

DNA Pitt Crew

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



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CANCER CENTER

Note from Director Robert L. Ferris, MD, PhD

At UPMC Hillman Cancer Center, we are enjoying a busy Fall. With our growth into the Assembly building, we have brought together more of our innovative cancer research to the Shadyside campus, which is enabling us to come together for meaningful scientific interchange, including our National Cancer Institute Cancer Center Support Grant Executive Advisory Board Meeting and our 34th Annual Scientific Retreat. We've also had an influx of new faculty; unveiled organizational-specific [mission, vision, and guiding principles](#); and launched a new fundraiser to support cancer research called [Rush to Crush Cancer](#). None of these things would be possible without the work from everyone across UPMC Hillman, including those within the Genome Stability Program (GSP). Working together, we are united in our pursuit to bring together compassionate care and transformative research to achieve the extraordinary – life without cancer.



Note from the Genome Stability Program Co-leaders, Patricia Opresko, PhD, and Bennett Van Houten, PhD

We are delighted to present the Fall 2022 edition of the DNA Pitt Crew newsletter, which provides recent information about UPMC Hillman Cancer Center Genome Stability Program (GSP) members, new recruits, and some of the exciting scientific accomplishments from this program.

It has been a pleasure attending meetings in person, and our annual GSP retreat, organized by and featuring our trainees, was held on June 21st in the new Assembly building. This year's featured keynote speaker was Professor Agnel Sfeir, PhD, who provided important insights into trainee presentations and presented a wonderful talk highlighting her recent work. The GSP was well represented at the recent 13th International Conference on Environmental Mutagens in Ottawa, Canada, with talks by faculty, postdocs, and students.

This edition includes four scientific highlights of recently published impactful studies: 1) showing persistent DNA damage and oncogenic stress-induced Trem1 promotes leukemia in mice (*Haematologica*); 2) a multi-center study evaluating the molecular landscape of pediatric thyroid modules through the use of a multigene genomic classifier in children (*JAMA Oncol.*); 3) explaining how telomeric 8-oxo-guanine drives rapid premature senescence in the absence of telomere shortening (*Nat Struct Mol Biol.*); and 4) defining how redox regulation of a critical cysteine in RAD51 by peroxiredoxin 1 impacts homologous recombination (*Redox Biol.*).

We are pleased to announce that GSP members have been awarded new grants and awards, including two R01's to Roderick J. O'Sullivan, PhD. This edition also includes a tribute to a remarkable colleague and scientist, Marcel Bruchez, PhD. We wish everyone good health and safety as we continue working during this challenging time of living in the age of COVID-19.



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Jonathan K. Alder, PhD

Faculty Spotlight: Jonathan K. Alder, PhD

Jonathan Alder, PhD, is an Assistant Professor of Medicine at the University of Pittsburgh and a member of the Genome Stability Group at UPMC Hillman Cancer Center. His research is focused on understanding how telomeres contribute to human health and disease.

Dr. Alder got his start in research when he answered an ad in the newspaper for a job at the University of Utah Human Genome Center. While he was grossly underqualified for the job posting, the Genome Center did need a full-time sequencing gel technician, and he began working the next day pouring sequencing gels for the human genome project. The environment at the Genome Center was electric and it did not take long before he was hooked on genetics and biomedical research. Following the completion of his bachelor's degree in chemistry at the University of Utah, Dr. Alder moved to the Baltimore-D.C. area to attend graduate school at Johns Hopkins University. His graduate work focused on a transcription factor, kruppel-like factor 4 (KLF4), that had been identified in many stem/progenitor populations. His work showed that KLF4 was necessary for the differentiation of subtypes of hematopoietic cells. While finishing his graduate work, Dr. Alder began a collaboration with a physician scientist, Mary Armanios, MD, that eventually led to a postdoctoral fellowship in her lab where he investigated the unexpected link between telomere dysfunction and pulmonary fibrosis.

The Alder lab focuses on the consequences of long and short telomeres on human disease. Short telomeres cause a spectrum of clinical phenotypes ranging from nail dystrophy to bone marrow failure. The most common clinical phenotype of short telomeres is pulmonary fibrosis. A primary research function of the lab is understanding why the lung is so sensitive to the length of caps on the ends of our chromosomes. His past work has shown that short telomeres can limit the capacity of the lung to repair itself after injury. On the other end of the spectrum, the Alder lab investigates how cancer cells escape mortality by lengthening their telomeres. Most cells in the body are limited in how many times they can divide by the shortening of their telomeres. Cancer cells must find a way to lengthen their telomeres to support unlimited growth. While mutations that increase the expression of telomerase, the enzyme responsible for synthesizing telomeres, are the most common, the Alder lab investigates additional mechanisms that are responsible for lengthening telomeres to support immortal growth of cancer cells. His recent work has demonstrated that promoter mutations in one of the proteins that coats telomeres and functions to recruit telomerase to the telomere increase its expression and work synergistically with telomerase to lengthen telomeres in cancer cells.

When he is not in the lab, Dr. Alder is driving his three kids around and trying to find time to hike and go fly fishing. Dr. Alder is a big fan of Pittsburgh and the University. He moved his lab here five years ago and is worried that everyone else is going to find out that this is the best place to live and do research in the U.S.



