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Metal Complexes that bind to the Amyloid-β Peptide of Relevance to Alzheimer's Disease

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Abstract:

Alzheimer's Disease (AD) is the most common form of dementia, and is a multi-faceted disease that is characterized by oxidative stress, metal-ion dysregulation, and the formation of intracellular neurofibrillary tangles of tau protein and extracellular amyloid-β (Aβ) aggregates. This review will focus on the interaction of metal complexes with the Aβ peptide, and how these interactions can modify the peptide aggregation pathway, oxidative stress, and overall toxicity of the Aβ peptide. While certain endogenous metal complexes such as heme can enhance toxicity, a large number of reports detail the potentially protective effect of discrete metal complexes in AD. These results will be discussed in the context of ligand design to target specific peptide residues for covalent binding, modulate peptide aggregation towards non-toxic species, and enhance blood brain barrier access. Additional features of metal complexes such as light-activated Aβ binding, catalytic antioxidant activity, and peptidase activity will be detailed.

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1. Introduction:

Neurodegenerative diseases (ND) are chronic and progressive disorders that share several common features, such as neuronal death in specific areas of the brain, synaptic damage and the accumulation of misfolded protein aggregates, causing memory and cognitive impairments, and eventually death.[1-3] Protein misfolding is common in ND, with genetic, neuropathological, cellular and biochemical studies supporting the theory that protein aggregation plays a role in these diseases.[4] Aggregation-prone proteins in NDs are: amyloid-β (Aβ) and tau in Alzheimer's disease (AD), α-synuclein (α-Syn) in Parkinson disease (PD), TAR DNA-binding protein 43 (TDP-43) in amyotrophic lateral sclerosis (ALS), and prion protein in prion disease (PrD). These proteins differ in function, sequence, expression level and size, however they have all been observed to misfold from their native state, forming intermolecular β-sheet-rich structures, which leads to a loss of protein function.[1, 2] These aggregates can vary from oligomeric species (ranging from dimers to larger protofibrils) to larger fibrillar structures, to which oligomers have demonstrated higher toxicity than the fibrillar structures in a number of diseases.[2]

Dementia is a process in which a ND leads to memory and cognitive decline, typically occurring above the age of 65, and in 2018 was estimated to affect 50 million people worldwide.[5] This number is expected to drastically increase over the next 30 years, reaching 152 million by 2050, in accordance with a global increase in life expectancy.[5, 6] AD is the most common form of dementia, representing 50-75% of the cases.[7] AD is classified as a proteinopathy and is characterized by the extracellular accumulation of Aβ aggregates (from oligomers to plaques) and intracellular formation of neurofibrillary tangles (NFTs) of tau.[8] The final diagnosis of AD requires *post-mortem* examination of the brain, however the development of molecular neuroimaging agents could allow for a diagnosis *ante-mortem*.[9] Positron emission tomography

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(PET) agents for the detection of amyloid are clinically available, such as ^{18}F-labelled tracers florbetapir, flutemetamol and florbetaben (**Figure 1**), however tau PET ligands are still in clinical development.[8] A number of metal-based diagnostic agents for AD have been reported, and this is a promising development due to the ability to tune the metal radionuclide decay properties to the pharmacokinetics of the imaging agent *vide infra*.[10-15]

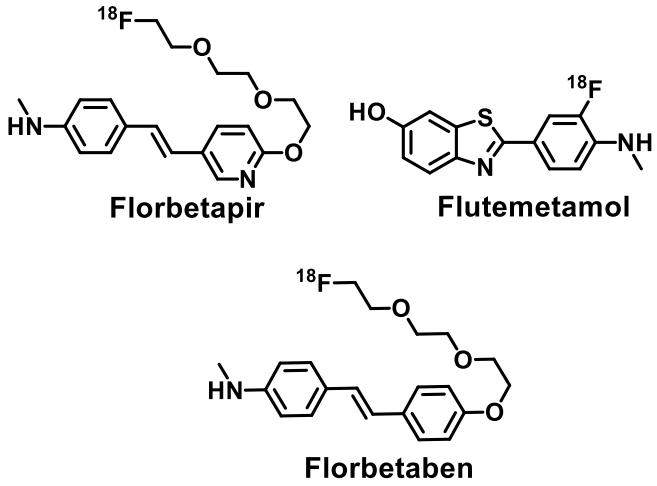

Figure 1: Structures of FDA-approved drugs for PET imaging of the brain (florbetapir, flutemetamol, florbetaben).

The FDA-approved drugs for treatment of AD are the acetyl cholinesterase (AChE) inhibitors donepezil, rivastigmine, and galantamine (**Figure 2**), and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (**Figure 2**). These drugs ameliorate the symptoms of the disease in its early stage, however disease modifying therapies could provide for a more effective approach for AD treatment.[14, 16-20] There are currently 64 agents in Phase II and 26 agents in Phase III clinical trials, to which 30% and 54% respectively are anti-amyloid (immunotherapy, β-secretase inhibitors and anti-aggregation) and 14% and 4% respectively are anti-tau

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(immunotherapy and anti-aggregation).[21] Efforts to develop new disease modifying therapies is of great interest for AD treatment.

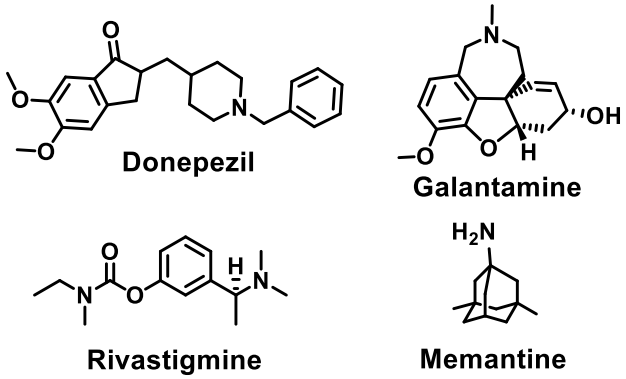

Figure 2: FDA-approved acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA antagonist memantine.

The Amyloid hypothesis has long been the dominant theory to explain the cause of AD, postulating that Aβ peptide oligomers and aggregates trigger a neurotoxic cascade in the brain.[20, 22-24] The Aβ peptide is a proteolytic cleavage product of the amyloid precursor protein (APP) by β- and γ-secretases, through the amyloidogenic pathway, producing fragments from 38 to 43 amino acids, forming in majority $A\beta_{1-40}$ (~90%) followed by $A\beta_{1-42}$ (~9%) (**Figure 3**).[25]

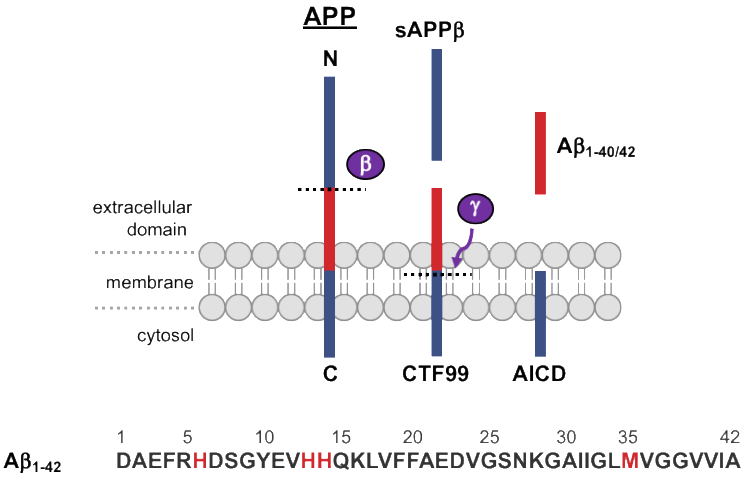

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Figure 3: Diagram of the transmembrane protein APP and the amyloidogenic pathway involving its cleavage by β- and γ-secretases producing $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides. The full amino acid sequence for $A\beta_{1-42}$ is also shown.

The APP protein can also be cleaved via a nonamyloidogenic pathway, when cleaved by α- and γ-secretases, forming products that have been hypothesized to have a role in brain development or in adult brain processes, such as synaptic plasticity and neurodegeneration protection.[26] Genetic mutations on the APP gene have been associated with higher production of $A\beta_{1-42}$ and are linked to early-onset familial AD.[27] A decrease in the level of $A\beta_{1-42}$ in the cerebrospinal fluid (CSF) was shown to be detected before the increase in tau and phosphorylated tau (P-tau),[8] supporting the hypothesis that Aβ plays a role in other brain processes leading to the disease.

Aβ monomers mostly exist as random coil structures, however, when these monomers fold to form α-helix and β-strand structures they can interact with other folded monomers *via* hydrophobic interactions. These interactions typically occur first at the hydrophobic C-terminal and/or at the self-recognition site (from Leu^{17} to Ala^{21}, **Figure 4**), leading to aggregate formation.[28-30] The Aβ peptide can be found in the brain in three general forms: membrane associated, aggregated and soluble.[31] Soluble, oligomeric Aβ species have been shown to have higher toxicity,[25, 31-34] and are better correlated with memory impairment and AD progression, leading to loss of dendritic spines and their synaptic connections.[28-30, 35] In addition, metal-ions such as Fe, Cu and Zn, have been shown to interact with the Aβ peptide, modulating its aggregation and increasing toxicity (**Figure 4**).[36]

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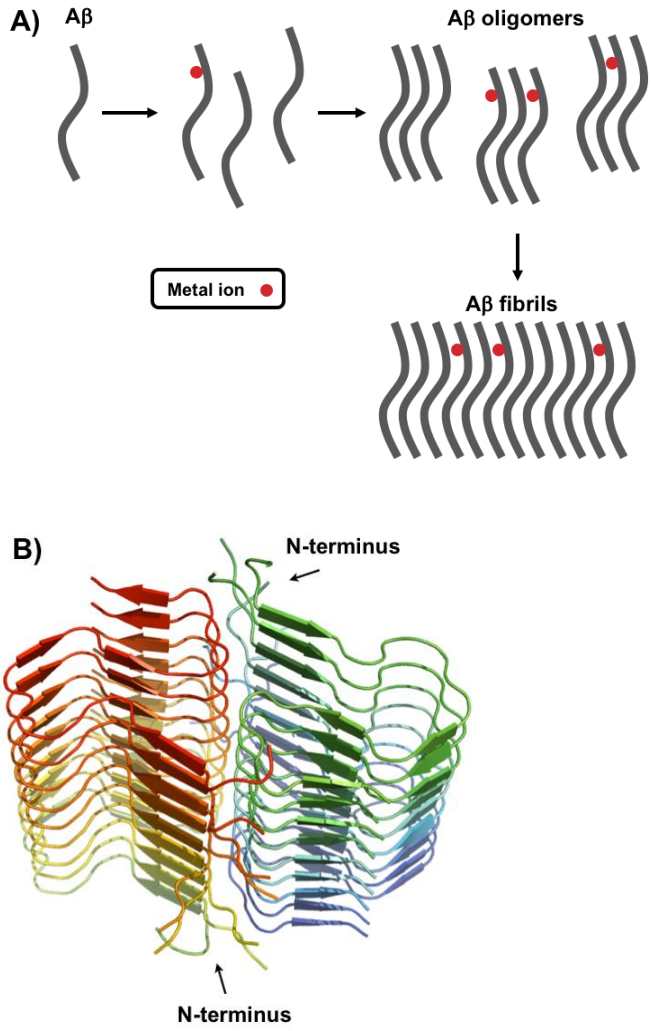

Figure 4. A) The aggregation process of the Aβ peptide including metal-ion interactions. **B)** Structure of $A\beta_{1\text{-}42}$ fibrils (PDB 5KK3) showing the 15-42 core structure and unstructured N-terminus (residues 1-14).

