University of California San Francisco **Prepared: 05/2010**

CURRICULUM VITAE

Name: **Yadong Huang, M.D., Ph.D.**

Position: Associate Investigator
Gladstone Institute of Neurological Disease
Gladstone Institute of Cardiovascular Disease

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EDUCATION:

1980 – 1985	Qingdao Medical University, Qingdao, P.R.China	M.D.	Medicine
1984 – 1985	Qingdao Medical University, Qingdao, P.R.China	Internship	Medicine
1985 – 1987	Peking Union Medical College, Beijing, P.R.China	Residency	Pathology
1985 – 1988	Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, P.R.China	M.Sc.	Cell Biology
1988 – 1991	Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, P.R.China (Advisor Name: Mingpeng She, M.D.)	Ph.D.	Biochemistry/ Pathology
1991 – 1995	Institute of Arteriosclerosis Research, University of Muenster, Germany (Advisor Name: Gerd Assmann, M.D.)	Postdoc	Lipid Biology
1995 – 1996	Gladstone Institute of Cardiovascular Disease, (Advisor Name: Robert W. Mahley, M.D., Ph.D.)	Postdoc	Lipid Metabolism
1996 – 1998	Gladstone Institute of Cardiovascular Disease, (Advisor Name: Robert W. Mahley, M.D., Ph.D.)	Research Scientist	Lipid Metabolism
1995 – 1998	University of California, San Francisco, CA (Advisor Name: Robert W. Mahley, M.D., Ph.D.)	Research Fellow	CVRI

PRINCIPAL POSITIONS HELD:

1990 – 1991	Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, P. R. China	Lecturer	Pathology

1998 – 1999	Gladstone Institute of Cardiovascular Disease,	Staff Research Scientist	
1999 – 2004	Gladstone Institute of Neurological Disease,	Staff Research Investigator	
1999 – 2004	Gladstone Institute of Cardiovascular Disease,	Staff Research Investigator	
1999 – 2005	University of California, San Francisco, CA	Assistant Adjunct Professor	Pathology
2004 – 2009	Gladstone Institute of Neurological Disease,	Assistant Investigator	
2004 – 2009	Gladstone Institute of Cardiovascular Disease,	Assistant Investigator	
2005 – 2009	University of California, San Francisco, CA	Assistant Professor in Residence	Pathology/ Neurology
2009 – now	Gladstone Institute of Neurological Disease,	Associate Investigator	
2009 – now	Gladstone Institute of Cardiovascular Disease,	Associate Investigator	
2009 – now	University of California, San Francisco, CA	Associate Professor in Residence	Pathology/ Neurology

HONORS AND AWARDS:

1991 – 1993	Boehringer-Ingelheim Postdoctoral Fellowship in Biomedical Research
1995	W. H. Hauss Award on Arteriosclerosis Research, German Arteriosclerosis Research Society
1996	Young Investigator Award, XII International Symposium on Drugs Affecting Lipid Metabolism, Houston, TX
2000	Young Investigator Award for Scientific Excellence, International Society for Arteriosclerosis Research
2009	New Faculty Award, California Institute for Regenerative Medicine (CIRM)

KEYWORDS/AREAS OF INTEREST:

Cellular and molecular mechanisms of neurodegeneration

- Cellular and molecular mechanisms of Alzheimer's disease
- Roles of apoE in Alzheimer's disease and other neurodegenerative disorders
- Roles of protein misfolding and/or aggregation in neurodegeneration
- Regulation of apoE expression in central nervous system
- Roles of apoE in neural stem cell development and differentiation

PROFESSIONAL ORGANIZATIONS:

Memberships:

1994 – now	American Heart Association (Council on Arteriosclerosis)
1997 – 2001	American Association for the Advancement of Science
1998 – 2001	New York Academy of Sciences
1999 – now	Society for Neuroscience
2003 – now	American Society for Biochemistry and Molecular Biology
2006 – 2008	New York Academy of Science
2005 – now	Alzheimer's Association
2010 – now	International Society to Advance Alzheimer Research and Treatment

Service to Professional Organizations:

2000 – 2004	Western Review Consortium's Peer Review Committee 4B, American Heart Association
2002	Ad hoc reviewer for Alzheimer's Association
2006	Ad hoc reviewer for American Medical Association Foundation
2006	Ad hoc reviewer for Catalan Agency for Health Technology Assessment and Research
2006	Co-Chair, Session of Disease Mechanisms (ApoE), 10th International Conference on Alzheimer's Disease and Related Disorders (July 15–20), Madrid, Spain.
2006	Chair, Session of Excitotoxicity, Inflammation, and Oxidative Stress, Neuroscience 2006 (Oct. 14–18), Atalanta, USA.
2007	Ad hoc reviewer for Alzheimer's Association
2007 – now	Advisor of Alzheimer Research Forum
2008	Chair, Session of Diseasse Mechanism (ApoE), 11th International Conference on Alzheimer's Disease and Related Disorders (July 26–31), Chicago, USA.
2010	Reviewer for American Federation for Aging Research (AFAR)

SERVICE TO PROFESSIONAL PUBLICATIONS:

2010 – Editorial Board Member
Frontiers in Alzheimer's Disease

1999 – now Ad hoc referee for the following Journals

American Journal of Medicine
American Journal of Pathology
American Journal of Physiology
Arteriosclerosis, Thrombosis, and Vascular Biology
Biochemical Journal
Biochemistry
Brain Research
Cell Stem Cell
Chemistry and Biology
European Journal of Human Genetics
FASEB Journal
Glia
Journal of Biological Chemistry
Journal of Clinical Investigation
Journal of Clinical Lipidology
Journal of Lipid Research
Journal of Medical Genetics
Journal of Neurochemistry
Journal of Neuroscience
Lipids
Metabolism
Molecular Neurodegeneration

Nature
Neuroscience
Neuroscience Letter
Proceedings of the National Academy of Sciences, USA
Trends in Molecular Medicine

INVITED PRESENTATIONS

INTERNATIONAL

Invited seminar: "Transgenic Animal Models of Type III Hyperlipoproteinemia," Institute of Arteriosclerosis Research, University of Muenster, Muenster, Germany (May 19, 1997)

Invited presentation: "Genetic Factors Modulating Type III Hyperlipoproteinemia," 4th Annual Scandinavian Atherosclerosis Conference. Copenhagen, Denmark (May 23, 1997)

Invited seminar: "Apolipoprotein E: from Heart Disease to Alzheimer's Disease," Institute of Arteriosclerosis Research, University of Muenster, Germany (May 16, 1999)

