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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Happy June, PCMM —

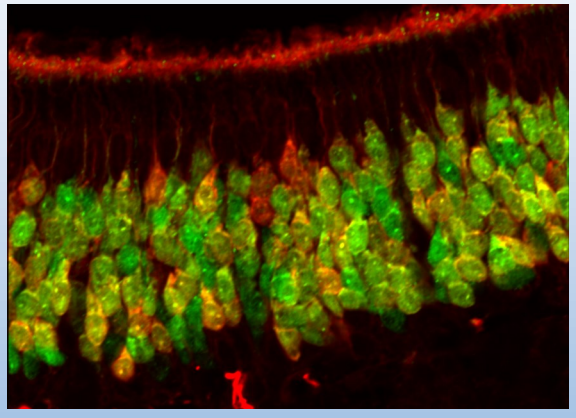
We would like to start highlighting PCMM alumnae careers. In this first run, we're highlighting a soon-to-be alum's success—Dr. Yu-San Huoh (Hur lab) recently accepted a tenure track assistant professor position! In future volumes, we'll continue highlighting alumnae career pathways from different fields, such as industry, scientific publishing, and others. As always, if you have any suggestions for the newsletter, please let contact us at vera.gaun@childrens.harvard.edu and colin.smith@childrens.harvard.edu.

In this issue

Call for Scientific Images

We're updating the PCMM website and are looking to showcase images from PCMM labs (microscopy, structural, etc.) In addition, we're looking for a banner image to display on the home page, similar to this and this BCH page.

Please send us your images in original resolution with a short description by July 7, 2025. We will try to include as many as possible! For questions, please contact Vera Gaun at vera.gaun@childrens.harvard.edu. Thanks!



Sample image: mouse olfactory epithelium sensory neurons. Green: mature neurons, red: surviving mature neurons from a given timepoint. Image generated by Vera Gaun, from a former lab.

Research Highlights

Exploring nucleosomes' inherent organizational properties

by Sangwoo Park and Vera Gaun

Eukaryotic cells' genome is organized at multiple levels: 147 base pair DNA stretches wind around histone proteins, forming nucleosomes as the basic packing unit, which further make up larger domains, such as topology-associated domains (TADs), and on a higher scale – open euchromatin and closed heterochromatin, referred to as compartments A and B. While it's known that specific proteins regulate the genomic architecture *in-trans* (i.e. cohesin is required for proper TAD maintenance, and readers and writers of histone post-translational modifications, or PTMs, affect chromatin structure), the role of inherent biophysical properties of chromatin itself in genome's structural organization is not as well defined.

Sangwoo Park

In a recent *Nature* publication from Dr. Taekjip "TJ" Ha's lab, Dr. Sangwoo Park et al. characterized nucleosomes' inherent biophysical properties. In this study, they developed the "condense-seq" assay to measure condensability: briefly, mononucleosomes were purified, condensed via spermine, and the resulting phase-separated condensed and non-condensed mononucleosome fractions were sequenced (figure 1). They then showed that, without any additional energy input or factors, such as chromatin readers or remodellers, purified native mononucleosomes can reproduce A/B compartments *in vitro*.

Taekjip Ha

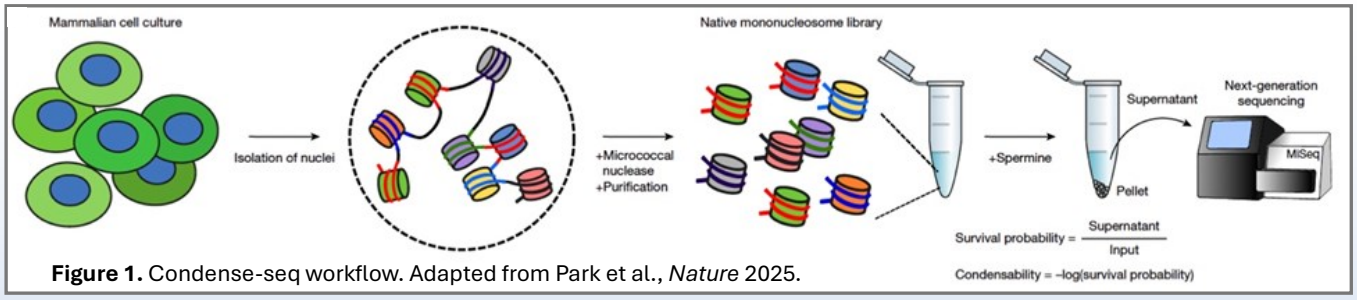


Figure 1. Condense-seq workflow. Adapted from Park et al., *Nature* 2025.

