BIOGRAPHICAL SKETCH

NAME: **Holly A. Ingraham, Ph.D.**

eRA COMMONS USER NAME (credential, e.g., agency login): **HOLLYI**

POSITION TITLE: **Professor of Cellular and Molecular Pharmacology, UCSF**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of California, San Diego (Revelle College)	B.A.	1975	Biology-High Honors
University of California, San Diego (Revelle College)	B.A.	1975	Psychology-High Honors
University of California, San Diego	Ph.D.	1981	Physiology/Pharmacology

A. Personal Statement

We study hormonal control of neuronal circuits in the female brain and peripheral tissues. We are particularly keen to understand how fluctuations or permanent loss of hormones during different life stages result in adaptive responses that affect **female physiology**. Defining the cellular and molecular basis of hormone action in responsive neurons and cells is highly relevant to chronic disorders that degrade the quality of life. Among the multiple diseases affecting men and women, our work is highly relevant to age-related metabolic decline, irritable bowel syndrome, osteoporosis, and frailty, which are all prevalent in females. My initial research program at UCSF focused on defining molecular pathways that control the early phases of mammalian sex determination. Today, we study natural biological variances in males and females that may contribute to chronic disease states in women. As evidenced by our publication record, we employ multifaceted approaches that span neuroscience, mouse genetics, and whole-animal physiology. Recent publications are listed below.

1. Venkataraman, A., Figueroa, EE, Casto, J., Castro-Navarro, FM., Soota, D., Brierley, SM., Julius, D. and **H.A. Ingraham**. A Cellular Basis for Heightened Gut Sensitivity in Females bioRxiv (2025), doi: 10.1101/2025.05.23.654927 May 28, PMID: 40501885, In Press at Science.
2. Babey ME, Krause WC, Chen K, Herber CB, Torok, Z., Nikkanen J, Rodriquez R, Zhang X, Castro-Navarro F, Wang Y, Villeda S, Wheeler, Leach, JK, Lane NE, Scheller EL, Chan CKF, Ambrosi TH, and **H.A. Ingraham**. A Maternal Brain Hormone that Builds Bone. bioRxiv (2023) Aug 29; PubMed PMID: 37693376; PMCID: PMC10491109, Nature (2024) AOP July 10th, PMID: 38987585, PMCID: PMC11306098.
3. Nikkanen, J. Leong, Y.A, Krause, W.C., Corbit, K.C., Tran, J.L., Dermadi, D., Masche, J.A., Van Ry, T., Cox, J.E., Weiss, E.J., Gokcumen, O., Chawla, A., and **H.A. Ingraham**. An evolutionary trade-off between host immunity and metabolism drives fatty liver in male mice. bioRxiv (2022) Science (2022) Oct 21;378(6617):290-295, PMID: 36264814, PMCID: PMC9870047.
4. Krause, W.C., R. Rodriguez, B. Gegenhuber, N. Matharu, A.N. Rodriguez, A.M. Padilla, K. Toma, C.B. Herber, S.M. Correa, X. Duan, N. Ahituv, J. Tollkuhn, and **H.A. Ingraham**, Oestrogen engages brain MC4R signaling to drive physical activity in female mice. bioRxiv (2020), Nature (2021) Nov;599(7883):131-135. Epub 2021 Oct 13, PMID: 34646010, PMCID: PMC9113400.

Another primary focus of my academic activities is mentoring younger scientists as they transition to faculty positions at R1 institutions. As the Director of an NIGMS training program, UCSF has successfully placed ~65% of Scholars in faculty positions at R1/R3 institutions over the past 10 years by utilizing individualized mentoring and career development plans. This approach includes assisting them with NIH K transition awards and faculty job applications. A recent Q&A session published in the November issue of Neuron highlights my reflections on my career path.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2020 – Pres. Herzstein Endowed Professor of Molecular Physiology
2016 – Pres. Director of UCSF IRACDA Scholar Program
2010 – 2020 Associate Vice-Chair, UCSF, Dept. of Cellular and Molecular Pharmacology
2004 – Pres. Professor, UCSF, Dept. Cellular and Molecular Pharmacology
2004 – 2020 Herzstein Distinguished Investigator in Molecular Physiology
2002 – 2007 Professor, UCSF, Department of Physiology with a joint appointment in the Department of OB/GYN and Reproductive Sciences
1999 – 2002 Associate Professor, UCSF, Department of Physiology with a joint appointment in the Department of Reproductive Sciences
1994 – 1999 Assistant Professor, Tenure Track UCSF, Department of Physiology with a joint appointment in the Department of Reproductive Sciences
1991 – 1994 Assistant Professor in Residence, with Joint appointment in the Department of Physiology University of California, San Francisco, and OB/GYN and Reproductive Sciences
1990 – 1991 Assistant Research Endocrinologist, Dept. of Medicine, University of California, San Diego
1987 – 1990 Research Associate with Dr. Michael Geoffrey Rosenfeld HHMI, University of California, San Diego
1981 – 1985 Postdoctoral Fellow and Research Associate with Drs. G.A. Evans and S.F. Heinemann, The Salk Institute for Biological Studies
1977 – 1981 Physiology and Pharmacology Graduate Student with Dr. M. Goulian, University of California, San Diego, Dept. of Medicine. Thesis "Effects of 5-Fluorodeoxyuridine on intracellular metabolism of deoxyuridylate."

