BIOGRAPHICAL SKETCH

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NAME: Shengkan "Victor" Jin

eRA COMMONS USER NAME (credential, e.g., agency login): jinsh1

POSITION TITLE: Associate Professor of Pharmacology

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.S.	07/1992	Biological Sciences
Cornell University Weill Medical College/ Sloan Kettering Cancer Center, New York	Ph.D.	02/1999	Pharmacology and Experimental Therapeutics (Kathleen Scotto Lab)
Rockefeller University, New York	Postdoctoral	02/2003	Cancer Biology (Arnold Levine Lab)

A. Personal Statement

The proposal is a proposal for developing off-the-shelf CAR-T using a new base editing technology. The technology was invented by my laboratory. The patent was awarded in US, European Union, China, Japan, and other countries. The project has the potential of establishing a new and safer platform technology for allogeneic CAR-T engineering and manufacturing. The Jin lab have the right combination of expertise and knowledge in cancer biology, gene editing, and experimental therapeutics to successfully execute the proposed research.

- I have extensive experience in cancer biology and cancer therapeutic development research. I did my Ph.D. in the Department of Molecular Pharmacology and Therapeutics at Cornell Weill Medical College/Memorial Sloan Kettering Cancer Center (Kathleen Scotto Lab). After graduation, I continued on cancer biology research in Dr. Arnold Levine Laboratory at the Rockefeller University, focusing on the cellular circuit regulated by tumor suppressor p53. After becoming an independent PI, my laboratory made important contributions in the fields of autophagy, cancer, and neutrient sensing pathways in tumorigenesis (see Scientific Contribution Section).
- My laboratory identified and characterized safe mammalian mitochondrial uncouplers for potential clinical use for treating diseases type 2 diabetes and cancer,[a] and further initiated an experimental drug development program leading to the identification of a promising lead compound for the treatment of Acute Lymphoblastic leukemia (ALL).[b]
- My laboratory invented the versatile Pin-point base editing technology in 2015, which can have broad applications for in cell therapy and gene therapy.[c,d]

Publications and work relevant to the current proposal:

a. Tao, H., Zhang, Y., Zeng, X., Shulman, GI, and Jin, S. (2014). Niclosamide Ethanolamine (NEN) Improves Blood Glycemic Control and Reduces Hepatic Steatosis in Mice. **Nature Medicine** 20,1263–1269. PMCID: PMC4299950
b. Victoria da Silva-Diz, Bin Cao, Olga Lancho, Eric Chiles, Amer Alasadi, Maya Aleksandrova, Shirley Luo, Amartya Singh, Hanlin Tao, David Augeri, Sonia Minuzzo, Stefano Indraccolo, Hossein Khiabanian,

Xiaoyang Su, Shengkan Jin,* and Daniel Herranz. A novel and highly effective mitochondrial uncoupling 1 drug in T-cell leukemia. **Blood,** 2021, in press. PMC Journal- in process. (SJ is a co-corresponding author)

c. Jin, Shengkan; Collantes, Juan. Nuclease-independent targeted gene editing platform and uses thereof. PCT/US16/42413, EP3322804A4. Priority date: July 15, 2015.
d. Collantes JC, Tan VM, Xu H, Ruiz-Urigüen M, Alasadi A, Guo J, Tao H, Su C, Tyc KM, Selmi T, Lambourne JJ, Harbottle JA, Stombaugh J, Xing J, Wiggins CM, Jin S. Development and Characterization of a Modular CRISPR and RNA Aptamer Mediated Base Editing System. **CRISPR J.** 2021 Feb;4(1):58-68. PMCID: PMC7898459.

