BIOGRAPHICAL SKETCH

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NAME: Junichi Sadoshima, MD, PhD

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

POSITION TITLE: Professor and Chair

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
Kyushu University, Fukuoka, Japan	MD	1983	Medicine
Kyushu University, Fukuoka, Japan	PhD	1989	Physiology
Kyushu University, Fukuoka, Japan		1983-1990	Resident, Internal Medicine, Cardiology
Beth Israel Hospital, Boston, MA		1990-1992	Postdoctoral Fellow, Molecular Biology

A. Personal Statement

My laboratory has been focusing on signaling mechanisms regulating the growth and death of cardiomyocytes in order to elucidate the underlying mechanisms of heart failure and aging. We are particularly interested in the signaling mechanisms of oxidative stress, mitochondria/metabolism, and autophagy/mitophagy and how they affect the survival and death of cardiomyocytes, protein quality control and mitochondrial function during heart failure, myocardial ischemia and aging. We use both *in vitro* molecular biology approaches, using cultured cardiomyocytes, including primary cultures of adult mouse cardiomyocytes, and state-of-the-art *in vivo* mouse physiology analyses. We also use proteomic analyses to evaluate how posttranslational protein modifications participate in cardiac hypertrophy and heart failure, acting as signaling mechanisms. Our laboratory has contributed significantly to a better understanding of the role of oxidative stress in the heart during heart failure and myocardial ischemia. Using genetically altered mouse models, we have demonstrated that thioredoxin 1 (Trx1) and NADPH oxidase 4 (Nox4) play important roles in the heart during pressure overload and myocardial ischemia. The mouse lines that we generated serve as unique tools to elucidate the roles of endogenous Trx1 and Nox4 and to identify the binding partners of Trx1 (Cell 2008; PNAS 2010; Cell Metabolism 2014; JCI 2016). Our goal is to understand how oxidative stress modulates the structures of signaling molecules, which, in turn, affect growth, death, gene expression, metabolism and other functions in the heart and the cardiomyocytes therein. In particular, *oxidative modifications of cysteine residues* affect subcellular localization, protein-protein interaction, protein stability and other functions in key signaling proteins in the heart. Our recent study elucidated the molecular mechanism through which Trx1 transfers NO to Atg7, an E1 like protein, thereby promoting autophagy and protection of the heart against ischemia (JCI in press).

Ongoing research support that I would like to highlight include:

NIH/NHLBI 1R01HL091469-13 **01/15/2008 –02/28/2023**
Cardioprotective Effects of Thioredoxin 1
Role: Principal Investigator
The goal of this project is to further delineate the molecular mechanisms by which Trx1 exerts its cardioprotective effects, including anti-hypertrophic and anti-apoptotic effects and the enhancement of mitochondrial function.

NIH/NHLBI 1R01 HL138720-04 **07/01/2017-05/31/2025**
Removal of damaged mitochondria by alternative autophagy
Role: Principal Investigator

The goal of this project is to elucidate the molecular mechanism of mitophagy and its functional significance in the heart during myocardial stress.

NIH/NHLBI 1R01HL112330-11 02/15/2012-1/31/2025

Regulation of Myocardial Growth and Death by the Hippo Pathway

Role: Principal Investigator

The overall goal of this project is to elucidate the role of the Hippo signaling pathway in mediating apoptosis and suppression of physiological hypertrophy.

NIH/NHLBI 1R01HL144626-02 07/01/2019-06/30/2023

FoxO1 protects the heart against ischemia

Role: Principal Investigator

The overall goal of this project is to elucidate the function of FoxO1 as a scaffold to stimulate C/EBP-β and protect the heart during ischemia and reperfusion.

Fondation Leducq Transatlantic Network of Excellence 01/01/2016-12/31/2022 (NCE)

Modulating Autophagy to Treat Cardiovascular Disease

Role: North American Coordinator

The overall goal is to conduct a transatlantic collaborative study on the functional role of autophagy and identify lead compounds to treat cardiovascular disease by modulating the activity of autophagy.

