BIOGRAPHICAL SKETCH

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NAME: Tseng, Yu-Hua

eRA COMMONS USER NAME (credential, e.g., agency login): TSENG_YU-HUA

POSITION TITLE: Professor of Medicine, Harvard Medical School; Senior Investigator, Joslin Diabetes Center

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	B.S.	06/89	Medical Technology
National Taiwan University, Taipei, Taiwan	M.S.	06/91	Microbio. & Immunology
University of Wisconsin-Madison, Madison, WI	Ph.D.	08/97	Cell. & Mol. Biology
Joslin Diabetes Center / Harvard Medical School, Boston, MA	Postdoc.	06/04	Diabetes & Obesity

A. **Personal Statement**

I have dedicated my career to researching obesity and diabetes, utilizing a broad range of cellular, molecular, and physiological techniques to explore the mechanisms regulating energy homeostasis. My work focuses on the unique energy-burning properties of brown fat and its associated 'beige' fat. Our lab, alongside others, has underscored the dynamic interactions between adipose-resident stem/progenitor cells and the inductive cues that guide the development and thermogenic function of brown and beige adipocytes. We discovered that developmental growth factors, such as BMPs and FGFs, play a crucial role in the differentiation of thermogenic adipocytes and metabolic regulation. By employing distinct cell surface markers, we have identified and isolated tissue-resident adipose precursors. Recently, through single-cell RNA sequencing and lineage tracing, we uncovered a novel progenitor population that originates from vascular smooth muscle cells for thermogenic adipocytes. My colleagues and I have demonstrated that adult human brown fat is located in specific areas of the neck, and that human brown fat precursors can be cultivated and differentiated in vitro. My lab has developed primary and immortalized human brown and white preadipocyte cell lines, which have been distributed to numerous labs worldwide. Using clonal human brown and white fat progenitor cells, we identified novel genetic biomarkers that predict the thermogenic potential of these cells once matured. Recently, we engineered human white preadipocytes to produce human brown-like cells using CRISPR technology to activate endogenous uncoupling protein 1 expression. Transplanting the CRISPR-engineered cells into mice has been shown to prevent diet-induced obesity and improve metabolic syndrome, underscoring the potential of this approach in combating obesity and metabolic diseases.

Beyond its role in energy expenditure, brown fat serves as an effective secretory tissue. Part of its beneficial effects are mediated through the production of signaling molecules that facilitate inter-organ communication in metabolic regulation. Our research, utilizing both targeted and untargeted lipidomics analyses, identifies novel brown fat-derived bioactive lipid mediators, specifically, 12,13-diHOME and 12-HEPE, which are capable of regulating fatty acid and glucose metabolism, respectively. Importantly, levels of these lipid mediators in human plasma are negatively correlated with BMI and insulin resistance, underscoring the potential of these bioactive lipids in counteracting obesity and metabolic disorders. Recently, we revealed that cold stimulation promotes BAT to produce maresin 2, a member of the specialized pro-resolving mediators of bioactive lipids, which aids in resolving inflammation associated with obesity. Our current ongoing research aims to identify the receptors for these lipid mediators and develop analogs or mimics of the bioactive lipids. These studies hold the promise of uncovering new therapeutic approaches for obesity and its associated metabolic complications.

Research support and representative publications are shown below:

R01 DK102898
Tseng (PI)
07/03/2015 – 03/31/2025
NIH/NIDDK

Fibroblast Growth Factor and Energy Metabolism

R01 DK132469
Tseng (PI)
04/06/2022 – 03/31/2027
NIH/NIDDK
Transcriptional and epigenetic regulation of thermogenic adipocyte program

R01 DK133528
Tseng (PI)
09/01/2022 – 08/31/2026
NIH/NIDDK
Dissecting the thermogenic adipose niche

(No Project Number)
Tseng (PI)
11/01/2022 – 3/31/2025 (NCE)
Joslin Diabetes Center, Beth Isreal Lahey Health
Cellular senescence and the pathogenesis of diabetes and its complications

