# Evaluation Board Decision on the Nomination for Appointment to Professor

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| **Masaryk University** | |
| **Faculty** | Faculty of Science |
| **Procedure field** | Biomolecular Chemistry |
| **Applicant** | doc. Mgr. Richard Štefl, Ph.D. |
| **Applicant's home unit, institution** | Faculty of Science, Masaryk University |
| **Board members** | |
| **Chair** | prof. RNDr. Vladimír Sklenář, DrSc.<br>*CEITEC, Masaryk University* |
| **Members** | prof. RNDr. Michal Otyepka, Ph.D.<br>*Univerzita Palackého v Olomouci*<br>Prof. Dr. Matthias Geyer<br>*University of Bonn, Germany*<br>prof. Petr Svoboda, Ph.D.<br>*Ústav molekulární genetiky AV ČR*<br>prof. Ing. Richard Hrabal, CSc.<br>*Vysoká škola chemicko - technologická Praha* |

## Evaluation of the applicant's scholarly/artistic qualifications

For the entire scientific career, Richard Štefl has been interested in structure and dynamics of biomolecules. He was trained in multiple disciplines, ranging from physical chemistry to biology. Currently, dr. Štefl employs a wide range of integrative structural biology tools, among which the main experimental technologies (NMR, X-ray crystallography, small-angle X-ray scattering, cryo-electron microscopy) are combined to link detailed atomic structure with cellular context and, consequently, with diseases.

During his Ph.D. years, Richard utilized computational methods, such as molecular dynamics simulations, to study the properties and behavior of nucleic acids. These studies revealed the molecular basis of guanine quadruplex stability and folding (Stefl et al, 2001a; Stefl et al, 2003; Fadrna et al, 2004), of sodium ions binding specificity in the minor groove of the AT-rich DNA sequences (Stefl and Koca, 2000), and of the unusual structure of a guanine-rich double helix (Stefl et al, 2001b; Trantirek et al, 2000a). These studies were carried out to complement the experimental data and to study very fast molecular events that cannot be grasped by standard experiments. He learned that computational methods complement experimental techniques and can enhance our understanding of biomacromolecular function. In this spirit, in which computational methods meet the experiment, he contributed to development and application of several new methods to aid the interpretation of nuclear magnetic resonance (NMR) data (Trantirek et al., 2000b; Trantirek et al., 2002). He also determined the solution structures of the DNA duplexes formed by d(GCAAAATTTTGC) and d(CGTTTTAAAACG) by NMR spectroscopy including refinement with residual dipolar couplings (Stefl et al, 2004).

To broaden experimental and theoretical expertise, dr. Štefl has decided to join the group of professor Frederic Allain at the ETH Zürich for a postdoctoral training in 2001. Major aim during this period was to gain a deep insight into modern molecular biology methods and improve his skills as an NMR spectroscopist for structural and functional studies utilising very high magnetic fields. His postdoctoral project aimed to understand the mechanism of posttranscriptional modifications mediated by an enzyme called adenosine deaminase acting on RNA 2 (ADAR2). ADAR2 site-selectively modifies adenosines to inosines within RNA transcript, thereby recoding genomic information. ADAR2 consists of two double-stranded RNA-binding motifs (dsRBMs) and an adenosine deamination domain. The obtained structural and functional data indicated that the specificity of ADAR2 is mediated by their dsRBMs (Stefl et al, 2006). These domains recognize certain irregularities in the double helical architecture of RNA and thus direct the catalytic domain to the specific editing site. This is an important finding since the dsRBMs were previously considered to be non-specific double-stranded RNA-binding modules. In this project, dr. Štefl also determined the solution structure of the RNA substrate; central region of the human GluR-B R/G pre-mRNA (Stefl and Allain, 2005). Richard assigned the resonances of a 32 kDa protein fragment of ADAR2 that is responsible for RNA-binding (Stefl et al, 2005) and subsequently, he determined the structure of the two dsRBMs of ADAR2 bound to a 71-nucleotide stem-loop pre-mRNA, GluR-B R/G (Stefl et al. 2010). In this paper, which was published in the highly respected journal Cell, he revealed an unexpected mode of sequence-specific RNA recognition by the two double-stranded RNA recognition motifs (dsRBMs) present in the N-terminal region of ADAR2 (A-to-I editing enzyme). The solution structure of the two dsRBMs of ADAR2 bound to a specific editing substrate (a 50 kDa complex that represents the largest protein-RNA complex structure ever solved in solution) revealed the general principle of the sequence-specific recognition by ADAR2 dsRBMs, which explains how ADAR2 selects its editing sites.

