

### Highlighting our PCGI Researchers

We could never achieve our mission without our PCGI researchers, and with this in mind, we sat down with two faculty members and two trainees to hear their perspectives on their work and a little on their lives outside of the lab.

PCGI Faculty members Mia Levine, PhD, and Kara Bernstein, PhD, graciously shared their thoughts with us this issue. Both Drs. Levine and Bernstein are part of the PCGI Core Leadership Council. Dr. Mia Levine is an Associate Professor in the Department of Biology and the Epigenetics Institute at the University of Pennsylvania. Dr. Levine received her PhD from the University of California, Davis under the mentorship of Dr. David Begun and conducted postdoctoral work with Dr. Harmit Malik at the Fred Hutchinson Cancer Research Center.

Dr. Kara Bernstein recently joined us from University of Pittsburgh where she was an Associate Professor of Microbiology and Molecular Genetics in the School of Medicine. She obtained her Ph.D. in 2006 from Yale University studying cell cycle regulation of ribosome biogenesis under the mentorship of Dr. Susan Baserga. She then studied DNA double-strand break repair as a postdoc in the laboratory of Dr. Rodney Rothstein at Columbia University.

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*Mia Levine, PhD (pictured on the top) and Kara Bernstein, PhD (shown below Dr. Levine) are both members of PCGI's Core Leadership Council.*

Welcome to the second Penn Center for Genome Integrity (PCGI) newsletter. Each quarter, we will highlight some of the innovations we're fostering within the Center.

Our overarching mission is to integrate cutting-edge research in basic and clinical sciences from several key disciplines in order to advance our fundamental understanding of genome integrity and its contributions to human biology. Since our founding in January 2020, despite the COVID-19 pandemic, we have continued to grow, successfully contributing to faculty recruitment, shared resources, and the creation of a vibrant scientific program centered on genome integrity and human disease. We hope to bring you monthly features, particularly to highlight our robust trainee program.



[www.med.upenn.edu/pcgi](http://www.med.upenn.edu/pcgi)

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## News Briefs

### Trainee Achievements

The PCGI is developing a community of trainees that represent diverse aspects of genome integrity and its relationship to human biology. We hold monthly trainee seminars that consist of two 30-minute trainee talks. Trainees are also presenting their work in our new PCGI Mini Symposia Series coming this Spring 2023, and they frequently chair sessions of our external faculty seminars. We celebrate the following PCGI trainee accomplishments:

- Nick Sapp, PhD of the Black Lab, has received the Provost's Postdoctoral Fellowship.
- Minn Lab PhD candidate Darwin Ye received a Parker Institute for Cancer Immunotherapy (PICI) Early Career Researcher Award for his project investigating how cells become resistant to immunotherapy to inform design of more effective cancer clinical trials. More on this achievement: <https://www.parkerici.org/the-latest/ecr22/>.
- Postdoctoral Researcher in the Black Lab, Ramya Billur, PhD, was awarded a Basser Fellowship.
- Noa Erlitzki, an MD/PhD Candidate in the Kohli Lab, was awarded a Genetics T32 Training Grant.
- This past July 2022, Black Lab mentee Nikaela Bryan, PhD, successfully defended her thesis *"Utilizing HXMS to uncover the structural basis of protein phase separation."*
- Discher Lab Postdoc, Larry Dooling, PhD, received the Overall Best Talk recognition at the NCI Junior Investigator Annual Meeting August 25-26, 2022 for his talk *"Cooperative phagocytosis underlies macrophage immunotherapy of solid tumors and initiates a broad anti-tumor IgG response."*
- Arunika Das, a Postdoc in the Black and Lampson Labs, received honorable mention for the Porter Prize for Research Excellence from the American Society for Cell Biology.

