BIOGRAPHICAL SKETCH

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NAME: Yu, Liqing

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

POSITION TITLE: Professor

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
Hubei Medical University at Xianning, Hubei, China	M.D.	1985	Medicine
The Third Military Medical University, Chongqing, China	Master of Pathology	1988	Pathology
Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China	Ph.D.	1995	Molecular and pathological basis of atherosclerosis
University of Alberta School of Medicine, Alberta, Canada	Postdoc.	1996-1998	Lipid metabolism
University of Texas Southwestern Medical Center, Dallas, Texas	Postdoc.	1998-2000	Lipid metabolism

A. Personal Statement

My long-term goal is to identify the molecular mechanisms underlying lipid metabolism and transport and to define how these mechanisms influence the pathogenesis of common diseases, such as obesity, insulin resistance, diabetes, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases. I have a broad background in biomedicine through clinical practice (Pathologist and Cardiologist) and basic research. I completed my postdoctoral training first in the lipid and lipoprotein group at the University of Alberta in Canada with Dr. Luis B. Agellon and later in the Department of Molecular Genetics at UT Southwestern Medical Center in Dallas with Dr. Helen H. Hobbs. In 2004 I started my own lab at Wake Forest University School of Medicine, working on the role of NPC1L1 in cholesterol transport and metabolic disease, and recently on the role of intracellular lipid droplet lipolysis in the pathogenesis of metabolic disorders. I singlehandedly created several transgenic and knockout mouse models, and served as the Director of the Institutional Transgenic Mouse Core Facility at Wake Forest University School of Medicine for more than 7 years, demonstrating my strong background on molecular biology, genetics and genetic manipulations of mice. In 2005, I started teaching students the advanced topics of Molecular and Cell Biology as well as Lipid Metabolism first at Wake Forest and later at University of Maryland, which ensures timely update of my knowledge in these areas. As a core faculty in the Georgia State University's Center for Molecular and Translational Medicine, and now in the Division of Endocrinology, Diabetes and Nutrition at University of Maryland School of Medicine, I have close interactions with colleagues who share common research interests. These daily intellectual exchanges secure successful completion of our research projects.

B. Positions and Honors

Positions and Employment

1988-1990 Assistant Professor, Department of Pathology, The Third Military Medical University, China
1990-1992 Medical Residency, Department of Cardiology, Southwestern Hospital, China
1995-1996 Attending Doctor and Lecturer, Department of Cardiology, Southwestern Hospital, China
2000-2001 Assistant Instructor, Department of Molecular Genetics, UT Southwestern Medical Center
2001-2004 Instructor, Department of Molecular Genetics, UT Southwestern Medical Center, Dallas, TX
2004-2011 Assistant Professor, Departments of Pathology and Biochemistry, Wake Forest University

Health Sciences, Winston-Salem, NC
2004-2011(July 31) Director, The Transgenic Mouse Core Facility, Wake Forest University Health Sciences,
2011(July 1)-2011 (July 31) Associate Professor, Department of Biochemistry, Wake Forest University Health Sciences, Winston-Salem, NC
2011-2016 Associate Professor with tenure, Department of Animal & Avian Sciences, University of Maryland, College Park, MD; Department of Biochemistry & Molecular Biology (Joint), University of Maryland School of Medicine, Baltimore, MD
2016-2018 Professor with tenure, Center for Molecular and Translational Medicine, Institute for Biomedical Sciences, Georgia State University, Atlanta, GA
2018-present Professor with tenure, Department of Medicine Division of Endocrinology, Diabetes & Nutrition, University of Maryland School of Medicine, Baltimore, MD

