	AAV-DJ-CaMKIIa hChR2(E123T/T159C)-mCherry-WPRE
GVVC-AAV-028	AAV-DJ-EF1-DIO-hChR2 (E123T/T159C)-eYFP
GVVC-AAV-029	AAV-DJ-CaMKIIa hChR2 (E123T/T159C)-p2A-EYFP-WPRE
GVVC-AAV-030	AAV-DJ-CaMKIIa hChR2 (E123T/T159C)-p2A-mCherry-WPRE
GVVC-AAV-031	AAV-DJ EF1a DIO NpHR3.0-mCherry
GVVC-AAV-032	AAV-DJ-EF1 DIO hChR2 (E123T/T159C)-p2A-eYFP-WPRE
GVVC-AAV-033	AAV-DJ-EF1 DIO hChR2 (E123T/T159C)-p2A-mCherry-WPRE
GVVC-AAV-034	AAV-DJ-EF1-DIO hChR2 (C128S/D156A)-eYFP
GVVC-AAV-035	AAV-5-CaMKIIa hChR2(H134R)-eYFP
GVVC-AAV-036	AAV-DJ-CaMKIIa hChR2(H134R)-eYFP
GVVC-AAV-037	AAV-DJ-CaMKIIa hChR2(H134R)-mCherry
GVVC-AAV-038	AAV-DJ-EF1-DIO hChR2(H134R)-eYFP
GVVC-AAV-039	AAV-DJ-EF1-DIO hChR2(H134R)- mCherry
GVVC-AAV-040	AAV-DJ-hSyn1 hChR2(H134R)-eYFP
GVVC-AAV-041	AAV-DJ-hSyn1 hChR2(H134R)-mCherry
GVVC-AAV-042	AAV-DJ-CamKIIa hChR2 (T159C)-p2A-EYFP-WPRE
GVVC-AAV-043	AAV-DJ-CamKIIa hChR2 (T159C)-p2A- mCherry-WPRE
GVVC-AAV-044	AAV-DJ-CaMKIIa C1V1 (E122T/E162T)-TS-EYFP
GVVC-AAV-045	AAV-DJ-CaMKIIa C1V1 (E122T/E162T)-TS-P2A-EYFP-WPRE
GVVC-AAV-046	AAV-DJ-CaMKIIa C1V1 (E122T/E162T)-TS-P2A-mCherry-WPRE

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Stanford University

GVVC-AAV-047	AAV-DJ-CaMKIIa C1V1 (E162T)-TS-p2A-EYFP-WPRE
GVVC-AAV-048	AAV-DJ-CaMKIIa C1V1 (E162T)-TS-p2A-mCherry-WPRE
GVVC-AAV-049	AAV-DJ-EF1a DIO C1V1 (E122T/E162T)-TS-p2A-eYFP-WPRE
GVVC-AAV-050	AAV-DJ-EF1a DIO C1V1 (E122T/E162T)-TS-p2A-mCherry-WPRE
GVVC-AAV-051	AAV-DJ-EF1a DIO C1V1 (E162T)-TS-p2A-eYFP-WPRE
GVVC-AAV-052	AAV-DJ-EF1a DIO C1V1 (E162T)-TS-p2A-mCherry-WPRE
GVVC-AAV-053	AAV-DJ-CaMKIIa eArch3.0-eYFP
GVVC-AAV-054	AAV-5-CaMKIIa eArch3.0-eYFP
GVVC-AAV-055	AAV-DJ-EF1-DIO eArch3.0-eYFP
GVVC-AAV-056	AAV-5-EF1a-DIO eArch3.0-eYFP
GVVC-AAV-057	AAV-DJ-CaMKIIa NpHR3.0-eYFP
GVVC-AAV-058	AAV-DJ-EF1a-DIO NpHR3.0-eYFP
GVVC-AAV-064	AAV-DJ-EF1-ChETA-eYFP
GVVC-AAV-065	AAV-DJ-EF1-DIO ChETA-eYFP
GVVC-AAV-066	AAV-DJ-EF1-ChIEF-eYFP
GVVC-AAV-072	AAV-DJ CaMKIIa-hChR2 (E123A)-mCherry
GVVC-AAV-075	AAV-DJ nEF Con/Fon hCHR2(H134R)-eYFP-WPRE
GVVC-AAV-076	AAV-DJ nEF Con/Foff hCHR2(H134R)-eYFP-WPRE
GVVC-AAV-077	AAV-DJ nEF Coff/Fon hCHR2(H134R)-eYFP-WPRE
GVVC-AAV-079	AAV-DJ hSyn Con/Fon hCHR2(H134R)-eYFP-WPRE
GVVC-AAV-081	AAV-DJ hSyn Con/Foff hCHR2(H134R)-eYFP-WPRE
GVVC-AAV-083	AAV-DJ hSyn Coff/Fon hCHR2(H134R)-eYFP-WPRE
GVVC-AAV-087	AAV-DJ EF1a fDIO hChR2(H134R)-eYFP-WPRE
GVVC-AAV-106	AAV-8-CaMKIIa-iC++-EYFP

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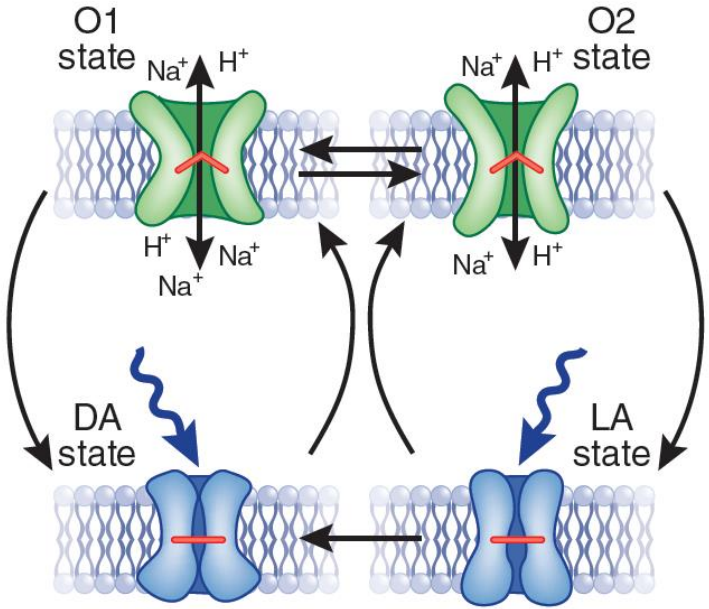
GVVC-AAV-163	AAV-8-hSyn-SwiChR++-mCherry
GVVC-AAV-173	AAV-8-hSyn-hChR2(E123T/T159C)-eYFP
GVVC-AAV-174	AAV-8-CaMKIIa-FLASH-eYFP
GVVC-AAV-175	AAV-8-hSyn-FLASH-eYFP
GVVC-AAV-176	AAV-8- Ef1a-DIO FLASH-eYFP
GVVC-AAV-179	AAV-8-CaMKIIa-bReaches-TS-p2A-mCherry
GVVC-AAV-183	AAV-8-hSyn-ChRmine-mScarlet-WPRE
GVVC-AAV-184	AAV-8-hSyn-ChRmine-mScarlet-Kv2.1-WPRE
GVVC-AAV-185	AAV-8-hSyn-ChRmine-eYFP-WPRE
GVVC-AAV-186	AAV-8-hSyn-ChRmine-eYFP-Kv2.1-WPRE
GVVC-AAV-188	AAV-8-Ef1a-DIO-ChRmine-mScarlet-WPRE
GVVC-AAV-189	AAV-8-Ef1a-DIO-ChRmine-mScarlet-Kv2.1-WPRE
GVVC-AAV-190	AAV-8-Ef1a-DIO-ChRmine-eYFP-WPRE
GVVC-AAV-191	AAV-8-Ef1a-DIO-ChRmine-eYFP-Kv2.1-WPRE
GVVC-AAV-193	AAV-8-CaMKIIa-ChRmine-mScarlet-WPRE
GVVC-AAV-194	AAV-8-CaMKIIa-ChRmine-mScarlet-Kv2.1-WPRE
GVVC-AAV-195	AAV-8-CaMKIIa-ChRmine-eYFP-WPRE
GVVC-AAV-196	AAV-8-CaMKIIa-ChRmine-eYFP-Kv2.1-WPRE
GVVC-AAV-199	AAV-8-CaMKIIa-eNpHR3.0-mCherry
GVVC-AAV-200	AAV-8-hSyn-eNpHR3.0-mCherry
GVVC-AAV-201	AAV-8-Ef1a-DIO eArch 3.0-mCherry
GVVC-AAV-202	AAV-8-Ef1a-DIO bReaChES-mCherry
GVVC-AAV-207	AAV-8-hSyn-DIO-ChR2-eYFP
GVVC-AAV-209	AAV-8-CaMKIIa-ChRmine-oScarlet WPRE

A simplified kinetic model of ChR function



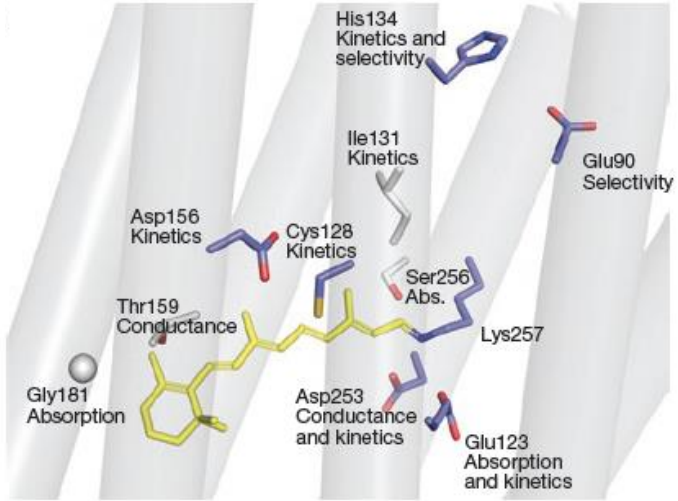
2 closed dark states
DA dark adapted
LA light adapted

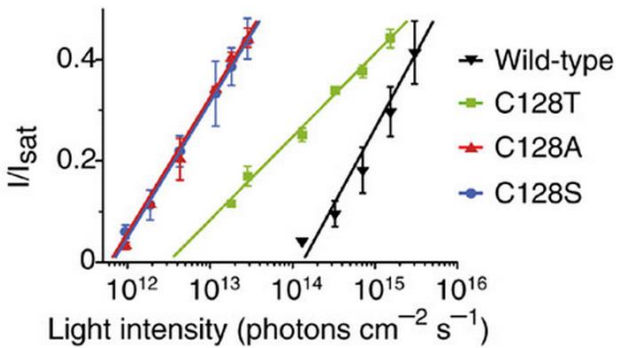
O2 results in reduced current amplitudes

Hegeman 2011 *ChR engineering and exploration of new optogenetic*

Opsin photoreaction and structure

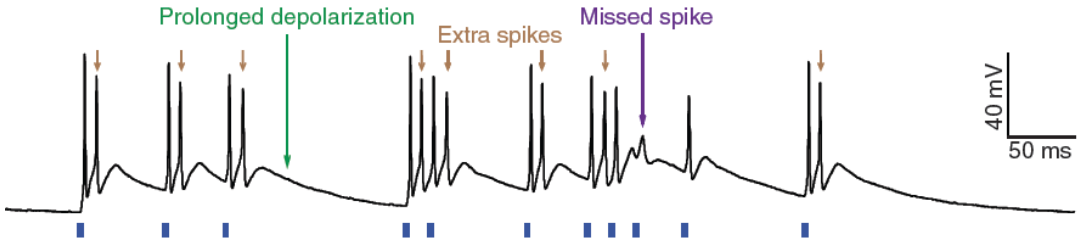
Mutations of aa residues are known to substantially influence optical and kinetic properties.



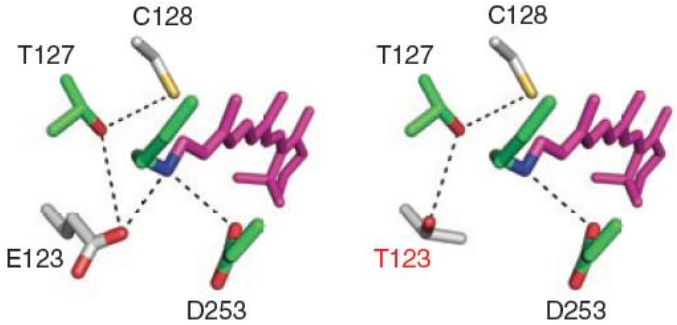


Hegeman et al. ChR engineering and exploration of new optogenetic tools. Nature methods, 2011

Engineering channelrhodopsin for speed and precision



Solution: mutate key residues in retinal binding pocket to improve channel kinetics



Gunaydin et al. Ultrafast optogenetic control. Nature Neuro, 2010

Spectrally-shifted opsins

JGI

Volvox carteri f. nagariensis v1.0

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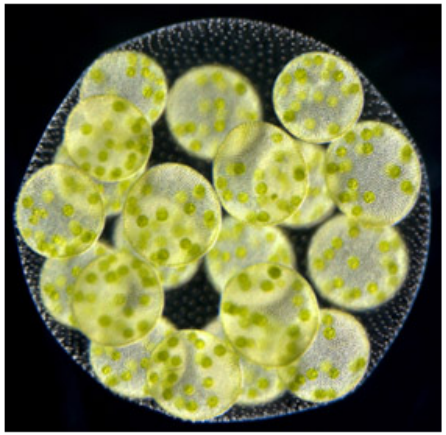


Photo by: Ichiro Nishii

Volvox carteri, the 'fierce roller', is a multicellular chlorophyte alga, closely related to the single-celled *Chlamydomonas reinhardtii*. *Volvox* normally reproduces as an asexual haploid, but can be induced to undergo sexual differentiation and reproduction. The 48-hour life cycle allows easy laboratory culture and includes an embryogenesis program that features many of the hallmarks of animal and plant development. These features include embryonic axis formation, asymmetric cell division, a gastrulation-like inversion, and differentiation of germ and somatic cells. The ~2000 somatic cells in a *Volvox* spheroid are biflagellate and adapted for motility, while the ~16 large germ cells contained within the spheroid are non-motile and specialized for growth and reproduction. *Volvox* embryogensis generates the coordinated arrangement of somatic flagella and photosensing eye spots needed for the organism's characteristic forward rolling motion.

The draft sequence of the *Volvox* genome will provide fascinating insights into the evolution of multicellularity in the green algal lineage and beyond. Moreover, the Volvocales, the family that includes single-celled *Chlamydomonas* (whose genome sequence is already available) and *Volvox*, also includes several multicellular or colonial species with intermediate cell numbers and less complex developmental programming. Comparative genomic studies within this group promises further insights into the origin and evolution of multicellularity in eukaryotes.

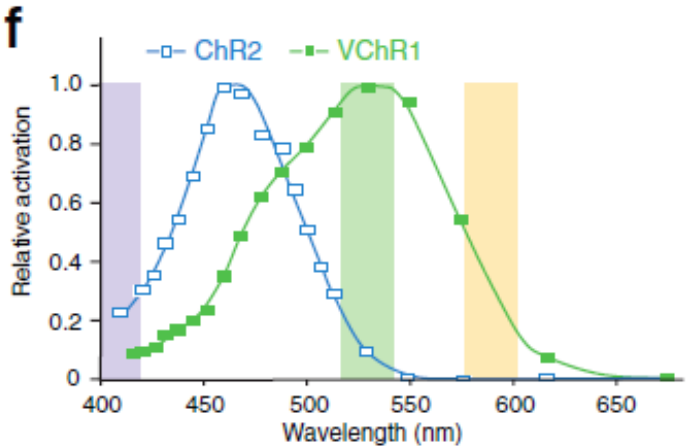
Comments/Questions

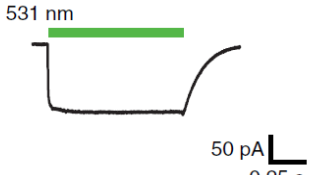
Zhang et al, 2008

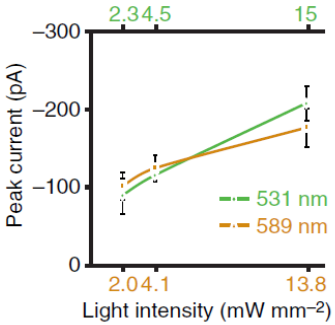
Opsin mining: VChR1

Red-shifted optogenetic excitation: a tool for fast neural control derived from *Volvox carteri*

Feng Zhang[1], Matthias Prigge[2], Florent Beyrière[2], Satoshi P Tsunoda[2], Joanna Mattis[1], Ofer Yizhar[1], Peter Hegemann[2] & Karl Deisseroth[1]

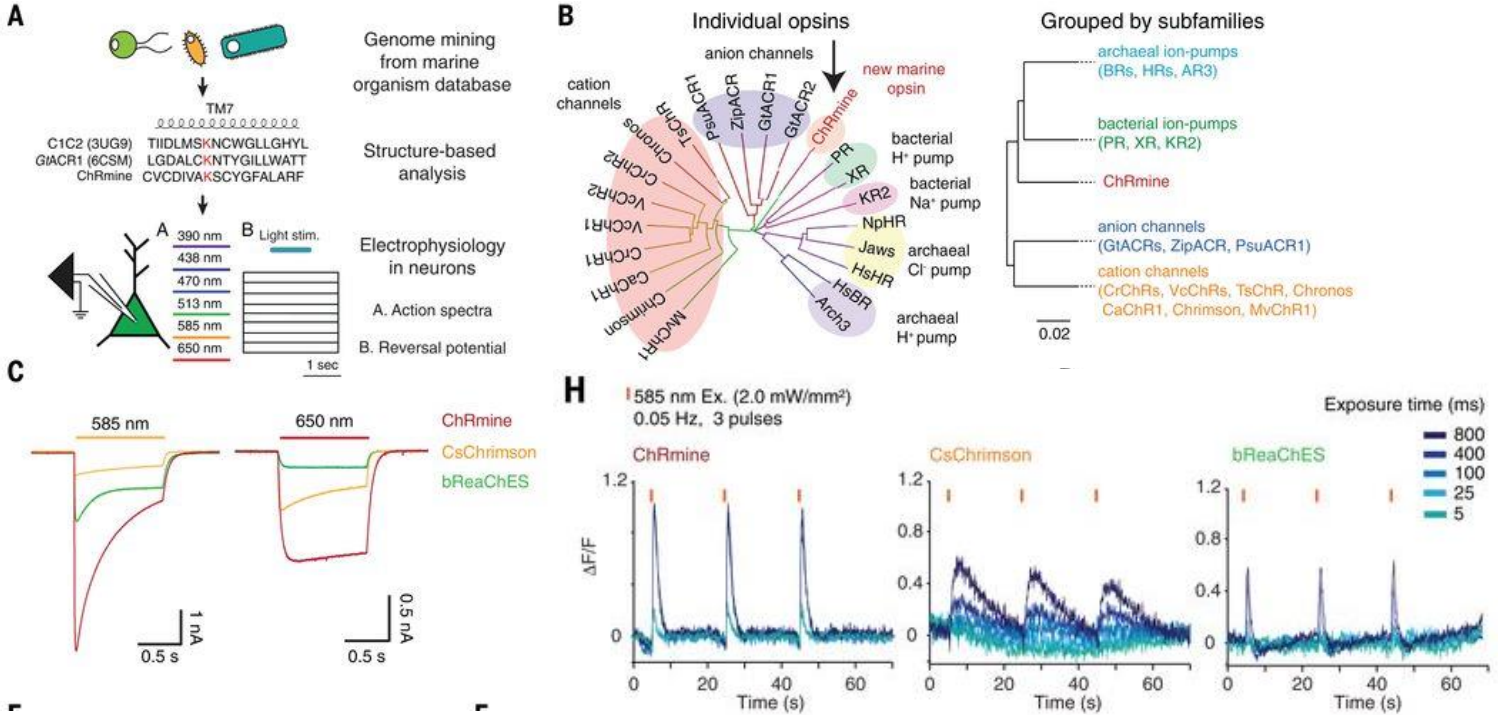






Zhang et al, 2008

Novel red opsin: ChRmine



Marshel*, Kim*, Machado*, Quirin* et al, Science 2019

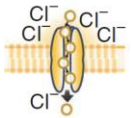
Inhibitory opsins

Probing archaea for new opsins for optogenetic control

Lake Zug, Wadi Natrun, Sahara Desert
The amount of water varies greatly during the year and lakes may disappear.

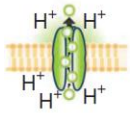
Local archaea express light-activated chloride pumps (halorhodopsins).

Natronomonas pharaonis belongs to the order of Halobacteriales, which also includes *Halobacterium salinarum* (HsHR).

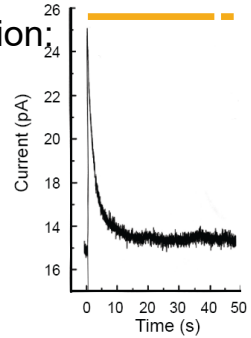


Possible optical approaches for inhibition:

-Halorhodopsin (**chloride pump**)

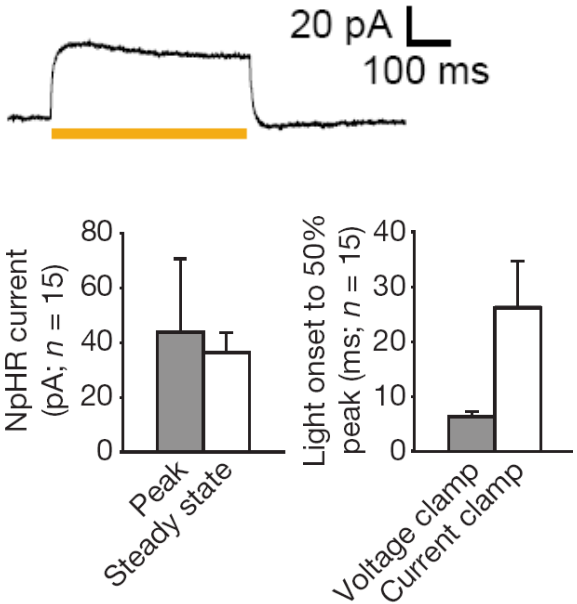


-Bacteriorhodopsin (**proton pump**)

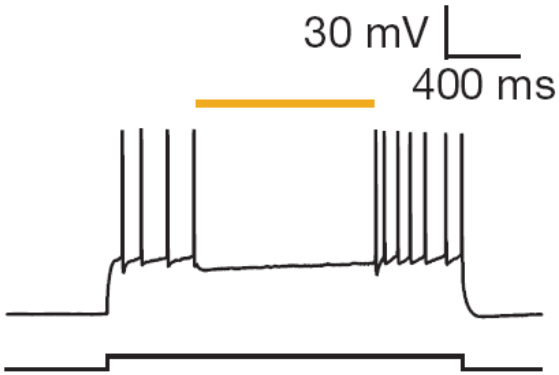


Halorhodopsin (NpHR)

