Daniel Bayless – Edward Mallinckrodt, Jr. Foundation Grant – 1-page LOI for Salk ApCom

Project title: Developing novel tools to image and study brain-derived estrogens and behavior

The Edward Mallinckrodt, Jr. Foundation supports "early-stage biomedical investigators engaged in basic and translational research that has the potential to make fundamental advances in biomedical science". The studies proposed here have potential to fundamentally extend and reshape our understanding of the actions of estrogens in the brain. We will develop and use novel research tools to study estrogen signaling and its role in modulating neural activity and behavior at an unprecedented level of temporal and spatial specificity. The classic model of estrogenic effects in the brain follows a path from estradiol (the primary bioactive estrogen) produced in the gonads reaching cells in the brain and then activating nuclear estrogen receptors[1]. Over the course of hours to days, this causes gene expression changes that lead to alterations in neural activity, connectivity, and behavior[2]. These slow-acting classical hormone mechanisms are important, but in the last two decades, it has become increasingly clear that estrogens also have acute effects occurring in seconds to minutes via activation of G-protein coupled estrogen receptors[3], and moreover, studies indicate that estradiol might even be locally synthesized and released via neurons[4]. However, the research tools needed to definitively prove this have been lacking. Here, we will develop molecular genetic techniques in mice to overcome two barriers that have prevented the study of neuronal release (Specific Aim 1, SA1) and function (SA2) of fast-acting brain-derived estrogens.

SA1: One current barrier is the lack of a method to reliably measure estradiol concentrations in individual brain regions across time. Studies in rodents and birds have shown that estradiol levels can vary across brain regions and developmental timepoints[5–7]. However, these methods either involve collecting the brain at a single timepoint or have sampling rates of ~30 minutes which makes it difficult to correlate these fluctuations to specific behaviors. To overcome this barrier, in collaboration with Yulong Li's lab, we are developing a fluorescent GPCR-Activation-Based (GRAB) sensor[8] for estradiol ($GRAB_{E2}$) (Fig 1). The Li lab generated the sensor construct, which sensitively reports estradiol concentrations with a temporal resolution of seconds. All *in vivo* imaging and behavioral studies will be conducted in my lab. Estrogens are implicated in many behaviors. Our initial studies will particularly focus on social behavior, memory, and anxiety. Using fluorescent imaging techniques in mice, we will actively monitor estradiol concentrations simultaneously in multiple brain regions during behavior to precisely determine if/how estradiol levels fluctuate and when/what stimuli elicit neuronal estradiol release. This technology will allow us to distinguish if estrogen levels in brain regions that are millimeters apart fluctuate differently, which would provide the first definitive proof of local estrogen release in the brain.

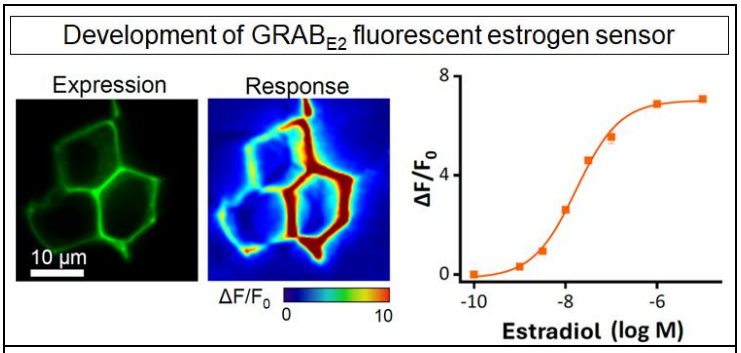

Fig 1: Florescence level of $GRAB_{E2}$ increases with increasing estradiol concentration. *Unpublished data from Yulong Li Lab*.

SA2: Another barrier has been the lack of a method to disrupt neuronal estrogen synthesis in adults without altering estrogens during development. If neuronal synthesis of estradiol occurs, it must occur via neurons that express the gene aromatase (Aro), the final and rate-limiting enzyme in the estradiol synthesis pathway[4]. Aro is expressed in discrete regions throughout the brain. To disrupt neuronal estrogen synthesis at specific timepoints and in specific brain regions, we have generated Aro^{Flox} mice that have the Aro gene flanked by loxp sites. Exposure to Cre causes recombination leading to loss of Aro expression (Fig 2). Therefore, we will perform brain region-specific knockouts of estrogen synthesis by delivering Cre to specific brain regions at specific developmental and adult timepoints, to understand the role of brain-derived estrogens in modulating social behavior, memory, and anxiety.

