

BIOGRAPHICAL SKETCH

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NAME: Lee, Lu-Yuan

eRA COMMONS USER NAME (credential, e.g., agency login): LU-YUAN.LEE

POSITION TITLE: Fred Zechman Professor of Physiology

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 |
|---|---------------------------|----------------------------|-------------------------|
| National Taiwan University, Taipei | BS | 1969 | Mechanical Engineering |
| University of Mississippi, Jackson, MS | MS | 1972 | Mechanical Engineering |
| University of Mississippi, Jackson, MS | PhD | 1975 | Physiology & Biophysics |
| University of California San Francisco, San Francisco, CA | Postdoctoral Fellow | 1978 | Pulmonary Physiology |

A. Personal Statement

My laboratory has been studying the properties and functions of airway sensory nerves and their regulation of airway functions in health and in diseases with NIH support for more than 35 years. One of our major research focuses is to uncover the transduction mechanisms involved in the airway responses to inhaled irritants; and how their regulatory functions are altered under various pathophysiological conditions.

The vagal bronchopulmonary C-fiber sensory terminals located superficially in the airway mucosa play an important role in defending the lung against inhaled irritants. Stimulation of these sensory endings elicits protective reflex responses such as cough and secretion of mucus. During acute or chronic airway inflammatory reaction (e.g., allergic asthma exacerbation), the excitability of these chemosensitive nerve endings innervating the airways is drastically elevated, which plays a pivotal role in triggering various symptoms of airway hypersensitivity such as airway irritation, excessive coughing, increased airway secretion and bronchial constriction, in these patients.

Several projects are currently conducted in our lab aimed specifically to uncover the underlying mechanisms of hypersensitivity of bronchopulmonary C-fiber neuron induced by certain endogenous chemical mediators and pro-inflammatory cytokines, and to identify the specific ion channels and the signal transduction pathways involved. Ongoing translational studies are also conducted to investigate the role of these nerve endings in the manifestation of these symptoms in patients with various airway inflammatory diseases.

Some of our recent representative publications are listed below:

- Khosravi M, Lin RL, Maskey AP, Pandey S, Lin AH, Lee LY. A distinct difference between air and mucosal temperatures in human respiratory tract. *Front Med (Lausanne)*. 2021 Jul 30;8:650637. PubMed PMID: [34395460](#)
- Lin AH, Hsu CC, Lin YS, Lin RL, Lee LY. Mechanisms underlying the stimulatory effect of inhaled sulfur dioxide on vagal bronchopulmonary C-fibres. *J. Physiol. (London)*. 598(5): 1093-1108, 2020. PubMed PMID: [31891193](#)
- Sun H, Lin AH, Ru F, Patil MJ, Meeker S, Lee LY, Udem BJ. KCNQ/M-channels regulate mouse vagal bronchopulmonary C-fiber excitability and cough sensitivity. *J Clin Invest (Insight)*. 2019 Mar; 4(5):e124467. PubMed PMID: [30721152](#)
- Lin AH, Athukorala A, Gleich GJ, Lee LY. Cough responses to inhaled irritants are enhanced by eosinophil major basic protein in awake mice. *Am J Physiol*. 317(1):R93-R97, 2019. PubMed PMID: [30995073](#)

Complete List of Published Work in My Bibliography:

<http://www.ncbi.nlm.nih.gov/myncbi/lu-yuan.lee.1/bibliography/47994128/public/?sort=date&direction=ascending>

(Google Scholar: h-index: 45; i10-index: 120)

