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INTERVIEW

Transitions in development – an interview with Bhavana Muralidharan

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Bhavana Muralidharan is an Assistant Professor at the Institute for Stem Cell Science and Regenerative Medicine (inStem), where her research focuses on chromatin-mediated regulation of neurodevelopment and neuropsychiatric disorders, and the development of cerebral organoids for modelling these disorders *in vitro*. We caught up with Bhavana over Zoom to discuss her research, the recent EMBO organoid meeting hosted at inStem and her creative performances outside of the lab.

When did you first become interested in science?

I have been interested in science since school, especially physics and biology. I remember being fascinated by light refraction and how it could be used to design lenses for eyesight problems. To me, science is a way to understand nature and create solutions for people's issues. My high school biology teacher particularly sparked my interest in biology; she taught from first principles, explaining how cells form tissues, then organ systems and finally the entire body. This left a lasting impression on me, inspiring me to explore the complex nature of biology and understand human physiology.

I understand you did your PhD at the National Centre for Cell Science in RNA biology. What exactly did your research focus on here?

My PhD focused on studying the post-transcriptional regulation of genes. My research shed light on the translational control mechanism of a very crucial biomolecule in the body – insulin. When glucose enters through the bloodstream and reaches the pancreatic islet β-cells, the islets first secrete their stored reserves of insulin. This reserve is then immediately replenished by an upregulation in the translation of the insulin mRNA, and all this happens within 30 min. However, the mechanism of translation driving this rapid protein synthesis was unknown.

I identified a stem-loop secondary structure in the 5′ untranslated region of the insulin mRNA that regulates its translation and also an essential role for the endoplasmic reticulum (ER) resident protein, protein disulfide isomerase, in glucose-stimulated insulin translation. From my doctoral work I delineated crucial aspects of nutrient-regulated insulin translation in the β-cell that shed light on broader metabolic aspects of β-cell physiology.

After a post-doc in Shubha Tole's lab in Mumbai, you then made an international move to Adrian Isaacs' lab at University College London – what spurred this decision to move to London?

As I considered my next steps before starting an independent lab, I felt compelled to shift my research towards a more clinical or translational approach after completing my post-doc in neurodevelopmental biology. Consequently, I joined Prof. Adrian Isaacs' lab at the UK Dementia Research Institute, UCL, London, which investigates the molecular mechanisms of genetic causes for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia – neurodegenerative and aging disorders. In his lab, I used patient-derived iPSCs and spinal cord motor neurons to study neurodegeneration mechanisms in a human *in vitro* disease model system.

You then moved back to India to start your own lab at inStem – what was the reasoning behind this decision?

My aim was to start my lab in India while finishing my first post-doc in Mumbai. Moving to the UK was intended to acquire new skills. My goal was always to contribute to India's research ecosystem and train the next generation of scientists. inStem is one of the country's premier research institutes within the Bangalore Life Science cluster, fostering a multi-institutional setup ideal for large collaborative programs, such as partnerships with clinicians or other neuroscientists. As India's first stem cell research institute, inStem focuses on frontier areas of stem cell research and capacity building, making it the perfect place to begin my career as a group leader.

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And how did you find the transition from post-doc to group leader?

The transition was both exciting and challenging. The excitement came from starting an independent career and developing my own research program. However, the responsibility of nurturing this 'baby' presented numerous challenges, such as lab setup, ordering reagents and equipment, establishing research protocols and training lab members. Balancing these tasks with grant writing, paper writing, teaching courses and administrative duties proved demanding. Overall, the experience was thrilling but extremely challenging, requiring preparedness for both aspects of the job.

The onset of the pandemic added to the challenge. Just a few months after settling into the new place, we had lockdowns and had to repurpose our labs and institutes for COVID testing. inStem became the hub of testing and viral genome sequencing. Coping with the multiple uncertainties that came along with the pandemic added to the challenge during the initial years.

How important do you think mentorship is in navigating an academic career? Are there any mentors who have particularly helped you in your transition to group leader?

Mentorship is crucial at any stage of a research career, as it provides guidance and support for growth. I have been fortunate to have several mentors, both teachers and scientists, and two individuals made a significant impact at critical points in my career. First, my post-doc mentor, Professor Shubha Tole, was not only an exceptional scientist but also a supportive mentor. When I had a child during my post-doc, she provided a project assistant to keep my work progressing, demonstrating that personal milestones should not hinder career advancement. This gesture left a lasting impression on me, and I have done the same for a post-doc in my lab.

More recently, Prof. Apurva Sarin, the former director of inStem, supported me with resources and guidance upon starting my research career at inStem. She has continued to mentor me, offering advice and constructive criticism on grant and paper writing, helping me grow as a scientist.