NIH/NHLBI 1R01HL150881-02 12/01/2019-11/30/2023

PPARα induces IL-6 to trigger diabetic cardiomyopathy

Role: Principal Investigator

The overall goal in this project is to elucidate the role of PPARα in mediating the inflammatory responses in the heart during the early phase of diabetes induced by high fat diet consumption.

AHA Merit Award 20MERIT35120374 01/01/2020-12/31/2024

Prevention of myocardial injury by inhibition of autosis

Role: Principal Investigator

The overall goal of this project is to elucidate the role of autosis in mediating myocardial injury in response to stress and the underlying mechanisms.

Citations

1. Yamamoto M, Yang G, Hong C, Liu J, Holle E, Yu X, Wagner T, Vatner SF and **Sadoshima J.** Inhibition of thioredoxin in the heart increases oxidative stress and cardiac hypertrophy. *J Clin Invest*. 2003;112:1395-1406.PMC228400
2. Ago T, Liu T, Zhai P, Chen W, Li H, Molkentin JD, Vatner SF and **Sadoshima J**. A redox-dependent pathway for regulating class II HDACs and cardiac hypertrophy. *Cell*. 2008;133:978-993
3. Shao D, Oka S, Liu T, Zhai P, Ago T, Sciarretta S, Li H and **Sadoshima J**. A Redox-Dependent Mechanism for Regulation of AMPK Activation by Thioredoxin1 during Energy Starvation. *Cell Metab*. 2014;19:232-245.PMC3937768
4. Matsushima S, Kuroda J, Zhai P, Liu T, Ikeda S, Nagarajan N, Oka S, Yokota T, Kinugawa S, Hsu CP, Li H, Tsutsui H and **Sadoshima J**. Tyrosine kinase FYN negatively regulates NOX4 in cardiac remodeling. *J Clin Invest*. 2016;126:3403-3416.PMC5004961
5. Nagarajan N, Oka SI, Nah J, Wu C, Zhai P, Mukai R, Xu X, Kashyap S, Huang CY, Sung E, Mizushima W, Titus AS, Takayama K, Mourad Y, Francisco J, Liu T, Chen T, Li H and **Sadoshima J**. Thioredoxin 1 promotes autophagy through transnitrosylation of Atg7 during myocardial ischemia. *J Clin Invest*. 2022:e162326

B. Positions and Honors

2012-Present	Chair, Department of Cell Biology and Molecular Medicine, Rutgers-NJMS, Newark, NJ
2011-2012	Interim Chair, Department of Cell Biology and Molecular Medicine, UMDNJ, Newark, NJ
2010-Present	Executive Director of Cardiovascular Research Institute, Rutgers-NJMS, Newark, NJ
2005-2010	Vice-Chair, Department of Cell Biology and Molecular Medicine, UMDNJ, Newark, NJ
2003-Present	Professor, Cardiovascular Research Institute, Department of Cell Biology and Molecular Medicine and Department of Medicine, Rutgers-NJMS, Newark, NJ
2002-Present	Director, Molecular Biology and Associate Director of the Cardiovascular Research Institute, Department of Cell Biology and Molecular Medicine, Rutgers-NJMS, Newark, NJ
2000-2003	Associate Professor, Cardiovascular Research Institute, Department of Cell Biology and Molecular Medicine and Department of Medicine, UMDNJ-NJMS, Newark, NJ
1999-2000	Associate Professor, Department of Cellular and Molecular Physiology, Penn State University/College of Medicine, Weis Center for Research, Danville and Hershey, PA

1998-1999 Assistant Professor, Department of Internal Medicine, Cardiovascular and Pulmonary Research Institute, Allegheny University of the Health Sciences, Pittsburgh, PA
1994-1997 Assistant Professor, Department of Internal Medicine, University of Michigan, Ann Arbor, MI
1992-1994 Instructor, Harvard Medical School, Boston, MA

Professional Memberships: *2002-Present American Society of Clinical Investigation*

