CNS as a major target of Sepsis and a source of brain dysfunction

Magna Meeting
Brazilian Academy of Sciences - 8th May 2017 Rio de Janeiro

Pr Fabrice Chrétien – Institut Pasteur & Hôpital Sainte Anne – Paris
fabrice.chretien@pasteur.fr

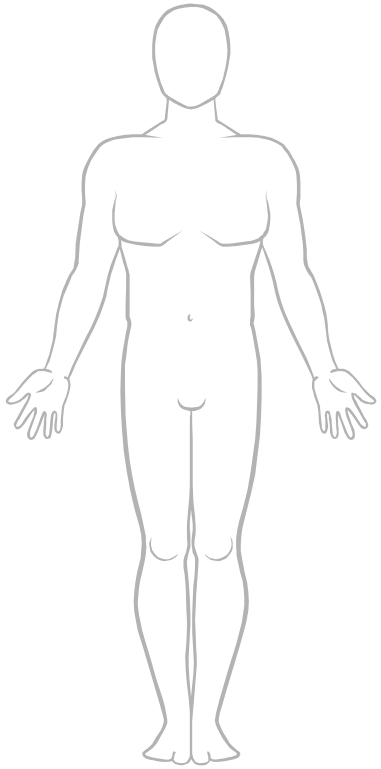
Institut Pasteur

SEPSIS

20-30
million patients / year

Increasing incidence

ICU
TREATMENT



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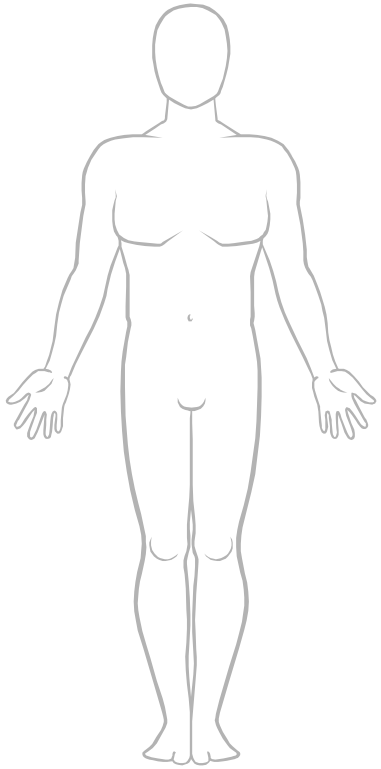


Shock ± **30%** **MORTALITY**

Multi organ failure

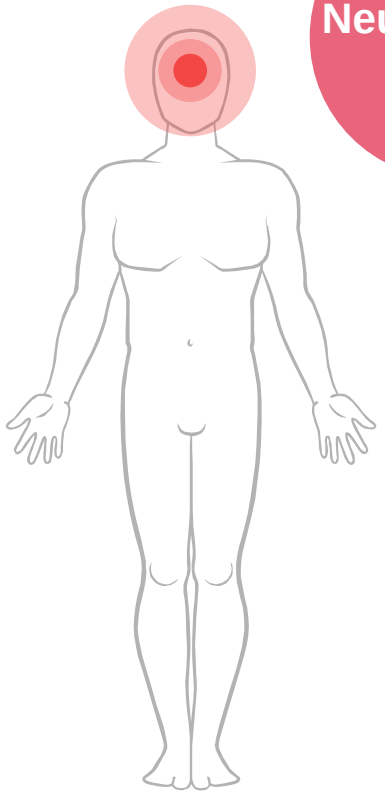
Short-term: **MORTALITY**

SEPSIS

20-30 million patients / year

Increasing incidence

ICU TREATMENT



Neurological failure

Encephalopathy **SiBD**

Shock ± **30%** **MORTALITY**

Multi organ failure

Short-term: **MORTALITY**

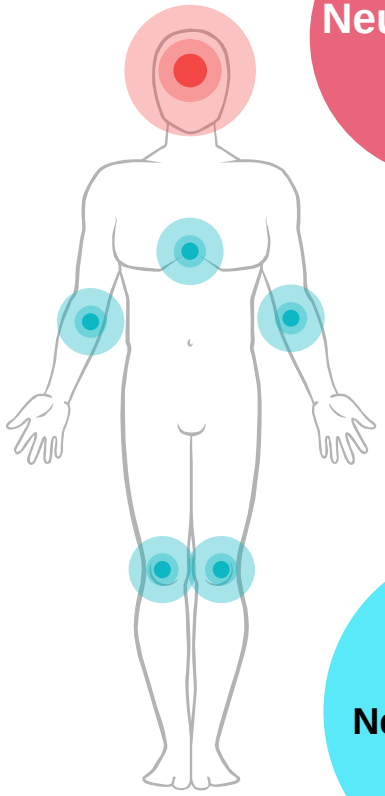
Long-term: **COGNITIVE DECLINE**

SEPSIS

20-30 million patients / year

Increasing incidence

ICU TREATMENT



Neurological failure

MUSCLE WEAKNESS DISABILLITIES

Encephalopathy **SiBD**

Shock ± **30%** **MORTALITY**

Multi organ failure

Short-term: **MORTALITY**

Acquired Neuromyopathy

Long-term: **COGNITIVE DECLINE**

OUR MAIN OBJECTIVE

NEURO-PATHOPHYSIOLOGY OF SEPSIS

- Acute and long-term brain and muscle dysfunction
- The impact of sequels
- Therapeutic innovations

OUR ORGANISATION

RESEARCH UNITS

Institut Pasteur

FIOCRUZ

NEURO-SEPSIS TASK FORCE

UNIVERSITY HOSPITALS

Centre hospitalier Sainte-Anne

TRIGGERSEP
TRIal Group for Global Evaluation and Research in SEPsis
F-CRIN Network

HÔPITAUX UNIVERSITAIRES PARIS OUEST
Hôpital européen Georges-Pompidou

Hôpitaux Universitaires Paris Ile-de-France Ouest
Site RAYMOND POINCARÉ

INDUSTRIAL PARTNERS

Air Liquide
creative oxygen

LIPOGEMS
Your cells for your health

ucb Pharma

OUR ORGANISATION

MULTI-DISCIPLINARY

RESEARCH UNITS

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NEURO-SEPSIS TASK FORCE

ADAPTABILITY

INTERNATIONAL

INDUSTRIAL PARTNERS

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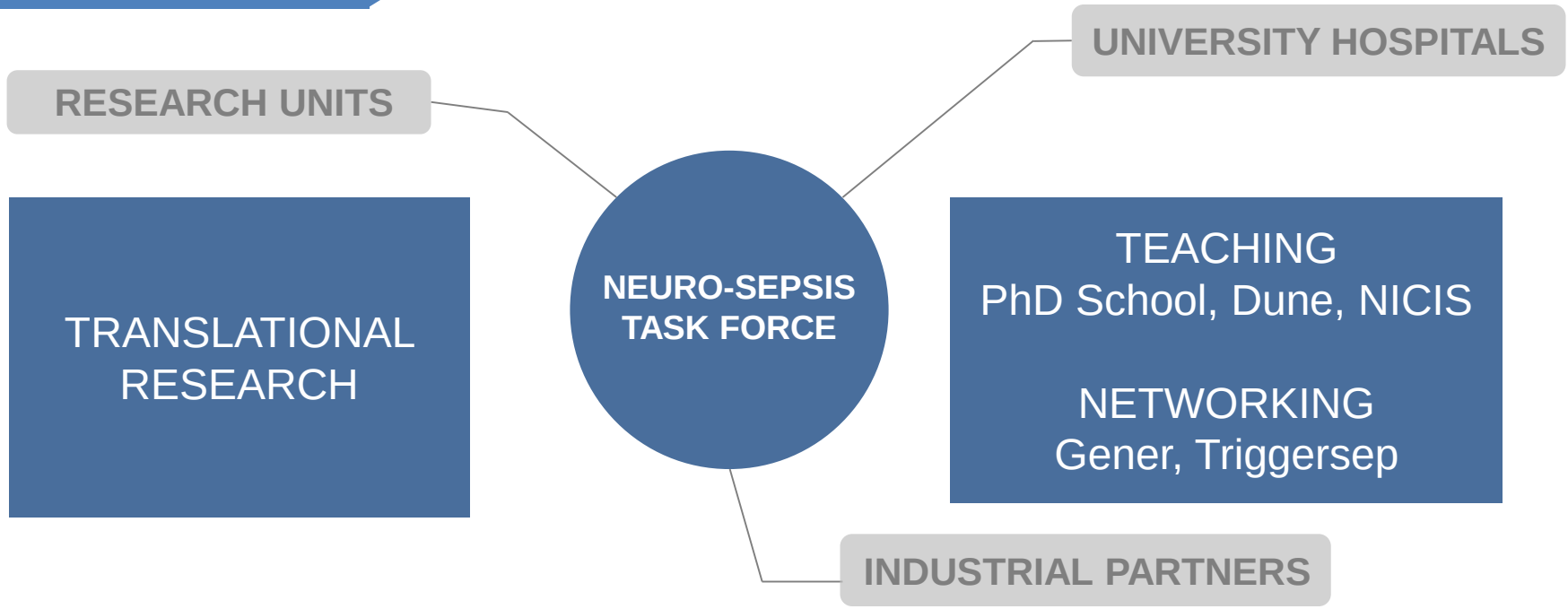
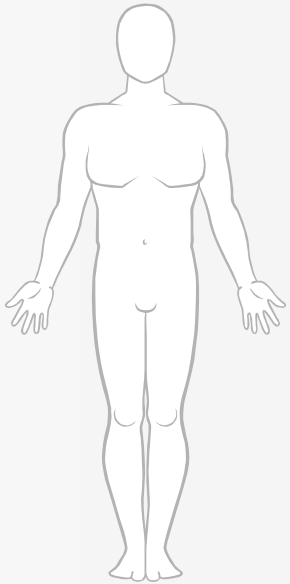
OUR ORGANISATION



A CLINICAL STORY



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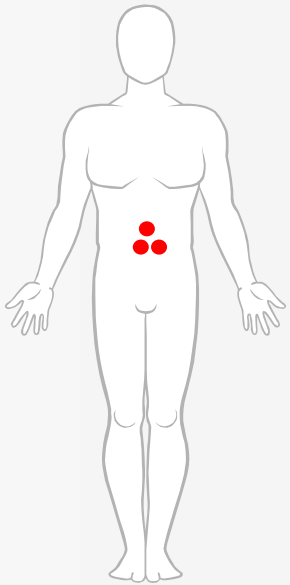


