



## **Hitoshi SHIMANO, MD, PhD**

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### **PROFILE**

My research goal has been to comprehend the whole biology, especially pathophysiology of different diseases in different organs in the light of diversity, dynamism and versatility of lipids and their metabolism hoping to bring a new concept into the central dogma of molecular biology.

Thanks to recent progress in omics and lipidomics, I enjoy the mystery of diversity of fatty acids in the membrane lipids, especially chain length of fatty acids highlighting importance of endogenous lipogenesis together with cholesterol metabolism in the various pathophysiology linking to signaling by nuclear receptors in atherosclerosis.

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### **EDUCATION**

**1978-1984**      **The University of Tokyo, Medical Department of Medicine.**

**1992**            **thesis (dissertation) Dr of Medical Science, the University of Tokyo:**  
"Effect of Overexpression of apolipoprotein E on Plasma Lipoprotein  
Metabolism in Transgenic Mice"

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### **PROJECT INTERESTS**

- Identification of upstream factors and mechanisms against regulation by transcription factors and co-factors involved in energy, especially lipid metabolism
- Effects of tissue fatty acid composition, especially chain length of C16 and C18 on a wide variety of pathophysiology

- Understanding of biological well-beingness in cells and bodies by identifying cellular sensors and effectors of energy metabolism to regulate cellular stress responses in homeostasis and allostasis
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## **Employment / Professional Experience**

- 1984-1986 Resident, Internal Medicine, Tokyo University Hospital, Tokyo, Japan
- 1986-1992 Medical and Research Staff, Third Department of Internal Medicine, Tokyo University Hospital, Tokyo, Japan
- 1992-1993 Postdoctoral research Fellow, Japan Society for the Promotion of Science for Japanese Junior Scientists, Japan
- 1993 Assistant Professor, Third Department of Internal Medicine, Tokyo University Hospital, Japan
- 1993-1996 Postdoctoral Research Fellow / Assistant Instructor of Molecular Genetics, Southwestern Medical Center, Dallas, TX
- 1996-1998 Instructor of Molecular Genetics, Southwestern Medical Center, Dallas, TX
- 1998-2000 Investigator of the Third Department of Internal Medicine, Tokyo University Hospital, Japan
- 2000-2005 Assistant Professor, Internal Medicine, University of Tsukuba, Japan
- 2002 -2008 Project Reader, Center for Tsukuba Advanced Research Alliance, University of Tsukuba, Japan
- 2004 - Division Head of Pathological Nutrition, Tsukuba University Hospital,
- 2005 - 2008 Associate Professor, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tokyo, Japan
- 2007- Clinical Professor, Tsukuba University Hospital, Tokyo, Japan
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## **QUALIFICATIONS AND MEMBERSHIPS**

- Qualified Medical Practitioner (Ministry of Health, Labor and Welfare, Japan, 1984)
- The Japan Society of Internal Medicine– Councilor
- The Japan Atherosclerosis Society – Director
- Japanese Society of Molecular Medicine – Director
- The Japan Endocrine Society – Councilor
- The Japan Diabetes Society – Councilor
- The Japan Diabetes Complication Society – Director
- The American Diabetes Association – member
- The American Heart Association – member

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## PROJECTS (major on-going national only)

### **AMED-CREST from Japan Agency for Medical Research and Development, AMED:**

Chain length of fatty acids, elucidation of mechanisms of disease control and development of fundamentals toward medical evolution

### **Grants-in-Aid from the Ministry of Science, Education, Culture and Technology of Japan:**

#### **the Scientific Research on Innovative Areas program "Inflammation Cellular Sociology"**

Elucidation of Molecular Basis of Inflammation and Fibrosis Regulated by Quantity and Quality of Organ Lipids in Inflammation Cellular Society and Development of New Preventive Strategy for Inflammatory Diseases

#### **Grant-in-Aid for Scientific Research (A)**

Molecular mechanism of organella homeostasis regulated by quantity and quality of lipids

#### **Grant-in-Aid for Challenging Research (Exploratory)**

Determination of physiological significance of cholesterol synthesis system in brain formation and its application to pathological conditions

Elucidation of the novel mechanism of the fatty acid-induced pancreatic beta-cell proliferation and its application to diabetes treatment

