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 the 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.

For the past twenty years, I have devoted myself to developing and applying high-resolution MS-based top-down proteomics to biomedical research. We have employed 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. By merging native MS with top-down proteomics, native top-down MS enables the characterization of macromolecular complexes, protein-ligand interactions, and comprehensive sequence mapping and proteoform characterization. Recently, my lab has taken a new direction by analyzing proteins and protein complexes in their native states, establishing an integrated native TDP (nTDP) approach to characterize the structure and function of proteins and protein complexes. Importantly, we developed a unified software package, MASH Native, for analyzing native TDP data, providing a 'one-stop shop' for characterizing both native protein complexes and proteoforms.

I have published over 200 papers, many of which have appeared in high-impact journals such as *Nature Methods, PNAS, Circ Res, Nature Communications, JACS,* and *Angewandte Chemie International Edition.* I am passionate about education and enjoy mentoring trainees from diverse backgrounds. I have successfully mentored 11 postdoctoral associates, 17 Ph.D. students, and 4 M.D. students (one with an honors thesis), as well as 47 undergraduate students at UW-Madison. I am currently mentoring 2 postdoctoral fellows, 12 graduate students, 1 M.D. student, and 6 undergraduate students.

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

2R01HL096971 Ge (PI) 8/2011–11/2022

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) 3/2013–6/2025

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) 6/2018–3/2023

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) 9/2015–12/2024

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 (***denatured***) top-down MS-based proteomics

Citations relevant to the proposed application I would like to highlight include:

- Roberts, D. S.; Loo, J. A.; Tsybin, Y. O.; Liu, X.; Wu, S.; Chamot-Rooke, J.; Agar, J. N.; Paša-Tolić, L.; Smith, L. M.; **Ge, Y.,** Top-down Proteomics. ***Nature Reviews Methods Primers*** **2024,** *4* (1), 38. PMCID: PMC11242913
- Chapman EA, Roberts DS, Tiambeng TN, Andrews J, Wang M-D, Reasoner EA, Melby JA, Li BH, Kim D, Alpert AJ, Jin S, **Ge Y.** Structure and Dynamics of Endogenous Cardiac Troponin Complex In Human Heart Tissue Captured By Native Nanoproteomics. ***Nature Commun.*** **2023**, 14, 8400. doi:10.1038/s41467-023-43321-z PMCID: PMC10728164
- 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, 120(19):e2222081120. PMCID: PMC10175728
- 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.

B. Positions, Scientific Appointments, and Honors

Positions and employment

2019-present	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
2015-2019	Associate Professor, Department of Cell and Regenerative Biology, School of Medicine and Public Health, and Department of Chemistry, 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
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
2004-2006	Research Scientist, Group Leader, Department of Analytical Development, PPD, Inc.
2003-2004	Senior Research Scientist I, Department of Chemical Technologies, Wyeth Research
2002-2003	Research Scientist III, Department of Chemical Technologies, Wyeth Research
1998-2002	Research Assistant, Department of Chemistry, Cornell University

Other Experience and Professional Memberships

2024- present	International Society for Heart Research (ISHR) North American Section Council
2022-2024	AHA Council on Basic Cardiovascular Sciences' Nominating Committee
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
2016-2020	Regular Member of NIH Study Section (Myocardial Ischemia and Metabolism)
2016-2018	Board of Directors for American Society for Mass Spectrometry
2015-present	Board of Directors for Top-down Proteomics Consortium
2015	NASA HERO Exercise and Cardiovascular Review Panel
2014	NIH Program Project Review Panel
2014	Ad hoc reviewer for United Kingdom Medical Research Council
2014	Ad hoc reviewer for Austrian Science Fund
2013-2015	AHA Cardiac Biology Regulation –Bsci6 Review Panel
2012	Ad hoc reviewer Swiss Science Foundation
2011	NIH Special Emphasis Panel (Cardiovascular and Respiratory Sciences)
2011	National Science Foundation Major Research Instrumentation (MRI) Program
2010-2015	Ad hoc reviewer for NIH Study Section (Myocardial Ischemia and Metabolism)
2009	Canada Foundation for Innovation Leaders Opportunity Fund Review Panel