a. Sugimoto S, Mena HA, Sansbury BE, Kobayashi S, Tsuji T, Wang CH, Yin X, Huang TL, Kusuyama J, Kodani SD, Darcy J, Profeta G, Pereira N, Tanzi RE, Zhang C, Serwold T, Kokkotou E, Goodyear LJ, Cypess AM, Leiria LO, Spite M, **Tseng YH**. Brown adipose tissue-derived MaR2 contributes to cold-induced resolution of inflammation. Nat Metab. 2022 Jun;4(6):775-790. *PMCID: PMC9792164.*
b. Shamsi F, Piper M, Ho L-L, Huang TL, Gupta A, Streets A, Lynes MD, **Tseng YH**. Vascular smooth muscle-derived TRPV1-positive progenitors are a source of cold-induced thermogenic adipocytes. Nat Metab 2021 Apr. *PMCID: PMC8076094*.
c. Leiria LO, Wang CH, Lynes MD, Yang K, Shamsi F, Sato M, Sugimoto S, Chen EY, Bussberg V, Narain NR, Sansbury BE, Darcy J, Huang TL, Kodani SD, Sakaguchi M, Rocha AL, Schulz TJ, Bartelt A, Hotamisligil GS, Hirshman MF, Leyen KV, Goodyear LJ, Bluher M, Cypess AM, Kiebish MA, Spite M, **Tseng YH**. 12-lipoxygenase regulates cold adaptation and glucose metabolism by producing the omega-3 lipid 12-HEPE from brown fat. Cell Metab 2019;30(4):768-783.e7. *PMCID: PMC6774888.*
d. Lynes M, Leiria L, Lundh M, Bartelt A, Shamsi F, Huang TL, Takahashi H, Hirshman MF, Schlein C, Lee A, Baer LA, May FJ, Gao F, Narain NR, Chen EY, Kiebish MA, Cypess AM, Blüher M, Goodyear LJ, Hotamisligil GS, Stanford KI, **Tseng YH**. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. Nat Med 2017; May;23(5):631-637. *PMCID: PMC5699924.*

B. Positions and Honors

Positions, Scientific Appointments, and Employment

2020-present	Professor of Medicine, Harvard Medical School
2016-present	Senior Investigator, Section on Integrative Physiology and Metabolism, JDC
2014-present	Faculty, Biological and Biomedical Sciences, Harvard Medical School
2011-present	Principal Faculty, Harvard Stem Cell Institute, Cambridge, MA
2022-present	Associate Member, the Broad Institute, Cambridge, MA
2007-present	Investigator, Harvard Nutrition Obesity Research Center, Cambridge, MA
2014-2020	Associate Professor of Medicine, Harvard Medical School
2012-2016	Investigator, Section on Integrative Physiology and Metabolism, JDC
2009-2014	Assistant Professor of Medicine, Harvard Medical School
2006-2012	Assistant Investigator, Section on Obesity and Hormone Action, JDC
2004-2009	Instructor of Medicine, Harvard Medical School, Boston, MA

Other Experience and Professional Memberships

2021	*Ad hoc* grant reviewer, Swiss National Science Foundation
2020	*Ad hoc* grant reviewer, National Science Foundation
2015-2019	Regular member, Cellular Aspects of Diabetes and Obesity Study Section, National Institutes of Health (NIH)
2015, 2018, 2021	*Ad hoc* grant reviewer, Special Emphasis Panel/Scientific Review Group, NIH
2014	*Ad hoc* grant reviewer of Peer Reviewed Medical Research Program, Department of Defense, U.S. Army Medical Research and Material Command

2014-present	Editorial Board, Genes & Diseases
2013-present	Director, Animal Facility, JDC
2013-present	Chair, Institutional Animal Care & Use Committee, JDC
2012-2018	Editorial Board, Scientific Reports
2011-present	Editorial Board, Adipocyte
2010-2012	Co-Director, Enrichment Core, Diabetes and Endocrinology Research Center, JDC
2010-present	Member, Responsible Conduct of Research Committee, JDC
2010-present	Editorial Board, Metabolism
2009-2014	Regular member, Research Grant Review Committee, American Diabetes Association

Honors

2024	WIELD Trailblazer: Women Shaping Diabetes and Metabolism Research and Care
2022	The Everfront Award, Pan Pacific Symposium on Stem Cells and Cancer Research, Taiwan
2021	The J Denis McGarry Prize, Montreal Diabetes Center, Montreal, Canada
2020	Honorary Master Degree, Harvard University, Cambridge, MA
2017	Armen Tashjian Award for Excellence in Endocrine Research, Harvard T.H. Chan School of Public Health, Boston, MA
2015	Keynote Lecture, Conference of Biomedical Science, Chinese Physiology Association, Taipei, Taiwan
2014	Hazel K. Stiebeling Lecture, Nutrition Department, Florida State University, Tallahassee, FL
2012-14	Visiting Professorship, National Defense Medical Center, Taipei, Taiwan
2011	Keynote Lecture, Celebration of 60th Anniversary of Southern Medical University, Guangzhou, China
2009	Keynote Lecture, Adiposcience Symposium, Osaka, Japan
2007	Travel Award, The Endocrine Society
2006	Travel Award, NIH “Lipodystrophy and Altered Fat Deposition” Workshop
2005	The Eleanor and Miles Shore Scholars in Medicine, Harvard Medical School
2001-2004	Individual National Research Service Award, NIH
2000	Travel Award, Keystone Symposia
1991	Outstanding Young Scientist in Immunology Award, Institute of Microbiology and Immunology, National Taiwan University
1989-1991	Graduate Fellowship, The Ministry of Education, Taiwan
1985-1991	The Tseng's Clansman Association Scholarship
1985-1991	Taipei Provincial Government Scholarships, Taipei, Taiwan
1985-1989	The Book Coupon Award, National Taiwan University, Taipei, Taiwan

