Penn Center for Genome Integrity

A Review of Achievements





A Message from the Director

The Penn Center for Genome Integrity (PCGI) was founded in 2019 to investigate provocative questions at the interface of genome integrity and different aspects of organismal biology. As we embark on the sixth year of operations, I wanted to take this moment to highlight how much we've been able to accomplish in the past year, while also emphasizing exciting plans for the coming year.

The mission of the PCGI is to understand how genome integrity impacts human biology. This requires a wholistic approach that connects laboratories engaged in the study the basic tenets of genome integrity with others that focus on the biological sequelae that are affected by genome instability. This philosophy distinguishes the PCGI from genome integrity centers at other institutions. We bring together research in basic mechanisms of DNA replication, DNA repair, and mitosis with laboratories that focus on immunology, stem cell function, neurobiology, virology, and development. Another distinguishing feature of the PCGI is the breadth of methodologies taken by participating laboratories, which range from molecular and cellular biology, structural biology, synthetic biology, evolutionary biology, chemical biology, and bioengineering. Such wideranging approaches were instrumental to the successful P01 application that examines the impact of genome instability on immune responses in cancer. Complementary approaches between PCGI laboratories have continued to lead to additional grant applications, trainee awards and fellowships, high impact collaborative publications, and translation of basic research, the most recent of which are highlighted within.

An important mission of the PCGI is to provide an environment that allows trainees to develop a broad range of skills and a network of colleagues from different fields. We have had 26 trainee speakers in the past year; they are a focal point of our mini-symposia series that include prominent faculty from other institutions. Trainees present at these symposia and often attend lunch or dinner with the keynote speakers, giving them unique access to a side of science not often experienced by students and postdocs. We hope this broadens the horizons of our trainees and gives them the opportunity to acquire important scientific and social interactions that are among the most enjoyable sides of academic science. We have also featured trainees at our annual PCGI retreats, which included keynote talks from scientific luminaries such as Jennifer Phillips-Cremins, TJ Ha, Sherry Gao, and Don Cleveland. Retreats have had additional enriching activities such as trainee roundtable discussions on entrepreneurial opportunities in academic science, strategies to land an academic faculty position, and bench to bedside translation of laboratory science.

The 2024/2025 academic year will bring more exciting developments, with planned mini symposia on topics such as "Double-stranded RNA recognition and signaling", "Targeting the Damage Response," and "Single molecular approaches to genome stability," as well as our annual retreat scheduled for June 10 at the Mütter Museum. We are looking even further into the future with a planned symposium in the 2025-2026 academic year centered on the P01 grant on Genomic instability and immune responses in cancer, featuring keynote talks by P01 external advisory board members Drs. Douglas Green, Karlene Cimprich, and Tarun Kapoor. We look forward to continued growth this year by welcoming new PCGI laboratories, purchasing shared equipment and resources, and expanding our presence on campus to shine light on how genome integrity shapes human biology.

-Roger A. Greenberg, MD, PhD



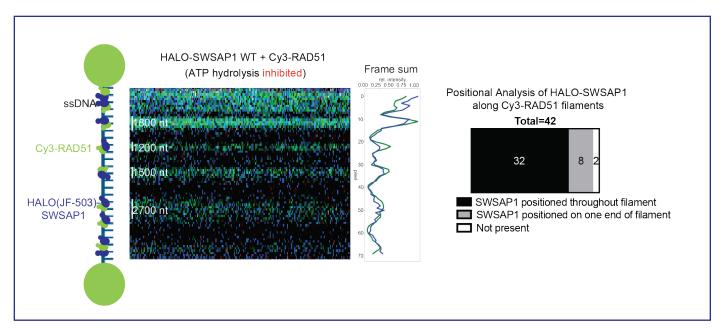
Bernstein Lab

Awards

- Dr. Kara Bernstein was named the George W. Raiziss II Professor of Biochemistry & Biophysics
- She also received the Discovery Boost Grant from the American Cancer Society to uncover new therapies for RAD51C deficient breast cancers and to identify therapeutically actionable cancer variants in RAD51C.
- Dr. Bernstein was featured in the local news for receiving the PA Breast Cancer Coalition Research Award for her lab's important work on triple negative breast cancer. <u>See the footage here</u>.
- Postdoctoral Researcher in the Bernstein Lab, Anna Palovcak, received the Mildred Cohn Award from the Biochemistry department. Additionally, she secured a slot for another year on CEET's NIH training grant.

