BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Richard I. Morimoto

POSITION TITLE: Bill and Gayle Cook Professor of Biology

EDUCATION

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Illinois, Chicago, IL	B.S.	06/1972	Biology
University of Illinois Medical Center, Chicago, IL	M.S.	06/1974	Pharmacology
The University of Chicago, Chicago, IL	Ph.D.	06/1978	Molecular Biology

A. Personal Statement: Protein quality control and cell stress responses are fundamental to all biological systems for integrity of the proteome, stress resilience and lifespan, and dysfunction of these essential cellular processes is associated with hundreds of human protein conformational diseases including neurodegenerative diseases, type II diabetes, metabolic pathologies and cancer. Imbalanced proteostasis in aging contributes substantially to proteome mismanagement and the expression of protein aggregates and other toxic species. Protein misfolding results in aberrant protein and membrane interactions, protein mislocalization, imbalanced stoichiometry of subunits of molecular machines, aggregation and improper degradation. Our research examines: (1) the regulation and functional properties of proteostasis networks and the heat shock response to to regulate the robustness and stability of the proteome, to detect damaged proteins and to protect against misfolding and aggregation, (2) how intertissue signaling communicates tissue function to prevent local proteotoxic damage from compromising organismal health and lifespan, (4) how aging leads to proteostasis collapse as the basis for age-associated degenerative diseases, and (6) the properties of small molecule proteostasis regulators as chemical-genetic tools to maintain and restore the proteome in health and disease.

B. Professional Experience: 1978-1981- Postdoctoral Fellow, Department of Biochemistry and Molecular Biology, Harvard University, mentor - Professor Matthew Meselson; **1978-1982-** Tutor in Biochemical Science, Harvard University; **1981-1982-** Research Fellow, Department of Biochemistry and Molecular Biology, Harvard University, mentor - M. Meselson; **1982-1988-** Assistant Professor of Biochemistry, Molecular & Cell Biology, Northwestern University; **1988-1993-** Associate Professor of Biochemistry, Molecular & Cell Biology; **1988-1993**- Director, Undergraduate Program in Biological Sciences; **1990-1993-** Associate Director, Medical Scientist Training Program; **1991-1993-** Arthur Andersen Professor; **1993-1998-** Professor & Chair, Department of Biochemistry, Molecular & Cell Biology; **1994-2005-** John Evans Professor of Molecular Biology; **1995-present-** Director-Rice Institute for Biomedical Research; **1998-2004-**, Dean of The Graduate School and Associate Provost of Graduate Education; **2002-present**- Scientific and Interim **(2019-)** Director of the Chicago Biomedical Consortium; **2005-present**- Bill and Gayle Cook Professor of Biology

Honors and Awards (since 1998): **1998-** Elected Fellow of the American Association for the Advancement of Science; AAAS Scientific Program Board; NIGMS Training Grant Review Panel; **1999-** Visiting Professor, Ecole Normale Superieure, Biologie Moleculaire, (Paris, France), Frank Rose Memorial Lecturer of the British Association for Cancer Research, External Advisory Committee, Kyoto University Institute for Frontier Medical Sciences; **2000-** MERIT award, National Institutes of General Medical Sciences, NIH, Percy Julian Memorial Lecture, Howard University; **2001-** Deans Lecture, Mount Sinai School of Medicine, William Potter Lecturer, Thomas Jefferson Medical School, Deans Lecture, University of Kentucky School of Medicine; **2003-** Visiting Professor, Kyoto University, Institute of Frontier Medical Sciences (Kyoto, Japan); **2004-** Leonardo da Vinci Lecture, San Raffaele Institute and Hospital (Milano Italy), Griffith Lecture, Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine; **2005-** Distinguished Lecturer, School of Molecular and Cell Biology, University of Illinois, Lynch Lecture in the Life Sciences, University of Notre Dame; **2006-** Visiting Professor, Abo Akademi-University of Turku Center for Biotechnology (Turku, Finland); **2007-** Visiting

