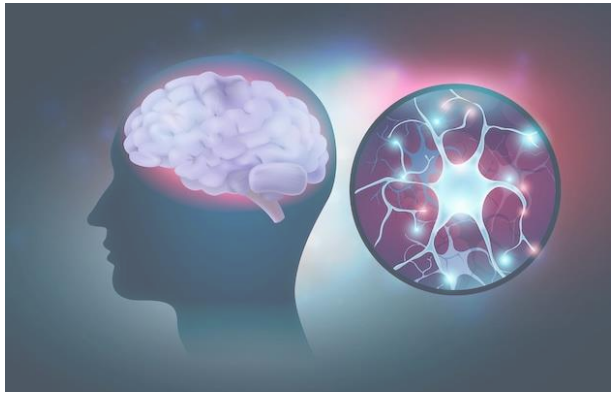
Synthesis of copper complexes for potential use in the diagnosis of Alzheimer's disease

Milena Salerno

Alzheimer’s disease

Neurodegenerative disease



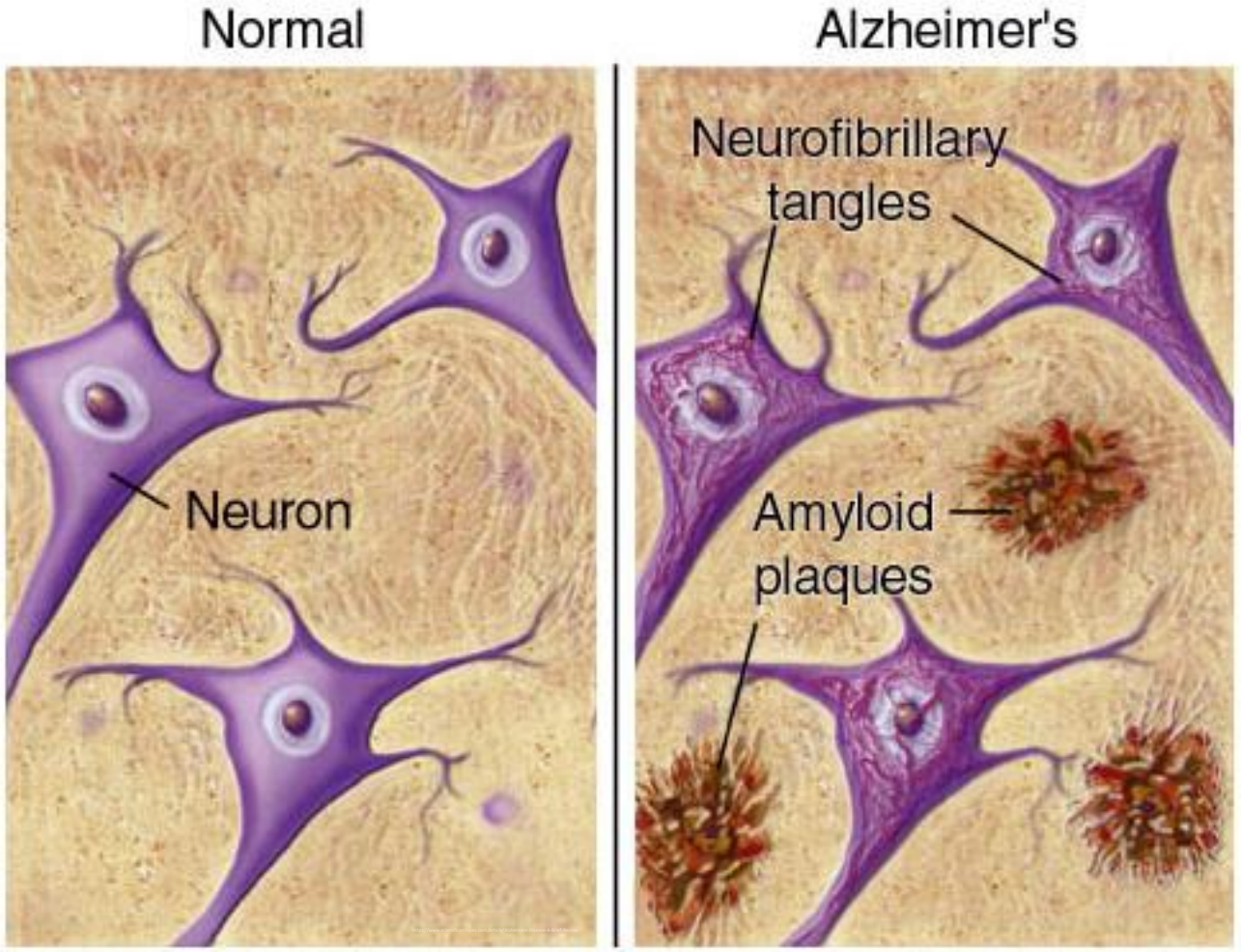
Multifactorial disease

Signs and Symptoms

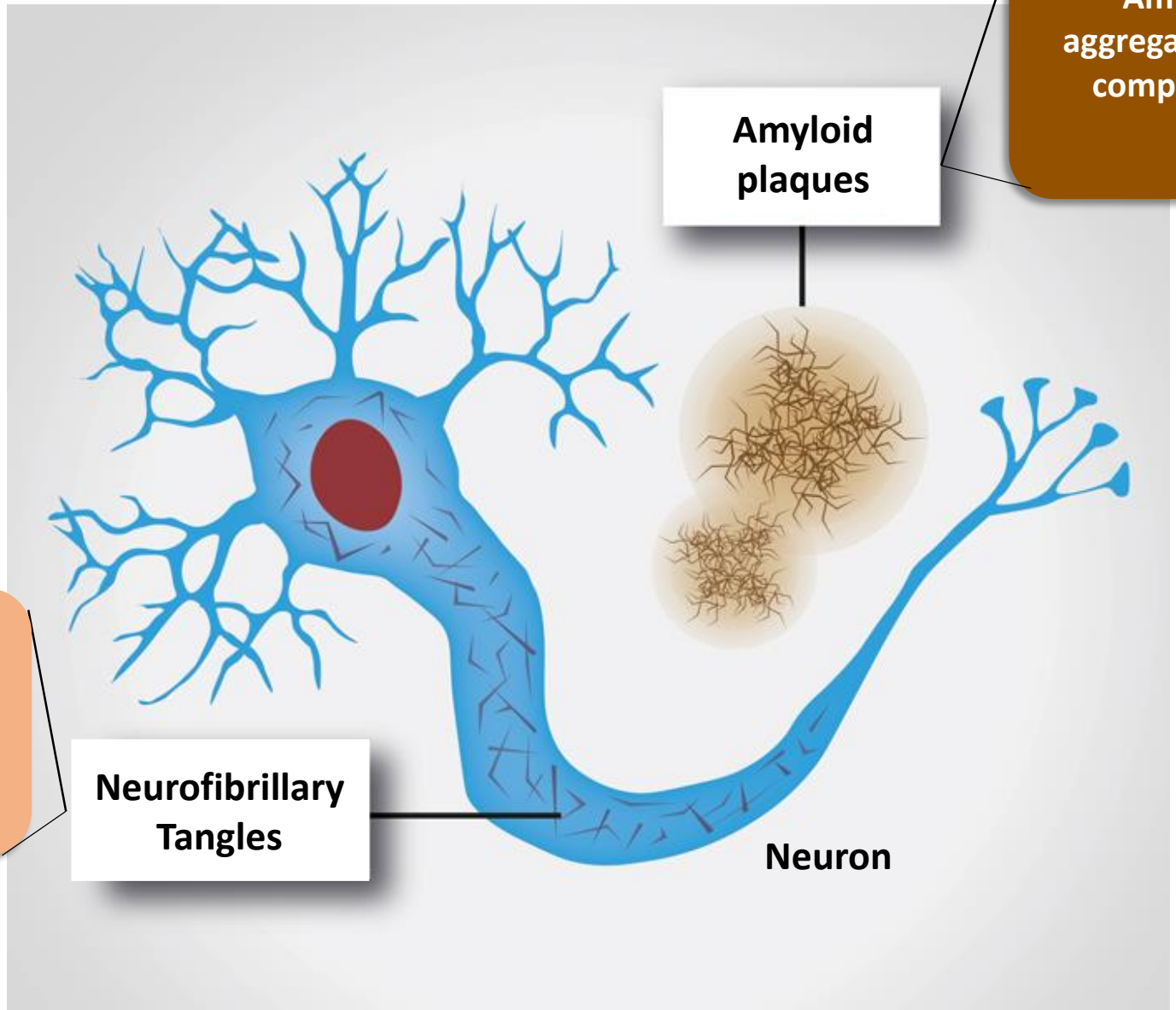
- MEMORY LOSS THAT DISRUPTS DAILY LIFE
- CONFUSION WITH TIME OR PLACE
- MISPLACING THINGS AND LOSING THE ABILITY TO RETRACE STEPS
- CHANGES IN MOOD AND PERSONALITY

Alzheimer’s disease

Pathological hallmarks



Amyloid protein aggregates are the main component of these plaques



Abnormal accumulation of tau protein inside brain neurons due to its hyperphosphorylation

Tau protein normally helps maintain the structure of neurons

Based on https://www.alzheimersresearchuk.org/news/taking-aim-at-amyloid/

Patients with Alzheimer's disease often require long-term care, which can be costly for families and healthcare systems

Providing care can significantly impact physical and mental well-being of the caregiver and all the family

According to Alzheimer Europe, the number of cases of Alzheimer's disease is expected to increase as Europe's population ages, reaching an estimated 115 million by 2050

https://www.europarl.europa.eu/doceo/document/E-9-2022-003066_EN.html#:~:text=Alzheimer's%20disease%20is%20now%20becoming,were%20suffering%20from%20this%20disorder.

