BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bunting, Samuel Francis

eRA COMMONS USER NAME: BUNTINGS

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Oxford, UK	MBiochem	06/2002	Biochemistry
University of Cambridge, UK	DPhil	08/2006	Developmental Genetics
National Cancer Institute, National Institutes of Health, Bethesda, MD	Postdoctoral	08/2012	Genome Integrity

A Personal Statement

I am a newly-tenured Associate Professor in the Department of Molecular Biology and Biochemistry, School of Arts and Sciences, Rutgers University. During my tenure period (2012-2019) I have used approaches based on mouse genetics to understand basic mechanisms for the regulation of DNA repair in mammals. My background in this field dates to my time as a postdoc at the National Cancer Institute, where I conducted experiments on BRCA1-deficient mice, I discovered that the DNA damage response regulator, 53BP1, is a key regulator of DNA repair, especially when BRCA1 is mutated. We showed that deletion of 53BP1 rescues embryonic lethality and tumor susceptibility in BRCA1-deficient mice, and demonstrated that these effects correlated with increased homologous recombination frequency after deletion of 53BP1. Based on these findings, we proposed a model in which 53BP1 controls choice of DNA double-strand break repair pathways by regulating the extent of resection at DNA double-strand breaks. This model has provided a basis for a substantial volume of subsequent research activity, including the recent discovery of the ‘shieldin’ complex acting downstream of 53BP1. My overall aim is to use mouse studies to understand how mammalian DNA double-strand break processes are regulated, and to develop appropriate treatments that can be tailored to individuals with defects in these pathways.

Rutgers University has been an excellent environment for my research program, thanks to the presence of three principal investigators at the Rutgers Cancer Institute of New Jersey (Rutgers Cancer Institute) who has very closely-related research interests to mine. Dr. Shridar Ganesan is a physician-scientist who studies the activity of BRCA1 and chromatin mechanisms regulating DNA repair. Dr. Zhiyuan Shen studies regulation of the BRCA2 tumor suppressor, with a particular interest in BCCIP (BRCA2 and CDKN1A interacting protein), which was identified by his lab. Dr. Bing Xia is the discoverer of PALB2 (Partner and Localizer of BRCA2), a factor that interacts with BRCA1 to mediate DNA repair by the homologous recombination pathway. Since 2012, members of my research group have been joining scientists from the Genesan, Shen and Xia labs for our monthly ‘DNA Double-Strand Break Joint Lab Meeting’. These meetings have been helpful for sharing research findings, technical approaches, and identifying reagents that can be shared between our groups to advance our science. This highly collaborative environment has led to me being a co-author on six research papers by colleagues at Rutgers University. I have co-authored four papers with Dr. Xia, two papers with Dr. Ganesan, and one paper with Dr. Shen. We have also attended conferences together, such as the Cold Spring Harbor ‘DNA Metabolism, Genomic Stability & Human Disease’ meeting in Suzhou, China in 2018. I am extremely happy that we are now building on our long-running collaborations on DNA double-strand break repair to put together a multi-investigator proposal that allows us to better integrate approaches in our respective labs. This proposal will also benefit from the inclusion of several core facilities offering new techniques, such as the Genome Editing Core, which will provide reagents that allows us to more rigorously address our research goals.

1. Her J, Ray C, Altshuler J, Zheng H, **Bunting SF**. 53BP1 Mediates ATR-Chk1 Signaling and Protects Replication Forks under Conditions of Replication Stress. Mol Cell Biol. 2018 Mar 29;38(8). pii: e00472-17. doi: 10.1128/MCB.00472-17. Print 2018 Apr 15. PubMed PMID: 29378830; PMCID: PMC5879462.
2. Misenko SM, Patel DS, Her J, **Bunting SF**. DNA repair and cell cycle checkpoint defects in a mouse model of 'BRCAness' are partially rescued by 53BP1 deletion. Cell Cycle. 2018 Apr 5:1-36. doi: 10.1080/15384101.2018.1456295. PubMed PMID: 29620483; PubMed Central PMCID: PMC6056228.
3. Patel DS, Misenko SM, Her J, **Bunting SF**. BLM helicase regulates DNA repair by counteracting RAD51 loading at DNA double-strand break sites. J Cell Biol. 2017 Sep 14. PubMed PMID: 28912125; PubMed Central PMCID: PMC5674892.
4. Li M, Cole F, Patel DS, Misenko SM, Her J, Malhowski A, Alhamza A, Zheng H, Baer R, Ludwig T, Jasin M, Nussenzweig A, Serrano L, **Bunting SF**. 53BP1 ablation rescues genomic instability in mice expressing 'RING-less' BRCA1. EMBO Rep. 2016 Sep 26. PubMed PMID: 27670884; PubMed Central PMCID: PMC5090706.