Invited presentation: "Differential Effect of Cytosolic ApoE3 and ApoE4 on Neurite Outgrowth and the Cytoskeleton," 6th International Conference on Neurodegenerative Disorders, Tobago, West Indies (April 13, 2000)

Invited presentation: "Pathogenesis of Type III Hyperlipoproteinemia: Lessons from Transgenic Animal Studies," Symposium of Genetics and Atherosclerosis, Aarhus, Denmark (June 24, 2000)

Invited presentation: "Apolipoprotein E Fragments and Alzheimer's Disease," the New Frontiers of Neruochemistry and Biophysics on Diagnosis and treatment of Neurological Disease, Florence, Italy (October 12, 2001)

Invited presentation: "Alternative Molecular Mechanisms Linking ApoE4 and Alzheimer's Disease," The 9th International Conference On Alzheimer's Disease and Related Disorders, Philadelphia (July 22, 2004)

Invited presentation: "Apolipoprotein E Proteolysis and Neurotoxicity," Neuroscience 2004, San Diego (October 23, 2004)

Invited presentation: "Role of Apolipoprotein E in A-beta Production, Neurodegeneration, and Alzheimer's Disease," Conference on Inclusion-Body Myositis (s-IBM): Frontiers of Research Potentially Relevant to Treatment, Marina Del Rey, CA (January 27, 2005)

Invited Seminar: "ApoE4 Fragments and Mitochondrial Dysfunction", GlaxoSmithKline, London, UK (January 18, 2006)

Invited presentation and session chair: "Profile and Regulation of Apolipoprotein E Expression in Central Nervous System in Mice with Targeting of Green Fluorescent protein Gene into the ApoE Locus". 10th International Conference on Alzheimer's Disease and Related Disorders. Madrid, Spain (July 19, 2006)

Invited presentation and session chair: "Apolipoprotein E Proteolysis as a Causative Factor and Therapeutic Target in Alzheimer's Disease". Symposium of Diagnosis, Mechanisms, and Treatment of Neurodegenerative Diseases. Beijing, P. R. China (May 15, 2007)

Invited presentation and a session chair: "ApoE Expression in the CNS: Role in Brain Injury". 11th International Conference on Alzheimer's Disease and Related Disorders. Chicago (July 29, 2008)

Invited presentation: "ApoE and Alzheimer's Disease". The Third Conference on Advances in Aging and Neurodegenerative Diseases. Ridgefield (April 23, 2009)

Invited presentation: "Mouse Models of ApoE in Alzheimer's Disease Research". Models of dementia: the good the bad, the future. Cambridge, UK (15 December 2010)

NATIONAL

Invited seminar: "Apolipoprotein E Proteolysis and Alzheimer's Disease," Department of Neuroscience and Neurology, Duke University (March 16, 2002)

Invited seminar: "Apolipoprotein E4: Molecular and Cellular Mechanisms Linking to Alzheimer's Disease," Eli Lilly and Company, Indianapolis (February 28, 2003)

Invited presentation: "Apolipoprotein E Proteolysis and Alzheimer's Disease," ApoE Catalyst Conference, The Institute for the Study of Aging, New York (May 29, 2003)

Invited presentation: "ApoE Genotype Accounts for the Vast Majority of AD Risk and AD Pathology," Challenging Views of Alzheimer's Disease, Cincinnati (July 26, 2003)

Invited presentation: "Apolipoprotein E: from Heart Disease to Alzheimer's Disease," Annual Graduate Research Symposium, University of Wyoming (April 28, 2006)

Invited Presentation: "Apolipoprotein Proteolysis: A Causative Factor and Therapeutic Target in Alzheimer's Disease". Symposium on the role of mitochondrial dysfunction in neurodegenerative disorders. New York Academy of Science, New York (May 22, 2006)

Invited Seminar: "Role of Apolipoprotein E in Heart Disease and Alzheimer's Disease". University of California, San Diego (July 2, 2007)

Invited presentation: "Apolipoprotein E Proteolysis as a Causative Factor and Therapeutic Target in Alzheimer's Disease". Symposium of the Role of Apolipoprotein E in Brain Aging and Alzheimer's Disease. National Institute of Aging, Bethesda (August 13, 2008)

REGIONAL AND OTHER INVITED PRESENTATIONS

Invited seminar: "Roles of ApoE in Neurodegenerative Disorders," Department of Neuroscience, Stanford University School of Medicine, Palo Alto (April 25, 2003)

Invited seminar: "ApoE Proteolysis and Alzheimer's Disease," Research Center for Aging, Stanford University School of Medicine, Palo Alto (May 23, 2003)

Invited seminar: "Animal Models of Alzheimer's Disease," Frontiers in Neurology and Neuroscience. University of California, San Francisco (January 7, 2004)

Invited seminar: "Apolipoprotein E and Alzheimer's Disease," Department of Nutritional Sciences & Toxicology, University of California, Berkeley (February 16, 2005)

Invited Seminar: "Apolipoprotein Proteolysis: A Causative Factor and Therapeutic Target in Alzheimer's Disease". The Stanford Initiative on Alzheimer's Disease (SIAD) Seminar, Stanford University, Palo Alto (May 17, 2006)

Invited Seminar: "Apolipoprotein E and Alzheimer's Disease". Rinat Neuroscience Corp. South San Francisco (July, 2006)

Invited presentation: "Apolipoprotein E4 and Alzheimer's Disease". Symposium on Bridging Cultures: Improving Evaluation and Treatment of Cognitive Disorders. San Francisco (March 8, 2008)

Invited seminar: "Apolipoprotein E4 as a Causative Factor and Therapeutic Target in Alzheimer's Disease". VA Hospital, UCSF, San Francisco (September 15, 2008)

Invited seminar: "Apolipoprotein E Proteolysis and Alzheimer's Disease". Elan. South San Francisco (December, 2008)

Invited seminal: "Induced Neural Stem Cells" iPierian, Inc. South San Francisco (March 11, 2010)

Invited seminar: "Apolipoprotein E4 Causes Tau-dependent GABAergic Interneuron Impairment, Leading to Learning and Memory Deficits in Mice". UCSF Memory and Aging Center (March 19, 2010)

Invited presentation: "Apolipoprotein E4 Causes Tau-dependent GABAergic Interneuron Impairment, Leading to Learning and Memory Deficits in Mice". Alzheimer's Researchers' Symposium. Berkeley (June 28, 2010)

