

## REVIEW

for the competition for the occupation of the academic position, . Associated Professor \* in higher education 4. Natural sciences, mathematics and informatics, professional field 4.3. Biological Sciences, scientific specialty "Virology" declared in the State Gazette. pcs. 93 of 26.1 01.2019 for the needs of the Department of Virology, Institute of Microbiology, BAS

Reviewer: Prof. Dr. Nelly Stoyanova Korsun, MD Scientific Degree: Virology

Institution: National Center for Infectious and Parasitic Diseases, Sofia

I declare that I do not have any common publications and participation in scientific forums and projects with the candidate.

### I. Materials received for the competition

I received all the materials for the competition in electronic form: CV; PDF copies of abstracts and publications; lists of publications, citations, participation in scientific forums and research projects; reference for the fulfillment of the minimum national requirements according to the Law; reference to original scientific contributions: documents for teaching at NBU and Sofia University "St. Kl.Ohridski ".

### II. Career development of the candidate

Assistant Professor Ivanka Nikolova Nikolova completed her secondary education at the Russian Language High School in Burgas in 1990. In 1995 she completed her higher education at Sofia University. Kliment Ohridski "and holds a Master's Degree in Biology and Chemistry. From 1998 to 2001 he was a full-time PhD student at the Institute of Microbiology (IMICB) Stefan Angelov at the Bulgarian Academy of Sciences, with scientific adviser Prof. Dr. AS Galabov, PhD. In 2004 she defended her thesis on Resistance and Dependent Mutants of the Coxsackie BI Virus to the Picornaviral Dexoxaryl Inhibitor and obtained the Doctor of Virology ONS. In the same year, she was appointed as a Research Fellow of the Department of Virology at IMICB and in 2008 she was appointed as Chief Assistant. From 2012 until now she has been the Head of the Laboratory for Experimental Chemotherapy for Enterovirus Infections, and since 2016 she has been the Head of the Virology Department. She is a member of the Union of Scientists in Bulgaria and she is secretary of the Foundation Acad. Stefan Angelov.

III. Candidate's compliance with the minimum national requirements contained in the Rules for the Implementation of the Law on the Application of the ZRASRB - Conditions and Procedure for Occupation of the Academic Position "Associated Professor" (amend. - SG 15/19 February 2019).

According to Art. Ia. (1) Applicants for the academic position of "Associated Professor" must meet the relevant national minimum requirements for scientific and teaching activity from the Rules for Implementation of the ZRARBB. Nikolova's evidence for the different groups of requirements of the PPZRARB for the occupation of the academic position "Associate Professor" collect 628 points and exceed the required number of 400 points.

### IV. General characteristics of the activity

Teaching

Assistant Professor Iv. Nikolova is a part-time lecturer in Virology for students at the New Bulgarian University (NBU) and at the Faculty of Physics at Sofia University "St. Kl.Ohridski ". The enclosed documents from the Dean of the BSU Faculty of NBU shows that the workload of Iv.Nikolova during the last 5 years (spring semesters 2014/2015 - 2018/2019) includes 150 hours of exercises and 28 hours of lectures. The documents from the Dean of the Faculty of Physics, Sofia University "Kl. Ohridski" shows classroom workload of 270 academic hours of lectures over the last 4 semesters (2015/2016 - 2018/2019). The total number of school hours in the period 2015-2019 is 448 hours.

#### Participation in research projects

Assistant Professor Iv. Nikolova participates in 9 research projects, 4 of which are funded by the National Research Fund of the Ministry of Education and Science. The other two projects are joint with the Serbian and Macedonian Academy of Sciences.

#### Scientific production and publication activity

For participation in this competition Iv. Nikolova presents 22 scientific papers that are not included in the dissertation for the PhD degree. These are 15 full-text publications in scientific publications, referenced and indexed in world-renowned scientific information databases (Scopus and Web of Science), 13 of them in Impact Factor journals (general IF 23.508); 2 full-text publications in non-refereed scientific peer-reviewed journals; 2 book chapters and 3 full length articles in international and national scientific collections. In the listed publications, Iv.Nikolova is the first author in 4 (18.2%), the second author - in 5 (22.7%) and the third or next author - in 13 (59.1%) publications, which speaks about her leading role in a considerable part of scientific research. After PhD Thesis, Assist. Prof. Iv. Nikolova has participated in 30 scientific forums, 15 of which - in scientific events abroad.

Assist. Prof. Iv. Nikolova has a total of 133 citations (without self quotations) of 7 publications, almost all in foreign editions. Candidate publications were cited in 118 publications. According to my reference in Scopus, it has 122 quotes (without self quotations). Her H-index in Scopus is 3. Quotations in world databases show the importance of the scientific topics developed by the candidate and the recognition of the international academic community.

