Welcome to the Department of Microbiology, Immunology & Parasitology

LSU Health Sciences Center
School of Medicine at New Orleans
http://www.medschool.lsuhsc.edu/microbiology

It is an exciting time to be involved in the study of microorganisms and their interactions with human and animal hosts. Recent advances in microbiology, immunology, and molecular genomics have provided tantalizing glimpses into the biology of these "bugs", how they cause disease and the influence of our own microbiota on the disease process, how the immune system has evolved to deal with the threat that they pose, and how, in turn, microorganisms have evolved complex survival strategies in the face of host defenses. The devastation caused by the COVID-19 pandemic is a stark reminder of these issues. SARS-CoV-2, along with recent outbreaks of Zika virus in Brazil and Ebola virus in West Africa and the ongoing problems of influenza virus, methicillin-resistant 'superbugs' (MRSA), HIV/AIDS, drug-resistant TB, Middle East respiratory syndrome (MERS), and serious fungal infections, among others, are constant reminders of the dynamic nature of our field.

Faculty in the Department of Microbiology, Immunology and Parasitology (MIP) direct translational research programs in immunology, virology, bacteriology, mycology and parasitology, linking basic and clinical sciences within the LSU Health Sciences Center and with researchers at other campuses. The Department provides a strongly interactive environment that has underpinned the development of several new interdisciplinary research and development programs with funding from the National Institutes of Health, Private Foundations and Industry. Our recent State-funded initiatives include the Louisiana Vaccine Center, established in collaboration with colleagues from Tulane and Xavier University with the aim of developing of new vaccines and therapies for infectious disease and promoting linkages with biotechnology. Members of our faculty have also forged strong linkages with related programs here at the Health Sciences Center, and the LSU School of Veterinary Medicine in Baton Rouge.

Each of these initiatives underpins a dynamic and integrated education program in MIP, that includes mentoring and career development of postgraduate students and postdoctoral trainees from Louisiana, across the United States, and around the globe. Students pursuing PhD and MS degrees in our program are mentored by an accomplished and dedicated faculty and supported by state-of-the art research facilities and core laboratories in genomics, proteomics, bioinformatics, flow cytometry, molecular interaction, and morphology and imaging.

Please contact us for further information concerning any aspect of our research and education programs.

Alistair Ramsay, Ph.D.
G. John Buddingh Professor and Head,
Department of Microbiology, Immunology & Parasitology
Director, Louisiana Vaccine Center

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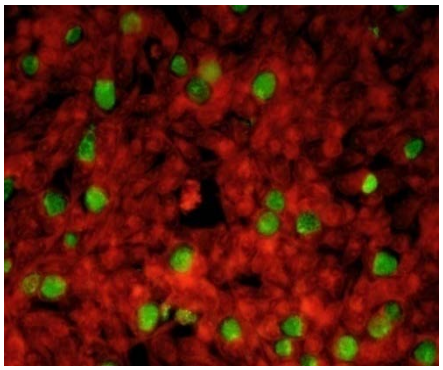
DEPARTMENT OF MICROBIOLOGY, IMMUNOLOGY, & PARASITOLOGY
FACULTY RESEARCH INTEREST

IMMUNOLOGY/INFECTIOUS DISEASES/CANCER

Pam Kozlowski, Ph.D. **[pkozlo@lsuhsc.edu; 568-6956; CSRB 606]**

Research in Dr. Kozlowski's laboratory is focused on the identification of mucosal and systemic IgA antibody responses that could protect against HIV-1 or SARS CoV-2 infection. IgA antibodies transported into mucosal fluids are ideally suited for host protection, and vaccines that induce HIV or SARS CoV-2-specific IgA antibodies in secretions could prevent transmission of these viruses at mucosal surfaces. Studies in the lab involve measuring the specificity and function of the antiviral antibodies produced in infected individuals or in nonhuman primates immunized with different types of vaccines.

Alison Quayle, Ph.D. **[aquayl@lsuhsc.edu; 568-4070; MEB 6240(6G1)]**



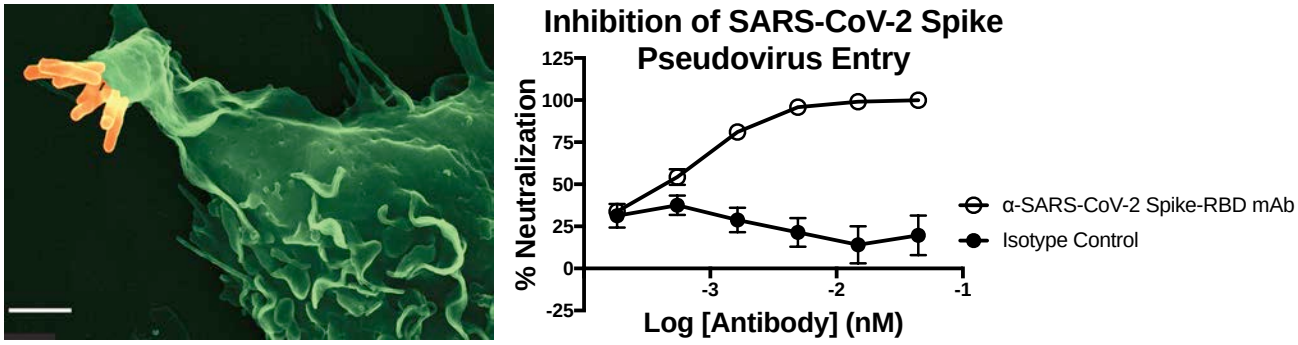
The central theme of our research is immune defense in the human female genital tract, with a focus on the unique obligate intracellular bacteria *Chlamydia trachomatis*, and HIV. Broadly, our research interests encompass the study of: (1) *Chlamydia trachomatis*-specific adaptive responses in the human endocervix, (2) immuno-evasive strategies used by *C. trachomatis* to adapt to, and survive in, the human genital milieu and (3) *C. trachomatis* and HIV co-infection and (4) the impact of a dysbiotic vaginal microbiome (bacterial vaginosis) on genital immunity. We collaborate with the LSU/Crescent Care Sexual Health Clinic for our clinical studies and use *in vitro* modeling in help elucidate basic mechanisms.

An endocervical isolate of Chlamydia trachomatis grown in HeLa cells. *Chlamydial lipopolysaccharide is stained green, visualizing the chlamydial inclusion, and structural proteins of the cell are stained red.*

Alistair Ramsay, Ph.D. **[aramsa@lsuhsc.edu; 568-8324; MEB 6206A]**

Current research interests of the Ramsay lab are centered on immune biology of pulmonary infections by intracellular pathogens with a view to the development of new or improved vaccine strategies. We are also interested in the development of novel, recombinant vaccine vectors that can effectively deliver key immunogens to different sites and tissues in the body and induce critical innate and adaptive immune responses. Our ultimate goal is to generate information that will inform the development of improved vaccines, particularly those that stimulate protective immunity at mucosal and systemic sites of infection.