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## HONORS

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| 2001 | Young Investigator Award, Japanese Society of Diabetes Mellitus and Complications |
| 2003 | Investigation Promoting Award, Japanese Society of Endocrinology                  |
| 2004 | Congress Award, Japanese Society of Clinical Molecular Medicine                   |
| 2006 | Investigation Promoting Award, Japan Medical Association                          |
| 2009 | Gotoh Yuichiro Award 2009 of Japan Atherosclerosis Society                        |

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## PROFESSIONAL PRESENTATIONS (invited only)

- Shimano H: A New Aspect of Organ Lipids in Metabolic Diseases:Lessons from Elovl6 ( "Metabolic complications of obesity" Journal of Internal Medicine:) 14th key symposium at St Catharine's College (Cambridge UK) 2017.9.21

- Shimano H, Matsuzaka T. A new aspect of organ lipids in various diseases, lessons from Elovl6. The 19<sup>th</sup> Takeda Science Foundation Symposium on Bioscience “Chronic Inflammation~Initiation, Progression and Resolution (Takeda Pharmaceutical Company Limited, Osaka) 2017.1.20-1.21
- Shimano H. : A new aspect of organ lipids in metabolic diseases, lessons from Elovl6. Homeodynamics in Clocks, Sleep and Metabolism —Tokyo Translational therapeutics meeting (at Ito Hall, Ito International Research Center, The University of Tokyo) 2014.9.24(水)
- Shimano H. : New Aspect of Organ Lipids in Metabolic Diseases and Atherosclerosis from Quantity to Quality: Lessons from Elovl6. 9<sup>th</sup> Metabolic Syndrome, Type 2 Diabetes and Atherosclerosis Congress (Kyoto International Conference Center, Kyoto), 2014.9.12-9.14
- Shimano H. : Journey for sightseeing energy metabolism from metabo to brain. The 1<sup>st</sup> Annual IIS Symposium (Tsukuba International Congress Center) 2013.3.27
- Shimano H. : Quantity control and quality control of fatty acids: new aspects of metabolic syndrome and atherosclerosis. China-Japan International Conference on Atherosclerosis 2012 (Lanzhou University, China) July 24-July 26, 2012
- Shimano H. : A New Aspect of Abnormal Tissue Lipids in Lipotoxicity: From Quantity to Quality. 8<sup>th</sup> International Diabetes Federation Western Pacific Region Congress (2010 IDF WPR Congress) (Busan, Korea) 2010.10.18
- Shimano H. : New aspect of abnormal tissue lipids in lipotoxicity: from quantity to quality (Symposia). ICE2010 (14<sup>th</sup> International Congress of Endocrinology: ICE 2010) at Kyoto2010.3.30
- Shimano H. : New aspect of abnormal tissue lipids in insulin resistance and metabolic syndrome. From quantity to quality of lipids U.S &#8211; Japan &#8211; Vietnam Joint Scientific Meeting Nutrition and Metabolism Panel(US-Japan Cooperative Medical Science Program) Ho Chi Minh City, Vietnam, October 28, 2008
- Shimano H. : New aspect of abnormal tissue lipids in insulin resistance A lesson from Elovl-6 deficient mice. Seoul Symposium on Obesity and Diabetes, Seoul, Korea, April 12, 2008
- Shimano H. : SREBP-1c and lipotoxicity, Symposia, The 6<sup>th</sup> International Group of Insulin Secretion (IGIS) France, 2007
- Shimano H. : Transcription factors that regulate insulin sensitivity in the liver and metabolic syndrome. (Symposia), The 5<sup>th</sup> Congress of Asian Pacific Society of Atherosclerosis and Vascular Diseases (APSAVD) Korea (International Convention Center, Jeju), 2006.4.12-4.15
- Shimano H. : Transcription factors that regulate insulin sensitivity in the liver and metabolic syndrome Japan-Korea Joint Symposium, 83th Japan Physiology Society at Guma, 2006
- Shimano H. : Transcriptional Regulation of Energy Metabolism and Insulin Resistance, International Academy Nutrition and Aging (IANA) International Symposium at Tokyo Luchon Seminar, 2004.10.1-2
- Shimano H. : Energy transcription factors and atherosclerosis, XIIIth International Symposium on Atherosclerosis Satellite Symposium (Kyoto) 2003.9.28-10.2
- Shimano H. : Transcriptional regulation of energy metabolism and atherosclerosis, XIIIth International Symposium on Atherosclerosis Workshop(Kyoto) 2003.9.28-10.2