Metal-ions such as Fe(II/III), Zn(II), Cu(I/II), Mn(II), Mg(II) and Ca(II) are essential for the functioning of critical processes in a healthy brain.[37] These biologically relevant metal-ions are tightly regulated in a healthy individual, however, an imbalance in their homeostasis can affect brain function. Metal dyshomeostasis can occur by disruption in the transport/utilization and/or the absence of specific metal binding proteins, and is observed in a number of ND.[38, 39] Amyloid plaques have been described as ‘metallic sinks’ on account of the remarkably high

concentrations (3-5 times when compared to aged-matched controls) of Cu (0.4 mM), Fe (0.9 mM), and Zn (1.0 mM) found within these deposits in AD brains.[36, 40-45] A nuclear magnetic resonance (NMR) solution structure of the $A\beta_{1-40}$ peptide (**Figure 5**) shows the metal-binding amino acid (aa) side-chains in the N-terminus, the central hydrophobic region (aa 17-21), and easily oxidized Met^{35} that are important to metal-ion binding, aggregation and biomolecule oxidation. The three Aβ His residues (His^6, His^{13} and His^{14}) are involved in the coordination of metal-ions, with dissociation constants (K_d) of ~10^{-10} M for Cu(II) and ~10^{-5} M for Zn(II).[46-51] Furthermore, residues Asp^1, Tyr^{10} and Glu^{11} also play a role in the binding of Aβ to Cu(II) and Zn(II).[52-55] Fe is typically found in the brain as naturally occurring iron porphyrins (heme, 95% of all Fe) or bound to biomolecules, such as ferritin.[56] Interestingly, depletion of complex IV (cell enzyme containing heme-a) occurs due to the binding of heme-a to Aβ in the brain of AD patients.[57] The binding of Cu(II) to Aβ depends on the pH of the solution, and at a pH lower than 7.8 the majority Cu(II) is bound to two His and Asp^1 (component I), while higher pH leads to the loss of one His and binding of a deprotonated amide (Ala^2) (component II) (**Figure 5**).[58]

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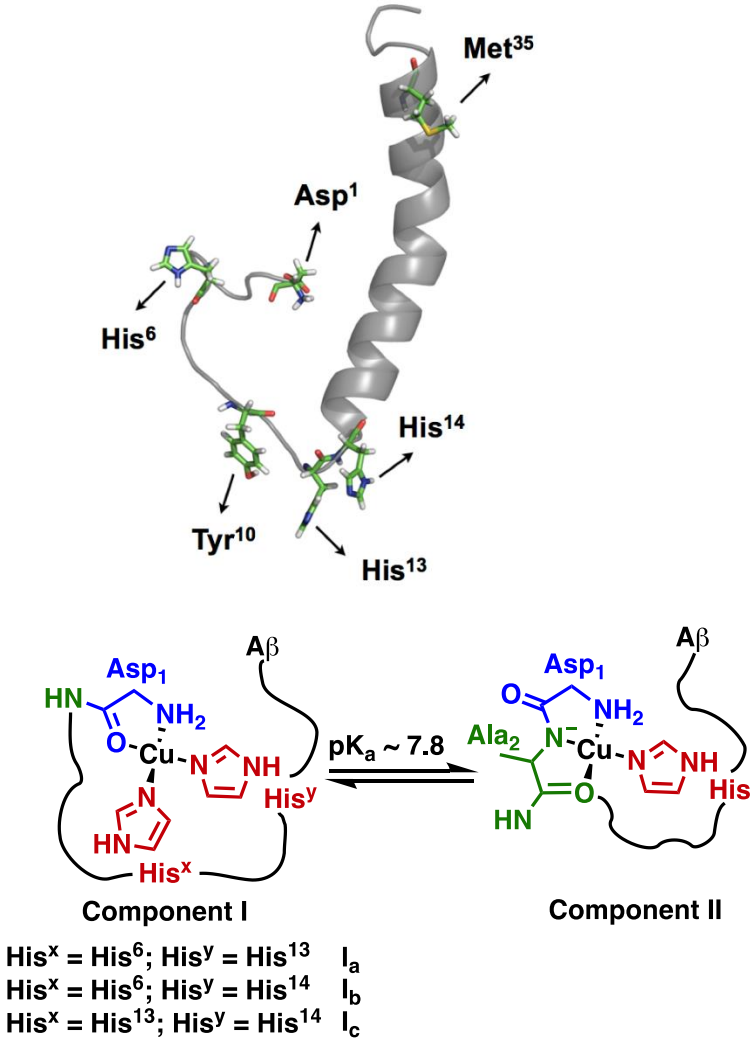

Figure 5. (Top) Solution structure of monomeric $A\beta_{1-40}$ (PDB 1BA4) showing the hydrophobic region and amino acid side-chains involved in metal-ion binding and peptide oxidation. (Bottom) Representation of Component I (Ia, Ib, Ic) and Component II, the two major pH-dependent Aβ-Cu(II) binding modes (modified from Borghesani *et al*, 2018).[58]

Metal-ion coordination to Aβ modulates its aggregation pattern, and potentiates the neurotoxicity of Aβ *via* redox-cycling and the production of ROS in the presence of dioxygen, playing an important role in oxidative stress.[47, 48, 59-68] The Aβ-Cu(II) complex generates ROS, such as $O_2^{\bullet-}$, H_2O_2 and $^{\bullet}OH$ by reducing O_2 in the presence of cholesterol and vitamin C.[69-

75] Due to the metal-ion dyshomeostasis observed in AD and the involvement of these metal-ions in protein aggregation, it is hypothesized that metal-ion dysregulation plays a significant role in AD development.[39] Two approaches for the prevention of metal-ion binding to Aβ are (1) to use ligands that can bind to Cu, Fe, and Zn,[76-78] and (2) discrete metal complexes that target Aβ peptide metal-binding residues and/or peptide aggregation. The latter approach will be discussed in this review.

This review will focus on the interaction of metal complexes with the Aβ peptide, and how these interactions can modify the peptide aggregation pathway, oxidative stress, and overall toxicity of the Aβ peptide. The use of metal complexes in medicine has many potential advantages in comparison to organic-based agents, and the development of the anticancer agent cis-platin (*cis*-$[Pt(NH_3)_2Cl_2]$) brought this field into the mainstream.[79] There are currently many metal-containing compounds with therapeutic potential, and metal complexes can interact with proteins and nucleic acids in unique ways in comparison to organic compounds, restoring function that was lost due to misfolding or introducing a new function not found naturally.[80-82] The general subject of metal complexes in the context of AD has been reviewed by other research groups, and we have chosen to only briefly discuss metal-based diagnostic agents as this area has been recently reviewed.[14, 28, 83-87] The aim of this article is to provide an up-to-date account of the field, with a focus on the interaction of discrete metal complexes with the Aβ peptide.

2. The Interaction of Metal Complexes with the Aβ Peptide

The design of metal complexes that interact with specific proteins related to ND has primarily focused on the Aβ peptide in AD.[83-86] A number of research groups have explored the interaction of discrete metal complexes with Aβ, including complexes of V, Mn, Re, Fe, Ru,

Co, Rh, Ir, Pt, and Cu. These complexes have been shown to interact with either monomeric or aggregated forms of the Aβ peptide, and modify peptide aggregation and toxicity in cells and animal models. **Table 1** details common characterization methods used to investigate the interaction of metal complexes with the Aβ peptide. The following sections will detail reported metal complexes, in the order of Group 5 to Group 11 transition metal ions.

Table 1. Example experimental and theoretical techniques used to study the interaction of metal complexes with the Aβ peptide.

Technique	**Readout**
Nuclear Magnetic Resonance (NMR)	Shift or broadening of specific peptide residue resonances due to binding. Shift in metal resonances (e.g. ^{195}Pt) with peptide interaction.
Electron Paramagnetic Resonance (EPR)	Changes in g-values/hyperfine with Aβ - metal complex interaction, shift in g-values/hyperfine for Cu-Aβ with metal complex interaction.
Mass Spectrometry	Metal complex – peptide adduct formation, MS-MS to determine specific binding residues.
Fluorescence	Peptide interaction in solution – interaction of metal complexes with Aβ aggregates in tissue samples etc.
Light Scattering	Changes in Aβ aggregate size in solution in the presence of metal complexes, changes in aggregation profile.
Thioflavin T fluorescence	Aβ fibrillization in the presence of metal complexes. Note many metal complexes interfere with this assay and thus alternate readouts are recommended.
Atomic Force Microscopy (AFM) and Transmission Electron Microscopy (TEM)	Changes in Aβ aggregate size and morphology in the presence of metal complexes.

Circular Dichroism (CD)	Changes in Aβ secondary structure and aggregation process in the presence of metal complexes.
X-ray Absorption Spectroscopy (XAS)	Binding of metal complexes to the Aβ peptide, identification of ligands bound to metal center.
Theoretical Calculations	Metal complex binding/interactions with the Aβ peptide, changes in folding in the presence of metal complexes via molecular dynamics.

2.1 Vanadium complexes: There are limited reports of the interaction of vanadium complexes with the Aβ peptide, with one recent publication detailing the use of a V(V) peroxo complex $[VO(O_2)_2(bipy)]^-$ (bipy = bipyridine, **Figure 6**) to reduce Aβ peptide fibril formation via Met-35 oxidation.[88] The atomic resolution structure of amyloid fibrils (**Figure 4**),[29, 30] highlights the importance of the Met-35 residue in fibril formation, and therefore targeted oxidation of this residue likely provides a selective method to limit fibril formation. The same group has also reported a similar strategy for modifying the aggregation of the prion protein,[89] and human islet amyloid polypeptide.[90]

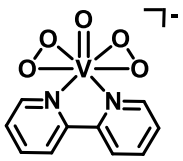

Figure 6: Structure of the $[VO(O_2)_2(bipy)]^-$ complex.

2.2 Manganese Complexes: Manganese is an essential trace element used as a cofactor for many enzymes and is important in processes that support development, growth and neuron function.[91] However, overexposure to Mn may induce neurotoxicity and contribute to neurodegeneration. A recent study by Hureau *et al.* investigated the use of a Mn superoxide dismutase (SOD) mimic (**Figure 7**) to target the Cu-induced formation of ROS and modulate Aβ aggregation.[92] The Mn complex was shown to remove Cu(II) from Aβ, reduce ROS, and prevent Cu-dependent peptide aggregation. The aforementioned activity of the Mn complex is due to metal exchange with Cu(II), thus sequestering the Cu(II) while releasing the Mn(II) from the complex. The Mn(II) complex was shown to be less toxic in comparison to the free ligand, and in addition the Mn complex exhibits SOD activity. This pro-drug strategy may be applicable to the use of Zn complexes to improve compound bioavailability which then undergo a similar transmetallation with Cu(II) in the brain.

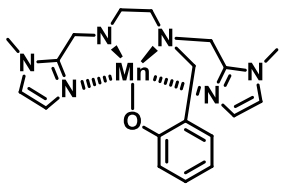

Figure 7: Mn(II) SOD complex the undergoes transmetallation with Cu(II) to limit Cu-induced ROS and Cu-Aβ interactions.

2.3 Re Complexes: A large number of Re complexes targeting Aβ-aggregates have been reported, and these studies have provided key information on the peptide aggregation process via luminescence, and for the development of ^{99m}Tc analogues for diagnostic imaging of AD.[12-14, 83, 93, 94] ^{99m}Tc is the most widely used radioisotope in nuclear medicine as it is readily obtained,

decays by emission of a γ-ray of suitable energy for imaging, and the 6 hour ½ life is compatible with biological localization. The development of an Aβ plaque imaging agent based on the ^{99m}Tc isotope would be of great benefit, providing the medical community with an easily accessible radiodiagnostic for AD.