### Faculty Achievements

PCGI Investigators are regularly receiving awards for their ground-breaking research:

- PCGI Co-Director Ben Black has received an NCI R01 to study how to tune PARP1 trapping and release from DNA breaks.
- Chengcheng Jin, PhD, was named a Pew Stewart

Scholar for Cancer Research

- Igor Brodsky was named Inaugural Robert R. Marshak Professor
- PCGI leadership submitted a P01 application on DNA damage activation of anti-tumor immune responses. While the first submission of this application did not receive a fundable score, there is considerable enthusiasm at the NCI for our re-submission and we have a very good chance at receiving funding this time around.
- Liling Wan, PhD, received the American Society of Hematology (ASH) Scholar Award. It is one of the Society's most prestigious research award programs, aiming to ease the transition period between completion of training and the establishment of an independent career for hematology researchers in the U.S. and Canada.
- Kenji Murakami has received an NSF Molecular and Cellular Biosciences grant for his proposal *"Investigations into the dynamic DNA recognition and processing during eukaryotic nucleotide excision repair."*
- Liling Wan, PhD, was granted the NIH Director's New Innovator Award. Part of the High-Risk, High-Reward Research program, this award supports exceptionally creative new investigators who propose highly innovative projects that have the potential for unusually high impact.
- Jennifer E. Phillips-Cremins received the International Society for Stem Cell Research (ISSCR) Susan B. Lim Outstanding New Investigator Award
- Liling Wan, PhD, was nominated and selected as one of the 2021 V Foundation Scholars. The V Scholar Grant supports young tenure-track faculty early in their cancer research careers by funding projects that are either laboratory-based fundamental research or translational research.
- Jennifer E. Phillips-Cremins, PhD, has obtained the National Institute of Health Pioneer Award.

PCGI Director Roger Greenberg was honored with several high-level speaking engagements:

- Vice Chair, Gordon Research Conference on Mammalian DNA Repair, in Ventura, CA, on February 5-10, 2023

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## Publications

The laboratories of PCGI Leaders Drs. Michael Lampson and Ben Black published a paper in *Nature Cell Biology* showing that centromere inheritance naturally minimizes fitness costs associated with weakened centromeres or epigenetic differences between parents:

- Arunika Das, Aiko Iwata-Otsubo, Aspasia Destouni, Jennine M Dawicki-McKenna, Katelyn G. Goese, Ben E. Black\*, Michael A. Lampson\*. [Epigenetic, genetic and maternal effects enable stable centromere inheritance](#). *Nat Cell Biol* 2022 May;24(5):748-756. (\*corresponding authors)

Using genetic engineering of deubiquitinating enzyme inactive knock-in mice and structural biology, the Greenberg Lab describes a model for autoinhibition of the BRCA1-A complex:

- Qinqin Jiang, Martina Foglizzo, Yaroslav I. Morozov, Xuejiao Yang, Arindam Datta, Lei Tian, Vaughn Thada, Weihua Li, Elton Zeqiraj, Roger A. Greenberg. [Autologous K63 deubiquitylation within the BRCA1-A complex licenses DNA damage recognition](#). *J Cell Biol*. 2022 Sep 5;221(9):e202111050. doi: 10.1083/jcb.202111050. Epub 2022 Aug 8.

The Black Lab highlights a previously unidentified molecular function for PI5P outside of the context of lipid mono- or bilayers and establishes a molecular paradigm for the allosteric regulation of complex, multidomain chromatin modulators by small cellular molecules:

- Papita Mandal, Karthik Eswara, Zhadyra Yerkesh, Vladlena Kharchenko, Levani Zandarashvili, Kacper Szczepksi, Dalila Bensaddek, Łukasz Jaremko, Ben E. Black, Wolfgang Fischle. [Molecular basis of hUHRL1 allosteric activation for synergistic histone modification binding by PI5P](#). *Sci Adv*. 2022 Aug 26;8(34):eabl9461. doi: 10.1126/sciadv.abl9461.

Looking at pre-clinical models, the Weitzman Lab identifies post-translational modification of CD19 as a mechanism of antigen escape from CAR T cell therapy:

- Amanda Heard, Jack H. Landmann, Ava R. Hansen, Alkmini Papadopoulou, Yu-Sung Hsu, Mehmet Emrah Selli, John M. Warrington, John

Lattin, Jufang Chang, Helen Ha, Martina Huang-Kroeper, Balraj Doray, Saar Gill, Marco Ruella, Katharina E. Hayer, Matthew D. Weitzman, Abby M. Green, Regina Fluhrer, Nathan Singh. [Antigen glycosylation regulates efficacy of CAR T cells targeting CD19](#). *Nat Commun*. 2022 Jun 11;13(1):3367.

The Black lab raises the question of whether it is the CENP-A nucleosome or the CCAN complex itself that provides the foundation for kinetochore assembly:

- Kathryn Kixmoeller, Praveen Kumar Allu, Ben E. Black. [Something's gotta give at the centromeric chromatin foundation of the kinetochore](#). *Mol. Cell* 2022 Jun 2;82(11):1976-1978. doi: 10.1016/j.molcel.2022.05.011.

