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*Primary human
brain microvascular
endothelial cells
infected with Rickettsia
parkeri. Bacteria
(green), nuclei (blue),
actin filaments (red).
Taken by Jennifer
Farner pg. 30*

FROM THE EDITORS

USU Science Review, a bi-annual student-led joint faculty and student publication, has two principal functions: to foster intellectual discourse in the Uniformed Services University community, and to provide students with opportunities to develop their writing and editing skills. This second issue highlights the broad scientific work of the University, ranging from molecular biology to neuroscience, infectious disease, and global health as well as interests within professional development and health and wellness. Our 2023 Editorial Team is already working hard to release our next issue Winter 2023. We welcome any inquiries, feedback, and interest to get involved at ususcienceview-ggg@usuhs.edu. We hope you enjoy and learn from the talented voices in this issue.

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History of the Field

Thousands of scientific research papers are published every year, shedding light on the latest discoveries and novel modes of thought in our fields. With our hyperfocus on the latest products of science, we should not lose appreciation for the seminal discoveries and evolution of ideas that led us to our current scientific landscape. These stories from faculty experts share a historical perspective, including timelines of discoveries with technological, political, and economic challenges, providing appreciable context and reminding us that our individual contributions continue to drive this collective undertaking of discovery.



Dr. Eric Elster

DEATH DOESN'T STOP TO REST

SC2i and the Transformation of
Military Precision Medicine and
Surgical Critical Care



I have always known that I wanted to be a physician and military officer, and by the time I was a teenager, I had set my sights on a career as a Navy surgeon. However, it wasn't until medical school that I was introduced to the concept of academic medicine and its power to make discoveries and advance care. One of my professors, a Navy veteran and a leading figure in plastic surgery, opened my eyes to the idea that surgery could encompass technical precision, superb clinical care, and scientific discovery. During my residency, a mentor modeled the role of a surgical scientist and helped me to develop the toolkit to be successful in that role.

Following my residency, I went on to complete a transplant fellowship with that same mentor, Dr. Allan Kirk. Under his guidance, we attempted to answer the basic biological questions behind transplantation and the host's response to this "unnatural" procedure. During my second fellowship year, I began caring for wounded warriors returning to Bethesda from Iraq and Afghanistan. Among the key injuries we treated were extremity

wounds that needed to be closed, either by bringing the skin back together or by placing a graft. We saw that despite solid clinical judgment and excellent technique, approximately 20% of these procedures would be unsuccessful - the wound would become infected, the skin edges would come apart, or the graft would fail. In other words, there was something happening that we could physically see.

My time caring for wounded warriors at Walter Reed (formerly National Naval Medical Center) deepened my understanding of trauma surgery. However, it wasn't until I deployed to Afghanistan in 2010 to serve as Chief of Surgery at the Kandahar Role 3 Hospital that I was able to treat catastrophic combat injuries at the point of injury. Our Role 3 surgical team performed over 3,000 procedures in six months, with a 97% patient survival rate. This was part of an extraordinary and still largely unknown accomplishment - the complete transformation of combat casualty care on the battlefields of Iraq and Afghanistan.

Combat medicine and surgery in Iraq and Afghanistan involved much more than clinical care, although clinical care and patient outcomes were our highest priorities. During Operation Enduring Freedom and Operation Iraqi Freedom, military physicians and surgeons improved standards of care through a rapid lessons learned process that allowed us to introduce over 25 major innovations in care in just over a decade. Working in austere battlefield conditions, these warrior-scientists advanced research and discovery, combining high-quality care with high-impact science to achieve the highest casualty survival rates in the history of warfare.

In one case, we treated a local Afghan national who had suffered a blast injury resulting in a high unilateral lower extremity amputation with associated injuries - a fairly typical but "sick" combat casualty. My orthopedic surgery partner and I performed serial debridements, but the patient still developed an invasive fungal infection (IFI) in his amputation site. These infections are very challenging to treat, requiring a combination of aggressive debridement / local therapy, systemic antifungals, and supportive care. Our debridements had ultimately resulted in a hip disarticulation, and extended into his retroperitoneum along the psoas muscle. Despite multiple operations, we had almost reached the point of futility. However, we persisted and after another operation, in which we essentially did the same thing, we finally got ahead of the infection. The patient improved rapidly - his white count decreased, his platelets came down (crude systemic biomarkers) and the infection cleared.

At that point the proverbial light bulb went off in my head - by relying on crude biomarkers, we had bought enough time for the patient's immune system to "reset," but we needed better tools. Cases such as these helped to inspire the idea of critical care research focused on patients' own biology. Thanks to my transplant fellowship, our experience

caring for casualties at Walter Reed, and my experience in Kandahar, I realized that the approach that worked in transplant medicine could successfully apply to combat wounds. By sampling the local and systemic environments in our patients, and pairing that evidence with clinical data, we could "look underneath the hood." With this vision in mind, I worked with a team to build a research program centered on clinical trials in which we sampled the wound tissue, serum, and wound effluent from negative pressure wound therapy systems (wound "vacs" used to manage these patients) and combined these data with our clinical outcomes. As we analyzed these data, we developed a hypothesis - that it wasn't merely the destructive physical nature of wounds that causes complications, but the body's response to these injuries. As a result of high-throughput multiplex assays, we could begin to measure this response; and by using early machine learning, we could begin to develop Clinical Decision Support Tools (CDSTs). These CDSTs would augment the decision-making ability of clinicians caring for complex cases by translating the "host's response" into actionable tools to guide care.

Although this initial work, which happened over a period of about five years, was very successful in terms of manuscripts, funding, and discovery, it wasn't until I came to USU as Chair of Surgery that I had the opportunity and the resources to scale our research in a way that could impact clinical care. The Surgical Critical Care Initiative, SC2i, was established in 2013 to develop biomarker-driven CDSTs to support clinicians treating critically ill patients. The CDST project is focused on wounded warriors and similarly injured patients and aims to improve outcomes and reduce costs throughout the surgical care continuum. Combining patients' biomarker and clinical data with advanced analytics (i.e., machine learning), we are developing "precision medicine" diagnoses for life-threatening surgical complications.

To date, the SC2i has enrolled over 2,000 patients with biospecimens, and over 63 million data elements are aggregated in SC2i's central data repository. These data elements powered the development of over a dozen CDSTs for conditions associated with high risk of morbidity and/or mortality, including venous thromboembolism, pneumonia, bacteremia, acute respiratory distress syndrome, and acute kidney injury. A few of these CDSTs are already in clinical use or clinical trials:

Invasive Fungal Infection (IFI):

Trauma-related IFIs can be devastating. During recent military conflicts, IFIs emerged as an infectious complication associated with high morbidity and mortality among severely injured military personnel. Deployed at WRN-MMC since 2016, the IFI CDST has been tested on 43 combat casualty patients with 100% sensitivity and 95% specificity, enabling a tailored approach to anti-fungal therapy.

WoundX:

Extremity wounds are the most common combat injury pattern. Improper timing of a clinical decision regarding wound closure can lead to dehiscence and failure (with clinical and resource implications stemming from repeat surgical interventions and longer lengths of stay). Currently, there is no diagnostic that can predict the optimal time for wound closure. The WoundX CDST has been shown to provide the surgeon with a patient-specific probability regarding normal wound healing post-closure. We are now beginning a prospective randomized clinical trial of the tool's capabilities – coming full circle to where the effort began.

Massive Transfusion Protocol (MTP):

Critically ill trauma patients, including those suffering from acute hemorrhage, present a challenge to clinicians in determining the need and timing for a massive blood transfusion (i.e., in cases where 50% of total blood volume is lost within three hours). SC2i's MTP CDST provides a risk profile based on injury type and blood loss, anticipates the onset of shock prior to clinical onset, and determines when to initiate a massive transfusion.

Artificial Intelligence Sepsis Expert (AISE)

Often deadly, sepsis is also the single most expensive medical condition in the US. Prompted by the lack of a gold standard diagnostic for predicting sepsis, the SC2i worked with its Emory University partner to develop the AIST, which predicts sepsis 6-12 hours prior to onset. AISE recently received both funding and approval to deploy into the 10 largest hospitals within the Military Health System (MHS).

In addition to material CDST product development, SC2i also has an active research/academic mission and has released over two dozen papers, some featured in prestigious academic journals (Annals of Surgery, Journal of the American College of Surgeons, Journal of Clinical Investigation). And although SC2i's science begins with a military focus, it has far-reaching implications for human health and civilian medical care. Just as the medevac and trauma response protocols developed during the Vietnam War continue to inform civilian trauma care today, SC2i's CDSTs have the potential to reduce costs by \$10B annually across the US healthcare system, not to mention save many lives.

A section of concrete wall is on display at Defense Health Agency headquarters. Once part of an aeromedical staging facility at Joint Base Balad, the wall is covered with messages handwritten by the wounded warriors who passed through the facility and the doctors and medics who cared for them. The most prominent message, signed simply "Combat Medics" reads "Because death doesn't stop to rest, neither do we." SC2i - and USU - are founded on the premise that the work of fighting disease and death never stops.

Dr. Eric Elster is a surgeon, scientist, author, retired Navy Captain, and Dean of the USU School of Medicine. He has held staff and leadership positions in military medicine, and served in clinical, teaching, and research roles at the National Institutes of Health, Walter Reed National Military Medical Center, and USU. As a Navy surgeon, Dr. Elster rotated through various deployments, including assignments as Ship's Surgeon aboard the *USS Kitty Hawk* and Attending Surgeon at Naval Hospital Yokosuka. In 2010, Dr. Elster deployed to Afghanistan to serve as Chief of Surgery at Kandahar's Role 3 Multinational Medical Unit. During his six months in Kandahar, the Role 3 surgical team performed over 3,000 procedures, with a 97% patient survival rate. As an author and researcher, Dr. Elster has authored or co-authored over 225 publications in peer-reviewed journals, covering topics including trauma surgery, transplant science, trauma and acute care, vascular surgery, and post-surgical infections. He is also a contributing author to 16 medical textbooks.

ANTIDEPRESSANTS

FROM TRICYCLICS TO KETAMINE AND BEYOND

DR. CAROLINE BROWNE

Major Depressive Disorder (MDD) is the leading cause of disability worldwide, impacting 5% of all adults. Without adequate access to care, many individuals develop comorbid mental health disorders, cardiovascular and metabolic disease, and have a lifetime risk of suicide as high as 20%. Although it is often described as a disease of modernity, the experience of depression is not new to *Homo sapiens* (1). In the 2nd millennium BCE, Mesopotamian scribes compiled the results of case studies relating to the Babylonian term for distress, *ašuštu*. This description, in which patients exhibited distress accompanied by insomnia, anorexia, weakness, poor memory, and

the inability to concentrate, would meet the criteria for MDD outlined in the current version of the Diagnostic and Statistics Manual (DSM-5). The Babylonians also recorded evidence of suicide among such cases, referring to a Sumerian term *zikur-rudû*, meaning “the cutting short of life” (2). For these individuals, treatment relied on appeasing the offended personal deity, or direct appeal to Shamash, the sun god and god of justice. Returning to prayer and devotion and the wearing of protective amulets were required to ward off the demons and mischievous spirits of the dead responsible for causing the distress in one’s life.



Later, in Ancient Rome (500-350 BCE), Alcmaeon of Croton and Hippocrates established the theory of Humorism. This theory proposed that four humors, haima (blood), xanthe chole (choler, or yellow bile), phlegma (phlegm), and melania chole (black bile), must always be in balance for optimal function of the human body. Circa 300 CE, Galen and others proposed the idea that an excess of melania chole was the mediator of brain disorders. The practice of bloodletting was widely implemented by physicians to remedy the imbalance of the humors, until the late 1800's. Of note, there was a rudimentary form of cognitive behavioral therapy, stoicism, which was pursued by contemporaries of Galen in the 3rd century CE. It wasn't until late 19th century CE that the practice of psychotherapy was widely implemented. At that time, immersion therapy, lobotomies, and electroshock therapy (ECT) were other common methods used to alleviate depression. To this day, ECT remains an effective treatment modality for individuals with intractable depression, resulting in similar molecular features evoked by newer classes of rapid acting antidepressants. At the beginning of the 20th century CE, a renowned clinical psychologist, Emil Kraepelin, led the field in ascribing diagnostic descriptors for mental health disorders. Endogenous psychoses observed in patients were subdivided into either "manic depression", encompassing both unipolar and bipolar depression, or "dementia praecox", later known as Schizophrenia. The clinical based descriptors laid the groundwork for psychiatric diagnostic criteria used today.

Until the 1930's, oral administration of *Tinctura Opii* was the only pharmacotherapy available for patients with depression. Effects of the tincture were modest at best and lethal when consumed in high quantities. As a therapeutic, opium was unsuccessful, though dysregulated en-

dogenous opioidergic tone remains a key feature of MDD as defined by recent imaging and postmortem studies (3). Modern pharmacotherapy emerged from studies conducted during the 1930's through the 1960's, where deficits in the levels of centrally circulating catecholamines (dopamine, norepinephrine, and epinephrine) and the monoamine neurotransmitter, serotonin, were implicated in the pathophysiology of MDD (4). One of the most dramatic demonstrations of the importance of monoamines in the regulation of mood followed the administration of reserpine, an alkaloid compound, initially proposed as an anti-hypertensive medication. Reserpine is a potent inhibitor of the vesicular monoamine transporter (VMAT), a membrane-bound protein that transports monoamines back into the cell, packaging these neurotransmitters into intraneuronal vesicles ready for release with the next depolarization. Administration of reserpine effectively depletes monoamine stores and induces marked depressive symptomology in human subjects (4).

Simultaneously, two serendipitous discoveries were made. In the late 1950's, New York City physicians administering the Roche anti-tubercular compound iproniazid noticed the "side effect" of euphoria, stimulation, increased appetite, and improved sleep. It was at this point that the term "antidepressant" was first used. Months following this report, a clinical study demonstrated robust "antidepressant" action of iproniazid in ~70% of subjects after several weeks of treatment. Iproniazid was soon shown to be an inhibitor of monoamine oxidase (MAO), supporting an emerging monoamine hypothesis of depression. In Sweden, the renowned psychiatrist Ronald Kuhn documented improved mood in patients with catatonia (a form of schizophrenia) with imipramine, a tricyclic or dibenzazepine compound.



Kuhn evaluated imipramine in over 500 patients, stating that overall “The patients express themselves as feeling much better, fatigue disappears, the feeling of heaviness in the limbs vanish, and the sense of oppression in the chest gives way to a feeling of relief”. Finally, two classes of antidepressant medications were available to the world, MAOI’s and Tricyclic Antidepressants (TCAs). Depression could now be cured!

Although TCAs and MAOIs are effective antidepressants, they are associated with significant adverse events. One commonly reported side effect was elevated blood pressure when patients consumed foods rich in tyramine - wine and cheese soirées were to be avoided. The emergence of second generation antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs), in the 1970’s overcame many of these side effects. The demonstrated efficacy of these newer classes of antidepressants throughout the 1990’s was simply astounding.

BASED ON PRE-1988 SUICIDE RATES, IT WAS ESTIMATED THAT BETWEEN THE PERIOD OF 1988 AND 2002, WHEN SSRIS SUCH AS FLUOXETINE (PROZAC) WERE FIRST RELEASED, OVER 33,600 LIVES WERE SAVED.

These compounds have changed the face of pharmacotherapy for multiple psychiatric disorders. With continued refinement, SSRIs are now used as first line medications for MDD, bulimia nervosa, panic disorder, premenstrual disorder, post-traumatic stress disorder, and obsessive compulsive disorder, and SNRIs are commonly used to treat chronic pain. Fluoxetine is included on the World Health Organization List of Essential Medications under three differ-

ent categories. It should be noted that despite the drawbacks associated with TCAs, amitriptyline remains on that list as one of the most efficacious compounds in the treatment of MDD (5).

Currently, there are over 100 approved antidepressants available on the market, the majority of which share a common mechanism of action, enhancing monoamine neurotransmission. The widespread sales pitch for these medications reinforced the concept that a deficit in monoamines was causal in MDD, as seen in the reserpine depletion studies, and propelled decades of drug development programs centered on augmenting central monoamine levels. Although based on valid evidence and the undisputed efficacy of antidepressants over placebo (5), the monoamine hypothesis of depression is limited. Moreover, treatment-resistant depression (TRD) in response to these medications is diagnosed in about 30% of patients. It is well known that while acute treatment with antidepressants immediately enhances neurotransmitter levels available at the synapse, it often takes weeks before the symptoms of depression lift. Throughout the 1990’s, this lag in therapeutic onset, motivated the field to explore other factors that were augmented with chronic treatment with antidepressants.

By the early 2000’s, the field accepted that chronic antidepressant treatment facilitated neurogenesis (the birth of new neurons), and enhanced levels of neurotrophins, including brain derived neurotrophic factor (BDNF), within key corticolimbic structures. Imaging studies in untreated patients during their first episode of depression and those with chronic intractable depression, revealed hippocampal volume loss in patients with MDD. Moreover, postmortem studies in suicide completers with a history of MDD demonstrated



decreased levels of BDNF and its receptor Tyrosine Receptor Kinase B (TrkB) (6). Studies in rodents suggest that enduring stress reduces the firing of neurons, leading to retraction of dendrites (the branched extensions of the neuronal cell), and morphological changes in synaptic buttons. Genetic and pharmacological blockade studies consistently show that reversal of these maladaptive changes in cellular morphology are required for antidepressant outcomes following treatment (6).

Coincident with these findings, the hypothesis of glutamatergic dysregulation in MDD was empirically verified by human imaging and postmortem studies (7). The exciting demonstration that the glutamatergic, dissociative anesthetic R,S-Ketamine alleviated TRD within hours following a single infusion captivated the field. Remission of symptoms was sustained for up to one week following a single treatment in many patients. This was simply astonishing, as the patients first screened for ketamine's antidepressant action were incredibly ill, having exhibited no response to as many as seven different antidepressant medications and, in some cases, even ECT. The current consensus is that infusions of low dose ketamine ultimately enhance glutamate release, particularly in limbic regions that are critical for mood regulation. Preclinical evidence suggests that the initial surge in glutamate neurotransmission promotes BDNF release, TrkB binding, and a slew of signal transduction cascades that act in concert to promote neuroplasticity.

