

2019 School of Medicine Research Round-up

To demonstrate the breadth of exceptional research done in the UNC School of Medicine, this inaugural publication is a compilation of the most noteworthy 1-2 research highlights provided by each Department over the past year.

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Department of Allied Health Sciences

Dr. Antoine Bailliard, Associate Professor in the Division of Occupational Science and Occupational Therapy, has received funding from the Los Angeles County Department of Mental Health through a subcontract with the University of California Los Angeles (UCLA) to design a specialized outreach team that will serve the most vulnerable homeless individuals with severe psychiatric disability across Los Angeles County. Dr. Bailliard joins Dr. Gary Cuddeback from UNC-CH's School of Social Work, and an interdisciplinary team at UCLA led by Dr. Elizabeth Bromley, to perform collaborative community-based research that will generate a description of the target population. The team will then build referral and triage tools to train outreach workers to identify and engage with the target population. Project deliverables include developing and piloting a Homeless Outreach Behavioral Screen, a Manual for Specialized Homeless Outreach and Mobile Engagement (HOME) teams, and training modules for the outreach teams.

Dr. Michael Lewek, Associate Professor in the Division of Physical Therapy, received funding from the NIH to identify a new approach for fall prevention. Individuals recovering from a stroke often experience injurious falls due to a stumble, or trip, while walking. Current fall prevention approaches teach reactive responses to a trip, or work to minimize the impairments associated with falls (e.g., strength, balance, range of movement). We are working towards a proactive, integrated, feed-forward control system to appropriately intervene, only when necessary. We are developing a novel monitoring system, that can accurately and reliably *predict*, in real-time, that a trip is about to occur. This work promises to have a tremendous impact on the field of walking recovery post-stroke and for other populations at-risk for trip-related falls. Successful completion of this project will establish a paradigm shift from reactive fall prevention to proactive trip and fall prevention.

Department of Anesthesiology

In the past year, Faculty in the Department of Anesthesiology published insights into the question, "Why are posttraumatic stress and pain more common in women"? Women have an additional X chromosome compared to men (XX vs XY), and in each cell of the body one of these X chromosomes is "turned off". However, studies have shown that a small fraction of the genes on the "turned off" X chromosome can "escape" inactivation. **Dr. Sarah Linnstaedt** and colleagues found that in women a much higher percentage of genes expressed from the X chromosomes were associated with posttraumatic stress and pain development than would be expected by chance. In addition, these genes were all more highly expressed in women than men, suggesting that genes "escaping" X chromosome inactivation may help account for the greater vulnerability of women to posttraumatic stress and pain. [Yu et al. Sept 2019](#)

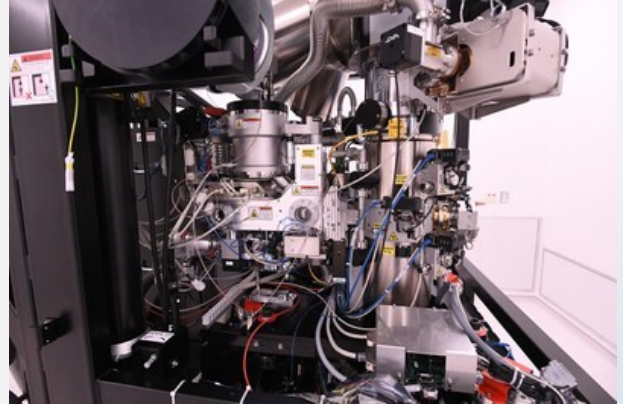
Department of Biochemistry and Biophysics

The laboratory directed by **Dr. Greg Wang**, Associate Professor of Department of Biochemistry and Biophysics and Lineberger Comprehensive Cancer Center, recently identified a gene termed PHF19 to be critically involved in the development of multiple myeloma, a malignant disease derived from plasma cells, and also provided proof-of-principle evidence supporting pharmacological targeting of this pathway for therapeutics of this common hematological cancer.



[These findings were recently published in BLOOD](#). Dr. Wang's team demonstrated the dependence of various myeloma models on PHF19 protein in malignant progression of the disease. They characterized the PHF19-dependent transcriptional programs in myeloma cells, and most importantly, provided evidence to show that PHF19 acts through Polycomb Repressive Complex 2 (PRC2) hyperactivation in tumorigenesis of myeloma. PRC2 can be druggable by a small-molecule inhibitor, UNC1999, initially developed at UNC. These results show early promise for PRC2 blockade as a new therapeutics of myeloma in the laboratory models.

UNC-CH opened a cryo-electron microscope (cryo-EM) core facility led by **Joshua Strauss PhD**, Assistant Professor. [In May 2019 UNC-CH acquired a cryo-EM](#) that uses accelerated electrons as a source of illumination. Electron microscopy enables researchers to obtain images of specimens at molecular resolution which makes it possible to design higher affinity drugs for the treatment of cancers and many other diseases. Atomic models of human proteins associated with genetic disorders will provide new structural information that researchers can use to gain a deeper understanding of the molecular basis of human diseases and the development of more accurate molecular diagnostic approaches. "CryoEM has profound implications for basic biomedical science research and our understanding of macromolecular structures," Joshua Strauss said. "Several applications have a direct impact on human health and medicine." The University collaborates with the Duke University and the National Institute for Environmental Health Science cryoEM facilities as part of the Molecular Microscopy Consortium.