C. Contributions to Science

1. **Establishing the interplays between inductive signals and resident progenitors in regulation of brown fat differentiation and function.** Brown adipose tissue (BAT) is specialized in energy expenditure and can counteract obesity and related metabolic disorders. In 2008, we made a fundamental discovery, which demonstrated that bone morphogenetic protein (BMP) 7, a member of the TGFβ superfamily of growth factors, specifically promotes brown adipocyte differentiation in committed and uncommitted adipose progenitors. We demonstrated an important role of BMP7 in promoting brown adipocyte differentiation and thermogenesis in vivo and in vitro and provide a potential novel therapeutic approach for the treatment of obesity. Recently, using scRNA-seq, we discovered a novel population of vascular smooth muscle-derived Trpv1-expressing adipose progenitors as the source of thermogenic adipocytes.
   a. Shamsi F, Piper M, Ho L-L, Huang TL, Gupta A, Streets A, Lynes MD, **Tseng YH**. Vascular smooth muscle-derived TRPV1-positive progenitors are a source of cold-induced thermogenic adipocytes. Nat Metabo 2021 Apr 12. DOI: 10.1038/s42255-021-00373-z. *PMCID: PMC8076094*
   b. Zhang H, Guan M, Townsend KL, Huang TL, An D, Yan X, Xue R, Schulz TJ, Winnay J, Mori M, Hirshman MF, Kristiansen K, Tsang JS, White AP, Cypess AM, Goodyear LJ, **Tseng YH**. MicroRNA-455 regulates brown adipogenesis via a novel HIF1an-AMPK-PGC1α signaling network. *EMBO Reports* 2015; 2015 Oct;16(10):1378-93. *PMCID: PMC4766451*
   c. Townsend KL, An D, Lynes MD, Huang TL, Zhang, H, Goodyear LJ, **Tseng YH.** Increased mitochondrial activity in BMP7-treated brown adipocytes, due to increased CPT1- and CD36-mediated fatty acid uptake. Antiox Redox Signal 2013; 19(3):243-257. *PMCID: PMC3691916*

d. **Tseng YH**, Kokkotou E, Schulz TJ, Huang TL, Winnay JN, Taniguchi CM, Tran TT, Suzuki R, Espinoza DO, Yamamoto Y, Ahrens MJ, Dudley AT, Norris AW, Kulkarni RN, Kahn CR. New role of bone morphogenetic protein-7 in brown adipogenesis and energy expenditure. Nature 2008; 454(7207): 1000-4. #Corresponding author. *PMCID: PMC2745972*

2. **Unraveling cross-talk between brown and beige fat depots in maintaining energy homeostasis**: Rodent data suggest the existence of two types of brown fat cells: the constitutive BAT (cBAT), which is of embryonic origin and anatomically located in the interscapular region of mice, and the recruitable BAT (rBAT) that resides within white adipose tissue. We created a unique mouse model with genetic ablation of type 1A BMP-receptor (BMPR1A) in brown adipogenic progenitor cells leading to a severe paucity of cBAT. This, in turn increases sympathetic input to WAT, thereby promoting the formation of rBAT within white fat depots. Interestingly, mice lacking insulin receptor in brown fat precursors also have decreased interscapular BAT mass and compensatory browning. These findings uncover a previously unknown compensatory mechanism aimed at restoring total brown fat-mediated thermogenic capacity in the body is sufficient to maintain normal temperature homeostasis as well as resistant to diet-induced obesity.
   a. Lynes MD, Schulz TJ, Pan AJ, **Tseng YH**. Disruption of insulin signaling in Myf5-expressing progenitors leads to marked paucity of brown fat, but normal muscle development. Endocrinology 2015 May;156(5):1637-47. *PMCID: PMC4398768*
   b. Huang P, Schulz TJ, Beauvais A, **Tseng YH**, Gussoni E. Intramuscular adipogenesis is inhibited by myo-endothelial progenitors with functioning Bmpr1a signaling. Nat Comm 2014; 5;5:4063. *PMCID: PMC4084855*
   c. Schulz TJ, Huang P, Huang TL, Xue R, McDougall LE, Townsend KL, Cypess AM, Mishina Y, Gussoni E, **Tseng YH.** Brown fat paucity due to impaired BMP signaling induces compensatory browning of white fat. Nature 2013; 495(7441):379-83. *PMCID: PMC3623555*
   d. Schulz TJ, Huang TL, Tran TT, Zhang H, Townsend KL, Shadrach J, Cerletti M, McDougall LE, Giorgadze N, Tchkonia T, Schrier D, Falb D, Kirkland JL, Wagers AJ, **Tseng YH.** Identification of inducible brown adipocyte progenitors residing in skeletal muscle and white fat. Proc Natl Acad of Sci U S A 2011; 108(1):143-8. *PMCID: PMC3017184*

