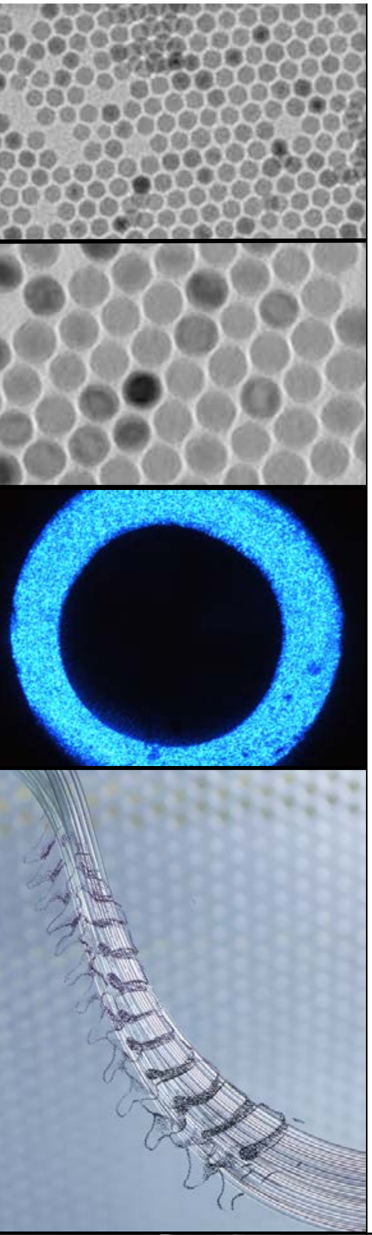
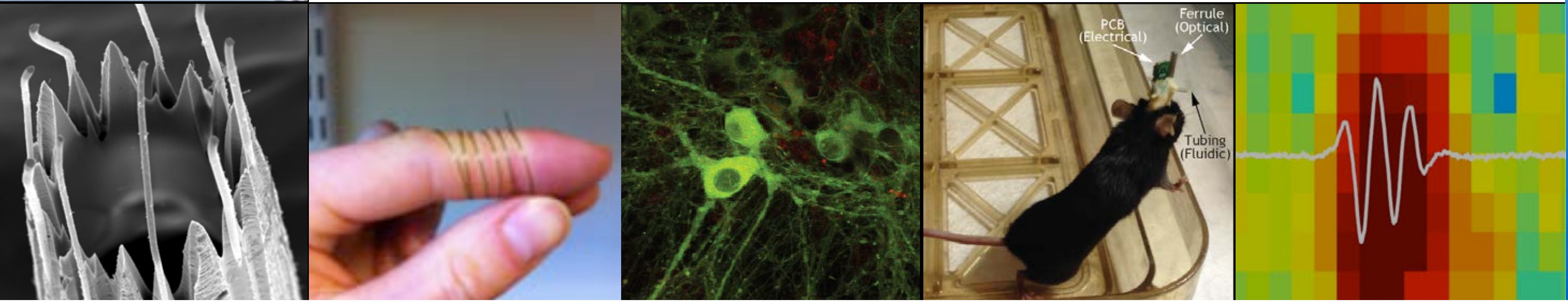


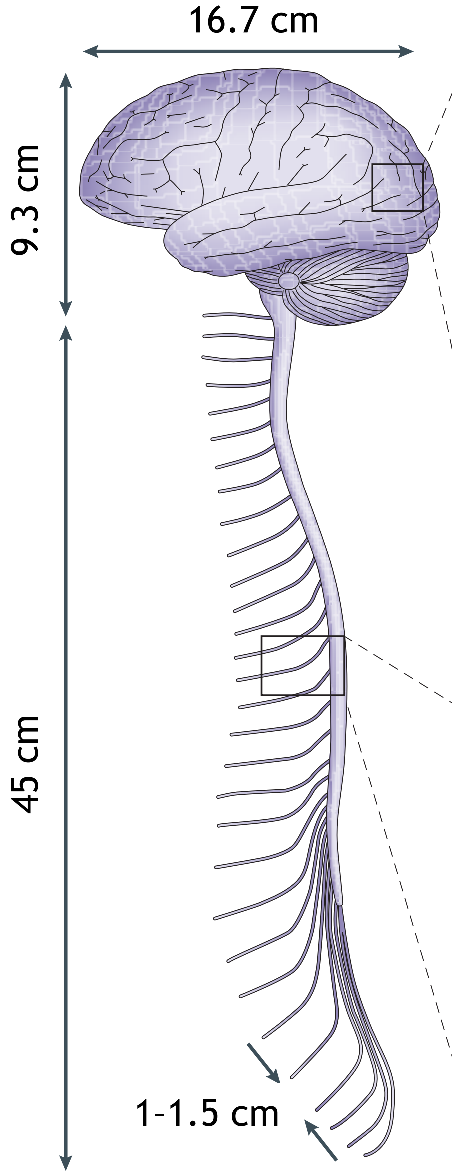
Harnessing Materials Design to Manipulate the Nervous System

Polina Anikeeva
Materials Science and Engineering
Brain and Cognitive Sciences
Research Laboratory of Electronics
McGovern Institute for Brain Research
Massachusetts Institute of Technology

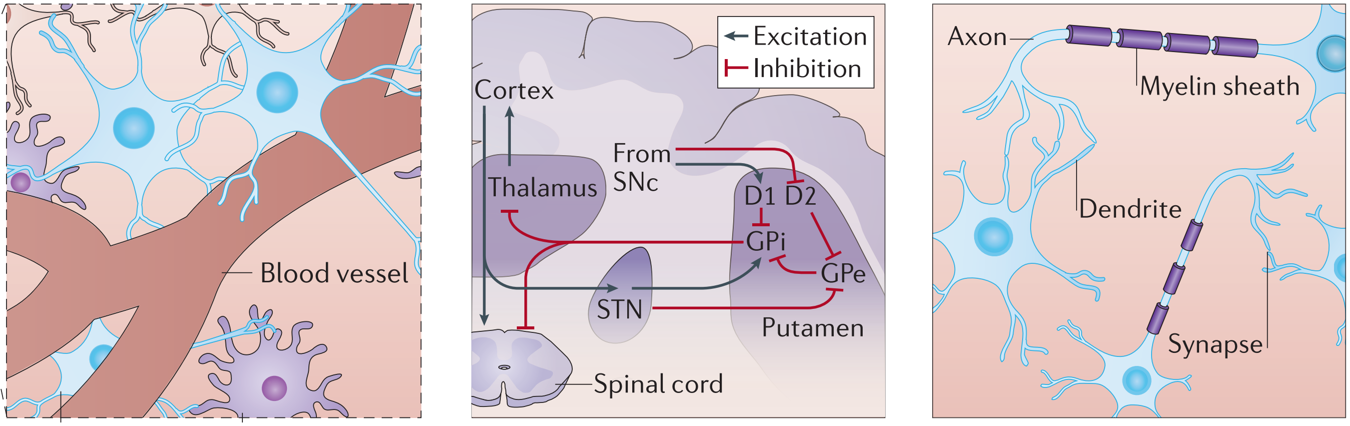
MIT Japan Conference, January 25th, 2019



Addressing Complexity of the Nervous System

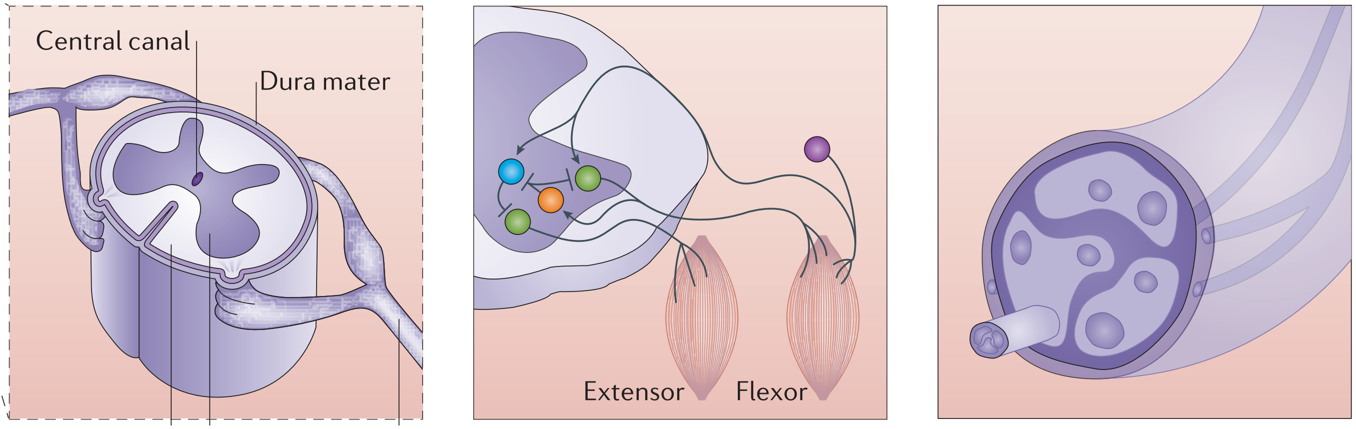


Complexity of the Brain Circuits



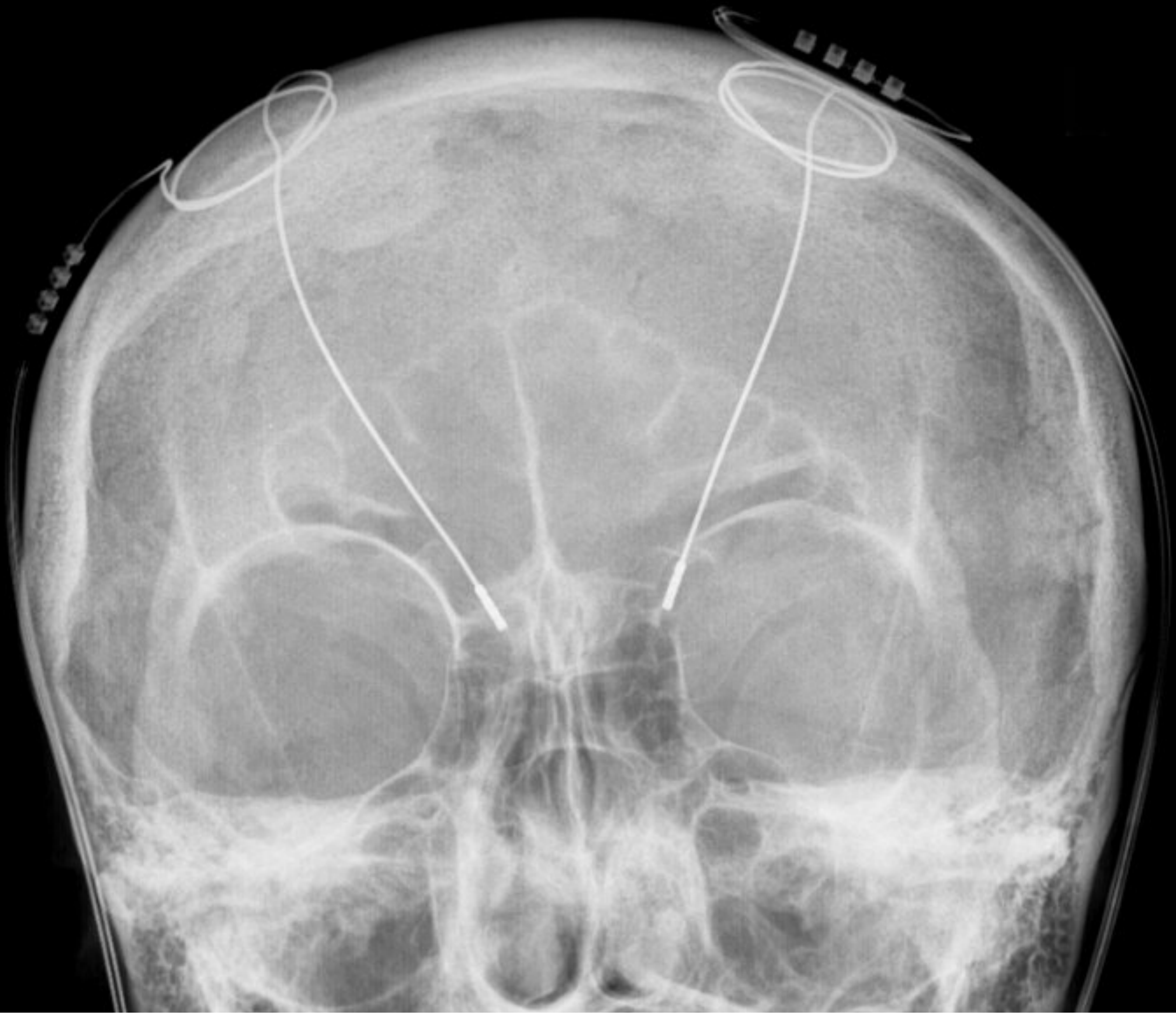
- 10^{11} neurons
- 10^{14} synapses
- 10^{2} neurotransmitters
- Elastic modulus ~kPa

Complexity of the Spinal Cord and Peripheral Circuits



- 10^{9} neurons
- >150,000 km of nerve fibers
- Elastic modulus kPa-MPa
- Repeated strain ~12%

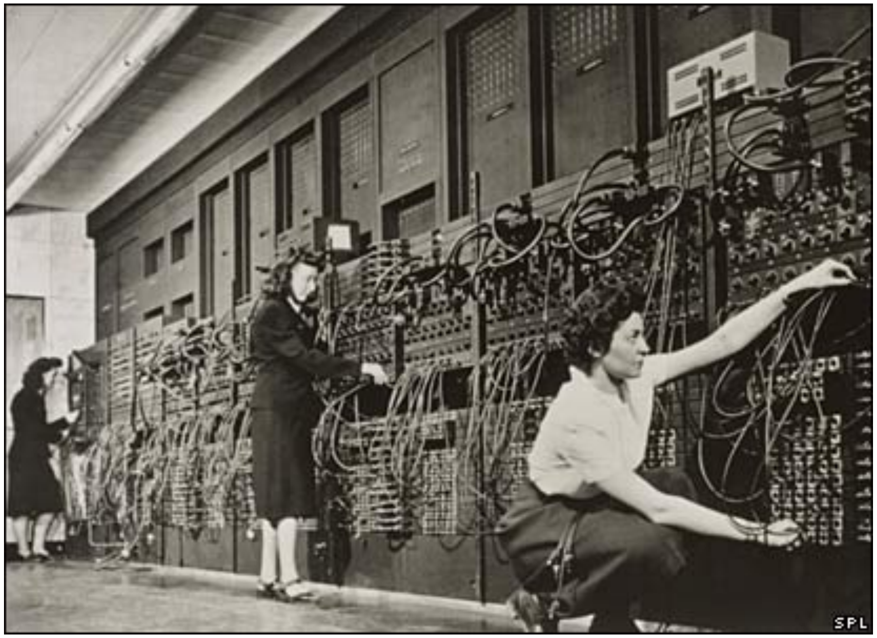
Chen, Canales, Anikeeva, Nat. Rev. Mater. 2017



Can We Just Make It Smaller?

Miniaturization:

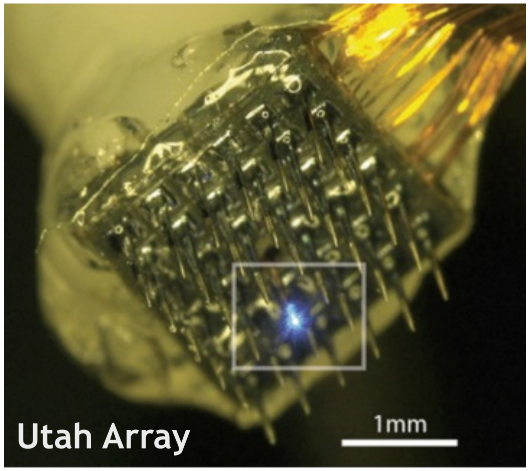
Could we apply what worked for silicon circuits to neural circuits?



