

To
The chairman of the scientific Jury,
determined by Order № P - /2020
of the Director of Institute of Microbiology – BAS

On your Protocol №1 / from
(date of the first meeting)

Attached hereby I present: Review
of the candidates under a competition for assuming the academic position of
"Professor" (Full Professor)
with scientific specialty "Immunology"
as announced in SG no. 47 of 22.05.2020, for the needs of the Laboratory
"Experimental Immunology", Department of Immunology, IMiB – BAS

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REVIEW

OF THE HABILITATION COMPETITION FOR ASSUMING THE ACADEMIC POSITION OF “PROFESSOR” (“FULL PROFESSOR”) IN PROFESSIONAL FIELD 4.3. BIOLOGICAL SCIENCES, SCIENTIFIC SPECIALTY: IMMUNOLOGY, ANNOUNCED IN SG NO. 47 OF 22.05.2020, FOR THE ACADEMIC DEVELOPMENT OF THE LABORATORY "EXPERIMENTAL IMMUNOLOGY", DEPARTMENT OF IMMUNOLOGY, IMiB - BAS

I. Analysis of the candidate's career profile

Assoc. Prof. Andrey Tchorbanov has a Master's degree in Genetics and Cell Engineering from Sofia University “St. Kliment Ohridski”, meeting with immunology, immunological methods and viral pathologies during the development of his Master thesis dissertation “Immunological and immunochemical methods for proving poliovirus infection.”. He has worked at NCIPD for 6 years (1992-1998), Section "Applied Immunology and Biotechnology" - Laboratory "Bacterial Vaccines" and have had a training under the program "Copernicus" as a guest researcher in 1997 in the Laboratory Experimental Immunology at the University of Utrecht, The Netherlands on “Modulation of the immune response by targeting genetically engineered antigens to certain cellular receptors”. In 1999 he had started working in Department of Immunology at the Institute of Microbiology – BAS (IMiB-BAS), where he has began working on topics concerning autoimmunity and responses eliciting auto-antibodies, as well as the development of protein and DNA chimeric molecules for the treatment of autoimmune diseases. In 2002 he defended his PhD dissertation on "Engineered and genetically engineered chimeric molecules as antigens" at the Institute of Microbiology - BAS. He has also visited the National University of Taipei, Taiwan (2003) as guest researcher. In 2009 he defended his habilitation for the academic position of "Associate Professor", and in 2011 he also became a guest lecturer at the University of Nis, Serbia.

II. General description of the submitted materials in the habilitation competition.

The materials presented by Assoc. Prof. Andrey Tchorbanov in his application fully cover the requirements of the habilitation competition and present specific evidence regarding the coverage of the required criteria for this competition, as well as they present the entire production of the applicant through lists of publications, citations and patents and within the content of the submitted Description of author contributions, Professional Resume, etc. The presented documentation is extremely well put together and very detailed. Digital copies of the publications presented as claim in his application for this habilitation competition are presented, as well as the abstracts of each presented work in both Bulgarian and English.

III. Evaluation of the candidate's scientific works for his overall academic development.

The materials presented by Assoc. Prof. Andrey Tchorbanov cover a wide range of original results and review materials, which show an extremely high level of expertise in the field of experimental and applied immunology, and include models and methods developed for *in vitro* and *in vivo* evaluation of candidates for therapeutic agents, prototype protein and genetically engineered chimeric molecules, and the generation of a variety of animal models for preclinical trials. His research over the years has focused on generating new tools for specific targeted therapy of diseases that pose serious societal challenges, such as allergic, autoimmune and oncological pathologies. The chosen strategy is highly innovative and includes different approaches for targeted interaction to specific cells, by creating molecular chimeras, involving hybrid antibodies, through protein and genetic engineering, as well as creating new animal models for their validation, and to study the pathogenesis of various diseases where modulation of the immune response may

serve as a major therapeutic approach. Assoc. Prof. Tchorbanov is undoubtedly an exceptional expert in the development of "humanized" models using immunodeficient SCID and NSG mice. Assoc. Prof. Tchorbanov and the scientific group developed by him over the years is a pioneer in the development of this field and the only one to my knowledge with such a level of expertise nationwide. As a result of his efforts, various prototype chimeric protein molecules have been constructed to suppress the pathological immune response in a number of pathologies related to changes in the immune system - systemic lupus erythematosus, autoimmune diabetes, allergies and asthma, infections, various cancers. An adequate model for preclinical study and analysis of the result of the experimental therapy has been developed for each of them. The results published by him and his scientific group in very renowned journals is a significant contribution in the field of experimental immunology and immunotherapy.

