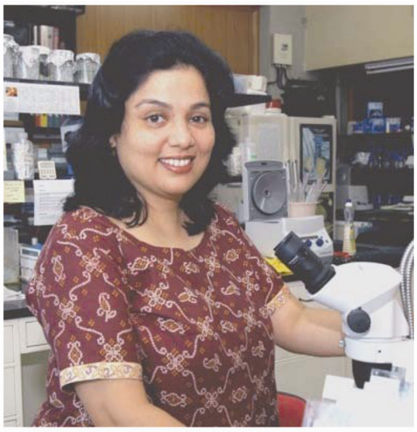
Shubha Tole



Shubha Tole is a neuroscientist at the Tata Institute of Fundamental Research, Mumbai. She has a host of awards to her name like the Wellcome Trust Senior International Fellowship (1999), the Swarnajayanti Fellowship (2005) from the Department of Science and Technology, the Research Award for Innovation in Neurosciences (2008) by the Society for Neuroscience, USA, Shanti Swarup Bhatnagar Award (2010). More recently she was awarded the Infosys Prize (2014) for her outstanding work on understanding how the brain develops in an embryo. In an interview with *Current Science*, she talks about her work and importance of why scientists should engage in science outreach programmes for the public.

What inspired you to take up neuroscience research as a career?

As a child I was curious about how things worked and why things were the way they were, and science was a natural extension of that curiosity. Scientists have the privilege of extending the phase of childhood wonder into their professional lives. Physics was my favourite subject in school, but by standard 12 it was overtaken by a fascination towards biology, especially the brain. During my undergraduate studies in the Life Science Department of St. Xaviers College, Mumbai, I used to do extra reading to present a topic of my interest to my classmates: how an embryo begins the earliest stages of its life, how the brain perceives vision, how transcription and translation are regulated, etc. When the time came for applying to universities for a Ph D programme, I applied to universities in the US, and chose Caltech as it had a good research programme in neuroscience.

What does your research focus on?

We have nestled in our heads the most amazing computer ever made – the brain. Unlike computers that are made of motherboards, IC circuits and wires, the brain has to be grown from a simple sheet of tissue in the embryo. An embryo faces an extraordinary challenge, as it has to form a brain with $10^{(11)}$ brain cells or neurons from a simple sheet of precursor cells. Neurons are of many types and the right ones have to be generated for use in a diverse array of brain structures. They are later wired up with extreme precision to ensure normal brain functions.

My work reveals insights into how the design of the brain, its ‘blueprint’ was made in evolution and also how the process of building the brain is executed during its development. In my laboratory we study the formation of the normal brain and the genetic strategies that are used to bring about the complicated process of cell division, migration and neural wiring, etc. Any compromise in these processes results in neurological disorders such as autism, schizophrenia, mental retardation, etc. Understanding the normal development of a brain therefore helps figuring out what goes wrong in the case of such disorders. I use the mouse model to uncover mechanisms that are likely to play out in human brain development as well. But even if cures were already available for brain disorders, the significance of understanding brain development would not be diminished. Our brain permits us to do many fantastic things. It allows us to build social networks and alter our environment to suit our needs. Our abilities and our inabilities arise from how the circuits are wired up in our brains. For example, we perceive the world as we see it in a limited range of the spectrum called the ‘visible’ spectrum, whereas a fly perceives the world differently as it can see ultraviolet light. How do these circuits form? This is one of the questions we work on in my laboratory.

Could you explain the function and importance of the gene Lhx2 in mice

Lhx2 is a multitasking master regulator of brain development. Very early in the development of the embryo, *Lhx2* acts as a molecular switch. Cells in which *Lhx2* is switched on produce neurons of the cerebral cortex. The ones in which it is switched off develop the ability to produce a potent cocktail of molecular signals and act as signalling centres. Just like lighthouses in a sea of immature cells, they respond to the signals and develop further. From a very early stage of growth of an embryo, a simple genetic switch decides which cells produce signals and which cells respond to them. In our laboratory we created embryos with many signalling cells (lighthouses) in a responding tissue. Normally, there is just one such lighthouse in each half of the brain, and the hippocampus – the structure where memories are formed – develops right next to it. The embryos with multiple lighthouses also has many extra hippocampi nestling within the brain. Therefore, we were able to understand the reason behind the positioning of the hippocampus. We are now working on finding out what factors determine the position of the signalling centres.

