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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Greetings, PCMM,

We hope that everyone is getting a chance to enjoy the weather (minus the humidity) and is also staying cool.

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

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Summer Greenery

Introductions: Young Hun Kim of the Ha Lab

Photo: courtesy of Dr. Kim

Tell us about your role here at PCMM.

I am a postdoctoral researcher in Dr. TJ Ha's lab and I joined August 2025. My project is to develop a DNA-based force spectroscopy platform using CRISPR-Cas9 protein for precise targeting. This new technique could contribute to understanding DNA-protein interactions such as DNA double strand breaks and DNA mismatch repairs.

Where were you before HMS?

Previously, I was at Memorial Sloan Kettering Cancer Center in New York, where I had the opportunity to collaborate with scientists across a wide range of disciplines, including cancer biology, immunology, developmental biology, and molecular biology. As a senior scientist, I've contributed to diverse research efforts by providing biophysical and mechanobiological insights from multiple perspectives. Using atomic force microscopy (AFM), I've imaged newly synthesized lipid nanoparticles, nucleosomes, DNA, and proteins for structural and functional characterization. I've also characterized mechano-biological properties spanning from single cells to human tissues to better understand processes involved in cancer metastasis and conducted ligand screening on extracellular vesicles (EVs). Collaborating with researchers who brought different scientific backgrounds and viewpoints was an especially valuable experience. These collaborations deepened my understanding of multiple research areas and allowed me to expand, integrate, and share knowledge and scientific perspectives across disciplines.

What's your favorite piece of lab equipment?

My favorite piece of equipment is the microscope. It is a powerful system to visualize data and to strongly support it. Seeing is believing!

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

"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less." (Marie Curie's quote)

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

Marine biologist, especially those who study whales. Whales are the largest mammals in the world, and even though they spend most of their lives underwater, they're incredibly well-adapted to stay submerged for long periods of time. Pretty impressive for an air-breathing mammal underwater!

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

A book I recently finished is *The Vegetarian* by Han Kang. I was really impressed by her writing style. In this book, she describes power and violence in such a calm, restrained way, which somehow makes it even more intense and unsettling.

Do you have any pets?

Not yet, but I love to have a cat as part of my family someday.

Lunch Conversations with Seminar Speakers

Dr. Ruaidhrí Jackson of Harvard Medical School visited PCMM back in April to give a seminar titled "The discovery of protein-coding chimeric mRNA in mammalian immunity." As part of his visit, he had lunch with PCMM trainees and shared his thoughts on a few topics.

Photo: courtesy of Dr. Jackson

Originally from Ireland, Dr. Jackson conducted his postdoctoral studies in Dr. Richard Flavell's lab at Yale. He then started his own lab at Harvard Medical School in 2019, had a slow start as the pandemic started, but is now up and running. Dr. Jackson's lab follows several lines of research: non-canonical genetics in the context of immunity, immune functions of neurons that innervate different organs, and immune cells' use of mechanosensory ion channels to trigger inflammation in response to mucosal infection and fibrosis. Dr. Jackson was able to secure funding for his novel/high-risk projects in part due to his strong publications from his postdoctoral training.

On how he chooses research projects: Dr. Jackson tries to choose topics that he thinks will be important, have high impact, and for which he can convince others to get funding. The other consideration for topics is whether they can be published in top scientific journals, since that is part of the academic funding and promotion process, for better or worse. The other practical part considered is the feasibility of the project. As the projects are carried out, they are periodically evaluated to see if they are worth pursuing further or if they should be terminated. Dr. Jackson pairs high-risk projects with low-risk ones and pitches to students, which greatly paid off for one of his students for the chimeric mRNA project. Dr. Jackson's philosophy is that he's interested in high-impact research, and if one is going to do a lot of hard work, one might as well do it on a high-impact topic.

On scientific collaboration: The chimeric mRNA project (that was the focus of his talk) was greatly facilitated by collaborating with PIs he met at other conferences, as they joined forces and collaborated on unpublished data. Additionally, the project was greatly facilitated with Hao Wu's and Judy Lieberman's labs, among others in the Longwood area. A reviewer's suggested experiment was made possible by one of Hao Wu's postdoctoral fellows, Gang Du, who now has his own lab in China. Collaboration is key in research, since one's lab has finite expertise and resources, and it's seemingly impossible to complete publications with current standards without collaboration. Dr. Jackson gave very appreciative feedback on the supportive environment he encountered at Harvard.