Awards and Honors

2026 Distinguished Public Lecture Series – Fralin Medical Center, Virginia Tech, VA
2026 Presidential Public Lecture Series – Simons Foundation, New York, NY
2026 Lois Taylor Ellison, MD Lecture – Medical College of Georgia, Augusta, GA
2026 Plenary Lecture - Federation of European Neuroscience Societies (FENS) – Barcelona, SPAIN
2026 **Harris Memorial Lectureship** – International Congress of Neuroendocrinology, Nagoya, JAPAN
2025 Lunenfeld-Tanenbaum Research Institute (LTRI) Distinguished Lecture, Toronto, CANADA
2025 Keynote Lecture, Cedars Sinai Women's Health Research, Los Angeles, CA
2025 Dolan Pritchett Honorary Lecture, Perlman School of Medicine, U. of Penn, Philadelphia, PA
2024 Keynote Lecture 1st Intl Conference on Steroid Hormones and Receptors, Albuquerque, NM
2024 Wu Lectureship, Institute for Human Nutrition, New York, NY
2024 **FASEB Excellence in Science Lifetime Achievement Award (**Keynote @ 2025 APS Summit)
2024 Keynote Lecture Women's History Month Symposium, UC Davis, Davis, CA
2023 **UCSF Lifetime Achievement in Mentoring Award**
2023 Marlene A. DeLuca Endowed Lectureship, UCSF, San Diego, CA
2023 Society of Endocrinology **Trans-Atlantic Medalist** and Lecture, Glasgow, UK
2023 Women in Medicine and Science (WIMS) Lectureship, U. of Arizona, Tucson, AZ
2023 Edwin B. Astwood Award for Outstanding Research in Basic Science, Endocrine Society
2022 Distinguished Bert O'Malley Endowed Lectureship, BCM, Houston, TX
2022 Kendall-Hench Lectureship in Endocrinology and Metabolism, Mayo Clinic, Rochester, MN
2022 John and Margaret Faulkner Lectureship, University of Michigan, MI
2021 Elected Member National Academy of Sciences **(NAS)**
2020 Senior Scholar Award - Global Consortium for Reproductive Longevity and Equality Found.
2020 Herzstein Endowed Professor in Molecular Physiology
2019 Elected Member American Academy of Arts and Sciences **(AAA&S)**
2019 42nd Steenbock Lectureship Award, U. of Wisconsin - Madison, WI
2018 Joseph Larner Memorial Lectureship Award in Pharmacology, U. of Virginia, VA
2018 Keynote Speaker - 8th Great Lakes Nuclear Receptors Conference, MN
2017 UCSF Chancellor's Martin Luther King, Jr. (MLK) Leadership Award
2012 Elected Fellow of the American Association for the Advancement of Science **(AAAS)**
2011 Named NIH College of Reviewers

2009, 2011 Plenary Lectureships Endocrine Society
2008 American Diabetes Association Champion Gala Honoree
2006-Pres. Herzstein Distinguished Investigator in Molecular Physiology
2003 UCSF Outstanding Faculty Mentorship Award Nominee
2002 Brook Byers Basic Science Award
2001 Williams Lectureship for Pediatric Research
2000 First Named Lectureship for Women in the Society of Andrology
1997-2002 NIH-Independent Scientist Development Award
1991-1992 Genentech Human Growth Foundation Award
1983-1984 W.M. Keck Foundation Fellow
1982-1983 J. Aaron Charitable Foundation Fellow
1981-1983 Muscular Dystrophy Fellowship

National Advisory Committees (Partial List)

