LEAPS MEETS LIFE SCIENCE CONFERENCE

Multilevel X-Ray Imaging Approach to Assess the Sequential Evolution of Multi-Organ Damage in Neurodegenerative Diseases

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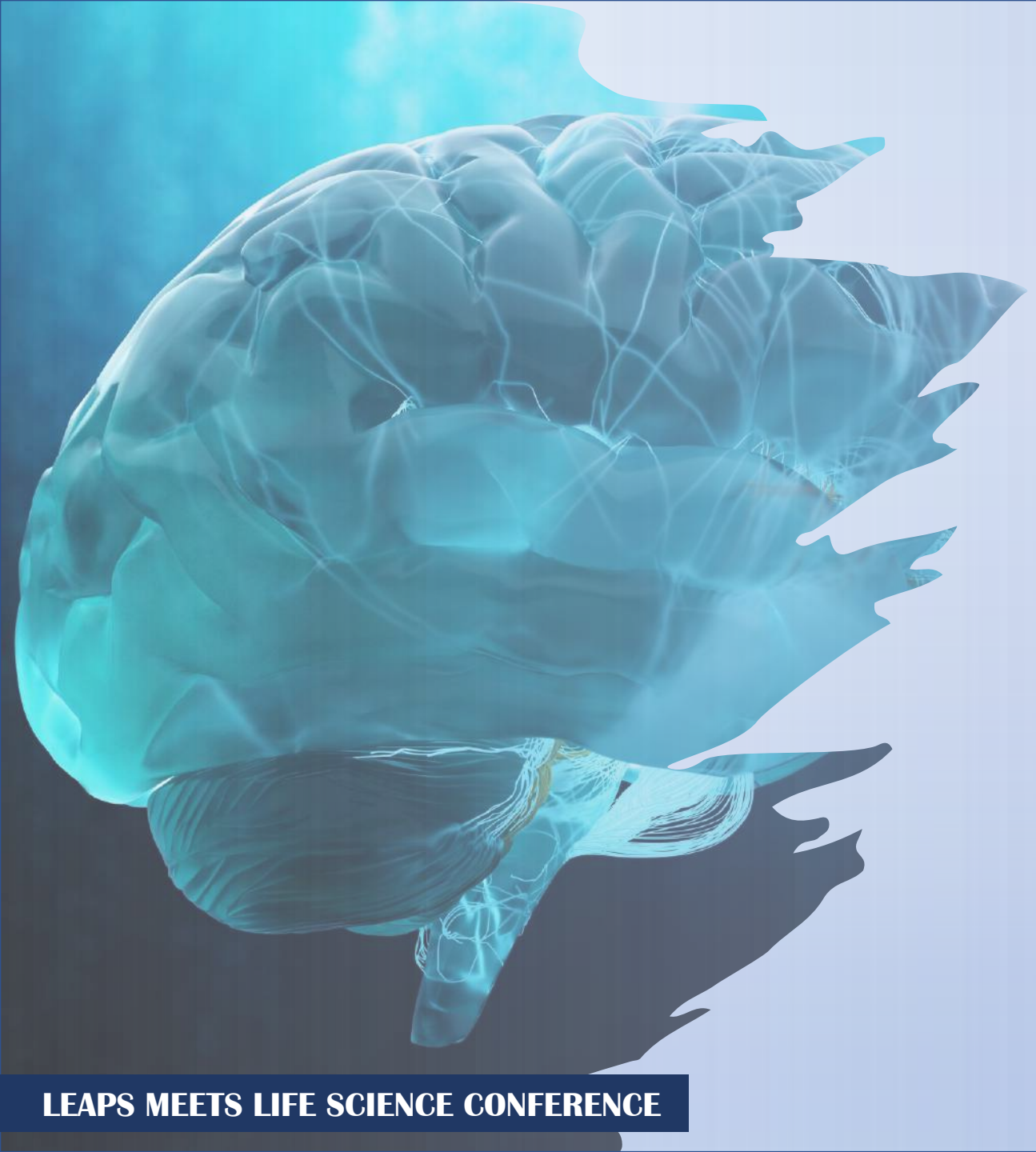
Elba Island, Italy

