BIOGRAPHICAL SKETCH

NAME: Ji-Yeon Shin

eRA COMMONS USER NAME (credential, e.g., agency login): js3444

POSITION TITLE: Assistant Member

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Chonnam National University, Chonnam, South Korea	B.S.	02/1996	Biology Education
GwangJu Institute of Science and Technology, GwangJu, South Korea	M.S.	02/1999	Developmental Biol
Emory University, Atlanta, GA	Ph.D.	05/2006	Genetics and Mol Biol

A. Personal Statement

My broad research interest is the nuclear envelope proteins in health and disease. One of my main research directions is to elucidate molecular mechanisms by which the nuclear envelope defects lead to dysregulation in cellular lipid metabolism and predisposition to neoplasia. I developed an interest in this fundamental research yet important medical problems after research training in diverse areas. For my doctoral degree, I studied neurogenetics, focusing on the non-cell autonomous contribution of glial cells to the selective neuropathology in Huntington's disease. I then obtained an additional year of training in neurogenetics as a postdoctoral UCSF. After I moved to New York due to a family issue, I worked with Drs. William Dauer and Howard Worman to understand the role of nuclear envelop proteins in normal development and various diseases. I initially focused on the interactions between a nuclear envelope protein LAP1 and other proteins and the implication of the protein-protein interactions in the pathology of muscular dystrophies. Subsequently, I made the unexpected discovery that depletion of LAP1 or its interacting partner, torsinA, from hepatocytes causes abnormal hepatic lipid metabolism and a predisposition to neoplasia. Some of this work was published in the *Journal of Clinical Investigation*. My more-recent senior author publication as an assistant professor was published in the *Journal of Lipid Research* and *JCI insight*. My research on the liver disease has led to my receiving a Pinnacle Research Award from the American Association for the Study of Liver Diseases and a Gilead Science Research Scholar Award. More recently, I received an R01 research grant (2023-2028) from NIH/NCI to study the causal roles of nuclear envelope defects in hepatic neoplasia. Equipped with my expertise and all the necessary tools and reagents that I have generated in previous studies, I am uniquely positioned to investigate the role of the nuclear envelope proteins in normal physiology and various diseases including muscular dystrophies and liver diseases.

Ongoing projects that I would like to highlight include:

R01 CA283566
Shin (PI) 09/01/2023 -08/31/2028
Nuclear envelope and predisposition to hepatic neoplasia

American Association for the Study of Liver Diseases
Shin (PI) 07/01/2021 – 07/30/2024
LAP1-torsinA Complex in NASH and HCC Development

Irving Institute for Clinical and Translational Research Precision Medicine Award
Shin (PI) 07/01/2023- 06/30/2024
Impaired cellular energetics and lipid metabolism in human iPSC-derived cardiomyocytes

Citations:

1. Östlund C, Hernandez-Ono A, Shin JY. The nuclear envelope in lipid metabolism and pathogenesis of NAFLD. *Biology (Basel)* 2020;9:338 PMCID: PMC7602593
2. Shin JY, Worman HJ. Molecular pathology of laminopathies. *Annu Rev Pathol* 2022;17:159-180 PMCID: PMC8881990

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments:

March 2024	Assistant Member, Hackensack Meridian Health Center for Discovery and Innovation
2019 - 2024	Assistant Professor of Medical Sciences (in Medicine), Columbia University
2011- 2019	Associate Research Scientist in Medicine, Columbia University
2010- 2011	Postdoctoral Research Scientist (mentor: William T. Dauer), Columbia University
2008-2009	Postdoctoral Fellow (mentor: William T. Dauer), Columbia University
2006-2007	Postdoctoral Fellow in Neruogenetics (mentors: Ying-Hui Fu and Louis J. Ptáček) University of California San Francisco

Honors:

2021	Pinnacle Research Award, American Association for the Study of Liver Diseases
2019	Gilead Science Research Scholar Award
2013	Finalist for a poster award in Muscular Dystrophy Association Scientific Conference
2013	Finalist for the presentation in the Department Medicine Grand Rounds (Columbia University)
2010-2013	Development Grant, Muscular Dystrophy Association
2004	Association of Korean Neuroscientists President's Outstanding Research Award
1996-1998	Recipient of Korean government scholarship, GwangJu Institute of Science and Technology
1996	Graduated with high honors, Chonnam National University, Korea
1992-1996	Full scholarship, Chonnam National University, Korea

