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: **Fu, Loning**

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

POSITION TITLE: **Associate 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
Beijing University, Beijing, China	B.S	07/1982	Cell Biology
Academia Sinica, Beijing, China	M.S	07/1985	Developmental Biology
University of Calgary, Alberta, Canada	Ph.D	10/1991	Molecular Biology
University of Toronto, Canada	Postdoctoral	2/1999	Molecular Biology
Baylor College of Medicine, Houston, U.S.A	Postdoctoral	2/2003	Molecular Genetics & Chronobiology

A. Personal Statement

I have a broad background in molecular and cellular biology, genetics, chronobiology, and integrative physiology. My earlier studies are centered on the mechanism of gene expression and the role of gene deregulation in early development and cancer. My research in the past 15 years is focused on defining the mechanism of circadian dysfunction in carcinogenesis. This led to my initial discovery of the role of mammalian circadian genes in DNA damage response, cell cycle control, and tumor suppression, and the recent demonstration of the role of the mammalian circadian clock in energy balance, metabolic homeostasis, and tumor suppression.

The Fu lab is instrumental for initiation of circadian research in the Yechoor, Moore, O'Malley, and York laboratories in Baylor College of Medicine. Our common interests in the role of circadian dysfunction in diseases and cancers have resulted in 8 publications from these collaborations in the past 8 years. Especially, the close collaboration between the Fu and Moore laboratories in the past few years has led to breakthrough discoveries that chronic circadian disruption is an independent risk factor of central leptin resistance, non-alcoholic fatty liver disease (NAFLD), and spontaneous hepatocellular carcinoma (HCC). We also found that circadian disruption induced sympathetic dysfunction is a key carcinogenetic mechanism promoting HCC initiation. These discoveries have laid a solid foundation to further investigate the pathophysiological mechanism of circadian disruption-induced spontaneous carcinogenesis, which is currently very poorly understood. Based on our exciting discoveries, this proposal is focused on defining the role of β-adrenergic receptor-mediated sympathetic dysfunction in circadian disruption induced liver pathologies and spontaneous hepatocarcinogenesis, identifying the sympathetic circadian dysfunction induced HCC-prone gene signature, and testing the role of β-blockers in prevention of circadian dysfunction induced HCC. The results generated from these studies will not only significantly advance our knowledge of spontaneous carcinogenesis but also open exciting new avenues for prevention and treatment of HCC, one of the deadliest human cancers.

1. **Fu L** and Lee CC. (2003) The circadian clock: pacemaker and tumor suppressor. ***Nature Rev. Cancer*** 3, 350–361. PMID: 12724733
2. **Fu L**, Kettner NM. (2013) The circadian clock in cancer development and therapy. ***Prog Mol Biol Transl Sci.*** 119:221-282, PMCID:PMC4103166
3. Kettner NM, Katchy CA and **Fu L**. (2014) Circadian gene variants in cancer. ***Ann Med***. 46:208-220. PMCID:PMC4153443

B. Positions and Honors

Positions

1985-1987	Junior faculty, Dept. of Biological Sciences and Technology, Tsinghua University, Beijing, China
1992-1999	Postdoc Fellow, Ontario Cancer Institute, University of Toronto, Ontario, Canada
1999-2002	Postdoc Fellow, Department of Molecular and Human Genetics, Baylor College of Medicine
2003-2006	Assistant Professor (non-tenure track), Dept. of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX
2006-2016	Assistant Professor (tenure track) Dept. of Pediatrics, Baylor College of Medicine, Houston, TX
2006-	Member, Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX
2007- 2016	Assistant Professor, Department of Molecular and Cell Biology, Baylor College of Medicine
2012-	Member, Center for Reproduction Medicine, Baylor College of Medicine
2016-	Associate Professor, Dept. of Pediatrics, Baylor College of Medicine, Houston, TX
2016-	Associate Professor, Dept. of Molecular and Cell Biology, Baylor College of Medicine, Houston, TX

Honors and Recognitions

2003 Press Conference: Circadian Genes Could Be Targets for New Cancer Drugs. The International Conference on Molecular Targets and Cancer Therapeutics, November, 2003, Boston, organized by AACR, NIH/NCI, and EIRTC (the European Organization for Research and Treatment of Cancer) (*http://www.prnewswire.com/news-releases/circadian-clock-genes-may-provide-targets-for-new-cancer-drugs-73074497.html*)

2011 The publication "Disrupting of Circadian Homeostasis of Sympathetic Signaling Promotes Tumor Development in mice" (PLoS ONE, 2010, 5, e10995) from the Fu lab was ranked among the top 7 research papers in Neuroscience by the Faculty of 1000 in 2011 (*http://thescientist.com/2011/08/ 23/top-7-in-neuroscience*)