*Back Left to Right: Daniel Sullivan, Jonathan Alder, Agustin Gil Silva, Angela Hinchie.
Front Left to Right: Anishka Parikh, Pattra Chun-on, Rachel Sutton*



Marcel Bruchez, PhD

Tribute to Marcel Bruchez, PhD

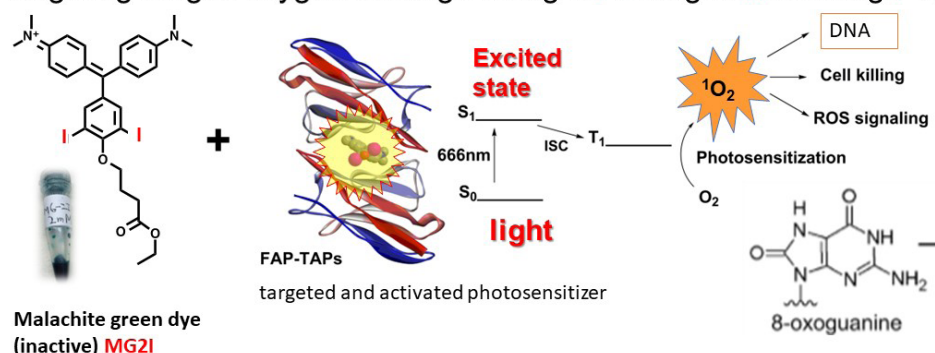
Contributed by Patty Opresko and Ben Van Houten

We were saddened to learn that Marcel Bruchez, PhD lost his heroic battle against brain cancer and died on August 27, 2022, at the age of 48. Dr. Bruchez was a remarkable scientist and a highly valued colleague to a large group of collaborators at the University of Pittsburgh and across the world. His career, while shortened prematurely due to his illness, was incredibly distinguished. Dr. Bruchez was an innovator in the field of optical measurements and perturbations in biological systems. He invented a new way to use Quantum Dots for biological detection. He was also a pioneer in the establishment of hybrid chemical/biological tagging approaches and an innovator in the development of genetically focused therapeutic approaches. Dr. Bruchez is the recipient of the Lord Rank Prize in Optoelectronics (2006), was cited as a TR100 innovator (2004), was the Leica Scientific Forum Keynote Lecturer (2010), and was the Elected Chair of CYTO2017. His products and innovations have won numerous awards, including the Science Magazine Top Ten Scientific Innovations of 2003, the R&D100 Award for Innovative Products (2004), the Larta Most Promising Innovation Award (2003), and the ELRIG Best New Technology Award (2013). He holds 31 U.S. patents and foreign patents that have been licensed to six companies. He is the founder of Quantum Dot Corporation and Sharp Edge Labs, has published one book and 81 research articles, and has an H-index of 45. Dr. Bruchez served as an Associate Editor for Frontiers in Genomic Assay Technology and was a standing member of the Instrument and Systems Development (ISD) study section at the NIH. Most recently Dr. Bruchez was inducted into the National Academy of Inventors in 2022.

We had the great fortune to work with Dr. Bruchez on a number of pioneering projects sharing a NIEHS R33 with him and Professors Ed Burton and Simon Watkins. This dream team of scientists were able to harness the power of an innovative chemoptogenetics approach developed by Dr. Bruchez. This system consists of a fluorogenic activating peptide (FAP) that binds avidly to an halogenated malachite dye. This dye, only when complexed to the FAP and illuminated by 660 nm light, produces singlet oxygen, a reactive oxygen species that due to its microsecond lifetime can only damage macromolecules within 200 nm of its formation. By fusing the FAP to specific proteins, this singlet oxygen bomb can be delivered to unique cellular locations with high spatial and temporal resolution (*Nat. Methods*, 2016). In a series of groundbreaking papers, this team was able to uniquely damage mitochondria in cells (*PNAS*, 2019) and ablate mitochondrial function in living zebrafish embryos (*Elife*, 2020). Opresko's team created a tagged FAP to a telomere-binding protein to direct Dr. Bruchez's "molecular sniper rifle" to produce 8-oxoguanine damage only at the tips of chromosomes, the telomeres (*Molecular Cell*, 2019). This allowed her team to demonstrate how this specific genotoxic damage directed only to telomeres affects cancer cells and, more recently, normal cells to produce cellular senescence (*NSMB* 2022). Dr. Bruchez's molecular sniper tool was described in a [SciShow YouTube video](#) that has received over 208,000 views.

We feel so fortunate to have known and worked with Marcel. He was a kind soul and a rare genius. Our lives were enriched by interactions with him. His brilliance helped to illuminate a new path of discovery for many scientists and transformed numerous research programs. There are no words to describe how much we will miss him.

Targeting singlet oxygen damage using a Fluorogen Activating Peptide



Nat. Methods, 2016



Nicole Kaminski

Trainee Spotlight: Nicole Kaminski

Contributed by Roderick J. O'Sullivan, PhD, and Nicole Kaminski

Nicole received her Bachelor of Science in Biochemistry from Virginia Tech. During this time, she studied the differential expression of chicken nutrient transporter proteins in the lab of Dr. Eric Wong. This work ultimately resulted in a first author paper in *Poultry Science*. She transitioned to the University of Pittsburgh where she joined Dr. Roddy O'Sullivan's lab as a Molecular Pharmacology Graduate Student.

In the O'Sullivan lab, Nicole has focused on projects involving post-translational modifications, transcription, lncRNAs, RAD51AP1, and their roles in the Alternative Lengthening of Telomeres (ALT) pathway. Since joining the O'Sullivan lab, Nicole has co-authored two journal articles, submitted a first author publication to *Molecular Cell*, and was awarded funding through T32 and F31 grants. Outside of the lab, Nicole has been very involved in the Biomedical Graduate Student Association, where she held three executive board positions, including President.

Nicole plans to continue researching DNA repair proteins in Boston where she will work as a Research Scientist for RADD Pharmaceuticals, a biotech company founded by Drs. Roger Greenberg and Tarun Kapoor.

Pitt Stop: Special Events and Visiting Speakers

Jaime Lopez, PhD

Dr. Jamie Lopez, Assistant Professor Department of Biology and Microbiology at South Dakota State University, presented a lecture entitled, "PARleying with DNA-protein crosslinks," on July 29, 2022. He first gave a fascinating account of how he identified SPRTN, a zinc metalloprotease, which processes DNA-protein crosslinks (DPC), and that was published in *Nature Genetics* in 2014. Families with mutations in the gene encoding this protein suffer premature aging and develop liver cancer at a young age. Several important anti-tumor compounds generate DPC including camptothecin (TOPOI), etoposide (TOPOII), and aza-C (DNMT). The repair of DPC is not well understood, and Dr. Lopez's research program is at the cutting edge of the molecular mechanism of how these replication-blocking lesions are processed. He then discussed new work suggesting that PARP1 interaction and PARylation of DPC is essential for efficient SPRTN processing. Trainees expressed how much they enjoyed speaking with Dr. Lopez, learning about his unique perspective on mentoring and establishing a new laboratory.