Voltage clamp, strong current

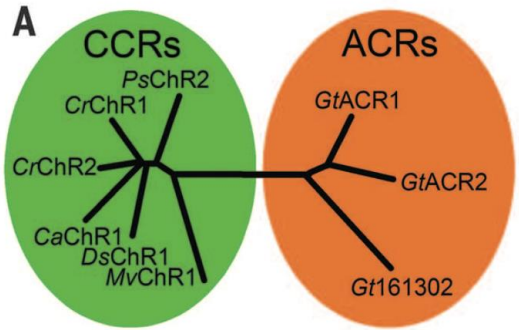


Current Clamp, inhibits firing

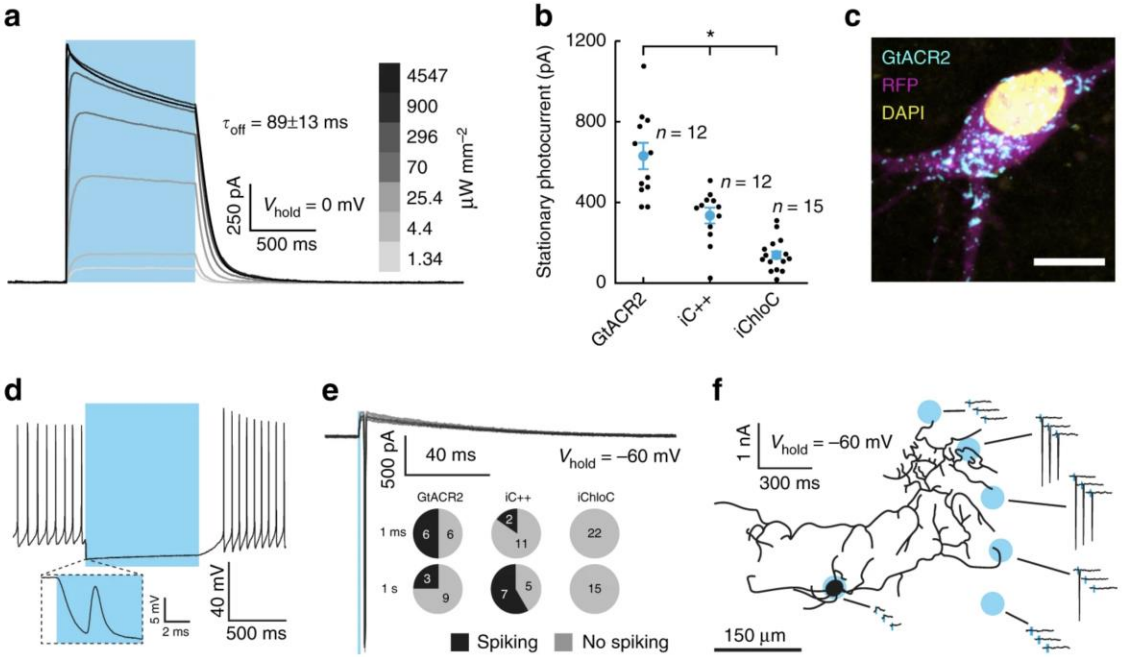


Zhang et al. Multimodal fast optical interrogation of neural circuitry. Nature, 2007

Anion-conducting channelrhodopsins (ACRs)



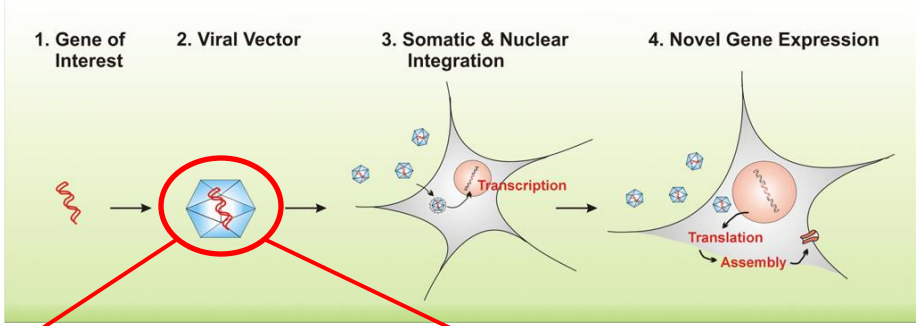
Govorunova et al., 2015

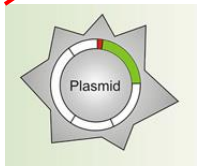


Mahn,…& Yizhar et al., Nature 2018

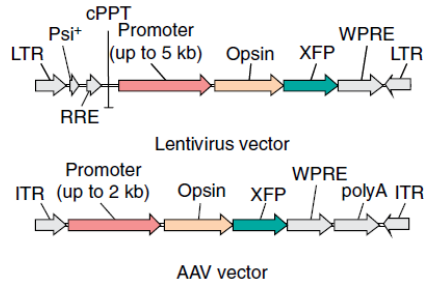
Viral delivery

- Rapid and flexible experimental implementation
- Potent (high gene copy number)
- Confer simultaneous genetic and anatomical specificity





•Adeno-associated virus (AAV2/5)
•Lentivirus
•Rabies virus
•Herpes simplex virus



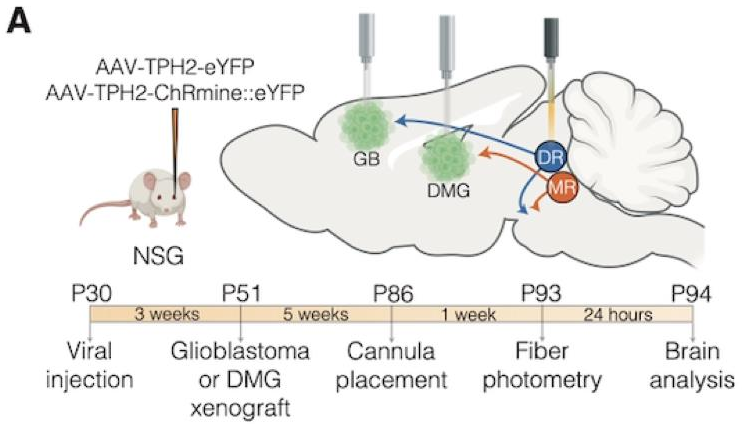
AAV engineered to cross the BBB

pAAV-S5E2-ChR2-mCherry (AAV PHP.eB)

Viral Prep	#135634-PHPeB
Purpose	Ready-to-use AAV PHP.eB particles produced from pAAV-S5E2-ChR2-mCherry (#135634). In addition to the viral particles, you will also receive purified pAAV-S5E2-ChR2-mCherry plasmid DNA. Expression of ChR2-mCherry under the control of the E2 regulatory element. These AAV were produced with the PHPeB serotype, which permits efficient transduction of the central nervous system. These AAV preparations are suitable purity for injection into animals.
Depositor	Jordane Dimidschstein
Article	Vormstein-Schneider et al Nat Neurosci. 2020 Dec;23(12):1629-1636.
Tags	mCherry
Available Since	Oct. 28, 2021
Availability	Academic Institutions and Nonprofits only

pAAV-hSyn-hChR2(H134R)-EYFP (AAV PHP.eB)

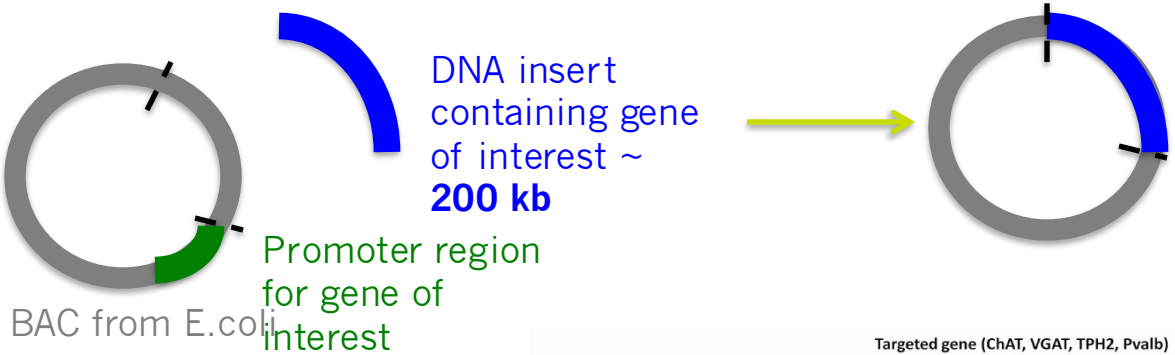
Viral Prep	#26973-PHPeB
Purpose	Ready-to-use AAV PHP.eB particles produced from pAAV-hSyn-hChR2(H134R)-EYFP (#26973). In addition to the viral particles, you will also receive purified pAAV-hSyn-hChR2(H134R)-EYFP plasmid DNA. hSyn-driven, humanized channelrhodopsin H134R mutant fused to EYFP for optogenetic activation. These AAV were produced with the PHPeB serotype, which permits efficient transduction of the central nervous system. These AAV preparations are suitable purity for injection into animals.
Depositor	Karl Deisseroth
Promoter	Syn
Tags	EYFP
Available Since	Sept. 8, 2020
Availability	Academic Institutions and Nonprofits only



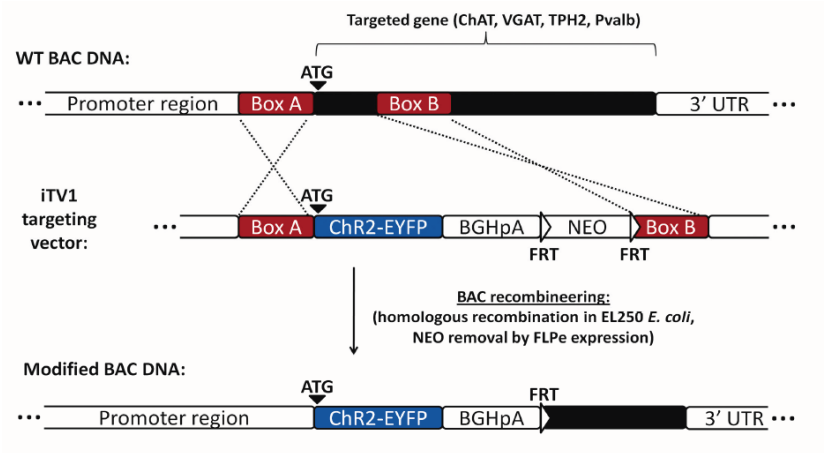
Addgene

Drexler et al, bioRxiv, 2025

Transgenic animals

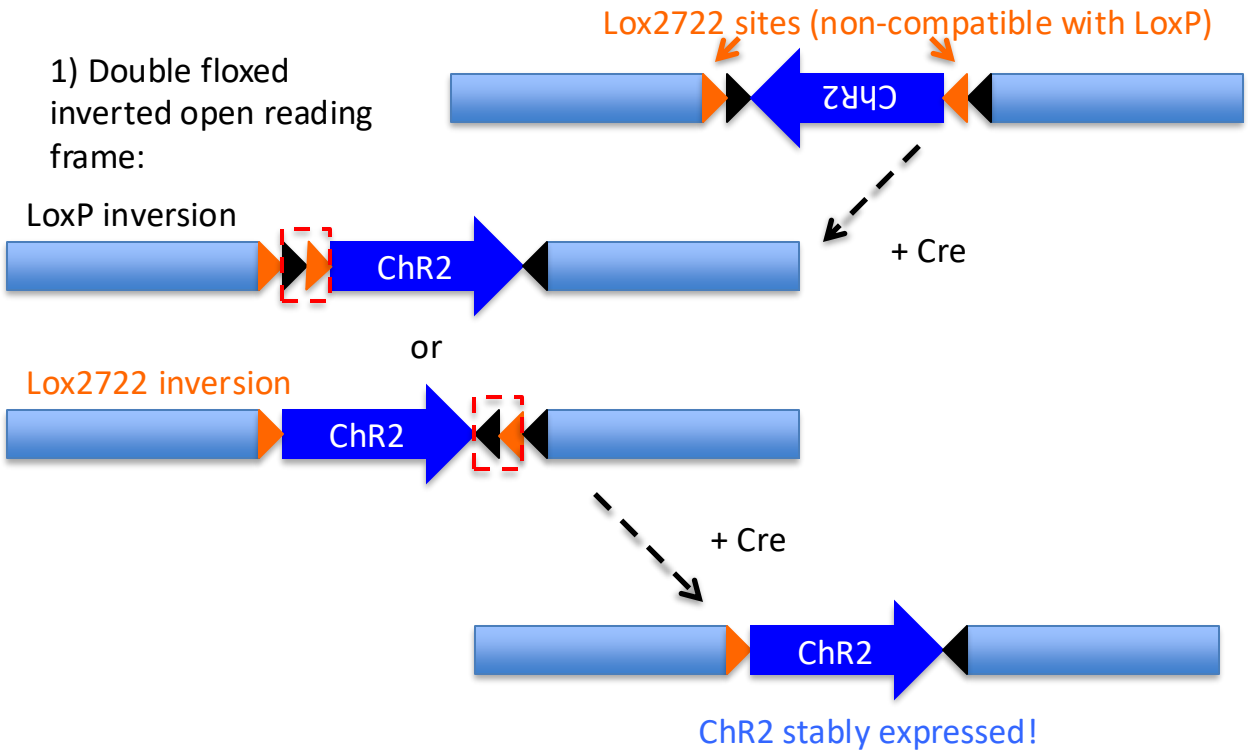


Injection of modified BAC DNA constructs into pronucleus of fertilized oocyte – then implanted into recipient female mouse uterus