- Shimano H. : RXR regulation of SREBP-1c and pathways of lipogenesis. FASEB Summer Conference : Molecular Biology of Intestinal Lipid Transport and Metabolism (Snowmass, Colorado) 2003.8.2-8.72
- Shimano H. : A crucial role of sterol regulatory element binding protein-1 in the regulation of lipogenic gene expression by polyunsaturated fatty acids. 4th Congress of the International Society for the Study of Fatty Acids and Lipids ISSFAL, 2000
- Shimano H., Yamada N, Ishibashi S, Yazaki Y. : Roles of apolipoprotein E in lipoprotein metabolism and atherosclerosis. 12 th Drugs Affecting Lipid Metabolism International Symposium, 1995
- Shimano H. : Overexpression of apo E in transgenic mice; disappearance of atherogenic lipoproteins. 12<sup>th</sup> SENRI Scientific Seminar at Osaka 1992

## REFERENCES

### Original Articles (selected only)

1. Nakagawa Y, Wang Y, Han SI, Okuda K, Oishi A, Yagishita Y, Kumagai K, Ohno H, Osaki Y, Mizunoe Y, Araki M, Murayama Y, Iwasaki H, Konishi M, Itoh N, Matsuzaka T, Sone H, Yamada N, Shimano H. Enterohepatic Transcription Factor CREB3L3 Protects Atherosclerosis via SREBP Competitive Inhibition. **Cell Mol Gastroenterol Hepatol**. 2021;11(4):949-971. doi: 10.1016/j.jcmgh.2020.11.004. Epub 2020 Nov 24. PMID: 33246135; PMCID: PMC7900604
2. Kawasaki M, Kambe A, Yamamoto Y, Arulmozhiraja S, Ito S, Nakagawa Y, Tokiwa H, Nakano S, Shimano H. Elucidation of Molecular Mechanism of a Selective PPAR $\alpha$  Modulator, Pemafibrate, through Combinational Approaches of X-ray Crystallography, Thermodynamic Analysis, and First-Principle Calculations. **Int J. Mol Sci**. 2020 Jan 6;21(1):361. doi: 10.3390/ijms21010361. PMID: 31935812; PMCID: PMC6981837
3. Matsuzaka T, Kuba M, Koyasu S, Yamamoto Y, Motomura K, Arulmozhiraja S, Ohno H, Sharma R, Shimura T, Okajima Y, Han SI, Aita Y, Mizunoe Y, Osaki Y, Iwasaki H, Yatoh S, Suzuki H, Sone H, Takeuchi Y, Yahagi N, Miyamoto T, Sekiya M, Nakagawa Y, Ema M, Takahashi S, Tokiwa H, Shimano H. Hepatocyte ELOVL Fatty Acid Elongase 6 Determines Ceramide Acyl-Chain Length and Hepatic Insulin Sensitivity in Mice. **Hepatology**. 2020 May;71(5):1609-1625. doi: 10.1002/hep.30953. Epub 2020 Feb 7. PMID: 31529722.
4. Shichino S, Ueha S, Hashimoto S, Otsuji M, Abe J, Tsukui T, Deshimaru S, Nakajima T, Kosugi-Kanaya M, Shand FH, Inagaki Y, Shimano H, Matsushima K. Transcriptome network analysis identifies protective role of the LXR/SREBP-1c axis in murine pulmonary fibrosis. **JCI Insight**. 2019 Jan 10;4(1). pii: 122163. doi: 10.1172
5. Nakamura Y, Matsuzaka T, Tahara-Hanaoka S, Shibuya K, Shimano H, Nakahashi-Oda C, Shibuya A. Elovl6 regulates mechanical damage-induced keratinocyte death and skin inflammation. **Cell Death Dis**. 2018 Dec 5;9(12):1181. doi: 10.1038

