

Kristyn Borrelli
Neuroscience Ph.D. Candidate
Department of Pharmacology & Experimental Therapeutics
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March 11, 2021

Dear Members of the Travel Awards Committee,

I am writing to request financial support of the upcoming virtual Genes, Brain, and Behavior Meeting this May. I am currently a fifth-year neuroscience Ph.D. candidate, working under the advisement of Dr. Camron Bryant in the Laboratory of Addiction Genetics at Boston University School of Medicine. Shortly after joining Dr. Bryant's laboratory in May of 2017, I took on the responsibility of implementing a behavioral approach never used in our lab previously. Over the course of several months, I had successfully laid the ground work to run intracranial self-stimulation (ICSS) experiments in mice. I presented a poster with results utilizing this approach at the 2019 iBANGS annual meeting in Edinburgh, Scotland, and this work has recently been accepted for publication in *Psychopharmacology*.

In 2018, I was appointed as a Transformative Training Program in Addiction Science (TTPAS) trainee. Through this training program, I have been exposed to the study and treatment of substance use disorders beyond basic laboratory research. During clinical rotations, I was able to interact with patients affected by substance use disorders, understand the rationale underlying appropriate treatment plans with clinicians, and witness first-hand the emotional and physical toll addictive disorders demand. During the course of this experience, I had taken on a new project in the lab. Currently, I am working to develop a model of Neonatal Opioid Withdrawal Syndrome (NOWS) in outbred mice. My research goals include discovery of developmental mechanisms impacted by perinatal opioid exposure, long-term behavioral implications including increased susceptibility to substance use disorders, and long-term changes in transcriptional profiles contributing to phenotypic risk. My training through TTPAS has only served to reinforce my hope that my work will benefit efforts to ameliorate the negative impact of substance use disorders, particularly those pertaining to opioids and cases of *in utero* exposure.

As a young researcher, I greatly value the opportunity to share my work others, particularly an audience with interests that align so closely with my own. I plan to share the work I described above at the IBANGS conference, and I hope to have the opportunity to gain insightful criticisms and suggestions for both this project and future experiments. I anticipate the potential to forge collaborative relationships and take advantage of the intellectual synergy my fellow scientists can offer me at this conference. A presentation at the IBANGS conference would additionally serve as a wonderful opportunity to further hone my skills in succinctly and effectively communicating my work, conveying both its broader real-world relevance as well as the fundamentals of the methods and implications of the results. My advisor, Dr. Camron Bryant, has held a faculty position at BU since 2012. Any financial support beyond our primary funding sources helps keep our experiments running at full throttle. The ability to attend conferences additionally bears the benefit of offering exposure to novel approaches in the field, fueling innovation in our own research.

I greatly appreciate you taking the time to review my application, and I look forward to hearing back from you.

Best Regards,
Kristyn Borrelli

Abstract (oral or poster presentation preferred):

PI Name: Camron Bryant (camron@bu.edu)

Neonatal morphine (P1-14) in CFW mice induces behavioral signs of withdrawal, sex-dependent transcriptomic profiles in brainstem (P15), and altered affective and psychostimulant-induced locomotor phenotypes in adolescence

Kristyn N. Borrelli¹, Emily J. Yao¹, William W. Yen², Qiu T. Ruan¹, Julia C. Kelliher¹, Melanie M. Chen¹, Richard K. Babbs¹, Jacob A. Beierle¹, Elisha M. Wachman^{3,4}, Alberto Cruz-Martin², Camron D. Bryant¹

¹Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics and Psychiatry, Boston University School of Medicine; ²Department of Biology and Pharmacology, Boston University; ³Department of Pediatrics, Boston Medical Center; ⁴Grayken Center for Addiction Medicine, Boston Medical Center

