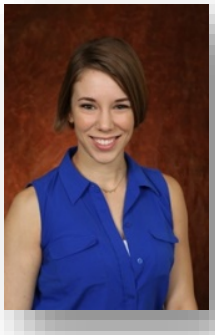
FSU Biomed

Florida State University College of Medicine

www.med.fsu.edu/BioSci

Student News

Congratulations to **Jamie Johnston** of the **Pinto lab**! Jamie successfully defended his dissertation this past month entitled "*Biophysical Defects Link Rare TNNC1 Variants to Cardiomyopathy*".



Congratulations to **Kristin Schoepfer** of the **Kabbaj lab**! Kristin successfully defended dissertation entitled "*Sex Differences and Effects of Estrous Stage on Hippocampal-prefrontal Theta Communications*" this past month as well.

Upcoming Events

July 8

Seminar Series: **Choogon Lee**

July 15

Seminar Series: **Gregg Stanwood**

July 22

Seminar Series: **Tim Megraw**

July 29

Seminar Series: **Sanjay Kumar**

July 31

End of Summer Semester

Student News Continued…

In May, BMS graduate student **Dingani Nkosi** of the **Meckes Lab** successfully defended his dissertation and will start residency training in Pathology at the University of Rochester this month.

The 22nd Annual Bryan Robinson Awards

The annual Bryan W. Robinson Awards took place on June 3rd via Zoom. This is a local endowment that has funded over 300 PhD candidates or physicians in training, with over $1 million in awards. The event celebrated the applicants for the 2020 Endowment, and additionally gave the 2019 Research Award recipients the opportunity to present their research. There was a total of 12 applicants, 3 of which were awarded grants of $3000, and additionally 3 honorable mentions awarded $1000 each. Of the 12 applicants, 10 were FSU students, including 7 from the Biomedical Sciences Department: **Maryam Ayazi, Sara Jones, Gloria Lee, Ernest Phillips, Connie Tenorio, Xiaoyan Yu, and Jiajing Zhang**.

Sara Jones of the **Bhide Lab** was one of three to be awarded a $3000 grant, and all three Honorable Mention grants of $1000 were awarded to FSU Biomed: **Maryam Ayazi** (**Ren Lab**), **Ernest Phillips** (**Gunjan Lab**), and **Connie Tenorio** (**Blaber Lab**).

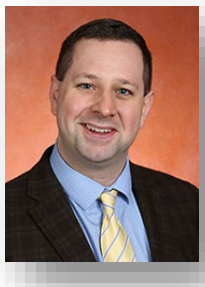
Bryan Robinson Awards Cont….

FSU Biomed Applicants and Research:

1. **Maryam Ayazi**, Myelin debris clearance by vascular pericytes contributes to neuroinflammation in spinal cord injury, FSU, **Yi Ren**, PhD
2. **Sara Jones**, Aspartame, anxiety and working memory deficit: Like father like son? FSU, **Pradeep Bhide**, PhD
3. **Gloria Lee**, The role of 14-3-3 proteins on NMDAR synaptic trafficking and schizophrenia-associated behavior, FSU, **Yi Zhou**, PhD
4. **Ernest Owen Nicandro Phillips**, The role of historic variant H3.3 in DNA repair and cancer, FSU, **Akash Gunjan**, PhD
5. **Connie A. Tenorio**, Perturbation of a folding nucleus in an all beta-protein can clue insights on evolution of protein folding pathways, FSU, **Michael Blaber**, PhD
6. **Xiaoyan Yu**, Deafferentation-induced FMRP responses and the association with stress granules, FSU, **Yuan Wang**, PhD
7. **Jiajing Zhang**, Investigating the role of hippocampus in psychomotor behaviors and its underlying neural circuits using a mouse model of schizophrenia, FSU, **Yi Zhou**, PhD

