

## Masashi Yanagisawa, M.D., Ph.D.

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### Professional membership:

American Academy of Sleep Medicine  
Japanese Society of Sleep Research, The Japan Neuroscience Society

### Education and Professional Appointments:

1985 M.D. (*summa cum laude*), 1985, University of Tsukuba  
1988 Ph.D. in Medical Sciences, 1988, University of Tsukuba  
1988 – 1989 Postdoctoral fellow, Department of Pharmacology, University of Tsukuba  
1989 – 1991 Assistant Professor of Pharmacology, University of Tsukuba  
1991 – 1991 Assistant Professor of Pharmacology, Kyoto University School of Medicine  
1991 – 1996 Associate Professor of Molecular Genetics, University of Texas Southwestern Medical Center at Dallas (UTSW); Associate Investigator, Howard Hughes Medical Institute (HHMI)  
1996 – 2014 Professor of Molecular Genetics, UTSW; Investigator, HHMI  
1998 – 2014 The Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science, UTSW  
2001 – 2007 Director, Yanagisawa Orphan Receptor Project (JST/ERATO)  
2010 – 2014 Professor and Director, FIRST program, University of Tsukuba  
2012 – Present Director, International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba  
2014 – Present Adjunct Professor of Molecular Genetics, UTSW

### Honors/Awards:

2003 Elected Member, National Academy of Sciences  
2016 Medal with Purple Ribbon, Government of Japan  
2017 Erwin Von Bälz Preis, Boehringer Ingelheim  
2018 The Asahi Prize, Asahi Shimbun Foundation  
2018 The Keio Medical Science Prize, Keio University Medical Science Fund  
2019 Takamine Memorial Daiichi Sankyo Prize, Daiichi Sankyo Foundation of Life Science  
2019 Person of Cultural Merit, Government of Japan  
2022 Toshihiko Tokizane Memorial Award, The Japan Neuroscience Society  
2022 2023 Breakthrough Prize in life sciences  
2023 Clarivate Citation Laureate

### Biographical Narrative:

In 1988, as a graduate student at University of Tsukuba, Yanagisawa discovered endothelin, a potent vasoconstrictor peptide from vascular endothelial cells, which sparked an intense research activity in the field. In the subsequent year, his group identified a G protein-coupled receptor for endothelin, which would become an important drug target; the endothelin receptor antagonist bosentan was approved in 2001 for the treatment of pulmonary hypertension. After moving to University of Texas Southwestern Medical Center at Dallas in 1991 as a young principal investigator, he identified the endothelin-converting enzyme, a metalloprotease that generate the active, mature endothelin peptides. Through gene-targeting experiments in mice, he also discovered in 1994 that the endothelin pathway is essential for embryonic development of certain neural crest derived tissues, and that endothelin-B receptor deficiency causes Hirschsprung disease in mice and humans. In 1996, he initiated a systematic search for endogenous ligands of “orphan” G protein-coupled receptors, which resulted in his 1998 discovery of orexin, a hypothalamic neuropeptide. He then discovered in 1999 that orexin deficiency causes the sleep disorder narcolepsy. This opened up a new avenue in sleep research, and led to a better understanding of sleep/wake switching mechanisms in the brain. The notion that orexin is an important endogenous waking agent led to the development of orexin receptor antagonists as sleep-inducing drug, first of which, suvorexant, was approved in 2014. Recognizing, however, that the fundamental mechanism for sleep homeostasis still remains a mystery, in 2010 he embarked upon a highly ambitious project of polysomnography (EEG/EMG)-based forward genetic screen for sleep/wake abnormalities in chemically mutagenized mouse cohort. This large-scale project is now continuing in Tsukuba, Japan, and has recently led to identification of several new genes that are importantly involved in the regulation of sleep amounts and the level of sleep need.

### Important Publications:

- 1) Yanagisawa, M., Kurihara, H., Kimura, S., Tomobe, Y., Kobayashi, M., Mitsui, Y., Yazaki, Y., Goto, K., Masaki, T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332: 411-415, 1988
- 2) Sakurai, T., Yanagisawa, M., Takawa, Y., Miyazaki, H., Kimura, S., Goto, K., Masaki, T. Cloning of a cDNA encoding a non-isopeptide selective subtype of the endothelin receptor. *Nature* 348: 732-735, 1990
- 3) Xu, D., Emoto, N., Giaid, A., Slaughter, C., Kaw, S., deWit, D., Yanagisawa, M. ECE-1: A membrane-bound metalloprotease that catalyzes the proteolytic activation of big endothelin-1. *Cell* 78: 473-485, 1994
- 4) Baynash, A.G., Hosoda, K., Giaid, A., Richardson, J.A., Emoto, N., Hammer, R.E., Yanagisawa, M. Interaction of endothelin-3 with endothelin-B receptor is essential for development of epidermal melanocytes and enteric neurons. *Cell* 79: 1277-1285, 1994
- 5) Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R.M., Tanaka, H., Williams, S.C., Richardson, J.A., Kozlowski, G.P., Wilson, S., Arch, J.R.S., Buckingham, R.E., Haynes, A.C., Carr, S.A., Annan, R.S., McNulty, D.E., Liu, W.S., Terrett, J.A., Elshourbagy, N.A., Bergsma, D.J., Yanagisawa, M. Orexins and orexin receptors: A family of hypothalamic neuropeptides and G