The Opioid Use Disorder epidemic has led to higher incidence of Neonatal Opioid Withdrawal Syndrome (NOWS). The neurobiological basis of NOWS is largely unknown, but mouse models will help facilitate mechanistic discovery. We aimed to induce repeated cycles of spontaneous opioid withdrawal during a sensitive period of neurodevelopment to understand both short- and long-term behavioral and neurodevelopmental implications of perinatal opioid exposure. We treated neonatal outbred Cartworth Farms White (CFW) mice (Swiss Webster) with morphine sulfate (MOR; 15.0 mg/kg, s.c.) once or twice daily from postnatal day 1 (P1) to P14, the approximate third trimester-equivalent of human gestation. Brainstem (containing pons and medulla) was collected on P15 and processed for transcriptome analysis via mRNA sequencing (RNA-seq). In a separate cohort, adolescent testing was performed from ~P25-36. MOR treatment resulted in weight deficits (P2- 14) that were sustained at P21 and P50. MOR also induced a delayed self-righting latency (P4, P7) and increased ultrasonic vocalizations (USVs; P7, P14). Thermal nociception via hot plate and tail withdrawal assays indicated thermal hyperalgesia in morphine mice (P7, P14). MOR-treated mice also exhibited anxiety-like behavior at P21 (open field). Brainstem transcriptome pathway analysis indicated opposing effects on ribosomal and mitochondrial gene expression by sex, as there was downregulation of genes within these networks in males and upregulation in females, potentially indicating sex-dependent modulation of metabolic function in response to perinatal MOR. During adolescence, MOR treatment was linked to decreased spatial memory performance, reduced anxiety-like behaviors, and increased locomotor activity following treatment with 2.0 mg/kg methamphetamine.

Kristyn Borrelli
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EDUCATION

Ph.D. Candidate in Neuroscience, 2016-present (Deg. Expected 2021)

Boston University School of Medicine – Boston, MA

Graduate Program for Neuroscience; Graduate Program in Biomolecular Pharmacology

GPA: 3.95

Bachelor of Science, 2016

University of Delaware – Newark, DE

Honors Degree with Distinction in Neuroscience, minor in Biological Sciences

GPA: 3.76

RESEARCH EXPERIENCE

Laboratory of Addiction Genetics, Boston University School of Medicine (March 2017-Present)

Advisor: Camron Bryant, Ph.D.

- Implementing intracranial self-stimulation (ICSS) to determine the impact of heterogeneous ribonucleoprotein H1 (hnRNP H1) dysfunction on methamphetamine-induced behavior in mice
- Developing a mouse model of Neonatal Opioid Withdrawal Syndrome (NOWS) to better understand the long-term behavioral and neurobiological implications of prenatal opioid exposure
- With Transformative Training Program in Addiction Science (TTPAS) co-mentor Elisha Wachman, M.D.: Evaluating DNA methylation patterns in postnatal placental tissue from patients who received opioid maintenance therapy during pregnancy

Pfizer, Cambridge, MA (Summer 2017)

Graduate Summer Intern: Precision Medicine Group, part of Clinical Research and Development at Pfizer supporting Inflammation/Immunology

Gained familiarity with next generation sequencing (NGS) technologies, immune-profiling, and high throughput single-cell sequencing (Chromium 10x platform) in clinical samples

Behavioral Epigenetics Neuroscience Laboratory, University of Delaware (2014-2016)

Undergraduate Research Assistant

Advisor: Tania L. Roth, Ph.D.

Investigated the effect of chronic, unpredictable prenatal stress on methylation of the brain-derived neurotrophic factor gene (*Bdnf*) in brain tissue of adult rats

Department of Cardiology, Copenhagen University Hospital Hvidovre (2015)

Research Assistant

Advisor: Ulrik Dixen, M.D./Ph.D.