3. **Human brown fat – anatomical locations, clonal analyses and gene profiling identify genetic biomarkers of human brown and white preadipocyte thermogenic potential**: While brown fat was once considered non-existent in adult humans, several seminal papers published in 2009 demonstrated that the neck, supraclavicular and spinal cord regions of adult humans contain substantial deposits of UCP1-positive adipocytes. We generated clonal cell lines from human neck fat and characterized their adipogenic differentiation and metabolic function *in vitro* and *in vivo* after transplantation into immune deficient nude mice. Using clonal analysis and gene expression profiling, we identified unique sets of gene signatures in human preadipocytes that could predict the thermogenic potential of these cells once matured in culture into adipocytes. These data highlight the cellular heterogeneity in human BAT and WAT. To test the utility of cell-based therapy, we generated human brown-like (HUMBLE) cells by engineering human white preadipocytes using CRISPR activation system. Transplantation of HUMBLE cells into mice could prevent diet-induced obesity and ameliorate metabolic syndrome.
   a. Wang, CH, Lundh M, Fu A, Kriszt R, Huang TL, Lynes MD, Leiria LO, Shamsi F, Darcy J, Greenwood BP, Narain NR, Tolstikov V, Smith KL, Emanuelli B, Chang YT, Hagen S, Danial NN, Kiebish MA, **Tseng YH**. CRISPR-engineered human brown-like adipocytes prevent diet-induced obesity and ameliorate metabolic syndrome in mice. Sci Transl Med 2020;12(558):1-14. *PMCID: PMC7704293*
   b. Xue R, Lynes MD, Dreyfuss JM, Shamsi F, Schulz TJ, Zhang H, Huang TL, Townsend KL, Li Y, Takahashi H, Weiner LS, White AP, Lynes MS, Rubin LL, Goodyear LJ, Cypess AM **Tseng YH.** Clonal analyses and gene profiling identify genetic biomarkers of human brown and white preadipocyte thermogenic potential. Nat Med 2015; 21(7):760-768. *PMCID: PMC4496292*
   c. Cypess AM, White AP, Vernochet C, Schulz TJ, Xue R, Sass C, Huang TL, Roberts-Toler C, Weiner LS, Sze C, Chacko A, Deschamps LN, Herder LM, Truchan N, Glasgow AL, Holman AR, Gavrila A, Hasselgren P-O, Mori MA, Molla M, **Tseng YH**. Anatomical localization, gene expression profiling, and functional characterization of human neck brown fat. Nat Med 2013; 19(5):635-9. *PMCID: PMC3650129*
   d. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, **Tseng YH**, Doria A, Kolodny GM, Kahn CR. Identification and significance of brown adipose tissue in human adult. N Engl J Med 2009; 360(15):1509-17. *PMCID: PMC2859951*

4. **Discovering new adipokines/lipokines secreted from activated brown fat and defining their roles in energy metabolism**: In addition to its well-recognized function in energy dissipation, at least part of brown fat's beneficial effect is due to its secretory function, and consequent capacity to affect metabolic functions

in other tissues. We revealed that FGF6 and FGF9 are adipokines that can regulate UCP1 expression in adipose precursors through a novel transcriptional network. Using unbiased lipidomics analyses, we unraveled dynamic lipid changes in adipose tissue in response to cold and identified new bioactive lipid mediators that mediate different beneficial effects of brown fat activation. 12,13 diHOME and 12-HEPE, which are secreted from brown fat in response to the challenge of cold, function to facilitate nutrient utilization and thermogenesis. More recently, we discovered that cold and β3-adrenergic stimulation promote BAT to produce maresin 2 (MaR2), a member of the specialized pro-resolving mediators of bioactive lipids, that play a role in the resolution of inflammation in obesity.