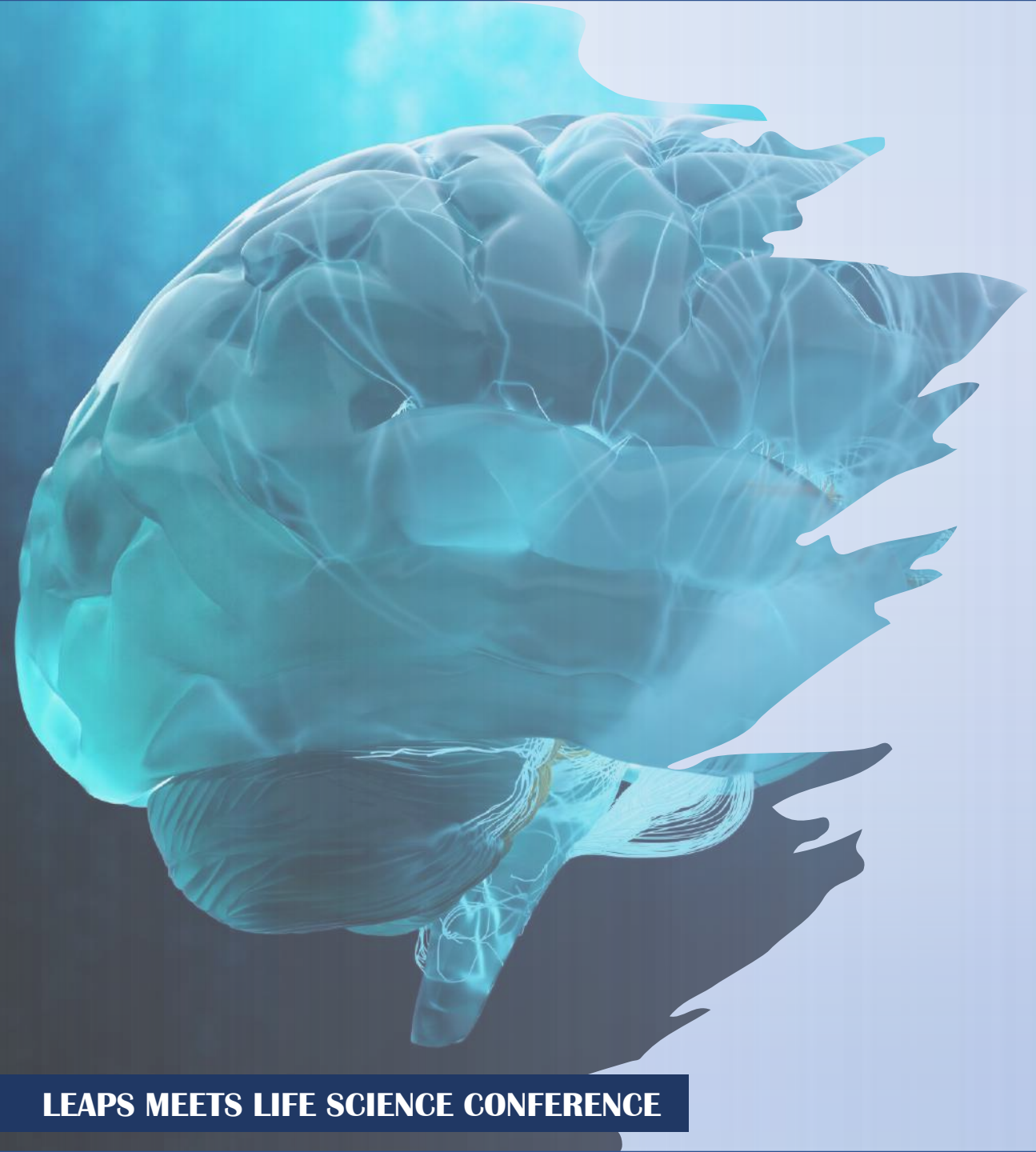


WHY MULTI-ORGAN INVESTIGATION?

TO DETECT THE DEGENERATION

1. SPATIAL PROGRESSION

2. EARLY BIO-MARKERS



A large and expending body of evidence indicates that the **gut-brain axis** likely plays a crucial role in neurological diseases

- bi-directional network of signal pathways between the nervous system and the gastrointestinal tract
- link between the external environment and the central nervous system

There are several mechanisms through which the gut may "talk" with the brain

1) ENTERIC NERVOUS SYSTEM: retrograde transportation of metabolites, small protein and molecules

2) Cross talk with the IMMUNE SYSTEM

3) SENSING MICROBIAL METABOLITES

1. ***GUT-BRAIN AXIS***
2. ANIMAL MODELS
3. XPCT
4. MULTIPLE SCLEROSIS
5. ALZHEIMER'S DISEASE

A pro-inflammatory intestinal environment and leaky gut induced by the alteration of intestinal microbiome could lead to an altered communication with the CNS.

GUT DYSBIOSIS

Increase in the gut barrier permeability

Increase in systemic circulation of microbes/microbial products and inflammatory factors

Increase in BBB permeability and changes in CNS immune response

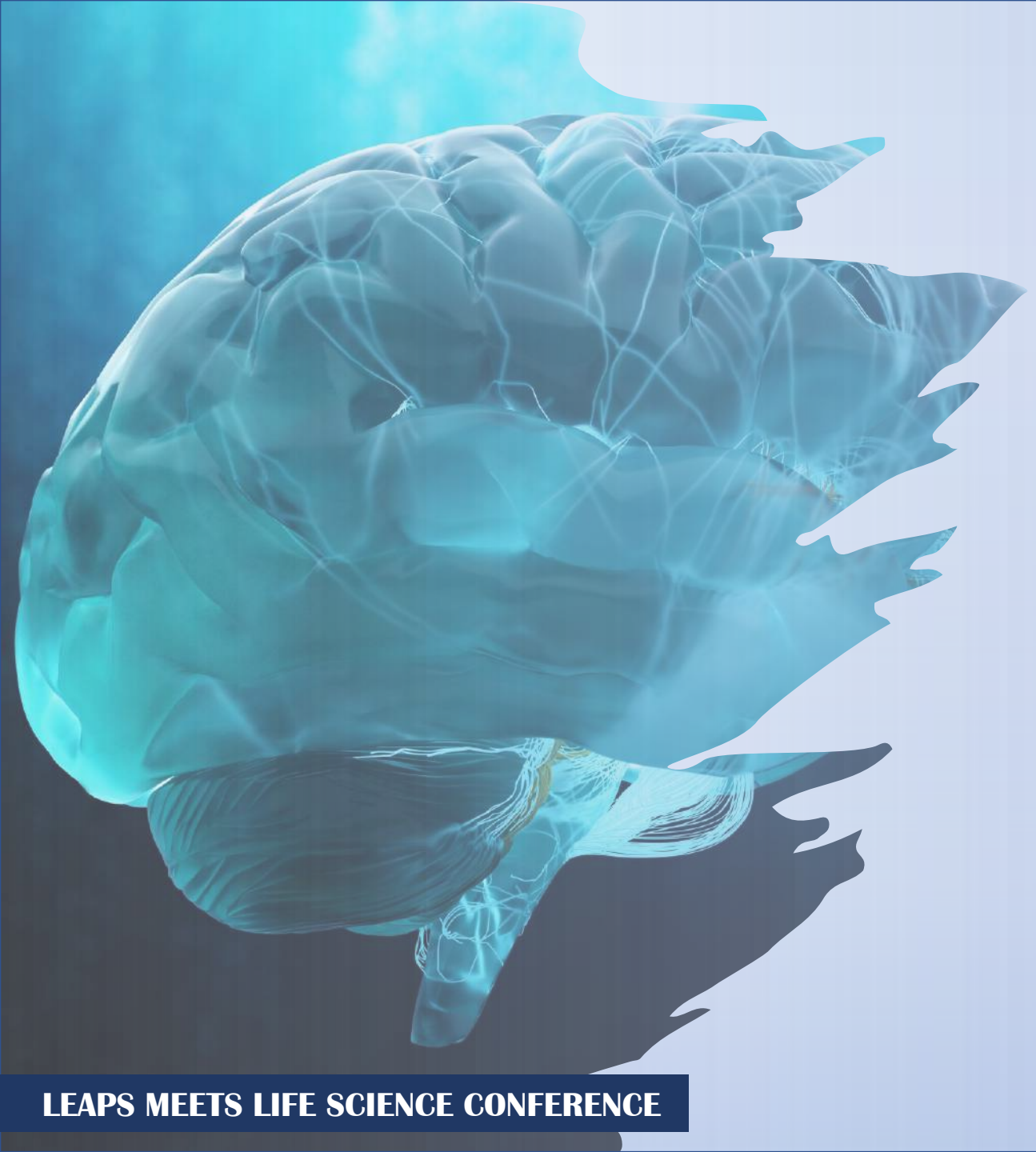
NEUROINFLAMMATION and NEURODEGENERATION

Accumulations of proteins in CNS

Abnormal aggregations of proteins in enteric nervous system

ADVANTAGES IN USING ANIMAL MODELS

- Rapid development and shorter life cycle
- Access to early stages of the disease
- Immunological surveillance
- Lower costs
- Control over experimental conditions