Unfortunately

No cure for the Alzheimer disease !

Lack of early and definitive diagnosis

Post-mortem diagnosis

Diagnosis

There is no single diagnostic test that can determine whether or not a person has Alzheimer's disease.

CLINICAL EXAMINATION :
(neurologists, neuropsychologists, geriatricians and geriatric psychiatrists)

Assessment :

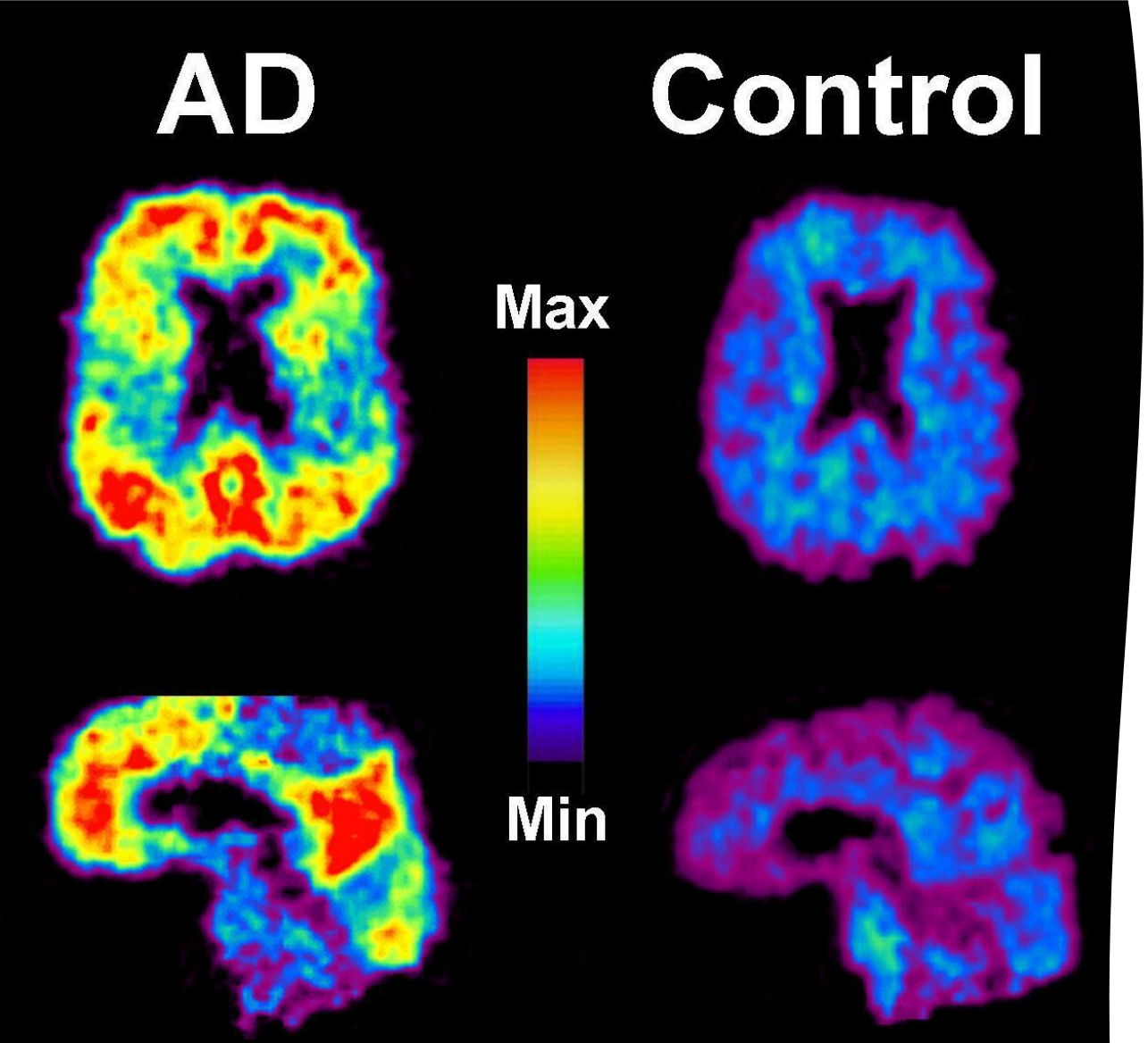
- Memory
- Language
- Motor skills
- Attention

PARACLINICAL EXAMINATIONS :
(radiologists)

- MRI (Magnetic Resonance Imaging)
- PET (Positron Emission Tomography)
- CSF (cerebrospinal fluid) analysis

Being able to make a diagnosis of Alzheimer's disease would help patients and families to have a diagnosis, plan for future care and improve their quality of life

Early diagnosis could contribute to the most effective treatment and help reduce costs and the financial burden on patients and their families



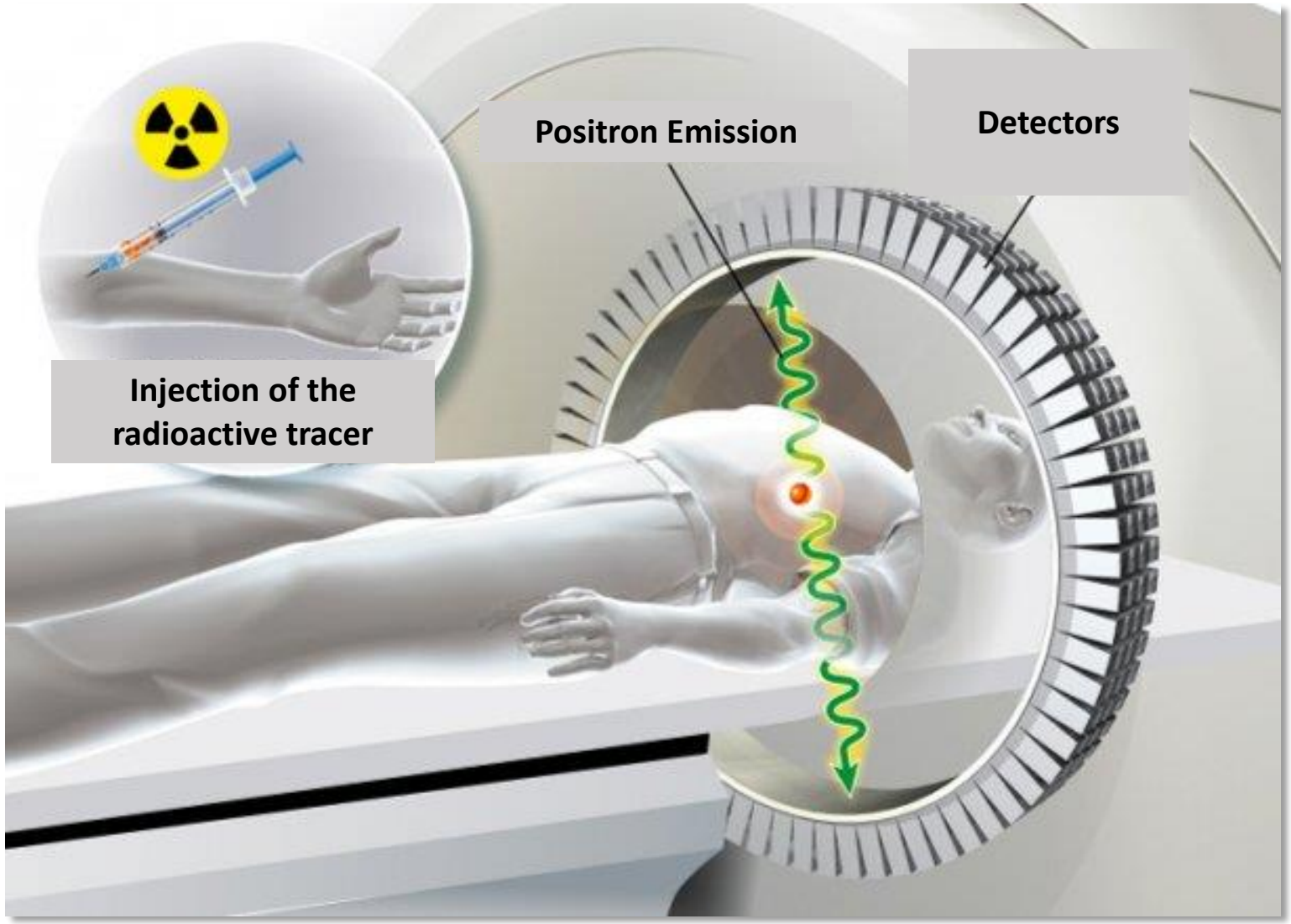
PET scan of a patient with Alzheimer's disease on the left and an elderly person with normal memory on the right.

Positron emission tomography (PET)

Aids in the diagnosis and monitoring of the disease progression

Positron emission tomography (PET)

PET is a medical imaging technique. It is based on the detection of radioactivity emitted after a radioactive tracer is injected into a patient and can detect changes at the molecular level.

