BIOGRAPHICAL SKETCH

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NAME: Hu, Patrick J.

eRA COMMONS USER NAME (credential, e.g., agency login): PATJHU ORCID: 0000-0002-5611-8062

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	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	06/1985	Biology
Robert Schumann Conservatory, Düsseldorf, Ger.	none	05/1986	Piano Performance
NYU School of Medicine, New York, NY	M.D., Ph.D.	05/1995	Biochemistry
The Johns Hopkins Hospital, Baltimore, MD	Residency	06/1998	Internal Medicine
Dana-Farber/Mass General Brigham, Boston, MA	Fellowship	06/2001	Adult Oncology
Massachusetts General Hospital, Boston, MA	Postdoc	06/2005	Genetics

A. Personal Statement. My lab uses the nematode *Caenorhabditis elegans* to elucidate fundamental mechanisms that govern development and aging. For many years, our research has focused on how the DAF-2 insulin-like signaling pathway influences life span. The DAF-2 insulin-like growth factor receptor ortholog controls development, metabolism, and longevity through a conserved PI 3-kinase/Akt pathway that inhibits the FoxO transcription factor DAF-16. We have executed numerous forward genetic screens that have revealed multiple new DAF-16/FoxO regulators. Based on our work on the conserved endoplasmic reticulum (ER) translocon component TRAP-1/SSR1, a modifier of DAF-16/FoxO activity, I have recently changed the research direction of my lab. We are now engaged in elucidating the role of ER stress and homeostasis in physiology and aging.

We discovered that TRAP-1/SSR1 plays a conserved role in promoting the biogenesis of insulin and insulin-like peptides. However, mammalian SSR1 is ubiquitously expressed, indicating that it must have a biological function distinct from its role in insulin biogenesis in pancreatic beta cells. Building on the observation that animals and cells with reduced TRAP-1/SSR1 activity exhibit constitutive activation of the ER unfolded protein response (UPR - a conserved ER quality control program that promotes equilibrium in response to protein misfolding and lipid bilayer stress), we have conducted two forward genetic screens to gain insight into ER UPR function and regulation *in vivo.* These screens have identified several ER UPR modifiers that promise to unveil mechanistic insights into how ER stress and homeostasis impact physiology and aging.

We are pursuing two major lines of investigation that have emerged from these screens. The first pertains to how collagen mutations impact cellular and organismal responses to protein misfolding. We have identified mutations in the triple helix domain of the *col-75* collagen gene that induce the ER UPR cell non-autonomously, implying that these mutations generate a cell-autonomous response distinct from the ER UPR that signals to the intestine. This data is aligned with observations that multiple missense mutations in human collagen genes impair collagen biogenesis without activating the canonical ER UPR. We hypothesize that disruption of collagen biogenesis activates a conserved and previously uncharacterized protein quality control program, which we refer to as the “unfolded collagen response” (UCR), that promotes homeostasis in response to collagen misfolding. As collagens are the most abundantly expressed proteins in the human body, the UCR will establish a new paradigm of protein quality control that will illuminate the regulation of collagen biosynthesis in humans and the pathogenesis of congenital collagenopathies as well as common diseases in the elderly that are characterized by fibrosis of the heart, lungs, liver, kidneys, and other organs. We are actively engaged in defining and characterizing the molecular components of the UCR.

In a second line of inquiry, we are investigating the role of the conserved gene *dsc-4,* the *C. elegans* ortholog of the gene encoding human microsomal triglyceride transfer protein (MTTP), in promoting protein homeostasis. Human MTTP acts in the liver to promote the biosynthesis of very low density lipoprotein (VLDL), the secretion of which generates the major source of atherosclerosis-promoting low density lipoprotein (LDL) in the bloodstream. Analogously, *C. elegans* DSC-4 may catalyze the biosynthesis of yolk lipoproteins that are secreted from the intestine and taken up by oocytes to provision embryos. We have identified two mutations in *dsc-4* that cause ER UPR induction. We hypothesize that DSC-4-catalyzed yolk lipoprotein biogenesis acts as an ER homeostasis checkpoint that conveys information about maternal homeostasis to progeny. If correct, this hypothesis will establish a new epigenetic mechanism through which offspring are informed about inputs from a parent's life experience that are integrated into an ER homeostat. As the basic machinery catalyzing lipoprotein assembly is conserved between *C. elegans* and humans, the proposed research promises to create new avenues of investigation into how lipoproteins may encode information about homeostasis both systemically and intergenerationally in humans. This will ultimately lead to unanticipated insights into the pathogenesis of common illnesses influenced by lipoproteins such as fatty liver disease, heart disease, and Alzheimer's disease as well as mechanisms that govern the influence of maternal dyshomeostasis on fetal health.