Publications

- The Bernstein Lab shows in Nature Communications that SWSAP1-SWS1 stimulates RAD51-dependent high-fidelity repair and may be an important new cancer therapeutic target: Hengel SR, Oppenheimer KG, Smith CM, Schaich MA, Rein HL, Martino J, Darrah KE, Witham M, Ezekwenna OC, Burton KR, Van Houten B, Spies M, Bernstein KA. The human Shu complex promotes RAD51 activity by modulating RPA dynamics on ssDNA. Nat Commun. 2024 Aug 21;15(1):7197. doi: 10.1038/s41467-024-51595-0.
- Raices M, Balmir F, Silva N, Li W, Grundy MK, Hoffman DK, Altendorfer E, Camacho CJ, Bernstein KA, Colaiácovo MP, Yanowitz J. Genetic and physical interactions reveal overlapping and distinct contributions to meiotic double-strand break formation in C. elegans. bioRxiv 2024 May 30:2024.02.23.581796. doi: 10.1101/2024.02.23.581796.
- Rein HL, Bernstein KA. <u>Variants in the first methionine of RAD51C are homologous recombination proficient due to an alternative start site</u>. *DNA Repair (Amst)*. 2024 Mar:135:103644. doi: 10.1016/j.dnarep.2024.103644. Epub 2024 Feb 1.



Human Shu complex proteins, SWSAP1-SWS1, decorate the RAD51 filament. Utilizing LUMICKS C-trap which combines single molecule confocal fluorescence microscopy with optical tweezers, positionally locates SWSAP1-SWS1 relative to RAD51 on ssDNA. Positions of RAD51 (Cy3-labeled) and SWSAP1 (HaloTag-JF503) were monitored over time as shown in the kymograph. The lab then quantified the positional localization of RAD51 relative to SWSAP1 on ssDNA. Surprisingly, positional analysis reveals that SWSAP1 is primarily decorated throughout the RAD51 filaments.



Black Lab

Awards

 Dr. Ben Black is among a small group of finalists for the Falling Walls Foundation Science Breakthrough of the Year 2024 Award for his groundbreaking work on Synthetic Human Chromosomes. Read more on the research.

Publications

- Research in the Black lab related to the aforementioned artificial chromosomes is highlighted in this *Science* paper: Gambogi CW, Birchak GJ, Mer E, Brown DM, Yankson G, Kixmoeller K, Gavade JN, Espinoza JL, Kashyap P, Dupont CL, Logsdon GA, Heun P, Glass JI, Black BE. Efficient formation of single-copy human artificial chromosomes. Science 2024 Mar 22;383(6689):1344-1349. doi: 10.1126/science. adj3566. Epub 2024 Mar 21.
- This study establishes HXMS as an approach to define the structural basis for phase separation:
 Bryan NW, Ali A, Niedzialkowska E, Mayne L, Stukenberg PT, Black BE. Structural basis for the phase separation of the chromosome passenger complex. Elife. 2024 Mar 8:13:e92709. doi: 10.7554/eLife.92709.
- The Lab uncovered unanticipated differences in local structure and changes in activation-coupled backbone dynamics between PARP1 and PARP2, in this posted study: Smith-Pillet ES, Billur R, Langelier M-F, Talele TT, Pascal JM, **Black BE**. A PARP2-specific active site α-helix melts to permit DNA damage-induced enzymatic activation. *BioRxiv* 2024 May 20:2024.05.20.594972. doi: 10.1101/2024.05.20.594972.
- Here the lab highlights a unique way to trigger PARP1 retention on DNA breaks: Velagapudi UK, Rouleau-Turcotte É, Billur R, Shao X, Patil M, **Black BE**, Pascal JM, Talele TT. <u>Novel modifications of PARP inhibitor veliparib increase</u> PARP1 binding to DNA breaks. *Biochem J* 2024 Mar 20;481(6):437-460. doi: 10.1042/BCJ20230406.
- The Black lab reveals new insight into kinetochore formation: Kixmoeller K, Chang Y-W, **Black BE**. <u>Centromeric chromatin clearings demarcate the site of kinetochore formation</u>. *BioRxiv* 2024 Apr 26:2024.04.26.591177. doi: 10.1101/2024.04.26.591177.