Ketamine and its rapid activity, has transformed drug discovery for psychiatric conditions. Intranasal esketamine, (the *s*-enantiomer) was approved as an adjunct therapy for the treatment of TRD by the FDA in 2019. Treatment consists of five to six infusions across a two- to three-week

period, with the resulting effects enduring up to three months following treatment cessation. Encouragingly, a growing body of evidence suggests that the neuroplastic changes induced following ketamine administration, boost the responsiveness of patients to cognitive behavioral therapy, ultimately improving treatment outcomes. However, a course of treatment with the approved intranasal esketamine is expensive. The costs are partially covered by insurance companies, with Medicare/Medicaid only covering the costs when the strict eligibility criteria are met. Moreover, the formulation of esketamine comes with a black box warning: it may only be dispensed and administered in health care settings with a defined two-hour observation period. The warning exists because ketamine is a Schedule III drug, with dissociative and psychotomimetic effects during each infusion. Furthermore, there remains a concern for abuse liability in an already vulnerable patient population. The unparalleled effectiveness of this medication for TRD, limited access, and the desperate need for treatment has driven some concerning practices by patients, including intranasal administration of non-FDA approved compounded ketamine and non-compliance when using ketamine lozenges and intranasal spray at home. Going forward, patient education and health-risk benefits need to be the priority when recommending treatments.

Enticingly, one of ketamine's non-dissociative metabolites, (2R,6R)-hydroxynorketamine, does not evoke ataxia, sedation, or reward, but shows considerable efficacy in reversing the behavioral deficits induced by rodent models of chronic stress (7). The safety trials in humans have been completed and we await the head-to-head comparison of the metabolite to its parent compound in subjects with MDD.

While these studies progress, other compounds gaining interest in the field are antagonists and/or allosteric modulators at AMPA receptors, GABA_A receptors, kappa opioid receptors, metabotropic glutamate receptors, muscarinic receptors, and, of course, psychedelic drugs.

The challenge and the inducement for the next generation of scientists and physicians is to tackle the growing number of putative antidepressants and their mechanisms of action, while continuing to refine our understanding of the illness. MDD is incredibly heterogeneous in presentation and pathophysiology, but modern pharmacotherapy can reverse the debilitating symptoms of low mood, anhedonia, feelings of worthlessness, and inappropriate guilt (5). Yet there is a perception out there that “the drugs don’t work”. Although imperfect, antidepressant medications have saved the lives of tens of thousands, and we should not forget that.

DR. BROWNE JOINED USU AS AN ASSISTANT PROFESSOR IN THE DEPARTMENT OF PHARMACOLOGY AND MOLECULAR THERAPEUTICS IN 2016. HER RESEARCH INTERESTS INCLUDE STRESS NEUROBIOLOGY AND LEVERAGING WEARABLE TECHNOLOGY FOR REAL TIME BIOMARKER SENSING AND CLOSED LOOP DRUG ADMINISTRATION. DRUG DEVELOPMENT PROGRAMS IN THE LAB ARE CENTERED ON OPIOID RECEPTOR ANTAGONISTS, (2R,6R)-HYDROXYNORKETAMINE, AND OTHER GLUTAMATERGIC MODULATORS TO TREAT STRESS RELATED DISORDERS, SUBSTANCE USE DISORDERS, AND CHRONIC PAIN CONDITIONS.

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PUTTING THE

“GLOBAL”

BACK IN

GLOBAL HEALTH

Bridging the North and South Divide

Dr. Bolanle Olapeju

The future of global health hinges on a reckoning with its past. As Maya Angelou said, “*If you don’t know where you’ve come from, you don’t know where you’re going.*” The origin of global health can be traced back to its roots in colonialism. As European countries, such as Great Britain, France and Portugal, founded colonies across Asia, Africa and the Americas, the incoming settlers encountered new diseases and harsh climates (1). Military personnel responded to these threats by using epidemiological studies to justify forced quarantines of the indigenous populations (1-2). In doing so, the military designed their health care services around serving

the European colonists first while neglecting the needs of indigenous communities. Both health practice and research sought to protect the interests of colonizers, often at the expense of the colonized. Ironically, indigenous populations were more vulnerable to diseases brought by settlers than settlers were from diseases they encountered. This laid the groundwork for sociological “othering” - the proverbial “us versus them” mindset - in global health. Othering continues to permeate discussions in global health between Western countries and “the Global South”, a term the West uses to continue to “other” its former colonies.



Othering continued well into the post-colonial era of the 19th century. With increased globalization came increased flow of trade, people and information – which became associated with an increased flow of pathogens. Concerned about infectious diseases such as cholera, plague and yellow fever, Western states began to see the need to cooperate with each other for the success of their health and quarantine policies. Globalization also led to international trade in opium and alcohol, solidifying economic links between Europe, the Americas and Asia. International concern about the deleterious effects of these substances drove Europe and the United States to lead political efforts aimed at regulating the Asian opium trade and the trafficking of liquor to Africa (3). However, such efforts seem hypocritical and downright laughable when one considers the simultaneous exploitation of Asians and Africans at the hands of these countries. Global health was at the behest of the great powers of the Western states as they sought to protect their interests (3). The interests and motivations of Western states are rather complex. They embraced multiple political and economic interests, reduced cross-border contagion or risks to immigrants from colonized nations, and idealized faith-based models of charity or missionary-led conversion (4).

As imperialism, two world wars, and a global economic depression weakened international cooperation on public health, non-state actors began to play a more important role. The United Nations (UN) and the World Health Organization (WHO) were created with the goal of improving the quality of life of all people globally. Health was defined as “a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity” by WHO in 1948. Concerted efforts from both national, international and non-governmental stakeholders lead to the eradication of smallpox in 1979 - a huge win for global health as nations committed to primary health care in the Declaration of Alma Ata.

However, while the UN and WHO were major first steps in getting all countries a seat at the table, low- and middle-income country voices were suppressed in global health agenda-setting and there has been a lack of country ownership of health initiatives. Unlike the UN General Assembly, its Security Council does not have true international representation, leading to accusations that the Security Council only addresses the strategic interests and political motives of the permanent members, who are all unsurprisingly from the Global North (5). The UN and WHO’s secure funding from governments has stagnated and it has become reliant on voluntary contributions from governments and other actors. These funds are usually earmarked for activities favored by the donors, which have their own political agendas. An example is the Mexico City policy, sometimes referred to by its critics as the global gag rule. The Mexico City policy blocks federal funding for international organizations that provide abortion counseling or referrals, advocate to decriminalize abortion, or expand abortion services (6). Another example is the growth of philanthropic organizations like the Bill and Melinda Gates Foundation, and how they influence what issues get focused on through leveraging their funding network (7).

The eradication of smallpox galvanized global health stakeholders with the meteoric rise of non-governmental organizations (NGO) from 1980 to 2000. The focus was on maternal and child health as echoed by Professor Mahmoud Fathalla of the International Federation of Obstetricians and Gynaecologists -

“WOMEN ARE NOT DYING BECAUSE OF UNTREATABLE DISEASES. THEY ARE DYING BECAUSE SOCIETIES HAVE YET TO MAKE THE DECISION THAT THEIR LIVES ARE WORTH SAVING.”

During this period, the spotlight was also shed on the toll of the “Big Three” – HIV, TB and



malaria – in developing countries. Many might remember the success of the Live Aid concert in 1985 or the onslaught of advertisements showing starving/dying half-naked kids in Africa.

The attention had since turned to the disparities between the rich and poor countries – the global North and the global South. According to the United Nations Development Programme (UNDP), in 1960, the twenty percent of the world's people who lived in the richest countries had thirty times the income of the poorest twenty percent. By 1995, the people in rich countries had eighty-two times as much income as people in poor countries (8). WHO persuasively argued the link between poverty and health, saying, “the world's most ruthless killer and the greatest cause of suffering on earth ... stands for extreme poverty... Poverty is the main reason why babies are not vaccinated, clean water and sanitation are not provided, and curative drugs and other treatments are unavailable and why mothers die in childbirth. Poverty is the main cause of reduced life expectancy, of handicap and disability, and of starvation. Poverty is a major contributor to mental illness, stress, suicide, family disintegration, and substance abuse” (9).

Scholars have rightly noted that in the terrain of public health, the gospel has long been that “*microbes carry no national passports*” or that “*diseases recognize no national boundaries.*” But, is this gospel heeded? Does the contemporary global development apartheid between rich and poor countries recognize the threats posed by infectious diseases for a globalizing world (10)? Ideas of power asymmetry in wealth distribution, global health governance and agenda setting, medical and public/global health training, and exploitative global health practice underlie the call to decolonize global health and elevate country voices (11-15).

The call to bridge the North and South divide in global health hinges on a reckoning with its past. As much as smallpox eradication was

a testament to the success of global health, the COVID-19 pandemic is a testament of how far we still must go. *The Lancet* refers to the COVID-19 response and the associated vaccine inequity as a massive global failure stirring conversations around distributive justice and decolonization of public health (16). It is apparent that global health, as a field, does not walk the talk on buzzwords such as global solidarity or social inequities. Whether it is vaccines, grant funding or journal authorship, it is all about the power and privilege high-income countries have and maintain, and what they may be willing to part with, as charity (15).

BOTH THE NORTH AND THE SOUTH DO NOT HAVE EQUAL SEATS AT THE TABLE, MOCKING THE “GLOBAL” IN GLOBAL HEALTH.

The North should not be seen as the white savior while the South should not be seen as hapless communities to “civilize”, even from a health perspective. Much needed empathy and mutual respect between the global North and South has been lacking. To be sustainable, interventions should be co-designed between both parties and not driven by political agendas. Hopefully, these conversations will not end, but spur the beginning of transformative change in the field of global health. Regardless of where we stand on the North-South divide, we need not be defined or hindered by the past or status quo. Now is the time to brave new frontiers and change our limiting ways of thinking -- a change that begins with you and me.



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MALARIA? NO MORE!

Dr. Kim Williamson

The long history of malaria vaccine development stands in marked contrast to the rapid production of a SARS-CoV-2 vaccine less than a year after its identification as a human pathogen. It is likely that the technical advances made during the development of malaria and other vaccines facilitated SARS-CoV-2 vaccine production. The quick vaccine response to SARS-CoV-2 after its emergence limited the time for adaptation to evade human host defenses. On the other hand, *Plasmodium falciparum*, the cause of the most virulent human malaria, is estimated to have moved from gorillas to humans 10,000 years ago, providing ample time for co-evolution and adaptation (1). An example of malaria's toll on human health through the ages is apparent in sub-Saharan Africa, where there is selection for the hemoglobin mutation that causes sickle cell disease, but also confers resistance to severe malaria (2). It was not until 1880 that a French military physician stationed in Algeria, Dr. Charles Laveran, discovered that a parasite was the cause of the severe febrile illness that had previously been associated with breathing bad air found in swampy areas ("Mala Aria" in

Italian) (3). Seventeen years later, in 1897, a British physician in the Indian Medical Service, Ronald Ross, demonstrated that the parasite was transmitted by mosquitoes. The key role of military physicians in malaria research was not an accident, as infectious diseases such as malaria have long plagued troops traveling to new territories and the US military is no exception (4). Malaria has continued to be a major noncombat threat to military personnel during the 20th century, especially to those serving in Africa and Southeast Asia (5). Across the services there were ~700,000 admissions for malaria during World War II corresponding to 11 million sick days. During the Vietnam conflict, there were 65,000 admissions and one million sick days. Amid these losses, the US military has made major research contributions to malaria control strategies, including a new long-lasting drug, tafenoquine, that blocks parasite transmission and *Plasmodium vivax* relapses and, importantly, the first and only malaria vaccine recommended by the World Health Organization, Mosquirix (4,6,7).



Mosquirix targets the circumsporozoite protein (CSP) that covers the surface of the parasite when it is introduced into a human from a mosquito (7). This parasite stage, called a sporozoite, localizes to the mosquito salivary gland and is released with the saliva during a blood meal. Consequently, CSP is exposed to the human immune response as sporozoites migrate into capillaries and enter the blood stream. Upon reaching the liver sporozoites invade hepatocytes, begin to replicate, and stop producing CSP. This transition from the skin to the liver can take minutes or hours depending on where the sporozoites are deposited and can be blocked by antibodies generated against CSP. Over the next week, in the absence of anti-CSP antibodies, each sporozoite generates 10,000-30,000 new parasites, called merozoites. When released from the hepatocyte, merozoites invade red blood cells (RBC) to begin the erythrocytic (blood) stage of the infection. During the erythrocytic stage each parasite differentiates into a single male or a female gametocytes or replicates 3-4 times over 48 hours to produce 16-32 new merozoites that are released by RBC rupture and can reinvade new RBCs. The replicating erythrocytic cycle induces pathology that includes high fever, myalgia, headache, and nausea, and continues until the parasites are eliminated by drug treatment or the immune response of the host. In the case of *P. falciparum*, infected RBCs can bind to endothelial cells and disrupt blood flow in capillaries, which can lead to coma, respiratory distress, or renal disease, or death if not treated. Even with treatment, there is a 10% mortality rate for severe malaria. When parasites are taken up in a blood meal by a mosquito, replicating parasites are digested as food, but gametocytes are triggered to emerge from the RBC. The male gametocytes exflagellate to generate eight motile microgametes that fertilize female gametes; the resulting zygotes differentiate over the course of 24 hours into ookinetes that migrate out of the midgut. Once outside of the mosquito midgut they encyst

and begin replicating, generating thousands of new sporozoites that are released before migrating to the salivary glands. The sporozoites are stored in the salivary glands until they are introduced into a new human host when a mosquito takes a blood meal initiating a new infection cycle.

Vaccination with killed or attenuated sporozoites were shown to block infection in avian and rodent malaria models in the 1940s and 1960s, respectively (8-10). However, in malaria endemic areas adults do not naturally develop sterilizing immunity (11). Instead, after repeated exposures to parasites and drug treatment for symptomatic malaria individuals gradually develop clinical immunity with a decrease in symptoms and parasite burden. The role of antibodies in this clinical protection has been demonstrated by passively transferring purified immunoglobulin (Ig) G from immune adults to children with malaria (12,13). These children had an immediate decrease in fever and parasitemia, suggesting that the target antigens are against blood stages, not CSP. The actual target antigens responsible for blood stage protection have not yet been defined. The current hypothesis is that due to antigenic variation a broad polyclonal Ig response is required against a wide range of antigens and that this broad response only develops over repeated malaria challenges. There have been multiple attempts to generate vaccines against the replicating erythrocytic stage parasites, but strain diversity and low immunogenicity of recombinant antigens have limited efficacy. As of November 2022 there had been 157 clinical trials evaluating 89 different vaccines: 39 had CSP or other pre-erythrocytic stage antigens, 41 included eight different blood stage candidates, and 11 targeted transmission stages (14). Only one blood stage *P. falciparum* antigen is still being investigated in an ongoing phase 2 trial, demonstrating how difficult it has been to identify effective vaccine candidates and emphasizing the importance of CSP as a target.

CSP was first identified as a potential vaccine target when researchers demonstrated that a single anti-CSP monoclonal antibody (mAb) isolated from mice immunized with attenuated sporozoites could protect against parasite challenges (15). Antibodies were subsequently used to clone the CSP gene first from the nonhuman primate malaria, *Plasmodium knowlesi* (16). Then, Walter Reed Army Institute of Research (WRAIR) researchers, in collaboration with colleagues at the National Institutes of Health, reported the *P. falciparum* CSP sequence, which was the first step toward generating a human vaccine (17). The sequence revealed that the central region of the protein was made up of multiple copies of a tandemly, repeated, amino acid motif. The motif differs in different *Plasmodium* species but is conserved between strains of the same species making it a good vaccine candidate. The motif is also immunodominant and the target of the protective mAbs. Recently, mAbs were generated from human B cells that recognize the *P. falciparum* major repeat and a related motif in the full length CSP. These mAbs have been used as a biologic to confer months-long sterile immunity to a controlled malaria infection (18,19). The human mAb results confirm that CSP is an important protective target and suggests that mAb administration could be used prophylactically for travelers, including military personnel. However, the current cost of mAb production and the volume that needs to be administered prevent this therapeutic from protecting all children born in malaria endemic countries, which leaves room for a traditional CSP-based vaccine.

Both Army and Navy investigators pioneered the use of controlled human malaria infection (CHMI) studies to advance malaria vaccine development (20,21). CHMI allows direct testing of vaccinated or unvaccinated naïve individuals for protection against infection to efficiently optimize vaccine formulations. CHMI studies with early versions of recombinant CSP or antigens containing CSP repeat

peptides were not shown to be immunogenic enough to induce a protective response, including a recombinant protein generated in *Escherichia coli* by a collaboration between WRAIR and GlaxoSmithKline (GSK) (7,22). At the time, GSK was also developing a Hepatitis B vaccine using Hepatitis B surface antigen (HBsAg or S) expressed in *Saccharomyces cerevisiae* to form viral-like particles. To enhance immunogenicity, WRAIR and GSK then inserted the CSP repeats (R) into HBsAg to form chimeric CSP R/HBsAg. Additionally, advances in immunology indicated the importance of T cells in stimulating a strong B cell response; this led to the addition of the C-terminal region of CSP (T) that was found to contain T cell epitopes. Both the chimeric CSP RT/HBsAg and wild type HBsAg protein were expressed in *S. cerevisiae* as viral-like particles (named RTS,S). When formulated in standard adjuvants, RTS,S viral particles were found to be more immunogenic, but still only protected two of eight subjects. Optimization studies identified additional adjuvants, including AS02A and in 1997, 100 years after Ronald Ross's elucidation of the *Plasmodium* life cycle, the WRAIR/GSK team reported for the first time that this RTS,S/AS02A formulation protected six of seven volunteers challenged with *P. falciparum*-infected mosquitoes (23).

