BISP 194 Special Topics in Modern Biology

Neural Prostheses

Winter 2008

Overview and Introduction

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Neural Prostheses
(*aka* Neural Prosthetics *aka* Neuroprosthetics)

(the art of designing) devices which restore or supplement function of the nervous system lost by disease or injury

- **Highly interdisciplinary subject**
  - at the interface between neuroscience and engineering
    - *analysis vs. synthesis*
- **Emerging discipline**
  - rapid advances in technology
  - slow transition from neuroscience/engineering research to medical practice
- **Several opportunities for learning**
  - learning about the latest advances in neurotechnology
  - learning to interpret and critically evaluate the literature

Neural Prostheses
Overview

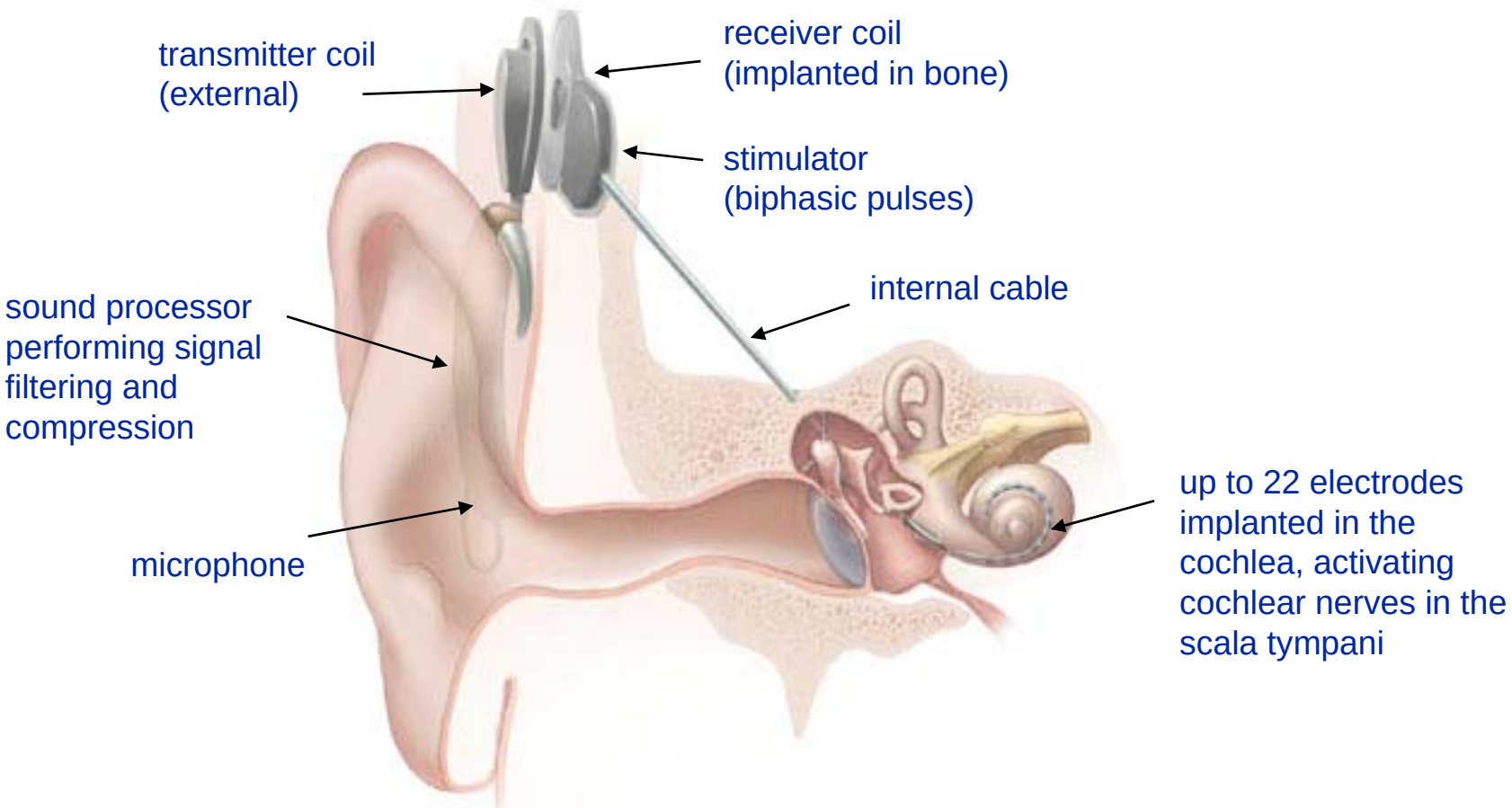
- **Sensory prostheses**
  - Cochlear implant for restored hearing
    - *The oldest, and the only widely used neural prosthesis*
  - Retinal implant for restored vision
    - *Largest current R&D investment (Second Sight in USA, and several groups in Taiwan, Japan, and Germany)*
- **Motor prostheses**
  - Functional neuromuscular stimulation
- **Brain prostheses**
  - Deep-brain stimulation
    - *Parkinson tremor remediation*
  - Neuromorphic and biomorphic systems

Sensory Prostheses

Cochlear Implant

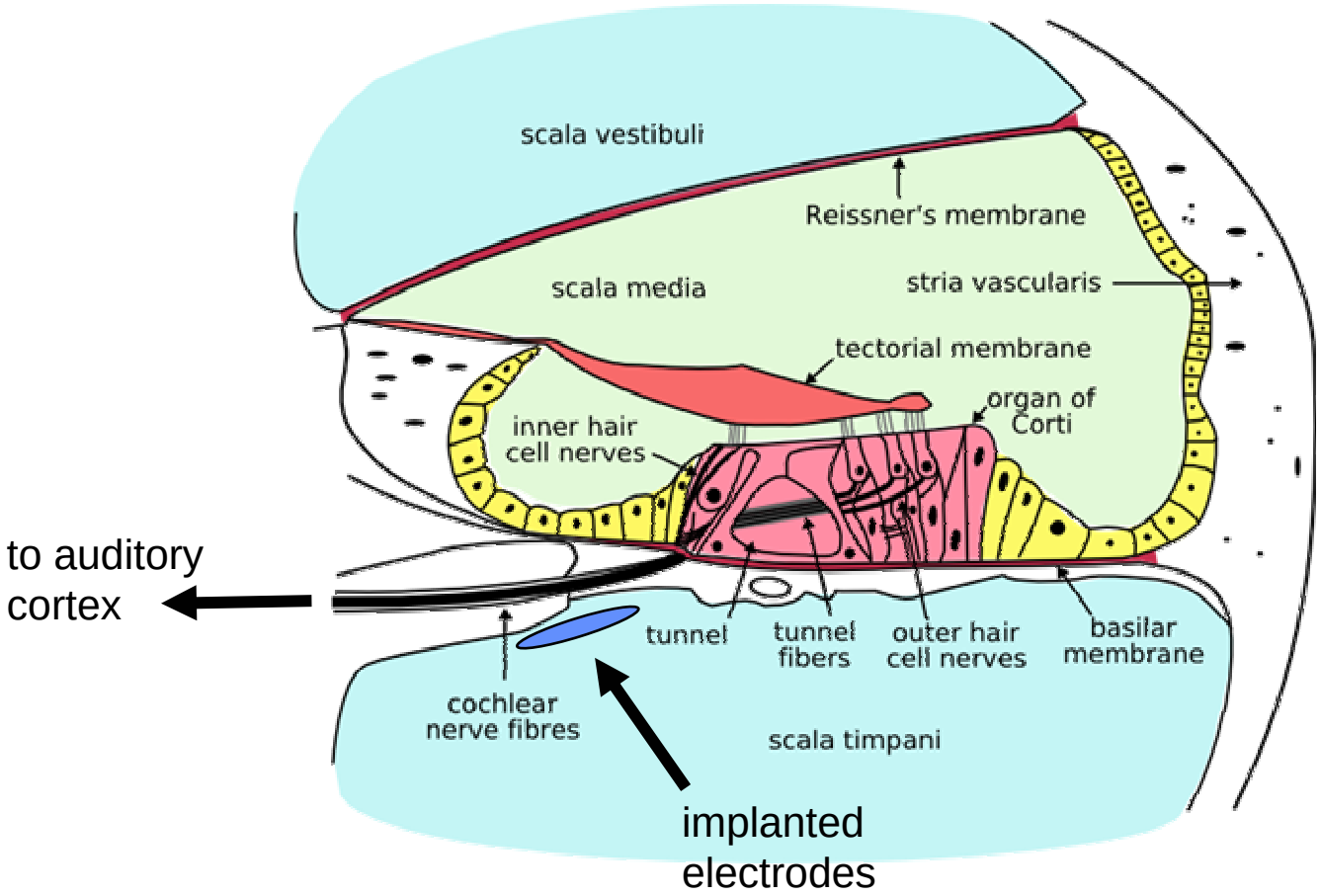
Retinal Implant

Cochlear Implant



- First cochlear implant by Djourno and Eyriès (1957)
- First multi-channel cochlear implant by Graeme Clark (1978)
- First audible-quality implant using Continuous Interleaving Conditioning (CIS) by Wilson et at (1991)