Due to the fact that there are no stable isotopes of technetium, stable isotopes of the third row congener rhenium are used to characterize metal complex stability and *in vitro* binding. While this review does not focus on diagnostic imaging agents, it is important to highlight the development of Re complexes as this provides important insight on the design features for optimal binding to Aβ aggregates, and also blood brain barrier (BBB) access. Example metal synthons include both the $[Re^{V}O]^{3+}$ and $[Re^{I}(CO)_3]^{+}$ cores as these are easily amendable to ^{99m}Tc radiotracer chemistry. For the $[Re^{V}O]^{3+}$ core, N_2S_2 donor ligands such as bis(aminoethanethiol) (BAT) and monoamine-monoamide dithiol (MAMA) have been used extensively as these provide a stable and overall neutral metal chelate. Examples are shown in **Figure 8**, in which both chelates can be attached to amyloid-targeting moieties such as substituted benzothiazole or benzofuran. In one example with the BAT chelate, the targeting moiety with R = NMe_2 (**Figure 8**) showed significant brain uptake, and Aβ-plaque binding in a Tg2576 mouse model.[95]

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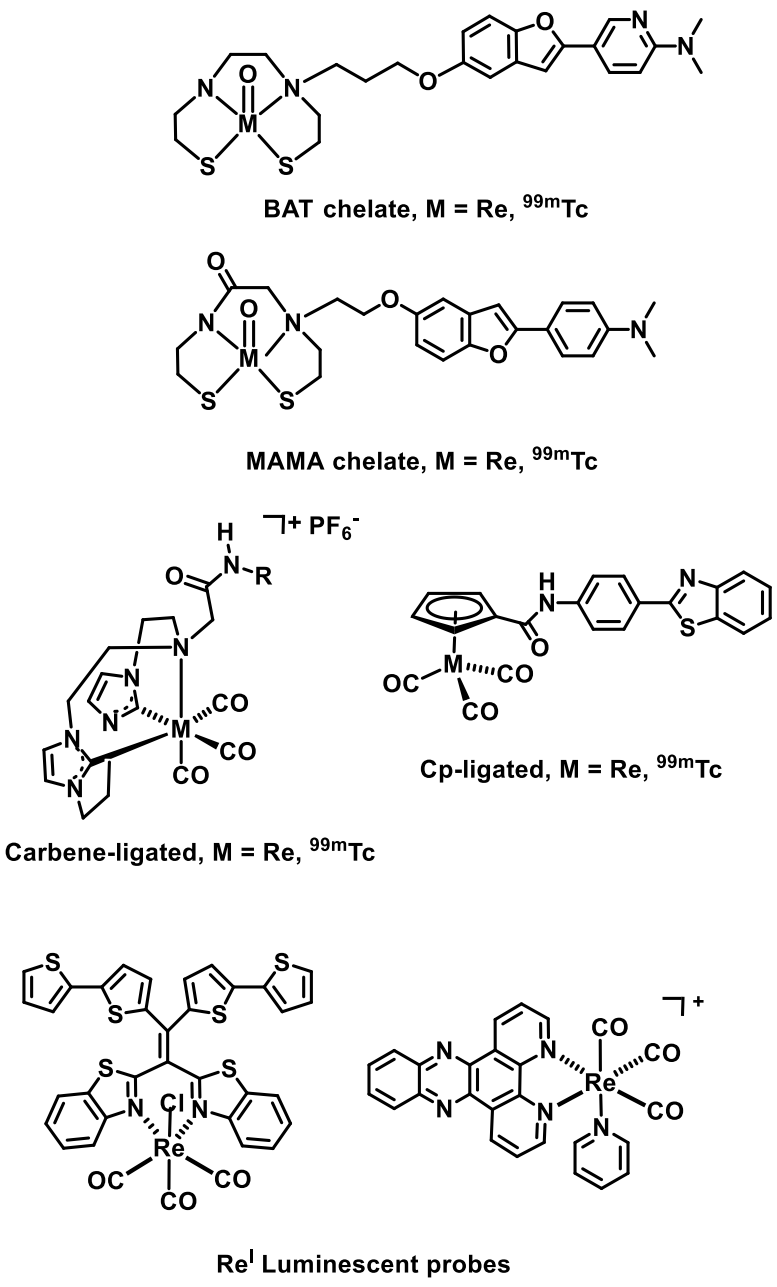

Figure 8: Example Re complexes that bind to Aβ-aggregates and act as cold surrogates for diagnostic imaging with ^{99m}Tc and/or luminescent probes.

While the bulk of the Re chemistry has focused on the $[Re^{V}O]^{3+}$ core, the low-valent $[Re^{I}(CO)_3]^{+}$ is an attractive alternative due to the stabilization afforded by the *fac*-CO ligands, and the development of a one-pot ^{99m}Tc radiolabelling protocol using sodium boranocarbonate as a

reducing agent and in situ source of carbon monoxide to form $[^{99m}Tc^{I}(CO)_3(H_2O)_3]^+$ from the pertechnetate ($[^{99m}Tc^{VII}O_4]^-$) starting material.[96, 97] Complex stability is generally maximized by using a tridentate ligand bound to the $[Re^{I}(CO)_3]^+$ core, and one recent example by Barnard and Donnelly *et al.* utilizes a bifunctional bis-N-heterocyclic carbene amine ligand with an attached stilbene moiety.[98] The resulting Re complex (**Figure 8**) was shown to bind to Aβ-plaque in human AD brain tissue via co-localization with the anti-amyloid-β antibody IE8. An alternative strategy is to employ a substituted cyclopentadienyl (Cp) capping ligand to form stable complexes of the $[Re^{I}(CO)_3]^+$ core.[99] One recent example by Pelecanou *et al.* connects a phenylbenzothiazole moiety to the Cp ligand via amide coupling, and the resulting Re complex (**Figure 8**) was shown to selectively stain Aβ-plaques in AD brain tissue sections.[100] Overall, the development of an FDA-approved ^{99m}Tc-derived Aβ-plaque imaging agent would be of significant benefit for the early detection of AD, and the staging of the disease for treatment.

The use of Re complexes as luminescent probes for Aβ aggregates has been reported by a number of research groups, both in the development of ^{99m}Tc imaging agents, and as stand-alone complexes for the identification of aggregates and light-induced peptide oxidation. As an example, Pigge *et al*. developed a Re tricarbonyl complex with pendant thiophene moieties (**Figure 8**) that displayed a 34-fold enhancement in luminescence, and a red-shift in emission wavelength, upon binding to Aβ aggregates.[101] Marti and co-workers developed a Re tricarbonyl complex with a dipyridophenazine (dppz) ligand that shows a large increase in photoluminescence upon binding to Aβ aggregates, and significant peptide oxidation.[102] Further work with this complex has elucidated the peptide binding location that is in close proximity to the place of oxidation.[103]

2.4 Fe Complexes:

2.4.1 Fe porphyrins: Most of the focus on iron complexes and their influence on the process of AD has centred on naturally occurring iron porphyrin complexes.[104, 105] Increased production of heme-a and heme-b (**Figure 9**) has been observed in the brain of AD patients, while there is depletion of complex IV (cell enzyme containing heme-a) due to the interaction of free heme with Aβ.[57] Several studies have shown that heme binds to Aβ leading to a red-shift in the heme Soret band.[57, 106, 107] In one of these studies, different mutants as well as different fragments of the Aβ peptide were incubated with heme in order to determine which residues are involved in the binding among His^{6}, $His^{13/14}$ or Tyr^{10}.[107] The single $Tyr^{10}Gly$ mutant of $A\beta_{1-16}$ (**Figure 10**) showed a red-shifted Soret band indicating binding, while the spectrum of fragments or mutants of Aβ without His residues were the same as heme alone, suggesting that His is essential for binding of heme to Aβ. For the double mutants that contained only one His, either 13 or 14, a similar change in the spectra was observed when compared to wild type Aβ, however the mutant that only contained His^{6} showed no significant change in the spectrum, suggesting that binding in the heme-Aβ complex is likely to occur at either His^{13} or His^{14}. In a different study, residues Phe^{19} and Phe^{20} were shown to be important for the interaction between the peptide and heme.[108] These studies also showed that the heme-Aβ complex acts as a peroxidase, with higher activity in comparison to heme alone. Interestingly the $A\beta_{10-20}$ fragment (**Figure 10**), even though it shows similar binding in comparison to $A\beta_{1-16}$ and $A\beta_{1-40}$, exhibited the same peroxidase activity as heme alone, suggesting that a residue in the 1-9 region must be involved in the peroxidase activity of the complex.[69] Acidic Arg residues have been shown to be present in the active site of the peroxidase enzyme and to play a crucial role in the activity.[109, 110] In fact, rodent Aβ (that

differs from human Aβ in the amino acids Arg^{5}Gly, Tyr^{10}Phe and His^{13}Arg (**Figure 10**) has been shown to bind less effectively to heme than human Aβ, with little to no change in the peroxidase activity when compared to heme alone.[111] However, it is important to note that even though the catalytic activity of heme-Aβ (0.042 s^{-1}) is higher than that of heme alone (0.01 s^{-1}), it is still very low when compared to that of HRP (45.5 s^{-1}).[112] The heme-Aβ complex was also shown to have increased pronitrative activity in NO_2-H_2O_2 dependent enolase nitrotyrosination, which could lead to impairment of protein function.[112, 113]

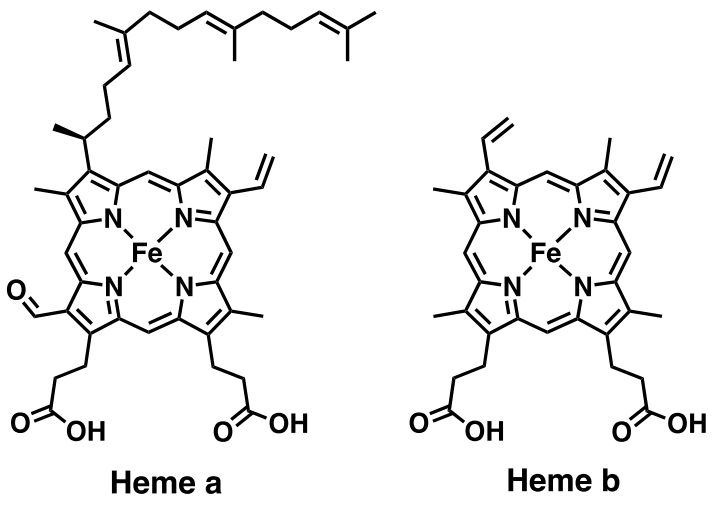

Figure 9. The structures of heme a and heme b.

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Figure 10. Full sequence of human and rat Aβ (hAβ and rAβ) highlighting the aa that differ, and the single and double mutants of $A\beta_{1\text{-}16}$.

Heme was also shown to change the aggregation pattern of Aβ with a decrease in Thioflavin T (ThT) fluorescence, and formation of smaller fibrils as shown by transmission electron microscopy (TEM).[106, 108] Both heme and Cu are known to bind to Aβ, and are found co-localized in Aβ plaques. Thus the concurrent binding of both Cu and heme to the peptide was investigated.[69] The absorption features of Aβ bound to both heme and Cu(II) were identical to Aβ bound to heme only, while EPR demonstrated that both the Cu and the heme were bound to the peptide with no observable interaction between the two metal centers. Interestingly, the electrochemical properties of the heme-Aβ-Cu species matched the individual Cu and heme Aβ complexes, and the peroxidase activity of the heme-Aβ-Cu species was similar to that of the heme-Aβ. Dey *et al.* concluded that under physiological conditions both heme and Cu(II) could be bound to Aβ, and both species have biologically-accessible redox responses that could generate ROS and

associated oxidative stress. Interestingly, the same group has recently reported that heme-bound Aβ-peptide forms compound I (Fe(IV)-oxo porphyrin radical), and that this potent oxidant is likely responsible or the oxidative degradation of neurotransmitters.[114]

2.4.2 Fe Complexes as Therapeutics: A series of chiral metallosupramolecular iron complexes (**Figure 11**), have been investigated for their ability to bind and limit aggregation of Aβ.[115] The compounds were found to bind to the peptide, with the *S* enantiomer for **Fe1** and *R* enantiomer for **Fe2** showing increased interaction with the peptide. An NMR study of the complex **Fe2**, showed a significant shift in the signal for residues Phe^{19} and Phe^{20} (present in the hydrophobic self-recognition region responsible for peptide-peptide interactions),[28] suggesting π-π interactions between the complex and the peptide. Interestingly the NMR shifts differed among the enantiomers, suggesting shape-specific interactions. Atomic force microscopy (AFM), a ThT assay and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) showed that complexes **Fe1** and **Fe2** led to a decrease in peptide aggregation. In addition, the complexes acted as SOD mimics and ROS scavengers. The complexes were shown to limit the toxicity of Aβ in PC12 cells in a concentration-dependent manner, with an enhanced effect observed for derivatives exhibiting a stronger interaction with the peptide. Finally, in an *in vivo* study, the complexes were shown to cross the BBB, exhibiting potential as therapeutics for AD.

