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An inclusive and collaborative spirit for global progress in genomics

Dimple Notani is principal investigator (PI) at the National Centre for Biological Sciences (NCBS) in Bangalore, India, studying gene regulation. *Nature Cell Biology* contacted Dimple to discuss the state of the field and her experience running a research lab in India through a pandemic and as a junior PI.

What inspired you to become a scientist and to study chromatin architecture and its role in gene expression regulation?

I am the first graduate and scientist from my family. Growing up, I had relatively limited exposure and access to science. A career in academia was not even a distant dream! Nevertheless, my science teacher inspired me to take up science as a major after high school. Curiosity determined my subsequent choices, and despite many hardships along the way, here I am today! In retrospect, I am glad I was bold enough to pursue this unknown path, and I am acutely aware of the difficulties faced by students who come from underprivileged backgrounds because I come from the same.

My interests widened from bookish science to experimental research during my master's degree, when I observed agarose gels displaying differential DNA amplicons from various mulberry species found in India. The differential DNA bands were the result of DNA base changes in those species. This fascinated me. How do single changes in the alphabet that makes up DNA (known as genetic variation) create phenotypic differences in a population? It was a humble start, but from this fascination grew my interest in gene regulation, driving me to pursue a PhD in gene regulation in India.

Gene regulation is a multifaceted phenomenon that involves the fine-tuned co-operation of many players — including transcription factors (TFs), histones and non-coding RNAs (ncRNAs) — on a genome, whose folding changes and which contains regulatory DNA elements. As a newcomer to the field, one can get lost if exposed to all these ideas simultaneously. I was exposed to these multiple facets in a stepwise manner, which allowed me to understand and appreciate these concepts deeply.

My PhD research in Sanjeev Galande's lab, then at National Centre for Cell Science, Pune, was focused on the regulatory roles of a TF in gene regulation. During my postdoc in the laboratory of Michael G. ('Geoff') Rosenfeld at University of California San Diego, I was prepared to interrogate the complex gene regulation 'cocktail', where all gene regulatory components mentioned above function together towards a common goal of fine-tuning gene expression in a spatio-temporal manner.

By 2009, when I started my postdoc, next-generation sequencing had begun revolutionizing genomics, enabling the discovery of a plethora of genomic elements, including enhancers. However, their functional understanding was lacking. I took advantage of genomic techniques to first understand if disease-associated genetic variation within enhancers had any effect on target genes. We observed that a disease-risk allele located in an enhancer affected binding of a key transcription factor, which in turn changed how cells carrying that allele responded to activation of that transcription factor in terms of long-range enhancer interactions and expression of neighbouring genes. These results, for the first time, revealed how genetic variation in an enhancer can alter the disease susceptibility of a population or individual. The findings convinced me to pursue these important elements to better understand them, and I am still hooked. My second project in Geoff's lab was to understand the functional role of enhancer-associated RNAs (eRNAs) as they had just been discovered but were perceived as 'transcriptional noise'. By utilizing chromatin conformation assays and genome-wide mapping of nascent RNA synthesis in the context of oestrogen receptor-α activation, we revealed the direct role of eRNAs in signalling-induced gene transcription and enhancer–promoter contacts. In spite of the field's intense focus on enhancers, our current knowledge of enhancers is just the tip of the iceberg. The unknowns continue to intrigue me and motivate me to pursue these fascinating regulatory elements in my laboratory.

What key research principles or methods did you take away from your post-doctoral training into your own research programme?

My postdoc mentor, Geoff, is the most intense scientist I have ever met. His passion and rigor for science is infectious. His lab has made seminal contributions to the field of nuclear receptors. Many aspects of signalling-induced transcription that we know come from research initiated in his laboratory. His approach to understanding the mechanisms of a biological phenomenon is deep and inspiring. He is not one to be satisfied with mere correlations of genomic data to arrive to a conclusion and requires that they are rigorously tested by various approaches, including genetic perturbation experiments. As an independent PI, I try to emulate his open-minded approach to science and the idea that genome-wide data-heavy and hypothesis-driven science can go together.

