Opinion

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According to a competition for the occupation of an academic position of associate professor in the field of higher education 4. "Natural sciences, mathematics and informatics", professional direction 4.3. "Biological Sciences" (Biophysics), for the needs of the "Electroinduced and Adhesive Properties" section at IBFBMI.

The announcement for the competition was published in the "State Gazette", no. 27/24/03/2023.

Only one candidate submitted documents for participation: assistant prof. Severina Yordanova Semkova PhD.

By order 344/19.05.2023 of the director of the IBFBMI-BAN, I have been appointed as a member of the scientific jury in the competition described above.

At the first meeting of the scientific jury, we got acquainted in detail with the materials presented by the assistant prof. Severina Semkova and we found that they meet the requirements of the law on the development of the academic staff of the Republic of Bulgaria.

Dr. Severina Semkova obtained the scientific and educational degree "Doctor" in the scientific specialty "Biophysics" in 2017, based on a dissertation on the topic: "Combined approach for *in vitro* and *in vivo* visualization of internalization and localization of fluorescent nanoparticles in tumors after electroporation".

In the presented materials for participation in the competition, the distribution of the scientific activities of the assistant professor Semkova is shown by points according to the minimum national requirements of the ZRAS of the Republic of Bulgaria.

As is clear from the presented documents, the results achieved by the assistant prof. Semkova cover, and in some indicators exceed, the requirements laid down in the law.

In group of indicators B (habilitation work) a list of six articles (B1-B6) is presented, which carry a total of 112 points 100 points are required for this indicator. The articles are distributed by quartiles as follows: Q1-1 issue, Q2-3 issue, Q3-1 issue, Q4-1 issue.

In indicator group D (scientific publications that are referenced and indexed in world-renowned databases of scientific information), 11 scientific publications are presented, which carry 222 points out of the required 200. Three of them were published in journals with rank Q1, 6 in journals Q2, 1 in Q3 and 1 in Q4. All articles are in journals with IF.

In group D indicators (citations in scientific publications, monographs, collective volumes and patents) with minimum national requirements 60 points a list of 73 citations distributed by articles is presented, which carry 146 points.

A list of participations or management of national/international scientific projects is also presented. According to the conditions of the competition for the academic position "Associate Professor", such activity is not required, but the candidate presents an impressive activity in this direction.

The presented scientific contributions of the Assistant Professor Dr. Severina Semkova are grouped as follows:

- Main scientific contributions (from the habilitation thesis)

- Contributions of scientific works according to indicator G7 (scientific publications that are referenced and indexed in world-renowned databases).

The attached reference presents a list of six scientific publications in refereed international scientific journals organized as habilitation work. A major scientific achievement derived from the habilitation work is: a thorough study of newly synthesized and/or unstudied biologically active substances of natural origin in combination/or not with electroporation. All test substances showed *in vitro* anticancer activity against a panel of human breast cancer cell lines.

Contributions of scientific works under indicator G7 (scientific publications that are referenced and indexed in world-renowned databases) are presented in subgroups:

1. Scientific contributions related to the development of modern platforms for visualizing the introduction and delivery of substances in cells and tissues in combination/or not with electroporation.

Electroporation has been shown to accelerate the release of organic dyes from the interior of nanoparticles, but not of quantum dots (publication G1).

2. Scientific contributions related to detailed research and proof of new aspects in the mechanism of action of conventional anticancer drugs:

Synergistic cytotoxicity specific to cells isolated from patients with acute lymphoblastic leukemia after treatment with Resveratrol in combination with conventional chemotherapeutics (Everolimus and Barasertib) was reported for the first time (publication G3).

The possibility of sensitization of cancer cells (colon) to SN38 (an active metabolite of the conventionally used chemotherapeutic agent Irinotecan) was investigated, as well as clarification of its mechanism of action after combined treatment with electroporation (EP). It was found that the combination of EP and SN38 affects cancer cell viability and cytoskeleton integrity (publication G6).

3. Scientific contributions related to the study of the redox status and its relation to cancer treatment.

An EPR methodology that allows the detection of superoxide overproduction in living cells and their differentiation (cancerous from non-cancerous) based on the intracellular redox status has been developed. The used (cell-penetrating) nitroxide radicals have been confirmed to be suitable contrast probes for distinguishing between non-proliferative, slow-proliferative and fast-proliferative cells, making them close to "perfect" redox sensors (publication G2).

Quantum sensors have been developed for tracking the total reducing capacity and/or oxidative stress in living objects by means of modern imaging techniques (EPR, MRI, optical imaging) based on specificity in their contrast characteristics (publication G9).

4. Scientific contributions related to the development of modern therapeutic approaches based on changes in redox homeostasis (research and proof of antiproliferative and cytotoxic effects of redox-active substances and their combinations (including those with conventional chemotherapeutics)).

The combination of redox active substances "Menadione Menadione/Ascorbate Ascorbate" M/A) (or "Pro Vitamin K3/Vitamin C", with trade name Apatone™) was investigated.

A synergistic dose-dependent antiproliferative and cytotoxic effect was established against cancer cells (cell lines of different origin and properties), but not against healthy cells of the same origin, especially at concentrations that are achieved *in vivo* after oral/parenteral administration.

M/A cytotoxicity was found to be associated with disturbances in oxidative phosphorylation and mitochondrial ATP depletion.

The M/A combination was found to strongly sensitize cancer cells to antitumor agents showing synergistic or additive cytotoxicity accompanied by impressive levels of apoptosis induction based on changes in cellular redox homeostasis.

It has been shown that oral intake of M/A can have a beneficial effect on the body's immune system, making cancer cells "visible" and possibly more vulnerable to natural immune cells (publications G4, G5, G7, G10).

5. Scientific contributions related to the identification and proof of new applications of approved and/or tested medical products, outside the scope of their original medical indication (the so-called "drug - repurposing").

Two different substances were studied: an antimalarial drug (Artemisinin) and an antiparasitic drug (Fenbendazole), administered alone or in combination with redox modulators on different cell lines, redox-related anticancer activity (antiproliferative and cytotoxic effects) was demonstrated (publications G8, G11).

The scientific contributions presented by the candidate correctly reflect the published results. A large part of them have an original character, and some have a potential applied character.

In conclusion, I believe that the parameters presented above, the presented scientific contributions, as well as the overall work of assistant professor Severina Semkova fully cover, and in some indicators exceed the requirements for acquiring the academic position of "associate professor", laid down in the regulations of the law on the Development of the Academic Staff of the Republic of Bulgaria and the additional requirements of IBFBMI-BAN.

My personal impressions of the candidate's work, as well as the duly submitted documents for the competition, give me reason to confidently recommend to the scientific jury to prepare a proposal to the Scientific Council of IBFBMI-BAN for the election of Severina Yordanova Semkova for the academic position of "associate professor" in scientific direction 4.3, Biological Sciences (Biophysics).

27.07.2023

Sofia

Signature:

/prof. Biliana Nikolova/