Man, 47, living in Paris, taxi driver

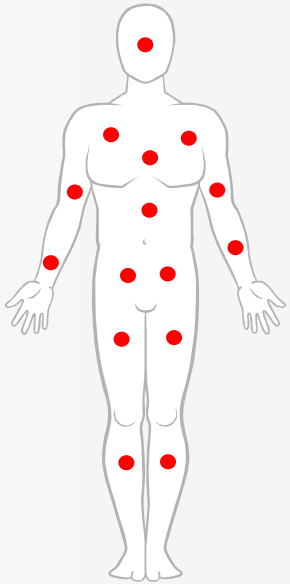
Abdominal infection

A PATHOLOGY STORY

EPIDEMIOLOGY

INITIAL INFECTION

A CLINICAL STORY



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Increasing deterioration

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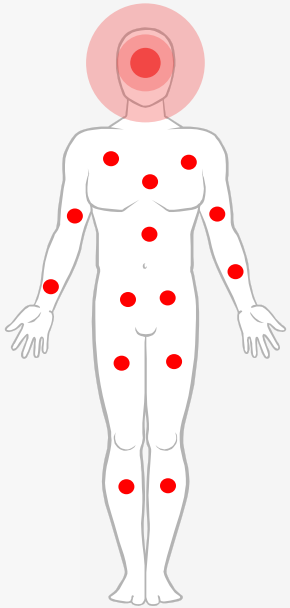
EPIDEMIOLOGY

INITIAL INFECTION

GENERALISATION
Systemic inflammation
SEPSIS

A CLINICAL STORY



Man, 47, living in Paris, taxi driver

Abdominal infection

Increasing deterioration

Hospitalization: Intensive care unit

A PATHOLOGY STORY

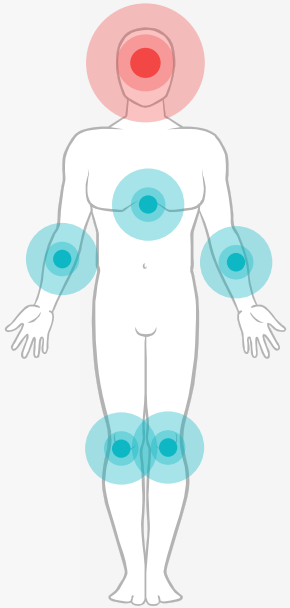
EPIDEMIOLOGY

INITIAL INFECTION

GENERALISATION
Systemic inflammation
SEPSIS

SEPSIS: Acute phase
Cell targets
Acute treatment

A CLINICAL STORY



Man, 47, living in Paris, taxi driver

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Increasing deterioration

Hospitalization: Intensive care unit

Convalescence
- Psychiatric
- Cognitive alterations
- Amyotrophy

A PATHOLOGY STORY

EPIDEMIOLOGY

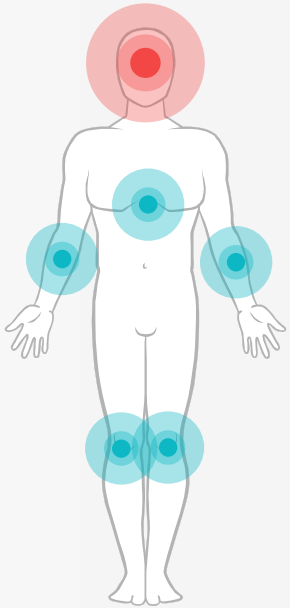
INITIAL INFECTION

GENERALISATION
Systemic inflammation
- SEPSIS

SEPSIS: Acute phase
- Cell targets
- Acute treatment

LONG-CONSEQUENCES
Degradation of tissues

A CLINICAL STORY



Man, 47, living in Paris, taxi driver

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Increasing deterioration

Hospitalization: Intensive care unit

Convalescence
- Psychiatric
- Cognitive alterations
- Amyotrophy

Various disabilities

A PATHOLOGY STORY

EPIDEMIOLOGY

INITIAL INFECTION

GENERALISATION
Systemic inflammation
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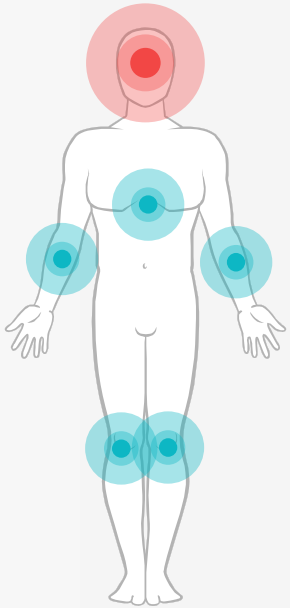
SEPSIS: Acute phase
- Cell targets
- Acute treatment

LONG-CONSEQUENCES
Degradation of tissues

SEQUELS

A CLINICAL STORY



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Convalescence

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Various disabilities

A PATHOLOGY STORY

EPIDEMIOLOGY

INITIAL INFECTION

GENERALISATION
Systemic inflammation
SEPSIS

HISTO UNIT

SEPSIS: Acute phase & Sequels

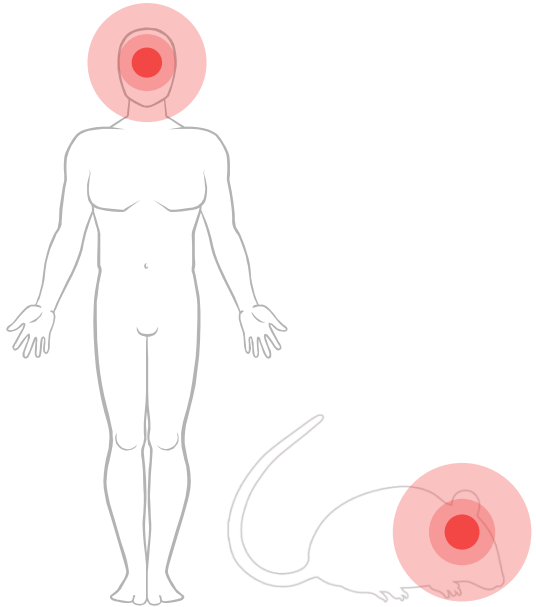
Clinical investigation

Physiopathology
- **. Cellular level**
- **. Cell interactions**
- **. Network / Function**

New treatments

RESULTS / PERSPECTIVES

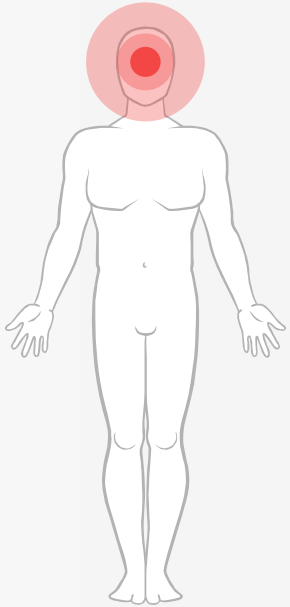
Brain & Sepsis



Sepsis induces brain dysfunction and sequels

Neuro-clinical investigation

T. Sharshar & J. Mantz



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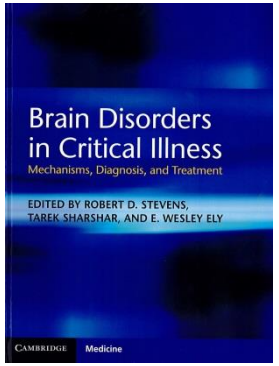
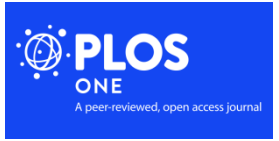
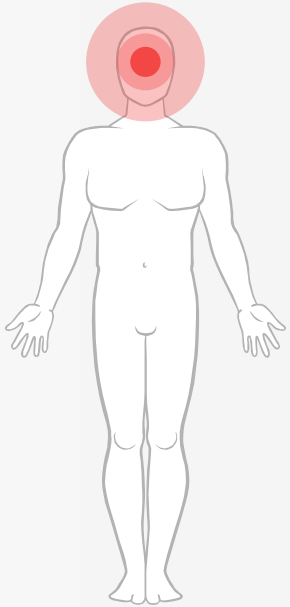
- Ponto-mesencephalic dysconduction (EP) is predictible of delirium
- EEG abnormalities are early predictible factors of death
- Brain stem dysfunction is an independant factor of gravity





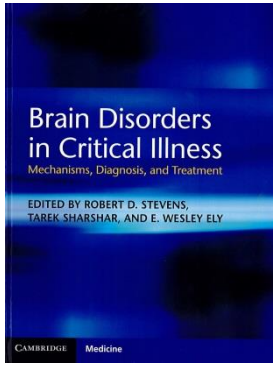
Azabou et al. In press
Azabou et al. 2015
Rohaut et al. In press

Sepsis induces brain dysfunction and sequels



Neuro-clinical investigation

T. Sharshar, F. Bozza & J. Mantz



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What are precisely the sequels?