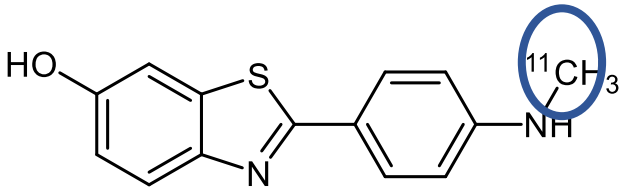


PET imaging

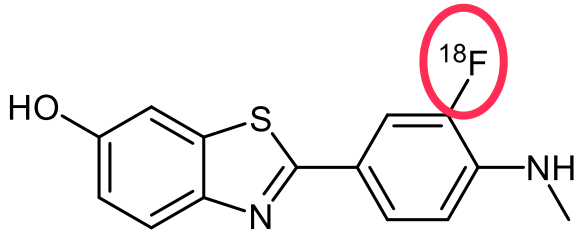
Alzheimer's diagnosis

Detection of amyloid plaques

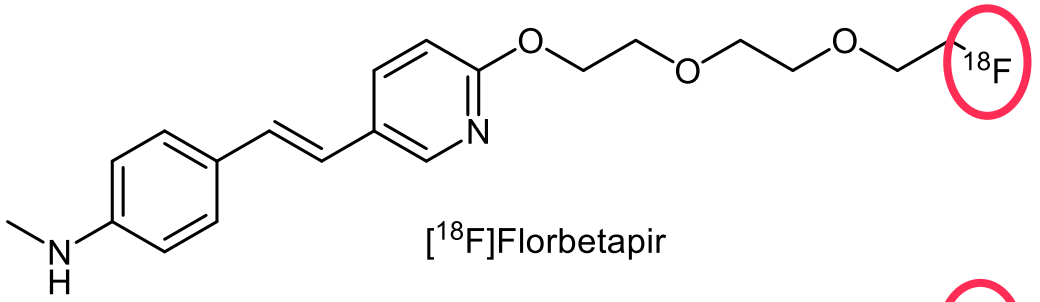
$t_{1/2}$: 20 min



Pittsburg Compound B ([^{11}C]PIB)

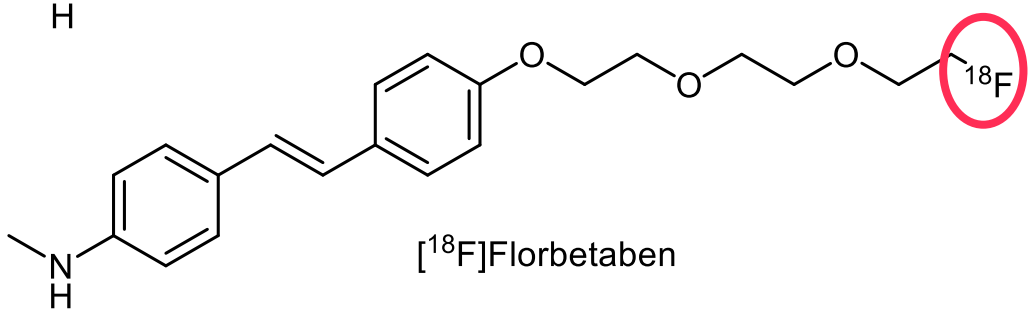


[^{18}F]Flutemetamol



[^{18}F]Florbetapir

$t_{1/2}$: 110 min



[^{18}F]Florbetaben

PET imaging

Alzheimer's diagnosis

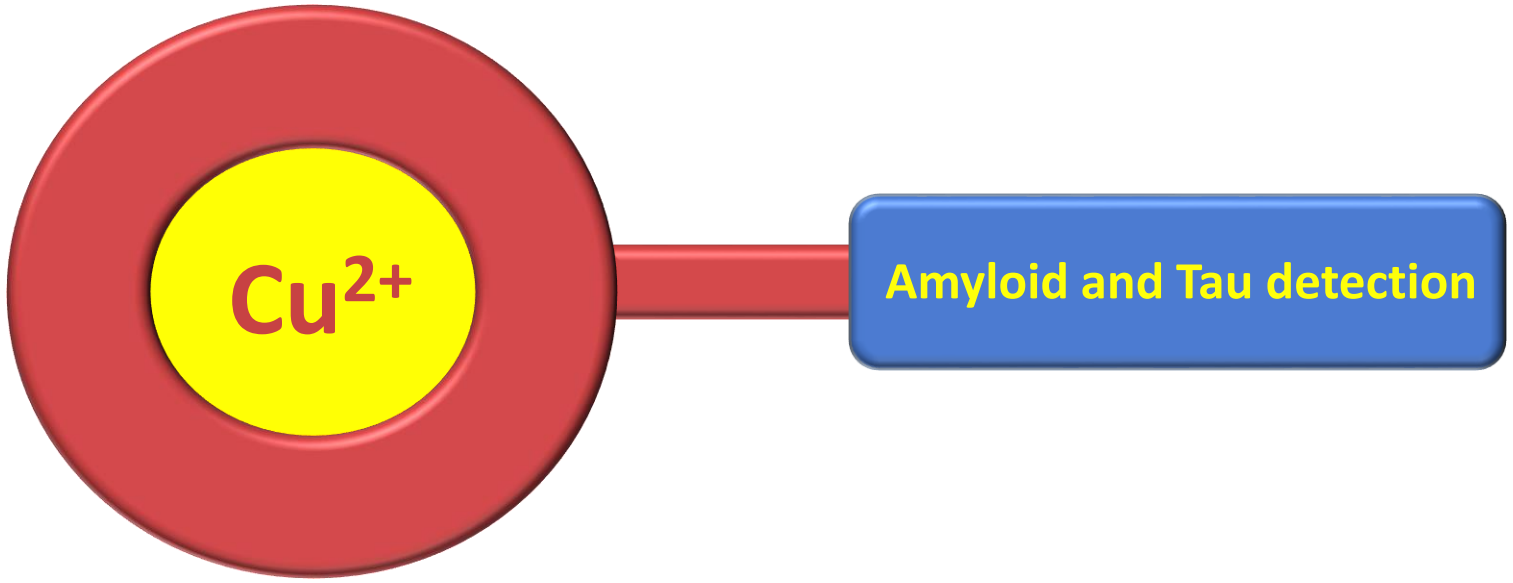
Detection of amyloid plaques

Alternative

The use of molecules with Cu radioisotopes could be a good alternative to obtain compounds with a longer $t_{1/2}$ time.

$t_{1/2}$ du ^{64}Cu = 12,7 h

Small New medical imaging agents for PET



The main characteristics of these complexes will be…

Sufficient stability to ensure their safe use in the human body by avoiding potential toxicity problems

Ability to specifically label amyloid plaques and tau pathology

Ability to cross the blood-brain barrier (BBB)

Simple diffusion

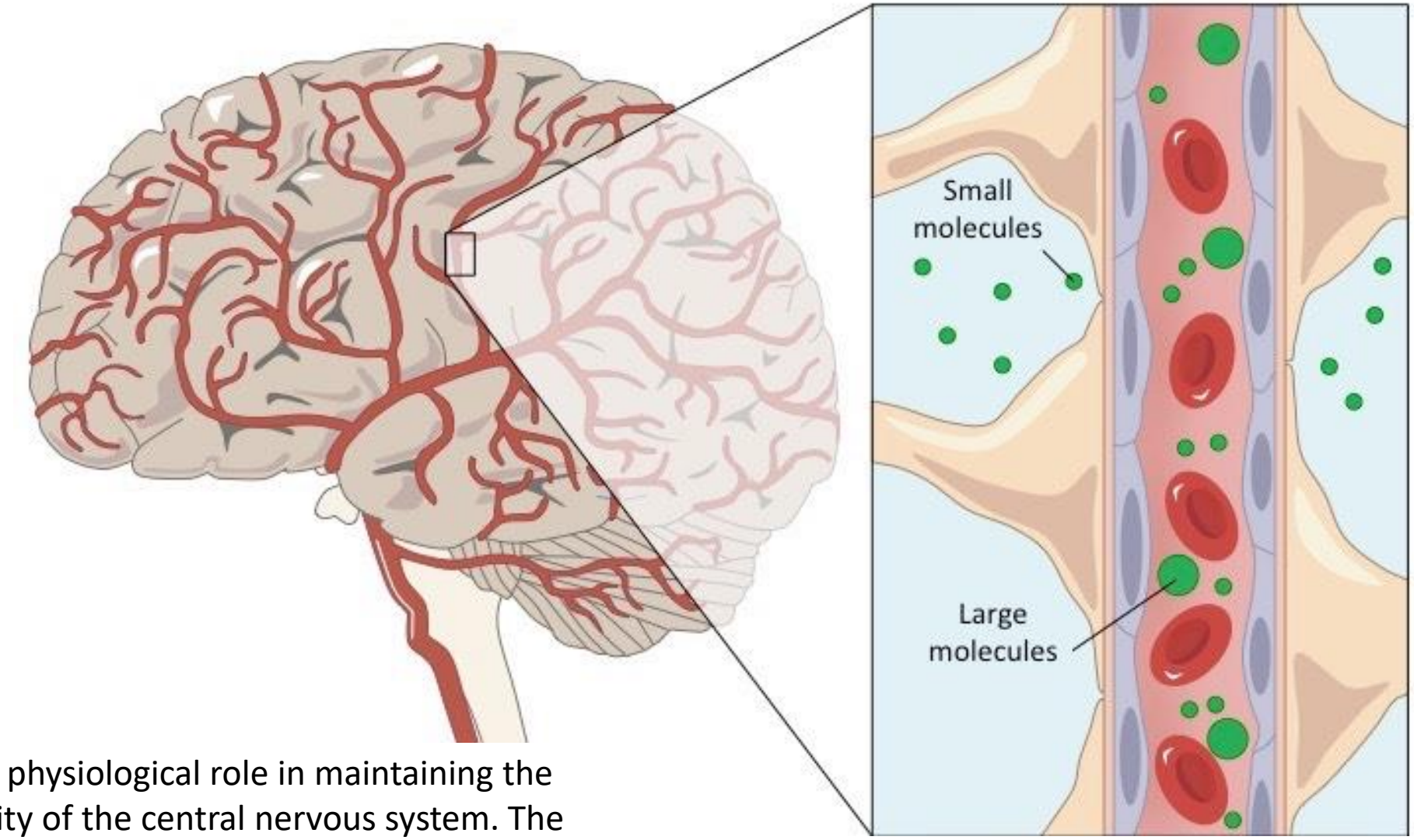
Alzheimer's disease

Copper complexes

Brain is the target!