- protein-coupled receptors that regulate feeding behavior. *Cell* 92: 573-585, 1998
- 6) Chemelli, R.M., Willie, J.T., Sinton, C.M., Elmquist, J.K., Scammell, T., Lee, C., Richardson, J.A., Williams, S.C., Xiong, Y., Kisanuki, Y., Fitch, T.E., Nakazato, M., Hammer, R.E., Saper, C.B., Yanagisawa, M. Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. *Cell* 98: 437-451, 1999
  - 7) Ikeda, Y., Kumagai, H., Skach, A., Sato, M., Yanagisawa, M. Modulation of circadian glucocorticoid oscillation through adrenal opioid-CXCR7 signaling alters emotional behavior. *Cell* 155: 1323-1336, 2013.
  - 8) Lee, I.T., Chang, A.S., Manandhar, M., Shan, Y., Fan, J., Izumo, M., Ikeda, Y., Motoike, T., Dixon, S., Seinfeld, E.J., Takahashi, S.J., Yanagisawa, M. Neuromedin S-Producing Neurons Act as Essential Pacemakers in the Suprachiasmatic Nucleus to Couple Clock Neurons and Dictate Circadian Rhythms. *Neuron* 85: 1086-1102, 2015.
  - 9) Nagahara, T., Saitoh, T., Kutsumura, N., Irukayama-Tomobe, Y., Ogawa, Y., Kuroda, D., Gouda, H., Kumagai, H., Fujii, H., Yanagisawa, M., Nagase, H. Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists. *J. Med. Chem.* 58: 7931-7937, 2015.
  - 10) Funato H., Miyoshi C., Fujiyama T., Kanda T., Sato M., Wang Z., Ma J., Nakane S., Tomita J., Ikkyu A., Kakizaki M., Hotta N., Kanno S., Komiya H., Asano F., Honda T., Kim J.S., Harano K., Muramoto H., Yonezawa T., Mizuno S., Miyazaki S., Connor L., Kumar V., Miura I., Suzuki T., Watanabe A., Abe M., Sugiyama F., Takahashi S., Sakimura K., Hayashi Y., Liu Q., Kume K., Wakana S., Takahashi J.S., Yanagisawa M. Forward genetic analysis of sleep in randomly mutagenized mice. *Nature* 539: 378-383, 2016
  - 11) Ogawa, Y., Irukayama-Tomobe, Y., Murakoshi, N., Kiyama, M., Ishikawa, Y., Hosokawa, N., Tominaga, H., Uchida, S., Kimura, S., Kanuka, M., Morita, M., Hamada, M., Takahashi, S., Hayashi, Y., Yanagisawa, M. Peripherally administered orexin improves survival of mice with endotoxin shock. *eLife* DOI: 10.7554/eLife.21055, 2016
  - 12) Nagase, H., Yamamoto, N., Yata, M., Ohru, S., Okada, T., Saitoh, T., Kutsumura, N., Nagumo, Y., Irukayama-Tomobe, Y., Ishikawa, Y., Ogawa, Y., Hirayama, S., Kuroda, D., Watanabe, Y., Gouda, H., Yanagisawa, M. Design and Synthesis of Potent and Highly Selective Orexin 1 Receptor Antagonists with a Morphinan Skeleton and Their Pharmacologies. *J. Med. Chem.* 60: 1018-1040, 2017
  - 13) Irukayama-Tomobe, Y., Ogawa, Y., Tominaga, H., Ishikawa, Y., Hosokawa, N., Ambai, S., Kawabe, Y., Uchida, S., Nakajima, R., Saitoh, T., Kanda, T., Vogt, K., Sakurai, T., Nagase, H., Yanagisawa, M. A non-peptide orexin type-2 receptor agonist ameliorates narcolepsy-cataplexy symptoms in mouse models. *Proc. Natl. Acad. Sci. USA* 114: 5731-5736, 2017
  - 14) Kaushik, M.K., Aritake, K., Imanishi, A., Kanbayashi, T., Ichikawa, T., Shimizu, T., Urade, Y., Yanagisawa, M. Continuous intrathecal orexin delivery inhibits cataplexy in a murine model of narcolepsy. *Proc. Natl. Acad. Sci. USA* 115:6046-6051, 2018
  - 15) Wang, Z., Ma, J., Miyoshi, C., Li, Y., Sato, M., Ogawa, Y., Lou, T., Ma, C., Gao, X., Lee, C., Yang, X., Zhou, S., Hotta-Hirashima, N., Klewe-Nebenius, D., Ikkyu A., Kakizaki, M., Kanno, S., Cao, L., Peng, J., Yu, Y., Funato, H., Yanagisawa, M., Liu, Q. Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. *Nature* 558: 435-439, 2018
  - 16) Honda, T., Fujiyama, T., Miyoshi, C., Ikkyu, A., Hotta-Hirashima, N., Kanno, S., Mizuno, S., Sugiyama, F., Takahashi, S., Funato, H., Yanagisawa, M. A single phosphorylation site of SIK3 regulates daily sleep amounts and sleep need in mice. *Proc. Natl. Acad. Sci. USA* 115: 10458-10463, 2018