GOVERNMENT AND OTHER PROFESSIONAL SERVICE:

2002 – 2004	Review Panel F, Alzheimer's Disease Research Program, Department of Health Services, California.
2005	Ad hoc reviewer for The Defense Advanced Research Projects Agency, US Department of Defense
2005	Ad hoc reviewer on Study Section of ZRG1 NDBG-A (Neurodegeneration, Neuroinflammation, Oxidative Stress, and Mitochondria), National Institute of Health
2006	Ad hoc reviewer on Study Section of ZRG1 NOMD-A (Neural Oxidative Stress, Mitochondria and Cell Death), National Institute of Health
2007	Ad hoc reviewer on Study Section of ZRG1 NOMD-A (Neural Oxidative Stress, Mitochondria and Cell Death), National Institute of Health
2007	Review Panel F, Alzheimer's Disease Research Program, Department of Health Services, California.
2009	Ad hoc reviewer, Health Research Awards Program, Health Research Board (HRB), Ireland.
2010	Reviewer for American Federation for Aging Research (AFAR)

UNIVERSITY AND PUBLIC SERVICE

UNIVERSITY SERVICE

GRADUATE PROGRAM SERVICE:

2005 – now	Served on interviewing BMS graduate program candidates.
2005 – now	Served as a faculty coach for 11 BMS students on their journal club presentation.
2005 – now	Served as a supervisor for eight BMS rotation students.
2005 – now	Served as a thesis supervisor for three BMS students.
2005 – 2009	Committee Member of Graduate Council, UCSF.
2006 – now	Served as a member on qualifying exam committees for five BMS students.
2007 – now	Served as a moderator in four classes for BMS program.
2010	Served as a member of a UCSF/Gladstone faculty search committee

DEPARTMENTAL (GLADSTONE INSTITUTES) SERVICE:

2001 – 2002	Tissue Culture Committee for Mission Bay New Building (Chair), Gladstone Institutes
2001	Annual Scientific Retreat Committee, Gladstone Institutes.
2001	Annual Scientific Retreat Committee, Gladstone Institutes.
2002	NIC Committee, Gladstone Institute of Neurological Disease.
2005 – 2009	Leadership Committee of Diversity, Gladstone Institutes.
2007 – now	Laboratory Animal Research Committee, Gladstone Institutes.

TEACHING and MENTORING

POSTGRADUATE AND OTHER COURSES

1999 – now Continuing Education, Gladstone Institutes, Gave 17 lectures or seminars to postdoctoral fellows, research associates, and administrative assistants.

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED:

Dates	Name	Program or School	Role	Current Position
2000	Jeffey Woldrich	Brown University	Summer intern supervisor	Medical student in UCSF
2003	Mark Yu	A high school in Houston	Summer intern supervisor	Undergraduate student in Case Western Reserve University
2004	Max Ma	UC, Berkeley	Summer intern supervisor	Medical student in Connell University
2005	Angela Sia	BMS program, UCSF	Rotation graduate student supervisor	Graduate student in BMS program, UCSF
2006–now	Bien-Ly Nga	BMS program, UCSF	Graduate student thesis supervisor	Graduate student in BMS program, UCSF
2007	Emily Elliott	BMS program, UCSF	Rotation graduate student supervisor	Graduate student in BMS program, UCSF
2007	Lauren Herl	BMS program, UCSF	Rotation graduate student supervisor	Graduate student in BMS program, UCSF
2008–now	Sachi Jain	BMS program, UCSF	Graduate student thesis supervisor	Graduate student in BMS program, UCSF
2008–now	Karen Ring	BMS program, UCSF	Graduate student thesis supervisor	Graduate student in BMS program, UCSF
2009	Candia Kenific	BMS program, UCSF	Rotation graduate student supervisor	Graduate student in BMS program, UCSF
2009	Dale Ando	BMS program, UCSF	Rotation graduate student supervisor	Graduate student in BMS program, UCSF
2009	Charles Wang	USC	Summer intern supervisor	Undergraduate student in USC
2009	Kanya Yan	UC Davis	Summer intern supervisor	Undergraduate student in US Davis
2010	Charles Wang	USC	Summer Intern	Undergraduate student in USC
2010	William Zhang	Yale University	Summer Intern	Undergraduate student in Yale University

POSTDOCTORAL FELLOWS AND RESIDENTS DIRECTLY SUPERVISED OR MENTORED:

Dates	Name	Fellow	Faculty Role	Current Position
1999–2001	Toru Kawamura, Ph.D.	Post-Doc Fellow	Research supervision	Scientist in a company in Japan
2002–2007	Qin Xu, Ph.D.	Post-Doc Fellow	Research Supervision	Scientist II in Gladstone Center for Translational Research
2002–2005	Shengjun Chang, Ph.D.	Post-Doc Fellow	Research Supervision	Postgraduate Researcher in Dept. of Neurology, UCSF
2004–2007	Jens Hans Brodbeck, Ph.D.	Post-Doc Fellow	Research Supervision	Scientist II in Gladstone Center for Translational Research
2005–2009	Gang Li, Ph.D.	Post-Doc Fellow	Research Supervision	Scientist II in a biotech company

2006–2007	Ligong Chen, Ph.D.	Post-Doc Fellow	Research Supervision	Postgraduate Researcher in UCSF
2007–2010	Mei Xiu Steele, Ph.D.	R&D Scientist II	Research Supervision	Scientist in a company in Bay Area
2007–now	Yaisa Andrews-Zwilling, Ph.D.	Post-Doc Fellow	Research Supervision	Post-Doc Fellow in my lab
2009–now	Laura Leung, Ph.D.	Post-Doc Fellow	Research Supervision	Post-Doc Fellow in my lab
2009–now	ChengZhong Wang, Ph.D.	Post-Doc Fellow	Research Supervision	Post-Doc Fellow in my lab

OTHERS:

See book chapters listed under "Non-Peer Reviewed Publications".
See lecture or seminar presentations listed under "Invited Presentations."