A primary focus of the lab at present is investigating host:pathogen interactions in *Mycobacterium tuberculosis* infection, using immune assays, genomics and bioinformatics. Related to this, we are interested in finding improved TB immunization strategies, based largely on the development and evaluation of recombinant BCG and viral vectors expressing immunogenic vaccine targets in *M. tuberculosis* and engineered for enhanced immunogenicity. More recently, we have developed a pseudovirus-based assay for neutralizing antibody responses against SARS-CoV-2 as a tool to help with our characterization of functional immunity in both SARS-CoV-2 convalescents and vaccines over time, as well as in a mouse model of infection (see Fig. overleaf).



Mycobacterium tuberculosis *associated with a macrophage cell (left), and evidence of blockade of entry of SARS-CoV-2 Spike glycoprotein pseudovirions (constructed in the lab) into permissive cells by anti-SARS CoV-2 S neutralizing antibodies.*

Guoshun Wang, D.V.M., Ph.D. **[gwang@lsuhsc.edu; 568-7908; CSRB 607]**

The Wang lab has two major research directions: 1) understanding cystic fibrosis (CF) disease pathogenesis, and developing CF gene and stem cell therapy, and 2) elucidating alcohol-induced anti-inflammation and immunosuppression.

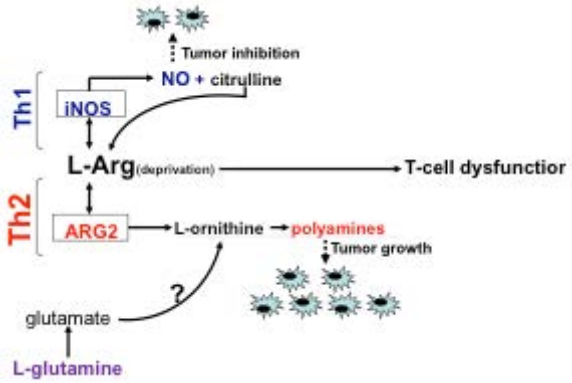
CF, the most common life-threatening genetic disorder in the Caucasian population, is caused by mutations in CF transmembrane conductance regulator (CFTR) gene, encoding a cAMP-activated chloride channel. Clinically, CF intestinal and lung diseases claim the most morbidity and mortality with the cardinal pathology characterized by infection, inflammation and obstruction. It is not fully established how the chloride channel defect leads to these clinical complications. The Wang lab made the initial discovery that the CFTR defect undermines chloride transport to neutrophil phagosomes, which impairs the production of hypochlorous acid (HOCl), a potent microbicide for effective bacterial killing. Such a defect compromises host defense against infection and host resolution of inflammation. Currently, the lab is further elucidating the contribution of this innate immune defect in CF lung and intestinal disease pathogenesis, and is also pursuing genomic editing to correct the root-causing defect of CF.

Alcohol is known to have anti-inflammatory and immunosuppressive effects. However, the molecular mechanisms underlying this long-observed phenomenon are not well defined. Previous research from this lab has shown that ethanol, in the absence of glucocorticoids, upregulates Glucocorticoid-Induced Leucine Zipper (GILZ), a critical steroid-responsive gene, through non-canonical activation of Glucocorticoid Receptor (GR). We are now characterizing how alcohol exploits the GR signaling pathway to modulate the body's immune system.

Arnold H. Zea, Ph.D. **[azea@lsuhsc.edu; 599-0906; CSRB 305]**

The Zea lab is focused in the immune biology of cancer and tuberculosis. In cancer, Dr. Zea is studying the mechanisms by which L-arginine and L-glutamine metabolism regulates tumor growth-inhibition and immune responses (see Figure below). This work will help to better understand mechanisms of resistance and tumor evasion and to develop new therapeutic strategies to control and possibly eradicate tumors. The knowledge and experience gained in cancer-related research has allowed Dr. Zea to explore whether similar mechanisms can occur in infections by *Mycobacterium tuberculosis* (*Mtb*) and Non-Tuberculous Mycobacteria (NTM). He is studying *in vitro* and *in vivo* mechanisms by which *Mtb*-cyclic-AMP and NTM-cyclic-AMP (cAMP) regulates arginase induction, nitric oxide and cytokine production used by *Mycobacteria* to survive and persist inside macrophages.

The main goal of these projects is to identify pathways involved in L-arginine metabolism that can be targeted to inhibit tumor and/or *Mycobacterial* growth/persistence. These findings could facilitate the development of new, unconventional therapies that could eliminate tumors and tuberculosis, based on their dependence on L-arginine or L-glutamine. It also has the potential to advance treatments for multi-drug and extensively-drug resistance tuberculosis, where current first line drug therapies are ineffective.



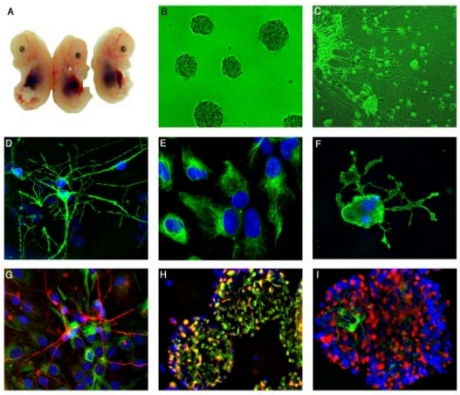
Impairment of antitumor immunity in patients with cancer (and TB) could be due to the shift from a Th1 to Th2 cytokine response*. This shift prompts the tumor microenvironment to produce high ARG2 and polyamine levels to sustain tumor growth, instead of high levels of INOS and NO to inhibit its proliferation. The depletion of L-Arginine (L-Arg) induces T-cell dysfunction as another advantage for tumor growth. The effect of L-glutamine on modulating L-arginine metabolism is being investigated.*

Krzysztof Reiss, Ph.D. **[kreiss@lsuhsc.edu; 210-2977; LCRC 710]**

Molecular strategies against Insulin-like Growth Factor I Receptor (IGF-IR) in brain tumors. Work from other laboratories and our recent findings strongly indicate that the signal from activated IGF-IR supports growth and survival of cancer cells, and the functional IGF-IR is required for supporting malignant transformation mediated by different cellular and viral oncogenic proteins. We are developing and testing different strategies aiming at the IGF-IR in vitro and in experimental animals. These include use of dominant negative mutants, antisense strategies, neutralizing antibodies, small inhibitory RNAs (siRNAs), and small molecular weight inhibitors of the IGF-IR tyrosine kinase activity.

The contribution of IGF-IR to JC virus T-antigen–mediated cellular transformation. Polyomaviruses are thought to participate in the development of cancer. A substantial body of evidence points to the role of human polyomavirus JC in brain tumors. The viral oncoprotein, JCV T-antigen, has the ability to transform cells in culture, is tumorigenic in experimental animals, and has been found in a significant number of brain tumor clinical samples including medulloblastomas and glioblastomas. By investigating functional association between JCV T-antigen and the IGF-IR system, we have found that: **(i)** cells with targeted disruption of the IGF-IR gene are resistant to JCV T-antigen –induced transformation; **(ii)** 1.5 x10^4 IGF-IR molecules *per* cell fully supports JCV T-antigen–mediated anchorage-independent growth *in vitro*; **(iii)** the major IGF-IR signaling molecule, IRS-1, directly interacts with JCV T-antigen, and translocates IRS-1 to the nucleus. In addition, we are testing molecular interplay between JC virus T-antigen and environmental contaminants, polycyclic aromatic hydrocarbons (PAHs) in the process of malignant transformation.