The Tong Lab published an article on the importance of ubiquitin-coordinated ribosome assembly in HSC regeneration:

- Kaosheng Lv, Chujie Gong, Charles Antony, Xu Han, Jian-Gang Ren, Ryan Donaghy, Ying Cheng, Simone Pellegrino, Alan J Warren, Vikram R Paralkar, Wei Tong. [HectD1 controls hematopoietic stem cell regeneration by coordinating ribosome assembly and protein synthesis](#). *Cell Stem Cell*. 2021 Jul 1;28(7):1275-1290.e9. doi: 10.1016/j.stem.2021.02.008.

This review article from the Greenberg Lab describes the importance of endogenous forms of DNA damage to genome instability and human disease:

- Vaughn Thada, Roger A. Greenberg. [Unpaved roads: How the DNA damage response navigates endogenous genotoxins](#). *DNA Repair (Amst)*. 2022 Oct;118:103383. doi: 10.1016/j.dnarep.2022.103383. Epub 2022 Aug 2.

The Lampson Lab published two review articles on the centromere drive:

- Tomohiro Kumon, Michael A. Lampson. [Evolution of eukaryotic centromeres by drive and suppression of selfish genetic elements](#). *Semin Cell Dev Biol*. 2022 Aug;128:51-60.

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*Highlighting PCGI Researchers, continued from p. 1...*

For our trainee perspective, we spoke with Tianpeng Zhang, PhD, and Vidhya Krishnamoorthy, PhD, both Postdoctoral Researchers in the Greenberg Lab. Dr. Krishnamoorthy pursued her PhD at the CSIR-Centre for Cellular and Molecular Biology, in Hyderabad, India under the mentorship of Dr. Veena K Parnaik. She joined the Greenberg lab after obtaining her PhD in 2019. Dr. Tianpeng Zhang received his Ph.D. from the Sun Yat-sen (Zhongshan) University, Guangzhou, China in 2017. He joined the Greenberg lab in 2018.

**Q: What project in your lab is exciting you the most right now?**

**ML:** Our newest publication explores the hazards of so called “junk DNA.” Junk DNA refers to those geneless, repeated units of non-coding DNA sequence. This “satellite DNA” accounts for millions of base pairs across the human genome, but its functional significance is poorly understood. Using the model fruit fly, we discovered that the very rapid evolution of satellite DNA drives the evolution of a DNA repair pathway. This pathway resolves dangerous crosslinks that form between protein and DNA and block various DNA transactions. We discovered that very rapid evolution of a DNA-protein crosslink repair factor is required to ensure the integrity of a large, rapidly evolving DNA satellite, and ultimately, female fertility. This publications established the first functional link between this repair pathway and DNA satellites and raises the possibility that seemingly inconsequential changes to junk DNA can actually have profound biological consequences. (see figure)

**KB:** It's hard to pick one project that I'm most excited about because they are all a little different and exciting in their own ways. It's like choosing a favorite child and it is just not possible because you love them all. Right now I think some of most innovative work is related to the Shu complex, which contains RAD51 paralogs.

We are exploring why the Shu complex functions to bypass DNA damage during S phase specifically and have uncovered a novel interaction between the Shu complex members and proteins involved in replication initiation.

**VK:** My research project on AAA ATPase complex and its functions in protein quality control of replisome proteins is very exciting. We have identified a novel complex, comprising of two AAA ATPases, SPATA5 and SPATA5L1, and two alpha helical proteins, C1orf109 and CINP, that plays an essential role in DNA replication progression, sister chromatid cohesion, and genome stability. This complex unfoldase activities are coupled to proteolytic turnover of replisome in S-phase. Our studies have defined a new paradigm of ubiquitin-

