Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

EN PARTENARIAT
ESPACE ÉTHIQUE
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Journée annuelle du comité d'éthique de l'Inserm

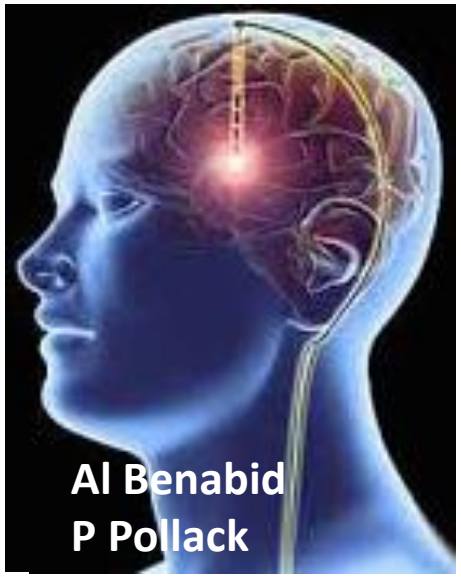
"Défis éthiques et utopie technologique d'essais cliniques « first-in-man » : un conflit d'intérêt ?"

PLAN

- **Le contexte**: Technologies implantées, micro-nano-Technologies et électronique et pathologies cérébrales.
- **« Case study »:** des technologies d'interface avec le cerveau: interfaces cerveau-machine et empreinte cérébrale.
- **Besoin clinique qui entraîne un devoir d'innovation versus utopies technologiques …et Transhumanisme**
- **Le premier patient ? Quand ? Comment ?**

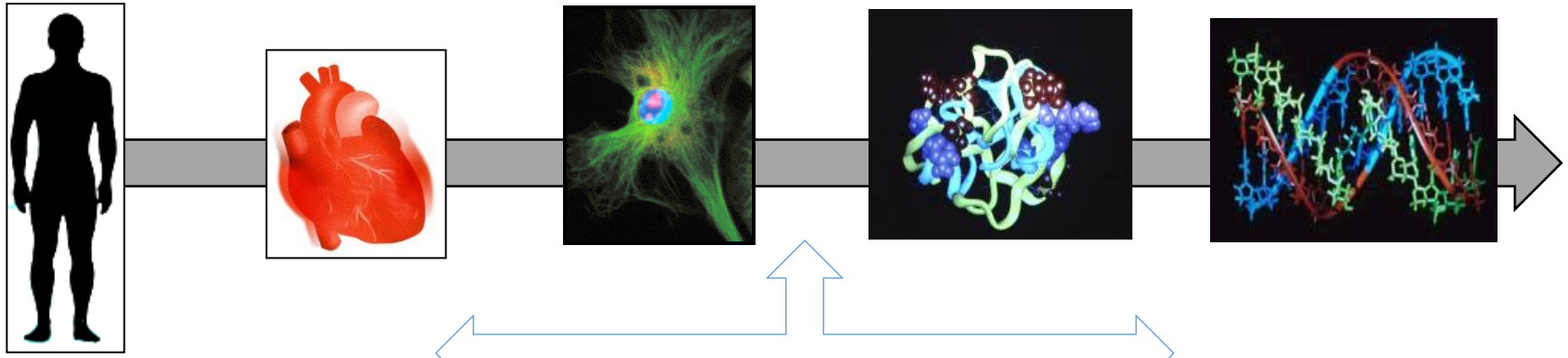
UN BESOIN MEDICAL MAJEUR:

- **Verrous des thérapie ciblées du cancer**
  - Pas de blockbuster, Hétérogénéité, complexité, résistance, microenvironnement …
- **Echec des thérapies ciblées pour les pathologies neurodégénératives**
  - L'inaccessibilité au cerveau, fonctionalité …



L'OPPORTUNITÉ « MEDTECH »

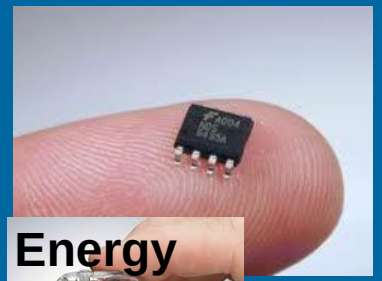
THE NANO-ELECTRONIC TOOLBOX TO RENOVATE MEDICINE ?

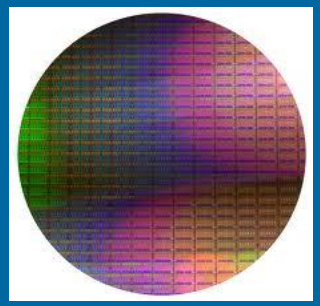


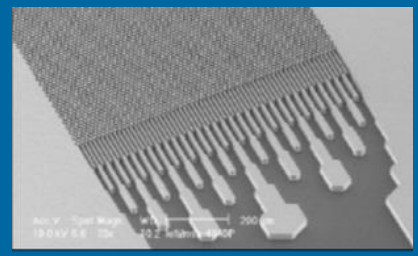
Communication network/wireless Hardware and softwares

