## BIOGRAPHICAL SKETCH

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NAME: Guo, (Jessie) Yanxiang

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

POSITION TITLE: Associate Professor (tenured)

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 Medical University (currently Peking University Health Science Center), Beijing, China | Bachelor of Medicine* | 07/1995 | Preventive Medicine |
| Institute of Basic Medical Sciences, Beijing, China | Master of Medicine | 07/1999 | Preventive Medicine and Immunology |
| Duke University, Durham, NC, USA | PhD | 12/2008 | Molecular Cancer Biology |
| Rutgers Cancer Institute of New Jersey, Rutgers University, New Brunswick, NJ, USA | Postdoc | 08/2015 | Autophagy and Cancer Metabolism |

* Equal to US MD

### A. Personal Statement

My general research interests are to elucidate the molecular mechanisms of tumorigenesis and identify potential targets for cancer therapy. Supervised by Dr. Sally Kornbluth at Duke University, I received extensive training in biochemistry, cell cycle, cell death, and cancer biology during my PhD study. During my postdoctoral training in the White laboratory at Rutgers Cancer Institute of New Jersey, I have been trained to use genetically engineered mouse models (GEMMs) that mimic human cancers, and mass spectrometry to study the role of autophagy in cancer metabolism and tumorigenesis. The training I have received allows me to continue achieving my ultimate goal to identify new targets for anti-cancer drugs.

I set up my independent laboratory in September 2015 and my research is focused on the field of cancer metabolism. By using isotope tracing labeling and mass spectrometry, I demonstrated for the first time that autophagy recycles intracellular macromolecules to support tumor cell metabolism and survival, which are essential to provide substrates to the TCA cycle for redox balance, energy homeostasis, and nucleotide synthesis. In collaboration with Dr. Rabinowitz at Princeton, I performed in vivo isotope tracing labeling and quantitative metabolic flux analysis in Kras-driven GEMMs for NSCLC and found that circulating lactate, not glucose, is the direct substrate used by lung tumors to extract energy from carbohydrates, an unexpected finding based on previous examination of nutrients used by cultured cancer cells. Furthermore, using GEMMs for Kras-driven NSCLC, I have demonstrated that both tumor-intrinsic autophagy and systemic autophagy are essential for Kras-driven lung tumorigenesis. These findings suggest that targeting cancer metabolism by inhibiting autophagy or blocking other circulating nutrient sources is a valuable strategy to treat lung cancer. Additionally, I am interested to identify other metabolic vulnerabilities that can potentially be targeted for the treatment of KRAS-driven NSCLC.

Recently, we found that G6PD, the first rate-limiting enzyme in oxPPP is not essential for Kras-mutant p53-deficient (KP) lung tumorigenesis using GEMM for NSCLC. oxPPP has been reported to generate cytosolic NADPH in cell culture studies. Our observation suggests that other metabolic pathways are involved in cytosolic NADPH generation during KP lung tumorigenesis. In this application, we propose to elucidate the cytosolic NADPH production routes and the NADPH-mediated metabolic pathways during KP lung tumorigenesis. By doing so, we expect to identify novel metabolic vulnerabilities that may be therapeutic targets for KRAS-driven NSCLC. My previous experience and training can ensure me to successfully complete this proposal.

Ongoing projects that I would like to highlight include:

1R01CA237347-01A1
Guo (PI) 02/01/2020-01/30/2025
*Elucidate the mechanism of autophagy in supporting Lkb1-deficient lung tumorigenesis and metastasis*

1R21CA263136-01A1
Guo (PI) 08/01/2022-07/31/2024
*Targeting autophagy to increase the sensitivity of LKB1-deficient lung tumors to angiogenesis inhibitor*

134036-RSG-19-165-01-TBG/American Cancer Society (ACS)
Guo (PI) 01/01/2020-12/31/2023
*Targeting Metabolic Vulnerabilities to Improve Kras-driven NSCLC Treatment*

Recently completed projects that I would like to highlight include:

GO2 Foundation for Lung Cancer's Young Innovators Team Awards
Guo (Leading PI) 12/01/2019-11/30/2022
*Targeting tumor cell metabolism to improve immunotherapy in KRAS-mutant NSCLC*

Lung Cancer Research Foundation Award
Guo (PI) 11/01/2018-01/31/2020
*Elucidate the mechanism of autophagy in supporting Lkb1-deficient lung tumorigenesis*

Citations:


1. Hui, S, Ghergurovich, J, Morscher, RJ, Cholsoon, J, Teng, X, Lu, W, Esparza, LA, Reya, T, Zhan, L, **Guo, JY**, White, E, and Rabinowitz, JD. Glucose feeds the TCA cycle via circulating lactate. **Nature**. 2017. doi:10.1038/nature24057 Pubmed PMID: 29045397
2. Bhatt V, Khayati K, Hu ZH, Lee A, Kamran W, Su X, **Guo JY**. Autophagy Modulates Lipid Metabolism to Maintain Metabolic Flexibility for Lkb1-Deficient Kras-Driven Lung Tumorigenesis. **Genes & development**. 2019. Epub 2019/01/30. doi: 10.1101/gad.320481.118. (Cover Article) PubMed PMID: 30692209.
3. Ghergurovich JM, Esposito M, Chen Z, Wang J, Bhatt V, Lan T, White E, Kang Y, **Guo JY*,** Rabinowitz JD*. Glucose-6-phosphate dehydrogenase is not essential for K-Ras-driven tumor growth or metastasis. **Cancer research**. 2020. Epub 2020/07/15. doi: 10.1158/0008-5472.CAN-19-2486. PubMed PMID: 32661137. ***co-corresponding author**
4. Khayati K, Bhatt V, Lan T, Alogaili F, Wang W, Lopez E, Hu ZS, Gokhale S, Cassidy L, Narita M, Xie P, White E, **Guo JY**. Transient Systemic Autophagy Inhibition is Selectively and Irreversibly Deleterious to Lung Cancer. **Cancer research**. 2022. Epub 20220926. doi: 10.1158/0008-5472.CAN-22-1039. PubMed PMID: 36156071.


## B. Positions, Scientific Appointments, and Honors

### Positions and Scientific Appointments

| | |
|---|---|
| 2022-Present | Associate Professor with tenure, Rutgers Cancer Institute of New Jersey, RBHS-Robert Wood Johnson Medical School, New Brunswick, NJ |
| 2022-Present | Adjunct Associate Professor with tenure, Department of Chemical Biology, Rutgers Ernest Mario School of Pharmacy, Piscataway, NJ |
| 2021-2022 | Associate Professor, Rutgers Cancer Institute of New Jersey, RBHS-Robert Wood Johnson Medical School, New Brunswick, NJ |
| 2021-2022 | Adjunct Associate Professor, Department of Chemical Biology, Rutgers Ernest Mario School of Pharmacy, Piscataway, NJ |
| 2015-2021 | Assistant Professor, Rutgers Cancer Institute of New Jersey, RBHS-Robert Wood Johnson Medical School, New Brunswick, NJ |
| 2015-2021 | Adjunct Assistant Professor, Department of Chemical Biology, Rutgers Ernest Mario School of Pharmacy, Piscataway, NJ |
| 2013-2015 | Assistant Research Professor, Rutgers Cancer Institute of New Jersey, Rutgers University Dr. Eileen White's laboratory, New Brunswick, NJ |
| 2011-2013 | Research Associate, Rutgers Cancer Institute of New Jersey, Rutgers University Dr. Eileen White's laboratory, New Brunswick, NJ |
| 2009-2011 | Research Assistant, Rutgers Cancer Institute of New Jersey, Rutgers University Dr. Eileen White's laboratory, New Brunswick, NJ |
| 2008-2009 | Postdoctoral Fellow, Rutgers Cancer Institute of New Jersey, Rutgers University |

| | |
|---|---|
| | Dr. Eileen White's laboratory, New Brunswick, NJ |
| 2003-2008 | Graduate Student, Department of Pharmacology and Cancer Biology, Duke University<br>Dr. Sally Kornbluth's laboratory, Durham, NC |
| 2001-2003 | Research Assistant, Animal Health Biotechnology Unit, Temasek Life Sciences Laboratory, Singapore |
| 1995-2001 | Research Assistant, Institute of Basic Medical Sciences, Beijing, China |