Department of Biomedical Engineering

In 2019, **Dr. Rahima Benhabbour**, Assistant Professor in the UNC/NC State Joint BME Department and an Adjunct Professor at the UNC Eshelman School of Pharmacy published work in Nature Communications on an ultra-long-acting tunable, biodegradable, and removable polymer-based implant that offers sustained drug delivery for up to one year for HIV treatment or prophylaxis. This study tested six antiretroviral drugs, and all kept their physical and chemical properties within the formulation and upon release. To quote Dr. Benhabbour: "To have an HIV prevention treatment that consists of an injection once or twice a year would make an incredible impact for patients." She adds, "This technology is not only promising for HIV, but for any kind of condition that requires a daily intake of medication. We're talking about a safe, removable, long-lasting injection that takes away the burden of adhering to a daily medication regimen."

BME Assistant Professor **Dr. Jason Franz's** group (the Applied Biomechanics Laboratory) recently published work in the Journal of Neuroengineering and Rehabilitation on the clinical utility of virtual reality as a training tool to enhance waking balance integrity in older adults. According to Dr. Franz "Older adults rely more on vision for balance than otherwise healthy younger people. Our group uses VR to essentially 'trick' the brain into thinking you're experiencing a fall while walking (through visual perception). Given older adults' susceptibility to that virtual instability, we asked whether a similar paradigm be used to increase balance confidence and reactive balance control." Subjects participated in a protocol that included 10 minutes of treadmill walking with (experimental session) and without (control session) optical flow perturbations.

Outcomes are promising, prolonged exposure to optical flow perturbations is found a useful training tool for corrective motor adjustments relevant to walking balance integrity in older adults.

Department of Cell Biology and Physiology

Department of Cell Biology and Physiology neuroscientists identify cellular templates for cerebral cortex development. Dr. Mark Zylka and Dr. Eva Anton, Professors of Cell Biology and Physiology in the UNC Neuroscience Center, performed single-cell transcriptome analysis of the cerebral cortex at key developmental time points to identify distinct cortical layer-specific cell types. Their paper, [published in *Nature Communications*](#), examined spatial and temporal expression patterns of hallmark genes and revealed cellular subtypes that associate with clinical phenotypes. Their study demonstrated how genetic and environmental factors affect cell composition, cell states, and cell fates during early mouse brain development and suggest that disease-linked gene mutations might form robust groupings based on their cell-type- and age-specific expression profiles. This work by Dr. Zylka and Dr. Anton suggests that expression-based genetic subtyping could have prognostic power for brain diseases such as Autism Spectrum Disorders (ASD), Alzheimer's disease, and schizophrenia.

Cell Biology and Physiology researchers uncovering the dangers of e-cigarettes. Pioneering work published in the [American Journal of Physiology - Lung Cellular and Molecular Physiology](#) from the laboratory of Dr. Robert Tarran, Professor and member of the Cystic Fibrosis Center, describes cellular defects and signaling dysregulation resulting from inhalation of e-liquids during "vaping". The Tarran Lab found that chronic inflammation, cell stress and abnormal cell growth resulted from flavored e-cigarette alteration of cellular calcium responses. The long-term harmful effects on respiratory health, including lung cancer and chronic obstructive pulmonary disease (COPD), may take decades to uncover, but in collaboration with Dr. Kathleen Caron, Professor and Chair, an impact on fertility has already been shown in mice. Published in the [Journal of the Endocrine Society](#), Dr. Caron and Dr. Tarran report impaired embryo implantation and poor fetal health due to e-cigarette exposure resulting in reduced pregnancy.

Department of Dermatology

Dr. Christopher Sayed, Associate Professor of the UNC Department of Dermatology and Director of the Hidradenitis Suppurativa Clinic, published the first North American clinical management guidelines for hidradenitis suppurativa (HS) in 2019 in the *Journal of the American Academy of Dermatology*. Dr. Sayed led a group of international experts in the United States and Canada, including Dr. Craig Burkhart of the UNC Department of Dermatology, in developing and publishing the guidelines. A comprehensive review of the available medical literature informed recommendations on diagnosis, disease assessment, comorbidity screening and medical and procedural management. These guidelines will widely impact dermatologists, surgeons and other physicians caring for patients with this common and devastating disease and inform future research efforts.

Department of Emergency Medicine

The Department has had a productive year, publishing over 50 peer-reviewed manuscripts and receiving its first three R01s awarded to **Drs. Michelle Meyer** and **Tim Platts-Mills**. With support from the National Institute of Justice, a multidisciplinary research team led by Dr. Platts-Mills completed a validation study of their elder abuse screening tool (the ED Senior AID tool). In the validation study, over 900 older adults were screened for elder abuse. The tool was found to be highly sensitive and specific for identifying elder abuse. Results will be presented at a national meeting this spring. The team is now partnering with The John A. Hartford Foundation to conduct an implementation study of the screening tool across five health care systems. Collaborators include Sheryl Zimmerman (UNC School of Social Work), Philip Sloane (UNC Family Medicine), Bryce Reeves (Duke Department of Population Health Sciences), and Sam McLean (UNC Department of Anesthesiology).

Department of Family Medicine

Sylvia Becker-Dreps, MD, MPH Associate Professor of Family Medicine published the study [“Effectiveness of prenatal tetanus, diphtheria, acellular pertussis vaccination in the prevention of infant pertussis in the US”](#) in the *American Journal of Preventive Medicine*.

Becker-Dreps and colleagues conducted a nationwide study, funded by the NIH-NIAID, of almost 700,000 mother-infant pairs using claims data to understand the benefits of prenatal Tdap vaccine. Infants of mothers who received prenatal Tdap experienced half the rate of pertussis as compared with infants of unimmunized mothers. They also examined the timing of Tdap vaccination, and results did not provide evidence to support changing the currently recommended timing of administration in pregnancy.



