Engineering Scaffold-Based Systems & Devices

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Outline

1. Intro
   - Background
   - Porous Collagen-Based Scaffolds

2. Research Focus
   - Regenerative Medicine
   - Medical Robotics
   - Brain-machine Interfaces
   - Tissue models

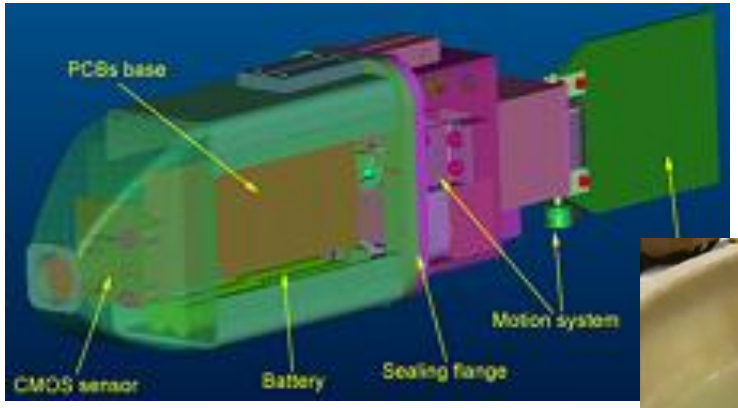
3. Leveraging Computational Science

Background

- Diploma Ing., Mechanical Engineering, **NTU Athens** — 2003
  - Design, dynamics & controls, robotics
- S.M., Mechanical Engineering, **MIT** — 2005
  - Dynamics and controls of space robotics & structures
- Ph.D., Mechanical Engineering, **MIT** — 2013
  - Biomaterials, nonlinear microscopy, regenerative medicine
- Post-doc, **NTU Athens** | Research Scientist, **Protavio Ltd** — 2013-2016
  - Cartilage degeneration, systems biology, multiplex proteomics
- Marie Curie Post-Doctoral Fellow, **IMBB-FORTH** — 2016-2019
  - Implants, CNS, stem cells, regenerative medicine
- Lecturer, Dept of Mechanical Engineering, **University of Cyprus** — 2019-2023
  - Biomedical engineering
- Assistant Prof., **University of Crete** | Collab. faculty, **IMBB-FORTH** — 2024-now
  - Biomedical engineering

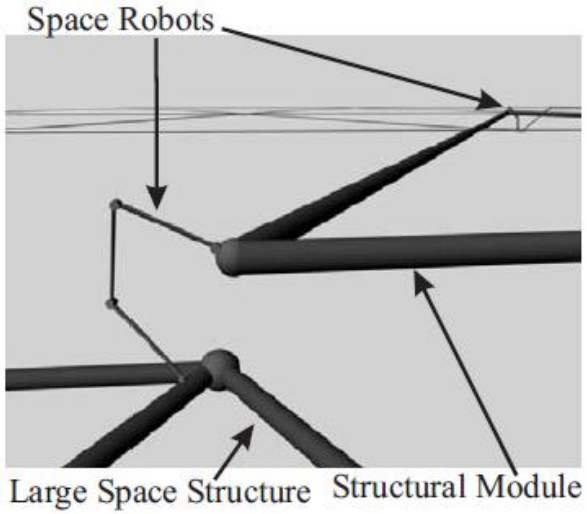
Roots: Underwater & Space Robotics

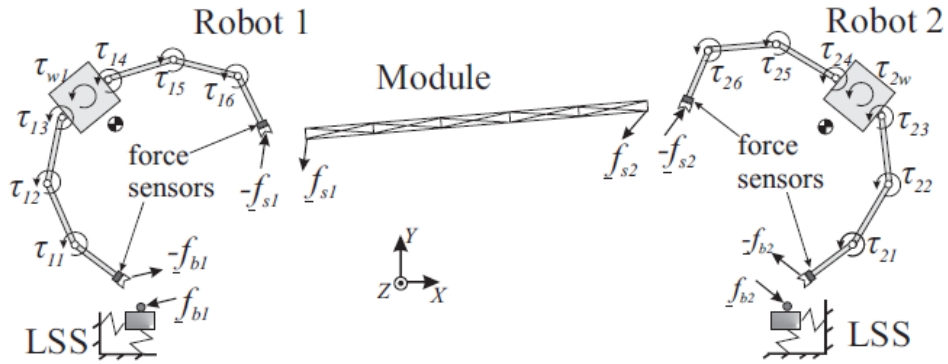
- Designed a small underwater robot
  - Best diploma thesis award, IEEE Greece



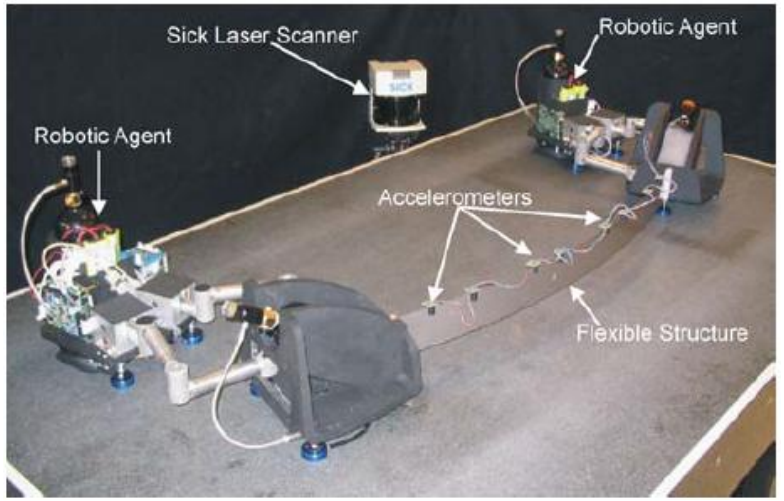
Robot fish in action (NTUA CSL Lab)

- Cooperative manipulation of large flexible structures by space robots





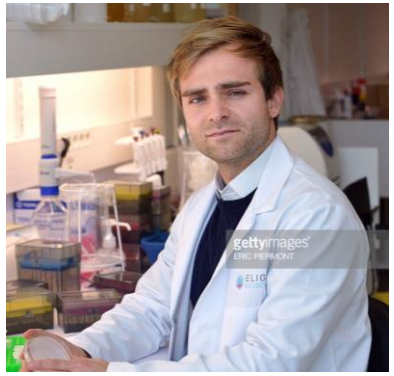
Cooperative manipulation of flexible structures



Research Objective

Engineer systems/devices that address important challenges of medicine

Challenges & Problems



Mechatronics

Computation

Optics

Engineering Design

Material science

Biology & Biotechnology

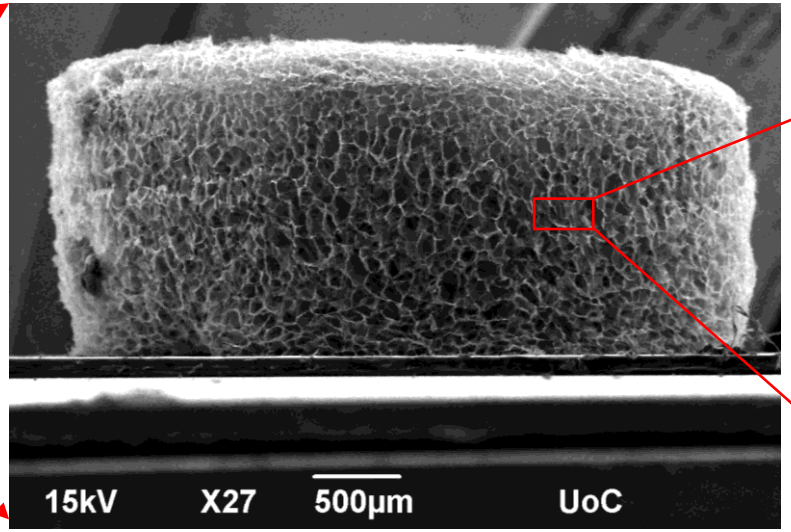
Clinical Practice

Systems, Devices

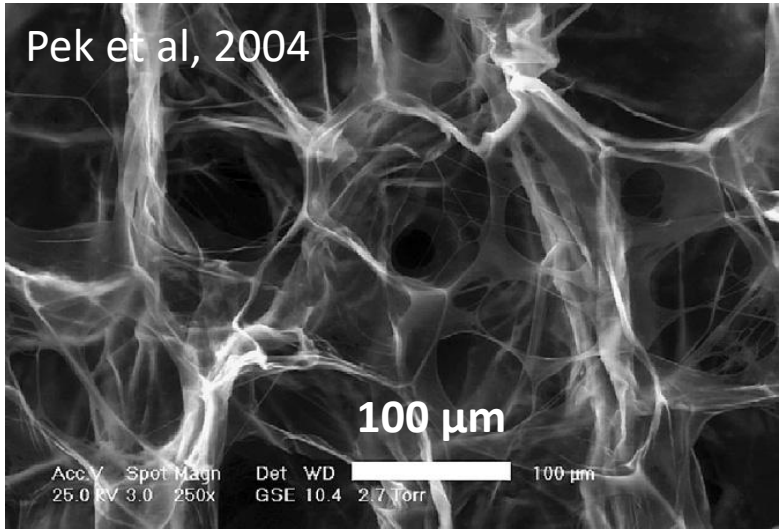
Porous Collagen-Based Scaffolds (PCS)

- Porous sponge-like biomaterials
- Made of microfibrillar collagen I
- FDA-approved grafts for regeneration

Integra® DRT®



A cylindrical PCS sample

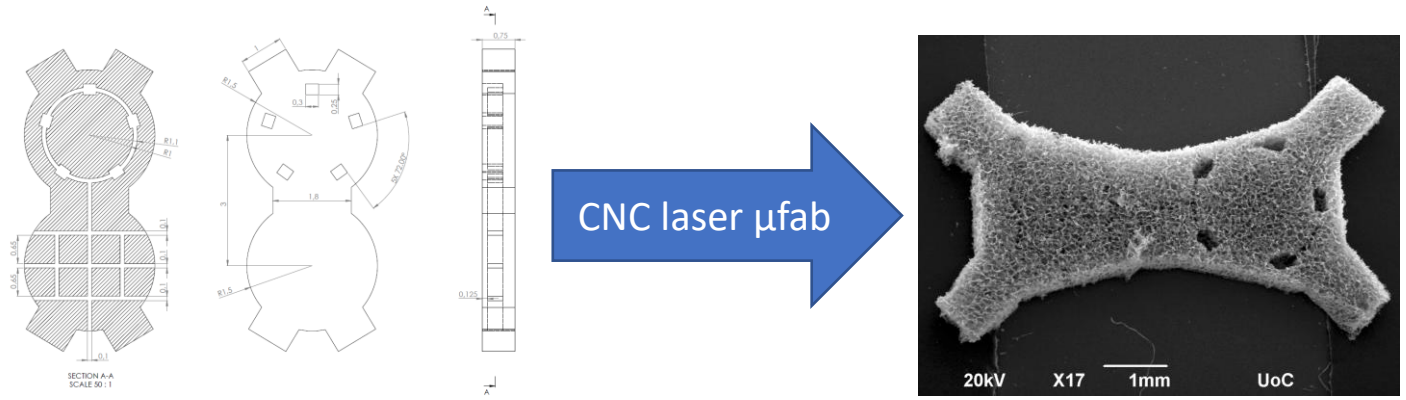


SEM of a PCS

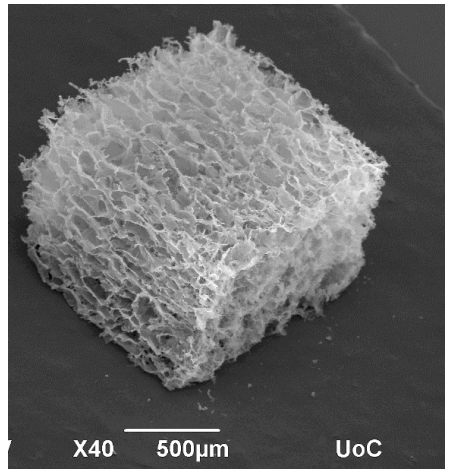
PCS Microfabrication

- Developed PCS microfabrication by laser ablation
  - High precision! Miniaturization! CNC!