B. Positions and Honors

Positions and Employment

| | |
|--------------|---|
| 1975-1978 | Postdoctoral Fellow, Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA |
| 1978-1984 | Assistant Professor, Department of Physiology and Biophysics, University of Kentucky, Lexington, KY |
| 1984-1992 | Associate Professor, Department of Physiology and Biophysics, University of Kentucky, Lexington, KY |
| 1985-1985 | Visiting Scholar, Department of Physiology & Biophysics, UTMB, Galveston, TX |
| 1992-present | Professor, Department of Physiology and Biophysics, University of Kentucky, Lexington, KY |
| 1992-1992 | Visiting Scholar, Department of Pharmacology, Karolinska Institute, Stockholm |
| 1994-1997 | Director of Research, Department of Physiology, University of Kentucky, Lexington, KY |
| 1997-1997 | Visiting Scientist, Novartis Institute for Medical Sciences, London, UK |
| 1997-2000 | Co-director of Graduate Studies, Department of Physiology, University of Kentucky, Lexington, KY |
| 2004-2012 | Coordinator, University of Kentucky Lung Biology Research Group, Lexington, KY |

Other Experience and Professional Memberships

| | |
|--------------|--|
| 1991-present | Ad Hoc Member, NIH/NHLBI Special Emphasis Panel and various other Study Sections |
| 1992-1995 | Fogarty Senior International Fellowship, NIH |
| 1995-1999 | Regular Member, NIH Respiratory and Applied Physiology Study Section |
| 2005-present | Editorial Board, Journal of Applied Physiology |
| 2007-present | Editorial Board, Respiration Physiology and Neurobiology |
| 2010-present | Editorial Board, Frontiers in Autonomic Neuroscience |
| 2010- | Fellow, Biomedical Engineering Society |
| 2011-present | Editorial Board, Frontiers in Respiratory Physiology |
| 2016- | Fellow, American Physiological Society |

Honors

| | |
|--------------|---|
| 1980-1983 | Young Investigator Research Award, NIH/NHLBI |
| 1983 | Silver Pointer Award (outstanding instructor elected by first-year medical class), University of Kentucky College of Medicine |
| 1994 | Master Teacher Award, University of Kentucky College of Medicine |
| 1996 | Master Teacher Award, University of Kentucky College of Medicine |
| 2000 | Abraham Flexner Master Educator Award, University of Kentucky College of Medicine |
| 2002-present | Fred W. Zechman Endowed Professor of Physiology, University of Kentucky |
| 2004-2020 | Wethington Award for Research, University of Kentucky College of Medicine |
| 2008 | Clinical and Translational Science Mentor Recognition Award, University of Kentucky |
| 2009 | Holsinger Teaching Award, University of Kentucky, Department of Physiology |
| 2014 | Outstanding Achievement Award, 10th Joint Meeting of International Symposium on Respiratory Diseases and ATS |
| 2018 | Golden Podium Award (course co-director, outstanding second year medical course) |
| 2020 | Golden Podium Award (course co-director, outstanding second year medical course) |

C. Contribution to Science

1. Role of vagal bronchopulmonary C-fibers in regulating respiratory functions: My longstanding research interest focuses on the functions and properties of airway sensory nerves. The research conducted in my lab during the last 30+ years has contributed to the existing knowledge about the role of vagal bronchopulmonary C-fibers in regulating various cardiopulmonary functions under both healthy and disease conditions. In particular, our recent investigations have uncovered some of the important mechanisms underlying the heightened activities of these afferents that developed during airway inflammation. These studies ranged from ion channels to human subjects; some representative invited reviews are listed below:

- a. Gu Q, Lee LY. TRP channels in airway sensory nerves. Neurosci Lett. 2021 Mar;748:135719. PubMed PMID: [33587987](#)
- b. Lee LY, Yu J. Sensory nerves in lung and airways (Invited Review). Comprehensive Physiol. 2014 Jan;4(1):287-324. PubMed PMID: [24692141](#).
- c. Gu Q, Lee LY. Airway irritation and cough evoked by acid: from human to ion channel (Invited Review). Curr Opin Pharmacol. 2011 Jun;11(3):238-47. PubMed PMID: [21543258](#).
- d. Burki NK, Lee LY. Mechanisms of dyspnea (Invited Review). Chest. 2010 Nov;138(5):1196-201. PubMed PMID: [21051395](#).

