BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Follow this format for each person.

NAME John David Symons	POSITION TITLE Professor, College of Health: Nutrition and Integrative Physiology; Department of Internal Medicine: Division of Endocrinology Metabolism, and Diabetes; Investigator: Molecular Medicine Program, University of Utah
eRA COMMONS USER NAME DSYMONS	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of British Columbia, Vancouver, BC, CA	B.P.E.	1980	Physical Education
University of Oregon, Eugene, OR, USA	M.S.	1982	Stress Physiology
University of Oregon, Eugene, OR, USA	Ph.D.	1984	Physiology

A. Personal Statement. I use endothelial cells, blood vessels, and anesthetized and conscious animal models to elucidate mechanisms responsible for vascular complications associated with obesity, insulin resistance, and diabetes. A new limb of research is interrogating the contribution from endothelial cell autophagy to vascular complications that occur in the process of healthy aging. This is relevant because the population worldwide is aging, aging-related cardiovascular complications are the primary cause of death in individuals ≥ 65 y old, and patient-management costs to the healthcare system are enormous and unsustainable. Current support for this work is provided by grants from the NIH NIA (RO3) and AHA (Grant-In-Aid). The process of autophagy is repressed in many cell types in the context of aging, and might play a role in neurodegenerative diseases such as Alzheimers and Parkinsons. One study reports that autophagy is repressed in primary endothelial cells from aged vs. adult humans, and might play a role in compromised arterial function that is associated with the process of aging. In 2014 we sought to determine whether genetic repression of autophagy *per se* influences the ability of endothelial cells to generate nitric oxide. We were the first to report that shear-stress induced nitric oxide generation is prevented when vascular autophagy is genetically compromised. A second manuscript currently in revision describes a novel mechanism that is responsible for this observation. Specifically, endothelial cells with compromised autophagy display impaired glycolysis, ATP production, and subsequent purinergic signaling to endothelial nitric oxide synthase (eNOS), the enzyme responsible for nitric oxide generation. Importantly, in older (24 month) vs. adult (5-month) mice that display compromised vascular autophagy, we show suppressed upregulation / initiation of vascular autophagy and eNOS activation in response to 60-min of treadmill-running (i.e., a physiological approach to increase vascular shear stress). Of note, nodes of dysfunction that exist in cells with genetic repression of autophagy, are recapitulated in primary endothelial cells from old vs adult mice, and primary endothelial cells from mice with inducible deletion of autophagy specifically in endothelial cells. It now is time to test the hypothesis that compromised endothelial cell autophagy in the context of aging, impairs physiological initiation of autophagy in primary arterial endothelial cells of older vs. adult humans, to an extent that impairs eNOS activation and subsequent arterial vasodilation. Thus, my new direction is a shift from basic research using cells, vessels, and animals, to clinical research using primary arterial endothelial cells from adult and older males and females. My new collaboration is with Dr. Joel Trinity from the Utah Vascular Research Laboratory (UVRL), who has developed a rhythmic handgrip model wherein brachial artery and radial artery shear-rate can be elevated similarly in adult and old subjects. Drs Ash Nelson and David Morgan, both Physician-Scientists associated with the UVRL and consultants on this project, will obtain primary endothelial cells from the radial artery before and after the exercise intervention, in adult and old patients. Results from this study will determine whether our findings from cells, vessels, and mice with genetic repression of autophagy can be translated to primary endothelial cells obtained from, and arterial function observed in, humans. Data obtained from these studies will lay important groundwork for Aims embedded in upcoming grant applications to address a “human component,” together with basic science-related Aims. Demonstrated experience with using these procedures will increase our competitiveness for extramural funding.

B. Positions and Honors

Research and/or Professional Experience

1985-1987	Natural Sciences and Engineering Research Council of Canada Visiting Fellowship; Defense and Civil Institute of Environmental Medicine, Environmental Physiology Section, Downsview, ON, Canada
1987-1990	Postdoctoral Fellowship; University of California-Davis, Department of Internal Medicine, Division of Cardiovascular Medicine, Davis, CA, USA.
1990-1994	Assistant Research Physiologist; University of California-Davis, Department of Internal Medicine, Division of Cardiovascular Medicine.
1994-1995	Visiting Senior Research Scientist, Cardiovascular Pharmacology, Alliance Pharmaceutical Corporation, San Diego, CA.
1995-2001	Assistant Adjunct Professor (non-tenure track); University of California-Davis, Department of Internal