- A novel biofabrication method
  - complementary to 3D printing



CAD drawing and resulting PCS implant



Spinal cord injury graft

PCS Engineering

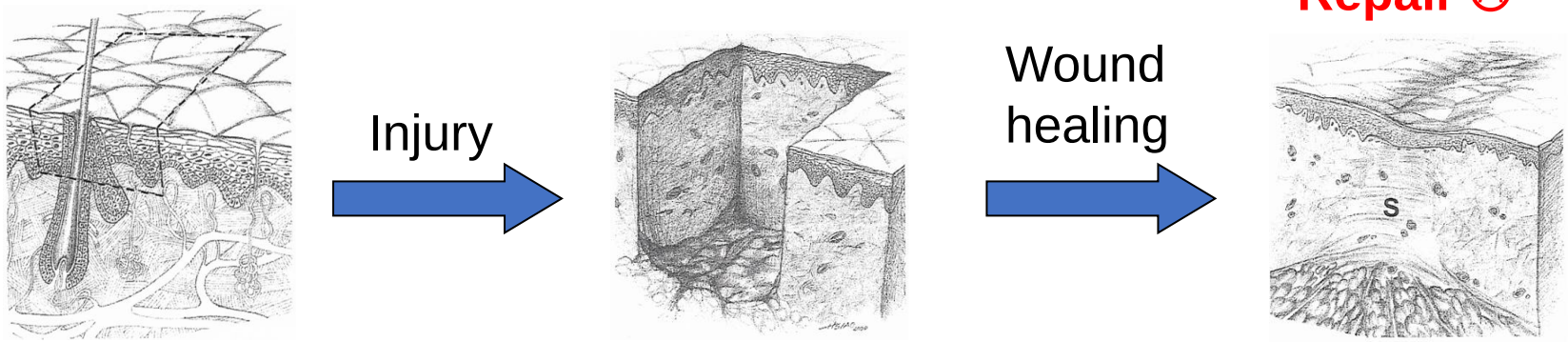
- Chemical Composition
- Mechanics
- Drug Delivery

Grafts for Regenerative Medicine

Clinical Need: The Irreversible Nature of Injury

- Injured/diseased organs do not heal spontaneously back to their original state
  - Huge social and financial impact
- Current solutions (Transplantations, Allografts) face severe limitations

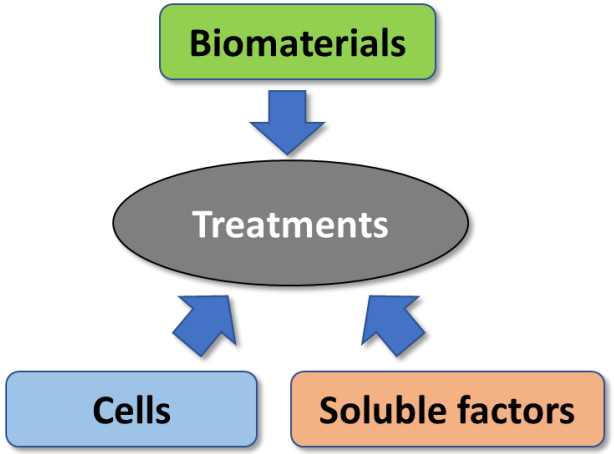
ACL injury (https://drrobertlaprademd.com)

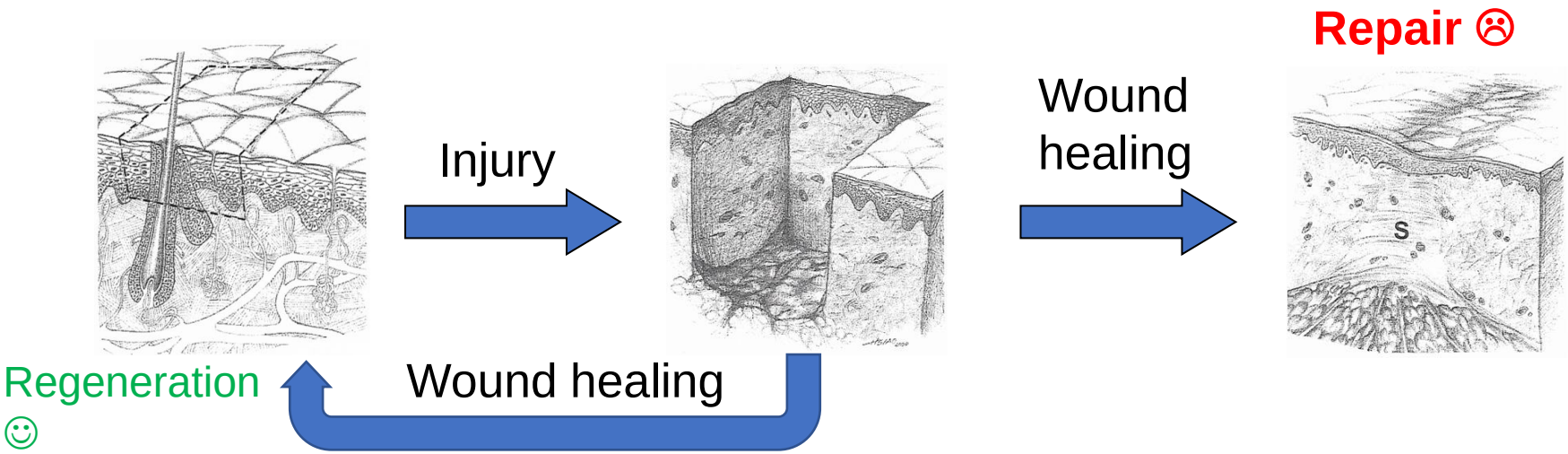


The Promise of Regenerative Medicine

- Modulate wound healing → *de novo* synthesis of normal tissue *in situ*

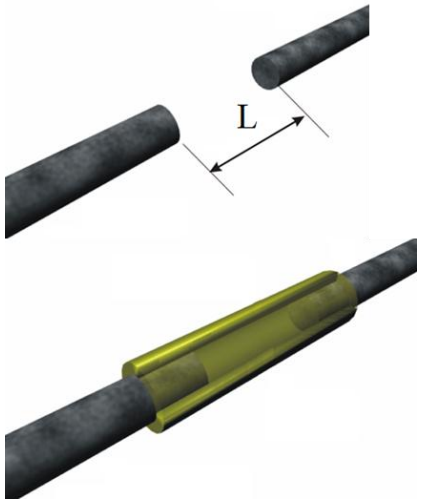
- Toolkit
  - Biomaterials
  - Cells
  - Soluble factors (small molecules, biologics)





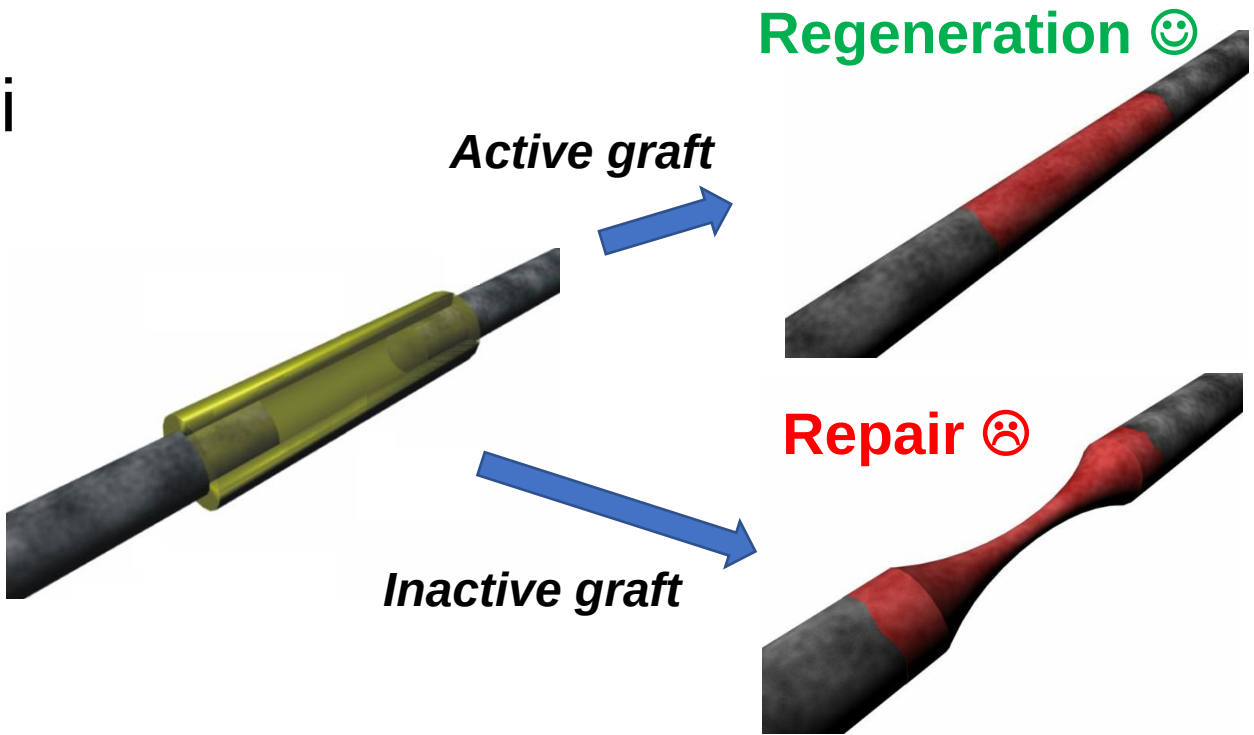
Treatments for Peripheral Nerve Injury

- PN injury (transection)
  - Caused by accidents
  - Causes loss of sensing/locomotion