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

New Jersey Commission on Cancer Research
COCR23PRG005, 7/2022-6/2025
Title: Developing Off-the-shelf CAR-T for treating Acute Lymphocytic Leukemia with a New Base Editing Technology.
This research Project is to develop off-the-shelf CAR-T for treatment ALL with a new base editing technology developed in the PI's laboratory
Role: PI

DOD, MD200088, 8/2021-7/2023
Title: Duchenne Muscular Dystrophy Research Program Idea Development Award
Title: Developing a Duchenne Muscular Dystrophy Therapeutic Agent With a New Base Editing Technology
The project is to develop a gene therapy agent for the treatment of Duchenne Muscular Dystrophy.
Role: PI

NIH/NIAAA R21, AA027050, 10/1/2018-7/31/2021 (with one-year no-cost extension)
Title: Prevention and treatment of ALD by inducing hepatic mitochondrial uncoupling
This research project is to test a new therapeutic strategy for alcoholic liver disease by inducing liver mitochondrial uncoupling.
Role: PI (Multi-PI Grant)

NIH/NCI R21 CA216604, 3/1/2017- 2/28/2020 (with one-year no-cost extension)
Title: Target cell metabolism for preventing and treating metastatic colon cancer
This research project is to test the novel strategy of treating metastatic colon cancer through mitochondrial uncoupling.
Role: PI

Rutgers University, TechAdvance Awards, 9/15/2018- 12/31/2019; 9/15/2020-12/31/2021
Title: New Base Editing Technology for Treating Cystic Fibrosis and Duchenne Muscular Dystrophy: Proof-of-concept in Cellular Models (2018-2019); New Base Editing Technology for Agriculture Applications (2020-2021)
This research project is to apply a new base gene editing technology for the potential treatment of cystic fibrosis and Duchenne muscular dystrophy using cellular models (2018-2019), and for potential agriculture use (2019-2020).
Role: PI.

Development of Experimental Therapeutics for Metabolic Disorders (PI: Jin) 10/01/2012 - 12/31/2020
Sponsor: Mito BioPharma, LLC
Title: Development of novel safe mitochondrial uncouplers for treating metabolic diseases and cancer
This research is to synthesize new safe mitochondrial uncouplers for type 2 diabetes, NASH, and cancer by modulating cell metabolism.
Role: Principal Investigator

Development of New Base Editing Platform for Precision Gene Editing (PI: Jin) 1/11/2019-4/30/2021
Sponsor: Horizon Discovery, Inc
Title: Development of novel CRISPR-RNA Aptamer mediated base editing platform for ex vivo and in vivo therapeutic development.

The project is to develop a new base editing platform technology as well as therapeutic leads for gene therapy and cell therapy by base editing.
Role: PI

B. Positions and Honors

Positions and Employment

2003-2008 Assistant Professor, Pharmacology Department, Rutgers University-Robert Wood Johnson Medical School, Piscataway, NJ.
2008-present Assoicate Professor, Pharmacology Department, Rutgers University- Robert Wood Johnson Medical School, Piscataway, NJ.
2003-present Member, the Cancer Institute of New Jersey, Rutgers University, New Brunswick, NJ.
2009-present Member, Center for Lipid Research, Rutgers University, New Brunswick, NJ
2010-present Member, The Cardivascular Institute of New Jersey, Rutgers University, New Brunswick, NJ.

Other Experience and Professional Memberships

2003-present Member, American Association for Cancer Research (AACR)
2003-present Member, Society of Chinese Biomedical Scientists in America (SCBA)
2006 Reviewer, NIH/NHLBI, Heart, Lung and Blood Program Project (PO1)
2007 *Ad hoc* reviewer, Association for International Cancer Research, UK
2007 Reviewer, NIH/NIA, Aging Systems and Geriatrics
2007-2013 Editorial Board Member, Autophagy
2008 Reviewer, NIH/NIA, Protein Homeostasis in Aging
2008-2010 *Ad hoc* reviewer, NIH, CAMP Study Section
2009-2011 *Ad hoc* reviewer, NIH, CMAD Study Section
2010-2011 *Ad hoc* reviewer, NIH SEP: Oxidative Stress, Aging, and Transmitters
2011 *Ad hoc* reviewer, NIH SEP: Disorders in Brain, Metabolism and Aging
2011-2014 *Ad hoc* reviewer, NIH, MBPP Study Section
2012,2017 *Ad hoc* reviewer, American Cancer Society, CCGC Study Section 2017
2017-19 Reviewer, NIH/NCI SEP: Clinical and Translational R21
2018 Reviewer, NIH/NCI Research Answers to NCI's Provocative Questions (R01, R21, P50)
2019 Ad hoc reviewer, NIH CMAD (Cellular Mechanism in Aging and Development) study section