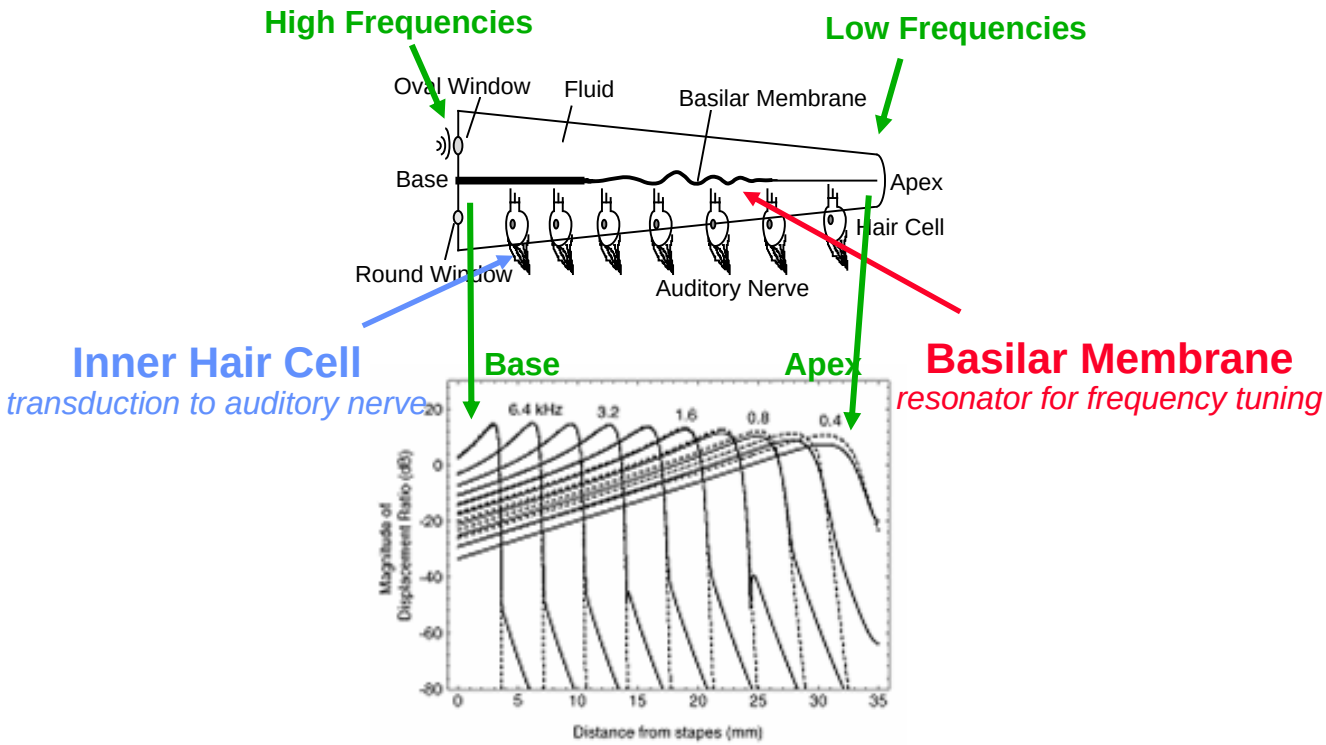
Cochlea Cross Section



- Inner hair cells excited by basilar membrane vibrations, amplified by outer hair cells, stimulate cochlear nerve fibers in the healthy cochlea.
- Electrodes in the cochlear implant stimulate cochlear nerve fibers with alternating current signals, of amplitude representative of sound intensity.

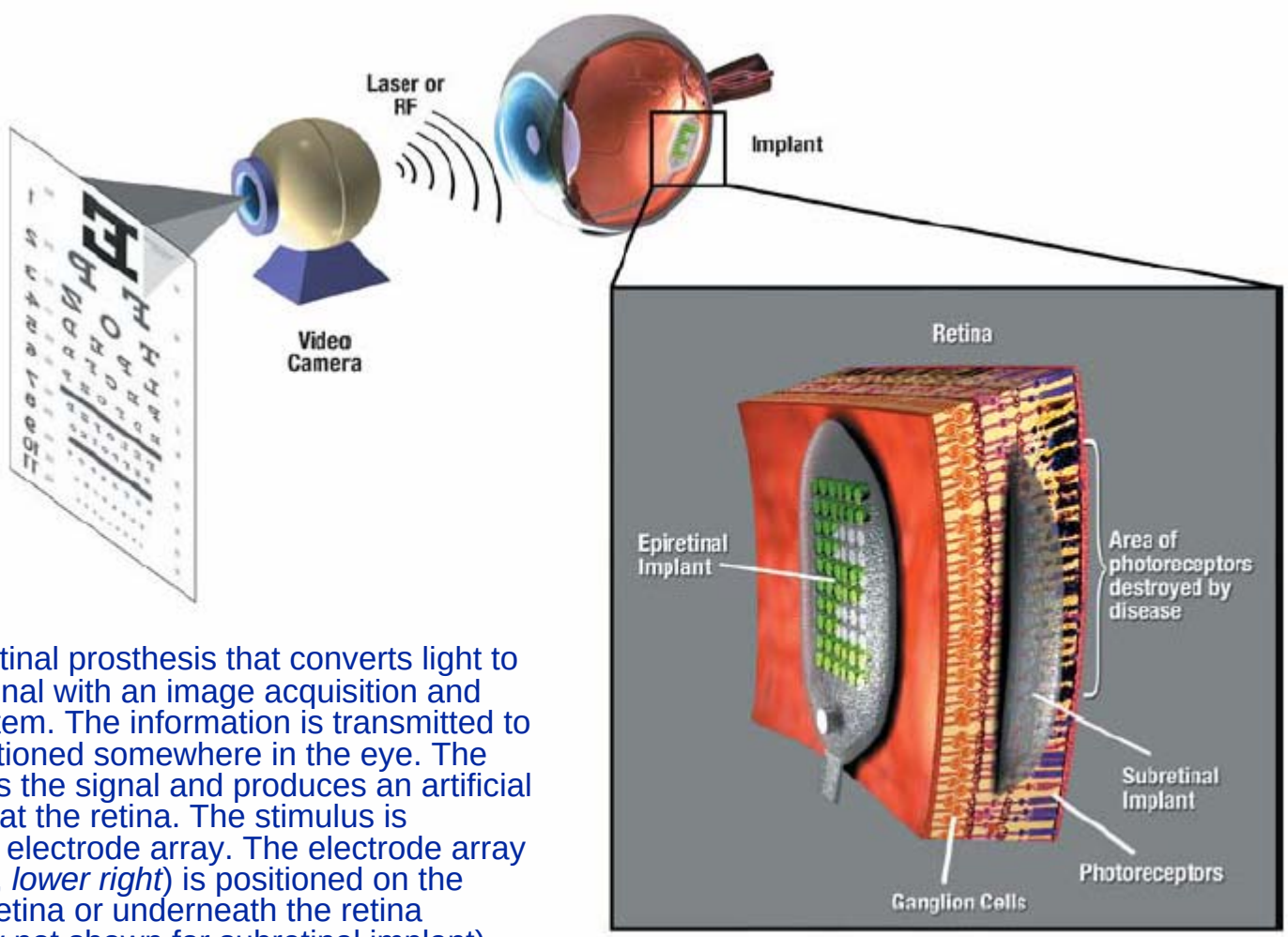
http://en.wikipedia.org/wiki/Image:Cochlea-crosssection.png

Silicon Cochlea and Auditory Periphery



- Fluid-filled cochlea transduces sound to resonant mechanical vibrations of the basilar membrane
  - *Characteristic frequency-space coding*
- Hair cells transduce membrane deflections to auditory nerve impulses
  - *Amplitude and time encoding with spikes*