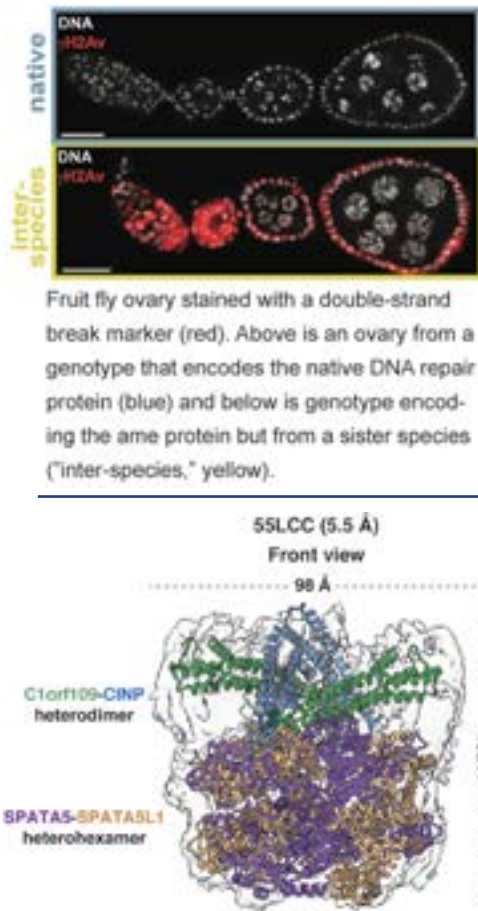
independent protein quality control on chromatin.

**TZ:** In the Greenberg lab, the scientific question [that] fascinated me most is how extensive homologous recombination dependent repair synthesis responds to complex secondary DNA structures that elicit replication stress at telomeres and elsewhere throughout genome. We established methodologies to acquire a comprehensive telomeric specific DNA damage response proteome. We revealed that long-tract DNA repair synthesis during break induced replication orchestrates template switch dependent lesion bypass, with SNM1A exonuclease activity as a critical effector of PCNA ubiquitination directed recombination in mammalian cells.

**Q: Which connections within other PCGI labs are you pursuing and/or wish to pursue more?**

**ML:** I am currently working closely with Michael Lampson. Together, we're exploring the consequences

of very rapid evolution of satellite DNA on the earliest moments of embryogenesis. We hypothesize that some proteins deposited by mom into the egg must recurrently evolve to recognize and/or process sperm-deposited paternal satellite DNA, which also evolves rapidly. We suspect that many cross-species



Top figure, Levine Lab. Bottom figure, Greenberg Lab: Structural organization of 55LCC complex by cryo-EM

incompatibilities arise at or even before the very first embryonic mitosis, linked to disrupted maternal protein - paternal DNA interactions.

**KB:** One of the primary reasons to moving to Penn was to collaborate with the PCGI labs and also members of the AFCRI. I would love to pursue some CRISPR screens and telomere analysis with Roger Greenberg's group, analyze new cell death mechanisms with combination treatments in RAD51 paralog deficient tumors with Cornelius Taabazuig, and perform innovative cell biology and structure/function analysis with Ben Black. I'm really inspired by the incredible science being done at the PCGI and I hope to learn from many of these scholars.

[RE: Other potential collaborations]: I would like to expand our basic science on the RAD51 paralogs into a more translational approach to have direct impact patient care. With that in mind, I'd like to collaborate with Susan Domcheck, Kara Maxwell, Kate Nathanson, and Fiona Simpkins who have similar interests in genes that impact breast and ovarian cancer development.

**Q: What are you most proud of having accomplished in your career as a scientist?**

**ML:** I am most proud of the profound intellectual and personal growth of my trainees. I strive to cultivate a supportive environment where undergraduate students, graduate students, and postdocs can evolve into the scientists and into the people that they want to be.

**KB:** During my career as a scientist, I'm most proud of having assembled a diverse team of incredible individuals and being able to foster a fun and exciting work environment while also leading a world-renown research program. I look forward to Monday morning and I want my trainees to feel the same way.

**VK:** I am happy to have contributed to the understanding of protein quality control mechanisms on chromatin especially in the process of DNA replication and repair. These findings can help target critical pathways for therapeutic interventions for rare neurodevelopmental



*Vidhya Krishnamoorthy, PhD (pictured above) and Tianpeng Zhang, PhD (below) are both Postdoctoral Researchers in the Greenberg Lab*



syndromes.

**TZ:** I am proud of being concentrated on the telomere biology for more than ten years since I was a graduate student. I established methodologies to study telomere maintenance mechanisms, and addressed several hardcore open questions, such as resolution of telomere replication problem, telomere specific DNA damage repair proteome, and molecular mechanism underlying break induced replication.

