BIOGRAPHICAL SKETCH

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NAME: Sara Park Faccidomo

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POSITION TITLE: Research Assistant Professor, Departments of Psychiatry & Bowles Center for Alcohol Studies

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tufts University, Medford, MA	B.A.	5/1998	Psychology
Tufts University, Medford, MA	M.S.	8/2003	Psychopharmacology
Tufts University, Medford, MA	Ph.D.	5/2006	Psychopharmacology
University of North Carolina, Chapel Hill, NC	Post Doc	5/2012	Behavioral Pharmacology

A. Personal Statement

I serve in three roles on this P60 ARC renewal application: co-I of Research Component 1 (CP1), co-PD of the Information Dissemination Core (IDC), and active researcher in the Scientific Resource Core (SRC). As noted below, I have the required education, training, research and leadership expertise to be successful in all of these roles.

I have been an active member of the preclinical alcohol research field for the past 20 years and have been working with Dr. Hodge for the past 15 years and with Dr. McElligott for the past 5 years. The proposed experiments are a natural extension of Dr. Hodge's R01, R37 and P60 awards, to which I have made extensive contributions in the prior funding cycle. Our research is focused on studying the neural mechanisms that modulate alcohol reinforcement and reinstatement. Recently, we have shown the mechanistic relevance of glutamatergic intracellular signaling pathways, involving AMPA, CAMKII, ERK1/2, using molecular strategies, and have functionally regulated the positive reinforcing effects of alcohol, via site-specific microinjection and viral vector strategies. We have recently discovered that TARP ɣ-8, a protein linked to CAMKII and that is required to anchor AMPA to the membrane, may be integral in modulating the positive reinforcing effects of alcohol self-administration in the BLA. The current research component (CP1) proposes to extend our prior work on non-dependent alcohol self-administration to delineate whether AMPAR receptor expression and function in the BLA→NAcb pathway is involved in regulating dependence-induced escalations in alcohol self-administration We will also elucidate the impact of alcohol dependence on novel PDZ domain proteins that regulate AMPAR function and use CRISPR technology to conduct mechanistic behavioral studies. Both of our labs are well-equipped to conduct the proposed studies and have both the equipment and personnel to successfully implement these novel molecular, electrophysiological, behavioral, and circuit-specific studies.

The Scientific Resource Core of the P60 ARC grant is a shared resource that provides investigators with extensive equipment and support for photometry, microscopy and molecular techniques (e.g., immunohistochemistry, microscopy, Western blots, RT-PCR) that are proposed in this application. One of my roles, as a research scientist on the SRC, is to provide molecular and microscopy scientific support for all of the research components, as needed. I have extensive expertise in the techniques offered by the SRC and I am responsible for maintaining the equipment and will help facilitate oversight of equitable use of resources.

The Information Dissemination Core of the P60 grant is focused on community education of existing and current research regarding brain development and function, alcohol's effects on the brain, alcohol drinking in youth and adults, and training scientists in effective community outreach. I have been an active participant in fulfilling the mission of this Core during the past 10 years with a particular focus on training scientists to engage in interactive community outreach and information dissemination. This past year, due to constraints generated by the pandemic, I created an IDC website, bringing our outreach opportunities to a virtual space. In this renewal application, I will share the leadership of this Core with Dr. Donita Robinson, and we have an outstanding team of personnel to lead all of the outreach activities proposed in the application. As Co-PD, I will facilitate communication between our ARC and BCAS teams and community groups, I will expand our online presence and I will create innovative interactive activities for teaching and learning. I am enthusiastic about this new role and look forward to being more involved in leading and fulfilling the mission of the IDC.

Overall, my training, research and outreach experiences provide me with a strong foundation to excel in all of these roles for the ARC and I will be fully devoted to elevating the impact and success of both the research and educational components of this application.

Ongoing and recently completed projects that are relevant to this application:

R01 AA028782 *05/10/21-03/31/2026*
Novel mechanism of alcohol self-administration and relapse
Role: Research Assistant Professor (Hodge, CW, PI)

5P60AA011605-22; Sub-Project ID: 5443, *12/01/17-11/30/22*
Limbic Glutamatergic Circuits in Ethanol Self-Administration (Component 1)
Role: Research Assistant Professor (Hodge, CW & McElligott, ZA, Component PIs; Kash, TL, P60 PI)

R37 AA014983 *07/01/16 – 6/30/21*
Molecular Mechanisms of Ethanol Reinforcement
Role: Research Assistant Professor (Hodge, CW, PI)