Professor, Kyoto University, Institute for Frontiers Medical Sciences (Kyoto, Japan), Visiting Professor, Ecole Normale Superieure (Paris, France); **2008-** Charlotte Haywood Lecture – Mt. Holyoke College; Honoris Causa, Abo Akademi University, Turku, Finland; **2009-** Outstanding Scientist Series, Burnham Institute for Medical Science (LaJolla, CA), C. David Marsden Lectureship, 13th International Congress of Parkinson's Disease and Movement Disorders (Paris, France); **2010-** Frontiers in Biology Lecture, Case Western Reserve University School of Medicine; **2011-** Heisenberg Lecture, von Siemens Foundation, Bavarian Academy of Sciences (Munich, Germany), Elected Fellow, American Academy of Arts and Sciences, Ellison Senior Fellow, Ellison Medical Foundation, MERIT award, National Institute on Aging, NIH. University of Illinois Alumni Achievement Award; **2012-** Honors Lecture, New York University Medical School, **2013-** Commandeur, Ordre des Palmes Academiques, Ministry of Education (France); **2014-** Fyodor Lynen Medal, German Society of Biochemistry and Molecular Biology (Germany); **2015-** Japan Society Promotion for Science Senior Fellow; **2019-** Plenary Lecture, Dynamic Codes of Proteins and Glycans in Stress Resilience and Diseases, Japan Agency for Medical Research and Development (Tokyo, Japan); Plenary Lecture, Bergamo Scienza 2019, Bergamo, Italy

C. Contributions to Science

1. Role of Molecular Chaperones in Protein Folding and the Regulation of the Heat Shock Response (HSR). We cloned the human Hsp70 gene (and other human chaperone genes) and developed *in vitro* assays to demonstrate how specific combinations of chaperones and co-chaperones "hold or fold" clients. We also established *in vivo* systems using mammalian cell culture and *C. elegans* to determine how chaperone networks regulate substrate activity and stress signaling. The properties of the HSR were revealed by cloning the four mammalian heat shock transcription factors (HSFs), the identification of genetic modifiers (HSBP-1, SIRT1, and other) that regulate HSF-1 in stress, development and aging.

- Freeman, B.C. and R.I. Morimoto. The Human Chaperones HSP90, HSP70 (HSC70) and HDJ-1 have Distinct Roles in Recognition of a Non-native Protein and Protein Refolding. EMBO Journal 15: 2969-2979 (1996).
- Freeman, B.C., D. Toft, and R.I. Morimoto. Molecular Chaperone Machines: Chaperone Activities of the Cyclophilin CyP-40 and the Steroid Aporeceptor Associated Protein p23. Science 274: 1718-1720 (1996).
- Shi, Y. D. Mosser, and R.I. Morimoto. Molecular Chaperones as HSF1 Specific Transcriptional Repressors. Genes and Development 12: 654-666 (1998).
- Satyal, S.H., D. Chen, S.G. Fox, J.M. Kramer, and R.I. Morimoto. Negative Regulation of the Heat Shock Transcriptional Response by HSBP1. Genes and Development 12: 1962-1974 (1998).
- Morley, J.F., and R.I. Morimoto. Regulation of Longevity in *C. elegans* by Heat Shock Factor and Molecular Chaperones. Mol. Biol. Cell 15: 657-664 (2004). PMCID: PMC329286
- Westerheide, S.D., J. Anckar, S. Stevens, L. Sistonen, and R.I. Morimoto. Stress-Inducible Regulation of Heat Shock Factor 1 by the Deacetylase SIRT1. Science 323: 1063-1066 (2009). PMCID: PMC3429349
- Li, J., L. Chauve, G. Phelps, R. Brielmann, and R.I. Morimoto. E2F Co-regulates an Essential HSF Developmental Program Distinct from the Heat Shock Response. Genes Dev. 30:2062-2075. (2016) PMCID: PMC5066613

2. Model Systems to Study Age-Associated Neurodegenerative Diseases. We have established dozens of *C. elegans* transgenic lines as folding sensors and models for protein conformational disease by expressing wild type and mutant Huntingtin, polyQ, Ataxin 1, Ataxin 3, Androgen Receptor, SOD1, TDP-43, FUS-1, Abeta, α-synuclein, tau and Sup35 prion domain in neurons, intestine and muscle cells. With these, we showed that the insulin signaling pathway (Age-1/Daf-2 and Daf-16) and HSF-1 regulate proteotoxicity and lifespan. These disease models were used in genome-wide RNAi screens to identify composition of the proteostasis network and to establish the mechanisms by which protein aggregation interferes with cellular function and lifespan.