Editorial Boards: Journal of Cardiovascular Aging (Associate Editor) 2021-Present. Nature Reviews Cardiology (Advisory Board) 2018-Present. Cardiovascular Research (Associate Editor) 2018-Present. Trends in Cardiovascular Medicine 2014-Present. Scientific Reports 2014-Present. PLoS One 2012-Present. Circulation 2012-2016. Journal of Cardiovascular Translational Research 2009-Present. Journal of Clinical Investigation 2009-Present. Autophagy (Associate Editor) 2009-2020, (Section Editor) 2020-Present. Journal of Cardiovascular Pharmacology 2008-Present. American Journal of Physiology-Heart and Circulatory Physiology (Editorial Board) 2007-Present, (Associate Editor) 2010-2020. Antioxidants and Redox Signaling 2006-Present. Journal of Molecular and Cellular Cardiology (Editorial Board) 1998-Present, (Associate Editor) 2018-2019, (Senior Consulting Editor) 2020-Present. Circulation Research (Editorial Board) 1998-Present, (Consulting Editor) 2009-2019. JACC Basic to Translational Science (Guest Associate Editor) 2021-Present.

Advisory Committees and Study Sections:

2012-2018 International Society of Heart Research, Council Member
2010-Present American Heart Association Committee for Scientific Sessions Program, BCVS SCILL Committee Member, BCVS Leadership Committee Member, BCVS Nominating Committee Member
2009-Present NIH Program Project Ad hoc Reviewer, CMAD Ad hoc Member, NIH College of CSR Reviewer, NIH RFA Special Emphasis Panel Reviewer, NIH ASG Ad hoc Reviewer
2009-2016 MIM Ad hoc Member, MIM Regular Member
2000-2007 NIH, CVA Ad hoc Member, CVA/CCHF, Regular Member
2002-2007 American Heart Association, Heritage Affiliate, Research Committee Member
1999-Present American Heart Association, National Cardiovascular (Patho) Physiology 1 Reviewer, Cellular and Molecular Genetics & Signaling Reviewer, Northeast 5 (2007-2008 Chair), Innovative Research Grant Peer Review Committee, Reviewer, Merit Award Reviewer
1999-Present NIH, SBIR, Program project grant, Conference grant, Special Emphasis Panel Member

Honors

2022 IACS Howard Morgan Distinguished Achievement Award Lecture; 2022 Keynote Lecture Oxford Longevity Project; 2022 The Edward J. Ill Excellence in Medicine Foundation, Outstanding Scientist Award; 2020 AHA Merit Award; 2017 ISHR President's Distinguished Lecture Award; 2017 AHA BCVS Distinguished Achievement Award; 2017 Organizer, Keystone Symposia Conference, Mitochondria, Metabolism and Heart; 2016 North American Coordinator, Fondation Leducq Transatlantic Network of Excellence; 2014 Thomas W Smith Memorial Lecture, AHA Scientific Sessions; 2013 Best Mentor Award, AHA BCVS; 2011 Co-Chair, AHA BCVS; 2010 Janice Pfeffer Distinguished Lecture Award, ISHR; 2001 First Prize Cardiovascular Research Prize Competition, American Heart Association; 1995 First Prize, Louis N Katz Basic Science Prize, American Heart Association

C. Contributions to Science

1. Regulation of Cell Signaling by Oxidative Stress in the Heart We have been focusing on how oxidative stress directly modulates the function of signaling molecules in the heart. Thioredoxin 1 (Trx1) is a 12-kD protein which has conserved cysteine residues that reduce (oxidized) proteins with disulfide bonds through a thiol-disulfide exchange reaction. Noxs are transmembrane proteins whose function is dedicated to generating either O_2^- or H_2O_2. We were the first to generate genetically altered mouse models to investigate the function of oxidative posttranslational modification of signaling molecules in the heart. We have identified HDAC4, AMPK, and mTOR as the main targets of Trx1 in the heart.

1. Ago T, Liu T, Zhai P, Chen W, Li H, Molkentin JD, Vatner SF, and **Sadoshima J**. A redox-dependent pathway for regulating class II HDACs and cardiac hypertrophy. *Cell* 133:978-993, 2008. PMID: 18555775
2. Shao D, Oka S, Liu T, Zhai P, Ago T, Sciarretta S, Li H, **Sadoshima J.** A Redox-Dependent Mechanism for Regulation of AMPK Activation by Thioredoxin1 during Energy Starvation. *Cell Metab* 19:232-245, 2014. PMC3937768.
3. Matsushima S, Kuroda J, Zhai P, Liu T, Ikeda S, Nagarajan, Oka S, Yokota T, Kinugawa S, Hsu CP, Li H, Tsutsui H, **Sadoshima J.** Tyrosine kinase Fyn negatively regulates Nox4 in cardiac remodeling. *J Clin Invest*: 126(9): 3403-3416, 2016. PMC5004961.

