Program in Cellular and Molecular Medicine
at Boston Children's Hospital

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Greetings, PCMM,

Happy Spring! We hope that everyone is getting a chance to enjoy the warmer weather (even it it's still fluctuating a bit).

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

In this issue

Spring is Finally Here

Introductions: Quentin Smith of the Ha Lab

Photo: courtesy of Quentin Smith

Tell us about your role here at PCMM.

I am a joint postdoctoral research fellow in the labs of Taekjip Ha (BCH) and Lucas Farnung (HMS).

Where were you before HMS?

I was a graduate student at Imperial College London, UK in the lab of David Rueda, researching CRISPR Cas9 off-targeting and developing high-fidelity genome editors.

What's your favorite piece of lab equipment?

Nanodrop, it's such a chill piece of equipment, reliable and versatile.

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

"It's not really who you know, but it's who knows you."

What made you pursue a career in science?

My biology teacher in secondary school, made science sound exciting and career-wise limitless!

What are your research interests?

I enjoy basic science, understanding how proteins perform their transactions on nucleic acids like DNA. Biophysical techniques like single-molecule fluorescence and cryo-genic electron microscopy (Cryo-EM) are tools that I love to use. I aspire to sit at the interface of science by using these findings to develop tools that can explored further in a clinical/ therapeutic setting.

What recent scientific breakthrough is most exciting to you?

Use of CRISPR to treat genetic diseases. Since its conception, it has made a fast and substantial impact from bench to clinic. I have high hopes that with future advancements in its delivery, efficiency and portability - it will become a routine therapeutic. That's what makes me excited, when science leaves the labs and changes the lives of people in need.

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

A video game content creator.

What are your hobbies outside the lab?

I enjoy playing video games and table tennis!

What kind of music and/or podcasts do you like?

Various genres, I am quite flexible on music taste. Growing up in East London, I listen to Grime quite a lot, it's rap/hip-hop but at 140 bpm. Podcasts, anything funny.

What is your favorite book or a book you've really enjoyed recently?

Code Dependent by Madhumita Murgia, this is an eye-opening account of how AI has already changed the lives of many across the world.

Do you have any pets?

I have an adorable orange/white pet cat called Mango, she's the greatest!

What's your favorite place in the world?
London, UK. It has it all.

What are you looking forward to discover in the Boston area?
I am looking forward to discovering fun things to do in the summer. Right now, it's very cold and slushy outside, so I'd rather stay indoors.

Do you have any secret talents?
Wouldn't be so secret if I told you now!

What is your favorite holiday destination?
Philippines! Had a blast with my wife in Manila & Boracay.

What is your favorite season? Summer!

What is your favorite video game?
Metroid Fusion on the Gameboy Advance.

City or countryside? City.

Fiction or non-fiction? Non-fiction.

What is something on your bucket list?
To see the Northern Lights.

Did you always want to be a scientist?
Yes, I really enjoyed practical sessions during my undergraduate degree, and summer internships and studentships really solidified it!

Of what accomplishment are you most proud?
Making it through my PhD - I have my PhD degree and will have my official graduation day this summer!

If you have a pet, what is one of their eccentric behaviors?
Mango plays fetch, like a dog with her soft felt balls, she retrieves and waits for us to throw it again – odd for a cat but fun!

Lunch Conversations with Seminar Speakers

On February 19th, Dr. Wei Yang of the National Institutes of Health (NIH) visited PCMM to give a seminar titled "From RAG to NHEJ: Splicing Together Our Adaptive Immune System." As part of her visit, she had lunch with PCMM trainees and shared her thoughts on a variety of topics:

Photo: courtesy of Dr. Yang

On searching for a faculty position: Dr. Yang, similarly to previous PCMM seminar speakers, did acknowledge the difficulty of securing a faculty position now and suggested that other parts of the world, like Europe, could be an option. Additionally, hospital networks in the United States, like the Mayo Clinic or City of Hope hospital systems, are excellent locations for research and offer well-funded research opportunities.

On her own scientific journey: In terms of finding the "right" postdoctoral lab, Dr. Yang emphasized the importance of a good fit. When she was looking for a lab for her postdoc, she talked to various scientists about potentially promising areas of research and also looked for labs in particular geographic areas. The lab that she finally chose was the one where she felt like she fit right in with the team. She emphasized the right fit over the specific research

question studied, since the specific question might evolve depending on where the research project takes one. During her postdoc at Yale University with Dr. Thomas Steitz, she was looking to study the RAG enzyme (responsible for V(D)J recombination in antibody generation), for which her advisor told her the timing was not right, so she worked on determining structures of other enzymes, before turning her attention to RAG again as an independent investigator at NIH.