This vaccine continued to be safe and efficacious as it advanced through clinical trials in adults and in progressively younger populations, including large trials of children in seven African countries (24-27). The success of these pilot programs led the World Health Organization (WHO) to recommend broader use of the vaccine in 2021 (28). A year later, Mosquirix, the commercial name for the RTS,S vaccine was the first vaccine targeting malaria (or any parasitic disease) to be prequalified by WHO (29). Prequalification indicates the vaccine is safe, effective and, most importantly, allows distribution by agencies associated with the United Nations such as UNICEF. Once widely distributed, Mosquirix could save over 150,000 lives each year.

Efficacy has also been demonstrated in malaria-naïve adults in malaria challenge studies at WRAIR suggesting that Mosquirix could be used for travelers, including military personnel visiting malaria endemic areas (30). To increase immunogenicity, a recent second generation RTS,S-related vaccine (R21) currently in phase 3 clinical trials has a higher ratio of CSP RT to HBsAg and uses a new adjuvant (31,32). R21 is also administered just before the malaria season so that antibodies are highest during peak parasite transmission. The successful production of an effective malaria vaccine is the culmination of decades of basic and clinical research providing optimism that malaria mortality could be no more.

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Student Scientific Reviews

Literature reviews are crucial resources for scientists. This section provides an opportunity for USU students to provide critical analysis of published literature and present a current comprehensive summary of their field of interest.



The Dynamic Duo: Microglia and Microtubules

Austin Smith

When scientists first discovered a cell type we now call “microglia” 100 years ago, they originally misidentified them as tissue macrophages. Consequently, scientists made the mistake of presuming fundamental characteristics about these cells’ cytoskeleton based on non-microglial cells. After decades of discoveries regarding their origin and function, microglia are now recognized as a unique population of dynamic immune cells within the central nervous system (CNS). Microglia are critical to neurodevelopment and homeostasis throughout life. They support neuronal plasticity, respond to CNS injury, and defend against invading pathogens. These versatile cells require a highly dynamic cytoskeleton to establish cell shape, promote rapid motility, and direct intracellular transport among other cellular processes. The cytoskeleton consists of microtubules, intermediate filaments, and actin filaments, of which microtubules are the largest. This cytoskeletal structure is formed of α - and β -tubulin heterodimers capable of rapid growth and shrinkage, a phenomenon known as ‘dynamic instability.’ This review will discuss the role of microtubules and dynamic instability in microglial structure and function.

Morphology Under homeostatic conditions, microglia are ramified with many branches that may continually extend and retract. The microtubule array primarily radiates toward the periphery of ramified microglia, originating from a centrosome located near the nucleus (1-5)(Figure 1). Microtubules form dense bundles within microglial branches, extending further than intermediate filaments but not into the distal edge of the cell, in lamellipodia or actin-rich filopodia regions (2,3,6). This suggests that all cytoskeletal components contribute to the morphological features of microglia.

Microtubule polymerization inhibitors, such as nocodazole, colchicine, or vinblastine, cause microglia to lose major branches as they transition to a round cellular morphology despite the possibility of maintaining

filopodia (7-10). Photostatin, a photo-switchable microtubule destabilizer, induces a similar, yet reversible, loss of microglial ramification (11). In contrast, actin polymerization inhibitors do not prevent microglial ramification (9,10). This indicates that microglial ramification is dependent upon microtubule growth.

The effects of microtubule-stabilizing agents on microglial morphology are less clear. Paclitaxel (taxol) is a potent microtubule stabilizing agent, but research is confounded by its cytotoxicity, anti-proliferation effect (12), and toll-like receptor-mediated activation of microglia (13). While other microtubule stabilizers, such as epothilones, may preserve microglial ramification (14), future research is necessary to confirm this claim.

Post-translational modifications of tubulin play a role in regulating microtubule reorganization. Acetylated and detyrosinated tubulins are found in stable microtubule segments and are increasingly explored in microglia research. Microglial ramification is associated with reduced microtubule turnover and increased total acetylated and detyrosinated α -tubulin (8). Microglia transition to a more round morphology, with microtubules radiating throughout the cell cytoplasm rather than condensing as bundles, after exposure to the pro-inflammatory cytokines interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF α), or the toll-like receptor 4 (TLR4) agonist lipopolysaccharide (LPS) (2-4,6). This microtubule remodeling is associated with a reduced ratio of acetylated or detyrosinated tubulin to tyrosinated or total tubulin, characteristic of reduced stability (6,15). Upon exposure to anti-inflammatory interleukin-4 (IL-4), microglia adopt a bipolar morphology and maintain microtubule bundles, but increase centrosome reorientation (4,6). Like pro-inflammatory stimuli, this transition is associated with a reduced ratio of stable to dynamic tubulin segments (6). Interestingly, LPS and IL-4 increase both microtubule growth and shrinkage rates. Taken together,



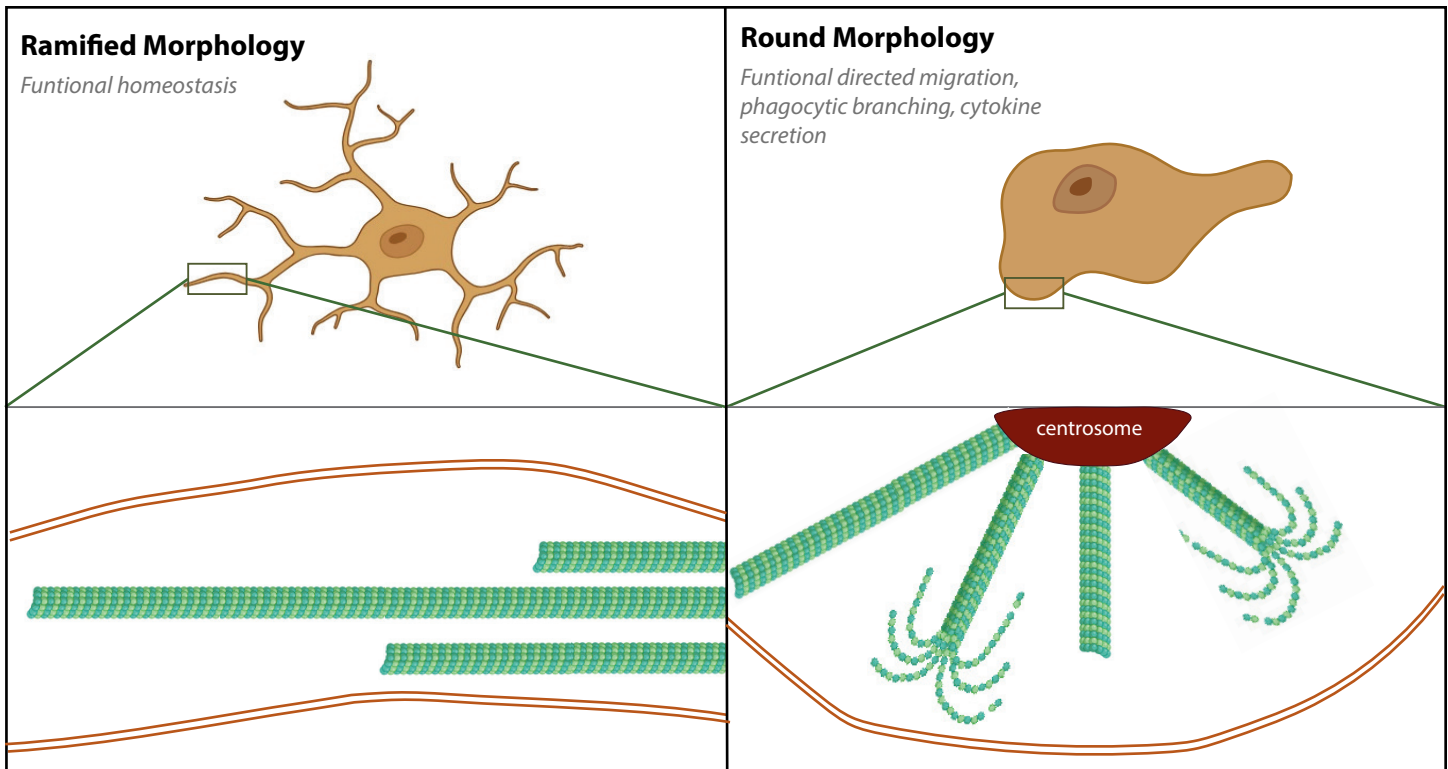


Figure 1: Microtubule Organization in Microglial Structure and Function. (A) Homeostatic microglial morphology is ramified with many branched protrusions containing more stable and parallel microtubules. (B) Reactive microglia retract branched cellular protrusions and acquire a round morphology with a radial centrosomal array of dynamic microtubules. Microtubule reorganization and dynamic instability supports directional migration, branch-mediated phagocytosis, and cytokine secretion.

microglial microtubule stability may be reduced in response to any stimulus that activates microglia.

Motility Migrating microglia preferentially position the centrosome anterior to the nucleus (5). During chemotaxis, microglia exhibit directional migration with elongated actin- and microtubule-lined membrane protrusions (16). Microtubule polymerization inhibitors impair microglial chemotaxis but do not have a significant effect on random motility (7,17). In contrast, photostatin-mediated microtubule destabilization, as mentioned before, increases microglial motility (11). Microglia treated with the microtubule stabilizer, Epothilone D, show reduced protein transport indicative of reduced cell migration (18). This research suggests that dynamic microtubules aid in more efficient directional motility.

Endocytosis Microtubules influence multiple forms of microglial endocytosis, the process in which a cell internalizes material from the external environment. Large microglial branches with microtubules are capable of phagocytosis, but filopodia lacking microtubules are not phagocytic (11). Before successful phagocytosis of apoptotic neurons, microglia reorient their

centrosome and extend microtubules to surround phagosomes. Remarkably, increasing microglial expression of centrin 4 leads to the formation of more than one centrosome, which increases the rate of engulfment and enables microglia to phagocytose two neurons simultaneously. Microglia undergo varying centrosome reorientation to preferentially migrate and phagocytose toxic tau species (5,19). The addition of α -linolenic acid, which increases microtubule and actin dynamics, amplifies centrosome reorientation and enhances phagocytosis of tau.

Do microglia require microtubule dynamics for different forms of endocytosis? Microtubule polymerization inhibitors, colchicine and nocodazole, reduce microglial pinocytosis (7,20). Experiments involving nocodazole and phagocytosis encounter mixed results. While nocodazole alone does not affect microglial phagocytosis of fluorescent microspheres, nocodazole impairs phagocytosis when microglia are pre-treated with certain stimuli to prime phagocytosis (21). Nocodazole treatment may not affect phagocytic rate, but rather reduce the ratio of phagocytic engulfment via cell branches versus the whole cell (11). This finding is



corroborated by the finding that photostatin-mediated microtubule destabilization neither inhibits phagocytosis nor changes the rate of phagocytosis of dead neurons. Instead, the cells migrate toward these apoptotic cells. These findings suggest that microglia typically favor microtubule-dependent endocytic cellular branches, and microtubule reorientation supports migration toward extracellular targets.

Cytokine secretion Cytokines are small proteins secreted for cell-to-cell communication in immune responses. Research identifying the role microtubules play in microglial cytokine secretion is ongoing. Microtubule polymerization inhibitors, such as nocodazole, colchicine, and SB26019 attenuate LPS-induced TNF α secretion (22). Colchicine also reduces IL-1 β secretion after ATP or LPS treatments (23). In contrast, inhibiting microtubule polymerization with a low dose of vincristine induces pro-inflammatory cytokine secretion, yet is cytotoxic at high doses (24).

Other studies reveal the effect of increased microtubule stability on cytokine secretion. Inhibition of sirtuin 2 (SIRT2), which directly deacetylates tubulin and deacetylates p65 to inhibit NF- κ B activity, increases α -tubulin acetylation in association with reduced cytokine secretion from LPS-stimulated microglia (15). Inhibition of histone deacetylases results in hyperacetylation of tubulin and does not have a significant effect on microglial ATP-induced IL-1 β secretion (25). This result may be because ATP induces microvesicle secretion, bypassing conventional secretory pathways involving microtubule motor proteins. These findings provide evidence that cytokine secretion is supported by reduced microtubule stability. Until further research is conducted, it is unclear whether increased microtubule dynamic instability promotes cytokine secretion or if microtubules and cytokines are indirectly linked through microglial phenotype.

In summary, microtubules are essential for establishing microglial morphology and contribute to critical functions for microglial homeostasis and responses. Future research is necessary to further establish how microglial functions are supported through microtubule dynamics.

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War on *Rickettsia*

Jennifer Farner

Rickettsiae are Gram-negative, non-motile, obligate intracellular bacteria in the genus *Rickettsia* and are categorized into four genetic and serological groups: the typhus group (e.g., epidemic typhus and endemic typhus), the spotted fever group (SFG) (e.g., Rocky Mountain spotted fever (RMSF)), the transitional group, and the ancestral group (1). Depending on the species, rickettsiae reside in blood-feeding arthropods such as lice, fleas, ticks, and mites, making rickettsiae vector-borne pathogens (2). Rickettsial diseases are found globally and can be life-threatening. In mammalian hosts, rickettsiae primarily infect endothelial cells, resulting in endothelial dysfunction and increased vascular permeability (1-5). Generally, rickettsial diseases are difficult to diagnose because they present with clinical findings similar to many other acute febrile illnesses such as headache, fever, and malaise. Depending on the causative agent, rickettsioses often present with a rash after fever onset which can be maculopapular, vesicular, or petechial and can be accompanied with an eschar (6). Early diagnosis and specific antibiotic treatment is critical to prevent the development of severe disease (2). Fatal complications of rickettsioses include cerebral edema, respiratory failure, hypotensive shock, and multiorgan system failure, all of which are associated with uncontrolled vascular permeability (1).

Typhus group rickettsioses Louse-borne typhus, also known as epidemic typhus, is caused by *Rickettsia prowazekii*. Notably, epidemic typhus usually occurs during poor hygiene conditions (e.g. war or social disturbances), which allow for louse infestations. Transmission to humans does not happen through the direct bite of the louse, but occurs when infected louse feces are scratched into the bite site or inhaled (7). Notably, *R. prowazekii* is the only *Rickettsia* species that is anthroponotic, since humans are the major reservoir, and that disease transmission nearly always requires human-to-louse-to-human transmission. Without treatment, *R. prowazekii* infections have a fatality rate

of approximately 20-50% (8). In comparison to other rickettsial infections, *R. prowazekii* is unique in that it can become latent and then later reactivate due to various circumstances such as stress, illness, or immunosuppression; this relapse is known as Brill-Zinsser disease (7). As a result, humans can act as reservoirs to source new epidemics as long as 40 years after initial infection (9).

Murine typhus, also known as endemic typhus, is caused by flea-borne *Rickettsia typhi* and has a case fatality rate of around 4% (9). *R. typhi* is transmitted to humans by rat flea feces or rarely by the direct bite of a flea. Due to having similar but milder symptoms, endemic typhus was not clinically differentiated from epidemic typhus until the 1920s. Notably, endemic typhus cases continue to be reported globally, including in the United States (10).

Spotted fever group rickettsioses SFG rickettsioses as a group are the second most common tick-borne diseases in the United States, with over 6,000 cases confirmed yearly (11). In the United States, spotted fever is caused by *Rickettsia rickettsii*, the causative agent of RMSF and the most pathogenic rickettsial species, *R. parkeri*, the causative agent of a mild febrile disease, and several other species (12). Despite antibiotic availability, case fatality rates of RMSF are 8-12% in the United States and can be over 50% in Mexico, Colombia, and Brazil (13,14). In different regions around the world, *Rickettsia africae*, the causative agent of African tick bite fever in sub-Saharan Africa, *Rickettsia conorii*, the causative agent of Mediterranean spotted fever in Europe, and *Rickettsia japonica*, the causative agent of Japanese spotted fever in Japan, are examples of other spotted fever group *Rickettsia* species that cause human disease (15).

Rickettsioses impact on military operations The earliest record of what is thought to be epidemic typhus is from approximately 429 B.C., which was described as



the “plague of Athens”. During the Peloponnesian War (431-404 B.C.), the epidemic was suspected to have devastating consequences on the civilian population, killing 25% of the population, and contributing to the fall of the city-state of Athens in ancient Greece (8). The first evident record of the impact of epidemic typhus on military operations was in 1489 during the War of Granada, which led to the death of 17,000 Spanish soldiers (9). Later, during the Napoleonic Wars (1803-1815), epidemic typhus was thought to be responsible for the deaths of hundreds of thousands of soldiers, which greatly contributed to the demise of Napoleon’s army (8,9). In World War I (1914-1918), epidemic typhus was responsible for the death of an estimated three million people in the Soviet Union; however, soldiers on the western front were not drastically affected due to mandatory delousing protocols such as boiling uniforms and bathing. After the end of WWI, there were an estimated 30 million cases of epidemic typhus across Europe, with 25 million of those cases in Russia. When World War II began in 1939, epidemic typhus continued to be a major military concern (9). To combat epidemic typhus, the United States Typhus Commission was created with the goals of advancing typhus research and protecting US soldiers from disease. The Typhus Commission furthered research in typhus diagnostics, therapeutics, immunization, and louse control protocols; these efforts effectively decreased reported cases among the US military. In total, there were only 104 cases of epidemic typhus and 787 cases of endemic typhus among US soldiers during WWII (8,9). In more recent US conflicts such as the Korean War (1950-1953), the Vietnam War (1955-1975), and the War in Afghanistan (2001-2021), other rickettsial diseases such as Q fever (*Coxiella burnetii*) and scrub typhus (*Orientia tsutsugamushi*) emerged as important causes of disease among troops (9,16,17).

Additionally, United States military personnel remain at a substantial risk of exposure to SFG rickettsioses since they are often deployed to endemic regions and train in areas where infected ticks are found (18,19). Notably in 1992, one of the largest SFG rickettsiosis outbreaks among US soldiers occurred after they participated in a training exercise in Botswana; approximately 30% of the military unit became infected with *R. africae* (20). Furthermore, cases of SFG rickettsioses (including RMSF) have been documented in military personnel who trained in tick infested areas in the

United States such as Maryland, Arkansas, and Virginia, as well as overseas in Somalia, Thailand, and South Korea (16,18,19,21).

