**BIOGRAPHICAL SKETCH**

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| NAME<br>Li, Xiang-An | POSITION TITLE<br>Professor |
|---|---|
| eRA COMMONS USER NAME<br>xiang-an.li | |

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 |
|---|---|---|---|
| Shandong University, China | B.S. | 1978-1982 | Chemistry |
| Shandong University, China | M.S. | 1982-1985 | Microbiology |
| Osaka University School of Medicine, Japan | Ph.D. | 1991-1994 | Biochemistry |
| National Cardiovascular Center, Japan. | Postdoc | 1998-2000 | Molecular Biology |
| University of Kentucky College of Medicine, Kentucky | Postdoc | 2000-2000 | Molecular/Cell Biology |

## A. Personal Statement

I have been studying scavenger receptor BI (SR-BI) and HDL, and focused on the roles of SR-BI and HDL in sepsis. I am a pioneer in this field first reporting that SR-BI is a critical protective factor in sepsis.

## B. Positions and Honors:

### Positions

| | |
|---|---|
| 1985-1986 | Research fellow, Department of Biochemistry, Taishan Medical College, China |
| 1987-1991 | Assistant Professor, Department of Biochemistry, Taishan Medical College, China |
| 1994-1997 | Professor, Department of Biochemistry, Taishan Medical College, China |
| 2000-2004 | Research associate, Department of Pediatrics/Physiology, University of Kentucky College of Medicine |
| 2004-2005 | Research assistant professor, Department of Pediatrics, University of Kentucky College of Medicine |
| 2006-2011 | Assistant Professor, Department of Pediatrics, University of Kentucky College of Medicine |
| 2008 - | Full member, Nutritional Sciences Center, University of Kentucky College of Medicine |
| 2013 - | Core member, Saha Cardiovascular Research Center, University of Kentucky College of Medicine |
| 2011-2016 | Associate Professor, Department of Pediatrics, University of Kentucky College of Medicine |
| 2016 - 2017 | Professor, Department of Pediatrics and Saha Cardiovascular Research Center, University of Kentucky College of Medicine |
| 2017 - | Professor, Department of Physiology and Saha Cardiovascular Research Center, University of Kentucky College of Medicine |

2017 - Director, HDL Receptor Laboratory, Saha Cardiovascular Research Center, University of Kentucky College of Medicine

### Professional Memberships

2000-2010 Member, American Heart Association (AHA)
2010-present Fellow, AHA (FAHA)
2001-present Member, American Society of Cell Biology
2009-present Member, Society of Critical Care Medicine
2011-present Member, Society for Leukocyte Biology
2014-present Member, Shock Society

### Honors

1995 National Outstanding Young Investigator Award, Department of Education of China
2009 Irvine H. Page Young Investigator Award, Council of Arteriosclerosis, Thrombosis and Vascular Biology, American Heart Association
2013 Mid-Career Investigator Award, Council of Peripheral Vascular Disease, American Heart Association

### Other Experiences

2010-present Editorial Board member, Journal of Nutritional Biochemistry
2009 Reviewer, NIH, Challenge Grants Panel Vascular and Hematology
2009 Reviewer, NIH, Challenge Grants Panel # 23
2009-2015 Reviewer, Italian Ministry of Health
2013-present Member, Lipids BSc2 study section, American Heart Association
10/2014 *ad hoc* reviewer, NIH SAT study section (Surgery, Anesthesiology and Trauma)
02/2015 *ad hoc* reviewer, NIH SAT study section (Surgery, Anesthesiology and Trauma)
10/2015 *ad hoc* reviewer, NIH SAT study section (Surgery, Anesthesiology and Trauma)
2016 Reviewer, MRC (Medical Research Council, UK)
05/2018 reviewer, ZRG1 BCMB-A (51) R RFA: NIH Transformative Research Awards (R01) Review

## C. Contributions to Science

My research focuses on the role of scavenger receptor BI (SR-BI) and high density lipoprotein (HDL) in sepsis. I am a leading investigator in this field.

**1. Identify SR-BI as a novel protective factor in sepsis in mice and establish SR-BI null mice as a relative adrenal insufficiency model -** I am a pioneer in the study of the role of SR-BI in sepsis. SR-BI is a well-established HDL receptor. It mediates intracellular cholesterol uptake from HDL which plays a key role in reducing cholesterol levels in circulation. Using endotoxemia and cecal ligation and puncture (CLP) sepsis models, my laboratory first identified SR-BI as a protective factor in sepsis. Numerous studies including ours further demonstrated that SR-BI protects against sepsis through multiple mechanisms, including preventing nitric oxide-induced toxicity, promoting LPS clearance, modulating LPS-TLR4 signaling and regulating corticosteroid production. Importantly, a number of laboratories including ours found that mice deficient in SR-BI fail to generate inducible glucocorticoid (iGC) in response to ACTH or septic stress, establishing SR-BI null mice as a relative adrenal insufficiency model. Using this unique animal model, we demonstrated, for the first time, that supplementation of GC benefits septic mice with adrenal insufficiency but harms septic mice without

adrenal insufficiency. Our study provide a “proof of concept” that GC therapy should be selectively used for septic individual with (but not without) relative adrenal insufficiency. Our long term goal is to translate the mechanistic study into improving GC therapy of septic patients.

