

Evaluation board decision on the nomination for appointment to professor

Masaryk University	
Faculty	Faculty of Science
Field of study	Biomolecular Chemistry
Applicant	<i>Mary O'Connell, Ph.D., MS</i>
Unit	Head – ERA Chair - Mary O'Connell Research Group

Board members

Chair	Prof. RNDr. Vladimír Sklenář, DrSc. <i>CEITEC Masaryk University, Brno</i>
Members	Prof. RNDr. Julius Lukeš, CSc. <i>Faculty of Science, University of South Bohemia, České Budějovice</i>
	Prof. RNDr. Ivan Raška, DrSc. <i>First Faculty of Medicine, Charles University, Prague</i>
	Prof. Mag. Dr. Renée Schröder <i>Max F. Perutz Laboratories, Vienna</i>
	Prof. RNDr. Jan Tachezy, Ph.D. <i>Faculty of Science, Charles University, Prague</i>

Evaluation of the applicant's scholarly / artistic qualifications

For most of her scientific career Dr. Mary O'Connell has been interested in RNA processing, in particular the conversion of adenosine to inosine (A-to-I) by RNA editing. The enzymes that catalyze this event are called ADAR, adenosine deaminases acting on RNA. They recognize adenosines for deamination within double stranded RNA (dsRNA). This enzyme activity has been proven to be important for a functional brain and several neurological diseases has been linked to altered A-to-I RNA editing. As a postdoctoral fellow in Prof. Walter Keller's laboratory, University of Basel, she was one of the first to clone a gene encoding an RNA editing enzyme (ADAR1) (O'Connell et al., 1995). Prior to the cloning, she had purified and characterized the ADAR1 enzyme from calf thymus (O'Connell et al., 1994). These efforts led to defining the general rules that apply to the recognition of site selectively edited substrates and also to the discovery of editing activity of another protein, ADAR2 (Maas et al., 1996, O'Connell et al., 1997, Gerber et al., 1997). Further analysis revealed that this enzyme is responsible for the editing event at the critical Q/R site in a transcript encoding subunit 2 of the AMPA glutamate receptor. The level of editing at this site is approximately 100%, and is essential in mammals. These key findings were at the forefront of the initial work on A-to-I editing and initiated a new research field that is still growing.

As a principal investigator at the Medical Research Council (MRC) Human Genetics Unit Dr. O'Connell continued to study RNA editing. Her group demonstrated that ADAR proteins function as dimers (Gallo et al., 2003). This has vastly contributed to the understanding of how ADAR recognize and interacts with its substrates. In collaboration with Prof. Carmo-Fonseca, Instituto de Medicina Molecular, Portugal, she was the first to surprisingly show that both of the RNA editing enzymes localize within the nucleolus in the cell nucleus (Desterro et al., 2003). Dr. O'Connell and Prof. Carmo-Fonseca demonstrated that the editing enzymes delocalize from the nucleolus upon expression of an editing substrate, indicating that the nucleolus may function as a storage unit for the ADAR enzymes and are recruited to specific targets upon expression.

Drosophila has been proven to be an important model system for studying RNA editing. In collaboration with Robert Reenan, Brown University, Mary initiated the work on editing in *Drosophila* demonstrating that editing is developmentally regulated and that *Drosophila* ADAR is itself regulated by editing (Palladino et al., 2000a). This was further analyzed and published in an article in *The EMBO Journal* (Keegan et al., 2005). RNA editing at most sites increases during fly development and it has been hypothesized that in the fly, RNA editing facilitates development of a complex adult nervous system that differs substantially from that of the embryo. Mary's laboratory has also been involved in the cloning and characterization of the fly *Adar* deletion mutants. There is extensive editing in *Drosophila* but only one *Adar* gene. In an article published in *Cell*, Dr. O'Connell and coworkers described that flies deficient for A-to-I editing are barely viable, sterile and suffer from neurodegeneration and lack of locomotion (Palladino et al., 2000b). It has been found that RNA editing is very similar in mammals and in *Drosophila*. Human ADAR2 is the ortholog of the fly gene and can rescue a deletion of it (Keegan et al., 2011).

Dr. O'Connell contributed to the interesting link between editing and RNA interference (RNAi). One of the most surprising finding was that ADARs can have editing independent functions and can bind to dsRNA and compete with the microRNA machinery (Heale et al., 2009). Mary has also studied the regulation of the ADAR enzymes and established that they are posttranslationally modified and this can influence their cellular localization and activity (Marcucci et al., 2011).

In collaboration with Yanick Crow, Dr. O'Connell demonstrated that mutations in *ADAR1* can cause Aicardi-Goutières syndrome (Rice et al., 2012). They were the first to demonstrate that inosine in endogenous RNA is critical for self, non-self-discrimination between host and pathogen (Mannion et al., 2014). Thus, ADARs are an essential element of the innate immune response.

In her current research, Mary continues to study ADAR activity, focusing primarily on the role of ADAR1 in innate immunity.

So far, Mary O'Connell has published 45 original papers and 8 chapters in a scholarly book publications. Web of Science and ResearchID (G-4740-2015) lists altogether 58 papers with 2546 citations (h-index=26). Eight papers have been cited more than 100 times.

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

Evaluation of the applicant's pedagogical experience

Having spent most of her career working in research institutes, Mary O'Connell had somewhat limited opportunities to teach. She gave two lectures/year (from 1997-2011) to PhD students while she was a Group Leader at the MRC Human Genetics Unit in Edinburgh.

At Stockholm University, Mary was course leader of a Masters course on Molecular Genetics (2013-2014) and a Methods Course (2014). The Masters course was based on the latest version of 'Gene' edited by Lewin. In addition to lectures in this course, she was organizing the lecture schedule and exams.

Currently, Mary gives 2 lectures/year in a course on RNA that is organized by Štěpánka Vaňáčková to PhD students at CEITEC MU. One lecture is on RNA modification and the other on RNA and Disease. In addition, she has been giving lectures on RNA modification in other Universities as part of their PhD courses, namely at Czech Academy of Sciences, Prague 2015, University Bicocca, Milan 2016, FMI Basel 2016, and Institute Curie, Paris 2017.

Dr. O'Connell established a non-profit organization GE&NE Africa to encourage scientists to travel to Africa and lecture for two weeks at African Universities. She has travelled to Ethiopia and taught an intensive course on genomics to PhD students in the University of Addis Ababa in 2015.

Mary O'Connell supervised 6 PhD students at the MRC from 1998-2014 who have graduated. Currently, she has been supervising 4 PhD students, 1 Master student and one under graduate student at CEITEC MU.

As ERA Chair, she has been shaping up both research and educational 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.

Evaluation of the applicant as a respected and recognized scholarly or artistic figure

Dr. Mary O'Connell is a leader in the field of RNA biology with an outstanding track-record of ground-breaking research. Her work was published in high impact journals including *Cell*, *The EMBO Journal*, *Nature Genetics*, *Nature Methods*, *PNAS*, and others. She made a number of seminal contributions at the forefront of the rapidly expanding areas of A and I RNA editing, an essential process increasing the degree of genetic variations.

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

Secret ballot results

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

Board decision

Based on the outcome of the secret ballot 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 Science of Masaryk University to

appoint the applicant professor of Biomolecular Chemistry

In Brno on September 26, 2017

Prof. RNDr. Julius Lukeš, CSc.

Prof. RNDr. Ivan Raška, DrSc.

Prof. Mag. Dr. Renée Schröder

Prof. RNDr. Tachezy, Ph.D.

Prof. RNDr. Vladimír Sklenář, DrSc.