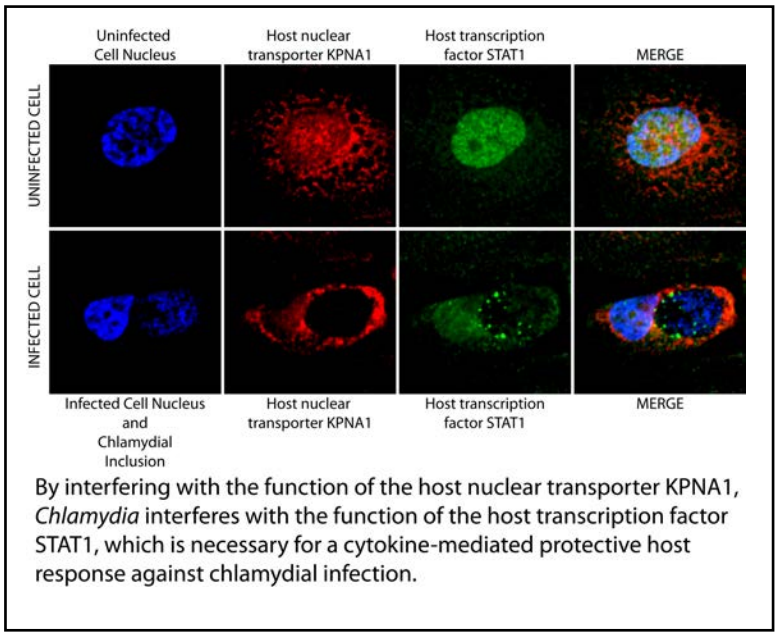
Role of IGF-I, and Tumor Necrosis Factor α (TNFα) in HIV associated dementia. In a substantial number of AIDS patients, HIV infection results in a serious neurological disorder of the central nervous system (CNS), HIV–associated dementia (HAD). Currently, there is no specific treatment for HAD, mainly because of an incomplete understanding of how HIV infection causes neuronal injury and apoptosis. The predominant pathogenesis of HAD is believed to involve activation of macrophages and microglia and their subsequent release of toxins that lead to neuronal and astrocytic dysfunction. Activation of the insulin-like growth factor I receptor (IGF-IR) represents a strong neuro-protective mechanism against a wide variety of insults. Therefore, our future task is to determine molecular pathways involved in cross-talk between IGF-I, TNFα receptors and HIV proteins in neural progenitors of the CNS.



Three-dimensional cultures of neural progenitors in which molecular interplay between IGF-IR and TNFα is being investigated.

BACTERIAL PATHOGENESIS

Ashok Aiyar, Ph.D. **[aaiyar@lsuhsc.edu; 568-4072; MEB6246 (6B11)]**



By interfering with the function of the host nuclear transporter KPNA1, *Chlamydia* interferes with the function of the host transcription factor STAT1, which is necessary for a cytokine-mediated protective host response against chlamydial infection.

My lab is interested in the molecular basis of pathogenesis associated with intraccellular microorganisms. We have previously studied pathogenesis associated with Epstein-Barr virus (EBV), a herpesvirus that was the first oncogenic human virus discovered. These studies were focused on the mechanisms by which viral DNA-binding proteins permitted EBV genomes to associate with human chromosomes and facilitate distinct programs of viral gene expression during oncogenesis. Currently we focus on *Chlamydia trachomatis*, an obligate intracellular bacterium that the leading bacterial sexually transmitted disease with consequences including infertility. In addition, chlamydial infections are the leading infectious cause of blindness (trachoma). We are particularly interested in determining how *Chlamydia* modulates intracellular signaling pathways to escape the protective effect of host cytokines. Our studies have focused on the effect of chlamydial infections on host transcription factors that drive this protective response. Additionally, we are interested in examining mechanisms by which the poly-microbial environment, present during natural human infections, ameliorates the effect of host cytokines on chlamydial infections. We anticipate the outcome of our studies to permit the discovery of novel therapeutics against *Chlamydia*, and facilitate the design of protective vaccines against this insidious bacterium.

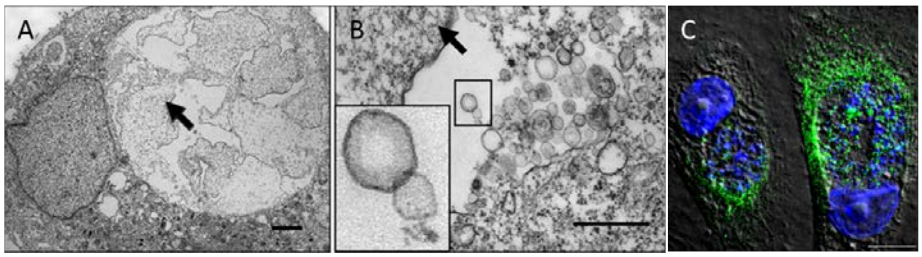
Jeffery Hobden, Ph.D. **[jhobde@lsuhsc.edu; 568-4077; MEB 6223 (6C21)]**

As the average American grows older, the incidence of osteoarthritis and rheumatoid arthritis (accompanied by type 2 diabetes and obesity) will dramatically rise, resulting in an increasing number of prosthetic knee and hip joint implant procedures. A serious and costly complication of prosthetic joint implantation is infection. In acute prosthetic joint infection (PJI), irrigation and debridement with prosthesis retention is preferred, but not always curative. There is little information on what variables lead to treatment failure. One factor that likely contributes to a poor prognosis is the propensity of bacteria, especially Methicillin-resistant *Staphylococcus aureus* (MRSA), to form biofilms on implant surfaces. Bacteria growing in biofilms are difficult, if not impossible, to clear by the host immune response and recalcitrant to antibiotic therapy.

Dr. Hobden's laboratory is currently developing clinically relevant model systems to gain an understanding of bacterial biofilm formation on various orthopedic substrates such as alloys of titanium, polymethyl methacrylate bone cement, and ultra-high density polyethylene. With these models, Dr. Hobden's laboratory is examining the efficacy of various antimicrobials and intervention strategies to eliminate or prevent Gram-positive (methicillin-resistant *Staphylococcus aureus* [MRSA, coagulase-negative staphylococci]) and Gram negative (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*) clinical isolates from growing as a biofilm on orthopedic substrates.