Other Experience and Professional Memberships

2004- Members of ASBMB and AHA
2009 – 2011: Action Medical Research United Kingdom – Ad hoc reviewer
2012: NIH EMNR-IRG Ad hoc reviewer (February); NIH IPOD Study Section, Temporary Reviewer (June); NIH EMNR-IRG Ad hoc reviewer (July); NIH EMNR-IRG Ad hoc reviewer (October)
2013 NIH IPOD Study Section, Temporary Reviewer (February)
2014 NIH R13 Special Emphasis Panel (February); NIH IPOD Study Section, Temporary Reviewer (February); NIH ZRG1EMNR-Q 50 Study Section (Nutrigenetics & Nutrogenomics) (July 9); NIH R13 Special Emphasis Panel (August); NIH HBPP Study Section, Temporary Reviewer (October 20-21)
2015 NIH IPOD Study Section, Temporary Reviewer (February 26-27); NIH ZRG1EMNR-V (55) R Study Section (Nutrigenetics & Nutrogenomics) (July 8); NIH HBPP Study Section (Oct. 19-20)
2016 NIH (IPOD Study Section, R13 Special Emphasis Panel, and Diabetic Complications Consortium); NIH MCE Study Section (Oct. 6-7)
2017 NIH MCE Study Section (Feb. 8-9), HBPP Study Section (Feb. 23-24), SCORE Study Section (Jun. 23), Temporary Reviewer
2017 Standing Member of NIH MCE Study Section (since July 1)

Honors

1988 Chinese Association of Cell Biology Award
1997 Ministry of Education of the People's Republic of China Award
2006 David L. Williams Memorial Lectureship Award, 2006 Aspen Lipid Conference
2006 Consultant, Merck & Co.

C. Contribution to Science

1. Discovery of the molecular mechanism responsible for hepatobiliary cholesterol secretion, a major pathway governing whole-body cholesterol homeostasis--While working in the laboratory of Dr. Helen Hobbs at UT Southwestern Medical Center in Dallas, I established transgenic and knockout mouse lines for ATP-binding cassette transporter G5 (ABCG5) and ABCG8, and demonstrated that the heterodimer of ABCG5/ABCG8 is the bona fide cholesterol transporter that is essential for secretion of cholesterol and noncholesterol sterols from hepatocytes into bile. Hepatocytes secrete three major lipids into bile: phospholipids, bile acids, and free cholesterol. It had been shown before our discovery that hepatocytes secrete phospholipids and bile acids into bile through ABCB4 and ABCB11, respectively. Thus, our findings closed a knowledge gap. Our findings also led to the best treatment for sitosterolemia, a genetic disease associated with premature coronary heart disease due to mutations in either ABCG5 or ABCG8.

a. Berge K.E., Tian T., Graf G.A., **Yu L.**, Grishim N.V., Schultz J., Kwiterovich P., Shan B., Barnes R., and Hobbs H.H. Accumulation of Dietary Cholesterol in Sitosterolemia Caused by Mutations in Adjacent ABC Transporters. **Science** 2000; 290:1771-1775
b. **Yu L.**, Hawkins J-L, Hammer R.E., Berge K.E., Horton J.D., Cohen J.C., and Hobbs H.H. Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol. **J. Clin. Invest.** 2002; 110: 671-680
c. **Yu L.**, Hammer R.E., Hawkins J-L, von Bergmann K., Lutjohann D., Cohen J.C. and Hobbs H.H. Disruption of *Abcg5* and *Abcg8* in mice reveals their crucial role in biliary secretion of cholesterol. **Proc. Natl. Acad. Sci. USA** 2002; 99:16237-16242

d. **Yu L.**, Gupta S., Xu F., Liverman A., Moschetta A., Mangelsdorf D., Repa J., Hobbs H.H., and Cohen J.C. Expression of ABCG5 and ABCG8 is required for regulation of biliary cholesterol secretion. **J. Biol. Chem.** 2005; 280:8742-8747

2. Discovery of liver as another target of ezetimibe, an intestinal cholesterol absorption inhibitor--The tissue distribution of NPC1L1 expression differs among species. Rodents express only a negligible amount of NPC1L1 in liver. In contrast, human livers have readily detectable levels of NPC1L1 mRNA and protein. My laboratory did the first study on NPC1L1 function in liver and for the first time demonstrated that liver is another site of ezetimibe action. Our studies also uncovered a novel mechanism responsible for biliary cholesterol excretion. Whereas ABCG5/G8 functions in liver to transport cholesterol out to bile, NPC1L1 inhibits ABCG5/ABCG8-mediated biliary cholesterol secretion. As a result, inhibition of hepatic NPC1L1 by ezetimibe may raise biliary cholesterol concentrations, which raised an important question: does ezetimibe increase biliary cholesterol concentrations in humans? Millions of people are taking ezetimibe. If the drug increases biliary cholesterol concentrations in humans, it may promote gallstone formation, particularly in individuals expressing more NPC1L1 in liver than intestine.

