DNA Pitt Crew

Summer 2025

The latest news and updates from the UPMC Hillman Cancer Center Genome Stability Program

University of Pittsburgh

UPMC | HILLMAN CANCER CENTER

Genome Stability Program GSP

Note from Genome Stability Program Leaders, Patricia Opresko, PhD & Roderick O'Sullivan, PhD

In this edition of the DNA Pitt Crew newsletter, we have lots of updates from the Genome Stability Program (GSP) to share - new discoveries and publications, awards, new faculty joining, and sadly some departures. We also enjoyed some fun events that showcasing genome stability related science across campus, as well as local efforts supporting cancer research.

In recent months, we have seen a lot of change here at UPMC Hillman Cancer Center. We bade farewell to Drs. Robert Ferris and Jeremy Rich. While a national search for a new director continues, we have been incredibly fortunate that Drs. Kathryn Schmitz and José Zevallos stepped up as interim Director and Deputy Director, respectively, and we appreciate their outstanding leadership and support for the research efforts of the GSP.

While navigating recent changes at UPMC Hillman, the GSP has remained highly productive, continuing to publish diverse high-impact basic and translational studies. The Opresko lab reported new findings on the impact and cellular response to oxidative damage at telomeres in Nature Communications. The Van Houten lab uncovered how thymidine DNA glycosylase finds 5-formylcytosine lesions in the DNA, a finding published in Nature Communications. Work from the Arndt lab reported the consequences of disrupting the Paf1 complex, a transcription elongation factor that is frequently mutated in cancer, in Cell Reports. A clinical study from Dr. Mowery and colleagues, revealed PD-1 inhibitor pembrolizumab combined with radiation therapy improves disease-free survival in patients with stage III sarcomas, published in Lancet.

This June, the Genome Stability Retreat took place at Alumni Hall on the University of Pittsburgh's main campus. Dr. Eros Lazzerini-Denchi, visiting from the National Cancer Institute, delivered an impressive keynote lecture to a packed room of GSP members and collaborators from other UPMC Hillman programs. We heard from faculty about their collaborative genome stability-related projects and participated in workshops on effectively mining TCGA and harnessing AlphaFold for protein interaction prediction. Throughout the day, the dynamic and collaborative research environment at UPMC Hillman was on full display. Stay tuned for more next year!

We thank our colleagues in the GSP for their contributions to advance the understanding of molecular pathways that maintain genome integrity and how these processes are altered in cancer cells and wish you all a wonderful summer!

Inside this Issue:

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Faculty Spotlight: Logan Myler, PhD

Logan Myler, PhD

Logan Myler, PhD, is an Assistant Professor in the Department of Pharmacology and Chemical Biology at the University of Pittsburgh and a member of the Genome Stability Program at UPMC Hillman Cancer Center. Dr. Myler's research focuses on the interplay of DNA double-strand break repair and telomere maintenance. He received his PhD from the University of Texas at Austin in Dr. Tanya Paull and Dr. Ilya Finkelstein's Labs, where he studied the basic mechanisms of DNA double-strand break repair using a single-molecule fluorescence microscopy technique called DNA curtains. There, Dr. Myler showed that the Mre11-Rad50-Nbs1 complex (MRN) could slide on DNA to recognize and initiate repair on even blocked DNA ends. This work reconsidered DNA repair pathway choice as a sequence model rather than a competition for end binding. He also characterized the regulation of the long-range resection machinery, which he coined as the "resectosome". Dr. Myler showed that the nuclease Exo1 is a processive enzyme that can resect 5 kilobases of DNA in vitro, but this enzyme is tightly regulated by the single-stranded DNA binding protein RPA. This likely prevents or limits Exo1 activity at inappropriate sites in the genome. Processivity factors such as the mismatch repair protein MutSalpha and MRN are able to retain Exo1 at mismatches and double-strand breaks, respectively, allowing repair only at specific sites. He published two first-author papers for this work as well as 10 co-author publications. Dr. Myler was also awarded a National Cancer Institute F99/K00 predoctoral-postdoctoral transition fellowship that funded his last two years of graduate work and the first four years of his postdoc.

