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First person – Asmahan Abu-Arish

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. Asmahan Abu-Arish is first author on 'Lipid-driven CFTR clustering is impaired in cystic fibrosis and restored by corrector drugs', published in JCS. Asmahan conducted the research described in this article while a Research Associate in John W. Hanrahan's lab at McGill University, Montreal, Canada. She is now an Assistant Professor at University of Saskatchewan, Saskatoon, Canada, where she is interested in uncovering the molecular players behind disease development in real time, namely in hyperinflammatory pulmonary diseases, such as cystic fibrosis and COPD.

Asmahan Abu-Arish

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

Cystic fibrosis (CF) is a genetic disease that affects many organs and leads to dehydration of the lungs and thick, sticky mucus in the airways. Mucus builds up, blocking the airways and increasing susceptibility to bacterial infections. CF is caused by mutations in the gene that codes for the CFTR, an ion channel that conducts chloride and bicarbonate ions through the apical cell membrane during secretion. The most prevalent mutation in the CFTR gene (F508del) causes retention of this protein inside the cell and so prevents normal ion and fluid secretion. Although the types of lipids in cell membranes differ in people with CF, little is known about their contribution to CFTR stability and regulation at the cell surface. We found that lipids determine the distribution of CFTR on the cell surface, with surprisingly little dependence on proteins that have been shown previously to interact with CFTR, such as NHERF1 and filamin A. Also, the recently approved triple combination drug Trikafta partially corrects trafficking of the mutants F508del-CFTR and S13F-CFTR to the cell surface, and restores their normal distribution, lateral mobility and ion channel function.

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

Working with live cells that are freshly isolated from the airways is challenging as they are highly sensitive to experimental conditions. This challenge was met through careful optimization, which required persistence and constantly checking the relevant literature. Reconciling the present results with earlier results from several groups including ours, which suggested CFTR localization might be determined by the scaffold proteins NHERF1 and filamin A, was also challenging. Our data revealed that lipids (and not the interacting proteome) mediate clustering and determine cell surface distribution and stability. Various mutations that eliminate CFTR interactions with other proteins were tested along with knockdown experiments and imaging-based assays of CFTR internalization. Taken together, these converging approaches showed the important role of lipids in determining CFTR localization and stability at the plasma membrane.

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

I had several such moments, and they are what makes research so rewarding. Based on the literature, I expected that elimination of the four amino acids (DTLR) at the C-terminus of CFTR that bind to NHERF1 would dramatically alter CFTR cell surface distribution, but to my great surprise it had no effect. Another moment came while investigating components of the newly developed CF therapy Trikafta and its effect on F508del CFTR localization and function. Unlike another corrector (VX-809) that I had studied previously, Trikafta greatly increased F508del CFTR translocation to the cell surface and restored its ability to form clusters and platforms, along with its ion channel function. It was exciting to visualize a therapeutic working in real time at the molecular level and appreciate what it means for patients not only with F508del CFTR, but also the S13F mutant, which was not expected based on previous studies.

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

The Journal of Cell Science is impactful, focuses on a wide range of cell biology topics, is committed to accepting excellent scientific research and has a diverse audience.

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

When I'd just joined the lab of Dr Hanrahan as a postdoctoral fellow, I had a lot of support from all lab members, which I

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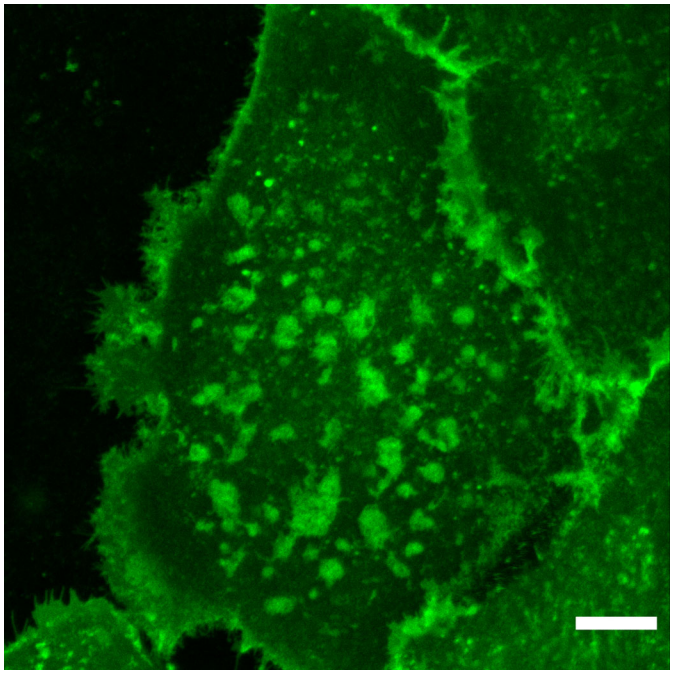

The distribution of C12-Sphingomyelin lipid inside large platforms after its hydrolysis into C12-Ceramide at the plasma membrane of human bronchial epithelial cells isolated from donor lungs. Scale bar: 8 µm.

appreciate. I would like to mention the support of Dr Jie Liao, a research associate in the lab. Her calm and kind demeanour helped me a lot. Dr Elvis Pandzic helped me with the programming aspect of my projects. Of course, the most impactful mentor was Dr Hanrahan. He provided me with both the scientific guidance and the freedom to pursue the scientific path of my choosing. Through his guidance, I learned how to answer important biological questions both profoundly and meaningfully.

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 was only introduced to science during my master's degree in the lab of Dr Michael Elbaum at the Weizmann Institute of Science. I fell in love with scientific research after my first experiment, because I felt that I am doing something nobody has done before. Being the first to answer a question is powerful. This feeling was surprisingly profound and continues with me until today. The most interesting moment in my scientific path was discovering my love for biology. I am a physicist who didn't enjoy biology before my master's degree. A course delivered by Dr Deborah Fass (Protein Structure and Function) led to a fascination with biology and directed me towards the biophysics field.

Who are your role models in science? Why?

I fortunately had several role models, and I learned different things from each one of them. The first is my master's supervisor, Dr Michael Elbaum. His patience, care and guidance helped place my feet on the path of science; he made it all possible. My PhD supervisor, Dr Cecile Fradin, was another role model. In her lab, I learned to be understanding, patient, independent and to take my responsibilities seriously. In the lab of Dr John Hanrahan, I learned how to approach real biological questions meaningfully. Dr Hanrahan generously provided me with all the needed financial and scientific support to freely define my scientific path, to pursue interesting biological problems and to grow as an independent scientist. Together, I learned how to be a scientist and how to deal with my trainees depending on where they are along their scientific path.

What's next for you?

I have just been appointed as an assistant professor at the University of Saskatchewan Collage of Medicine. Currently, my lab is interested in investigating inflammation regulation in hyperinflammatory pulmonary diseases. We use a combination of high-quality fluorescence confocal imaging of live cells and quantitative molecular biophysics techniques to fully understand the molecular determinants of inflammation regulation in real time and in relevant cell models.

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

I enjoy swimming very much; I feel as if I am flying 'in water'.

Reference

Abu-Arish, A., Pandžić, E., Luo, Y., Sato, Y., Turner, M. J., Wiseman, P. W. and Hanrahan, J. W. (2022). Lipid-driven CFTR clustering is impaired in cystic fibrosis and restored by corrector drugs. *J. Cell Sci.* **135**, jcs259002. doi:10.1242/jcs.259002