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UNIVERSITÉ
Grenoble
Alpes

Gaëlle Offranc Piret

Développement d'implants (cérébraux ultra-souples) biomimétiques pour y intégrer des capteurs et effecteurs dédiés à des fonctions théra-gnostiques

erc
European Research Council
Established by the European Commission

BRAINTECH LAB U1205,
THERANOSTIC TECHNOLOGIES FOR BRAIN MICRO-ENVIRONMENT DECIPHERING AND THERAPIES

CHU GRENOBLE ALPES

LUND UNIVERSITY

ESIEE PARIS

cea

iemn
Institut d'Electronique, de Microélectronique et de Nanotechnologie
UMR CNRS 8520

RENATECH
French national nanofabrication network

UNIVERSITÉ Grenoble Alpes

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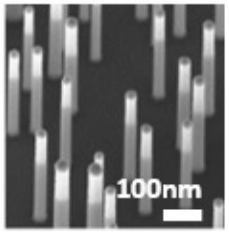
PhD and post-doc

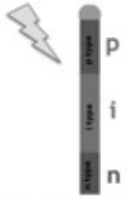


MICRO & NANOTECHNOLOGY

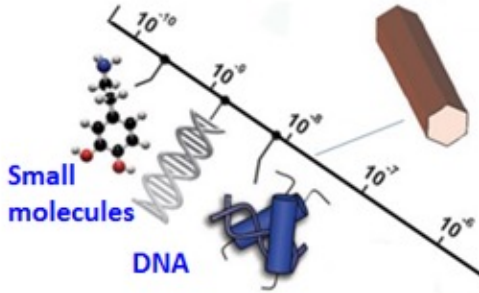
Nanowires

Surface chemistry

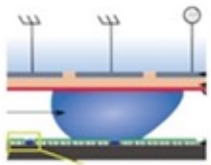
Lithography



Nanowire device delivering ~ 1V



Devices



Soft substrates

Soft tissue

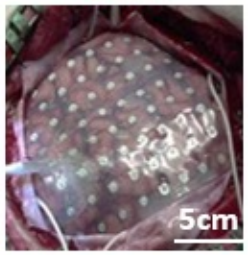
European Research Council
Established by the European Commission

UNDERSTANDING THE BRAIN
&
TREATING BRAIN DISEASES

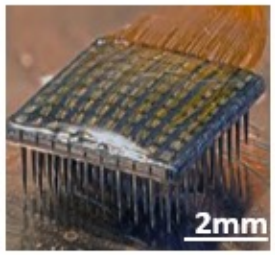
Model the brain ← Record and interface the brain

EEG

ECoG

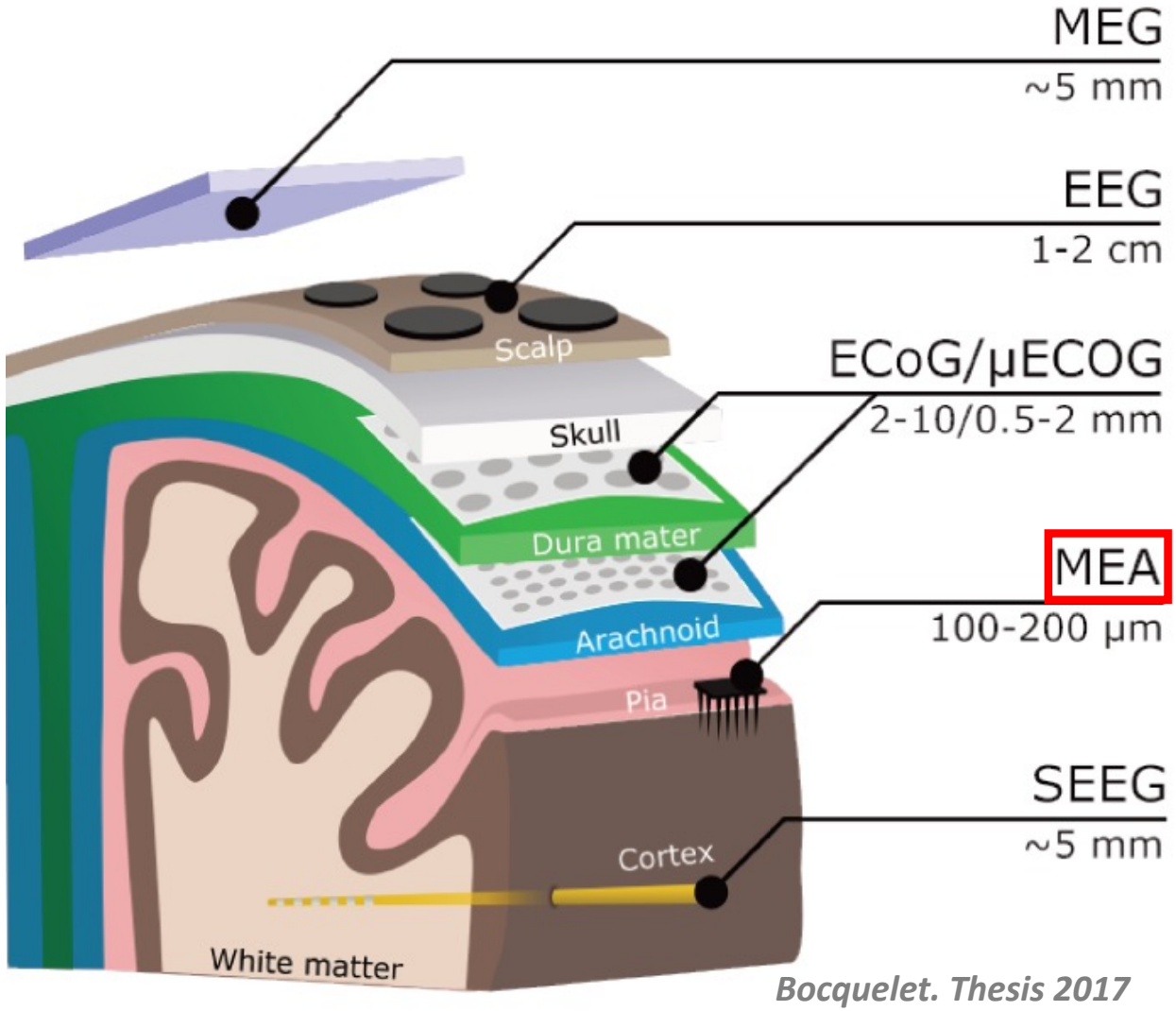


MEA



BRAIN MICRO SNOOPER

A mimetic implant for
low perturbation,
stable stimulation and recording
of neural units inside the brain

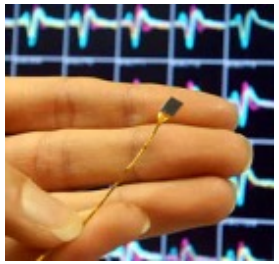


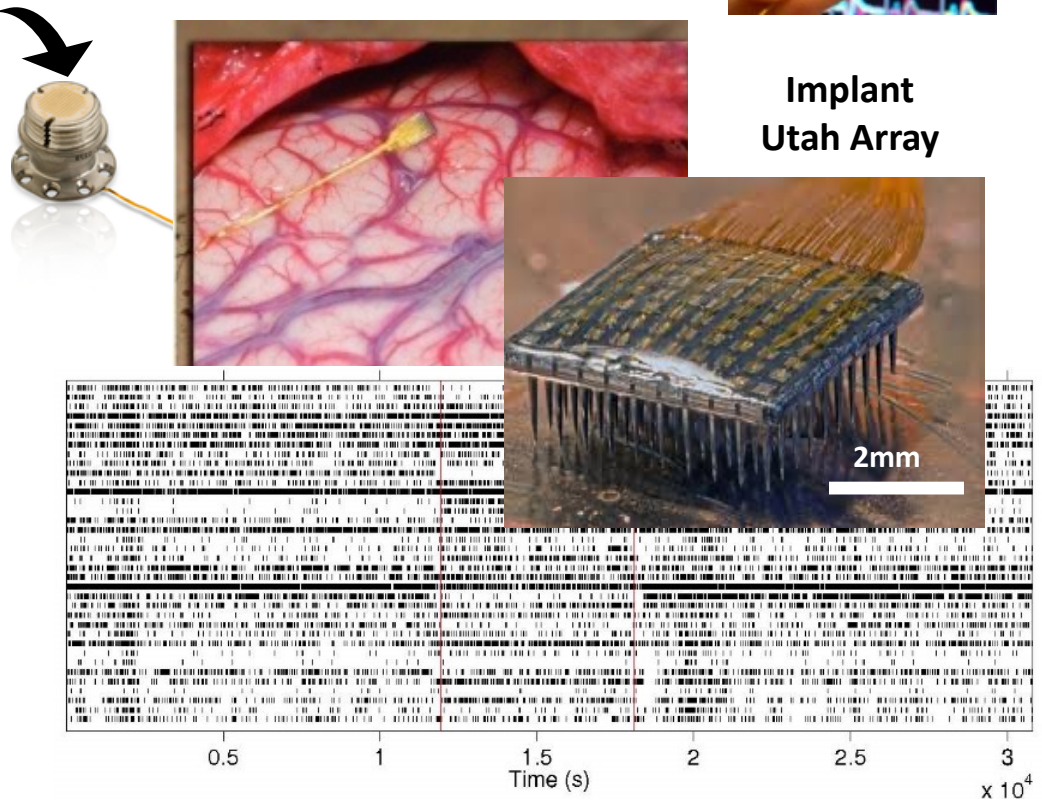
MICRO-ELECTRODES (20µm)

Bocquelet. Thesis 2017

Brain Computer Interface : BCI

- **Recording the activity of several neural units from the Cortex M1**
- **Enhancement of tetraplegic patient condition**
- **Robot hand and robot arm control**



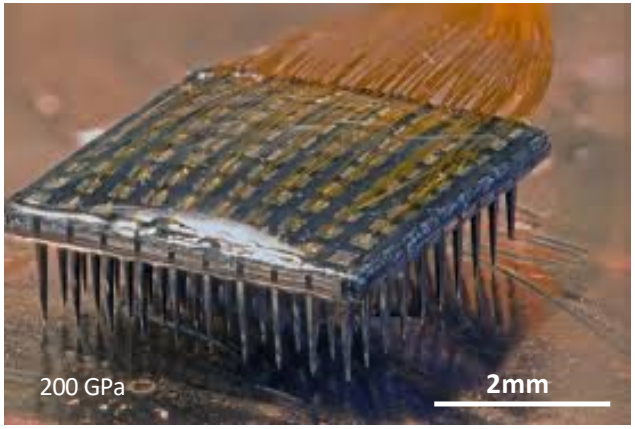


Hochberg, L. R. et al. (2006) Nature
Hochberg, L. R. et al. (2012) Nature
Collinger et al. (2013) Lancet
Woldinger et al. (2015) J Neural Eng

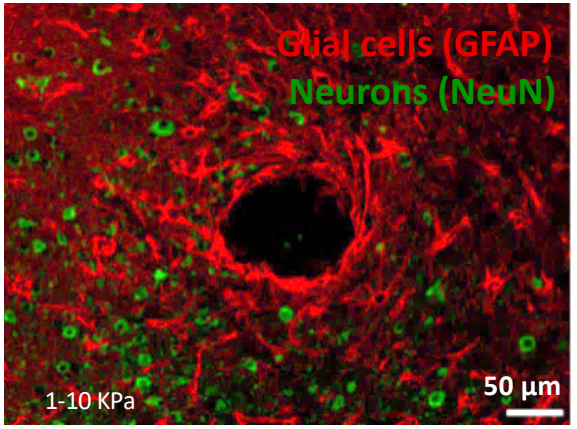
Main Issue

Long-term spike recording limitations :

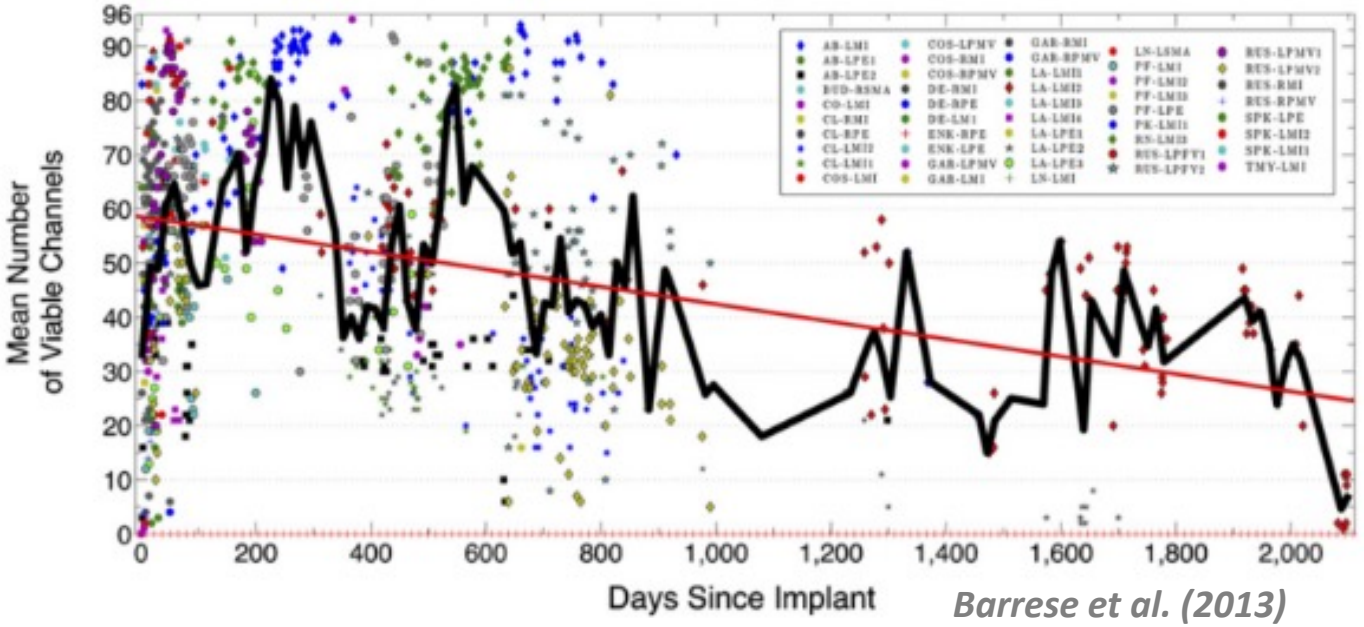
- Detachment of neurons from electrodes
- Glial scar



Utah Array (source: utah.edu)