a. Temel, R.E., Tang W., Ma Y, Rudel L.L, Willingham M.C., Ioannou Y.A., Davies J.P., Nilsson L-M, and **Yu L.** Hepatic Niemann-Pick C1-Like 1 regulates biliary cholesterol concentration and is a target of ezetimibe. **J. Clin. Invest.** 2007; 117:1968-1978
b. Tang W, Jia L, Ma Y, Xie P, Haywood J, Dawson PA, Li J, and **Yu L.** Ezetimibe restores biliary cholesterol excretion in mice expressing Niemann-Pick C1-Like 1 only in liver. **BBA-MCBL**. 2011; 1811: 549-555
c. Betters JL and **Yu L.** Transporters as drug targets: discovery and development of an NPC1L1 inhibitor. **Clin. Pharm. & Ther.** 2010; 87:117-121
d. Jia L, Betters JL, and **Yu L.** Niemann-Pick C1-Like 1 Protein in Intestinal and Hepatic Cholesterol Transport. **Ann. Rev. of Physiol.** 2011; 73: 239-259

3. Discovery of cholesterol-regulated trafficking of Niemann-Pick C1-Like 1 (NPC1L1) protein, a cholesterol transporter essential for intestinal cholesterol absorption and the molecular target of cholesterol-lowering drug ezetimibe--My laboratory was the first to demonstrate that the subcellular localization of NPC1L1 protein is regulated by cellular cholesterol availability and cell polarity, which explains why both cell surface and intracellular locations are observed for NPC1L1 protein. **In addition**, my laboratory was the first to show that cholesterol-regulated trafficking of NPC1L1 is coupled to its cholesterol-transporting ability. These findings have shed light on, and laid the foundation for further exploration of, the cellular and molecular mechanisms underlying NPC1L1-dependent cholesterol transport and its inhibition by drugs such as ezetimibe, an intestinal cholesterol absorption inhibitor that is widely prescribed clinically to low blood cholesterol. Furthermore, my laboratory was the first to establish an *in vitro* assay for measuring ezetimibe-sensitive NPC1L1-dependent cholesterol uptake, which was used to screen new NPC1L1 inhibitors by pharmaceutical companies, including Merck & Co.

a. Yu L. (**also the only corresponding author**), Bharadwaj, S., Brown, J.M., Ma, Y., Du, W., Davis, M.A., Michaely, P., Liu, P., Willingham, M.C., and Rudel, L.L. Cholesterol-regulated translocation of Niemann-Pick C1-Like 1 to the cell surface facilitates free cholesterol uptake. **J. Biol. Chem.** 2005; 281:6616-6624
b. Brown J.M., Rudel L.L., and **Yu L.** Niemann-Pick C1-Like 1 (NPC1L1) mediates sterol-specific unidirectional transport of unesterified cholesterol in McArdle-RH7777 hepatoma cells. **Biochem. J.** 2007; 406 (2):273-283
c. Petersen NH, Faergeman NJ, **Yu L**, and Wustner D. Kinetic imaging of NPC1L1 and sterol trafficking between plasma membrane and recycling endosomes in hepatoma cells. **J. Lipid. Res.** 2008; 49(9):2023-2037
d. **Yu L.** The structure and function of Niemann-Pick C1-Like 1 protein. **Curr. Opin. Lipidol.** 2008; 19(3):363-369

4. Demonstration of important roles of CGI-58 in regulating the pathogenesis of common metabolic disorders—My laboratory for the first time used CGI-58 antisense oligonucleotides (ASOs) to knock down CGI-58 in a few tissues and observed profound effects of CGI-58 knockdown in adult mice on glucose tolerance, insulin sensitivity and fatty liver. Using the conditional CGI-58 knockout mouse line we created, we demonstrated that liver CGI-58 deficiency directly causes advanced non-alcoholic fatty liver disease (NAFLD), including simple steatosis, nonalcoholic steatohepatitis (NASH) and hepatic fibrosis even in mice on a regular chow diet. This is the first animal model that shows the full spectrum of NAFLD pathologies in the absence of aggressive dietary

manipulations. Additionally, our studies with CGI-58 deletion in intestine, macrophages and muscle uncovered an unexpected role of CGI-58 in regulating cellular and/or whole-body cholesterol homeostasis in addition to intracellular triglyceride balance, glucose metabolism, insulin sensitivity and inflammation. Our studies on adipose CGI-58 have established a new paradigm for the role of adipose lipid droplet lipolysis in thermoregulation and metabolic health.