- Morley, J.F., H. Brignull, J. Weyers, and R.I. Morimoto. The Threshold for Polyglutamine-Expansion Protein Aggregation and Cellular Toxicity is Dynamic and Influenced by Aging in *C. elegans*. Proc. Natl. Acad. Science USA 99: 10417-10422 (2002). PMCID: PMC124929
- Nollen, E.A.A., S. Garcia, RG. Van Haaften, S. Kim, R.I. Morimoto, and R.H.A. Plasterek. Genome-wide RNAi Screen Identifies Novel Regulators of Polyglutamine Aggregation. Proc. Natl. Acad. of Science, USA 101: 6403-6408 (2004). PMCID: PMC404057
- Gidalevitz, T., Ben-Zvi, A., Ho, K., Brignull, H., and R.I. Morimoto. Progressive Disruption of Cellular Protein Folding in Models of Polyglutamine Diseases. Science 311: 1471-1474 (2006).
-Brignull, H., F. Moore, S. Tang, and R.I. Morimoto. Polyglutamine Proteins at the Pathogenic Threshold Display Neuron-Specific Aggregation in *C. elegans* Neurons. J. Neuroscience 26: 7597-7606 (2006).

-Gidalevitz, T., T. Krupinski, S.M. Garcia, and R.I. Morimoto. Toxicity of Mutant SOD1 is Directed by Protein Polymorphisms. PLoS Genetics 5(3): e1000399 (2009).
- Silva, M. C., S. Fox, H. Thakkar, M. J. Rivera Beam, M. D. Amaral, and R.I. Morimoto. A Genetic Screening Strategy Identifies Novel Global Regulators of the Proteostasis Network. PLoS Genetics.7(12): DOI:10.1371 (2011). PMCID: PMC3248563
- Gidalevitz, G., N. Wang, T. Deravaj, and R.I. Morimoto. Natural Genetic Variation Determines Susceptibility to Aggregation or Toxicity in a *C. elegans* model for Polyglutamine Disease. BMC Biology 11, 100, DOI: 10.1186 (2013).

3. Physical Chemical Properties of Protein Misfolding and Aggregation. We identified supersaturation as a shared physical biochemical property in Alzheimer's Disease, Huntington's Disease, ALS and muscle inclusion myositis. We showed that the deposition of insoluble, supersaturated proteins into aggregates and inclusions occurs when their cellular concentration is high relative to their intrinsic solubility. These characteristics likely define why aggregation is a systemic problem in age-associated diseases.
-Ciryam, P., G. G. Tartaglia, R. I. Morimoto, C. M. Dobson, and M. Vendruscolo. Neurodegenerative Diseases and Widespread Aggregation are Associated with Supersaturated Proteins. Cell Reports 5: 781-790, DOI: 10.1016, PMID: 24183671 (2013).
-Ciryam, P., R. Kundra, R. Freer, R. I. Morimoto, C. M. Dobson, and M. Vendruscolo. A Transcriptional Signature of Alzheimer's Disease is Associated with a Metastable Subproteome at Risk for Aggregation. Proc. Natl. Acad. Sci. U.S.A., DOI: 10.1073 (2016).
-Ciryam, P., I. Lambert-Smith, D. M. Bean, D. N. Saunders, M. R. Wilson, R. I. Morimoto, S. G. Oliver, C. M. Dobson, M. Vendruscolo, G. Favrin, and J. J. Yerbury. Tissue-specific Patterns of Supersaturation are Associated with Co-Aggregation in ALS Inclusion Bodies. Proc. Natl. Acad. Sci. USA., DOI:10.1073 (2017).
-Kundra, R., P. Ciryam, R. I. Morimoto, C. M. Dobson, and M. Vendruscolo. Protein Homeostasis of a Metastable Subproteome Associated with Alzheimer's Disease. Proc. Natl. Acad. Sci. USA., DOI: 10.1073/pnas.1618417114 (2017).
- Ciryam, P., M. Antelek, C. Dobson, A. Guttsches, R. Kley, K. Marcus, R. I. Morimoto, M. Vendruscolo, and C. Weihl. A Metastable Subproteome Underlies Inclusion Formation in Muscle Proteinopathies. Acta Neuropathol Commun. 7(1): 197. doi: 10.1186/s40478-019-0853-9 (2019).

