

CELL SCIENTISTS TO WATCH

Cell scientist to watch – Mahak Sharma

Mahak Sharma graduated with a bachelor's degree in biotechnology from the Guru Gobind Singh Indraprastha University, Delhi, India. She then moved to the laboratory of Steve Caplan at the University of Nebraska Medical Center, Omaha, USA, where she received her PhD in 2009. After post-doctoral research with Michael Brenner at the Department of Rheumatology, Immunology and Allergy at Harvard Medical School, she returned to India in 2011 as an Assistant Professor at the Indian Institute of Science, Education and Research (IISER) in Mohali. Mahak is the recipient of a Wellcome Trust/Department of Biotechnology (DBT) India Alliance Intermediate Fellowship. Her research group investigates the mechanisms of late endosome and lysosome trafficking, lysosome positioning, and how intracellular pathogens use the host trafficking machinery to their advantage for growth and survival.

What inspired you to become a scientist?

My parents, who are both clinicians by profession, and my mother especially, had a huge influence on me. She instilled the seed of curiosity and was my first teacher. She was using methods of active learning to teach me about scientific concepts and biology, like showing me a retina from a goat to explain how eyes and vision function. Today, my mother's still asking me what my next lecture or seminar is about and wants me to explain things in a simple way. Her interest in my work keeps me on my toes with regards to my science communication skills.

After your undergraduate studies you moved to the USA and returned to India to set up your lab in 2011. What influenced your decisions?

I wanted to explore the best labs in the world and experience the opportunities abroad, and that's when I decided to apply for a PhD in the USA. Initially, I joined as a graduate student at the University of Arkansas for Medical Science, but then I transferred to Nebraska where I joined the lab of my PhD mentor, Steve Caplan. At the end of my training in Steve's lab, the desire to go back to India had become very strong. Then, during my postdoc, I got a first author paper rather quickly and I started interviewing for a faculty position in India early on. I may have even hurried it a bit, having been only in my third year as a postdoc, but eventually, many institutes reviewed my CV favourably and that's when I got the job offer.

You mentioned your desire to return to India. What was your motivation there?

Family and also research. I had always enjoyed my life in India and I feel deeply connected to the culture. As for the research, the outlook was changing around 2008. Five Indian Institutes of Science, Education and Research (IISER) had opened and these places hired the best people from around the world. Also, the Wellcome Trust/DBT India Alliance had set up its funding with a very generous allowance. Many things were happening at the time and I felt it was



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the right time to return and apply for such funding opportunities to start my lab research.

Nearly a decade later, how is the funding situation in India, in general, in your opinion?

The funding opportunities are there, but the Wellcome Trust/DBT India Alliance grants are very different from other grants in the country in terms of the amount of funding and also the flexibility, which is extremely important. Furthermore, with this type of international funding the exposure that one gets is great. There's also an allowance for international travel and they highly encourage having collaborations outside India. So this is great, but we also need this kind of flexibility in other funding programmes. That's more difficult in this country. A lot of investigators in India want the government to change the funding model but it hasn't happened yet. Besides the Wellcome Trust/DBT India Alliance support, the support by IISER Mohali has also been very generous – so for me, funding has been pretty good so far. I would also like to take this opportunity to advocate for an increase in the funding of curiosity-driven, basic research, which is essential for scientific breakthroughs.

What challenges did you face when starting your own lab that you didn't expect?

When I returned I did not have any idea how challenging things would be as I hadn't done any real research before in India. I think

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Mahak with her lab members

that was actually good because if I had known the challenges I faced, maybe it would have taken me a little longer to decide whether I want to come back or not. IISER Mohali was also a new institute and it took time to establish the lab, to figure out how things work. The paperwork is something that's definitely a big part of our daily research life, and in general you need patience to deal with it. I think that I have also adjusted to this idea that things are going to take time, so we plan ahead a lot.

How are the challenges that you're facing now different?

As the lab is completely functional now, the challenge is to seek new funding as my current grant comes to an end soon. Also, I want to develop more challenging projects to avoid being stagnant in terms of the questions or the science that I'm doing. We're learning new techniques and we're incorporating new model systems in the lab. For instance, the Allen Institute for Cell Science are in the process of developing a wonderful resource for cell biologists by creating induced pluripotent stem (IPS) cells that are CRISPR-tagged at endogenous loci for different marker genes to visualize subcellular organelles and structures – I would like to incorporate this entire model of cell culture in my lab in the coming months.

What questions are your lab trying to answer just now?

