BIOGRAPHICAL SKETCH

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NAME: Parnell, Scott E.

eRA COMMONS USER NAME (credential, e.g., agency login): scott_parnell

POSITION TITLE: Associate Professor

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Texas A&M University, College Station, TX	BA	08/1994	08/1998	Biology
Texas A&M University, College Station, TX	PHD	08/1999	11/2004	Medical Sciences/ Neuroscience
University of North Carolina, Chapel Hill, NC	Postdoctoral Fellow	11/2004	09/2009	Neurotoxicology/ Embryology

A. Personal Statement

Research in my laboratory is focused on understanding the pathology and related pathogenic mechanisms underlying prenatal alcohol exposure (PAE) and other teratogens during early gestation. PAE induces a wide spectrum of deficits depending on a multitude on factors, including timing and amount of exposure, genetics, etc. In order to better understand this spectrum of effects, part of my research has been aimed at understanding the pathogenic mechanisms involved in developmental toxicology exposure. Towards this goal, a large part of my lab's focus is on the cellular events following ethanol exposure that lead to the observed dysmorphologies. For example, we have been exploring novel hypotheses involving primary cilia as a mediator of ethanol's effects during gestation. Alongside this research using genetically engineered mice and whole transcriptome sequencing (RNA-seq), we also aim to better understand the genes that alter susceptibility to the detrimental effects of early PAE.

I have mentored numerous scientists-in-training throughout my career. As a faculty member at UNC, I have mentored or co-mentored five postdoctoral fellows who have gone on to medical and industry positions, as well as their own independent faculty positions. I have served/am currently serving on the dissertation committee of numerous graduate students. Additionally, I have mentored numerous UNC undergraduates in my lab, many of whom have gone on to graduate school. In order to facilitate better mentorship, I only accept a limited number of students at each level at one time. As a faculty member, I find that this approach provides the time to tailor individual training plans for each person. In addition, when appropriate I seek out co-mentors for certain trainees to increase their scientific and academic exposure. For example, my most recent post-doc's K99/R00 was co-sponsored by Dr. Leslie Morrow, also a member of the Bowles Center for Alcohol Studies, who has vastly more experience in both training post-docs, but also molecular biology techniques that complement my own research expertise.

Ongoing and recently completed projects that I would like to highlight include:

R01 HD100584, National Institute of Child Health and Human Development (NICHD)
Kovarova/Parnell (Multi-PIs)

09/13/19-07/31/24
In vivo evaluation of safety and pharmacology of the sustained release formulation of Dolutegravir in pre-conception and early stages of pregnancy in animal models
Role: PI

R01 AA026068, National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Parnell (PI)
12/15/18-11/30/23
Cellular Mechanisms in Fetal Alcohol Spectrum Disorders
Role: PI

R01 AA031346, National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Parnell/Eberhart/Tarantino (Multi-PIs)
09/15/2023-07/31/2028
Characterizing the Genetics of FASD in Complementary Mouse and Fish Models
Role: PI

Bibliography: https://www.ncbi.nlm.nih.gov/myncbi/scott.parnell.1/bibliography/public/

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

- 07/2023 – Present: Associate Professor, Dept. of Cell Biology and Physiology, Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC
- 04/2019 – 07/2023: Assistant Professor, Dept. of Cell Biology and Physiology, Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC
- 08/2009-04/2019: Research Assistant Professor, Dept. of Cell Biology and Physiology, Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC
- 11/2004 - 07/2009: Postdoctoral Research Fellow, Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC
  - 2005-2006: Postdoctoral Fellowship, Bowles Center for Alcohol Studies, University of North Carolina School of Medicine.
- 08/1999 - 11/2004: Graduate Research Assistant, Alcohol and Brain Research Laboratory, Dept. of Human Anatomy and Medical Neurobiology, Texas A&M University System Health Science Center, College Station, TX
- 08/1998 - 08/1999: Research Assistant, Alcohol and Brain Research Laboratory, Dept. of Human Anatomy and Medical Neurobiology, Texas A&M University, College Station, TX

Honors:

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- 2021 Editor's Choice for the June issue of *Disease Models & Mechanisms* for "Transcriptomic analyses of gastrulation-stage C57BL/6J and C57BL/6NHsd mouse embryos with differential susceptibility to alcohol" Boschen KE, Ptacek TS, Berginski ME, Simon JM, & **Parnell SE**.
- 2020 Editor's Choice: Addiction and Top 100 in Neuroscience publications for "Cannabinoids exacerbate alcohol teratogenesis by a CB1-Hedgehog interaction" by Fish EW, Murdaugh LB, Zhang C, Boschen KE, Boa-Amponsem O, Mendoza-Romero HN, Tarpley M, Chdid L, Mukhopadhyay S, Cole GJ, Williams KP, & **Parnell SE**. *Scientific Reports*, 2019.
- 2019 Best Component Award – First year medical students – Gross Anatomy Component
- 2018 Wilson Publication Award for the best paper published in the Teratology Society's journal *Birth Defects Research* in 2017 for "Genetic vulnerabilities to prenatal alcohol exposure: Limb defects in sonic hedgehog and Gli2 heterozygous mice" by Fish EW, Murdaugh LB, Sulik KK, Williams KP, & **Parnell SE**, Teratology Society

- 2016 Best Component Award – First year medical students – Gross Anatomy Component
- 2013 Best Course Award – First year medical students – Structure and Development
- 2007 Junior Investigator Award, International Conference on Applications of Neuroimaging to Alcoholism (ICANA).

C. Contributions to Science

1. Pathogenic mechanisms and genetics of prenatal ethanol exposure

   Using our mouse model of FASD, we are starting to uncover some of the mechanisms underlying ethanol's teratogenesis, as well as numerous genetic factors involved in prenatal ethanol exposure. We have used two closely related strains of mice with differing sensitivities to ethanol identify numerous candidate genes that modify susceptibility to prenatal ethanol exposure. Furthermore, we have used other knockout mice to demonstrate that modifying key genes involved in primary cilia function and stability (Kif3a and Mns1) increase susceptibility to prenatal ethanol exposure. Conversely, we can knockout key genes involved in apoptosis (Bax) and completely block the effects of early gestational ethanol exposure. Together, these data and ongoing research are informing our knowledge of the underlying mechanisms and genetic factors involved in FAS.

   a. Fish EW, Mendoza-Romero HN, Love CA, Dragicevich CJ, Cannizzo MD, Boschen KE, Hepperla A, Simon JM, **Parnell SE**. 2022. The pro-apoptotic Bax gene modifies susceptibility to craniofacial dysmorphology following gastrulation-stage alcohol exposure. Birth Defects Res. 114:1229-1243.
   b. Boschen KE, Ptacek TS, Berginski ME, Simon JM, **Parnell SE**. 2021. Transcriptomic analyses of gastrulation-stage C57BL/6J and C57BL/6NHsd mouse embryos with differential susceptibility to alcohol. Dis Model Mech. 14(6):dmm049012.
   c. Fish EW, Tucker SK, Peterson, RL, Eberhart JK, **Parnell SE**. 2021. Loss of Tumor Protein 53 protects against alcohol-mediated facial malformations in mice and zebrafish. Alcohol Clin Exp Res. 45:1965-1979.
   d. Boschen KE, Gong H, Murdaugh LB, **Parnell SE**. Knockdown of Mns1 Increases Susceptibility to Craniofacial Defects Following Gastrulation-Stage Alcohol Exposure in Mice. Alcohol Clin Exp Res. 2018 42(11):2136-2143. PMID: 30129265.

2. Teratogenicity of cannabinoids, including THC and CBD.

   Marijuana and natural cannabinoids have long been suspected of altering brain development, but the results have been either subtle or mixed, depending on the variable being examined. However, through selective breeding, THC concentrations in marijuana is increasing leading to increased potencies and toxicity in adults. Perhaps more alarming, over the course of the last several years, synthetic cannabinoids are increasingly being abused. These synthetic cannabinoids have efficacies for the cannabinoid receptors as much as 50 times that of THC, leading to a greater degree of toxicity and emergency room visits by people abusing these drugs. To see if this same toxicity might extend to the developing embryo, we tested the teratogenicity of a prototypical synthetic cannabinoid, CP-55,940, in a mouse model at the beginning of neurulation, a very sensitive period in development. In this study, we discovered that synthetic cannabinoids are extremely teratogenic, inducing birth defects of the brain and craniofacies (eyes, lips, palate, etc) at dosages as low as 0.0625 mg/kg, a dose well within the range of human exposure. More recently, we have shown that THC and other cannabinoids such as CBD are also quite teratogenic in the developing embryo, and perhaps more importantly, these actions are synergistic when combined with even low doses of ethanol. Together, these data clearly indicate a need for further developmental evaluation of these synthetic cannabinoids and an increased awareness of their potential impact on public health.

