BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Lee, Eun-Sook Y.	Professor
eRA COMMONS USER NAME EunLee	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Hyo-Sung University, South Korea	B.S.	1985	Pharmacy
Florida A&M University, Tallahassee, FL	Ph.D.	1999	Pharmacology
Florida A&M University, Tallahassee, FL	Postdoctoral	2005	Neuropharmacology/Toxicology
Vanderbilt University Medical Center	Research Scholar	2007	Neurotoxicology

A. Personal Statement

The goal of our research is to get insight into the mechanism of manganese (Mn)-induced neurotoxicity at the transcriptional level. We focus on several genes that interact with Mn to modulate its neurotoxicity. One project is to investigate the role of the transcription factor yin yang 1 (YY1) in Mn-induced dysregulation of the astrocytic glutamate transporter GLT-1, which is the main glutamate transporter taking up most of excess glutamate from the synaptic clefts to prevent excitotoxic neuronal death. Impairment of this transporter is associated with various neurological disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and manganism (Mnism). The latter is caused by chronic exposure to Mn, causing PD-like pathological features. Understanding molecular mechanisms involved in Mn-induced dysregulation of GLT-1 is critical to advance developing strategies for treatment of Mn neurotoxicity as well as other neurological disorders associated with impairment of this transporter. We use several experimental tools to study the role of YY1 in Mn-induced impairment of astrocytic GLT-1 such as genetic manipulation strategies by generating an astrocyte-specific YY1 conditional knockout (YY1 cKO) mouse model and applying adeno-associated viral vectors to delete astrocytic YY1 in the specific regions of interest in the brain.

Another focusing area is to understand the mechanisms of RE1-silencing transcription factor (REST)-induced protection against Mn neurotoxicity in astrocytes and dopaminergic neurons. This is based on our recent findings that both Mn and YY1 repress REST, while overexpression of REST attenuated Mn-induced toxicity in dopaminergic neurons as well as astrocytes, suggesting that REST could be a potential molecular target to protect against Mn neurotoxicity. REST exerts neuroprotective effects in aging and AD patients.

We are also investigating the role of leucine rich repeat kinase 2 (LRRK2) in Mn neurotoxicity. Genetic variants of LRRK2 are substantial risk factors for familial and sporadic PD cases and implicated in its interaction with environmental factors. Elucidation of mechanism of the interaction between Mn and LRRK2 in PD pathogenesis will greatly advance our understanding of gene-environmental interaction in PD, Mnism and neurological diseases.

I have a broad background in neurotoxicology, neurochemistry, neuropharmacology, molecular biology and genetic engineering. I have extensive experiences of training undergraduate, pharmacy & medical students, Ph.D. students, postdocs and junior faculty. I also contribute my expertise to the scientific research community by serving as a regular member of the NIH grant review (NAL study section) as well as a research grant advisory board member of Ed and Ethel Moore Alzheimer's Disease Research Program in Florida Health Department. I am a licensed pharmacist (Florida, USA, #PS38968).

B. Positions and Honors

Research Positions and Professional Experience

2000-2005 Research Associate, Neuroscience Laboratory, College of Pharmacy, Florida A&M University (FAMU), Tallahassee, Florida

2001-2005	Adjunct Professor of Organic Chemistry, Department of Chemistry, FAMU
2005-2007	Research Assistant Professor, Division of Neurobiology/Neurotoxicology, Meharry Medical College, Nashville, TN
2007-2010	Assistant Professor, Department of Neurology, Meharry Medical College, Nashville, TN
2007-2013	Adjunct Assistant Professor, Division of Pediatric Toxicology, Vanderbilt University Medical Center, Nashville, TN
2010-2013	Assistant Professor, Department of Physiology, Meharry Medical College, Nashville, TN
2013-2016	Associate Professor, Department of Physiology, Meharry Medical College, Nashville, TN
2013-2016	Adjunct Associate Professor, Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN
2016-present	Professor, Department of Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL

Honors

1984	Outstanding student scholarship, Hyo-Sung University
1997-98	Outstanding graduate student scholarship, Florida A&M University
2010	Scholarship award for Glia meeting, Cold Spring Harbor Laboratory, New York
2015	Exemplary Award, Excellence in Research, Meharry Medical College
2017	Researcher of the year, College of Pharmacy, Florida A&M University

Professional Memberships and Other Experience

1996-Present	Member, Experimental Biology
1996-Present	Member, Society for Neuroscience
2012-Present	Member, Society of Toxicology
2005-Present	Ad-Hoc Reviewer, Journal of Neural Transmission
2007-Present	Ad-Hoc Reviewer, Cell Biology and Toxicology
2008-Present	Ad-Hoc Reviewer, Neuroscience
2012	Ad-Hoc NIH grant reviewer: NAL study section
2015	Ad-Hoc NIH grant reviewer: ONES (Outstanding New Environmental Scientist) award study section
2016	Ad-Hoc NIH grant reviewer: NAL (Neurotoxicology and Alcoholism) study section
2017-2023	Regular Member NIH grant reviewer: (Neurotoxicology and Alcoholism) study section
2017-2020	Advisory board member of Ed and Ethel Moore Alzheimer's Disease Research Program in Florida Health Department

