BIOGRAPHICAL SKETCH

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NAME: Chang, Ta Yuan

eRA COMMONS USERNAME (credential, e.g., agency login): TYCHANG

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
National Taiwan University, Taipei, Taiwan	BS	06/1967	Chemistry
University of North Carolina at Chapel Hill, NC	PhD	06/1973	Biochemistry
Washington University Med School, St. Louis, MO	Postdoc	1973-1976	Biochemistry

A. PERSONAL STATEMENT

Our laboratory (with Dr. Catherine Chang as a Co-I) at Dartmouth has been working on cellular cholesterol metabolism in health and in diseases for many years. Our laboratory identified the gene that encodes ACAT1 and has been working on biochemical characterization and pathophysiological functions of ACAT1 for many years. ACAT1 is now considered to be a promising drug target to treat several human diseases, in part through the effort of the Chang lab at Dartmouth. Below, I list four refences that are most relevant to the current proposal. These references demonstrate that I am scientifically and technically well-qualified as the PI of this proposal.

1. Bryleva, E. Y., M. A. Rogers, C. C. Chang, F. Buen, B. T. Harris, E. Rousselet, N. G. Seidah, S. Oddo, F. M. LaFerla, T. A. Spencer, W. F. Hickey, and **T. Y. Chang**. 2010. *ACAT1* gene ablation increases 24(S)-hydroxycholesterol content in the brain and ameliorates amyloid pathology in mice with AD. *Proc Natl Acad Sci U S A* **107**: 3081-3086. *PMCID: PMC2840286*

2. Shibuya, Y., C. C. Chang, L. H. Huang, E. Y. Bryleva, and **T. Y. Chang**. 2014. Inhibiting ACAT1/SOAT1 in microglia stimulates autophagy-mediated lysosomal proteolysis and increases Abeta1-42 clearance. *J Neurosci* **34**: 14484-14501. *PMCID: PMC4813549*

3. De La Torre, A. L., C. Smith, J. Granger, F. L. Anderson, T. C. Harned, M. C. Havrda, C. C. Y. Chang, and **T. Y. Chang**. 2022. Facile method to incorporate high-affinity ACAT/SOAT1 inhibitor F12511 into stealth liposome-based nanoparticle and demonstration of its efficacy in blocking cholesteryl ester biosynthesis without overt toxicity in neuronal cell culture. *J Neurosci Methods* **367**: 109437. PMCID: PMC8775100

4. Rogers, M. A., C. C. Y. Chang, R. A. Maue, E. M. Melton, A. A. Peden, W. S. Garver, J. Lee, P. Schroen, M. Huang, and **T. Y. Chang**. 2022. *Acat1*/*Soat1* knockout extends the mutant Npc1 mouse lifespan and ameliorates functional deficiencies in multiple organelles of mutant cells. *Proc Natl Acad Sci U S A* **119**: e2201646119. PMCID: PMC9170141

<u>Ongoing and recent supported research that I would like to highlight includes:</u>

RO1 AG063544
PI Chang
09/30/2018–05/31/2023
Alleviating lysosomal defects in ADRDs by blocking cholesterol storage

R01 AG037609
PI Chang
07/01/2010–04/30/2020

B. POSITIONS AND HONORS

Positions and Employment

2021–2023 Associate Editor, *Frontiers in Aging Neuroscience*
2018–2021 Editorial Board member, *Journal of Lipid Research*
2016–present Ad hoc member, multiple NIH special emphasis panels
2009–2014 Editorial Board Member, *Journal of Biological Chemistry*
2008–present Professor, Biochemistry Dept, Geisel School of Medicine at Dartmouth
2005–2009 NIH Integrative Nutrition & Metabolic Process Study Section Member
2001–2006 Editorial Board Member, *Journal of Biological Chemistry*
2000–2008 Professor and Chair, Biochemistry Dept, Dartmouth Medical School
1997–2001 AHA National Research Study Committee Member
1995–2000 Visiting Professor, Biochemistry Dept, Kumamoto University Medical School, Japan
1995–2000 Editorial Board Member, *Journal of Biological Chemistry*
1976–2000 Assistant/Associate/Full Professor, Biochemistry Dept, Dartmouth Medical School