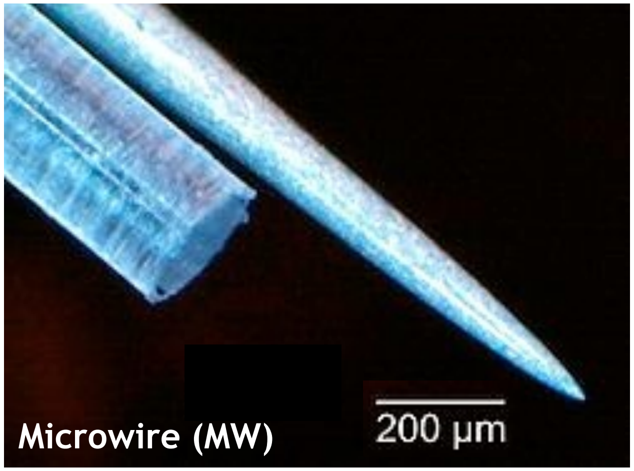
1950s

Today

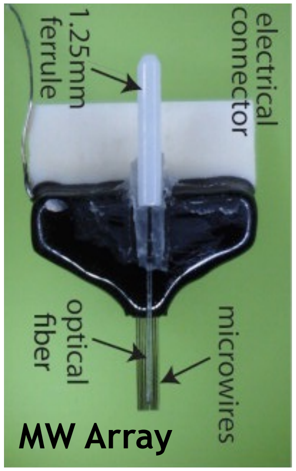
Neural Probes vs. Neural Tissues: Elastic Mismatch



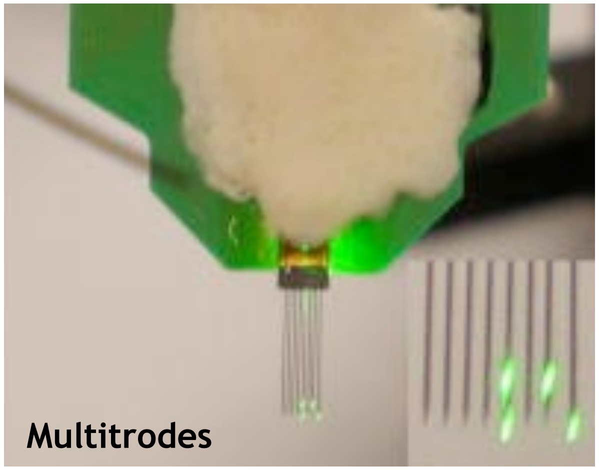
Utah Array



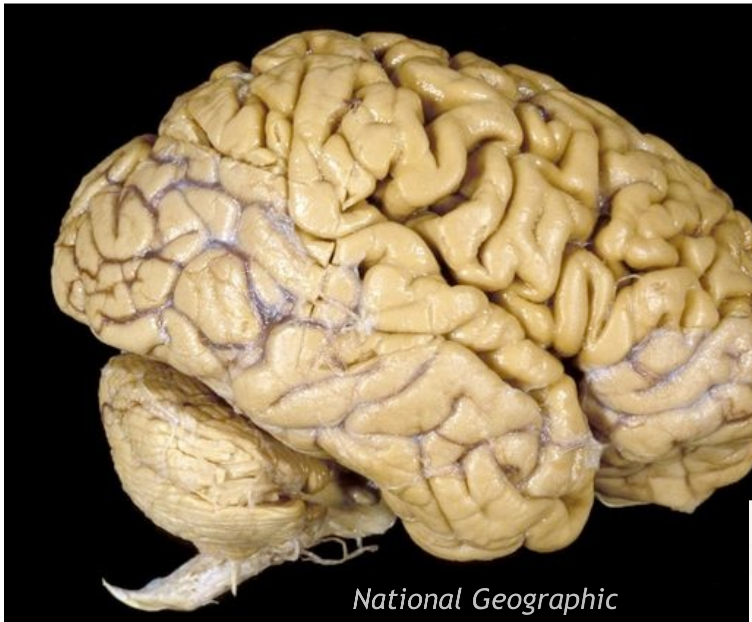
Microwire (MW)



MW Array



Multitrodes

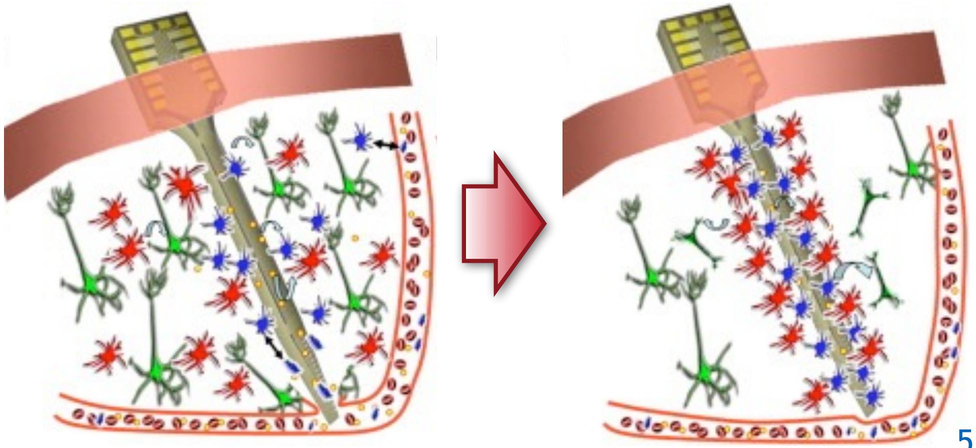


National Geographic

- Brain has a highly developed surface
- Consistency of pudding (kPa-MPa)

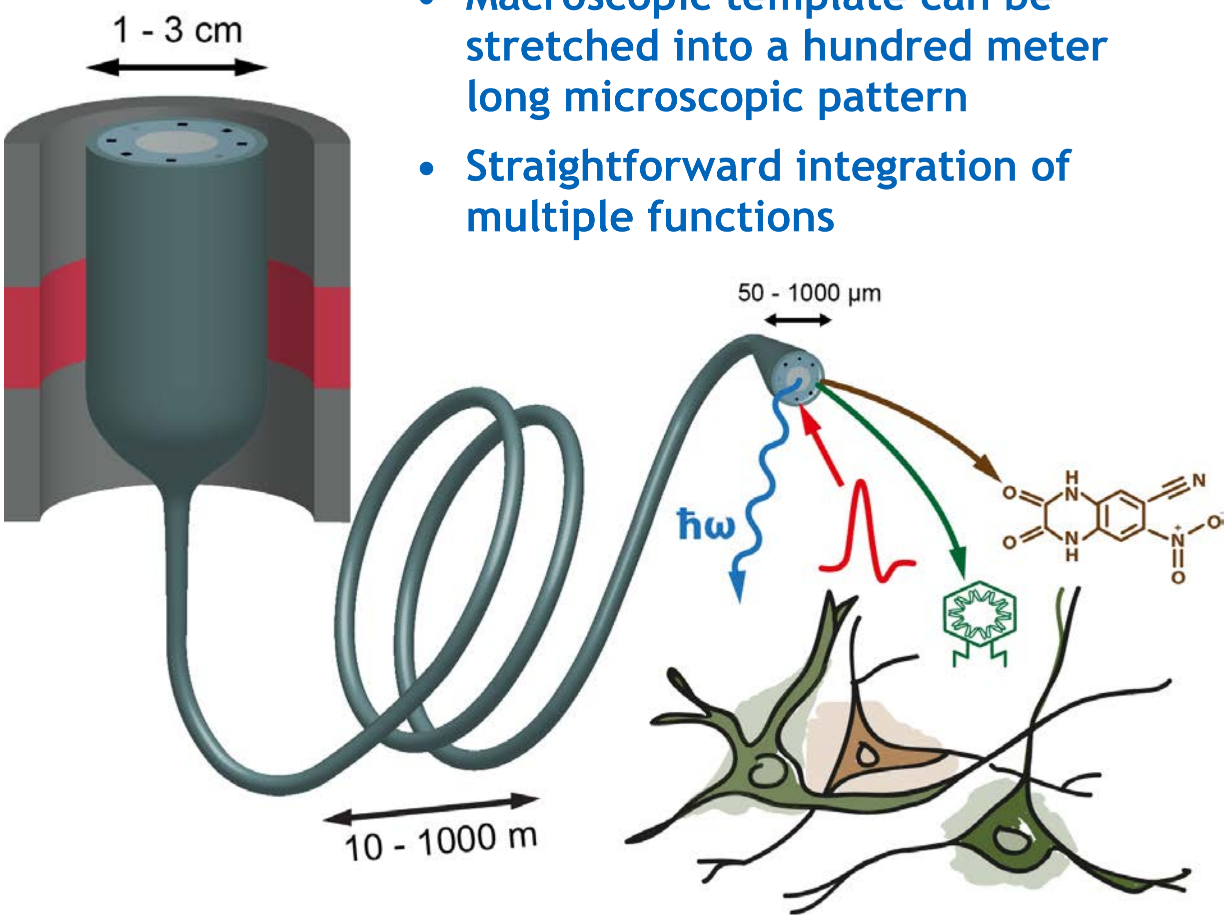
- Elastic moduli of neural probes ~ 10-100 GPa
- Chronic tissue damage during “micromotion”
- Blood-brain barrier breach
- Disruption of glial networks

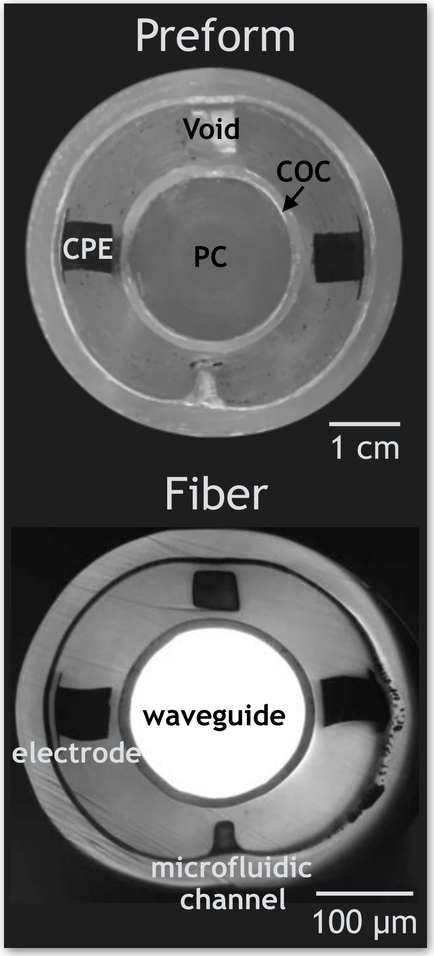
Formation of glial scar and loss of function



Learning from Photonics: Fiber-Based Fabrication

- Macroscopic template can be stretched into a hundred meter long microscopic pattern
- Straightforward integration of multiple functions



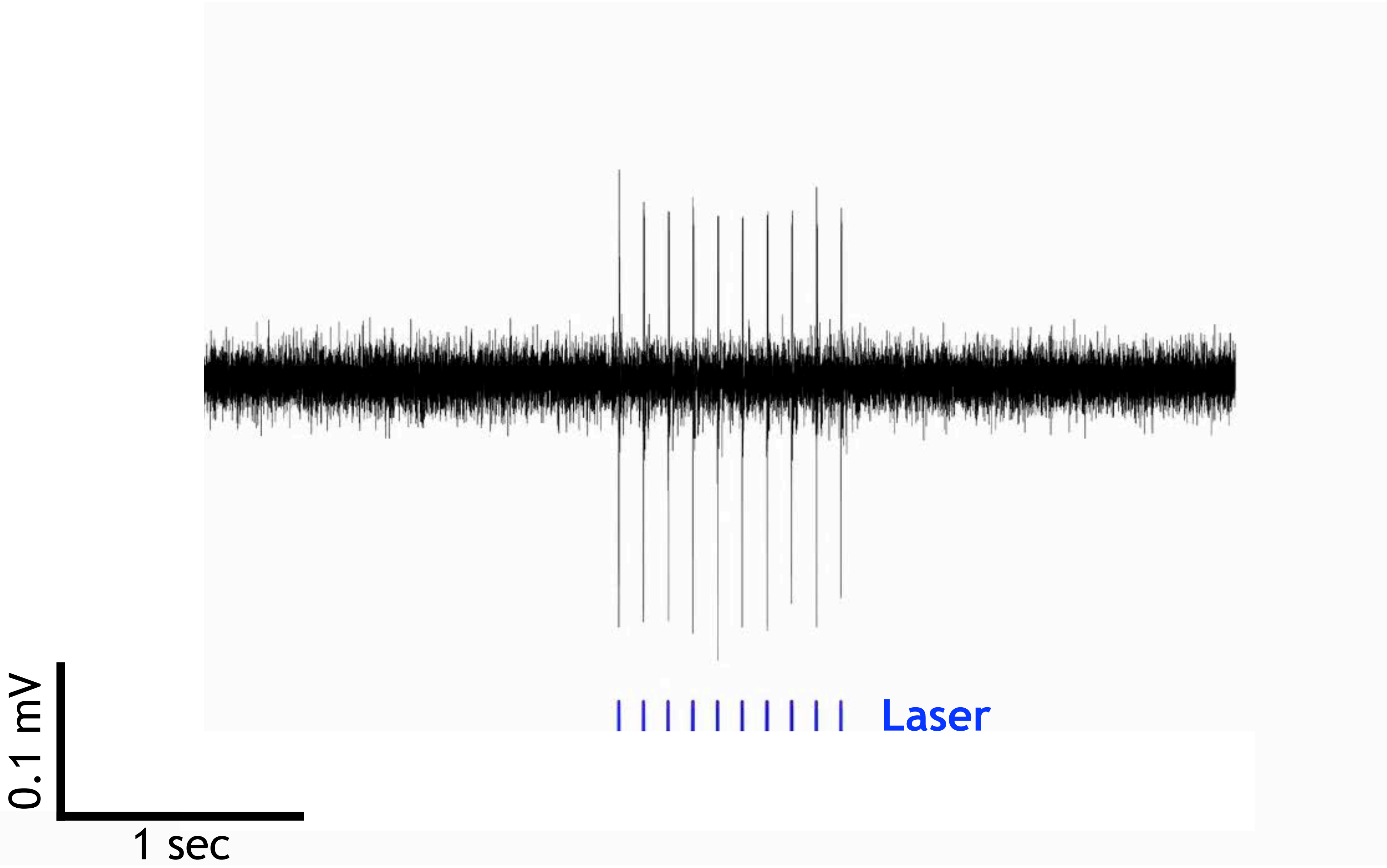


PC = polycarbonate, COC = cyclic olefin copolymer
CPE = carbon-loaded conductive polyethylene

- Virtually arbitrary pattern can be defined
- Features down to ~nm can be produced
- Combined processing of multiple materials: polymers, metals, glasses
- Control over elastic modulus: softer materials – reduced tissue damage

