

**TO TEACHING SCIENTIFIC COUNCIL, FACULTY OF MEDICINE, UNIVERSITY OF
BELGRADE**

**Report on the Evaluation of the Scientific Basis of the Proposed Doctoral Dissertation
Topic**

"Correlation of Human Papillomavirus Infection in Preinvasive and Invasive Skin and
Ectocervical Tumors of Squamous Cell Origin with Expression of the Transcription Factor
FOXP3"

Candidate: Boba Kotlica, MD

By decision of Teaching Scientific Council of the Faculty of Medicine, University of Belgrade, dated 17.03.2026., No. 7/XIV-3/1-BK, a Committee for the Evaluation of the Scientific Basis of the Proposed Doctoral Dissertation Topic entitled "Correlation of Human Papillomavirus Infection in Preinvasive and Invasive Skin and Ectocervical Tumors of Squamous Cell Origin with Expression of the Transcription Factor FOXP3" submitted by candidate Boba Kotlica, MD, was appointed, composed of the following members:

Name and surname of the Committee member	Title	Scientific field	Institution of employment
Saša Kadija, MD	Full Professor	Gynecology and Obstetrics	Faculty of Medicine, University of Belgrade
Ivana Likić Lađević, MD	Full Professor	Gynecology and Obstetrics	Faculty of Medicine, University of Belgrade
Ana Banko, MD	Associate Professor	Microbiology	Faculty of Medicine, University of Belgrade
Aleksandar Krunić, MD	Assistant Professor	Dermatovenereology	Northwestern University, Chicago, United States of America
Olivera Levakov, MD	Assistant Professor	Dermatovenereology	Faculty of Medicine, University of Novi Sad

Mentors name and surname	Title	Scientific field	Institution of employment
Katarina Stefanović, MD	Associate Professor	Gynecology and Obstetrics	Faculty of Medicine, University of Belgrade
Giuseppe Argenziano, MD	Full Professor	Dermatovenereology	University of Campania Luigi Vanvitelli, Naples, Italy

Based on the analysis of the submitted documentation regarding the proposed doctoral dissertation topic, following a discussion with the candidate and in accordance with the criteria for assessing the scientific validity of doctoral dissertation topic, the members of the Committee submit the following to the Teaching Scientific Council of the Faculty of Medicine, University of Belgrade:

REPORT

A. Candidate information:

Boba Kotlica was born on 16 February 1999 in Belgrade. She enrolled in the Faculty of Medicine, University of Belgrade in 2017 and graduated in 2023 with an average grade of 9.80. Since 2024, she has been employed at the Department of Dermatovenereology, Clinical Hospital Center Zvezdara. In April 2025, she enrolled in residency training in Dermatovenereology at the Faculty of Medicine, University of Belgrade. She enrolled in doctoral studies in Gynecology and Gynecological Oncology in 2023 at the Faculty of Medicine, University of Belgrade, under the mentorship of Assoc. Prof. Katarina Stefanović, MD. Additionally, she is a member of the Serbian Association of Dermato-Venereologists, the International Dermoscopy Society, the European Association of Dermato-oncology, the European Society of Human Reproduction and Embryology, and the Serbian Genetics Society. She is the recipient of the 2021 St. Sava Award for year 2021 (Ministry of Education, Science and Technological Development of the Republic of Serbia, Belgrade, Serbia).