**a**. **Li XA***, Guo L, Asmis R, Nikolova-Karakashian M, Smart EJ: Scavenger receptor BI prevents nitric oxide-induced cytotoxicity and endotoxin-induced death. *Circ Res* 2006, 98:e60-5.
**b**. Guo L, Song Z, Li M, Wu Q, Wang D, Feng H, Bernard P, Daugherty A, Huang B, **Li XA***: Scavenger Receptor BI Protects against Septic Death through Its Role in Modulating Inflammatory Response. *J Biol Chem* 2009, 284:19826-34. PMC2740408
**c**. Guo L, Zheng Z, Ai J, Huang B and **Li XA*.** Hepatic scavenger receptor BI protects against polymicrobial-induced sepsis through promoting LPS clearance in mice. *J Biol Chem* 2014; 289: 14666-14673. PMC4031522.
**d**. Ai J, Guo L, Zheng Z, Wang SX, Huang B and **Li XA*.** Corticosteroid therapy benefits septic mice with adrenal insufficiency but harms septic mice without adrenal insufficiency. *Critical Care Medicine* 2015; 43:e490-8.

**2. Establish low HDL as a risk factor for sepsis and develop synthetic HDL for sepsis therapy -** I am a leading scientist in the study of the role of HDL in sepsis. Septic patients have low HDL levels, which is associated with a poor prognosis. However, whether low HDL is a cause of septic death or simply a marker of sepsis remains unclear. Using ApoA-I knockout mice as a HDL-deficient animal model, we demonstrated that a deficiency of ApoA1 leads to a significant decrease in survival in CLP-induced sepsis. We further demonstrated that HDL has multiple protective roles in CLP-induced sepsis: in addition to its well-established role in neutralization of LPS, HDL exerts its protection against sepsis through promoting LPS clearance, modulating corticosterone production and leukocyte recruitment, and regulating thymocyte apoptosis. Combined with the earlier clinical findings, our study reveals low HDL as a risk factor of sepsis and supports efforts to raise HDL levels as a therapeutic approach for sepsis. We recently obtained a new R01 funding to study the role of synthetic HDL in sepsis. Our long term goal is to develop synthetic HDL for sepsis therapy and for the treatment of other inflammatory diseases.

**a**. Feng H and **Li XA***. Dysfunctional HDL. *Curr Opin Endocrinol Diabetes Obese* 2009; 16:156-162. PMC3065374
**b**. Guo L, Ai J, Zheng Z, Deborah AH, Daugherty A, Huang B and **Li XA***. HDL protects against polymicrobial-induced sepsis in mice. *J Biol Chem* 2013; 288:17947-17953. PMC3689940.
**c**. Guo L, Zheng Z, Ai J, Deborah AH, Mittelstadt PR, Thacker S, Daugherty A, Ashwell JD, Remaley A and **Li XA***. Scavenger receptor BI and HDL regulate thymocyte apoptosis in sepsis. *Arterioscler Thromb Vasc Biol* 2014; 34: 966-975. PMC4010389
**d**. Morin E, Guo L, Schwendeman A, and **Li XA***. HDL in sepsis - risk factor and therapeutic approach. *Front. Pharmacol.* 2015; 6: 244. doi:10.3389/fphar.2015.00244

**3. Identify SR-BI as a novel regulator of autoimmune disease -** My laboratory first reported that mice deficient in SR-BI and impaired T cell homeostasis. We further showed that the aged SR-BI null develop autoimmune disease.

**a**. Feng H, Guo L, Wang D, Gao H, Hou G, Zheng Z, Ai J, Forman O, Daugherty A and **Li XA*.** Impaired lymphocyte homeostasis and autoimmune disorder in mice deficient in HDL receptor SR-BI. *Arterioscler Thromb Vasc Biol* 2011; 31: 2543-2551. PMC3220294
**b**. Zheng Z, Ai J and **Li XA*.** Scavenger receptor BI and immune dysfunctions. *Curr Opin Endocrinol Diabetes Obese* 2014; 21: 121-128.

**Complete List of Published Work in MyBibliography:**

http://www.ncbi.nlm.nih.gov/sites/myncbi/xiang-an.li.1/bibliography/41165489/public/?sort=date&direction=descending

## D. Research Support

### Ongoing Research Support

1. R01GM113832 Li (MPIs, Contact PI) 01/01/2015 – 11/30/2019
Synthetic HDL_a potential sepsis therapy
The goal of this grant is to understand mechanism(s) of sHDL vascular protection, and to tailor the sHDL composition and treatment regimen specifically for sepsis.

2. 1R01GM121796 Li (PI) 09/01/2017 – 08/31/2021
Mechanism of adrenal insufficiency as a risk factor for sepsis
The goal of this project is to elucidate the role of adrenal insufficiency in sepsis.

3. 1R01HL142640 ZY LI (PI, XA Li Co-I) 04/01/2019 – 03/31/2023
Inflammasome activation triggers systemic coagulation in sepsis
The goal of this project is to assess the mechanism of how Inflammasome activation triggers systemic coagulation in sepsis.

### Completed Research Support

1. R01GM085231 Li (PI) 08/2008 – 05/2015
Role of SR-BI in LPS detoxification
The goal of this project is to determine the mechanism underlying SR-BI protection against LPS toxicity in sepsis.

2. R01GM085231-02S1 Li (PI) 08/2009 – 08/2012
Role of SR-BI in LPS detoxification
The goal of this supplemental project is to determine the role of SR-BI in adaptive immunity in sepsis, to backcross SR-BI null mice to C57BL/6J background and to generate loxP-SR-BI mice.

3. R01GM085231-05S1 Li (PI) 09/2012 – 05/2015
Role of SR-BI in LPS detoxification
The goal of this supplemental project is to determine the role of SR-BI in adaptive immunity in sepsis.