Citations that highlight experience, qualifications, and collaborative efforts within the ARC:

1. Hoffman JL*, Faccidomo S*, Saunders BL, Taylor S, Kim M, Hodge CW. Inhibition of AMPA receptors containing TARP γ-8 with JNJ-55511118 shows preclinical efficacy for pharmacotherapeutic treatment of chronic repetitive alcohol self-administration, Alcohol Clin Exp Res (2021) July; 45(7):1424-1435. PMID: 34086361; PMCID: PMC8336716
2. Faccidomo S, Cogan ES, Hon OJ, Hoffman JL, Saunders BL, Eastman VR, Kim M, Taylor S, McElligott ZA, Hodge CW. Calcium-Permeable AMPA Receptor Activity and GluA1 Trafficking in the Basolateral Amygdala Regulate Operant Alcohol Self-Administration, Addiction Biology (2021) Sept; 26(5). PMID: 33955100; PMCID: PMC8376775
3. Torruella-Suarez ML, Vandenberg JR, Cogan ES, Tipton GJ, Teklezghi A, Dange K, Patel GK, McHenry JA, Hardaway JA, Kantak PA, Crowley NA, DiBerto JF, Faccidomo SP, Hodge CW, Stuber GD, McElligott ZA (2020) Manipulations of Central Amygdala Neurotensin Neurons Alter the Consumption of Ethanol and Sweet Fluids in Mice. J Neurosci (2020) Jan 15; 40(3):632-647. PMID: 31744862; PMCID: PMC6961987
4. Salling MC, Faccidomo SP, Li C, Psilos K, Galunas C, Spanos M, Agoglia AE, Kash TL, Hodge CW. Moderate alcohol drinking and the amygdala proteome: Identification and validation of CaMKII as a novel molecular mechanism of the positive reinforcing effects of alcohol. Biological Psychiatry (2016) March; 79(6):430-42. PMID: 25579851; PMCID: PMC4417085.

B. Positions, Scientific Appointments, and Honors
Positions

2021-present Adjunct Instructor, University of North Carolina-Chapel Hill, BBSP Program
2020-present Research Assistant Professor, University of North Carolina-Chapel Hill, Departments of Psychiatry & Bowles Center for Alcohol Studies
2011-2020 Research Associate, University of North Carolina-Chapel Hill, Bowles Center for Alcohol Studies (PI, Clyde W Hodge)

2006-2011 Postdoctoral Research Trainee, University of North Carolina-Chapel Hill, Bowles Center for Alcohol Studies (PI, Clyde W Hodge)
2000-2005 Graduate Teaching Assistant, Tufts University, Department of Psychology (PI, Klaus A Miczek)
2000-2006 Graduate Research Assistant, Tufts University, Department of Psychology (PI, Klaus A Miczek)
1998-1999 Research Assistant, Tufts University, Department of Psychology (PI, Klaus A Miczek)

Scientific Appointments & Honors

1999-present Society for Neuroscience
2005-present Research Society on Alcoholism
2006-present Peer reviewer for 12 journals
2007, 2008, 2009 Research Society for Alcoholism Junior Investigator Award
2005 Research Society for Alcoholism Student Merit Award
2004-2011 New York Academy of Sciences

C. Contributions to Science

1) Glutamatergic molecular mechanisms that regulate alcohol self-administration and reinforcement: role for protein kinases, calcium signaling and AMPA receptor activity. Glutamate signaling in the brain influences diverse neural processes that result in altered synaptic activity and neuronal plasticity. Both ERK and CAMKII are critically important substrates that are known to modulate both learning and memory and excitatory neurotransmission in the brain. Both acute and chronic alcohol self-administration alter the activity levels of these proteins, which reflects concomitant neuronal plasticity that contributes to the development of addiction and relapse to drugs of abuse. My early post-doctoral work showed that systemic inhibition of ERK specifically and selectively increased operant alcohol but not sucrose self-administration. Further, we found that levels of pERK immunoreactivity were increased in alcohol self-administering mice in reward-related brain regions, suggesting that alcohol-induced molecular changes in ERK phosphorylation could have functional consequences. Indeed, we used site-specific microinjection to directly inhibit ERK in multiple brain regions and found that increased operant responding was observed after direct microinjection into the PFC. We have also extensively studied whether there is a functional role for CAMKII, and AMPAR activity on non-dependence alcohol self-administration and relapse. Indeed, we have found that both CAMKII and the GluA1 subunit of the AMPAR are key substrates of alcohol self-administration and are elevated after multiple models of alcohol drinking. Moreover, direct inhibition of both CAMKII and GluA1-containing AMPARs in the basolateral amygdala (BLA), potently decreases operant responding for alcohol. We have also explored AMPAR accessory proteins such as TARP ɣ-8, which is integral in anchoring GluA1-containing AMPARs to the membrane. Functional inhibition of this relationship also blunts operant responding for alcohol. Common features of these proteins are that they are all involved in modulating neuronal excitatory activity. Thus, we suggest that neuronal signaling pathways that interact with AMPARS, are important mechanisms for regulating the positive reinforcing properties of alcohol, especially in regions that project to the NAC, such as the BLA and PFC.