Jaime Lopez, PhD

Arvind Panday, PhD

Dr. Arvind Panday, Instructor in Medicine Harvard Medical School in Dr. Scully's laboratory, presented a lecture entitled "Therapeutic Potential of FANCM for BRCA1-linked Cancer," virtually on June 20, 2022. Dr. Panday described his recent work on FANCM regulation of repair pathway choice at stalled replication forks, which was published in *Molecular Cell* and led to a funded NCI K99/R00 award. He introduced FANCM protein and the elegant system he used involving an engineered Tus/Ter replication fork barrier to study replication fork stalling at a defined locus in mammalian cells. He also constructed a series of mutations in defined domains of the endogenous FANCM gene. He then described how mutations that inactivate the FANCM ATPase activity eliminated the protein's repair functions and trapped FANCM at stalled forks. He also shared his exciting result that FANCM ATPase mutants are synthetically lethal with Brca1 mutations, thereby raising the possibility for FANCM as a "druggable" new target in BRCA1-linked cancers. Dr. Panday visited UPMC Hillman in person the following week and met with several faculty



Arvind Panday, PhD

Pitt Stop: Special Events and Visiting Speakers (continued)

2022 GSP Mini-Retreat Featuring Agnel Sfeir, PhD

This past June, the Genome Stability Program held its annual mini-retreat co-chaired by graduate student Michelle Lynskey (O'Sullivan Lab) and Matt Schaich, PhD (Van Houten Lab). The retreat showcased eight trainees from the GSP (listed below). After our trainees gave their talks, we welcomed our keynote lecturer Dr. Agnel Sfeir, the Paine Webber Chair in Cancer Genetics, Professor, and Member of Sloan Kettering Institute. Dr. Sfeir has made significant contributions toward understanding DNA repair in the context of telomeres and mitochondria, and has continued to dedicate time to trainee development. She gave an exemplary talk entitled, "A tale of two genomes: DNA repair in the mitochondria and the nucleus," in which she described two exciting projects her lab is currently investigating. After the keynote lecture, there was a poster session highlighting the amazing work being done at UPMC Hillman. Dr. Sfeir participated and made sure to learn more about each student's project.

It was great to be back in person at the new Assembly Building this year, and we are already looking forward to next year's retreat! The keynote speaker for next year will be Professor Roger Greenberg from the University of Pennsylvania. We appreciate Ragini Bhargava, PhD (O'Sullivan lab), and Daniela Muoio, PhD (Fouquerel lab), for volunteering to co-chair the retreat in 2023.



Michelle Lynskey, Agnel Sfeir, PhD and Matt Schaich, PhD

2022 GSP Mini-Retreat Trainee Talks:

Andrew Cipriano (Bakkenist Lab)

"Caffeine induces origin firing without inhibiting ATR kinase"

Limei Wu, PhD (Du Lab)

"Persistent DNA damage and oncogenic stress-induced Trem1 promotes leukemia in mice"

Ryan Barnes, PhD (Opresko Lab)

"Telomeric 8-oxo-guanine induces premature senescence by disrupting telomere replication"

Brittani Schnable (Van Houten Lab)

"Stimulation of thymine DNA glycosylase by UV-damage DNA binding protein"

Kaylee Ermine (Zhang Lab)

"Restoring necroptosis in colorectal cancer to overcome therapeutic resistance"

Poulomi Nath, PhD (Nechemia-Arbely Lab)

"Mechanisms of CENP-A overexpression induced genomic instability"

Pattra Chun-on (Alder Lab)

"TPP1 promoter mutations synergize with TERT promoter mutations to lengthen telomeres in melanoma"

Li Wan, PhD (Chang-Moore Lab)

"Merkel cell polyomavirus (MCPyV) small T antigen (sT) enhances genome replication by facilitating Large T antigen (LT) binding to the MCPyV viral origin"



GSP mini retreat poster session. Picture courtesy P. Opresko.

Scientific Conference Highlights and Awards



53rd Annual Meeting of Environmental Mutagenesis and Genomics Society

August 27 - September 1, 2022 — Ottawa Canada

Each year, the Education, Student and New Investigator Affairs Committee (ESNIA) invites students and new investigators to submit abstracts for either poster or oral presentations. Submissions are automatically entered in the Best Presentation/Poster Competition, which takes place at the EMGS Annual Meeting, this year in conjunction with the 13th International Conference on Environmental Mutagens.

- **Ryan Barnes, PhD**, co-chaired the DNA Repair Special Interest Group Meeting and the session “Polynucleotide signatures and regulation of genotoxin stress response.” He won best poster for a new investigator sponsored by Mutation Research Fundamental and Molecular Mechanisms titled “Telomeric 8-Oxo-Guanine drives rapid premature senescence in the absence of telomere shortening.” He also received a travel award.
- **Matthew Schaich, PhD**, came in second place for Best New Investigator poster titled “Single-molecule analysis of damage detection by UV-DDB and OGG1 from nuclear extracts.”
- **Mariarosaria de Rosa, PhD**, gave a talk entitled “The processing of 8-oxoG at telomeres promotes cellular senescence.” She also presented a poster with the same title, was young investigator co-chair of a session entitled “DNA repair advances,” and received a travel award.
- **Sanjana Thosar** from Dr. Opresko’s lab presented a poster and gave a 10-minute talk at the DNA Repair Special Interest Group. The title of both the poster and talk was “Telomeric 8-oxoG promotes replication stress driven ALT.”
- **Sripriya Raja** from Dr. Van Houten’s lab was awarded a travel grant to attend the meeting. She gave both a poster and oral presentation. The title was “Understanding the role of UV-DDB in the SMUG1-mediated repair of the oxidative DNA lesion, 5-hydroxymethyl-2-deoxyuridine.”

