A Nervous Future

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Texas Biomedical Device Center, Alan G. MacDiarmid Nanotech Institute, Center for Engineering Innovation
The University of Texas at Dallas

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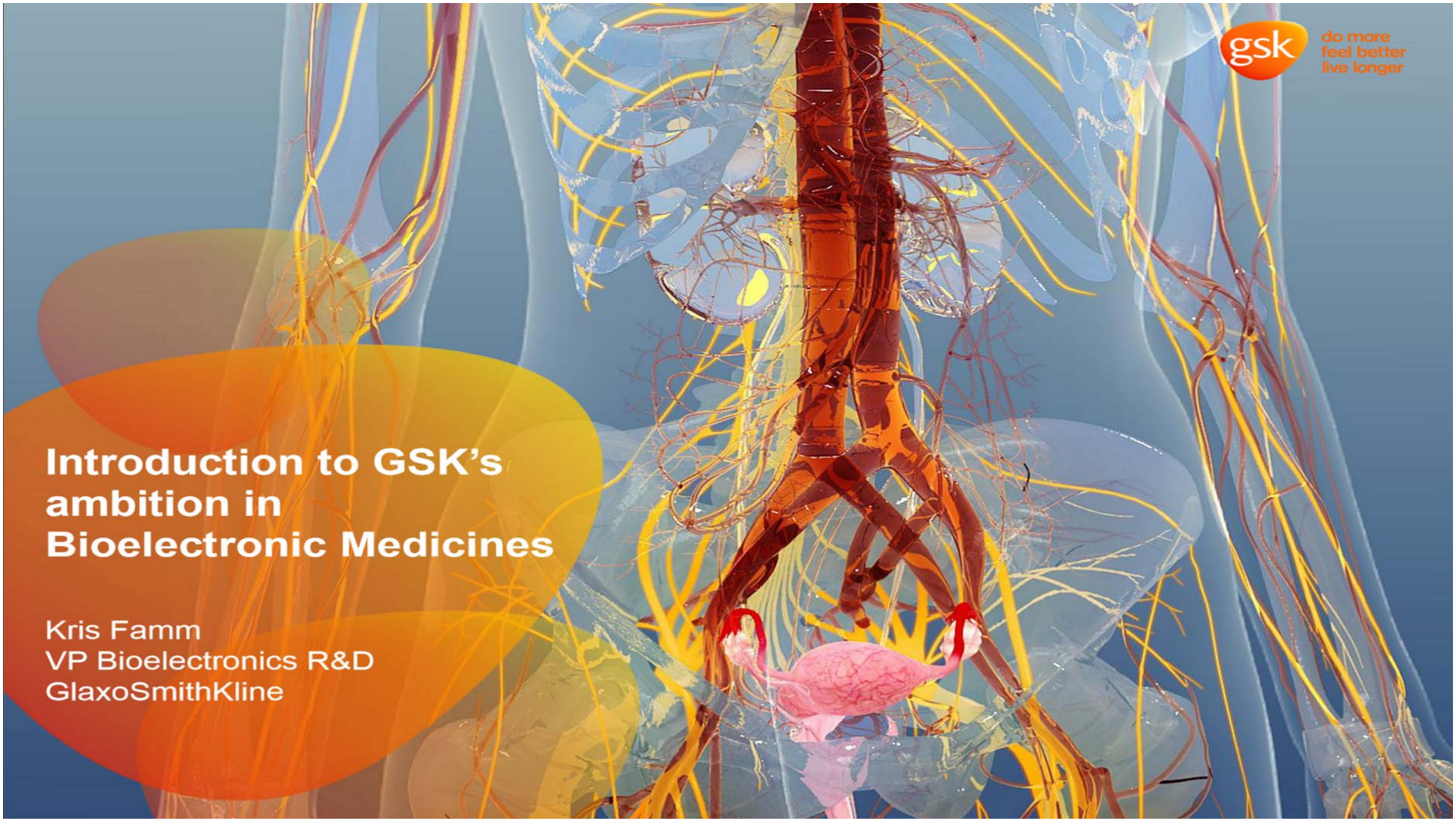
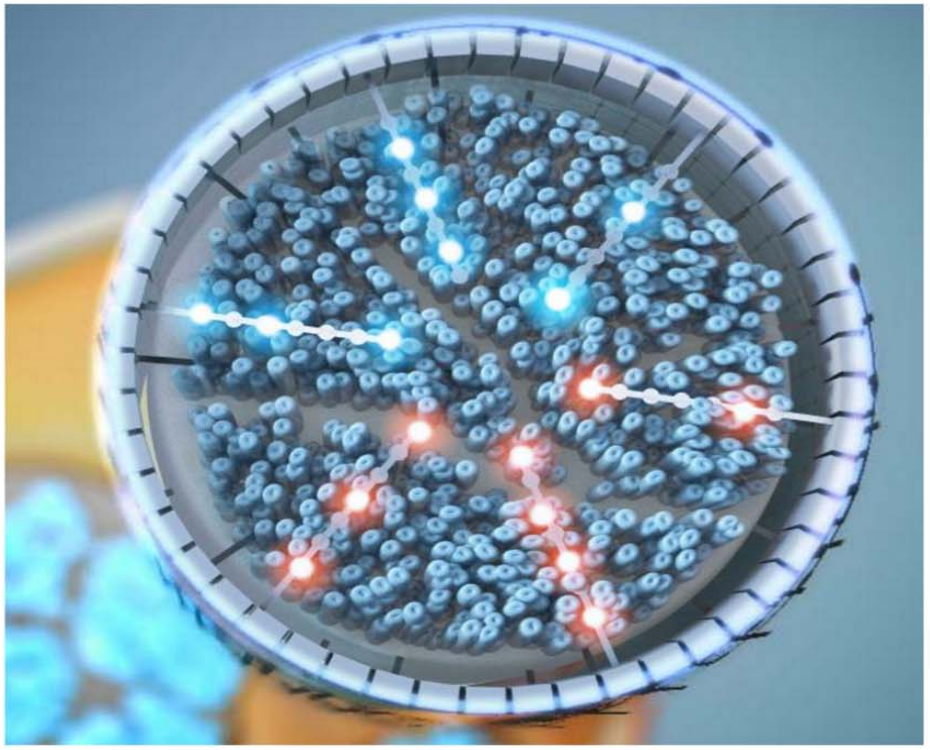

gsk
do more
feel better
live longer
Introduction to GSK's ambition in Bioelectronic Medicines
Kris Famm
VP Bioelectronics R&D
GlaxoSmithKline

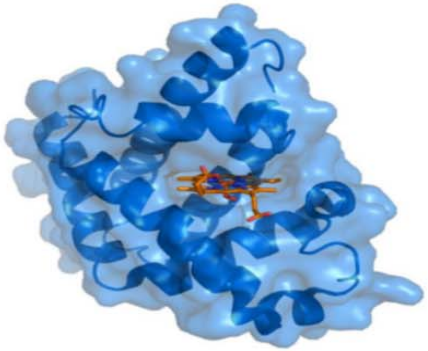
Hallmarks of bioelectronic medicines GSK aims to advance over the next 1-2 decades

- Use naturalistic neural signalling as a **treatment modality**
- Target **visceral peripheral nerves** to modulate functions of organs central in major chronic diseases
- Take a **technology leap** towards closed-loop, miniaturised devices



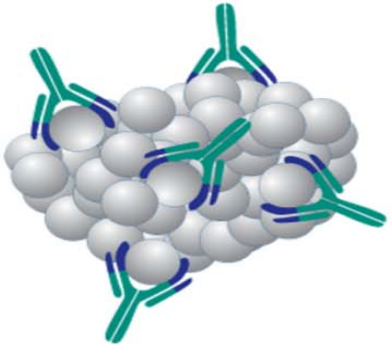
Treatment modality: Leveraging fundamental control systems in biology

Cell signalling control



Small molecule drugs cause naturalistic shifts in signalling cascades

Immune system control



Vaccines and **antibody drugs** leverage the immune system

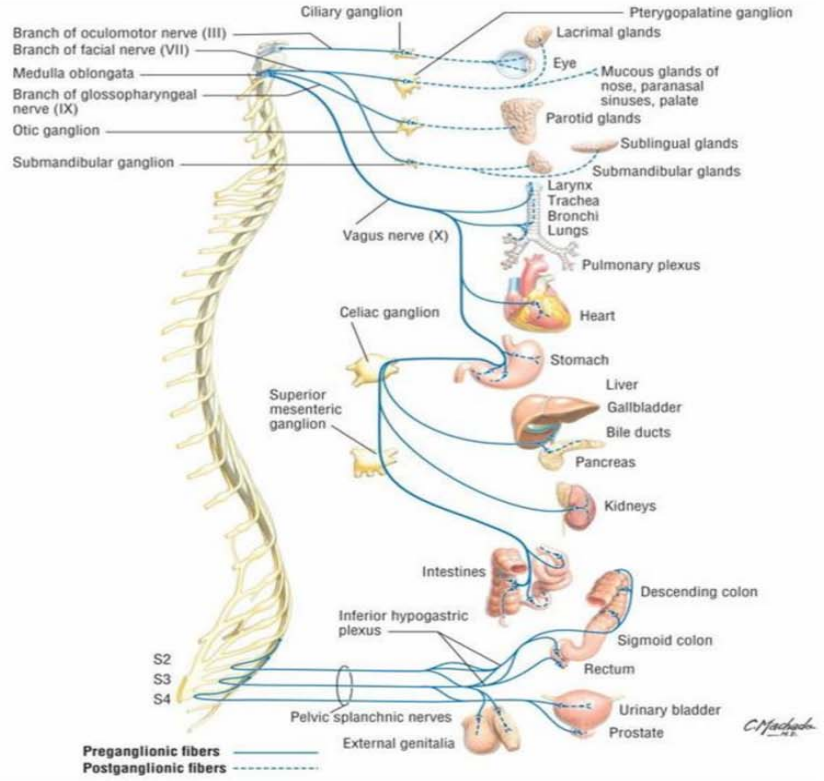
Neural control

Bioelectronic medicines will "piggyback" on the body's precision wiring

Image source: http://en.wikipedia.org/wiki/Ligand_(biochemistry); http://www.rndsystems.com/resources/images/6295.gif; http://www.empowher.com/media/reference/x-linked-adrenoleukodystrophy

