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: Binfeng Lu

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

POSITION TITLE: Member Scientist

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
Tsinghua University, Beijing, China	B.Sc.	07/92	Biology
Columbia University, New York, NY	Ph.D.	07/98	Immunology
Yale School of Medicine	Postdoc	04/03	Immunology

A. Personal Statement

I have extensive and deep expertise in tumor immunology through studying signaling molecules, transcription factors, cytokines, and co-inhibitory molecules in T cell-mediated antitumor immune responses. We have discovered a signaling transduction pathway (Gadd45/p38 axis) that plays an important role in T helper cell-mediated immune responses and have established its critical role in tumor immunity (published in Immunity, Nature Immunology, Science and Journal of Experimental Medicine). In addition, our lab has demonstrated that T-bet and Eomes are required for adaptive anti-tumor immune responses. And we have further shown that upregulation of T-bet in TIL correlates with better overall survival of esophageal cancer patients. Recently, we have made several discoveries of molecular pathways that can be targeted to enhance adaptive antitumor immune responses. We have first shown that stimulation of the “danger” signal IL33 directly increases $CD8^+$ T cell effector function and expression of IL-33 in tumor inhibits tumor growth. In addition, we have discovered that IL-36γ promotes antitumor immunity through directly activating type 1 lymphocytes such as CD8 T cells, NK cells, and gamma delta T cells (published in Cancer Cell). Our lab was the first to report that TIM-3 is highly and specifically expressed in intratumoral Tregs and found that its expression on Tregs correlates with human lung cancer progression. We have also established new cancer therapeutic modality combining chemo, radio frequency ablation and immunotherapy (published in Nature Nanotechnology, Nature Communication and Clinical Cancer Research). My lab is also interested in understanding T cell autophagy and metabolism. We were the first to show that that T cell undergo autophagy upon activation. This line of work has been published in Cell Report and Cell Death and Differentiation. In summary, we have demonstrated record of successful and innovative research projects in an area of T cell-mediated tumor immunity.

Research Support

1R01CA254274-01A1 06/16/2021-05/31/2026
Role: PI
Source: NIH
Study of the IL-33-driven immune cell organization underpinning responses to immune checkpoint blockade cancer therapy. This main aim of this grant to study how IL-33 regulates antitumor immune cell function.

R01CA239716 07/01/2019 - 06/30/2024

Role: PI (**multi-PI**)
Source: NIH
Study of Interleukin 33 as a new immunotherapy of lung cancer. This main aim of this grant to deliver IL-33 gene as a part of nanoparticle formulation for therapy.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

09/2022 -present Member and Director, Center for Discovery and Innovation of Hackensack Meridian Health.
01/2021 – 08/2022: Professor with tenure, Department of Immunology, University of Pittsburgh School of Medicine.
09/2016 - 01/2022: Faculty director, Transgenic and Gene Targeting Core, Department of Immunology, University of Pittsburgh School of Medicine.
04/2004 - 08/2022: Member, University of Pittsburgh Cancer Institute.
08/2009 – 12/2021: Associate Professor with tenure, Department of Immunology, University of Pittsburgh School of Medicine.
04/2003 - 07/2009: Assistant Professor, Department of Immunology, University of Pittsburgh School of Medicine.
09/1998 - 03/2003: Postdoctoral Fellow, Section of Immunobiology, Yale University School of Medicine.

Honors and Awards

04/2006 American Association of Immunologists travel award.
12/2005 Overseas young scientist award, Natural Science Foundation of China.
05/2004 Cancer Research Institute Young Investigator Award.
04/2003 Mentored Research Scientist Development Award KO1, NIH.
3/2001 Postdoctoral Fellowship, the Arthritis Foundation.
1992 Graduate Fellowship, Columbia University.

Professional Memberships and Service

2020 to 2024 Standing member, Transplantation, Tolerance, and Tumor Immunology Study Section–TTT
2018-present Member of scientific advisory board, Anwita Biosciences Inc, CA.
2020-2022 Reviewer, Mission Boost Grant Committee-S20, American Cancer Society,
2019-2020 Reviewer, Developmental Therapeutics (DT) study section
2019 Reviewer, Transplantation, Tolerance, and Tumor Immunology Study Section – TTT
2012-2020 NIH Immunology Fellowships and AREA Grants study section.
2019 Reviewer of R21 and R03 NIH Special Emphasis Panel Immune Oncology
2018 Reviewer, NIH, Immune System Plasticity in Dental, Oral, and Craniofacial Diseases Meeting
2017 NCI Clinical and Translational R21 and Omnibus R03.
2017 Reviewer, the Cancer Immunopathology and Immunotherapy study section – CII
2016 NIH- SBIR/STTR Special Emphasis Panel/Scientific Review Group.
2015 Special Emphasis Panel (SEP) ZRG1 IMM-H(02)M “Immune Mechanisms”.
2016-present Member - Society for the Immunotherapy of Cancer (SITC).
2010-present Member - American Association for Cancer Research (AACR).
1998-present Member - American Association of Immunologists (AAI).