- Cognitive and psychiatric disorders

Innate immunity involvement in depression

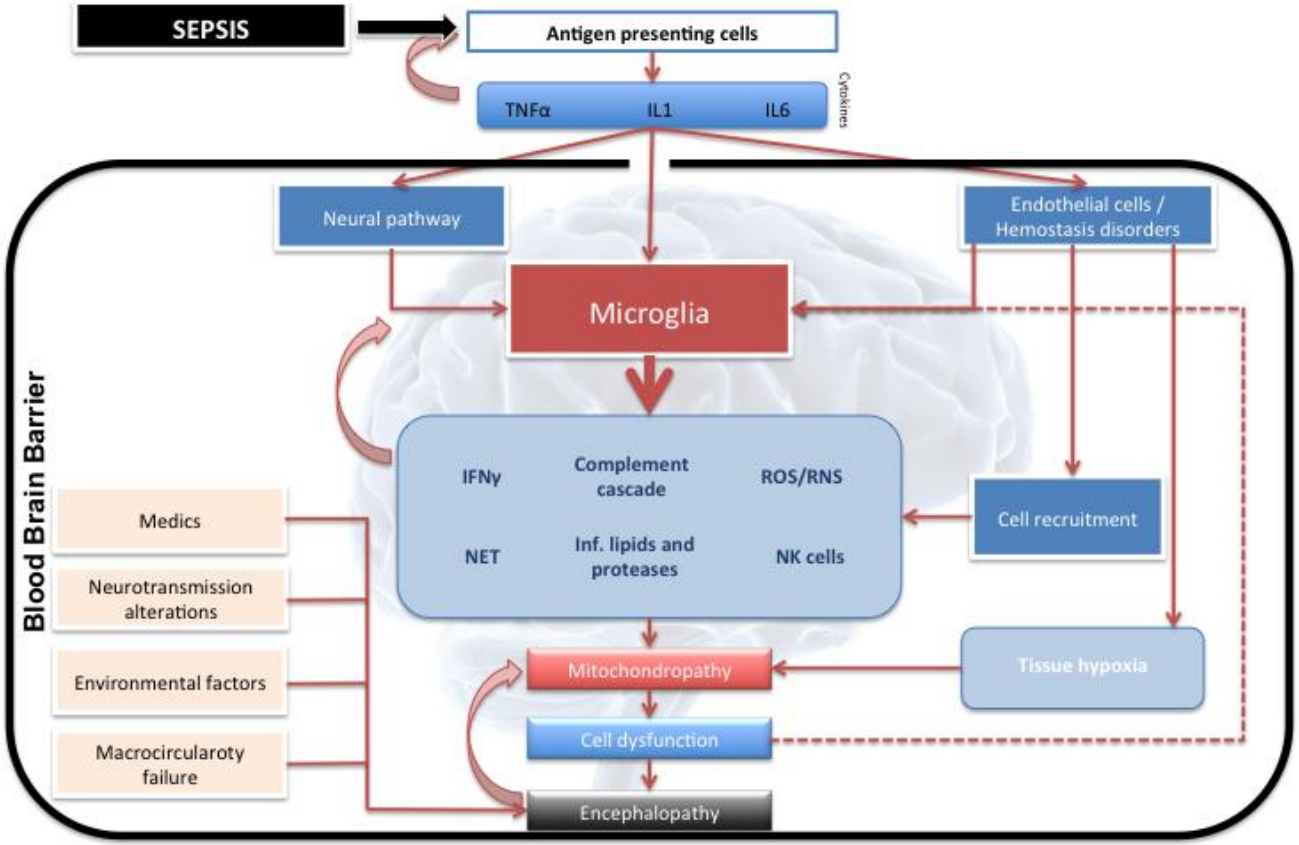
R. Gaillard

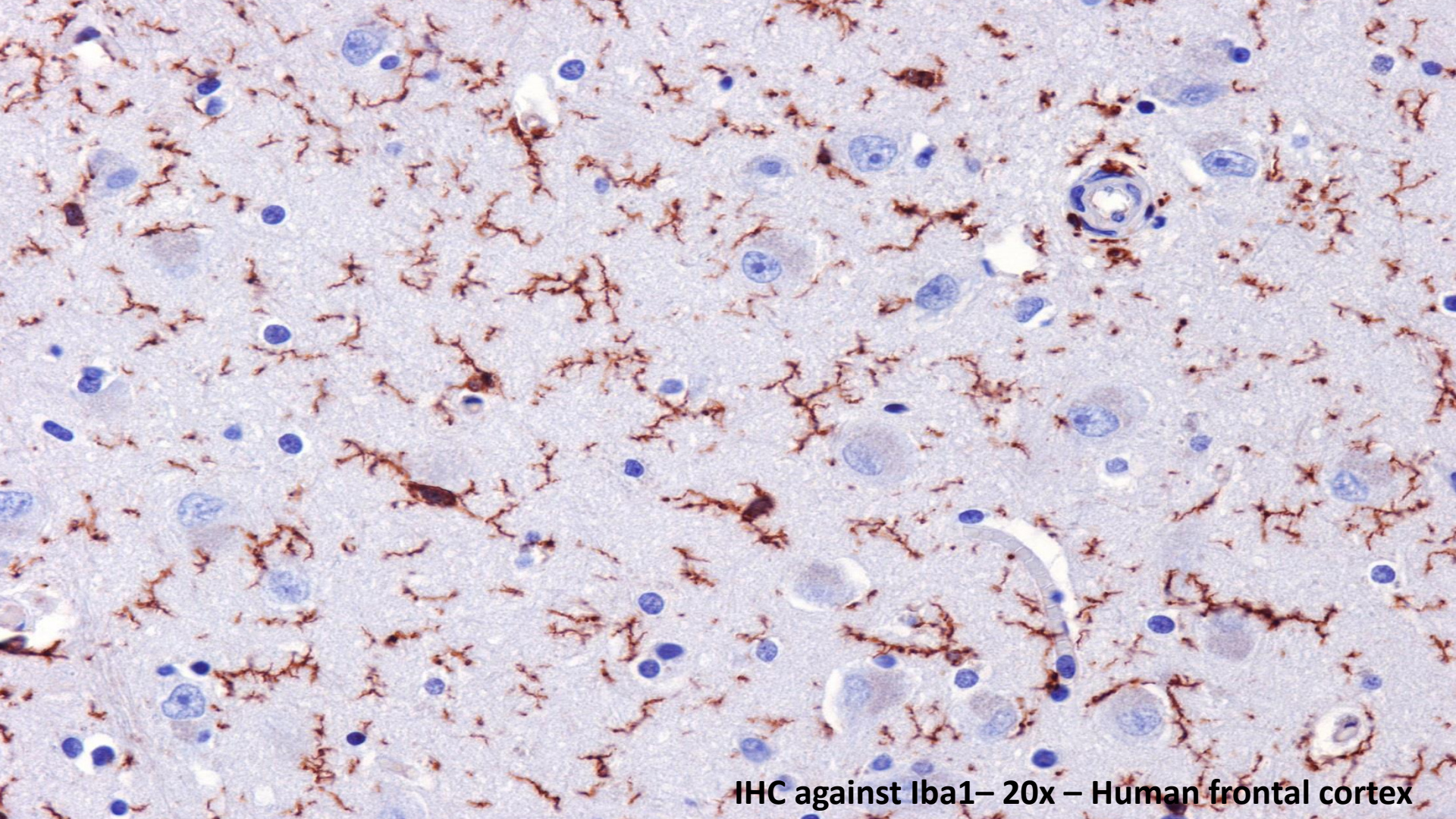
CLINICAL STUDY	ProReTro study	120/400
	Brasilian SAE BRICNet study	110/310
	Pan ICU study	400/400
	SuiviRea Trial	494/520

Azabou et al. In press
Azabou et al. 2015
Rohaut et al. In press
Georgin-Lavialle et al. 2016

