BIOGRAPHICAL SKETCH

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NAME: Brandt F. Eichman

eRA COMMONS USER NAME (credential, e.g., agency login): beichman

POSITION TITLE: Professor and Chair of Biological Sciences, William R. Kenan, Jr. Chair

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Mississippi, Oxford, MS	BS	12/1993	Chemistry
Oregon State University, Corvallis, OR	PHD	10/2000	Biochemistry & Biophysics
Harvard Medical School Boston, MA (Advisor: Tom Ellenberger)	Postdoctoral Fellow	05/2004	Structural Biology of DNA Replication and Repair

A. Personal Statement

Research in my laboratory is focused on the mechanisms by which DNA processing proteins maintain integrity of the genome. We apply a combination of structural/biophysical, biochemical, and genetic methods to understand (1) excision repair of DNA alkylation damage and (2) assembly, progression, and repair of the eukaryotic DNA replication machinery. I have a broad background in physical biochemistry, extensive training and experience in protein and DNA structure determination by X-ray crystallography, and significant experience in protein and nucleic acid chemistry and enzymology. My graduate training involved determination of crystal structures of DNA-psoralen interstrand crosslinks and DNA recombination intermediates. I expanded these research interests as an NIH postdoctoral fellow at Harvard Medical School to include structural enzymology of DNA repair and replication proteins, and further developed the technical skills and biological background directly relevant to the current focus of my laboratory. I have expanded my structural toolbox to include NMR, SAXS and EM through collaborations at Vanderbilt and elsewhere. As an independent investigator at Vanderbilt University, I have demonstrated success in coordinating personnel, collaborations, and budgets for multiple research programs by maintaining continued funding from no less than two concurrent grants from the NIH, NSF, and American Cancer Society, publishing high-impact peer reviewed articles, and training postdoctoral fellows and students at both the graduate and undergraduate levels. For example, one of my current postdoctoral research associates has published seven first author publications in *Nature*, *Nature Chemical Biology*, and *PNAS*, among others. I hold appointments in both the College of Arts & Science and School of Medicine, in which I teach undergraduate and graduate level biochemistry courses full time throughout the academic year in addition to directing a research lab with a steady state of 10 people. I integrate training in the classroom with laboratory research by providing opportunities for trainees at all levels to serve as teaching assistants in my biochemistry courses and as research mentors to younger students. In the past 13 years, I have mentored 6 postdoctoral scholars, 13 graduate students, and 15 undergraduates in the laboratory, all of whom subsequently continued with scientific training or careers in medical school, graduate school, government, and industry. Of the 5 current graduate students in my laboratory, three are women and two are underrepresented minorities that entered Vanderbilt through the Initiative for Maximizing Student Diversity (IMSD), an NIH funded program that promotes diversity by developing and supporting graduate students underrepresented in biomedical science as they pursue a Ph.D. degree. My commitment to training the next generation of scientists is highlighted by the fact that I developed and served as co-director for Vanderbilt's first undergraduate major in Biochemistry & Chemical Biology.

1. Mullins EA, Shi R, Parsons ZD, Yuen PK, David SS, Igarashi Y, and Eichman BF (2015) The DNA glycosylase AlkD uses a non-base-flipping mechanism to excise bulky lesions. ***Nature***, 527: 254-258. (PMC4896645)

2. Kile AC, Chavez DA, Bacal J, Eldirani S, Korzhnev DM, Bezsonova I, Eichman BF*, Cimprich KA* (2015) HLTF's Ancient HIRAN Domain Binds 3′-DNA Ends to Drive Replication Fork Reversal. ***Mol Cell***, 58: 1090-1100. (PMC4475461)
3. Mullins EA, Shi R, and Eichman BF (2017) Toxicity and repair of DNA adducts produced by the natural product yatakemycin. ***Nat Chem Biol***, 13: 1002-1008. (PMC5657529)
4. Thompson PS§, Amidon KM§, Mohni KN, Cortez D*, and Eichman BF*. (2019) Protection of abasic sites during DNA replication by a stable thiazolidine protein-DNA crosslink. ***Nat Struct Mol Biol***, 26: 613-618 (PMC6628887)

