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FIRST PERSON

First person – Leeanne McGurk

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. Leeanne McGurk is first author on 'TDP-43, a protein central to amyotrophic lateral sclerosis, is destabilized by tankyrase-1 and -2', published in JCS. Leeanne conducted the research described in this article while a post-doc in Dr Nancy M. Bonini's lab at University of Pennsylvania. She is now a PI at the School of Life Sciences, University of Dundee, UK, investigating the biology of the aging brain.

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

We understand very little about how our brain ages but for some individuals, the aging process occurs much faster, specific brain cells degenerate, and certain brain functions are lost. For example, in amyotrophic lateral sclerosis (ALS), motor neurons deteriorate, and the patients become completely paralyzed and die within 2–5 years of symptomatic onset. We think that a protein called TDP-43 may be central to ALS because it is mutated in a small proportion of patients, and in the majority of patients (>95%), TDP-43 is mislocalised from the nucleus to the cytoplasm of affected motor neurons. We are interested in knowing what may cause this change in TDP-43 as this may help us to understand what triggers ALS.

In this paper, we found that when we purified TDP-43 from human and monkey cells we also purified enzymes called tankyrase-1 and -2 (tankyrase-1/2). Tankyrase-1/2 binds to proteins that have a short stretch of amino acids that are collectively called a tankyrase-binding motif, and the TDP-43 protein has a region that resembles this motif. When we removed the tankyrase-binding motif from TDP-43 the protein no longer co-purified with tankyrase-1/2, suggesting that tankyrase-1/2 may regulate TDP-43. Using a number of different experimental approaches, we found that the TDP-43 protein is stabilized by tankyrase-1/2 and we think it does so by promoting the localization of TDP-43 to the cytoplasm where it is degraded more slowly. Our work highlights tankyrase-1/2 as a protein that may control disease-aspects of TDP-43 and that perhaps targeting tankyrase-1/2 may have therapeutic potential.

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

We anticipated that tankyrase would help degrade TDP-43. Once we got all of the different pieces of the experiments optimized, we found the opposite to be true. After many repetitions, we concluded that we had disproved one of our hypotheses and we then had to develop a new one. We took a different approach and we looked at the cells under the microscope. We found evidence that suggests that TDP-43 is degraded in the nucleus and that tankyrase helps to keep TDP-43 in the cytoplasm where its degradation dynamics appear to be slower.

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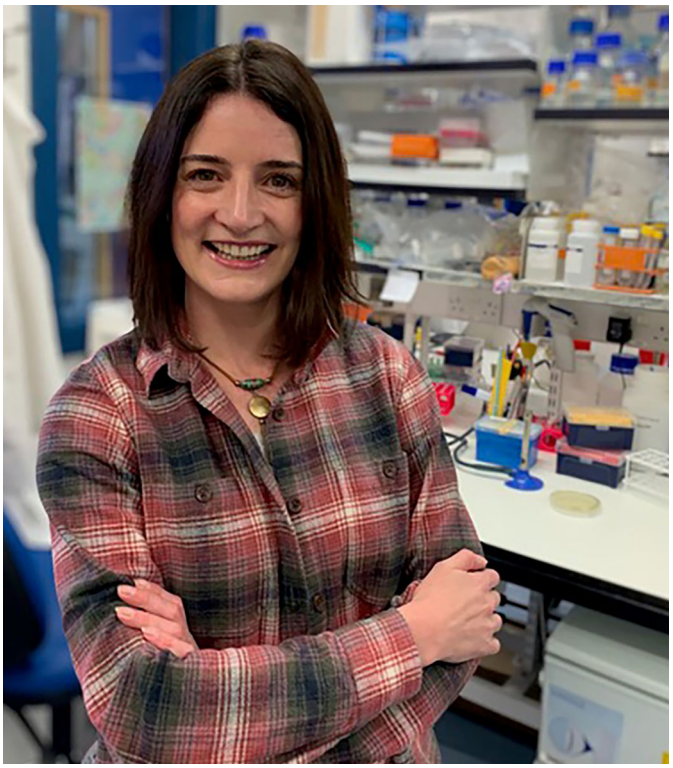

Leeanne McGurk

"…we concluded that we had disproved one of our hypotheses and we then had to develop a new one."

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

I did a lot of this work with Olivia Rifai when she was an undergraduate student. We were both embarking on types of experiments that neither of us had done before. We definitely said 'yay' the day Olivia came running to my bench to show me that deletion of the tankyrase-binding domain prevented TDP-43 from co-purifying with tankyrase.

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

The scope of the cell biology that is published by the Journal of Cell Science is broad and has included impactful research papers focused on TDP-43 and neurodegenerative disease.

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

Like a lot of other people in science, I was shy and not very confident. I have had great mentors that have helped me with this. Prof. Mary Bownes (University of Edinburgh) encouraged me to embark upon a PhD even though I thought I would never be able to do it. Prof. Mary O'Connell (now CEITEC) encouraged me to aim

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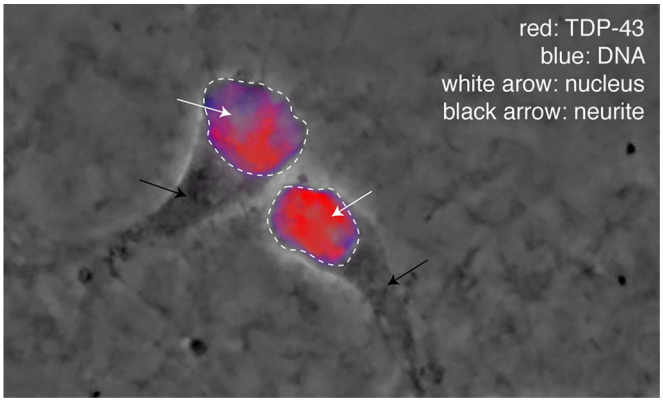

Two healthy rat cortical neurons grown in a laboratory dish.

high and do a postdoc in an area of science that I loved, and Dr Nancy Bonini, among many things, encouraged me to speak up.

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?

One part of being a scientist that you cannot get from lectures is how much fun it is to be doing the experiments and at the same time be working on real-life problems. You have the opportunity to work with and meet people from all over the world who have different backgrounds and experiences, and you learn a lot from just interacting with the people around you.

Who are your role models in science? Why?

The mentors I mentioned above are three women that have excelled as scientists, and I have learned a lot from them. Other role models include the scientists whom I cite in this publication as it is their papers that inspired a lot of the work, co-workers who have approaches and traits that I admire, and seminar speakers who motivate me to strive further.

What's next for you?

I have recently started my own lab at the School of Life Sciences at the University of Dundee. We plan to continue to look at the cellular processes that are responsible for our brain deteriorating as we age.

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

I'm a crazy cat lady!

Reference

McGurk, L., Rifai, O. M. and Bonini, N. M. (2020). TDP-43, a protein central to amyotrophic lateral sclerosis, is destabilized by tankyrase -1 and -2. *J. Cell Sci.* **133**, jcs245811. doi:10.1242/jcs.245811