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: XIA, BING

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

POSITION TITLE: Professor

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
Wuhan University, China	BS	07/1992	Biochemistry
Rutgers University	PhD	07/2001	Biochem & Mol Biol
Dana-Farber Cancer Institute and Harvard Medical School	Postdoctoral Fellow	08/2007	Cancer Genetics (David Livingston)

A. Personal Statement

The major goal of my research is to understand how hereditary cancers develop and how to prevent and better treat them. Our primary focus is the cellular and genetic mechanisms of cancer development associated with mutations in BRCA1/2 and PALB2 tumor suppressors. Specifically, we study the mechanisms of the BRCA1-PALB2-BRCA2 axis in the DNA damage response and the roles of DNA damage, oxidative stress, and autophagy in BRCA/PALB2-associated cancer development. I have made significant contributions to the DNA repair and cancer genetics fields, particularly through the discovery of the PALB2 tumor suppressor and the establishment of the BRCA1-PALB2-BRCA2 DNA damage response and tumor suppression pathway. Additionally, work from my laboratory has shed light on the roles of oxidative stress and autophagy in breast cancer. Originally trained in biochemistry and molecular biology, I have expertise in mechanistic studies of tumor suppressor genes. Moreover, I have been working on mouse models since 2006 and have accumulated significant experience in modeling breast cancer. Over the years, I have collaborated with basic scientists, physician scientists, human geneticists, and pathologists. Since starting my lab in 2007, I have obtained seven R01-level grants from the NIH and American Cancer Society (ACS) and successfully guided most postdocs in the lab to compete for fellowships from federal and state agencies. Therefore, I have the qualifications to direct the relevant parts of research and training in this program project.

Ongoing and recently completed projects that I would like to highlight include:

R01 CA262227-01, National Cancer Institute (NCI)
Xia, Bing (PI)
07/01/21-06/30/26
Regulation of DNA replication kinetics by BRCA2 after DNA damage

P01 CA250957-01A1, National Cancer Institute (NCI)
Xia, Bing (PL)
05/01/21-04/30/26
(Project 2) Targeting DNA replication in BRCA-associated breast cancer

R01 CA138804-11, National Cancer Institute (NCI)
Xia, Bing (PI)
07/01/20-06/30/25
Role of PALB2 in the DNA Damage Response and Cancer Suppression

R01 CA188096-01A1, National Cancer Institute (NCI)
Xia, Bing (PI)
06/01/15-05/31/20
Targeting Autophagy in Hereditary Breast Cancer

Citations:

1. Kang Z, Fu P, Alcivar AL, Fu H, Redon C, Foo TK, Zuo Y, Ye C, Baxley R, Madireddy A, Buisson R, Bielinsky AK, Zou L, Shen Z, Aladjem MI, Xia B. BRCA2 associates with MCM10 to suppress PRIMPOL-mediated repriming and single-stranded gap formation after DNA damage. Nat Commun. 2021 Oct 13;12(1):5966. PubMed Central PMCID: PMC8514439.
2. Foo TK, Vincelli G, Huselid E, Her J, Zheng H, Simhadri S, Wang M, Huo Y, Li T, Yu X, Li H, Zhao W, Bunting SF, Xia B. ATR/ATM-mediated phosphorylation of BRCA1 T1394 promotes homologous recombinational repair and G2/M checkpoint maintenance. Cancer Res. 2021 Jul 23; PubMed PMID: 34301763.
3. Huo Y, Selenica P, Mahdi AH, Pareja F, Kyker-Snowman K, Chen Y, Kumar R, Da Cruz Paula A, Basili T, Brown DN, Pei X, Riaz N, Tan Y, Huang YX, Li T, Barnard NJ, Reis-Filho JS, Weigelt B, Xia B. Genetic interactions among *Brca1*, *Brca2*, *Palb2*, and *Trp53* in mammary tumor development. NPJ Breast Cancer. 2021 Apr 23;7(1):45. doi: 10.1038/s41523-021-00253-5. PubMed PMID: 33893322; PubMed Central PMCID: PMC8065161.
4. Anantha RW, Simhadri S, Foo TK, Miao S, Liu J, Shen Z, Ganesan S, Xia B. Functional and mutational landscapes of BRCA1 for homology-directed repair and therapy resistance. Elife. 2017 Apr 11;6 PubMed Central PMCID: PMC5432210.