Canales, Jia, Froriep, Koppes et al., Nat. Biotech. 2015

Multifunctional Interfaces with Neural Circuits

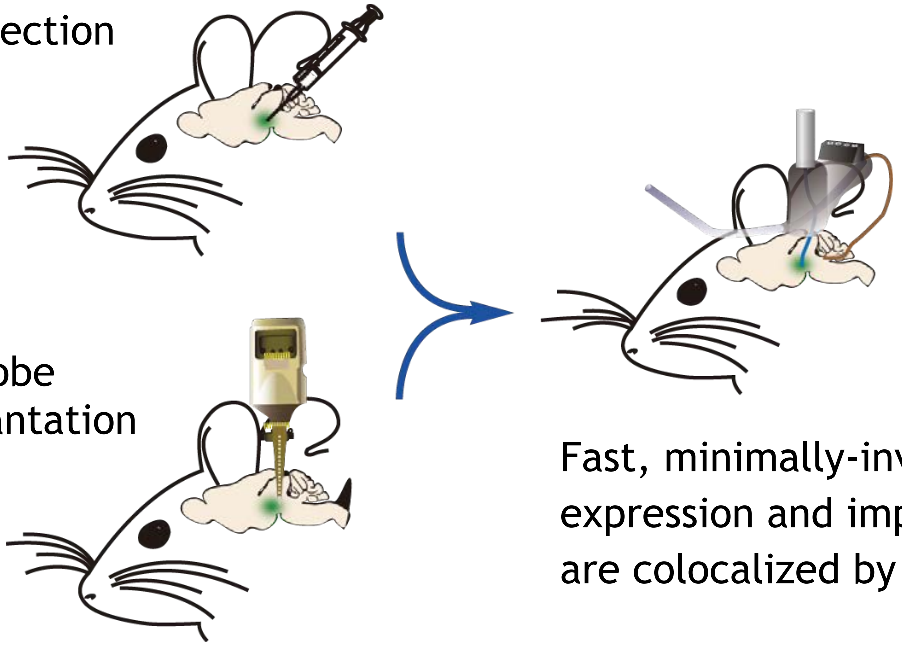


Canales,.. Anikeeva et al., Nat. Biotechnol. 2015

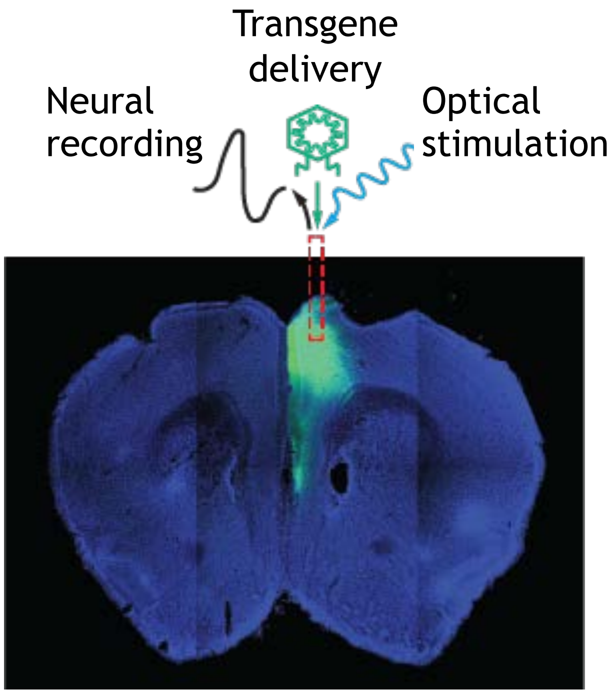
One-Step Optogenetics

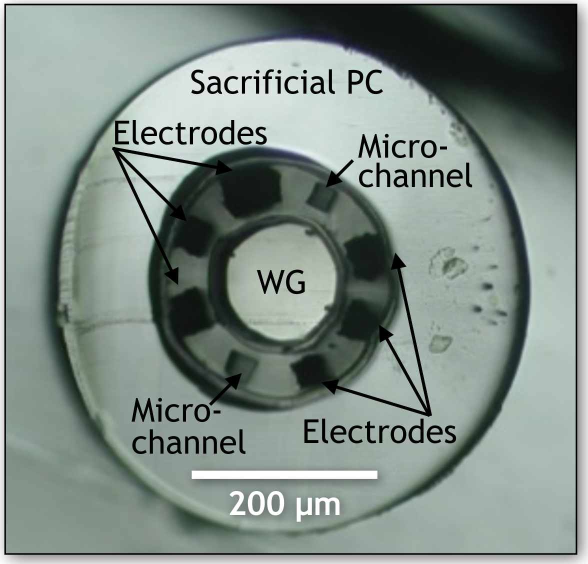
1. Injection

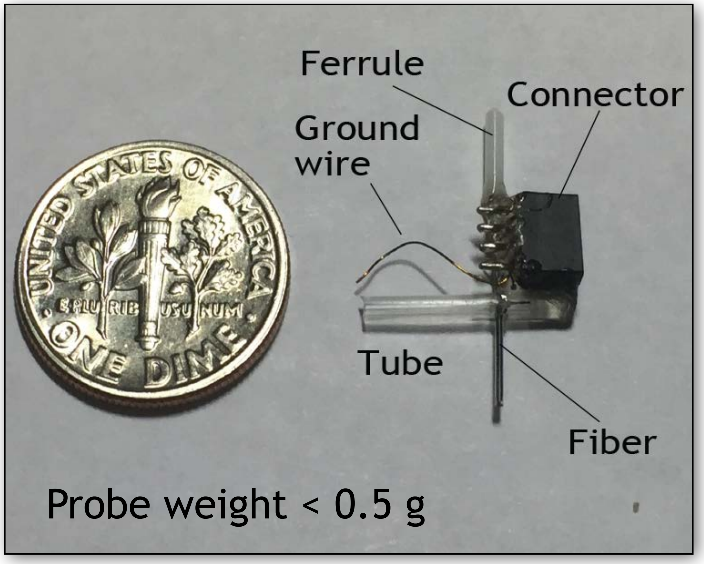
2. Probe implantation



Fast, minimally-invasive, expression and implantation are colocalized by design





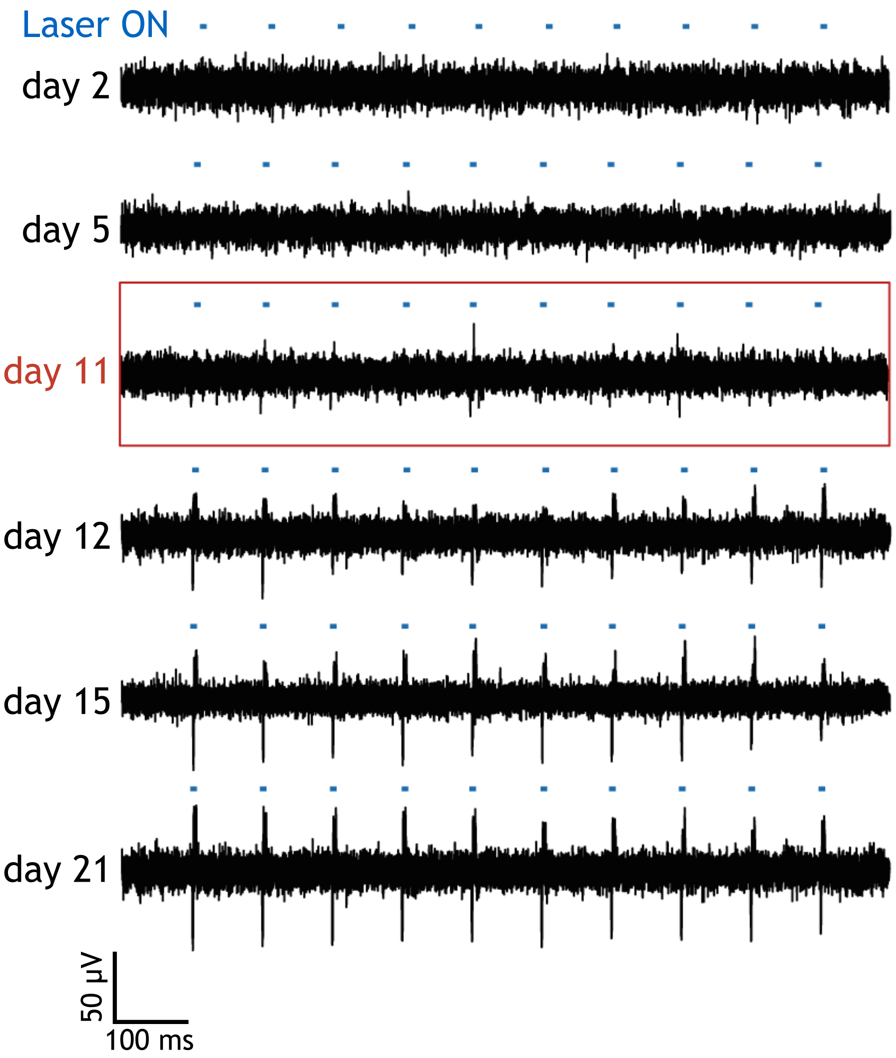


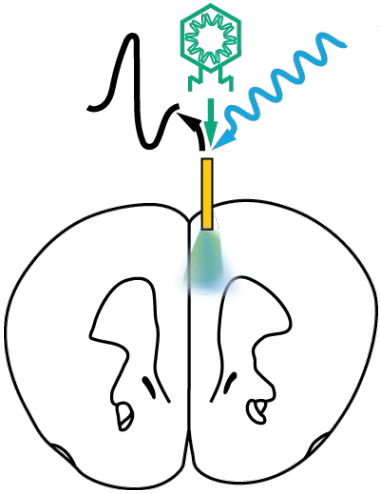
Probe weight < 0.5 g

Park et al., Nat. Neurosci. 2017

One-Step Optogenetics: Monitoring Opsin Expression

Manipulation of cortical activity





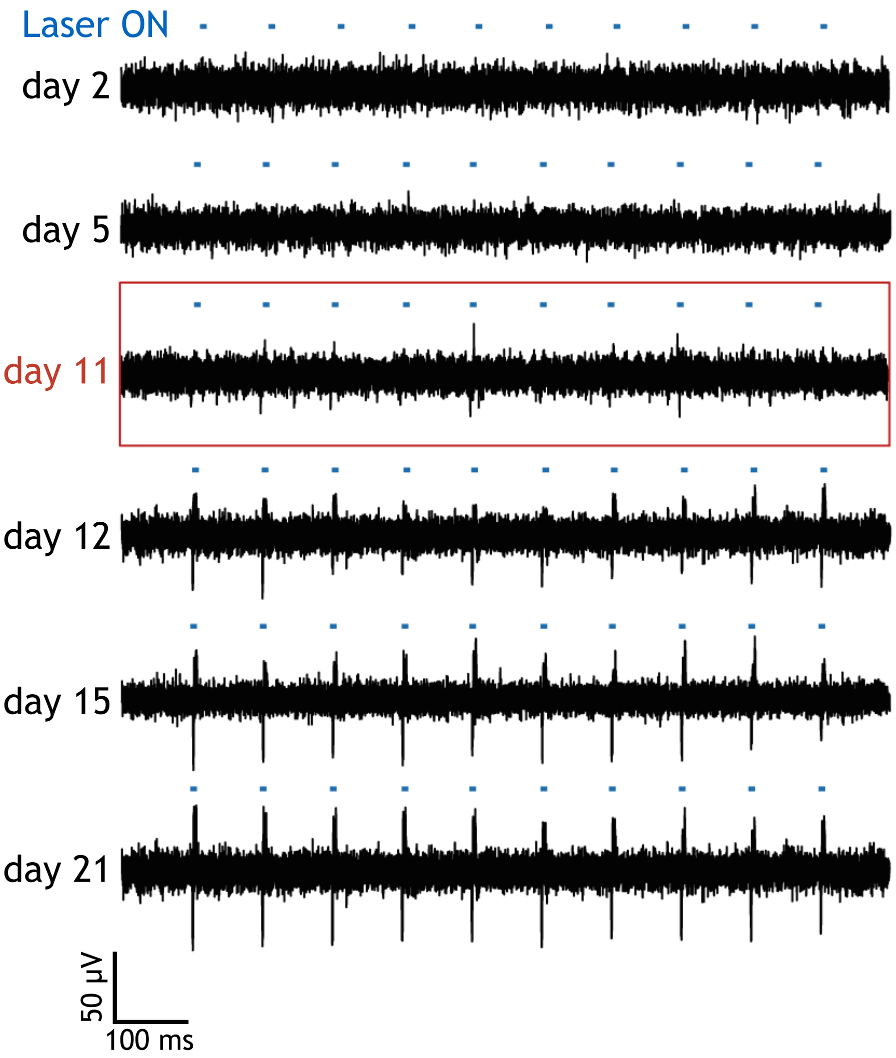
Multifunctional fiber probe:

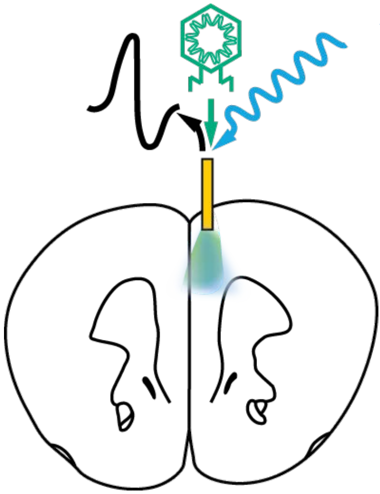
- Microfluidic delivery of opsin genes e.g. *AAV5-CamKIIa::ChR2-eYFP*
- Electrophysiological recording during optical stimulation reveals onset of opsin expression

Park et al., Nat. Neurosci. 2017

One-Step Optogenetics: From Surgery to Behavior

Manipulation of cortical activity

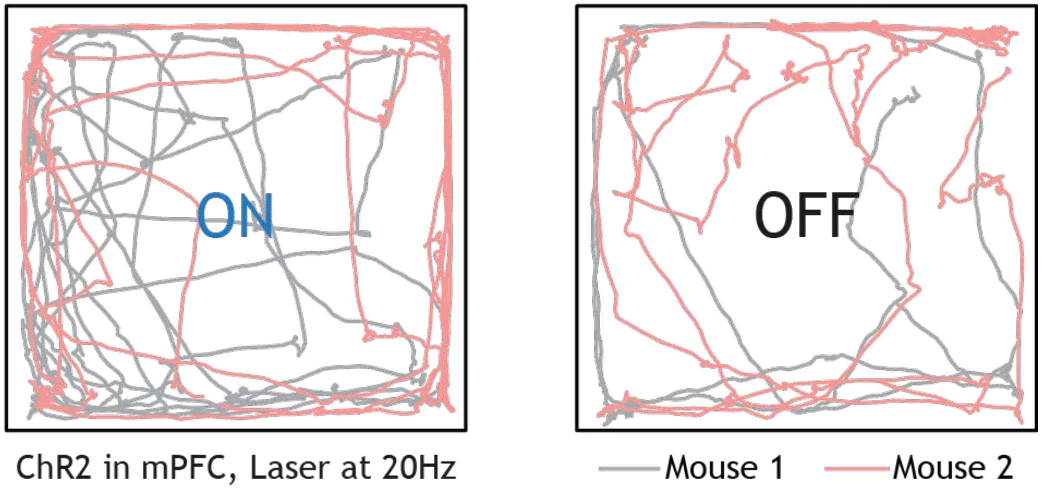




Multifunctional fiber probe:

- Microfluidic delivery of opsin genes e.g. *AAV5-CamKIIa::ChR2-eYFP*
- Electrophysiological recording of optically evoked activity confirms expression 11±1 days after surgery
- Evoked activity in the motor cortex stimulates locomotor activity