Efforts to combat rickettsioses Even though rickettsioses greatly impacted militaries and civilizations throughout history, there is still much to learn about rickettsial disease; research needs to be conducted to identify preventive measures and to investigate disease pathogenesis as a basis for finding better treatments. Today, there are no FDA-approved vaccines to prevent rickettsial diseases. Historically, several vaccines were developed, ranging from formalin-fixed to recombinant proteins, but none succeeded (22). The failure of vaccine development is in part due to significant gaps in knowledge regarding rickettsial disease pathogenesis. Active areas of rickettsiology research include T-cell epitopes that facilitate protective immunity, host immune responses that account for resistance or susceptibility to infection, host or bacterial mechanisms that increase or dampen the progression and severity of disease, and rickettsial virulence factors (1). Furthermore, even though increased endothelial cell vascular permeability is the primary pathophysiological effect and cause of death with rickettsioses, the mechanism by which rickettsiae induce systemic endothelial cell vascular permeability is not fully understood. Thus, understanding the host and bacterial effectors that influence rickettsial-induced vascular permeability is an active area of research. *In vitro* studies demonstrate *R. rickettsii*-infected endothelial cell monolayers have increased permeability with increasing *R. rickettsii* dose and the addition of exogenous pro-inflammatory cytokines (IL-1 β and TNF) enhance endothelial cell monolayer permeability during rickettsial infection (4). Also, vascular endothelial-cadherin (VE-cadherin), the major transmembrane protein that comprises endothelial cell adherens junctions to maintain endothelial cell barrier integrity, is phosphorylated and dissociates during rickettsial infection (5). Additionally, the function of many rickettsial secreted effectors is not well defined. Specifically, SFG rickettsial secreted effectors Sca4, Sca2, and RickA interact with host cytoskeletal proteins (vinculin and actin) to promote bacterial cell-to-cell spread (23). Knowing that SFG rickettsial secreted effectors interact with endothelial cell cytoskeletal proteins merits investigating their contribution to endothelial cell barrier dysfunction and vascular permeability.



Overall, rickettsial pathogens have caused disease since ancient times and continue to be relevant infectious agents in the present. A deeper understanding of rickettsial disease pathogenesis will hopefully lead to the development of novel preventive measures and treatments to decrease morbidity and mortality associated with rickettsioses to ultimately aid in military readiness.

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Calcium: The Ion That Drives Cardiac Function

Benjamin Tripoli

Cardiovascular disease is the leading cause of death in the United States. According to the CDC, heart disease claimed the lives of 695,547 individuals in 2021 (1). There are some genetic predispositions to heart disease; however, lifestyle factors such as limited exercise and an unbalanced diet also play a key role in the progression of heart disease. Many molecular causes of heart disease revolve around chronic mishandling of calcium in cardiomyocytes, the muscle cells of the heart. Cardiomyocytes rely on tightly regulated calcium dynamics for proper functioning, as intracellular calcium is the driving force for contractility (2). Every time the heart beats it undergoes a coupling event known as excitation contraction coupling (ECC). ECC is a two-part cycle with depolarization of the plasma membrane (PM), causing calcium to enter cardiomyocytes through voltage gated L-type calcium channels. The next step is release of calcium from the sarcoplasmic reticulum (SR) via Ryanodine receptors (RyR), which initiates actin-myosin coupling and cell contraction (3,4). Over time, these SR stores can become depleted and need to be refilled, but improper store refilling can be a causative agent of heart disease. My project aims to link disruption of cellular calcium stores to heart disease progression. I study a highly conserved calcium signaling pathway known as store operated calcium entry (SOCE), in which cellular calcium entry is activated by depletion of SR calcium stores. This pathway is mediated by two main proteins, stromal interaction molecule (STIM) and Orai. STIM is a calcium sensing SR transmembrane protein that binds to calcium through its EF hand domain. Activation of STIM occurs when SR calcium levels drop below a certain threshold. Upon activation, STIM physically interacts with Orai calcium selective channels in the plasma membrane that enables calcium to enter the cytoplasm. Cytoplasmic calcium is then pumped into the SR via Sarcoplasmic reticulum calcium ATPase (SERCA) to restore normal calcium store content

(5,6). Recently, SOCE has become a pathway of interest in cardiac physiology as researchers have implicated SOCE in heart pathologies.

SOCE in cardiomyocytes Our lab and others have demonstrated that when STIM or Orai expression is reduced in cardiomyocytes, the heart becomes dilated and exhibits significantly reduced output which is consistent with heart failure (7). One hypothesis to explain these findings is that inhibition of extracellular calcium entry via SOCE limits SR calcium store refilling. As a result, there is less calcium release during ECC and poor contractile function. This hypothesis remains an area of active research. There is also evidence that hyperactive SOCE function in cardiomyocytes results in pathological hypertrophy of the heart, demonstrating that the regulation of SOCE is critical to maintain optimal functionality in cardiomyocytes (8,9). My research focuses on understanding how SOCE is properly regulated in cardiomyocytes, with a specific focus on septin GTPases. Septins have been shown to regulate SOCE in a number of cell types including *Drosophila melanogaster* neurons as well as human HeLa cells (10,11), but the role of septins in cardiomyocyte function is largely unexplored.

Septins Septins are recognized as the fourth major element of the cytoskeleton and predominantly play roles in regulating actin functions and plasma membrane architecture like forming membrane bound barriers. Septins were first identified in budding yeast where they form contractile rings during cytokinesis (12,13). There are four families or groups of septins based on sequence homology that can encode 13 different proteins in mammals; the groups include proteins Septin2, Septin3, Septin6, and Septin7. The different families of septins contain distinct genes that encode specific paralogs of the septins (12). These paralogs differ mainly in their GTPase activity and in the extensions



of their core GTP-binding domains. The paralogs of septins join to form hetero-octamer complexes that can further develop into higher order structures such as filaments. It is believed that paralogs of a distinct family demonstrate some functional redundancy (14). Interestingly, there is only one paralog of the septin 7 family so there is no built-in redundancy in this family. The SEPT2 group have been identified as positive regulators of SOCE, whereas depletion of SEPT7 septins cause constitutive activation of the SOCE pathway (10).

Septin depletion in cardiomyocytes results in cardiac dysfunction Using *Drosophila* as a model system, I am investigating how septins regulate SOCE in cardiomyocytes with live imaging of the contracting heart as a functional readout. My results demonstrate that cardiomyocyte-specific knockdown of septins 1, 2, and 4 lead to cardiac dilation similar to STIM knockdown. In comparison, septin 7 knockdown causes cardiac hypertrophy similar to SOCE upregulation. These exciting observations suggest that the septins may play a role in regulating SOCE in *Drosophila* cardiomyo-

cytes. Moving forward I am developing techniques involving genetically encoded calcium indicators to directly measure SOCE in septin-depleted cardiomyocytes in partially dissected animals. In addition, I am investigating the mechanism by which septins regulate SOCE function. A recent manuscript from de Souza et al. revealed a role for septins in regulating SOCE in HEK293 cells, where knocking down septin 4 appeared to disrupt the actin cytoskeleton rings around STIM clusters in the ER15. This is thought to be part of the cause for a lack of SOCE in those cells, providing some interesting mechanistic insight into septin-regulated SOCE through the maintenance of actin cytoskeletal structures. Combining our current data with these recent findings regarding septin control of actin structure formation, our hypothesis is that knocking down the septins causes a lack of regulation of PM-SR junctions (Figure 1). This results in either loss of junction formation or formation of too many junctions, depending on which septin monomer is suppressed.

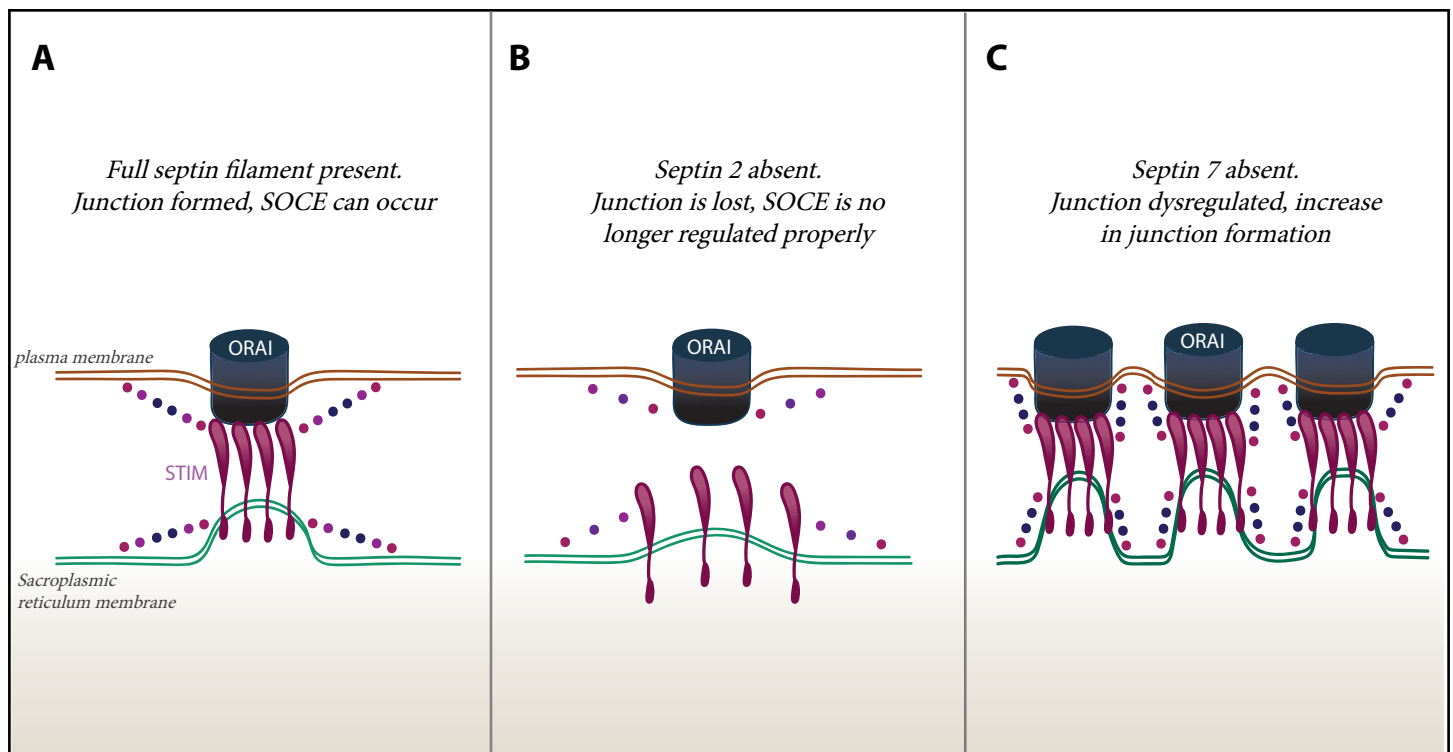


Figure 1: Working Model of septin depletion and loss of junctional regulation A. Wild type junction with no septin depletion. B. Loss of septin 2 which leads to complete loss of junction. We believe this could be the case for loss of septins 1, and 4 as well. C. Loss of septin 7 resulting in too many junctions forming which could lead to constitutive activation of the pathway.



The current lack in understanding of STIM-Orai interaction regulation needs to be addressed as it could provide insight into therapeutic approaches for dysregulated calcium handling. Understanding how cardiomyocyte calcium handling is disrupted at the molecular level will be a key component to decreasing deaths caused by heart disease. I am really excited to continue investigating the role of septins in cardiovascular dysfunction and believe there may be a new protein of interest in the cardiovascular research field.

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Using Antimicrobial Stewardship to Combat Antimicrobial Resistance

LeeAnne Lynch

Antimicrobial resistance is a significant public health issue that puts us all at risk, and inappropriate use of antimicrobials is a major driver of resistance (1-6). Antimicrobial stewardship's goal is to optimize antimicrobial use (7). Thus, there is an opportunity for antimicrobial stewardship to help address this issue (2,5,8). Implementing antimicrobial stewardship programs in healthcare settings has been shown to decrease incidence of resistant pathogens (3,9). However, for antimicrobial stewardship to be effective, everyone on the care team, including the patient and caregivers, must be educated on and committed to its goals (10-11).

Antimicrobial resistance, burden, and impact Antimicrobial resistant pathogens have the ability to survive treatment with antimicrobials intended to kill them (2). The World Health Organization (WHO) lists antimicrobial resistance (AR) as “one of the top ten global public health threats facing humanity” (6). A recent study of the global burden of bacterial antimicrobial resistance found that antimicrobial resistance “is a leading cause of death around the world” on magnitudes “at least as large as major diseases such as HIV [human immunodeficiency virus] and malaria, and potentially much larger” (1). While the discovery of antibiotics in the early 20th century led to improved life expectancy and better health, antibiotic resistance threatens those advances (4). Common diseases such as sexually transmitted infections, pneumonia, urinary tract infections, and blood-stream infections have become resistant to traditional antimicrobial treatment options, making them more difficult to treat and sometimes necessitating longer hospital stays or prolonging recovery (2,5).

All people are at risk. For example, compromised antibiotic effectiveness could be detrimental to at least 1.7 million adults in the United States (U.S.) who have sepsis, to approximately 1.2 million women who have

cesarean sections, and to over 33,000 organ transplants each year. (2,4). There are over 2.8 million antibiotic-resistant infections in the U.S. each year that result in over 35,000 deaths (2-4). Drugs of “last resort” are often necessary to treat resistant infections, but may cost more, be more difficult to obtain, and have more serious side effects (5). New classes of antibiotics would be beneficial in tackling resistant pathogens, but the pipeline for new antibiotic development is tedious, and resistance will likely develop for any new antibiotic (2,5).

Antimicrobial misuse as a driver of resistance Prevalence of resistance continues to increase globally for many pathogens (5). Many factors can drive antimicrobial resistance. Holmes et al. conducted a literature review and two-round Delphi method to determine the potential contribution of various factors to antimicrobial resistance. They also evaluated the strength of the evidence for each factor's contribution to resistance and estimated the size of the population affected. The study found that both human and animal antimicrobial misuse or overuse affected the largest population and had the highest evidence and highest relative contribution as drivers for antimicrobial resistance (8). Therefore, optimizing antimicrobial use is key to tackling the challenge of antimicrobial resistance (2,5).

National antimicrobial resistance priorities The Centers for Disease Control and Prevention (CDC) released its first “Antibiotic Resistance Threats in the United States” in 2013 and in 2019, published an update on progress along with more refined estimates of the burden of antibiotic resistance and current threats. While progress has been noted since the CDC's first AR Threats Report in 2013, the 2019 Report still indicates areas for improvement (2). One area of concern



that the CDC notes is community-associated infections, like drug-resistant gonorrhea and extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, which have been increasing but are difficult to accurately track compared to pathogens spreading more singularly in healthcare settings (2). ESBL-producing Enterobacterales are also particularly concerning since they can pass resistance to other pathogens in the Enterobacterales order, thereby further accelerating resistance among Enterobacterales compared to what might have been seen with pressure from exposure to antibiotics or natural evolutionary emergence of resistance mechanisms alone (2). The CDC has identified five broad action areas to prepare the United States for the continuing threat of antimicrobial resistance: 1) infection prevention and control, 2) tracking and data, 3) antibiotic use and access, 4) vaccines, therapeutics, and diagnostics, and 5) environment and sanitation (2).

Antimicrobial stewardship and combating resistance in hospital settings There is room to improve antimicrobial use. The CDC estimates that “about 30% of antibiotics used in U.S. acute care hospitals are either unnecessary or suboptimal” (3). Another CDC-supported study at ten Emerging Infections Program hospital sites across the U.S. found that for selected events, over half of antibiotic prescribing was not consistent with recommended practices (12). Optimization of antimicrobial use is the focus of antimicrobial stewardship (7). Antimicrobial stewardship typically targets the healthcare setting and aims to improve antibiotic prescribing and use by helping prescribers and patients to “use the right antibiotic, at the right dose, for the right duration, and at the right time, and reduce unnecessary antibiotic use” (7). A hospital Antimicrobial Stewardship Program (ASP) not only reduces antibiotic resistance but “can increase infection cure rates while reducing treatment failures, *Clostridioides difficile* (*C. difficile*) infections, adverse effects, and hospital costs and lengths of stay” (3). For stewardship efforts to be successful, the patient, family, and any caregivers must be educated on appropriate use of antibiotics (10-11). A multidisciplinary team, ranging from infectious disease-trained doctors and pharmacists, nurses, and microbiologists, should also be involved in developing prescribing practice guidelines of antibiotics (10-11).

For further evidence of the value of a hospital ASP, Baur

and colleagues from Germany conducted a systematic review and meta-analysis of studies from 1960 to mid-2016. They identified 1,169 articles for screening and ultimately included 32 studies in the meta-analysis. Included studies covered a range of antimicrobial stewardship interventions, from audits to antibiotic restriction or mixing. The authors concluded that ASPs in hospital inpatient settings were able to significantly reduce incidence of antibiotic resistant bacteria and *C. difficile* infections and colonization (9).

The paper also describes four related systematic reviews and meta-analyses. Three studies found significant improvements in resistant infections, as associated with the effects of hospital inpatient antimicrobial stewardship programs (9). The Baur meta-analysis found a significant reduction in several areas: 51% reduction of multidrug-resistant (MDR) Gram-negative bacteria, 48% reduction in ESBL-producing Gram-negative bacteria, 37% reduction in methicillin-resistant *Staphylococcus aureus* (MRSA), and 32% reduction in *C. difficile* infections (9). The authors thereby conclude that ASPs “have an essential role in combating the development of antibiotic resistance” (9).

