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: Yan, Zhen

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

POSITION TITLE: Professor of Medicine, Pharmacology, and Molecular Physiology & Biological Physics

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
Medical Worker's College of Jiangsu Province	B.S. (M.D.)	05/1986	Medicine
Univ of Illinois at Urbana-Champaign	M.S.	05/1991	Exercise Physiology
Univ of Texas Health Science Center at Houston	Ph.D.	05/1995	Physiology & Cell Biology
Univ of Texas Southwestern Medical Center at Dallas	Post-doc	04/1999	Molecular Cardiology

A. Personal Statement

Non-communicable diseases account for more than 60% of the death and more than 75% of health care costs in America. On the other hand, it is undisputed that regular exercise has profound health benefits and is the most powerful intervention for prevention and treatment of these chronic diseases. We employ the state-of-the-art molecular and imaging technologies in a variety of animal models to elucidate the underlying molecular and signaling mechanisms of exercise training-induced adaptations and their impacts on health and disease. Trained as a physician scientist, I have 30 years of research experience with private and federal funding (>30) and have established a rigorous research program to achieve my long-term goal to unveil the underlying mechanisms of exercise training and its impact on health and diseases and *vice versa*.

1. Akimoto T, Pohnert SC, Li P, Zhang M, Gumbs C, Rosenberg PB, Williams RS, **Yan Z**. Exercise stimulates Pgc-1alpha transcription in skeletal muscle through activation of the p38 MAPK pathway. J Biol Chem. 2005 May 20;280(20):19587-93. PubMed PMID: 15767263.
2. Laker RC, Lillard TS, Okutsu M, Zhang M, Hoehn KL, Connelly JJ, **Yan Z**. Exercise prevents maternal high-fat diet-induced hypermethylation of the Pgc-1α gene and age-dependent metabolic dysfunction in the offspring. Diabetes. 2014 May;63(5):1605-11. PubMed Central PMCID: PMC5860829.
3. Laker RC, Drake JC, Wilson RJ, Lira VA, Lewellen BM, Ryall KA, Zhang M, Saucerman JJ, Goodyear LJ, Kundu M, **Yan Z**. AMPK phosphorylation of Ulk1 is required for lysosome targeting of mitochondria in mitophagy induced by exercise. Nat Commun. 2017 Sep 15;8(1):548. PubMed Central PMCID: PMC5601463.
4. Call JA, Donet J, Martin KS, Sharma AK, Chen X, Zhang J, Cai J, Galarreta CA, Okutsu M, Du Z, Lira VA, Zhang M, Mehrad B, Annex BH, Klibanov AL, Bowler RP, Laubach VE, Peirce SM, **Yan Z**. Muscle-derived extracellular superoxide dismutase inhibits endothelial activation and protects against multiple organ dysfunction syndrome in mice. Free Radic Biol Med. 2017 Dec;113:212-223. PubMed Central PMCID: PMC5740866.

B. Positions and Honors

Positions and Employment

1981-1988 Lecturer of Pharmacology and Surgery, Nanjing Health School, Nanjing, China
1982-1983 Guest Surgeon, Nanjing First Hospital, Nanjing, China
1995-1999 Post-doctoral Research Fellow, UTSW Medical Center, Dallas, TX
1999-2000 Instructor of Internal Medicine, UTSW Medical Center, Dallas, TX
2000-2002 Assistant Prof of Pharmacology and Internal Medicine, UTSW Medical Center, Dallas, TX

2002-2007	Assistant Research Prof of Medicine, Duke University Medical Center, Durham, NC
2003-2008	Adjunct Assistant Prof, Department of Cell and Molecular Physiology, UNC-Chapel Hill, NC
2008-2008	Adjunct Principal Investigator, Singapore Institute for Clinical Sciences
2006-2008	Associate Prof, Duke-NUS Graduate Medical School, Singapore
2007-2008	Associate Prof of Medicine, Duke University Medical Center, Durham, NC
2013-2016	Distinguished Visiting Professor, Dalian Medical University First Affiliated Hospital
2009-2017	Associate Prof of Medicine (tenured), Departments of Medicine, Pharmacology, Molecular Physiology and Biological Physics, and Director, Center for Skeletal Muscle Research at the Robert M. Berne Cardiovascular Research Center, University of Virginia, Charlottesville, VA
2017-current	Distinguished Visiting Professor, Tianjin University of Sport, Tianjin China
2017-current	Professor, Departments of Medicine, Pharmacology and Molecular Physiology & Biological Physics, and Director, Center for Skeletal Muscle Research, the Robert M. Berne Cardiovascular Research Center, University of Virginia, Charlottesville, VA

