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| PhD Program | MEDICINAL CHEMISTRY |
| Project title: | Novel gelator molecules incorporating short A β - fragments. Minimalist design of aggregated A β -peptide. |
| Research field: | Project belongs to bioorganic and medicinal chemistry fields. Molecules capable to self-assemble into nano-sized fibrous aggregates and containing selected fragments of the Alzheimer's disease involved A β -protein will be designed using molecular modeling. Their self-assembly motifs at molecular and supramolecular levels will be investigated by spectroscopic methods (FTIR, ¹ H-NMR, UV, CD and fluorescence) electronic microscopy (TEM SEM) and AFM. |
| Institution where the experimental work will be performed | Ruđer Bošković Institute 10000 Zagreb, Bijenička 54 URL: http://www.irb.hr/hr/str/zokb/labs/04_lsnc/ |
| Supervision | The investigation will be supervised by Prof. dr. sc. Mladen Žinić |
| Achievement | The candidate will acquire broad knowledge in organic synthesis, spectroscopy, electronic microscopy and supramolecular chemistry including principles of molecular recognition, self-assembly and self-organization. After PhD degree, candidate will acquire knowledge of principles and methods of modern chemistry and should be able to successfully compete for either an academic position, or position in chemical or pharmaceutical industry. |
| Abstract | <p>Aggregation and disaggregation are central phenomena in nature and the formation of fibers through self-assembly is of particular interest as common building principles are found in both living and nonliving (synthetic) systems. Protein fibers are involved in intra- and extra-cellular functions, but also in a group of diseases that feature pathological changes in protein conformation. One of the best studied examples is the amyloid β-peptide (Aβ), a cleavage product of the amyloid precursor protein (APP), which is causally implicated in Alzheimer's disease (AD) and other neurodegenerative disorders. As proposed by different models, β-sheets form within Aβ, and the peptide then assembles into fibrils, which subsequently aggregate into hierarchical assemblies. Hydrogen bonds and hydrophobic interactions between the peptide molecules are responsible for this assembly process. A consequence of the Aβ self-assembly process is the formation of extra-cellular amyloid plaques composed of aggregated Aβ.</p> <p>On the other hand, fibers and fibrils can be generated from specially designed small molecules encoded with information for unidirectional self-assembly. In many cases such self-assembly that occurs in specific solvents results in formation of gels. In this PhD thesis, novel gelling molecules containing short selected fragments of Aβ-peptide (2-5 amino acids) will be designed and synthesized. Their gelling properties toward water and various organic solvents will be assessed. The self-assembly motifs existing at the molecular and supramolecular levels will be studied by spectroscopic methods (FTIR, ¹H-NMR, UV, fluorescence, CD), electron microscopy (TEM, SEM) and atomic force microscopy (AFM). The results of structural studies are expected to provide detailed information on non-covalent interactions that stabilise fibrous gel aggregates. The successful design is expected to provide minimalist model of aggregated Aβ-peptide suitable for screening purposes. In addition, the interactions between the molecules earlier shown to bind on aggregated Aβ-peptide and the minimalist model could be studied in more detail using appropriate spectroscopic methods and may reveal the precise mode of binding. With such information in hand, stronger binders to aggregated Aβ could be designed which have a potential for development of advanced diagnostic tools or potential drugs for AD treatment.</p> |