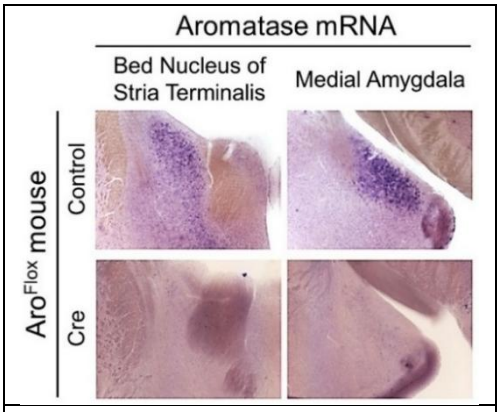

Fig 2: Aro mRNA is absent in Aro^{Flox} mice following exposure to Cre. *Unpublished*.

These tools will provide the scientific community with the ability to study brain-derived estrogens with exceptional temporal and spatial specificity. These studies will also provide excellent data for obtaining NIH R01-level funding for this research in my lab. Gaining a detailed understanding of the local synthesis of estrogens in the brain and their acute effects will radically expand how we think about the actions of sex hormones in modulating neural activity and behavior. This has implications for our fundamental understanding of the neural basis of behaviors influenced by estrogens, such as social behaviors, memory, and anxiety, as well as for neurological disorders that are affected by sex hormones or present with sex differences.

References

1. Fuentes, N., and Silveyra, P. (2019). Chapter Three - Estrogen receptor signaling mechanisms. In Advances in Protein Chemistry and Structural Biology Intracellular Signalling Proteins., R. Donev, ed. (Academic Press), pp. 135–170. https://doi.org/10.1016/bs.apcsb.2019.01.001.
2. Lawal, O.O., Lin, D., and Lischinsky, J.E. (2025). Estrogen Control of Social Behaviors. Annu Rev Neurosci. https://doi.org/10.1146/annurev-neuro-112723-041639.
3. Rudolph, L.M., Cornil, C.A., Mittelman-Smith, M.A., Rainville, J.R., Remage-Healey, L., Sinchak, K., and Micevych, P.E. (2016). Actions of Steroids: New Neurotransmitters. J Neurosci *36*, 11449–11458. https://doi.org/10.1523/JNEUROSCI.2473-16.2016.
4. Spool, J.A., Bergan, J.F., and Remage-Healey, L. (2022). A neural circuit perspective on brain aromatase. Front Neuroendocrinol *65*, 100973. https://doi.org/10.1016/j.yfrne.2021.100973.
5. Konkle, A.T.M., and McCarthy, M.M. (2011). Developmental time course of estradiol, testosterone, and dihydrotestosterone levels in discrete regions of male and female rat brain. Endocrinology *152*, 223–235. https://doi.org/10.1210/en.2010-0607.
6. Remage-Healey, L., Maidment, N.T., and Schlinger, B.A. (2008). Forebrain steroid levels fluctuate rapidly during social interactions. Nat Neurosci *11*, 1327–1334. https://doi.org/10.1038/nn.2200.
7. de Bournonville, M.-P., de Bournonville, C., Vandries, L.M., Nys, G., Fillet, M., Ball, G.F., Balthazart, J., and Cornil, C.A. (2021). Rapid changes in brain estrogen concentration during male sexual behavior are site and stimulus specific. Sci Rep *11*, 20130. https://doi.org/10.1038/s41598-021-99497-1.
8. Wu, Z., Lin, D., and Li, Y. (2022). Pushing the frontiers: tools for monitoring neurotransmitters and neuromodulators. Nat Rev Neurosci *23*, 257–274. https://doi.org/10.1038/s41583-022-00577-6.

