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

My lab studies how hormones influence the nervous system to understand better how age-related or drug-induced hormone changes alter female physiology. My initial work at UCSF began by dissecting gonadal differentiation, and today we continue to study sex differences in the gut and brain. We are particularly keen to understand the cellular and molecular basis of metabolic/behavioral disorders that exhibit sex biases in women. As evidenced by our publication record, we engage in multi-faceted approaches that focus on central and peripheral physiological systems. Current studies seek to define the role of sex-steroid hormone signaling acting through nuclear receptors in highly responsive tissues, including the brain and gut. I am excited by our three recent studies (2021 *Nature*, 2022 *Science,* 2023 *Nature & BioRxiv*) aimed at dissecting **hormone-sensitive programs** for understanding the molecular origins of sex-biased behavior, metabolism, and visceral pain.

Another primary focus of my academic activities is directed toward the most vulnerable population in our nation's biomedical educational pipeline – women and minority postdoctoral fellows. As such, I serve as the **Director of the NIGMS-IRACDA program at UCSF**, which provides a cohort of 12 funded and 5-to-8 associated scholars with individualized mentoring and career development plans for future success at R1 and R3 institutions, including helping them with K01 and K99 applications. The success of our program in placing our scholars at R01 and R3 institutions has allowed us to extend the funding period of this award for an additional year (2023).

Newer lab publications:

a. 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) DOI:10.1101/2022.01.07.475423v1, Science (2022) Oct 21;378(6617):290-295, doi: 10.1126/science.abn9886, PMID: 36264814.

b. *Bayrer, J.R., Castro, J., Venkataraman, A., Touhara, K.K., Rossen, N.D., Morrie, R.D., Hendry, Madden, A.J., Braverman, K.N., Schober. G., Brizuela, M., Castro-Navarro, F., Bueno-Silva, C., ***Ingraham, H.A.**, *Brierley, S.M. and D. Julius. Gut Enterochromaffin Cells are Critical Drivers of Visceral Pain and Anxiety BioRxiv (2022) DOI:10.1101/2022.04.04.486775 (In Press, Nature). ***Co-corresponding Author**

c. **Ingraham, HA,** Herber, C.B., and Krause, W.C., Running the Female Power Grid Across Lifespan Through Brain Estrogen Signaling. Annual Reviews of Physiology, 2022, Vol 84:25 1-25.

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 signaling to drive physical activity in female mice. Nature (2021) Nov;599(7883):131-135. Epub 2021 Oct 13.PMID: 34646010.

Ongoing research support:

1. **1R01AG062331-01 (Ingraham – PI)** 10/01/19-09/30/24
   NIH-NIA
   Arcuate ERa Signaling in Central Control of Female Bone Metabolism

   This new R01 application will manipulate, map projections, and define the organizational differences of estrogen Kiss1 arcuate neurons in increasing bone mass in female mice.

2. **K12GM081266 (Ingraham – PI)** (Extended to 2023 Per Program) 08/01/17-07/31/23

   NIH-NIGMS Institutional Research and Academic Career Development Award

   This institutional training award aims to build a diverse group of highly trained biomedical research scientists nationally. Postdoctoral scholars (12 slots) are supported to carry out impactful and innovative biomedical research with an appropriate research mentor for up to three years.

3. **R01DK121657-01A1 (Ingraham - PI)** 03/01/20-02/29/25
   NIH-NIDDK
   Dissecting a hormone-responsive processor for female activity

   This new R01 application will manipulate a hormone-dependent node by CRISPRa, map projections, and define the neuronal cell types in the VMHvl that direct physical activity in females.

4. **GCRLE Senior Scholar Award 0320 (Ingraham – PI)** 09/01/20-01/31/23

   Global Consortium for Reproductive Longevity and Equality Foundation (Buck Institute)

   Identifying Novel Drivers in Central Control of Female Reproduction

   This award, administered by the Buck Institute and funded by the GCRLE, seeks to define novel clusters of neurons that optimize ovarian function in female mice.

5. **R01DK 135714-01 (Ingraham/Julius – Multi-PI)** 04/01/23-03/31/28

   Anticipated Start Date (Impact Score 3%)

   Understanding Mechanisms and Sex-Differences in Visceral Pain

   This award extends our efforts focused on understanding the basic science and sex bias of visceral pain in female mice as it relates to irritable bowel syndrome.

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 to Promote Diversity
2010 – 2020 Associate Vice-Chair, UCSF, Dept. of Cellular and Molecular Pharmacology
2004 – Pres. Professor, UCSF, Dept. Cellular and Molecular Pharmacology
2004 – Pres. 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, UCSD
1987 – 1990 Research Associate with Dr. Michael Geoffrey Rosenfeld Howard Hughes Medical Institute, 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

2023 Society of Endocrinology Transatlantic 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.
2019 Elected Member American Academy of Arts and Sciences **(AAA&S)**
2019 42nd Steenbock Lectureship Award, U. of Wisconsin - Madison, WI
2019 Elsevier Keynote Speaker – Society for Behavioral Neuroendocrinology Conference, IN
2018 Joseph Larner Memorial Lectureship Award in Pharmacology, U. of Virginia, VA
2018 Keynote Speaker - 8th Great Lakes Nuclear Receptors Conference, MN
2018 Keynote Speaker - Ray E. Burger Research Colloquium, UC Davis
2017 UCSF Chancellor's Martin Luther King, Jr. (MLK) Leadership Award
2012 Elected Fellow of the American Association for 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)

2023 – Pres. Scientific Advisory Board – K. Lisa Yang Brain-Body Center, MIT
2022 Ad-Hoc 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. Organization for Study of Sex Differences**,** Elected Council Member
2016 – 2020. Pennington NORC, Advisory Board Member
2015 – 2020. Chair, NIDDK-B Review Panel, Permanent Member
2015 – 2019. American Diabetes Association, Grant Review Panel Member
2006 – 2019 Annual Review of Physiology-Endocrinology and Metabolism Section Editor
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 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 NIH Challenge Grants, Distinguished Editor for Physiological and Pathological Sciences
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

All Publications Link: http://www.ncbi.nlm.nih.gov/pubmed?term=Ingraham H

1. Role Hormone Signaling in Hypothalamic Function

My lab has defined important hormone-sensitive neuron clusters in the hypothalamus that mediate sex-dependent aspects of metabolism and skeletal health.

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. DOI: 10.1016/j.celrep.2014.12.011. 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. DOI: 10.1016/j.jsb.2015.09.012. (2015) PMCID: PMC4651778.

3. Ligands for NR5A Nuclear Receptors

My lab has led efforts to define the 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 these signaling lipids (PIP_2 and PIP_3) bind with high affinity to NR5A receptors and then later 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, Fitch,M., Nyangau, E., Hellerstein, M., 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). Molecular and Cellular Biology 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.