Editorial Boards

J Appl Physiol (1999-2002); J Biol Chem (2011-2017); Am J Physiol (2011-present); Associate Editor of Sports Medicine and Health Science (2018-2021)

Grant Review Panels

AHA Council on Basic Cardiovascular Sciences (1999-2000); Muscular Dystrophy Campaign ad hoc reviewer (2003-2004); AHA Integrative Cardiac Biology/Regulation Study Group (2005-2007); Alberta Heritage Foundation for Medical Research ad hoc reviewer (2007); NIH Study Section for R3 Grants (2006-2008); NIH Board of Scientific Counselors (BSC) for the Intramural Research Programs (2009); NIH NHLBI ad hoc reviewer R01 Grants (2009); Chinese Oversea Fellowship invited reviewer (2010-present); Italian Ministry of Health Invited Reviewer for Young Italian Researcher Grant (2010-2012); AHA Basic Cell CSS 3 Study Section ad hoc reviewer (2011-2012); NIH/NIAMS ad hoc reviewer for SMEP study section (2012-present); Invited reviewer of the Association Française contre les Myopathies; NIH/CSR ad hoc reviewer for CMAD study section (2012-2013); NIH CSR ad hoc reviewer for MOSS Q14 Skeletal Muscle SBIR/STTR (2014); Academie Universitaire Louvain Concerted Research Actions (CRA) reviewer (2014); NIH/CSR regular member of CMAD study section (2014-2018); Co-chair of CMAD study section (2016); The VA Cellular and Molecular Medicine (CAMM) Merit review panel *ad hoc* reviewer (2016); PADOH Formula Grants Final Performance Reviewer; NIH/CSR ZRG1 CB-Z (50) R Reviewer (2018); NIH/CSR ZDK1 GRB-N (O1) 1 Reviewer (2018); FLDOH Biomedical Reviews Reviewer (2019); NIDDK ZDK1 GRB-N (M4) Review Panel Reviewer (2019)

Honors

University of Illinois Graduate School Thesis Award (1990); 8th International Conference of Exercise Biochemistry Travel Grant (1991); NIH NRSA-Postdoctoral Fellow (1995-1999); Duke-NUS Outstanding Innovator Award (2010); UVA Department of Medicine Outstanding Research Award (2011); UVA Department of Medicine Outstanding Research Award (2016); Blue Flame Award from Addgene (2016); Induction into the MilliPub Club for 2018.

C. Contribution to Science

1. Exercise-induced mitophagy and its role in contractile and metabolic adapations. This research focuses on a fundamental question in exercise science: how does endurance exercise improve mitochondrial function. I proposed a “cash for clunker” hypothesis that mitohcondrial biogenesis and clearance are both important for mitochondrial qaulity control. I showed that endurance exercise training promotes autophagy gene expression and autophagy flux. Taking advantage of the state-of-the-art imaging, genetic and physiological exercise models in mice, I have gained significant insights into exercise-induced mitophagy and provided the first direct evidence that AMPK controls Ulk1 for activation of mitophagy under the condition of exercise. These insightful findings will significantly impact the research in mitochondrial quality control.

a. Lira VA, Okutsu M, Zhang M, Greene NP, Laker RC, Breen DS, Hoehn KL, **Yan Z**. Autophagy is required for exercise training-induced skeletal muscle adaptation and improvement of physical performance. FASEB J. 2013 Oct;27(10):4184-93. PubMed Central PMCID: PMC4046188.

b. Laker RC, Xu P, Ryall KA, Sujkowski A, Kenwood BM, Chain KH, Zhang M, Royal MA, Hoehn KL, Driscoll M, Adler PN, Wessells RJ, Saucerman JJ, **Yan Z**. A novel MitoTimer reporter gene for mitochondrial content, structure, stress, and damage in vivo. J Biol Chem. 2014 Apr 25;289(17):12005-15. PubMed Central PMCID: PMC4002107.