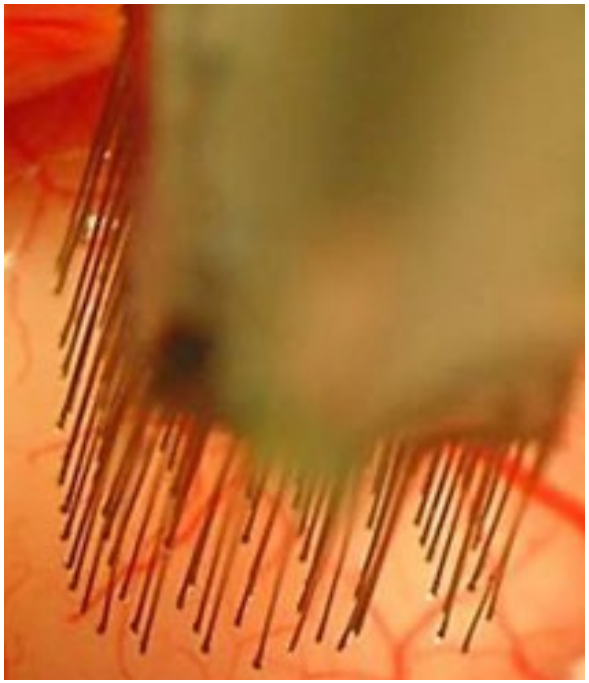
Marin, C et al. (2010)

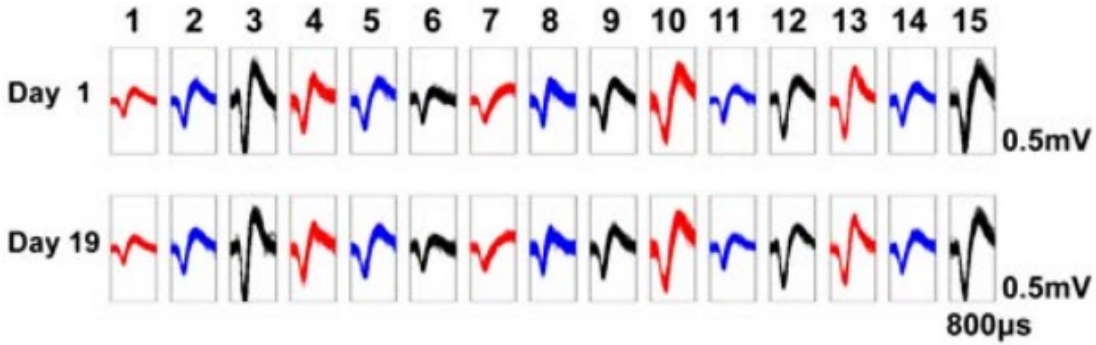


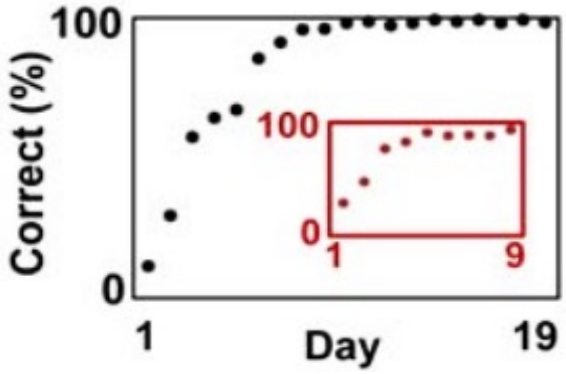
Barrese et al. (2013)

Need of signal stability : BCI performances enhanced + easier interpretation of brain signals

Penetrating microwire network : 3 weeks stability for 15 electrodes







Ganguly, K et al. (2009)
PLoS Biology
Ganguly, K et al. (2011)
Nature Neuroscience

- Faster learning of BCI tasks
- Performance of more complexe tasks (velocity, freedom in action)
- Low biocompatibility
- Need of signal stability over a longer time period

=> ERC

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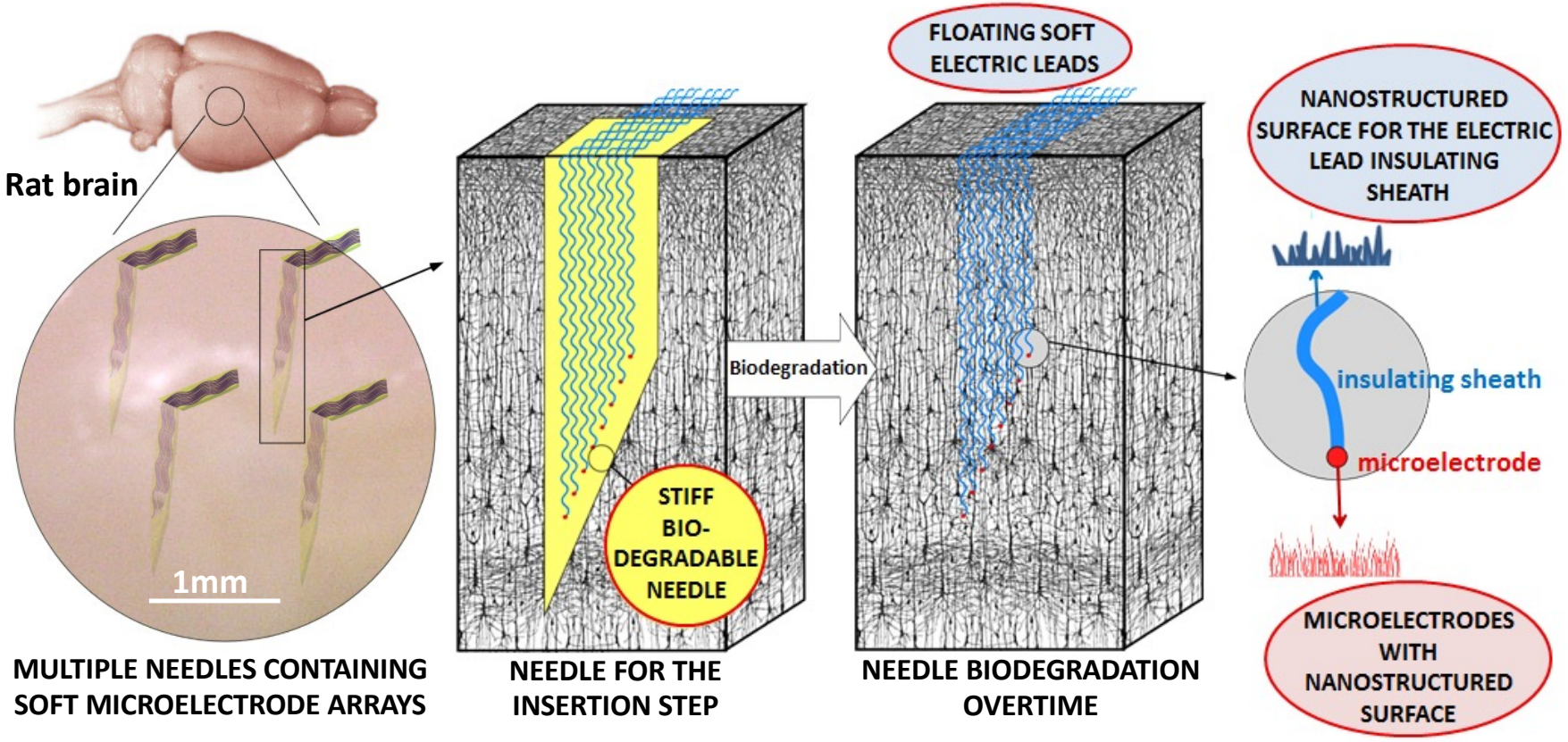
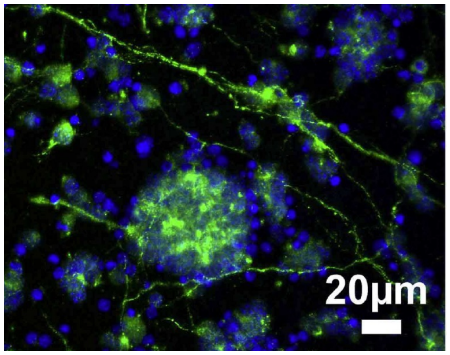
ERC BRAIN MICROSNOOPER (1.5Meuros)

– Research Team with 3 to 6 people from 2015

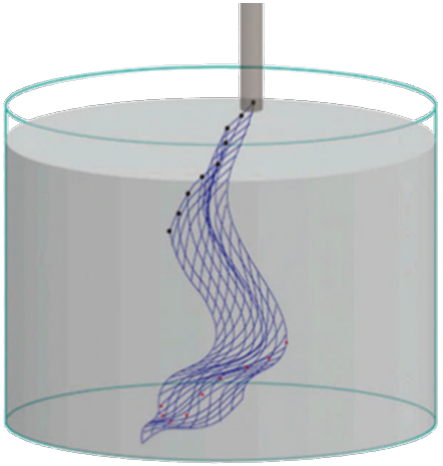
STABLE AND HIGH RESOLUTION NEURAL UNIT RECORDING



Main goals

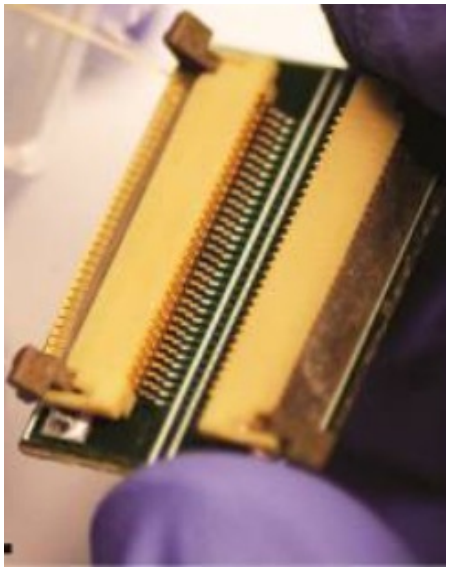


Piret et al, 2013



Zhou et al, 2017

Tien et al, 2013



Schuhmann et al, 2017

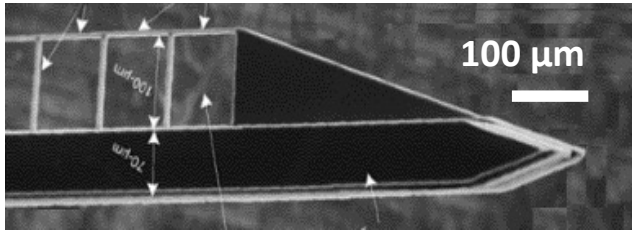
Neuron-sized

Flexible

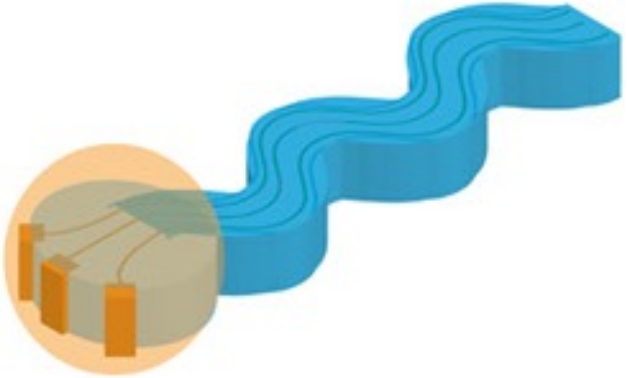
Implantable

Easy to connect

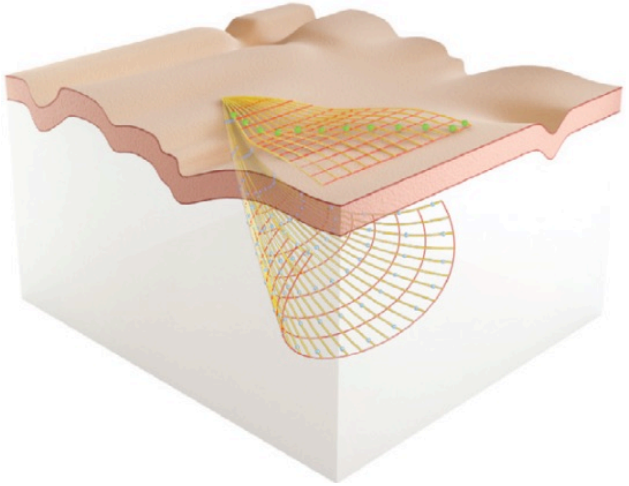
Main goals



Seymour, J. P et al. (2007)



