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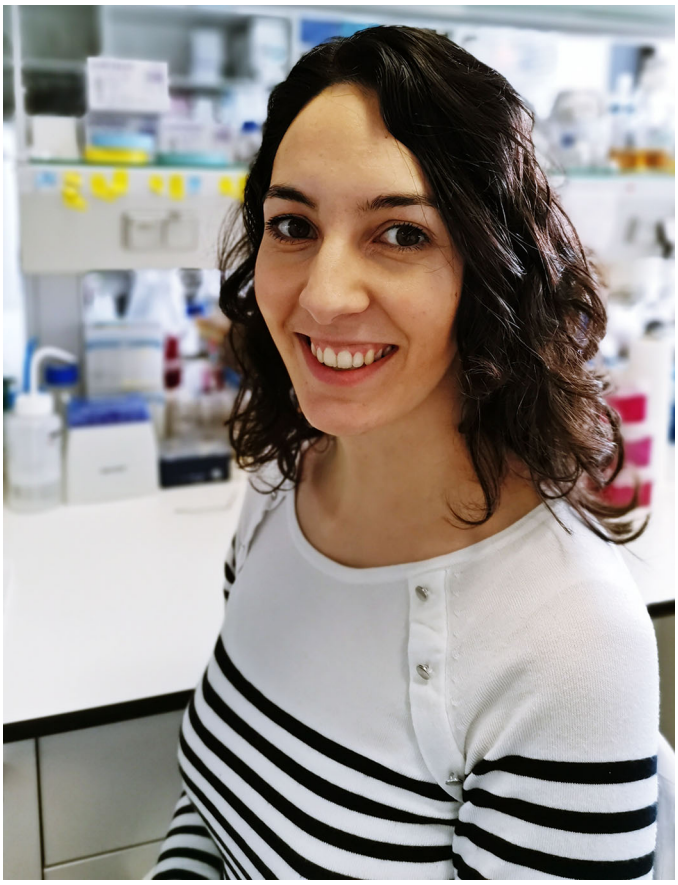
FIRST PERSON

First person – Mirjana Malnar

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Mirjana Malnar is first author on 'SFPQ regulates the accumulation of RNA foci and dipeptide repeat proteins from the expanded repeat mutation in *C9orf72*', published in JCS. Mirjana is a PhD student in the lab of Boris Rogelj at Jožef Stefan Institute, Ljubljana, Slovenia, investigating RNA biology and the involvement of non-coding RNAs in various diseases.



Mirjana Malnar

How would you explain the main findings of your paper in lay terms?

We studied the mechanisms of two devastating and incurable diseases affecting neurons – amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). ALS is a disease that affects neurons enabling movement, swallowing and breathing. FTD is a type of dementia primarily affecting behavior and speech. Both diseases share some mechanisms at the molecular level. One of these mechanisms is associated with a mutation in the *C9orf72* gene. This mutation causes formation of RNAs that form specific structures in cells and can impair the function of different cellular proteins. The mutation is also a source of toxic proteins, which have been found in neurons of ALS and FTD patients. In this research we studied the impact of SFPQ protein on the consequences of *C9orf72* mutation. We show that lower levels of SFPQ in cells lead to lower numbers of toxic RNAs and proteins from the *C9orf72* mutation, and that higher levels of SFPQ lead to higher numbers of toxic RNAs and proteins. Therefore, we have discovered an important role of SFPQ protein in this mutation, and its role in lowering the levels of toxic RNAs and proteins from the *C9orf72* mutation presents a potential therapeutic approach.

Were there any specific challenges associated with this project? If so, how did you overcome them?

The major challenges in this project were actually not with the research itself. Of course, we spent a lot of time on protocol optimization for repeatability and robustness of experimental procedures. We also had to be very careful about proper RNA foci quantification, as microscopy analysis always requires special attention. However, our main challenge first came with the closure of the lab in the middle of the research due to the COVID-19 pandemic. This caused our research to stall at its most exciting point, and it was very hard to wait for the day we could proceed with our studies. But our troubles didn't stop there. As we returned to the lab, we found that our confocal microscope stopped working, and every time we fixed a certain bug another one somehow appeared. We had to spend an additional few months in apprehension before we could finish our research and find out the long-expected outcome of our experiments. We definitely got training in patience during this study.