B. Positions and Honors

Positions and Employment

2004-2010 Assistant Professor of Biological Sciences, Vanderbilt University, Nashville, TN
2007-2010 Assistant Professor of Biochemistry, Vanderbilt University Medical Center, Nashville, TN
2010-2016 Associate Professor of Biological Sciences and Biochemistry, Vanderbilt University
2016-present Professor of Biological Sciences and Biochemistry, Vanderbilt University
2016-2019 Co-Director, Undergraduate Program in Biochemistry and Chemical Biology, Vanderbilt Univ
2018-present William R. Kenan, Jr. Chair at the College of Arts & Science, Vanderbilt University
2019-present Chair, Department of Biological Sciences, Vanderbilt University

Other Experience and Professional Membership

1991-present Member, American Chemical Society (1991-present), American Crystallographic Association (1998-present), American Society of Photobiology (2001), American Society for Biochemistry and Molecular Biology (2008-present), Sigma Xi Scientific Research Society (2008-present)
2004-present Member, Vanderbilt Center for Structural Biology, Center in Molecular Toxicology (2006-present), Institute of Chemical Biology (2005-present), Vanderbilt-Ingram Cancer Center (2005-present)
2004-present Ad Hoc Reviewer: *Nature, Nature Struct and Mol Bio, Nature Communications; Molecular Cell, Cell Reports, PNAS*, *EMBO Journal*, *Journal of Biological Chemistry*, *Structure*, *Molecular and Cellular Biology*, *Nucleic Acids Research*, and others
2007-2016 Educational Testing Service GRE Biochemistry Subject Test, Author and Reviewer
2011-2015 Vanderbilt College of Arts & Science Curriculum Committee (Chair 2014-15)
2011-present NSF Division of Molecular and Cellular Biosciences: *ad hoc* reviewer
2012-2014 Vanderbilt Chapter of Sigma Xi President
2013-present Faculty of 1000 member and reviewer, Structural Biology / Structure: Replication and Repair
2014 Co-organizer, FASEB Summer Conference, *Machines on Genes: Nucleic Acid Enzymes*
2014 Co-organizer, Southeast Regional Meeting of the ACS, *Frontiers in Nucleic Acids Symposium*
2014-present Italian Association for Cancer Research (AIRC), ad hoc grant reviewer
2015 NIH Macromolecular Structure and Function A (MSFA) Study Section, ad hoc member
2016 NIH Macromolecular Structure and Function A (MSFA) Study Section, mail-in reviewer
2016 NIH NCI Program Project P01 Special Emphasis Review Panel ZCA1 RPRB-F
2017 NIH Macromolecular Structure and Function C (MSFC) Study Section, ad hoc member
2018 NIH NCI Program Project P01 Special Emphasis Review Panel ZCA1 RTRB-E

Honors

1989-1993 Kelly Gene Cook full academic scholarship, University of Mississippi
1995 Kelly Gene Cook graduate scholarship, Oregon State University
2002-2004 Ruth L. Kirschstein National Research Service Award, NIH Postdoctoral Fellowship
2002 American Cancer Society Postdoctoral Fellowship, Declined
2007 American Cancer Society Research Scholar
2009 Sigma Xi Young Investigator Award
2011 Vanderbilt Chancellor's Award for Research
2011 Keynote speaker at Argonne National Laboratory Annual Users Meeting, Argonne, IL
2012 Elected Co-Organizer of 2014 FASEB Science Research Conference: *Nucleic Acids Enzymes*
2013 Appointed to Faculty of 1000
2010-2017 Vanderbilt-Ingram Cancer Center Impact Award (three time winner, 2010, 2015, 2017)
2018 William R. Kenan, Jr. Chair at the College of Arts & Science