Honors

2021 Elected National Academy of Sciences Member
2011 Elected AAAS Fellow
1994–2004 NIH MERIT Award
1982–1987 NIH Research Career Development Award

Consultantships

2002–2016 Institute of Biotechnology and Pharmaceutical Research, NHRI, Taiwan
1998–2001 Chugai Pharmaceuticals, Gotemba, Japan
1998–2000 Pierre-Fabre Pharmaceutical Laboratories, Castres, France
1992–1994 Parke-Davis Pharmaceuticals, Ann-Arbor, MI

Invited Presentations in National/International Meetings (Since 2010)

2021 One of two organizes for the special issue of Exploration in Neuroprotection Therapy on "Cholesterol dyshomeostasis in neurological diseases" (2021)
2020 Diabetes Virtual Summer Camp, Wellesley, Massachusetts (2020)
2019 One of two Keynote Speakers, 3rd Annual National Conference on Metabolic Biology, Shanghai, China (2019).
2019 92nd Japan Biochemical Society Symposium, Japan (2019)
2017 Meeting the Challenge of Healthy Aging, EuroSciCon, London (2017)
2017 One of two organizers for JLR thematic series on "ApoE and Lipid Homeostasis in Alzheimer's Disease (2017)
2015 The 2015 Alzheimer's Disease Congress, London, UK (2015)
2015 Drug Discovery and Therapy World Congress, Boston (also as session co-chair) (2015)
2015 Neurological Disorders Summit, San Francisco (also as session chair) (2015)
2014 FASEB Meeting in Lipid Droplets (as session chair), VT (2014)
2013 Cold Spring Harbor Asia Meeting in Metabolism and Obesity, Suzhou (as special lecturer) (2013)
2011 The 84th Japan Biochemical Society Symposium, Japan (2011)
2010 Gordon Research Conference on Lipoprotein Metabolism, NH (2010)
2010 The18th International Symposium on Molecular Cell Biology of Macrophages, Japan (2010)
2010 The 1st International Symposium on Lipids: Cell Biology and Metabolism, China (also as session chair) (2010)

C. CONTRIBUTIONS TO SCIENCE

The Chang laboratory has been working on cellular cholesterol metabolism in health and in diseases since 1976. Our contributions in science can be categorized into four following areas:

1. In the early years, our laboratory used somatic cell genetics to study cholesterol metabolism. We mutagenized Chinese hamster ovary cells and isolated four classes of cholesterol mutants (1978-1994). Two of these mutants were used as cloning vehicles in the Brown and Goldstein laboratory to identify the *Scap* gene (1996) and the *S2p* gene (1997), which mediate the sterol regulatory element binding protein (SREBP) and its transcriptional control of many genes in lipid metabolism. The third mutant was used as a cloning vehicle in the Pentchev laboratory at the NIH to help identify the Niemann-Pick type C1 (*Npc1*) gene (1997), which plays a key role in intracellular cholesterol transport.

a. Chang, T. Y., and J. S. Limanek. 1980. Regulation of cytosolic acetoacetyl coenzyme A thiolase, 3-hydroxy-3-methylglutaryl coenzyme A synthase, 3-hydroxy-3-methylglutaryl coenzyme A reductase, and mevalonate kinase by low density lipoprotein and by 25-hydroxycholesterol in Chinese hamster ovary cells. *J Biol Chem* **255**: 7787-7795.

b. Rawson, R. B., N. G. Zelenski, D. Nijhawan, J. Ye, J. Sakai, M. T. Hasan, T. Y. Chang, M. S. Brown, and J. L. Goldstein. 1997. Complementation cloning of S2P, a gene encoding a putative metalloprotease required for intramembrane cleavage of SREBPs. *Mol Cell* **1**: 47-57.

c. Cadigan, K. M., D. M. Spillane, and T. Y. Chang. 1990. Isolation and characterization of Chinese hamster ovary cell mutants defective in intracellular low density lipoprotein-cholesterol trafficking. *J Cell Biol* **110**: 295-308.

