Tarun Kapoor: In the right position to study chromosomes

Kapoor uses small molecule inhibitors and high-resolution microscopy to explore metaphase chromosome alignment.

Properly positioning a cell's chromosomes at the center of the mitotic spindle is a tricky business. Errors or failures in spindle attachment can cause chromosome mis-segregation, leading to cell death or to cancer. Scientists are finally starting to get a handle on this problem, thanks in part to the work of Tarun Kapoor.

Kapoor approaches cell biology from a chemist's perspective, using techniques he learned during his graduate studies with Stuart Schreiber at Harvard. There, Kapoor merged combinatorial chemistry with rational drug design to develop inhibitors to probe the function of SH3 protein domains (1). Kapoor later joined Tim Mitchison's lab, also at Harvard, for his postdoctoral work, and was introduced to motor proteins, their role in mitosis, and the microscopy techniques needed to study these topics (2).

Now, as a tenured professor at Rockefeller University, Kapoor uses high-resolution microscopy and targeted drug design to probe the mechanisms behind spindle attachment and mitotic positioning of chromosomes (3–5). We called him to find out how chromosomes reach the middle ground.

SPACE RACE

What first got you interested in science?

I grew up in Calcutta, a major city in eastern India. As a child I went to the equivalent of a private school. It had a very science-centric curriculum, which I enjoyed. But I think the thing that most inspired me to pursue a career in science was when I saw the television broadcast of the first Indian astronaut in space, Rakesh Sharma. Television was just starting to spread in India, so there were only a few hours of coverage on the event, but I vividly remember him waving into the camera and saying that the most beautiful place that he could see on Earth was India. It was just one of those magical moments.

My friends and I all wanted to be astronauts after that. Ultimately I did not make it into space, of course, but it's one of the things that got me halfway around the world to the United States.

Is that what inspired you to pursue your undergraduate degree in the US?

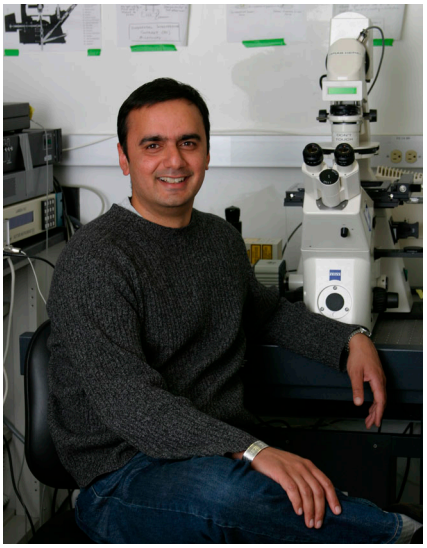
I'd done very well on my exams in India, and people really encouraged me to go abroad for college. I wanted to go to a technical school, like MIT or the California Institute of Technology. It was tough deciding where to go: there was no Internet then, so the information was rather fragmented. I had to get an old catalogue from the United States Education Foundation in India, and it was somewhat out of date [laughs]. I went to Caltech thinking that Richard Feynman was alive, but it turned out that he had died a few years previously.

Once I got there, I expected to major in physics, but then I got a work-study job in Barbara Imperiali's chemistry lab. I'd never really done any wet work in India. My science education there didn't involve much practical training, so this was all new to me. I got into playing around in the lab, and I just had a blast. I became a real "lab rat."

> "It was extremely cool to learn about all the complexities of cytoskeletal biology from one of the masters of the subject."

So, having fallen in love with chemistry, you decided to pursue a graduate degree in it, too?

Yes. I thought very carefully about where I wanted to go for graduate school. I got really excited by Stuart Schreiber at Harvard because there was a lot going on in his lab. I joined a subgroup of the lab that was studying Src homology 3 (SH3) protein domains, and teamed up with another graduate student, James Chem. We set about designing small chemicals that would inhibit SH3 domains' binding to their cognate ligands.



Tarun Kapoor

We ended up taking a semi-rational, semi-combinatorial approach to the problem: using a few rules about how molecules bind proteins, we tried to make every possible combination of chemical motifs that obeyed these rules, and tested them all to see if any of them worked. We found some compounds that worked in vitro, but it was frustrating because none of them did anything to cells; they were completely boring from a cell biology point of view.

INNER SPACE

How did you transition from studying SH3 domains to studying kinesin in your postdoc?

Tim Mitchison visited Stuart's lab for a sabbatical. I started talking to him, and it was extremely cool to learn about all the complexities of cytoskeletal biology from one of the masters of the subject. I decided to do my postdoc with him, and apply chemical approaches to biological problems.