Retinal Implant

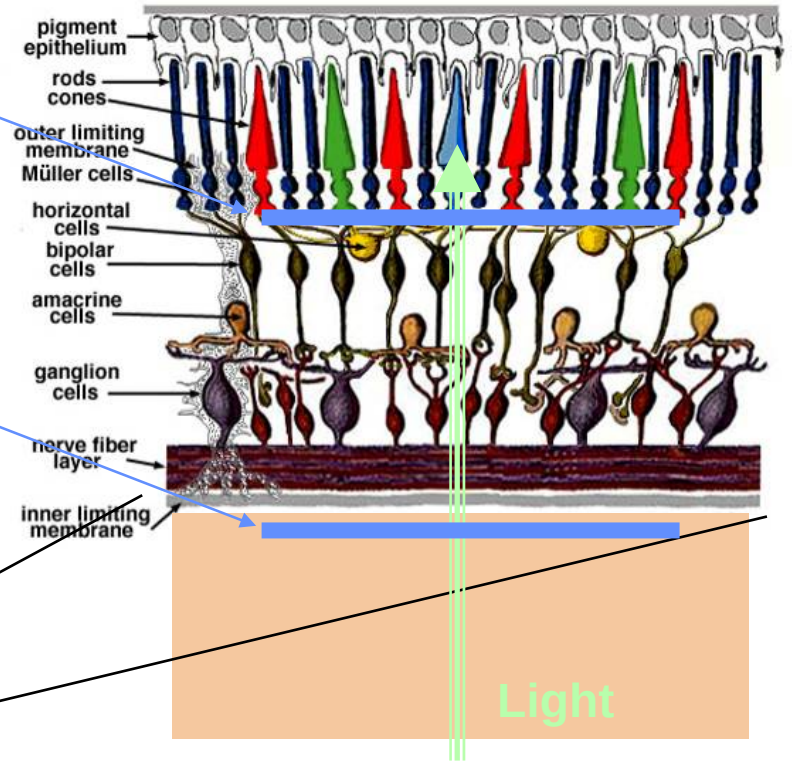


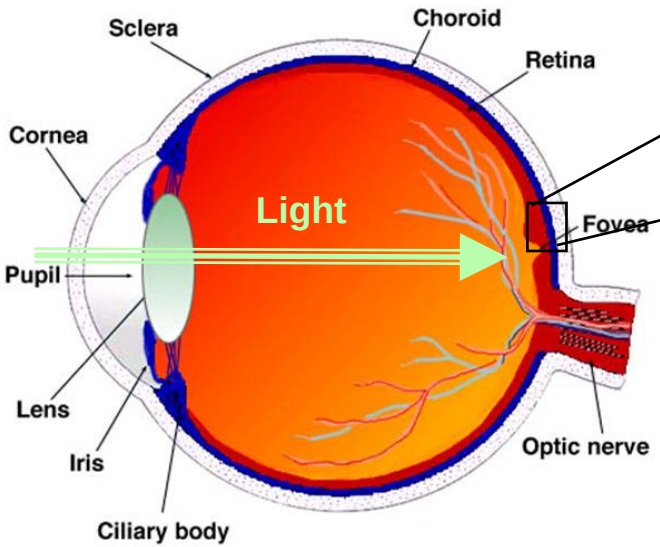
Concept of a retinal prosthesis that converts light to an electrical signal with an image acquisition and processing system. The information is transmitted to an implant positioned somewhere in the eye. The implant receives the signal and produces an artificial stimulus signal at the retina. The stimulus is delivered by an electrode array. The electrode array (*shown in inset*, *lower right*) is positioned on the surface of the retina or underneath the retina (electrode array not shown for subretinal implant).

J.D. Weiland, W. Liu, M.S. Humayun, Ann. Rev. Biom. Eng., vol. 7, 2005

Retina and Visual System

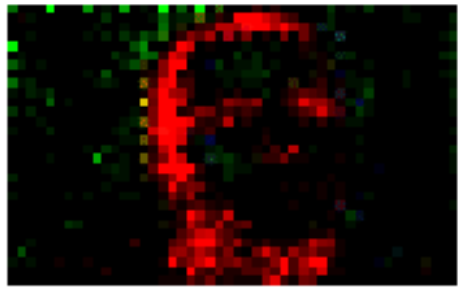
- **Subretinal implant**
  - uses intact retinal processing, accessing bipolar cells
  - surgically more involved, constraining device sizing
- **Epiretinal implant**
  - uses silicon retina to emulate retinal processing
  - easier to integrate and interface





J.D. Weiland and M.S. Humayun, IEEE EMB Mag., Sept/Oct 2006.

Silicon Retina



- Mimics retinal processing in a silicon chip
  - *Neuromorphic*
    - *imitating form and function of neurobiology*
  - *Integrated photosensors (rods)*

Boahen, "Neuromorphic Chips", Scientific American, May 2005

Brain Prostheses

Deep Brain Stimulation

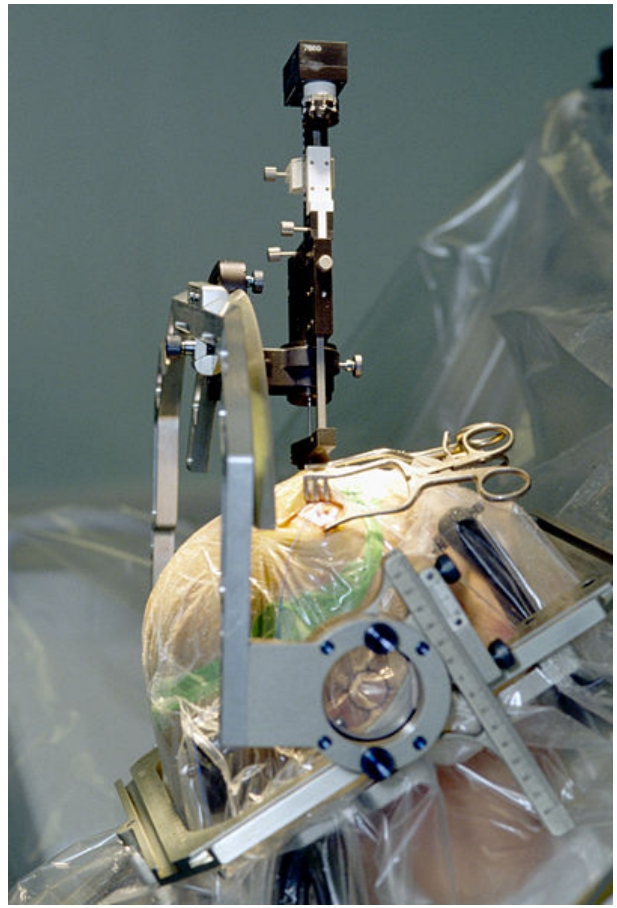
Cortical Vision Prostheses

Implantable Electrode Arrays

Deep Brain Stimulation (DBS)

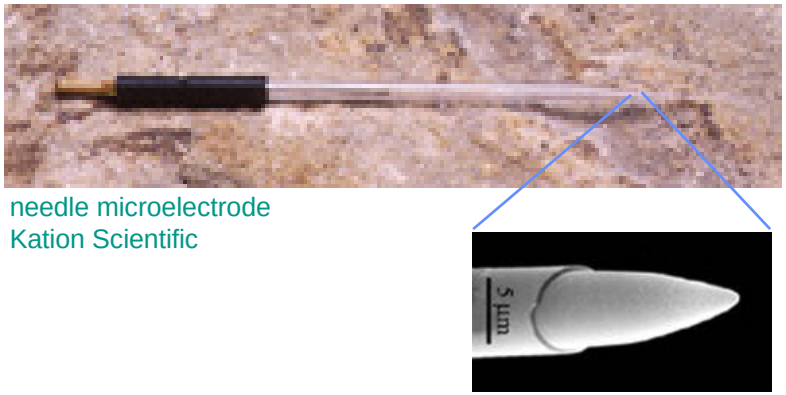
for Parkinson's Disease Tremor Remediation

- "Brain's pacemaker"
  - *Electrode is implanted in the brain's thalamus*
  - *Periodic (130-185Hz) activation of electrical impulses delivered by the electrode suppresses Parkinson-induced tremor*
- Invasive procedure
  - *Surgical insertion of electrode and stimulation electronics*
  - *Battery needs to be replaced*



Surgery to insert electrode deep in the brain. Parkinson's patient remains awake during surgery. http://en.wikipedia.org/wiki/Deep_brain_stimulation

Electrodes



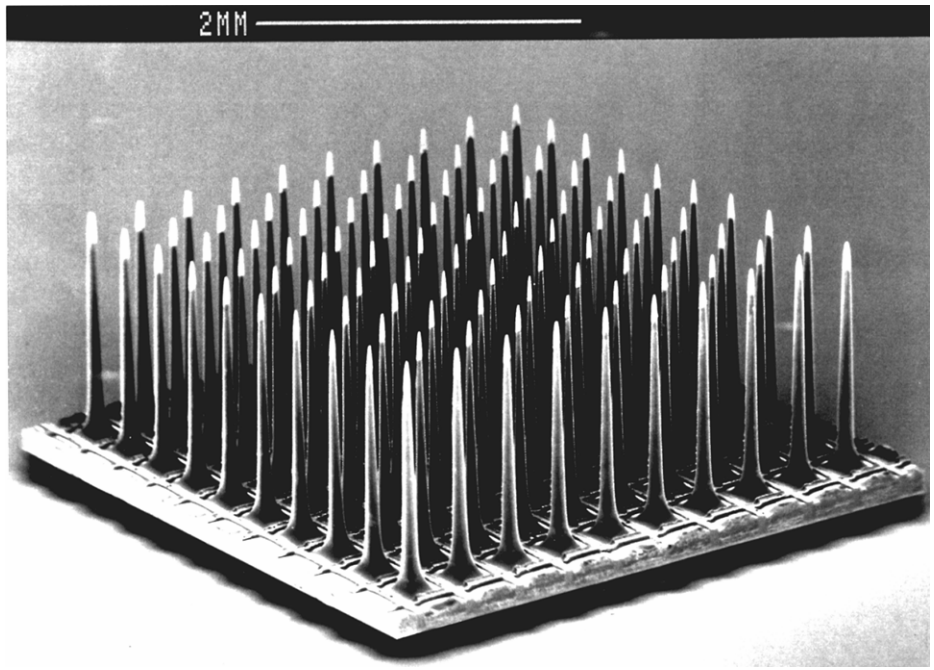
needle microelectrode
Kation Scientific

- **Needle electrode**
  - Metal, typically Tungsten
  - Electrical contact impedance in 10kΩ to 1MΩ range
  - Penetration through neural tissue

active EEG gel-contact electrode
Biosemi

- **Flat electrode**
  - Higher impedance
  - Mostly for external use and on neural surface
    - *scalp EEG (electroencephalogram) recording*
    - *retinal implants*

