Program in Cellular and Molecular Medicine



at Boston Children's Hospital

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Greetings, PCMM -

Happy Halloween! As daylight saving time ends this Sunday, the clocks "fall back" one hour, and the days are getting shorter on sunlight, we hope everyone is stocking up on vitamin D as needed!

As always, if you have any suggestions for the newsletter, please contact us at vera.gaun@childrens.harvard.edu.

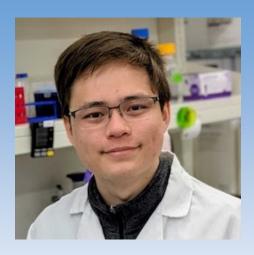
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Introductions: Tylar Matsuo of the Ha Lab



Tell us about your role here at PCMM.

I am a research assistant in TJ Ha's lab investigating chromatin organization and DNA repair using molecular dynamics simulations and microscopy experiments.

Where were you before HMS?

I was an undergraduate student at Amherst College, where I double-majored in physics and law, jurisprudence, and social thought. For my honors thesis research, I induced three-dimensional skyrmions, a type of non-trivial topological excitation, in spin-2 Bose-Einstein condensates. These skyrmions, which had not previously been experimentally observed, possess interesting discrete symmetries arising from the Bose-Einstein condensate's quantum state, and have potential applications in information storage and quantum simulation.

What's your favorite piece of lab equipment?

My favorite pieces of lab equipment are the centrifuges. They're conceptually simple, but without them many of my experiments would not be possible. They also almost always work.

What are your research interests?

I am investigating protein-DNA interactions. I am interested in how proteins are recruited to and reshape chromatin following DNA damage. I have been using molecular dynamics simulations to uncover the role of loop-extruding factors in homologous recombination, and I am involved with microscopy experiments using the Ha lab's new GOLDFISH-X genome imaging technique.

If you could solve one scientific or medical mystery, what would it be and why?

I would find an effective and reliable method for delivery of large biomolecules, such as Cas9, to cells in animal models. This would open the door to many further experiments as well as to the development of new therapeutics.

Do you have any pets?

I have two adorable Havanese dogs back home in Maryland.

What's your favorite place in the world?

Airports. They're full of adventure and possibility — from an airport I can get almost anywhere else in the world. Also, sometimes they have good food.

What are you looking forward to discover in the Boston area?

I have been trying out many of the restaurants around Boston. Many of them have excellent food, especially in the North End and Brookline!

Introductions: Saket Bagde of the Springer Lab



Photo: courtesy of Xuanwei Huang

Tell us about your role here at PCMM.

I'm a Postdoctoral Research Fellow in Dr. Timothy Springer's lab. I'm a protein engineer and I am developing novel tools to reliably grow 'organoids' - miniature organs or patient-derived tissues - in a dish.

Where were you before HMS?

I was at Cornell University in Ithaca, New York, where I did my Ph.D. in Dr. Chris Fromme's lab. My thesis focused on understanding the design principles of large, modular protein complexes. I studied membrane trafficking, the cell's 'postal service', and investigated the activation of Rab GTPases that serve as "molecular barcodes" and regulate membrane trafficking.

I also studied the molecular assembly lines that produce antibiotics and captured the first high-resolution structure of an intact polyketide synthase (PKS) module. This revealed a surprisingly asymmetric 'pendulum mechanism' for how it works, which provides a new blueprint for engineering PKSs to produce novel therapeutics.

What's your favorite piece of lab equipment?

I'd have to say the centrifuge. It's both terrifying and incredibly useful. It's the only machine in the lab that sounds like it's preparing for takeoff, which really adds a sense of highstakes drama to just pelleting cells.

What is the best piece of advice you've ever received?

I did most of my Ph.D. on yeast, so when I was about to start learning mammalian cell culture, I was intimidated. I remember my advisor said, 'Don't worry, it's just like growing yeast... they just have a fancier diet.'

I believe it was his way of reminding me that even a complex new skill is built on the same core principles of care and rigor I already knew. I'm finding it just as true for learning to grow organoids - which have an even fancier diet.

What made you pursue a career in science?

After high school, I started in a mechanical engineering program in India but soon realized I missed biology. I decided to switch to research, an unpopular move, as it meant leaving a secure career path for an uncertain one; but my family supported me. My father is both an engineer and a social worker. Growing up, I'd asked him why he bothered with social work instead of just focusing on engineering. When I told him I wanted to switch, he asked me why. I said, 'I'll be happier doing this, and it's a path where I can ultimately help people.' He replied, 'Now you have the answer to why I do social work.' That motivation helps me to this day.

Introductions: Saket Bagde of the Springer Lab

What are your research interests?