C. Contributions to Science

1. Investigating cytokine signaling mechanisms in Th1 cells.
During my graduate training with Dr. Paul Rothman at Columbia University and my postdoctoral training with Dr. Richard Flavell at Yale University, I have focused on studying signaling in Th1 cells. As a graduate student, I generated IFN-γR2 deficient mice using gene “knockout” technology. Using this new mouse strain, I further studied the role of IFN-γR2 in infection and autoimmunity. Our work established a critical role of IFN-γR2 in listeria resistance in mice and elucidated the underlying mechanisms. During my postdoctoral training at Yale, I carried out a series of genomic studies combining cDNA representational difference analysis (RDA) and house-made DNA microarrays to look for genes expressed specifically in Th1 cells. I discovered several genes using this approach. I focused on Gadd45g and Gadd45b because these proteins have been shown to potentiate MAP kinase pathways and are highly expressed in Th1 cells. We hypothesized that Gadd45

mediated hyper-activation of MAP kinases in Th1 cells. To test this hypothesis, I generated Gadd45g and Gadd45b "knockout" mice. Our work eventually established that Gadd45b and Gadd45g were critical for MAP kinase hyper-activation in Th1 cells and played important role in IFN-γ production and Th1 biology.

a. **Lu B**, Ebensperger C, Dembic Z, Wang Y, Kvatyuk M, Lu T, Coffman RL, Pestka S, Rothman PB. (1998) Targeted disruption of the interferon-gamma receptor 2 gene results in severe immune defects in mice. *Proc Natl Acad Sci U S A.* 7;95(14):8233-8. PMCID:PMC20959
b. **Lu B**, Ferrandino A, Flavell RA. (2004) Gadd45beta is important for perpetuating cognate and inflammatory signals in T cells. *Nat Immunol.* 5(1):38-44.
c. Sun***** H**, Lu* B**, Li R, Flavell RA and Taneja R. (2001) Defective T-cell activation and autoimmune disorder in Stra13-deficient mice. (***** These authors contribute equally) *Nature Immunology*. 2(11): 1040-7.
d. **Lu B**, Yu H, Chow C, Li B, Zheng W, Davis RJ, Flavell RA.(2001) GADD45gamma Mediates the Activation of the p38 and JNK MAP Kinase Pathways and Cytokine Production in Effector T(H)1 Cells. *Immunity.* 14(5):583-90.

2. Study autophagy and amino acid metabolism in T cell-mediated immune responses.

One focus of my lab is to understand T cell autophagy and metabolism. Our lab was first to show that T cell undergo autophagy upon activation. We then showed that autophagy is required for cytokine-withdrawal cell death. Using T cell-specific beclin 1 deficient mice generated in our lab, we further demonstrated that autophagy played an important role in autoimmunity in mice. Besides cell death and survival, we demonstrated that autophagy is actively involved in T cell metabolism and regulated by mTORC1. Another important regulator of T cell metabolism is a transcription factor called ATF4. Recently, we have published a paper in Cell Report demonstrating that ATF4 drives reprogramming of amino acid metabolism in T cells through directly regulating mTORC1, glycolysis, and glutaminolysis.