B. List of the Candidate's Fully Published Papers

1. Jovičić Pavlović S, Simić Ogrizović S, Bukumirić Z, Erić M, Pavlović N, **Kotlica B**, Novaković I. Impact of the fetuin gene polymorphisms in coronary artery calcification and mortality of patients with chronic kidney disease and renal transplant. *Genetika*. 2022; 54(1):457-72. M23, IF 2021= 0,753.
2. **Kotlica B**, Ristanović M, Novaković I. Analiza polimorfizma RS34637584 u genu LRRK2 kod bolesnika sa Parkinsonovom bolešću. *MedPodml*. 2022; 73(3):33-7. M52, IF none
3. Todorovic D, Stojanovic M, Gopcevic K, Medic A, Stankovic S, **Kotlica B**, Labudovic Borovic M, Djuric D. Effects of four weeks lasting aerobic physical activity on cardiovascular biomarkers, oxidative stress and histomorphometric changes of heart and aorta in rats with experimentally induced hyperhomocysteinemia. *Mol Cell Biochem*. 2023; 478(1):161-72. M22, IF 2023= 3,5.
4. Tulic L, Tulic I, Stojnic J, Bila J, Vukovic Z, **Kotlica B**. Different doses of recombinant FSH and determining parameters of oxidative stress. *J Med Biochem*. 2024; 43(2):219-25. M23, IF 2024= 1,5.
5. Jovandaric MZ, Jovanovic K, Raus M, Babic S, Igic T, **Kotlica B**, Milicevic S. The Significance of Plant Nutrition in the Creation of the Intestinal Microbiota-Prevention of Chronic Diseases: A Narrative Review. *Medicina*, 2024, 60(12):1969. M21, IF 2024= 2,4.
6. Ivanović K, Tulić I, Stojnić J, Micić J, Bila J, Ivanović S, Ivanović M, Babović I, **Kotlica B**, Tulić L. Unraveling infertility- most frequent causes and essential predictors of assisted reproductive technologies outcomes. *Srp Arh Celok Lek*, 2025, 153(9-10):465-70. M23, IF 2024= 0,2.

C. RATIONALE- JUSTIFICATION OF THE TOPIC:

1. SCIENTIFIC FIELD:

MEDICINE (Dermato-Oncology, Gynecologic Oncology)

2. SUBJECT OF THE WORK :

The subject of this study is the analysis of the presence of Human Papillomavirus (HPV) infection in preinvasive and invasive squamous cell tumors of the skin, vulva, and ectocervix, as well as the assessment of FOXP3 protein expression in these tumors. The study will also determine the frequency of genotypes and alleles at specific *FOXP3* gene loci and evaluate their association with FOXP3 protein expression.

3. RESEARCH AIMS:

1. To examine the presence and determine the genotypes of HPV infection in cervical smear samples of preinvasive ectocervical tumors (low-grade squamous intraepithelial lesion, i.e. L-SIL and high-grade squamous intraepithelial lesion, i.e. H-SIL) and invasive ectocervical tumors (squamous cell carcinoma), as well as biopsies of preinvasive skin tumors (actinic keratosis and Bowen's disease) and invasive skin tumors (squamous cell carcinoma) and preinvasive vulvar skin tumors (low-grade squamous intraepithelial lesion, i.e. VIN-1, high-grade squamous intraepithelial lesion, i.e. VIN-2 and VIN-3) and invasive vulvar skin tumors (squamous cell carcinoma).
2. To determine FOXP3 protein expression in biopsies of preinvasive ectocervical tumors (low-grade squamous intraepithelial lesion i.e. L-SIL and high-grade squamous intraepithelial lesion i.e. H-SIL) and invasive ectocervical tumors (squamous cell carcinoma), as well as in biopsies of preinvasive skin tumors (actinic keratosis and Bowen's disease) and invasive skin tumors (squamous cell carcinoma) and preinvasive vulvar skin tumors (low-grade squamous intraepithelial lesion i.e. VIN-1, high-grade squamous intraepithelial lesion i.e. VIN-2 and VIN-3) and invasive vulvar skin tumors (squamous cell carcinoma).
3. To determine the genotype and allele frequencies of the rs2280883 and rs3761548 loci of the *FOXP3* gene in blood samples from research participants with preinvasive ectocervical tumors (low-grade squamous intraepithelial lesion, i.e. L-SIL and high-grade squamous intraepithelial lesion, i.e. H-SIL) and invasive ectocervical tumors (squamous cell carcinoma), as well as preinvasive skin tumors (actinic keratosis and Bowen's disease) and invasive skin tumors (squamous cell carcinoma) and preinvasive vulvar skin tumors (low-grade squamous intraepithelial lesion, i.e. VIN-1, high-grade squamous intraepithelial lesion, i.e. VIN-2 and VIN-3) and invasive vulvar skin tumors (squamous cell carcinoma) and their association with FOXP3 protein expression in the aforementioned preinvasive and invasive tumor tissues of the ectocervix, skin and vulvar skin.