2015 The publication "Circadian Dysfunction Induces Leptin Resistance in Mice" (Cell Metabolism 2015, 22:448-459) from the Fu lab was selected as Editor's Choice by Science Translational Medicine in July, 2015 (http://stm.sciencemag.org/content/7/298/298ec131)

2016 The publication "Circadian Homeostasis of Liver Metabolism Suppresses Hepatocarcinogenesis" (Cancer Cell, 2016, 30, 909-924) from the Fu lab was selected for Cell Press Release in 2016: Jet lag and obesity share similar pathways to liver cancer. November 23, 2016 (*http://www.cell.com/cancer-cell/fulltext/S1535-6108(16)30494-9*).

2018 NIH/NCI Chronomedicine Webinar "Tumor Suppression Is a Clock Controlled Physiological Function", March 20th, 2018

C. Contribution to Science

1. The mechanism and biological significance of translational regulation.
   My earlier publications address the mechanism of translational regulation of gene expression and the role of dysregulation of translational initiation in early development and DNA damage response. My initial studies discovered an important role of the secondary structures in 5'untranslated regions (5'UTR) of maternal mRNAs in translational regulation during early development. I then found that a 3'UTR sequence in the *p53* mRNA controls p53 response to γ-radiation in human acute myeloid leukemia (AML), and identify a cytoplasmic RNA binding protein that controls p53 mediated radiation response by interacting with the p53 3'UTR sequence. Together, my studies not only significantly improved our understanding of the mechanism of translational regulation but also demonstrated the biological relevance of translational regulation in early development and tumor suppression. I served as the primary investigator in all these studies.
   a. **Fu L**, Ye R, Browder LW and Johnston RN. Translational potentiation of mRNA with stable secondary structure in Xenopus. ***Science*****,** 251, 807-810 (1991). PMID: 1990443

b. **Fu L,** Minden M and Béchamel S. Translational regulation of human p53 gene expression. ***EMBO J.*** 15, 4392-4401 (1996) PMID: 8861966
c. **Fu L** and Benchimol S. Participation of the human p53 3'UTR in translational repression and activation following γ-irradiation. ***EMBO J.*** 16, 4117-4125 (1997). PMID: 9233820
d. **Fu L,** Ma W and Benchimol S. A translation repressor element resides in the 3' untranslated region of human p53 mRNA. ***Oncogene***.18, 6419-6424 (1999). PMID: 10597243

2. The tumor suppression function of the molecular clock.

I was the first to report the role of mammalian circadian genes in cancer genetics by demonstrating that loss of function in the core circadian gene *Period2* abolishes cell cycle checkpoints, deregulates DNA damage response, and increases γ-radiation-induced tumorigenesis in mice. Subsequently, I found that loss of function in *Period, Cryptochrome,* or *Bmal1* genes leads to a similar neoplastic growth phenotype in bone. Further studies in my laboratory demonstrated that mice lacking either positive or negative loops of circadian genes all display increased spontaneous and radiation-induced carcinogenesis, and that chronic circadian disruption increases radiation induced tumorigenesis in wild-type (WT) mice and also accelerates carcinogenesis in *p53*-null mice. Togehter, these studies discovered that the clock control is a novel mechanism of tumor suppression *in vivo*. I served as the primary investigator in all these studies.

a. **Fu L,** Pelicano H, Liu J, Huang P and Lee CC. (2002) The circadian gene *mPer2* plays an important role in DNA-damage response and tumor suppression *in vivo*. ***Cell*** 111, 41-50. PMID: 12372299
b. **Fu L,** Petal M**,** Bradley A, Wagner, EF and Karsenty G. (2005) The molecular clock and AP1 mediate the leptin-dependent sympathetic regulation of bone formation. ***Cell*** 122, 803-815. PMID: 16143109
c. Lee S, Donehower LA, Herron AJ, Moore DD and **Fu L.** (2010) Disrupting circadian homeostasis of sympathetic signaling promotes tumor development in mice. ***PLoS ONE,*** 5, e10995. PMCID:PMC2881876