c. **Yan Z***, Kronemberger A, Blomme J, Call JA, Caster HM, Pereira RO, Zhao H, de Melo VU, Laker RC, Zhang M, Lira VA*. Exercise leads to unfavourable cardiac remodeling and enhanced metabolic homeostasis in obese mice with cardiac and skeletal muscle autophagy deficiency. Sci Rep. 2017 Aug 11;7(1):7894. PubMed PMID: 28801668; PubMed Central PMCID: PMC5554260. (*Corresponding authors)

d. Laker RC, Drake JC, Wilson RJ, Lira VA, Lewellen BM, Ryall KA, Zhang M, Saucerman JJ, Goodyear LJ, Kundu M, **Yan Z**. AMPK phosphorylation of Ulk1 is required for lysosome targeting of mitochondria in mitophagy induced by exercise. Nat Commun. 2017 Sep 15;8(1):548. PubMed Central PMCID: PMC5601463.

2. p38 MAPK in control of PGC-1α in exercise-induced skeletal muscle adaptation. My research has also focused on the importance of the master gene of mitochondria and oxidative metabolism, PGC-1α, in muscle adaptation. Specifically, I revealed the critial role of PGC-1α in mitochondrial biogenesis and angiogenesis, but confirmed that it is not obligatory to fiber type transformation. Importantly, I discovered the critical role of γ isoform of p38 MAPK in PGC-1α gene regulation in response to exercise training. These findings genetically separate the metabolic adaptations from contractile adaptations in skeletal muscle, prompting a wave of investigations into the mechnims underlying endurance exercise-induced mitochondrial biogenesis.

a. Akimoto T, Pohnert SC, Li P, Zhang M, Gumbs C, Rosenberg PB, Williams RS, **Yan Z**. Exercise stimulates Pgc-1alpha transcription in skeletal muscle through activation of the p38 MAPK pathway. J Biol Chem. 2005 May 20;280(20):19587-93. PubMed PMID: 15767263.

b. Pogozelski AR, Geng T, Li P, Yin X, Lira VA, Zhang M, Chi JT, **Yan Z**. p38gamma mitogen-activated protein kinase is a key regulator in skeletal muscle metabolic adaptation in mice. PLoS One. 2009 Nov 20;4(11):e7934. PubMed Central PMCID: PMC2775956.

c. Geng T, Li P, Okutsu M, Yin X, Kwek J, Zhang M, **Yan Z**. PGC-1alpha plays a functional role in exercise-induced mitochondrial biogenesis and angiogenesis but not fiber-type transformation in mouse skeletal muscle. Am J Physiol Cell Physiol. 2010 Mar;298(3):C572-9. PubMed Central PMCID: PMC3353735.

d. **Yan Z**, Okutsu M, Akhtar YN, Lira VA. Regulation of exercise-induced fiber type transformation, mitochondrial biogenesis, and angiogenesis in skeletal muscle. J Appl Physiol (1985). 2011 Jan;110(1):264-74. PubMed Central PMCID: PMC3253006.

3. Endurance exercise in prevention and treatment of chronic diseases. Exercise has since antiquity been known to improve physical performance and health; however, direct scientific evidence has been scanty. I set a rigorous research program using mouse models of exercise and revealed profound positive impacts of endurance exercise training on metabolism, oxidative stress, inflammation and microbiome. For example, I have found for the first time that obese pregnancy in mice led to *Pgc-1α* hypermethylation (-260 CpG) in offspring skeletal muscle along with early onset of glucose intolerance, whereas maternal exercise during pregnancy completely mitigated these epigenetic and metabolic abnormalities in the offspring. I have also contributed significantly to the very first study showing life-long voluntary wheel running defined an anti-inflammatory gut microbiota signature in mice. More recently, I have found that voluntary running in a mouse genetic model of Friedrich's ataxia completely mitigated the symptomatic onset of the disease. These findings have paved the way for more thorough studies of exercise training-mediated protection against chronic diseases.

a. Lira VA, Benton CR, **Yan Z***, Bonen A*. PGC-1alpha regulation by exercise training and its influences on muscle function and insulin sensitivity. Am J Physiol Endocrinol Metab. 2010 Aug;299(2):E145-61. PubMed Central PMCID: PMC2928513. (*Corresponding authors)

b. Zhang C, Li S, Yang L, Huang P, Li W, Wang S, Zhao G, Zhang M, Pang X, **Yan Z**, Liu Y, Zhao L. Structural modulation of gut microbiota in life-long calorie-restricted mice. Nat Commun. 2013;4:2163. PubMed Central PMCID: PMC3717500.

c. Laker RC, Lillard TS, Okutsu M, Zhang M, Hoehn KL, Connelly JJ, **Yan Z**. Exercise prevents maternal high-fat diet-induced hypermethylation of the Pgc-1α gene and age-dependent metabolic dysfunction in the offspring. Diabetes. 2014 May;63(5):1605-11. PubMed Central PMCID: PMC5860829.