Li Shen, M.D., Ph.D. **[lshen@lsuhsc.edu; 568-4076; MEB 6217 (6C15)]**

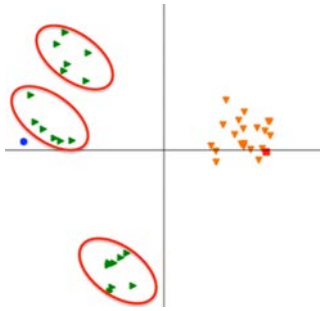
Research in Dr. Shen's lab is focused on pathogenesis of human intracellular pathogens, such as *Chlamydia trachomatis* that cause the most prevalent sexually transmitted bacterial infections with serious reproductive complications in both men and women. Molecular, genetic, biochemical, cell biology, and RNA-sequencing approaches are utilized in combination. (i) *Control of the virulence associated type III secretion system (T3SS) in C. trachomatis*. *Chlamydia* uses the T3SS to deliver virulence proteins termed 'effectors' to counteract host innate immunity. Evidence emerges that there is an intimate link between gene expression and the T3SS in *C. trachomatis*. We are interested in defining the mechanisms that are utilized by *Chlamydia* to carefully regulate the T3SS activity at multiple steps, including gene expression, substrate recognition, and spatiotemporal effector secretion. (ii) *Mechanisms and consequences of C. trachomatis responses to antimicrobial insults.* Despite aggressive diagnosis and antibiotic treatment program, rates of *C. trachomatis* infections continue to rise. We seek to develop novel tools that allow us to quantitatively probe diverse developmental forms of *C. trachomatis* during infection. We will characterize key signaling pathways, in *C. trachomatis* and its host cells, that contribute to *Chlamydia* adaptation and survival during exposure to external and internal antimicrobial insults. It is expected that insights obtained will pave the way for the future development of novel therapies targeting the pathways against *Chlamydia* infections.



Chlamydial persistent forms (A) and the member vesicles induced by ampicillin in HeLa cells (B). Translocation of virulence factor CPAF (green) into the cytosol of human primary endocervcal epithelial cells (C).

Christopher Taylor, Ph.D. **[ctay15@lsuhsc.edu; 568-4065; CSRB 601A]**

The human body is host to diverse communities of microbial organisms collectively referred to as the human microbiome. These communities include bacteria, fungi and archaea, some of which perform important metabolic functions. Interventions such as antibiotic treatment and environmental interaction can disrupt these communities and changes in community structure have been shown to play a major role in several diseases. We use 16S ribosomal RNA collected from these communities in tandem with high-throughput sequencing to study and analyze these microbial communities and their relationship with human health and disease. The primary focus of the lab is computational analysis and visualization of microbial community structure performed in collaboration with clinicians and basic scientists. In addition to the human microbiome, we also investigate microbial communities in model organisms such as mouse, rat, and non-human primate studies with a focus on translational research. In addition to 16S rRNA analysis of microbial community structures, we also use shotgun metagenomic sequencing to assess microbial communities. The primary source of funding for our lab is NIAID with several grants to study the reproductive tract and interactions of microbiota with sexually transmitted infections (primarily Chlamydia) and bacterial vaginosis.

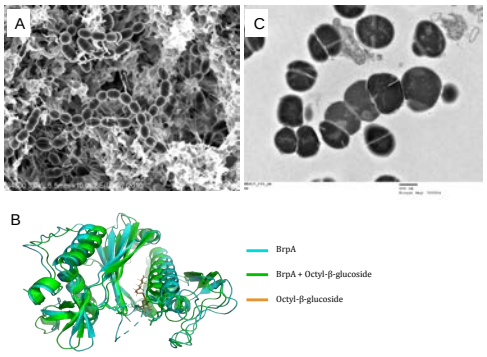


***Principle Coordinates Analysis Plot** of mice given a gut microbiota transplant (green triangles) from mice on a high-fat diet (blue circle) and mice given a gut microbiota transplant (orange triangles) from mice on a standard chow diet (red square). The gut microbial communities of mice receiving the transplant are most similar to each respective transplant donor community. Red ovals surround samples from mice that were housed in the same cage illustrating that gut microbial community drift is impacted by cohabitation.*

Z. Tom Wen, Ph.D. **[zwen@lsuhsc.edu; 941-8465; Dental School 6305]**

The focus of Dr. Wen's research is on molecular characterization of oral biofilms and identification of novel strategies against human dental caries. Major efforts are being directed to (i) identification of genes required for biofilm formation by *S. mutans,* the key etiological agent of dental caries; (ii) uncovering how different species of bacteria communicate affecting the development and stability of the complex microbial communities and ultimately, oral health; and (iii) identification of novel strategies including natural compounds effective against cariogenic biofilms and dental caries. In addition, Dr. Wen also works with the Xu Group in biomaterials on development of novel antibacterial dental composites.

With the support of NIH, Dr. Wen has recently shown that biofilm regulatory protein BrpA in *S. mutans* is a surface-associated protein with critical roles in cell envelope biogenesis, stress tolerance response and biofilm formation, and that deficiency of BrpA almost completely abolishes the ability of the bacterium to colonize the tooth surface and causes carious lesions *in vivo*. Currently, Dr. Wen and his collaborators are working on uncovering the *cis*- and *trans*-acting factors that regulate BrpA expression and proteins that interact with BrpA in functions mediated by BrpA and on small molecules that modulate BrpA-regulated virulence.



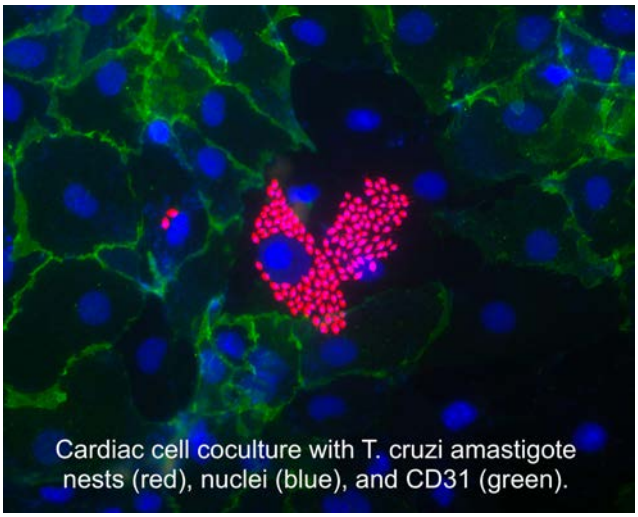
A. SEM image of *S. mutans* biofilms at x10.0k; B. BrpA structure with and without Octyl-β-glucoside; C. TEM image of a *mecA* mutant featuring major defects in cell division at x10.0k.

An adaptor, MecA forms complex with ATPase ClpC playing an important role in protein homeostasis, stress tolerance, genetic competence and virulence in *S. mutans*. However, recent studies by Dr. Wen have shown that besides interacting with ClpC, MecA can also regulate the expression of various genes critical to *S. mutans'* pathophysiology, including cell division and biofilm formation. Another major effort in Dr. Wen's lab is to uncover the scope of the MecA regulon and the underlying mechanisms and the potential of targeting MecA in virulence modulation of *S. mutans*.

