OPINION

by Assoc. prof. Ivan Nedkov Ivanov, MD, PhD

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Subject: Doctoral thesis for the acquisition of educational and scientific degree "Doctor" in professional field 4.3. Biological Sciences, PhD program "Genetics", by Georgi Dimitrov Blazhev, full-time PhD student at the Department of Genetics, Faculty of Biology, Sofia University "St. Kliment Ohridski". Kliment Ohridski".

Doctoral thesis topic: "A multi-omics approach to analyze the biological and clinical heterogeneity of some rare malignant diseases"

Scientific supervisor of the PhD student: Assoc. prof. Velizar Stefanov Shivarov, MD, PhD.

1. General presentation of the procedure and the PhD student

The presented Doctoral thesis and abstract are prepared in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, and the Regulations for its implementation and the Regulations on the terms and conditions for acquiring academic degrees and occupying academic positions at Sofia University "St. Kliment Ohridski". Kliment Ohridski".

The Doctoral thesis is structured in the usual way, according to the requirements, spread over 102 pages, including 173 references . It is illustrated with figures, tables and graphs. The autoreferate has an usual structure, written on 43 pages.

Presented with the Doctoral thesis are two publications in international journals (one of which in a periodical with impact factor) and one participation in a scientific forum. The PhD student has provided a reference showing the successful implementation of the individual curriculum for full-time doctoral studies according to the requirements of Sofia University. There is a fulfillment of the minimum requirements set out in the Law on the Development of the Academic Staff in the Republic of Bulgaria.

2. Assessment of the topicality of the problem.

In the introduction and review of the Doctoral thesis, the PhD student discusses the epidemiology and problems associated with rare oncological diseases. Main emphasis is placed on malignant pleural mesothelioma, its etiology, pathogenesis, diagnosis and unfavorable prognosis. The introduction shows the social significance of the disease. Performing systemic biomedical testing by combining omics data is an approach with the

potential to identify biomarkers and potential therapeutic targets in malignant pleural mesothelioma. This demonstrates the relevance of the problem in modern medical diagnostic and therapeutic activity, as well as research, medico-biological practice.

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3. Knowledge of the problem

The literature review is structured in several sections, according to the tasks set in the Doctoral thesis. The first main focus of the review examines in synthesized form the main aspects related to epidemiology, etiology and pathogenesis, as well as the diagnosis and morphological classification of malignant pleural mesothelioma. In detail, the PhD student represents the genetic aspects of the disease. The second focus of the literature review is devoted to the basic concepts and essence of omics technologies. In general, the literature data presented are modern and sufficient, without unnecessary circumstantiality.

The hypothesis, the purpose of the Doctoral thesis and the defined nine tasks are relevant and logically subordinate to the title of the dissertation. The Doctoral thesis is identified as a scientific study aimed at translating known biological data into conclusions with a clinically related meaning.

4. Doctoral thesis methodology

The analytical approach used is modern, consistent with the available omics data on malignant mesothelioma of the pleura. The author points out the databases used and the approach when working with them. The methodology is consistent with the purpose and objectives of the study. The author demonstrates that he is proficient in and applies the described methods.

5. Evaluation of the results of the Doctoral thesis

The results are described in sufficient detail, arranged and illustrated. They follow the tasks set. The author derived a two-gene predictive score (2-PS) using a classical treminating transcriptional data set. A predictive value of the binary 2-PS score was demonstrated in one training and in two validation datasets. It was studied to what extent the binary 2-PS score defined subgroups of patients with malignant pleural mesothelioma with different biological characteristics.

Further analysis in the subgroups demonstrated that the score correlated with calculated infiltration by certain types of immune cells.

The potential of 2-PS as prognostic in survival and predictive of response to certain types of therapy is identified. In this context, the correlation of 2-PS in different cell lines malignant mesothelioma of the pleura with their sensitivity to specific antitumor medications administered in vitro was investigated. This work outlines an approach of work that is applicable to other malignant neoplasms for which available and sufficient omics data are available.

The discussion presents in a summarized form the meaning and role of the results obtained, and they are compared with the results of other similar studies in the available literature. The author discusses briefly the possibility of implimentation of artificial intelligence in future development of predictive models.

The conclusions are five in number, clear and plausible, corresponding to the tasks set and the results described. They are a consequence of the implementation of the tasks set and the analysis of the results obtained.

6. Evaluation of the contributions formulated

The contributions proposed by the PhD student are four in number original and three of a confirmatory nature. Contributions are objective and can be accepted.

7. Conclusion

Georgi Blazhev's Doctoral thesis is in line with the current state of biomedical sciences and is dedicated to a contemporary topic. In the course of the development of the Doctoral thesis, the PhD student has acquired sufficient theoretical knowledge and practical skills to allow him to independently carry out similar scientific research.

I believe that the dissertation presented in this form meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and I give a positive opinion on the award of the PhD student Georgi Blazhev to PhD degree in the scientific specialty "Genetics" from professional field 4.3 "Biological Sciences".

15.05.2024 г. .....

Pleven (Assoc. prof. Ivan Nedkov Ivanov, MD, PhD)