d. Carstea, E. D., J. A. Morris, K. G. Coleman, S. K. Loftus, D. Zhang, C. Cummings, J. Gu, M. A. Rosenfeld, W. J. Pavan, D. B. Krizman, J. Nagle, M. H. Polymeropoulos, S. L. Sturley, Y. A. Ioannou, M. E. Higgins, M. Comly, A. Cooney, A. Brown, C. R. Kaneski, E. J. Blanchette-Mackie, N. K. Dwyer, E. B. Neufeld, T. Y. Chang, L. Liscum, J. F. Strauss, 3rd, K. Ohno, M. Zeigler, R. Carmi, J. Sokol, D. Markie, R. R. O'Neill, O. P. van Diggelen, M. Elleder, M. C. Patterson, R. O. Brady, M. T. Vanier, P. G. Pentchev, and D. A. Tagle. 1997. Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. *Science* **277**: 228-231.

2. The most significant research accomplishment of the Chang laboratory was to have opened the molecular era for the key cholesterol storage enzyme acyl-CoA: cholesterol acyltransferase 1 (ACAT1; named as sterol O-acyltransferase 1 and abbreviated as SOAT1 in GenBank). The ACAT enzyme activity was first identified by Alfin-Slater and colleagues in 1958; however, the molecular identity of ACAT remained elusive for the next 35 years. In 1993, our laboratory used the fourth “Chang mutant”, which is deficient in cholesterol esterification, as the cloning vehicle to identify the first ACAT gene *Acat1/Soat1.* I received a MERIT Award from NIH for this work. Our laboratory then purified the recombinant ACAT1 to homogeneity and demonstrated that ACAT1 is a single membrane protein regulated through substrate-driven allosteric control. We also showed that ACAT1 is a homo-tetrameric enzyme, a two-fold dimer, with nine membrane-spanning domains, and with its active site histidine embedded within the 7th transmembrane domain (1993–2005).

a. Cadigan, K. M., J. G. Heider, and T. Y. Chang. 1988. Isolation and characterization of Chinese hamster ovary cell mutants deficient in acyl-coenzyme A:cholesterol acyltransferase activity. *J Biol Chem* **263**: 274-282.

b. Chang, C. C., H. Y. Huh, K. M. Cadigan, and T. Y. Chang. 1993. Molecular cloning and functional expression of human acyl-coenzyme A:cholesterol acyltransferase cDNA in mutant Chinese hamster ovary cells. *J Biol Chem* **268**: 20747-20755.

c. Chang, C. C., C. Y. Lee, E. T. Chang, J. C. Cruz, M. C. Levesque, and T. Y. Chang. 1998. Recombinant acyl-CoA:cholesterol acyltransferase-1 (ACAT-1) purified to essential homogeneity utilizes cholesterol in mixed micelles or in vesicles in a highly cooperative manner. *J Biol Chem* **273**: 35132-35141.

d. Guo, Z. Y., S. Lin, J. A. Heinen, C. C. Chang, and T. Y. Chang. 2005. The active site His-460 of human acyl-coenzyme A:cholesterol acyltransferase 1 resides in a hitherto undisclosed transmembrane domain. *J Biol Chem* **280**: 37814-37826.

3. More recently, our laboratory has been investigating ACAT1 as a promising target for treating Alzheimer’s disease. Mechanistically, we demonstrated that blocking ACAT1 increases the capacity of

lysosomes to degrade denatured proteins/peptides, including oligomeric Abeta peptides and misfolded tau protein. We are also involved in demonstrating that ACAT1 in macrophages is a target for treating atherosclerosis, and diet-induced obesity (2010-present).

