JCB Journal of Cell Biology

PEOPLE & IDEAS

Dorothy Schafer: Sculpting the next generation of microglia researchers

Lucia Morgado-Palacin

Dorothy Schafer investigates the role of microglia in neural circuit development and plasticity with a special focus on neurological disorders.

Every student has a favorite teacher. For Dorothy (Dori) Schafer, these were her biology teachers in middle and high schools, who imprinted on her a passion for the life sciences. Dori was one of the few students of Clarksville, a small town in southern Indiana, that went to a 4-yr college right after finishing high school. She attended Mount Holyoke College—a liberal arts, gender-diverse women's college that was originally created to provide women with educational opportunities equal to those available at the traditionally all-male Ivy League colleges. Dori would later pursue a career in science. However, not being more exposed to scientific career paths—as the daughter of an elementary teacher and a sales representative—brought out insecurities, when among peers or mentors, that she had to learn to overcome.

During her undergraduate years at Mount Holyoke College, Dori fell for the neuroscience field while doing research under the guidance of Dr. Will Millard. For her PhD, she studied the contribution of neuro–glia interactions to axon organization in the lab of Dr. Matthew Rasband at the University of Connecticut Health Center. Captivated by glial cells, Dori committed herself to investigating how microglia, the resident immune cells of the brain, contribute to neural circuit development and plasticity. As a postdoc in the lab of Dr. Beth Stevens, at the Boston Children's Hospital, and the Harvard Medical School, she discovered that microglia engulf presynaptic axon terminals of less active retinal ganglion cells to help mature the connections in the developing visual system (Schafer et al., 2012). In 2015, she started her own lab at the University of Massachusetts Chan Medical School, where she continues to unravel the role of microglia in synaptic connectivity and brain development. We talked with Dori about her current and future projects and her vision of running a lab.

What interested you about microglia in neural circuit development and plasticity?

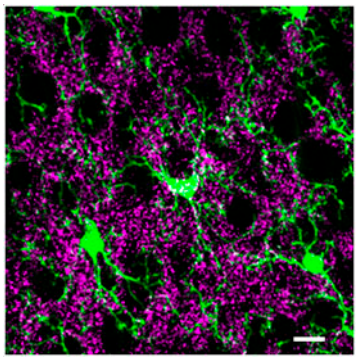
As a graduate student, I was working in the glial field but then became equally fascinated by neural–immune interactions. I found microglia to be right at the intersection of these two passions. I tend to gravitate towards projects that bring two fields together, which can often lead to discoveries that were previously overlooked. In this case, neuroscience and immunology intersect beautifully. The question of how immune cells and immune molecules are co-opted by the nervous system to regulate normal function is absolutely fascinating and also highly relevant to disease.

What are you currently working on and what is up next for you?

We have two major themes in my lab. On one end, we are interested in how neural activity instructs microglia to remodel synapses. We discovered that neurons with reduced activity—arising, for instance, from a peripheral sensory lesion—instruct microglia to eliminate synapses through fractalkine ligand-receptor signaling (Gunner et al., 2019). A postdoc and a graduate student are currently working on a project to identify how microglia and astrocytes work together to remodel synapses in response to changes in neural circuit activity in this paradigm. The other part of the lab is, in contrast, focused on disease with a particular emphasis on understanding how microglia and synapses are impacted during neurodegeneration related to multiple sclerosis (MS). We have shown that targeting the alternative complement cascade in an inflammatory demyelinating context, such as that of MS, prevents microglia from removing synapses of retinal cells and lessens the loss of visual acuity (Werneburg et al., 2020). Some of our new projects in this area include determining how chronic engulfment of cellular material may drive inflammation, identifying how senescence impacts microglia function, and determining whether certain

Dorothy Schafer. Photo by Dorothy Schafer.

lmorgado@rockefeller.edu.



Microglia (green) and synaptic compartments, labeled by the Homer protein (pink), in the mouse developing cortex. Image courtesy of the Schafer lab.

neurons and their synapses are more vulnerable to microglia-mediated synapse removal and why.

What kind of approach do you bring to your work?

I am very curious by nature. As a result, I select people in my lab that are curious and highly self-motivated. Then, I encourage them to use their creativity to design the most exciting set of experiments. Related to the first point, I don't want people to be limited by methods—if we don't have the experimental tools at hand, we seek out opportunities to learn the most powerful strategies for answering our questions. I also am a strong believer in the power of collaboration. It seems counterproductive to operate in a silo—it's not as fun and it causes anxiety and isolation. I will always reach out to collaborate and to connect my people. Finally, I am a mentor. This is a strong passion of mine and I believe the people in my lab are my legacy. Strong mentorship breeds happiness, productivity, and success for everyone.

You feel strongly about the need of solid mentorship for success in science...