Visceral peripheral nerves: The autonomic nerves reach many organs implicated in chronic diseases

Parasympathetic nervous system



Sympathetic nervous system

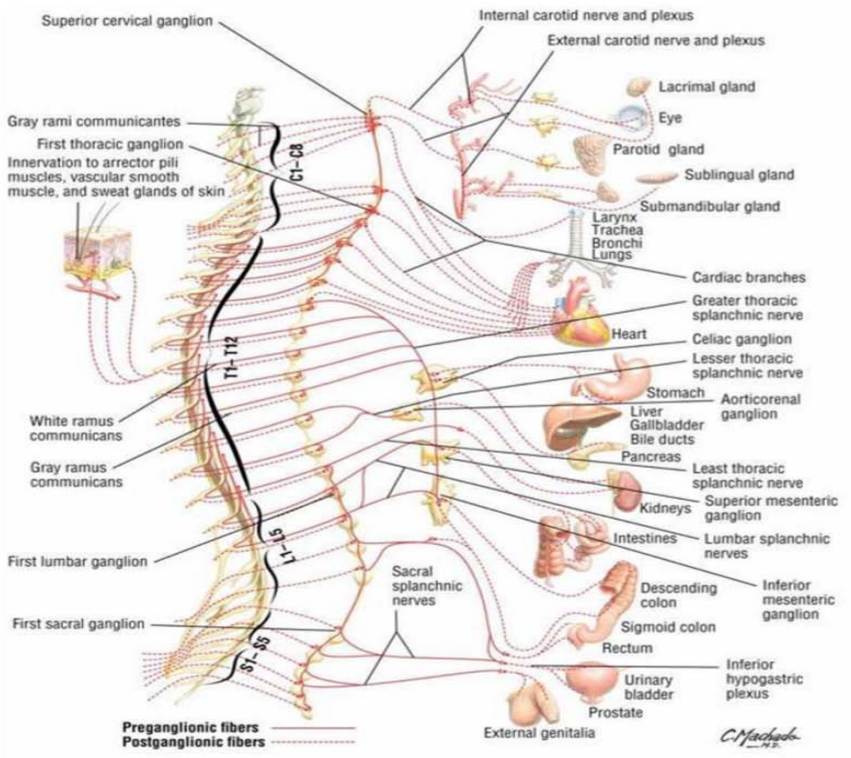
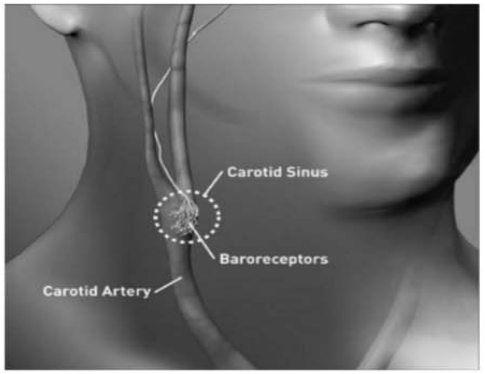
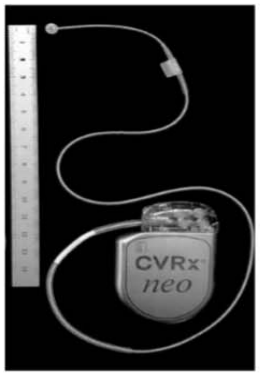
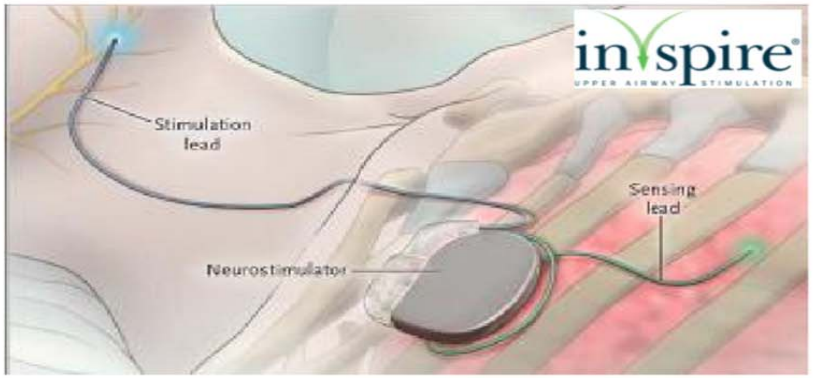


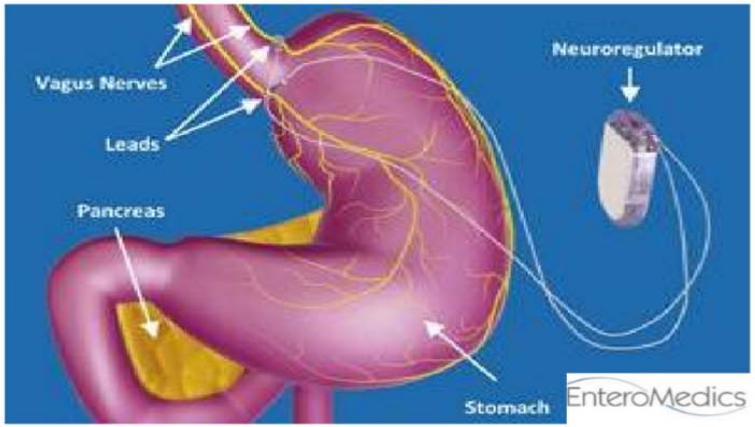
Image source: Atlas of Human Anatomy, 5th edition, Frank H Netter

Technology leap… from today's full nerve approaches



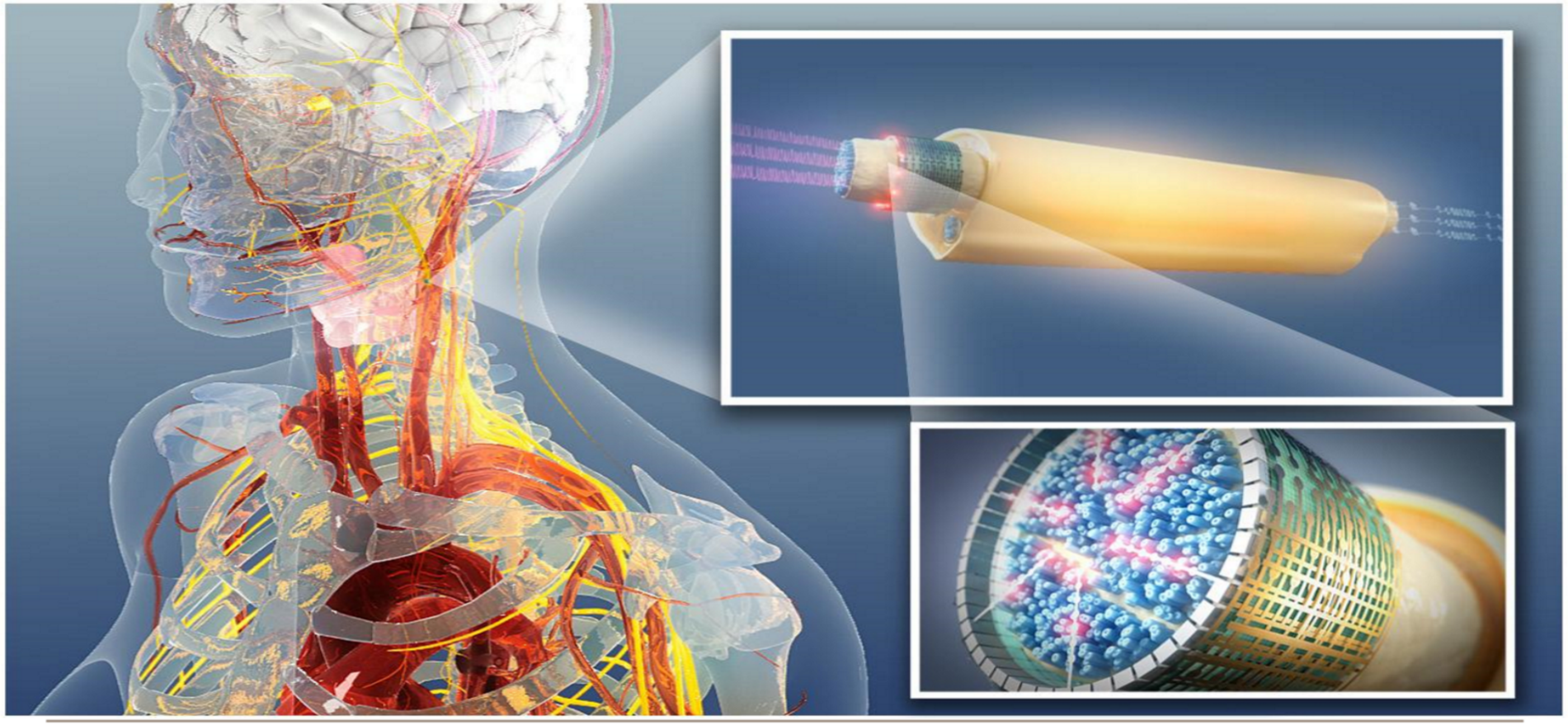


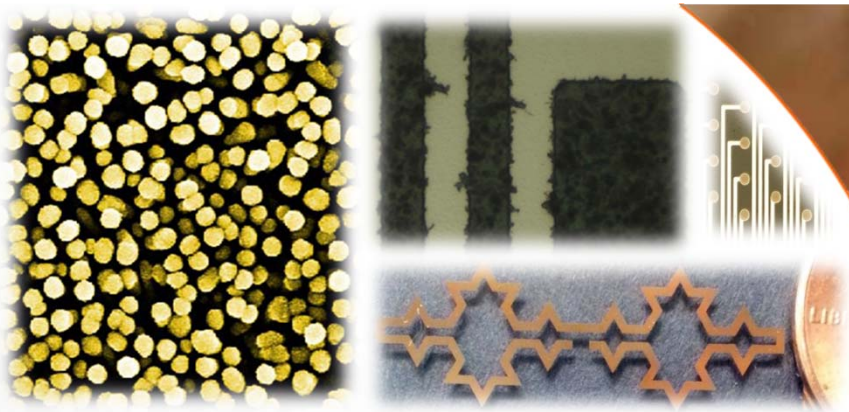




Source:CVRx; SetPoint Medical; inspiresleep.com; N Engl J Med 2014;370:139-49; http://www.bariatricnews.net/?q=news/11179/vbloc-therapy-new-dawn