C. Contributions to Science

1. *Invented a New CRISPR Base Editing Platform for Gene Therapy and Cell Therapy, Licensed to Horizon Discovery*

Gene inactivation by the conventional CRISPR gene editing technology requires generating of DNA double-strand break (DSB), which is potentially oncogenic. Thus, there are major hurdles to applying CRISPR technology for general therapeutic use. Base editing technology is the second generation CRISPR therapeutic platform for therapeutic development. David Liu group invented a base editing platform by a direct fusion of a nucleotide deaminase to a nuclease- deficient Cas9. We invented a base editing platform based on the targeted recruitment of the nucleotide deaminase through an RNA aptamer (encoded in gRNA).[a,b,c] The technology was licensed to a UK public company, Horizon Discovery, to develop therapeutics and basic research reagents. This set of work laid the foundation of the current proposal of applying the new base editing technology for off-the-shelf CAR-T engineering.

a. Jin, Shengkan; Collantes, Juan. Nuclease-independent targeted gene editing platform and uses thereof. PCT/US16/42413, Priority date: July 15, 2015.
b. Jin, Shengkan and Collantes, Juan. Targeted Gene Editing Platform Independent of DNA Double Strand Break and Uses Thereof PCT/US18/12304. Priority Date: 1/5/2017.

c. Collantes JC, Tan VM, Xu H, Ruiz-Urigüen M, Alasadi A, Guo J, Tao H, Su C, Tyc KM, Selmi T, Lambourne JJ, Harbottle JA, Stombaugh J, Xing J, Wiggins CM, Jin S. Development and Characterization of a Modular CRISPR and RNA Aptamer Mediated Base Editing System. **CRISPR J.** 2021 Feb;4(1):58-68. PMCID: PMC7898459.

2. Autophagy, cell metabolism, and cancer:

In the 1990s, the process of autophagy was first identified in yeast. Through a collaborative effort with Zhenyu Yue from Nat Heintz lab we characterized the first mammalian organism with an autophagy gene deletion, and demonstrated that autophagy deficiency leads to tumorigenesis.[a] This work, which has been cited over 2200 times, unequivocally showed that autophagy plays an important functional role in a mammalian organism. This pioneering work was followed by an era of intensive autophagy research in human health and diseases by many other researchers around the world which culminated with the recognition of 2016 Nobel Prize to Ohsumi, the discoverer of autophagy genes and machinery in yeast. I have made other important contributions to autophagy and cancer. For example, our 2005 work that elucidated the communication between genotoxic signal (p53) and nutrient signal (AMPK-mTOR) to coordinately regulate cell metabolism and autophagy has been cited over 1300 times.[b] Later on, I helped investigated the mechanism by which autophagy is involved in tumorigenesis, including the regulation of autophagy by p53,[b] and through degradation of mitochondria[c] and by handling metabolic stress.[d]

a. Z. Yue, S. Jin, A.J. Levine and N. Heintz. (2003) *Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor.* **Proc. Nat. Acad. Sci.** 100 (25): 15077-15082. PMCID: PMC299911
b. Z. Feng, H. Zhang, A.J. Levine, and S. Jin. (2005) *The Coordinate Regulation of the p53 and mTOR Pathways in Cells.* **Proc. Nat. Acad. Sci**., 102(23):8204-9. PMCID: PMC1142118
c. Y. Zhang, H. Qi, R. Taylor, W. Xu, L. F. Liu, and S. Jin. (2007) *The role of autophagy in mitochondria maintenance: characterization of mitochondrial functions in autophagy-deficient S. cerevisiae strains.* **Autophagy**. 9;3(4): 337-46. PMCID: PMC17404
d. Degenhardt, K., Mathew, R., Beaudoin, B., Bray, K., Anderson, D, Chen, G., Mukherjee, C., Shi, Y., Gelinas, C., Nelson, D.A., Jin, S., and White, E. (2006). *Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis.* **Cancer Cell**. 10(1):51-64. PMCID: PMC2857533