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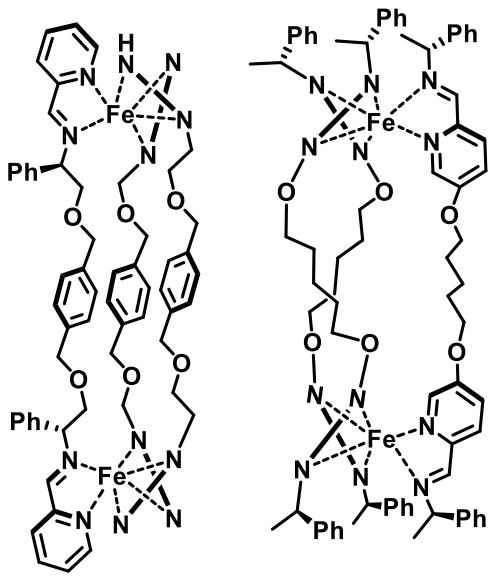

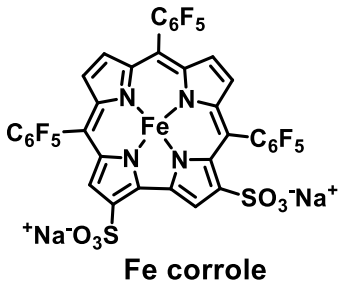

Figure 11. (a) The structure of chiral metallosupramolecular iron complexes (**Fe1** and **Fe2**; note not all Py groups drawn for clarity), and (b) a Fe corrole catalytic antioxidant.

Recently, we reported the Aβ-peptide binding and catalytic antioxidant activity of an Fe corrole complex (**Figure 11**).[116] This complex has been previously reported by Gross *et al.* to exhibit exceptional catalase and superoxide dismutase activity,[117, 118] and this activity is maintained when bound to an axial His (and albumin). The Fe corrole complex also binds to and protects cholesterol-carrying lipoproteins from oxidative stress; and oral administration of this

compound to a mouse model of atherosclerosis leads to a decrease in atherosclerotic lesions.[119] The Fe corrole complex was determined to have moderate affinity for the Aβ peptide ($K_D \sim 10^{-7}$), binding via a His residue to form a 5-coordinate complex, and limit aggregation of the peptide in solution. The higher stability of the 5-coordinate mono-axial ligated Fe(III)-corrole, in comparison to the 6-coordinate bis-axial coordinated species, is opposite to that for Fe(III) porphyrins.[120-122] Upon bis-axial ligation Fe(III) porphyrins gain more crystal field stabilization energy (CFSE) as they transform from high-spin to low-spin, while Fe(III) corroles only transform from intermediate-spin to low-spin.[121, 122] Additional EPR and ESI-MS experiments showed that the Fe corrole complex did not compete with Cu ($K_D \sim 10^{-10}$) for binding, and both Cu and the Fe corrole could bind to the Aβ peptide simultaneously. This result is similar to that reported by Dey *et al.* for Fe porphyrins.[69] Interestingly, the Fe corrole maintains its exceptional antioxidant activity when bound to the Aβ peptide, limiting the generation of peroxide and the hydroxyl radical from Cu-Aβ. Further work is on-going with this complex to determine therapeutic potential in cell models.

2.5 Ru Complexes: The interaction of Ru complexes with the Aβ peptide have highlighted the key role of ligand design in peptide binding and associated toxicity. In general, Ru compounds are considered to be less toxic in comparison to Pt compounds, and were thus attractive candidates for further development in AD.[123] Valensin *et al.* first reported a *fac*-$[Ru(CO)_3Cl_2(N^1\text{-thz})]$ complex (**Figure 12**) that selectively targeted His residues on Aβ.[124] Peptide adducts were confirmed using ESI-MS, with selective His ligation determined from NMR experiments. Further testing of the anticancer candidates PMru20, NAMI-A and KP1019 (**Figure 12**) showed that the

axial ligands had a significant effect on the biological properties.[125] PMru20 was determined to limit Aβ aggregation to the greatest extent, and in addition protected rat cortical neurons from both $A\beta_{1\text{-}42}$ and the truncated $A\beta_{25\text{-}35}$ (without His) toxicity. Further investigation of KP1019 showed a concentration-dependent effect of this Ru(III) complex on $A\beta_{1\text{-}42}$ aggregation, and formation of His-adducts *via* EPR spectroscopy.[126] For KP1019, and likely other Ru(III) complexes, significant interference in the standard ThT aggregation assay can occur, and thus alternate aggregation assays are advised such as dynamic light scattering and/or gel electrophoresis/Western blotting. Interestingly, KP1019 was found to promote the formation of amorphous high molecular weight aggregates of the Aβ peptide. Finally, KP1019 was determined to have a concentration-dependent rescuing effect on human neuroblastoma (SH-SY5Y) cells in the presence of the $A\beta_{1\text{-}42}$ peptide. Of note, in the case of both PMru20 and KP1019, pre-incubation of the complex with the Aβ peptide was necessary to show a protective effect in cells, highlighting the need for new Ru compounds that selectively target the Aβ peptide. Our group has recently reported on a series of NAMI-A analogues, in which the size of the apical N-heterocycle is increased, and how changing the size the apical ligand effects Aβ peptide binding and aggregation (**Figure 12**).[127] The complexes were shown to bind to the peptide, likely via a His residue, by ^{1}H NMR and ESI-MS measurements. In addition, the Ru complexes promoted the formation of insoluble fibrils at the 24 hour timepoint, in comparison to peptide alone which formed large amorphous aggregates. These results point to an interesting difference between the Fe corrole analogue (discussed above) that promotes formation of low molecular weight aggregates, while the Ru(III) complexes stabilize large peptide aggregates. One hypothesis is that additional ligand exchange reactions occur with the Ru(III) complexes providing multiple peptide binding sites for aggregate formation. Indeed,

X-ray crystallography studies of Ru(III) complexes such as NAMI-A with a number of target proteins show complete loss of the original ligands in the structures.[123]

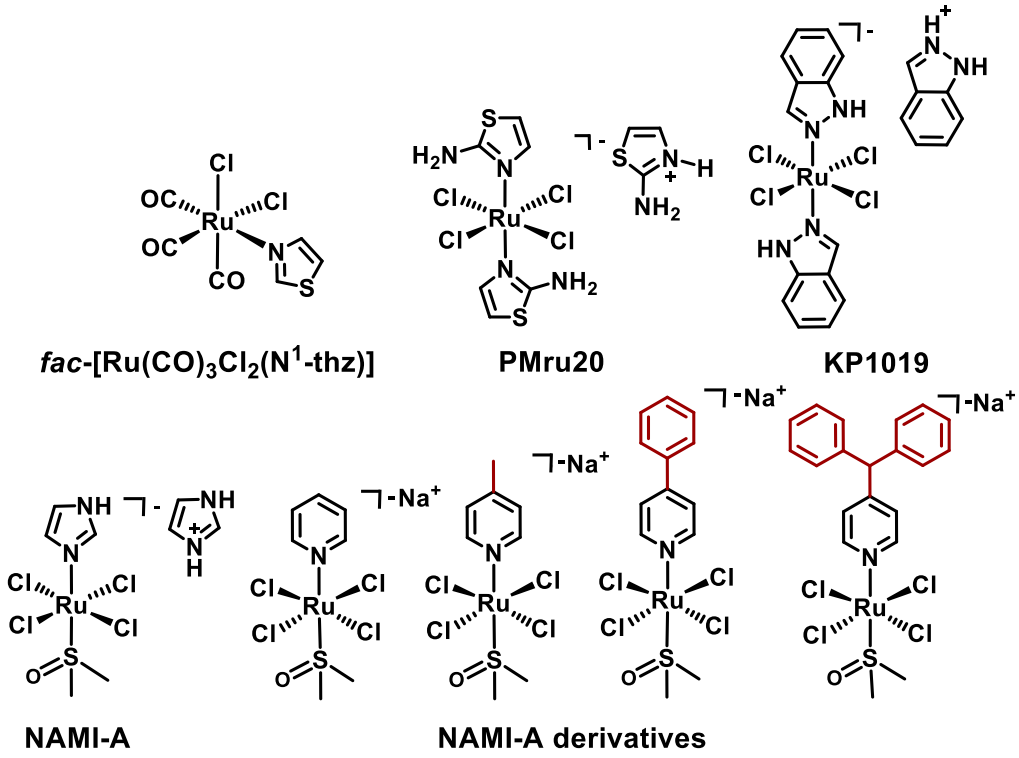

Figure 12: Ru complexes that bind to the Aβ peptide, altering aggregation patterns, and lowering toxicity in cell models.

2.5.1 Ru(II) Polypyridyl Complexes: Ru(II) polypyridyl complexes have been extensively investigated in the last few decades due to their interesting electrochemical, photophysical, and biological properties.[128, 129] These complexes find wide application in several research areas, such as conversion of solar energy, fabrication of molecular devices, DNA intercalation, and protein binding. Stable Ru(II) polypyridyl complexes can be activated with light leading to ligand dissociation to afford a metal complex capable of binding to biological targets, and/or generation of ROS such as singlet oxygen ($^1O_2$).[130]

A series of Ru(II) polypyridyl complexes (**Figure 13**) have been investigated for their ability to interact with Aβ peptide,[131-133] and due to the hydrophobic nature of the bpy/phen ligands, these complexes can form π-π interactions with the peptide.[131, 132] For example, photoactivation of $[Ru(bpy)_3]^{2+}$ (**Figure 13**) in the presence of the Aβ peptide leads to amino acid oxidation and destabilization of peptide secondary structure.[131] After exposure to light, $[Ru(bpy)_3]^{2+}$ demonstrated the ability to disassemble highly stable Aβ aggregates, generating small and less toxic Aβ fragments, showing the possibility of using Ru(II) complexes as anti-Aβ agents. Ru(II) polypyridyl complexes can also be used as sensitive fluorescent probes for Aβ aggregates. For example, the interaction of $[Ru(bpy)_2(dppz)]^{2+}$ (**Figure 13**) with Aβ fibrils results in an enhancement of luminescence likely due to the limited ability of water to quench the excited state of the complex once bound to the peptide aggregates.[134] A similar process occurs with $[Ru(bpy)_2(dpqp)]^{2+}$, however this complex can be used to monitor oligomer formation (**Figure 13**).[135, 136] The Ru(II) complex containing an extended polypyridyl ligand ($[Ru(bxbg)]^{2+}$ (**Figure 13**) inhibited acetylcholinesterase (AChE), with inhibitory values similar to that of the FDA approved drug tacrine.[132] This complex completely inhibits Aβ aggregation as well, demonstrated by ThT fluorescence and TEM. Another series of Ru(II) complexes, ($[Ru(Apy)]^{2+}$ (**Figure 13**), were shown to protect against ROS and had an inhibitory effect against AChE.[133] Interestingly, their luminescence increases in the presence of Aβ aggregates, allowing for the visualization of these species within 3 hours of aggregation, while a ThT signal only increases after 24 hours, making this a promising compound for the visualization of Aβ aggregates in the early stages of fibrilization.