Electrode Arrays



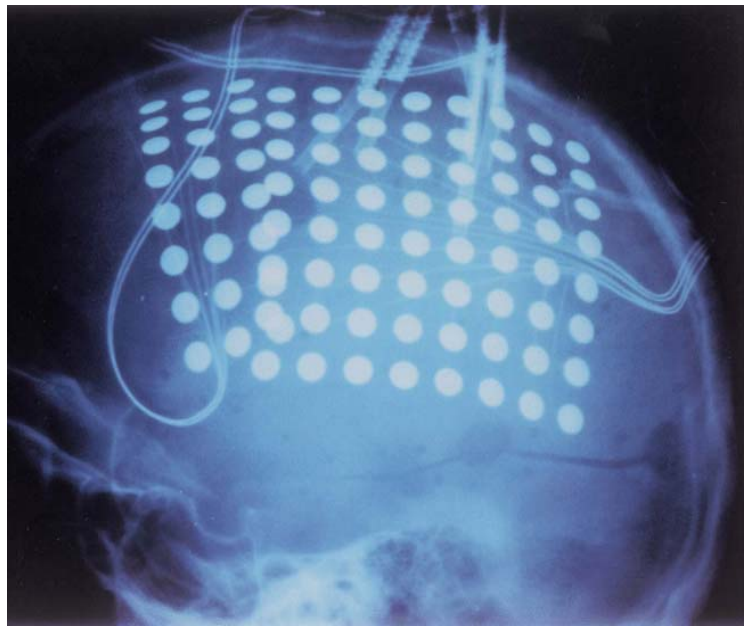
"Utah array"
Normann laboratory, University of Utah, 2003

- **Penetrating electrode arrays**
  - Typically silicon based, fabricated in MEMS (microelectromechanical systems) process
  - Cortical vision implants
- **Flat electrode arrays**
  - Retinal implants
  - Electrocorticogram (ECoG) monitoring systems

Electrocorticogram (ECoG)

Implanted epilepsy grid electrodes

www.mayoclinic.com



- **Cortical surface electrodes**
  - Higher spatial resolution than scalp EEG
- **Epilepsy monitoring**
  - Preparation for surgery to remove focus of epileptic activity, avoiding critical brain functional areas

Implantable Wireless Telemetry

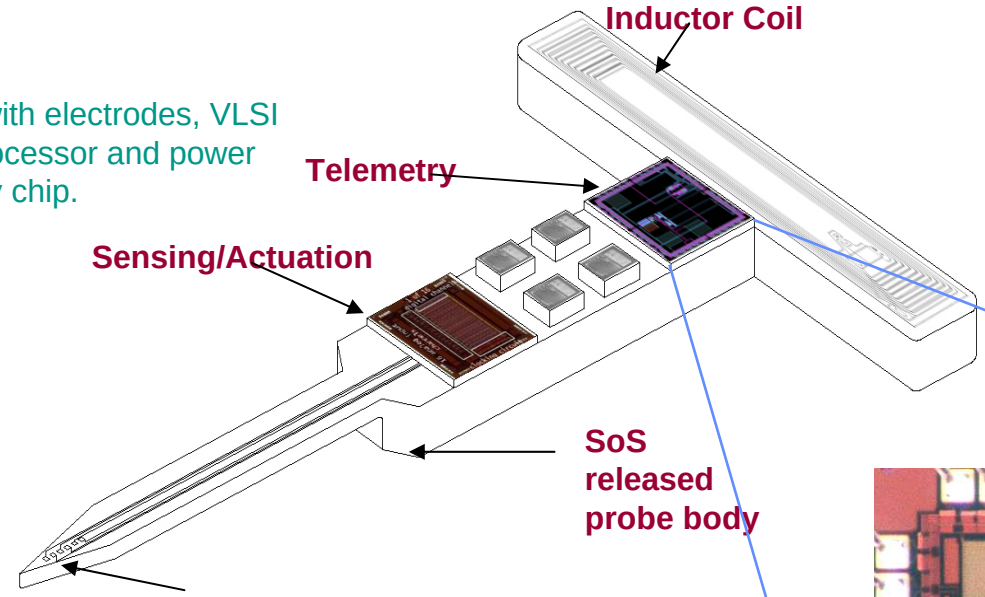
- **Transcutaneous wires limit the application of implantable sensing/actuation technology to neural prostheses**
  - Risk of infection
    - *Opening through the skin reduces the body's natural defense against invading microorganisms*
  - Limited mobility
    - *Tethered to power source and data logging instrumentation*

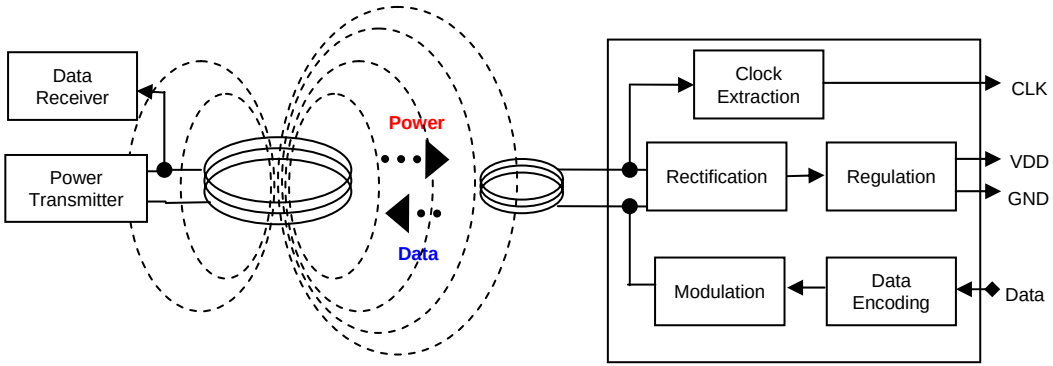
- **Wireless technology is widely available, however:**
  - Frequency range of radio transmission is limited by the body's absorption spectra and safety considerations
    - *Magnetic (inductive) coupling at low frequency, ~1-4 MHz*
    - *Very low transmitted power requires efficient low-power design*

Sauer, Stanacevic, Cauwenberghs, and Thakor, 2005

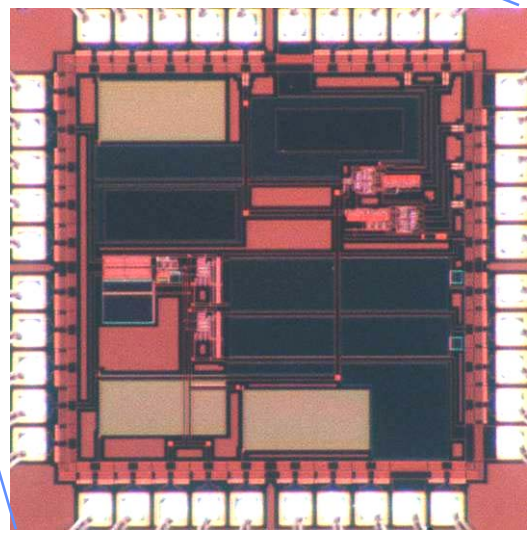
Implantable Wireless Telemetry

Implantable probe with electrodes, VLSI sensor/actuation processor and power harvesting telemetry chip.