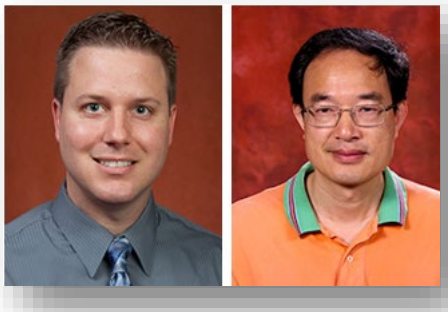
In addition to the above, the 2019 recipients, including **Samantha Pavlock** (**Bhide Lab**), **Grace Hammel** (**Ren Lab**), and **Xiaoyan Yu** (**Yuan Wang Lab**), presented their research via zoom.

Faculty News



Dr. Robert Tomko Jr. was granted a patent (Patent #10,676,519) entitled "*Chimeric proteins and their use in identifying anti-deubiquitinase compounds*". This technology involves chimeric proteins having deubiquitinase activity and methods of identifying anti-deubiquitinase compounds using the chimeric proteins. These methods and assays can be adapted to high throughput screening procedures to assay for anti-cancer drugs effecting deubiquitinase activity. Disrupting the Rpn11 deubiquitinase function is a validated strategy for treatment of human cancers.

Funding News



Dr. David Meckes was awarded a pilot grant from FSU with Co-I's Drs. **Zucai Suo** and Sam Grant to develop a mesenchymal stem cell extracellular vesicles-based therapy for COVID-19. He was also awarded a pilot and feasibility grant from the NIH as part of the Center for Engineered Human CNS Tissue Models for Neurotropic Viruses (NIAID Grant U19 AI131130) to study extracellular vesicle-mediated transmission of Zika virus.

The Gunjan Lab received the Clinical and Translational Science Institute's (CTSI) Precision Health Initiative pilot funding in the amount of $50,000 for applying genomic sequencing-based approaches to understand the underlying causes of keloids and their variable response to steroid therapy.

Publications

Dr. Yanchang Wang recently had a research article accepted for publication by the journal, *Cell Reports*. The article titled "The Cdc48 complex alleviates the cytotoxicity of misfolded proteins by regulating ubiquitin homeostasis" was additionally written by **Ryan Higgins, Marie-Helene Kabbaj, Delaney Sherwin, Lauren A. Howell, Alexa Hatcher,** and **Robert J. Tomko Jr.**

Manuscript Number: CELL-REPORTS-D-20-02061R2

Graduate students **Dingani Nkosi**, **Leanne Duke,** and postdoctoral fellow **Li Sun,** along with contributions from Nilkumar Patel, Sunil K. Surapaneni, Mandip Singh, and **David G. Meckes, Jr.** have a new publication in *MBio* entitled "*Epstein-Barr Virus LMP1 Promotes Syntenin-1- and Hrs Induced Extracellular Vesicle Formation for Its Own Secretion to Increase Cell Proliferation and Migration*".

LMP1 is a notable viral protein that contributes to the modification of EV content and tumor microenvironment remodeling. LMP1-modified EVs enhance tumor proliferation, migration, and invasion potential and promote radioresistance. Currently, the mechanisms surrounding LMP1 incorporation into the host EV pathways are not well understood. This study revealed that LMP1 utilizes Hrs, Syntenin-1, and specific components of the ESCRT-III complex for release from the cell, enhancement of EV production, and metastatic properties of cancer cells. These findings begin to unravel the mechanism of LMP1 EV trafficking and may provide new targets to control EBV-associated cancers.