Arndt Lab Awardees

- **Alex Francette** received the Carl Storm Underrepresented Minority (CSURM) Fellowship to participate in the Gordon Research Conference on Chromatin Structure and Function in Castelldefels, Spain. He also was awarded the Outstanding Presenter Award for the Dietrich School of Arts and Science Grad Expo 2022.
- **Sanchirmaa Namjilsuren** received the Andrew Mellon Predoctoral Fellowship.

Hot Papers

- Kiesel, B. F., J. J. Deppas, J. Guo, R. A. Parise, D. A. Clump, C. J. Bakkenist and J. H. Beumer (2022). [“Dose-dependent bioavailability, absorption-rate limited elimination, and tissue distribution of the ATR inhibitor BAY-1895344 \(elimusertib\) in mice.”](#) *Cancer chemotherapy and pharmacology* 89(6): 795–807.
- Lin, Q., L. Wu, S. Chatla, F. A. Chowdhury, N. Atale, J. Joseph and W. Du (2022). [“Hematopoietic stem cell regeneration through paracrine regulation of the Wnt5a/Prox1 signaling axis.”](#) *The Journal of clinical investigation* 132(12): e155914.
- Li, X., S. Chatla, A. F. Wilson, L. Wu, N. Atale and W. Du (2022). [“Persistent DNA damage and oncogenic stress-induced Trem1 promotes leukemia in mice.”](#) *Haematologica*, 10.3324/haematol.2021.280404. Advance online publication.
- Wang, H., J. Lu, F. Alencastro, A. Roberts, J. Fiedor, P. Carroll, R. N. Eisenman, S. Ranganathan, M. Torbenson, A. W. Duncan and E. V. Prochownik (2022). [“Coordinated Cross-Talk Between the Myc and Mlx Networks in Liver Regeneration and Neoplasia.”](#) *Cellular and molecular gastroenterology and hepatology* 13(6): 1785–1804.
- Hense, J. D., D. N. Garcia, J. V. Isola, J. A. Alvarado-Rincón, B. M. Zanini, J. B. Prosczek, M. B. Stout, J. B. Mason, P. T. Walsh, M. A. Briño-Enríquez, I. Schadock, C. C. Barros, M. M. Masternak and A. Schneider (2022). [“Senolytic treatment reverses obesity-mediated senescent cell accumulation in the ovary.”](#) *GeroScience* 44(3): 1747–1759.
- Rodriguez, C. P., H. Kang, J. L. Geiger, B. Burtress, C. H. Chung, C. R. Pickering, C. Fakhry, Q. T. Le, S. S. Yom, T. J. Galloway, E. Golemis, A. Li, J. Shoop, S. Wong, R. Mehra, H. Skinner, N. F. Saba, E. R. Flores, J. N. Myers, J. M. Ford, R. Karchin, R. L. Ferris, C. Kunos, J. M. Lynn and S. Malik (2022). [“Clinical Trial Development in TP53-Mutated Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma.”](#) *Journal of the National Cancer Institute*, djac163. Advance online publication.
- Gallant, J. N., S. C. Chen, C. A. Ortega, S. L. Rohde, R. H. Belcher, J. L. Netteville, N. Baregamian, H. Wang, J. Liang, F. Ye, Y. E. Nikiforov, M. N. Nikiforova and V. L. Weiss (2022). [“Evaluation of the Molecular Landscape of Pediatric Thyroid Nodules and Use of a Multigene Genomic Classifier in Children.”](#) *JAMA oncology*, 8(9): 1323–1327.
- Hamade, D. F., A. Espinal, J. Yu, B. J. Leibowitz, R. Fisher, W. Hou, D. Shields, J. P. van Pijkeren, A. Mukherjee, M. W. Epperly, A. M. Vlad, L. Coffman, H. Wang, M. Saiful Huq, R. Patel, J. Huang and J. S. Greenberger (2022). [“Lactobacillus reuteri Releasing IL-22 \(LR-IL-22\) Facilitates Intestinal Radioprotection for Whole-Abdomen Irradiation \(WAI\) of Ovarian Cancer.”](#) *Radiation research* 198(1): 89–105.
- Barnes, R. P., M. de Rosa, S. A. Thosar, A. C. Detwiler, V. Roginskaya, B. Van Houten, M. P. Bruchez, J. Stewart-Ornstein and P. L. Opresko (2022). [“Telomeric 8-oxo-guanine drives rapid premature senescence in the absence of telomere shortening.”](#) *Nature structural & molecular biology* 29(7): 639–652.
- Jofré, D. M., D. K. Hoffman, A. S. Cervino, G. M. Hahn, M. Grundy, S. Yun, F. Amrit, D. B. Stolz, L. F. Godoy, E. Salvatore, F. A. Rossi, A. Ghazi, M. C. Cirio, J. L. Yanowitz and D. Hochbaum (2022). [“The CHARGE syndrome ortholog CHD-7 regulates TGF- \$\beta\$ pathways in *Caenorhabditis elegans*.”](#) *Proceedings of the National Academy of Sciences of the United States of America* 119(15): e2109508119.
- Skoko, J. J., J. Cao, D. Gaboriau, M. Attar, A. Asan, L. Hong, C. E. Paulsen, H. Ma, Y. Liu, H. Wu, T. Harkness, C. M. Furdui, Y. Manevich, C. G. Morrison, E. T. Brown, D. Normolle, M. Spies, M. A. Spies, K. Carroll and C. A. Neumann (2022). [“Redox regulation of RAD51 Cys319 and homologous recombination by peroxiredoxin 1.”](#) *Redox biology*, 56: 102443.

Cool Science

Persistent DNA damage and oncogenic stress-induced Trem1 promotes leukemia in mice.