4. Oka S, Byun J, Huang CY, Imai N, Ralda G, Zhai P, Xu X, Kashyap S, Warren JS, Maschek JA, Tippetts TS, Tong M, Venkatesh S, Ikeda Y, Mizushima W, Kashihara T, **Sadoshima J**. Nampt potentiates anti-oxidant defense in diabetic cardiomyopathy. *Circ Res* 129, 114-130, 2021. PMC8513534.
5. Nagarajan N, Oka S, Nah J, Wu C, Zhai P, Mukai R, Xu X, Kashyap S, Huang CY, Sung EA, Mizushima W, Titus AS, Takayama K, Mourad Y, Francisco J, Liu T, Chen T, Li H, **Sadoshima J**. Thioredoxin 1 promotes autophagy through transnitrosylation of Atg7 during myocardial ischemia. *J Clin Invest*: (in press) 2023. PMID: 36480290.

2. Signaling Mechanisms of Cardiac Hypertrophy

I started my career by studying the molecular mechanism of stretch-induced cardiac hypertrophy and identified autocrine secretion of angiotensin II and activation of Gαq-mediated signaling mechanisms as playing an important role in mediating cardiac hypertrophy. I have been focusing on the signaling mechanism by which pathological hypertrophy is induced and heart failure develops, using genetically altered mouse models and state-of-the-art -omics approaches.

1. Matsuda T, Zhai P, Maejima Y, Hong C, Gao S, Tian B, Goto K, Takagi H, Tamamori-Adachi M, Kitajima S, and **Sadoshima J**. Distinct roles of GSK-3alpha and GSK-3beta phosphorylation in the heart under pressure overload. *Proc Natl Acad Sci U S A* 105:20900-20905, 2008. PMC2634936.
2. Yang Y, Del Re DP, Nakano N, Sciarretta S, Zhai P, Park J, Sayed D, Shirakabe A, Matsushima S, Park Y, Tian B, Abdellatif M, **Sadoshima J.** miR-206 mediates YAP-induced cardiac hypertrophy and survival. *Circ Res* 117:891-904, 2015. PMC26333362.
3. Nakamura M, **Sadoshima J.** Mechanisms of physiological and pathological hypertrophy. *Nat Rev Cardiol.* 15:387-407, 2018. PMID: 29674714.
4. Kashihara T, Mukai R, Oka S, Zhai P, Nakada Y, Yang Z, Mizushima W, Nakahara T, Warren JS, Abdellatif M, **Sadoshima J.** YAP mediates compensatory cardiac hypertrophy through aerobic glycolysis in response to pressure overload. *J Clin Invest*,132(6): e150595, 2022. PMC8920343.

3. The Hippo Signaling Pathway in the Heart

Signaling mechanisms controlling cell survival and death play an important role in mediating the progression of heart failure. We found that mammalian sterile 20-like kinase 1 (Mst1) is strongly activated when cardiomyocytes undergo apoptosis and that Mst1 plays an important role in mediating apoptosis and suppressing autophagy in the heart. Mst1 is the main component of the Hippo signaling pathway (Yamamoto et al *JCI* 2002). Our group was the first to investigate the role of the Hippo signaling pathway in heart failure.

