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's having a good summer. It's that time of the year again to register for the annual PCMM retreat — if you haven't already, please use this link to register by July 31st, and let us know if you have any questions!

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

In this issue

PCMM Retreat (2025)

Introductions: Stephanie Miceli of the Li and Wagner Labs

Photo: courtesy of Dr. Miceli

Tell us about your role here at PCMM.

I am a program coordinator for both Dr. Denisa Wagner and Dr. Julia Li. I'm a research admin, involved in personnel onboarding, finances, grant submissions, and coordinating the many aspects of daily research life. I'm also very involved in editing scientific manuscripts, abstracts, and grant proposals, which is my favorite part!

Where were you before HMS?

Before joining the admin part of science, I was a scientist myself. I did my PhD at Radboud University in the Netherlands, investigating the effects of antidepressant use on cortical microcircuitry in utero. I also did a postdoctoral fellowship at the Max Planck Institute in Bonn, Germany, where I established an electrophysiology lab for *in vivo* patch clamp in *Drosophila*. There, I got very involved in grant administration, equipment procurement, and budgeting, and I came to really appreciate the multiple aspects of project and research management. After that, I became a lab and department manager at the Cologne Excellence Cluster on Aging and Aging-Associated Diseases (CECAD). I loved the fast pace of the admin world, having to interact with so many different people and problem-solve. I moved to the US in 2024 and got my permanent residency. Now I'm here, in one of the greatest research hubs in the world, learning all about the American scientific environment, grant system, and more. It's very interesting.

What profession would you choose if you weren't in administration?

Probably scientific editing or publishing. I really enjoy the writing and critical review side of my work, reading across broad medical and scientific fields, getting the front-row to new findings. It would be a natural fit. But for now, I get all the work satisfaction I need in my coordination job! I've already learned about neutrophil extracellular traps, as well as how viral repeats cause genetic instability and cancer. It's important for me to work with passionate people, and my teams here at PCMM definitely are.

Favorite piece of equipment?

The amplifier. It allows you to measure tiny, electric signals from different cell types, and lets you record neural activity like action and local field potentials. Once you get comfortable with all the different knobs and settings, it becomes such a fun piece of equipment. You can use different gains and filters to visualize rhythms and strengths of brain networks. It's true that I sometimes miss the lab!

What's your favorite place in the world?

I lived in Germany for almost 20 years, and Berlin on a Sunday is the best. On Sunday, all shops and groceries are closed. People walk around the city, but there's no consuming, apart from ice cream! People walk, drink coffee, and look through the storefront windows. The streets are actually all pretty empty, and it's such a flash to feel this calm in one of the biggest metropoles in the world.

Lunch Conversations with Seminar Speakers

On May 21st, Dr. Steven Banik of Stanford University visited PCMM to give a seminar titled "Detecting and rewiring cellular interactomes." As part of his visit, he had lunch with PCMM trainees and shared his thoughts on a few topics.

Photo: courtesy of Dr. Banik

Dr. Banik did his Ph.D. in Chemistry and Chemical Biology at Harvard University and conducted his postdoctoral studies at the lab of Dr. Carolyn Bertozzi (2022 Chemistry Nobel Prize winner) at Stanford. For his postdoc, Dr. Banik switched from chemistry to synthetic and chemical biology, a pivoting decision in part based on the fact that he wanted to differentiate himself from others in the field of chemistry. He started his own lab at Stanford in 2021.

On the current academic job market: Dr. Banik agreed that the job market continues to be difficult. As part of a faculty search committee, he saw first-hand the challenge for the candidates to get hired for a position of Assistant Professor of Chemistry. Of the three finalist candidates in chemistry, the committee ended up not making an offer to any of them due to a non-optimal fit. In general, having a computational background is a big advantage, but one needs to show that this approach is the best for a given problem studied, and not just tacked on to fit the position description. The reviewers can usually tell the difference when looking at an application. [Having said that, different institutions have varying degrees of how specific of a skillset they're looking for in a professor candidate]. Additionally, the candidate should be prepared to have a plan of how/with whom one will collaborate on their research plan projects if the interviewing institution doesn't have the computational or other capabilities.