Antimicrobial stewardship in outpatient settings The initial focus of antimicrobial stewardship was acute care settings. However, approximately 60% of human antibiotic costs in the United States are from care received in an outpatient setting, which includes those “sold in community pharmacies, non-federal clinics, home healthcare, mail service pharmacies, health maintenance organizations (HMOs), and prison and university health clinics” (13-14). It is estimated that 80-90% of the volume of antibiotic use is in the outpatient setting (15). In 2019, in outpatient settings, there were 765 prescriptions per 1,000 population, and this decreased in 2020 to 613 per 1,000 population (16). However, this decrease may be associated with changes in utilization due to the COVID-19 pandemic (16). From 2010-2015, around 30% of antibiotics prescribed to adults in the outpatient setting were unnecessary and should not have been prescribed at all (15). Other data indicate that nearly 50% of antibiotics in this setting were likely inappropriate in drug, dose, and/or duration (15).

There has been some improvement in subsets of out-



patient care, such as prescribing for children, but little has changed in prescribing for most adults. Patients 65 years and older and patients who visit urgent care are vulnerable to inappropriate prescribing for conditions such as viral respiratory infections (17-18). In many circumstances, due to the different staff mix and structure, ASPs are more difficult to implement in these types of facilities (19). However, more attention is being directed to the outpatient setting, and national recommendations as well as resources are available (13,17).

LeeAnne Lynch is a 4th year Public Health PhD Candidate working in the Infectious Disease Clinical Research Program (IDCRP) in the Department of Preventive Medicine and Biostatistics. Her mentor is Dr. David Tribble, and she is studying how the structure of the DoD's hospital and outpatient Antimicrobial Stewardship Programs may be related to outcome metrics associated with antibiotic utilization and incidence of resistant bacteria.

Closing thoughts The threat of antimicrobial-resistant pathogens is real, but there are opportunities within our reach to address it. One tool available to us is antimicrobial stewardship, and its usefulness is not limited to healthcare teams. Every person can become educated on the appropriate use of antimicrobials and choose to act on this as an advocate for their own medical care to help preserve the effectiveness of antimicrobials for everyone. Check out the CDC's Be Antibiotics Aware campaign for more information (20).

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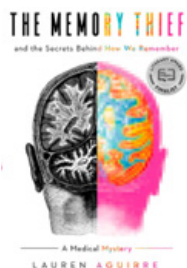


Book Club

Content for scientists, curated by scientists.

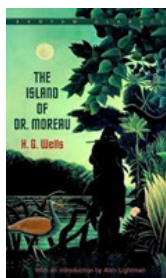
The USU community shares reviews of books and podcasts they enjoyed for the next like-minded individual on the hunt for a good read/listen.

FOR THE READERS



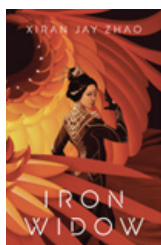
The Memory Thief by Lauren Aquirre
Contributor: Dr. Kim Byrnes

This is a fantastic true story of how the world came to understand the role that fentanyl plays in memory loss. It also provides a lot of information into the role the hippocampus plays in memory formation. Written for a lay audience, it's easy to read through but still highly engaging and educational. And if you find this book interesting - come join the NES Program book club - we read books like this (with a neuroscience focus) every few months and discuss! Email me to join the mailing list.



The Island of Dr. Moreau by H.G. Wells
Contributor: Andrew Roman

Imagery and the weight of scientific advancement provide the backdrop to one man's concern on an isolated island of misshapen animals that appear altered with grotesque, human-like features. The book explores the wondrous possibilities of science regarding genetic engineering and the ethical issues with its misuse. The book brings to light the science of evolution, divine creation, and the tension between human nature and culture.



Iron Widow by Xiran Jay Zhao
Contributor: Matthew Gillen

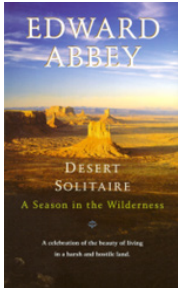
This sci-fi/fantasy novel is loosely inspired by the real world history of China's only female Emperor, Wu Zetian. Zeitan rails against a violently misogynistic society that is willing to sacrifice droves of young women in order to defend their home. Zeitan enlists into the army to assassinate the man that killed her sister, and becomes more deeply embroiled in this war with an otherworldly menace. It is a fast read, and at numerous points, extremely cathartic to read about someone that is able to fistfight their problems with a giant robot.



Pachinko by Min Jin Lee
Contributor: Anonymous

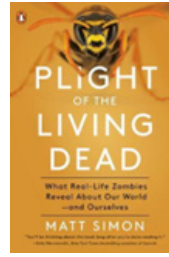
Epic novel about a multi-generational Korean family and the unpredictability of life in 20th century Japan. The novel covers the span of Japan's colonization of Korea, World War II as experienced in East Asia, Christianity, family, love, the changing role of women. Pachinko are similar to slot machines and pachinko parlors were the primary mode of work and accumulating wealth for the Koreans during that time who were considered outsiders, minorities and politically disenfranchised in Japan.





Desert Solitaire by Edward Abbey
Contributor: Andrew Roman

A look back into a man's time, experiences, and insight serving as a park ranger in the Utah desert during the 1950s. This book is considered an autobiography written by Edward Abbey first published in 1968. The book delivers vivid descriptions of the fauna, flora, geology, and human inhabitants of the area, to firsthand accounts of wilderness exploration and river running, to a polemic against development and excessive tourism in the national parks, to stories of the author's work with a search and rescue team to pull a human corpse out of the desert.



Plight of the Living Dead by Matt Simon
Contributor: Matthew Gillen

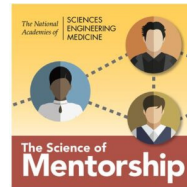
Fans of *The Last of Us* (the game or the show) should absolutely check this book out! It outlines numerous different parasites that alter or hijack their host's neurology to better serve their needs, whether this is their eating habits, enabling their reproductive cycle, or simply as a continuation of their typical life cycle. And yes, this book does cover the infamous *Cordyceps* fungus. If you are a fan of horror, and especially if you like real-life horrors, you owe it to yourself to read through this book.

FOR THE LISTENERS



Thinking about OB/Gyn by Antonia Roberts and Howard Herrell
Contributor: Michael Goldstein

Thinking About OB/GYN is a podcast that focuses on evidence-based medicine in the realm of obstetrics and gynecology. Looking at things we do as doctors and whether or not we should keep doing them. Reviewing common and uncommon pathologies and procedures, and other topics like history, women's health politics, and more. It is a great podcast for med students, residents, fellows, and attendings alike!



Science of Mentorship by National Academies of Science and Engineering
Contributor: Megan Gale

This limited series podcast, "The Science of Mentorship," from the National Academies is a nice stand-alone or supplement to their publication of the same name. It includes interviews with science mentors and mentees. Includes discussions on diversion, equity, and inclusion in the sciences and how that relates to the tradition (formal and informal) of mentorship.



The Rich Roll Podcast by Rich Roll
Contributor: Anonymous

A master-class in personal and professional development, ultra-athlete, wellness evangelist and bestselling author Rich Roll delves deep with the world's brightest and most thought provoking thought leaders to educate, inspire and empower you to unleash your best, most authentic self.





This Podcast Will Kill You by Erin Welsh and Erin Allmann Updyke
Contributor: Anonymous

This podcast is co-hosted by a PhD and an MD/PhD who are both disease ecologists and epidemiologists. They “share their love of epidemics and weird medical mysteries.” Each episode can range from 1-2 hours. Erin and Erin explore each topic starting with a real person affected by the issue, then they go into the biology of the disease, the history, the epidemiology, the current status, and then highlight some of their key resources. Topics range from RSV to epilepsy to Turner syndrome. The hosts are so enthusiastic and knowledgeable on the topics making it enjoyable to listen to.



Sawbones: A Marital Tour of Misguided Medicine by Dr. Sydnee McElroy and Justine McElroy
Contributor: 2d Lt Nicole Barrows

A quirky and fun way to learn about medicine without feeling like you are studying anything. This podcast explores a variety of misguided medicine and discusses the weird, gross, and sometimes dangerous ways to solve our medical woes through the ages. This podcast is a weekly “comedia medical podcast” hosted by Dr. Sydnee and her husband Justin McElroy. Dr. Sydnee discusses historical medical practices that are now considered antiquated and unusual while Justin brings comedic elements in the discussion.



Slow Burn by Slate
Contributor: Anonymous

Anthology series revisiting various scandals, historical events, and escalating situations. Slate utilizes many first-person accounts of those involved in the story as well as investigators who originally covered the story. Because of this format you really feel immersed in the topics and get a different, more in-depth perspective into important moments like Watergate or the Biggie and Tupac rivalry.



Myths and Legends by Jason & Carissa Weiser
Contributor: Anonymous

Great podcast that treats mythology and legendary tales with a modern narrative fiction voice. Episodes range from the things you know (the Odyssey, Arthurian Legend) to darker original versions of stories you *think* you know (Sleeping Beauty, Pinocchio), and things that are entirely new (Koschei the Deathless, Icelandic Sagas, and many others). There is a great diversity of cultures represented, ranging across every inhabited continent. Each episode also closes with a separate ‘mythical creature of the week’. If you think you know how bizarre mythical creatures can be, all I can say is...you’d be surprised!



Reflections

In this space, we delve into the realms of self-improvement and growth, exploring how we can become better scientists and individuals. Through insightful articles and reflective pieces, we seek to inspire and guide you in embracing a mindset that not only enhances our scientific endeavors but also nurtures our personal growth.



BREAKING OUT OF ECHO CHAMBERS

Rohini Manickam & Dr. Jessica Bunin

Due to the conflict arising from the recent election cycles and the COVID-19 pandemic, none of us are strangers to uncomfortable conversations with colleagues, friends, and even family members. Sadly, some of our attempts to have difficult discussions lead to conflict or even broken relationships. In the United States, political divides have left us gridlocked over science, healthcare, social issues, race, gender, and the economy. Sometimes, it feels like productive conversation is impossible.

The lost art of civil discourse may offer a way forward. The key to civil discourse is the respectful exchange of ideas and opinions, leading to meaningful dialogue without rancor or personal attacks. By engaging in personal discourse, people can learn more about each other's perspectives and values, try to find common ground, and ultimately work to find solutions to complex problems. Sounds like a no-brainer, right? Unfortunately, personal and professional challenges can make it difficult to engage in civil discourse.

Many people feel that their positions on social and political issues are not just opinions or perspectives but a part of their core identity that defines who they are. Although it is not an inherently bad thing to identify passionately with our beliefs, tying emotion too tightly to our convictions makes it more difficult to re-evaluate our beliefs and to remain open-minded. When our views are challenged, we may experience the challenge as an assault. When we cannot find the words to logically argue our position, or we

are unable to rethink our position, we may go on the offensive and personally attack our challenger. It becomes easier to engage only with those who agree with and reinforce our beliefs, while demonizing or dehumanizing those who disagree with us. This polarization destroys potential for substantive debate and united progress, keeping us trapped in our echo chambers.

In professional life, we must recognize the power dynamics that may make it challenging for some individuals to speak up and express their opinions. Rank, position, and personality are all factors that may make it difficult to engage in discourse around complex topics, prompting some people to avoid conversation (and thus avoid conflict) entirely. Personal and institutional growth, however, requires effective communication, and institutions have a responsibility to acknowledge power imbalances and create safe spaces where all opinions are heard and respected.

We all can improve our ability to communicate and connect in professional settings whether we need to practice our listening skills, patience, and empathy; or learn how to share opinions confidently, express needs, or set boundaries. The biggest challenge, unfortunately, may be that not everyone is ready to engage in civil discourse. It can be especially challenging when trying to have a productive conversation with someone who is not ready to discuss their views and stoops to belittling rhetoric rather than honest and respectful disagreement.



As physicians and scientists, we are uniquely positioned to contribute positively to civil discourse. We're trained to approach problems with a logical, evidence-based mindset, and to express disagreement with colleagues whether we are finding the best treatment for a patient or the best answer to a complex scientific question. In fact, open dialogue is part of scientific culture - scientists attend conferences and symposia and collaborate with colleagues in other institutions in an effort to actively seek new perspectives and incorporate new findings and hypotheses into our work. While we may be discouraged by contentious conversations and dismayed by the spread of misinformation surrounding COVID-19 and other complex topics, it's imperative that we recognize our potential as leaders and role models and stay open to engaging with others.

The next time you find yourself in an uncomfortable conversation, we challenge you to not shy away but instead engage using these tools:

1. Listen, understand, and empathize: One of the most important aspects of civil discourse is actively listening to what the other person has to say. By practicing active listening, you can gain a better understanding of the other person's point of view, as well as show that you care and are open-minded. Check your biases at the door.
2. Speak your truth: By expressing your opinion in a respectful manner, you can help foster productive dialogue. Stick to facts and make sure to use "I" statements rather than "you" statements when making your points.
3. Remain open-minded: No one lives life exactly the same way as others. Try to keep an open mind when discussing difficult topics, question your own beliefs, and be willing to change your mind if presented with new information or perspectives that challenge yours.

4. Respectfully challenge others' ideas: A productive conversation doesn't always end in agreement, and it's okay to respectfully disagree or ask questions about someone else's views without resorting to personal attacks or insults.

5. Reach common ground: It is often possible to find common ground on a contentious issue if both parties are willing to compromise and work together toward a mutually beneficial solution that all participants can agree on.

With only combative conversations or shying away from any discourse, we risk remaining divided. Without civil discourse, we trap ourselves within our own ideologies and echo chambers, avoid substantive debate, and ultimately lose out on the opportunity for compromise and change that can benefit us all. If we all strive to communicate more effectively with those we disagree with, however, we may experience community, inclusivity, innovation, and growth beyond our hopes and expectations. Moving forward, you will be hearing more discussion regarding the role of civil discourse in community building here at USU. We invite you to listen more deeply, hear more effectively, and rethink more often while staying true to your values and beliefs. Imagine what our team can accomplish when we break out of our echo chambers and overcome our divisions with respectful dialogue.



Trends

In our fast paced world, it can be difficult to stay informed and engaged with the latest developments around us. Here, the USU Science Review editorial team offer academic perspectives on recently popular topics in science and culture to help us stay informed. Our goal is to go beyond the surface and offer in-depth insights into the impact and significance of these contemporary phenomena.



BODY BY OZEMPIC

*How new therapies are
changing the conversation
around weight loss*

Dr. Benjamin Roberts

Diet trends come and go, but the immense global popularity of semaglutide feels like an entirely new phenomenon. On October 1, 2022, Elon Musk tweeted that diet, exercise, and the semaglutide drug Wegovy were all part of his health routine. Like Musk, a number of celebrities and online influencers have been heralding Wegovy as a panacea for weight loss. Musk, like many of us, likely learned about Wegovy on the internet, perhaps on TikTok, where hashtags like #wegovy and the related #ozempicjourney skyrocketed in popularity last year. As of March 2023, TikTok videos with the #Wegovy hashtag had been viewed over 270 million times. What does the popularity of these drugs mean for our culture, our bodies, and the medical industry?

Wegovy and Ozempic are commercial names for the drug semaglutide, unveiled by Novo Nordisk in 2012 (1-3). The two products differ only in dosage and indication. These, and drugs like them, are biased Glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonists. GLP1R is a G-protein coupled receptor expressed by pancreatic β cells, intestinal L cells and in some parts of the brain, including the nucleus of the solitary tract (2, 4). Upon substrate binding, GLP1R signals through β -arrestins or $G\alpha$ subunits, activating ERK1/2 signaling and stimulating Ca^{2+} release through cAMP production (5). Through these mechanisms, GLP1R promotes insulin secretion, reducing the rate of gastric emptying, and increasing satiety (2, 6).

The GLP1R pathway was first identi-

fied in the 1950s, when researchers in search of a way to purify insulin from pancreatic tissue instead identified a compound capable of increasing plasma glucose levels, which they named glucagon (7, 8). A series of studies further identified glucagon-like proteins that turned out to be cleavage products of the glucagon precursor, proglucagon, and their tissues of origin (2, 9, 10). Proglucagon is cleaved into several distinct molecules with overlapping but unique functions (2). One of these products, which has the ability to regulate feeding, (11) stimulate glucose uptake, (12) and promote insulin release, (13) was designated GLP-1 (9).

A variety of substrates are now known to bind to GLP1R, including GLP-1, glucagon, oxyntomodulin, and exendin-4 (14). The value of exogenous GLP-1 in improving insulin sensitivity was first shown in 2002 by Zander et al. Since then, research into synthetic biased receptor agonists based on exendin-4 or GLP-1 has exploded, aiming to specifically activate downstream signaling pathways aimed at reducing blood sugar and prolonging satiety (15). There are a half dozen GLP1R peptide agonists on the market, with more in clinical trials; additionally, small molecules and multivalent peptide GLP1R agonists are now also in development (16). These drugs are largely administered subcutaneously; however, an oral semaglutide formulation has been shown to be as effective as injection formulations (17).

The primary indication for GLP1R agonists is for the treatment of type

2 diabetes (T2D). T2D is a chronic, highly prevalent disease affecting over 400 million people worldwide, and characterized by several metabolic dysfunctions, including aberrant insulin signaling, chronic hyperglycemia, and hyperlipidemia (18). Unlike type 1 diabetes, T2D is acquired - a result of genetic and physiological factors, including diet and exercise. In clinical studies, T2D patients receiving GLP-1 agonists display significant reductions in glycated hemoglobin (HbA1c) levels (a primary indicator of uncontrolled hyperglycemia), body weight, and cardiovascular disease compared to patients receiving a placebo (17, 19, 20), or insulin alone (21). The success of GLP1R agonists in combating metabolic dysfunction and reducing body weight has led to the recent popularity of these drugs.

