FrenchBIC Webinar

Cu(I)-targeting ligand in Alzheimer disease context

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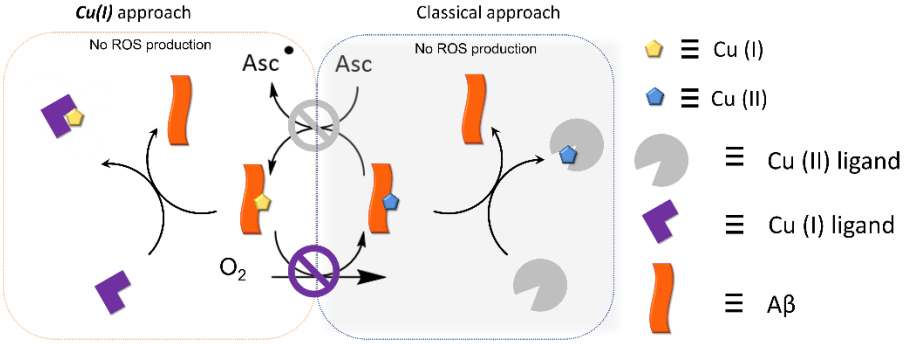
Alzheimer disease (AD) is the most common cause of dementia, affecting more than 30 million people in the world, characterized by a brain deterioration leading to difficulties with memory, behaviour, and thinking. According to the "amyloid cascade hypothesis" an abnormal amyloid deposits formation composed of amyloid-β peptides (Aβ), a 40-42 amino acids peptide, occurs in AD brain in extracellular locations at the early stage of the disorder.[1] Aggregation of Aβ is linked to an accumulation of the peptide induced by an imbalance between its clearance and its production. Due to the presence of a huge concentration of d-metal ions in the senile plaques (up to mM) and an overall disturbed metal homeostasis the role of metal ions in the disease has been widely studied.[2]

It has been shown over the last decade that Cu ions bound to Aβ is able to catalyze the production of reactive oxygen species (ROS) through incomplete reduction of dioxygen.[3, 4] This ROS production in assumed to be part of the enhancement of the oxidative stress found in AD brain that drive the disease. These findings led to the development of therapeutic approaches based on the chelation of Cu(II) with the description of a large number of ligands. Promising effects have been observed with different class of ligands such as hydroxyquinoline moieties, stilbene-like molecules, benzothiazole derivatives, macrocyclic and peptidic ligands.[5, 6] Nevertheless, until now, attempts to use Cu ligands in AD clinical treatment has failed.

Tow ways are possible to achieve the inhibition of the Cu-Aβ toxicity. One way, which has been largely developed, is to remove Cu(II) from Aβ leading to a Cu(II)-complex resistant to the reduction. The other way is to design ligands able to remove Cu(I) from Aβ and leading to a redox inert species.



Inhibition of Cu−Aβ*-induced ROS production either by the chelation of the Cu(II) by classical ligands (grey part), either by the chelation of the Cu(I) by Cu(I) ligand (violet part).*

The targeting of Cu(I) in the therapy by chelation approach is an emerging and promising idea as Cu(I) is the entity directly reacting with O_2.

Here we will present recent results obtained within the group that demonstrate the importance of the Cu(I) redox state when studying Cu ligand. The rational design of Cu(I) ligand fulfilling all the criteria to be a good ligand in AD context will also be presented.

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