BIOGRAPHICAL SKETCH

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NAME: **Jianhua Zhang**

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POSITION TITLE: **Associate Professor**

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
University of Science & Technology of China	B.S.	1984	Biology
University of Texas Southwestern Medical Center	Ph.D.	1991	Cell & Molecular Biology
Whitehead Institute for Biomedical Research	Postdoc	1995	Molecular Biology

A. Personal statement

I came to the US in 1985 via a CUSPEA program, trained with Dr. Joseph Sambrook at UT Southwestern on molecular cloning and cellular retinoic acid binding protein structure/function relationships, and from 1991 to 1995 with Dr. Rick Young in the Whitehead Institute on the genetics of RNA polymerase holoenzyme and coactivator functions. From 1996 to 2005 I had been working with genetically engineered mouse models of (i) dopamine receptors, (ii) immediate early gene transcription factor c-fos, and (iii) DNA fragmentation factors in neuroplasticity and apoptosis at the Univ of Cincinnati, by generating and analyzing conventional and conditional mouse knockout and transgenic models. In 2005 I became a tenure track assistant professor in UAB where I focused my research program on how the autophagy-lysosomal pathway plays a role in neuronal function and survival, in the context of Parkinson's disease. **A.** The work my laboratory and collaborators published in Molecular Brain in 2008 established, in mouse and *C. elegans* models, that lysosomal cathepsin D plays an essential role in degradation of alpha-synuclein. Following that, my laboratory published a series of studies investigating the impact of cathepsin D haploinsufficiency and dominant negative mutant of cathepsin D on alpha-synuclein degradation and neurotoxin-induced cell survival. **B.** With my collaborators we extended our models of autophagy by generating novel mouse models of autophagy-lysosomal protein knockouts and overexpression, including conditional knockout of VPS34 which is defective for PI3P production and autophagosomal formation, conditional overexpression of serine/cysteine protease inhibitor SCCA1 (SERPINB3) which suppresses, and cathepsin D which enhances, lysosomal protein turnover. **C.** Our recent endeavors are to integrate autophagy, bioenergetics and oxidative stress to understand the underlying mechanisms contributing to neurodegenerative disease. To achieve this I have built a robust collaborative network and our recent studies have provided substantial evidence supporting the role of autophagy in the mitochondrial quality control in response to environmental toxins and endogenous oxidants in a variety of cell settings. We proposed have recently proposed the novel hypothesis that autophagy is an essential cellular antioxidant pathway responsible for clearance of oxidant-induced cellular damage which has attracted a great deal of attention in the field. Importantly, autophagy is at the same time regulated by and regulates cellular metabolism and bioenergetics, and plays an essential role in programming and reprogramming during differentiation and disease pathogenesis.

Our collaborators at UAB include Drs. Victor Darley-Usmar and Scott Ballinger on mitochondrial function, Drs. David Standaert, Rita Cowell, Matthew Goldberg, and Laura Volpicelli-Daley on Parkinson's disease, Drs. Kevin Roth and John Shacka on neuropathology, Drs. Fineberg and Cofield on experimental design, power analyses and statistics. Our collaborators outside of UAB include Drs. Wei-Xing Zong, Luc Van Kaer, on the

role of autophagy in liver, heart and immune systems, Dr. Ling Li on Alzheimer's disease models, Dr. Huaibin Cai on alpha-synuclein conditional mouse models.

Representative publications pertinent to this grant application include:

- Jegga A, Schneider L, Ouyang X, **Zhang J** (2011) Systems biology of the autophagy-lysosomal pathway. Autophagy 7:5, 1-13. PMCID:PMC3127210 cited 52 times
- Jaber N, Dou Z, Chen JS, Catanzaro J, Jiang YP, Ballou LM, Selinger E, Ouyang X, Lin R, **Zhang J***, Zong WX* (2012) The Class III PI3K Vps34 plays an essential role in autophagy and in the heart and liver function. Proc Nat Acad Sci USA 109:2003-2008. *Co-corresponding author. PMCID:PMC3277541 cited 98 times
- Lee J, Giordano S, **Zhang J** (2012) Autophagy, mitochondrial and oxidative stress: cross-talk and redox signaling. Biochemical Journal. 441:523-540. PMCID:PMC3258656 cited 349 times
- Giordano S, Darley-Usmar V, **Zhang J** (2013) Autophagy as an essential cellular antioxidant pathway in neurodegenerative disease. Redox Biology 2:82–90. PMCID:PMC3909266 cited 29 times