The dearth of physicians focused on discovery research is threatening the future of the academic medical enterprise in this country. Over the past decade, I have been actively involved in promoting the interests of physician-scientist trainees as Director of the Physician-Scientist Training Program (PSTP) in the Department of Medicine at Vanderbilt University Medical Center and Director of the Office of Medical Student Research and Assistant Dean for Physician-Researcher Training at Vanderbilt University School of Medicine. I am very excited and fortunate to have the opportunity to take on a new challenge as the incoming Director of the Medical Scientist Training Program (MSTP) at the University of Colorado School of Medicine (CUSOM). My extensive background in overseeing research training in both undergraduate and graduate medical contexts has provided me with the experience and expertise needed to help CUSOM MSTP students maximize their chances of future success as physician-scientists and independent investigators. As an active laboratory scientist and MSTP Director, I am committed to scientific rigor, training, and mentoring, as well as to promoting inclusive, safe, and supportive scientific environments.

1. Alam, H., Williams, T., Dumas, K.J., Guo, C., Yoshina, S., Mitani, S., and **Hu, P.J.** 2010. EAK-7 controls development and life span by regulating nuclear DAF-16/FoxO activity. *Cell Metabolism* 12:30-41. PMC2907918
2. Chen, A. T.-Y., Guo, C., Dumas, K.J., Ashrafi, K., and **Hu, P.J.** 2013. Effects of *C. elegans sgk-1* mutations on life span, stress resistance, and DAF-16/FoxO regulation. *Aging Cell* 12:932-940. PMC3824081
3. Chen, A. T.-Y., Guo, C., Itani, O.A., Budaitis, B.G., Williams, T.W., Hopkins, C.E., McEachin, R.C., Pande, M., Grant, A.R., Yoshina, S., Mitani, S., and **Hu, P.J.** 2015. Longevity genes revealed by integrative analysis of isoform-specific *daf-16/FoxO* mutants of *Caenorhabditis elegans*. *Genetics* 201:613-629. PMC4596673
4. Li, X., Itani, O.A., Haataja, L., Dumas, K.J., Yang, J., Cha, J., Flibotte, S., Shih, H.-J., Delaney, C.E., Xu, J., Qi, L., Arvan, P., Liu, M., and **Hu, P.J.** 2019. Requirement for translocon-associated protein (TRAP) α in insulin biogenesis. *Science Advances* 5, eaax0292.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2025-present	Associate Professor, Department of Medicine, University of Colorado School of Medicine
2016-2025	Associate Professor, Departments of Medicine and Cell and Developmental Biology, Vanderbilt University School of Medicine
2014-2016	Associate Professor, Departments of Internal Medicine and Cell and Developmental Biology; Research Associate Professor, Institute of Gerontology, University of Michigan Medical School
2013-2014	Research Assistant Professor, Institute of Gerontology, University of Michigan Medical School
2005-2013	Research Assistant Professor, Life Sciences Institute, University of Michigan
2005-2014	Assistant Professor, Departments of Internal Medicine and Cell and Developmental Biology, University of Michigan Medical School
2001-2005	Assistant in Medicine, Mass General Hospital; Instructor in Medicine, Harvard Medical School

Other Experience and Professional Memberships

2025-present Director, Medical Scientist Training Program, University of Colorado School of Medicine
2025-present Associate Dean for Medical Education, University of Colorado School of Medicine
2022-2025 Assistant Dean for Physician-Researcher Training, Vanderbilt University School of Medicine
2022-2025 Director, Office of Medical Student Research, Vanderbilt University School of Medicine
2022-present Member, Board of Reviewing Editors, *eLife*
2022 Member, Cancer Stem Cell Consortium peer review committee, American Cancer Society
2018-2025 Member, Cancer Education Advisory Committee, Vanderbilt-Ingram Cancer Center
2017-2025 Director, Physician-Scientist Training Program, Department of Medicine, Vanderbilt University Medical Center
2017-2025 Member, Admissions Subcommittee, Vanderbilt Medical Scientist Training Program
2017-present Member, American Association for the Advancement of Science
2017-present Member, Genetics Society of America
2017-2018 Vice-Chair, Development, Differentiation, and Cancer peer review committee, American Cancer Society
2016-2022 Associate Editor, *Oncogene*
2016-present Member, Advisory Board, *Caenorhabditis* Genetics Center
2016-2025 Member, Beta cell Interest Group (BIG), Vanderbilt Diabetes Research and Training Center
2016-2025 Member, Vanderbilt Diabetes Research and Training Center
2016-2017 Associate Director, Physician-Scientist Training Program, Department of Medicine, Vanderbilt University Medical Center
2015-2016 Member, Center for Organogenesis, University of Michigan
2015 *ad hoc* member, R13 Special Emphasis Panel study section, NIDDK, NIH
2014-2020 Member, Development, Differentiation, and Cancer peer review committee, American Cancer Society
2013-2016 Member, Institute of Gerontology, University of Michigan
2012-present Editorial Board, *Frontiers in Genetics of Aging*
2012-2013 *ad hoc* member, Development, Differentiation, and Cancer peer review committee, American Cancer Society
2012 *ad hoc* member, Innovative Research Grant peer review committee, American Heart Association
2011-present Member, National Scientific Advisory Council, American Federation for Aging Research
2011-2016 Member, University of Michigan Institute of Gerontology Aging Training Program
2005-2016 Core Member, University of Michigan Comprehensive Cancer Center
Member, Michigan Diabetes Research Center
Member, Michigan Metabolomics and Obesity Center