After completion of the post-doctoral training in 2007, Richard Štefl established his own laboratory at Masaryk University and switched to a new research field focused on transcription termination machineries of RNA polymerase II and the overall structure and composition of RNA polymerase II CTD interactome. His work helped to decipher the basic rules that govern the readout of the CTD code. The concept of the CTD code has been suggested some time ago, but the mechanisms and signals that promote recruitment of specific termination and processing factors were unclear. On the route, Richard solved structures related to the recognition of termination signals for non-coding genes (Hobor et al. 2011; Holub et al. 2012; Kubicek et al., 2011; Kubicek et al., 2012; Porrua et al., 2012; Bacikova et al., 2014; Tudek et al. 2014; Hrossova et al., 2015) and protein-coding genes (Jasnovidova et al., 2017a; Jasnovidova et al., 2017b). These pioneering studies revealed new structural features and modes of recognition that have had a considerable impact in biological fields. For example, in a 2012 Genes & Development paper, dr. Stefl reported that the CTD recognition by Nrd1 requires both phosphorylation and isomerization of RNAPII CTD. This suggests that the coupling of covalent and non-covalent changes in the CTD structure regulated by kinases/phosphatases and isomerases are

crucial for the dynamical process of recruitment and displacement of appropriate processing factors during the transcriptional cycle. In a 2014 Molecular Cell paper, Richard reported a new function of the Nrd1-Nab3-Sen1 (NNS) complex, which controls pervasive transcription in yeast by terminating transcription of cryptic transcripts and directing these RNAs to degradation by the exosome. In this work, he showed structural and functional evidence demonstrating that the CTD Interaction Domain (CID) of Nrd1p interacts with RNA polymerase II (RNAPII) and Trf4p in a mutually exclusive manner, which defines two distinct forms of the NNS-complex, one involved in termination and the other in degradation. He proposed that the dynamics of factors interacting with the CTD of RNAPII throughout the transcription cycle is regulated not only by the enzymes responsible for CTD modifications and proline isomerization, but also by competitive interactions with proteins containing CTD-like motifs (CTD mimics). In a 2017 PNAS paper, dr. Štefl reported the use of integrative structural biology to visualize the architecture of RNAPII CTD in complex with Rtt103, a 3'-end RNA-processing and transcription termination factor. Rtt103 forms homodimers via its long coiled-coil domain and associates densely on the repetitive sequence of the phosphorylated CTD via its N-terminal CTD-interacting domain. The CTD-Rtt103 association opens the compact random coil structure of the CTD, leading to a beads-on-a-string topology in which the long rod-shaped Rtt103 dimers define the topological and mobility restraints of the entire assembly. These findings underpin the importance of the structural plasticity of the CTD, which is templated by a particular set of CTD-binding proteins.

Above described discoveries represent just several examples of new structural features revealed in the laboratory of dr. Štefl, which may have a considerable impact in several areas of functional biology. Furthermore, because a number of genetic disorders or human diseases (including neurodegenerative diseases or cancer) relate to abnormalities in RNA processing and ribonucleoprotein assembly, it is anticipated that the detailed knowledge of mechanisms regulating the co-transcriptional processing will be of clinical value in the long term