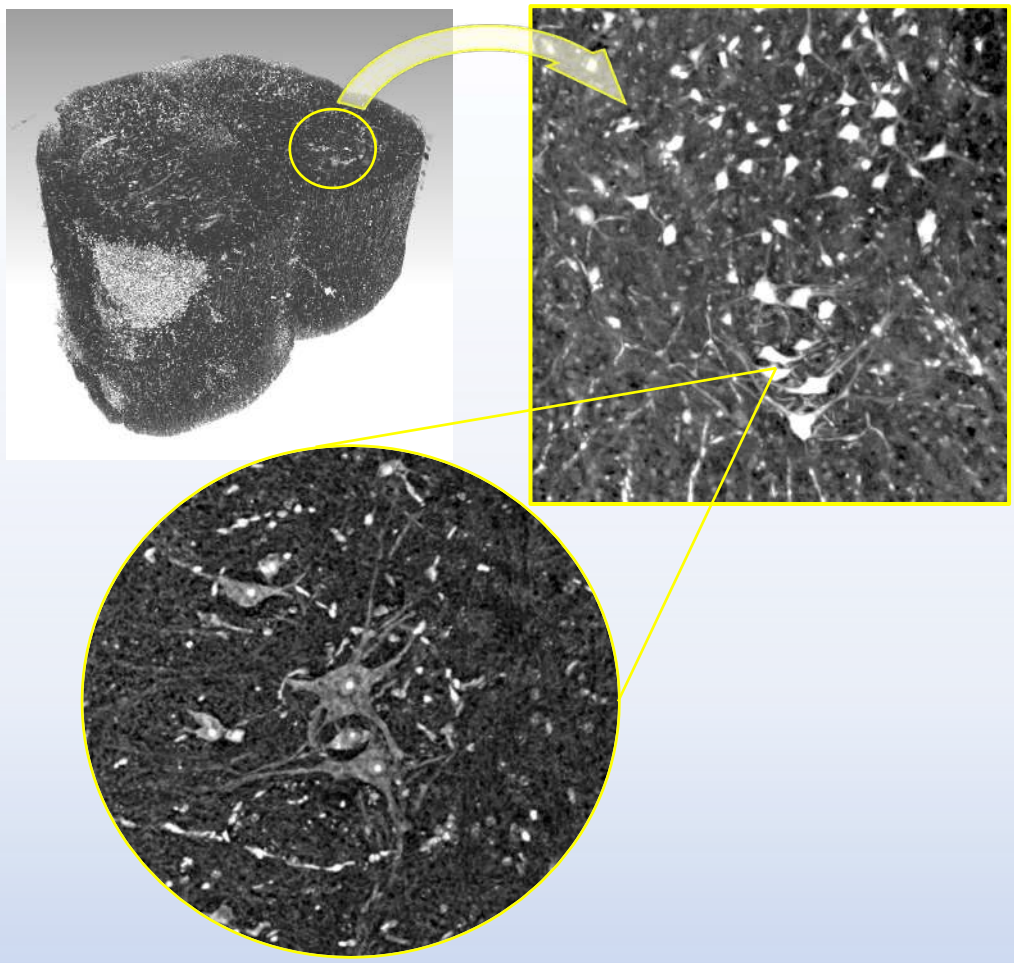
WHY X-RAY PHASE CONTRAST TOMOGRAPHY?

X-RAY PHASE CONTRAST TOMOGRAPHY

ADVANTAGES OF XPCT FOR PRECLINICAL STUDIES

1. 3D imaging of the entire organ down to single cell

2. Higher contrast of soft low-absorbing tissues without chemical aggressive and slicing sample preparation



X-RAY PHASE CONTRAST TOMOGRAPHY

1. GUT-BRAIN AXIS
2. ANIMAL MODELS
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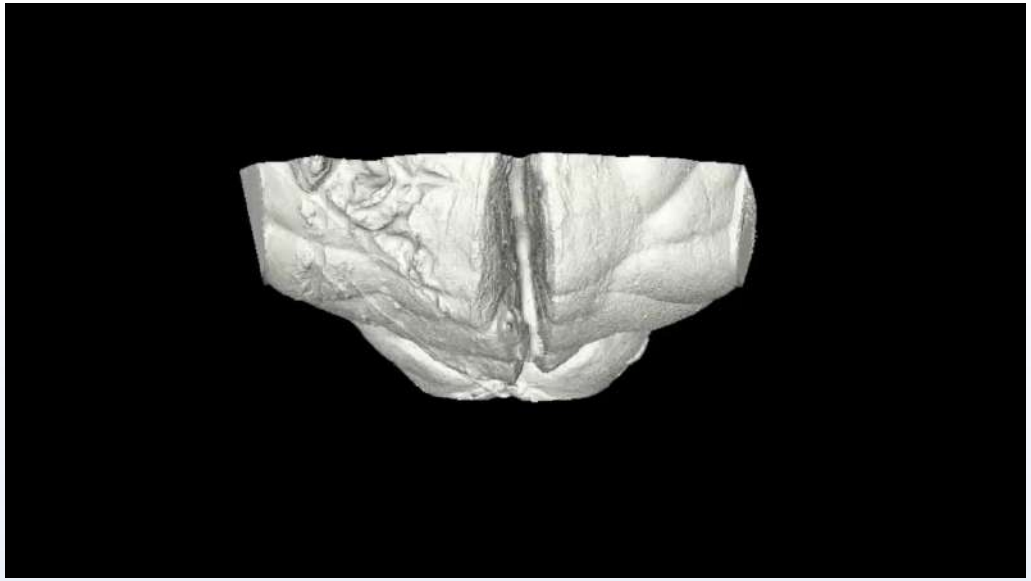
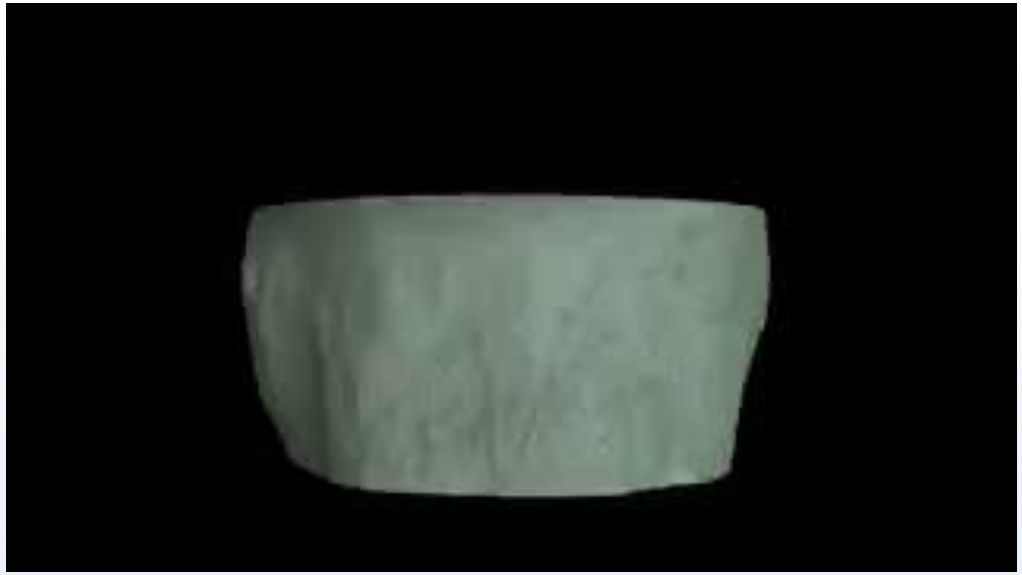