C. Contributions to Science

1. 1. My recent research has primarily focused on the study of hepatic lipid metabolism and liver diseases. I was led in that direction by following up on a serendipitous discovery: when I conditionally depleted LAP1 from mouse hepatocytes in a control experiment, I observed abnormal fat accumulation in the cells. I discovered that depletion of inner nuclear membrane protein LAP1 from hepatocytes causes hepatic steatosis and steatohepatitis secondary to defective liver VLDL secretion. The AAA+ ATPase torsinA binds to LAP1 in the perinuclear space of the nuclear envelope. I then depleted torsinA from hepatocytes and demonstrated that the mice had an even more significant decrease in hepatic VLDL secretion and developed profound steatosis. I have also led a study on the formation and regulation of nuclear lipid droplets in mice with depletion of LAP1 from hepatocytes. Most recently, we have examined the role of another torsinA activity, LULL1, in low-density lipoprotein secretion and steatosis and its interaction with LAP1 in regulating them.
    a. Shin JY, Hernandez-Ono A, Fedotova T, Östlund C, Lee MJ, Gibeley SB, Liang CC, Dauer WT, Ginsberg HN, Worman HJ. Nuclear envelope-localized torsinA-LAP1 complex regulates hepatic VLDL secretion and steatosis. *J. Clin. Invest.* 2019;130:4885-4900 PMCID: PMC6819140
    b. Östlund C, Hernandez-Ono A, Turk SJ, Dauer WT, Ginsberg HN, Worman HJ, Shin JY. Hepatocytes deficient in nuclear envelope protein lamina-associated polypeptide 1 are an ideal mammalian system to study intranuclear lipid droplets. *J. Lipid Res.* 2022;63:100277 PMCID: PMC9587410
    c. Hernandez-Ono A, Zhao Y P, Murray JW, Östlund C, Lee MJ, Dauer WT, Worman HJ*, Ginsberg HN*, Shin JY* Dynamic regulation of hepatic lipid metabolism by torsinA and its activators. *JCI insight* 2024; 9(3): e175328 [*Co-corresponding authors]

2. My Ph.D. thesis project was focused on glial cell dysfunction caused by mutant huntingtin (HTT), which contributes to the selective neuropathology in Huntington's disease (HD). Before I started this project, the studies on HD pathology were mainly focused on the pathogenic mechanisms by expression and accumulation of mutant HTT in neurons. However, I made a keen observation that the accumulation of

mutant HTT also occurs in glial cells in HD brain sections, although the expression level was lower than in neurons. This observation made me formulate a hypothesis that glial cell dysfunction caused by mutant HTT contributes to the selective neuropathology of medium-sized spiny neurons in HD. I demonstrated that HTT expressing glial cells have impaired ability of glutamate clearance, and lead to increased excitotoxicity to neurons. To extend the finding to *in vivo* model, I established transgenic mice expressing mutant HTT only in glial cells. The mouse showed age-dependent neurological phenotypes proving that HTT expressing glial cells is sufficient to cause the HD pathology.

a. Shin JY, Fang ZH, Yu ZX, Wang CE, Li SH, Li XJ. Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. *J. Cell Biol.* 2005;171:1001-1012 PMCID: PMC2171327
b. Bradford J, Shin JY, Robert M, Wang CE, Sheng G, Li SH, Li XJ. Expression of mutant huntingtin in mouse brain astrocytes causes neurological symptoms in mice via transcriptional dysregulation of glutamate transporter. *Proc. Natl. Acad. Sci. USA* 2009;106:22480-22485 PMCID: PMC2799722
c. Bradford J*, Shin JY*, Roberts M, Wang CE, Sheng G, Li SH, Li XJ. Mutant huntingtin in glial cells exacerbates neurological symptoms of Huntington disease mice. *J. Biol. Chem.* 2010;285:10653-10661 [*Co-first authors] PMCID: PMC2856273

3. My project at UCSF as a postdoctoral fellow was focused on the characterization of the molecular basis of human clock gene, *Period 2*, using novel mouse and cell models. I also initiated a new project on the role of microRNAs in brain development, in particular, oligodendrocyte proliferation and differentiation. I established a mouse line in which *Dicer* is selectively depleted in the oligodendrocyte lineage. The mice display multiple neurological impairment with premature death before 6 months of age and the mouse model was instrumental to the follow up studies even after I left the laboratory.

a. Xu Y, Toh KL, Jones CR, Shin JY, Fu YH, Ptácek LJ. Modeling of a human circadian mutation yields insights into clock regulation by PER2. *Cell* 2007;128:59-70 PMCID: PMC1828903
b. Shin D, Shin JY, McManus MT, Ptácek LJ, Fu YH. Dicer ablation in oligodendrocytes provokes neuronal impairment in mice. *Ann. Neurol*. 2009;66:843-57 PMCID: PMC2885004