4. Effects of Aging and Cell Stress on Proteostasis Networks. We discovered that the four major cell stress responses; the heat shock response (HSR), the ER and mitochondrial unfolded protein responses, and antioxidant stress responses of *C. elegans* decline simultaneously at reproductive maturity. This coincides with the misfolding of temperature-sensitive folding sensors and the appearance of insoluble aggregates. The transcriptional dysregulation of the HSR occurs by altered epigenetic repressive marks at genes encoding molecular chaperones, leading to reduced binding of HSF-1 and RNA pol II at target promoters. Collapse of the HSR is suppressed by removal of germ line stem cells and enhancing expression of the jumonji demethylase, revealing that reproduction is tightly coupled with somatic proteostasis. We propose that the age-dependent collapse of proteostasis observed for the HSR extends to all cell protective mechanisms and represents an early event that triggers age-dependent decline. Extending our observations to human brain aging, the expression of 1/3rd of the human chaperome of 340 genes declines in Alzheimer's, Huntington's and Parkinson's disease, and together with functional RNAi assays for protein aggregation we identified a core chaperome of 16 genes that are essential to prevent misfolding and proteotoxicity in brain aging.
- Ben-Zvi-A., E.A. Miller, and R.I. Morimoto. The Collapse of Proteostasis Represents an Early Molecular Event in *C. elegans* Aging. Proc. Natl. Acad. Sci. USA. 106: 14914-14919 (2009). PMCID: PMC2736453
- Kirstein-Miles, J., A. Scior, E. Duerling, and R.I. Morimoto. The Nascent Polypeptide Associated Complex is a Key Regulator of Proteostasis. The EMBO Journal 32(10): 1451-1468, PMID: 23604074 DOI: 10.1038 (2013).
- Brehme, M., C. Voisine, T. Rolland, S. Wachi, J. Soper, Y. Zhu, K. Orton, A. Villella, D. Garza, M. Vidal, H. Ge, and R.I. Morimoto. A Chaperome Sub-Network Safeguards Protein Homeostasis in Aging and Neurodegenerative Disease. Cell Reports 9: 1135–1150, DOI: 10.1016/j (2014). PMCID: PMC4255334
- Kirstein, J., D. Morito, T. Kakihana, M. Sugihara, A. Minnen, M.S. Hipp, C. Nussbaum-Krammer, F.U. Hartl, K. Nagata, and R.I. Morimoto. Proteotoxic Stress and Ageing Triggers the Loss of Redox Homeostasis Across Cellular Compartments. EMBO Journal 34: 2334-2349, PMID:26228940 (2015).
-Labbadia, J. and R.I. Morimoto. Repression of the Heat Shock Response is a Programmed Event at the Onset of Reproduction. Molecular Cell 59: 639-650, DOI 10.1016/j. molcel.2015.06.027 PMID: 266212459 (2015).

- Labbadia, J., R. Brielmann, M. Neto, Y.-F. Lin, C.M. Haynes, and R.I. Morimoto. Mitochondrial Stress Restores the Heat Shock Response and Prevents Proteostasis Collapse During Aging. Cell Reports 21: 1481-1494, DOI.org/10.1016/j.celrep.2017.10.038 (2017).
- Kirstein, J., K. Arnsburg, A. Scior, A. Szlachcic, D. Lys Guilbride, R.I. Morimoto, B. Bukau. and N.B. Nillegoda. In vivo Properties of the Disaggregase Function of J-domain Proteins and Hsc70 in *C. elegans* Stress and Aging. Aging Cell, 16:1414-1424, DOI: 10.1111/acel.12686 (2017).