B1. Positions

1996-2005	Research Assistant Professor, Department of Cell Biology, Neurobiology and Anatomy, University of Cincinnati College of Medicine
2005-2011	Tenure Track Assistant Professor, Department of Pathology, University of Alabama at Birmingham
2010-2013	Investigator, Birmingham VA Medical Center
2011-present	Associate Professor, Department of Pathology, University of Alabama at Birmingham
2012-present	Associate Professor with tenure, Department of Pathology, University of Alabama at Birmingham

B2. Memberships and services

ad hoc review: Transformative R01, CDIN and SEP (NIH), Alzheimer's association, Parkinson's UK Career Development Award

Editorial board:

2010-present	Brain Research Bulletin
2013-present	Redox Biology
2013-present	American Journal of Pathology
2013-present	PLoS ONE

Membership:

2005-present	Chinese Biologic Investigator Society (CBIS)
2006-present	Society of Chinese Bioscientists in America (SCBA)
2006-present	Birmingham Chinese Professor Association (BCPA, president from 2006)
2010-present	Association for Neurons and Diseases (AND)
2010-present	Society for Free Radical Biology and Medicine (SFRBM, council member from 2012)

C. Contribution to Science:

Dr. Zhang has published 69 peer reviewed research articles, 17 peer reviewed review articles, and 11 book chapters. Her citation indices are: H-factor 34, i10-index 64, total citation 6759.

1. Novel transcription regulation mechanisms, behavioral/pathological significance of conditional knockout of an immediate early gene. Working as a postdoctoral associate with Dr. Richard Young in the Whitehead Institute for Biomedical Research I identified the first cyclin in the general transcription machinery, and demonstrated that a kinase and cyclin pair exists in the RNA polymerase II holoenzyme and performs coactivator functions. This paper has been cited over 373 times and was the foundation for other studies in the field. Furthermore, I and other have found that the RNA polymerase II is associated with a large pre-formed multi-subunit complex. This was important because it challenged the traditional view that the RNA polymerase II undergoes a stepwise assembly process with general transcription factors to initiate transcription every time a promoter is about to be activated. Rather, we found that the RNA polymerase II pre-exists in a complex with the general transcription factors. I then began my first studies in the basic neurobiology with investigation of

the mechanisms of how c-fos regulates neuronal excitability and neuronal cell survival. This was a significant departure from the prevailing view at the time as c-fos as a neuronal activity marker, induced by a variety of activities, light, feeding, electric stimulation, but no study established causality of c-fos in various neuronal functions In the course of these studies I developed my expertise in generating novel animal models with region-specific c-fos knockout in the forebrain or in D1 dopamine receptor-containing neurons, respectively. These studies were the first to demonstrate that c-fos regulates neuronal excitability and neuronal cell survival, and to demonstrate the causality between lack of c-fos and lack of electrophysiological, neuromorphological, molecular and behavioral response to abusive drugs. The mice are of significant value in investigating how gene expression are regulated and how regulated gene expression dictate the adaptation and mal-adaptation of the nervous system to physiological and pathological stimulations. Our findings had a major impact on future studies of the expression and regulation of psychostimulants actions in the context of long term effect of drug abuse.