**Q: What is your favorite thing to do outside of the lab?**

**ML:** I love spending time with my delightful sons, husband, and golden retriever.

**KB:** I enjoy walking, gardening, and eating ice cream with my kids on a hot summer day. In Philly, there are quite a few of those!

**VK:** Running, hiking, traveling, and reading are some of the activities I enjoy outside of lab.

**TZ:** My favorite things outside the lab are reading and exploring the unknowns. With reading, I can experience the life

I have no chance to live in. With exploring, I can get access to those I am not prepared for.

*Because they are just beginning their career tracks, we asked a few additional questions of our postdocs:*

**Q: What research areas interest you the most and why?**

**VK:** My research interests lie across the areas of DNA replication and repair and proteolytic turnover mechanisms. These pathways often underlie the defects in several cancers and neurological disorders. Mechanistic understanding of these processes will help in the design of novel therapeutics targeting these complex diseases.

**TZ:** I am devoted to addressing fundamental questions on telomere maintenance mechanisms and pursuing potential cancer therapeutic strategies based on telomere biology.

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## PCGI Mini Symposia

The PCGI is excited to announce we will soon be hosting a new mini symposia series on a broad range of topics in genome integrity. Each mini symposium will feature two external faculty speakers, and two internal trainee speakers. **We will hold these talks from 2:00 to 5:00 pm (with a coffee break in-between) in the BRB II/III Glen Gaulton Auditorium.** We hope you can join us for the following sessions:

### Monday, February 13, 2023

Session Topic: *“Repetitive DNA and development”*  
Speakers: Todd Macfarlan, PhD (NIH/NICHHD), Xin Chen, PhD (HHMI/JHU), Damian Dudka (Lampson Lab), and Sung-Ya Lin (Levine Lab, tentatively).

### Monday, March 6, 2023

Session Topic: *“Recombination Mechanisms”*  
Speakers: Jean Gautier (Columbia), Eros Lazzerini Denchi (NIH/NCI), Mikael Garabedian (Good lab), and Tianpeng Zhang (Greenberg Lab)

### Monday, April 17, 2023

Session Topic: *“Molecular machines in genome stability”*  
Speakers: Edward Twomey (JHU), Tarun Kapoor (Rockefeller) and Vidhya Krishnamoorthy (Greenberg Lab), and TBA trainee from the Murakami Lab.

Talk titles and additional details are coming soon. If you would like to be added to our mailing list, or would like more information, please contact Laura Murillo via email at [murillo@upenn.edu](mailto:murillo@upenn.edu).

Scan this QR code for our full events calendar:



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(Roger Greenberg, continued)

- Plenary Speaker, NSW Cancer Conference, Sydney, Australia
- Keynote Speaker, 30th Annual Japanese Breast Cancer Symposium, Yokohama, Japan, June 30-July 2, 2022
- Keynote Speaker for the Gordon Research Conference entitled “Genome Stability and Integrity” in Ventura California in June 2022
- Keynote Speaker, Canadian Symposium on Telomeres and Genomic Integrity, Alberta CA
- Keynote Speaker, University of Pittsburgh Genome Stability Program (GSP) mini-retreat, Pittsburgh, PA.

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**(TZ, continued):** Telomere maintenance mechanisms are adopted to overcome replicative senescence in cancer cells, which is a unique feature in contrast to somatic cells. In the past decade, cancer therapeutic approaches, such as targeting the telomere sequence, telomerase, and the alternative lengthening of telomeres have been developed. Unfortunately, none have advanced to late-stage clinical trials yet. Thus, it is essential to comprehensively understand the molecular basis of telomere maintenance mechanisms, so that we can innovate drug development.

**Q: *Where do you see yourself going after your postdoctoral work is complete?***

**VK:** I am interested in pursuing a research career either in academia or industry after my postdoc with a goal of working at the interface of basic and translational science.

**TZ:** I will search for independent scientific research opportunities in research institutes. I will be continuously focusing on the telomere biology in order to reveal its contribution to carcinogenesis and senescence.

We would like to thank Drs. Levine, Bernstein, Krishnamoorthy, and Zhang for taking the time to share their work and interests, both professional and personal, with us. We are continually impressed by the dedication and collaborative spirit of our researchers, and looking forward to sharing more in the next issue.

*Publications, continued from p. 3...*

- Damian Dudka, Michael A. Lampson. [Centromere drive: model systems and experimental progress](#). *Chromosome Res.* 2022 Jun 22. doi:10.1007/s10577-022-09696-3. Online ahead of print.

