The objective of this project was to investigate the potential of the natural protein, metallothionein as a treatment for Alzheimer’s disease.

We found that metallothionein had a powerful ability to block the injurious effect of Aβ on cultured neurons. It did this by an unexpected mechanism involving an exchange between metallothionein-bound zinc and Aβ-bound copper. Furthermore, this process inhibited the formation of the plaque-associated form of Aβ. Thus, metallothionein is likely to oppose the accumulation of toxic Aβ, and to simultaneously protect neurons from damage.

We compared the ability of different types of metallothionein, including novel synthetic forms we designed, to protect neurons and were able to identify the key structural components of metallothionein responsible for its properties. We performed two animal trials administering metallothionein to animals with a genetic predisposition to Alzheimer’s disease. In one trial metallothionein clearly decreased formation of Aβ plaques but disappointingly we were not able to replicate this in the second trial. We believe this was due to difficulties in administering metallothionein to these animals, and because of the unexpectedly low levels of Aβ deposited in the animals’ brains. We therefore studied the distribution of metallothionein in mice following administration and found that indeed small amounts did reach the brain and could be found within neural cells, suggesting that we need to repeat these trials in a more robust model of the disease (this work is currently underway, funded by the NHMRC).

An unexpected outcome from this project was the development of a cell-based assay for screening potential therapeutic agents for their ability to inhibit Aβ plaque formation and stability. This may have significant potential for the rapid analysis of large numbers of novel molecules and is under further development in our laboratory.