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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Volume 10

JANUARY 2026 NEWSLETTER

Greetings, PCMM,

We hope that everyone is staying warm and healthy in this winter weather.

Just one more month of winter left!

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

In this issue

Introductions: Andrés M. Mier Valdivia of the Ha Lab

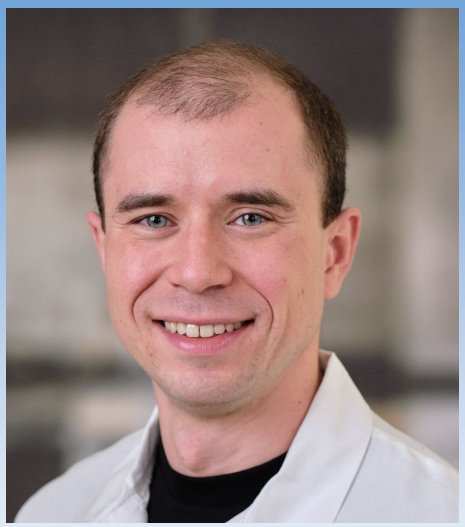


Photo: courtesy of Andrés Mier Valdivia

Tell us about your role here at PCMM. I joined the Ha lab as a postdoctoral fellow in September 2025. I'm interested in developing new techniques for generating and measuring forces with single molecule resolution. I'm hoping to apply these methods to study the mechanical response of cells.

Where were you before HMS?

I completed my PhD in June 2025 on the other side of the river, in the applied physics program at Harvard. My doctoral research was completely unrelated to biophysics. I studied the optical and electronic properties of two-dimensional materials, layered compounds that are only a few atoms thick. Specifically, I was looking at how the interactions between electrons and photons can give rise to collective and synchronized light emission, a phenomenon termed superradiance. Although such cooperative emission has been reported in other systems, our group was the first to see this effect (with a few new twists, as well) in two-dimensional semiconductors, which offer many advantages over atomic gases and conventional semiconductors. We're working on publishing the results!

The example above was a case in which the individual components of a larger system – and their intractable interactions – give rise to measurable, macroscopic phenomena that are a priori difficult or even impossible to predict in some cases. This idea is what drew me condensed matter physics, and likewise what has now motivated me to pivot to biophysics. Life itself is the ultimate emergent phenomenon with maximal complexity!

What's your favorite piece of lab equipment?

The microscope. It creates beautiful images and, if I'm using it, it means I'm generating data!

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

Never stop learning.

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

I think quantum technologies are promising for the development of new types of probes to study biological systems. I would use unlimited funds to work on marrying cell biology with quantum materials, like the ones I studied in my PhD. I hope to take my research in that direction someday.

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

I would try to be a fiction writer. Maybe I would work as a journalist as well to make sure I could pay the bills!

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

One of my favorite novels is *One Hundred Years of Solitude* by Gabriel García Márquez. I enjoy re-reading it every few years to see how my interpretation of it changes. Recently, I finished reading La conversación que somos: Linderos de la utopía (The conversation that we are: the boundaries of utopia), a collection of interviews by the Puerto Rican poet Ángel Darío Carrero. It contains a lot of interesting perspectives on life. He's one of my favorite poets but sadly I don't think he's been translated to English yet!

Do you have any pets?

No, which is why I try to befriend people who have cats.

Lunch Conversations with Seminar Speakers

On December 18th, Dr. Dan Littman of New York University School of Medicine visited PCMM to give a seminar titled "T cell homeostasis in response to food and intestinal microbiota." As part of his visit, he had lunch with PCMM trainees and shared his thoughts on a variety of topics:

Photo: courtesy of Dr. Littman

To postdoctoral fellows searching for faculty positions:

Dr. Littman did acknowledge the difficulty of securing a faculty position now and mentioned that one of his postdoctoral fellows ended up not finding a position during last cycle. He suggested that other countries could also present an option: there are additional opportunities in Asia and Europe.

On whether conducting science has fundamentally changed the past few decades: Dr. Littman commented that there is now much more pressure on getting grants early at the start of one's career, which competes with the PI's time for doing benchwork and training their mentees. However, we all agreed that fundamentally the way science is done is still the same, and people who become a faculty member have a strong passion for solving puzzles and get a certain "high" from solving questions, which for some people lasts a long time until next discovery. Some of Dr. Littman's favorite memories of doing science include, as a postdoc staying in the lab at 2 a.m with other researchers including Fred Alt there, some pipetting away and some discussing various techniques.

On recruiting lab members: Dr. Littman (like Dr. Zhang last month) acknowledged that recruiting the right lab members is a difficult aspect and recommended not to hire people just for the sake of hiring. He said that he primarily looks for an applicant's passion and tries to tell whether they're "in it" for the long run. (This is all in addition to the regular application materials, i.e. reference letters, CV, and publication record). Dr. Littman mentioned that the late Dr. Baltimore had a knack for finding people who would be successful after finishing in his lab,

even though others might not have picked up on it.