B. Positions, Scientific Appointments, and Honors

2022-2022	Grant reviewer, ZCA1 RPRB-8 (M1) S NCI SPORE (P50) Review I
2020-2020	Ad hoc reviewer, NIH Cancer Etiology (CE) Study Section
2019-	Professor, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey and Robert Wood Johnson Medical School
2015-2018	Grant reviewer, NIH Special Emphasis Panels
2015-2016	Ad hoc reviewer, NIH Tumor Cell Biology (TCB) Study Section
2013-2019	Associate Professor, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey and Robert Wood Johnson Medical School
2012-2019	Grant reviewer, Cancer Research UK. Medical Research Council UK, Breast Cancer Campaign UK, Research Grant Council Hong Kong, Basser Research Center for BRACA, French National Research Agency
2010-2014	Ad hoc reviewer, NIH Cancer Etiology (CE) Study Section
2010	Research Scholar Award, American Cancer Society
2009-2019	Scientist reviewer, DOD Breast Cancer Research Program
2007-2013	Assistant Professor, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey and Robert Wood Johnson Medical School
2007	Member, American Association of Cancer Research
2006	Best Basic Science Abstract, The 18th Fanconi Anemia Research Fund Scientific Symposium
2002	Postdoctoral Fellowship, DOD Breast Cancer Research Program
2001-2007	Research Fellow, Department of Cancer Biology, Dana-Farber Cancer Institute and Harvard Medical School
1996-2001	Graduate Student, Department of Biochemistry, Rutgers Robert Wood Johnson Medical

School

C. Contributions to Science

1. Mechanisms of the Cold Shock Response in E.coli. The cold shock response is critical for bacteria to survive and grow at low temperature. During my PhD studies, I generated a quadruple knockout of the major cold shock protein CspA and its family members CspB, CspE and CspG. My work clearly demonstrated that the CspA family is essential for E.coli to survive low temperature. I also made significant contribution to the regulation of CspA induction and ribosomal function at low temperature. My studies significantly advanced our understanding of the cold shock response and contributed to new design strategies to produce proteins at low temperature to achieve with better solubility and biological activity.

   a. Xia B, Ke H, Shinde U, Inouye M. The role of RbfA in 16S rRNA processing and cell growth at low temperature in Escherichia coli. J Mol Biol. 2003 Sep 19;332(3):575-84. PubMed PMID: 12963368.
   b. Xia B, Ke H, Jiang W, Inouye M. The Cold Box stem-loop proximal to the 5'-end of the Escherichia coli *cspA* gene stabilizes its mRNA at low temperature. J Biol Chem. 2002 Feb 22;277(8):6005-11. PubMed PMID: 11741997.
   c. Xia B, Ke H, Inouye M. Acquirement of cold sensitivity by quadruple deletion of the cspA family and its suppression by PNPase S1 domain in Escherichia coli. Mol Microbiol. 2001 Apr;40(1):179-88. PubMed PMID: 11298285.
   d. Bae W, Xia B, Inouye M, Severinov K. Escherichia coli CspA-family RNA chaperones are transcription antiterminators. Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7784-9. PubMed Central PMCID: PMC16622.

2. Discovery of PALB2 as DNA damage response factor and tumor suppressor. BRCA1 and BRCA2 are important tumor suppressor proteins playing key roles in homologous recombination (HR)-mediated DNA double strand break repair (DSBR) and cell cycle checkpoint control. During my postdoctoral training I discovered PALB2 as a major BRCA2 binding partner critical for its DNA repair and tumor suppression functions. Subsequently, we and others found PALB2 mutations in familial breast cancer and Fanconi anemia (FA) patients, establishing PALB2 as a breast cancer tumor suppressor and a FA protein in its own right. To date, mutations in PALB2 have been found in cancer families in much of the world, and PALB2 has been widely considered as a key breast cancer susceptibility gene and the de facto BRCA3.