Family Medicine’s **Adam Goldstein, MD, MPH** was awarded a \$2.7 million R01 grant from NCI to investigate more effective health warnings for little cigars and cigarillos. There are few research studies on the topic, despite little cigars and cigarillos being the most popular cigar products, and his work will fill those gaps by studying which warning characteristics are the most influential in reducing use. He will also examine how additional policies such as removal of flavor descriptions could influence the impact of warnings. The study will provide evidence to policymakers on how such warnings impact user behavior. [Press Release](#)

Department of Genetics

Dr. Karen Mohlke, Professor of Genetics, led a multi-institutional team to examine the gene expression of adipose tissue, which is associated with increased cardiometabolic risk and mortality. Described [in an exciting paper in](#) *The American Journal of Human Genetics*, the team examined RNA-sequencing expression data from participants in the METabolic Syndrome in Men Study and identified and characterized genes that colocalize with genome-wide association study loci for BMI, cholesterol and triglyceride levels, waist-hip ratio, type 2 diabetes and other cardiometabolic traits.

Importantly, they were able to identify genes that show the strongest evidence of mediating the variant to trait associations by comparing gene expression level with cardiometabolic trait levels in the participants. Overall, the team identified hundreds of genes that may act in adipose tissue to influence cardiometabolic traits, indicating that these genes should be prioritized for future functional analysis.

As part of the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, **Dr. Patrick Sullivan**, Distinguished Professor of Genetics, and colleagues published [a breakthrough paper in *Nature Genetics*](#) that refines the basis of major depressive disorder – a common illness accompanied by considerable morbidity, mortality, costs, and heightened risk of suicide. The team conducted a genome-wide association meta-analysis based on over 400,000 studies and identified 44 independent and significant loci associated with clinical features of this disease. Furthermore, the genetic findings implicated brain regions exhibiting anatomical differences in many cases. Importantly, they also found that lower educational attainment and higher body mass were putatively causal factors related to the genetic risk for major depression whereas major depression and schizophrenia reflected a partly shared biological etiology. These findings have neurobiological clinical, and therapeutic relevance for major depression, and suggests that continuous measure of risk underlies the clinical phenotype.

Department of Medicine

John Buse MD PhD (Division Director for Endocrinology and Metabolism, Director of NC TraCS) is one of, if not “THE”, world experts in design, conduct and analysis of drug trials for diabetes. UNC celebrates Dr. Buse’s extraordinary leadership in bringing the GLP-1 drugs into global standard treatment regimens for people with diabetes. It is now fully accepted that GLP-1 use improves cardiovascular outcomes, as first shown in the LEADER study ([NEJM 10.1056/NEJMoa1901118](#)) led by Dr. Buse. Many related trials underlining this finding were also performed under Dr. Buse’s guidance. While it is difficult to select from a virtual tsunami of his 2019 publications guiding diabetes treatment, his 2019 *Lancet Diabetes and Endocrinology* paper “[Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes \(PIONEER 7\): a multicentre, open-label, randomised, phase 3a trial](#)” exemplifies the rapid progress being made in this field.

J. Victor Garcia, PhD continues to make substantial contributions in the understanding of HIV treatment and prophylaxis. His 2019 *Nature Communications* paper “[Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery](#)” nicely dovetails [a previous manuscript](#) also in *Nature Communication* describing the use of these ultra-long acting formulations for HIV treatment and prevention. As part of a team that also includes the laboratories of Drs. Benhabbour and Kovarova, an implantable system capable of delivering multiple anti-HIV drugs was developed. The polymer-based biodegradable, multi-drug delivery system allows flexibility in dosing to achieve target release kinetics and drug concentrations for up to one year. Translation of this formulation into humans promises to revolutionize delivery of complex drug regimens to at risk patient populations.

Department of Microbiology and Immunology

The emergence of antibiotic resistant bacteria is endangering the efficacy of antibiotics, which have transformed medicine and saved millions of lives. Therefore, combatting resistance by inhibiting its emergence or by re-sensitizing resistant strains is of major importance. Aminoglycosides are a major class of antibiotics that target the protein synthesis machinery in bacteria. Penetration of aminoglycosides into the bacterial cell is dependent on active respiration and bacteria can resist aminoglycoside antibiotics by entering a non-respiring state. **The Conlon laboratory** in the Department of Microbiology and Immunology has shown that [rhamnolipids, biosurfactant molecules produced by *Pseudomonas aeruginosa*, can alter the *Staphylococcus aureus* cell membrane](#), leading to induction of aminoglycoside uptake, even in a non-respiring bacterial cell. Rhamnolipids dramatically increase the potency of aminoglycosides, inhibit the rise of aminoglycoside resistant mutants, and re-sensitize aminoglycoside-resistant strains. These findings are of high impact because they demonstrate a new approach to combat antibiotic resistance.



Clostridioides difficile (commonly “*C. diff*”) causes life-threatening diarrhea and colitis and is considered an urgent antibiotic-resistance threat by the Centers for Disease Control and Prevention. *C. difficile* employs a strategy called “phase variation” to generate behaviorally and physiologically distinct subpopulations of bacteria within a genetically identical population. Research from **the Tamayo Laboratory** in the Department of Microbiology and Immunology [has identified a regulatory system, CmrRST](#), which undergoes phase variation through a genetic switch, generating subpopulations of *C. difficile* with distinct properties—including the ability to cause disease. This heterogeneity is poised to benefit *C. difficile* by balancing the need to produce factors necessary for survival in a host with changing environmental selective pressures against those factors, helping ensure the survival of the population as a whole. Recognition of the heterogeneous potential of a single strain of *C. difficile* may impact diagnostic, therapeutic, and prevention strategies for these infections.

