



## **Targets for eliminating misfolded proteins that cause human diseases (e.g. neurodegenerative diseases)**

**The Challenge:** Alzheimer's (AD), Huntington's (HD) and Parkinson's Diseases (PD) are neurodegenerative disorders characterized clinically by progressive memory loss and neuropathologically by extensive neuronal cell death and accumulation of misfolded proteins in the brain. In fact, there is growing evidence that accumulation of misfolded proteins in cells and tissues cause not only neurodegenerative diseases but also many other human diseases. For example, several human disorders are associated with an expansion of a continuous stretch of glutamine or alanine amino acids in proteins: nine different human disorders are linked to expansion of a reiterated stretch of glutamine amino acid, and another nine to expansion of alanine amino acids (collectively called polyglutamine or polyalanine disorders, respectively). A classical example of a polyglutamine expansion disorder is Huntington's disease. The mechanisms by which expanded polyglutamine and polyalanine proteins cause disease is still not fully understood. One apparently abnormal feature of proteins containing expanded polyglutamine and polyalanine tracts is their tendency to misfold and aggregate, which has been linked to their toxicity. Discovery of factors that eliminate or clear misfolded proteins from cells could provide an attractive means to treat or prevent disease caused by protein misfolding. UMBI scientists have shown that overexpression of the protein ubiquilin reduces protein aggregates and toxicity of both expanded polyglutamine and polyalanine proteins.

**UMBI Solution:** Overexpression of ubiquilin can clear polyalanine and polyglutamine aggregates thereby reducing protein aggregates, toxicity and cell death. Thus, ubiquilin is likely to be useful for preventing or clearing the accumulation of misfolded protein aggregates in cells. Methods to modulate ubiquilin expression might have utility to treat diseases not only associated with expanded polyalanine and polyglutamine proteins, but also diseases associated with misfolding and aggregation of other unrelated proteins. UMBI investigators also showed that ubiquilin interacts with presenilins, mutations in which cause Alzheimer's disease. It therefore appears that ubiquilin interacts with key proteins involved in a number of human diseases and could provide an attractive therapeutic target for treating Alzheimer's, Huntington's and other human diseases.

### **Commercial Applications:**

- **Drug Development:** targets for development of therapeutics to treat neurodegenerative disorders and other diseases characterized by expanded polyalanine and polyglutamine proteins
- **Research use:** provides assayable probe for the characterization of important biochemical pathways in neurodegenerative diseases and the discovery of novel drug targets

**Advantages:** Platform technology – may be used as a platform for developing a drug to treat Alzheimer's, Huntington's and Parkinson's patients

**Stage of Development:** Proteins have been shown to interact and be regulated in a predictable way *in vitro*, in cell-lines and in nematode model systems. Experiments need to be carried out in higher animal models and the development of a reporter cell-line or assay system is underway to allow HTS of therapeutics.

**Patent Status:** U.S. and PCT patent applications are pending

**Licensing Potential:** UMBI is seeking exclusive or non-exclusive licensees to all or part of this technology portfolio. The UMBI Inventor would welcome the opportunity to collaborate with any licensee to further refine the invention or extend its capabilities.

**Lead Inventor & UMBI References:** Monteiro, 00-023; 05-007; 06-023

**Relevant Publications:**

1. Mah, A.L., G. Perry, M.A. Smith, and M.J. Monteiro. 2000. Identification of ubiquilin, a novel presenilin interactor that increases presenilin protein accumulation. *J Cell Biol.* 151:847-62.
2. Wang H, Lim PJ, Yin C, Rieckher M, Vogel BE, and Monteiro M.J. (2006) Suppression of Polyglutamine-Induced Toxicity in Cell and Animal Models of Huntington's Disease by Ubiquilin. *Hum Mol Genet.* 15:1025-1041.
3. Wang H, and Monteiro MJ. (2007) Ubiquilin overexpression reduces GFP-polyalanine-induced protein aggregates and toxicity. *Exp Cell Res* 313:2810-2820.
4. Wang H, and Monteiro MJ. (2007) Ubiquilin overexpression enhances the degradation of expanded polyglutamine proteins. *Biochem Biophys Res Commun.*360:423-427.

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