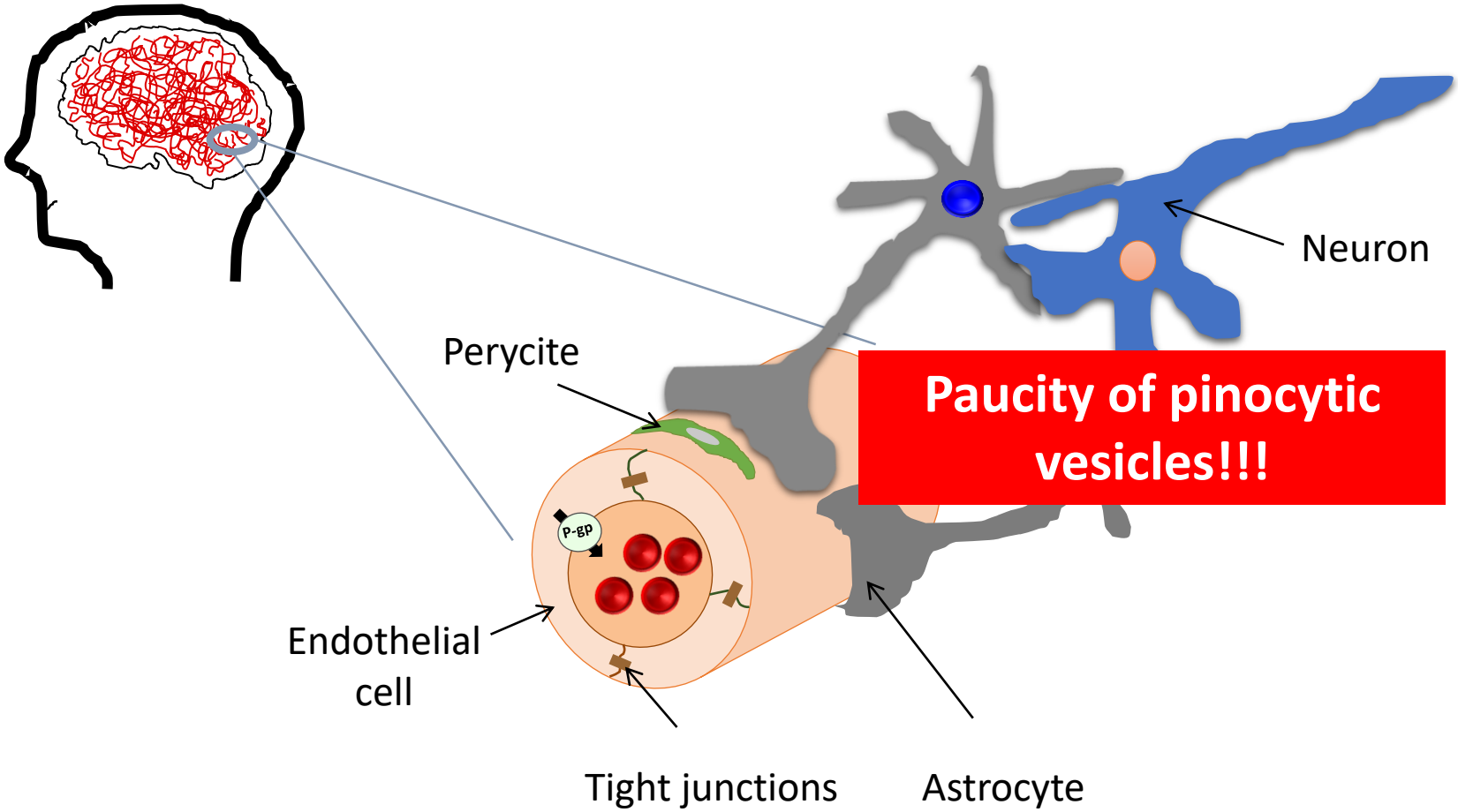
Special attention will be given to the design of new tracers considering the specific characteristics of the BBB

The blood-brain barrier



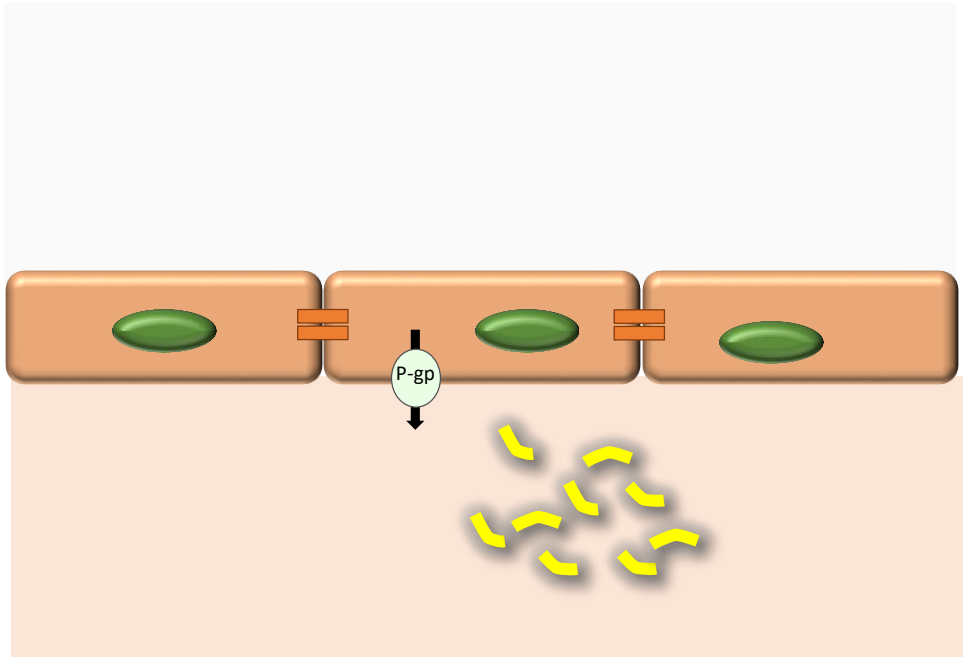
The BBB plays a crucial physiological role in maintaining the homeostasis and integrity of the central nervous system. The BBB's low permeability significantly restricts the passage of diagnostic or therapeutic synthetic molecules to the brain.

Blood brain barrier (BBB)



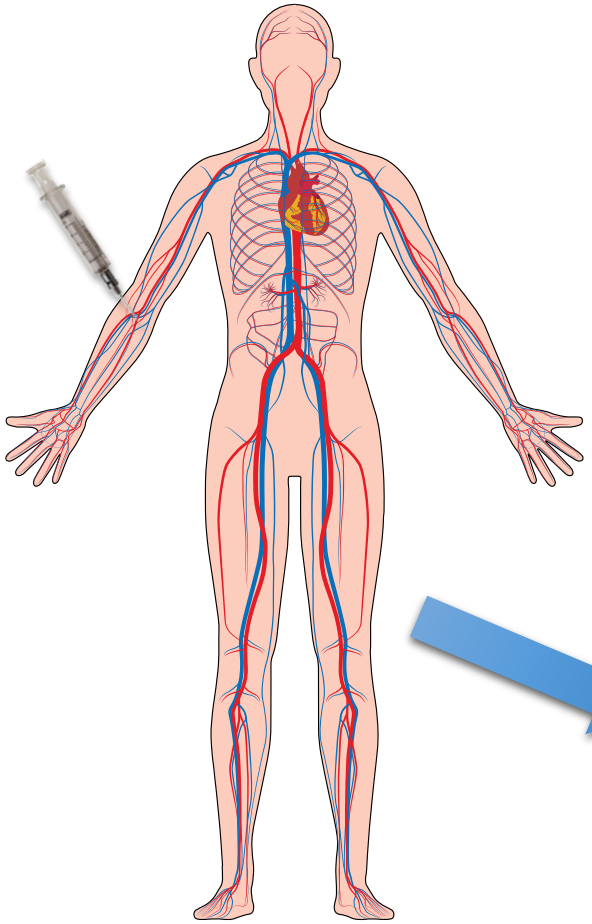
Rowinska-Zyrek et al., 2014

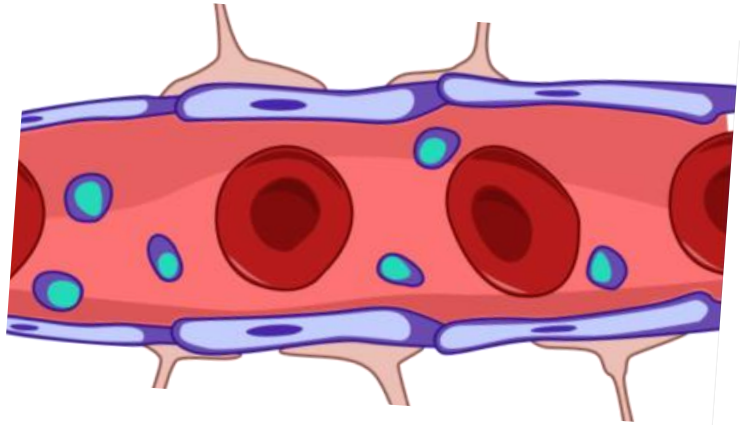
Efflux of a molecule by P-Glycoprotein (P-gp)