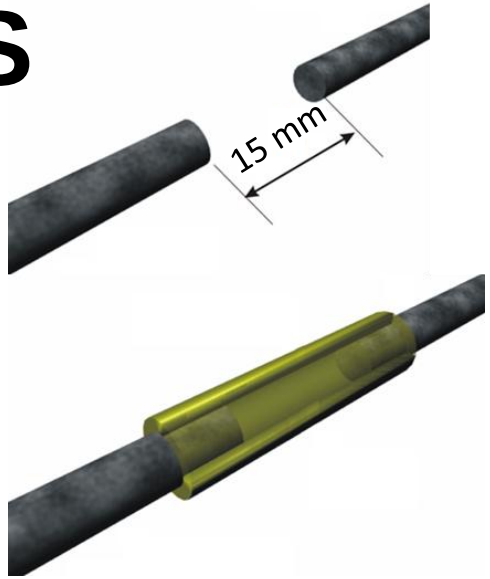
PN transection and conduit grafting

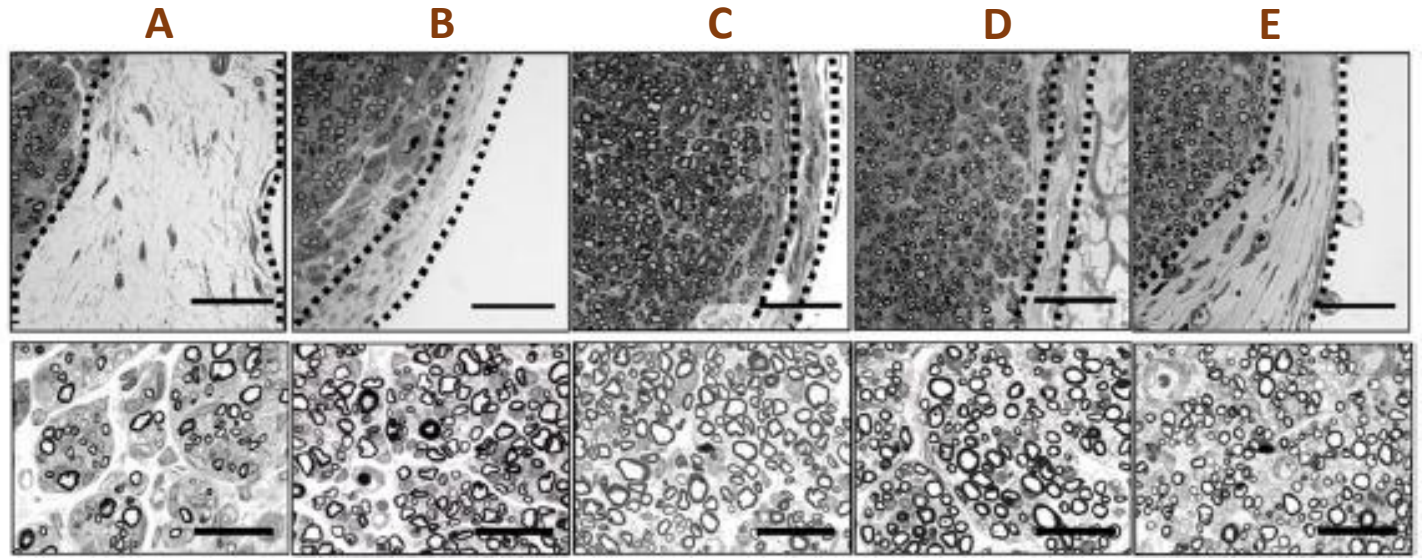
- PCS Conduit Treatments for PNi
  - WH outcome depends strongly on conduit properties!
  - Still, don't understand why

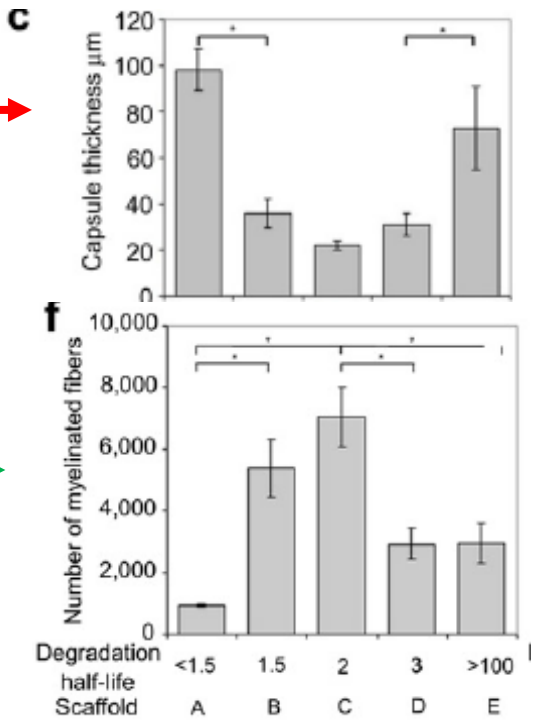


Regulation of PN Wound Healing by PCS

- Studied transected rat PNs grafted with 5 PCS types
  - increasing x-linking
- Results show strong inverse correlation between axon regeneration & wound contraction







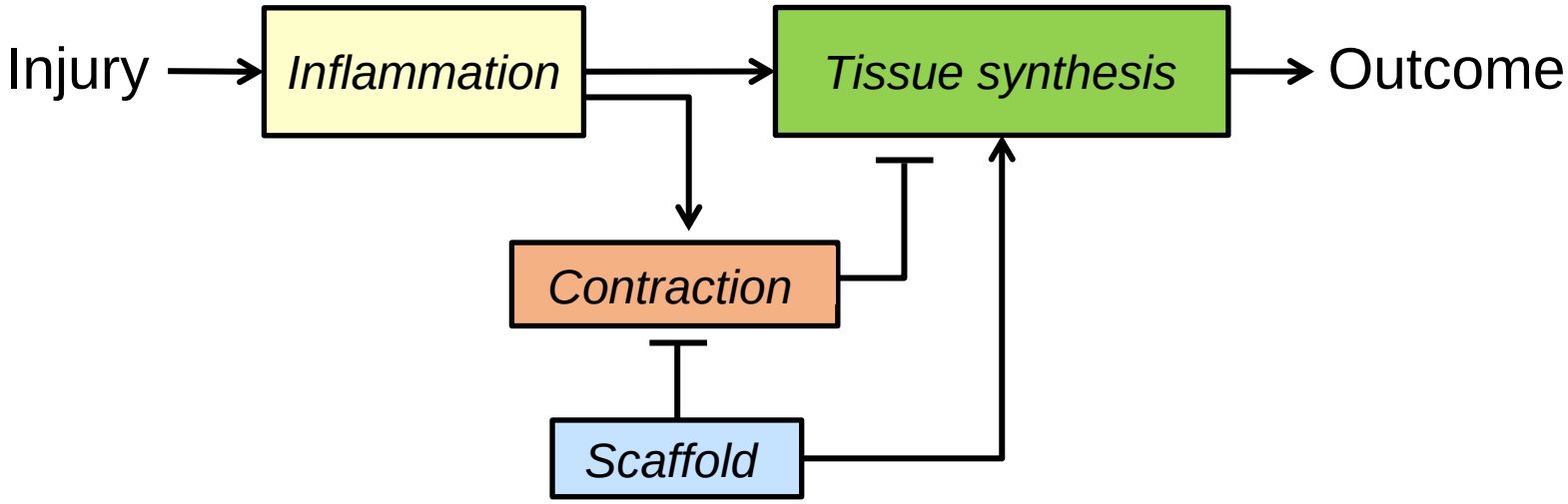
***Top**: capsule thickness. **Bottom**: myelinated axons in the gap middle (9 weeks post injury)*

Soller, Tzeranis et al. 2012

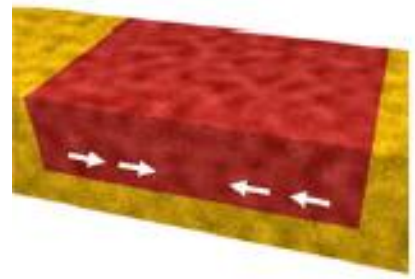
Hypothesis: Regeneration VS Wound Contraction

- A key role of biomechanics observed in
  - Induced regeneration (skin, PNS)
  - Animals that spontaneously regenerate tissues

- Blocking wound contraction proposed as a key mechanism that can drive regeneration



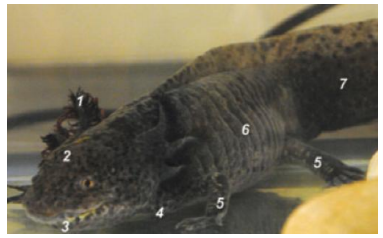
Stress field (Skin)



Stress field (PN)

A. Kempi mouse

Axolotl



Yannas & Tzeranis, *npj regen medicine* 2021

Treatments for CNS Injuries

- Brain trauma, stroke, spinal cord injury
  - Major unmet clinical need

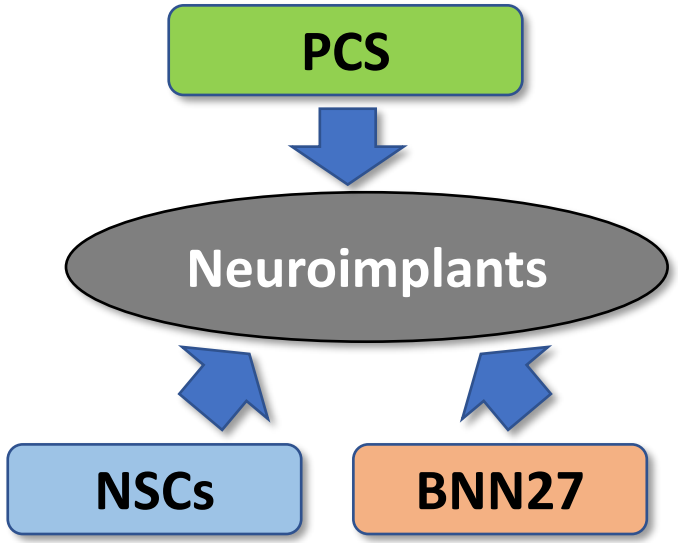
- CNSi are much harder to treat than PNSi
  - Loss of neural cells
  - Inhibitors of axonal elongation