Power delivery and data transmission over the same inductive link



Telemetry chip (1.5mm X 1.5mm)

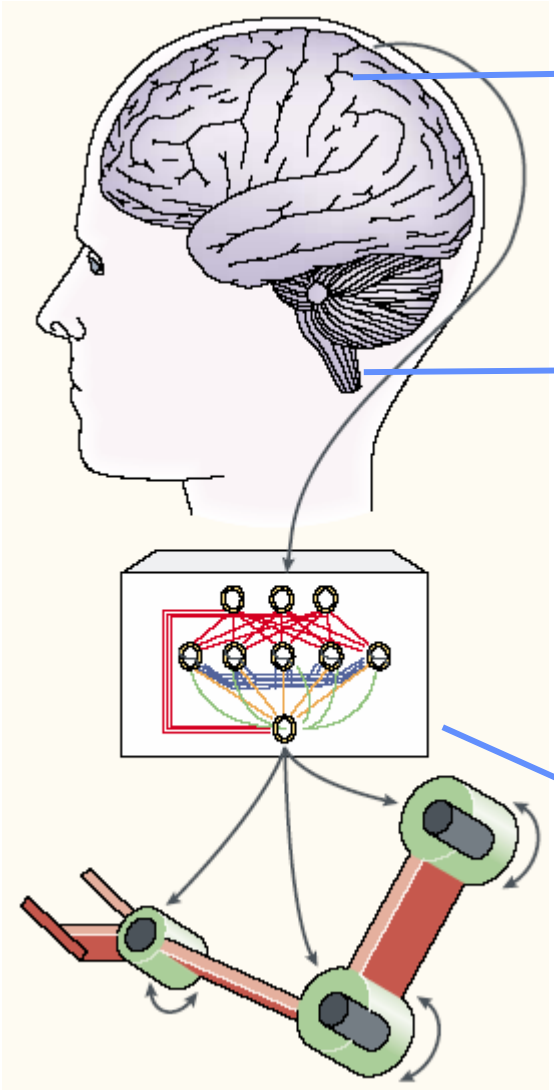
Sauer, Stanacevic, Cauwenberghs, and Thakor, 2005

Motor Prostheses

Brain Machine (Computer) Interfaces

Implantable Electrode Arrays

Brain Computer Interfaces and Motor Control



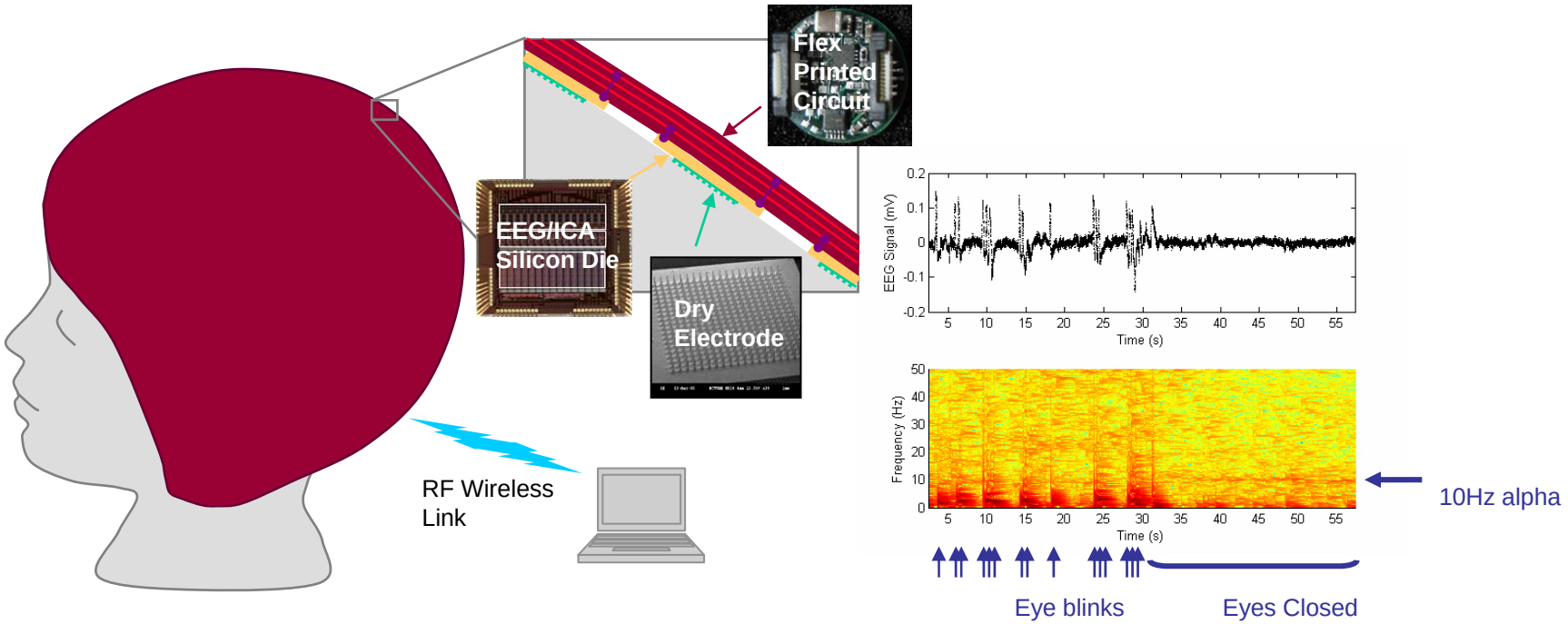
- **The brain's motor commands …**
  - Parietal/frontal cortex
    - *Implanted electrodes*
    - *Electroencephalogram (EEG)*
      - *Cortical signals, noninvasive*
      - *Low bandwidth (seconds)*
  - Nerve signals
    - *Spinal cord electrodes*
    - *Electromyogram (EMG)*
      - *Muscle signals, noninvasive*
      - *Higher bandwidth (milliseconds)*

… translated into motor actions

- Machine learning/signal processing
- Neuromorphic approaches
  - *Central pattern generators (CPGs)*

Nicolelis, Nature Rev. Neuroscience 4, 417, 2003

Wireless EEG/ICA Neurotechnology



- **Integrated EEG/ICA wireless EEG recording system**
  - Scalable towards 1000+ channels
  - Dry contact electrodes
  - Wireless, lightweight
  - Integrated, distributed independent component analysis (ICA)

Sullivan, Deiss, Jung and Cauwenberghs, 2007

Emerging Technologies

Nanotechnology

- Nanoparticles interacting with cells
- Carbon nanofibers for enduring nanoelectrodes

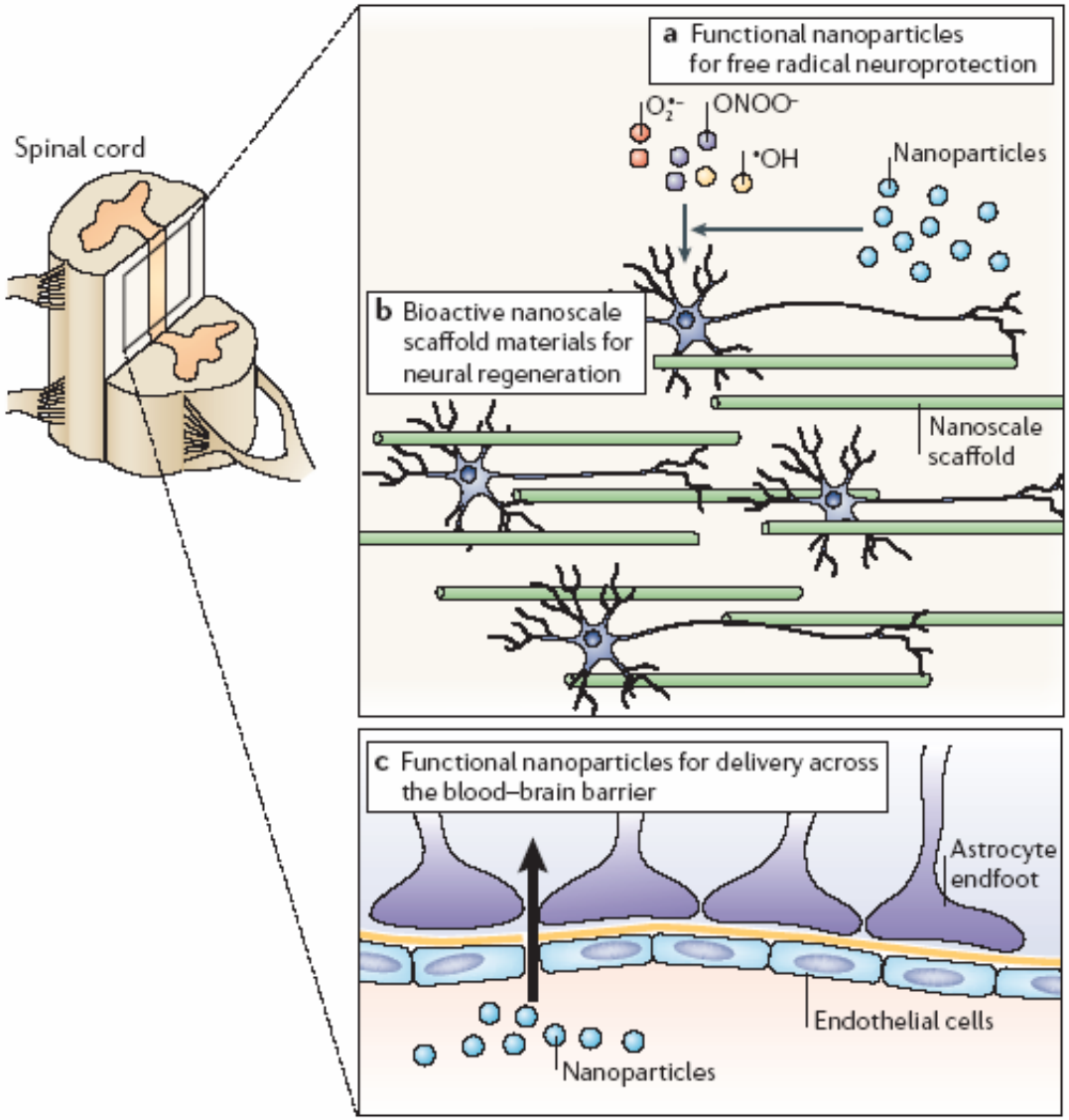
Molecular optics

- ChR2 optical activation of targeted neurons
- NPhR optical inactivation of targeted neurons

Spinal cord regeneration

Others …

Clinical Neuroscience Nanotechnology



Applications of nanotechnology in clinical neuroscience.