Investigated the risk factors for patients with non-ischemic heart failure in treatment with an implantable cardioverter defibrillator (ICD)

HONORS AND AWARDS

Recipient, Boston University Genome Science Institute RNA-Sequencing Research Award (2020)

Fellow, Boston University's Transformative Training Program in Addiction Science (2018 – 2020)

Recipient, National Institute of General Medical Sciences (NIGMS) T32 Instructional Training Grant (2017-2018)

Recipient, American Association of University Professors (AAUP) Student Scholarship (2016)

Recipient, University of Delaware General Honors Award (2014)

MENTORSHIP

Undergraduates: Kyra Dubinsky (BU, 2017-2018), Wendolin Marmol (Quinnipiac University, NIDA Summer Intern, 2018), Carly Langan (BU, 2018-2020), Chih-Cheng Wu (BU, 2018-2020), Rhea Bhandari (BU, 2020-present), Catalina Zamorano (BU, 2020-present)
Rotation Ph.D. Students: Chinyere Kemet (2021)

PUBLICATIONS

Borrelli KN, Langan CR, Dubinsky KR, Szumlinski KK, Carlezon WA, Chartoff EH, Bryant CD. Intracranial self-stimulation and concomitant behaviors following systemic methamphetamine administration in *Hnmph1* mutant mice. Accepted, March 2021. *Psychopharmacology*. Pre-print: <https://www.biorxiv.org/content/10.1101/2020.06.05.137190v2.full>

Blaze J, Asok A, **Borrelli KN**, Tulbert C, Bollinger J, Ronca AE, Roth TL. (2017) Intra-uterine exposure to maternal stress alters *Bdnf IV* DNA methylation and telomere length in the brain of adult rat offspring. *Int J Dev Neurosci*. 62:56-62. PMID: 28330827

MANUSCRIPTS IN PREPARATION

Borrelli KN, Yao EJ, Yen WW, Ruan QT, Chen MM, Kelliher JC, Langan CR, Scotellaro JL, Babbs RK, Beierle JC, Johnson WE, Wachman EM, Cruz-Martin A, Bryant CD. Sex differences in behavioral and brainstem transcriptomic neuroadaptations following neonatal opioid exposure in outbred mice. Manuscript in preparation.

ORAL AND POSTER PRESENTATIONS

Borrelli KN, Yao EJ, Yen WW, Ruan QT, Chen MM, Kelliher JC, Langan CR, Scotellaro JL, Babbs RK, Beierle JC, Johnson WE, Wachman EM, Cruz-Martin A, Bryant CD. Automated facial grimace tracking to assess spontaneous withdrawal following neonatal morphine (P1-14) in CFW mice and altered affective phenotypes in adolescence. Poster Presentation. *Virtual American College of Neuropsychopharmacology Annual Meeting. December 6-9, 2020.*

Borrelli KN, Yao EJ, Yen WW, Ruan QT, Chen MM, Kelliher JC, Langan CR, Scotellaro JL, Babbs RK, Beierle JC, Johnson WE, Wachman EM, Cruz-Martin A, Bryant CD. Neonatal morphine administration (P1-14) in CFW mice induces behavioral signs of withdrawal, sex-dependent transcriptomic profiles in brainstem (P15), and altered affective and psychostimulant-induced locomotor phenotypes in adolescence. Oral Presentation. *Boston University Genome Science Institute Virtual Symposium. November 12, 2020.*

Borrelli KN, Yao EJ, Yen WW, Ruan QT, Chen MM, Kelliher JC, Langan CR, Scotellaro JL, Babbs RK, Beierle JC, Johnson WE, Wachman EM, Cruz-Martin A, Bryant CD. Neonatal morphine administration (P1-14) in outbred CFW mice induces enhanced behavioral signs of withdrawal in females and distinct patterns of transcriptional activation and brainstem gene expression. Oral Presentation. *International Behavioural & Neural Genetics Society Virtual Trainee Symposium. September 23, 2020.*

Borrelli KN, Yao EJ, Yen WW, Ruan QT, Chen MM, Kelliher JC, Langan CR, Scotellaro JL, Babbs RK, Beierle JC, Johnson WE, Wachman EM, Cruz-Martin A, Bryant CD. Neonatal morphine administration (P1-14) in CFW mice induces behavioral signs of withdrawal, sex-dependent transcriptomic profiles in brainstem (P15), and altered affective and psychostimulant-induced locomotor phenotypes in adolescence. Poster Presentation. *Neurogenetics Virtual Conference. July 29, 2020.*

