BIOGRAPHICAL SKETCH

NAME: YAMANAKA, Naoki

POSITION TITLE: Associate Professor of Entomology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Tokyo, Tokyo, Japan	B.S.	03/2002	Agriculture
University of Tokyo, Tokyo, Japan	Ph.D.	03/2007	Biological Science
University of Tokyo, Tokyo, Japan	Postdoctoral	09/2007	Biological Science
University of Minnesota	Postdoctoral	03/2014	Developmental Genetics

A. Personal Statement

Throughout my career, I have been working on the neuroendocrine control of insect development. More specifically, the major focus of my research has been on signaling pathways that are working both upstream and downstream of the production and release of ecdysone, a lipophilic steroid hormone in insects. As a PI of the NIH Director's New Innovator Award (DP2; 2018-2023) and the Pew Biomedical Scholars Award from the Pew Charitable Trusts (2017-2021), I am leading a project to reveal the molecular mechanisms of the production, release, and uptake of ecdysone in the fruit fly *Drosophila melanogaster*, which has successfully led to some groundbreaking findings and relevant publications as listed below:

1. Okamoto N, **Yamanaka N**. (2020) Steroid Hormone Entry into the Brain Requires a Membrane Transporter in *Drosophila*. *Curr. Biol.* 30:359-366.e3.
1. Okamoto N, Viswanatha R, Bittar R, Li Z, Haga-Yamanaka S, Perrimon N, **Yamanaka N**. (2018) A Membrane Transporter Is Required for Steroid Hormone Uptake in *Drosophila*. *Dev. Cell* 47:294-305.
3. Ohhara Y, Kobayashi S, **Yamanaka N**. (2017) Nutrient-Dependent Endocycling in Steroidogenic Tissue Dictates Timing of Metamorphosis in *Drosophila melanogaster*. *PLoS Genet.* 13(1):e1006583.
4. **Yamanaka N**, Marqués G, O'Connor MB. (2015) Vesicle-Mediated Steroid Hormone Secretion in *Drosophila melanogaster*. *Cell* 163:907-919.

B. Positions and Honors

Positions and Employment

2006 – 2007 Research Fellow (DC2), Japan Society for the Promotion of Science (research fellowship for graduate students; supervisor: Hiroshi Kataoka)
2007 – 2008 Research Fellow (PD), Japan Society for the Promotion of Science (postdoctoral research fellowship; supervisor: Hiroshi Kataoka)
2008 – 2010 Postdoctoral Associate, Howard Hughes Medical Institute at the University of Minnesota (supervisor: Michael B. O'Connor)
2010 – 2012 Postdoctoral Fellow, Japan Society for the Promotion of Science (postdoctoral research fellowship for research abroad; supervisor: Michael B. O'Connor)
2012 – 2014 Postdoctoral Associate, University of Minnesota (supervisor: Michael B. O'Connor)
2014 – Assistant Professor, Department of Entomology, University of California, Riverside
2020 – Associate Professor, Department of Entomology, University of California, Riverside

Other Experience and Professional Memberships

2003 – Member, Japan Society for Bioscience, Biotechnology, and Agrochemistry
2009 – Member, Genetics Society of America
2014 – Member, Entomological Society of America

Honors

2009 25th Inoue Research Award for Young Scientists, Inoue Foundation for Science (awarded to the top 30 academic dissertations accepted in Japan in past 3 years)
2012 Pathway to Independence Award (K99/R00), NIH/NICHD
2017 Pew Biomedical Scholar
2018 NIH Director's New Innovator Award (DP2), NIH

C. Contributions to Science

1. As an independent investigator, I am currently leading an effort to characterize how steroid hormone production, release, and uptake are regulated at the molecular level in fruit flies. This resulted in an unexpected finding that the insect steroid hormone ecdysone is accumulated into vesicles and released from the steroidogenic tissue, the prothoracic gland (PG), via exocytosis (2015). We also identified and characterized an evolutionarily conserved membrane transporter required for cellular uptake of ecdysone (2018), and most recently we also identified its critical function in the blood-brain barrier to incorporate ecdysone into the brain (2020). Altogether, these results challenge the prevailing assumption that all steroid hormones can freely pass through the phospholipid bilayer of cell membranes by simple diffusion, and may therefore have an enormous impact on both basic and clinical aspects of steroid hormone biology.

