

FIRST PERSON

First person – Sarah O’Keefe

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. Sarah O’Keefe is first author on ‘Ipomoeassin-F inhibits the *in vitro* biogenesis of the SARS-CoV-2 spike protein and its host cell membrane receptor’, published in JCS. Sarah is a postdoc in the lab of Stephen High at the School of Biological Sciences, University of Manchester, UK, where she is developing small molecule inhibitors for the benefit of human health.

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

Viral pandemics like those caused by Ebola, Zika and SARS-CoV-2 are a major threat to human health. However, we currently lack ‘broad-spectrum’ drugs effective against different viruses, including those yet to emerge. Viruses use host cellular machineries that are crucial for their replication and propagation. Hence, drugs that target these machineries have potential as new, broad-spectrum, antiviral therapeutics. We have shown that the compound ipomoeassin-F selectively reduces the production of several proteins important for SARS-CoV-2 viral infection, including the viral spike protein and its cellular receptor. Our work highlights the possibility of developing ipomoeassin-F as a broad-spectrum, antiviral agent that may contribute to preparations for future pandemics.

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

The biggest challenges of this project were not related to the technicalities of the experiments, but rather were a consequence of reduced access to the laboratory; firstly, due to the closure of the university campus as a measure to control the SARS-CoV-2 pandemic and, secondly, due to the death of a close family member. In the first instance, we arranged collaborative access to plasmids encoding the relevant SARS-CoV-2 proteins and meticulously planned our experiments, cloning strategies and how to implement new lab safety procedures whilst waiting for the re-opening of the lab. In the second instance, the support and understanding from my colleagues and supervisor Stephen High were invaluable and, looking back now, I am delighted with the study that we carried out during this difficult period.

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

Based on our previous characterisation of the powerful inhibitor of the Sec61 membrane translocation complex, ipomoeassin-F (Zong et al. 2019), and the topology of the SARS-CoV-2 spike protein, we speculated that its ER membrane insertion would be strongly inhibited by ipomoeassin-F. However, whilst our predictions regarding the sensitivity of other SARS-CoV-2 proteins were rapidly proved correct by our experiments, I initially struggled to synthesise the extremely long and complex viral spike protein using our typical cell-free system. When I found the conditions to successfully produce the full-



Sarah O’Keefe

length spike protein, which then enabled our original prediction to be tested and confirmed, that was my ‘eureka’ moment.

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

We wanted to publish our findings quickly and reach a wide readership in order to raise awareness and prompt further studies of Sec61 inhibitors as potential broad-spectrum antivirals. The opportunity to publish our study as a ‘Short Report’ in Journal of Cell Science fitted these aspirations extremely well.

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?

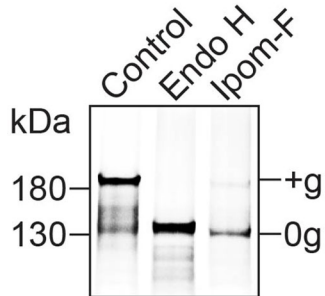
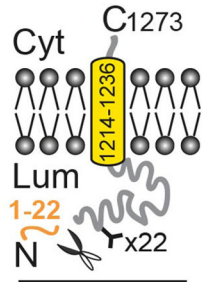
I first became inspired to pursue a career in small molecule drug discovery during my training in Medicinal Chemistry, primarily through my enjoyment of the research projects I did during my master’s degree. Following a year working as a synthetic organic chemist, I originally began my PhD hoping to ‘gain some biological skills’ to further my career as a chemist. Little did I know that I’d wake up one day as a fully-fledged cell biology postdoc who only occasionally dabbles in some chemical synthesis!

What’s next for you?

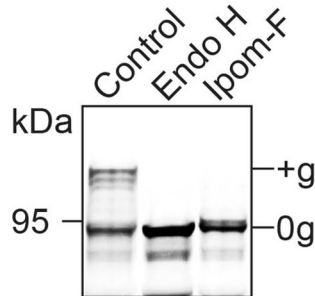
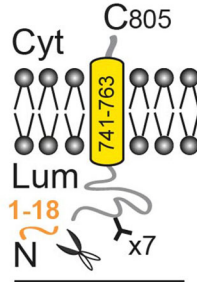
After my current postdoc, I hope to find another postdoctoral research opportunity that will allow me to keep learning new techniques and provide answers to currently unresolved questions.

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SARS-CoV-2 spike protein



Human ACE2



Ipomoeassin-F inhibits the biogenesis of the SARS-CoV-2 spike protein and its host cell receptor, human ACE2, in canine pancreatic microsomes.

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

I absolutely adore penguins!

References

- O'Keefe, S., Roboti, P., Duah, K. B., Zong, G., Schneider, H., Shi, W. Q. and High, S. (2021). Ipomoeassin-F inhibits the *in vitro* biogenesis of the SARS-CoV-2 spike protein and its host cell membrane receptor. *J. Cell Sci.* **134**, jcs257758. doi:10.1242/jcs.257758
- Zong, G., Hu, Z., O'Keefe, S., Tranter, D., Iannotti, M. J., Baron, L., Hall, B., Corfield, K., Paatero, A., Henderson, M. et al. (2019). Ipomoeassin F binds Sec61 α to inhibit protein translocation. *J. Am. Chem. Soc.* **141**, 8450-8461. doi:10.1021/jacs.8b13506