The immune receptor TREM1 (Triggering receptor expressed on myeloid cells 1) is a master regulator of inflammatory response. Compelling evidence suggests important pathological roles for TREM1 in various types of solid tumors. However, the role of TREM1 in hematologic malignancies is not known. Previous work from Dr. Du's laboratory showed that TREM1 cooperates with diminished DNA damage response to induce expansion of pre-leukemic hematopoietic stem cells (HSCs) in mice deficient for the Fanconi anemia gene *Fanca*. In this new article, the authors studied TREM1 in leukemogenesis using mouse models of the DNA repair-deficient *Fanca*^{-/-} and the oncogenic *MLL-AF9* or *Kras*^{G12D} and found that TREM1 was highly expressed in pre-leukemic HSCs and leukemia stem cells (LSCs). By selective deletion of the TREM1 gene in the hematopoietic compartment, they showed that ablation of TREM1 reduced leukemogenic activity of the pre-leukemic HSCs and LSCs in mice. TREM1 was required for the proliferation of the pre-leukemic HSCs and LSCs. Further analysis revealed that TREM1 expression in pre-leukemic HSCs and LSCs was associated with persistent DNA damage, prolonged oncogenic stress, and a strong inflammatory signature. Targeting several top TREM1 inflammatory signatures inhibits the proliferation of pre-leukemic HSCs and LSCs. Collectively, the lab's observations uncover previously unknown expression and function of TREM1 in malignant stem cells and identify TREM1 as a driver of leukemogenesis.

Impact: Targeting several top TREM1 inflammatory signatures inhibits the proliferation of pre-leukemic HSCs and LSCs. Collectively, these observations uncover previously unknown expression and function of TREM1 in malignant stem cells and identify TREM1 as a driver of leukemogenesis and suggest a new drug target in the treatment of leukemia.

Funding: R01HL151390 (W.D.)

Source: Li, X., S. Chatla, A. F. Wilson, L. Wu, N. Atale and W. Du (2022). "[Persistent DNA damage and oncogenic stress-induced Trem1 promotes leukemia in mice.](#)" *Haematologica*, 10.3324/haematol.2021.280404. Advance online publication.

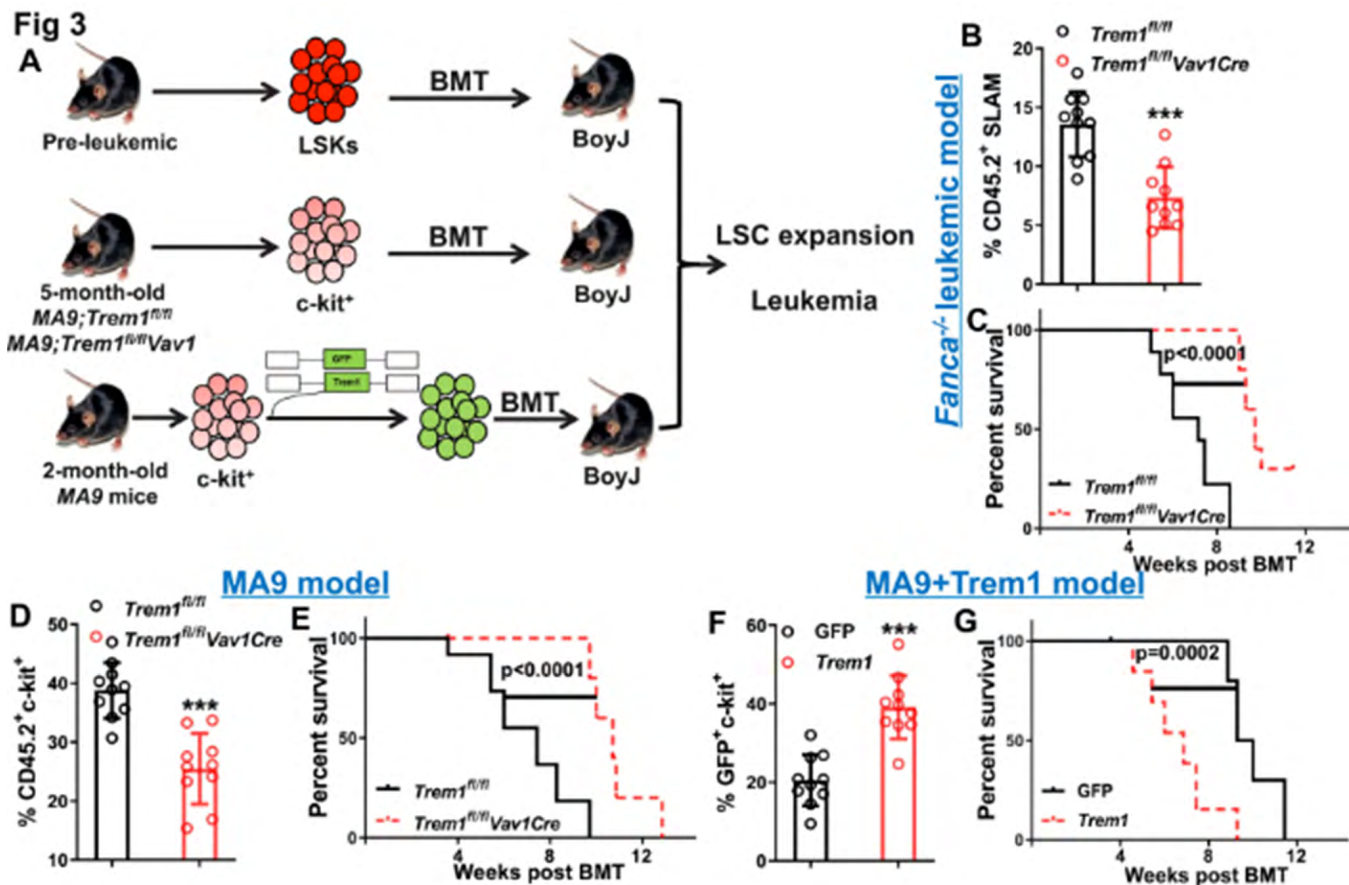


Figure Legend: TREM1 in leukemogenesis using mouse models of the DNA repair-deficient *Fanca*^{-/-} and the oncogenic *MLL-AF9* or *Kras*^{G12D}.