Sohal et al. 2014



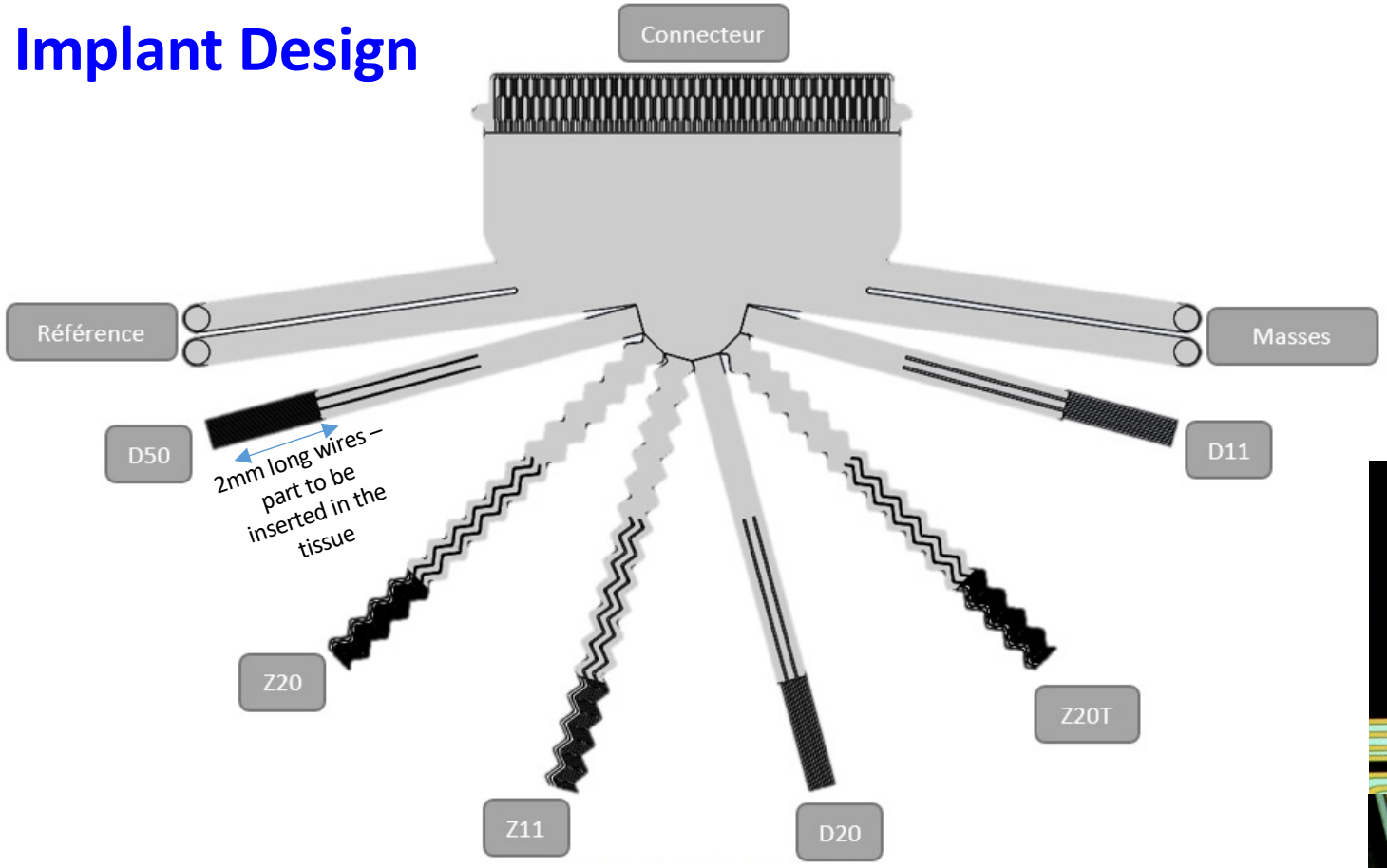
Liu et al. 2015

Low dimension for neuron repopulation

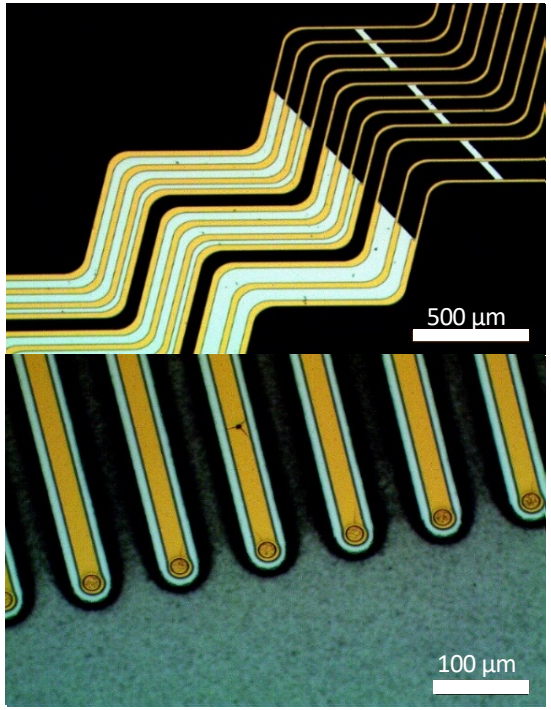
Wavy shape for brain movement absorption

Wires to be free of mechanical strains

Implant Design



- 71 Pads to adapt commercial connector ZIF
- 2 References et 2 grounds
- 6 arrays of 11 very thin and soft wires
- A the tip of each wire: 1 electrode (diameter 16 µm)



- 8µm thick wires with widths of 11, 20 or 50 µm (gold/platinum tracks 5, 10 or 20µm)

-> Evaluate the effect of different widths on tissue reaction

- SU8 or polyimide **-> Evaluate the effect of different insulator materials**
- Wavy or straight wires **-> Evaluate the effect of different wire shape**

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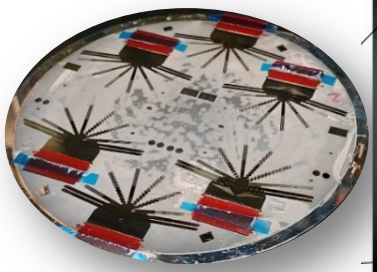
CLEAN ROOM PLATEFORM NETWORK for BRAINTECH device prototypes + clinical trial transfer

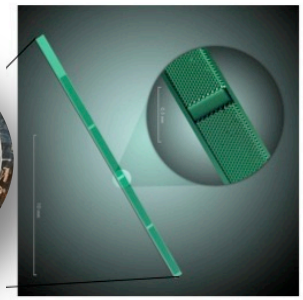
RENATECH
ESIEE
NEEL
PTA (CNRS/CEA)
PICTIC
LETI-3S
DTSI

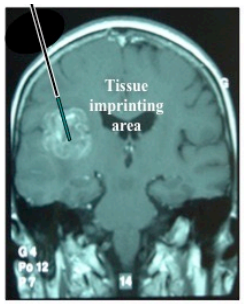
CIC-IT

- Start-ups
- Clinical trials
- Industrial partnership (CATIN/DEKER)

CLINICAL trials (ANSM Approval) :
Living human primary cell culture in the real micro-environment state

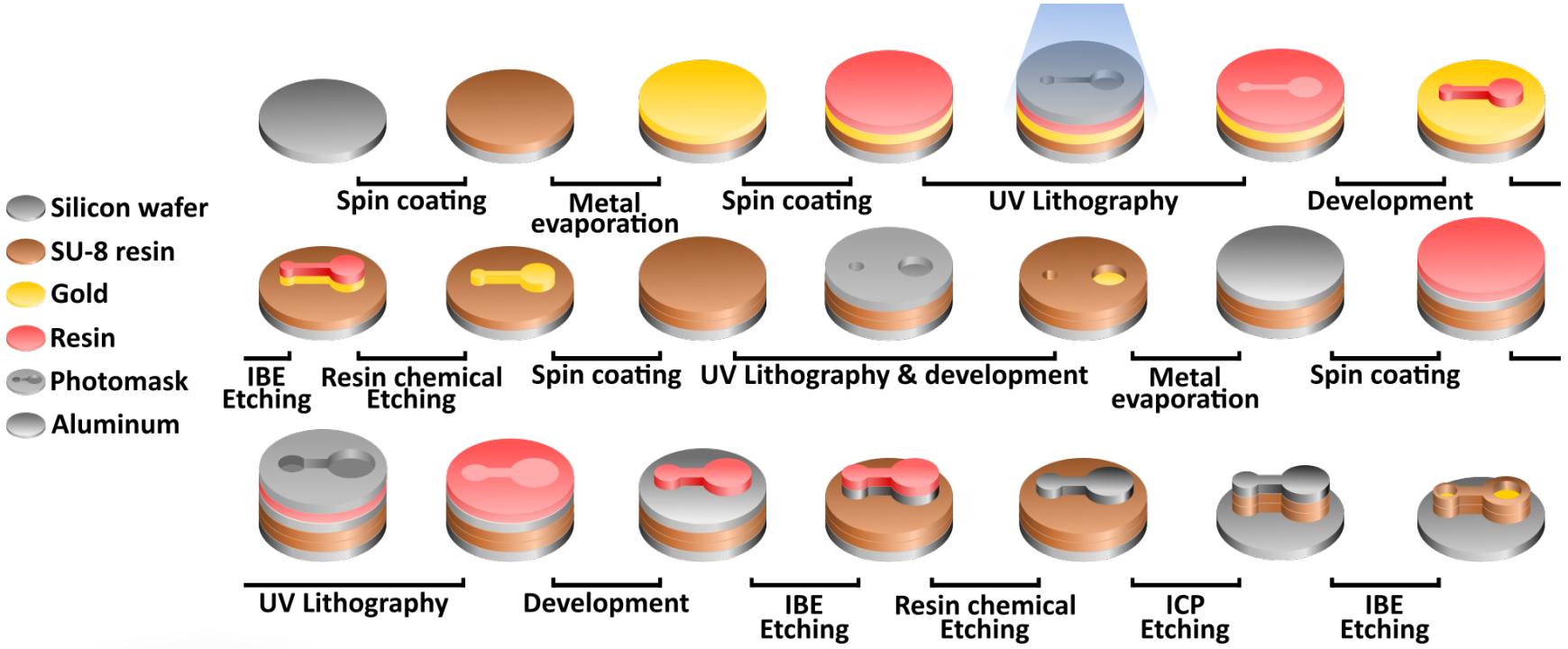






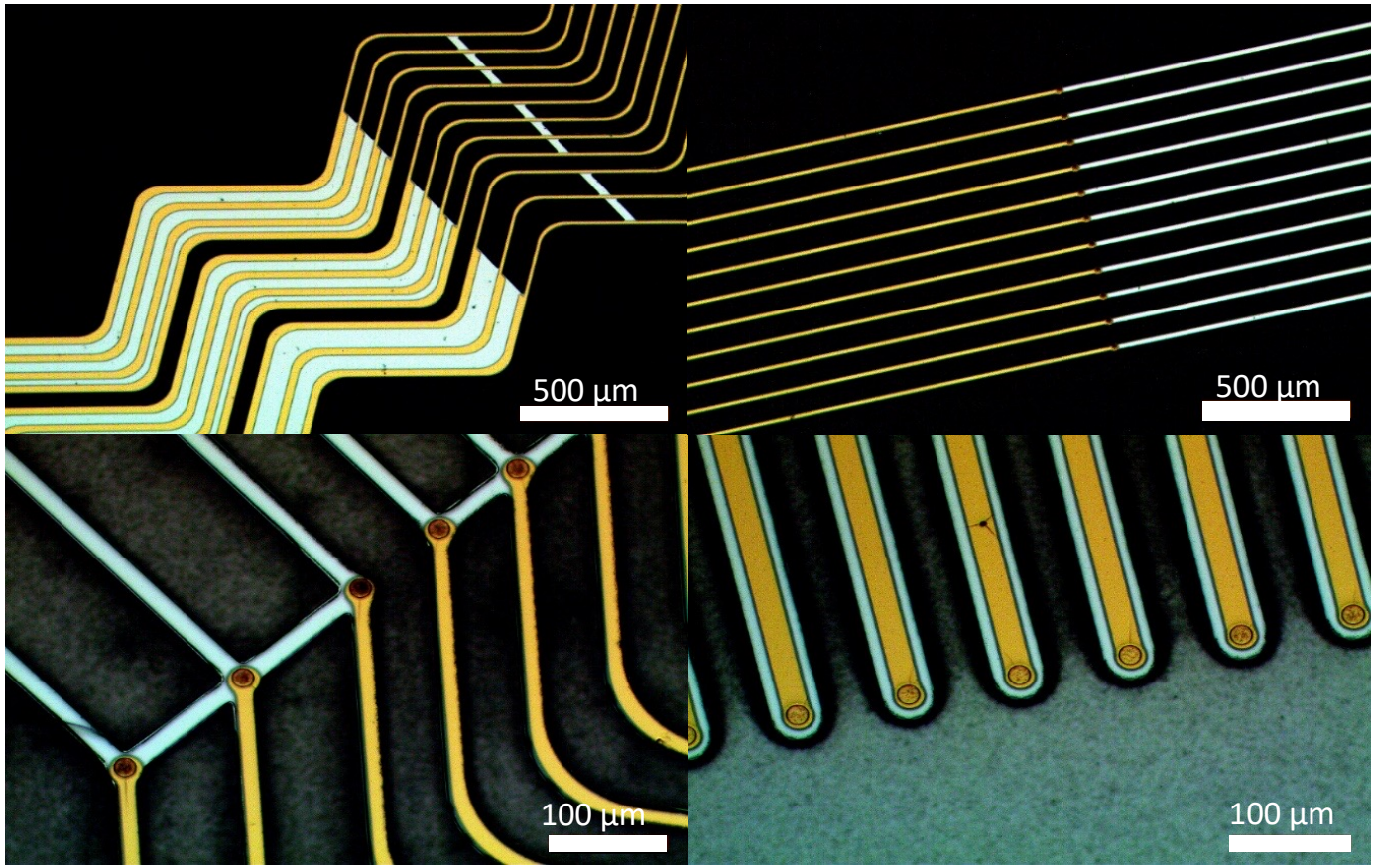
Start Up:
IN VIVO DATA BANK for finding new biomarkers and adapt better the treatments

Clean Room Process : using IBE to favor an industrial transfer



6 implants/wafer
Implant thickness: 8 µm
Gold thickness: 200 nm

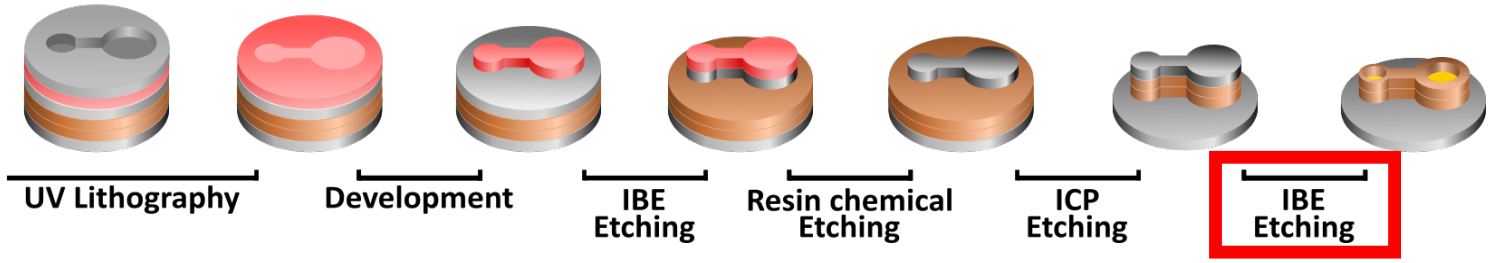
Microscopy Characterization

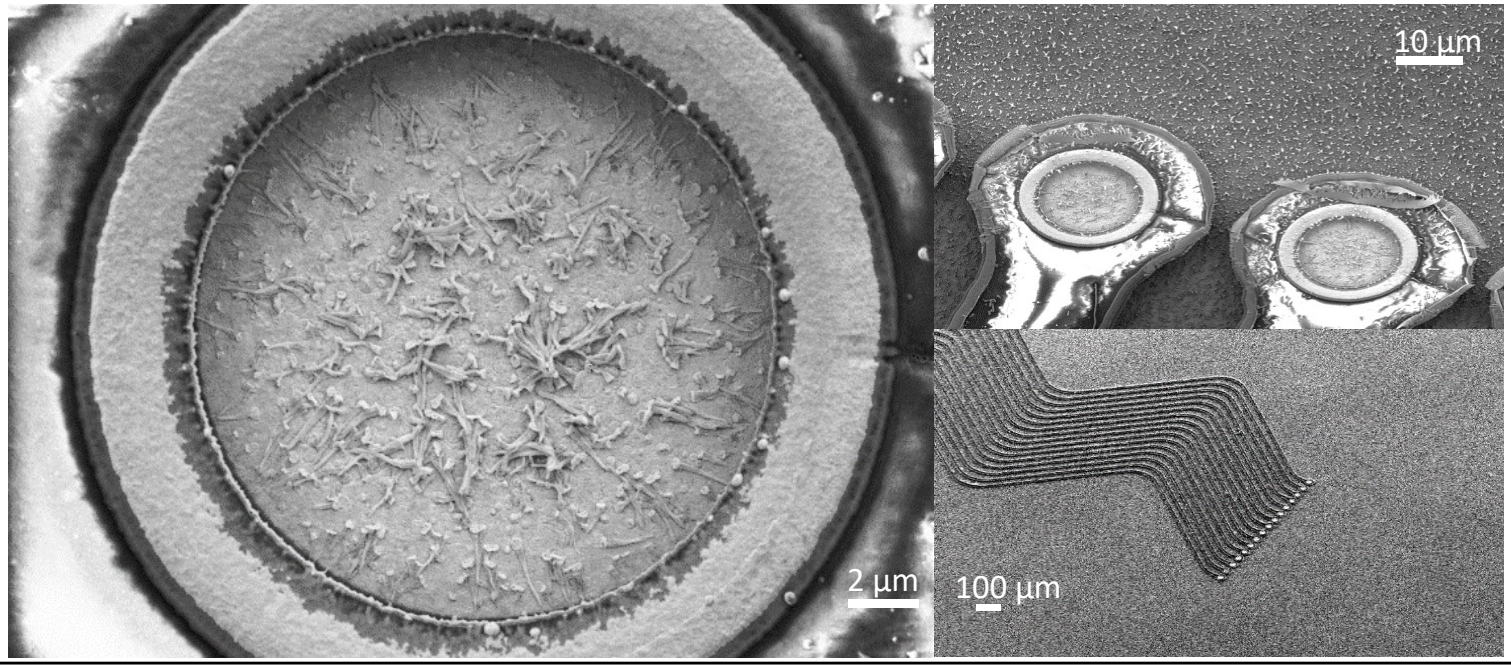


Different patterns:

- Wavy or straight wires
- 11 or 20 or 50 µm width wires
- 5 or 10 or 20 µm width gold tracks
- 20 µm diameter electrodes

Scanning Electron Microscopy Characterization

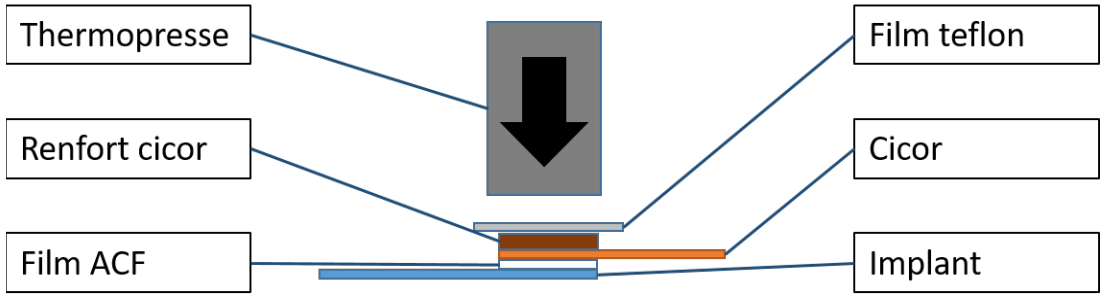


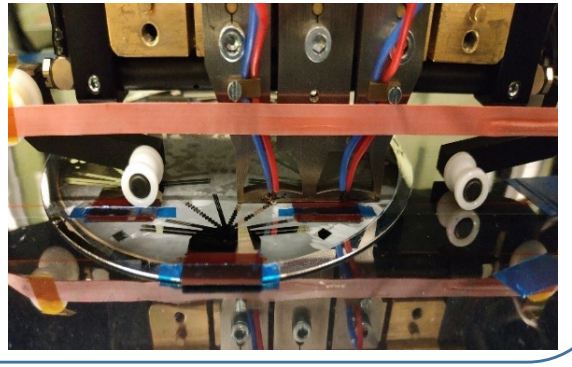


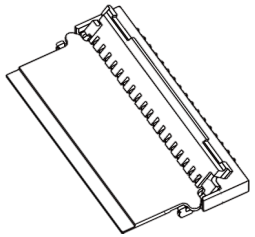
Ion beam electron (IBE) nanostructures gold electrode.
Nanostructures improve neuron adhesion *(Piret et al, 2013)* and neural recording performances *(Piret et al, 2015).*

Connection to a PCB board : PICTIC platform

Thermopress : 71 channels implant pad bonded with a « flex extension » with ACF (Anisotropic Conductive Film)

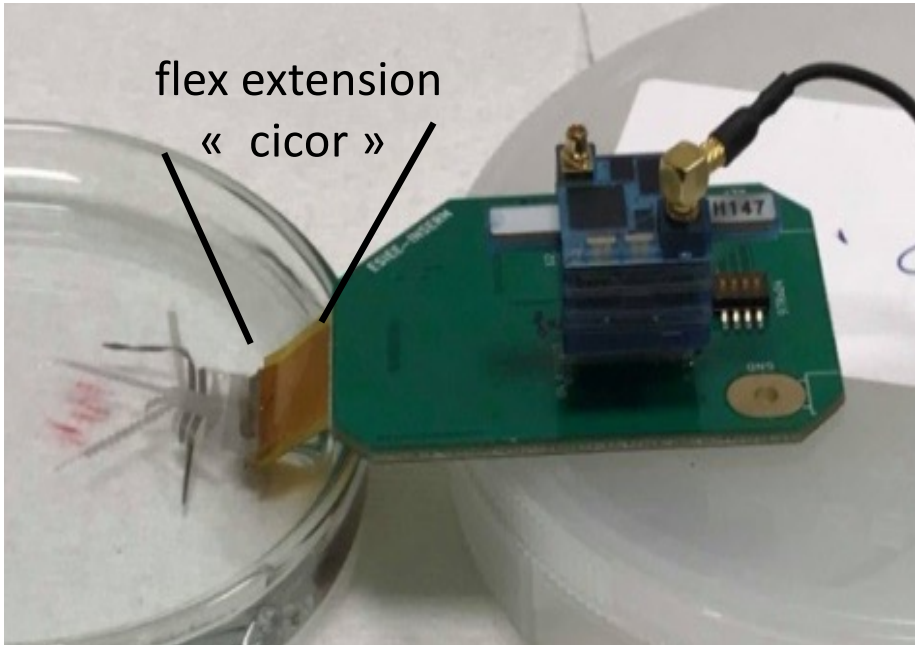






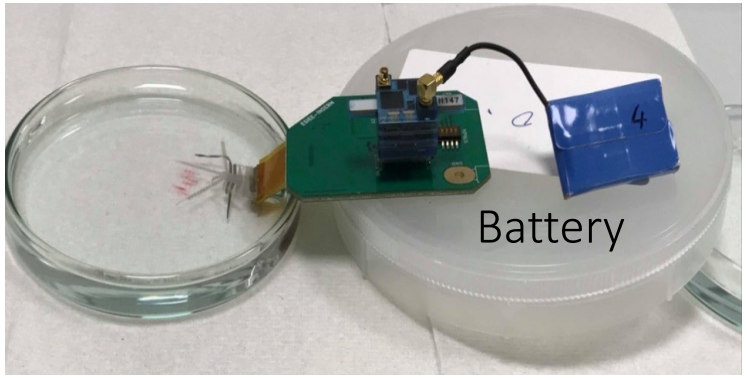
Flex inserted into a ZIF = Zero Insertion Force

PCB Board : ZIF connected with two Omnetics and wireless MCS headstages

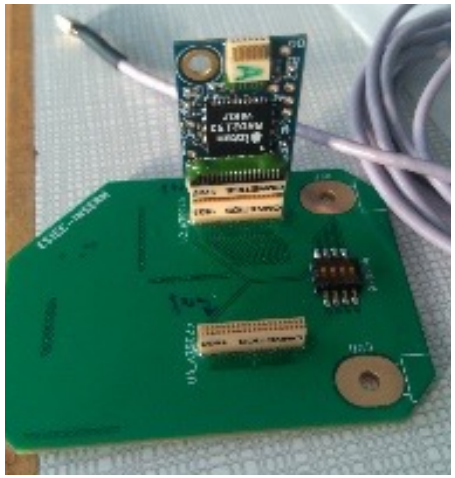


Electrical characterization: impedances and cyclic voltametry

Amplifier and wireless system: MCS

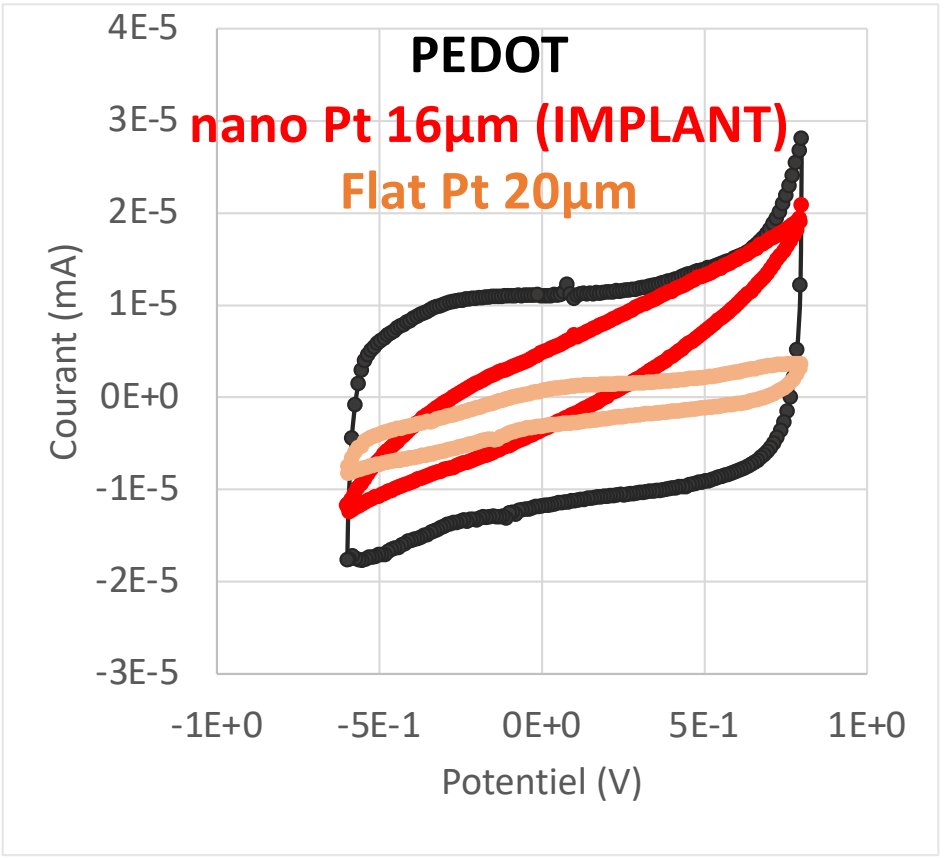


Amplifier and wired system: Intan



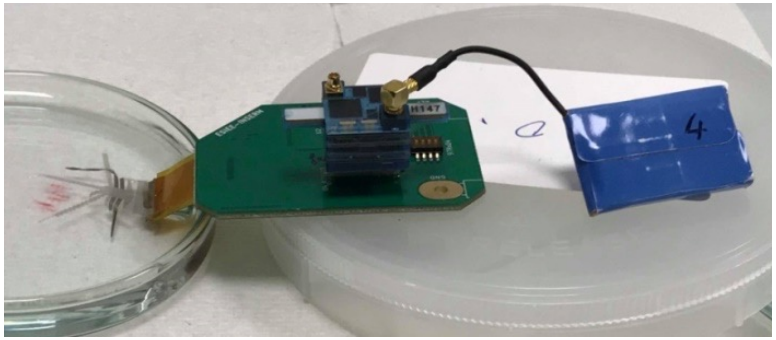
A lot of variation in the measures

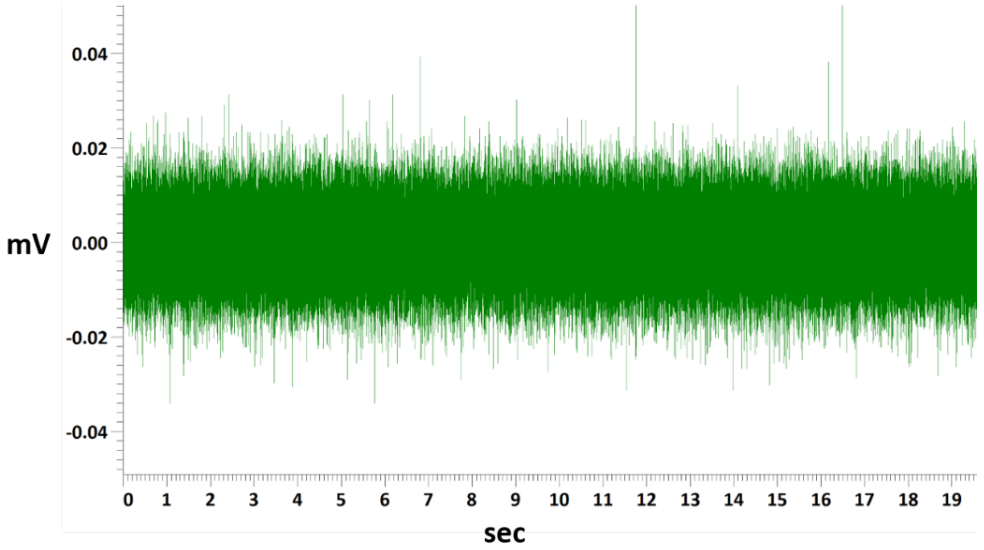
Low impedances :
1,8 Mohm for
16 µm nanostructured electrode diameter



Charge Storage Capacity CSC :
Nanostructured implant (red)
> flat platinum (brown)

Noise measurement





Bruit (µV)	60-6	60-5	60-4	60-3	60-2	60-1	59-4	59-1
Moyenne	10,31	25,29	28,85	23,30	29,67	105,41	62,87	86,62
Mediane	8,48	25,24	25,32	17,01	30,13	109,17	35,97	72,08
ecartype	5,15	6,33	9,79	39,83	8,42	27,66	61,82	49,00

A lot of variations… Movement of electrodes in the solution?
Noise measurement do not correspond to impedance measurement
⇒ Check the alignement of the connexion
⇒ Check PCB cards