The Pathophysiology

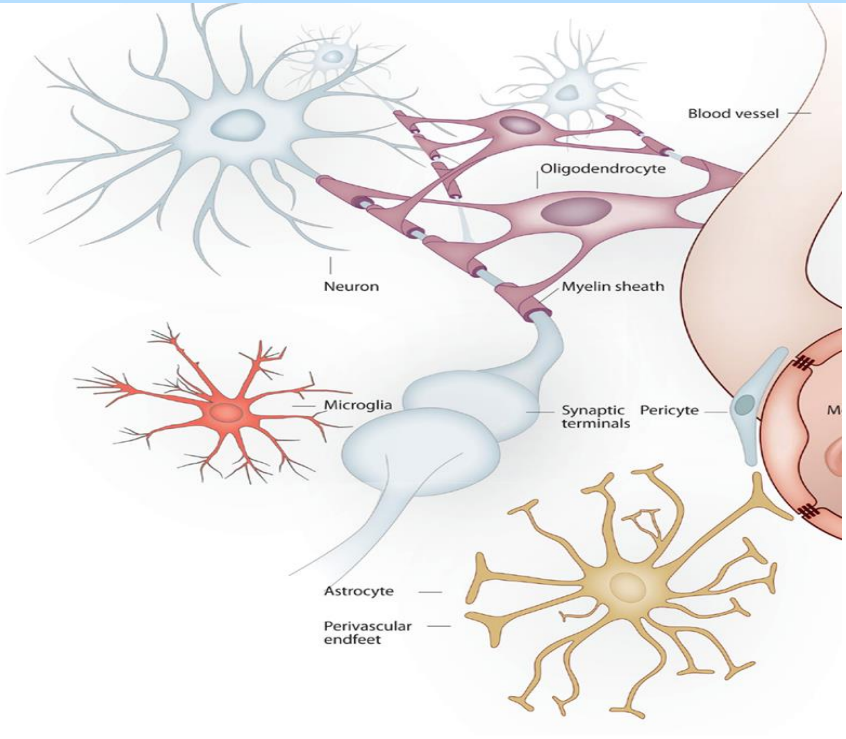
HYPOTHESIS




IHC against Iba1– 20x – Human frontal cortex

Microglia: an amasing keeper of the brain

Healthy brain



Microglia: an amasing keeper of the brain

Healthy brain

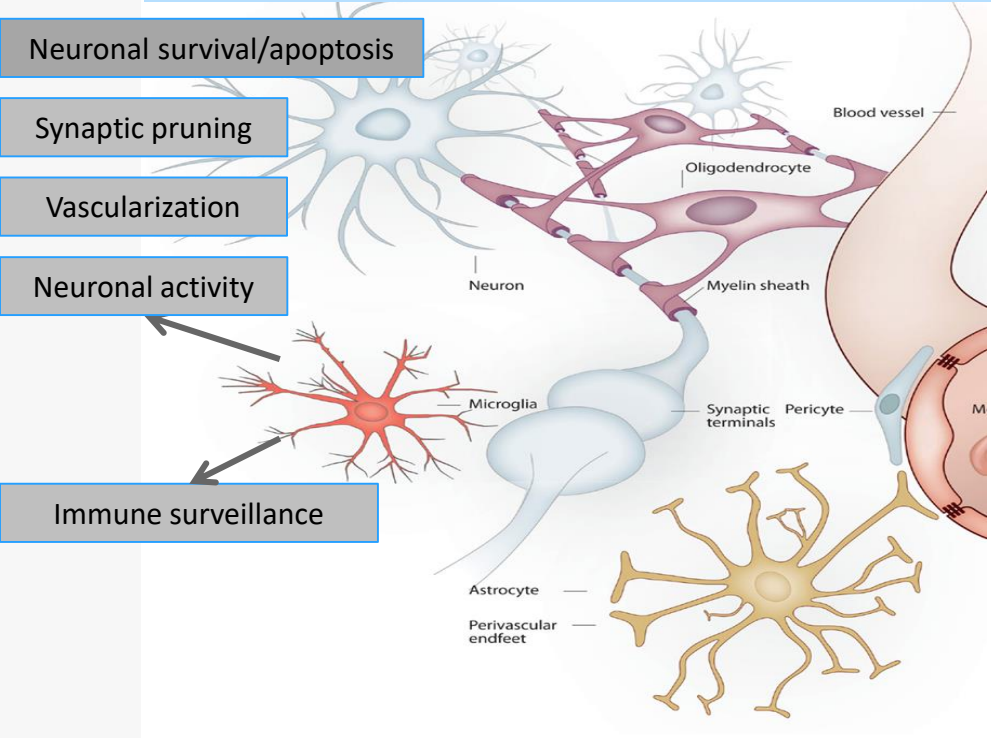
Neuronal survival/apoptosis

Synaptic pruning

Vascularization

Neuronal activity

Immune surveillance



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Damaged brain

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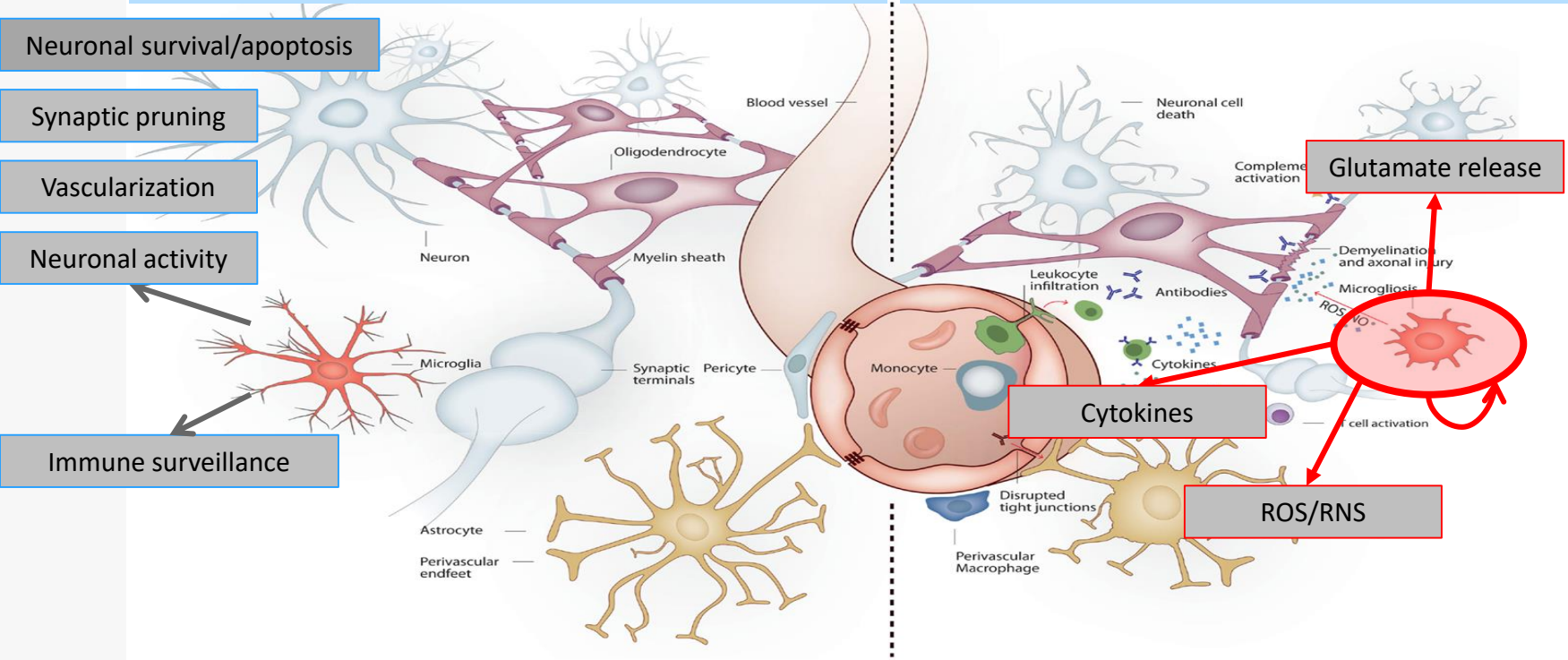