- Biomaterials by themselves cannot induce regeneration

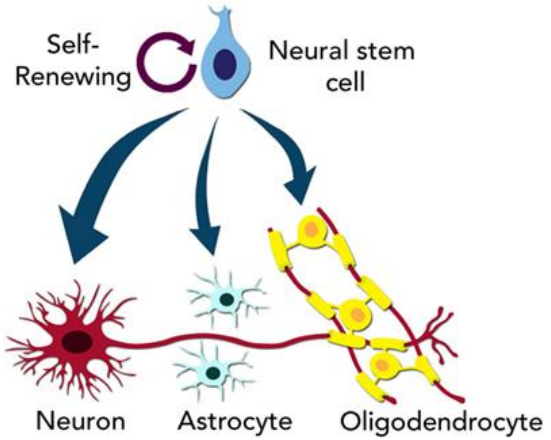
Spinal cord injury (wikipedia)

PCS-based Grafts for CNS Injuries

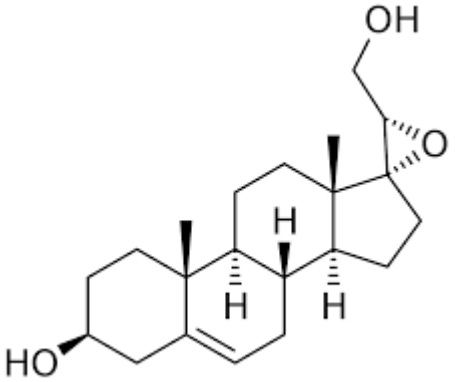
- **Neuroimplants**: PCS Grafts that deliver Stem Cells and drugs at spinal cord injury (SCI) lesions



- Neural stem cells (NSCs)
  - Progenitors of neurons & glia



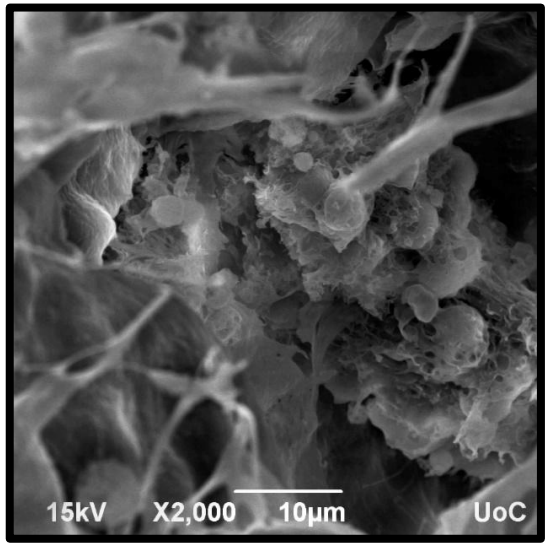
- BNN27
  - Small-molecule analog of NGF
  - Neuroprotective & neurogenic activity



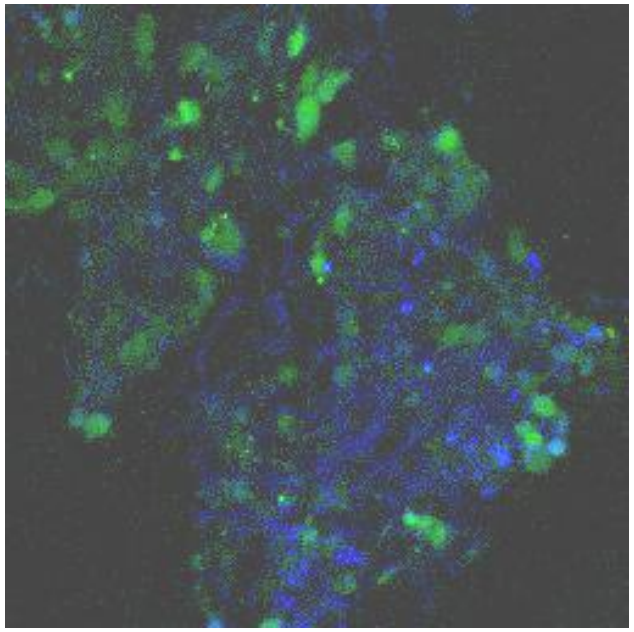
In collaboration with Prof. A. Gravanis & I. Charalampopoulos (U Crete)

Neuroimplant Design

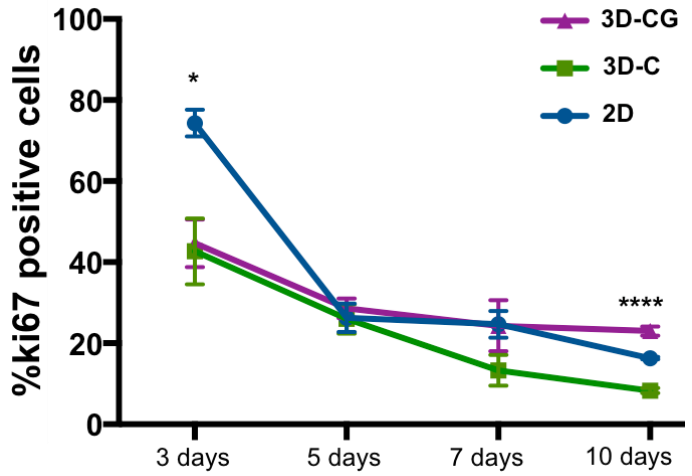
- Evaluate PCS grafts based on *in vitro* 3D culture of NSC in PCS



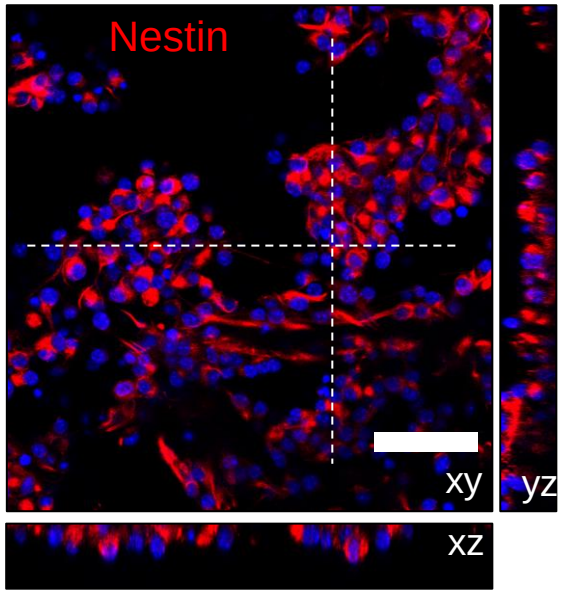
NSCs inside a PCS (neuroimplant)



Ca^{+2} imaging of NSCs in PCS



NSC proliferation study



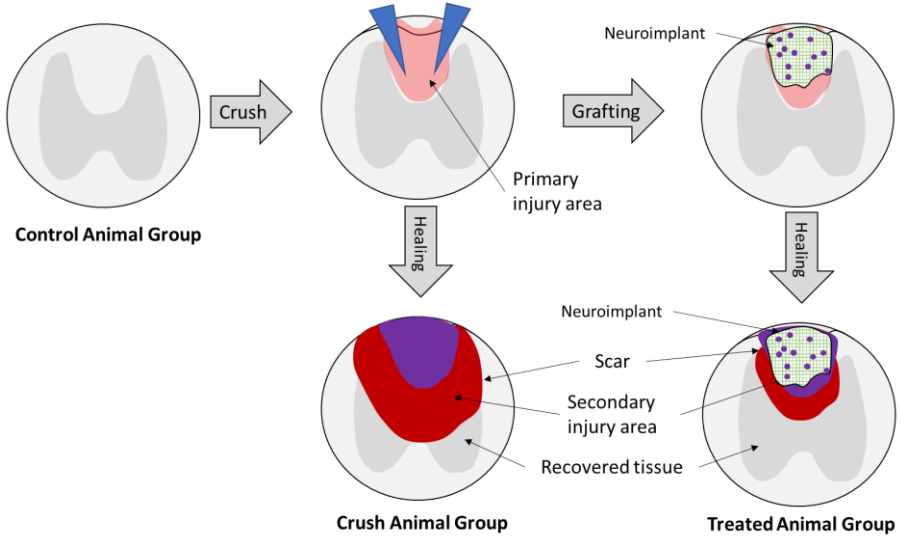
$Nestin^{+}$ NSCs inside a CS

Kourgiantaki, et al., npj Regen. Med. 2020

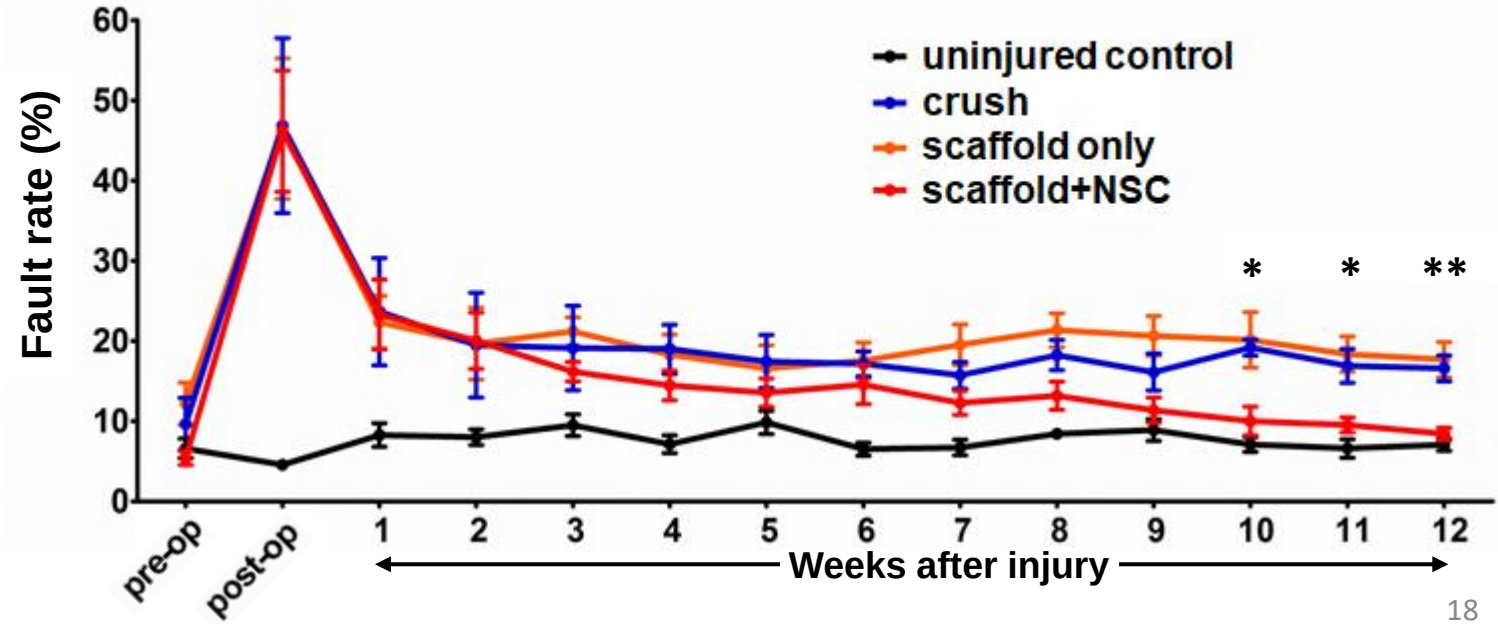
Neuroimplant Effects on Spinal Cord Injury