- Liao S-M*, **Zhang J*,** Jeffrey DA, Koleske AJ, Thompson CM, Chao DM, Viljoen M, van Vuuren HJJ,Young RA (1995) A kinase-cyclin pair in the RNA polymerase II holoenzyme. Nature 374:193-196 *(*co-first author) (with news and views by O'Neill EM and Erin O'Shea: "Transcriptional regulation. Cyclins in initiation"*) cited 376 times
- Hengartner CJ, Thompson CM, **Zhang J,** Chao DM, Liao S-M, Koleske AJ, Young RA (1995) Association of an activator with an RNA polymerase II holoenzyme. Genes & Dev 9:897-910 cited 230 times
- **Zhang, J.,** Zhang, D., McQuade, J.S., Behbehani, M., Tsien, J. & Xu, M. (2002) C-fos regulates neuronal excitability and survival. Nature Genet. 30:416-420. Cited 54 times
- **Zhang J,** Zhang L, Jiao H, Zhang Q, Zhang D, Lou D, Katz JL, Xu M (2006) c-Fos facilitates the acquisition and extinction of cocaine-induced persistent changes. J Neurosci 26:13287-13296 cited 66 times

2. Apoptotic DNA fragmentation factors. DNA fragmentation factor was identified by biochemistry to be involved in apoptosis. To understand its role in vivo, I generated DNA fragmentation factor 45 (DFF45) knockout mice. We found that DFF45 is important for DNA fragmentation activity in vivo. Furthermore, in a follow-up paper, we for the first time demonstrated that regulation of DNA fragmentation influences the completion of apoptosis. The knockout mice benefited a lot of researchers in the field. They facilitated the identification of additional nucleases, and brought to a better understanding of nucleases in apoptosis, neurodegeneration, autoimmunity and cancer. After the identification of a second apoptotic endonuclease, EndoG, we generated mice deficient in EndoG and studied its role in pre-implantation embryogenesis and normal apoptosis.

- **Zhang J**, Liu X, Scherer DC, Van Kaer L, Wang X, Xu M (1998) Resistance to DNA fragmentation and chromatin condensation in mice lacking the DNA fragmentation factor 45. Proc Natl Acad Sci USA 95: 12480-12485 (*with commentary by Susan Cory: "Cell death throes"*) PMCID:PMC22856 cited 192 times
- **Zhang J,** Wang X, Bove K, Xu M (1999) DNA fragmentation factor 45 deficient cells are more resistant to apoptosis and exhibit different dying morphology than wild-type control cells. J Biol Chem 274:37450-37454 cited 83 times
- Review: **Zhang J,** Xu M (2002) Apoptotic DNA degradation and tissue homeostasis. Trends Cell Biol 12:84-89 cited 106 times
- **Zhang J,** Dong M, Li L, Fan Y, Pathrie P, Dong J, Olivares-Villagom D, Lou D, Wells J, Van Kaer L, Wang X, Xu M (2003) Endonuclease G is required for early embryogenesis and normal apoptosis in mice. Proc Natl Acad Sci USA 100:15782-15787 co-corresponding author cited 97 times

3. Autophagy and lysosomal functions. When I came to UAB in 2005 I continued to pursue my interest in apoptosis with a particular emphasis on its interface with the process autophagy. Early in my career I effectively used a systems biology approach to understand the mechanisms of transcription in the nervous system and apoptosis. We recently extended this concept to autophagy with a recent paper in Autophagy which revealed some previously unknown interactions and regulation of autophagy genes, lipid metabolism and calcium regulated proteases. Following the theme of understanding in depth the regulation of protein function in neurodegenerative diseases we have used molecular approaches to define the role of lysosomal enzymes in neurodegenerative diseases such as Parkinson's and Huntington's diseases. We demonstrated using mouse and *C. elegans* models, that lysosomal cathepsin D, but not cathepsin B or L or mutated cathepsin D, is required for degradation of alpha-synuclein. Following that, my laboratory published a series of

studies investigating the impact of cathepsin D haploinsufficiency and dominant negative mutant of cathepsin D on autophagy and cell survival, as well as impact of other cathepsins in mutant huntingtin toxicity.