3. The role of circadian disruption in metabolic diseases.

I also significantly contributed to the understanding of the mechanism of obesity epidemics in modern societies. Using a mouse model of human nightshift schedule, my lab demonstrated that chronic circadian disruption, which has reached the epidemic level in our society, induces spontaneous central leptin resistance, a hallmark of obesity in humans, independent of all previously identified obesity risk factors. This study not only defined a critical role for chronic circadian disruption in the prevalence of obesity and metabolic syndrome, but also established jet-lagged WT mice as a clinic relevant animal model for studying the mechanism of obesity and obesity-related diseases. In collaboration with other BCM research teams, we have also shown that disruption of the molecular clock increases the risk of diabetes, and that the steroid receptor coactivator SRC2 plays an active role in regulating the molecular clock and liver metabolism. Disruption of the SRC2 signaling aggravates circadian disruption induced hepatic pathology. I served as the primary or co-investigator in all these studies.

a. Kettner NM, Mayo SA, Hua J, Lee C, Moore DD and **Fu L**. (2015) Circadian disruption induces Leptin resistance in mice. ***Cell Metabolism***, 22, 448-459, PMCID: PMC4558341
b. Lee J, Kim MS, Li R, Liu VY, **Fu L**, Moore DD, Ma K and Yechoor VK. (2011) Loss of Bmal1 leads to uncoupling and impaired glucose-stimulated insulin secretion in β-cells. ***Islets*** 3, 381-388. PMID: 22045262
c. Stashi E, Lanz RB, Mao J, Reineke L C, Kettner N, Stevenson C, Dasgupta S, Dean A, Sivasubramanian N, Reineke EL, York B, DeMayo F, **Fu L**[¶], and O'Malley BW[¶]. (2014) SRC-2 is an essential coactivator for BMAL1:CLOCK in orchestrating circadian rhythm and metabolism. ***Cell Report*** 6, 633-645 PMCID: PMC4096300, [¶]Equal contribution.
d. Fleet T, Stashi E, Zhu B, Rajapakshe K, Marcelo KL, Kettner NM, Gorman BK, Coarfa C, **Fu L**, O'Malley BW and York B. (2016) Genetic and environmental models of circadian disruption link SRC-2 function to hepatic pathology. ***J Biol Rhythm*** 31,443-460, PMCID: PMC5248931

4. Tumor suppression is a physiological function of the mammalian circadian clock

My lab plays a vital role in discovering that tumor suppression is a clock-controlled physiological function. Especially, we provided the first experimental evidence that neuroendocrine circadian dysfunction is an independent risk factor of spontaneous carcinogenesis. By a close collaboration with the Moore laboratories in BCM, we demonstrated that circadian dysfunction not only induces leptin resistance, hyperinsulinemia, hyperglycemia, and dyslipidemia at the organismal level, and non-alcoholic fatty liver disease (NAFLD),

cholestasis, and fibrosis in the liver, but also the progression from NAFLD to spontaneous hepatocarcinogenesis. Importantly, we found that the pathway of hepatocarcinogenesis in jet-lagged WT mice follows a mechanism strikingly similar to that observed in obese humans. Our extensive molecular, metabolomics, and genetic analyses identified a jet-lag induced hepatic gene signature that drives liver metabolic dysfunction and tumorigenesis, with nuclear receptor controlled cholesterol/bile acid metabolism as the top deregulated pathways. We demonstrated that cholestasis is a key proximal drive of NAFLD-induced hepatocellular carcinoma (HCC), and that all key players controlling bile acid homeostasis, such as the essential bile acid synthesis enzyme CYp7A1, the bile acid receptor FXR, the xenobiotic receptor CAR, and the co-suppressor SHP are controlled by the clock in the liver. We further demonstrated that circadian dysfunction induces sympathetic malfunction, and that both *Fxr* and *Car* are the first order clock-controlled genes directly targeted by rhythmic sympathetic signaling in the liver. Blocking jet lag induced sympathetic dysfunction or CAR activation can completely inhibit NAFLD-induced spontaneous hepatocarcinogenesis. Together, our studies established a clinic relevant model for spontaneous hepatocarcinogenesis and also opened exciting opportunities for studying novel therapeutic strategies of HCC prevention, early diagnosis, and treatment.

a. Ma, K., Xiao, R., Tseng, H., Shan, L., **Fu, L** and Moore DD. (2009) Circadian dysregulation disrupts bile acid homeostasis. ***PLoS ONE***. 4, e6843. PMID: 1971844
b. Wu N, Ho Kim K, Zhou Y, Man Lee J, Kettner NM, Mamrosh JL, Choi S, **Fu L** and Moore DD. (2016) Small heterodimer partner (NR0B2) coordinates nutrient signaling and the circadian clock in Mice. ***Mol Endocrinol***, 30, 988-995, PMCID: PMC5004116
c. Kettner NM, Voicu H, Coarfa C, Sreekumar A, Putluri N, Finegold MJ, Katchy CA, Lee C, Moore DD and **Fu L**. (2016) Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. ***Cancer Cell*** 30, 909-924. PMCID: PMC5695235

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

Research Support

Active

USDA/ARS 3092-5-001-060 Fu (PI) 10/31/14-09/30/19
USDA
The Role of Leptin in Diet-Induced Obesity
This objective of this study is to investigate the role of leptin in controlling energy homeostasis and diet induced obesity.
Overlap: None.