Borrelli KN, Yao EJ, Yen WW, Ruan QT, Chen MM, Kelliher JC, Langan CR, Scotellaro JL, Babbs RK, Beierle JC, Johnson WE, Wachman EM, Cruz-Martin A, Bryant CD. Neonatal morphine administration (P1-14) in outbred CFW mice induces enhanced behavioral signs of withdrawal in females and a distinct brainstem transcriptomic profile. Poster Presentation. *National Institute on Drug Abuse Genetics Consortium Meeting. Rockville, MD. Jan 13-14, 2020.*

Borrelli KN, Yao EJ, Yen WW, Ruan QT, Chen MM, Kelliher JC, Langan CR, Scotellaro JL, Babbs RK, Beierle JC, Johnson WE, Wachman EM, Cruz-Martin A, Bryant CD. Neonatal morphine administration (P1-P14) in outbred CFW mice induces signs of withdrawal and behavioral evidence for a developmental delay. Poster Presentation. *International Narcotics Research Conference. New York, New York. July 7-11, 2019.*

Borrelli, KN, Carlezon A Jr, Chartoff EH, Bryant CD. Reward sensitivity in *Hnrnp1^{+/-}* mice following acute methamphetamine administration as measured via intracranial self-stimulation. Poster Presentation. *International Behavioural and Neural Genetics Society Annual Meeting. Edinburgh, UK. May 10-14, 2019.*

Borrelli, KN, Carlezon A Jr, Chartoff EH, Bryant CD. Reward sensitivity in *Hnrnp1^{+/-}* mice following acute methamphetamine administration as measured via intracranial self-stimulation. Poster Presentation. *National Institute on Drug Abuse Genetics Consortium Meeting. Rockville, MD. Jan 14-15, 2019.*

Borrelli, KN, Carlezon A Jr, Chartoff EH, Bryant CD. Reward sensitivity as measured via intracranial self-stimulation in *Hnrnp1^{+/-}* mice with reduced methamphetamine addictive behaviors. Poster Presentation. *Boston University Genome Science Institute Symposium. Boston, MA. November 15, 2018.*

Borrelli, KN, Carlezon A Jr, Chartoff EH, Bryant CD. Reward sensitivity as measured via intracranial self-stimulation in *Hnrnp1^{+/-}* mice with reduced methamphetamine addictive behaviors. Poster Presentation. *Society for Neuroscience Annual Meeting, San Diego, CA. November 3-7, 2018.*

Borrelli, K, Blaze, J, Asok, A, Roth, TL, Ronca, AE. Unpredictable variable prenatal stress (UVPS) alters *Bdnf* DNA methylation and telomere length in behaviorally-relevant brain regions of adult rat offspring. Poster Presentation. *Society for Neuroscience, Delaware Center for Neuroscience Research Symposium. Newark, Delaware. December 2015.*

Borrelli, K, Boas, R, Mizrak, I, Fanø, S, Dixen, U. Nature and severity of ventricular arrhythmia in non-ischemic heart failure: A DANISH Holter substudy. Poster Presentation. *National Scientista Foundation Annual Symposium. Microsoft, New York, New York. October 2015.*

Borrelli, K, Boas, R, Mizrak, I, Fanø, S, Dixen, U. Nature and severity of ventricular arrhythmia in non-ischemic heart failure: A DANISH Holter substudy. Poster Presentation. *Danish Institute for Study Abroad Research Practicum Symposium. Copenhagen, Denmark. May 2015.*



Camron D. Bryant, Ph.D.