Nanotechnology can be used to limit and/or reverse neuropathological disease processes at a molecular level or facilitate and support other approaches with this goal. **a**: Nanoparticles that promote neuroprotection by limiting the effects of free radicals produced following trauma (for example, those produced by CNS secondary injury mechanisms). **b**: The development and use of nanoengineered scaffold materials that mimic the extracellular matrix and provide a physical and/or bioactive environment for neural regeneration. **c**: Nanoparticles designed to allow the transport of drugs and small molecules across the blood–brain barrier.

Gabriel A. Silva, "Neuroscience nanotechnology: progress, opportunities and challenges," *Nature Reviews Neuroscience,* vol. 7, pp. 65-74, January 2006.

Carbon Nanofibers for Enduring Nanoelectrodes

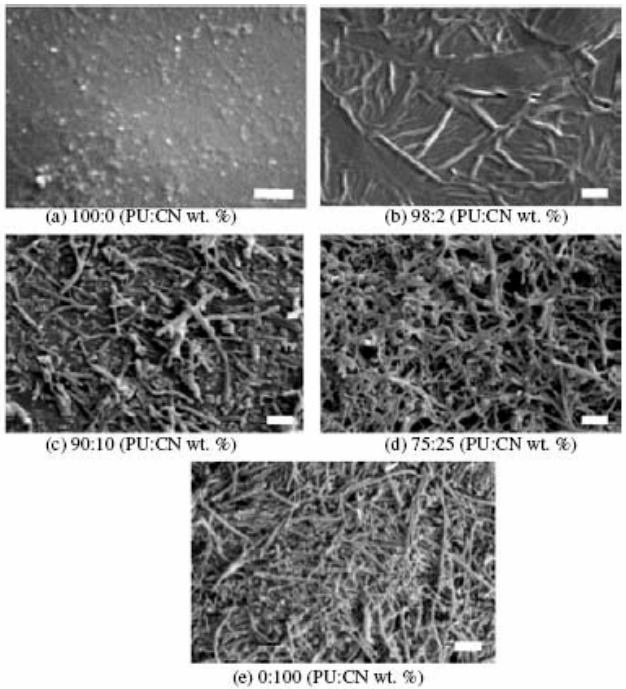


Figure 1. Representative SEM images of PU:CN composites. Scale bar = 1 μm.

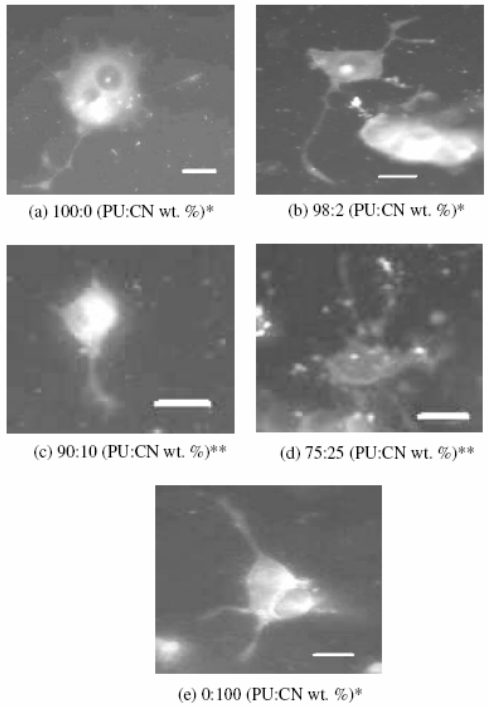


Figure 3. Representative images of optimal neurite extension for neurons cultured on all PU:CN materials. *Scale bar = 10 μm; **scale bar = 20 μm.

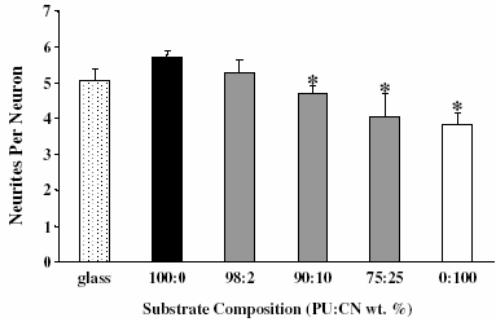


Figure 2. Optimal neurite extension for neurons cultured on all PU:CN materials. Time = 3 d. Values are mean +/− SEM; $n = 3$; * $p < 0.1$ compared to 100:0 PU:CN wt%.

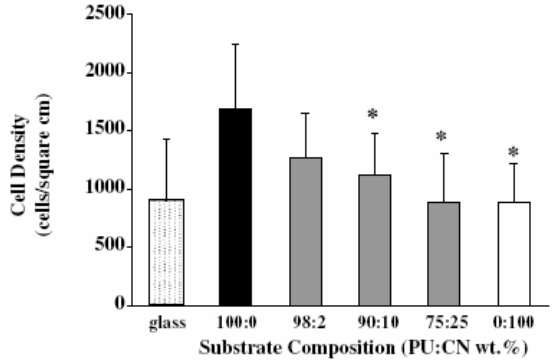
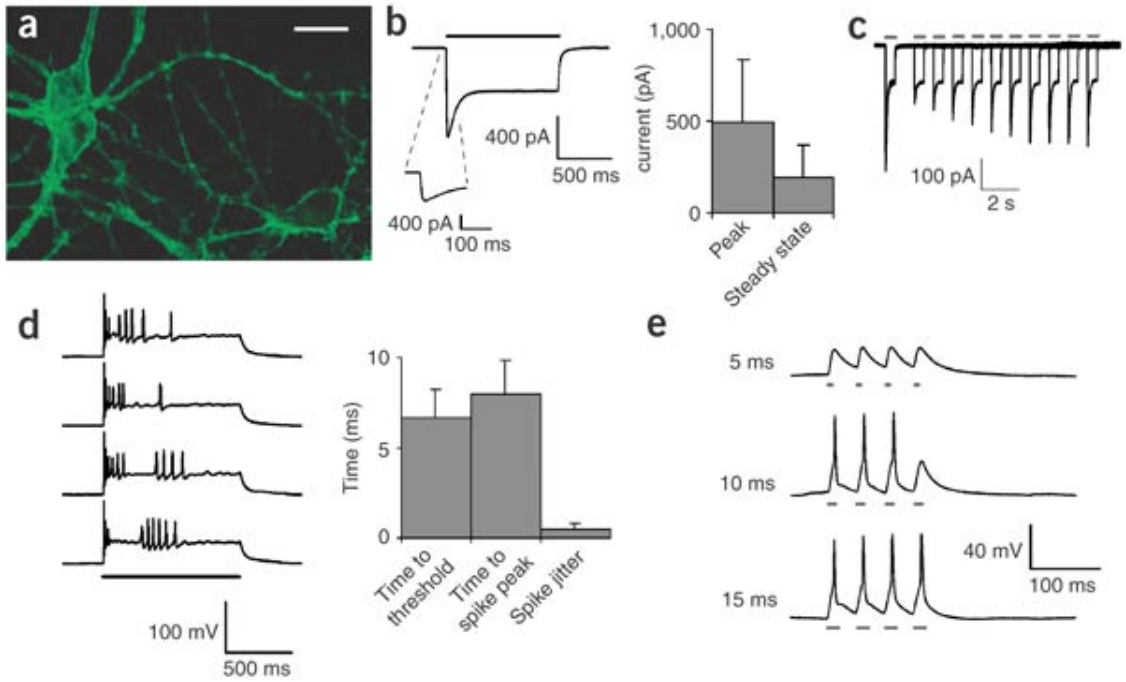


Figure 4. Decreased astrocyte cell adhesion density with increased numbers of CNs in PU. Values are mean +/− SEM; $n = 3$; * $p < 0.1$ compared to 100:0 PU:CN wt%.

- **Carbon nanofiber (CN) reinforced polycarbonate urethane (PU)**
  - increased nerve cell adhesion for neural prostheses
  - decreased astrocyte adhesion reduces glial scar formation for enduring electrode function

Thomas Webster, Michael Waid, Janice McKenzie, Rachel Price, and Jeremiah Ejiofor, "Nano-biotechnology: carbon nanofibres as improved neural and orthopaedic implants," *Nanotechnology*, vol. 15, pp. 48-54, 2004.

