BIOGRAPHICAL SKETCH

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NAME: Eckert, Kristin

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POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Pennsylvania State University, University Park, PA	BS	05/1982	Microbiology
University of Wisconsin-Madison, Madison, WI	PhD	12/1988	Oncology
National Institute of Environmental Health Science, Research Triangle Park, NC	Postdoctoral Fellow	06/1993	Molecular Genetics

A. Personal Statement

Education administration and mentoring experience: I am the Associate Director for Cancer Research Training and Education for the Penn State Cancer Institute (PSCI). In this capacity, I am responsible for coordinating cancer research career development activities for trainees across the entire continuum, from K-12 education through faculty levels. This role gives me an intimate knowledge of the nuances of cancer research education and training at all career stages. To stay abreast of current national standards in all aspects of cancer research training, I am a member of the Board of Directors for the Cancer Biology Training Consortium (CABTRAC), which gives me first-hand knowledge of current trends and best practices in mentoring and career advancement, including diversity training. I currently am MPI of an NCI-R25 research training grant ("PROMISE") that provides undergraduate students from diverse backgrounds with a holistic understanding of cancer as a disease (how it is prevented, controlled, and treated), while stimulating interest in oncology careers and providing the skills needed for participants to have durable research careers. I recently served a 5-year appointment as Director of the Penn State College of Medicine's Office of Postdoctoral Affairs, where I was responsible for the career and professional development of the ~100 postdoctoral scholars at our institution. These responsibilities included oversight of the required postdoctoral Responsible Conduct of Research (RCR) training, implementing University policies governing postdoctoral scholars, and creating specific postdoctoral programs and workshops. My current position as Chief of the Experimental Pathology Division provides me with professional development and mentoring responsibilities for both non-tenure track and tenure-track junior faculty.

Since beginning my independent research career, I have successfully mentored over 35 trainees across the full spectrum of learners in my cancer research laboratory: high school, undergraduate science and medical, graduate, postdoctoral, resident, faculty and professional (science teacher) levels. Through my extensive and wide-ranging educational experiences, I am highly familiar with all aspects of training and mentorship. My previous mentees enjoy a broad range of scientific careers, including traditional academia (tenured professors), along with government, biotech industries and the private sector. In recognition of my administrative leadership, teaching and mentoring excellence, I was named a Distinguished Educator of the Penn State College of Medicine in 2015. I have successfully mentored several undergraduate minority students who now hold positions as Assistant Professor (MD) at Vanderbilt University, Research Associate at Mount Sinai, and NSF graduate research fellow at the University of Michigan.

My direct mentorship and training experiences, together with my administrative roles within the Penn State Cancer Institute, give me insight into the varied problems and challenges facing trainees, as well as practical experiences in how to overcome such obstacles. *These experiences have given me profound insights into how best to translate an NIH-funded research program into productive projects for learners in the REACH program*.

Research expertise: My research career has been devoted to studying mechanisms of mutagenesis in human cells, particularly in relation to tumor cell evolution. I have >25 years of basic genetics and biochemistry research and interdisciplinary NIH grant leadership experience in the fields of DNA polymerase fidelity,

mutational mechanisms within microsatellite DNA sequences, and DNA damage-induced mutagenesis. My lab uses integrated biochemical, molecular biology, genetics and genomics approach to study how human cells orchestrate the activities of over 15 DNA polymerases. A central focus of my laboratory has been to elucidate how repetitive regions of the human genome are replicated in an efficient and high fidelity manner. Microsatellite DNA instability is a well-known genetic signature found in many types of cancer. We use both *ex vivo* (nontumorigenic and tumorigenic human cell lines) and *in vitro* biochemical approaches to elucidate the contributions of DNA polymerase fidelity and mismatch repair to microsatellite instability. My research program also includes an interdisciplinary, collaborative a genomics approach to study microsatellite stability within individual human genomes. Recently, my laboratory has made new discoveries regarding the human cell responses to DNA replication stress, particularly ATR signaling and DNA polymerase regulation. This research is at the leading edge of a new field studying replication stress and the effects on Difficult-to-Replicate Sequences, such as fragile sites and G-quadruplexes, regions of the genome correlated with increased genome instability and structural variation in tumor cells.