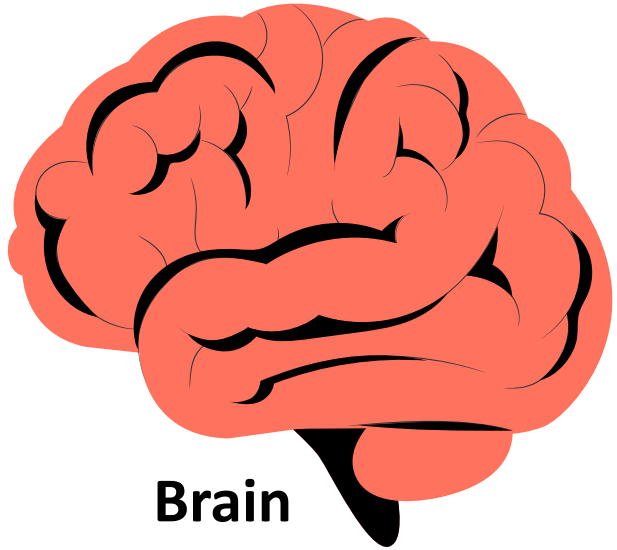
Highly selective barrier protecting the brain

Only certain molecules can pass through

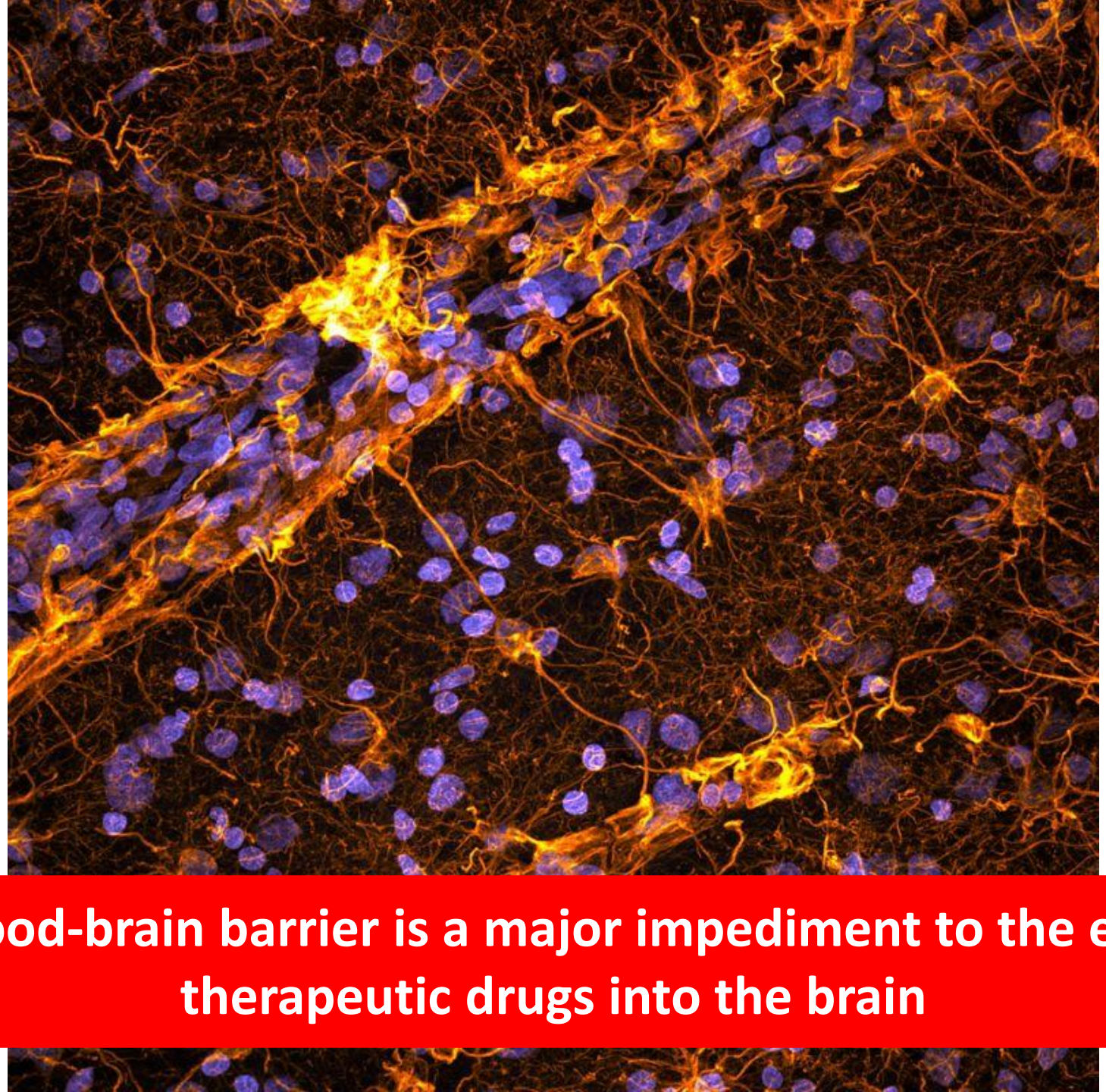




BBB



Brain



The blood-brain barrier is a major impediment to the entry of therapeutic drugs into the brain

Rational synthesis of new molecules targeting the brain

Predictive models

Predict the ability of molecules to be absorbed by the organism

Strategy

- Lipinski's rule
- Log BB

Predictive models

Lipinski's rule

Lipinski's rule is a tool used to predict the druglikeness of a synthetic molecule. According to this rule, a good absorption and permeability is likely if :

- Molecular weight is lower than 500 Daltons
- Oil/water distribution coefficient (LogP) is lower than 5
- Hydrogen bond donors lower than 5 (expressed as the sum of OHs and NHs)
- Hydrogen bond acceptor lower than 10 (expressed as the sum of Ns and Os)

Predictive models

Log BB

$$Log\ BB = \frac{Concentration\ in\ the\ brain}{Concentration\ in\ the\ bloob}$$

A higher log BB value indicates better penetration of the BBB, which means that the compound is more likely to reach therapeutic concentrations in the brain. Log BB values can be derived experimentally either *in vivo* using animals or *in vitro* using cellular BBB models

Predictive models

Log BB

Experimentally determined **log BB** values are correlated with various molecular descriptors using mathematical models

Several studies have evaluated the ability of molecules to cross the BBB by calculating the Log BB value

$$\text{Log BB} = 0{,}5159 \log P - 0{,}0277 TPSA - 0{,}3462$$

Vilar et al., 2010

Predictive models

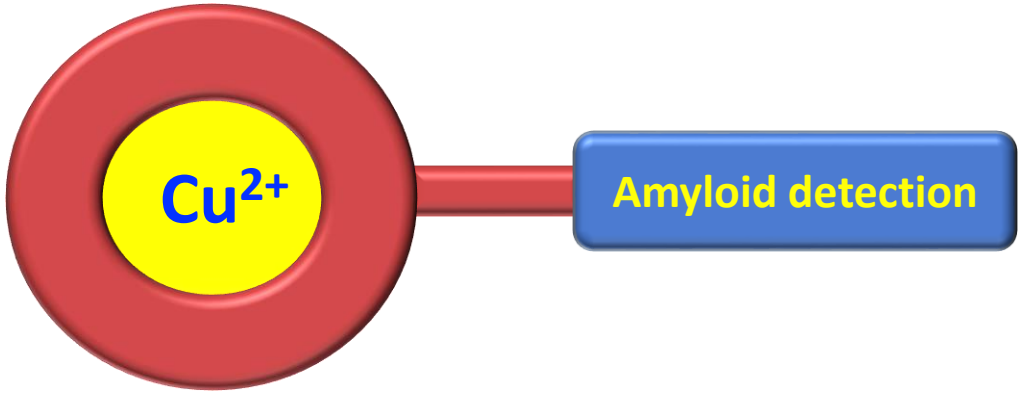
Log BB

If the Log BB value is **less than -1**, the compound may not be able to cross the BBB