5. Organismal Control of Cell Stress and Proteostasis Networks by Cell Non-Autonomous Regulation. The most unexpected observation has been intertissue communication and cell non-autonomous regulation of organismal proteostasis. Metazoans have established a complex trans-cellular stress-signaling pathway that communicates between neurons to somatic tissues and between somatic tissues. This was shown: (1) for the HSR that is regulated by the AFD thermosensory neurons to provide centralized control over the induction of the HSR in other tissues, (2) at the neuromuscular junction involves cholinergic and GABA-ergic signaling, and involves release of Ca^{2+} and activation of HSF-1, (3) transcellular chaperone signaling between somatic tissues and neurons to ensure that local proteotoxic damage within any single cell or tissue is protected by a community organism-wide response from adjacent tissues. This ensures that the unique complement of proteins expressed within each tissue is maintained by a combination of autonomous and non-autonomous quality control to prevent misfolding and aggregation from dominating the health of a tissue and compromising the health of the organism, and (4). That the fertilized egg quality resets maternal stress resilience and proteostasis.
- Garcia, S., M.O. Casanueva, C. Silva, M. Amaral, and R.I. Morimoto. Neuronal Signaling Modulates Protein Homeostasis in *C.* elegans Postsynaptic Muscle Cells. Genes and Development: 21: 3006-3016 (2007). PMCID: PMC2049200
- Prahlad, V., Cornelius, T., and R.I. Morimoto. Regulation of the Cellular Heat Shock Response in *Caenorhabditis elegans* by Thermosensory Neurons. Science 320: 811-814 (2008). PMCID: PMC3429343
- van Oosten-Hawle, P., R. Porter, and R. I. Morimoto. Regulation of Organismal Proteostasis by Transcellular Chaperone Signaling. Cell 153: 1366-1378, DOI:10.1016 (2013). PMCID: PMC3955170
- Silva, M. C., M. D. Amaral, and R.I. Morimoto. Neuronal Reprogramming of Protein Homeostasis by Calcium Dependent Regulation of the Heat Shock Response. PLoS Genetics 9(8), DOI: 10.1371, e1003711 (2013).
-Tatum, M.C., M.D. Chikka, F.K. Oi, L. Chauve, L.A. Martinez-Velazquez, H.W.M. Steinbusch, R.I. Morimoto, and V. Prahlad. Optogenetic Stimulation of Serotonin Release Activates the Heat Shock Response in Distal Tissues of *C. elegans.* Current Biology 25: 163-174, DOI: 10.1016/j.cub.2014.11.040 (2015).
- Sala, A.J., L.C. Bott, R.M. Brielmann, and R.I. Morimoto. Embryo Integrity Regulates Maternal Proteostasis and Stress Resilience. Genes and Development. 34: 678-687, doi:10.1101/gad.335422.119(2020).

6. Small Molecule Pharmacological Regulation of the Heat Shock Response for Age-Associated Conformational Diseases. We identified small molecules that induce the HSR, that are HSF-1 selective and pan-stress responsive. These include celastrol, non-steroidal anti-inflammatory drugs (salicylate, indomethacin) and ~300 previously unidentified small molecules identified from a ~ 1mil molecule screen for chaperone regulators that suppress aggregation in *C. elegans* and tissue culture models of mutant SOD1, Huntingtin, and Atx-1. We have employed these small molecule proteostasis regulators in multiple mammalian cell-based systems to alter the course of protein misfolding and aggregation and to restore cellular health.
- Jurivich, D., L. Sistonen, R. Kroes and R.I. Morimoto. Effects of Sodium Salicylate on the Human Heat Shock Response. Science 255, 1243-1245 (1992).
- Westerheide, S., J. Bosman, B. Mbadugha, T. Kawahara, G. Matsumoto, W. Gu, S. Kim, J. Devlin, R. Silverman, and R.I. Morimoto. Celastrols as Inducers of the Human Heat Shock Response and Cytoprotection J. Biol. Chem. 279: 56053-60 (2004). PMID: 15509580
- Westerheide, S., T. Kawahara, K. Orton, and R.I. Morimoto. Triptolide, an Inhibitor of the Human Heat Shock Response that Enhances Stress-Induced Cell Death. J. Biol. Chem. 281: 9616-9622 (2006). PMID: 16469748
- Calamini, B., C. Silva, F. Madoux, D. M. Hutt, S. Khanna, M. Chalfant, P. Hodder, B. Tait, D. Garza, W. Balch, and R.I. Morimoto. Small Molecule Proteostasis Regulators for Protein Conformational Disease. Nature Chemical Biology DOI. 10.1038 (2011). PMCID: PMC3262058
- Yu, A., Y. Shibata, B. Shah, B. Calamini, D. Lo, and R.I. Morimoto. Protein Aggregation Inhibits Clathrin-Mediated Endocytosis by Chaperone Competition. Proc. Natl. Acad. Sci. USA 111: E1481-1490. DOI: 10.1073/pnas.1321811111 (2014).
- Yu, A., S.G. Fox, A. Cavallini, C. Kerridge, M. J. O'Neill, J. Wolak, S. Bose, and R. I. Morimoto. Tau Protein Aggregates Inhibit the Protein-Folding and Vesicular Trafficking Arms of the Cellular Proteostasis Network. J. Biological Chemistry 294(19): 7917-7930 DOI:10.1074/jbc.RA119.007527 (2019).