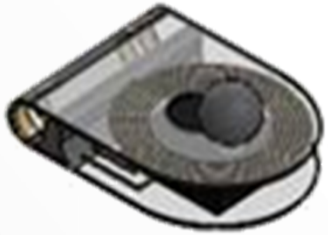
Technology leap... to intelligent, miniaturised devices



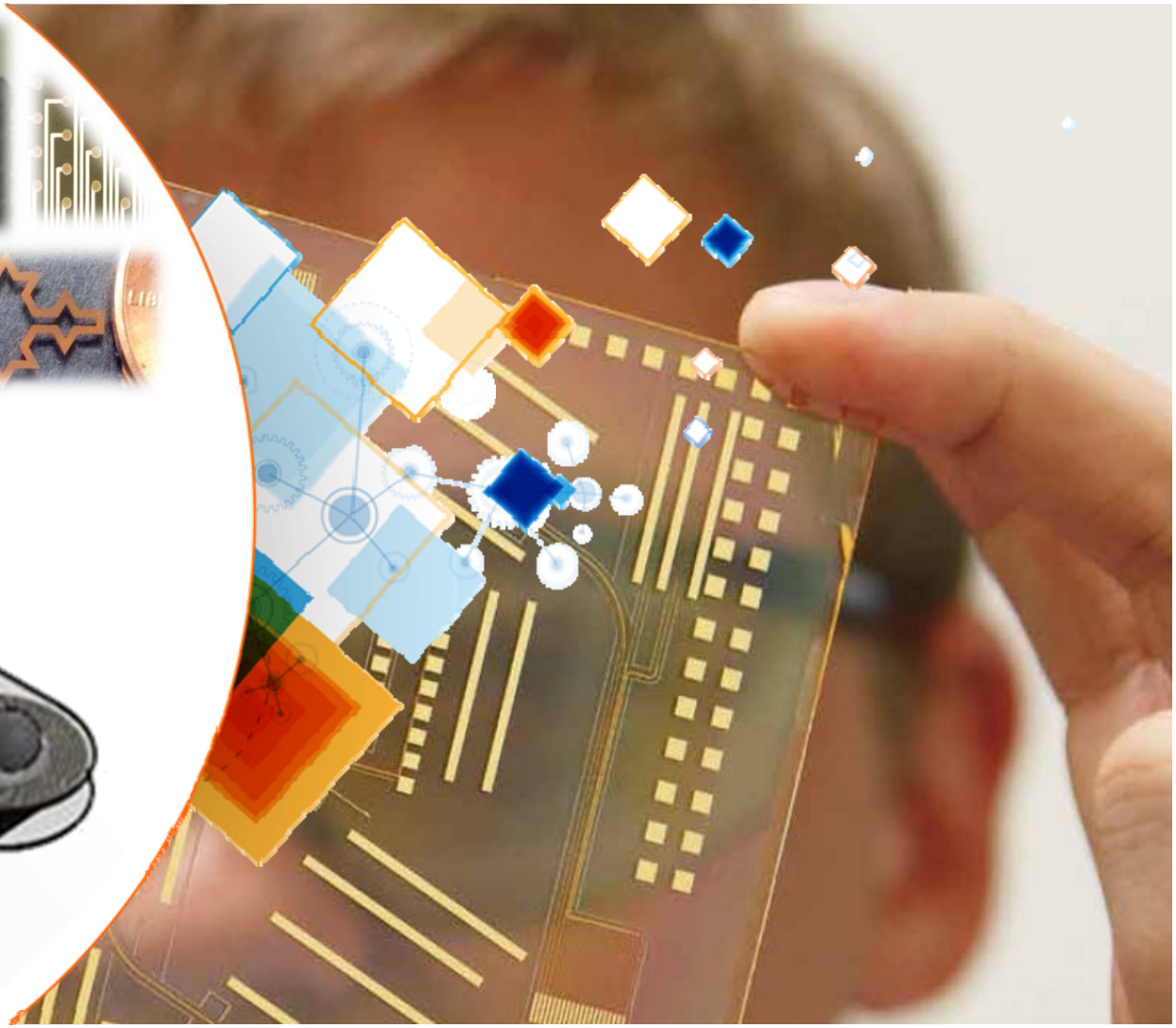


NerveTags™

A *Bioelectronics* Solution
from UT Dallas



UT DALLAS
The University of Texas at Dallas

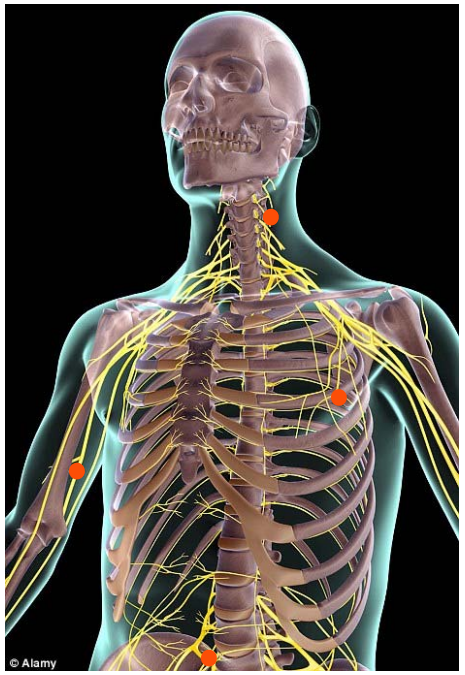


Objective

Create a universal platform for interrogating and manipulating peripheral nerves

Desired features of this platform:

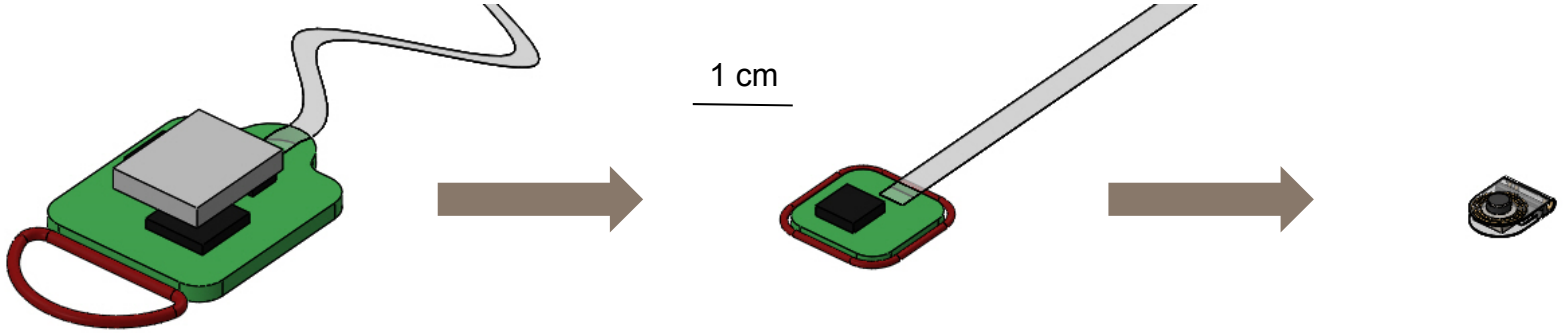
- System of distributed wireless “tagged nerve” nodes (no leads, no central unit)
- NerveTags™ are directly attached to individual nerve branches for functional specificity
- Each tag can record, stimulate and block nerve activity
- Tags are inductively charged and store energy for >24 hours
- Tags communicate wirelessly using 2.45GHz digital radio
- Inexpensive (<$100) and mass producible



Strategic approach - electronics

Phased miniaturization using commercial components/processes

- Technology to create NerveTags™ already exists and is tested to industry standards
- Minimize risk and development time by using commercial silicon (no custom ASICs)



Prototype 1
- Full featured
- ~10 chips on PCB
- Silicone encapsulation
- Battery rechargeable

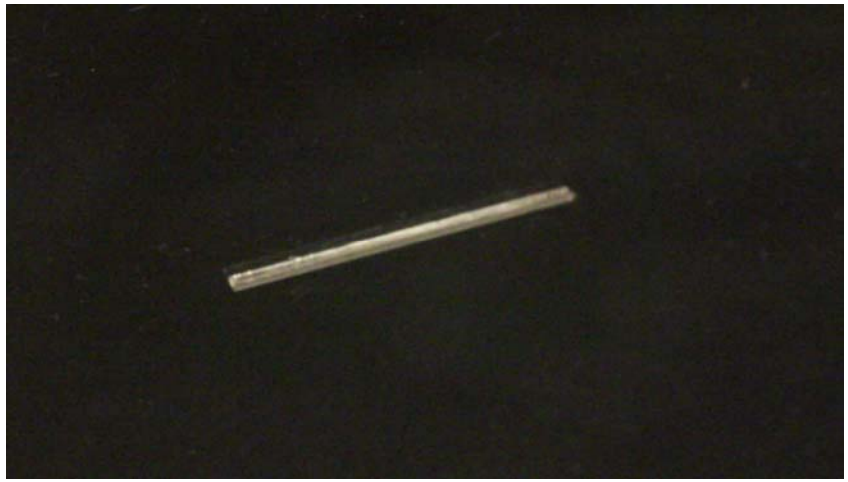
Prototype 2
- Minimum necessary features
- 2-3 chips on PCB
- Silicone encapsulation
- Supercap. rechargeable

Nerve Tag
- Multi-chip module
- Hermetic ceramic package
- Polymer substrate
- Supercap. rechargeable

Strategic Approach - chronic neural interfaces

Problem: Neural interfaces fail prematurely for biotic and abiotic reasons

- **Approach**: Provide stable neural interfaces on softening polymers for easy insertion with chronic moduli approaching soft tissue.
- **Modes**: Wirelessly record, stimulate and block neural signals.
- **Targets:** spinal cord, cochlea, dorsal root ganglia, stomach, other visceral organs and the pudendal, splenic, carotid sinus, hypogastric, sciatic, tibial, sural, vagus and splanchnic nerves.

