

FSU Biomed

Florida State University College of Medicine

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Student News

The Fall 2022 semester saw five students from BMS successfully defend their dissertations!

Maicon Landim Vieira (Pinto Lab) – *Elucidating new mechanisms of cardiac muscle regulation and myofilament dysfunction.*

Delaney Sherwin (Yanchang Wang Lab) – *The balance of protein kinases and phosphatases at the kinetochore in accurate chromosome segregation.*

Jennifer Warnock (Tomko Lab) – *Regulation of proteasome function and quality control by short, flexible motifs in the ATPase motor.*

Xiaoyan Yu (Yuan Wang Lab) – *FMRP mechanism of circuit development and dynamics in the auditory brainstem.*

Sara Jones (Bhide Lab) – *Transgenerational transmission of changes in behavior and gene expression following aspartame consumption.*

Additionally, **Daniel Zuniga** with the **Bhide Lab** successfully defended his Honors in the Major Thesis entitled “Nicotine and the developing brain”.

Congratulations to all!!!



Upcoming Events

January 9

Spring Semester Begins

January 11

Seminar Series: **Michelle Rodriguez Garcia**

January 16

MLK Holiday: University Closed

January 18

Seminar Series: **Kwangjun Lee**

January 25

Seminar Series: Melissa Ehringer

February 1

Seminar Series: **Isabella Coscarella**

February 3

CoM Research Fair

February 8

Seminar Series: Sakhitivel Sadayappan

Community News

In October, **BMS** had the opportunity to represent **Florida State University** and the College of Medicine through participation in the 11th Annual Tallahassee Science Festival!!!



Faculty News

In October, **Dr. Sanjay Kumar** was featured in an interview with Dr. Andrew Wilner on *ReachMD*. The interview titled "Advances in Temporal Lobe Epilepsy Research", discusses recent research conducted by the Kumar Lab. Link to the interview: <https://reachmd.com/programs/neurofrontiers/advances-in-temporal-lobe-epilepsy-research/13956/>

Fall Awards Ceremony

In November, the **Biomedical Sciences Department** was the recipient of numerous awards at the Annual College of Medicine Awards Ceremony!

Outstanding Senior Faculty Educator – **Dr. Gregg Stanwood**

Outstanding Junior Faculty Educator – **Dr. Raed Rizkallah**

Outstanding Senior Faculty Researcher – **Dr. Gregg Stanwood**

Outstanding Junior Faculty Researcher – **Dr. Stephen Chelko**

Exemplary Staff Team or Group – **Biomedical Sciences Staff**

Publications

Recent PhD Graduate, **Sara Jones**, with the **Bhide Lab** published a paper in the *Proceedings of the National Academy of Sciences*, entitled "Transgenerational transmission of aspartame induced anxiety, and changes in glutamate-GABA signaling and gene expression in the amygdala". Additional authors include **Deirdre M. McCarthy**, **Cynthia Vied**, **Gregg D. Stanwood**, **Chris Schatschneider** and **Pradeep G. Bhide**. Link and abstract are below.

Link: www.pnas.org/doi/10.1073/pnas.2213120119

Abstract: We report the effects of aspartame on anxiety-like behavior, neurotransmitter signaling and gene expression in the amygdala, a brain region associated with the regulation of anxiety and fear responses. C57BL/6 mice consumed drinking water containing 0.015% or 0.03% aspartame, a dose equivalent of 8-15%

of the FDA recommended maximum human daily intake, or plain drinking water. Robust anxiety-like behavior (evaluated using open field test and elevated zero maze) was observed in male and female mice consuming the aspartame-containing water. Diazepam, an allosteric modulator of the GABA-A receptor, alleviated the anxiety. RNA sequencing of the amygdala followed by KEGG biological pathway analysis of differentially expressed genes showed glutamatergic and GABAergic synapse pathways as significantly enriched. Quantitative PCR showed upregulation of mRNA for the glutamate NMDA receptor subunit 2D (*Grin2d*) and metabotropic receptor 4 (*Grm4*), and downregulation of the GABA-A receptor associated protein (*Gabarap*) mRNA. Thus, taken together, our diazepam and gene expression data show that aspartame consumption shifted the excitation-inhibition equilibrium in the amygdala toward excitation. Even more strikingly, the anxiety-like behavior, its response to diazepam, and changes in amygdala gene expression were transmitted to male and female offspring in two generations descending from the aspartame-exposed males. Extrapolation of the findings to humans suggests that aspartame consumption at doses below the FDA recommended maximum daily intake may produce neurobehavioral changes in aspartame-consuming individuals and their descendants. Thus, human population at risk of aspartame's potential mental health effects may be larger than current expectations, which only include aspartame consuming individuals.