SUMMARY OF TEACHING HOURS:

2003–2004: 300 total hours of teaching (including preparation).
Informal teaching hours: 40 hours
Mentoring hours: 260 hours

2004–2005: 360 total hours of teaching (including preparation).
Informal teaching hours: 100 hours
Mentoring hours: 260 hours

2005–2006: 420 total hours of teaching (including preparation).
Informal teaching hours: 130 hours
Mentoring hours: 290 hours

2006–2007: 450 total hours of teaching (including preparation).
Informal teaching hours: 150 hours
Mentoring hours: 320 hours

2007–2008: 560 total hours of teaching (including preparation).
Formal teaching in BMS program: 10 hours
Informal teaching hours: 150 hours
Mentoring hours: 400 hours

2008–2009: 570 total hours of teaching (including preparation).
Formal teaching in BMS program: 20 hours
Informal teaching hours: 150 hours
Mentoring hours: 400 hours

RESEARCH AND CREATIVE ACTIVITIES

RESEARCH AWARDS AND GRANTS

CURRENT ACTIVE

1. Gladstone Annual Funds (PI, Yadong Huang) 01/2010–12/2010
   Funds for Pilot Studies $210,000 direct/yr

2. New Faculty Award (PI, Yadong Huang) 03/2009–02/2014
   California Institute for Regenerative Medicine (CIRM)
   Defining the Isoform-Specific Effects of ApoE on the $300,000 direct/yr 2
   Development of iPS cells into Functional Neurons $1,500,000 direct/yrs 1–5

3. Tau Consortium Grant (PI, Yadong Huang) 05/2010–04/2012
   Generation of Induced Pluripotent Stem (iPS) Cells and
   Induced Neural Stem Cells (iNSC) from $160,000 direct/yr 1
   Human Dermal Fibroblasts Carrying A Tau Mutation $320,000 direct/yrs 1–2

4. P01 AG022074 renewal (PI, Lennart Mucke) 06/2008–05/2013
   NIH/NIA
   Project-3 (PL, Yadong Huang) $209,340 direct/yr 2
   Apolipoprotein E in Alzheimer's Disease: Cellular Mechanisms $1,025,000 direct/yrs 1–5

5. P01 AG022074 renewal (PI, Lennart Mucke) 06/2008–05/2013
   NIH/NIA
   Core B (CL, Yadong Huang) $109,797 direct/yr 2
   Cell Culture Core $533,000 direct/yrs 1–5

6. Research Agreement with Merck (PI, Robert Mahley) 11/2006–10/2010
   ApoE4 Modulators for the Treatment of Alzheimer's Disease
   ApoE protease and mitochondria projects (PI) $651,042 direct/yr 4
   $2,604,168 direct/yrs 1–4

7. Two graduate students and two postdoctoral fellows in my lab received fellowship grants.

PENDING

1. Renewal of Research Agreement with Merck (PI, Robert Mahley) 11/2010–10/2012
   ApoE4 Modulators for the Treatment of Alzheimer's Disease
   ApoE protease and mitochondria projects (PI) $650,000 direct/yr 1
   $1,300,000 direct/yrs 1–2

PAST

1. Postdoctoral Fellowship (PI) 1991–1993
   Boehringer-Ingelheim $26,000 direct/yr 1
   Roles of apolipoprotein AI and E in Cholesterol Efflux $52,000 direct/yrs 1–2

2. Beginning Grant-in-Aid 9960050Y (PI) 1999–2001
   American Heart Association $59,925 direct/yr 1
   Apolipoprotein E as a Modulator of Hepatic VLDL Metabolism $119,831 direct/yrs 1–2

3. Research Project Award 8RT-0130 (PI) 1999–2002
   UC Tobacco-Related Disease Research Program (UC-TRDRP) $142,761 direct/yr 1
   Apolipoprotein E: Remnant Metabolism and Atherosclerosis $445,522 direct/yrs 1–3

4. R01 HL64162 (PI) 2000–2005
   NIH/NHLBI $169,143 direct/yr 1
   Apolipoprotein E Expression Level Modulates VLDL Metabolism $887,184 direct/yrs 1–5

5. Research Contract (PI) 2003–2004
   GlasoSmithKline $100,000 direct/yr 1
   Apolipoprotein E4 and Alzheimer's Disease

6. R01 HL037063 (PI) 04/01/00–03/31/05
   NIH/NHLBI $210,000 direct/yr 1
   Regulation of Apolipoprotein Synthesis $1,050,000 direct/yrs 1–5

7. Research Contract (PI) 09/2005–12/2006
   GlasoSmithKline $250,000
   Identification of the Mitochondrial Protein Targets of the apoE4 Fragment

PEER REVIEWED PUBLICATIONS:

1. **Huang Y,** von Eckardstein A, and Assmann G (1993) Cell-derived unesterified cholesterol cycles between different HDLs and LDL for its effective esterification in plasma. *Arterioscler. Thromb.* 13:445–458.
2. **Huang Y,** von Eckardstein A, Wu S, Maeda N, and Assmann G (1994) A plasma lipoprotein containing only apolipoprotein E and with gamma-mobility on electrophoresis releases cholesterol from cells. *Proc. Natl. Acad. Sci. USA.* 91:1834–1838.
3. **Huang Y**, von Eckardstein A, Wu S, and Assmann G (1995) Effects of the apolipoprotein E-polymorphism on uptake and transfer of cell-derived cholesterol in plasma. *J. Clin. Invest.* 96:2693–2701.
4. **Huang Y**, von Eckardstein A, Wu S, and Assmann G (1995) Cholesterol efflux, cholesterol esterification, and cholesterol ester transfer by LpA-I and LpAI/A-II in native plasma. *Arterioscler. Thromb. Vasc. Biol.* 15: 1412–1418.
5. **Huang Y,** von Eckardstein A, Wu S, Langer C, and Assmann G (1995) Generation of pre-β_1-HDL and conversion into α-HDL: Evidence for disturbed HDL conversion in Tangier Disease. *Arterioscler. Thromb.Vasc. Biol.* 15:1746–1754.
6. von Eckardstein A, **Huang Y**, Wu S, Funke H, Noseda G, and Assmann G (1995) Reverse cholesterol transport in plasma of patients with different forms of familial HDL deficiency. *Arterioscler. Thromb. Vasc. Biol.* 15:691–703
7. von Eckardstein A, **Huang Y**, Wu S, Saadat Sarmadi A, Schwarz S, Steinmetz A, and Assmann G (1995) Lipoproteins containing apolipoprotein A-IV but not apolipoprotein A-I take up and esterify cell-derived cholesterol in plasma. *Arterioscler. Thromb. Vasc. Biol.* 15:1755–1763
8. von Eckardstein A, Jauhiainen M, **Huang Y**, Metso J, Langer C, Pussinen P, Wu S, Ehnholm C, and Assmann G (1996) Phospholipid transfer protein-mediated conversion of high density lipoproteins (HDL) generates preβ_1-HDL. *Biochiim. Biophys. Acta* 1301:255–262.
9. **Huang Y**, Schwendner SW, Rall SC Jr, and Mahley RW (1996) Hypolipidemic and hyperlipidemic phenotypes in transgenic mice expressing human apolipoprotein E2. *J. Biol. Chem.* 271:29146–29151.
10. Miccoli R, Zhu Y, Daum U, Wessling J, **Huang Y**, Navalesi R, Assmann G, and von Eckardstein A (1997) A natural apolipoprotein A-I variant, apoA-I(L141R)pisa, interferes with the formation of α-high density lipoproteins (HDL) but not with the formation of preβ1-HDL and influences efflux of cholesterol into plasma. *J. Lipid Res.* 38:1242–1253.
11. **Huang Y**, Schwendner SW, Rall SC Jr, and Mahley RW (1997) Apolipoprotein E2 transgenic rabbits: Modulation of the type III hyperlipoproteinemic phenotype by estrogen and occurrence of spontaneous atherosclerosis. *J. Biol. Chem.* 272:22685–22694
12. **Huang Y**, Rall SC, and Mahley RW (1997) Genetic factors precipitating type III hyperlipoproteinemia in hypolipidemic transgenic mice expressing human apolipoprotein E2. *Arterioscler. Thromb. Vasc. Biol.* 17:2817–2824.
13. **Huang Y**, von Eckardstein A, Zhu Y, Langer C, Raabe M, Wu S, Seedorf U, Maeda N, and Assmann G (1997) Effects of genotype and diet on cholesterol efflux into plasma and lipoproteins of normal, apolipoprotein A-I-, and apolipoprotein E-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* 17:2010–2019.