Research Highlights

The Alt Lab Identifies Convergent Antibody Solutions Using Focused Humanized Mouse Models

A study, from the laboratory of *Dr. Frederick Alt*, led by Himanshu Batra and collaborators, reports a remarkable molecular convergence in antibody responses generated from humanized mouse models with a focused immunoglobulin gene repertoire.

Fred Alt and Himanshu Batra

The exons that encode Variable regions of antibody heavy (HC) and light (LC) chains are assembled from germline immunoglobulin V (variable), D (Diversity), and J (Joining) gene segments during B-cell development by V(D)J recombination. Antibodies mostly recognize an antigen through complementarity-determining regions (CDRs). Two CDRs (CDR1 and CDR2) are encoded by each of the approximately 100 V_H and V_L gene segments, with their sequence usually unique to a particular V_H or V_L. In contrast, CDR3 sequences of given HC or LC variable regions are encoded by $V_H(D)J_H$ and V_LJ_L junctional sequences, respectively. Because junctional diversification creates far greater sequence diversity than V_H and V_L assortment alone, CDR3 is by far the major source of primary antibody repertoire diversity. The number of CDR3 sequences that can be generated through junctional diversification exceeds the number of B cells in mammalian immune systems by many orders of magnitude. Thus, the relative size of the primary B cell receptor (BCR) repertoire in humans and mice is determined by the number of primary B cells in their immune system.

Standard Immunoglobulin (*Ig*) gene-humanized mice that have been used to discover many clinically important humanized antibodies, rearrange the full complement of human *Igh* and *IgL* variable region gene segments. Therefore, a single antibody discovery mouse of this type expresses only a tiny fraction (0.1%) of the CDR3 diversity present in a primary human BCR repertoire, because a mouse has 1000-fold fewer B cells than a human. To attempt to enhance discovery of antibodies based on focused diverse CDR3s, Dr. Alt's group generated a humanized antibody discovery mouse model that generates a primary humanized B cell receptor repertoire exclusively from a single human V_H1-2 and, dominantly, from a human Vκ1-33, each in association with an immense diversity of CDR3s. Immunization of this model with SARS-CoV-2 D614G spike elicited an antibody that potently neutralized SARS-CoV-2 variants through Omicron BA.2.75.4.

A new study published in PNAS (*Batra et al.*), describes a modified version of their original antibody discovery mouse model in which they introduced human D3-3-J_H6 rearrangement cassette in place of the proximal mouse D and J_H1-4 segments in their original V_H1-2/Vκ1-33 rearranging mouse model to generate the "single V_H1-2/hD3-3-hJ_H6/Vκ1-33" rearranging mouse model. The hD3-3-hJ_H6 junctional combination also can encode human-like HC-CDR3 sequences that are much longer than those encoded by mouse D and J_H combi-

nations. Thus, this new model provides a modified version of their original antibody discovery model that expresses a broader length range and a largely different set of human-like HC-CDR3 sequences. They immunized both original and newly generated antibody discovery mouse models with the same Omicron BA.4/5 spike-ferritin nanoparticles. Upon immunization, each model yielded four independent antibodies that broadly and potently neutralized most downstream Omicron variants. Surprisingly, the Omicron bnAbs from both models had 12AA HC-CDR3s, despite the new model predominantly generating much longer CDR3s. In addition, all but one of bNAbs from both models contained pairs of adjacent aromatic residues in the center of their HC-CDR3s. Remarkably, all 8 of these Omicron bnAbs targeted the same conserved Omicron-specific epitope. A leading antibody from each set protected mice from lethal Omicron BQ.1.1 challenge.

This study highlights how viral evolution can create new antibody vulnerabilities while enabling escape from prior immunity. In Omicron, the variant founding S373P mutation and associated conformational changes in the receptor binding domain (RBD) created a previously inaccessible epitope that was recognized by each of the 8 neutralizing antibodies primarily through their CDR3 sequences. Thus, the convergent neutralizing antibodies identified in this study exploit an Omicron-specific structural vulnerability that was not present in earlier pre-Omicron SARS-CoV-2 variants. This convergence also illustrates a broader immunological principle: despite the enormous diversity of possible antibody sequences, structural compatibility between antibody and antigen can strongly constrain the most effective neutralization pathways. Understanding these constraints can help guide the discovery of potent antibodies and inform vaccine strategies designed to elicit protective antibody lineages against evolving viral pathogens.

Beyond vaccine design implications, the study further validates the utility of single-human-V_H- and Vκ-rearranging mice for discovering humanized antibodies that neutralize emerging pathogens. By restricting V_H and Vκ usage while preserving extensive CDR3 diversity, this strategy increases the likelihood of generating antibodies with rare CDR3-driven binding modes that may not be present in other types of antibody discovery mouse models. The model also provides an experimental system for studying how antibody sequence diversity is translated into antigen recognition and protective immunity.