a. **Faccidomo S,** Besheer J, Stanford PC, Hodge CW (2009) Increased operant responding for ethanol in male C57BL.6J mice: specific regulation by the ERK1/2, but not JNK, MAP kinase pathway. Psychopharmacology, 204:135-147
b. **Faccidomo S,** Salling MC, Galunas C, Hodge CW (2015) Operant ethanol self-administration increases extracellular-signal regulated protein kinase (ERK) phosphorylation in reward-related brain regions: selective regulation of positive reinforcement in the prefrontal cortex of C57BL/6J mice. Psychopharmacology, 232:3417-30
c. **Faccidomo S,** Reid GT, Agoglia AE, Ademola SA, Hodge CW (2016) CAMKII inhibition in the prefrontal cortex specifically increases the positive reinforcing effects of sweetened alcohol in C57BL/6J mice. Behav Brain Res, 298:286-90
d. Salling MC, Hodge CJ, Psilos KE, Eastman VR, **Faccidomo SP,** Hodge CW (2017) Cue-induced reinstatement of alcohol-seeking behavior is associated with increased CAMKII T286 phosphorylation in the reward pathway of mice. Pharmacol Biochem Behav, 163:20-29
e. Stevenson RA, Hoffman JL, Maldonado-Devincci AM, **Faccidomo S,** Hodge CW. MGluR5 activity is required for the induction of ethanol behavioral sensitization and associated changes in ERK

MAP kinase phosphorylation in the nucleus accumbens shell and lateral habenula. Behavioural Brain Research, 367:19-27; 2019

f. **Faccidomo S,** Cogan ES, Hon OJ, Hoffman JL, Saunders BL, Eastman VR, Kim M, Taylor S, McElligott ZA, Hodge CW. Calcium-Permeable AMPA Receptor Activity and GluA1 Trafficking in the Basolateral Amygdala Regulate Operant Alcohol Self-Administration, Addiction Biology (2021) Sept; 26(5). PMID: 33955100; PMCID: PMC8376775

g. Hoffman JL*, **Faccidomo S*,** Saunders BL, Taylor S, Kim M, Hodge CW. Inhibition of AMPA receptors containing TARP γ-8 with JNJ-55511118 shows preclinical efficacy for pharmacotherapeutic treatment of chronic repetitive alcohol self-administration, Alcohol Clin Exp Res (2021) July; 45(7):1424-1435. PMID: 34086361; PMCID: PMC8336716

2) Identification of novel protein targets of alcohol self-administration: exploration of the nucleus accumbens and amygdala proteome. Alcohol addiction is a prevalent and significant public health problem and the currently available medications prescribed to curb alcohol drinking and relapse are marginally effective and not widely prescribed. Proteomics can be used as an unbiased novel approach to identify key biological networks of proteins that are up- and down-regulated in reward-relation brain regions as a consequence of alcohol self-administration. Our lab has successfully used this strategy to understand the effects of chronic, voluntary alcohol drinking on the amygdala proteome and most recently, the nucleus accumbens proteome. In both of these experiments, we followed some of the most interesting protein changes that emerged (CAMKII for amygdala and GSTP-1 for nucleus accumbens) and found that we could selectively attenuate the reinforcing effects of alcohol via pharmacological modulation of these pathways. Moreover, we found that the upstream regulators of the networks of proteins that were altered are key proteins involved in neurodegeneration including Tau, APP & Presenilin and we havre recently published data showing that alcohol drinking exacerbates learning and memory deficits, and Tau pathology, in a mouse model of pathological aging. These studies show that proteomics is a useful preclinical method to identify novel and unexpected brain mechanisms that mediate the reinforcing effects of alcohol and that could lead to drug discovery.