2025 – 2028 **Elected Officer**, Class II Biological Sciences, National Academy of Sciences (NAS)
2025 Editorial Board Reviewer, NIH Director's New Innovator Award Program (DP2)
2024 Participant, The Next Frontier in Women's Health Panelist, **The White House,** Washington, DC
2024 Ad-Hoc Reviewer, NIH BNRS Panel
2024 – Pres. Panelist, Task Force for Scientific Advancement, American Physiological Society
2023 – 2024 Scientific Advisor, Nutritional, Obesity Research Center, Baylor College of Medicine
2023 – 2024 Member, NASEM Committee on **Assessment of NIH Research on Women's Health**
2023 – Pres. Scientific Advisory Board – K. Lisa Yang Brain-Body Center, MIT
2022 Ad-Hoc Reviewer, NIH CSME Panel
2021 Ad Hoc Inaugural NIH MPOD Panel, NINDS Blueprint for Neuroscience Panel
2020 Ad Hoc Reviewer NIA – ERP Panel
2019 ASBMR – Invited Contributor to Workshop on Aging – Sept 22, 2019
2018 – Pres. Lead Organizer and Coordinator for UCSF Women in Discovery Science
2018 – Pres. Elected Council Member, Organization for the Study of Sex Differences**,**
2016 – 2020 Advisory Board Member, Pennington NORC,
2015 – 2020 **Chair**, NIDDK-B Review Panel, Permanent Member
2015 – 2019 Grant Review Panel Member, American Diabetes Association,
2006 – 2019 Section Editor, Annual Review of Physiology-Endocrinology and Metabolism
2014 & 2018 Ad-Hoc Reviewer NIH IPOD Panel, NIDDK Program Project Review
2014 **Co-Chair**, NIH Directors SEP – Illuminating the Druggable Genome
2013 – 2016 American Heart Association Review Panel
2012 – 2013 As Hoc Reviewer, NIH-NIDDK ZRG-SEP, ZEG-SEP, and ZDK1-SEP Panels
2012 ADA Ad-Hoc Reviewer for Neurohormonal Control of Metabolism
2011 **Chair**, NIH-NIDDK Program Project Review
2011 NIDDK Stage 2 Editorial Board Review for R24 Collaborative Team Science
2009 Distinguished Editor for Physiological and Pathological Sciences, NIH Challenge Grants
2008 – 2009 NIH-NIDDK SEP Panels Feb 2008, Aug 2008, Feb 2009, March 2009
2008 & 2009 **Co-Chair**, American Heart Association Review Panel
2008 **Chair**, SEP NIH Panel
2006 **Chair**, Special Review Panel
2004 – 2006 **Chair**, Molecular and Cellular Endocrinology NIH Study Section

C. Contributions to Science

1. Hormone Signaling in Sex-Specific Hypothalamic Function

My lab has defined important hormone-sensitive neuron clusters in the hypothalamus mediating sex-dependent metabolic and skeletal health relevant to female physiology.

a. Cheung, C., Kurrasch, D.M., Liang, J., and **H.A. Ingraham**, Genetic Labeling Of SF-1 Neurons Reveals VMH Circuitry Beginning at Neurogenesis and The Emergence of a Separate Non-SF-1 Neuronal Cluster in the Ventrolateral VMH, Journal of Comparative Neurology (2013) Apr 15;521(6):1268-88. PMCID: PMC4324838.

b. Correa, SM, Newstrom, DW., Warne, JP., Cheung, C.C., Flandin, P., Pierce, AA., Xu, AW, Rubenstein, J.R. and **H.A. Ingraham**. An estrogen-responsive module in the ventromedial hypothalamus selectively drives sex-specific activity in females. Cell Reports (2016) Jan 6;10(1):62-74. Epub 2014 Dec 24. (2015) PMCID: PMC4324838.

c. Herber, CH, Krause, W.C., Wang, L-P., Bayrer, J.R., Li, A., Reid, MS, Fields, A., Hsiao, EC, Nomura, D., Nissenson, RA., Correa, SM and **H.A. Ingraham**, Estrogen signaling in arcuate Kiss1 neurons suppresses a sex-dependent female circuit promoting dense, strong bones, Nat. Commun. (2019). **10**: 163 PMID: 30635563 (BioRxiv 2018).

