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. My research is highly interdisciplinary that cuts across the traditional boundaries of chemistry, biology, and medicine. I received my Ph.D. from Cornell University under the joint supervision of Prof. Fred McLafferty, a pioneer in mass spectrometry, and Prof. Tadhg Begley, a well-known chemical biologist/enzymologist. Thus I have a strong background in chemical biology, analytical chemistry and extensive training/experience in mass spectrometry. After graduate school, I explored a career in pharmaceutical industry and had practical working experience in both drug discovery and development in pharmaceutical industry. Although I enjoyed my industrial experience, my ultimate interests were in academia for the freedom of pursuing independent research. In 2006, I joined UW-Madison to establish the Human Proteomics Program. In 2012, I started my tenure track position in the Department of Cell and Regenerative Biology and Department of Chemistry at UW-Madison and have established a vibrant and externally funded research program in cardiovascular proteomics and systems biology. I have developed innovative technologies that can provide transformative insights into the understanding of cardiovascular disease and regeneration, to identify new molecular targets for diagnosis, and ultimately provide novel treatments for cardiovascular diseases.

I have published over 170 papers including several in high impact journals such as Nature Methods, PNAS, Circ Res, Nature Communications, and JACS. I have been awarded three NIH R01 grants as PI, and one as MPI, 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 medicine graduate programs. I have successfully mentored 10 post-doc associates, 14 PhD students, and 4 MD students (1 with an honors thesis), as well as 31 undergraduate students at UW-Madison. I am currently mentoring 3 post-doc fellows, 12 graduate students, 1 MD student, as well as 6 undergraduate students in my research group.

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

2R01HL096971 Ge (PI) 8/5/2011–11/30/2022
Top-Down Proteomics of Myofilaments in Heart Failure

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.

2R01HL10980-05A1 Ge (PI) 3/1/2013 - 6/30/2025
Deciphering Myofilament Modifications in Ischemic Cardiomyopathy
Goals: To understand the molecular mechanism in ischemic cardiomyopathy and identify novel targets for diagnosis and treatment of ischemic heart diseases through novel multi-omics strategy.

R01GM125085 Ge (PI) 6/01/2018 - 3/31/2023
MASH Explorer, a Comprehensive Software Environment of Top-Down Proteomics
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

2R01GM117058 Jin and Ge (MPI) 9/22/2015 - 6/30/2024
Enabling Top-down Proteomics through Material Chemistry and Nanotechnology
Goals: To develop novel approaches enabled by nanotechnology and materials chemistry to address the challenges in top-down MS-based proteomics.

R01HL148059 Palecek (PI), Ge (co-I) 07/2019-06/2024
Multi-Omics Approach to Discover Metabolic Critical Quality Attributes for Cardiomyocyte Biomanufacturing
Goals: 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.

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.
2006-2019 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 Director, Human Proteomics Program, School of Medicine and Public Health, 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

Other Experience and Professional Memberships

2009 Canada Foundation for Innovation Leaders Opportunity Fund Review Panel
2010-2015 *Ad hoc* reviewer for NIH Study Section (Myocardial Ischemia and Metabolism)
2011 NIH Special Emphasis Panel (Cardiovascular and Respiratory Sciences)
2011 National Science Foundation Major Research Instrumentation (MRI) Program
2012 *Ad hoc* reviewer Swiss Science Foundation
2013-2015 AHA Cardiac Biology Regulation –Bsci6 Review Panel
2014 *Ad hoc* reviewer for United Kingdom Medical Research Council
2014 *Ad hoc* reviewer for Austrian Science Fund
2014 NIH Program Project Review Panel
2015 NASA HERO Exercise and Cardiovascular Review Panel
2015-present Board of Directors for Top-down Proteomics Consortium
2016-2018 Board of Directors for American Society for Mass Spectrometry

2016-2020 Regular Member of NIH Study Section (Myocardial Ischemia and Metabolism)
2021 External Advisory Committee for Beijing Proteome Research Center "Research on Multi-dimensional Proteome System"
2021 *Ad Hoc* Reviewer for NIH Study Section: Special Emphasis Panel ZRG1 CVRS-K 02 M
2021 *Ad Hoc* Reviewer for Dutch Research Council
2022-2024 AHA Council on Basic Cardiovascular Sciences' Nominating Committee

Honors

2007-2010 American Heart Association Scientist Development Grant
2011 The Academy of Cardiovascular Research Excellence Young Investigator Award
2014 Shaw Scientist Finalist
2016 Georges Guiochon Faculty Fellowship
2018 H. I. Romnes Faculty Fellowship
2019 The Top 100 Analytical Scientist Power List (on a global scale)
2020 American Society for Mass Spectrometry Biemann Medal
2020 The Top 10 Analytical Scientist Power List (in North America)
2021 Human Proteome Organization (HUPO) Clinical & Translational Proteomics Sciences Award

C. Contribution to Science (from over 170 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. 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.
c. 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.
d. Tiambeng T, Roberts DS, Brown KA, Zhu Y, Chen B, Wu Z, Mitchell SD, Guardado-Alvarez TM, Jin S, **Ge Y.*** Nanoproteomics enables proteoform-resolved analysis of low-abundance proteins in human serum. *Nature Commun.* **2020**, *11*, 3903. PMCID:PMC7411019