PATHOGENIC EUKARYOTES

Doug Johnston, Ph.D. **[djoh13@lsuhsc.edu; 568-4071; CSRB 609]**

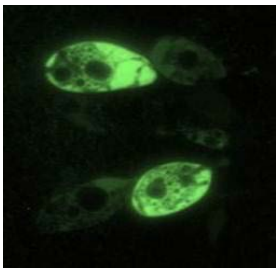
The Johnston lab focuses on defining mechanisms of the human host response to infection by the fungus *Candida albicans* and the parasite *Trypanosoma cruzi*. We are particularly interested in the roles played by host endothelial cells, which line the vasculature and form the most significant barrier against tissue invasion by bloodborne pathogens. In addition to providing barrier functions the endothelium is a critical regulator of tissue homeostasis and plays key roles in inflammation and wound healing. While *C. albicans* is a common commensal, changes in host immune status allow the fungus to penetrate the skin or mucosa, where it gains access to the bloodstream. Once bloodborne, *Candida* is capable of escaping the vasculature and invading nearly every tissue of



the body. Mortality attributed to disseminated candidiasis is often greater than 50%, even with aggressive antifungal treatment. *T. cruzi*, a kinetoplastid parasite transmitted through hematophagous insect vectors, is the causative agent of Chagas' Disease (CD) and accounts for more than 10,000 deaths annually, with an estimated 8 million infections worldwide. Chronic CD most often results in cardiac remodeling and *T. cruzi*-induced fibrosis is a major contributor to heart failure, but the underlying mechanisms remain mostly uncharacterized. We use molecular, genetic, biochemical, immunochemical, and cell-based approaches to define endothelial responses to adherence, invasion, and damage by *C. albicans* and *T. cruzi*. Vascular dysfunction in these settings likely contributes to the establishment and maintenance of deep tissue infections. We believe that clinical manipulation of the endothelial response to these pathogens will help to preserve vascular barrier function and lead to enhanced immunity and decreased pathology.

Ben Kelly, Ph.D. **[bkell2@lsuhsc.edu; 568-6115; MEB 6111)]**

Dr. Kelly's laboratory studies the biology of the protozoan pathogens, *Leishmania* and *Trypanosoma cruzi*. These parasites are transmitted via the bite of their insect vectors and are the etiologic agents of leishmaniasis and Chagas disease, respectively. Currently, there are no really effective treatments to combat these debilitating and often fatal diseases that have infected approximately 20 million people worldwide. Research in my laboratory focuses primarily on understanding molecular functions of specific parasite proteins required for viability and virulence. We are especially interested in identifying important molecular functions unique to these parasites, as these may represent potential drug targets for better, low toxicity therapies against these diseases. Current research in the lab includes use of conventional and CRISPR-based gene-knockout and gene-tagging approaches to understand how a molecular scaffolding protein, termed "LACK", promotes expression of parasite genes important for virulence and survival in the mammalian host.



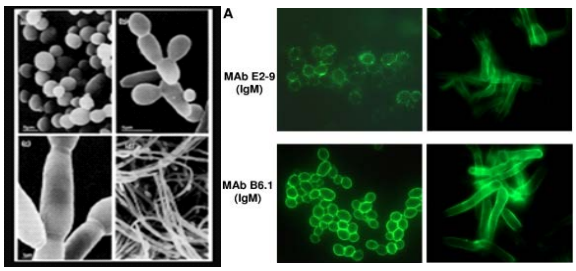
Leishmania parasites expressing a LACK–Green Fluorescent Protein chimeric transgene.

Joy Sturtevant, Ph.D. **[jsturt@lsuhsc.edu; 568-6116; MEB 6207 (6C4: Lions 669)]**

Pathogens have evolved to thwart our immune response and/or 'peacefully' reside within our body. How do they do this? Our laboratory focused on the initial interactions between pathogen and host, and the intracellular signaling events that dictate a response in either host or pathogen. Our major pathogen of interest is *Candida albicans*, the most common opportunistic fungal pathogen and the 4th most common nosocomial infectious agent but also a member of the normal microbiota. We have expertise in molecular genetic methods, mutations, proteomic, cell culture and cell biology techniques. Currently the lab also has a major focus on medical education with emphasis on organizing the delivery of basic science by using active techniques and granulated learning objectives. Sharing our resources and expertise is our current research goal. We love to talk science, troubleshoot and collaborate.

Hong Xin, M.D., Ph.D. **[hxin@lsuhsc.edu; 568-8121, MEB 6265 (6A6)]**

Hematogenously disseminated candidiasis in humans has become the third leading cause of hospital-acquired blood stream infections and despite antifungal therapy at least 40% of affected individuals will die of this disease. As there is no approved antifungal vaccine for use in humans and significant therapeutic challenges remain, our approach is disease prevention through active vaccination and/or passive immunization with protective antibodies. We first reported that a tetanus toxoid conjugated

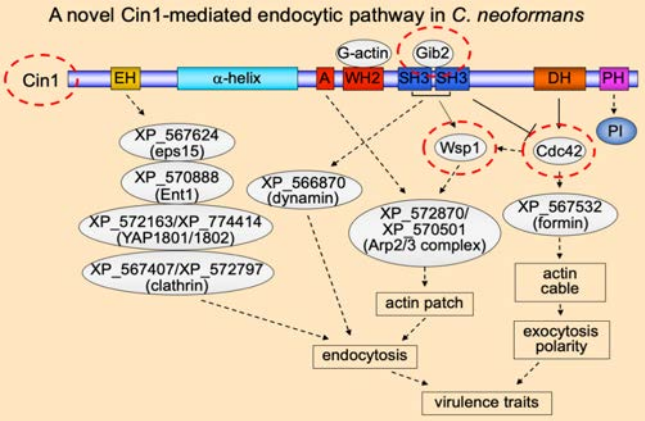


Candida albicans Antibodies bind to *Candida*

glycopeptide vaccine induced dual (double) antibody-dependent protective immunity without the need for adjuvant, which is feasible for human use. We have demonstrated a novel double chimeric peptide vaccine that functions synergistically to improve the level of protection against disseminated candidiasis. Up to now, we have developed a panel of protective monoclonal antibodies (mAbs), which are specific for fungal cell-surface glycan and peptides with high homologous among all medically relevant *Candida* species, including *C. auris.* Furthermore, we showed that the combination of two mAbs is a much more effective immunoprotective approach as compared to single mAb treatment. Strikingly, these "universal" mAbs, as an adjunct to the existing therapy, greatly enhanced efficacy of antifungal treatment against the diseases in immunocompromised mouse models, indicating the great clinical relevance. Our research goal is to develop the multi-epitope vaccine and mAb-based therapy that protects against medically significant *Candida* species in humans, as well as addressing fundamental questions concerning vaccine-induced immunity in high-risk, immune compromised populations.

Ping Wang, Ph.D. **[pwang@lsuhsc.edu; 568-2446; MEB 6118]**

Research in my laboratory is focused on understanding the molecular basis of pathogenesis using two human fungal pathogens, *Cryptococcus neoformans* and *Rhizopus delemar,* as model organisms. For *C. neoformans,* we examine how G protein-binding proteins and their regulators mediate signal transduction pathways that coordinate cellular growth and differentiation required for virulence. We also dissect a novel intersectin (Cin1)-mediated intracellular trafficking in the secretion of virulence factors and determine whether Cin1 alternative splicing has a role in the neurotropic property of the fungus, a unique mechanism of cryptococcal pathogenesis.