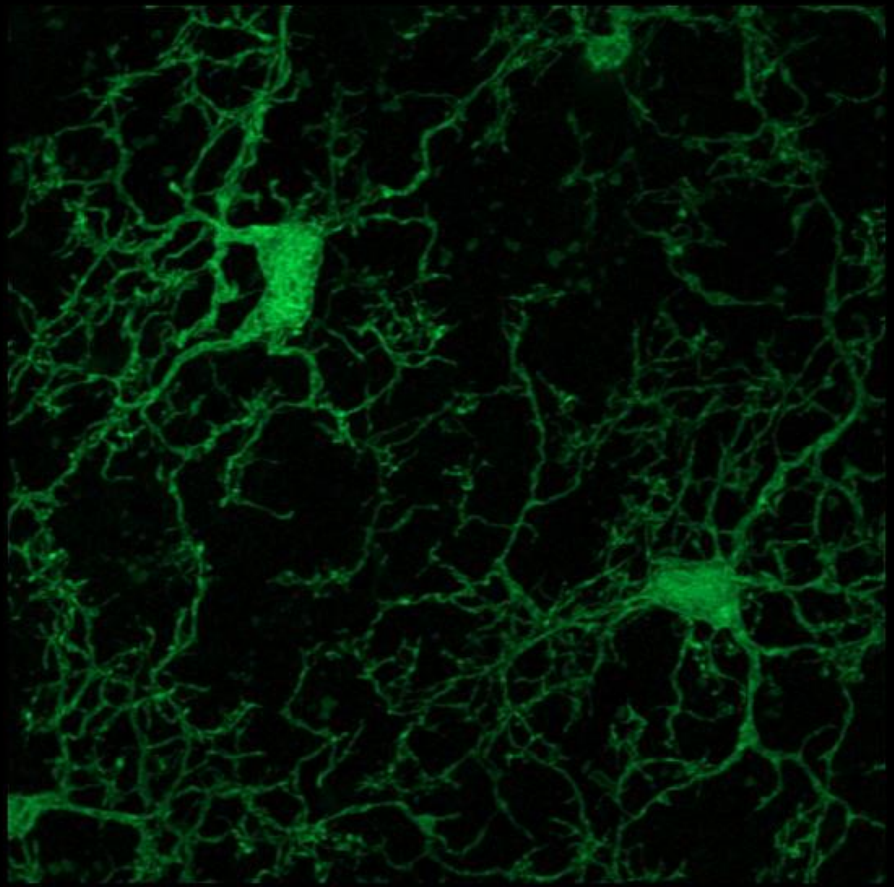
Glutamate release

Cytokines

ROS/RNS

An appropriate animal model

An appropriate animal model

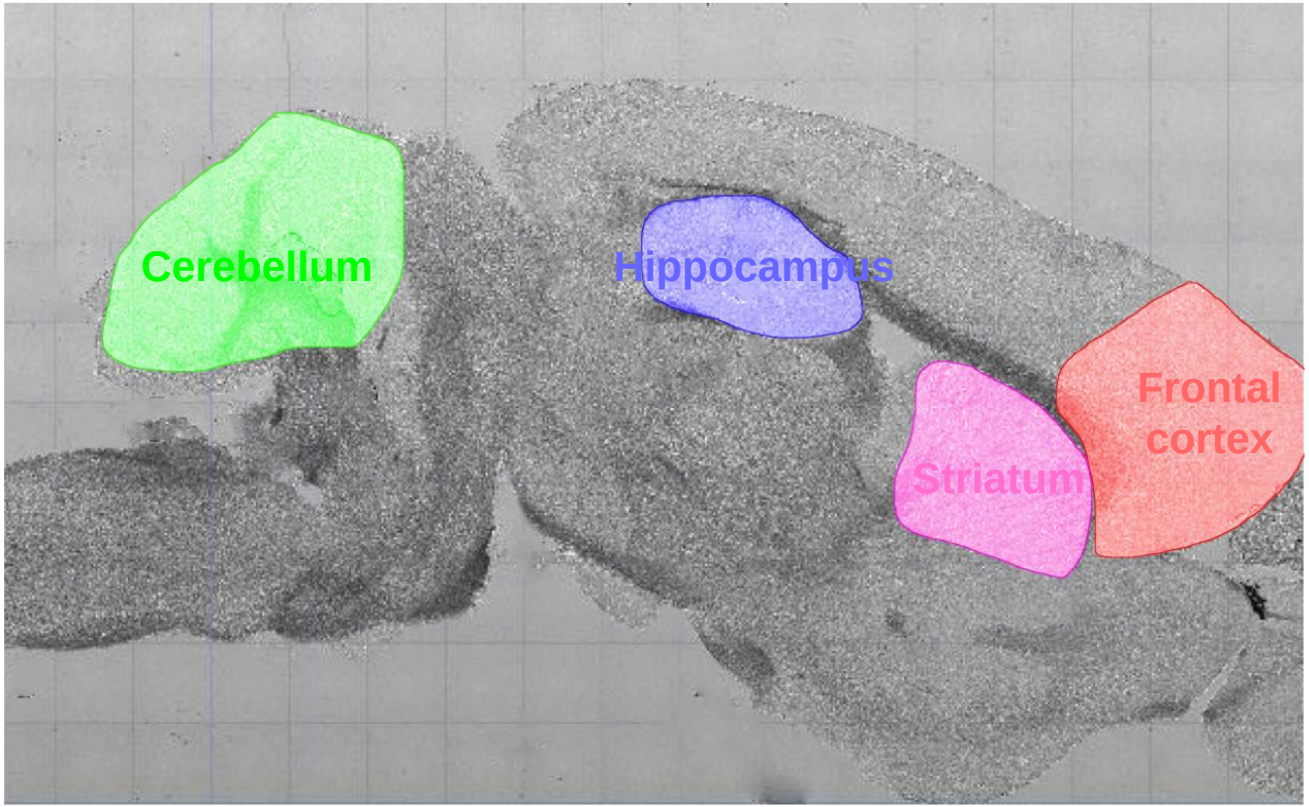


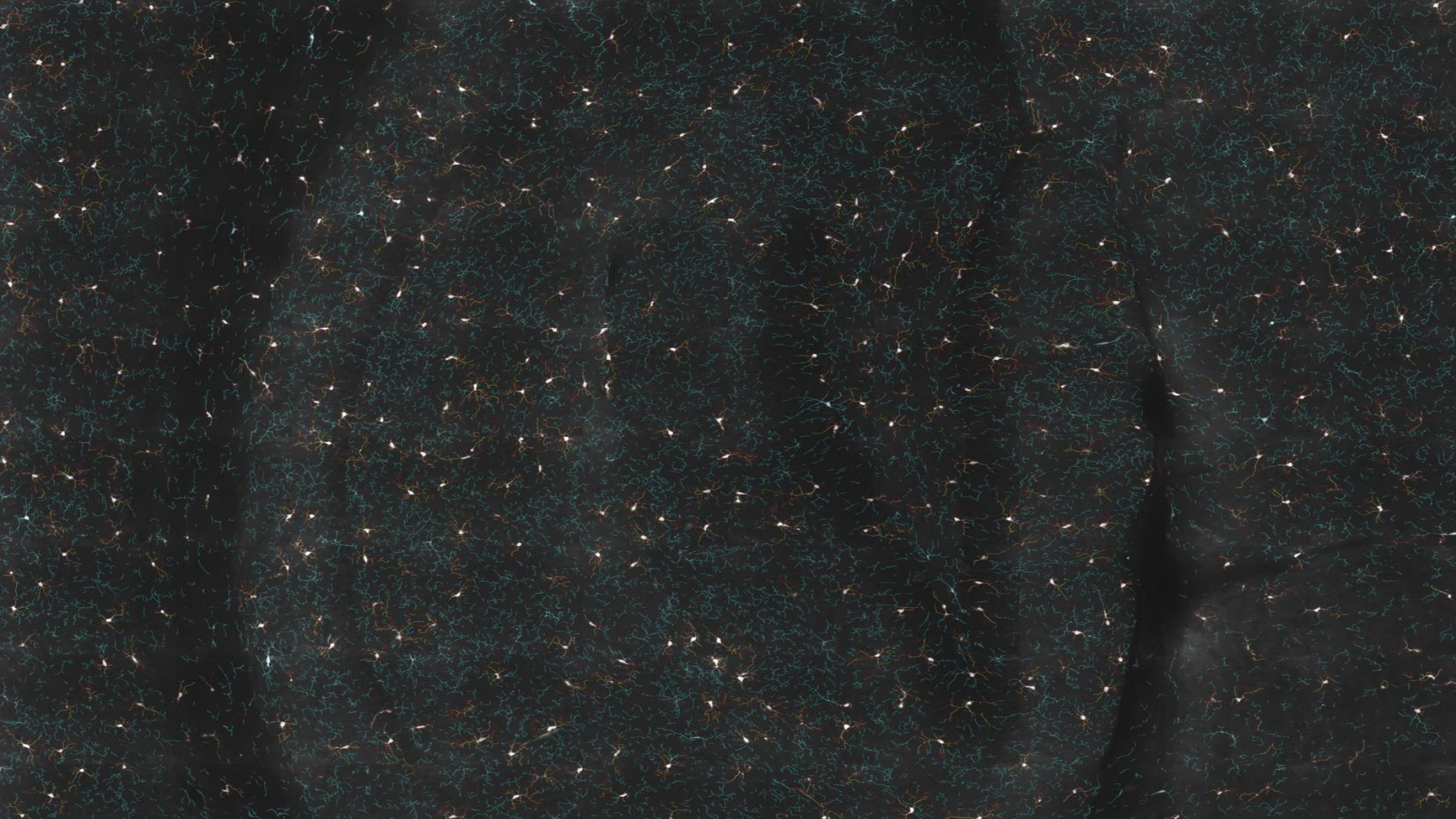
An automated imaging system

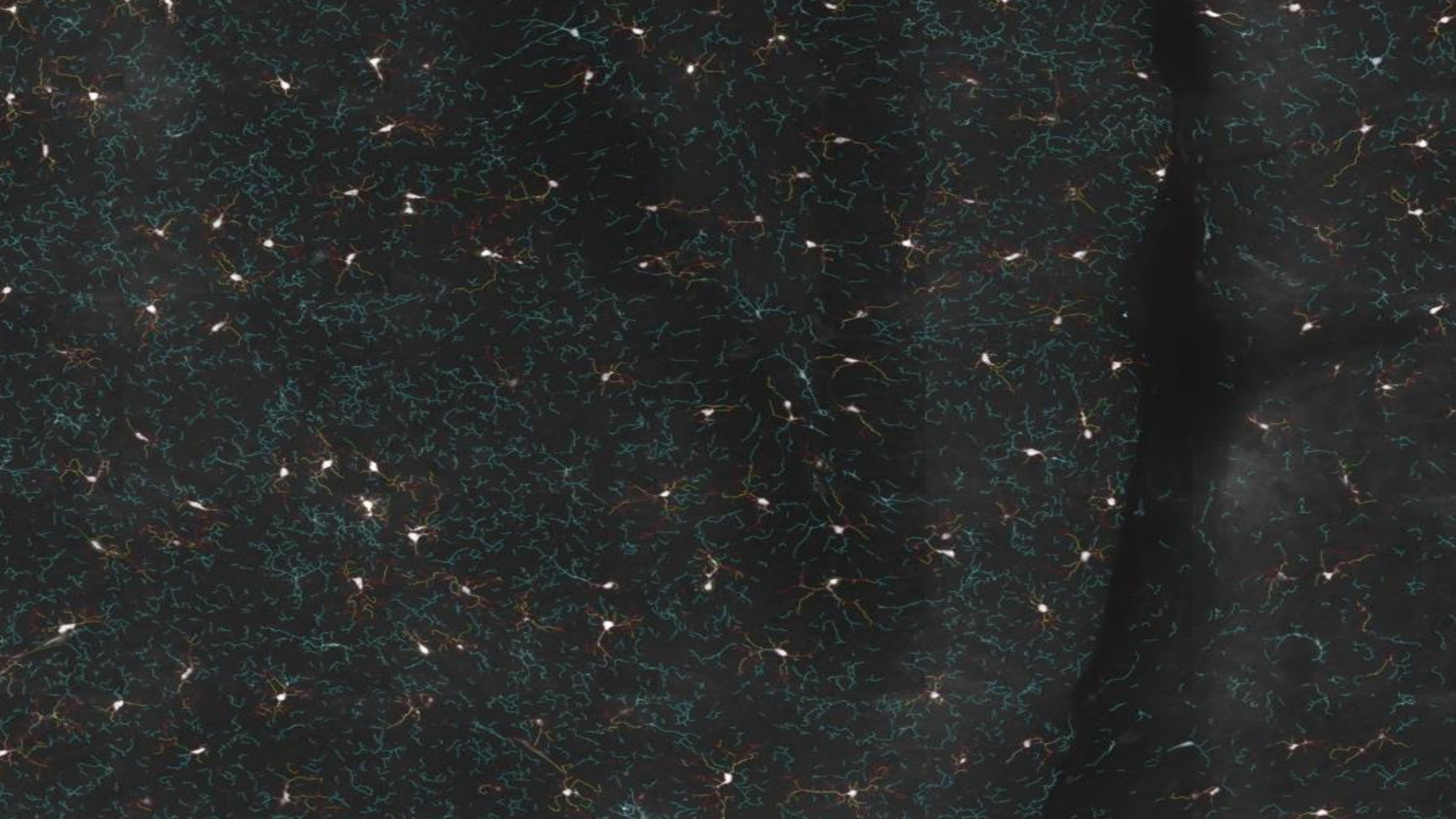
In collaboration with the Imagopole,
Dr **Anne Danckaert**, Institut Pasteur.

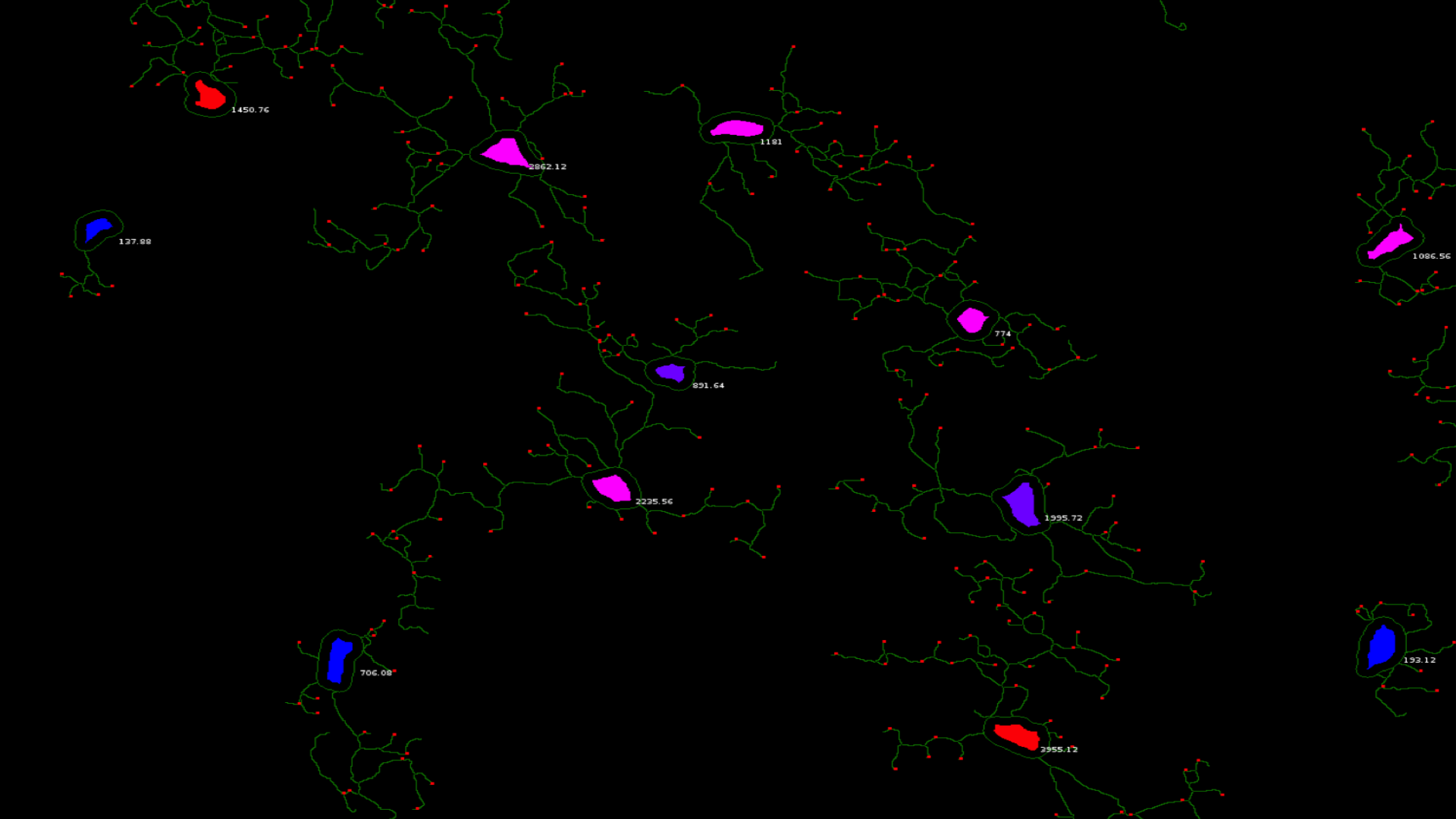
Cell Voyager - CV1000 – Yokogawa , 10x, BF