1. Del Re DP, Matsuda T, Zhai P, Gao S, Clark GJ, Van Der Weyden L, and **Sadoshima J.** Proapoptotic Rassf1A/Mst1 signaling in cardiac fibroblasts is protective against pressure overload in mice. *J Clin Invest* 120:3555-3567, 2010. PMC2947240.
2. Del Re, D.P., Matsuda, T., Zhai, P., Maejima, Y., Jain, M.R., Liu, T., Li, H., Hsu, C.-P., **Sadoshima, J.** Mst1 promotes apoptosis through phosphorylation and inhibition of Bcl-xL in cardiomyocytes. *Mol Cell* 54:639-650, 2014. PMC4074544.
3. Ikeda S, Mizushima W, Sciarretta S, Abdellatif M, Zhai P, Mukai R, Fefelova N, Oka SI, Nakamura M, Del Re D, Farrance I, Park JY, Tian B, Xie LH, Kumar M, Hsu CP, Sadayappan S, Shimokawa H, Lim DS, **Sadoshima J**. Hippo defficiency leads to cardiac dysfunction accompanied by cardiomyocyte dedifferentiation during pressure overload. *Circ Res*. 124: 292-305, 2019. PMC 30582455.
4. Ikeda S, Mukai R, Mizushima W, Zhai P, Oka SI, Nakamura M, Del Re D, Sciarretta S, Hsu CP, Shimokawa H, **Sadoshima J.** Yes-associated proten facilitates pressure overload induced dysfunction in the diabetic heart. *JACC Basic to Transl Sci* 4:611-622, 2019. PMC6872826.
5. Ikeda S, Nah J, Shirakabe A, Zhai P, Oka S, Sciarretta S, Guan KL, Shimokawa H, **Sadoshima J.** YAP plays a crucial role in the development of cardiomyopathy in lysosomal storage diseases. *J Clin Invest.* 131:e143173, 2021. PMC7919732.

4. Autophagy and Mitophagy in the Heart

We are one of the first groups in the field to report the functional significance of autophagy during stress in the heart (Yan et al *PNAS* 2005). We are focusing on the signaling mechanism by which autophagy is regulated in the heart. Thus far, we have discovered, thus far, that autophagy is stimulated by FoxO, whereas it is inhibited by the mTOR-Rheb pathway and Mst1. We also demonstrated the importance of mitophagy, mediated through both conventional and alternative mechanisms, as *a critical mechanism of mitochondrial quality control* during myocardial ischemia and heart failure. In addition, we have shown that excessive autophagy induces cell death with unique morphological and biochemical features, called autosis, in cardiomyocytes.

1. Maejima Y, Kyoi S, Zhai P, Liu T, Li H, Ivessa A, Sciarretta S, Del Re DP, Zablocki DK, Hsu CP, Lim D, Isobe M, **Sadoshima J.** Mst1 inhibits autophagy by promoting Beclin-1Bcl-2 interaction. *Nature Med* 19: 1478-1488, 2013. PMC3823824.

2. Shirakabe A, Zhai P, Ikeda Y, Saito T, Maejima Y, Hsu CP, Nomura M, Egashira K, Levine B, **Sadoshima J**. Drp1-dependent mitochondrial autophagy plays a protective role against pressure-overload-induced mitochondrial dysfunction ad heart failure. *Circulation*. 133:1249-1263, 2016. PMC4811679.
3. Shirakabe A, Ikeda Y, Sciarretta S, Zablocki DK, **Sadoshima J.** Aging and Autophagy in the Heart. *Circ Res.* 118(10):1563-76, 2016. PMC4869999.
4. Sciarretta S, Maejima Y, Zablocki D, **Sadoshima J**. The role of autophagy in the heart. *Annu Rev Physiol* 80:1-26, 2018. PMID: 29068766.
5. Sciarretta S, Yee D, Nagarajan N, Bianchi F, Saito T, Valenti V, Tong M, Del Re DP, Vecchione C, Schirone L, Fonte M, Rabattu S, Shirakabe A, Boppana VS, Volpe M, Frati G, Zhai P, **Sadoshima J.** Trehalose-induced activation of autophagy improves cardiac remodeling after myocardial infarction. *J Am Coll Cardiol*. 71:1999-2010, 2018. PMC 6347412.
6. Saito T, **Nah J**, Oka S, Mukai R, Monden Y, Maejima Y, Ikeda Y, Sciarretta S, Liu T, Li H, Baljinnyam E, Fraidenraich D, Fritzky L, Zhai P, Ichinose S, Isobe M, Hsu CP, Kundu M, **Sadoshima J.** An alternative mitophagy mediated by Rab9 protects the heart against ischemia. *J Clin Invest* 129:802-819, 2019. PMC6355232.
7. Tong M, Saito T, Zhai P, Oka SI, Mizushima W, Nakamura M, Ikeda S, Shirakabe A and **Sadoshima J**. Mitophagy is essential for maintaining cardiac function during high fat diet-induced diabetic cardiomyopathy. *Circ Res*. 124:1360-1371, 2019. PMC6483841.
8. Nah J, Zhai P, Huan CY, Fernandez AF, Mareedu S, Levine B, **Sadoshima J.** Upregulation of rubicon promotes autosis during myocardial ischemia/reperfusion injury. *J Clin Invest* 130:29078-2992, 2020. PMC7260042.
9. Tong M, Saito T, Zhai P, Oka SI, Mizushima W, Nakamura M, Ikeda S, Shirakabe A, **Sadoshima J**. Alternative Mitophagy Protects the Heart Against Obesity-Associated Cardiomyopathy. *Circ Res.* 129:1105-1121, 2021. PMID: 34724805.
10. Nah J, Shirakabe A, Mukai R, Zhai P, Sung EA, Ivessa A, Mizushima W, Nakada Y, Saito T, Hu C, Jung YK, **Sadoshima J**. Ulk1-dependent Alternative mitophagy plays a protective role during pressure overload in the heart. Cardiovasc Res 118(12):2638-2651, 2022. PMID: 35018428.

