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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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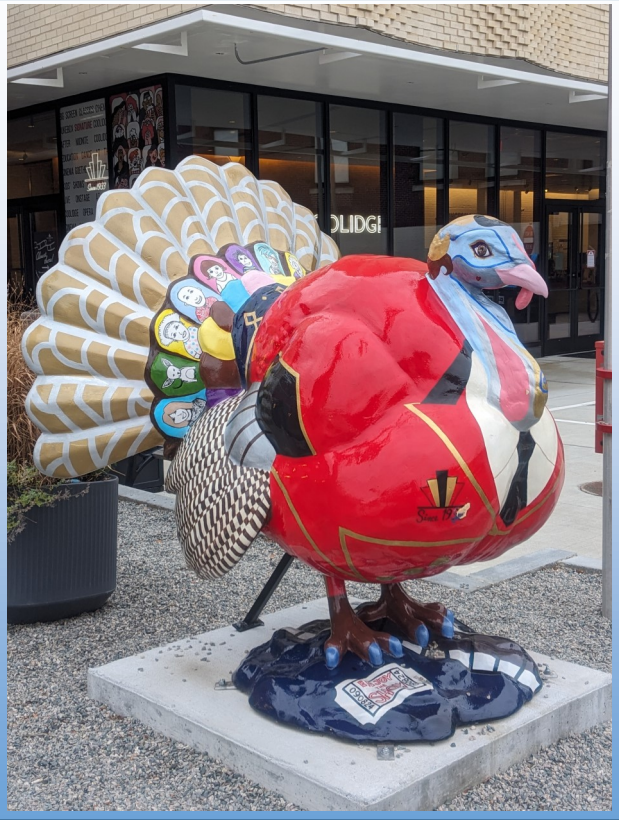
Greetings, PCMM,

We hope that those who celebrate had a good Thanksgiving, and to all — please enjoy the sculpture turkeys below. More of the public art turkeys can be found in the neighboring town of Brookline, and make for a fun scavenger hunt activity.

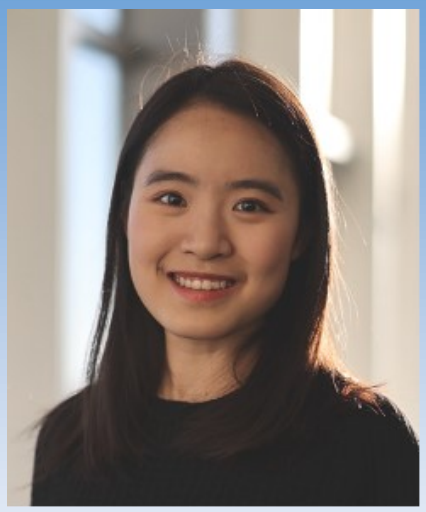
As always, if you have any suggestions for the newsletter, please contact us at vera.gaun@childrens.harvard.edu.

In this issue

Spotted Around Town



Introductions: Rena Ren of the Zhang Lab



Tell us about your role here at PCMM.

I'm a Postdoctoral Research Fellow in Dr. Yi Zhang's lab. I'm an RNA imaging technology developer and I'm currently developing new tools to visualize RNA dynamics in early embryos.

Where were you before HMS?

I was at MIT and Broad Institute in Cambridge, where I did my PhD in Dr. Xiao Wang's lab in the Department of Chemistry. My thesis focused on developing imaging-based spatiotemporal RNA sequencing technologies. As a graduate student, I developed new tools to study spatially resolved post-transcriptional RNA dynamics. Using them, I profiled spatiotemporal transcriptomes with 1-hour resolution in time and subcellular resolution in space in human induced pluripotent stem cell-derived cardiomyocytes and primary human skin cells. This led me discover that the kinetic steps of RNA life cycle were highly connected to their cellular functions, post-transcriptional modifications, cell types and time-sensitive cell cycle states.

What's your favorite piece of lab equipment?

