

# **REVIEW**

By: Prof. Dr. **Anton Bozhidarov Tonchev**, MD, DSc - Head of the Department of Anatomy and Cell Biology, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

On: Dissertation for obtaining scientific degree "Doctor of Science" for Higher Education in the field 7. Health and Sport, Professional Field 7.1. Urology, specialty "Urology", on the topic "*The role of NGF, BDNF and their TrkA, TrkB and p75NTR receptors for the onset and metastasis of prostate carcinoma*"

Candidate: Assoc. Prof. Nikolay Todorov Evtimov MD, Unit of Urology, Department of Surgical Diseases, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

By a Decision of the Faculty Council of the Faculty of Medicine No. 16 / 10.12.2018 and an Executive Order of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna No. R-109-662 from 14.12.2018, I have been appointed as a member of the Scientific Jury evaluating the dissertation of Assoc. Prof. Nikolay Todorov Evtimov MD, for acquiring the scientific degree "Doctor of Science". By Protocol 1 / 14.12.2019 from a meeting of the Scientific Jury I was assigned to prepare a Review of the thesis.

## **I. Biographical information on Assoc. Prof. Nikolay Evtimov, MD, PhD**

Nikolay Todorov Evtimov was born on May 21, 1960 in the city of Varna. He graduated from secondary school in Varna, at 1975. From 1978 to 1984 Nikolay Evtimov has studied medicine at the Medical University – Varna. After receiving a Master's degree in Medicine he worked as a general practitioner at the hospital of Tutrakan as a surgeon, and was consecutively appointed Head of the department and Director of the same hospital, until 1995. From 1995 Dr Evtimov moved to Varna, where he worked as a plastic surgeon at the Clinic of and Plastic and Skin Reconstruction Surgery/Military Medical Academy - Varna (until March 31, 2000).

Since 1992 Dr. Evtimov is a specialist in Surgery, and since 1998 - also in Urology. After 2000 he has worked as a surgeon, and since 2005 - as an urologist at "St. Anna" Hospital - Varna. In 2006 he has been working at the University Clinic of Urology in Halle-Wittenberg, Germany. Dr Evtimov had specialized in Bulgarian and in foreign clinics, as follows:

- 2007 - Laparoscopic and Multi-Organ Explantation and Kidney Transplantation - Halle, Germany;
- 2010 - Robotic Surgery - Pleven, Bulgaria;
- 2010 - Robotic Surgery in Cluj-Napoca, Romania;
- 2010 - University Clinic of Urology and Andrology - Salzburg, Austria;
- 2011 - University Clinic of Urology and Andrology - Salzburg, Austria;
- 2018. - Robotic surgery at University Clinic of Urology, Andrology and Transplantology - Halle, Germany

In 2013, he successfully defends a dissertation on "Systemic inflammatory response in laparoscopic and classical radical prostatectomy in prostate carcinoma. Surgical and Functional Comparison". The same year, Dr Evtimov has commenced teaching as an Assistant Professor on tuition at the Medical University - Varna. In 2015, he was elected as an Assistant Professor on a permanent contract with the university, and from 2017 onwards, he is Associate Professor at the Department of Surgical Diseases, Faculty of Medicine, Medical University - Varna.

Nikolay Evtimov speaks fluent Russian, German, English and French.

**Summary: During his career, Assoc. Prof. Nikolay Evtimov has more than 35 years of clinical and scientific work, including five years of teaching, in Urology.**

## **II. Overview of the dissertation of Assoc Prof. Dr. Evtimov**

Assoc. Prof. Evtimov's dissertation is spread over 212 standard printed pages (excluding the pages of the bibliography). The thesis has the following chapters:

1. Abbreviations
2. Introduction
3. Literature review
4. Aim and objectives
5. Materials and methods
6. Results
7. Discussion
8. Summary of data
9. Conclusions
10. Original contributions of the dissertation
11. Publications related to the dissertation
12. Participations at scientific events
13. Literature used

The thesis includes 58 figures and 44 tables that visualize the gathered data and analyze them. The literature contains more than 200 different publications.

### **III. Evaluation of the significance of the topic of the dissertation**

The prostate carcinoma is the most frequent urological malignancy and one of the most frequent neoplasms in males. Clarification of the mechanisms of the genesis of the prostate cancer would help in the assessment and treatment of this disease. A significant role in the prostate oncogenesis is attributed to the paracrine signaling between the stromal and the epithelial cells in the gland. A part of those intercellular interactions are mediated by a family of molecules named “neurotrophins” due to their effects on the neuronal system, where they were firstly found. Due to their potent biological activity, the neurotrophins are considered powerful regulators of the processes of cell division and differentiation in any system they operate. Neurotrophins consists of a few ligands and their receptors. The ligands are the Nerve growth factor (NGF), Brain-derived neurotrophic factor (BDNF), Neurotrophin-3 (NT3), NT4/5, and the receptors are TrkA, TrkB, TrkC, and the common receptor for all neurotrophins known as p75NTR. In his dissertation, Dr Evtimov has focused on two of the ligands (NGF и BDNF) and their receptors (TrkA, TrkB и p75NTR) in the context of the prostate carcinoma. To this day, the information about the connection of the neurotrophins and this cancer is insufficient, and research in this field may help the assessment and treatment of the disease.