More Cool Science

Evaluation of the molecular landscape of pediatric thyroid nodules and use of a multigene genomic classifier in children.

This was a retrospective consecutive case series and multigene genomic classifier (GC) testing of fine-needle aspiration (FNA) and formalin-fixed paraffin-embedded (FFPE) tissues from sequential pediatric thyroidectomies performed between January 2003 and December 2019 at a single tertiary academic medical center. The study included 95 patients (median [range] age, 16.3 [4.8 to 21.1] years; 75 [79%] female) who underwent surgery for a thyroid nodule. Of the 95 patients, 75 (79%) were female, and the median (IQR) age was 16.3 (14.0-17.3) years. Next-generation sequencing confirmed the unique molecular landscape of malignant pediatric thyroid nodules (compared with adults), which is dominated by gene fusions (most commonly RET and NTRK), rare BRAF/RAS alterations, and no TP53 or TERT promoter pathogenic variants. Several poorly differentiated thyroid cancers harbored DICER1 variants. Benign nodules appeared to be almost exclusively associated with TSHR and DICER1 alterations. The test demonstrated a 96% sensitivity (95% CI, 87%-99%) and 78% specificity (95% CI, 64%-88%). The negative predictive value was 95% (95% CI, 88%-98%) and the positive predictive value was 83% (95% CI, 74%-89%). The concordance of GC between 23 pairs of matched FFPE and FNA tissues was 96%.

Impact: The study results suggest that although the molecular landscape of pediatric thyroid nodules is different than in adults, it remains amenable to multigene genomic classification. The multigene GC test, with high sensitivity and reasonably high specificity, represents a potential addition to the diagnostic workup of children with thyroid nodules which may help prevent potentially unnecessary diagnostic surgeries.

Funding: This work was funded by the American Society of Cytopathology (Young Investigator Award to Dr. Weiss), American Thyroid Association (2019-0000000090 to Dr. Weiss), National Cancer Institute (VCORCDP K12CA090625 and K08CA240901-01A1 to Dr. Weiss), V Foundation for Cancer Research (Scholar Award to Dr. Weiss), Children's Cancer Research Fund (Research Award to Dr. Weiss), and American Cancer Society (133934-CSDG-19-216-01-TBG to Dr. Weiss).

Source: Gallant, J. N., S. C. Chen, C. A. Ortega, S. L. Rohde, R. H. Belcher, J. L. Netteville, N. Baregamian, H. Wang, J. Liang, F. Ye, Y. E. Nikiforov, M. N. Nikiforova and V. L. Weiss (2022). "Evaluation of the Molecular Landscape of Pediatric Thyroid Nodules and Use of a Multigene Genomic Classifier in Children." *JAMA oncology*, 8(9): 1323-1327.

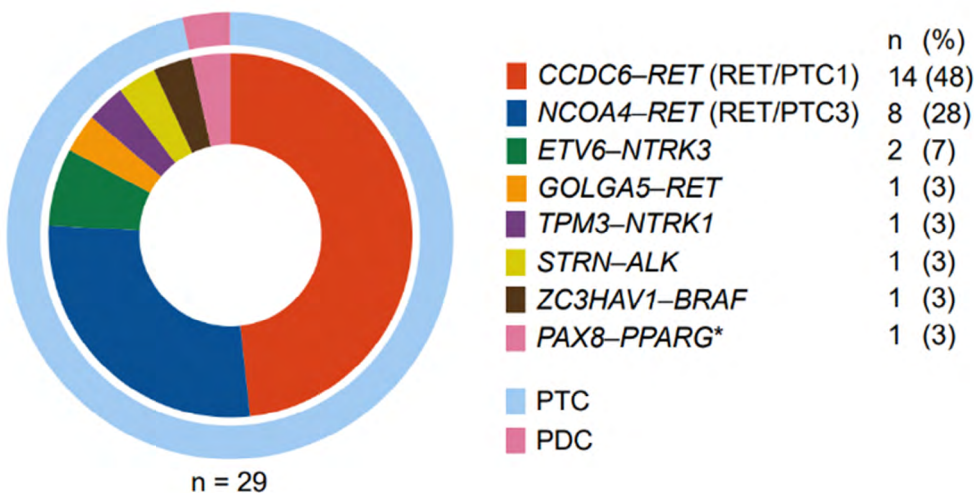


Figure Legend: Gene fusions identified in malignant pediatric thyroid nodules pie chart demonstrating the breakdown of gene fusions identified in pediatric malignant thyroid nodules. The inner ring breaks down the different gene fusions, and the outer ring highlights the nodule pathology. Abbreviations: PTC, papillary thyroid cancer (and variants); PDC, poorly differentiated carcinoma. The PAX8-PPARG (asterisk) fusion was also identified in a benign nodule (follicular adenoma). TREM1 in leukemogenesis using mouse models of the DNA repair-deficient Fanca^{-/-} and the oncogenic MLL-AF9 or Kras^{G12D}.

More Cool Science

Telomeric 8-oxo-guanine drives rapid premature senescence in the absence of telomere shortening.

Oxidative stress and inflammation contribute to the etiology of numerous human diseases including cancer and is associated with increased telomere dysfunction and premature senescence. Telomeric DNA is highly susceptible to formation of the common oxidative lesion 8-oxo-guanine (8-oxoG), which had been proposed to accelerate telomere shortening. In this collaboration, Dr. Opresko and colleagues tested this theory directly using a chemoptogenetic tool to selectively induce 8-oxoG damage only at the telomeres. They showed that acute 8-oxoG formation at telomeres is sufficient to trigger rapid premature senescence without telomere shortening or telomere losses in primary and hTERT expressing human fibroblasts and epithelial cells. Instead, they observed that oxidative damage induced telomere fragility, DNA damage response (DDR) signaling, and replication stress at telomeres. Mechanistically, their data is consistent with a model in which 8-oxoG itself, and/or repair intermediates, stall DNA replication at the telomeres, leading to a robust induction of p53 signaling to arrest cell growth and enforce premature senescence.