B. Positions and Honors

Positions and Employment

2012- 2018 Assistant Professor, Department of Molecular Biology and Biochemistry, Rutgers, The State University of New Jersey
2019- Associate Professor with tenure, Department of Molecular Biology and Biochemistry, Rutgers, The State University of New Jersey

Other Experience and Professional Memberships

2013- Member, New York Academy of Sciences

Honors

2001 Scholar of New College, Oxford
2004 Chibnall Bursary from Clare College, Cambridge for research into molecular biochemistry
2005 British Society for Immunology Travel Award
2007 NCI Director's Intramural Innovation Award for research proposal 'Mapping Chromosome Breaks in B Lymphocytes using ChIP-Seq'
2009 Fellow's Award for Research Excellence
2010 Fellow's Award for Research Excellence (second award)
2011 National Cancer Institute Director's Intramural Innovation Award (second award)
2018 'Hit the Ground Running' Award for early-career contributions to the graduate program Awarded by the directors of the Rutgers Graduate Programs in Molecular Biosciences
2018 Directors' Early Career Award for outstanding contributions to the graduate program. Awarded by the directors of the Rutgers Graduate Programs in Molecular Biosciences

C. Contribution to Science

1. My previous research training has included characterization of tumor phenotypes in transgenic and gene-targeted mice, with a particular focus on lymphocytes and hematopoietic stem cells. In particular, I jointly authored a paper on lymphomas that appear in AID-transgenic mice as a consequence of a recurrent translocation involving c-myc and the micro-RNA gene, miR-155.
    a. Bolland DJ, Wood AL, Johnston CM, **Bunting SF**, Morgan G, Chakalova L, Fraser PJ, Corcoran AE. Antisense intergenic transcription in V(D)J recombination. Nat Immunol. 2004 Jun;5(6):630-7. PubMed PMID: 15107847.
    b. Vigorito E, Perks KL, Abreu-Goodger C, **Bunting SF**, Xiang Z, Kohlhaas S, Das PP, Miska EA, Rodriguez A, Bradley A, Smith KG, Rada C, Enright AJ, Toellner KM, Maclennan IC, Turner M. microRNA-155 regulates the generation of immunoglobulin class-switched plasma cells. Immunity. 2007 Dec;27(6):847-59. PubMed PMID: 18055230; PubMed Central PMCID: PMC4135426.
    c. Murga M, **Bunting SF**, Montaña MF, Soria R, Mulero F, Cañamero M, Lee Y, McKinnon PJ, Nussenzweig A, Fernandez-Capetillo O. A mouse model of ATR-Seckel shows embryonic

replicative stress and accelerated aging. Nat Genet. 2009 Aug;41(8):891-8. PubMed PMID: 19620979; PMCID: PMC2902278.

d. Robbiani DF, **Bunting SF**, Feldhahn N, Bothmer A, Camps J, Deroubaix S, McBride KM, Klein IA, Stone G, Eisenreich TR, Ried T, Nussenzweig A, Nussenzweig MC. AID produces DNA double-strand breaks in non-Ig genes and mature B cell lymphomas with reciprocal chromosome translocations. Mol Cell. 2009 Nov 25;36(4):631-41 PubMed PMID: 19941823; PubMed Central PMCID: PMC2805907.