Yes, I do. I was extremely fortunate to have two gifted mentors: Dr. Matthew Rasband, my PhD mentor, and Dr. Beth Stevens, my postdoc mentor. They offered support in different ways but both approaches were kind and hugely beneficial to my career. The single most important thing that I learned from Matt and Beth was to be supportive to the people in your lab—this laid the foundation for how I treat my team.

Good mentorship has also been instrumental for me to learn to navigate the ups and downs of being a PI. My chair and vice chair of my department, Drs. Vivian Budnik and Mark Freeman, were extremely giving of their time and mentored me early on when I started my lab. They continue to be mentors and I'm grateful.

In your experience as both a mentee and a mentor, what is the best mentoring approach?

Hmm... that should be plural. There is no one-size-fits-all approach; each person is different and requires a different mentoring style. This takes a lot of time, emotional energy, and introspective thought—I didn't fully appreciate this until I started my own lab. Mentoring people that work in a completely different manner than I do, along with providing feedback that might be difficult to hear, has been extremely challenging. I really want people to succeed, so when my mentees are under-performing and struggling, it is very difficult for me and I tend to internalize it, which is emotionally exhausting.

So, how does one minimize the emotional drain of mentoring?

My approach is to bring people into my lab that I have a good confidence will succeed under my mentorship. The best advice I was given was to be selective with the people that join my lab. Looking back, not everyone who started with me was a great fit for me, and I wasn't a great fit for them. It's fine to admit that and help trainees find the better mentee–mentor relationship.

You mentioned before that you don't want the people in your lab to be limited by methods. What technical challenges have you found in your field of research and how have you overcome them?

Well, until about two weeks ago in a recent publication, microglia were not amenable to transduction by adeno-associated virus vectors or similar vectors in vivo. Therefore, any in vivo experiment has required making or obtaining new genetically engineered mouse models—hopefully, this is now going to change with this recent publication. Moreover, microglia are quite particular in culture, and new methods have emerged to culture these cells, particularly for human-derived iPSCs. However, these still aren't perfect and getting more in vivo–like cells to study biology in culture remains a huge need. How to overcome these challenges? There is only one way forward, I think: seek out collaborations and opportunities to learn new strategies.

I can see how the dependence of your field on in vivo tools is quite a challenge. Generating new mouse lines isn't a trivial task, obviously. I guess that, when doing revisions for a study, you may have to think wisely regarding which definitive experiments would satisfactorily respond the reviewers in the most cost- and time-effective way for your lab, and this can potentially be applied to any field. Is there anything you would implement in the reviewing process to ease this task?

Implementing more open conversations between reviewers of papers and authors. I don't think that this would ever happen but, in a perfect world, it would be wonderful if the two sides could talk openly about the specific findings and define ways to revise a manuscript satisfactorily. This would require that everyone approaches this effort with the best intentions, but it would create a more collegial scientific atmosphere, faster and more efficient scientific progress, and a fairer review process. This is probably totally unrealistic though. I also see how it would be more difficult for junior PIs... but I think it would be worth trying.

We like to always ask for the biggest accomplishments inside and outside the lab so far. What have been yours?

Easy to answer both questions [smiles]. Inside the lab, my biggest accomplishments so far are having three students earn their PhDs and one postdoc that just recently got his own academic position! And outside the lab, raising two amazing kids—something I'm doing together with my husband, who, by the way, could also qualify as a scientific mentor of mine, hehe. We met in our PhD lab and he has always pushed and challenged me. Having many late-night scientific discussions and

Celebration at the Schafer lab; first postdoc, Sebastian Werneburg, to get his own lab. Photo by the Schafer lab.

disagreements with him has taught me a lot about compromise and seeing someone else's point of view. It has taught me to be a better scientist and mentor.

Many useful insights that you have shared with us, thanks so much! Would you try and give us some tips for a successful research career?

Above all, you must love it. I truly love my career. It's a lot of time and often we are sacrificing other things in our lives to achieve success. You have to feel fulfilled by this career path. Also, be creative and don't be afraid to ask the big questions. If it requires a unique technique that you don't have, seek collaboration. You may be amazed at the giving and helpful nature of your colleagues. The worst they can say is "no." Beyond that, seek good mentorship and be a good mentor. The single most important decision you will make is your mentors. They will truly steer your career path. In turn, be a kind and generous mentor. You will find this comes back 100-fold in personal fulfillment and growth of your lab and career.

References

Gunner, G., et al. 2019. *Nat. Neurosci.* https://doi.org/10.1038/s41593-019-0419-y

Schafer, D.P., et al. 2012. *Neuron.* https://doi.org/10.1016/j.neuron.2012.03.026

Werneburg, S., et al. 2020. *Immunity.* https://doi.org/10.1016/j.immuni.2019.12.004