4. Muscle-derived extracellular superoxide dismutase (EcSOD) in exercise benefits. In line with my interest in the impact of exercise training on health and diseases, I have studied skeletal msucle-derived antioxidant enzyme, EcSOD and found that exercise training and nitric oxide (NO) donor can both enhance EcSOD expression in skeletal muscle, which lead to a wide range of protections in skeletal muscle and remote organs/tissues, including muscle wasting, diabetic cardiomyopathy and sepsis-induced multiple organ

dysfunction syndrome. These findings are highly significantly in providing not only the direct evidence of exercise benefit, but also revelation of important underlying mechanisms.

a. Geng T, Li P, Yin X, **Yan Z**. PGC-1α promotes nitric oxide antioxidant defenses and inhibits FOXO signaling against cardiac cachexia in mice. Am J Pathol. 2011 Apr;178(4):1738-48. PubMed Central PMCID: PMC3078433.
b. Okutsu M, Call JA, Lira VA, Zhang M, Donet JA, French BA, Martin KS, Peirce-Cottler SM, Rembold CM, Annex BH, **Yan Z**. Extracellular superoxide dismutase ameliorates skeletal muscle abnormalities, cachexia, and exercise intolerance in mice with congestive heart failure. Circ Heart Fail. 2014 May;7(3):519-30. PubMed Central PMCID: PMC4080303.
c. Call JA, Chain KH, Martin KS, Lira VA, Okutsu M, Zhang M, **Yan Z**. Enhanced Skeletal Muscle Expression of EcSOD Mitigates Streptozotocin-Induced Diabetic Cardiomyopathy by Reducing Oxidative Stress and Aberrant Cell Signaling. Circ Heart Fail. 2015 Jan;8(1):188-97. PubMed Central PMCID: PMC4445759.
d. Call JA, Donet J, Martin KS, Sharma AK, Chen X, Zhang J, Cai J, Galarreta CA, Okutsu M, Du Z, Lira VA, Zhang M, Mehrad B, Annex BH, Klibanov AL, Bowler RP, Laubach VE, Peirce SM, **Yan Z**. Muscle-derived extracellular superoxide dismutase inhibits endothelial activation and protects against multiple organ dysfunction syndrome in mice. Free Radic Biol Med. 2017 Dec;113:212-223. PubMed Central PMCID: PMC5740866.

Complete List of Published Work in MyBiobliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/zhen.yan.1/bibliography/40433180/public/?sort=date&direction=descending with 110 peer-reviewed publications with 16296 citations and h-index of 50 (Google Scholar).

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

Ongoing Research Support

5R01AR050429-13 NIH/NIAMS Yan (PI) 08/01/18–06/30/23
AMPK-Ulk1 in exercise-induced mitophagy in skeletal muscle
The proposed studies focus on the regulation and functional role of AMPK-Ulk1-mediated mitophagy induced by endurance exercise in skeletal muscle adaptation.
Role: PI

R01GM109473 NIH/NIGMS Yan (PI) 04/01/15 - 03/31/19
Muscle-derived EcSOD in protection against multiple organ dysfunction syndrome
The study focuses on elucidating the role and mechanism by which muscle-derived EcSOD provides protection against multiple organ dysfunction syndrome in mouse models of sepsis.
Role: PI

FARA General Research Grant Yan (PI) 03/01/17 – 2/28/19
Endurance and resistance exercise mitigate Friedreich's ataxia
The objective of this proposal is to elucidate how two different modes of exercise may prevent the onset of symptomatic Friedreich's Ataxia in mice.
Role: PI

UVA Pan-University Institute Yan (PI) 05/12/16-
UVA Healthspan Institute Initiative
This is to develop a pan-university institute to foster multidisciplinary research that supports delivering holistic, personalized interventions to promote research to maximize healthspan across the whole lifespan.
Role: PI

1R01HL130082-01A1 NIH/NILBI Yang (PI) 04/01/16-03/30/21
The splenic CD4 T cells mediate myocardial ischemia reperfusion injury
This research project will determine that the splenic CD4+ T cells mediate the myocardial post-IR injury, and how substances released from damaged heart activate splenic CD4+ T cells, which amplify the inflammatory response and exaggerate myocardial infarction.
Role: Co-Investigator