Impact: This study uncovered a novel mechanism of rapid telomere-driven senescence triggered by a common oxidative stress-induced base lesion, that is distinct from “replicative senescence” and has important implications for cellular senescence linked to oxidative stress. Identifying mechanisms of cellular senescence is critical because senescent cells secrete factors that can promote tumor growth.

Funding: R01CA207209 (R.J.O.) and P30CA047904, F32AG067710-01, K99ES033771 (R.P.B.), R01EB017268 (M.P.B.) and R35ES031638 (B.V.H), and R35ES030396, R01CA207342 (P.L.O). Glenn Award for Research in Biological Mechanisms of Aging (P.L.O).

Source: Barnes, R. P., M. de Rosa, S. A. Thosar, A. C. Detwiler, V. Roginskaya, B. Van Houten, M. P. Bruchez, J. Stewart-Ornstein and P. L. Opresko (2022). [“Telomeric 8-oxo-guanine drives rapid premature senescence in the absence of telomere shortening.”](#) *Nature structural & molecular biology* **29**(7): 639–652.

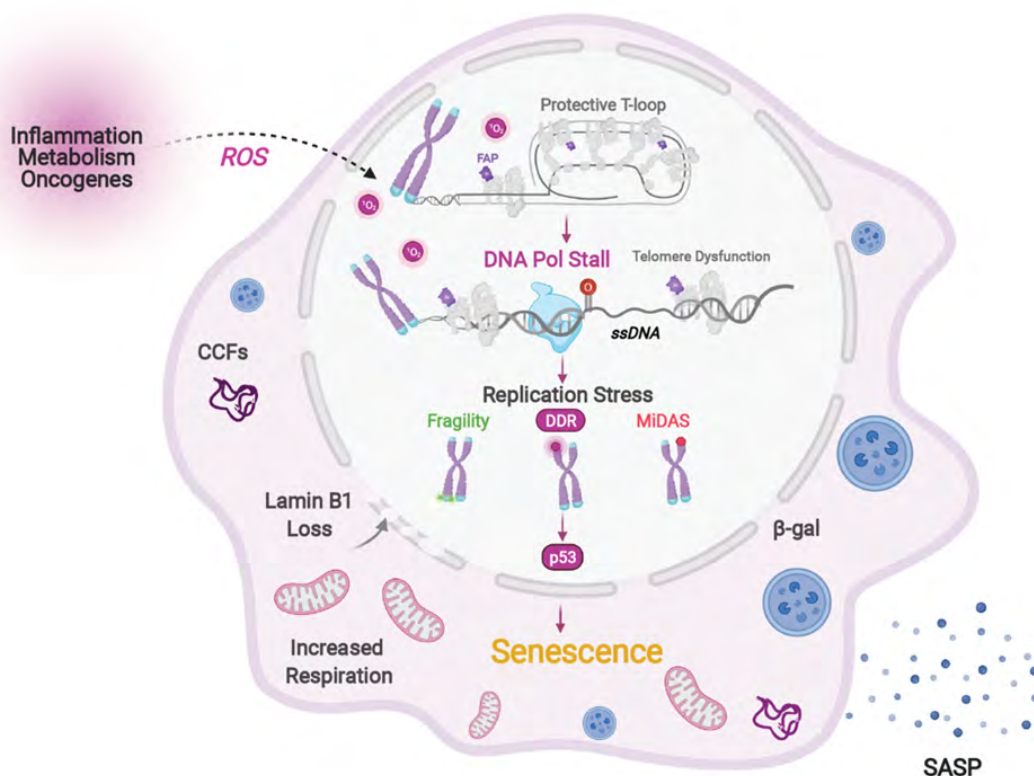


Figure Legend: Model for telomere 8-oxoG induced senescence. Under oxidative stress (ROS) telomeres are susceptible 8-oxoG formation. Replication fork stalling at 8-oxoG in the telomere can result in excess single stranded DNA and replication stress, which leads to telomere fragility, localized DDR signaling, and mitotic DNA synthesis (MiDAS) at the telomere. Telomeric DDR activates p53 which promotes hallmarks of cellular senescence. Image created with BioRender.com.

More Cool Science

Redox regulation of RAD51 Cys319 and homologous recombination by peroxiredoxin 1.

Reactive species from exogenous and endogenous sources can damage both proteins and DNA. Peroxiredoxin 1 (PRDX1) scavenges excess peroxides by reducing them and coordinates the signaling of interacting proteins. In this collaborative study Carola Neumann, MD, and colleagues showed that PRDX1 modulates the oxidation of Cysteine 319 of the RAD51 recombinase protein, which is essential for homologous recombination (HR) of chromosome breaks and collapsed replication forks. The loss of PRDX1 inhibits RAD51 foci formation and represses HR-mediated repair after the induction of DNA double strand breaks by ionizing radiation. PRDX1-deficient human breast cancer cells and mouse embryonic fibroblasts show disrupted RAD51 foci formation and decreased HR, leading to increased cellular sensitivity to irradiation. PRDX1 deficient cells also show increased incorporation of a sulfenylation probe in RAD51 Cys319, a thiol important for RAD51 function which PRDX1 maintains in a reduced state. Molecular dynamics (MD) simulations show tight binding of poly-dT DNA by a non-oxidized RAD51 protein, but dissociation of poly-dT DNA from an oxidized Cys319 RAD51 filament. These novel data establish RAD51 Cys319 as a functionally important site for the redox regulation of HR and cellular responses to IR, and PRDX1 as a critical regulator of HR.

Impact: This study highlights the importance of PRDX1 in maintaining homologous recombination repair by protecting the functionally important Cys319 residue in RAD51 from oxidation. Factors that regulate homologous recombination are important targets for sensitizing cells to PARP inhibitor cancer therapy.

