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First person – Jan Steinkühler

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. Jan Steinkühler is the first author on "Membrane fluctuations and acidosis regulate cooperative binding of 'marker of self' protein CD47 with the macrophage checkpoint receptor SIRPα", published in Journal of Cell Science. Jan conducted the work in this article while a PhD student in the lab of Rumiana Dimova at the Max Planck Institute of Colloids and Interfaces, Potsdam, Germany, on a collaborative visit to Dennis Discher's lab at the University of Pennsylvania, USA. He is now a postdoc in Rumiana Dimova's lab, investigating biointerfaces through the use of biomembrane models.

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

In multicellular organisms like humans, cells constantly communicate with each other in order to perform functions vital to the survival of the organism. Protein interactions are universal players in signal transmission between cells. We studied the interaction between the proteins CD47 and SIPRA, which help the killer cells of the immune system to differentiate between 'self' and foreign, potentially malignant, cells. To be able to perform detailed studies on these proteins, we reconstituted CD47 into membrane models by directly breaking apart sheets of the cell membrane. These sheets then close up into spheres (blebs) and retain functional CD47 protein on their surface. This approach leads to a reduction in complexity, which can be nicely seen in the figure overleaf. Interaction between the spherical blebs and surfaces coated with the SIPRA protein again imposes constraints on the shape, and the blebs adopt a spherical cap-like shape. Such simple morphologies allow for detailed measurements. In this way, we were able to connect simulations and theoretical predictions to the actual results obtained in our experiments, and found good agreement between measured and calculated efficiency of CD47–SIPRA complex formation. It is known that CD47–SIPRA interactions have broad implications for the response of the immune system to cancers, which often exhibit an acidic environment. Our study here indicates that, under acidic conditions, CD47–SIPRA interactions are weakened. Indeed, in cell assays performed under acidic conditions, we saw an increase in activity of the killer cells of the immune system.

"[…] working in [another] lab was a great opportunity to understand the work of my PhD in a different context."

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

Most of the experimental work was done within a half-year-long visit to Dennis Discher's lab at the University of Pennsylvania.

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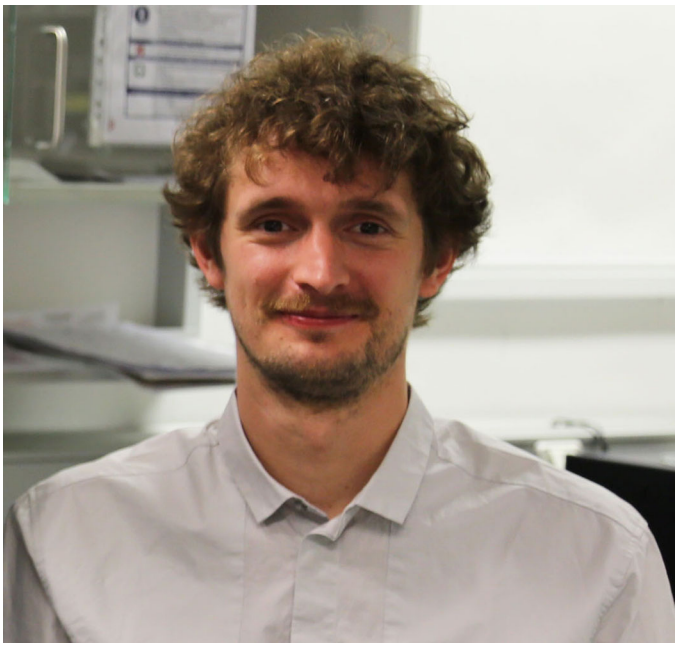

Jan Steinkühler

The short duration of the stay was indeed a challenge. At the same time, working in a cell biology-driven environment, compared to the more physics-oriented lab at home, was a great opportunity to understand the work of my PhD in a different context. Both abroad and at home, the trick that helped to overcome time constraints was working long hours.

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

I was aware of the theoretical work on membrane–membrane adhesion led by Reinhard Lipowsky from my home institution, and it was indeed an exciting moment when I understood that the system we were studying at the University of Pennsylvania might provide the missing link between the theory and experiments. It is fascinating that even if the isolated membranes are compositionally very complex, we can describe them accurately using only a few parameters that can be measured directly. It was also nice to see how well the simulations and calculations performed by the co-authors of the paper matched the experimental results.

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

The topic of this special issue, 'reconstituting cell biology', fits very well with our work. We have used plasma membrane vesicles expressing functional CD47 protein. Plasma membrane vesicles are somewhat undefined in terms of exact composition but should capture more of the complexity that arises from lipid–lipid and lipid–protein interactions. In addition, the approach used is potentially less time-consuming than the usual recombinant protein expression and reconstitution into synthetic membranes. I believe that the methods and results of this work should be interesting to the audience of Journal of Cell Science, in particular for studies of protein complex formation.

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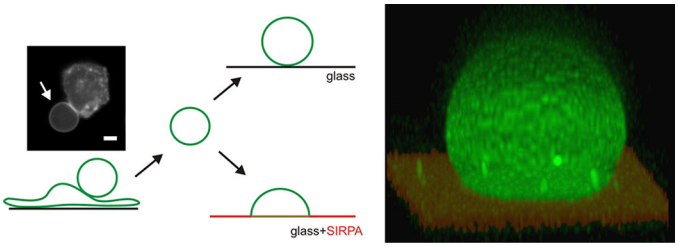

Spherical plasma membrane sheets are lysed from cells expressing CD47–GFP (shown in grey on the left) and spontaneously detach. This allows for studies where no interactions between proteins are present (top), or vesicles adhere to a SIRPA-modified substrate (red) and maximize the adhesion area for CD47–SIRPA complexes (bottom). Right: three-dimensional reconstruction of a vesicle adhering to a SIRPA-coated surface.

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?

The moment of a true discovery, the look through the microscope at something that no-one else has seen before, has fascinated me ever since my undergrad studies and has kept me in science up to now. While working in science, I have come to understand that not only can this first moment of a discovery be pleasing, but also how understanding of a system is built up and slowly leads to a more complete picture. More broadly speaking, I'm very happy that our society allows for the funding of research into basic aspects of science, the benefits of which appear only later.

"The moment of a true discovery, the look through the microscope at something that no-one else has seen before, has fascinated me ever since my undergrad studies."

What's next for you?

Originating from this work, we have discovered some additional interesting aspects of this system, which I'm currently working on to get published. For the rest of 2018, I will be studying the effect of protein absorption on membrane morphology using synthetic lipid bilayers and light-sensitive proteins. I plan to change labs in 2019 for a second postdoc.

Reference

Steinkühler, J., Różycki, B., Alvey, C., Lipowsky, R., Weikl, T. R., Dimova, R. and Discher, D. E. (2019). Membrane fluctuations and acidosis regulate cooperative binding of 'marker of self' protein CD47 with the macrophage checkpoint receptor SIRPα. *J. Cell Sci.* **132**, jcs216770.