

FIRST PERSON

First person – Alexander Whitehead

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping researchers promote themselves alongside their papers. Alexander Whitehead is first author on 'AP-1 signaling modulates cardiac fibroblast stress responses', published in JCS. Alexander conducted the research described in this article while an NSF GRFP Graduate Fellow in Adam Engler's lab at Sanford Consortium for Regenerative Medicine, La Jolla, USA. He is now a Hartwell Postdoctoral Fellow in the lab of Bruce Klein at Microbial Sciences Building, Madison, USA. His research interests include regenerative medicine, stem cell modeling, immunity and fibrosis.

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

When you have a heart attack, cells called cardiac fibroblasts create a scar to quickly patch up the damage. Unfortunately, this scar impedes the ability of the heart to pump, conduct electrical signals and coordinate cellular responses. In this study, we found that several of the damage signals that are induced after a heart attack converge to activate a protein complex called AP-1 that is responsible for scar formation. We also found that certain common genetic mutations at a site in the genome called 9p21 alter the function of the AP-1 protein complex, ultimately impacting proteins that help cells communicate.

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

Fibroblasts are most relaxed in an environment that recapitulates the tissue they live in within the body. For practical reasons, we usually grow fibroblasts in plastic dishes, which means that at any given time they are a little bit stressed. It took a lot of optimization to find conditions that made the cells happy enough to dissect some of these stress pathways.

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

Because our previous work with cardiomyocytes implicated JNK/p38 in 9p21-mediated stress responses, I was very encouraged to find a strong difference in AP-1 activation in cardiac fibroblasts, as AP-1 is frequently phosphorylated by JNK. Because the composition and expression of AP-1 as well as its location of genomic binding varies greatly between cell types, it made sense that this pathway could yield different dysfunctional phenotypes across different types of cardiac cells through a conserved mechanism. Furthermore, as AP-1 is a stress-inducible protein, this might explain why some patients with common variants in 9p21 do not experience heart problems until later in life, as opposed to these variants being embryonically lethal.

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

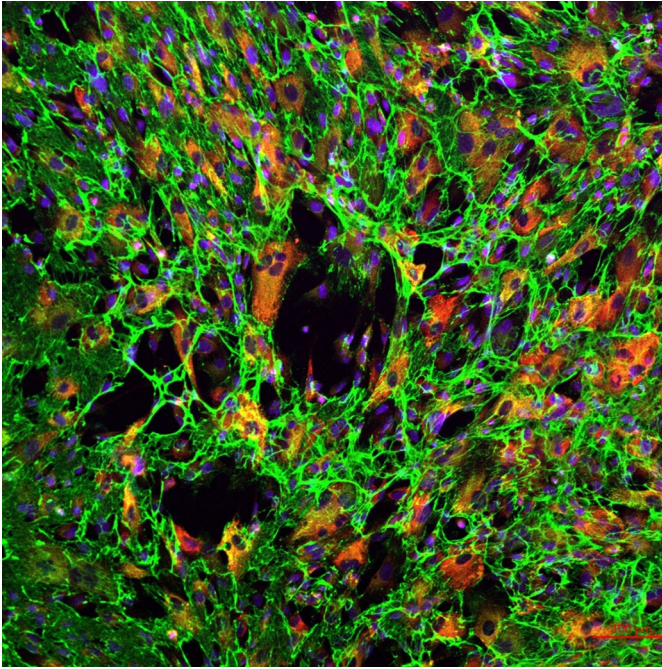
Journal of Cell Science was a good fit for our work because of their emphasis on foundational cell biology and answering mechanistic questions.

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

I would like to thank Adam Engler for guiding this work and establishing strong collaborations (especially with Bing Ren and Jake Hocker) to push the mechanistic understanding further. Tatiana Kisseleva's experience with primary stellate cells was critical in establishing our *in vitro* culture system and troubleshooting our assays.

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?

Initially, I was very interested in engineering tissues for therapeutic applications to improve quality of life for patient. When I learned



Cardiac fibroblasts with mutations at the 9p21 genomic site respond to inflammatory stimuli, upregulating smooth muscle actin (red) and assembling fibrillar fibronectin (green). DAPI nuclear stain is shown in blue.

about regenerative medicine, my interest shifted – what if we could induce the body to heal itself rather than design artificial replacements in the lab? This led to my interest into regenerative models, such as the neonatal mouse heart, that helped to identify the AP-1 pathway. During this time, my understanding of immunology also developed. Immune cells are not only involved in defense against pathogens, but also in sterile inflammation and tissue regeneration. This sparked my interest in immunology and regulation of stress and repair pathways that led to my current postdoctoral project in fungal immunology and vaccine design.

What's next for you?

I'm currently doing a postdoc with Bruce Klein at the University of Wisconsin, Madison working on designing fungal vaccines. Through this opportunity, I'm expanding my understanding of immunology, gaining experience working with *in vivo* systems, and continuing to improve my computational biology skills by identifying determinants of vaccine efficacy.

Reference

Whitehead, A. J., Atcha, H., Hocker, J. D., Ren, B. and Engler, A. J. (2023). AP-1 signaling modulates cardiac fibroblast stress responses. *J. Cell Sci.* **136**, jcs261152. doi:10.1242/jcs.261152