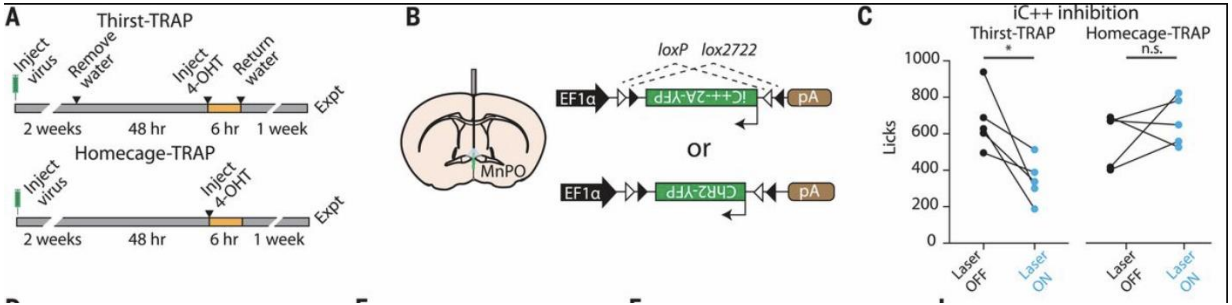


Zhao et al, 2011

Recombinase-based approaches for optogenetic tools



The neural basis for thirst

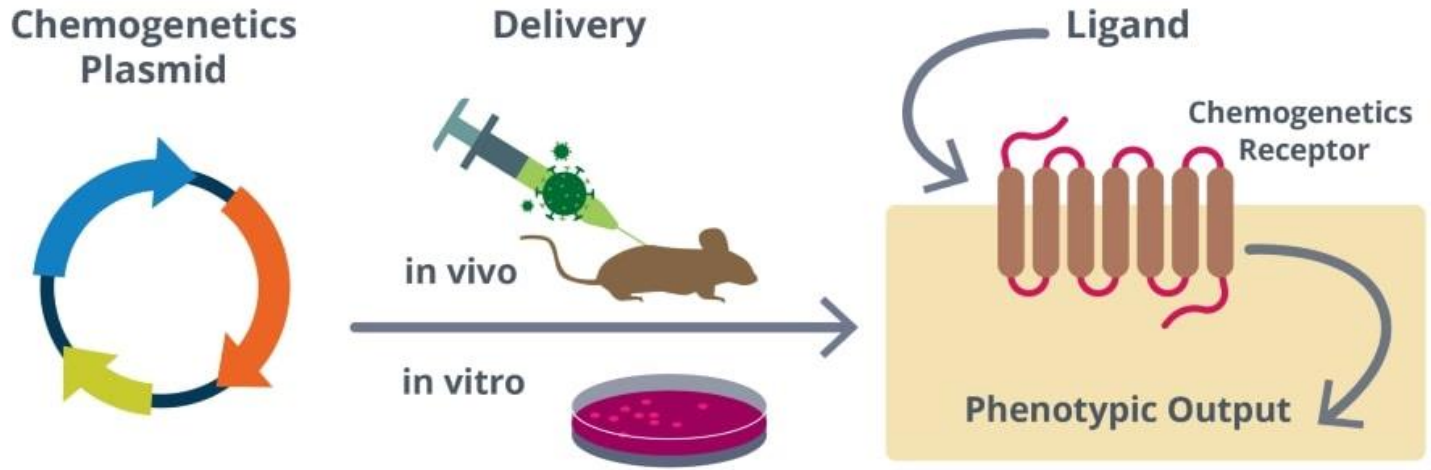


Allen et al., Science 2017

Behavioral output

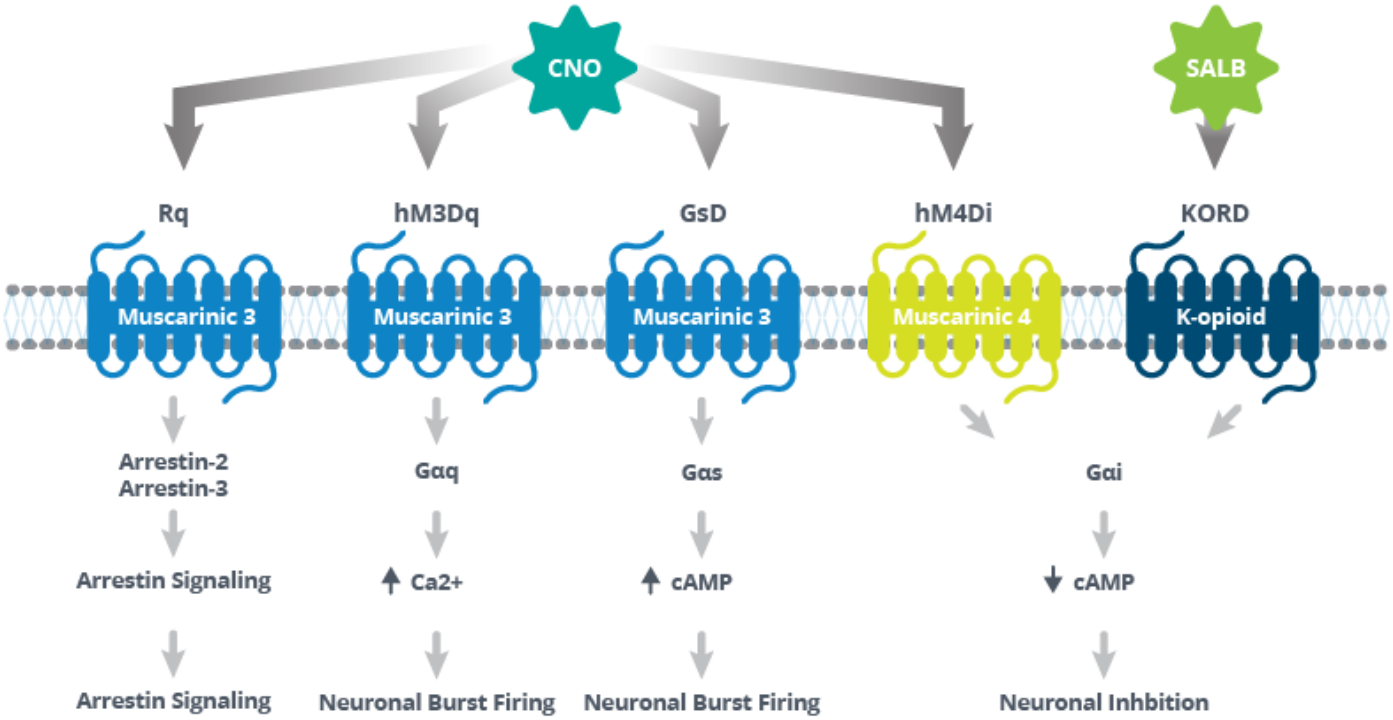
Gibson *et al*., Science, 2014

Chemogenetics



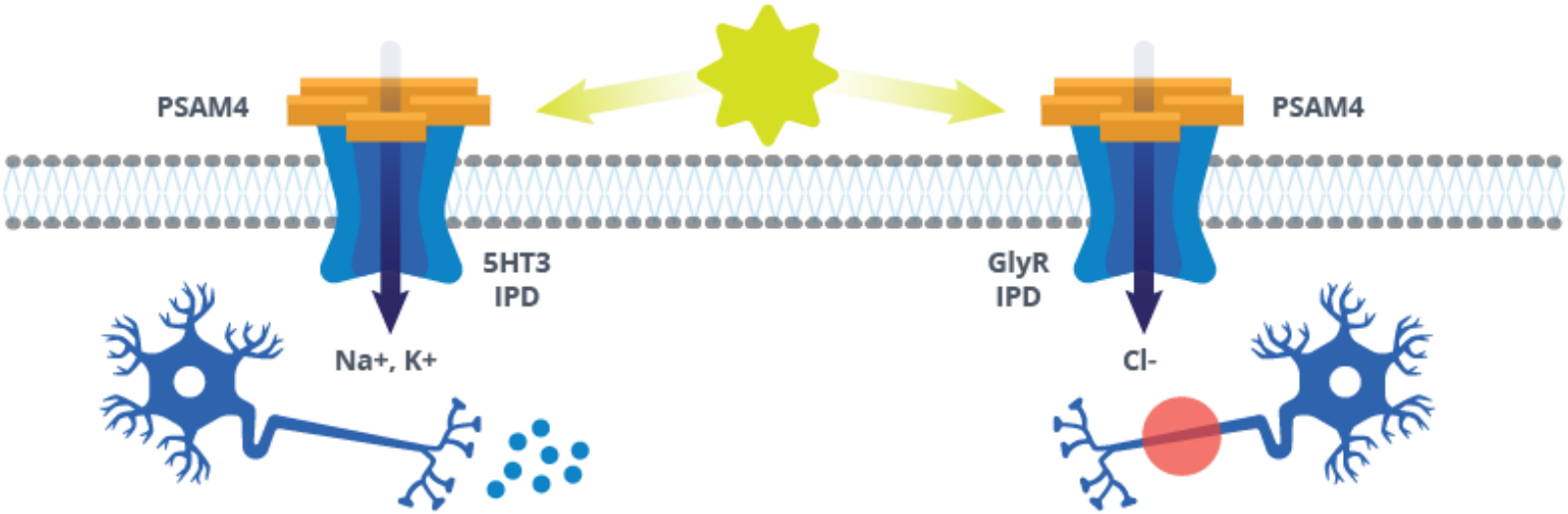
Sourced from addgene.org

Chemogenetics - DREADDs

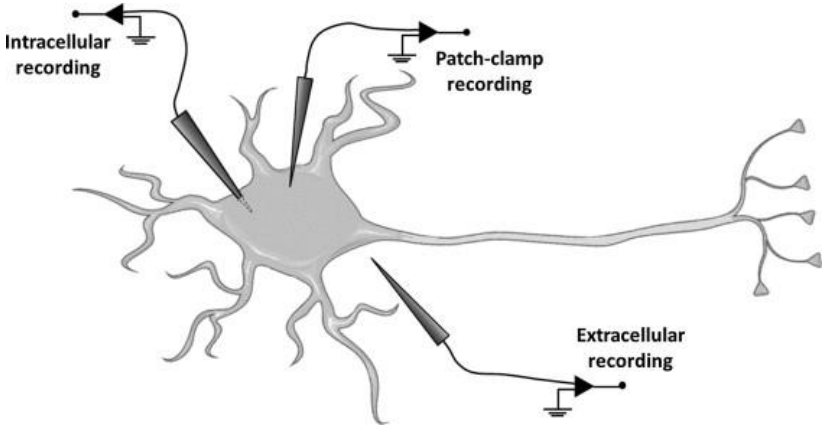


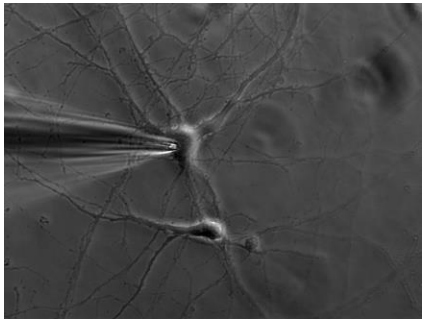
Sourced from addgene.org

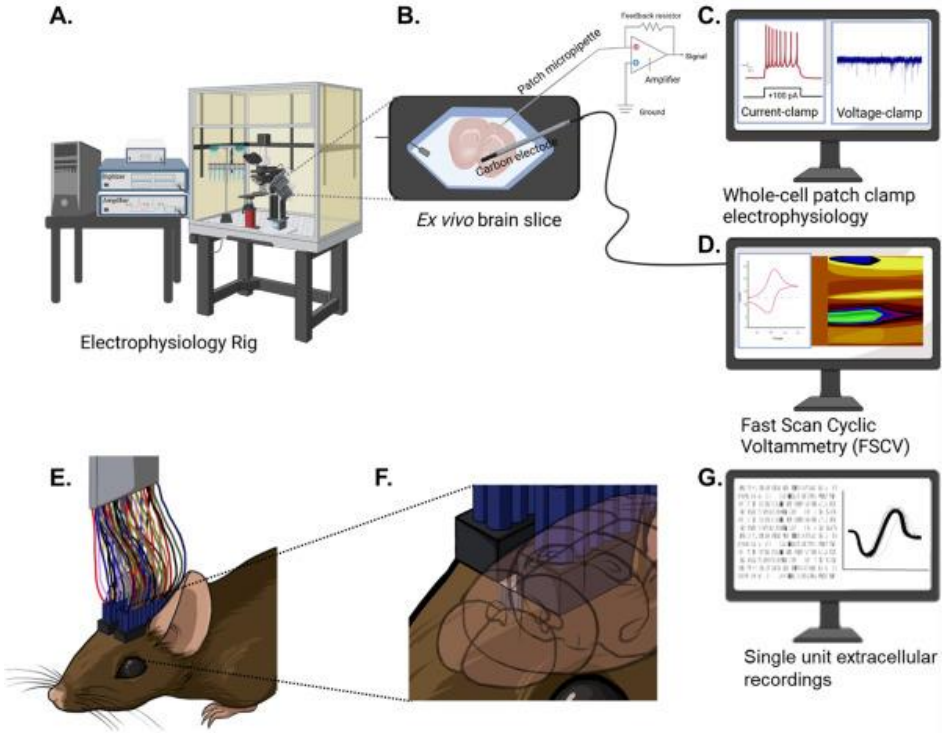
Chemogenetics - PSAMs



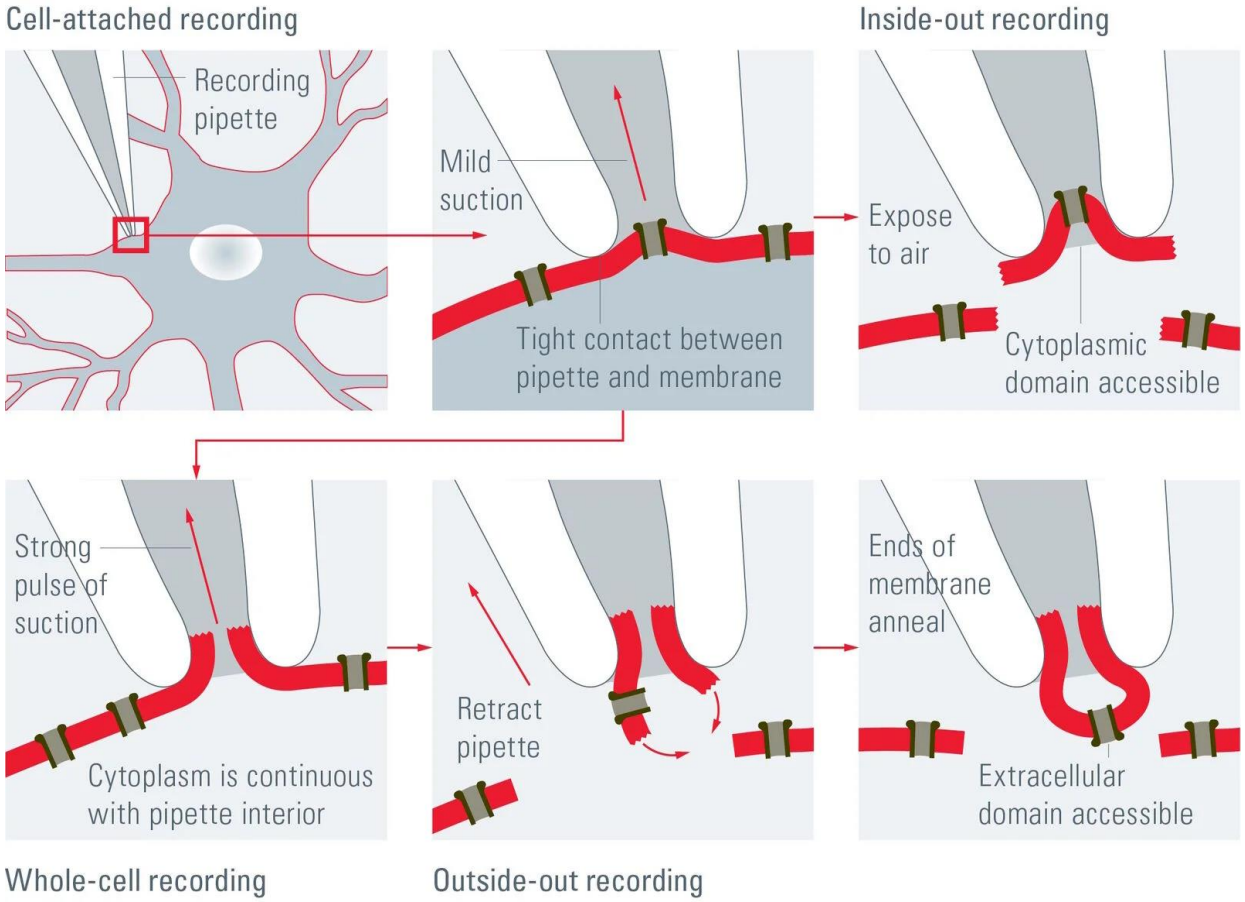
Electrophysiology



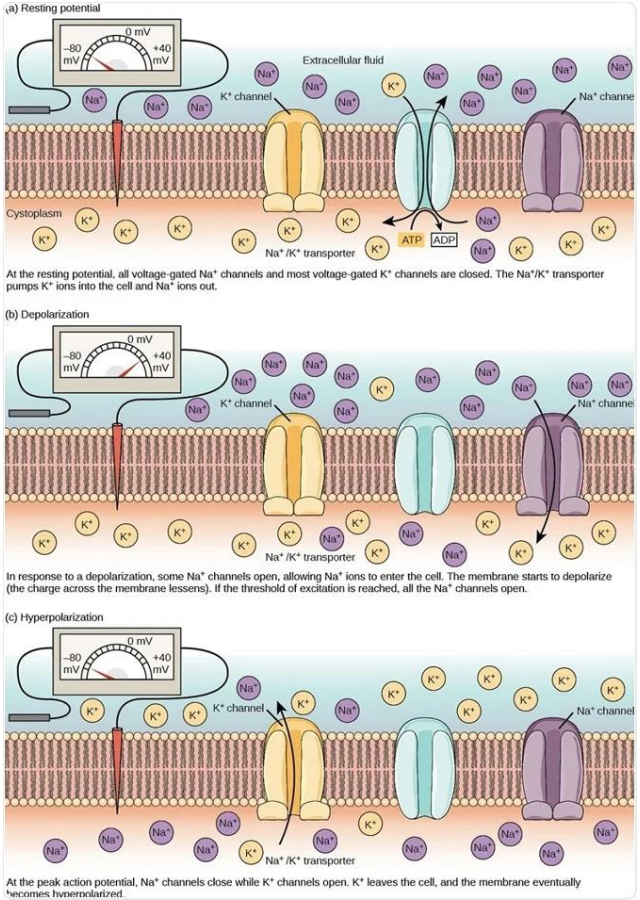


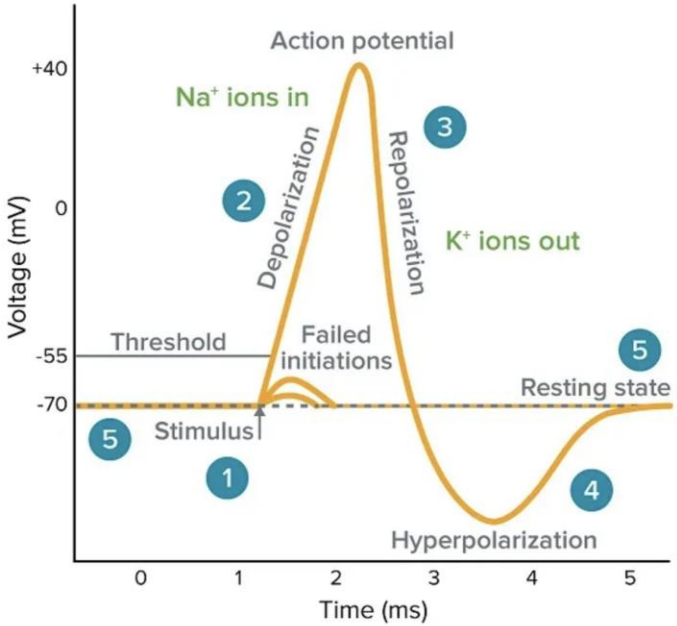


Patch clamping

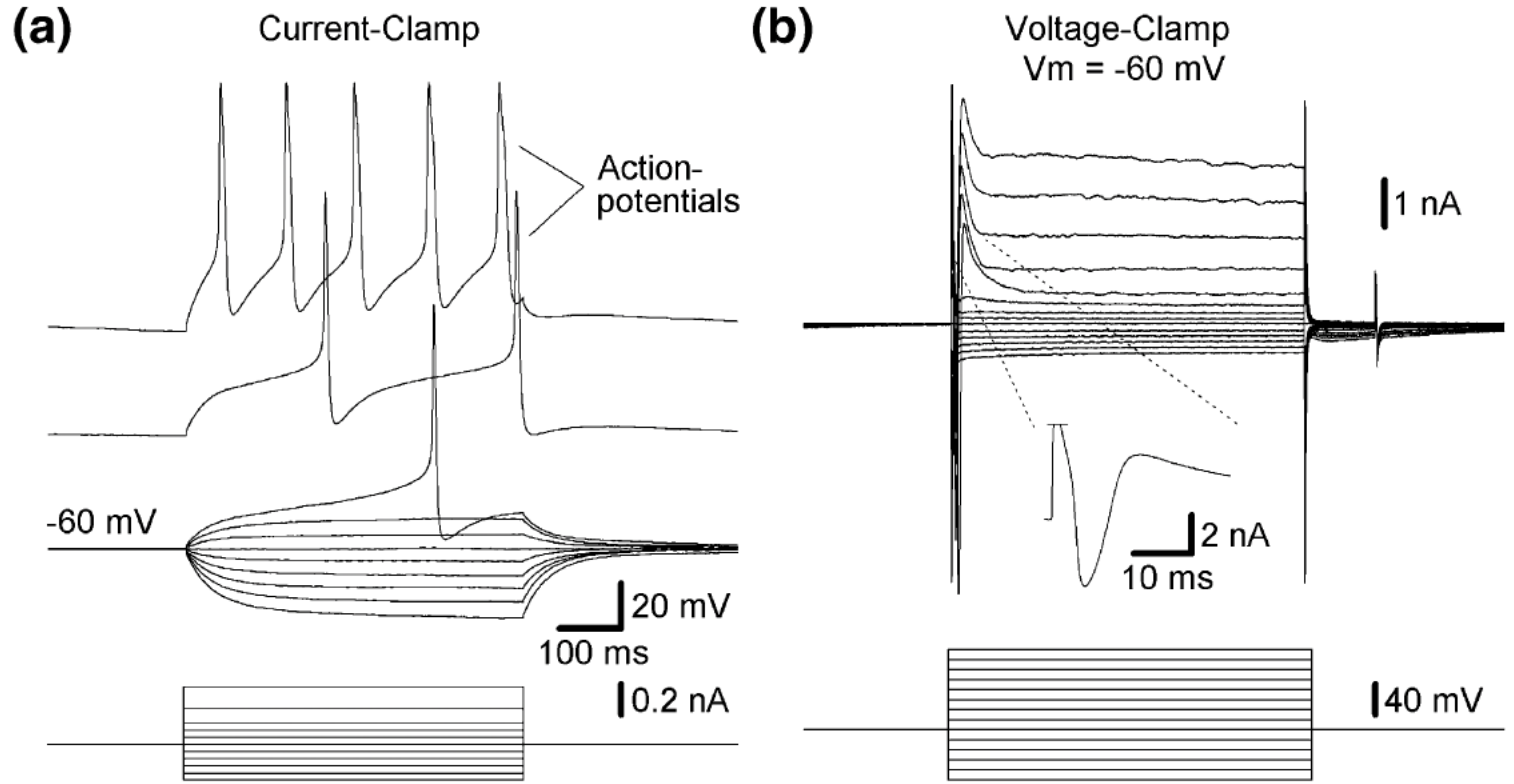


Changes in membrane potential





Voltage clamp vs current clamp



Neuronal tracing - labeling

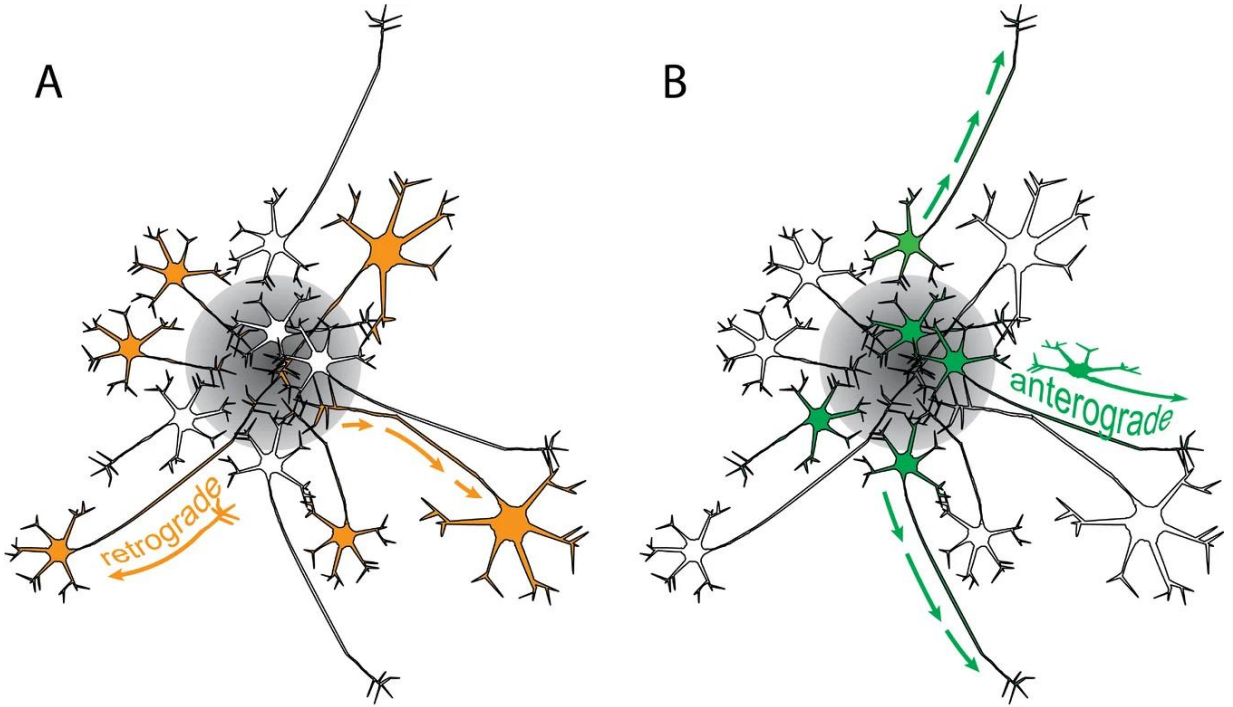
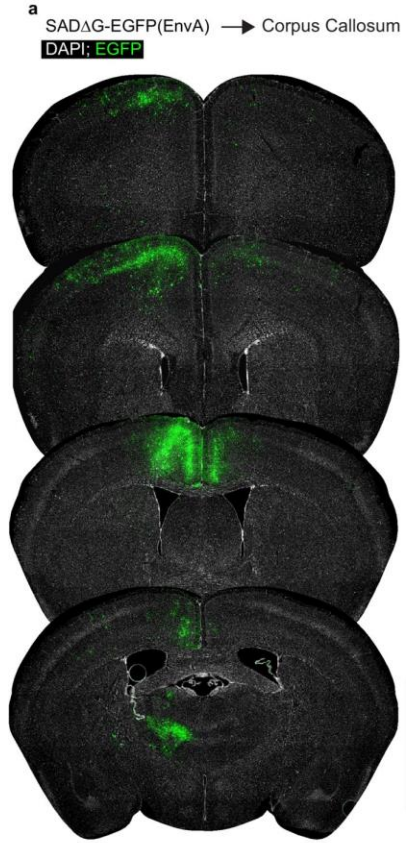


Figure 1. Neuronal tracers are delivered to a particular location (gray). *(A) Retrograde tracers mark neurons that send information to that area (visualized in orange). (B) Anterograde tracers mark neurons that receive information from that area (visualized in green).*

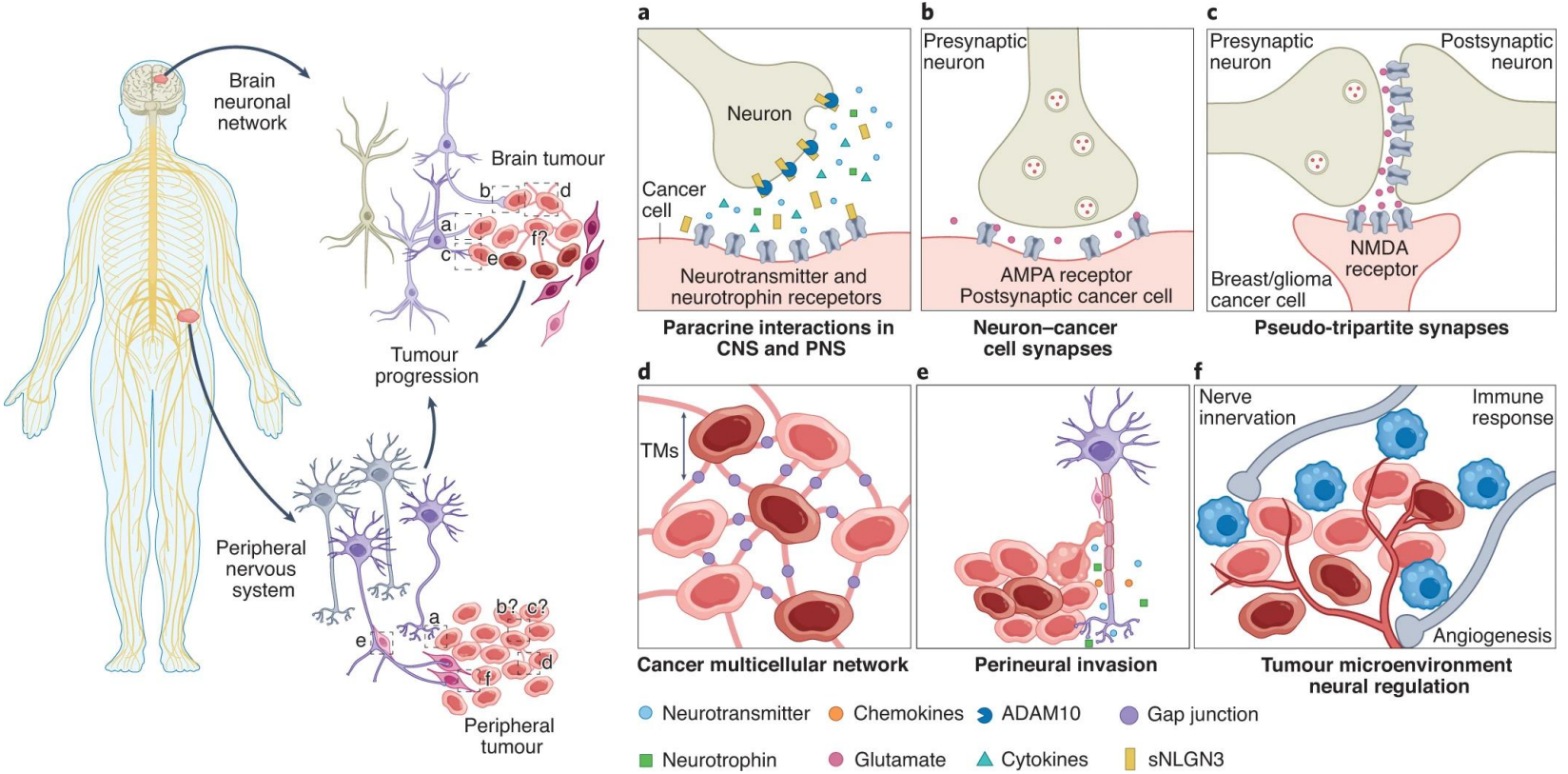
Neuronal tracing – monosynaptic using rabies virus



Mount et al., eLife, 2019

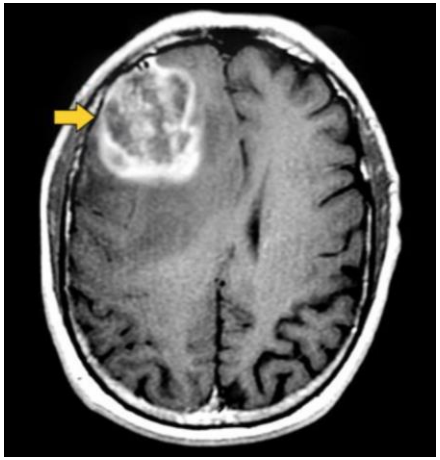
Neuron-cancer interactions

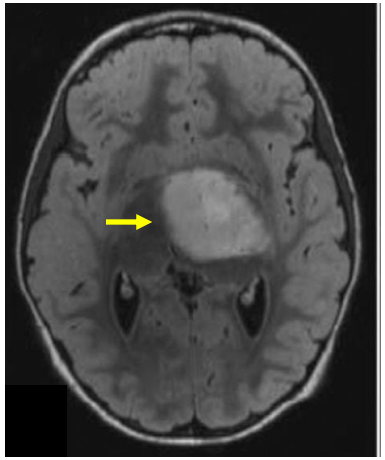
Neural inputs drive cancer progression

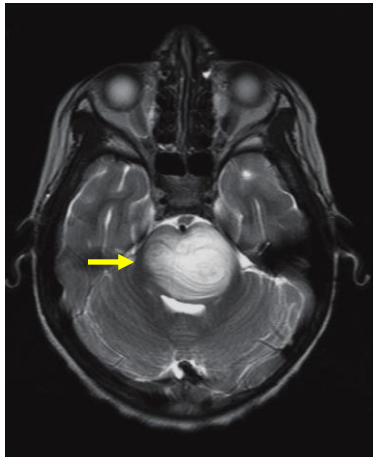


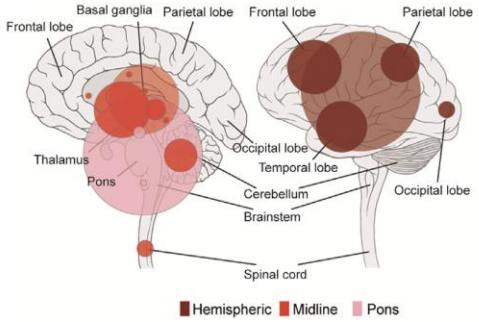
Pan and Winkler, *Nature Cell Biology*, 2022.

