FSU Biomed

Florida State University College of Medicine

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A final note…

This will be my final newsletter compiled and distributed on behalf of the Biomedical Sciences Department. As of February 3rd, 2023, I will no longer be with Florida State University, as I leave for new opportunities and a fresh start. During my time with the department, I have enjoyed working with the numerous students, staff, and faculty that have come through this program and the College of Medicine.

I was offered this position with no prior experience in the field, and leave with four years of it, having navigated unexpected pandemics, personal and professional challenges, and even an enjoyable emergency appendectomy! This place afforded me the opportunity to pursue numerous academic endeavors, while assisting FSU towards achieving its institutional goals, and continuing my musical endeavors with a nearby professional sports team (Go Jags!!!). And I am forever grateful for the great people I have had the opportunity to know.

Go 'Noles!!

Ryan Teston

Upcoming Events

February 3

CoM Research Fair

February 15

Seminar Series: Patrick O'Brien

February 22

Seminar Series: Nina Zamani & Nastaran Aziz

Publications

Two recent publications from the **Blaber Lab** (invited book chapters):

1. Blaber, Michael (2023) Protein Symmetry, Function and Stability. In: Bradshaw Ralph A., Hart Gerald W. and Stahl Philip D. (eds.) Encyclopedia of Cell Biology, Second Edition, vol. 1, pp. 123-131. Oxford: Elsevier.

2. Longo, L. M., & Blaber, M. (2023). Folding, Misfolding, Disordered Proteins, and Related Diseases. In: Bradshaw Ralph A., Hart Gerald W. and Stahl Philip D. (eds.) Encyclopedia of Cell Biology, Second Edition, vol. 1, Oxford: Elsevier.

Additionally, **Dr. Blaber** has had an invited editorial "Symmetry in Protein Architecture: Evolution, Design, Structure-function Relationship and Applications" accepted for publication in Frontiers in Molecular Biosciences, section Structural Biology.

Lastly, a new US Patent is accredited to the **Blaber lab**. US Patent 11,479,590 "Synthetic foldable proteins generated from peptide segments of folding nuclei of reference proteins", inventors Michael Blaber and Liam Longo.

Maicon Landim-Vieira, Dr. Jose Pinto, and Dr. Stephen Chelko recently published the manuscript entitled "**Efficacy and Safety of Angiotensin Receptor Blockers in a Pre-Clinical Model of Arrhythmogenic Cardiomyopathy"** in **IJMS**. This was a collaborative project with Dr. Nuria Amat-Alarcon from School of Medicine, Johns Hopkins University and Dr. Daniel P. Judge from the Medical University of South Carolina.

Link: https://pubmed.ncbi.nlm.nih.gov/36430389

Abstract: Arrhythmogenic Cardiomyopathy (ACM) is a familial heart disease, characterized by contractile dysfunction, ventricular arrhythmias (VAs), and the risk of sudden cardiac death. Currently, implantable cardioverter defibrillators and antiarrhythmics are the mainstays in ACM therapeutics. Angiotensin receptor blockers (ARBs) have been highlighted in the treatment of heart diseases, including ACM. Yet, recent research has additionally implicated ARBs in the genesis of VAs and myocardial lipolysis via the peroxisome proliferator-activated receptor gamma (PPAR) pathway. The latter is of particular interest, as fibrofatty infiltration is a pathological hallmark in ACM. Here, we tested two ARBs, Valsartan and Telmisartan, and the PPAR agonist, Rosiglitazone, in an animal model of ACM, homozygous Desmoglein-2 mutant mice (Dsg2mut/mut). Cardiac function, premature ventricular contractions (PVCs), fibrofatty scars, PPAR/ protein levels, and PPAR-mediated mRNA transcripts were assessed. Of note, not a single mouse treated with Rosiglitazone made it to the study endpoint (i.e., 100% mortality: n = 5/5). Telmisartan-treated Dsg2mut/mut mice displayed the preservation of contractile function (percent ejection fraction [%EF]; 74.8 6.8%EF) compared to Vehicle- (42.5 5.6%EF) and Valsartan-treated (63.1 4.4%EF) mice. However, Telmisartan-treated Dsg2mut/mut mice showed increased cardiac wall motion abnormalities, augmented %PVCs, electrocardiographic repolarization/depolarization abnormalities, larger fibrotic lesions, and increased expression of PPARγ-regulated gene transcripts compared to their Dsg2mut/mut counterparts. Alternatively, Valsartan-treated Dsg2mut/mut mice harbored fewer myocardial scars, reduced %PVC, and increased Wnt-mediated transcripts. Considering our findings, caution should be taken by physicians when prescribing medications that may increase PPARγ signaling in patients with ACM.