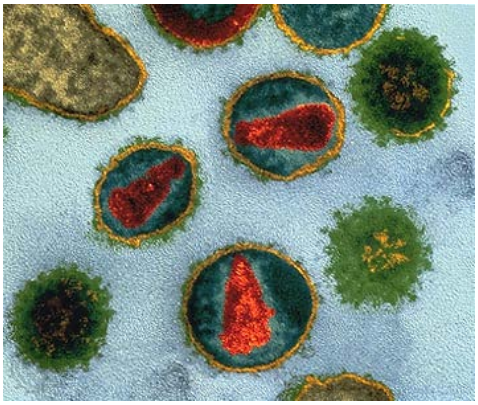


For *Rhizopus delemar,* our focus is to develop tools that can advance genetic studies of mucormycosis virulence mechanisms. We have started with adopting CRISPRCas9 technology for gene editing, whose optimization will facilitate the construction of mutant libraries. Such technical development would promote the discovery of novel targets for antifungal therapy

MOLECULAR VIROLOGY AND VIRAL PATHOGENESIS

Angela Amedee, Ph.D. **[aamede@lsuhsc.edu; 568-5608; MEB 6254]**

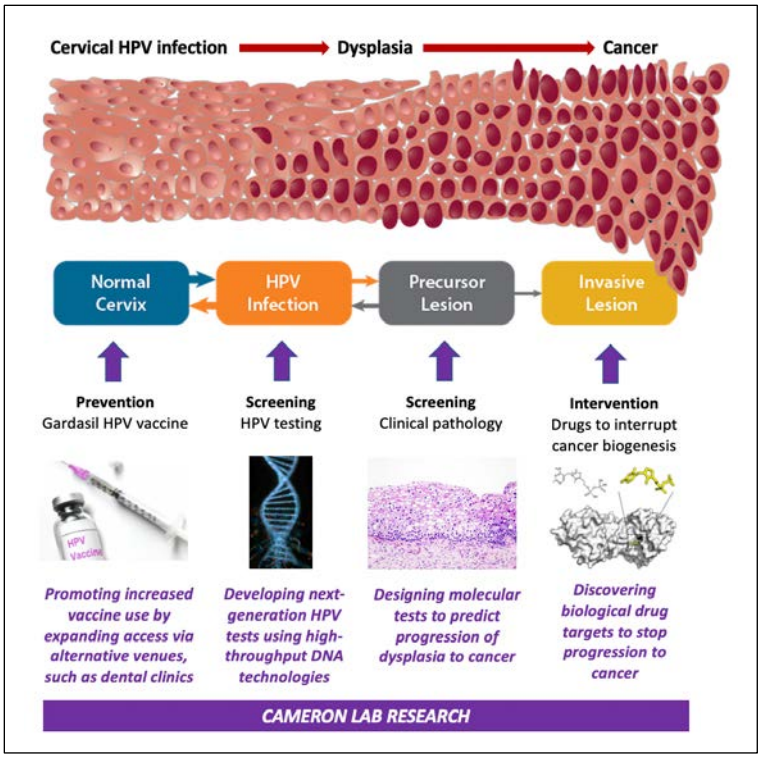
The Amedee laboratory investigates the pathogenesis of Human Immunodeficiency Virus (HIV), with a focus on the viral and host factors responsible for transmission. The laboratory conducts animal model studies utilizing the nonhuman primate model of HIV disease, as well as clinical translational studies in HIV-infected populations and cell culture models of HIV infection. One area of research in the laboratory involves collaborative projects with scientist from the LSUHSC Alcohol and Drug Abuse Center of Excellence to investigate the effects of alcohol consumption and drug abuse on HIV transmission and pathogenesis. Many of these studies are done with macaques infected with Simian Immunodeficiency Virus (SIV) and are designed to identify the mechanisms responsible for sexual transmission and viral shedding mechanisms responsible for sexual transmission and



HIV color-enhanced electron microscope image. (Oliver Meckes and Gelderblom/Art Resource, New York).

viral shedding in the genital mucosa. Parallel studies in clinical populations are also ongoing. Other studies in the laboratory investigate the mechanisms involved in mother-to-infant transmission of HIV and the establishment and maintenance of viral reservoirs in women. This work focuses on the selection and evolution of viral genotypes in the infant, as well as viral reservoirs, viral expression, and pathogenesis in females, using both clinical and animal model studies. The Amedee laboratory also has ongoing collaborative projects with other LSUHSC faculty that investigate the interaction of sexually-transmitted diseases with HIV. These studies are designed to decipher the dynamics of HIV replication and genital shedding, as well as susceptibility to HIV infection in the presence of co-infections using both clinical and *in vitro* cell culture studies.

Jennifer E. Cameron, Ph.D **[jcame2@lsuhsc.edu; 568-2196; MEB 6243]**



It is estimated that at least 10% of cancers worldwide are caused by infections with 'tumor viruses'. One of the most common tumor viruses is human papillomavirus (HPV), which causes cervical cancer in women as well as anal cancers and some oral and throat cancers in both men and women. We seek to understand the underlying molecular biology of HPV cancer biogenesis so that we can apply that knowledge to improve cancer prevention strategies. For example, our work has recently focused on the expression patterns of tiny regulatory molecules known as microRNAs that can differentiate aggressive from benign dysplasia, the precursor to HPV cancer. Additionally, our work has revealed compelling clinical evidence that when two tumor viruses - HPV and Epstein-Barr virus (EBV) - share a biological niche, they may coordinately promote dysplasia development. Therefore, we are interested in unraveling the biological consequences of HPV-EBV co- infection to reveal key aspects of cancer biogenesis that can be exploited for effective medical intervention. The Cameron lab employs cutting-edge genomic technologies to investigate these and other clinically important questions in specimens donated by patients with HPV infection.

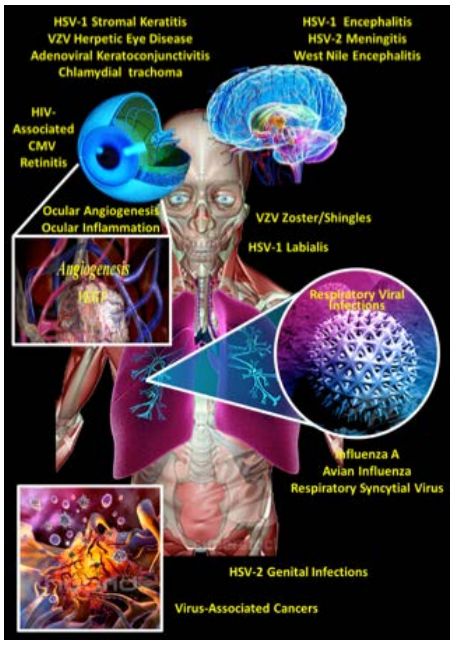
In response to the emergence of SARS coronavirus type 2, Dr. Cameron's lab has participated in research to characterize the innate and adaptive immune responses important for protection against COVID-19 morbidity and mortality. The lab is also evaluating protease inhibitor compounds that interfere with SARS-CoV-2 replication by blocking the activity of the two viral proteases. Promising compounds will enter the developmental pipeline as potential antiviral therapies for COVID-19.

Timothy Foster, Ph.D. **[tfoste@lsuhsc.edu; 568-4075; MEB 6259 (6A1)]**

The Foster lab investigates cellular and molecular virus-host interactions that can be utilized to simultaneously inhibit pathogen replication and suppress deleterious host-mediated inflammatory responses, especially within the eye. To ensure visual clarity and acuity, the eye is normally maintained as an avascular immunologically privileged organ. However, infection of the ocular surface by common viral or bacterial

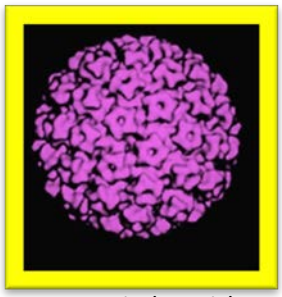
pathogens can result in vision-threatening vascularization and host-mediated inflammatory responses that cannot be resolved by current anti-pathogen treatment regimens. Through our studies, we have developed targeted therapeutics that modulate host metabolic pathways that are required for both pathogen replication and induction of inflammation-associated disease sequelae (US patent applications 61/664,464, 13/828,669, & 14/039909 and international patent application PCT/US13/31623 by Foster *et al*.).

