BIOGRAPHICAL SKETCH

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NAME: Ying Ge

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

POSITION TITLE: 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
Peking University, Beijing, P.R. China	BS	1997	Chemistry
Cornell University, Ithaca, NY	PhD	2002	Chemistry

A. Personal Statement

My career goal is to redefine molecular mechanisms in heart failure and cardiac regeneration through systems biology approaches and translate the bench discoveries to the clinic for precision medicine. I have established a highly interdisciplinary research program that cuts across the traditional boundaries of chemistry, biology, and medicine, based on my unique training and diverse research experiences. I was trained as an analytical chemist and a biochemist at Cornell University under the joint supervision of Fred McLafferty (a pioneer in mass spectrometry) and Tadhg Begley (a renowned enzymologist) working on biological mass spectrometry (MS) and thiamin biosynthesis. At the University of Wisconsin-Madison, I have developed a keen interest in cardiac biology/physiology and established a vibrant and externally funded research program in cardiac proteomics and systems biology. By creatively integrating my expertise in chemistry/proteomics/metabolomics with cardiac biology, I aim to develop innovative technologies that can provide transformative insights into the understanding of cardiac diseases, to identify new molecular targets for diagnosis, and ultimately provide novel treatments for heart failure. I have published 117 papers and am the corresponding author for 63 of them with several in high impact journals such as Nature Methods and PNAS. I have been awarded a Scientist Development Grant by American Heart Association and three NIH R01 grants and a high-end instrument grant. Moreover, I have been a regular reviewer for NIH, *ad hoc* reviewer for AHA, NSF and other domestic and international grant agencies.

I am very passionate about education and find genuine fulfillment in inspiring young scientists. My satisfaction comes when I see students develop critical thinking and problem solving ability and thrive in their career development stages. In my lab, I aim to create a stimulating and nurturing research environment to train the young generation of scientists from diverse backgrounds. I have been mentoring students from chemistry, biology and medical scientist graduate programs. I have successfully mentored 10 post-doc associates, 5 PhD students, and 1 MD student (with honor thesis) as well as 25 undergraduate students at UW-Madison. I am currently mentoring 11 graduate students as well as 9 undergraduate students and 1 MD student in my research group.

B. Positions and Honors

Positions and employment

1998-2002 Research Assistant, Department of Chemistry, Cornell University
2002-2003 Research Scientist III, Department of Chemical Technologies, Wyeth Research
2003-2004 Senior Research Scientist I, Department of Chemical Technologies, Wyeth Research
2004-2006 Research Scientist, Group Leader, Department of Analytical Development, PPD, Inc.
2006-present Director of Mass Spectrometry, Human Proteomics Program, School of Medicine and Public Health, University of Wisconsin-Madison

2006-2012 Assistant Scientist, Department of Physiology, School of Medicine and Public Health, University of Wisconsin-Madison

2012-2015 Assistant Professor, Department of Cell and Regenerative Biology, School of Medicine and Public Health, and Department of Chemistry, University of Wisconsin-Madison

2015-2019 Associate Professor, Department of Cell and Regenerative Biology, School of Medicine and Public Health, and Department of Chemistry, University of Wisconsin-Madison

2019-present Professor, Department of Cell and Regenerative Biology, School of Medicine and Public Health, and Department of Chemistry, University of Wisconsin-Madison

Selected honors and professional activities

H. I. Romnes Faculty Fellowship (2018), Georges Guiochon Faculty Fellowship (2016), Regular Member of NIH Study Section (Myocardial Ischemia and Metabolism, 2016-2022); Board of Directors for American Society for Mass Spectrometry (2016-2018); Board of Directors for Top-down Proteomics Consortium (2015-present); Shaw Scientist Finalist (2014); The Academy of Cardiovascular Research Excellence Young Investigator Award (2011); Scientist Development Grant from the American Heart Association Greater Midwest Affiliate (2007-2010); University of Kentucky Cardiovascular Research Center Visiting Professor (2009); Canadian Society for Mass Spectrometry Student Award (2001); North American FT-ICR Society Student Award (2001)

Ad hoc Reviewer for: NIH Study Section (Myocardial Ischemia and Metabolism) (2010, 2012, 2014, 2015); NIH Program Project Review Panel (2014); NIH Special Emphasis Panel (Cardiovascular and Respiratory Sciences) (2011); AHA Cardiac Biology Regulation –Bsci6 Review Panel (2013, 2014, 2015); NASA HERO Exercise and Cardiovascular Panel (2015); United Kingdom Medical Research Council (2014); Austrian Science Fund (2014); Swiss Science Foundation (2012), National Science Foundation Major Research Instrumentation (MRI) Program (2011); Canada Foundation for Innovation Leaders Opportunity Fund; Pacific Northwest National Laboratory EMSL Peer Review Panel (2009); Ontario Research Fund - Global Leadership Round in Genomics & Life Sciences Competition (2009).