They then used purified mononuclesomes from H1 embryonic stem cells (H1 hESCs) to demonstrate an anticorrelation between gene expression and condensability at 1Mb resolution (figure 2).

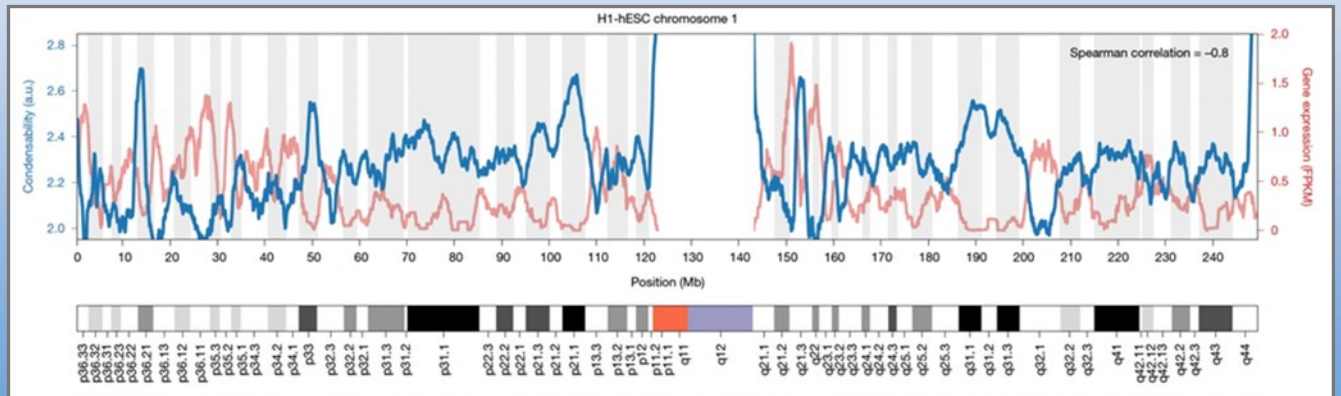


Figure 2. Anticorrelation between gene expression (via RNA-seq) and condensability in H1-hESCs at the 1 Mb scale. Adapted from Park et al., *Nature* 2025.

Sangwoo and the team then showed that a cell type-dependent property, such as the differentiation state, is associated with condensability, whereas a cell type-independent property, such as AT content, is not a major determinant factor for it. They additionally demonstrated the importance of histone PTMs in condensability by using reconstituted nucleosomes (with PTM-free histones) and showing that the reconstituted nucleosomes couldn't reproduce the native chromatin condensation without histone PTMs.

Next, Sangwoo and the team tested how individual histone PTMs affect nucleosome condensation. Using a synthetic nucleosome library, made of identical DNA sequence and histones with various PTM modifications, they have shown that (surprisingly) most PTMs reduce condensability. Ubiquitylation and acetylation had the strongest effect on reducing condensability, while methylation had a weaker, but also reducing effect. Furthermore, they showed that electrostatic forces are a major driving force of 3D genome organization: the addition of various polycations resulted in chromatin condensation, similar to polyamines'.

Potential Relevance in Disease

Since polyamines affect T cell activation and differentiation, and polyamine deficiency misregulates T cell development, Sangwoo et al. chose this cell type to examine the nucleosomes' condensability states. Polyamine depletion via using knockout mice or chemical treatment in cells resulted in hyperpolarization, i.e. condensed chromatin becoming even more condensed, and the less condensed nucleosomes becoming less condensed. This mechanism might play a role in polyamine deficiency phenotypes.

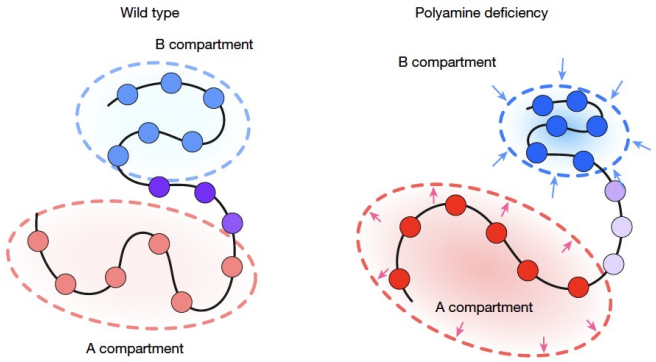


Figure 3. Polyamine deficiency results in hyperpolarization of nucleosomes in T cells. Adapted from Park et al., *Nature* 2025.

Sangwoo concludes: "Native nucleosomes know where to go! We were surprised at the finding that simple biophysical properties of nucleosomes can predict the complex biological structure and functions. Our novel bottom-up approach illuminates this basic biophysical principle of genome organization."

