OPINION

by Assoc. Prof. Dr. Lilia Ivanova Ivanova MD,

City Lab SMDL - Varna

Subject: Documents from Assistant Professor Ivanka Nikolova Nikolova, PhD, for participation in the competition for awarding the academic position "Associated Professor" for the needs of the Department of Virology, Institute of Microbiology of the Bulgarian Academy of Sciences, in the field of higher education 4. Natural sciences, professional field 4.3. Biological sciences, mathematics and informatics, specialty - virology. The competition has been announced in the State Gazette no. 93 / 26.11.2019 and the only candidate is Ivanka Nikolova Nikolova, db.

As a member of the Scientific Jury, determined by a decision of the SC of IMicB-BAS (Minutes 12 / 28.11.2019 and 13 / 17.12 / 2019) and appointed by order of the Director of IMicB-BAS 130 / 23.12.2019 I have been selected to submit an opinion on the procedure for occupation of the academic position of Associated Professor at the Department of Virology, Institute of Microbiology of BAS in the field of higher education 4. Natural sciences, professional field 4.3. Biological sciences, mathematics and informatics, specialty - virology.

Dear members of the Scientific Jury,

Short biographical information:

Assistant Professor Ivanka Nikolova Nikolova was born on 12.11.1972. Graduated Russian language high school in Burgas and higher education at Sofia University "St. Kliment Ohridski" Master Degree in biology and chemistry. She has worked consecutively as a biologist - specialist, scientific associate of the III degree, Assist. Prof., head of the laboratory "Experimental chemotherapy of enterovirus infections" in the Department of Virology of the Institute of Microbiology of the Bulgarian Academy of Sciences. From 2016 until now she is the Head of the Virology Department of the Institute of Microbiology of BAS. As a full-time doctoral student in Virology at the same Department of BAS on the topic: "Coxsackie B1 Resistant and Dependent Mutants to the Picornaviral Disexaril Inhibitor," with Academician Angel S. Galabov, PhD.

Participates in the implementation of 3 international scientific projects, jointly with Israel, the Serbian Academy of Sciences, the Macedonian Academy of Science and Art together with the Medical University of Sofia. She is involved in the implementation of 4 projects of the Research Fund of the Ministry of Education and Science and is the scientific leader of 2 projects funded by BAS.

Since 2015 she has been the secretary of the General Virology Seminar and of the Foundation "Acad. Prof. Dr. Stephan Angeloff".

She is a member of the Union of Scientists in Bulgaria. She achieved reward for best young scientist in Bulgaria in the field of microbiology for 2003.

Submitted materials:

In this competition, Assist. Prof. Assistant Ivanka Nikolova Nikolova participates with a total of 25 publications, 3 of them - related to the dissertation, 2 articles in books, 4 scientific articles in collections of national and international scientific forums. An abstract of the dissertation is also provided. The publications are in English and 15 of them are in scientific journals with IF and 4 in journals without IF. Total IF - 26,842. In 7 of the publications the candidate is the first author, in 5 - the second author, in 13 - the third and subsequent author. The citations are 133 without quotes.

She has participated in a total of 36 scientific forums, of which 12 - in Bulgarian scientific forums with international participation, 6 - in Balkan scientific forums ("Microbiologia Balkanica") and 18 - in world and European scientific forums.

Learning activity

Assist. Prof. Ivanka Nikolova Nikolova has been teaching since 2014/2015 - 30 teaching hours of Bachelor's Degree in Virology at the New Bulgarian University. During the academic year 2015/2016 and 2016/2017, the academic load is 89 hours per year, taking place at the New Bulgarian University and the Faculty of Physics at Sofia University "Kliment Ohridski". In 2017/2018 and 2018/2019, the academic load is 120 hours per year.

