INSTITUTE OF BIOCHEMISTRY AND BIOPHYSICS
POLISH ACADEMY OF SCIENCES

1. **Research Unit:** Laboratory of Chemical Biology of Metal Ions
2. **Supervisor:** Prof. Dr hab. Wojciech Bal
3. **Supervisor (email):** wbal@ibb.waw.pl
4. **Project title (English):** Establishment of partition of Aβ peptides related to Alzheimer's disease between the water and phospholipid phases and search for molecules modifying this partition.
5. **Project title (Polish):** Ustalenie partycji peptydów Aβ związanych z chorobą Alzheimera między fazą wodną i fosfolipidową i poszukiwanie cząsteczek modyfikujących tę partycję.
6. **Description of the project (up to 500 words)**:

Alzheimer's Disease (AD) is a progressive and inevitably lethal dementia, caused by massive death of neurons in brain structures dealing with memory and emotions. The age is the main risk factor and no treatment can revert or even halt its progress. The best available recommendation is to maintain a healthy lifestyle. Although a number of aberrant processes were identified in AD brains and many drugs were developed to curb them, none has been successful in human clinical trials.

Soluble aggregated Aβ peptides are the best documented early toxic species in AD and many therapies were directed against these species. Those therapies, although successful in experimental animals, did not work in patients. This indicates that something crucial is missing in our understanding of Aβ physiology and pathology. The aim of this project is to clarify one such physiological aspect on the molecular level.

The Aβ peptides are soluble both in water and body fluids and in phospholipid bilayers constituting cellular membranes. When present in a membrane-like phospholipid environment, these peptides remain there and do not form toxic aggregates, but, once in aqueous solution, these aggregates are formed spontaneously within hours. In contrast, the disease progress takes many years, suggesting that until this time the Aβ peptides are not released to brain fluids in significant amounts. Based on prior evidence we propose that in normal brain the Aβ peptides reside mainly in the phospholipid environment and the molecules or processes affecting their biomembrane solubility may contribute to the progress of AD. These molecules or processes may be targeted by future AD therapies.

The aims of the project include determination how much of main Aβ peptides, Aβ1-40, Aβ1-42 and Aβ4-42, can be dissolved in phospholipid bilayers of various compositions, modelling the physiological variability of cellular membranes. In such environment Aβ peptides remain monomeric, assume a partially α-helical conformation. Monomeric Aβ peptides in solution do not have a fixed shape, while the toxic Aβ aggregates contain β-sheet structures. We want to explain what causes the α-helical Aβ monomers to leave the membrane environment and get transformed into toxic aggregates. Such aggregates return to the membrane and damage it. Our further aim is to correlate the membrane leaving and membrane destructing propensity of Aβ peptides with is composition. We will also study how biological metal ions Cu(II) and Zn(II) contribute to these phenomena. Finally, we will search for molecules that could stabilize α-helices in Aβ peptides, thus reducing the risk of their aggregation and gain of toxicity. Such molecules may become AD drug candidates.

To achieve our goals we will chemically synthesize Aβ1-40, Aβ1-42 and Aβ4-42 peptides and optimize the experimental procedures of their handling in order to assure good reproducibility of experiments. Our main studies will be performed using state of the art techniques of biomembrane research, including measurements of ionic currents flowing through microscale phospholipid bilayers and determining bilayer fluidity using spin labels detected by EPR. Finally, we will employ computer simulations and experiments to screen for molecules able to enhance α-helical Aβ.

7. **References related to conducted /planned research (maximum 3)**:

    - E. Stefaniak, E. Atrian-Blasco, W. Goch, L. Sabater, C. Hureau,W. Bal, The aggregation pattern of Aβ1-40 is altered by the presence of N-truncated Aβ4-40 and/or Cu(II) ions in a similar way via ionic interactions. Chem. Eur. J. 27, 2798-2809, 2021.
    - M. Mital, K. Szutkowski, K. Bossak-Ahmad, P. Skrobecki, S. C. Drew, J. Poznański, I. Zhukov, T. Frączyk, W. Bal, The Palladium(II) Complex of $A\beta_{4-16}$ as Suitable Model for Structural Studies of Biorelevant Copper(II) Complexes of N-Truncated Beta-Amyloids, Int. J. Mol. Sci. 21, art. no. 9200, 2020, doi:10.3390/ijms21239200
    - N. E. Wezynfeld, E. Stefaniak, K. Stachucy, A. Drozd, D. Płonka, S. C. Drew, A. Krężel, W. Bal, Resistance of Cu(Aβ4-16) to copper capture by metallothionein 3 supports a function of Aβ4-42 peptide as a synaptic Cu^{II} scavenger, Angew. Chem. Int. Ed. 55, 8235–8238, 2016.

8. **Scholarship amount (net):** please contact the project supervisor.