Optical cortical control of locomotion



Park et al., Nat. Neurosci. 2017

Hydrogel Integration of Multifunctional Fibers

Several slides of unpublished data

Minimally Invasive Interfaces

GFAP – Astrocytes

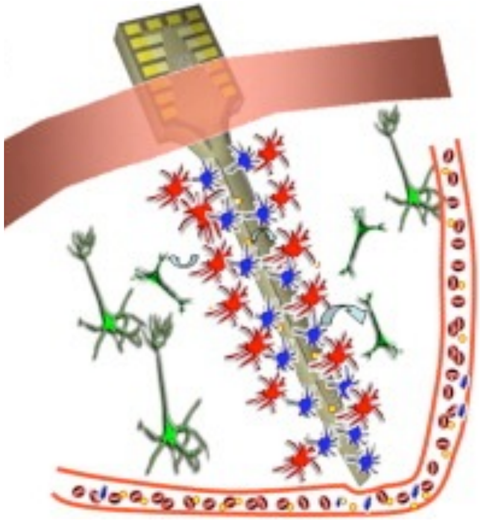
Iba1 – Glia

ED1 – Macrophages

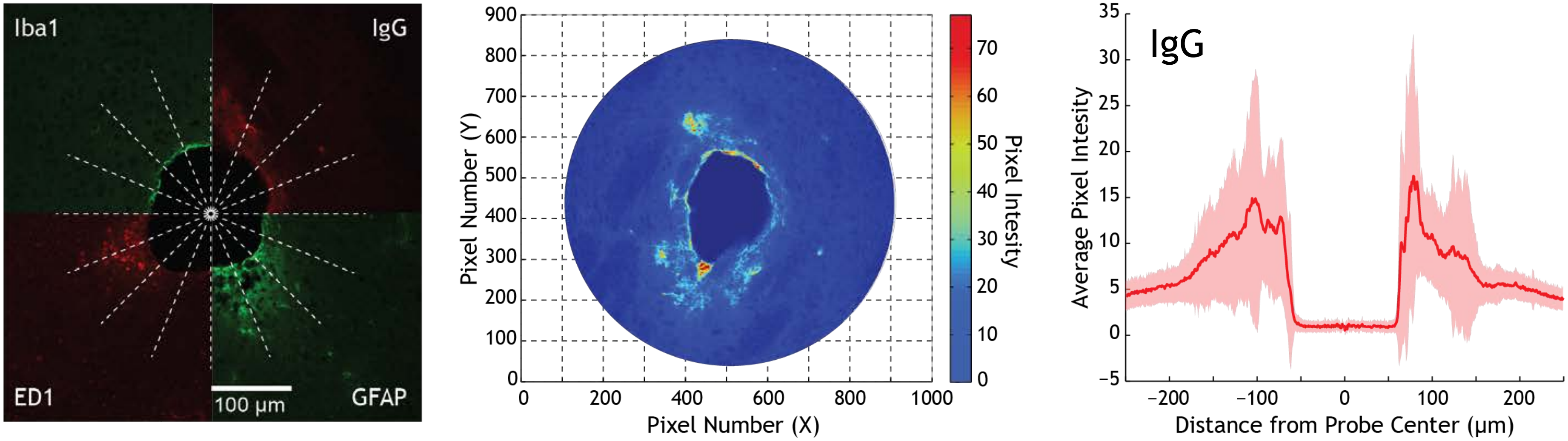
Ward et al., Brain Res. 2009

IgG – Disruption of BBB

Saxena et al., Biomaterials 2013



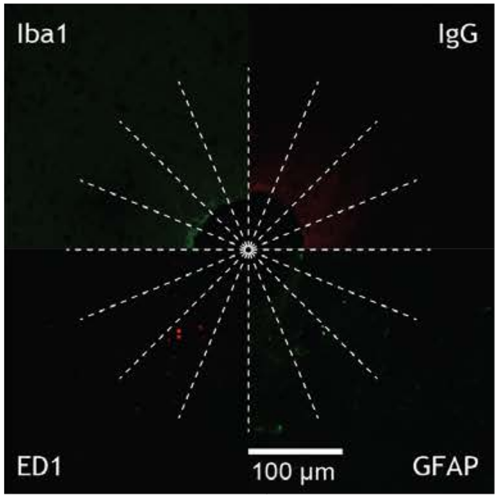
Tissue response to a steel microwire

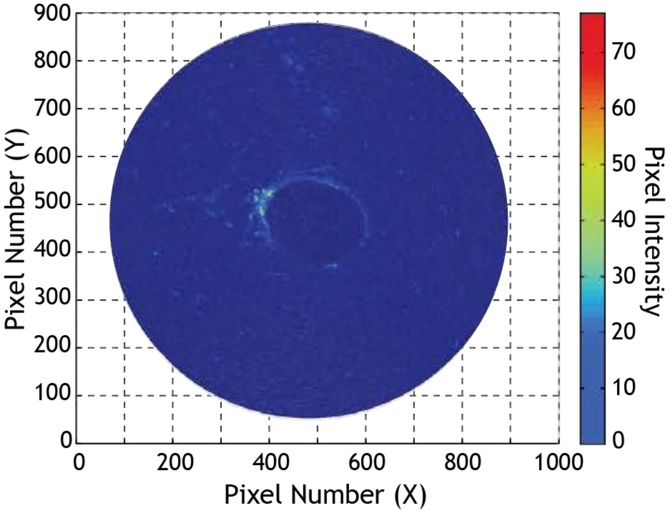


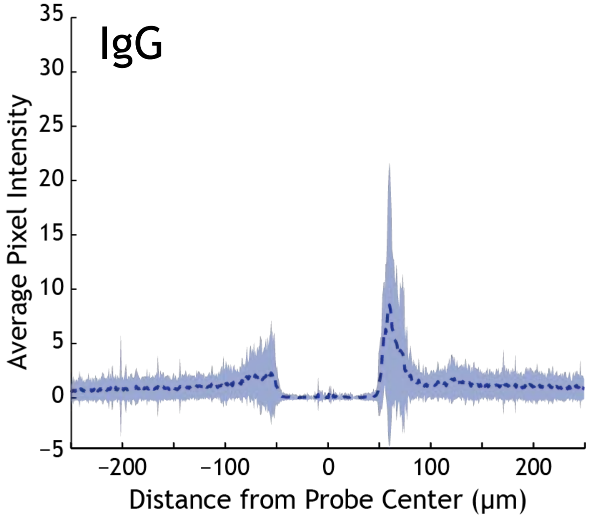
Canales, Jia, Froriep, Koppes et al., Nat. Biotech. 2015

Minimally Invasive Interfaces

Tissue response to a multielectrode fiber probe







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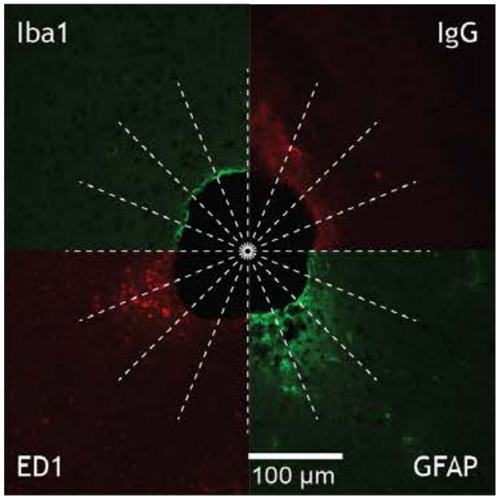
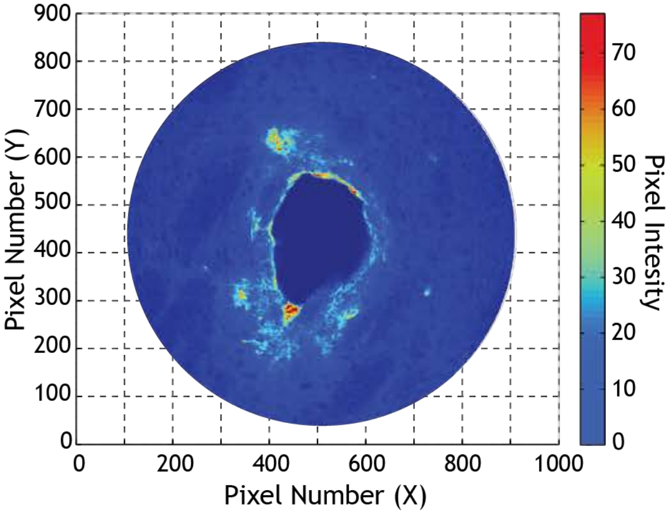
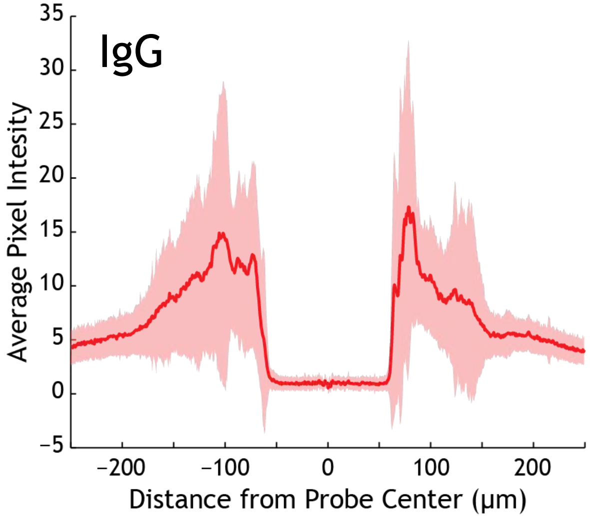






Canales, Jia, Froriep, Koppes et al., Nat. Biotech. 2015

Minimally Invasive Neural Stimulation

Electrical stimulation

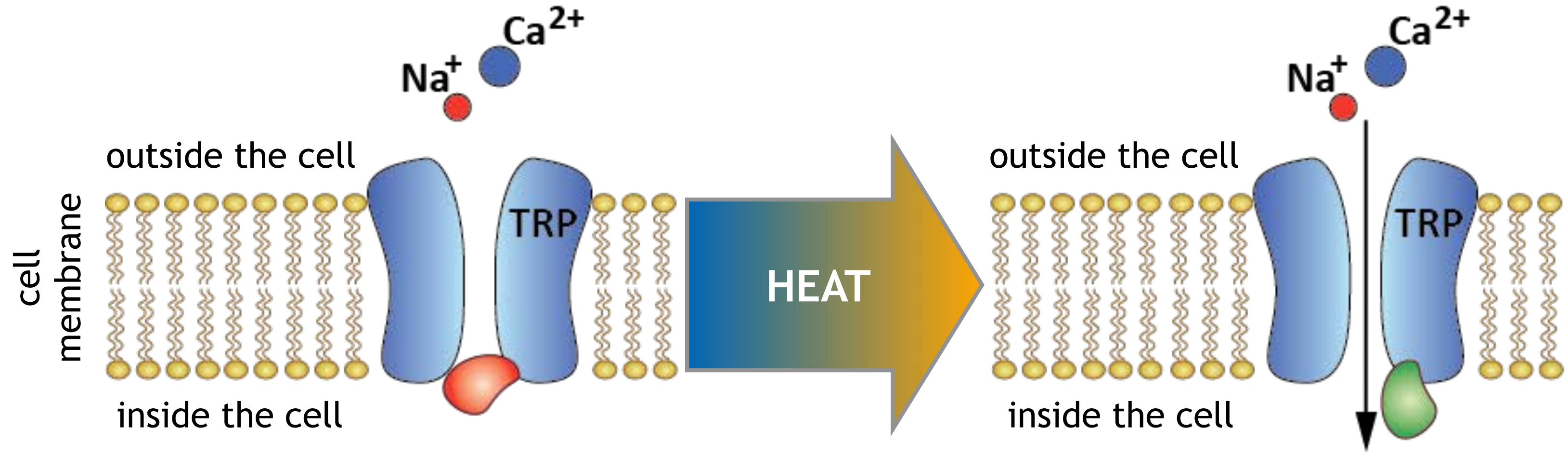
Cyberonics, Inc.

Remote stimulation

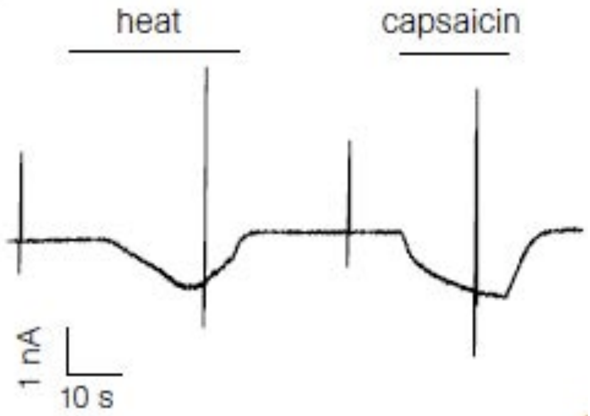
Using GSK graphics

Sensitivity to Local Temperature Increase

- **Capsaicin receptor (TRPV1) is activated by heat as well as chili peppers.**
  (Caterina et al., Nature 1997; Caterina et al., Nature 1999)
- **Expressed throughout peripheral nervous system. Also present in central nervous system.**
- **Major player of pain pathway in the spinal cord.**



Ionic Currents Evoked
by Temperature and Capsaicin



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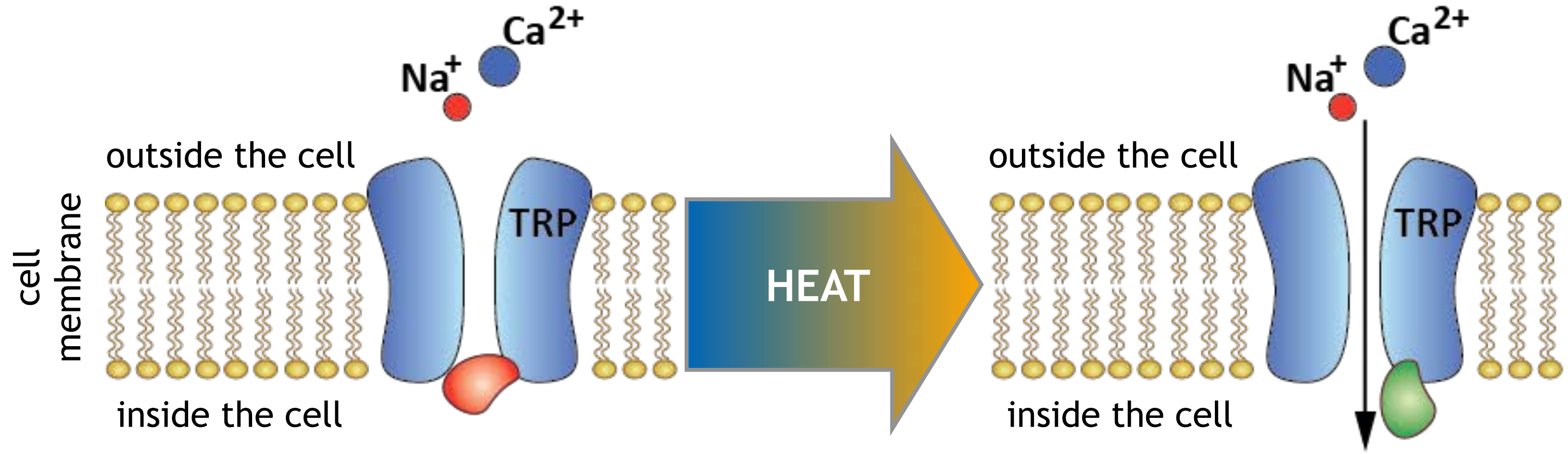
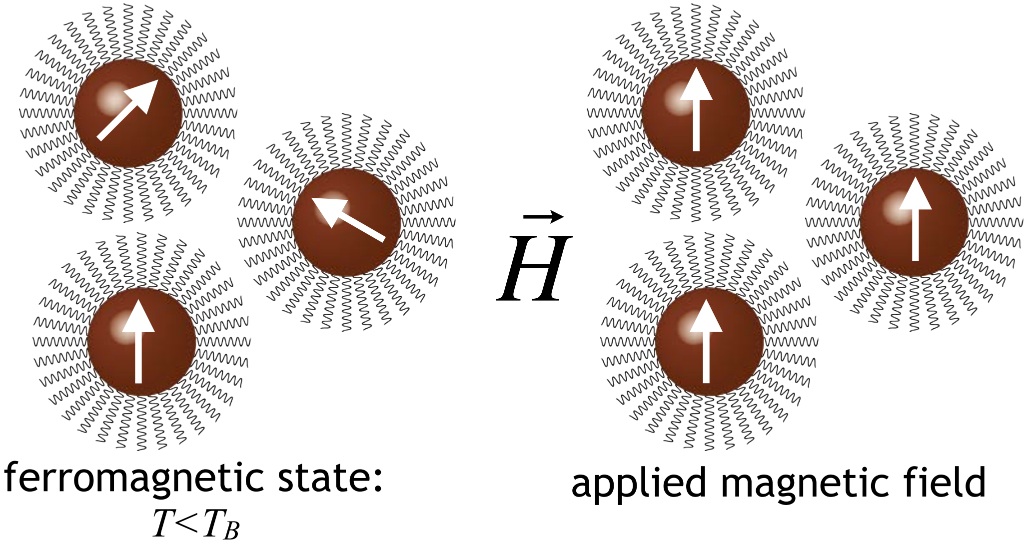