The Rules of Procedure for Acquisition of Academic Degrees and Occupation of Academic Positions at IMICB have additional requirements for occupying the academic post of Associate Professor: number of publications in IF journals, monographs, chapters of monographs, collections of international forums published in full text - 20: in 5 of them - 1st author: 1F (for the whole scientific career) - 20; H index (for the whole scientific career) - 5; participation in research projects - 3. Assistant Professor Ivan Nikolova has a total of 18 publications meeting the first requirement; its total IF is 26,842; has participated in 9 research projects, which fulfills most of the additional IMICB criteria.

#### Main directions of scientific activity

The scientific studies of Assistant Professor Ivanka Nikolova focuses on experimental chemotherapy for viral infections and in particular enterovirus infections. The relevance of these studies stems from the important clinical relevance of enterovirus infections, which occur in many cases with severe clinical manifestations (meningitis, encephalitis, paralysis, myocarditis, etc.). The rapid formation of drug resistance in the viruses is one of the reasons for the lack of licensed etiotropic treatment preparations. The candidate's main scientific contributions are the following:

## 1. Experimental chemotherapy for enterovirus infections

1. The development of resistant enterovirus mutants in vivo and in vitro to one of the most effective inhibitors of enteroviruses - disoxaryl (a blocker of the hydrophobic pocket of VP1 protein) has been demonstrated.
2. A package of phenotypic markers (MIC<sub>50</sub> value, size and shape of agar plates, resistance at 50 ° C, pathogenicity in mice) has been introduced to characterize viral drug mutants (resistant and dependent) as an important step in the study of inhibitors of enteroviruses.
3. Continuous cultivation of a resistant mutant (Coxsackie virus VG) in cell cultures in the presence of disoxaryl yields a mutant dependent mutant to this antiviral agent.
4. Molecular bases of drug resistance were determined on the model of disoxaryl mutants of Coxsackie B1 virus by sequencing the genome and performing amino acid analysis of the VP1 protein.
5. Combined effects of selective enterovirus replication inhibitors with different mechanisms of sequential alternative administration (CAA) have been investigated. The results of the administration of CAA in Coxsackie virus infections in mice indicate that this treatment regimen prevents the development of drug resistance and provides clear antiviral activity.
6. Amino acid analysis of enterovirus isolates in mice subjected to CAA was performed in which no drug resistance is formed and sensitivity to antiviral drugs is maintained.
7. In vitro synthesis and screening for anti-enterovirus activity of over 70 new compounds - analogues of MDL-860 (a key compound for the construction of a triple anti-enterovirus combination) was performed. Of these, 17 novel compounds exhibit distinct activity and 7 exhibit particularly high in vitro activity. Six low-toxic compounds with potent inhibitory effect on the replication of Coxsackievirus B1 were included in in vivo studies in neonatal mice; one of the compounds showed the most pronounced protective effect at a dose of 50 mg / kg (50% protective index). Several selected active compounds are included in combined administration in vitro with Pleconaril, Oxoglaucine and Guanidine.

## II. Broad-based screening aimed at detecting promising inhibitors of viral replication of enteroviruses, herpes viruses, adenoviruses and RSV.

1. Test of silanes (organosilicones) for in vitro anti-viral activity against 8 model virus strains.
2. Testing of merocyanins and violoric acid salts for Herpes simplex virus type 1 replication in cell cultures.
3. Testing for the antiviral activity of monoterpene alcohol geraniol against a broad spectrum of viruses in cell cultures.
4. Testing of elagitanins (isolated from plant source and synthetic derivatives) on the replication of Herpes simplex virus type 1 in cell cultures.
5. Test of ethanol extracts of the plant vortex (*Tanacetum vulgare* L.) against viral strains of different taxonomic groups (Picornaviridae, Herpesviridae and () rthomvxoviridae).

## III. Detection, genotyping and genetic analysis of various DNA viruses (cytomegalovirus and papilloma viruses) in samples from Bulgarian patients

- I. Detection of cytomegalovirus DNA in patients with unidentified ocular disease.

2. Genotyping of human papilloma virus proven in patients with throat cancer.

3. Genomic changes in cervical precancerous lesions and tumors induced by different types of human papillomaviruses in Bulgarian patients were investigated by microchip CGH analysis for the first time.

#### CONCLUSION

Presented by Assistant Professor Ivanka Nikolova materials for this competition show that she meets the mandatory and specific conditions and scientometric criteria for occupying the academic position of "Associate Professor". I give a positive assessment of the candidate's educational and research activities and recommend that the Honorable Scientific Jury award the Assistant Professor Ivanka Nikolova Associate Professor Academic Position in Higher Education 4. Natural Sciences, Mathematics and Informatics; professional field 4.3. Biological Sciences; scientific specialty "Virology".