The future plans for the development of the scientific group are to create new experimental animal models generating various diseases, as well as to create prototypes of drugs and vaccines for future therapy. More detail is presented in his academic evaluation analysis.

✓ ***General characteristics of the scientific production and publication activity;***

The scientific contributions of Assoc. Prof. Tchorbanov, presented in the form of publications and projects in this competition can be summarized in three main areas, which does not end his significant scientific activity: *selective suppression of the pathological response by chimeric molecules in mice and human models of autoimmunity; design and generation of new types of DNA and protein-engineered vaccines and adjuvants; application of newly synthesized cyanine dyes for analysis of various cellular processes.*

As it concerns chronology and scientific aims, one of the main focuses of Assoc. Prof. Tchorbanov's research is the generation of chimeric molecules with different complexity of genetic engineering approaches, including the creation of fusion (chimeric) protein molecules constructed from peptides mimicking double-stranded DNA epitopes, receptor fragments and / or variable antibody fragments aimed at binding to and activating various immune cell inhibiting molecules. These studies have an evolutionary character with constant upgrading to new and more complex chimeras, validated in classical, but often in original author's conceived experimental humanized mouse models of systemic lupus erythematosus, as well as type 1 diabetes.

Chimeric molecular constructs blocking pathogenetic cell lineages of auto-antigen-producing B-cells represent a very innovative approach and are a research instrument with very high potential, as this allows for a multimodal interaction with immune cells of virtually any kind. These complex fusion molecular complexes can, on the one hand, "recognize" antigen-specific cells, carrying a modality containing an auto-antigenic epitope, and, on the other hand, "act" on the same cell through a second or even third modality, inhibiting proliferation or secretion, by binding to specific receptors on its surface. Assoc. Prof. Tchorbanov and his group have employed a number of implementations of the approach, as for ex. in models of systemic lupus they have created, they applied and successfully validated: molecular chimeras between DNA mimicking (mimotopic) peptides and monoclonal antibodies (mAb) against surface inhibitory peptides (such as CD32 (FcγRIIb)); two- and three-specific chimeric antibodies, with high affinity for a particular antigen; mimotope decapeptide DWEYSVWLSN and mAb against the T- and B-lymphocyte inhibitory activity receptor - complement receptor type 1 (CR1).

A further point in the evolution of the developed technological approaches by Assoc. Prof. Tchorbanov in direction of creating antiviral vaccines with internal adjuvant properties is the design of an extremely interesting and innovative combination of chimeric (fusion) molecule with B-cell activating and internal adjuvant effect, encoding T- and B-cell epitopes (like haemagglutinin from influenza A virus) associated with a sequence encoding single-stranded variable antibody fragments (scFv) specific for co-stimulating B-cell complement receptor types 1 or 2 (CR1/2). The construct was administered as a DNA vaccine and tested *in vivo*, in a mouse model, with a demonstrated complement-receptor specific adjuvant cytotoxic and humoral response.

The next stage in the development of these advances is the stimulation of an immune response to low-immunogenic constant viral epitopes, which would allow a long-lasting effect and resistance of anti-viral vaccines to the constant variability of pathogens. For this purpose, Assoc. Prof. Tchurbanov and his team have developed chimeras consisting of single-stranded variable fragments (scFv) of murine anti-human Fc γ RI monoclonal antibody, possessing cellular stimulation activity, fused to peptide sequences containing T- and B-cell epitopes of influenza A virus hemagglutinin. The DNA vaccine has been successfully tested *in vitro* in a state-of-the-art experimental humanized NOD SCID gamma mouse model, demonstrating efficacy in generating virus-specific antibodies and highly cytotoxic T-cell response. Another approach put in use by his group with good results is the use of natural exogenous adjuvants, such as hemocyanins, isolated from marine gastropods or land snails, leading to an enhanced cytotoxic and humoral response.