MOUSE BRAIN



MOUSE SPINAL CORD

X-RAY PHASE CONTRAST TOMOGRAPHY

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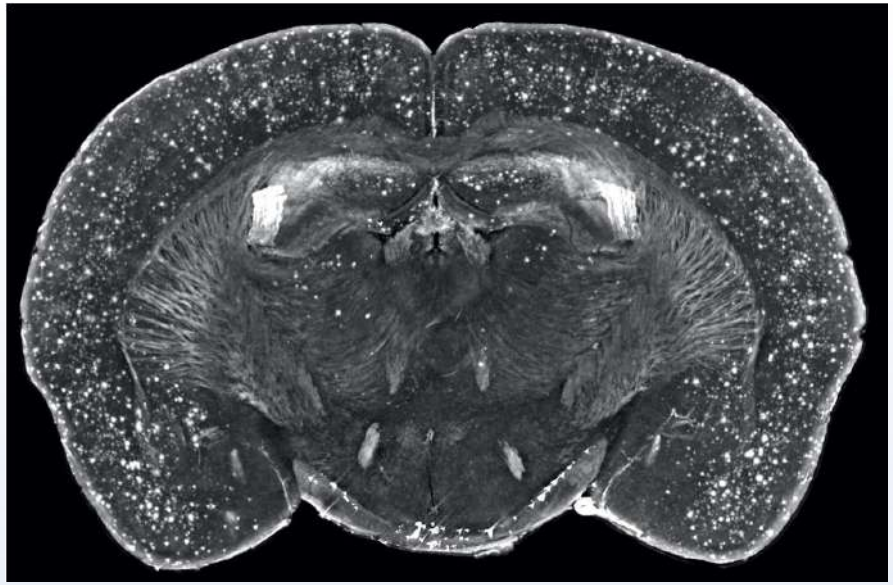
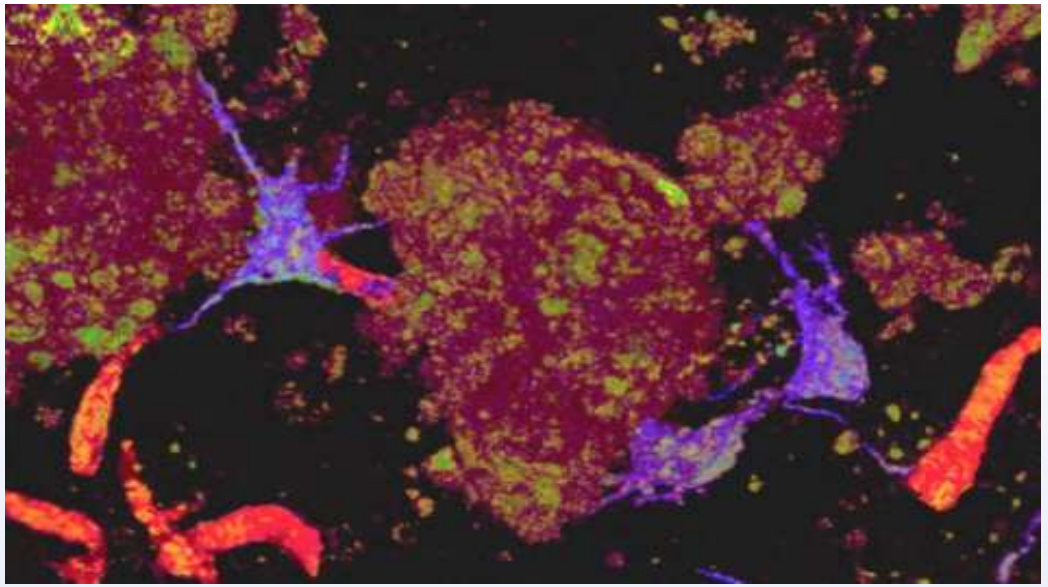


MICRO-XPCT

Resolution~10 um



NANO-XPCT

Resolution~150 nm

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MULTIPLE SCLEROSIS

MULTIPLE SCLEROSIS

CLINICAL MANIFESTATIONS

Neurological and motor deficIts

Long-term irreversible disability

BIOLOGICAL FEATURES

Neuroinflammation

Demyelination

Infiltration of lymphocytes into CNS

Axonal loss

Infectious agents have long been suspected as trigger for autoimmune response against CNS constituents.

MULTIPLE SCLEROSIS

- Which are the anatomical regions involved?
- How does the disease spread over time?
- What might be the imaging indicators that can act as markers to recognize the disease early?

MULTIPLE SCLEROSIS

WHERE

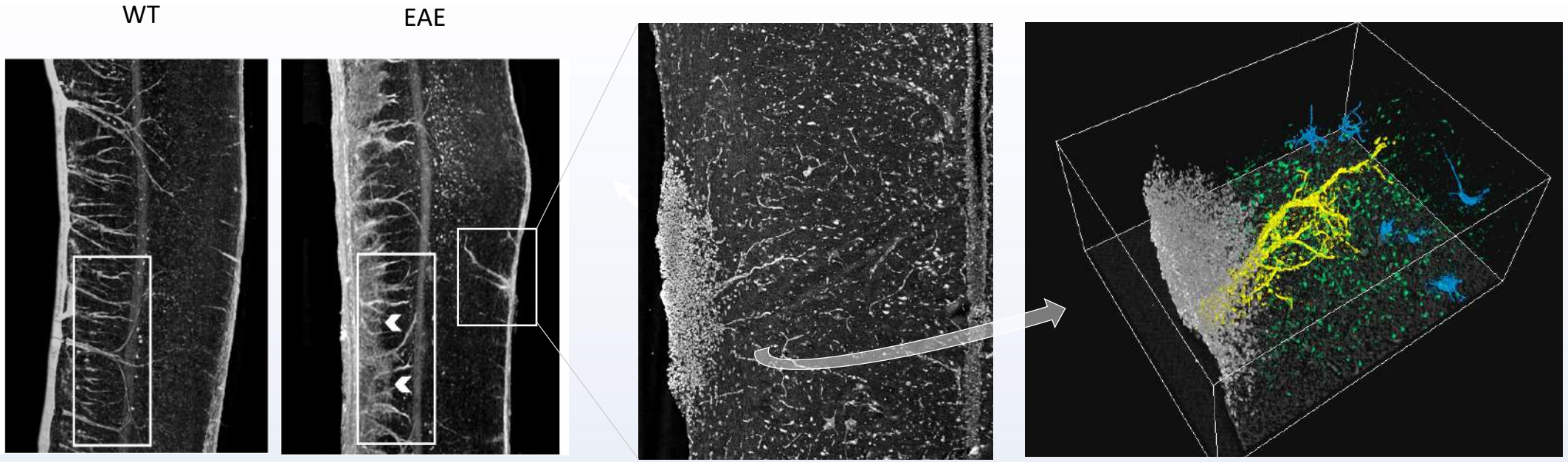
- Brain
- Spinal cord
- Intestine
- Optic nerve

WHEN

- Zero-time (wild time mice)
- 3 days post induction
- 7 days post induction
- Disease onset (11-13 dpi)

MULTIPLE SCLEROSIS

Blood barrier impairment



Palermo et al, Commun. Phys. 2022

- Large accumulation of cells localized around the vessels which would be commensurate with infiltrating inflammatory T cells and macrophages typical of an EAE lesion.