During all stages of his career, dr. Štefl was highly independent and creative to secure his own funding. At the postdoctoral level, he was a European Molecular Biology Organization (EMBO) long-term fellowship awardee and Human Frontier Science Program Organization (HFSPO) long-term fellowship recipient. His laboratory was established through competitive start-up grants from Howard Hughes Medical Institute, European Molecular Biology Organization, and Human Frontier Science Program. Currently, he is primarily funded by the ERC Consolidator Grant. He is a head of the Centre for Structural Biology at CEITEC and has strong commitments to the structural biology field by serving the community as the member of executive board and the vice-president of the Czech Structural Biology Society since 2015. His results attracted international attention and Richard was invited to deliver 10 invited lectures at various institutions. Among them, invited lectures at Oxford University (2018), FEBS-EMBO Conference in Paris (2014), and at the Fifteenth Annual Meeting of the RNA Society in Seattle (2010) are to be emphasized. He also received a number of awards, including highly prestigious Neuron Impulse Award (2015).

So far, Dr. Štefl has published 38 original papers with 1727 citations in Web of Science or 1373 citations if all self-citations are excluded (h-index=24; Web of Science).

**Conclusion:** The applicant's scholarly qualifications ***meet*** the requirements expected of applicants participating in a professor appointment procedure in the field of Biomolecular Chemistry.

**Conclusion**: The applicant's scholarly/artistic capabilities **meet** the requirements expected of applicants participating in a professor appointment appointment procedure in the field of Biomolecular Chemistry.

**Evaluation of the applicant's pedagogical experience**

Having spent most of his career working in research institutes, dr. Štefl had somewhat limited opportunities to teach. Since 2007, he delivers course on Protein-RNA Interactions at Masaryk University. Since 2014, he teaches the course on Structural and Molecular Biology of RNA (with the contribution of Štěpánka Vaňáčová and Peter J. Lukavsky). In addition, he regularly delivers his courses within the frame of the course Advances in Molecular Biology and Genetics at Academy of Sciences in Prague.

Dr. Štefl is very active in training students at various levels. So far, he has supervised 8 bachelor's and 8 master's students who successfully defended their theses and has supervised 12 doctoral candidates. Till January 2020, 7 candidates successfully defended their Ph.D. theses. Richard Štefl has also overseen research projects of 3 postdoctoral fellows who joined his laboratory.

As an ERC Consolidator grantee, he has been shaping up research, educational, and PR activities at CEITEC MU.

**Conclusion:** The applicant's pedagogical capabilities ***meet*** the requirements expected of applicants participating in a professor appointment procedure in the field of Biomolecular Chemistry.

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**Evaluation of the applicant as a respected and recognized scholarly or artistic figure in a given field**

Dr. Richard Štefl is a leader in the field of RNA structural biology with an outstanding track-record of ground-breaking research. His work was published in high impact journals including Cell, Genes & Development, Molecular Cell, PNAS, EMBO Journal, EMBO Reports, and others.

He made a number of seminal contributions at the forefront of the rapidly expanding area of RNA structural biology, which links the detailed atomic structure with cellular context and, subsequently, with diseases.

**Conclusion:** The applicant ***is*** a respected and recognized scholarly figure in his field. The applicant ***has*** made a significant contribution to the development of his field. The applicant ***constitutes*** a leading figure in his field of scholarship or research.

**Conclusion**: The applicant **is** a respected and recognized scholarly figure in his/her field. The applicant **has** made a significant contribution to the development of his/her field. The applicant **constitutes** a leading figure in his/her field of scholarship or research.

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# Evaluation Board Decision on the Nomination for Appointment to Professor

**Secret vote results**

Voting took place: electronically

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| Number of board members | | 5 |
| Number of votes cast | | 5 |
| of which | in favour | 5 |
| | against | 0 |

**Board decision**

Based on the outcome of the secret vote and following an evaluation of the applicant's scholarly or artistic qualifications, pedagogical experience and role as a respected and recognized scholarly or artistic figure,the board hereby submits a proposal to the scientific board of the Faculty of Faculty of Science of Masaryk University to **appoint the applicant professor** of Biomolecular Chemistry.

In Brno on 21.02.2020

prof. RNDr. Vladimír Sklenář, DrSc.