Guest editor for a special issue on “Cardiovascular Proteomics in Clinical and Translational Application” for *Proteomics-clinical application* (2014). Reviewer for 20+ scientific journals including Science, Nature, PNAS.

C. Contribution to Science (from a total of 110 publications)

1. ***Technology Development for Top-Down Proteomics***

Proteomics is essential for deciphering how proteins interact as a system and for understanding the functions of cellular systems in human diseases. However, the unique characteristics of the human proteome, which include the large dynamic range of protein expression and the extreme complexity resulting from a plethora of post-translational modifications (PTMs) and sequence variations, make such analyses difficult. The emerging top-down mass spectrometry (MS)-based proteomics, which is based on analysis of intact proteins, is arguably the most powerful method to comprehensively characterize proteoforms that arise from genetic variations, alternative splicing, and PTMs. I have made significant advances in top-down MS for analysis of large intact proteins purified from complex biological samples including cell and tissue lysate as well as body fluids. We have shown that top-down MS has unique advantages for unraveling the molecular complexity, quantifying modified protein forms, deep sequencing of intact proteins, mapping modification sites with full sequence coverage, discovering unexpected modifications, identifying and quantifying positional isomers and determining the order of multiple modifications. Recently, we are employing a multi-pronged approach to address the challenges in top-down proteomics in a comprehensive manner by developing new MS-compatible surfactants for protein solubilization, novel materials and new strategies for multi-dimensional chromatography separation of proteins, novel nanomaterials for enrichment of low-abundance proteins. Additionally, we are developing a new comprehensive user-friendly software package for top-down proteomics.

a. Hwang, L.; Ayaz-Guner, S.; Cai, W.; Gregorich Z. R.; Jin, S.; **Ge, Y.*** Specific enrichment of phosphoproteins using functionalized multivalent nanoparticles, *J. Am. Chem. Soc*., **2015**, *137*, 2432-2435. PMCID: PMC4372338.

b. Valeja, S. G.; Xiu, L.; Gregorich Z. R.; Guner, H.; Jin, S.; **Ge, Y.*** Three dimensional liquid chromatography coupling IEC/HIC/RPC for effective protein separation in top-down proteomics***,*** *Anal. Chem.* **2015***, 87,* 5363-5371*.* PMCID: PMC4575680.

c. Cai, W.; Guner, H.; Gregorich, Z. R.; Chen, A. J.; Ayaz-Guner, S.; Peng, Y.; Valeja, S. G.; Liu, X.; **Ge, Y.*** MASH Suite Pro: A comprehensive software tool for top-down proteomics, *Mol. Cell Proteomics* **2016**, *15*, 703-714. PMCID: PMC4739683.

d. Brown, K. A.; Chen, B.; Guardado-Alvarez, T.; Lin, Z.; Hwang, L.; Ayaz-Guner, S.; Jin, S.; **Ge, Y.** A cleavable surfactant for top-down proteomics. *Nature Methods* **2019**, 16, 417-420. PMCID: PMC6532422.

2. The Role of Myofilament Modifications in Heart Failure

A major biological research objective in my lab is to understand how myofilament modifications regulate cardiac contractility in health and disease using top-down proteomics in conjunction with *in vivo*, *ex vivo*, and *in vitro* functional measurements. Myofilament proteins of the sarcomeres not only play essential roles in cardiac contractility, but are also critical elements in signal reception and transduction during the onset and progression to heart failure (HF). I have made important contributions to myofilament proteomics and muscle biology. We have comprehensively characterized all types of detectable PTMs including phosphorylation, acetylation, proteolytic degradation, splicing isoforms and single amino acid polymorphisms of cardiac troponin (cTn)/tropomyosin (Tm), a key thin filament regulatory complex, purified directly from animal and human heart tissues. Furthermore, we have identified all the phosphorylation sites in a thick filament protein, cardiac myosin-binding protein C. More importantly, we have linked altered myofilament PTMs to contractile dysfunction in HF using both animal models and human clinical samples.