Department of Nutrition

Barry H. Popkin, PhD, W. R. Kenan Jr. Distinguished Professor of Nutrition was the lead author of “[Dynamics of the double burden of malnutrition and the changing nutrition reality](#)”, the first paper in a 4-paper report published in *The Lancet* in December 2019. Popkin and his co-authors show that the double burden of high levels of both undernutrition and overweight occurs primarily in the lowest-income countries. The paper explores the trends behind the double burden of malnutrition, the societal and food system changes that may be causing it, its biological explanation and effects, and policy measures that may help address malnutrition in all its forms. The other three papers in The Lancet series build on the work of Popkin and his team, exploring the physiological impacts of the double burden of malnutrition and recommending “double-duty” interventions that simultaneously reduce the risk of nutritional deficiencies while preventing obesity and related diseases.

The Robert Wood Johnson Foundation’s Health Eating Research program recognized [NAPSACC](#) (Nutrition and Physical Activity Self-Assessment for Child Care) for having the “best evidence for

impact” on obesity prevention in young children in a brief published in March 2019. NAPSACC was developed by the [Children’s Healthy Weight Research Group](#), which is directed by **Dianne Ward, EdD**, Professor of Nutrition. NAPSACC is an evidence-based program with a proven track record of reducing childhood obesity risk by guiding child care providers through a five-step process to help them create environments that foster healthy eating and physical activity. The brief recommended that NAPSACC be incorporated into states’ existing Quality Rating and Improvement Systems as a way to maximize its reach, concluding that the program “shows the best evidence for impact on early childhood obesity risk among interventions specifically targeted to children under five.” Go NAPSACC currently is in use by 20 states and continues to expand.

Department of Neurology

A team led by **Tim Gershon, MD, PhD** and **Kirk Wilhelmsen, MD, PhD**, published the first study to use high-throughput single cell gene expression analysis to study how the diversity of cells within brain tumors allows tumors to overcome targeted therapy. This work, which will be published in *Nature Communications* with Gershon and Wilhelmsen as co-senior authors, showed that brain tumors include many different types of cells, and that while some of these cell types are treatment responsive, others are treatment resistant. The work makes a strong case for the idea that cancers contain cells resistant to specific treatments even before treatment starts, and that combinations of therapies will be needed to treat all of the different cell types within a brain tumor.

The journal “*The Scientist*” recognized **Todd Cohen, PhD**, as one of the eight “Rising Stars” in neuroscience for his research on neurodegenerative disease. His goal is to identify drugs that we could move into human clinical trials. In his lab at The University of North Carolina at Chapel Hill, he works to understand protein quality control in neurodegenerative diseases. Suppressing abnormal protein aggregation may be a promising avenue for age-related disease treatments. We want to understand neurodegeneration as a whole, so we study many of the proteins that cause brain cells to die, not just in Alzheimer’s disease but also muscle and motor disorders. The implications are obvious – if you understand the proteins mode of action, then you can find drugs and therapies for many different neurological diseases.

Department of Neurosurgery

The Department of Neurosurgery along with the fetal care program published 2 fetal myelomeningocele outcomes articles in *Neurosurgical Focus* this October highlighting the unique fetal care that we do at UNC alongside the department of Maternal Fetal Medicine. **Dr. Carolyn Quinsey** studied [Thirty-day Medical and Surgical Readmission Following Prenatal Versus Postnatal Myelomeningocele Repair](#) to determine readmission outcomes between these two groups and their etiologies. By looking at 24 prenatal and 34 postnatal myelomeningocele repair procedures, Dr. Quinsey concluded that patients with prenatal myelomeningocele repair had fewer hospital readmissions at 30 days, 60 days, and 1 year versus the postnatal repair group despite similar NICU lengths of stay.

The second paper examining fetal myelomeningocele outcomes was published by **Dr. Scott Elton**. Dr. Elton studied the [Cost of Prenatal Versus Postnatal Myelomeningocele Closure for Both Mother and Child at 1 Year of Life](#) by conducting a retrospective review of a database of patients undergoing

prenatal and postnatal myelomeningocele between 2011 and 2018 with 1-year follow-up. Dr. Elton ultimately concluded that the median cost of prenatal versus postnatal myelomeningocele closure did not significantly differ from a hospital perspective at 1 year, however considering the mother alone prenatal closure was costlier. Dr. Quinsey's and Dr. Elton's papers were both presented at the National Pediatric Neurosurgery Section Meeting and UNC remains a major center for fetal care and research on fetal myelomeningocele repair.

Department of Obstetrics and Gynecology

National Multi-Center Comparative Effectiveness Study on Treatment Options for Women with Symptomatic Uterine Fibroids: Hysterectomy and myomectomy are the two most common surgical options for uterine fibroids, but there are few studies comparing treatment effectiveness or provide comparisons across surgical approach, age or race/ethnicity. Led by **Wanda Nicholson, MD MPH MBA, Andrea Knittel, MD PhD**, Division of Obstetrics and Gynecology, and **Lauren Schiff, MD**, Division of Minimally Invasive Gynecologic Surgery, the **COM**paring Options for Management: **PA**tient-Centered **RE**sults for Uterine Fibroids (**COMPARE-UF**) study enrolled a diverse study cohort involving 3,094 women (45% were African American) to conduct comparative effectiveness research to assess fibroid-specific health-related quality of life (HRQOL) and symptom severity at 6-12 weeks and annually up to 3-years after surgery. Results of this work showed that substantial improvements in HRQOL and symptom severity scores were found in both the myomectomy and hysterectomy groups and across age and race/ethnicity.