The **Yuan Wang Lab** recently published 4 manuscripts!!! Title, link, and abstract for each are below.

1. Curnow E, Wang Y. 2022. New Animal Models for Understanding FMRP Functions and FXS Pathology. *Cells*. 2022 May 12;11(10):1628. doi: 10.3390/cells11101628. PMID: 35626665; PMCID: PMC9140010.

<https://pubmed-ncbi-nlm-nih-gov.proxy.lib.fsu.edu/35626665/>

Abstract: Fragile X encompasses a range of genetic conditions, all of which result as a function of changes within the FMR1 gene and abnormal production and/or expression of the FMR1 gene products. Individuals with Fragile X syndrome (FXS), the most common heritable form of intellectual disability, have a full-mutation sequence (>200 CGG repeats) which brings about transcriptional silencing of FMR1 and loss of FMR protein (FMRP). Despite considerable progress in our understanding of FXS, safe, effective, and reliable treatments that either prevent or reduce the severity of the FXS phenotype have not been approved. While current FXS animal models contribute their own unique understanding to the molecular, cellular, physiological, and behavioral deficits associated with FXS, no single animal model is able to fully recreate the FXS phenotype. This review will describe the status and rationale in the development, validation, and utility of three emerging animal model systems for FXS, namely the nonhuman primate (NHP), Mongolian gerbil, and chicken. These developing animal models will provide a sophisticated resource in which the deficits in complex functions of perception, action, and cognition in the human disorder are accurately reflected and aid in the successful translation of novel therapeutics and interventions to the clinic setting.

2. Fan Q, Zhang X, Wang Y, Wang X. 2022. Dissecting Cell-Autonomous Function of Fragile X Mental Retardation Protein in an Auditory Circuit by In Ovo Electroporation. *JoVE (Journal of Visualized Experiments)*: 2022 Jul 6;(185). doi: 10.3791/64187. PMID: 35876562.

<https://pubmed-ncbi-nlm-nih-gov.proxy.lib.fsu.edu/35876562/>

Abstract: Fragile X mental retardation protein (FMRP) is an mRNA-binding protein that regulates local protein translation. FMRP loss or dysfunction leads to aberrant neuronal and synaptic activities in fragile X syndrome (FXS), which is characterized by intellectual disability, sensory abnormalities, and social communication problems. Studies of FMRP function and FXS pathogenesis have primarily been conducted with *Fmr1* (the gene encoding FMRP) knockout in transgenic animals. Here we report an in vivo method for determining the cell-autonomous function of FMRP during the period of circuit assembly and synaptic formation using chicken embryos. This method employs stage-, site-, and direction-specific electroporation of a drug-inducible vector

system containing Fmr1 small hairpin RNA (shRNA) and an EGFP reporter. With this method, we achieved selective FMRP knockdown in the auditory ganglion (AG) and in one of its brainstem targets, the nucleus magnocellularis (NM), thus providing a component-specific manipulation within the AG-NM circuit. Additionally, the mosaic pattern of the transfection allows within-animal controls and neighboring neuron/fiber comparisons for enhanced reliability and sensitivity in data analyzing. The inducible vector system provides temporal control of gene editing onset to minimize accumulating developmental effects. The combination of these strategies provides an innovative tool to dissect the cell-autonomous function of FMRP in synaptic and circuit development.

3. Wang X, Fan Q, Yu X, Wang Y. 2023. Cellular distribution of the Fragile X mental retardation protein in the inner ear: a developmental and comparative study in the mouse, rat, gerbil, and chicken. *J Comp Neurol*. 2023 Jan;531(1):149-169. doi: 10.1002/cne.25420. Epub 2022 Oct 12. PMID: 36222577; PMCID: PMC9691623.