14. Fan J, Ji ZS, **Huang Y**, de Silva H, Sanan D, Mahley RW, Innerarity TL, and Taylor JM (1998) Increased expression of apolipoprotein E in transgenic rabbits results in reduced levels of very low density lipoproteins and an accumulation of low density lipoproteins in plasma. *J. Clin. Invest.* 101:2151–2164.
15. von Eckardstein A, **Huang Y**, Kastelein JJP, Geisel J, Real JT, Kuivenhoven JA, Miccoli R, Noseda G, and Assmann G (1998) Lipid-free apolipoprotein (apo) A-I is converted into alpha-migrating high density lipoproteins by lipoprotein-depleted plasma of normolipidemic donors and apo A-I-deficient patients but not of Tangier disease patients. *Atherosclerosi*s 138:25–34.
16. **Huang Y**, Liu XQ, Rall SC, and Mahley RW (1998) Apolipoprotein E2 reduces low density lipoprotein cholesterol in transgenic mice by impairing lipoprotein lipase-mediated lipolysis of triglyceride-rich lipoproteins. *J. Biol. Chem.* 273:17483–17490.
17. **Huang Y**, Liu XQ, Rall SC, Taylor JM, von Eckardstein A, Assmann G, and Mahley RW (1998) Overexpression and accumulation of apolipoprotein E as a cause of hypertriglyceridemia. *J. Biol. Chem.* 273:26388–26393.
18. **Huang Y**, Ji ZS, Brecht WJ, Rall SC, Taylor JM, and Mahley RW (1999) Overexpression of apolipoprotein E3 in transgenic rabbits causes combined hyperlipidemia by stimulating hepatic very low density lipoprotein (VLDL) production and impairing VLDL lipolysis. *Arterioscler. Thromb. Vasc. Biol.* 19:2952–2959.
19. Langer C, **Huang Y**, Cullen P, Wiesenhutter B, Mahley RW, Assmann G, and von Eckardstein A (2000) Endogenous apolipoprotein E modulates cholesterol efflux and cholesterol ester hydrolysis mediated by high density lipoprotein 3 and lipid-free apolipoproteins in mouse peritoneal macrophages. *J. Mol. Med.* 78:217-227**.**
20. **Huang Y**, Liu XQ, Wyss-Coray T, Brecht WJ, Sanan DA, Mahley RW (2001) Apolipoprotein E fragments present in Alzheimer's disease brains induce neurofibrillary tangle-like intracellular inclusions in neurons. *Proc. Natl. Acad. Sci. USA.* 98:8838–8843.
21. Buttini M, Yu GQ, Shockley K, **Huang Y,** Jones B, Masliah E, Mallory M, Yeo T, Longo M, and Mucke L (2002) Modulation of Alzheimer-like synaptic and cholinergic deficits in transgenic mice by human apolipoprotein E depends on isoform, aging, and overexpression of amyloid peptides but not on plaque formation. *J. Neurosci.* 22:10539–10548.
22. Ji ZS, Miranda RD, Newhouse YM, Weisgraber KH, **Huang Y,** and Mahley RW (2002) Apolipoprotein E4 potentiates amyloid β peptide-induced lysosomal leakage and apoptosis in neuronal cells. *J. Biol. Chem.* 277:21821–21828.
23. Harris FM, Walter JB, Xu Q, Tesseur I, Kekonius L, Wyss-Coray T, Fish JD, Masliah E, Hopkins PC, Scearce-Levie K, Weisgraber KH, Mucke L, Mahley RW, and **Huang Y** (2003). Carboxyl-terminal-truncated apolipoprotein E4 causes Alzheimer's disease-like neurodegeneration and behavioral deficits in transgenic mice. *Proc. Natl. Acad. Sci. USA.* 100:10966–10971.
24. Harris FM, Tesseur T, Brecht WJ, Xu Q, Mullendorff K, Chang S, Wyss-Coray T, Mahley RW, and **Huang Y** (2004) Astroglial regulation of apolipoprotein E expression in neuronal cells: Implications for Alzheimer's disease. *J. Biol. Chem.* 279:3862–3868.
25. Brecht WJ, Harris FM, Chang S, Tesseur I, Yu GQ, Xu Q, Wyss-Coray T, Buttini M, Mucke L, Mahley RW, and **Huang Y** (2004) Neuron-specific apolipoprotein E4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. *J. Neurosci.* 24:2527–2534.