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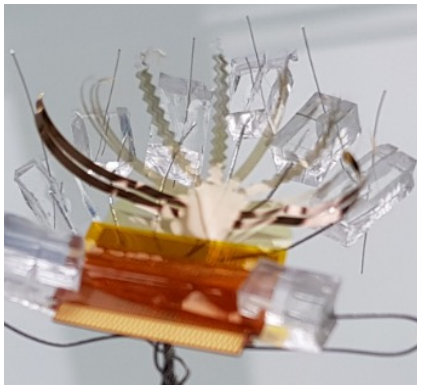
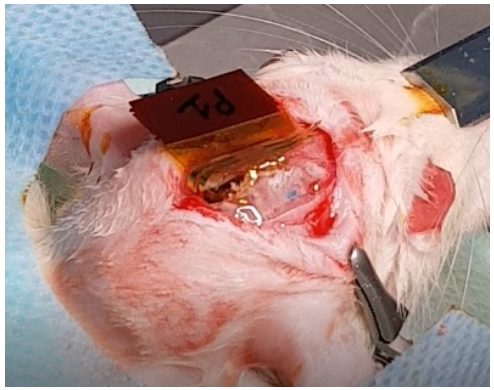
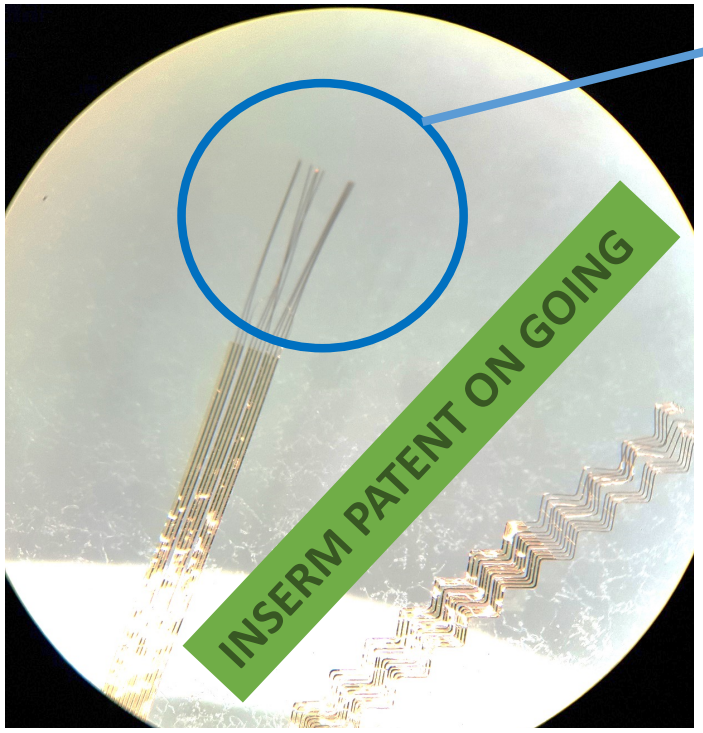
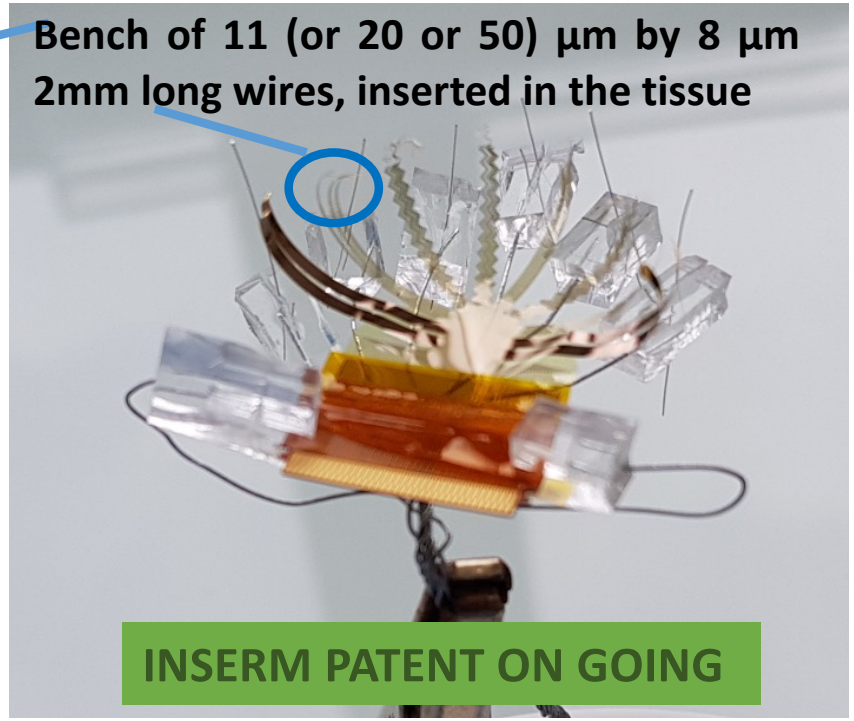
Wifi in vivo recording of rats with the BRAIN MICRO SNOOPER tool: intracortical soft implant with 64 micro-nano-electrodes





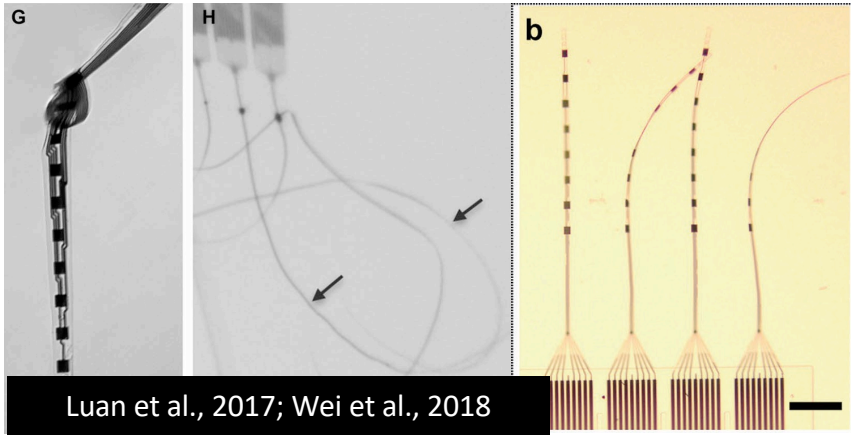
Wifi in vivo recording





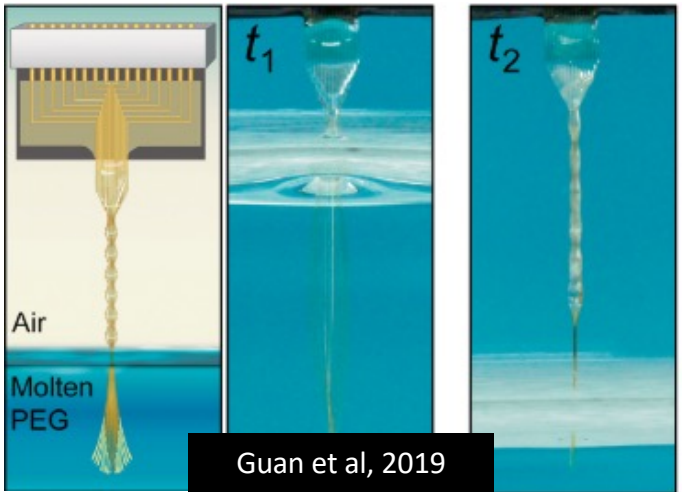
Literature state of the art

Nano-electronic thread; SU-8 = 1µm



Luan et al., 2017; Wei et al., 2018

Neurotassel Polyimide = 1.5µm



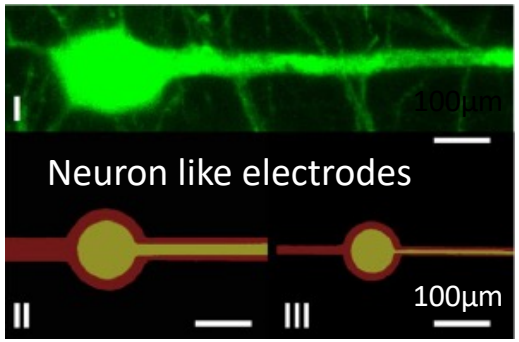
Guan et al, 2019

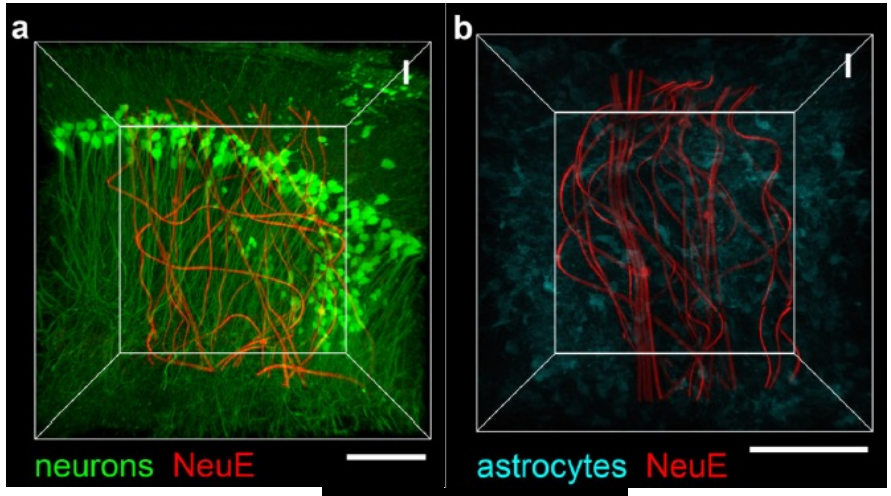
Stentrode; platinum = 50µm

Oxley et al., 2016

Macroporous brain probe; SU-8 ~ 1µm

Stiffness (structure, geometry)