Medicine, Division of Cardiovascular Medicine
2001-2005 Assistant Professor, University of Utah, College of Health, Salt Lake City, UT.
2005-2013 Associate Professor, University of Utah, College of Health, Salt Lake City, UT.
2006 - Adjunct Appointment, University of Utah, Department of Nutrition, Salt Lake City, UT.
2007 - Adjunct Appointment, University of Utah, Dept of Internal Medicine, Div of Endocrinology, Metabolism, and Diabetes, Salt Lake City, UT.
2013 - Professor, University of Utah, College of Health, Salt Lake City, UT.
2014 - Investigator, University of Utah Molecular Medicine Program

Journal reviewer Journals of the American Physiological Society (APS), American Heart Association (AHA), American College of Sports Medicine (ACSM); American College of Cardiology (ACC), American Diabetes Association (ADA), Diabetologia, Journal of Molecular and Cellular Cardiology, European Journal of Applied Physiology, British Journal of Pharmacology, Cardiovascular Research, Scientific Reports, Obesity, American Journal of Clinical Nutrition, Journal of Physiology, Life Sciences, Experimental Physiology, Chinese Journal of Physiology, Journal of Cardiovascular Medicine, Endocrinology, Cell Death and Disease, Prostaglandins and other Lipid Mediators, Cell Death and Discovery, Cardiovascular Diabetologia, Heart and Vessels, Journal of Vascular Research.

Grant reviewer AHA WSA; External reviewer-Medical Research Council of Canada; Alberta Heart and Stroke Foundation; Veterans Affairs Merit Review-External Grant Examiner; Alcoholic Beverage Medical Research Foundation; UU UROP, UU VP for Research; UU Research Committee; UU COH Research Committee; UU Center on Aging.

Honors

1985-1987 Visiting Fellowship, Natural Sciences and Engineering Research Council of Canada
1989 American Heart Association Young Investigator Travel Award
1993 Elected Fellow, American College of Sports Medicine
1993, 1998 Recognition by the University of California for outstanding commitment and participation in mentorships for undergraduate researchers in Agriculture, Letters, and Science Program
1991-2000 Academic Federation Research Travel Award
1999 Clinical Nutrition Research Unit New Investigator Award
2000 American College of Sports Medicine Visiting Scholar Award
2000 American Physiological Society Research Career Enhancement Award
2000 Scientist Development Award, American Heart Association, National Affiliate, Scientist Development Award
2006 Elected Fellow, Cardiovascular Section, American Physiological Society
2010 Finalist, University Professor Award
2011 University of Utah, College of Health, Outstanding Researcher Award
2013 Editorial Board, American Journal of Physiology; Endocrinology and Metabolism
2013 University of Utah, College of Health, Distinguished Mentor Award

Service

Laboratory host: UU Undergraduate research opportunities program (UROP), APS and AHA Summer Research Fellowship Programs, Biology UROP, Honors College, LEAP Program; UU Medical Student Research Program, Native American Research Internship Program. Moderator / organizer – multiple times for UU Undergraduate research conference (URC), UCUR, AHA Summer Research Roundtable meeting; Mentor for APS Minority Travel Award Program; Minority Undergraduate Internship Program (American Diabetes Association).

University: UU Research Committee; UU IACUC; UU SOM Awards Committee College/Departmental: COH Research Committee; Faculty search committees (ESS and NUTR); Chair search committee (ESS); RPT Committee (2-time chair ESS) and NUTR; Nutrition Department Chair Search Committee; Student award committee; Organized outside seminar speakers to COH, ESS, Nutrition; ESS Curriculum streamlining committee; ESS Graduate student selection committee; Chair, COH College Council; Chair, Nutrition and Integrated Physiology RPT Committee, COH Realignment Committee; Graduate Curriculum Committee; Deans Advisory Committee. National: APS Cardiovascular Section Fellowship Committee.

C. Contributions to Science

1. *Postdoctoral Fellowship.* I developed/refined a minipig model to study mechanisms responsible for coronary collateral growth and development. Swine were instrumented to evaluate regional and global myocardial function and to quantify regional blood flow at rest and during dynamic exercise. We reported that : (i) myocardial ischemia is not requisite to precipitate collateral development; (ii) flow-induced shear stress was an important requirement for collateral development; (iii) collateral vessels that do grow and develop are adequate to maintain function at rest but are inadequate to do so during the stress of dynamic exercise.

