

БЪЛГАРСКА АКАДЕМИЯ НА НАУКИТЕ  
И-Т ПО ЕКСПЕРИМЕНТАЛНА МОРФОЛОГИЯ,  
ПАТОЛОГИЯ И АНТРОПОЛОГИЯ С МУЗЕЙ  
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СОФИЯ

## OPINION

By Assoc. Prof. Ivaylo Petrov Ivanov

Member of the Scientific Jury, appointed by Order RD-15-27 of the Director of IEMPAM-BAS

**Subject:** Dissertation for obtaining the scientific degree "Doctor of Science" in the specialty "Biochemistry" (01.06.10) from Professional field 4.3 "Biological Sciences" on "Biochemical basis of Alzheimer's disease" by Prof. Ludmil Penuv Kirazov.

Prof. Kirazov has presented a full set of excellently made and neatly arranged documents, in full compliance with the requirements of the Law for Development of the Academic Staff in the Republic of Bulgaria (LDASRB) and its Regulations.

Ludmil Penuv Kirazov has been a professor of Biochemistry since 2016 at IEMPAM-BAS after successfully applying for an announced competition. The scientific career of Professor Kirazov is impressive with his specializations in Germany, as well as his publications in prominent international and national journals, with h-index 9 according to Scopus, presentation of the results of scientific forums at home and abroad and a large number (425) noticed quotes. The dissertation includes 31 publications with a total impact factor of 30.23, as well as 45 scientific papers on the topic of the dissertation. The reference to the requirements for acquiring the scientific degree "Doctor of Sciences" from the Regulations of IEMPAM for application of the LDASRB shows 652 points, which is almost twice the required minimum of 350 points.

Alzheimer's disease is the most common degenerative disease affecting the human brain and is the predominant type of dementia. In the last two decades, there has been an increase in mortality from this disease, with age being the main risk factor. With the changing demographic structure of society, characterized by an increasing number of older people, Alzheimer's disease has become a serious social and economic problem. Despite the accumulated vast information, the causes of the disease are not well understood, which the reason for the lack of effective therapy is. According to the above, the topic of the dissertation is very relevant, and the aim of the research is to contribute to clarifying the etiology of Alzheimer's disease and to create appropriate experimental models.

The presented dissertation is written on 279 pages and contains the standard sections, as 149 pages are dedicated to the presentation of the results and their discussion and 27 pages for the experimental part. The results are presented in 9 tables and 86 figures, 697 literature sources are cited.

The literature review is purposeful and written concisely and clearly. The membrane form of the amyloid precursor protein and its processing, the amyloid  $\beta$ -peptide and its forms and the role of these substances in normal and Alzheimer's disease are described. Due attention has been paid to the mixed pathology of this disease.

The applied methods are described in detail, in view of the possibility of repeating them. A wide range of biochemical, genetic, immune and other methods have been used. The effectiveness of the applied methods at a certain stage of the work was subjected to a thorough analysis. As a result, improvements have been made to these methods or other suitable methods have been tried. This shows that an opportunity has been sought to obtain the most reliable results.

The presented scientific publications show that the scientific activity of Professor Ludmil Kirazov is in the field of biochemistry, as the main scientific contributions can be grouped as follows:

It has been found that monomeric amyloid  $\beta$ -peptides affect the concentration-dependent and reversible electrical activity of neuronal cells, whereas A $\beta$ 1-42 fibrils do not have such an effect. Based on the obtained data, it was concluded that the reduction of electrical activity by monomeric amyloid  $\beta$ -peptides, which disrupts communication between neurons, is key to the development of Alzheimer's disease, i.e. senile plaques are the result of the disease, not the cause. Amyloid  $\beta$ -peptides have been shown to act as agonists of the neurotransmitter receptors  $\gamma$ -amino butyric acid and glycine.

The neurotransmitter glutamate modulates the processing of amyloid precursor protein and a change in balance is important in the development of Alzheimer's disease. There was no feedback between the amount of soluble amyloid precursor protein and its secretion.

The study of the influence of vascular endothelial growth factor on the processing of amyloid precursor protein has shown that it leads to transient inhibition of amyloid  $\beta$ -protein fibrillogenesis.

Interleukin-1 $\beta$  has been shown to play an important role in the pathogenic mechanisms leading to cholinergic deficiencies in patients with Alzheimer's disease.

The role of cholinergic innervation in the processing of amyloid precursor protein has been demonstrated in vivo using transgenic models of Alzheimer's disease. By appropriate treatment, an improved animal model of Alzheimer's disease with a pathology closer to human has been obtained, which can be used in future studies of this disease.

The role of amyloid precursor protein in synaptogenesis and maintenance of normal synaptic function has been convincingly demonstrated. Studies on mRNA expression of various isoforms of amyloid precursor protein in ontogenesis confirm its role in synaptogenesis.

For the first time, a comparative study of the transcriptome in the synaptosomal fraction of young and adult mice was performed. As a result of these studies, a number of previously undescribed long intervening non-coding RNAs and circular RNAs have been found in adult synaptosomes. These results are the basis for future research on some of the molecular mechanisms of the disease.

The abstract adequately reflects the content of the dissertation.

**Conclusion:** The dissertation of Professor Ludmil Kirazov is significant in volume and quality, carried out at a high professional level. The style is clear and concise, with strictly processed data, detailed original results, accurate conclusions and contributions. This scientific work significantly enriches the knowledge of the biochemical mechanisms of the pathogenesis of Alzheimer's disease. The obtained results have found very good citations in the scientific literature. Both the work and the scientometric indicators of Professor Kirazov fully comply with the requirements of LDASRB and its Regulations.

Based on the above, with deep conviction I recommend the honorable Scientific Jury to award Prof. Ludmil Penuv Kirazov the degree "Doctor of Science" in Biochemistry (01.06.10) from the Professional Field 4.3 "Biological Sciences".

05/17/2021

Signature: 