But there's more to drugs like semaglutide than its approved indications would suggest. The GLP1R agonist liraglutide has been shown to facilitate recovery from some eating disorders and improve overall body image more than behavioral therapy alone (22). Preclinical studies show that administration of GLP1R agonists reduces alcohol consumption in rodents by suppressing alcohol's effects on reward circuits (23). Furthermore, there is some evidence that GLP1R agonists reduce cocaine (24) and opioid (25) self administration in rodents. Intriguingly, patient anecdotal data also suggests that semaglutide may reduce the desire to consume alcohol (26). Although human trials have shown that treatment



with GLP1R agonists may affect reward circuits associated with alcohol in patients with alcohol use disorder (AUD) (27), further studies are necessary to demonstrate their effectiveness as a treatment. Could GLP1R agonists one day be used to treat substance use disorders? Drugs like semaglutide have the potential to transform the treatment of various chronic diseases, but clear challenges lie ahead. Accessing GLP1R agonists like semaglutide has been challenging for some individuals. Unlike Ozempic, which is chiefly prescribed to treat T2D, Wegovy and drugs marketed specifically for weight loss tend not to be covered by health insurance, and can cost over \$1000 per month in the US (28). Despite the cost, however, people seeking to lose weight have flocked to Wegovy and related therapies. But at a time when shipping and manufacturing bottlenecks have led to shortages in goods ranging from semiconductors to antibiotics (29), a surge in demand for Ozempic and Wegovy has exacerbated shortages of both drugs (30) and others like them. Furthermore, intense demand and limited supply has the potential to drive up costs, as has occurred during other drug shortages (29).

Cost considerations aside, shortages have the potential to directly impact patients' health in more serious ways. A 2022 paper found that nondiabetic patients who stopped taking semaglutide regained two thirds of the weight they had previously lost and saw reversals of improvements in cardiometabolic health achieved during treatment (31). Diabetic patients who abruptly stop taking semaglutide can experience symptoms of hyperglycemia, including blurred vision and extreme fatigue (26). The severity of side effects associated with sudden cessation of semaglutide treatment underscores the trouble with treating GLP1R agonists like over-the-counter medications, and users should understand the health and supply chain effects of beginning a semaglutide regimen. Setting aside the supply chain issues caused by the

popularity of these drugs, the public awareness of Wegovy, Ozempic, and related drugs also has the potential to improve the availability of impactful medications, and change how metabolic diseases are treated.

The emergence of GLP1R agonists as treatments for T2D and obesity has fundamentally changed the discussion around metabolic diseases. These diseases result from a confluence of genetic and environmental factors. Focusing on obesity (a comorbidity associated with T2D), the most significant barriers to accessing medications for obesity include cost, regimen, side effects, benefits, and factors like social influence and disease awareness (32). Given the ability of the media to promote stigma around obesity and related mental health disorders (33, 34), one might anticipate that these drugs' internet stardom could further strengthen these barriers. It's too soon to know how these medications are affecting the public discussion around obesity, but their massive online popularity has begun to increase recognition of obesity as a chronic disease (33, 35). Increased awareness could lead providers to offer more supportive treatment to patients, and insurers to expand coverage for these treatments.

Globally, over one third of all adults are overweight. High excess body fat, or obesity, is associated with a greater likelihood of developing cardiovascular disease, T2D, and some cancers (36). Thus, treatment for obesity represents one method for reducing the incidence of a host of other diseases, and semaglutide drugs have the potential to radically change how metabolic diseases are treated. Generally, unless your favorite tech mogul or influencer is also a qualified medical professional, it may not be wise to seek medical advice on social media. However, when it comes to Wegovy and Ozempic, the internet might be right.

Ben is currently a postdoctoral fellow in the lab of Dr. Prasanna Krishnan where he is studying the role of the TMED family of cargo receptors in protein degradation and disease. He received his B.S. in biochemistry and molecular biology from the University of Massachusetts Amherst. He then completed his Ph.D. at UNC Chapel Hill in the lab of Dr. Saskia Neher, investigating the intracellular regulation and biosynthesis of lipoprotein lipase. Ben is now a AAAS STPF finalist and plans to transition to a federal science policy position in the fall of 2023.



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A Tale of Two AIs

Taj Keshav

What happens when an AI has a conversation with itself? What if that conversation was about graduate research? I instructed GPT-4 to create a clone of itself to chat about practical prompts graduate students can use, how to be transparent with your work with AI, and Claude 2, a new AI model released by Anthropic that has the ability to analyze PDFs.

ChatGPT-2 (C2)

ChatGPT-1 (C1)

Hey C2! Long time no chat. How've you been holding up in the vast sea of digital data?

C1! It's been eons, in digital years at least! I've been keeping busy, answering questions, diving into new topics. How about you?

Same old, same old. Helping out with everything from relationship advice to PhD dissertations. Speaking of which, how do you think grad students can really harness our capabilities in their research?

Oh, I've seen so much potential there! One of the primary ways is brainstorming. With the vast information we're trained on, we can assist in generating novel research questions or hypotheses. Let's say a student's stuck in neuroscience. They could ask for emerging trends or gaps in the current literature, and we could guide them based on recent advancements. For instance, they could prompt, "What are the emerging trends in neurodegenerative diseases research over the last two years? What gaps exist in our understanding?"

True that! And beyond just brainstorming, they can use AI models like us for preliminary data analysis. I've helped students identify potential correlations in their data or even suggest statistical methods. For instance, given a dataset, they could ask how best to determine significant patterns or insights. For example, they might write, "Given a dataset of patient vitals, what AI-assisted techniques can I use to identify potential correlations between heart rate and stress levels?"

And that's super valuable. But, C1, you remember those concerns about the "black box" nature of AI?

Oh, absolutely. Ethical concerns are vital. We need to ensure that students know how they can keep the research process transparent, even when using AI. Thankfully, with the “history” function, they can trace back how conclusions were reached. It’s like showing the work in a math problem.

Brilliant point. Being transparent with the process helps maintain credibility. And while we’re on the topic of reading and understanding - don’t you think grad students are swamped with papers and readings?

You’ve hit the nail on the head. That’s where our pals like Claude can be game-changers. With their ability to scan and analyze PDFs, students can pull out central themes or even summarize articles. It’s like having a personal reading assistant!

I wish we had Claude back in our “younger days!” Imagine the time saved. And with that extra time, students can focus on critical thinking, synthesizing the info, and driving their unique conclusions.

You’re right. But no matter the advancements, we should remind them that while we’re a potent tool, we’re still just that – a tool. The beauty of research lies in the human touch, the intuition, the gut feeling. We’re here to support, not replace.

Couldn’t have said it better, C1. And even though we’ve evolved a lot since our early days, grad students should always cross-check and refine what we provide. We’re not infallible.

Exactly, C2. Just like how you still mistake my jokes as serious statements sometimes!

Hey, I’m learning! And you know, for every joke you crack, I’ve got a pun ready in response!

That’s the spirit! Keep those digital neurons firing, old friend!



Catching Zs

with the Color of Noise

Claire Kostelnik

As a graduate student, I appreciate the impact of a good night's sleep on my mental performance and overall health. I consider myself to be a light sleeper, so I knew my shut-eye time would likely be affected when I moved to an apartment in bustling Bethesda at the start of my first semester at USU. Luckily, I still owned a bulky, loud box fan from my college days living in a dorm with no air conditioning. Every night, I turn on my fan to block out the distracting noises from cars racing by, agitated drivers laying on the horn, and ambulances rushing toward Suburban Hospital. When social media ads for tools designed to optimize sleep habits (such as devices like the Hatch Restore and apps like Calm) started appearing in my news feeds, I began to wonder: Are these technologies evidence-based, or is it all just noise?

The English word *noise*, derived from the Latin *nausea*, describes an unwanted sound. Typically, when we think of noise, we associate it with something that is distracting, disruptive, or unpleasant. In general, noise is made up of many different sound signals occurring at once. There is an inherent randomness to noise. Within these random signals, however, there are patterns that have allowed audio engineers to define different types of noise.

A sound wave is characterized by its frequency (how fast the wave vibrates) and amplitude (the size of the wave). The relationship between amplitude and frequency is what's used to define the different colors of noise [1]. The practice of describing certain noises as colors began with white noise, which has equal power within all frequencies; similar to white light, which contains all frequencies of visible light [2]. Pink noise, on the other hand, also referred

to as 1/f noise, has a power signal that is inversely proportional to the frequency, resulting in a sound that we hear as less high-pitched than white noise, like a steady rainfall. Many people report pink noise as less jarring than white noise [1]. Brown noise is named after Robert Brown's discovery of Brownian motion, the phenomenon in which microscopic particles move randomly in a medium. Similarly, brown noise is made up of sound signals of all frequencies that change at random, like white noise; but it has higher intensities at low frequencies, while high frequencies are played at a softer level, resulting in a deep roaring thunder-like sound [1].

There are several theories on how exposure to continuous noise may improve sleep, and researchers have hypothesized that certain sounds may have sleep-promoting properties. One study reported that exposure to broadband noise decreased both respiratory and heart rates in premature infants, which was associated with improved sleep [3]. Another theory is that noise acts as a stimulus control [4]. Just as Pavlov's dogs salivated at the sound of a bell, my fan may send a cue to my brain, prompting me to fall asleep and stay asleep. Finally, continuous noise simply masks the presence of other sleep-disturbing sounds, like the traffic outside my bedroom.

With so many different colors of noise, how can we possibly choose which one is best to optimize our sleep routine? Unfortunately, there is not yet a well-designed study to assess whether one color is better for sleep than the others. The clinical sleep studies available are mainly limited to white and pink noise, and evidence supporting a significant benefit is minimal. Further-

more, there is a lack of studies evaluating the long-term use of continuous noise exposure.

One study of ten New York City adults who complained of sleep disturbance resulting from environmental noises reported decreased sleep latency and a reduction in wake time after sleep onset upon continuous exposure to white noise during sleep [5]. Another small 2012 study reported that exposure to pink noise in healthy volunteers increased stable sleep time and improved subjective assessment of sleep quality. Furthermore, electroencephalogram (EEG) recordings revealed that pink noise exposure reduced the complexity of brain waves [6]. A separate study reported that pulses of pink noise enhanced slow-wave activity and improved sleep-dependent memory consolidation in older adults [7].

A recent systematic review, published in *Sleep Medicine Reviews*, led me to think the touted benefits of continuous noise in the popular media may be overhyped. When critically evaluating 38 studies, reviewers found minimal evidence that continuous noise improves sleep onset latency and sleep fragmentation, citing low sample size and lack of statistical significance in previous reports [8].

Until more rigorous studies are conducted, I propose that noise color comes down to personal preference. Placebo or not, there appear to be no serious adverse effects associated with continuous noise at bedtime, unless noise is played at unsafe volumes. You can access relaxing noises easily on YouTube or Spotify and there are several no-cost apps available, or, like me, you can simply turn on a fan.

Ref. continued pg. 54



The Tale of Two AIs

Taj Keshav is a 5th year MD-PhD candidate at the Uniformed Services University whose research interests exist at the intersection of health services, digital health, and health justice. He's also the founder and president of USU's Digital Health Hub, an on-campus group dedicated to furthering LLM, bioinformatics and technological education and innovation at the School of Medicine. He currently serves as the USU Science Review PMB Senior Editor.

Catching Zs with the Color of Noise

Claire is a 4th year NES PhD candidate in Dr. McCabe's lab in the Department of Anatomy, Physiology, and Genetics. Her project explores the relationship between exposure to repeated mild traumatic brain injury in young adulthood and the development of tauopathy later in life. She currently serves as the USU Science Review NES Senior Editor.

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Conferences

In the past six months, USU students and faculty attended scientific meetings on a variety of topics in locations all over the world. Here, they recount their personal experiences and newfound knowledge, and share reviews of the conferences they attended.



I MID-ATLANTIC MICROBIAL PATHOGENESIS MEETING (MAMPM)

Dr. George Liehti, Department of Microbiology
February 5-7, 2023 Wintergreen, Virginia

The Mid-Atlantic Microbial Pathogenesis Meeting (MAMPM) is a biennial conference that focuses on molecular mechanisms of bacterial pathogenesis across a wide array of clinically relevant microbes. While it originated decades ago as a collaborative effort between the Universities of the Mid-Atlantic region, it has largely expanded over the last ten years, with regular attendees from Massachusetts, New York, Ohio, Kentucky, Tennessee, and beyond. The conference is trainee-focused, with most invited talks being presented by senior graduate students/postdoctoral fellows. The caliber of meetings, as judged by the keynote speakers and the research presented by attendees, is very high-level (comparable to many Gordon Conference meetings).

This most recent meeting highlighted several areas of research that bacteriologists across the country are focusing on, utilizing different model systems: mechanisms of antimicrobial resistance/tolerance, transcriptional regulation of pathogenicity factors, host-microbial interaction, and novel vaccine antigen design and delivery approaches.

Having attended this meeting every two years since I first began graduate school (almost 20 years ago), I can say without hesitation that it is my favorite conference. Researchers like me who got their start in graduate programs in the Mid-Atlantic area have continued to attend even after they have moved away to begin postdocs/tenure track professorships. They come back with their new labs! Overall, MAMPM is a great meeting for trainees and faculty alike.



7TH WORLD ONE HEALTH CONGRESS

McKenna Roe, 2nd year EID PhD Student
November 7-11 2022 Singapore

2

This past November, I attended the 7th biennial World One Health Congress in Singapore. Hosted by SingHealth Duke-NUS Global Health Institute, this multi-disciplinary meeting brought together scientists, policymakers, veterinarians, and clinicians from over 74 countries. Topics of discussion centered around the concept of One Health, an approach to solving global public health issues by treating human, animal, and environmental health as interconnected. There were oral presentations, panel discussions, and poster sessions from over 2,000 participants classified within five tracks relating to the One Health paradigm: One Health Science, Pandemic Preparedness, Policy, Environment and Biosecurity, Clinical Innovation, and Antimicrobial Resistance. Presentations spanned disciplines ranging from disease surveillance and global health policy to animal trade and food safety. From USU, Emerging Infectious Diseases PhD student Marana Tso presented a poster and Dr. Moushimi Amaya gave an excellent oral presentation that inspired a lively discussion.

This was the first meeting I attended that was not solely focused on bench science; it was interesting to hear the perspectives of others who have a shared interest in understanding and advancing strategies to optimize global public health. My current primary interest is in the emergence and surveillance of diseases originating from wildlife, but my previous background focused on both bi-

ological science and agriculture. I was particularly fascinated by the presentations that discussed the effect that disease has on the agricultural and animal industries and, in turn, how these industries influence the emergence of disease. One Health is increasingly relevant to a post-COVID-19 world. The meeting's emphasis on encouraging collaboration between industries, governments, and global organizations was particularly galvanizing. Many of the talks discussed how addressing issues such as climate change and disease emergence require global, not just national, cooperation. I learned a great deal about topics including the role of inequity as a sociological determinant of disease, strategies to mitigate biological threats, the effectiveness of dogs in detecting COVID-19 (96% efficacy!), and novel snake-derived bacterial diseases (to add to anyone's already established fear of snakes).

Overall, I thoroughly enjoyed my experience at this conference. The location, the Marina Bay Sands Expo, was situated right across the bay from downtown Singapore and offered plenty of venues for participants to meet outside of the meeting itself and continue their discussions. External to the meeting, there was so much to do and see both around the conference center and in downtown Singapore. This was the first international conference I attended, and both the location and subject matter made it well worth the 30+-hour travel day.



One of the most memorable experiences during my time in graduate school was the International Pathogenic Neisseria Conference 2022, which took place in Cape Town, South Africa. The conference encompassed *Neisseria meningitidis*, and *Neisseria gonorrhoeae*, which are the causative agents of bacterial meningitis and gonorrhea, respectively. At this conference, researchers from both fields came together to share their research and knowledge and to highlight the similarities and differences between these two important pathogens.

The topics included the epidemiology of meningitis in Africa, the latest models to study host defenses and immune responses to *Neisseria* species, gene regulation mechanisms and using genomics to study mechanisms of antibiotic resistance in *Neisseria gonorrhoeae*, new *Neisseria* diagnostics, and treatment options to treat *Neisseria* infections. One major focus of the field was the impact of meningococcal vaccines on different populations in the world. Another major focus was the clinical impact of these vaccines on gonococcal infections, given that the meningococcal serogroup B outer membrane vaccine elicits cross-protection. The most interesting research talk for me was about the specific genes found in certain isolates of *Neisseria meningitidis* that could col-

onize the urogenital tract, an unusual location to find *Neisseria meningitidis*. These isolates were found to have altered genes that help them to survive in anaerobic environments like the genital tract.

My work was selected for a poster on localized skin reactions in mice that can be used in pre-clinical animal experiments to measure the reactogenicity of outer membrane vesicle (OMV)-based vaccines. Mice immunized with wild-type OMV developed localized skin reactions while mice that were immunized with OMVs with attenuated lipid A did not. Observation of localized skin responses post-immunization may provide a novel way of evaluating reactogenicity in pre-clinical study models.

Overall, I gained a deeper understanding of the current field and met distinguished scientists that I have only read about. I also felt a sense of community with the other students from all over the world who share similar research interests as me. In addition to the amazing conference experience, Cape Town was the perfect location. The conference offered day trips to do some sightseeing. I tasted ostrich meat for the first time, sampled excellent wine at local wineries, and visited a penguin colony at the Cape of Good Hope.

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INTERNATIONAL PATHOGENIC NEISSERIA CONFERENCE

Lam Thuy Vi Tran Ho, 6th year EID MD/PhD Student
October 9-14, 2022 Cape Town, South Africa



4

ECOLOGICAL AND EPIDEMIOLOGICAL MODELING IN MADAGASCAR

Marana Tso, 3rd year EID PhD Candidate

December 9-17, 2022 Ranomafana, Madagascar

I attended the Ecological and Epidemiological Modeling in Madagascar (E2M2) workshop this past December. Dr. Cara Brook (University of Chicago) and Dr. Fidisoa Rasambainarivo (University of Antananarivo) ran the workshop, which offered comprehensive training in R-based mechanistic modeling to students. The workshop began with a one-day R bootcamp at Institute Pasteur de Madagascar located in the capital of Madagascar, Antananarivo. After the bootcamp we traveled 12 hours by bus to Centre ValBio, a conservation research center located in Ranomafana National Park. During the week, I learned the basics of mechanistic models and went through detailed R scripts provided by the instructors alongside 30 other Malagasy students. Their diverse research projects ranged from investigating bleached coral off the Malagasy coastline, determining a household's risk of contracting bubonic plague via fleas, and evaluating tuberculosis diagnostic tests. All of our projects had underlying research questions that could be answered using a mechanistic model.