ABSTRACT: Extracellular vesicles (EVs) are important mediators of cell-to-cell communication that are involved in both normal processes and pathological conditions. Latent membrane protein 1 (LMP1) is a major viral oncogene that is expressed in most Epstein-Barr virus (EBV)-associated cancers and secreted in EVs. LMP1-modified EVs have the ability to influence recipient cell growth, migration, and differentiation and regulate immune cell function. Despite the significance of LMP1-modified EVs in EBV malignancies, very little is understood about how this protein hijacks the host EV pathway for secretion. Using the biotin identification (BioID) method, we identified LMP1-proximal interacting proteins that are known to play roles in EV formation and protein trafficking. Analysis of the identified LMP1-interacting proteins revealed an enrichment in the ESCRT pathway and associated proteins, including CD63, Syntenin-1, Alix, TSG101, Hrs, and charged multivesicular body proteins (CHMPs). LMP1 transcriptionally upregulated and increased the protein expression of EV biogenesis and secretion genes. Nanoparticle tracking and immunoblot analysis revealed reduced levels of LMP1 EV packaging and of vesicle production following the knockdown of Syntenin-1, Alix, Hrs, and TSG101, with altered endolysosomal trafficking observed when Syntenin-1 and Hrs expression was reduced. Knockdown of specific ESCRT-III subunits (CHMP4B, -5, and -6) impaired LMP1 packaging and secretion into EVs. Finally, we demonstrate that the efficient secretion of LMP1-modified EVs promotes cell attachment, proliferation, and migration and tumor growth. Together, these results begin to shed light on how LMP1 exploits host ESCRT machinery to direct the incorporation of the viral oncoprotein into the EV pathway for secretion to alter the tumor microenvironment.

The Gunjan Lab in collaboration with **Dr. Branko Stefanovic** and dermatologist Dr. George Cohen recently published an article regarding their study entitled "Treatment of Keloids with a Single Dose of Low Energy Superficial X-ray Radiation to Prevent Recurrence After Surgical Excision: An in Vitro and in Vivo Study". The article written by **Yuna Son**, **Ernest Owen Nicandro Phillips**, Kristin Magrini Price, Laurence Zalmon Rosenberg, **Branko Stefanovic**, Christopher Michael Wolfe, Tarek Samir Shaath, Amit Om, George Franklin Cohen and **Akash Gunjan** was published in the Journal of American Academy of Dermatology last month. Link and abstract are below

Link: https://pubmed.ncbi.nlm.nih.gov/32540415/

Abstract for "*Epstein-Barr Virus LMP1 Promotes Syntenin-1- and Hrs Induced Extracellular Vesicle Formation for Its Own Secretion to Increase Cell Proliferation and Migration*":

Keloids are common but benign (non-cancerous) skin tumors that often cause major discomfort and are very difficult to treat. Their occurrence is highly skewed towards dark skinned individuals, occurring predominantly in African Americans with an estimated 1 in 5 individuals being affected, compared to about 1 in 1000 for white Americans. Keloids are typically treated by surgical removal but without any additional therapy, they regrow in nearly 100% of the cases. Post-surgical therapy to reduce recurrence often involves radiation or steroid therapy. However, evidence-based radiation doses for keloid therapy have not been established, while only a third of the patients benefit from steroid therapy. Only humans appear to develop keloids and so animal models to study keloids are unavailable, which makes their study challenging. Hence, we cultured keloid tissues and cells in dishes following their surgical removal from patients to determine the most effective radiation parameters for preventing the growth of keloid cells. We found that *a single low dose of low energy X-ray radiation delivered just skin deep within ~3 months of surgery is highly effective in preventing recurrence* with very minimal adverse effects. Hence, higher doses or multiple rounds of radiation are not required for keloid therapy and these may in fact be harmful due to the significant adverse effects associated with such radiation protocols that are typically used for cancer therapy. Finally, our data also suggest that our radiation parameters are likely to be effective in preventing keloid recurrence even in patients that do not respond to steroids.

A manuscript entitled "*A Bell-Shaped Dose Response of Topical FGF-1 in Dermal Wound Healing of Aged Female BALB/cByJ Mice*" authored by Brooke Hagerott has been accepted for publication in *J. Prot. Proteomics*. This study describes an atypical dose-response curve of topical FGF-1 as a pharmacotherapy in treating the age-related impairment of dermal wound healing in aged female mice. This study involved undergraduate researchers Hagerott, McGarry, Cohen, and Powell. Also participating in the study was FSU College of Medicine, class of 2021 student, Alli Blumstein. **Connie Tenorio**, a graduate student in the **Blaber Lab** also participated. Dr. Tamas Nagy, University of Georgia College of Veterinary Medicine, collaborated on the histopathology analyses. The abstract is below.