d. Krause, W.C., R. Rodriguez, B. Gegenhuber, N. Matharu, A.N. Rodriguez, A.M. Padilla, K. Toma, C.B. Herber, S.M. Correa, X. Duan, N. Ahituv, J. Tollkuhn, and **H.A. Ingraham**, Oestrogen engages brain MC4R signalling to drive physical activity in female mice. Nature (2021) Nov;599(7883):131-135. Epub 2021 Oct 13.PMID: 34646010. Highlighted in *NYT*, *Nature, Cell Metabolism*, and *Faculty Reviews.*

2. Structural Analyses of NR5A Nuclear Receptors (SF-1 and LRH-1)

In collaboration with the Fletterick lab, my lab led the initial efforts to understand how members of the NR5A family are ligand-activated. We showed that these receptors have large ligand-binding pockets and that the rodent LRH-1 is perfectly stable without ligands. However, we subsequently established that all other species of the NR5A subfamily could bind phospholipids, with the highest affinity ligands found to be the signaling phosphatidylinositols, PIP_2, and PIP_3.

a. Krylova, I.N., Sablin, E.P., Moore, J., Xu, R.X., Waitt, G.M., MacKay, J.A., Juzumiene, D., Bynum, J.M., Madauss, K., Montana, V., Lebedeva, L., Suzawa, M., Williams, J.D., Williams, S.P., Guy, R.K., Thornton, J.W., Fletterick, R.J., Willson, T.M. and **H.A. Ingraham**, Structural analyses reveal phosphatidyl inositols (PI) as ligands for the NR5 orphan receptors SF-1 and LRH-1. Cell 120:343-355 (2005). PMID: 15707893

b. Sablin, E., Krylova, I., Fletterick, R.J. and **H.A. Ingraham**, Structural basis for ligand-independent activation of the orphan nuclear receptor LRH-1. Molecular Cell 11:1575-1585 (2003). See Review "Activation Incarnate" by Martin L. Privalsky in Developmental Cell (2003). PMID: 12820970

c. Sablin, E.P., Blind, R., Krylova, I.N., Ingraham, J.G., Cai, F., Williams, J.D., Fletterick, R.J., and **H.A. Ingraham**, Structure of SF-1 Bound by Different Phospholipids: Evidence for Regulatory Ligands. Mol Endocrinology 23(1):25-34 (2009). PMCID: PMC2646595.

d. Sablin EP, Blind RD, Uthayaruban R, Chiu HJ, Deacon AM, Das D, **Ingraham** HA, and Fletterick RJ. Structure of human LRH-1 LBD bound to the signaling phospholipid, PIP_3. J Struct Biol. Sep 28. pii: S1047-8477(15)30067-8. (2015) PMCID: PMC4651778.

3. Phospholipid Ligands for NR5A Nuclear Receptors

My lab has led efforts to define endogenous and synthetic ligands for the NR5A family. We have worked on developing assays to assess the effects of synthetic ligands on NR5A activity. Importantly, we were the first to discover that signaling lipids (PIP_2 and PIP_3) bind with high affinity to NR5A receptors. Later, we linked the production of diverse AA-phospholipid species to LRH-1 activity and hepatic lipid storage.

a. Whitby, R.J., Stec, J., Blind, R.D., Dixon, S., Leesnitzer, L.M., Orband-Miller, L.A., Williams, S.P., Willson, T.M., Xu, R., Zuercher, W.J., Cai, F. and **H. A. Ingraham**, Small Molecule Agonists of the Orphan Nuclear Receptors Steroidogenic Factor-1 (SF-1, NR5A1) and Liver Receptor Homologue-1 (LRH-1, NR5A2). Journal of Med Chem 54(7):2266-81 (2011). PMCID: PMC4151520.

b. Blind, R.D., Suzawa, M. and **H.A. Ingraham**, Direct modification and regulation of the nuclear protein-lipid complex NR5A1-PIP_2 by the PI3-kinase IPMK. (**Cover and Podcast**) Science Signaling Jun 19;5(229) (2012) PMCID: PMC3395721.

c. Blind, R.D., Sablin, E.P, Kuchenbecker, K., Chui, H-J. Deacon, A., Das, D., Fletterick, R.J. and **H.A. Ingraham**, The Signaling Phospholipid PIP3 Binds SF-1 Creating A New Interaction Surface at the Entrance of the Ligand Binding Pocket, Proc Nat Acad Sci Oct 21;111(42):15054-9 (2014) PMCID: PMC4210282.

d. Miranda, D.A., W.C. Krause, A. Cazenave, D.S. M. Suzawa, Escusa, Foo, J.C. Shihadih, A. Stahl, M. Fitch, E. Nyangau, M. Hellerstein, M.R. Wenk, D.L. Silver, and **H.A. Ingraham**. LRH-1 Regulates Hepatic Lipid Homeostasis and Maintains Arachidonoyl Phospholipid Pools Critical for Phospholipid Diversity, JCI Insight (2018) March 8th, Mar 8;3(5). pii: 96151. PMID:29515023.