The Black lab highlights recent progress on identifying regions within the cell nucleus that permit efficient formation of the centromeric chromatin that guards genome integrity at cell division:

- Janardan N. Gavade, Ben E. Black\*. 2022. Chromosomes: a nuclear neighborhood conducive to centromere formation. *Curr. Biol.*, in press.

The Discher lab shows the potential of combination CD47-SIRP $\alpha$  disruption and tumor-opsonizing IgG in molecular and cellular therapies:

- Jason C Andrechak, Lawrence J Dooling, Michael P Tobin, William Zhang, Brandon H Hayes, Justine Y Lee, Xiaoling Jin, Jerome Irianto, Dennis E Discher. [CD47-SIRP \$\alpha\$  Checkpoint Disruption in Metastases Requires Tumor-Targeting Antibody for Molecular and Engineered Macrophage Therapies](#). *Cancers (Basel)*. 2022 Apr 11;14(8):1930. doi: 10.3390/cancers14081930.

This perspective from the Greenberg Lab examines recently published findings from the Branzei lab that describe molecular mechanisms of DNA damage tolerance:

- Tianpeng Zhang, Roger A. Greenberg. [The inner workings of replisome-dependent control of DNA damage tolerance](#). *Genes Dev.* 2022 Feb 1;36(3-4):103-105.

Using well-characterized DRS datasets supported by independent meRIP-Seq and miCLIP-Seq datasets, the Weitzman Lab showed that Detection of Ribonucleic acid Modifications Manifested in Error Rates (DRUMMER) operate with high sensitivity and specificity:

- Jonathan S. Abebe, Alexander M. Price, Katharina E. Hayer, Ian Mohr, Matthew D. Weitzman, Angus C. Wilson, Daniel P. Depledge. [DRUMMER-Rapid detection of RNA modifications through comparative nanopore sequencing](#). *Bioinformatics*. 2022 Apr 15;38(11):3113-3115.

Through a collaboration with the Ernst Lab at UMB, the Shin and Brodsky Labs published two companion papers:

- Erin M Harberts, Daniel Grubaugh , Daniel C Akuma, Sunny Shin, Robert K Ernst, Igor E Brodsky. [Position-Specific Secondary Acylation Determines Detection of Lipid A by Murine TLR4 and Caspase-11](#). *Infect Immun.* 2022 Aug 18;90(8):e0020122. doi: 10.1128/iai.00201-22.
- Jasmine Alexander-Floyd, Antonia R Bass, Erin M Harberts, Daniel Grubaugh, Joseph D Buxbaum, Igor E Brodsky, Robert K Ernst, Sunny Shin. [Lipid A Variants Activate Human TLR4 and the Noncanonical Inflammasome Differently and Require the Core Oligosaccharide for Inflammasome Activation](#). *Infect Immun.* 2022 Aug 18;90(8):e0020822. doi: 10.1128/iai.00208-22.

This review from the Discher Lab discussed the importance of regulating lamin levels for mechanically active tissue constructs and organoids as well as cell therapies:

- Mai Wang, Irena Ivanovska, Manasvita Vashisth, Dennis E Discher. [Nuclear mechanoprotection: From tissue atlases as blueprints to distinctive regulation of nuclear lamins](#). *APL Bioeng.* 2022 Jun 15;6(2):021504. doi: 10.1063/5.0080392.

This *Molecular Cell* article from the Murakami Lab reveals a dynamic state of TFIIH, the largest of GTFs, in PIC/ITC with distinct functional consequences at multiple steps on the pathway to elongation:

- Chun Yang, Rina Fujiwara, Hee Jong Kim, Pratik Basnet, Yunye Zhu, Jose J. Gorbea Colón, Stefan Steimle, Benjamin A. Garcia, Craig D. Kaplan, Kenji Murakami. [Structural visualization of de novo transcription initiation by \*Saccharomyces cerevisiae\* RNA polymerase II](#). *Mol Cell.* 2022 Feb 3;82(3):660-676.e9.

*Did we miss your article? Your good news? Don't forget to notify PCGI Administrative Director Laura Murillo when your lab receives an award, publishes research, or has an interesting research story to share: [murillo@upenn.edu](mailto:murillo@upenn.edu).*