When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

Yes, there was a 'eureka' moment; however, we did not fully give in to it at first. We had some results on the influence of SFPQ on the numbers of sense RNA foci from our previous research, and we had already shown that SFPQ binds to the sense RNA. At the start of this research, we found that SFPQ doesn't bind to antisense RNA, so we expected we would have a lot of negative results where SFPQ would not influence the antisense RNA foci. However, we wanted to study the antisense RNA foci in any case and, after performing the first experiments in cells, we were very surprised that SFPQ expression levels impacted the antisense RNA foci numbers as well. We were very skeptical about this result, but after performing multiple experiments and confirming the initial findings, we became really excited that there must be some other underlying mechanism. At that point, we decided to check the expression of dipeptide repeat proteins (DPRs) and were even more excited when we saw the impact of SFPQ expression on the synthesis of DPRs. After these initial exciting findings, confirming our results in multiple cell lines and multiple repeats was a very gratifying work. We are very excited to research the diverse roles of SFPQ even further.

Why did you choose Journal of Cell Science for your paper?

We find Journal of Cell Science a great resource for a variety of research on cell mechanisms. We also published our previous work on this subject in JCS (Bajc Česnik et al., 2019), and thought that the current work would be a great 'sequel' to it. The work was mostly performed in various cell lines, and we thought it would fit perfectly with the scope of this journal.

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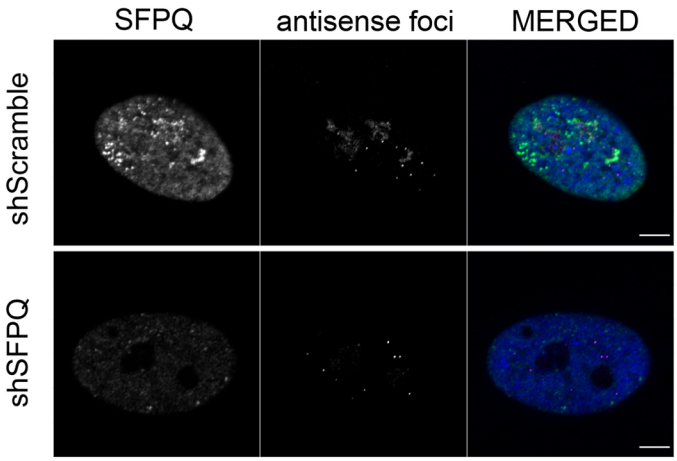

SFPQ knockdown in *C9orf72* mutation-positive patient-derived cells reduces the number of sense and antisense RNA foci and their derived dipeptide repeat protein expression. The image presents reduction of antisense RNA foci in control (shScramble) and SFPQ-knockdown (shSFPQ) *C9orf72* mutation-positive fibroblasts. Antisense RNA foci are labeled in magenta, SFPQ is labeled in green.

Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?

Besides my PhD mentor Professor Dr Boris Rogelj, who is always there to remind me about the importance of the scientific novelty and enthusiasm for research, all the members of our lab form a great support system. The past year has been especially stressful, as it is the final year of my PhD and at the same time the COVID-19 pandemic year. For all the support during this time, I am extremely thankful to Assistant Professor Dr Helena Motaln and Dr Janja Božič, as they are always ready to help in any way possible and provide their advice and motivating words when these are most needed.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

I gather most of my motivation from the enthusiasm seen in others. My first chemistry teacher was an extremely enthusiastic chemist who could make you fall in love with chemistry in one second. From my initial enthusiasm for chemistry, I became more interested in the biochemical world. I was very lucky to have great professors giving lectures during my biochemistry studies, as they always expressed their eagerness to learn and discover, which is something I am drawn to. After my great experience during my Bachelor's thesis, which was done under the supervision of Assistant Professor Dr Tadeja Režen and Professor Dr Damjana Rozman, I was sure to pursue science.

"I gather most of my motivation from the enthusiasm seen in others."

Who are your role models in science? Why?

My greatest role models are scientists who remain humble regardless of their great achievements, remain kind in spite of stressful situations, and are ready to take their time to share their knowledge and cooperate with others. I am lucky to have met multiple scientists like that and learn from them.

What's next for you?

I am currently working on another project regarding expanded repeats in ALS and FTD, and am in the process of finishing my PhD. After that, I plan to pursue a postdoc position and I am looking forward to studying new scientific questions.

Tell us something interesting about yourself that wouldn't be on your CV

My time-management skills involve pipetting with both hands.

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