

OPINION

on the dissertation for the award of the scientific degree "Doctor of Biological Sciences" in the Field of Higher Education 4. "Natural Sciences, Mathematics and Informatics", professional direction 4.3. Biology, specialty "Molecular Biology" at the "Chromatin Structure and Function" section, IMB, BAS

Thesis topic: Common target, different agents: Fundamental vulnerabilities of the tumor cell as a basis for selective antitumor action

Author: Prof. Dr. Iva Ugrinova

by Prof. Dr. Tanya Ivanova Topuzova-Hristova, Faculty of Biology of Sofia University "St. Kliment Ohridski", member of the scientific jury, determined by order No. 150-OB of 13.07.2026 of the Director of the Institute of Molecular Biology, BAS

1. Brief biographical information about the candidate

Prof. Iva Ugrinova graduated from the Faculty of Biology of Sofia University in 1992 with a degree in "Biotechnology", specialization in "Genetic and Cellular Engineering". She obtained her educational and scientific degree "PhD" at the Institute of Molecular Biology, Bulgarian Academy of Sciences in 2002 with a dissertation defense on the topic: "Post-synthetic acetylation of the non-histone protein HMGB1 - characterization and DNA binding properties". She has specializations at the Ecole Normale Supérieure de Lyon - Lyon, France with funding from NATO -2004-2005 and from the Région Rhône-Alpes - 2007. Her entire scientific career has been connected to the Institute of Molecular Biology-Bulgarian Academy of Sciences, where she successively passed through all academic positions from doctoral student to the academic position of "Professor", which she holds in 2019. From 2013 to the present, she has been the head of the "Chromatin Structure and Functions" section, and from 2014 to 2022 she combines this position with the position of Director of the Institute of Molecular Biology, and from 2022 to the present, she is the deputy director of the same institute. She was a visiting professor at École Normale Supérieure de Lyon – Lyon, France in 2008 and 2014.

Prof. Dr. Iva Ugrinova Zlatkova works actively in the field of molecular biology and epigenetics. The main focus of her research is the structural organization of chromatin and the role of non-histone HMGB proteins in the regulation of processes in the cell nucleus. This problem is logically related to the elucidation of mechanisms of ontogenesis and a significant contribution to experimental oncology, as well as the development of new antitumor therapies. In this regard, Prof. Ugrinova's team is involved in the testing of new compounds (coamorphic drug structures, metal complexes and nanomaterials), investigating their capacity for targeted cytotoxic action against tumor cells. These studies find a logical continuation in the developments included in the dissertation. She is the head of two national projects funded by the National Science Foundation of the Ministry of Education and Science, on the topic of the dissertation: D01/217 of 30.11.2018. Topic: "Innovative low-toxic biologically active agents for precision medicine" (completed) and KP06-H61/1 of 13.12.2022. Topic: "Antitumor activity and mechanism of action of newly synthesized DNA intercalating heterocyclic condensed naphthalimides" (ongoing). Part of the research was funded by three more national research projects, in which Prof. Ugrinova is a participant and to which she has expressed gratitude in the dissertation.

2. General characteristics and relevance of the dissertation work

Quantitative indicators: The volume of the dissertation is 275 pages, which are distributed in 12 chapters, following the generally accepted scheme for such work: Introduction, Literature review (55 pages), Objective supported by five specific scientific tasks, Results (187 pages), Summary discussion, Conclusion, Contributions, Conclusions, Perspectives and future development of the research and Lists of abbreviations, publications and cited literature. The Results chapter presents the individual publications summarized in the dissertation work, which are fully integrated into the text, including cited literature for each of them. This way of presenting a dissertation work for the acquisition of the scientific degree "Doctor of Sciences" is permissible, according to item 2.2 of the Regulations for the implementation of the law on the development of the academic staff at the Institute of Molecular Biology "Acad. Rumen Tsanev" (IMB) at the Bulgarian Academy of Sciences. The publications are grouped into three thematic areas, corresponding to the main research areas of the dissertation. 158 papers are cited, of which 105 (over 66%) are from the last 5-6 years.

Relevance: Oncological diseases are still a challenge in biomedical research, due to the great impact on society and the difficulties encountered in their treatment. The drugs used for chemotherapy often have low selectivity and lead to a significant deterioration in the quality of life of patients, which makes the search for new approaches, drugs and targets in the treatment of cancer particularly relevant. The results obtained outline several promising directions for future research: 1) study of heterocyclic-cancelled naphthalimide derivatives and elucidation of their mechanisms of action; 2) creation of a new generation of functionalized polymer nanosystems for combined delivery of siRNA, antitumor drugs and natural biologically active molecules; 3) fractionation and identification of active antitumor components of the hemolymph of *Rapana venosa* and 4) the study of natural products obtained through modern environmentally friendly technologies in order to identify highly selective substances with antitumor activity.

Aim and tasks: The aim of this dissertation is to show that structurally different synthetic and natural biologically active agents can achieve a selective antitumor effect by affecting a limited number of fundamental vulnerabilities of the tumor cell, and to develop approaches to increase their pharmaceutical applicability through modern polymer nanosystems. The tasks set in this regard are excellently planned, as a cell model has been applied that allows the assessment of cellular response in the presence or absence of functional p53 and when attacking key processes in cancer cells related to the maintenance of genomic stability, redox homeostasis and cell survival programs. These three main target areas are attacked with preparations of different composition and the cellular response is assessed with adequate modern cell and molecular biological approaches.