   a. **Yamanaka N**, Marqués G, O'Connor MB. (2015) Vesicle-Mediated Steroid Hormone Secretion in *Drosophila melanogaster*. *Cell* 163:907-919.
   b. Okamoto N, Viswanatha R, Bittar R, Li Z, Haga-Yamanaka S, Perrimon N, **Yamanaka N**. (2018) A Membrane Transporter Is Required for Steroid Hormone Uptake in *Drosophila*. *Dev. Cell* 47:294-305.
   c. Okamoto N, **Yamanaka N**. (2020) Steroid Hormone Entry into the Brain Requires a Membrane Transporter in *Drosophila*. *Curr. Biol.* 30:359-366.e3.

2. During early stages of my career, I focused on identifying and characterizing novel neuropeptide signaling pathways that regulate steroidogenesis in insects. Traditionally, the regulation of insect steroidogenesis has been described within a simple framework, where steroid production is only stimulated by a brain neuropeptide called the prothoracicotropic hormone (PTTH). On the contrary, my early publications clearly showed that there are other neuropeptides that finely regulate the production of steroids in insects. These findings are now described in insect physiology textbooks.

   a. **Yamanaka N**, Hua YJ, Mizoguchi A, Watanabe K, Niwa R, Tanaka Y, Kataoka H. (2005) Identification of a novel prothoracicostatic hormone and its receptor in the silkworm *Bombyx mori*. *J. Biol. Chem.* 280:14684-14690.
   b. **Yamanaka N**, Zitnan D, Kim YJ, Adams ME, Hua YJ, Suzuki Y, Suzuki M, Suzuki A, Satake H, Mizoguchi A, Asaoka K, Tanaka Y, Kataoka H. (2006) Regulation of insect steroid hormone biosynthesis by innervating peptidergic neurons. *Proc. Natl. Acad. Sci. U.S.A.* 103:8622-8627.
   c. **Yamanaka N**, Hua YJ, Roller L, Spalovská-Valachová I, Mizoguchi A, Kataoka H, Tanaka Y. (2010) *Bombyx* prothoracicostatic peptides activate the sex peptide receptor to regulate ecdysteroid biosynthesis. *Proc. Natl. Acad. Sci. U.S.A.* 107:2060-2065.

3. I was also committed to an effort to identify the receptor for PTTH (2009). This work opened up an opportunity to investigate detailed functions of this classical insect hormone, which led to the unexpected finding of its function in regulating light avoidance behavior (2013).

   a. Rewitz KF, **Yamanaka N**, Gilbert LI, O'Connor MB. (2009) The insect neuropeptide PTTH activates receptor tyrosine kinase torso to initiate metamorphosis.
   Science 326:1403-1405.
   b. **Yamanaka N***, Romero NM*, Martin FA*, Rewitz KF, Sun M, O'Connor MB, Léopold P. (2013) Neuroendocrine control of *Drosophila* larval light preference.
   Science 341:1113-1116. (*=equal contributions)

4. I joined two international collaborations aimed to characterize genes functioning in the PG in a comprehensive manner. These studies have established this endocrine gland as an ideal model for studying molecular machineries of steroidogenesis.

   a. Danielsen ET, Moeller ME, **Yamanaka N**, Ou Q, Laursen JM, Soenderholm C, Zhuo R, Phelps B, Tang K, Zeng J, Kondo S, Nielsen CH, Harvald EB, Faergeman NJ, Haley MJ, O'Connor KA, King-Jones K, O'Connor MB, Rewitz KF. (2016) A *Drosophila* Genome-Wide Screen Identifies Regulators of Steroid Hormone Production and Developmental Timing.
   Dev. Cell 37(6):558-70.
   b. Ou Q, Zeng J, **Yamanaka N**, Brakken-Thal C, O'Connor MB, King-Jones K. (2016) The Insect Prothoracic Gland as a Model for Steroid Hormone Biosynthesis and Regulation.
   Cell Rep. 16(1):247-62.