Milestones

• Luca Busino, PhD, has received tenure in his promotion to Associate Professor of Cancer Biology.

Publications

Findings from the Busino Lab, through collaborations with two other PCGI Labs, uncover an endogenous, cell autonomous function of DCAF15 in sustaining AML proliferation through post-translational control of cohesin dynamics: Grothusen GP, Chang R, Cao Z, Zhou N, Mittal M, Datta A, Wulfridge P, Beer T, Want B, Zheng N, Tang H-Y, Sarma K, Greenberg RA, Shi J, **Busino L**. <u>DCAF15 control of cohesin dynamics sustains acute myeloid leukemia</u>. *Nat Commun*. 2024 Jul 3;15(1):5604. doi: 10.1038/s41467-024-49882-x.



Dr. Ben Black (left) shown with his Graduate Student, Gabriel Birchak. Image courtesy of Falling Walls Foundation.



Discher Lab

Milestones

• Larry Dooling, PhD, will be finishing his postdoctoral research in the Discher lab and will be an Assistant Professor at The University of Houston, TX starting in January 2025.

Publications

• Hayes BH, Wang M, Zhu H, Phan SH, Andrechak JC, Chang AH, Dooling LJ, Tobin MP, Marchena T, **Discher DE**. Chromosomal instability can favor macrophage-mediated immune response and induce a broad, vaccination-like anti-tumor lgG response. *eLife*. 2024 May 28:12:RP88054. doi: 10.7554/eLife.88054.

Good Lab

Awards

- Dr. Matt Good was named co-leader of the NSF Material Research Science and Engineering Center interdisciplinary research group, IRG2 in October 2023. This project focuses on building condensed phase materials in cells
- Dr. Good was awarded a PCGI pilot award: "Programming the Dynamics of End-Joining Condensates at DNA Breaks"

Publications

Good Lab study reveals principles governing disordered protein assembly into discrete membraneless compartments: Welles RM, Sojitra KA, Garabedian MV, Xia B, Wang W, Guan M, Regy RM, Gallagher ER, Hammer DA, Mittal J, Good MC. <u>Determinants that enable disordered protein assembly into discrete condensed phases</u>. *Nat Chem.* 2024 Jul;16(7):1062-1072. doi: 10.1038/s41557-023-01423-7. Epub 2024 Feb 5.

*This work was highlighted in News and Views from Nature: "Rules of selective condensation in cells." Nature Chemistry (2024). 10.1038/s41557-024-01525-w

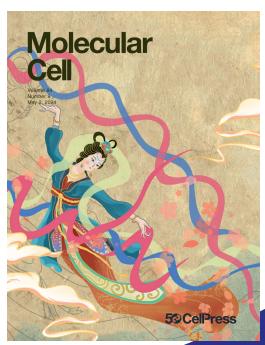
Greenberg Lab

Milestones

- Tianpeng Zhang, PhD, a former Postdoctoral Researcher in the Greenberg lab, has became an Assistant Professor in the Department of Radiation Oncology at the University of Virginia Medical School.
- Vidhya Krishnamoorthy completed her postdoctoral research in the Greenberg lab April 2024, and started a position as Scientist at Nava Therapeutics.

Publications

- Co-authors Drs. Haoyang Jiang and Tianpeng Zhang published an article in *Molecular Cell* that was featured on the cover: Jiang H, Zhang T, Kaur H, Shi T, Krishnan A, Kwon Y, Sung P, **Greenberg RA**. <u>BLM helicase unwinds lagging strand substrates to assemble the ALT telomere damage response</u>. *Molecular Cell* 2024 April; 84(9):1684-1698 .e9.doi: 10.1016/j.molcel.2024.03.011. Epub 2024 Apr 8.
- Krishnamoorthy V, Foglizzo M, Dilley RL*, Wu A, Datta A, Dutta P, Campbell LJ, Degtjarik O, Musgrove LJ, Calabrese AN, Zeqiraj E*, and Greenberg RA*. <u>The SPATA5-SPATA5L1 ATPase complex directs</u> <u>replisome proteostasis to ensure genome integrity</u>. *Cell* March 2024 187(9):2250-2268. * co-corresponding authorship





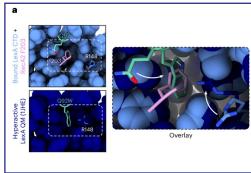
Kohli Lab

Awards

• Kohli Lab postdoc Dr. Noa Erlitzki has been named a Doctors For America 2024/25 Copello Health Advocacy Fellow. See more on the <u>Doctors for America Copello fellowship page</u>.