The Tomko lab recently published a paper entitled "Assembly chaperone Nas6 selectively destabilizes 26S proteasomes with defective regulatory particle-core particle interfaces" in the Journal of Biological Chemistry. Authors were former graduate student and current Emory postdoc Jenny Warnock, undergraduate Gabriel Jobin, current Harvard student Sandhya Kumar (Sanjay's daughter!), and myself. The article, which is published online ahead of print, was also selected to be featured as the Editor's pick for the issue!!

Link: https://pubmed.ncbi.nlm.nih.gov/36634850/

Abstract: The 26S proteasome is a 66-subunit chambered protease present in all eukaryotes that maintains organismal health by degrading unneeded or defective proteins. Defects in proteasome function or assembly are known to contribute to the development of various cancers, neurodegeneration, and diabetes. During proteasome biogenesis, a family of evolutionarily conserved chaperones assemble a hexameric ring of AAA+ family ATPase subunits contained within the proteasomal regulatory particle (RP) and guide their docking onto the surface of the proteolytic core particle (CP). This RP-CP interaction couples the substrate capture and unfolding process to proteolysis. We previously reported a mutation in the proteasome that promoted dissociation of the RP and CP by one of these chaperones, Nas6. However, the nature of the signal for Nas6-dependent proteasome disassembly, and the generality of this post-assembly proteasome quality control function for Nas6 remains unknown. Here, we use structure-guided mutagenesis and in vitro proteasome disassembly assays to demonstrate that Nas6 more broadly destabilizes 26S proteasomes with a defective RP-CP interface. We show that Nas6 can promote dissociation of mature proteasomes into RP and CP in cells harboring defects on either side of the RP-CP interface. This function is unique to Nas6 and independent from other known RP assembly chaperones. Further biochemical experiments suggest that Nas6 may exploit a weakened RP-CP interface to dissociate the RP from the CP. We propose that this post-assembly role of Nas6 may fulfill a quality control function in cells by promoting the recycling of functional subcomplexes contained within defective proteasomes.