Honors

2011 Innovative Research Grant, American Heart Association
2011 Member-elect, American Society for Clinical Investigation
2010 Research Scholar Grant, American Cancer Society
2008 Kimmel Scholar, Sidney Kimmel Foundation for Cancer Research
2005 Biological Sciences Scholar, University of Michigan
2002 NIDDK K08 Mentored Clinical Scientist Development Award (DK062884)
1999 Howard Hughes Medical Institute Postdoctoral Research Fellowship for Physicians
1994 Alpha Omega Alpha Honor Medical Society, New York University School of Medicine

C. Contributions to Science

1. <u>*Developing innovative genetic screens to reveal the mechanistic basis for developmental plasticity*</u>: In *C. elegans,* the conserved DAF-2 insulin-like signaling (ILS) pathway controls developmental plasticity by promoting reproductive development in low stress conditions. In the presence of population stress, a constitutively elaborated complex mixture of lipophilic molecules known as ascarosides and collectively

referred to as “pheromone” induces larvae to enter an alternative developmental pathway that culminates in a state of diapause known as dauer arrest. While it has been known for some time that pheromone induces dauer arrest by inhibiting DAF-2 ILS, how it does so is poorly understood. As insulin and insulin-like growth factor signaling pathways in humans are influenced by environmental stress and dysregulated in common diseases such as diabetes and cancer, understanding how stress impacts these pathways will lead to new approaches to prevent and treat common human diseases.

We have discovered several new regulators of *C. elegans* DAF-2 ILS and developmental plasticity through innovative genetic screens. We identified a new conserved pathway, the EAK pathway, which acts in parallel to canonical PI3K/Akt signaling to inhibit dauer arrest. We have also uncovered unexpected roles for dosage compensation, the conserved histone H4 lysine 20 methyltransferase SET-4, and the conserved ER membrane protein TRAP-1 in the control of developmental plasticity.

a. Alam, H., Williams, T., Dumas, K.J., Guo, C., Yoshina, S., Mitani, S., and **Hu, P.J.** 2010. EAK-7 controls development and life span by regulating nuclear DAF-16/FoxO activity. *Cell Metab* 12:30-41. PMC2907918
b. Dumas, K.J., Delaney, C.E., Flibotte, S., Moerman, D.G., Csankovszki, G., and **Hu, P.J.** 2013. Unexpected role for dosage compensation in dauer arrest, insulin-like signaling, and FoxO transcription factor regulation in *Caenorhabditis elegans*. *Genetics* 194:619-629. PMC3697968
c. Delaney, C.E., Chen, A.T., Graniel, J.V., Dumas, K.J., and **Hu, P.J.** 2017. A histone H4K20 methyltransferase couples environmental cues to sensory neuron control of developmental plasticity. *Development* 144:1273-1282.
d. Li, X., Itani, O.A., Haataja, L., Dumas, K.J., Yang, J., Cha, J., Flibotte, S., Shih, H.-J., Delaney, C.E., Xu, J., Qi, L., Arvan, P., Liu, M., and **Hu, P.J.** 2019. Requirement for translocon-associated protein (TRAP) α in insulin biogenesis. *Science Advances* 5, eaax0292. PMC6892615

2. <u>*Expanding the landscape of proteins that influence ER homeostasis*</u>: Although TRAPα/SSR1 was first discovered more than 30 years ago as a protein that binds to the nascent signal peptide of preprolactin, its biological function has remained obscure. In an unbiased forward genetic screen for new DAF-16/FoxO regulators, we isolated a null mutation in *trap-1,* the *C. elegans* ortholog of TRAPα/SSR1. Our work indicates that TRAP-1 and mammalian TRAPα/SSR1 have conserved roles not only in the biogenesis of insulin but also in the maintenance of ER homeostasis. This discovery underscores the important role of the translocon in choreographing cotranslational protein folding in the ER and has engendered a change in the scientific direction of my laboratory.