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. 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.
d. Tucholski, T.; Cai, W.; Gregorich, Z.; Bayne, E.; Mitchell, S.; de Lange, W.; McIlwain, S.; Wrobbel, M.; Karp, H.; Hite, Z.; Vikhorev, P. G., Marston, S. B.; Lal, S.; Li, A.; dos Remedios, C.; Kohmoto, T.; Hermsen, J.; Kamp, T.; Ralphe J. C.; Moss, R.L.; **Ge, Y.*** Distinct hypertrophic cardiomyopathy genotypes result in convergent sarcomeric proteoform profiles revealed by top-down proteomics, *Proc. Natl. Acad. Sci. U. S. A.* 2020, 117, 24691-24700. PMCID:PMC7547245 *This article is a PNAS Direct Submission.

3. 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. Prof. Timothy Kamp and Carter Raphe).

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.* 2019*, 125,* 936-953. PMC:PMCID6852699.

4. The Role of AMPK in Cardiac Health and Disease

AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase that is essential in regulating energy metabolism in all eukaryotic cells. We and others have proved recently that AMPK can regulate cardiac contractility. We have demonstrated that AMPK can directly phosphorylate cardiac troponin I (cTnI) at Ser150

in vitro and this site is also phosphorylated on ischemia in whole hearts. Treatment of cardiomyocytes with the AMPK activator, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), resulted increased cTnI phosphylation at Ser150 and increased myocyte contractility and prolonged relaxation. Meanwhile, we and our collaborators provided in vivo evidence that AMPK phosphorylates cTnI to increase cardiac contraction and blunt the effects of cTnI protein kinase A phosphorylation. Taken together, these studies demonstrated that activated AMPK improves contractility via phosphorylating cTnI at Ser150 and thus increasing the Ca^{2+} sensitivity.

a. Sancho Solis, R.; **Ge, Y.***; Walker, J. W. A preferred AMPK phosphorylation site in the inhibitory loop of cardiac and skeletal troponin I, *Protein Sci.* 2011, *20*, 894-907. **(Ge, Y. Corresponding author)**

b. Oliveira, S.M.; Zhang, Y.H.; Sancho Solís, R.; Isackson, H.; Bellahcene, M.; Yavari, A.; Pinter, K.; Davies, J.D., **Ge, Y.;** Ashrafian, H.; Walker, J. W.; Carling, D.; Watkins, H.; Casadei, B.; Redwood, C. AMP-activated protein kinase phosphorylates cardiac troponin I and alters contractility of murine ventricular myocytes, *Circ. Res*., 2012, *110*, 1192-1201.

c. Chen, S.; Zhu, P.; Guo, H.; Wang, Y.; Ma, Y.; Wang, J.; Gao, J.; Chen, J.; **Ge, Y.;** Zhuang, J.; Li, J. α-1 catalytic subunit of AMPK modulates contractile function of cardiomyocytes through phosphorylation of troponin I, *Life Sci*., 2014, *98*, 75-82.

d. Yu, D.; Peng, Y.; Ayaz-Guner, S.; Gregorich Z. R.; **Ge, Y**.* Comprehensive characterization of AMP-activated protein kinase catalytic domain by top-down mass spectrometry, *J. Am. Soc. Mass Spectrom. 2016, 27, 220-232.* **(Ge, Y. Corresponding author)**

5. Multi-omics on skeletal muscle in sarcopenia

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. Moreover, we have 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. Furthermore, we utilized top-down proteomics to elucidate sarcopenia-related changes in the fast- and slow-twitch skeletal muscles of aging rats. Top-down quantitative proteomics identified significant changes in the PTMs of critical myofilament proteins in the fast-twitch skeletal muscles, in accordance with the vulnerability of fast-twitch muscles to sarcopenia. Age-related alterations in the phosphorylation of proteins in the Z-discs in striated muscles were also noted in the fast-twitch skeletal muscle of aging rats, representing the first report of changes in the phosphorylation of Z-disc proteins in skeletal muscle during aging. More recently, we have made a major technological breakthrough in the development of high-sensitivity top-down proteomics for analysis of single muscle fibers (multinucleated single cells) which captures single muscle cell heterogeneity at the proteoform level even for large proteins such as myosin heavy chain (223 kDa).

a. 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

b. 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

c. Jin, Y.; Diffee, G. M.; Colman, R. J.; Anderson, R. M.; **Ge, Y.*** Top-down mass spectrometry of sarcomeric protein post-translational modifications from non-human primate skeletal muscle, *J. Am. Soc. Mass Spectrom.* 2019*. 30,* 2460-2469. PMCID: PMC6722035

d. Melby, J.A.; Brown, K.A.; Gregorich, Z.R.; Roberts, D.S.; Chapman, E.A.; Ehlers, L.E.; Gao, Z.; Larson, E.J.; Jin, Y.; Lopez, J.; Hartung, J.; Zhu, Y.; Wang, D.; Guo, W.; Diffee, G.M.; **Ge, Y.**; High Sensitivity Top-down Proteomics Captures Single Muscle Cell Heterogeneity in Large Proteoforms. *Proc. Natl. Acad. Sci. U. S. A.* 2023, *Accepted*, doi: 10.1101/2022.12.29.521273

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