License: A Registered Pharmacist in Florida (License#: PS38968)

C. Contribution to Science

1. Role of phospholipid methylation in Parkinson's disease: my earlier work is to understand the etiology of Parkinson's disease (PD). Excess methylation has been proposed as a mechanism of pathogenesis of PD. I have found that excess methylation of phospholipids resulted in increased production of lyso-phosphatidylcholine that is toxic and produces PD symptoms. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a prodrug to the neurotoxin MPP^+, which causes permanent symptoms of Parkinson's disease, also increased methylation of phospholipids.
    a. **Lee** ES, Chen H, Shepherd KR, Lamango NS, Soliman KF, Charlton CG (2004). Inhibitory effects of lysophosphatidylcholine on the dopaminergic system. Neurochemical Research 2004 29(7):1333-42. PMID: 15202762
    b. **Lee** ES, Soliman KF, Charlton CG (2005). Lysophosphatidylcholine decreases locomotor activities and dopamine turnover rates in rats. Neurotoxicology. 26, 27-38. PMID: 15527871
    c. **Lee** ES, Chen H, Soliman KF, Charlton CG (2005). Effects of homocysteine on the dopaminergic system and behavior in rodents. *Neurotoxicology*. 26, 361-371. PMID:15935208

d. **Lee** ES, Chen H, Charlton CG, Soliman KF. (2005). The role of phospholipid methylation in 1-methyl-4-phenyl-pyridinium ion (MPP^+)-induced neurotoxicity in PC12 cells. *NeuroToxicology* 26, 945-957. PMID:15950286

2. Enhancing effects of estrogens and selective estrogen receptor modulators (SERMs) on expression of astrocytic glutamate transporters (GLAST and GLT-1) which are responsible for preventing excitotoxic neuronal injury in the brain. I have found that estrogenic compounds increased expression of both GLAST and GLT-1 at the transcriptional level by activating the NF-kB and CREB pathways.
    a. **Lee** E, Sidoryk-Wegrzynowicz M, Yin Z, Webb A, Son DS, Aschner M. (2012). Transforming Growth Factor-α Mediates Estrogen-Induced Upregulation of Glutamate Transporter GLT-1 in Rat Primary Astrocytes. *Glia*. 60(7):1024-36. PMID: 22488924.
    b. Karki P, Webb A, Smith K, Lee K, Son DS, Aschner M and **Lee** E (2013). cAMP response element-binding protein (CREB) and nuclear factor κB mediate the tamoxifen-induced up-regulation of glutamate transporter 1 (GLT-1) in rat astrocytes. *J Biol Chem*. 288:28975-86. PMC3789995
    c. Karki P, Webb A, Zerguine A, Choi J, Son DS and **Lee** E (2014). Mechanism of Raloxifene-induced Upregulation of Glutamate Transporter GLT-1 in Rat Primary Astrocytes. *Glia* 62(8):1270-83. PMC4061260
    d. Pajarillo E, Johnson J Jr, Kim J, Karki P, Son DS, Aschner M, **Lee** E (2018). 17β-estradiol and tamoxifen protect mice from manganese-induced dopaminergic neurotoxicity. *NeuroToxicology.* 65:280-288. PMID: 29183790
3. Mechanism of manganese (Mn)-induced repression of astrocytic glutamate transporters at the transcriptional level. I have found that Mn increased expression of transcription factor yin yang 1 (YY1) at transcription level via activating NF-κB pathway. This Mn-enhanced YY1 bound to its consensus sites of the promoter regions of GLT-1 and GLAST, respectively, resulting in repression of both GLT-1 and GLAST, while knockdown of YY1 reversed the Mn effects on these transporters. YY1 also interacted with NF-κB, a main positive regulator of both GLT-1/GLAST, and completely abolished NF-κB's positive effects on these transporters. YY1 also interacted with epigenetic modifier histone deacetylases (HDACs) which acted as co-repressors of YY1 on the regulation of GLT-1 and GLAST.
    a. Karki P, Webb A, Smith K, Johnson Jr. J, Lee K, Son DS, Aschner M and **Lee** E (2014)**.** Yin Yang 1 is a Repressor of EAAT2 and it Mediates Manganese-induced Decrease of EAAT2 Expression in Astrocytes. *Mol Cell Biol*. 34(7):1280-9. PMID: 24469401.
    b. Karki P, Smith K, Johnson Jr. J, Aschner M and **Lee** E (2015). Genetic dys-regulation of astrocytic glutamate transporter EAAT2 and its implications in neurological disorders and manganese toxicity. *Neurochem Res.* 40(2):380-8. PMID: 25064045
    c. Karki P, Johnson J Jr, Son DS, Aschner M, **Lee** E (2017). Transcriptional regulation of human transforming growth factor-α in astrocytes. *Mol Neurobiol.* 54(2):964-976. PMID: 26797516.
    d. Karki P, Hong P, Johnson J Jr, Pajarillo E, Son DS, Aschner M, **Lee** E (2018). Arundic Acid Increases Expression and Function of Astrocytic Glutamate Transporter EAAT1 Via the ERK, Akt, and NF-κB Pathways. Mol Neurobiol. 55(6):5031-50462017. PMID: 28812276.
4. Epigenetic mechanism of Mn-induced repression of astrocytic glutamate transporters. The role of histone deacetylases (HDACs) in Mn-induced repression of astrocytic glutamate transporters has been studied. I have found that inhibitors of HDACs attenuated Mn-induced dopaminergic neurotoxicity as well as reversed Mn-repressed astrocytic glutamate transporters.
    a. Johnson J Jr, Pajarillo E, Taka E, Reams R, Son DS, Aschner M, **Lee** E. (2017). Valproate and sodium butyrate attenuate manganese-decreased locomotor activity and astrocytic glutamate transporters expression in mice. *NeuroToxicology*. 64:230-239. PMID: 28610743.
    b. **Lee E**, Karki P, Johnson J Jr, Hong P, Aschner M (2017). Manganese Control of Glutamate Transporters' Gene Expression. Adv Neurobiol. 16:1-12. PMID: 28828603
    c. Johnson J Jr, Pajarillo E, Karki P, Kim J, Son DS, Aschner M, **Lee** E (2018). Valproic acid attenuates manganese-induced reduction in expression of GLT-1 and GLAST with concomitant changes in murine dopaminergic neurotoxicity. Neurotoxicology. 67:112-120. PMID: 29778792.
5. Roles of proinflammatory chemokines on the progression of cancers: recently, I have been working on cancers in collaboration with other investigators. This research is to define roles of proinflammatory chemokines in the progression of ovarian and breast cancers. We have found that proinflammatory chemokines promote the progression of these cancers by driving an inflammatory burden via NF-κB and EGFR mediated signaling.