What is your lab focusing on? What approaches do you use?

To drive developmental programmes, enhancers are born de novo to regulate target genes. However, the genes that respond to signalling are regulated by constitutive enhancers that

undergo cycles of activation and inactivation upon every round of ligand stimulation. Interestingly, the molecular mechanisms behind the dynamic behaviours of enhancers are not clearly understood. My laboratory uses publicly available genome-wide data to formulate hypotheses and chromatin conformation assays, transcriptomics, high-resolution microscopy and carefully designed enhancer perturbation approaches to identify molecular mechanisms of enhancer functions.

My lab's expertise has poised us to delve deeply into the genetic basis of diseases that are relevant to India. We are exploring how germline mutations in regulatory elements impact gene expression to understand the susceptibility of the Indian population to diseases with a major socio-economic burden, such as congenital glaucoma, cardiac hypertrophy and metabolic disorders. The recent focus of Indian funding agencies on disease-relevant research adds impetus to our research.

Tell us about your lab's guiding principles.

As a lab, we support diversity, including in terms of gender and LGBTQIA+ identity, religion and regional background. We are of course aware of the geo-political differences and disturbances in India, but we do not let them affect us. Once you join the lab, you are treated as an equal and expected to treat others the same, with respect. We hope to provide an environment that encourages open discussions, compassion and a collaborative spirit. My lab is much like a family; we deeply care about each other, while simultaneously conducting rigorous, and country-relevant research to justify taxpayer funds spent on research. Genomics is still not mainstream in India. We are a collaborative lab. One of our goals is to try and enable other Indian researchers in resource-poor settings to perform genome-wide experiments.

What are the field's directions you're most excited about?

There has never been a better time to be in this field, especially owing to the technological advances in single-cell genomics, high-resolution microscopy and ways to label chromatin to track regulatory elements in live cells. Owing to such diverse sets of data, the field is also highly multi-disciplinary, which pushes its boundaries. We are now able to ask fundamental questions pertaining to the regulatory links between enhancers, gene transcription rate, chromatin folding and the spatial location of a gene at a single-cell level. I am excited about the possibility of examining the understanding of transcriptional regulation that emerged from population averaging to a single-cell level.

What do you think are the main challenges for the field?

Any field progresses from a balance between curiosity- and hypothesis-driven science. Because genomics is mainstream now, this has resulted in the perceived compulsion to make conclusions genome-wide. This contrasts with locus-based studies, which have provided most of the fundamental understanding of gene regulation. Drifting away from locus-based approaches has allowed the field to generate enormous genome-wide data but has negatively impacted rigorous hypothesis-driven science. The experiments suggest that transcriptional mechanisms that are mediated by enhancers are rather heterogeneous and do not follow a one-size-fits-all. Therefore, testing genome-wide concepts with locus-based studies is crucial.

Technological advancements in microscopy and single-cell approaches now allow us to ask fundamental questions; however, only labs that are resource-abundant can ask these questions and be at the forefront. A more inclusive and collaborative spirit is important to allow less resourceful labs to contribute to this exciting time in the gene regulation field.

What are unique aspects of running a successful lab in India?

Our individual grants are too small to do resource-heavy research. However, this provides us with an opportunity to think and try to do something out of the box that otherwise wouldn't receive funding in western countries. For example, I challenged the perceived notion that enhancer clusters are superior and work as a sum-of-all enhancers by testing the impact of enhancer deletions, one by one, within a dense enhancer cluster. We rely on such laborious but important approaches that are not resource-intensive. One advantage of running a research lab in India is that we get to work with excellent masters and PhD students who have a great deal of hunger, creativity, sharpness and do not shy away from hard work. Many of them are first-generation graduates just like me. Shaping their career with world-class science gives me a unique opportunity, privilege and satisfaction to inspire this and future generations of scientists directly or indirectly. This is something I cherish; it makes my career in India worth it!