We also found a completely different function of *Lhx2* at a later stage in the development of the embryo, when the circuitry for high-resolution signal processing becomes connected up in the brain. Our sensory system has the ability to discriminate signals coming in from various sensory modalities such as visual, auditory or somatosensory (touch) pathways at a very high resolution. For example, when you pick up a cup, you need to be able to know where the top and the bottom of the handle are. Have you ever wondered where your brain would get this information from? In order for the brain to perceive the two as physically distinct, nerves carrying sensation from the two fingers – one on the top and one at the bottom of the handle – must connect to two separate points on the cerebral cortex in order for the brain to perceive the two points as physically distinct. It is similar for every bit of our skin. We get sensation from different parts, because the nerves carrying information connect to different points in the brain. We discovered that *Lhx2* controls this circuitry in the mouse, in which the whiskers serve as fingers to sense the environment. Without *Lhx2* functioning, the nerves fail to wire up properly and the mouse does not have a normal sensory 'map' in its brain.

Why are mice used as model systems in many of the neuroscience research experiments?

Animal models are chosen for their suitability to the question one wants to study. For example, the development of spinal cord is similar in birds and mammals. As chicks grow in eggs, they are preferred in studies focusing on the spinal cord where in one needs to access a developing embryo to overexpress or knock down a gene of interest. Similarly, fruit flies are used to understand molecular mechanisms, as many of the proteins that guide nerve growth are common in both insects and mammals. As I am interested in the cerebral cortex, a structure unique to mammals, I use the mouse as my model system of choice. Mice are easy to maintain, and in addition, there exists technology to test what happens if a particular gene is removed or misexpressed in new locations. Such studies help understand development of the human brain, since the mechanisms we examine are likely to be common across mammals.

Is it possible to extrapolate the results of the experiments done on mice to humans?

To a large extent, yes. One has to choose the questions wisely and the model systems just as wisely. The cerebral cortex, if flattened out, is about the size of a one rupee coin in a mouse, a small chapatti in monkeys and that of a large pizza in humans. But in all three, the map remains the same, only their size differs. So if we can understand how the map is created in a mouse, then it gives us answers for the map of the human brain as well.

What are the current trends in neuroscience research in India?

India is still young in the field of neuroscience. Today's students are tomorrow's scientists, but neuroscience is not well represented in the undergraduate curriculum. As a consequence, the neuroscience community in India is not very large. In countries like USA, neuroscience is one of the areas with intense on-going research. The annual meeting of the Society for Neurosciences in USA draws over 35,000 people. Though these large numbers are not seen in India, there are a few neuroscientists doing excellent research in the country, and the numbers are growing. Some of our Ph D students who went abroad for postdoctoral training have returned and taken up faculty positions at institutions around the country. The Indian neuroscience scene will change rapidly in the coming decade and I am looking forward to it.

How difficult is it for scientists early in their careers to avail funding opportunities in India?

There are many schemes from DST, DBT, CSIR, ICMR and the Wellcome-DBT India alliance, to name a few. However, the limitation in India is not the funds but the mind-set of people at various stages in the system. The administrators of funding need to make funds flexible and disburse them in a timely fashion, if a scientist is to compete effectively on the international scene. The institutional leaders or senior scientists can make a huge difference in helping younger colleagues. Most importantly, early career scientists need to have the foresight to plan their careers, the will to succeed and the ambition to aim high.

What are the caveats of doing science research in India?

Each place comes with its own challenges. Things are not perfect anywhere. In India, scientists struggle mostly with infrastructure and management issues. Regular maintenance of high-end equipment needs trained and skilled personnel. Apart from this, grants not being released in a timely fashion and the lack of foreign travel funds make interaction and collaboration with international community difficult. Scientists abroad do not face these hardships.