  - 17) Miyoshi, C., Kim, S.J., Ezaki, T., Ikkyu, A., Kanno, M., Kakizaki, M., Yamada, M., Wakana, S., Yanagisawa, M., Funato, H. Methodology and theoretical basis of forward genetic screening for sleep/wakefulness in mice. *Proc. Natl. Acad. Sci. USA* 116: 16062-16067, 2019
  - 18) Yamabe, M., Horie, K., Shiokawa, H., Funato, H., Yanagisawa, M., Kitagawa, H. MC-SleepNet: Large-scale Sleep Stage Scoring in Mice by Deep Neural Networks. *Scientific Reports* 9: 15793, 2019
  - 19) Takahashi, T., Sunagawa, G., Soya, S., Abe, M., Sakurai, K., Ishikawa, K., Yanagisawa, M., Hama, H., Hasegawa, E., Miyawaki, A., Sakimura, K., Takahashi, M., Sakurai, T. A discrete neuronal circuit induces a hibernation-like state in rodents. *Nature* 583: 109-114, 2020
  - 20) Kumar, D., Koyanagi, I., Carrier-Ruiz, A., Vergara, P., Srinivasan, S., Sugaya, Y., Kasuya, M., Yu, T.S., Vogt, K., Muratani, M., Ohnishi, T., Singh, S., Teixeira, C.M., Chérasse, Y., Naoi, T., Wang, S.H., Nondhalee, P., Osman, B.A., Kaneko, N., Sawamoto, K., Kernie, S.G., Sakurai, T., McHugh, T.J., Kano, M., Yanagisawa, M., Sakaguchi, M. Sparse Activity of Hippocampal Adult-Born Neurons during REM Sleep Is Necessary for Memory Consolidation. *Neuron* 107: 552-565, 2020
  - 21) Hirose, Y., Kitazono, T., Sezaki, M., Abe, M., Sakimura, K., Funato, H., Handa, H., Vogt, K., Yanagisawa, M. Hypnotic effect of thalidomide is independent of teratogenic ubiquitin/proteasome pathway. *Proc. Natl. Acad. Sci. USA* 117: 23106-23112, 2020
  - 22) Ogawa, Y., Miyoshi, C., Obana, N., Yajima, K., Hotta, N., Ikkyu, A., Kanno, S., Soga, T., Fukuda, S., Yanagisawa, M. Gut microbiota depletion by chronic antibiotic treatment alters the sleep/wake architecture and sleep EEG power spectra in mice. *Scientific Reports* 10: 19554, 2020
  - 23) Kaushik, M.K., Aritake, K., Imanishi, A., Kanbayashi, T., Urade, Y., Yanagisawa, M. Induction of narcolepsy-like symptoms by orexin receptor antagonists in mice. *Sleep* 44: zsab043, 2021
  - 24) Iwasaki, K., Fujiyama, T., Nakata, S., Park, M., Miyoshi, C., Hotta, N., Ikkyu, A., Kakizaki, M., Sugiyama, F., Mizuno, S., Abe, M., Sakimura, K., Takahashi, S., Funato, H., Yanagisawa, M. Induction of mutant *Sik3* Sleepy allele in neurons in late infancy increases sleep need. *Journal of Neuroscience* 41: 2733-2746, 2021
  - 25) Suzuki-Abe, H., Sonomura, K., Nakata, S., Miyanishi, K., Mahmoud, A., Hotta-Hirashima, N., Miyoshi, C., Sato, T., Funato, H., Yanagisawa, M. Metabolomic and pharmacologic analyses of brain substances associated with sleep pressure in mice. *Neuroscience Research* 117: 16-24, 2022
  - 26) Kim, S.J., Hotta-Hirashima, N., Asano, F., Kitazono, T., Iwasaki, K., Nakata, S., Komiya, H., Asama, N., Matsuoka, T., Fujiyama T., Ikkyu, A., Kakizaki, M., Kanno, S., Choi, J., Kumar, D., Tsukamoto, T., Mahmoud, A., Mizuno, S., Miyazaki, S., Tsuneoka, Y., Sugiyama, F., Takahashi, S., Hayashi, Y., Muratani, M., Liu, Q., Miyoshi, C., Yanagisawa, M., Funato, H. Kinase signalling in excitatory neurons regulates sleep quantity and depth. *Nature* published online, 2022
  - 27) Zhou, R., Wang, G., Li, Q., Meng, F., Liu, C., Gan, R., Ju, D., Liao, M., Xu, J., Sang, D., Gao, X., Zhou, S., Wu, K., Sun, Q., Guo, Y., Wu, C., Chen, Z., Chen, L., Shi, B., Wang, H., Wang, X., Li, H., Cai, T., Bin, L., Wang, F., Funato, H., Yanagisawa, M., Zhang, E.E., Liu, Q. A signaling pathway for transcriptional regulation of sleep amount in mice. *Nature* published online, 2022