4. RESEARCH HYPOTHESES:

Infection with different HPV types in preinvasive and invasive squamous cell tumors of the skin and ectocervical is associated with increased FOXP3 protein expression and polymorphisms in the *FOXP3* gene.

5. RESEARCH METHODS:

This research was designed as a prospective multicenter cohort study. The study is conducted at the following institutions: the Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia (UCCS), Clinic for Burns, Plastic and Reconstructive Surgery UCCS, Clinic for Otorhinolaryngology and Maxillofacial Surgery UCCS, Institute for Oncology and Radiology of Serbia, Clinic for Gynecology and Obstetrics "Narodni front", Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade (FMUB), Institute of Pathology FMUB and Institute of Human Genetics FMUB.

The research period extends from July 2025 to the end of December 2026. Ethical approval was obtained from the Ethics Committee of the UCCS (decision number 1128/23 of July 3, 2025, amendment number 1500/48 of September 29, 2025), the Ethics Committee of the Institute of

Oncology and Radiology of Serbia (decision number 01-1/25/2106 of July 11, 2025) and the Ethics Committee of the Gynecological and Obstetric Clinic "Narodni Front" (decision number 2208/2025/021590 of October 9, 2025). Additional consents were also obtained from: Clinic for Gynecology and Obstetrics UCCS (number 2380 dated June 9, 2025), Clinic for Burns, Plastic and Reconstructive Surgery UCCS (number 600 dated June 4, 2025), Clinic for Otorhinolaryngology and Maxillofacial Surgery UCCS (number 965 dated September 22, 2025), Institute of Oncology and Radiology of Serbia (number 01-1/25/2017 dated July 4, 2025), Gynecological and Obstetric Clinic "Narodni Front" (number 29023-2025-011731 dated June 12, 2025), Institute of Microbiology and Immunology FMUB (number 130 dated June 5, 2025), Institute of Pathology of the FMUB (number 02-582/25 of June 2, 2025) and the Institute of Human Genetics of the FMUB (number 108 of June 5, 2025).

The study will include 168 women aged 18 years and older, consecutively enrolled upon presentation for treatment at the participating institutions, who undergo surgery for preinvasive (L-SIL and H-SIL) and invasive ectocervical tumors (squamous cell carcinoma); preinvasive (actinic keratosis and Bowen's disease) and invasive skin tumors (squamous cell carcinoma); as well as preinvasive (VIN-1, VIN-2, and VIN-3) and invasive vulvar tumors (squamous cell carcinoma). The exclusion criterion for the study was the absence of histopathologically confirmed preinvasive or invasive squamous cell tumors of the skin, vulvar skin, or ectocervix. The data will be used solely for scientific purposes and in accordance with the provisions of the Personal Data Protection Act. Study participants data and analyses will be anonymized. The study was designed to be free of risk for the participants. Written informed consent will be obtained from all study participants prior to participation in the study. The following data will be collected: 1) demographic data (age, occupation, place of residence, body mass index, smoking status and alcohol consumption); 2) anamnestic data (symptoms, duration of symptoms, previous therapies and interventions, first menstrual period, regularity of menstrual cycles, childbirth, miscarriages, sun exposure habits, surgical history, injuries, allergies, chronic diseases, family history of skin and gynecological tumors and chronic diseases); 3) dermatological and dermoscopy examination data (hair, skin, genital and oropharyngeal mucosa, and nail plates of hands and feet); 4) gynecological examination data (vulva inspection, speculum examination, bimanual and ultrasound examination, and Papanicolaou smear results); and 5) histopathological findings.