- Tested Neuroimplants in a Mouse SCI model
  - Dorsal column crush
  - NSC delivery

- Neuroimplants improved locomotion recovery 10-12 weeks post-injury

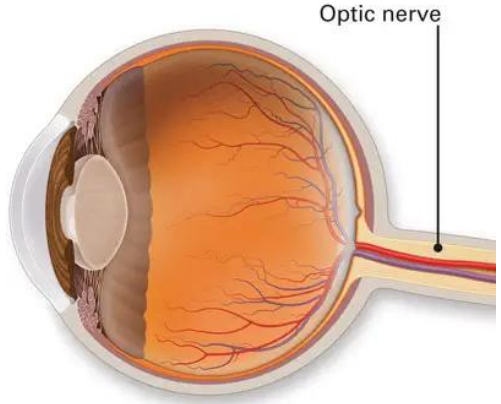


Kourgiantaki et al., npj Regen. Med. 2020
Georgelou et al., biomedicines 2023

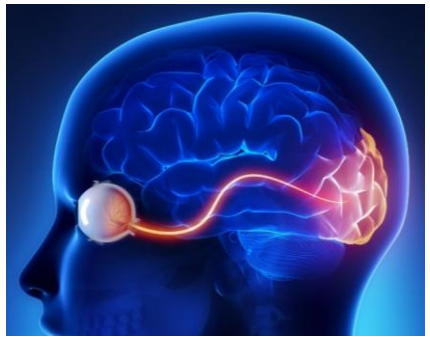


Graft-mediated BNN27 Delivery After Optic Nerve Injury

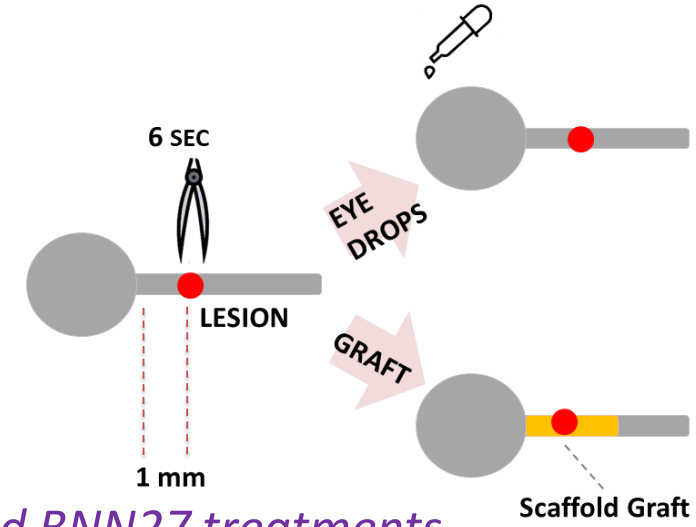
- Optic Nerve Injury (ONI)
  - Side-effect of accidents
  - Induces Retinal Ganglion Cells (RGCs) death → blindness



www.aao.org



- BNN27 delivery in a mouse ONI model via biomaterial grafts
  - Biomaterial-in-a-biomaterial approach



ONI model and BNN27 treatments

In collaboration with Prof. D. Karagogeos & Dr. M. Savvaki (U Crete)

K. Georgelou et al. submitted

Medical Robotics

Soft Growing Robots (SGR)

- Ordinary **medical robots**
  - made of stiff components
  - emphasize precision & haptic interfaces

- Emerging **Soft Robots**
  - made of soft deformable materials
  - Diverse properties & capabilities

- **Soft Growing Robots (vine robots)**
  - Expand via eversion
  - Adapt shape to environment, navigate via narrow lumen
  - Minimal friction forces to environment
  - Can contain a tool-holding catheter

daVinci medical robot

SGR can pass narrow holes

Catheter with SGR

https://tia.ucsb.edu/vine-robot-technology

Soft Growing Robots Challenges

- Miniaturization
- Fabrication
- Steering
- Sensing
- Actuation
- MRI compatibility

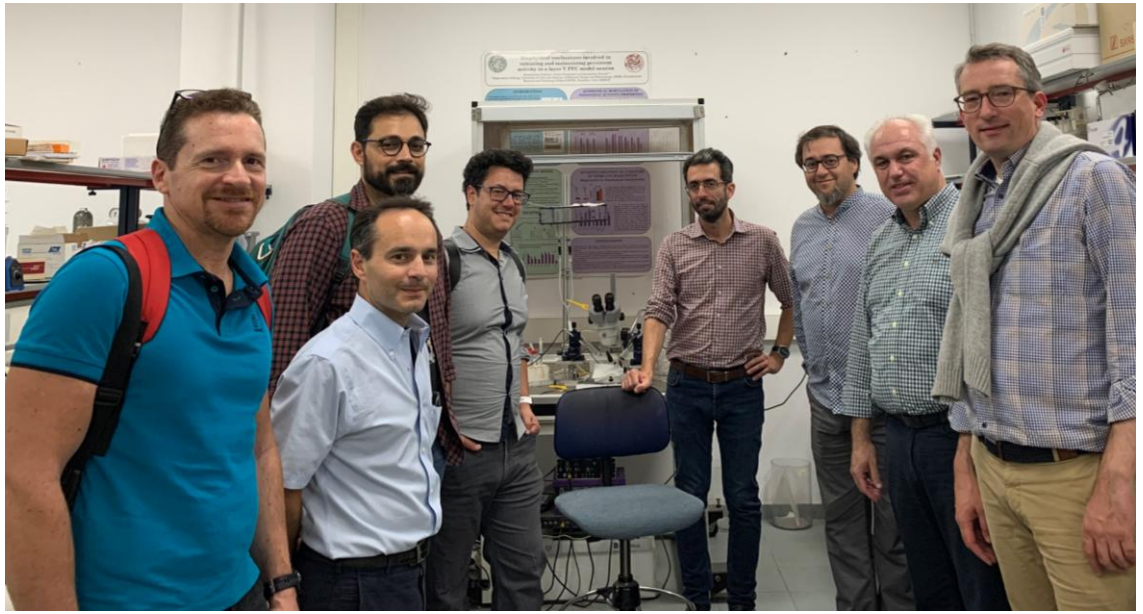
SGR catheter steering

Extension of a SGR with a catheter (KCL, UTH)

Project SoftReach

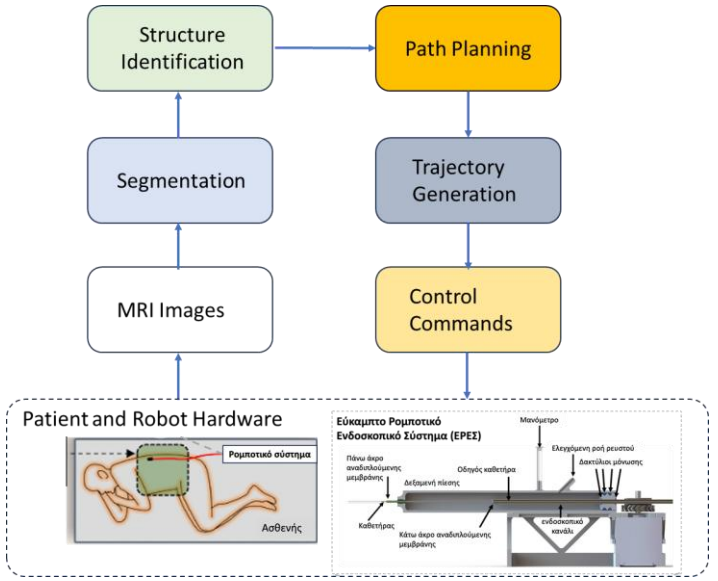
European Innovation Council

- Engineer an MRI-guided SGR for delivery of therapeutics-loaded PCS deep in the brain
- Provide minimally-invasive access to the brain
- Demo targeted delivery in the brain
- FORTH
  - Implant design & fabrication
  - Study therapeutic effects in mice

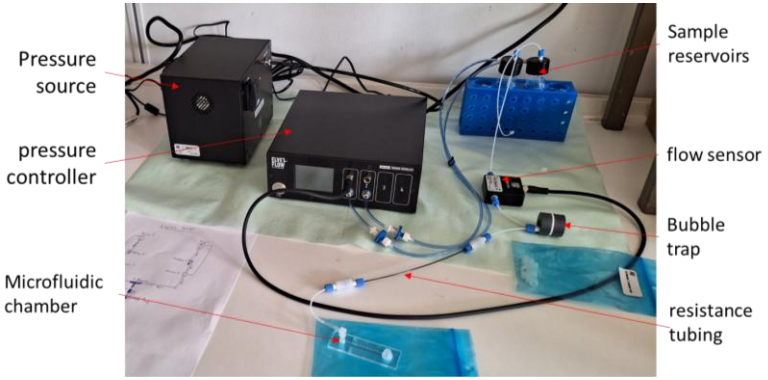


Project SoftReach

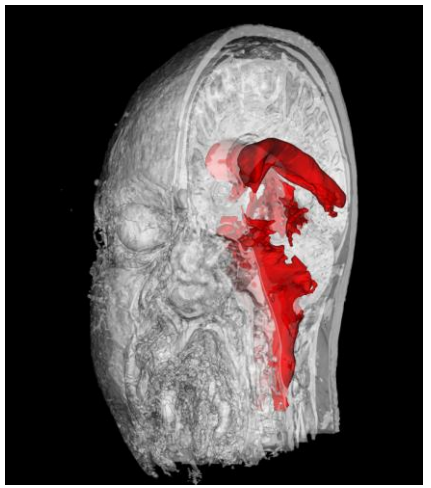
- Robot hardware design & fab
- MRI-based robot navigation
- Robot control
- Implant design, fabrication & attachment
- Therapeutic delivery in mice brain
- Design brain phantoms



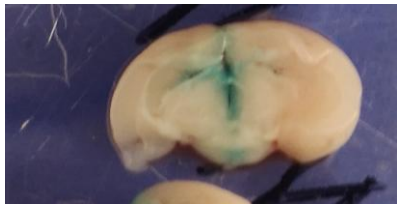
Robot control architecture (UTH)