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Scholarly Profile

The research mission of the Bayless Lab is to increase our understanding of the neural circuits that underlie social behavior and the factors that alter these neural circuits. Our experiments focus on how sex hormones, genes associated with human disorders, and aging shape and modulate these neural circuits. The neural circuits that underlie innate social behaviors, such as social approach, mating, and aggression, are intermingled among circuits that regulate unrelated neural processes and behaviors. To isolate and selectively study neural circuits that encode and generate fundamental elements of social behaviors, we use advanced molecular genetic techniques in mice.

Academic Positions

2023 – Present	**Assistant Professor**	The Salk Institute	Molecular Neurobiology

Education and Training

2019 – 2023	**Basic Life Research Scientist**	Stanford University Advisor: Dr. Nirao Shah	Neurobiology
2016 – 2019	**Postdoctoral Fellow**	Stanford University Advisor: Dr. Nirao Shah	Neurobiology
2014 – 2016	**Postdoctoral Fellow**	UC-San Francisco Advisor: Dr. Nirao Shah	Neurobiology
2012 – 2014	**Ph.D.**	Tulane University Advisor: Dr. Jill Daniel	Behavioral Neuroscience
2009 – 2012	**M.S.**	Tulane University Advisor: Dr. Jill Daniel	Behavioral Neuroscience
2004 – 2008	**B.A.**	University of Oklahoma	Psychology

Publications

1. Jantarachanatanthiti P., **Bayless D.W.** The rhythm of sequential behavioral transitions: Neuromodulatory dynamics and male sexual behavior. *Preview*, Neuron, 113, 1124-1126 (2025) (link to pdf)
2. **Bayless D.W.**, Davis C.O., Yang R., Wei Y., Carvalho V.M., Knoedler J.K., Yang T., Livingston, O., Lomvardas A., Martins G.J., Vicente A.M., Ding J.B., Luo L., Shah N.M. A neural circuit for male sexual behavior and reward. Cell, 186, 3862-3881 (2023) (link to pdf)
3. Yang T., **Bayless D.W.**, Wei Y., Landayan D.S., Marcelo I., Wang Y., DeNardo L.A., Luo L., Druckmann S., Shah N.M. Hypothalamic neurons that mirror aggression. Cell, 186: 1-17 (2023). (link to pdf)
4. Knoedler J.R., Inoue S., **Bayless D.W.**, Yang T., Tantry A., Davis C.O., Leung N.Y., Parthasarathy S., Wang G.D., Alvarado, M., Rizvi A.H., Fenno L.E., Ramakrishnan C., Deisseroth K., Shah N.M. A functional cellular framework for sex and estrous cycle-dependent gene expression and behavior. Cell, 185: 654-671 (2022). (link to pdf)

5. Darling J.S., **Bayless D.W.**, Dartez L.R., Taylor J.H., Mehrotra A., Smith W.L., Daniel J.M. Sex differences in impulsivity in adult rats are mediated by organizational actions of neonatal gonadal hormones and not by hormones acting at puberty or in adulthood. Behavioural Brain Research, 395: 112843 (2020). (link to pdf)
6. **Bayless D.W.**, Yang T., Mason M.M., Susanto A.A.T., Lobdell A., Shah N.M. Limbic neurons shape sex recognition and social behavior in sexually naïve males. Cell, 176: 1190-1205 (2019). (link to pdf)
7. **Bayless D.W.**, Shah N.M. Genetic dissection of neural circuits underlying sexually dimorphic social behaviours. *Invited Review* in Themed Issue, "Multifaceted origins of sex differences in the brain", Phil. Trans. R. Soc. B, 371: 20150109 (2016). (link to pdf)
8. **Bayless D.W.**, Daniel J.M. Sex differences in myelination within and strength of projections from the orbital frontal cortex to the dorsal striatum in adult rats: Implications for sex differences in inhibitory control. Neuroscience, 300: 286-296 (2015). (link to pdf)
9. **Bayless D.W.**, Perez M.C., Daniel J.M. Comparison of the validity of the use of the spontaneously hypertensive rat as a model of attention deficit hyperactivity disorder in males and females. Behavioural Brain Research, 286: 85-92 (2015). (link to pdf)
10. **Bayless D.W.**, Darling J.S., Daniel J.M. Mechanisms by which neonatal testosterone exposure mediates sex differences in impulsivity in prepubertal rats. Hormones and Behavior, 64(5), 764-769 (2013). (link to pdf)
11. **Bayless D.W.**, Darling J.S., Stout W.J., Daniel J.M. Sex differences in attentional processes in adult rats as measured by performance on the 5-choice serial reaction time task. Behavioural Brain Research, 235, 48-54 (2012). (link to pdf)

