BIOGRAPHICAL SKETCH

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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

Trained as a physician scientist, I have >25 years of experience in biomedical research on a broad range of topics related to the mechanisms and benefits of exercise training. As a PI on privately and federally funded grants (total 32), I have established a rigorous research program and generated and applied unique genetic models ranging from cultured cells, fruit flies to mice. My long-term research goal is to improve our understanding of the molecular and signaling mechanisms of exercise and its impact on health and diseases (i.e. diabetes, heart failure, mitochondrial disease (FRDA) and sepsis etc.) 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. (528 citations) PubMed PMID: 15767263.
2. 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 PMID: 24523418; (19 citations) PubMed Central PMCID: PMC4080303.
3. 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. (55 citations) PubMed PMID: 24430439.
4. 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 (accepted)

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

Editorial Boards

J Appl Physiol (1999-2002); J Biol Chem (2011-2017); Am J Physiol (2011-present)

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)

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 of Medicine Outstanding Research Award (2016); Blue Flame Award from Addgene (2016).

C. Contribution to Science

1. Elucidated AMPK-Ulk1 in exercise-induced mitophagy in skeletal muscle and its role in contractile and metabolic adapations. I focused on a fundamental question in exercise science: how does exercise training induce muscle adaptation. I proposed a “cash for clunker” hypothesis that mitohcondrial biogenesis and clearance are both important for mitochondrial qaulity control. I showed that exercise training promotes the 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 insights into exercise-induced mitophagy, a sepcific process of clearance of damaged/dysfunctional mitochondria, in skeletal muscle, which is critical for the maintenance of metabolic homeostasis and prevention of insulin resistance. I provided the first direct evidence that AMPK controls Ulk1 in mediating mitophagy in skeletal muscle under the condition of exercise. These insightful findings will significantly impact the research in mitochondrial quality control and its role in physiology and disease development.
   a. **Yan Z**, Lira VA, Greene NP. Exercise training-induced regulation of mitochondrial quality. Exerc Sport Sci Rev. 2012 Jul;40(3):159-64. (92 citations) PubMed Central PMCID: PMC3384482.
   b. 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. (126 citations) PubMed Central PMCID: PMC4046188.
   c. Drake JC, Wilson RJ, **Yan Z**. Molecular mechanisms for mitochondrial adaptation to exercise training in skeletal muscle. FASEB J. 2016 Jan;30(1):13-22. (24 citations) PubMed PMID: 26370848.
   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 (accepted)

2. Revealed the role of p38γ MAPK in control of PGC-1α in exercise-induced skeletal muscle adaptation. My lab focused on the importance of the master gene of mitochondria and oxidative metabolism, PGC-1α, in

muscle adaptation. Specifically, we revealed the critial role of PGC-1α in mitochondrial biogenesis and angiogenesis, but not in fiber type transformation. Importantly, we discovered that p38γ MAPK plays a critical role in PGC-1α gene expression in skeletal muscle in response to exercise training. These findings genetically separate the metabolic adaptations from contractile adaptations, providing strong scientific evidence for regular exercise in prevention and treatment of chronic diseases.

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. (528 citations) 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. (121 citations) 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. (171 citations) 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. (175 citations) PubMed Central PMCID: PMC3253006.

3. Obtained direct evidence of the benefits of endurance exercise in prevention and treatemtn of chronic diseases. Exercise has since antiquity been known to promote physical performance and improve health. 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 that obese pregnancy leads to *Pgc-1*α hypermethylation (-260 CpG) in offspring skeletal muscle along with early onset of glucose intolerance, while maternal exercise during pregnancy can completely mitigated the epigenetic and metabolic abnormalities in the offspring. These findings for the first time revealed a link between obese pregnancy and a negative epigenetic influence on a master gene of oxidative metabolism in the offspring and confirm the beneficial impact of maternal exercise. I have also found that endurance exercise training in mouse enetic model of Friedrich's ataxia can completely mitigate the symptomatic onset of the disease. These findings have paved the way for more thorough studies of exercise training-mediated protection against chronic diseases in animal and humans

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. (200 citations) 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. (108 citations) 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. (55 citations) PubMed PMID: 24430439.
d. Laker RC, Taddeo EP, Akhtar YN, Zhang M, Hoehn KL, **Yan Z**. The Mitochondrial Permeability Transition Pore Regulator Cyclophilin D Exhibits Tissue-Specific Control of Metabolic Homeostasis. PLoS One. 2016 Dec 22;11(12):e0167910. (1 citation) PubMed Central PMCID: PMC5179060.

4. Revealed muscle-derived extracellular superoxide dismutase (EcSOD) in exercise benefits. Trained as a physician, I am extremely interested in the impact of exercise training on health and diseases. Skeletal msucle-derived antioxidant enzyme, EcSOD, is of particular interest. I have found that exercise training and nitric oxide (NO) donor can both enhance skeletal muscle EcSOD expression, which can exert a wide range of protections locally and systemically, including catabolic muscle wasting, diabetic cardiomyopathy and sepsis-induced multiple organ dysfunction syndrome. These findings are highly significantly as they provide not only the evidence for the benefits of exercise training in prevention of oxidative stress-related diseases, but also reveal a important underlying molecular/signaling mechanism.

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. (63 citations) 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. (19 citations) 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. (11 citations) PubMed PMID: 25504759.

d. Leitner LM, Wilson RJ, **Yan Z**, Gödecke A. Reactive Oxygen Species/Nitric Oxide Mediated Inter-Organ Communication in Skeletal Muscle Wasting Diseases. Antioxid Redox Signal. 2017 Jan 4. (2 citations) PubMed PMID: 27835923.

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 100 peer-reviewed publications with 10672 citations and h-index of 46 (Google Scholar).

D. Research Support

Ongoing Research Support

R01GM109473 NIH/NIGMS Yan (PI) 04/01/15 - 03/31/20
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 CCPH Pilot Grant Program Yan, Davis-Slack (MPI) 03/31/17-03/31/18
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

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

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, the period in one's life during which a person is generally healthy and free from serious physical, mental, and social disorders, across the whole lifespan from pre-conception to the end of life care.
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, not the circulating CD4+ T cells, mediate the myocardial post-ischemic reperfusion injury, and explore how substances released from damaged heart activate splenic CD4+ T cells, which amplify the inflammatory response and exaggerate myocardial infarction.
Role: Co-Investigator

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

Completed Research Support in last five years

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