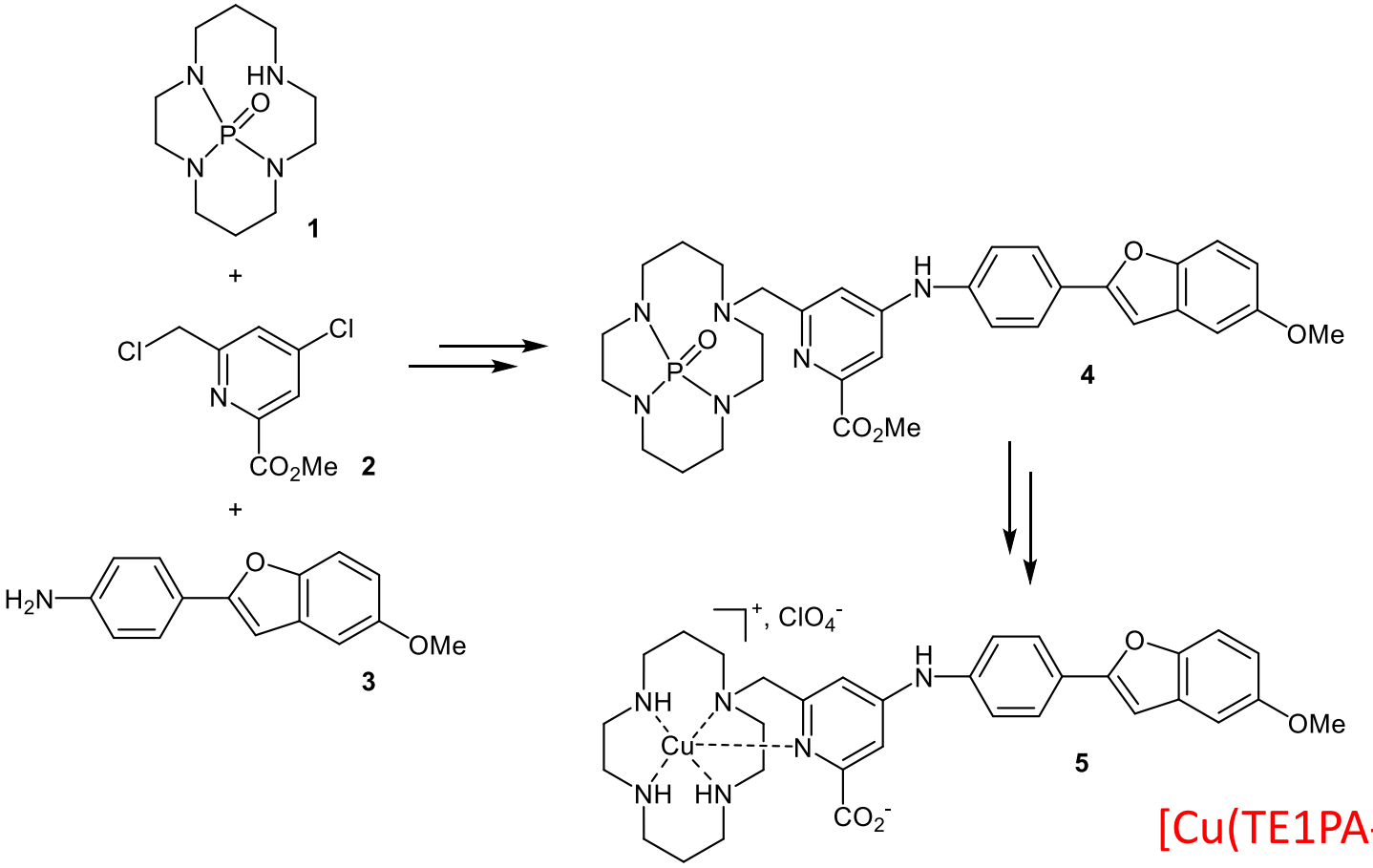
If the Log BB value is **greater than 0.3**, the compound may be able to cross the BBB and distribute to the brain

Our goal

Using the predictive models, we propose to design different molecules (ligands) that allow the synthesis of the corresponding copper complexes. These ligands have a part capable of chelating copper and another part capable of recognizing amyloid plaques



Synthesis

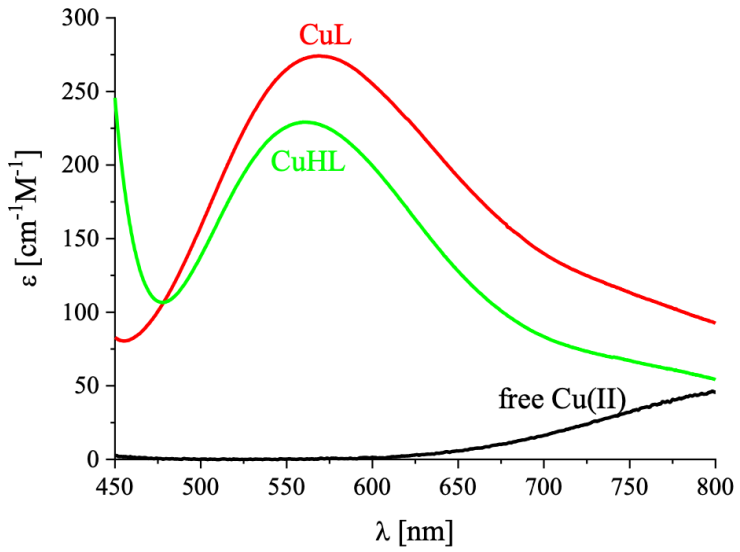


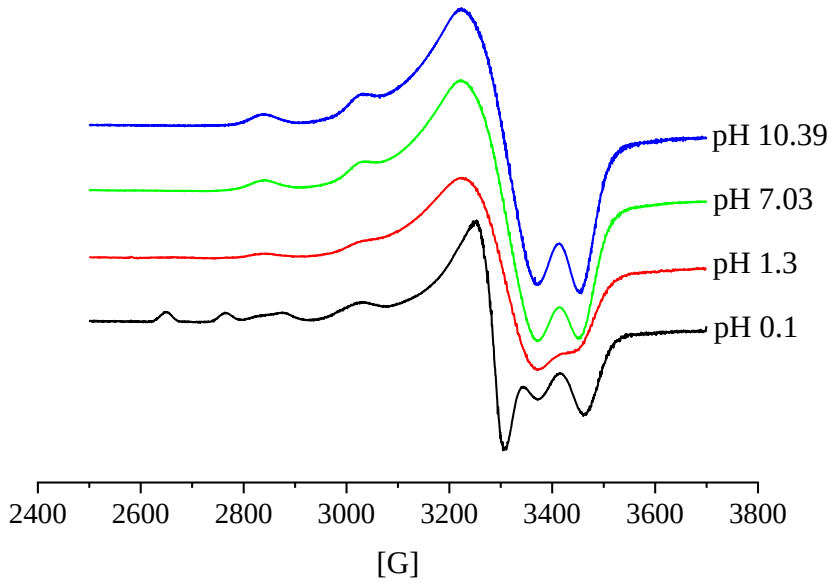
10 steps

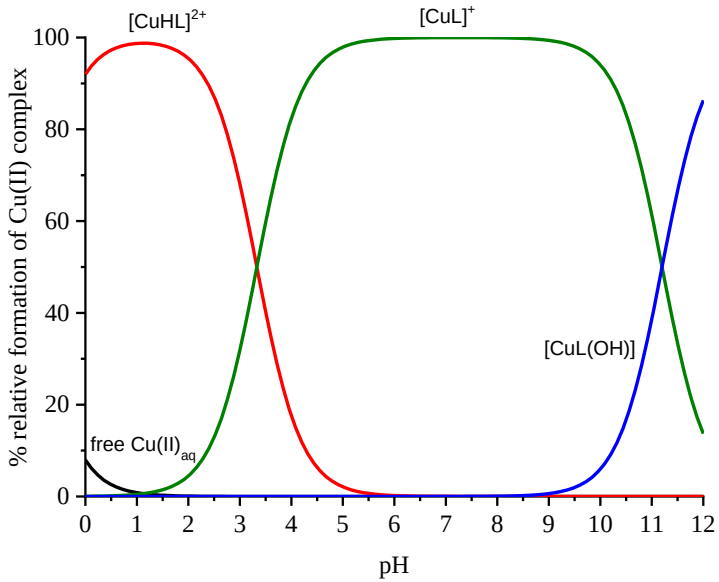
Dellal et al., 2023

Our strategy combines three building blocks: the protected cyclam 1, the picolinate derivative 2, and the 5-methoxy-2-(4-aminophenyl)benzofuran 3, which should be able to target amyloid plaques. The combination of these three fragments would yield the product 4. Finally, deprotection of the cyclam moiety of 4 and subsequent complexation with copper would yield the expected complex 5.