**Other Experience and Professional Memberships**

| | |
|---|---|
| 2015-Present | Full Member, Rutgers Cancer Institute of New Jersey |
| 2015-Present | Scientific Review: *Swiss Cancer League/Swiss Cancer Research (Swiss); NIH/NCI/TCB study section; California's Tobacco-Related Disease Research Program (TRDRP) Trainees – Cancer and Oral Biology Review Panel; ZCA1 SRB-5 (O1) SEP-4: NCI Clinical and Translational R21 and Omnibus R03; NIH Oncological Sciences F09C fellowship review panel* |
| 2015-Present | Journal Peer Review: *Autophagy, Cancer Prevention Research, Cell Death & Disease, Genes &Development, Cell Biochemistry Function, Scientific Reports, Nature Communication, Cell Death & Disease, Current Pharmacology Report, Cell Report, Clinical Cancer Research, Cell Metabolism, JCMM, Nature Metabolism, Molecular Oncology* |
| 2010-Present | Active Member, American Association for Cancer Research (AACR) |

**Honors**

| | |
|---|---|
| 2020 | ACS Research Scholar Award |
| 2020 | Rutgers Seed Funding for Large Multi-PI Awards |
| 2019 | Rutgers and Princeton Collaboration Seed Funding Pilot Award |
| 2019 | GO2 Foundation for Lung Cancer's Young Innovators Team Awards |
| 2018 | Lung Cancer Research Foundation Award |
| 2017 | ACS Pilot Award |
| 2016 | OASIS Women in Leadership Program |
| 2015 | The NCI Transition Career Development Award (K22) |
| 2013 | Gallo Awards from Annual Retreat on Cancer Research in New Jersey |
| 2012 | Gallo Awards from Annual Retreat on Cancer Research in New Jersey |
| 2011 | Gallo Awards from Annual Retreat on Cancer Research in New Jersey |
| 2010 | FEBS Transcontinental YOUTH TRAVEL FUND (YTF) grant |
| 2007 | Conference Travel Fellowship, Duke University Graduate School |
| 2007 | Pharmacology Departmental Symposium Poster Award |
| 2006 | Conference Travel Fellowship, Duke University Graduate School |
| 2003-2005 | NIH Training Fellowship, Cell and Molecular Biology program, Duke University |

## C. Contributions to Science

### 1. Cell cycle

As a graduate student with Dr. Sally Kornbluth at Duke University, I utilized cell-free extracts prepared from eggs of the *Xenopus laevis* to study the regulation of cell cycle events and apoptotic processes *in vitro*. I found that the Aven protein, a previously reported apoptotic inhibitor, when overexpressed, acts as an ataxia-telangiectasia mutated (ATM) activator to inhibit G2/M progression. Additionally, in collaboration with other graduate students, I found that protein phosphatase-1 (PP1) activity is suppressed during early mitosis by dual inhibition through Cdc2 phosphorylation and the binding of inhibitor 1 (I1). At late mitosis, a drop in Cdc2 activity following cyclin B degradation and auto-dephosphorylation of PP1 at its Cdc2 phosphorylation site (Thr 320) allows partial PP1 activation, which further promotes PP1-regulated dephosphorylation at the activating site of I1 (Thr 35) followed by dissociation of the I1-PP1 complex. Then fully activated PP1 dephosphorylates mitotic proteins and promotes mitotic exit. I also contributed to the understanding of the mechanism of early mitotic inhibitor 2 (Emi2) on cytostatic factor arrest and meiosis I-meiosis II transition.