Evaluation of research activities

The research activity of Assist. Prof. Ivanka Nikolova Nikolova is predominantly in the field of experimental virology and in particular experimental chemotherapy of viral infections in several major directions: 1. Detects the development of resistant enterovirus mutants to WIN compounds in vitro and in vivo and is mutant-dependent. Clarifies the phenomenon of drug resistance to the capsid inhibitor disoxaryl in neurotropic coxsackie B1 viral infection in a mouse model. Defines the phenotypic characteristics of resistant and dependent mutants by introducing a package of phenotypic markers. Determination of the molecular genetic basis of resistance by RNA sequencing, and upon comparative analysis of the amino acid sequence of the capsid VP1 of the resistant mutant and the original strain, finds two point mutations (M213H and F237L) in the genome of the resistant mutant. 2. Develops a new approach for the combined in vivo administration of mouse model antiviral preparations - sequential alternative administration (CAA) of triple combinations of inhibitors with different mechanism of action on enterovirus replication. Establishes sustained and increased sensitivity of the virus to the partner drugs in the combination during the course of treatment. Genomic analysis of mouse isolates subjected to CCA that did not show drug resistance and showed increased sensitivity to antiviral drugs was performed. RNA mutations were detected in regions 5, UTR, 2A, and 2B and amino acid substitutions in the VP3 region. 3. A large-scale trial of a wide range of substances of natural or synthetic origin was conducted to search for antiviral activity and more specifically inhibit the replication of many clinically relevant viruses - enteroviruses, herpes viruses, adenoviruses, respiratory syncytial virus. 4. A study was conducted for the detection, genotyping and genetic analysis of various DNA viruses in samples from Bulgarian patients. For the first time, genomic changes in cervical precancerous lesions and tumors induced by different types of human papillomaviruses in Bulgarian patients were examined using microarray CGH analysis.

The original scientific contributions of Assist. Prof. Ivanka Nikolova is in the field of experimental chemotherapy for enterovirus infections that are still incurable and of great clinical importance. The high mutation frequency of these viruses and the rapid development of drug resistance are the cause of the failure of monotherapy with virtually all inhibitors of enterovirus replication, demonstrated for the first time even by the disoxaril - blocker of the hydrophobic pocket of capsid VP1. The mouse model in vivo for the first time demonstrated the development of drug resistance to WIN compounds in neurotropic coxsackie B viral infection due to the accumulation of drug resistant mutants in the target organ - the brain. It introduces a package of phenotype markers to characterize these mutants and the molecular bases of drug resistance are defined by RNA sequencing. It is extremely innovative to introduce for the first time the combined use of selective inhibitors of enterovirus replication with different mechanisms of action, avoiding the so-called "dose pressure" characteristic of monotherapy that favors the rapid selection of resistant mutants. Develops a treatment course on the scheme of

sequential alternative introduction of triple combination enterovirus inhibitors in mice. This raises the hope of creating effective treatment for enterovirus infections in humans as well.

More than 70 new analogues of MDL-860 (oxoglaucine), an important compound in the triple combination, have been synthesized and screened. Six leading compounds were selected that are low toxic and have good synergistic effects in in vivo experiments in neonatal mice. Broad-based screening was conducted to identify promising replication inhibitors of enteroviruses, herpes viruses, adenoviruses, and respiratory syncytial virus such as silanes, merocyanins, and salts of violanic acid, monoterpenic alkaline extracellular synthalenic alcohol derivatives the plant is spinning. For the first time, genomic changes in cervical precancerous lesions and tumors induced by different types of human papillomaviruses in Bulgarian patients and microchip CGH analysis were investigated, in collaboration with a team of the Medical University - Sofia. Works on detection, genotyping and genetic analysis of DNA viruses (CMV and HPV).

The scientific activity is focused on topical and highly perspective problems. She works with various partners - Institute of Organic Chemistry - BAS, Medical University - Sofia, Institute Pasteur-Paris. Shows that she can work in a team and create a team.

According to the minimum national requirements for the scientific and teaching activity of the ZRASRB it shows, according to Indicator A - 50 points, Indicator C - 102 points, Indicator D - 217 points, Indicator D - 266 points. According to the additional requirements of IMicB there is a total IF of 26,842, citations - 133 and H factor - 3.

In conclusion, I believe that the presented materials from the scientific production and the teaching activity of Assistant Professor Ivanka Nikolova Nikolova, PhD cover and exceed the minimum requirements of the ZRASRB, of the Regulations for the acquisition of scientific degrees and for the occupation of academic positions of BAS and the additional requirements of IMnebB in the academic position of Associated Professor. I wish she continue to expand her multidisciplinary and implementation approach.

Because of the above, I recommend that the venerable members of the Scientific Jury vote positively for the award of the academic position of Associated Professor to the Assistant Professor Ivanka Nikolova NikolovaPhD as I will do.

Assoc. Prof. Dr. Lilia Ivanova Ivanova MD