2. Involvement of TRPV1 thermal sensitivity in airway inflammation-induced hypersensitivity: In the last ten years, our research team has carried out a series of studies demonstrating that a slight increase in temperature within the normal physiological range can activate and sensitize bronchopulmonary sensory neurons, and this action is mediated primarily through the thermal-sensitive properties of the transient receptor potential vanilloid type 1 (TRPV1) channels. In addition, we have demonstrated that both the expression and sensitivity of TRPV1 in pulmonary sensory nerves are up-regulated in an animal model of allergic asthma. These novel findings, supported by our more recent studies in patients with asthma and allergic rhinitis, begin to unveil the important role of the TRPV1 thermal sensitivity in the manifestation of various symptoms in airway inflammatory diseases. The current proposal aims to further investigate the possible involvement of TRPV1 as a potential trigger of the pathophysiology during asthma exacerbation.

- a. Hayes D Jr, Collins PB, Khosravi M, Lin RL, Lee LY. Bronchoconstriction triggered by breathing hot humid air in patients with asthma: role of cholinergic reflex. Am J Respir Crit Care Med. 2012 Jun 1;185(11):1190-6. PubMed PMID: [22505744](#); PubMed Central PMCID: [PMC3373066](#).
- b. Lee LY, Gu Q. Role of TRPV1 in inflammation-induced airway hypersensitivity. Curr Opin Pharmacol. 2009 Jun;9(3):243-9. PubMed PMID: [19269247](#); PubMed Central PMCID: [PMC2704095](#).
- c. Ni D, Lee LY. Effect of increasing temperature on TRPV1-mediated responses in isolated rat pulmonary sensory neurons. Am J Physiol Lung Cell Mol Physiol. 2008 Mar;294(3):L563-71. PubMed PMID: [18178674](#).
- d. Zhang G, Lin RL, Wiggers M, Snow DM, Lee LY. Altered expression of TRPV1 and sensitivity to capsaicin in pulmonary myelinated afferents following chronic airway inflammation in the rat. J Physiol. 2008 Dec 1;586(Pt 23):5771-86. PubMed PMID: [18832423](#); PubMed Central PMCID: [PMC2655410](#).

3. Interaction between TRPV1 and transient receptor potential ankyrin type 1 (TRPA1) in Pulmonary Sensory Neurons: TRPA1 and TRPV1 receptors are co-expressed in vagal pulmonary C-fiber sensory nerves. Because both these channels are sensitive to a number of endogenous inflammatory mediators, they are likely activated simultaneously during airway inflammation. In an ongoing series of studies, our research team has reported a distinct potentiating effect induced abruptly by simultaneous activations of TRPA1 and TRPV1 by their respective selective agonists at near-threshold concentrations. This synergistic effect was dependent upon the extracellular Ca²⁺, and totally absent when either the TRPA1 or the TRPV1 agonist was replaced by a non-TRPA1 and non-TRPV1 chemical activator of these neurons, demonstrating the selectivity of the interaction between these two TRP channels. These findings suggest that the TRPA1-TRPV1 interaction may play an important role in regulating the function and excitability of pulmonary sensory neurons during airway inflammation.

- a. Lee LY, Hsu CC, Lin YJ, Lin RL, Khosravi M. Interaction between TRPA1 and TRPV1: Synergy on pulmonary sensory nerves. Pulm Pharmacol Ther. 2015 Aug 14; PubMed PMID: [26283426](#).
- b. Hsu CC, Lee LY. Role of calcium ions in the positive interaction between TRPA1 and TRPV1 channels in bronchopulmonary sensory neurons. J Appl Physiol. 2015 Jun 15;118(12):1533-43. PubMed PMID: [25858491](#); PubMed Central PMCID: [PMC4469923](#).