a. Yang X, Xia R, Yue C, Zhai W, Du W, Yang Q, Cao H, Chen X, Obando D, Zhu Y, Chen X, Chen JJ, Piganelli J, Wipf P, Jiang Y, Xiao G, Wu C, Jiang J, **Lu B**. ATF4 Regulates $CD4^+$ T Cell Immune Responses through Metabolic Reprogramming. *Cell Rep*. 2018 May 8;23(6):1754-1766. PMCID: PMC6051420
b. Kovacs J, Yang Q, Gonzalez-García I, Li C, Ju S, Gonzales-Garcia I, Chen X, Zhang X, and **Lu B**, Autophagy promotes T-cell survival through degradation of proteins of the cell death machinery. *Cell Death Differ*. 2012 Jan;19(1):144-52. doi: 10.1038/cdd.2011.78. Epub 2011 Jun 10. PubMed PMID: 21660048
c. Li C, Capan E, Zhao Y, Zhao J, Stolz D, Watkins S, Jin S, **Lu B**. Autophagy is induced in $CD4^+$ T cells and important for the growth factor-withdrawal cell death. *J Immunol*. 2006 Oct 15;177(8):5163-8. PubMed PMID: 17015701.
d. Liu L, Tran E, Zhao Y, Huang Y, Flavell R, **Lu B**. Gadd45 beta and Gadd45 gamma are critical for regulating autoimmunity. *J Exp Med*. 2005 Nov 21;202(10):1341-7. Epub 2005 Nov 14. PubMed PMID:16287712; PubMed Central PMCID: PMC2212988.

3. Study novel checkpoint molecules in tumor immunity.

In the past 10 years we have focused on studying the immune suppressive mechanisms in tumor immunology. We have discovered that TIM-3 is uniquely expressed by tumor infiltrating lymphocytes (TIL). Our lab was the first to report that TIM-3 is preferentially expressed on tumor infiltrating Treg and its expression correlated with poor outcome of human lung cancer patients. Many labs have subsequently confirmed our studies. We further demonstrated that $TIM\text{-}3^+$ Treg are the most potent regulatory T cells and showing features of effector tissue Treg cells.

a. Wang W, Wu S, Cen Z, Yixin Zhang Y, Chen Y, Huang Y, Cillo AR, Prokopec JS, Quarato G, Vignali DA, Stewart-Ornstein J, Li S, Lu B*, and Gong Y*. *Co-corresponding authors. Mobilizing Phospholipids on Tumor Plasma Membrane Reveals Phosphatidylserine Externalization Blockade for Cancer Immunotherapy. *Cell Reports.* (in press) 2022
b. Yang M, Du W, Yi L, Wu S, He C, Zhai W, Yue C, Sun R, Menk AV, Delgoffe GM, Jiang J, **Lu B**. Checkpoint molecules coordinately restrain hyperactivated effector T cells in the tumor microenvironment. *OncoImmunology*. 2020 Jan 30;9(1):1708064. doi: 10.1080/2162402X.2019.1708064.PubMed PMID: 32076578; PubMed Central PMCID: PMC6999836.
c. Liu Z, McMichael EL, Shayan G, Li J, Chen K, Srivastava R, Kane LP, **Lu B**, Ferris RL. Novel Effector Phenotype of $Tim\text{-}3^+$ Regulatory T Cells Leads to Enhanced Suppressive Function in Head and Neck Cancer Patients. *Clin Cancer Res*. 2018 Sep 15;24(18):4529-4538.PubMed PMID: 29712685; PubMed Central PMCID: PMC6139056.
d. Gao X, Zhu Y, Li G, Huang H, Zhang G, Wang F, Sun J, Yang Q, Zhang X, **B Lu**. TIM-3 expression

characterizes regulatory T cells in tumor tissues and is associated with lung cancer progression. *PLoS One*. 2012;7(2):e30676. doi: 10.1371/journal.pone.0030676. Epub 2012 Feb 17. PubMed PMID: 22363469; PubMed Central PMCID: PMC3281852.

4. Study tissue-derived cytokines in tumor immune surveillance and antitumor immunity. My lab also focuses on studying novel positive signals that can promote antitumor immunity. Recently, our lab first discovered that danger signals IL-33 and IL-36 can promote effector function in Th1 cells, CD8 T cells, NK cells and gamma delta T cells, and thereby promoting antitumor immunity. These cytokines are expressed in normal epithelial tissues and down-regulated in tumor epithelial cells. We hypothesize that down-regulation of these alarmin cytokines by tumor cells is a major immune evasion mechanism that allows cancer progression. A major theme of the lab is to further test this hypothesis and investigate the in-depth mechanisms. We are also actively exploring these molecules as therapeutic agents for immunotherapy of cancer.