a. Bryleva, E. Y., M. A. Rogers, C. C. Chang, F. Buen, B. T. Harris, E. Rousselet, N. G. Seidah, S. Oddo, F. M. LaFerla, T. A. Spencer, W. F. Hickey, and T. Y. Chang. 2010. ACAT1 gene ablation increases 24(S)-hydroxycholesterol content in the brain and ameliorates amyloid pathology in mice with AD. *Proc Natl Acad Sci U S A* **107**: 3081-3086. *PMCID: PMC2840286*
b. Shibuya, Y., C. C. Chang, L. H. Huang, E. Y. Bryleva, and T. Y. Chang. 2014. Inhibiting ACAT1/SOAT1 in microglia stimulates autophagy-mediated lysosomal proteolysis and increases Abeta1-42 clearance. *J Neurosci* **34**: 14484-14501. *PMCID: PMC4205563*
c. Huang, L. H., E. M. Melton, H. Li, P. Sohn, M. A. Rogers, M. J. Mulligan-Kehoe, S. N. Fiering, W. F. Hickey, C. C. Chang, and T. Y. Chang. 2016. Myeloid Acyl-CoA:Cholesterol Acyltransferase 1 Deficiency Reduces Lesion Macrophage Content and Suppresses Atherosclerosis Progression. *J Biol Chem* **291**: 6232-6244. *PMCID: PMC4813549*
d. Huang, L. H., E. M. Melton, H. Li, P. Sohn, D. Jung, C. Y. Tsai, T. Ma, H. Sano, H. Ha, R. H. Friedline, J. K. Kim, E. Usherwood, C. C. Y. Chang, and T. Y. Chang. 2018. Myeloid-specific Acat1 ablation attenuates inflammatory responses in macrophages, improves insulin sensitivity, and suppresses diet-induced obesity. *Am J Physiol Endocrinol Metab* **315**: E340-E356. *PMCID: PMC6171008*

4. Our laboratory has made significant contributions towards understanding the function of the Niemann-Pick type C1 protein in intracellular cholesterol trafficking: We demonstrated that, in the mutant NPC mouse brain, cholesterol accumulation can be observed as early as postnatal day 9; we showed that Niemann-Pick type C1 protein is a cholesterol-binding protein. We also demonstrated that vesicular trafficking is involved in transporting a significant portion of LDL-derived cholesterol from the NPC1-containing endosomal compartment to the TGN compartment via vesicular trafficking. More recently, we have demonstrated that *Acat1*/*Soat1* KO extends mutant *Npc1* mouse lifespan and ameliorates functional deficiencies in multiple organelles in mutant *Npc1* cells. (2004-present).

a. Reid, P. C., N. Sakashita, S. Sugii, Y. Ohno-Iwashita, Y. Shimada, W. F. Hickey, and T. Y. Chang. 2004. A novel cholesterol stain reveals early neuronal cholesterol accumulation in the Niemann-Pick type C1 mouse brain. *J Lipid Res* **45**: 582-591.
b. Ohgami, N., D. C. Ko, M. Thomas, M. P. Scott, C. C. Chang, and T. Y. Chang. 2004. Binding between the Niemann-Pick C1 protein and a photoactivatable cholesterol analog requires a functional sterol-sensing domain. *Proc Natl Acad Sci U S A* **101**: 12473-12478.
c. Urano, Y., H. Watanabe, S. R. Murphy, Y. Shibuya, Y. Geng, A. A. Peden, C. C. Chang, and T. Y. Chang. 2008. Transport of LDL-derived cholesterol from the NPC1 compartment to the ER involves the trans-Golgi network and the SNARE protein complex. *Proc Natl Acad Sci U S A* **105**: 16513-16518. *PMCID: PMC2575451*
d. Rogers, M. A., C. C. Y. Chang, R. A. Maue, E. M. Melton, A. A. Peden, W. S. Garver, J. Lee, P. Schroen, M. Huang, and T. Y. Chang. 2022. Acat1/Soat1 knockout extends the mutant Npc1 mouse lifespan and ameliorates functional deficiencies in multiple organelles of mutant cells. *Proc Natl Acad Sci U S A* **119**: e2201646119. *PMCID: PMC9170141*

Complete List of Published Work in My Bibliography (No. of publications: 133):
https://www.ncbi.nlm.nih.gov/myncbi/ta%20yuan.chang.1/bibliography/public/