**Conclusion: I assess the dissertation topic as highly significant and up-to-date.**

### **IV. Evaluation of the sections “Introduction” and “Literature review”**

In the Introduction, we observe the need to expand the knowledge in the field of the dissertation. The author has concisely reviewed the known data as well as the topics

where more research is needed. The used literature, written on 55 standard printed pages, demonstrates the high competence of Dr Evtimov on the available literature on neurotrophins, their receptors, and the genesis of the prostate cancer. The fact, that in he used more than 200 title (many of them from the last years) indicates the ability of handling an information avalanche during his work on the thesis – a thing, which in my opinion Assoc. Prof. Evtimov has achieved successfully.

## **V. Evaluation of the Aim and the Objectives of the dissertation**

The Aim and Objectives of the dissertation are clearly formulated. The aim is the link between immunohistochemical expression of neurotrophin NGF and BDNNF and their receptors (TrkA, TrkB and p75NTR) in prostate cancer and their correlation with the different clinical indicators. The aim is clearly diffined with steps toward the objective. **Given the methodologies presented, I conclude that the aim as feasible.**

## **VI. Evaluation of the section “Materials and methods”**

The inclusion and exclusion criteria for the patient selection, the methods for the morphological and laboratory analysis of the samples and the statistical evaluation are clearly defined.

**Conclusion: Materials and methods are described in great detail in a way that allows experiments to be repeated by independent researchers.**

## **VII. Evaluation of the results**

The results are spread over 73 standard pages, illustrated by 58 figures and 44 tables. The figures are of a very good quality and clearly visualize the points of the dissertation. An analysis was performed on the localization and expression of the

major neurotrophins NGF and BDNF, and their receptors (TrkA, TrkB and p75NTR) in the parenchymal and stromal cells of the prostate cancer and benign hyperplasia. Of particular novelty is the finding showing expression of neurotrophins and their receptors in periprostatic fat tissue. An analysis on such a large scale contains a genuine potential for the discovery of new mechanisms for development of prostate cancer.

The data for the expression is correlated with clinical-laboratory indications such as prostate gland weight, prostate specific antigen (PSA) plasma mass index, body mass index, and clinical staging (TNM and Gleason score) of the tumor. The author's data suggest that differences in neurotrophin expression for neurotrophins in various areas of prostate carcinoma and periprostatic tissues contribute to a more accurate diagnosis, especially in complex cases to be solved. A strong expression of NGF and BDNF is associated with invasiveness and increased proliferative activity. This suggests that neurotrophin receptors represent powerful new targets for pharmacological treatment and/or markers of prognostic and predictive significance in prostate cancer.

**Conclusion: the presented results are with high quality and support the conclusions of the dissertation.**

### **VIII. Evaluation of sections “Discussion”, “Summary of data”, and “Conclusions”**

The discussion is detailed (in a volume of nearly 30 pages) and again demonstrates the good competence on the existing literature as well as the analytical thinking of Assoc. Prof. Evtimov. The results are discussed in the light of an in-depth synthesis of the known literature data.

The *Summary of data* section formulates 12 main points of the thesis reflecting the most important results of the author. I accept them as corresponding to the results.

A separate chapter *Conclusion* helps summarizing the results and sheds light on the prospects for further research. Associate Prof. Evtimov has elaborated on the phases of tumorigenesis of prostate carcinoma and the position of his own original data reported in the thesis in the overall concept of the oncogenic process of this malignant tumor.

**Conclusion: The presented "Discussion", "Summary of data", and "Conclusions" correctly and precisely discuss and summarize the main points of the dissertation work.**

## **IX. Evaluation of the original contributions of the dissertation**

The main original contribution of the dissertation are the presented results on density of expression of NGF and BDNF and their specific receptors, showing a significant proportional dependence between the expression of NGF and BDNF, and the malignancy of prostate cancer. For the first time a combination score is done between expressions of BDNF, NGF according the values of Gleason score/PSA/TNM classification. There are 7 listed original contributions of the dissertation, which I accept.

**Conclusion: I consider the contributions are sufficient for awarding the scientific degree „Doctor of science“.**

## **X. Assessment of the sciencemetrics of Assoc. Prof. N. Evtimov**

A reference is attached from the Library of MU-Varna, showing that the total impact factor of Dr. N. Evtimov is 20.4. The Google Scholar database shows that the works of Assoc. Prof. Evtimov have currently over 30 citations.

### **Integral conclusion on the dissertation**

The dissertation of Assoc. Prof. Dr. Nikolay Todorov Evtimov, MD, PhD from the Unit of Urology of the Department of Surgical Diseases, Faculty of Medicine, Medical University „Prof. Dr. Paraskev Stoyanov"-Varna is dedicated on an extremely up-to-date problem. The author has presented numerous original results, via the application of clinical, laboratory and morphological methods, which the author had skillfully used to solve the objectives of the study. The dissertation is with a clear interdisciplinary range and includes original scientific data from at least several medical fields, including urology, oncology and neuroscience. I conclude that the presented dissertation completely fulfils the Bulgarian Law on the Career Development of the Academic Staff and local regulations of MU-Varna in this respect for acquiring the scientific degree „Doctor of Science". That is why I will vote in favor for awarding him with the Degree and allow myself to recommend the same to the other members of the honored Scientific Jury, appointed with an Executive Order No R-109-662 from 14.12.2018 of the Rector at Medical University-Varna.



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