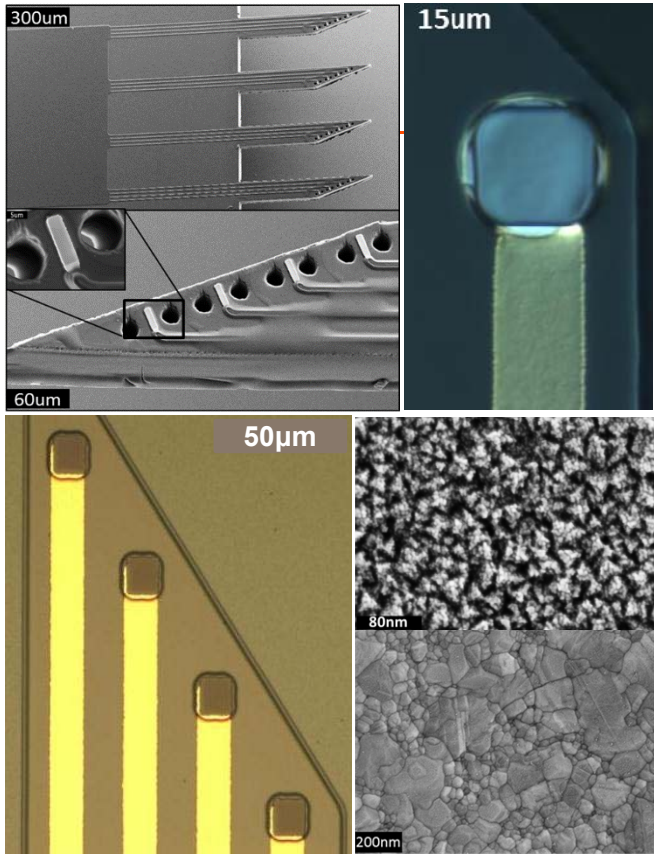


Video: Self-coiling shape memory polymer transistor array

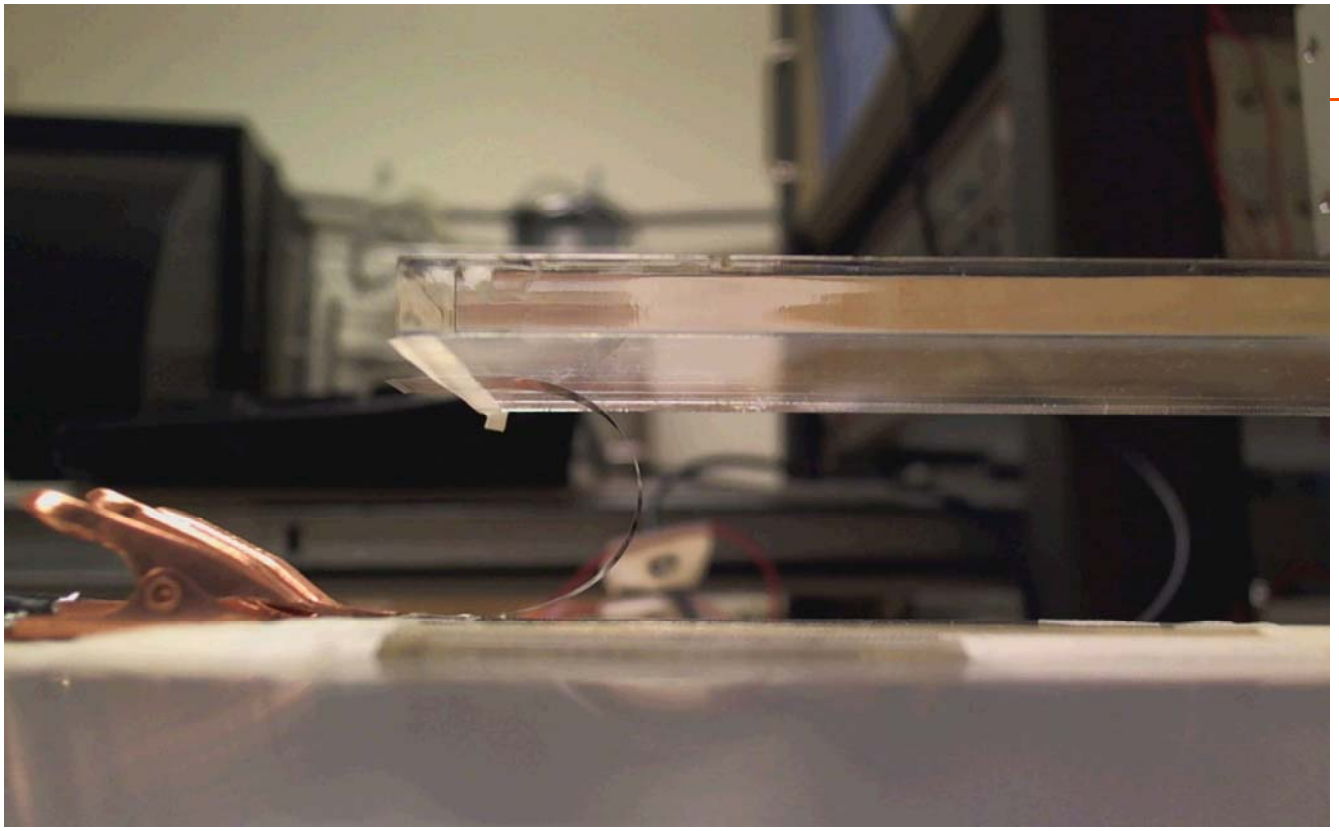
Funding Sources: DARPA Young Faculty Award; DARPA Director's Fellowship; GSK Forward Research Award; GSK De-risking Award; NIH SBIR; DoD CDMRP Award

Design Overview

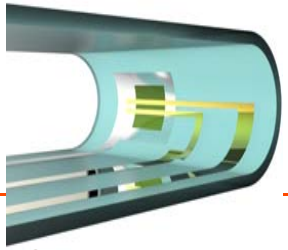
- Broad platform from technical innovation
  - **Design** shape memory polymers (SMPs)
  - **Process** softening flexible electronics
  - **Integrate** thin-film transistor technologies onto devices
  - **Enhance** charge injection capacity (CIC) for microstimulators
  - **Differentiate** single unit action potentials for recording
  - **Enable** hypothesis-driven neuroscience and brain research



We evaluate flexibility limits

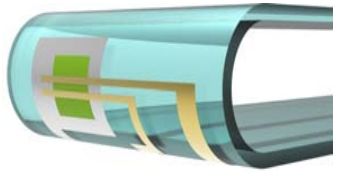


Bending an Organic Thin Film Transistor from r = 10 mm to r = 100 µm.