- Mammalian tissues are transparent to AMF with RF frequencies (100s kHz-10s MHz)
- **Magnetic nanoparticles (MNPs) convert alternating magnetic field (AMF) into heat via hysteresis**
- Heating depends on magnetic properties of MNPs, amplitude and frequency of AMF

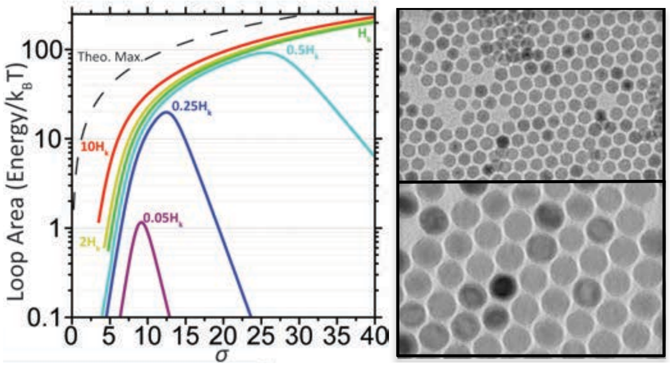
Pankhurst et al., J. Phys. D (2002)



Enabling Neuronal Magnetic Sensitivity

Materials Chemistry and Physics

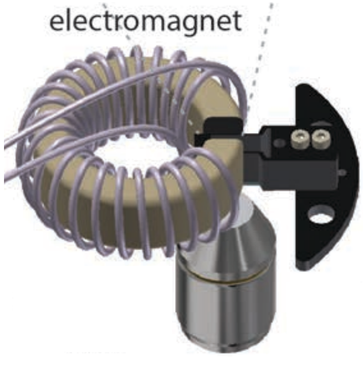
- Superparamagnetic nanoparticles with optimal AMF-to-heat conversion
- Size and magnetic anisotropy tuning through synthesis

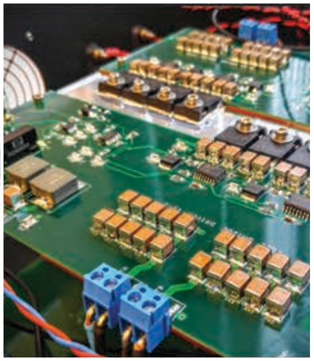


Chen et al. ACS Nano 2013
Chen et al. Nano Lett. 2016

Electronics

- Developing electromagnets and circuits that produce AMF to achieve heating in MNPs
- Simultaneous AMF stimulation and imaging apparatuses

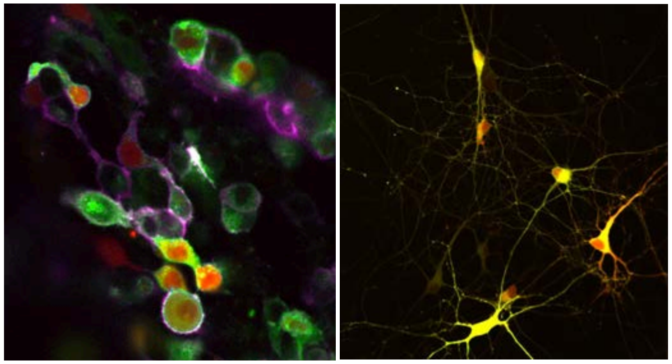




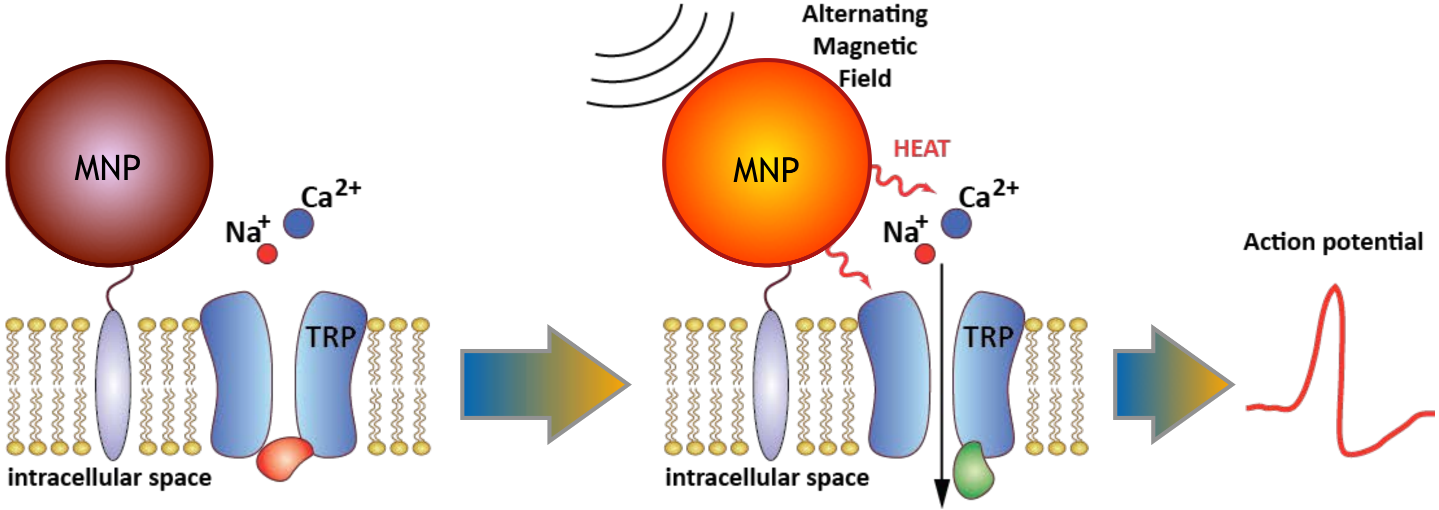
Christiansen et al. Appl. Phys. Lett 2014
Christiansen et al. Rev. Sci. Instr. 2017

Biology

- Thermo-genetic toolkit
- Nanoparticles conjugation to mammalian cells
- Excitation of heat-sensitive membrane proteins

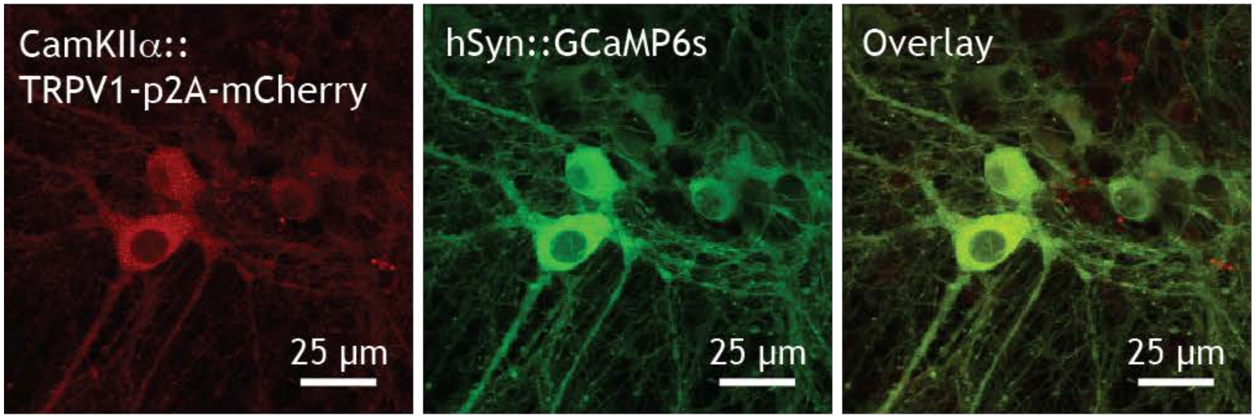


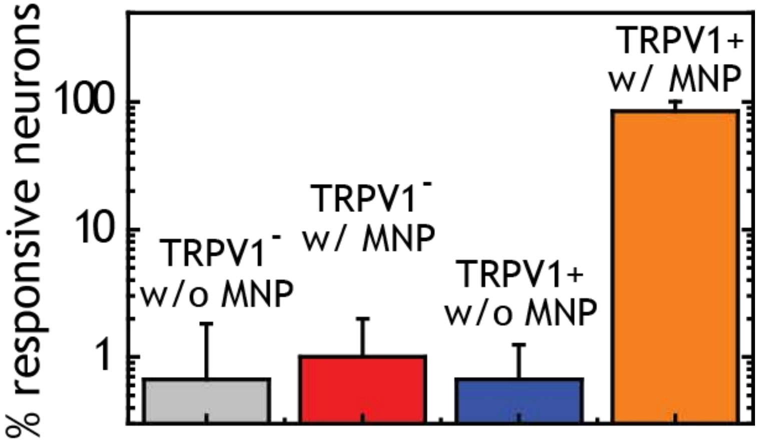
Chen et al. Science 2015
Romero et al. Adv. Funct. Mater. 2016



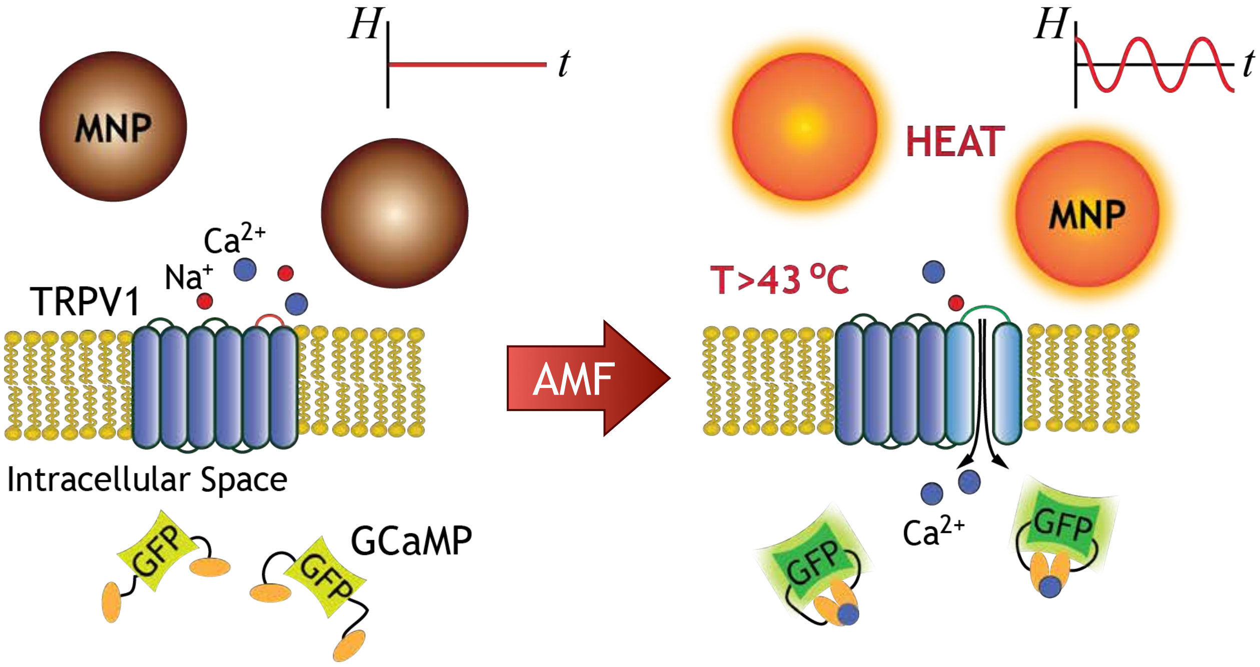
Huang et. al, Nat. Nano. 5 602-606 (2010), Stanley et. al, Science 336 604-608 (2012)

Magnetothermal Neural Stimulation





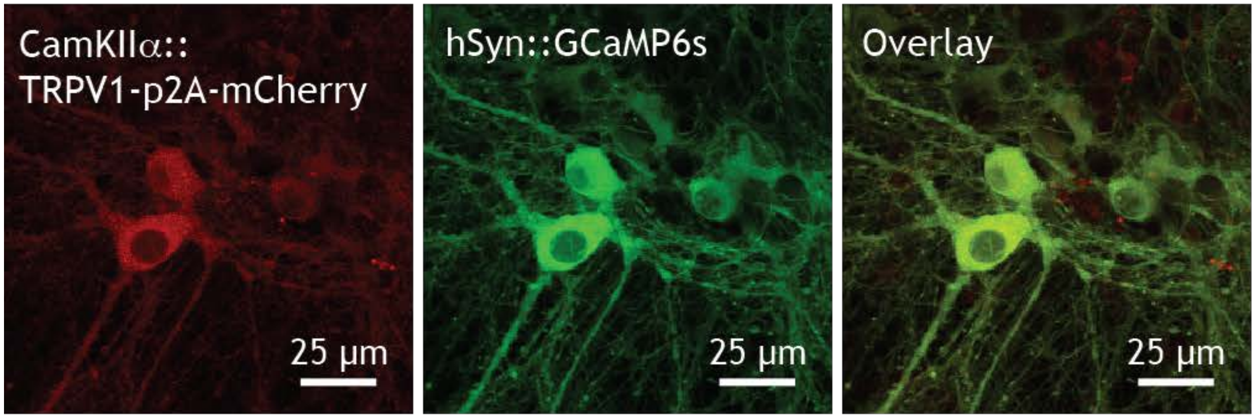
- Viral delivery enables 56% co-transfection efficiency for heat-sensor TRPV1 and Ca^{2+} indicator GCaMP6s

