BIOGRAPHICAL SKETCH

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NAME: Lithgow, Gordon J.

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

POSITION TITLE: Professor and Chief Academic Officer

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
University of Strathclyde, Glasgow, Scotland	B.Sc. Honours	06/1985	Applied Microbiology
University of Glasgow, Scotland	Ph.D.	06/1985-05/1989	Genetics
Post-doctoral Research Fellowship, Ciba Giegy AG, Biotechnology Unit, Basel, Switzerland (Mentor: Albert Hinnen)		1989-1991	Yeast Genetics and Biochemistry
Post-doctoral Research Fellowship, Institute for Behavoral Genetics, University of Colorado at Boulder (Mentor: Thomas E. Johnson)		1991-1996	*C. elegans* aging

A. Personal Statement

I have the experience, leadership, training, expertise, and motivation necessary to successfully lead the proposed research project. I am very experienced in leading an interdisciplinary team such as the one proposed here. From 2007 to 2013, I was the Principal Investigator of the Interdiciplinary Research Consortium on Geroscience, which was an eleven-component project with a $28 million budget over five years. Prior to that, I was the co-director of aging research in the UK (the SAGE initiative). I am an expert in the molecular biology of aging and a leader in the sub-field of pharmacological extension of lifespan in model organisms. My laboratory utilizes molecular genetics and biochemistry to define aging processes and through extensive collaborations, we apply a range of leading edge technologies including proteomics and metabolomics as described in this application. Whilst historically we focused on lifespan extension as a measure of aging rate, we have now moved significantly toward attempting to understand what causes age-related pathology and chronic disease. I am particularly interested in discovering molecular and biochemical aspects of normal aging that could explain why aging is a prominent risk factor for diseases such as Alzheimer's. This has led to deeper collaborations with labs such as Dr. Julie Andersen's on the role of aging in neurodegeneration focused on proteostasis, including autophagy. Since 2013, the Lithgow lab has been one of three nodes for the *Caenorhabditis* Intervention Testing Program (CITP). This consortium has established a rigorous platform for the testing how chemical compounds affect lifespan and healthspan. This is important for this proposal as the use of chemical interventions is subject to the protocols established for the CITP. I have 13 publications co-authored with the other PIs in this proposal.

B. Positions and Honors

1989-1991 Post-doctoral Research Fellowship; yeast cell biology, Ciba Giegy AG, Biotechnology Unit, Basel, Switzerland.

1991-1995 Post-doctoral Research Fellowship; *C. elegans* aging, Institute for Behavioral Genetics, University of Colorado, Boulder, Colorado.

1995-2001 Lecturer in Molecular Gerontology, School of Biological Sciences, University of Manchester, Manchester, England.

1999-2001	Senior Lecturer in Molecular Gerontology, School of Biological Sciences, University of Manchester, England.
2001-2009	Associate Professor, Buck Institute for Age Research, Novato, California, USA.
2007-2013	Principle Investigator, Interdisciplinary Research Consortium in Geroscience, Buck Institute for Research on Aging
2008-present	Center Coordinator of the Larry L. Hillblom Center for Integrative Studies of Aging, Buck Institute for Research on Aging
2009-present	Professor, Buck Institute for Research on Aging, Novato, California, USA
2013-2014	Director of Interdisciplinary Research, Buck Institute
2014-present	Chief Academic Officer, the Buck Institute
1997	The Hans Selye Award, Budapest, Hungary
2001	The Ewald W. Busse Research Award in Biomedical Sciences, Gerontological Society of America
2001	The Bennett J. Cohen Memorial Lecture, University of Michigan, Ann Arbor
2002	Nathan W. Shock Memorial Lecture, National Institute on Aging (NIA)
2004	Chair, Biology of Aging, Gordon Research Conference
2013	The 2013 Tenovus Medal Lecturer for Outstanding Research in Biomedicine. University of Glasgow, Scotland.
2019	Denham Harman Research Award. Given by the American Aging Association to researchers who have made significant contributions to biomedical aging research.

Other Experience and Professional Memberships, selected

1997	Organizer, BBSRC Workshop on the Science of Ageing, Warwick, England
1999	Organizer, First European Molecular Biology Organization (EMBO) Workshop on Cellular and Molecular Ageing, Switzerland
2000	Coordinator, BBSRC Network on Science of Ageing SAGE
2000	BBSRC Genomes in Animal Function (GAIN) Panel
2000	Cambridge University Government Policy Forum Program
2000-present	Associate Editor, *Biogerontology*
2001-2005	Editorial Board, *Aging Cell*
2002-2006	NIA B Special Studies Study Section, Biological Aging Review Committee, permanent member
2004	Chair, Access Committee, Aging Interventional Testing Program (NIA)
2004	Ad Hoc Reviewer, Cellular Mechanisms in Aging and Development (CMAD)
2005	Section Editor, Aging Cell
2006-2011	Board of Scientific Counselors, National Institute on Aging
2006-2007	Biological Sciences Section Program Committee, the Gerontological Society of America
2007-2011	Editorial Board, *Gerontology*
2010	The Gerontological Society of America, Biological Sciences Section, Chair
2012-2014	Founding Editor, *Longevity and Healthspan*

C. Contribution to Science

My early publications in aging research established a relationship between long-lived genetic variants and the resistance to multiple forms of environmental stress, even in young animals. This resulted in a number of investigators establishing an association between stress resistance and longevity across a wide range of aging interventions. We have exploited this relationship in a number of ways, including uncovering stress response factors that determine aging, identifying the role of a DNA damage checkpoint signaling pathway in longevity, and identifying an age-related molecular pathology and protein insolubility to link longevity to age-related diseases.