We are studying the protein machinery that regulates cargo trafficking towards the lysosomes. Lysosomes have been on the side-line for a very long time, being called the dead-end organelle or trash can of the cell. But work in the past few years from the labs of Andrea Ballabio and David Sabatini has shown that lysosomes are the control centre of cell homeostasis, which highlights the importance of this organelle. We are trying to study how it receives cargo – this cargo could be an endosome, it could be an autophagosome, it could be a vacuole/phagosome that contains bacteria. We are studying the protein machinery that regulates the fusion of lysosome and cargo-containing compartments, such as the tethering factors and small GTPases. Furthermore, we want to know how intracellular pathogens such as *Salmonella* or *Mycobacterium* modulate or manipulate this machinery to their advantage. Recent work has also suggested that lysosome position within the cell is very important – there is a sub-class of lysosomes, peripheral lysosomes, which are very important for cell migration, bone remodelling and plasma membrane repair. We want to study how the factors that regulate lysosome positioning would contribute to these cellular processes in specialised cells.

What has been the most influential publication or work in your field recently?

The advances made in imaging techniques has helped the field, but I would like to specifically point to the work of a couple of people that I follow and who have inspired me: the lab of Sergio Grinstein has recently shown that there are differences between peripheral and perinuclear lysosomes with regards to protein content and pH. Equally, Paul Luzio's group put forward the notion that lysosomes could be neutral pH compartments and serve as a storage organelle for proteases. As I mentioned, the Ballabio and Sabatini labs demonstrated that lysosomes are centre stage for cell homeostasis and nutrient signalling and that has contributed substantially to my understanding and my excitement about this field. The current project that we have in the lab on manipulation of host vesicle fusion machinery by intracellular pathogens has immensely benefitted from the research done in the labs of Michael Hensel and Albert Haas, who have explained the mechanistic basis of interactions between host endosomal machinery and pathogens, as well as defined the minimum machinery required for these interactions to take place.

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How do you achieve a work-life balance when you're trying to establish yourself as an independent investigator?

In the beginning, I would stress out over small things and I've learned along the way that you just have to be patient. It was difficult to maintain a balance, even without any family responsibilities like many of my colleagues whom I commend for doing such a fantastic job. I would try to take the weekend off or I would just go for a short trip to the beautiful hills we have nearby the city, or I'd watch a movie or enjoy good theatre. It takes your mind off research and that helps to rejuvenate for the coming week.

What is the best science-related advice you ever received?

From my PhD, I am still very close to my mentors Steve Caplan and Naava Naslavsky. We still email a lot and they give me feedback. Advice that Steve gave me early on is that each student needs a different style of mentoring, and that I should modulate my strategy according to each student. This was very helpful. Another very important thing that he pointed out was that being a group leader can be a lonely job because you cannot necessarily share the apprehensions and disappointments along the way with your students that much – you want to keep them motivated (*laughs*). Therefore, he advised that one finds happiness in small things: a nice experiment or a new hypothesis that seems very exciting. My postdoc advisor Michael Brenner told me to un-plug myself routinely, to 'smell the roses along the way' – all these things have definitely contributed and proven to be helpful.

What is the most important advice you would give to someone about to start their own lab?

I've seen many people establishing their labs and they have a plan and definitely think about each and every step, which is fantastic. So I'm not sure I can give them any advice on planning how to do things. If I had to mention one thing, I'd say don't overwhelm yourself with several big projects when you're starting your lab. It's important to keep a focus in the initial few years and to show that

you're productive. For that, talk to your students regularly and orientate them early towards a publication in terms of writing a draft in their second or third year. If they get a paper early during their PhD it's very helpful for them, as well as for their CV as a young group leader.

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What is your advice on establishing good collaborations?

It helps if you have a specific experiment or question in mind, for example addressing something in a different model system. I think this will kick off things because your collaborator can see that there is a concrete idea and understand your vision. I wouldn't keep a collaboration too open-ended because then it generally does not take off.

How do you get the most out of the meetings you attend, particularly in the early stages of your career?

I do some homework to make sure that I get the most out of a meeting, especially for the big conferences like the ASCB. You

have to seek out people who can give you very good feedback on the work, give advice on the project or have the special expertise that I'm looking for. For instance, I tried to learn about new techniques at the last ASCB meeting, such as BioID and super-resolution imaging. It's great if you can talk to the people who invented it or use it routinely – you can get direct information on the trouble shooting of these new challenging techniques.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

I really love to read poetry, specifically poetry written in Urdu. It has a really soothing and calming effect on me. I attend many recitals of Urdu poetry and I find a lot of peace in that language, in the meaning of these couplets. I sometimes recite these couplets when I have a gathering of my family members or my friends and I enjoy this beautiful language. The other thing is that I'm the movie critic of the lab and my department. My students and colleagues routinely ask me whether I've seen this new movie and so on and I like to dissect the story line and review it in length. It takes my mind off research.

Mahak Sharma was interviewed by Manuel Breuer, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.