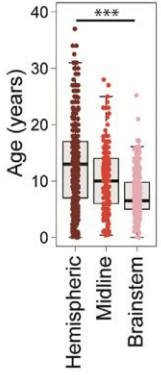
Pediatric high-grade glioma

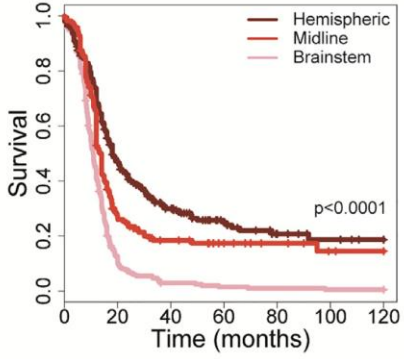








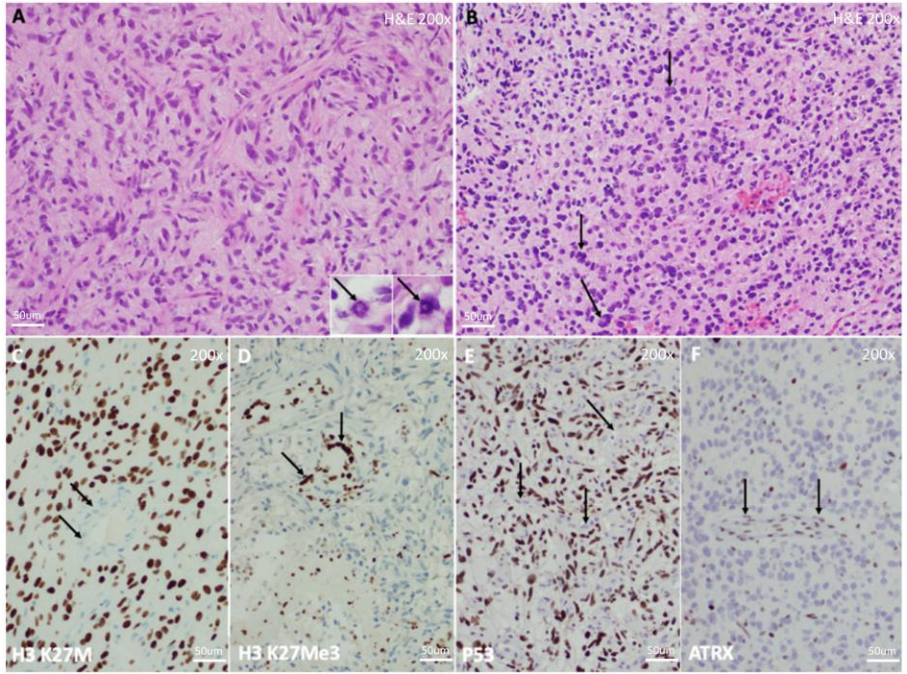


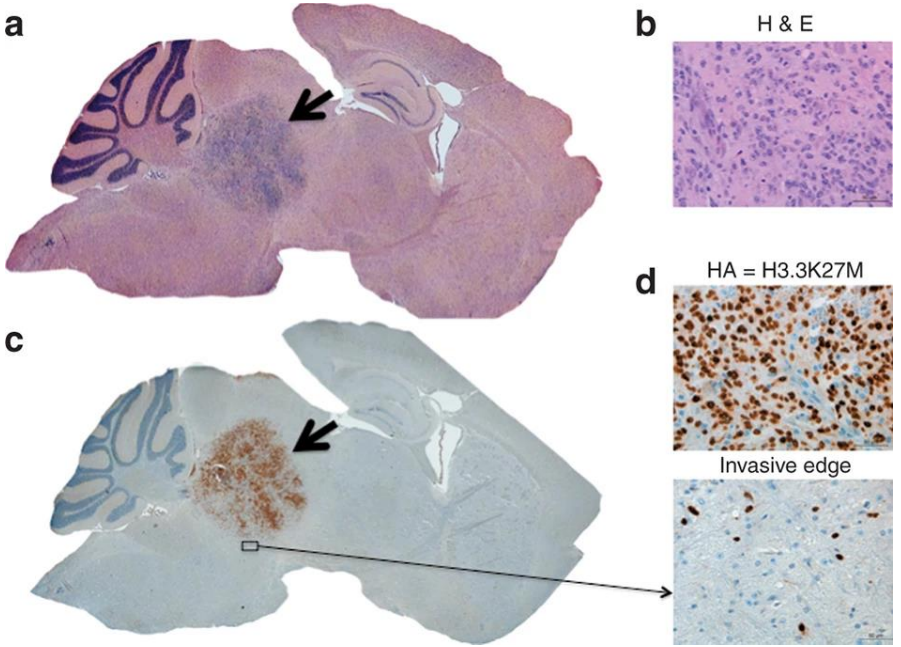


Mackay et al., *Cancer Cell*, 2017.

Glioma are diffusely infiltrating brain tumors

Diffuse intrinsic pontine glioma

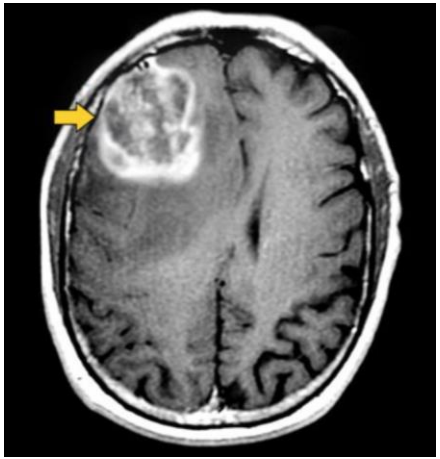


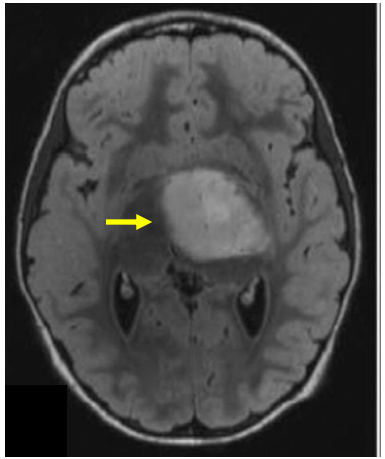


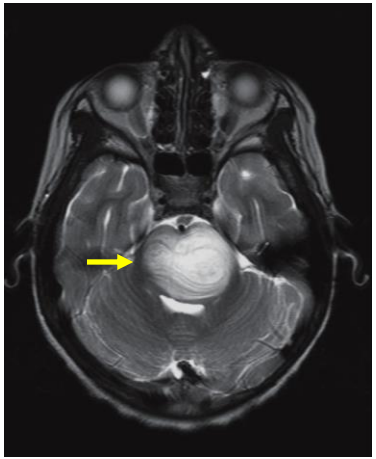
Damodharan et al., *J. Pers. Med*, 2022, Schroeder et al., *Ped Res*, 2013.

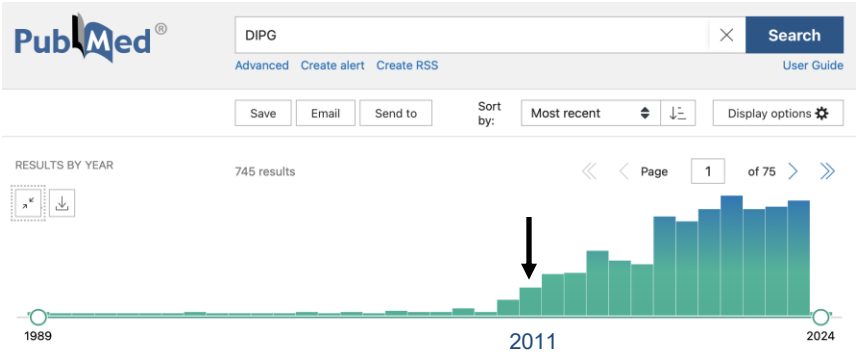
Pediatric high-grade glioma

DIPG



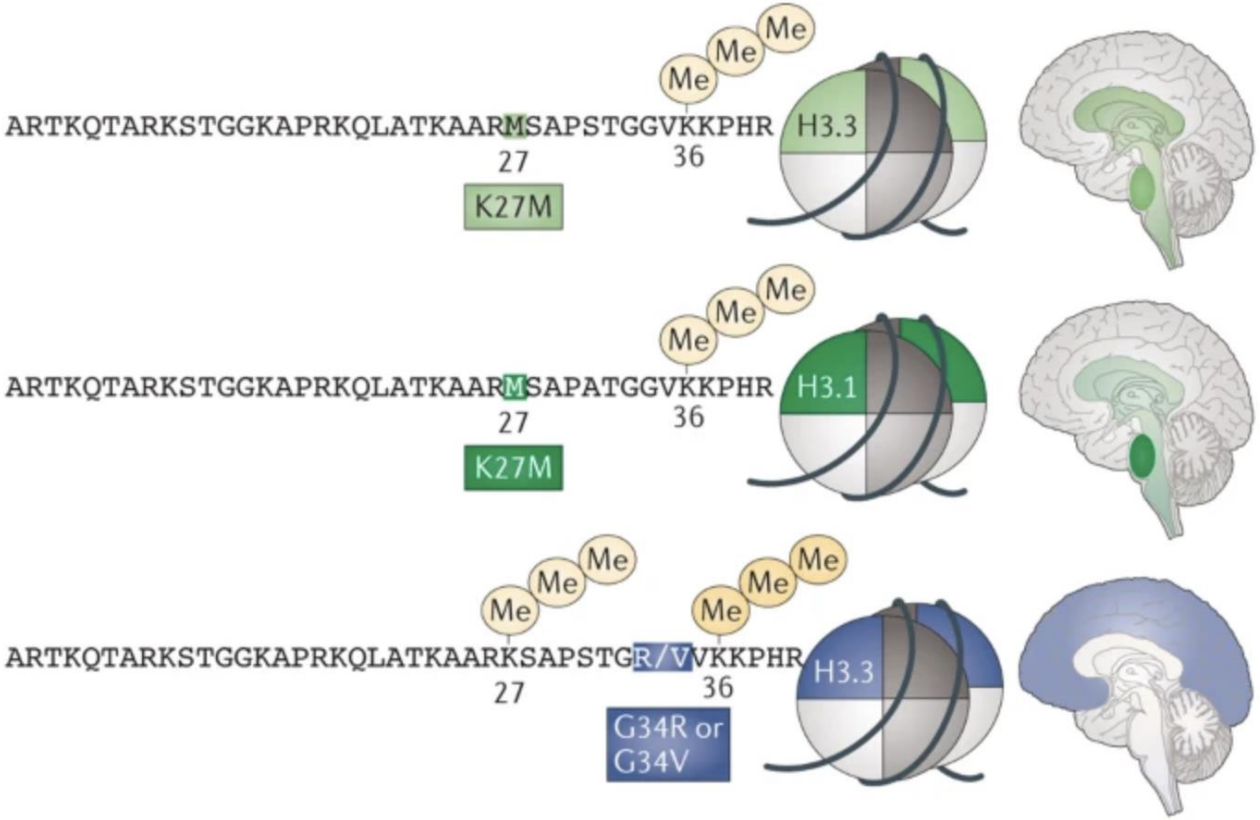


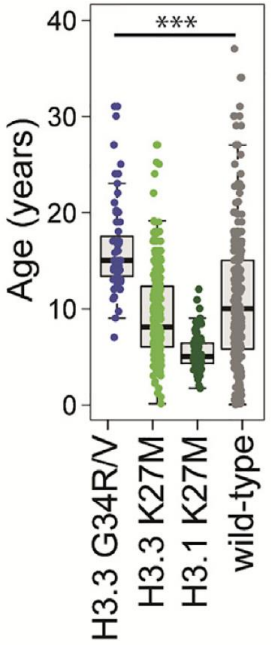




- Lack of knowledge on the biology of DIPG
- No patient tumor tissue samples
- Limited models

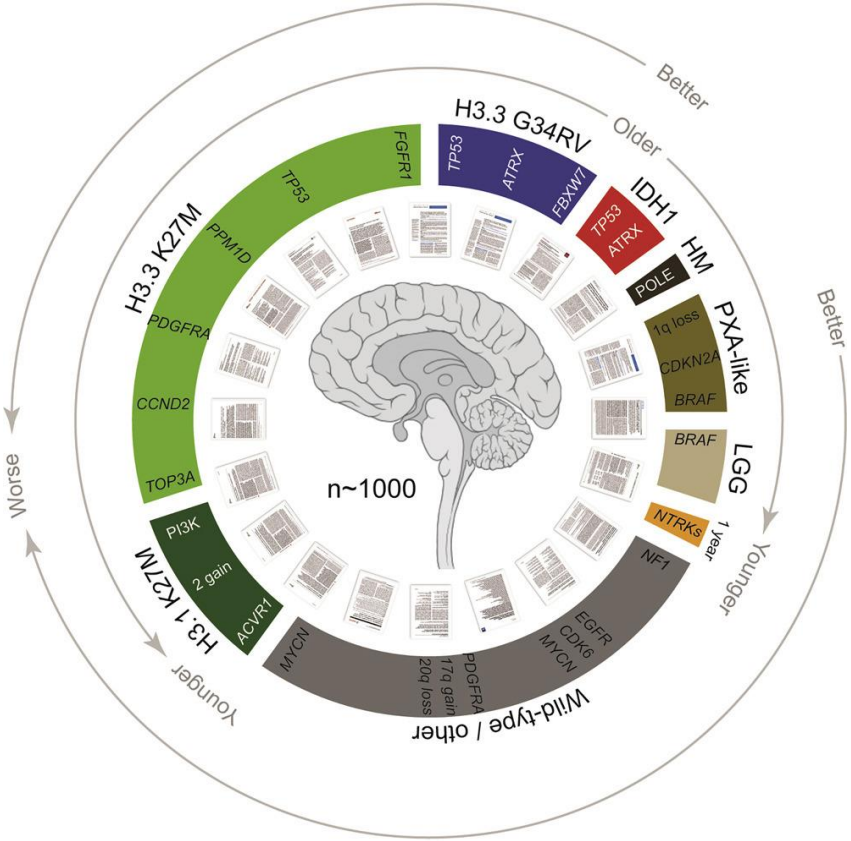
Histone mutations in pediatric glioma





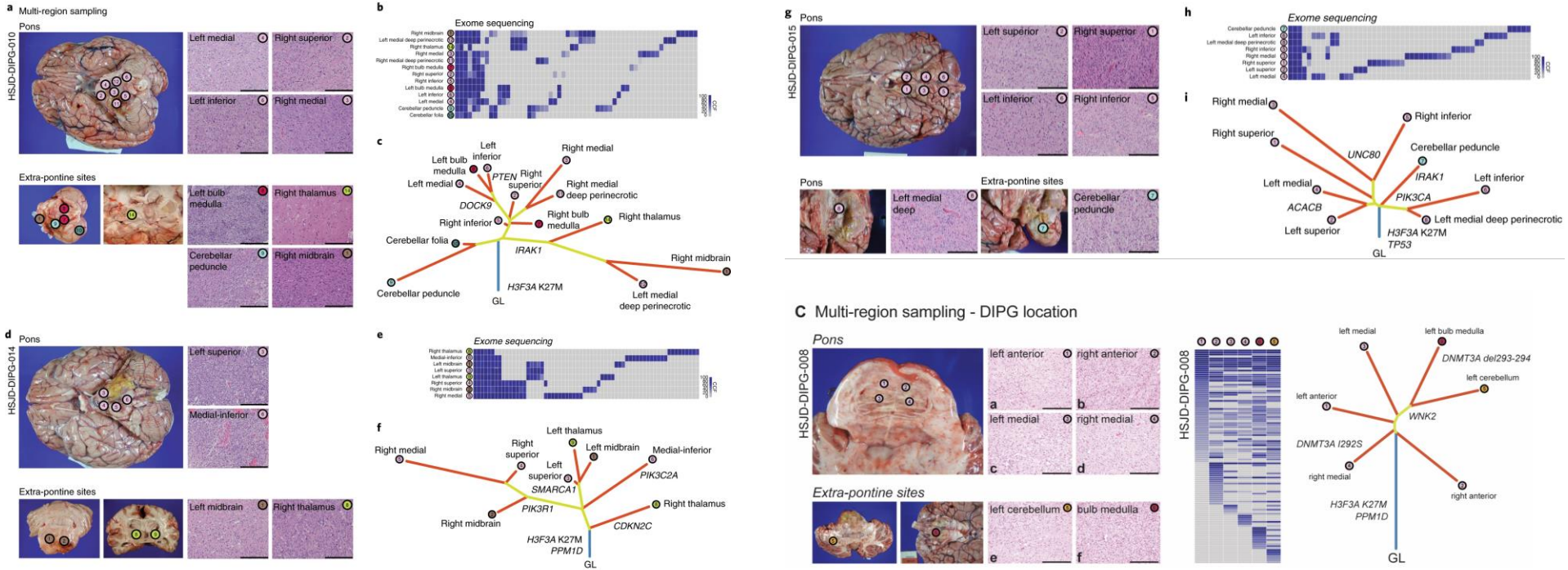
Wu et al., *Nat Gen*, 2012,
Schwartzentruber et al., Nature, 2012.

Molecular subtypes of glioma

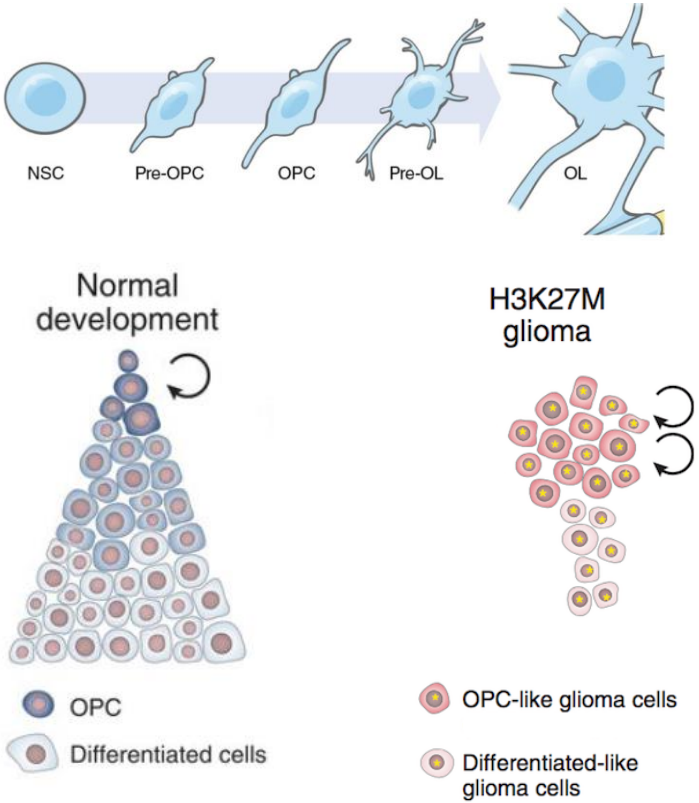


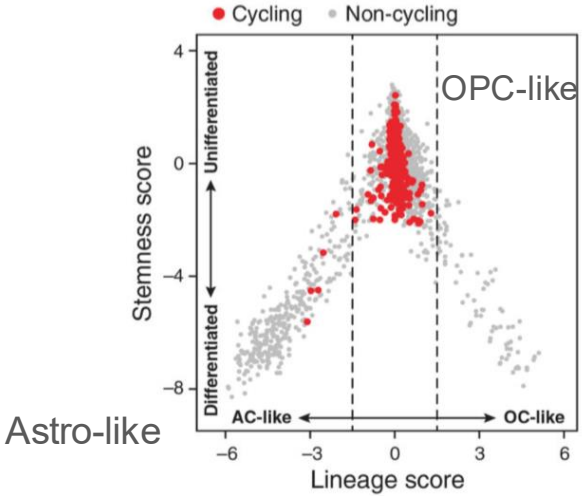
Mackay et al., *Cancer Cell*, 2017.

DIPG genotypic evolution



Pediatric midline glioma resemble glial progenitor cells





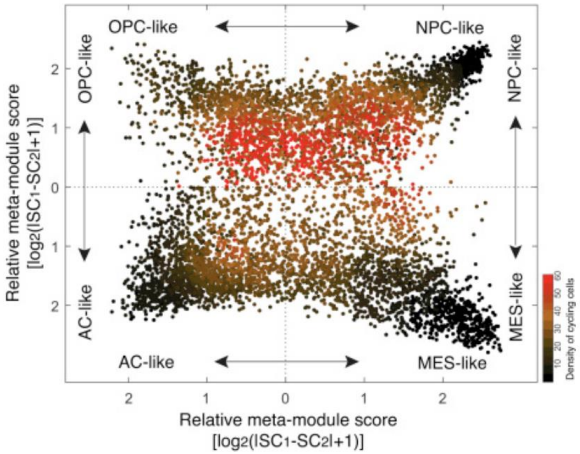
Astro-like

OL-like

Filbin et al., *Science*, 2018.
Reviewed : Filbin & Monje, *Nat Med*, 2019.

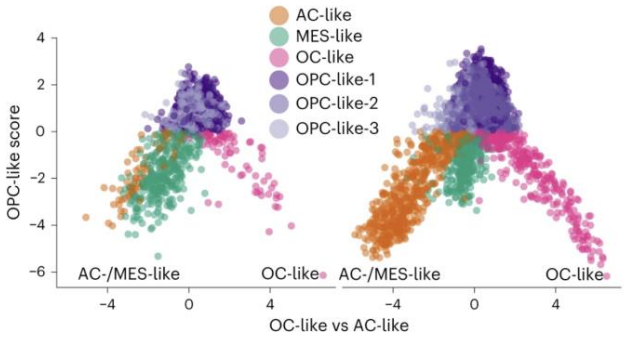
Cellular populations in glioma

IDH-WT glioma



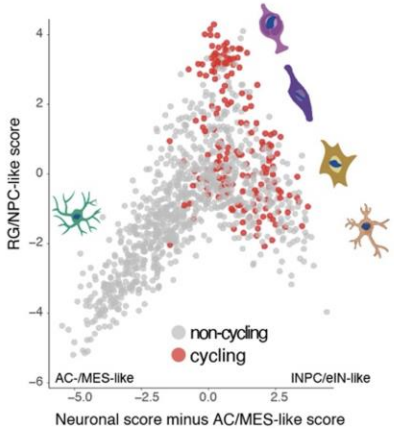
Neftel et al. Cell, 2019.

H3 K27M-mutant glioma



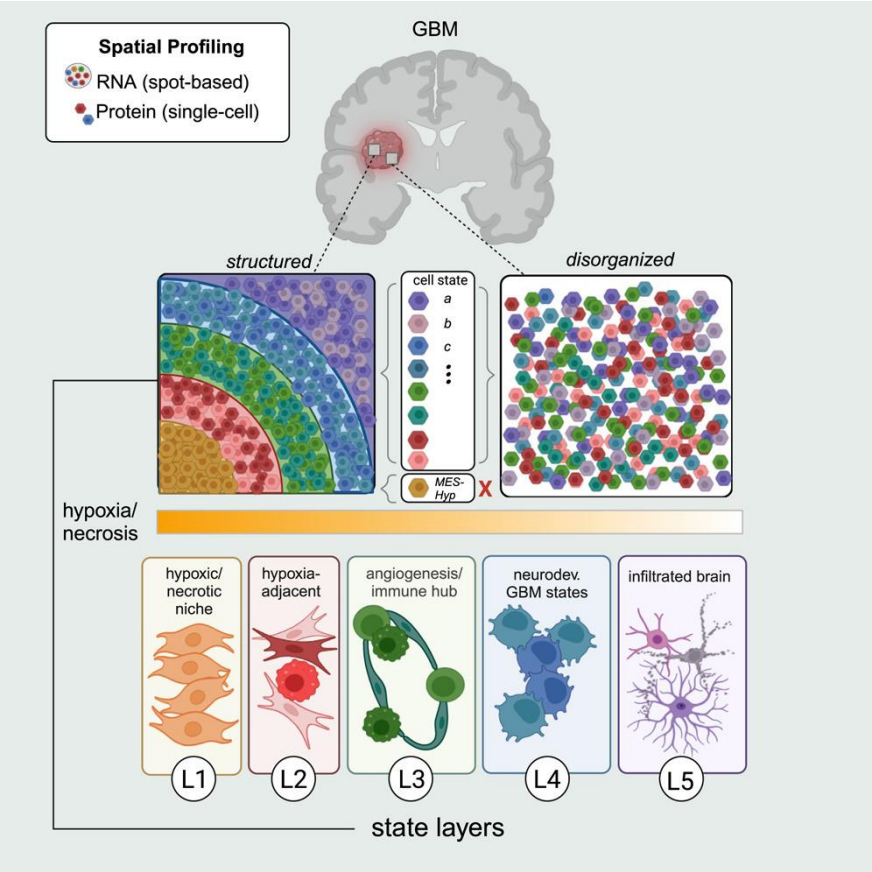
Filbin et al., Science, 2018. Liu et al., Nat Genet 2022.

H3 G34R/V-mutant glioma



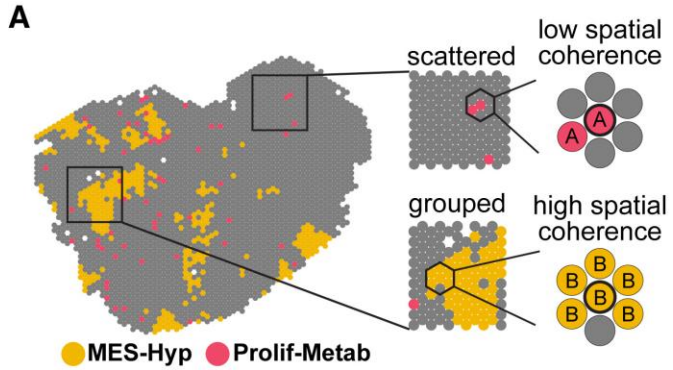
Liu et al., Cancer Cell, 2024.
Chen et al., Cell 2020.