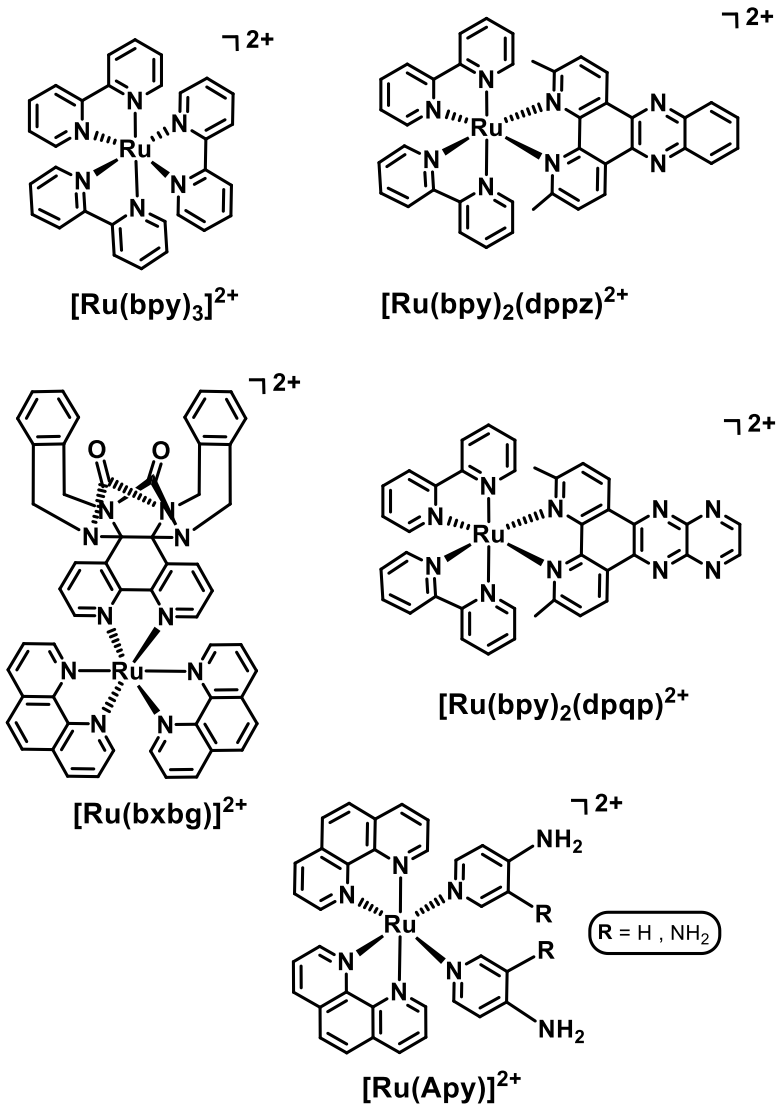

Figure 13: Ru(II) polypyridyl complexes that interact with the Aβ peptide.

2.6 Co Complexes: A number of Co complexes have been investigated for their interaction with the Aβ peptide, and in addition, promote peptide cleavage reactions. The Co(III) Schiff base complex (Co(III)-acacen, **Figure 14**) was shown to bind to one or two His of $A\beta_{1\text{-}16}$, with a preference for His^{6} and one of $His^{13/14}$, according to NMR studies and density functional theory (DFT) calculations.[48] $A\beta_{1\text{-}42}$ aggregated differently in the presence of Co(III)-acacen, with a

concentration-dependent stabilization of high MW oligomeric species (30 to 160 kDa). The presence of the complex also led to a reduction of the binding of the $A\beta_{1-42}$ peptide to differentiated hippocampal neurons. Recent work with a structural analogue by both experimental and computational methods shows that covalent binding to peptide His residues results in decreased formation of β-sheet structures, destabilization of pre-formed β-sheets, and suppression of aggregation.[137] In a different approach, researchers have shown that Co complexes can induce Aβ peptide cleavage.[138, 139] Firstly, a series of Co(III)-cyclen complexes (**Figure 14**) were shown to induce cleavage of monomers and oligomers of $A\beta_{1-40}$ and $A\beta_{1-42}$, while the formation of fibrils limited the percentage of cleavage fragments observed by matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry.[138] In a more recent report by Lim *et al.*, a Co(II) complex of a tetra-N-methylated cyclam (Co(II)-TMC, **Figure 14**) was shown to decrease the $A\beta_{1-40}$ peptide monomer concentration by 60% through amide bond hydrolytic cleavage.[139] The control complex Co(II)-EDTA did not induce cleavage, while the simple salt $Co(II)(NO_3)_2$ induced cleavage of $A\beta_{1-40}$ at different sites than those produced by the Co(II) complex (**Figure 14)**. Co(II)-TMC can bind covalently to Aβ and alter the aggregation of both $A\beta_{1-40}$ and $A\beta_{1-42}$. Interestingly, the complex was shown to protect cells from the toxicity induced by Aβ and was demonstrated to cross the BBB. A number of Co(III) complexes have been investigated as redox-activated anticancer agents, whereby reduction to Co(II) in a hypoxic tumour environment leads to ligand exchange and release of a toxic payload.[140, 141] By tuning the Co(II)/Co(III) redox potential it may be possible to enhance binding of a kinetically inert Co(III) complex to the Aβ peptide in the pro-oxidant environment of the AD brain.[142]

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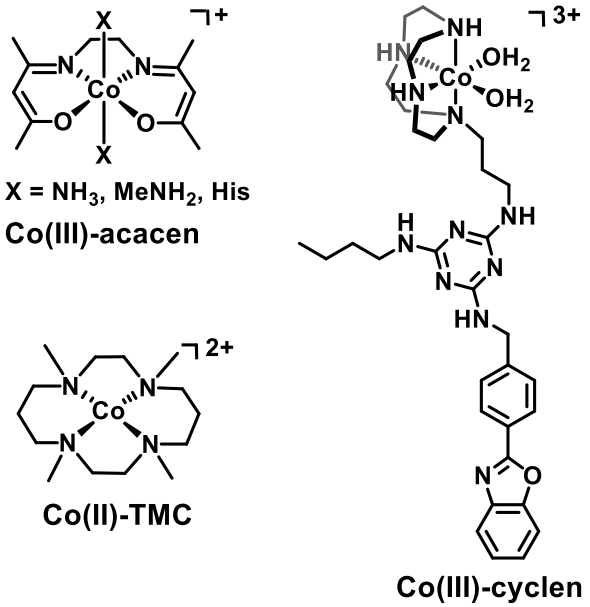

Figure 14: The structures of Co(III)-acacen, Co(II)TMC and Co(III)-cyclen.

2.7 Rh and Ir Complexes: The covalent interaction of Rh and Ir transition metal complexes with the Aβ peptide has also shown considerable promise. A series of cyclometallated Rh(III) and Ir(III) complexes (**Figure 15**, **A** and **B**) were shown to bind covalently to the Aβ peptide, leading to a reduction in fibril length for $A\beta_{1\text{-}40}$.[143] Electrospray ionization-MS (ESI-MS) measurements indicated 1:1 Aβ-Rh(III) adduct formation. Interestingly, the Rh(III) complex, as opposed to the Ir(III) complex, exhibited a more pronounced effect on aggregation, almost completely inhibiting the formation of high molecular weight species for $A\beta_{1\text{-}40}$. The Rh(III) derivative exhibited an anti-aggregating effect at a low concentration relative to peptide (1:10 complex to peptide concentration ratio), indicating the complex blocks fibril elongation. As for the Ir(III) complexes investigated, complex **B** (**Figure 15**) containing the smaller aromatic ligand of the series showed the most pronounced disruption of the fibrillization process when compared to the complex with the ligand

phenylquinoline, possibly due to steric effects. These complexes demonstrated enhanced emission in the presence of fibrils, and the Ir(III) complexes containing the more bulky ligands were more suited for cellular labelling applications. This study shows that ligand exchange rates (Rh(III) vs. Ir(III)) and steric bulk of co-ligands play a significant role in Aβ peptide binding, and associated aggregation and toxicity. More recently, the same group developed derivatives based on complex **B** in **Figure 15**, in which a third bidentate ligand was incorporated, instead of exchangeable H_2O ligands. All twelve complexes prepared by Lu *et al.* interacted with $A\beta_{1\text{-}40}$ monomers and fibrils differently, however complex **C** in **Figure 15** showed the highest affinity for fibrils.[144] Even though no covalent binding was observed between the Ir(III) complex **C** and peptide, the complex completely inhibited aggregation of $A\beta_{1\text{-}40}$. These results show that non-covalent interactions, when strong enough, can inhibit $A\beta_{1\text{-}40}$ aggregation. The presence of monomers or fibrils of $A\beta_{1\text{-}40}$ led to an increase in complex luminescence, possibly due to hydrophobic interactions with the peptide, protecting the complex from non-radioactive decay by solvent quenching. Lastly, the Ir(III) complex **C** was shown to be neuroprotective against $A\beta_{1\text{-}40}$ toxicity in human neuroblastoma SH-SY5Y cells and mouse primary cortical cells. Lim *et al.* have reported on an Ir complex which leads to the light-activated oxidation of the Aβ peptide (complex **D** in **Figure 15**).[145] Histidine, tyrosine, and methionine were identified as sites of peptide oxidation. Very recently, Lim *et al.* reported a series of cyclometallated Ir complexes with two exchangeable *cis*-aqua ligands that coordinate to the Aβ peptide and promote the photo-induced oxidation of the peptide in the presence of O_2 (based on complex **E** in **Figure 15**).[146] Specific amino acid residues are targeted for oxidation, including His13/His14 and Met35. Overall, these studies show that Rh and Ir complexes in a variety of different geometries bind to the Aβ peptide and can limit associated aggregation and toxicity.

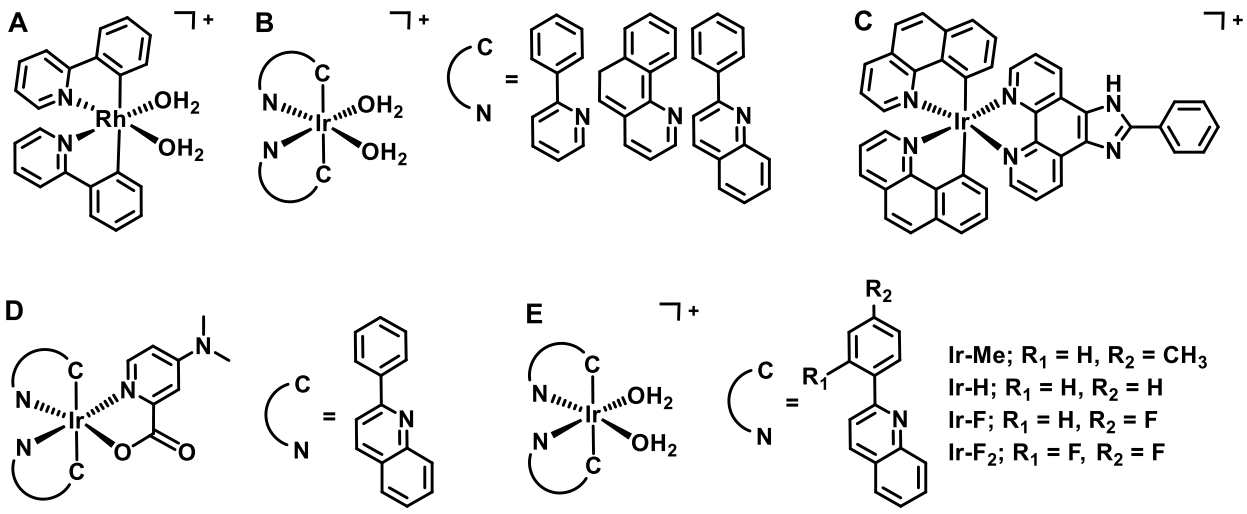

Figure 15: Structures of cyclometallated Rh(III) and Ir(III) derivatives studied in the context of Aβ peptide interactions in AD.