a. Wu JQ*, **Guo JY***, Tang W*, Yang CS, Freel CD, Chen C, Nairn AC, Kornbluth S. PP1-mediated dephosphorylation of phosphoproteins at mitotic exit is controlled by inhibitor-1 and PP1 phosphorylation. **Nature cell biology**. 2009;11(5):644-51. doi: 10.1038/ncb1871. PubMed PMID: 19396163; PubMed Central PMCID: PMC2788612. ***co-equal first author**
b. Tang W*, Wu JQ*, **Guo JY***, Hansen DV, Perry JA, Freel CD, Nutt L, Jackson PK, Kornbluth S. Cdc2 and Mos regulate Emi2 stability to promote the meiosis I-meiosis II transition. **Molecular biology of the**

**cell**. 2008;19(8):3536-43. doi: 10.1091/mbc.E08-04-0417. PubMed PMID: 18550795; PubMed Central PMCID: PMC2488281. ***co-equal first author**

c. **Guo JY*,** Yamada A*, Kajino T, Wu JQ, Tang W, Freel CD, Feng J, Chau BN, Wang MZ, Margolis SS, Yoo HY, Wang XF, Dunphy WG, Irusta PM, Hardwick JM, Kornbluth S. Aven-dependent activation of ATM following DNA damage. **Current biology**. 2008;18(13):933-42. doi: 10.1016/j.cub.2008.05.045. PubMed PMID: 18571408; PubMed Central PMCID: PMC2691717. ***co-equal first author**

d. Wu Q, **Guo JY**, Yamada A, Perry JA, Wang MZ, Araki M, Freel CD, Tung JJ, Tang W, Margolis SS, Jackson PK, Yamano H, Asano M, Kornbluth S. A role for Cdc2- and PP2A-mediated regulation of Emi2 in the maintenance of CSF arrest. **Current biology**. 2007;17(3):213-24. doi: 10.1016/j.cub.2006.12.045. PubMed PMID: 17276914; PubMed Central PMCID: PMC2790409.

**2. <u>Autophagy and cancer metabolism</u>**

I started to investigate the role of autophagy in tumorigenesis since my postdoc training with Dr. Eileen White at Rutgers Cancer Institute of New Jersey. There I discovered that Ras activation causes "autophagy addiction" and that the mechanism of this process is that tumor cells require autophagy to maintain the pool of functioning mitochondria to support metabolism during nutrient deprivation. Furthermore, by using the *Kras*-driven GEMMs for human NSCLC, I discovered that autophagy is required to maintain mitochondrial function, tumor cell growth and survival, and that autophagy inhibition causes adenomas and carcinomas to be converted to more benign oncocytomas. These findings suggest that mutations in essential autophagy genes may be the genetic basis for the development of oncocytomas and NSCLC can be converted to more benign oncocytomas by inhibiting autophagy. Additionally, I contributed to the findings that circulating arginine supplied by host autophagy is required for tumorigenesis and host autophagy ablation causes tumor cell disintegration prior to damage to most normal tissues, suggesting a therapeutic window by using autophagy inhibition for cancer treatment. I also contributed to the discovery that autophagy promotes the lung tumor growth in a GEMM driven by $Braf^{V600E}$. My findings indicate both tumor-intrinsic autophagy and tumor non-autonomous autophagy play important roles in cancer cell metabolism and tumor growth.

a. **Guo JY***, Chen HY*, Mathew R*, Fan J*, Strohecker AM, Karsli-Uzunbas G, Kamphorst JJ, Chen G, Lemons JM, Karantza V, Coller HA, Dipaola RS, Gelinas C, Rabinowitz JD, White E. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. **Genes & development**. 2011;25(5):460-70. doi: 10.1101/gad.2016311. PubMed PMID: 21317241; (Cover Article) PubMed Central PMCID: PMC3049287. ***co-equal first author**