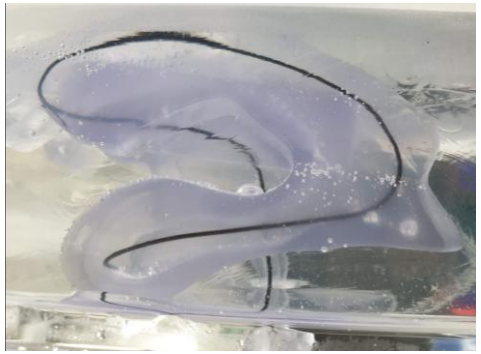
Microfluidic systems (FORTH)



T2 MRI (KCL, GRIT)



Dye delivered in mouse brain (FORTH)



Catheter elongation inside a phantom (KCL)

Project SoftReach

www.softreach.eu

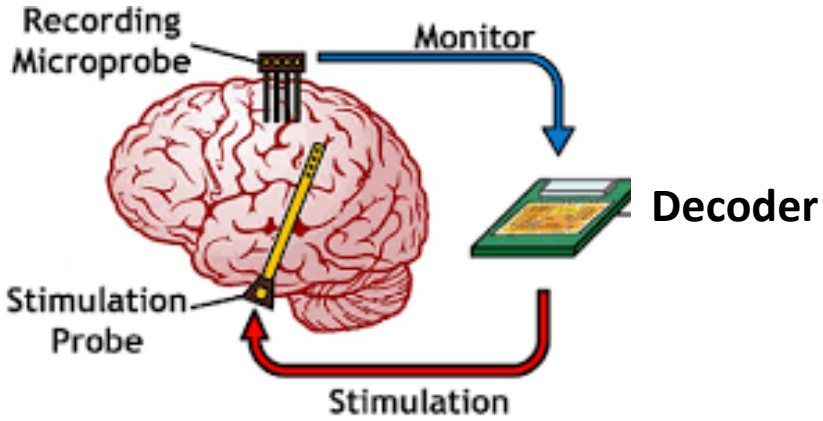
Brain Machine Interfaces

Brain Machine Interfaces

- Direct communication links between the CNS electrical activity and an external device

- BMI rely on
  - **Electrodes** to record/stimulate CNS
  - **Decoding algorithms** acquired brain signals

- Applications
  - Disease monitoring and therapy
  - Assistive technology



Closed loop BMI

BMI for SCI treatment (EPFL)

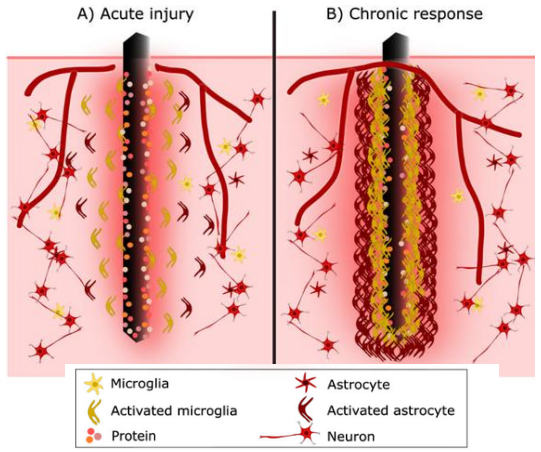
Project BioHySiC (Synergy grant)

FOUNDATION FOR RESEARCH AND TECHNOLOGY - HELLAS

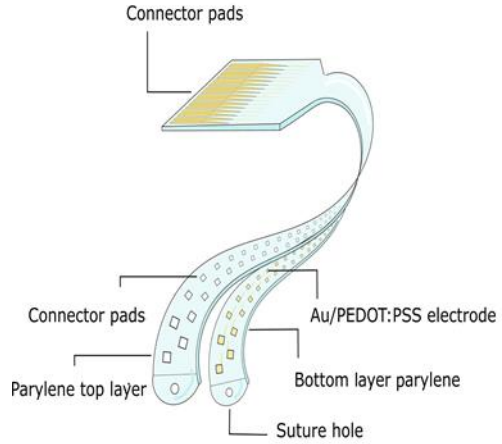
- BMI are limited by electrode longevity
  - Abiotic response → delamination
  - Biotic response → inflammation

- Proposed solution: novel electrode designs
  - Novel SiC electrodes
  - Novel biomaterial coatings

- Design and characterize a novel epidural μECoG device for spinal cord monitoring



Chronic response around implanted electrodes



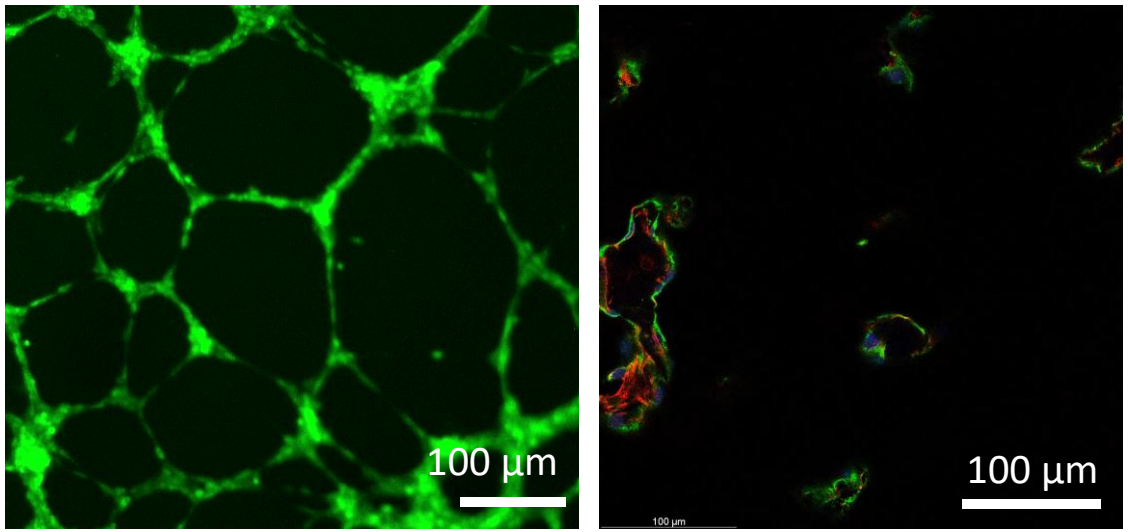
μECoG design (Woodington et al., 2024)

Tissue Models

3D Tissue Models

- Ordinary cell culture poorly mimics *in vivo* environment
  - Questions result validity

- 3D tissue models better emulate tissues
  - Cells grown inside biomaterials
  - Mimic structure of specific tissues

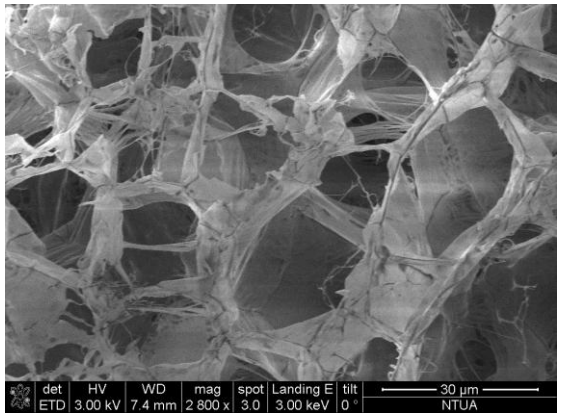


Vessel-like structures formed by endothelia grown on a Matrigel (left) or inside a PCS (right)

- Applications
  - Implant design
  - Drug discovery
  - Basic science

3D Tissue Models Based on PCS

- Key device specs
  - Low cost
  - Simple to use
  - High-throughput quantification



- Quantify neural cell ensembles in PCS via automated microscopy

Operetta HCS (IMBB-FORTH)

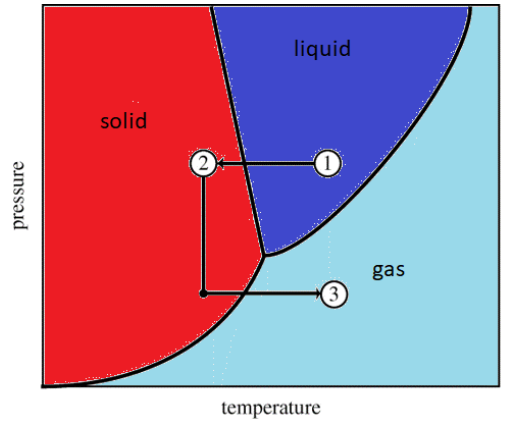
3D Tissue Models Based on PCS

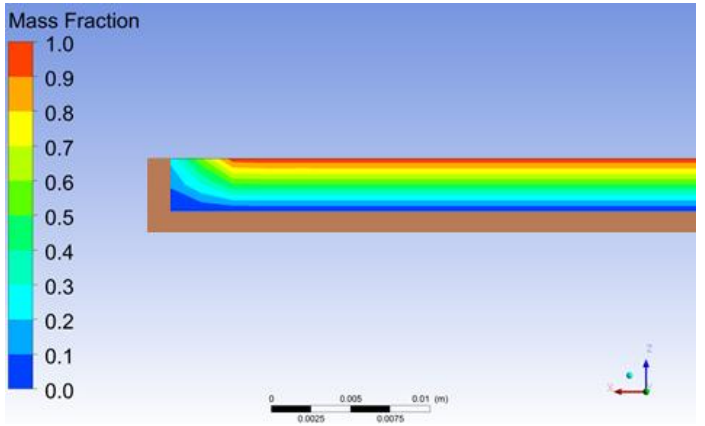
- Design devices to facilitate cell culture & quantification in PCS
  - House PCS
  - Interface fluidics
  - Automate manipulations
  - Enhance repeatability

Leveraging Computational Science

Simulation of Complex Systems

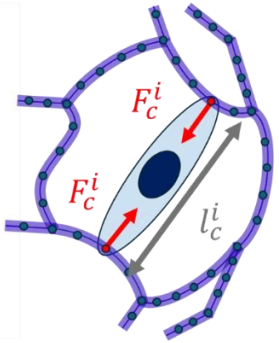
- PCS fabrication
  - Lyophilization
  - Crystal growth
  - Rheology





CFD of water freezing during lyophilization

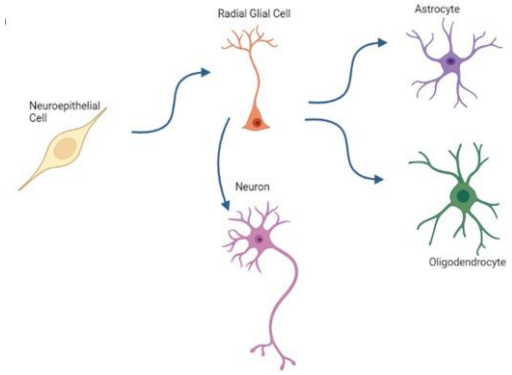
- Scaffold Mechanics
  - µm-scale to cm-scale
  - Nonlinear effects
  - Interactions with environment
  - Fluid flow

