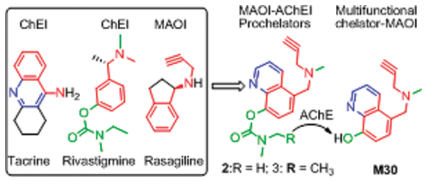
# In this ISSUE

## A Three-Pronged Attack on Alzheimer's

Alzheimer's disease, a progressive neurodegenerative disorder, is characterized by the presence of two forms of protein-derived aggregates, called β-amyloid plaques and neurofibrillary tangles, in the brain. Increased levels of biometals such as iron, copper, and zinc have been implicated in such aberrant protein aggregation events, and evidence suggests that compounds that can regulate biometal concentrations, such as metal chelating agents, may have therapeutic potential. However, typical metal chelators lack selectivity and do not necessarily penetrate the blood-brain barrier well. Now, Zheng *et al.* (DOI: 10.1021/cb900264w) report the rational design of a novel class of prodrugs that can launch a three-pronged attack on Alzheimer's disease.

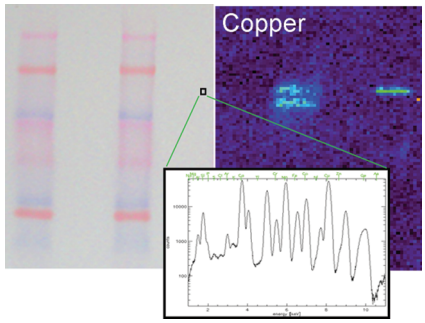
The prodrugs are designed to inhibit two enzymes implicated in Alzheimer's pathophysiology, acetylcholinesterase (AChE) and monoamine oxidase. However, upon AChE inhibition, the prodrug cleverly releases its third weapon, an active metal chelator, which is poised to modulate the local metal concentration, decrease oxidative stress, and possibly reduce unwanted protein aggregation processes. This innovative strategy may prove useful in targeting other metal-related diseases as well, such as Parkinson's disease.




## X-ray Exploitation

Metal ions play critical roles in protein function, and evidence suggests that their concentrations and distributions across cells are highly influenced by both physiological processes and the external environment. However, little is known about the dynamic regulation of metal ions, in part due to the lack of effective methods for their detection and quantification in complex environments. Finney *et al.* (DOI: 10.1021/cb1000263) now present a simple yet powerful approach to identify and quantify metal ions associated with metalloproteins in complex samples.

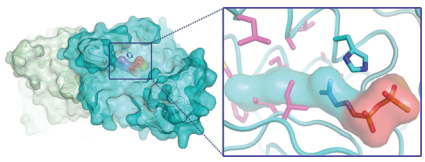
The approach exploits the fact that metals are fluorescent when excited at X-ray energies. After gel electrophoresis to separate proteins in complex mixtures, the existence, amount, and chemical state of the metal ions associated with a given protein could be determined using two X-ray based techniques, synchrotron X-ray fluorescence and X-ray absorption spectroscopy. The utility of the approach was demonstrated by examining the binding of different chromium species to blood serum proteins and by evaluating changes in iron speciation that result from oxygen depletion in the metal-metabolizing bacteria *Shewanella oneidensis*.




## Accessing Isoprenoids from Archaea

From archaea to humans, isoprenoids play key roles in many biological processes, such as membrane stability, steroid biosynthesis, and protein localization. Archaea, however, appear to utilize a distinct pathway for the formation of isopentenyl diphosphate (IPP), a key precursor in isoprenoid biosynthesis. Isopentenyl phosphate kinase (IPK) is a recently discovered enzyme that catalyzes the formation of IPP in archaea, and Dellas *et al.* (DOI: 10.1021/cb1000313) now report the crystal structure and biochemical characterization of IPK from the archaeon *Methanocaldococcus jannaschii*.

Analysis of the IPK crystal structure revealed the pivotal role of an active site histidine residue, which interacts with both the substrate and the product of the reaction. Moreover, the information gained from mutational studies facilitated the design of engineered enzymes capable of producing nonnatural isoprenoid diphosphates. Such engineered enzymes and their products have numerous applications, including the recycling of isoprenyl monophosphates in isoprenoid production, and the creation of various isoprenoid analogues for use as molecular tools in the exploration of isoprenoid biology.



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