

|                       |   |
|-----------------------|---|
| <b>Title</b>          | <b>Provide a title for the research project</b>   |
| <b>PI</b>             | POLVERINO DE LAURETO Patrizia   |
| <b>Research Group</b> | Protein Chemistry   |
| <b>Curriculum</b>     | Scienze Farmaceutiche   |
| <b>Contact</b>        | <b>web:</b> <a href="http://www.dsfarm.unipd.it/patrizia-polverino-de-laureto-0">http://www.dsfarm.unipd.it/patrizia-polverino-de-laureto-0</a> |
|                       | <b>email:</b> <a href="mailto:patrizia.polverinodelaureto@unipd.it">patrizia.polverinodelaureto@unipd.it</a>                                    |

### Molecular basis of the interaction between $\alpha$ -synuclein and compounds with anti-fibrillogenic properties

#### Project description:

- The research activity of our lab focuses on protein folding and misfolding studies and issues related to protein aggregation. Systematic studies are carried out with the aim of clarifying at the molecular level the protein amyloid aggregation mechanism using spectroscopic (circular dichroism, fluorescence, Fourier transform infrared, dynamic light scattering), biochemical (limited proteolysis) and morphological (electronic microscopy) techniques. A topic of current interest concerns the study of aggregated states of human alpha-synuclein, a protein involved in Parkinson's disease. Considering that this protein is present in free brain districts or presynaptic terminals, interaction studies with synthetic membranes and fatty acids are ongoing. Actually we are involved in a project focused on the study of the molecular interaction between the protein and small molecules of natural origin able to inhibit its amyloid aggregation process. These investigations into the structure–activity relationships of natural products may guide the design of novel therapeutic drugs in Parkinson's disease with enhanced properties.

#### Publications:

- E. Frare, M. F. Mossuto, P. Polverino de Laureto, M. Dumoulin, C. M. Dobson and A. Fontana. Identification of the Core Structure of Lysozyme Amyloid Fibrils by Proteolysis. *J.Mol.Biol.* 361, 551–561 (2006).
- P. Picotti, G. De Franceschi, E. Frare, B. Spolaore, M. Zambonin, F. Chiti, P. Polverino de Laureto, A. Fontana. Amyloid Fibril Formation and Disaggregation of Fragment 1-29 of Apomyoglobin: Insight into the effect of pH on Protein Fibrillogenesis. *J.Mol.Biol.* 367, 1237–1245 (2007).
- G. De Franceschi, E. Frare, L. Bubacco, S. Mammi, A. Fontana, and P. Polverino de Laureto. Molecular Insights into the Interaction between alpha-Synuclein and Docosahexaenoic Acid. *J. Mol Biol.* 394, 94–107 (2009).
- M.F. Mossuto, A. Dhulesia, G. Devlin, E. Frare, Kumita Jr, P. Polverino De Laureto, M. Dumoulin, A. Fontana, C.M. Dobson, X. Salvatella. The Non-core Regions of Human Lysozyme Amyloid Fibrils Give Rise to Cytotoxicity. *J. Mol Biol.* 402, 783–796 (2010).
- G. De Franceschi, E. Frare, M. Pivato, A. Relini, A. Penco, E. Greggio, L. Bubacco, P. Polverino de Laureto. Structural and morphological characterization of aggregated species of alpha-synuclein induced by docosahexaenoic acid. *J.Biol.Chem.*, 286, 22262–22274 (2011).
- M. Pivato, G. De Franceschi, L. Tosatto, E. Frare, D. Kumar, D. Aioanei, M. Brucale, I. Tessari, M. Bisaglia, B. Samori, P. Polverino de Laureto, L. Bubacco. Covalent  $\alpha$ -synuclein dimers: chemico-physical and aggregation properties. *PLoS One* 7(12). doi: 10.1371/journal.pone.0050027 (2012).
- C. Fecchio, G. De Franceschi, A. Relini, E. Greggio, M. Dalla Serra, L. Bubacco, P. Polverino de Laureto.  $\alpha$ -Synuclein oligomers induced by docosahexaenoic acid affect membrane integrity. *PLoS One.* 8(11), e82732. doi:10.1371/journal.pone.0082732. (2013).
- Y. Feng, G. De Franceschi, A. Kahraman, M. Soste, A. Melnik, P. Boersema, P. Polverino de Laureto, Y. Nikolaev, A. P. Oliveira and P. Picotti. Probing protein structural transitions in complex biological backgrounds. *Nature Biotechnology* 32, 1036–1044, doi:10.1038/nbt.2999 (2014).
- J. R. da Palma, D. J. Burri, J. Oppliger, M. Salamina, L. Cendron, P. Polverino de Laureto, N. G. Seidah, S. Kunz, A. Pasquato. Zymogen Activation and Subcellular Activity of Subtilisin Kexin Isozyme-1/Site-1 Protease. *J.Biol.Chem.* 289, 35743–35756, doi: 10.1074/jbc.M114.588525 (2014).



- 
10. G. De Franceschi, C. Fecchio, R. Sharon, A.H. Schapira, C. Proukakis, V. Bellotti, P. Polverino de Laureto.  $\alpha$ -Synuclein Structural Features Inhibit Harmful Polyunsaturated Fatty Acids Oxidation, Suggesting Roles in Neuroprotection. *J.Biol.Chem.* 292(17):6927-6937 (2017).

**Collaborations/Network:**

University of Florence  
University of Tuscia (Viterbo)  
University College of London  
Lausanne University Hospital