These approaches are unlike current drugs in that: 1) Disruption of these pathways prevents replication of a broad range of intracellular pathogens, including most viruses and some bacteria such as *Chlamydia*; 2) Targeting of host pathways, rather than pathogen-specific mechanisms, constrains development of drug resistance; 3) They can be used for treatment of current drug resistant pathogens; 4) They block formation of vision-threatening host-mediated sequelae by modulating inflammatory responses; 5) They inhibit pathological vascularization, a current area of intense research for ophthalmic, as well as for anti-cancer therapeutics; 6) They promote healing of traumatic wounds induced either surgically or through pathogen replication. Therefore, our lab's efforts have broad reaching implications that go far beyond exploring a single pathogen or disease presentation. Consequently, we employ a broad range of cellular and molecular techniques, as well as animal models in order to discern therapeutic efficacy of a drug and its potential mechanisms of action.



Virus and Inflammation-Associated Disease Processes Targeted by Metabolic Therapeutics in Development.

Michael Hagensee, M.D., Ph.D. **[mhagen@lsuhsc.edu; 210-3324; LCRC 708]**



HPV viral particle

The Hagensee laboratory studies the role of human papillomavirus (HPV) in human malignancies. Studies are focused on the increase in HPV-related cervical cancer in HIV+ women and the increase in oral cancer in HIV+ men and women.

A new area of focus is the role of HPV in anal cancer from basic biology to clinical trials and similar increases in anal cancer rates in HIV+ individuals. This increase may be due, in part, to an interaction with another DNA virus, Epstein Barr Virus (EBV) which also causes human cancers. Current projects include detection of HPV and EBV in clinical specimens, determination of the systemic and local immune response against each virus, in-vitro modeling techniques and development of xenograft mouse models. Results from these studies will aid in improved diagnostics and preventive measures for these cancers. Additional projects include development of self-testing methods to detect HPV DNA to improve cervical cancer screening and studies into improvement of HPV vaccine implementation. More recently, we have started to explore the serological response to SARS-COV-2 namely detection of serum antibodies against COVID-19, how long do they last after natural infection or vaccination and responses to the new variants of COVID-19.

Francesca Peruzzi, Ph.D. **[fperuz@lsuhsc.edu; 210-2978; LCRC 606]**

People living with HIV (PLWH) are at high risk of developing cancer. Although combined antiretroviral therapy (cART) reduces the viral load and increases the life span of these patients, it does not fully restore the fitness of immune cells, sensitizing them to secondary infections and other pathologies, including cancer. Recent studies indicate the presence of specific epigenetic changes in monocytes of PLWH that are associated with

dysfunctional immune responses observed in these cells. While analyses of epigenetic changes of innate immune cells of HIV$^+$ individuals could reveal novel mechanisms underlying cancer development and/or progression, this area of research requires further investigation.

Our experimental model involves isolation of CD14$^+$ monocytes from HIV$^+$ patients and healthy age- matched controls and the *in vitro* analysis of these cells following their polarization toward a pro-inflammatory (M1-like) macrophage phenotype, defined as monocyte-derived macrophages (MDMs). When exposed to environmental signals, such as β-glucan or lipopolysaccharide (LPS) endotoxins, normal monocytes will execute two types of innate programming called "trained immunity" and "tolerance" characterized by either hyper-responsiveness or hypo-responsiveness to secondary stimuli, respectively. Our data show that this delicate balance between trained immunity and tolerance is defective in monocytes of HIV$^+$ individuals. Our current project investigates the molecular mechanisms linking epigenetic modifications underlying a dysfunctional immune response to the susceptibility to cancer development in HIV$^+$ individuals with low or undetectable viral load.

DEPARTMENT OF MICROBIOLOGY, IMMUNOLOGY, & PARASITOLOGY
CURRENT (AND RECENT) GRADUATE STUDENTS (*alphabetically by mentor)*

AMEDEE LAB:

James Prusak (graduated MS May, 2021)

James investigated the impact of alcohol abuse on HIV pathogenesis and disease utilizing the SIV-infected rhesus macaque model, monitoring the development of drug resistant virus in animals receiving three-drug combination antiretroviral therapy. His project also involved characterizing the replicative capacity of virus in tissue reservoirs through the use of an *ex vivo* quantitative viral outgrowth assay. These issues are of importance for control and treatment of HIV infection and associated comorbidities

CAMERON LAB:

Ashley Winters

Ashley's PhD project is focused on miRNAs as biomarkers for identifying women who will advance from low grade cervical intraepithelial neoplasia (LG-CIN) to high grade cervical intraepithelial neoplasia (LG-CIN). Her project uses RNA extracted from biopsy samples from patients who have progressed from LG-CIN to HG-CIN, or from control samples, to identify dysregulated miRNAs and their target transcripts using several approaches including bioinformatics. Her work is part of an overall lab focus aimed at the development of a clinical test, currently lacking, that predicts the prognosis of LG-CIN and which could obviate the need for medical observation and indicate treatment intervention for women at risk of progression to HG-CIN and cancer.

FOSTER LAB:

Diana Battaglia (graduated PhD May, 2021)

Diana's project focused on evaluation of the efficacy of two novel therapeutics against ocular herpetic infections. Ocular herpetic infections are the leading cause of infectious blindness and over 90% of the US population is infected with some type of herpes virus. Currently available therapeutics do not treat all aspects of the disease. The Foster lab is currently developing and evaluating two novel classes of therapeutics that function through modulating the metabolism of arginine and serotonin. In order to determine if these new therapies are superior to those currently available, Diana tested their antiviral, antiangiogenic, and anti-inflammatory properties, utilizing both *ex vivo* and *in vitro* models that have provided promising results. The

lab is testing these therapies using *in vivo* models of chronic inflammation- and vascularization-associated disease.

Nazary Nebeluk (graduated PhD December, 2020)
Nazary, a recent MD/PhD student in the Department, evaluated a novel therapeutic that modulates host cell arginine metabolism as a treatment for viral infection and disease. Developed in the Foster lab, this approach has the potential to prevent viral replication and spread, as well as damaging inflammation-mediated disease sequelae. Nazary demonstrated that, unlike current antiviral therapeutics specific to a single pathogen, this agent has broad antiviral activity against a number of human viral pathogens, and began to elucidate its mechanisms of action. The lab will utilize these findings to help understand the role of host metabolic pathways in viral replication and viral-induced disease in order to identify new targets and develop new therapeutics.

