How would you explain the main findings of your paper in lay terms?
The causative agent of gastroenteritis, Salmonella Typhimurium (STm), targets several important molecular pathways of the host to ensure a successful infection. One of these pathways is SUMOylation, a post-translational modification (PTM) mechanism. Certain cellular proteins have PTMs that result in modified function/fate. In this way, SUMOylation of proteins also modulates the functions of crucial regulatory proteins and thereby alters several fundamental processes of a cell. Our previous work showed that STm ‘tinkers’ with two critical enzymes of SUMOylation pathway, Ubc9 and PIAS1, during infection. This interference by STm is known to be required for the alteration of the global SUMOylation of the host. These changes in turn are necessary and sufficient to reprogram the inflammatory signaling of the host. However, the details of how STm exerts these rapid changes was not fully understood. In current work, for the first time, we reveal the regulation of SUMO machinery enzymes Ubc9 and PIAS1 in the context of STm infection. Using the power of bioinformatics and molecular biology tools, we show that a master regulator of the cell known as activator protein-1 (or AP-1) directly binds to the host DNA encoding PIAS1. The most interesting aspect of the study was the reciprocal regulation of AP-1 activity by SUMOylation. This regulation of AP-1 confers a selective and differential regulation of its targets, highlighting the complexity of molecular circuits and how pathogens manipulate them.

Were there any specific challenges associated with this project? If so, how did you overcome them?
In our quest to identify the mechanism of regulation of SUMOylation pathway genes (Ubc9 and PIAS1) during Salmonella infection, we realized there was a role for a master regulator: AP-1. Transcription factors such as AP-1 display an extremely complex mode of regulation in different cellular contexts. For example, during a Salmonella infection, AP-1 activates only a selective subset of the thousands of its bona fide targets. In the current study, using computational tools and sophisticated molecular biology assays, we identified a PTM-dependent target-gene selective regulation by AP-1 during Salmonella infection. This was an extremely challenging aspect to study since it required replacing the endogenous AP-1 from the cell with a SUMOylation-deficient mutant. For this, a genetically engineered stable murine embryonic fibroblast cell line that expressed these variants (particularly c-Fos) was used. Microscopy and cell fractionation experiments of SUMOylated and non-SUMOylated AP-1 revealed that PTMs, particularly SUMOylation and phosphorylation, control their localization in the cell during infection. Furthermore, specific experimental assessment of the binding of SUMOylated versus non-SUMOylated forms of AP-1 to the promoter of various targets was achieved using chromatin immunoprecipitation and electrophoretic gel mobility shift assays performed with customized antibodies that recognize only one or the other forms of AP-1.

When doing the research, did you have a particular result or ‘eureka’ moment that has stuck with you?
This study contributes two key aspects to the field. Firstly, the regulation of SUMOylation pathway genes Ubc9 and PIAS1 by AP-1, and secondly, the bidirectionality between AP-1 and genes involved in SUMOylation. The exciting moment that our team remembers is identifying the direct binding of c-Fos, a subunit of AP-1, to promoters of both Ubc9 and PIAS1. STm infection of murine fibroblasts genetically engineered to express SUMOylation-deficient c-Fos resulted in a massive transcriptional upregulation of immune pathway genes. This meant that these transcription factors can be tuned to preferentially activate immune genes via their PTM modifications.
Why did you choose Journal of Cell Science for your paper?
Journal of Cell Science is a highly respected cell biology journal, which has a very rigorous, fast and smooth review process. The current work covers a very important area of host cell and pathogen interplay, an area that is within the scope of JCS. We have also contributed to JCS previously, and we have seen that our work has received a wide readership and citations. The advance posting policy of JCS wherein the journal publishes accepted articles on its ‘Accepted manuscripts’ page is also attractive. These features attracted us to submit this work to JCS.

Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?
Yes, being a PhD student, I am pursuing my research journey under the mentorship of Dr C. V. Srikanth. He always teaches, supports, motivates and gives me the freedom to think and plan my research, which is very much required for the overall development of a PhD candidate. From him, I have learnt to analyze, interpret and construct a logical scientific outcome, even from results that might appear ‘negative’ at first glance. He also nurtured and mentored me to evolve as an independent researcher.

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?
After my undergraduate course, I always wanted to contribute my knowledge in the field of human diseases for the improvement and betterment of society. Gastroenteritis is a communicable disease with a high mortality rate, which is a serious health burden worldwide. At the end of this journey, I have been able to contribute an important concept to the field of host–pathogen interaction, which is extremely satisfying. Furthermore, the techniques and training that I have acquired during this work now allow me to dare to enter newer and more challenging areas, such as gene therapy and human diseases, which is my dream.

Who are your role models in science? Why?
Instead of giving one name I would like to say that I have always been motivated by the great mentors and teachers around me. I was very fortunate, always blessed with great mentors who teach, guide, support and help me in direct or indirect ways. I try to learn from the experiences and incidents. I believe some quotes about how having a never give up attitude, being always willing to learn, and that consistency and determination are the key to success. This kept me motivated and helped me to accomplish my goals during tough times.

What’s next for you?
I would like to do research in the future. I would like to pursue a career in the field of gene therapy or vaccine development, which is a promising, potential therapeutic emerging area necessary for the advancement of research.

Tell us something interesting about yourself that wouldn’t be on your CV
Of course, outside the world of research, I love to play badminton, which keeps me healthy both physically and mentally. I also love music, singing and travelling to new places. I also like to spend time with my family, colleagues and friends.

Reference