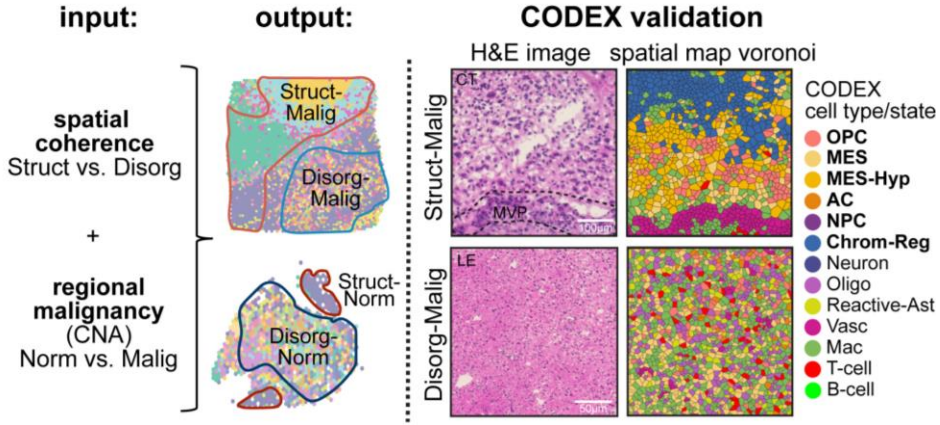
Multilayered organization of glioblastoma



Greenwald, *Cell*, 2024.

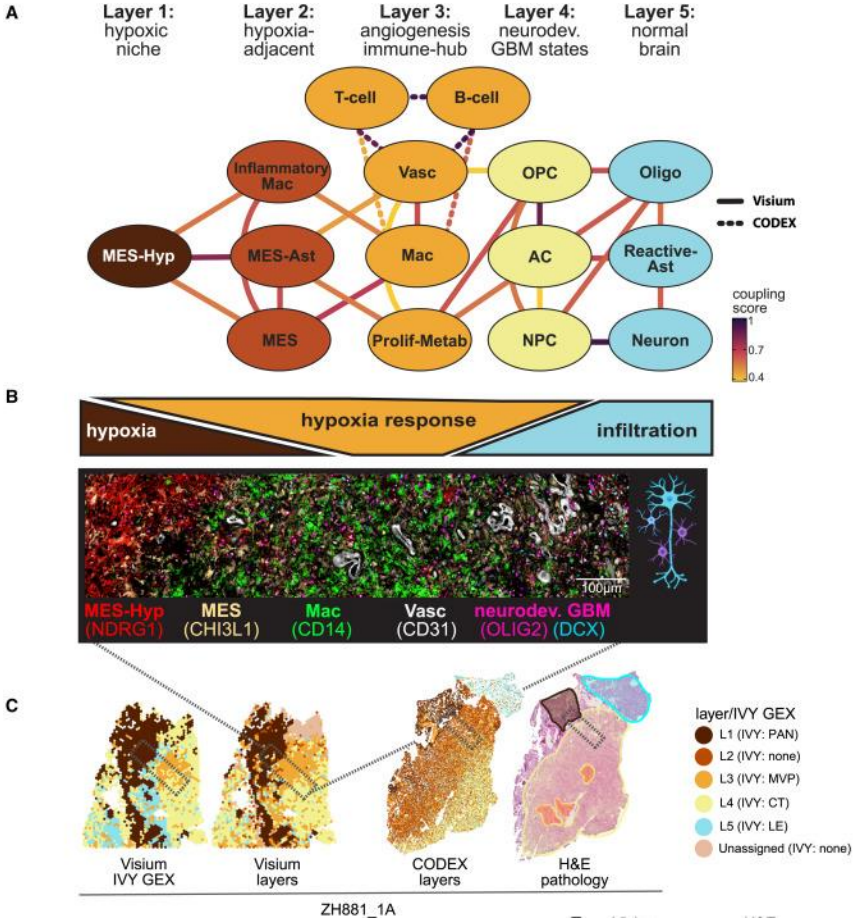
“Disorganized” vs “Structured” regions





Greenwald, *Cell*, 2024.

Layered regions



Greenwald, *Cell*, 2024.

Neuron-cancer interactions

THE AMERICAN
JOURNAL OF CANCER

A Continuation of The Journal of Cancer Research

VOLUME XXXIV NOVEMBER, 1938 NUMBER 3

STRUCTURAL DEVELOPMENT IN GLIOMAS

H. J. SCHERER, M.D.

(From the Department of Pathology, Bunge Institute, Antwerp, Belgium)

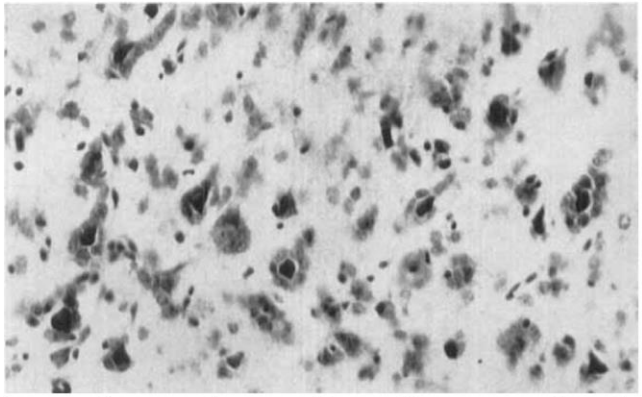
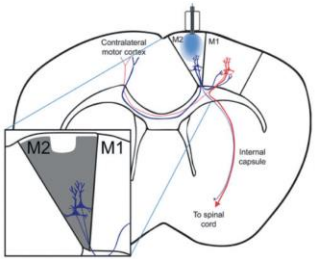
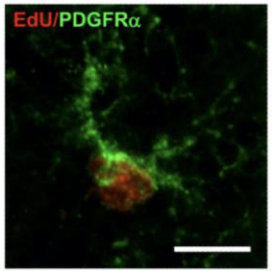


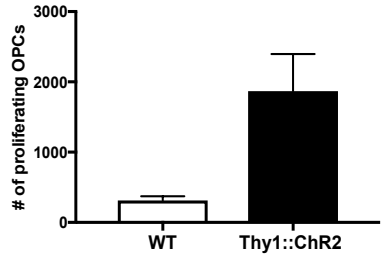
FIG. 1. PRECOCIOUS PERINEURAL STRUCTURES FORMING CAPSULES ABOUT NERVE CELLS. CASE 6/36 NISSL

OPCs respond to neuronal activity

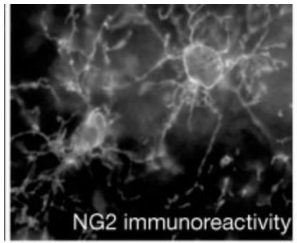
OPC proliferation

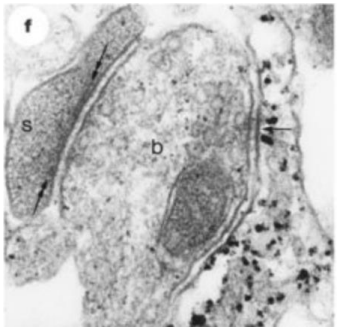






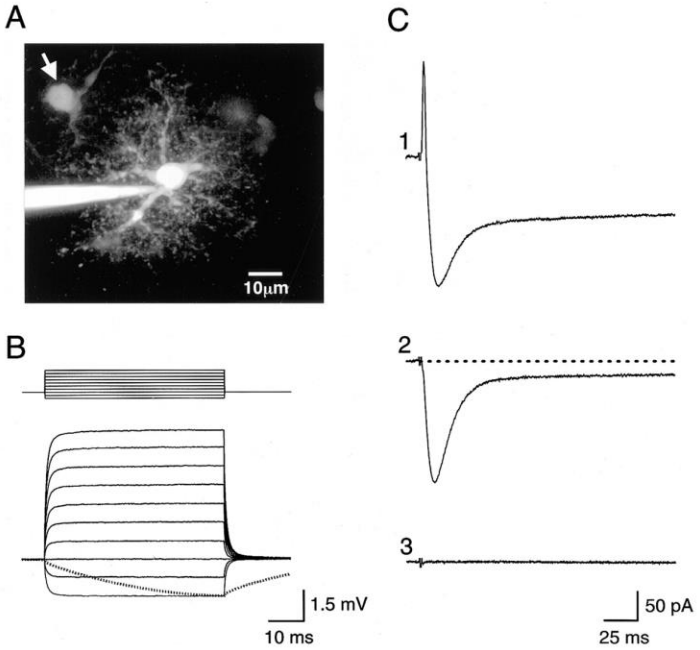
Neuron-OPC synapses

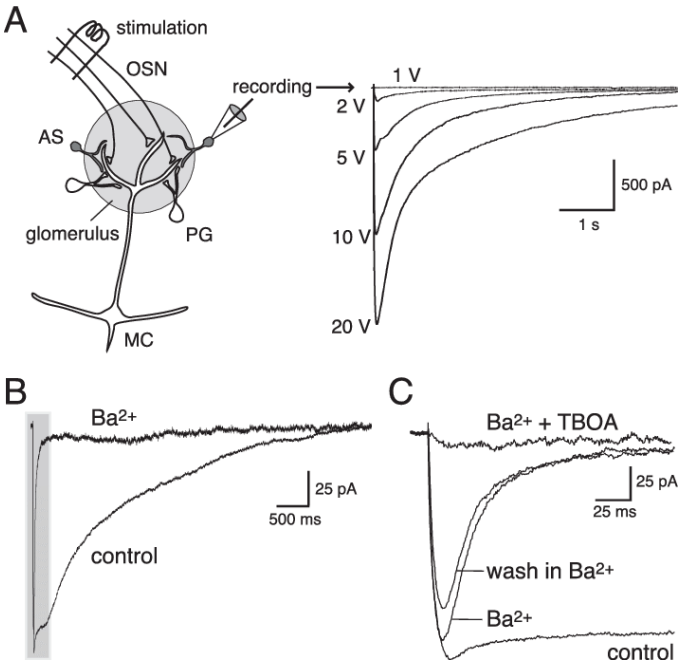




Gibson et al., *Science*, 2014; Bergles et al., *Nature*, 2000. Reviewed: Mount & Monje, *Neuron*, 2017; Yalçin & Monje, *Dev Cell*, 2021.

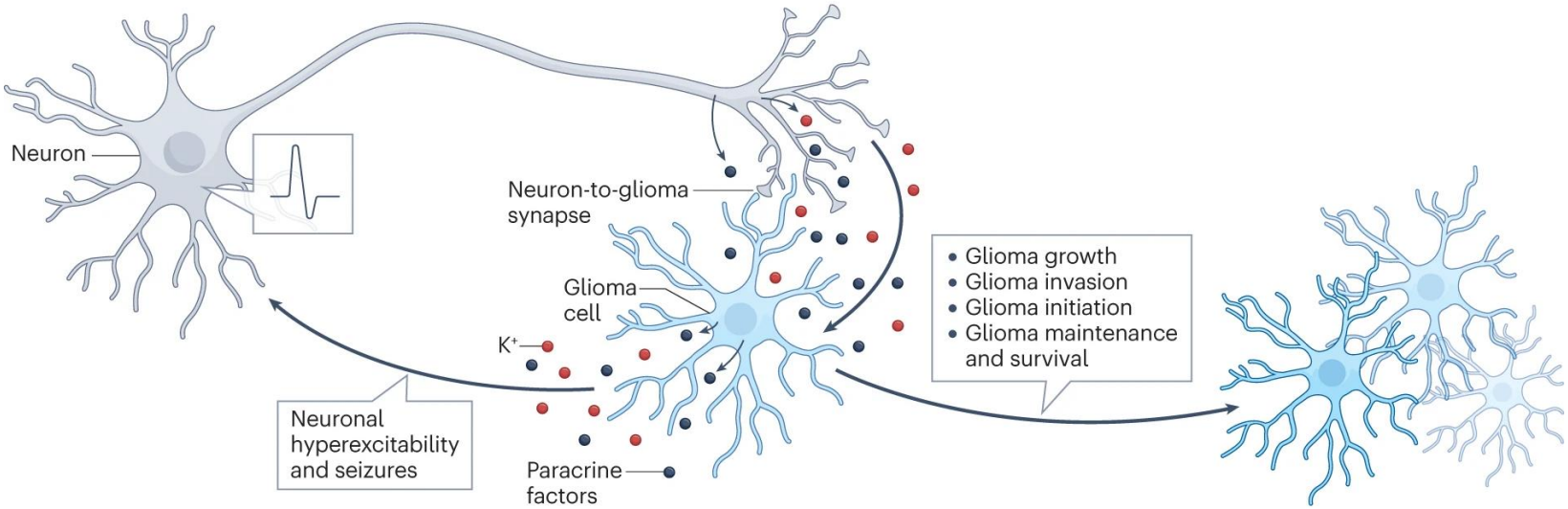
Astrocytes respond to neuronal activity





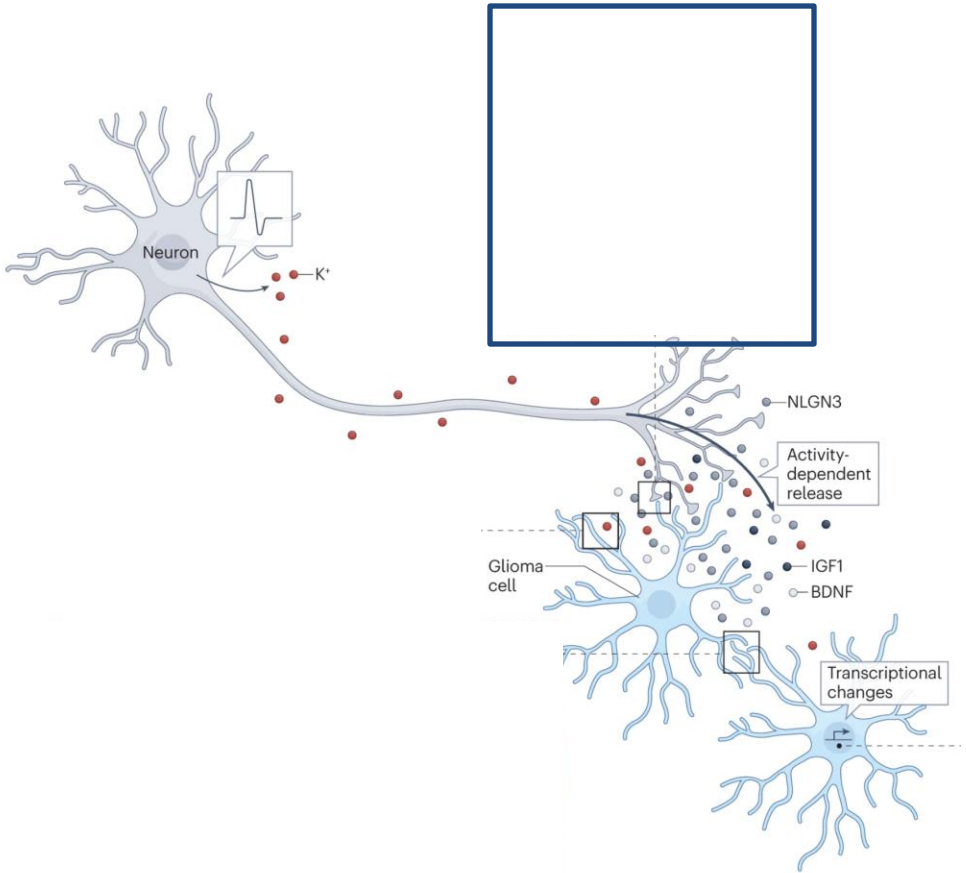
Bergles et al., *Neuron*, 1997. De Saint Jan et al., *J Neurosci*, 2005.

Neuron-glioma interactions drive glioma pathobiology



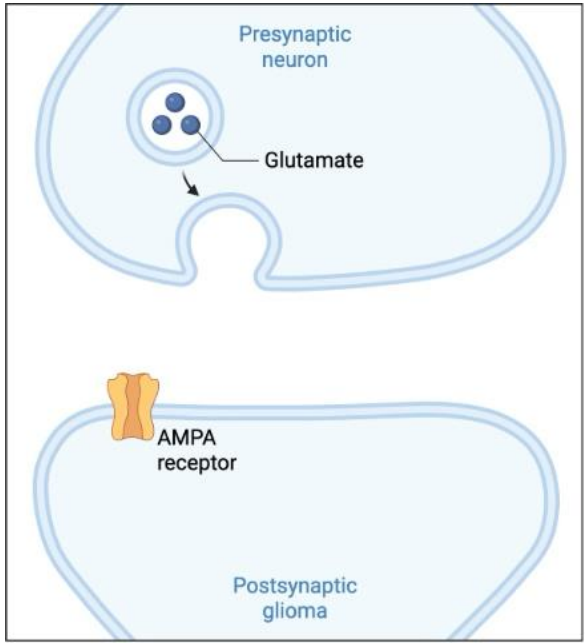
Taylor & Monje, *Nature Neurosci Rev*, 2023

Neuronal activity-regulated mechanisms of glioma growth

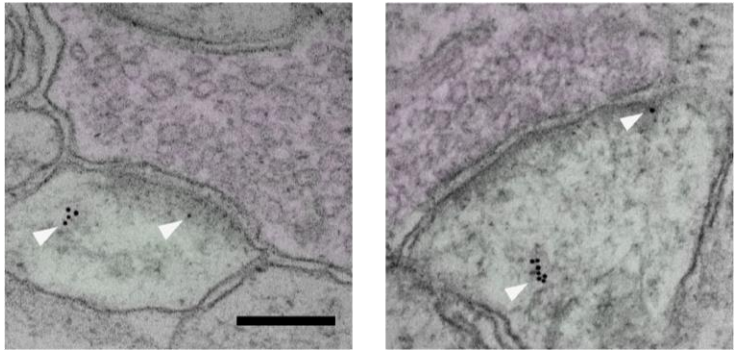


Taylor & Monje, *Nature Neurosci Rev*, 2023

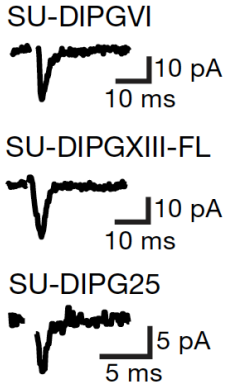
Glutamatergic neuron-to-glioma synaptic signaling

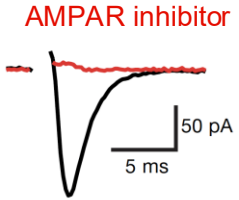


Immuno-electron microscopy of glioma



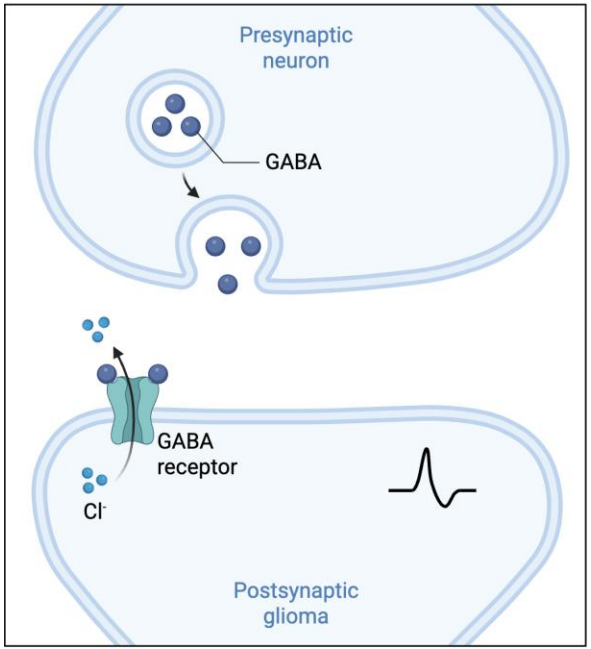
Whole cell patch clamp electrophysiology of glioma



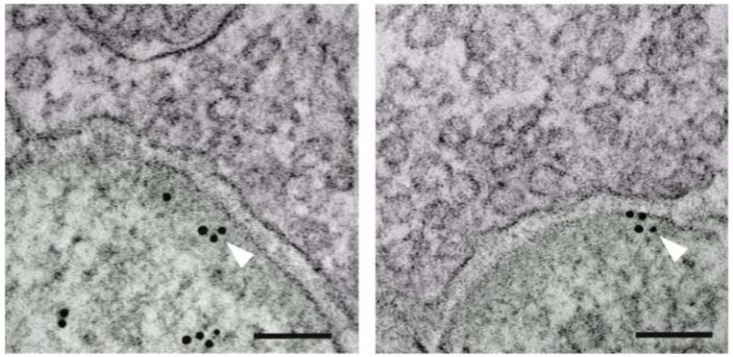


Venkatesh et al., *Nature*, 2019, (Taylor et al., *Nature,* 2023)

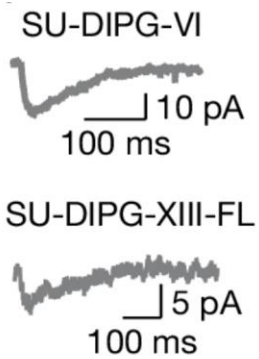
GABAergic neuron-to-glioma synaptic signaling

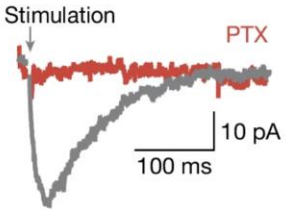


Immuno-electron microscopy of glioma



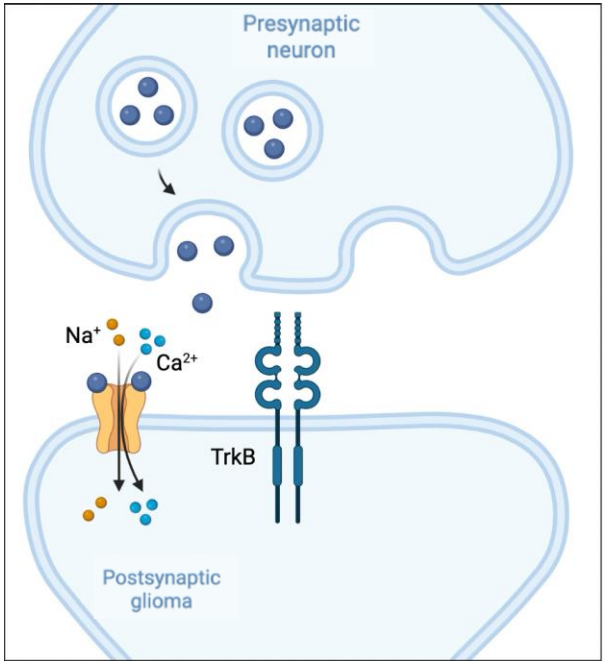
Whole cell patch clamp electrophysiology of glioma



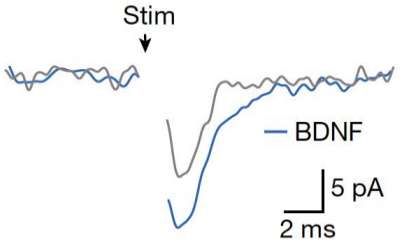


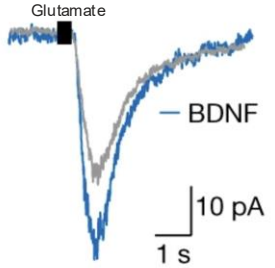
Barron et al., *Nature*, 2025.