MULTIPLE SCLEROSIS

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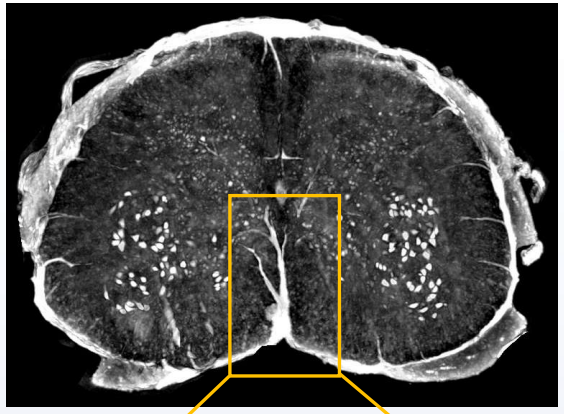
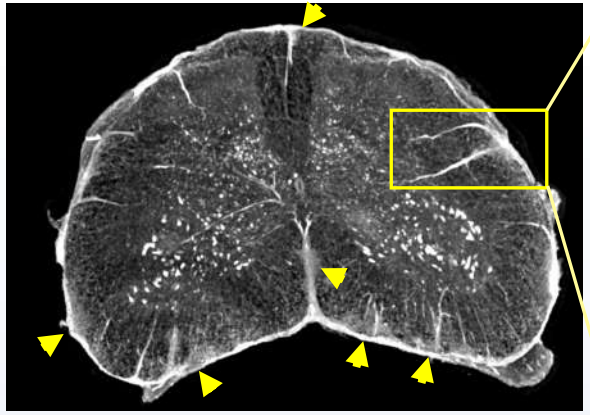
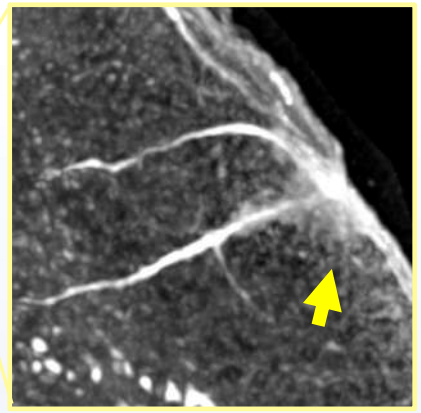
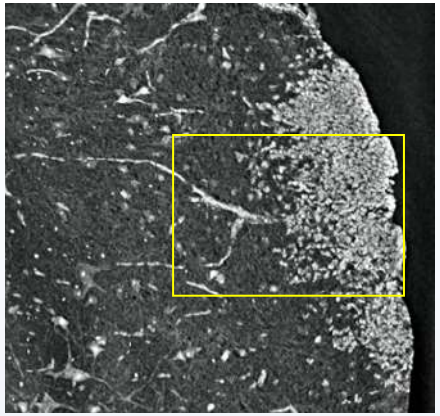
7 DPI

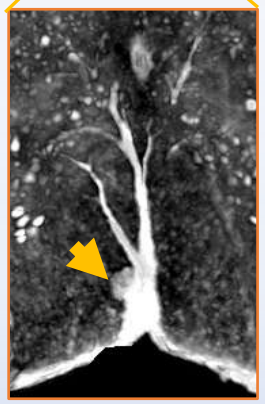


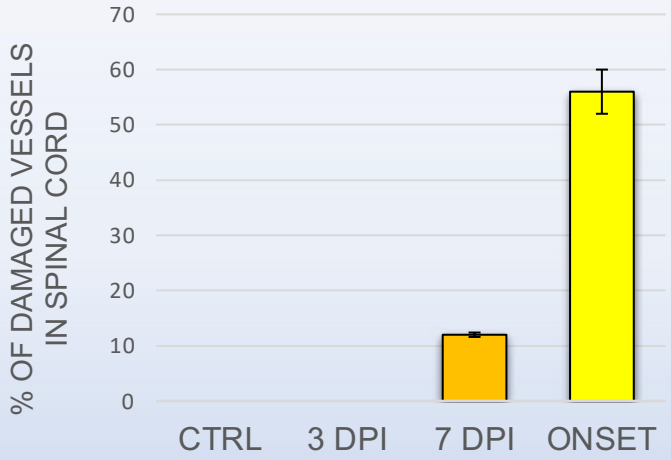
11 DPI -onset











- Inflammation imaging markers appearing at presymptomatic stage
- Inflammation foci at the base of blood vessels