Dr. Myler then went on to a postdoc at Rockefeller University with Dr. Titia de Lange. There, he began characterizing the evolutionary history of shelterin, a 6-subunit protein complex that protects the natural ends of our chromosomes from being inappropriately recognized as DNA damage. He identified that shelterin originated as a 5-subunit complex in invertebrates prior to a duplication of the TRF subunit that gave rise to TRF1 and TRF2. The original TRF subunit likely acted more like TRF2, and it contained an iDDR domain, which had been shown to regulate the DNA damage response and bind to the MRN complex. Dr. Myler went on to show that the iDDR domain interacts with the Rad50 subunit of MRN and prevents its interaction with the co-factor CtIP at telomeres. This prevents its nuclease activity from acting on telomeres following replication. This work not only identified a mechanism of regulation of the MRN complex at telomeres, but also showed for the first time how MRN interacts with CtIP, which has broad implications for its function at double-strand breaks. These two first-author papers were published in *Genes & Development, Nature Structural and Molecular Biology*. Dr. Myler then started his lab at Pitt/UPMC in September 2024 and continues to study how the MRN complex is regulated at double-strand breaks and telomeres. His preliminary data suggest that the iDDR domain can also affect MRN's ability to activate the signaling kinase ATM, a protein often mutated in cancer cells. His lab is beginning to identify the mechanisms by which MRN activates ATM and of how CtIP stimulates the nuclease activity of MRN. Additionally, his lab is interested in other facets of DNA repair and telomere maintenance, including how the reverse transcriptase Telomerase is regulated by the DNA damage response. Telomerase is upregulated in ~90% of cancer cells and represents a potential therapeutic target. Collectively, the lab is working to identify the basic mechanisms of double-strand break repair and telomere maintenance to develop new understanding and treatment mechanisms for cancer.

In his free time, Dr. Myler enjoys watching Pittsburgh sports with his wife and son (especially the Pittsburgh Penguins), working on his 100-year-old house, and visiting local breweries.

Trainee Spotlight: Ragini Bhargava, PhD

Ragini Bhargava, PhD

Ragini Bhargava earned her PhD in Cancer Biology from the Irell and Manella Graduate School of Biological Sciences at the City of Hope Cancer Center in Duarte, CA. She conducted her doctoral research on DNA double-strand break repair in Dr. Jeremy M. Stark's lab. There, she developed CRISPR-based assays to model large-scale deletion rearrangements, demonstrating that the loss of the ATM kinase, often mutated in cancers, can affect the contribution of the canonical non-homologous end-joining (c-NHEJ) repair pathway. During her investigation, Dr. Bhargava found that the c-NHEJ pathway primarily mediates error-free repair. She applied these findings to create the first chromosomal reporter assay for modeling repair by c-NHEJ, outside of V(D)J recombination. While at the Stark lab, she also contributed to the foundation for studies on single-strand annealing and microhomology-mediated end joining. Dr. Bhargava's PhD work culminated in three first-author research manuscripts, a first-author review article, and four additional co-author manuscripts. After completing her PhD, motivated by a desire to study the interplay between epigenetic regulation and DNA repair at telomeres, Dr. Bhargava joined Dr. Roderick O'Sullivan's lab as a recipient of the Hillman Postdoctoral Fellowship.

In this position, she began developing proteomics-based approaches to decipher the significance of the G2 phase of the cell cycle concerning the Alternative Lengthening of Telomeres (ALT) pathway for telomere maintenance. Through this work, she identified the protein TRIM24 as a potential new regulator of the ALT mechanism. Fortuitously, Dr. Kyle Miller's lab was on the verge of a similar discovery, which has resulted in a co-1st authorship on a manuscript recently published in *Molecular Cell*. Concurrently, she has also been focused on her primary project characterizing novel genomic rearrangements in human cancer cells utilizing ALT. This project has involved collaborations with the GSP's Arbely lab and has employed several new technologies. Her 1st author manuscript detailing this work is in preparation. Dr. Bhargava presented her findings at the GRC on Epigenetics, where she received a Best Poster award, as well as at the Mammalian DNA Repair meeting held in Ventura last Spring. In the future, Ragini aims to transition to an independent position with the goal of further understanding how cells adapt to the epigenetic rewiring often associated with cancer. When in the lab, Dr. Bhargava is often found teasing her lab mates with her excessive science puns. Outside the lab, she enjoys watching reality television, cooking for her friends and family, and being outsmarted by her husky, Summer.