Algorithm
Deep learning
Artificial intelligence

Miniaturization Multifunctional integration

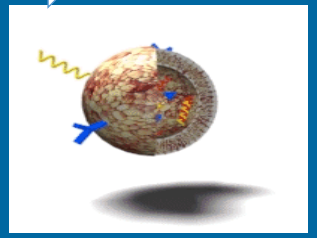




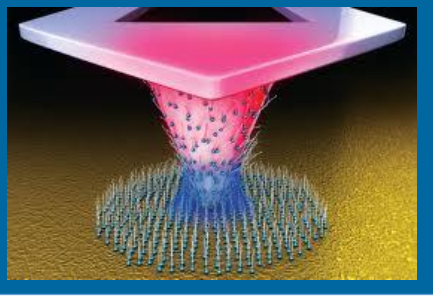


Micro-nano-fluidic

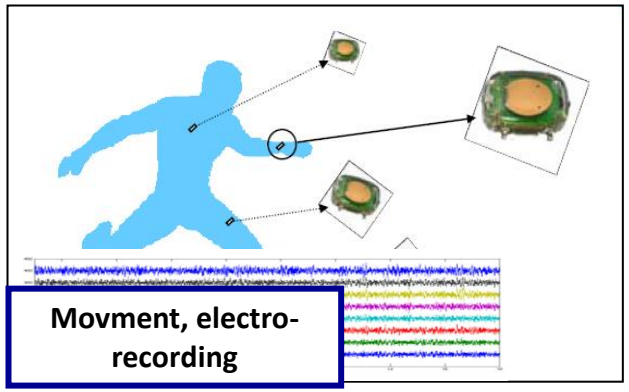
Nano-particles



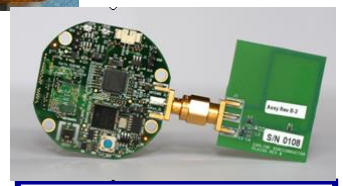
Surface modification: nanolithography



ACTIVE IMPLANTED NEUROPROSTHETIC DEVICES FOR DIAGNOSIS AND THERAPY

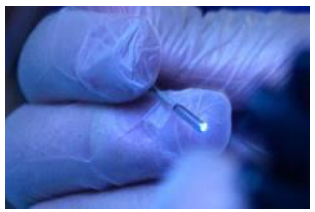


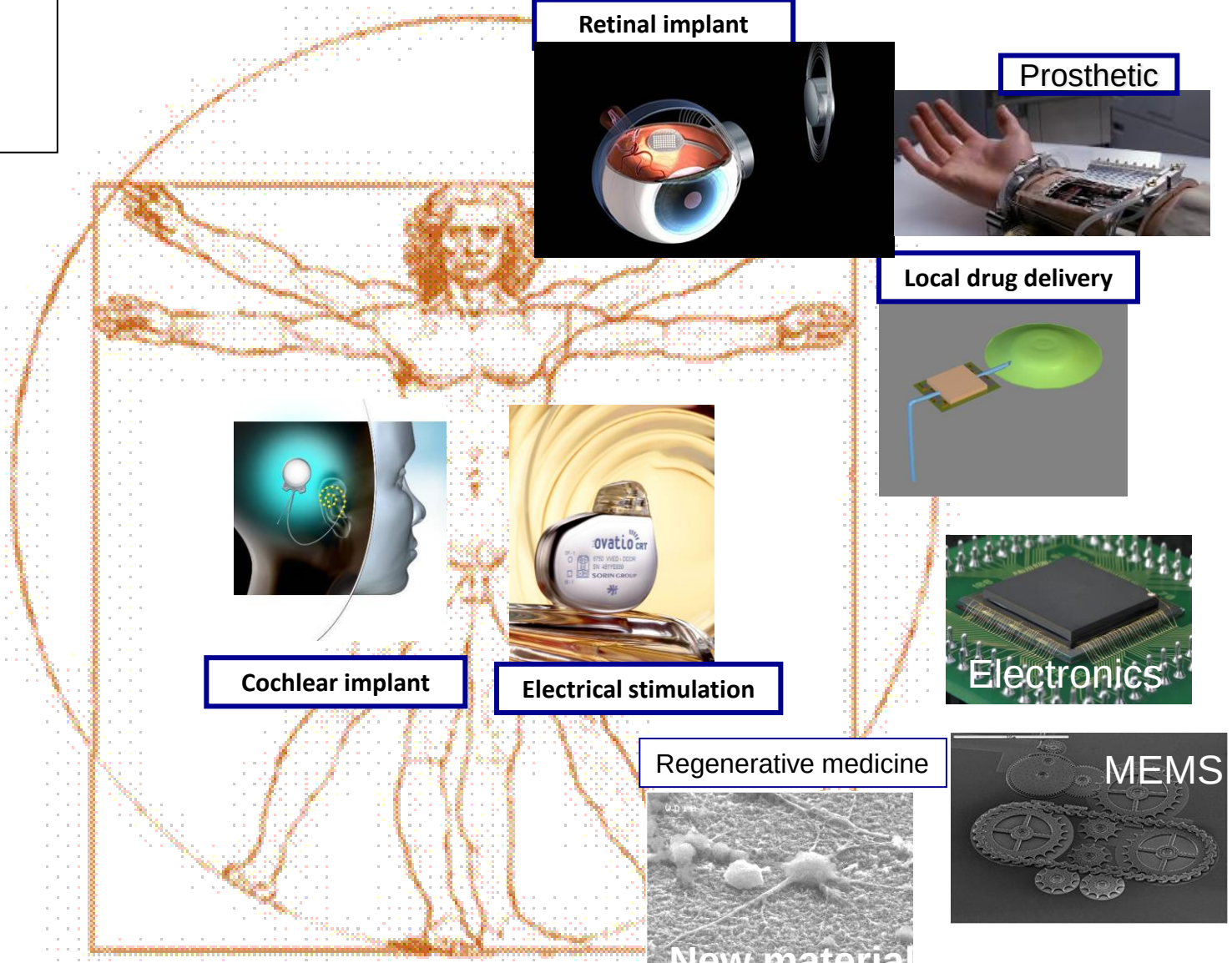
Movment, electro-recording



Brain cumputer interface

Micro-imaging





Retinal implant

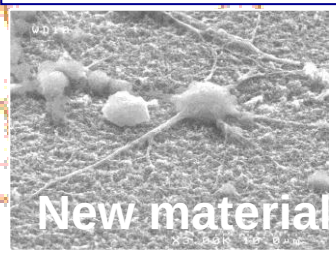
Prosthetic

Local drug delivery

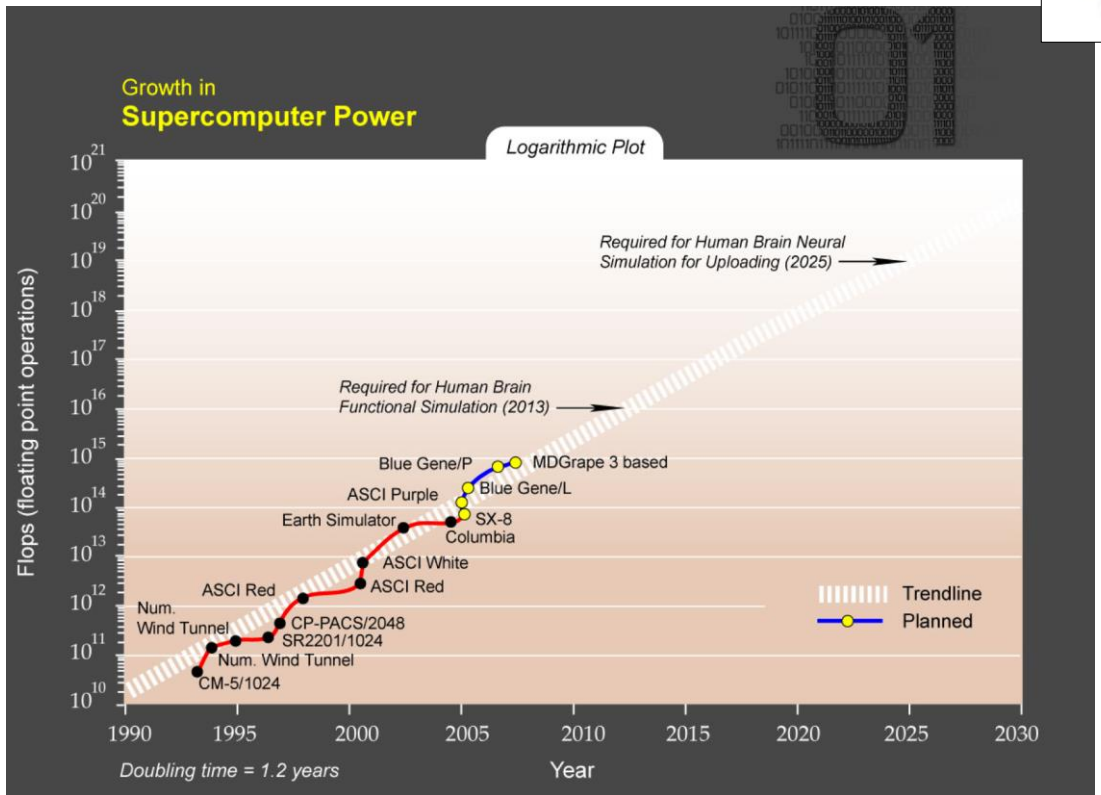
Cochlear implant

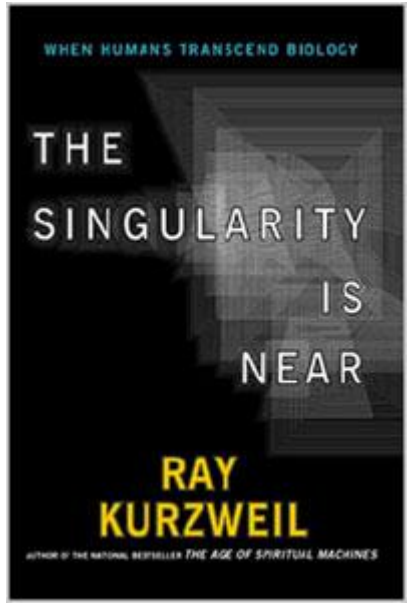
Electrical stimulation

Regenerative medicine

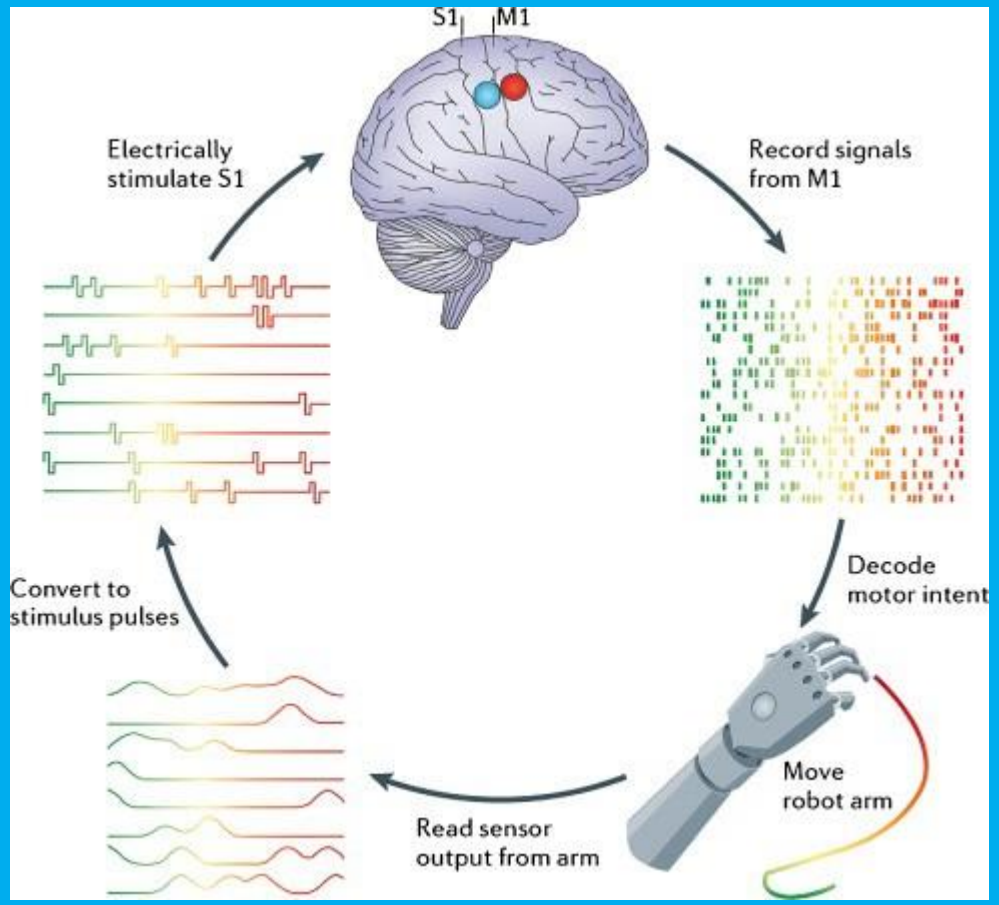


LES UTOPIES TECHNOLOGIQUES: QU'EST-CE QUI EST POSSIBLE, SOUHAITABLE ET ETHIQUE ?





BRAIN COMPUTER INTERFACE STRATEGIES



EEG

EEG Helmet

ElectroEncephalogram

- Non invasive
- Few degrees of freedom
- Large range of applications

https://www.youtube.com/watch?v=fZrvdODe1QI

Miguel A.L. Nicolelis, Duke University Center for Neuroengineering and the Department of Neurobiology, 2014

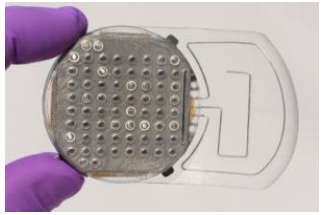
- Médiatisation à outrance
- Technologie immature
- « Survente »
- Inadéquation clinique
- **Le besoin patient ? Les usages ?**

ECoG

ECoG array

ElectroCorticoGram

- Many degrees of freedom
- Invasive few risks
- Medical Applications



Andrew B Schwartz, Department of Neurobiology, University of Pittsburgh (Collinger et al., The Lancet 2013), (Wang, W., *PloS one* , **2013**

http://onlinelibrary.wiley.com/doi/10.1002/ana.22613/full

Toshiki Yoshimine, University Medical School, Osaka.
(Yanagisawa et al., **2012**. Ann Neurol.)

4,44

INTRACORTICAL ARRAY

MicroElectrode array

- Possibly large number of degrees of freedom
- Very invasive, long term problems

BlackRock array

BlackRock array

2006

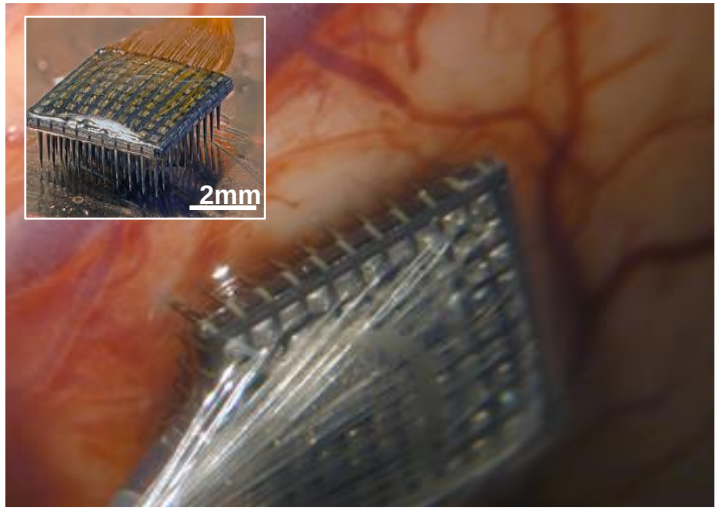
2,13

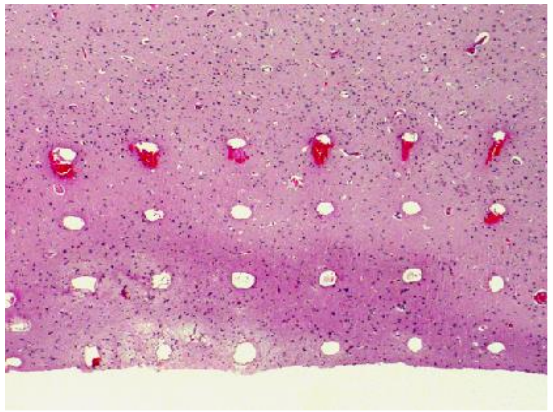
3,11

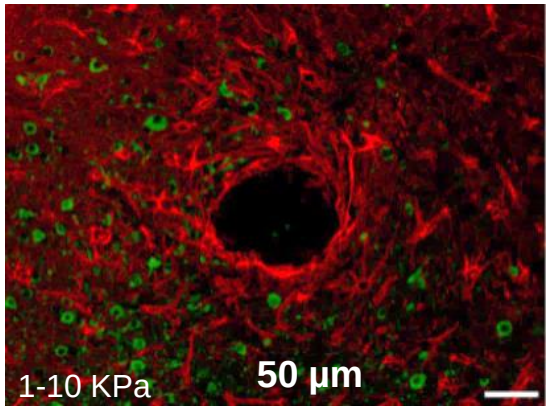
- **John P. Donoghue & R. Hochberg , Cyberkinetics Neurotechnology, Brown University, Massachusetts General Hospital** Hochberg, et al *Nature* (**2006**) , Hochberg, et al *Nature* (**2012**)

2,44

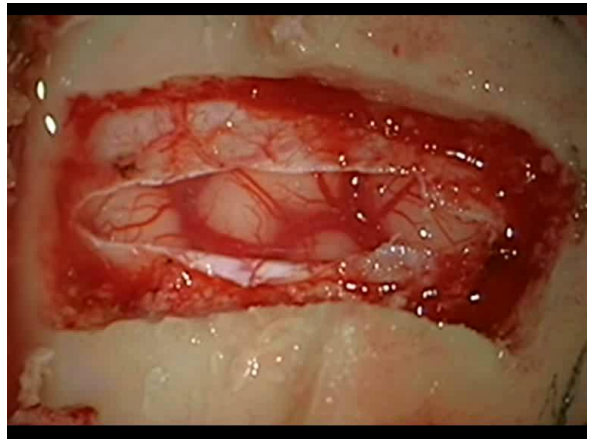
LONG TERM STABILITY IS A MAJOR CONCERN

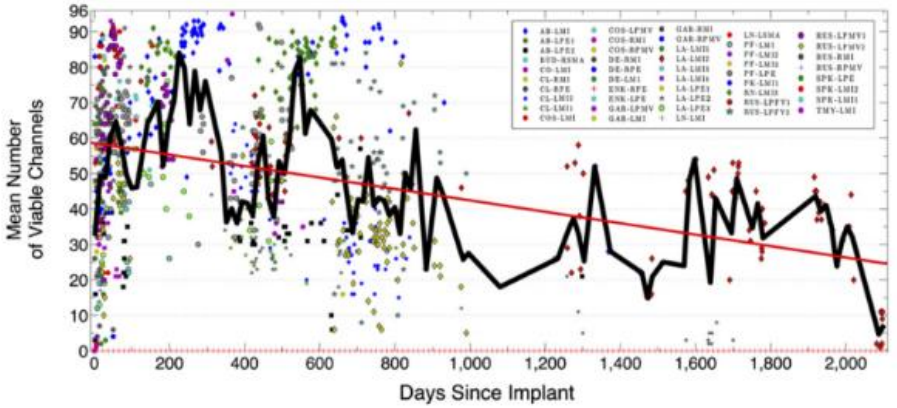






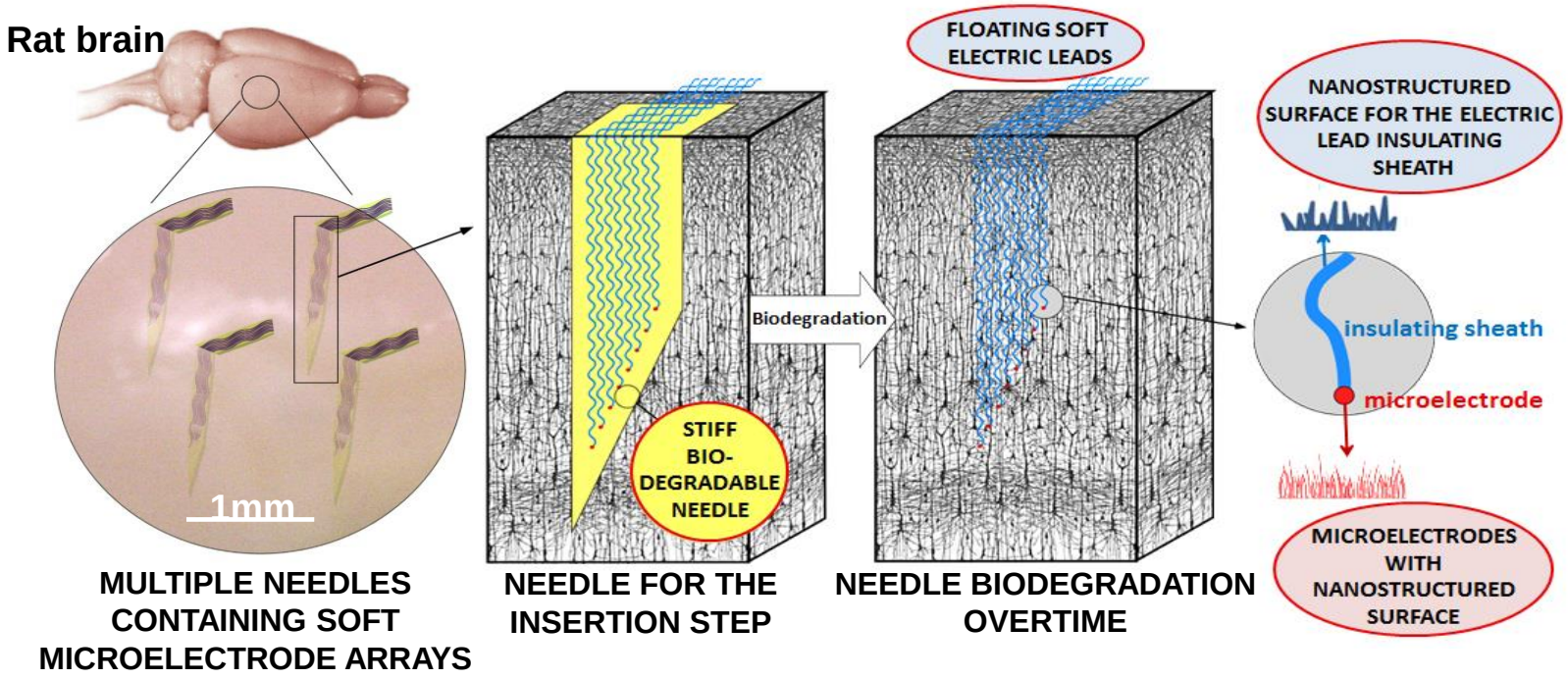
Marin, C et al. (2010)
Front Neuroengineering