AWARDS

2022	Nominee for 2022 Stanford Postdoc JEDI (Justice, Equity, Diversity, and Inclusion) Champion Award
2021	Honorable Mention for Stanford.Berkeley.UCSF Next Generation Faculty Symposium
2013	First Place, Outstanding Graduate Research Award, Tulane University Science and Engineering Research Day
2011	Tulane University Flowerree Summer Research Fund Award
2008	Graduated with Special Distinction from the University of Oklahoma
2007	Psi Chi Honor Society
2006	National Society of Collegiate Scholars
2006	Phi Kappa Phi Honor Society
2005	Alpha Lambda Delta Honor Society
2005	R. Boyd Gunning Scholar, Top 1% of Freshman Class, University of Oklahoma

RESEARCH SUPPORT

Current

1. Brain Research Foundation Seed Grant 06/01/2024 – 05/31/2026
Grant Number: *BRFSG-2024-02*
Understanding the Impact of ASD-linked Genes on Subcortical Processing of Social Cues
Funding: $80,000
Role: Principal Investigator

Completed

1. Pilot Funding for Autism Research 12/19/2022 – 08/14/2023
Autism Research Working Group at Stanford University
Functional significance of ASD-linked gene expression in a sexually dimorphic subcortical nucleus
Funding: $21,700
Role: Principal Investigator

2. NIH T32 Postdoctoral Training Grant 12/01/2014 – 11/30/2015
Grant Number: *T32 HD007263, Mellon (PI)*
National Institute of Child Health & Human Development
Integrated Training in Reproductive Sciences
Genetic imaging and manipulation of sexually dimorphic neurons during reproductive behaviors
Role: Trainee

3. State of Louisiana Board of Regents Graduate Fellowship 08/01/2009 – 05/15/2014
Grant Number: *LEQSF (2009-2014)-GF-13, Daniel (PI)*
Role: Trainee

4. Tulane University Flowerree Research Award 06/01/2011 – 08/20/2011
Effect of Neonatal Hormone Exposure on Impulsivity in Prepubertal Rats
Role: Principal Investigator

TEACHING AND MENTORSHIP

Teaching Philosophy

Educating and mentoring students and trainees is one of the most influential and long-lasting impacts that a research scientist can have. Scientific knowledge is continually built upon the discoveries that came before it. Therefore, it is paramount to provide an excellent education and learning environment for students and trainees, so that the next generation of scientists is fully equipped to advance the scientific knowledge of today and so that those who choose career paths outside of research remain true advocates for trusting and funding scientific research. I have worked as a high school science teacher, graduate teaching assistant, and undergraduate course lecturer.

Classroom Instruction

2025-present Lecturer, Module on Biology and Sex/Gender
BILD 60: Diversity, Equity, and Inclusion (DEI) and Human Biology,
University of California, San Diego

2013-14 Teaching assistant, Undergraduate Neuroscience Lab,
NSCI 6515: Biopsychology Laboratory, Tulane University, New Orleans, LA
(Lead Instructor: Dr. Thomas Hebert)

2012-14 Teaching assistant, High School Neuroscience Summer Program,
NSCI 1015: Basic Neuroscience with Laboratory, Tulane University, New Orleans, LA
(Lead Instructor: Dr. Thomas Hebert)

2008-09 Substitute teacher, Norman Public Schools, Norman, OK
(Supervisor: Robbi Mullinax)

Scientific Research Mentorship

As an assistant professor at the Salk Institute:

2024-present Lisa Tatsumi, (*PhD Student, UCSD Biology Program*)

2024-present Caliope Marin, (*PhD Student, UCSD Biology Program*)

2024-25 Sarah Gharagozlou, (*High School Student*)