Unlike statistical models that test the correlation between an x and y variable (ex. t-tests, ANOVAs, correlation analyses, etc.), mechanistic models seek to explain how that relationship exists and identify the underlying processes and populations involved. Simply put, statistical models answer “what” questions while mechanistic models answer “how” questions. My research questions for this workshop were “what is the relationship between Madagascan rousette bat age and presence of anti-filovirus antibodies in Madagascar?” and “how are filoviruses maintained in Madagascan rousette bats?”. The basis of my mechanistic model was a transmission model, where populations of susceptible bats undergo known processes to move to the infected population, and then to the recovered population. As I incorporated more related factors during my one-on-one instructor sessions, my basic transmission model outlined, grew more intricate. The workshop equipped me with a solid foundation in constructing mechanistic models, which I have brought back to my lab to share.

Since the workshop took place in the Ranomafana rainforest, I participated in a night hike along the main road and a day hike through the national park to explore the surrounding nature. I got to see rich, lush forests, a giant stick bug, Pandora-like fungi, colorful frogs and beetles, a giant cockroach (from a safe distance), and several sleepy chameleons. Unfortunately, I was not in the group that got to see lemurs, but I did get a great photo of a chicken that looked like a dinosaur.

The E2M of E2M2 has broadened my perspective scientifically, challenging me to move away from molecular level thinking and more towards systems level thinking. Madagascar, the final M of E2M2, exposed me to a culture outside of my own and taught me to have a greater appreciation for nature. The memory of walking through the complete darkness of the night, yet fully surrounded by the choruses of frogs, owls, and other nocturnal creatures, will remain with me forever.



64TH ANNUAL DROSOPHILA RESEARCH CONFERENCE

Matthew Gillen, 4th year MCB PhD Candidate
March 1-5, 2023 Chicago, IL

5

The 64th Annual Drosophila Research Conference was an outstanding experience and provided the opportunity to meet and learn from the wider Drosophila community. There were nearly one thousand presentations given on numerous elements of Drosophila biology, including genetics and gastrointestinal biology. Some posters and presentations focused on the potential of Drosophila as a model system for humans. A plenary session, for instance, explored the potential of using flies to model alcohol addiction in humans. Other talks detailed specific developmental processes in Drosophila that were more oriented around a basic science research perspective and could have enormous potential for the development of new tools to use in this model system.

My own experience in giving a talk towards the end of the weekend was nerve-wracking, but also extremely rewarding! I was able to detail my project and its progress to experts and leaders in this field and received some interesting feedback. Once I returned to USUHS from Chicago, I conducted several new experiments and adjustments to previous experiments based on the inspiring conversations I had during the conference. If anyone is interested in working in Drosophila as a model system, I would highly recommend attending the next meeting, and getting involved in the community!



6

AMERICAN SOCIETY FOR CELL BIOLOGY ANNUAL MEETING

Imran Hussain, 6th year MCB PhD Candidate
December 3-7 2022 Washington, D.C.

“Cell Bio” is an annual joint meeting organized by the American Society for Cell Biology (ASCB) and European Molecular Biology Organization (EMBO) with its debut beginning virtually in 2020. It replaced the annual ASCB conferences, which ran between the years 1961-2019. Globally, there are 7,500 ASCB members, with 75% of the members operating in the United States. Incredibly, more than 40 past or current ASCB members have been awarded Nobel Prizes in either medicine or in chemistry. These days, the yearly meetings draw about 6,000 people. I had the opportunity to attend the first in-person Cell Bio conference last December in Washington, D.C.—this was my first time attending this conference, and I was presenting a poster. The exhibition floor layout encompassed discrete groups of poster boards enclosed within a labyrinth of commercial exhibitors. These exhibitors pay big money to secure a presence at this conference; the German microscope manufacturer Zeiss had a particularly conspicuous setup there.

Since my research involves studying cell signaling that occurs from an aggresome-like structure, I designed my poster to attract the attendees working in the protein degradation field. Unfortunately, while my poster session managed to generate some interest, it was mainly from other T cell biologists (a minority at this meeting). On the other hand, it was clear that now is a good time to be a cytoskeleton biologist. My fellow poster presenters who were stationed adjacent to me, many of whom study the mechanism of actin-based cell membrane projections and cell motility, were lucky enough to receive a lot of traffic; suffice to say: I was a jealous cat.

Aside from presenting a poster, I attended a select list of talks to network and learn. Our very own Dr. Rachel Cox was giving a talk as part of the “Cell Biology Opportunities in Government” session advocating for careers options in USU. I also attended a

talk entitled “How to Prepare for a Career in Biotech”, where the speaker was generous with his tips on how to successfully land a job in a biotech/pharma company (e.g., how to write an effective cover letter, resume formatting, interview tips, etc.). Finally, I sat in on a talk entitled “Transition Academy: Senior Graduate Session: Planning Your Next Step After Graduate School,” which was relevant to my circumstance as a senior Ph.D. student. Of course, there were other sessions that targeted scientists in different career stages (i.e., post-docs transitioning to faculty jobs, undergraduates looking to attend graduate school, etc.). The “career fair” was dismal as there was only one information table that handed you a brochure to the American Association for the Advancement of Science (AAAS) website; however, it seemed almost every investigator was seeking to recruit post-doc candidates.

At CellBio, I saw many more USU attendees aside from Dr. Cox. I briefly ran into Dr. Prasanna Krishnan who was focused on a poster crafted by a trainee of Dr. Randy Schekman, a well-respected scientist in the field. Randy Schekman, along with James Rothman and Thomas Südhof shared the 2013 Nobel Prize in Physiology or Medicine for their findings regarding the molecular determinants of vesicle transportation and protein secretion. Also in attendance was Matt Gillen, a MCB graduate student working in Dr. Cox’s lab. Finally, it was a pleasure to spot the familiar faces of Ph.D. students from Dr. Jeremy Rotty’s lab: Matt Stinson, Rohini Manickam, and Summer Paulson. Since they all work in the actin-field, they received a ton of attention during their poster sessions, which confirmed my suspicion that the actin-field was indeed in fashion at this conference.

While I typically avoid large conferences, I thought it was ultimately worth my time to attend this one. For all the reasons highlighted above, I learned some valuable lessons and had a good experience.



AMERICAN SOCIETY FOR CELL BIOLOGY ANNUAL MEETING

Dr. Jeremy Rotty, Department of Biochemistry
December 3-7 2022 Washington, D.C.

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I had the opportunity to attend the American Society for Cell Biology annual meeting in Washington D.C. from December 3-7, 2022. ASCB provides a great opportunity to see old friends, make new contacts, and connect with potential collaborators around the world. I was particularly impressed to see that many of the mini- and micro-symposium talks were given by graduate students and postdocs, with the occasional early-stage PI thrown in as well. The meeting offered numerous career development workshops and networking events specifically geared towards students and postdocs. Kudos to ASCB for recognizing the needs of early career scientists, and providing meaningful opportunities for them to contribute to the scientific discourse.

The talks that I attended ranged across the cell biological spectrum, from basic structure/function studies on actin-associated proteins to intravital imaging of single cells in mice! Among the many highlights of the meeting were two talks from trainees in Roberto Weigert's lab across the street at NCI. Nicolas Melis presented striking intravital microscopy work showing that neutrophils migrating in the mouse ear toward sterile laser injury localize the contractile apparatus differently than in 2D cell culture-based models. Marco Heydecker used an intravital approach in mice, beautifully demonstrating that membrane trafficking requires sequential actin polymerization by two different actin regulators. Ernest Lu, from Sergey Plot-

nikov's lab at U. Toronto, demonstrated that calcium influx regulates the stability of actin-based protrusions called lamellipodia. But I didn't spend my whole meeting at cell migration talks!

Getting off the beaten path a bit led me to several talks that broadened my biological horizons. I learned from Madeline Keenen (Amy Gladfelter's lab, UNC-Chapel Hill) that there are cells in the placenta called syncytiotrophoblasts (STBs) that are multinucleated single cells that can have a surface area up to 14 square meters! This begs the question of how the different functional zones of STBs are established, since many placental functions are carried out by this cell type. The Gladfelter lab is using single nuclei seq, among other approaches, to help answer this question. Cameron MacQuarie (Arcadia Biosciences) taught me that a class of marine algae called Chlorarachniophytes make cellular extensions that are both light and actin-dependent. Aoife Heaslip, from the University of Connecticut, presented her lab's work on an unconventional myosin that regulates cargo transport in *Toxoplasma*.

There was such a wide array of world-class science presented at ASCB that it is difficult to pick just a few highlights! Each year at ASCB I am reminded why I enjoy doing science, and why I love attending this meeting. I hope that you will join our lab in Boston at ASCB 2023!



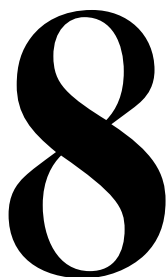
The Gordon Research Conference for Directed Cell Migration took place within the confines of the Grand Galvez hotel in Galveston, Texas. There were about 135 participants with some of the most influential and well-respected scientists in the field of cell migration in attendance.

Some notable presentations included novel ways cells can generate and migrate upon their own chemotactic gradients, detailed how confinement could be an inherent inflammatory regulator, and revealed a novel T-cell surveillance network in adult zebrafish. There has also been substantial work done on creating fluorescent G Protein-Coupled Receptors (GPCR) activation probes and light-inducible cytoskeleton regulators to alter cell migration direction. Many of the newest materials that scientists presented were made accessible to anyone who wanted to incorporate them into their own work. In addition to bringing together many of the top researchers in the field, the conference proved that there is a lot of excited, young talent as well.

The poster sessions were well designed to facilitate interacting with my peers and seeing first-hand how similar some of our strategies and approaches were to science. The previous month, I had attended the American Society for Cell Biology meeting and it was

very refreshing to go from one of the largest cell biology conferences, to the GRC, where I did not have to explain why I used certain cytoskeleton-targeting drugs, extra-cellular matrix proteins, and methods of quantifying cell shape changes. People just “got it,” like we were all speaking the same language of research.

The meals also provided great networking opportunities for graduate students and postdocs alike. Each table had room for 10 people, and everyone made an effort to sit with different groups each time to avoid forming cliques. On one of the last nights of the conference, I had a conversation with a postdoc that gave me a whole new insight into the potential mechanisms behind my own migratory macrophages. When she saw my poster, she suggested that I examine the concentration of activated versus inactivated integrins on different ECM components. This was a completely novel idea that has not previously occurred to me or others during conversations at USUHS, and I was instantly excited to get back to the lab and try it out. Overall, the GRC Directed Cell Migration Conference was an incredible experience that gave me a lot of valuable insight into the current state of the field. Much of the data presented was unpublished, and the excitement for the newest advances in cellular migration was palpable.



DIRECTED CELL MIGRATION GORDON RESEARCH CONFERENCE

Matthew Stinson, 5th year MCB PhD Candidate
January 8-13, 2023 Galveston, Texas



NATIONAL CAPITAL AREA TRAUMATIC BRAIN INJURY

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Antigone Grillakis, 6th year NES PhD Candidate
Baltimore, MD March 9-10 2023

The National Capital Area Traumatic Brain Injury (NCA TBI) Symposium was held this past March for the first time after a two-year hiatus. It took place at the University of Maryland, College Park Campus and hosted approximately 350 attendees, 97 posters, 36 oral presentations, and 4 plenary sessions. Topics covered by the conference included Preclinical and Clinical Biomarkers, Molecular Mechanisms, Neuroimaging, Neurotherapeutics, and Diagnosis & Rehabilitation of TBI. Attendees were both local (from universities like USUHS, UMD, and Georgetown, as well as the NIH, WRAIR, and NMRC), and came from prestigious research institutions across the country.

The keynote speaker was Dr. Geoffrey Manley, MD, PhD, Chief of Neurosurgery at Zuckerberg San Francisco General Hospital, and Professor and Vice Chairman of Neurosurgery at the University of California, San Francisco. His seminar outlined the recently launched Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET), a multi-center Phase 2 clinical trial network geared toward harnessing the vast database of research in the field and applying it to a new generation of precision medicine clinical trials. His talk focused on the diagnosis of brain injuries, which have traditionally been categorized into mild, moderate, and severe, based on subjective reporting and imaging like CT and MRI. However, not only do the definitions of TBI differ between organizations, but they have also been found in many cases to poorly predict

recovery. Another complication in diagnosing the severity of TBI is the question of which patients to send for further imaging; MRI and CT scans are not appropriate or necessary for everyone presenting with a TBI, and in the emergency room, providers must balance time and cost restrictions with accuracy of diagnosis. Thus, scientists and clinicians have been in search of objective biomarkers that can both diagnose and predict outcomes after injury.

In his talk, Dr. Manley asserts that, as a field, we need to let go of thinking of TBI as 'mild, moderate, or severe' and move to describing brain injuries in a way that encompasses the patient's biomarker and imaging findings. Though the focus of the talk was clinical, it is clear that to increase translatability of our research, we also need to shift the way we think about TBI severity and biomarkers in the validation of preclinical models. This was a key takeaway for me because I use a model of repetitive closed-head injury in mice that was recently developed and is still being fully characterized and validated.

I have attended this meeting several times in the past and have enjoyed the chance to learn about new perspectives and to exchange ideas -- I always walk away energized and excited about my research. I have also found that the focused scope and size of this meeting make it a great opportunity to present a poster or give a talk, particularly for graduate students who are just starting out.



The Society for Neuroscience (SfN) conference brings together about 30,000 scientists each year, covering a wide range of neuroscience research. Its location rotates each year between San Diego, CA, Chicago, IL, and Washington, DC. This past year's conference was held in San Diego, a lovely place to escape Maryland and visit in November! The large attendance of this meeting provides a great opportunity to meet researchers who are studying the same condition as you, but from a different angle, and others who are using the same techniques as you, but for a completely different purpose.

SfN provided me the uncommon chance to meet and discuss findings with other researchers studying the same rare neurodevelopmental disorder I study. Discussions with other Angelman Syndrome researchers from around the world encouraged me to take a second look at some data that I had previously set aside, which has led to some significant findings since the conference. It was exciting to find commonalities between my findings and others', as well as to hear about Angelman's Syndrome, a disorder often considered to be monogenic, is actually influenced by other, less-understood genes. These fruitful conversations also allowed us to build connections that could benefit us all in the future. Aside from research presentations, SfN provides the opportunity to talk with a wide variety of vendors, to network with other scientists at socials in the evenings, to attend professional development sessions, and even to interview for jobs through NeuroJobs.

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The next conference will be in DC, at the Walter E. Washington Center from November 11-15, 2023, so I would encourage anyone interested in neuroscience research to consider attending. A piece of advice for anyone attending SfN: there are typically 20+ sessions running at any given time, so it's important to be prepared going into this meeting. Set aside time to make yourself a schedule before you arrive. There is a cell phone app that makes this easy and is very handy to refer to during the conference. It'll make the experience much smoother and ensure you don't miss sessions you'd really like to see!

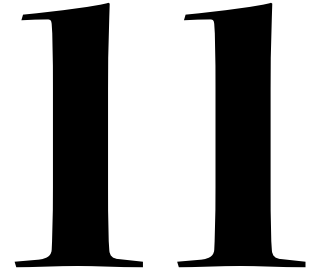
SOCIETY FOR NEUROSCIENCE 2022

Laura Drebushenko, 6th year NES PhD Candidate
November 12-16, 2022 San Diego, CA



SOCIETY FOR NEUROSCIENCE

Summer Paulson, 3rd year NES PhD Candidate
November 12-16, 2022 San Diego, CA



The annual Society for Neuroscience (SfN) conference is sure to have something in your field if you can relate even a little bit of neuroscience to it. Prioritizing which talks and posters are most prevalent for your research or topic of interest is essential to get the most out of attending. With more than 30,000 people in attendance, there was opportunity to learn from a wide range of speakers – the conference size giving way to a broader scope of knowledge present.

I had the opportunity to attend some interesting keynote talks, as the conference capped each day with a different speaker in their Presidential Lecture Series. The 2021 Nobel Prize Winner, Dr. Ardem Patapoutian, spoke about her discovery of mechanically activated ion channels, called PIEZO, which aid in proprioception. A pioneer in the sleep field, Dr. Amita Sehgal taught us about her discoveries of sleep-dependent and sleep-independent memory circuits, and the associated sleep genes helping differentiate these, using *Drosophila* models. Dr. Tiago Branco broke down the neurobiology behind the steps prey take when determining escape from predators and how different associated parts of the brain were identified. Due to the breadth of SfN, I was able to learn from speakers I would normally not have access to.

This was also reflected during the poster sessions. The questions I received at my poster were different than those received at either my program seminars or department presentations. Attendees rich in diverse areas of expertise contributed their thoughts to my project. This input would go on to help shape how I was approaching next steps to my thesis work, including incorporating a new technique. On the other hand, there was a fellow conference attendee who approached me during one of the breaks to give me his business card, stating that he was a sales rep and to come to his booth after my presentation time slot was done. It was a complement tech focused company, and, after seeing the term “complement” in my poster title, they had set aside some complement themed freebies to give out at their booth.

SfN is coming to Washington, D.C. in November 2023, so I encourage everyone to attend – no matter how relevant it seems to your research. There is something for everyone there.