C. Contribution to Science

1. *DNA glycosylase repair of DNA alkylation damage.* DNA alkylation represents the most abundant and devastating type of genotoxic damage to the cell, and is the basis for the use of alkylating agents in chemotherapy. My lab has made important contributions to our understanding of how various types of alkylation damage derived from reactive metabolites, microbial toxins, and anti-cancer drugs are located and repaired by DNA glycosylases, which initiate the base excision repair (BER) pathway. The predominant view for years was that BER is confined to small lesions because DNA glycosylases achieve specificity and catalysis by flipping the damaged base out of the DNA helix and into an active site pocket. Through our work on several enzymes that remove bulky adducts and interstrand crosslinks derived from bacterial toxins, we discovered that base flipping is not required for damage recognition and excision by DNA glycosylases, and that this novel mechanism enables glycosylases to excise larger chemical adducts than previously known, which has opened the door to discovery of new repair enzymes and genotoxic agents important for beneficial and pathogenic host-microbe relationships.
    a. Mullins EA, Shi R, Parsons ZD, Yuen PK, David SS, Igarashi Y, and Eichman BF (2015) The DNA glycosylase AlkD uses a non-base-flipping mechanism to excise bulky lesions. ***Nature***, 527: 254-258. (PMC4896645)
    b. Mullins EA, Shi R, and Eichman BF (2017) Toxicity and repair of DNA adducts produced by the natural product yatakemycin. ***Nat Chem Biol***, 13: 1002-1008. (PMC5657529)
    c. Mullins EA, Warren GM, Bradley NP, Eichman BF (2017) Structure of a DNA glycosylase that unhooks interstrand cross-links. ***Proc Natl Acad Sci USA***, 114: 4400-4405 (PMC5410837)
    d. Shi R, Mullins EA, Shen X, Lay K, Yuen P, David SS, Rokas A, Eichman BF (2018) Selective base excision repair of DNA damage by the non-base-flipping DNA glycosylase AlkC. ***EMBO J***, 37: 63-74 (PMC5753038)
2. *Repair of stalled replication forks.* My laboratory has provided some of the first structural evidence for how replication forks that have stalled as a consequence of DNA damage are recognized and stabilized by proteins that aid in origin-independent replication restart. Humans possess at least three specialized DNA fork remodeling proteins (SMARCAL1, HLTF, ZRANB3) that use ATP-dependent DNA motor activity to convert fork DNA structures into a four-way junctions, which serve as an important intermediate for replication restart. Despite our knowledge of replication fork reversal as a means of tolerating or repairing damaged DNA during S-phase, the mechanisms of the fork reversal reaction, and the cellular roles of individual remodelers is unknown. We provided the first structural and biochemical information for SMARCAL1 and HLTF, which has provided a rationale for how these enzymes translocate on duplex DNA and catalyze strand reannealing, replication fork reversal, and branch migration of 4-way junctions. Together with their cell biology (in collaboration with David Cortez at Vanderbilt and Karlene Cimprich at Stanford), our mechanistic work has pushed the field toward an understanding of how these novel enzymes achieve specificity for different types of stalled forks and how fork reversal might operate in cells. In addition, we have also recently characterized a novel replication-dependent repair mechanism for abasic sites, a potent block of replication forks, through structural studies of SRAP domain-containing proteins.
    a. Mason AC, Rambo RP, Greer BH, Pritchett M, Tainer JA, Cortez D, and Eichman BF (2014) A structure-specific nucleic acid binding domain conserved among DNA repair proteins. ***Proc Natl Acad Sci USA***, 111: 7618-7623. (PMC4040553)
    b. Kile AC, Chavez DA, Bacal J, Eldirani S, Korzhnev DM, Bezsonova I, Eichman BF*, Cimprich KA* (2015) HLTF's Ancient HIRAN Domain Binds 3′-DNA Ends to Drive Replication Fork Reversal. ***Mol Cell***, 58: 1090-1100. (PMC4475461)
    c. Chavez DA, Greer BH, Eichman BF (2018) The HIRAN domain of helicase-like transcription factor positions the DNA translocase motor to drive efficient DNA fork regression. ***J Biol Chem***, 293: 8484-94 (PMC5986216)
    d. Thompson PS, Amidon KM, Mohni KN, Cortez D*, and Eichman BF*. (2019) Protection of abasic sites during DNA replication by a stable thiazolidine protein-DNA crosslink. ***Nat Struct Mol Biol***, in press (PMC article in process)
3. *Structural biology of eukaryotic DNA replication*. My laboratory provided some of the first structural information for the eukaryotic DNA replication machinery. Despite knowledge of enzymes involved in bacterial replication, at the time I started my laboratory at Vanderbilt the field knew very little about the mechanisms by which eukaryotic replisomes are assembled and activated, replication is initiated, and how