2. My work on BRCA1 and 53BP1 has led to a significant development in our understanding of DNA repair and tumor predisposition. I showed that co-deletion of the gene for 53BP1 in *Brca1*-deficient mice rescues genomic instability and embryonic lethality. The tumor predisposition normally observed in *Brca1*-deficient mice is also alleviated by ablation of 53BP1. My 2010 paper in 'Cell' (cited 487 times) showed that 53BP1 regulates resection of DNA double-strand breaks, influencing the choice of mutagenic vs error-free DNA repair pathways. I have added to this work on BRCA1 by publishing additional studies aimed at further clarifying repair activities associated with BRCA1, and better understanding the impact of 53BP1 on BRCA1 activity at damage sites.
    a. Cao L, Xu X, **Bunting SF**, Liu J, Wang RH, Cao LL, Wu JJ, Peng TN, Chen J, Nussenzweig A, Deng CX, Finkel T. A selective requirement for 53BP1 in the biological response to genomic instability induced by Brca1 deficiency. Mol Cell. 2009 Aug 28;35(4):534-41 PubMed PMID: 19716796; PubMed Central PMCID: PMC3392030.
    b. **Bunting SF**, Callén E, Wong N, Chen HT, Polato F, Gunn A, Bothmer A, Feldhahn N, Fernandez-Capetillo O, Cao L, Xu X, Deng CX, Finkel T, Nussenzweig M, Stark JM, Nussenzweig A. 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell. 2010 Apr 16;141(2):243-54. PubMed PMID: 20362325; PubMed Central PMCID: PMC2857570.
    c. Bothmer A, Robbiani DF, Di Virgilio M, **Bunting SF**, Klein IA, Feldhahn N, Barlow J, Chen HT, Bosque D, Callen E, Nussenzweig A, Nussenzweig MC. Regulation of DNA end joining, resection, and immunoglobulin class switch recombination by 53BP1. Mol Cell. 2011 May 6;42(3):319-29. PubMed PMID: 21549309; PubMed Central PMCID: PMC3142663.
    d. **Bunting SF**, Callén E, Kozak ML, Kim JM, Wong N, López-Contreras AJ, Ludwig T, Baer R, Faryabi RB, Malhowski A, Chen HT, Fernandez-Capetillo O, D'Andrea A, Nussenzweig A. BRCA1 functions independently of homologous recombination in DNA interstrand crosslink repair. Mol Cell. 2012 Apr 27;46(2):125-35 PubMed PMID: 22445484; PubMed Central PMCID: PMC3340543.

3. My lab at Rutgers University continues to study mechanisms involved in the response to DNA damage, using cellular and genetic approaches, transgenic mouse models and advanced microscopy. In collaboration with our colleagues in the School of Arts and Sciences and Cancer Institute of New Jersey, we have identified how the tumor suppressors BRCA1 and PALB2 collaborate during repair of DNA double-strand breaks.
    a. Her J, **Bunting SF**. How cells ensure correct repair of DNA double-strand breaks. J Biol Chem. 2018 Feb 5. pii: jbc.TM118.000371. doi: 10.1074/jbc.TM118.000371. PubMed PMID: 29414795; PubMed Central PMCID: PMC6036189.
    b. Li M, Cole F, Patel DS, Misenko SM, Her J, Malhowski A, Alhamza A, Zheng H, Baer R, Ludwig T, Jasin M, Nussenzweig A, Serrano L, **Bunting SF**. 53BP1 ablation rescues genomic instability in mice expressing 'RING-less' BRCA1. EMBO Rep. 2016 Sep 26. PubMed PMID: 27670884; PubMed Central PMCID: PMC5090706.
    c. Bowman-Colin C, Xia B, **Bunting SF**, Klijn C, Drost R, Bouwman P, Fineman L, Chen X, Culhane AC, Cai H, Rodig SJ, Bronson RT, Jonkers J, Nussenzweig A, Kanellopoulou C, Livingston DM. Palb2 synergizes with Trp53 to suppress mammary tumor formation in a model of inherited breast cancer. Proc Natl Acad Sci U S A. 2013 May 21;110(21):8632-7 PubMed PMID: 23657012; PubMed Central PMCID: PMC3666744.
    d. Simhadri S, Peterson S, Patel DS, Huo Y, Cai H, Bowman-Colin C, Miller S, Ludwig T, Ganesan S, Bhaumik M, **Bunting SF**, Jasin M, Xia B. Male fertility defect associated with disrupted BRCA1-PALB2 interaction in mice. J Biol Chem. 2014 Aug 29;289(35):24617-29. PubMed PMID: 25016020; PubMed Central PMCID: PMC4148885.