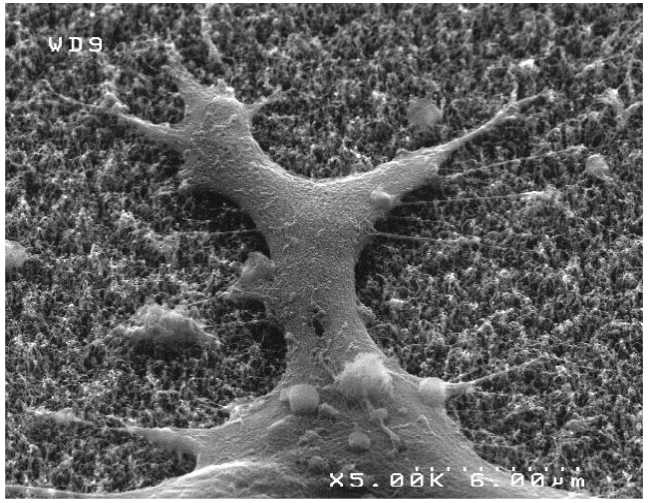


Barrese et al. (2013) J Neural Eng

NEED TO COME BACK TO BASIC RESEARCH !

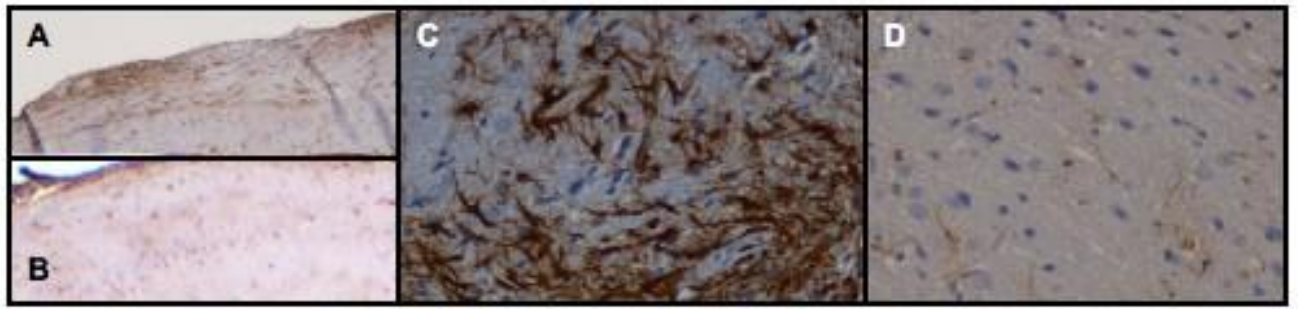


TOWARD MORE PHYSIOLOGIC INTEGRATION



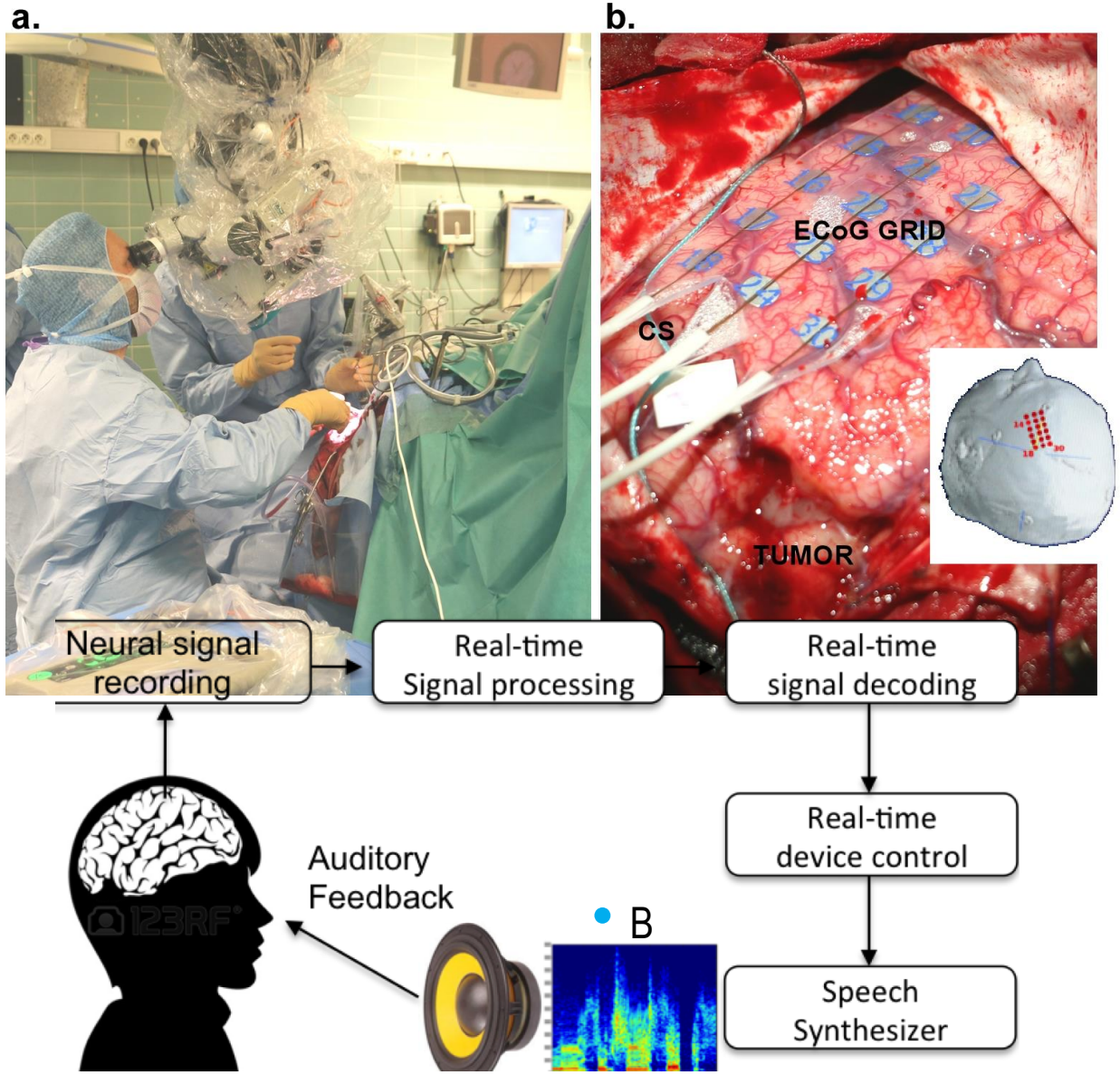
European Research Council
Established by the European Commission

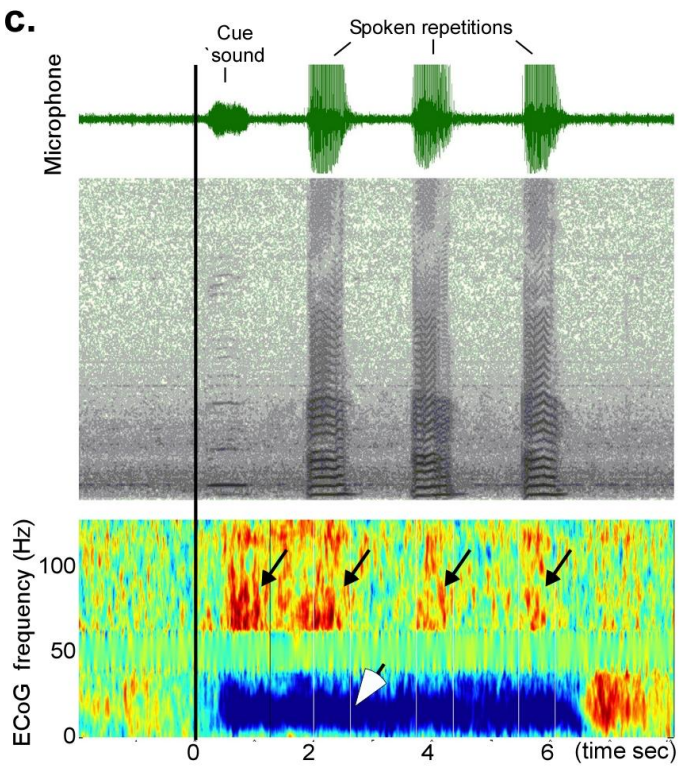
Gael Piret



Sauter 2013

BRAINSPEAK





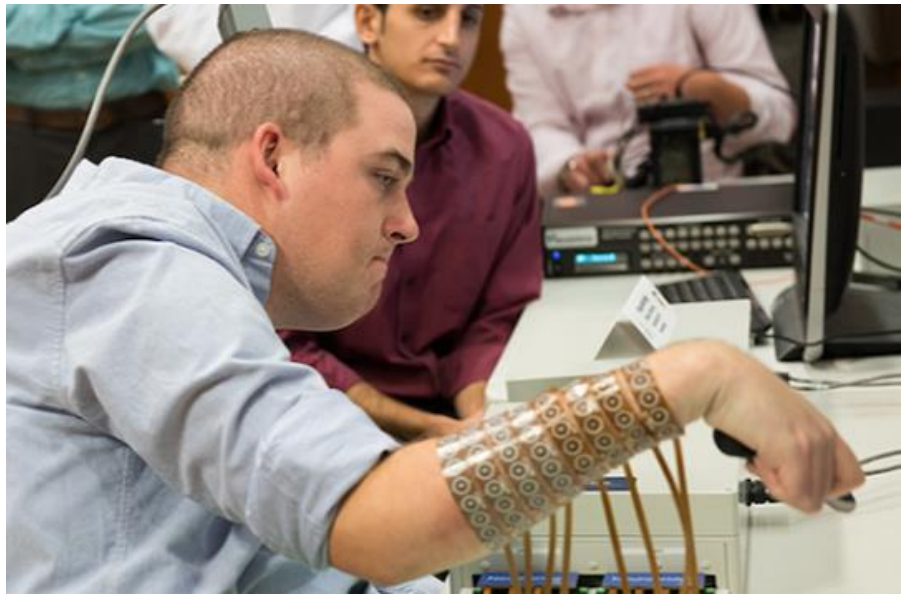
Blaise Yvert

FONDATION RECHERCHE MÉDICALE

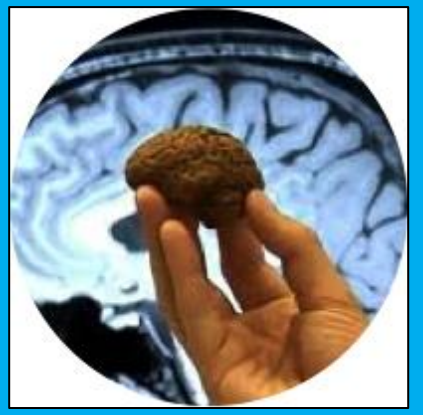
First acute validation during functional awake surgery for gliomas

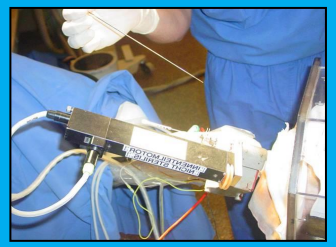
EN CONCLUSION

- Une opportunité pour les patients
- Le bénéfice reste très faible après plus de 10 ans de recherche
- Problème de la stabilité à long terme
- Risque bénéfice quand sujet atteint de handicap ? Un membre de l'équipe de recherche ?
- Recherche incrémentale versus miracle annoncé (et savoir retourner à la recherche plus fondamentale)



EXPLORING AND DECIPHERING THE INACESSIBLE BRAIN ?
A NEW BIOMEDICAL PROCEDURE: BRAINPRINT TECHNOLOGY



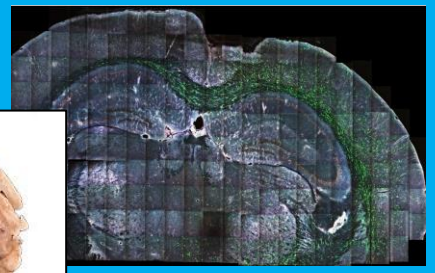


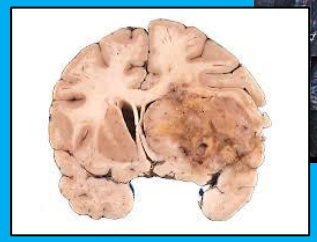
Non lesional access to the Brain- neuromodulation