Pitt Stops: Special Events and Visiting Speakers

Caroline Kisker, PhD

Caroline Kisker, PhD

Professor, Co-Director of the Rudolf Virchow Center for Integrative and Translational Bioimaging. Vice President for Research and Academic Career Development, Julius-Maximilians-Universität Würzburg, Germany

Visit: October 17 & 18, 2024

Contributed by Bennett Van Houten, PhD

On October 17th, Professor Kisker presented a lecture on her studies of structure and function of nucleotide excision repair (NER) proteins. She started her presentation with a quote from the 2015 Nobel laurate, Professor, Tomas Lindahl that our DNA is constantly being damaged by endogenous and exogenous factors, and if it was not for multiple repair pathways, this level of damage would be incompatible with life. After reviewing the known structures of NER proteins, she discussed her published work on how two

Pitt Stops: Special Events and Visiting Speakers (continued)

subunits of TFIIH, p52 and p8, alter the translocatse and ATPase activity a third subunit of TFIIH, XPB (Nucleic Acids Res. 2020 Dec 2;48(21):12282-12296.) She then discussed unpublished work on the role of a specific RED motif in XPB and some single molecule studies of XPB's translocase activity. Finally, she summarized her team's recent work-up of the structure of XPD stalled at a DNA interstrand crosslink, which gave us new insights into damage recognition by this subunit of TFIIH. We greatly enjoyed her visit and the time she spent meeting with faculty and trainees.

Ben E. Black, PhD

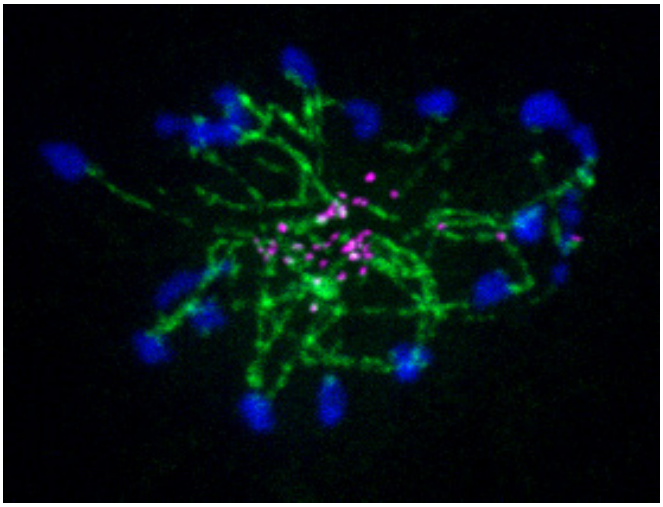
Eldridge Reeves Johnson Foundation Professor

Perelman School of Medicine

University of Pennsylvania

Visit: April 3, 2025

Contributed by Roderick O'Sullivan, PhD



Catastrophic displacement of centromeric chromatin in HMGA1-depleted oocytes. Image provided by Ben E. Black from Dudka et al. (2024).

Professor Black gave a seminar titled "Managing and Bypassing Repetitive Centromere DNA". He is a recognized leader in the field of centromere biology. His recent publication in Cell — which employs state-of-the-art cryo-electron tomography to study chromatin during kinetochore formation— demonstrates his group's continued innovation at the forefront of chromosome biology.

His work has significantly advanced our understanding of how centromeres function, including strategies to bypass repetitive DNA sequences when engineering functional centromeres on human artificial chromosomes. These achievements, published in top-tier journals such as Cell, Nature and Science, have earned his group recognition among recent "Breakthroughs of the Year." In addition to his centromere research, Professor Black has explored PARP protein activation mechanisms, with important findings published in Science and Molecular Cell.

Jean-Yves Masson, PhD, FCAHS

Director FRQS-Oncopole Cancer Network

CHU de Québec Research Center Oncology Axis

Laval University, Québec

Visit: April 7, 2025

Contributed by Elise Fouquerel, PhD

Dr. Jean-Yves Masson gave a seminar titled "Decoding DSB Repair: From PARP Activation to Strand Invasion in Homologous Recombination". He is a Fellow of the Canadian Academy of Health Sciences and a globally recognized expert in DNA repair mechanisms. His groundbreaking research continues to shape our understanding of genome stability and offers new avenues for targeted cancer therapies.