26. Xu Q, Brecht WJ, Weisgraber KH, Mahley RW, and **Huang Y** (2004) Apolipoprotein E4 domain interaction occurs in living neuronal cells as determined by fluorescence resonance energy transfer. *J. Biol. Chem*. 279:25511–25516.
27. Harris FM, Brecht WJ, Xu Q, Mahley RW, and **Huang Y** (2004) Increased tau phosphorylation in apolipoprotein E4 transgenic mice is associated with activation of extracellular signal-regulated kinase: Modulation by Zinc. *J. Biol. Chem.* 279:44795-44801.
28. Chang S, Ma TR, Miranda RD, Balestra ME, Mahley RW, and **Huang Y** (2005) Lipid-and receptor-binding regions of apolipoprotein E4 fragments act in concert to cause mitochondrial dysfunction and neurotoxicity. *Proc. Natl. Acad. Sci. USA*. 102:18694–18699.
29. Ramaswamy G, Xu Q, **Huang Y**, and Weisgraber KH (2005) Effect of domain interaction on apolipoprotein E levels in mouse brain. *J. Neurosci.* 16:10658–10663.
30. Hodoglugil U, Williamson DW, **Huang Y**, and Mahley RW (2005) An interaction between the TaqIB polymorphism of cholesterol ester transfer protein and smoking is associated with changes in plasma high-density lipoprotein cholesterol levels in Turks. *Clin. Genet.* 68:118–127.
31. Hodoglugil U, Williamson DW, **Huang Y**, and Mahley RW (2005) Common polymorphisms of ATP binding cassette transporter A1, including a functional promoter polymorphism, associated with plasma high-density lipoprotein cholesterol levels in Turks. *Atherosclerosis* 183:199–212.
32. Ye S, **Huang Y**, Mullendorff K, Dong L, Giedt G, Meng EC, Cohen FE, Kuntz ID, Weisgraber KH, and Mahley RW (2005) Apolipoprotein E4 enhances amyloid β peptide production in cultured neuronal cells: ApoE structure as a potential therapeutic target. *Proc. Natl. Acad. Sci. USA.* 102:18700–18705.
33. Ji ZS, Mullendorff K, Cheng IH, Miranda RD, **Huang Y**, and Mahley RW (2006) Reactivity of apolipoprotein E4 and amyloid beta peptide: lysosomal stability and neurodegeneration. *J. Biol. Chem*. 281:2683–2692.
34. Hodoglugil U, Tanyolac S, Williamson DW, **Huang Y**, and Mahley RW (2006) Apolipoprotein A-V: a potential modulator of plasma triglyceride levels in Turks. *J. Lipid Res*. 47:144–153.
35. **Huang Y** and Mahley RW (2006) Commentary: "Perspective on a pathogenesis and treatment of Alzheimer's disease." Apolipoprotein E and the mitochondrial metabolic hypothesis. *Alzheimer's and Dementia.* 2:71–73.
36. Mahley RW, Weisgraber KH, and **Huang Y** (2006) Apolipoprotein E4: A causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc. Natl. Acad. Sci. USA.* 103:5644–5651.
37. Xu Q, Bernardo A, Walker D, Kanegawa T, Mahley RW, and **Huang Y** (2006) Profile and regulation of apolipoprotein (apo) E expression in central nervous system in mice with targeting of green fluorescent protein to the apoE locus. *J. Neurosci.* 26:4985–4994.
38. Mahley RW, **Huang Y**, and Weisgraber KH (2006) Commentary: "Apolipoprotein E facilitates reverse cholesterol transport by allowing cholesterol ester-rich core expansion in HDL." *J. Clin. Invest*. 116:1226–1229.
39. Brodbeck J, Balestra ME, Saunders AM, Roses AD, Mahley RW, and **Huang Y** (2008) Rosiglitazone increases dendritic spine density and rescues spine loss caused by apolipoprotein E4 in primary cortical neurons. *Proc. Natl. Acad. Sci. USA.* 105:1343–1346.
40. Xu Q, Walker D, Bernardo A, Brodbeck J, Malestra ME, and **Huang Y** (2008) Intron-3 retention/splicing controls neuronal expression of apolipoprotein E in the central nervous system. *J. Neurosci.* 28:1452–1459.

41. Burt TD, Agan BK, Marconi VC, He W, Kulkarni H, Mold JE, Cavrois M, **Huang Y,** Mahley RW, Dolan MJ, McCune JM, Ahuja SK (2008) Apolipoprotein apoE4 influences HIV-1 cell entry *in vitro* and the *ApoE* ε4/ε4 genotype accelerates HIV disease progression. *Proc. Natl. Acad. Sci. USA* 105:8718–8723.
42. Tesseur I, Zhang H, Brecht WJ, Corn J, Gong JS, Yanagisawa K, Michikawa M, Weisgraber KH, **Huang Y,** and Wyss-Coray T (2009) Bioactive TGF-β associates with lipoproteins and is enriched in those containing apolipoprotein E3. *J. Neurochem.* 110:1254–1262.
43. Li G, Bien-Ly N, Andrews-Zwilling Y, Xu Q, Bernardo A, Ring K, Halabisky B, Deng C, Mahley RW, and **Huang Y** (2009) GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knock-in mice. *Cell Stem Cell.* 5:634–645.

MANUSCRIPTS SUBMITTED:

1. Andrews-Zwilling Y, Bien-Ly N, Xu Q, Li G, Bernardo A, Yoon SY, Zwilling D, Yan TX, Chen L, and **Huang Y**. Apolipoprotein E4 causes age- and tau-dependent impairment of GABAergic interneurons, leading to learning and memory deficits in mice. *Submitted to Neuron.*
2. Bien-Ly N, Xu Q, Bernardo A, Walker D, and **Huang Y**. A unique conformation of the lipid-binding domain of apolipoprotein E determines its isoform-dependent interaction with amyloid-β peptides. *Submitted to J. Biol. Chem*.
3. Brodbeck J, Balestra M, Freedman S, Weisgraber KH, Mahley RW, and **Huang Y**. Apolipoprotein E4 causes structure- and neuronal activity-dependent impairment of mitochondrial dynamics in neuronal cells. *Submitted to J. Neurosci.*

INVITED PUBLICATIONS AND OTHER CREATIVE ACTIVITIES:

Review Articles:

1. von Eckardstein A, **Huang Y**, and Assmann G (1994) Physiological role and clinical relevance of high density lipoprotein subclasses. *Curr. Opin. Lipidol.* 5:404–416.
2. Assmann G, Schulte H, von Eckardstein A, and **Huang Y** (1996) High density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implication for reverse cholesterol transport. *Atherosclerosis* 124 (Suppl.):S11–S20.
3. von Eckardstein A, **Huang Y**, and Assmann G (1996) Uptake, transfer, and esterification of cell-derived cholesterol in plasma of patients with familial HDL-deficiency. *Z Gastroenterol.* 34 (Suppl.) 3:143–144.
4. Mahley RW and **Huang Y** (1999) Apolipoprotein E: From atherosclerosis to Alzheimer's disease and beyond. *Curr. Opin. Lipidol.* 10:207–217.
5. Mahley RW, **Huang Y**, and Rall SC (1999) Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia): Questions, quandaries, and paradoxes. *J. Lipid Res.* 40:1933–1949.
6. **Huang Y,** Weisgraber KH, Mucke L, and Mahley RW (2004) Apolipoprotein E: Diversity of cellular origins, structural and biophysical properties, and effects in Alzheimer's disease. *J. Mol. Neurosci.* 23:187–202.
7. Raber J, **Huang Y,** and Ashford JW (2004) ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol. Aging.* 25:641–660.
8. **Huang Y** (2006) Apolipoprotein E and Alzheimer's Disease. *Neurology* 24:S79–85.

