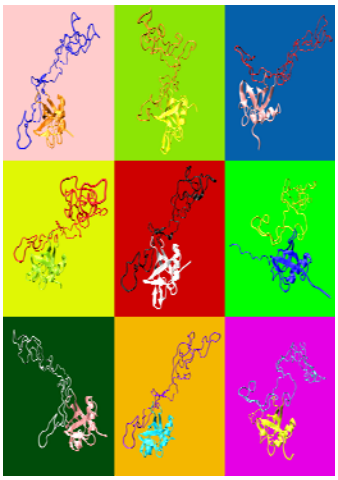
Madrid, Wednesday May 30th 2012

A study reveals common features in the proteins that trigger neurodegenerative diseases

- **The results may provide new targets for prevention, early diagnosis and therapy of these devastating diseases**

- **It has been published in the last issue of 'PLoS Biology', being selected as a journal cover with a special comment**



Artistic rendering of the conformational polymorphism of a neurotoxic protein. Neurodegenerative diseases like Alzheimer's or Parkinson's have been causally related to specific proteins that typically do not have a defined structure. Using single-molecule force spectroscopy one can monitor their rich fluctuating behaviour, which is on the basis of the key process that triggers the pathological cascade, making it an ideal target for therapy, diagnostics and prevention. This conformational polymorphism is closely associated to disease and can be inhibited by a potential therapeutic agent. *Image generated using CESGA resources and the VMD program.*

Neurotoxic proteins are those proteins that as we grow older, and under certain circumstances, can trigger neurodegenerative diseases like Alzheimer's or Parkinson's. They are involved in a variety of cellular functions and, though they posses very different sequences, they share the final steps of the process of aggregation and fibril formation, which is associated to these diseases. A study leaded by the Cajal Institute (CSIC) has revealed that these proteins share common features also from the beginning of the neurodegeneration cascade. These results may help to perform early diagnostics and to design drugs to treat or prevent these disorders. This study has

counted with the participation and funding of the Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas and the participation of IMDEA Nanociencia.

Thanks to an atomic force microscope, the researchers have been able to stretch and deconstruct these proteins, one molecule at a time, to individually analyze they structures they form. “We have discovered that all representative neurotoxic proteins before they start to associate and form their characteristic aggregates, they adopt a rich collection of structures the formation of which has been associated to cellular toxicity and neurodegeneration”, explains the CSIC researcher Mariano Carrión-Vázquez, from the Cajal Institute.

Blockade of ‘molecular malignization’

This study has also uncovered that a pharmacological agent (termed QPB1) is able to block the “molecular malignization” of neurotoxic proteins like the one involved in Parkinson’s disease and a prion model similar to those causing mad caw disease or its equivalent in humans. The curative potential of QBP1 was previously demonstrated by other group in animal models that reproduced Huntigton’s disease.

“This polyvalent potential drug reduces the formation of the stable structures we detect in these proteins and, considering their association to disease development, we propose they are the ones that may trigger the disease. The mechanical blockade of molecular motors, a kind of molecular seizing, of the protein recycling machinery of the cell may be a possible mechanism that could initiate these diseases”, adds Carrión-Vázquez.

Prevention, diagnostics and treatment

The researchers, which have published this study in the last issue of *PLoS Biology*, think that some of the observed structures may serve as a target for treatment as well as prevention and early diagnostics of these diseases.

“Our work opens the door to understand the molecular mechanism that triggers the toxicity of neurotoxic proteins. This may allow to elucidate the primary cause of these diseases and represents a critical step forward for prevention, diagnostics and for designing more specific and efficient drugs”, concludes the researcher.

Rubén Hervás, Javier Oroz, Albert Galera-Prat, Oscar Goñi, Alejandro Valbuena, Andrés M Vera, Àngel Gómez-Sicilia, Fernando Losada-Urzáiz, Vladimir N. Uversky, Margarita Menéndez, Douglas V Laurents, Marta Bruix, Mariano Carrión-Vázquez (2012). **Common Features at the Start of the Neurodegeneration Cascade**. *PLoS Biol* 10(5): e1001335. doi:10.1371/journal.pbio.1001335.

Janelle Weaver (2012) **Single-Molecule Technique Links Structural Fluctuations of Proteins to Brain Diseases**. *PLoS Biol* 10(5): e1001338. doi:10.1371/journal.pbio.1001338.