5. I collaborated with Naoki Okamoto to identify and characterize the first insulin-like growth factor (IGF) in insects. Although it was known that insects have insulin-like peptides that consist of A- and B-chains like mammalian insulin, nobody had previously reported a single chain, IGF-like peptide in insects. Our studies identified and characterized such IGF-like peptides in insects for the first time, and demonstrated the significance of studying insulin/IGF signaling in insects.

   a. Okamoto N, **Yamanaka N**, Satake H, Saegusa H, Kataoka H, Mizoguchi A. (2009) An ecdysteroid-inducible insulin-like growth factor-like peptide regulates adult development of the silkmoth *Bombyx mori*.
   FEBS J. 276:1221-1232.
   b. Okamoto N*, **Yamanaka N***, Yagi Y, Nishida Y, Kataoka H, O'Connor MB, Mizoguchi A. (2009) A fat body-derived IGF-like peptide regulates postfeeding growth in *Drosophila*.
   Dev. Cell 17:885-891. (*=equal contributions)
   c. Okamoto N, **Yamanaka N**. (2015) Nutrition-dependent control of insect development by insulin-like peptides.
   Curr. Opin. Insect Sci. 11:21-30.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/naoki.yamanaka.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

DP2 GM132929 Yamanaka (PI) 09/30/2018 – 05/31/2023
NIH – Office of the Director
Membrane steroid hormone transporters in development and reproduction
The goal of this study is to elucidate the function of Ecdysone Importer (EcI), a membrane transporter we recently found to be required for cellular uptake of ecdysone, in flies and mosquitoes to develop novel methodologies for controlling insect development and reproduction.
Role: PI

Pew Biomedical Scholars Program Yamanaka (PI) 08/01/2017 – 07/31/2021
The Pew Charitable Trusts
Transporter-mediated steroid hormone uptake by animal cells
The goal of this study is to elucidate the function of EcI in other animal species.
Role: PI

Agriculture and Food Research Initiative (AFRI) Yamanaka (PI) 09/01/2019 – 08/31/2021
USDA/NIFA
Characterizing unique gustatory abilities in bumble bees
The goal of this project is to identify cellular and molecular components controlling bumble bee gustation.
Role: PI

W. M. Keck Foundation Medical Research Grant Haga-Yamanaka (PI) 02/01/2018 – 01/31/2021
W. M. Keck Foundation
Functional analysis of membrane steroid hormone importers
The goal of this study is to elucidate the function of EcI and its homologs in both *Drosophila* and mammals, and develop chemical reagents that can control the function of these potential steroid hormone importers.
Role: Co-Investigator

2017188 Bloch (PI) 11/01/2018 – 10/31/2022
US - Israel Binational Science Foundation (BSF)
Regulation of body size-based caste differentiation in bumble bees
The goal of this study is to elucidate molecular pathways controlling bumble bee caste differentiation.
Role: Co-Investigator

Completed Research Support

K99/R00 HD073239 Yamanaka (PI) 07/20/2012 – 12/31/2017
NIH – NICHD
Molecular mechanisms of steroid hormone secretion and trafficking
The goal of this project was to elucidate the machinery and regulatory mechanisms of steroid hormone release and trafficking, by using the fruit fly *Drosophila* as a model organism.
Role: PI

Agriculture and Food Research Initiative (AFRI) Woodard (PI) 03/01/2018 – 02/29/2020
USDA/NIFA
Improving commercial pollination by manipulating bumble bee development
The goal of this project is to identify molecular components controlling bumble bee development and establish methodologies to manipulate their functions.
Role: Co-Investigator