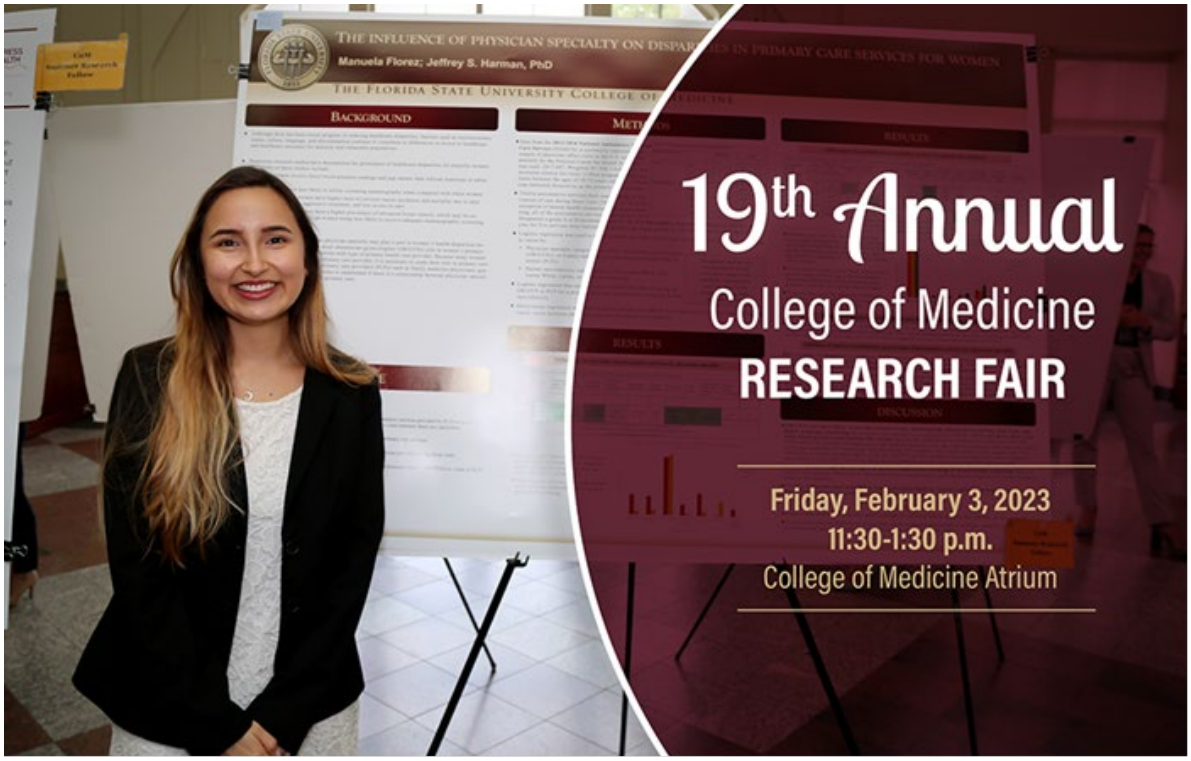
The **Irianto Lab** published a paper entitled "Genomic heterogeneity in pancreatic cancer organoids and its stability with culture" in npj Genomic Medicine. Authoris include Olalekan H. Usman, Liting Zhang, Gengqiang Xie, Hemant M. Kocher, Chang-il Hwang, Yue Julia Wang, Xian Fan Mallory, and Jerome Irianto.

Link: https://www.nature.com/articles/s41525-022-00342-9

Abstract: The establishment of patient-derived pancreatic cancer organoid culture in recent years creates an exciting opportunity for researchers to perform a wide range of in vitro studies on a model that closely recapitulates the tumor. One of the outstanding question in pancreatic cancer biology is the causes and consequences of genomic heterogeneity observed in the disease. However, to use pancreatic cancer organoids as a model to study genomic variations, we need to first understand the degree of genomic heterogeneity and its stability within organoids. Here, we used single-cell whole-genome sequencing to investigate the genomic heterogeneity of two independent pancreatic cancer organoid lines, as well as their genomic stability with extended culture. Clonal populations with similar copy number profiles were observed within the organoids, and the proportion of these clones was shifted with extended culture, suggesting the growth advantage of some clones. However, sub-clonal genomic heterogeneity was also observed within each clonal population, indicating the genomic instability of the pancreatic cancer cells themselves. Furthermore, our transcriptomic analysis also revealed a positive correlation between copy number alterations and gene expression regulation, suggesting the "gene dosage" effect of these copy number alterations that translates to gene expression regulation.

Funding News

Drs. Jerome Irianto and **Branko Stefanovic** were recently awarded the Live Like Bella Pediatric Cancer Research Initiative from Florida Health. The labs will receive $124,025 for the project entitled "Evaluation of LARP6 inhibitor for the treatment of pediatric glioblastoma". This project will verify the impact of LARP6 inhibition on the growth and invasion potential of pediatric glioblastoma organoids and elucidate the mechanism behind it.



Save the Date

Wednesday, Mar. 1st	Seminar Series: Louis Muglia
Wednesday, Mar. 8th	Seminar Series: Bernhard Luscher
Wednesday, March 15th	Seminar Series: **Alana Chang** & **Tomiwa Lawal**
Wednesday, March 22nd	Seminar Series: Paul Janssen