My favorite lab equipment is a small vacuum aspirator called VACUSIP. This is the most useful tool I relied on throughout my PhD, and it was the first thing I asked to order when I started my postdoc. My experiments involve lots of adding and removing chemical solutions from solid-phase tissue samples, and this device makes my workflow fast and easier. It's also much easier to clean up than a normal vacuum filtration system.

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

"Surround yourself with kind and intellectually curious people."

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

If given unlimited funds, I'd be interested in studying the origins of life and origins of human consciousness.

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

I'd like to be a retrotransposon: a little unpredictable and always finding new places to belong.

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

One book I really enjoyed this year is *Why Fish Don't Exist* by Lulu Miller. It's an eye-opening example of how the past rigid scientific systems can shape our assumptions and the danger of scientists clinging to fixed labels. Plus, it turned out to be a fun education on fish.

Research Highlights

Uncoupling autoreactive B cell receptor expression from the breakdown of tolerance in lupus

by Kristine Oleinika and Vera Gaun, November 12th, 2025

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multisystem involvement, arising from the breakdown of B cell tolerance and the subsequent production of pathogenic autoantibodies. Many existing mouse models of lupus either yield inconsistent results or fail to recapitulate the natural progression of disease, so in 2017 the Carroll lab established a mixed bone marrow chimera model, in which autoreactive B cell receptor (BCR) knock-in B cells (564Igi) recruit wild type (WT) B cells into germinal centers (GCs). This WT B cell activation results in antibody diversification, referred to as epitope spreading, recapitulating lupus progression (Figure 1). Characterization of the WT B cell clones recruited into GCs within 564Igi:WT chimeras provided an opportunity to address key mechanistic questions, such as whether the WT B cell clones that undergo a break of tolerance can initiate autoimmunity independently, and what governs the inclusion of new B cell clones into GCs.

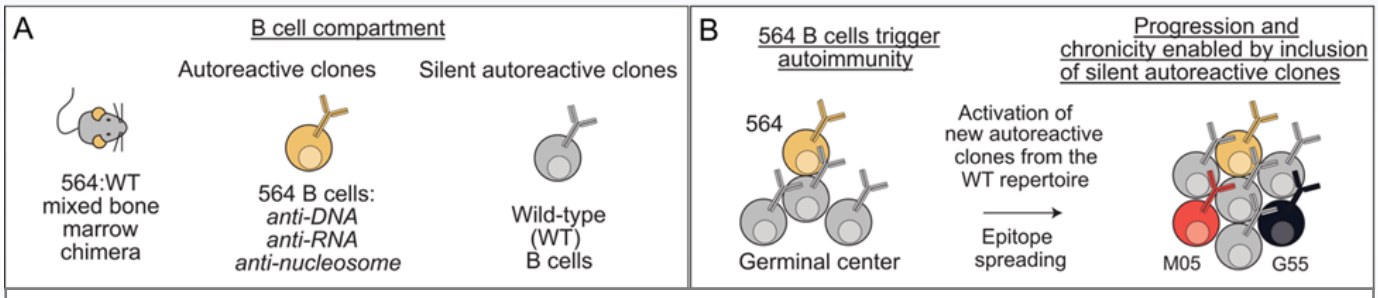
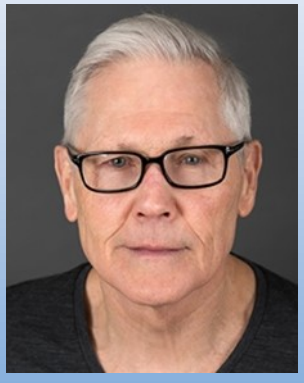


Figure 1. A) B cell repertoire dynamics and antibody diversification in autoreactive germinal centers can be modeled using mixed bone marrow chimeras. Silent autoreactive clones are B cells with intrinsic autoreactive potential that remain functionally inactive – unable to expand or become antibody-secreting cells – unless tolerance is overcome. B) Germinal center response in mixed bone marrow chimeras: autoreactive 564Igi B cells initiate the autoimmune response and recruit WT B cells into germinal centers, enabling the diversification of the autoantibody repertoire and lupus progression.