Publications

- Erlitzki N, Kohli RM. An Overview of Global, Local, and Base-Resolution Methods for the Detection of 5-Hydroxymethylcytosine in Genomic DNA. Methods Mol Biol. 2024:2842:325-352. doi: 10.1007/978-1-0716-4051-7_17.
- Cory MB, Li A, Hurley CM, Carman PJ, Pumroy RA, Hostetler ZM, Perez RM, Venkatesh Y, Li X, Gupta K, Petersson EJ, Kohli RM. <u>The LexA-RecA* structure reveals a cryptic lock-and-key mechanism for SOS activation</u>. *Nat Struct Mol Biol*. 2024 May 16. doi: 10.1038/s41594-024-01317-3.
 Online ahead of print.
- Prasasya RD, Caldwell BA, Liu Z, Wu S, Leu NA, Fowler JM, Cincotta
 SA, Laird DJ, **Kohli RM**, Bartolomei MS. <u>Iterative oxidation by TET1</u>
 is required for reprogramming of imprinting control regions and
 patterning of mouse sperm hypomethylated regions. *Dev Cell*. 2024 Apr 22;59(8):1010-1027.e8. doi: 10.1016/j. devcel.2024.02.012. Epub 2024 Apr 2.



Lampson Lab

Awards

Michael Lampson, PhD, Professor of Biology, SAS, and Core PCGI Investigator, was elected a 2024 American
Association for the Advancement of Science (AAAS) Fellow for his contributions to cell biology, in particular
advancing our understanding of chromosome segregation in cell division and inheritance through the germline.
Read more about it here and in Penn Today.

Publications

Clark FE, Greenberg NL, Silva DMZA, Trimm E, Skinner M, Walton RZ, Rosin LF, Lampson MA, Akera T. An egg-sabotaging mechanism drives non-Mendelian transmission in mice. Curr Biol. 2024 Jul 24:S0960-9822(24)00901-1. doi: 10.1016/j.cub.2024.07.001. Online ahead of print.

Levine Lab

Awards

- Nick Brown, 2nd year graduate student in the Levine Lab, received a T32 award from the Cell and Molecular Biology Training Grant for his proposal entitled, "Telomere establishment caught in a molecular arms race"
- Sung-Ya Lin, 5th year graduate student in the Levine Lab, received the Graduate Student Excellence Award from the Society for Molecular Biology and Evolution.
- Mia Levine received the Penn Biology Department Undergraduate Teaching Award

Publications

- The Levine lab identified two histone modifications that determine reproductive lifespan extension in Drosophila: Brand CL, Oliver GT, Farkas IZ, Buszczak M, Levine MT. Recurrent Duplication and Diversification of a Vital DNA Repair Gene Family Across Drosophila. Mol Biol Evol. 2024 Jun 1;41(6):msae113. doi: 10.1093/molbev/msae113.
- This review from the collaborations of the PCGI Labs discusses telomere regulation during the earliest embryonic cell cycles: Jeon H-J, **Levine MT, Lampson MA**. <u>Telomere Elongation During Pre-Implantation Embryo</u> Development. *Adv Anat Embryol Cell Biol*. 2024:238:121-129. doi: 10.1007/978-3-031-55163-5 6.

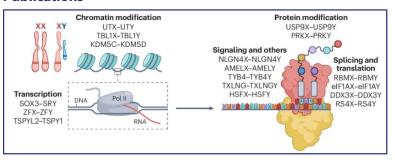


Liu Lab

Awards

Dr. Kathy Liu was awarded the St. Baldrick's foundation Research Grant Award. Read more about it here.

Publications



Owens MC, Yanas A, Liu KF, *Nat Struct Mol Biol* Figure 1a: The many roles of sexually dimorphic protein pairs in the cell.