Compressive strain, parallel channel

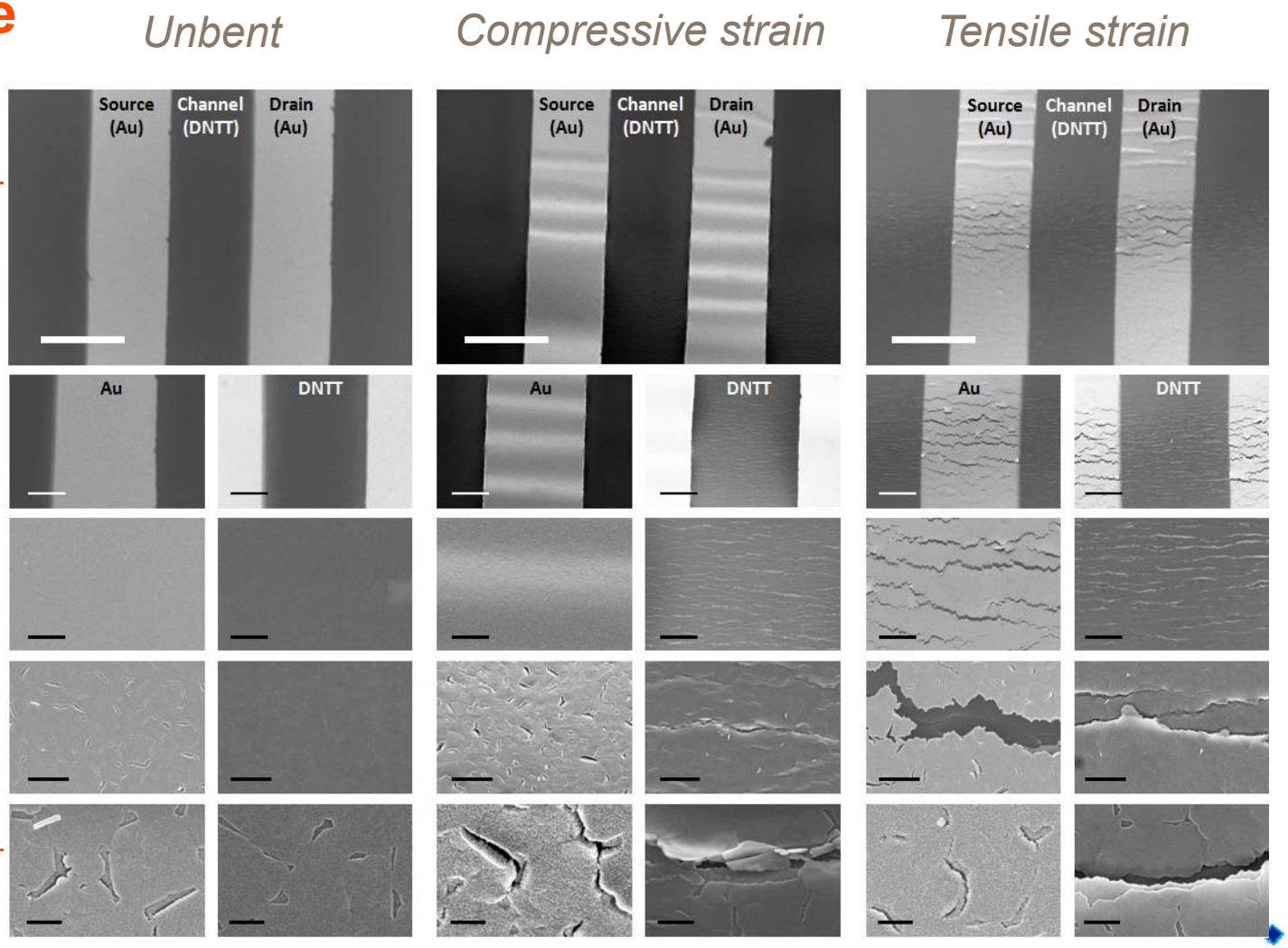
Compressive strain, perp. channel



Tensile strain, parallel channel

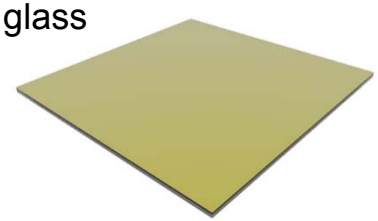
Tensile strain, perp. channel

We analyze materials' failures

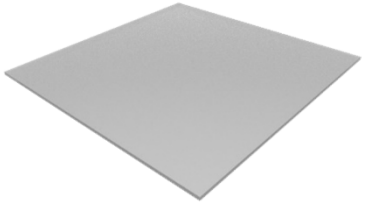


We utilize photolithographic processes to fabricate 16-channel titanium nitride electrodes on SMPs

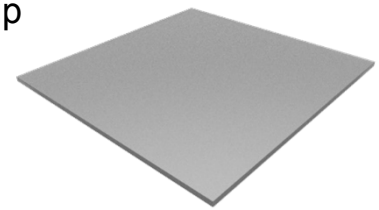
1. Evaporate gold on glass



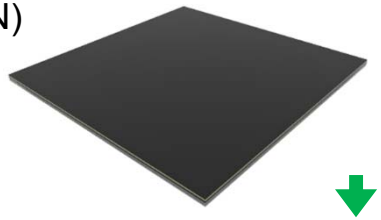
2. Deposit Parylene-C



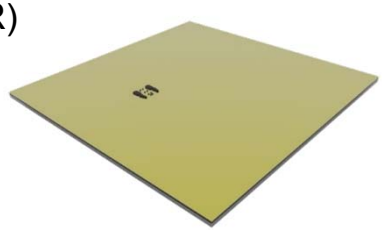
3. Polymerize SMP and flip



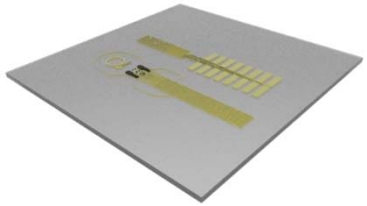
4. Sputter Titanium Nitride (TiN)



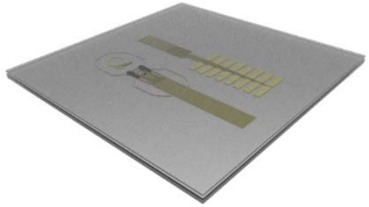
5. Etch TiN via photoresist (PR)



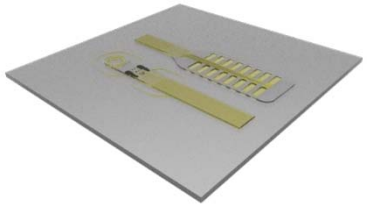
6. Etch gold via PR



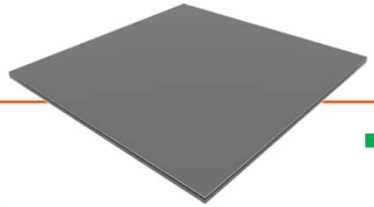
7. Deposit Parylene-C



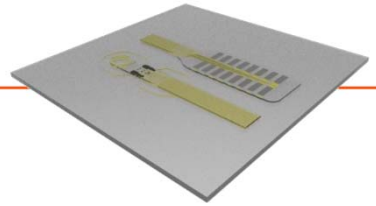
8. Etch Parylene-C via PR



9. Evaporate nickel



10. Etch nickel via PR

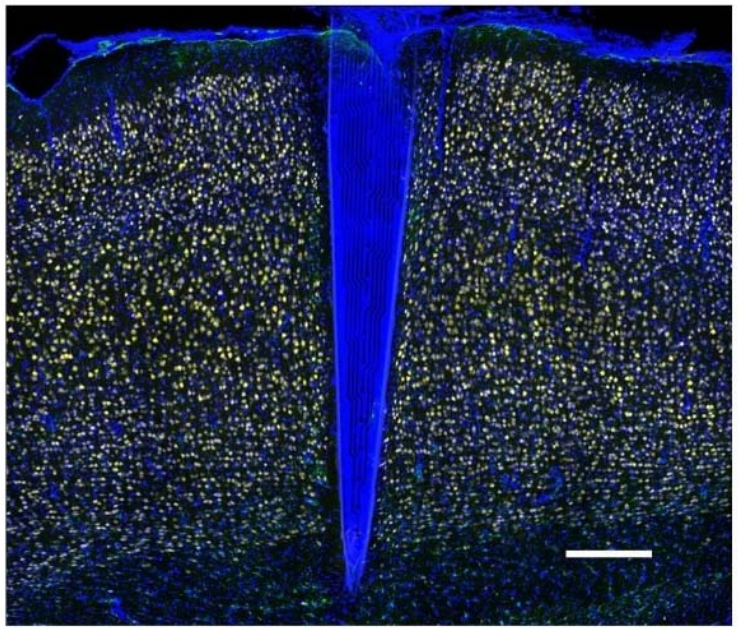


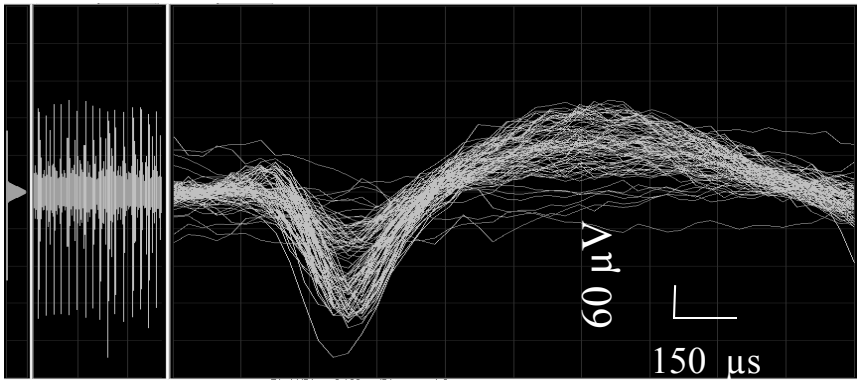
11. Plasma etch w/ oxygen via hard mask

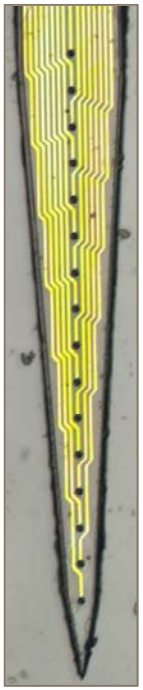
12. Solder wired connector

Early animal work lends credibility to softening hypothesis

Clinical Validation Lab: Joe Pancrazio (GMU → UTD)







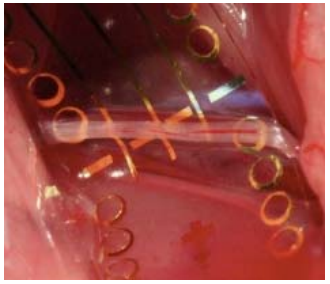
Left: Device capture histology from animal implanted for 77 days in motor cortex with SMP-based intracortical probe. Activated astrocytes (GFAP) in green, neurons (NeuN) in yellow, all other cell types in blue (DAPI).

Top: Single unit neural activity from the motor cortex after one week implanted in a rat from electrode pictured right.

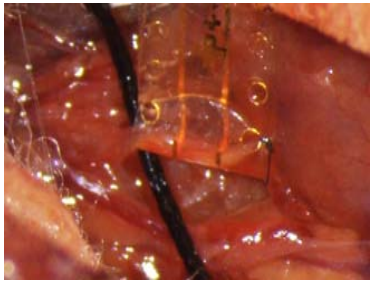
Recently awarded DoD CDMRP 3-year grant with Pancrazio, Capadona based on further testing this hypothesis

Generations of NerveTag™ Cuff Interfaces (Romero Lab)

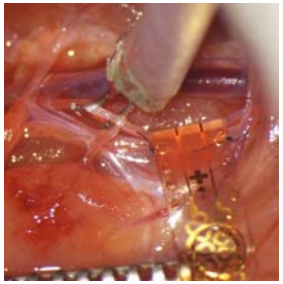
Increasingly small, flexible photolithographically defined nerve cuffs