DNA unwinding and synthesis activities are coordinated. We characterized the domain architecture and binding properties of Mcm10, a central mediator in eukaryotic replication initiation and elongation. Our biochemistry and structural biology of Mcm10 provided a model for how Mcm10 serves to coordinate multiple activities within the multiprotein replisome machine. We also determined some of the first crystal structures of human DNA polymerase α-primase subunits (p58, p48), which initiates DNA synthesis at the start of each Okazaki fragment. This research program has paved the way to a current understanding of initiation of DNA replication.

a. Warren EM, Vaithiyalingam S, Haworth J, Greer B, Smith JA, Bielinsky AK, Chazin WJ, and Eichman BF (2008) Structural Basis for DNA Binding by Replication Initiator Mcm10. ***Structure***, 16: 1892-1901. (PMC2636851)
b. Warren EM, Huang H, Fanning E, Chazin WJ, and Eichman BF (2009) Physical interactions between Mcm10, DNA, and DNA polymerase α. ***J Biol Chem***, 284: 24662-24672 (PMC2782055)
c. Vaithiyalingam S, Warren EM, Eichman BF*, Chazin WJ* (2010) Insights into eukaryotic DNA priming from the structure of the unique iron-sulfur cluster domain of human DNA primase. ***Proc Natl Acad Sci USA***, 107: 13684-13689. (PMC2922289)
d. Vaithiyalingam S, Arnett DR, Aggarwal A, Eichman BF, Fanning E*, and Chazin WJ* (2014) Insights into eukaryotic priming from structures of the p48 subunit of human DNA primase in pre-catalytic conformations. ***J Mol Biol***, 426: 558-69 (PMC3946992)

4. *Structures of DNA junctions and interstrand crosslinks.* As a graduate student, I determined the first crystal structure of a Holliday junction, the four-stranded DNA intermediate formed during homologous recombination, from an inverted-repeat DNA sequence. This long-awaited structure revealed the atomic details of intrinsic DNA crossover geometry in the absence of protein, and thus provided important insight into how nucleic acid processing proteins recognize and manipulate higher order DNA tertiary structure. This breakthrough was a result of my work to understand how interstrand DNA crosslinking agents and other therapeutically important DNA adducts perturb the double-helix. I determined the first crystal structures of DNA crosslinked by psoralen, a plant natural product used clinically to treat psoriasis and as a laboratory DNA crosslinking reagent. I discovered the molecular details for how the crosslink distorts and destabilizes the DNA, and most importantly that the drug is capable of inducing the formation of four-way junctions, which was one of the first structural examples supporting a role for recombination in DNA damage repair.
    a. Eichman BF, Vargason JM, Mooers BHM, and Ho PS (2000) The Holliday junction in an inverted repeat sequence: Sequence effects on the structure of four-way junctions. ***Proc Nat Acad Sci, USA***, 97: 3971-3976. (PMC18126)
    b. Eichman BF, Mooers BHM, Alberti M, Hearst JE, and Ho PS (2001) The crystal structures of psoralen cross-linked DNA: Drug dependent formation of Holliday junctions. ***J Mol Biol***, 308: 15-26. (PMID 11302703)
    c. Ho PS and Eichman BF (2001) The crystal structures of DNA Holliday junctions. ***Curr Op Struct Biol***, 11: 302-308. (PMID 11406378)
    d. Eichman BF, Ortiz-Lombardía M, Aymamí J, Coll M, and Ho PS (2002) The inherent properties of DNA four-way junctions: Comparing the crystal structures of Holliday junctions. ***J Mol Biol***, 320: 1037-1051. (PMID 12126623)