Channel Rhodopsin-2 (ChR2) Optogenetics



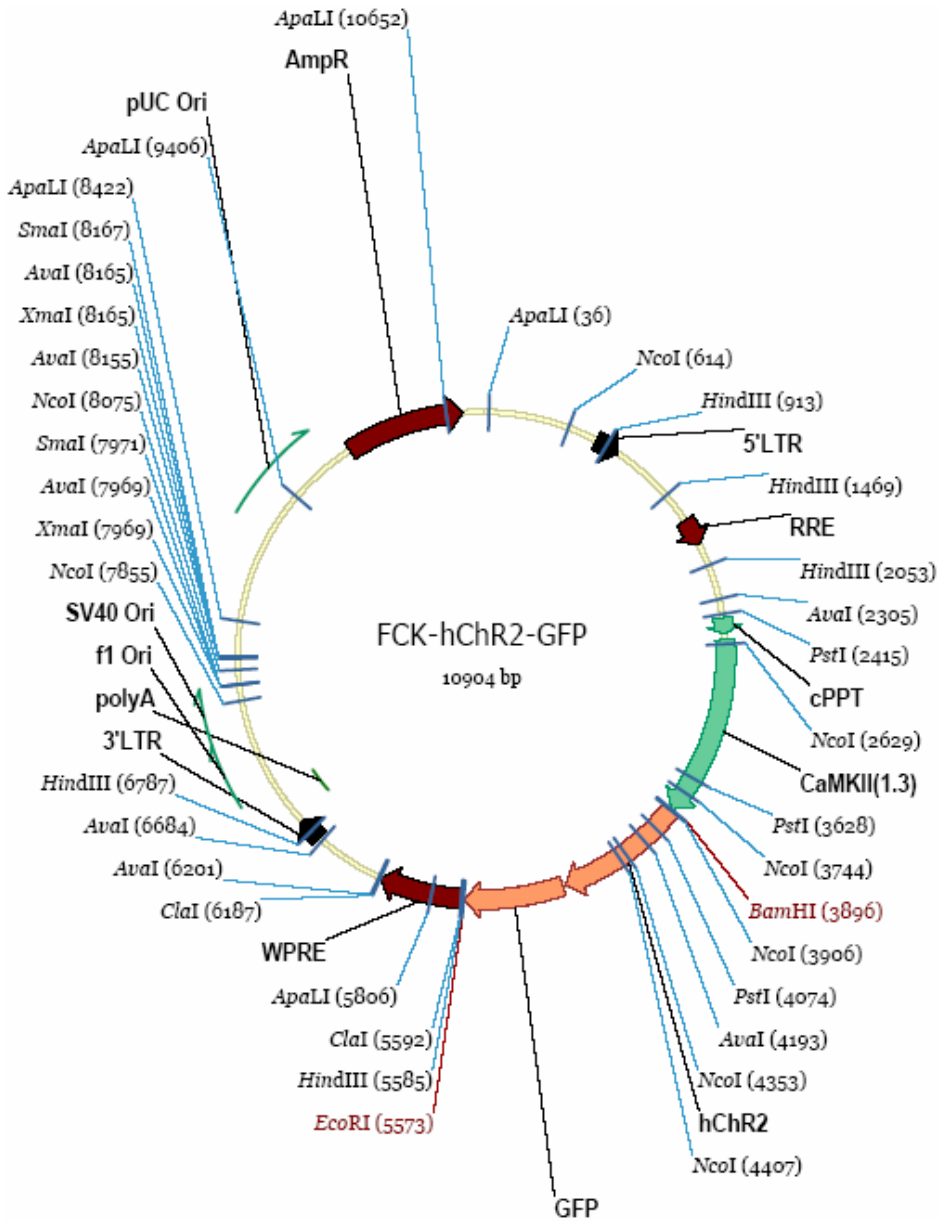
ChR2 enables light-driven neuron spiking.

(**a**) Hippocampal neurons expressing ChR2-YFP (scale bar 30 m). (**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-clamped hippocampal neuron (left) evoked by 1-s periods of light (gray bar). Right, properties of the first spike elicited (*n* = 10): latency to spike threshold, latency to spike peak, and jitter of spike time. (**e**) Voltage traces in response to brief light pulse series, with light pulses (gray bars) lasting 5 ms (top), 10 ms (middle) or 15 ms (bottom).

- **Precise control over neural activation**
  - ChR2 channel protein activated by light
  - lentiviral gene, delivered to targeted neurons, expresses ChR2 protein
  - msec timing precision for generation of precise action potentials

Edward Boyden, Feng Zhang, Ernst Bamberg, Georg Nagel, Karl Deisseroth, "Millisecond-timescale, genetically targeted optical control of neural activity," *Nature Neuroscience*, vol. 8, pp. 1263-1268, 2005.

Lentiviral Gene Plasmid Map

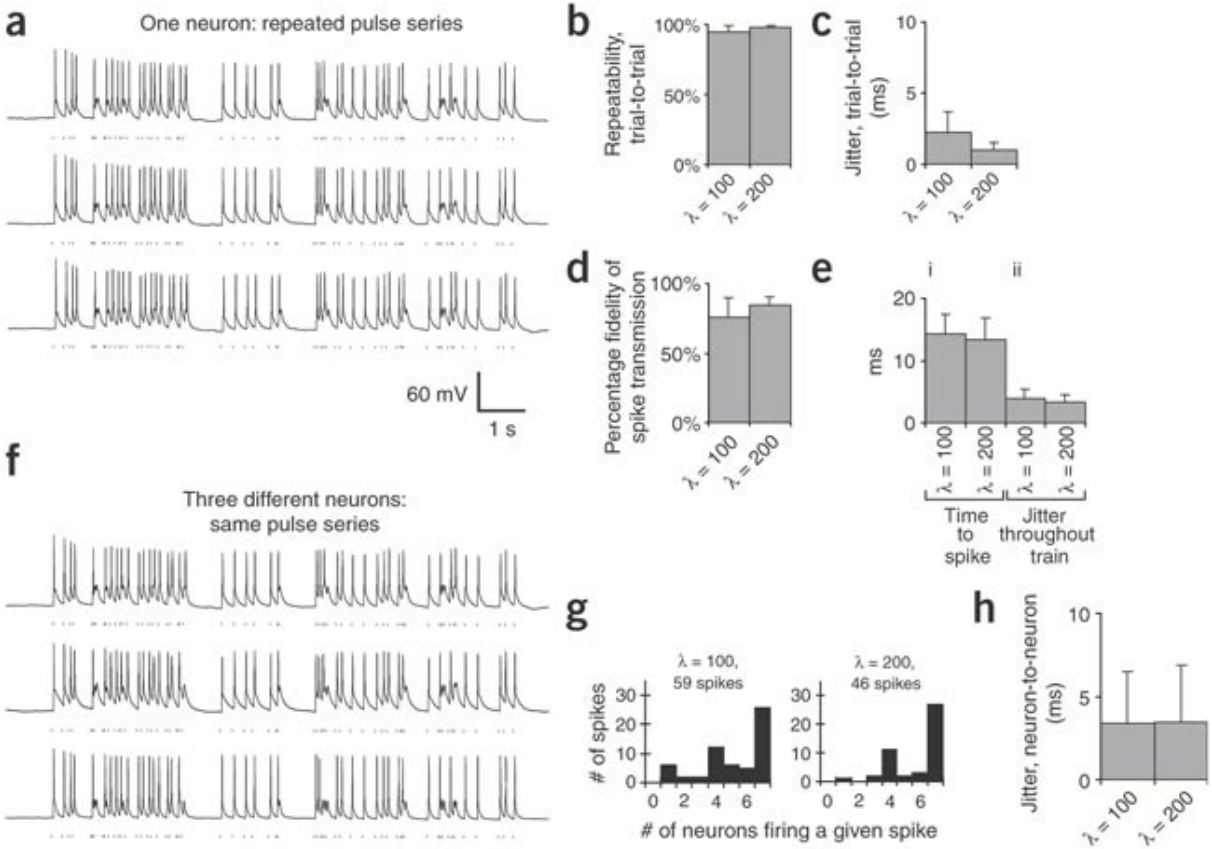


- **Mammalian codon-optimized C. reinhardtii channelrhodopsin-2 ("hChR2")**
  - lentivirus
  - fused to GFP
  - CaMKII promoter

Lentivirus plasmid (or vector), showing all unique restriction sites

Edward Boyden, posted at http://edboyden.org/05.09.boyden.html

ChR2 Repeatable Activation of Precise, Single Action Potentials



Realistic spike trains driven by series of light pulses.

(**a**) Voltage traces showing spikes in a single current-clamped hippocampal neuron, in response to three deliveries of a Poisson train (with mean interval = 100 ms) of light pulses (gray dashes). (**b**) Trial-to-trial repeatability of light-evoked spike trains, as measured by comparing the presence or absence of a spike in two repeated trials of a Poisson train (either = 100 ms or = 200 ms) delivered to the same neuron (*n* = 7 neurons). (**c**) Trial-to-trial jitter of spikes, across repeated light-evoked spike trains. (**d**) Percent fidelity of spike transmission throughout entire 8-s light pulse series. (**e**) Latency of spikes throughout each light pulse series (i) and jitter of spike times throughout train (ii). (**f**) Voltage traces showing spikes in three different hippocampal neurons, in response to the same temporally patterned light stimulus (gray dashes) used in **a**. (**g**) Histogram showing how many of the seven neurons spiked in response to each light pulse in the Poisson train. (**h**) Neuron-to-neuron jitter of spikes evoked by light stimulation.