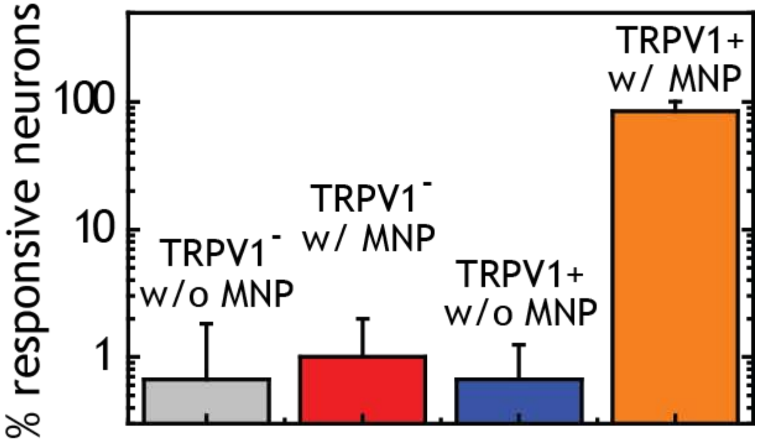


Chen, et al., Science 2015

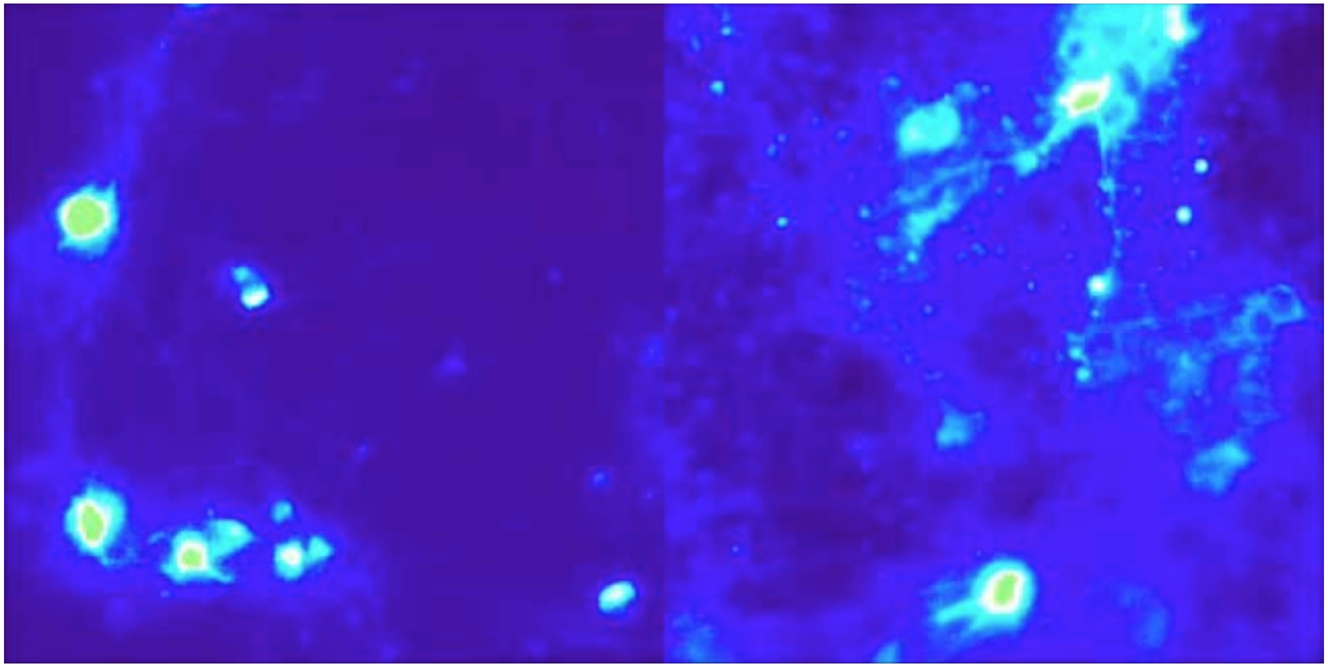
AMF = alternating magnetic field, H_0 = 15 kA/m, f = 500 kHz

Magnetothermal Neural Stimulation





- Viral delivery enables 56% co-transfection efficiency for heat-sensor TRPV1 and Ca^{2+} indicator GCaMP6s
- AMF robustly evokes neural activity in heat-sensitized primary neurons in the presence of MNP solutions



TRPV1$^-$, AMF ON TRPV1$^+$, AMF ON

Chen, et al., Science 2015

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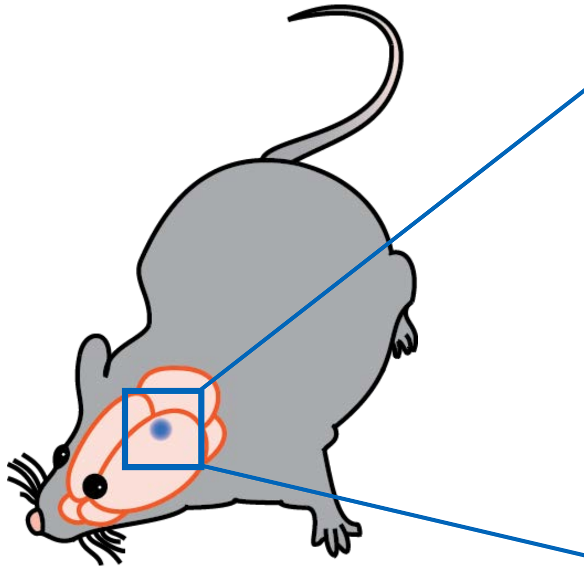
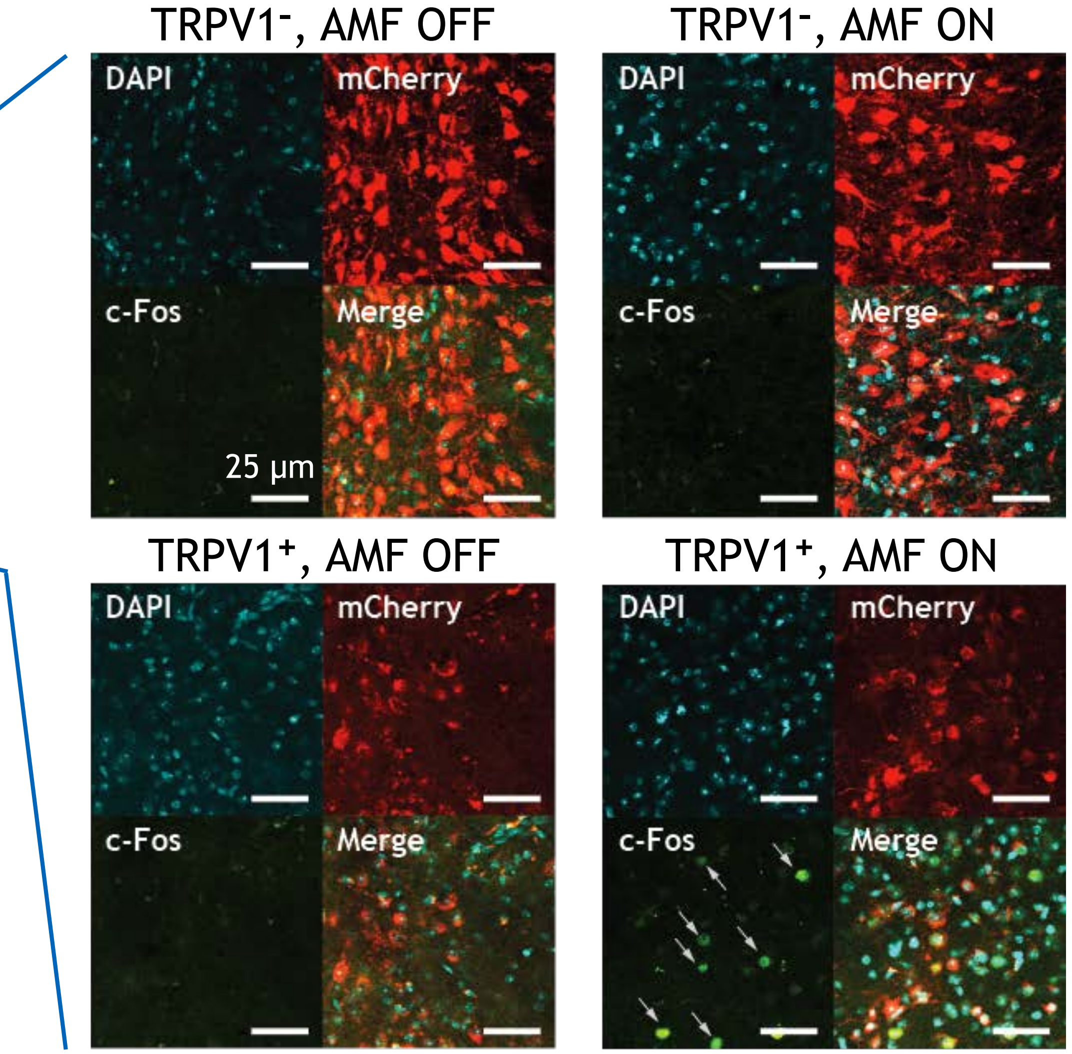
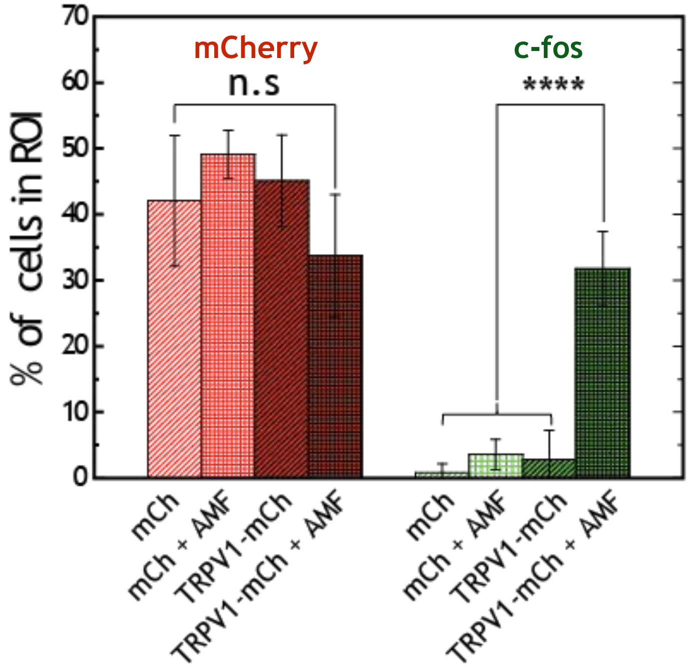
Magnetothermal Stimulation *In Vivo*







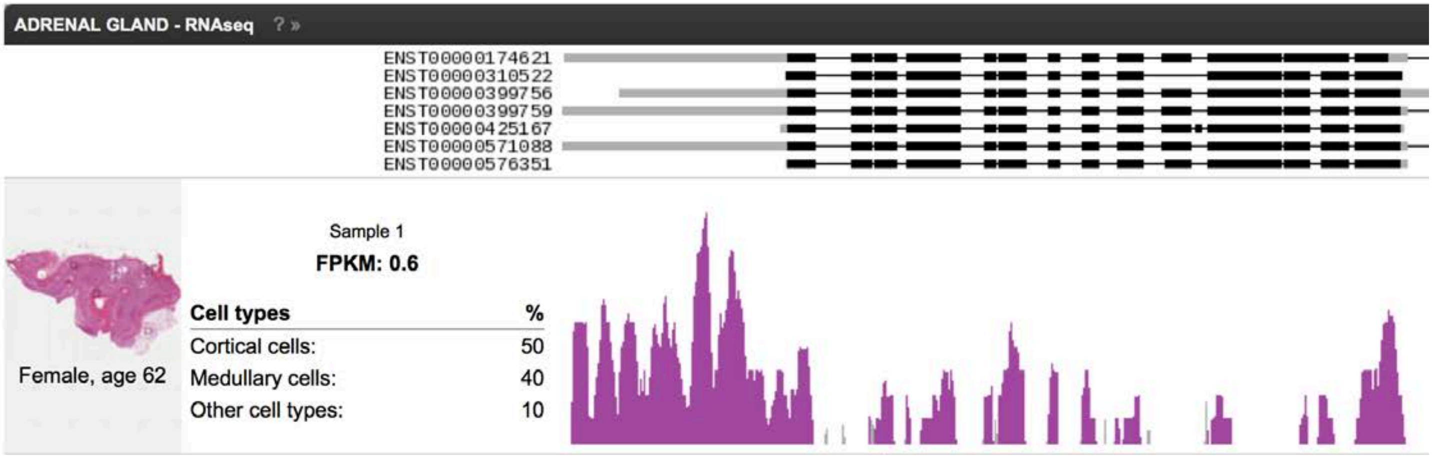
- MNP injection and AMF stimulation evokes neural activity *in vivo* (immediate early gene c-fos)
- No activity in the absence of AMF, MNPs, or TRPV1

Chen, et al., Science 2015

Beyond Transgenes: Endogenous TRPV1 Expression

Natural expression of TRPV1 in humans and rodents

(The Human Protein Atlas (http://www.proteinatlas.org), Yu et al. Mol. Biol. Rep. 2012)



ADRENAL GLAND - RNAseq ? »

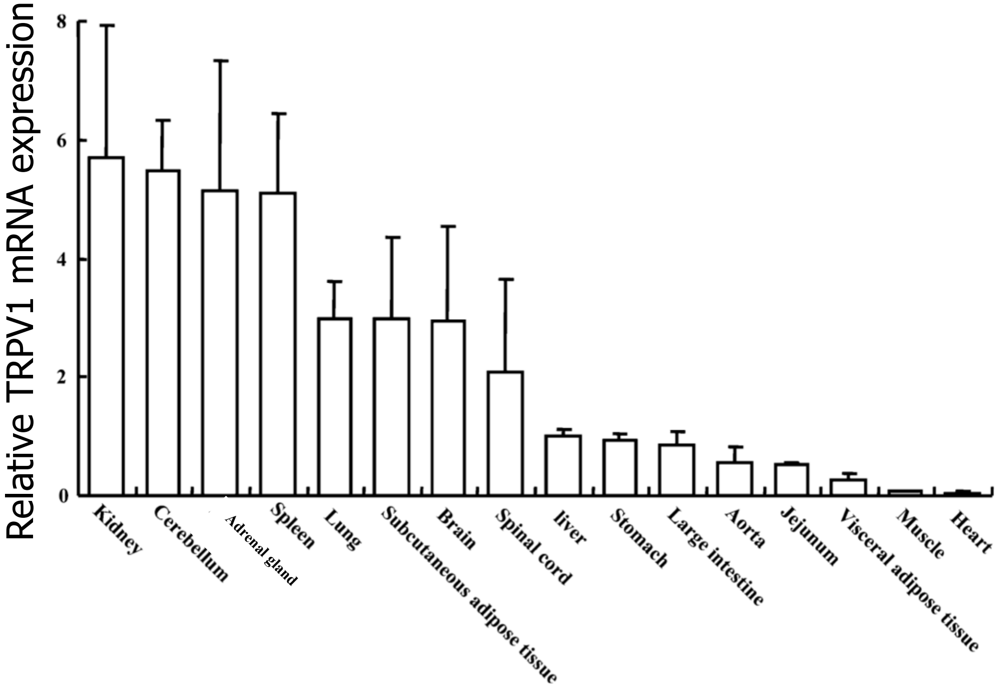
ENST00000174621
ENST00000310522
ENST00000399756
ENST00000399759
ENST00000425167
ENST00000571088
ENST00000576351