   a. Li, X., Itani, O.A., Haataja, L., Dumas, K.J., Yang, J., Cha, J., Flibotte, S., Shih, H.-J., Delaney, C.E., Xu, J., Qi, L., Arvan, P., Liu, M., and **Hu, P.J.** 2019. Requirement for translocon-associated protein (TRAP) α in insulin biogenesis. *Science Advances* 5, eaax0292. PMC6892615

3. <u>*Accelerating forward genetics through up-front whole genome sequencing (WGS)*</u>: We pioneered the approach of up-front sequencing of mutant genomes immediately after mutant isolation, prior to mapping or outcrossing. This has revolutionized forward genetics in *C. elegans* and other organisms. By defining the full complement of mutagen-induced variants present in every isolated mutant, up-front WGS facilitates the identification of causal mutations in many strains prior to genetic mapping and permits the prioritization and deprioritization of specific mutant strains for detailed analysis. By obviating mapping in many isolated mutants, up-front WGS enables screens in complex genetic backgrounds. Moreover, up-front WGS permits the identification and characterization of causal complex genomic rearrangements that may not be stably transmitted to progeny. While forward genetics has always been a powerful tool for researchers, the “sequence first” approach has transformed it such that the efficiency of genetic screens is now commensurate with their value.

   a. Dumas, K.J., Delaney, C.E., Flibotte, S., Moerman, D.G., Csankovszki, G., and **Hu, P.J.** 2013. Unexpected role for dosage compensation in dauer arrest, insulin-like signaling, and FoxO transcription factor regulation in *Caenorhabditis elegans*. *Genetics* 194:619-629. PMC3697968
   b. **Hu, P.J.** Whole genome sequencing and the transformation of *C. elegans* forward genetics. 2014. *Methods* 68:437-440.

c. Itani, O.A., Flibotte, S., Dumas, K.J., Moerman, D.G., and **Hu, P.J**. 2016. Chromoanasynthetic genomic rearrangement identified in a *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis screen in *Caenorhabditis elegans. G3: Genes, Genomes, Genetics* 6:351-356. PMC4751554
d. Itani, O.A., Flibotte, S., Dumas, K.J., Guo, C., Blumenthal, T., and **Hu, P.J.** 2016. *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis reveals an intronic residue critical for *Caenorhabditis elegans* 3' splice site function *in vivo*. *G3: Genes, Genomes, Genetics* 6:1751-1756. PMC4889670

4. *Elucidating new mechanisms of life span extension*: Although the role of FoxO transcription factors in extending life span was discovered nearly 25 years ago, how FoxO transcription factors extend life span remains obscure. In *C. elegans,* most DAF-16/FoxO target genes have not been interrogated for functions in life span control. This is largely due to the significant logistical hurdle of performing life span assays after either mutational or RNAi-based inactivation of each of thousands of DAF-16/FoxO target genes.

We have devised a strategy to prioritize tractable subsets of DAF-16/FoxO target genes for detailed phenotypic analysis. By combining whole transcriptome profiling with life span assays of several long-lived strains in the context of wild-type and mutant DAF-16/FoxO proteins, we have identified 138 DAF-16/FoxO target genes, the DAF-16/FoxO-dependent regulation of which is correlated with longevity. Our initial functional studies on these genes have revealed ten DAF-16/FoxO target genes that significantly influence life span, several of which had not previously been implicated in DAF-16/FoxO-dependent longevity. One of these genes, *cest-1.1,* encodes a conserved carboxylesterase that is required for the biosynthesis of two novel nucleoside-like ascarosides termed uglas#1 and uglas#11. This investigation into the function of CEST-1.1 and uglas compounds has the potential to establish roles for an unprecedented class of modular metabolites in life span control. In light of the association of common genetic variants in human *FoxO* genes with extreme longevity, mechanistic insights into how conserved DAF-16/FoxO target genes such as *cest-1.1* promote longevity will lead to new strategies to improve human health by harnessing the longevity-promoting effects of FoxO transcription factors and new classes of small molecules such as uglas#1 and uglas#11.

a. Chen, A. T.-Y., Guo, C., Itani, O.A., Budaitis, B.G., Williams, T.W., Hopkins, C.E., McEachin, R.C., Pande, M., Grant, A.R., Yoshina, S., Mitani, S., and **Hu, P.J.** 2015. Longevity genes revealed by integrative analysis of isoform-specific *daf-16/FoxO* mutants of *Caenorhabditis elegans*. *Genetics* 201:613-629. PMC4596673
b. Le, H.H., Wrobel, C.J.J., Cohen, S.M., Yu, J., Park, H., Kruempel, J.C., Helf, M.J., Curtis, B.J., Rodrigues, P.R., **Hu, P.J.,** Sternberg, P.W., and Schroeder, F.C. 2020. Modular metabolite assembly in *C. elegans* depends on carboxylesterases and formation of lysosome-related organelles. *eLife* 9:e61886

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/patrick.hu.1/bibliography/public/