Adaptive plasticity of malignant synapses

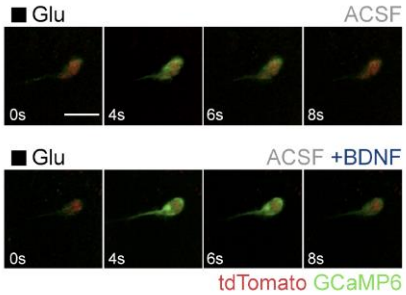


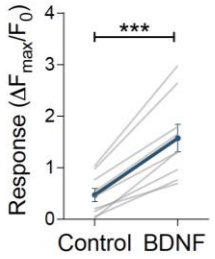
Whole cell patch clamp electrophysiology of glioma





Calcium imaging of GCaMp6s-expressing glioma

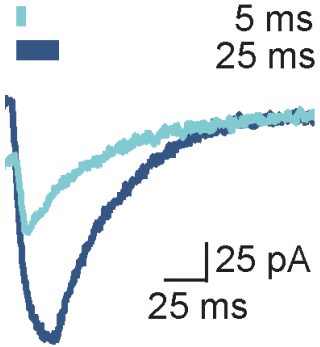




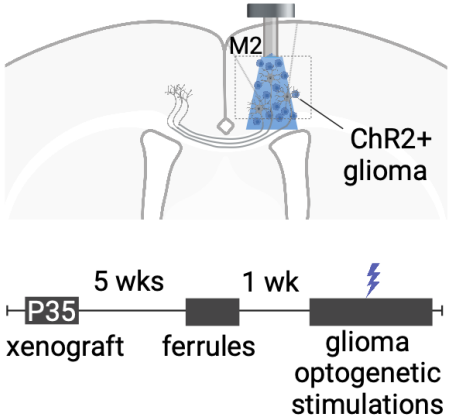
Taylor et al., *Nature*, 2023

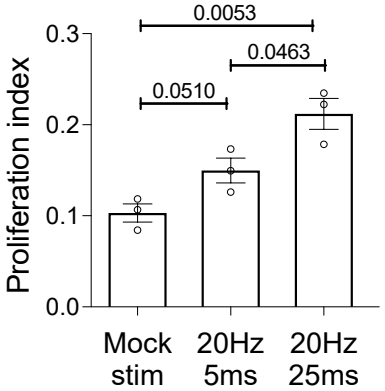
Membrane depolarization induces glioma proliferation

ChR2-expressing glioma
Whole-cell patch clamp recording



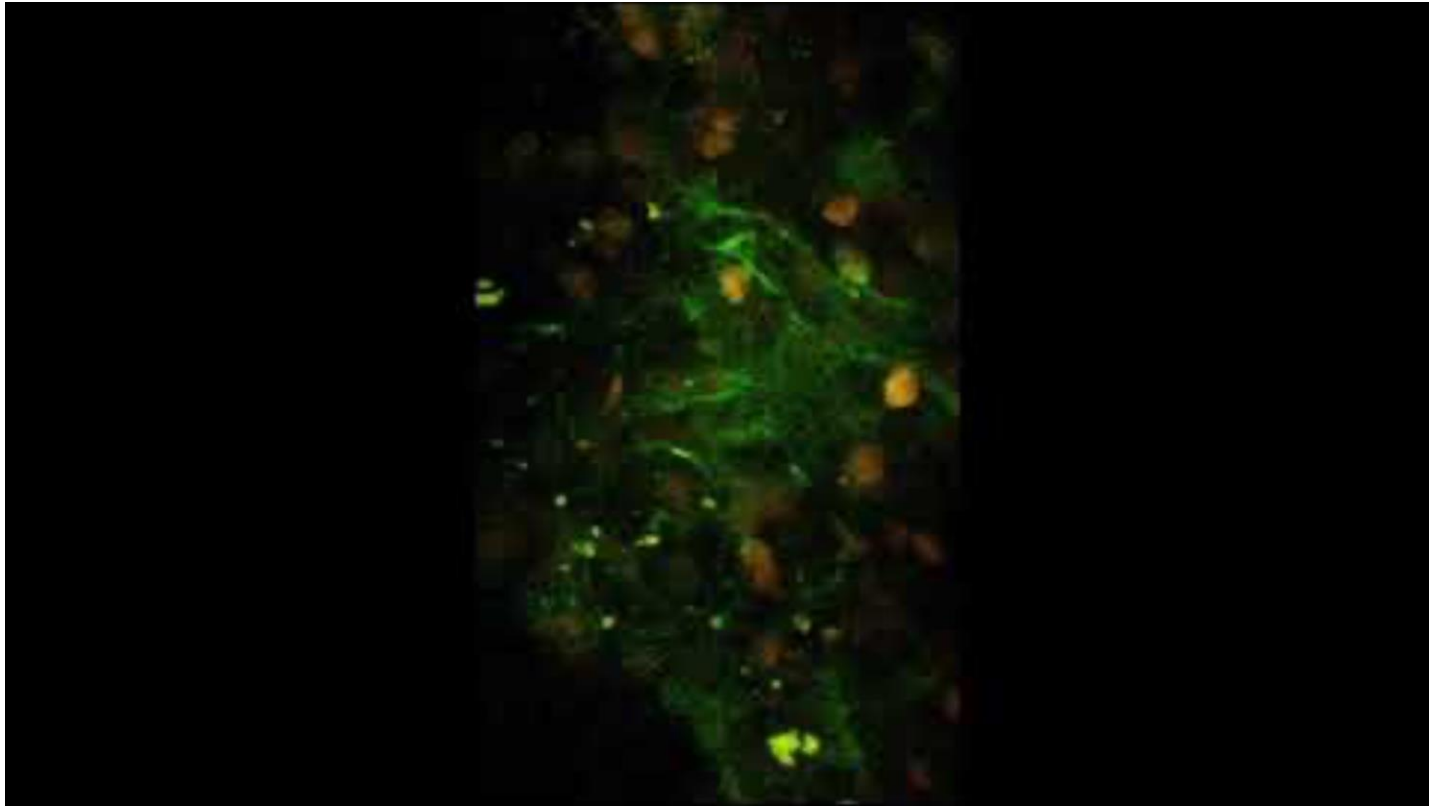
Glioma optogenetic stimulation





Taylor et al., *Nature*, 2023

Neuronal activity induced glioma calcium transients

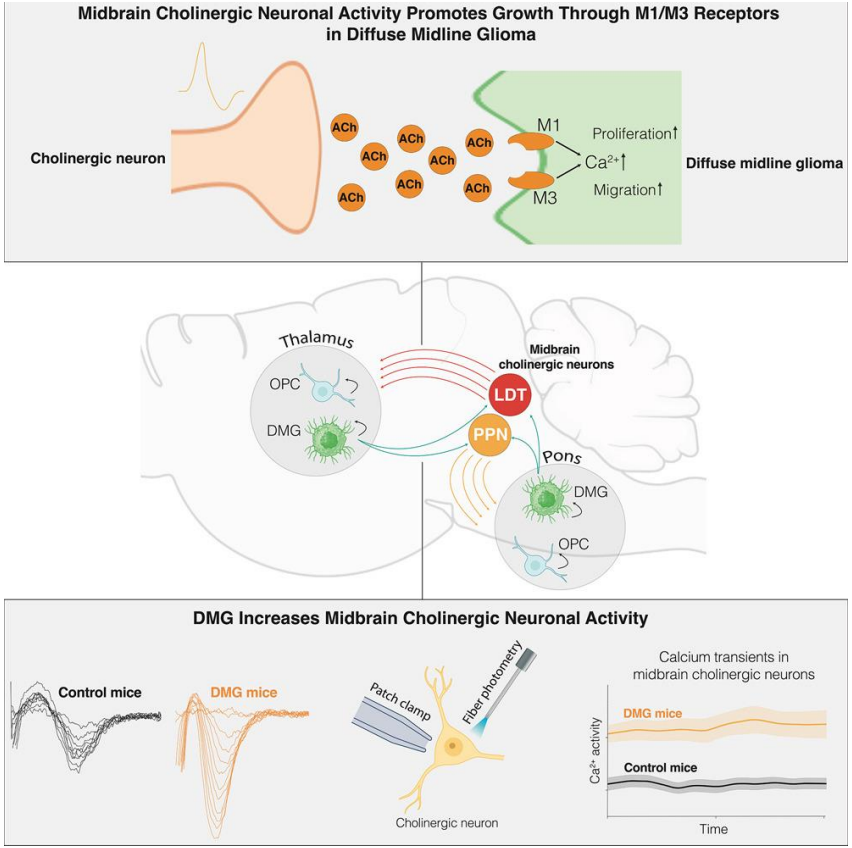


Venkatesh et al., *Nature*, 2019

Glioma integrates into neural networks

Tetzlaff et al., 2025 *Cell*

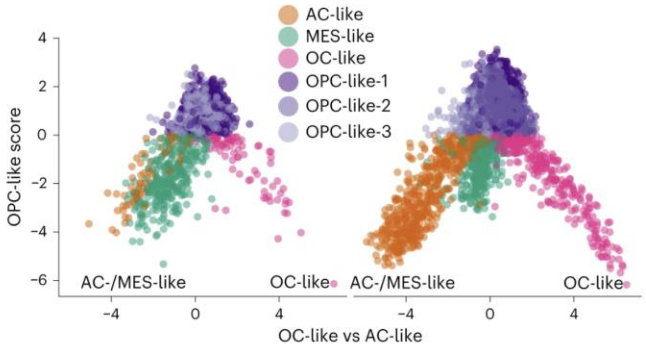
Cholinergic signaling in glioma



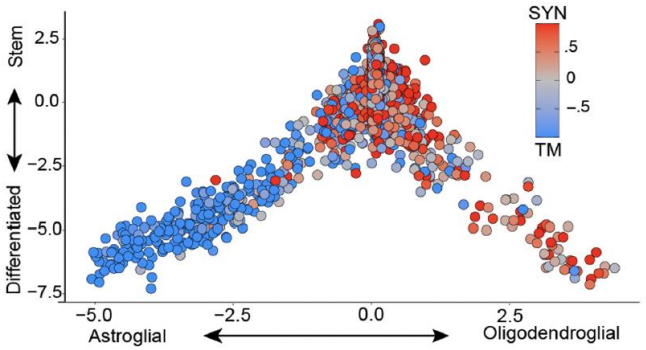
Drexler et al., 2025 *Cell*

Distinct neuron-glioma interactions by cellular subpopulations

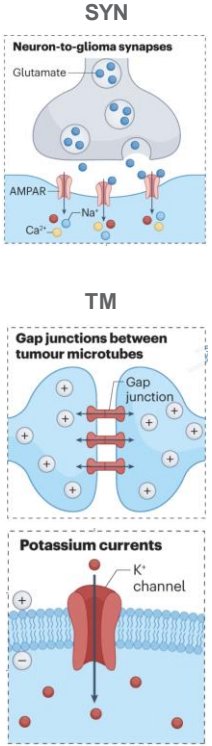
H3 K27M-mutant glioma



Filbin et al., *Science*, 2018. Liu et al., *Nat Genetics* 2022.



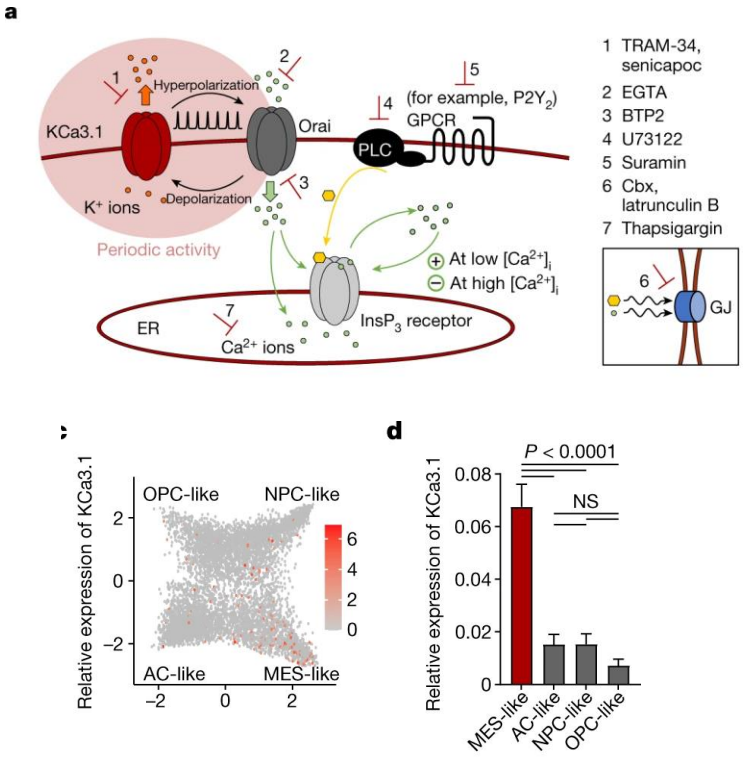
Taylor *et al*. *Nature*, 2023.
Taylor & Monje, *Nature Neurosci Rev*, 2023.



Autonomous rhythmic activity in GBM

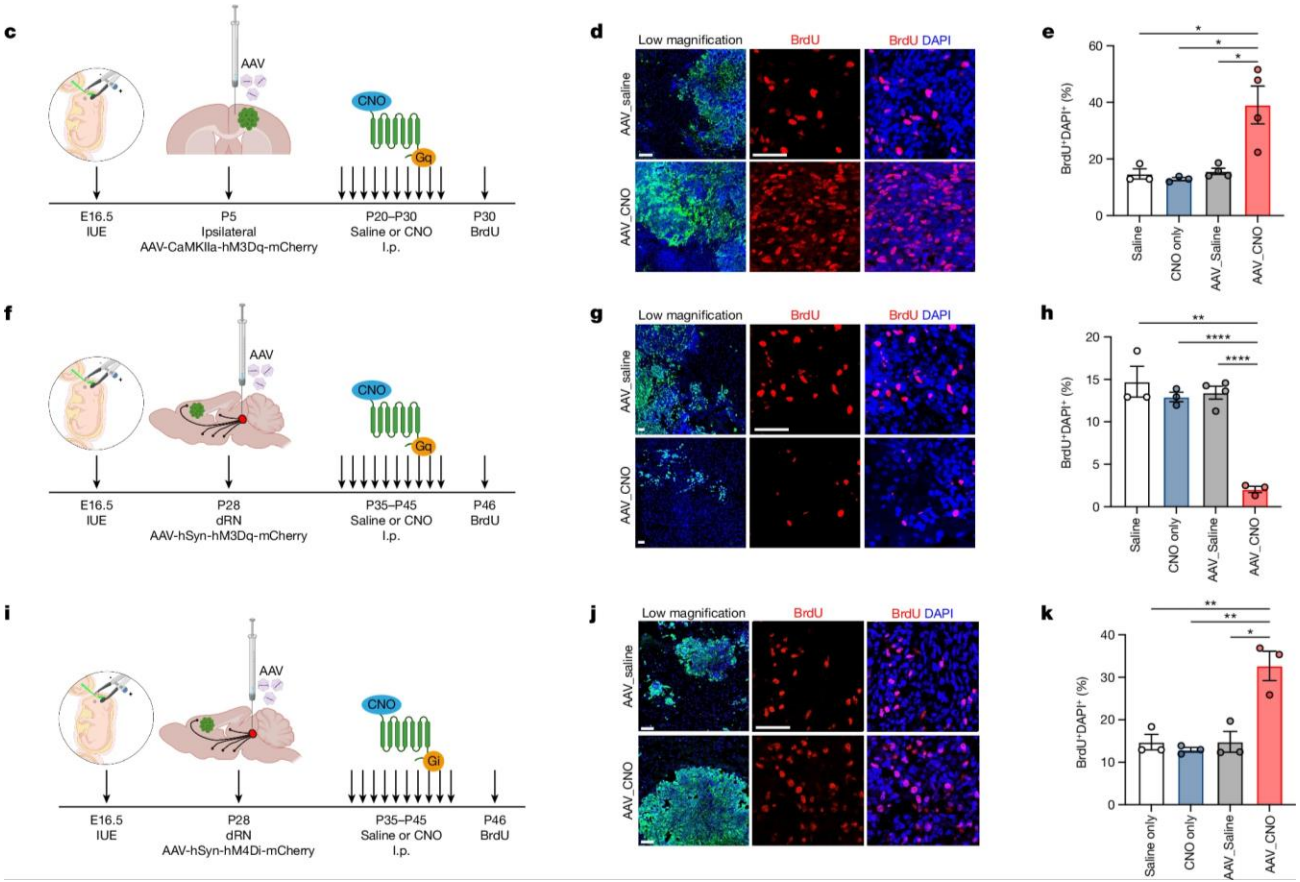
Patient-derived Human Glioblastoma Cells (S24 Line)
Xenograft in Mouse Brain

Calcium imaging with multiphoton microscopy in awake mouse demonstrating the autonomous calcium activity of periodic cells.



Hausmann et al., *Nature*, 2023.

Serotonergic signaling in ependymoma



Chen et al., *Nature*, 2024.

Neuron-cancer interactions

VOLUME II JANUARY, 1897 No. 1

THE JOURNAL
OF
EXPERIMENTAL MEDICINE

ON THE PRESENCE OF NERVES IN TUMORS AND OF OTHER STRUCTURES IN THEM AS REVEALED BY A MODIFICATION OF EHRLICH'S METHOD OF "VITAL STAINING" WITH METHYLENE BLUE.

BY HUGH H. YOUNG, M. D.
(*From the Anatomical Laboratory of the Johns Hopkins University.*)

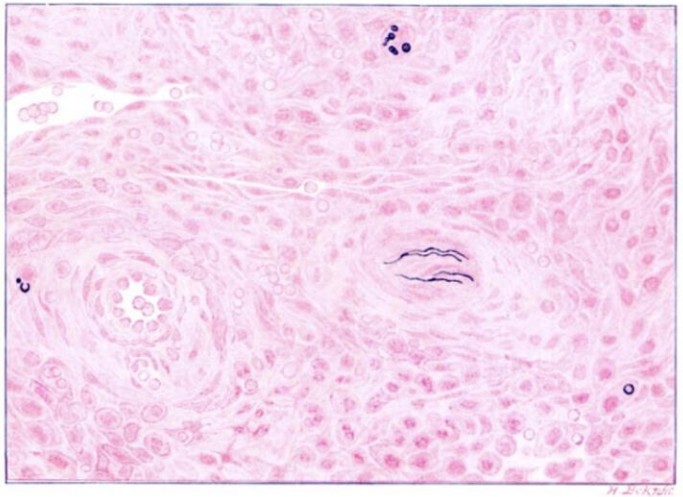
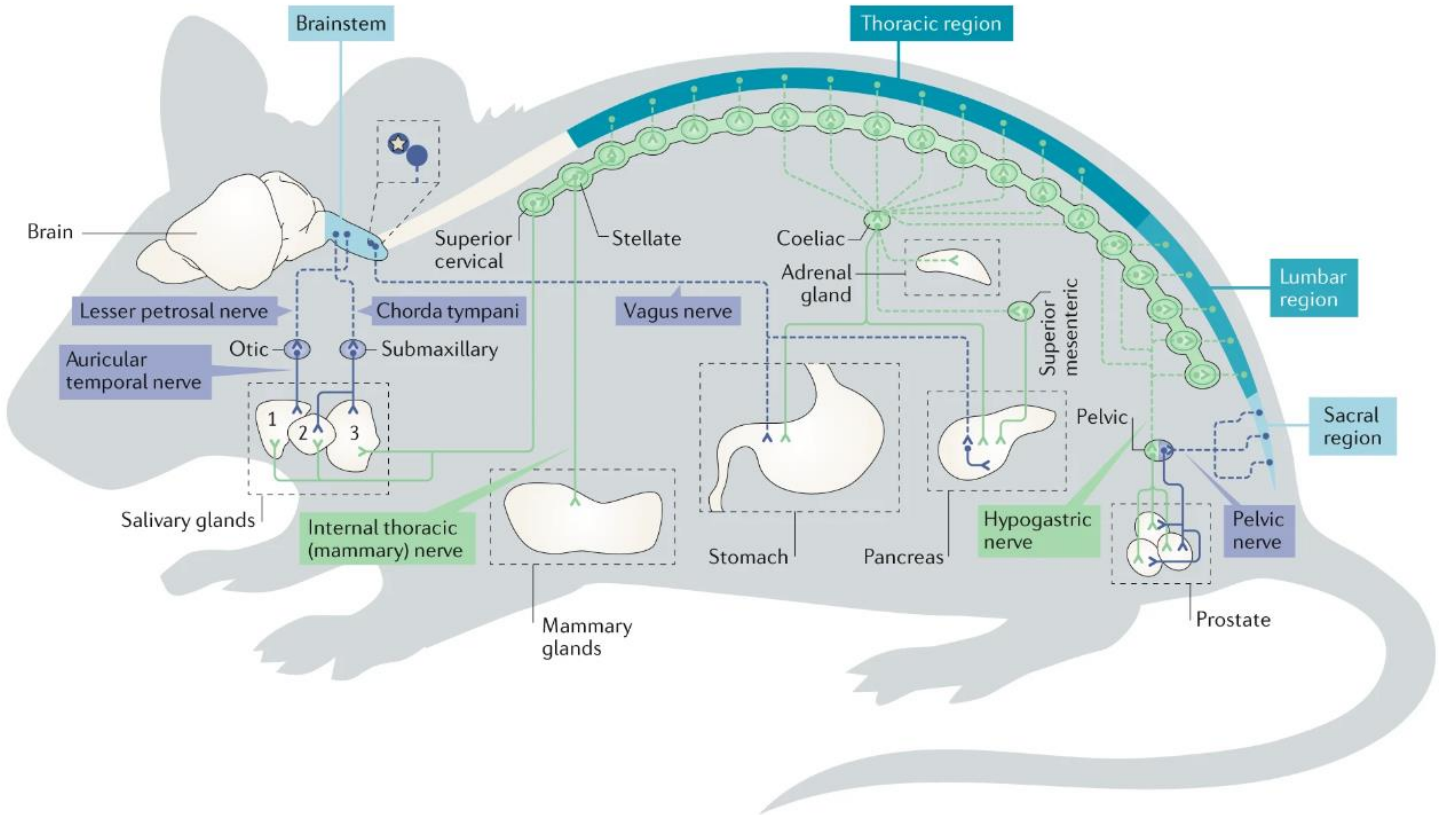


FIG. 1.

the living patient. The present studies pretend to no degree of completeness, but since they include a number of observations which would seem to be entirely new, and because for unavoidable reasons the research must for the present be discontinued, I have decided to put the results on record, with the hope that others may be sufficiently interested in them to make further experiments along similar lines.