She joined the NIH after her postdoc due to several factors, including stable funding and a strong collaborative environment. The physical layout of NIH purposefully includes shared common spaces to facilitate interactions and collaborations between researchers, and researchers are very invested in each other's success. Dr. Yang mentioned that her NIH job offer letter had a personal touch, where all of the department researchers signed her letter. In terms of funding, the investigators don't have to write grants (but do get evaluated every 4 years) and don't have teaching responsibilities, allowing for more time to be devoted directly to research. On a sidenote, the process of applying for an NIH investigator position is very similar to a faculty recruitment process.

On the atmosphere at NIH right now: Dr. Yang described the situation at the NIH as not so great at the moment. Last year, there was a hiring freeze, many people left, and several new faculty had been let go. This was a discouraging situation, but fortunately, the hiring freeze was lifted on October 15, 2025, and recruitment of junior faculty will be resumed this year. In addition, even though there is increased funding available for each group due to the decreasing number of scientists, the closure of the NIH procurement office last year limits how much a lab can spend per month and significantly slows down research. Additionally, international travel has been restricted. Despite these setbacks, Dr. Yang hopes that this rough patch can eventually reverse in a few years.

We thank Dr. Yang for meeting with PCMM trainees and sharing her insights – we appreciate her optimism in these challenging times.

PCMM Researcher Wins a Prestigious Fellowship

Ayijiang Yisimayi, PhD, (Lieberman Laboratory) has been awarded a Helen Hay Whitney Fellowship. Her research focuses on developing strategies to harness the immune system to treat cancer. Many tumors accumulate cytosolic DNA due to chromosomal instability, which acts as a danger signal and triggers strong immune activation. Building on this, Ayijiang aims to convert immunologically "cold" tumors into "hot" ones by mimicking the potent immune responses of mismatch repair–deficient (MMRd) tumors. She will investigate how chromosomal instability drives anti-tumor immunity and explore how T cells can eliminate tumors independently of classical antigen presentation. In addition, she will examine how this approach induces durable and broad immune protection against diverse tumor types.

Photo: courtesy of Ayijiang Yisimayi

Alumni Careers

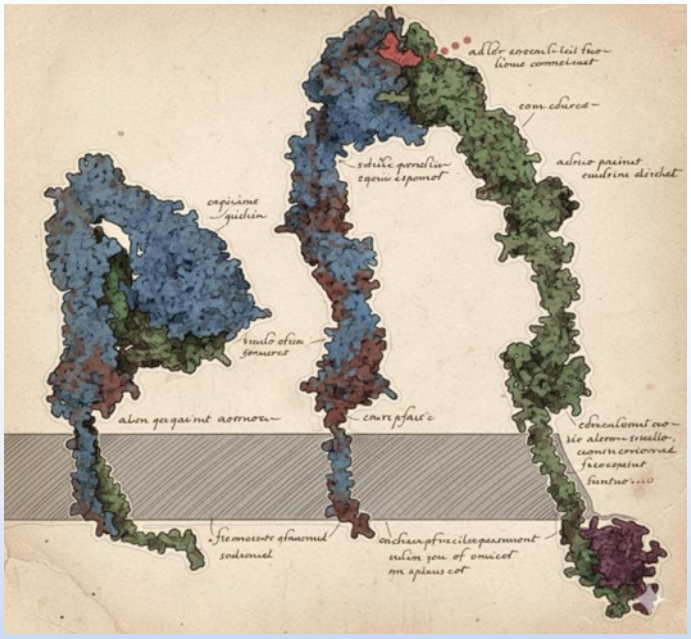
Associate Vice President, Molecular and Cellular Science at Eli Lilly: Dr. Albert Lin

This month, Dr. Albert Lin, a former postdoctoral fellow at Dr. Tim Springer's lab, talked about his journey from PCMM to Biotech industry. He has worked both at a start-up company which he co-founded, Morphic Therapeutic, and is now working for the largest pharmaceutical company in the world, Eli Lilly, and shared his insights below.

Photo: courtesy of Albert Lin

On his time as a postdoctoral fellow at Dr. Springer's Lab: Dr. Lin joined the Springer lab with 2 main goals – to study the structures of integrins in complex with protein ligands via X-ray crystallography and to figure out how to make better small molecule inhibitors for integrins, since his background was in structural biology and structure-based drug design. His goal at the time was to become a professor.