a. Chen L, Sun R, Xu J, Zhai W, Zhang D, Yang M, Yue C, Chen Y, Li S, Turnquist H, Jiang J, and **Lu B**. Tumor-derived interleukin 33 promotes tissue resident CD8+ T cells and is required for checkpoint blockade tumor immunotherapy. *Cancer Immunology Research* Nov;8(11):1381-1392. doi: 10.1158/2326-6066.CIR-19-1024. PMID: 32917659; PMCID: PMC7642190. (Cover story).
b. Wang X, Zhao X, Feng C, Weinstein A, Xia R, Wen W, Lv Q, Zuo S, Tang P, Yang X, Chen X, Wang H, Zang S, Stollings L, Denning TL, Jiang J, Fan J, Zhang G, Zhang X, Zhu Y, Storkus W, **Lu B**. IL-36γ transforms the tumor microenvironment and promotes type 1 lymphocyte-mediated antitumor immune responses. *Cancer cell* 2015 28: 296-306.PMID:26321222. PMCID: PMC4573903
c. Gao X, Wang X, Yang Q, Zhao X, Wen W, Li G, Lu J, Qin W, Qi Y, Xie F, Jiang J, Wu C, Zhang X, Chen X, Turnquist H, Zhu Y, **Lu B**. Tumoral Expression of IL-33 Inhibits Tumor Growth and Modifies the Tumor Microenvironment through $CD8^+$ T and NK Cells. *J Immunol*. 2014 Nov 26. pii: 1401344. [Epub ahead of print] PubMed PMID: 25429071. PMCID: PMC4272901
d. Yang Q, Li G, Zhu Y, Liu L, Chen E, Turnquist H, Zhang X, Finn OJ, Chen X, **Lu B.** IL-33 synergizes with TCR and IL-12 signaling to promote the effector function of $CD8^+$ T cells. *Eur J Immunol*. 2011 Nov;41(11):3351-60. doi: 10.1002/eji.201141629. Epub 2011 Oct 13. PubMed PMID: 21887788; PubMed Central PMCID: PMC3332117.

5. Development of cytokine-based cancer immunotherapy. Cytokines are among the earliest clinically approved immune therapies for cancer. However, the pleiotropic property of cytokines and poor pharmacokinetic profiles limit broader clinical application. Our lab, in close collaboration with others, has been keen on developing novel classes of cytokine-based cancer immunotherapies through engineering , combination with oncolytic viruses, and nanoparticles.

a. Chen Y, Huang Y, Li Q, Luo A, Zhang A, Huang H, Sun J, Zhang L, Sun R, Baind DJ, Conwaye J, **Lu B***, and Li S*. *Co-corresponding authors. Targeting Xkr8 via Nanoparticles-Mediated In Situ Codelivery of SiRNA and Chemotherapy Drugs for Cancer Immunochemotherapy. *Nature Nanotechnology* (accepted). 2022
b. Yang M, Giehl E, Feng C, Feist M, Chen H, Dai E, Liu Z, Ma C, Ravindranathan R, Bartlett D, **Lu B***, and Guo Z*. *co-corresponding authors. IL-36g-armed Oncolytic Virus Exerts Superior Efficacy through Induction of Potent Adaptive Antitumor Immunity. *Cancer Immunology and Immunotherapy. 2021 Feb 4. doi: 10.1007/s00262-021-02860-4. Online ahead of print. PMID: 33538860. 2021.* 2021
c. Wan Z, Sun R, Liu YW, Li S, Sun J, Li J, Zhu J, Moharil P, Zhang B, Ren P, Ren G, Zhang M, Ma X, Dai S, Yang D, **Lu B**, Li S. Targeting metabotropic glutamate receptor 4 for cancer immunotherapy. Sci Adv. 2021 Dec 10;7(50):eabj4226. doi: 10.1126/sciadv.abj4226. Epub 2021 Dec 10. PMID: 34890233
d. Wu S, Sun R, Tan B, Chen b, Zhou W, Gao DS, Zhong J, Huang H, Jiang J and **Lu B** The Half-Life-Extended IL21 can Be Combined with Multiple Checkpoint Inhibitors for Tumor Immunotherapy. *Front Cell Dev Biol. 2021*
e. Chen Y, Xia R, Huang Y, Zhao W, Li J, Zhang X, Wang P, Venkataramanan R, Fan J, Xie W, Ma X, **Lu B**, Li S. An immunostimulatory dual-functional nanocarrier that improves cancer immunochemotherapy. *Nat Commun*. 2016 Nov 7;7:13443. doi:10.1038/ncomms13443. PubMed PMID: 27819653; PubMed Central PMCID: PMC5103075.

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40172651/?sort=date&direction=descending