Physico-chemical characterization



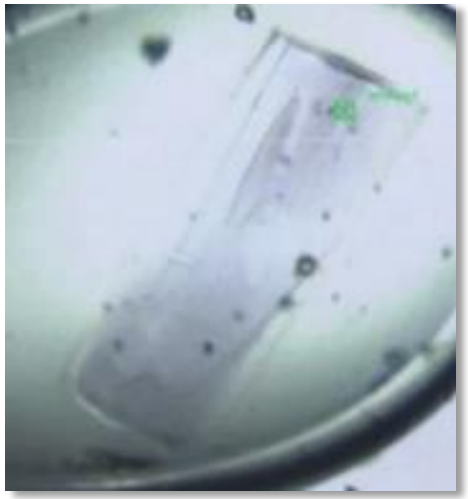


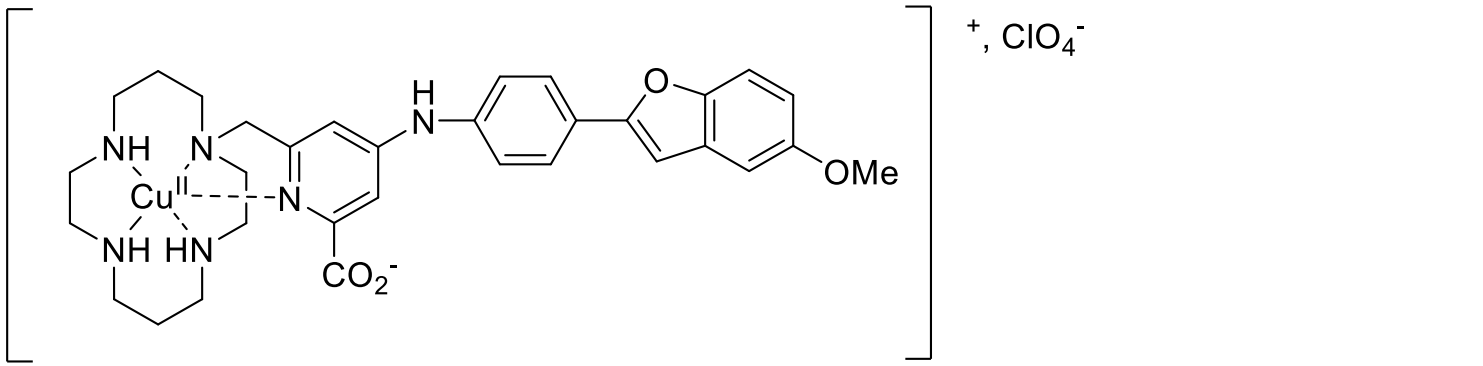


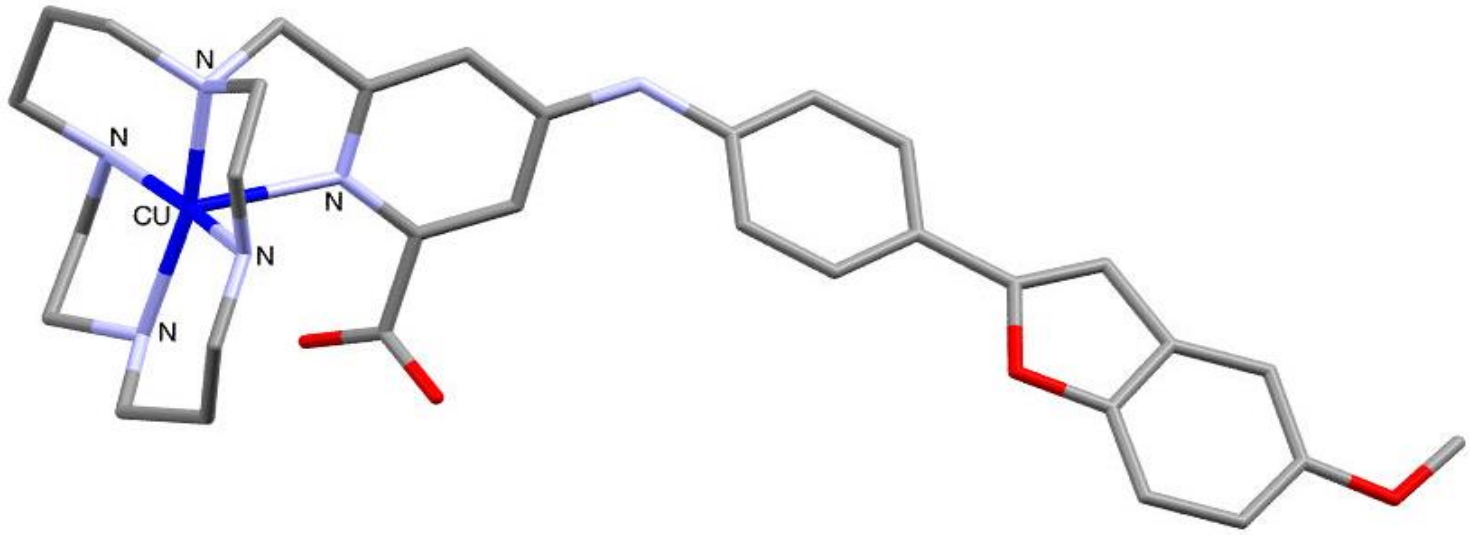
The studies in solution revealed the properties of [Cu(TE1PA-ONO)] + , highlighting its structure and thermodynamic stability.

Physico-chemical characterization

Crystallography

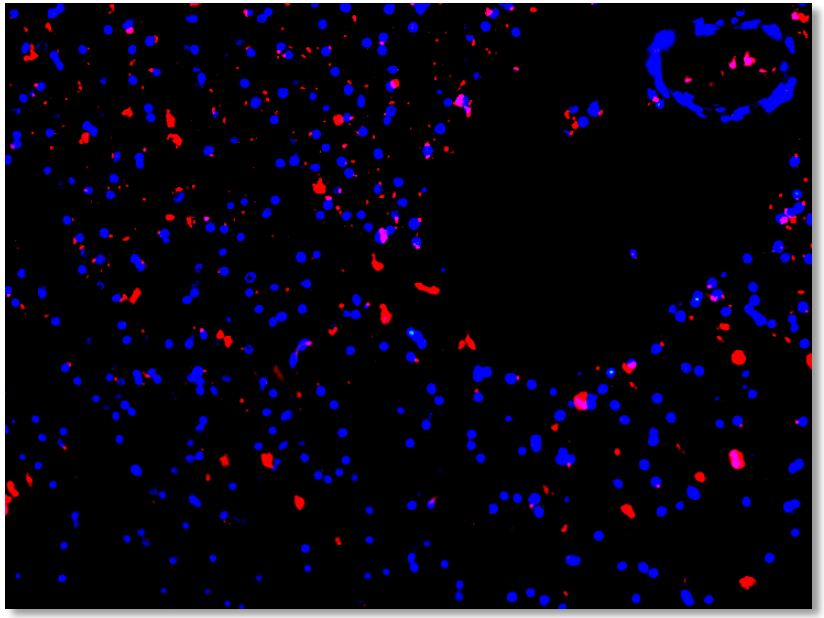




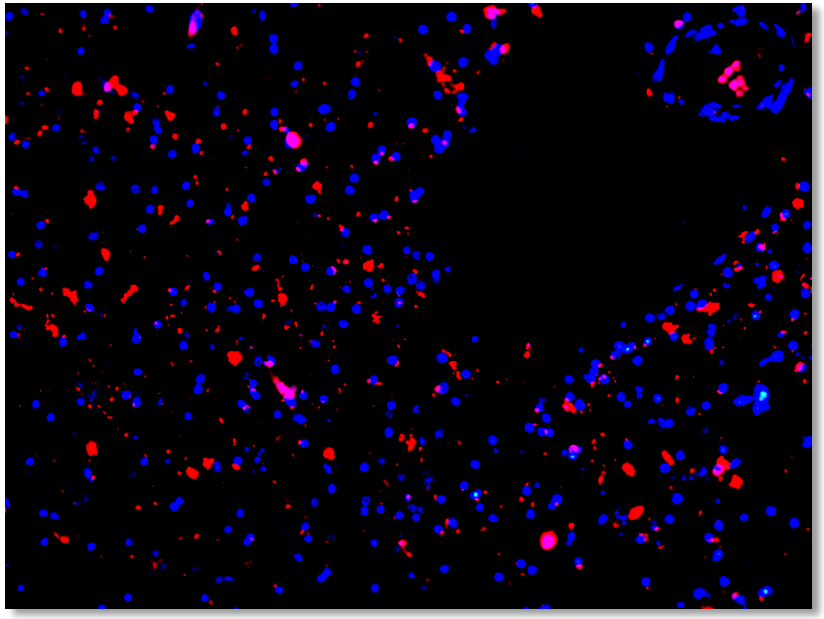


Labelling of amyloid plaques on brain sections of Alzheimer's disease patients

Anti-β amyloid



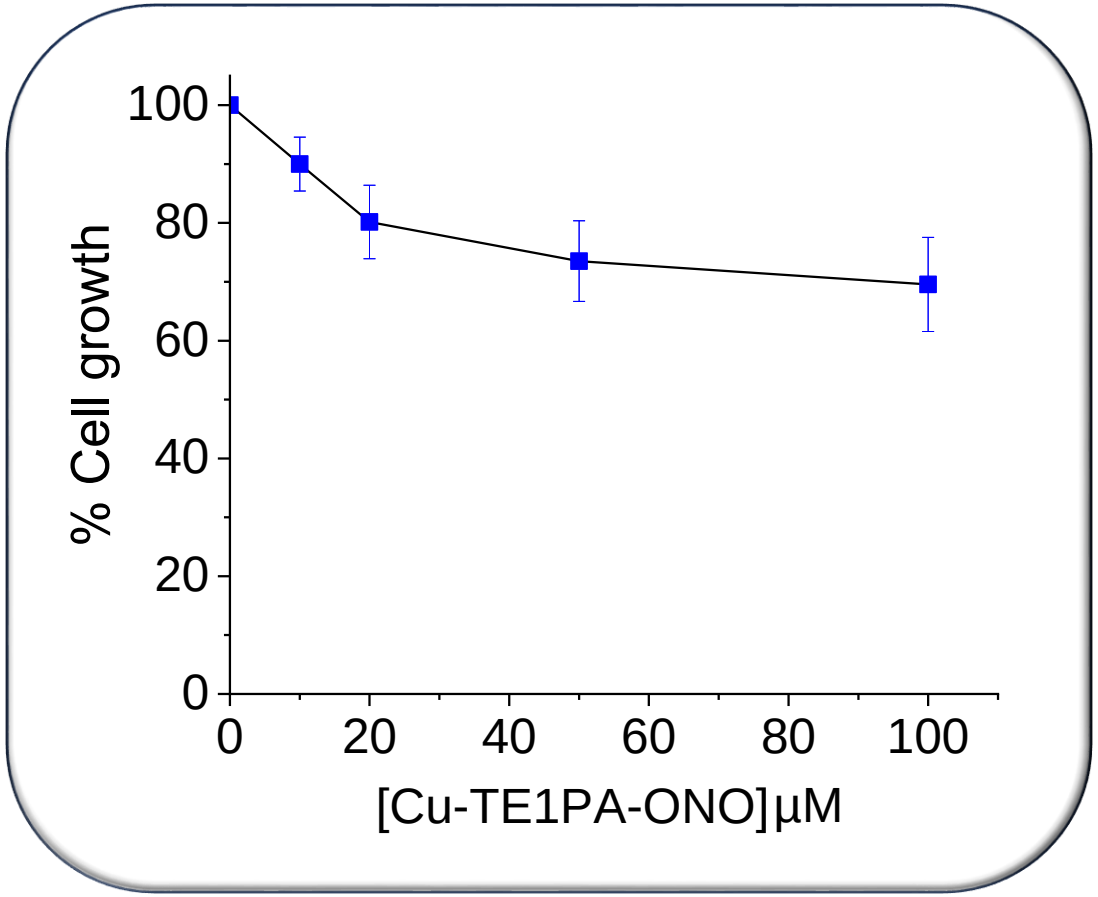
[Cu(TE1PA-ONO)]$^{+}$



Similar distribution and density of amyloid plaques were observed using anti-amyloid antibodies and [Cu(TE1PA-ONO)]$^{+}$ on brain sections, indicating that our copper complex could be used to detect beta amyloid deposits.