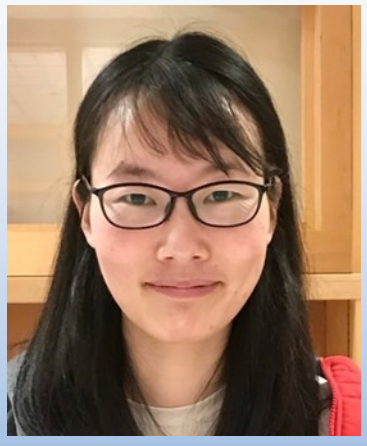
On successfully challenging some established ideas in science: Often scientific dogma takes a while to change, so how can scientists with potentially controversial discoveries "convince" the field that their finding is real? Dr. Littman suggested the answer in genetics, i.e. functionally proving that the finding has a functional significance. (Imaging provides a good start of correlation, but genetic analysis is the ultimate proof of causation). He also mentioned that differing and opposing ideas can also be a sign of an actively developing field.

On the importance of educating the general public on the science behind treatments such as vaccines: For example, RNA vaccine research government funding for $500 million was recently stopped. Dr. Littman commented: "The leaders at HHS (U.S. Department of Health and Human Services) are stating that the public does not trust RNA vaccines, hence they are cutting the funding (rather than engaging the scientists who are expert in the field to guide research policies). This kind of populist approach to science, which is amplified by the current administration, with their frequent posting of misinformation on social media, will lead to rapid erosion of our leadership position in science and technology." Thus, it's very important to educate the public on the basic science and effectiveness of newly developed treatments and let the scientific experts guide research policies.

We thank Dr. Littman for meeting with PCMM trainees and sharing his insights - we'll be collecting more perspectives from visiting PCMM speakers in the future.

PCMM Researcher Wins a Prestigious Fellowship

Zhouping Hong, PhD, (Wu Laboratory) has been awarded the Irvington Postdoctoral Fellowship from CRI. The innate immune system is the body's first line of defense, relying on inflammasomes, signaling platforms built from NOD-like receptors (NLRs), to detect danger and initiate inflammation. Although individual inflammasomes are well characterized, whether distinct NLRs cooperate remains unknown. Zhouping's research explores the concept that different NLRs can assemble into super-inflammasome complexes that amplify immune signaling and may play key roles in inflammation, autoimmune disease, and cancer. Focusing on NLRP3 and NLRP1, Zhouping combines biochemical, biophysical, and structural approaches to define how these inflammasomes interact, how their cooperation enhances immune activation, and what molecular mechanisms govern their assembly. By establishing the first mechanistic framework for super-inflammasome formation, her work could reshape our understanding of innate immune regulation and reveal new therapeutic targets for inflammatory diseases.



Delving into the biophysical properties of FUS nanoclusters

by Vera Gaun and Tapas Paul, January, 2026

In the past few decades, membraneless biomolecular condensates have emerged as key organizers of cellular biochemistry, yet the earliest molecular events that precede condensate formation remain poorly understood. Various phase-separating proteins can form condensates, including Fused in sarcoma (FUS), an RNA-binding protein implicated in neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS). Recently, even smaller FUS assemblies than conventional condensates, termed nanoclusters, have been observed both *in vitro* and *in vivo*. These structures form at concentrations far below those required for macroscopic condensate formation, yet their physical properties and biological relevance have remained largely unexplored.

To address this gap, Yingda Ge, Tapas Paul, et al. from the Myong Lab, along with collaborators from Johns Hopkins University, report a comprehensive biophysical characterization of FUS nanoclusters in a recent *Nature Communications* article.


Yingda Ge


Tapas Paul


Sua Myong

The standard method of FUS preparation involves expressing FUS with a solubility tag and cleaving the tag in solution using TEV protease, a step that is often inefficient and limits precise kinetics measurements. By developing an improved protocol that enables efficient cleavage and purification while maintaining FUS solubility, the team obtained well-defined, pre-cleaved FUS (PC-FUS). This approach allowed more accurate quantification of protein concentration and more precise tracking of nanocluster formation compared to conventionally prepared TEV-cleaved FUS (TC-FUS). Notably, PC-FUS exhibited a lower apparent saturation concentration and enabled direct visualization of nanocluster species. At sub-micromolar concentration (e.g., ~200 nM), well below those required for condensate formation (~1 µM), nanoclusters with characteristic sizes of several hundred nanometers were detected using Dynamic Light Scattering (DLS) (Figure 1).