On choosing research projects: Coming from a chemistry background, Dr. Banik was interested in a variety of different biological problems. He chose a question that he could do excellent science on, and by which he could differentiate himself from other researchers. Additionally, he ran his research direction ideas by his postdoc mentor, Dr. Bertozzi, who approved them and his hiring decision. Dr. Banik's research directions ended up as: addressing protein (mis)localization and how manipulation thereof could provide therapeutic use and detecting and discovering rare pharmacologies through synthetic biology circuit development. An important technique currently being developed in his lab is for measuring small (but potentially functionally significant) differences in protein concentration during real time, which can be missed by standard techniques like Western Blot.

Research Highlights

Rejuvenating effects of interleukin-4 on blood stem cells

by Jingfei Yao and Vera Gaun, July 17, 2026

The processes of aging and chronic inflammation exhibit an imbalance in blood cell populations, leading to an expansion of myeloid cells (neutrophils and monocytes) while decreasing lymphoid cells (B cells and T cells). This, in turn, can further increase the levels of pro-inflammatory cytokines, driving a feed-forward loop and contributing to systemic dysfunction across multiple tissues.

Jingfei Yao

In a recent *Immunity* cover story publication, Jingfei Yao (first author) and Yuting Wang from the Zhang lab have identified the cytokine interleukin –4 (IL-4) as a signaling molecule that can restore the balance of lymphoid and myeloid cell populations, in turn resulting in positive systemic effects. Additionally, they further elucidated the underlying molecular mechanism.

Yi Zhang

For the initial screen, they tested a set of known pro- and anti-inflammatory cytokines *in vitro*. Only IL-4 resulted in inhibition of the myeloid differentiation. Additionally, they identified the particular blood cell populations responsive to IL-4: IL-4 promoted the transition of MPP2 and MPP3 cells toward the lymphoid-biased MPP4 state (Figure 1).

In addition, the authors have shown the signaling mechanism to be via the FLT3-STAT6 pathway (Figure 2). This was demonstrated both *in vitro* with STAT6 pathway inhibitors, as well as *in vivo* using STAT6 KO mice.