It should be dully noted that these studies are not self-serving development of new therapeutic approaches, but integrated studies of the auto-immune processes themselves, in the process of which new experimental therapeutic models were used, but also new phenomena related to the studied diseases were found, as is the case e.g. with the deposition of complement C3 on nuclear antigens reflecting disease progression in a murine model of SLE, et al.

Very interesting are the studies of the group of Assoc. Prof. Chorbanov regarding the development of newly synthesized cyanine dyes not only as adjuvants but also as potential analogues of Thiazole Orange, allowing them to be used for analysis of DNA content in living cells and for analysis of cellular apoptosis. The team successfully tested other hemocyanins as *in vivo* anti-tumour and anti-proliferative agents in a mouse model of colon cancer developed by them.

In a large part of the publications Assoc. Prof. Tchurbanov is the leading author, making a strong impression on the very good international recognition of the team, allowing a solid level of be published papers in prestigious scientific journals with high impact factor / quartile by an entirely national scientific team.

The project activity of Assoc. Prof. Tchurbanov is impressive. He has so far participated in 33 successfully completed projects, and currently actively participates in 13 new projects, of which he is either PI, or Co-PI or Coordinator for his organization. He is respectively the Coordinator / Project Leader of two major projects under the Operational Program "Science and Education for Smart Development" 2014-2020 - Infrastructure project "Construction and Development of Centres of Competence" and the Operational Program "Innovation and Competitiveness" 2014-2020, procedure "Development of product and production innovations" - a joint project between IM-BAS and NEOPHARM Bulgaria EOOD. These data show that in addition to being a strong scientist, the candidate is able to skilfully lead complex administrative projects, as well as projects related to R&D activities. It should be emphasized that some of the projects led by him are with foreign funding, incl. one of his latest projects related to the development of a new multi-epitope vaccine against the causative agent of COVID-19, as well as its validation in a new humanized mouse model for vaccine testing.

IV. Evaluation of the habilitation thesis or its equivalent in published papers submitted for participation in the competition for "PROFESSOR" by the candidate.

Publications equivalent to the habilitation thesis / monograph, exceeding the requirements of „RULES FOR IMPLEMENTATION OF THE LAW ON THE DEVELOPMENT OF THE ACADEMIC COMPOSITION IN THE REPUBLIC OF BULGARIA“ (RILDACRB), mainly on the topic of hybrid molecules modulating the auto-immune response in diseases such as systemic lupus erythematosus, are presented.

V. Reflection (citation) of the candidate's publications in the national and foreign literature (publication image).

The presented total number of citations, as well as the citations for the last years are in a significant volume, as their number also exceeds the requirements of RILDACRB and the Regulations of IMiB - BAS. The level of publications is of rank Q1, Q2, as the impact factor is high, incl. exceeding 6 on some articles.

Assoc. Prof. Tchorbanov is an inventor in 2 international patents - "AN AGENT FOR SELECTIVE SUPPRESSION DISEASE-ASSOCIATED AUTO-REACTIVE B-CELLS", "SUPPRESSOR OF DISEASE-ASSOCIATED AUTOREACTIVE B LYMPHOCYTES."

He has 6 prestigious awards over the years, of which he has twice won the "Diploma of Excellence" of Union of Scientists in Bulgaria (BuSI) and also twice won the highest award for scientific activity in Bulgaria - Pythagoras: Winner of the Pythagorean Award for Biomedical science - 2012; Winner of the Pythagorean Prize for established scientist for biomedical sciences - 2017. He is a member of prestigious international scientific societies: 1. Chairman of the section "Immunology" at the Union of Scientists in Bulgaria (BuSI). 2. EFIS - European Federation of Immunological Associations. 3. EASD - European Association for the Study of Diabetes.