2.8 Pt Complexes: Pt(II) phenanthroline complexes, Pt(phen)Cl_2, and Pt(ϕ-phen)Cl_2 (**Figure 16**) were reported to bind to the Aβ peptide, altering its aggregation pattern and limiting its neurotoxicity.[147] The Pt(II) phenanthroline complexes were compared with cisplatin, with the former binding to His in the N-terminus region and reducing peptide neurotoxicity, while cisplatin targeted Met^{35} and was shown to be inactive. The free ligands and Pt(II) salts exhibited a low affinity for Aβ, indicating that the planar hydrophobic phenanthroline ligand was necessary for the observed activity. NMR, X-ray absorption spectroscopy (XAS), mass spectrometry (MS), and molecular modelling investigations further confirmed that the planar hydrophobic ligand stabilized histidine-protein adducts.[148-150] NMR experiments showed that the phenanthroline ligand interacts with the protein *via* non-covalent interactions, while the Pt(II) center binds directly to two His residues, potentially limiting the coordination of Cu(II) and Zn(II).[148] Other Pt(II)

complexes containing planar hydrophobic ligands have been investigated by Hureau *et al.*, such as Pt(ϕ-MePy)(DMSO)Cl (**Figure 16**).[151, 152] This complex bound to the Aβ peptide similarly to the phenanthroline analogues, although the results suggest binding of the Pt complex to just one His instead of two. Cu(II) and Zn(II) typically bind to Aβ His residues, and the presence of Pt(II) complexes modulated the metal binding properties of Aβ, although Aβ-Cu ROS generation was not inhibited completely.[147, 152, 153] Electron paramagnetic resonance (EPR) analysis shows a change in the peptide Cu(II) binding site in the presence of Pt(ϕ-MePy)(DMSO)Cl, with the initial two His Cu(II) coordination (component I) shifting to only one His bound (component II). The interaction of Zn(II) with Aβ results in aggregation enhancement, however the presence of the Pt(ϕ-MePy)(DMSO)Cl complex limited Zn-induced Aβ aggregation.[152] A bifunctional complex, containing one or two cyclen metal-binding moieties attached to a bipyridine Pt(II) binding unit (**Figure 16**, **PC1**) was shown to limit Cu/Zn aggregation and associated toxicity through His binding and metal scavenging ability.[154]

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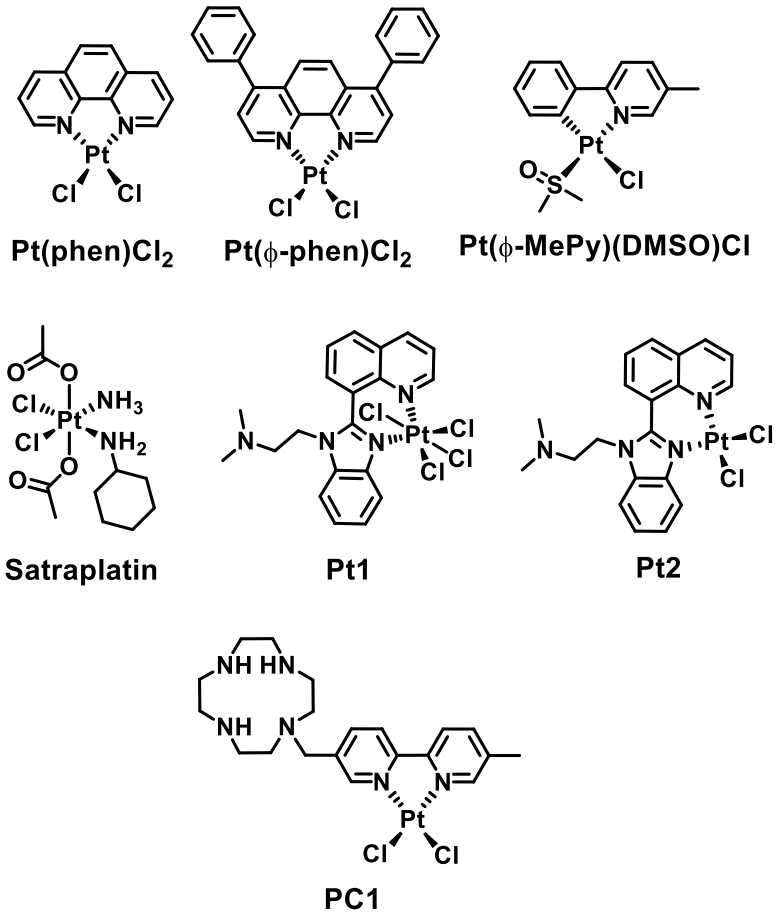

Figure 16: The structure of representative Pt complexes that interact with the Aβ peptide, disrupt metal binding, and show promise in cell and animal models.

It is possible to tune the therapeutic effects of these Pt(II) complexes *via* alteration of ligand exchange kinetics and overall charge of the complex.[155] Pt(IV) complexes, such as Satraplatin (**Figure 16**), exhibit slow ligand exchange kinetics, making them biologically stable and orally bioavailable.[156-158] With that in mind, Barnham *et al.*[159] synthesized an orally bioavailable Pt(IV) pro-drug with a hydrophobic diamine, and its Pt(II) analogue (Pt1 and Pt2, respectively, **Figure 16**) as modulators of Aβ peptide aggregation and toxicity. The Pt(IV) complex showed increased brain uptake in comparison to the Pt(II) complex, and upon reduction to Pt(II), was

shown to limit peptide aggregation and toxicity in cortical neurons. The treatment of an APP/PS1 mouse model of AD (**Figure 16,** Pt1) showed a statistically significant reduction in CSF $A\beta_{1-42}$ levels and reduction in plaque load. Thus, the Pt(IV) pro-drug strategy was shown to be promising for the development of Pt-complexes that cross the BBB and selectively target Aβ.

2.9. Cu Complexes: A number of ^{64}Cu complexes have been reported that incorporate amyloid-binding moieties into the molecule for Aβ plaque binding. The longer half-life of the ^{64}Cu isotope ($t_{1/2}$ = 12.7 hours) versus the ^{18}F isotope ($t_{1/2}$ = 110 min) currently used in approved plaque imaging agents (see **Figure 1**), could provide significant benefits including use over a longer period and shipment to sites remote from cyclotron facilities. Donnelly *et al.* reported a Cu complex with a styrylpyridine group (**Figure 17**) which bound to Aβ plaques in human brain tissue.[11] The ^{64}Cu-labelled derivative showed significant brain uptake in wild-type mice with fast washout. More recently, Mirica *et al.* reported on a ^{64}Cu agent with a pyridine-amine macrocycle attached to a benzothiazole (**Figure 17**).[10] This ^{64}Cu complex was shown to bind to Aβ aggregates in transgenic AD mouse brain sections, and showed promising uptake in Tg2576 transgenic mice. Both of the studies highlighted above have demonstrated the feasibility of using ^{64}Cu agents in brain imaging applications.

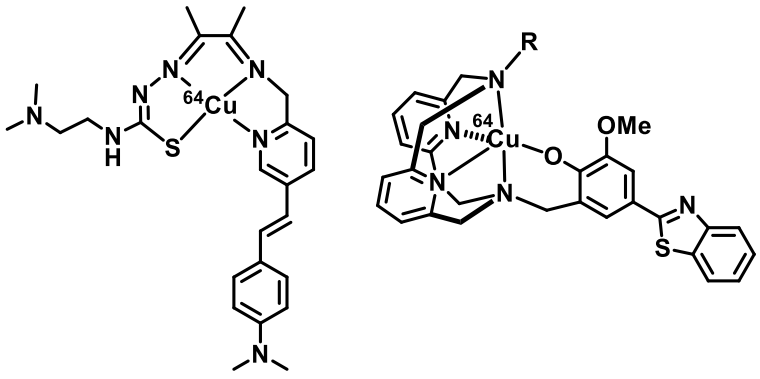

Figure 17: ^{64}Cu complexes used as plaque imaging agents in AD.

3. Outlook: This review highlights the binding of discrete metal complexes to the Aβ peptide of relevance to Alzheimer's disease. While in the majority of cases the studied complexes show a potential therapeutic benefit, complexes such as heme have been shown to promote ROS and toxicity associated with the disease. Thus one needs to use caution when designing transition metal complexes as potential therapeutics in this disease, and analyze for changes in reactivity of the complex once bound to the biological target. Recent results highlighted in this review show that in addition to metal complex interaction with the Aβ peptide, and resulting changes to the peptide aggregation pattern, additional properties of metal complexes such as catalytic antioxidant activity, photo-induced oxidation, and peptidase activity can be used to provide additional therapeutic benefit. Protein misfolding and aggregation are common characteristics of other neurodegenerative diseases such as Parkinson's disease, Creutzfeldt Jakob disease, and Amyotrophic Lateral Sclerosis.[76, 77] Specific proteins of interest include α-synuclein (Parkinson's), tau (AD), and the prion protein (Creutzfeldt Jakob disease). Indeed, metal complex interactions with the prion protein,[160] and tau[161] have been recently reported. Thus, the development of metal compounds that selectively target specific protein aggregates may provide new diagnostic tools, and selective therapies. Important considerations in this area include blood brain barrier (BBB) permeability, off-target toxicity, and possible accumulation of metal ions in the brain as a result of chronic administration. As we continue to learn more about the etiology of neurodegeneration, and of specific diseases such as AD, new opportunities will be presented for transition metal complexes.

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5. References:

[1] C.A. Ross, M.A. Poirier, Nature Med., 10 (2004) S10.

[2] C. Soto, S. Pritzkow, Nature Neurosci., 21 (2018) 1332-1340.

[3] A.D. Gitler, P. Dhillon, J. Shorter, Dis. Mod. Mech., 10 (2017) 499-502.

[4] M. Goedert, Science, 349 (2015) 1255555.

[5] C. Patterson, in, Alzheimer's Disease International, London, 2018.

[6] https://www.alz.co.uk/research/statistics, in, 2017.

[7] A.W. Martin Prince, Maëlenn Guerchet, Gemma-Claire Ali, Yu-Tzu Wu, Matthew Prina, World Alzheimer Report 2015. The Global Impact on Dementia. An Analysis of Prevalence, Incidence, Cost and Trends, 2015.

[8] F.M. Elahi, B.L. Miller, Nature Rev. Neurol., 13 (2017) 457.

[9] H.W. Querfurth, F.M. LaFerla, New Engl. J. Med., 362 (2010) 329-344.

[10] N. Bandara, A.K. Sharma, S. Krieger, J.W. Schultz, B.H. Han, B.E. Rogers, L.M. Mirica, J. Am. Chem. Soc., 139 (2017) 12550-12558.

[11] J.L. Hickey, S. Lim, D.J. Hayne, B.M. Paterson, J.M. White, V.L. Villemagne, P. Roselt, D. Binns, C. Cullinane, C.M. Jeffery, R.I. Price, K.J. Barnham, P.S. Donnelly, J. Am. Chem. Soc., 135 (2013) 16120-16132.

[12] S.P. Fletcher, A. Noor, J.L. Hickey, C.A. McLean, J.M. White, P.S. Donnelly, J. Biol. Inorg. Chem., 23 (2018) 1139-1151.

[13] D.J. Hayne, J.M. White, C.A. McLean, V.L. Villemagne, K.J. Barnham, P.S. Donnelly, Inorg. Chem., 55 (2016) 7944-7953.

[14] J.L. Hickey, P.S. Donnelly, Coord. Chem. Rev., 256 (2012) 2367-2380.

[15] L.E. McInnes, A. Noor, K. Kysenius, C. Cullinane, P. Roselt, C.A. McLean, F.C.K. Chiu, A.K. Powell, P.J. Crouch, J.M. White, P.S. Donnelly, Inorg. Chem., 58 (2019) 3382-3395.

[16] V.H. Finder, J. Alzh. Dis., 22 (2010) S5-S19.

[17] E.D. Roberson, L. Mucke, Science, 314 (2006) 781-784.

[18] P.A. Adlard, S.A. James, A.I. Bush, C.L. Masters, Drugs of Today, 45 (2009) 293-304.

[19] M. Citron, Nature Rev. Drug. Disc., 9 (2010) 387-398.

[20] D.J. Selkoe, Nature Med., 17 (2011) 1693-1693.

[21] J. Cummings, G. Lee, A. Ritter, K. Zhong, Alzh, Dementia, 4 (2018) 195-214.

[22] A. Abbott, Nature, 456 (2008) 161-164.

[23] J. Hardy, D.J. Selkoe, Science, 297 (2002) 353-356.

[24] D.J. Selkoe, J. Hardy, EMBO Mol. Med., 8 (2016) 595-608.

[25] C.A. McLean, R.A. Cherny, F.W. Fraser, S.J. Fuller, M.J. Smith, K. Beyreuther, A.I. Bush, C.L. Masters, Ann. Neurol., 46 (1999) 860-866.