2024-25 Elina Thode, (*High School Student*)
2024-present Alisa Kudo, (*UCSD Undergrad*)
2024-present Annika Torres, (*UCSD Undergrad*)
2024-present Ashrika Paudyal, (*UCSD Undergrad*)
2024-present Dr. Subhalakshmi Guha, (*Postdoctoral Fellow*)
2024-present Dr. Seungjoon Lee, (*Postdoctoral Fellow*)
2024-24 Leanne Lehmann, (*Rotating PhD Student*, *UCSD Neuroscience Program*)
2023-24 Joycelyn Yiu, (*Rotating PhD Student*, *UCSD Bioengineering Program*)
2023-present Pom Jantarachanatanthiti, (*Research Assistant I*)

As a postdoctoral researcher in Nirao Shah's lab at Stanford University and UCSF:

2022-22 Oscar Livingston, (*High School Student*)
2021-23 Leonardi Gozali, (*PhD Student*, *Stanford Biology Program*)
2019-19 Chelsea Nnebe, (*M.D./Ph.D. Student, Stanford School of Medicine*)
2018-19 Victoria Flagg, (*Master's Student, Stanford Neurosciences Program*)
2018-23 Chung-ha Davis, (*PhD Student, Stanford Neurosciences Program*)
2018-19 Ilana Zucker-Scharff, (*PhD Student, Stanford Neurosciences Program*)
2017-18 Corey Fernandez, (*PhD Student, Stanford Neurosciences Program*)
2018-18 Lexi Lobdell, (*Mount Holyoke Undergrad*)
2017-18 Albert Susanto, (*UC Berkeley Undergrad*)
2015-17 Matthew Mason, (*UC Berkeley Undergrad*)
2015-15 Gabriel Chan, (*UCLA Undergrad*)

As a graduate student in Jill Daniel's lab at Tulane University:

2013-14 Jacob Rosenblum, (*Tulane Undergrad*)
2012-14 Maria Perez, (*Tulane Undergrad*)
2010-13 Jeffrey Darling, (*Tulane Undergrad*)

INVITED TALKS AND SEMINARS

1. UCLA Neuroendocrinology Seminar Series, Los Angeles, CA, June 6, 2025, "Illuminating the neural circuits that generate social behavior."
2. Stanford Autism Working Group Seminar Series, Stanford, CA, March 2, 2023, "Neural circuits for innate but flexible social behavior."
3. UC-Santa Cruz NeuroClub Seminar Series, Santa Cruz, CA, May 11, 2021, "Sex on the brain: Neuropeptidergic modulation of sex recognition and mating behavior."
4. Eco-Evo Lunch Seminar Series, Virtual Zoom talks given by early career ecology and evolution scientists, November 17, 2020, "Sex on the brain: Sexually differentiated regulation of sex recognition and mating behavior."
5. Max-Planck Institute - Munich Winter Conference on Stress, Garmisch-Partenkirchen, Germany, March 17, 2019, "Neural pathway for innate sex recognition."
6. Stanford Center for Molecular Neuroscience in Health and Disease - Member Meeting, Stanford, CA, July 19, 2018, "A neural substrate for sex recognition."
7. Stanford Neurobiology Lab Evening, Stanford, CA, November 30, 2017, "Neurobiology of social interactions."

8. UCSF Center for Reproductive Sciences Workshop, San Francisco, CA, February 5, 2016, "Genetic dissection of the neural circuits underlying reproductive behavior in mice."
9. Tulane Graduate Studies Student Association Colloquium Series, New Orleans, LA, November 6, 2013, "Sex differences in impulsivity: Role of neonatal testosterone exposure."
10. Tulane University Psychology Colloquium Series, New Orleans, LA, March 2, 2012, "Sex differences in attention and impulsivity in prepubertal and adult rats."