HPV detection and genotyping in cervical swab samples and biopsies of vulvar and skin tumors will be performed at the Virology Laboratory, Institute of Microbiology and Immunology, FMUB. After collection, swab and biopsy samples will be placed in sterile tubes containing saline solution. The extraction of DNA will be performed using automated QiaCube Connect system (Qiagen, Hilden, Germany) and extracted DNA will be stored at -20°C until further analysis. Following DNA isolation, HPV DNA will be amplified by commercial Real-time polymerase chain reaction (RT-PCR) kit (Bosphore HPV Screening Kit V1, IVD, Anatolia Geneworks, Istanbul, Turkey) on ABI QuantStudio5 RT PCR System (Life Technologies, USA), with primary data processing conducted by the integrated software. In addition, HPV DNA will be amplified using traditional PCR with primers specific to the *E1* and *L1* viral genes and obtained PCR products will be analyzed by electrophoresis on a 2% agarose gel, using a DNA ladder as a molecular size standard and ethidium bromide for DNA visualization. HPV genotyping will be performed using direct Sanger sequencing. This process includes purification of PCR products of *E1* and *L1* genes using the MiniElute PCR Purification Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions, followed by bidirectional cycle sequencing using the ABI BigDye Terminator v3.1 kit (Applied Biosystems, Foster City, USA), with the same primers used for PCR amplification. Following purification with isopropanol and denaturation with formamide, the sequencing reaction products will be loaded onto an automated DNA sequencer (ABI PRISM 3500 Genetic Analyzer; Applied Biosystems, Foster City, USA). The sequences will be analyzed

using Sequence Analysis 5.1 and SeqScape 2.5 software packages (Applied Biosystems, Foster City, CA, USA). HPV genotyping for each isolate will be conducted by comparing obtained sequences with reference sequences in the NCBI database (National Center for Biotechnology Information, USA) using the BLAST algorithm. The nucleotide sequence will be assigned to an HPV type if it corresponded in more than 95% similarity with a known HPV genotype.

FOXP3 protein expression will be analyzed at the Institute of Pathology, FMUB, using immunohistochemical staining on formalin-fixed, paraffin-embedded tissue sections. Staining will be performed using anti-FOXP3 antibody (recombinant mouse monoclonal antibody, clone 236A/E7, Abcam, Cambridge, UK, USA), at a dilution of 1:100 and incubated at room temperature for 60 minutes. The reaction will be detected using the UltraVision Quanto HRP Detection System (Eprelia, USA) with 3,3'-diaminobenzidine (DAB) as the chromogen. Immunohistochemically stained tissue sections will be evaluated using a light microscope by counting FOXP3-positive cells in five high-power fields (400x magnification). FOXP3 expressions will be quantified as the average number of FOXP3-positive cells per field of view.

For the analysis of *FOXP3* gene polymorphisms, whole blood samples (10 mL) anticoagulated with EDTA will be collected from all research participants by peripheral venipuncture and transported to the laboratory of the Institute of Human Genetics, FMUB. Genomic DNA will be isolated using the Miller salting-out method. Genotyping of the *FOXP3* polymorphic loci rs2280883 and rs3761548 will be performed using qPCR, with commercially available TaqMan SNP Genotyping assays (Thermo Fisher Scientific, USA). This method uses allele-specific oligonucleotide probes labeled with distinct fluorophores, together with sequence-specific qPCR primers. Fluorescence emission from each probe indicates the presence of the corresponding allele in the sample, with results automatically recorded by the software. The analysis will be performed on an ABI 7500 RT PCR System (Life Technologies, USA), with primary data processing conducted by the integrated 7500 Software.

For an alpha significance level of 0.05 and a statistical power of the 1-beta test of 80%, the required total sample size was calculated to be 168 patients. Data will be described using measures of central tendency (arithmetic mean and median), measures of variability (variation interval and standard deviation), relative numbers, and tabular and graphical presentations, considering data type and distribution. Normality of data distribution will be assessed using statistical (Shapiro-Wilk test) and graphical methods (histogram and box plot). For comparisons between two independent groups, Student's *t*-test or the Mann-Whitney *U* test will be used for numerical variables, depending on data distribution, while the chi-square test or Fisher's exact test will be applied for categorical variables. Comparisons involving three or more independent groups will be conducted using the chi-square test, one-way analysis of variance (ANOVA) and Kruskal-Wallis test. Binary logistic regression analysis will be used to estimate the probability of belonging to one of the two comparison groups based on the examined factors. All statistical hypotheses will be tested at a significance level of 0.05, with results considered statistically significant if the *p*-value is less than 0.05. Statistical analyses will be performed using IBM SPSS Statistics, version 31 (IBM Corporation, Armonk, NY, USA).