<https://pubmed-ncbi-nlm-nih-gov.proxy.lib.fsu.edu/36222577/>

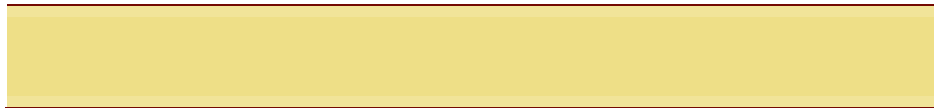
Abstract: The Fragile X mental retardation protein (FMRP) is an mRNA binding protein that is essential for neural circuit assembly and synaptic plasticity. Loss of functional FMRP leads to Fragile X syndrome (FXS), a neurodevelopmental disorder characterized by sensory dysfunction including abnormal auditory processing. While the central mechanisms of FMRP regulation have been studied in the brain, whether FMRP is expressed in the auditory periphery and how it develops and functions remains unknown. In this study, we characterized the spatiotemporal distribution pattern of FMRP immunoreactivity in the inner ear of mice, rats, gerbils, and chickens. Across species, FMRP was expressed in hair cells and supporting cells, with a particularly high level in immature hair cells during the prehearing period. Interestingly, the distribution of cytoplasmic FMRP displayed an age-dependent translocation in hair cells, and this feature was conserved across species. In the auditory ganglion (AG), FMRP immunoreactivity was detected in neuronal cell bodies as well as their peripheral and central processes. Distinct from hair cells, FMRP intensity in AG neurons was high both during development and after maturation. Additionally, FMRP was evident in mature glial cells surrounding AG neurons. Together, these observations demonstrate distinct developmental trajectories across cell types in the auditory periphery. Given the importance of peripheral inputs to the maturation of auditory circuits, these findings implicate involvement of FMRP in inner ear development as well as a potential contribution of periphery FMRP to the generation of auditory dysfunction in FXS.

4. Yu X, Wang Y. 2022. Tonotopic differentiation of presynaptic neurotransmitter-releasing machinery in the auditory brainstem during the prehearing period and its selective deficits in Fmr1 knockout mice. *J Comp Neurol*. 2022 Dec;530(18):3248-3269. doi: 10.1002/cne.25406. Epub 2022 Sep 6.

<https://pubmed-ncbi-nlm-nih-gov.proxy.lib.fsu.edu/36067267/>

Abstract: Tonotopic organization is a fundamental feature of the auditory system. In the developing auditory brainstem, the ontogeny and maturation of neurotransmission progress from high to low frequencies along the tonotopic axis. To explore the underlying mechanism of this tonotopic development, we aim to determine whether the presynaptic machinery responsible for neurotransmitter release is tonotopically differentiated during development. In the current study, we examined vesicular neurotransmitter transporters and calcium sensors, two central players responsible for loading neurotransmitter into synaptic vesicles and for triggering neurotransmitter release in a calcium-dependent manner, respectively. Using immunocytochemistry, we characterized the distribution patterns of vesicular glutamate transporters (VGLUTs) 1 and 2, vesicular gamma-aminobutyric acid transporter (VGAT), and calcium sensor synaptotagmin (Syt) 1 and 2 in the developing mouse medial nucleus of the trapezoid body (MNTB). We identified tonotopic gradients of VGLUT1, VGAT, Syt1, and Syt2 in the first postnatal week, with higher protein densities in the more medial (highfrequency) portion of the MNTB. These gradients gradually flattened before

the onset of hearing. In contrast, VGLUT2 was distributed relatively uniformly along the tonotopic axis during this prehearing period. In mice lacking Fragile X mental retardation protein, an mRNA-binding protein that regulates synaptic development and plasticity, progress to achieve the mature-like organization was altered for VGLUT1, Syt1, and Syt2, but not for VGAT. Together, our results identified novel organization patterns of selective presynaptic proteins in immature auditory synapses, providing a potential mechanism that may contribute to tonotopic differentiation of neurotransmission during normal and abnormal development.



Save the Date

Wednesday, Feb. 15th

Seminar Series: Patrick O'Brien

Wednesday, Feb. 22nd

Seminar Series: **Nina Zamani and
Nastaran Aziz**

Wednesday, Mar. 1st

Seminar Series: Louis Muglia

Wednesday, Mar. 8th

Seminar Series: Bernhard Luscher

Do you have news you wish to share in the Biomed Newsletter? Contact Ryan Teston at:
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