Dr. Masson's work centers on how cells respond to DNA damage caused by ionizing radiation and toxic chemicals, particularly agents that interfere with DNA replication. These stressors can result in DNA double-strand breaks (DSBs)—one of the most lethal forms of DNA damage. If not repaired accurately, DSBs can trigger cell death or give rise to genetic mutations, chromosomal abnormalities, and, ultimately, cancerous transformation.

Pitt Stops: Special Events and Visiting Speakers (continued)

Elise Fouquerel, PhD &
Jean-Yves Masson, PhD, FCAHS

A significant focus of his research has been understanding the molecular players involved in the DNA damage response. Among his most notable discoveries is the identification of a critical vulnerability in PALB2-deficient cells, which exhibit extreme sensitivity to PARP inhibitors—a class of drugs that block a key DNA repair pathway. This insight has opened the door to new, targeted treatment strategies for individuals with hereditary breast and ovarian cancers, particularly those carrying mutations in PALB2, BRCA1, or BRCA2.

Beyond his research on PALB2 and PARP inhibition, Dr. Masson has contributed extensively to characterizing the complex network of proteins that detect and repair DNA breaks, helping to delineate pathways such as homologous recombination repair. His work not only deepens our understanding of how healthy cells maintain genetic integrity but also informs the development of precision medicine approaches that exploit the unique vulnerabilities of cancer cells.

Dr. Masson's research is widely published in leading scientific journals, and his leadership in the field has earned him recognition both in Canada and internationally. His work stands at the intersection of basic science and clinical application, demonstrating how fundamental discoveries can directly inform and improve cancer diagnosis and treatment.

Beth Ann Sullivan, PhD

Associate Dean for Research Training

James B. Duke Distinguished Professor

Duke University School of Medicine

Visit: April 22, 2025

Contributed by Yael Nechemia-Arbely, PhD

The seminar held on Tuesday, April 22nd featured Dr. Beth Sullivan, James B. Duke Distinguished Professor of Molecular Genetics and Microbiology at Duke University. Dr. Sullivan is a recognized leader in chromosome biology, and her research focuses on the organization and function of the centromere—an essential region for proper chromosome segregation.

Yael Nechemia-Arbely, PhD &
Beth Ann Sullivan, PhD

Her laboratory has made significant contributions to the understanding of centromere genomics and epigenetics and was part of the Telomere-to-Telomere (T2T) Consortium. This collaborative effort achieved the first complete, gapless human genome assembly using ultra-long-read sequencing and optical mapping, resolving many previously unassembled regions, including centromeres.

At the time of the seminar, Dr. Sullivan's lab was investigating how chromosomes are packaged into inherited chromatin domains and how disruptions in this organization lead to abnormalities associated with reproductive issues and cancer. Her talk provided valuable insights into centromere and neocentromere architecture and their evolution, both genomically and epigenetically, genome stability, and the broader implications for human health.

Scientific Conference Highlights and Awards

Wei Du, MD, PhD

Wei Du, MD, PhD – DNA damage, immune response, aging and leukemia

Dr. Wei Du, Associate Professor of Medicine, was recently award the Leukemia & Lymphoma Society Scholar award. Alterations in cell intrinsic pathways or bone marrow microenvironment affect hematopoietic stem cell (HSC) function and potentially lead to leukemogenesis. DNA damage response and immune response are two fundamental processes that play critical roles in genomic integrity and surveillance against tumors, including leukemia. Dr. Du's research program employs novel preclinical mouse models to investigate the mechanisms that promote leukemogenesis, with the focus on interplay between DDR and immune response, stem cell-niche interaction; aging, and oncogenic stress-induced complex formation. Her goal is to develop new approaches to improve HSC function for leukemia therapy.

About Leukemia & Lymphoma Society (LLS) Scholar award

The LLS Scholar award supports rising stars in the blood cancer research field. Scholars are highly qualified investigators who have shown a capacity for independent, sustained, and original investigation in the field of hematologic malignancies and/or relevant pre-malignant conditions. They must hold an independent, tenure-track faculty-level position, below the level of full professor, and must have substantial research support awarded from a national agency. Scholar applicants are primarily basic and translational researchers.