CRPIT MIRA RP150587 El-Serag (PI) 12/01/15 – 11/30/20
CPRIT
Circadian Disruption and Bile Acids as HCC Risk Factors
The goal of this component in this multi-Investigator project is study the impact of circadian disruption and CAR oncogenic activation as independent risk factors for human liver cancer.
Role: Co-investigator
Overlap: None

R01CA230848 Fu (PI) 09/01/2018 - 08/31/2023
NIH/NCI
Nuclear Receptor Mechanisms in Circadian Disruption Induced Hepatocarcinogenesis
The goals of this study is to define the nuclear receptor FXR and CAR controlled gene signatures, the role of p53 and β-Catenin mutations in spontaneous HCC initiation, and the FXR agonist obeticholic acid (OCA) and CAR inverse agonist androstanol (ANDR) in prevention of NAFLD-induced HCC.
Role: PI
Overlap: None

Pending

1 R01 CA238988-01 Fu (PI) 04/01/2019 - 03/31/2024

NIH/NCI
Sympathetic circadian dysfunction in obesity-related hepatocarcinogenesis
The goals of this study is to define the role of sympathetic circadian dysfunction in obesity-related spontaneous hepatocarcinogenesis and the role of β-blockers in prevention and treatment of NAFLD-induced HCC.
Role: PI
Overlap: None

3092-51000-060 Fu (PI) 04/01/2019 – 3/31/2024
USDA/ARS
Metabolic Consequences of Obesity
The goal of this study is to define the role of chronic circadian disruption in chronic sympathetic dysfunction and peripheral leptin resistance, and the role of hypertension and peripheral leptin resistance in the development of obesity related NAFLD and hepatic fibrosis.
Role: PI
Overlap: None

Completed

R01 CA137019-01A1 (PI: Fu) Fu (PI) 08/01/10-07/31/17
NIH/NCI
The Study of the Circadian Rhythm in p53 Signaling
The objective of this study is designed to study the mechanism of circadian control of tumor suppressor p53.
Role: PI

NIH/NIDDK P01DK059820-11A1 O'Malley (PI) 09/14/12 – 06/30/17
NIH/NIDDK
Genetic and Metabolic Fingerprints of Co-activators
The objectives of this project are to define the role coactivator SRC-2 in controlling energy homeostasis.
Role: Co-investigator

6250-51000-055 Fu (PI) 10/09-09/14
USDA/ARS
The Circadian Clock in Nutritional Metabolism and Obesity
The objective of this project to study the role of chronic circadian disruption of energy homeostasis in obesity.

RO3 CA107821-01A1 (PI) Fu (PI) 09/04-06/06
NIH/NCI
Study of the Circadian Clock-controlled DNA-Damage Response
The goal of this study is to investigate the role of the circadian clock in DNA damage response

Scholastic Performance

2010-2018 Journal Review
Aging Cell, Annals of Oncology, Annals Medicine, Biochimica et Biophysica Acta, BioMed Central, Cell Report, Chronobiology International, EMBO Reports, Endocrinology, Hepatology, International Journal of Cancer, Journal of Biological Chemistry, Journal of Biological Rhythms, Molecular Cell, Molecular Oncology, Oncogene, Nature Communications, Nature Medicine, PLoS Biology, Scientific Report, SL Gastroenterology, SRL Gastroenterology & Hepatology

2006-2018 Grant Review
External Reviewer, MIHGH Neurogenetics Consortium Seed Grant Program, the Maine Institute of Human Genetics and Health, University of Maine, Orono, ME, USA
External Reviewer, the Molecular and Cellular Medicine Board, Medical Research Council

External Reviewer, Prostate Cancer UK
Ad hoc reviewer, the NIH/NCI study section of Cell Signaling and Regulatory Systems
External Reviewer, the Health Research Council of New Zealand
External Reviewer, the Israel Science Foundation (ISF)
External Reviewer, the French National Research Agency (ANR)

2018 Member, the Peer-Review Panel for the National Toxicology Program (NTP) Monograph on Shift Work at Night, Light at Night, and Circadian Disruption as Carcinogens.