a. **Ge, Y.***; Rybakova, I.; Xu, Q.; Moss, R. L. Top-down high resolution mass spectrometry of cardiac myosin binding protein C revealed that truncation alters protein phosphorylation state, *Proc. Natl. Acad. Sci. U. S. A.* 200*9,106,* 12658-12663. PMCID: PMC2722289 *This article is a PNAS Direct Submission

b. Zhang, J.; Guy, J. M.; Norman, H. A.; Chen, Y.; Dong, X.; Wang, S.; Kohmoto, T.; Young, K. H.; Moss, R. L.; **Ge, Y.*** Top-Down quantitative proteomics identified phosphorylation of cardiac troponin I as a candidate biomarker for chronic heart failure, *J. Proteome Res.* 2011, 10,4054-4065. PMCID: PMC3170873

c. Dong, X.; Sumandea, C. A.; Chen, Y.; Garcia-Cazarin, M. L.; Zhang, J.; Balke, C. M.; Sumandea, M. P.; **Ge, Y**.* Augmented phosphorylation of cardiac troponin I in hypertensive heart failure, *J. Biol. Chem*. 2012, *287*, 848-857. PMCID: PMC3256890

d. Peng, Y.; Gregorich Z. R.; Valeja, S. G.; Zhang, H.; Cai, W.; Chen, Y.; Guner, H.; Chen, A. J.; Schwahn, D. J.; Hacker, T. A.; Liu, X.; **Ge, Y.*** Top-down proteomics reveals concerted reductions in myofilament and Z-disc protein phosphorylation after acute myocardial infarction, *Mol. Cell. Proteomics* 2014, *13*, 2752-2764. PMCID: PMC4189000.

3. Top-down Proteomics of Skeletal Muscle in Aging

We have established an integrated approach combining top-down high-resolution MS-based proteomics with mechanical functional measurement to study the role of myofilament protein modifications in skeletal muscle during the process of aging and sarcopenic muscle dysfunction. We have comprehensively characterized skeletal muscle troponin and tropomyosin. Our recent study uncovered a progressive age-related decline in the phosphorylation of myosin regulatory light chain (RLC), a critical protein involved in the modulation of muscle contractility, in the skeletal muscle of aging rats, which contributes to sarcopenic muscle dysfunction.

a. Chen, Y.; Sumandea, M. P.; Larsson, L.; Moss, R. L.; **Ge, Y.*** Dissecting human skeletal muscle troponin proteoforms by top-down mass spectrometry, *J. Muscle Res. Cell Motil.* 2015, *36*, 169-181. PMCID: PMC4427557.

b. Gregorich, Z. R.; Cai, W.; Jin, Y.; Wei, L.; Chen, A. J.; McKiernane, S. H.; Aiken, J. M.; Moss, R. L.; Diffee, G. M.; **Ge, Y.*** Top-down targeted proteomics reveals decrease in myosin regulatory light chain phosphorylation that contributes to sarcopenic muscle dysfunction, *J. Proteome Res.* 2016, *15,* 2706-2716. PMCID: PMC4975644.

c. Wei, L.; Gregorich, Z. R.; Lin, Z.; Cai, W.; Jin, Y.; McKiernan, S. H.; Mcilwain, S.; Aiken, J. M.; Moss, R. L.; Diffee, G. M.; **Ge, Y**.* Novel sarcopenia-related alterations in sarcomeric protein post-translational modifications in skeletal muscles identified by top-down proteomics, *Mol. Cell. Proteomics* 2018, *17*, 134-145. PMCID: PMC5750843.

4. Stem Cell and Cardiac Regeneration

A new direction in my research program is to investigate the molecular mechanism in cardiac regeneration via systems biology approaches. The stem cell treatments have beneficial functional improvement for post-MI left ventricular (LV) remodeling, however, the underlying mechanisms remain poorly defined. Thus, we are undertaking a systems biology approach to comprehensively delineate the molecular signaling pathways underlying cardiac regeneration in response to stem cell transplantation (in collaboration with Prof. Jianyi Zhang). Using a swine acute myocardial infarction model with tri-lineage cardiovascular cell transplantation, we provided the direct evidence that the functionally beneficial effects of cell therapy is accompanied by changes in the protein

expression profiles of the myocardial cells in the recipient myocardium—leading to the induction of beneficial signaling pathways Recently, we demonstrated that the MI-induced changes in sarcomeric proteins phosphorylation were reversed by cell transplantation of human cardiac muscle patches derived from human induced-pluripotent stem cells in clinically relevant dimensions four weeks after MI injury. Moreover, we are harnessing the power of innovative top-down proteomics-based systems biology with patient specific hiPSC-derived cardiomyocytes (CMs) in engineered cardiac tissue to study hypertrophic cardiomyopathy (HCM) (in collaboration with Prof. Carter Raphe and Prof. Timothy Kamp).