[26] M. Korte, Science, 363 (2019) 123-124.

[27] F. Kametani, M. Hasegawa, Front. Neurosci., 12 (2018) 25-25.

[28] J.-M. Suh, G. Kim, J. Kang, M.H. Lim, Inorg. Chem., 58 (2019) 8-17.

[29] M.T. Colvin, R. Silvers, Q.Z. Ni, T.V. Can, I. Sergeyev, M. Rosay, K.J. Donovan, B. Michael, J. Wall, S. Linse, R.G. Griffin, J. Am. Chem. Soc., 138 (2016) 9663-9674.

[30] M.A. Wälti, F. Ravotti, H. Arai, C.G. Glabe, J.S. Wall, A. Böckmann, P. Güntert, B.H. Meier, R. Riek, Proc. Nat. Acad. Sci., 113 (2016) E4976-E4984.

[31] S. Lesne, M.T. Koh, L. Kotilinek, R. Kayed, C.G. Glabe, A. Yang, M. Gallagher, K.H. Ashe, Nature, 440 (2006) 352-357.

[32] A.D. Watt, V.L. Villemagne, K.J. Barnham, Journal of Alzheimer's disease : JAD, 33 Suppl 1 (2013) S283-293.

[33] R. Nortley, N. Korte, P. Izquierdo, C. Hirunpattarasilp, A. Mishra, Z. Jaunmuktane, V. Kyrargyri, T. Pfeiffer, L. Khennouf, C. Madry, H. Gong, A. Richard-Loendt, W. Huang, T. Saito, T.C. Saido, S. Brandner, H. Sethi, D. Attwell, Science, 365 (2019) eaav9518.

[34] B. Zott, M.M. Simon, W. Hong, F. Unger, H.-J. Chen-Engerer, M.P. Frosch, B. Sakmann, D.M. Walsh, A. Konnerth, Science, 365 (2019) 559-565.

[35] N.R. Stallings, M.A. O'Neal, J. Hu, E.T. Kavalali, I. Bezprozvanny, J.S. Malter, Sci. Signal., 11 (2018) eaap8734.

[36] R. Squitti, Front. Biosci., 17 (2012) 451-472.

[37] R. González-Domínguez, T. García-Barrera, J.L. Gómez-Ariza, BioMetals, 27 (2014) 539-549.

[38] A.I. Mot, P.J. Crouch, Chapter 1 - Biometals and Alzheimer's Disease, in: A.R. White, M. Aschner, L.G. Costa, A.I. Bush (Eds.) Biometals in Neurodegenerative Diseases, Academic Press, 2017, pp. 1-17.

[39] J.S. Cristóvão, R. Santos, C.M. Gomes, Ox. Med. Cell Longevity, 2016 (2016) 13.

[40] M.A. Lovell, J.D. Robertson, W.J. Teesdale, J.L. Campbell, W.R. Markesbery, J. Neurol. Sci., 158 (1998) 47-52.

[41] L.M. Miller, Q. Wang, T.P. Telivala, R.J. Smith, A. Lanzirotti, J. Miklossy, J. Struct. Biol., 155 (2006) 30-37.

[42] M.G. Savelieff, A.S. DeToma, J.S. Derrick, M.H. Lim, Acc. Chem. Res., 47 (2014) 2475-2482.

[43] K.P. Kepp, Chem. Rev., 112 (2012) 5193-5239.

[44] A.S. Pithadia, A. Kochi, M.T. Soper, M.W. Beck, Y.Z. Liu, S. Lee, A.S. DeToma, B.T. Ruotolo, M.H. Lim, Inorg. Chem., 51 (2012) 12959-12967.

[45] P. Faller, C. Hureau, Dalton Trans., (2009) 1080-1094.

[46] L.Q. Hatcher, L. Hong, W.D. Bush, T. Carducci, J.D. Simon, J. Phys. Chem. B, 112 (2008) 8160-8164.

[47] F. Hane, Z. Leonenko, Biomolecules, 4 (2014) 101-116.

[48] M.C. Heffern, P.T. Velasco, L.M. Matosziuk, J.L. Coomes, C. Karras, M.A. Ratner, W.B. Klein, A.L. Eckermann, T.J. Meade, Chembiochem : a European journal of chemical biology, 15 (2014) 1584-1589.

[49] C. Cheignon, M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, F. Collin, Redox Biol, 14 (2018) 450-464.

[50] B. Alies, A. Conte-Daban, S. Sayen, F. Collin, I. Kieffer, E. Guillon, P. Faller, C. Hureau, Inorg. Chem., 55 (2016) 10499-10509.

[51] I. Zawisza, M. Rózga, W. Bal, Coord. Chem. Rev., 256 (2012) 2297-2307.

[52] Y. Miller, B. Ma, R. Nussinov, Coord. Chem. Rev., 256 (2012) 2245-2252.

[53] V. Wineman-Fisher, D.N. Bloch, Y. Miller, Coord. Chem. Rev., 327-328 (2016) 20-26.

[54] S. Parthasarathy, F. Long, Y. Miller, Y. Xiao, D. McElheny, K. Thurber, B. Ma, R. Nussinov, Y. Ishii, J. Am. Chem. Soc., 133 (2011) 3390-3400.

[55] Y. Miller, B. Ma, R. Nussinov, Proc. Nat. Acad. Sci., 107 (2010) 9490-9495.

[56] J. Hooda, A. Shah, L. Zhang, Nutrients, 6 (2014) 1080-1102.

[57] H. Atamna, W.H. Frey, Proc. Nat. Acad. Sci., 101 (2004) 11153-11158.

[58] V. Borghesani, B. Alies, C. Hureau, Eur. J. Inorg. Chem., 2018 (2018) 7-15.

[59] X. Huang, C.S. Atwood, M.A. Hartshorn, G. Multhaup, L.E. Goldstein, R.C. Scarpa, M.P. Cuajungco, D.N. Gray, J. Lim, R.D. Moir, R.E. Tanzi, A.I. Bush, Biochemistry, 38 (1999) 7609-7616.

[60] K. Reybier, S. Ayala, B. Alies, J.V. Rodrigues, S. Bustos Rodriguez, G. La Penna, F. Collin, C.M. Gomes, C. Hureau, P. Faller, Angewandte Chemie, 55 (2016) 1085-1089.

[61] G. La Penna, C. Hureau, P. Faller, AIP Conference Proceedings, 1618 (2014) 112-114.

[62] T. Rival, R.M. Page, D.S. Chandraratna, T.J. Sendall, E. Ryder, B. Liu, H. Lewis, T. Rosahl, R. Hider, L.M. Camargo, M.S. Shearman, D.C. Crowther, D.A. Lomas, Eur. J. Neurosci., 29 (2009) 1335-1347.

[63] T. Kanti Das, M.R. Wati, K. Fatima-Shad, Arch. Neurosci., 2 (2015) e60038.

[64] R.J. Ward, D.T. Dexter, R.R. Crichton, J. Trace Elem. Med. Biol., (2015).

[65] A. Lakatos, B. Gyurcsik, N.V. Nagy, Z. Csendes, E. Weber, L. Fulop, T. Kiss, Dalton Trans., 41 (2012) 1713-1726.

[66] S.L. Leong, T.R. Young, K.J. Barnham, A.G. Wedd, M.G. Hinds, Z. Xiao, R. Cappai, Metallomics, 6 (2014) 105-116.

[67] A.S. Pithadia, M.H. Lim, Curr. Opin. Chem. Biol., (2012) 67-73.

[68] F. Bousejra-ElGarah, C. Bijani, Y. Coppel, P. Faller, C. Hureau, Inorg. Chem., 50 (2011) 9024-9030.

[69] D. Pramanik, C. Ghosh, S.G. Dey, J. Am. Chem. Soc., 133 (2011) 15545-15552.

[70] K. Reybier, S. Ayala, B. Alies, J.V. Rodrigues, S.B. Rodriguez, G.L. Penna, F. Collin, C.M. Gomes, C. Hureau, P. Faller, Angew. Chem. Int. Ed., 55 (2016) 1085-1089.

[71] X. Huang, M.P. Cuajungco, C.S. Atwood, M.A. Hartshorn, J.D.A. Tyndall, G.R. Hanson, K.C. Stokes, M. Leopold, G. Multhaup, L.E. Goldstein, R.C. Scarpa, A.J. Saunders, J. Lim, R.D.

Moir, C. Glahe, E.F. Bowden, C.L. Masters, D.P. Fairlie, R.E. Tanzi, A.I. Bush, J. Biol. Chem., 274 (1999) 37111-37116.

[72] X. Huang, C.S. Atwood, M.A. Hartshorn, G. Multhaup, L.E. Goldstein, R.C. Scarpa, M.P. Cuajungco, D.N. Gray, J. Lim, R.D. Moir, R.E. Tanzi, A.I. Bush, Biochemistry, 38 (1999) 7609-7616.

[73] G.F.Z. da Silva, L.J. Ming, Angew. Chem. Int. Ed., 44 (2005) 5501-5504.

[74] C. Cheignon, P. Faller, D. Testemale, C. Hureau, F. Collin, Metallomics, 8 (2016) 1081-1089.

[75] C. Hureau, Metal Ions and Complexes in Alzheimer's Disease: From Fundamental to Therapeutic Perspectives, in: Encyclopedia of Inorganic and Bioinorganic Chemistry, 2018, pp. 1-14.

[76] K.J. Barnham, A.I. Bush, Chem. Soc. Rev., 43 (2014) 6727-6749.

[77] M.G. Savelieff, G. Nam, J. Kang, H.J. Lee, M. Lee, M.H. Lim, Chem. Rev., 119 (2019) 1221-1322.

[78] L.E. Scott, C. Orvig, Chem. Rev., 109 (2009) 4885-4910.

[79] B. Rosenberg, L. VanCamp, J.E. Trosko, V.H. Mansour, Nature, 222 (1969) 385-386.

[80] K.D. Mjos, C. Orvig, Chem. Rev., 114 (2014) 4540-4563.

[81] G. Jaouen, A. Vessieres, S. Top, Chem. Soc. Rev., 44 (2015) 8802-8817.

[82] B. Bertrand, A. Casini, Dalton Trans., 43 (2014) 4209-4219.

[83] D.J. Hayne, S. Lim, P.S. Donnelly, Chem. Soc. Rev., 43 (2014) 6701-6715.

[84] H. Liu, Y.W. Qu, X.H. Wang, Future Med. Chem., 10 (2018) 679-701.

[85] T.A. Sales, I.G. Prandi, A.A. de Castro, D.H.S. Leal, E.F.F. da Cunha, K. Kuca, T.C. Ramalho, Int. J. Mol. Sci., 20 (2019).

[86] X.H. Wang, X.Y. Wang, Z.J. Guo, Coord. Chem. Rev., 362 (2018) 72-84.

[87] J.J. Miller, Gomes, L. M., Storr, T. and Casini, A., The Interaction of Metal Compounds with Protein Targets: New Tools in Medicinal Chemistry and Chemical Biology, in: Encyclopedia of Inorganic and Bioinorganic Chemistry, 2016, pp. 1-13.

[88] L. He, X. Wang, D. Zhu, C. Zhao, W. Du, Metallomics, 7 (2015) 1562-1572.

[89] B. Zhang, D. Zhu, W. Wang, G. Gong, W. Du, RSC Advances, 6 (2016) 17083-17091.

[90] J. Xu, B. Zhang, G. Gong, X. Huang, W. Du, J. Inorg. Biochem., 197 (2019) 110721.

[91] A.C. Martins, Jr., P. Morcillo, O.M. Ijomone, V. Venkataramani, F.E. Harrison, E. Lee, A.B. Bowman, M. Aschner, Int. J. Environ. Res. Public Health, 16 (2019) 3546.

[92] A. Conte-Daban, V. Ambike, R. Guillot, N. Delsuc, C. Policar, C. Hureau, Chem. Eur. J., 24 (2018) 5095-5099.

[93] M. Sajjad, E. Saeed, H. Seyed Jalal, Current Med. Chem., 26 (2019) 2166-2189.

[94] M. Ono, H. Saji, Int. J. Mol. Imaging, 2011 (2011) 543267-543267.