- Owens MC, Yanas A, **Liu KF**. <u>Sex chromosome-encoded protein homologs: current progress and open questions</u>. *Nat Struct Mol Biol*. 2024 Aug;31(8):1156-1166. doi: 10.1038/s41594-024-01362-y. Epub 2024 Aug 9.
- Lavorando E, Owens MC, **Liu KF.** Comparing the roles of sex chromosome-encoded protein homologs in gene regulation. *Genes Dev.* 2024 Aug 20;38(13-14):585-596. doi: 10.1101/gad.351890.124.
- Owens MC, Shen H, Yanas A, Mendoza-Figueroa M, Lavorando E, Wei XY, Him S, Tang HY, and Goldman

Y, **Liu KF**. Specific catalytically impaired DDX3X mutants form sexually dimorphic hollow condensates. *Nat. Commun.*, accepted, (2024).

 Yanas A, Him S, Owens M, Liu KF, Goldman Y. DDX3X and DDX3Y constitutively form nanometer-scale RNA-protein clusters that foster enzymatic activity. Curr. Biol., accepted (2024).

Modzelewski Lab

Awards

- Graduate Student Katie Toohill has received a Developmental Biology Training Grant (DBT32).
- Dr. Andrew Modzelewski has received an NIH MIRA (R35).

Publications

Basavaraja R, Zhang H, Holczbauer Á, Lu Z, Radaelli E, Assenmacher CA, George SS, Nallamala VC, Beiting DP,
Meyer-Ficca ML, Meyer RG, Guo W, Fan Y, Modzelewski AJ, Spiegelman VS, Cohen MS, Fuchs SY. PARP11 inhibition
inactivates tumor-infiltrating regulatory T cells and improves the efficacy of immunotherapies. Cell Rep Med. 2024
Jul 16;5(7):101649. doi: 10.1016/j.xcrm.2024.101649.

Tong Lab

Awards

- Dr. Wei Tong with Dr. Larry Holzman and other Penn/CHOP faculties received a large training center grant, The
 Philadelphia Program for Mentored Research Training in Kidney, Urologic, and Hematologic Diseases (PERFORMKUH U2C/TL1). It provides mentored training and professional development for 4 predoctoral and 7 postdoctoral
 trainees in 5 institutions within the Philadelphia region.
- Dr. Wei Tong and Dr. Sinica Dovat from Penn State received a CURE grant from the Department of Health of PA, entitled "Precision medicine approach to reduce health disparity in pediatric leukemia."



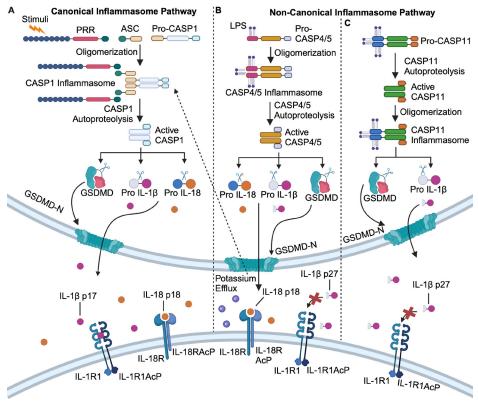
Taabazuing Lab

Awards

Dr. Cornelius Taabazuing received an NIGMD R35 MIRA Award that will fund his lab for 5 years

Publications

- Bourne CM, **Taazazuing CY**. <u>Harnessing Pyroptosis for Cancer Immunotherapy</u>. *Cells* 2024 Feb 16;13(4):346. doi: 10.3390/cells13040346.
- The Taabazuing Lab published a review in mBio discussing the recent advances in our understanding of caspase substrate specificities, with a focus on inflammatory caspases: Exconde PM, Bourne CM, Kulkarni M, Discher BM, Taazazuing CY. Inflammatory caspase substrate specificities. mBio 2024 Jul 17;15(7):e0297523. doi: 10.1128/mbio.02975-23. Epub 2024 Jun 5.
- The Brodsky and Taabazuing labs reveal in a Science Advances article that functionally interconnected but distinct death complexes mediate pyroptosis and IL-1β release in response to pathogen blockade of immune signaling: Wertman RS, Yost W, Herrmann BI, Bourne CM, Sorobetea D, Go CK, Saller BS, Groß O, Scott P, Rongvaux A, Taazazuing CY, Brodsky IE. Distinct sequential death complexes regulate pyroptosis and IL-1β release in response to Yersinia blockade of immune signaling. Sci Adv. 2024 Jul 26;10(30):eadl3629. doi: 10.1126/sciadv.adl3629. Epub 2024 Jul 26.
- Akuma DC, Wodzanowski KA, Schwartz Wertman R, Exconde PM, Vázquez Marrero VR, Odunze CE, Grubaugh D, Shin S, Taabazuing CY, Brodsky IE. <u>Catalytic activity and autoprocessing of murine caspase-11 mediate noncanonical inflammasome assembly in response to cytosolic LPS</u>. *Elife* 2024 Jan 17:13:e83725. doi: 10.7554/eLife.83725.