INTERVENTIONAL AND MULTIMODAL IMAGING

Micro-environment

Optics
Poly-omics





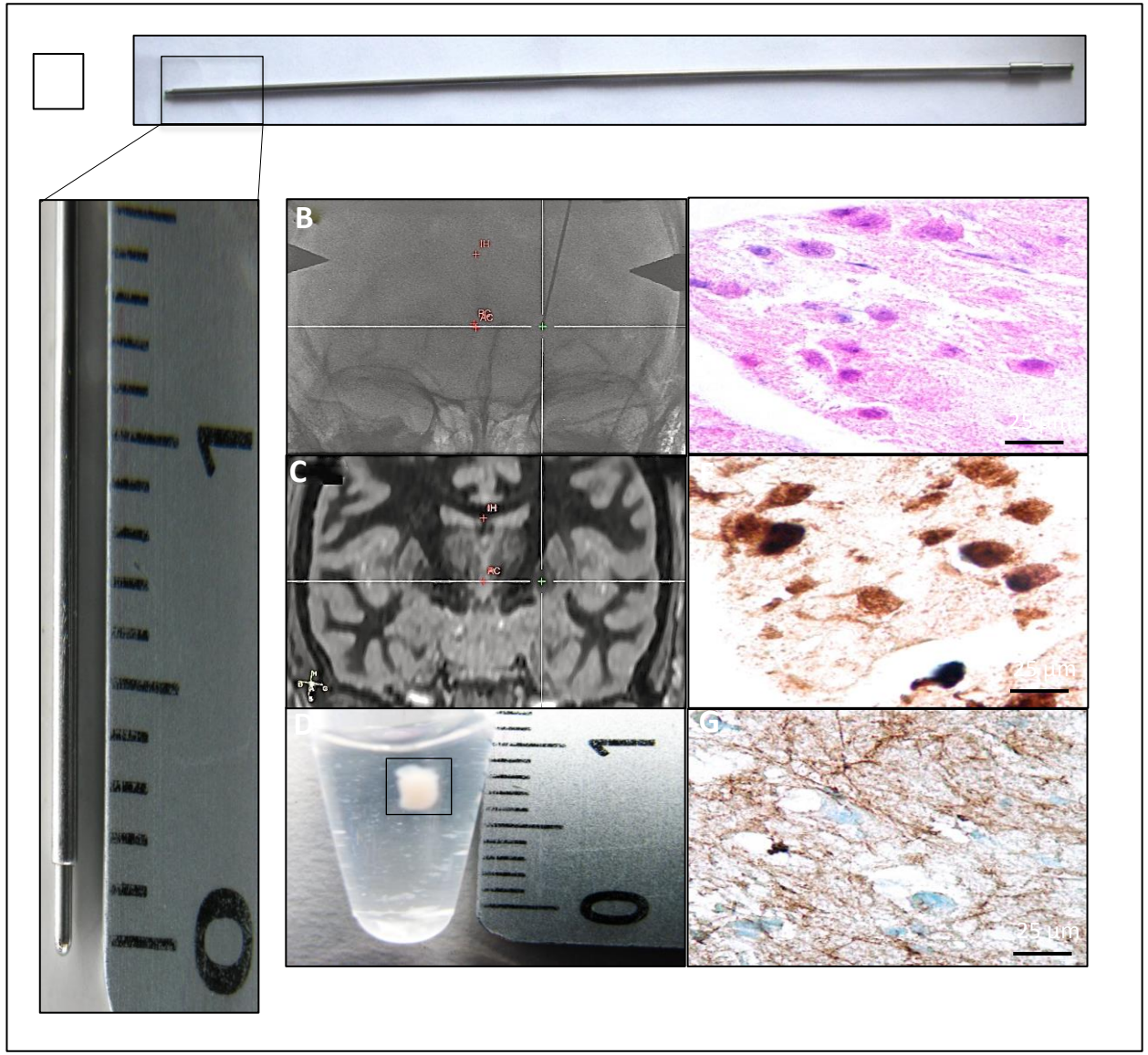
Tumor-neurodegenerative heterogeneity/complexity invasion

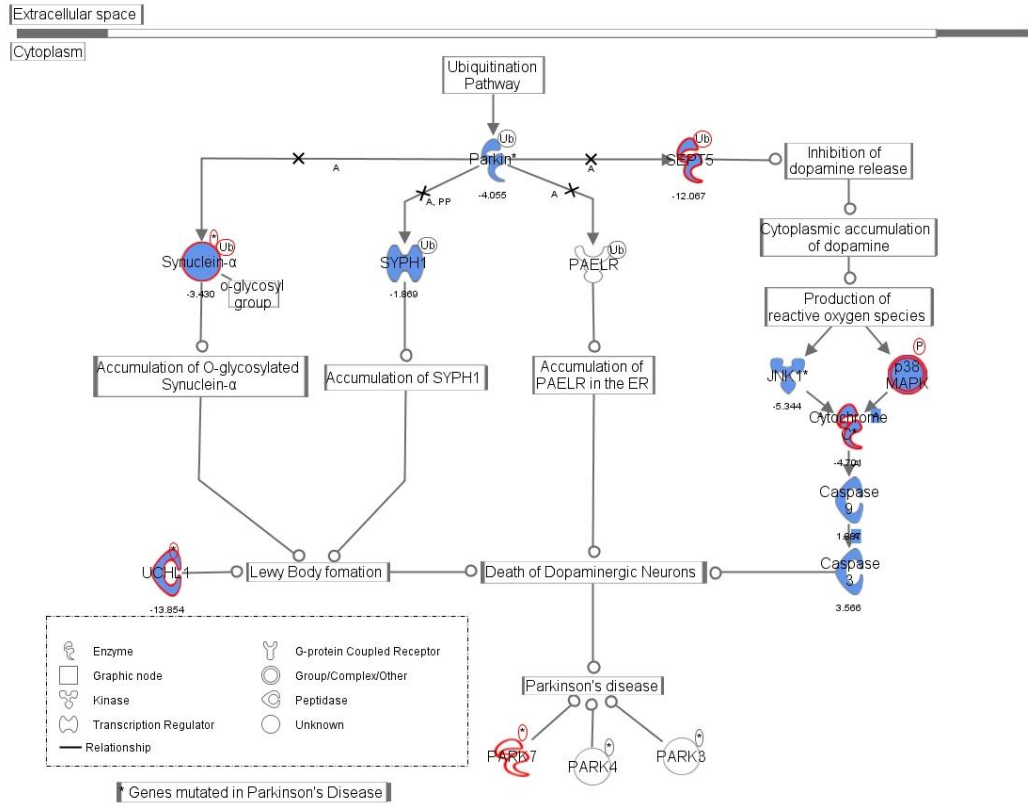
Innovative technologies

DEEP BRAIN FINGERPRINT DURING DBS

- **Deep-Brain-Stimulation is a paradigme for non-lesional « physical » intervention in the brain: living micro-brain fragment can be recovered from the stylet in contact with the cerebral tissues**

MICRO-SAMPLES OF HUMAN “LIVING” BRAIN FROM INACCESSIBLE TERRITORIES !

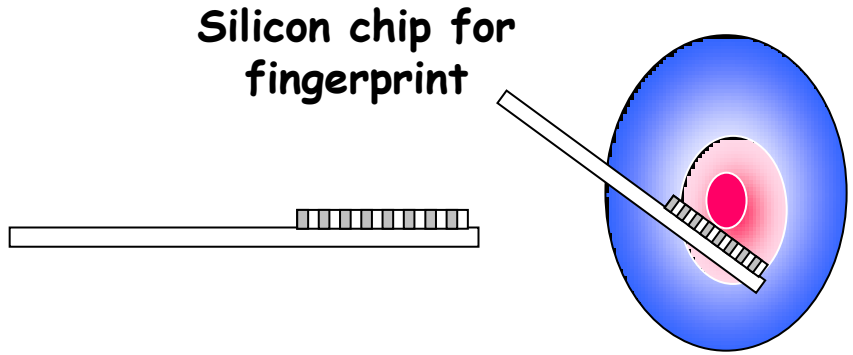




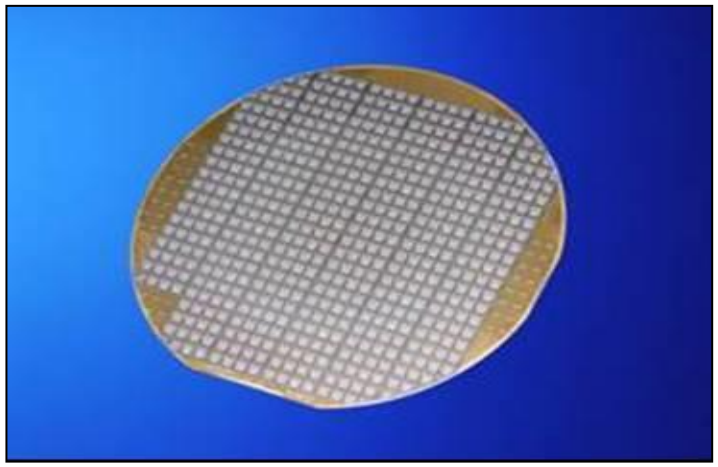
Compatible with poly-omics investigations

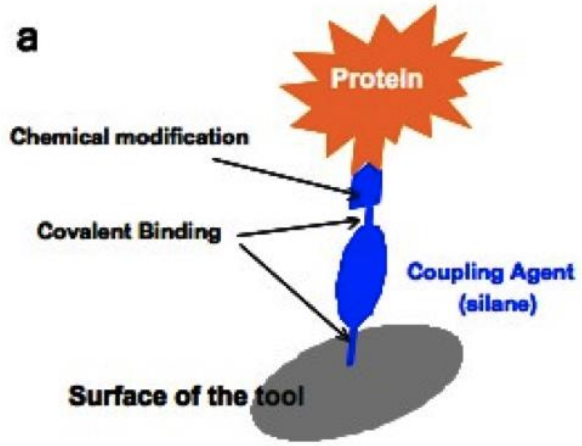
Molecular neurodeg 2016

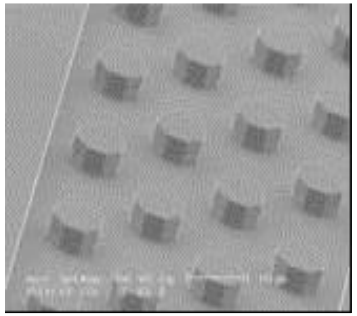
OPTIMIZING THE BRAIN FINGERPRINT ? AN INNOVATIVE SILICON BRAINPRINT TECHNOLOGY



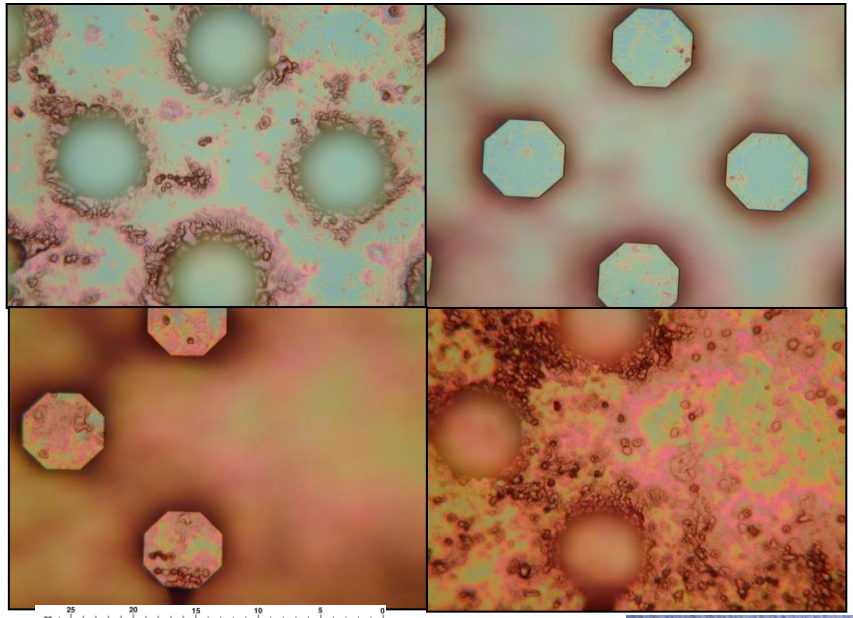
- **Micro-nano-chemomodified interacting surfaces**