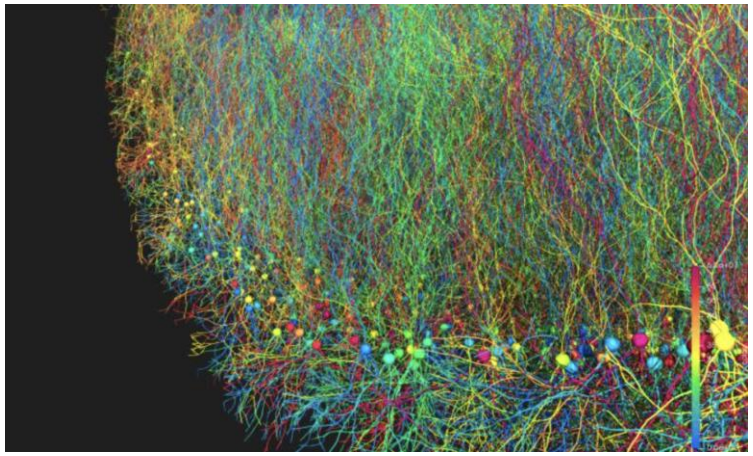


FEA of PCS lattices reveals the matrix stiffness perceived by cells grown in PCS

Simulation of Complex Systems

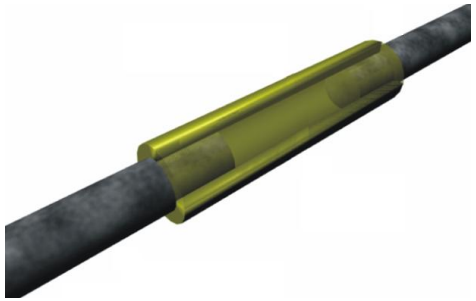
- Tissue construct response
  - Mechanobiology
  - Biomechanics
  - Stem cell differentiation
  - Scaffold remodeling

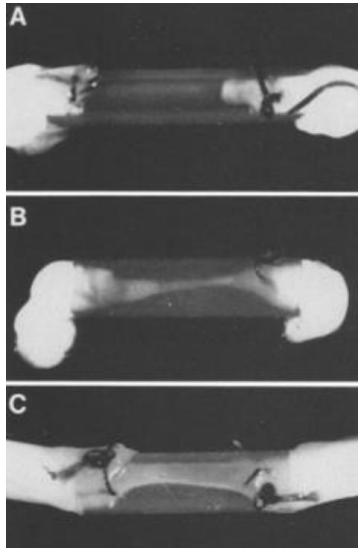


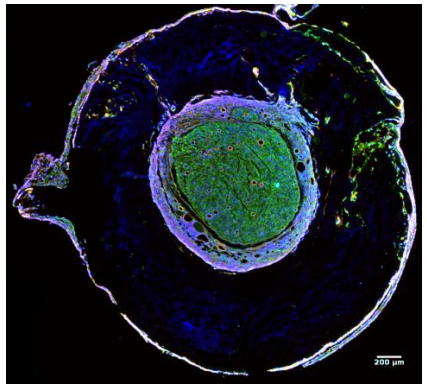


Agent-based modeling and stochastic simulation of NSC differentiation and neuronal elongation (Biodynamo)

- Wound Healing response
  - PNi
  - CNS (SCIi) response
  - Around electrodes



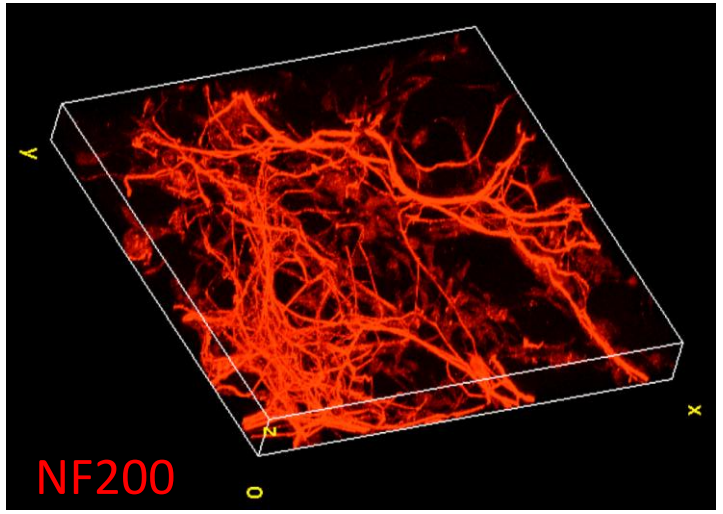




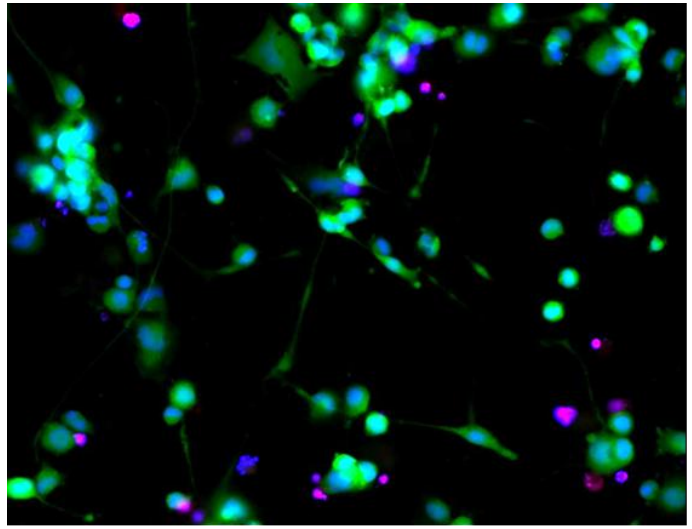
Time response of wound healing following PNi

Data Analysis

- Large 3D imaging datasets
  - Classification
  - Single-cell image informatics
  - Statistics



Confocal z-stack of DRG neurons grown inside PCS (A. Kourgiantaki)



HCS images of NSC34 cells (O. Sarlidou)

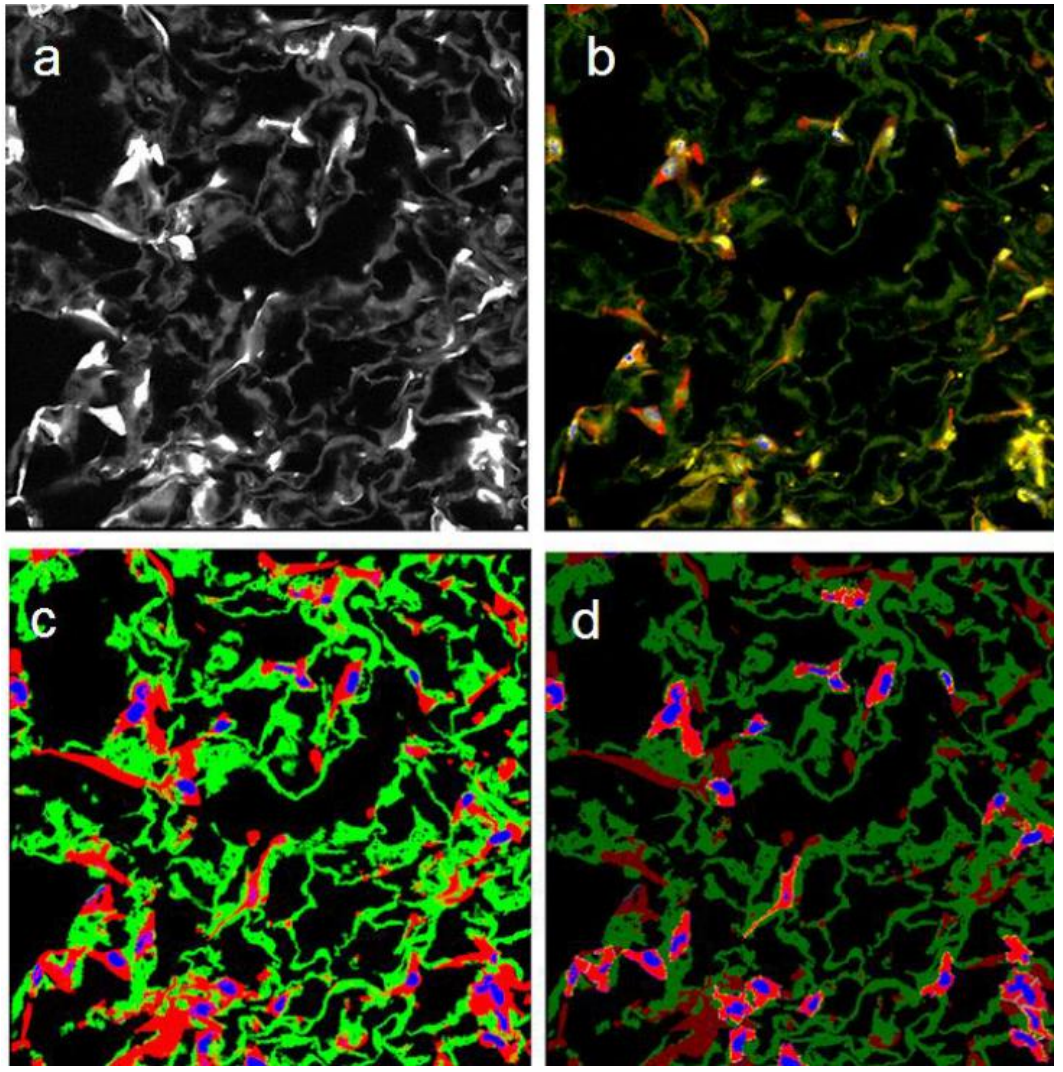
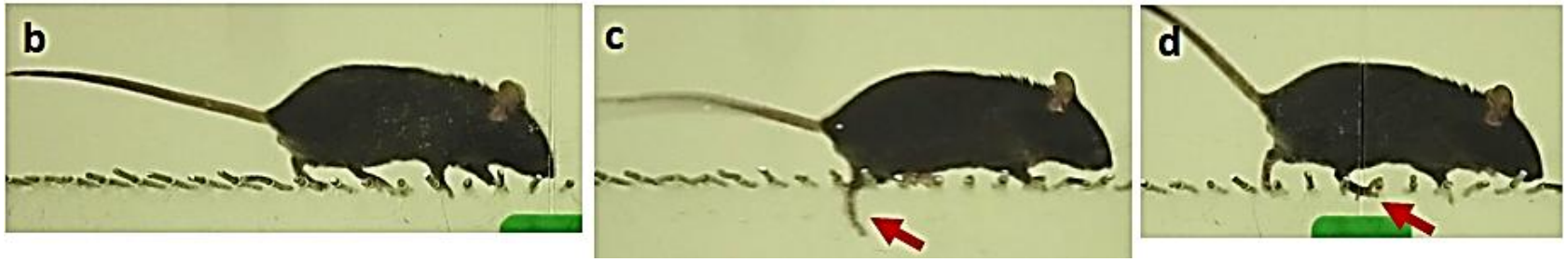