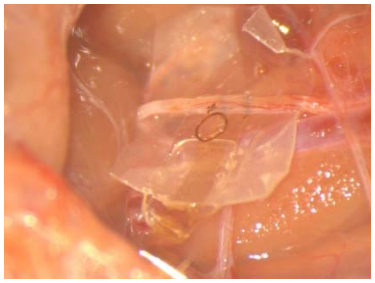
Gen 1: Vagus

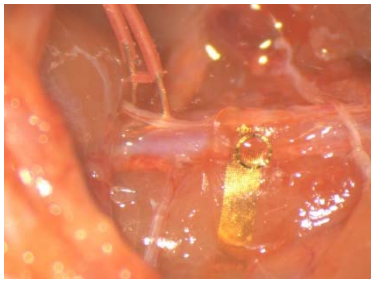


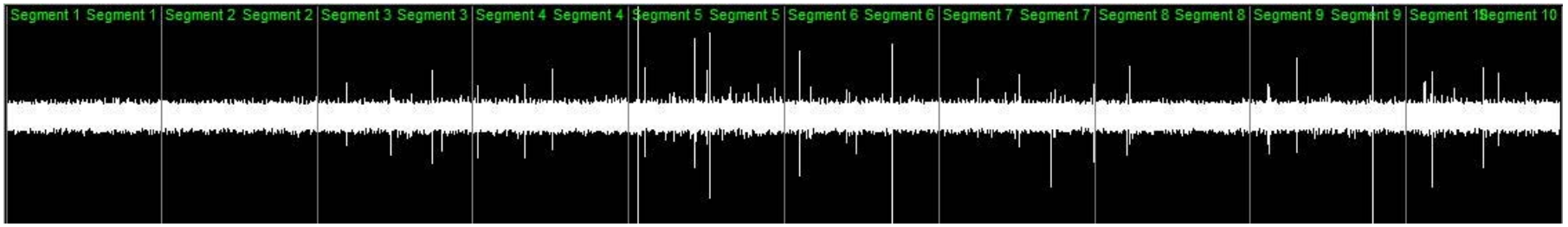
Gen 2: Splanchnic and cervical vagus



Gen 3: Vagus and with upstream proximal hook

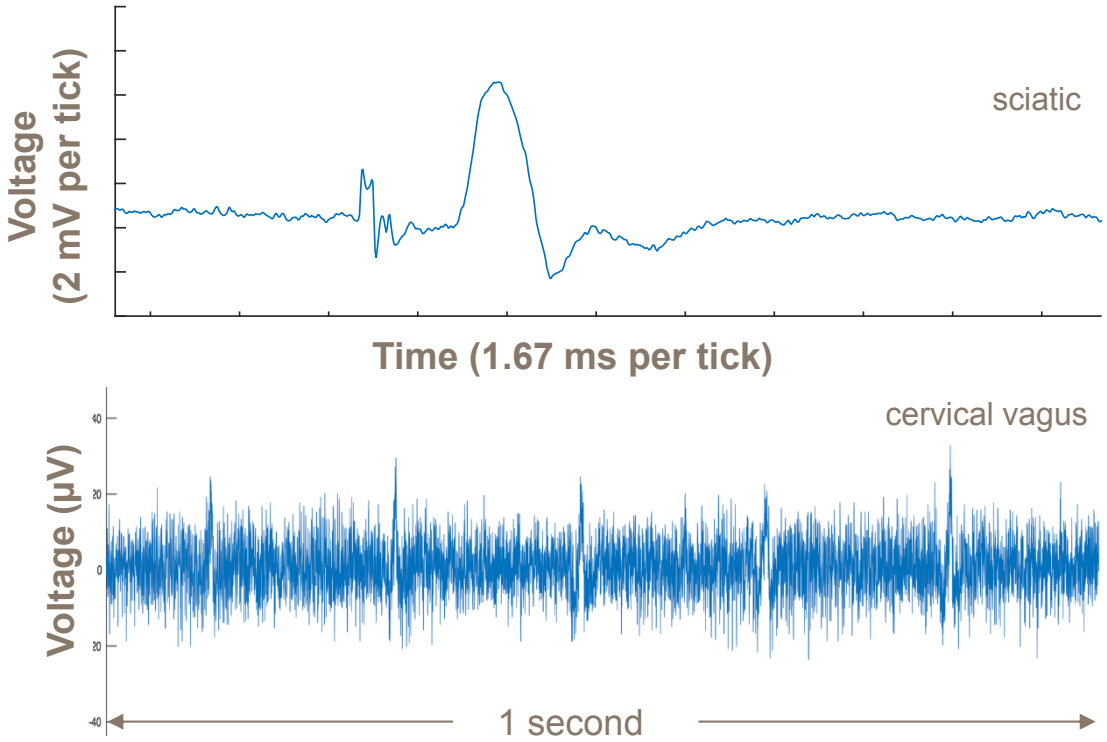


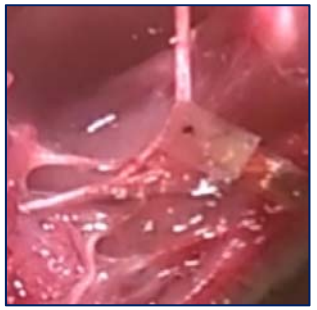




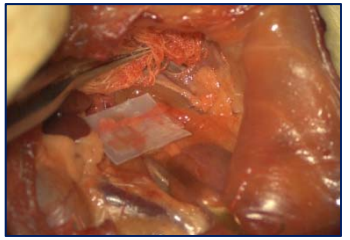
The Gen 3 softening cuff fit snug around the vagus nerve and stayed for 30+ min; we recorded baseline and induced hypoxia; baseline noise was 50uV (peak-to-peak)

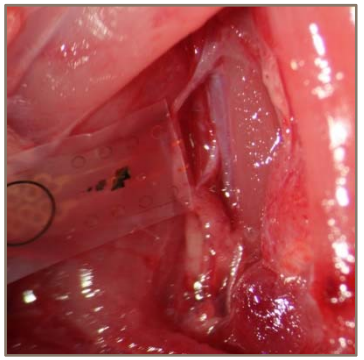
Acute neural recording, blocking, stimulation (Rutgers Lab – Georgia Tech)



