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The Chair of the Scientific Council
Institute of Bioorganic Chemistry
Polish Academy of Sciences in Poznan

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Review of the Doctoral Dissertation of Ms. Alicja Komur entitled "The C. elegans "hibernation": surviving cold through ferritin-mediated iron detoxification"

The Ph. D. dissertation I have reviewed describes original experiments performed and analyzed by Ms. Alijca Komur in the Institute of Bioorganic Chemistry, Polish Academy of Sciences (IChB PAS) in Poznan. Prof. Rafal Ciosk and Dr. Daria Sobanska supervised the research presented in the Dissertation.

Cold is a potentially lethal hazard. How plants and animals rewire cellular programs to survive cold is a fascinating problem. In the case of animals, hibernation is a physiological response to temperature decrease, which correlates with metabolic rate reduction without any negative consequences for the health and survival of the organism. The detailed cellular mechanisms underlying entrance or exit to the hibernation state have yet to be entirely determined. The aim of the Thesis was to uncover molecular processes involved in the hibernation-like response, employing a simple model organism that enters a hibernation-like state, the nematode *Caenorhabditis elegans*. The study started from the previous observation that nematodes lacking the ETS-4 transcription factor exhibited improved cold survival. Among the genes whose regulation was altered by the absence of ETS-4, the upregulation of *ftn-1* mRNA was observed. *ftn-1* encodes an ortholog of mammalian ferritin heavy chain (FTH1). Therefore, the objectives of this study were focused on determining whether FTN-1 was involved in cold protection in *C. elegans* and a better understanding of the processes underlying the proposed *C. elegans* ferritin-mediated cold protection during hibernation-like response.

The main findings of this Thesis were: (i) High levels of FTN-1 enhances cold resistance in *C. elegans* (ii) The ferroxidase activity of FTN-1 is required for cold protection. (iii) Most likely, FTN-1 acts as an antioxidant in the protection against

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reactive oxygen species (ROS) generated by cold exposure (iv) Additional factors, aside from ETS-4, such as ELT-2 and HIF-1, contribute to the regulated expression of FTN-1 in cold conditions (v) Two RNA- binding proteins, RLE-1 and REGE-1 collaborate to silence the *ets-4* mRNA during cold response.

The structure of the Ph. D. Thesis is standard. It includes the relevant and required chapters, i.e., theoretical introduction, precisely formulated objectives, description of performed materials and methods, obtained results and discussion, conclusions plus summary, and references. The introduction presents the necessary information about the major topics addressed in the Thesis. It provides all facts important for understanding the experimental chapters. Materials and methods are adequately described and support the analysis of obtained results. Chapter Results, divided into appropriate parts, forms the most extensively elaborated section. The author performed solid experimental work using various genetic, molecular, and cell biology approaches. The experiments described in the Thesis are thoroughly planned, and the rationale for the used approaches is clear and logical; experiments are of high technical quality and, in most cases, are accompanied by appropriate controls. The discussion section is comprehensive and well-composed. This section summarizes the presented work's outcome and offers additional exciting and insightful points. It is focused on the ferritin role in cold protection in *C. elegans* and the extrapolation of these results to higher animals. Also, the discussion includes a section on future perspectives on this work.

Ms. Alicja Komur presents in her Ph.D. thesis original results, which have allowed her to suggest a central role of ferritin in the cold-protection response in *C. elegans*, which is the most outstanding achievement of this work. The Ph. D. student has performed excellent research, and proof of it is that the results obtained by her were part of two research articles in two prestigious journals (Nucleic Acid Research and Nature Communications). Moreover, the obtained data open new exciting directions for future

studies in cold survival, which is the best indication of high-quality scientific results. The candidate could design and carry out molecular biology and biochemical experiments and interpret the results of the experiments performed critically. Moreover, Ms. Alicja Komur has shown that she knows all scientific literature concerning the cold-response field well and can confront her observations with the results that other researchers have obtained.

The Dissertation being the subject of the review, fulfills the conditions laid down in the Act of July 20, 2018, The Law on Higher Education and Science (Journal of Laws 2018, item 1668 as amended), the Act of July 3, 2018, Provisions Introducing the Act – The Law on Higher Education and Science (Journal of Laws 2018, item 1669 as amended), and The Rules of Proceeding in the Matter of Awarding the Doctoral Degree in the Institute of Bioorganic Chemistry PAS (Resolution of the Scientific Board of IBCH PAS No. 99/2022/Internet of June 9, 2022) and I recommend that the Scientific Board of the Institute of Bioorganic Chemistry PAS allows it to further steps in Ph.D. defense process.

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