   a. Fish EW, Murdaugh LB, Zhang C, Boschen KE, Boa-Amponsem O, Mendoza-Romero HN, Tarpley M, Chdid L, Mukhopadhyay S, Cole GJ, Williams KP, **Parnell SE**. Cannabinoids Exacerbate Alcohol Teratogenesis by a CB1-Hedgehog Interaction. Sci Rep, 9:16057, 2019. PMID: 31690747
   b. Gilbert MT, Sulik KK, Fish EW, Baker LK, Dehart DB**, Parnell SE**. Dose-dependent teratogenicity of the synthetic cannabinoid CP-55,940 in mice. Neurotoxicol Teratol. 2016 58:15-22. PMID: 26708672.

c. Fish, E.W., Boschen, K.K., Murdaugh, L.B., Mendoza-Romero, H.N., Williams, K.P., **Parnell, S.E**. (2017). Alcohol exacerbates the teratogenic effects of prenatal cannabinoid exposure in a C57BL/6J mouse model. Alc Clin Exp Res S1:105

3. Adaptation of high-resolution MRI to an FASD animal model of stage-dependent defects.

PAE induces a wide spectrum of deficits depending on several factors that have been shown to modify ethanol's teratogenesis, the most important of which is probably timing of exposure, particularly during early gestation (gastrulation – neurulation stages) when the brain is undergoing key formative processes. This is reflected in the fact that gastrulation stage PAE (gestational day [GD] 7 in the mouse) results in the classic craniofacial features associated with FAS and brain defects in the holoprosencephaly (HPE) spectrum, however, exposure just one day later (GD 8) at the start of neurulation induces more subtle defects. In order to better understand the stage-specific effects of early gestational PAE, we began a series of experiments in which we exposed pregnant mice at varying stages of their pregnancy and then examined the offspring to determine the resultant brain malformations. For this, we pioneered the use of high-resolution magnetic resonance imaging (MRI – sometimes referred to as magnetic resonance microscopy) which uses high field strength magnets (7-9.4 T) to obtain images at resolutions of 10-50 □m. This allows for a detailed examination of the specific pattern of regional brain changes resulting from varying patterns of acute ethanol exposure. In contrast to the HPE brain and facial phenotypes observed following a GD 7 (gastrulation) exposure that resulted from a general lack of midline tissue, PAE during neurulation resulted in only eye defects in the face, along with more subtle, yet consistent defects in the brain (Parnell et al., 2009, 2013; O'Leary-Moore et al., 2010). The more significant effects include dysgenesis of the cerebellum and a consistent rostroventral midline expansion, an opposite effect relative to exposure during gastrulation. Although there were small variations in regional brain effects across the days of exposure during neurulation (GD 8, 9, 10), the effects on the rostroventral midline expansion were consistent in all of these exposure periods, suggesting a neurulation-stage specific dysmorphology. Furthermore, this midline expansion has also been replicated in our diet exposure model in which a moderate level of ethanol exposure throughout the period of neurulation resulted in similar effects. This is significant as it demonstrated a pathogenic origin of PAE-induced hypertelorism observed in some children with FASD and provides clues to a basic cellular mechanism underlying this pathology.

a. Fish EW, Holloway HT, Rumple A, Baker LK, Wieczorek LA, Moy SS, Paniagua B, **Parnell SE**. Acute alcohol exposure during neurulation: Behavioral and brain structural consequences in adolescent C57BL/6J mice. Behav Brain Res. 2016 Sep 15;311:70-80. PubMed PMID: 27185739.
b. **Parnell SE**, Holloway HE, Baker LK, Styner MA, Sulik KK. Dysmorphogenic effects of first trimester-equivalent ethanol exposure in mice: a magnetic resonance microscopy-based study. Alcohol Clin Exp Res. 2014 Jul;38(7):2008-14. PubMed PMID: 24931007.
c. **Parnell SE**, Holloway HT, O'Leary-Moore SK, Dehart DB, Paniaqua B, Oguz I, Budin F, Styner MA, Johnson GA, Sulik KK. Magnetic resonance microscopy-based analyses of the neuroanatomical effects of gestational day 9 ethanol exposure in mice. Neurotoxicol Teratol. 2013 Sep-Oct;39:77-83. PubMed PMID: 23911654.
d. **Parnell SE**, O'Leary-Moore SK, Godin EA, Dehart DB, Johnson BW, Allan Johnson G, Styner MA, Sulik KK. Magnetic resonance microscopy defines ethanol-induced brain abnormalities in prenatal mice: effects of acute insult on gestational day 8. Alcohol Clin Exp Res. 2009 Jun;33(6):1001-11. PubMed PMID: 19302087.