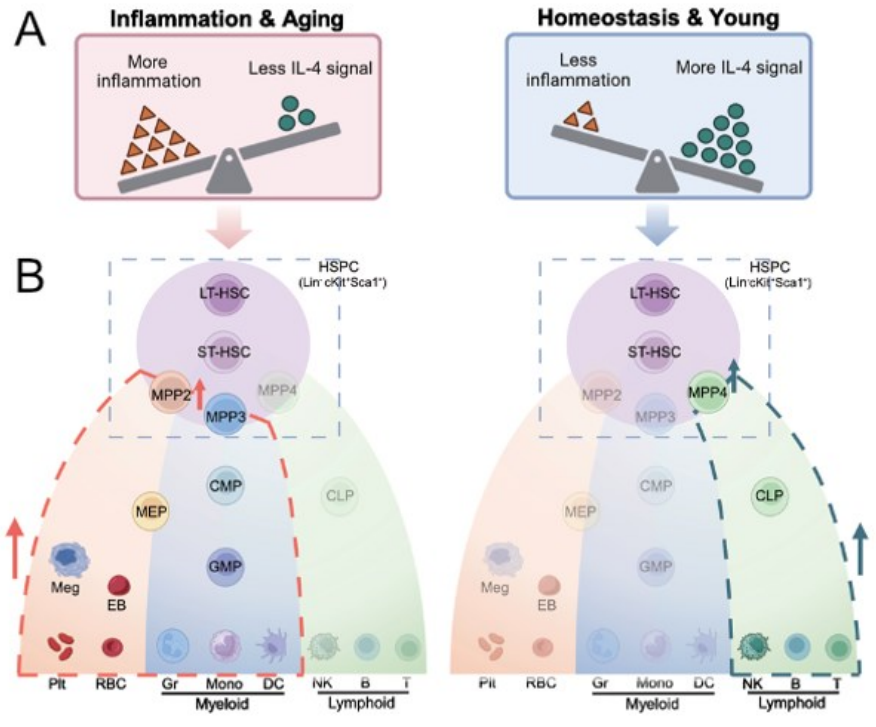

Figure 1. The balance of the myeloid and lymphoid lineages during different conditions. A) IL-4 signaling shifts hematopoiesis toward lymphoid output under homeostatic conditions. B) The hematopoietic cell hierarchy: long-term hematopoietic stem cells (LT-HSCs) differentiate into short-term HSCs (ST-HSCs), which then differentiate into lineage-restricted multipotent progenitors (MPP) 2, 3 and 4, which give rise to different cell lineages. Image: courtesy of Jingfei Yao.

Notably, IL-4 signaling was down-regulated in aged mice. Importantly, administration of IL-4 in mice with chronic inflammation and old age reversed the myeloid bias and restored B-cell and naïve T-cell production while reducing exhausted T cells, resulting in significantly improved overall systemic function (cognitive and muscle) and metabolic parameters.

Thus, IL-4 is a promising candidate for reversing age- and chronic inflammation-related myeloid bias and the accompanying negative systemic effects. How exactly IL-4 -mediated rebalancing of the lymphoid/myeloid cell populations affects different organs would be an interesting avenue to study. IL-4 can be a multifaceted therapeutic, since it could also be combined with immunotherapies to modulate them.

Despite its therapeutic promise, systemic IL-4 administration may carry potential risks because IL-4 is also involved in type 2 inflammation and has been implicated in tumor progression in certain contexts. Future strategies that enable targeted or transient delivery may maximize therapeutic benefits while minimizing adverse effects.

Jingfei concludes: "Our findings suggest that restoring lymphoid balance, rather than broadly suppressing inflammation, may represent a promising strategy to promote healthier immune aging."

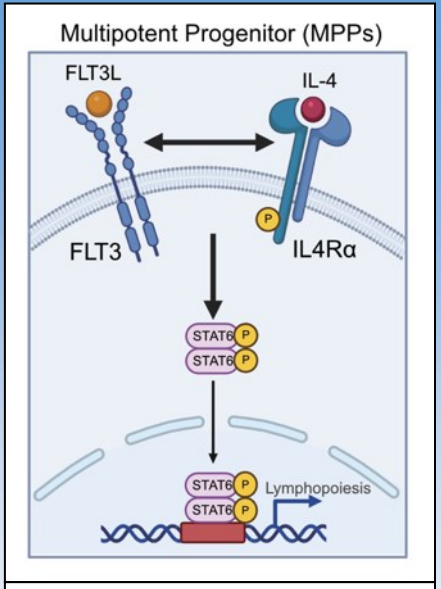

Figure 2. The IL4-FLT3-STAT6 axis is responsible for increased lymphopoiesis in MPP4 cells. The FLT3 receptor is selectively expressed on MPP4 cells and potentiates the effects of IL-4, resulting in increased STAT6 signaling and activation of the downstream lymphopoiesis transcription program. Image: courtesy of Jingfei Yao.