   a. Tischkowitz M, Xia B (co-first author), Sabbaghian N, Reis-Filho JS, Hamel N, Li G, van Beers EH, Li L, Khalil T, Quenneville LA, Omeroglu A, Poll A, Lepage P, Wong N, Nederlof PM, Ashworth A, Tonin PN, Narod SA, Livingston DM, Foulkes WD. Analysis of PALB2/FANCN-associated breast cancer families. Proc Natl Acad Sci U S A. 2007 Apr 17;104(16):6788-93. PubMed Central PMCID: PMC1871863.
   b. Erkko H, Xia B (co-first author), Nikkilä J, Schleutker J, Syrjäkoski K, Mannermaa A, Kallioniemi A, Pylkäs K, Karppinen SM, Rapakko K, Miron A, Sheng Q, Li G, Mattila H, Bell DW, Haber DA, Grip M, Reiman M, Jukkola-Vuorinen A, Mustonen A, Kere J, Aaltonen LA, Kosma VM, Kataja V, Soini Y, Drapkin RI, Livingston DM, Winqvist R. A recurrent mutation in PALB2 in Finnish cancer families. Nature. 2007 Mar 15;446(7133):316-9. PubMed PMID: 17287723.
   c. Xia B, Dorsman JC, Ameziane N, de Vries Y, Rooimans MA, Sheng Q, Pals G, Errami A, Gluckman E, Llera J, Wang W, Livingston DM, Joenje H, de Winter JP. Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. Nat Genet. 2007 Feb;39(2):159-61. PubMed PMID: 17200672.
   d. Xia B, Sheng Q, Nakanishi K, Ohashi A, Wu J, Christ N, Liu X, Jasin M, Couch FJ, Livingston DM. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell. 2006 Jun 23;22(6):719-729. PubMed PMID: 16793542.

3. Establishment of the BRCA1-PALB2-BRCA2 DNA damage response and tumor suppression pathway. Prior to the discovery of PALB2, BRCA1 and BRCA2 had long been known to associate each other and co-localize at DNA damage sites. Yet, how they function together in the DNA damage response remained elusive for nearly a decade. Following the discovery of PALB2, we and others co-discovered that PALB2 also directly binds BRCA1 and that BRCA1 functions upstream of PALB2 and promotes the recruitment of

the PALB2/BRCA2 complex to DNA damage sites. We have also conducted a series of functional characterizations of patient-derived PALB2 and BRCA1 missense variants, which further cemented the critical role of BRCA1-PALB2-BRCA2 pathway in DNA repair and tumor suppression. Recently, we demonstrated that the 3 proteins play similar roles in the G2/M checkpoint response and that PALB2 also links BRCA1 and BRCA2 in the process.

a. 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. 2019 Mar;38(10):1585-1596. PubMed Central PMCID: PMC6408219.
b. Foo TK, Tischkowitz M, Simhadri S, Boshari T, Zayed N, Burke KA, Berman SH, Blecua P, Riaz N, Huo Y, Ding YC, Neuhausen SL, Weigelt B, Reis-Filho JS, Foulkes WD, Xia B. Compromised BRCA1-PALB2 interaction is associated with breast cancer risk. Oncogene. 2017 Jul 20;36(29):4161-4170. PubMed Central PMCID: PMC5519427.
c. Anantha RW, Simhadri S, Foo TK, Miao S, Liu J, Shen Z, Ganesan S, Xia B. Functional and mutational landscapes of BRCA1 for homology-directed repair and therapy resistance. Elife. 2017 Apr 11;6 PubMed Central PMCID: PMC5432210.
d. Zhang F, Ma J, Wu J, Ye L, Cai H, Xia B (co-corresponding author), Yu X. PALB2 links BRCA1 and BRCA2 in the DNA-damage response. Curr Biol. 2009 Mar 24;19(6):524-9. PubMed Central PMCID: PMC2750839.