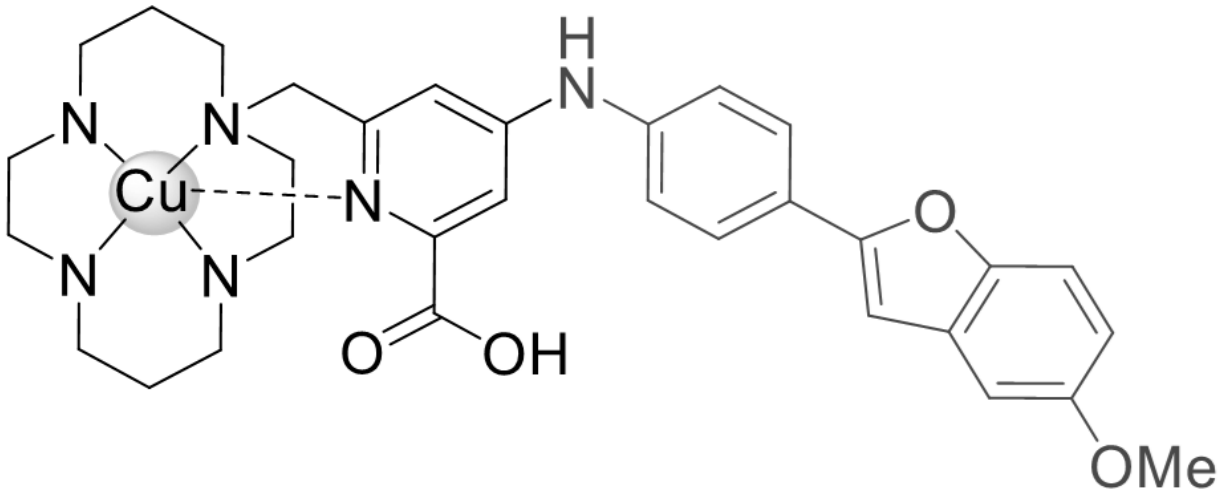
Cytotoxicity tests

- On human neuronal cells
- Incubation with the complex at different concentrations for 48 hours.
- Cellular growth is 70% after incubation with **[Cu-TE1PA-ONO]** at 100µM for 48h



Low toxicity towards neuronal cells

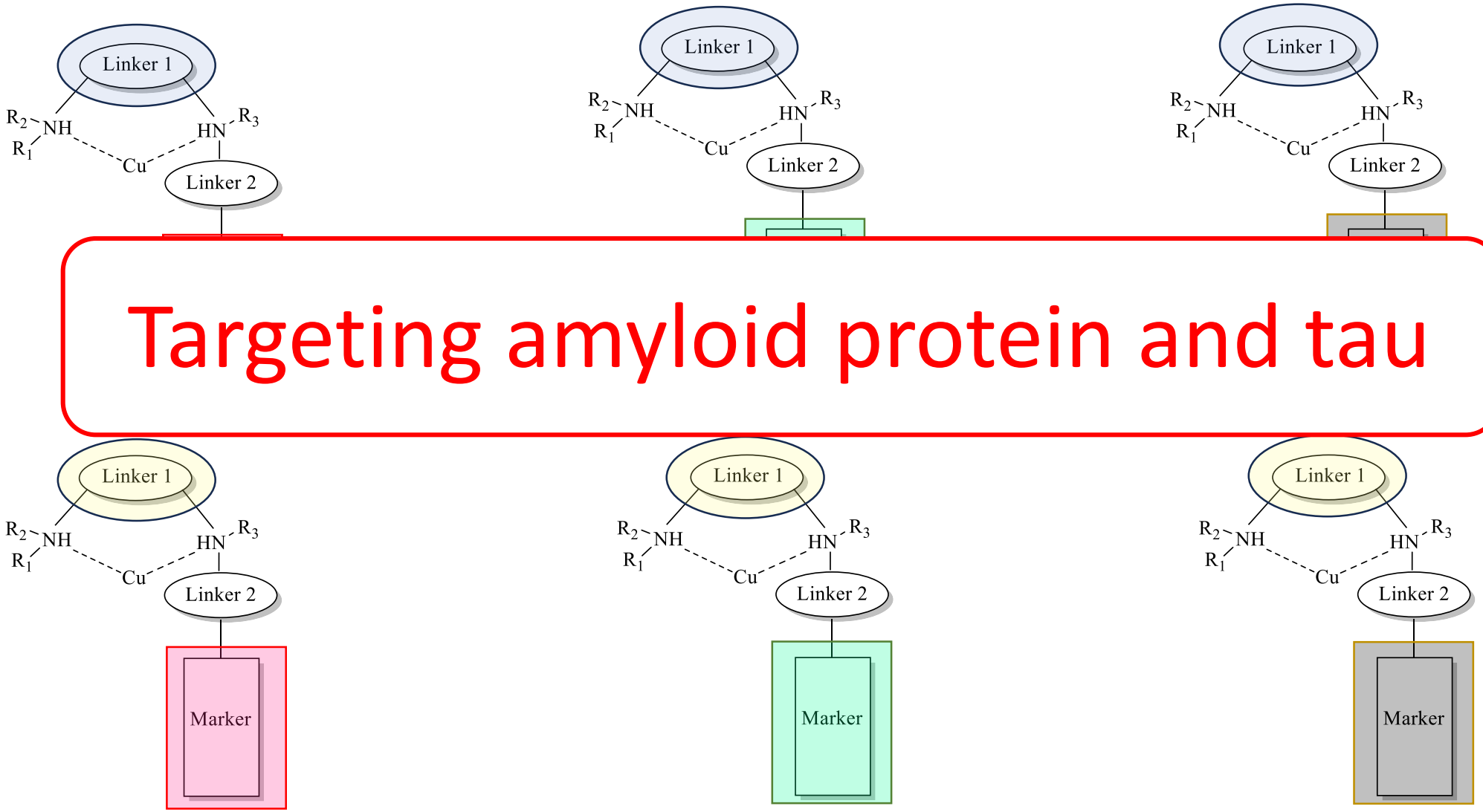
Conclusion



[Cu(TE1PA-ONO)]$^{+}$

Could open new perspectives for the development of new copper complexes with potential use in PET imaging to detect beta-amyloid plaques in the diagnosis of Alzheimer's disease

Ongoing work



Improve the specificity of the diagnosis of AD

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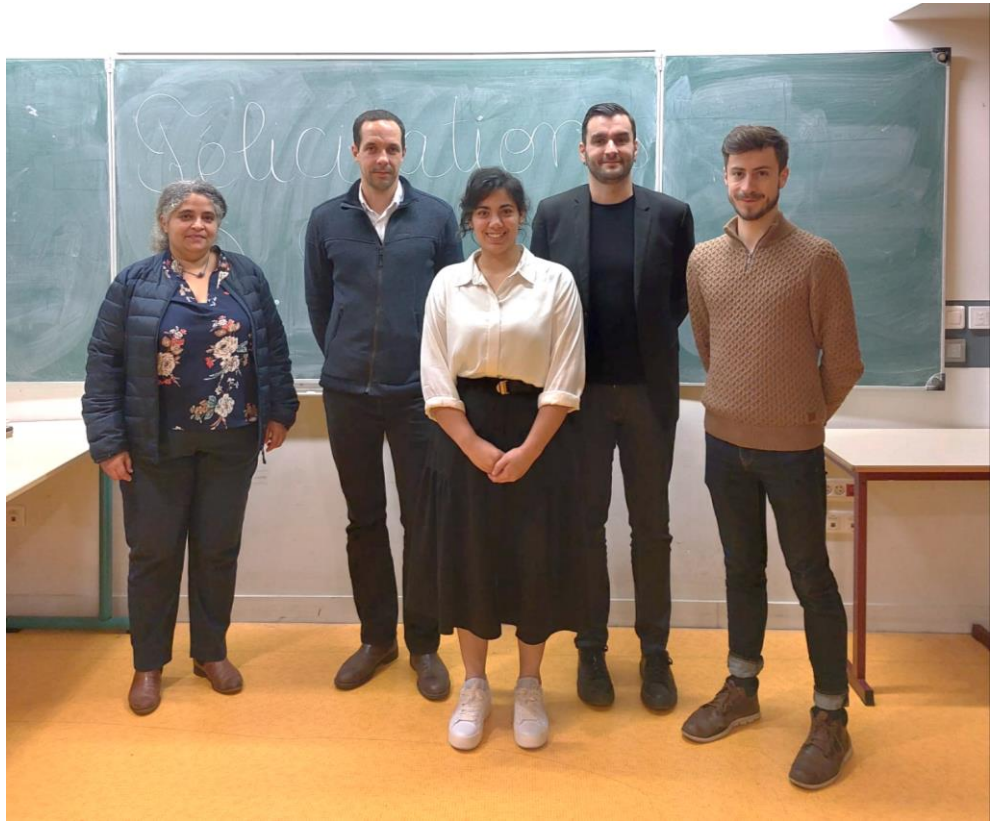

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