9. Xu Q and **Huang Y** (2006) Lipid metabolism and neurodegenerative disorders. *Future Lipidology*. 1:441–453.
10. Mahley RW and **Huang Y** (2006) Apolipoprotein (apo) E4 and Alzheimer's disease: Unique conformational and biophysical properties of apoE4 can modulate neuropathology. *Acta Neurol Scand Suppl.* 185:8–14.
11. **Huang Y** (2006) Molecular and cellular mechanisms of apolipoprotein E4 neurotoxicity and potential therapeutic strategies. *Curr. Opin. Drug Discov. Developm.* 9:627–641.
12. Roses AD, Saunders AM, **Huang Y,** Strum J, Weisgraber KH, and Mahley RW (2007) Complex disease-associated pharmacogenetics: Drug efficacy, drug safety, and confirmation of a pathogenetic hypothesis (Alzheimer's disease.) *Pharmacogenomics J.* 7:10–28.
13. Mahley RW, **Huang Y,** Weisgraber KH (2007) Detrimental effects of apolipoprotein E4: Potential therapeutic targets in Alzheimer's disease. *Curr. Alzheimer Res.* 4:537–40.
14. Mahley RW, Weisgraber KH, and **Huang Y** (2009) Apolipoprotein E: Structure determines function from altherosclerosis to Alzheimer's disease to AIDS. *J. Lipid Res.* 50:S183–S188.
15. Mahley RW and **Huang Y** (2009) Alzheimer disease: multiple causes, multiple effects of apolipoprotein E4, and multiple therapeutic approaches. *Annals of Neurology*. 65:623–625.
16. Huang Y (2010) Aβ-independent roles of apolipoprotein E4 in the pathogenesis of Alzheimer's disease *Trends Mol. Med.* In press.
17. Huang Y (2010) Mechanisms linking apolipoprotein E isoforms with cardiovascular and neurological diseases. *Curr. Opin. Lipidol.* In press.

Books and Chapters:

1. Assmann G, von Eckardstein A, **Huang Y**, and Wu S (1995) A lipoprotein present in normal and HDL-deficient plasmas releases cholesterol from cells. *Atherosclerosis X, Woodford, F.P. Editor.* p 662–665.
2. von Eckardstein A, **Huang Y**, and Assmann G (1996) Role of high density lipoprotein subclasses in reverse cholesterol transport. *Proceedings of the Symposium on HDL-Deficiency and Atherosclerosis.* Kluwver Verlag, p 17–23.
3. von Eckardstein A, **Huang Y**, Wu S, and Assmann G (1996) Role of apoE for reverse cholesterol transport. *Proceedings of the C.B. Pennington Conference on Nutrition, Genetics, and Heart Disease.* Baton Rouge, LA, USA. p 189.
4. **Huang Y** and Mahley RW (1999) Apolipoprotein E and human disease. In *Plasma Lipids and Their Role in Diseases.* Editor, Barter PJ. p257–284.
5. Mahley RW and **Huang Y** (2003) Apolipoprotein E: structure and function in lipid metabolism and neurobiology. In *The Molecular and Genetic Basis of Neurological Disease.* Editors: Rosenberg RN, Prusiner SB, DiMauro S, and Barchi RL, Nestler EJ. Butterworth Heinemann, Newton, MA. p565–573.
6. **Huang Y** (2004) Transgenic and gene-targeted mouse models in hypoxic pulmonary hypertension research. In *Hypoxic Pulmonary Vasoconstriction: Cellular and Molecular Mechanisms*. Editor: Jason XJ. Yuan. P559–568.
7. **Huang Y** (2006) Transgenic and gene-targeted mouse models of hyperlipidemia. In *A Handbook of Mouse Models for Cardiovascular Research,* Editor: Qingbo Xu. P33–42.
8. **Huang Y** and Mahley RW (2007) Apolipoprotein E: structure and function in lipid metabolism and neurobiology. In *The Molecular and Genetic Basis of Neurological Disease.* Editors: Rosenberg RN,

DiMauro S, Henry Paulson, Louis Ptacek, and Nestler EJ. Butterworth Heinemann, Newton, MA. P590–602.

PATENTS ISSUED OR PENDING:

2000 Methods and Compositions for Use in the Treatment for Hyperlipidemia (US Case No. 09/544,910)
Inventors: **Yadong Huang**, Robert W. Mahley, and John Taylor.

2002 Methods of Treating Disorders Related to ApoE (US Case No. 10/033,526)
Inventors: **Yadong Huang** and Robert W. Mahley

2003 Methods of Diagnosing Alzheimer's disease (US Case No. 10/627,447)
Inventor: **Yadong Huang**

2005 Methods of Identifying Agents that Modulate Mitochondrial Function (GLAD-031 PRV)
Inventors: **Yadong Huang** and Jens Brodbeck

2005 Agents that Reduce ApoE-Induced Impairment of Mitochondria and Methods of Use Thereof (GLAD-030 PRV)
Inventors: **Yadong Huang** and Robert W. Mahley

2006 Regulation of Neuronal Expression of Apolipoprotein E (ApoE) (UC-GL2007-803-1)
Inventors: **Yadong Huang** and Qin Xu

2006 Role of Apolipoprotein E (ApoE) in Neurogenesis (UC-GL2007-802-1)
Inventors: **Yadong Huang**, Gang Li, Robert W. Mahley, and Qin Xu

2008 Apolipoprotein E Cleaving Enzyme (GLAD-375PRV)
Inventors: **Yadong Huang**, Robert W. Mahley, et al.

2009 Methods for Treating Apolipoprotein E4-Associated Disorders (GLAD 383PRV)
Inventors: **Yadong Huang** and Gang Li

2009 Methods of Generating Induced Neural Stem Cells (GLAD-379 PRV)
Inventors: **Yadong Huang** and Karen Ring

2009 Methods for Preventing ApoE4-Associated Disorders (GLAD 384PRV)
Inventors: **Yadong Huang** and Yaisa Andrews-Zwilling

RESEARCH PROGRAM (SEPARATE SUMMARY)

Five Significant recent publications:

1. Brecht WJ, Harris FM, Chang S, Tesseur I, Yu GQ, Xu Q, Wyss-Coray T, Buttini M, Mucke L, Mahley RW, and **Huang Y** (2004) Neuron-specific apolipoprotein E4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. *J. Neurosci.* 24:2527–2534.