4. Role of PTMs in Nuclear Receptor Activity and Tissue Development

My lab led efforts to understand the role of sumoylation on nuclear receptor activity. We were the first to establish that sumoylation modifies receptor activity and leads to the selective activation of SUMO-sensitive genes using both in vitro and in vivo data by knocking in a SUMO-less form of the receptor, which results in endocrine abnormalities and inappropriate steroid hormone production.

a. Campbell, L.A., Faivre, E., Show, M.D., Ingraham, J.G., Flinders, J., Gross, J.D. and **H.A. Ingraham**, Decreased Recognition of SUMO-Sensitive Target Genes following Modification of SF-1 (NR5A1). Mol Cell Bio 28(24):7476-86 (2008). PMCID: PMCID: PMC2593425.

b. Lee, F.Y., Faivre, E.J., Suzawa, M., Lontok, E., Ebert, D., Cai, F., Belsham, D.D. and **H.A. Ingraham**. Eliminating SF-1 (NR5A1) Sumoylation In Vivo Results in Ectopic Hedgehog Signaling and Disruption of Endocrine Development. (**Cover, Preview, and Podcast**), Developmental Cell 21:315-327 (2011), PMCID: PMC3157481.

c. Suzawa, M, Miranda, D.A., Ramos, K. A, Faivre, EJ, Ang, K.-H., Wilson, CG, Arkin, MR, Kim, Y-S., Diaz, A., Schneekloth, J.S. and **H. A. Ingraham.** Tannic Acid Identified in a Phenotypic Screen Inhibits Sumoylation and Activates SUMO-sensitive Transcriptional Programs In Vivo. Elife. 2015 Dec 11;4. pii: e09003, PMCID: PMC4749390, PMCID: PMC5675444.

d. Xing, Y, Zubir, M., Morohashi, K-H., **Ingraham, H.A.**, and G.D. Hammer. Timing of Adrenal Regression Controlled by Synergistic Interaction between Sf1 SUMOylation and Dax1, Development (2017) Oct 15;144(20):3798-3807, PMID:28893949.

5. Role of NR5A1 (SF-1) in Endocrine Tissue Development

My lab identified SF-1 as a major determinant of male sex differentiation by showing that this nuclear receptor regulates an essential peptide hormone (MIS, AMH) in the development of the bi-potential urogenital ridge. MIS leads to the destruction of the female reproductive tract in males. We went on to show that haploinsufficiency of SF-1 in mice leads to adrenal hypoplasia, similar to what has now been found in human heterozygous *SF-1* mutants.

a. Shen, W-H., Moore, C.C.D., Ikeda, Y., Parker, K.L. and **H.A. Ingraham**, The orphan nuclear receptor, SF-1 regulates Müllerian inhibiting substance expression, a link in the sex determination pathway. Cell 77:651-661 (1994). PMID: 8205615

b. **Ingraham, H.A.**, Lala, D., Ikeda, Y., Luo, X., Shen, W-H., Nachtigal, M., Abbud, R., Nilson, J.H., and K.L. Parker, The nuclear receptor steroidogenic factor 1 acts at multiple levels of the reproductive axis. Genes & Development (1994) 8:2302-2312. PMID: 7958897

c. Nachtigal, M.W., Hirokawa, Y., VanHouten-Enyeart, D., Flanagan, J.N., Hammer, G.D. and **H.A. Ingraham**, Wilms' Tumor and Dax-1 modulate the orphan nuclear receptor, SF-1 in sex-specific gene expression. Cell 93:445-454 (1998). PMID: 9590178

d. Bland, M.L., Jamieson, C., Akana, S., Bornstein, S.R., Eisenhofer, G., Dallman, M., and **H.A. Ingraham**, Haploinsufficiency of steroidogenic factor-1 in mice disrupts adrenal development leading to an impaired stress response. Proc Nat Acad Sci 97:14488-14493 (2000), PMCID: PMC18946.

All Publications Link: https://www.ncbi.nlm.nih.gov/myncbi/holly.ingraham.1/bibliography/public/