Daniel Bayless – 1907 Foundation Trailblazer Award – One page summary

Project title: ***Understanding Sex Differences in Alzheimer's Disease to Identify Targets for Treatment***

Abbreviated answers to the application questions: [I will provide more details and discussion in the full application.]

1) What is the novel idea and what is the potential impact to the field?

Women are twice as likely as men to develop Alzheimer's Disease (AD) at some point in their lives (1 in 5 women vs. 1 in 10 men)[1–5]. Any factor that increases a person's likelihood of developing a neurodegenerative disease by two-fold warrants further investigation. My novel idea is that if we can understand the neurological factors that cause this increased risk in women, then we can use that information to develop treatments aimed at reducing the likelihood of developing AD. Women, on average, exhibit better episodic memory than men[6–8]. I hypothesize that sex differences in gene expression resulting from the process of sexual differentiation endow women with enhanced episodic memory but also make them more vulnerable to developing AD during aging. Memory impairments caused by AD result from neurodegeneration of cells in a brain area called the hippocampus, which is essential for memory formation and retrieval[1,9]. I propose to use my lab's expertise in advanced molecular genetic techniques in mice to identify and study genes that are 1) differentially expressed in the hippocampus of females and males and 2) have the potential to cause females to be more vulnerable or males to be more resilient to developing AD.

2) What is the scientific rationale of the idea given current gaps in knowledge?

It is currently unknown why women have a higher prevalence of AD than men. Women typically live longer than men, and age is the greatest risk factor for AD[1,10,11]. While this surely contributes to the increased lifetime prevalence in women, it is unlikely to account for all of the two-fold increase[11]. Some researchers have suggested that environmental factors, such as education, occupation, and health behaviors, contribute to the prevalence disparity[1,12]. We believe that biological factors, such as hormonal and gene expression differences, contribute to the sex difference in AD prevalence, and we believe that we can utilize the information that we learn about these biological factors to design treatments to improve AD prognosis in women and men.

3) If your Novel Idea is true and everything goes to plan, how will this improve health outcomes, and for whom?

If successful, these studies will impact the field of AD research first by increasing our understanding about how AD differentially affects women and men and then by providing molecular targets (candidate genes that we identify as important for the resilience to AD in males) that can then be used in the development of potential therapeutics for AD in women and men. In addition, if our hypothesis is correct, then our studies will establish an experimental framework for utilizing sex differences in the prevalence of a psychiatric or neurodegenerative disorder as a mechanism to identify neurological factors that exert resiliency to the disorder. This concept could be applied to any disorder that is expressed differently in men and women.

4) What is your execution plan and why are you uniquely positioned to execute?

Employing the same single nucleus RNA sequencing strategy used in my postdoctoral work[13], we will identify genes that are differentially expressed in the hippocampus of male and female mice. Then, we will use neural activity monitoring in control and AD model mice to compare how these genes alter the activity of hippocampal neurons and memory performance in males and females.

I am uniquely positioned to execute these experiments because my doctoral training was in neuroscientific research methods to analyze sex differences in the brain and behavior, and my postdoctoral work used molecular genetic techniques in mice to functionally characterize multiple populations of neurons that process social cues and generate fundamental social behaviors. My postdoctoral research resulted in a series of high impact publications[13–16] (all published in Cell - two as first author and two as second author).

5) Why is 1907 Foundation best positioned to partner with you?

I established my lab in September 2023, and one goal that I have for my lab is to expand our basic neuroscience research to include studies aimed at understanding the mechanisms that underlie neurological disorders. This 1907 Trailblazer Award is the perfect mechanism to help me achieve that goal because these experiments are not well suited for traditional funding sources because my lab does not have prior experience conducting AD mouse model studies and we do not have preliminary data yet. But at the heart of the proposed studies is employing molecular genetic techniques in mice to examine sex differences in neurobiology and behavior, and my lab is exceptionally well positioned to perform these types of experiments. In addition, my lab is part of a world-renowned research institute that has multiple research groups currently performing AD research studies. These labs are all highly collaborative and happy to support my lab as we conduct these AD mouse model studies.