My research addresses a fundamental question: How are specialized tissue and organ structures formed and how are these processes disrupted in disease? Organoids are powerful models to study this, but their utility is severely limited by the undefined and inconsistent nature of the growth substrate used in current protocols.

My current focus is on replacing this substrate. I'm using a multidisciplinary approach of structural biology and protein engineering to develop a fully-defined, synthetic basement membrane mimic. The goal is to establish the fundamental design principles of cell-matrix adhesion and then use those rules to engineer a substrate that can potentiate the growth of robust, reproducible organoids for therapeutic testing and, ultimately, 'patient avatars'.

If you had unlimited funds, what kind of research would you conduct?

I would conduct this exact research, but at a scale that's currently impossible. My project is high-risk and aims to build something new from the ground up, which is tough to fund through traditional grants.

With unlimited funds, I would build a high-throughput 'Organoid Foundry.' We could use Al-driven protein design and robotics to create and test thousands of different 'smart soil' compositions in parallel, not just for epithelial organoids, but for complex, multi-cell type systems, like organoids with their own integrated immune systems, and eventually make full organs! We could finally crack the code for personalized medicine!

If you were a molecule or a protein, what kind would you be and why?

I'd have to say an integrin. Integrins act like molecular hands, reaching out to grab the matrix outside the cell. But what I love is that they aren't just static anchors. To do their job and send signals inside the cell, they undergo these massive, beautifully choreographed conformational changes - they bend, extend, and move with real purpose.

As a trained Indian contemporary dancer, that idea really resonates with me. It's a perfect connection between intricate, purposeful movement and communicating a vital message.

What profession would you choose if you weren't a scientist?

I would absolutely be an artist. My mother inspired my love for painting and dance, and it's a huge part of who I am.

I'd probably split my time between a canvas and a dance studio. In a way, I already try to bring that artistic side into my science; my interest in dance helps me appreciate the 'choreography' of proteins, and solving and illustrating protein structures feels like getting to paint the beautiful, intricate machines of life.

What are your hobbies outside the lab?

I love to paint and I'm also a huge Bollywood fan, so I'm always trying to learn hook steps from the latest songs. When I need to relax, I enjoy hiking, gardening, and surprisingly - watching a good horror movie.

Faculty News

Sun Hur Elected to National Academy of Medicine



Sun Hur, PhD, was one of almost 100 individuals elected to the National Academy of Medicine (NAM) this October. The NAM website states: "Election to the Academy is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service." Dr. Hur is cited "for elucidating the self versus non-self RNA discrimination mechanism for the RIG-I-like receptors, revealing macromolecular assemblies that set a paradigm for sensing foreign nucleic acids in the innate immune system. Her recent findings on FOXP3 and AIRE expanded these mechanisms to transcription factors, with far-reaching implications beyond immunology."

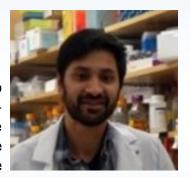
Congratulations to Sun on achieving this high honor!

Alumni Careers

Senior Scientist in Biotech Industry: Dr. Setu Vora

This month, <u>Dr. Setu Vora</u>, a former postdoctoral fellow at <u>Wu lab</u>, talked about his experience in biotech industry, from his role as a Senior Scientist at <u>Evolved by Nature</u>. Here are some of his thoughts:

General outlook: Dr. Vora applied to industry positions in 2022, when the job market was still strong. Many companies were hiring, there was a lot of investment into biotech, and the interest rates were low. Overall, it was a good time for finding an industry job, whereas now the job market is tough. In general, the environment in biotech industry can be less stable than in academia, and one



needs to keep track of the current market trends. For example, if a company's drug patent is running out, that means they will have less funding at some point, with potential implications for employment rates.

The application process/interview: During the strong 2022 season, Setu landed 3 interviews in total, by just applying for the positions online. [The current, much more competitive 2025 job market certainly requires additional efforts, like networking]. For the interview talks, Dr. Vora advises to focus on one's previous research that's most relevant to the company's work (if one has a choice). Specifically, focus on 1 relevant project as opposed to talking about 2 projects, where one is relevant and the other - not. Additionally, for negotiating the offer, since each situation is different, Setu suggested consulting with an independent recruiter.

The position: Setu's drug discovery background helped him secure the position, in which he conducted assay validation. The important skills that helped Setu in the biotech setting were collaboration and communication to a broad audience. In the Wu lab, Setu has worked on drug discovery and collaborated with scientists from different backgrounds (i.e. chemists, physicians, etc). Additionally, at the biotech company, he had to present his progress to a wide audience (including company members without a scientific background), so being able to convey the major points without too many technical details is an important skill to have.

Thanks to Dr. Vora for taking the time to talk about his experience! We'll be continuing talking to PCMM alumni in biotech industry.