An automated imaging system








1450.76
2862.12
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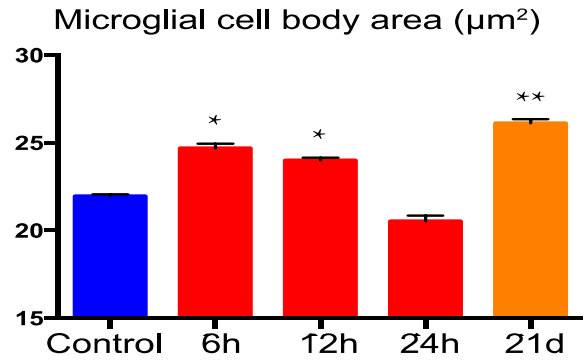
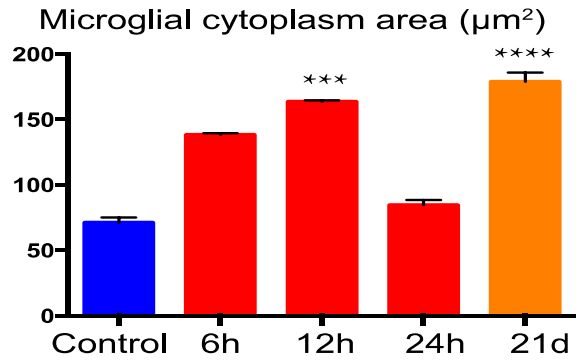
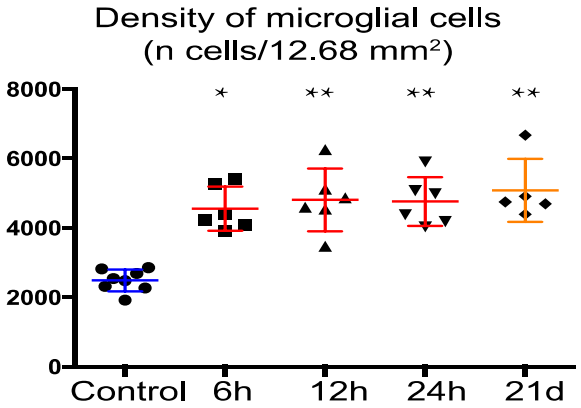
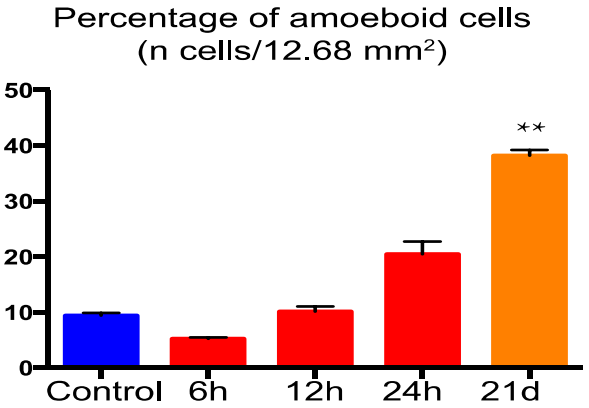
774
891.64
2235.56
1995.72
706.08
193.12
3955.12