Completed Research Support in last five years

UVA CCPH Pilot Grant Program Yan, Davis-Slack (MPI) 03/31/17-09/30/18
Combined Endurance and Resistance Exercise in Ovarian Cancer Prevention in Mice
The study focuses on the impact of combined endurance and resistance exercise on the development of ovarian cancer in novel MADM model in mice.
Role: MPI

3R01CA166458-03S1 NIH/NCI Bullock (PI) 06/1/15-12/31/17
BLIMP-1 mediated regulation of CD8+ TIL
The proposed studies of the parent grant are to understand the impact of BLIMP1 expression on tumor infiltrating CD8+ T lymphocyte function.
Role: Co-Investigator

UVA-AZ Alliance Program Yan (PI) 04/01/17-09/30/17
Small molecule screen in MitoTimer flies and mice for diabetic cardiomyopathy
The project focuses on screening for small molecules in promoting mitophagy and mitochondrial health using cardiomyocytes from MitoTimer mice.
Role: PI

2R01AR050429 NIH/NIAMS Yan (PI) 07/01/11–06/30/17 NCE
p38 MAPK a regulator of muscle contractile and metabolic functions
The proposed studies focus on molecular mechanism and functional role of p38 MAPK in skeletal muscle metabolic and contractile function in cachexia and type 2 diabetes.
Role: PI

FARA 183 General Research Grant Yan (PI) 12/15/14 – 3/31/17
Exercise Impacts on Mitochondria and Muscle Function in Friedreich's Ataxia
The objective of this proposal is to elucidate how exercise affects mitochondria in skeletal muscle and the heart and their function in a mouse model of Friedreich's Ataxia.
Role: PI

14PRE20380254 AHA Predoctoral Fellowship Wilson (PI) 07/01/14-06/30/16
Protein S-nitrosylation Protects Against Ischemia-Reperfusion Injury in Skeletal Muscle
The proposed studies focus on the role of protein s-nitrosylation in protection against Ischemia-Reperfusion induced mitochondrial oxidative stress in skeletal muscle.
Role: Mentor

14POST20450061 AHA Postdoctoral Fellowship Laker (PI) 07/01/14-06/30/16
Epigenetic influence of maternal exercise on offspring metabolic and cardiovascular outcomes
The proposed studies focus on the impact of maternal exercise on offspring from obese dams.
Role: Mentor

Thelma R. Swortzel Award Saucerman (MPI) 06/01/14–11/30/15
MitoTimer reporter in human fibroblasts for diagnosis of mitochondrial diseases
This study explores MitoTimer in human fibroblasts as a diagnostic tool for human mitochondrial diseases.
Role: MPI

12POST12030231 AHA Postdoctoral Fellowship Call (PI) 07/01/12-06/30/14
Skeletal muscle-heart crosstalk in prevention of diabetic cardiomyopathy
The proposed studies focus on the necessity and sufficiency of extracellular superoxide dismutase in exercise training prevention of diabetic cardiomyopathy.
Role: Mentor

1-11-BS-181 ADA Basic Science Award Yan (PI) 01/01/11–12/31/13
Mitochondrial permeability transition and mitophagy in type 2 diabetes
The study focuses on the importance of mitochondrial maintenance in skeletal muscle in type 2 diabetes.
Role: PI

1-11-JF-17 ADA Junior Faculty Award Hoehn (PI) 01/01/11-12/31/13
The role of the mitochondrial permeability pore (mPTP) in the etiology of insulin resistance
This project tests the hypothesis that mitochondrial superoxide production modifies the mitochondrial permeability pore and increases its susceptibility to opening to drive insulin resistance
Role: Co-investigator

1R21HD068953, NIH/NICHD Lynch (PI) 12/01/11–11/30/13
Mitochondrial Lipid Kinase
The goals of this project are to ultimately identify the reaction catalyzed by AGK, determine AGK function in mitochondria in the fate of cell lineages in the mouse.
Role: Co-investigator

1R21AR060444-01, NIH/NIAMS Yan (PI) 09/01/11–08/31/13
NO-dependent SOD3 protection against cachexia

The studies focus on NO-dependent regulation of SOD3 in protection against catabolic muscle wasting.
Role: PI