4. We have recently applied structural biology approaches to determine how DNA repair factors interact at the molecular level. Specifically, we have focused on the interaction between BRCA1 and PALB2, which associate through formation of a 'coiled coil' module in which helical regions from each protein bind to each other. Using NMR spectroscopy and other biophysical techniques, we have revealed the solution structure of homo-oligomeric PALB2. Using information about interface residues gained from these structural biology approaches, we have conducted mutagenesis experiments to test the importance of specific residues for complex formation. These studies are ongoing, with a current focus on the heterodimeric interaction between BRCA1 and PALB2.
    a. Song F, Li M, Liu G, Gurla S, Daigham N, Xia B, Montelione G, **Bunting SF**. Antiparallel Coiled-Coil Interactions Mediate Homodimerization of the DNA Damage Repair Protein, PALB2. Biochemistry. 2018 Oct 5. doi: 10.1021/acs.biochem.8b00789. [Epub ahead of print] PubMed PMID: 30289697; PubMed Central PMCID: PMC6652205.

5. As an active participant in the Rutgers Cancer Institute of New Jersey DNA Repair Interest group, I support my colleagues' research by conducting cytogenetic and cell biology assays on B cells from genetically-modified mice. We have also performed preclinical studies of molecules that affect the DNA damage research, to generate preliminary data for planned clinical trials. These studies have led to a number of collaborative publications.
    a. Khan AJ, Misenko SM, Thandoni A, Schiff D, Jhawar SR, **Bunting SF**, Haffty BG. VX-984 is a selective inhibitor of non-homologous end joining, with possible preferential activity in transformed cells. *Oncotarget*. 2018 May 25; 9(41):25833-25841. PubMed PMID: 29899825; PubMed Central PMCID: PMC5995231.
    b. Simhadri S, Vincelli G, Huo Y, Misenko S, Foo TK, Ahlskog J, Sørensen CS, Oakley GG, Ganesan S, **Bunting SF**, Xia B. PALB2 connects BRCA1 and BRCA2 in the G2/M checkpoint response. Oncogene. 2018 Oct 18. doi: 10.1038/s41388-018-0535-2. PubMed PMID: 30337689; PubMed Central PMCID: PMC6408219
    c. Sharma P, Mullen JR, Li M, Zaratiegui M, **Bunting SF**, Brill SJ. A Lysine Desert Protects a Novel Domain in the Slx5-Slx8 SUMO Targeted Ub Ligase To Maintain Sumoylation Levels in Saccharomyces cerevisiae. Genetics. 2017 May 26. PubMed PMID: 28550017; PubMed Central PMCID: PMC5560789.
    d. Hong X, Liu W, Song R, Shah JJ, Feng X, Tsang CK, Morgan KM, **Bunting SF**, Inuzuka H, Zheng XF, Shen Z, Sabaawy HE, Liu L, Pine SR. SOX9 is targeted for proteasomal degradation by the E3 ligase FBW7 in response to DNA damage. Nucleic Acids Res. 2016 Oct 14;44(18):8855-8869. PubMed PMID: 27566146; PubMed Central PMCID: PMC5062998.

Complete List of Published Work in Pubmed:
https://www.ncbi.nlm.nih.gov/pubmed/?term=bunting+sf+OR+(bunting+AND+nussenzweig)+OR+(bunting+AND+vigorito)+or+(bunting+AND+Fischer)

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NIH R01 CA190858 (PI) 09/01/15 – 08/31/20
Control of commitment steps in mammalian homologous recombination
The goals of this project are to test contributions of DNA damage response genes to maintenance of genomic integrity, evaluate the impact of 53BP1 on DNA repair efficiency in postmitotic cells, and use structural biology to solve structures of protein complexes involving PALB2.

Completed Research Support

NIH R00 CA160574-03 (PI) 09/01/12 – 08/31/15
Targeted therapies to correct genomic instability in Brca1-deficient cells
The goals of this project are to use genetics to test whether 53BP1 deletion can rescue genomic instability in cells with deficiencies in homologous recombination, dissect the domains of 53BP1 required for its activity and develop assays to screen for small molecule inhibitors of 53BP1.