a. Ignacio RM, Kabir SM, **Lee** ES, Adunyah SE, Son DS. NF-κB-Mediated CCL20 Reigns Dominantly in CXCR2-Driven Ovarian Cancer Progression. PLoS One. 2016;11(10):e0164189. PMID: 27723802
b. Choi H, Ignacio RMC, **Lee** ES, Roby KF, Terranova PF, Son DS (2017). Localization of Serum Amyloid A3 in the Mouse Ovary. Immune Netw. 17(4):261-268. PMID: 28860955.
c. Ignacio RMC, Dong YL, Kabir SM, Choi H, **Lee** ES, Wilson AJ, Beeghly-Fadiel A, Whalen MM, Son DS (2018). CXCR2 is a negative regulator of p21 in p53-dependent and independent manner via Akt-mediated Mdm2 in ovarian cancer. Oncotarget. 9(11):9751-9765. PMID: 29515768
d. Ignacio RMC, Gibbs CR, **Lee** ES, Son DS. The TGFα-EGFR-Akt signaling axis plays a role in enhancing proinflammatory chemokines in triple-negative breast cancer cells. Oncotarget. 2018 Jun 29;9(50):29286-29303. PMID: 30034618

Pubmed: https://www.ncbi.nlm.nih.gov/sites/myncbi/eun sook.lee.1/bibliography/44072553/public/?sort=date&direction=descending

RESEARCH SUPPORT

Ongoing Research Support

R01 R01 ES024756 08/15/2015 -06/30/2020
Mechanism of manganese-induced impairment of astrocytic glutamate transporters.
The goal of this project is to elucidate the mechanism of manganese (Mn)-induced neurotoxicity via dysregulation of glutamate transporters at the transcriptional level.
Role: PI

R01 Supplement 3R01 ES024756-05S1 07/24/2018 -06/30/2020
The goal of this project is creat a region-specific YY1 knockout mouse by microinjecting recombinant adeno-associated viral (rAAV) vectors that express Cre recombinase using stereotaxic injections into the striatum of YY1-loxP homogenous mice.
Role: PI

U54 U54CA233396 Reams (PI) 09/19/2018 – 08/31/2023
1/3 Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center
The goal of this project is to eliminate cancer health disparities, and will determine the molecular, genetic and epigenetic factors that contribute to the early development of pancreatic ductal adenocarcinoma.
Role: Co-I on the Pilot project

Recently Completed Research Support

SC1 GM089630-01 Lee (PI) 06/10/2010 – 05/31/2017
Estrogen-neuroprotection due to astroglial Glu transporters occurs via TGF-α/β1.
Goal: to elucidate the neuroprotective mechanisms of 17β-estradiol (E2) and selective estrogen receptor modulators (SERMs) and develop strategies for the discovery of suitable SERMs that can be used as neuroprotectants without risks of cancer for women or of feminizing effects for men.
Role: PI

VICTR Pilot grant VR9584 06/01/2014-06/30/2016
Title: Mechanism of Tamoxifen-Induced Suppression of Malignant Brain Tumor Growth by Inhibiting PKC-Dependent Translocation of FGF/FGFR1 to the Nucleus
Goal: to identify the molecular target for the Treatment of Malignant Brain Tumors.
Role: PI