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7. Zhao H, Matsuzaka T, Nakano Y, Motomura K, Tang N, Yokoo T, Okajima Y, Han SI, Takeuchi Y, Aita Y, Iwasaki H, Yatoh S, Suzuki H, Sekiya M, Yahagi N, Nakagawa Y, Sone H, Yamada N, Shimano H. Elovl6 Deficiency Improves Glycemic Control in Diabetic db/db Mice by Expanding  $\beta$ -Cell Mass and Increasing Insulin Secretory Capacity. **Diabetes**. 2017 Jul; 66(7): 1833-1846.
8. Oishi Y, Spann NJ, Link VM, Muse ED, Strid T, Edillor C, Kolar MJ, Matsuzaka T, Hayakawa S, Tao J, Kaikkonen MU, Carlin AF, Lam MT, Manabe I, Shimano H, Saghatelian A, Glass CK. SREBP1 Contributes to Resolution of Pro-inflammatory TLR4 Signaling by Reprogramming Fatty Acid Metabolism. **Cell Metab**. 2017 Feb 7; 25(2): 412-427.
9. Nakagawa Y, Satoh A, Tezuka H, Han SI, Takei K, Iwasaki H, Yatoh S, Yahagi N, Suzuki H, Iwasaki Y, Sone H, Matsuzaka T, Yamada N, Shimano H. CREB3L3 controls fatty acid oxidation and ketogenesis in synergy with PPAR $\alpha$ . **Sci Rep**. 2016 Dec 16; 6: 39182.
10. Sunaga H, Matsui H, Anjo S, Syamsunarno MR, Koitabashi N, Iso T, Matsuzaka T, Shimano H, Yokoyama T, Kurabayashi M. Elongation of Long-Chain Fatty Acid Family Member 6 (Elovl6)-Driven Fatty Acid Metabolism Regulates Vascular Smooth Muscle Cell Phenotype Through AMP-Activated Protein Kinase/Krüppel-Like Factor 4 (AMPK/KLF4) Signaling. **J Am Heart Assoc**. 2016 Nov 23; 5(12). e004014.
11. Kikuchi T, Orihara K, Oikawa F, Han SI, Kuba M, Okuda K, Satoh A, Osaki Y, Takeuchi Y, Aita Y, Matsuzaka T, Iwasaki H, Yatoh S, Sekiya M, Yahagi N, Suzuki H, Sone H, Nakagawa Y, Yamada N, Shimano H. Intestinal CREBH overexpression prevents high-cholesterol diet-induced hypercholesterolemia by reducing Npc111 expression. **Mol Metab**. 2016 Sep 17; 5(11): 1092-1102.
12. Takeuchi Y, Yahagi N, Aita Y, Murayama Y, Sawada Y, Piao X, Toya N, Oya Y, Shikama A, Takarada A, Masuda Y, Nishi M, Kubota M, Izumida Y, Yamamoto T, Sekiya M, Matsuzaka T, Nakagawa Y, Urayama O, Kawakami Y, Iizuka Y, Gotoda T, Itaka K, Kataoka K, Nagai R, Kadowaki T, Yamada N, Lu Y, Jain MK, Shimano H. KLF15 Enables Rapid Switching between Lipogenesis and Gluconeogenesis during Fasting. **Cell Rep**. 2016 Aug 30; 16(9): 2373-2386.
13. Nakagawa Y, Oikawa F, Mizuno S, Ohno H, Yagishita Y, Satoh A, Osaki Y, Takei K, Kikuchi T, Han SI, Matsuzaka T, Iwasaki H, Kobayashi K, Yatoh S, Yahagi N, Isaka M, Suzuki H, Sone H, Takahashi S, Yamada N, Shimano H. Hyperlipidemia and hepatitis in liver-specific CREB3L3 knockout mice generated using a one-step CRISPR/Cas9 system. **Sci Rep**. 2016 Jun 13;6:27857.
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17. Sunaga H, Matsui H, Ueno M, Maeno T, Iso T, Syamsunarno MR, Anjo S, Matsuzaka T, Shimano H, Yokoyama T, Kurabayashi M. Deranged fatty acid composition causes pulmonary fibrosis in Elovl6-deficient mice. **Nat Commun.** 2013; 4: 2563.
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- IRS-2-mediated insulin signaling in the liver. **Nature Cell Biology** 6(4): 351-7, 2004 Apr [Epub 2004 Mar 14]
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- Dual regulation of mouse delta-5 and-6 desaturase gene expression by SREBP-1 and PPARalpha. **J Lipid Res** 43(1): 107-14, 2002 Jan
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