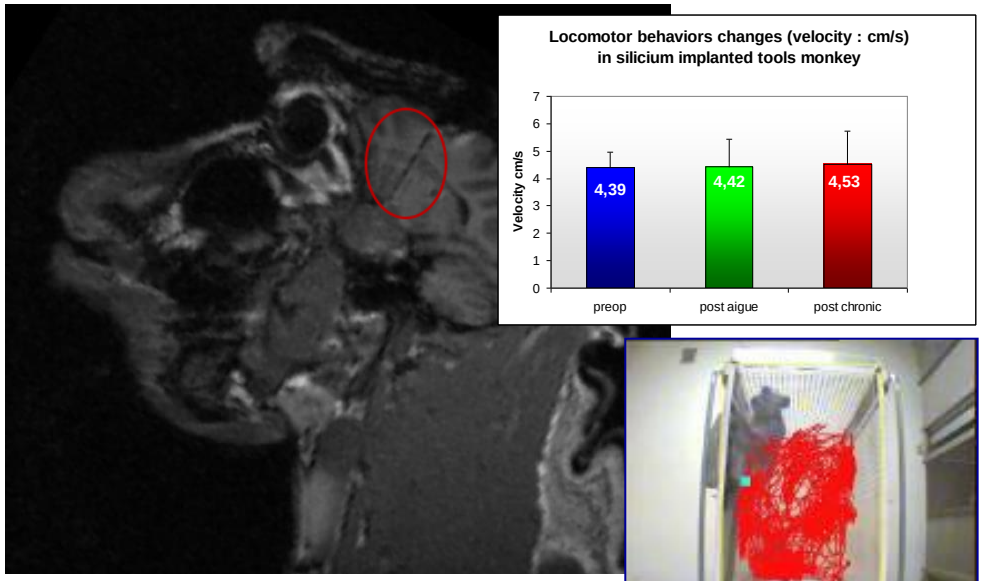


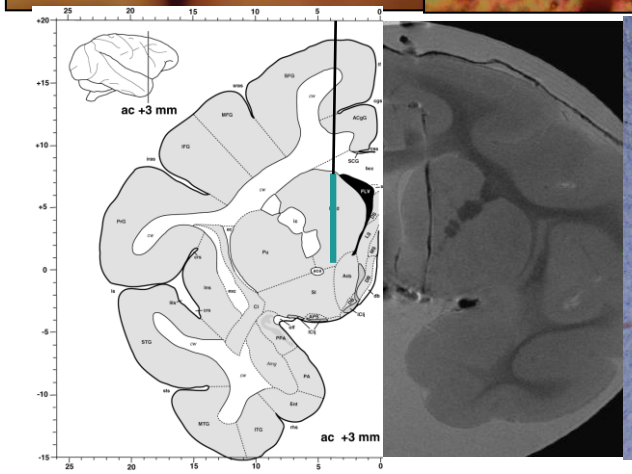


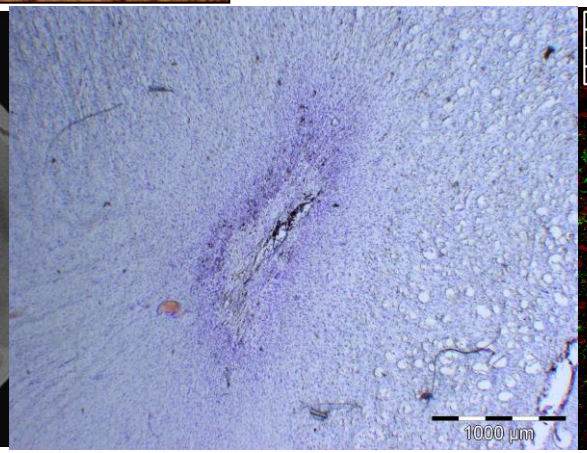


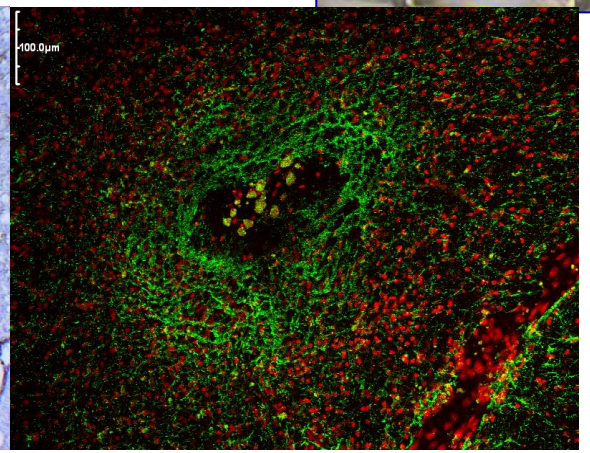
PRECLINICAL TOXICOLOGY







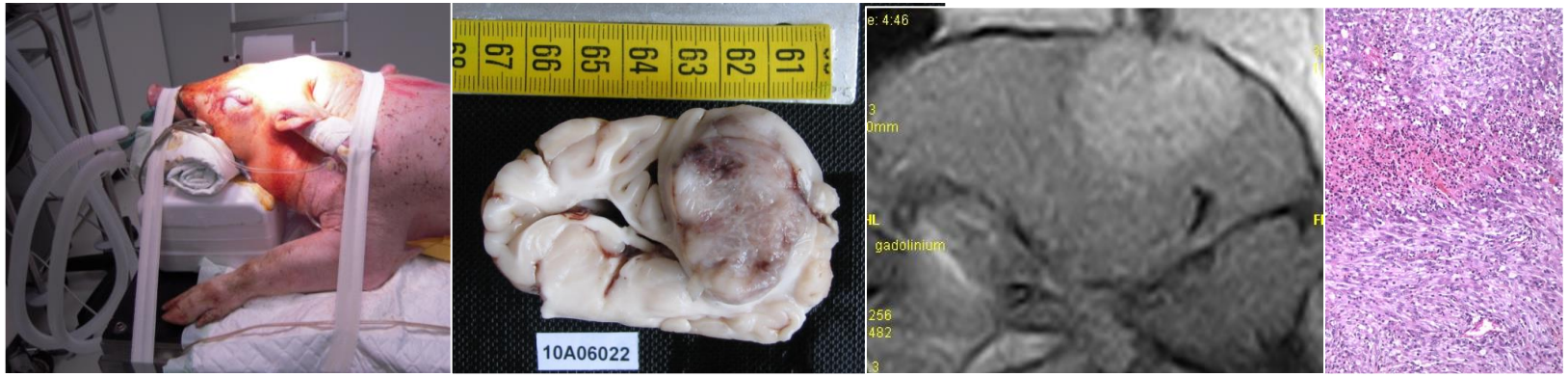




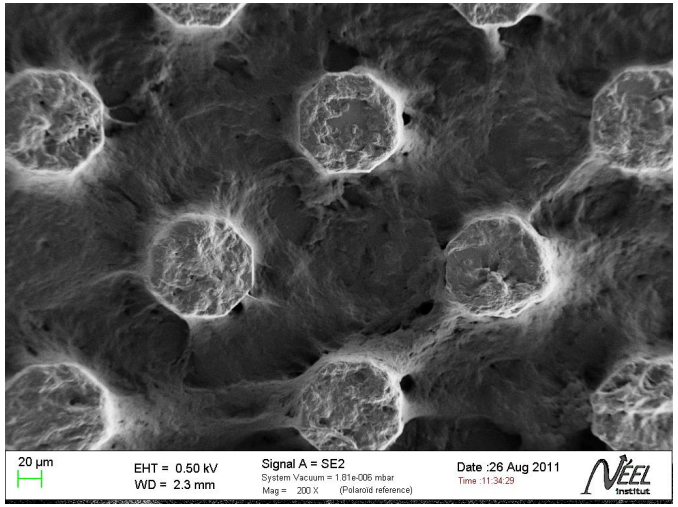
Long term tox ? 2 years

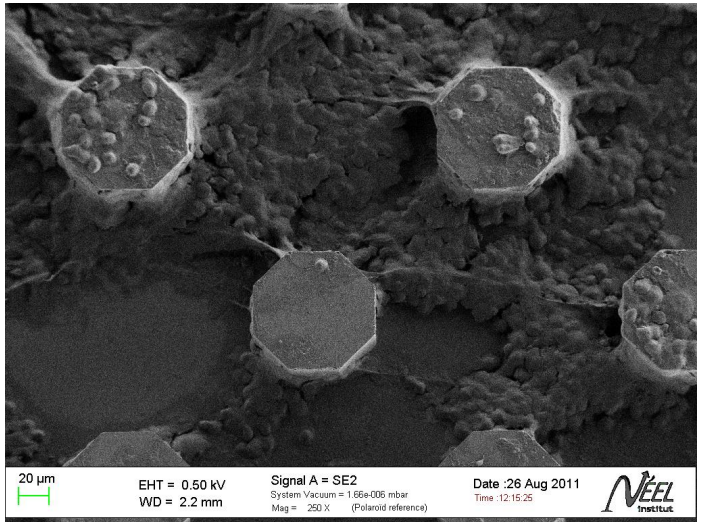
PRECLINICAL PROOF OF CONCEPT IN REAL NEUROSURGICAL CONDITIONS

L SELEK
2014



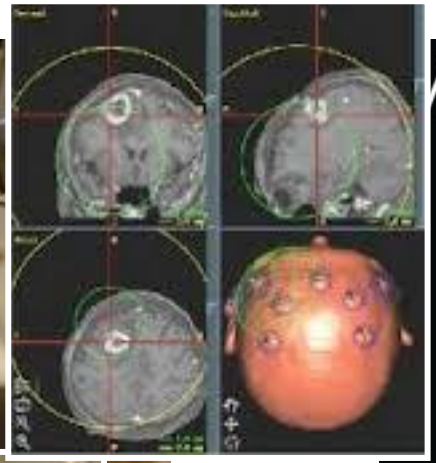
From Non human primate to swine

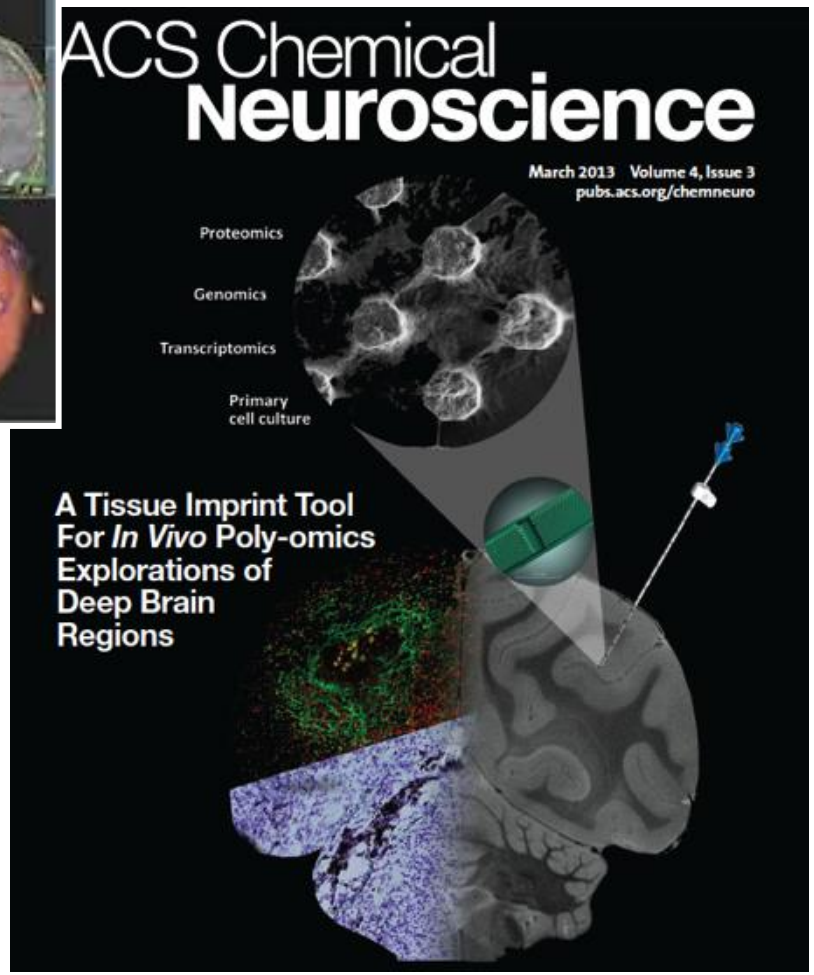




A NEW "POST-BIOPSY POST-HYSTOLOGY" MEDICAL PROCEDURE: "NON LESIONAL TISSUE-FINGERPRINT"

CLINICAL TRIAL: « BRAIN-PRINT »

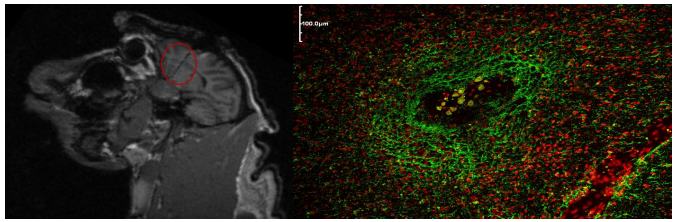




- **Synergistic association: Stereotaxy, 3D MRI, Neuronavigation, bio-robotic (Medtech-Rosa), Medical device industrialisation (Alcys)**

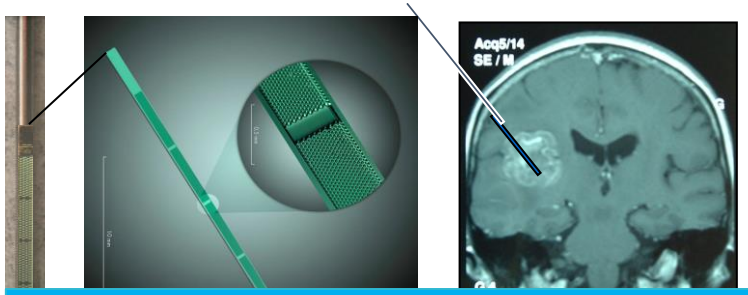
FROM CONCEPT TO INDUSTRIALIZATION AND THERAPEUTICAL TRIAL

Preclinical toxicology



Clinical operability

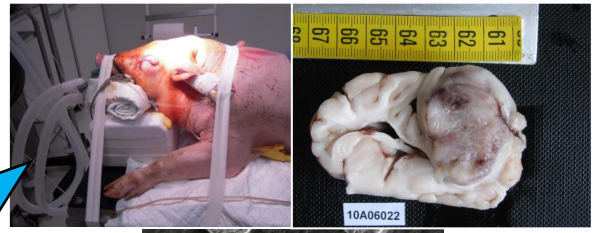
Specific informed consent, GBM

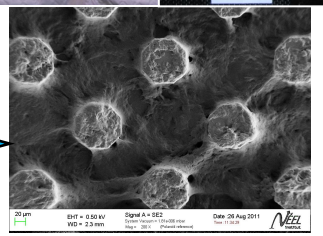


ANSM Aproval and HUMAN trial

CHU Angers (Pr Menei), Saint-Anne (Pr Devaux)-H Chneiweiss, Henry Mondor (Pr Palfi)
Grenoble (Pr Chabardes, Pr Gay)