Yvonne Mowery, MD, PhD – Advancing Immunotherapy for Sarcoma

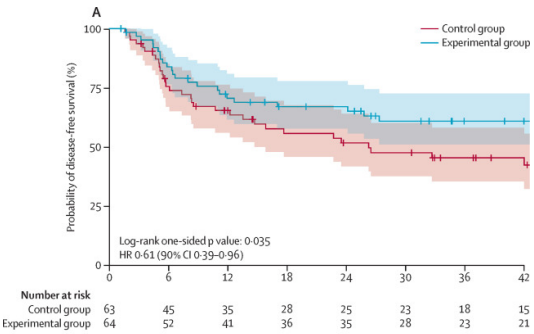
Yvonne Mowery, MD, PhD

Dr. Yvonne Mowery, a physician-scientist, Associate Professor of Radiation Oncology, has led transformative research that is reshaping the treatment landscape for certain subtypes of high-risk soft tissue sarcoma (STS). Her innovative preclinical work culminated in the design and execution of SU2C-SARC032, a landmark clinical trial that was recently published in *Lancet*.

Dr. Mowery worked with David Kirsch, MD, PhD, to develop SU2C-SARC032, a randomized phase II clinical trial that tested the addition of perioperative pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, to neoadjuvant radiotherapy and surgery in patients with stage III undifferentiated pleomorphic sarcoma or pleomorphic/dedifferentiated liposarcoma of the extremity. Conducted across multiple academic centers in the US, Canada, Italy, and Australia, the trial demonstrated a 15% absolute improvement in 2-year disease-free survival with the addition of pembrolizumab to standard of care radiotherapy and surgery. This disease-free survival benefit, primarily driven by improved distant disease control, marks the first randomized evidence that immunotherapy enhances outcomes when combined with standard local therapy for resectable high-risk soft tissue sarcoma. Correlative studies from this clinical trial are ongoing, including evaluation of circulating tumor DNA and the tumor microenvironment.

As Radiation Oncology PI for the trial, Dr. Mowery not only guided its scientific direction but also helped secure critical funding from Stand Up to Cancer and the Merck Investigator Studies Program to support the study. Her work on SU2C-SARC032 represents one of the most important advances in sarcoma treatment in decades and has already begun to influence clinical practice.

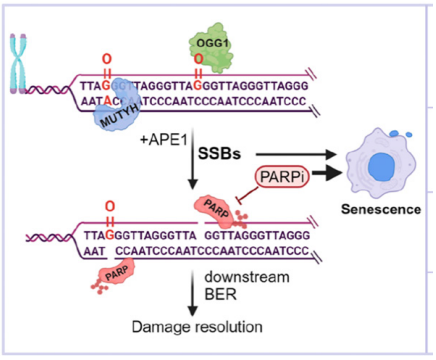
Hot Papers



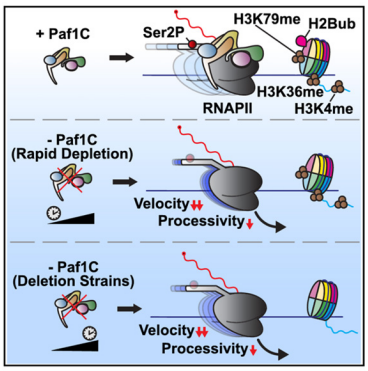
Mowery YM, Ballman KV, Hong AM, Schuetze SM, Wagner AJ, Monga CV, Heise RS, Attis S, Choy W, Burgess M, Bae S, Pryor DI, Van Tine BA, Tinoco G, Chmielowski B, Freeman C, Gronchi A, Meyer CF, Dickson MA, Hartner L, Davis LE, Powers BC, Moding EJ, Weinhold KJ, van de Rihn M, Brigman BE, Riedel RF, Kirsch DG. **"Safety and efficacy of pembrolizumab, radiation therapy, and surgery versus radiation therapy and surgery for stage III soft tissue sarcoma of the extremity (SU2C-SARC032): an open-label, randomised clinical trial."** *Lancet*. 2024 Nov 23;404(10467):2053-2064. doi: 10.1016/S0140-6736(24)01812-9. Epub 2024 Nov 12. PubMed PMID: 39547252. PMCID: PMC11842127.

Impact: This study found that addition of anti-PD-1 pembrolizumab to preoperative radiotherapy and surgery improves disease-free survival for patients with stage III sarcoma and liposarcoma, which establishes a promising new treatment option for these patients.