3. *Safe mitochondrial uncouplers and treatment of type 2 diabetes and cancer*

Type 2 diabetes has reached an epidemic level in the developed world. The disease leads to severe and sometimes fatal complications, such as stroke, heart failure, hypertension, kidney failure, and blindness, if the hyperglycemic condition is not controlled. Unfortunately, the current FDA- approved drugs only treat the hyperglycemia symptom. None treats the cause of insulin resistance. Intracellular accumulation of cytotoxic lipids is one primary cause of insulin resistance. Mitochondrial uncoupling is an effective way for burning intracellular fat and an excellent strategy for treating insulin resistance. However, the challenge is to discover a safe mitochondrial uncoupler for practical use. We identified an FDA- approved drug, niclosamide, and demonstrated that its ethanolamine salt (NEN) can safely induce mitochondrial uncoupling *in vivo* and greatly improve glycemic control in diabetic mouse models.[a] This study has immediate translational implications for treating type 2 diabetes. In continuation of this work, we performed medicinal chemistry studies and invented many new chemical compounds for safely uncoupling mitochondria. Moreover, we have conducted proof-of-concept studies in some colon cancer models.[b,c,d]

b. Tao, H., Zhang, Y., Zeng, X., Shulman, GI, and Jin, S. (2014). *Niclosamide Ethanolamine (NEN) Improves Blood Glycemic Control and Reduces Hepatic Steatosis in Mice.* **Nature Medicine** 20,1263–1269. PMCID: PMC4299950
c. Amer Alasadi, Michael Chen, G.V.T. Swapna, Hanlin Tao, Jingjing Guo, Juan Collantes, Noor Fadhil, Gaetano T. Montelione, and Shengkan Jin. Effect of mitochondrial uncouplers niclosamide ethanolamine (NEN) and oxyclozanide on hepatic metastasis of colon cancer. **Cell Death and Disease**. 2018; 9(2):215. doi:10.1038/s41419-017-0092-6. PMC5833462.
d. Alasadi, A; Cao B; Guo, J; Tao, H; Collantes, J; Tan, VM; Su, X; Augeri, D; and Jin, S. Mitochondrial Uncoupler MB1-47 is Efficacious in Treating Hepatic Metastasis of Pancreatic Cancer in Murine Tumor Transplantation Models. **Oncogene**, 40, 2285-2295 (2021). PMC Journal – In Process

e. Victoria da Silva-Diz, Bin Cao, Olga Lancho, Eric Chiles, Amer Alasadi, Maya Aleksandrova, Shirley Luo, Amartya Singh, Hanlin Tao, David Augeri, Sonia Minuzzo, Stefano Indraccolo, Hossein Khiabanian, Xiaoyang Su, Shengkan Jin,* and Daniel Herranz. A novel and highly effective mitochondrial uncoupling 1 drug in T-cell leukemia. **Blood,** 2021, in press. PMC Journal- in process. (SJ is a co-corresponding author)

4. Autophagy and adipocyte differentiation

Obesity has become a pandemic in the US and the developed nations. The direct cause of obesity is the accumulation of excessive white adipose tissue. Understanding how adipose tissues are formed may help fight the obesity pandemic. White adipocytes have a unique cellular structure, in which the cytosol is occupied primarily by one gigantic unilocular lipid droplet while the rest of the cellular components occupied minimal space. It was unclear *what cellular processes* are responsible for the *massive cellular re-organization* during adipogenesis, in particular for the clearance of cytosolic components such as mitochondria, to make room for the big lipid droplet. By generating an adipose tissue- specific autophagy gene knockout mouse model, we demonstrated that autophagy is critical in normal adipocyte differentiation and adipose tissue development. In particular, we found that autophagy is essential for the degradation of mitochondria during adipogenesis.[a,b] This study was *a hallmark work for introducing autophagy research into the field of adipose biology and adipose function.* Interestingly, mice with autophagy deficiency in adipose tissue are resistant to diet-induced obesity and type 2 diabetes. The utilization of autophagy inhibition as a potential mitochondrial uncoupling approach was filed for patent application.[c]