Read the full findings by Batra et al., and a deeper summary of the system and the significance of the findings in the *PNAS commentary** that accompanied this article.

* For access to the full commentary, please contact Himanshu Batra at Himanshu.Batra@childrens.harvard.edu.

PCMM Researchers Win Prestigious Fellowships

Photo: courtesy of dr. Zhang

Sherry Zhang, Ph.D., an instructor in the Hur Laboratory, has been awarded an NIH Exploratory/Developmental Research Project Grant R21. The transcription regulator Aire plays a pivotal role in immune tolerance by enforcing the ectopic expression of peripheral tissue antigens (PTAs) for negative selection of autoreactive T cells in the thymus. Defects in Aire result in manifestations of autoimmune polyglandular syndrome type 1 (APS-1). The goal of this grant is to elucidate the molecular mechanism of Aire in transcriptional regulation, with a specific focus on dissecting the spatial and temporal relationships between Aire transcriptional condensates and Aire-targeted PTA loci. This project is expected to address key gaps in our understanding of how Aire regulates PTA gene expression and have a broad impact on the field of transcriptional regulation.

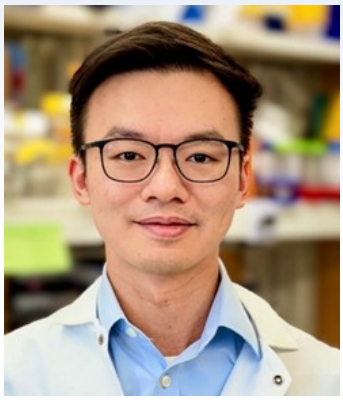

Photo: courtesy of dr. Chen

Po-Ta Chen, Ph.D. (Ha Laboratory), has been awarded a Cancer Research Institute Irvington Postdoctoral Fellowship. Po-Ta will study why exhausted CD8 T cells in tumors often remain dysfunctional despite PD-1 immune checkpoint blockade. His project focuses on whether the three-dimensional folding of DNA helps stabilize the molecular program of T cell exhaustion. To investigate this, Po-Ta developed GOLDFISH-X, a genome imaging technique that avoids heat denaturation and can measure DNA organization, gene activity, and local protein environments in the same single cells. He will apply this platform to key exhaustion-associated genes with the goal of identifying mechanisms that could be targeted to improve the durability of cancer immunotherapy.

Faculty News

Photo: Greg Kahn / HHMI

Dr. Yi Zhang, Ph.D. was one of the 120 individuals elected to the National Academy of Sciences this year. Members are elected "in recognition of their distinguished and continuing achievements in original research." Dr. Zhang's pioneering work in epigenetics and chromatin biology has included the discovery and characterization of novel histone methyltransferases and the JmjC histone demethylase family; 5-formylcytosine and 5-carboxylcytosine as new intermediates in the DNA demethylation pathway, and their generation by Tet proteins; and H3K27me3-mediated genomic imprinting and its role in X-inactivation and animal cloning efficiency. Of particular note, he established the canonical model of how the Polycomb group (PcG) proteins silence gene expression, a longstanding mystery in the fields of development and genetics, showing that Polycomb repressive complex 2 (PRC2) trimethylates lysine 27 of histone H3 (H3K27me3), recruiting Polycomb repressive complex 1 (PRC1) to catalyze ubiqutination of lysine 119 of histone H2A (H2AK119ub).

Photo: courtesy of Dr. Springer

Timothy Springer, Ph.D. was named as one of America's 250 greatest innovators by Forbes magazine. The innovators were selected based on their creativity, breadth, engagement, disruption, and commercial impact, part of a yearlong series of special reports to celebrate the 250th anniversary of the United States. Forbes describes the innovators as not "just inventors; they're business leaders who bring their breakthroughs to market, transforming entire industries and creating new ones." Prof. Springer is cited for discovering the immune "keys" to fight disease and for cofounding Moderna.

Dr. Springer was also named as one of the year's 150 Most Influential Bostonians by Boston Magazine. The yearly list aims to "highlight the people shaping how Boston lives, works, thinks, and feels." Dr. Springer's mention describes him as follows: "The founding investor behind Moderna is also a Harvard professor, a serial biotech entrepreneur, a philanthropist who has endowed programs and professorships all over town – and an obsessive collector of gongshi, the ancient Chinese scholars' rocks he loves so much, he named a biotech company, Scholar Rock, after them."