- c. Lin YJ, Lin RL, Ruan T, Khosravi M, Lee LY. A synergistic effect of simultaneous TRPA1 and TRPV1 activations on vagal pulmonary C-fiber afferents. *J Appl Physiol*. 2015 Feb 1;118(3):273-81. PubMed PMID: [25414245](#); PubMed Central PMCID: [PMC4312849](#).
- d. Hsu CC, Lin RL, Lee LY, Lin YS. Hydrogen sulfide induces hypersensitivity of rat capsaicin-sensitive lung vagal neurons: role of TRPA1 receptors. *Am J Physiol Regul Integr Comp Physiol*. 2013 Oct 1;305(7):R769-79. PubMed PMID: [23842678](#); PubMed Central PMCID: [PMC3798805](#).

4. Airway hypersensitivity induced by eosinophil granule-derived cationic proteins: Eosinophils and other inflammatory cells infiltrate into the airways during anaphylactic reaction and mucosal inflammation. A number of low molecular weight, highly cationic, cysteine/arginine-rich proteins are synthesized and secreted by eosinophils, and play a key role in the mucosal injury and asthma pathogenesis. In a series of studies in collaboration with Dr. Gerald Gleich (Mayo Clinic), we have demonstrated that human eosinophil granule-derived cationic proteins can stimulate vagal bronchopulmonary C-fiber endings, and enhance the excitability of isolated rat vagal pulmonary neurons to capsaicin, proton and ATP by inhibiting the sustained delayed-rectifier voltage-gated K⁺ current and the A-type, fast-inactivating K⁺ current in these sensory neurons. These novel findings have provided new insights into the mechanisms and involvement of vagal bronchopulmonary sensory nerves in the airway hypersensitivity induced by eosinophil infiltration and inflammation.

- a. Lee LY, Gu Q, Lin AH, Khosravi M, Gleich G. Airway hypersensitivity induced by eosinophil granule-derived cationic proteins. *Pulm Pharmacol Ther*. 2019 Aug;57:101804. PubMed PMID: [31096035](#)
- b. Lin AH, Athukorala A, Gleich GJ, Lee LY. Cough responses to inhaled irritants are enhanced by eosinophil major basic protein in awake mice. *Am J Physiol Regul Integr Comp Physiol*. 2019 Apr;317(1):R93-R97. PMID: [30995073](#)
- c. Gu Q, Lim ME, Gleich GJ, Lee LY. Mechanisms of eosinophil major basic protein-induced hyperexcitability of vagal pulmonary chemosensitive neurons. *Am J Physiol Lung Cell Mol Physiol*. 2009 Mar;296(3):L453-61. PubMed PMID: [19136577](#); PubMed Central PMCID: [PMC2660213](#).
- d. Gu Q, Wiggers ME, Gleich GJ, Lee LY. Sensitization of isolated rat vagal pulmonary sensory neurons by eosinophil-derived cationic proteins. *Am J Physiol Lung Cell Mol Physiol*. 2008 Mar;294(3):L544-52. PubMed PMID: [18178677](#).

5. Role of nicotine in airway irritation evoked by cigarette smoke inhalation: Inhaled cigarette smoke causes airway irritation, cough and reflex bronchoconstriction, and is one of the most common inhaled irritants to the human respiratory tract. Our research team has conducted several study series spanning over thirty years in both human subjects and electrophysiological recording of vagal bronchopulmonary sensory nerves and isolated neurons. Our studies have established the first evidence that nicotine is primarily responsible for the airway irritation and coughing caused by cigarette smoke inhalation, and the action is mediated through an activation of nicotinic acetylcholine receptors expressed on the sensory terminals innervating the airway mucosa. This finding has completely changed the previously existing concept in the literature that the irritant effects of cigarette smoke was caused mainly by the particulate matter contained in the smoke.