a. Brown J.M., Chung S., Das A., Shelness G., Rudel L.L., and **Yu L.** CGI-58 facilitates mobilization of cytoplasmic triglyceride for lipoprotein secretion in hepatoma cells. **J. Lipid Res.** 2007; 48:2295-2305; Brown JM, Betters JL, Lord C, Ma Y, Han X, Yang K, Alger HM, Melchior J, Sawyer J, Shah R, Wilson MD, Liu X, Graham MJ, Lee R, Crooke R, Shulman GI, Xue B, Shi H, and **Yu L.** CGI-58 knockdown in mice causes hepatic steatosis but prevents diet-induced obesity and glucose intolerance. **J. Lipid Res.** 2010; 51, 3306-3315
b. Guo F, Ma Y, Kadegowda AK, Xie P, Liu G, Liu X, Miao H, Ou J, Su X, Zheng Z, Xue B, Shi H, and **Yu L.** Deficiency of Liver Comparative Gene Identification-58 (CGI-58) Causes Steatohepatitis and Fibrosis in Mice. **J. Lipid Res.** 2013; 54, 2109-2120
c. Miao H, Ou J, Ma Y, Guo F, Yang Z, Wiggins M, Liu C, Song W, Han X, Wang M, Cao Q, Chung BH, Yang D, Liang H, Xue B, Shi H, Gan L and **Yu L**. Macrophage CGI-58 deficiency activates ROS-inflammasome pathway to promote insulin resistance in mice. **Cell Rep.** 2014; 7(1):223-235
   Xie P, Kadegowda AK, Ma Y, Guo F, Han X, Wang M, Groban L, Xue B, Shi H, Li H and **Yu L.** (2015) Muscle-specific deletion of comparative gene identification-58 (CGI-58) causes muscle steatosis but improves insulin sensitivity in male mice. **Endocrinology** 2015; 156(5):1648-1658
d. Shin H, Shin H, Ma Y, Chanturiya T, Cao Q, Wang Y, Kadegowda AKG, Jackson R, Rumore D, Xue B, Shi H, Gavrilova O, and **Yu L**. Lipolysis in Brown Adipocytes Is Not Essential for Cold-Induced Thermogenesis in Mice. **Cell Metabolism** 2017; 26(5):764-777

5. Discovery of a cancer-suppressing role of intracellular fat lipolysis in the development and progression of colorectal cancer--CGI-58 (also known as Abhd5) is a lipid droplet-associated protein and ubiquitously expressed. In vitro studies have shown that CGI-58 activates intracellular triglyceride hydrolysis. Mutations in human CGI-58 causes an inherited disease called Chanarin-Dorfman syndrome that is characterized by scaly dry skin and cytosolic lipid droplet accumulation in almost all cell types. My laboratory is among the first groups working on CGI-58. We demonstrated that CGI-58 limits intracellular lipid accumulation by inhibiting triglyceride catabolism, not by increasing lipid synthesis. Since global CGI-58 knockout mice die neonatally due to defective skin barrier functions, we created a CGI-58-floxed mouse line. Intestine-specific CGI-58 knockout causes lipid droplet accumulation in enterocytes as a result of inhibition of lipid droplet hydrolysis. We found that CGI-58 deletion in the intestine of Apc(Min/+) mice, an animal model of colorectal cancer, promotes intestinal carcinogenesis and the malignant transformation of intestinal adenomatous polyps. Mechanistically we demonstrated that CGI-58 deficiency in colorectal cancer cells induces epithelial-mesenchymal transition (EMT) by suppressing the AMPKα-p53 pathway, which is attributable to increased aerobic glycolysis. In human colorectal cancer, CGI-58 expression falls substantially and correlates negatively with malignant features. Our findings are the first to link a lipolytic activator to colorectal cancer pathogenesis and suggest that one mechanism for cancer cells to develop aerobic glycolysis is by suppressing CGI-58-mediated intracellular fat lipolysis, which opened a new direction in the field.

