Copper, an essential trace element in all oxygen-dependent living organisms, plays a vital role in many physiological processes ranging from energy metabolism to DNA synthesis.¹ The easy interconversion between the Cu(I) and Cu(II) oxidation states allows this element to coordinate a variety of ligands and also holds the key to the function of many important enzymes and proteins.² Among these are superoxide dismutase, cytochrome c oxidase, tyrosinase and amyloid precursor protein.² Copper-containing proteins can also catalyze oxidation-reduction reactions with molecular oxygen to produce free radicals via a Fenton-type reaction.³ Hence, copper homeostasis is strictly regulated by a system of copper transporters and chaperons.³ Defects in any part of these homeostatic mechanisms lead to disease. Well studied examples include Menkes and Wilson’s disease.⁴ In studying these diseases, both of which involve altered copper homeostasis, new insights have been gained into other disorders in which altered metal homeostasis is also observed. It has now been established that the amyloid precursor protein (APP), a cell surface transmembrane glycoprotein containing two copper binding domains, is part of the pathogenesis of Alzheimer’s disease (AD).⁵ Thus, understanding the metallopathology of this disease is key. Building on this knowledge can then lead to therapeutic agents capable of treating and possibly even curing this disease.

Alzheimer’s disease (AD) is characterized by extracellular accumulation of aggregated forms of the amyloid-β (Aβ) peptide in the neocortex of the brain, and intracellular formation of neurofibrillary tangles.⁶,⁷ Greatest neurotoxicity is exhibited by Aβ aggregation pathway
intermediates, particularly lower-molecular-mass dimers and trimers.\textsuperscript{8-10} The high levels of copper found in these Aβ deposits, along with the observation that copper co-purifies with the Aβ from AD brains, indicate that copper plays an essential role in AD pathogenesis.\textsuperscript{11,12} Since copper is in excess in the plasma but deficient within the cell, therapeutic strategies are focused on either removal of extracellular copper via copper chelating agents or increasing copper bioavailability to the deficient cell through a copper complex. Currently, there are four different drugs approved for treatment of AD, none of whose mechanisms of action involve cell homeostasis of copper, the main cause of cognitive decline. To remedy this lack, researchers have begun making and testing various copper chelating agents as well as copper complexes.

In order to accelerate clinical trials, the chelating agents chosen for study all had established toxicology profiles.\textsuperscript{6} The molecules discussed in detail in this presentation are shown in Figures 2 and 3. The most thorough studies have been carried out for the quinoline and quinolone drug class. A first generation compound of this class, clioquinol (CQ), is a known Cu/Zn chelator. NMR spectroscopy revealed that CQ selectively removes Cu from Aβ. Furthermore, in a nine week transgenic mouse study, oral treatment with CQ caused a 49\% decrease in brain Aβ deposition.\textsuperscript{10} PBT2, a second generation 8-OH quinoline, has several advantages over CQ, including easier chemical synthesis, higher solubility and increased blood-brain-barrier (BBB) permeability.\textsuperscript{7} Phase IIa clinical trials show PBT2 attenuates cognitive decline, in conjunction with decreasing plasma Aβ levels.\textsuperscript{13} AD model mice studies also indicate that PBT2 lowers both interstitial Aβ levels and phosphorylated tau proteins.\textsuperscript{14} Another potential drug, PD-109, was specifically designed to selectively bind Zn and Cu. With a high lipophilicity, PD-109 can also effectively cross the BBB. Results showed it facilitates the transition of Aβ from insoluble to soluble forms in the cerebrum.\textsuperscript{15} Commercially available pyrrolidine dithiocarbamate (PDTC) also shows some promise by decreasing tau phosphorylation and stimulating protective signaling pathways.\textsuperscript{16}

The second therapeutic strategy, increasing copper bioavailability, appears to be just as effective as the chelation strategy. Here, glyoxalbis(N(4)-methyl-3-thiosemicarbazonato) copper (II), or Cu(II)(gtsm), demonstrated that inhibition of GSK3β, a kinase that regulates the neurotoxic pathways of AD, actually increased intracellular bioavailability of copper.\textsuperscript{7} In addition, Cu(II)(gtsm) also decreased the amount of Aβ trimers and

**Figure 2. Chelating ligands with promising potential in the treatment of AD.\textsuperscript{6,13-16}**

**Figure 3. Cu(II)(gtsm) shows much promise as an AD therapeutic.\textsuperscript{7}**
phosphorylated tau in AD mice, a decrease that correlated with the restoration of cognitive ability to that of a normal mouse.⁷

References