Sepsis induces very early microglial activation

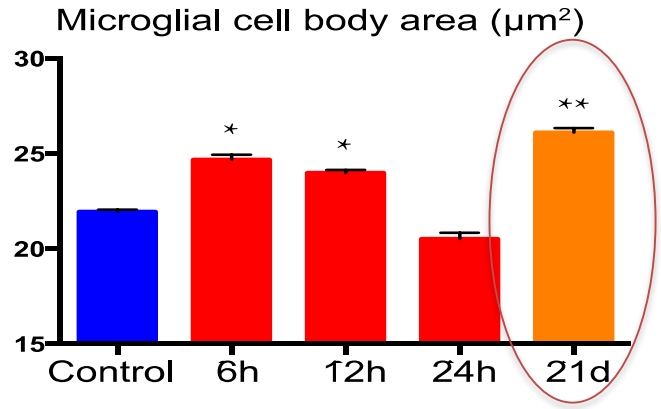


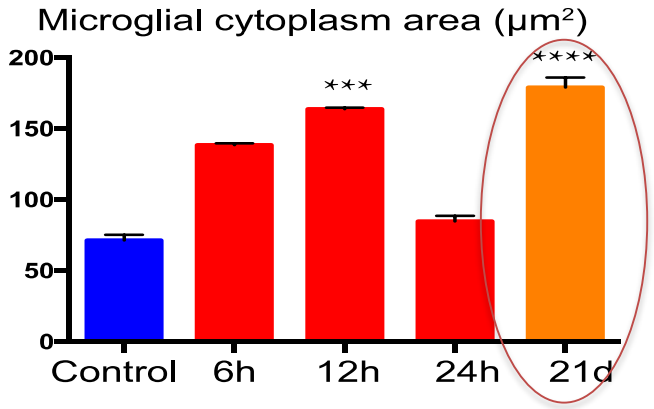


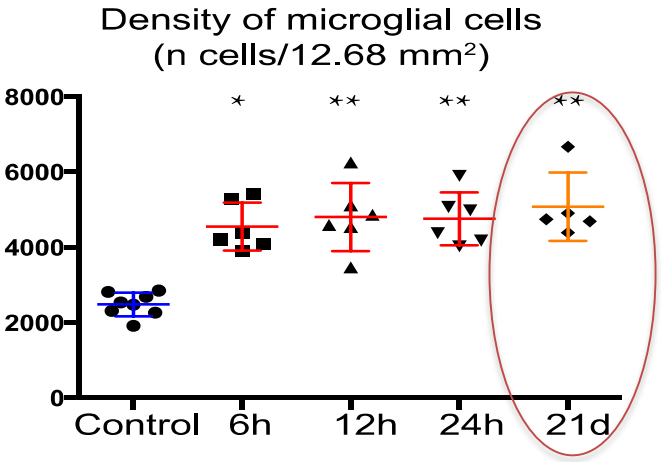


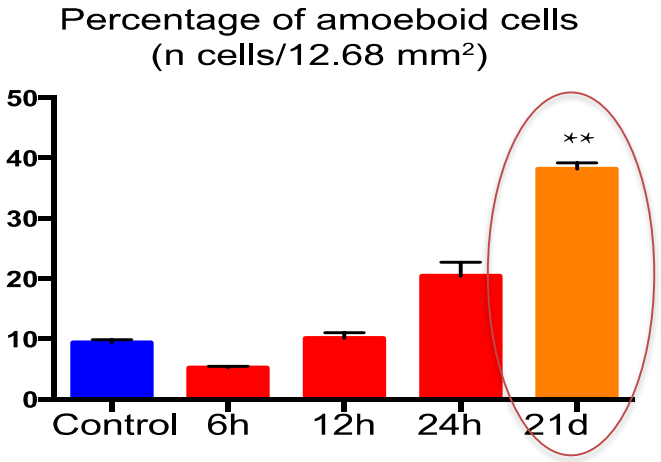


Sepsis induces sequels in microglial cells









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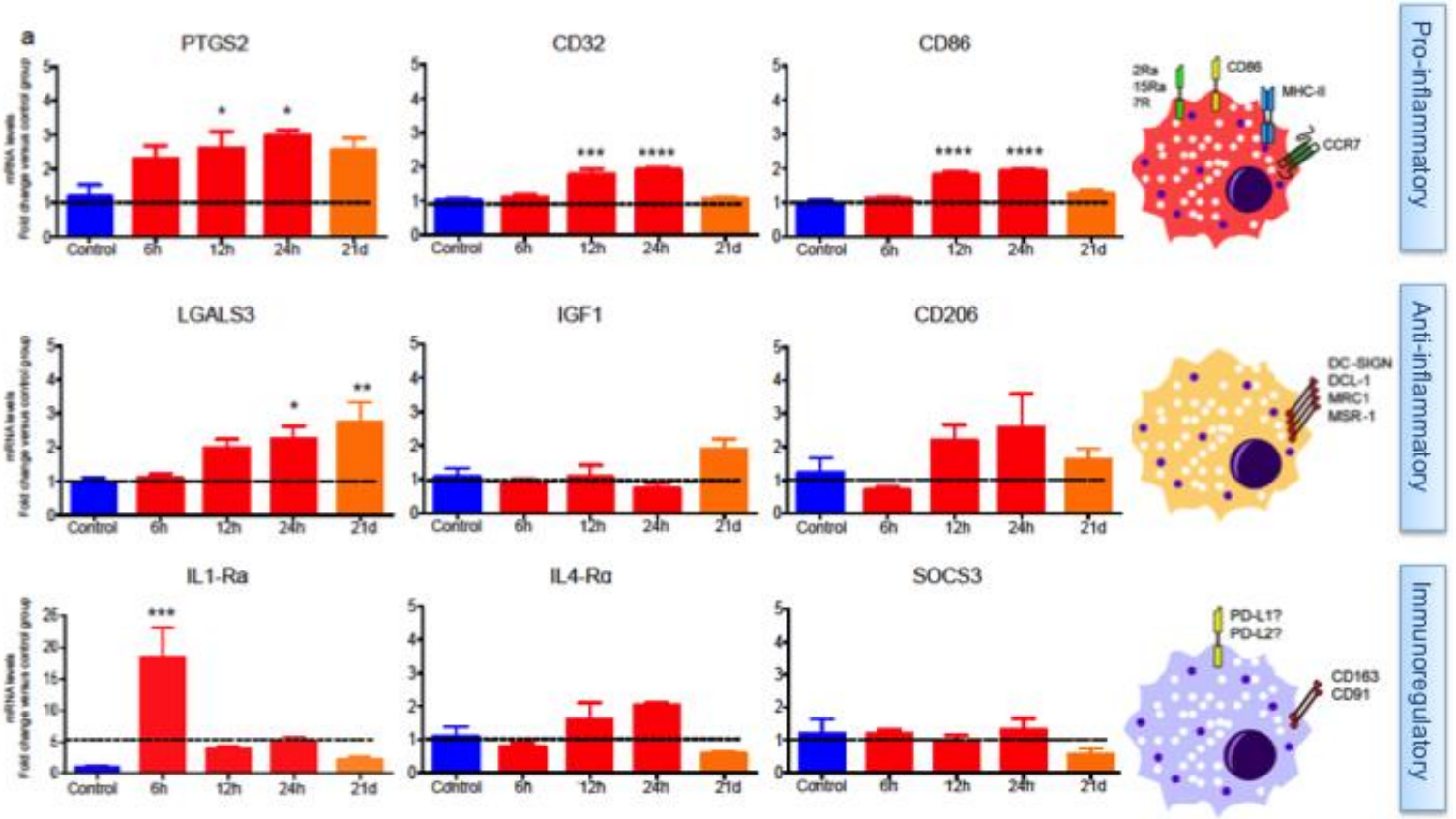
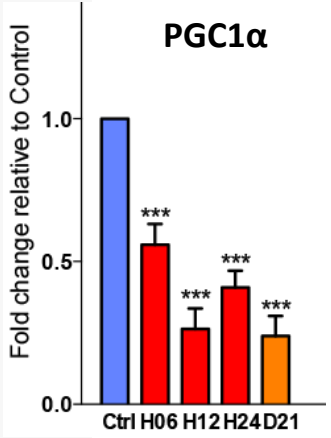
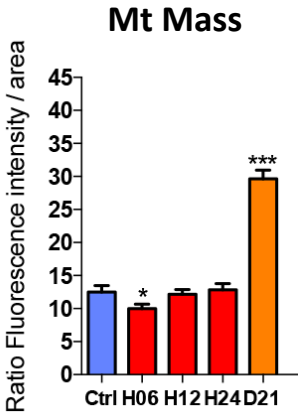
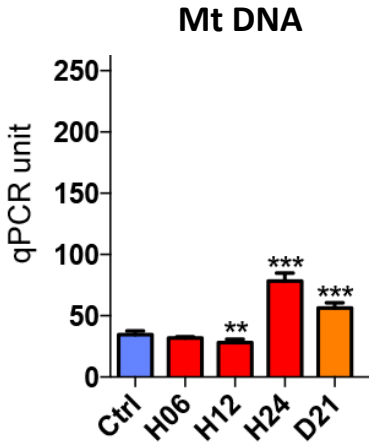


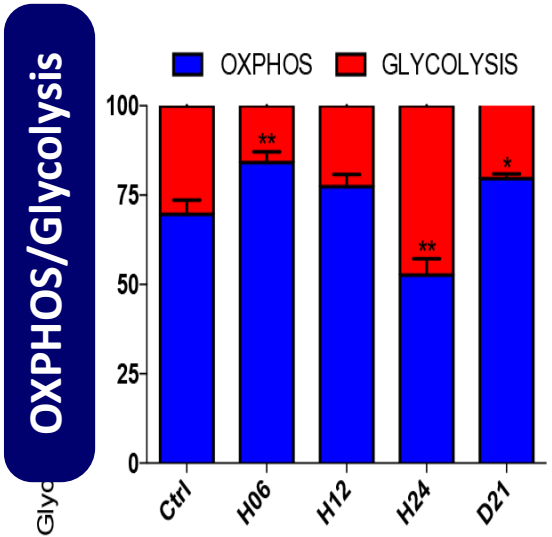
Sepsis induces durable mitochondrial dysfunction

Mitochondrial biogenesis, mass and content









Correlated with severe anxiety and cognitive decline in mice

Microglia and primary neuro-inflammation

Institut Pasteur

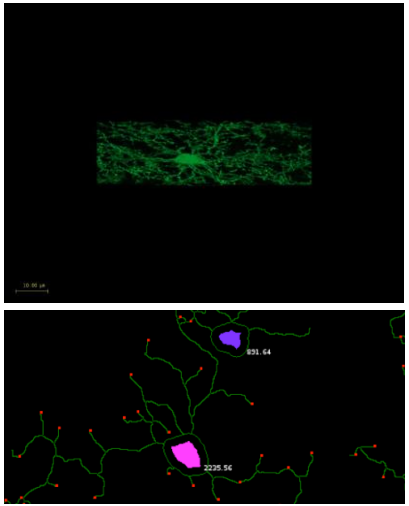
Anne Danckaert
Imagopôle

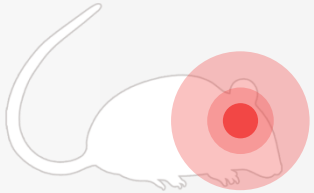
Laurent Chatre
Stem Cells & Development

F. Verdonk & F. Chrétien

Cellular Level

- New software for 3D cell imaging
- Microglial cells
  - Early activation and scar
  - Source of cytokines (No BBB permeability)
- Mitochondrial dysfunction





Mouse model of sepsis

- CLP
- CX3CR1 $^{GFP/+}$ mice

Verdonk et al. 2016

Microglia and primary neuro-inflammation

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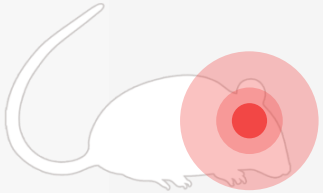
Stem Cells & Development

Pierre-Marie Lledo
Perception et Mémoire



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F. Verdonk & F. Chrétien

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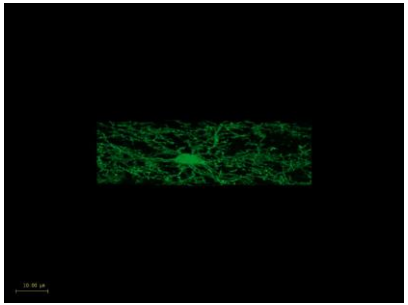
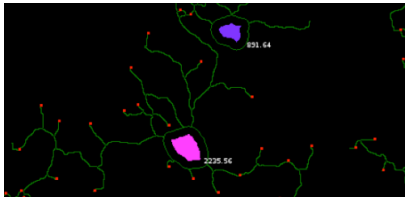
  - Source of cytokines (No BBB permeability)
- Mitochondrial dysfunction

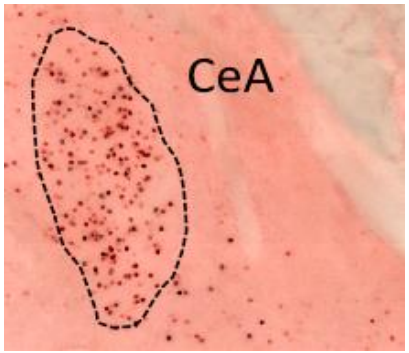




Inter-cellular Level

A. Mazeraud & T. Sharshar

- Central amygdala nuclei is activated
- Sepsis induces a PTSD-like phenotype
- Pharmacogenetic / Pharmacological silencing

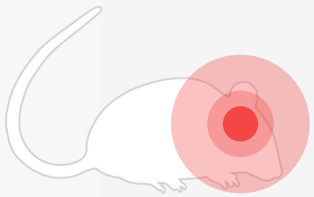


Functional Level

- Interconnectivity between brain areas and networks

Verdonk et al. 2016
Mazeraud et al. In Prep.

Microglia modulation



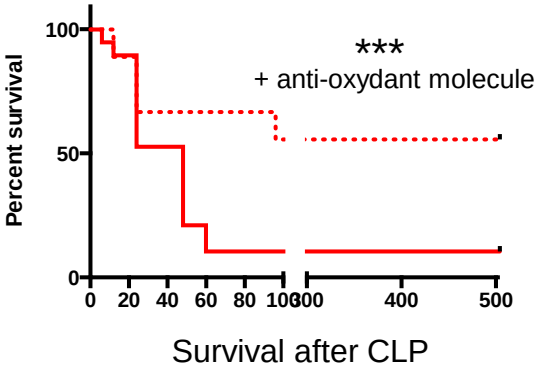
Mouse model of sepsis
- CLP
- CX3CR1 $^{GFP/+}$ mice

- MnTBAP → ~~Oxidative stress~~
- Ketamine → ~~Depression~~
- Levetiracetam → ~~PTSD~~
- Statins → ~~Cognitive impairments~~

