How would you explain the main findings of your paper in lay terms?
Most people are familiar with ALS (Lou Gehrig’s disease) due to the ‘ice bucket challenge’ that was popular several years ago. However, it is not as widely known that ALS is currently thought to be similar to diseases such as Alzheimer’s, where protein aggregates in the brain cause neurons to die. We show in this paper that there is a complex role these protein aggregates play in neurodegeneration, and they are not simply toxic clumps. We discovered that when a neuron lacks the correct expression of a specific protein (TDP-43) in the nucleus, its DNA becomes damaged. We linked the DNA damage seen to the presence of R-loop structures, which form on DNA and are still poorly understood. We propose that TDP-43 plays a major role in maintaining genomic integrity through its splicing activity by managing R-loop accumulation. Understanding the genomic instability associated with TDP-43 loss may be key in determining the central pathology behind ALS and other TDP-43 associated diseases.

Were there any specific challenges associated with this project? If so, how did you overcome them?
The biggest challenge we overcame was optimizing the expression levels of TDP-43. Because this protein is essential and regulates its own mRNA, TDP-43 cannot be easily depleted or depleted for extended periods of time before cells begin to undergo apoptosis. We overcame this issue by depleting TDP-43 using siRNA, which required several rounds of transfection to significantly reduce protein levels. Depleting TDP-43 also became increasingly difficult in non-cycling cells. We unsuccessfully utilized several post-mitotic cell types before collaborating with another lab to effectively deplete TDP-43 in mouse neurons.

When doing the research, did you have a particular result or ‘eureka’ moment that has stuck with you?
When forming a hypothesis about which TDP-43 domains are critical for DNA damage regulation, we originally thought that the C-terminal domain (CTD) would be the most important. The CTD is known to be critical for protein–protein interactions with several other essential splicing factors, making this domain an obvious target at the beginning. However, after our data showed that truncation of the entire CTD did not perturb replication progression, the narrative of our story changed significantly. Ultimately, we discovered that TDP-43 mutations that disturb its ability to bind RNA or localize to the nucleus played critical roles in cellular R-loop regulation.

Why did you choose Journal of Cell Science for your paper?
We chose Journal of Cell Science because we wanted to publish in a journal that would reach scientists from multiple areas of study, as our research covers various disciplines and sets a basis for future studies.

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 have always enjoyed studying science. During my undergraduate studies, I focused on medical laboratory science before becoming a bench technologist for a small period of time. Fatefully, while my graduate education has focused more on basic science research, I have gravitated back to medical lab science and hope to join a laboratory medicine fellowship following my PhD.

Describe what you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?
Decades of research still has not resulted in a distinct cause, detection method or cure for ALS. Because there is so much unknown about...
disease onset and almost 90% of cases are sporadic and non-hereditary, disease tracking and research has been severely limited. I think improving disease diagnosis techniques will help address the complex nature of ALS and further its research to ultimately improve mechanistic understanding of disease progression. While there have been significant improvements in disease detection, there are still no agreed-upon techniques that would allow for more accurate non-invasive human studies or creation of precise mouse models.

**What’s next for you?**
I am entering the fifth year of my PhD. I am currently working on collaborative projects with other researchers and continuing the research story presented in this paper. After graduation, I hope to join a laboratory medicine fellowship in order to combine my basic science experience with my passion for clinical applications.

**Tell us something interesting about yourself that wouldn’t be on your CV**
In my free time I enjoy home-brewing, watching college basketball and playing the tuba.

**Reference**