PRESENTATIONS

1. **Bayless D.W.**, Flagg V.G., Shah N.M. A sexually dimorphic neuronal circuit for innate sex/mate recognition in mice. *Poster Presentation*, Cold Spring Harbor Laboratory, Neuronal Circuits Meeting; Cold Spring Harbor, NY (2020).
2. **Bayless D.W**., Shah N.M. Genetic imaging and manipulation of sexually dimorphic neurons during reproductive behaviors. *Poster Presentation*, Center for Reproductive Sciences, UCSF Annual Retreat; San Francisco, CA (2015).
3. **Bayless D.W.**, Daniel J.M. Sex differences in the strength of projections from the orbital frontal cortex to the dorsal striatum in adult rats: Implications for sex differences in inhibitory control. *Poster Presentation*, Society for Neuroscience Annual Meeting; Washington, DC (2014).
4. **Bayless D.W.**, Noonan M.M., Fitzpatrick M.E., Daniel J.M. (2013). Mechanism by which neonatal testosterone exposure mediates sex differences in impulsivity in prepubertal rats. *Poster Presentation*, Society for Neuroscience Annual Meeting; San Diego, CA (2013).
5. **Bayless D.W.**, Daniel J.M. Sex differences in myelination in the adult rat orbital frontal cortex and striatum: Implications for sex differences in inhibitory control. *Poster Presentation*, Society for Behavioral Neuroendocrinology Annual Meeting; Atlanta, GA (2013).
6. **Bayless D.W.**, Noonan M.M., Fitzpatrick M.E., Daniel J.M. Mechanism by which neonatal testosterone exposure mediates sex differences in impulsivity in prepubertal rats. *Poster Presentation*, Organization for the Study of Sex Differences Annual Meeting; Weehawken, NJ (2013).
7. **Bayless D.W.**, Darling J.S., Rosenblum, J.D., Daniel J.M. Effect of gonadectomy on attentional processes in adult male rats on the 5-choice serial reaction time task. *Poster Presentation*, Society for Neuroscience Annual Meeting; New Orleans, LA (2012).
8. **Bayless D.W.**, Darling J.S., Koster A.J., Daniel J.M. Sex differences in impulsive choice in prepubescent and adult rats. *Poster Presentation*, Society for Neuroscience Annual Meeting; Washington, DC (2011).
9. **Bayless D.W.**, Perez M.C., Daniel J.M. Sex differences in attentional processes in the spontaneously hypertensive rat, a rodent model of attention-deficit/hyperactivity disorder. *Poster Presentation*, Organization for Study of Sex Differences Annual Meeting; Oklahoma City, OK (2011).
10. **Bayless D.W.**, Stout W.J., Darling J.S., Daniel J.M. Effect of biological sex on attentional processes in adult rats. *Poster Presentation*, Society for Neuroscience Annual Meeting; San Diego, CA (2010).

PROFESSIONAL SERVICE AND MEMBERSHIPS

2025-present Faculty representative, Salk Society of Research Fellows (graduate student and postdoc association at Salk)

2024-present Member, UCSD Neurosciences PhD Program Admissions Committee

2024-25 Member, Salk Institute Thursday Seminar Series Committee

2024-present Ad hoc scientific consultant, STAT News

2023-present Ad hoc peer reviewer, Nature, eLife, Current Opinion in Neurobiology

2021-22 Creator/editor, Stanford Neurobiology Community monthly newsletter

2021-21 Co-coordinator, Stanford Neurobiology Anti-Oppression Summer Reading Group, 8 bi-weekly meetings focused on discussion/praxis related to oppression in STEM.

2020-23 Coordinator, Stanford Neurobiology "Research in Progress" series, bi-weekly talks given by post-docs and grad students in the Neurobiology Department

2020-23 Founding member, Diversity, Equity, Inclusion, and Belonging Committee for the Stanford Neurosciences Ph.D. Program

2020-23 Founding member, Diversity, Equity, and Inclusion Committee for the Stanford Neurobiology Department

2013-14 Coordinator, Tulane Uptown Neuroscience Meetings, monthly presentations given by neuroscience labs at Tulane University

2011-present Member, Organization for the Study of Sex Differences

2010-present Member, Society for Behavioral Neuroendocrinology

2009-present Member, Society for Neuroscience

2009-14 Member, Greater New Orleans Society for Neuroscience

PATENTS

1. Methods to Elicit Desire to Mate and Mating Behavior. US Patent Application No. 63/292,986. Filed 12/22/2022. Inventors: Daniel Bayless, Chung-ha Davis, Sayaka Inoue, Joseph Knoedler, and Nirao Shah.

REFERENCES

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