

ACADEMIC REVIEW

By **Prof. Dr. Julian Rumenov Ananiev, MD, PhD**

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Subject: PhD-thesis for the award of an educational and scientific degree

"PhD"

To **Dr. Plamen Petrov Vasilev**

PhD-thesis topic: **"APOPTOSIS AND NECROPTOSIS IN BASAL CELL AND
SQUAMOUS CELL SKIN CARCINOMA"**

Professional direction: 7.1. Medicine

PhD program: "Pathologic anatomy and cytopathology"

Scientific supervisor: Prof. Dr. Maria Angelova Tsaneva, MD, PhD

Short details of the PhD student

Dr. Plamen Petrov Vassilev was born on 13.10.1974. In 1992 he graduated from "G. S. Rakovski" school in Burgas. Two years later he began studying medicine at the Medical University of Sofia, and in 2000 he graduated as a doctor. From 2005 to 2010 he specialized in "Clinical Laboratory" at the Medical University "Prof. Dr. Paraskev Stoyanov" Varna and the University Hospital Burgas. In the period between 2013 and 2017 he specialized in "General and Clinical Pathology" at the Medical University "Prof. Dr. Paraskev Stoyanov" Varna and the University Hospital St. Marina - Varna. He is a PhD-student in the PhD-program "Pathoanatomy and Cytopathology" until 2025 at the Medical University of Varna. He worked as a medical doctor - clinical laboratory at the University Hospital Burgas, Medical Center "St. Stiliyan" - Varna, Medical Center "St. Iv. Rilski" Varna, as well as a doctor in general and clinical pathology at the University Hospital "Veliki Preslav", University Hospital "St. Marina", Military

Medical Academy Hospital Varna and University Hospital Burgas. He has a good level of English proficiency.

Relevance, description and significance of the PhD-thesis

The PhD work of Dr. Vasilev is a thorough and interesting morphological study on the role of some markers related to program cell death in patients with epithelial skin tumors in search of their predictive value. The work includes: introduction, literature review, aim and objectives, material and methods, results and discussion, conclusion, contributions of the PhD work, publications related to the PhD work and literature.

After presenting the abbreviations used, the PhD work begins with an **introduction**, in which the author makes a brief overview of malignant skin diseases and emphasizes the relationship between the occurrence, therapeutic behavior, as well as the importance of programmed cell death and the molecular and signaling pathways involved in their development.

The **literature review** follows, and the author generally divides it into two subchapters and gradually presents and summarizes the information related to: 1) *basal cell carcinoma* - epidemiology and risk factors for its development; tumorigenesis of the neoplasm with a main emphasis on mutations and changes in the Sonic Hedgehog- and Hippo-YAP-signaling pathways of induction, genetic polymorphisms and somatic mutations found in the respective neoplasm; morphological characteristics, staging and prognostic and predictive parameters in it; 2) *squamous cell carcinoma* - and here again follows a presentation of the epidemiology, etiological and risk factors for the development of carcinoma; summarized and synthesized information regarding tumorigenesis, again including gene mutations and the participation of other signaling pathways, such as: NOTCH1 and NOTCH2, the RAS-RAF-MEK-ERK signaling pathway, as well as the PI3K/AKT/mTOR signaling pathway. In the same subchapter, Dr. Vasilev presents two types of programmed cell death - apoptosis and necroptosis, and at the end makes a brief conclusion, which is also a natural transition to summarizing the information and configuring the goal of the dissertation.

The **aim** of the PhD-thesis is to study the immunohistochemical expression of the apoptosis marker Caspase-3 and the necroptosis marker Receptor-interacting kinase 3 (RIPK3)

in patients with basal cell and squamous cell carcinoma of the skin and to determine their predictive value. Seven tasks are presented - directly related to the aim of the dissertation, with one part of them being related to the study of the clinical and morphological parameters of patients from both groups, and another - to IHC examination and analysis of the results obtained with the available data.

In the presented **material and methods**, the doctoral student includes a total of 91 patients, of which 46 are with basal cell carcinoma and 45 with squamous cell carcinoma of the skin, collected for the period 2015 - 2021. Inclusion and exclusion criteria, tumor staging and morphological description; routine fixation and staining, as well as IHC examination protocols, relevant components and expression reporting are indicated. At the end of the chapter, the statistical methods used to analyze the obtained results and data are listed.

The chapter "**Results and Discussion**" follows, where the presented data logically follow the set aim and tasks. In the first part of this chapter, an analysis of the clinical and morphological characteristics of patients with both types of neoplasms was performed. A number of available data were compared and presented with microphotographs of a large part of the types of neoplasms. The second subchapter includes an analysis of the data on the expression of Caspase-3 in the tumor tissue of both types of tumors, as well as in adjacent healthy tissue. The distribution is presented, as well as a comparison of the dependencies between the expression of the marker in healthy and tumor tissue, as well as a number of indicators, such as: age, gender, risk groups, degree of differentiation, necrosis, lymphocytic infiltration, etc. In the third subchapter, a similar analysis was performed regarding the expression of RIPK3 in the tumor and healthy tissue of both neoplasms and the same characteristics. The data are presented in tabular form, accompanied by information on significance, as well as photographic material.

In the **conclusion**, the author informs about new information on the expression and localization of RIPK3 and Casp-3 in the two types of studied neoplasms, outlining the possibility that these markers can be used in the future as auxiliary diagnostic and prognostic tools and emphasizing the need for additional study with larger cohorts.

A total of 16 **conclusions** are formulated.

Two groups of **contributions** are summarized: two scientific contributions of an original nature and eight scientific contributions of a practical-applied nature.

Two more **scientific publications** in Varna Medical Forum are presented.

The PhD-thesis is written on a total of 139 pages and is illustrated with: 35 figures and 66 tables.

The bibliography includes 355 literary sources, of which 6 in Cyrillic and 349 in Latin.

Conclusion

Based on the above, I think that the PhD work of Dr. Plamen Petrov Vasilev represents an **interesting, in-depth and fully completed scientific work with significant results, conclusions and contributions.**

I give my positive assessment and will vote "Positive" the awarding of the ESD "PhD" to Dr. Plamen Petrov Vasilev in the Field of Higher Education: 7. Health and Sports, Professional Area: 7.1. Medicine, PhD program: "Pathologic anatomy and cytopathology", and I also recommend the honorable members of the scientific jury to vote positively.

01.11.2025

Stara Zagora

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