OBGYN has received \$20 million in new funding from the Bill and Melinda Gates Foundation to develop technologies to make pregnancy safer. The **Fetal Age Machine Learning Initiative (FAMLI)** is developing a portable obstetric ultrasound for settings where expert sonographers are not available. We have partnered with Google to build computer vision AI models that can be deployed on a smart phone. Field testing will begin in mid 2020. The **LABOR Study** is leveraging new tools in wearable sensors and AI to make the intrapartum period safer. We are enrolling 15,000 pregnant women in Zambia, Ghana, and India and monitoring maternal and fetal physiology with wearables. These data – coupled with an exhaustive documentation of all diagnoses, interventions, and outcomes – will allow precision medicine experts at the School of Public Health to develop new models to risk-stratify women in labor and diagnose pregnancy complications before they occur.

Department of Ophthalmology

Glaucoma is the leading cause of irreversible blindness worldwide. The disease disproportionately affects people of West African descent. UNC Ophthalmology published the first glaucoma incidence study in a West African population in the journal *Ophthalmology* this year, which is our specialty's highest impact factor journal. Twelve hundred Ghanaians over age 40 were followed over 8 years and the incidence of new cases of glaucoma was 4.7%. When comparing this to similarly performed incidence studies throughout the world, we demonstrated that West Africans have the highest incidence of glaucoma globally. Concurrent with this study, we contributed the largest number of cases and controls of DNA samples to a glaucoma genetics study of people of African descent. This study, published in 2019 in the *Journal of the American Medical Association*, found a strong association with the gene that codes for amyloid- β A4, suggesting that glaucoma is a central nervous system disease.

Department of Orthopaedics

From the department of Orthopaedic Surgery **Drs. Carter Clement, MD, Paula Strassle PhD, and Robert Ostrum, MD** published an interesting paper looking at volume outcomes and their relationship to adverse events in the *Journal of Orthopaedic Trauma*. In the paper, [“Do Hospital or Surgeon Volume affect Outcomes after Surgical Management of Tibial Shaft Fractures?”](#) they used the New York SPARCS database and examined whether low volume orthopaedic surgeons or low volume hospitals had a greater incidence of complications versus high volume practitioners and institutions. After reviewing 9,147 patients the authors concluded that there was no difference in re-operation or adverse events when comparing large and small volume providers. They concluded that most surgeons and hospitals can effectively manage the typical tibia shaft fracture but stress that more complex injuries should be referred to higher volume surgeons for more complex care.

Anterior cruciate ligament (ACL) tears and ruptures are among the most severe knee injuries and many people undergo surgical intervention to reconstruct the ligament and stabilize the knee. However, there is limited information about the clinical epidemiology of these procedures. **Dr. Jeffrey Spang** and colleagues from the School of Global Public Health Dr. Herzog and Dr. Marshall address this gap in a paper titled [“Trends in Incidence of ACL Reconstruction and Concomitant Procedures Among Commercially Insured Individuals in the United States, 2002-2014”](#). They show that incidence rates of isolated ACL reconstruction and rates of concomitant meniscal surgery have increased, particularly among children and adolescents. A renewed focus on adoption of injury prevention programs is needed to mitigate these trends. Additionally, there is a need for research on long-term patient outcomes and postoperative health care utilization after ACL reconstruction, with a focus on understanding the sex disparity in concomitant meniscal surgery.

Department of Otolaryngology

The FDA approves cochlear implantation for single-sided deafness:

A cochlear implant is a surgically implanted device used to treat patients with moderate-to-severe hearing loss and poor speech perception in both ears. The UNC Cochlear Implant Clinical Research Lab recently conducted a clinical trial evaluating cochlear implantation for patients with single-sided deafness. Study participants had moderate-to-profound hearing loss in one ear, and in the other ear they had either normal hearing or mild-to-moderate hearing loss. The research question was whether a cochlear implant would help these patients perform better on tests evaluating spatial hearing and speech perception. Our data demonstrated that the cochlear implant supported significant improvements for sentence recognition in noise, sound source localization, and quality of life. Based on UNC’s data, the FDA approved the study device for use in adult and pediatric patients with unilateral and asymmetric hearing loss. Click [here](#) to read the full press release.



Participant performing a test of auditory localization

Demethylation as a potential therapy for HPV-associated head and neck cancer: Human papillomavirus-associated head and neck squamous cell carcinoma (HPV+ HNSCC) is the most frequently diagnosed HPV-associated cancer in the US. UNC’s Head and Neck Oncology Lab recently received funding from NIH NIDCR to study demethylation therapy as a potential treatment in HPV+ HNSCC using 5-azacytidine, an FDA approved agent used clinically to treat myelodysplastic syndromes and refractory cases of acute myelogenous leukemia. This agent works by reactivating

tumor suppressors and causing DNA damage. Experiments currently under way will determine mechanisms of 5-azacytidine toxicity that are specific to HPV-positive tumors, and investigate the use of 5-azacytidine alone or in combination with chemotherapeutic agents to suppress HPV-associated HNSCC metastasis and inhibit growth using xenografts. These studies will lay the groundwork for a new targeted therapy for HPV+ HNSCC, which is desperately needed to treat patients with recurrent or metastatic HPV+ HNSCC.