1. Lithgow GJ, White TM, Melov S, Johnson TE. (1995). Thermotolerance and extended life-span conferred by single-gene mutations and induced by thermal stress. **PNAS** 1;92(16):7540-4. PMCID: PMC41375
2. Walker GA and Lithgow GJ (2003) Lifespan extension in *C. elegans* by a molecular chaperone dependent upon insulin-like signals. **Aging Cell.** 2(2):131-9.
3. Olsen A, Vantipalli MC and Lithgow GJ (2006). Checkpoint Proteins Regulate Survival of the Post-Mitotic Adult Soma in *Caenorhabditis elegans.* **Science** 312(5778): 1381-85. PMCID: PMC2568993
4. McColl G, Rogers AN, Alavez S, Hubbard AE, Melov S, Link CD, Bush AI, Kapahi P and Lithgow GJ (2010). Insulin-like Signaling Determines Survival during Stress via Post Transcriptional Mechanisms in *C. elegans*. **Cell Metabolism***,* 12(3):260-72. PMCID: PMC2945254.

My lab has also contributed to the evolutionary biology of aging by demonstrating that lifespan-determining genes are consistent with antagonistic pleotropy in laboratory conditions. Through laboratory-based natural selection experiments, we showed that long-lived alleles of genes in the insulin signalling pathway have significant fitness defects compared to wild-type alleles.

1. Lithgow GJ and Kirkwood TBL (1996) Mechanisms and evolution of aging. **Science**. 5; 273:80.
2. Jenkins, NL, M^{c}Coll, G, Walker, DW, Harris J, and Lithgow, GJ (2000). The Evolution of *C. elegans* Lifespan. **Nature**, 405(6784): 296-7.
3. Jenkins NL[1], McColl G, Lithgow GJ. **Proc Biol Sci.** (2004) Fitness cost of extended lifespan in *Caenorhabditis elegans* 271:2523-6.
4. Lithgow GJ and Gill MS (2003) Physiology: Cost-free longevity in mice? **Nature.** 421(6919): 125-6.

We have made a major contribution to the sub-field of pharmacological manipulation of lifespan, which is relevant to the current application. We published the first account of pharmacological lifespan extension in an animal in a high profile journal, which prompted a pursuit to find lifespan-extending compounds in scores of labs for the last 17 years. We have recently focused on compounds that promote protein homeostasis and metal homeostasis. We have also identified new pathways that modulate aging through this chemical biology approach.

1. Melov S, Ravenscroft J, Malik S, Gill MS, Walker D, Clayton P, Wallace D, Malfroy B, Doctrow S and Lithgow GJ (2000). Extension of lifespan with superoxide dismutase/catalase mimetics. **Science**. 289(5484):1567-9.
2. Alavez S, Vantipalli MC Zucker, DJS, Klang I, Lithgow GJ (2011). Amyloid-binding compounds maintain protein homeostasis during ageing and extend lifespan. **Nature** 472(7342): 2326-9. PMCID: PMC3610427
3. Lucanic M, Held, JM, Vantipalli MC, Klang IM, Graham JB, Gibson BW, Lithgow GJ, Gill MS (2011). N-acylethanolamine signaling mediates the effect of diet on lifespan in *C. elegans*. **Nature**. 473(7346) :226-9. PMCID: PMC3093655.
4. Lucanic M, Plummer WT, Chen E, Harke J, Foulger AC, Onken B, Coleman-Hulbert AL, Dumas KJ, Guo S, Johnson E, Bhaumik D, Xue J, Crist AB, Presley MP, Harinath G, Sedore CA, Chamoli M, Kamat S, Chen MK, Angeli S, Chang C, Willis JH, Edgar D, Royal MA, Chao EA, Patel S, Garrett T,

Ibanez-Ventoso C, Hope J, Kish JL, Guo M, Lithgow GJ, Driscoll M, Phillips PC. Impact of genetic background and experimental reproducibility on identifying chemical compounds with robust longevity effects. **Nat Commun**. 8:14256 (2017).

Most directly relevant to this application is a series of discoveries indicating that a wide range of protein becomes insoluble during normal aging in *C. elegans*. These proteins are of diverse function and predicted tissue expression, but they are enriched for proteins that determine lifespan. These proteins are collectively called the insolublome. We have demonstrated that the formation of the insolublome during aging can be accelerated (by iron feeding) or slowed (by vitamin D feeding).