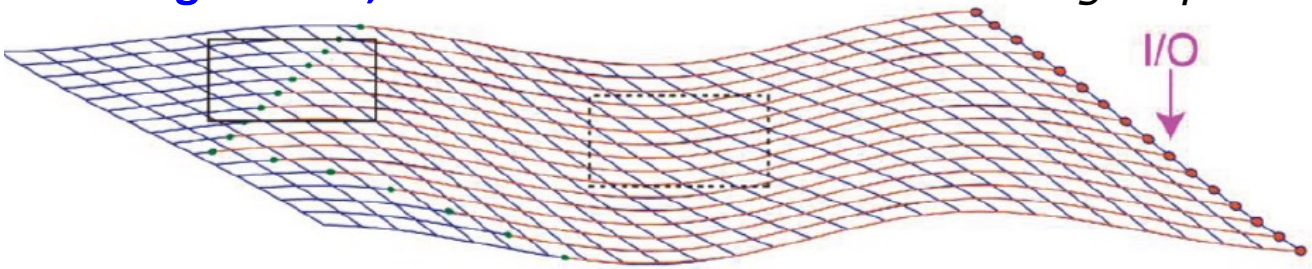


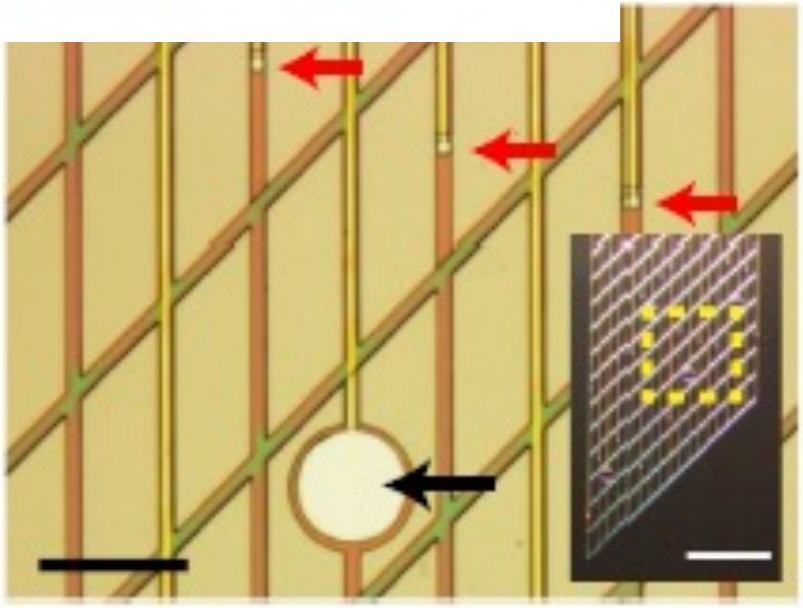


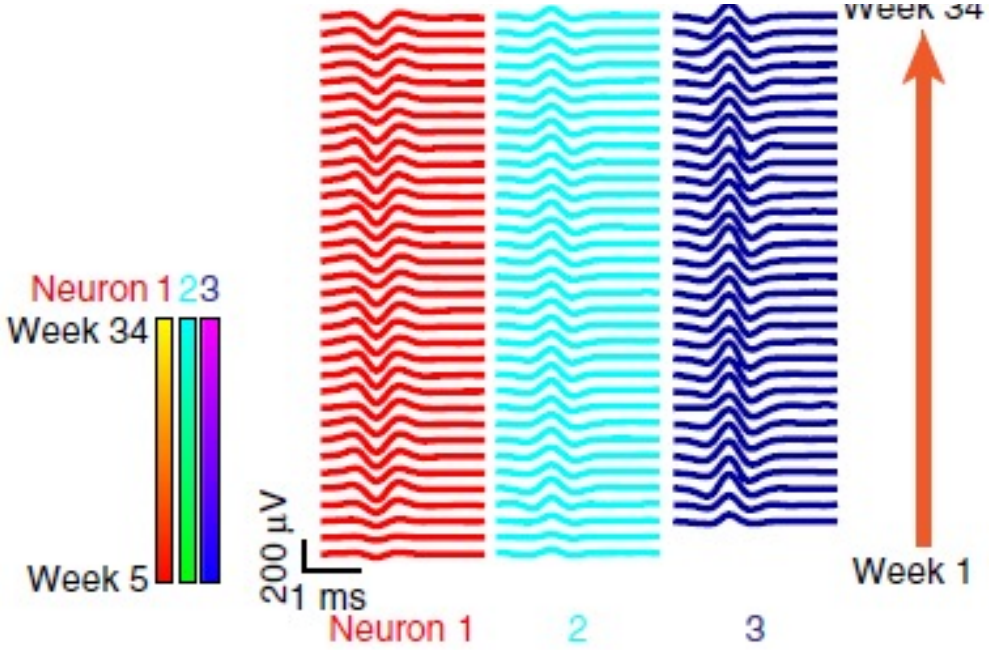
Yang et al, 2019

Stable 8 month chronic mouse brain recording at the single-neuron level

Tian-Ming Fu et al, nature methods 2016 - *Lieber's group*

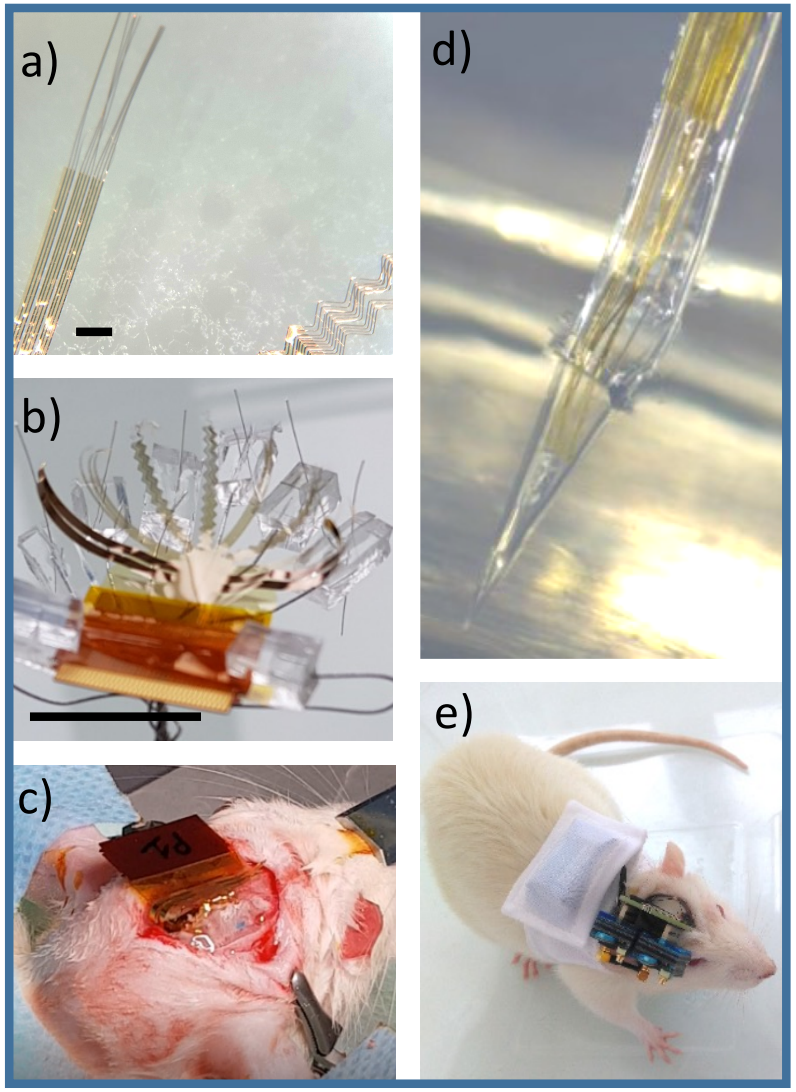


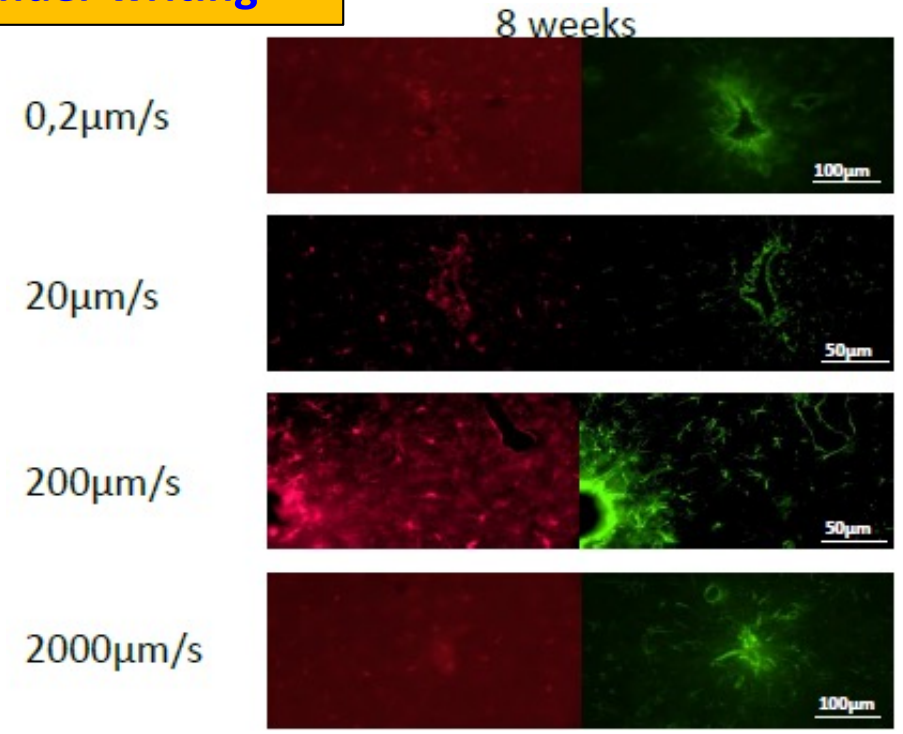




- **Method for sterilization ?**
- **Use for bigger animals ?**

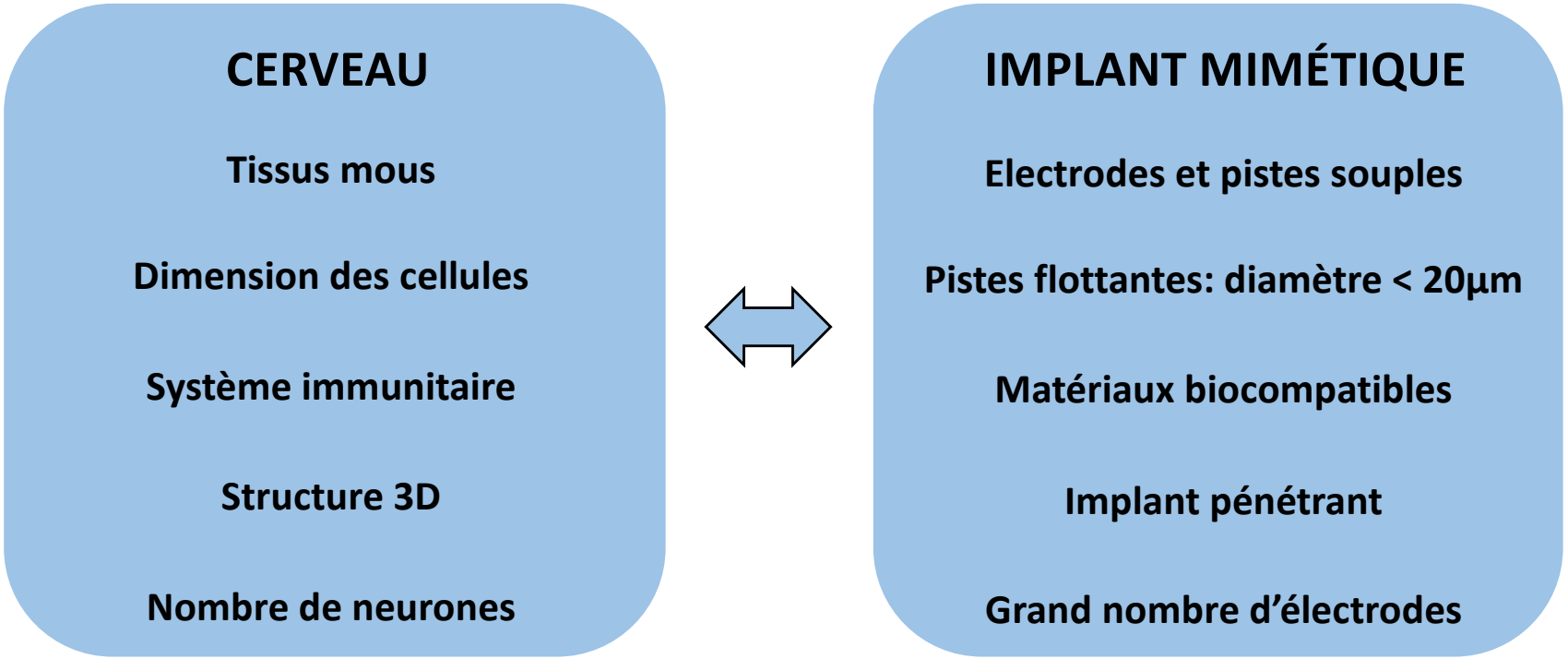
Darlot F, et al, paper under writing





- ✓ **The 0.2µm/s insertion often fails**
- ✓ **No effect of implantation speed on tissues**
- ✓ **A scar size with a diameter of about 50µm**
- ✓ **During PFA procedure, the rat brains don't present infections like it was the case with the shuttle method for the implant insertion**

Projet CR: Implants de haute résolution et stables sur le long terme



- **Axe 1– Implant stable: microélectrodes souples et « flottantes »**
- **Axe 2– Nanostructuration: implant adhésif et détection sensible**
- **Axe 3– Densité de microélectrodes**

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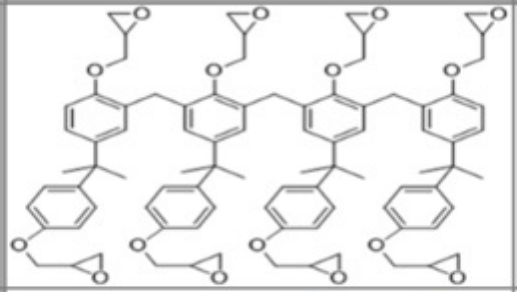
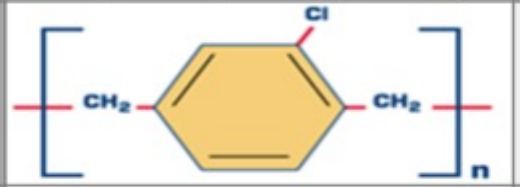
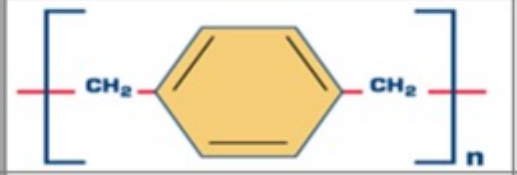
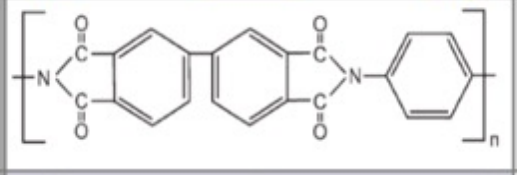
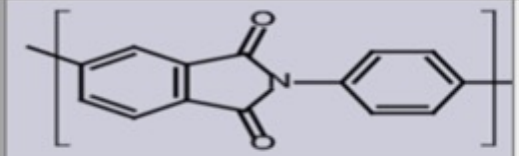
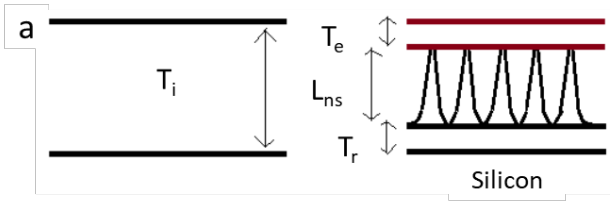
tech Inserm

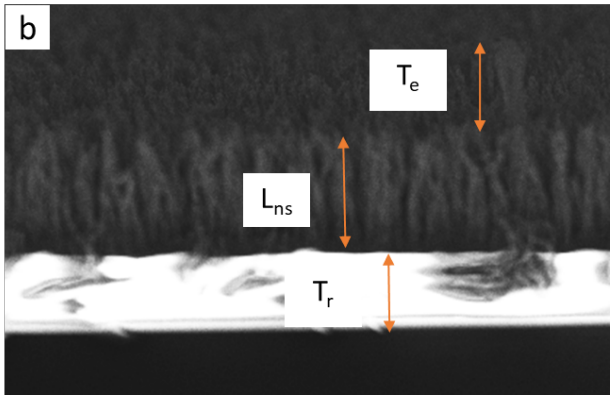
Improving implant adhesion and biocompatibility with the tissue:

Nanostructuration of potential implant insulators

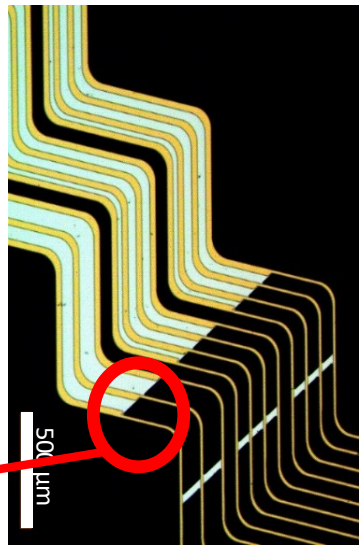
Polymer	Formula	Thickness
SU-8		8 µm (2 layers) or 12 µm (3 layers)
Parylene C		12 µm
Parylene HT		25 µm
Parylene N		4 µm
PI-2611		8 µm
PI-LTC9320		20 µm