Note: for free access to the full article as well as the *Immunity* preview highlighting the study, please contact Dr. Yao at Jingfei.Yao@childrens.harvard.edu

PCMM Researchers Win Prestigious Fellowships

Photo: courtesy of dr. Le

Viet Le, PhD, an instructor in the Springer Laboratory, has been awarded an NIH R03 grant from the National Institute of Diabetes and Digestive and Kidney Diseases. Renal fibrosis is a pivotal factor in the progression of acute kidney injury to chronic kidney disease and ultimately end-stage kidney disease. Transforming growth factor β2 (TGF-β2) is an emerging mediator of renal fibrosis and therapeutic target. Viet's research focuses on understanding how integrin αVβ6 activates the latent form of TGF-β2. His R03 project will use super-resolution microscopy to map upregulation of proTGF-β2 and integrin αVβ6 as well as TGF-β2 activation in the renal fibrotic niche and investigate whether abolishing αVβ6-mediated TGF-β2 activation *in vivo* attenuates renal fibrosis using a newly developed mouse model. The overall goal of the project is to validate αVβ6-mediated TGF-β2 activation as a therapeutic target for preventing kidney fibrosis.

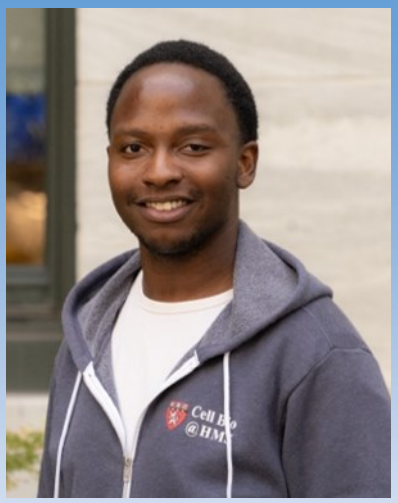

Photo: courtesy of dr. Smith

Quentin Smith, PhD (Ha & Farnung Laboratories) has been awarded an EMBO Postdoctoral Research Fellowship. Faithful cell division and proliferation depend on the careful coordination of essential molecular processes including transcription, DNA replication and repair. Although each process is vital, collisions between their molecular machines can threaten genome stability. Factors such as Transcription Termination Factor I act as critical roadblocks that help prevent these conflicts. As an EMBO Fellow, Quentin will develop biochemical, single-molecule, and structural approaches to characterize these interactions across scales. This work will advance our understanding of how essential chromatin-based processes are coordinated throughout the cell cycle.

Photo: courtesy of dr. Bi

Xiaotian Bi, PhD (Ha Laboratory) has been awarded a fellowship through the Protecting the Talent Pipeline in Neurodegeneration Program at BCH. Xiaotian is investigating the molecular mechanisms that drive CAG repeat instability in Huntington's disease (HD). Somatic expansion of the CAG repeat in the HTT gene is thought to contribute to disease progression, and DNA mismatch repair (MMR) proteins have emerged as key drivers of this process. However, how CAG repeat-containing DNA structures are recognized and processed to produce expansion or contraction remains poorly understood. Xiaotian's work uses single-molecule FRET to visualize the dynamics of CAG repeat DNA structures and their interactions with MMR proteins. She is also developing a sequencing-based MMR-seq platform in mammalian cells to connect defined slip-out DNA structures with cellular repair outcomes. By integrating single-molecule mechanistic measurements with sequencing-based outcome readouts, this work will help reveal the molecular events that bias repeat DNA toward expansion or contraction and provide a mechanistic framework for evaluating therapeutic strategies for HD.

Photo: courtesy of dr. Sun

Ninghe Sun, PhD (Zhang Laboratory) has been awarded a fellowship through the Protecting the Talent Pipeline in Neurodegeneration Program at BCH. Aging is the greatest risk factor for neurodegenerative diseases, including Alzheimer's disease, but how aging increases vulnerability to cognitive decline remains incompletely understood. Ninghe's research focuses on how age-associated molecular changes contribute to neurodegeneration, with a particular focus on Clusterin (Clu), a secreted protein that regulates amyloid formation in Alzheimer's disease. The induction of Clu is associated with aging, cellular stress responses, and decreased neuronal protection. By integrating molecular, cellular, and *in vivo* approaches, his work seeks to reveal the mechanisms linking Clu regulation to aging biology and progression of neurodegenerative disease, with the goal of identifying new strategies to preserve brain function, cognitive health, and to promote healthy aging.