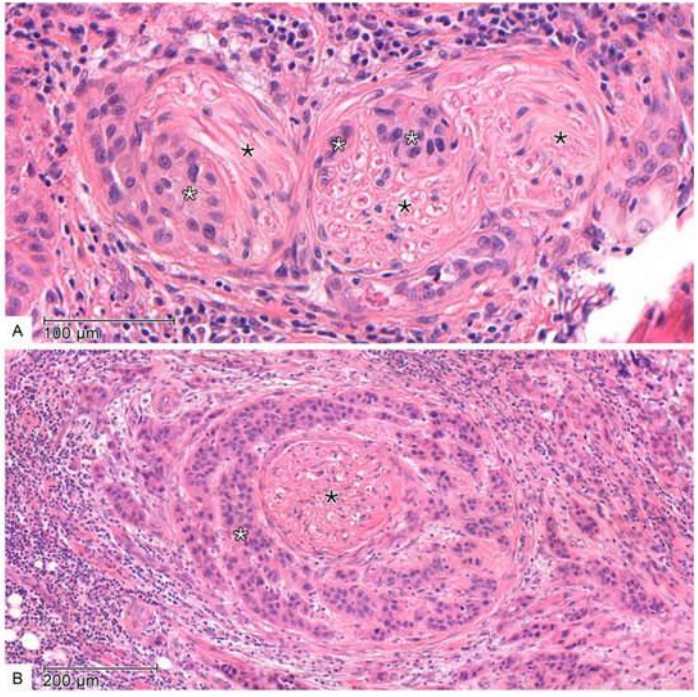
Innervation of peripheral organs



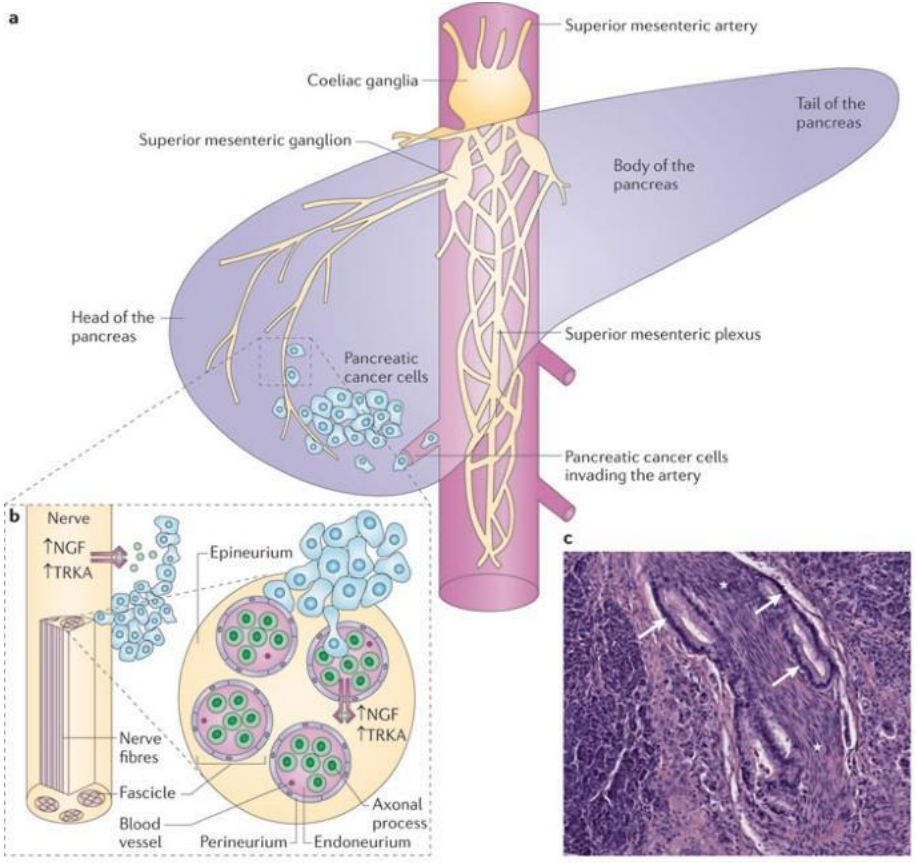
Zahalka & Frenette, 2020 *Nat Rev Canc*

Perineural invasion

Oral squamous cell carcinoma

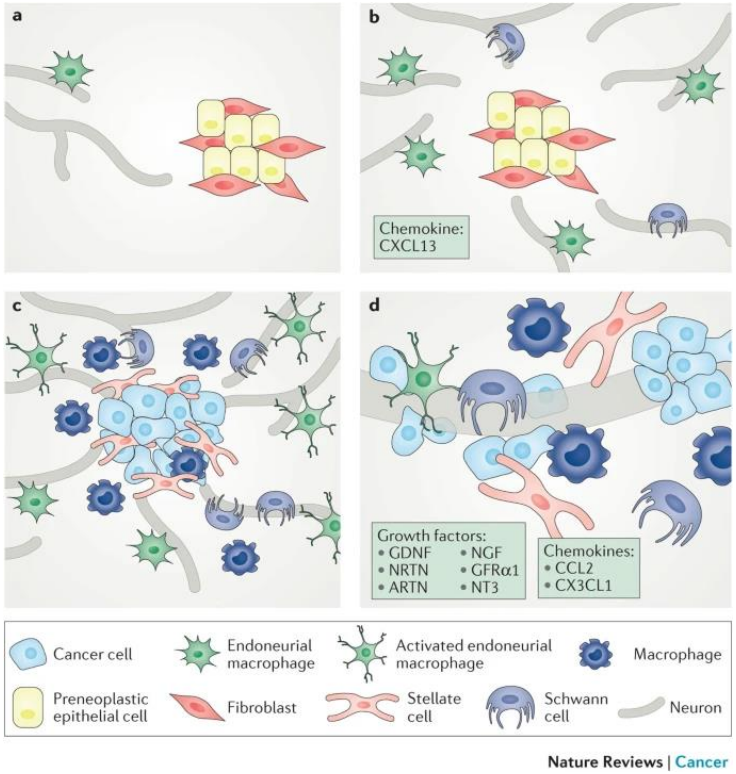


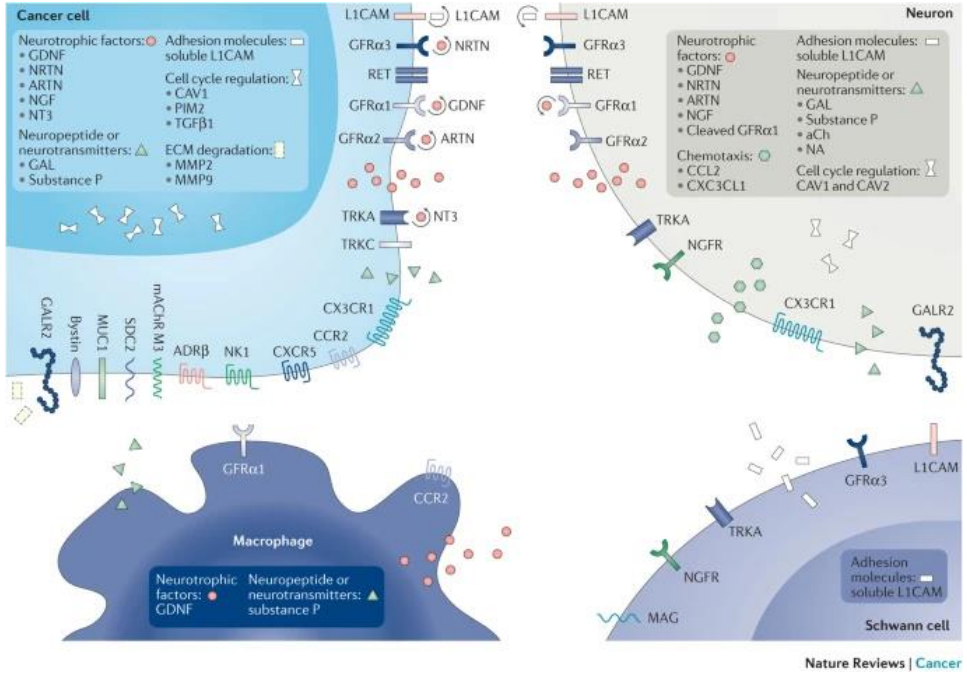
Hakim, Cancers, 2025



Bapat, Nature Reviews Cancer, 2011

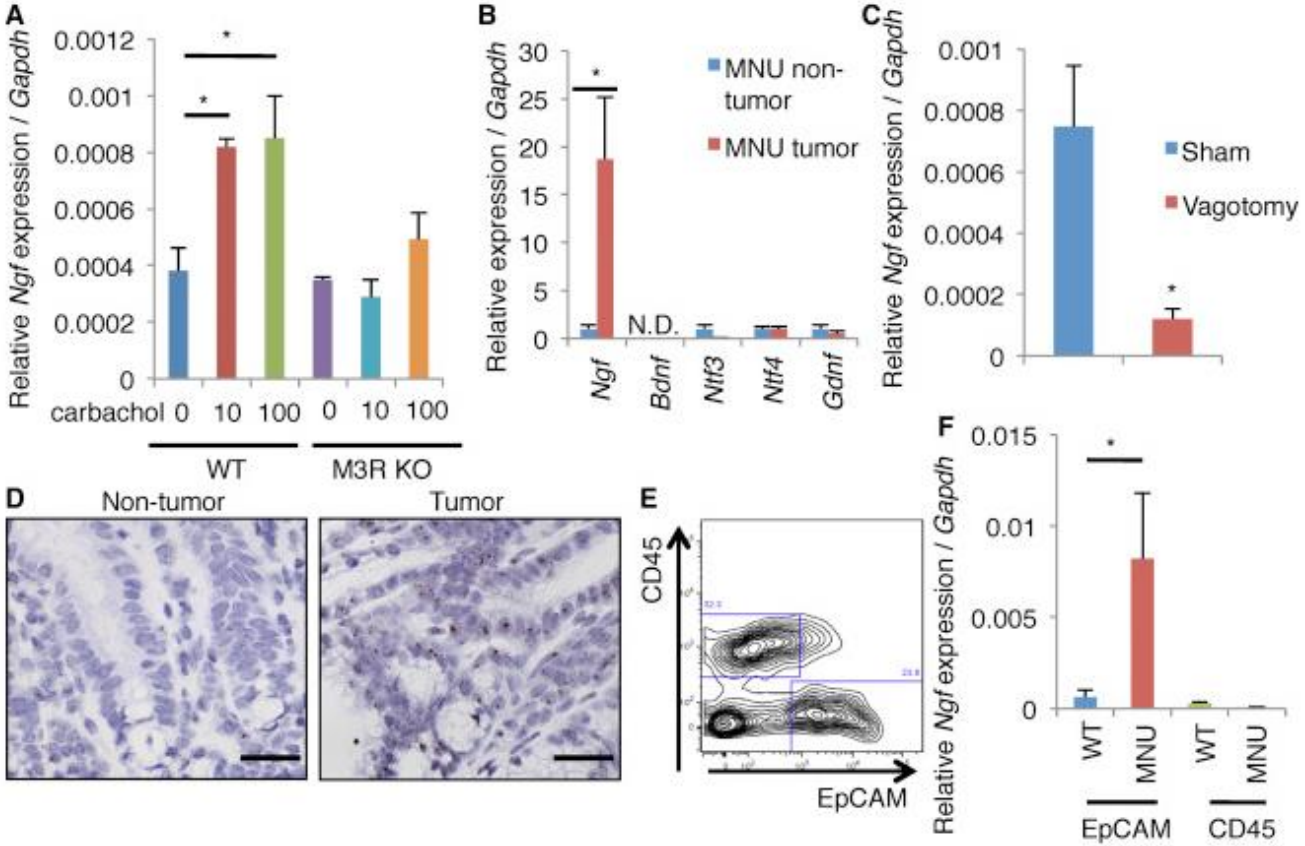
Mechanisms of cancer dissemination along nerves





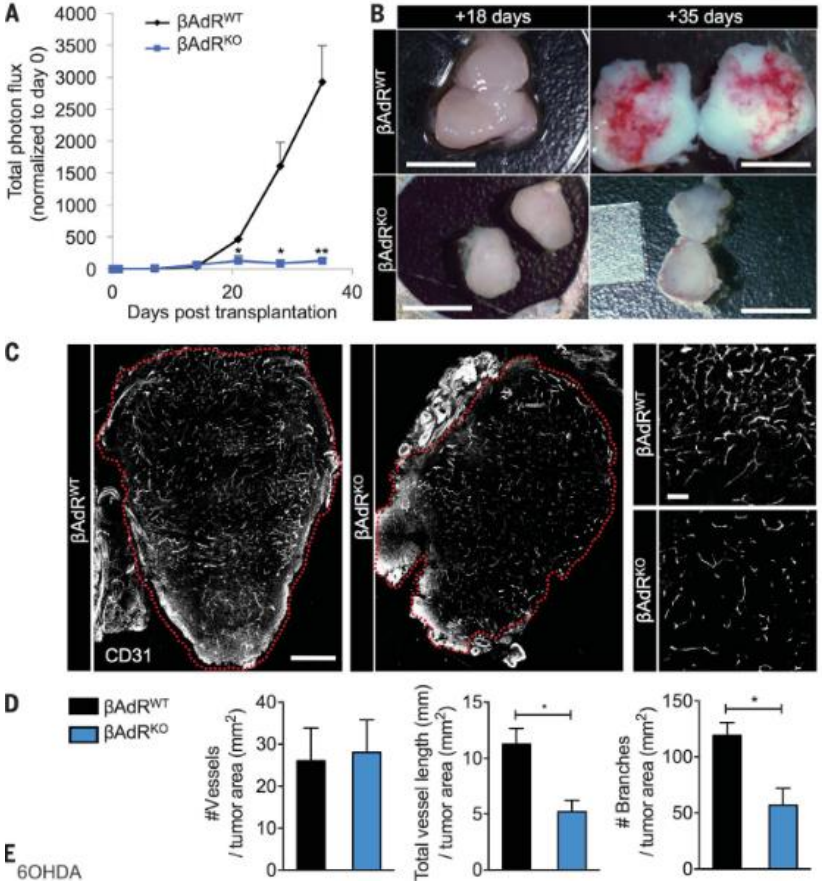
Amit, Na'ara and Gil., *Nature Rev Cancer*, 2016.

Tumors provide trophic support for neurons



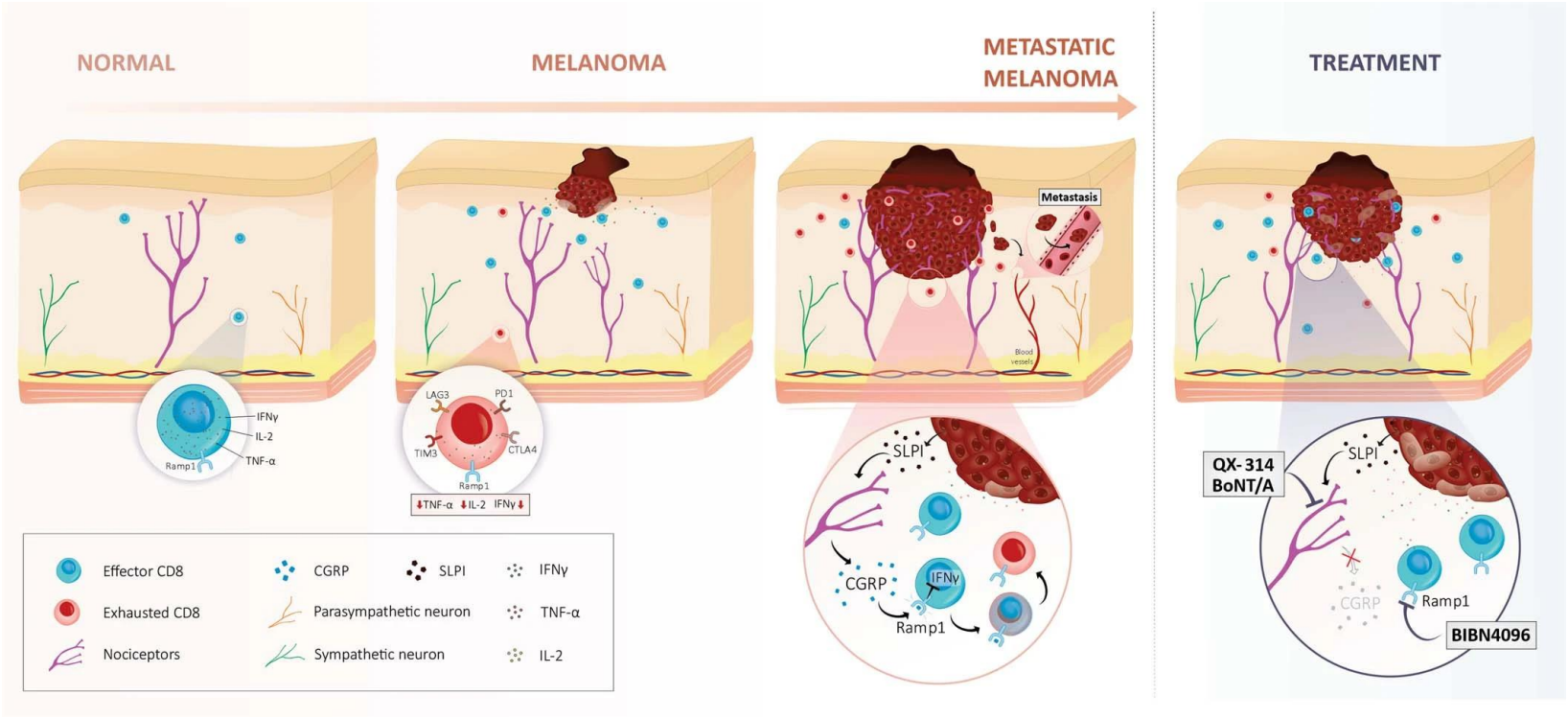
Hayakawa et al., 2017 *Cancer Cell*

Nerves modify the TME



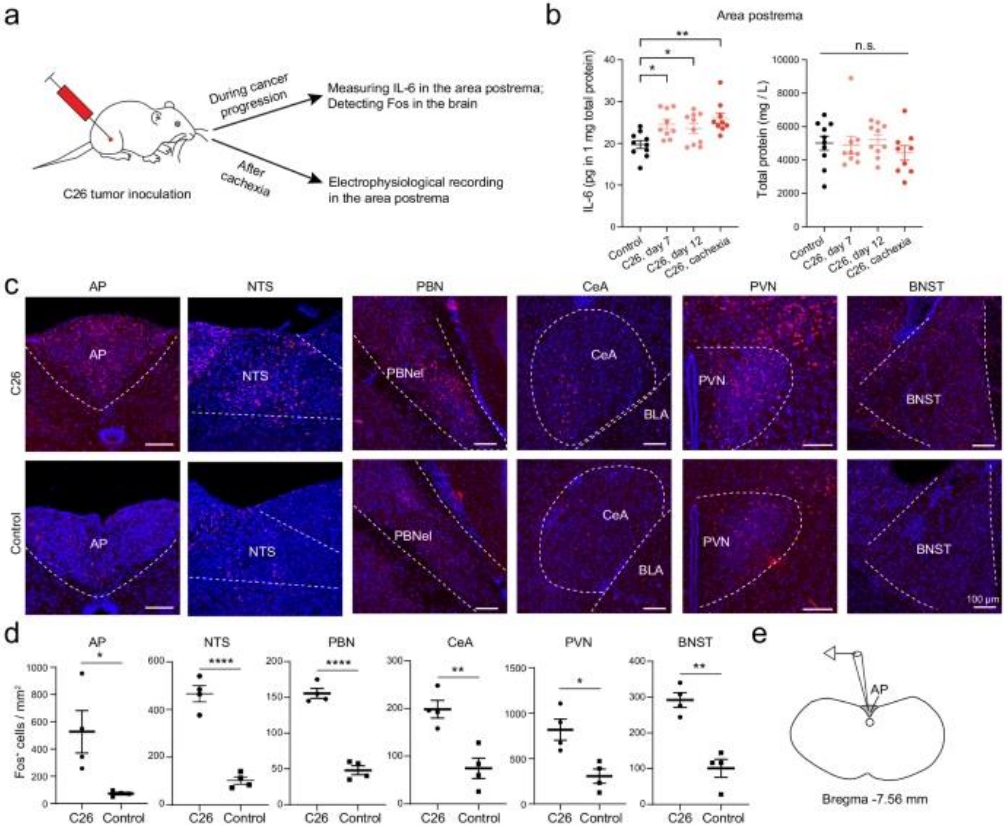
Zahalka et al, 2017 *Science*

Nerves modulate antitumor immunity



Balood et al.,, Nature, 2022

Peripheral cancers can alter brain activity



Sun et al., 2024 *Nat Comm*

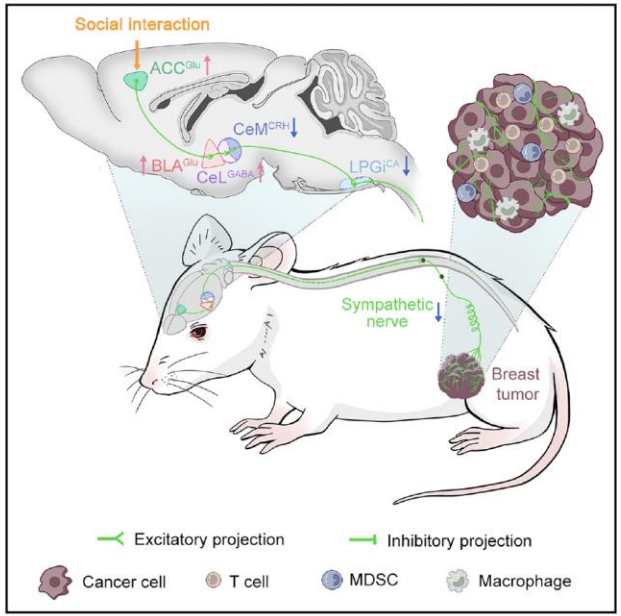
Brain activity can alter peripheral cancer growth

Neuron

Article

Social interaction in mice suppresses breast cancer progression via a corticoamygdala neural circuit

Graphical abstract



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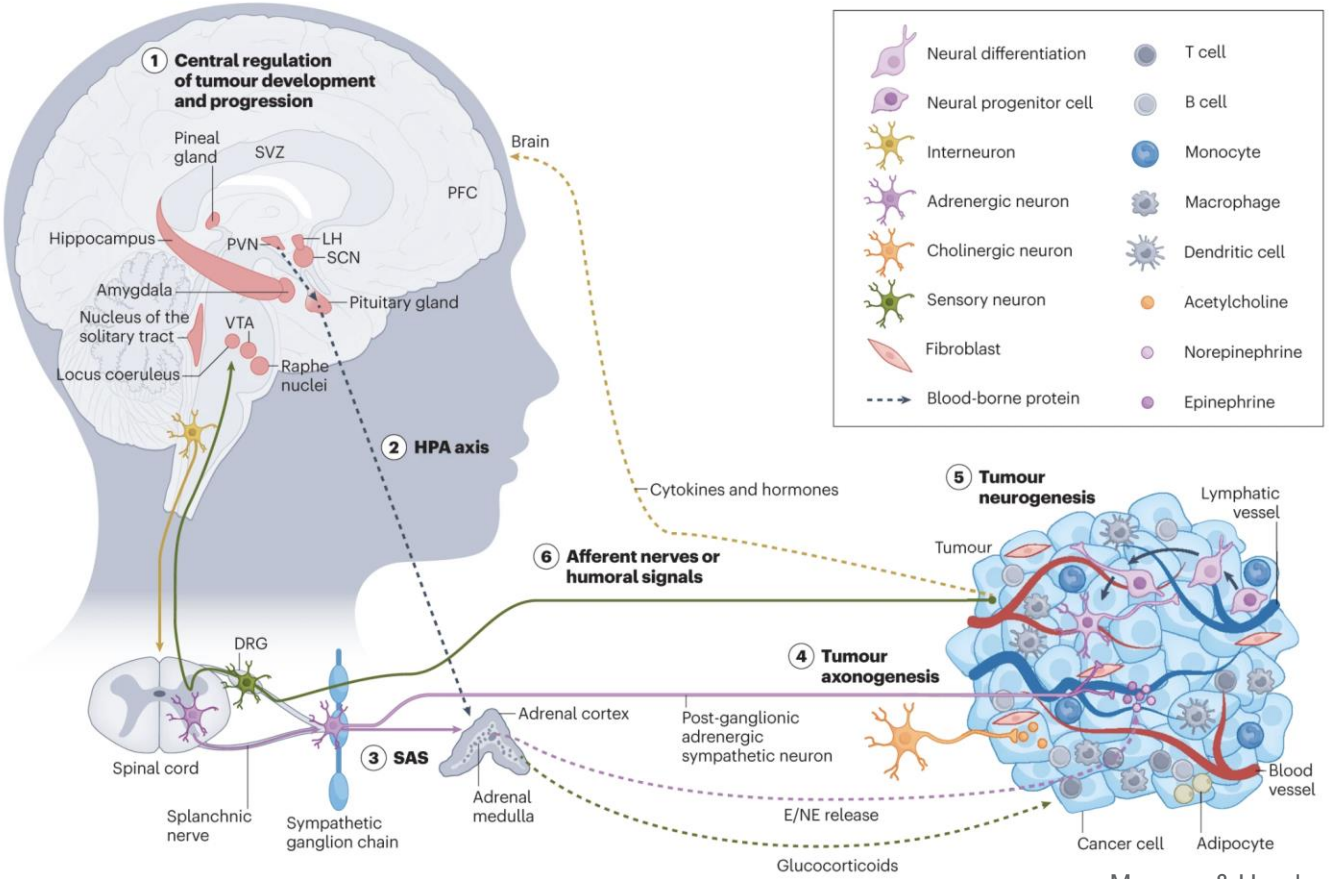
In brief

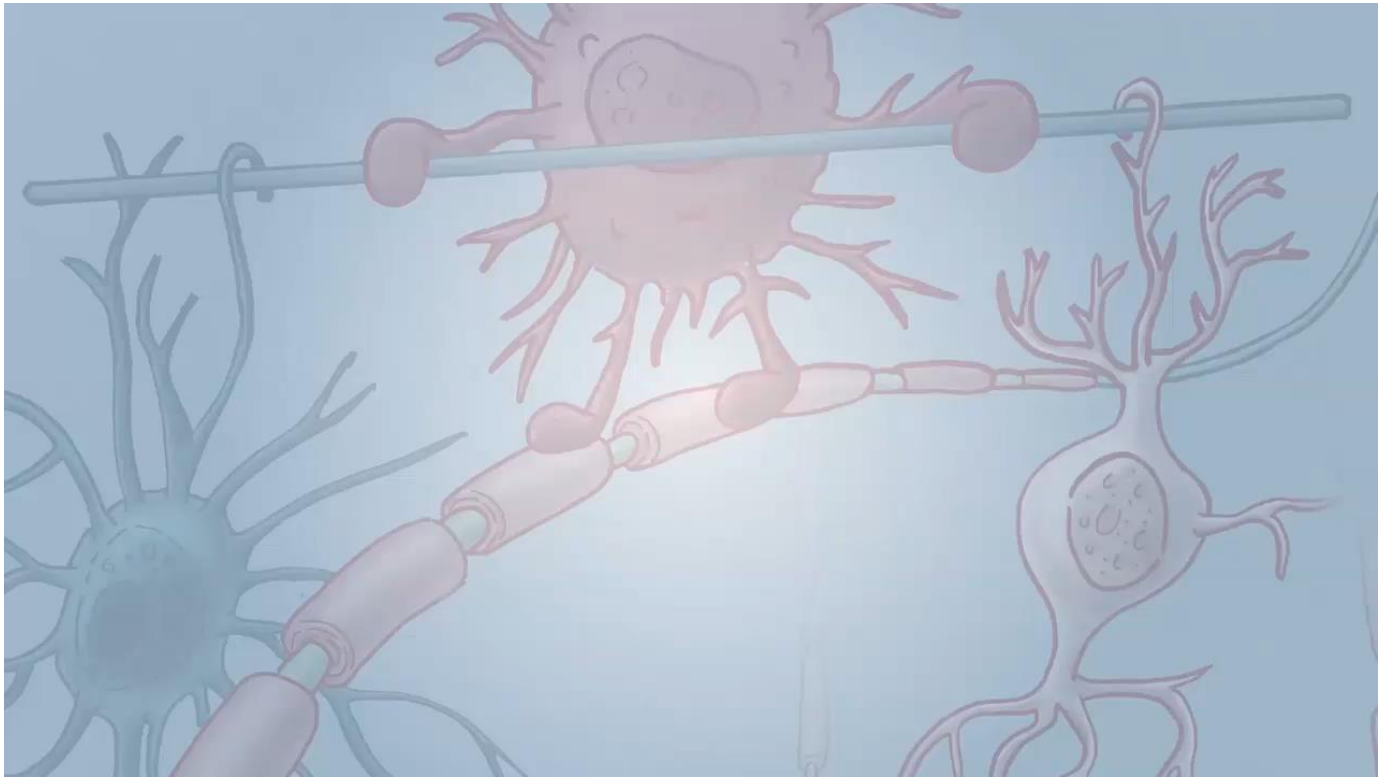
Wen et al. reveal that social interaction reduces breast cancer progression by activating ACC^{Glu}→BLA^{Glu} circuits, inhibiting intratumoral sympathetic activity. This neural mechanism enhances antitumor immunity, offering new therapeutic insights.