a. Ye, L.; Chang, Y. H.; Xiong Q.; Zhang P.; Somasundaram, P.; Lepley M.; Swingen C.; Su, L.; Wendel, J. S.; Guo, J.; Jang, A.; Rosenbush, D.; Zhang, L.; Greder, L.; Dutton, J. R.; Zhang, J.; Kamp, T. J.; Kaufman, D.S.; **Ge, Y.;** Zhang, J. Cardiac repair in a porcine model of acute myocardial infarction with human induced pluripotent stem cell-derived cardiovascular cells, *Cell Stem Cell* 2014, *15*, 750-761. PMCID: PMC4275050

b. Chang, Y.; Ye, L.; Cai, W.; Lee, Y-K.; Guner, H.; Lee, Y-S.; Kamp, T. J.; Zhang, J.; **Ge, Y.*** Quantitative proteomics reveals differential regulation of protein expression in recipient myocardium after trilineage cardiovascular cell transplantation, *Proteomics*, 2015, *15*, 2560-2567. PMCID: PMC4690722

c. Gao, L.; Gregorich, Z. R.; Zhu, W.; Mattapally, S.; Lou, X.; Borovjagin, A. V.; Walcott, G. P.; Pollard, A. E.; Fast, V. G.; **Ge, Y.;** Zhang, J. Large cardiac-muscle patches engineered from human induced-pluripotent stem-cell–derived cardiac cells improve recovery from myocardial infarction in swine. *Circulation,* 2018, 137, 1712-1730. PMCID:PMC5903991

d. Cai, W.; Zhang, J.; de Lange, W. J.; Gregorich, Z. R.; Karp, H.; Farrell, E. T.; Lin, Z.; Mitchell, S. D.; Tucholski, T.; McIlwain, S.; Ralphe, C. J.; Kamp, T. J.; **Ge, Y.** Unbiased proteomics method to assess the maturation of human pluripotent stem cell-derived cardiomyocytes, *Circ. Res.* Epub ahead of print.

For a more complete list of published work visit MyBibliography
https://www.ncbi.nlm.nih.gov/sites/myncbi/ying.ge.1/bibliography/41605245/public/?sort=date&direction=descending

D. Research Support

Ongoing

"Top-Down Proteomics of Myofilaments in Heart Failure"
Principal Investigator: **Ge** Agency: NIH/NHLBI
Type: R01 Period: 8/5/2011 – 11/30/2022
Goals: To develop top-down mass spectrometry-based proteomics technologies for analysis of key myofilament regulatory proteins and to understand the disease mechanism in left ventricular hypertrophy and failure using a pressure overload animal model and hypertrophic cardiomyopathy.
Impact/Priority Score: 18, Percentile: 8.0 (reviewed by CCHF study section)
Renewal: Impact/Priority Score: 21, Percentile: 3.0 (reviewed by CCHF study section)

"Enabling Top-down Proteomics through Material Chemistry and Nanotechnology"
Principal Investigator: **Ge and Jin (MPI)** Agency: NIH/NIGMS
Type: R01 Period: 9/22/2015 - 8/31/2020 (no cost extension)
Goals: To develop novel approaches enabled by nanotechnology and materials chemistry to address the challenges in top-down MS-based proteomics.
Impact/Priority Score: 20, Percentile: 2.0 (reviewed by ISD study section)

"MASH Explorer, a Comprehensive Software Environment of Top-Down Proteomics"
Principal Investigator: **Ge** Agency: NIH/NIGMS
Type: R01 Period: 6/01/2018 - 3/31/2022
Goals: To develop MASH Explorer, a comprehensive, user-friendly, and universal software environment for top-down proteomics, to process data from various vendor formats and incorporate multiple algorithms for deconvolution and database search with user-friendly graphical interfaces
Impact/Priority Score: 18, Percentile: 2.0 (reviewed by EBIT study section)