a. Sugimoto S, Mena HA, Sansbury BE, Kobayashi S, Tsuji T, Wang CH, Yin X, Huang TL, Kusuyama J, Kodani SD, Darcy J, Profeta G, Pereira N, Tanzi RE, Zhang C, Serwold T, Kokkotou E, Goodyear LJ, Cypess AM, Leiria LO, Spite M, Tseng YH. Brown adipose tissue-derived MaR2 contributes to cold-induced resolution of inflammation. Nat Metab. 2022, 4(6):775-790. *PMCID: PMC9792164.*
b. Shamsi F, Xue R, Huang TL, Lundh M, Liu Y, Leiria LO, Lynes MD, Kempf E, Wang CH, Sugimoto S, Nigro P, Landgraf K, Schulz T, Li Y, Emanuelli B, Kothakota S, Williams LT, Jessen N, Pedersen SB, Böttcher Y, Blüher B, Körner A, Goodyear LJ, Mohammadi M, Kahn CR, **Tseng YH**. FGF6 and FGF9 regulate UCP1 expression independent of brown adipogenesis. Nat Comm 2020, 11(1): 1421. *PMCID: PMC7078224*.
c. Leiria LO, Wang CH, Lynes MD, Yang K, Shamsi F, Sato M, Sugimoto S, Chen EY, Bussberg V, Narain NR, Sansbury BE, Darcy J, Huang TL, Kodani SD, Sakaguchi M, Rocha AL, Schulz TJ, Bartelt A, Hotamisligil GS, Hirshman MF, Leyen KV, Goodyear LJ, Bluher M, Cypess AM, Kiebish MA, Spite M, **Tseng YH**. 12-lipoxygenase regulates cold adaptation and glucose metabolism by producing the omega-3 lipid 12-HEPE from brown fat. Cell Metab 2019;30(4):768-783.e7. *PMCID: PMC6774888*.
d. Lynes M, Leiria L, Lundh M, Bartelt A, Shamsi F, Huang TL, Takahashi H, Hirshman MF, Schlein C, Lee A, Baer LA, May FJ, Gao F, Narain NR, Chen EY, Kiebish MA, Cypess AM, Blüher M, Goodyear LJ, Hotamisligil GS, Stanford KI, **Tseng YH**. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. Nat Med 2017; May;23(5):631-637. *PMCID: PMC5699924*

5. **Establishing the role insulin receptor substrates in survival and differentiation of brown adipocytes**: Insulin promotes adipocyte differentiation via a complex signaling network involving multiple insulin receptor substrates (IRSs). In 2002-2005, we investigated the role of the IRS proteins in brown adipocyte differentiation by using brown fat precursor cell lines derived from all four IRS KO mice. Combining microarray analyses and molecular approaches, we revealed a highly coordinated pattern of gene expression changes that predict the potential of brown preadipocytes to become adipocytes.
   a. Cypess AM, Zhang H, Schulz TJ, Huang TL, Espinoza DO, Kristiansen K, Unterman TG, **Tseng YH.** Insulin/IGF-1 regulation of necdin and brown adipocyte differentiation via CREB- and FoxO1-associated pathway. Endocrinology 2011; 152(10):3680-9. *PMCID: PMC3176640*
   b. **Tseng YH**, Butte AJ, Kokkotou E, Yechoor VK, Taniguchi CM, Kriauciunas KM, Cypess AL, Niinobe M, Yoshikawa K, Patti ME, Kahn CR. Prediction of preadipocyte differentiation by gene expression reveals role of insulin receptor substrates and necdin. Nat Cell Biol 2005; 7(6):601-11. PMID: 15895078
   c. **Tseng YH**, Kriauciunas KM, Kokkotou E, Kahn CR. Differential roles of insulin receptor substrates in brown adipocyte differentiation. Mol Cellular Biol 2004; 24(5):1918-29. *PMCID: PMC350563*
   d. **Tseng YH**, Ueki K, Kriauciunas KM, Kahn CR. Differential roles of insulin receptor substrates in the anti-apoptotic function of insulin-like growth factor-1 and insulin. J Biol Chem 2002; 277(35): 31601-11. *PMCID: PMC350563*.

Complete List of Published Work in MyBibliography: http://www.ncbi.nlm.nih.gov/pubmed/?term=yu-hua+tseng