Female, age 62

Sample 1

FPKM: 0.6

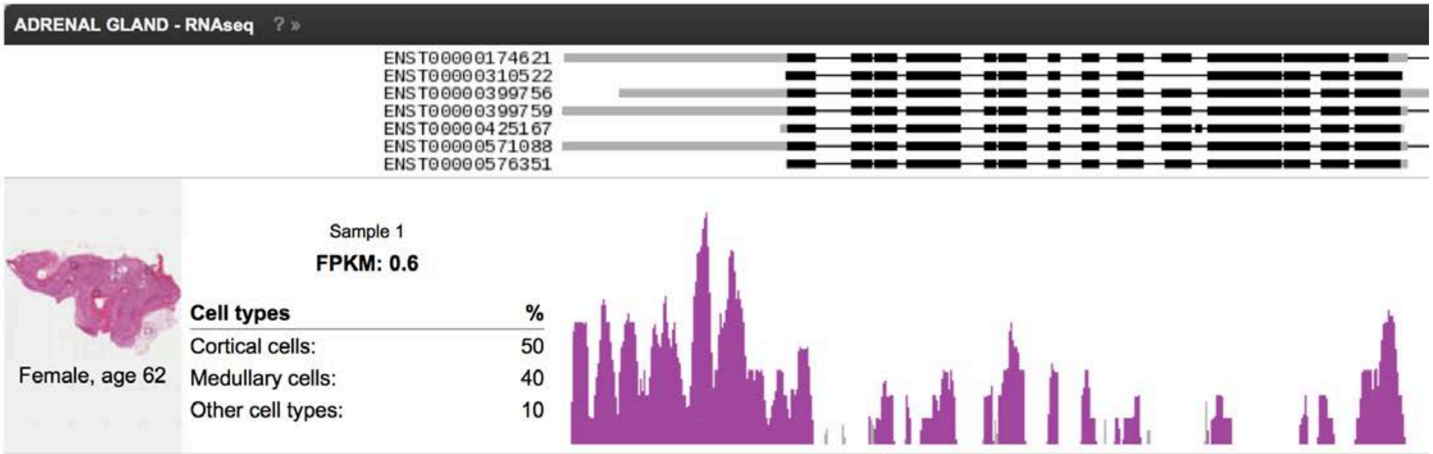
Cell types	%
Cortical cells:	50
Medullary cells:	40
Other cell types:	10



TRPV1 Expression in Adrenal Gland

Natural expression of TRPV1 in humans and rodents

(The Human Protein Atlas (http://www.proteinatlas.org), Yu et al. Mol. Biol. Rep. 2012)



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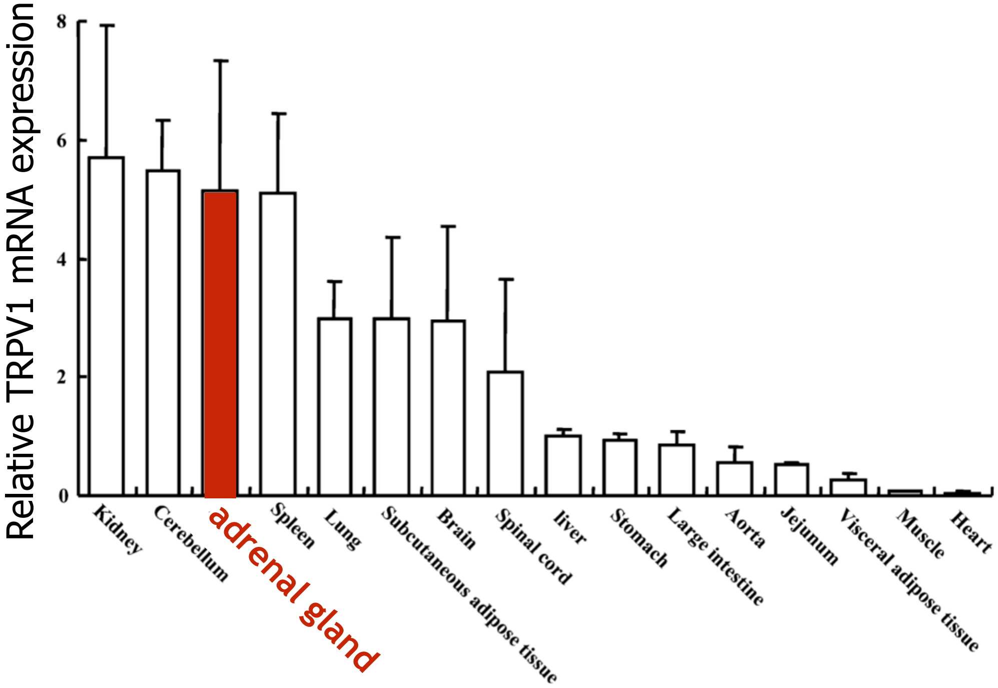


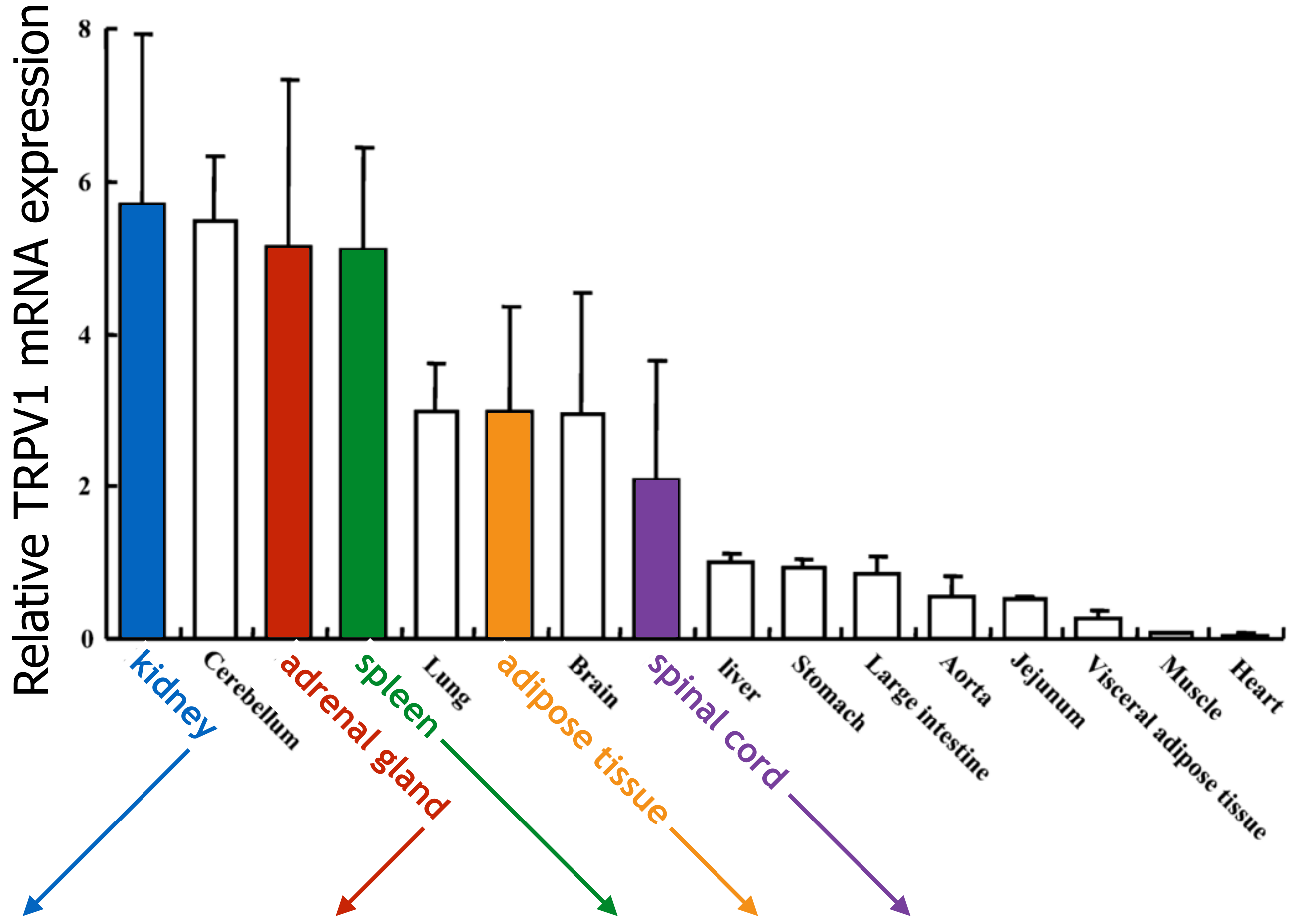
Magnetic Control of Adrenal Function

Several slides of unpublished data

TRPV1 Expression: Therapeutic Opportunities

Natural expression of TRPV1 in humans and rodents

(The Human Protein Atlas (http://www.proteinatlas.org), Yu et al. Mol. Biol. Rep. 2012)



Inflammation
Renal failure

Depression
Anxiety
Traumatic stress
Hypertension

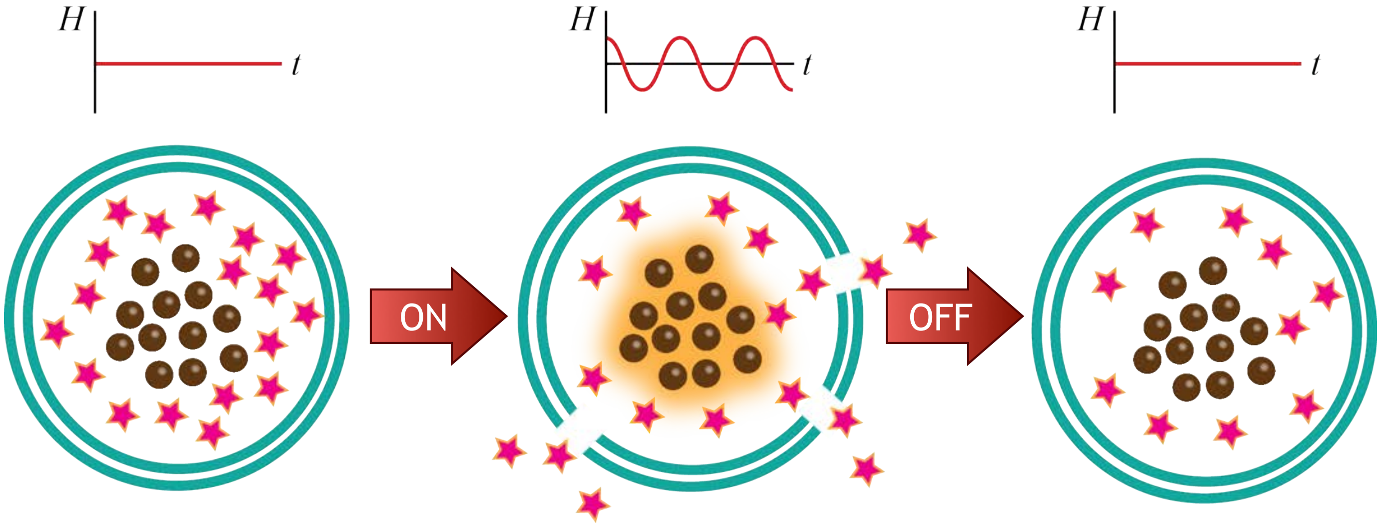
Infection
Anemia

Obesity

Pain

Magnetic Control of Drug Delivery

- Liposomes loaded with MNPs may allow for multiple cycles of drug release
- Liposomes are (mostly) agnostic to the pharmacological payload chemistry



Schuerle et al., Nano Lett. 2016
Rao et al., under review

Magnetic Control of Drug Delivery

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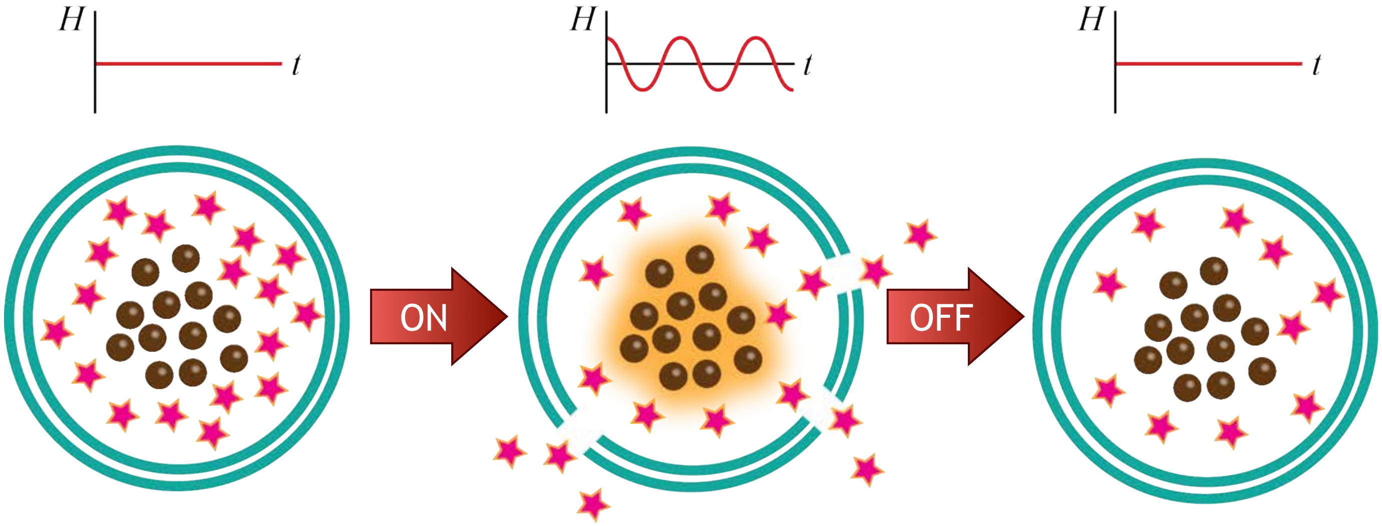
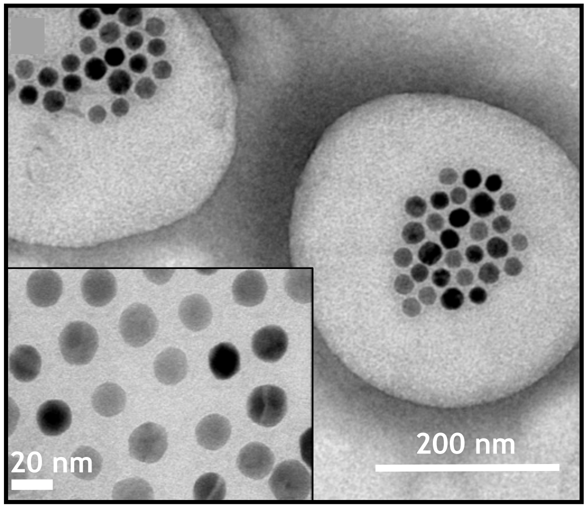
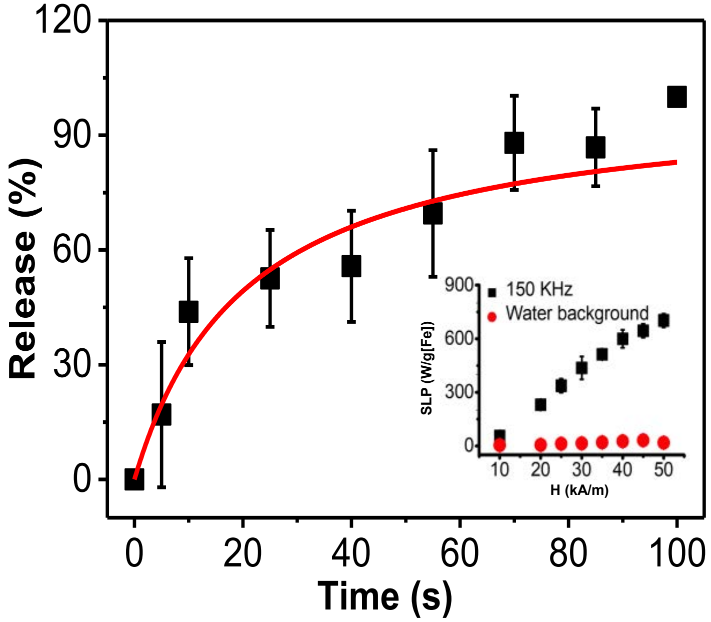