I started working on rational approaches for making chemical inhibitors for kinesins. Meanwhile, another postdoc

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

in the lab, Thomas Mayer, was screening chemical collections for compounds that block mitosis. He found monastrol, a chemical that caused monopolar spindles in cells. On a whim, we threw it in my assays to see if it could inhibit a kinesin—and it did!

Having a specific inhibitor for a kinesin was a big boost experimentally?

It became extremely clear to me that you could learn a lot with a small molecule. The real advantage of a small chemical that can get into a cell to block protein function is that it acts very fast. In a couple of seconds, you can observe a perturbation. But, that advantage is of no consequence unless you can track the dynamics on the same timescale.

That's what got me interested in high-resolution imaging. I was lucky that around that time, Tim started to spend his summers at Woods Hole Marine Biological Laboratory—and I got to go with him. I worked in the Cell Division Group with Tim and Ted Salmon. Ted was very generous—we all stayed at his house. We'd have breakfast talking about the experiments from the previous night, and dinners talking about what we'd do when we got back to the lab that evening. We'd go to work, then take off in the middle of the day for a swim, and then go back to the lab. It was an amazing experience, sort of like boot camp for microscopy and cell biology.

> "Woods Hole was an amazing experience, sort of like boot camp for microscopy and cell biology."

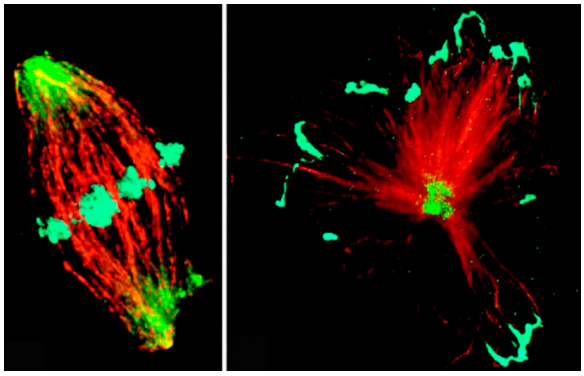
Boot camp with a break for a swim at the beach?

Actually, in the last few years I've gone back to swimming. Everyone says it's the most boring thing in the world to do, but I think putting my head into the water is where I get all my thinking done. I can just shut out all the sounds of New York and all the chaos around me. There's this rhythm that you get into after your 20th lap or so. You can tune everything else out and find your zone.

LAB SPACE

What have you found in your zone?

In the last few years, the mitosis field has advanced to the point where I'm starting to feel that, while the problem isn't yet solved, at least it is bounded. The individual proteins involved have been identified, which is great for me, because I never had any training in genetics. Now we can get in there with our small molecule inhibitors and try to tease apart individual proteins' functions. Our approach is really a chemist's approach; we break apart a reaction mechanism to find key intermediates. We can trap the intermediate stages with our chemicals, observe them in microscopes, and then try to reconstruct the path to accurate mitosis. Since arriving at Rockefeller I've been working on two questions. One is, how do chromosomes attach to the spindle, and then how they get positioned at the middle of the spindle, at the metaphase plate? But once things find the middle, the question then becomes: How does the chromosome really know it's properly attached? What's the mechanism underlying that?



Mitotic spindles in the absence (left) and presence (right) of the Eg5 kinesin inhibitor monastrol.

What kind of checks do chromosomes use to determine they are properly attached to the spindle?

I think it really comes down to mechanical sensing. The chromosome acts like a little nano-machine or a tensiometer. When it's properly attached to both poles, it's being pulled in opposite directions simultaneously and is under high tension. So, we are going back to the approach that Bruce Nicklas pioneered, using needles to pull on chromosomes and exploring how they sense these forces. But this time around, we have better tools: we've been collaborating with Shin'ichi Ishiwata's lab in Japan, using cantilevers and force-calibrated needles. These let us apply very controlled and precise forces to the spindle, which we can use to explore the forces involved, the proteins that sense them, and how those proteins respond.

Do you still want to be an astronaut?

Actually I love being a scientist. It's like having a hobby as your job. I hope to contribute some more to studies on mitosis, but professionally, my only other ambition is to someday help advance science in India. I go back whenever I can, partly to see family, but also to attend meetings, to try to support the community there. I want to help others be inspired just as I was.

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3. Lampson, M.A., et al. 2004. *Nat. Cell Biol.* 6:232–237.
4. Kapoor, T.M., et al. 2006. *Science.* 311:388–391.
5. Itabashi, T., et al. 2009. *Nat. Methods.* 6:167–172.

A detour to Bhutan on a recent trip to India.