De Luigi, A., Mariani, A., De Paola, M., Re Depaolini, A., Colombo, L., Russo, L., Rondelli, V., Brocca, P., Adler-Abramovich, L., Gazit, E., Del Favero, E., Cantù, L., Salmona. M. Doxycycline hinders phenylalanine fibril assemblies revealing a potential novel therapeutic approach in phenylketonuria. ***Sci. Rep.***; 2015: 5

Abstract: A new paradigm for the aetiopathology of phenylketonuria suggests the presence of amyloid-like assemblies in the brains of transgenic mouse models and patients with phenylketonuria, possibly shedding light on the selective cognitive deficit associated with this disease. Paralleling the amyloidogenic route that identifies different stages of peptide aggregation, corresponding to different levels of toxicity, we experimentally address for the first time, the physico-chemical properties of phenylalanine aggregates via Small Angle, Wide Angle X-ray Scattering and Atomic Force Microscopy. Results are consistent with the presence of well-structured, aligned fibres generated by milliMolar concentrations of phenylalanine. Moreover, the amyloid-modulating doxycycline agent affects the local structure of phenylalanine aggregates, preventing the formation of well-ordered crystalline structures. Phenylalanine assemblies prove toxic in vitro to immortalized cell lines and primary neuronal cells. Furthermore, these assemblies also cause dendritic sprouting alterations and synaptic protein impairment in neurons. Doxycycline counteracts these toxic effects, suggesting an approach for the development of future innovative non-dietary preventive therapies.