[95] Y. Cheng, M. Ono, H. Kimura, M. Ueda, H. Saji, J. Med. Chem., 55 (2012) 2279-2286.

[96] R. Alberto, K. Ortner, N. Wheatley, R. Schibli, A.P. Schubiger, J. Am. Chem. Soc., 123 (2001) 3135-3136.

[97] R. Alberto, R. Schibli, A. Egli, A.P. Schubiger, U. Abram, T.A. Kaden, J. Am. Chem. Soc., 120 (1998) 7987-7988.

[98] C.Y. Chan, A. Noor, C.A. McLean, P.S. Donnelly, P.J. Barnard, Chem. Commun., 53 (2017) 2311-2314.

[99] M. Wenzel, J. Labelled Compd. Radiopharm., 31 (1992) 641-650.

[100] C. Kiritsis, B. Mavroidi, A. Shegani, L. Palamaris, G. Loudos, M. Sagnou, I. Pirmettis, M. Papadopoulos, M. Pelecanou, ACS Med. Chem. Lett., 8 (2017) 1089-1092.

[101] M.T. Gabr, F.C. Pigge, Chemistry-a European Journal, 24 (2018) 11729-11737.

[102] A. Aliyan, B. Kirby, C. Pennington, A.A. Martí, J. Am. Chem. Soc., 138 (2016) 8686-8689.

[103] A. Aliyan, T.J. Paul, B. Jiang, C. Pennington, G. Sharma, R. Prabhakar, A.A. Marti, Chem, 3 (2017) 898-912.

[104] D. Pramanik, C. Ghosh, S. Mukherjee, S.G. Dey, Coord. Chem. Rev., 257 (2013) 81-92.

[105] C. Ghosh, M. Seal, S. Mukherjee, S. Ghosh Dey, Acc. Chem. Res., 48 (2015) 2556-2564.

[106] H. Atamna, K. Boyle, Proc. Nat. Acad. Sci., 103 (2006) 3381-3386.

[107] D. Pramanik, S.G. Dey, J. Am. Chem. Soc., 133 (2011) 81-87.

[108] C. Yuan, Z. Gao, Chem. Res. Toxicol., 26 (2013) 262-269.

[109] J.N. Rodriguez-Lopez, A.T. Smith, R.N. Thorneley, The Journal of biological chemistry, 271 (1996) 4023-4030.

[110] A. Henriksen, A.T. Smith, M. Gajhede, J. Biol. Chem., 274 (1999) 35005-35011.

[111] H. Atamna, W.H. Frey Ii, N. Ko, Arch. Biochem. Biophys., 487 (2009) 59-65.

[112] G. Thiabaud, S. Pizzocaro, R. Garcia-Serres, J.-M. Latour, E. Monzani, L. Casella, Angew. Chem. Int. Ed., 52 (2013) 8041-8044.

[113] C. Yuan, L. Yi, Z. Yang, Q. Deng, Y. Huang, H. Li, Z. Gao, J. Biol. Inorg. Chem., 17 (2012) 197-207.

[114] I. Pal, A.K. Nath, M. Roy, M. Seal, C. Ghosh, A. Dey, S.G. Dey, Chem. Sci., 10 (2019) 8405-8410.

[115] M. Li, S.E. Howson, K. Dong, N. Gao, J. Ren, P. Scott, X. Qu, J. Am. Chem. Soc., 136 (2014) 11655-11663.

[116] L.M.F. Gomes, A. Mahammed, K.E. Prosser, J.R. Smith, M.A. Silverman, C.J. Walsby, Z. Gross, T. Storr, Chem. Sci., 10 (2019) 1634-1643.

[117] A. Mahammed, Z. Gross, J. Am. Chem. Soc., 127 (2005) 2883-2887.

[118] M. Eckshtain, I. Zilbermann, A. Mahammed, I. Saltsman, Z. Okun, E. Maimon, H. Cohen, D. Meyerstein, Z. Gross, Dalton Trans., (2009) 7879-7882.

[119] A. Haber, M. Aviram, Z. Gross, Chem. Sci., 2 (2011) 295-302.

[120] C.A. Joseph, P.C. Ford, J. Am. Chem. Soc., 127 (2005) 6737-6743.

[121] E. Vogel, S. Will, A.S. Tilling, L. Neumann, J. Lex, E. Bill, A.X. Trautwein, K. Wieghardt, Angewandte Chemie-International Edition in English, 33 (1994) 731-735.

[122] S. Will, J. Lex, E. Vogel, V.A. Adamian, E. VanCaemelbecke, K.M. Kadish, Inorg. Chem., 35 (1996) 5577-5583.

[123] E. Alessio, L. Messori, Molecules, 24 (2019) 1995.

[124] D. Valensin, P. Anzini, E. Gaggelli, N. Gaggelli, G. Tamasi, R. Cini, C. Gabbiani, E. Michelucci, L. Messori, H. Kozlowski, G. Valensin, Inorg. Chem., 49 (2010) 4720-4722.

[125] L. Messori, M. Camarri, T. Ferraro, C. Gabbiani, D. Franceschini, ACS Med. Chem. Lett., 4 (2013) 329-332.

[126] M.R. Jones, C. Mu, M.C.P. Wang, M.I. Webb, C.J. Walsby, T. Storr, Metallomics, 7 (2015) 129-135.

[127] L.M.F. Gomes, J.C. Bataglioli, A.J. Jussila, J.R. Smith, C.J. Walsby, T. Storr, Front. Chem., 7 (2019).

[128] T. Mede, M. Jäger, U.S. Schubert, Chem. Soc. Rev., 47 (2018) 7577-7627.

[129] F.E. Poynton, S.A. Bright, S. Blasco, D.C. Williams, J.M. Kelly, T. Gunnlaugsson, Chem. Soc. Rev., 46 (2017) 7706-7756.

[130] F. Heinemann, J. Karges, G. Gasser, Acc. Chem. Res., 50 (2017) 2727-2736.

[131] G. Son, B.I. Lee, Y.J. Chung, C.B. Park, Acta Biomaterialia, 67 (2018) 147-155.

[132] N.A. Vyas, S.S. Bhat, A.S. Kumbhar, U.B. Sonawane, V. Jani, R.R. Joshi, S.N. Ramteke, P.P. Kulkarni, B. Joshi, Eur. J. Med. Chem., 75 (2014) 375-381.

[133] D.E.S. Silva, M.P. Cali, W.M. Pazin, E. Carlos-Lima, M.T. Salles Trevisan, T. Venâncio, M. Arcisio-Miranda, A.S. Ito, R.M. Carlos, J. Med. Chem., 59 (2016) 9215-9227.

[134] N.P. Cook, M. Ozbil, C. Katsampes, R. Prabhakar, A.A. Martí, J. Am. Chem. Soc., 135 (2013) 10810-10816.

[135] B. Jiang, A. Aliyan, N.P. Cook, A. Augustine, G. Bhak, R. Maldonado, A.D. Smith McWilliams, E.M. Flores, N. Mendez, M. Shahnawaz, F.J. Godoy, J. Montenegro, I. Moreno-Gonzalez, A.A. Martí, J. Am. Chem. Soc., 141 (2019) 15605-15610.

[136] A. Aliyan, N.P. Cook, A.A. Martí, Chem. Rev., 119 (2019) 11819-11856.

[137] A. Iscen, C.R. Brue, K.F. Roberts, J. Kim, G.C. Schatz, T.J. Meade, J. Am. Chem. Soc., 141 (2019) 16685-16695.

[138] J. Suh, S.H. Yoo, M.G. Kim, K. Jeong, J.Y. Ahn, M.-s. Kim, P.S. Chae, T.Y. Lee, J. Lee, J. Lee, Y.A. Jang, E.H. Ko, Angew. Chem. Int. Ed., 46 (2007) 7064-7067.

[139] J.S. Derrick, J. Lee, S.J.C. Lee, Y. Kim, E. Nam, H. Tak, J. Kang, M. Lee, S.H. Kim, K. Park, J. Cho, M.H. Lim, J. Am. Chem. Soc., 139 (2017) 2234-2244.

[140] A.K. Renfrew, Metallomics, 6 (2014) 1324-1335.

[141] N. Graf, S.J. Lippard, Adv. Drug. Deliv. Rev., 64 (2012) 993-1004.

[142] C. Cheignon, M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, F. Collin, Redox Biol., 14 (2018) 450-464.

[143] B.Y.-W. Man, H.-M. Chan, C.-H. Leung, D.S.-H. Chan, L.-P. Bai, Z.-H. Jiang, H.-W. Li, D.-L. Ma, Chem. Sci., 2 (2011) 917-921.

[144] L. Lu, H.-J. Zhong, M. Wang, S.-L. Ho, H.-W. Li, C.-H. Leung, D.-L. Ma, Science Rep., 5 (2015) 14619.

[145] J. Kang, S.J.C. Lee, J.S. Nam, H.J. Lee, M.G. Kang, K.J. Korshavn, H.T. Kim, J. Cho, A. Ramamoorthy, H.W. Rhee, T.H. Kwon, M.H. Lim, Chemistry-a European Journal, 23 (2017) 1645-1653.

[146] J. Kang, J.S. Nam, H.J. Lee, G. Nam, H.-W. Rhee, T.-H. Kwon, M.H. Lim, Chem. Sci., 10 (2019) 6855-6862.

[147] K.J. Barnham, V.B. Kenche, G.D. Ciccotosto, D.P. Smith, D.J. Tew, X. Liu, K. Perez, G.A. Cranston, T.J. Johanssen, I. Volitakis, A.I. Bush, C.L. Masters, A.R. White, J.P. Smith, R.A. Cherny, R. Cappai, Proc. Nat. Acad. Sci., 105 (2008) 6813-6818.

[148] G. Ma, F. Huang, X. Pu, L. Jia, T. Jiang, L. Li, Y. Liu, Chem. Eur. J., 17 (2011) 11657-11666.

[149] V.A. Streltsov, V. Chandana Epa, S.A. James, Q.I. Churches, J.M. Caine, V.B. Kenche, K.J. Barnham, Chem. Commun., 49 (2013) 11364-11366.

[150] M. Turner, J.A. Platts, R.J. Deeth, J. Chem. Theor. Comput., 12 (2016) 1385-1392.

[151] I. Sasaki, C. Bijani, S. Ladeira, V. Bourdon, P. Faller, C. Hureau, Dalton Trans., 41 (2012) 6404-6407.

[152] F. Collin, I. Sasaki, H. Eury, P. Faller, C. Hureau, Chem. Commun., 49 (2013) 2130-2132.

[153] G. Ma, E. Wang, H. Wei, K. Wei, P. Zhu, Y. Liu, Metallomics, 5 (2013) 879-887.

[154] X. Wang, X. Wang, C. Zhang, Y. Jiao, Z. Guo, Chem. Sci., 3 (2012) 1304-1312.

[155] C. Hureau, P. Faller, Dalton Trans., 43 (2014) 4233-4237.

[156] J.L. Carr, M.D. Tingle, M.J. McKeage, Cancer Chemother. Pharmacol., 50 (2002) 9-15.

[157] A.R. Khokhar, Y. Deng, S. al-Baker, M. Yoshida, Z.H. Siddik, J. Inorg. Biochem., 51 (1993) 677-687.

[158] M. Galanski, B.K. Keppler, Inorg. Chem., 35 (1996) 1709-1711.

[159] V.B. Kenche, L.W. Hung, K. Perez, I. Volitakes, G. Ciccotosto, J. Kwok, N. Critch, N. Sherratt, M. Cortes, V. Lal, C.L. Masters, K. Murakami, R. Cappai, P.A. Adlard, K.J. Barnham, Angew. Chem. Int. Ed., 52 (2013) 3374-3378.

[160] X. Wang, D. Zhu, C. Zhao, L. He, W. Du, Metallomics, 7 (2015) 837-846.

[161] N.V. Gorantla, V.G. Landge, P.G. Nagaraju, P. Priyadarshini Cg, E. Balaraman, S. Chinnathambi, ACS Omega, 4 (2019) 16702-16714.