References

1. Alzheimer's Association (2023). 2023 Alzheimer's disease facts and figures. Alzheimer's & Dementia *19*, 1598–1695. 10.1002/alz.13016.
2. Cao, Q., Tan, C.-C., Xu, W., Hu, H., Cao, X.-P., Dong, Q., Tan, L., and Yu, J.-T. (2020). The Prevalence of Dementia: A Systematic Review and Meta-Analysis. J Alzheimers Dis *73*, 1157–1166. 10.3233/JAD-191092.
3. Dumurgier, J., and Sabia, S. (2020). [Epidemiology of Alzheimer's disease: latest trends]. Rev Prat *70*, 149–151.
4. Li, R., and Singh, M. (2014). Sex differences in cognitive impairment and Alzheimer's disease. Front Neuroendocrinol *35*, 385–403. 10.1016/j.yfrne.2014.01.002.
5. Tahami Monfared, A.A., Byrnes, M.J., White, L.A., and Zhang, Q. (2022). Alzheimer's Disease: Epidemiology and Clinical Progression. Neurol Ther *11*, 553–569. 10.1007/s40120-022-00338-8.
6. Asperholm, M., Högman, N., Rafi, J., and Herlitz, A. (2019). What did you do yesterday? A meta-analysis of sex differences in episodic memory. Psychol Bull *145*, 785–821. 10.1037/bul0000197.
7. Spalek, K., Coynel, D., de Quervain, D., and Milnik, A. (2023). Sex-dependent differences in connectivity patterns are related to episodic memory recall. Hum Brain Mapp *44*, 5612–5623. 10.1002/hbm.26465.
8. Beltz, A.M., Kelly, D.P., and Berenbaum, S.A. (2020). Sex differences in brain and behavioral development. In Neural Circuit and Cognitive Development (Second Edition), J. Rubenstein, P. Rakic, B. Chen, and K. Y. Kwan, eds. (Academic Press), pp. 585–638. 10.1016/B978-0-12-814411-4.00027-5.
9. DeTure, M.A., and Dickson, D.W. (2019). The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener *14*, 32. 10.1186/s13024-019-0333-5.
10. Kawas, C., Gray, S., Brookmeyer, R., Fozard, J., and Zonderman, A. (2000). Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology *54*, 2072–2077. 10.1212/wnl.54.11.2072.
11. Shaw, C., Hayes-Larson, E., Glymour, M.M., Dufouil, C., Hohman, T.J., Whitmer, R.A., Kobayashi, L.C., Brookmeyer, R., and Mayeda, E.R. (2021). Evaluation of Selective Survival and Sex/Gender Differences in Dementia Incidence Using a Simulation Model. JAMA Netw Open *4*, e211001. 10.1001/jamanetworkopen.2021.1001.
12. Rocca, W.A., Mielke, M.M., Vemuri, P., and Miller, V.M. (2014). Sex and gender differences in the causes of dementia: a narrative review. Maturitas *79*, 196–201. 10.1016/j.maturitas.2014.05.008.
13. Knoedler, J.R., Inoue, S., Bayless, D.W., Yang, T., Tantry, A., Davis, C.-H., Leung, N.Y., Parthasarathy, S., Wang, G., Alvarado, M., et al. (2022). A functional cellular framework for sex and estrous cycle-dependent gene expression and behavior. Cell *185*, 654-671.e22. 10.1016/j.cell.2021.12.031.
14. Bayless, D.W., Davis, C.-H.O., Yang, R., Wei, Y., de Andrade Carvalho, V.M., Knoedler, J.R., Yang, T., Livingston, O., Lomvardas, A., Martins, G.J., et al. (2023). A neural circuit for male sexual behavior and reward. Cell *186*, 3862-3881.e28. 10.1016/j.cell.2023.07.021.
15. Bayless, D.W., Yang, T., Mason, M.M., Susanto, A.A.T., Lobdell, A., and Shah, N.M. (2019). Limbic Neurons Shape Sex Recognition and Social Behavior in Sexually Naive Males. Cell *176*, 1190-1205.e20. 10.1016/j.cell.2018.12.041.
16. Yang, T., Bayless, D.W., Wei, Y., Landayan, D., Marcelo, I.M., Wang, Y., DeNardo, L.A., Luo, L., Druckmann, S., and Shah, N.M. (2023). Hypothalamic neurons that mirror aggression. Cell *186*, 1195-1211.e19. 10.1016/j.cell.2023.01.022.

Daniel W. Bayless, Ph.D.

Assistant Professor
Salk Institute for Biological Studies
10010 N Torrey Pines Rd
La Jolla, CA 92037

dbayless@salk.edu
(918) 521-9111
bayless.salk.edu

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 past experiences and sex hormones 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**	University of California, 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. **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)
2. 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)
3. 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)

4. 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)
5. **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)
6. **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)
7. **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)
8. **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)
9. **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)
10. **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

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
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
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 and as a graduate teaching assistant leading group discussions, lectures, and experiments. In addition, I am passionate about actively promoting diversity and equity in science, and I foster an environment of belonging and respect in the classroom and lab. I am the first person in my family's history to earn a doctorate degree, so I understand the value of sharing my experiences with and teaching and mentoring the next generation of teachers, policymakers, and scientists.