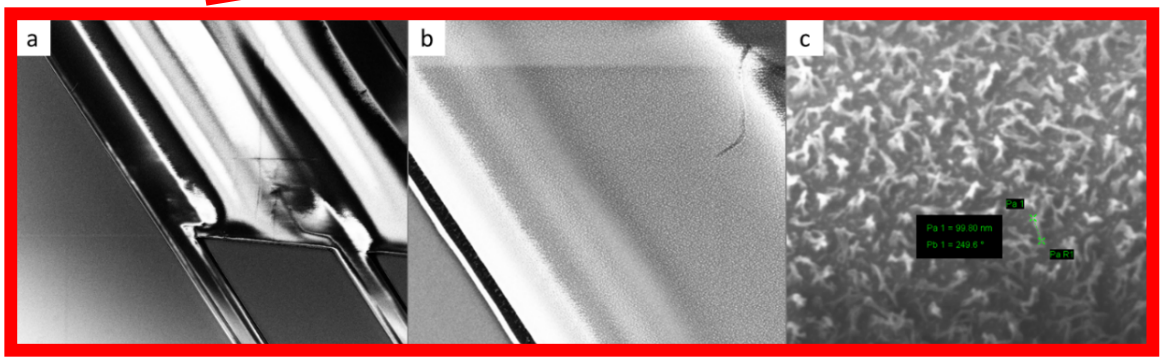
O_2 plasma etching





Integration in the SU8 implant fabrication process





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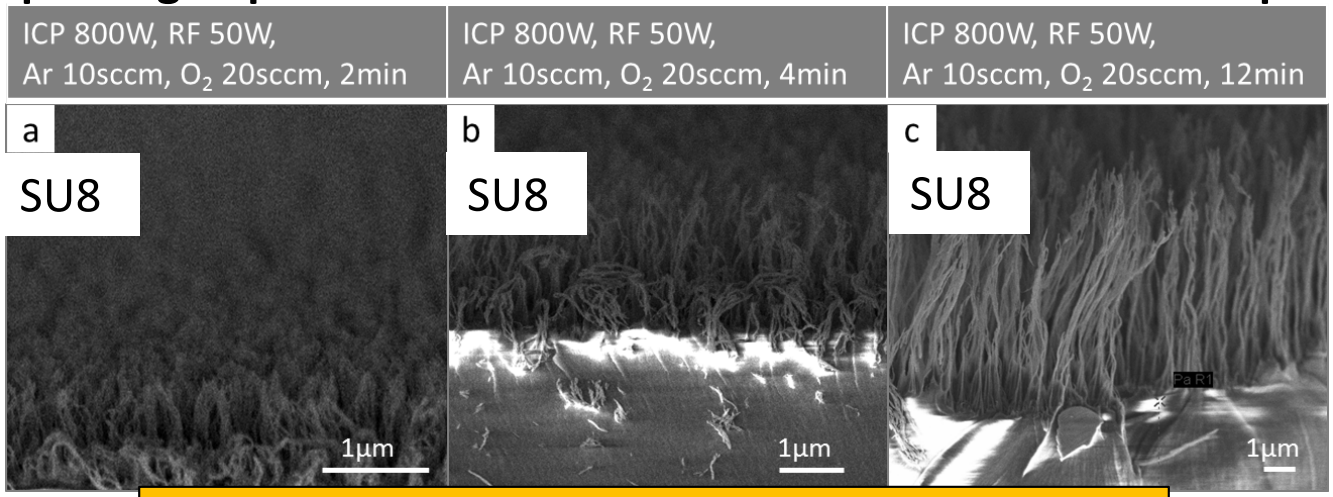
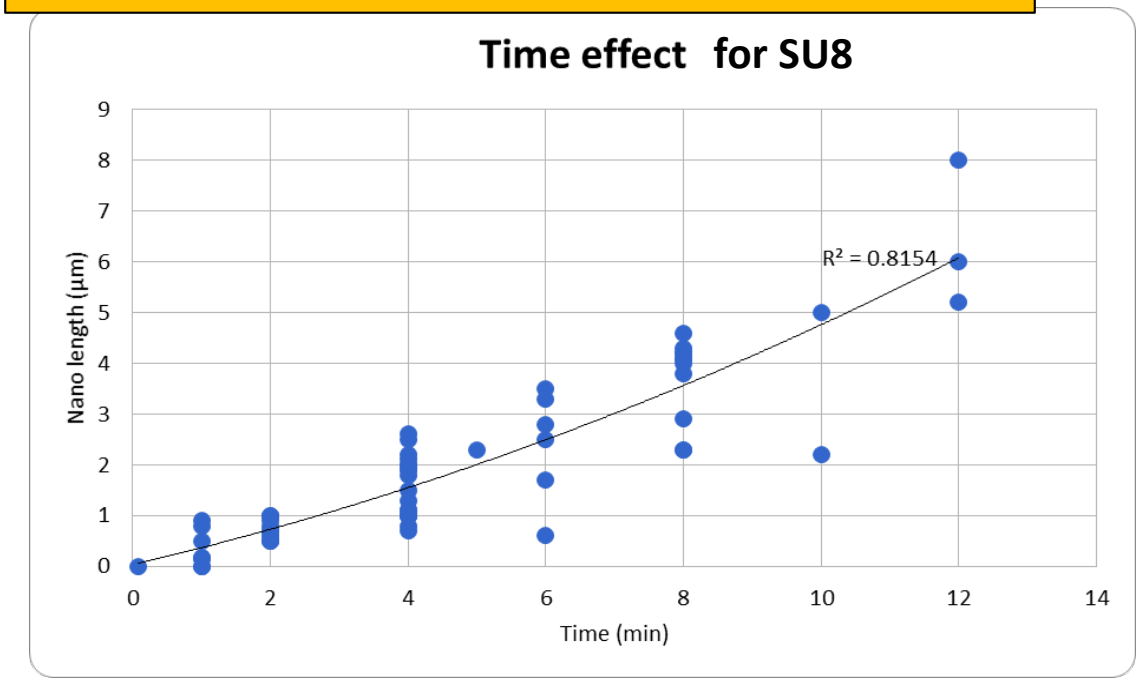
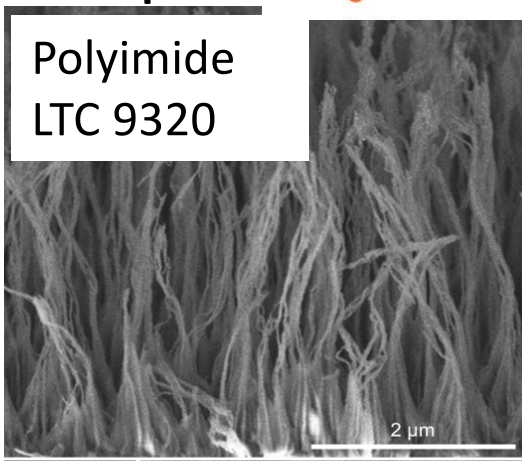
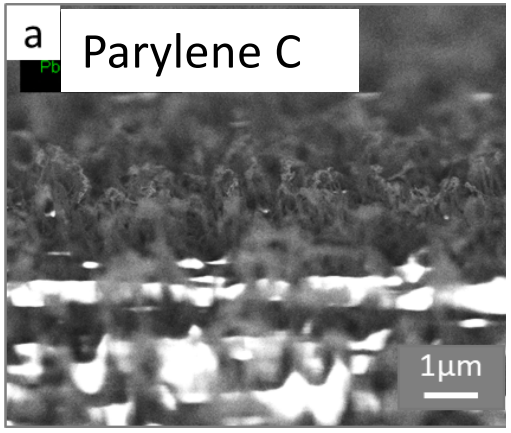
Improving implant adhesion to tissues: Nanostructuration of potential implant

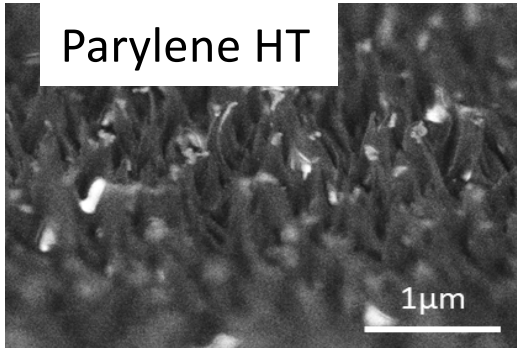


Mayaudon et al, 1st paper in preparation









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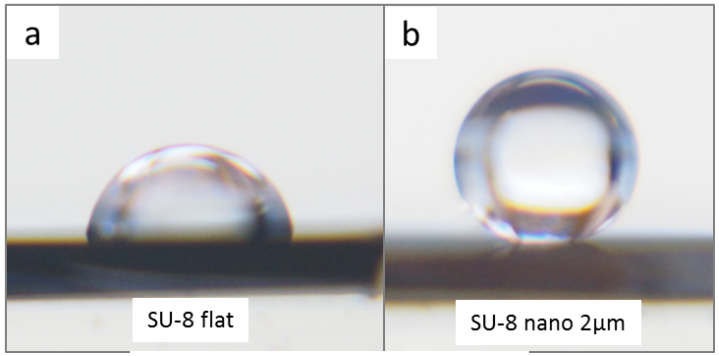
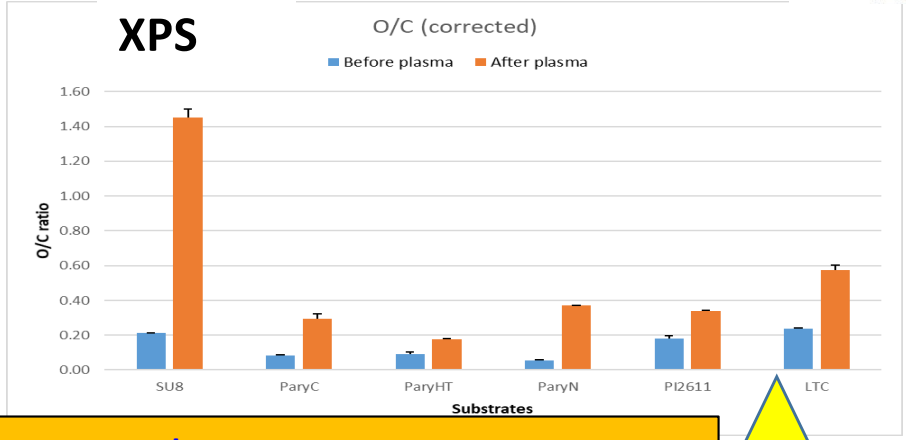
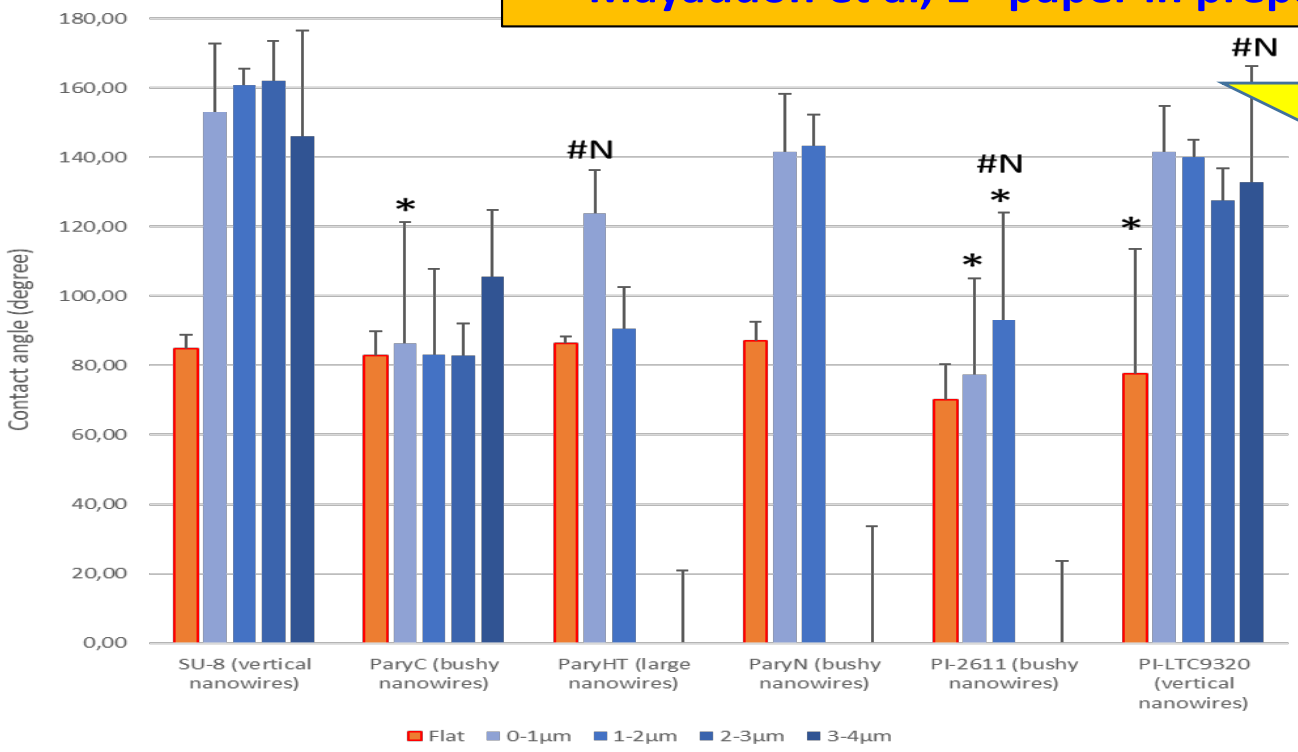
Nanostructuration : increase of oxygen/carbon ratio, increase of CA





Contact Angle

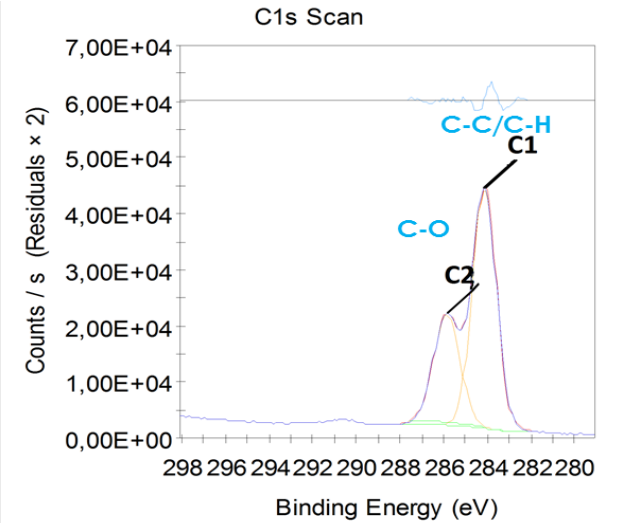
Mayaudon et al, 1st paper in preparation



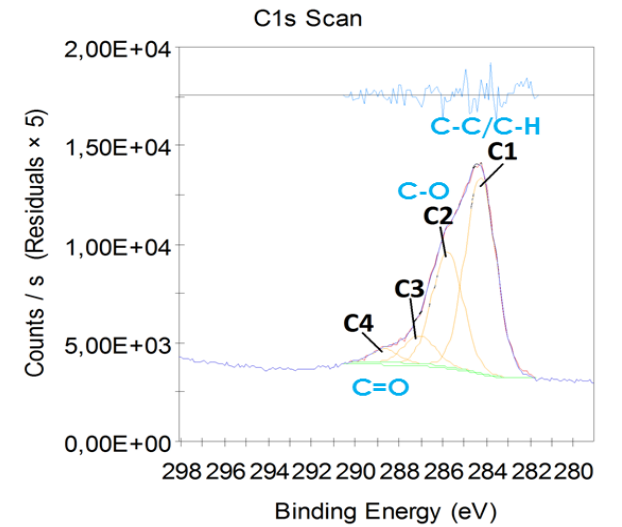
SU8
parylene N
PI LTC9320

The shape of nanostructures might explain the Contact Angle after nanostructuration (rather than the surface chemistry)