b. **Guo JY**, Karsli-Uzunbas G, Mathew R, Aisner SC, Kamphorst JJ, Strohecker AM, Chen G, Price S, Lu W, Teng X, Snyder E, Santanam U, Dipaola RS, Jacks T, Rabinowitz JD, White E. Autophagy suppresses progression of K-ras-induced lung tumors to oncocytomas and maintains lipid homeostasis. **Genes & development**. 2013;27(13):1447-61. doi: 10.1101/gad.219642.113. PubMed PMID: 23824538; PubMed Central PMCID: PMC3713426. ** featured on the journal cover

c. Karsli-Uzunbas G, **Guo JY**, Price S, Teng X, Laddha SV, Khor S, Kalaany NY, Jacks T, Chan CS, Rabinowitz JD, White E. Autophagy is required for glucose homeostasis and lung tumor maintenance. **Cancer discovery**. 2014;4(8):914-27. doi: 10.1158/2159-8290.CD-14-0363. PubMed PMID: 24875857; PubMed Central PMCID: PMC4125614.

d. Poillet-Perez L, Xie X, Zhan L, Yang Y, Sharp DW, Hu ZS, Su X, Maganti A, Jiang C, Lu W, Zheng H, Bosenberg MW, Mehnert JM, **Guo JY**, Lattime E, Rabinowitz JD, White E. Autophagy maintains tumour growth through circulating arginine. **Nature**. 2018;563(7732):569-73. Epub 2018/11/16. doi: 10.1038/s41586-018-0697-7. PubMed PMID: 30429607.

**3. <u>Autophagy and Kras-driven lung cancer</u>**

Since I started my independent laboratory in September 2015, my research focus is to understand the mechanism of autophagy in supporting Kras-driven lung tumorigenesis and potential translatability of autophagy inhibition to the treatment of lung cancer. I found that autophagy is required to recycle metabolites to maintain redox state and energy homeostasis, and to prevent fatal nucleotide pool depletion for *Kras*-driven lung cancer cells to survive starvation. Using the *Kras*-driven GEMMs for human NSCLC, I found that the extent of tumor growth inhibition by autophagy ablation is much more dramatic in Kras-mutant Lkb1-deficient (KL) lung tumor than that in Kras-mutant p53-deficient (KP) lung tumor. Furthermore, I generated a novel autophagy switchable GEMM for Kras-driven NSCLC and found that transient loss of systemic autophagy causes irreversible damage to tumors by suppressing cancer cell metabolism and promoting anti-tumor immunity. Recently, we demonstrated that autophagy upregulation in KL tumors causes resistance to

MEK inhibitor and the combination of HCQ and Trametinib induced ferroptosis in KL cancer cells, leading to tumor regression. Therefore, a combination of autophagy and MEK inhibition could be a novel therapeutic strategy to specifically treat NSCLC bearing co-mutations of LKB1 and KRAS. These findings provide theoretical support for the clinical application of autophagy inhibitor in the treatment of KRAS-mutant NSCLC.

a. **Guo JY#**, Teng X, Laddha SV, Ma S, Van Nostrand SC, Yang Y, Khor S, Chan CS, Rabinowitz JD, White E#. Autophagy provides metabolic substrates to maintain energy charge and nucleotide pools in Ras-driven lung cancer cells. **Genes & development**. 2016;30(15):1704-17.PMID: 27516533. **# co-corresponding author**
b. Bhatt V, Khayati K, Hu ZH, Lee A, Kamran W, Su X, **Guo JY**. Autophagy Modulates Lipid Metabolism to Maintain Metabolic Flexibility for Lkb1-Deficient Kras-Driven Lung Tumorigenesis. **Genes & development**. 2019. Epub 2019/01/30. doi: 10.1101/gad.320481.118. (Cover Article) PubMed PMID: 30692209. ** featured on the journal cover
c. Khayati K, Bhatt V, Lan T, Alogaili F, Wang W, Lopez E, Hu ZS, Gokhale S, Cassidy L, Narita M, Xie P, White E, **Guo JY**. Transient Systemic Autophagy Inhibition is Selectively and Irreversibly Deleterious to Lung Cancer. **Cancer research**. 2022. Epub 20220926. doi: 10.1158/0008-5472.CAN-22-1039. PubMed PMID: 36156071.
d. Bhatt V, Lan T, Wang W, Kong J, Lopes EC, Wang J, Khayati K, Raju A, Rangel M, Lopez E, Hu ZS, Luo X, Su X, Malhotra J, Hu W, Pine SR, White E, **Guo JY**. Inhibition of autophagy and MEK promotes ferroptosis in Lkb1-deficient Kras-driven lung tumors. **Cell Death Dis.** 2023;14(1):61. Epub 20230126. doi: 10.1038/s41419-023-05592-8. PubMed PMID: 36702816; PMCID: PMC9879981.