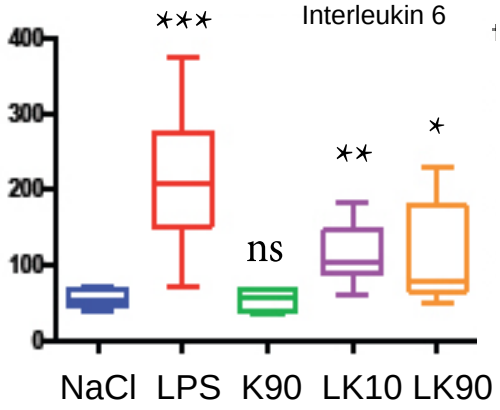
CLINICAL STUDY TRIAL POCK 1/880

F. Verdonk & R. Gaillard

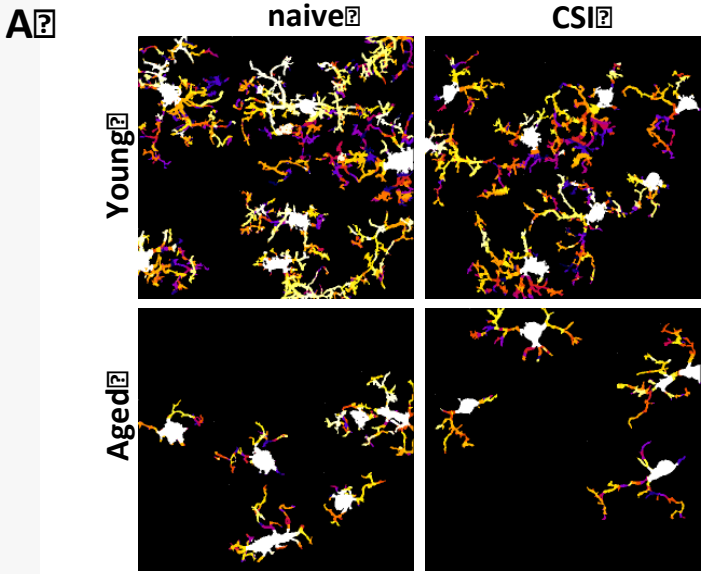
MnTBAP

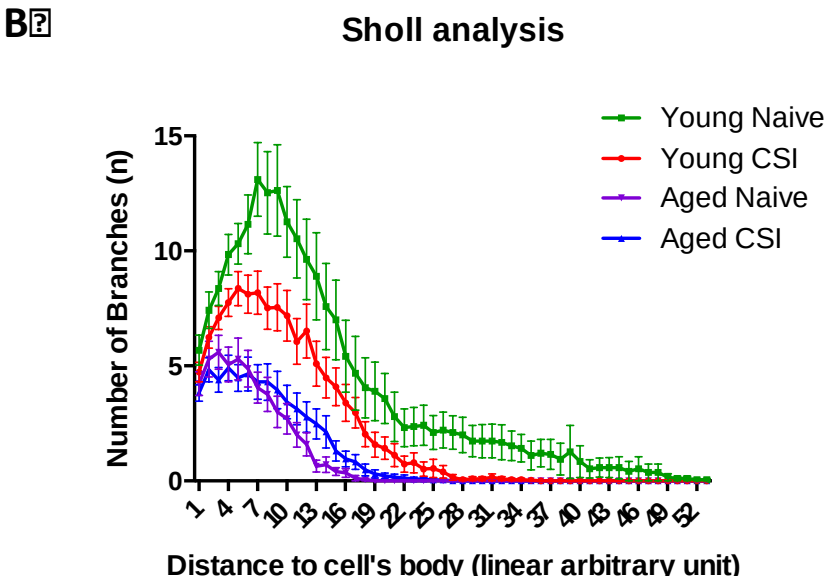


Ketamine



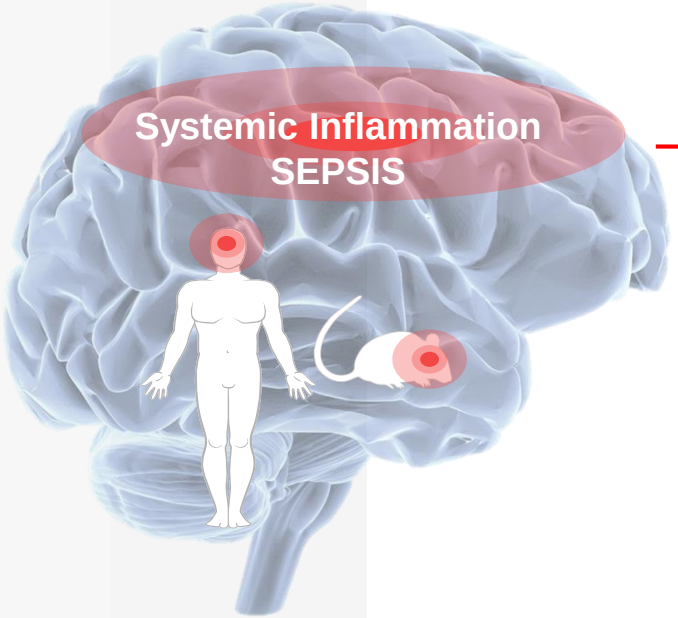
And in aged mice?





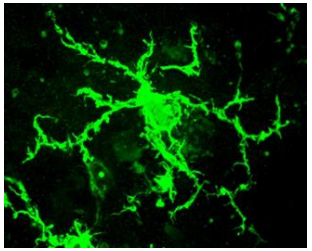
J. D'Avila & F. Bozza - FioCruz

Sepsis impact on Central Nervous System



NEUROINFLAMMATION

Long-term clinical alteration
Neuro-anatomical sequels
Psychological sequels



Microglia

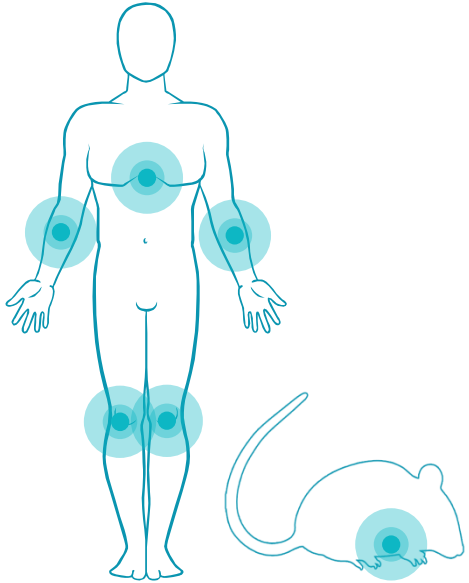
Early activation
Specific localisations
The problem of priming

Mechanisms
Mitochondria alterations
Immunologic alterations
Brain connections

Modulation/Prevention/Treatments

RESULTS / PERSPECTIVES

Muscle & Sepsis



Muscle regeneration, stem cells and sepsis

LESION

Normal context: *Ad integrum* regeneration

Pathology context: Regeneration atypia

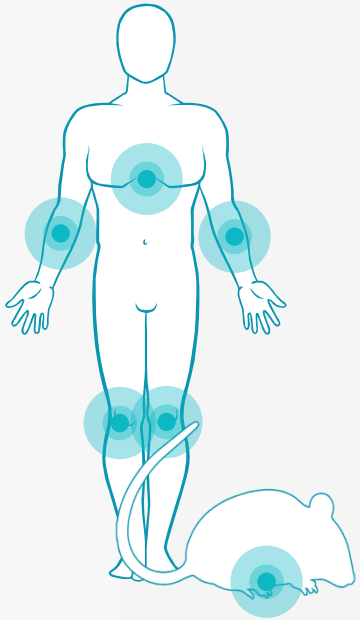
Alteration of stem cells
Alteration of environment
Alteration of cell partners

MSC

Mechanisms
Mitochondria
Role of immune system
MSC

Modulation / Prevention / Treatments

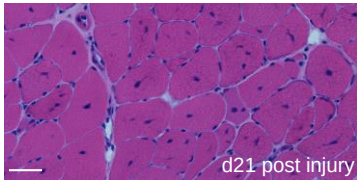
Sepsis and muscle pathology

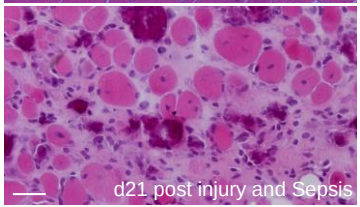


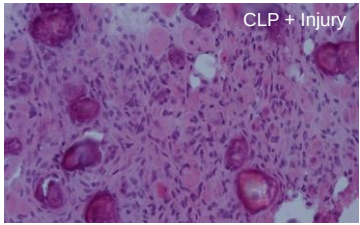
Mouse models
- Pax7-nGFP
- Flk1$^{GFP/+}$

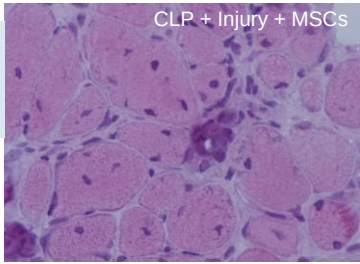
P. Rocheteau & F. Chrétien

- **Alteration of muscle regeneration**
- **SC are intrinsically impaired**
- **MSC injection leads to better regeneration**
  - Fibrosis/Cytokine regulation
  - Mitochondrial parameters
  - Muscle force









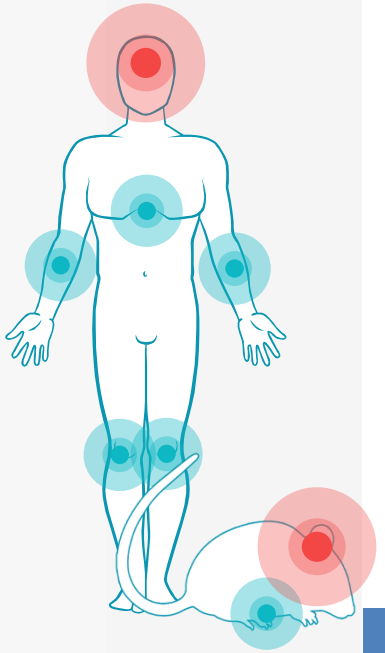
CLINICAL STUDY DISCUSS 24/96 *P. Rocheteau & A. Bouglé*
PHRC Trial *T. Lescot*

Rocheteau et al. 2016

nature COMMUNICATIONS

And the peripheral nervous system?

The neurological impairment during sepsis



- Early
- Durable
- Very severe

- An independent factor of mortality, sequels, neurological disorders
- Neuroinflammation is a key element in the pathophysiology

- Muscle and brain are concomitantly affected
- Mitochondria are a main target with severe sequels accumulated

- Even after recovery sequels in cells is the substratum of disabilities

. The need to combined both pathophysiological and clinical research

. To propose new innovative treatments

Fabrice Chrétien

Laurence Fiette

Grégory Jouvion

David Briand

Magali Tichit

Sabine Maurin

Adrien Bouglé

Wagih Ben Hassen

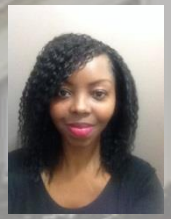
Lorna Guéniot

Tarek Sharshar

Raphaël Gaillard

Pierre Rocheteau

Patricia Flamant



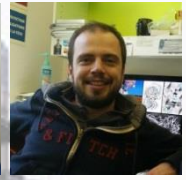
Ines Moyokolo

Pierre Goossens

Richard Lo-Man

Jean Mantz

Franck Verdonk



Aurélien Mazeraud

Cyril Gittiaux

Olivier Langeron

Thomas Lescot

Dania Zhivaki

Nassima Messal

Cédric Thépenier

Baptiste Duceau, Sergio Sanchez, Oumaima Stambouli, Cyril Longé, Mylène Fefeu, Emmanuel Pardo, Myriam Akbal, Victoria Lepère, Lucile Boccara, Margot Delabarre

THANK YOU !

Institut Pasteur