•**Symons JD**, Pitsillides KF, Longhurst JC. Chronic reduction of myocardial ischemia does not attenuate coronary collateral development in miniswine. *Circulation*. 1992 86 (2) : 660-71. PMID: 1638730

•**Symons JD**, Firoozmand E, Longhurst JC. Repeated dipyridamole administration enhances collateral-dependent flow and regional function during exercise: a role for adenosine. *Circ Res*. 1993 73 (3) : 503-13. PMID: 8348693

•**Symons JD**, Longhurst JC, Stebbins CL. Response of collateral-dependent myocardium to vasopressin release during prolonged intense exercise. *Am J Physiol*. 1993 264 : H1644-52. PMID: 7684576

•**Symons JD**, Rendig SV, Fu LW, Longhurst JC. Endothelin-1 limits increases in blood flow to native and collateral-dependent myocardium. *Am J Physiol*. 1997 273 : R41-8. PMID: 9249531

2. *Very early independence.* Myocardial ischemia and reperfusion impair coronary vascular function. Exercise training improves coronary vascular function. I developed a rodent model to determine whether prior exercise training is protective concerning subsequent myocardial ischemia. We reported that : (i) while exercise-training is protective in this regard; (ii) high-intensity interval training is even more efficacious; and that (iii) the Na-H exchanger contributes importantly to ischemia-induced coronary vascular dysfunction.

•**Symons JD**, Rendig SV, Stebbins CL, Longhurst JC. Microvascular and myocardial contractile responses to ischemia: influence of exercise training*. J Appl Physiol*. 2000 88 (2) : 433-42. PMID:10658008

•**Symons JD**, Hayashi Y, Ensunsa JL. Improved coronary vascular function evoked by high-intensity treadmill training is maintained in arteries exposed to ischemia and reperfusion. *J Appl Physiol.* 2003 95 (4) : 1638-47. PMID:12819213

•**Symons JD**, Correa SD, Schaefer S. Na-H exchange inhibition with cariporide limits functional impairment caused by repetitive ischemia*. J Cardiovasc Pharmacol*. 1998 32 (6) : 853-62. PMID: 9869490

•**Symons JD**, Schaefer S. Na(+)/H(+) exchange subtype 1 inhibition reduces endothelial dysfunction in vessels from stunned myocardium. *Am J Physiol Heart Circ Physiol*. 2001 281 (4) : H1575-82. PMID:11557546

3. *Early independence.* Hyperhomocysteinemia was hypothesized to be a cardiovascular disease risk factor, but its impact on vascular function was unknown. I developed several rodent models to show that endogenously produced pathophysiological concentrations of homocysteine are sufficient to: (i) impair endothelial function in resistance and conductance sized arteries, (ii) increase vascular permeability, and (iii) evoke arterial stiffening.

•**Symons JD**, Mullick AE, Ensunsa JL, Ma AA, Rutledge JC. Hyperhomocysteinemia evoked by folate depletion: effects on coronary and carotid arterial function. *Arterioscler Thromb Vasc Biol*. 2002 22 (5) : 772-80. PMID:12006389

•Mullick AE, Zaid UB, Athanassious CN, Lentz SR, Rutledge JC, **Symons JD**. Hyperhomocysteinemia increases arterial permeability and stiffness in mice. *Am J Physiol Regul Integr Comp Physiol*. 2006 291 (5) : R1349-54. PMID:16793933

•**Symons JD**, Rutledge JC, Simonsen U, Pattathu RA. Vascular dysfunction produced by hyperhomocysteinemia is more severe in the presence of low folate. *Am J Physiol Heart Circ Physiol*. 2006 290 (1) : H181-91. PMID:16143648

•**Symons JD**, Zaid UB, Athanassious CN, Mullick AE, Lentz SR, Rutledge JC. Influence of folate on arterial permeability and stiffness in the absence or presence of hyperhomocysteinemia. *Arterioscler Thromb Vasc Biol*. 2006 26 (4) : 814-8. PMID:16424349

4. *Independence (lipotoxicity focus).* Obesity and T2DM precipitate endothelial dysfunction but precise mechanisms are unclear. I have used cell systems, isolated vessels, and intact animals with / without genetic manipulation to show that endothelial dysfunction and hypertension that exist in the context of diet-induced obesity is secondary to : (i) elevated free fatty acids (FFAs) in general; and (ii) the FFA metabolite ceramide in particular. Further, we have shown that (iii) ceramide disrupts interactions among Akt-Hsp90-eNOS by activating protein phosphatase 2A (PP2A) in a manner that can be prevented in vivo by using a novel small molecule PP2A inhibitor.