Edward Boyden, Feng Zhang, Ernst Bamberg, Georg Nagel, Karl Deisseroth, "Millisecond-timescale, genetically targeted optical control of neural activity," *Nature Neuroscience,* vol. 8, pp. 1263-1268, 2005.

Multimodal Optogenetic Control

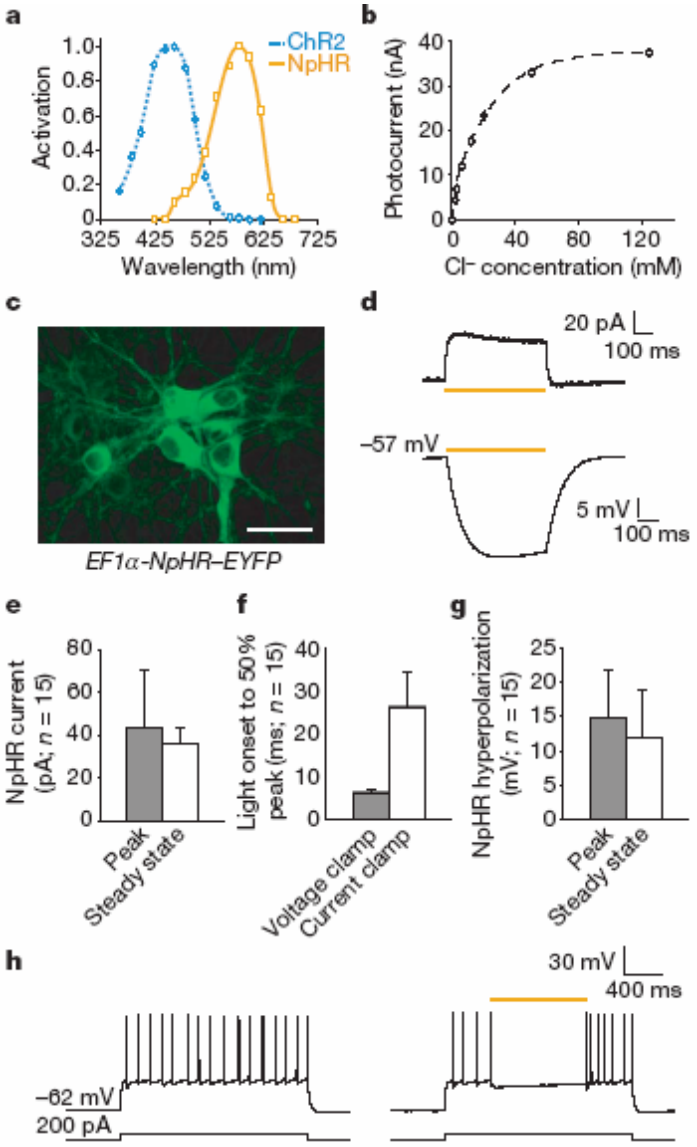
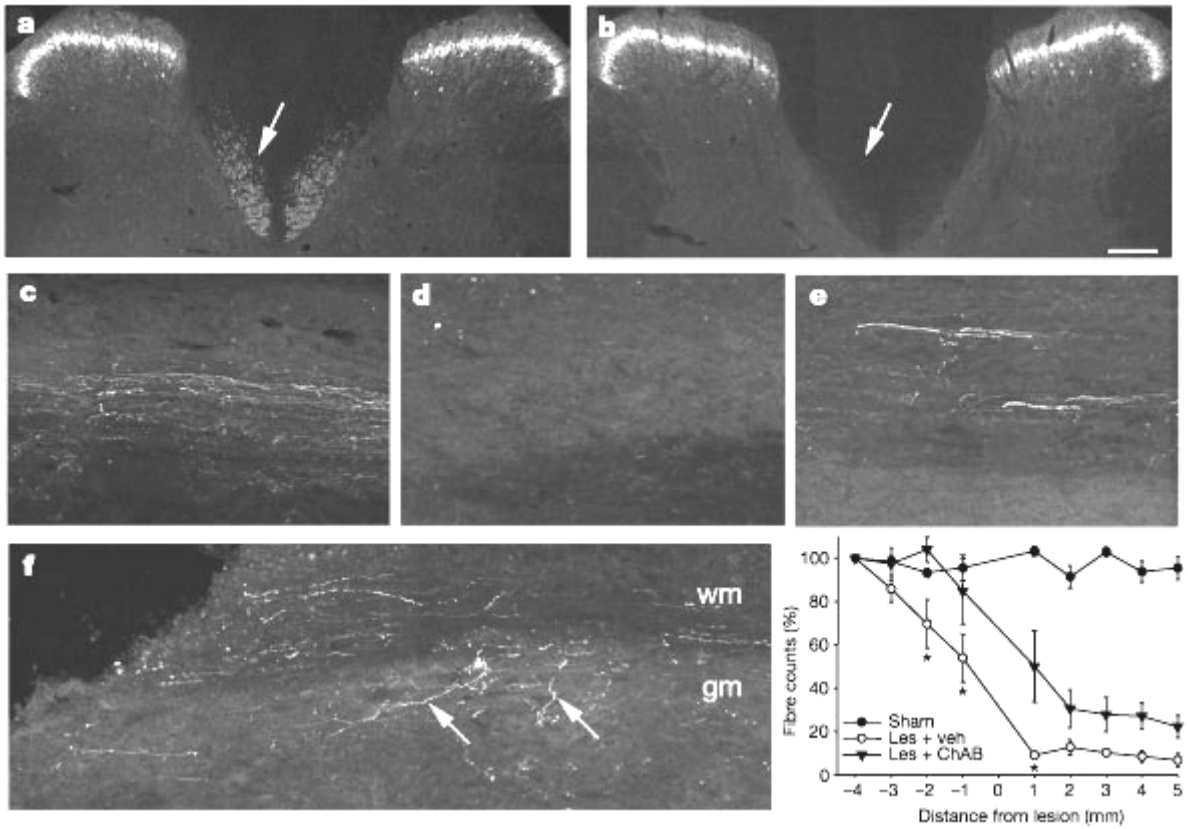


Figure 1 | Electrophysiological properties of NpHR in oocytes and hippocampal neurons. **a**, Action spectrum of NpHR in oocytes held at −50 mV, determined by 20 nm narrow bandwidth interference filters. The ChR2 action spectrum is provided for comparison[4]. **b**, Extracellular [Cl^-] dependence of NpHR pump currents indicates a simple Michaelis–Menten type saturation with a K_M of 16 mM (dashed fit curve). **c**, Hippocampal neurons expressing NpHR–EYFP (scale bar 50 μm). **d**, Yellow light (593 nm)-induced outward photocurrent in neurons (top panel, voltage clamp) and membrane hyperpolarization (bottom panel, current clamp); illumination duration is indicated by the yellow bar. **e**, NpHR peak versus steady-state current (mean ± s.d.; $n = 15$). **f**, Latency of NpHR activity measured from light onset to 50% of the peak current or hyperpolarization (mean ± s.d.; $n = 15$). **g**, NpHR peak versus steady-state membrane hyperpolarization (mean ± s.d.; $n = 15$). **h**, Illumination with yellow light potently inhibited neuronal firing.

- **Activation by ChR2**
- **Inactivation by NpHR**
  - Differentiation by wavelength selection
  - Differentiation by gene expression

F. Zhang, L.-P. Wang, M. Brauner, J. Liewald, K. Kay, N. Watzke, P. Wood, E. Bamberg, G. Nagel, A. Gottschalk, and K. Deisseroth, "Multimodal fast optical interrogation of neural circuitry," *Nature,* vol. 446, pp. 633-639, 2007.

ChABC Mediated Spinal Regeneration



ChABC promotes regeneration of corticospinal tract axons.

a, In control lumbar spinal cord, PKC-immunoreactivity is present in the dorsal horn and the CST. **b**, After a dorsal column lesion, PKC- immunoreactivity is no longer present in the CST (arrows in **a** and **b**), confirming a complete lesion. **c**, BDA-labelled CST fibres in the cervical spinal cord of controls. **d**, **e**, In lesioned animals BDA-labelled fibres are not observed below the injury site after vehicle infusions (**d**), but are present after ChABC infusions (**e**). **f**, In a ChABC-treated animal many axons are observed at the lesion site and appear to send collaterals (arrows) from white matter (wm) to grey matter (gm), indicating terminal arborization of regenerating axons. Quantification data (right) are percentages (means s.e.m.; asterisks denote significant difference between vehicle and ChABC treatment, $P<0.05$, two-way ANOVA, Tukey post-hoc). Scale bar, 200 m (**a**–**e**); 100 m (**f**). Les, lesion; veh, vehicle.

- **Chondroitinase ABC (ChABC):**
  - suppresses glial scar tissue buildup near spinal cord injury,
  - promotes corticospinal axonal regrowth.

E.J. Bradbury, L.D. Moon, R.J. Popat, V.R. King, G.S. Bennett, P.N. Patel, J.W. Fawcett, and S.B. McMahon, "Chondroitinase ABC promotes functional recovery after spinal cord injury," *Nature,*, vol. 416(6881), pp. 636-40, 2002.