- Qiao L, Hamamichi S, Caldwell KA, Caldwell GA, Yacoubian TA, Wilson S, Xie ZL, Speake LD, Parks R, Crabtree D, Liang Q, Crimmins S, Schneider L, Uchiyama Y, Iwatsubo T, Zhou Y, Peng L, Lu YM, Standaert DG. Walls KC, Shacka JJ, Roth KA, **Zhang J** (2008) Lysosomal enzyme cathepsin D protects against α-synuclein aggregation and toxicity. Molecular Brain 1:17. PMCID:PMC2600785 cited 96 times
- Shacka J, Roth K, **Zhang J** (2008 Jan) The autophagy-lysosomal degradation pathway: role in neurodegenerative disease and therapy. Frontiers in Bioscience 13:718-36 cited 102 times
- Liang Q, Ouyang X, Schneider L, **Zhang J** (2011) Reduction of mutant huntingtin accumulation and toxicity by lysosomal cathepsins D and B in neurons. Molecular Neurodegeneration 6:37. PMCID:PMC3164227 cited 12 times
- Crabtree D, Dodson M, Ouyang X, Boyer-Guittaut M, Liang Q, Ballestas M, Fineberg N, **Zhang J** (2013) Overexpression of an inactive mutant cathepsin D increases endogenous alpha-synuclein and cathepsin B activity in SH-SY5Y cells. Journal of Neurochemistry 128:950-61. PMCID:PMC3951679 cited 4 times

4. In vivo functions of autophagy lysosomal proteins, and novel regulation of autophagy by LC3 homolog GABARAPL1 and mitochondrial SIRT3 deacetylase. We developed novel conditional mouse models and used both knockdown model in breast cancer cells and mouse embryonic mouse fibroblasts developed by collaborators to investigate autophagy lysosomal functions in autophagy and disease pathologies. Our conditional knockout of VPS34 which is defective for PI3P production and autophagosomal formation, as well as conditional overexpression of serine/cysteine protease inhibitor SCCA1 (SERPINB3) which suppresses and cathepsin D which enhances lysosomal protein turnover, helped identifying the role of these autophagy lysosomal activity modulators in liver, heart, immune system, and breast cancer pathologies. We also found that GABARAPL1 and mitochondrial SIRT3 deacetylase play critical roles in regulation of autophagic flux and integration of bioenergetics and mitochondrial quality.

- Parekh VV, Wu L, Boyd KL, Williams, JA, Gaddy JA, Olivares-Villagomez D, Cover TL, Zong WX, **Zhang J**, Van Kaer L (2013) Impaired autophagy, defective T cell homeostasis and a wasting syndrome in mice with a T cell-specific deletion of Vps34. Journal of Immunity 190(10):5086-101. PMCID:PMC3646937 cited 16 times
- Sheshadri N, Catanzaro J, Bott A, Sun Y, Ullman E, Chen E, Pan J-A, Wu S, Crawford H, **Zhang J,** Zong WX (2014) SCCA1/SerpinB3 promotes epithelial-mesenchymal transition and oncogenic transformation via unfolded protein response and IL-6 signaling. Cancer Research 74:6318-29 PMCID:PMC4216755
- Liang Q, Benavides G, Vasilopoulos A, Gius D, Darley-Usmar V, **Zhang J** (2013) Bioenergetic and autophagic control by Sirt3 in response to nutrient deprivation in mouse embryonic fibroblasts. Biochemical Journal 454:249-257. PMCID:PMC3927421 cited 6 times
- Boyer-Guittaut M, Poillet L, Liang Q, Bôle-Richard E, Ouyang X, Benavides GA, Chakrama F-Z, Fraichard A, Darley-Usmar VM, Despouy G, Jouvenot M, Delage-Mourroux R, **Zhang J** (2014) The role of GABARAPL1 (GEC1) in autophagic flux and mitochondrial quality control in MDA-MB-436 breast cancer cells. Autophagy 10:6,986-1003 PMCID:PMC4091181 cited 4 times