Indian research is mostly run by these marvelous PhD students and not by postdocs, as most PhD graduates understandably go abroad for a postdoc. However, unlike for postdocs, the learning curve for students is rather steep, which can slow the progress of a competitive project, but once they are at the crest, they are superb and an outstanding resource for Indian labs.

The main challenge for a lab like mine is continual evolution to keep up with this technology-driven field. Owing to a limited number of labs with similar interests in India and the unavailability of skilled postdocs, I often rely on either developing the technology in the lab or collaborating with a lab abroad — both of which become challenging as the former needs infrastructure and funding, and the latter needs collaborators and travel grants.

Starting a new lab is difficult anywhere owing to challenges faced everywhere, and these challenges can feel pronounced as one readjusts to expectations and resources of doing first-rate research here having transitioned back from abroad. However, once steady work is published and recognized, getting international funding is easier than for someone with similar credentials in the West. Recruiting talented students to my lab has not been an issue.

Tell us about the transition becoming a group leader. Any mentoring advice for junior investigators learning to manage a team?

The advice I would give to junior investigators who wish to start a lab in India is to have an open mind. You are sure to encounter a mix of successes and obstacles. Have a strategic plan in terms of funding, infrastructure and administrative support to help navigate the system. To start my lab, I was fortunate to get a tenure-track position at the NCBS with a state-of-the-art genomics and microscopy facility. Generous start-up from NCBS-TIFR and funding from India Alliance DBT–Wellcome Trust (a partnership between Wellcome Trust, UK, and the Department of Biotechnology, India) allowed me to kick start the lab. Later, for networking and skill development, I got access to courses, meetings and some funding thorough the EMBO Global Investigator Program. Both India Alliance DBT–Wellcome Trust and EMBO have changed the research landscape in India and have inspired a whole generation of scientists to return to India for their scientific career. I would advise new investigators to have collaborators and mentors early on. Do not hesitate to ask for help from a lab in India or abroad. I was pleasantly surprised by the generosity of the international community to build and support science in India.

You started your lab before the COVID-19 pandemic, and we hope you and your colleagues have been well. How has the pandemic affected your research?

I started my lab in February 2016 and had almost settled down before the start of the pandemic. The labs were closed both during the initial nationwide lockdown in 2020 and again during the devastating Delta wave in 2021, when only lab maintenance was allowed. Collectively, we lost momentum and work is slowly going back to the pre-pandemic pace. Initially, coming back to the lab in shifts required a lot of effort as a team, wherein students helped each other to finish long experiments. This made my team more cohesive and efficient, something positive and desired. As the lab was new, manuscripts were still under revision. It took us a long time to finish the work, both owing to fewer working hours as well as the availability of reagents, which was severely affected. Fortunately, my group did not suffer physically because of the pandemic; I am most grateful for that. Another positive side of the outbreak was the commendable initiative of moving worldwide meetings online. This allowed my lab members to both participate and listen to speakers from all over world, something that would often be impossible due to funding and visa issues.

Thinking about life outside of the lab: how do you balance your personal time with leading a research group? What hobbies do you enjoy?

I would love to give you a good answer to this, but the reality is that there is no balance. Sometimes, it is the family that takes centerstage and at other times it is work. Especially as a parent of a young child, planning and execution is very challenging. Fortunately, the nature of our work provides flexibility. I do not shy away from expressing my transient focus on personal life to my lab. This allows my team to also understand the importance of taking personal time away from work. In short stretches of free time, I enjoy making soaps, candles and natural lotions. When I find time, I like to go to the rainforests in the southern part of India that is close to Bangalore, but I am always looking forward to what my lab will tell me when I return.

Interviewed by Melina Casadio

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