•**Symons JD**, McMillin SL, Riehle C, Tanner J, Palionyte M, Hillas E, Jones D, Cooksey RC, Birnbaum MJ, McClain DA, Zhang QJ, Gale D, Wilson LJ, Abel ED. Contribution of insulin and Akt1 signaling to endothelial nitric oxide synthase in the regulation of endothelial function and blood pressure. *Circ Res*. 2009 104 (9) : 1085-94. PMID 19342603 PMCID: PMC2936913

•Zhang QJ, Holland WL, Wilson L, Tanner JM, Kearns D, Cahoon JM, Pettey D, Losee J, Duncan B, Gale D, Kowalski CA, Deeter N, Nichols A, Deesing M, Arrant C, Ruan T, Boehme C, McCamey DR, Rou J, Ambal K, Narra KK, Summers SA, Abel ED, **Symons JD**. Ceramide mediates vascular dysfunction in diet-induced obesity by PP2A-mediated dephosphorylation of the eNOS-Akt complex. *Diabetes*. 2012 61 (7): 1848-59. PMID: 22586587

•**Symons JD** and Abel ED. Lipotoxicity contributes to endothelial dysfunction : a focus on the contribution from ceramide. *Reviews in Endocrine and Metabolic Disorders.* 2013 14 (1) 59-68. doi: 10.1007/s11154-012-9235-3 PMID: 23292334

•Bharath LP, Ruan T, Li Y, Ravindran A, Wan X, Nhan JK, Walker M, Deeter L, Goodrich R, Johnson E, Munday D, Mueller R, Kunz D, Jones D, Reese V, Summers SA, Babu PVA, Holland WL, Zhang QJ, Abel ED, **Symons JD.** Ceramide initiated protein phosphatase 2A activation contributes to arterial dysfunction in vivo. *Diabetes*. 2015 64 (11): 3914-3926. PMID: 26253611

5. *Independence (autophagy focus).* The mechanism whereby vascular autophagy contributes cardiovascular function is unclear. In 2014 we showed that autophagy could be upregulated in: (i) endothelial cells by nutrient deprivation; (ii) blood vessels by 14 h fasting in mice; and (iii) blood vessels from mice in response to acute exercise. Further, after showing that a protein required for autophagosome formation (Atg3) was lower in arteries from aged vs. adult mice, we silenced Atg3 in endothelial cells and reported that shear-induced NO generation was prevented. A manuscript in R-1 reveals a novel mechanism responsible for this observation in vitro. Ongoing studies are determining whether this (or other) mechanism(s) can be translated aged humans.

•Bharath LP, Mueller R, Li YY, Ruan T, Kunz D, Goodrich R, Mills T, Deeter L, Sargsyan A, Babu PVA , Graham TE, **Symons JD.** Impairment of autophagy in endothelial cells prevents shear-stress induced increases in nitric oxide bioavailability. *Can J Physiol Pharmacol.* 2014 92 (7) : 605–612. PMID 24941409

•Bharath LP, Ruan T, Li YY, Mueller R, Bean T, Reese V, Richardson RS, Sargsyan A, Pires, K, Babu PVA, Boudina S, Graham TE, **Symons JD.** Endothelial cell autophagy maintains shear-stress-induced nitric oxide generation via glycolysis-dependent purinergic signaling to eNOS. R-1 2017

•Zhang QJ, Zhu Y, Tsushima K, Jaishy B, Riehle C, Jones D, **Symons JD**, Abel ED. An Akt1-Hsp90β-Atg13 complex initiates fasting-induced autophagy in cardiomyocytes independently of mTOR. Submitted 2017

A complete list of ~70 publications is at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1hc1qC8WC8iAe/bibliography/46643892/public/?sort=date&direction=descending

D. Current Research Support

• 16GRNT31050004 American Heart Association Western States Affiliate Grant-In-Aid
07/01/2016 – 06-30-2018
Aging limits autophagic flux in endothelial cells
154K over 2 years Role: PI
The purpose of this grant is to determine the time course of autophagy repression in endothelial cells during aging.

• 1RO3 AGO52848-01A1 National Institutes of Health
01/01/2017 – 12-31-2019
Characterizing the phenotype of young and old mice with disrupted vascular autophagy
149K over 2 years Role: PI
The purpose of this grant is to elucidate mechanisms whereby compromised autophagy limits endothelial cell nitric oxide generation.

• 16UFEL31810001 American Heart Association Western States Affiliate Undergraduate Fellowship
07/01/2016 – 06/30/2017
Vascular adaptations require intact endothelial cell autophagy
$6,500 Student (G Hestwood) Mentor (JD Symons)
The purpose of this grant is to determine whether EC autophagy must be intact for training-induced vascular adaptations to be observed.