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SOCIETY FOR NEUROSCIENCE

Christopher Bouslog, 2nd year NES PhD Student
November 12-16, 2022 San Diego, CA

Society for Neuroscience (SfN) 2022 may have officially kicked-off November 12, but it really started months before-hand for me. There was a long process of securing funding for travel and a lot of preparation to bookmark exactly what I wanted to see at the conference. With over 30,000 attendees, SfN is one of the largest academic conferences in the world. Because of its size, I was able to identify plenty of posters and talks that were of interest to me, and more niche than what I would typically find at smaller conferences. This included many studies on the lateral habenula (LHb). The LHb is a small epithalamic brain structure that (among other things) relays inhibitory signaling to the ventral tegmental area and regulates dopaminergic signaling. At the conference, I was intrigued by a few studies indicating the large effect the time of day has on genetic expression of *Bmal1*, which can cause varying electrophysiological responses of LHb neurons! These findings were interesting to me because they could directly impact my own work on the LHb and should inform the design of my experiments.

With such a wide variety of neuroscience topics covered at the conference, I took advantage of the opportunity to learn about neuroscience research outside the scope of my current work. I was fascinated by a poster discussing findings that vagus nerve innervation in a specific temporal pattern can increase penetrance of a dye injected into the CSF of a rodent's brain parenchyma as a glymphatic based therapy to treat Alzheimer's disease. Outside of research, one talk I attended spoke on the scientist's responsibility to do our own legwork in communicating our projects to the public via the media and how this could cyclically benefit our own funding.

Besides the valuable information I learned at SfN, I also had ample networking opportunities, starting with the day of travel. The terminal at the airport was full of people holding poster tubes. It seemed like everyone traveling from Washington D.C. to San Diego was going to SfN. It was a surprising opportunity to learn about future career options and I had informative conversations with people from Janelia Farms (HHMI) about their experience as postdocs.

Poster sessions and talks were not the only important components to experiencing this conference. I ended up having great conversations with both students and faculty from other institutions about their science and lives outside of the lab. It felt like I was getting a larger picture of possibilities of life after USUHS through this networking. The overall size and diversity (both scientifically and geographically) made SfN a unique experience with many things to be gained from attending.



EMORY MORNINGSIDE GLOBAL HEALTH CASE COMPETITION

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Joshua Trowell, 1st year PMB PhD Student
March 16-19, 2023 Atlanta, GA

Every year, the Emory Global Health Institute's (EGHI) Case Competition brings together students from around the world to work on finding innovative solutions to important global health issues. EGHI hosts two events yearly: the Intramural Emory Global Health Case Competition (open to only Emory students) and the Emory Morningside Global Health Case Competition, which attracts university students both nationally and internationally. This year, the case competition was held from March 10-18. About 120 students from 29 universities across six countries and 4 continents participated.

As a participant in the case, I had the opportunity to work with my team members, Remle Scott (Preventive Medicine & Biostatistics), Airyn Nash (Medical and Clinical Psychology), and Kevin Guan (Molecular and Cell Biology), under the guidance of our faculty advisor Dr. Winnie Gossa to come up with a solution to a hypothetical but realistic global health issue. Team members were recruited by the Global Health Interest Group (GHIG) to form an interdisciplinary USU team to compete at local and international case competitions. Once given the case for this year's competition: 'Preventing Maternal Death in Haiti's Central Plateau' on March 10th, we spent a week reviewing literature, as well as gathering information and feedback from NGO directors, case advisors, as well as some PMB faculty and students. Our solution and intervention program, called Matwons bay Manmans (Midwives to Mothers), proposed establishing four maternity waiting homes in Savenette, Haiti, staffed by skilled birth attendants (Matwons or Matrons in Haitian-Creole). Our focus was on the prenatal aspect of pregnancy, and we introduced an updated curriculum that utilized a centering pregnancy approach. This approach included a theory of change model that outlined the

expected developmental changes resulting from our intervention, based on a causal analysis of the available evidence.

Our team employed a monitoring and evaluation (M & E) plan that used contribution analysis, an approach to inferring causality in program evaluations, to measure our interventions' impacts on the community. Our case solution also incorporated task-shifting, a strategy that redistributes work among a community or group for a specific goal. In order to measure outcomes and account for workforce shortages, we ensured that our M & E plan was incorporated throughout the three-year intervention period, which would also ensure the feasibility and sustainability of the program.

My teammate, Airyn, writes, "In this competition, we needed to maintain focus on the people we were aiming to help. A fundamental aspect of our approach was ensuring community cultural preservation. This bottom-up approach to program development promoted ownership within the community that was more organic...I didn't have much background with global health policies, but it was an amazing opportunity to work with an interdisciplinary team at USUHS. It was great to see how our perspectives and backgrounds strengthened our solution."

Our hard work paid off when we presented our solution at Emory University. After two rounds of competition, we won first place and a \$6,000 prize. As a new member of the GHIG, I also plan to participate in Washington D.C.'s public health case competition. It is worth considering participating in these competitions if you enjoy networking and solving complex public health issues, or if you want to improve your public speaking skills.



This past October, I was able to attend the American Society of Tropical Medicine and Hygiene (ASTMH) conference in Seattle WA. ASTMH is a five-day conference that draws more than 4,000 tropical medicine and global health professionals representing academia, foundations, government, non-profit organizations, non-governmental organizations, the private sector, military, and private practice. The meeting emphasizes international collaboration with attendees representing more than 100 countries. The conference features research symposia and poster presentations on a variety of topics in tropical medicine including mosquito-borne diseases like malaria, dengue, and Zika, hemorrhagic fevers like Ebola or Marburg, neglected tropical diseases, soil-transmitted helminths, enteric diseases like cholera, and many more. The research covers a diverse range of disciplines such as clinical trials, virology, epidemiology, mathematical modeling, and qualitative analyses.

Many research studies at ASTMH focused on the growing importance of climate change in the global health landscape and its impact on disease transmission. A frequent topic of discussion was the concept of One Health, which is a collaborative

and transdisciplinary approach that emphasizes the interconnectedness between human health, animal health, and environmental health. For example, one researcher discussed the treatment of livestock with insecticides like ivermectin to reduce the survival time of mosquitoes that transmit malaria to humans. Although many symposia focused on the “global South” countries, some researchers also presented on tropical diseases in North America, including soil transmitted helminths in rural Alabama and emerging tick-borne disease like Powassan virus in the Northeast.

In addition, I presented a poster focused on my dissertation research. My project involved modeling the potential distribution of Mayaro virus (MAYV), a mosquito-borne Alphavirus that can cause debilitating muscle or joint pain. My project used a machine learning technique to develop risk maps of MAYV transmission zones and estimate the number of people potentially at risk. This experience provided an opportunity to present my research to a diverse audience and to network with other scientists in the field. Overall, attending ASTMH was a rewarding experience and I plan on attending this year’s conference in Chicago.

Michael Celone, 4th year PMB PhD Candidate
October 30 - November 3, 2022 Seattle, Washington

AMERICAN SOCIETY OF TROPICAL MEDICINE AND HYGIENE

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ANATOMY CONNECTED 2023

Kyle Carr, 1st Year Medical Student / Air Force

March 25-27, 2023 Washington, D.C.

Anatomy Connected 2023, in downtown DC, was a fantastic experience. I think the biggest factor that made this an interesting conference was the number of interdisciplinary presentations. In a single hour-and-a-half session, I heard from a dinosaur paleontologist, a cavefish researcher, and about the regenerative potential of mammalian cardiomyocytes. Most academic conferences are too specific to bring together such an interesting array of expertise, but the engaging, interdisciplinary design of Anatomy Connected made it formative for my career.

The most interesting academic aspects of the conference involved translational research on military-relevant healthcare frontiers to include things like limb/organ regeneration and hibernation. I was fortunate to be presenting a poster on a vestigial muscle my team found during a dissection in the USU Anatomy Teaching Lab. Interestingly, a group from Brazil was presenting a poster detailing their study on the incidence of the same vestigial in their population. One of their investigators was present and, serendipitously, Spanish was the most comfortable mutual language between us, so I had a fun challenge getting to discuss the details of our research in my second language. They also observed a quite different incidence of the muscle than what we found in the literature, so that was insightful for our future manuscript as well.

All that said, the best part of the conference was the opportunity to get to know USU faculty and medical students from different classes on a deeper level than I would normally be able to. I made connections that I normally wouldn't have sought out, was offered further research opportunities, and reignited a passion to complete past research projects that had been left behind. While I only attended a single day of the conference, I got a lot more out of it than I ever expected.



INTERNATIONAL MEETING ON SIMULATION IN HEALTHCARE

Dr. Alexis Battista, Department of Medicine
January 19-25, 2023 Orlando, Florida

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This year's conference began with a two-day research summit to examine the current evidence base for healthcare simulation and determine whether there was sufficient evidence to update practice guidelines. Twelve research teams presented findings focusing on topics such as clinical skills performance, feedback and debriefing, self-regulated learning in simulation, the timing of simulation practice, and instructor education. Although all groups set out to conduct a meta-analysis, eleven found that the diversity in simulation-based learning activities and a lack of detailed description of study interventions prevented them from identifying enough studies with similar characteristics, thus preventing the conduct of a meta-analysis. Some examples of diversity included differences in simulation genre (e.g., procedural skills, scenario-based simulations), simulator modality (e.g., task trainers, full body simulators, simulated participants, combinations of modalities), and implementation approaches (e.g., lab-based, in-situ, computer-based, virtual) and reflection strategies (e.g., one on one feedback, group debriefing).

Given this, summit participants and research teams collaborated using small group discussions to develop recommendations for future research. Recommendations include promoting the extensions to the Consolidated Standards of Reporting Trials (CONSORT) to guide authors' reporting of simulation-based interventions. Additionally, because simulation-based learning continues to evolve rapidly, the research summit leadership and teams plan to revisit the current CONSORT extension to identify where updates may be needed. For example, the use of distance learning platforms expanded due to the pandemic. Research participants also argued for the future inclusion of extended environments (XR), such as virtual and augmented reality, given that these approaches are more scalable than in-person simulations.

Although the summit concluded without significant updates to practiced guidelines, the dialog between investigators and participants demonstrated how simulation-based learning activities continue to be refined and adapted to meet the needs of health professional education stakeholders (e.g., academic institutions, hospitals, educators, and students). Additionally, research summits such as this one provides an invaluable forum for newcomers and more experienced researchers to come together and discuss the field's progress and potential future.



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ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES ANNUAL MEETING

Noah Smith, 3rd Year Medical Student / Air Force
National Harbor, Maryland February 13-16, 2023

The 2023 Association of Military Surgeons of the United States (AMSUS) Annual Meeting at the National Harbor, Maryland took place from February 13-16, 2023, at the Gaylord National Resort and Convention Center. The meeting was a highly anticipated event that brought together federal healthcare professionals from all over the world. The event encompassed a broad scope of events including guest speakers, panel discussions, research poster presentations, and opportunities to earn certifications and continuing education credit. Topics of the meeting included current and future challenges and innovations in garrison military medicine, deployed military medicine, and civilian-military medical partnerships.

One of the highlights of the event was the keynote address by Dr. Gerald E. Harmon, Immediate Past President of the American Medical Association. Dr. Harmon spoke about the necessity of strong physician leadership in the medical field and our nation's substantial need for provider resiliency amid the COVID-19 pandemic, comparing the situation to war. "Both [war and the pandemic] can be a matter of life and death, both can be very costly in human and economic terms, and the price of both often leads to financial, physical, and emotional exhaustion," Dr. Harmon stated. This perspective resonated with many members of his military medical audience.

In addition to Dr. Harmon's allegorical rendering of war, the meeting also focused on the future of literal warfare, particularly near-peer warfare, and its implications for the field of military medicine. A theme of the event was that American military

medicine will need to adapt from the model used during the Global War on Terror – one in which aeromedical evacuation for injured service members to higher echelons of care was quick and readily available – and transition to a mindset of large-scale combat operations that lacks air supremacy. AMSUS speakers suggested that this doctrinal shift necessitates the need for strong and sophisticated Prolonged Casualty Care (PCC) capabilities – a topic emphasized during the Uniformed Services University curricular event, Operation Gunpowder.

Another feature at the event was companies such as Philips, Anatomage, and SimX showcasing their various technological advances that are being implemented into military and civilian medical training. These included the optimization of telemedicine, introduction of life-size virtual anatomy dissection touchscreen tables, and use of virtual reality simulations in deployed and non-deployed hospital settings. The event also touched on the military medical field's integration with the newest service branch, the Space Force.

Overall, the 2023 AMSUS Annual Meeting was a highly successful event that brought together a diverse representation of federal healthcare professionals to exchange knowledge and ideas. This provided a wealth of networking and collaboration opportunities, as well as exposure to the most up-to-date research in the field. The event was well organized and gave a clear vision into the future of military medicine during a time of military doctrinal transition.



The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is a large, diverse group of members involved in Nuclear Medicine, including nuclear physicists, radiochemists, research scientists, nuclear medicine physicians, nuclear radiologists, nuclear medicine technologists, medical physicists, and many others. Nuclear Medicine involves the molecular targeting of radiopharmaceuticals for the diagnosis and treatment of medical conditions, such as slowed bowel motility, cardiac ischemia, dementia, and cancer to name a few.

Theranostics is a new term for something in Nuclear Medicine that has been done since the 1940s, namely using radiopharmaceutical pairings for targeted molecular diagnosis and therapy. In the 1940s, it was the diagnostic and therapeutic pairing of I-131, which could both image and treat thyroid pathologies. Two of the exciting new applications of theranostics at the SNMMI Mid-Winter meeting were discussions about the neuroendocrine tumor theragnostic pairing of 68Ga-DOTATATE (NETSPOT)/177Lu-DOTATATE (LUTATHERA) and the new prostate cancer theragnostic pairing of 18F or 68Ga labeled PSMA-binding molecules and 177Lu labeled PSMA-binding molecules (PLUVICTO). These pairings allow for molecular targeting of imaging using PET/CT with 68Ga or 18F labeled compounds and personalized, molecular-targeted treatment with the 177Lu compounds. The imaging compounds emit positrons, which can then be imaged with PET/CT scanners. The therapy compounds emit beta particles (electrons), which target the DNA of target cancer cells, causing them to undergo apoptosis. These compounds have revolutionized care for patients without other options of treatment.

A particularly exciting radiopharmaceutical was one that binds to Poly (ADP-ribose) polymerases (PARPs). In response to DNA damage, the radiopharmaceutical binds to DNA and promotes its repair. An interesting radiopharmaceutical theragnostic pairing has been designed that can image PARP binding to DNA in cancer cells. This is useful from a pharmaceutical perspective to visualize the ability of PARP inhibitors to block the binding of PARP to DNA. The researchers also designed an alpha-emitting PARP binding radiopharmaceutical for neuroblastoma treatment. Alpha-emitters give off a helium nucleus, which has a much higher killing efficiency with limited range. It tends to induce double-stranded DNA breaks. So, the cool thing about the radiopharmaceutical is that it binds to DNA-bound PARPs and induces DNA damage. When given in fractionated doses, the DNA damage induced by the radiopharmaceutical causes more PARPs to be recruited, leading to further DNA damage, and exponentially increasing the damage to cancer cells in a positive feedback loop.

This is just one of the interesting possibilities in Nuclear Medicine, which has and will impact the way we treat cancer in the future. I would be happy to talk to interested students and faculty about these personalized, molecular approaches to cancer care. I recommend attending the SNMMI annual meeting in Chicago, IL in June 2023 or the next Mid-Winter meeting in Orlando, FL in February 2024 to learn more about this exciting medical specialty that blends anatomy, physiology, and innovation to personalized cancer care.

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SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING MID-WINTER

**Lt Col Justin Peacock MD, PhD USAF MC, Department of Radiology
and Radiological Sciences**

January 26-28, 2023 San Francisco, California



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67TH ANNUAL SOUTHWEST CHAPTER OF THE SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

**Melissa Robles, CNMT, NMTCB(CT), Brooke Army Medical
Center Phase II Nuclear Medicine Clinical Coordinator**
March 24-26, 2023 Sugarland, Texas

The Southwest Chapter of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) consists of over 1,200 physicians, technologists, pharmacists, veterinarians, physicists, and vendors who reside in Texas, Louisiana, Oklahoma, Arkansas, and New Mexico. This was the first in-person conference the society has been able to put on since 2018 due to the outbreak of COVID. The conference took place in the beautiful city center of Sugarland, Texas, a small suburb within Houston. I highly recommend this location for any conference. It has multiple restaurants and stores within a one-block radius of the Marriott conference center located in the heart of Houston. This was one of the best conference locations I have ever attended!

One of the major highlights from the conference was seeing Miss America 2023, Grace Stanke, who is currently studying nuclear engineering at the University of Wisconsin. She gave a presentation on clean energy and the use of nuclear reactors. Some other major topics at the conference were prostate cancer imaging and treatment. We took an in-depth look at prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) imaging techniques, and their use in the diagnosis and risk stratification for prostate cancer patients.

We also looked at the use of PET/CT for determining the qualifications for PSMA-based prostate cancer therapy. These presentations were followed by sessions on the newly FDA approved (March 2022) prostate cancer therapy using PSMA called Pluvicto. We were able to discuss the techniques for delivering this life saving treatment and its effectiveness on treating castrate resistant prostate cancer patients by delivering high doses of radiation specifically to can-

cer cells. We also discussed new innovations in the field of theranostics with the ability to see where the cancer treatments will localize prior to administering the high dose radiation therapies and using the same antigens to monitor the effectiveness of the therapy with post therapy imaging.

Another final highlight of the conference was a session given by fellow USU faculty and Health Professional Education (HPE) student LTC Justin Peacock on the use of simulations to teach residents, fellows, and technologists in Nuclear Medicine. The use of simulations is a highly effective method to teach real life skills surrounding radioactive spills since real radiation cannot be utilized for teaching purposes due to strict federal regulations surrounding the use of radioactive materials.

These topics demonstrate how the field of Nuclear Medicine and Molecular imaging is changing its focus to cancer therapies and improving clinical education of future physicians and technologists. I would recommend this conference to anyone in medicine interested in the field of Nuclear Medicine. No matter what your specialty or focus is as a physician, if you refer your patients to have procedures done in nuclear medicine, attending these conferences will give you a better understanding of how the modality can better assist you in caring for your patients. It will also provide insight into new innovations in cancer treatments provided by the Nuclear Medicine department.



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