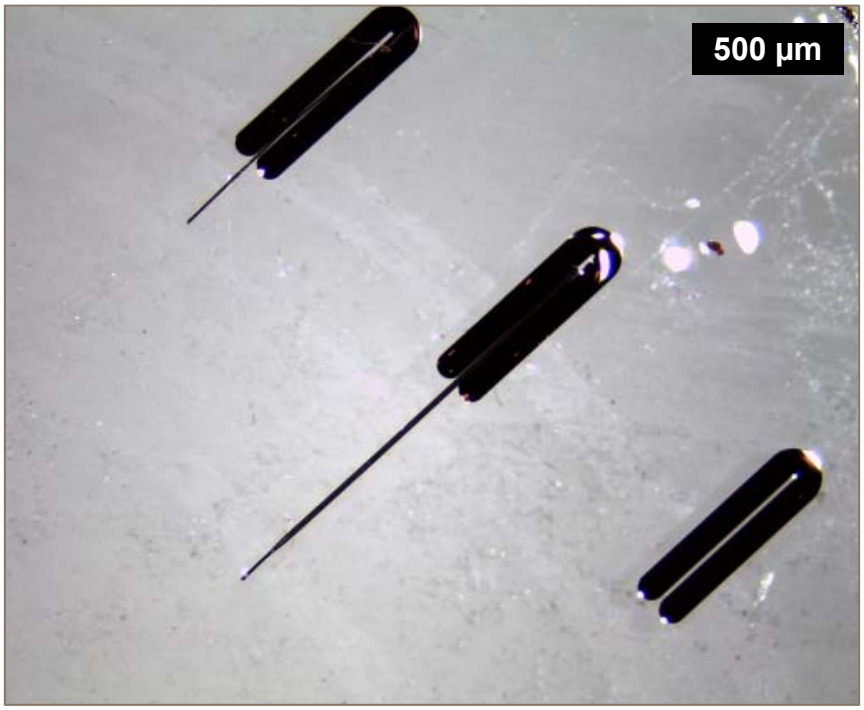


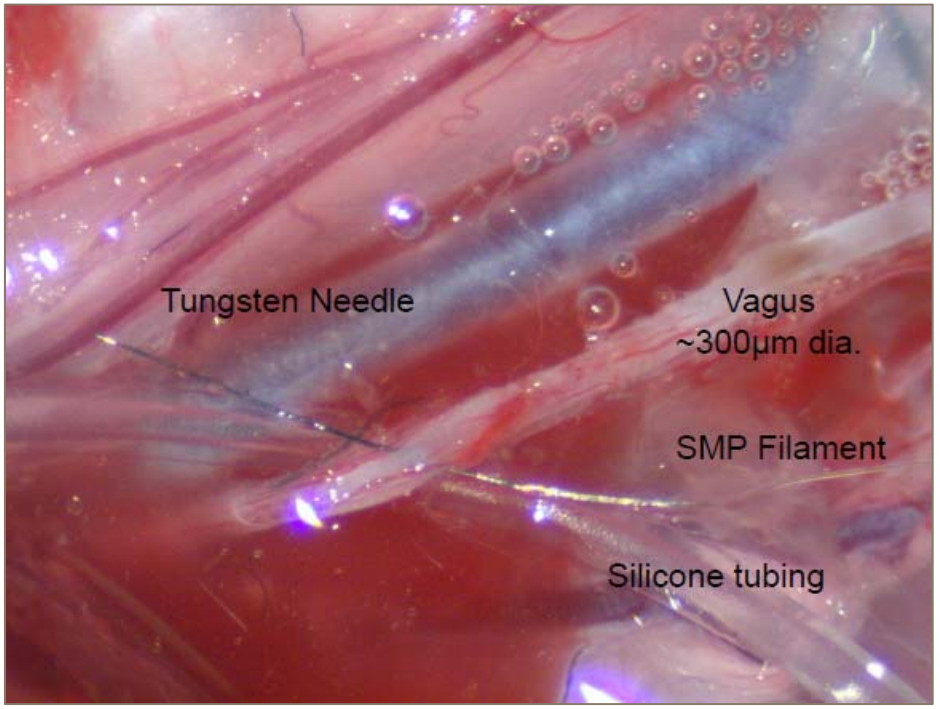
greater sphlanchnic





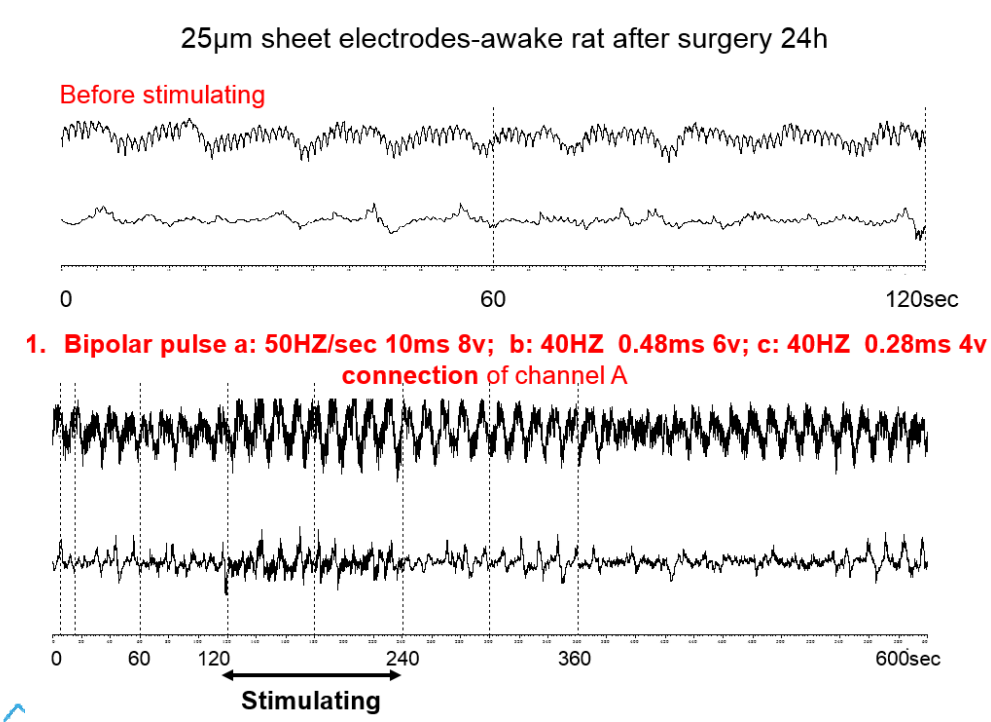
Penetrating intrafascicular electrodes (Yoshida Lab – Indiana Univ.-Purdue Univ. Indianapolis)

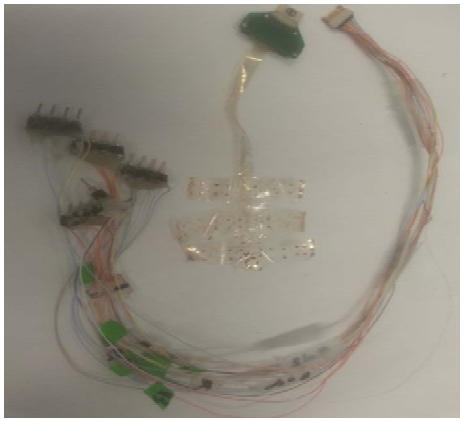




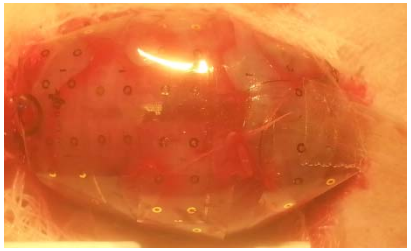
Left: We were able to trap tungsten wires into polymer holders which allow us to align multiple needles precisely. This way we can align them relative to our photomasks. **Right:** Pulling a test SMP filament through the Vagus nerve.

Plexus blanket demonstration (Pasricha Lab – Johns Hopkins University)

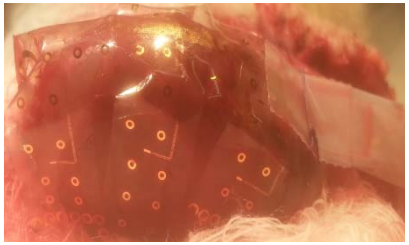




Put the sheet on the stomach before we put it into abdomen



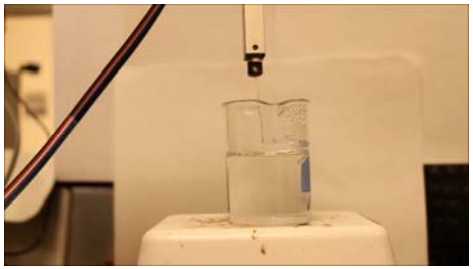
After 1 day: electrostimulating and recording gastric myo-electrical activity-slow waves



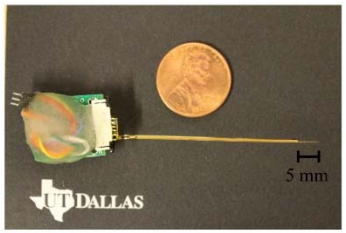
Toward a high-channel count, self-coiling cochlear implant (Lee Lab – UT Southwestern Medical School)

Straight insertion - Cochlear

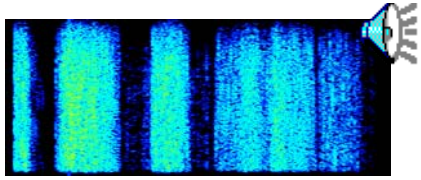
Self-coiling insertion - UTD



Insertion Tool - UTD

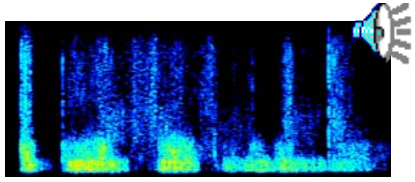


6 channel prototype

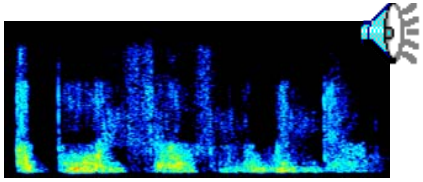


1 channel

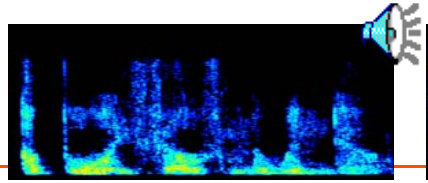
2 channels



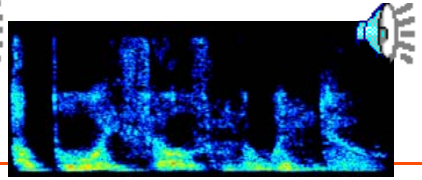
4 channels



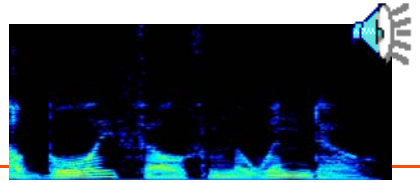
8 channels



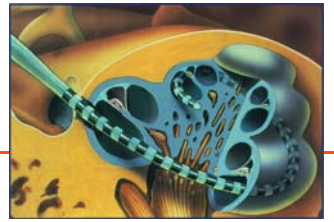
16 channels



32 channels



unfiltered signal



GSK Innovation Challenge Team at UT Dallas

Bioengineering, Mat. Sci. and Eng., Mech. Eng., Electrical Eng., Chemistry

Voit

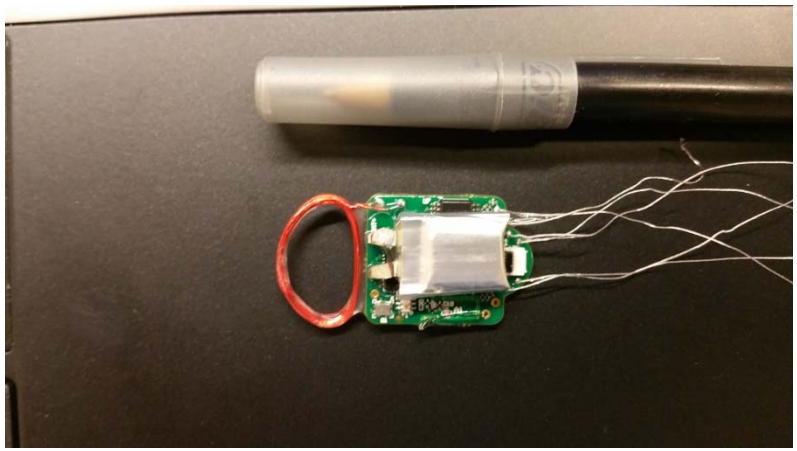
Rennaker

Grasse

Team Members: Dane Grasse, Walter Voit, Rob Rennaker, Ken O, Stuart Cogan, Mario Romero-Ortega, Mike Kilgard, Shalini Prasad, Seth Hayes, >30 graduates, >15 post docs, >100 undergraduates, 8 cleanroom staff (right), 8 vivarium staff

First Generation of NerveTag™ Wireless Electronics

Fabricated entirely with off-the-shelf low cost commercial components



Working with Texas Instruments Components

Features

- Battery powered (Li-po, 10mAh)
- Inductive recharging (13.56MHz)
- 1 channel nerve recording (12kHz, 40kS/s)
- 1 channel ECG recording (500Hz, 1kS/s)
- 1 channel nerve stimulation
  - Switched-electrode stimulation
- 2.4 GHz proprietary digital radio
- Silicone encapsulation
- Softening polymer cuff electrodes

Pressure and Temperature Sensors

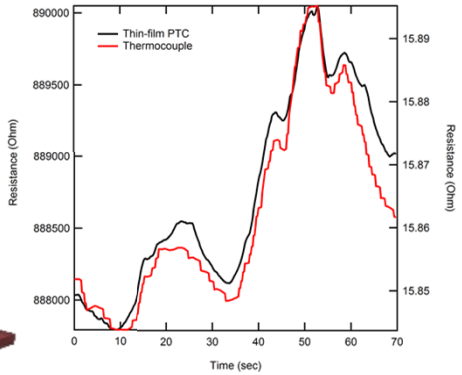
Pascalor

Pascalor, Inc.