Systemic cancer neuroscience



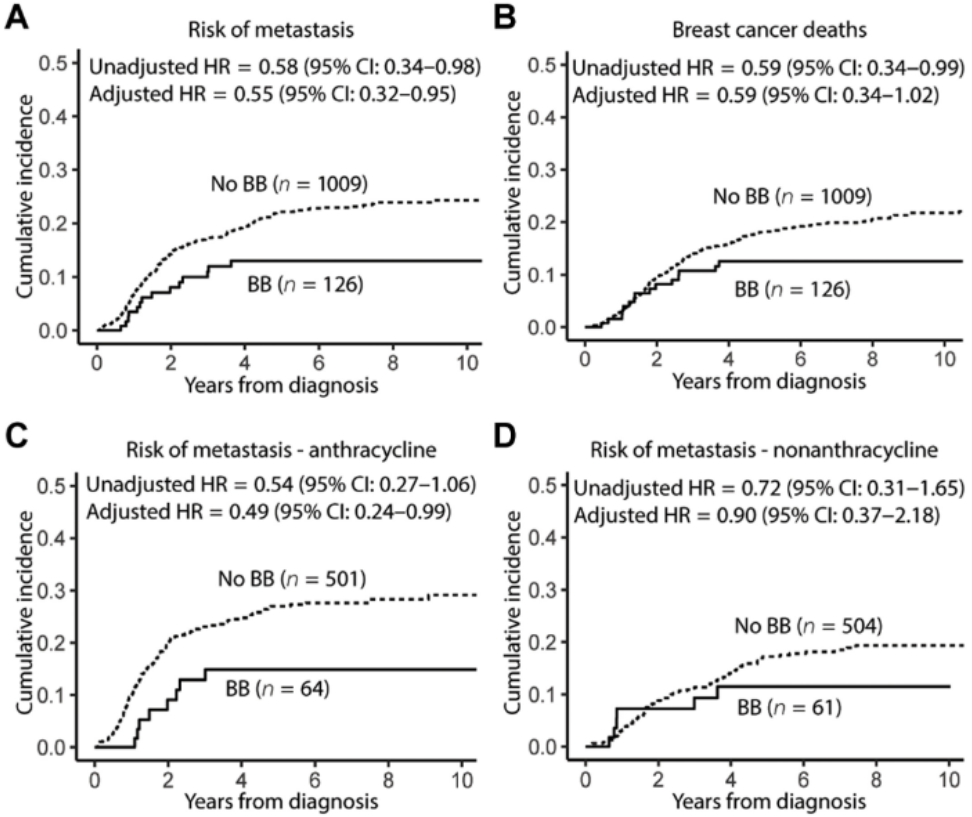
Magnon & Hondermarck, 2023 *Nat Rev Canc*

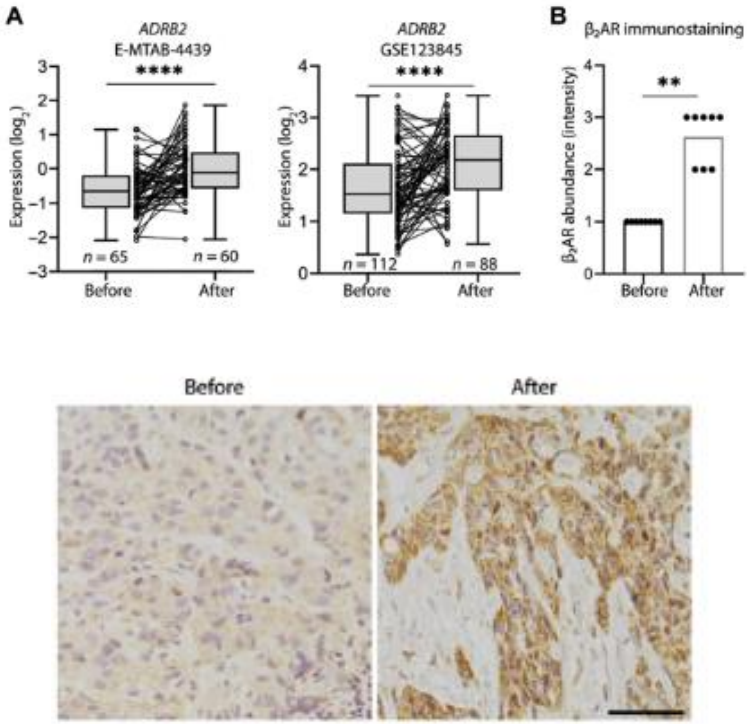
Cancer treatment effects the nervous system



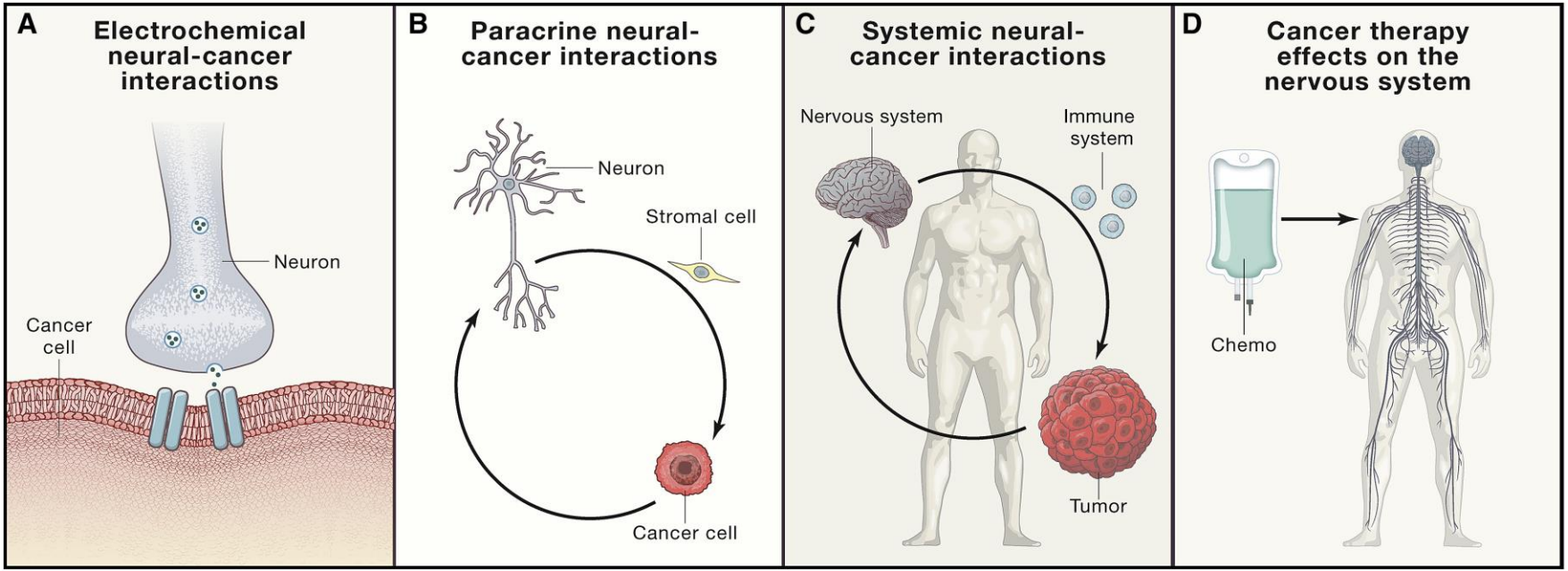
Gibson et al., 2019 *Cell*

Manipulating the nervous system can influence therapy efficacy





Cancer Neuroscience



Monje et al., *Cell*, 2020.

Design your own cancer neuroscience project

Cancer?
Neuron?
TME?
Techniques?
Outcome?

Cancer neuroscience problem

Emerging evidence suggests that the nervous system can regulate cancer initiation, progression and dissemination in multiple tumor types. As part of you PhD project you are interested in understanding if neurons play a role in driving the cancer type you are studying.

Please design an experiment to investigate how neuronal activity regulates the behavior of cancer cell biology. You may choose the cancer type and experimental model system. Your answer should clearly state the biological question and hypothesis, and include:

1. the experimental model you would use
2. the key manipulations and controls
3. the main readouts / outcome measures
4. how the results would be interpreted
5. at least one limitation of your approach and one alternative strategy

ARTICLE

https://doi.org/10.1038/s41586-019-1563-y

Electrical and synaptic integration of glioma into neural circuits

Humsa S. Venkatesh[1], Wade Morishita[2,3], Anna C. Geraghty[1], Dana Silverbush[4,5,6], Shawn M. Gillespie[1], Marlene Arzt[1], Lydia T. Tam[1], Cedric Espenel[7], Anitha Ponnuswami[1], Lijun Ni[1], Pamelyn J. Woo[1], Kathryn R. Taylor[1], Amit Agarwal[8,15], Aviv Regev[5,6,9], David Brang[10], Hannes Vogel[1,11,12], Shawn Hervey-Jumper[13], Dwight E. Bergles[8], Mario L. Suvà[4,5,6], Robert C. Malenka[2,3] & Michelle Monje[1,2,11,12,14]*

High-grade gliomas are lethal brain cancers whose progression is robustly regulated by neuronal activity. Activity-regulated release of growth factors promotes glioma growth, but this alone is insufficient to explain the effect that neuronal activity exerts on glioma progression. Here we show that neuron and glioma interactions include electrochemical communication through bona fide AMPA receptor-dependent neuron–glioma synapses. Neuronal activity also evokes non-synaptic activity-dependent potassium currents that are amplified by gap junction-mediated tumour interconnections, forming an electrically coupled network. Depolarization of glioma membranes assessed by in vivo optogenetics promotes proliferation, whereas pharmacologically or genetically blocking electrochemical signalling inhibits the growth of glioma xenografts and extends mouse survival. Emphasizing the positive feedback mechanisms by which gliomas increase neuronal excitability and thus activity-regulated glioma growth, human intraoperative electrocorticography demonstrates increased cortical excitability in the glioma-infiltrated brain. Together, these findings indicate that synaptic and electrical integration into neural circuits promotes glioma progression.

Fig. 1. Transcriptomic and structural evidence for glioma synapses.

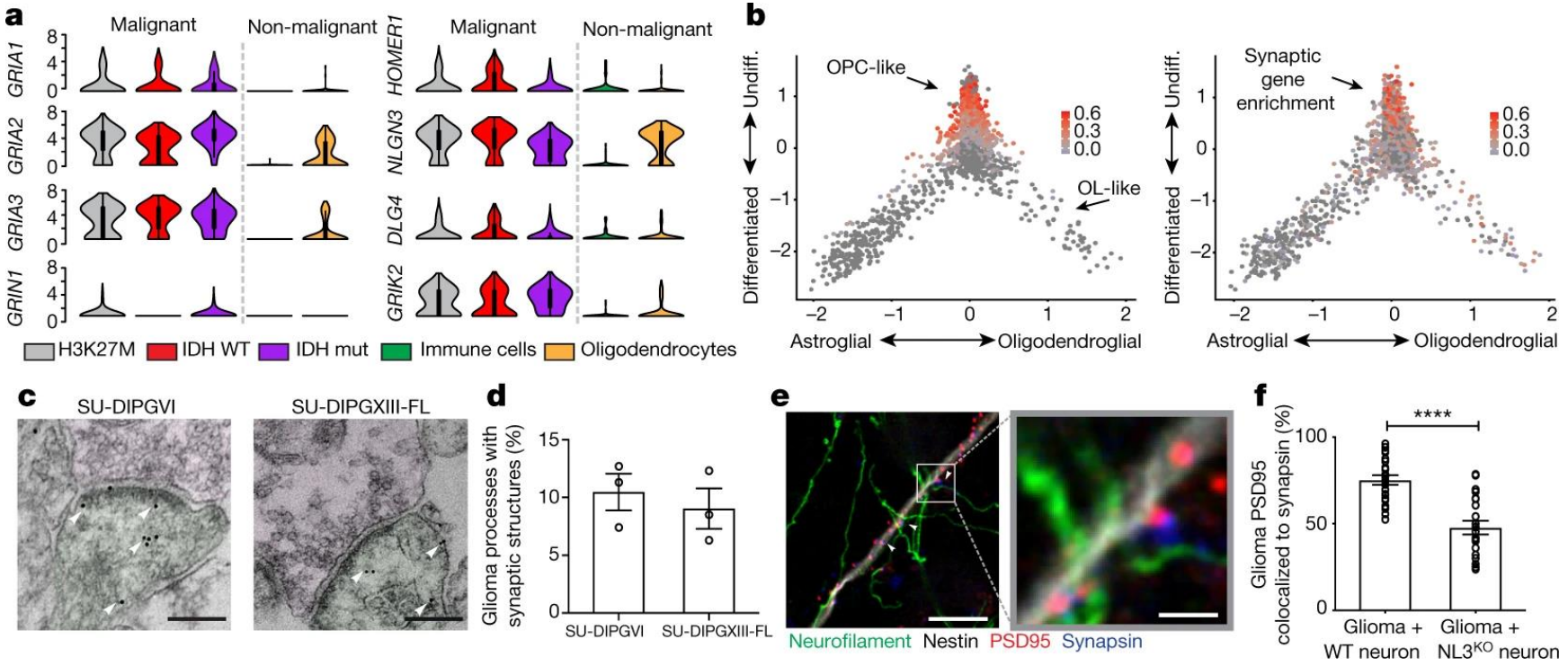


Fig. 2. Synaptic AMPAR-mediated EPSCs in glioma.

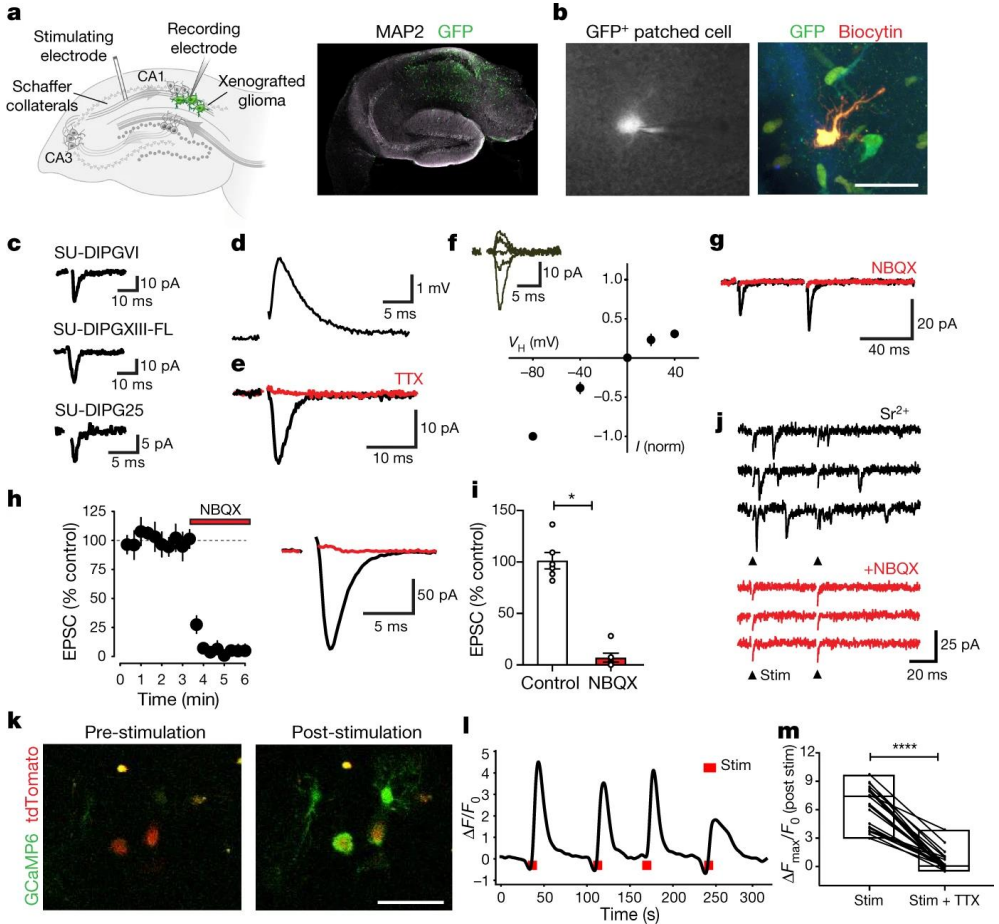


Fig. 3. Neuronal activity-dependent potassium currents in glioma.

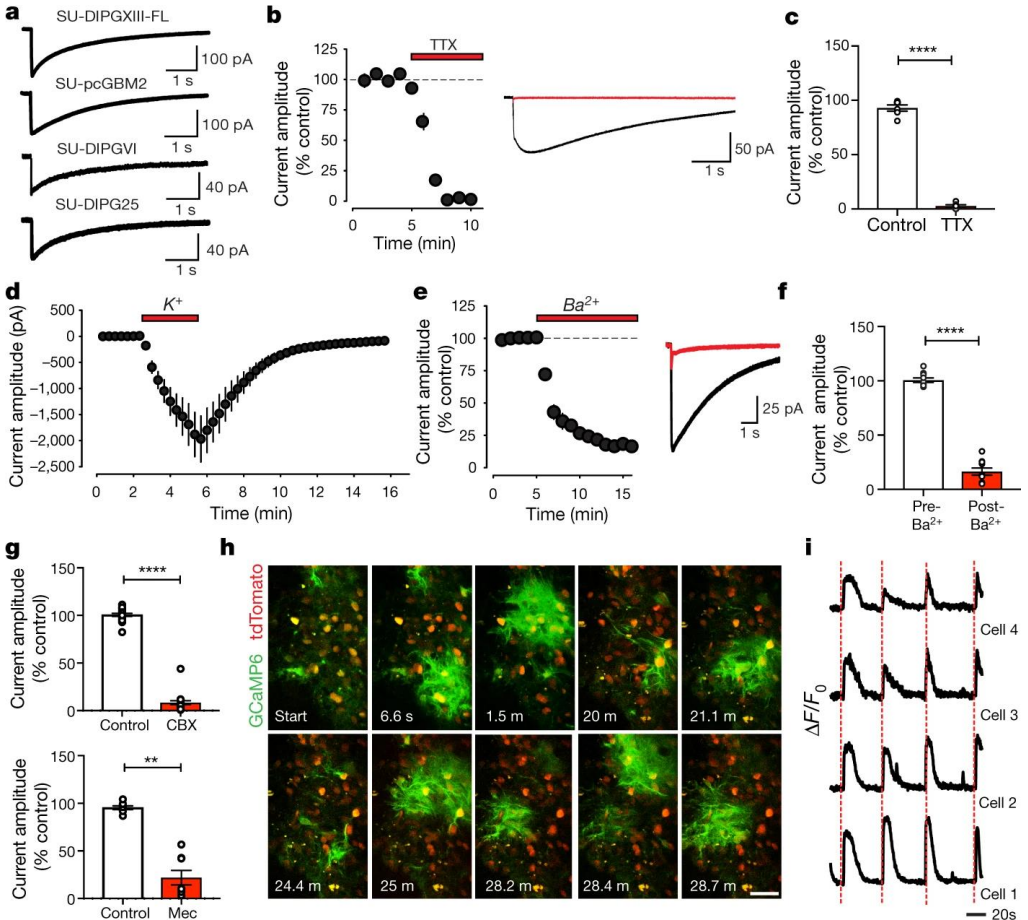


Fig. 4. Glioma membrane depolarization promotes glioma progression.

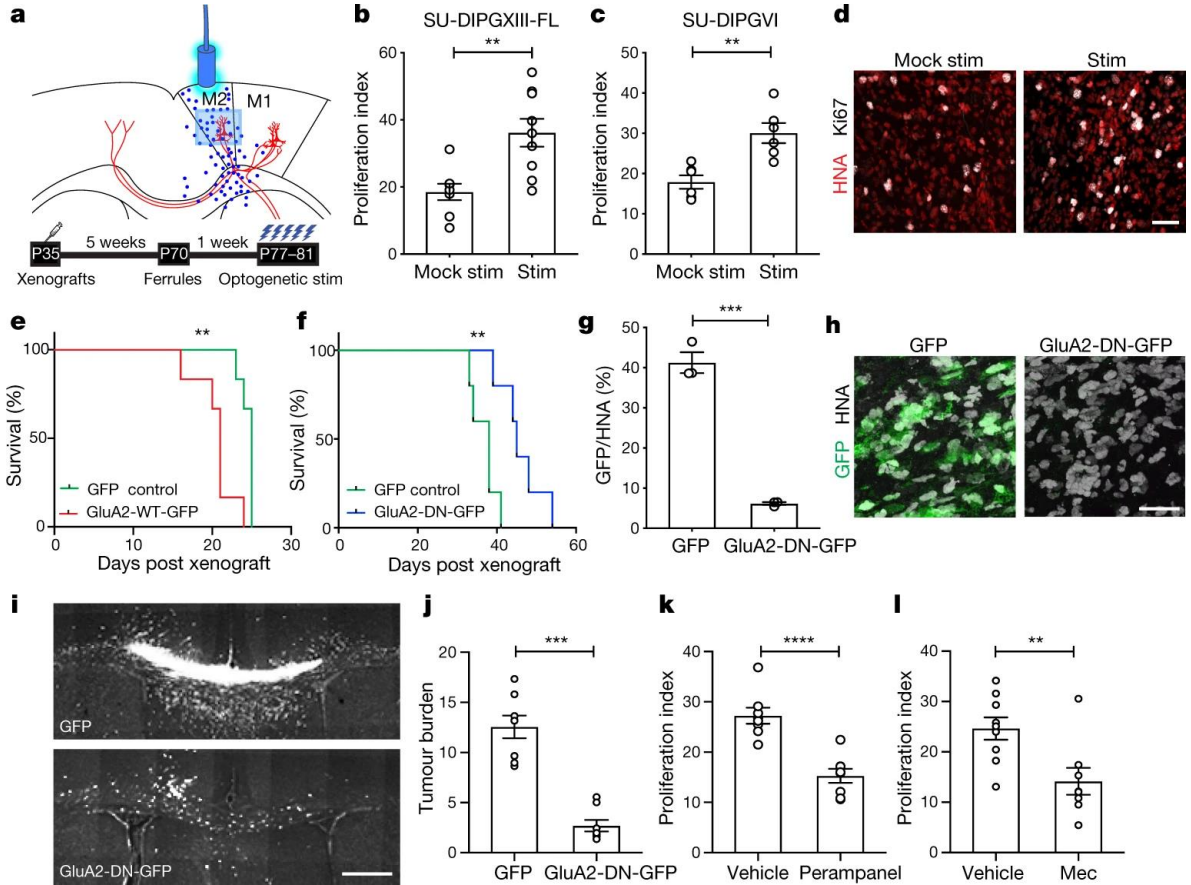


Fig. 5. Increased neuronal excitability in glioma-infiltrated brain.