**4. <u>Autophagy and adult mice homeostasis</u>**

As a master of energy sensor, LKB1 plays an essential role for tissues to respond to energy crises. I previously have made great contributions to understanding the importance of autophagy in adult mice survival and response to starvation. I further explored the interaction of Lkb1 and autophagy in sustaining adult mouse survival by conditionally and systemically deleting Lkb1 and autophagy essential gene *Atg7*. I found that Lkb1 is required for survival in adult mice, and that autophagy temporarily compensates for the loss of Lkb1. The underlying mechanism is that acute systemic deletion of Lkb1 in adult mice led to impaired intestine barrier function, hypoglycemia, p53 induction and disturbed serum metabolism, which is partially rescued by the Lkb1 loss-induced autophagy upregulation. These findings for the first time elucidate the interplay of Lkb1 and autophagy in supporting adult mouse homeostasis.

a. Uzunbas G, **Guo JY**, Price S, Teng X, Laddha SV, Khor S, Kalaany NY, Jacks T, Chan CS, Rabinowitz JD, White E. Autophagy is required for glucose homeostasis and lung tumor maintenance. **Cancer discovery**. 2014;4(8):914-27. doi: 10.1158/2159-8290.CD-14-0363. PubMed PMID: 24875857; PubMed Central PMCID: PMC4125614.
b. Karsli- Khayati K, Bhatt V, Hu ZS, Fahumy S, Luo X, **Guo JY**. Autophagy compensates for Lkb1 loss to maintain adult mice homeostasis and survival. **Elife**. 2020;9. Epub 2020/11/26. doi: 10.7554/eLife.62377. PubMed PMID: 33236987; PMCID: PMC7714393.

**5. <u>G6PD and Kras-driven tumorigenesis</u>**

G6PD is a major contributor to NADPH production and redox homeostasis, and its expression is upregulated and correlated with negative patient outcomes in multiple human cancer types. Recently, we employed modern genetic tools to evaluate the role of G6PD in lung, breast, and colon cancer driven by oncogenic KRAS. We found that although G6PD may matter more in other cancers, in the studied KRAS tumor models, G6PD at most modestly promotes disease progression and is not strictly essential for solid tumorigenesis or metastatic spread. In particular, G6PD is not required for KP lung tumorigenesis. Our findings suggest that G6PD is likely to be particularly important in the context of tumor type or oncogenes. Hence, identification of tumors that are particularly sensitive to G6PD loss is an important ongoing area for investigation. Moreover, elucidating the metabolic pathways involved in maintaining cytosolic NADPH in KP lung tumors is essential for discovering new metabolic therapeutic targets.

a. Ghergurovich JM, Esposito M, Chen Z, Wang J, Bhatt V, Lan T, White E, Kang Y, **Guo JY*,** Rabinowitz JD*. Glucose-6-phosphate dehydrogenase is not essential for K-Ras-driven tumor growth or metastasis. **Cancer research**. 2020. Epub 2020/07/15. doi: 10.1158/0008-5472.CAN-19-2486. PubMed PMID: 32661137. ***co-corresponding author**

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https://www.ncbi.nlm.nih.gov/myncbi/12u_YqpM6nu5g/bibliography/public/