Clinical need + Innovative technology

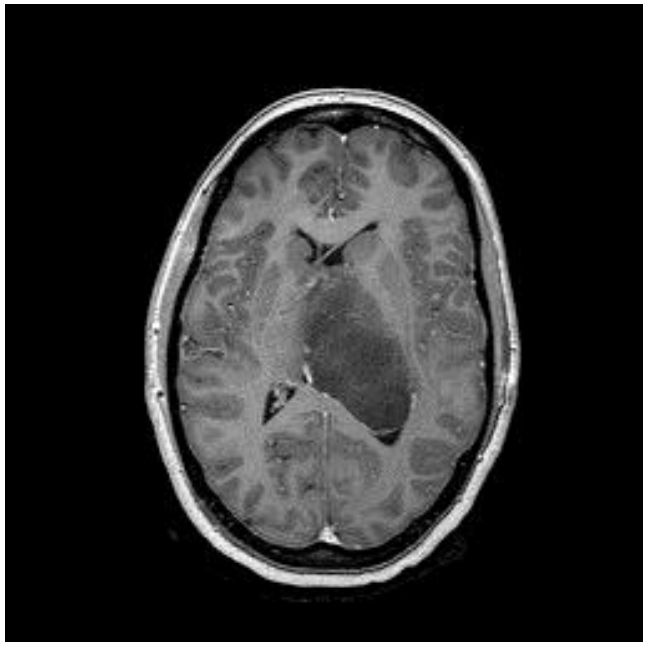


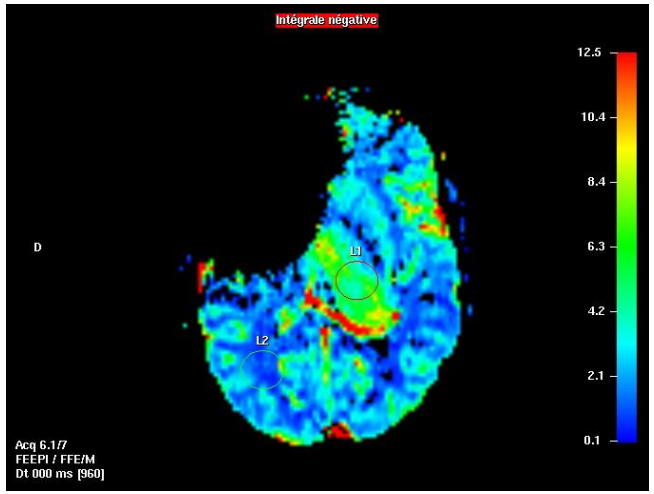


Regulatory tests done independently

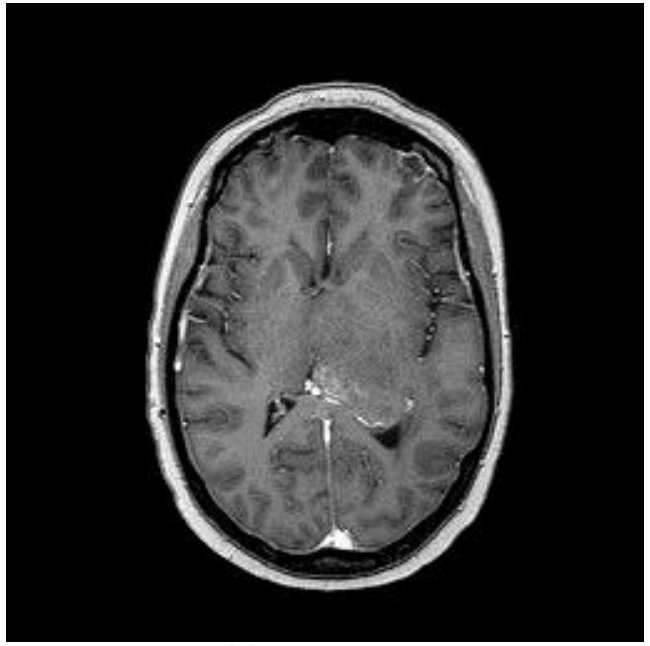
First 5 patients multimodal investigation in CLINATEC was mandatory for approval and dissemination

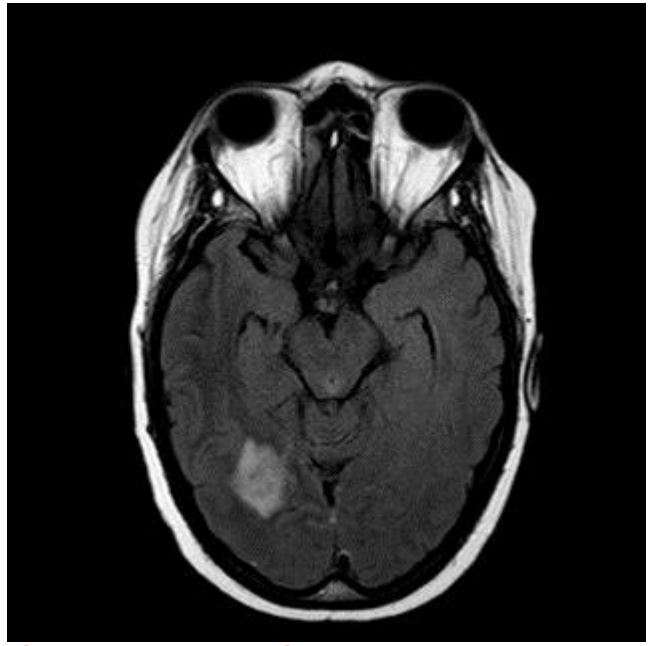
PREMIER PATIENT GLIOPRINT



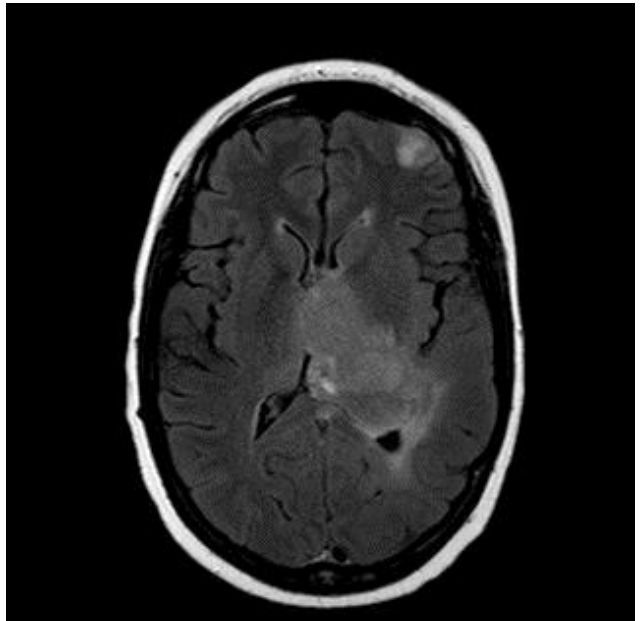


- Corticoïdes
- Radiothérapie
- Temodal

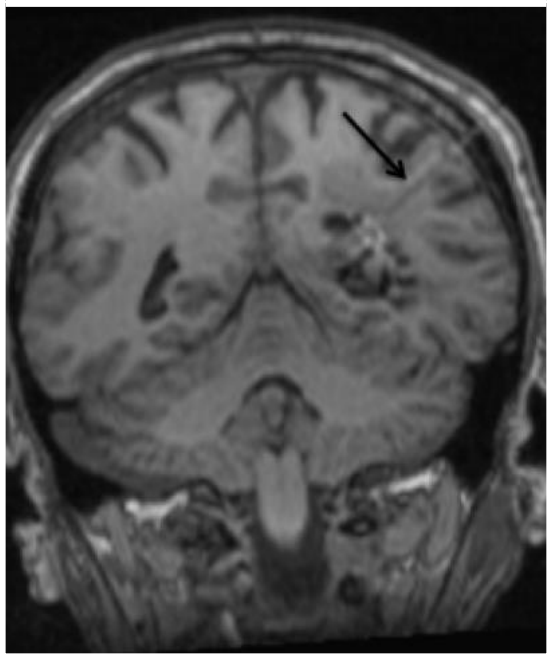




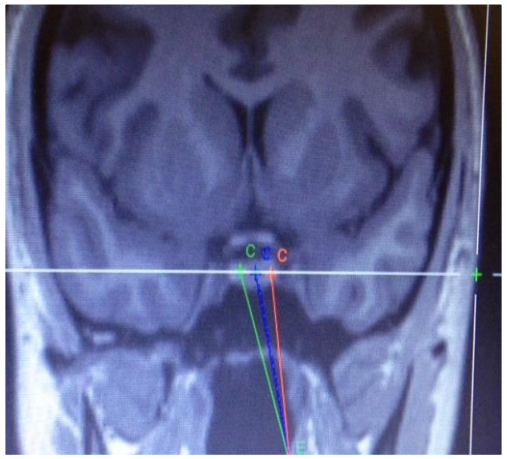
Effet secondaire lié aux matériaux ?



FIRST HUMAN VALIDATION

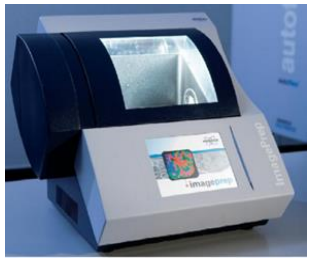


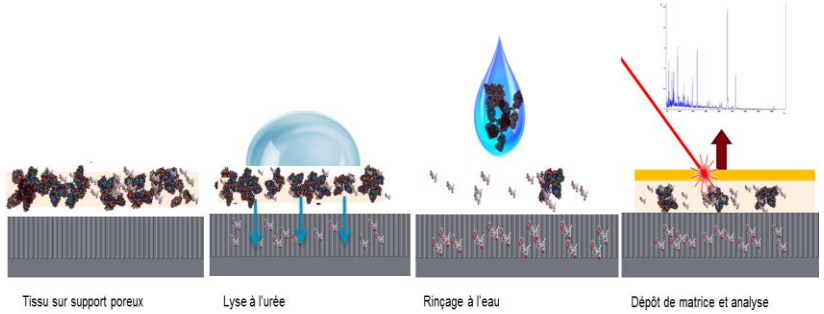
EXTENSION TO PITUITARY SURGERY

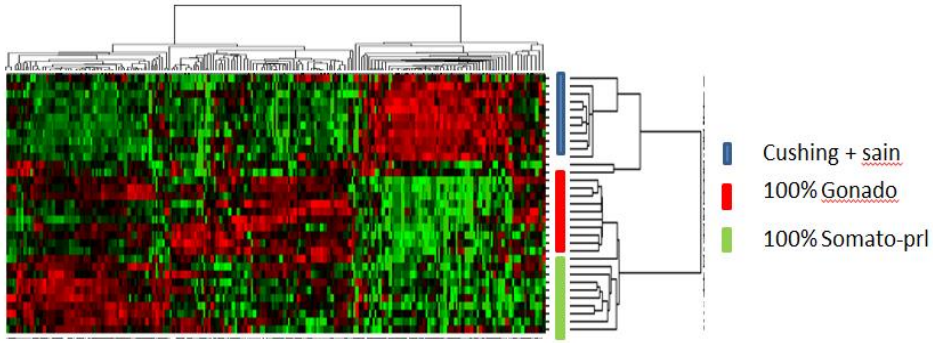


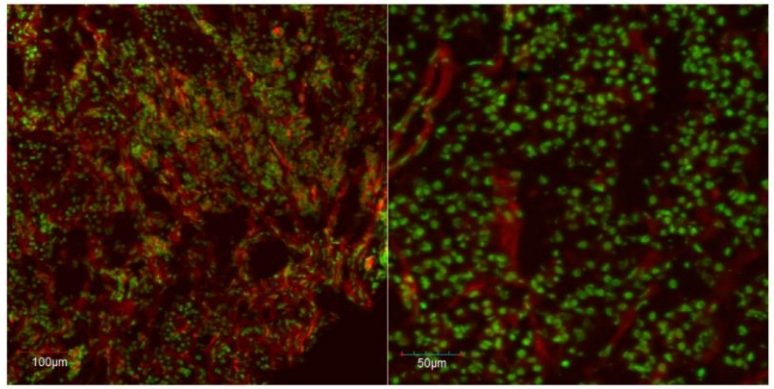
- Intra-operative MRI
- Endoscopy
- Robotic to define Baintprint trajectory
- **Do we have enough data to extend to a non lethal pathology ?**