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/brandt.eichman.2/bibliography/public/

D. Research Support

Ongoing Research Support

R01 GM117299-01 Eichman (PI) 01/20/16 - 12/31/19
NIH / NIGMS
Mechanisms of Replication Fork Repair
The major goals of this grant are to determine the molecular mechanisms of SMARCAL1 and HLTF, two DNA motor proteins that stabilize vulnerable replication forks that stall upon encountering DNA damage and other

forms of replicative stress. Structural, biochemical, and cell biological approaches will be used to define how SMARCAL1 and HLTF catalyze the remodeling of DNA forks to 4-way junctions.

MCB-1928918 Eichman (PI) 09/01/19 – 08/31/23
NSF / MCB-Genetic Mechanisms
DNA Repair Mechanisms of Self-Resistance to Genotoxic Secondary Metabolites
The goals are to understand the specialized base excision repair mechanism of resistance against toxic cyclopropylpyrroloindole natural products in *Streptomyces*. The aims of the proposal are to (1) characterize the specificity of AlkD homologs for CPI-DNA adducts, (2) elucidate the role of base excision repair in yatakemycin YTM resistance, and (3) characterize the role of AlkC in 3mC and 1mA repair in bacteria.

1R01 ES030575-A1-01 Cortez (PI) 04/01/19 – 03/31/24
NIH / NIEHS
Functions of SRAP domain proteins in DNA metabolism
The major goal of this proposal is to utilize biochemical, genetic, and structural approaches in human, yeast, and bacterial systems to determine how SRAP proteins maintain genome stability. Completing these studies will generate paradigm setting discoveries within the fields of environmental toxicology, DNA repair, DNA replication, epigenetic control, and enzymology.
Role: Co-Investigator

5P01 CA092584-16 Tainer (PI) 09/01/16 - 08/31/21
NIH / NCI
Structural Cell Biology of DNA Repair Machines / Project 2: Replication Fork Repair and Signaling (Cortez, PI)
The major goals of this grant are to determine the structures and cellular functions of human DNA motor proteins (SMARCAL1, HLTF, and ZRANB3) involved in restart of stalled/damaged DNA replication forks. The role of the Eichman lab is to use structural information for these proteins to guide experiments designed to test the role of these proteins in the cell.
Role: Sr. Investigator

Completed Research Support

R01 ES019625-05 Camps (PI) 07/25/11 - 06/30/17 NCE
NIH / NIEHS
Mechanisms of Selective Excision and Oxidative Repair of Alkylated DNA
The major goals of this project are to understand how alkylated DNA from endogenous and exogenous sources is processed. My role is to determine the structural and biochemical basis for 3-methyladenine and 1,N^6-ethenoadenine selectivity by human ABH2 dioxygenase and MAG glycosylase DNA repair enzymes.
Role: Co-Investigator

MCB-1517695 Eichman (PI) 08/01/15 - 07/31/19
NSF / MCB-Genetic Mechanisms
A New Structural Architecture for Recognition of DNA Damage
The goals are to determine 1) the molecular details by which tandem helical repeat proteins discriminate among aberrant DNA, 2) the fundamental chemical and physical basis for recognition and removal of positively charged alkylpurines from DNA, 3) the mechanism of removal of bulky yatakemycin-DNA adducts, which represent an important class of chemotherapeutic agents, and 4) the rationale for multiple alkyl-DNA glycosylases in *Bacillus*.

Discovery Grant Eichman, Chazin, Ohi (co-PI) 07/01/15 – 06/30/17
Vanderbilt College of Arts & Science
Coordination of RNA and DNA Synthesis Activities in Polymerase α-Primase
The major goals of this project are to collect preliminary data aimed at understanding 1) the range of intermolecular motions in DNA polymerase α-primase during its catalytic cycle, and 2) the role of the iron-sulfur cluster in the DNA primase subunit