4. Prevention of ethanol-induced brain defects.

Prenatal alcohol exposure is one of the leading causes of birth defects, and research is continually finding new ways in which alcohol can harm the developing brain. In spite of these facts and ongoing, robust prevention campaigns, the incidence of FASD has not changed. In order to test potential therapeutic strategies, we tested the ability of two compounds to ameliorate the effects of early PAE. For this series of experiments, we used a FASD mouse model that we developed involving dietary ethanol exposure that demonstrated consistent ethanol-induced ocular defects as a measure of ethanol's teratogenesis as eye and forebrain development is intimately linked in early development. (Parnell et al., 2006). First we tested the efficacy of SAL (SALLRSIPA), a nine amino acid fragment of activity-dependent neurotrophic factor

(ADNF). When administered in the ethanol-containing liquid diet during early gestation (gastrulation and neurulation), SAL reduced the incidence of eye defects to a level approximately two-thirds that of ethanol alone; a level not much higher than the spontaneous incidence of eye defects in this mouse strain (Parnell et al., 2007). The second compound we tested was n-acetylcysteine (NAC), a drug used to increase glutathione level. Using the same mouse model and exposure paradigm in the previous SAL study, we demonstrated that NAC could also ameliorate the effects, although to a lesser extent compared to SAL (Parnell et al., 2010). However, these data do begin to suggest cellular mechanisms such as altered reactive oxygen species (ROS) homeostasis that may underlie ethanol's pathogenesis.

a. **Parnell SE**, Dehart DB, Wills TA, Chen SY, Hodge CW, Besheer J, Waage-Baudet HG, Charness ME, Sulik KK. Maternal oral intake mouse model for fetal alcohol spectrum disorders: ocular defects as a measure of effect. Alcohol Clin Exp Res. 2006 Oct;30(10):1791-8. PubMed PMID: 17010146.
b. **Parnell SE**, Chen SY, Charness ME, Hodge CW, Dehart DB, Sulik KK. Concurrent dietary administration of D-SAL and ethanol diminishes ethanol's teratogenesis. Alcohol Clin Exp Res. 2007 Dec;31(12):2059-64. PubMed PMID: 17949468.
c. **Parnell SE**, Sulik KK, Dehart DB, Chen SY. Reduction of ethanol-induced ocular abnormalities in mice through dietary administration of N-acetylcysteine. Alcohol. 2010 44(7-8):699-705. PMID: 21112471.

5. Nicotine lowers blood alcohol concentrations (BAC).

Ethanol (alcohol) and nicotine are the two most commonly co-abused drugs, so it is natural to study their teratogenicity together. In one of these initial studies in a rat model of third trimester ethanol exposure, we discovered that when ethanol and nicotine were administered together, the peak BAC was lower in these pups compared to pups administered ethanol alone (Chen et al., 1998). In a follow-up study in neonatal rat pups, we confirmed this finding that nicotine lowers BACs and demonstrated that it does so in a dose-dependent manner (Chen et al., 2001). Although these findings were exciting, it was unknown if this phenomenon was isolated to neonatal ages and the mechanism by which nicotine lowered BACs was unclear. To answer these questions, we then co-administered nicotine and ethanol in adult rats who demonstrated a similar response to the neonates (Parnell et al., 2006). It was previously known that nicotine was able to slow gastric emptying, so we hypothesized that nicotine lowered BACs by prolonging the time that ethanol remained in the stomach undergoing metabolism via gastric alcohol dehydrogenase (gADH) prior to being absorbed via the small intestine. To test this hypothesis, we conducted an experiment in which we demonstrated that nicotine could only lower peak BACs when ethanol was administered intragastrically as opposed to it being given through an intraperitoneal injection, thus bypassing the stomach. These novel findings were the first to show that nicotine could lower BACs.

a. Chen WJ, **Parnell SE**, West JR. Neonatal alcohol and nicotine exposure limits brain growth and depletes cerebellar Purkinje cells. Alcohol. 1998 Jan;15(1):33-41. PubMed PMID: 9426835.
b. Chen WJ, **Parnell SE**, West JR. Nicotine decreases blood alcohol concentration in neonatal rats. Alcohol Clin Exp Res. 2001 Jul;25(7):1072-7. PubMed PMID: 11505035.
c. **Parnell SE**, West JR, Chen WJ. Nicotine decreases blood alcohol concentrations in adult rats: a phenomenon potentially related to gastric function. Alcohol Clin Exp Res. 2006 Aug;30(8):1408-13. PubMed PMID: 16899044.