MULTIPLE SCLEROSIS

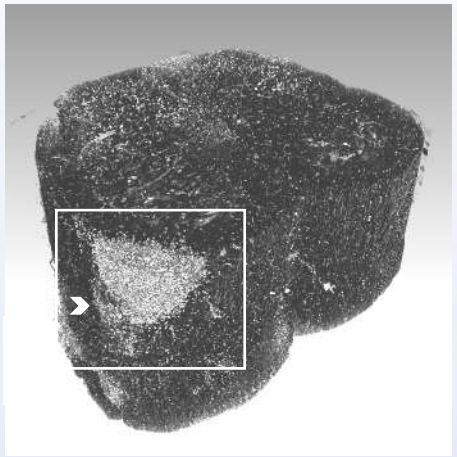
Inflammation timeline in the CNS

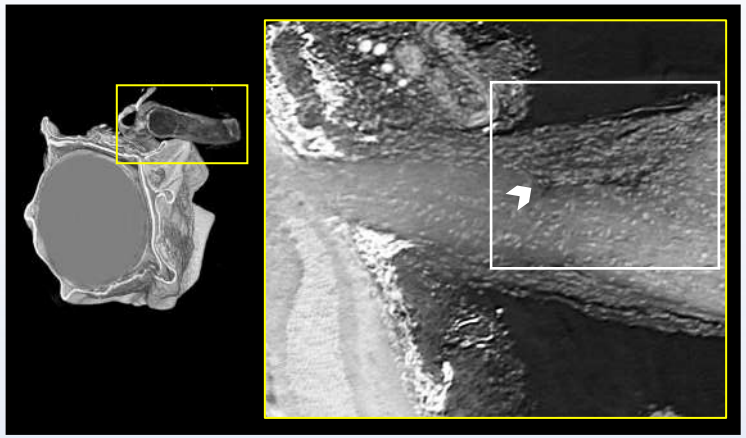
SPINAL CORD

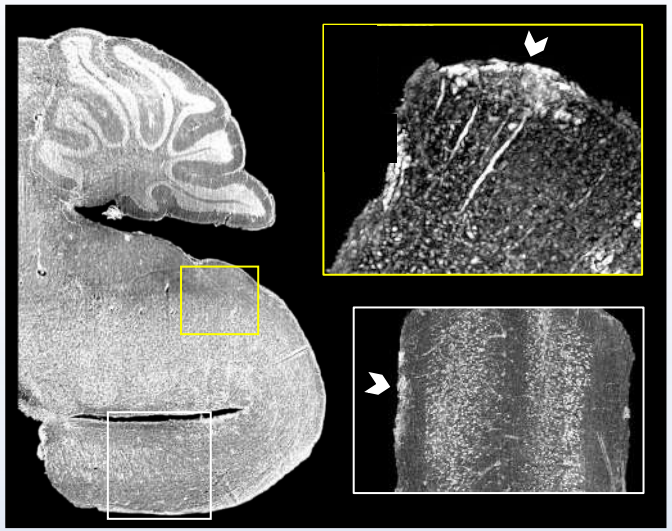
OPTIC NERVE

BRAIN

MICRO-XPCT



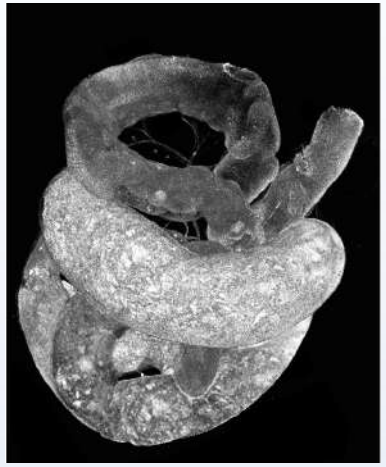


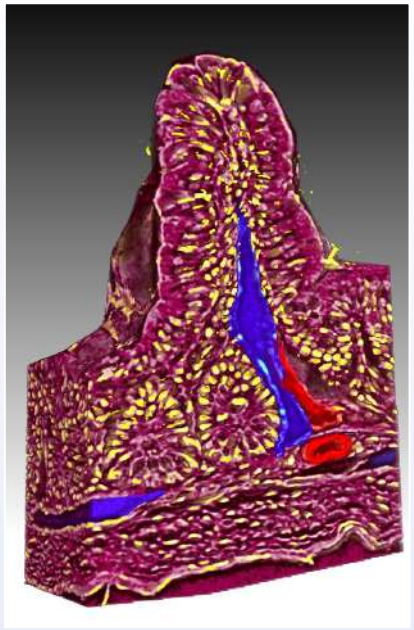


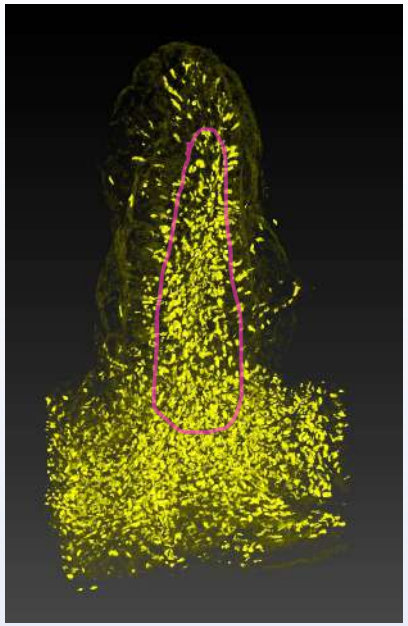
- Optical neuritis
- Infiltrating cells in the brainstem