4. *Palb2* conditional knockout and knockin mouse models. Like *Brca1* and *Brca2*, systemic knockout of *Palb2* leads to embryonic lethality. In collaboration with Dr. David Livingston's group, we created a floxed allele of *Palb2*. We then independently generated a mouse model of *Palb2*-associated breast cancer. We further demonstrated that p53 is a barrier to tumor development upon loss of PALB2 and that autophagy promotes tumor development by overcoming the p53 barrier. Moreover, we generated a Palb2 knockin strain in which the endogenous PALB2-BRCA1 interaction is disrupted. Through this study we demonstrated that the interaction between the two proteins is important for DNA repair in vivo, male fertility and the suppression of both spontaneous and radiation-induced tumor development. Using the same strain, we recently provided evidence of tissue-specific DNA damage response and demonstrated a key role of NFκB in promoting cell survival and tumorigenesis in *Palb2* mutant tissues after DNA damage. These studies substantially advance our understanding of PALB-associated tumor development and the in vivo significance of the BRCA1-PALB2 interaction.

   a. Huo Y, Selenica P, Mahdi AH, Pareja F, Kyker-Snowman K, Chen Y, Kumar R, Da Cruz Paula A, Basili T, Brown DN, Pei X, Riaz N, Tan Y, Huang YX, Li T, Barnard NJ, Reis-Filho JS, Weigelt B, Xia B. Genetic interactions among *Brca1*, *Brca2*, *Palb2*, and *Trp53* in mammary tumor development. NPJ Breast Cancer. 2021 Apr 23;7(1):45. PubMed Central PMCID: PMC8065161.
   b. Mahdi AH, Huo Y, Tan Y, Simhadri S, Vincelli G, Gao J, Ganesan S, Xia B. Evidence of Intertissue Differences in the DNA Damage Response and the Pro-oncogenic Role of NF-κB in Mice with Disengaged BRCA1-PALB2 Interaction. Cancer Res. 2018 Jul 15;78(14):3969-3981. PubMed Central PMCID: PMC6050088.
   c. 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 Central PMCID: PMC4148885.
   d. Huo Y, Cai H, Teplova I, Bowman-Colin C, Chen G, Price S, Barnard N, Ganesan S, Karantza V, White E, Xia B. Autophagy opposes p53-mediated tumor barrier to facilitate tumorigenesis in a model of PALB2-associated hereditary breast cancer. Cancer Discov. 2013 Aug;3(8):894-907. PubMed Central PMCID: PMC3740014.

5. Regulation of the KEAP1-NRF2 oxidative stress response pathway. NRF2 is a master antioxidant transcription factor that drives the expression of a large battery of oxidative stress response genes. KEAP1 binds to NRF2 and targets NRF2 for ubiquitylation and degradation. We found that PALB2 directly binds to KEAP1 with a highly conserved "ETGE" motif that is identical to that of NRF2, thereby titrating KEAP1 and protects NRF2 from destruction. Later, using cells from Palb2 conditional knockout mice, we showed that

loss of PALB2 leads to impaired NRF2 accumulation in the nucleus. Moreover, we recently identified DPP3 as an oxidative stress-inducible binding protein of KEAP1 and showed that DPP3 is required for NRF2 induction by oxidative stress (hydrogen peroxide) and that DPP3 upregulation correlates with high NRF2 activity and poor prognosis in breast cancer. In addition, we also contributed to another study that identified IQGAP1 as an interacting partner and regulator of NRF2.

a. Lu K, Alcivar AL, Ma J, Foo TK, Zywea S, Mahdi A, Huo Y, Kensler TW, Gatza ML, Xia B. NRF2 Induction Supporting Breast Cancer Cell Survival Is Enabled by Oxidative Stress-Induced DPP3-KEAP1 Interaction. Cancer Res. 2017 Jun 1;77(11):2881-2892. PubMed Central PMCID: PMC5464605.
b. Kim JH, Xu EY, Sacks DB, Lee J, Shu L, Xia B, Kong AN. Identification and functional studies of a new Nrf2 partner IQGAP1: a critical role in the stability and transactivation of Nrf2. Antioxid Redox Signal. 2013 Jul 10;19(2):89-101. PubMed Central PMCID: PMC3689176.
c. Ma J, Cai H, Wu T, Sobhian B, Huo Y, Alcivar A, Mehta M, Cheung KL, Ganesan S, Kong AN, Zhang DD, Xia B. PALB2 interacts with KEAP1 to promote NRF2 nuclear accumulation and function. Mol Cell Biol. 2012 Apr;32(8):1506-17. PubMed Central PMCID: PMC3318596.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/1h1BjzoH77yQv/bibliography/public/