Apart from research, Assoc. Prof. Tchorbanov also participates in a wide range of expert activities: He is a member of the National Commission for Ethical Work with Laboratory Animals at the Ministry of Agriculture and Food as a representative of BAS, 2006-2012; European Union research and innovation "Horizon 2020" - Commission "Challenges for the European Bioeconomy: Food Security, Sustainable Agriculture and Forestry, Maritime, Marine and Inland Water Research", since 2013; At the Ministry of Education and Science he participates in the "Commission for consideration of requests for national co-financing for the preparation and participation of Bulgarian teams in research projects under the EC Framework Programs in the field of research." 2014-2016; "Commission for determination of the Pythagorean Awards for 2017", 2018 and the Commission for updating the rules of operation of the National Contact Network under the Horizons 2020 Framework Program, 2018.

Assoc. Prof. Tchorbanov is a member of the Scientific Council of the Stefan Angelov Institute of Microbiology - BAS and of General Assembly - BAS.

VI. Complex, qualitative assessment of the teaching-methodical and teaching activity, incl. scientific guidance of students, doctoral students, postgraduates.

Currently, the working group of Assoc. Prof. Andrey Tchorbanov consists of 3 main assistants, 2 assistants, 3 full-time doctoral students (plus two future ones from January) and 8 graduates and interns. The group developed models of mouse metabolic syndrome, 2 mouse and humanized models of autoimmune diabetes, mouse model of collagenase-induced arthritis, 2 mouse and humanized lupus models, mouse and humanized model of asthma, mouse and humanized models for testing anti-viral vaccines, mouse and humanized models of colorectal cancer, glioblastoma and melanoma. The prototypes of the developed drugs range from various plant extracts, proteins and their derivatives, to new probiotic strains, new virus vaccines, phage display and chimeric protein and DNA molecules. The influence of various hormones in reproductive biology under conditions of autoimmunity, as well as the influence of various epigenetic factors on the development of the autoimmune process are also tested.

VII. Critical remarks and recommendations.

-none

VIII. General assessment of the applicant's compliance with the mandatory conditions and the mandatory quantitative criteria and scientometric indicators:

The documents submitted by the only candidate, Assoc. Prof. Andrey Chorbanov, with an extremely vibrant appearance, clearly show coverage of the minimum national criteria of the RILDACRB and those of IMIKB - BAS:

- According to the minimum requirements of RILDACRB, for Subject field 4. Natural sciences, mathematics and informatics, with Professional subtopic 4.3. Biological sciences, in Group A, Indicator 1 (defended PhD thesis) 50 points are required and covered, in Group B, indicators 3 and 4 (publications as habilitation work) are covered 120 points out of the required 100 points, and in Group D indicators 5-10 (additional publications outside the habilitation ones) are covered 250 points out of the required 200 points. The fact that the publications in groups B and D are mostly with rank Q1 (63%) and partly Q2 (37%) is extremely good). Of the 100 citations required in Group D, 466 curated in the Web of Science and Scopus databases are presented. Group E covered 465,376 points out of 150 required points, indicating 5 of the large number of defended doctoral students under the guidance of Assoc. Prof. Tchorbanov, and 5 projects with attracted funds totalling BGN 201 880, and 1050 hours of teaching activities were conducted by 2012 so far.
- According to the local criteria of IMikB - BAS, 32 out of 20 required articles with impact factor are presented, all being published after habilitation in the academic position "Associate Professor". Assoc. Prof. Chorbanov is a leading author in 23 of them, with 16 articles required, where the candidate is a leading author. He has presented a total of 476 citations out of 400 required, and his works total impact factor is 141.754 out of required 40, with an h-index of 13 (11, according to Scopus, with auto citations excluded), where 10 is required. The requirements for successful project management and doctoral students are also significantly exceeded.

IX. In conclusion, the scientific merit indicators demonstrated by Assoc. Prof. Andrey Tchorbanov significantly outrank the requirements stipulated by the Rule of application of the National Law of Academic Staff Development as well as they significantly outrank the elevated local criteria of the Institute of Microbiology at BAS, which taken together with his scientific and teaching achievements, makes strong application for assuming the academic position of "Professor" (Full Professor). Assoc. Prof. Andrey Tchorbanov fully meets the mandatory and specific conditions and scientometric criteria for the academic position " Professor ", something I am fully convinced in, and I vote for it as a member of Scientific Jury!

X. As the only candidate in the competition, the need for ranking candidates is eliminated and the choice of this proposal for the position is unambiguous, natural and fully deserved!

Prof. Soren Hayrabyan, MD, PhD, DSC