5. Regulation of Aging and Metabolism by Sirtuins and PPARα in the Heart

The incidence of heart disease is dramatically increased by aging. My laboratory is interested in investigating the molecular mechanisms promoting and counteracting aging in the heart. According to the hormesis hypothesis, aging may be controlled by accumulation of stress resistance activated by low levels of stress, such as caloric restriction. Sirtuin family proteins are important in mediating lifespan extension in response to caloric restriction. My laboratory was the first to describe the function of Sirt1 in the heart by generating genetically altered mouse models of Sirt1. We found that Sirt1 is activated by fasting and other stresses and promotes cardiomyocyte survival. Sirt1 inhibits PPARα-mediated transcription by inducing downregulation of ERR target genes in cardiomyocytes. This work is one of the first to show the molecular link between Sirt1 and metabolism.

1. Yan L, Vatner DE, O'Connor JP, Ivessa A, Ge H, Chen W, Hirotani S, Ishikawa Y, **Sadoshima J**, and Vatner SF. Type 5 adenylyl cyclase disruption increases longevity and protects against stress. *Cell:* 130(2):247-58, 2007. PMID: 17662940.
2. Hsu CP, Oka S, Shao D, Hariharan N, **Sadoshima J**. Nicotinamide phosphoribosyltransferase regulates cell survival through NAD+ synthesis in cardiac myocytes. *Circ Res*: 105, 481-491, 2009. PMC2765790.
3. Hsu CP, Zhai P, Yamamoto T, Maejima Y, Matsushima S, Harinaran N, Shao D, Takagi H, Oka S, **Sadoshima J.** Sirt1 protects the heart from ischemia/reperfusion. *Circulation*: 122, 2170-2182, 2010. PMC3003297.
4. Oka S, Alcendor R, Zhai P, Park JY, Shao D, Cho J, Yamamoto T, Tian B, **Sadoshima J.** PPARalpha-Sirt1 complex mediates cardiac hypertrophy and failure through suppression of the ERR transcriptional pathway. *Cell Metab* 14:598-611, 2011. PMC3217210.
5. Nakamura M, Tong L, Husain S, Zhai P, Warren J.S., Hsu C.P., Matsuda T, Phiel C.J., Cox J.E., Tian B, Li H, **Sadoshima J**. Glycogen Synthase Kinase-3α Promotes Fatty Acid Uptake and Lipotoxic Cardiomyopathy. *Cell Metab*: 29, 1119-1134, 2019. PMC6677269.
6. Chen Y, Maejima Y, Shirakabe A, Yamamoto T, Ikeda Y, **Sadoshima J**, Zhai P. Ser9 phosphorylation of GSK-3β promotes aging in the heart through suppression of autophagy. *J Cardiovasc Aging* 1:9, 2021. PMC 8589323.

Complete List of Published Work

http://www.ncbi.nlm.nih.gov/pubmed/?term=Sadoshima+J