The objective of this study was to characterize the therapeutic dose–response characteristics for topical FGF-1 in the full-thickness dermal healing of aged female BALB/cByJ mice. The approach utilized a splinted excisional model of dermal healing, and a novel fine-sampled photographic methodology, to quantify key wound healing parameters for different doses of topical FGF-1. The histology of healed wounds, representative of each dose cohort, was also evaluated by section and staining. The results show that topical FGF-1 pharmacotherapy for accelerating dermal healing in aged BALB/cByJ female mice yields a narrow dose–response curve, with diminished therapeutic effect at high concentration (i.e., "bell-shaped" dose–response). The physiological response of FGF-1 in wound healing involves a combination of cell types (including vascular endothelial cells, epidermal keratinocytes and dermal fibroblasts). These individual cells types in culture can have different FGF-1 dose–response curves; however, only the response of fibroblasts is bell-shaped. The bell-shaped dose–response in dermal healing, therefore, principally reflects the effect upon fibroblasts. A narrow bell-shaped dose–response requires precise dosing of FGF-1 for therapeutic benefit. The results identify the practical dose range to elicit such a benefit.

A manuscript entitled "Conserved Buried Water Molecules Enable the β-Trefoil Architecture" and authored by **Dr. Michael Blaber** has been accepted for publication in Protein Science. Link and abstract are below.

Link: https://doi.org/10.1002/pro.3899

Available high-resolution crystal structures for the family of β-trefoil proteins in the structural databank were queried for buried waters. Such waters were classified as either: 1) unique to a particular domain, family, or superfamily, or 2) conserved among all β-trefoil folds. Three buried waters conserved among all β-trefoil folds were identified. These waters are related by the threefold rotational pseudo-symmetry characteristic of this protein architecture (representing three instances of an identical structural environment within each repeating trefoil-fold motif). The structural properties of this buried water are remarkable and include: residing in a cavity space no larger than a single water molecule, exhibiting a positional uncertainty (i.e., normalized B-factor) substantially lower than the average Ca atom, providing essentially ideal H-bonding geometry with three solvent-inaccessible main chain groups, simultaneously serving as a bridging H-bond for three different β-strands at a point of secondary structure divergence, and orienting conserved hydrophobic sidechains to form a nascent core-packing group. Other published work supports an interpretation that these interactions are key to the formation of an efficient folding nucleus and folded thermostability. The fundamental threefold symmetric structural element of the β-trefoil fold is therefore, surprisingly, a buried water molecule.

Notice to Faculty

This year we will once again honor and celebrate the achievements of one of our postdocs with the **Outstanding Achievement as a Postdoctoral Scholar** award.

Recipients for this COM postdoc achievement award are selected by the GPC, based on outstanding scholarship, including publications, fellowships, awards, conference presentations, etc.

The recipient of this award will be announced at the annual retreat on ***Friday, August 21st***. The recipient will receive a certificate and $250 to spend on books and electronics.

Nominations usually come from the Postdoc's mentor. Please send your nominations for this year's annual **Outstanding achievement as a postdoctoral scholar** award by **Friday, July 31st**.

To nominate an outstanding postdoc **please contact Tim Megraw** with **the nominee's CV and a brief outline, in one paragraph, of the achievements of the postdoc** you wish to nominate for this award. The GPC will evaluate the nominations.

Save the Date

Wednesday, August 5th	Seminar Series: **Gloria Lee**
Monday, August 24th	Fall Semester Begins

Do you have news you wish to share in the May Biomed Newsletter? If so, please contact Ryan Teston at: ryan.teston@med.fsu.edu

The July Deadline for Submissions: Wednesday, July 29th at 12pm