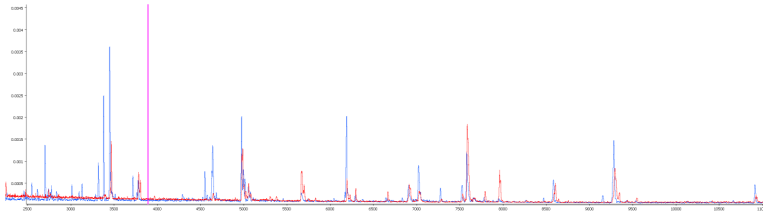
EXTEMPORANEOUS PROTEOMIC PROFILING TO DISCRIMINATE ADENOMATOUS TISSUES



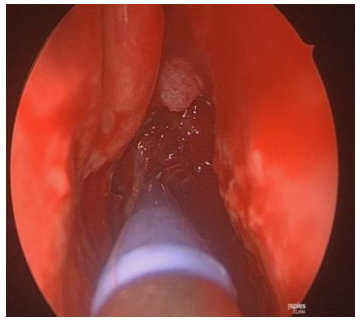


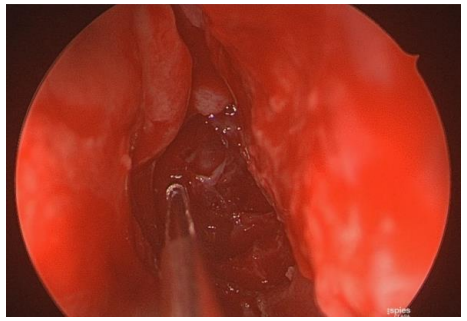


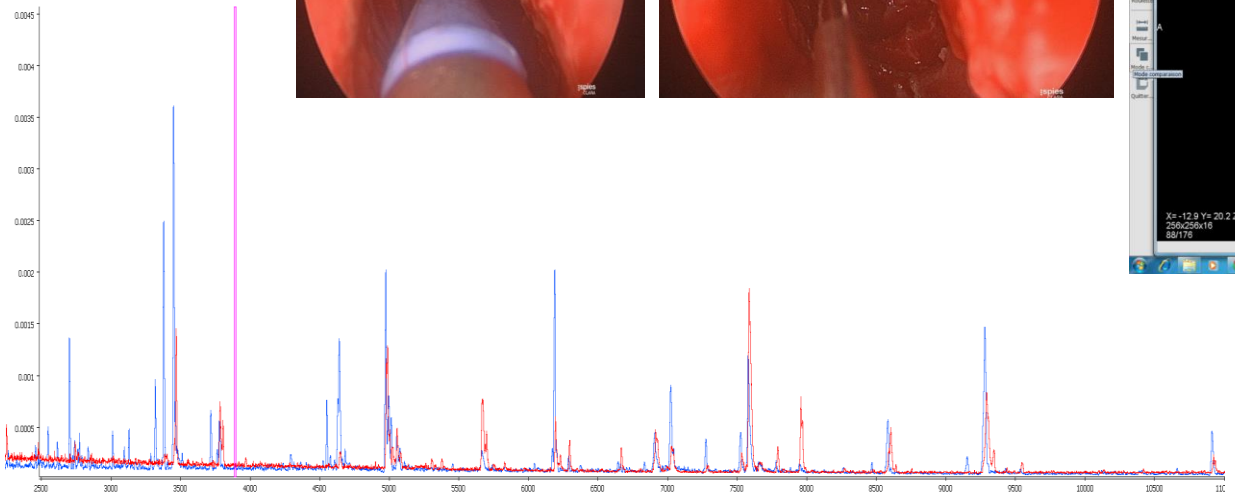




VALIDATION OF A PITUITARY ENDOSCOPIC SURGERY ASSOCIATING INTERVENTIONAL MRI AND MOLECULAR PROFILING



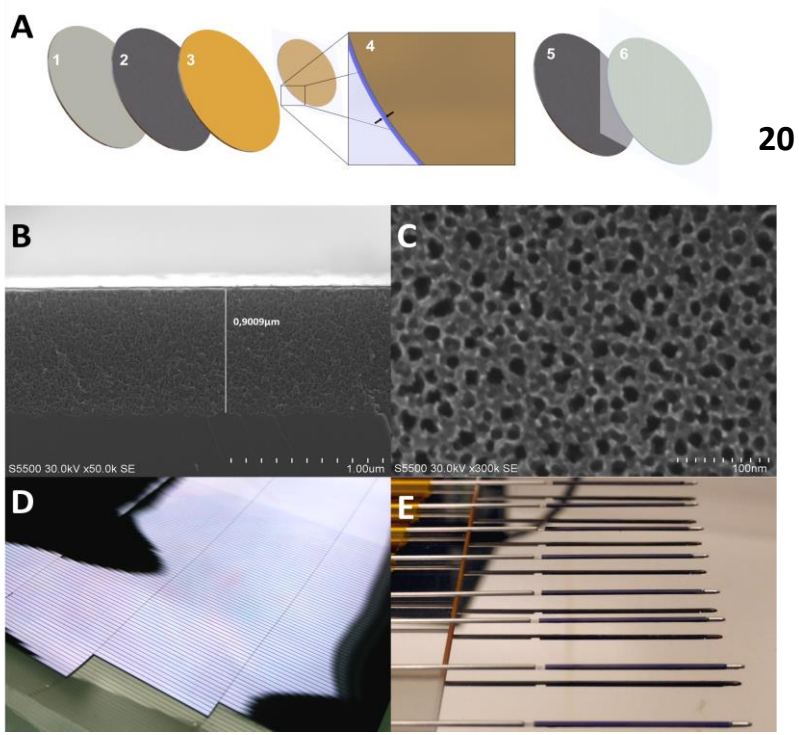




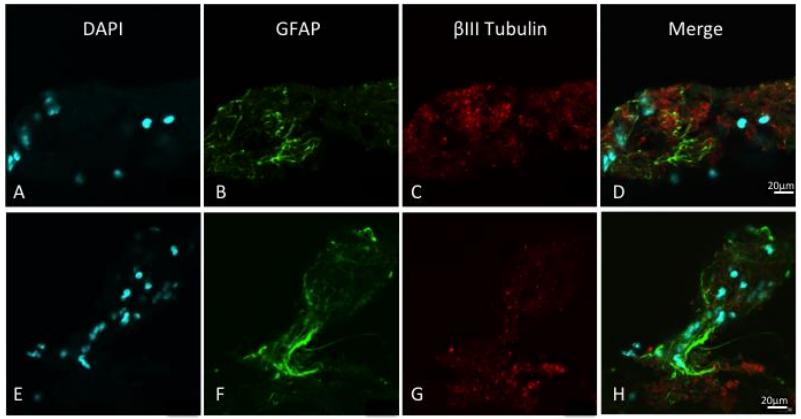
- **Modification of the device during the clinical trial in a CE norm methodology !**
- **Industrial level is mandatory**
- **But can generate conflict of interest**

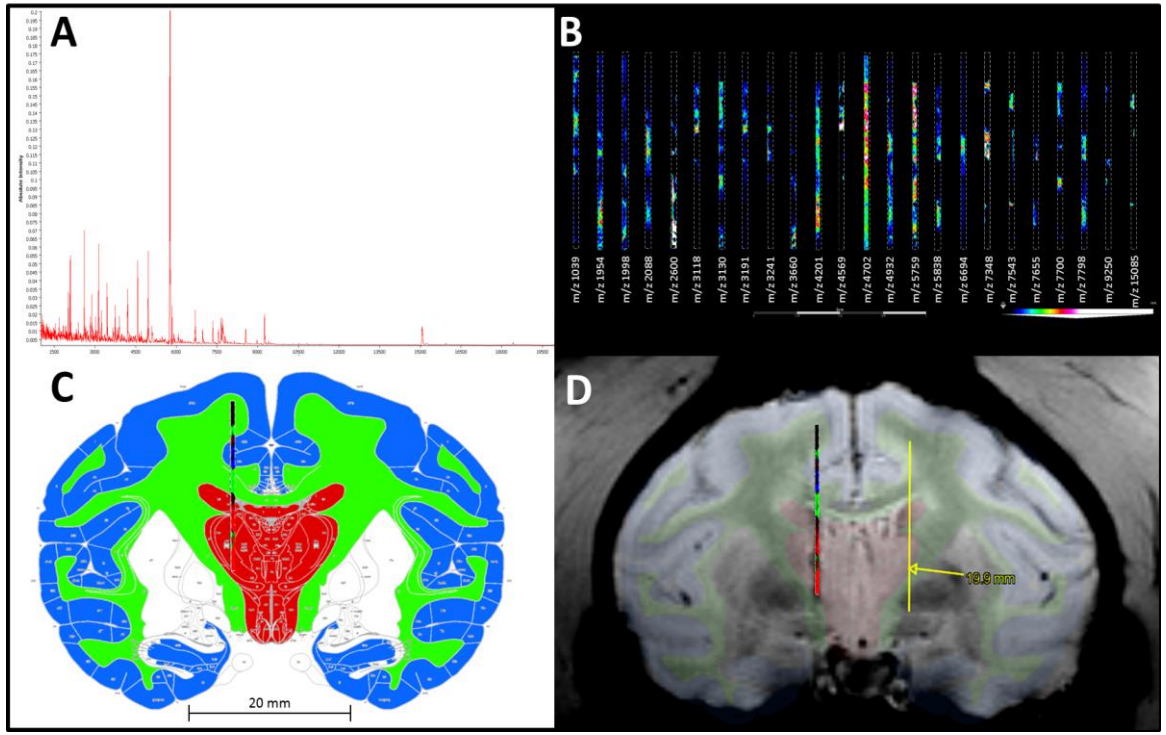
MEDIMPRINT
MEDICAL DEVICES AND DIAGNOSTICS

NEXT-GENERATION DEVICE USING NANOPOROUS SILICON FOR NEURODEGENERATIVE DISEASES INVESTIGATIONS



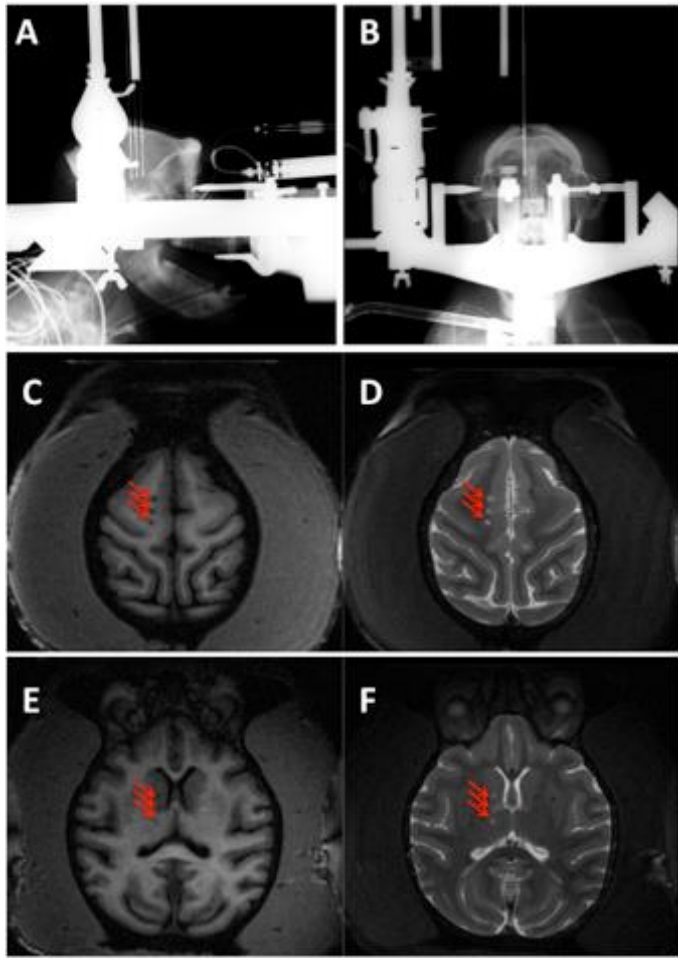
20 nm

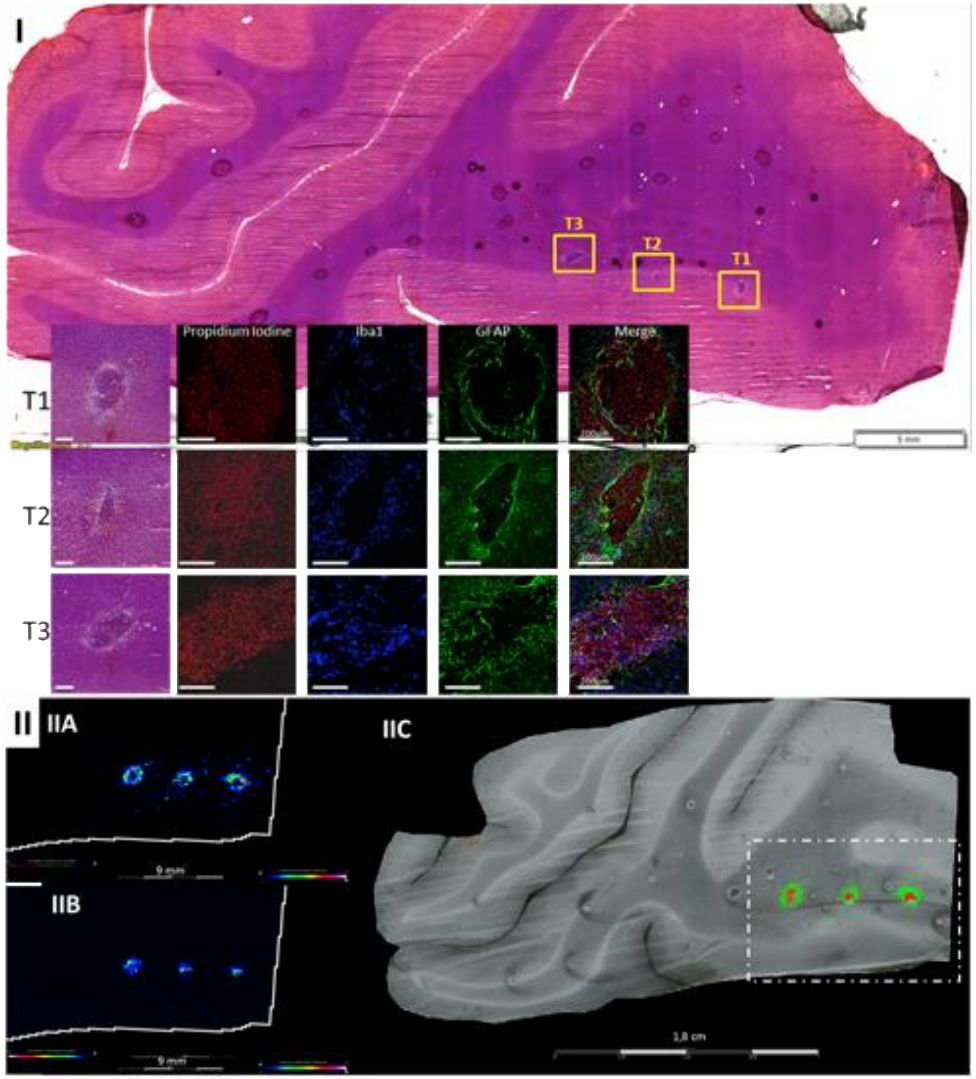




- HIGH RESOLUTION IN SITU MAPPING
- NO CHEMISTRY
- IMMEDIATE CAPTURE
- High miniaturisation

