

OPINION

by Professor Dr. Peter Ivanov Ghenev, PhD, Department of
General and Clinical Pathology at the Medical University of Varna

RE: scientific work for awarding educational and scientific degree "Doctor of medical sciences" in the field of higher education 7. Health and sport, professional field 7.1. Medicine, scientific specialty "Urology".

Thesis theme

"The role of NGF, BDNF and their receptors TrkA, TrkB and p75NTR
for the occurrence and metastasis of prostate carcinoma "

Candidate: Assoc. Prof. Dr. Nikolay Todorov Evtimov, MD, Associate Professor at the Department of Surgical Diseases at the Faculty of Medicine of the Medical University "Prof. P. Stoyanov" - Varna.

By order of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" Varna № P-109-662 from 14.12.2018 I was nominated as a member of the Scientific Jury and with Protocol № 1 / 14.12.2018 of a meeting of the same Scientific Jury I was instructed to draw up an opinion on the scientific work submitted for evaluation by Assoc. Prof. Dr. Nikolay Todorov Evtimov.

Biographical data:

Associate Professor Dr. Nikolay Todorov Evtimov, PhD. was born on 21.05.1960 in Varna. He graduated from the Medical University of Varna (1978-1984). After graduation he worked as a surgeon in the Regional hospital - Tutrakan as a surgeon, head of department and director until 1995. After that he moved to Varna and until 31.03.2000 he worked as a plastic surgeon at the Burn and Plastic Surgery Clinic of the Military Medical Academy in Varna. He successfully passed a specialty exam, in 1992 in Surgery and in 1998 in Urology. Since 2000 he has been focusing on urology and has been working consecutively as individual practitioner, at the St. Anna University Hospital in Varna and at the Urology Clinic in Halle-Wittenberg, Germany. Over the years Dr. Evtimov has specialized in the country and abroad: laparoscopic and multi-organ transplantation and renal transplantation at Martin-Luther University, Halle, Germany; Robot Surgery Da Vinci in Pleven and Cluj-Napoca, Romania. In 2009 and 2011 he gained international experience by working as a urologist at the Urology and Andrology University Clinic - Saint-John Salzburg Austria. In 2013, he defended a dissertation on "Systemic inflammatory response in laparoscopic and classic radical prostatectomy in prostate cancer. Surgical and Functional Comparison" and acquired PhD degree in the scientific specialty "Urology". He began teaching as a paid assistant at the Medical University - Varna. In 2015 he was elected as a regular assistant, and in 2017 he was an Associate Professor at the Department of Surgical Diseases at Medical University - Varna.

Associate Professor Evtimov has more than 35 years of work experience, which includes five years of teaching.

Assessment of dissertation:

Prof. Evtimov provided all necessary materials for the dissertation on the topic: "The Role of NGF, BDNF and Their Receptors TrkA, TrkB and p75NTR for the Origin and Metastasis of Prostate Cancer" at the Scientific Department of the Medical University - Varna.

Dissertation is based on 22 full-text publications related to the topic (of which nine are in reference journals) and participations in forums with printed abstracts, including Impact Factor. A monograph on the topic: "NEUROTROPHINS Physiological and pathogenic multifunctionality" is also presented.

The dissertation contains a total of 251 pages, well illustrated with 58 figures and 44 tables. Microphotographs, including immunohistochemicals, are of high quality and properly interpreted. The bibliography includes 290 titles, current for the moment. The individual parts - overview, results, discussion are within the conventional ratio.

The study was conducted on 257 prostatectomy materials for localized prostate carcinoma. In addition to a surgical examination, an in-depth morphological study of biopsied tissues (prostate gland, carcinoma, periprostatic adipose tissue), including immunohistochemical study of neurotrophins and their receptors was carried out.

The main focus of dissertation work is an extremely actual topic dedicated to the study of the most important neurotrophins and their receptors in the process of tumor transformation and the progression of prostate carcinoma. Neurotrophins are a family of growth factors that act by binding to specific transmembrane receptors that are found initially in normal cells of the nervous system - sympathetic, sensory and cholinergic brain neurons, and later in other normal cell types such as

cardiomyocytes, adipocytes, immune, epithelial, smooth muscle and endothelial cells. This circumstance gives rise to the extremely pleiotropic effect of neurotrophins and their ability to mediate functions of other cell types. Of particular importance is the fact that they are also expressed in tumor-transformed cells, which implies involvement in carcinogenesis. The choice of Dr Evtimov to focus on neurotrophins obviously emerges from the empirical fact that perineural invasion is a very characteristic morphological finding in the spreading of prostate cancer. It is precisely these details, to which Dr Evtimov adheres - initially, in a meaningful, comprehensive, contemporary and adequate literary review. The main objective of the review was to identify and evaluate the localization and semiquantitative immunohistochemical expression of major neurotrophins (NGF and BDNF) as well as their tyrosine kinase receptors (specific TrkA, TrkB and the universal p75^{NTR}) in parenchymal and stromal cells of the prostate gland in carcinoma and benign hyperplasia, as well as in individual areas of periprostatic adipose tissue.

The results obtained are compared with anatomical and clinical-laboratory data such as prostate gland weight, plasma prostate specific antigen (PSA) concentration, body mass index (BMI), TNM and Gleason score of the tumor. Different neurotrophic expressions in individual areas of prostate carcinoma and periprostatic tissues contribute to accurate diagnosis in problematic cases. Strong expression of NGF and BDNF is associated with invasiveness and increased proliferative activity. This suggests that the expression of neurotrophin NGF, BDNF and their specific TrkA and TrkB receptors is confirmed as a factor of potential prognostic and predictive significance.

Personal impressions

I have known Dr. Evtimov personally since 2000 when he started working in Varna and appeared as a surgeon with a certain inclination to morphological diagnostics. He was interested in every detail of the morphological activity that was important to the quality of the operative work and to determining the subsequent behavior of the particular patient. These circumstances give me reason to appoint Dr. Evtimov as a well-trained surgeon with a rich theoretical experience and proven skills in many areas of surgical practice.

Conclusion:

The submitted documentation is in full volume and meets the procedural requirements of the Medical University of Varna.

The scientific output of the applicant meets the necessary criteria. I accept the reference for scientific contributions without any comments. I am impressed by the candidate's personal and professional qualities and I think he fully meets the conditions for acquiring the degree.

For these reasons, I am particularly pleased to fulfill my duties and to vote positively to Associate Professor Dr. Nikolay Todorov Evtimov, PhD, to be awarded the scientific degree "Doctor of Medical Sciences".

Signature:

01.02.2019

Professor Dr. Peter Ghenev, PhD