Active Grant Support

R01 CA237153
Eckert (PI)
04/01/2019-3/31/2024
Pro-tumorigenic functions of human DNA polymerases eta and kappa during genome duplication under physiological replication stress conditions

R25 CA272184
Eckert (MPI)
09/01/2022 - 08/31/2027
Penn State Research training in Oncology and Medicine to Inspire Student Engagement (PROMISE)

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2019-present	Chief, Division of Experimental Pathology, Department of Pathology
2017-present	Associate Director for Cancer Research Training and Education, Penn State Cancer Institute
2015-2020	Director, Office of Postdoctoral Affairs, Penn State University, Hershey campus
2023-2025	Board of Directors, Cancer Biology Training Consortium (CABTRAC)
2021	Chair, Cancer Genomics Special Emphasis Panel
2021	Panel member, NCI Program Project Review III (ZCA SRB-K M1)
2020	Panel member, F09A Fellowships: Oncology review panel
2019	Panel member, NCI Oncology 1-Special Emphasis panel
2018	Panel member, NCI SPORE grant review
2017	Panel member, NCI Predoctoral to Postdoctoral Fellow Transition Award ZCA RTRB-0
2014 - 2015	Ad Hoc Member, NIH/CSR panel member: NCI Omnibus R21/R03; Cancer Etiology
2014	Member, Oncology 2 - Translational Clinical IRG (OTC) IRG integrated review group
2013 - 2019	Editorial Board, Cancer Research
2012	Panel Member, Radiation Therapeutics SEP ZRG1 OTC-C
2011	Panel Member, Basic & Translational Molecular Oncology P01 SEP NCI
2008	Chair, NIH/CSR Special Emphasis Panel ZRG1 ONC-H(02)
2007-present	Professor, Pennsylvania State University College of Medicine
2006-present	Member, Penn State Hershey Cancer Institute
2006 - 2010	Member, Radiation Therapeutics and Biology Study Section, NIH/CSR (Acting Co-chair)
1999 - 2007	Associate Professor (with tenure), Pennsylvania State University College of Medicine
1993 - 1999	Assistant Professor, Pennsylvania State University College of Medicine, Hershey, PA

Honors

2020	Penn State Hershey Commission for Women, "Commitment, Community, Change" Award
2015	Distinguished Educator, Pennsylvania State University College of Medicine
1997	American Cancer Society Research Scholar, American Cancer Society
1995	Gertrude Elion Cancer Research Award, American Association for Cancer Research

C. Contributions to Science

1. *Mechanisms of Human Genome Replication through* DiToRS. DNA polymerases encounter many Difficult-To-Replicate Sequences, or DiToRS, within repetitive genome regions that cause replication fork stalling. If not navigated efficiently, DiToRS lead to double strand breaks and structural variation, particularly during tumorigenesis. My laboratory is at the leading edge of a new field studying DNA polymerase activities required for efficient DiToRS replication. We discovered that replicative DNA polymerases are significantly inhibited with specific types of repetitive DNA sequences, thereby contributing to replication stress. We demonstrated that specialized DNA polymerases eta and kappa are required for efficient common fragile site stability, and that polymerase eta prevents tumor cell death under conditions of replication stress in human cells.
   a. Shah SN, Opresko PL, Meng X, Lee MY, **Eckert KA**. DNA structure and the Werner protein modulate human DNA polymerase delta-dependent replication dynamics within the common fragile site FRA16D. Nucleic Acids Res. 2010 Mar; 38(4):1149-62. PubMed PMID: 19969545; PubMed Central PMCID: PMC2831333.
   b. Barnes RP, Tsao WC, Moldovan GL, **Eckert KA**. DNA Polymerase Eta Prevents Tumor Cell Cycle Arrest And Cell Death During Recovery from Replication Stress. Cancer Res. 2018 Dec; 78(23):6549-60. PubMed PMID: 30297532.
   c. Kaushal, S., C E. Wollmuth, K Das, SE Hile, SB Regan, RP Barnes, A Haouzi, SM Lee, NCM House, Mi Guyumdzhyan, **KA Eckert**, and CH Freudenreich. Sequence and nuclease requirements for breakage and healing of a structure-forming (AT)n sequence within fragile site FRA16D. Cell Reports 2019; 27(4):1151-1164. PMID:31018130
   d. Tsao WC, R. Buj, K. M. Aird, J. M. Sidorova, and **KA Eckert** . Overexpression of oncogenic H-Ras in hTERT-immortalized and SV40 transformed human cells targets replicative and specialized DNA polymerases for depletion. PLoS ONE 2021 May 7;16(5):e0251188. PMID: 33961649.