De Rosa M, Barnes RP, Detwiler AC, Nyalapatla PR, Wipf P, Opresko PL. **"OGG1 and MUTYH repair activities promote telomeric 8-oxoguaine induced senescence in human fibroblasts".** *Nature Communications*. 2025 Jan 21;16(1):893. doi: 10.1038/s41467-024-55638-4. PubMed PMID: 39837827. PMCID: PMC11751180.



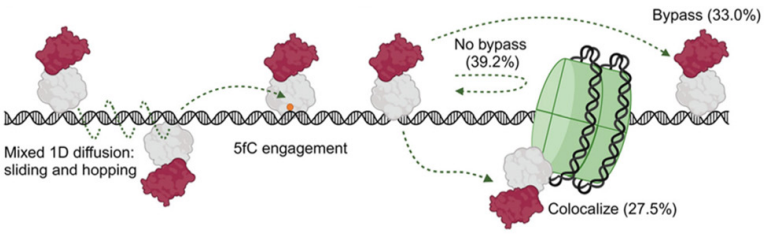
Impact: This study revealed that DNA single strand breaks intermediates that arise during base excision repair of 8-oxoguanine at telomeres triggers cellular senescence by disrupting telomere function. MUTYH mutations cause cancer predisposition, and this study uncovered a potential role for MUTYH in p53 signaling from persistent unrepaired 8-oxoguanine lesions to protect against tumorigenesis.



Francette AM, Arndt KM. **"Multiple direct and indirect roles of the Paf1 complex in transcription elongation, splicing, and histone modifications".** *Cell Reports*. 2024 Sep 24;43(9):114730. doi: 10.1016/j.celrep.2024.114730. Epub 2024 Sep 7. PubMed PMID: 39244754. PMCID: PMC11498942.

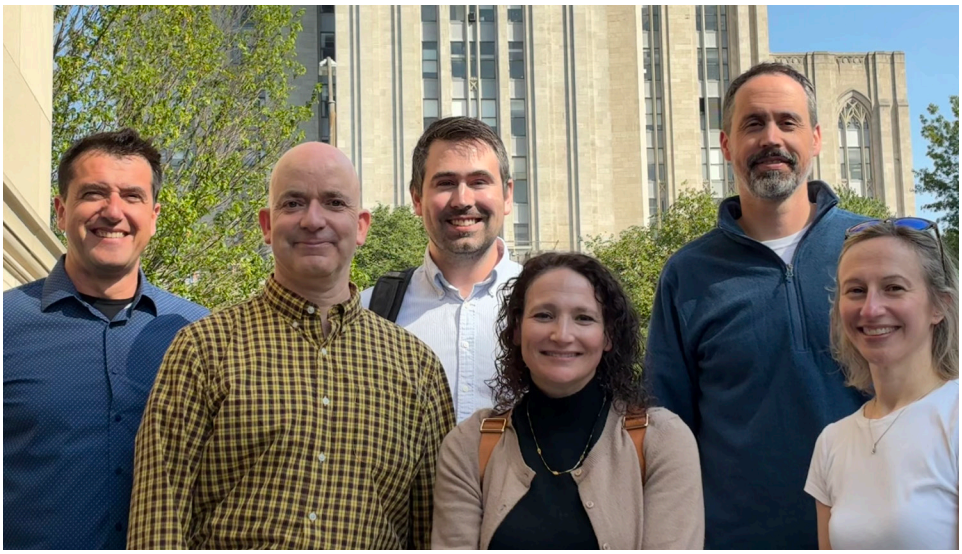
Impact: Mutations in the Paf1 complex, a core transcription elongation factor, lead to cancer. This study investigated the immediate and extended dysregulation of transcription and transcription-coupled processes in the absence of Paf1 complex. Results demonstrated direct effects of Paf1C subunits on RNAPII processivity and elongation rate and indirect effects on transcript splicing and repression of antisense transcripts.

Schnable BL, Schaich MA, Roginskaya VR, Leary LP, Weaver TM, Freudenthal BD, Drohat AC, Van Houten B. **"Thymine DNA glycosylase combines sliding, hopping, and nucleosome interactions to efficiently search for 5-formylcytosine."** *Nature Communications*. 2024 Oct 25;15(1):9226. doi: 10.1038/s41467-024-53497-7. PMID: 39455577. PMCID: PMC11512004.