Selected Award and Honors

2024	The Analytical Scientist Power List (on a global scale): Top 20 Human Health Heros
2022-2023	Vilas Distinguished Achievement Professorship
2021	Human Proteome Organization (HUPO) Clinical & Translational Proteomics Sciences Award
2020	The Top 10 Analytical Scientist Power List (in North America)
2020	American Society for Mass Spectrometry Biemann Medal
2019	The Top 100 Analytical Scientist Power List (on a global scale)
2018	H. I. Romnes Faculty Fellowship
2016	Georges Guiochon Faculty Fellowship
2014	Shaw Scientist Finalist
2011	The Academy of Cardiovascular Research Excellence Young Investigator Award
2007-2010	American Heart Association Scientist Development Grant

C. Contributions to Science (> 200 peer-reviewed 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. We have employed 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. Recently, we have developed native nanoproteomics platform to characterize the structure of dynamics of protein complexes.

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. 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.

c. Tiambeng, T.; Roberts, D.S.; Brown, K. A.; Zhu, Y.; Chen, B.; Wu, Z.; Mitchell, S.D.; Guardado-Alvarez, T.M.; Jin, S.; **Ge, Y.*** Nanoproteomics enables proteoform-resolved analysis of low-abundance proteins in human serum. *Nature Commun.* **2020**, *11*, 3903. PMCID:PMC7411019

d. Chapman, E. A.; Roberts, D.S, Tiambeng TN, Andrews J, Wang M-D, Reasoner EA, Melby JA, Li BH, Kim D, Alpert AJ, Jin S, **Ge Y.** Structure and dynamics of endogenous cardiac troponin complex in human heart tissue captured by native nanoproteomics. *Nature Commun.* **2023**, 14, 8400. doi:10.1038/s41467-023-43321-z. PMCID: PMC10728164

2. Technology Development for Bottom-up Proteomics, Metabolomics and Multi-omics

My lab has developed a high-throughput bottom-up proteomic method using the MS-compatible surfactant Azo for robust protein extraction, rapid digestion, and MS analysis after UV degradation. This method enhances integral membrane protein analysis and streamlines workflows for clinical applications. Subsequently, we developed an ultrafast and reproducible proteomics from small amounts of heart tissue enabled by azo. Moreover, we have expanded the use of Azo-enabled bottom-up proteomics to extracellular matrix (ECM) proteomics and exosome proteomics. My lab also developed an ultra-high-resolution MS-based metabolomics platform with high-throughput and high reproducibility for analysis of both polar and nonpolar metabolite features from plasma samples. Recently, we implemented parallel metabolite extractions and high-resolution MS-based methods to obtain a comprehensive analysis of the human heart metabolome. Furthermore, we have developed a multi-omics strategy enabled by sequential extraction to capture metabolites and proteins from the same sample and analyzed these extracts using high-resolution MS.

a. Brown, K; Tucholski, T; Eken, C; Knott, S; Zhu, Y; Jin, S; **Ge, Y.** High-throughput proteomics enabled by a photocleavable surfactant. *Angew. Chemie. Int. Ed.* 2020, *132*, 8406-8410. PMCID: PMC7230032

b. Knott, S.J.; Brown, K.A.; Josyer, H.; Carr, A.; Inman, D.; Jin, S.; Friedl, A.; Ponik, S.M.; **Ge, Y.** Photocleavable surfactant-enabled extracellular matrix proteomics. *Anal. Chem*, 2020, *92*, 15693-15698. PMCID: PMC7961849

c. Zhu, Y.; Wancewicz, B.; Schaid, M.; Tiambeng, T.N.; Wenger, K.; Jin, Y.; Heyman, H.; Thompson, C.J.; Barsch, A.; Cox, E.D.; Davis, D.B.; Brasier, A.R.; Kimple, M.; **Ge, Y.** Ultrahigh-resolution mass spectrometry-based platform for plasma metabolomics applied to type 2 diabetes research, *J. Proteome Res.*, 2020, *20*, 463-473. PMCID: PMC7775897

d. Wancewicz, B.; Pergande, M. R.; Zhu, Y.; Gao, Z.; Shi, Z.; Plouff, K.; **Ge, Y.** Comprehensive Metabolomic Analysis of Human Heart Tissue Enabled by Parallel Metabolite Extraction and High-Resolution Mass Spectrometry. *Anal Chem* **2024,** *96,* 5781-5789. PMCID: PMC11057979

3. ***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. 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

c. 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.

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, 120(19):e2222081120. PMCID: PMC10175728

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. 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

For a more complete list of published work visit MyBibliography
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