   Role/contribution: I am the senior author and also responsible for study concept and design, data analysis, and writing and revision of the manuscript.

2. Xu Q, Bernardo A, Walker D, Kanegawa T, Mahley RW, and **Huang Y** (2006) Profile and regulation of apolipoprotein (apo) E expression in central nervous system in mice with targeting of green fluorescent protein to the apoE locus. *J. Neurosci.* 26:4985–4994.

   Role/contribution: I am the senior author and also responsible for study concept and design, data analysis, and writing and revision of the manuscript.

3. Brodbeck J, Balestra ME, Saunders AM, Roses AD, Mahley RW, and **Huang Y** (2008) Rosiglitazone increases dendritic spine density and rescues spine loss caused by apolipoprotein E4 in primary cortical neurons. *Proc. Natl. Acad. Sci. USA.* 105:1343–1346.

   Role/contribution: I am the senior author and also responsible for study concept and design, data analysis, and writing and revision of the manuscript.

4. Xu Q, Walker D, Bernardo A, Brodbeck J, Malestra ME, and **Huang Y** (2008) Intron-3 retention/splicing controls neuronal expression of apolipoprotein E in the central nervous system. *J. Neurosci.* 28:1452–1459.

   Role/contribution: I am the senior author and also responsible for study concept and design, data analysis, and writing and revision of the manuscript.

5. Li G, Bien-Ly N, Andrews-Zwilling Y, Xu Q, Bernardo A, Ring K, Halabisky B, Deng C, Mahley RW, and Huang Y (2009) GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knock-in mice. *Cell Stem Cell.* 5:634–645.

   Role/contribution: I am the senior author and also responsible for study concept and design, data analysis, and writing and revision of the manuscript.

Current Research Interest/Program:

My current research interest/program focuses on the role of apoE in neurobiology and neurodegeneration, particularly Alzheimer's disease (AD). ApoE4 is the major known genetic risk factor for AD and has a gene-dose effect on the risk and age of onset of AD. Although several hypotheses have been proposed to explain this association, the underlying mechanisms are still not clear.

Studies from my laboratory have demonstrated a biological event that could play a major role in apoE4-related neuropathology. Specifically, apoE is subject to cleavage by a neuron-specific chymotrypsin-like serine protease that generates bioactive carboxyl-terminal-truncated forms of apoE *(Brecht et al., J. Neurosci. 2004, 24:2527–2534; Harris et al., Proc. Natl. Acad. Sci. USA. 2003, 100:10966–10971).* ApoE4 is more susceptible to cleavage than apoE3. The apoE fragments are found at higher levels in the brains of AD patients than in age- and sex-matched controls. When expressed in cultured neuronal cells or added exogenously to the cultures, the truncated apoE4 is neurotoxic, leading to cytoskeletal disruption and mitochondrial dysfunction and finally cell death *(Huang et al., Proc. Natl. Acad. Sci. USA. 2001, 98:8838–8843; Chang et al., Proc. Natl. Acad. Sci. USA. 2001, 102:18694–18699)*. Furthermore, expression of the carboxyl-terminal-truncated apoE4 causes AD-like neurodegeneration and behavioral deficits in transgenic mice *(Harris et al., Proc. Natl. Acad. Sci. USA. 2003, 100:10966–10971)*. Since we have demonstrated that apoE is synthesized by neurons under diverse physiological or pathological conditions *(Harris et al., J. Bio. Chem. 2004, 279:3862–3868; Xu et al., J. Neurosci. 2006, 26:4985–*4994; Xu et al., *J. Neurosci.* 2008, 28:1452–1459*)*, this cleavage could represent an early event in apoE4-related neuropathology (*Harris et al., J. Biol. Chem. 2004, 279:44795-44801).*

Based on these *in vitro* and *in vivo* observations, I hypothesize that apoE4 produced in neurons in response to stress or injury (*e.g.*, aging, Aβ toxicity, brain trauma, or oxidative stress) is uniquely susceptible to proteolytic cleavage by an apoE cleaving enzyme (AECE) and that the resulting bioactive carboxyl-terminal-truncated fragments, probably together with other AD related factors (*e.g.,* Aβ) induce neuropathology and associated behavioral deficits. Thus, AECE represents a new therapeutic target for AD drug development. In addition, protection of the apoE4 fragment interaction with cytoskeletal components or mitochondria might also be beneficial for treatment or prevention from AD. Currently, I have a 4-year research agreement with Merck Research Laboratory to develop anti-AD drugs targeting these two apoE4-related detrimental effects in CNS.

Recently, we also demonstrated that apoE4 impairs adult hippocampal neurogenesis (*Li et al., Cell Stem Cell. 2009, 5:634–645*). Mouse neural stem cells express apoE. ApoE knockout mice have significantly less hippocampal neurogenesis, but significantly more astrogenesis, than wildtype mice due to decreased Noggin expression in neural stem cells. In contrast, neuronal maturation in apoE4 knock-in mice is impaired due to reduced survival and function of GABAergic interneurons in the hilus of the hippocampus, and a $GABA_A$ receptor potentiator rescues the apoE4-associated decrease in hippocampal neurogenesis. Thus, apoE contributes to adult hippocampal neurogenesis, and apoE4 impairs GABAergic input to newborn neurons, leading to decreased neurogenesis.

Ongoing studies in my research program are to investigate the regulatory mechanisms of neuronal expression of apoE, to study the underlying mechanisms of apoE4's detrimental effect on GABAergic interneurons and its contribution to learning and memory deficits, to assess the mechanisms underlying apoE4's susceptibility to proteolysis, to determine the mechanisms by which apoE4 and its fragments cause neuronal and cognitive deficits, to identify and characterize the AECE and develop its inhibitors, and to test the inhibitors in our animal models and, ultimately, in AD patients.