Department of Pathology and Laboratory Medicine

Our collaboration with the McAllister Heart institute has resulted in a long-standing history of impactful research in the molecular mechanisms of cardiac injurious stimuli, such as ischemic necrosis, hypertrophy secondary to hypertension, and diabetic cardiomyopathy, and the response to these injuries. To highlight our findings in molecular mechanisms of cardiac cell growth and morphology, **Dr. Li Qian**, Associate Professor, and colleagues used single-cell transcriptomics to determine the molecular factors involved in human cardiac reprogramming. [This article in *Cell Stem Cell*](#) also provides detailed datasets and rigorous analytical pipelines for predicting cell fate conversion. Also in 2019, **Dr. Jiandong Liu**, Associate Professor, found that Lin28a promotes pathological cardiac hypertrophic growth through Pck2-mediated anabolic synthesis. These findings were [published in *Circulation*](#).

To next highlight our advances in genetic determinants of cardiac disease, **Dr. Joan Taylor** and team conducted a novel genome-wide siRNA screen to identify modulators of calcium-induced necrosis in human muscle cells, and revealed multiple molecular circuitries involved in cardiomyocyte necrosis [in a publication in *ACS Pharmacology and Translational Science*](#). In June of this year, **Dr. Nobuyo Maeda** and colleagues identified the rate-limiting factor in reactive oxygen species production that potentiates diabetic cardiomyopathy. These findings can be found in *JCI insight* [here](#).

Department of Pediatrics

Drs. Charles Esther and **Marianne Muhlebach**, working with several UNC investigators and researchers from Australia, performed comprehensive analyses on lower-airway samples from young preschool children with cystic fibrosis and compared them to non-cystic fibrosis controls. At this early age, they determined that mucus in these children's lungs was elevated and often found in abnormal "flakes" that were highly resistant to commonly used therapies. Samples from these children were largely sterile by both standard and molecular based analyses, but showed high levels of inflammation when compared to controls. This inflammation, as well as levels of oxidative stress, correlated with total amounts of mucins and mucus "flakes". These findings suggest that early inflammatory processes and lung damage starts early in cystic fibrosis, before lower airway bacterial infection is established; and that novel treatments are needed to address abnormal mucus buildup and early inflammation in cystic fibrosis. ([PMID 30944166](#))

Dr. Toni Darville's group in Pediatric Infectious Diseases has made important strides in understanding which immune system responses are important for mediating resistance to infection/reinfection and which are associated with increased risk for progression/ascension of genital tract infections of chlamydia in women ([PMID 30820577](#) & [30784128](#)). These data indicate that an effective chlamydial vaccine must induce T cell immunity to be effective. This and previous work contributed to Dr. Darville's group being awarded a U19 earlier this year to fund the UNC-Chlamydial Vaccine Initiative (1U19AI144181-01). Darville and her collaborators will continue to advance our

understanding of Chlamydia infection and effective immune responses in order to help create a vaccine development pipeline. Despite public health efforts, chlamydia and several other sexually transmitted infections are still significant causes of morbidity in both developed and developing countries. Effective vaccines, especially for high-risk populations, would have tremendous public health impact.

Department of Pharmacology

Justin English, a postdoc in **Bryan Roth's** lab (and formerly a PHCO grad student in the **Dohlman lab**), has received nice press for his breakthrough development in the field of directed evolution, recently published in *Cell*. Whereas previous approaches have relied on bacteria or yeast expressions systems. Justin's method used a mammalian expression system to rapidly evolve single chain antibodies - which can be functionally expressed inside cells - that modulate the activity of serotonin and dopamine receptors. You can read more about this directed evolution method [here](#).

Kirsten Bryan was one of three winners of the Pagano award, given every year to LCCC postdocs: Kirsten, who is now a research Assistant Professor in the Department of Pharmacology, was recognized for her work on a study published in *Nature Medicine*. She helped lead the study while working as a postdoctoral fellow in the lab of UNC Lineberger's **Channing Der**, PhD, which detailed findings for a possible new therapeutic strategy for pancreatic cancer that involves blocking the cancer cells' energy source. The announcement about her receipt of the Pagano Award [can be found here](#). Kirsten's *Nature Medicine* publications has received significant recognition and has been featured by multiple venues, including [CBS](#) and [NBC](#).

Department of Physical Medicine and Rehabilitation

Systematic Review and Meta-Analysis Highlights Usefulness of Mind-body Therapies for Opioid-related Pain Management: PM&R faculty members **Susan Gaylord, PhD** and **Kim Faurot, PhD** participated in a multi-institution systematic review and meta-analysis on Mind-Body Therapies for Opioid-Treated Pain, recently published in *JAMA Internal Medicine*. Researchers evaluated the efficacy of meditation, hypnosis, relaxation, guided imagery, therapeutic suggestion and cognitive behavioral therapy for modulating pain and opioid use in 6000+ patients taking opioids for clinical pain. Overall, mind-body therapies were significantly associated with reduction in pain intensity and opioid dosing for painful health conditions, with moderate to large effect size improvements in pain outcomes for meditation, hypnosis, suggestion, and cognitive behavioral therapy. The study, published online in *JAMA Internal Medicine* on November 4, 2019 (Garland et al.) represents the first systematic evaluation of therapeutic benefits of mind-body therapies for opioid-treated clinical pain, highlighting their usefulness for opioid-related pain management and opioid-misuse reduction.