2. *Repetitive DNA and Genome Evolution*: In collaborative research, we have extensively studied repetitive DNA evolution in the human genome to discover the underlying "why" and "how" of mutagenesis, rather than simply providing descriptive analyses of the types of genome changes. Our pioneering work describing the definition of a microsatellite based on mutational behavior has been extensively cited by microsatellite researchers in both the genome evolution and disease fields. Our novel studies of DNA polymerase errors within microsatellites and other repetitive sequences that form alternative DNA secondary structures (collectively called non-B DNA) have provided new insights into the mechanisms stabilizing the human genome, and the contribution of microsatellites to chromosome fragility.
   a. Fungtammasan A, Walsh E, Chiaromonte F, **Eckert KA***, Makova KD*. A genome-wide analysis of common fragile sites: what features determine chromosomal instability in the human genome?. Genome Res. 2012 Jun;22(6):993-1005. PubMed PMID: 22456607; PubMed Central PMCID: PMC3371707. *co-corresponding authors.
   b. Ananda G, Hile SE, Breski A, Wang Y, Kelkar Y, Makova KD, **Eckert KA***. Microsatellite interruptions stabilize primate genomes and exist as population-specific single nucleotide polymorphisms within individual human genomes. PLoS Genet. 2014 Jul;10(7):e1004498. PubMed PMID: 25033203; PubMed Central PMCID: PMC4102424. *co-corresponding authors
   c. Guiblet, W.M., M.A. Cremona, M. Cechova, R.S. Harris, I.Kejnovska, E. Kejnovsky, **K. Eckert**, F. Chiaromonte, and K.D. Makova. Long-read sequencing technology indicates genome-wide effects of non-B DNA on polymerization speed and error rate. Genome Res. 2018; 28(12):1767-1778. PMID: 30401733.

d. Guiblet, W., M A. Cremona, R. S. Harris, D Chen, **K A Eckert**, F Chiaromonte, YF Huang, and KD Makova. Non-B DNA: A major contributor to small- and large-scale variation in nucleotide substitution frequencies across the genome. Nucleic Acids Research, 2021; 49(3):1497-1516. PMID: 33450015.

3. *DNA Polymerase Functions in Genome Duplication:* We demonstrated, for the first time, that specialized DNA polymerases can replicate microsatellite sequences more accurately than replicative polymerases. These and other studies advanced a new paradigm in which specialized polymerases have adopted critical functions in DNA duplication, beyond DNA translesion synthesis, as higher eukaryotic genomes have acquired increased repetitive DNA content.
   a. Hile SE, Wang X, Lee MY, **Eckert KA**. Beyond translesion synthesis: polymerase κ fidelity as a potential determinant of microsatellite stability. Nucleic Acids Res. 2012 Feb;40(4):1636-47. PubMed PMID: 22021378; PubMed Central PMCID: PMC3287198.
   b. Walsh E, Wang X, Lee MY, **Eckert KA**. Mechanism of replicative DNA polymerase delta pausing and a potential role for DNA polymerase kappa in common fragile site replication. J Mol Biol. 2013 Jan 23;425(2):232-43. PubMed PMID: 23174185; PubMed Central PMCID: PMC3540124.
   c. Barnes, RP, Hile, SE, Lee, MY, and **Eckert KA**. DNA polymerases eta and kappa exchange with the replicative polymerase delta holoenzyme to complete common fragile site synthesis. DNA Repair, 2017; 57: 1-11. PMID:28605669
   d. Stein, ME, Hile S, Weissensteiner M, Lee MY, Zhang S, Kejnovsky E, Kejnovská I, Makova KD, and **Eckert KA** (2022) Variation in G-quadruplex Sequence and Topology Differentially Impacts Human DNA Polymerase Fidelity. DNA Repair 119:103402. PMID: 36116264.