Classroom Instruction

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, (Lead Instructor: Dr. Thomas Hebert)
2008-09	Substitute teacher, Norman Public Schools, Norman, OK (Supervisor: Robbi Mullinax)

Scientific Research Mentorship

2023-present	Pom Jantarachanatanthiti, Salk Institute Research Assistant
2022	Oscar Livingston, (*High School Student*), Stanford Summer Research Internship
2021-23	Leonardi Gozali, (*Stanford Grad Student*), Stanford Biology Program
2019	Chelsea Nnebe, (Stanford *M.D./Ph.D. Student*), Stanford School of Medicine
2018-19	Victoria Flagg, (*Stanford Master's Student*), Stanford Neurosciences Program
2018-23	Chung-ha Davis, (*Stanford Grad Student*), Stanford Neurosciences Program
2018-19	Ilana Zucker-Scharff, (*Stanford Grad Student*), Stanford Neurosciences Program

2017-18 Corey Fernandez, (*Stanford Grad Student*), Stanford Neurosciences Program

2018 Lexi Lobdell, (*Mount Holyoke Undergrad*), Stanford Summer Research Internship

2017-18 Albert Susanto, (*UC Berkeley Undergrad*), Stanford Research Assistant

2015-17 Matthew Mason, (*UC Berkeley Undergrad*), UCSF/Stanford Research Technician

2015 Gabriel Chan, (*UCLA Undergrad*), UCSF Summer Research Internship

2013-14 Jacob Rosenblum, (*Tulane Undergrad*), Tulane Research Assistant

2012-14 Maria Perez, (*Tulane Undergrad*), Tulane Research Assistant

2010-13 Jeffrey Darling, (*Tulane Undergrad*), Tulane Research Assistant

INVITED TALKS AND SEMINARS

1. Stanford Autism Working Group Seminar Series, Stanford, CA, March 2, 2023, "Neural circuits for innate but flexible social behavior."
2. UC-Santa Cruz NeuroClub Seminar Series, Santa Cruz, CA, May 11, 2021, "Sex on the brain: Neuropeptidergic modulation of sex recognition and mating behavior."
3. 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."
4. Max-Planck Institute - Munich Winter Conference on Stress, Garmisch-Partenkirchen, Germany, March 17, 2019, "Neural pathway for innate sex recognition."
5. Stanford Center for Molecular Neuroscience in Health and Disease - Member Meeting, Stanford, CA, July 19, 2018, "A neural substrate for sex recognition."
6. Stanford Neurobiology Lab Evening, Stanford, CA, November 30, 2017, "Neurobiology of social interactions."
7. UCSF Center for Reproductive Sciences Workshop, San Francisco, CA, February 5, 2016, "Genetic dissection of the neural circuits underlying reproductive behavior in mice."
8. Tulane Graduate Studies Student Association Colloquium Series, New Orleans, LA, November 6, 2013, "Sex differences in impulsivity: Role of neonatal testosterone exposure."
9. 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

2023-present	Ad hoc peer reviewer, eLife
2021-2022	Creator/editor, Stanford Neurobiology Community monthly newsletter
2021	Co-coordinator, Stanford Neurobiology Anti-Oppression Summer Reading Group, 8 bi-weekly meetings focused on discussion/praxis related to oppression in STEM.
2020-2023	Coordinator, Stanford Neurobiology “Research in Progress” series, bi-weekly talks given by post-docs and grad students in the Neurobiology Department
2020-2023	Founding member, Diversity, Equity, Inclusion, and Belonging Committee for the Stanford Neurosciences Ph.D. Program
2020-2023	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

Nirao Shah, M.D., Ph.D.
Professor
Dept. of Psychiatry
and Dept. of Neurobiology
Stanford University
1201 Welch Rd, Rm P106
Stanford, CA 94305
(650) 725-5735
nirao@stanford.edu

Jill Daniel, Ph.D.
Professor
Dept. of Psychology
Tulane Brain Institute
Tulane University
200 Flower Hall
New Orleans, LA 70118
(504) 862-3301
jmdaniel@tulane.edu

Gary Dohanich, Ph.D.
Professor
Dept. of Psychology
Tulane University
3047 Percival Stern Hall
New Orleans, LA 70118
(504) 862-3307
dohanich@tulane.edu

Thomas Clandinin, Ph.D.
Professor
Dept. of Neurobiology
Stanford University
299 W. Campus Dr, Rm D200
Stanford, CA 94305
(650) 725-3958
trc@stanford.edu