a. Ou J, Miao H, Ma Y, Guo F, Deng J, Wei X, Zhou J, Xie G, Shi H, Xue B, Liang H and **Yu L.** Loss of Abhd5 (CGI-58) promotes colorectal tumor development and progression by inducing aerobic glycolysis and epithelial-mesenchymal transition. **Cell Rep.** 2014; 9(5):1798-1811.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/liqing.yu.1/bibliography/41162508/public/?sort=date&direction=ascending

D. Research Support
Ongoing Research Support
R01 (NIH/NIDDK) 07/18/2016—06/30/2020
Cellular and Molecular Mechanisms of Fatty Liver Disease
The major goal of this project is to identify the cellular and molecular bases for nonalcoholic fatty liver disease (NAFLD) progression using a novel mouse model that develops NASH and hepatic fibrosis on regular chow.
Role: PI

AHA (Grant-in-Aid) 07/01/2017—06/30/2019
Macrophage Triglyceride Hydrolysis and Atherosclerosis
The major goal of this project is to determine whether deficiency of lipid droplet lipolysis in macrophages influences atherogenesis in apoE knockout mice.
Role: PI

ADA 1-18-IBS-346 01/01/2018—12/31/2020
Brown fat lipolysis deficiency-induced thermoregulation and metabolic adaptation
The major goal of this project is to examine the effects of brown fat CGI-58 gene deficiency on thermogenesis and energy metabolism.
Role: PI

R01 (NIH/NIDDK) 06/15/2018 – 05/31/2022
The Role of Adipose Lipolysis in Thermoregulation
The major goal of this project is to molecularly define how adipose lipolysis regulates thermogenesis and metabolic health under different environmental and nutritional conditions.
Role: PI

R01 (NIH/NIDDK) 05/25/2018 – 04/30/2022
Epigenetic programming of beta-klotho in non-alcoholic fatty liver disease
The major goal of this project is to define how FGF21 resistance occurs and promotes fatty liver during chronic overnutrition.
Role: Co-I

Pending Support
R01 (NIH/NIDDK) 04/01/2019 – 03/30/2024
Coactivator regulates hepatic lipid metabolism and insulin signaling in obesity
The major goal of this project is to molecularly define how P300 coactivator regulates the pathogenesis of fatty liver and insulin resistance.
Role: Co-PI (Lead PI: Ling He at Johns Hopkins)

Completed Research Support
R01 (NIDDK) 04/01/2010-- 09/30/2016
NPC1L1 and Metabolic Diseases
The major goal of this project is to define how deficiency of a cholesterol transporter named NPC1L1 protects mice from high fat diet-induced obesity, glucose intolerance and insulin resistance.
Role: PI

Hisun Pharm (Industry) Grant 06/15/2013—06/14/2015
Hisun Pharm compound HS-25 and NPC1L1-dependent cholesterol absorption
The major goal of this project is to test whether HS-25 is an inhibitor of NPC1L1-depedent cholesterol absorption
Role: PI

Scientist Development Grant 07/01/2006 – 06/30/2010
American Heart Association
Ezetimibe modification of hepatic Niemann-Pick C1-Like 1 function
The major goal of this project is to determine whether ezetimibe inhibits hepatic NPC1L1
Role: PI

ZETIA/VYTORIN Investigator-Initiated Studies 011/01/2008-10/31/2010
Merck, Co.
The role of hepatic NPC1L1 and ezetimibe in reverse cholesterol transport
The major goal of this project is to determine whether hepatic NPC1L1 inhibits reverse cholesterol absorption
Role: PI

ZETIA/VYTORIN Investigator-Initiated Studies 08/01/2008-07/31/2010
Merck, Co.
Effects of intestinal overexpression of NPC1L1 on cholesterol metabolism
The major goal of this project is to genetically demonstrate a critical role of intestinal cholesterol absorption in production of atherogenic lipoprotein-cholesterol.
Role: PI

Pfizer Pharmaceuticals Atorvastatin Research Award 07/01/2005 – 06/30/2006
Pfizer, Co.
Role of the sterol-sensing domain in Niemann-Pick C1-Like 1 trafficking and function.
The major goal of this project it to define how the sterol-sensing domain (SSD) of NPC1L1 regulates NPC1L1's subcellular localization in response to cells' cholesterol availability.
Role: PI