6. EXPECTED RESULTS:

Considering that HPV infection is associated with the development of one of the most common malignancy in women - cervical carcinoma, as well as squamous cell carcinoma of photoexposed skin sites, the detection of certain HPV genotypes is expected in cervical swab samples from women with preinvasive and invasive ectocervical tumors or skin biopsies (photoexposed areas) and vulvar biopsies (photounexposed areas) with preinvasive or invasive squamous cell tumors. Although FOXP3 expression has been described in certain malignancies, it has not been

thoroughly investigated in keratinocyte-derived tumors of the ectocervix, skin, and vulva. In vitro models have demonstrated that increased FOXP3 expression may promote the proliferation of cervical cancer cells; therefore, elevated FOXP3 expression is expected in the examined tumor tissue. Furthermore, analysis of polymorphisms in the *FOXP3* gene sequence may identify potential genetic predisposition factors for the development of preinvasive and invasive squamous cell tumors of the skin and ectocervix.

7. SCIENTIFIC CONTRIBUTION:

The planned doctoral dissertation will analyze the presence of Human Papillomavirus infection in preinvasive and invasive tumors of the skin, vulva, and ectocervix, including precise HPV genotyping by sequencing viral DNA. In order to examine the role and importance of T regulatory lymphocytes in the development and progression of these tumors, the expression of the FOXP3 protein, which is an indicator of the identity of this type of lymphocyte, will be analyzed in the affected tissue. The analysis will also include genetic determinants of FOXP3 expression, so that potential predisposing factors for the occurrence of tumors can be determined. The proposed research is of particular importance due to its interdisciplinary nature, as it integrates virological, immunohistochemical, and genetic data with clinical and histopathological findings. The collected data are expected to contribute significantly to the understanding of the etiology and pathogenesis of keratinocyte tumors of the skin and ectocervix, which could potentially facilitate the development of more effective prevention and treatment strategies. In addition to its general scientific relevance, a specific contribution of this doctoral dissertation lies in the identification of HPV genotypes as well as *FOXP3* gene variants present in the local population. Should an association between FOXP3 expression and gene polymorphisms be demonstrated, this may provide a basis for novel therapeutic approaches in the management of these tumors. Furthermore, knowledge of specific molecular profiles may facilitate the development of algorithms for a personalized approach to patient care, which is of clear scientific and clinical importance.

8. LIST OF USED REFERENCES:

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D. CONCLUSION

Based on the analysis of the submitted documentation, the members of the Committee believe that the proposed topic of the doctoral dissertation entitled "Correlation of Human Papillomavirus Infection in Preinvasive and Invasive Skin and Ectocervical Tumors of Squamous Cell Origin with Expression of the Transcription Factor FOXP3" submitted by candidate Boba Kotlica, MD is scientifically significant and relevant.

The topic fully meets the requirements for an original scientific contribution to research related to determining the frequency of HPV genotypes, examining the significance of the level of expression of the transcription factor FOXP3 and connection with gene polymorphisms for the *FOXP3* gene in women with preinvasive and invasive skin and ectocervical squamous cell tumors.

The previous professional and scientific work of candidate Boba Kotlica, MD as well as mentor1, Assoc. Prof. Katarina Stefanović and mentor2, Prof. Giuseppe Argenziano, together with the relevance of the proposed topic, provide a solid basis for conducting the research in a competent and contemporary manner.

Accordingly, based on the overall analysis of the submitted material, the Committee unanimously concludes that, in addition to all legal requirements, all other formal requirements have been fulfilled and, on this basis, proposes to the Teaching Scientific Council of the Faculty of Medicine, University of Belgrade to approve the preparation of the doctoral dissertation of candidate Boba Kotlica, MD, on the proposed topic.

Committee:

Belgrade, 14 May 2026

1. Prof. Saša Kadija, MD

2. Prof. Ivana Likić Lađević, MD

3. Assoc. Prof. Ana Banko, MD

4. Asst. Prof. Aleksandar Krunić, MD

5. Asst. Prof. Olivera Levakov, MD