Exconde PM, et. al. Figure 1. See Legend online for details.



Weitzman Lab

Awards

- Amber Abbott, a Graduate Student in the Weitzman lab, was awarded a Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship (F31). She was also awarded a poster prize for her presentation at RNA Day at Penn.
- Tanner Tessier, PhD, Postdoctoral Fellow in the Weitzman lab, received a 3-year Canadian Institutes of Health Research Fellowship.
- Namrata Kumar, PhD, Postdoctoral Fellow was awarded the best poster award at the FASEB Genetic Recombination and Genome Rearrangements meeting.
- Former Postdoctoral Fellow, Alex Price, PhD, has become an Assistant Professor at the Wistar Institute.
- Matthew Weitzman was Elected Fellow of the American Academy of Microbiology.

Publications

- Packard JE, Kumar N, Weitzman MD, Dembowski JA. <u>Identifying</u>
 <u>Protein Interactions with Viral DNA Genomes during Virus Infection</u>.

 Viruses. 2024 May 25;16(6):845. doi: 10.3390/v16060845.
- Fingerman DF, O'Leary DR, Hansen AR, Tran T, Harris BR, DeWeerd RA, Hayer KE, Fan J, Chen E, Tennakoon M, Meroni A, Szeto JH, Devenport J, LaVigne D, Weitzman MD, Shalem O, Bednarski J, Vindigni A, Zhao X, Green AM. The SMC5/6 complex prevents genotoxicity upon APOBEC3A-mediated replication stress. EMBO J. 2024 Aug;43(15):3240-3255. doi: 10.1038/s44318-024-00137-x. Epub 2024 Jun 17.

Unphosphorylated Phosphorylated

Y
N
Phosphorylation of the adenovirus L1-52K packaging protein promotes liquid-like behaviour of 52K condensates formed *in vitro*.

Grams et al., EMBO Journal (2024)

Grams N, Charman M, Halko E, Lauman R, Garcia BA, **Weitzman MD**. Phosphorylation regulates viral biomolecular condensates to promote infectious progeny production. *EMBO J*. 2024 Jan;43(2):277-303. doi: 10.1038/s44318-023-00021-0. Epub 2024 Jan 2.

We hope we didn't miss your lab's achievements!

Please share your good news with us any time by emailing

Laura Murillo at murillo@upenn.edu.

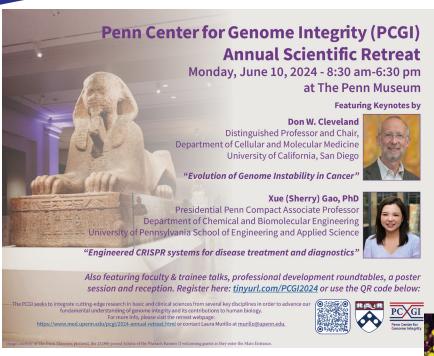
We are happy to share it next time, and on social media.

Follow us on X PennGenomeInteg to stay updated

on the latest.



Events Hosted







Click here to see full-sized images of all our event fliers



PCGI Trainees becoming Faculty

We are immensely proud of the following trainees from PCGI Labs who have now moved on to Faculty positions:



Arunika Das, PhD, who completed her postdoctoral work in the PCGI Labs of Drs. Ben Black and Mike Lampson, is now an Assistant Professor of Biomedical Sciences at Cornell University College of Veterinary Medicine.

Tianpeng Zhang, PhD, a former Postdoctoral Researcher in the Greenberg lab, has became an Assistant Professor in the Department of Radiation Oncology at the University of Virginia Medical School.





Larry Dooling, PhD will be finishing his postdoctoral research in the Discher lab and will be an Assistant Professor at The University of Houston, TX starting in January 2025.

Marisa Egan, PhD is now an Assistant Professor of Biology at Swarthmore University after completing her CAMB PhD studies in the Shin Lab.





Alexander Price, PhD, formerly a postdoc in the Weitzman lab, has become an Assistant Professor at The Wistar Institute in the Gene Expression and Regulation Program of the Ellen and Ronald Caplan Cancer Center.