Sangwoo Park, PhD, was the first author of the article, and Taekjip Ha, PhD, was the senior author. Other authors include Raquel Merino-Urteaga, Violetta Karwacki-Neisius, PhD*, Gustavo Ezequiel Carrizo, MSc*, Advait Athreya*, Alberto Marin-Gonzalez, PhD, Nils A. Benning, Jonghan Park, Michelle M. Mitchener, Natarajan V. Bhanu, Benjamin A. Garcia, Bin Zhang, Tom W. Muir, and Erika L. Pearce, PhD.*
**These authors contributed equally.*

Alumnae Careers

(Soon-to-be) Tenure Track Assistant Professor: Dr. Yu-San Huoh

Photo: courtesy of Dr. Huoh

Congratulations to Dr. Yu-San Huoh, an Instructor in the Hur lab who recently got a tenure track assistant professor position at SUNY Downstate Health Sciences University! She talked to us about her experience of applying for tenure track (TT) faculty positions. Here are some take away messages we got:

Overall: From Yu-San's experience, the most important components of a successful faculty application are:

I. Publication record
II. Funding. This, along with publication record, is often used to triage applicants. Depending on your postdoctoral stage, having a transition award (such as an NIH K99/R00) is very likely essential.
III. Letters of recommendation
IV. Future research plan

The latter two are critical for advancing in the process. Most positions require three recommendation letters, occasionally four, so be sure to ask early. These letters should explicitly speak to your potential to 1) lead an independent research program, 2) secure grant funding, and 3) mentor and train researchers. If your postdoctoral mentor supports you continuing aspects of your current work, that should also be clearly stated in their letter. To ensure alignment, have an early and candid conversation with your postdoctoral mentor about what parts of your work you can bring to your independent lab.

Additionally, Yu-San referred us to this useful HMS guide (compiled by Johannes Walter, PhD, Harvard Medical School) that provides detailed insights on the TT application process.

Application process: Over two academic job search cycles, Yu-San submitted 40+ applications, using job postings listed at high-impact journals, like *Science* and *Nature,* as well as Academic Jobs Online. That may seem like a daunting amount of recommendation letters to write, but from Yu-San's experience, her referees were more than happy to help. In addition, many institutions use academic faculty application platforms like Interfolio to manage and collect application materials like letters of recommendation.

Research statement: Your research statement needs to be written in a clear, accessible format so readers outside your specific field can understand and appreciate your research vision. Since committees are reviewing dozens of applications, incorporating a memorable phrase or recurring theme throughout your research statement will help readers retain a strong impression of your focus. A useful exercise is to come up with one sentence that captures what you do and what you want to be known for. For example: "Yu-San investigates how biomolecular condensates regulate immune gene expression."

Chalk talk: The chalk talk is to assess how clearly you can articulate your research plan and how well you can think on your feet. Search committees will likely give very specific instructions (such as format and time constraints), so be sure to follow them. It's very helpful to practice beforehand with as many of your colleagues that are willing to listen. After practicing a few times, get feedback from PIs, as they have been through the process recently or served on search committees.

You should be familiar with the funding mechanisms and typical budget ranges for the grants you plan to pursue. One valuable piece of advice Yu-San received was to assess the feasibility of each project in terms of time, personnel, and cost. It's also important to understand the institutional research model. For example, at SUNY Downstate, research is primarily graduate student–driven, so projects should be designed with that in mind.

Throughout the process: Again and again, PIs told Yu-San that applying for a faculty position is one of the hardest parts of an academic career. Even when an interview didn't result in an offer, Yu-San used the experience and feedback to improve for the next one. Messages of encouragement, including Fred Modell's talk on persistence (delivered as part of the 2024 Jeffrey Modell Award at the PCMM retreat), helped Yu-San stay motivated. A strong support system makes a real difference. This applies not just in academia, but across all career paths.

Negotiating the offer: A department's willingness to negotiate your start-up package is a good sign that they're invested in your success. But to make a compelling case, your requests should be clearly tied to your research needs. Effective negotiation requires knowing what things cost. Yu-San shared a useful strategy: she made an Excel spreadsheet listing prices for key items to plan her budget and justify her requests. It's important to identify the equipment you'll need early on, since start-up funds are often distributed annually. If big-ticket items are >75% of your first-year budget, you may need to ask for additional funding or a different distribution schedule to leave room for hiring.

Again, thanks to Dr. Huoh for taking the time to share her experience applying for TT positions, and we wish her continued success as she soon embarks on a new journey!