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March 12, 2021

RE: Letter of Recommendation for Kristyn Borrelli for a 2021 IBANGS Travel Award

Dear Members of the Travel Awards Committee:

I am writing to provide my highest recommendation for my student, Kristyn Borrelli, for a Travel Award to attend the 2020 annual IBANGS meeting. Kristyn is a fifth year Ph.D. student in the Graduate Program for Neuroscience who joined my lab in the Spring of 2017. In year first year, she elected to take a concentrated course of study in biomolecular pharmacology in order to strengthen her foundational knowledge critical to our work. She was awarded with financial support from two separate sources since joining my lab, speaking to her high standard of academic achievement and level of commitment to her research. These accomplishments include support from our Program in Biomolecular Pharmacology training grant (T32) as well as a 2-year fellowship through our Transformative Training Program in Addiction Sciences (TTPAS) at BU (awarded in the Fall of 2018). Her desire to participate in this interdisciplinary program suggests strong interest in the translational relevance of our work, extending beyond the bench.

Kristyn has successfully tackled challenging and new projects in the lab with a high level of independence. Upon first joining in 2017, she implemented a new behavioral technique from scratch (intracranial self-stimulation), including ordering and setting up the equipment and writing the code to run the various protocols. ICSS is now a mainstay technique in the lab that is a critical component of our addiction research. This technique is notoriously difficult to implement in mice, as it requires surgical techniques and rigorous behavioral training, but she was able to persevere and troubleshoot her way to success. **Very recently, her first, first author paper was accepted in *Psychopharmacology*** which used ICSS to measure innate reward threshold and changes in reward processing under the influence of methamphetamine in *Hnrnp1* mutant mice. This was a very difficult paper to write, given that I had no hands-on experience with this technique which was front-and-center in the publication. We went through several renditions of packaging the data for publication and Kristyn was almost entirely responsible for crafting this manuscript, with only big-picture suggestions and minimal edits from me. After setting up the ICSS procedure, Kristyn developed a model of early life stress that she applied toward *Hnrnp1* mutants and observed long-term effects on emotional and cognitive behaviors in adulthood as well as changes in methamphetamine sensitivity that interacted with *Hnrnp1* genotype.

Kristyn demonstrated further flexibility in moving between projects; in 2018 she transitioned to working on neonatal opioid withdrawal syndrome (NOWS) and has further optimized the procedures for assessing the short-term effects on behaviors (withdrawal – pain, USVs, etc.) and has developed procedures for testing long-term effects on behavior and brain adaptations in adolescence and adulthood. She has two NOWS manuscripts that she will prepare for publication this year. In addition to behavioral analysis, Kristyn successfully analyzed RNA-sequencing data from mice generated from our NOWS model and is currently performing immunohistochemical analyses of brain tissue from these mice. In addition, because Kristyn is a TTPAS trainee, one of the requirements is that they must work with another investigator to learn a new approach/technique/subject matter outside of their home lab environment that can be applied to addiction research. Here, Kristyn is working with both Drs. Elisha Wachman (BMC, NICU) and Huiping Zhang (BUSM Psychiatry) to analyze methylome data from the placental tissues of mothers dependent on opioids. These training activities will result in another co-authored publication for Kristyn.

Considering that Kristyn came to my lab without any experience running animal behavior and with limited experience in data analysis, big data, or manuscript preparation, her level of progress and productivity over the last four years is very impressive. In addition to acquiring these skills, she has also successfully managed numerous undergraduate research assistants during this time and hosted her first two PhD rotation students this year. Kristyn is an effective mentor and always ensures her students understand their contributions and why

this work is important in a broader sense. As an example, with the help of Kristyn, her undergraduate student Catalina Zamorano procured her own UROP funding to complete a semester project. Cat is also completing an undergraduate thesis project that Kristyn is supervising.

Your financial support would be greatly appreciated in supporting Kristyn to attend the 2021 IBANGS conference which will certainly benefit her ongoing development as a scientist, and I know she will take full advantage of the opportunity to share her current work, gain insight relevant to both her professional and scientific improvement, and constructively engage with the IBANGS community. I give my strongest recommendation for Kristyn to receive a travel award for the 2021 IBANGS conference.

Best Regards,

A handwritten signature in black ink, appearing to read 'C. D. Bryant', written in a cursive style.

Camron D. Bryant, Ph.D