1. Reis-Rodrigues P, Czerwieniec G, Peters TW, Evani US, Alavez S, Gaman EA, Vantipalli M, Mooney SD, Gibson BW, Lithgow GJ, Hughes RE (2012). Proteomic analysis of age-dependent changes in protein solubility identifies genes that modulate lifespan. **Aging Cell** 11:120-7. PMCID: PMC3437485.
2. Klang IM, Schilling B, Sorensen DJ, Sahu AK, Kapahi P, Andersen JK, Swoboda P, Killilea DW, Gibson BW, Lithgow GJ. (2014) Iron promotes protein insolubility and aging in *C. elegans*. **Aging** 6:975-91. PMCID: PMC4276790.
3. Mark KA, Dumas KJ, Bhaumik D, Schilling B, Davis S, Oron TR, Sorensen DJ, Lucanic M, Brem RB, Melov S, Ramanathan A, Gibson BW, Lithgow GJ (2016). Vitamin D Promotes Protein Homeostasis and Longevity via the Stress Response Pathway Genes *skn-1, ire-1*, and *xbp-1*. **Cell Reports.** 17:1227-1237. PMID: 27783938.

We have also published a series of studies on the role of metals in aging, microRNAs in aging, the nuclear hormone receptor DAF-12 and other topics. The role of DAF-12 in autophagy and neurological disease is currently a focus of our collaboration with the Andersen lab.

1. Lucanic M, Graham J, Scott G, Bhaumik D, Benz CC, Hubbard A, Lithgow GJ, Melov S. (2013) Age-related micro-RNA abundance in individual *C. elegans*. **Aging** 5(6):394-411. PMCID: PMC3824409
2. Fisher AL and Lithgow GJ (2005) The Nuclear hormone receptor DAF-12 has opposing effects on *Caenorhabditis elegans* lifespan and regulates genes repressed in multiple long-lived worms. **Aging Cell** 5(2):127-38.
3. Held JM, White MP, Fisher AL, Gibson BW, Lithgow GJ, Gill MS (2006). DAF-12 dependent rescue of dauer formation in *Caenorhabditis elegans* by (25S) cholestenoic acid. **Aging Cell:** 2006 5(4):283-91.

http://www.ncbi.nlm.nih.gov/sites/myncbi/gordon.lithgow.1/bibliography/40530030/public/?sort=date&direction=descending.

D. Research Support

ONGOING RESEARCH SUPPORT

R01 AG029631 (Lithgow) 05/1/14 − 04/30/19
NIH/NIA
Pharmacology of Lifespan Extension
Identify the mechanism of lifespan extension with focus on vitamin D – shown to maintain protein homeostasis and extend lifespan in C.elegans. This will uncover novel mechanisms for interventions in aging and age related disease.

R03AG056938 (Brem) 07/1/17 – 06/30/19
NIH/NIA
Screening potassium and phosphate binder drugs for lifespan and healthspan effects in invertebrates
This project aims are: 1) Testing phosphate and potassium binders for longevity effects in yeast. 2) Testing phosphate and potassium binders for pro-lifespan, pro-healthspan effects in the nematode *C. elegans*.
Role: Co-Investigator

U01 AG045844 (Lithgow) 08/15/13 - 03/31/22
NIH/NIA
Caenorhabditis Intervention Testing Program – Buck Institute Compound Testing
The aims of this project are to: 1) to uncover compounds with robust effects on lifespan, 2) to discover compounds with reproducible effects on lifespan.

U01 AG045844 -06S1 (Lithgow) 08/15/13 - 03/31/22
NIH/NIA
Supplement to Caenorhabditis Intervention Testing Program – Buck Institute Compound Testing
The aims of this project are to: 1) to uncover compounds with robust effects on lifespan, 2) to discover compounds with reproducible effects on lifespan.

RF1AG057358-01 (MPI: Lithgow, Andersen) 09/15/17 - 06/30/22
NIA/NIH
A temporal bioenergetic, metabolomics, and proteomic map of Alzheimer's disease in invertebrate models
This project proposes a new deeper understanding of AD by undertaking a holistic systems biology-based approach to examine overall cellular functions and, in doing so, discover new therapeutic approaches for the disease.

COMPLETED RESEARCH SUPPORT

R21 AG048528 (Lithgow) 7/1/14 − 6/30/16
NIH/NIA
Vitamin D metabolism and lifespan determination
There is considerable debate about how much vitamin D supplements we should all be taking with some experts believing just about everyone over 65 is vitamin D deficient. If this is true, then it is a major public health issue because low vitamin D levels are associated with everything from cancer to Alzheimer's and Parkinson's disease.

U01 AG045844 (Lithgow) 8/15/13 − 5/31/16
NIH/NIA
The *Caenorhabditis* Intervention Testing Program
This consortium award addresses the issue of reproducibility of aging interventions between labs but also addresses the issue of robustness across series of highly variable genetic backgrounds.

U01 AG045844-03S1 (Lithgow) 08/01/15-5/31/17
NIH/NIA **supplement**
Caenorhabditis Intervention Testing Program – Buck Institute Compound Testing
The aims of this project are to: 1) to uncover compounds with robust effects on lifespan, 2) to discover compounds with reproducible effects on lifespan.