5. Autophagy lysosomal impact on cellular bioenergetics and mitochondrial quality control. One key direction we recently focus on is to identify molecular and cellular mechanisms integrating autophagy regulation with cellular bioenergetic dysfunction, oxidative stress, and neurodegeneration. In collaboration with co-workers at UAB we developed these concepts in a series of review articles exploring the interaction between oxidative stress, mitochondrial quality control and autophagy. Methods of these studies were also published in a series of articles. Furthermore, in a series of research articles, we have gained considerable insight into neurotoxin toxicity, mitochondrial dysfunction, oxidative stress and protective mechanisms of autophagy-lysosomal activities. Highlights include:

a. We have established methods to assess cellular bioenergetic dysfunction in a variety of cell models and in response to diverse oxidative stressors. In human dopaminergic neuroblastoma cells, we further assessed differentiation induced changes in cellular bioenergetics, cellular bioenergetic dysfunction and toxicity in response to MPTP, 6-hydroxydopamine and rotenone.

b. We have investigated cellular bioenergetic dysfunction in response to a variety of pro-oxidant, protein accumulation, protein modification, oxidative and metabolic stress, including nitric oxide under hypoxia, the lipid peroxidation product 4-hydroxynonenal, and rotenone in primary neurons, and demonstrated that autophagy plays an important role in protecting cellular function and survival in various cellular injury models.

- Dranka BP, Benavides GA, Diers AR, Giordano S, Zelickson BR, Reily C, Zou L, Chatham J, Hill BG, **Zhang J**, Landar A, and Darley-Usmar VM (2011) Assessing bioenergetic function in response to oxidative stress by metabolic profiling. Free Radical Biology and Medicine 51:1622-1635 PMCID:PMC3548422 cited 77 times
- Dodson M, Liang Q, Johnson M, Redmann M, Fineberg N, Darley-Usmar V, **Zhang J** (2013) Inhibition of glycolysis attenuates 4-hydroxynonenal-dependent autophagy and exacerbates apoptosis in differentiated SH-SY5Y neuroblastoma cells. Autophagy 9:1996-2008. PMCID:PMC4028343 cited 9 times
- Benavides GA, Liang Q, Dodson M, Darley-Usmar V, **Zhang J** (2013) Inhibition of autophagy and glycolysis by nitric oxide during hypoxia-reoxygenation impairs cellular bioenergetics and promotes cell death in primary neurons. Free Radical Biology and Medicine PMCID:PMC3859859 cited 9 times
- Giordano S, Dodson M, Ravi S, Ouyang X, Redmann M, Darley-Usmar, **Zhang J** (2014) Bioenergetic adaptation in response to autophagy regulators during rotenone exposure. J Neurochem 131:625-33 PMID:25081478 [PubMed - in process] cited 2 times

Complete List of Published Work in googlescholar:
http://scholar.google.com/citations?user=nHLXgEAAAAAJ&hl=en

D. Research Support:

ONGOING

R01NS064090 (Zhang, Jianhua) 04/15/2010 – 03/31/2015
"Alpha-synuclein Degradation Mechanisms"
NIH/NINDS
Alpha-synuclein aggregation is a hallmark of Parkinson's and other Lewy body diseases. Mutations of alpha-synuclein or its gene triplication are responsible for a subset of familial Parkinson's disease. We study how cathepsin D haploinsufficiency and AAV-cathepsin delivery impact alpha-synuclein accumulation and dopaminergic neuron death in alpha-synuclein transgenic mice.
Role: PI

R21ES024027 (Matalon) 09/24/2013 – 08/31/2015
NIH/NIEHS
Mitochondrial Bioenergetic Dysfunction and Chlorine Toxicity
Chlorine generates strong oxidants which promote mitochondrial degradation and causes lung injury and inflammation. The goal of this project is to develop therapeutics against chlorine toxicity that work through a mitochondrial mechanism.
Role: Co-Investigator

COMPLETED for the past three years

"Novel mechanism of neuroprotection against neurotoxins" 2010 - 2013
Veteran Affairs, USA
VA Merit Award
Mitochondrial neurotoxins induce dopaminergic neurodegeneration in mouse models. We study how cathepsin D haploinsufficiency and AAV-cathepsin delivery affect susceptibility of dopaminergic neurons to MPTP.
Role: PI