XPS analysis

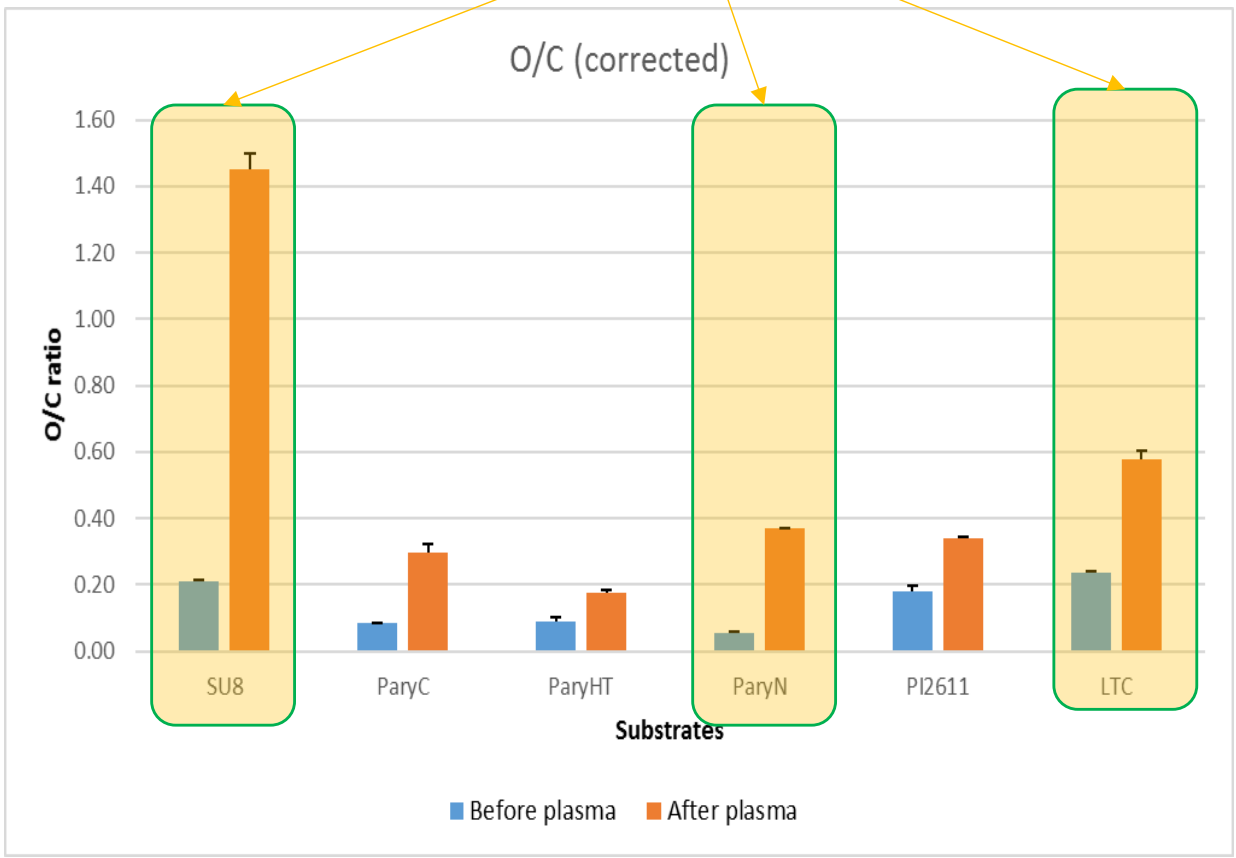


SU-8 flat



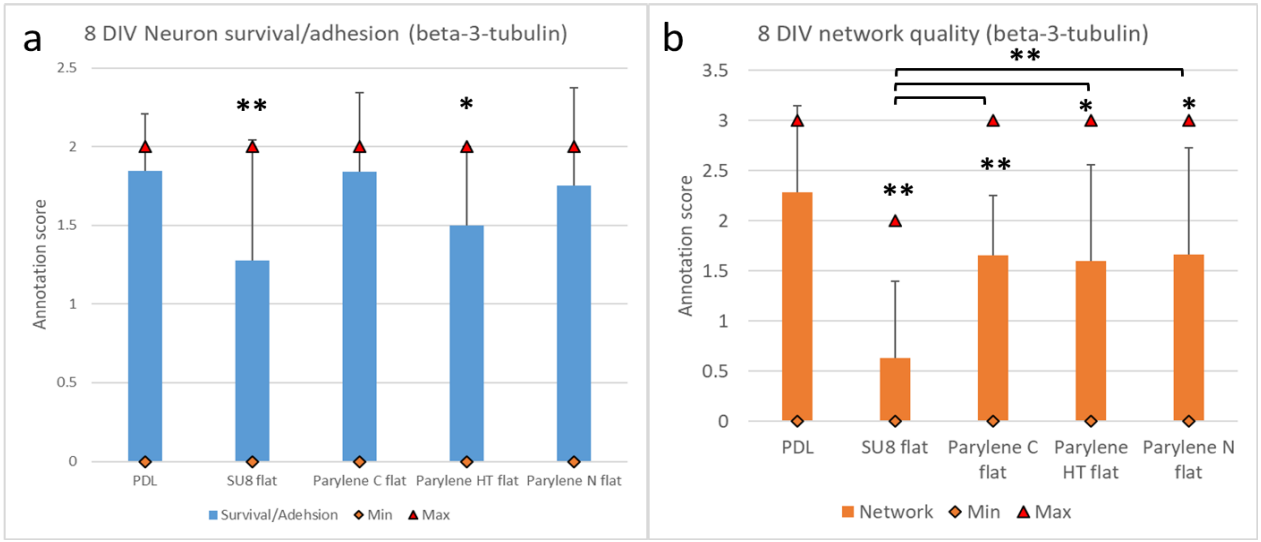
SU-8 nano

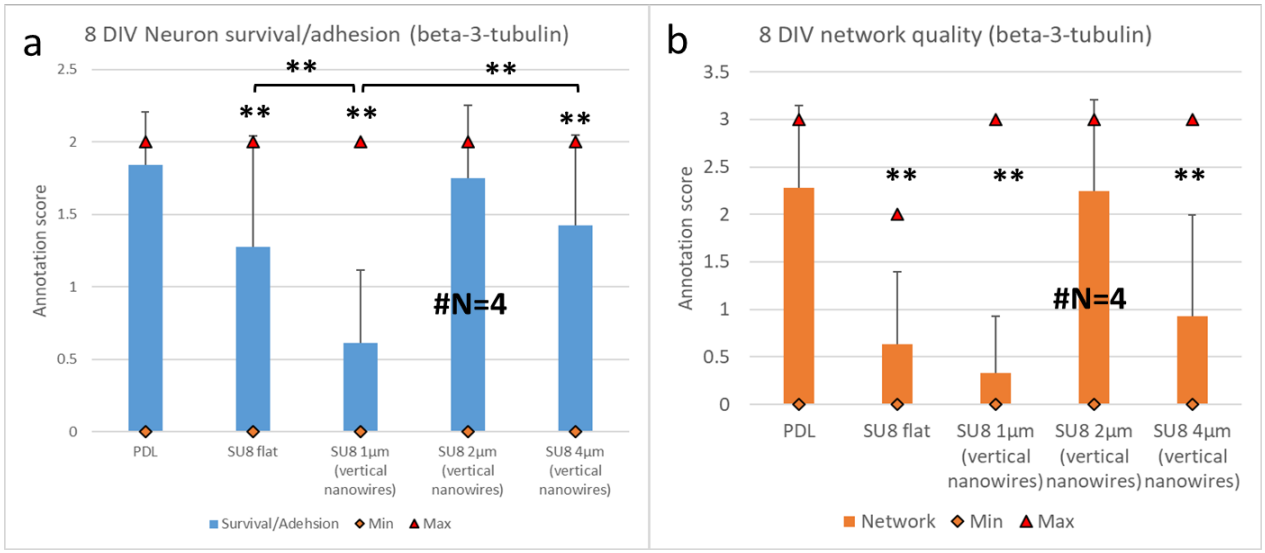
Superhydrophobic surfaces



- no direct correlation with the wettability

Neural cell culture (2 to 6 days post-natal rat cortical cells):
An effect of both surface chemistry and nanostructure length





Flat Parylene is better than flat SU-8

SU8 4µm long nanostructures seems better than flat SU-8

Mayaudon et al, 2nd paper in preparation

Flat SU-8 are better than SU-8 1µm long nanostructures

Flat Parylene are better than Parylene 2µm long nanostructures

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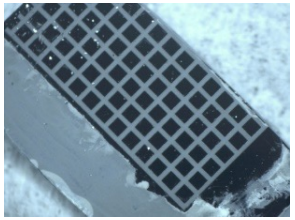
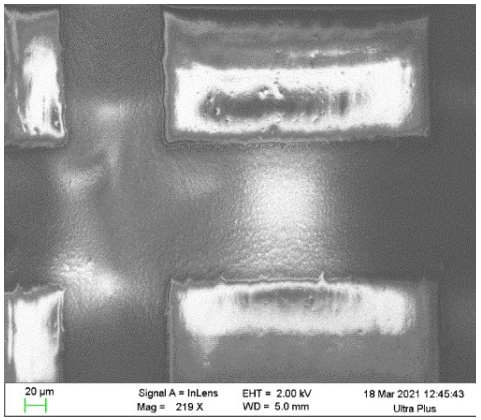
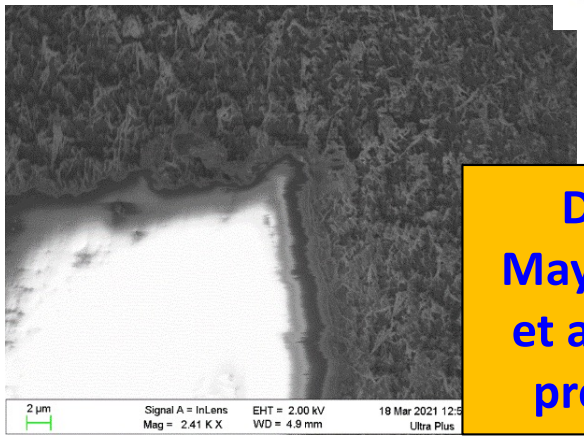
10x



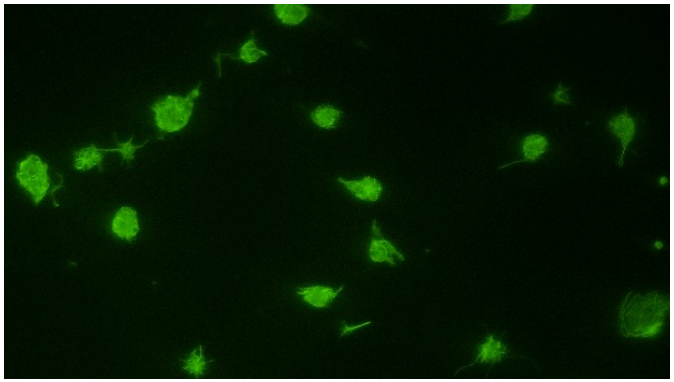


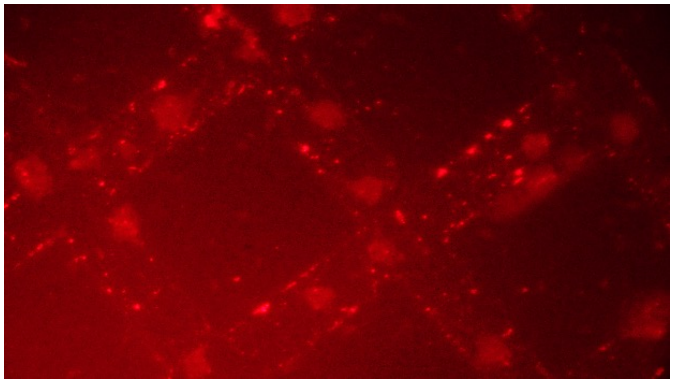


- GFAP
- B tubuline III

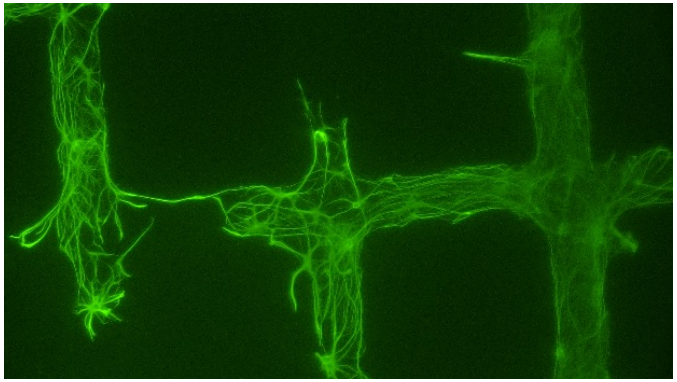
Darlot F , Mayaudon JM, et al, paper in preparation

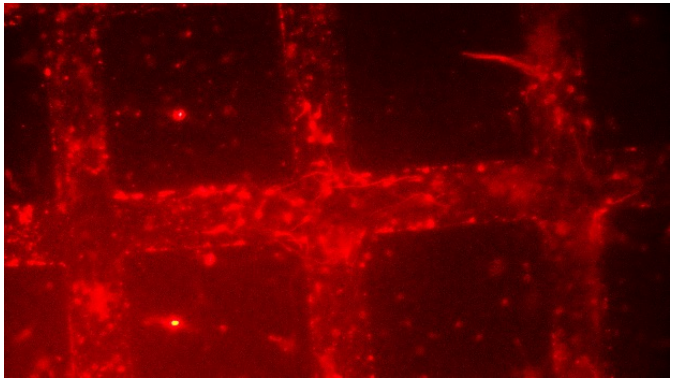
P5 ; 6DIV





P5 ; 12DIV





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2022 – 2027 and + Objectives

BRAIN MICRO SNOOPER TOOL

Produce generic MICROSNOOPER implants for fundamental and clinical applications

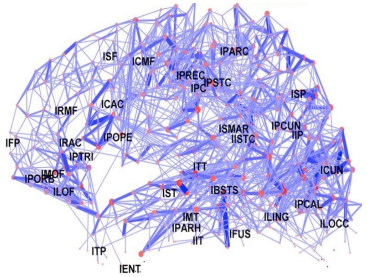
- ❑ In vivo RECORDING/STIMULATION IN MINIPIGS (cortical, peri-tumoral)
- ❑ In vivo RECORDING IN RATS (spike sorting for correlation of signals and behaviour)
- ❑ Improve the LONG TERM use of the implant (nanostructuration, surface chemistry)

2 years

- ❑ Adding micro sensors to the tool
- ❑ CLINICAL TRIALS
- ❑ In vitro tumoral tissue recordings

INSTITUT DE LA VISION

PIXIUM VISION

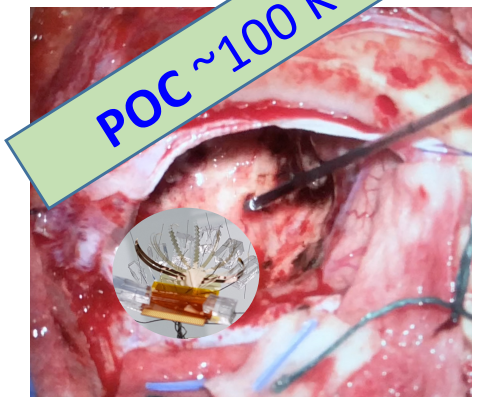


Cortical dynamics, plasticity of healthy and pathologic brain – chronic implants

EU partners – application to grant calls on going

Toward other applications:
Neural pain
Neuroprotection (Alzheimer)

POC ~100 K€



Peritumoral/ Epilleptic tissue electrical characterization
3/5 years

Robot **5/10 years**
Control of external devices using brain signals

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Brain Storming ATSG

- Conferences to share our « on-going » work each year
- Collect encountered issues: help each other, communicate issues to UGA and national instances/authorities
- Detect potential innovative projects to apply to European calls: gathering 2 or more ATSG research group expertises.
- A webpage to propose Internship projects (Licence to Master) to join activities of 2 or more ATSG research groups?
- SHS bridges with other non SHS ATSG research groups: Internships for exploration of clinical needs? Litterature to identify our strength in Grenoble?


Thank you
Gaelle Piret
Fannie Darlot
François Berger
Braintech lab – INSERM
Grenoble, France