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Source: Skoko, J. J., J. Cao, D. Gaboriau, M. Attar, A. Asan, L. Hong, C. E. Paulsen, H. Ma, Y. Liu, H. Wu, T. Harkness, C. M. Furdui, Y. Manevich, C. G. Morrison, E. T. Brown, D. Normolle, M. Spies, M. A. Spies, K. Carroll and C. A. Neumann (2022). [“Redox regulation of RAD51 Cys319 and homologous recombination by peroxiredoxin 1.”](#) *Redox biology*, **56**: 102443.

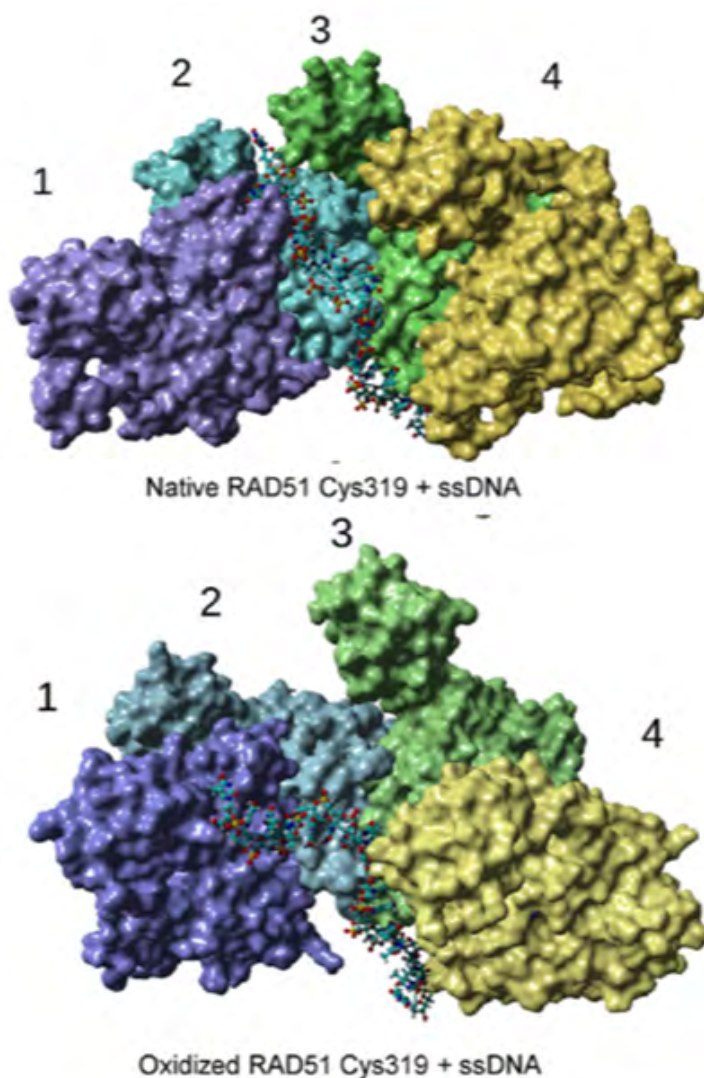


Figure Legend: MD simulations of a tetrameric RAD51-DNA filament show sulfenylation of Cys319 destabilizes ssDNA binding. The last snapshot of a refined MD for native (upper) and oxidized (lower) RAD51 filaments with different protomers colored in purple, blue, green, and yellow demonstrated ssDNA (poly-dT ball and stick) was destabilized in the oxidized RAD51 filament from binding residues in loops 232-237 and 278-288 present in the native RAD51 Cys319 filament.

Faculty and Staff News



Carola Neumann, MD

Carola Neumann, MD & Patricia Opresko, PhD elected to lead societies.

Congratulations to Dr. Carola Neumann for being elected as the next SfRBM President-Elect! Dr. Neumann is currently Associate Professor and Vice Chair for Precision and Translational Pharmacology. Her research focuses on redox biology in cancer development and treatment. Dr. Neumann has been an SfRBM Council Member since 2018, serving first as Free Radical School Committee Chair and is currently the Marketing - Internal Chair, responsible for The Dot newsletter. She has also been a conference abstract reviewer and Young Investigator Award judge. Dr. Neumann is also SfRBM's current representative on FASEB's Science Policy Committee, and she will assume the role of SfRBM President in 2025.



Patricia Opresko, PhD

Congratulations also to Dr. Patricia L. Opresko for being elected as the next Vice President-elect to the Environmental Mutagenesis and Genomics Society. She will serve as President next. Dr. Opresko is a Professor of Environmental and Occupational, and of Pharmacology and Chemical Biology. She has been highly active in EMGS since joining in 2005 and has regularly participated in the annual meetings by presenting and chairing sessions. Dr. Opresko served on the Program, Awards and Honors, Finance, and Executive Committees. She was elected as a Counselor and as the DNA Repair SIG Representative to the Program Committee. Dr. Opresko values EMGS for the opportunities to participate in a scientific society that shares her interests in genome stability, genotoxic exposures, and human health, and looks forward to continued EMGS growth and advancement.



Benjamin A.
Nacev, MD, PhD

Benjamin A. Nacev, MD, PhD, joins UPMC Hillman Cancer Center.

Dr. Nacev earned his MD and PhD degrees from the Johns Hopkins University School of Medicine, where his work focused on the mechanisms of small-molecule inhibitors of angiogenesis. Following his doctoral training, he completed his internal-medicine residency in the Osler training program at the Johns Hopkins Hospital before joining Memorial Sloan Kettering for a Medical Oncology/Hematology fellowship. After completing his fellowship, Dr. Nacev joined the faculty of the Sarcoma Medical Oncology Service at Memorial Sloan Kettering. Dr. Nacev's research is focused cancer-associated mutations in histone genes and on understanding genetic alterations in epigenetic regulators in sarcomas.



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 in order 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/>