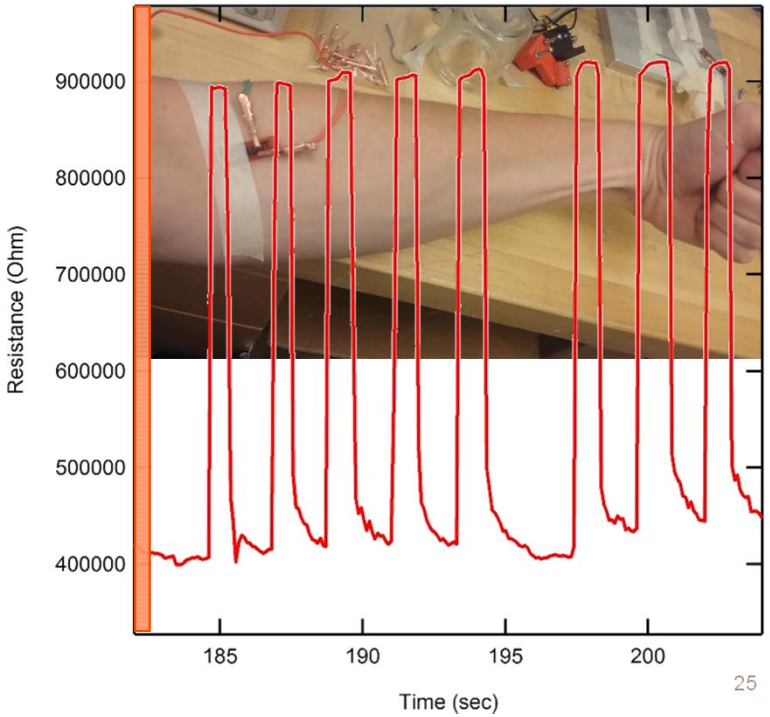
We are trying to…

…transform any contoured 2D surface into a rich, interactive 3D experience

Tracking finger height within centimeters of a sensor

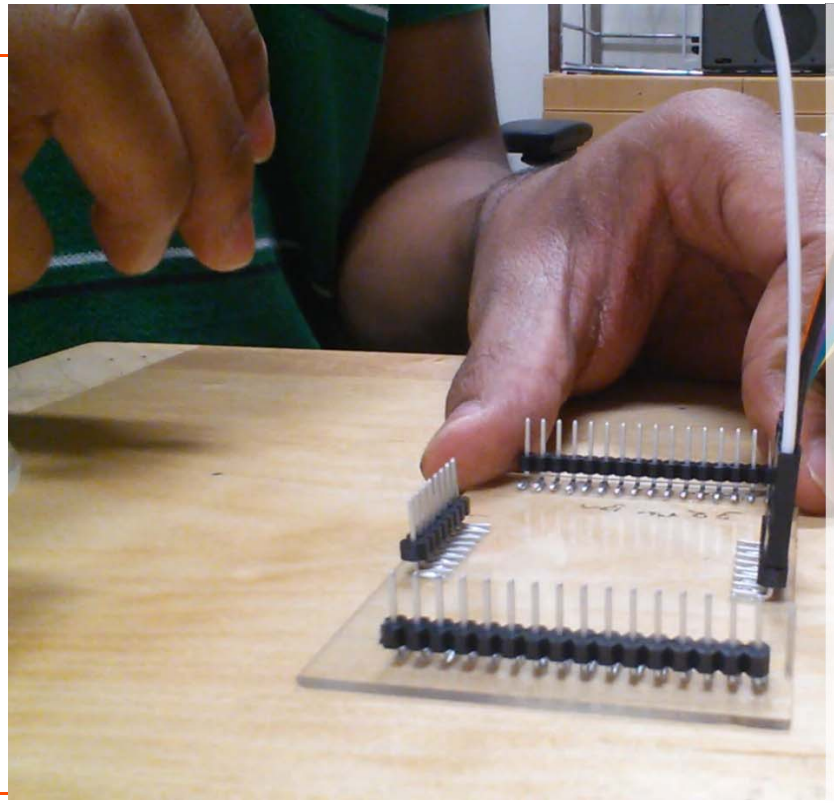


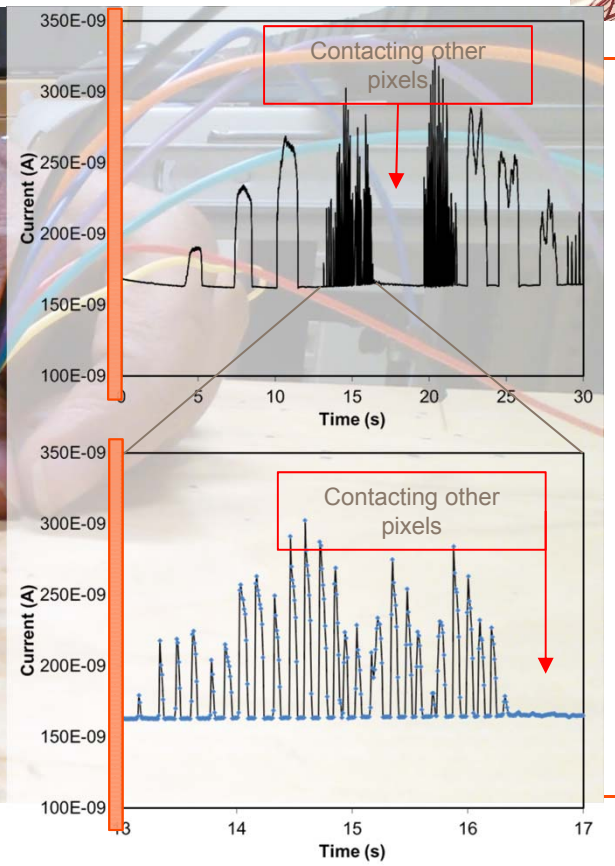
Brachial artery delivers warm blood to forearm muscles



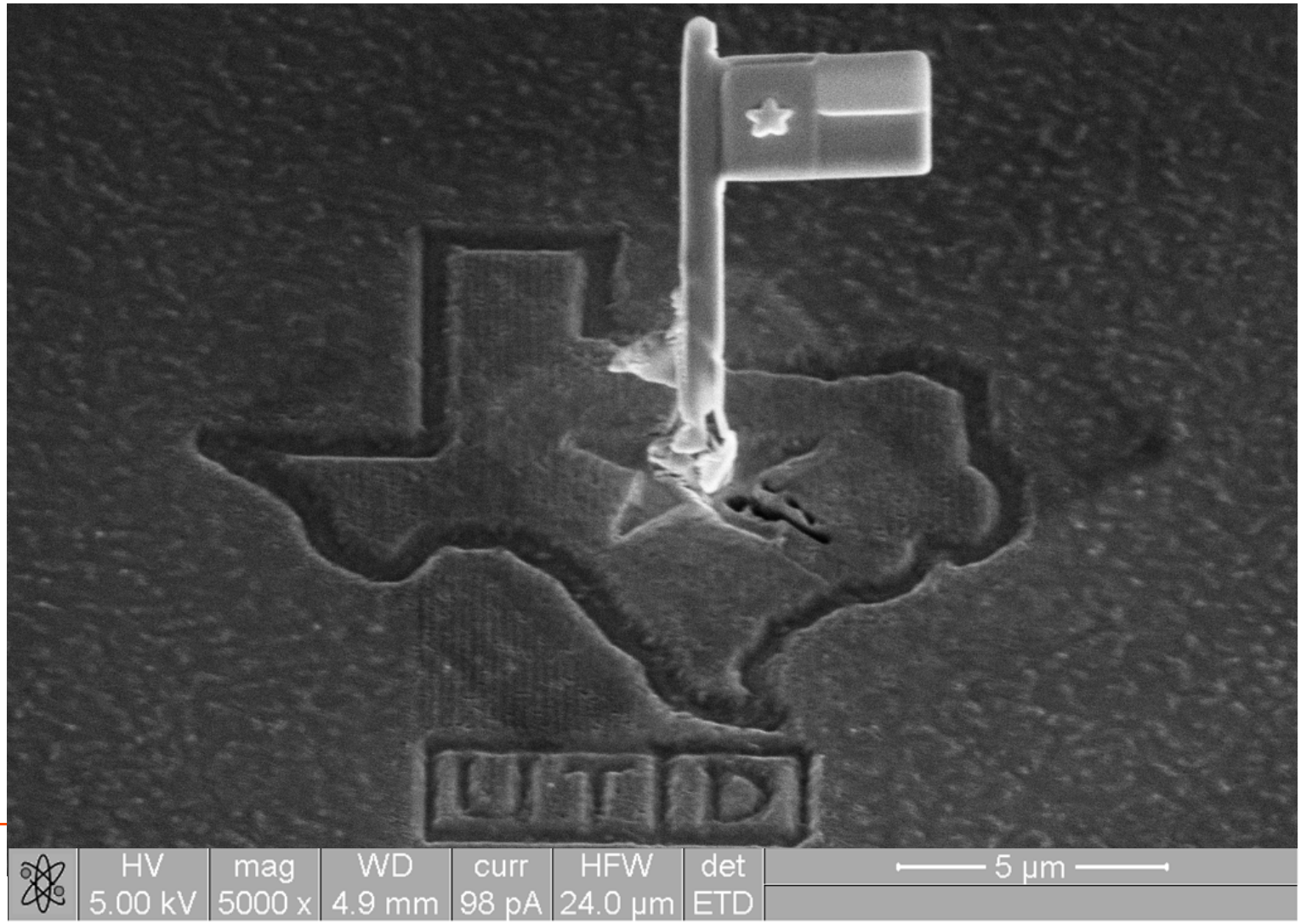
Transparent array: testing one pixel

Pascalor





Thinking Small



Inner Space: Bioelectronics and Medicine's Future

March 11-12, 2016 | Austin, TX | South by Southwest

Thanks

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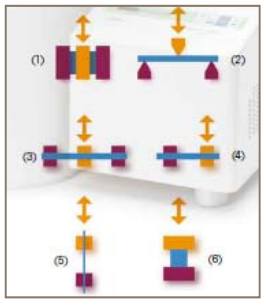
Adaptive 3D Technologies

Equipment

Dynamic Mechanical Analysis



Deformation Modes

Differential Scanning Calorimetry

DMA 3 point bend fixture – Load Cell: 40N, multi-frequency

DSC Robotic Autosampler – Temp range -100 °C to 700 °C

DMA Shear Clamp: Up to 1000 Hz

Universal Testing Machine

Thermo Gravimetric Analysis

Human Capital