Impact: Epigenetic alterations are common in cancer, and base excision repair of 5-formylcytosine by thymidine DNA glycosylase (TDG) is involved in active DNA demethylation. Using single molecule fluorescence experiments, this study advanced mechanistic understanding for how TDG search for modified DNA bases in the context of chromatin.

Faculty and Staff News



From left to right: Drs. Eros Lazzerini Denchi, Orlando Schärer, Logan Myler, Yael Nechemia-Arbely, Jonathan Alder & Patricia Opresko

Genome Stability Program Mini Retreat Recap

On June 2, 2025, the GSP hosted a dynamic and inspiring Mini Retreat at the University of Pittsburgh's Alumni Hall. The event brought together program members and collaborators for a full day of science, discussion, and community-building focused on the latest research in genome stability and cancer biology.

The retreat kicked off with a warm welcome from Co-Leaders Drs. Opresko and O'Sullivan, setting the stage for engaging presentations and collaborative dialogue.

Highlights from the morning included:

- Dr. Carola Neumann's keynote on novel DNA repair-inhibiting nitro-fatty acids as a therapeutic avenue for triple-negative breast cancer.
- Dr. Elise Fouquerel's investigation into oxidative stress at centromeres.
- A highly anticipated AlphaFold3 structural modeling workshop led by Dr. Logan Myler.
- Presentations from Drs. Sarah Hainer and Katherine Aird exploring chromatin remodeling and the metabolic control of homologous recombination, respectively.

The keynote address was delivered by Dr. Eros Lazzerini Denchi, who discussed the intricate roles of telomere dynamics in both pluripotent stem cells and cancer progression. He is a Senior Investigator and head of the Telomere Biology Unit in the Laboratory of Genome Integrity at the National Cancer Institute's Center for Cancer Research. He earned his M.S. in Biology from the Università Statale di Milano and his Ph.D. in Molecular Oncology from the European Institute of Oncology in Milan. After postdoctoral training with Dr. Titia de Lange at Rockefeller University, he led his own research at Scripps Research Institute before joining NIH in 2021.

Dr. Lazzerini Denchi's lab investigates how telomeres—protective caps at chromosome ends—ensure genome stability by preventing DNA damage responses, including how telomere-associated proteins manage telomere length and integrity in stem cells and cancer. His team is known for discoveries like the telomere-trimming protein TZAP and key insights into shelterin-mediated telomere protection.

The afternoon featured additional cutting-edge talks, including:

- Dr. Dayana Rivadeneira's work on telomere protection in T cells and its therapeutic implications.
- Dr. Jonathan Alder's translational research on telomeres in both lab and clinical settings.
- A hands-on TCGA/genomic sequencing workshop led by Dr. Adrian Lee.
- Final presentations from Drs. Yvonne Mowery and Christopher Bakkenist on combination radiation therapies and novel immune signaling mechanisms.

Faculty and Staff News (continued)

The retreat concluded with informal networking and refreshments at The Porch, capping off a highly successful day of science and connection. Special thanks to all speakers and attendees for their contributions to an exciting and enriching event. The GSP continues to thrive through the innovation and collaboration of its vibrant scientific community.

Rush to Crush Cancer: Benefiting UPMC Hillman Cancer Center

GSP members participated in the Rush to Crush Cancer events May 15, 16, 17 and 18, 2025. Now in its third year, events included an evening party, a survivors' walk, and, of course, bike rides! All funds raised support vital cancer research here at UPMC Hillman.

Thank you to all riders, donors, and volunteers who made these events a success.

From left to right: Drs. Bruce Freeman, Sam Sanford, Orlando Schärer, Tanya Myler, Logan Myler & Ben Van Houten

Prepared by Sarah O'Melia / Edited by Gera Jochum

About the Genome Stability Program

UPMC Hillman Cancer Center's Genome Stability Program works to gain new insights into the molecular pathways that maintain genome integrity and how these processes are altered in cancer cells. The Genome Stability Program works synergistically with other UPMC Hillman Cancer Center programs to translate their novel, basic insights into development of new targets, drug discovery, and recognition of biomarkers to ultimately provide clinical applications for cancer prevention and treatment.

Learn more about the Genome Stability Program at:
https://hillmanresearch.upmc.edu/research/programs/genome-stability/