3. Evaluation of the publications and the candidate's personal contribution

The dissertation includes a total of 10 scientific publications, of which 8 have an impact factor and rank Q1, one with a rank Q3, and one with a rank Q4. In all ten of the mentioned publications, Prof. Ugrinova is the last (leading) author, which is an indicator of a significant personal contribution to the development and design of these publications. The author's reference for compliance lists three more publications with an impact factor and rank Q1 in the year of publication, which were published immediately before the period specified in the dissertation and are related to the topic of the dissertation. The publications are grouped into three different areas, according to the group of compounds used: 1) study of ferrocene-camphor-sulfonamide derivatives (DK-164, CC-78) and their nanoformulation; 2) presenting benzodioxin- and benzofuran-terminated naphthalimide derivatives

as inducers of replication stress and DNA damage, with dual p53-dependent and p53-independent activity; and 3) testing of biologically active substances from natural sources for antitumor activity.

Financially, the research is supported by a total of four national projects, funded by the National Science Foundation of the Ministry of Education and Science, and the National Scientific Program "Innovative Low-Toxic Biologically Active Agents for Precision Medicine" - BioActiveMed of the Ministry of Education, Contract No. D01/217.

Citation information: The presented dissertation includes 10 scientific publications, mostly with rank Q1, published in the period 2021–2026, with a total impact factor of 48.9 and 87 independent citations. High citation rate is a good indicator of the significance of the scientific problem under consideration.

Scientometric indicators: From the above, it is clear that the scientometric indicators exceed the requirements of the Law on the State of the Republic of Bulgaria on the State of the Republic of Bulgaria and the dissertation fully meets the criteria for awarding the scientific degree "Doctor of Sciences". In addition to the fixed 50 points for educational and the academic degree of Doctor and 100 points for the presented dissertation work (group of indicators A and B), Prof. Iva Ugrinova participated with 227 points for indicator D (with 200 required) and 174 points for indicator E (with 100 required), thus exceeding the requirements of the Law and the Regulations by 22%.

4. Scientific and applied scientific contributions

The dissertation summarizes a consistent research program – from the discovery of new synthetic and natural antitumor agents, through the elucidation of their molecular mechanisms of action, to the development of effective delivery systems. Another great advantage of the dissertation work is the hypothesis that structurally different synthetic and natural agents can induce an antitumor effect through convergence to common cellular mechanisms. This allows to draw the relevant conclusions and conclusions regarding the antitumor effect of individual drugs and provides guidance in the search for new drugs applicable in antitumor therapies and the development of approaches to increase their selectivity and pharmaceutical applicability.

The dissertation formulates four contributions of a fundamental nature regarding the main vulnerabilities of tumor cells and the key role of p53 in the stress-induced cellular response; four experimental contributions concerning the characterization of the antitumor potential and molecular mechanism of action of a series of ferrocene-camphor-sulfonamide derivatives, heterocyclic-annulled benzodioxin- and benzofuran-containing naphthalimide derivatives, as well as natural products from hemolymph fractions of the Black Sea snail *Rapana venosa*, of plant and fungal origin, including cannabidiol, extracts of *Croton lechleri* and *Amanita muscaria*; one applied contribution concerning biodegradable polymer nanosystems providing improved solubility, stability and pharmaceutical applicability

I fully accept the applied and experimental contributions, which are undoubtedly original and reflect the new knowledge achieved in the implementation of the scientific projects. The fundamental contributions are formulated more generally and the third (on the existence of alternative p53-independent mechanisms for inducing cell death) is rather confirmatory. However, the dissertation work shows a different aspect of the mechanisms of antitumor action and provides guidelines in the search for new, more effective and highly selective antitumor drugs.

6. Critical notes and recommendations

Including the full texts of the publications in the dissertation work itself is a non-standard approach to presenting the results and interrupts the text of the scientific work, but is compensated by the general

overview and their summarized discussion afterwards. This way of presentation complies with the Regulations for the implementation of the ZRASRB in the IMB, BAS. However, this disrupts the balance between the individual chapters and the final work contains parts in both English and Bulgarian, which is also unusual for this type of scientific work, disrupts the logic of the text and makes it difficult to generally perceive the large amount of information. The abstract presents only the first pages of the publications with their abstracts, which significantly reduces its volume, but the reader has to search for the publications themselves in order to gain a full idea of the results discussed. It would be more appropriate to include selected significant results to support the discussion and conclusions.

The chapter Perspectives and future development of research makes a good impression, in which the next steps in the future development of the presented research program are clearly outlined.

5. Conclusion

In conclusion, the presented dissertation work on the topic "Common target, different agents: Fundamental vulnerabilities of the tumor cell as a basis for selective antitumor action" with the author Prof. Dr. Iva Ugrinova is in the form of a collection of scientific publications accompanied by a comprehensive literature review and connecting discussion. The dissertation, as well as the scientific publications included in it, fully meet and exceed the scientometric requirements of the ZRASRB and the Regulations of the IMB, BAS. The hypothesis has been formulated and proven that structurally different synthetic and natural agents can induce an antitumor effect through convergence to common cellular mechanisms. The presented scientific program lays the foundation for several promising future directions of research, which will ensure continuity and sustainability of scientific research in the group led by Prof. Iva Ugrinova.

Everything said so far gives me reason for a positive assessment and I strongly recommend that the esteemed jury award the scientific degree "Doctor of Sciences" to Prof. Iva Ugrinova.

Sofia

14.09.2026

Signature:

(Prof. Dr. Tanya Topuzova-Hristova)