a. Baerga, R., Zhang, Y., Chen, P., Goldman, P., and Jin, S. (2009) *Targeted deletion of autophagy-related 5 (atg5) impairs WAT adipogenesis in a cell culture model and in mice.* **Autophagy**, 5(8):1118-30. PMCID: PMC2873687
b. Zhang, Y., Goldman, S., Baerga, R., Zhao, Y., Komatsu, M., and Jin, S. (2009) *Adipose-Specific Deletion of the Autophagy-Related Gene 7 (atg7) Reveals a Role in Adipogenesis.* **Proc. Natl. Acad. Sci.** 106(47):19860-5. PMCID: PMC2785257
c. Jin, Shengkan. Inhibiting obesity progression by inhibiting adipocyte differentiation with a pre-adipocyte autophagy inhibitor. US Patent App. No. US 13/059,994, PCT No. PCT/US2009/054464

5. p53 and tumor suppression

In 1999, I joined Arnie Levine laboratory at Rockefeller University as a postdoctoral fellow. At the time, Celera decided to sequence human genome with the shot-gun approach and used *Drosophila* genome for a test run. *I was able to identify Drosophila p53 (dp53) and helped establish its fundamental evolutionary role*: protecting genome integrity of the germline cells (as a proud side note, Micheal Young, the 2017 Nobel Prize Laureate, was a co-author in this paper).[a] This work also enabled *Drosophila* as a convenient genetic organism model for the study of p53, one of the two most important tumor suppressor genes in human. Interestingly, dp53 activates cell death in a unique way: instead of directly activating the pro-apoptotic genes, it induces inhibitors of IAPs (inhibitors of apoptosis). Using a proteomic approach, I was able to identify a similar pathway in the mammalian systems.[b] Importantly, with the advent of full human genome information at the time, it was critically important to develop a tool for genome-wide search and validation of the genes that are transcriptionally regulated by p53. We developed and validated an algorithm and computational tool for that purpose.[c,d] It greatly facilitated the effort of systematical understanding of the functional circuitry of tumor suppressor p53.

a. S. Jin, S. Martinek, J. R. Wortman, W. S. Joo, N. Mirkovic, A. Sali, N. P. Pavletich, M. D. Yandell, M.W. Young and A. J. Levine. (2000) *Identification and Characterization of a p53 Homologue in Drosophila melanogaster.* **Proc. Nat. Acad. Sci**. 97 (13): 7301-7306. PMCID: PMC16540.
b. S. Jin, M. Kalkum, M. Overholtzer, B.T. Chait and A.J. Levine. (2003) *CIAP1 and the Serine Protease HTRA2 are Involved in a Novel p53-dependent Apoptotic Pathway in Mammals*. **Genes and Dev.** 17:359-367. PMCID: PMC195984
c. J. Hoh**,** S. Jin***,** T. Parrado, J. Edington, A. J. Levine, J. Ott. (2002) *The p53MH algorithm and its application in detecting p53-responsive genes.* **Proc. Nat. Acad. Sci**. 99 (13): 8467-8472. (*S. Jin is a co-first author). PMCID: PMC124275
d. Z. Feng, S. Jin***,** A. Zupnick, J. Hoh, E. de Stanchina, S. Lowe, C. Prives, and A. J. Levine.(2006) *p53*

tumor suppressor protein regulates the levels of huntingtin gene expression. (*S.Jin. is an equal contribution first author). **Oncogene**. 25(1):1-7. PMID:16278683

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