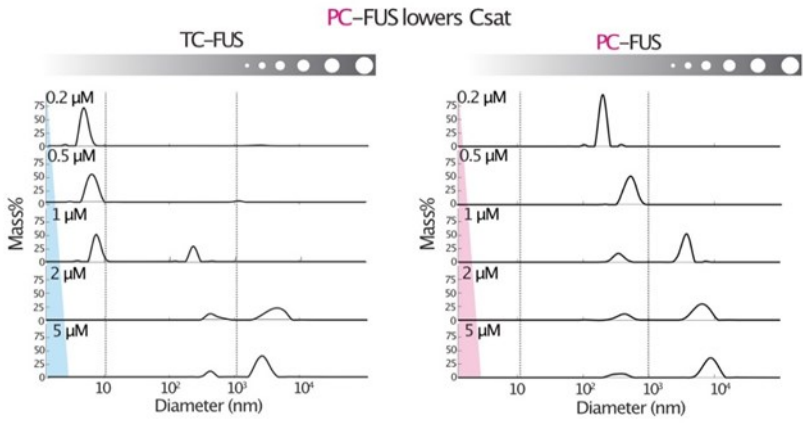


Figure 1. Pre-cleaved FUS (PC-FUS) forms nanoclusters at sub-micromolar concentrations (~200-500 nM) and undergoes condensate formation at higher concentrations (~1 µM). In contrast, conventionally prepared TEV cleaved FUS (TC-FUS) does not allow the same level of precision in tracking early assembly kinetics.

To further probe nanocluster properties, the team employed an innovative technique known as the Single Cluster Pull-down assay (SiCluP), which enabled visualization and quantitative analysis of individual nanoclusters (Figure 2). These measurements revealed that nanoclusters display kinetics distinct from condensate and exhibit liquid-like behavior, including dynamic exchange with their surroundings (data not shown).

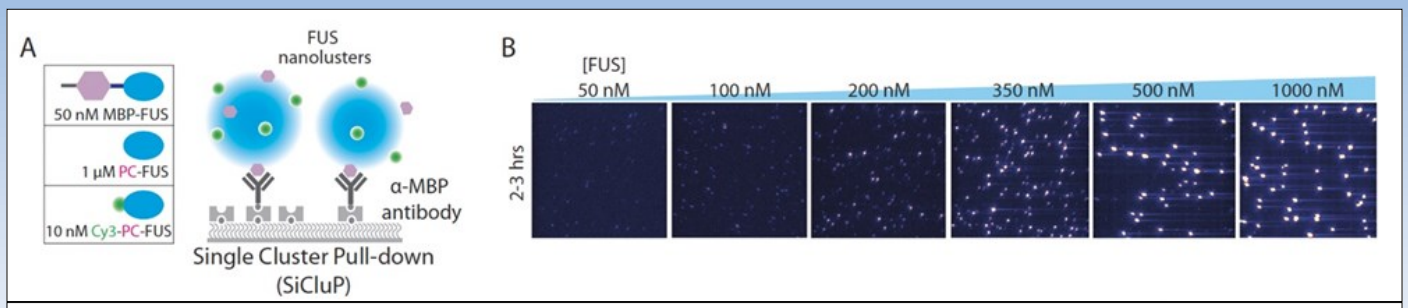


Figure 2. (A) Schematic of the Single Cluster Pull-down assay (SiCluP). Solubility-tagged FUS (MBP-FUS) is immobilized on the surface via an anti-MBP antibody, allowing added PC-FUS including fluorescently labeled Cy3-PC-FUS, to associate and enable visualization of individual FUS nanoclusters. (B) Representative images showing that nanocluster size increases with FUS concentration within the nanocluster regime (200-350 nM), before the onset of microscopic condensate formation at higher concentrations.

In addition, nanoclusters and condensates were found to rely on different intermolecular forces. While both assemblies are influenced by electrostatic interactions, nanoclusters are significantly less dependent on hydrophobic interactions compared to condensates over the concentration range tested. This distinction highlights nanoclusters as a physically unique assembly state rather than simply small condensates.

Finally, the study demonstrates that RNA modulates nanocluster size and that an ALS-linked FUS mutation (G156E) leads to the formation of significantly smaller FUS-RNA nanoclusters. These findings suggest that disease-associated mutations can perturb FUS assembly at very early stages, well before condensate formation.

Together, these results establish FUS nanoclusters as distinct, liquid-like intermediates along the phase-separation pathway, providing new insight into the molecular continuum underlying biomolecular condensation and its potential relevance to neurodegenerative disease.

“Our findings show that phase separation is not a binary process,” conclude Yingda Ge and Tapas Paul. “FUS nanoclusters represent a stable, liquid-like intermediate that exists far below saturation, offering a new framework for understanding how biomolecular condensates emerge and how disease-linked mutations may alter this process.”

Yingda Ge and Tapas Paul, PhD, were the first co-authors and Sua Myong, PhD was the senior author. Other authors are Margarita Gordiychuk, Nilimesh Das, PhD, and Yaojun Zhang, PhD.

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Collaboration note: the SiCluP technique developed in this work is also being used in collaboration with Hao Wu’s lab to investigate the pyrin condensate which supports ASC filament growth (manuscript under revision).