Department of Psychiatry

Brexanolone (Zulresso): *The FDA approval of the first drug developed to treat postpartum depression--brexanolone (Zulresso), an allosteric modulator of both synaptic and extra-synaptic GABA_A receptors, in March 2019. Dr. Samantha Meltzer-Brody, MD, MPH, was the academic principal investigator of the clinical trials. UNC's Perinatal Psychiatry Unit was the first and only site to initially administer the drug in the open label trial and participate in the full clinical trial program. An [integrated analysis](#) of results from the three double-blind, placebo-controlled trials of ZULRESSO was published in [The Lancet](#).* The GABA pathway may play a key role in regulating hormones

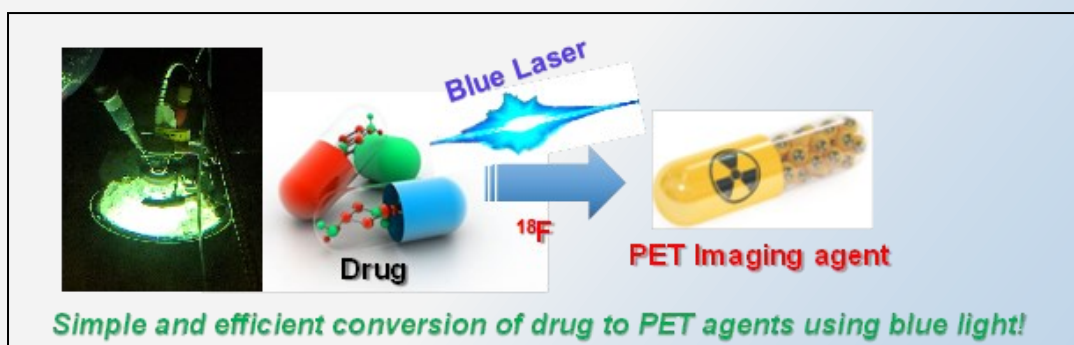
important in PPD. Since becoming commercially available in June 2019, ZULRESSO is available as an IV infusion across the US to patients under a Risk Evaluation and Mitigation Strategy in medically supervised settings that provide monitoring to mitigate risk from excessive sedation or sudden loss of consciousness.

Anorexia Nervosa GWAS Findings: *A large-scale genome-wide association study conducted by Dr. Cynthia Bulik, PhD and colleagues identified eight genetic variants significantly associated with anorexia nervosa (AN) and was published in [Nature Genetics](#) (July 2019). The study is the first to demonstrate that the origins of this disorder appear to be both metabolic and psychiatric.* Bulik and a multinational group of researchers combined data collected through collaborative consortium efforts. The data set included 16,992 anorexia nervosa cases and 55,525 controls of European ancestry from 17 countries. Other findings include: 1) the genetic basis of AN overlaps with other psychiatric disorders like obsessive-compulsive disorder, depression, anxiety, and schizophrenia; 2) genetic factors associated with AN also influence physical activity, which could help explain the tendency for people with AN to be highly active; 3) the genetic basis of AN overlaps with metabolic (including glycemic), lipid (fats), and anthropometric (body measurement) traits.

Department of Radiation Oncology

Dr. Bisham Chera and **Dr. Gaorav Gupta** in the Department of Radiation Oncology have co-invented a novel blood test that detects tumor-modified HPV DNA released from HPV positive head and neck cancers. By applying the blood test to patients enrolled in clinical trials at UNC-Lineberger, they have demonstrated high sensitivity and specificity of the blood test for identifying patients with HPV positive cancers. Their work also indicates that the blood test enables precise monitoring of treatment responses, which may help guide treatment decisions in future clinical trials. Finally, Drs. Chera, Gupta, and colleagues have demonstrated that the blood test can help physicians monitor patients after treatment completion—allowing for earlier detection of cancer recurrence than standard clinical followup. Collectively, these findings suggest that this blood test has the potential to improve clinical management and treatment outcomes for patients with HPV positive cancers.

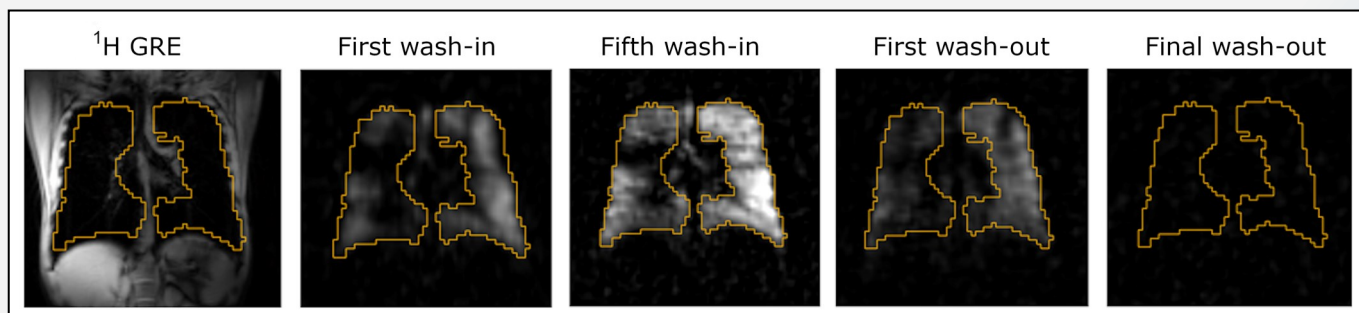
Department of Radiology



Positron emission tomography (PET) is a powerful and developing technology that plays key roles in medical imaging and drug discovery/development. Unfortunately, the availability of PET agents is limited in many situations due to the lack of efficient and simple labeling methods to modify biologically active small molecules/drugs. In this report, we discovered a mild method for the [^{18}F]-fluorination of aromatic C-H bonds using blue laser illumination. This is a collaboration between Li and Nicewicz labs, which represents an entirely new method for incorporation of [^{18}F]F into aromatic compounds using late stage radiolabeling. Mild conditions coupled with easy access to the required

precursors will allow for the unprecedented access to novel aromatic PET tracers of use in neurology, oncology, and other research areas, which will generate high impact in those fields. More on this work led by **Zibo Li, PhD** Associate Professor, Director of cyclotron and radiochemistry research program, can be found [here](#).