- a. Lee LY, Lin RL, Khosravi M, Xu F. Reflex bronchoconstriction evoked by inhaled nicotine aerosol in guinea pigs: role of the nicotinic acetylcholine receptor. *J Appl Physiol*. 2018 Jul;125(1):117-123. PubMed PMID: [29369741](#)
- b. Khosravi M, Lin RL, Lee LY. Inhalation of Electronic Cigarette Aerosol Induces Reflex Bronchoconstriction by Activation of Vagal Bronchopulmonary C-fibers. *Am J Physiol Lung Cell Mol Physiol*. 2018 Oct;315(4):L467-L475. PubMed PMID: [29847989](#)
- c. Lee LY, Gu Q. Cough sensors. IV. Nicotinic membrane receptors on cough sensors. *Handb Exp Pharmacol*. 2009; PubMed PMID: [18825337](#).
- d. Xu J, Yang W, Zhang G, Gu Q, Lee LY. Calcium transient evoked by nicotine in isolated rat vagal pulmonary sensory neurons. *Am J Physiol Lung Cell Mol Physiol*. 2007 Jan;292(1):L54-L61. PubMed PMID: [16920888](#)

D. Research Support

Ongoing Research Support

MISP# 100107

Merck Sharp & Dohme

Lee, Lu-Yuan (PI)

09/29/21-09/28/23

This research project aims to investigate the role of the P2X3 receptor expressed in airway sensory nerves in the cough hypersensitivity to inhaled irritants induced by allergic airway inflammation.

Role: PI

P30 ES026529-04S1

Hahn/Lee (MPI)

09/17/20-03/31/22

National Institute of Environmental Health Sciences

Administrative Supplement Grant for "Center for Appalachian Research in Environmental Sciences"

This study aims to investigate the stimulatory effect of inhaled SO₂ on vagal bronchopulmonary C-fibers and its role in the pulmonary defense function against inhaled irritants.

Role: PI

U01 AI123832-01 (NCE)

Lee, Lu-Yuan (PI)

01/15/16-12/31/20

National Institute of Allergy and Infectious Diseases

Role of TRPV1 in asthma exacerbation.

This study aims to investigate: if both the thermal sensitivity and the TRPV1 expression are enhanced in pulmonary sensory neurons by chronic airway allergic inflammation; and if the airway temperature is elevated in asthmatics during the allergic inflammatory reaction.

Role: PI

UL1TR001998

Lee & Khosravi (Co-PIs)

12/15/19-12/31/21

NIH/NCATS / Center for Clinical and Translational Science (CCTS)

CTSA Pilot Project: Assessing effects of electronic cigarettes on airway function in asthma.

This grant was awarded by the University of Kentucky CCTS funded by the NIH National Center for Advancing Translational Sciences to support a pilot study of the pulmonary effects of inhaling e-cigarettes on the airway functions in patients with asthma.

Role: Co-PI

R25 GM125680-01

Frazier (PI)

09/01/18-08/31/23

National Institute of General Medical Sciences

Interactive Mentoring to Enhance Research Skills (IMERS)

This IMERS Project aims to organize workshops and provide innovative trainings for the minority college faculty members in the preparation of competitive grant applications and research proposals.

Role: Co-investigator

T32 GM118292-01A1

Smith Bret (PI)

07/01/2017-06-30/22

National Institute of General Medical Sciences

Graduate Training in Integrative Physiology

To fund training for PhD students studying integrative aspects of physiology at the behavioral, systems, cellular, and molecular levels.

Role: Faculty Mentor

Completed Research Support

R01 HL96914

Lee, Lu-Yuan (PI)

09/01/09-12/31/17

National Heart, Lung and Blood Institute

Role of TRPV1 in Airway Hypersensitivity Induced by Allergic Inflammation

This project aimed to determine whether the airway hypersensitivity caused by allergic inflammation results from increased excitability of the bronchopulmonary C-fiber sensory nerves in an animal model of asthma.

Role: PI

R01 AI123832-Administrative Supplement

Lee, Lu-Yuan (PI)

08/05/16-12/31/17

National Institute of Allergy and Infectious Diseases

Role of TRPV1 in asthma exacerbation.

This administrative supplement provides additional funds to support the hiring of a Clinical Research Coordinator to join our clinical study on role of TRPV1 and asthma exacerbation using the technique of the segmental bronchoprovocation with allergen in patients with asthma.

Role: PI