•Undergraduate student support through University of Utah Undergraduate Research Opportunities Program (UROP), 3 students at present x 2400.00 per award.

Completed Research Support ***relevant to this application***

• WU13237P02917459W Washington University (WU) Diabetes Research Center (DRC) Pilot / Feasibility Grant
Pathophysiological and genetic disruption of EC autophagy lowers endothelial cell NO production
12/2015-11/2016
40K / 1 year Role:PI
This is an NIH NIDDK award to Washington University, that solicits applications externally for Pilot/Feasibility Grants

• University of Utah, Diabetes and Metabolism Center : Pilot and Feasibility Grant
Characterizing a mouse model to study vascular autophagy in obesity and type 2 diabetes
01-01-2015 – 12-12-2016
25K / 2 year Role: PI
This grant is designed to provide funds to generate / characterize iecAtg3KO mice.

• University of Utah, Center on Aging : Pilot and Feasibility Grant
Links among autophagy, mitophagy, and nitric oxide bioavailability in aging vasculature.
01-01-2015 – 12-12-2015
20K / 1 year Role: PI
This grant is designed to provide funds to collect preliminary data for extramural applications.

•Undergraduate student support through University of Utah Undergraduate Research Opportunities Program (UROP), 4 students x 2400.00 per award; American Heart Association, 2 students x 6000.00 per award; American Physiological Society, 1 student x 7500.00 per award; American Diabetes Association Minority Undergraduate Internship Award, 1 student x 3000.00; Native American Research Internship Program, 1 student x 6000.00 per award; 2 students x Science Without Borders program; Brazil).

Completed Research Support – last 4 years only

• 2R15HL091493-02 National Institutes of Health
The role of ceramide in contributing to vascular dysfunction in diet-induced obesity.
08/2012 – 07-2016
100K/year 3 years Role: PI

This grant provides undergraduate students with research training experience.

• 1-12-BS-208 American Diabetes Association Research Grant 01/2012 – 12/2014
Mechanisms whereby endogenous ceramide impairs eNOS signaling and arterial function
This grant is a renewal that uses intact animals, isolated vessels and cell systems assays to determine mechanisms responsible for ceramide-induced vascular dysfunction.
100K per year / 3 years Role: PI

•UU Research Committee Faculty and Research and Creative Grant 07/2008 – 06/2010
Determining the contribution from ceramide to cardiovascular complications associated with obesity in Sptlcb2+ mice. The goal of this research is to determine whether ceramide evokes endothelial dysfunction in a tissue autonomous manner using a genetic approach. Role: PI

•UU Interdisciplinary Research Grant 01/2010 – 12/2010
Determination of reactive oxygen / nitrogen species in cell culture models of oxidant stress using electron paramagnetic spectroscopy (EPR). Optimize the use of EPR to test the hypothesis that ceramide accumulation generates superoxide anion which combines with nitric oxide to form peroxynitrite and disrupt agonist mediated eNOS dimerization. Role: PI

•1R15HL091493-01 01/2008 – 11/2011
National Institutes of Health R15 A.R.E.A. Grant; The role of ceramide in contributing to vascular dysfunction in diet-induced obesity. To provide undergraduate students with research training experience. Role: PI

•7-08-RA-164 07/2008 – 11/2011
American Diabetes Association Research Grant
Role of ceramide in obesity-related vascular dysfunction.
To test the hypotheses that ceramide contributes to lowering nitric oxide bioavailability using cell culture, isolated vessel, and whole animal systems. Role: PI

•University of Utah Funding Incentive Seed Grant 07/2011 – 06/2012
Mechanisms for ceramide-mediated vascular dysfunction; This grant provides funds for investigators to obtain preliminary data to be used for extramural grant applications. These funds will be used to optimize cell imaging studies for mapping intracellular protein movement. 28 K per year; 1 year; Role: PI

•University of Utah College of Health Research and Creative Grant Fund 06/2011 – 05/2012
Ceramide binds I2PP2A and activates PP2A. This grant funds preliminary experiments to determine how ceramide activates PP2A. 6K per year; 1 year, Role: PI

Pending Research Support

• 1RO1 HL135592-A1 National Institutes of Health
07/01/2017 – 06-30-2022
Autophagy maintains vascular function through a novel glycolysis-linked pathway regulating eNOS
2,097,000 over 5 y Role: PI
The purpose of this grant is to elucidate mechanisms whereby compromised autophagy limits endothelial cell nitric oxide generation.

• UU Office of Vice President – Research Instrumentation Grant
55K to purchase an additional isobaric pressure perfused myograph apparatus
Submitted 01-15-2017