A problem underlying some of the above is that collaboration is perceived negatively rather than as a positive aspect by some members of the Indian scientific community. If you have foreign authors on your papers, those publications are not given the value they deserve. I would say we have things backwards – if people elsewhere want to collaborate with you, that means they think your work or your interaction is valuable. Sometimes you contribute a reagent or an idea or a piece of data to a larger story someone else is working on. Other times, you request someone for a reagent, a transgenic mouse, or a piece of data that fits well with your own work. Either way, it is healthy and for the good of Indian science. The present attitude towards collaborations needs to change. Otherwise, the aspirations of young scientists will be curtailed, because of the lack of interaction with a wider scientific community.

How important is it to convey the research results to the common man?

As a scientist who has the luxury of exploring the most fascinating subject, I believe that I owe it to the taxpayer, who funds my research to share some of the excitement. I also feel scientists should, as part of their jobs, engage actively with the student community. Helping the next generation as much as possible is the best way of inspiring the younger generation. With this aim, I write blogs for the student and teacher community on the website www.indiabioscience.org. Topics that I have covered conclude 'Taking the ME out of mentorship', 'How to decide which Institution to join', and one that helps students applying for projects entitled 'Calling all teachers, please help'.

What is your opinion on researchers engaging themselves in science outreach programmes?

I admire scientists who have taken the trouble to enhance their communication skills and engage in public outreach. Science communication is an integral part of research skills, and all research students should be trained to have them. At TIFR we have a wonderful outreach programme called 'Chai and Why', which is the brainchild of Arnab Bhattacharya. Chai and Why is on Facebook, and runs on two Sundays a month at Prithvi Theater and Ruparel College. The sessions are interactive and are available on YouTube. I encourage readers to view them. I also teach 'Science communication' in a course that is offered to students at TIFR each year, and it is well appreciated. Involvement of researchers and scientists in public outreach will encourage and inspire youngsters to take up science as a career.

What is your opinion on the quality of science education in the schools and colleges in the country? What are the aspects which need improvement?

I have been privileged to have been taught by a few really exceptional teachers and I frequently come across students who are enthusiastic about learning something new. What is missing is a modern syllabus and a method of education that removes emphasis on rote-learning. We need appreciation of science as an on-going process of discovery, not a 'product' enshrined in a textbook that needs to be memorized. Learning is not memorization and biology is not drawing diagrams. Yet, this is what we communicate to our students, as we do not know how else to evaluate them. Since the beginning, our school system is based on the format that the teacher has all the answers and the students have to ask the questions. Here, the burden is not on the students to find the answers, but rather on the teachers. Our education system needs to change in what is expected of the students. Our teachers need to be able to transfer the burden of discovery to the students, because this encourages creativity. Independent thinking by students must be encouraged. Examinations must be designed to test the understanding and not the memory of the students. Teachers have to be encouraged and allowed to experiment with out-of-the-box methods of teaching. We need a social change in what is expected from each side. All the elements of the equation have to change the way of how we have been doing things. This will trigger more thoughtful approach towards education and that is when you get science-minded students. It is impressive that we have good scientists in our country, in spite of the limitations of our education system.

Students also should not limit their learning to the school curriculum as exam scores are neither a measure of learning nor a measure of how well one will do in his or her life.

The focus now a days is very much on women scientists, pursuing a successful career in science. Do you believe there is a gender bias or disparity in the field? If so, what were the challenges you faced and how did you get past the hurdles?

There is certainly a gender disparity. This problem begins early and needs to be addressed at the school level itself. That is where young women compromise, which sets them on a track that will not lead them to the high leadership roles they could very well play. I had a wonderful role-model in my mother who was an occupational therapist at Tata Memorial Hospital. She faced all odds and struggled with seemingly impossible challenges, but still never gave up working to her fullest. My own career path was much clearer, as my parents gave me their complete support and had faith in me. They have raised me to make my own choices from the beginning and have trusted my decisions to deal with the challenges that come my way.

The challenges I faced in my career are similar to those faced by any woman professional in any field. The solutions are also very similar. There are different ways of resolving problems and different solutions to choose from. One just has to have the strength of purpose to follow one's heart and not give up on one's own dreams. Prioritizing what is important and working out plans accordingly is the key. Do not let anyone make you feel bad for the choices you have made. Follow a path you decide on after thoughtful consideration of the options, taking all the advice you need, but finally make your own decision.

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