"KCNJ2 Mutation-Induced Arrhythmia Mechanisms in CPVT Phenotypes"
Principal Investigator: **Eckhardt** (**Ge, Co-investigator)** Agency: NIH/NHLBI
Type: R01 Period: 8/1/2018 – 7/31/2022

Goals: to determine the biophysical properties, Ca^{2+} sensitivity, phosphorylation state and arrhythmia mechanism of KCNJ2 (ion channel Kir2.1) mutations associated with a catecholaminergic polymorphic ventricular tachycardia or an Adersen-Tawil syndrome phenotype and compare that to a heart failure model.

"A Multi-Omics Approach to Discover Metabolic Critical Quality Attributes for Cardiomyocyte Biomanufacturing"
Principal Investigator: **Palecek** (**Ge, Co-investigator)** Agency: NIH/NHLBI
Type: R01 Period: 7/1/2019 – 6/30/2023
Goals: This study aims to provide fundamental new insights into metabolic transitions during iPSC-CM differentiation and maturation, will identify novel multivariate metabolic CQAs that will facilitate efforts to mature iPSC-CMs, and generate tools to enable assessment of iPSC-CM differentiation and maturation during biomanufacturing.

"Signaling Pathways in Skin Patterning and Polarity"
Principal Investigator: **Chang** (**Ge, Co-investigator)** Agency: NIH/NIGMS
Type: R01 Period: 4/1/2019 – 6/30/2024
Goals: to reveal fundamental insights into the mechanisms of the mammalian planar cell polarity (PCP) pathway and improve our understanding of the pathogenesis of PCP-related diseases.

"Epithelial Innate Signaling in Airway Inflammation and Remodeling"
Principal Investigator: **Garofalo** (**Ge, Co-investigator)** Agency: NIH/NIAID
Type: P01 Period: 9/1/2018 – 8/31/2023
Goals: To test the hypothesis that NFkB/RelA-activated BRD4 HAT- chromatin remodeling complex (CRC) links RSV infection with the remodeling program.

Completed

"Deciphering Myofilament Modifications in Ischemic Cardiomyopathy"
Principal Investigator: **Ge** Agency: NIH/NHLBI
Type: R01 Period: 3/1/2013 - 2/28/2018 (NCE)
Goals: To understand the molecular mechanism in ischemic cardiomyopathy and identify novel targets for diagnosis and treatment of ischemic heart diseases through identification of ischemia-induced myofilament protein modifications.
Impact/Priority Score: 17, Percentile: 6.0 (reviewed by MIM study section)

"Ultra High-Resolution Mass Spectrometer for Biomedical Research"
Principal Investigator: **Ge** Agency: NIH/Office of the Director
Type: High-end instrument grant Period: 3/1/2015-2/29/2016
Goals: To obtain an ultra high-resolution Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer to support 21 NIH-funded research projects at the University of Wisconsin (UW)-Madison.

"Bioenergetics in Hypertrophied and Remodeled Left Ventricle"
Principal Investigator: Zhang (**Ge**, **Co-investigator**) Agency: NIH/NHLBI
Type: R01 Period: 8/10/2012-8/31/2016
Goals: To determine the energetics in hypertrophied and remodeled left ventricle towards a better understanding of the underlying mechanism in heart failure.

"Nanotechnology Enabled Top-Down Mass Spectrometry-Based Phosphoproteomics"
Principal Investigator: Jin (**Ge, Co-investigator**) Agency: NIH/NIBIB
Type: R21 Period: 2/01/2012-1/30/2015
Goals: To solve the challenge towards a comprehensive analysis of the human phosphoproteome by developing a class of smart multivalent nanoparticle reagents for capturing phosphoproteins globally out of human proteome followed by top-down proteomics of intact phosphoproteins.
Impact/Priority Score: 20, Percentile: 4.0 (reviewed by NANO study section)

"Deciphering Cardiac Troponin Modifications for Diagnosis of Heart Diseases"
Principal Investigator: **Ge** Agency: AHA, Greater Midwest Affiliate
Type: Scientist Development Grant Period: 07/1/07-6/30/11 (NCE)
Goals: To gain a better understanding of the molecular mechanism in the development of heart failure via characterization of modifications in cardiac troponin associated with heart diseases using top down mass spectrometry based methodologies.