4. My postdoctoral and subsequent research as an Associate Research Scientist at Columbia University was focused on elucidating the roles of nuclear envelope proteins in normal physiology and pathology. Mutations in genes encoding nuclear envelope proteins are linked to many human disorders. However, only limited information was available about pathogenic mechanisms and the cell biology of nuclear envelope proteins. Using an unbiased proteomics approach, I discovered an interaction between a poorly-characterized inner nuclear membrane protein, LAP1, and the Emery-Dreifuss muscular dystrophy protein, emerin, which is also localized to the inner nuclear membrane. Using conditional knockout mice, I then demonstrated that the deletion of LAP1 from mouse striated muscle leads to either abnormal striated muscle development or muscular dystrophy, depending upon the developmental stage at which the protein is depleted. I also demonstrated the role of LAP1 in normal heart function and how depletions of multiple nuclear envelope proteins affect the postnatal development of mice.

a. Shin JY, Méndez-López I, Wang Y, Hays AP, Tanji K, Lefkowitch JH, Schulze PC, Worman HJ, Dauer WT. Lamina-associated polypeptide-1 interacts with the muscular dystrophy protein emerin and is essential for skeletal muscle maintenance. *Dev. Cell* 2013;26:591-603 PMCID: PMC3798056
b. Shin JY, Le Dour C, Sera F, Iwata S, Homma S, Joseph LC, Morrow JP, Dauer WT and Worman HJ Depletion of lamina-associated polypeptide 1 from cardiomyocytes causes cardiac dysfunction in mice. *Nucleus* 2014;5:260-268 PMCID: PMC4133221
c. Shin JY, Méndez-López I, Hong M, Wang Y, Tanji K, Wu W, Shugol L, Krauss RS, Dauer WT, Worman HJ. Lamina-associated polypeptide 1 is dispensable for embryonic myogenesis but required for postnatal skeletal muscle growth. *Hum. Mol. Genet.* 2017;26:65-78 PMCID: PMC6075563
d. Wang Y*, Shin JY*, Nakanishi K, Homma S, Kim GJ, Tanji K, Joseph LC, Morrow JP, Stewart CL, Dauer WT, Worman HJ. Postnatal development of mice with combined genetic depletions of lamin A/C, emerin and lamina-associated polypeptide 1. *Hum. Mo.l Genet.* 2019;28:2486-2500 [*Co-first authors] PMCID: PMC7590221

5. I have contributed to other research on diseases and developmental defects caused by mutations in genes encoding nuclear lamins. I studied the effects of a novel lamin A/C gene mutation that blocks prelamin A protein farnesylation in a patient with a progeroid disorder. I have also contributed to preclinical research on a novel agent for the treatment of cardiomyopathy caused by lamin A/C gene mutation and a project on

developmental defects with combined deletions of multiple nuclear envelope proteins. Contributing to these research projects has expanded by understanding of the role of nuclear lamins in pathology.

a. Wang Y, Lichter-Konecki U, Anyane-Yeboa K, Shaw JE, Lu JT, Östlund C, Shin JY, Clark LN, Gundersen GG, Nagy PL, Worman HJ. A mutation abolishing the ZMPSTE24 cleavage site in prelamin A causes a progeroid disorder. *J. Cell Sci.* 2016;129:1975-1980 PMCID: PMC4878994
b. Wu W, Chordia MD, Hart BP, Kumarasinghe ES, Ji MK, Bhargava A, Lawlor MW, Shin JY, Sera F, Homma S, Muchir A, Khire UR, Worman HJ. Macrocyclic MEK1/2 inhibitor with efficacy in a mouse model of cardiomyopathy caused by lamin A/C gene mutation. *Bioorg. Med*. *Chem*. 2017;25:1004-1013 PMCID: PMC5291759
c. Wang Y*, Shin JY*, Nakanishe K, Homma S, Kim GJ, Kurenai T, Joseph CL, Morrow JP, Stewart CL, Dauer WT, Worman HJ. Postnatal development of mice with combined genetic depletion of lamin A/C, emerin, and lamina-associated polypeptide 1. *Hum. Mol. Genet.* 2019;28: 2486–2500 PMCID: PMC7590221 [*Co-first authors]
d. Wang Y, Shilagardi K, Hsu T, Odinammadu K, Maruyama T, Wu W, Lin C-H, Damoci CB, Eric D. Spear ED, Shin JY, Hsu W, Michaelis S, and Worman HJ. Abolishing the prelamin A ZMPSTE24 cleavage site leads to progeroid phenotypes with near-normal longevity in mice *Proc. Natl. Acad. Sci. USA* 2022;119:e2118695119 PMCID: PMC8892526

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/ji-yeon.shin.1/bibliography/48010547/public/?sort=date&direction=ascending