Schuerle et al., Nano Lett. 2016
Rao et al., under review

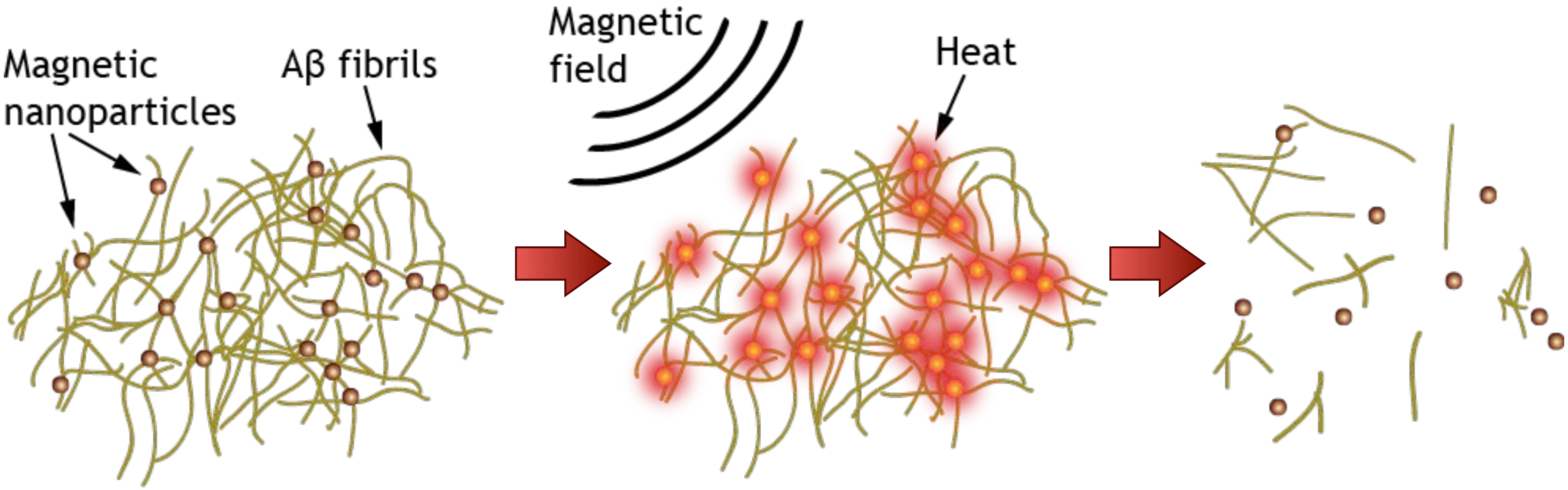
Magnetic Control of Drug Delivery

Several slides of unpublished data

Targeting Protein Aggregates with Nanoparticles

Hypothesis:

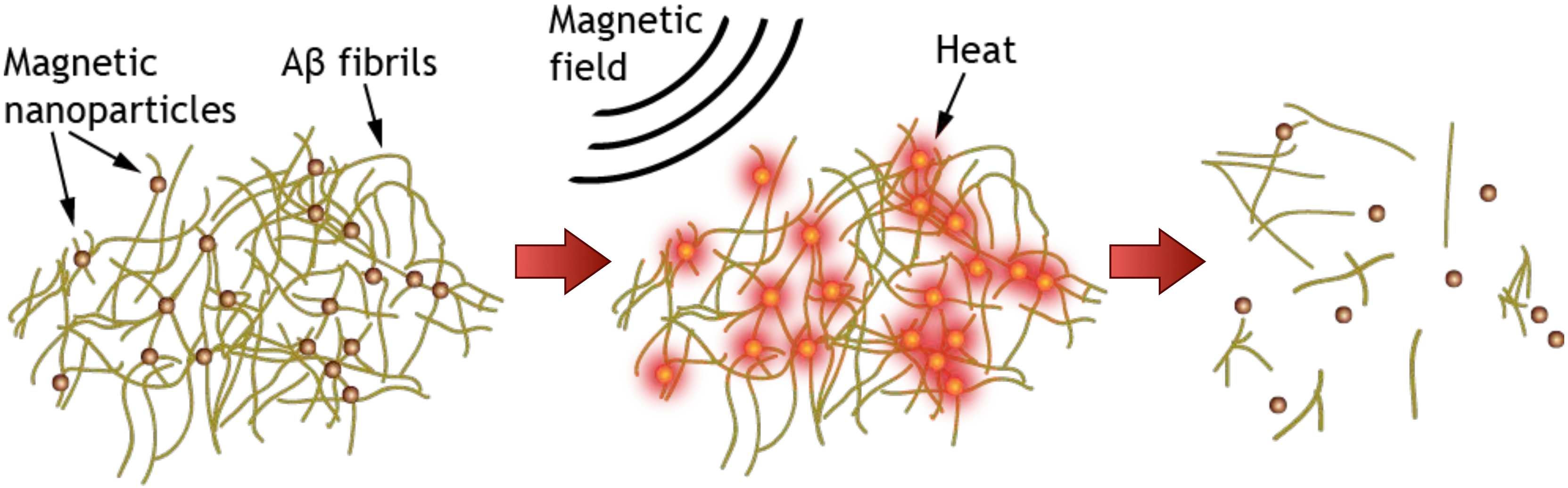
Local heating of magnetic nanoparticles (MNPs) in alternating magnetic fields (AMF) can destabilize ß-sheet structure and disaggregate Aß deposits:

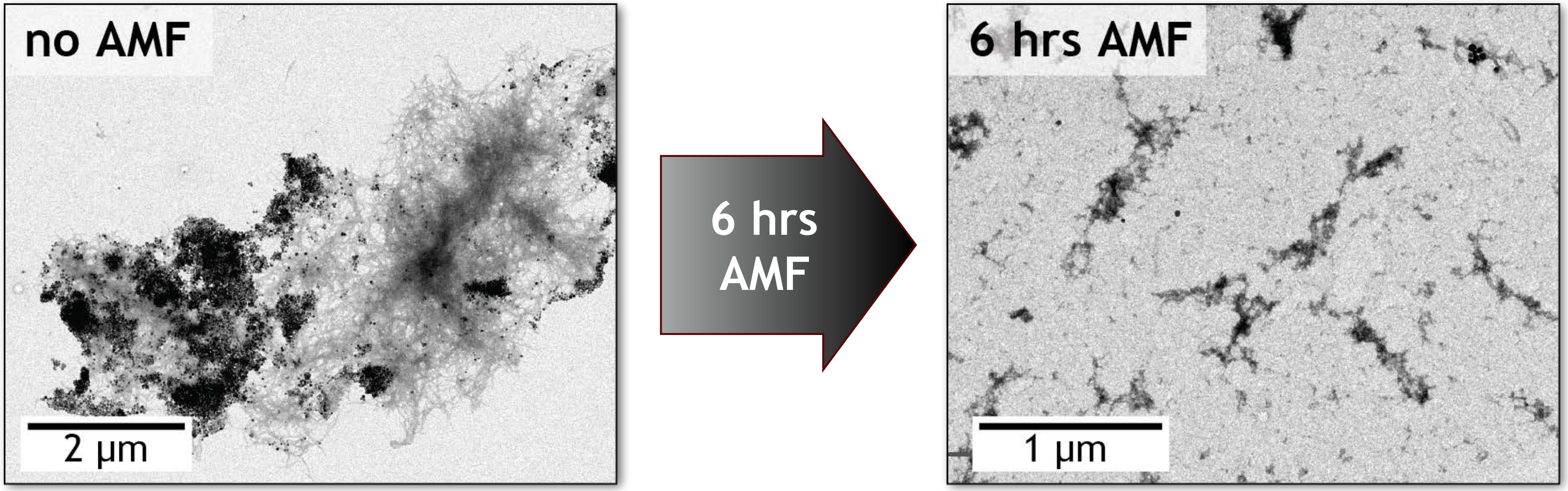


Loynachan, Romero, Christiansen, et al., Adv. Healthcare Mater. 2015

Targeting Protein Aggregates with Nanoparticles

Magnetic heating of targeted MNPs breaks up microscale Aβ aggregates into nanoscale fibrils.

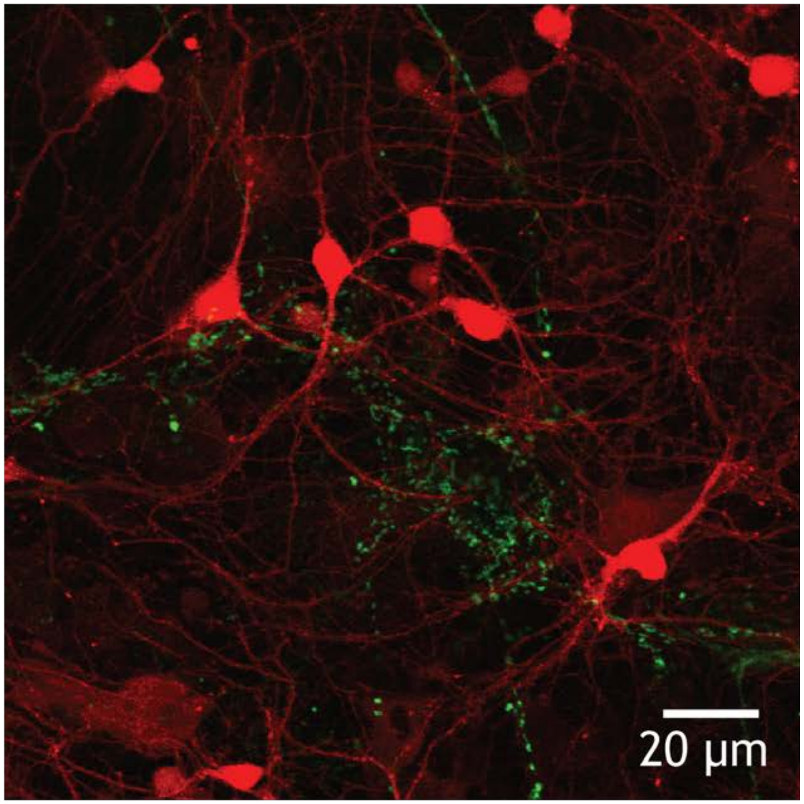


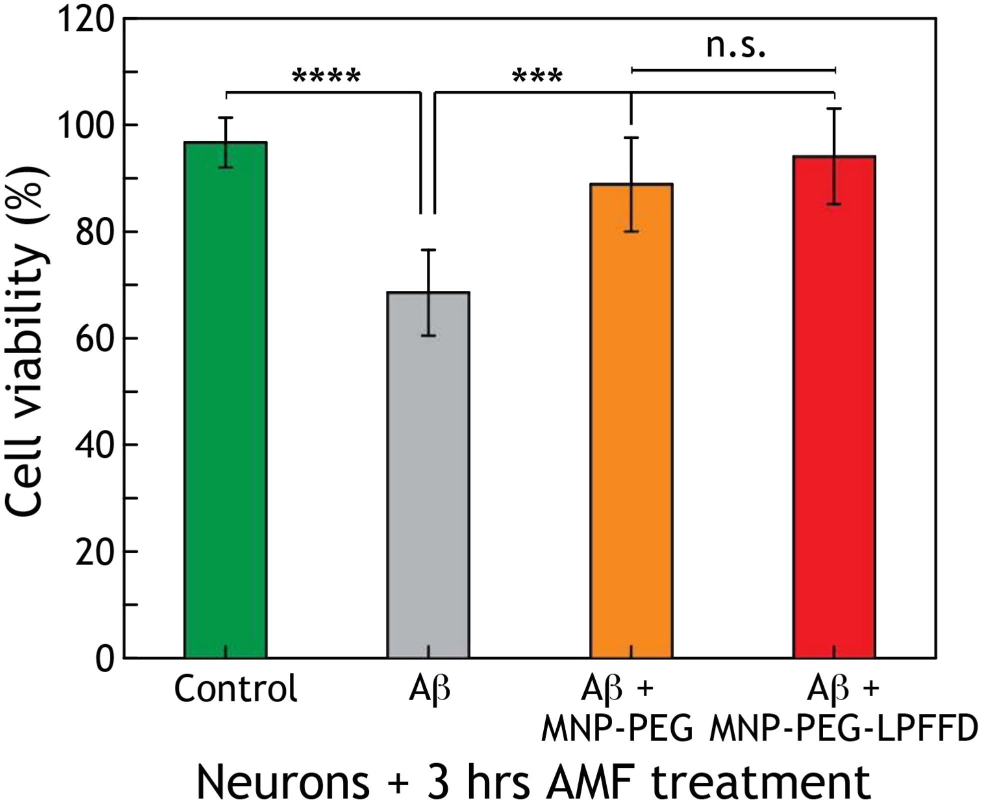


Loynachan, Romero, Christiansen, et al., Adv. Healthcare Mater. 2015

Targeting Protein Aggregates with Nanoparticles

Targeted magnetothermal disaggregation of Aß deposits improves neuronal viability *in vitro*.

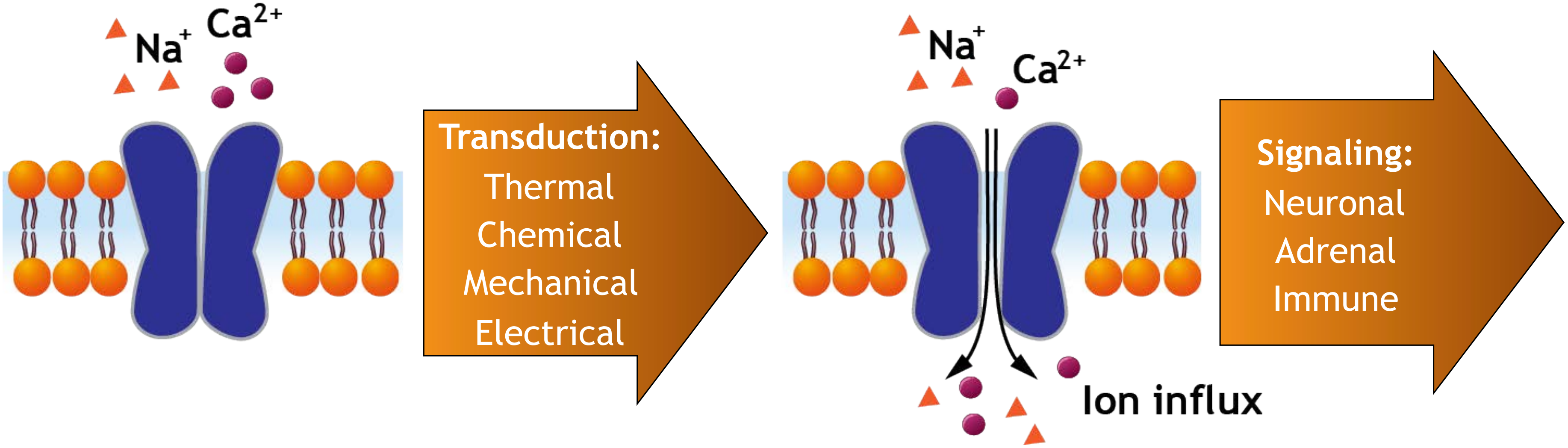




Loynachan, Romero, Christiansen, et al., Adv. Healthcare Mater. 2015

Materials Design for Future Theranostics

- Interfacing with the nervous system implies embracing complexity:
  Billions of neurons, trillions of synapses, hundreds of (known) neurotransmitters
- Ion channels and receptors are nanometer-sized “biological machines”
  Interfacing with these nano-machines demands nanoscale tools
- Materials design may deliver “interpreters” between the languages
  of synthetic electronics and those of ion channels or neural circuits.



Transduction:
Thermal
Chemical
Mechanical
Electrical

Signaling:
Neuronal
Adrenal
Immune

Fiber-Based Actuators

Several slides of unpublished data

rle AT MIT

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CMSE MIT Center for Materials Science and Engineering
MTL microsystems technology laboratories massachusetts institute of technology
NSF
NIH National Institute of Mental Health
DARPA
NIH National Institute of Neurological Disorders and Stroke