MULTIPLE SCLEROSIS

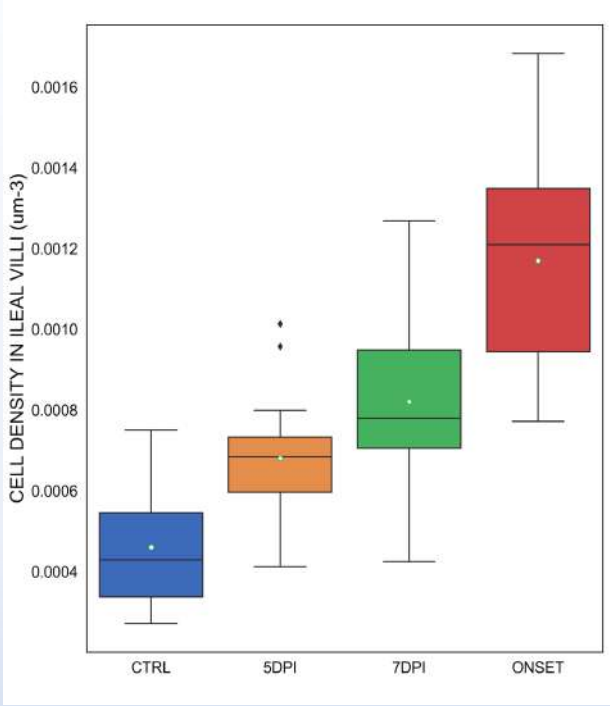
Insight into the Role of Gut-brain Axis





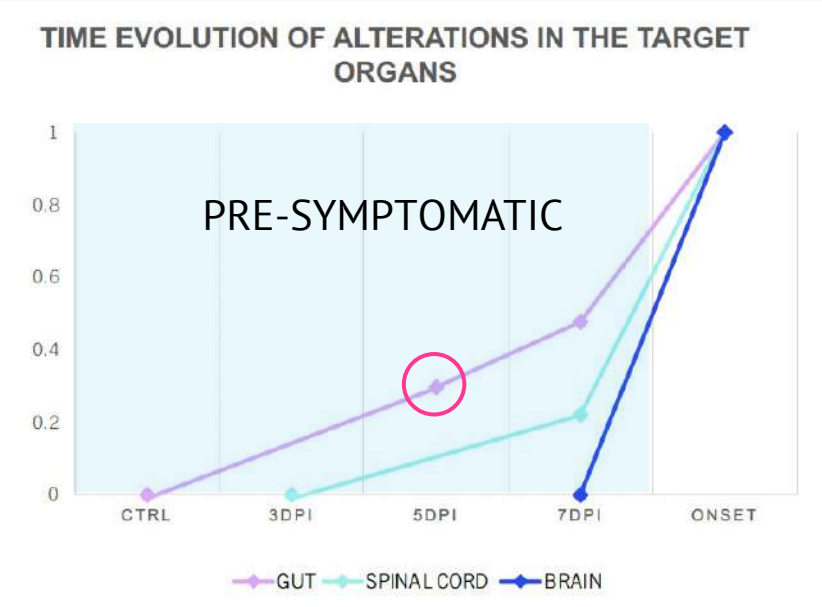


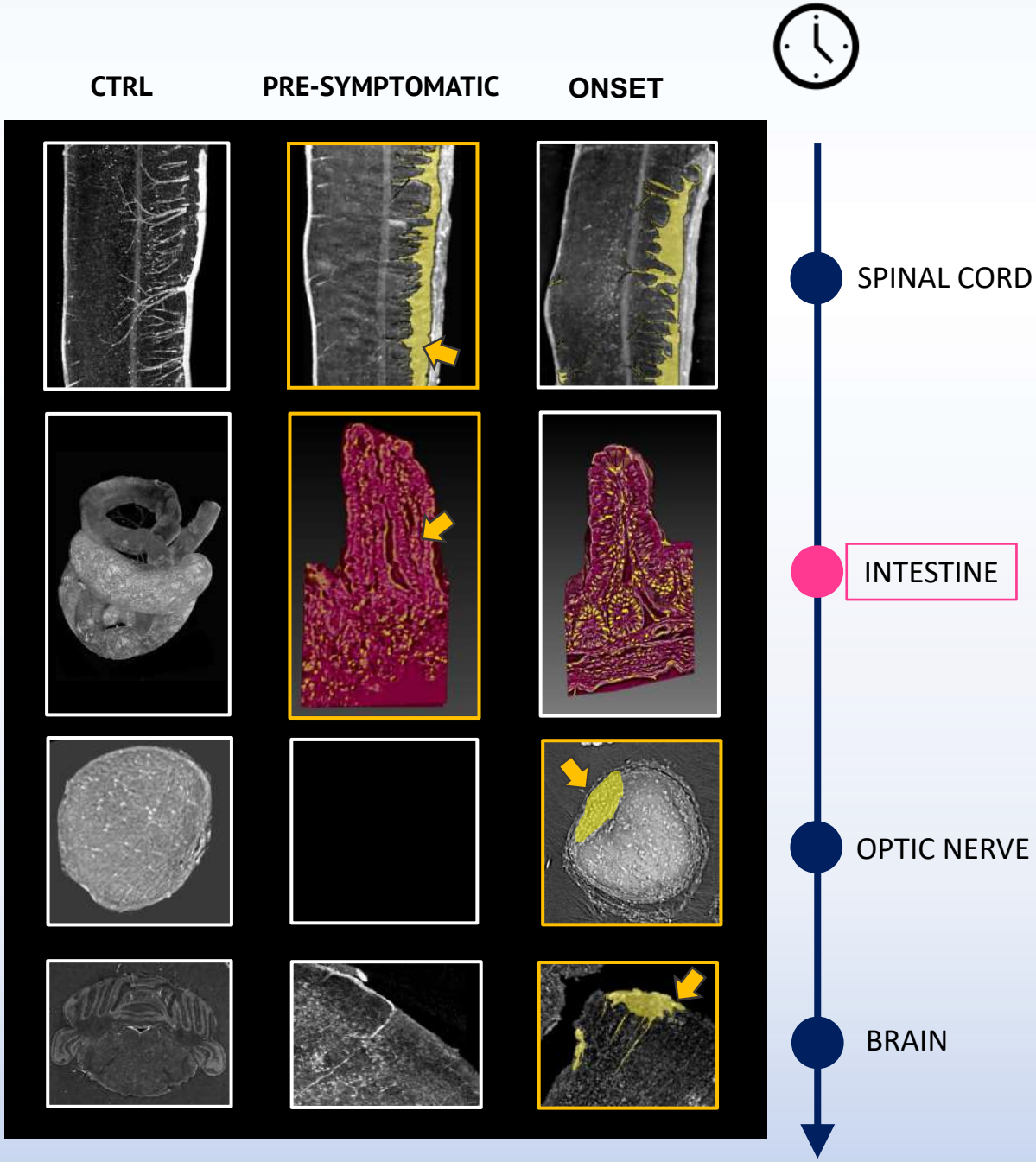
- Increment of cell density in the intestinal mucosa of EAE-induced mice from pre-symptomatic stages.



MULTIPLE SCLEROSIS

Inflammation markers over time





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ALZHEIMER'S DISEASE

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ALZHEIMER'S DISEASE

CLINICAL MANIFESTATIONS

Progressive and irreversible loss of superior cognitive functions

BIOLOGICAL FEATURES

Aggregates of Beta-amyloids (plaques)