4. *Mechanisms of Microsatellite Instability in Human Cells*: Our laboratory published seminal work that contributed to our understanding the mechanisms of microsatellite instability in human cells. We demonstrated that microsatellites of various motif sequences have intrinsically low mutation rates during replication in non-tumorigenic somatic cells (a, d). We demonstrated that loss of distinct mismatch repair proteins, such as those associated with Lynch Syndrome, create strong mutational biases within microsatellites (b,c). Our work illuminated the biochemical mechanisms underlying different molecular phenotypes observed diagnostically with microsatellites in tumor cells, such as MSI-low and EMAST (d).
   a. Hile SE, Yan G, **Eckert KA**. Somatic mutation rates and specificities at TC/AG and GT/CA microsatellite sequences in nontumorigenic human lymphoblastoid cells. Cancer Res. 2000 Mar 15;60(6):1698-703. PubMed PMID: 10749142.
   b. Shah SN, **Eckert KA**. Human postmeiotic segregation 2 exhibits biased repair at tetranucleotide microsatellite sequences. Cancer Res. 2009 Feb 1;69(3):1143-9. PubMed PMID: 19155293; PubMed Central PMCID: PMC3642623.
   c. Baptiste BA, Ananda G, Strubczewski N, Lutzkanin A, Khoo SJ, Srikanth A, Kim N, Makova KD, Krasilnikova MM, **Eckert KA**. Mature microsatellites: mechanisms underlying dinucleotide microsatellite mutational biases in human cells. G3 (Bethesda). 2013 Mar;3(3):451-63. PubMed PMID: 23450065; PubMed Central PMCID: PMC3583453.
   d. Hile SE, Shabashev S, **Eckert KA**. Tumor-specific microsatellite instability: do distinct mechanisms underlie the MSI-L and EMAST phenotypes?. Mutat Res. 2013 Mar-Apr;743-744:67-77. PubMed PMID: 23206442; PubMed Central PMCID: PMC3610773.

5. *DNA Polymerase Fidelity*: My studies of DNA polymerase structure/function and DNA polymerase error discrimination mechanisms (i.e., fidelity) began as a postdoctoral fellow at NIEHS. My independent laboratory continued this research, focusing on DNA polymerase structure/function (a,c) and polymerase fidelity when replicating alkylated DNA lesions (b). Our expertise in DNA polymerase fidelity is both nationally and internationally recognized, as many collaborators have asked us to characterize DNA polymerases, including the newly identified PrimPol (d).
   a. Opresko PL, Shiman R, **Eckert KA**. Hydrophobic interactions in the hinge domain of DNA polymerase beta are important but not sufficient for maintaining fidelity of DNA synthesis. Biochemistry. 2000 Sep 19;39(37):11399-407. PubMed PMID: 10985785.

b. Hamid S, **Eckert KA**. Effect of DNA polymerase beta loop variants on discrimination of O^6-methyldeoxyguanosine modification present in the nucleotide versus template substrate. Biochemistry. 2005 Aug 2;44(30):10378-87. PubMed PMID: 16042415.

c. Donigan, K.A., S. E. Hile, **K.A. Eckert** and J.B. Sweasy (2012) The human gastric cancer-associated DNA polymerase ß variant D160N is a mutator that induces cellular transformation, DNA Repair, 11:381-390. PubMed PMID: 22341651; PMCID: PMC3624760

d. Guilliam TA, Jozwiakowski SK, Ehlinger A, Barnes RP, Rudd SG, Bailey LJ, Skehel JM, **Eckert KA**, Chazin WJ, Doherty AJ. Human PrimPol is a highly error-prone polymerase regulated by single-stranded DNA binding proteins. Nucleic Acids Res. 2015 Jan;43(2):1056-68. PubMed PMID: 25550423; PubMed Central PMCID: PMC4333378.

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