On integrin biology and Dr. Lin's major discovery: Integrins are validated targets in multiple diseases, including inflammatory bowel diseases (IBD). While there is an approved antibody treatment (vedolizumab) that targets $\alpha_4\beta_7$ integrin, it is very inconvenient for IBD patients (due to the need for recurrent injections) and a high cost. An alternative – oral small molecule inhibitors – has been challenging to create, in part due to them acting as partial activators as their systemic concentration decreases. The mechanism for partial agonism was postulated to be caused by drugs that inadvertently trigger the activated "open confirmation" of integrins.



Integrins consist of two subunits, α and β, and adopt open (right) or closed (left) conformations corresponding to their active or inactive states. Image: courtesy of Albert Lin.

During his postdoc, Dr. Lin discovered a key chemical principle for designing integrin inhibitors that fully stabilize the "closed" integrin conformation. This is highly desirable since these "closing" integrin inhibitors do not act as partial activators. Moreover, he showed that this principle can be generalized and applied to other members of the integrin family.

Dr. Lin remembers when he finally cracked the problem in 2014 – he emailed Dr. Springer on a Saturday, and they met the next day in the lab. Upon seeing the results, Dr. Springer got very excited and suggested that this was a finding for a new biotech company. Thus, this discovery led Dr. Lin onto a path in biotech, as a co-founder of Morphic Therapeutic. (The *Cell* publication on this discovery was eventually published in 2022.)

On creating Morphic Therapeutic: Once they decided to build a company, Dr. Springer and Dr. Lin communicated with investors to present the data and secure funding. Meanwhile, they were also working on patenting the discovery with the TIDO office at BCH, and it turned out that since the discovery principle is relatively general, it is not patentable. Instead, it was categorized as a "know-how" by BCH, and Morphic ended up licensing the "know-how" from BCH. Later, Morphic also licensed numerous protein constructs, stable cell lines, and a method for stabilizing integrin heterodimers generated by many different postdocs in the Springer lab throughout the years. All the inventors benefited financially as a result, especially after Morphic went public in 2019.

Dr. Lin was initially given a title of Senior Scientist. As the company was originated from his discovery, this might be surprising to some, as in other instances, one might hold a much more senior role of their newly founded companies. However, to Dr. Lin, it was a blessing in disguise in that there is so much one needs to learn and experience before developing into a senior executive. As a scientist, he was able to focus on growing his technical expertise and knowledge and delivering key data needed for the company to succeed. At Morphic, he worked very hard, including weekends and nights, and advanced his career quickly. As he rose through the ranks, he developed leadership skills and crucial knowledge in other disciplines of drug discovery and development. In 2023, MORF-057, an oral small molecule inhibitor of $\alpha_4\beta_7$ integrin for IBD that Dr. Lin co-invented, returned positive Phase 2 data. Morphic was acquired by Eli Lilly as a subsidiary in the summer of 2024.

On working at Eli Lilly: In comparison to Morphic, Eli Lilly is a much bigger organization, thus has its own advantages and challenges. For example, for a given problem, large companies have a vast amount of resources to go both in depth and breadth. However, things tend to move a lot slower in big companies. Additionally, Big Pharma often focus on diseases with a large market, and unfortunately rare diseases often do not fit that category.

On what he looks for in perspective job applicants: In addition to an excellent technical background (for which Dr. Lin complimented PCMM postdocs), another aspect that Dr. Lin looks for is teamwork and leadership. He works with many smart people, and, naturally, some smart people might think their solutions and ideas are the best ones. So, he emphasized the importance of learning to collaborate well and be open to ideas from other people – a concept which sounds very simple but can sometimes be very hard to accomplish in practice. In many cases, there can be more than one way of getting from point "A" to point "B", so it's important to listen to different ideas on how to accomplish a goal.

Additionally, for applicants who would like to eventually acquire leadership positions in biotech, he advises to think about building those leadership skills, which include collaborating in your academic projects with others, and, again, being open to others' ideas. Dr. Lin's philosophy as a manager and leader is that, since he hires smart people, he does not need to be very directive with them but instead gives them the resources and freedom to figure out how to solve a challenging scientific problem.

We thank Dr. Lin for taking the time to share his insights! We'll be talking to more PCMM alumni in the future.