JOHNSTON LAB:

Lyndsey Nash Gisclair
Lyndsey's PhD project is focused on evaluating endothelial cell responses to infection with the parasite *Trypanosoma cruzi*, the causative agent of Chagas' Disease. About 30% of infected individuals will develop severe life-threatening cardiomyopathy as a result of excessive inflammation and fibrosis. While the roles of fibroblasts and cardiomyocytes are well studied, the contributions of infected endothelial cells to cardiac remodeling remain largely undefined. *In vitro*, infected cardiac endothelial cells respond to infection by undergoing endothelial-to-mesenchymal transition, where these cells lose their endothelial phenotype and become pro-fibrotic. Lyndsey's project will include the development of a novel 3D multicellular cardiac coculture model to more accurately characterize the endothelial response to *T. cruzi* infection and to help identify endothelial dysfunction that may inform potential therapies for the treatment and/or prevention of Chagas' Disease.

KELLY LAB:

Kourtni Goutierrez (graduated MS May, 2021)
Kourtni's Masters project involved CRISPR-based approaches to the study of essential genes in the parasite *Leishmania*, using this approach to better understand the important molecular functions of the *Leishmania* molecular scaffold protein, LACK. Kourtni also investigated new ways to apply CRISPR technology in *Leishmania* and is currently developing a multi-round CRISPR targeting strategy for sequential gene-targeting and gene-tagging.

Isabel Stephany-Brassesco
Isabel's PhD project is focused on identification of RACK1-proximal proteins in parasitic trypanosomatids and the importance of rsp17 in ribosome LACK interactions and LACK function. This work is a key component of the lab emphasis on molecular understanding of the function and regulation of trypanosomatid protein pathways towards improved drug therapies.

KOZLOWSKI LAB:

Justin Smith
Justin's PhD project is focused on evaluating potential effector functions of IgA from rhesus macaques immunized with newly developed trimeric HIV envelope proteins. IgA antibodies in this species are not well characterized and it remains unclear if they can efficiently neutralize virus or mediate Fc-dependent antiviral effector functions. He will compare HIV neutralization by IgG and IgA from these animals and evaluate Fc-mediated IgA functions, such as phagocytosis and antibody-dependent cellular cytotoxicity using monocytes and neutrophils from macaques and humans to determine if human cells can be used to effectively measure

macaque IgA effector functions. These studies will inform development of new methods for measuring functions of IgA antibodies generated by HIV vaccine candidates and their correlation with protection.

PERUZZI LAB:

Celeste Faia
Celeste's PhD project is an investigation of dysregulation of microRNAs (miRNAs) in both innate myeloid immune cells and in circulating exosomes. The incidence of both AIDS- and non-AIDS-associated malignancies is highly prevalent in the infected population compared to uninfected individuals. This increased susceptibility for developing cancer may be attributed to continued immune dysfunction in patients on anti-retroviral therapy (ART), the underlying molecular mechanisms of which are largely undefined. Celeste's hypothesis is that primary monocytes and macrophages of HIV-infected individuals exhibit a dysfunctional phenotype caused by both the transcriptional dysregulation of cellular miRNAs and the post-transcriptional dysregulation of genes targeted by miRNAs in circulating exosomes.

QUAYLE LAB:

Caleb Ardizzone
Caleb's PhD project is focused on eludicating protective immunity to *Chlamydia trachomatis* in the female genital tract, and the factors that compromise this. Specifically, he is: determining the functional capacity of antibodies of different isotypes and specificities to inhibit *Chlamydia trachomatis* infection, (ii) identifying, growing and using relevant clinical isolates *Chlamydia trachomatis* in our *in vitro* models, and (iii) investigating the role of a dysregulated vaginal microbiome (bacterial vaginosis) in instances where *Chlamydia trachomatis* is able to evade clearance by the local immune response. He works extensively with the LSU Crescent Care Sexual Health Clinic for these clinical studies.

RAMSAY LAB:

Jared Sheehan
Jared's PhD project is focused on characterizing the development and decay of both binding isotypes and functional (virus-neutralizing) antibody responses against SARS-CoV-2 over time, both in sera from subjects given the COVID-19 mRNA vaccine and in convalescent sera from patients who were infected with SARS-COV-2. He is also characterizing early immune responses, in particular innate lymphoid cell (ILC) responses, in mice given different recombinant vaccine vectors - including adenovirus, fowlpoxvirus, and modified vaccinia Ankara strain (MVA) – with a view to selecting the most appropriate vaccine vector for subsequent vaccination studies in a mouse model of SARS-CoV-2 infection. These involve evaluation of ILC responses, adaptive immune responses, and protective efficacy following vector/protein-based heterologous prime-boost vaccination.

TAYLOR LAB:

Jacob Elnaggar
Jacob is an MD/PhD student working on assessment of the vaginal microbiome through the use of 16S rRNA sequencing, shotgun metagenomic sequencing, and qPCR assays. Sexually transmitted infections alter the vaginal community in women, and understanding their pathogenesis and interactions with the commensal microbiome is crucial in order to develop more effective treatments. Jacob is developing informatics methods to analyze and visualize the microbial composition of vaginal samples over time using both sequencing methodologies and qPCR assays to obtain better assessments of the abundances of microbial organisms. These methods will help to shed light on the complex interactions between microbial organisms in the reproductive tract and various sexually transmitted infections including chlamydia and bacterial vaginosis.

WANG, G LAB:

Dianne Wellems
Dianne's PhD project concerns elucidation of the role of cystic fibrosis transmembrane conductance regulator (CFTR) in myeloid cells in cystic fibrosis (CF). The aims of her project are to determine how CFTR deletion in myeloid cell lineages affects host resolution of inflammation and/or host lung defense against infection, and to characterize the response of *Pseudomonas* to CF neutrophil phagocytosis.

Callie Scull
Callie's PhD is concerned with how the function of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in innate immune cells affects the intestinal microbiota, a potential mechanism underlying cystic fibrosis (CF) intestinal disease that clinically manifests as intestinal infection, inflammation, and obstruction. She is also testing CRISPR/Cas9-mediated gene correction to rectify the intestinal disease.

XIN LAB:

Abby Adams (graduated PhD May, 2021)
Abby's project focused on evaluation of the protective efficacy of peptides derived from the *C. albicans* cell wall proteins fructose bisphosphate aldolase (Fba) and methionine synthase (Met6), and underlying immune mechanisms, in a murine model of disseminated candidiasis. Her work showed that vaccination with these peptides reduced fungal burden, increased survival, and generated robust humoral responses, while she also demonstrated the necessity of complement for vaccine-based protection, and the ability of vaccine-induced antibodies to increase phagocytosis. This project is a key part of work ongoing in the Xin lab, with the goal of establishing an effective and mechanistically defined preventive against disseminated candidiasis for which there are no immunoprophylactics currently available.

Jonothan Colon
Jonothan's PhD project concerns the development of immunotherapeutic strategies to protect the host from multidrug-resistant *Candida auris* infection. The specific aims of his project are to evaluate, using established mouse models: (i) currently available multi-peptide vaccines as a novel immunotherapeutic for invasive *C. auris* infection, and (ii) a panel of peptide-related monoclonal antibodies as a passive vaccination strategy against invasive *C. auris* infection.

FIRST YEAR GRADUATE STUDENTS:

Samantha Demers and **Thomas Galbato** entered the MIP graduate program in August 2021. They are scheduled to begin full-time PhD research in a MIP lab in the summer of 2021 following three laboratory rotations.