Two novel mouse models to dissect lupus initiation

Kristine Oleinika

In a recent *Cutting Edge* article published in the *Journal of Immunology* by the Carroll lab, Kristine Oleinika et al. addressed these questions by uncoupling autoreactive BCR expression from the activation cues that allow them to initiate autoimmunity. Using CRISPR, the team generated two new autoreactive BCR knock-in mouse strains, based on WT clones selected from the GCs in 564Igi:WT chimeras (Figure 1B): G55, which recognizes the Smith D2 protein, and M05, with specificity for single-stranded DNA and the chemokine CCL22. Both M05 and G55 reflect autoantibody specificities characteristic of human lupus. The authors then showed that these trans-



Michael Carroll

genic mice were not autoimmune – lacking GCs and autoantibodies – and that receptor editing contributed to establishing tolerance. However, in bone marrow chimeras with 564Igi B cells, both M05 and G55 clones were activated, enriched in GCs, and produced autoantibodies (Figure 2). Thus, not all autoreactive BCRs are equal at spreading autoreactivity, and a presence of autoreactive BCR is not sufficient to produce autoimmunity.

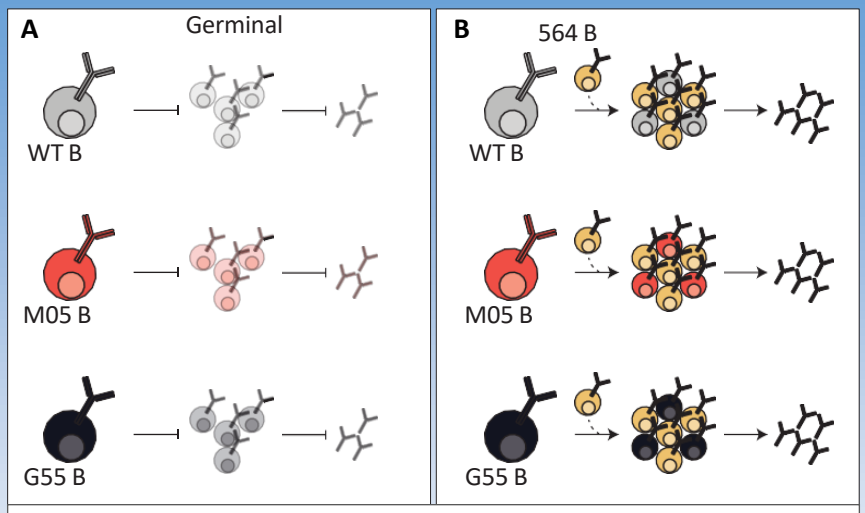


Figure 2. A) Peripheral tolerance is maintained in autoreactive BCR knock-in mice (M05 and G55). B) Tolerance is breached in germinal center niches established by 564Igi B cells.

Additionally, the authors observed that compared to WT B cells, M05 and G55 enabled greater autoantibody production by 564Igi B cells, suggesting inter-clonal modulation of autoantibody responses in lupus.

Further parsing the mechanism

The 2 novel autoreactive BCR transgenic mouse models enable deeper dissection of the mechanisms governing B cell tolerance breakdown. They demonstrate that the immune context – not just autoreactive BCR expression – determines whether autoimmunity is initiated. These models allow investigators to probe the cues that dictate why some autoreactive B cells can initiate lupus-like autoimmunity, while others remain functionally silenced. Potential mechanisms suggested by the authors include a threshold requirement for both T cell help and autoantigen displayed as immune complexes on follicular dendritic cells.

Kristine concludes: “Identifying the checkpoints that govern the early transition from B cell tolerance to autoreactivity will uncover the origins of systemic autoimmunity and guide the development of strategies to restore lasting immune balance.”

Kristine Oleinika, PhD, was the first author on the paper, and Michael Carroll, PhD, was the senior author. Other authors include: Alexia Correia Ferreira, Selma Mouftakir, Carlos Castrillon, PhD, Lisa Madungwe, Usha Nair, PhD, and Facundo D. Batista, PhD.