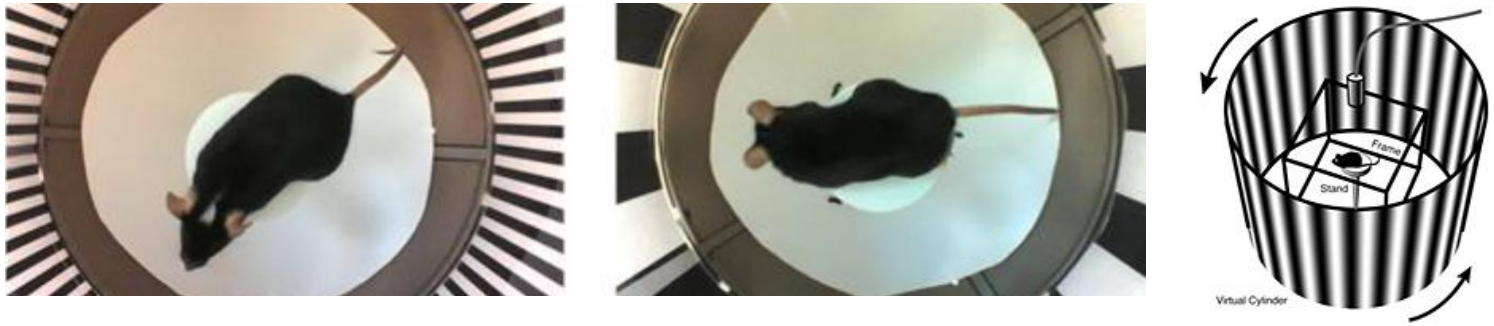
Image analysis of 16-channel z-stacks for single-cell identification and analysis

Data Analysis

- Analysis of behavioral assays videos
  - Crucial to evaluate wound healing response, drug effects
  - Need efficacy, objectivity



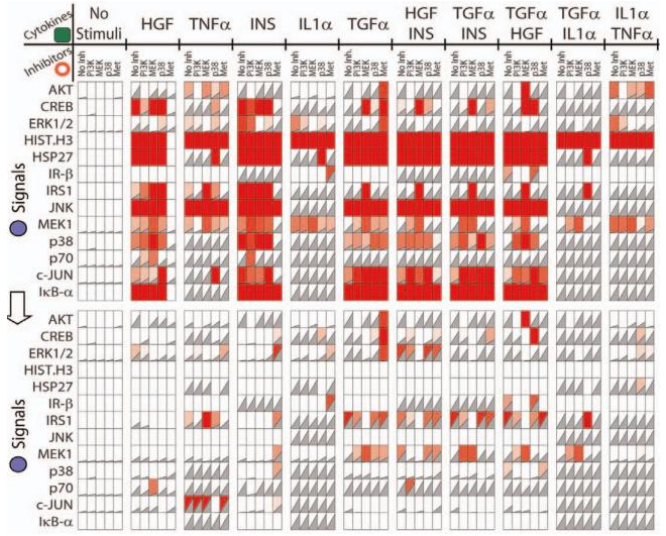
Video snapshots from the horizontal ladder walking assay (top) and the optomotor assay (bottom)



Data Analysis

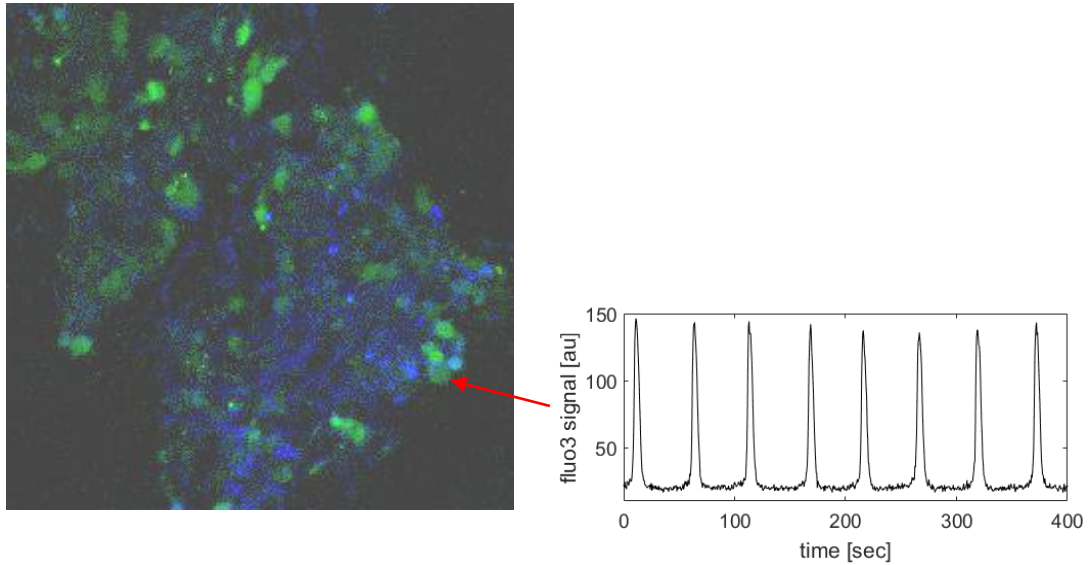
- Multi-omics
  - Imaging
  - Proteomics
  - Transcriptomics

Luminex phosphoproteomic dataset (Mitsos et al. 2009)



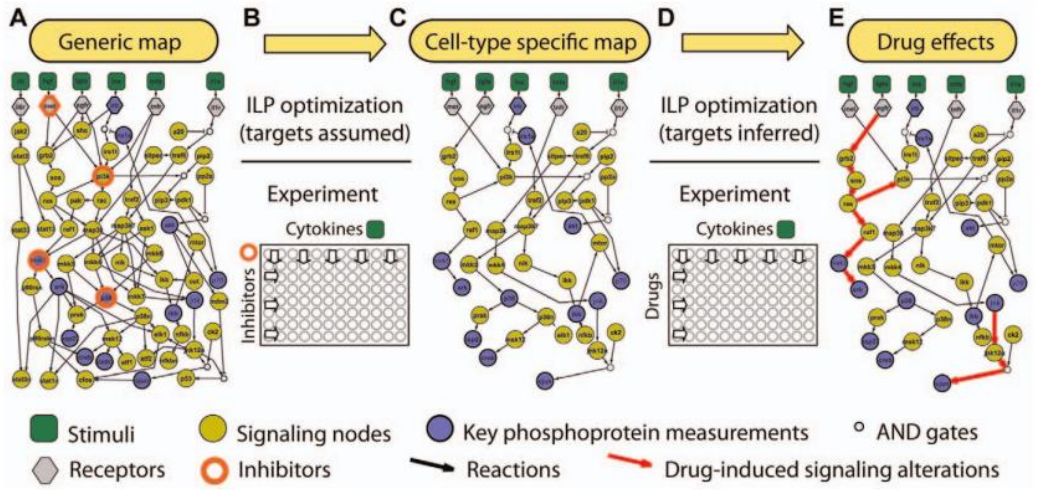
- Analysis of neural networks
  - Decoding electrode datasets
  - Ca^{+2} imaging datasets

Ca+2 imaging of walking assay (top) and the optomotor assay (bottom)



Optimization & Design

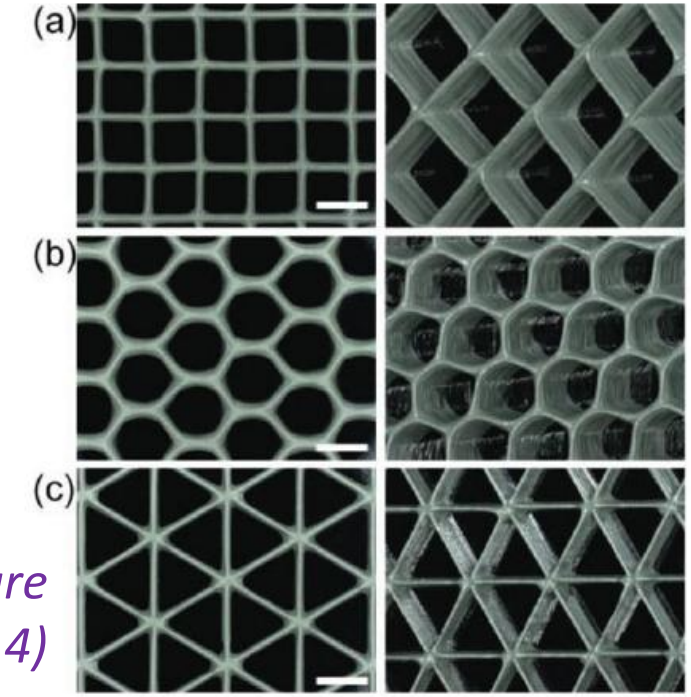
- Signal transduction Pathway Analysis
  - ILP for Drug mode of action analysis



Mode of action analysis (Mitsos et al. 2009)

- Biomaterial & graft design
  - Structure
  - Cell content
  - Stem cell fate manipulation

- Robot design



Optimization of lattice structure (Compton and Lewis 2014)

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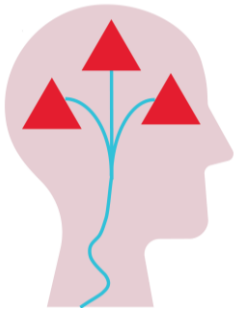
Job Openings (PostDoc, PhD)

- Project *Softreach*
  - Biofabrication, fluidics, mechatronics
  - Cell-biomaterial interactions
  - Drug delivery *in vivo*, neurogenesis



European Innovation Council

- Project *BioHySiC*
  - Electrode engineering, SiC fabrication
  - Biomaterial-CNS interactions

FORTH
FOUNDATION FOR RESEARCH AND TECHNOLOGY - HELLAS

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Reneurocell Therapeutics

- A new spinoff of FORTH & UoC

- Secured seed funding to develop human SCI grafts

- Job Openings
  - Stem cell engineering
  - Neural engineering
  - Mouse models
  - Biofabrication
  - Entrepreneurship

info@reneurocell.com

Thank you!

Questions?