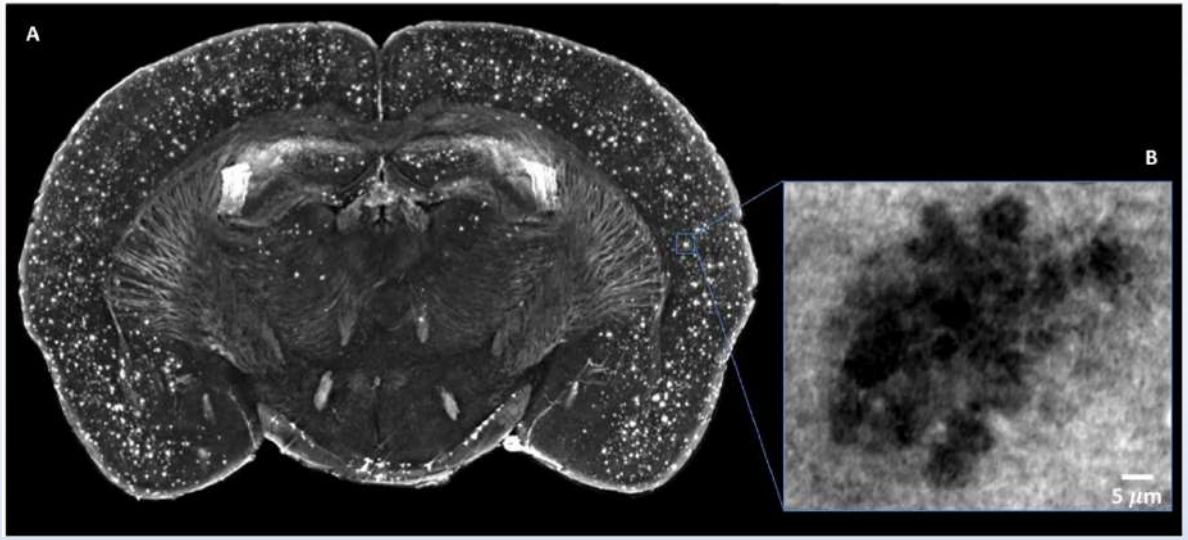
Neurofibrillary tangles of tau protein

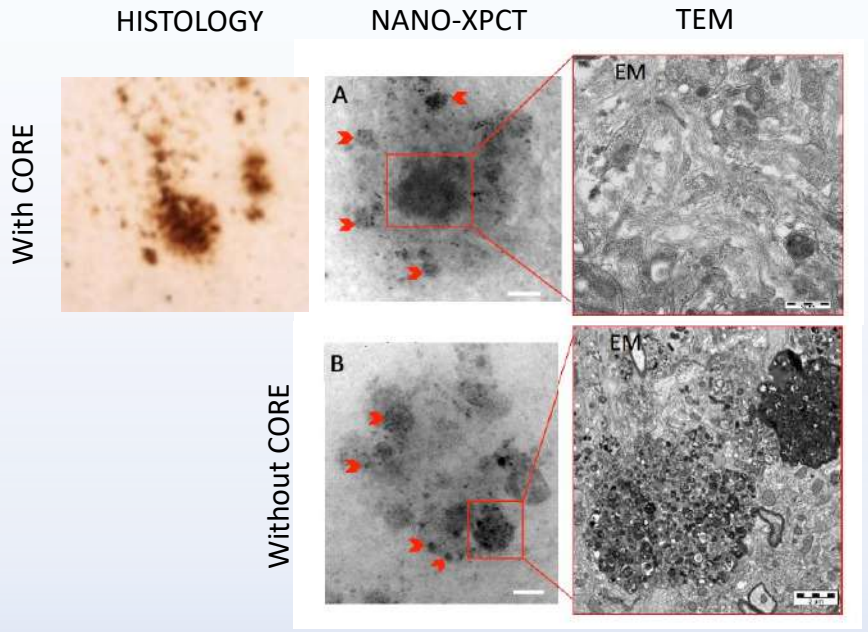
- APP/PS1 - Model for familial AD → 5 %
- SAMP8 - Model for sporadic AD → 95 %

APP/PS1 - Model for familial AD

Exploring the brain

APP/PS1 are double transgenic mice expressing a chimeric mouse/human amyloid precursor protein and a mutant human presenilin 1 (PS1-dE9), both directed to CNS neurons.





Massimi et al, Neuroimage 2019
Palermo et al, Front. Neurosci. 2020

ESRF
The European Synchrotron

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NANO-XPCT

APP/PS1 - Model for familial AD

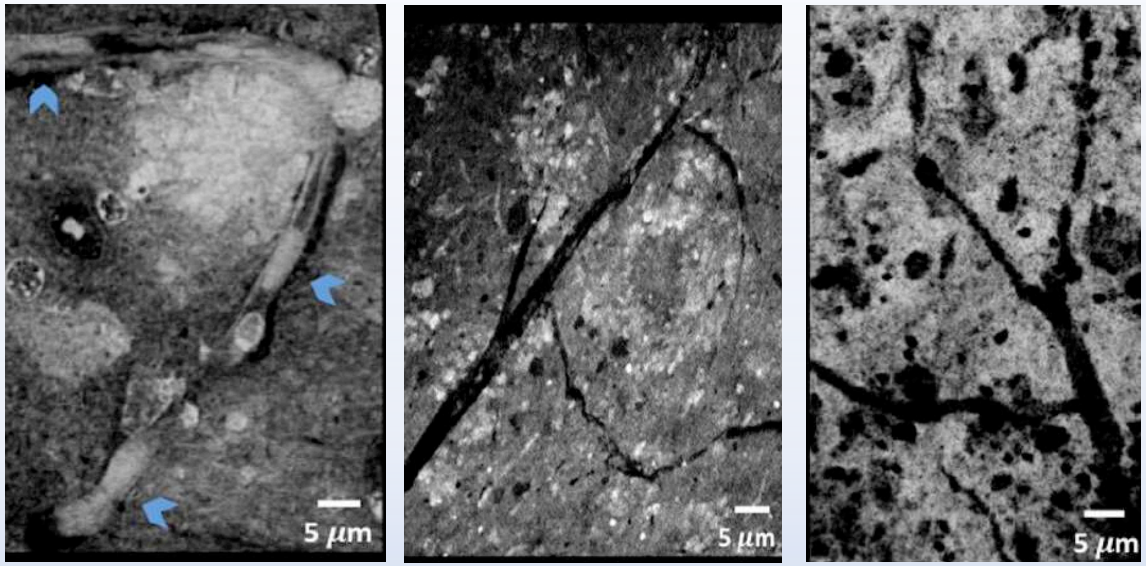
Monitoring the effects of novel therapies

Intranasal delivery of mesenchymal stem cell secretome repairs the brain of Alzheimer's mice

Giulia Santamaria [1], Edoardo Brandi [1], Pietro La Vitola [1], Federica Grandi [1], Giovanni Ferrara [2], Francesca Pischiutta [1], Gloria Vegliante [1], Elisa R Zanier [1], Francesca Re [3], Antonio Uccelli [2,4], Gianluigi Forloni [1], Nicole Kerlero de Rosbo [2], Claudia Balducci [5]

- INDUCED MEMORY RECOVERY
- INCRESED NUMBER OF DETECTED NEURONS
- NO REDUCTION OF THE PLAQUE LOAD

APP/PS1 APP/PS1 w/ treatment WT



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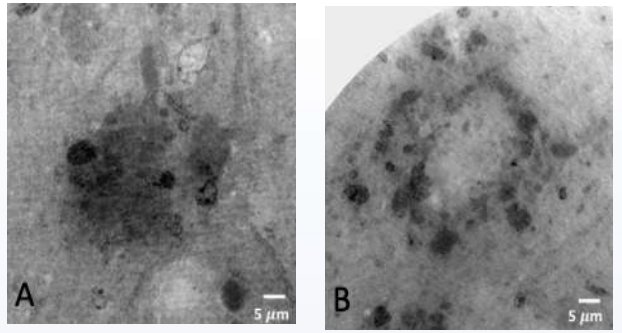
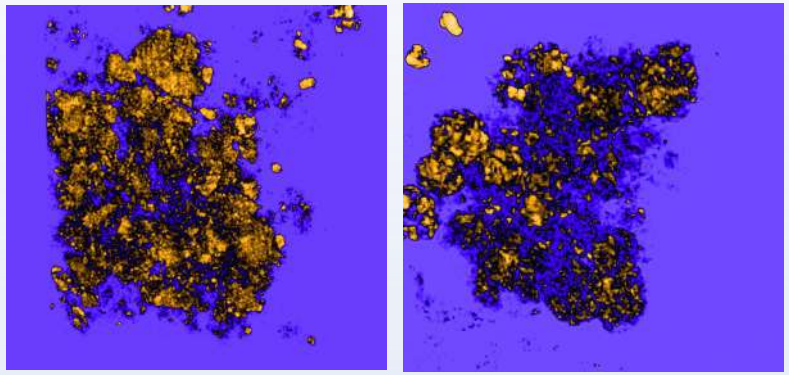
APP/PS1 APP/PS1 w/ treatment





- Improved condition of vessels
- Treatment appears associated to disrupted plaques composed by an high-density corona and a less dense core

SAMP8 - Model for sporadic AD

Senescence-accelerated mouse-prone 8 is a spontaneous animal model of accelerated aging. It is considered a robust model for exploring the etiopathogenesis of sporadic AD.

PRECLINICAL STUDIES:
IN-VIVO tests and EX-VIVO XPCT

FUTURE PERSPECTIVES

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SYNCHROTRON RADIATION FACILITIES

ESRF The European Synchrotron

SOLEIL SYNCHROTRON

PAUL SCHERRER INSTITUT PSI

diamond

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