NEXT GENERATION NANOTOXICOLOGY ?

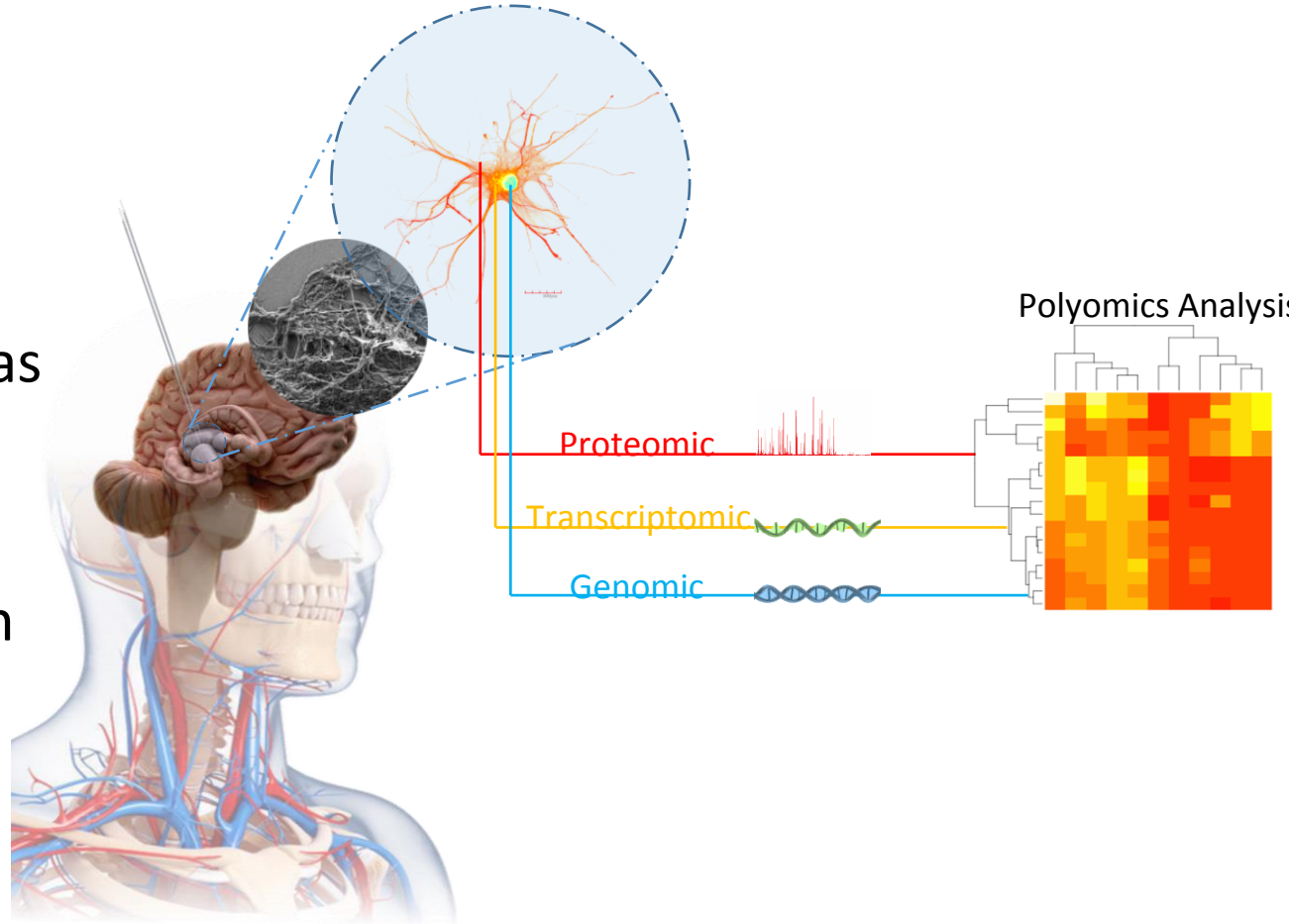




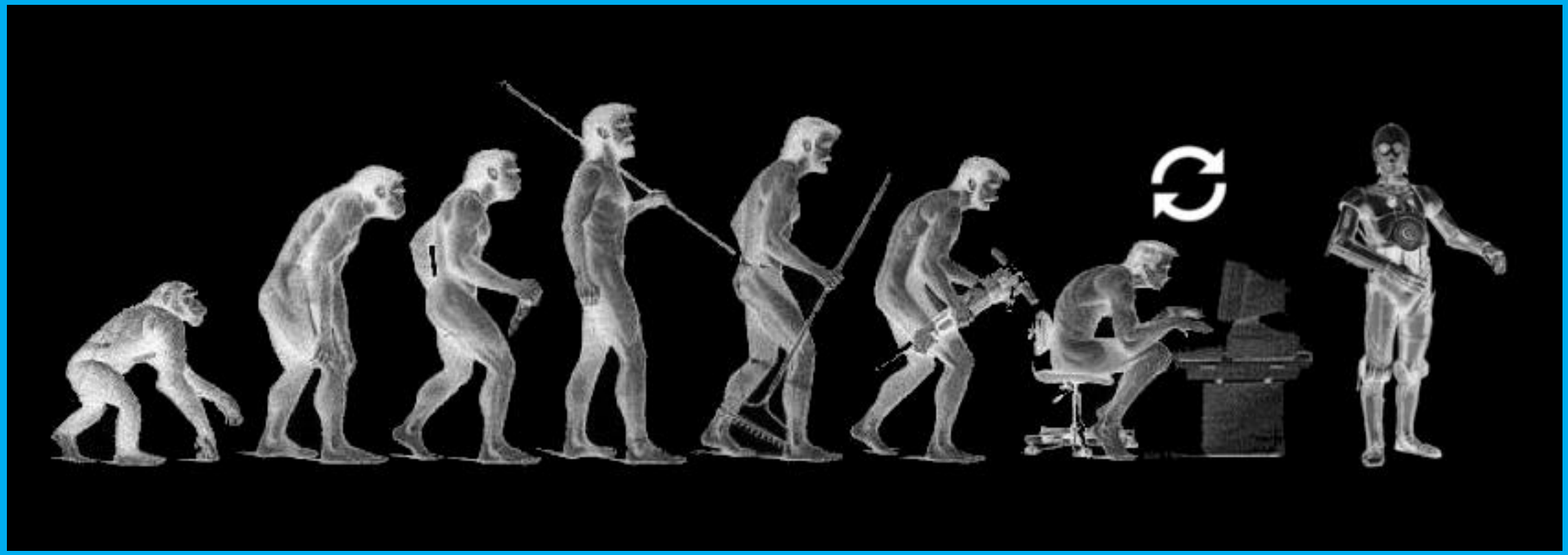
More than the norm ? And again long term tox …

EN CONCLUSION

- Une nouvelle procédure médicale avec un impact potentiel pour trouver des cibles plus curatrices (Cancer, neurodégénératif)
- Première introduction de silicium chimiquement modifié chez l'homme
- D'où le choix princeps du glioblastome
- Puis extension à une pathologie ne mettant pas en jeu le pronostique vital
- Un consentement éclairé spécifique
- Pour la seconde génération utilisant le silicium nanoporeux, devons nous aussi avoir une première phase GBM ?



LES REFLEXIONS ÉTHIQUES D’UN CLINICIEN NAÏF



LES UTOPIES TECHNOLOGIQUES

- **Conflit d'intérêt:**
  - Attirer les patients avec des rêves
  - « Survente » pour attirer des supports financiers..
  - Des pseudosciences auquel nous contribuons parfois…
- **Un erreur épistémologique:**
  - La réflexion éthique et philosophique se focalise sur la science fiction et non sur la nouveauté qui émerge à l'interface avec le vivant lors des premiers essais

ACCEPTANCE SOCIETALE

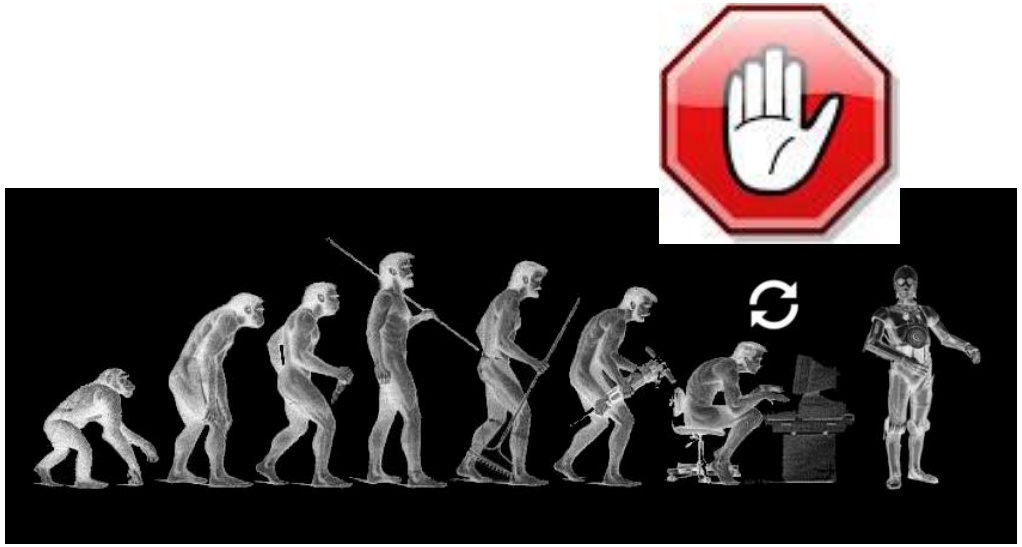
- Mieux communiquer avec le grand public
- Éviter les communications de type science fiction avec des images clinquantes
- Formations à l'interface entre la biologie, la médecine, et l'ingeniérie.

L'INVENTION DU BIEN-ÊTRE ET LA REVENDICATION D'UNE LIBERALISATION DE L'INTERVENTION SUR LE CORPS

- La discrimination-évolutive- entre le normal et le pathologique est la base de la médecine
- Toute intervention sur le corps peut entrainer des effets secondaires , inacceptables en l'absence de pathologie
- Régulation indispensable des technologies intervenants à l'interface avec le vivant
- Le wellness ne doit pas conforter une marchandisation dérégulée du corps et de ses informations

POSITION FERME CONTRE L'IDEOLOGIE TRASNHUMANISTE

- "next-generation transhumanisme" passant du socialisme des années 30 à l'hyperlibéralisme
- Charlatanisme scientifique
- Marchandisation du corps sans barrière de régulation ni protection de la privacité (« vous êtes un bioconservateur »)
- **La modification du cerveau comme celle du germen doit rester un interdit**



PERSPECTIVES ?

- Une méthodologie translationnelle pour **accélérer le transfert au lit du patient de technologies innovantes tout en diminuant le risque de la nouveauté** ?
- **Protocole de phase 0 cognitif** considérant le patient comme le vrai modèle et utilisant au mieux la potentialité des investigations multimodales pour suivre les mécanismes et l'impacts de la technologie introduite pour la première fois chez l'homme ?
- **Un consentement éclairé plus actif** et un statut rénové du patient plus acteur de la recherche ?
- **Les sciences humaines et sociales doivent avoir un rôle actif** et précoce dans le processus du transfert clinique de l'innovation technologique.
- **Plutôt qu'un principe de précaution « bloquant » une surveillance active de l'impact des protocoles de phase précoces modifiant potentiellement les caractéristiques fondamentales de l'humain**.

MERCI POUR VOTRE ATTENTION