a. Salling MC, **Faccidomo SP,** Li C, Psilos K, Galunas C, Spanos M, Agoglia AE, Kash TL, Hodge CW (2016) Moderate alcohol drinking and the amygdala proteome: Identification and validation of Calcium/Calmodulin dependent kinase II and AMPA receptor activity as novel molecular mechanisms of the positive reinforcing effects of alcohol. Biol Psychiatry, 79:430-42

b. **Faccidomo S,** Swaim KS, Saunders BL, Santanam TS, Taylor SM, Kim M, Reid GT, Eastman VR, Hodge CW (2018) Mining the nucleus accumbens proteome for novel targets of alcohol self-administration in male C57BL/6J mice. Psychopharmacology, 235:1681-1696

c. Hoffman JL*, **Faccidomo S*,** Kim M, Taylor SM, Agoglia AE, May AM, Smith EN, Wong LC, Hodge CW (2019) Alcohol drinking exacerbates neural and behavioral pathology in the 3xTg-AD mouse model of Alzheimer's Disease. Int Rev Neurobiol, 148:169-230

3) Maladaptive persistent consequences of maternal separation stress: influence on anxiety-like behavior and addiction. Both acute and chronic maternal separations are highly stressful to both the pups and the dam and, depending on the length and intensity of the separation, can lead to long-lasting maladaptive behavioral and neurochemical consequences in adulthood. I studied the anxiety-like behavior of mouse pups that are separated from their mother with the goal of identifying novel and selective therapeutics that would attenuate anxiety-like behavior under these conditions. Unlike classic animal models of anxiety, acute separation-induced ultrasonic vocalizations at this age occur independently from motor effects and thus, the efficacy of anxiolytic drugs can be evaluated based on their effect on vocalizations rather than on a locomotor-dependent measure of anxiety. Importantly, we found that many of the novel (at the time) SSRI's, GABAergic positive modulators and mixed glutamatergic antagonists were efficacious in reducing anxiety-like behavior in mouse pups. Secondly, we used chronic early maternal separation stress to investigate whether this type of early life stress predisposes individuals to show greater behavioral responses to drugs of abuse in adulthood. Indeed, we found that repeated maternal separation in the first 2 weeks of life led to an increase in behavioral sensitization to cocaine and was associated with dysregulated HPA-axis in adulthood. Together, these findings show that adequate maternal care during the first several weeks of life is essential for preventing the development of appropriate stress responses, drug-taking and possibly anxiety-like behavior in adulthood.

a. Fish EW, **Faccidomo S,** Gupta S, Miczek KA (2004) Anxiolytic effects of escitalopram, citalopram, and R-citalopram in maternally separated mouse pups. J Pharm Exp Ther, 308:474-480

b. Kikusui T, **Faccidomo S,** Miczek KA (2005) Repeated maternal separation: Differences in cocaine-induced behavioral sensitization in adult male and female mice. Psychopharmacology, 178:202-210
c. Takahaski A, Yap JJ, Bohager DZ, **Faccidomo S,** Clayton T, Cook JM, Miczek KA (2009) Glutamtergic and GABAergic modulations of ultrasonic vocalizations during maternal separation distress in mouse pups. Psychopharmacology, 204:135-147

4) Neurobiology of alcohol and aggression. My graduate work primarily focused on understanding the effects of alcohol on the social behavior of mice. Specifically, I studied the neurobiology underlying the individual differences between mice that were prone to exhibit excessive aggression after consumption or injection of a moderate dose of alcohol vs. those who remained placid. In particular, my contribution to this field centered on the discovery that activation of 5-HT1B receptors selectively attenuate alcohol-heightened aggression to a greater degree than their effect on species-typical levels of aggression. Moreover, modulation of these receptors within the DRN to PFC pathway specifically increases both heightened aggression and extracellular cortical levels of 5-HT. These finding support prior research indicating that genetic differences in 5-HT related genes may confer susceptibility to individuals, making them more likely to drink excessively and more likely to engage in violence when intoxicated.

a. Miczek KA, Maxson SC, Fish EW, **Faccidomo S** (2001) Aggressive behavioral phenotypes in mice. Behav Brain Res, 125(1-2):167-181
b. **Faccidomo S,** Bannai M, Miczek KA (2008) Escalated aggression after alcohol drinking in male mice: dorsal raphe and prefrontal cortex serotonin and 5-HT1B receptors. Neuropsychopharmacology, 33:2888-2999
c. **Faccidomo S,** Quadros IM, Takahashi A, Fish EW, Miczek KA (2012) Infralimbic and dorsal raphe microinjection of the 5-HT1B receptor agonist CP-93,129: attenuation of aggressive behavior in CFW male mice. Psychopharmacology, 222:117-2

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