You mentioned the support you received during your pregnancy and maternity leave; would you say this type of support is something that should be more widely available to women in science?

Absolutely, what Shubha did was quite uncommon. Though there is much more awareness and sensitivity today, as a community, we have a long way to go. I hope more people will follow her example, as support during maternity leave and child-rearing can make a huge difference in a career. I'm now a faculty member in India with a strong research program and numerous competitive fellowships thanks to her timely support. So I believe we need systemic changes to ensure continued success. It may take time, but that change is crucial.

What advice would you give to people starting their own labs?

The starting years are the most critical and challenging, filled with uncertainties in building your team and research program. So you need a big dose of patience to slowly but steadily establish a solid foundation. It's also important to seek out mentors, especially ones who understand your institute's specific issues and can offer tailored advice. Lastly, don't forget to maintain the right balance, as burnout risk is high. There is a lot of work, both at the bench and behind the scenes, so having hobbies or passions outside science can really help you recharge and maintain your enthusiasm and energy.

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Can you summarise the research themes of your group?

My lab focuses on how chromatin and epigenetic mechanisms affect the development of the cerebral cortex in healthy and disease states. Chromatin regulation plays a critical role in neurodevelopment, from stem cell proliferation and neuronal differentiation to axon pathfinding and synapse formation. Thus, mutations in chromatin modifiers have been linked to a wide range of neurodevelopmental disorders.

We use an integrative approach, combining functional genomics with mouse genetics, human iPSCs and cerebral organoids to unravel the molecular and cellular processes underlying neurodevelopment. A major line of investigation in the lab uses the resources of a program at inStem called the accelerator program for discovery in brain disorders using stem cells (ADBS). Through this, we have access to deep-sequenced genetic data, clinical phenotyping information and iPSCs from individuals with bipolar disorder. ADBS has recruited 300 clinically dense Indian families with a strong history of mental illnesses, including patients, unaffected family controls and unrelated healthy individuals (population controls). To elucidate the mechanisms of the neuropathology of bipolar disorder, we establish cerebral organoids from patients and control iPSCs.

Your research involves working with both mouse and stem cell-based models – what are the benefits of using both these models for studying neural development?

We work with both model systems to study the brain and interconnectivity between different parts. The mouse is a complete and physiologically relevant model for this purpose. However, there are many human-specific differences that the mouse cannot encapsulate. To study the differences between the mouse and human brains, a human model system is necessary, for which we currently use stem cell-derived cerebral organoids. Going forward, a humanized mouse model would be ideal. Investigating the uniqueness of the human and integrating it into a complete system are essential aspects to consider in model systems.

I understand you were an organizer of the recent EMBO workshop on 'modelling development and disease with human tissue organoids' at your institute, inStem. How did this come about and what were the notable outputs from the meeting?

Orly Reiner, Carol Schuurmans and Shubha Tole, who were my co-organizers, conceived the idea of a meeting in India to address the lack of researchers in the organoid biology field here. As a new faculty member starting work with organoids at inStem, I was excited to be asked to be the local organizer and host. The meeting was particularly beneficial for Indian post-docs and students, who often face financial constraints that limit their access to international conferences. Thus, the opportunity to attend a local meeting where they could meet scientists from across the

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globe, discuss their work and receive valuable feedback was significant.

At the conference, alongside world-class scientific presentations, we included a symposium on biomedical ethics to draw attention to ethical concerns surrounding human stem cell and organoid research. We emphasized the significance of developing healthcare solutions with global reach and accessibility. We also organized a mentoring session, which focused on career guidance, diversity, inclusion and work-life balance, and featured a round-table discussion. This session was a major highlight of our event.

I see you're on Twitter. What are your thoughts on social media for scientists?

Twitter, as a platform, is extremely helpful for staying up to date on current research findings; researchers often post informative Twitter threads about their work, which is useful for keeping up with current trends. For some, it is also a great place to get information on openings, access to talent, conferences, grants, etc. However, I must concede, it can also be distracting and sometimes overwhelming for early-career researchers. Comparing one's own trajectory with that of their peers can lead to unhealthy comparisons. Thus, it is essential to strike a balance and be cognisant that each person's lived experience is different. It is worth remembering that science happens in the lab, not on Twitter.

Finally, is there anything Development readers would be surprised to learn about you?

I was on track to become a professional performing artist in classical dance, training under the renowned Guru Saroja Vaidyanathan for 15 years (she received the Padma Bhushan award, India's third highest civilian honour!). I also earned a national level scholarship from the Center for Cultural Resources and Training and performed in India and abroad. Despite this, my growing interest in biology and science led me to give up performing and pursue a career in scientific research, but I still enjoy an occasional artistic performance or activity.