Cystic fibrosis is an inherited, life-threatening disease that causes severe damage to the lungs and digestive system beginning in infancy. Accurate assessments of lung function are needed by clinicians to evaluate disease progression, identify exacerbations in patients, and assess new therapies. A collaborative research effort by the Department of Radiology and the Marsico Lung Institute led by **Yueh Lee, MD, PhD** and **Jennifer Goralski, MD** have demonstrated that a novel MRI ventilation imaging approach offers high sensitivity to the respiratory changes in CF patients, adding a powerful tool for clinicians to more accurately evaluate patient's lung function. The technique utilizes an inert gas mixed with oxygen, and a fast 5 minute MRI scan to provide quantitative 3-D ventilation information across the lung. Ongoing work by the team will extend these efforts to younger subjects and for understanding other lung diseases.



Department of Social Medicine

Lauren Brinkley-Rubinstein, PhD, [Assistant Professor of Social Medicine](#) and core faculty in the [Center for Health Equity Research](#), was first author on a [study](#) analyzing the health effects of solitary confinement. Solitary confinement during incarceration is associated with poor health outcomes, but little is known about its association with mortality. Dr. Brinkley-Rubinstein and her coauthors conducted a retrospective cohort study that included 229,274 individuals who were incarcerated and released from the North Carolina prison system from January 2000 to December 2015. Individuals who spent any time in solitary confinement were more likely to die in the first year after release (especially from suicide and homicide), to die of an opioid overdose in the first 2 weeks after release, or become re-incarcerated. These findings suggest that solitary confinement is associated with an increased risk of death during community reentry, and indicate a need to find alternatives to its use.

Department of Surgery

Researchers develop method for separating tissue types in tumor samples: Jen Jen Yeh, MD, is a UNC Lineberger member, Professor and the Vice Chair for Research in the Department of Surgery. In the journal *Nature Communications*, her group reported a new computational method, DECODER, for separating the different compartments in a particular tumor sample – whether that is stroma, immune cells or cancer cells. DECODER can help understand the biology of the tumor and tumor micro environment. In the future, DECODER may be used to identify the cancer for a patient that has a cancer of unknown origin.

Pancreatic cancer tumor classification could optimize treatment choices: In the journal *Clinical Cancer Research*, a journal of the American Association for Cancer Research, researchers led by UNC Lineberger's **Jen Jen Yeh, MD** in the Department of Surgery, and Naim Rashid, PhD, in the Department of Biostatistics, reported findings for how two subtypes of pancreatic cancer respond to treatments differently. Importantly, they found that one subtype of the disease showed poor responses to common therapies, and also had worse survival. They are working to bring their classification algorithm, which they called PurlST, into a form that can be used in future clinical trials at the North Carolina Cancer Hospital, the University of Rochester and the Medical College of Wisconsin. Clinical trials will be needed to try to understand how the tumor subtypes can inform how patients respond to treatment.

Department of Urology

Earlier this year, the [Patient-Centered Outcomes Research Institute \(PCORI\)](#) Board of Governors approved \$8.5 million to fund research for the [Comparison of Intravesical Therapy and Surgery as Treatment Options for Bladder Cancer\(CISTO\)](#). [Dr. Angela Smith](#) of UNC Urology and [Dr. John Gore](#) of the University of Washington are co-Principal Investigators in partnership with the [Bladder Cancer Advocacy Network \(BCAN\)](#). The study compares bladder-removal surgery with a treatment that delivers therapeutic agents to the bladder to treat recurrent non-muscle invasive bladder cancer (NMIBC). The study will engage patients and ask about their experiences and outcomes following their treatment for NMIBC and analyze their reasons for picking a specific treatment option. In addition to BCAN, partners in this study include the [American Urological Association \(AUA\)](#), which will incorporate the results in educational materials and practice guidelines to ensure the results are utilized when informing patients about their treatment options.

Opioid prescribing guidelines result in fewer opioid prescriptions without compromising patient pain control. Recent studies have implicated surgical prescriptions as a contributor to the opioid crisis, prompting efforts to reduce post-operative opioid prescriptions. However, to allow for post-operative recovery, we must ensure adequate pain control. In collaboration with Drs. Peggy McNaull, Brooke Chidgey, and Nathan Woody from the Department of Anesthesia and Jami Mann from Pharmacy among others, our Department, [led by resident Kathryn Gessner, MD PhD](#), utilized patient opioid use data to develop procedure-specific evidence-based Standard Opioid Prescribing Schedules. Using these guidelines, patients were surveyed regarding opioid prescription amounts, usage amounts, pain interference, and patient satisfaction. We showed that implementation of these prescription guidelines decreased opioid prescription and use amounts without compromising patient satisfaction or pain control. These efforts have been presented at national meetings and received national media coverage, and are being disseminated throughout the UNC Healthcare system.